Utilization of Electrophilic Benzannulated Heterocycles for Accessing Novel Heteroacenes

by

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10CC18A39016

A thesis submitted to the
Academy of Scientific & Innovative Research
for the award of the degree of
DOCTOR OF PHILOSOPHY
in
SCIENCE

Under the supervision of
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November 2023

CSIR-National Institute for Interdisciplinary Science and Technology
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ACKNOWLEDGEMENTS

It is with immense pleasure and great respect that I place on record my deep sense of gratitude to my research supervisors, ***Dr. Jubi John*** *and* ***Dr. Sunil Varughese****, for suggesting the research topic and for their inspiring guidance, immense knowledge, endearing care, constant support, and motivation, leading to the successful completion of this work.*

I wish to thank Dr. C. Anandharamakrishnan and Dr. A. Ajayaghosh, present and former Directors of CSIR-National Institute for Interdisciplinary Science and Technology, Thiruvananthapuram, for providing me with the necessary facilities for carrying out the work.

I sincerely acknowledge Dr. R. Luxmi Varma, Dr. C. H. Suresh, and Dr. V. Karunakaran, former and present AcSIR coordinators, CSIR-NIIST for the timely help and advice for the academic procedures of AcSIR.

I am very much thankful to Dr. K. V. Radhakrishnan, Dr. U. S. Hareesh, and Dr. V. K. Praveen, my Doctoral Advisory Committee members, for their help, support, suggestion and encouragement throughout my PhD period.

I would like to express my gratitude to Dr. K. V. Radhakrishnan, Dr. P. Sujatha Devi, and Dr. R. Luxmi Varma present and former Heads, Chemical Sciences and Technology Division for their endless support.

I like to thank all the AcSIR faculty members of CSIR-NIIST for their help and support during the course work period.

I would like to thank Dr. L. Ravi Sankar, Dr. B. S. Sasidhar, Dr. Kaustabh Kumar Maiti, Dr. A. Kumaran, and Dr. Adarsh Ashok, and all other scientists of the Chemical Sciences and Technology Division, for all the help and support extended to me.

I would like to acknowledge Dr. Jomon Mathew (St. Joseph's College, Calicut) for computational studies, Dr. Sunil Varughese (CSIR-NIIST), Prof. Mahesh Hariharan, Mr. Alex Andrews (IISER-Thiruvananthapuram) and Dr. Jagadeesh Babu Nanubolu (CSIR-IICT) for single crystal X-ray analysis.

I would also like to thank Mrs. Saumini Mathew for recording NMR spectra, Mrs. Viji for mass spectral analysis, Mr. Robert Philip for the general help, Ms. Neethu K. K., and Ms. Divya Pillai, for helping me with the various experiments.

I greatly acknowledge my seniors Dr. Santhini P. V. and Dr. Nitha P.R., for their help and support throughout the studies.

I am grateful to my present and former members of JJ family, Dr. Nitha P. R., Dr. Vishnu K. Omanakuttan, Mr. Rahul P., Mr. Akhil Krishnan R., Dr. Dipankar Paul, Ms. Angel Johny, Ms. Reshma, Dr. Jagadeesh Krishnan, Ms. Anjana S., Ms. Nandana S. K., Mr. Surya, Mr. Shanif and Ms. Anjana J. for their love, care and support throughout my research period. I also thank my M. Sc. project students Ms. Rajalekshmi A. R., Ms. Namitha Paul, Ms. Varsha P. V., Ms. Aparna A., Ms. Malavika Mohan, Ms. Nafiya. for helping me to carry out some of my lab work.

I also thank all the present and former members of the Chemical Sciences and Technology Division and friends at other Divisions of CSIR-NIIST for their help and cooperation.

I am forever grateful to my dear friends Susu, Shibu, Indu, Vishnu, Nishna and Vyshnapriya for always being a source of happiness, love and support.

I would also like to thank Dr. G. Anil Kumar, School of Chemical Sciences, M.G. University Kottayam, and all my beloved teachers for their help and blessings.

I am deeply indebted to my Pappa, Mummy, sister Dr. Shelene, brother Dr. Jesu, and my cute little nephews Jayden and Johan, my in-laws, and other family members for their continued energy, unconditional love, and unerring support in my life. I am deeply grateful to my partner Prince for all the patience, understanding, love, and support.

Finally, I sincerely thank the CSIR-JRF and SRF for financial assistance.

Above all, I thank Almighty for all his blessings.

Sheba Ann Babu

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LIST OF ABBREVIATIONS

Å	Angstrom
Ac	Acetyl
AcOH	Acetic acid
Ar	Argon
Ar-	Aryl
Bn	Benzyl
BoC	*tert*-Butyloxycarbonyl
Calcd	Calculated
CCDC	Cambridge Crystallographic Data Centre
$CHCl_3$	Chloroform
°C	Degree celsius
DCE	Dichloroethane
DCM	Dichloromethane
d	Doublet
dd	Doublet of doublets
DMF	N, N-Dimethylformamide
DMSO	Dimethyl sulfoxide
DFT	Density functional theory
dr	Diastereomeric ratio
dt	Doublet of triplets
ee	Enantiomeric excess
equiv.	Equivalent
er	Enantiomeric ratio
ESI	Electron spray ionization

Et	Ethyl
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
et al.	Et allii/alia
FT-IR	Fourier transform infrared spectroscopy
h	Hour
HRMS	High resolution mass spectrometry
Hz	Hertz
^{i}Pr	Isopropyl
$^{i}PrOH$	Isopropyl alcohol
J	Coupling constant
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m	Meta
MCR	Multicomponent reaction
Me	Methyl
MeOH	Methanol
mg	Milligram
MHz	Mega hertz
min	Minutes
mL	Millilitre
mmol	Millimolar
mol%	Mole percent
MP	Melting point
MS	Molecular sieves
MW	Microwave

NIS	N-iodosuccinimide
Na	Sodium
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
Pd	Palladium
Ph	Phenyl
PTSA	*p*-Toluenesulfonic acid
q	Quartet
rt	Room temperature
Rh	Rhodium
Ru	Ruthenium
s	Singlet
t	Triplet
TBAI	Tetra-n-butylammonium iodide
tert	Tertiary
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
TMS	Tetramethylsilane
Tol	Tolyl
Ts	Tosyl
H_2O	Water
δ	NMR chemical shift in parts per million

PREFACE

Heteroacenes are considered promising candidates in the field of organic semiconductors, light-emitting diodes, field-effect transistors, and photovoltaics. The huge potential of heteroacenes can be attributed to the presence of heteroatoms and the possibility of variation of conjugation lengths, both of which have beneficial effects on their optoelectronic properties. Because of them being the subject of extensive research in material applications, several groups have come up with versatile and efficient synthetic strategies for polyring-fused heterocycles. Despite these interesting properties, the wide application of these heteroacenes is limited due to the lack of short and efficient synthetic routes. At this point, electrophilic indoles turned out to be useful in synthesizing *N*-heteroacenes, such as indole-fused heteroacenes, which show similar analogous properties. This thesis focuses on the use of electrophilic benzannulated heterocycles for accessing novel heteroacenes, in which we have demonstrated the reactivity of 3-nitroindoles/benzothiophenes towards different electron-rich species such as isoquinolinium, pyridinium ylides and 2-amino pyridines.

Our efforts focused on developing new synthetic methodologies towards fused heteroacenes from electrophilic benzannulated heterocycles. Our initial efforts were focused towards the synthesis of polyring-fused imidazo[1,2-*a*]pyridines from the annulation of electrophilic indoles with 2-aminopyridines and 2-aminoquinolines. Nitration reactions were carried out to obtain different substituted electrophilic indoles, and optimization studies were carried out towards the synthesis of indole-fused imidazo[1,2-*a*]pyridines and indolo-imidazo[1,2-*a*]quinolines with varied substitution pattern. Next, we turned our attention towards the dipolar cycloaddition of isoquinolinium and pyridinium methylides to electrophilic indoles for accessing functionalized pyrrolo[2,1-*a*]isoquinolines and indolizines, respectively. Here, different heteroaromatic *N*-ylides were prepared and treated with various electrophilic indoles. Finally, we have developed an efficient method to synthesize complex polyring fused *N*-heterocycles *via* Pd-catalyzed site-selective C–H activation from the above obtained pyrrolo[2,1-*a*]isoquinolines and indolizines.

The thesis has been divided into four chapters

Chapter 1 gives a brief introduction to the synthesis of *N*-heterocycles using electrophilic benzannulated heterocycles and the recent developments in this field. Herein, we present an overview of the reactivities of 3-nitroindoles towards different electron rich species, particularly in cycloaddition or annulation reactions.

In **Chapter 2,** we have developed a copper-catalyzed methodology for the synthesis of heteroacenes. By the annulation of electrophilic indole with 2-aminopyridine, we could generate indole-fused imidazo[1,2-*a*]pyridine, an interesting seldom-explored tetracene. We could also synthesize pentacene from electrophilic indole by performing annulation with 2-aminoquinoline. The present annulation was found to be general as a range of indole-fused imidazo[1,2-*a*]pyridines and indolo-imidazo[1,2-*a*]quinolines could be synthesized in moderate to good yields. The basic photophysical properties of representative examples of the synthesized heteroacenes were evaluated in order to assess their suitability in material applications. Finally, we could also extend the Cu-catalyzed annulation for the synthesis of benzothiophene-fused imidazo[1,2-*a*]pyridine.

In **Chapter 3A,** we have carried out a domino reaction involving a 1,3-dipolar cycloaddition and a ring-opening between isoquinolinium ylides and electrophilic benzannulated heterocycles. This hitherto unknown methodology gives easy access to a series of highly functionalized pyrrolo[2,1-*a*] isoquinolines starting from different isoquinolinium methylides and 3-nitroindoles. In addition, we observed the formation of S–S bridged bis-pyrrolo[2,1-*a*]isoquinolines from the reaction of 3-nitro benzothiophene and isoquinolinium methylides.

In **Chapter 3B,** a palladium-catalyzed site-selective C–H functionalization of the above obtained pyrrolo[2,1-*a*]isoquinolines towards the synthesis of complex polyring fused *N*-heterocycles was investigated. These observations were made on the 5-benzoylpyrrolo[2,1-*a*]isoquinoline scaffold, where we could identify three sites for C−H functionalization and an *N*-center which could participate in C−H amination. The experimental and theoretical investigations have shown that there is a preference for Pd-catalyzed cross-dehydrogenative coupling toward 8*H*-indeno-pyrrolo[2,1-*a*]isoquinolinone derivatives. Then, during our attempts for selective C−H amination, we came across a unique and previously unknown O_2 induced chemoselectivity forcing the formation of the 9*H*-indolo-pyrrolo[2,1-*a*]isoquinoline scaffold over the CDC product. We believe that this selectivity is induced by O_2, which gets incorporated in the active Pd-species, driving the reaction to take a Wacker-type pathway leading to C−H amination. When we tried the Pd catalyzed C−H amination with a substrate bearing a NO_2-group on the benzoyl moiety of the starting substrate, we found that the C−H amination was taking place preferentially at the isoquinoline ring. This result can be attributed to the higher electron density at the reactive center on the isoquinoline ring and the stability of the multiring fused benzazepine compared with the pentacene regioisomer.

In **Chapter 4A,** we came across another unexpected route towards the synthesis of indolizines. In the previous chapter, we utilized the reactivity of isoquinolinium ylides as the nucleophile for the 1,3-dipolar cycloaddition with electrophilic indoles, and here, we have planned to have pyridinium methylide as the nucleophilic partner. The reaction parameters were then optimised, and substrate scope was studied with differently substituted 3-nitroindoles and *N*-ylides. The reaction was found, in general, to yield the products in good yields.

In **Chapter 4B,** we observed a palladium-catalyzed site-selective C–H functionalization on the benzoyl-substituted indolizine scaffold. Here also, we could identify two sites for C−H functionalization and an *N*-center which could participate in C−H amination. The experimental investigations have shown that under Pd-catalyzed cross dehydrogenative coupling, an intramolecular cyclization takes place between the two C-H centres affording the corresponding 6*H*-indeno-indolizines and an intramolecular C-H amination takes place between the C-H and *N*-centers towards the synthesis of indolizino[2,1-*b*]indoles. The reaction is applicable to a range of substrates with various functional groups in moderate to good yields.

Chapter 1

An Overview of Recent Developments in the Synthesis of *N*-Heterocycles from Electrophilic Indoles

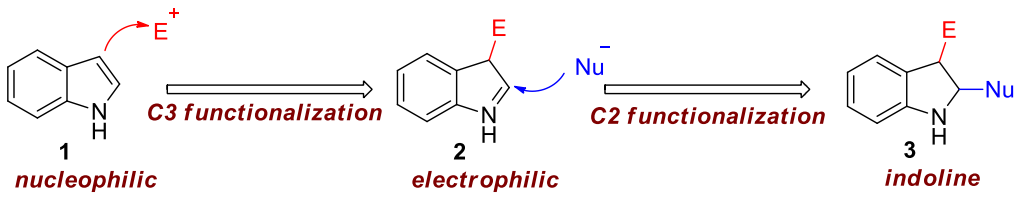
1.1 Abstract

Over the past two decades, the chemistry of electrophilic benzannulated heterocycles was extensively investigated, and several dipolar cycloadditions, metal and organo-catalyzed transformations were introduced for the generation of fused heterocycles. While the electron-rich character of the indole motif has been extensively studied over the years, recent research has focused on harnessing the electrophilic reactivity of 3-nitroindole derivatives. In this chapter, we study a series of reactions using benzannulated heterocycles acting as electrophiles with various electron-rich species towards the synthesis of fused N-heterocycles.

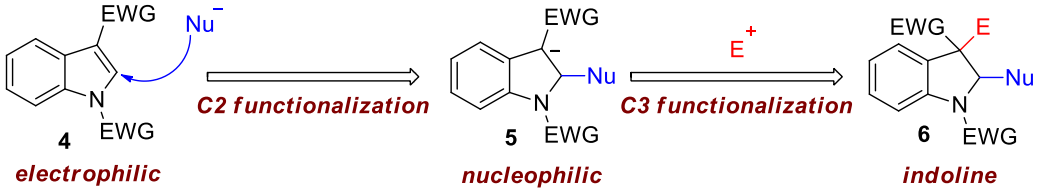
1.2 Introduction

Indole is generally considered an electron-rich species due to the characteristic nucleophilicity at the 3rd position.[1] But, if the *N*-atom and the 2nd or 3rd position of indole are substituted with electron-withdrawing substituents, the nucleophilic character is overturned.[2] As a result, the C2=C3-NO_2 part acts as an electron-deficient alkene that can participate in annulation reactions (Scheme 1.1). The nucleophilic part of the reactant will add to the 2nd position of electrophilic indole. The nucleophilic centre, thus formed at the 3rd position, will react with the electrophilic part of the reactant to form an annulated moiety.

Normal reactivity of indole



Reactivity of electrophilic indole



Scheme 1.1 Reactivity pattern of indole substrates

The creation of materials for organic semiconductors, light-emitting diodes, field-effect transistors, and photovoltaics is the consequence of significant developments in the study of polycyclic aromatic hydrocarbons during the recent decades.[3] When one or more of the C-H bonds in an acene (polycyclic aromatic compound) is substituted by a heteroatom such as N, S, O, etc., it becomes a heteroacene. Recent research has uncovered various heteroacenes containing S- or N-atoms that exhibit intriguing properties that could be used as functional materials.[4] These heteroacenes have several advantages over conventional polycyclic aromatic hydrocarbons, such as electron-richness, stability and tunable properties.[5] This has led to the quest for simple synthetic methods for accessing conjugated heteroacenes.[6] At this point, electrophilic indoles turned out to be useful in synthesizing *N*-heteroacenes, such as indole-fused heteroacenes (figure 1), which show similar analogous properties.

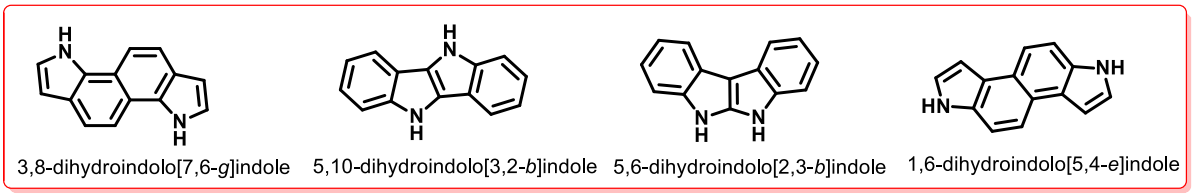


Figure 1. Indole-fused heteroacenes

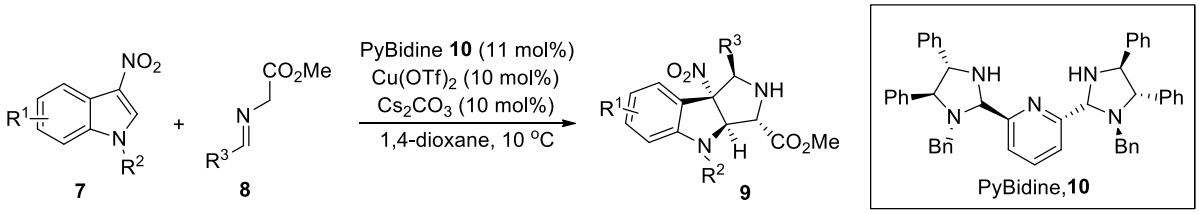
This thesis focuses on the use of electrophilic benzannulated heterocycles for accessing novel heteroacenes, and herein, we present an overview of the reactivities of electrophilic indoles towards different electron-rich species,[7] with particular attention to their participation in cycloaddition and annulation reactions.

1.3 Reactions of Electrophilic Indoles towards *N*-heterocycles

1.3.1 [3+2] cycloaddition reactions

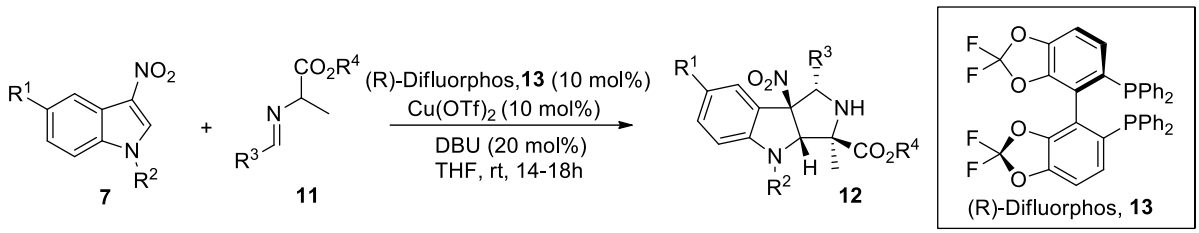
Cycloaddition reaction is one of the most important reactions in organic synthesis. It is a pericyclic reaction which involves an addition between two unsaturated molecules, affording a cyclic product. In recent years, the construction of heterocycles from arenes and heteroarenes has been made possible through [3+2] cycloaddition reactions.[8]

In 2014, for the first time, Arai *et al*. developed an enantioselective [3+2] cycloaddition reaction using electrophilic indoles with the help of PyBidine/Copper catalyst.[9] Promising results were obtained by using 11 mol% of PyBidine **10**, 10 mol% of $Cu(OTf)_2$ and 10 mol% Cs_2CO_3 as the base in 1,4-dioxane solvent at 10 °C. On investigating the substrate scope, it was found that the reaction proceeded well with various *N*-Ts-protected indoles **7** (Scheme 1.2). The cycloaddition reactions were also carried out with various imino esters **8**, affording the products with high enantioselectivity.



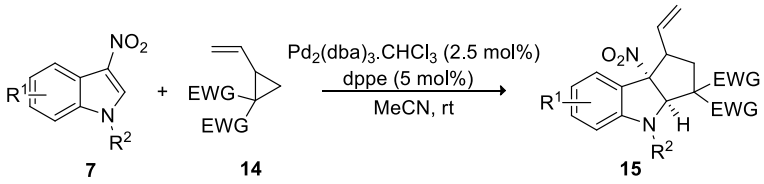
Scheme 1.2 Enantioselective [3+2] cycloaddition of 3-nitroindoles using PyBidine/Cu catalyst

In 2016, Stanley and coworkers successfully used a catalyst prepared from $Cu(OTf)_2$ and (*R*)-Diflurophos, in carrying out enantioselective dearomative [3+2] cycloadditions of indoles with azomethine ylides.[10] Screening of reaction conditions revealed that the reaction was influenced by the catalyst. The reaction was carried out using different types of imino esters **11**, derived from alanine methyl ester and a variety of aromatic aldehydes, in THF solvent at room temperature for 14-18 hours affording the corresponding products in moderate to good yields (Scheme 1.3).



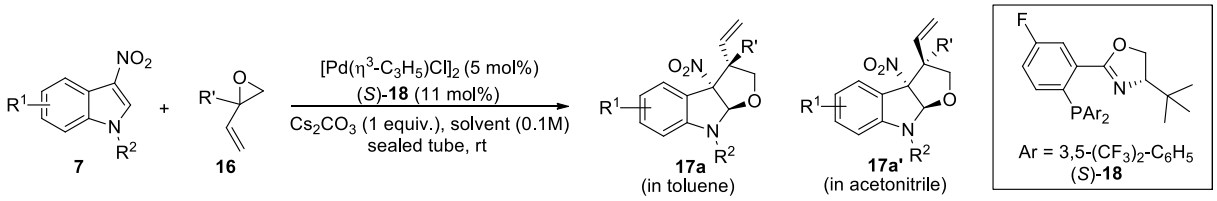
Scheme 1.3 Synthesis of pyrroloindoline derivatives

A Pd(0)-catalyst was used to catalyze a [3+2] cycloaddition of 3-nitroindoles **7** with vinyl cyclopropanes **14** , thereby leading to the synthesis of 2,3-fused cyclopentannulated indoline derivatives (Scheme 1.4). [11] The best results were obtained when 2.5 mol% of $Pd_2(dba)_3.CHCl_3$ and 5 mol% of dppe were used with MeCN (0.2M) as solvent at room temperature for 45 minutes.



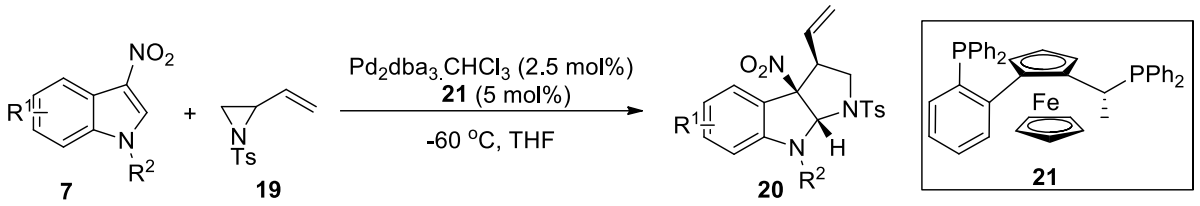
Scheme 1.4 Synthesis of 2, 3-fused cyclopentannuated indoline derivatives

An asymmetric [3+2] cycloaddition of 3-nitroindoles with epoxy butenes **16** was realized under palladium catalysis, [12] using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as the catalyst, affording the corresponding tetrahydrofuroindoles in high yields with good diastero- and enantioselectivities (Scheme 1.5).



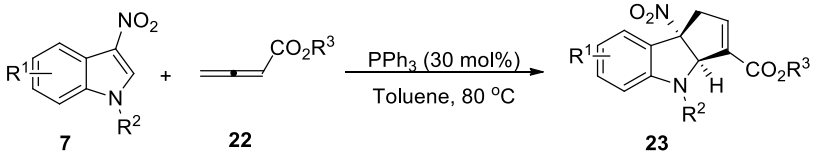
Scheme 1.5 [3+2] cycloaddition between 3-nitroindoles and epoxy butenes

Synthesis of pyrroloindolines through palladium catalyzed [3+2] cycloaddition of nitroindoles with vinyl aziridines was developed. [13] Using $Pd_2dba_3.CHCl_3$ (2.5 mol%), Walphos **21** (5 mol%) as the ligand at -60 ^oC in THF solvent led to the corresponding products in high yields and high diasteroselectivity and enantioselectivity (Scheme 1.6).



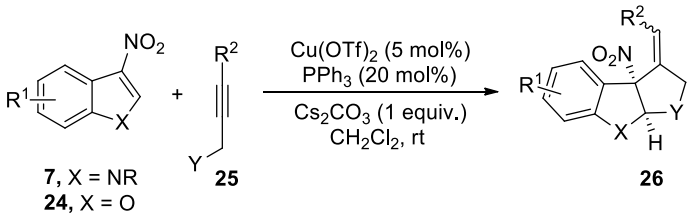
Scheme 1.6 Reaction of 3-nitroindoles with vinyl aziridines in the presence of Walphos ligand

The formation of an indole fused five membered ring *via* a [3+2] cyclization reaction between 3-nitroindoles and allene esters **22** catalyzed by PPh_3 (30 mol%) with toluene as solvent at 80 °C was reported in 2012 by Shi and coworkers (Scheme 1.7).[14] It was through this work where the authors put forward an idea of using various 1, 3-dipoles for carrying out [3+2] cyclizations with 3-nitroindoles.



Scheme 1.7 A phosphine catalyzed reaction between 3-nitroindoles and allene esters

Vitale *et al*. reported a copper catalyzed approach towards the synthesis of cyclopenta[*b*]indolines by a dearomative [3+2] cycloaddition process between 3-nitroindoles and propargyllic nucleophiles **25**.[15] The reaction was performed using $Cu(OTf)_2$ (5 mol%), PPh_3(20 mol%), Cs_2CO_3 (1 equiv.) as base in DCM solvent at room temperature to afford the corresponding indolines in moderate to good yield. Starting from 3-nitrobenzofuran, this methodology could also be applied to the synthesis of cyclopenta[*b*]benzofurans (Scheme 1.8).

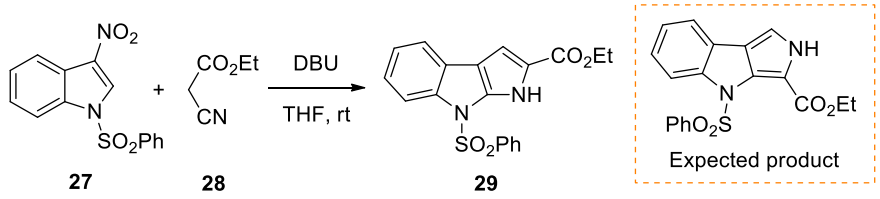


Scheme 1.8 Copper catalyzed reaction between 3-nitroindoles and propargyllic nucleophiles

1.3.2 1,3-dipolar cycloaddition

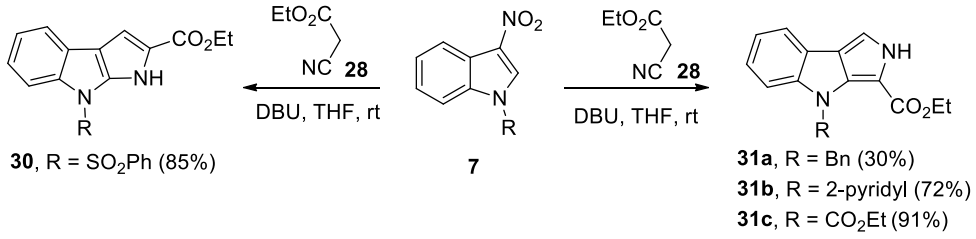
1,3-dipolar cycloaddition stands as an effective method for the regio and stereoselective synthesis of 5-membered heterocycles. The reaction takes place between a 1,3-dipole and a dipolarophile to form a 5-membered ring.[8] Here, indole substrates are put forward for accessing fused rings by acting as suitable dipolarophiles.

Gribble and coworkers reported the synthesis of pyrrolo[2,3-*b*]indole from electrophilic indole *via* an abnormal Barton-Zard reaction.[16] In the presence of DBU as the base, 3-nitro-*N*-(phenylsulfonyl)indole **27** was treated with ethyl isocyanoacetate **28.** In contrary to the expectation of product ethyl 4-(phenylsulfonyl)-2,4-dihydro-pyrrolo[3,4-*b*]indole-3-carboxylate, the authors isolated ethyl-8-(phenylsulfonyl)-1,8-dihyropyrrolo[2,3-*b*]indole-2-carboxylate **29** in 85% yield (Scheme 1.9).



Scheme 1.9 Synthesis of pyrrolo[2,3-*b*]indole from electrophilic indole

The unprecedented observation of formation of pyrrolo[2,3-*b*]indole from the reaction of electrophilic indole and ethyl isocyanoacetate in the presence of a base was later investigated in detail by the same group (Scheme 1.10).

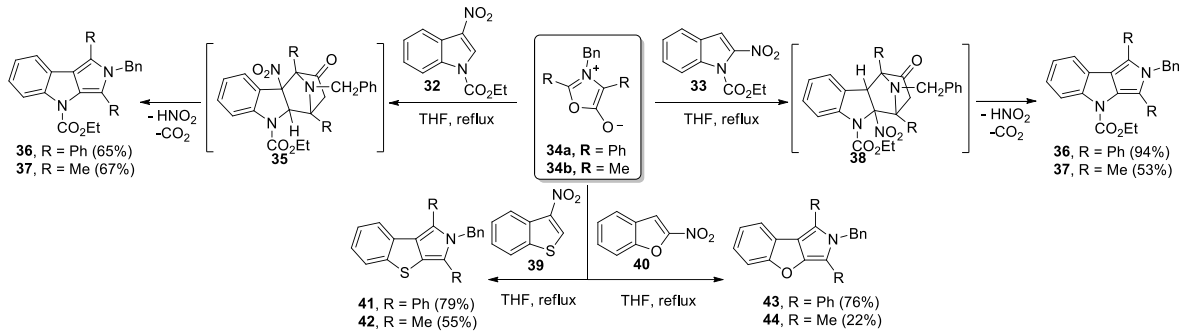


Scheme 1.10 Synthesis of pyrrolo[2,3-*b*]indoles and pyrrolo[3,4-*b*]indoles from electrophilic indole

They hypothesized that the ring-opening observed in the Michael adduct was due to the presence of a highly electron-withdrawing substituent such as phenylsulfonyl group. It was

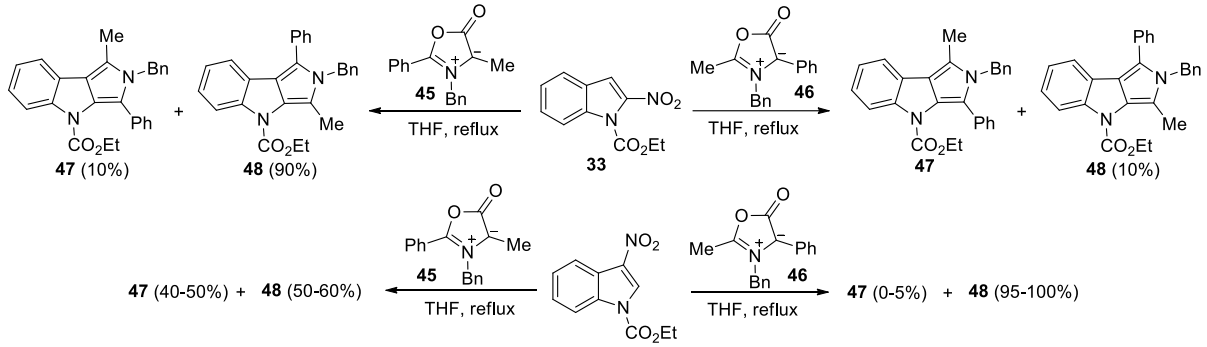
found that the electrophilic indoles with Bn, 2-pyridyl and CO_2Et as *N*-substituents furnished pyrrolo[3,4-*b*]indoles in satisfactory to good yields (Scheme 1.10).

Later in 1998, the same group reported a 1,3-dipolar cycloaddition reaction of electrophilic benzannulated heterocycles towards the synthesis of pyrrolo[3,4-*b*]indoles, benzo[*b*]furo[2,3-*c*]pyrroles and benzo[*b*]thieno[2,3-*c*]pyrroles.[17] Pyrrolo[3,4-*b*]indoles were generated from the dipolar cycloaddition of Münchnones **34a** and **34b** (1,3-oxazolium-5-olates) with electrophilic indoles. Following the same approach, the authors synthesized other heteroacenes such as benzo[*b*]furo[2,3-*c*]pyrrole **43-44** from 2-nitrobenzofuran and benzo[*b*]thieno[2,3-*c*]pyrroles **41-42** from 3-nitrobenzo[*b*]thiophene (Scheme 1.11).



Scheme 1.11 Synthesis of pyrrolo[3,4-*b*]indoles, benzo[*b*]furo[2,3-*c*]pyrroles and benzo[*b*]thieno[2,3-*c*]pyrroles from Münchnones

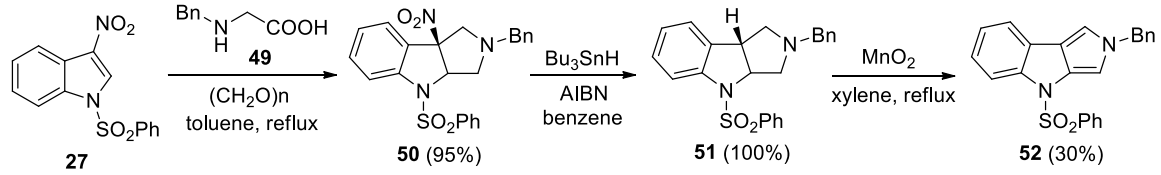
Unsymmetrical Münchnones were then utilized by the same group for the synthesis of pyrrolo[3,4-*b*]indoles from electrophilic indoles (Scheme 1.12).[18]



Scheme 1.12 Synthesis of pyrrolo[3,4-*b*]indoles from unsymmetrical Münchnones

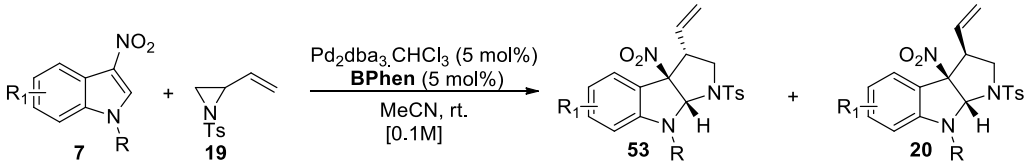
The reaction was carried out by treating various *N*-protected 2 and 3-nitroindoles with unsymmetrical mesoionic Münchnones **45-46** in THF at reflux conditions (Scheme 1.12).

Another method was adopted by Gribble and coworkers, which involved a 1,3-dipolar cycloaddition of 2- or 3-nitroindoles with azomethine ylides towards the synthesis of pyrrolo[3,4-*b*]indoles.[19] The reaction of both *N*-Ts-3-nitro-indole **7** and with the azomethine ylide (generated *in situ* from substituted glycine and paraformaldehyde) went smoothly, thereby affording the cycloadduct **50** in excellent yield (Scheme 1.13). The NO_2 group present in the cycloadduct was eliminated by treatment with Bu_3SnH/AIBN in benzene. Finally, pyrrolo[3,4-*b*]indole **52** was generated by MnO_2 mediated oxidation of **51** in refluxing xylene.



Scheme 1.13 Synthesis of pyrrolo[3,4-*b*]indole

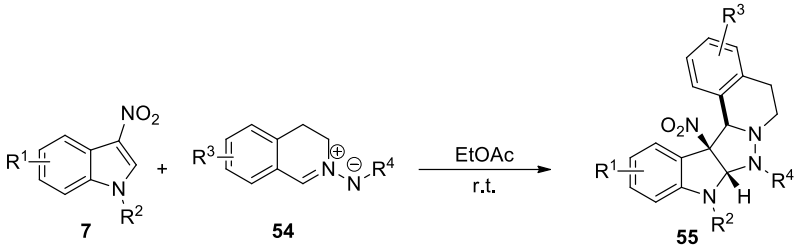
Another report suggested the use of a Palladium catalyst ($Pd_2(dba)_3 \cdot CHCl_3$) for the cycloaddition of vinylaziridines to 3-nitroindoles.[20] Out of the several ligands, BPhen (15 mol%) proved to be the best and afforded upto 81% yield. Varying substitutions at the *N*-position as well as on the phenyl ring of the indole moiety, and with different vinyl functionalities, afforded the corresponding products in good yields. (Scheme 1.14).



Scheme 1.14 Palladium catalyzed reaction between 3-nitroindoles and vinyl aziridines

In 2017, Wang *et al.* reported a 1,3-dipolar cycloaddition of C,N-cyclic azomethine imines with 3-nitroindoles towards the synthesis of 5-ring fused tetrahydroisoquinolines in the absence of a catalyst.[21] On screening the reaction conditions, best results were obtained on using ethyl acetate as solvent in the absence of a metal catalyst at room temperature. Overall,

this method provides easy access for the incorporation of two important scaffolds i.e. tetrahydroisoquinoline and indoline (Scheme 1.15).

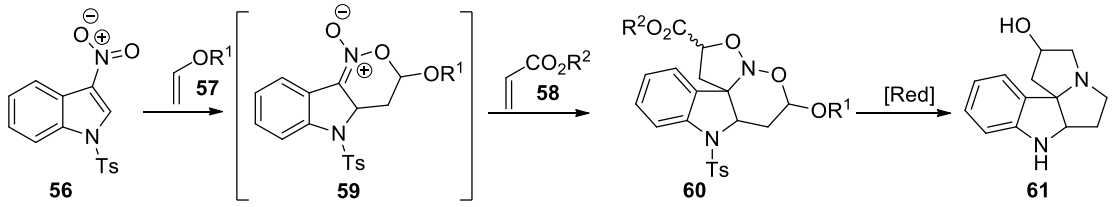


Scheme 1.15 1, 3-dipolar cycloaddition of 3-nitroindoles with C,N-cyclic azomethine imines

1.3.3 [4+2] Cycloaddition reactions

[4+2] cycloaddition reaction or the Diels Alder reaction is the one which involves the formation of two bonds between a diene and a dienophile, to form a cyclohexene skeleton.[22] For many years, indoles have been used in combination with electron rich dienes in such kind of [4+2] cycloadditions.

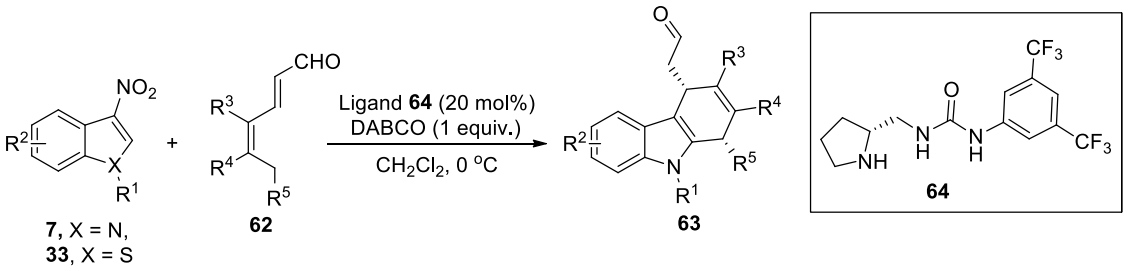
Synthesis of 4-membered *N*-fused heterocycles was carried out using [4+2]/ [3+2] cycloadddition of 3-nitroindole and 3-nitro pyrrole derivatives.[23] The synthetic route involves two steps, i.e, a [4+2] cycloaddition occurring between the nitroalkenic part of the indole/pyrrole and the electron rich dienophile **57** (alkyl vinyl ether) under high pressure, followed by a [3+2] cycloaddition between this nitronate dipole intermediate and the electron-deficient dipolarophile **58** (acrylate). Finally, the reduction of the N-O bonds would lead to the formation of *N*-fused heterocycles. (Scheme 1.16). The above transformation was achieved using Raney Nickel hydrogenation.



Scheme 1.16 [4+2]/ [3+2] cycloadddition of 3-nitroindole derivatives

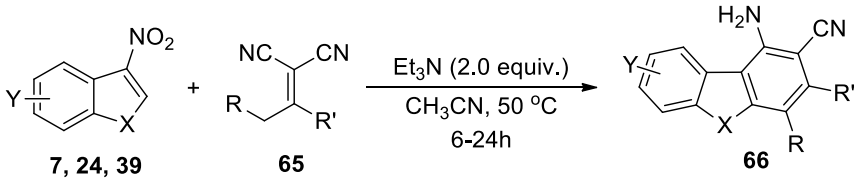
For the first time, Jorgensen and coworkers reported [4+2] cycloaddition between 3-nitroindoles and 2, 4-dienals using organocatalysts.[24] Synthesis of dihydrocarbazole scaffolds

were achieved in the presence of an urea based catalyst (20 mol%), DABCO (1 equiv.) in DCM at 0 °C. The reaction afforded the corresponding products in good to moderate yields and enantioselectivity (Scheme 1.17). The stereoselective approach of the dienophile to the amino-activated diene functionality was achieved by employing a hydrogen-bonding organocatalyst and a nitro group at the 3rd position of indole.



Scheme 1.17 An organocatalyzed reaction between 3-nitroindoles and 2, 4-dienals *via* a [4+2] cycloaddition

Yang and co-workers showed that carbazole-4-amine derivatives could be synthesized *via* a [4+2] annulation between 3-nitroindoles and alkylidene malononitriles.[25] Best results were obtained when Et_3N (2.0 equiv.) was used as the base in acetonitrile at 50 °C for 24 h (Scheme 1.18). The reaction was found to be general with a variety of substituted alkylidene malononitriles and they could also extend the reaction to synthesize functionalized dibenzofuran and dibenzothiophene.

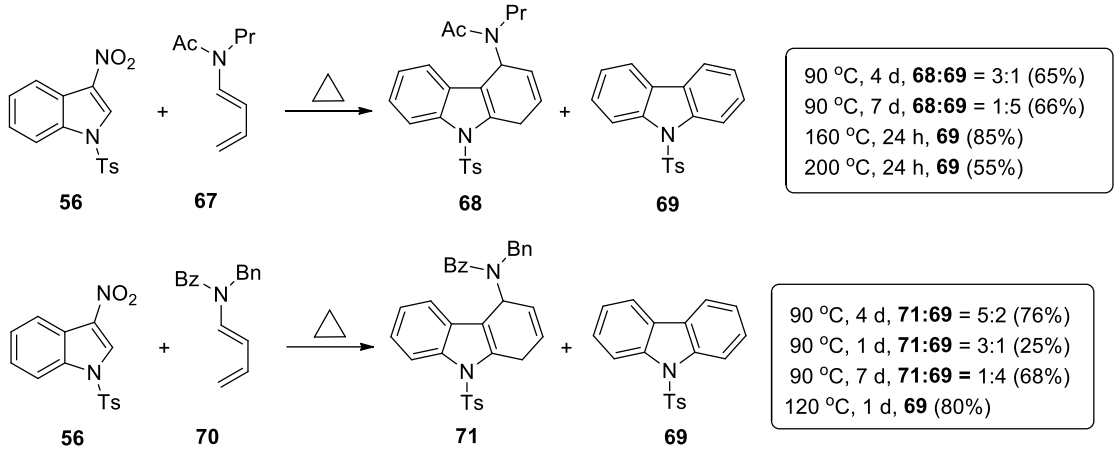


Scheme 1.18 [4+2] annulation of electrophilic benzannulated heterocycles with alkylidene malononitrile

1.3.4 Diels-Alder Reactions

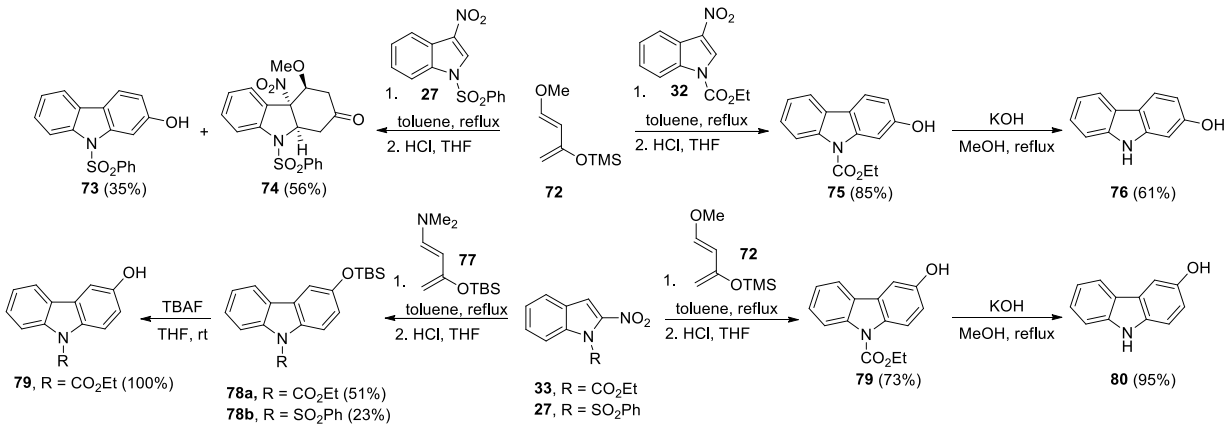
Mancini and coworkers reported the synthesis of intermediates of Aspidosermine alkaloids *via* Diels-Alder reactions of electrophilic indole and dienamides.[26] The studies carried out by treating 1-(*N*-acyl-*N*-alkylamino)-dienes **67** with *N*-Ts-3-nitroindole. When the diene **67** was treated with electrophilic indole **56** at 90 °C for 4 days, a mixture of *N*-Ts-dihydrocarbazole

68 and *N*-Ts-carbazole **69** was obtained in a ratio of 3:1 and in 65% total yield. On increasing the reaction time to 7 days, the product ratio of *N*-Ts-dihydrocarbazole **68**: *N*-Ts-carbazole **69** turned out to be 1:5 with an overall yield of 66%. The highest yield of 85% was obtained for *N*-tosyl carbazole **69** when the temperature was increased to 160 ^{o}C for 24 h. On further increasing the temperature to 200 ^{o}C, the yield of **69** was found to decrease to 55% due to detosylation of the *N*-tosyl carbazole (Scheme 1.19). Similar studies were carried out with indole **56** and diene **70** affording a mixture of dihydrocarabazole **71** and carbazole **69**.



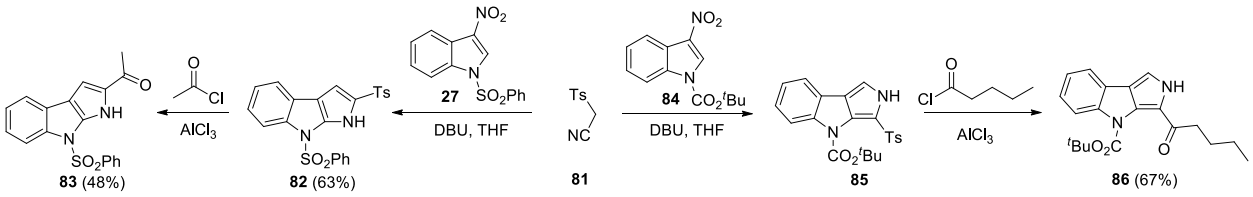
Scheme 1.19 Diels-Alder reactions of *N*-tosyl-3-nitroindoles and dienamides

Another facile method for the synthesis of hydroxycarbazole was introduced in 2001 by Gribble and co-workers from electrophilic indole. The methodology utilized Diels Alder reactions of 2- and 3-nitroindoles with Danishefsky's dienes **72** and **77** (Scheme 1.20)[27]. When *N*-Ts-3-nitroindole **27** was treated with diene **72** in toluene followed by acid hydrolysis furnished a mixture of exo adduct **74** (56%) and carbazole **73** (35%). In the case of electrophilic indole **32**, only carbazole **75** (85%) was obtained without the formation of any cycloadduct. Again, cycloaddition of 2-nitroindole with **72** gave carbazole **79** in 73% after acid hydrolysis. The reaction of diene with *N*-carboxyethyl-2-nitroindole afforded the carbazole **78a** in 51 %. When the reactivity of 2-nitro-1-(phenylsulfonyl)indole with dienes **72** and **77** were compared, it was noticed that only **77** reacted properly with 2-nitro -1-(phenylsulfonyl)indole to afford the carbazole **78b**, and that too in low yield (23%) (Scheme 1.20).



Scheme 1.20 Diels-Alder cycloaddition of electrophilic indoles with Danishefsky's diene

Gribble and co-workers extended their methodology for synthesizing pyrroloindoles for accessing further functionalized moieties. The dipolar cycloaddition of *N*-Boc-substituted-3-nitro-indole with TosMIC yielded pyrrolo[3,4-*b*]indole **85**. The treatment of **85** with valeryl chloride resulted in an ipso acylation-detosylation reaction furnishing acylated analogue pyrrolo[3,4-*b*]indole **86**.[28] In the same way, acyl-substituted pyrrolo[2,3-*b*]indole **83** was synthesized from **82** which was obtained from the dipolar cycloaddition of *N*-SO_2Ph-substituted-3-nitro-indole with TosMIC (Scheme 1.21).



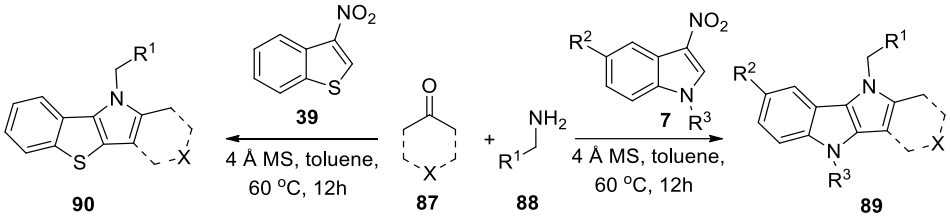
Scheme 1.21 Synthesis of acyl-substituted pyrroloindoles *via* ipso-acylation-detosylation reaction

1.3.5 Multicomponent Reactions

Multicomponent reactions have gained widespread attention for the stereoselective formation of several bonds in one pot.[29] These reactions have discovered practical applications in synthesizing valuable organic compounds as well as in the construction and functionalization of indoles.

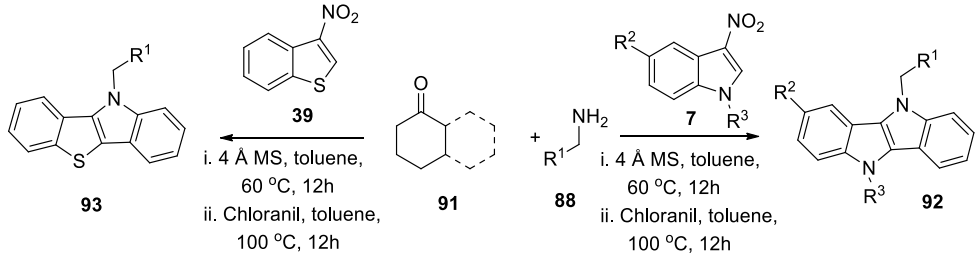
In 2017, we came across a multicomponent reaction involving an enolizable ketone, a primary amine and an *N*-protected 3-nitroindole for the synthesis of pyrrolo[3,2-*b*]indole.

Under the optimized conditions, which consisted of 4 Å M.S., toluene as the solvent at 60 °C, the reaction was found to be general for a range of amines (aliphatic and aromatic), cyclic and acyclic ketones and electrophilic indoles affording the corresponding pyrroloindoles in moderate to good yields (Scheme 1.22). The multicomponent reaction of 3-nitrobenzothiophene was also carried out using the same conditions towards the synthesis of benzothieno[3,2-*b*]pyrroles (Scheme 1.22).



Scheme 1.22 A multicomponent reaction towards pyrrolization of indoles and benzothiophenes

Then, we introduced a sequential multicomponent reaction-oxidation approach towards the synthesis of indolo[3,2-*b*]indoles and benzothieno[3,2-*b*]indoles.[30] The reaction was planned in such a way that the intermediate pyrrolo[3,2-*b*]indole formed from the multicomponent reaction could be oxidized in situ using chloranil (Scheme 1.23).



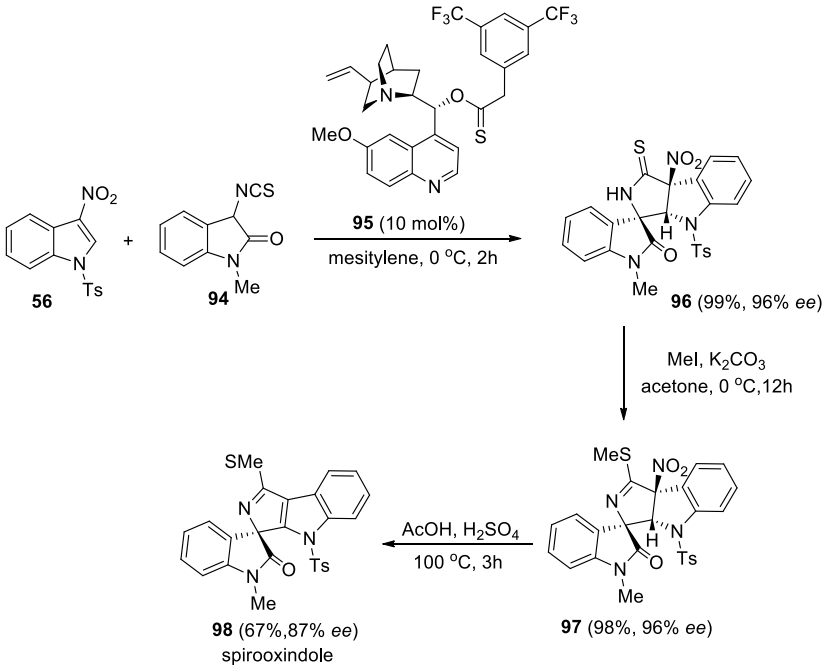
Scheme 1.23 A one-pot approach towards the synthesis of indolo[3,2-*b*]indole and benzothieno[3,2-*b*]indole

The synthesized indoloindoles were also subjected to synthetic modifications in order to evaluate their photophysical properties. By using this strategy, we could make unsymmetrical indolo[3,2-*b*]indoles, which were hard to access prior to this report. In addition, we could also synthesize halogenated indolo[3,2-*b*]indole moieties, which were further functionalized

for DSC applications.[6] The reaction was also extended for accessing benzothieno[3,2-*b*]indoles when started from 3-nitrobenzothiophene (Scheme 1.23).

1.3.6 Miscellaneous

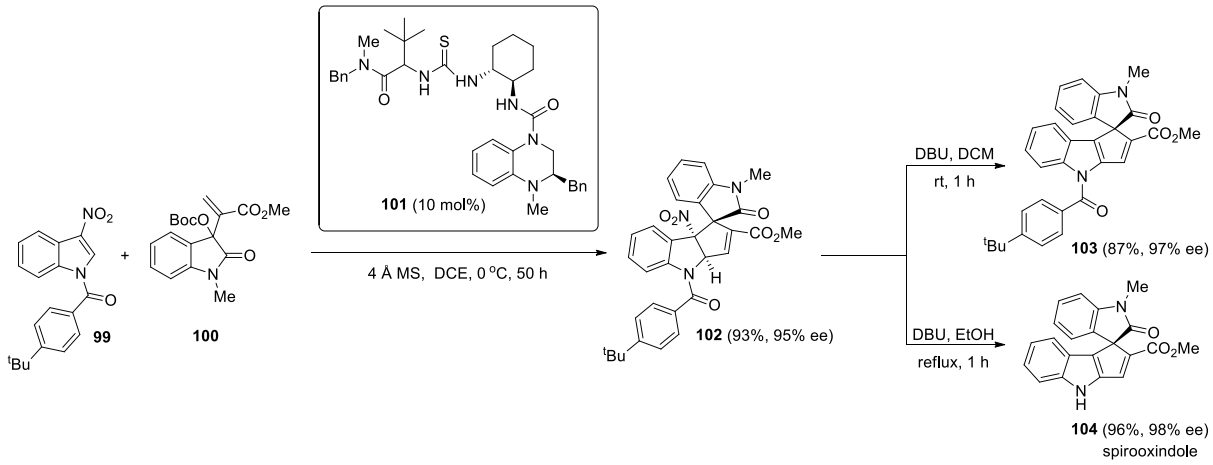
In 2015, Yuan and coworkers reported that the aminothiocarbamate catalyst **94** smoothly promoted the asymmetric Michael/Cyclization Cascade Reaction of 3-Isothiocyanato Oxindoles and 3-Nitroindoles (scheme 1.24).[31] This reaction provides a method for the preparation of diverse and enantioenriched polycyclic spirooxindoles in high yields and excellent diastero- and enantioselectivities.



Scheme 1.24 Reaction of 3-Isothiocyanato Oxindoles with 3-Nitroindoles *via* asymmetric Michael/Cyclization Cascade reaction

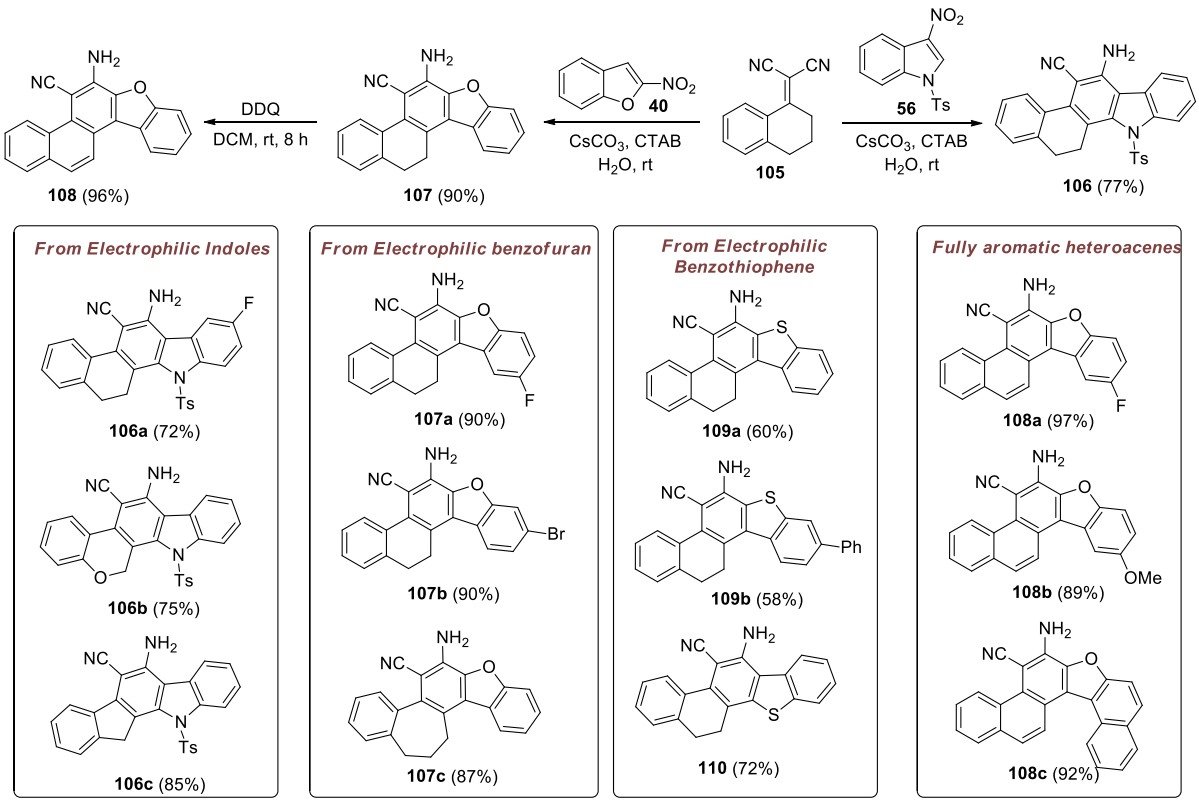
In 2020, the synthesis of polycyclic spirooxindoles was carried out using [3+2] annulations of isatin-derived MBH-carbonates and 3-nitroindoles.[32] The authours made efforts to improve the stereoselectivity of the reaction using novel chiral DMAP-thiourea bifunctional catalyst **101**. Further transformation of these spirooxindole products also led to the formation of annulated heterocycles. i.e., treatment of spirooxindole **102** with DBU in DCM at room temperature, led to the formation of **103**, with the elimination of HNO_2 in 87% yield and

97% *ee*. With DBU in EtOH at reflux, acyl group got removed to give **104** with 96% yield and 98% *ee* (Scheme 1.25).



Scheme 1.25 [3+2] annulations of 3-nitroindoles with isatin-derived MBH-carbonates

Yuan and coworkers developed an eco-friendly method for the synthesis of dibenzoheterocyclic compounds *via* a Michael addition process of electrophilic benzannulated heterocycles such as 2-nitrobenzofurans, 2-nitrobenzothiophenes, 3-nitrobenzothiophenes, and 3-nitroindoles with α,α-dicyanoalkenes (Scheme 1.26).[33] This [4+2] annulation reaction took place in the presence of 1 equiv. of Cs_2CO_3 and 5 mol% of CTAB in water at room temperature. Being fascinated by the importance of fused polycyclic heteroaromatic compounds, they further carried out an oxidative dehydrogenation reaction of **107** using 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) to afford the corresponding products **108a-c** in excellent yields.



Scheme 1.26 [4+2] annulation of electron deficient nitrobenzoheterocycles and α,α-dicyanoalkenes

1.4 Conclusions

Recent research in the field of organic chemistry has revealed a fascinating array of heteroacenes—polycyclic aromatic compounds that incorporate heteroatoms like sulfur (S), nitrogen (N) or oxygen (O) into their structures. These compounds have exhibited intriguing properties that have the potential for a wide range of applications in functional materials. As research in this field continues, it is likely to lead to even more innovative applications and discoveries.

Electrophilic indoles have proven to be versatile electron-deficient heterocyclic compounds. Their use as an electrophile with different nucleophiles has been well documented in various reactions, which includes [3+2], [4+2], 1, 3-dipolar cycloadditions and multicomponent reactions. Metal catalyzed and non-catalyzed reactions also utilized these indoles for the synthesis of various substituted carbazoles, pyrroloindoles and indoloindoles, etc. The versatility of electrophilic indoles has been confirmed by numerous asymmetric dearomative

cascade reactions. Research in this field has shown significant advancements and continues to reveal novel synthetic routes towards fused indole heterocyclic moieties.

Our efforts were focused on the development of new synthetic methodologies towards fused heteroacenes from electrophilic benzannulated heterocycles. Our initial efforts were focused towards the synthesis of polyring-fused imidazo[1,2-*a*]pyridines from the annulation of electrophilic indoles with 2-aminopyridines and 2-aminoquinolines. Next, we turned our attention towards the dipolar cycloaddition of isoquinolinium and pyridinium methylides to electrophilic indoles for accessing functionalized pyrrolo[2,1-*a*]isoquinolines and indolizines, respectively. Here, different heteroaromatic *N*-ylides were prepared and treated with various electrophilic indoles. Finally, we have developed an efficient method to synthesize complex polyring fused *N*-heterocycles *via* Pd-catalyzed site-selective C–H activation from the above obtained pyrrolo[2,1-*a*]isoquinolines and indolizines.

1.5 References

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Chapter 2

Copper-Catalyzed Annulation of Electrophilic Benzannulated Heterocycles with 2-Aminopyridine and 2-Aminoquinoline: Direct Access toward Polyring-Fused Imidazo[1,2-*a*] pyridines

2.1 Abstract

We have developed a direct method for the synthesis of polyring-fused imidazo[1,2-a]pyridines via a copper-catalyzed annulation of electrophilic benzannulated heterocycles with 2-aminopyridine and 2-aminoquinoline. From 3-nitroindoles and 2-aminopyridine, we could synthesize tetracenes viz. indole fused imidazo[1,2-a]pyridines and by starting from 2-aminoquinoline, we could generate pentacenes viz. indoloimidazo[1,2-a]quinolines. In addition, we could also extend the methodology towards the synthesis of benzothienoimidazo[1,2-a]pyridines starting from 3-nitrobenzothiophene. Furthermore, the basic photophysical properties of these synthesized heteroacenes were evaluated.

2.2 Introduction

Heteroacenes are considered promising candidates in the field of organic semiconductors, light-emitting diodes, field-effect transistors, and photovoltaics.[1] The reason for the huge potential of heteroacenes can be attributed to the presence of heteroatoms and the possibility of variation of conjugation lengths, both of which have beneficial effects on their optoelectronic properties.[2] As the subject of extensive research in material applications, several groups have developed versatile and efficient synthetic strategies towards polyring-fused heterocycles.[3] Inspired by the tremendous utilization of heteroacenes, we were interested in finding synthetic routes towards seldom explored ones and herein, we report a copper catalyzed strategy towards the synthesis of polyring-fused imidazo[1,2-*a*]pyridines.

2.2.1 Introduction to 2-aminopyridines

2-Aminopyridine, a pyridine ring with an *ortho*-substituted amine functionality, is a heavily utilized synthon in the field of pharmaceuticals.[4] Due to its binucleophilic nature, a plethora of heterocycles can be synthesized from this simple starting material, wherein the exocyclic amino group or endocyclic pyridinium nitrogen initiates the reaction.

During the past decades, several methods were developed for deriving pharmacologically active heterocyclic compounds from 2-aminopyridine, among which imidazo[1,2-*a*]pyridine[5] is recognized as the most important one. Synthesis of this moiety is desirable due to its tremendous use in the field of medicinal chemistry and material science (Fig. 1).[5]

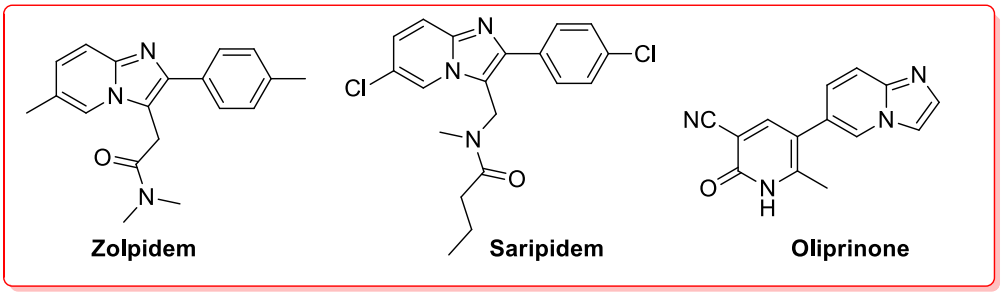
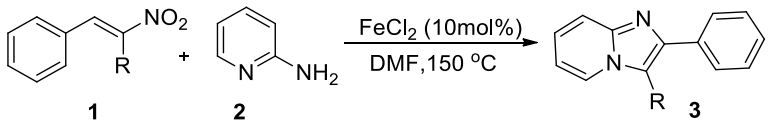


Figure 1. Various drugs with imidazo[1,2-*a*]pyridine moiety

Accordingly, various synthetic strategies have been developed towards imidazo[1,2-*a*] pyridine derivatives out of which the coupling between 2-aminopyridine and nitro olefins seems to be attractive.

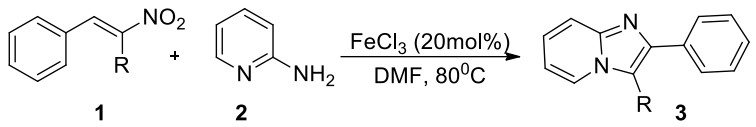
2.2.2 Reactivity of 2-aminopyridine with nitroolefins towards imidazo[1,2-*a*]pyridine derivatives

The first reports in this line came from the groups of Yan and Huang *et al.* towards the synthesis of 3-methyl-2-arylimidazo[1,2-*a*]pyridine derivatives using $FeCl_2$ as catalyst[6] *via* a Michael addition/intramolecular cyclization of 2-aminopyridines with 2-methylnitroolefins (Scheme 2.1).



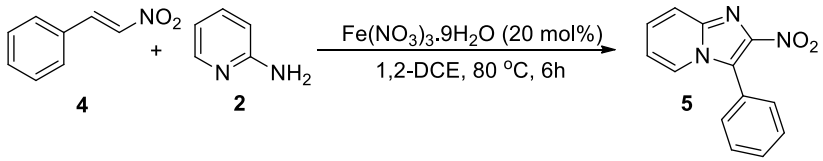
Scheme 2.1 Tandem coupling of 2-aminopyridines with 2-methylnitroolefins

Hajra *et al.* also developed a simple and efficient methodology for the synthesis of 2-arylimidazo[1,2-*a*]pyridines through an iron (III) catalyzed reaction between nitroolefins and 2-aminopyridines.[7] (Scheme 2.2).



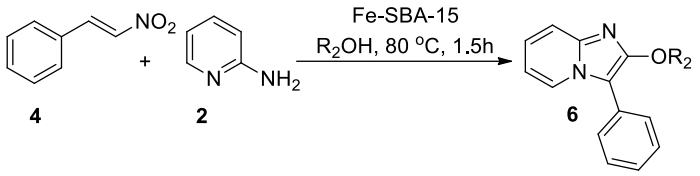
Scheme 2.2 Iron (III) catalyzed reaction between nitroolefins and 2-aminopyridines

Later in 2015, Hajra *et al*. reported the synthesis of 2-nitro-3-aryl imidazo[1,2-*a*]pyridines from simple nitroalkenes and 2-aminopyridine. Mild aerobic conditions were maintained throughout the protocol, and an iron catalyst ($Fe(NO_3)_3.9H_2O$) helped to tune the methodology. The nitro group in the imidazo[1,2-*a*]pyridine was found to be retained as such [8](Scheme 2.3).



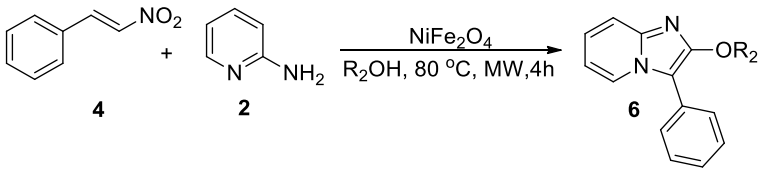
Scheme 2.3 Synthesis of 2-nitro-3-aryl imidazo[1,2-*a*]pyridines

Banerjee *et al*. synthesized imidazo[1,2-*a*]pyridines *via* a mesoporous silica (Fe-SBA-15) catalyzed reaction between 2-aminopyridines with β-nitrostyrenes in alcohol (Scheme 2.4).



Scheme 2.4 Synthesis of imidazo[1,2-*a*]pyridines from 2-aminopyridines and *β*-nitrostyrenes

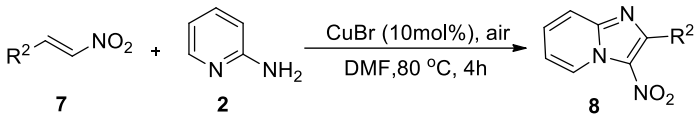
The same group also used nano $NiFe_2O_4$ as catalyst instead of mesoporous silica to synthesise imidazo[1,2-*a*]pyridines in the presence of alcohol under microwave irradiation[9].



Scheme 2.5 Synthesis of imidazo[1,2-*a*]pyridines using $NiFe_2O_4$

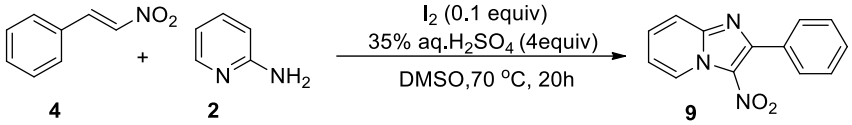
The mechanism involved an aza-Michael addition, imine formation, and a nucleophillic ligand transfer. The main advantages of these nanoparticles are that they serve both as a catalyst and an oxidant (Scheme 2.5).

A Cu-catalyzed method to synthesize polysubstituted imidazo[1,2-*a*]pyridines using air as the oxidant was reported by Yan and co-workers[10] (Scheme 2.6).



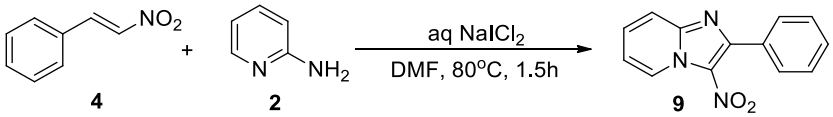
Scheme 2.6 Synthesis of polysubstituted imidazo[1,2-*a*]pyridines

Tachikawa *et al.* reported a metal free synthesis of imidazopyridines from nitroalkene and 2-aminopyridine in the presence of catalytic amount of Iodine and aqueous hydrogen peroxide[11] (Scheme 2.7).



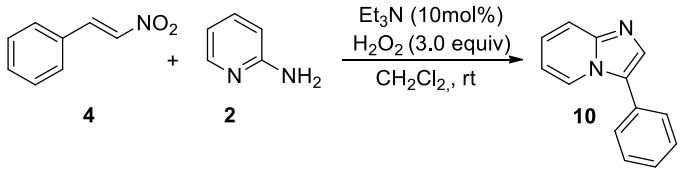
Scheme 2.7 Metal free synthesis of imidazopyridines

In 2014, Telvekar *et al.* reported the synthesis of 3-nitro-2-arylimidazo[1,2-*a*] pyridines using soidium dichloroiodide [12] (Scheme 2.8).



Scheme 2.8 Synthesis of 3-nitro-2-aryl imidazo[1,2-*a*] pyridines

Maheswari *et al.* reported a facile, metal-free, base catalysed construction of 3-arylimidazo[1,2-*a*] pyridine from *β*-nitrostyrene and 2-aminopyridines employing H_2O_2 (30% aqueous) as the oxidant.

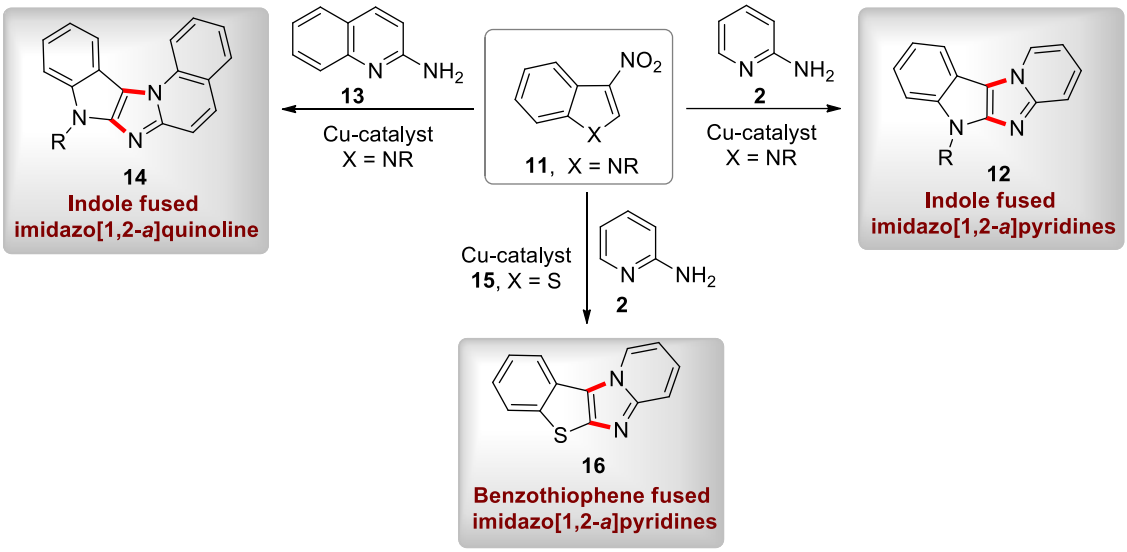


Scheme 2.9 Base catalysed synthesis of 3-arylimidazo[1,2-*a*] pyridine

The use of an inexpensive base and facile reaction conditions has made this strategy a practical alternative for the synthesis of 3-arylimidazo[1,2-*a*] pyridines [13] (Scheme 2.9).

2.3 Statement of the problem

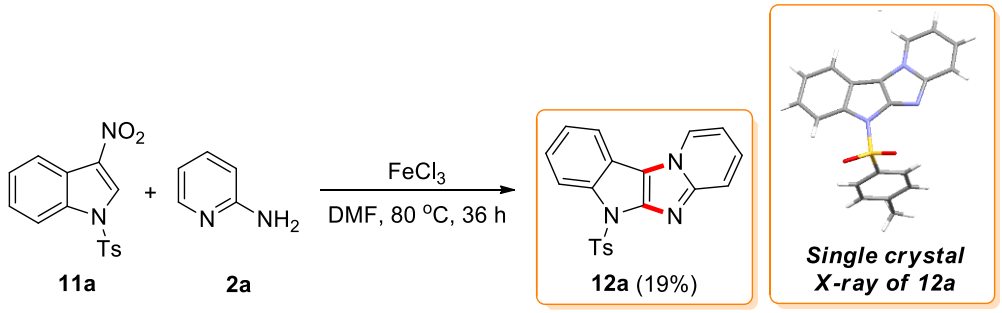
Due to our continued interest in the chemistry of electrophilic benzannulated heterocycles and also due to our search for novel heteroacenes for material applications[14] we hypothesized that the reaction of 2-aminopyridine with electrophilic benzannulated heterocycles should result in an annulation process and the results of the investigations in this line are disclosed here (Scheme 2.10).



Scheme 2.10 Annulation reaction of electrophilic benzannulated heterocycles with 2-aminopyridine.

2.4 Results and discussion

Our investigations commenced with 3-nitro-*N*-tosyl indole **11a** and 2-aminopyridine **2a** as substrates. The initial reaction between **11a** (1.0 equiv.) and **2a** (1.5 equiv.) was carried out in the presence of $FeCl_3$ (10 mol%) as a catalyst in DMF at 80 ^oC. After 36 hours, as expected, we could isolate indole fused imidazo[1,2-*a*]pyridine **12a** in 19% yield (Scheme 2.11).



Scheme 2.11 Synthesis of indole fused imidazo[1,2-*a*]pyridine *via* the Cu-catalyzed annulation of 3-nitro-*N*-tosyl indole with 2-aminopyridine (X-Ray of **12a** (CCDC: 2237083, 50% ellipsoid contour probability level).

The structure of **12a** established by various spectroscopic analyses was further confirmed from single crystal x-ray crystallographic data. High-quality single crystals of **12a** in white colour were obtained by slow vaporization of its saturated solution in CH_2Cl_2/hexane (1:2 vol/vol).

In the ^{1}H NMR spectrum, aromatic protons were found to resonate in the region δ 8.31–6.95 ppm.

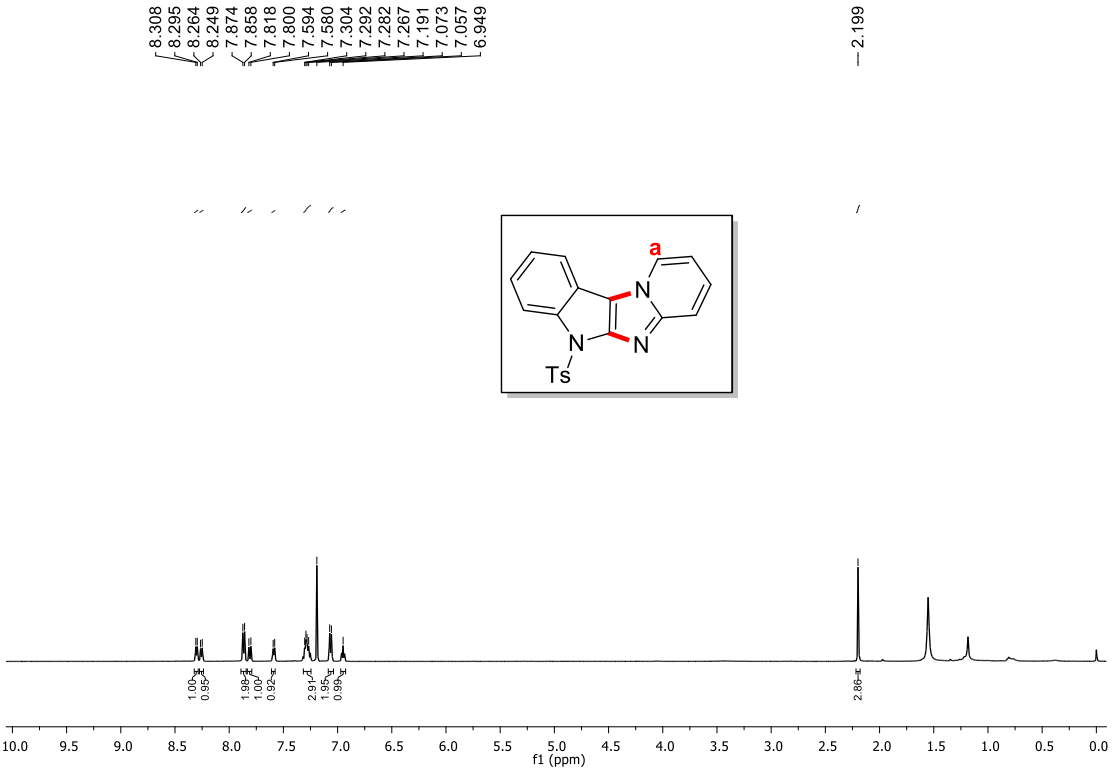


Figure 2. ^{1}H NMR spectra of **12a**

The proton on the pyridine ring attached near to the *N* atom (a) resonated at 8.30 ppm as a doublet. The methyl protons of the tosyl group resonated as singlet at δ 2.20 ppm. The ^{1}H NMR spectrum of the compound is shown in figure 2.

In the ^{13}C spectrum (Figure 3), characteristic peaks at δ 148.8 (a) and 148.0 (b) ppm which corresponds to the highly deshielded aromatic carbons flanked between the *N*-atoms of the indolo-imidazo and pyrido-imidazo rings respectively. All the other aromatic carbons resonated in the region δ 144.9-112.7 ppm. The methyl carbons of the tosyl group showed a sharp peak at δ 21.6 ppm. All other peaks in the ^{1}H and ^{13}C NMR were in good agreement with the assigned structure.

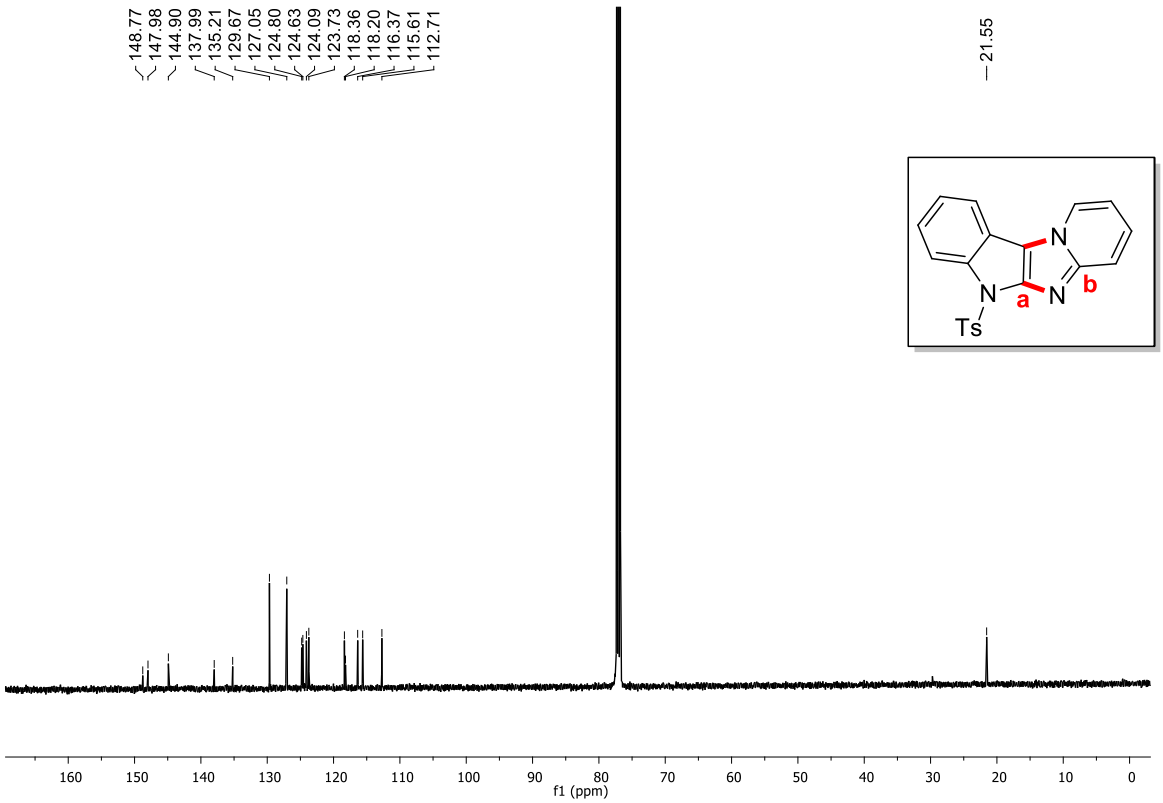
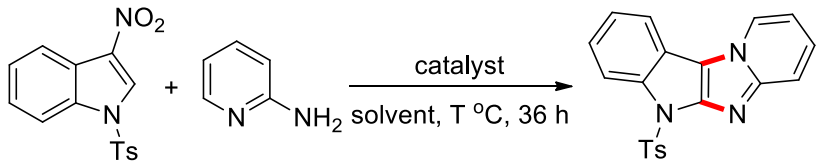


Figure 3. ^{13}C NMR spectra of **12a**

Inspired by this result, we went on with the optimisation of reaction conditions. First, we checked the efficacy of different metal salts such as $FeCl_3$, $FeCl_2$, CuBr, CuI, CuCl and $Cu(OAC)_2$, $Cu(OTf)_2$; out of which the CuI-catalyzed reaction afforded indole fused imidazo[1,2-*a*]pyridine **12a** in 41% yield (Table 1, entries 1-7). To our delight, increasing the

reaction temperature to 100 °C resulted in an improvement of the yield of **12a** to 60% (Table 1, entry 8). The screening of different solvents such as DMF, DMSO, DMA, DCE, NMP, MeCN, chlorobenzene, toluene and ethanol showed that DMF was the best medium for the present annulation (Table 1, entries 8-16). Next, we turned our attention in checking the effect of concentration on the outcome of the reaction. Changing the concentration to 0.1 mmol as well as 0.3 mmol did not have a positive influence on the reaction yield (Table 1, entries 17-18). Our next attempt was to check the effect of increasing and decreasing the amount of **2a** used in the reaction (Table 1, entries 19-20). From these reactions, the one with 1.2 equivalents of **2a** afforded the indole fused imidazo[1,2-*a*]pyridine in 70% yield. Next, on using PTSA as an acid catalyst, the reaction produced a yield of 50% (Table 1, entry 21). Finally, an increase in the catalyst loading led to a drop in the yield of **12a** to 42% and the reaction failed to proceed in the absence of the catalyst (Table 1, entries 22-23).

Table 1. Optimization studies[a]



11a **2a** **12a**

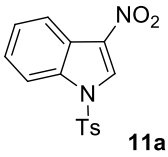
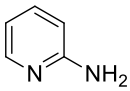
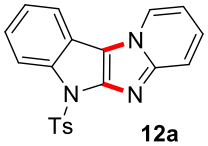
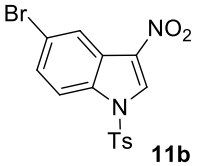
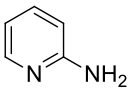
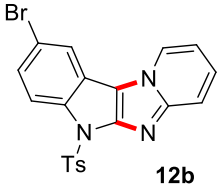
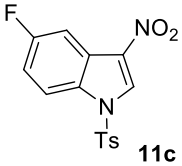
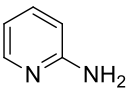
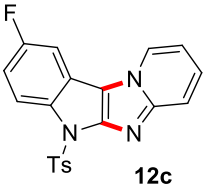
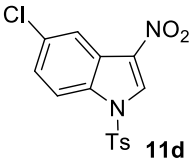
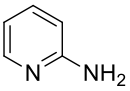
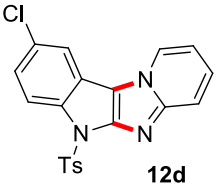
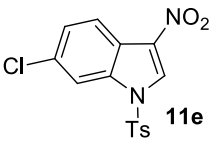
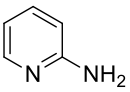
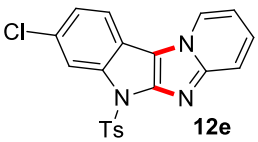
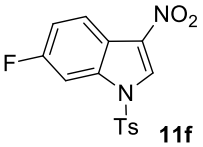
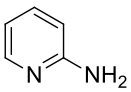
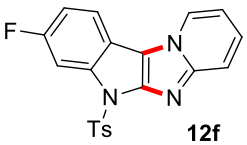
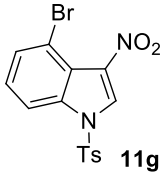
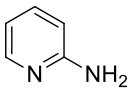
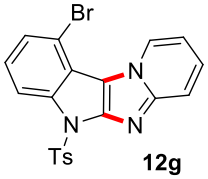
Entry	Catalyst	Solvent	Temperature (°C)	Yield of **12a** (%)
1	$FeCl_3$	DMF	80	19
2	$FeCl_2$	DMF	80	NR
3	CuBr	DMF	80	23
4	CuI	DMF	80	41
5	CuCl	DMF	80	26
6	$Cu(OAc)_2$	DMF	80	22
7	$Cu(OTf)_2$	DMF	80	traces
8	CuI	DMF	100	60
9	CuI	DMSO	100	58
10	CuI	DMA	100	traces

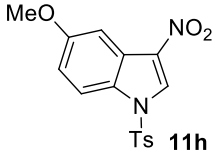
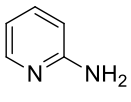
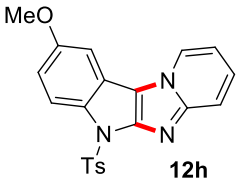
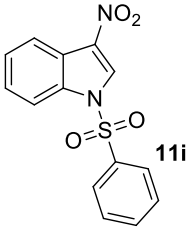
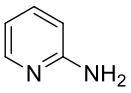
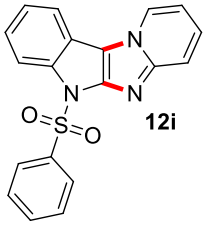
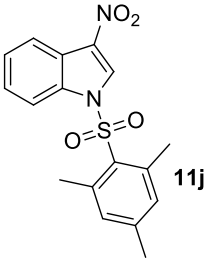
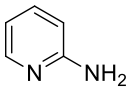
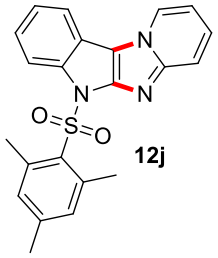
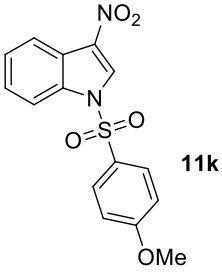
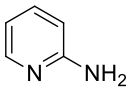
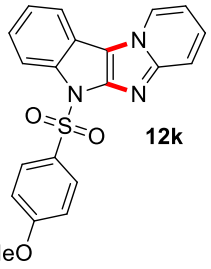
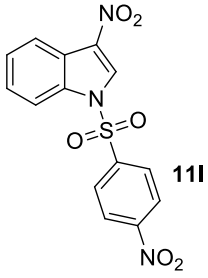
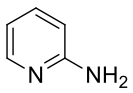
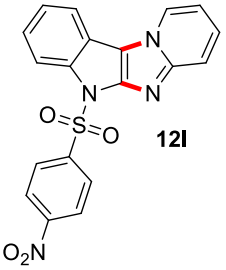
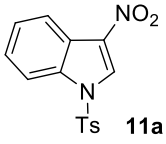
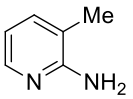
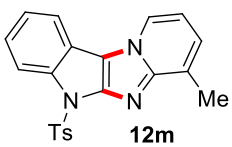
11	CuI	DCE	100	41
12	CuI	NMP	100	48
13	CuI	MeCN	100	37
14	CuI	chlorobenzene	100	35
15	CuI	toluene	100	traces
16	CuI	EtOH	100	55
17[b]	CuI	DMF	100	40
18[c]	CuI	DMF	100	25
19[d]	**CuI**	**DMF**	**100**	**70**
20[e]	CuI	DMF	100	66
21[f]	CuI	DMF	100	50
22[g]	CuI	DMF	100	42
23	-	DMF	100	NR

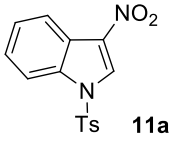
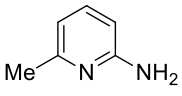
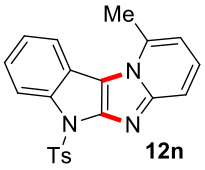
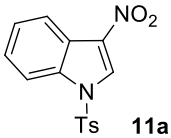
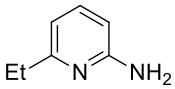
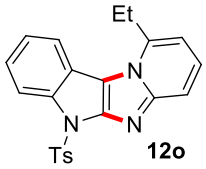
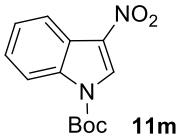
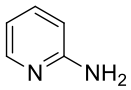
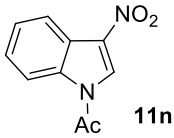
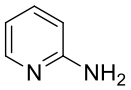
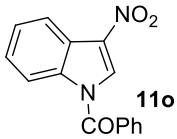
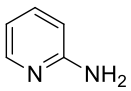
Reaction conditions: [a] **11** (1.0 equiv.), **2a** (1.5 equiv.), catalyst (10 mol%), solvent (0.15 mM), T °C, 36 h, isolated yields; [b] solvent (0.1 mM); [c] solvent (0.3 mM); [d] **2a** (1.2 equiv.); [e] **2a** (2.0 equiv.); [f] PTSA (1.2 equiv.); [g] catalyst (20 mol%); NR = no reaction.

With the optimized conditions in hand [3-nitro-*N*-tosyl indole (1.0 equiv.), 2-aminopyridine (1.2 equiv.), CuI (10 mol%), DMF (0.15 mmol), 100 °C, 36 h], we examined the reactivity of a series of substituted 2-aminopyridines and 3-nitro-*N*-tosyl indoles to establish the generality of this annulation (Table 2). First, the Cu-catalyzed annulation of **11a** with **2a** was repeated by starting with 1.0 g of **11a** from which indole fused imidazo[1,2-*a*]pyridine **12a** was isolated in 61% yield. Then, we checked the reactivity of halogenated electrophilic indoles in the present annulation reaction. In this line, we could install halogens such as F, Cl and Br at different positions of the indole moiety of the fused imidazo[1,2-*a*]pyridine as in **12b** to **12g**. In accordance with our previous observations, the presence of an electron-donating substituent (OMe) on the indole motif hindered the annulation process and **12h** was not obtained.

Table 2. Generality of indole fused imidazo[1,2-*a*]pyridine synthesis[a]

Entry	Indole	2-Aminopyridine	Product	Yield
1	 **11a**	 **2a**	 **12a**	70, 61[b]
2	 **11b**	 **2a**	 **12b**	55
3	 **11c**	 **2a**	 **12c**	45
4	 **11d**	 **2a**	 **12d**	41
5	 **11e**	 **2a**	 **12e**	40
6	 **11f**	 **2a**	 **12f**	43
7	 **11g**	 **2a**	 **12g**	45

Entry	Indole	2-Aminopyridine	Product	Yield
8	 **11h**	 **2a**	 **12h**	NR
9	 **11i**	 **2b**	 **12i**	50
10	 **11j**	 **2a**	 **12j**	50
11	 **11k**	 **2a**	 **12k**	47
12	 **11l**	 **2a**	 **12l**	55
13	 **11a**	 **2b**	 **12m**	35

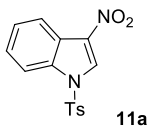
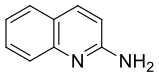
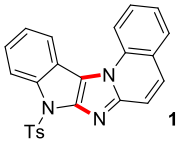
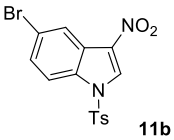
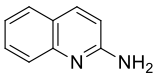
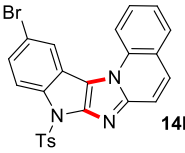
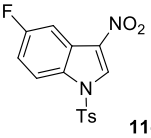
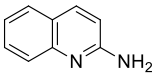
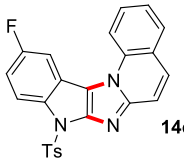
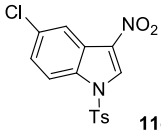
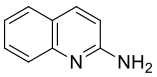
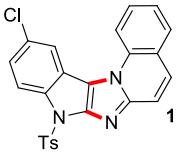
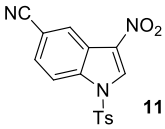
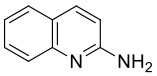
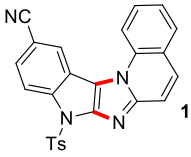
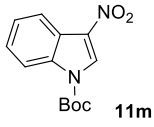
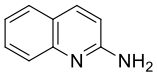
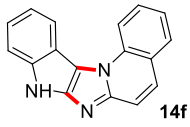
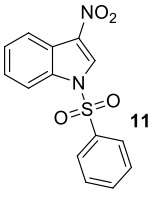
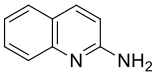
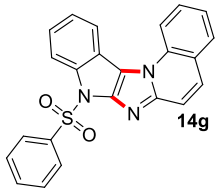
Entry	Indole	2-Aminopyridine	Product	Yield
14	 **11a**	 **2b**	 **12n**	32
15	 **11a**	 **2c**	 **12o**	35
16	 **11m**	 **2a**	 **12p**	35
17	 **11n**	 **2a**	 **12p**	37
18	 **11o**	 **2a**	 **12p**	traces

Reaction conditions: [a] **11** (1.0 equiv.), **2** (1.2 equiv.), CuI (10 mol%), DMF (0.15 mM), 100 °C, 36 h; [b] starting from 1.0 gram of **1**; NR = no reaction.

Next, we tried the reaction by starting with electrophilic indoles having different aryl sulphonyl groups on the *N*-atom (Table 2). The Cu-catalyzed annulation of these resulted in the formation of indole fused imidazo[1,2-*a*]pyridines **12i** to **12l** in satisfactory yields. Further investigations were focused on evaluating the reactivity of different 2-aminopyridines, among which 3-methyl, 5-methyl and 6-ethyl substituted 2-aminopyridine furnished the corresponding products **12m, 12n** and **12o** in poor yields.[15] The reason for the drop in the yield with substituted 2-aminopyridines is not properly understood at the moment.

Surprisingly, by changing the electron withdrawing substituent on the *N*-atom of indole to Boc, Ac and benzoyl groups, we observed the formation of **12p** with the *N*-substituents cleaved probably by 2-aminopyridine after the annulation process (Table 2).

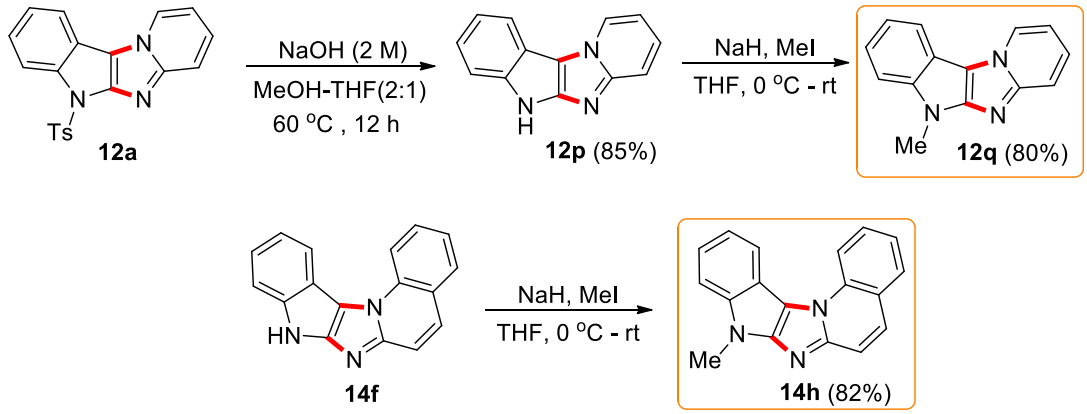
Table 3. Generality of indoloimidazo[1,2-*a*]quinolone synthesis[a]

Entry	Indole	2-Aminoquinoline	Product	Yield
1	 **11a**	 **13**	 **14a**	65
2	 **11b**	 **13**	 **14b**	50
3	 **11c**	 **13**	 **14c**	45
4	 **11d**	 **13**	 **14d**	45
5	 **11p**	 **13**	 **14e**	48
6	 **11m**	 **13**	 **14f**	55
7	 **11i**	 **13**	 **14g**	60

Reaction conditions: [a]**11** (1.0 equiv.), **13** (1.2 equiv.), CuI (10 mol%), DMF (0.15 mM), 100 °C, 36 h.

After establishing the generality of the annulation of electrophilic indoles with 2-aminopyridine toward tetracenes, we planned to utilize 2-aminoquinoline for the annulation with the idea of generating pentacenes (Table 3). The Cu-catalyzed reaction of 3-nitro-*N*-tosyl indole **11** with 2-aminoquinoline **13** under the optimized conditions afforded indoloimidazo[1,2-*a*]quinoline **14a** in 65% yield. The annulation of halogenated electrophilic indoles with 2-aminoquinoline also resulted in the formation of expected products **14b** to **14d** in moderate yields. We also introduced CN-group to the indole part of **14e** by starting from appropriately substituted electrophilic indole. As observed earlier, we could see that with *N*-Boc-3-nitro-indole, the annulated product **14f** was obtained after the Boc-group cleavage. Finally, indole with SO_2Ph-substituent on *N*-atom (**11i**) also furnished the desired product **14g** in 60% yield.

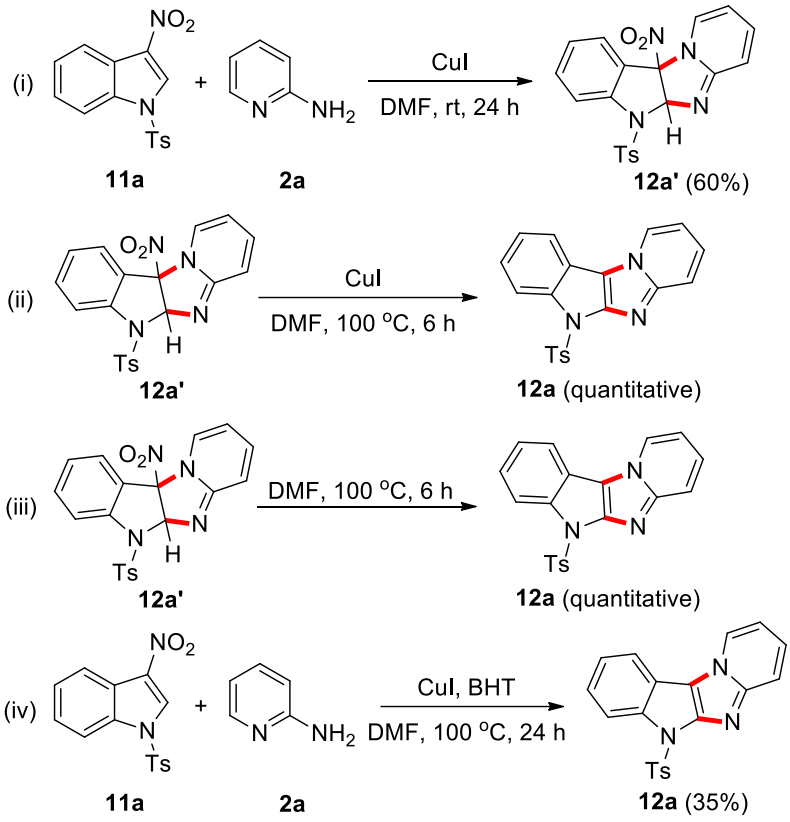
To further highlight the developed methodology, we attempted Ts-deprotection[17(a)] in the synthesized indole fused imidazo[1,2-*a*]pyridine (Scheme 2.12). Upon subjecting **12a** to basic conditions in a mixture of THF and MeOH, the expected Ts-deprotected compound **12p** was obtained in 85% yield. Then, **12p** was easily *N*-alkylated by treating with methyl iodide under basic conditions to give **12q** in 80% yield. The *N*-alkylation of **14f** was also attempted in a similar way as mentioned above, and the corresponding product **14h** was obtained in 82% yield.



Scheme 2.12 Synthetic transformations of pyridoimidazo[4,5-*b*]indole and indoloimidazo[1,2-*a*]quinoline

In order to get an insight into the mechanism of this Cu-catalyzed annulation, we carried out some control experiments (Scheme 2.13). To our surprise, when the optimised reaction was

carried out at room temperature, we obtained the annulated product (non-aromatic) **12a'** which we believe is the intermediate of the present annulation reaction (Scheme 2.13(i)). Then, **12a'** was subjected to two reaction conditions (DMF, 100 °C, 6 h) in the presence and absence of CuI and from both the reactions, the product **12a** was obtained in quantitative yields (Scheme 2.13(ii) & 2.13(iii)).

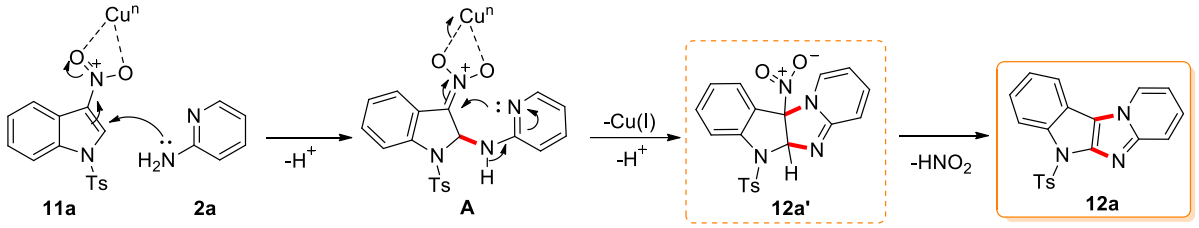


Scheme 2.13 Control experiments for elucidating the mechanism

This observation proves that the Cu-catalyst is not required in the aromatization stage. Finally, in order to check whether the reaction is proceeding via a radical pathway, we repeated the optimised reaction in the presence of 1.0 equivalent of BHT (butyrated hydroxyl toluene) from which we could observe the formation of the product **12a** (Scheme 2.13(iv)).

Based on the above observations and literature precedents,[16-17] we propose a mechanism for the annulation reaction as shown in Scheme 2.14. The first step is the Michael addition of 2-aminopyridine to the C-2 of 3-nitroindole wherein the Cu-catalyst (acting as a Lewis acid) coordinates with the oxygens of the nitro-group in **11a**.[15] This will make the C-2 of **11a** more

electrophilic, thereby enabling Michael addition of **2a** to happen to furnish intermediate **A**. Then, the annulation is completed by the attack of lone pair on the pyridine *N*-atom to the C-3 of **1** along with protodemetallation. This step affords the intermediate **12a'**, which we could isolate as depicted in Scheme 2.13(i). This is followed by the elimination of nitrous acid and subsequent aromatization to furnish indole fused imidazo[1,2-*a*]pyridine **12a**.[16]



Scheme 2.14 Mechanism for the synthesis of pyridoimidazo[4,5-*b*]indoles

In order to explore the material aspects of these heteroacenes, we investigated the preliminary photophysical properties of indole fused imidazo[1,2-*a*]pyridine and indoloimidazo[1,2-*a*]quinolone. The normalized UV–vis absorption and the steady-state photoluminescence (PL) spectra of these compounds recorded in chloroform (1×10^{-5} M) are shown in Fig. 4 and the corresponding photophysical parameters are expressed in Table 4.

From Figure 4. it is clear that when compared to indole fused imidazo[1,2-*a*]pyridines (**12a, 12f, 12n, 12p, 12q**), the indoloimidazo[1,2-*a*]quinolines derivatives (**14a, 14d, 14f, 14g, 14h**) showed a red shifted absorption due to the extended π-congugation in it. This also reflects in the emission profile of the corresponding compounds with a red shifted emission maximum. The absorption and emission properties of all these compounds are summarized in Table 4.

In addition, we have recorded the fluorescence quantum yield of compounds **12a**, **12q**, **14a** and **14h** (Table 5). We observed higher fluorescence quantum yields for pentacenes (**14a, 14h**) than tetracenes (**12a, 12q**). All these findings reveal the structure-property relationship of *N*-heterocyclic systems that would benefit the development of novel materials with advanced functionalities.

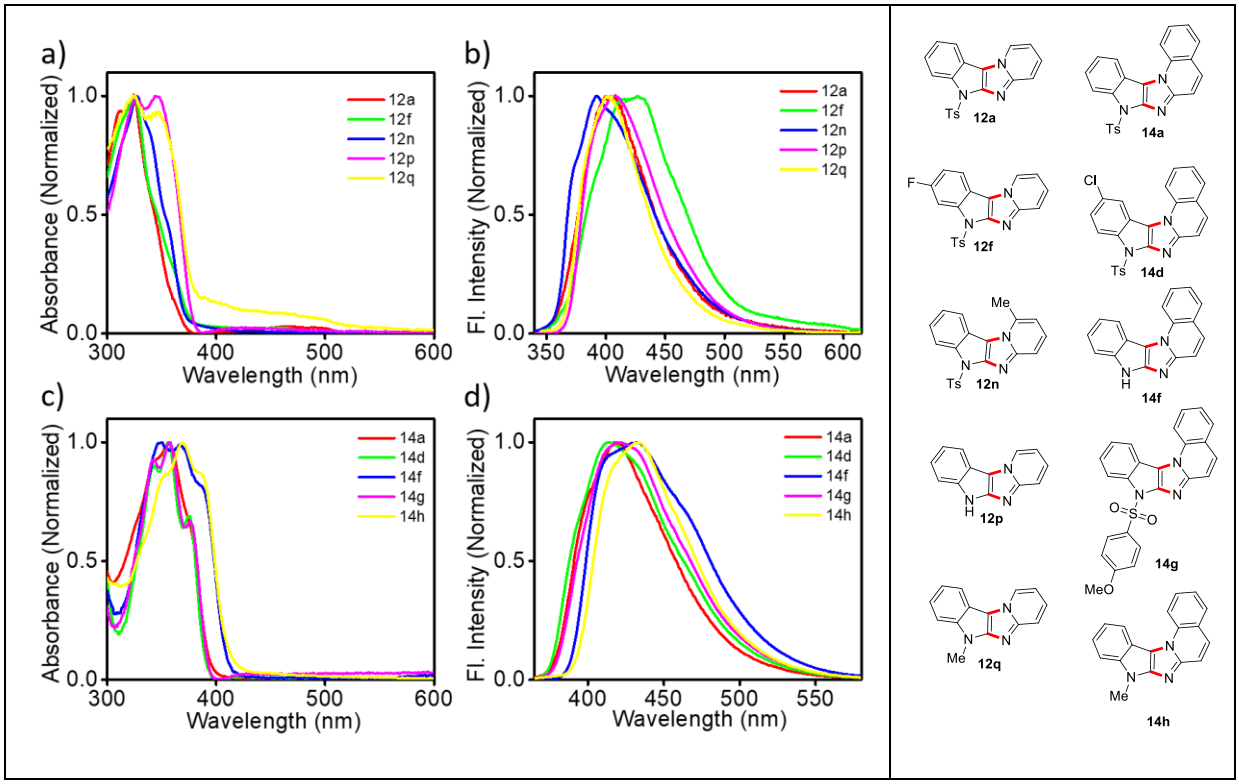


Figure 4. Normalized a) absorption and b) emission spectra of indole fused imidazo[1,2-*a*]pyridines; Normalized c) absorption and d) emission spectra of indoloimidazo[1,2-*a*]quinolines in $CHCl_3$ [conc. = 1 x 10^{-5} M].

Table 4. Absorption maximum, extinction coefficient (ε) and emission maximum in $CHCl_3$ (1 x 10^{-5} M).

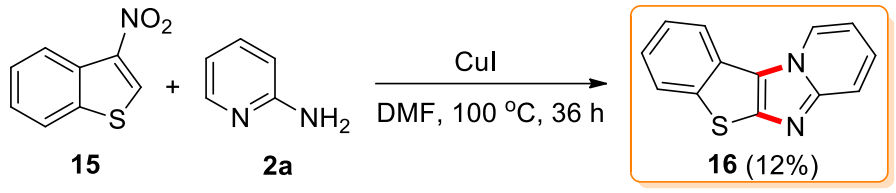
Compound	**λ_{abs} (nm)**	**ε x 10^5 (M^{-1} cm^{-1})**	**λ_{em} (nm)**
12a	311, 324	0.13, 0.14	400
12f	325	0.30	421
12n	327	0.37	392
12p	325, 345	0.08, 0.08	408
12q	324, 345	0.06, 0.05	402
14a	342, 357	0.18, 0.19	419

14d	342, 356, 375	0.06, 0.07, 0.04	414
14f	348, 367, 388	0.04, 0.04, 0.03	432
14g	342, 357, 376	0.07, 0.08, 0.05	420
14h	352, 369, 386	0.11, 0.12, 0.11	433

Table 5. Fluorescence quantum yield (Φ_f) in $CHCl_3$ (1 x 10^{-5} M).

12a Φ_f **(%)**	**12q** Φ_f **(%)**	**14a** Φ_f **(%)**	**14h** Φ_f **(%)**
2.15	1.63	10.59	26.89

Finally, we wanted to extend this annulation to electrophilic benzothiophene and when 3-nitrobenzothiophene **15** was treated with 2-aminopyridine **2a** under the optimized conditions, the expected annulated product benzothiophene fused imidazo[1,2-*a*]pyridine **16** was obtained in 12% yield (Scheme 2.15). From this reaction we could isolate both the unreacted starting materials which warrants for further optimization and this will be done in due course.



Scheme 2.15 Synthesis of benzothiophene fused imidazo[1,2-*a*]pyridine *via* the Cu-catalyzed annulation of 3-nitrobenzothiophene with 2-aminopyridine.

2.5 Conclusions

To conclude, we have successfully developed a Cu-catalyzed methodology for the synthesis of heteroacenes. By the annulation of electrophilic indole with 2-aminopyrydine, we could generate indole fused imidazo[1,2-*a*]pyridine, an interesting but seldom explored tetracene. We could also synthesize pentacenes from electrophilic indole by performing the annulation

with 2-aminoquinolines. The present annulation was found to be general as a range of indole fused imidazo[1,2-*a*]pyridines and indoloimidazo[1,2-*a*]quinolones could be synthesized in moderate to good yields. We have proposed a mechanism which involves a Cu-catalyzed Michael addition and ring-closing to furnish a non-aromatic intermediate which was isolated. The basic photophysical properties of representative examples of the synthesized heteroacenes were evaluated in order to assess their suitability in material applications. Finally, we could also extend the Cu-catalyzed annulation for the synthesis of benzothiophene fused imidazo[1,2-*a*]pyridine. The application of these heteroacenes as components of dyes for DSC's are currently progressing in our lab.

2.6 Experimental section

2.6.1 General experimental methods

All reactions were conducted in oven-dried glass wares. Solvents used for the experiments were distilled and degassed with Argon. All other reagents were purchased from local suppliers. All reactions were monitored by TLC (Silica gel 60 F254, 0.25 mm, Merck), visualization was effected with UV and/or by staining with Enholm yellow solution. Gravity column chromatography was performed using 100-200 mesh silica gel and mixtures of hexane- ethyl acetate were used for elution. Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer FT-IR spectrometer. Nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C{^{1}H} NMR). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (double doublet); m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C{^{1}H} NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). Mass spectra were recorded under ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer. Absorption spectra were measured using a Shimadzu UV-visible 3101 PC NIR spectrophotometer using a quartz cell with a 1 cm path length. Fluorescence spectra were

recorded using a SPEX-Fluorolog F112X spectrofluorometer equipped with a 450 W xenon arc lamp. The spectra were corrected using the program installed by the manufacturer. The fluorescence quantum yields in the solution state were determined relative to a standard compound, quinine sulphate (0.1 M H_2SO_4; ϕ_F = 0.546), using optically matching solutions. The diffraction data of single crystals were collected on a Bruker Apex-II diffractometer using graphite monochromated Mo-Kα radiation. The data was processed with the SMART software suite. The structure solution was carried out by direct methods, and the refinements were performed by full-matrix least-squares on F2 using the SHELXTL suite of programs. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments.

All chemicals were purchased from TCI Chemicals, Sigma-Aldrich or Spectrochem.

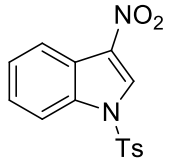
2.6.2 Synthesis and Characterization

Procedure for the synthesis of electrophilic benzannulated heterocycles. 3-Nitroindoles and 3-nitrobenzothiophene were prepared by following a literature report.[18]

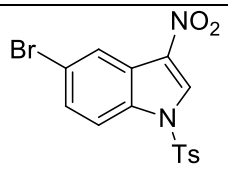
Preformed acetyl nitrate was generated by the dropwise addition of neat yellow 90% HNO_3 (30.0 mmol, 1.35 mL) to cooled (0 °C) acetic anhydride (20 mL) followed by standing at r.t. for 10 min and was used immediately. To a stirred solution of indole 3 (10.0 mmol) in acetic anhydride (50 mL) at –70 °C was added a solution of the preformed acetyl nitrate dropwise via addition funnel over 30 min. The mixture was kept at this temperature until the reaction was found to be complete by TLC. The mixture was then poured onto ice (50 g) and stirred for 1 h with external cooling. If a precipitate formed, it was collected by suction filtration. The aqueous solution was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (300 mL), dried (Na_2SO_4), and concentrated in vacuo to give a crude solid. The crude was then purified by column chromatography (ethyl acetate/hexane) to give the desired 3-nitroindole and 3-nitrobenzothiophene.

3-nitro-1-tosyl-1*H*-indole (**11a**)[18]. Column chromatography (5% ethyl acetate/hexane) gave **11a** as white solid (928 mg, 80%).

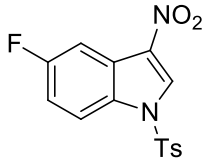
	Mp: 135 - 136 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.59 (s, 1H), 8.26 (d, *J* = 8.5

	Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.49 – 7.48 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 146.8, 133.8, 133.6, 130.5, 127.9, 127.5, 126.8, 125.9, 121.8, 121.3, 113.6, 21.8 ppm.

5-bromo-3-nitro-1-tosyl-1*H*-indole (**11b**)[18]. Column chromatography (5% ethyl acetate/hexane) gave **11b** as white solid (896 mg, 80%).

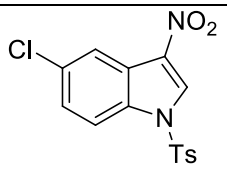
	**Mp**: 230 -232 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.46 (s, 1H), 8.32 (s, 1H), 7.80 (t, *J* = 9.0 Hz, 3H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H) 2.34 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 147.1, 133.5, 132.2, 130.7, 130.3, 130.0, 128.6, 127.5, 126.9, 124.0, 123.2, 119.9, 115.0, 21.8 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{15}H_{11}BrN_2NaO_4S$, 416.9515; found, 416.9530.

5-fluoro-3-nitro-1-tosyl-1*H*-indole (**11c**). Column chromatography (5% ethyl acetate/hexane) gave **11c** as white solid (808 mg, 70%).

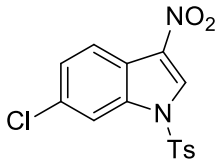
	**Mp:** 199 -201 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.60 (s, 1H), 8.00 - 7.97 (m, 1H), 7.93 - 7.91 (m, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.24 - 7.20 (m, 1H), 2.43 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 161.0 (d, *J* = 244 Hz), 147.1, 133.6, 130.6, 129.9, 129.1, 127.5, 123.0, 122.9, 115.4, 115.2 (d, *J* = 29.14 Hz), 115.0, 107.4, 107.2, 21.8 ppm.

5-chloro-3-nitro-1-tosyl-1*H*-indole (**11d**)[18]. Column chromatography (5% ethyl acetate/hexane) gave **11d** as white solid (573 mg, 50%).

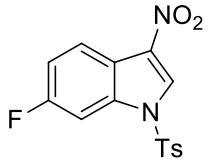
	Mp: 198 - 200 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.49 (s, 1H), 8.17 (s, 1H), 7.87 (d, *J* = 9.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 9.0 Hz,

	1H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.34 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 147.1, 133.6, 132.3, 131.8, 130.7, 130.3, 128.8, 127.5, 127.3, 122.8, 121.0, 114.8, 21.8 ppm. **HRMS (ESI-Orbitrap) m/z:** $(M+Na)^+$ calcd for $C_{15}H_{11}ClN_2NaO_4S$ 373.0020; found 373.0035

6-chloro-3-nitro-1-tosyl-1*H*-indole (**11e**)[18]. Column chromatography (5% ethyl acetate/hexane) gave **11e** as white solid (745 mg, 65%).

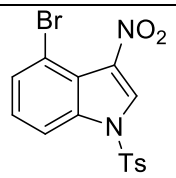
	**Mp:** 190 -192 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.45 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.96 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.35 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 147.2, 133.8, 133.6, 133.1, 130.7, 128.1, 127.5, 126.7, 122.2, 120.3, 113.8, 21.8 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{15}H_{11}ClN_2NaO_4S$, 373.0020; found, 373.0033.

6-fluoro-3-nitro-1-tosyl-1*H*-indole (**11f**). Column chromatography (5% ethyl acetate/hexane) gave **11f** as white solid (736 mg, 64%).

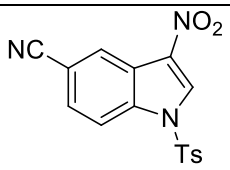
	**Mp:** 196 - 198 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.55 (s, 1H), 8.23 – 8.20 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.23 (t, *J* = 8.5 Hz, 1H), 2.44 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 161.7 (d, *J* = 245 Hz), 147.1, 133.6, 130.7, 127.99, 127.96, 127.5, 122.7, 122.6, 114.8, 114.6, 101.2, 101.0, 21.8 ppm.

4-bromo-3-nitro-1-tosyl-1*H*-indole (**11g**). Column chromatography (5% ethyl acetate/hexane) gave **11g** as white solid (672 mg, 60%).

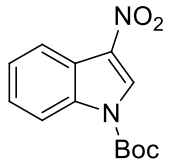
	Mp: 188 - 190 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.42 (s, 1H), 7.94 (t, *J* = 8.5

	Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 2.34 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 147.0, 134.7, 133.6, 131.1, 130.6, 130.4, 128.4, 127.5, 127.3, 120.7, 113.6, 112.8, 21.9 ppm.

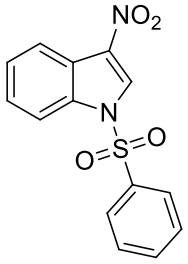
5-cyano-3-nitro-1-tosyl-1*H*-indole (**11p**)[18]. Column chromatography (5% ethyl acetate/hexane) gave **11p** as white solid (783 mg, 68%).

	**Mp:** 220 -222 °C. **^1H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.58 (s, 1H), 8.54 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.35 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 147.6, 134.9, 133.3, 130.9, 129.61, 129.55, 127.6, 126.4, 121.9, 118.2, 114.8, 110.0, 21.8 ppm.

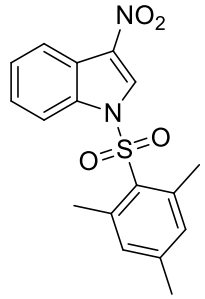
tert-butyl 3-nitro-1*H*-indole-1-carboxylate (**11m**)[18]. Column chromatography (5% ethyl acetate/hexane) gave **11m** as a yellow solid (600 mg, 50%).

	**Mp:** 136 - 138 °C. **^1H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.48 (s, 1H), 8.21 – 8.19 (m, 1H), 8.17 – 8.16 (m, 1H), 7.40- 7.38 (m, 2H), 1.64 (s, 9H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 148.2, 127.9, 126.7, 125.5, 121.6, 120.8, 115.5, 86.7, 28.0 ppm..

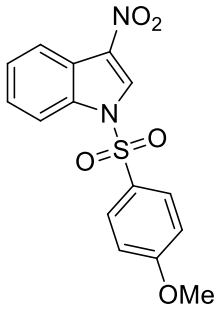
3-nitro-1-(phenylsulfonyl)-1*H*-indole. (**11i**)[18]. Column chromatography (10% ethyl acetate/hexane) gave **11i** as white solid (587 mg, 50%).

	**Mp:** 139 -141 °C. **^1H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.60 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.05 – 8.02 (m, 3H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.50 – 7.49 (m, 2H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 136.9, 135.2, 133.6, 129.9, 127.8, 127.4, 126.9, 126.0, 121.8, 121.3, 113.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{14}H_{10}N_2NaO_4S$, 325.0253; found, 325.0269.

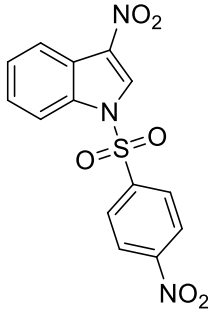
1-(mesitylsulfonyl)-3-nitro-1*H*-indole (**11j**). Column chromatography (5% ethyl acetate/hexane) gave **11j** as white solid (862 mg, 75%).

	**Mp:** 210-212 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.49 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.34 - 7.25 (m, 3H), 2.49 (s, 6H), 2.24 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 145.8, 140.7, 133.6, 133.0, 128.3, 126.5, 125.6, 121.4, 121.3, 112.8, 22.8, 21.2 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{17}H_{16}N_2NaO_4S$, 367.0723; found, 367.0741.

1-((4-methoxyphenyl)sulfonyl)-3-nitro-1*H*-indole (**11k**). Column chromatography (10% ethyl acetate/hexane) gave **11k** as white solid (810 mg, 70%).

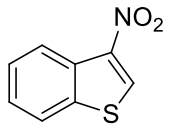
	**Mp:** 205-207 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.59 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.48 – 7.47 (m, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 3.86 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 164.9, 133.5, 129.9, 127.90, 127.87, 126.7, 125.8, 121.8, 121.2, 115.1, 113.6, 55.9 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{15}H_{12}N_2NaO_5S$, 355.0359; found, 355.0373.

3-nitro-1-((4-nitrophenyl)sulfonyl)-1*H*-indole (**11l**). Column chromatography (10% ethyl acetate/hexane) gave **11l** as white solid (459 mg, 40%).

	**Mp:** 218-220 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.35 (d, *J* = 8.5 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H), 8.12 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.38 (t, *J* = 7.5 Hz, 1H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 144.0, 132.7, 130.2, 128.9, 126.0, 125.8, 125.5, 125.0, 124.5, 124.4, 115.8, 114.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{14}H_9N_3NaO_6S$

	370.0104; found 370.0111.

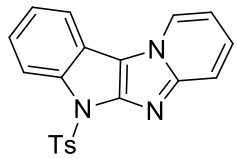
3-nitro-benzothiophene (**15**). Column chromatography (hexane) gave **15** as a yellow solid (465 mg, 35%).

	**Mp:** 130 - 132 ^{o}C. **^{1}H NMR (500 MHz, CDCl$_3$, TMS)**: δ 8.62 (s, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H) ppm. **^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$)**: δ 142.7, 138.7, 132.7, 130.0, 127.1, 126.4, 124.0, 123.0 ppm.

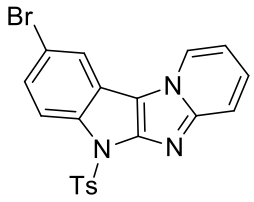
Procedure for the reaction of 3-nitro-*N*-tosyl indole and 2-aminopyridine. A mixture of 3-nitro-*N*-tosyl indole (1.0 equiv.), 2-aminopyridine (1.2 equiv.) and copper iodide (10 mol%) was weighed into a dry reaction tube. Dry DMF (0.15 mmol) was added and the mixture was allowed to stir at 100 ^{o}C in an oil bath for 36 hours. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products. **2.6.4 Synthesis and characterization of indole fused imidazo[1,2-*a*]pyridines**

6-Tosyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12a**). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **11a** (100 mg, 0.32 mmol), 2-aminopyridine **2a** (36 mg, 0.38 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100^{o}C for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12a** as a white solid in 70% yield (81 mg).

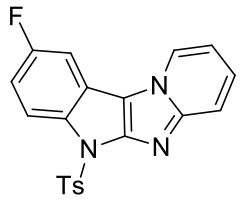
	Mp: 228-230 ^{o}C. **^{1}H NMR (500 MHz, CDCl$_3$, TMS)**: δ 8.30 (d, *J* = 6.5 Hz, 1H), 8.26 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 9.0 Hz,

	1H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.30 - 7.25 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 6.5 Hz, 1H), 2.20 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 148.8, 148.0, 144.9, 138.0, 135.2, 129.7, 127.0, 124.8, 124.6, 124.1, 123.7, 118.4, 118.2, 116.4, 115.6, 112.7, 21.6 ppm. **IR (neat) ν_{max}**: 2929, 1595, 1526, 1430, 1405, 1374, 1245, 1172, 1121, 1088, 1023, 933, 816, 738, 677, 568, 540, 421 cm^{-1}. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{20}H_{16}N_3O_2S$, 362.0957; found, 362.0969.

9-Bromo-6-tosyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12b**). The reaction was performed according to general procedure with 5-bromo-3-nitro-*N*-tosyl indole **11b** (100 mg, 0.25 mmol), 2-aminopyridine **2a** (28 mg, 0.3 mmol) and copper iodide (5 mg, 0.025 mmol) in DMF (0.15 mmol) at 100 °C for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12b** as a white solid in 55% yield (61 mg).

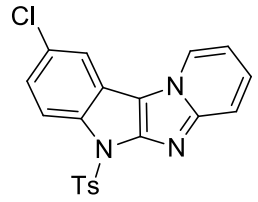
	**Mp:** 203-205 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.27 (d, *J* = 6.5 Hz, 1H), 8.12 (d, *J* = 9 Hz, 1H), 7.85 - 7.80 (m, 3H), 7.71 (s, 1H), 7.37 (d, *J* = 8 Hz, 1H), 7.31 (t, *J* = 8 Hz, 1H), 7.08 (d, *J* = 8 Hz, 2H), 6.97 (t, *J* = 6.5 Hz, 1H), 2.21 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 148.5, 145.2, 136.6, 134.9, 129.8, 127.1, 126.3, 125.4, 124.9, 119.6, 119.1, 118.5, 117.5, 116.9, 113.0, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{20}H_{15}BrN_3O_2S$, 440.0063; found: 440.0067.

9-Fluoro-6-tosyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12c**). The reaction was performed according to general procedure with 5-flouro-3-nitro-*N*-tosyl indole **11c** (100 mg, 0.30 mmol), 2-aminopyridine **2a** (34 mg, 0.36 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 ºC for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12c** as a white solid in 45% yield (51 mg).

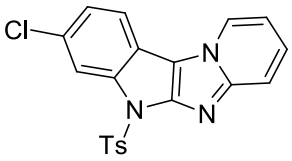
	**Mp:** 235 - 237 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.24 (d, *J* = 6.5 Hz, 1H), 8.20 - 8.17 (m, 1H), 7.84 - 7.79 (m, 3H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.00 - 6.96 (m, 2H), 2.20 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 159.0, 149.1 (d, *J* = 184 Hz), 145.1, 134.9, 134.0, 129.7, 127.0, 125.3, 124.9, 118.4, 116.65, 116.58, 113.0 (d, *J* = 24.5 Hz), 103.0 (d, *J* = 26.0 Hz), 21.6 ppm. **^{19}F NMR (470 MHz, $CDCl_3$)**: δ -117.6 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{20}H_{15}FN_3O_2S$, 380.0864; found, 380. 0860.

9-Chloro-6-tosyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-b]indole (**12d**). The reaction was performed according to general procedure with 5-chloro-3-nitro-*N*-tosyl indole **11d** (100 mg, 0.28 mmol), 2-amino-pyridine **2a** (32 mg, 0.34 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 ºC for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12d** as a brown solid in 41% yield (46 mg).

	Mp: 260 - 262 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.26 (d, *J*= 6.5 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.54 (s, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J*= 8.5 Hz, 1H),

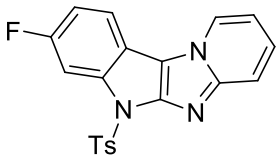
	7.07 (d, *J* = 8.0 Hz, 2H), 6.97 (t, *J* = 6.5 Hz, 1H), 2.21 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 148.4, 145.3, 136.2, 134.8, 130.0, 129.8, 127.0, 125.5, 125.0, 123.6, 119.2, 118.3, 116.5, 116.2, 113.1, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{20}H_{15}ClN_3O_2S$, 396.0568; found, 396.0570.

8-Chloro-6-tosyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-b]indole (**12e**). The reaction was performed according to general procedure with 6-chloro-3-nitro-*N*-tosyl indole **11e** (100 mg, 0.28 mmol), 2-amino-pyridine **2a** (32 mg, 0.34 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12e** as a white solid in 40% yield (44 mg).

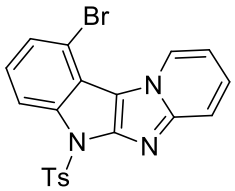
	**Mp:** 238-240 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.24 (m, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.09 (d, *J*= 8.0 Hz, 2H), 6.95 (t, *J*= 6.5 Hz, 1H), 2.21 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 148.9, 148.1, 145.3, 138.1, 135.0, 129.8, 129.3, 127.1, 125.0, 124.8, 124.4, 118.4, 116.8, 116.5, 115.8, 113.0, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{20}H_{15}ClN_3O_2S$, 396.0568; found, 396.0581.

8-Fluoro-6-tosyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12f**). The reaction was performed according to general procedure with 6-fluoro-3-nitro-*N*-tosyl indole **11f** (100 mg, 0.30 mmol), 2-aminopyridine **2a** (34 mg, 0.36 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C stirred for 36 hours. After workup, the residue was purified by

silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12f** as a white solid in 43% yield (49 mg).

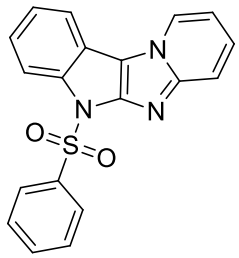
	**Mp:** 244-246 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.23 (d, *J* = 6.5 Hz, 1H), 7.99 (d, *J* = 10.5 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.48 -7.46 (m, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 8.5 Hz, 1H), 6.94 (t, *J* = 6.5 Hz, 1H), 2.21 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 160.8 (d, *J* = 240.4 Hz), 148.8, 147.6, 145.2, 138.3, 138.2, 135.0, 129.8, 127.1, 124.6, 124.6, 118.3, 116.8, 116.7, 114.6, 112.8, 112.1, 111.7 (d, *J* = 23.8 Hz), 103.8 (d, *J* = 29.2 Hz), 29.7 ppm. **^{19}F NMR (470 MHz, $CDCl_3$)**: δ -115.8 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{20}H_{15}FN_3O_2S$, 380.0864; found, 380.0864.

10-Bromo-6-tosyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-b]indole (**12g**). The reaction was performed according to general procedure with 4-bromo-3-nitro-*N*-tosyl indole **11g** (100 mg, 0.25 mmol), 2-amino-pyridine **2a** (28 mg, 0.30 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12g** as a white solid in 45% yield (50 mg).

	**Mp:** 228-230 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.58 (d, *J* = 6.5 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.23 – 7.18 (m, 3H), 6.99 (t, *J* = 6.5 Hz, 1H), 2.31 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 149.2, 149.1, 138.6, 134.9, 129.8, 128.1, 127.9, 127.1, 125.6, 124.4, 120.7, 118.2, 114.2, 112.4,

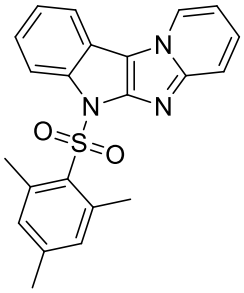
	111.8, 109.8, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{20}H_{14}BrN_3NaO_2S$, 461.9882; found, 461.9905.

6-(Phenylsulfonyl)-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12i**). The reaction was performed according to general procedure with 3-nitro-1-(phenylsulfonyl)-1H-indole **11i** (100 mg, 0.33 mmol), 2-aminopyridine **2a** (37 mg, 0.39 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 ^oC for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12i** as a white solid in 50% yield (61 mg).

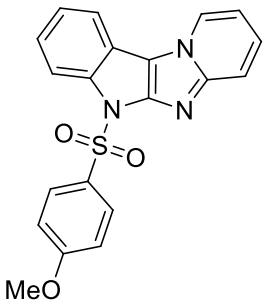
	**Mp:** 170-172 ^oC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.28 (d, *J* = 7.0 Hz, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31-7.24 (m, 5H), 6.94 (t, *J* = 7.0 Hz, 1H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 148.6,148.0,138.1, 137.9, 133.8, 129.1, 127.0, 124.84, 124.75, 124.2, 123.8, 118.3, 118.2, 116.4, 115.5, 112.8 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{19}H_{14}N_3O_2S$, 348.0801; found, 348.08087.

6-(Mesitylsulfonyl)-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12j**). The reaction was performed according to general procedure with 1-(mesitylsulfonyl)-3-nitro-1H-indole **11j** (100 mg, 0.29 mmol), 2-aminopyridine **2a** (33 mg, 0.35 mmol) and copper iodide (6mg, 0.03 mmol) in DMF (0.15 mmol) at 100 ^oC for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12j** as a white solid in 50% yield (57 mg).

	Mp: 201-203 ^oC.

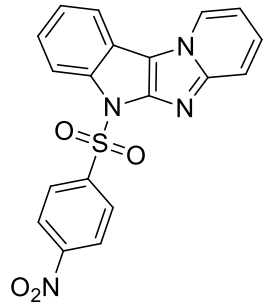
	**^{1}H NMR (500 MHz, $CDCl_3$, TMS):** 8.32 (d, *J* = 6.5 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.21 - 7.14 (m, 2H), 6.91 (t, *J* = 6.5 Hz, 1H), 6.86 (s, 2H), 2.58 (s, 6H), 2.18 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 149.4, 147.9, 143.8, 140.8, 138.1, 133.7, 132.2, 124.8, 124.3, 123.3, 123.2, 118.2, 117.1, 116.4, 114.8, 112.5, 111.4, 22.9, 21.1 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{22}H_{20}N_3O_2S$, 390.1271; found, 390.1295.

6-((4-Methoxyphenyl)sulfonyl)-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12k**). The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1H-indole **11k** (100 mg, 0.30 mmol), 2-amino-pyridine **2a** (34 mg, 0.36 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12k** as a white solid in 47% yield (53 mg).

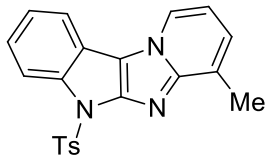
	**Mp:** 262-264 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.30 (d, *J* = 6.5 Hz, 1H), 8.25 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.80 (d, *J* = 9.5 Hz, 1H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.31 – 7.25 (m, 3H), 6.95 (t, *J* = 6.5 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 3.65 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 183.8, 148.6, 147.9, 138.0, 129.7, 129.3, 124.8, 124.7, 124.1, 123.7, 118.3, 118.2, 116.4, 115.6, 114.2, 112.8, 55.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{20}H_{16}N_3O_3S$, 378.0907; found, 378.0921.

6-((4-Nitrophenyl)sulfonyl)-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12l**). The reaction was performed according to general procedure with 3-nitro-1-((4-nitrophenyl)sulfonyl)-1H-indole **11l** (100 mg, 0.29 mmol), 2-amino-pyridine **2a** (33 mg, 0.35 mmol) and copper iodide (6 mg,

0.03 mmol) in DMF (0.15 mmol) at 100 ºC for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12l** as a white solid in 55% yield (63 mg).

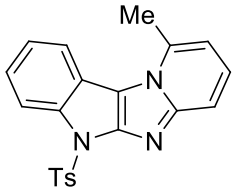
	**Mp:** 210-212 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.31 (d, *J* = 6.5 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 9.0 Hz, 2H), 8.10 (d, *J* = 9.0 Hz, 2H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.30 (m, 3H), 6.99 (t, *J* = 6.5 Hz, 1H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 150.8, 148.1, 143.0, 128.4, 125.3, 125.0, 124.3, 124.2, 118.4, 116.7, 115.6, 113.2 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{19}H_{13}N_4O_4S$, 393.0652; found, 393.0653.

4-Methyl-6-tosyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12m**). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **11a** (100 mg, 0.32 mmol),2-amino-3-methyl-pyridine **2b** (41 mg, 0.38 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 ºC for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12m** as a white solid in 35% yield (42 mg).

	**Mp:** 229-231 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.25 (d, *J* = 7.5 Hz, 1H), 8.17 (d, *J* = 6.5 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.08 – 7.05 (m, 3H), 6.86 (t, *J* = 6.5 Hz, 1H), 2.70 (s, 3H), 2.21 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 148.3, 144.8, 138.1, 135.1, 129.6, 128.4, 127.1, 124.1, 123.9, 123.6, 122.6, 118.5, 116.2, 115.7, 112.6, 21.5, 17.6 ppm.

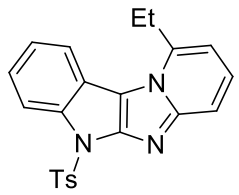
	HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{21}H_{18}N_3O_2S$, 376.1114; found, 376.1148.

1-Methyl-6-tosyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12n**). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **11a** (100 mg, 0.32 mmol), 2-amino-6-methylpyridine **2c** (41 mg, 0.38 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12n** as a white solid in 32% yield (38 mg).

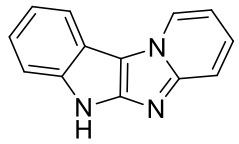
	**Mp:** 215-217 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.27 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.0 Hz, 1H), 7.27 – 7.24 (m, 3H), 7.08 (d, *J* = 7.5 Hz, 2H), 6.69 (d, *J* = 6.5 Hz, 1H), 3.09 (s, 3H), 2.21 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 149.3, 144.9, 137.9, 135.2, 134.8, 129.6, 127.1, 125.7 124.0, 123.5, 118.9, 117.7, 115.7, 115.6, 112.1, 22.3, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{21}H_{18}N_3O_2S$, 376.1114; found, 376.1121.

1-Ethyl-6-tosyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-b]indole (**12o**). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **11a** (100 mg, 0.32 mmol), 2-amino-6-ethylpyridine **2d** (46 mg, 0.38 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12o** as a white solid in 35% yield (43 mg).

	Mp: 220-222 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.30 - 8.28 (m, 1H), 7.86 (d,

	*J* = 8.0 Hz, 2H), 7.70 – 7.69 (m, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.25 – 7.23 (m, 3H), 7.06 (d, *J*= 8.5 Hz, 2H), 6.67 (d, *J* = 7.0 Hz, 1H), 3.38 (q, *J* = 7.5 Hz, 2H), 2.20 (s, 3H), 1.43 (t, *J* = 7.5 Hz, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$):** δ 149.4, 144.9, 140.3, 137.9, 135.2, 129.6, 127.1, 125.8, 124.1, 123.4, 118.9, 117.8, 115.8, 115.5, 112.4, 109.8, 27.9, 21.6, 12.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{22}H_{20}N_3O_2S$, 390.1271; found, 390.1279.

6*H*-Pyrido[1',2':1,2]imidazo[4,5-*b*]indole (**12p**). The reaction was performed according to general procedure with 3-nitro-*N*-Boc indole **11m** (100 mg, 0.38 mmol.), 2-aminopyridine **2a** (42 mg, 0.45 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100°C for 36 hours. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **12p** as a white solid in 35% yield (28 mg).

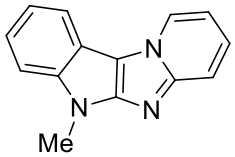
	**Mp:** 238-240 °C. **^1H NMR (500 MHz, Acetone-d_6, TMS):** δ 10.32 (s,1H), 8.77 (d, *J* = 6.5 Hz, 1H), 7.89 (d, *J* = 7.0 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.93 (t, *J* = 6.5 Hz, 1H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6):** δ 139.3, 125.6, 123.4, 121.4, 119.4, 116.5, 116.3, 115.0, 112.0, 110.9 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{13}H_{10}N_3$, 208.0869; found, 208.0880.

Procedure for the scale up of 12a. A mixture of 3-nitro-*N*-tosyl indole **11a** (1.0 g, 3.16 mmol), 2-aminopyridine **2a** (356 mg, 3.79 mmol) and copper iodide (60 mg, 0.316 mmol) was weighed into a dry reaction tube. Dry DMF (0.15 mmol) was added and the mixture was allowed to stir at 100 °C in an oil bath for 36 hours. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed

under vacuum. The residue was then purified by silica gel column chromatography (30% ethyl acetate in hexane) to afford the desired product **12a** (695 mg, 61%).

Procedure for the deprotection of 12a. A solution of NaOH (2.0 M, 2.0 mL) in MeOH was added to a stirring solution of **12a** (100 mg, 0.28 mmol) in dry THF, and the resulting mixture was refluxed in an oil bath under nitrogen for overnight. Upon completion, the reaction mixture was concentrated under reduced pressure, water was added, and the mixture extracted with EtOAc. The organic layer washed successively with brine, the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the residue on activated neutral alumina column chromatography (30% ethyl acetate in hexane) yielded the deprotected compound **12p** as white solid (50 mg, 85%)

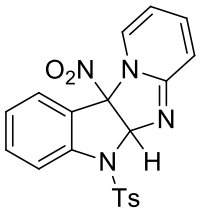
Synthesis and characterization of 6-methyl-6*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (12q). To a stirred solution of **12p** (100 mg, 0.48 mmol) in dry THF, NaH (23 mg, 0.96 mmol) was added portion wise under nitrogen atmosphere at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 30 min. The reaction mixture was cooled again to 0 °C and methyl iodide (135 mg, 0.96 mmol) was added dropwise and stirred at room temperature for 3 h. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **12q** as a white solid in 80% yield (85 mg).

	**Mp:** 200 - 210 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.44 (d, *J* = 6.5 Hz,1H), 7.74 (t, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 6.5 Hz, 1H), 3.92 (s, 1H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 149.2, 146.5, 139.9, 125.1, 124.7, 121.9, 119.9, 116.4, 116.1, 114.3, 112.4, 109.9, 109.3, 29.7 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{14}H_{12}N_3$,

	222.1026; found, 222.1033.

Control Experiments

Synthesis and characterization of 10*b*-nitro-6-tosyl-6,10*b*-dihydro-5a*H*-pyrido[1',2':1,2]imidazo[4,5-*b*]indole (12a'). A mixture of 3-nitro-*N*-tosyl indole **11a** (100 mg, 0.32 mmol), 2-amino-pyridine **2a** (36 mg, 0.38 mmol) and copper iodide (6 mg, 0.03 mmol) was weighed into a dry reaction tube. Dry DMF (0.15 mmol) was added and the mixture was allowed to stir at room temperature for 24 hours. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was purified by silica gel chromatography (20% ethyl acetate in hexane) to afford the desired product **12a'** as a brown solid in 60% yield (79 mg).

	**Mp:** 140-142 ^oC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.74 (d, *J*= 8.0 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.92 (t, *J* = 7.5Hz, 1H), 6.68 (s, 1H), 6.54 (d, *J* = 9.0 Hz, 1H), 5.89 (t, *J* = 6.5 Hz, 1H), 2.31 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 159.0, 145.0, 144.6, 138.3, 134.2, 133.2, 130.5, 129.9, 127.8, 124.6, 123.9, 123.0, 116.5, 116.0, 106.7, 106.2, 93.5, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{20}H_{17}N_4O_4S$, 409.0965; found, 409.0979.

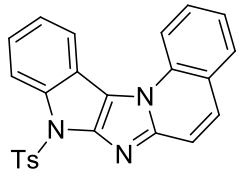
Procedure for the reaction of 11a and 2a in the presence of BHT. A mixture of 3-nitro-*N*-tosyl indole **11a** (100 mg, 0.32 mmol), 2-amino-pyridine **2a** (36 mg, 0.38 mmol), BHT (71 mg, 0.32 mmol) and copper iodide (6 mg, 0.03 mmol) was weighed into a dry reaction tube. Dry DMF (0.15 mmol) was added and the mixture was allowed to stir at 100 ^oC in an oil bath. After 24 hours, the reaction was stopped, water added and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was purified by silica gel

chromatography (30% ethyl acetate in hexane) to afford the product **12a** as a white solid in 35% yield (41 mg).

Procedure for the reaction of 3-nitro-*N*-tosyl indole and 2-aminoquinoline. A mixture of 3-nitro-*N*-tosyl indole (1.0 equiv.), 2-aminoquinoline (1.2 equiv.) and copper iodide (10 mol%) was weighed into a dry reaction tube. Anhydrous DMF (0.15mmol) was added and allowed to stir at 100°C in an oil bath for 36 hours. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by activated neutral alumina column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and characterization of indoloimidazo[1,2-*a*]quinolines

8-Tosyl-8*H*-indolo[2',3':4,5]imidazo[1,2-*a*]quinoline (**14a**). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **11a** (100 mg, 0.32 mmol), 2-aminoquinoline **13** (55 mg, 0.38 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100°C for 36 hours. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **14a** as a white solid in 65% yield (86 mg).



Mp: 248-250 °C.

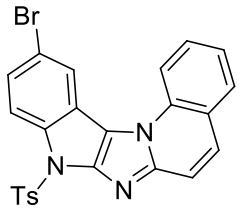
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.32 (t, *J* = 7.0 Hz, 2H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 9.5 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 9.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 2.15 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.1, 146.8, 145.0, 138.3, 135.0, 132.8, 129.7, 129.1, 128.5, 127.1, 127.0, 124.8, 124.1, 124.0, 123.6, 118.44, 118.37, 117.8, 116.8, 115.7, 114.7, 21.5 ppm.

IR (neat) ν_{max}: 3051, 1595, 1539, 1483, 1436, 1413, 1369, 1300,

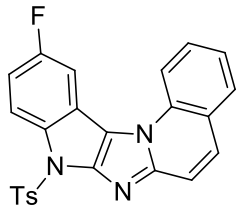
	1215, 1178, 1132, 1090, 1026, 951, 812, 796, 671, 659, 614, 571, 538, 505, 432 cm^{-1}. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{24}H_{18}N_3O_2S$, 412.1114; found, 412.1129.

11-Bromo-8-tosyl-8*H*-indolo[2',3':4,5]imidazo[1,2-*a*]quinoline (**14b**). The reaction was performed according to general procedure with 5-bromo-3-nitro-*N*-tosyl indole **11b** (100 mg, 0.25 mmol), 2-aminoquinoline **13** (43 mg, 0.30 mmol) and copper iodide (4 mg, 0.02 mmol) in DMF (0.15 mmol) at 100 ºC for 36 hours. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **14b** as a white solid in 50% yield (61 mg).

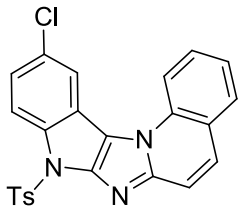
	**Mp:** 282-284 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.32 (d, *J* = 8.5 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.15 (s, 1H), 7.85 (d, *J* = 7.5 Hz, 3H), 7.78 – 7.73 (m, 2H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H) 2.20 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 147.5, 145.3, 136.9, 134.8, 129.8, 129.4, 129.0, 127.7, 127.1, 126.6, 125.1, 123.7, 121.0, 120.0, 117.8, 117.5, 117.0, 116.7, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{24}H_{17}BrN_3O_2S$, 490.0219; found, 490.0235.

11-Fluoro-8-tosyl-8*H*-indolo[2',3':4,5]imidazo[1,2-*a*]quinoline (**14c**). The reaction was performed according to general procedure with 5-fluoro-3-nitro-*N*-tosyl indole **11c** (100 mg, 0.30 mmol), 2-aminoquinoline **13** (52mg, 0.36 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 ºC for 36 hours. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **14c** as a white solid in 45% yield (58 mg).

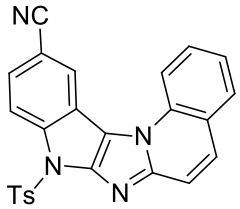
	Mp: 232-234 ºC.

	**^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.34 – 8.31 (m, 2H), 7.84 (d, *J* = 8.0 Hz, 3H), 7.74 (t, *J* = 8.5 Hz, 3H), 7.64 (d, *J* = 9.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.08 – 7.05 (m, 3H), 2.20 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 149.4, 147.4, 145.2, 134.8, 132.9, 129.7, 129.4, 128.9, 127.6, 127.1, 125.1, 124.1, 123.7, 119.4, 117.9, 116.8, 116.6, 111.1 (d, *J* = 24.0 Hz), 105.1 (d, *J* = 27.0 Hz), 21.6 ppm. **^{19}F NMR (470 MHz, $CDCl_3$):** δ -117.0 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{24}H_{17}FN_3O_2S$, 430.1020; found, 430.1036

11-Chloro-8-tosyl-8*H*-indolo[2',3':4,5]imidazo[1,2-*a*]quinoline (**14d**). The reaction was performed according to general procedure with 5-chloro-3-nitro-*N*-tosyl-indole **11d** (100 mg, 0.29 mmol), 2-aminoquinoline **13** (50 mg, 0.34 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 ºC for 36 hours. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **14d** as a yellow solid in 45% yield (58 mg).

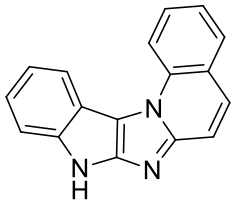
	**Mp:** 278-280 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.36 (d, *J* = 8.5 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.02 (s, 1H), 7.88 – 7.77 (m, 5H), 7.72 – 7.67 (m, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 2H), 2.21 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 145.3, 136.5, 134.8, 132.9, 132.5, 129.8, 129.4, 129.0, 127.7, 127.1, 125.1, 123.8, 123.7, 119.6, 118.2, 117.8, 116.7, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{24}H_{17}ClN_3O_2S$, 446.0725; found, 446.0742.

8-Tosyl-8*H*-indolo[2',3':4,5]imidazo[1,2-*a*]quinoline-11-carbonitrile (**14e**). The reaction was performed according to general procedure with 5-cyano-3-nitro-*N*-tosyl-indole **11p** (100 mg, 0.29 mmol), 2-aminoquinoline **13** (50 mg, 0.34 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 hours. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **14e** as a white solid in 48% yield (60 mg).

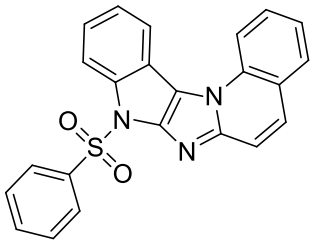
	**Mp:** 220-222 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.48 (d, *J* = 8.5 Hz, 1H), 8.38 (s, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 9.5 Hz, 1H), 7.71 (d, *J* = 9.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 2H), 2.23 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 149.4, 148.0, 145.8, 139.9, 134.8, 132.9, 130.0, 129.6, 129.3, 128.3, 127.2, 127.0, 125.4, 123.7, 122.2, 118.5, 117.8, 116.5, 116.1, 113.2, 107.4, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{25}H_{16}N_4NaO_2S$, 459.0886; found, 459.0899.

8*H*-indolo[2',3':4,5]imidazo[1,2-*a*]quinoline (**14f**). The reaction was performed according to general procedure with 3-nitro-*N*-Boc-indole **11m** (100 mg, 0.38 mmol), 2-aminoquinoline **13** (66 mg, 0.45 mmol) and copper iodide (8 mg, 0.04 mmol) in DMF (0.15 mmol) at 100 °C for 36 hours. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **14f** as a white solid in 55% yield (54 mg).

	Mp: 158-160 °C. **^{1}H NMR (500 MHz, dmso-d_6, TMS):** δ 11.74 (s, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.40 (d, *J* = 6.5 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 1H), 7.99 (t, *J* = 7.0 Hz, 1H), 7.86 (d, *J* = 9.5 Hz, 1H), 7.71 (d, *J* = 9.5 Hz,

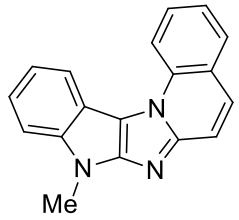
	1H), 7.64 – 7.58 (m, 2H), 7.31 – 7.30 (m, 2H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, dmso-d_6):** δ 150.2, 146.3, 139.7, 133.7, 132.9, 129.6, 126.3, 125.2, 124.6, 123.1, 122.1, 119.8, 118.5, 117.4, 113.5, 113.0, 111.1 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{17}H_{12}N_3$, 258.1026; found, 258.1037.

8-(Phenylsulfonyl)-8*H*-indolo[2',3':4,5]imidazo[1,2-*a*]quinoline (**14g**). The reaction was performed according to general procedure with 3-nitro-1-(phenylsulfonyl)-1H-indole **11i** (100 mg, 0.35 mmol), 2-aminoquinoline **13** (60 mg, 0.42 mmol) and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 hours. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **14g** as a white solid in 60% yield (83 mg).

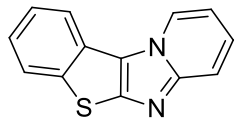
	**Mp:** 190-192 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.50 (d, *J* = 8.5 Hz, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.41 – 7.34 (m, 3H), 7.29 (t, *J* = 7.5 Hz, 2H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 148.2, 147.0, 138.3, 138.0, 133.9, 129.2, 129.1, 128.6, 127.1, 127.0, 124.9, 124.2, 124.1, 123.7, 118.4, 117.9, 116.9, 115.8 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{23}H_{16}N_3O_2S$, 398.0958; found, 398.0970.

Synthesis and characterization of 8-methyl-8*H*-indolo[2',3':4,5]imidazo[1,2-*a*]quinoline (14h). To a stirred solution of **14f** (100 mg, 0.39 mmol) in dry THF, NaH (19 mg, 0.78 mmol) was added portion wise under nitrogen atmosphere at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 30 min. The reaction mixture was cooled again to 0 °C and methyl iodide (109 mg, 0.78 mmol) was added dropwise and stirred at room temperature for 3 h. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was

dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14h** as a white solid in 82% yield (87 mg).

	**Mp:** 200 -220 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.70 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 9.5 Hz, 1H), 7.63 (d, *J* = 9.5 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.36 – 7.29 (m, 2H), 3.99 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 140.2, 129.0, 128.6, 124.4, 123.4, 122.0, 119.7, 118.3, 117.1, 110.1, 29.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{18}H_{14}N_3$, 272.1182; found, 272.1195.

Synthesis and characterization of benzo[4',5']thieno[2',3':4,5]imidazo[1,2-*a*]pyridine (16). The reaction was performed according to general procedure with 3-nitro-benzothiophene **15** (100 mg, 0.56 mmol), 2-aminopyridine **2a** (63 mg, 0.67 mmol) and copper iodide (11 mg, 0.06 mmol) in DMF (0.15 mmol) at 100 °C for 36 hours. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **16** as a white solid in 12% yield (15 mg).

	**Mp:** 200-202 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.54 (d, *J* = 6.5 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 9.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.00 (t, *J* = 6.5 Hz, 1H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 149.3, 139.6, 125.3, 125.13, 125.08, 124.74, 124.66, 123.8, 118.1, 117.4, 112.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{13}H_9N_2S$,

	225.0481; found, 225.0489.

.

2.7 References

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15. In all reactions depicted in tables 2 and 3, we could observe the formation of a yellow-coloured intractable band both in TLC and during column chromatography. This might be the reason for the comparatively low yield of the reaction

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Chapter 3A

Domino Dipolar Cycloaddition-Ring Opening Reaction of Isoquinolinium Ylides with Electrophilic Benzannulated Heterocycles

3A.1 Abstract

We have come across an unexpected domino dipolar cycloaddition-ring opening reaction between electrophilic indoles and isoquinolinium methylides for accessing functionalized pyrrolo[2,1-a]isoquinolines. The reaction was found to be general, yielding the products in good yields and scalable to gram-scale. We also observed the formation of S-S bridged bis-pyrrolo[2,1-a]isoquinolines from the reaction of 3-nitro benzothiophene and isoquinolinium methylides.

3A.2 Introduction

As discussed in previous Chapter 1, reports on the dipolar cycloaddition utilizing electrophilic indole as the dipolarophile towards annulated heterocycles made us devise dipolar cycloaddition reactions towards novel heteroacenes.

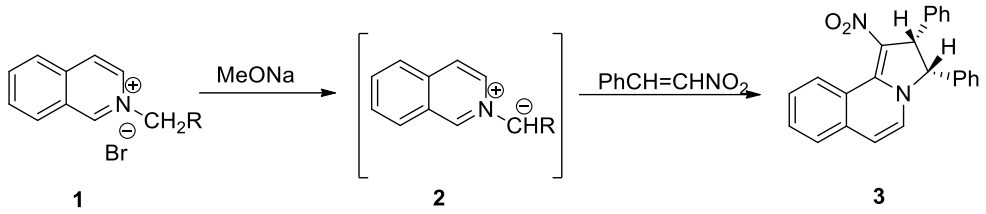
3A.2.1 Heteroaromatic *N*-ylides

Heteroaromatic *N*-ylides are a class of dipoles which were comprehensively studied for the generation of highly functionalized carbocycles and heterocycles. [1] In particular, isoquinolinium methylides were utilized in dipolar cycloaddition reactions with several dipolarophiles, such as electron-deficient alkenes and alkynes, to access fused *N*-heterocyclic scaffolds.[2]

3A.2.2 Initial reports on the dipolar cycloaddition reactions using isoquinolinium methylides

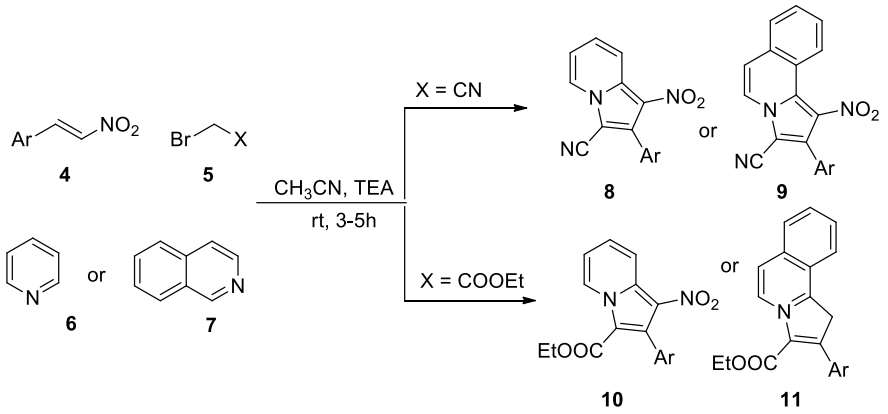
The first report on 1,3-dipolar cycloaddition of isoquinolinium methylides to nitrostyrenes was published in the year 1990, where 1-nitro-2-phenyl-3-R-2,3-dihydrobenzo[*g*]indolizine

was synthesized by the reaction between *β*-nitrostyrene and isoquinolinium methylide [3] (scheme 3A.1).



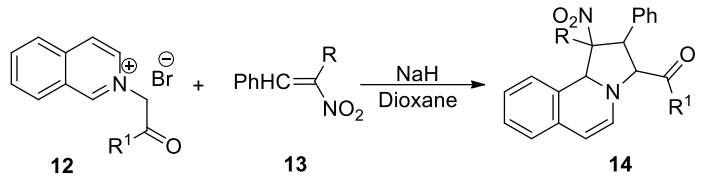
Scheme 3A.1 Synthesis of 1-nitro-2-phenyl-3-R-2,3-dihydrobenzo[*g*]indolizines

Muthusaravanan and co-workers reported the synthesis of novel tri-/disubstituted indolizines and pyrrolo[2,1-*a*]isoquinolines for the first time *via* a three component domino one pot reaction of pyridinium/isoquinolinium ylide, generated *in situ* from pyridine/isoquinoline, with bromoacetonitrile or ethyl bromoacetate and *β*-nitrostyrene. The reaction afforded a maximum yield of the product when a molar equivalent of triethylamine was employed. These compounds also display significant anti mycobacterial activities (Scheme 3A.2).[4]



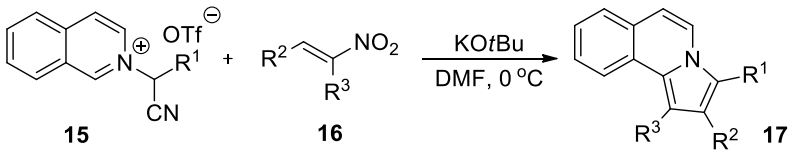
Scheme 3A.2 Synthesis of novel indolizines and pyrrolo[2,1-*a*]isoquinolines

In 2009, Nosachev and his co-workers extended the studies in the field of 1,3-dipolar cycloaddition by treating substituted 1-nitro-2-phenylethenes with *N*-phenacyl and *N*-acetonylisoquinolinium bromides**.** The reaction afforded its maximum yield with sodium hydride as a base in dry dioxane (Scheme 3A.3).[5]



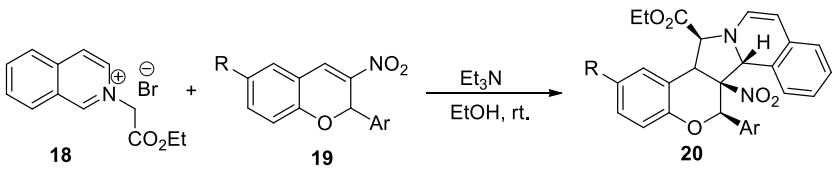
Scheme 3A.3 1,3-dipolar cycloaddition of substituted 1-nitro-2-phenylethenes

Later Kucukdisli and Opatz reported the reaction of different heteroaromatic *N*-ylides (including isoquinolinium methylides) with *β*-nitrostyrene[6] (scheme 3A.4) and found that aromatized products were obtained after the elimination of HNO_2.



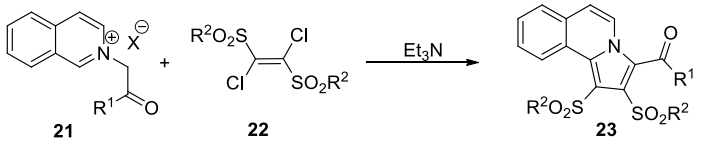
Scheme 3A.4 Synthesis of polysubstituted indolizines

In 2014, the dipolar cycloaddition of isoquinolinium methylides to 3-nitrochromenes was reported to furnish azadibenzo[a,g]fluorene derivatives[7] (scheme 3A.5).



Scheme 3A.5 Reaction of isoquinolinium salts with 3-nitrochromenes.

In 2017, Dontsova *et al.* reported the synthesis of substituted 1,2-di(alkylsulfonyl)indolizines and 1,2-di(alkylsulfonyl) pyrrolo[2,1-*a*]isoquinolines from the corresponding heteroaromatic *N*-ylides in the presence of three-fold excess of Et_3N (Scheme 3A.6).[8]

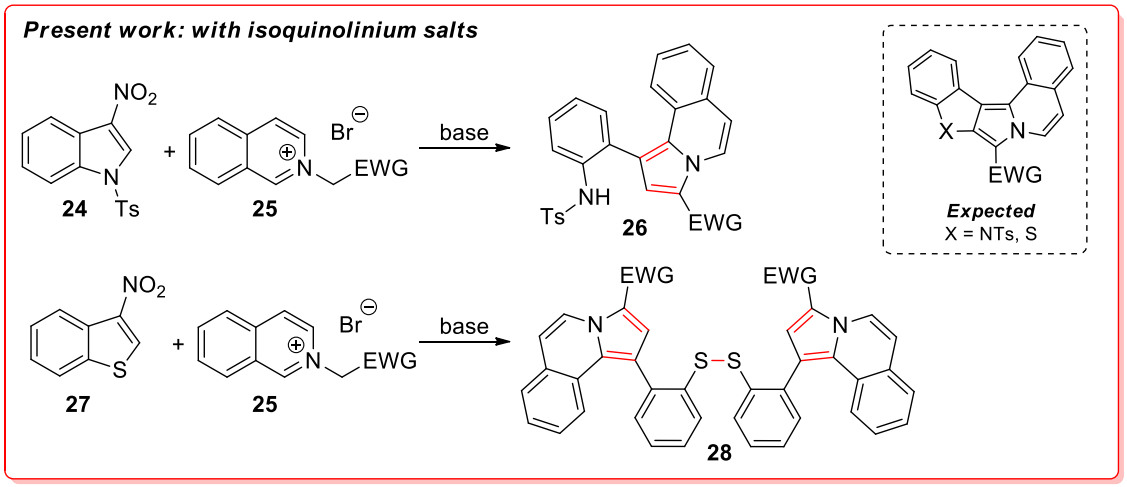


Scheme 3A.6 Synthesis of substituted 1,2-di(alkylsulfonyl) pyrrolo[2,1-*a*]isoquinolines

3A.3 Statement of the problem

Inspired by the above reports on the dipolar cycloaddition of isoquinolinium methylides to nitrostyrenes, we hypothesized that the reactions of these heteroaromatic *N*-ylides with

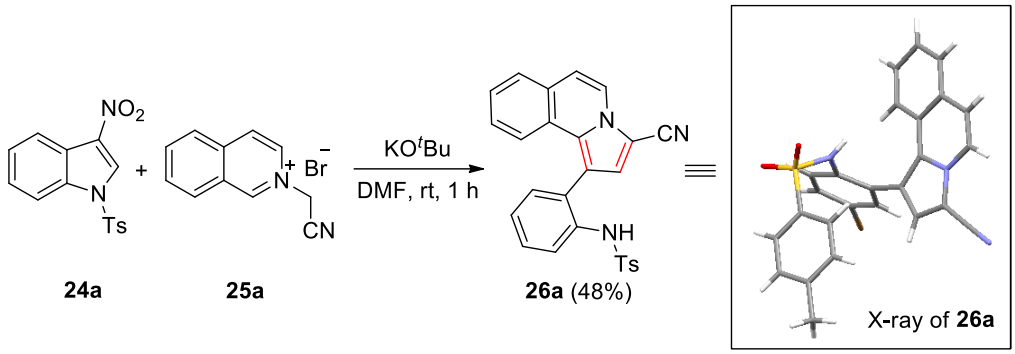
electrophilic benzannulated heterocycles would result in the development of novel heteroacenes (Scheme 3A.7). We believed that the heteroaromatic *N*-ylide would participate in a dipolar cycloaddition with electrophilic benzannulated heterocycle followed by the elimination of HNO_2 to afford multi-ring fused heterocyclic moieties as shown in the scheme below.



Scheme 3A.7 Dipolar cycloaddition of electrophilic benzannulated heterocycles with isoquinolinium salts

3A.4 Results and discussion

We commenced our studies by selecting *N*-tosyl-3-nitro indole **24a** and 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** as model substrates. Initially **24a** (1.0 equiv.) and **25a** (1.1 equiv.) were treated in the presence of *t*BuOK (4.0 equiv.) in DMF at room temperature for an hour. Contrary to our expectation of a pentacene as depicted in scheme 3A.7, the 1,3-dipolar cycloaddition reaction between **24a** and **25a** resulted in the formation of functionalized pyrrolo[2,1-*a*]isoquinoline **26a** in 48% yield (Scheme 3A.8). The structure assigned to the product on the basis of spectroscopic analysis was unambiguously confirmed by single crystal X-ray analysis of **26a.**



24a **25a** **26a** (48%)

Scheme 3A.8 1,3-dipolar cycloaddition of isoquinolinium methylides with electrophilic indoles

In the ^{1}H NMR spectrum, aromatic protons were found to resonate in the region δ 8.09-7.09 ppm. The proton on the isoquinoline ring attached near to the N atom (a) resonated at 8.09 ppm as a doublet. The singlet observed at δ 6.38 (b) and 6.44 (c) ppm was attributed to the NH proton attached to the tosyl group and the proton of the pyrrole ring, respectively. The methyl protons of the tosyl group resonated as a singlet at δ 2.37 ppm. The ^{1}H NMR spectrum of the compound is shown in figure 1.

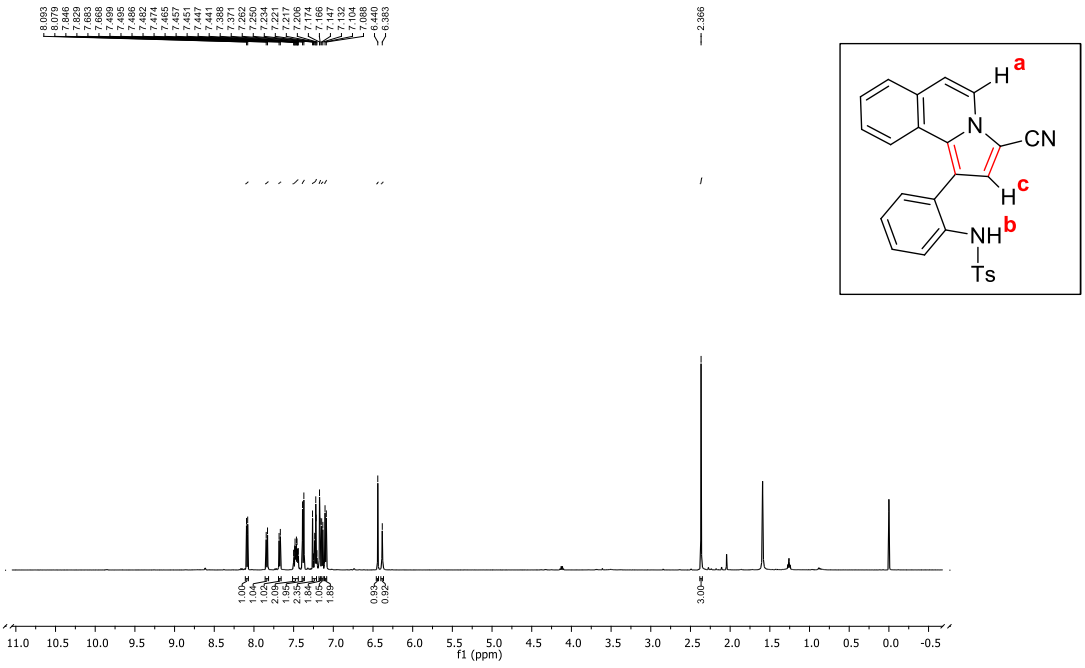


Figure 1. ^{1}H NMR spectra of **26a**

In the ^{13}C spectrum (Figure 2), the aromatic carbons resonated in the region δ 144.1-112.9 ppm. The carbon attached to the CN group in the pyrrole ring resonated at δ 98.0 ppm (a), and the one attached to NH moiety resonated at δ 144.0 ppm (b). The methyl carbon of the tosyl group showed a peak at δ 21.5 ppm. All other peaks in the ^{1}H and ^{13}C NMR were in good agreement with the assigned structure.

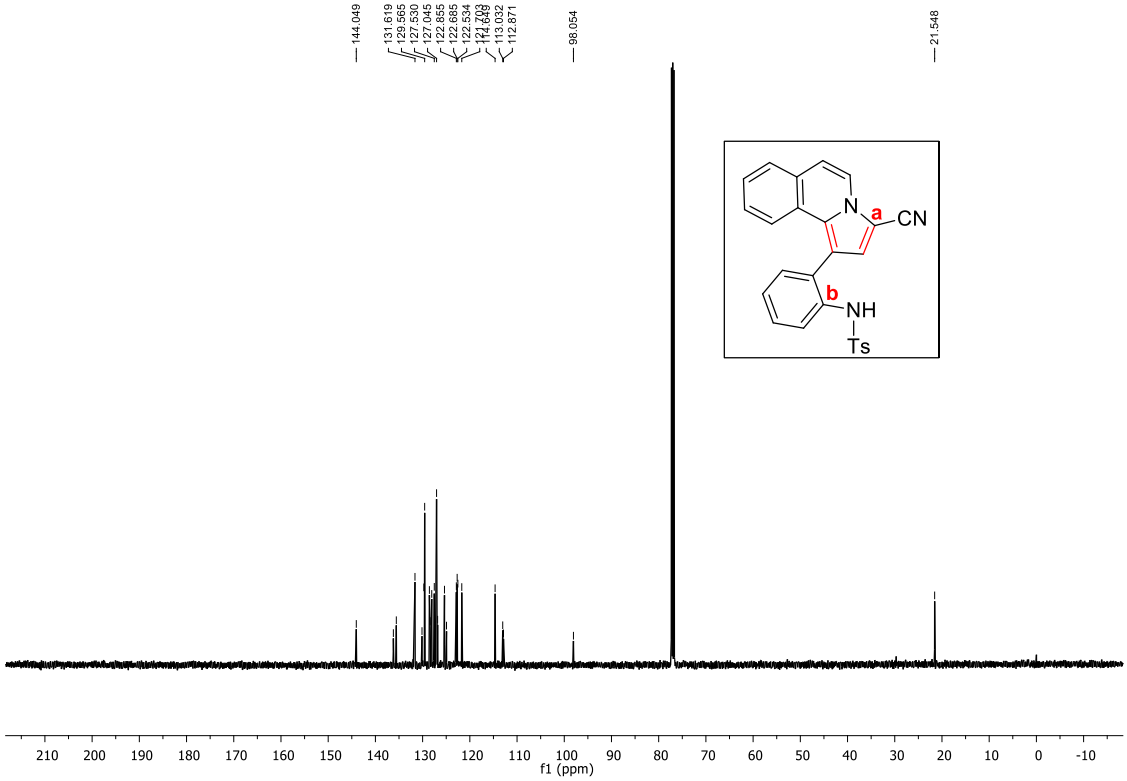


Figure 2. ^{13}C NMR spectra of **26a**

The structure assigned was further confirmed by high resolution mass spectral analysis, which showed (M+H) peak at *m/z* = 460.11007. The structure assigned to the product on the basis of spectroscopic analysis was unambiguously confirmed by single crystal X-ray analysis of **26a.**

Pyrrolo[2,1-*a*]isoquinoline moieties[9] are important fused *N*-heterocycles found in plenty as core structures of natural products such as crispine A & B, trolline, lamellarins, erythrina alkaloids etc. (figure 3) which were found to possess interesting anticancer, antiviral and antibacterial activities.[10]

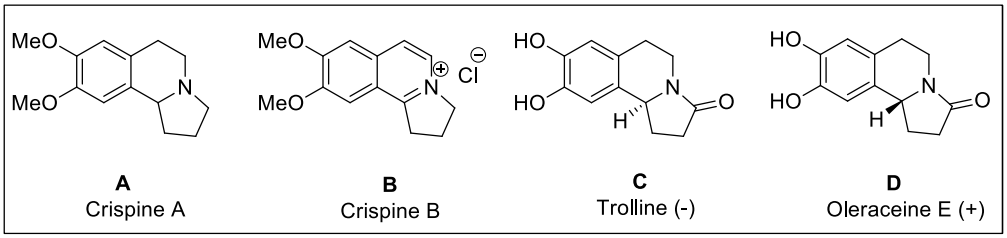


Figure 3. Pyrrolo-isoquinoline alkaloids endowed with cytotoxic activity (**A** and **B**) antibacterial/antiviral (**C**) and antioxidant activity (**D**)

The synthetic pyrrolo[2,1-*a*]isoquinolines were also found to exhibit a plethora of biological properties such as anticancer, MDR reversal, estrogen receptor modulator, DNA chelating, antimicrobial, antiplatelet and anti-inflammatory.[11] In addition, these fused *N*-heterocycles were utilized in developing different metal cation and organic sensors.[12] The two well-known strategies to access pyrrolo[2,1-*a*]isoquinolines are by the annulation of appropriate rings to a substituted pyrrole or a *N*-functionalized isoquinoline.[17, 19a, 13] In 2019, Dong and Huang reported the synthesis of substituted indolizines from the reaction of chromones and pyridinium salts.[14] This reaction proceeded via a 1,3-dipolar cycloaddition-ring opening and aromatization cascade.

Intrigued by the unexpected synthesis of substituted pyrrolo[2,1-*a*]isoquinoline moiety, we optimised the reaction conditions with **24a** and **25a** as substrates. Screening of different bases such as *t*BuOK, *t*BuONa, NaOMe, Cs_2CO_3, K_2CO_3, Na_2CO_3, KOH, NaOH, LiOH, NaH and DIPEA (Table 1, entries 1-11) revealed that KOH was the most suitable base furnishing the product in 54% yield. Then, we focused on the effect of different solvents on the reaction outcome (Table 1, entry 12-16). Among the screened solvents, DMF was found to be the most effective one, giving the product in 54 % yield. The reaction yield was found to decrease when the base amount was decreased to 2.0 equivalents (Table 1, entry 19). Finally, we turned our attention towards the effect of substrate concentration on the reaction. To our delight, the use of 1.5 equivalents of **25a** increased the yield of **26a** to 88% (Table 1, entry 18).

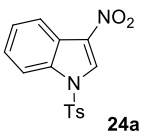
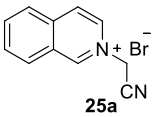
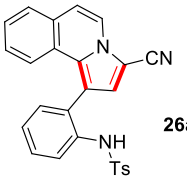
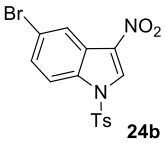
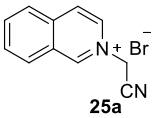
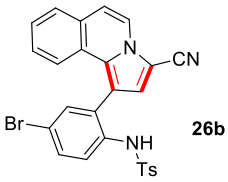
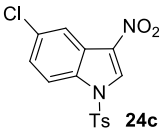
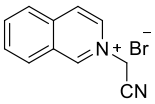
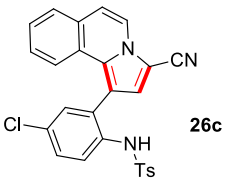
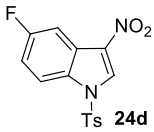
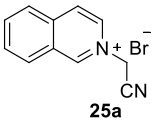
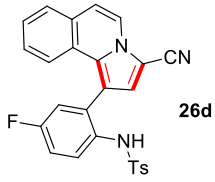
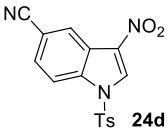
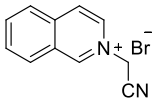
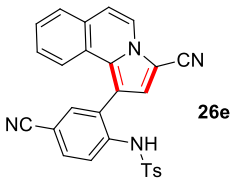
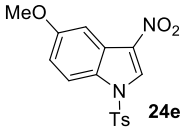
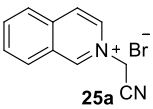
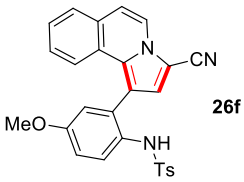
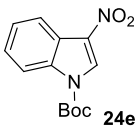
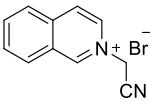
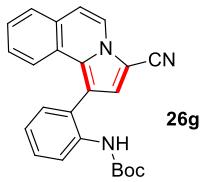
Table 1. Optimization studies[a]

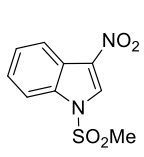
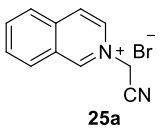
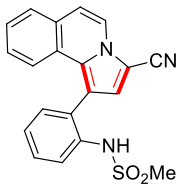
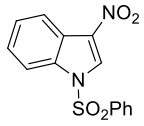
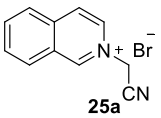
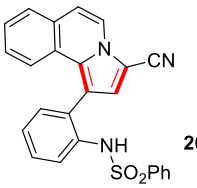
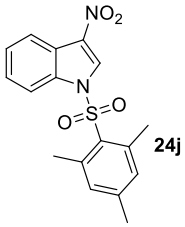
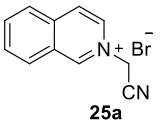
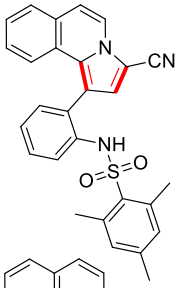
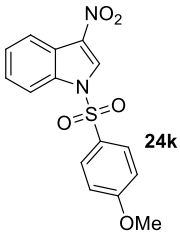
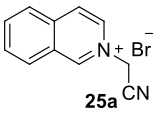
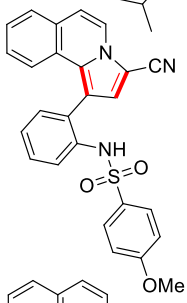
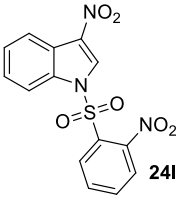
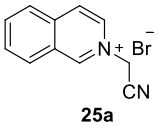
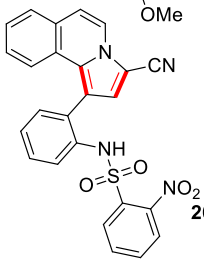
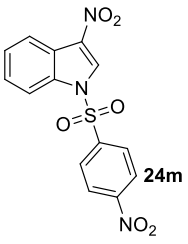
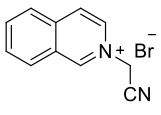
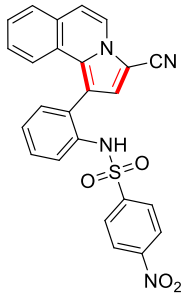
Entry	Base	Solvent	Time (h)	Yield of 26a (%)
1	^{t}BuOK	DMF	1	48
2	^{t}BuONa	DMF	1	21
3	NaOMe	DMF	1	-
4	Cs_2CO_3	DMF	1	37
5	K_2CO_3	DMF	1	16
6	Na_2CO_3	DMF	1	Trace
7	KOH	DMF	1	54
8	NaOH	DMF	1	49
9	LiOH	DMF	1	43
10	NaH	DMF	1	38
11	DIPEA	DMF	1	-
12	KOH	1,4-dioxane	1	16
13	KOH	EtOH	1	-
14	KOH	CH_3CN	1	26
15	KOH	EtOAc	1	-
16	KOH	THF	1	22
17	KOH	DMF	12	61
18[b]	**KOH**	**DMF**	**1**	**88**
19[c]	KOH	DMF	1	10

[a]Reaction conditions: **24a** (1.0 equiv., 0.16 mmol), **25a** (1.1 equiv.), base (4.0 equiv.), solvent (1.0 mL), rt; [b]**25a** (1.5 equiv.); [c]base (2.0 equiv.)

With the optimized conditions in hand [1.0 equiv. of **24a**, 1.5 equiv. of **25a**, 4.0 equiv. of KOH, DMF, rt], we then explored the scope of the 1,3-dipolar cycloaddition of isoquinolinium methylides using different substituted electrophilic indoles, the results of which are summarized in Table 2. In this line, the generality of different 3-nitro-indoles **1** with the model substrate 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** was studied.

Table 2. The generality of 1,3-dipolar cycloaddition reaction of isoquinolinium methylides with substituted electrophilic indoles

Entry	Indole	Isoquinolinium methylide	Product	Yield
1	 **24a**	 **25a**	 **26a**	88
2	 **24b**	 **25a**	 **26b**	75
3	 **24c**	 **25a**	 **26c**	72
4	 **24d**	 **25a**	 **26d**	71
5	 **24d**	 **25a**	 **26e**	52
6	 **24e**	 **25a**	 **26f**	NR
7	 **24e**	 **25a**	 **26g**	75

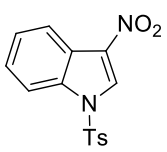
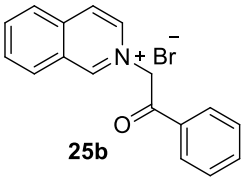
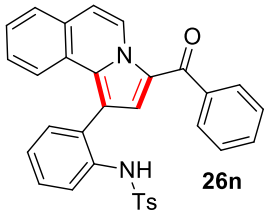
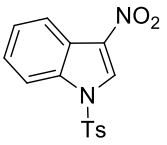
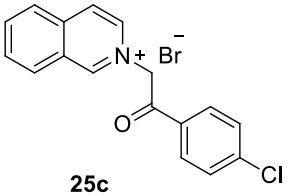
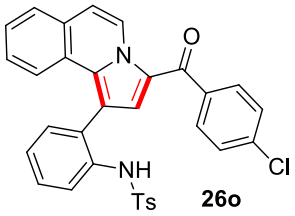
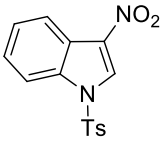
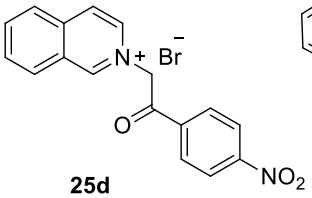
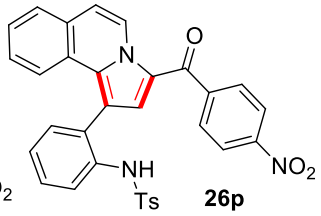
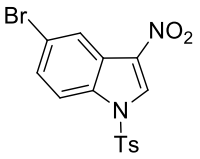
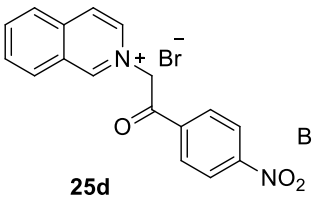
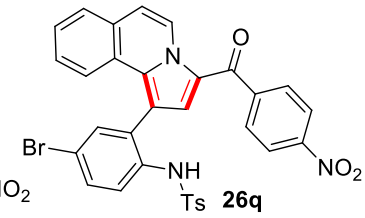
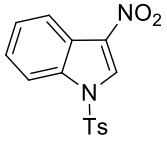
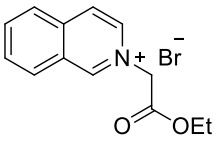
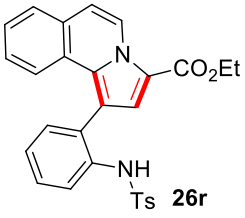
Entry	Indole	Isoquinolinium methylide	Product	Yield
8	 **24h**	 **25a**	 **26h**	52
9	 **24i**	 **25a**	 **26i**	61
10	 **24j**	 **25a**	 **26j**	57
11	 **24k**	 **25a**	 **26k**	91
12	 **24l**	 **25a**	 **26l**	49
13	 **24m**	 **25a**	 **26m**	40

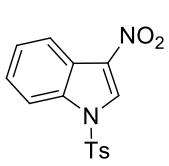
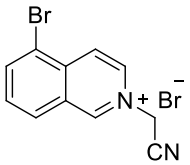
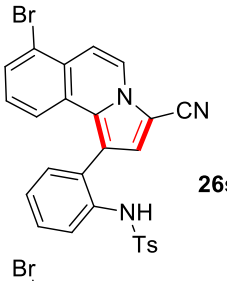
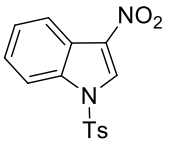
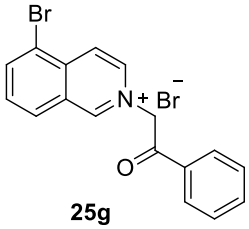
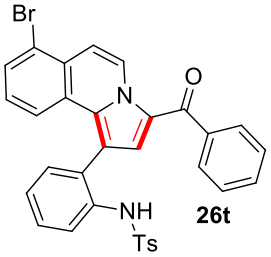
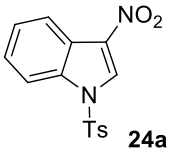
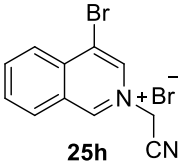
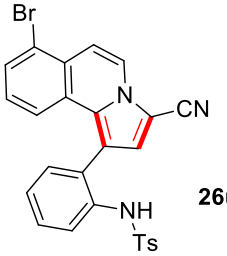
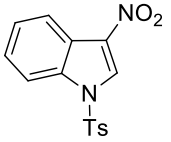
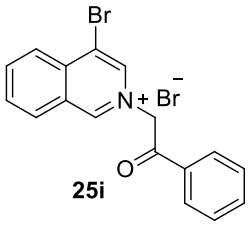
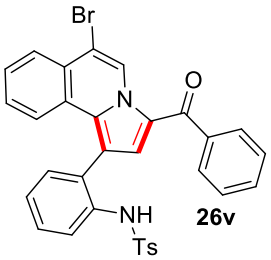
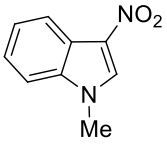
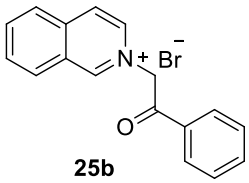
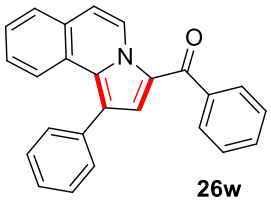
[a] Reaction conditions: **24** (1.0 equiv., 0.32 mmol), **25a** (1.5 equiv.), KOH (4.0 equiv.), DMF (2.0 mL), rt, 1 h

The reactions with halogen (Br, F, Cl)-substituted nitroindoles proceeded well, affording the products **26b**, **26c** and **26d** in good yields (Table 2). The dipolar cycloaddition of **25a** with 3-nitro-1-tosyl-1H-indole-5-carbonitrile afforded the corresponding substituted pyrrolo[2,1-*a*]isoquinoline **26e** in 52% yield. With electron-releasing OMe-substituent (5-methoxy-3-nitro-1-tosyl-1H-indole), even after heating to reflux in DMF for a prolonged period of time, the reaction failed, which might be due to the reduced electrophilicity (**26f**). Next, the electron-withdrawing substituent on the *N*-atom of the indole was changed to Boc, in which case the expected product **26g** was isolated in 75% yield. The reactions with electrophilic indole substrates with SO_2Me and SO_2Ph on the *N*-atom afforded **26h** and **26i** in 52% and 61% yield. Finally, other sulphonyl substituents on the *N*-atom of the indole were found to influence the outcome of the reaction from which the products **26j** to **26m** were obtained in moderate to excellent yields (Table 2).

Further investigations were focused on evaluating the reactivity of different isoquinolinium bromides in the present dipolar cycloaddition with electrophilic indoles (Table 3). The reactions with isoquinolinium methylides **25b-25d** (with different substituents on the para-position of phenyl ring) afforded the products **26n-26p** in good yields (Table 3). The isoquinolinium methylides **39e** with ethoxycarbonyl -group as the electron-withdrawing moiety also afforded the corresponding pyrrolo[2,1-*a*]isoquinoline **26r** in 62% yield. Finally, isoquinolinium bromides **39f-39i** prepared from 4-bromo isoquinoline and 5-bromo isoquinoline were tested for reactivity in the present transformation, and the products **26s-26v** were isolated from the reactions in satisfactory yields (Table 3). *N*-Methyl-protected 3-nitroindole led to the formation of pyrrolo[2,1-*a*] isoquinoline **26w**, wherein we observed the elimination of the *N*-methyl group (Table 3).

Table 3. Generality of 1,3-dipolar cycloaddition reaction with various isoquinolinium bromides

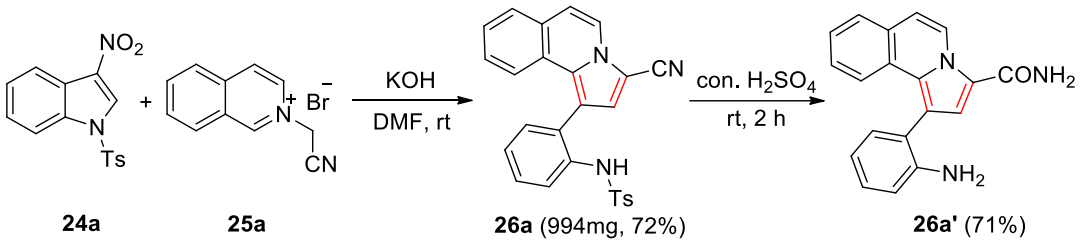
Entry	Indole	Isoquinolinium methylide	Product	Yield
1	 **24a**	 **25b**	 **26n**	68[b]
2	 **24a**	 **25c**	 **26o**	73
3	 **24a**	 **25d**	 **26p**	75
4	 **24b**	 **25d**	 **26q**	71
5	 **24a**	 **25e**	 **26r**	62

Entry	Indole	Isoquinolinium methylide	Product	Yield
6	 **24a**	 **25f**	 **26s**	59
7	 **24a**	 **25g**	 **26t**	52[b]
8	 **24a**	 **25h**	 **26u**	54
9	 **24a**	 **25i**	 **26v**	48
10	 **24n**	 **25b**	 **26w**	33

Reaction conditions: [a]**24** (1.0 equiv., 0.32 mmol), **25**[a] (1.5 equiv.), KOH (4.0 equiv.), DMF (2.0 mL), rt, 1 h, [b]4 h

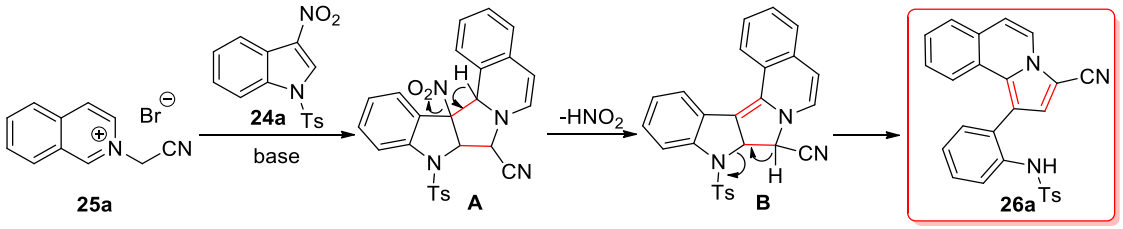
We also attempted a gram-scale synthesis (starting from 1.0 g of **24a**) of pyrrolo[2,1-*a*]isoquinoline **26a**, and the compound was obtained in 72% yield (Scheme 3A.9). The compound **26a** was then subjected to Ts-deprotection by treating with concentrated H_2SO_4

for 2 hours which furnished the pyrrolo[2,1- *a*]isoquinoline **26a'**. In compound **26a'** not only was the Ts-group got removed, but the CN-moiety was also converted to the corresponding amide.



Scheme 3A.9 Gram-scale reaction of **24a** with **25a** and *N*-Ts deprotection of pyrrolo[2,1-*a*]isoquinoline **26a**

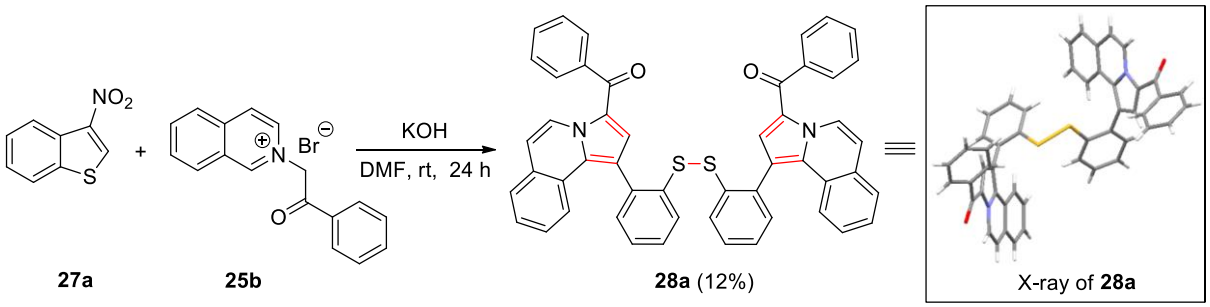
Based on our observations and on the reported literature,[14-16] we have proposed a plausible mechanism for the present domino dipolar cycloaddition-ring opening process happening during the reaction of electrophilic indole and isoquinolinium methylide (Scheme 3A.10). First step is the deprotonation of the activated methylene group of isoquinolinium salt by KOH to generate the corresponding *N*-ylide. This dipole will then participate in a 1,3-dipolar cycloaddition with the dipolarophile, *N*-tosyl-3-nitroindole **24a** to generate the corresponding cycloadduct **A** (Scheme 3A.10). Subsequent elimination of HNO_2 from **A** generates the intermediate **B** which upon aromatization results in a strain induced cleavage of the C-N bond furnishing the final product pyrrolo[2,1-*a*]isoquinoline **26a**.



Scheme 3A.10 Plausible mechanism for the synthesis of pyrrolo [2,1-*a*] isoquinoline **26**

The unexpected domino transformation observed from the reaction of electrophilic indoles and isoquinolinium methylides prompted us to check the reactivity of electrophilic benzothiophenes. The initial experiment was performed by reacting 3-nitro benzothiophene **27a** with 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **25b** in the presence of KOH (2.0 equiv.) in DMF at room temperature. After 24 h, a bis-pyrrolo[2,1- *a*]isoquinoline **28a**

linked with a S-S bond was isolated in 12% yield (Scheme 3A.11). The structure assigned to the product on the basis of spectroscopic analysis was unambiguously confirmed by single crystal X-ray analysis of **28a.**



Scheme 3A.11 Synthesis of bis-pyrrolo[2,1- *a*]isoquinoline **28a** from 3-nitrobenzothiophene and **25b**

In the ^{1}H NMR spectrum, aromatic protons were found to resonate in the region δ 9.62-7.05 ppm.

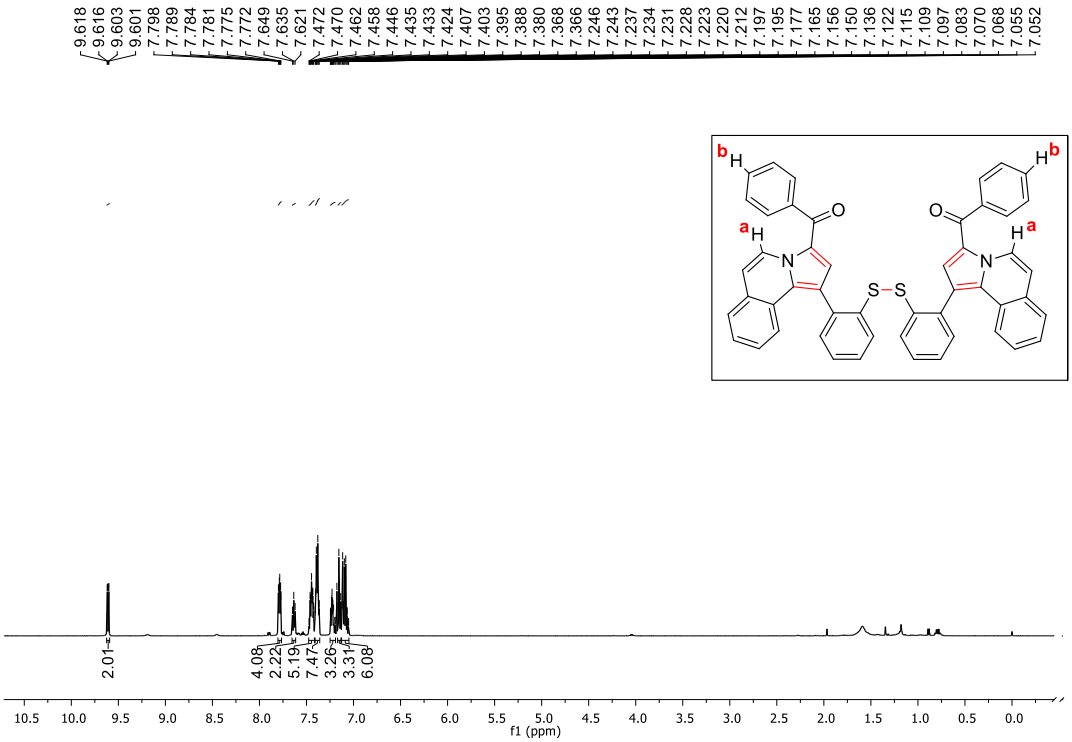


Figure 4. ^{1}H NMR spectra of **28a**

The doublet of doublet at δ 9.61 ppm (a) is attributed to the proton attached to the N-atom on the isoquinoline ring and the triplet at δ 7.63 ppm (b) corresponds to the proton on the COPh

ring. All the rest of the protons are seen to resonate as multiplets. The ^{1}H NMR spectrum of the compound is shown in figure 4.

In the the ^{13}C spectrum (Figure 5), the aromatic carbons resonated in the region δ 185.6-114.0 ppm. The carbon of the carbonyl group resonated at δ 185.6 ppm (a). The carbon attached to S-S moiety resonated at δ 131.3 ppm (b). All other peaks in the ^{1}H and ^{13}C NMR were in good agreement with the assigned structure.

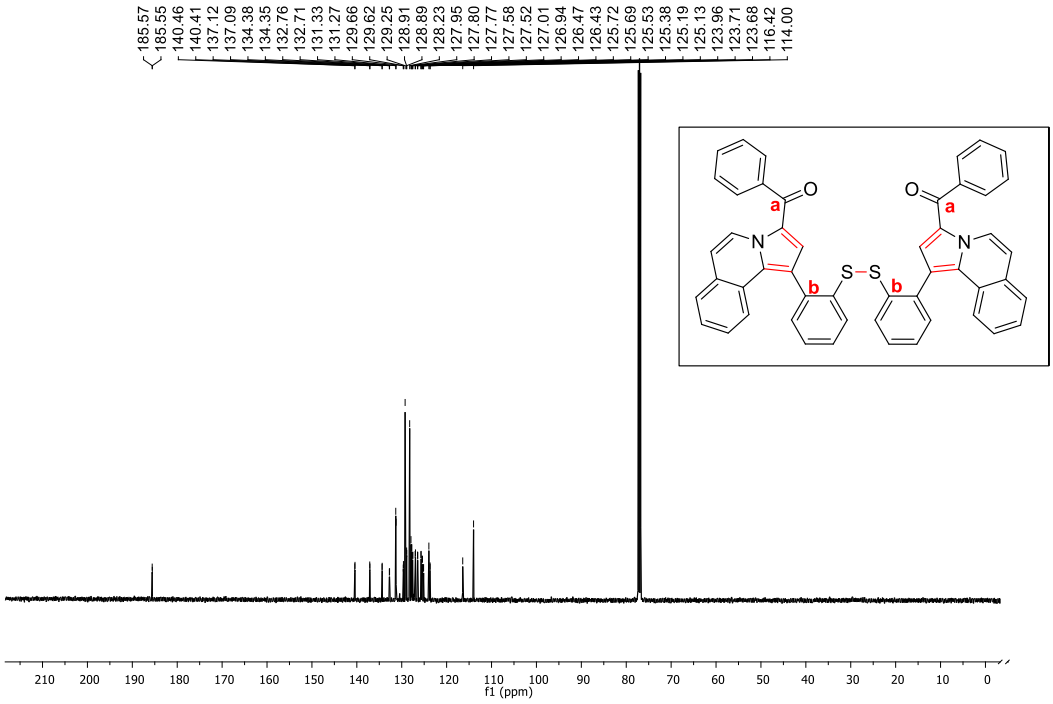


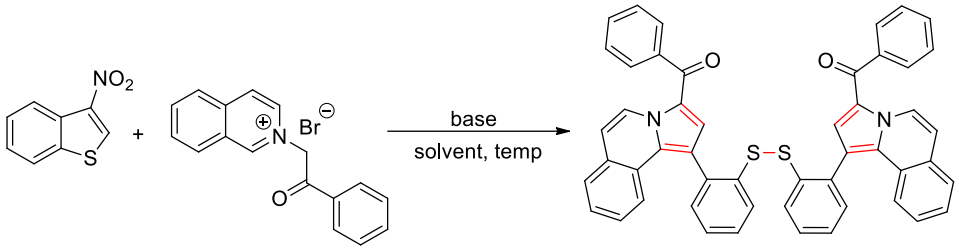
Figure 5. ^{13}C NMR spectra of **28a**

The structure assigned was further confirmed by high resolution mass spectral analysis which showed (M+H) peak at *m/z* = 757.20007.

The poor yield obtained for the synthesis of bis-pyrrolo[2,1- *a*]isoquinoline **28a** prompted us to optimize the reaction conditions with **27a** and **25b** as substrates. Increasing the equivalents of base and **25b** was found not to have a positive outcome on the reaction yield (Table 4, entry 2-3). A slight increase in the yield of **28a** was noted by carrying out the reaction at 60 ^{o}C (Table 4, entry 4). Screening of different bases such as K_2CO_3, K_3PO_4, Na_2CO_3, Cs_2CO_3, NaOH, KOH and KO*t*Bu (Table 4, entries 4-10) revealed that K_3PO_4 was more efficient. Further screening of solvents showed that CH_3CN gave better results in comparison to other solvents such as DMF, THF, EtOH, DMA, 1,4-dioxane and DMSO (Table 4, entries 7, 11-

16). Also, performing the reaction in the presence of an oxidant, $Cu(OAc)_2.H_2O$ was found to be less efficient (Table 4, entry 17-18). In all the reactions mentioned above, complete consumption of 3-nitrobenzothiophene **27a** was not observed.

Table 4. Optimization studies[a]



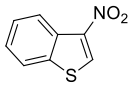
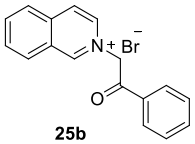
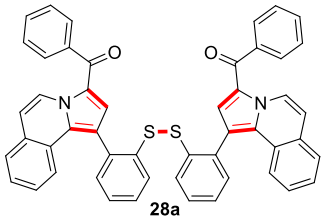
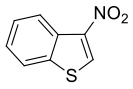
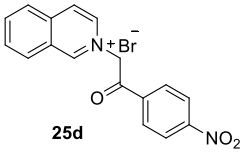
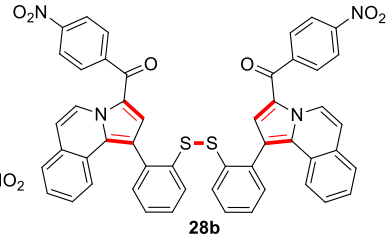
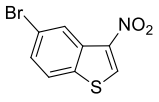
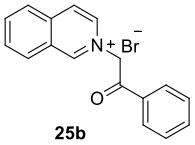
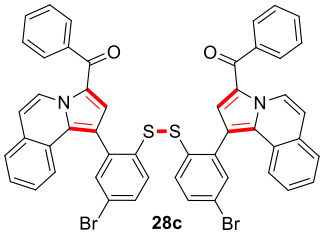
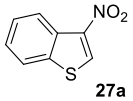
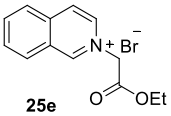
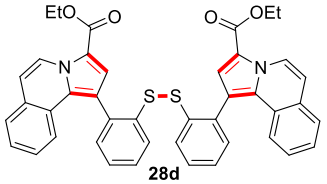
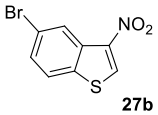
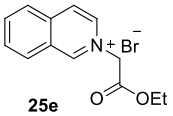
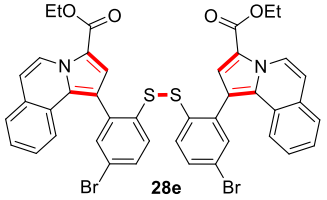
27a **25b** **28a**

Entry	Base	Solvent	Temp. (ºC)	Yield of 28a (%)
1	KOH	DMF	rt	12
2[b]	KOH	DMF	rt	10
3[c]	KOH	DMF	rt	10
4	KOH	DMF	60	14
5	^{t}BuOK	DMF	60	14
6	NaOH	DMF	60	10
7	K_3PO_4	DMF	60	29
8	K_2CO_3	DMF	60	14
9	Na_2CO_3	DMF	60	-
10	Cs_2CO_3	DMF	60	12
11	K_3PO_4	EtOH	60	-
12	K_3PO_4	THF	60	-
13	K_3PO_4	1,4-dioxane	60	-
14	**K_3PO_4**	**CH_3CN**	**60**	**80**
15	K_3PO_4	DMA	60	14
16	K_3PO_4	DMSO	60	20
17	K_3PO_4, $Cu(OAc)_2.H_2O$	DMF	60	trace
18[d]	2,6-Lutidine, $Cu(OAc)_2.H_2O$	DMF	60	trace

[a]Reaction conditions: **27a** (1.0 equiv., 0.28 mmol), **25b** (1.5 equiv.), base (2.0 equiv.), solvent (1.0 mL), rt, 24 h; [b]base (4.0 equiv.); [c]**25b** (3.0 equiv.); [d]base (5.0 equiv.); $Cu(OAc)_2.H_2O$ (1.5 equiv.)

With the optimized conditions in hand [1.0 equiv. of **27a**, 1.5 equiv. of **25b**, 2.0 equiv. of K_3PO_4, CH_3CN (1ml), 60 ^oC], the scope of the reaction for the synthesis of bis-pyrrolo[2,1-*a*]isoquinoline was investigated (Table 5).

Table 5. Generality of 1, 3-dipolar cycloaddition reaction of various isoquinolinium methylides with 3-nitrobenzothiophene

Entry	3-nitrobenzothiophene	Isoquinolinium methylide	Product	Yield
1	 **27a**	 **25b**	 **28a**	80
2	 **27a**	 **25d**	 **28b**	61
3	 **27b**	 **25b**	 **28c**	66
4	 **27a**	 **25e**	 **28d**	48
5	 **27b**	 **25e**	 **28e**	40

Reaction conditions: [a]**27** (1.0 equiv., 0.56 mmol), **25** (1.5 equiv.), K_3PO_4 (2.0 equiv.), CH_3CN (2.0 mL), 60 ^oC, 24 h.

The presence of a phenylethanone substitution on the isoquinolinium *N*-atom resulted in a better reaction furnishing the corresponding S-S bridged bis-pyrrolo[2,1- *a*]isoquinolines **28a-28c** in good to excellent yields (Table 5). Reactions of isoquinolinium methylide **25e** with ethoxycarbonyl group as the electron-withdrawing substituent afforded the corresponding products **28d** and **28e** in satisfactory yields (Table 5). In all the reactions mentioned above, unreacted 3-nitrobenzothiophene **27a** was recovered.

3A.5 Conclusions

In short, we have developed a domino reaction involving a 1,3-dipolar cycloaddition and a ring-opening between isoquinolinium ylides and electrophilic benzannulated heterocycles. This hitherto unknown methodology gives an easy access towards a series of highly functionalized pyrrolo[2,1-*a*] isoquinolines starting from different isoquinolinium methylides and 3-nitroindoles. In addition, we observed the formation of S-S bridged bis-pyrrolo[2,1-*a*]isoquinolines from the reaction of 3-nitro benzothiophene and isoquinolinium methylides. We have also demonstrated the applicability of this cycloaddition reaction for the generation of pyrrolo[2,1-*a*] isoquinolines on a gram-scale.

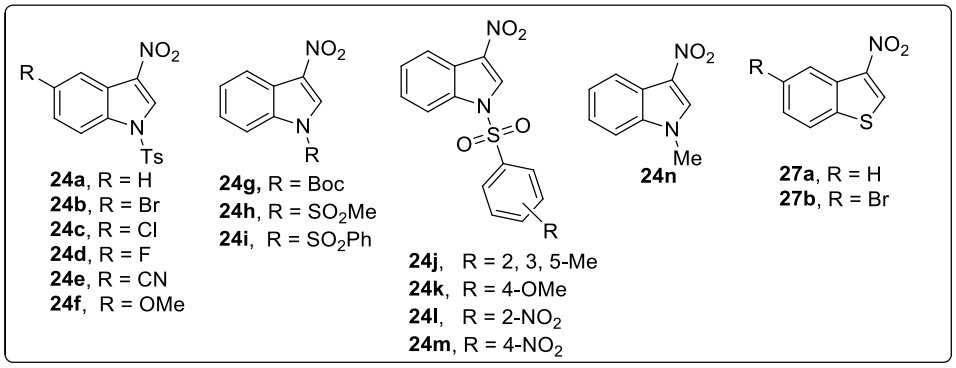
3A.6 Experimental Section

3A.6.1 General experimental methods: All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the methods in the literature and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets pre-coated with silica gel containing a fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using neutral alumina, and mixtures of ethyl acetate hexanes were used for elution melting points which were determined using a calibrated digital melting point apparatus (Büchi 530 melting point apparatus). Infrared spectra were recorded on a Bruker FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker Avance-300 (300 MHz for 1H NMR, 75 MHz for $^{13}C\{^{1}H\}$ NMR) and Bruker AMX-500 (500 MHz for ^{1}H NMR, 125 MHz for $^{13}C\{^{1}H\}$ NMR) instruments. All spectra were measured at 300 K, unless otherwise

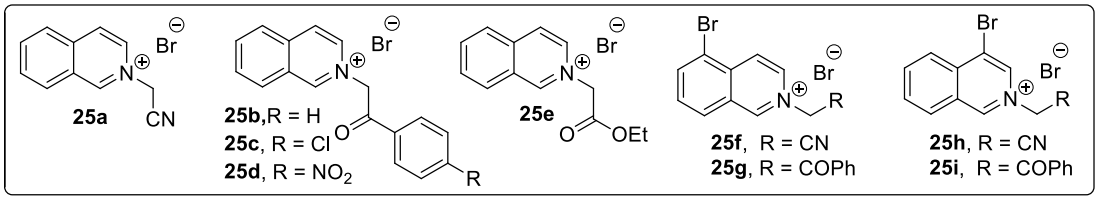
specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. 1H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were recorded with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with a JMS-T100GC spectrometer or with an ESI/HRMS at 60 000 resolution using a Thermo Scientific Exactive mass spectrometer with orbitrap analyzer. Gas chromatographic analysis was performed using GCMS-TQ8030 SHIMADZU.

3A.6.2 Synthesis and characterization:

Procedure for the synthesis of electrophilic benzannulated heterocycles 24 and 27: 3-Nitroindoles (**24a-24n**) and 3-nitrobenzothiophenes (**27a-27b**) were prepared by following a literature report.[15]



Procedure for the synthesis of isoquinolinium salts (25a-25i): All isoquinolinium salts (**25a-25i**) were prepared by following a previously reported procedure.[16] To isoquinoline dissolved in acetone at 0 ^{o}C, α-halocarbonyl compound was added and the mixture was stirred at room temperature for a period of time. After the completion of the reaction, the precipitate formed was filtered and washed with diethyl ether to get the pure product.

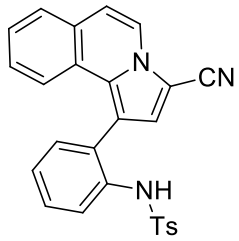


Experimental procedure for the reaction between 3-nitro-*N*-tosyl indole and isoquinolinium salt

A mixture of 3-nitro-*N*-tosyl indole (100 mg, 1.0 equiv.), isoquinolinium salt (1.5 equiv.) and KOH (4.0 equiv.) was weighed into a dry reaction tube. Dry DMF was added and the reaction mixture was allowed to stir at room temperature. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (neutral alumina, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and characterization of pyrrolo[2,1-*a*]isoquinolines (26a-26v)

***N*-(2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4methylbenzenesulfonamide (26a).** The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **24a** (100 mg, 0.32 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (118 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26a** as a pale yellow solid (122 mg, 88%).



Mp: 147−150 °C.

IR (neat) ν_{max}: 3884, 3822, 3732, 3485, 3010, 2356, 1546, 1493, 1452, 1334, 1161, 1091, 903, 762 cm−1.

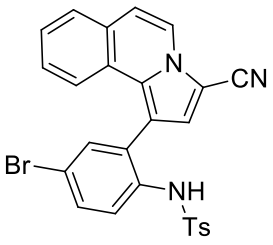
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.09 (d, J = 7 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.50-7.44 (m, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.25-7.21 (m, 2H), 7.17-7.13 (m, 3H), 7.10 (d, J = 8 Hz, 2H), 6.44 (s, 1H), 6.38 (s, 1H), 2.37 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.0, 136.2, 135.6, 131.6, 130.1, 129.7, 129.6, 128.6, 128.4, 128.1, 127.5, 127.0, 126.8, 125.4, 124.9, 122.8, 122.7, 122.5, 121.7, 114.6, 113.0, 112.9, 98.0, 21.6 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{26}H_{19}N_3NaO_2S$ 460.10902, found 460.11007.

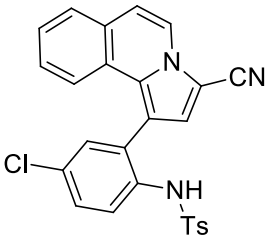
***N*-(4-bromo-2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methyl benzene sulfonamide (26b)**. The reaction was performed according to general procedure with 5-

bromo-3-nitro-*N*-tosyl indole **24b** (100 mg, 0.25 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (95 mg, 0.38 mmol) and KOH (57 mg, 1.01 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (25% ethyl acetate in hexane) to afford the desired product **26b** as a brown solid (98 mg, 75%).

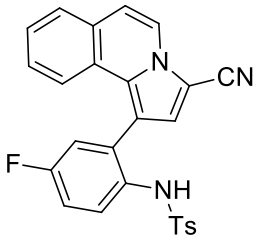
	**Mp**: 208−210 °C. **IR (neat) ν_{max}**: 3837, 3747, 3534, 3463, 3273, 2959, 2205, 1721, 1451, 1269, 1116, 1069, 885, 740 cm−1. **^{1}H NMR (500 MHz, $(CD_3)_2CO$, TMS)**: δ 8.20 (d, J = 7.5 Hz, 1H), 8.13 (s, 1H), 7.85 (d, J = 8 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.71 (dd, J_1 = 9 Hz, J_2 = 1.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 1.5 Hz, 1H), 7.44 (d, J = 8 Hz, 2H), 7.35 (d, J = 7.5 Hz, 1H), 7.29-7.24 (m, 2H), 7.17 (d, J = 7.5 Hz, 2H), 6.73 (s, 1H), 2.36 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2CO$)**: δ 143.7, 137.3, 136.1, 134.4, 132.2, 130.5, 130.4, 129.4, 128.6, 128.2, 127.9, 127.6, 126.8, 125.1, 124.9, 123.2, 122.8, 122.6, 117.5, 114.3, 112.6, 112.5, 97.8, 20.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{26}H_{18}BrN_3NaO_2S$ 538.01953, found 538.02063.

***N*-(4-chloro-2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methyl benzene sulfonamide (26c)**. The reaction was performed according to general procedure with 5-chloro-3-nitro-*N*-tosyl indole **24c** (100 mg, 0.28 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (106 mg, 0.42mmol) and KOH (64 mg, 1.14 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26c** as a yellow solid (96 mg, 72%).

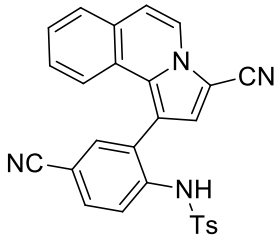
	Mp: 190−192 °C. **IR (neat) ν_{max}**: 3839, 3751, 3570, 3481, 3265, 3239, 3142, 3048, 2952, 2207, 1595, 1490, 1327, 1160, 1087, 890, 778, 674 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.02 (d, J = 7.5 Hz, 1H), 7.72

	(d, *J* = 9 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.42-7.37 (m, 2H), 7.29 (d, *J* = 8 Hz, 2H), 7.16-7.05 (m, 6H), 6.32 (s, 1H), 6.25 (s, 1H), 2.32 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 144.4, 135.9, 134.3, 131.4, 130.7, 130.1, 129.8, 129.7, 128.8, 128.6, 128.5, 128.3, 127.7, 127.0, 124.7, 123.1, 122.7, 122.5, 114.8, 112.6, 111.6, 98.3, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{26}H_{18}ClN_3NaO_2S$ 494.07004, found 494.07205.

***N*-(2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)-4-fluorophenyl)-4-methyl benzene sulfonamide (26d).** The reaction was performed according to general procedure with 5-Flouro-3-nitro-*N*-tosyl-indole **24d** (100 mg, 0.29 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (111 mg, 0.44 mmol) and KOH (67 mg, 1.19 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethylacetate in hexane) to afford the desired product **26d** as a brown solid (97 mg, 71%).

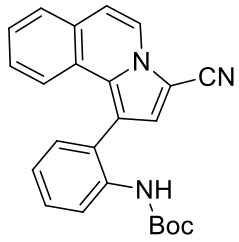
	**Mp**: 172−174 °C. **IR (neat) ν_{max}**: 3869, 3805, 3714, 3622, 3479, 3326, 3190, 2214, 1546, 1453, 1324, 1154, 1087, 784, 662 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.07 (d, *J* = 7 Hz, 1H), 7.85-7.82 (m, 1H), 7.69 (d, *J* = 8 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8 Hz, 2H), 7.25-7.17 (m, 3H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.10 (d, J = 7.5 Hz, 2H), 6.94 (d, *J* = 8 Hz, 1H), 6.27 (s, 1H), 6.26 (s, 1H), 2.38 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 144.8, 140.2, 135.6, 134.6 (d, *J* = 243 Hz), 130.3, 129.9, 128.8, 128.6, 128.4, 127.8, 127.1, 126.4, 124.5, 124.1, 122.6, 122.6, 122.4, 122.0, 120.7, 119.8, 119.3, 118.0, 115.1, 112.4, 111.0, 110.0, 108.0, 102.7, 99.0, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z:** $(M + Na)^+$ calcd for $C_{26}H_{18}FN_3NaO_2S$ 478.09960, found 478. 10168.

***N*-(4-cyano-2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methyl benzene sulfonamide (26e)**. The reaction was performed according to general procedure with 5-cyano-3-nitro-*N*-tosyl-indole **24e** (100 mg, 0.29 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (110 mg, 0.44 mmol) and KOH (66 mg, 1.17 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (25% ethyl acetate in hexane) to afford the desired product **26e** as a yellow solid (71 mg, 52%).

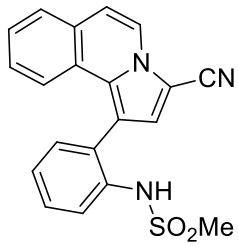
	**Mp**: 217−220 °C. **IR (neat) ν_{max}**: 3920, 3870, 3815, 3750, 3674, 3535, 3463, 2906, 2209, 1523, 1490, 1334, 1163, 901 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.13 (d, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 9 Hz, 1H), 7.72 (t, *J* = 7 Hz, 2H), 7.53-7.46 (m, 4H), 7.22-7.15 (m, 4H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.76 (s, 1H), 6.69 (s, 1H), 2.40 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 161.0, 159.1, 144.2, 135.9, 131.6, 131.6, 129.9, 129.7, 129.6, 128.8, 128.5, 128.3, 127.7, 127.0, 125.0, 124.9, 124.6, 122.6, 122.5, 122.4, 118.3, 118.1, 116.8, 116.6, 114.8, 112.7, 112.0, 98.1, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{27}H_{18}N_4NaO_2S$ 485.10427, found 485.10656.

Tert-butyl(2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)carbamate (26g). The reaction was performed according to general procedure with 3-nitro-*N*-Boc indole **24g** (100 mg, 0.38 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (143 mg, 0.57 mmol) and KOH (85 mg, 1.53 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **26g** as a colourless solid (110 mg, 75%).

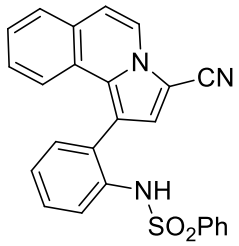
	Mp: 157−160 °C. **IR (neat) ν_{max}**: 3804, 3586, 3533, 3506, 3365, 2992, 2359, 2326, 2206, 1717, 1513, 1452, 1151, 1021, 829, 763, 739, 702 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.14 (d, *J* = 8 Hz, 1H), 8.07(d,

	*J* = 7.5 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.42-7.39 (m, 2H), 7.26-7.22 (m, 2H), 7.19 (s, 1H), 7.17 (s, 1H), 7.10-7.07 (m, 2H), 6.22 (s, 1H), 1.23 (s, 9H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 152.7, 137.1, 131.3, 130.1, 129.4, 128.6, 128.4, 128.0, 127.2, 125.4, 124.2, 123.5, 123.4, 123.2, 122.7, 119.8, 114.5, 114.3, 113.3, 98.2, 80.6, 28.1 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{24}H_{21}N_3NaO_2$ 406.15260, found 406.15397.

***N*-(2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)methanesulfonamide (26h)**. The reaction was performed according to general procedure with 1-(methylsulfonyl)-3-nitro-1H-indole **24h** (100 mg, 0.42 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (155 mg, 0.62 mmol) and KOH (93 mg, 1.66 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26h** as a colourless solid (78 mg, 52%).

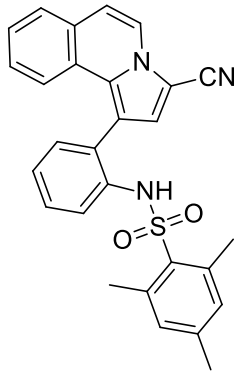
	**Mp**: 167−169 °C. **IR (neat) ν_{max}**: 3884, 3769, 3688, 3546, 3478, 3269, 2903, 2206, 1569, 1485, 1385, 1326, 1157, 1101, 969, 768 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.08 (d, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.47 (t, *J* = 8 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.24-7.19 (m, 2H), 7.12-7.10 (m, 2H), 6.22 (s, 1H), 2.78 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 136.0, 132.2, 130.2, 128.7, 128.6, 128.4, 127.8, 125.4, 125.0, 124.9, 122.9, 122.7, 122.7, 118.8, 114.9, 112.9, 112.8, 98.6, 39.9 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{20}H_{15}N_3NaO_2S$ 384.07772, found 384.07822.

***N*-(2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)benzenesulfonamide (26i)**. The reaction was performed according to general procedure with 3-nitro-1-(phenylsulfonyl)-1H-indole **24i** (100 mg, 0.33 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (124 mg, 0.50 mmol) and KOH (74 mg, 1.32 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26i** as a colourless solid (85 mg, 61%).

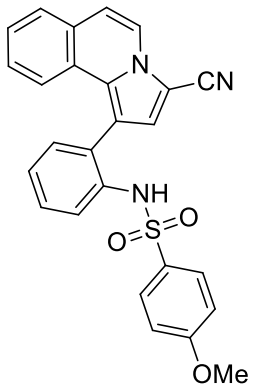
	**Mp**: 203−205 °C. **IR (neat) ν_{max}**: 3870, 3848, 3726, 3675, 3536, 3451, 3301, 3260, 2876, 2355, 2196, 1576, 1487, 1445, 1386, 1329, 1159, 1092, 896 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.02 (d, *J* = 7 Hz, 1H), 7.77 (d, *J* = 8 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.45-7.38 (m, 5H), 7.28-7.25 (m, 1H), 7.19-7.11 (m, 5H), 7.08 (d, *J* = 8 Hz, 1H), 6.31 (s, 2H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 139.0, 135.4, 133.1, 131.7, 130.1, 129.8, 129.0, 128.7, 128.4, 128.2, 127.6, 127.0, 126.9, 125.5, 124.9, 122.8, 122.6, 122.5, 121.7, 114.7, 112.9, 98.1 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{25}H_{17}N_3NaO_2S$ 446.09337, found 446.09430.

***N*-(2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-2,4,6-trimethyl benzene sulfonamide (26j)**. The reaction was performed according to general procedure with 1-(mesitylsulfonyl)-3-nitro-1H-indole **24j** (100 mg, 0.29 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (109 mg, 0.44 mmol) and KOH (65 mg, 1.16 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26j** as a colourless solid (77 mg, 57%).

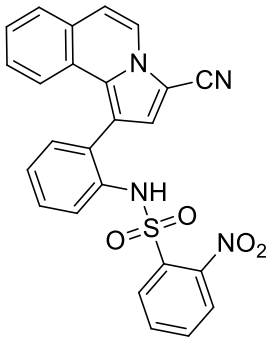
	Mp: 213−215 °C. **IR (neat) ν_{max}**: 3895, 3788, 3669, 3636, 3531, 3436, 3300, 3123, 2922, 2794, 2340, 2207, 1573, 1485, 1441, 1330, 1258, 1156, 1011, 791 cm^{-1}.

	**^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.02 (d, *J* = 7 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.41-7.38 (m, 2H), 7.19-7.18 (m, 2H), 7.15-7.13 (m, 2H), 7.07 (d, *J* = 7 Hz, 1H), 6.59 (s, 1H), 6.57 (s, 2H), 6.45 (s, 1H), 2.11 (s, 3H), 2.04 (s, 6H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 142.4, 138.8, 135.3, 133.9, 131.8, 131.6, 129.9, 129.5, 128.6, 128.4, 128.2, 128.0, 127.5, 125.9, 124.9, 123.8, 122.9, 122.6, 122.4, 114.6, 113.7, 112.9, 98.1, 22.8, 21.0 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{28}H_{23}N_3NaO_2S$ 488.14032, found 488.14207.

***N*-(2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methoxy benzene sulfonamide (26k)**. The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1H-indole **24k** (100 mg, 0.30 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (112 mg, 0.45 mmol) and KOH (68 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (25% ethyl acetate in hexane) to afford the desired product **26k** as a brown solid (125 mg, 91%).

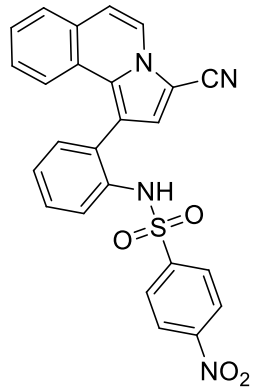
	**Mp**: 183-185 °C. **IR (neat) ν_{max}**: 3838, 3728, 3675, 3644, 3459, 3217, 2319, 1700, 1543, 1402, 1324, 1153, 1091, 1019, 892, 836, 785, 660 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.02 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8 Hz, 1H), 7.43-7.34 (m, 4H), 7.17-7.15 (m, 2H), 7.10-7.06 (m, 3H), 6.68 (d, *J* = 8.5 Hz, 2H), 6.43 (s, 1H), 6.30 (s, 1H), 3.75 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 163.2, 135.6, 131.6, 130.6, 129.8, 129.2, 128.6, 128.4, 128.1, 127.5, 126.7, 125.3, 124.9, 122.9, 122.7, 122.5, 121.5, 114.7, 114.1, 113.0, 55.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{26}H_{19}N_3NaO_3S$ 476.10393, found 476.10366.

***N*-(2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-2-nitrobenzenesulfonamide (26l)**. The reaction was performed according to general procedure with 3-nitro-1-((2-nitrophenyl)sulfonyl)-1H-indole **24l** (100 mg, 0.29 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (108 mg, 0.43 mmol) and KOH (64 mg, 1.15 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (25% ethyl acetate in hexane) to afford the desired product **26l** as a yellow solid (66 mg, 49%).

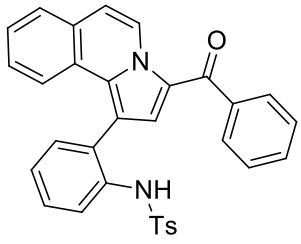
	**Mp**: 132−135 °C. **IR (neat) ν_{max}**: 3865, 3803, 3680, 3605, 3453, 3112, 2203, 1635, 1582, 1532, 1400, 1349, 1173, 1121, 898, 850, 777, 733 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 7.94 (d, *J* = 7 Hz, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.45-7.38 (m, 3H), 7.36-7.33 (m, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.23-7.19 (m, 2H), 7.04-7.00 (m, 3H), 6.42 (s, 1H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$):** δ 147.1, 135.0, 133.7, 132.9, 132.4, 131.5, 130.5, 130.2, 129.8, 129.0, 128.6, 128.5, 128.0, 127.7, 126.9, 125.5, 125.1, 124.9, 122.5, 122.2, 114.6, 113.5, 112.8 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{25}H_{16}N_4NaO_4S$ 491.07845, found 491.07918.

***N*-(2-(3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-nitrobenzenesulfonamide (26m)**. The reaction was performed according to general procedure with 3-nitro-1-((4-nitrophenyl)sulfonyl)-1H-indole **24m** (100 mg, 0.29 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (108 mg, 0.43 mmol) and KOH (65 mg, 1.15 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (25% ethyl acetate in hexane) to afford the desired product **26m** as a yellow solid (54 mg, 40%).

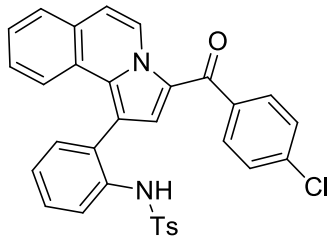
	Mp: 209−212 °C. **IR (neat) ν_{max}**: 3825, 3711, 3630, 3484, 3187, 2364, 1562, 1520, 1338, 1156, 862, 754, 679 cm^{-1}.

	**^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.03 (d, *J* = 7.5 Hz, 1H), 7.80-7.76 (m, 3H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.49-7.44 (m, 3H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.24-7.19 (m, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.82 (s, 1H), 6.64 (s, 1H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 149.8, 144.8, 134.5, 132.0, 130.1, 130.0, 128.3, 128.2, 128.2, 127.9, 127.7, 127.3, 126.3, 124.7, 123.8, 122.6, 122.4, 122.3, 122.2, 114.8, 112.8, 112.6, 98.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{25}H_{16}N_4NaO_4S$ 491.07845, found 491.08002.

***N*-(2-(3-benzoylpyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methyl benzene sulfonamide (26n)**. The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **24a** (100 mg, 0.32 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **25b** (156 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 4 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26n** as a yellow solid (111 mg, 68%).

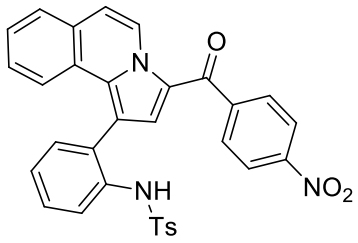
	**Mp**: 223−226 °C. **IR (neat) ν_{max}:** 3843, 3741, 3633, 3438, 3251, 2371, 1608, 1487, 1436, 1334, 1231, 1159, 905, 871, 807 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.59 (d, *J* = 7.5 Hz, 1H), 7.78-7.76 (m, 3H), 7.64 (d, *J* = 8 Hz, 1H), 7.54-7.52 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.42-7.36 (m, 2H), 7.24 (s, 1H), 7.21- 7.19 (m, 2H), 7.15-7.11 (m, 3H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8 Hz, 2H), 6.65 (s, 1H), 6.46 (s, 1H), 2.07 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 185.4, 143.7, 140.2, 136.0, 135.7, 132.7, 131.7, 131.5, 129.6, 129.5, 129.3, 129.2, 128.4, 128.0, 127.8, 127.2, 127.0, 127.0, 126.8, 125.5, 125.0, 124.6, 124.0, 123.4, 120.5, 114.3, 113.1, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+H)^+$ calcd for $C_{32}H_{25}N_2O_3S$ 517.15804, found 517.15996.

***N*-(2-(3-(4-chlorobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (26o)**. The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **24a** (100 mg, 0.32 mmol), 2-(2-(4-chlorophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **25c** (172 mg, 0.47 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26o** as a yellow solid (127 mg, 73%).

	**Mp**: 215−218 °C. **IR (neat) ν_{max}**: 3837, 3750, 3478, 3247, 2360, 1606, 1433, 1365, 1331, 1155, 1084, 900, 804 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.54 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8 Hz, 1H), 7.43-7.36 (m, 4H), 7.26 (d, J = *8* Hz, 2H), 7.20-7.12 (m, 4H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 2H), 6.60 (s, 1H), 6.44 (s, 1H), 2.11 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 183.9, 143.8, 138.5, 137.8, 136.0, 135.7, 133.0, 131.7, 130.5, 129.6, 129.3, 128.7, 128.2, 127.9, 127.1, 127.0, 126.7, 125.4, 125.0, 124.5, 123.7, 123.4, 120.5, 114.5, 113.3, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{33}ClN_2NaO_3S$ 573.10101, found 573.10307.

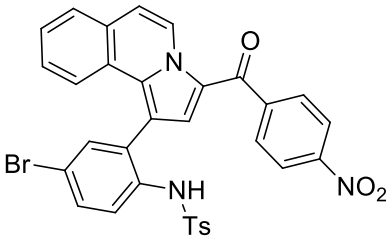
4-methyl-*N*-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)benzenesulfonamide (26p). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **24a** (100 mg, 0.32 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **25d** (177 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26p** as a bright yellow solid (134 mg, 75%).

	Mp: 199−203 °C.

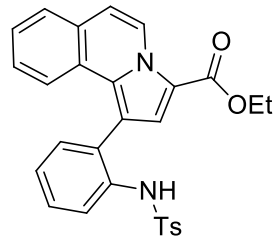
	**IR (neat) ν_{max}:** 3876, 3831, 3798, 3717, 3573, 3463, 3404, 3229, 2348, 1740,1650, 1587, 1523, 1440, 1333, 1161, 1086, 798, 704 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.61 (d, *J* = 7.5 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8 Hz, 1H), 7.68 (d, *J* = 8 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8 Hz, 2H), 7.20-7.19 (m, 2H), 7.16-7.11 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8 Hz, 2H), 6.73 (s, 1H), 6.45 (s, 1H), 2.12 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$**): δ 182.7, 149.3, 145.6, 143.8, 136.1, 135.7, 133.7, 131.7, 129.9, 129.8, 129.4, 128.5, 128.1, 127.3, 127.2, 127.0, 126.5, 125.4, 124.9, 124.4, 124.6, 123.6, 123.2, 120.1, 115.1, 114.0, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{32}H_{23}N_3NaO_5S$ 584.12506, found 584.12785.

***N*-(4-bromo-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4 methylbenzene sulfonamide (26q)**. The reaction was performed according to general procedure with 5-bromo-3-nitro-*N*-tosyl indole **24b** (100 mg, 0.25 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **25d** (142 mg, 0.38 mmol) and KOH (57 mg, 1.01 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26q** as a yellow solid (115 mg, 71 %).

	Mp: 250−252 °C. **IR (neat) ν_{max}:** 3937, 3870, 3792, 3726, 3597, 3560, 3527, 3396, 3337, 3238, 3043, 2927, 1729, 1694, 1589, 1518, 1468, 1435, 1334, 1163, 802, 702 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.59 (d, *J* = 7.5 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8 Hz, 2H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 9 Hz, 1H), 7.49-7.46 (m, 2H),

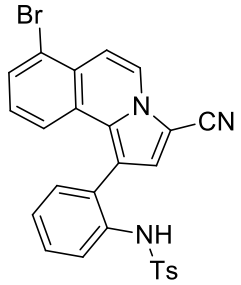
	7.34 (s, 1H), 7.28 (s, 1H), 7.21-7.19 (m, 2H), 7.16-7.10 (m, 2H), 6.81 (d, *J* = 7.5 Hz, 2H), 6.69 (s, 1H), 6.42 (s, 1H), 2.14 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 182.8, 149.4, 145.4, 144.0, 135.9, 135.0, 134.3, 133.5, 132.7, 129.9, 129.8, 129.5, 128.7, 128.5, 128.3, 127.3, 127.1, 127.0, 125.4, 124.1, 123.6, 123.5, 123.4, 121.5, 117.6, 115.2, 112.4, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{32}H_{22}BrN_3NaO_5S$ 662.03558, found 662.03709.

Ethyl 1-(2-(4-methylphenylsulfonamido)phenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (26r). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **24a** (100 mg, 0.32 mmol), 2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium-bromide **25e** (140 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26r** as a colourless solid (95 mg, 62%).

	**Mp**: 125−126 °C. **IR (neat) ν_{max}**: 3904, 3831, 3700, 3437, 3267, 2837, 1684, 1544, 1493, 1447, 1380, 1332, 1290, 1203, 1158, 1079, 954, 902, 790, 742 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.23 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 8 Hz, 1H), 7.38-7.30 (m, 2H), 7.27 (d, *J* = 8 Hz, 2H), 7.18-7.10 (m, 2H), 7.04 (d, *J* = 8 Hz, 1H), 7.00-6.95 (m, 2H), 6.87-6.86 (m, 3H), 6.54 (s, 1H), 4.35 (q, *J* = 7 Hz, 2H,), 2.19 (s, 3H), 1.37 (t, *J* = 7 Hz, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 161.1, 143.6, 136.0, 135.5, 131.7, 131.1, 130.3, 129.4, 129.3, 128.5, 127.7, 127.6, 127.4, 127.0, 127.0, 127.0, 125.0, 125.0, 124.6, 122.9, 122.0, 120.8, 116.3, 113.5, 112.3, 60.3, 21.6, 14.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M+Na)^+$ calcd for $C_{28}H_{24}N_2NaO_4S$

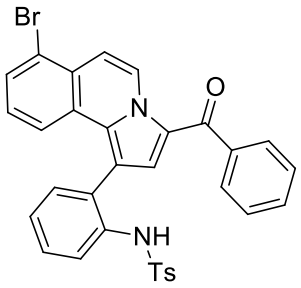
	507.13490, found 507.13644.

***N*-(2-(7-bromo-3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (26s).** The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **24a** (100 mg, 0.32 mmol), 5-bromo-2-(cyanomethyl)isoquinolin-2-ium-bromide **25f** (156 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (10% ethylacetate in hexane) to afford the desired product **26s** as a colourless solid (96 mg, 59%).

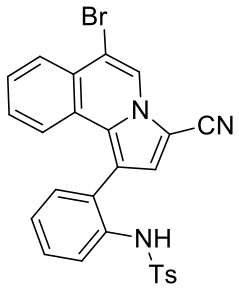
	**Mp**: 74−76 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.13 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.50-7.46 (m, 1H), 7.36 (d, *J* = 8 Hz, 2H), 7.24-7.14 (m, 3H), 7.08 (d, *J* = 8 Hz, 2H), 6.98 (t, *J* = 8 Hz, 1H), 6.50 (s, 1H), 6.40 (s, 1H), 2.37 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 144.1, 136.1, 135.5, 131.9, 131.5, 130.0, 129.6, 129.3, 129.0, 127.6, 127.0, 126.5, 126.4, 125.5, 123.7, 123.4, 122.5, 122.1, 121.8, 113.8, 113.2, 112.5, 98.3, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{26}H_{18}BrN_3NaO_2S$ 538.01953, found 538.02089.

***N*-(2-(3-benzoyl-7-bromopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (26t).** The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **24a** (100 mg, 0.32 mmol), 5-bromo-2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **25g** (192 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 4 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26t** as a yellow solid (98 mg, 52%).

	Mp: 243−247 °C.

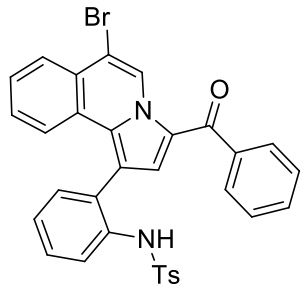
	**IR (neat) ν_{max}:** 3916, 3877, 3804, 3670, 3529, 3444, 2957, 2450, 1727, 1673, 1618, 1334, 1162, 911, 867, 787 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.62 (d, *J* = 7.5 Hz, 1H), 7.79-7.75 (m, 3H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.55-7.53 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.40-7.37 (m,1H), 7.25 (d, *J* = 8 Hz, 2H), 7.17-7.11 (m, 3H), 6.86 (t, *J* = 8 Hz, 1H), 6.74 (d, *J* = 8 Hz, 2H), 6.71 (s, 1H), 6.42 (s, 1H), 2.08 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 185.5, 143.8, 139.9, 136.0, 135.6, 131.8, 131.8, 131.7, 131.6, 129.7, 129.3, 129.2, 128.6, 128.4, 128.2, 127.0, 127.0, 126.7, 126.1, 125.1, 124.0, 122.8, 122.0, 120.8, 113.7, 112.8, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for 617.05050, found 617.05084.

***N*-(2-(6-bromo-3-cyanopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (26u).** The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **24a** (100 mg, 0.32 mmol), 4-bromo-2-(cyanomethyl)isoquinolin-2-ium-bromide **25h** (156 mg, 0.47 mmol) and KOH (70 mg, 1.26 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **26u** as a yellow solid (88 mg, 54%).

	**Mp**: 167−170 °C. **IR (neat) ν_{max}:** 3917, 3847, 3803, 3619, 3448, 3227, 2204, 1591, 1489, 1434, 1331, 1159, 1086, 915, 811 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.37 (s, 1H), 8.04 (d, *J* = 8 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.56-7.53 (m, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.28-7.21 (m, 4H), 7.09 (d, *J* = 7.5 Hz, 2H), 6.46 (s, 2H), 2.38 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 144.0, 136.2, 135.6, 131.5, 129.9, 129.5, 129.4, 128.6, 127.3, 127.2, 127.0, 126.4, 125.4, 125.0,

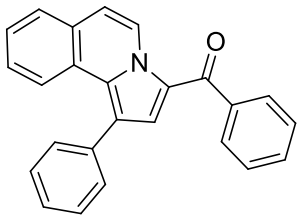
	123.6, 123.1, 122.9, 121.8, 113.6, 112.4, 110.8, 98.0, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{26}H_{18}BrN_3NaO_2S$ 538.01953, found 538.02112.

***N*-(2-(3-benzoyl-6-bromopyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (26v).** The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **24a** (100 mg, 0.32 mmol), 4-bromo-2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **25i** (192 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 4 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **26v** as a yellow solid (90 mg, 48%).

	**Mp**: 230−234 °C. **IR (neat) ν_{max}:** 3878, 3744, 3638, 3557, 3492, 3264, 3059, 1744, 1708, 1649, 1613, 1428, 1335, 1160, 1089, 980, 903, 814, 762, 727 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.92 (s, 1H), 8.02 (d, *J* = 8 Hz, 1H), 7.77-7.74 (m, 3H), 7.53 (t, *J* = 7 Hz, 1H), 7.50-7.43 (m, 3H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 8 Hz, 2H), 7.19-7.12 (m, 3H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 8 Hz, 2H), 6.67 (s, 1H), 6.43 (s, 1H), 2.07 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 185.4, 143.8, 139.8, 136.0, 135.6, 131.8, 131.7, 131.6, 129.7, 129.3, 129.2, 128.7, 128.5, 128.2, 126.9, 126.9, 126.9, 126.6, 126.6, 125.2, 124.5, 123.8, 123.5, 120.9, 113.5, 110.6, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{23}BrN_2NaO_sS$ 617.05050, found 617.05255.

Phenyl(1-phenylpyrrolo[2,1-a]isoquinolin-3-yl)methanone (26w). The reaction was performed according to general procedure with 3-nitro-*N*-methyl indole **24n** (100 mg, 0.57 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **25b** (279 mg, 0.85 mmol) and

KOH (128 mg, 2.28 mmol) at rt for 4 h. After workup, the residue was purified by activated neutral alumina column chromatography (5% ethyl acetate in hexane) to afford the desired product **26w** as a yellow solid (65 mg, 33%).

	**Mp**: 183−185 °C. **IR (neat) ν_{max}**: 3700, 3643, 3531, 3557, 3358, 2328, 1911, 1764, 1730, 1598, 1566, 1443, 1393, 1364, 1331, 1282, 1195, 902, 790, 747, 718 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.30 (d, *J* = 8 Hz, 1H), 8.19 (d, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.59-7.55 (m, 2H), 7.52 (d, *J* = 8 Hz, 2H), 7.19 (t, *J* = 7 Hz, 1H), 7.15-7.13 (m, 3H), 7.09-7.04 (m, 6H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 187.6, 139.7, 138.1, 135.8, 134.8, 131.2, 130.1, 129.8, 128.9, 127.9, 127.7, 127.7, 127.5, 126.9, 126.6, 125.3, 124.7, 123.4, 122.0, 113.0, 103.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{25}H_{18}NO$ 348.13829, found 348.13923.

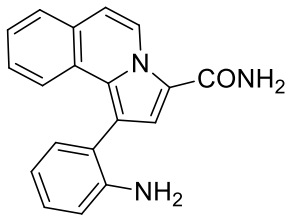
Procedure for scale up of 26a

A mixture of 3-nitro-*N*-tosyl indole **24a** (1.0 g, 3.16 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **25a** (1.18 mg, 4.74 mmol) and KOH (708 mg, 12.64 mmol) was weighed into a dry reaction tube. Dry DMF (18.0 mL) was added and allowed to stir at room temperature for 12 h. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford **26a** (994 mg, 72%).

Synthesis and characterization of 26a'

The compound **26a** (100 mg, 0.23 mmol) was treated with concentrated H_2SO_4 (2.0 equiv.) at room temperature for 2 hours. After completion of the reaction as indicated from the TLC, the reaction mixture was cooled and quenched by drop-wise addition of saturated $NaHCO_3$

solution and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by activated neutral alumina column chromatography (50% ethyl acetate in hexane) to afford the pyrrolo[2,1- *a*]isoquinoline **26a'** as a brown solid (49 mg, 71%).



Mp: 118-120 °C.

^{1}H NMR (500 MHz, $(CD_3)_2CO$, TMS): δ 9.45 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.24 (s, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8 Hz, 1H), 6.75 (d, *J* = 8 Hz, 1H), 6.60 (t, *J* = 7 Hz, 1H), 4.28 (s, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2CO$): δ 163.3, 146.7, 131.2, 129.0, 128.7, 128.1, 127.0, 126.6, 126.5, 126.0, 125.2, 123.4, 121.3, 118.7, 118.5, 116.8, 115.7, 115.1, 114.6, 112.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{19}H_{16}N_3O$ 302.12879, found 302.12991.

Optimization studies towards the synthesis of thiol

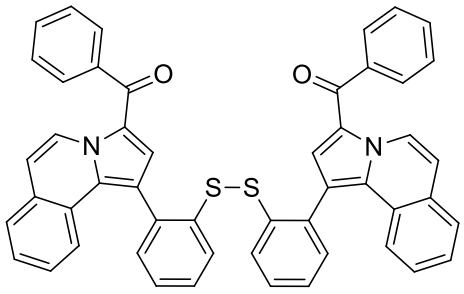
A dry reaction was also carried out with a mixture of 3-nitrobenzothiophene **27a** (100 mg, 1.0 equiv.), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **25b** (1.5 equiv.) and K_3PO_4 (2.0 equiv.) in CH_3CN under Argon atmosphere. The reaction was then allowed to stir at 60 ^oC for 24 hours. Here also, we obtained the disulfide bis-pyrrolo[2,1-*a*]isoquinoline **28a** and we were not able to isolate any other intermediates from the reaction mixture.

Experimental procedure for the reaction between 3-nitrobenzothiophene and isoquinolinium salt

A mixture of 3-nitrobenzothiophene (100 mg, 1.0 equiv.), isoquinolinium salt (1.5 equiv.) and K_3PO_4 (2.0 equiv.) was weighed into a dry reaction tube. Dry CH_3CN was added and allowed to stir at 60 ^oC for 24 hours. After completion of the reaction, the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and characterization of bis-pyrrolo[2,1-a]isoquinolines (28a-28e)

(1,1'-(disulfanediylbis(2,1-phenylene))bis(pyrrolo[2,1-a]isoquinoline-3,1-diyl))bis(phenylmethanone) (28a). The reaction was performed according to general procedure with 3-nitrobenzo[b]thiophene **27a** (100 mg, 0.56 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **25b** (275 mg, 0.84 mmol) and K_3PO_4 (237 mg, 1.12 mmol) at 60 °C for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **28a** as a yellow solid (169 mg, 80%).



Mp: 249-252°C.

IR (neat) ν_{max}: 3945, 3846, 3779, 3682, 3538, 2961, 2363, 1728, 1613, 1414, 1331, 1227, 1168, 1121, 1072, 1031, 965, 932, 871, 791, 756, 727, 688 cm^{-1}.

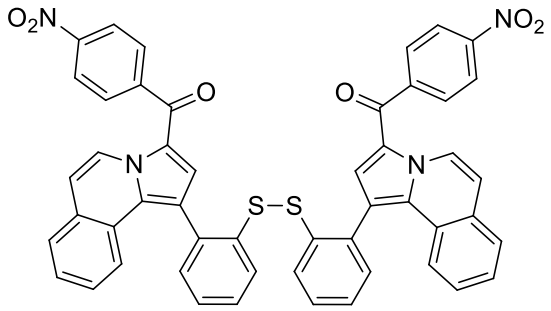
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.61 (dd, J_1 = 7.5 Hz, J_2 = 1 Hz, 2H), 7.80-7.77 (m, 4H), 7.63 (t, J = 7 Hz, 2H), 7.47-7.42 (m, 5H), 7.41-7.37 (m, 7H), 7.25-7.20 (m, 3H), 7.17-7.14 (m, 3H), 7.12-7.05 (m, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.6, 185.5, 140.5, 140.4, 137.1, 137.1, 134.4, 134.4, 132.8, 132.7, 131.3, 131.3, 129.7, 129.6, 129.2, 128.9, 128.9, 128.2, 127.9, 127.8, 127.8, 127.6, 127.5, 127.0, 126.9, 126.5, 126.4, 125.7, 125.7, 125.5, 125.4, 125.2, 125.1, 124.0, 123.7, 123.7, 116.4, 114.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{50}H_{33}N_2O_2S_2$ 757.19780, found 757.20007.

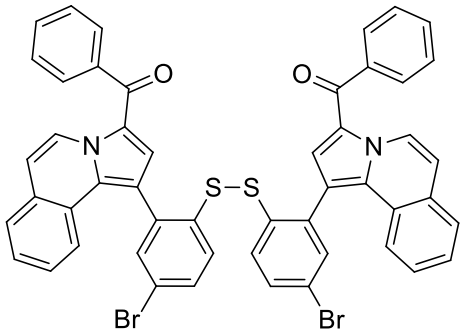
(1,1'-(disulfanediylbis(2,1-phenylene))bis(pyrrolo[2,1-a]isoquinoline-3,1-diyl))bis((4-nitrophenyl)methanone) (28b). The reaction was performed according to general procedure with 3-nitrobenzo[b]thiophene **27a** (100 mg, 0.56 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium-bromide **25d** (312 mg, 0.84 mmol) and K_3PO_4 (237 mg, 1.12 mmol) at 60 °C for 24 h. After solvent removal, the residue was purified by silica gel column

chromatography (20% ethyl acetate in hexane) to afford the desired product **28b** as a yellow solid (145 mg, 61%).

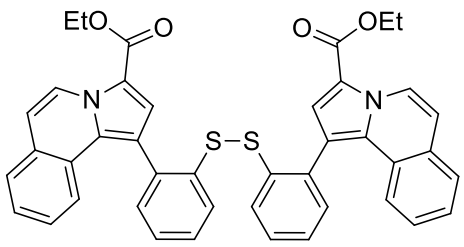
	**Mp**: 290-292 °C. **IR (neat) ν_{max}**: 3900, 3822, 3722, 3650, 3430, 2959, 2918, 2336, 1727, 1616, 1519, 1334, 1282, 1119, 1072, 853, 798, 729, 697 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.62 (d, *J* = 7.5 Hz, 2H), 8.26-8.24 (m, 4H), 7.93-7.90 (m, 4H), 7.69 (t, *J* = 7 Hz, 2H), 7.50-7.36 (m, 7H), 7.27-7.23 (m, 3H), 7.17-7.06 (m, 8H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 182.8, 182.7, 149.2, 145.9, 145.9, 137.0, 137.0, 134.0, 133.9, 133.8, 133.7, 131.3, 129.9, 129.1, 129.1, 128.5, 128.4, 127.9, 127.9, 127.8, 127.8, 127.2, 127.1, 126.7, 126.7, 125.6, 125.5, 125.0, 124.9, 124.1, 123.5, 123.1, 123.0, 117.2, 117.2, 114.7 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{25}H_{15}N_2O_3S$ 847.16795, found 847.16754.

(1,1'-(disulfanediylbis(3-bromo-6,1phenylene))bis(pyrrolo[2,1-a]isoquinoline-3,1 diyl))bis(phenylmethanone) (28c). The reaction was performed according to general procedure with 5-bromo-3-nitrobenzo[b]thiophene **27b** (100 mg, 0.39 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium -bromide **25b** (191 mg, 0.58 mmol) and K_3PO_4 (165 mg, 0.78 mmol) at 60 °C for 24 h. After solvent removal, the residue was purified by activated neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **28c** as a light yellow solid (117 mg, 66%).

	Mp: 230-232 °C. **IR (neat) ν_{max}**: 3952, 3803, 3390, 3072, 2958, 2922, 2357, 1722, 1606, 1572, 1457, 1328, 1279, 1118,

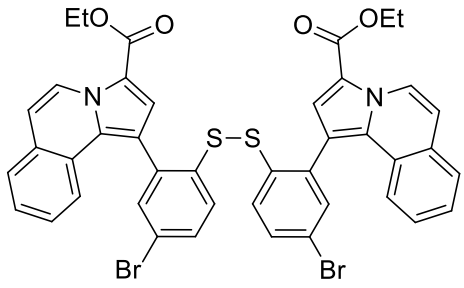
	1070, 938, 868, 791, 742, 687 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.60 (d, *J* = 7.5 Hz, 2H), 7.78 (t, *J* = 7 Hz, 4H), 7.70-7.66 (m, 2H), 7.50-7.46 (m, 3H), 7.44-7.39 (m, 8H), 7.33 (d, *J* = 8 Hz, 1H), 7.26-7.22 (m, 2H), 7.18-7.05 (m, 8H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$):** δ 185.6, 185.6, 140.3, 140.2, 136.4, 136.4, 136.3, 133.9, 132.6, 132.4, 131.9, 131.8, 131.5, 129.7, 129.6, 129.2, 128.3, 128.3, 128.2, 128.2, 127.7, 127.6, 127.5, 127.5, 127.4, 127.3, 127.2, 127.1, 125.7, 125.6, 124.9, 124.8, 123.9, 123.8, 123.7, 120.4, 120.4, 114.9, 114.9, 114.2, 114.2 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{50}H_{31}Br_2N_2O_2S_2$ 915.01677, found 915.01770.

Diethyl1,1'-(disulfanediylbis(2,1-phenylene))bis(pyrrolo[2,1-a]isoquinoline-3-carboxylate) (28d). The reaction was performed according to general procedure with 3-nitrobenzo[b]thiophene **27a** (100 mg, 0.56 mmol), 2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium-bromide **25e** (248 mg, 0.84 mmol) and K_3PO_4 (237 mg, 1.12 mmol) at 60 °C for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (5% ethyl acetate in hexane) to afford the desired product **28d** as a colourless solid (93 mg, 48%).

	**Mp**: 248-250°C. **IR (neat) ν_{max}**: 3898, 3841, 3732, 3598, 3357, 2917, 2846, 2312, 1738, 1477, 1444, 1374, 1331, 1203, 1074, 693, 665 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.26 (d, *J* = 7.5 Hz, 2H), 7.60-7.58 (m, 2H), 7.48-7.46 (m, 1H), 7.42 (dd, J_1 = 8 Hz, J_2 = 1 Hz, 1H), 7.39-7.32 (m, 6H), 7.23-7.20 (m, 2H), 7.18-7.10 (m, 6H), 6.99 (d, *J* = 7.5 Hz, 2H), 4.36-4.29 (m, 4H), 1.36-1.32 (m, 6H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$):** δ 161.4, 161.4,

	137.1, 137.0, 134.6, 131.3, 131.2, 131.1, 128.8, 128.7, 128.6, 128.5, 127.5, 127.4, 127.2, 126.9, 126.8, 126.3, 126.3, 125.6, 125.6, 125.3, 125.2, 124.8, 124.8, 123.5, 122.6, 115.9, 115.9, 115.6, 115.6, 60.2, 14.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{42}H_{32}N_2NaO_4S_2$ 715.16957, found 715.17230.

Diethyl 1,1'-(disulfanediylbis(3-bromo-6,1-phenylene))bis(pyrrolo[2,1-a]isoquinoline-3-carboxylate) (28e). The reaction was performed according to general procedure with 5-bromo-3-nitrobenzo[b]thiophene **27b** (100 mg, 0.39 mmol), 2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium-bromide **25e** (172 mg, 0.58 mmol) and K_3PO_4 (165 mg, 0.78 mmol) at 60 ºC for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **28e** as a colourless solid (66 mg, 40%).

	**Mp**: 237-240 °C. **IR (neat) ν_{max}**: 3911, 3840, 3754, 3681, 3603, 3564, 3263, 3130, 2361, 1691, 1457, 1375, 1340, 1214, 1077, 801, 745, 691, 638 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.26 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 2H), 7.64-7.60 (m, 2H), 7.43-7.38 (m, 4H), 7.34-7.31 (m, 2H), 7.28-7.27 (m, 2H), 7.22-7.14 (m, 6H), 7.03-7.00 (m, 2H), 4.37-4.29 (m, 4H), 1.36-1.32 (m, 6H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 161.3, 161.2, 136.7, 136.3, 136.3, 133.9, 133.9, 131.8, 131.7, 131.1, 130.9, 128.6, 128.6, 127.6, 127.6, 127.5, 127.5, 127.4, 127.1, 127.0, 125.3, 125.2, 124.8, 124.8, 123.2, 122.4, 122.3, 120.3, 120.3, 116.2, 116.1, 114.2, 114.1, 113.4, 113.4, 60.3, 60.3, 14.5, 14.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{42}H_{30}Br_2N_2NaO_4S_2$ 872.98855, found 872.98987.

3A.7 References

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Chapter 3B

Discovery of Oxygen Induced Chemoselectivity in Pd-Catalyzed C–H Functionalization: Cross-Dehydrogenative Coupling *vs* C–H Amination

3B.1 Abstract

We have come across a substrate, namely, 5-benzoyl-pyrrolo[2,1-a]isoquinoline, in which three different functionalizable C-H bonds were identified that could be judiciously transformed site selectively for the generation of complex polyring fused N-heterocycles. A Pd-catalyzed cross-dehydrogenative coupling of 5-benzoyl-pyrrolo[2,1-a]isoquinoline afforded 8H-indeno-pyrrolo[2,1-a]isoquinolinone and an oxygen induced palladium catalyzed selective C-H amination in the same substrate provided a pentacene viz., 9H-indolo-pyrrolo[2,1-a]isoquinoline. We also observed the formation of a multiring fused benzazepine scaffold by the site selective C-H amination in 5-(4-nitro benzoyl)-pyrrolo[2,1-a]isoquinoline.

3B.2 Introduction

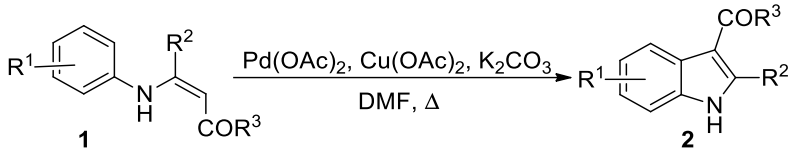
Organic synthesis has taken a huge stride with the advancements in the functionalization of unactivated C-H bonds directly to carbon-carbon or carbon-heteroatom bonds.[1] The initial reports on selective C-H functionalization relied on free radical transformations followed by the development of metal complexes that could activate C-H bonds.[2] For the last 2 decades, organic chemists have tasked with designing substrates or environments that would enable selective functionalization of unactivated C-H bonds.[3] These developments have shortened the way that retrosynthetic approaches are planned towards complex organic molecules, thereby improving step and atom economy.

Cross-dehydrogenative coupling (CDC) or dual C-H activation is presently considered as an inevitable tool for the generation of carbon-carbon bonds both in intermolecular and intramolecular fashion. This powerful methodology which doesn't require any preactivation

of reaction centers have been utilized for the synthesis of carbocycles and heterocycles under both transition metal catalyzed and metal-free conditions.

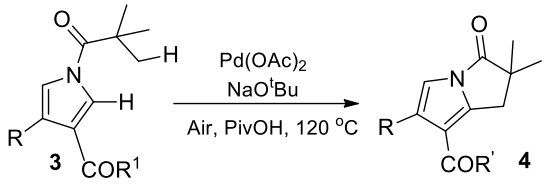
3B.2.1 Cross-dehydrogenative coupling or dual CH activation towards C-C bond formation

It was in 2008 when Glorius and co-workers reported the intramolecular oxidative coupling of commercially available anilines **1** in the presence of palladium catalyst towards functionalized indoles (Scheme 3B.1.). This transformation was carried out *via* the cyclization of *N*-aryl enamine carboxylates to give the corresponding indoles.[4]



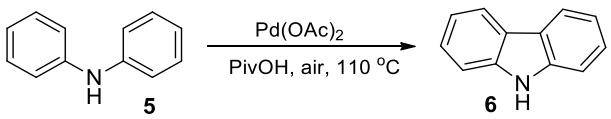
Scheme 3B.1 Palladium-catalyzed oxidative cyclization of *N*-aryl enamines

In the same year, Fagnou and coworkers reported an intramolecular palladium-catalyzed coupling of arenes with unactivated alkanes leading to the formation of a new $C(sp^2)$-$C(sp^3)$ bond. These reactions showed high regioselectivity for both the azole and alkane moieties, and was carried out with air as the terminal oxidant (Scheme 3B.2). [5]



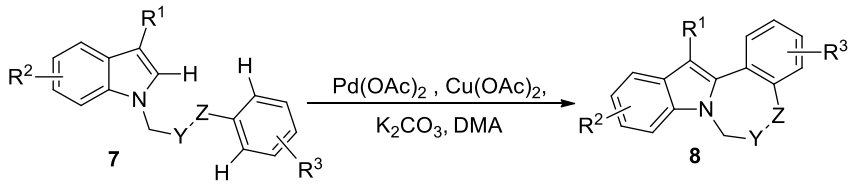
Scheme 3B.2 Palladium-catalyzed arene-alkane coupling reaction

Again, the same group reported another intramolecular palladium(II)-catalyzed oxidative carbon-carbon bond formation under air (Scheme 3B.3). Use of electron-rich diarylamines as substrates with pivalic acid as the solvent afforded the corresponding carbazole products with improved yields and scope.[6]



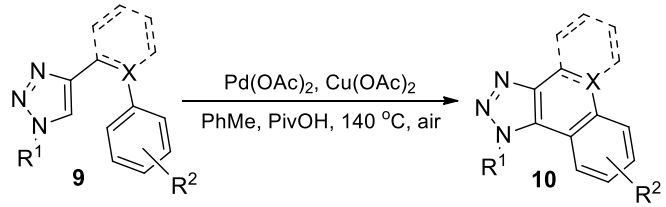
Scheme 3B.3 Palladium(II)-catalyzed oxidative biaryl synthesis

In 2010, for the first time Greaney *et al.* reported the intramolecular oxidative C-H coupling for the synthesis of annulated heterocycles. The reaction tolerates a wide range of functional groups by using a simple catalyst system of $Pd(OAc)_2$, K_2CO_3 and $Cu(OAc)_2$ with DMA as the solvent (Scheme 3B.4). [7]



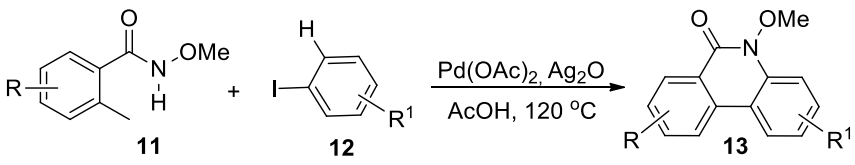
Scheme 3B.4 Intramolecular oxidative coupling of indole with heteroarenes

Later, in the same year, Ackermann and coworkers reported a palladium-catalyzed intramolecular dehydrogenative arylation of 1,2,3-triazoles towards annulated phenanthrenes through a reaction sequence comprising of two distinct catalytic C-H bond functionalization reactions (Scheme 3B.5).[8]



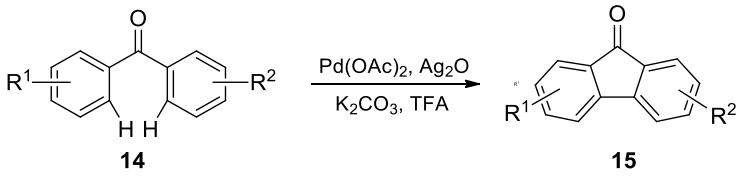
Scheme 3B.5 Cyclodehydrogenative arylations of 1,2,3-triazoles

Another method was adopted by Wang and coworkers for the synthesis of phenanthridinones *via* a palladium catalyzed dual C-H activation (Scheme 3B.6). This reaction took place between *N*-methoxybenzamides and aryl iodides which was achieved through a one-pot formation of C-C and C-N bonds. On screening the reaction conditions, best results were obtained on using a catalytic system of $Pd(OAc)_2$, and Ag_2O in the presence of AcOH as the solvent. [9]



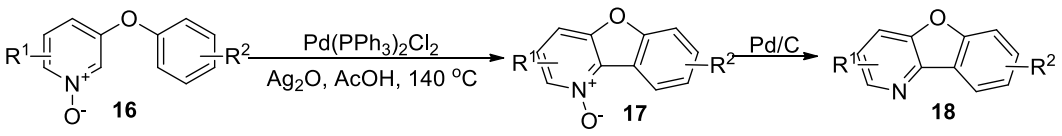
Scheme 3B.6. Palladium-catalyzed reaction of *N*-methoxybenzamides with phenyl iodides

The synthesis of fluorenones *via* a palladium-catalyzed dual C-H functionalization pathway was reported by Shi and coworkers in 2012. This reaction, which stands as an effective route towards fluorenone derivatives, involves an oxidative dehydrogenative cyclization of benzophenones with good functional group tolerance (Scheme 3B.7). [10]



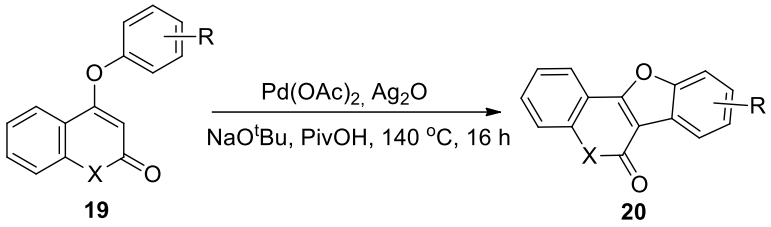
Scheme 3B.7 Palladium-catalyzed dual C-H functionalization towards fluorenones

Wang and co-workers later reported an efficient catalytic system for the synthesis of benzofuro[3,2-*b*]pyridine 1-oxides by Pd-catalyzed intramolecular dual C–H activation (Scheme 3B.8). Also, they could observe an efficient oxidative cyclisation, thereby resulting in the corresponding benzofuro[3,2-*b*]pyridines in excellent yields.[11]



Scheme 3B.8 Synthesis of benzofuro[3,2-*b*]pyridines

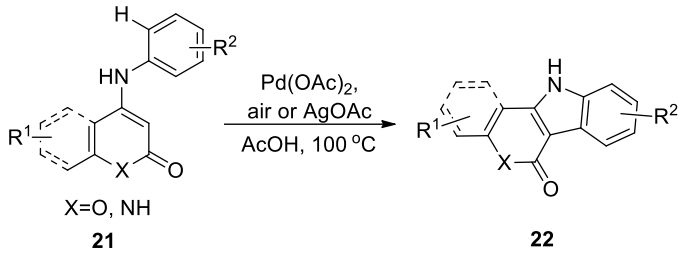
In 2016, McGlacken and coworkers reported a double C–H activation of 4-phenoxy-2-coumarins to the corresponding cyclized products. This approach provides access to various substitution patterns (on the phenoxy ring) that would be difficult to accomplish through other means (Scheme 3B.9).[12]



Scheme 3B.9 Cyclization of 4-Phenoxy-2-coumarins *via* a double C–H activation

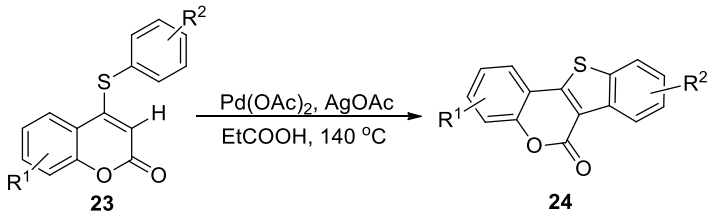
In the same year, Xu *et al.* developed a base-free technique for synthesizing indole-fused polyheterocycles using a highly efficient palladium catalyzed intramolecular cross

dehydrogenetive coupling (CDC) reaction with 4-aniline substituted coumarins, quinolinones, and pyrones (Scheme 3B.10). The reaction afforded the corresponding indolo[3,2-*c*]coumarins, indolo[3,2-*c*]quinolinones, and indolo[3,2-*c*]pyrones with good to exceptional yields (up to 99%).[13]



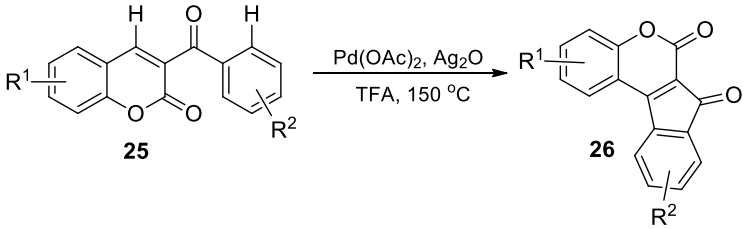
Scheme 3B.10 Synthesis of indole-fused polyheterocycles *via* CDC coupling

In 2019, a palladium-catalyzed cross-dehydrogenative coupling of 4-arylthiocoumarins through C–H activation was described to synthesize benzothiophenes. A broad range of substituted benzothiophenes using this method could be easily achieved in moderate to good yields (Scheme 3B.11).[14]



Scheme 3B.11 Pd-catalyzed CDC for the synthesis of benzothiophenes using coumarins

Very recently, Weng *et al*. disclosed a palladium-catalyzed cross-dehydrogenative coupling of 3-benzoyl substituted coumarins *via* C-H activation to produce indeno[2,1-*c*]chromene-6,7-diones (Scheme 3B.12). The reaction demonstrates good functional group tolerance and broad substrate scope with moderate to good yields.[15]

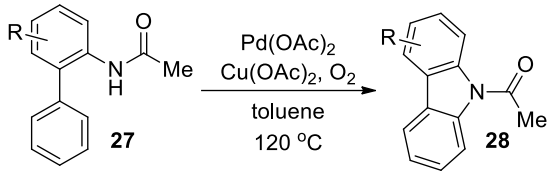


Scheme 3B.12 Intramolecular C–H activation cross-dehydrogenative coupling of coumarin fused heterocycles

Another equally important transformation is C-H amination which also is a heavily relied strategy for generating substituted amines or *N*-heterocycles.

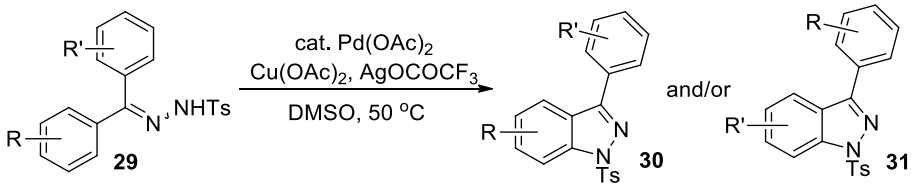
3B.2.2 C-H amination towards C-N bond formation

It was in 2005 when Buchwald *et al*. reported an intramolecular C-H amination towards the synthesis of substituted carbazoles (Scheme 3B.13). This transformation was carried out *via* the cyclization of substituted 2-arylacetanilides under palladium catalysis. Herein, they have disclosed a new method which involves a combination of C-H functionalization and C-N bond-forming processes.[16]



Scheme 3B.13 Pd-catalyzed amidation towards the synthesis of substituted carbazoles

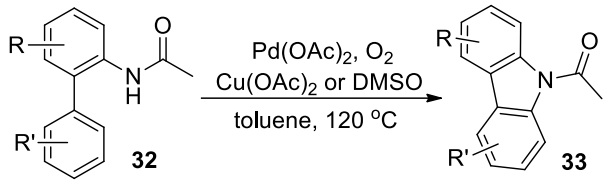
In 2007, Hiroya *et al*. described the synthesis of indazoles *via* a direct C-H activation and intramolecular amination of hydrazone compounds in the presence of palladium catalyst. On screening the reaction conditions, the best results were obtained by using a catalytic system of $Pd(OAc)_2$, $Cu(OAc)_2$ and $AgOCOCF_3$ in the presence of DMSO as the solvent. The reactions proceed under relatively mild conditions, allowing high functional group tolerance (Scheme 3B.14).[17]



Scheme 3B.14 Intramolecular C-H amination towards the synthesis of indazoles

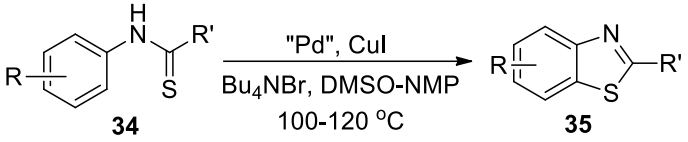
Again in 2008, Tsang and co-workers reported an intramolecular conversion of an arene C-H bond to a C-N bond to synthesise unsymmetrical carbazoles (Scheme 3B.15). The method is

compatible with various functional groups using a catalytic system of $Pd(OAc)_2$ and $Cu(OAc)_2$ with toluene as the solvent under oxygen atmosphere.[18]



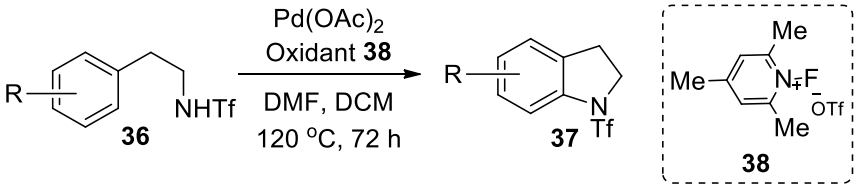
Scheme 3B.15 Pd-catalyzed synthesis of unsymmetrical carbazoles *via* C-N bond formation

In 2008, a palladium catalyzed C-H amination of thiobenzanilides through C−H functionalization/C−S bond formation was described to synthesize 2-substituted benzothiazoles. The use of a catalytic system consisting of 10 mol % of Pd(II), 50 mol % of Cu(I), and 2 equivalents of Bu_4NBr afforded the corresponding benzothiazoles in improved yield and scope (Scheme 3B.16).[19]



Scheme 3B.16 Pd-catalyzed synthesis of 2-substituted benzothiazoles

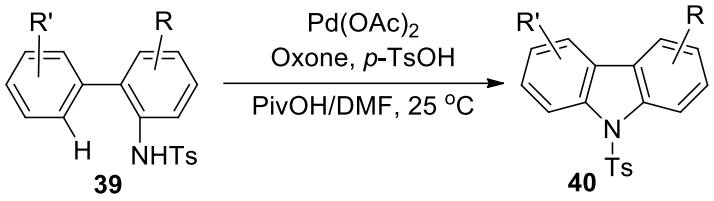
In 2009, Yu and co-workers reported a palladium catalyzed C-H amination using a two - electron F^+ source as an oxidant (Scheme 3B.17). This reaction, which is an effective route towards synthesising indoline derivatives, involves an intramolecular amination of trifluoroamide-protected alkylamines with good functional group tolerance.[20]



Scheme 3B.17 Pd-catalzyed intramolecular C-H amination towards substituted indolines

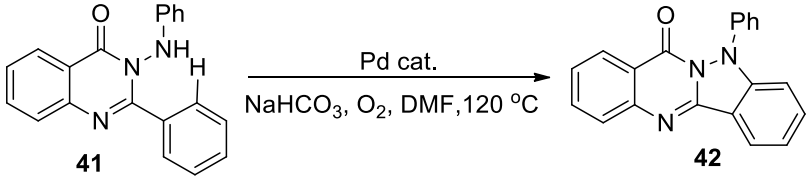
Another method was adopted by Youn and co-workers in 2011 towards synthesizing carbazoles *via* intramolecular oxidative C-H amination of *N*-Ts-2-arylanilines using palladium as a catalyst and oxone as an oxidant. The salient features of this protocol are broad substrate

scope, good functional group tolerance and practicality of using oxone as a green and safe oxidant under mild conditions (Scheme 3B.18).[21]



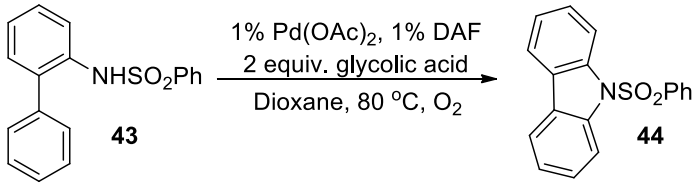
Scheme 3B.18 Pd-catalyzed synthesis of *N*-heterocycles from 2-arylanilines

In 2014, Yang and coworkers reported a new palladium-catalyzed intramolecular C-H amination of 2-aryl-3-(arylamino)quinazolinones towards a series of substituted indazolo[3,2-*b*]quinazolinone derivatives with oxygen as the terminal oxidant (Scheme 3B.19). The reaction demonstrates good functional group tolerance and broad substrate scope with moderate to good yields.[22]



Scheme 3B.19 Pd-catalyzed C-H amination towards indazolo[3,2-*b*]quinazolinone derivatives

Again, in the same year Stahl *et al.* reported an aerobic carbazole synthesis *via* an intramolecular aryl C-H amination with a (DAF)Pd(OAc)$_2$ system. In this reaction, *in situ* generation of a peroxide-based oxidant from O_2 and the solvent, 1,4-dioxane promotes the C–H amination of 2-aminobiphenyl derivatives (Scheme 3B.20).[23]



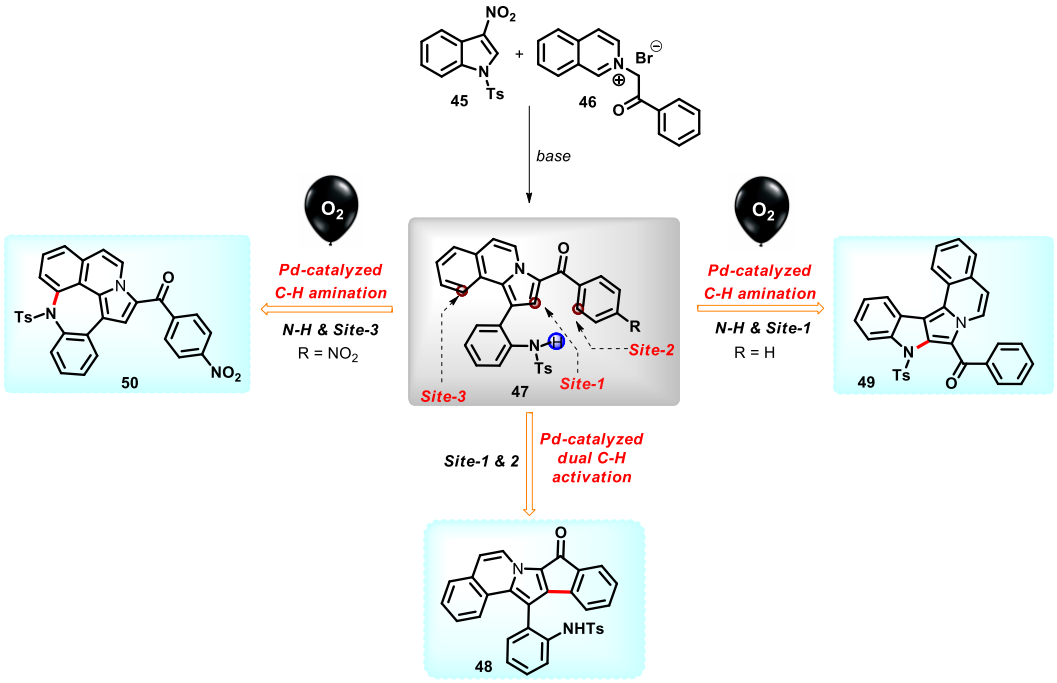
Scheme 3B.20 Intramolecular C-H amination of 2-aminobiphenyl derivatives

Achieving high position selectivity in C-H functionalization among similar reactive sites is still a challenging task for chemists.[24] Site selective C-H functionalization is now a days effected by either utilizing the stereoelectronic differences in reactive centers or by installing

appropriate directing groups that can limit the reactivity to particular centers of interest.[25] In this chapter, we report our observations on site-selective C-H functionalization between three different reactive centers towards polyring fused *N*-heterocycles.

3B.3 Statement of the problem

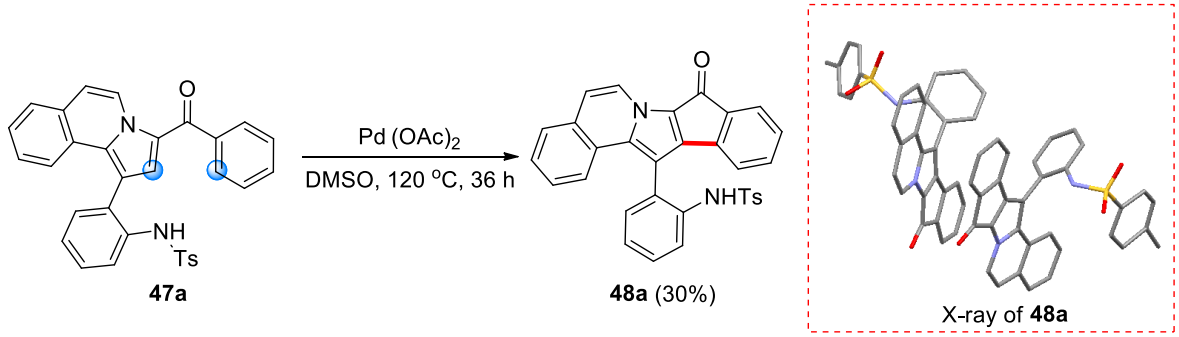
In the substrate 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline **47a** (Scheme 3B.21), we identified two fucntionalizable C-H centers, at site-1 & site-2. Under Pd-catalyzed cross-dehydrogenative coupling conditions, we hypothesized that an intramolecular cyclization will happen between site-1 and site-2 affording 8H-indeno-pyrrolo[2,1-*a*]isoquinolinone moiety **48a**. In addition, by tuning the reaction conditions, we postulated that a C-H amination could be effected between N-H and site-1 for the synthesis of 9-tosyl-9*H*-indolo-pyrrolo[2,1-*a*]isoquinoline **49a**. These investigations resulted in unraveling an oxygen induced chemoselectivity which, to the best of our knowledge, is unknown thus far. Finally, during the investigations on the generality of C-H amination reaction, we came across an unprecedented observation of formation of a polyring fused azepine **50a** by the C-H amination between N-H and site-3. Herein, we describe in detail about our examinations on Pd-catalyzed cross-dehydrogenative coupling and C-H aminations towards polyring fused *N*-heterocycles.



Scheme 3B.21 C-H functionalization towards synthesis of *N*-heterocycles

3B.4 Results and discussion

We initiated our investigations by synthesizing 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline **47a** from 3-nitro-*N*-tosyl indole **45a** and 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **46a** (Scheme 3B.21). By keeping **47a** as a substrate, we planned to examine the possibility of Pd-catalyzed cross-dehydrogenative coupling for activating C-H bonds at sites 1&2 as shown in Scheme 1. The test reaction was set up with **47a** in the presence 10 mol% of $Pd(OAc)_2$ in DMSO at 120 °C for 36 h (Scheme 3B.22). As expected, we could isolate the product 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-one **48a** formed by dual C-H activation in 30% yield. The structure of **48a** was established with various spectroscopic methods and single crystal X-ray analysis.



Scheme 3B.22 Pd(II) mediated cross-dehydrogenative coupling of pyrrolo[2,1-*a*]isoquinolines

In the ^{1}H NMR spectrum, aromatic protons were found to resonate in the region δ 8.27-6.14 ppm. The proton on the isoquinolium ring attached near to the N atom (a) resonated at 8.29 ppm as a doublet. The singlet observed at δ 6.65 (b) was attributed to NH proton attached to the tosyl group. The methyl protons of tosyl group resonated as singlet at δ 2.05 ppm. The ^{1}H NMR spectrum of the compound is shown in figure 1.

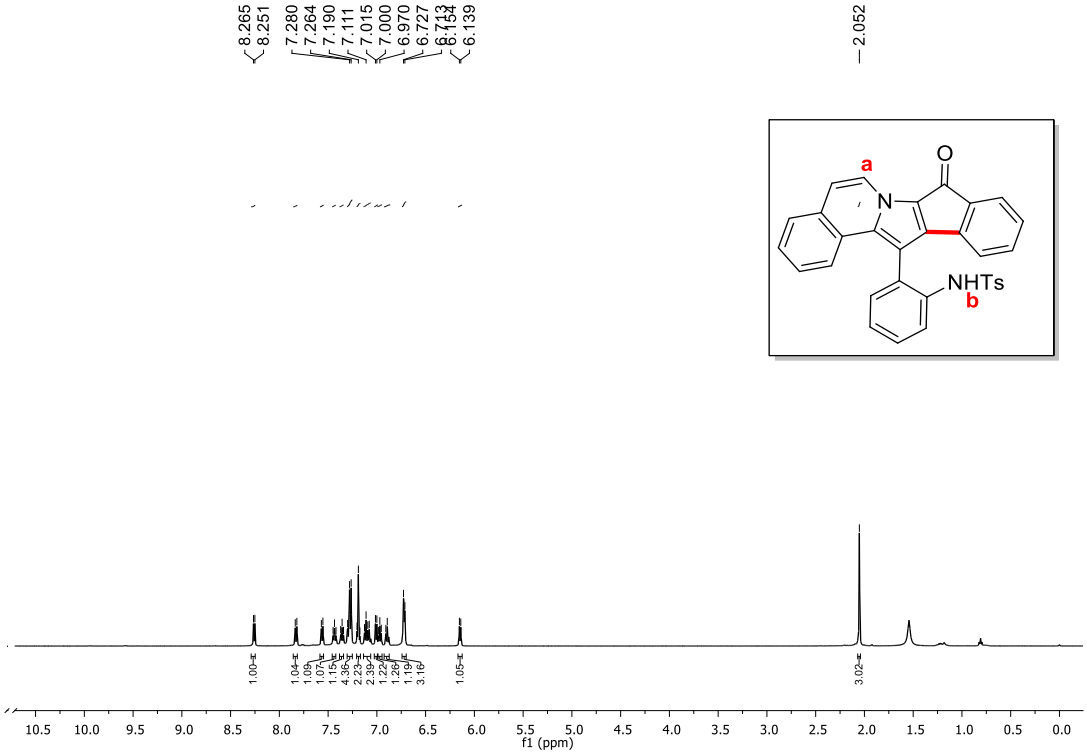


Figure 1. ^{1}H NMR spectra of **48a**

In the ^{13}C NMR spectrum (Figure 2), the aromatic carbons resonated in the region δ 179.4-108.5 ppm. The carbonyl carbon resonated at δ 179.4 ppm (a). The methyl carbon of the tosyl group showed a peak at δ 21.6 ppm. All other peaks in the ^{1}H and ^{13}C NMR were in good agreement with the assigned structure.

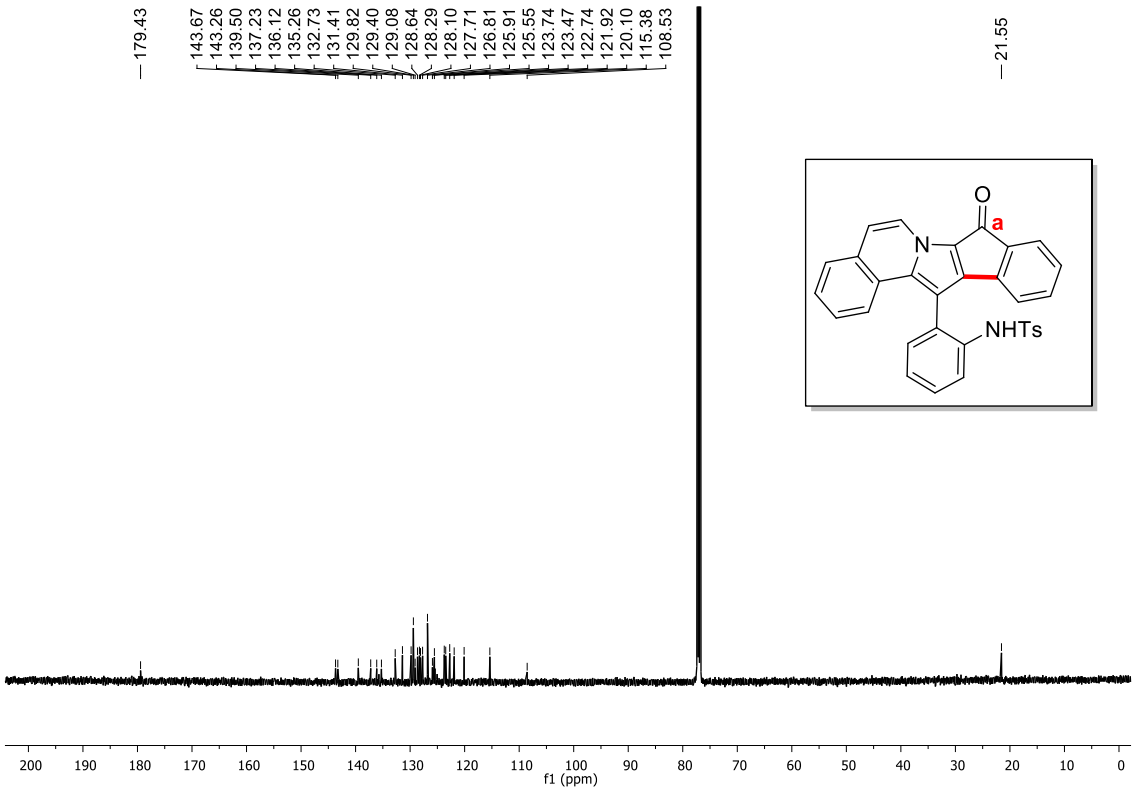
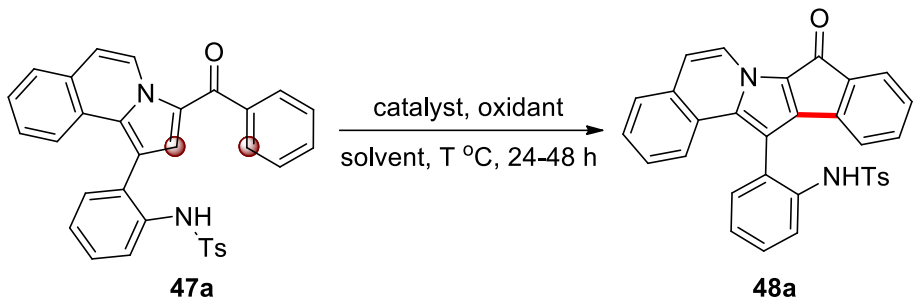


Figure 2. ^{13}C NMR spectra of **48a**

The optimization of Pd(II) mediated cross-dehydrogenative coupling towards functionalized 8H-indenopyrrolo[2,1-*a*]isoquinolin-8-one was carried out with **47a** as the substrate. At first, we checked the efficiency of reoxidants such as $K_2S_2O_8$, AgOAc and $Cu(OAc)_2$ (Table 1, entries 2-4) among which $Cu(OAc)_2$ turned out to be crucial for the reaction. Systematic screening of various palladium sources revealed that $Pd(OAc)_2$ was found to be the best catalyst for the present cross-dehydrogenative coupling (Table 1, entries 2, 5-8). Next, we screened various solvents such as PiVOH, DMF, Toluene and Xylene in addition to DMSO (Table 1, entries 2, 9-11). From these reactions, toluene was found to be the best medium for the Pd-catalyzed dual C-H activation. We found that an increase in the amount of catalyst to 20 mol% improved the yield of **48a** to 84% (Table 1, entry 12). Finally, an increase in the reaction temperature to 140 ^oC by using xylene as the solvent did not have any positive impact on the yield of the reaction (Table 1, entry 13).

Table 1. Optimisation studies with **47a** towards cross-dehydrogenative coupling [a]



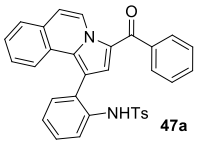
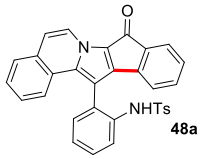
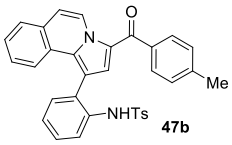
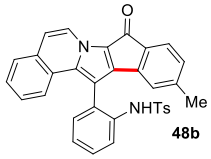
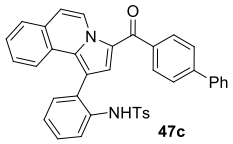
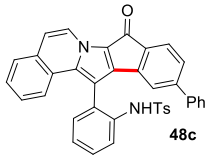
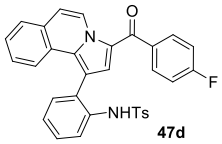
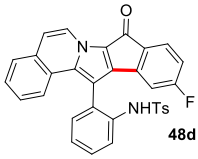
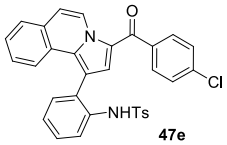
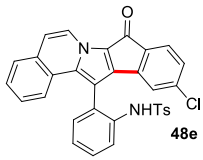
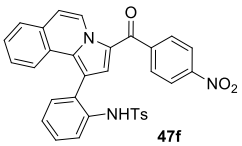
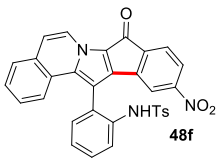
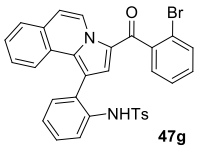
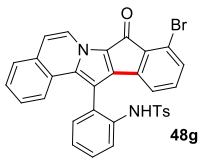
47a **48a**

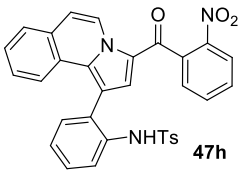
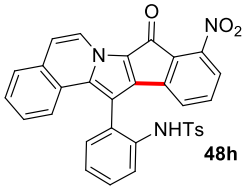
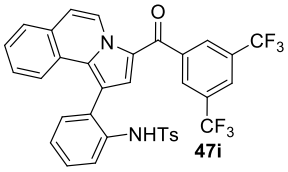
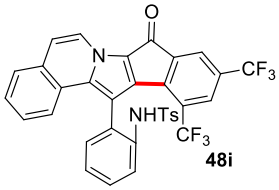
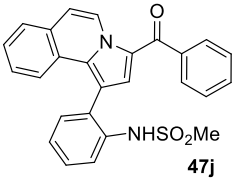
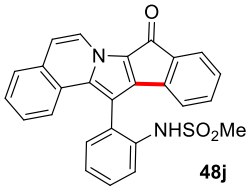
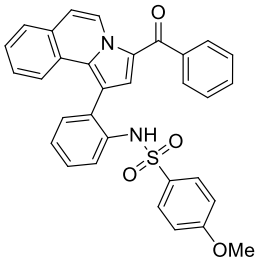
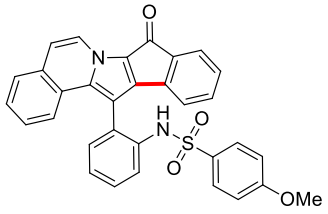
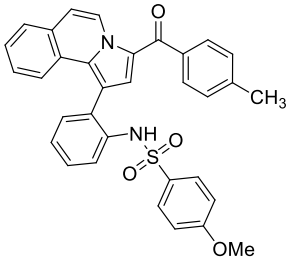
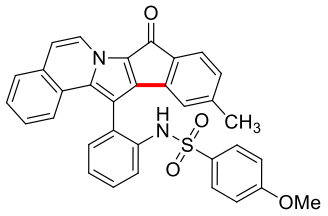
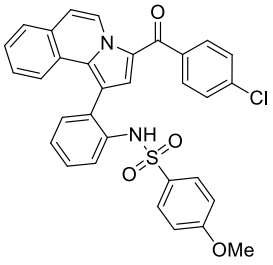
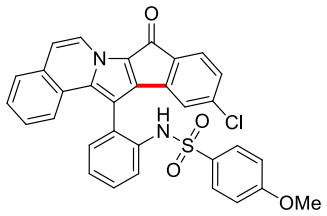
Entry	Catalyst	Oxidant	Solvent	Time (h)	Yield of 48a (%)
1	$Pd(OAc)_2$	-	DMSO	36	30
2	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	24	71
3	$Pd(OAc)_2$	$K_2S_2O_8$	DMSO	24	trace
4	$Pd(OAc)_2$	AgOAc	DMSO	24	40
5	$PdCl_2$	$Cu(OAc)_2$	DMSO	24	40
6	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$	DMSO	24	36
7	$Pd(tfa)_2$	$Cu(OAc)_2$	DMSO	24	44
8	$Pd(dba)_2$	$Cu(OAc)_2$	DMSO	24	32
9	$Pd(OAc)_2$	$Cu(OAc)_2$	PiVOH	24	nr
10	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	24	42
11	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	48	75
12[b]	**$Pd(OAc)_2$**	**$Cu(OAc)_2$**	**toluene**	**36**	**84**
13[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	xylene	36	80

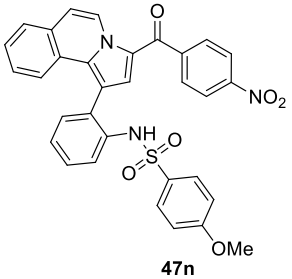
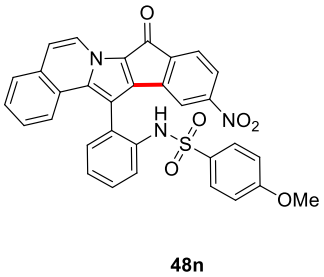
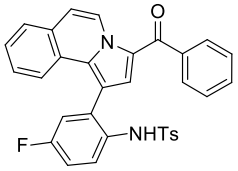
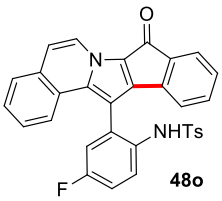
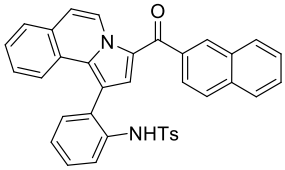
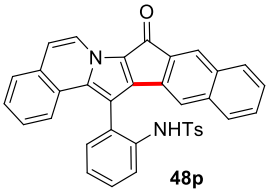
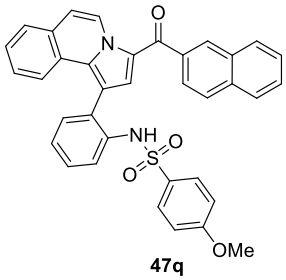
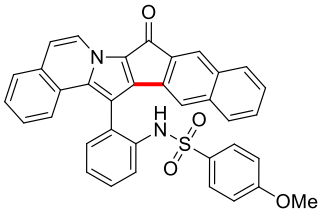
Reaction conditions: [a] **47a** (1.0 equiv., 0.10 mmol), catalyst (10 mol%), oxidant (1.0 equiv.), solvent (1.0 mL), 120 °C; [b] catalyst (20 mol%); [c] catalyst (20 mol%), 140 °C.

Under the optimized conditions [$Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv.), toluene, 120 °C, 36 h] for the Pd-catalyzed cross-dehydrogenative coupling towards functionalized 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-one, we explored the scope of the reaction using different 5-benzoyl pyrrolo[2,1-*a*]isoquinolines, the results of which are summarized in Table 2.

Table 2. Generality of Pd-catalyzed cross-dehydrogenative coupling[a]

Entry	Pyrrolo[1,2-*a*]isoquinoline	Product	Yield
1	 **47a**	 **48a**	84, 80[b]
2	 **47b**	 **48b**	70
3	 **47c**	 **48c**	64
4	 **47d**	 **48d**	40
5	 **47e**	 **48e**	64
6	 **47f**	 **48f**	70
7	 **47g**	 **48g**	50

Entry	Pyrrolo[1,2-*a*]isoquinoline	Product	Yield
8	 **47h**	 **48h**	40
9	 **47i**	 **48i**	53
10	 **47j**	 **48j**	60
11	 **47k**	 **48k**	62
12	 **47l**	 **48l**	55
13	 **47m**	 **48m**	52

Entry	Pyrrolo[1,2-*a*]isoquinoline	Product	Yield
14	 **47n**	 **48n**	51
15	 **47o**	 **48o**	49
16	 **47p**	 **48p**	60
17	 **47q**	 **48q**	55

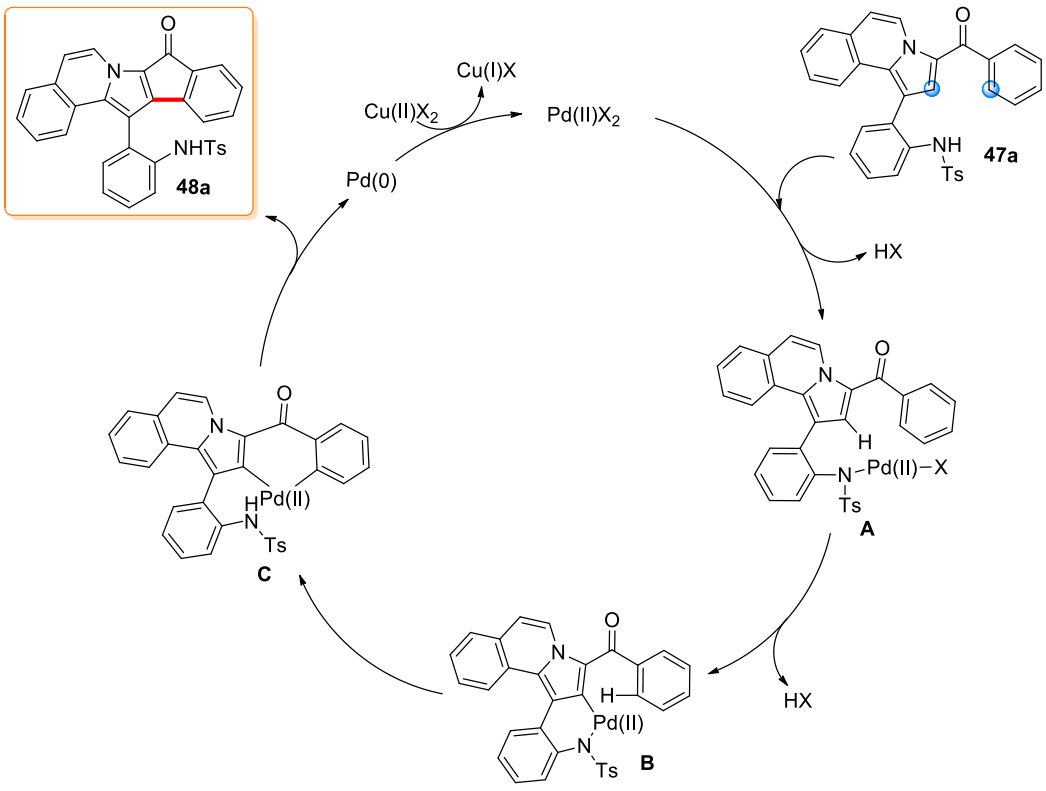
[a]Reaction conditions: **47** (1.0 equiv., 0.20 mmol), $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv.), toluene (2.0 mL), 120 °C, 36 h, starting material was recovered in the cases where yields were moderate. [b]From 1.0 g of **47a**.

Different starting substrates **47** for this study was synthesized from a series of electrophilic indoles and isoquinolinium salts as shown in the experimental section.

We initiated the studies (Table 2) by using 5-benzoyl pyrrolo[2,1-*a*]isoquinolines with substituents on the benzoyl moiety. In this line, we could introduce methyl (in **48b**) and phenyl (in **48c**) substituents on the indanone ring. Next, we were able to synthesize 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-ones **48d** and **48e** with halogen substitutions (F and Cl) on

the indanone ring. The Pd-catalyzed cross-dehydrogenative coupling conditions also worked well with a NO_2-group on the benzoyl moiety thereby furnishing **48f** in 70% yield. By the synthesis of **48g**, **48h** and **48i**, we could demonstrate that substituents can be introduced at any position of the indanone ring by starting with the appropriately functionalized 5-benzoyl pyrrolo[2,1-*a*]isoquinolines. We also tried reactions with substrates having different *N*-substituents such as -SO_2Me and -SO_2Ph-4OMe and all these afforded the corresponding products **48j** to **48n** in moderate to good yields. We could synthesize **48o** in 49% yield with a F-substituent on the aryl group attached to the pyrrole ring. Finally, the methodology could be extended for the synthesis of six-ring fused heteroacenes **48p** and **48q** by starting from suitably substituted 5-naphthoyl pyrrolo[2,1-*a*]isoquinolines. The reaction of 1.0 g of **47a** afforded the product 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-one **48a** in 80% yield.

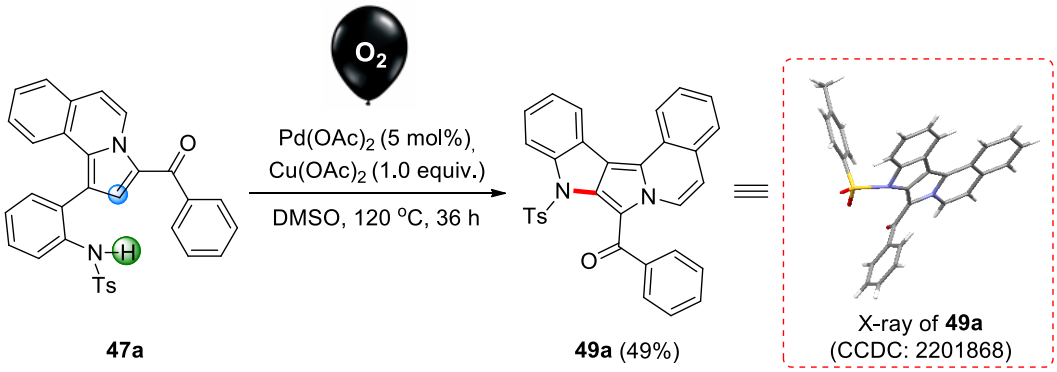
Based on our observations and by following reported literature, we propose a mechanism for the Pd-catalyzed cross-dehydrogenative coupling towards indenopyrrolo[2,1-*a*]isoquinolines (Scheme 3B.23).[265,6,15]



Scheme 3B.23 Plausible mechanism for the synthesis of indenopyrrolo[2,1-*a*]isoquinolines [X = OAc]

The first step of the catalytic cycle will be the formation of N-Pd bond as in intermediate **A** from **3a** and the Pd-catalyst.[27] Next, a selective activation of the C-H bond in pyrrole ring takes place to form a six-membered palladacycle **B**.[28] A Fujiwara-Moritani type process is then believed to occur in intermediate **B** *via* a C-H bond activation in the benzoyl moiety to furnish the new six-membered cyclic Pd(II) intermediate **C**.[27,29] Subsequently, the reductive elimination occurs in **C** affording the product **48a** and Pd(0). Finally, the Pd(II) species is regenerated by the oxidation with $Cu(OAc)_2$ to complete the catalytic cycle (Scheme 3B.23).

The metal-catalyzed intramolecular C−H amination provides a straightforward approach for the synthesis of *N*-containing heterocycles such as carbazoles, benzimidazoles, indazoles, indolines etc. In this line, we targeted the C-H amination between the N-H and site-1 of pyrrolo[2,1-*a*]isoquinolines (Scheme 3B.24) towards the synthesis of indolo-pyrrolo[2,1-*a*]isoquinoline. During our optimization studies on Pd-catalyzed cross-dehydrogenative coupling with **47a**, we came across a combination of $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv.) under O_2 atmosphere in DMSO. The reaction at 120 °C was allowed to continue for 36 h after which we could isolate indolo-pyrrolo[2,1-*a*]isoquinoline **49a** in 49% yield along with **48a** in minor amounts (Scheme 3B.24). Interestingly, in the present observation, the presence of oxygen has changed the course of the reaction furnishing the C-H amination product in major quantity and such an oxygen induced chemoselective transformation is rare.



Scheme 3B.24 Pd(II) catalyzed site-selective C-H activation towards indolo[3',2':3,4]pyrrolo[2,1-*a*]isoquinoline

In the ^{1}H NMR spectrum, aromatic protons were found to resonate in the region δ 8.96-6.76 ppm. The proton on the isoquinolium ring attached near to the N atom (a) resonated at 8.96

ppm as a doublet. The methyl protons of tosyl group resonated as singlet at δ 2.06 ppm. The ^{1}H NMR spectrum of the compound is shown in figure 3.

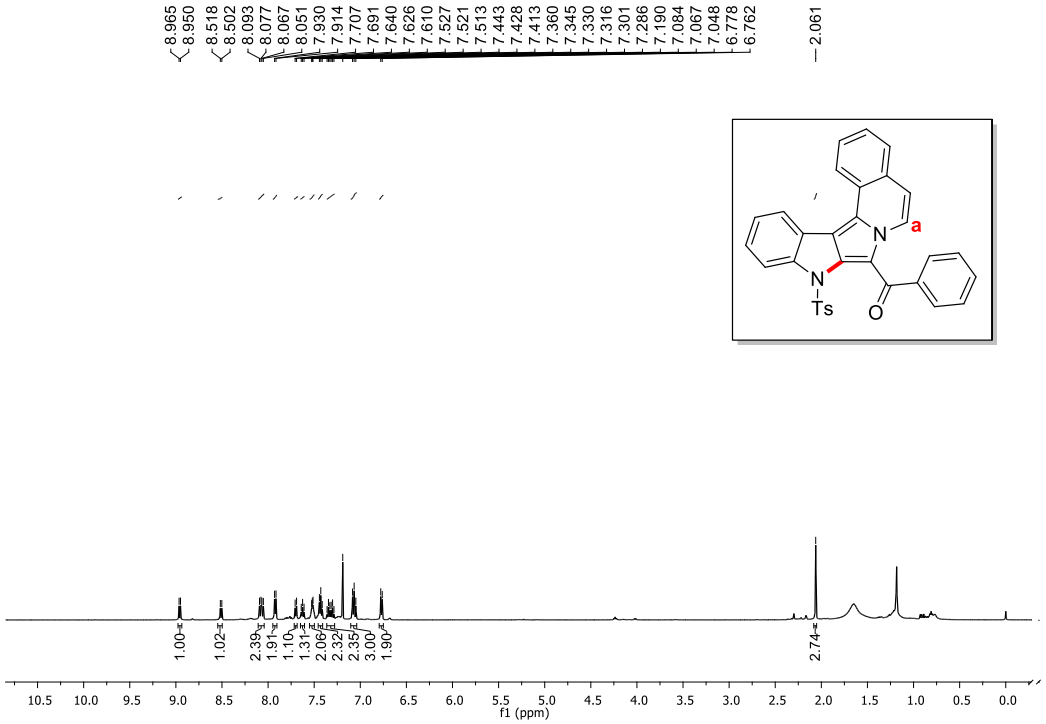


Figure 3. ^{1}H NMR spectra of **49a**

In the ^{13}C spectrum (Figure 4), the aromatic carbons resonated in the region δ 187.3-113.2 ppm. The carbonyl carbon resonated at δ 187.3 ppm (a). The methyl carbon of the tosyl group showed a peak at δ 21.5 ppm. All other peaks in the ^{1}H and ^{13}C NMR were in good agreement with the assigned structure.

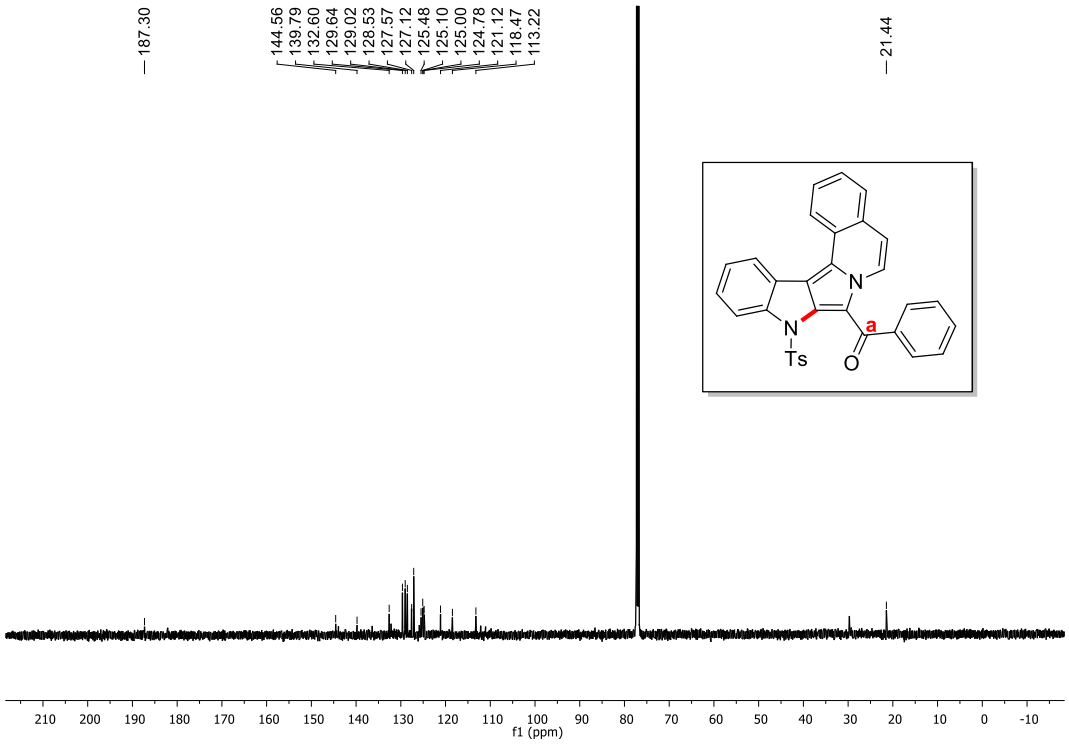
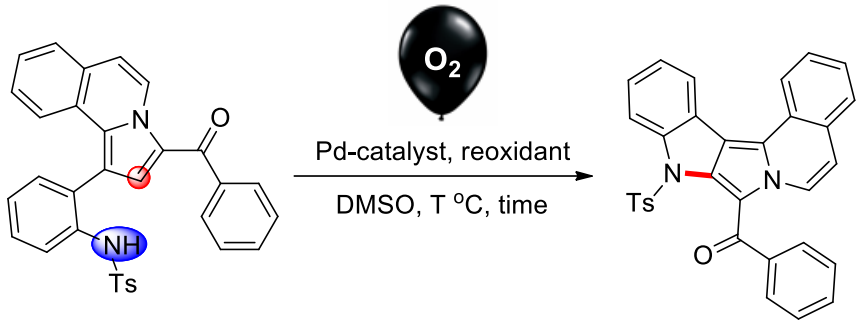


Figure 4. ^{13}C NMR spectra of **49a**

A systematic investigation was carried out to find the best condition for Pd-catalyzed site selective C-H amination with **47a** as the substrate. Initially, we looked at different reoxidants such as $Cu(OAc)_2$, $Cu(OTf)_2$, $CuCl_2$ and benzoquinone out of which $Cu(OAc)_2$ was found to be the best option (Table 3, entries 1-4). Next, the screening of different Pd-catalysts ($Pd(OAc)_2$, $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(tfa)_2$, $Pd(dba)_2$, $[Pd(allyl)Cl]_2$) was done and the highest yield for **49a** was obtained with $Pd(OAc)_2$ (Table 3, entries 1, 5-9). The reaction was then repeated in different solvents such as toluene, DCE and DMF but DMSO was found to be the best medium for the present Pd-catalyzed site selective C-H amination (Table 3, entries 1, 10-12). An increase in the loading of the catalyst or the equivalents of the reoxidant did not have a positive influence on the yield of 5a (Table 3, entries 13-14). The Pd-catalyzed site selective C-H amination of **47a** was attempted in the absence of reoxidant $Cu(OAc)_2$, and the formation of **49a** was not observed in this case. A decrease in the reaction time from 36 to 12 h slightly improved the yield of **49a** to 54% (Table 3, entry 15). Finally, a reaction was repeated by increasing the temperature to 150 ^oC, and this attempt also proved to be futile. From all these

reaction mixtures, we could observe the formation of the product from dual C-H activation in trace amounts.

Table 3: Optimisation studies with **47a** towards site selective C-H amination[a]



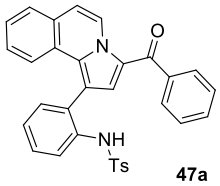
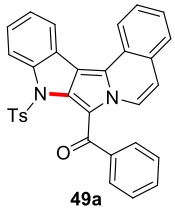
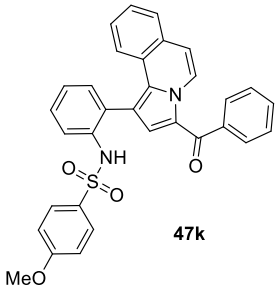
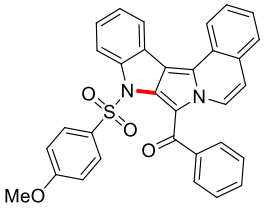
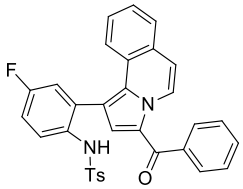
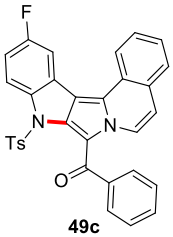
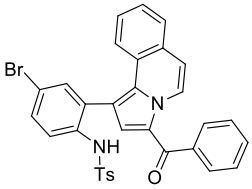
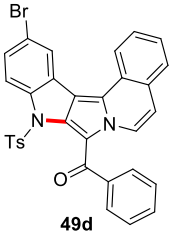
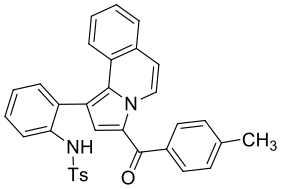
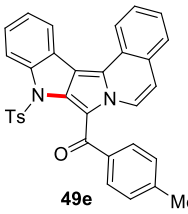
47a **49a**

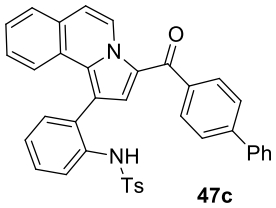
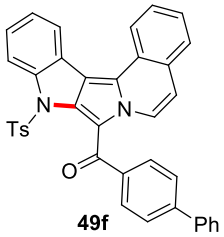
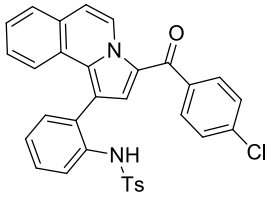
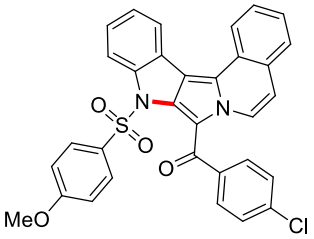
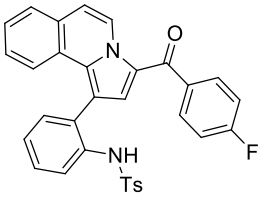
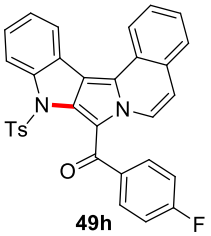
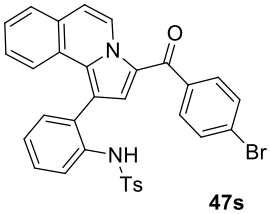
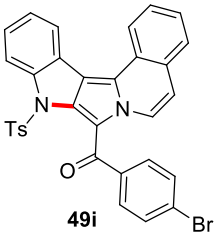
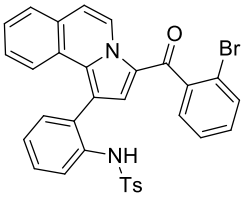
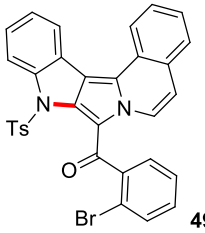
Entry	Catalyst	Reoxidant	Solvent	Yield of **49a** (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	49
2	$Pd(OAc)_2$	$Cu(OTf)_2$	DMSO	NR
3	$Pd(OAc)_2$	$CuCl_2$	DMSO	NR
4	$Pd(OAc)_2$	Benzoquinone	DMSO	NR
5	$PdCl_2$	$Cu(OAc)_2$	DMSO	traces
6	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$	DMSO	42
7	$Pd(tfa)_2$	$Cu(OAc)_2$	DMSO	traces
8	$Pd(dba)_2$	$Cu(OAc)_2$	DMSO	45
9	$[Pd(allyl)Cl]_2$	$Cu(OAc)_2$	DMSO	traces
10	$Pd(OAc)_2$	$Cu(OAc)_2$	Toluene	nr
11	$Pd(OAc)_2$	$Cu(OAc)_2$	DCE	nr
12	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	20
13[b]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	25
14[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	30
15	$Pd(OAc)_2$	-	DMSO	NR
16[d]	**$Pd(OAc)_2$**	**$Cu(OAc)_2$**	**DMSO**	**54**
17[e]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	20

Reaction conditions: [a] **47a** (1.0 equiv., 0.10 mmol), Pd-catalyst (5 mol%), reoxidant (1.0 equiv.), solvent (1.0 mL), 120 °C, 36 h; [b] $Pd(OAc)_2$ (10 mol%); [c] $Cu(OAc)_2$ (2.0 equiv.); [d] 12 h; [e] 150 °C, 12 h.

With the optimized conditions in hand [$Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv.), DMSO, O_2, 120 ^oC, 12 h], we explored the scope of the reaction using different pyrrolo[2,1-*a*]isoquinolines, the results of which are summarized in Table 4.

Table 4. Pd-catalyzed C-H amination of pyrrolo[2,1-*a*]isoquinolines towards indolopyrrolo[2,1- *a*]isoquinolines[a]

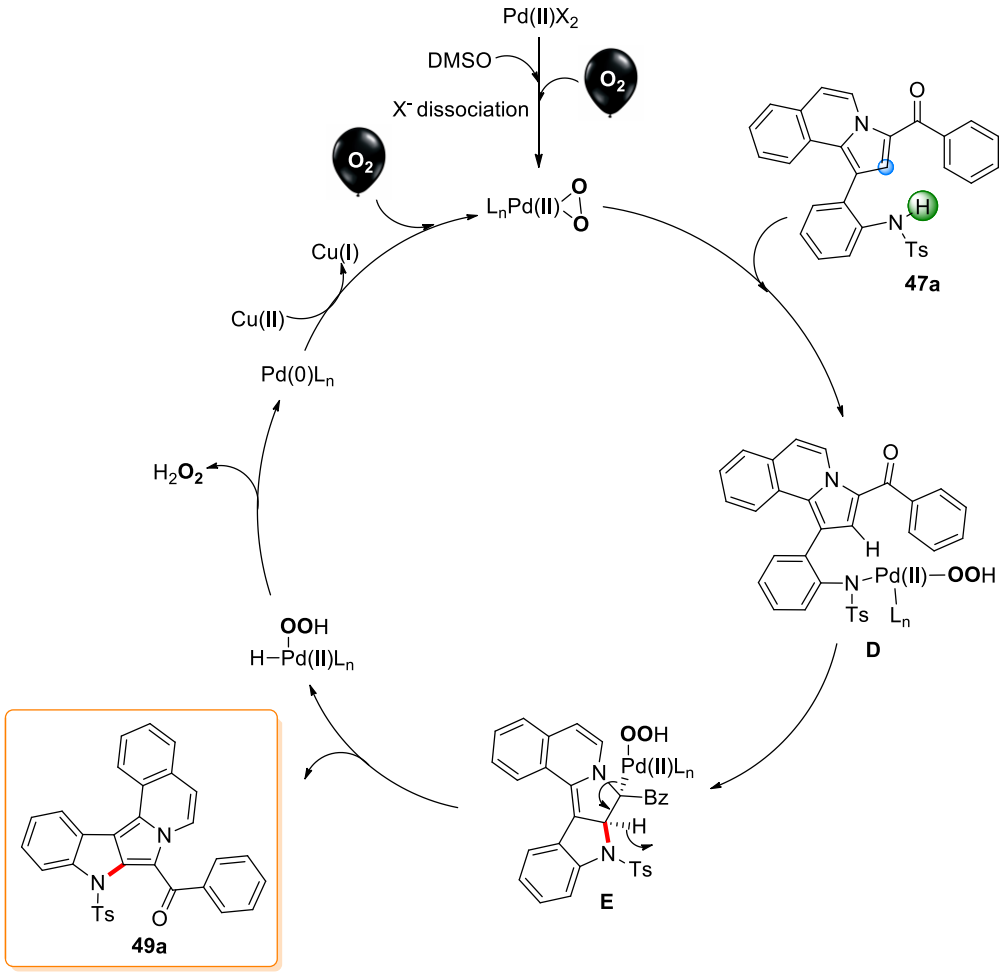
Entry	Pyrrolo[1,2-*a*]isoquinoline	Product	Yield
1	 **47a**	 **49a**	54, 49[b]
2	 **47k**	 **49b**	53
3	 **47o**	 **49c**	50
4	 **47r**	 **49d**	49
5	 **47b**	 **49e**	45

Entry	Pyrrolo[1,2-*a*]isoquinoline	Product	Yield
6	 **47c**	 **49f**	44
7	 **47e**	 **49g**	40
8	 **47d**	 **49h**	39
9	 **47s**	 **49i**	40
10	 **47g**	 **49j**	41

[a]Reaction conditions: **47** (1.0 equiv., 100 mg), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv.), O_2 (1.0 atm), DMSO (0.1 M), 120 °C, 12 h, formation of indenopyrrolo[2,1-a]isoquinolines **48** in trace amounts detected in all cases. [b]From 1.0 g of **47a**.

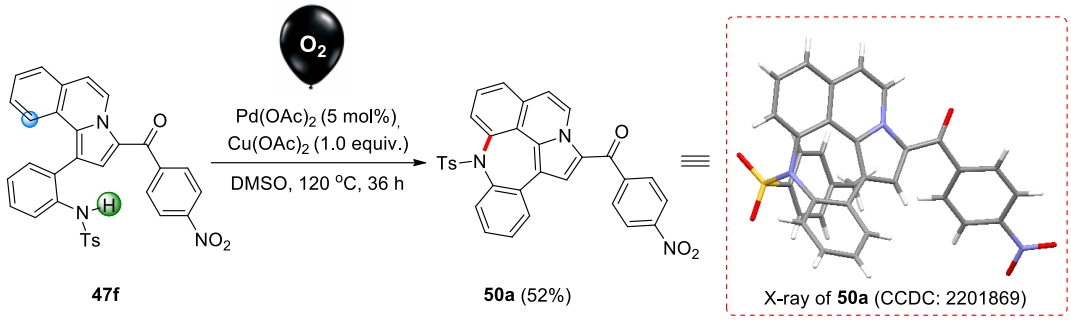
First, we repeated the Pd-catalyzed C-H amination with **47a**, from which the product **49a** was obtained in 54% yield. Then, we changed the substituent at the *N*-atom from Ts- to 4-OMe-C_6H_4-SO_2- and from the reaction, the corresponding indolo-pyrrolo[2,1-*a*]isoquinoline **49b** was isolated in 53% yield (Table 4). We could synthesize indole fused pyrrolo[2,1-*a*]isoquinolines **49c** and **49d** with halogens such as F and Br on the indole ring in satisfactory yields (Table 4). Next, we evaluated the variations in substitutions on the benzoyl group attached to the pyrrole ring. The reaction was found to be compatible with electronically diverse functionalities at the para position, including electron donating methyl (**49e**) and phenyl groups (**49f**). In addition, halogens such as F, Cl and Br on different positions of the benzoyl group were also tolerated under these reaction conditions, affording the products **49g** to **49j** (Table 4). In all the above cases, we could observe the formation of indenopyrrolo[2,1-*a*]isoquinolines in trace amounts. The reaction of 1.0 g of **47a** afforded the product indolo-pyrrolo[2,1-*a*]isoquinoline **49a** in 49 % yield (Table 4).

This oxygen-induced chemoselective synthesis of indolo-pyrrolo[2,1-*a*]isoquinoline **49** made us believe that oxygen might be involved from the start of the catalytic cycle. We hypothesize that initially DMSO interacts with the catalyst $Pd(OAc)_2$ to form a $Pd(0)(DMSO)_n$ species as per the theoretical investigations carried out by Zierkiewicz and Privalov.[30] Stahl and co-workers have investigated in detail on the Pd-catalyzed aerobic oxidations promoted by ligands.[31] By following the literature precedents,[32] we believe that $Pd(0)(DMSO)_n$ is then oxidized by oxygen to form the active η^2-peroxo-Pd(II) species. We consider that the presence of oxygen forces the reaction to take a Wacker-like pathway, as proposed by Buchwald and Monguchi for the oxygen promoted Pd-catalyzed synthesis of carbazoles.[29, 33] In this line, the complexation of η^2-peroxo-Pd(II) intermediate to the *N*-centre in **3a** takes place, generating the amide **D**. Next, a Wacker-like addition of the Pd-species across the pyrrole double bond will give rise to the intermediate **E**. A β-hydride elimination then happens in **E**, releasing the indolo-pyrrolo[2,1-*a*]isoquinoline **49** and H-Pd(II)Ln-OOH moiety. Reductive elimination happens in H-Pd(II)Ln-OOH, releasing the $Pd(0)L_n$ and H_2O_2. The $Pd(0)L_n$ is then reoxidized by $Cu(OAc)_2$ and O_2 to continue the catalytic cycle (Scheme 3B.25).



Scheme 3B.25 Plausible mechanism for the O_2 induced Pd-catalyzed C-H amination for synthesis of *N*-Ts-indolopyrrolo[2,1-*a*]isoquinolines [X = OAc, L = DMSO]

We came across a serendipitous observation of the activation of C-H bond in the isoquinoline ring (site-3, Scheme 3B.21) in **47f** during the generality studies of Pd-catalyzed C-H amination. The reaction of appropriately functionalized 5-(4-nitro benzoyl)-pyrrolo[2,1-*a*]isoquinolines **47f** under the optimized conditions for O_2 promoted Pd-catalyzed C-H amination furnished tetra-ring-fused azepine **50a** in 52% yield. The structure of **50a** was established by various spectroscopic analyses and further confirmed by single crystal X-ray analysis (Scheme 3B.26). We observed that the reaction does not proceed further after 36 h, and from this reaction mixture, we could recover unreacted **47f**.



Scheme 3B.26 Pd-catalyzed site-selective C-H activation towards tetra-ring-fused azepine **50a**

In the ^{1}H NMR spectrum, aromatic protons were found to resonate in the region δ 9.26-6.61 ppm. The proton on the isoquinolium ring attached near to the N atom (a) resonated at 9.25 ppm as a doublet. The singlet observed at δ 7.10 (b) was attributed to the proton of the pyrrole ring. The methyl protons of tosyl group resonated as singlet at δ 2.06 ppm. The ^{1}H NMR spectrum of the compound is shown in figure 5.

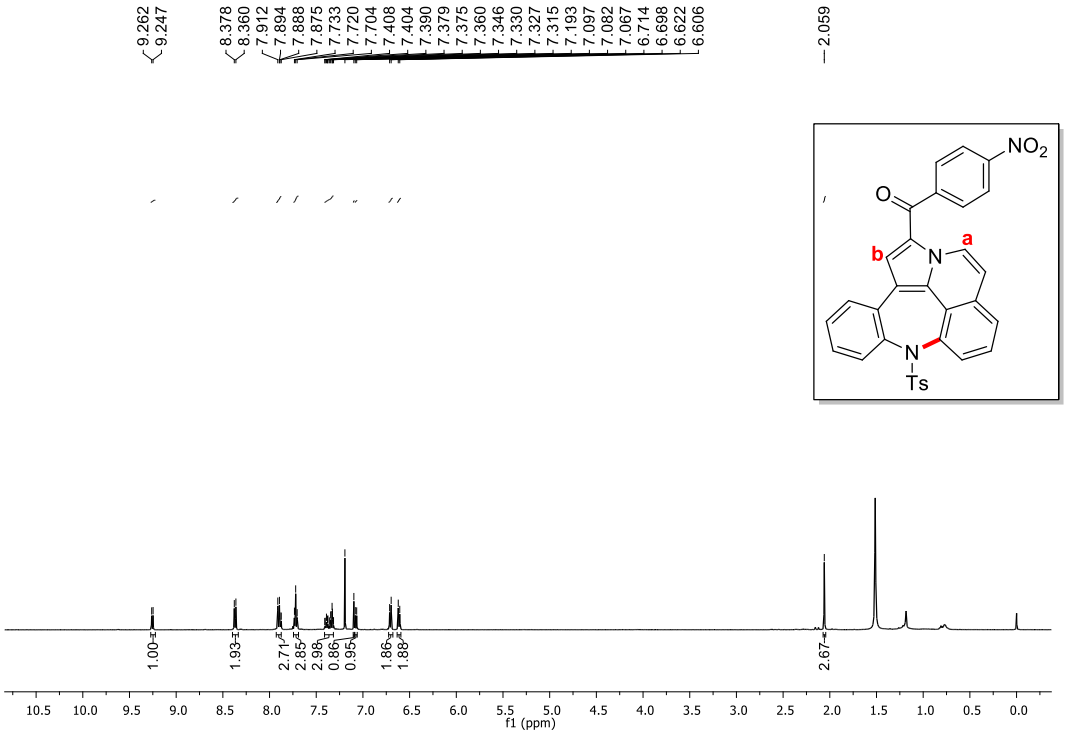


Figure 5. ^{1}H NMR spectrum of **50a**

In the ^{13}C spectrum (Figure 6), the aromatic carbons resonated in the region δ 182.9-113.8 ppm. The carbonyl carbon resonated at δ 182.9 ppm (a). The methyl carbon of the tosyl group

showed a peak at δ 21.3 ppm. All other peaks in the ^{1}H and ^{13}C NMR were in good agreement with the assigned structure.

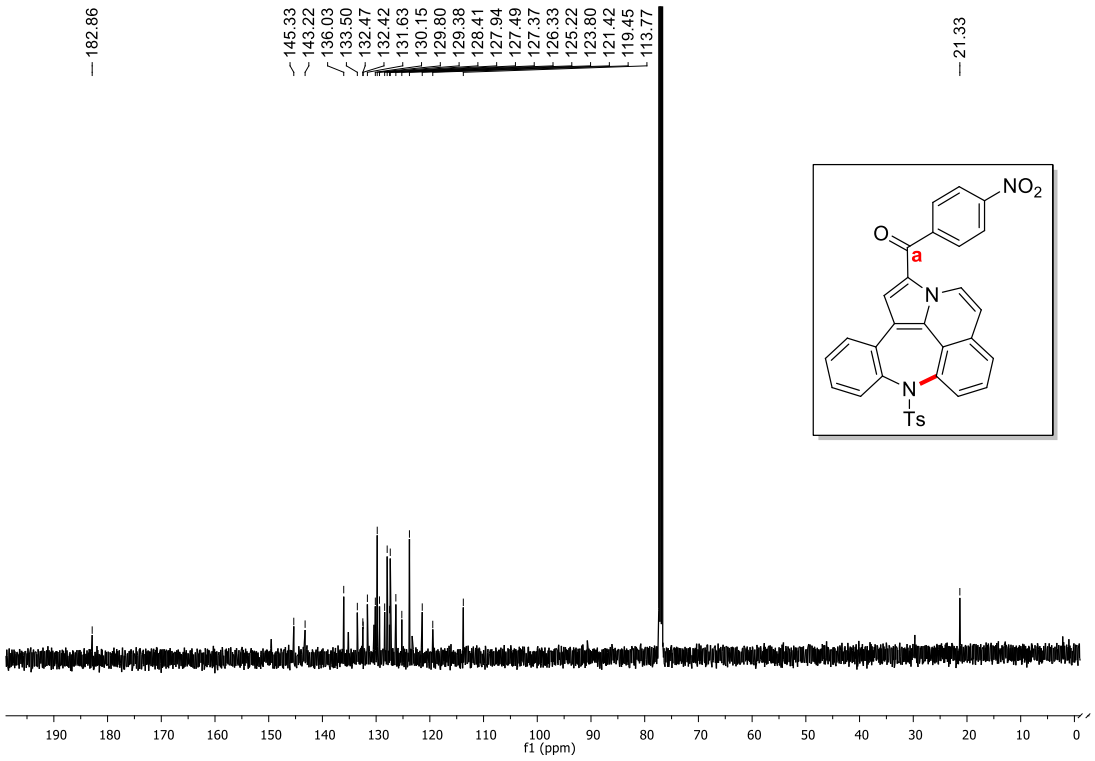
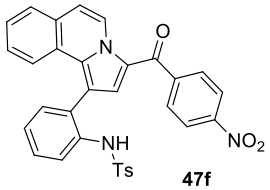
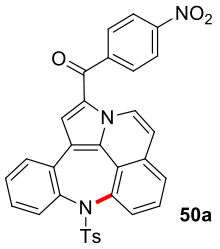
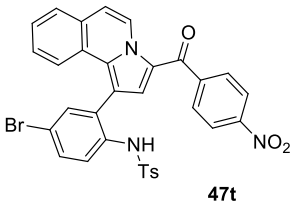
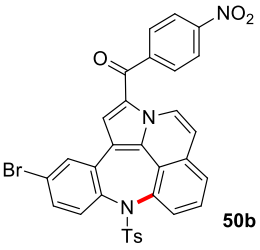
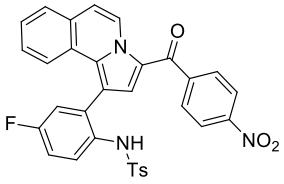
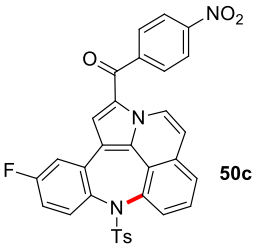
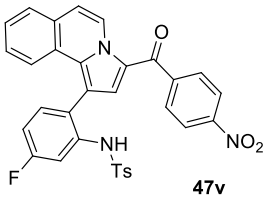
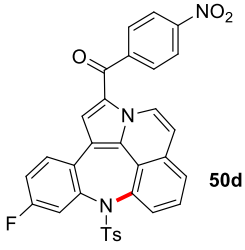
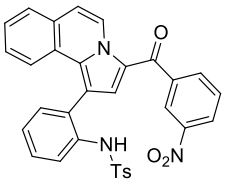
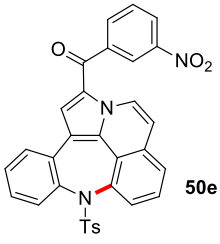


Figure 6. ^{13}C NMR spectrum of **50a**

We were excited to observe the formation of this multiring fused azepine scaffold, and we went on to explore the scope of the reaction by starting from different 5-benzoyl-pyrrolo[2,1-*a*]isoquinolines with NO_2-group on the phenyl ring (Table 5). With this methodology, we could introduce halogens such as Br and F on the fused benzene ring, thereby generating multiring fused azepines **50b**, **50c** and **50d** in moderate yields. Moreover, changing the nitro group to the meta position of the benzene ring in the benzoyl substituent also gave a positive result, and we isolated the corresponding product **50e** in 51% yield. As mentioned above, we could recover unreacted starting compounds in all cases.

Table 5. Pd-catalyzed C-H amination of pyrrolo[2,1-*a*]isoquinolines towards multiring fused azepines[a]

Entry	Pyrrolo[1,2-*a*]isoquinoline	Product	Yield
1	 **47f**	 **50a**	52
2	 **47t**	 **50b**	50
3	 **47u**	 **50c**	53
4	 **47v**	 **50d**	45
5	 **47w**	 **50e**	51

[a]Reaction conditions: **47** (1.0 equiv., 100 mg), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv.), O_2 (1.0 atm), DMSO (0.1 M), 120 °C, 36 h, and unreacted starting compounds were recovered in all cases.

The factors influencing the site selective C-H functionalization towards different fused N-heterocycles were then analyzed. The single crystal X-ray structures of **47a** and **47f** (Figure 7) and density functional theory calculations at the B3LYP-D3/6-31G(d,p)[34] level showed that the orientation of tosylamine group, C-H bond electron density at the sites 1 and 3 and the thermodynamic stability of possible products will be decisive in the site selective C-H amination.

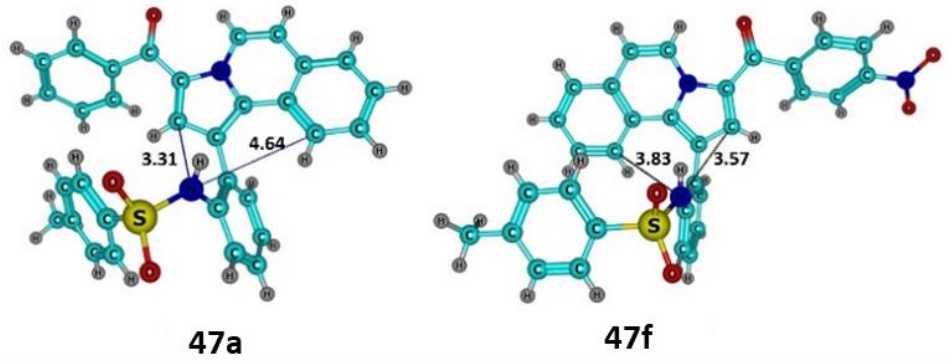


Figure 7. X-ray structures of **47a** (CCDC: 2201867) and **47f** (CCDC: 2174937). [N-C distances are given in Å]

The X-ray structure of **47a** shows the closeness of *N*-centre to site-1 (3.31 Å) compared to site-3 (4.64 Å). Therefore, the binding of $Pd(OAc)_2$ to nitrogen would lead to the C-H activation at site-1. It can further proceed to the C-H activation of phenyl ring (site-2) forming **48a** which is thermodynamically more stable than the possible C-H aminated products (Figure 8).

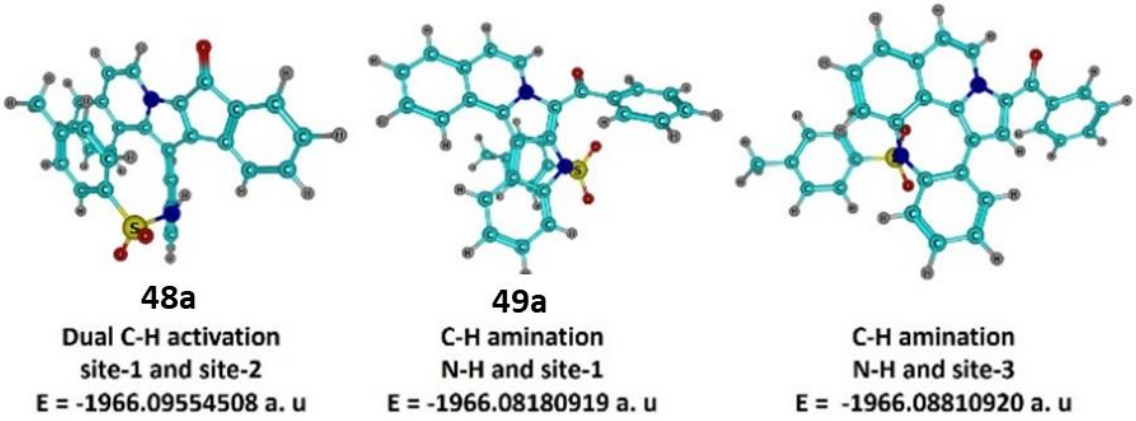


Figure 8. Optimized structures of the possible C-H activation products of **47a** along with energy values

Binding of oxygen to $Pd(OAc)_2$ would hinder the phenyl C-H activation and results in C-H amination to form **49a**. In the case of **47f**, dual C-H activation product is thermodynamically more stable than the possible C-H amination products and therefore **48f** forms (Figure 9). Binding of oxygen to Pd center hinders the activation of phenyl C-H (site-2) and the isoquinoline C-H undergoes activation to form **50a** albeit N is slightly closer to site-1 (3.57 Å) than site -3 (3.83 Å). This can be accounted to the higher electron density at site-3 and the stability of **49a** (more stable than site -1 C-H aminated product by 3 kcal/mol). Molecular electrostatic potential at the carbon nucleus on site -1 is -14.74153 a. u while that at site -3 is -14.74500 a. u suggests a higher electron density at site-3 than site-1.[35]

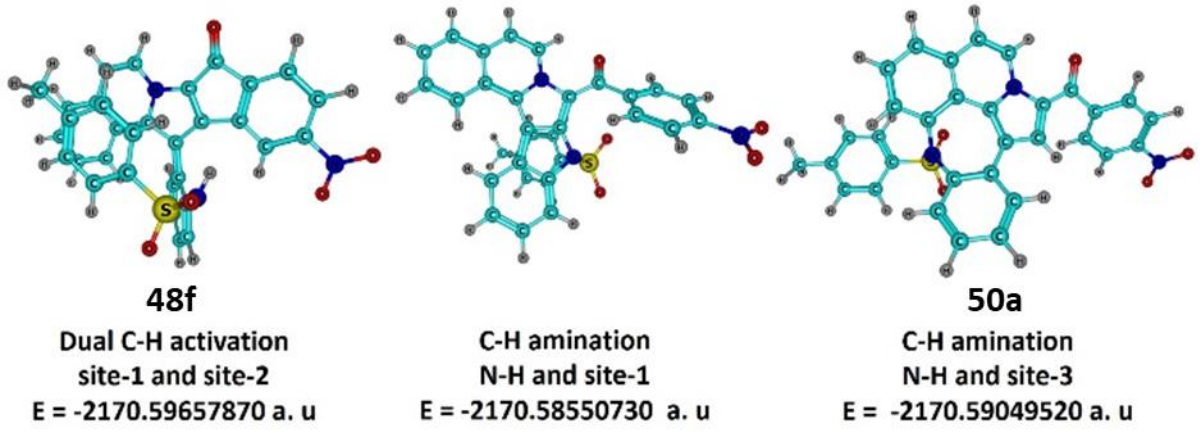


Figure 9. Optimized structures of the possible C-H activation products of **47f** along with energy values.

3B.5 Conclusions

To conclude, we have unraveled an interesting Pd-catalyzed site selective C-H functionalization towards multiring fused *N*-heterocycles. These observations were made on 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline scaffold, where we could identify three sites for C-H functionalization and a *N*-centre which could participate in C-H amination. The experimental and theoretical investigations have shown that there is a preference for Pd-catalyzed cross dehydrogenative coupling towards 8*H*-indeno-pyrrolo[2,1-*a*]isoquinolinone derivatives. Then during our attempts for selective C-H amination, we came across a unique and previously unknown O_2 induced chemoselectivity forcing the formation of 9*H*-indolo-pyrrolo[2,1-*a*]isoquinoline scaffold over the CDC product. We believe that this selectivity is induced by

O_2 which gets incorporated in the active Pd-species driving the reaction to take Wacker-type pathway leading to C-H amination When we tried the Pd-catalyzed C-H amination with a substrate bearing a NO_2-group on the benzoyl moiety of starting substrate, we found that the C-H amination was taking place preferentially at the isoquinoline ring. This result can be attributed to the higher electron density at the reactive centre on isoquinoline ring and also to stability of multiring fused benzazepine in comparison with the pentacene regioisomer. Currently we are investigating the reaction pathway in detail both experimentally and theoretically and also are trying to apply the site selectivity in similar scaffolds.

3B.6 Experimental section

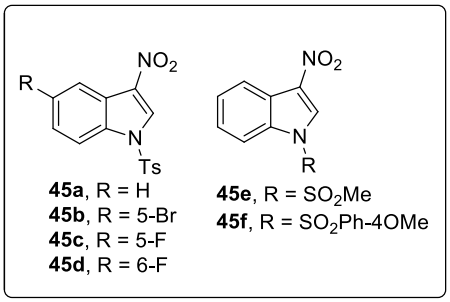
3B.6.1 General experimental methods: All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets precoated with silica gel containing fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using neutral alumina, silica gel, and mixtures of ethyl acetate−hexanes for elution.Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer FT-IR spectrometer. Nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX-500 (500 MHz for ^{1}H NMR, 125 MHz for $^{13}C\{^1H\}$ NMR). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (double doublet); m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra ($^{13}C\{^1H\}$ NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). Mass spectra were recorded under ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer. The diffraction data of single crystals were collected on a Bruker Apex-II diffractometer using graphite monochromated Mo-Kα radiation. The data was processed with the SMART software suite. The structure solution was carried out by direct methods, and the refinements were performed by full-matrix least-squares on F2 using the SHELXTL suite of programs. Structural

assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments.

3B.6.2 Synthesis and characterization

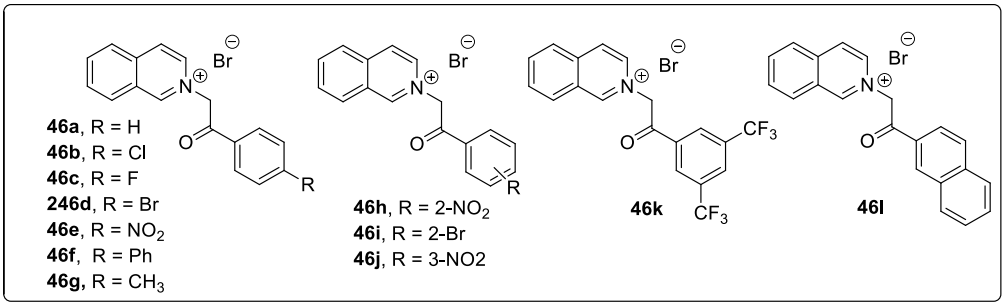
Procedure for the synthesis of electrophilic benzannulated heterocycles

3-Nitroindoles (**45a-45f**) were prepared by following a literature report.[36]



Procedure for the synthesis of isoquinolinium salts

All isoquinolinium salts (**46a-46l**) were prepared by following a previously reported procedure.[37] To isoquinoline dissolved in acetone at 0 °C, the α-halocarbonyl compound was added and the mixture was stirred at room temperature for a period of time. After the completion of the reaction, the precipitate formed was filtered and washed with diethyl ether to get the pure product.

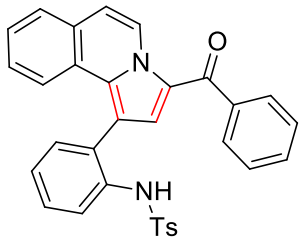


Experimental procedure for the reaction between 3-nitro-*N*-tosyl indole and isoquinolinium salt: A mixture of 3-nitro-*N*-tosyl indole (100 mg, 1.0 equiv.), isoquinolinium salt (1.5 equiv.) and KOH (4.0 equiv.) was weighed into a dry reaction tube. Dry DMF was added and the reaction mixture was allowed to stir at room temperature. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was

removed under vacuum. The residue was then purified by column chromatography (neutral alumina, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

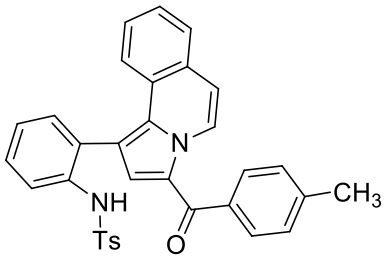
Synthesis and characterization of pyrrolo[2,1-a]isoquinolines

N-(2-(3-benzoylpyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methyl benzene sulfonamide (47a). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **46a** (156 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 4 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47a** as a yellow solid (111 mg, 68%).

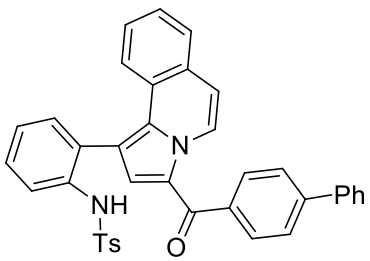
	**Mp**: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.59 (d, *J* = 7.5 Hz, 1H), 7.78-7.76 (m, 3H), 7.64 (d, *J* = 8 Hz, 1H), 7.54-7.52 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.42-7.36 (m, 2H), 7.24 (s, 1H), 7.21- 7.19 (m, 2H), 7.15-7.11 (m, 3H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8 Hz, 2H), 6.65 (s, 1H), 6.46 (s, 1H), 2.07 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 185.4, 143.7, 140.2, 136.0, 135.7, 132.7, 131.7, 131.5, 129.6, 129.5, 129.3, 129.2, 128.4, 128.0, 127.8, 127.2, 127.0, 127.0, 126.8, 125.5, 125.0, 124.6, 124.0, 123.4, 120.5, 114.3, 113.1, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{25}N_2O_3S$ 517.1580, found 517.1599.

4-methyl-N-(2-(3-(4-methylbenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)benzene sulfonamide (47b). The reaction was performed according to general procedure with 3-nitro-N-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-oxo-2-(p-tolyl)ethyl)isoquinolin-2-ium bromide **46g** (164 mg, 0.48 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47b** as a pale yellow solid (128 mg, 75%).

	Mp: 230 - 232 °C.

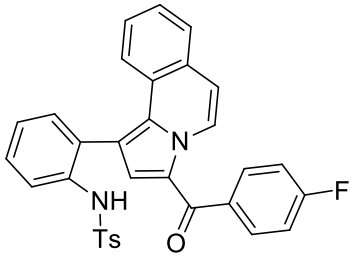
	**^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.56 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.26 – 7.24 (m, 4H), 7.21 (brs, 1H), 7.15 – 7.10 (m, 3H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.62 (s, 1H), 6.45 (s, 1H), 2.40 (s, 3H), 2.06 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 185.3, 143.7, 142.2, 137.4, 135.9, 135.6, 132.5, 131.7, 129.5, 129.4, 129.3, 129.1, 128.0, 127.8, 127.4, 127.0, 126.6, 125.5, 125.0, 124.1, 123.3, 120.6, 114.2, 112.9, 21.6, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{33}H_{27}N_2O_3S$ 531.1737, found 531.1750.

N-(2-(3-([1,1'-biphenyl]-4-carbonyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methyl benzenesulfonamide (47c). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)isoquinolin-2-ium bromide **46f** (192 mg, 0.48 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47c** as a pale yellow solid (142 mg, 75%).

	**Mp**: 138 - 140 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.59 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.64 (m, 3H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.44 – 7.33 (m, 5H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.23 – 7.21 (m, 1H), 7.16 – 7.12 (m, 3H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 6.70 (s, 1H), 6.47 (s, 1H), 2.00 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 185.0, 144.4, 143.8, 140.0, 138.9, 135.7, 131.7, 129.8, 129.3, 129.0, 128.1, 127.2,

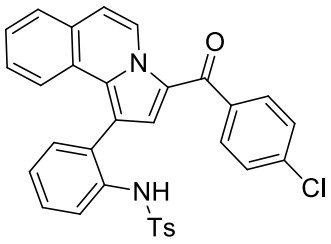
	127.1, 127.04, 127.02, 126.8, 125.5, 125.0, 124.6, 124.1, 123.4, 120.6, 114.4, 113.2, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{38}H_{28}N_2NaO_3S$ 615.1713, found 615.1743.

N-(2-(3-(4-fluorobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (47d). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-(4-fluorophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46c** (164 mg, 0.48 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47d** as a pale yellow solid (116 mg, 68%).

	**Mp**: 210 - 212 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.54 (d, *J* = 7.5 Hz, 1H), 7.82 – 7.79 (m, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.21 – 7.19 (m, 1H), 7.14 (t, *J* = 7.0 Hz, 5H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.64 (s, 1H), 6.46 (s, 1H), 2.10 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 183.8, 143.7, 136.3, 136.0, 135.7, 132.8, 131.7, 131.61, 131.54, 129.6, 129.5, 129.3, 128.1, 127.9, 127.1, 127.0, 126.6, 125.4 (d, *J* = 255 Hz), 125.0, 124.6, 123.8, 120.5, 115.57, 115.39, 114.4, 113.2, 21.4 ppm. **^{19}F NMR (470 MHz, CDCl3):** δ -107.6 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{23}FN_2NaO_3S$ 557.1306, found 557.1329.

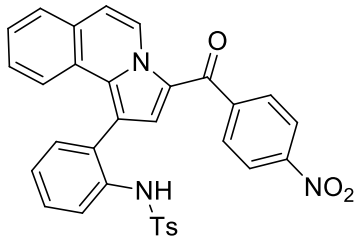
*N-(2-(3-(4-chlorobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (**47e**).* The reaction was performed according to general procedure

with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-(4-chlorophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46b** (172 mg, 0.47 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47e** as a yellow solid (127 mg, 73%).

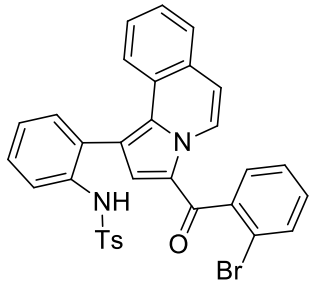
	**Mp**: 215−218 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.54 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8 Hz, 1H), 7.43-7.36 (m, 4H), 7.26 (d, J = *8* Hz, 2H), 7.20-7.12 (m, 4H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 2H), 6.60 (s, 1H), 6.44 (s, 1H), 2.11 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 183.9, 143.8, 138.5, 137.8, 136.0, 135.7, 133.0, 131.7, 130.5, 129.6, 129.3, 128.7, 128.2, 127.9, 127.1, 127.0, 126.7, 125.4, 125.0, 124.5, 123.7, 123.4, 120.5, 114.5, 113.3, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{23}ClN_2NaO_3S$ 573.1010, found 573.1030

*4-methyl-N-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)benzenesulfonamide **(47f).*** The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46e** (177 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47f** as a bright yellow solid (134 mg, 75%).

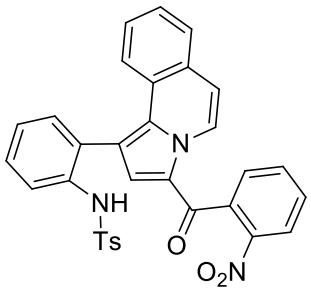
	Mp: 199−203 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.61 (d, *J* = 7.5 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8 Hz, 1H), 7.68 (d, *J* = 8 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8 Hz, 2H), 7.20-7.19

	(m, 2H), 7.16-7.11 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8 Hz, 2H), 6.73 (s, 1H), 6.45 (s, 1H), 2.12 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 182.7, 149.3, 145.6, 143.8, 136.1, 135.7, 133.7, 131.7, 129.9, 129.8, 129.4, 128.5, 128.1, 127.3, 127.2, 127.0, 126.5, 125.4, 124.9, 124.4, 124.6, 123.6, 123.2, 120.1, 115.1, 114.0, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{23}N_3NaO_5S$ 584.1250, found 584.1278.

*N-(2-(3-(2-bromobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methyl benzenesulfonamide (**47g**)*. The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-(2-bromophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46i** (193 mg, 0.48 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47g** as a pale yellow solid (137 mg, 72%).

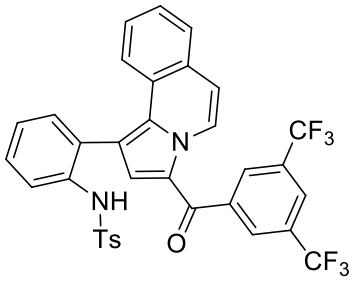
	**Mp**: 205 - 206 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.80 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.77 – 7.73 (m, 2H), 7.53 – 7.50 (m, 2H), 7.48 – 7.38 (m, 5H), 7.29 – 7.28 (m, 1H), 7.25 – 7.13 (m, 4H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.64 (s, 1H), 6.58 (s, 1H), 2.19 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 184.2, 143.6, 141.6, 135.9, 135.6, 133.3, 131.7, 130.9, 129.6, 129.3, 129.2, 127.9, 127.4, 127.2, 127.1, 127.0, 125.6, 124.8, 124.5, 123.6, 120.3, 114.9, 113.8, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{24}BrN_2O_3S$ 595.0686, found 595.0702.

*4-methyl-N-(2-(3-(2-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)benzenesulfonamide (**47h**)*. The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-(2-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46h** (177 mg, 0.48 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47h** as a yellow solid (129 mg, 72%).

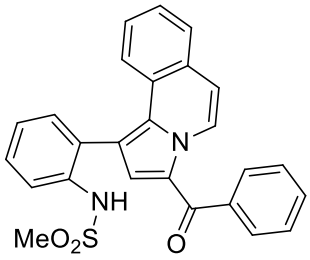
	**Mp**: 140 - 142 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.63 (d, *J* = 7.5 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.73 – 7.60 (m, 6H), 7.43 – 7.40 (m, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.14 – 7.13(d, *J* = 7.0 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 6.52 (s, 1H), 6.47 (s, 1H), 2.10 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 181.6, 147.2, 143.5, 135.2, 136.1, 135.5, 133.7, 133.5, 131.8, 130.5, 129.7, 129.61, 129.57, 129.3, 128.3, 127.9, 127.1, 127.0, 126.7, 125.6, 125.4, 124.9, 124.6, 124.4, 123.6, 123.5, 120.6, 115.0, 113.9, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{23}N_3NaO_5S$ 584.1251, found 584.1271.

*N-(2-(3-(3,5-bis(trifluoromethyl)benzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methyl benzenesulfonamide (**47i**)*. The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-(3,5-bis(trifluoromethyl)phenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46k** (220 mg, 0.48 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47i** as a yellow solid (146 mg, 70%).

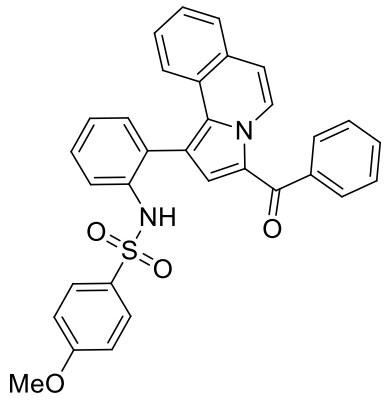
	Mp: 125 - 128 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.57 (d, *J* = 7.5 Hz, 1H), 8.21 (s, 2H), 8.01 (s, 1H), 7.68 (t, *J* = 8.5 Hz, 2H), 7.44

	(t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.21 – 7.19 (m, 2H), 7.15 – 7.13 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.70 (s, 1H), 6.45 (s, 1H), 2.09 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 181.5, 143.7, 142.1, 136.1, 135.7, 133.0 (q, *J* = 228 Hz), 131.84, 131.77, 129.8, 129.3, 129.0, 128.6, 128.2, 127.2, 127.0, 126.9, 126.3, 125.3, 124.9, 124.7, 124.3, 123.6, 123.0, 120.1, 115.2, 114.3, 21.4 ppm. **^{19}F NMR (470 MHz, CDCl3):** δ -62.8 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{34}H_{23}F_6N_2O_3S$ 653.1328, found 653.1355.

N-(2-(3-benzoylpyrrolo[2,1-a]isoquinolin-1-yl)phenyl)methanesulfonamide ***(47j).*** The reaction was performed according to general procedure with 1-(methylsulfonyl)-3-nitro-1H-indole **45e** (100 mg, 0.42 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **46a** (207 mg, 0.63 mmol) and KOH (94 mg, 1.68 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47j** as a pale yellow solid (126 mg, 68%).

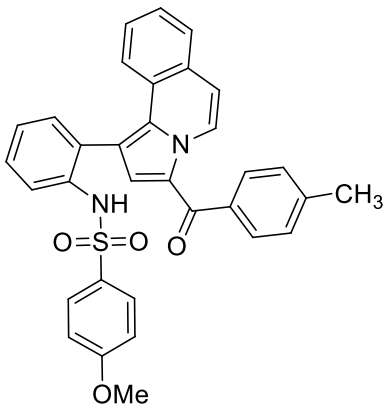
	**Mp**: 179 - 181 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.69 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 7.0 Hz, 2H), 7.79 – 7.74 (m, 2H), 7.58 – 7.48 (m, 6H), 7.43 – 7.41 (m, 1H), 7.31 – 7.27 (m, 2H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.19 (s, 1H), 6.40 (s, 1H), 2.82 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 185.6, 140.1, 136.0, 132.2, 131.5, 129.8, 129.1, 128.3, 127.9, 127.3, 127.0, 125.7, 124.8, 124.4, 123.2, 118.6, 114.4, 113.0, 39.9 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{26}H_{21}N_2O_3S$ 441.1267, found 441.1278.

*N-(2-(3-benzoylpyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide (**47k**).* The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1H-indole **45f** (100 mg, 0.30 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **46a** (148 mg, 0.45 mmol) and KOH (67 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47k** as a pale yellow solid (83 mg, 52%).

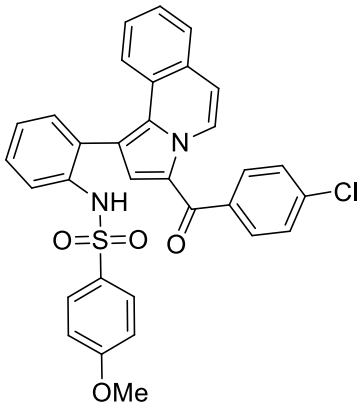
	**Mp**: 228 - 230 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.59 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.74 (m, 3H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.0 Hz, 1H), 7.46 – 7.43 (m, 2H), 7.41 – 7.35 (m, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.21 (brs, 1H), 7.13 – 7.10 (m, 3H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.78 (s, 1H), 6.50 (s, 1H), 6.42 (d, *J* = 8.5 Hz, 2H), 3.60 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 185.5, 162.3, 140.1, 135.7, 131.8, 131.5, 130.5, 129.5, 129.1, 128.5, 128.4, 128.0, 127.8, 127.0, 126.9, 125.5, 124.9, 123.4, 120.3, 114.4, 113.8, 113.2, 55.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{25}N_2O_4S$ 533.1530, found 533.1559.

*4-methoxy-N-(2-(3-(4-methylbenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)benzene sulfonamide (**47l**).* The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1H-indole **45f** (100 mg, 0.30 mmol), 2-(2-oxo-2-(p-tolyl)ethyl)isoquinolin-2-ium bromide **46g** (155 mg, 0.45 mmol) and KOH (68 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47l** as a pale yellow solid (115 mg, 70%).

	Mp: 200 - 202 °C.

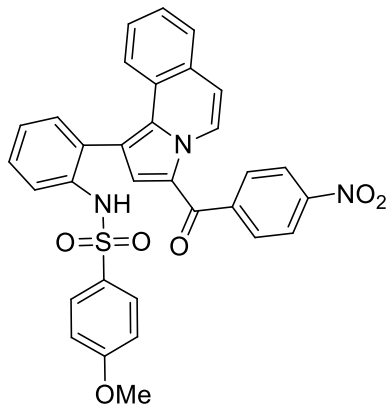
	**^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.65 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.28 (m, 1H), 7.23 – 7.19 (m, 3H), 7.14 – 7.11 (m, 1H), 6.85 (s, 1H), 6.58 (s, 1H), 6.51 (d, *J* = 9.0 Hz, 2H), 3.70 (s, 3H), 2.06 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 185.3, 162.9, 142.2, 137.4, 135.7, 132.4, 131.8, 130.5, 129.4, 129.3, 129.1, 129.0, 127.9, 127.8, 127.2, 127.0, 126.6, 125.5, 124.9, 124.6, 123.3, 120.4, 114.2, 113.8, 113.0, 55.3, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{33}H_{26}N_2NaO_4S$ 569.1505, found 569.1522.

*N-(2-(3-(4-chlorobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methoxy benzenesulfonamide (**47m**)*. The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1H-indole **45f** (100 mg, 0.30 mmol), 2-(2-(4-chlorophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46b** (164 mg, 0.45 mmol) and KOH (68 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47m** as a yellow solid (122 mg, 72%).

	**Mp**: 145 - 147 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS**): δ 9.55 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.37 (m, 4H), 7.30 (d, *J* = 9.0 Hz, 2H), 7.21 – 7.19 (m, 1H), 7.15 – 7.13 (m, 3H), 7.07 – 7.04 (m, 1H), 6.67 (s, 1H), 6.44 (d, *J* = 9.0 Hz, 3H), 3.63 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 183.9, 163.0, 138.4, 137.8, 135.7, 131.7, 130.5, 129.6, 129.1, 128.6, 128.2, 127.9, 127.1, 126.7, 125.4, 125.0, 124.5, 123.4, 120.6, 114.5, 113.8, 113.4, 55.4 ppm.

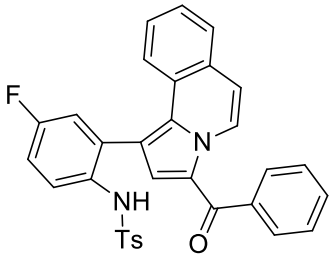
	HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{24}ClN_2O_4S$ 567.1140, found 567.1167.

*4-methoxy-N-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl) benzenesulfonamide (**47n**).* The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1H-indole **45f** (100 mg, 0.30 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46e** (168 mg, 0.45 mmol) and KOH (68 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47n** as a yellow solid (130 mg, 75%).

	**Mp**: 140 - 142 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.61 (d, *J* = 7.5 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.21 – 7.19 (m, 2H), 7.16 – 7.13 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.63 (s, 1H), 6.43 (d, *J* = 8.5 Hz, 2H), 6.38 (s, 1H), 3.63 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 182.8, 162.9, 149.4, 145.6, 135.7, 131.7, 130.6, 129.9, 129.8, 129.1, 128.6, 128.2, 127.3, 127.2, 125.4, 125.1, 124.4, 123.6, 123.5, 120.6, 115.1, 114.1, 113.8, 55.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{23}N_3NaO_6S$ 600.1200, found 600.1225.

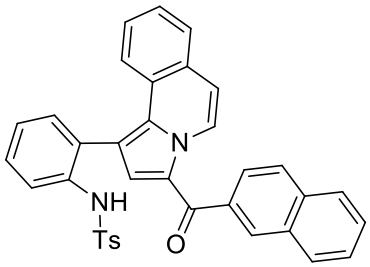
*N-(2-(3-benzoylpyrrolo[2,1-a]isoquinolin-1-yl)-4-fluorophenyl)-4-methylbenzenesulfonamide (**47o**).* The reaction was performed according to general procedure with 5-Flouro-3-nitro-*N*-tosyl indole **45c** (100 mg, 0.30 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **46a** (148 mg, 0.45 mmol) and KOH (67 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column

chromatography (20% ethyl acetate in hexane) to afford the desired product **47r** as a pale yellow solid (83 mg, 52%).

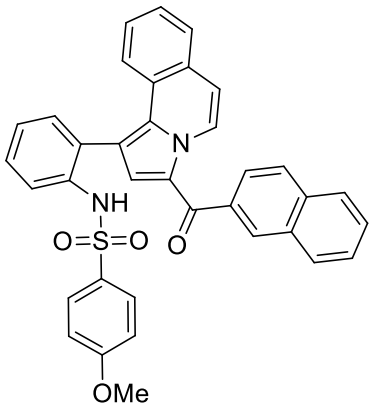
	**Mp**: 200 - 202 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.56 (d, *J* = 7.5 Hz, 1H), 7.77 – 7.74 (m, 3H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.48 – 7.42 (m, 3H), 7.18 – 7.10 (m, 6H), 6.95 – 6.93 (m, 1H), 6.70 (d, *J* = 8.0 Hz, 2H), 6.52 (s, 1H), 6.34 (s, 1H), 2.02 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 185.4, 143.8, 140.0, 135.6, 132.4, 131.7, 130.0, 129.6, 129.3, 129.2, 128.5, 128.3, 128.0, 127.0, 126.4, 126.3 (d, *J* = 223 Hz), 124.3, 124.0, 123.5 (d, *J* = 28.2 Hz), 123.1, 118.4, 118.3, 116.4, 116.3, 114.5, 21.4 ppm. **^{19}F NMR (470 MHz, $CDCl_3$):** δ -116.6 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{24}FN_2O_3S$ 535.1486, found 535.1488.

*N-(2-(3-(2-naphthoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **(47p)***. The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-(naphthalen-2-yl)-2-oxoethyl)isoquinolin-2-ium bromide **46l** (181 mg, 0.48 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47p** as a yellow solid (132 mg, 73%).

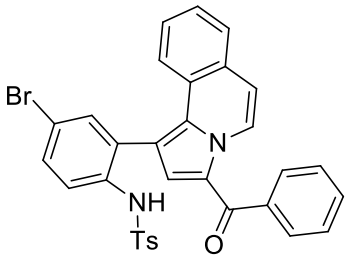
	Mp: 215 - 217 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.60 (d, *J* = 7.5 Hz, 1H), 8.24 (s, 1H), 7.92 – 7.86 (m, 4H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.41 – 7.34 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 3H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.14 – 7.12 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.64 (s, 1H), 6.56 (d, *J* = 8.0 Hz, 2H), 6.49 (s 1H), 1.76 (s, 3H) ppm.

	**$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 185.3, 143.7, 137.5, 135.8, 135.7, 134.9, 132.8, 132.4, 131.8, 129.9, 129.6, 129.5, 129.3, 129.2, 128.3, 128.1, 128.0, 127.8, 127.1, 127.0, 126.9, 125.8, 125.5, 125.0, 124.6, 124.2, 123.4, 120.6, 114.4, 113.2, 21.0 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{36}H_{27}N_2O_3S$ 567.1737, found 567.1751.

*N-(2-(3-(2-naphthoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide **(47q)***. The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1H-indole **45f** (100 mg, 0.30 mmol), 2-(2-(naphthalen-2-yl)-2-oxoethyl)isoquinolin-2-ium bromide **46l** (171 mg, 0.45 mmol) and KOH (68 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47q** as a yellow solid (129 mg, 74%).

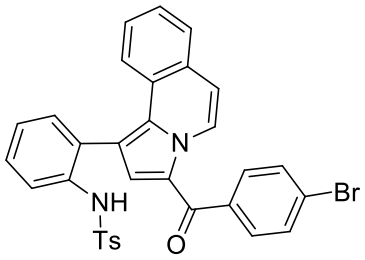
	**Mp**: 185 - 187 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.71 (d, *J* = 7.5 Hz, 1H), 8.37 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.98 – 7.96 (m, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.52 – 7.45 (m, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.21 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.86 (s, 1H), 6.58 (s, 1H), 6.41 (d, *J* = 8.5 Hz, 2H), 3.45 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 185.4, 162.9, 137.4, 135.7, 134.9, 132.7, 132.4, 131.8, 130.4, 129.9, 129.6, 129.5, 129.3, 129.1, 128.3, 128.1, 127.9, 127.8, 127.1, 126.8, 125.6, 125.5, 124.9, 124.6, 124.3, 123.4, 120.5, 114.4, 113.8, 111.3, 55.1 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{36}H_{27}N_2O_4S$ 583.1686, found 583.1713.

*N-(2-(3-benzoylpyrrolo[2,1-a]isoquinolin-1-yl)-4-bromophenyl)-4-methylbenzenesulfonamide (**47r**).* The reaction was performed according to general procedure with 5-Bromo-3-nitro-*N*-tosyl indole **45b** (100 mg, 0.25 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **46a** (125 mg, 0.38 mmol) and KOH (56 mg, 1.00 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47r** as a pale yellow solid (101 mg, 68%).

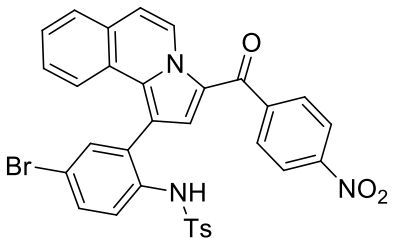
	**Mp**: 265 - 267 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.57 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.67 – 7.65 (m, 2H), 7.54 – 7.49 (m, 1H), 7.48 – 7.42 (m, 4H), 7.36 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.16 – 7.09 (m, 3H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.59 (s, 1H), 6.41 (s, 1H), 2.08 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 185.4, 144.0, 140.0, 135.6, 135.0, 134.3, 132.6, 132.4, 131.7, 129.6, 129.4, 129.3, 129.2, 129.0, 128.4, 128.3, 128.1, 127.2, 127.0, 126.7, 125.5, 124.3, 124.1, 123.2, 122.0, 117.8, 114.5, 111.5, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{24}BrN_2O_3S$ 595.0686, found 595.0656.

*N-(2-(3-(4-bromobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methyl benzenesulfonamide (**47s**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-(4-bromophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46d** (195 mg, 0.48 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47s** as a pale yellow solid (137 mg, 72%).

	Mp: 235 - 237 °C.

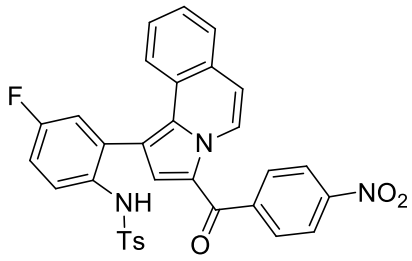
	**^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.55 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 3H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.37 (m, 3H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.0 Hz, 3H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.59 (s, 1H), 6.43 (s, 1H), 2.12 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 184.0, 143.8, 139.0, 135.9, 135.7, 133.1, 131.7, 131.6, 130.7, 129.6, 129.6, 129.3, 128.2, 127.9, 127.1, 127.0, 126.8, 126.3, 125.4, 125.0, 124.5, 123.6, 123.4, 120.5, 114.6, 113.3, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{24}BrN_2O_3S$ 595.0686, found 595.0673.

N-(4-bromo-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4 methylbenzene sulfonamide **(47t).** The reaction was performed according to general procedure with 5-bromo-3-nitro-*N*-tosyl indole **45b** (100 mg, 0.25 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46e** (142 mg, 0.38 mmol) and KOH (57 mg, 1.01 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47t** as a yellow solid (115 mg, 71 %).

	**Mp**: 250−252 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.59 (d, *J* = 7.5 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8 Hz, 2H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 9 Hz, 1H), 7.49-7.46 (m, 2H), 7.34 (s, 1H), 7.28 (s, 1H), 7.21-7.19 (m, 2H), 7.16-7.10 (m, 2H), 6.81 (d, *J* = 7.5 Hz, 2H), 6.69 (s, 1H), 6.42 (s, 1H), 2.14 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 182.8, 149.4, 145.4, 144.0, 135.9, 135.0, 134.3, 133.5, 132.7, 129.9, 129.8, 129.5, 128.7, 128.5, 128.3, 127.3, 127.1, 127.0, 125.4,

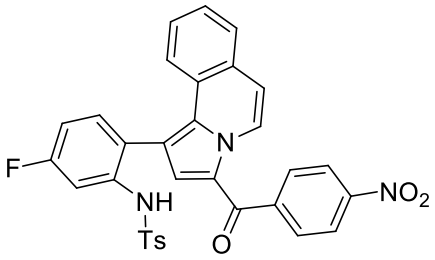
	124.1, 123.6, 123.5, 123.4, 121.5, 117.6, 115.2, 112.4, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{22}BrN_3NaO_5S$ 662.0355, found 662.0370.

*N-(4-fluoro-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (**47u**).* The reaction was performed according to general procedure with 5-Flouro-3-nitro-*N*-tosyl indole **45c** (100 mg, 0.30 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46e** (168 mg, 0.45 mmol) and KOH (67 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47u** as a pale yellow solid (122 mg, 70%).

	**Mp**: 198 - 200 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.60 (d, *J* = 7.5 Hz, 1H), 8.32 (d, *J* = 8.5 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.24 – 7.21 (m, 3H), 7.17 – 7.11 (m, 3H), 6.95 – 6.93 (m, 1H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.65 (s, 1H), 6.30 (s, 1H), 2.08 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 182.8, 149.5, 145.4, 143.8, 136.1, 133.4, 129.9, 129.3, 128.7, 128.3, 127.3, 127.0, 126.8, 126.3 (d, *J* = 248 Hz), 124.1, 123.6, 123.4,123.1, 118.5, 118.3, 116.7, 116.5, 115.2, 21.4 ppm. **^{19}F NMR (470 MHz, CDCl3):** δ -116.5 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{23}FN_3O_5S$ 580.1337, found 580.1316.

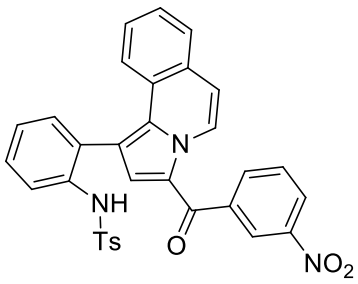
*N-(5-fluoro-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (**47v**).* The reaction was performed according to general procedure

with 6-Flouro-3-nitro-*N*-tosyl indole **45d** (100 mg, 0.30 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46e** (168 mg, 0.45 mmol) and KOH (67 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47v** as a pale yellow solid (125 mg, 72%).

	**Mp**: 205 - 207 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.62 (d, *J* = 7.5 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.22 – 7.21 (m, 2H), 7.16 - 7.12 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.76 (s, 1H), 6.49 (s, 1H), 2.17 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 182.8, 149.4, 145.6, 144.2, 137.3, 137.2, 134.8 (d, *J* = 240 Hz), 133.0, 132.9, 129.9, 129.8, 128.6, 128.2, 127.5, 127.3, 127.0, 125.4, 124.2, 123.6, 123.4, 121.5, 115.2, 112.8, 111.7, 111.6, 107.0, 106.8, 21.5 ppm. **^{19}F NMR (470 MHz, CDCl3)**: δ -109.4 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{23}FN_3O_5S$ 580.1337, found 580.1328.

4-methyl-N-(2-(3-(3-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)benzenesulfonamide (47w). The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **45a** (100 mg, 0.32 mmol), 2-(2-(3-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **46j** (179 mg, 0.48 mmol) and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **47w** as a pale yellow solid (117 mg, 65%).

	Mp: 190 - 192 °C.

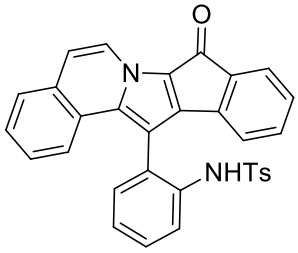
	**^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.60 (d, *J* = 7.5 Hz, 1H), 8.61 (s, 1H), 8.37 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 7.5 Hz, 1H), 7.71 – 7.65 (m, 3H), 7.46 – 7.43 (m, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.22 – 7.21 (m, 2H), 7.16 – 7.12 (m, 2H), 7.07 – 7.04 (m, 1H), 6.79 (d, *J* = 7.5 Hz, 2H), 6.77 (s, 1H), 6.45 (s, 1H), 2.11 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 182.2, 148.1, 143.7, 141.7, 136.1, 135.6, 134.7, 131.8, 129.7, 129.6, 129.4, 128.5, 128.1, 127.2, 127.0, 126.4, 125.8, 125.4, 124.9, 123.9, 123.6, 123.2, 120.1, 115.0, 114.0, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{24}N_3O_5S$ 562.1431, found 562.1436.

Experimental procedure for the Pd-catalyzed cross-dehydrogenative coupling of pyrrolo[2,1-*a*]isoquinolines: A mixture of pyrrolo[2,1-*a*]isoquinoline **47** (1.0 equiv.), $Pd(OAc)_2$ (20 mol%) and $Cu(OAc)_2$ (1.0 equiv.) was weighed into a dry reaction tube. Dry toluene was added and the reaction mixture was allowed to stir at 120 °C in an oil bath for 36 h. After completion of the reaction as indicated from the TLC, the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and characterization of indenopyrrolo[2,1-a]isoquinolinones (48a – 48q)

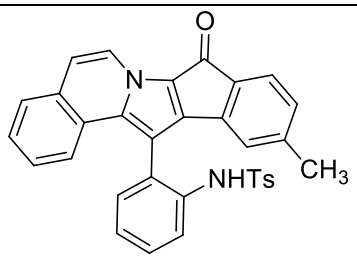
*4-methyl-N-(2-(8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**48a**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47a** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.036 mmol) and $Cu(OAc)_2$ (35 mg, 0.19 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48a** as an orange solid (84 mg, 84%).

	Mp: 264 - 268 °C.

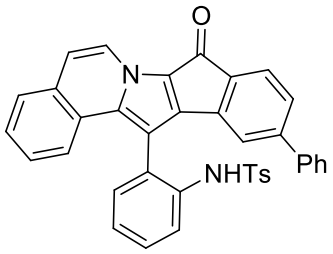
	**IR (neat) ν_{max}**: 3253, 2922, 1686, 1612, 1489, 1385, 1332, 1158, 1097, 896, 792, 722, 660, 565, 538 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.29 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 7.0 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.0 Hz, 1H), 7.32 – 7.29 (m, 2H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.22 – 7.19 (m, 1H), 7.13 - 7.09 (m, 2H), 7.04 (d, *J* = 7.0 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 7.5 Hz, 2H), 6.65 (s, 1H), 6.15 (d, *J* = 7.0 Hz, 1H), 2.05 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$):** δ 179.4, 143.7, 143.3, 139.6, 137.2, 136.1, 135.3, 132.7, 131.4, 129.8, 129.4, 129.1, 128.6, 128.3, 128.1, 127.7, 126.8, 125.9, 125.6, 123.7, 123.5, 122.7, 121.9, 120.1, 115.4, 108.5, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{23}N_2O_3S$ 515.1424, found 515.1447.

*4-methyl-N-(2-(11-methyl-8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**48b**)*. The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-methylbenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide **47b** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.038 mmol) and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in toluene at 120 ºC for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48b** as an orange solid (70 mg, 70%).

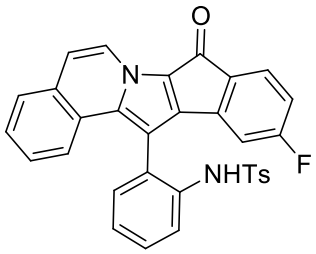
	Mp: 216 - 220 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.27 (d, *J* = 7.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.30-7.26 (m, 3H), 7.22 - 7.19 (m, 3H), 7.09 – 7.04 (m, 1H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.72 - 6.69 (m, 3H), 5.98 (s, 1H), 2.07 (s, 3H), 2.04 (s, 3H) ppm.

	**$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$):** δ 179.6, 143.6, 143.5, 142.9, 137.6, 137.0, 136.2, 135.4, 135.3, 131.4, 129.8, 129.3, 129.0, 128.5, 128.3, 127.9, 127.7, 126.8, 126.0, 125.5, 123.7, 123.5, 122.7, 121.9, 121.4, 115.2, 108.4, 21.9, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{33}H_{25}N_2O_3S$ 529.1580, found 529.1589.

*4-methyl-N-(2-(8-oxo-11-phenyl-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**48c**)*. The reaction was performed according to general procedure with *N*-(2-(3-([1,1'-biphenyl]-4-carbonyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methyl benzenesulfonamide **47c** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (8 mg, 0.034 mmol) and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in toluene at 120 ºC for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48c** as a pale orange solid (64 mg, 64%).

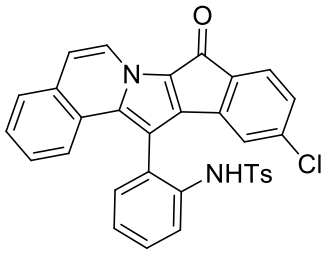
	**Mp**: 255 - 257 °C. **IR (neat) ν_{max}**: 3079, 2930, 2843, 1682, 1603, 1489, 1394, 1341, 1150, 1080, 904, 792, 747, 660, 565, 538 cm^{-1}. **^1H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.31 (d, *J* = 7.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.39 – 7.37 (m, 2H), 7.34 – 7.32 (m, 3H), 7.30 - 7.27 (m, 5H), 7.23 - 7.20 (m, 2H), 7.18 – 7.16 (m, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.0 Hz, 1H), 6.72 (s, 1H), 6.66 (d, *J* = 8.0 Hz, 2H), 6.43 (s, 1H), 1.89 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 179.2, 145.6, 143.8, 142.7, 139.9, 138.4, 138.2, 136.2, 135.7, 135.3, 131.4, 129.9, 129.4, 129.1, 128.9, 128.7, 128.2, 127.7, 126.83, 126.76, 126.7, 125.5, 123.9, 123.7, 122.7, 121.9, 118.9, 115.4, 108.7, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{38}H_{27}N_2O_3S$ 591.1737, found 591.1759.

*N-(2-(11-fluoro-8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)-4-methylbenzenesulfonamide (**48d**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-fluorobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47d** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.038 mmol) and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48d** as an orange solid (40 mg, 40%).

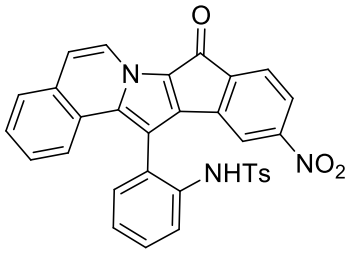
	**Mp**: 290 - 292 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.27 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.0 Hz, 1H), 7.31 - 7.26 (m, 4H), 7.22 - 7.21 (m, 2H), 7.17 – 7.14 (m, 2H), 7.07 (d, *J* = 7.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.60 (s, 1H), 5.70 (d, *J* = 8.0 Hz, 1H), 2.10 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 178.2, 144.0, 136.0, 135.5 (d, *J* = 211.5 Hz), 131.2, 130.1, 129.6, 129.0, 128.9, 128.3, 127.8, 126.9, 125.6, 125.5, 125.4, 125.2, 125.02, 124.94, 123.6, 122.7, 121.5, 115.8, 109.0, 108.6, 21.4 ppm. **^{19}F NMR (470 MHz, $CDCl_3$):** δ -105.6 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: (M - H) calcd for $C_{32}H_{20}FN_2O_3S$ 531.1173, found 531.1176

*N-(2-(11-chloro-8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)-4-methylbenzenesulfonamide (**48e**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-chlorobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47e** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.36 mmol) and $Cu(OAc)_2$ (33 mg, 0.18 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48e** as an orange solid (64 mg, 64%).

	Mp: 295 - 298 °C.

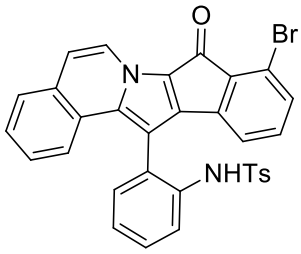
	**^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.28 (d, *J* = 7.0 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.41 – 7.38 (m, 1H), 7.30 - 7.27 (m, 3H), 7.23 - 7.19 (m, 2H), 7.17 - 7.14 (m, 2H), 7.07 (d, *J* = 7.0 Hz, 1H), 6.97 - 6.95 (m, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.59 (s, 1H), 5.98 (d, *J* = 1.5 Hz, 1H), 2.10 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 178.1, 143.9, 141.8, 139.0, 138.6, 137.7, 136.0, 135.4, 131.2, 130.2, 129.4, 129.1, 128.9, 128.4, 127.8, 126.9, 125.6, 125.4, 125.2, 124.2, 123.6, 122.7, 121.6, 120.6, 115.8, 108.8, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: (M - H) calcd for $C_{32}H_{20}ClN_2O_3S$ 547.0877, found 547.0881.

*4-methyl-N-(2-(11-nitro-8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**48f**)*. The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide **47f** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.035 mmol) and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48f** as an orange solid (70 mg, 70%).

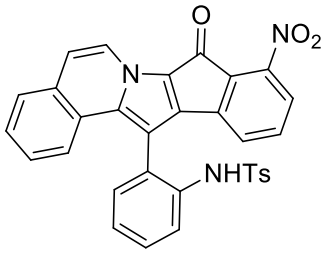
	**Mp**: 260 - 262 °C. **IR (neat) ν_{max}**: 2922, 2852, 1673, 1498, 1402, 1324, 1272, 1158, 1080, 904, 809, 722, 660, 556, 538 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.30 (d, *J* = 7.0 Hz, 1H), 7.90 - 7.86 (m, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.45 - 7.41 (m, 2H), 7.31 - 7.25 (m, 5H), 7.12 (d, *J* = 7.0 Hz, 1H), 6.77 - 6.74 (m, 3H), 6.62 (s, 1H), 2.04 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 176.0, 150.8, 144.9, 141.3, 136.2, 131.1, 130.6, 129.5, 129.4, 129.2, 128.9, 127.9,

	127.0, 125.8, 125.3, 124.4, 123.7, 123.2, 123.0, 121.4, 116.4, 114.2, 109.6, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{21}N_3NaO_5S$ 582.1094, found 582.1100.

*N-(2-(9-bromo-8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)-4-methylbenzenesulfonamide (**48g**).* The reaction was performed according to general procedure with *N*-(2-(3-(2-bromobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47g** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (8 mg, 0.034 mmol) and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48g** as an orange solid (50 mg, 50%).

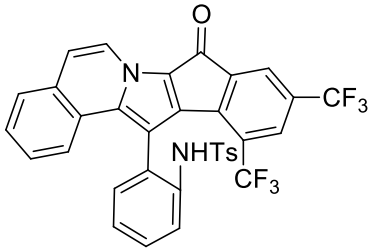
	**Mp**: 255 - 258 °C. **IR (neat) ν_{max}:** 3245, 2922, 2852, 1673, 1603, 1498, 1402, 1158, 1088, 887, 800, 757, 669, 565, 530 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.28 (d, *J* = 7.0 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.46 - 7.42 (m, 1H), 7.38 - 7.35 (m, 1H), 7.32 - 7.29 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.21 - 7.20 (m, 1H), 7.13 - 7.09 (m, 2H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.65 (s, 1H), 6.15 (d, *J* = 7.5 Hz, 1H), 2.05 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 179.4, 143.7, 143.3, 139.5, 137.2, 136.1, 135.7, 135.3, 132.7, 131.4, 129.8, 129.4, 129.1, 128.6, 128.3, 128.1, 127.7, 126.8, 125.9, 125.5, 125.4, 123.7, 123.4, 122.8, 121.9, 120.1, 115.4, 108.6, 21.6 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{22}BrN_2O_3S$ 593.0529, found 593.0536.

*4-methyl-N-(2-(9-nitro-8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**48h**).* The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(2-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide **47h** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.036 mmol) and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in toluene at 120 ºC for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48h** as an orange solid (40 mg, 40%).

	**Mp**: 238 - 240 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.28 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.29 - 7.27 (m, 3H), 7.24 - 7.21 (m, 3H), 7.15 – 7.13 (m, 2H), 7.09 (d, *J* = 7.0 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.63 (s, 1H), 6.30 (d, *J* = 7.0 Hz, 1H), 2.10 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 167.1, 154.1, 153.7, 153.0, 143.8, 136.9, 133.7, 133.3, 131.3, 130.2, 129.4, 129.0, 128.7, 127.9, 126.8, 125.7, 125.4, 125.3, 123.6,122.8, 122.6, 122.1, 116.3, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{22}N_3O_5S$ 560.1275, found 560.1288.

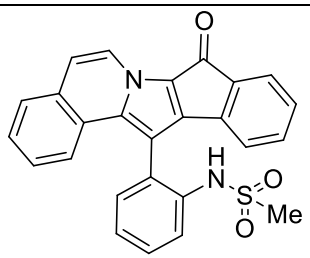
*4-methyl-N-(2-(8-oxo-10,12-bis(trifluoromethyl)-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**48i**).* The reaction was performed according to general procedure with *N*-(2-(3-(3,5-bis(trifluoromethyl)benzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methyl benzenesulfonamide **47i** (100 mg, 0.15 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol) and $Cu(OAc)_2$ (28 mg, 0.15 mmol) in toluene at 120 ºC for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48i** as a pale orange solid (53 mg, 53%).

	Mp: 290 - 292 °C.

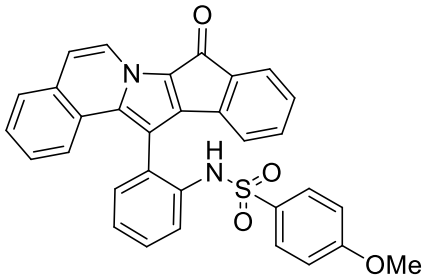
	**IR (neat) ν_{max}**: 3253, 3061, 2922, 2852, 1690, 1595, 1498, 1398, 1332, 1280, 1158, 1131, 1080, 914, 782, 757, 695, 561, 538 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.44 (d, *J* = 7.0 Hz, 1H), 7.74 – 7.71 (m, 2H), 7.56 – 7.54 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.34 – 7.32 (m, 3H), 7.17 - 7.15 (m, 1H), 7.13 - 7.11 (m, 2H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.57 – 6.56 (m, 2H), 2.17 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 175.6, 143.5, 142.2, 138.3, 137.5, 136.5, 132.2 (q, *J* = 233 Hz), 129.5, 129.2, 128.9, 128.4, 127.7, 127.0, 125.4, 124.4, 123.4, 123.3, 122.9, 122.4, 118.64, 118.56, 117.4, 112.5, 21.4 ppm. **^{19}F NMR (470 MHz, CDCl3):** δ -62.5 (s), -63.5 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{34}H_{21}F_6N_2O_3S$ 651.1172, found 651.1183.

*N-(2-(8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)methanesulfonamide (**48j**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)methanesulfonamide **47j** (100mg, 0.22 mmol), $Pd(OAc)_2$ (10 mg, 0.045 mmol) and $Cu(OAc)_2$ (41mg, 0.22 mmol) in toluene at 120 ºC for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48j** as an orange solid (60 mg, 60%).

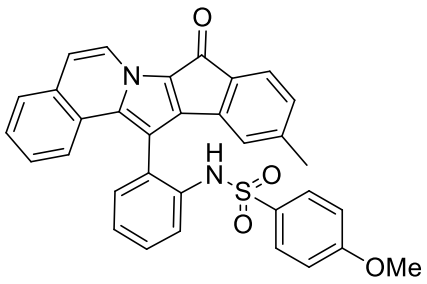
	Mp: 250 - 252 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.27 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 6.5 Hz, 1H), 7.39 - 7.35 (m, 2H), 7.29 - 7.21 (m, 3H), 7.01 - 6.97 (m, 3H), 6.60 (s, 1H), 6.48 (d, *J* = 6.5 Hz, 1H), 2.76 (s, 3H) ppm.

	**$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 179.4, 143.4, 139.6, 137.4, 136.0, 132.9, 131.9, 130.2, 129.2, 128.6, 128.3, 127.9, 125.5, 125.2, 124.9, 123.8, 123.7, 122.7, 119.9, 119.5, 115.5, 108.09, 39.8 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{26}H_{19}N_2O_3S$ 439.1111, found 439.1115.

*4-methoxy-N-(2-(8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**48k**)*. The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide **47k** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.038 mmol) and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in toluene at 120 ºC for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48k** as an orange solid (62 mg, 62%).

	**Mp**: 150 - 152 °C. **IR (neat) ν_{max}**: 2930, 2852, 1686, 1603, 1498, 1402, 1262, 1167, 1088, 1028, 887, 722, 652, 565, 535 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.29 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.46 - 7.35 (m, 4H), 7.33 - 7.29 (m, 4H), 7.11 - 7.08 (m, 2H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.91 – 6.88 (m, 1H), 6.63 (s, 1H), 6.38 (d, *J* = 9.0 Hz, 1H), 6.13 (d, *J* = 7.0 Hz, 1H), 3.56 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 179.4, 162.8, 139.5, 137.2, 135.4, 132.8, 131.4, 129.8, 129.1, 129.0, 128.8, 128.3, 128.1, 127.7, 125.5, 123.7, 123.4, 122.8, 121.8, 120.0, 115.4, 113.8, 55.3 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{23}N_2O_4S$ 531.1373, found 531.1383.

*4-methoxy-N-(2-(11-methyl-8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**48l**).* The reaction was performed according to general procedure with 4-methoxy-N-(2-(3-(4-methylbenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide **47l** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.036 mmol) and $Cu(OAc)_2$ (33 mg, 0.18 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48l** as an orange solid (55 mg, 55%).



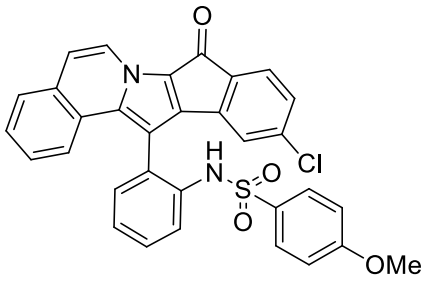
Mp: 260 - 262 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.26 (d, *J* = 7.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.0 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.33 - 7.31 (m, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.21 -7.16 (m, 3H), 7.08 – 7.07 (m, 2H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.68 (s, 1H), 6.37 (d, *J* = 7.5 Hz, 2H), 5.92 (s, 1H), 3.54 (s, 3H), 2.05 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 179.6, 162.8, 143.6, 142.9, 137.6, 136.9, 135.5, 135.4, 131.4, 130.6, 129.8, 129.0, 128.6, 128.3, 127.9, 127.6, 125.9, 125.5, 125.4, 123.7, 123.4, 122.7, 121.7, 121.3, 115.3, 113.7, 108.4, 55.2, 21.9 ppm.

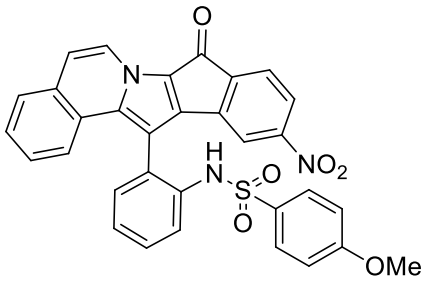
HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{33}H_{25}N_2O_4S$ 545.1530, found 545.1541.

*N-(2-(11-chloro-8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)-4-methoxybenzenesulfonamide (**48m**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-chlorobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methoxy benzenesulfonamide **47m** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.036 mmol) and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48m** as an orange solid (52 mg, 52%).

	**Mp**: 230 - 232 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.23 (d, *J* = 7.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.37 – 7.33 (m, 3H), 7.26 (d, *J* = 7.0 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.16 - 7.11 (m, 3H), 7.01 (d, *J* = 6.5 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 6.44 (d, *J* = 9.0 Hz, 2H), 5.99 (s, 1H), 3.60 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 178.0, 162.9, 141.8, 139.0, 138.6, 137.6, 136.1, 135.5, 131.2, 130.5, 130.1, 129.1, 129.0, 128.9, 128.3, 127.73, 127.72, 125.5, 125.4, 25.2, 125.2, 124.2, 123.6, 122.7, 121.4, 120.5, 115.8, 113.8, 108.9, 55.3 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{21}ClN_2NaO_4S$ 587.0803, found 587.0822.

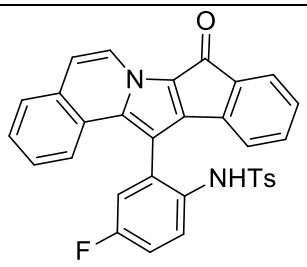
*4-methoxy-N-(2-(11-nitro-8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**48n**)*. The reaction was performed according to general procedure with 4-methoxy-*N*-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl) benzenesulfonamide **47n** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (8 mg, 0.035 mmol) and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48n** as an orange solid (51 mg, 51%).

	Mp: 230 - 232 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.23 (d, *J* = 7.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.37 – 7.33 (m, 3H), 7.26 (d, *J* = 7.0 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.16 - 7.11 (m, 3H), 7.01 (d, *J* = 6.5 Hz, 1H), 6.90 (d, *J* = 8.0 Hz,

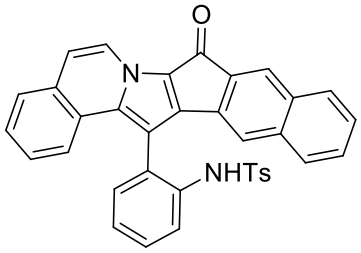
	1H), 6.71 (s, 1H), 6.44 (d, *J* = 9.0 Hz, 2H), 5.99 (s, 1H), 3.60 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 178.0, 162.9, 141.8, 139.0, 138.6, 137.6, 136.1, 135.5, 131.2, 130.5, 130.1, 129.1, 129.0, 128.9, 128.3, 127.73, 127.72, 125.5, 125.4, 25.2, 125.2, 124.2, 123.6, 122.7, 121.4, 120.5, 115.8, 113.8, 108.9, 55.3 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{21}ClN_2NaO_4S$ 587.0803, found 587.0822.

*N-(4-fluoro-2-(8-oxo-8H-indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)-4-methylbenzenesulfonamide (**48o**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)-4-fluorophenyl)-4-methylbenzenesulfonamide **47o** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.38 mmol) and $Cu(OAc)_2$ (35 mg, 0.19 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48o** as an orange solid (49 mg, 49%).

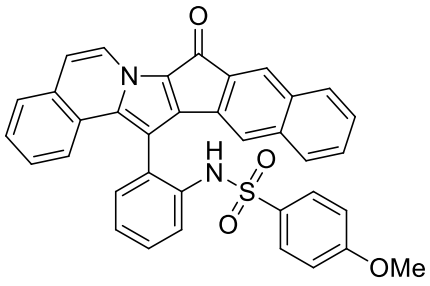
	Mp: 249 - 251 °C. **IR (neat) ν_{max}**: 2956, 2922, 2843, 1682, 1595, 1481, 1402, 1341, 1258, 1163, 1088, 1018, 887, 792, 722, 669, 547, 512 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.28 (d, *J* = 7.0 Hz, 1H), 7.85 – 7.82 (m, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.0 Hz, 1H), 7.32 (d, *J* = 7.0 Hz, 1H), 7.18 – 7.11 (m, 5H), 7.06 – 7.03 (m, 2H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.95 (t, *J* = 7.0 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 2H), 6.52 (s, 1H), 6.20 (d, *J* = 7.0 Hz, 1H), 2.01 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 179.4, 143.8, 142.9, 139.4, 136.5 (d, *J* = 124 Hz), 132.9, 131.2, 129.4, 129.1, 128.8, 128.4, 128.3, 127.9, 126.6, 125.4, 125.3, 125.2, 125.1, 123.6 (d, *J* = 32.9

	Hz), 122.4, 120.0, 118.0, 117.8, 116.8, 116.6, 116.1, 115.5, 21.5 ppm. **^{19}F NMR (470 MHz, $CDCl_3$):** δ -115.5 (s) ppm. **HRMS (ESI-Orbitrap) m/z:** $(M + H)^+$ calcd for $C_{32}H_{22}FN_2O_3S$ 533.1330, found 533.1342.

*4-methyl-N-(2-(8-oxo-8H-benzo[5',6']indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-15-yl)phenyl)benzenesulfonamide (**48p**).* The reaction was performed according to general procedure with N-(2-(3-(2-naphthoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47p** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.035 mmol) and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in toluene at 120 ºC for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48p** as a yellow solid (60 mg, 60%).

	**Mp**: 240 - 242 °C. **IR (neat) ν_{max}:** 3069, 2930, 2860, 1673, 1621, 1489, 1406, 1332, 1167, 1088, 904, 800, 765, 669, 565, 547 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.37 (d, *J* = 7.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.37 – 7.36 (m, 1H), 7.32 – 7.31 (m, 3H), 728 - 7.26 (m, 3H), 7.24 -7.21 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.72 (s, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 6.37 (s, 1H), 1.71 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 178.1, 143.7, 143.2, 138.8, 136.7, 136.1, 135.8, 135.5, 133.4, 132.0, 131.5, 130.3, 129.9, 129.3, 128.8, 128.5, 127.8, 126.9, 126.7, 125.3, 124.3, 123.8, 123.1, 121.7, 118.9, 115.1, 108.1, 21.0 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{36}H_{25}N_2O_3S$ 565.1580, found 565.1583.

*4-methoxy-N-(2-(8-oxo-8H-benzo[5',6']indeno[1',2':4,5]pyrrolo[2,1-a]isoquinolin-15-yl)phenyl)benzenesulfonamide (**48q**).* The reaction was performed according to general procedure with *N*-(2-(3-(2-naphthoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide **47q** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (8mg, 0.34 mmol) and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **48q** as an orange solid (55 mg, 55%).



Mp: 254 - 256 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.27 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.56 – 7.49 (m, 3H), 7.39 – 7.36 (m, 4H), 7.32 – 7.31 (m, 2H), 7.29 – 7.21 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.96 (s, 1H), 6.87 (d, *J* = 7.0 Hz, 1H), 6.40 (s, 1H), 6.30 (d, *J* = 9.0 Hz, 2H), 3.22 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 178.0, 162.7, 143.2, 138.7, 134.8, 135.7, 133.4, 131.5, 130.7, 130.2, 129.9, 129.4, 129.0, 128.7, 128.6, 128.3, 128.3, 127.7, 126.6, 125.8, 125.4, 125.3, 124.3, 123.7, 123.1, 121.4, 118.8, 115.0, 113.7, 108.2, 54.9 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{36}H_{24}N_2NaO_4S$ 603.1349, found 603.1358.

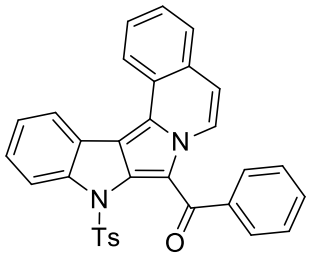
Procedure for scale up of 48a

A mixture of *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methyl benzene sulfonamide **47a** (1.0 g, 1.9 mmol), $Pd(OAc)_2$ (90 mg, 0.36 mmol) and $Cu(OAc)_2$ (350 mg, 1.9 mmol) was weighed into a dry reaction tube. Dry toluene was added and the reaction mixture was allowed to stir at 120 °C in an oil bath for 36 h. After completion of the reaction as indicated from the TLC, the solvent was removed under vacuum. The residue was then purified by column chromatography (20% ethyl acetate in hexane) to afford the desired product **48a** as an orange solid (800 mg, 80%).

Experimental procedure for the Pd-catalyzed CH amination of Pyrrolo[2,1-*a*]isoquinolines towards indolopyrrolo[2,1-*a*]isoquinolines: A mixture of pyrrolo[2,1-*a*]isoquinoline **47** (1.0 equiv), $Pd(OAc)_2$ (5 mol%) and $Cu(OAc)_2$ (1.0 equiv.) was weighed into a dry Schlenk tube. Dry DMSO was added and the reaction mixture was stirred at 120 ^oC in an oil bath for 12 h under O_2 atmosphere. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and characterization of indolo[3',2':3,4]pyrrolo[2,1-*a*]isoquinolines (49a-49j)

*phenyl(9-tosyl-9H-indolo[3',2':3,4]pyrrolo[2,1-a]isoquinolin-8-yl)methanone (**49a**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47a** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.038 mmol) and $Cu(OAc)_2$ (35 mg, 0.19 mmol) in DMSO under O_2 atmosphere at 120 ^oC for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **49a** as a pale yellow solid (54 mg, 54%).



Mp: 220 -222 °C.

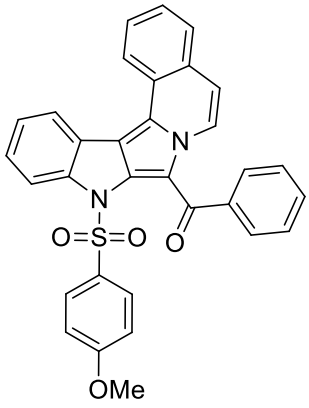
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.96 (d, *J* = 7.5 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.09 - 8.05 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.53 – 7.51 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.36 - 7.29 (m, 2H), 7.08 – 7.05 (m, 3H), 6.77 (d, *J* = 8.0 Hz, 2H), 2.06 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 187.3, 144.6, 139.8, 132.6, 129.6, 129.0, 128.5, 127.6, 127.1, 125.5, 125.1, 125.0, 124.8, 121.1, 118.5, 113.2, 21.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{22}N_2NaO_3S$ 537.1243, found 537.1270.

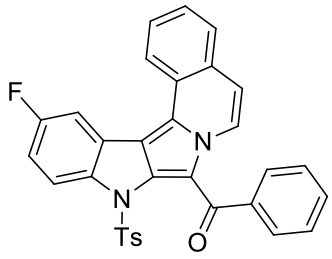
*(9-((4-methoxyphenyl)sulfonyl)-9H-indolo[3',2':3,4]pyrrolo[2,1-a]isoquinolin-8-yl)(phenyl)methanone (**49b**).* The reaction was performed according to general procedure with

N-(2-(3-benzoylpyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide **47k** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol) and $Cu(OAc)_2$ (34 mg, 0.18 mmol) in DMSO under O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **49b** as a yellow solid (53 mg, 53%).

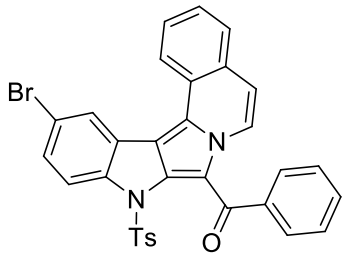
	**Mp**: 125 - 128 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.95 (d, *J* = 7.5 Hz, 1H), 8.52 (d, *J* = 8.0 Hz, 1H), 8.10 - 8.06 (m, 2H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.53 - 7.51 (m, 2H), 7.44 – 7.42 (m, 2H), 7.37 - 7.29 (m, 2H), 7.13 (d, *J* = 9.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 9.0 Hz, 2H), 3.54 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 187.3, 163.5, 144.1, 139.8, 136.4, 132.6, 129.6, 129.3, 129.1, 128.5, 127.6, 127.1, 126.0, 125.5, 125.1, 125.0, 124.8, 121.1, 118.5, 113.5, 113.2, 55.3 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{23}N_2O_4S$ 531.1373, found 531.1388.

(12-fluoro-9-tosyl-9H-indolo[3',2':3,4]pyrrolo[2,1-a]isoquinolin-8-yl)(phenyl)methanone ***(49c)***. The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)-4-fluorophenyl)-4-methylbenzenesulfonamide **47o** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (2 mg, 0.0095 mmol) and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in DMSO under O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **49c** as a yellow solid (50 mg, 50%).

	Mp: 282 - 284 °C. **IR (neat) ν_{max}:** 3069, 2982, 2912, 1690, 1630, 1577, 1394, 1332, 1158, 1088, 957, 792, 660, 590, 538 cm^{-1}.

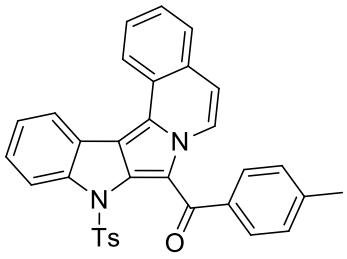
	**^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.95 (d, *J* = 7.5 Hz, 1H), 8.36 (d, *J* = 8.5 Hz, 1H), 8.04 - 8.01 (m, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.72 - 7.70 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.10 - 7.03 (m, 3H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 2.08 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 187.2, 144.8, 139.6, 137.2, 132.7, 131.8, 129.6, 129.1, 128.6, 127.9, 127.8, 126.2 (d, *J* = 275 Hz), 127.1, 124.9, 124.6, 119.4, 119.3, 113.6, 111.8, 111.6, 111.2, 108.1, 107.9, 21.5 ppm. **^{19}F NMR (470 MHz, CDCl3):** δ -116.2 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{22}FN_2O_3S$ 533.1330, found 533.1342.

(12-bromo-9-tosyl-9H-indolo[3',2':3,4]pyrrolo[2,1-a]isoquinolin-8-yl)(phenyl)methanone ***(49d)***. The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)-4-bromophenyl)-4-methylbenzenesulfonamide **47r** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085 mmol) and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **49d** as a yellow solid (49 mg, 49%).

	**Mp**: 215 - 218 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.93 (d, *J* = 7.0 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 8.14 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 7.0 Hz, 1H), 7.56 - 7.52 (m, 2H), 7.47 - 7.40 (m, 4H), 7.09 (t, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 2.10 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 187.2, 144.9, 142.7, 139.6, 132.8, 132.0, 129.6, 129.2, 128.6, 127.9, 127.6, 127.3, 127.1, 125.0, 124.6, 123.9, 119.5, 118.9, 113.6, 21.5 ppm.

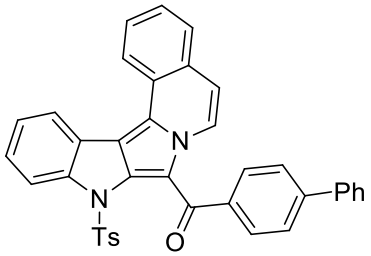
	HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{22}BrN_2O_3S$ 593.0529, found 593.0549.

p-tolyl(9-tosyl-9H-indolo[3',2':3,4]pyrrolo[2,1-a]isoquinolin-8-yl)methanone ***(49e)***. The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-methylbenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide **47b** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol) and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in DMSO under O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **49e** as a yellow solid (45 mg, 45%).

	**Mp**: 203 - 205 °C. **IR (neat) ν_{max}**: 2974, 2922, 2860, 1700, 1586, 1376, 1332, 1254, 1167, 1088, 1036, 809, 757, 669, 565, 538 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.87 (d, *J* = 7.5 Hz, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.0 Hz, 1H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.36 - 7.29 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H), 2.06 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 187.1, 144.5, 144.1, 143.9, 143.9, 143.4, 137.2, 135.9, 132.2, 129.8, 129.3, 129.3, 129.0, 129.0, 127.5, 127.5, 127.5, 127.4, 127.1, 125.9, 125.4, 125.4, 125.1, 125.0, 124.7, 121.11, 121.10, 118.4, 113.1, 113.0, 112.0, 21.8, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{33}H_{25}N_2O_3S$ 529.1580, found 529.1580.

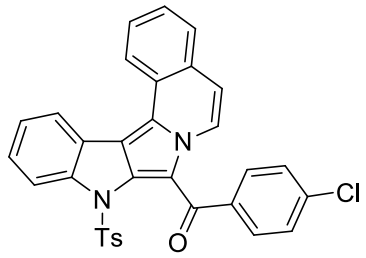
[1,1'-biphenyl]-4-yl(9-tosyl-9H-indolo[3',2':3,4]pyrrolo[2,1-a]isoquinolin-8-yl)methanone ***(49f)*****.** The reaction was performed according to general procedure with *N*-(2-(3-([1,1'-

biphenyl]-4-carbonyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methyl benzenesulfonamide **47c** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085 mmol) and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **49f** as a yellow solid (44 mg, 44%).

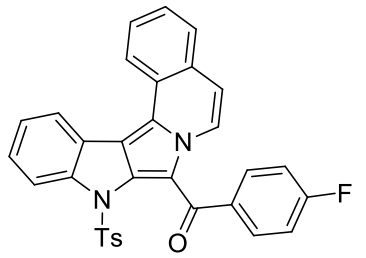
	**Mp**: 205 -207 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.92 (d, *J* = 7.5 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 7.5 Hz, 3H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.41 – 7.38 (m, 2H), 7.36 - 7.30 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H) 2.06 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 186.9, 144.6, 144.0, 140.3, 138.6, 136.1, 132.2, 130.2, 129.0, 128.8, 128.0, 127.6, 127.4, 127.2, 127.1, 125.9, 125.5, 125.1, 125.14, 125.07, 124.8, 121.2, 118.5, 113.2, 112.1, 111.1, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{38}H_{27}N_2O_3S$ 591.1737, found 591.1740.

*(4-chlorophenyl)(9-tosyl-9H-indolo[3',2':3,4]pyrrolo[2,1-a]isoquinolin-8-yl)methanone (**49g**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-chlorobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47e** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol) and $Cu(OAc)_2$ (33 mg, 0.18 mmol) in DMSO under O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **49g** as a yellow solid (40 mg, 40%).

	Mp: 198 - 200 °C. **IR (neat) ν_{max}:** 2974, 2930, 2843, 1682, 1638, 1586, 1372, 1324, 1158, 1088, 809, 739, 660, 573, 538 cm^{-1}.

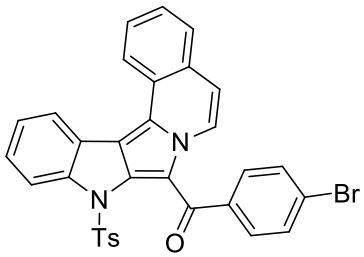
	**^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.97 (d, *J* = 7.5 Hz, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.54 – 7.59 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.36 - 7.30 (m, 2H), 7.06 (t, *J* = 8.5 Hz, 3H), 6.77 (d, *J* = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 185.8, 144.7, 144.0, 138.8, 136.6, 132.0, 131.0, 130.3, 129.2, 129.0, 128.9, 127.8, 127.7, 127.2, 127.1, 125.8, 125.6, 125.1, 125.0, 125.0, 125.0, 124.8, 121.2, 118.6, 113.4, 112.3, 110.8, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{22}ClN_2O_3S$ 549.1034, found 549.1032.

(4-fluorophenyl)(9-tosyl-9H-indolo[3',2':3,4]pyrrolo[2,1-a]isoquinolin-8-yl)methanone ***(49h)***. The reaction was performed according to general procedure with *N*-(2-(3-(4-fluorobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47d** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol) and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in DMSO under O_2 atmosphere at 120 ºC for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **49h** as a pale yellow solid (39 mg, 39%).

	**Mp**: 250 - 252 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.95 (d, *J* = 7.5 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 7.95 – 7.92 (m, 2H), 7.77 – 7.75 (m, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.37 – 7.30 (m, 2H), 7.11 – 7.06 (m, 4H), 6.77 (d, *J* = 8.0 Hz, 2H), 2.06 (s, 3H) ppm **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 185.7, 144.6, 144.0, 136.4, 136.2, 132.1, 132.0, 130.3, 129.0, 127.7, 127.6, 127.1,

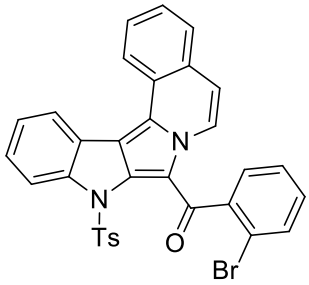
	125.9, 125.6, 125.1, 125.0, 124.8, 121.1, 118.60, 118.56, 115.7, 115.6, 112.2, 111.3 (d, J = 243 Hz), 21.4 ppm. **^{19}F NMR (470 MHz, $CDCl_3$)**: δ -106.2 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{22}FN_2O_3S$ 533.1330, found 533.1343.

(4-bromophenyl)(9-tosyl-9H-indolo[3',2':3,4]pyrrolo[2,1-a]isoquinolin-8-yl)methanone ***(49i)***. The reaction was performed according to general procedure with *N*-(2-(3-(4-bromobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methyl benzenesulfonamide **47s** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085 mmol) and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under O_2 atmosphere at 120 ºC for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **49i** as a pale yellow solid (40 mg, 40%).

	**Mp**: 210 - 212 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.97 (d, J = 7.5 Hz, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.56 - 7.51 (m, 3H), 7.37 - 7.30 (m, 2H), 7.08 – 7.05 (m, 3H), 6.77 (d, J = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 186.0, 144.7, 144.0, 138.8, 136.6, 131.8, 131.1, 129.0, 127.8, 127.7, 127.2, 127.1, 125.1, 125.0, 124.8, 121.2, 118.6, 113.4, 112.3, 110.7, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{22}BrN_2O_3S$ 593.0529, found 593.0549.

(2-bromophenyl)(9-tosyl-9H-indolo[3',2':3,4]pyrrolo[2,1-a]isoquinolin-8-yl)methanone ***(49j)***. The reaction was performed according to general procedure with *N*-(2-(3-(2-bromobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methyl benzenesulfonamide **47g**

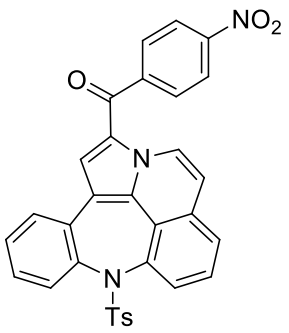
(100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085) and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under O_2 atmosphere at 120 ºC for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **49j** as a yellow solid (41 mg, 41%).

	**Mp**: 244 - 248 °C. **IR (neat) ν_{max}:** 2969, 2912, 2852, 1690, 1630, 1577, 1394, 1376, 1336, 1167, 1088, 800, 739, 660, 573, 530 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 8.96 (d, *J* = 7.5 Hz, 1H), 8.51 (d, *J* = 8.5 Hz, 1H), 8.09 - 8.05 (m, 2H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 6.5 Hz, 2H), 7.43 - 7.41 (m, 2H), 7.34 - 7.29 (m, 2H), 7.08 – 7.05 (m, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 187.3, 144.6, 143.9, 139.8, 136.4, 132.6, 132.2, 129.6, 129.1, 129.0, 128.5, 127.6, 127.6, 127.1, 125.9, 125.5, 125.1, 125.0, 124.8, 124.7, 121.1, 118.5, 113.2, 112.1, 111.0, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{22}BrN_2O_3S$ 593.0529, found 593.0542.

Experimental procedure for the Pd-catalyzed C-H activation of pyrrolo[2,1-*a*]isoquinolines towards multiring fused azepines: A mixture of pyrrolo[2,1-*a*]isoquinoline **47** (1.0 equiv), $Pd(OAc)_2$ (5 mol%) and $Cu(OAc)_2$ (1.0 equiv.) was weighed into a dry Schlenk tube. Dry DMSO was added and the reaction mixture was stirred at 120 ºC in an oil bath for 36 h under O_2 atmosphere. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

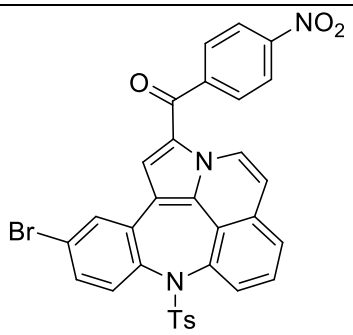
Synthesis and characterization of fused azepines (50a-50e)

*(4-nitrophenyl)(6-tosyl-6H-6,12a-diazacyclopenta[gh]pleiaden-12-yl)methanone (**50a**).* The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide **47f** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol) and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in DMSO under O_2 atmosphere at 120 °C for 36 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **50a** as a yellow solid (52 mg, 52%).

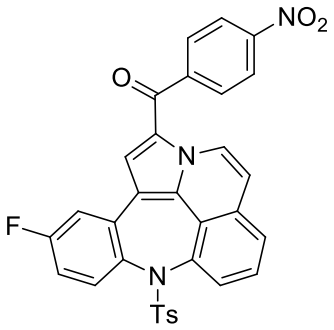
	**Mp**: 260 - 262 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.25 (d, *J* = 7.5 Hz, 1H), 8.37 (d, *J* = 9.0 Hz, 2H), 7.91 - 7.88 (m, 3H), 7.73 - 7.70 (m, 3H), 7.41 - 7.32 (m, 3H), 7.10 (s, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 182.9, 145.3, 143.2, 136.0, 135.5, 135.2, 132.5, 132.4, 131.6, 130.2, 129.8, 128.4, 127.9, 127.5, 127.4, 126.3, 125.2, 123.8, 121.4, 119.4, 113.8, 21.3 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{21}N_3NaO_5S$ 582.1094, found 582.1088.

*(9-bromo-6-tosyl-6H-6,12a-diazacyclopenta[gh]pleiaden-12-yl)(4-nitrophenyl)methanone (**50b**).* The reaction was performed according to general procedure with *N*-(4-bromo-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47t** (100 mg, 0.16 mmol), $Pd(OAc)_2$ (2 mg, 0.008 mmol) and $Cu(OAc)_2$ (29 mg, 0.16 mmol) in DMSO under O_2 atmosphere at 120 °C for 36 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **50b** as a yellow solid (50 mg, 50%).

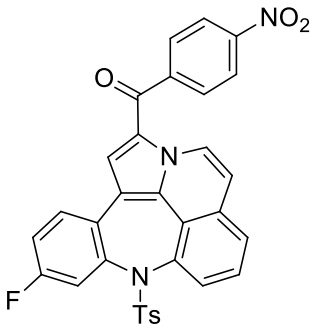
	Mp: 257 − 259 °C. **IR (neat) ν_{max}**: 2912, 1708, 1621, 1481, 1341, 1237, 1158, 1088, 939, 809, 757, 669, 573, 530 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.25 (d, *J* = 7.5 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 2H), 7.90 - 7.86 (m, 3H), 7.75 - 7.74

	(m, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.43 (s, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.06 (s, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.63 (d, *J* = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$):** δ 182.6, 145.2, 143.2, 136.9, 135.0, 131.2, 130.4, 130.0, 128.0, 127.4, 125.2, 123.9, 121.6, 121.3, 118.5, 117.9, 113.9, 21.3 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{21}BrN_3O_5S$ 638.0380, found 638.0377.

(9-fluoro-6-tosyl-6H-6,12a-diazacyclopenta[gh]pleiaden-12-yl)(4-nitrophenyl)methanone ***(50c).*** The reaction was performed according to general procedure with *N*-(4-fluoro-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47u** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085 mmol) and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under O_2 atmosphere at 120 °C for 36 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **50c** as a yellow solid (53 mg, 53%).

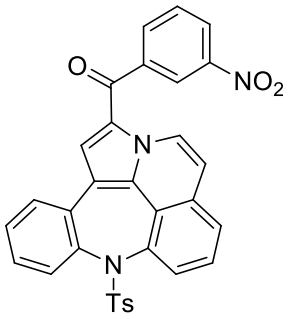
	**Mp**: 279 - 281 °C. **^1H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.25 (d, *J* = 7.5 Hz, 1H), 8.38 (d, *J* = 8.0 Hz, 2H), 7.90 - 7.87 (m, 3H), 7.75 - 7.74 (m, 2H), 7.69 – 7.66 (m, 1H), 7.10 - 7.06 (m, 2H), 7.04 (s, 1H), 6.97 (d, *J* = 7.0 Hz, 1H), 6.71(d, *J* = 7.5 Hz, 2H), 6.63 (d, *J* = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$):** δ 183.0, 149.7, 144.2 (d, *J* = 211 Hz), 136.0, 135.4, 135.3, 135.1, 131.6, 130.4, 130.3, 129.8, 128.0, 127.4, 126.4, 125.2, 123.8, 121.4, 115.4, 115.4, 115.2, 114.0, 21.3 ppm. **^{19}F NMR (470 MHz, $CDCl_3$):** δ -112.0 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{21}FN_3O_5S$ 578.1180, found 578.1176.

(8-fluoro-6-tosyl-6H-6,12a-diazacyclopenta[gh]pleiaden-12-yl)(4-nitrophenyl)methanone ***(50d)***. The reaction was performed according to general procedure with *N*-(5-fluoro-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **47v** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085 mmol) and $Cu(OAc)_2$ (31 mg, 0.17mmol) in DMSO under O_2 atmosphere at 120 °C for 36 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **50d** as a yellow solid (45 mg, 45%).

	**Mp**: 180 - 182 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.25 (d, *J* = 7.5 Hz, 1H), 8.37 (d, *J* = 7.5 Hz, 2H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.86 – 7.85 (m, 1H), 7.74 - 7.73 (m, 2H), 7.45 (d, *J* = 9.5 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.10 – 7.07 (m, 2H), 7.04 (s, 1H), 6.72 (d, *J* = 7.5 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 2H), 2.06 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 182.9, 144.3 (d, *J* = 221 Hz), 135.8, 131.8, 130.4, 130.2, 129.8, 128.0, 127.4, 126.5, 125.2, 123.8, 123.3, 121.1, 120.3, 118.6, 117.1, 113.8, 21.3 ppm. **^{19}F NMR (470 MHz, CDCl3):** δ -113.4 (s) ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{20}FN_3NaO_5S$ 600.1000, found 600.1005.

(3-nitrophenyl)(6-tosyl-6H-6,12a-diazacyclopenta[gh]pleiaden-12-yl)methanone ***(50e)***. The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(3-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide **47w** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol) and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in DMSO under O_2 atmosphere at 120 °C for 36 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **50e** as a yellow solid (51 mg, 51%).

	Mp: 295 - 298 °C. **IR (neat) ν_{max}**: 2956, 2912, 2852, 1725, 1682, 1612, 1533, 1472, 1341, 1254, 1158, 1088, 817, 747, 660, 565, 530 cm^{-1}.

	**^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.25 (d, *J* = 7.5 Hz, 1H), 8.58 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 6.5 Hz, 1H), 7.74 – 7.71 (m, 4H), 7.41 – 7.32 (m, 3H), 7.13 (s, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 2H), 2.05 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 182.3, 143.4, 141.4, 136.1, 135.2, 134.6, 133.5, 132.4, 131.6, 130.3, 130.1, 129.4, 128.4, 128.0, 127.5, 127.4, 126.3, 126.2, 125.2, 123.8, 121.3, 121.2, 119.5, 113.7, 22.7 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{21}N_3NaO_5S$ 582.1094, found 582.1107.

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Chapter 4A

Domino Dipolar Cycloaddition-Ring Opening Reaction of Pyridinium Ylides with Electrophilic Indoles

4A.1 Abstract

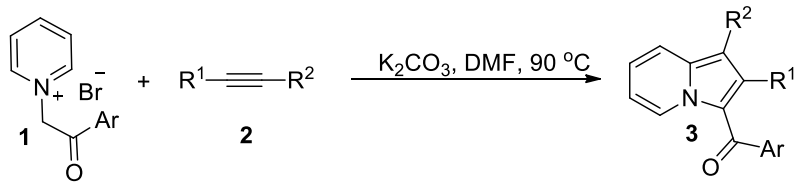
A simple and efficient synthetic approach for constructing a variety of structurally novel indolizines has been developed from electrophilic indoles and pyridinium ylides. The synthetic protocol involves a 1,3-dipolar cycloaddition reaction followed by a strain-induced ring opening aromatization. A series of indolizines bearing different substituents were obtained in moderate to good yields.

4A.2 Introduction

Pyridinium ylides are versatile building blocks for synthetic heterocyclic chemistry. They are widely utilized as synthons for accessing heterocycles due to their ease of preparation and strong reactivity as nucleophiles, 1,3-dipoles, and electrophiles.[1] The 1,3-dipolar cycloaddition of pyridinium ylides with 1,3-dipolarophiles, such as electron-deficient alkenes and alkynes, has become one of the most convergent and straightforward approaches toward functionalized indolizines.[1]

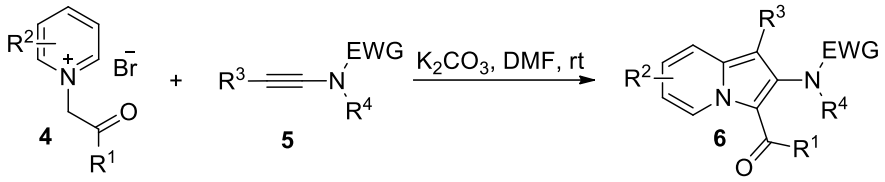
4A.2.1 Reports on reactions of 1,3-dipolar cycloaddition reactions of Pyridinium *N*-ylides

Yongjia Shang and his co-workers reported the 1,3-dipolar cycloaddition between pyridinium salt **1** and alkyne **2**. The reaction proceeded under basic conditions and afforded the corresponding indolizine derivatives **3** in good yield (Scheme 4A.1).[2]



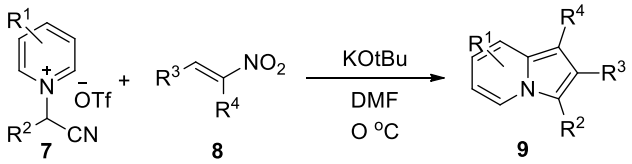
Scheme 4A.1 Reaction of pyridinium ylides with alkynes

Later, *N*-ethynylamides **5**, having an electron-withdrawing substituent at the triple bond, were also successfully involved in a 1,3-dipolar cycloaddition with stabilized pyridinium ylides towards the synthesis of highly functionalized 2-aminoindolizines **6** (Scheme 4A.2).[3]



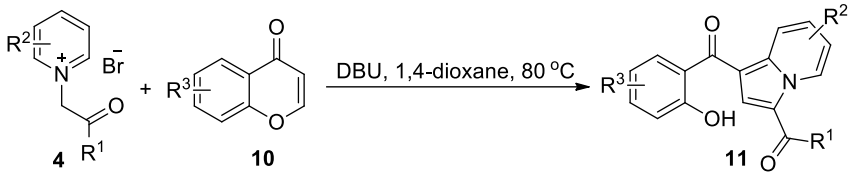
Scheme 4A.2 Synthesis of 2-aminoindolizines

Kucukdisli and Opatz generated a synthetic route for accessing highly substituted indolizines and *N*-fused pyrrole containing heterocycles using pyridinium salts and nitroalkenes **8** (Scheme 4A.4).[4]



Scheme 4A.3 Reaction of pyridinium ylides with nitroalkenes

Dong *et al*. also reported a metal-free synthesis of indolizines **11** bearing a phenolic hydroxy group from structure-specific alkenes such as chromones **10**.



Scheme 4A.4 Synthesis of indolizines from chromones and pyridinium salts

The reaction proceeded *via* a 1,3-dipolar-cycloaddition reaction followed by ring-opening isomerization (Scheme 4A.3).[5]

Indolizines are an important class of nitrogen-containing heterocycles that exhibit a variety of biological activities, including anti-cancer, anti-inflammatory, anti-convulsant and phosphodiesterase inhibitory effects (Figure 1).[6] Besides, indolizine motifs are also known to have diverse photophysical properties.[7] Due to the widespread use of this heterocyclic moiety as a preferred scaffold, researchers in organic chemistry and material science are now looking into effective methods for synthesising multisubstituted indolizine derivatives.

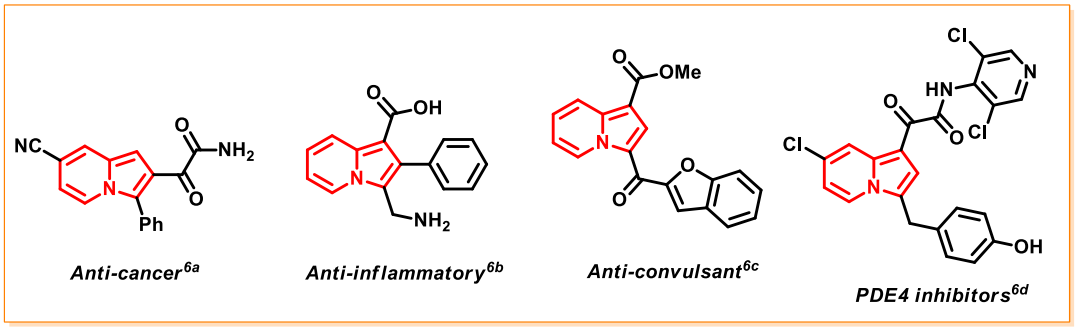
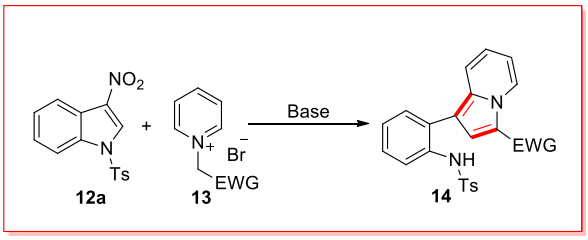


Figure 1. Bioactive Indolizines

4A.3 Statement of the problem

Recently, much attention has been paid to investigating the electrophilic reactivity of 3-nitro indoles. Notably, it has been shown that by incorporating electron-withdrawing groups on the *N*-atom and C-2 or C-3 carbon atoms of indole resulted in reversing its intrinsic nucleophilic character, thus making the system quite electrophilic (described in detail in Chapter 1). Our interest in the chemistry of electrophilic benzannulated heterocycles led us towards the synthesis of functionalized pyrrolo[2,1-*a*]isoquinolines *via* a domino dipolar cycloaddition-ring opening reaction of electrophilic indoles with isoquinolinium methylides[8] (Chapter 3A). Inspired by the above reports, we hypothesized that the reactions of pyridinium *N*-ylides with electrophilic indoles would develop novel indolizine derivatives (Scheme 4A.5).

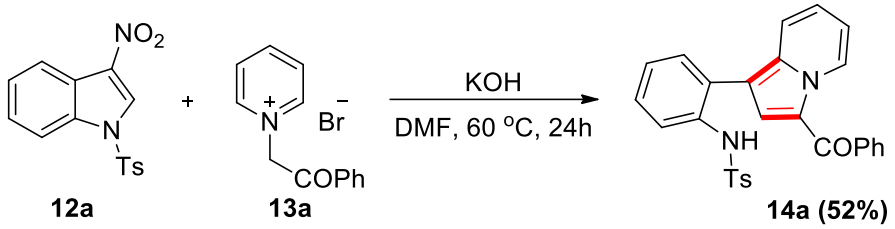


Scheme 4A.5 Reactivity of electrophilic indoles with pyridinium ylides

4A.4 Results and discussion

With this knowledge in mind, we began our investigations by studying the reactions of *N*-tosyl 3-nitroindole (**12a**) with 1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide (**13a**) in DMF with KOH (4 equiv.) as base at 60 °C for 24 h. As depicted in Scheme 4A.5, the 1,3-dipolar cycloaddition reaction between **12a** and **13a** resulted in the formation of functionalized

indolizine **14a** in 52% yield (Scheme 4A.6). The structure of **14a** was established by various spectroscopic analyses.



Scheme 4A.6 1,3-dipolar cycloaddition of pyridinium methylides with electrophilic indole.

In the ^{1}H NMR spectrum, aromatic protons were found to resonate in the region δ 9.92-6.54 ppm. The proton on the pyridinium ring attached near to the N atom (a) resonated at 9.91 ppm as a doublet. The singlet observed at δ 6.54 (b) ppm was attributed to NH proton attached to the tosyl group. The methyl protons of tosyl group resonated as singlet at δ 2.18 ppm. The ^{1}H NMR spectrum of the compound is shown in figure 2.

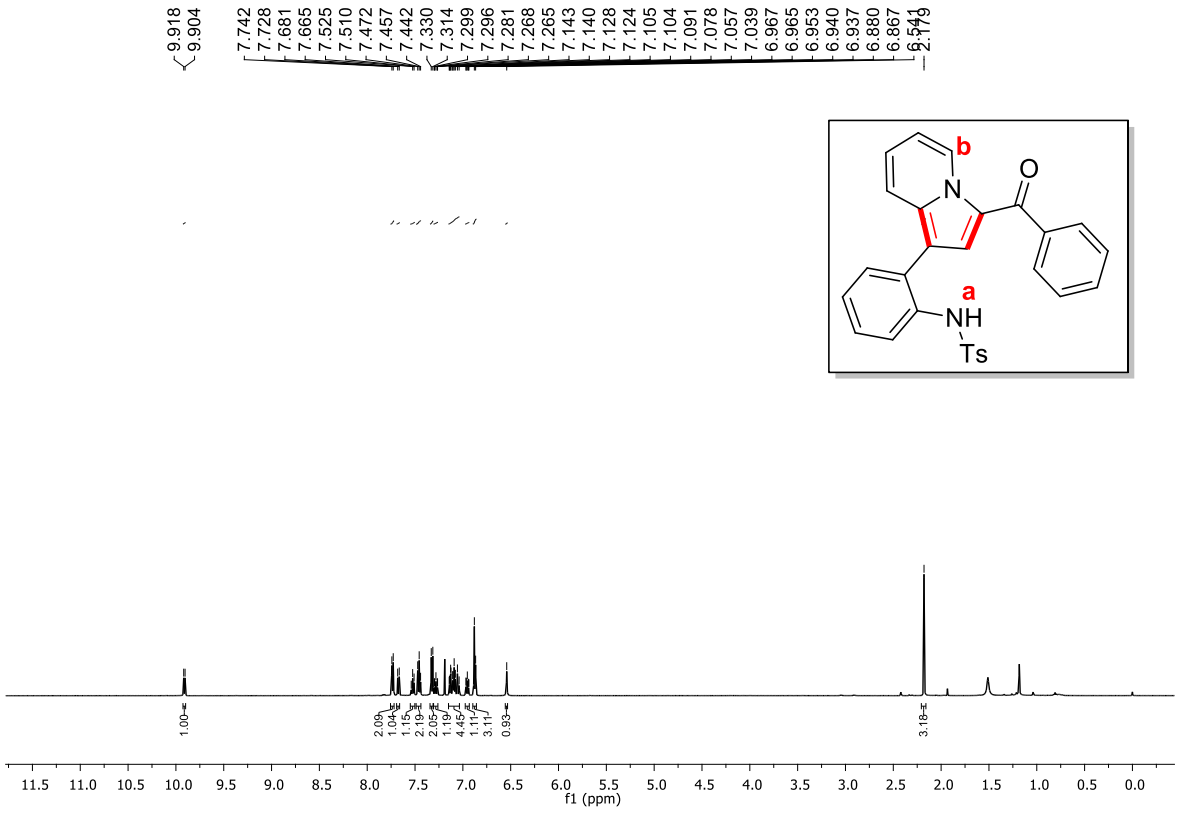


Figure 2. ^{1}H NMR Spectra of **14a**

In the ^{13}C spectrum (Figure 3), the aromatic carbons resonated in the region δ 184.7-111.1 ppm. The carbonyl carbon (a) resonated at δ 184.7 ppm and the methyl carbon of the tosyl group showed a peak at δ 21.5 ppm. All other peaks in the ^{1}H and ^{13}C NMR were in good agreement with the assigned structure.

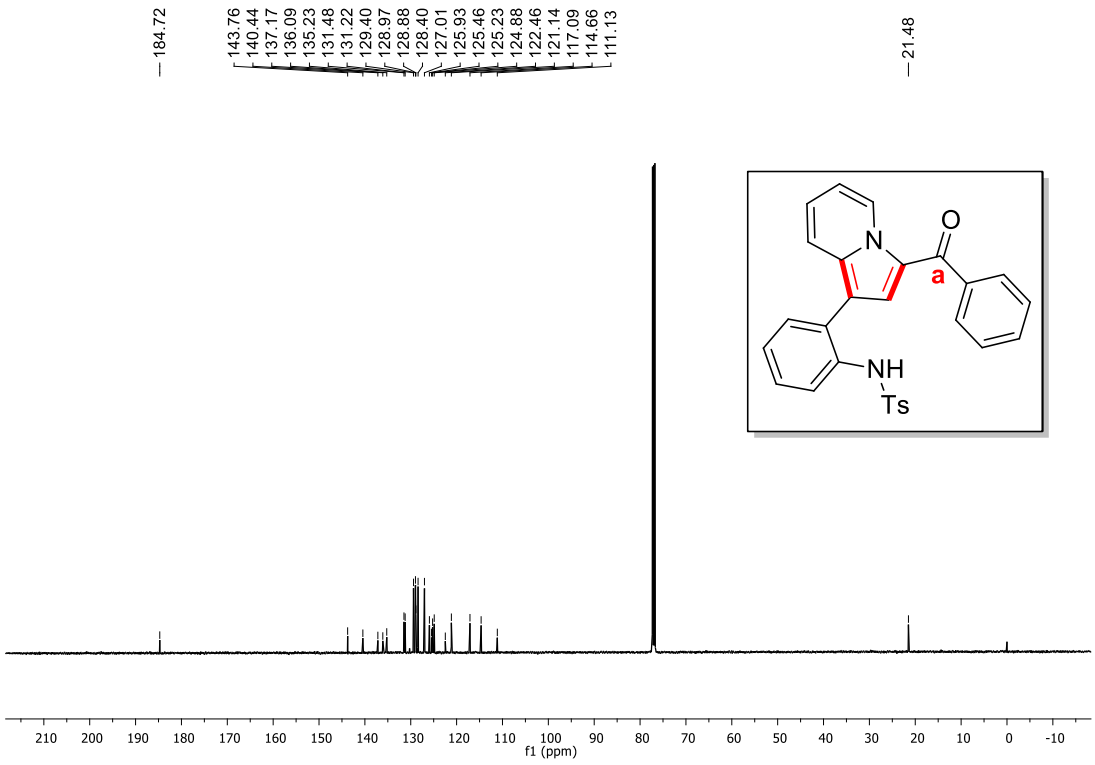


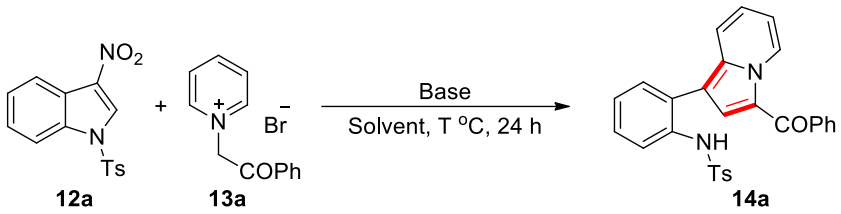
Figure 3. ^{13}C NMR Spectra of **14a**

The structure assigned was further confirmed by high resolution mass spectral analysis which showed (M+H) peak at *m/z* = 467.1442.

Detailed optimization studies were carried out with *N*-tosyl 3-nitro indole **12a** (1.0 equiv.) and 1-(2-oxo-2-phenylethyl)pyridine-1-ium bromide **13a** (1.1 equiv.) as model substrates (Table 1). After screening different solvents and bases (entries 2-12), the combination of CH_3CN and K_3PO_4 emerged as the best option. The amounts of K_3PO_4 and **13a** were also optimized (entries 13-17), and 4.0 equiv. of K_3PO_4 and 1.2 equiv. of **13a** proved to be the best choice (entry 17). Next, we turned our attention to checking the effect of concentration on the outcome of the reaction. Changing the concentration to 0.1 mmol as well as 0.3 mmol

did not have a positive influence on the reaction yield. For further improvement of yields, we also increased the reaction temperature but it led to a drop in yield of **14a** to 30% (entry 15).

Table 1: Optimization studies[a]

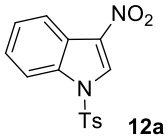
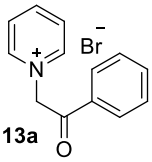
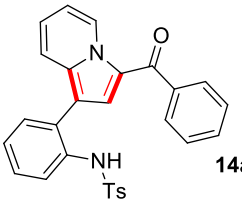
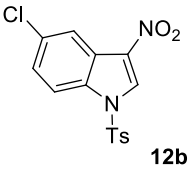
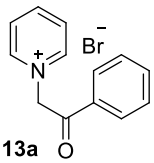
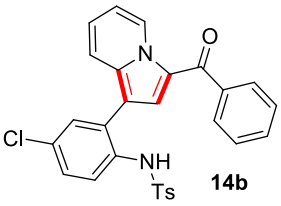
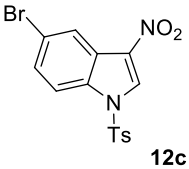
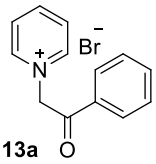
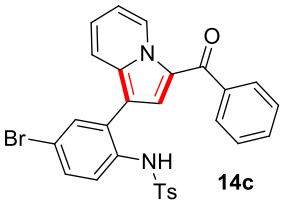
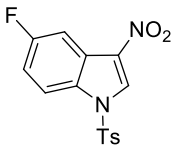
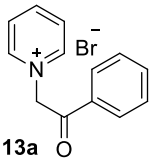
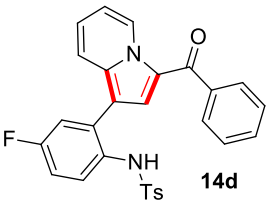
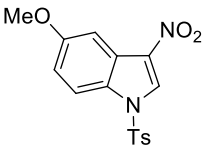
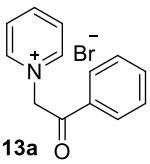
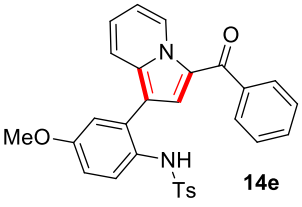


Entry	Oxidant	Solvent	Temp (° C)	Yield of **14a** (%)
1	KOH	DMF	rt	15
2	KOH	DMF	60	52
3	KOH	1,4-dioxane	60	30
4	KOH	CH_3CN	60	58
5	KOH	THF	60	27
6	DBU	CH_3CN	60	32
7	Et_3N	CH_3CN	60	traces
8	KO*t*Bu	CH_3CN	60	47
9	NaOH	CH_3CN	60	36
10	K_3PO_4	CH_3CN	60	64
11	LiOH	CH_3CN	60	traces
12	K_2CO_3	CH_3CN	60	traces
13[b]	K_3PO_4	CH_3CN	60	39
14[c]	K_3PO_4	CH_3CN	60	33
15	K_3PO_4	CH_3CN	90	30
16[d]	K_3PO_4	CH_3CN	60	74
17[e]	**K_3PO_4**	**CH_3CN**	**60**	**77**
18[f]	K_3PO_4	CH_3CN	60	65
19[g]	K_3PO_4	CH_3CN	60	26
20[h]	K_3PO_4	CH_3CN	60	33

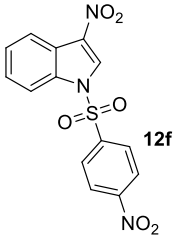
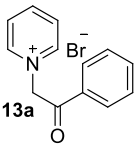
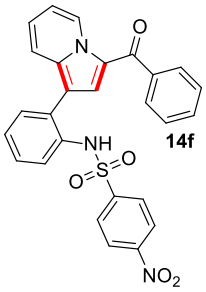
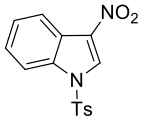
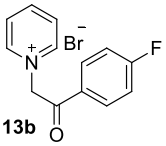
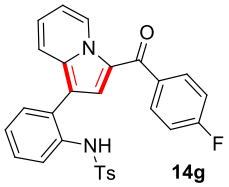
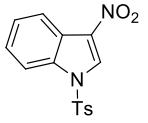
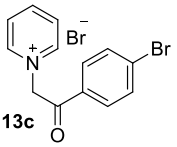
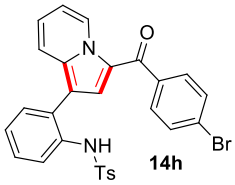
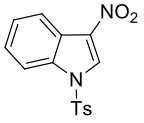
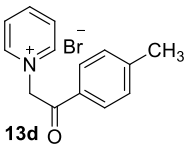
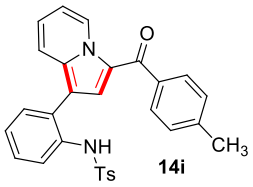
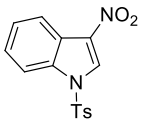
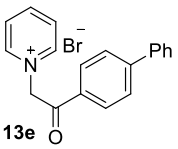
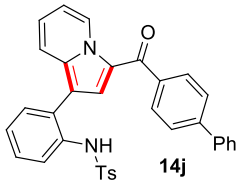
Reaction conditions: [a] **12a** (1.0 equiv., 0.16 mmol), **13a** (1.5 equiv.), base (4.0 equiv.), solvent (0.15 mM), 60 °C; [b]base (3.0 equiv.); [c]base (5.0 equiv.); [d]**13a** (1.1 equiv.); [e]**13a** (1.2 equiv.); [f]**13a** (1.3 equiv.), [g]solvent (0.1 mM), [h]solvent (0.3 mM).

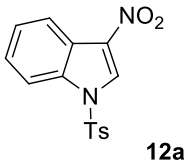
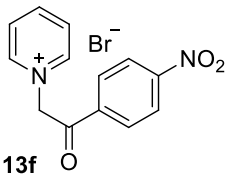
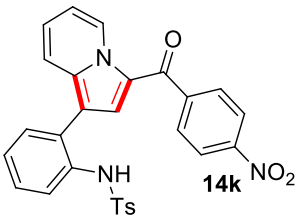
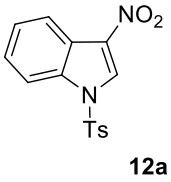
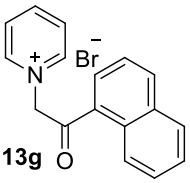
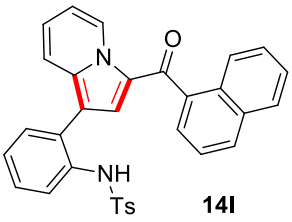
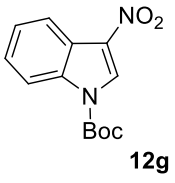
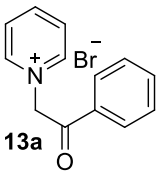
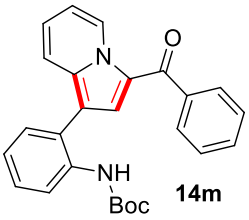
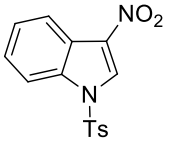
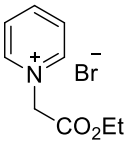
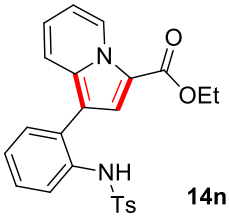
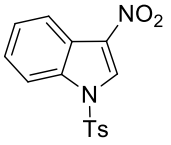
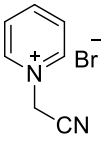
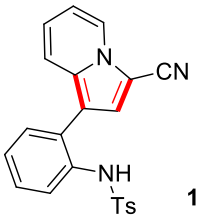
With the optimized conditions in hand [1.0 equiv. of **12a**, 1.2 equiv. of **13a**, K_3PO_4 (4 equiv.), CH_3CN (1ml), 60 ^oC], a series of 3-nitroindoles and pyridinium salts were applied to establish the scope and generality of the protocol**,** the results of which are summarized in Table 2. First, the generality of different 3-nitro indoles on the model substrate 1-(2-oxo-2-phenylethyl)pyridine-1-ium bromide (**13a**) were studied (Table 2, entry 1-6).

Table 2. Generality of 1,3-dipolar cycloaddition of pyridinium methylides with substituted electrophilic indoles[a]

Entry	Indole	Pyridinium methylide	Product	Yield
1	 **12a**	 **13a**	 **14a**	77
2	 **12b**	 **13a**	 **14b**	66
3	 **12c**	 **13a**	 **14c**	44
4	 **12d**	 **13a**	 **14d**	42
5	 **12e**	 **13a**	 **14e**	NR

The reactions with halogen (Cl, Br, F)-substituted nitroindoles proceeded well, affording the products **14b**, **14c** and **14d** in moderate yields (Table 2). No desired product was obtained on using 5-methoxy-3-nitroindole as the substrate (**14e**) (Table 2). The reaction with 3-nitro-1-((4-nitrophenyl)sulfonyl)-1H-indole afforded the corresponding indolizine in moderate yield (**14f**) (Table 2).

Entry	Indole	Pyridinium methylide	Product	Yield
6	 **12f**	 **13a**	 **14f**	48
7	 **12a**	 **13b**	 **14g**	50
8	 **12b**	 **13c**	 **14h**	52
9	 **12a**	 **13d**	 **14i**	54
10	 **12a**	 **13e**	 **14j**	62

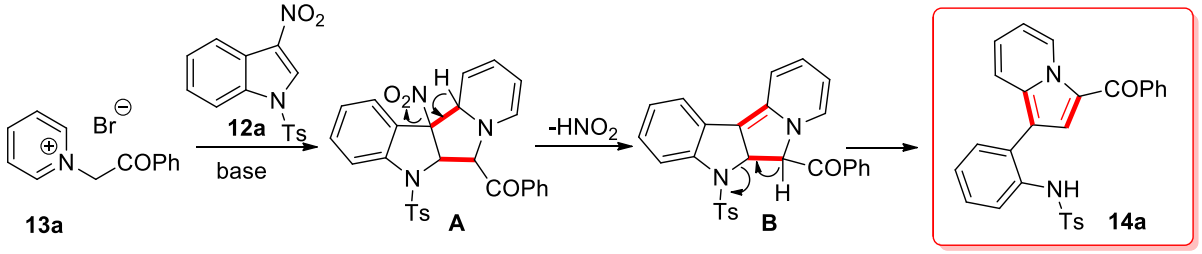
Entry	Indole	Pyridinium methylide	Product	Yield
11	 **12a**	 **13f**	 **14k**	63
12	 **12a**	 **13g**	 **14l**	65
13	 **12g**	 **13a**	 **14m**	NR
14	 **12a**	 **13h**	 **14n**	NR
15	 **12a**	 **13i**	 **14o**	NR

Reaction conditions: [a]**1** (1.0 equiv., 100 mg), **2** (1.2 equiv.), K_3PO_4 (4.0 equiv.), CH_3CN (0.15 mM), 60 ^oC, 24 h.

Next, the influence of the nature of pyridinium salts was examined. To this end, various pyridinium salts bearing different electron withdrawing groups were tested (Table 2, entry 7-15). The reactions of pyridinium bromides (with different substituents on the para position of

the phenyl ring) afforded the products in good yield (**14g-14k**) (Table 2). Finally, the pyridinium methylide **13l** with naphthoyl group as the electron-withdrawing moiety furnished the corresponding indolizine in satisfactory yield (**14l**). With 3-nitro *N*-Boc indole, we could only observe the formation of an intractable band (**14m**). Ethoxycarbonyl and cyano-substituted pyridinum salts also failed to participate in the reaction (**14n, 14o**) (Table 2).

Based on our observations and on the reported literature,[4,8] we have proposed a plausible mechanism for the present domino dipolar cycloaddition-ring opening process happening during the reaction of electrophilic indole and pyridinium methylide (Scheme 4A.7). This reaction proceeded *via* a 1,3-dipolar cycloaddition-ring opening and aromatization cascade (Scheme 4A.7). The first step is the conversion of the pyridinium salt **13a** to the corresponding *N*-ylide in the presence of a base. Next, a 1,3-dipolar cycloaddition takes place between the dipolarophile, *N*-tosyl-3-nitroindole **12a** and the *N*-ylide to generate the corresponding cycloadduct **A.** Subsequent elimination of HNO_2 from **A** generates the unstable intermediate **B**, which upon aromatization, results in a strain-induced cleavage of the C-N bond furnishing the final product indolizine **14a**.



Scheme 4A.7 Plausible mechanism for 1,3-dipolar cycloaddition of pyridinium ylides with electrophilic indoles

4A.5 Conclusions

In conclusion, we have developed a novel method for the synthesis of complex indolizines from various 3-nitroindoles and pyridinium methylides *via* a 1,3-dipolar cycloaddition-ring opening reaction. This protocol is compatible with a wide range of functional groups and represents a simple, efficient, and economical method of producing indolizine derivatives with moderate to good yields. Furthermore, the presence of two functionalizable C-H bonds

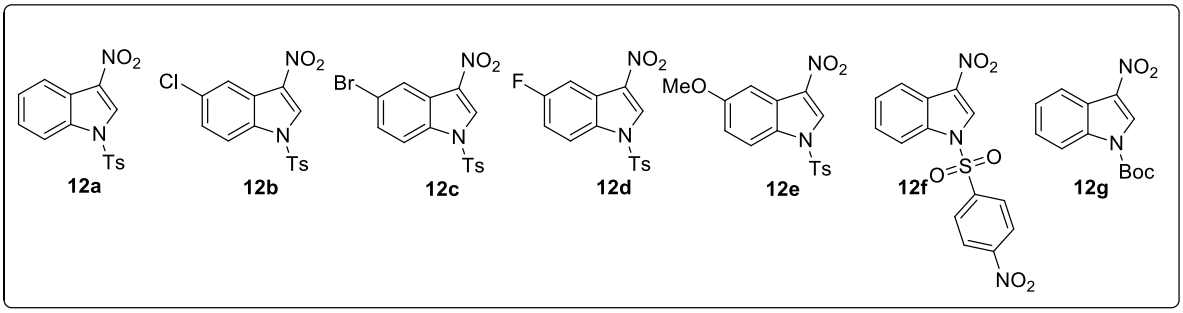
in these indolizine motifs makes it attractive for accessing fused indolizine scaffolds, the details of which will be discussed in Chapter 4B.

4A.6 Experimental section

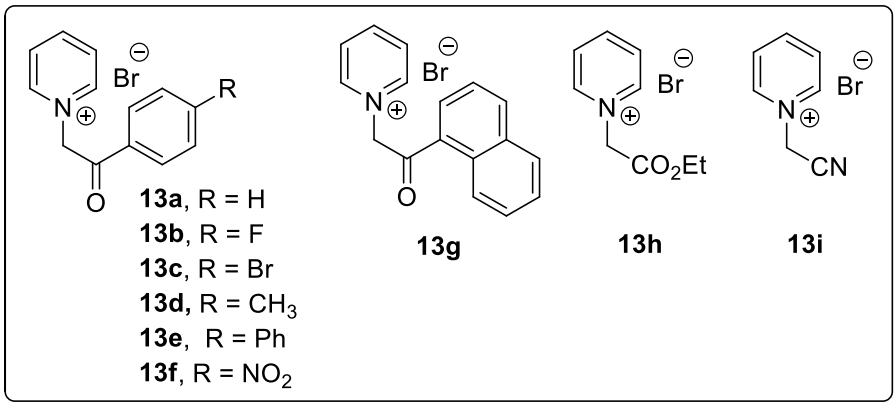
4A.6.1 General experimental methods: All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets pre-coated with silica gel containing fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using neutral alumina, silica gel and mixtures of ethyl acetate hexanes for elution. Melting points were determined using a calibrated digital melting point apparatus (Büchi 530 melting point apparatus). NMR spectra were recorded with Bruker AMX-500 (500 MHz for 1H NMR, 125 MHz for $^{13}C\{^{1}H\}$ NMR) instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were performed with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with a ESI/ HRMS at 60,000 resolution using ThermoScientificExactive mass spectrometer with orbitrap analyzer.

4A.6.2 Synthesis and characterization:

Procedure for the synthesis of 3-Nitroindoles: 3-Nitroindoles (**12a-12g**) were prepared by following a literature report.[9]



Procedure for the synthesis of pyridinium salts (13a-13i): All pyridinium salts (**13a-13i**) were prepared by following a previously reported procedure.[10] To pyridine dissolved in acetone at 0 °C, α-halocarbonyl compound was added and the mixture was stirred at room temperature for a period of time. After the completion of the reaction, the precipitate formed was filtered and washed with diethyl ether to get the pure product.



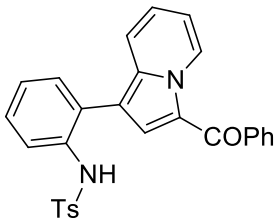
Experimental procedure for the reaction between 3-nitro-*N*-tosyl indole and pyridinium salt

A mixture of 3-nitro-*N*-tosyl indole (100 mg, 1.0 equiv.), pyridinium salt (1.2 equiv.) and K_3PO_4 (4.0 equiv.) was weighed into a dry reaction tube. Dry CH_3CN was added and the reaction mixture was allowed to stir at 60 °C for 24 h. After completion of the reaction as indicated from the TLC, the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

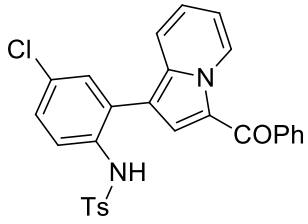
Synthesis and characterization of indolizines

*N-(2-(3-benzoylindolizin-1-yl)phenyl)-4-methylbenzenesulfonamide (**14a**).* The reaction was performed according to general procedure with 3-nitro-N-tosyl indole **12a** (100 mg, 0.32 mmol), 1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide **13a** (105 mg, 0.38 mmol) and K_3PO_4 (272 mg, 1.28 mmol) at 60 °C for 24 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14a** as a yellow solid (114 mg, 77%).

	Mp: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.91 (d, *J* = 7.0 Hz, 1H), 7.74

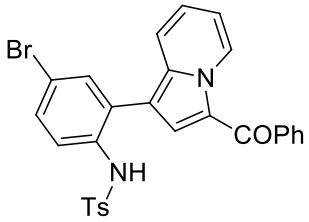
	(d, *J* = 7.0 Hz, 2H), 7.67 (d, *J* = 8 Hz, 1H), 7.54-7.51 (m, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.30-7.26 (m, 1H), 7.14-7.04 (m, 4H), 6.97-6.94 (m, 1H), 6.87 (d, *J* = 6.5 Hz, 3H), 6.54 (s, 1H), 2.18 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 184.7, 143.8, 140.4, 137.2, 136.1, 135.2, 131.5, 131.2, 129.4, 129.0, 128.9, 128.4, 127.0, 125.9, 125.5, 125.2, 124.9, 122.5, 121.1, 117.1, 114.7, 111.1, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{23}N_2O_3S$: 467.1424, found 467.1442.

N-(2-(3-benzoylindolizin-1-yl)-4-chlorophenyl)-4-methylbenzenesulfonamide ***(14b)***. The reaction was performed according to general procedure with 5-Cl-3-nitro-*N*-tosyl indole **12b** (100 mg, 0.28 mmol), 1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide **13a** (94 mg, 0.34 mmol) and K_3PO_4 (238 mg, 1.12 mmol) at 60 ºC for 24 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14b** as a yellow solid (92 mg, 66%).

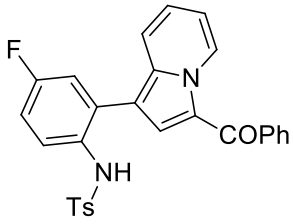
	**Mp**: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.86 (d, *J* = 6.5 Hz, 1H), 8.01 (d, *J* = 7.0 Hz, 1H), 7.71 (d, *J* = 7.0 Hz, 2H), 7.54-7.51 (m, 2H), 7.44 (t, *J* = 7.0 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.12-7.03 (m, 2H), 6.95-6.94 (m, 1H), 6.88-6.86 (m, 2H), 6.64 (s, 1H), 2.17 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 184.8, 171.4, 144.1, 140.2, 137.0, 135.8, 134.5, 134.1, 133.7, 131.7, 131.4, 130.2, 129.5, 129.0, 128.5, 128.4, 127.0, 126.0, 125.7, 122.8, 122.6, 117.9, 116.9, 114.8, 109.8, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{22}ClN_2O_3S$: 501.1034, found 501.1055.

N-(2-(3-benzoylindolizin-1-yl)-4-bromophenyl)-4-methylbenzenesulfonamide ***(14c)***. The reaction was performed according to general procedure with 5-Br-3-nitro-*N*-tosyl indole **12c**

(100 mg, 0.25 mmol), 1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide **13a** (83 mg, 0.30 mmol) and K_3PO_4 (212 mg, 1.00 mmol) at 60 ºC for 24 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14c** as a yellow solid (60 mg, 44%).

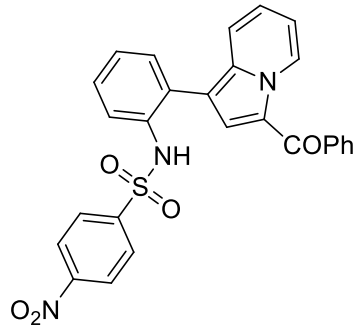
	**Mp**: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.97 (d, *J* = 6.0 Hz, 1H), 7.80 (d, *J* = 7.0 Hz, 2H), 7.64-7.59 (m, 2H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.47-7.45 (m, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 2.5 Hz, 1H), 7.21-7.19 (m, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 7.06-7.03 (m, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.91 (s, 1H), 6.57 (s, 1H), 2.18 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 184.8, 144.1, 134.5, 134.1, 131.8, 131.4, 129.5, 129.0, 128.49, 128.46, 127.5, 127.04, 127.00, 125.8, 125.6, 122.5, 118.2, 117.8, 116.8, 114.8, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{22}BrN_2O_3S$: 545.0529, found 545.0547.

N-(2-(3-benzoylindolizin-1-yl)-4-fluorophenyl)-4-methylbenzenesulfonamide ***(14d)***. The reaction was performed according to general procedure with 5-F-3-nitro-*N*-tosyl indole **12d** (100 mg, 0.30 mmol), 1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide **13a** (100 mg, 0.36 mmol) and K_3PO_4 (255 mg, 1.20 mmol) at 60 ºC for 24 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14d** as a yellow solid (61 mg, 42%).

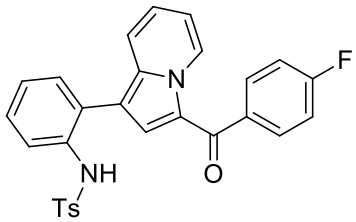
	**Mp**: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.86 (d, *J* = 7.0 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 2H), 7.63-7.61 (m, 1H), 7.51 (t, *J* = 7.0 Hz, 1H), 7.46-7.43 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.12-7.08 (m, 1H), 7.02-6.96 (m, 2H), 6.93 (t, *J* = 6.5 Hz, 1H), 6.87-6.84 (m, 1H), 6.81 (d, *J* = 9.5 Hz, 3H), 6.52 (d, *J* = 5.0 Hz, 1H) 2.13 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 184.8, 159.9 (d, *J* = 245 Hz),

	143.8, 140.3, 136.8, 135.8, 131.4, 131.1, 129.4, 129.0, 128.9, 128.5, 126.9, 125.6, 125.5, 124.4, 124.3, 122.5, 118.0, 117.8, 116.8, 115.7, 115.5, 114.8, 110.2, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{22}FN_2O_3S$: 485.1330, found 485.1343.

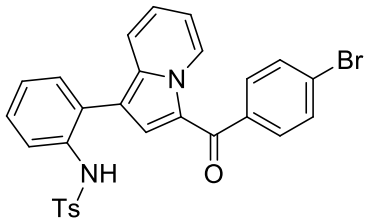
*N-(2-(3-benzoylindolizin-1-yl)phenyl)-4-nitrobenzenesulfonamide (**14f**).* The reaction was performed according to general procedure with 3-nitro-1-((4-nitrophenyl)sulfonyl)-1H-indole **12f** (100 mg, 0.29 mmol), 1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide **13a** (97 mg, 0.35 mmol) and K_3PO_4 (246 mg, 1.16 mmol) at 60 ºC for 24 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14f** as a yellow solid (69 mg, 48%).

	**Mp**: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.89 (d, *J* = 7.0 Hz, 1H), 7.78 (d, *J* = 7.0 Hz, 2H), 7.74 (d, *J* = 8 Hz, 1H), 7.64-7.62 (m, 1H), 7.51-7.48 (m, 3H), 7.45-7.41 (m, 2H), 7.37-7.34 (m, 2H), 7.32-7.27 (m, 3H), 7.13-7.06 (m, 2H), 6.99-6.96 (m, 1H), 6.90 (s, 1H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 184.4, 140.3, 137.2, 134.5, 133.1, 132.2, 131.6, 131.2, 13.4, 128.91, 128.87, 128.4, 126.7, 126.0, 125.8, 125.4, 125.1, 122.2, 116.5, 114.4, 111.7 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{27}H_{20}N_3O_5S$: 498.1118, found 498.1108.

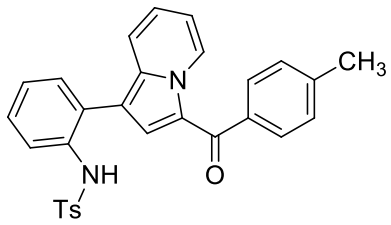
*N-(2-(3-(4-fluorobenzoyl)indolizin-1-yl)phenyl)-4-methylbenzenesulfonamide (**14g**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **12a** (100 mg, 0.32 mmol), 1-(2-(4-fluorophenyl)-2-oxoethyl)pyridin-1-ium bromide **13b** (112 mg, 0.38 mmol) and K_3PO_4 (272 mg, 1.28 mmol) at 60 ºC for 24 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14g** as a green solid (77 mg, 50%).

	**Mp**: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.94 (d, *J* = 5.5 Hz, 1H), 7.83 (m, 2H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.0 Hz, 2H), 7.36 (t, *J* = 6.5 Hz, 1H), 7.20-7.12 (m, 6H), 7.02-6.96 (m, 4H), 6.63 (s, 1H), 2.28 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 183.2, 143.8, 136.5, 136.2 (d, J = 254 Hz), 131.5, 131.4, 131.3, 129.4, 129.0, 128.8, 127.0, 125.8, 125.4, 125.3, 124.9, 122.2, 121.1, 117.1, 115.6, 115.4, 114.8, 111.2, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{22}FN_2O_3S$: 485.1330, found 485.1342.

*N-(2-(3-(4-bromobenzoyl)indolizin-1-yl)phenyl)-4-methylbenzenesulfonamide(**14h**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **12a** (100 mg, 0.32 mmol), 1-(2-(4-bromophenyl)-2-oxoethyl)pyridin-1-ium bromide **13c** (135 mg, 0.38 mmol) and K_3PO_4 (272 mg, 1.28 mmol) at 60 ºC for 24 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14h** as a green solid (91 mg, 52%).

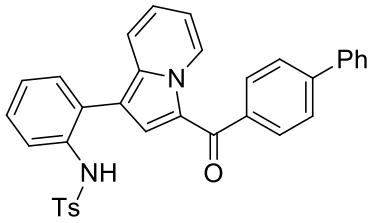
	**Mp**: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.84 (d, *J* = 7.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.59-7.55 (m, 4H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.13-7.05 (m, 4H), 6.93 (t, *J* = 6.5 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 2H), 6.83 (s, 1H), 6.58 (s, 1H), 2.21 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 183.2, 143.9, 139.2, 137.5, 136.2, 135.2, 131.6, 131.5, 130.6, 129.4, 129.0, 128.9, 127.0, 125.93, 125.87, 125.6, 125.4, 125.0, 122.1, 121.2, 117.2, 114.9, 111.5, 21.5 pm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{22}BrN_2O_3S$: 545.0529, found 545.0529.

4-methyl-N-(2-(3-(4-methylbenzoyl)indolizin-1-yl)phenyl)benzenesulfonamide ***(14i)***. The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **12a** (100 mg, 0.32 mmol), 1-(2-oxo-2-(p-tolyl)ethyl)pyridin-1-ium bromide **13d** (111 mg, 0.38 mmol) and K_3PO_4 (272 mg, 1.28 mmol) at 60 ºC for 24 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14i** as a green solid (83 mg, 54%).

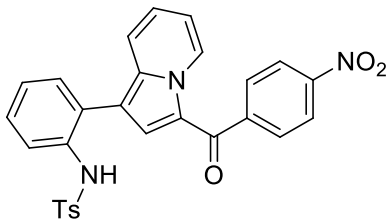
	**Mp**: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.88 (d, *J* = 7.0 Hz, 1H), 7.68-7.64 (m, 3H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.28-7.25 (m, 3H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.11-7.03 (m, 3H), 6.93 (t, *J* = 6.5 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 3H), 6.55 (s, 1H), 2.41 (s, 3H), 2.18 (s, 3H) ppm. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)**: δ 184.7, 143.7, 141.7, 137.7, 137.0, 136.1, 135.2, 131.5, 129.4, 129.14, 129.07, 128.8, 127.0, 125.8, 125.6, 125.0, 124.9, 122.6, 121.2, 117.0, 114.5, 110.9, 21.6, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{29}H_{25}N_2O_3S$: 481.1580, found 481.1600.

N-(2-(3-([1,1'-biphenyl]-4-carbonyl)indolizin-1-yl)phenyl)-4-methylbenzenesulfonamide ***(14j)***. The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **12a** (100 mg, 0.32 mmol), 1-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)pyridin-1-ium bromide **13e** (134 mg, 0.38 mmol) and K_3PO_4 (272 mg, 1.28 mmol) at 60 ºC for 24 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14j** as a green solid (107 mg, 62%).

	Mp: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 10.00 (d, *J* = 7.0 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.77-7.74 (m, 3H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.43-7.40 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.24-7.13 (m, 4H), 7.05-7.02 (m, 2H), 6.95

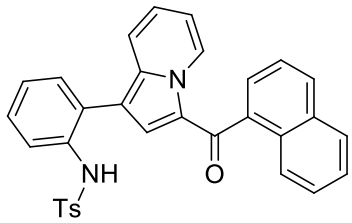
	(d, *J* = 8.0 Hz, 2H), 6.65 (s, 1H), 2.19 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 184.3, 175.3, 144.1, 140.1, 139.1, 137.2, 136.1, 135.2, 131.5, 129.6, 129.4, 129.0, 128.9, 128.1, 127.3, 127.1, 127.0, 125.9, 125.5, 125.3, 124.9, 122.5, 121.1, 117.1, 114.7, 111.2, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{34}H_{27}N_2O_3S$: 543.1737, found 543.1763.

*4-methyl-N-(2-(3-(4-nitrobenzoyl)indolizin-1-yl)phenyl)benzenesulfonamide (**14k**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **12a** (100 mg, 0.32 mmol), 1-(2-(4-nitrophenyl)-2-oxoethyl)pyridin-1-ium bromide **13f** (122 mg, 0.38 mmol) and K_3PO_4 (272 mg, 1.28 mmol) at 60 °C for 24 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14k** as a green solid (103 mg, 63%).

	**Mp**: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.93 (d, *J* = 6.5 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.0 Hz, 1H), 7.18-7.09 (m, 4H), 7.03 (t, *J* = 6.5 Hz, 1H), 6.96-6.95 (m, 3H), 6.52 (s, 1H), 2.22 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)**: δ 181.8, 149.2, 145.9, 143.9, 138.0, 136.4, 135.2, 131.5, 129.8, 129.5, 129.14, 129.10, 127.0, 126.3, 126.2, 125.0, 123.6, 121.9, 121.1, 117.4, 115.4, 112.3, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{22}N_3O_5S$: 512.1275, found 512.1293.

*N-(2-(3-(1-naphthoyl)indolizin-1-yl)phenyl)-4-methylbenzenesulfonamide (**14l**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **12a** (100 mg, 0.32 mmol), 1-(2-(naphthalen-1-yl)-2-oxoethyl)pyridin-1-ium bromide **13g** (124 mg, 0.38 mmol) and K_3PO_4 (272 mg, 1.28 mmol) at 60 °C for 24 h. After workup, the residue was purified by

silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **14l** as a yellow solid (107 mg, 65%).

	**Mp**: 223−226 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 10.17 (d, *J* = 6.5 Hz, 1H), 8.17 (d, *J* = 6.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 6.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 6.5 Hz, 1H), 7.57 (d, *J* = 7.0 Hz, 3H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 6.5 Hz, 3H), 7.18-7.09 (m, 4H), 6.68 (d, *J* = 7.5 Hz, 2H), 6.56 (s, 1H), 6.50 (s, 1H), 2.09 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)**: δ 185.6, 143.7, 138.2, 137.7, 135.7, 135.2, 133.8, 131.5, 131.0, 130.2, 129.3, 129.1, 128.9, 128.3, 127.2, 126.8, 126.6, 126.4, 126.3, 125.8, 125.6, 125.2, 124.8, 124.6, 123.7, 121.1, 117.2, 115.0, 111.3, 21.3 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{32}H_{25}N_2O_3S$: 517.1580, found 517.1598.

4A.7 References

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Chapter 4B

Pd(II)–mediated C–H Functionalization of Indolizines towards Polyring Fused *N*-Heterocycles

4B.1 Abstract

The presence of two functionalizable C-H bonds in 5-benzoyl-substituted indolizine makes it attractive for accessing fused indolizine scaffolds. In this line, we have introduced a palladium-mediated site-selective C-H functionalization, where the N-centre and the two C-H centres of the indolizine moiety can be readily functionalized to generate fused N-heterocycles. A Pd-mediated cross-dehydrogenative coupling afforded 6H-indeno-indolizine, and an oxygen-induced palladium catalyzed selective C-H amination in the same substrate provided a tetracene viz., indolizino[2,1-b]indoles.

4B.2 Introduction

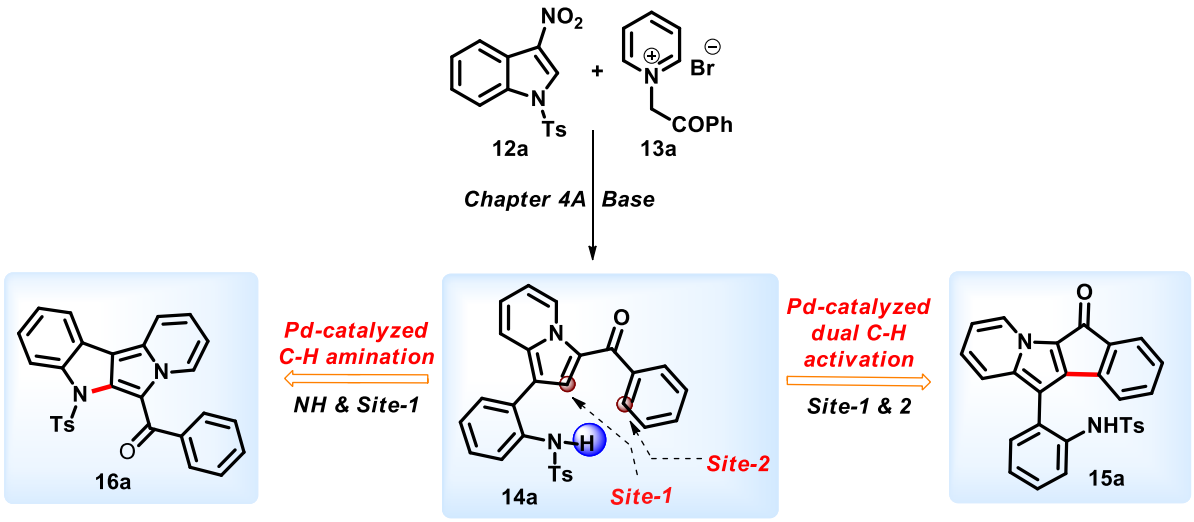
For the past few years, the scientific community has been exploring novel approaches toward the functionalization of unactivated C-H bonds, creating carbon-carbon or carbon-heteroatom bonds.[1] Initially, site-selective C-H functionalization relied on free radical transformations[2], followed by the development of metal complexes capable of activating C-H bonds.[3] Over the past two decades, organic chemists have embraced the task of developing advanced methodologies and new strategies for C-H functionalization at unactivated sites.[4]

4B.3 Statement of the problem

In an effort to synthesize *N*-fused heterocycles, our interest was to make indolizine fused heterocycles amenable by a short and efficient synthetic methodology. Based on our previous report on C-H functionalization of pyrrolo[2,1-*a*]isoquinolines (described in Chapter 3B), we hypothesized that a similar strategy can also be applied to site-selective C-H functionalization of the indolizine moiety **14a** (isolated in Chapter 4A) *via* cross-

dehydrogenative coupling and C-H amination reaction towards the formation of fused indolizine scaffolds.

In this particular substrate *N*-(2-(3-benzoylindolizin-1-yl)phenyl)-4-methylbenzene sulfonamide **14a** (Scheme 4B.1), we identified two functionalizable C-H centers, at site-1 & site-2. Under Pd-catalyzed cross-dehydrogenative coupling conditions, we hypothesized that an intramolecular cyclization would happen between site-1 and site-2, affording 6*H*-indeno-indolizine moiety **15a**. In addition, by tuning the reaction conditions, we postulated that a C-H amination could be effected between N-H and site-1 to synthesise indolizino[2,1- *b*]indole moiety **16a.**

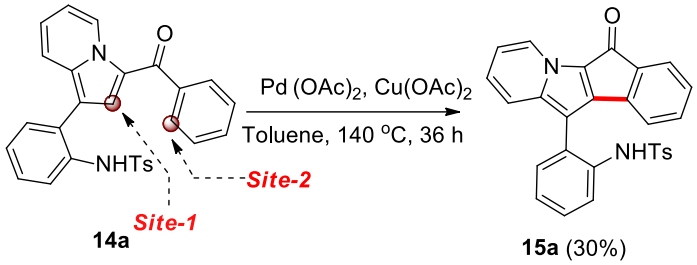


Scheme 4B.1 Pd(II) mediated C-H functionalziation of indolizines

4B.4 Results and Discussion

Cross dehydrogenative coupling (CDC),[5] a technique based on C-H activation that makes it easier to produce carbon-carbon bonds from the direct coupling of two C-H bonds, has emerged as an attractive and competitive way of producing a range of fused heterocyclic rings. In this line, we targeted the Pd-catalyzed cross-dehydrogenative coupling reaction between site-1 and site-2 of indolizine **14a** towards 6*H*-indeno-indolizine moiety **15a** (Scheme 4B.1). To verify the feasibility of our proposed assumption, we started the investigation by synthesizing *N*-(2-(3-benzoylindolizin-1-yl)phenyl)-4-methylbenzene sulfonamide **14a** from 3-nitro-*N*-tosyl indole **12a** and 1-(2-oxo-2-phenylethyl)pyridin-1-ium

bromide **13a** (Scheme 4B.1, described in Chapter 4A). The test reaction was set up with **14a** in the presence of 20 mol% of $Pd(OAc)_2$ in toluene at 140 °C for 24 h (Scheme 4B.2). As expected, we could isolate the product 6*H*-indeno[1,2-*b*]indolizin-6-one **15a** formed by dual C-H activation in 30% yield. The structure of **15a** was established by various spectroscopic analyses.



Scheme 4B.2 Pd(II) mediated dual C-H activation of indolizines

In the ^{1}H NMR spectrum, aromatic protons resonated in the region δ 8.45-6.53 ppm. The proton on the pyridine ring attached near to the *N*-atom (a) resonated at δ 8.45 ppm as a doublet.

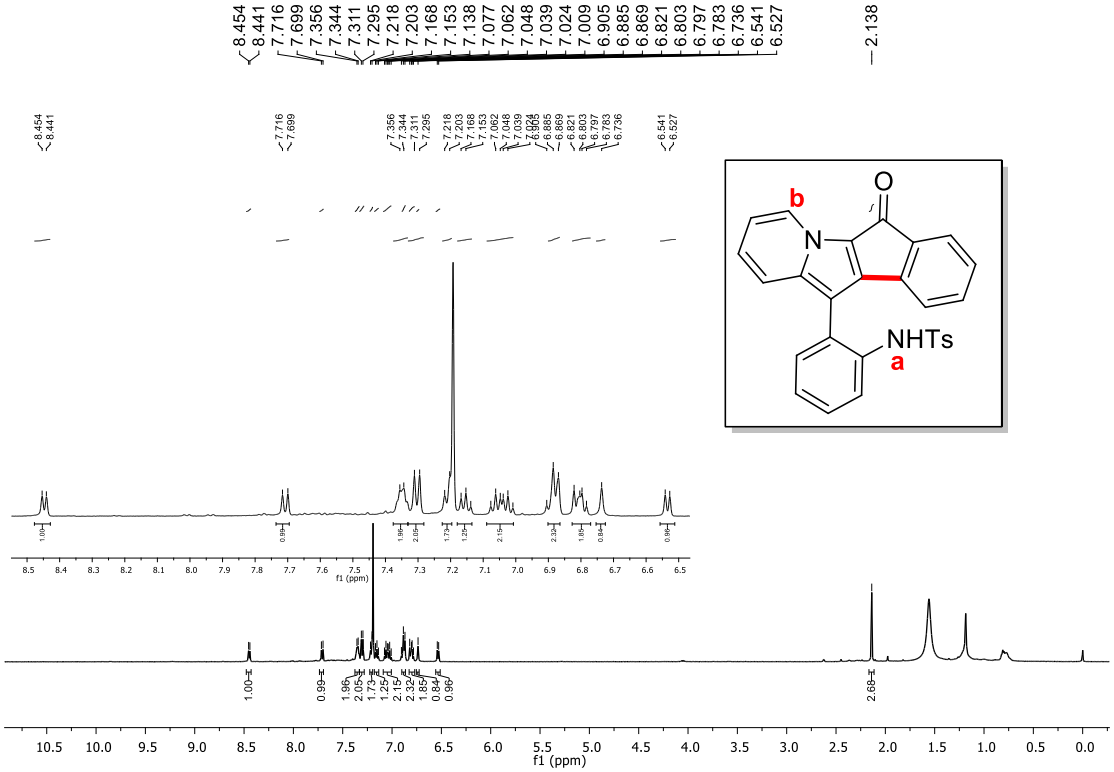


Figure 1. ^{1}H NMR Spectra of **15a**

The singlet observed at δ 6.74 ppm (b) was attributed to NH proton attached to the tosyl group. The methyl protons of tosyl group resonated as singlet at δ 2.14 ppm. The ^{1}H NMR spectrum of the compound is shown in figure 1.

In the ^{13}C spectrum (Figure 2), the aromatic carbons resonated in the region δ 178.1-106.5 ppm. The carbonyl carbon resonated at δ 178.1 ppm (a). The methyl carbon of the tosyl group showed a peak at δ 21.5 ppm. All other peaks in the ^{1}H and ^{13}C NMR were in good agreement with the assigned structure.

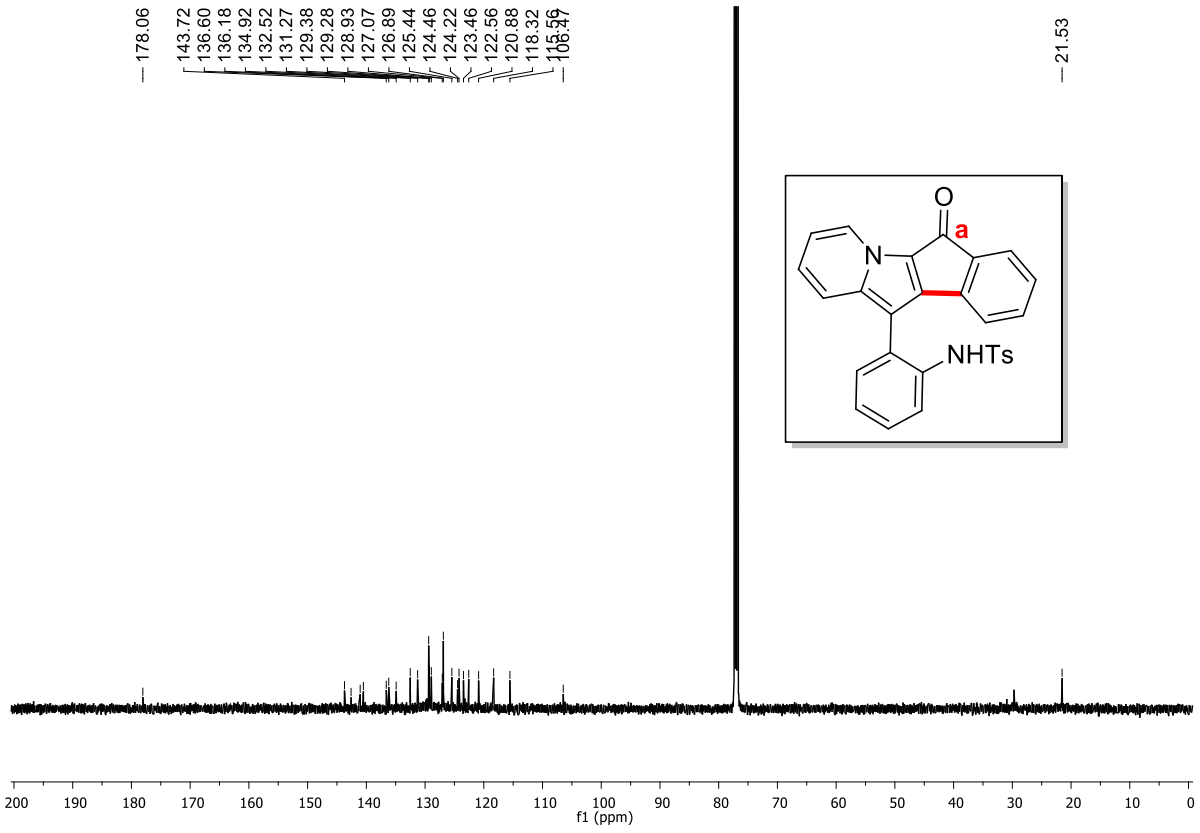
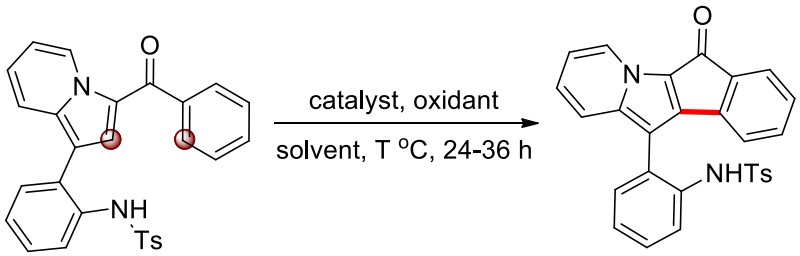


Figure 2. ^{13}C NMR Spectra of **15a**

We commenced further optimization studies with **14a** as a test substrate to determine the influence of various reaction parameters, the results of which are summarized in Table 1. Initially, the reaction was carried out by employing 20 mol% of $Pd(OAc)_2$ and 1.0 equiv. of $Cu(OAc)_2$ in toluene medium, and the desired product was obtained only in 30% yield after 24 hours. On changing the oxidants from $Cu(OAc)_2$ to $K_2S_2O_8$ and AgOAc, we could not

observe any increase in the reaction yield (Table 1, entry 1-3). Other palladium catalysts such as $PdCl_2$, $PdCl_2(PPh_3)_2$ and $Pd(tfa)_2$ afforded poor results, hence revealing that $Pd(OAc)_2$ is the best one (Table 1, entry 1). An increase in the amount of catalyst loading and oxidant led to a drop in yield to 25% and 20%, respectively (Table 1, entry 7-8). To our delight, increasing the reaction time to 36 h increased the yield upto 40% (Table 1, entry 9). This observation prompted us to further increase the reaction time to 60 h, but it did not have any positive outcome on the reaction (Table 1, entry 10). In order to improve the reaction conditions, we also screened various solvents, among which only toluene afforded the best yield (Table 1, entry 11-16). In all these cases, **14a** remained, which made us try another reaction with a catalyst system comprising $Pd(OAc)_2$, AgOAC with PivOH as the solvent (Table 1, entry 17). Herein, we could observe an increase in the yield of the reaction up to 52%. We further tried the same reaction with different silver oxidants, such as AgOAc and AgO, and in all these cases, the reaction failed to proceed (Table 1, entry 18-19). In order to be sure whether the palladium catalyst is regenerated or not, we tried another reaction consisting of 1.0 equivalent of $Pd(OAc)_2$ in PivOH medium, which led to a yield of 92% (Table 1, entry 20), which stands as a clear evidence for the low yield of the reaction due to catalyst poisoning.

Table 1. Optimisation studies[a]



14a **15a**

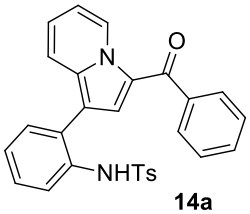
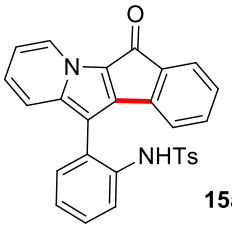
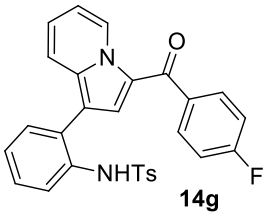
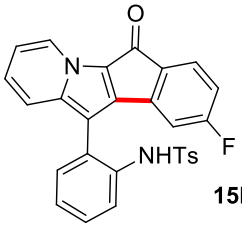
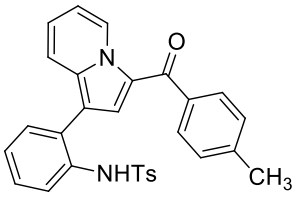
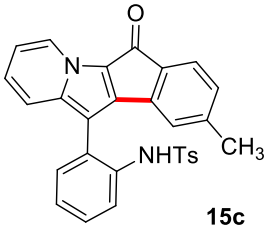
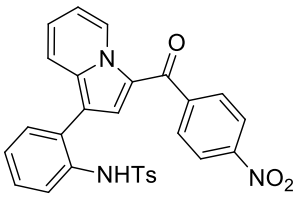
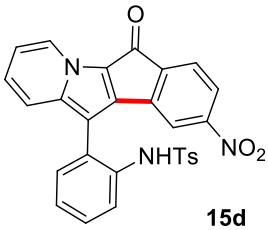
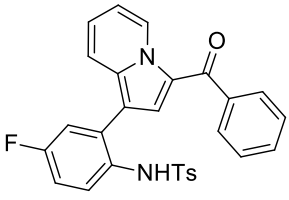
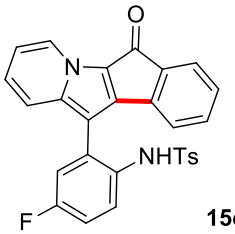
Entry	Catalyst	Oxidant	Solvent	Time (h)	Yield of **15a** (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2$	Toluene	24	30
2	$Pd(OAc)_2$	$K_2S_2O_8$	Toluene	24	traces
3	$Pd(OAc)_2$	Ag(OAc)	Toluene	24	30
4	$PdCl_2$	$Cu(OAc)_2$	Toluene	24	traces
5	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$	Toluene	24	20

6	$Pd(tfa)_2$	$Cu(OAc)_2$	Toluene	24	traces
7[b]	$Pd(OAc)_2$	$Cu(OAc)_2$	Toluene	24	25
8[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	Toluene	24	20
9	$Pd(OAc)_2$	$Cu(OAc)_2$	Toluene	36	40
10	$Pd(OAc)_2$	$Cu(OAc)_2$	Toluene	60	40
11	$Pd(OAc)_2$	$Cu(OAc)_2$	Xylene	36	traces
12	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	36	trace
13	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	36	20
14	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	36	30
15	$Pd(OAc)_2$	$Cu(OAc)_2$	TFA	36	nr
16	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH	36	Trace
17	**$Pd(OAc)_2$**	**AgOAc**	**PivOH**	**36**	**52**
18	$Pd(OAc)_2$	Ag_2O	PivOH	36	nr
19	$Pd(OAc)_2$	Ag_2CO_3	PivOH	36	nr
20	$Pd(OAc)_2$	-	PivOH	36	92

Reaction conditions: [a] **14a** (1.0 equiv., 0.10 mmol), catalyst (20 mol%), oxidant (1.0 equiv.), solvent (0.5 M), 140 °C; [b] catalyst (30 mol%); [c] oxidant (2.0 equiv.).

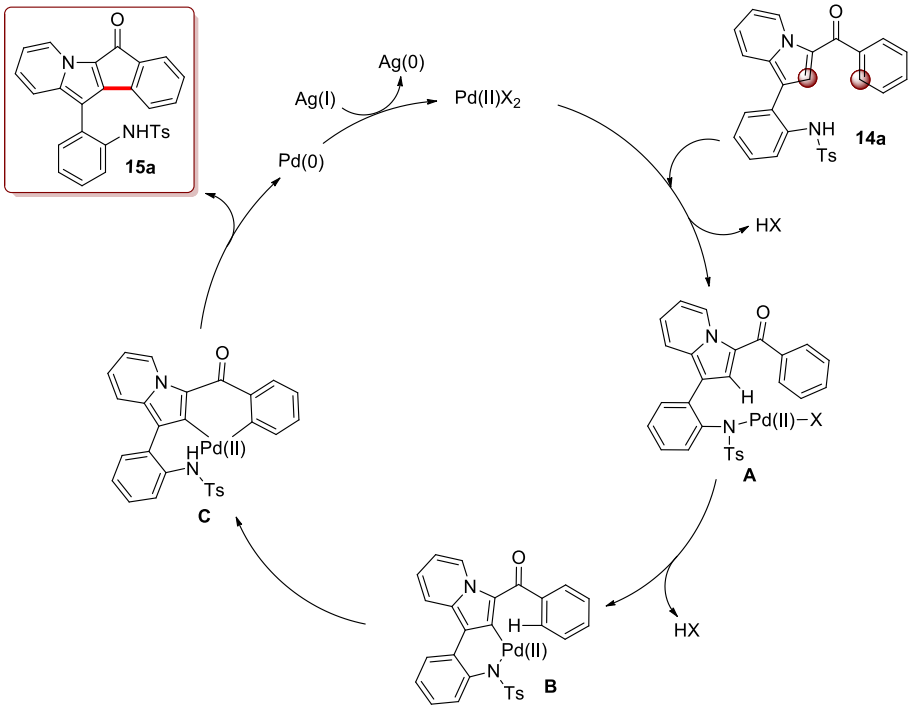
With the optimized conditions in hand [**14a** (1.0 equiv., 0.10 mmol), $Pd(OAc)_2$ (20 mol%), AgOAc (1.0 equiv.), PiVOH (0.5 M), 140 °C], we explored the substrate scope of this reaction under both catalytic and stoichiometric amounts of $Pd(OAc)_2$ in PivOH. Initially, we started the reaction by using various benzoyl-substituted indolizines (Table 2), wherein we could introduce halogens such as F (**15b**) on the indanone ring. The Pd-catalyzed cross-dehydrogenative coupling conditions also worked well with a CH_3 and NO_2-group on the benzoyl moiety, thereby furnishing **15c** and **15d** in good to moderate yields. We also tried reactions with F substituent on the aryl part of the pyrrole ring (**15e**), affording the corresponding product in good yield.

Table 2. Generality of Pd-mediated cross-dehydrogenative coupling[a]

Entry	Indolizine	Product	Yield
1	 **14a**	 **15a**	92, *52
2	 **14g**	 **15b**	88, *25
3	 **14i**	 **15c**	94, *36
4	 **14k**	 **15d**	91, *27
5	 **14d**	 **15e**	92, *40

[a]Reaction conditions: 1. **14** (1.0 equiv., 100 mg), $Pd(OAc)_2$ (1.0 equiv.), PivOH (0.5 M), 140 °C, 36 h. 2.* **14** (1.0 equiv., 100 mg), $Pd(OAc)_2$ (20 mol%), AgOAc (1.0 equiv.), PivOH (0.5 M), 140°C, 36 h.

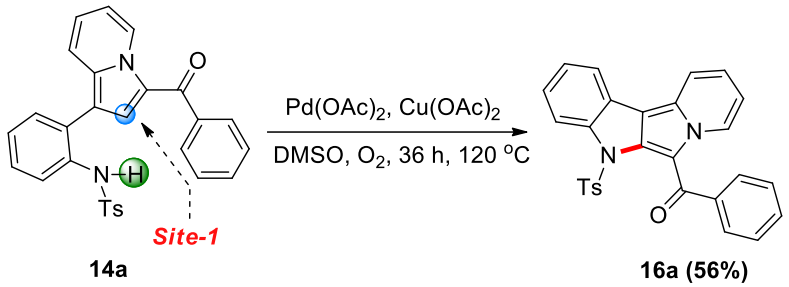
Based on our observations and following the reported literature, we propose a mechanism for the Pd-catalyzed cross-dehydrogenative coupling towards 6*H*-indeno-indolizines (Scheme 4B.3).[5,6] The formation of the N-Pd bond, as seen in intermediate **A** from **14a** and the Pd-catalyst, will mark the beginning of the catalytic cycle.[7,8] The C-H bond in the pyrrole ring is then selectively activated to form a six-membered palladacycle **B**.[9] The new six-membered cyclic Pd(II) intermediate **C** is then believed to be produced *via* a Fujiwara-Moritani type reaction in intermediate **B** *via* a C-H bond activation in the benzoyl moiety.[5,10] Reductive elimination then occurs in **C**, forming the product **15a** and Pd(0). Finally, the catalytic cycle is completed by the regeneration of the Pd(II) species through oxidation with AgOAc.



Scheme 4B.3 Plausible mechanism for the synthesis of 6*H*-indeno-indolizines

It is important to mention that C-H amination has also established itself as a powerful tool for generating substituted amines or *N*-heterocycles.[7-9] In this line, we targeted the C-H amination between the N-H and site-1 of indolizines (Scheme 4B.1) for the synthesis of indolizino[2,1-*b*]indoles. During our optimization studies on Pd-catalyzed cross-dehydrogenative coupling with **14a**, we came across a combination of $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv.) under an O_2 atmosphere in DMSO. The reaction at 120 ^oC was

allowed to continue for 36 h, after which we could isolate indolizino[2,1-*b*]indoles **16a** in 56% yield (Scheme 4B.4). It is interesting to note that in the current observation, oxygen was present, and this altered the reaction's path to produce the C-H amination product. This type of oxygen-induced chemoselective transformation is uncommon.



Scheme 4B.4 Pd(II) mediated C-H amination of indolizines

In the ^{1}H NMR spectrum, aromatic protons were found to resonate in the region δ 9.66-6.85 ppm. The proton on the pyridine ring attached near to the N atom (a) resonated at δ 9.66 ppm as a doublet. The methyl protons of the tosyl group resonated as singlet at δ 2.17 ppm. The ^{1}H NMR spectrum of the compound is shown in Figure 3.

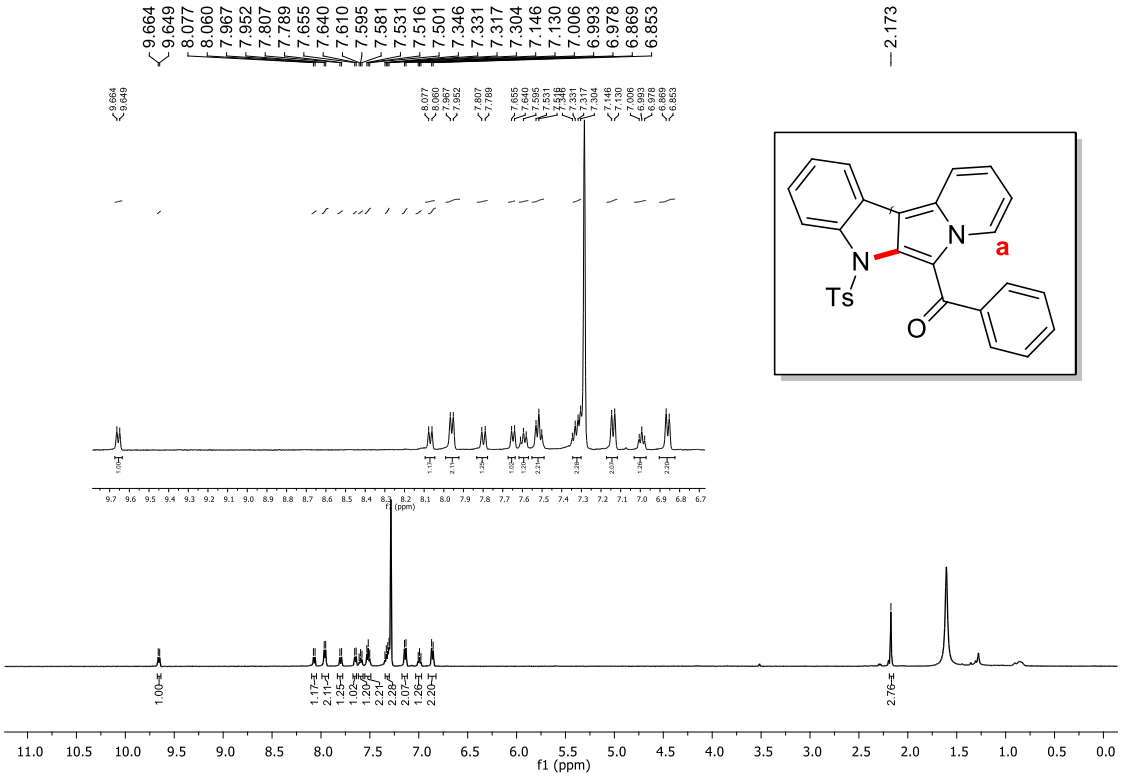


Figure 3. ^{1}H NMR Spectra of **16a**

In the ^{13}C spectrum (Figure 4), the aromatic carbons resonated in the region δ 186.4-113.6 ppm. The carbonyl carbon resonated at δ 186.4 ppm (a). The methyl carbon of the tosyl group showed a peak at δ 21.4 ppm. All other peaks in the ^{1}H and ^{13}C NMR were in good agreement with the assigned structure.

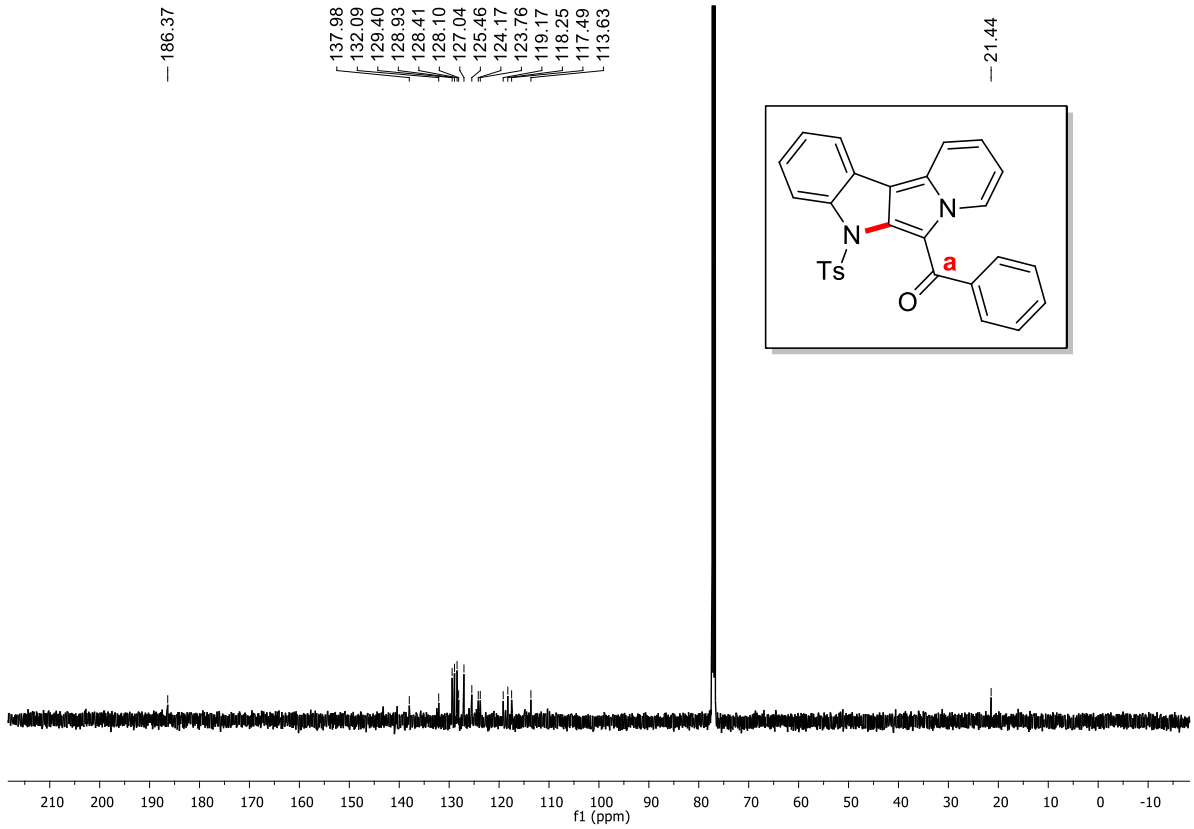
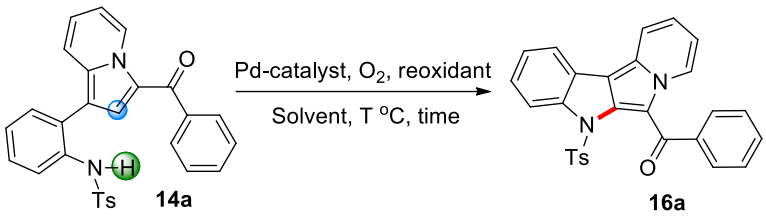


Figure 4. ^{13}C NMR Spectra of **16a**

We commenced our investigations with **14a** as the test substrate to find suitable reaction conditions for the palladium catalyzed C-H amination using various Pd-catalysts, oxidants and solvents (Table 3). Screening of various solvents, such as DMSO, DMF and toluene, revealed DMSO to be the best (Table 3, entry 1-3). Other palladium catalysts such as $PdCl_2(PPh_3)_2$, $Pd(tfa)_2$, $PdCl_2$, and $Pd(dba)_2$ were screened, and we observed an increase in yield of the reaction up to 76% when $PdCl_2$ was used as the catalyst (Table 3, entry 4-7). Attempts to use different oxidants such as AgOAc, AgO and benzoquinone were also unsuccessful, hence revealing $Cu(OAc)_2$ to be the best (Table 3, entry 8-10).

Table 3. Optimisation studies[a]

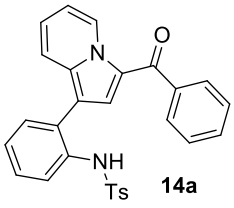
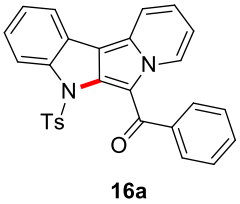
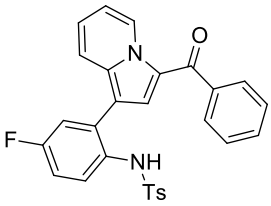
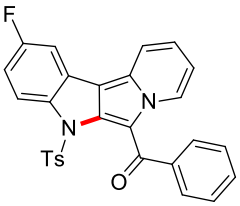
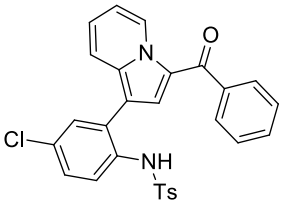
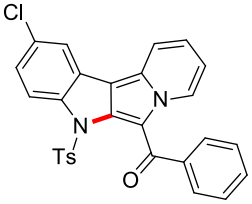
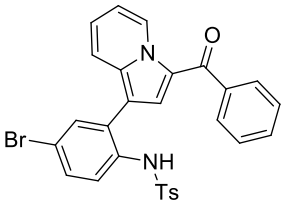
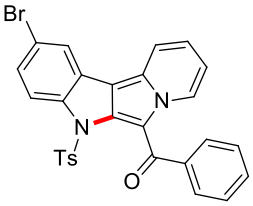
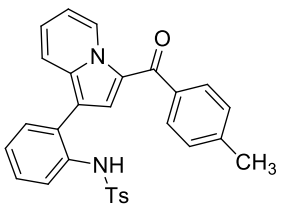
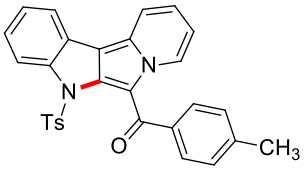


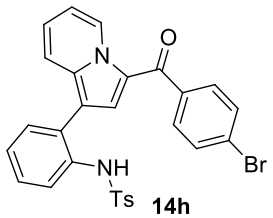
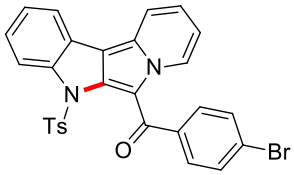
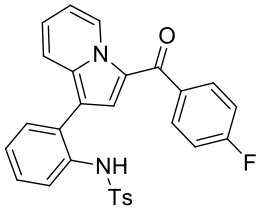
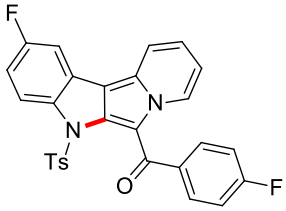
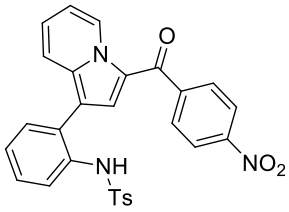
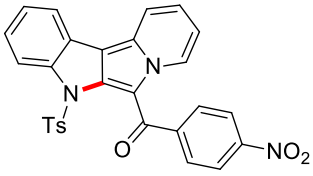
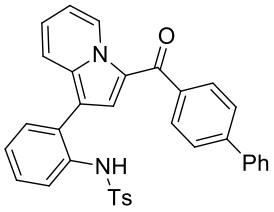
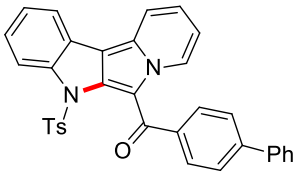
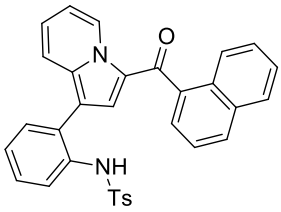
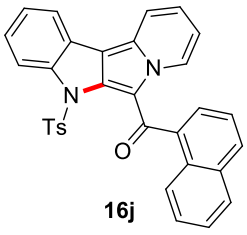
Entry	Catalyst	Oxidant	Solvent	Time (h)	Yield of **16a** (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	36	56
2	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	36	40
3	$Pd(OAc)_2$	$Cu(OAc)_2$	Toluene	36	Nr
4	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$	DMSO	36	44
5	$Pd(tfa)_2$	$Cu(OAc)_2$	DMSO	36	40
6	**$PdCl_2$**	**$Cu(OAc)_2$**	**DMSO**	**36**	**76**
7	$Pd(dba)_2$	$Cu(OAc)_2$	DMSO	36	40
8	$PdCl_2$	AgOAc	DMSO	36	Nr
9	$PdCl_2$	AgO	DMSO	36	Nr
10	$PdCl_2$	Bezoquinone	DMSO	36	Nr

Reaction conditions: [a]**14a** (1.0 equiv., 0.10 mmol), catalyst (5 mol%), oxidant (1.0 equiv.), solvent (0.1 M), 120 °C.

With the aforementioned optimized reaction protocol in hand [**14a** (1.0 equiv.), $PdCl_2$ (5 mol%), $Cu(OAc)_2$(1.0 equiv.), DMSO, O_2, 120 °C, 36 h], we explored the substrate scope of this reaction using different indolizines, the results of which are summarized in Table 4. Initially, we started the reaction with F, Cl and Br substituents on the aryl part of the indole ring (**16b**, **16c, 16d**), affording the corresponding products in good yield. The Pd-catalyzed C-H amination also worked well with electron-donating and electron-releasing substituents on the para position of benzoyl moiety attached to the pyrrole ring (**16e-16i**) in moderate to good yields. We could also synthesize **16j** in 70% yield by starting from suitably substituted 5-naphthoyl indolizine.

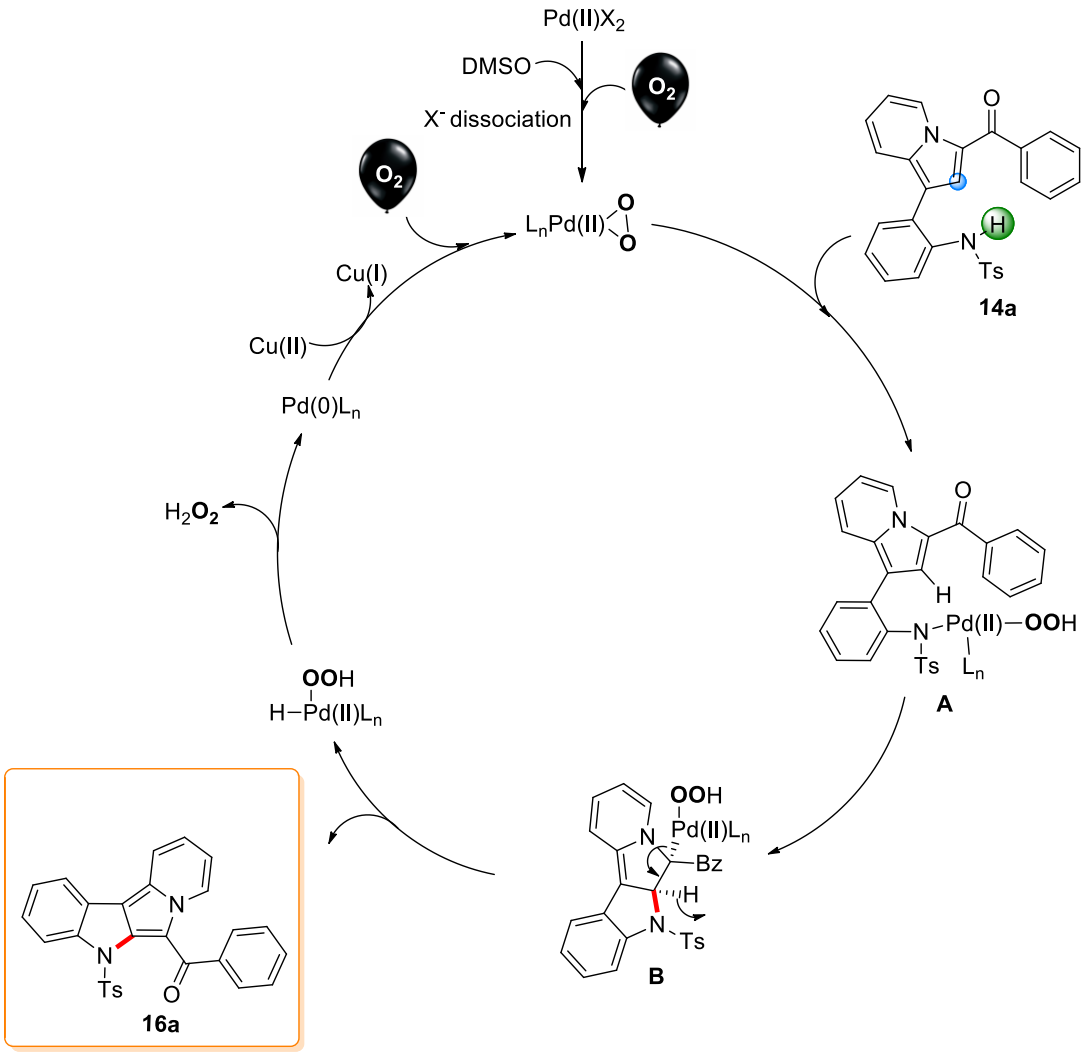
Table 4. Generality of Pd-catalyzed C-H amination of indolizines towards indolizino[2,1-*b*]indoles.

Entry	Indolizine	Product	Yield
1	 **14a**	 **16a**	76
2	 **14d**	 **16b**	70
3	 **14b**	 **16c**	70
4	 **14c**	 **16d**	70
5	 **14i**	 **16e**	74

Entry	Indolizine	Product	Yield
6	 **14h**	 **16f**	72
7	 **14g**	 **16g**	72
8	 **14k**	 **16h**	74
9	 **14j**	 **16i**	68
10	 **14l**	 **16j**	70

Reaction conditions: **14a** (1.0 equiv., 100 mg), $PdCl_2$ (0.05 equiv.), $Cu(OAc)_2$ (1.0 equiv.), DMSO (0.1 M), O_2, 120 ^oC, 36 h.

Based on our observations and following the reported literature, we propose a mechanism for the Pd-catalyzed site-selective activation towards indolizino[2,1- *b*]indoles (Scheme 4B.5).



Scheme 4B.5 Plausible mechanism for the synthesis of indolizino[2,1-*b*]indoles

According to the theoretical studies of Zierkiewicz and Privalov, we assume that DMSO initially interacts with the catalyst $PdCl_2$ to generate a Pd(0)(DMSO)n species.[11] Stahl and co-workers have extensively researched the ligand-supported Pd-catalyzed aerobic oxidations.[12] We assume that Pd(0)(DMSO)n is subsequently oxidized by oxygen to produce the active η^2-peroxo-Pd(II) species by adhering to the literature precedents.[13] We believe that oxygen compels the reaction to follow the Wacker-like pathway described by Buchwald and Monguchi for the oxygen-promoted Pd-catalyzed synthesis of carbazoles.[9,14] In this line, the intermediate η^2-peroxo-Pd(II) intermediate complexes with the *N*-center in **14a** to produce

amide **A**. The intermediate **B** will then be produced by a Wacker-like addition of the Pd-species across the pyrrole double bond. Then, in **B**, a ß-hydride elimination takes place, releasing the H-Pd(II)L_n-OOH moiety and indolizino[2,1-*b*]indoles (Scheme 4B.5). H-Pd(II)L_n-OOH undergoes reductive elimination, releasing Pd(0)L_n and H_2O_2. Pd(0)Ln is reoxidized by $Cu(OAc)_2$ and O_2 to complete the catalytic cycle.

The factors influencing the site-selective C-H functionalization towards different fused *N*-heterocycles were then analysed. Structures of **15a** and **16a** are optimized at the B3LYP-D3/6-311G(d,p) level of density functional theory[15] using Gaussian 16 suite of programs[16](Figure 5). The formation of the dual C-H activation product, **15a**, is rationalized by the fact that **15a** is 6.10 kcal/mol more thermodynamically stable than the C-H amination product, **16a**. In the presence of O_2, the phenyl C-H activation is hindered by the binding of O_2 with $Pd(OAc)_2$, leading to the formation of the C-H amination product **16a**.

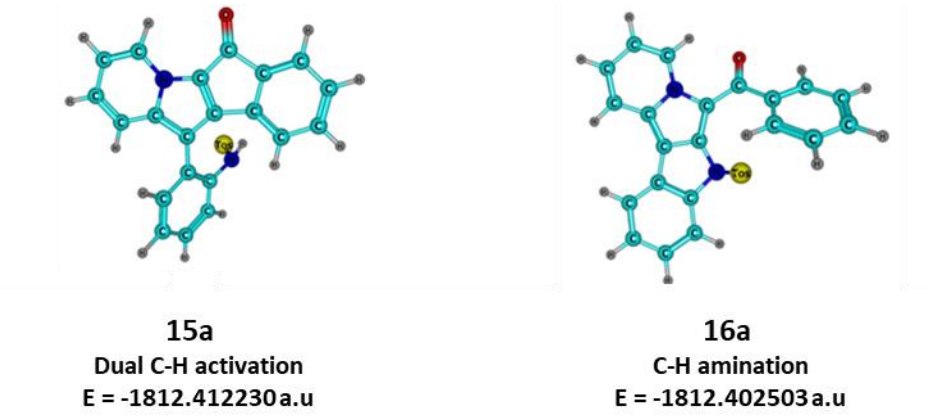


Figure 5. Optimized structures of **15a** and **16a** along with the SCF energy values. Tosyl groups are not shown for clarity.

4B.5 Conclusions

In conclusion, we have discovered an intriguing Pd-catalyzed site-selective C-H functionalization toward multiring fused *N*-heterocycles. These observations were made on benzoyl-substituted indolizine scaffold, where we could identify two sites for C-H functionalization and an *N*-centre that could participate in C-H amination. The experimental and theoretical studies support that there is a preference for Pd-catalyzed cross-dehydrogenative coupling towards 6*H*-indeno-indolizine moiety derivatives. The potential of this method is further established by a broad substrate scope.

4B.6 Experimental section

4B.6.1 General experimental methods: All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets pre-coated with silica gel containing fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using neutral alumina, silica gel and mixtures of ethyl acetate hexanes for elution. Melting points were determined using a calibrated digital melting point apparatus (Büchi 530 melting point apparatus). NMR spectra were recorded with Bruker AMX-500 (500 MHz for 1H NMR, 125 MHz for $^{13}C\{^{1}H\}$ NMR) instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were performed with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with a ESI/ HRMS at 60,000 resolution using ThermoScientificExactive mass spectrometer with orbitrap analyzer.

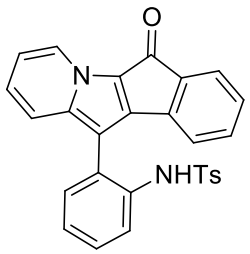
4B.6.2 Synthesis and characterization:

Synthesis and characterization of indolizines 14: Detailed description given in experimental section of Chapter 4A.

Experimental procedure for the Pd-catalyzed cross-dehydrogenative coupling of indolizines: A mixture of indolizine **14** (1.0 equiv.), $Pd(OAc)_2$ (20 mol%) and AgOAc (1.0 equiv.) was weighed into a dry reaction tube. Pivalic acid was added and the reaction mixture was allowed to stir at 140 ^{o}C in an oil bath for 36 h. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

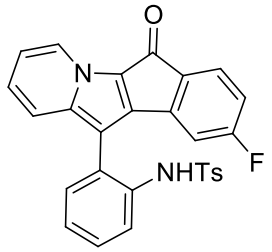
Synthesis and characterization of 6*H*-indeno indolizines (15a – 15e)

4-methyl-N-(2-(6-oxo-6H-indeno[1,2-b]indolizin-11-yl)phenyl)benzene sulfonamide (***15a***). The reaction was performed according to general procedure with *N*-(2-(3-benzoylindolizin-1-yl)phenyl)-4-methylbenzenesulfonamide **14a** (100 mg, 0.21 mmol), $Pd(OAc)_2$ (9 mg, 0.042 mmol) and AgOAc (35 mg, 0.1 mmol) in PivOH at 140 ºC for 36h. After workup, the residue was purified by column chromatography (20% ethyl acetate/hexane) to afford the desired product **15a** as a red solid. (52 mg, 52%). The same reaction was repeated with $Pd(OAc)_2$ (47 mg, 0.21 mmol) in PivOH to obtain **15a** (92 mg, 92%).

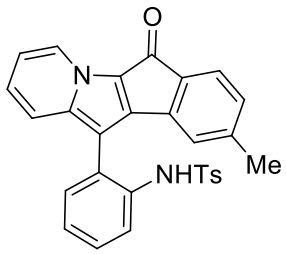
	**Mp**: 260-262 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.45 (d, *J* = 6.5 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.36-7.34 (m, 2H), 7.30 (d, *J* = 8 Hz, 2H), 7.22 – 7.20 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.08 - 7.01 (m, 2H), 6.91 - 6.87 (m, 2H), 6.82 - 6.78 (m, 2H), 6.74 (s, 1H), 6.53 (d, *J* = 7.0 Hz, 1H), 2.14 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 178.1, 143.7, 142.6, 141.1, 140.5, 136.6, 136.2, 134.9, 132.5, 131.3, 129.4, 129.3, 128.9, 127.1, 126.9, 125.4, 124.5, 124.2, 123.5, 122.6, 120.9, 118.3, 115.6, 106.5, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{28}H_{20}N_2NaO_3S$: 487.1087, found 487.1107.

N-(2-(8-fluoro-6-oxo-6H-indeno[1,2-b]indolizin-11-yl)phenyl)-4-methylbenzene sulfonamide ***(15b)***. The reaction was performed according to general procedure with *N*-(2-(3-(4-fluorobenzoyl)indolizin-1-yl)phenyl)-4-methylbenzenesulfonamide **14d** (100 mg, 0.21 mmol), $Pd(OAc)_2$ (9 mg, 0.042 mmol) and AgOAc (35 mg, 0.21 mmol) in PivOH at 140 ºC for 36h. After workup, the residue was purified by column chromatography (20% ethyl acetate/hexane) to afford the desired product **15b** as a red solid (25 mg, 25%). The same reaction was repeated with $Pd(OAc)_2$ (47 mg, 0.21 mmol) in PivOH to obtain **15b** (88 mg, 88%).

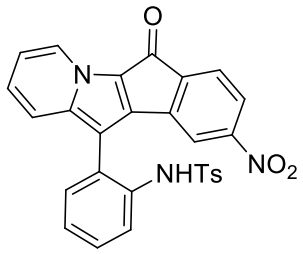
	Mp: 266-268 ºC.

	**^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.42 (d, *J* = 6.5 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 3H), 7.30-7.28 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 3H), 6.91-6.89 (m, 2H), 6.81 (t, *J* = 6.5 Hz, 1H), 6.76 (s, 1H), 6.68 (t, *J* = 8.0 Hz, 1H), 6.16 (d, *J* = 8.0 Hz, 1H) 2.17 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 176.9, 144.0, 140.9, 136.2, 135.1, 130.4 (d, *J* = 220 Hz), 129.5, 127.0, 125.3, 125.0, 124.5, 123.6, 121.8, 118.5, 115.9, 114.3, 114.1, 109.8, 109.6, 106.7, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{20}FN_2O_3S$: 483.1173, found 483.1192.

*4-methyl-N-(2-(8-methyl-6-oxo-6H-indeno[1,2-b] indolizinyl) phenyl)benzene sulfonamide (**15c**).* The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-methylbenzoyl)indolizin-1-yl)phenyl)benzenesulfonamide **14i** (100 mg, 0.21 mmol), $Pd(OAc)_2$ (9 mg, 0.042 mmol) and AgOAc (35 mg, 0.21 mmol) in PivOH (0.5 M) at 140 °C for 36h. After workup, the residue was purified by activated neutral alumina chromatography (20% ethyl acetate/hexane) to afford the desired product **15c** as a red solid. (36 mg, 36%). The same reaction was repeated with $Pd(OAc)_2$ (47 mg, 0.21 mmol) in PivOH to obtain **15c** (94 mg, 94%).

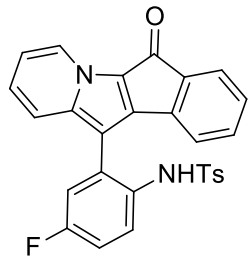
	**Mp**: 290-292 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.43 (d, *J* = 7.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.25-7.22 (m, 2H), 7.16 (s, 1H), 6.88 - 6.84 (m, 4H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.74 (s, 1H), 6.38 (s, 1H), 2.15 (s, 3H), 2.13 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 178.1, 136.2, 131.2, 129.3, 129.2, 129.0, 126.9, 125.5, 123.8, 123.6, 123.5, 122.8, 122.1, 118.3, 115.4, 21.9, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{29}H_{23}N_2O_3S$: 479.1424, found 479.1437.

*4-methyl-N-(2-(8-nitro-6-oxo-6H-indeno[1,2-b]indolizin-11-yl)phenyl)benzene sulfonamide (**15d**).*The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-nitrobenzoyl)indolizin-1-yl)phenyl)benzenesulfonamide **14k** (100 mg, 0.20 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol) and AgOAc (33 mg, 0.20 mmol) in PivOH (0.5 M) at 140 °C for 36h. After workup, the residue was purified by activated neutral alumina chromatography (20% ethyl acetate/hexane) to afford the desired product **15d** as a red solid (27 mg, 27%). The same reaction was repeated with $Pd(OAc)_2$ (45 mg, 0.20 mmol) in PivOH to obtain **15d** (91 mg, 91%).

	**Mp**: 250-252 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.48 (d, *J* = 6.5 Hz, 1H), 7.96 (d, *J* = 6.0 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.42-7.38 (m, 3H), 7.22-7.21 (m, 3H), 7.07-7.01 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.89 (t, *J* = 6.5 Hz, 1H), 6.74 (s, 1H), 2.16 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 181.8, 149.2, 145.9, 143.9, 138.0, 136.4, 135.2, 131.5, 129.8, 129.5, 129.2, 129.1, 127.0, 126.3, 126.2, 125.0, 123.6, 121.9, 121.0, 117.3, 115.4, 112.3, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{20}N_3O_5S$: 510.1118, found 510.1137.

*N-(4-fluoro-2-(6-oxo-6H-indeno[1,2-b]indolizin-11-yl)phenyl)-4-methylbenzene sulfonamide (**15e**)*. The reaction was performed according to general procedure with *N*-(2-(3-benzoylindolizin-1-yl)-4-fluorophenyl)-4-methylbenzenesulfonamide **14g** (100 mg, 0.21 mmol), $Pd(OAc)_2$ (9 mg, 0.042 mmol) and AgOAc (35 mg, 0.21 mmol) in PivOH (0.5 M) at 140 °C for 36h. After workup, the residue was purified by activated neutral alumina chromatography (20% ethyl acetate/hexane) to afford the desired product **15e** as a red solid (40 mg, 40%). The same reaction was repeated with $Pd(OAc)_2$ (47 mg, 0.21 mmol) in PivOH to obtain **15e** (92 mg, 92%).

	Mp: 258-260 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 8.44 (d, *J* = 6.5 Hz, 1H),

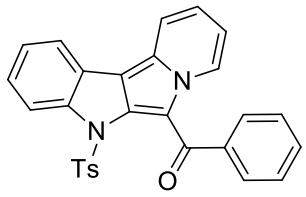
	7.72-7.69 (m, 1H), 7.37 (d, *J* = 6.5 Hz, 1H), 7.20-7.19 (m, 2H), 7.09 - 7.06 (m, 3H), 6.94 - 6.90 (m, 2H), 6.82 - 6.78 (m, 4H), 6.61 (s, 1H), 6.56 (d, *J* = 6.5 Hz, 1H), 2.10 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 177.0, 159.2 (d, *J* = 252 Hz), 142.7, 141.3, 139.6, 139.3, 135.4, 135.0, 131.7, 129.78, 129.76, 128.6, 128.3, 128.1, 127.0, 126.0, 125.7, 125.2, 125.1, 123.4, 122.6, 119.7, 117.0, 116.7, 116.5, 115.2, 115.0, 114.6, 104.5, 20.5 ppm. **HRMS (ESI-Orbitrap) m/z:** $(M + H)^+$ calcd for $C_{28}H_{20}FN_2O_3S$: 483.1173, found 483.1189.

Experimental procedure for the Pd-catalyzed CH amination of indolizines towards indolizino[2,1-*b*]indoles: A mixture of indolizine **14** (1.0 equiv), $PdCl_2$ (5 mol%) and $Cu(OAc)_2$ (1.0 equiv.) was weighed into a dry Schlenk tube. Dry DMSO was added and the reaction mixture was stirred at 120 ºC in an oil bath for 36 h under O_2 atmosphere. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

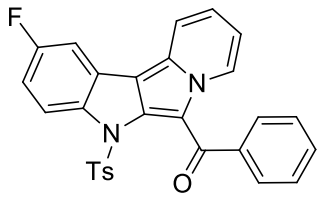
Synthesis and characterization of indolizino[2,1-*b*]indoles (16a – 16j)

*phenyl(5-tosyl-5H-indolizino[2,1-b]-6-yl)methanone (**16a**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylindolizin-1-yl)phenyl)-4-methylbenzenesulfonamide **14a** (100 mg, 0.21 mmol), $PdCl_2$ (2 mg, 0.01 mmol) and $Cu(OAc)_2$ (38 mg, 0.21 mmol) under O_2 atmosphere in DMSO at 120 ºC for 36h. After workup, the residue was purified by silica chromatography (10% ethyl acetate/hexane) to afford the desired product **16a** as a yellow solid. (76 mg, 76%).

	Mp: 258-260 ºC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.66 (d, *J* = 7.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 2H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.0 Hz, 1H), 7.52 (t,

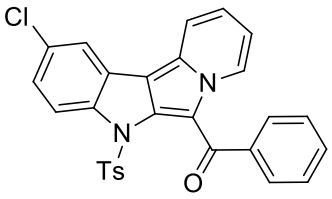
	*J* = 7.5 Hz, 2H), 7.35 - 7.30 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.01-6.98 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 2.17 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 186.4, 138.0, 132.1, 129.4, 128.9, 128.4, 128.1, 127.0, 125.5, 124.2, 123.8, 119.2, 118.2, 117.5, 113.6, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{28}H_{20}N_2NaO_3S$: 487.1087, found 487.1087.

*(2-fluoro-5-tosyl-5H-indolizino[2,1-b]indol-6-yl)(phenyl)methanone (**16b**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylindolizin-1-yl)-4-fluorophenyl)-4-methylbenzenesulfonamide **14d** (100 mg, 0.21 mmol), $PdCl_2$ (2 mg, 0.01 mmol) and $Cu(OAc)_2$ (38 mg, 0.21 mmol) under O_2 atmosphere in DMSO at 120 °C for 36h. After workup, the residue was purified by silica chromatography (10% ethyl acetate/hexane) to afford the desired product **16b** as a yellow solid (70 mg, 70%).

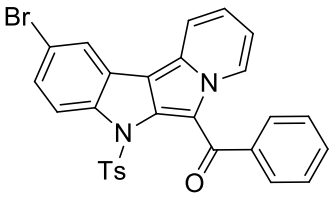
	**Mp**: 262-264 °C **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.55 (d, *J* = 7.0 Hz, 1H), 7.91-7.86 (m, 3H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.44-7.41 (m, 2H), 7.25-7.22 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.94 - 6.87 (m, 2H), 6.79 (d, *J* = 8.0 Hz, 2H), 2.10 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 186.3, 144.7, 140.2, 138.9, 138.4 (d, *J* = 190 Hz), 132.2, 132.1, 129.4, 129.0, 128.4, 128.2, 127.0, 124.2, 119.3, 119.2, 117.4, 113.9, 110.9, 106.0, 105.8, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{20}FN_2O_3S$: 483.1173, found 483.1186.

*(2-chloro-5-tosyl-5H-indolizino[2,1-b]indol-6-yl)(phenyl)methanone (**16c**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylindolizin-1-yl)-4-chlorophenyl)-4-methylbenzenesulfonamide **14b** (100 mg, 0.20 mmol), $PdCl_2$ (2 mg, 0.01 mmol) and $Cu(OAc)_2$ (36 mg, 0.20 mmol) under O_2 atmosphere in DMSO at 120 °C for 36h.

After workup, the residue was purified by silica chromatography (10% ethyl acetate/hexane) to afford the desired product **16c** as a yellow solid (70 mg, 70%).

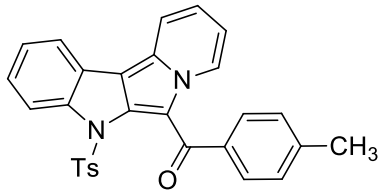
	**Mp**: 266-268 ^{o}C. **^{1}H NMR (500 MHz, CDCl$_3$, TMS)**: δ 9.60 (d, *J* = 7.0 Hz, 1H), 7.93-7.89 (m, 3H), 7.76-7.74 (m, 2H), 7.59-7.56 (m, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 6.5 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 2.18 (s, 3H) ppm. **^{13}C NMR (125 MHz, CDCl$_3$)**: δ 186.4, 164.1, 144.8, 141.9, 140.2, 132.3, 129.4, 129.2, 128.5, 128.2, 127.0, 126.8, 124.2, 122.1, 119.4, 117.4, 114.0, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: (M + H)$^{+}$ calcd for $C_{28}H_{20}ClN_2O_3S$: 499.0878, found 499.0878.

(2-bromo-5-tosyl-5H-indolizino[2,1-b]indol-6-yl)(phenyl)methanone ***(16d)***. The reaction was performed according to general procedure with *N*-(2-(3-benzoylindolizin-1-yl)-4-bromophenyl)-4-methylbenzenesulfonamide **14c** (100 mg, 0.18 mmol), $PdCl_2$ (2 mg, 0.009 mmol) and $Cu(OAc)_2$ (33 mg, 0.18 mmol) under O_2 atmosphere in DMSO at 120 ^{o}C for 36h. After workup, the residue was purified by silica chromatography (10% ethyl acetate/hexane) to afford the desired product **16d** as a yellow solid (70 mg, 70%).

	**Mp**: 270-272 ^{o}C. **^{1}H NMR (500 MHz, CDCl$_3$, TMS)**: δ 9.60 (d, *J* = 6.5 Hz, 1H), 7.92 – 7.89 (m, 2H), 7.76-7.74 (m, 2H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.49 (t, *J* = 7.0 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.32-7.29 (m, 2H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.00 (t, *J* = 6.5 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 2.18 (s, 3H) ppm. **^{13}C NMR (125 MHz, CDCl$_3$)**: δ 186.4, 144.8, 132.3, 130.2, 129.4, 129.2, 128.5, 128.2, 127.0, 126.8, 124.2, 122.1, 119.4, 117.4, 114.0, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: (M + Na)$^{+}$ calcd for

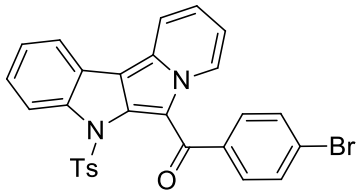
	$C_{28}H_{19}BrN_2NaO_3S$: 565.0192, found 565.0214.

*p-tolyl(5-tosyl-5H-indolizino[2,1-b]indol-6-yl)methanone (**16e**).* The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-methylbenzoyl)indolizin-1-yl)phenyl)benzenesulfonamide **14i** (100 mg, 0.21 mmol), $PdCl_2$ (2 mg, 0.01 mmol) and $Cu(OAc)_2$ (38 mg, 0.21 mmol) under O_2 atmosphere in DMSO at 120 °C for 36h. After workup, the residue was purified by silica chromatography (10% ethyl acetate/hexane) to afford the desired product **16e** as a yellow solid (74 mg, 74%).

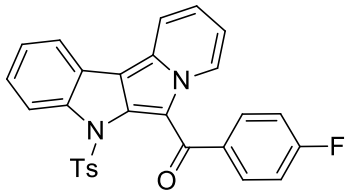
	**Mp**: 276-278 °C **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.47 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 9.5 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.25 - 7.21 (m, 5H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.87 (t, *J* = 7.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H), 2.08 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 183.6, 146.8, 143.2, 142.8, 137.7, 129.5, 129.2, 128.9, 128.0, 127.0, 126.1, 125.4, 124.1, 123.4, 119.2, 118.2, 117.5, 113.4, 110.5, 21.8, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{29}H_{23}N_2O_3S$: 479.1424, found 479.1439.

*(4-bromophenyl)(5-tosyl-5H-indolizino[2,1-b]indol-6-yl)methanone (**16f**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-bromobenzoyl)indolizin-1-yl)phenyl)-4-methylbenzenesulfonamide **14h** (100 mg, 0.18 mmol), $PdCl_2$ (2 mg, 0.009 mmol) and $Cu(OAc)_2$ (33 mg, 0.18 mmol) under O_2 atmosphere in DMSO at 120 °C for 36h. After workup, the residue was purified by silica chromatography (10% ethyl acetate/hexane) to afford the desired product **16f** as a yellow solid (72 mg, 72%).

	Mp: 264-268 °C **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.57 (d, *J* = 7.0 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.73-7.70 (m, 3H), 7.55-7.53(m, 3H), 7.26-7.22 (m, 3H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.92 (t, *J* =

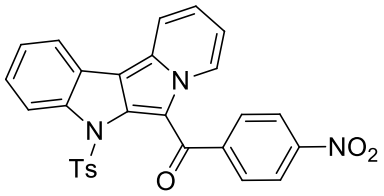
	6.5 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 2H), 2.09 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 188.4, 144.6, 143.2, 139.4, 131.7, 130.9, 129.0, 128.2, 127.5, 127.0, 125.6, 124.3, 124.2, 119.2, 118.4, 117.5, 113.8, 110.0, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{28}H_{19}BrN_2NaO_3S$: 565.0192, found 565.0213.

*(4-fluorophenyl)(5-tosyl-5H-indolizino[2,1-b]indol-6-yl)methanone (**16g**)*. The reaction was performed according to general procedure with *N*-(2-(3-(4-fluorobenzoyl)indolizin-1-yl)phenyl)-4-methylbenzenesulfonamide **14g** (100 mg, 0.21 mmol), $PdCl_2$ (2 mg, 0.01 mmol) and $Cu(OAc)_2$ (38 mg, 0.21 mmol) under O_2 atmosphere in DMSO at 120 °C for 36h. After workup, the residue was purified by silica chromatography (10% ethyl acetate/hexane) to afford the desired product **16g** as a yellow solid (72 mg, 72%).

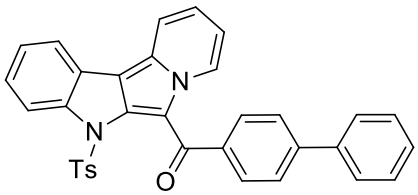
	**Mp**: 268-270 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.61 (d, *J* = 7.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.96-7.94 (m, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.33-7.28 (m, 3H), 7.16 (t, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 2H), 6.97 (t, *J* = 6.5 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 2H), 2.15 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 184.8, 165.2 (d, *J* = 251 Hz), 144.5, 143.2, 137.9, 132.4, 131.8, 131.7, 129.6, 128.9, 128.5, 128.1, 127.3, 127.0, 126.0, 125.6, 124.3, 123.9, 119.2, 118.3, 117.5, 115.6, 115.4, 113.7, 110.1, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{28}H_{20}FN_2O_3S$: 483.1173, found 483.1193.

*(4-nitrophenyl)(5-tosyl-5H-indolizino[2,1-b]indol-6-yl)methanone (**16h**)*. The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-nitrobenzoyl)indolizin-1-yl)phenyl)benzenesulfonamide **14k** (100 mg, 0.20 mmol), $PdCl_2$ (2 mg, 0.01 mmol) and $Cu(OAc)_2$ (36 mg, 0.20 mmol) under O_2 atmosphere in DMSO at 120 °C for 36h. After

workup, the residue was purified by silica chromatography (10% ethyl acetate/hexane) to afford the desired product **16h** as a yellow solid (74 mg, 74%).

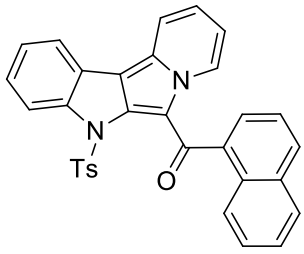
	**Mp**: 250-252 °C. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.86 (d, *J* = 7.5 Hz, 1H), 8.35 (d, *J* = 7.5 Hz, 2H), 8.06 (d, *J* = 7.5 Hz, 3H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.36-7.31 (m, 2H), 7.10 (d, *J* = 7.0 Hz, 3H), 6.86 (d, *J* = 7.5 Hz, 2H), 2.18 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 183.4, 149.4, 146.1, 144.8, 143.2, 132.1, 130.1, 129.0, 128.6, 127.0, 125.8, 125.3, 124.6, 123.6, 119.3, 118.4, 117.6, 114.5, 110.8, 110.2, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{28}H_{19}N_3NaO_5S$: 532.0938, found 532.0959.

*[1,1'-biphenyl]-4-yl(5-tosyl-5H-indolizino[2,1-b]indol-6-yl)methanone (**16i**)*. The reaction was performed according to general procedure with *N*-(2-(3-([1,1'-biphenyl]-4-carbonyl)indolizin-1-yl)phenyl)-4-methylbenzenesulfonamide **14j** (100 mg, 0.18 mmol), $PdCl_2$ (2 mg, 0.009 mmol) and $Cu(OAc)_2$ (33 mg, 0.18 mmol) under O_2 atmosphere in DMSO at 120 °C for 36h. After workup, the residue was purified by silica chromatography (10% ethyl acetate/hexane) to afford the desired product **16i** as a yellow solid (68 mg, 68%).

	**Mp**: 274-278 °C **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.59 (d, *J* = 7.5 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 9.5 Hz, 1H), 7.71 (t, *J* = 8.5 Hz, 4H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.46 (t, *J* = 7.0 Hz, 3H), 7.37 (t, *J* = 7.0 Hz, 1H), 7.33-7.28 (m, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.96 (t, *J* = 6.5 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 2H), 2.14 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 185.9, 144.6, 144.5, 140.4, 139.2, 137.8, 132.5, 130.0, 129.0, 128.8, 128.1,

	127.8, 127.4, 127.1, 127.0, 126.1, 125.5, 124.2, 123.7, 119.2, 118.3, 117.5, 113.6, 110.3, 109.9, 21.5 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + H)^+$ calcd for $C_{34}H_{25}N_2O_3S$: 541.1580, found 541.1600.

*naphthalen-1-yl(5-tosyl-5H-indolizino[2,1-b]indol-6-yl)methanone (**16j**)*. The reaction was performed according to general procedure with *N*-(2-(3-(1-naphthoyl)indolizin-1-yl)phenyl)-4-methylbenzenesulfonamide **14l** (100 mg, 0.19 mmol), $PdCl_2$ (2 mg, 0.01 mmol) and $Cu(OAc)_2$ (34 mg, 0.19 mmol) under O_2 atmosphere in DMSO at 120 ^oC for 36h. After workup, the residue was purified by silica chromatography (10% ethyl acetate/hexane) to afford the desired product **16j** as a yellow solid (70 mg, 70%).

	**Mp**: 290-292 ^oC. **^{1}H NMR (500 MHz, $CDCl_3$, TMS)**: δ 9.84 (d, *J* = 7.5 Hz, 1H), 8.80 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.85-7.81 (m, 2H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.60-7.56 (m, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.0 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.23-7.21 (m, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.00-6.96 (m, 3H), 6.75 (d, *J* = 8.0 Hz, 2H), 2.07 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 187.2, 144.3, 143.3, 138.8, 138.0, 134.3, 132.2, 132.0, 129.0, 128.8, 128.5, 128.3, 127.2, 126.9, 126.7, 126.1, 125.3, 124.4, 124.1, 119.1, 118.2, 117.5, 114.0, 111.5, 110.0, 21.4 ppm. **HRMS (ESI-Orbitrap) m/z**: $(M + Na)^+$ calcd for $C_{32}H_{22}N_2NaO_3S$: 537.1243, found 537.1262.

4B.7 References

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Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian, Inc., *Wallingford CT*, **2016**.

ABSTRACT

Name of the Student**:** **Ms. Sheba Ann Babu** Registration No**.:** 10CC18A39016
Faculty of Study**:** Chemical Sciences Year of Submission**:** 2023
AcSIR academic centre/CSIR Lab**:** CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST)
Name of the Supervisors**: Dr. Jubi John & Dr. Sunil Varughese**
Title of the thesis: **Utilization of Electrophilic Benzannulated Heterocycles for Accessing Novel Heteroacenes**

Recent research in organic chemistry has revealed a fascinating array of heteroacenes with diverse properties and applications in electronics, optoelectronics, and renewable energy. These heteroacenes have several advantages over conventional polycyclic aromatic hydrocarbons, such as electron-richness, stability and tunable properties. However, the broad utilization of these heteroacenes is constrained by the absence of concise and efficient synthetic pathways. At this point, electrophilic indoles turned out to be useful in synthesizing *N*-heteroacenes, such as indole-fused heteroacenes, which show similar analogous properties. Electrophilic benzannulated heterocycles such as indole, benzothiophene, or benzofuran, substituted with a nitro group at the 2nd or 3rd position, can be used with suitable dipoles or appropriately synthesized bis-reactive species for accessing novel heteroacenes. This thesis focuses on the use of electrophilic benzannulated heterocycles towards the synthesis of *N*-fused heterocycles in which we have demonstrated the reactivity of 3-nitroindoles/benzothiophenes towards different electron-rich species such as isoquinolinium, pyridinium ylides and 2-amino pyridines.

Chapter 1 begins with a brief introduction to the reactivity of electrophilic indoles towards synthesising *N*-fused heterocycles.

In Chapter 2, we have developed a copper-catalyzed methodology for the synthesis of heteroacenes, such as indole-fused imidazo[1,2-*a*]pyridines and indolo-imidazo[1,2-*a*]quinolones by the annulation of electrophilic indole with 2-aminopyridine and 2-aminoquinoline respectively. We could also extend the methodology towards the synthesis of benzothiophene-fused imidazo[1,2-*a*]pyridines.

Chapter 3A describes the domino reaction dipolar cycloaddition- ring-opening reaction between isoquinolinium ylides and electrophilic benzannulated heterocycles towards the synthesis of pyrrolo[2,1-*a*] isoquinolines starting from different isoquinolinium methylides and 3-nitroindoles. Formation of S–S bridged bis-pyrrolo[2,1-*a*]isoquinolines was also observed using electrophilic 3-nitro benzothiophene as the substrate.

In Chapter 3B, we synthesized complex polyring fused N-heterocycles *via* a palladium-catalyzed site-selective C–H functionalization of the above obtained pyrrolo[2,1-*a*]isoquinolines. We could identify three sites for C−H functionalization and a *N*-center on the 5-benzoylpyrrolo[2,1-*a*]isoquinoline scaffold. At first, the activation of C-H bonds was effected by a Pd-catalyzed cross-dehydrogenative coupling to synthesize 8*H*-indeno-pyrrolo[2,1-*a*]isoquinolinone. An oxygen induced palladium catalyzed selective C-H amination in the same substrate furnished a pentacene, 9*H*-indolo-pyrrolo[2,1-*a*]isoquinoline. Finally, the site-selective C-H amination in 5-(4-nitro benzoyl)-pyrrolo[2,1-*a*]isoquinoline led to the formation of a multiring fused benzazepine scaffold.

In Chapter 4A, we developed a simple and efficient synthetic approach for generating a library of structurally novel indolizines *via* a 1,3-dipolar cycloaddition-ring opening cascade.

In Chapter 4B, we have introduced a palladium-catalyzed site-selective C–H functionalization in these indolizine motifs for accessing fused indolizine scaffolds. A Pd-mediated cross-dehydrogenative coupling of 5-benzoyl-substituted indolizine afforded 6*H*-indeno-indolizine and a tetracene viz., indolizino[2,1-*b*]indoles was produced in the same substrate by an oxygen-induced palladium-catalyzed selective C-H amination.

List of Publications Emanating from the Thesis

1. **Sheba Ann Babu**, Rajalekshmi A. R., Nitha P. R., Vishnu K. Omanakuttan, Rahul P., Sunil Varughese and Jubi John, Unprecedented access to functionalized pyrrolo[2,1-a]isoquinolines from the domino reaction of isoquinolinium ylides and electrophilic benzannulated heterocycles. *Org. Biomol. Chem*., **2021**, *19*, 1807.

2. **Sheba Ann Babu**, Varsha P. V, Susanna Poulose, Sunil Varughese, and Jubi John, Copper-Catalyzed Annulation of Electrophilic Benzannulated Heterocycles with 2-Aminopyridine and 2-Aminoquinoline: Direct Access toward Polyring-Fused Imidazo[1,2-a]pyridines. *J. Org. Chem*., **2023,** *88,* 10027.

3. **Sheba Ann Babu**, Sunil Varughese, Jomon Mathew and Jubi John, Discovery of Oxygen Induced Chemoselectivity in Pd-Catalyzed C−H Functionalization: Cross-Dehydrogenative Coupling *Vs* C−H Amination. *J. Org. Chem*., **2023**, *88*, 9877.

4. **Sheba Ann Babu**, Jijy E. and Jubi John, Annulation Reactions of Electrophilic Benzannulated Heterocycles towards Heteroacenes. *Chem. Commun*., **2024**, *60*, 1674.

5. **Sheba Ann Babu**, Aparna A., Malavika Mohan, Namitha Paul, Jomon Mathew and Jubi John, Tandem Reactions of Electrophilic Indoles towards Indolizines and their Subsequent Transformations through Pd(II)-Mediated C-H Functionalization to Access Polyring Fused *N*-Heterocycles (Manuscript submitted).

List of Publications not Related to Thesis Work

1. P. V. Santhini, **Sheba Ann Babu**, Akhil Krishnan R, E. Suresh, and Jubi John, Heteroannulation of 3-Nitroindoles and 3-Nitrobenzo[b]thiophenes: A Multicomponent Approach toward Pyrrole-Fused Heterocycles. *Org. Lett*., **2017**, *19*, 2458.

2. P. V. Santhini, Akhil Krishnan R, **Sheba Ann Babu**, Betna Shamlin Simethy, Gourab Das, Vakayil K. Praveen, Sunil Varughese, and Jubi John, One-Pot MCR-Oxidation Approach toward Indole-Fused Heteroacenes. *J. Org. Chem*., **2017**, *82*, 10537.

3. **Sheba Ann Babu**, K. Keerthi Krishnan, S. M. Ujwaldev, and Gopinathan Anilkumar, Applications of Pybox Complexes in Asymmetric Catalysis. *Asian J. Org. Chem*., **2018**, *7*, 1033.

4. **Sheba Ann Babu**, Salim Saranya, K. R. Rohit, and Gopinathan Anilkumar, Ligand-Free Cu-Catalyzed Suzuki Coupling of Alkynyl Bromides with Boronic Acids in Ethanol Under Microwave Irradiation. *Chemistry Select*., **2019**, *4*, 1019.

5. Rahul Pulikkodan, Nitha P. Ravi, Vishnu. K. Omanakuttan, **Sheba Ann Babu**, Sasikumar Parameswaran, Vakayil. K. Praveen, Henning Hopf, Jubi John, Superbase-Mediated Indirect Friedländer Reaction: A Transition Metal-Free Oxidative Annulation toward Functionalized Quinolines. *Eur. J. Org. Chem*., **2020**, 3081.

6. Akhil Krishnan R., **Sheba Ann Babu**, Nitha P. R., Jagadeesh Krishnan, and Jubi John, Synthesis of Benzothienobenzofurans via Annulation of Electrophilic Benzothiophenes with Phenols. *Org. Lett*., **2021**, *23*, 1814.

7. Akhil Krishnan R., **Sheba Ann Babu**, Nitha P. Ravi, Sreeja Thulasi, and Jubi John, Base-Mediated Annulation of Electrophilic Benzothiophene with Naphthols and Phenols: Accessing Benzothiophene-Fused Heteroacenes. *J. Org. Chem*., **2022**, *87*, 8017.

8. Nandana S. K., Rahul P., **Sheba Ann Babu**, Jubi John and Henning Hopf, A Review on the Synthetic Methods towards Benzothienobenzothiophenes (Manuscript submitted).

List of Papers/Posters Presented in Conference

1. Domino Dipolar Cycloaddition-Ring Opening Reaction of Isoquinolinium Ylides with Electrophilic Benzannulated Heterocycles: Unprecedented Access of Functionalized Pyrrolo[2,1-*a*]isoquinolines, **Sheba Ann Babu**, Sunil Varughese and Jubi John, Online National Conference on Organic Chemistry "NITT Organic Chemistry Conference (NITTOCC)" organized by Department of chemistry, National Institute of Technology Tiruchirappalli (NITT), on December 16th – 18th, 2021.

2. Pd-Catalyzed Site Selective and Chemoselective C-H Functionalization towards Polyring Fused *N*-Heterocycles, **Sheba Ann Babu** and Jubi John, 30th CRSI-NSC & 16th CRSI-RSC Symposium Series in Chemistry at Jawaharlal Nehru University, New Delhi, February 2023.

Organic & Biomolecular Chemistry

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PAPER

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Cite this: *Org. Biomol. Chem.*, 2021, **19**, 1807

Unprecedented access to functionalized pyrrolo[2,1-*a*]isoquinolines from the domino reaction of isoquinolinium ylides and electrophilic benzannulated heterocycles†

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Received 2nd January 2021,
Accepted 25th January 2021

DOI: 10.1039/d1ob00005e

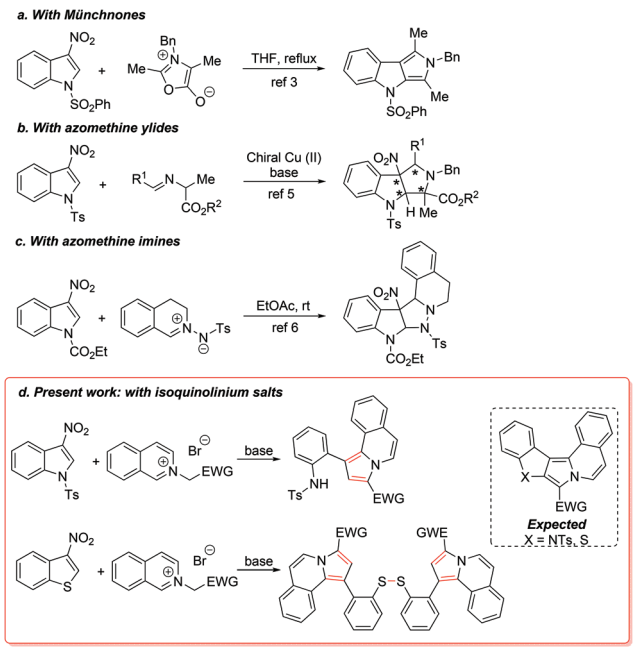
rsc.li/obc

We have come across an unexpected reaction between electrophilic indoles and isoquinolinium methylides for accessing functionalized pyrrolo[2,1-*a*]isoquinolines. The reaction was found in general to yield the products in good yields. We also observed the formation of S–S-bridged bis-pyrrolo[2,1-*a*]isoquinolines from the reaction of 3-nitro benzothiophene and isoquinolinium methylides.

Introduction

Electrophilic benzannulated heterocycles, which exhibit unusual reactivity can be generated by installing electron-withdrawing substituents at precise positions.[1] In this way, an indole moiety can be made electrophilic by placing electron-withdrawing groups on the N-atom and C-2 or C-3 carbon atoms. The chemistry of electrophilic indoles was extensively investigated by several groups for the synthesis of functionalized (or fused) indoline/indole moieties.[2] Dipolar cycloaddition utilizing an electrophilic indole as the dipolarophile towards annulated heterocycles has been reported by different groups. The first of these reports came from Gribble's group in 1998 in which they synthesized pyrrolo[3,4-*b*]indoles *via* the dipolar cycloaddition of münchnones with an electrophilic indole (Scheme 1a).[3] Later, the same group also reported the reaction of azomethine ylides with electrophilic indoles, furnishing hexahydropyrrolo[3,4-*b*]indoles.[4] The asymmetric version of azomethine ylide addition to an electrophilic indole was independently reported by Arai and Stanley (Scheme 1b).[5] In 2017, Wang and co-workers reported the synthesis of five-ring-fused tetrahydroisoquinolines from azomethine imines and electrophilic indoles (Scheme 1c).[6] Our interest in the chemistry of electrophilic benzannulated heterocycles[7] made us devise dipolar cycloaddition reactions towards novel heteroacenes (Scheme 1d).

Heteroaromatic N-ylides are a class of dipoles which have been comprehensively studied for the generation of highly functionalized carbocycles and heterocycles.[8] In particular, isoquinolinium methylides have been utilized in dipolar cycloaddition reactions with several dipolarophiles, such as electron-deficient alkenes and alkynes to access fused



Scheme 1 Dipolar cycloadditions involving electrophilic benzannulated heterocycles.

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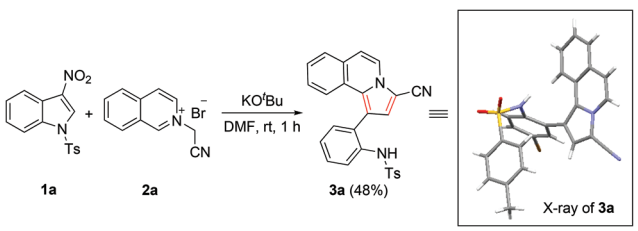
†Electronic supplementary information (ESI) available. CCDC 2042168 and 2042169. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob00005e

N-heterocyclic scaffolds.[9] The 1,3-dipolar cycloaddition of isoquinolinium methylides to nitrostyrenes has been reported previously. The first work in this line was published in 1990 when 1-nitro-2-phenyl-3-*R*-2,3-dihydrobenzo[*g*]indolizine was synthesized *via* the reaction between β-nitrostyrene and isoquinolinium methylide.[10] Later, Kucukdisli and Opatz reported the reaction of different heteroaromatic N-ylides (including isoquinolinium methylides) with β-nitrostyrene and found that aromatized products were obtained after the elimination of HNO_2.[11] In 2014, the dipolar cycloaddition of isoquinolinium methylides to 3-nitrochromenes was reported to furnish azadibenzo[*a*,*g*]fluorene derivatives.[12] Inspired by these reports on the dipolar cycloaddition of isoquinolinium methylides to nitrostyrenes, we hypothesized that the reactions of these heteroaromatic N-ylides with electrophilic benzannulated heterocycles would result in the development of novel heteroacenes (Scheme 1d).

Results and discussion

We commenced our studies by selecting *N*-tosyl-3-nitro indole **1a** and 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** as model substrates. Initially, **1a** (1.0 equiv.) and **2a** (1.1 equiv.) were treated in the presence of potassium *t*-butoxide (^{t}BuOK, 4.0 equiv.) in dimethylformamide (DMF) at room temperature for 1 h. Contrary to our expectation of the formation of a pentacene, as depicted in Scheme 1d, the 1,3-dipolar cycloaddition reaction between **1a** and **2a** resulted in the formation of functionalized pyrrolo[2,1-*a*]isoquinoline **3a** in 48% yield (Scheme 2). The structure of **3a** established by various spectroscopic analyses was further confirmed from X-ray crystallographic data.

Pyrrolo[2,1-*a*]isoquinoline moieties[13] are important fused N-heterocycles that are found in plenty of core structures of natural products, such as crispine A and B, trolline, lamellarins, and erythrina alkaloids, which are found to show interesting anticancer, antiviral and antibacterial activities.[14] Synthetic pyrrolo[2,1-*a*]isoquinolines have also been found to exhibit a plethora of biological properties, such as anticancer effects, multidrug resistance (MDR) reversal, estrogen receptor modulation, deoxyribonucleic acid (DNA) chelation, and antimicrobial, antiplatelet and anti-inflammatory effects.[15] In addition, these fused N-heterocycles have been utilized in developing different metal cation and organic sensors.[16] Two well-known strategies to access pyrrolo[2,1-*a*]isoquinolines are the annulation of appropriate rings to a substituted pyrrole or an N-functionalized isoquinoline.[13,15a,17] In 2019, Dong and Huang reported the synthesis of substituted indolizines from the reaction of chromones and pyridinium salts.[18] This reaction proceeded *via* a 1,3-dipolar cycloaddition-ring opening and aromatization cascade.

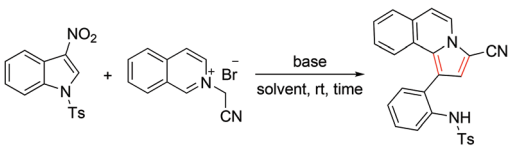


Scheme 2 1,3-Dipolar cycloaddition of an isoquinolinium methylide with an electrophilic indole.

Intrigued by the unexpected synthesis of the substituted pyrrolo[2,1-*a*]isoquinoline moiety, we went on with the optimization of the reaction conditions with **1a** and **2a** as substrates. Screening of different bases, such as ^{t}BuOK, ^{t}BuONa, NaOMe, Cs_2CO_3, K_2CO_3, Na_2CO_3, KOH, NaOH, LiOH, NaH and DIPEA (Table 1, entries 1–11) revealed that KOH was the most suitable base, furnishing the product in 54% yield. Then, we focused on the effect of different solvents on the reaction outcome (Table 1, entries 12–16). Among the screened solvents, DMF was found to be the most effective, giving the product in 54% yield. The yield of the reaction was found to decrease when the amount of base was decreased to 2.0 equivalents. In this case, the starting material was found to remain unreacted and no by-product was observed (Table 1, entry 19). Finally, we turned our attention towards the effect of substrate concentration on the reaction. To our delight, the use of 1.5 equivalents of **2a** increased the yield of **3a** to 88% (Table 1, entry 18).

With the optimized conditions in hand (1.0 equiv. of **1a**, 1.5 equiv. of **2a**, 4.0 equiv. of KOH, DMF, rt), we then explored the scope of the 1,3-dipolar cycloaddition of isoquinolinium

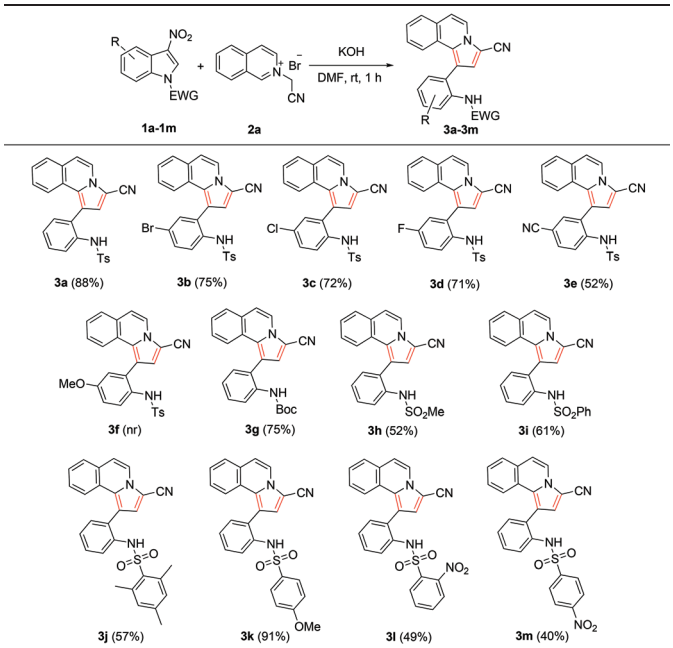
Table 1 Optimization studies[a]



Entry	Base	Solvent	Time (h)	Yield of **3a** (%)
1	^{t}BuOK	DMF	1	48
2	^{t}BuONa	DMF	1	21
3	NaOMe	DMF	1	—
4	Cs_2CO_3	DMF	1	37
5	K_2CO_3	DMF	1	16
6	Na_2CO_3	DMF	1	Trace
7	KOH	DMF	1	54
8	NaOH	DMF	1	49
9	LiOH	DMF	1	43
10	NaH	DMF	1	38
11	DIPEA	DMF	1	—
12	KOH	1,4-Dioxane	1	16
13	KOH	EtOH	1	—
14	KOH	CH_3CN	1	26
15	KOH	EtOAc	1	—
16	KOH	THF	1	22
17	KOH	DMF	12	61
18[b]	KOH	DMF	1	88
19[c]	KOH	DMF	1	10

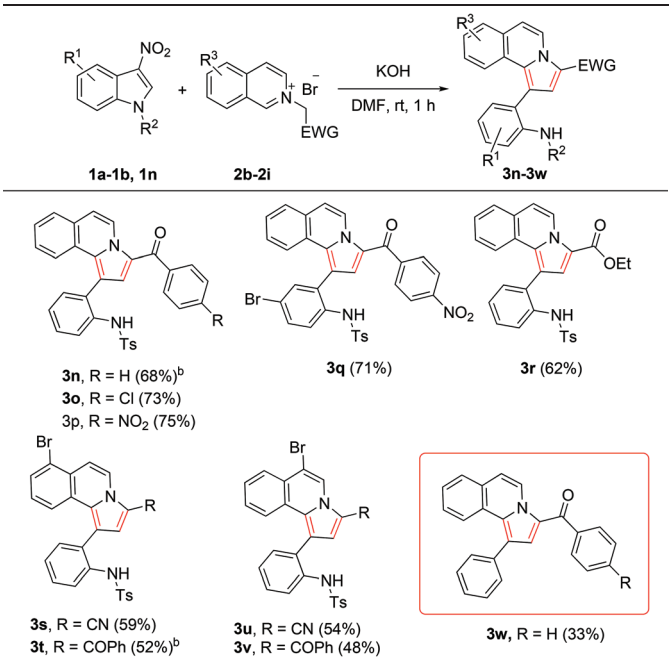
[a] Reaction conditions: **1a** (1.0 equiv., 0.16 mmol), **2a** (1.1 equiv.), base (4.0 equiv.), solvent (1.0 mL), rt. [b] **2a** (1.5 equiv.). [c] Base (2.0 equiv.).

Table 2 Generalization of 1,3-dipolar cycloaddition of isoquinolinium methylides with substituted electrophilic indoles[a]



[a] Reaction conditions: **1** (1.0 equiv., 100 mg), **2a** (1.5 equiv.), KOH (4.0 equiv.), DMF (0.16 M), rt, 1 h.

Table 3 Generalization of 1,3-dipolar cycloaddition reaction with various isoquinolinium bromides[a]



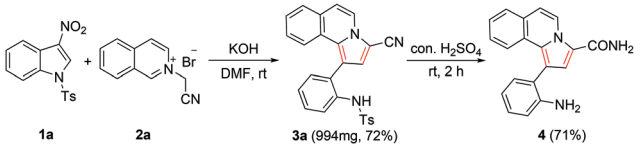
Reaction conditions: [a] **1** (1.0 equiv., 100 mg), **2a** (1.5 equiv.), KOH (4.0 equiv.), DMF (0.16 M), rt, 1 h. [b] 4 h.

methylides using different substituted electrophilic indoles, the results of which are summarized in Table 2. In this way, the generalization of different 3-nitro-indoles **1** with the model substrate 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** was studied. Reactions with halogens (Br, F, Cl)-substituted nitroindoles proceeded well, affording products **3b**, **3c** and **3d** in good yields. The dipolar cycloaddition of **2a** with 3-nitro-1-tosyl-1*H*-indole-5-carbonitrile afforded the corresponding substituted pyrrolo[2,1-*a*]isoquinoline **3e** in 52% yield. With an electron-releasing OMe-substituent (5-methoxy-3-nitro-1-tosyl-1*H*-indole), even after heating to reflux in DMF for a prolonged period of time, the reaction failed, which might be due to the reduced electrophilicity (**3f**). Next, the electron-withdrawing substituent on the N-atom of the indole was changed to Boc, in which case the expected product **3g** was isolated in 75% yield. The reactions with electrophilic indole substrates with SO_2Me and SO_2Ph on the N-atom afforded **3h** and **3i** in 52% and 61% yields. Finally, other sulfonyl substituents on the N-atom of the indole were found to influence the outcome of the reaction from which products **3j** to **3m** were obtained in moderate to excellent yields.

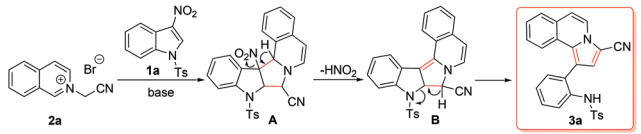
Further investigations were focused on evaluating the reactivity of different isoquinolinium bromides in the present dipolar cycloaddition with electrophilic indoles (Table 3). The reactions with isoquinolinium methylides **2b–2d** (with different substituents on the *para*-position of the phenyl ring) afforded the products **3n–3p** in good yields. The isoquinolinium methylides **2e** with an ethoxycarbonyl-group as the electron-withdrawing moiety also afforded the corresponding pyrrolo[2,1-*a*]isoquinoline **3r** in 62% yield. Finally, isoquinolinium bromides **2f–2i** prepared from 4-bromo isoquinoline and 5-bromo isoquinoline were tested for reactivity in the present transformation and products **3s–3v** were isolated from the reactions in satisfactory yields. *N*-Methyl-3-nitroindole led to the formation of pyrrolo[2,1-*a*] isoquinoline **3w**, wherein we observed the elimination of the *N*-methyl group.

We also attempted a gram-scale synthesis (starting from 1.0 g of **1a**) of pyrrolo[2,1-*a*]isoquinoline **3a**, and the compound was obtained in 72% yield (Scheme 3). Compound **3a** was then subjected to Ts-deprotection by treating it with concentrated H_2SO_4 for 2 hours, which furnished pyrrolo[2,1-*a*]isoquinoline **4**. In compound **4** not only was the Ts-group removed but the CN-moiety was also converted to the corresponding amide.

Based on our observations and on the reported literature,[10–12] we propose a plausible mechanism for the present domino dipolar cycloaddition-ring opening process that takes place during the reaction of electrophilic indole and



Scheme 3 Gram-scale reaction of **1a** with **2a** and *N*-Ts deprotection of pyrrolo[2,1-*a*]isoquinoline **3a**.

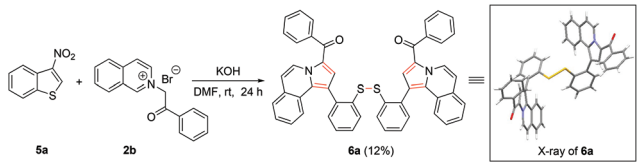


Scheme 4 Plausible mechanism for the synthesis of pyrrolo[2,1-*a*]isoquinoline **3**.

isoquinolinium methylide (Scheme 4). The first step is the deprotonation of the activated methylene group of the isoquinolinium salt by KOH to generate the corresponding N-ylide. This dipole then participates in a 1,3-dipolar cycloaddition with the dipolarophile, *N*-tosyl-3-nitroindole **1a** to generate the corresponding cycloadduct **A** (Scheme 4). Subsequent elimination of HNO_2 from **A** generates intermediate **B**, which upon aromatization results in a strain-induced cleavage of the C–N bond, furnishing the final product pyrrolo[2,1-*a*]isoquinoline **3a**.

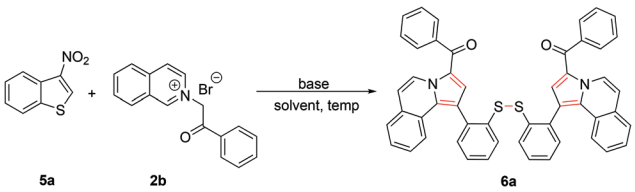
The unexpected domino transformation observed from the reaction of electrophilic indoles and isoquinolinium methylides prompted us to check the reactivity of electrophilic benzothiophenes. The initial experiment was performed by reacting 3-nitro benzothiophene **5a** with 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **2b** in the presence of KOH (2.0 equiv.) in DMF at room temperature. After 24 h, a bis-pyrrolo[2,1-*a*]isoquinoline **6a** linked with an S–S bond was isolated in 12% yield (Scheme 5). The structure of **6a** was established by various spectroscopic analyses and confirmed from X-ray crystallographic data.

The poor yield obtained for the synthesis of bis-pyrrolo[2,1-*a*]isoquinoline **6a** prompted us to optimize the reaction conditions with **5a** and **2b** as substrates. Increasing the equivalents of base and **2b** was found not to have a positive outcome on the reaction yield (Table 4, entries 2 and 3). A slight increase in the yield of **6a** was noted by carrying out the reaction at 60 °C (Table 4, entry 4). Screening of different bases, such as K_2CO_3, K_3PO_4, Na_2CO_3, Cs_2CO_3, NaOH, KOH and KO*t*Bu (Table 4, entries 4–10), revealed that K_3PO_4 was more efficient. Further screening of solvents showed that CH_3CN gave better results in comparison to other solvents, such as DMF, THF, EtOH, DMA, 1,4-dioxane or DMSO (Table 4, entries 7, 11–16). Also, performing the reaction in the presence of an oxidant, $Cu(OAc)_2{\cdot}H_2O$, was found to be less efficient (Table 4, entries 17 and 18). Finally, we carried out the reaction under an inert atmosphere to see whether the oxidation of intermediate thiol to an S–S bond bridged bis-pyrrolo[2,1-*a*]isoquinoline could be prevented (Table 4, entry 19). From this reaction, **6a** was isolated in low yield and we were not able to isolate the thiol or any other intermediates. Complete consumption of 3-nitrobenzothiophene **5a** was not observed in any of the reactions mentioned above.



Scheme 5 Synthesis of bis-pyrrolo[2,1-*a*]isoquinoline **6a** from 3-nitro benzothiophene and **2b**.

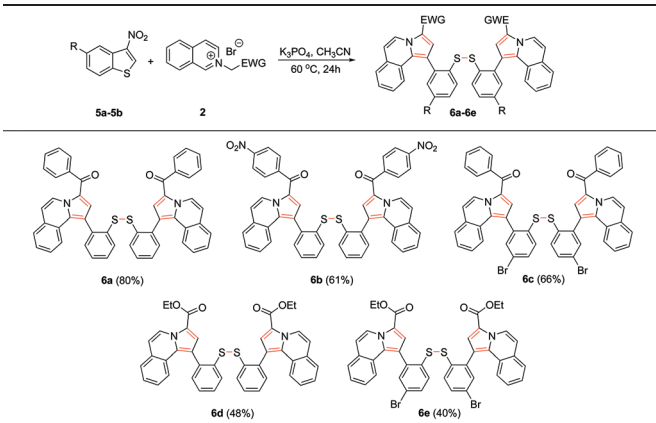
Table 4 Optimization studies[a]



Entry	Base	Solvent	Temp. (°C)	Yield of **6a** (%)
1	KOH	DMF	rt	12
2[b]	KOH	DMF	rt	10
3[c]	KOH	DMF	rt	10
4	KOH	DMF	60	14
5	^{t}BuOK	DMF	60	14
6	NaOH	DMF	60	10
7	K_3PO_4	DMF	60	29
8	K_2CO_3	DMF	60	14
9	Na_2CO_3	DMF	60	—
10	Cs_2CO_3	DMF	60	12
11	K_3PO_4	EtOH	60	—
12	K_3PO_4	THF	60	—
13	K_3PO_4	1,4-Dioxane	60	—
14	K_3PO_4	CH_3CN	60	80
15	K_3PO_4	DMA	60	14
16	K_3PO_4	DMSO	60	20
17	K_3PO_4, $Cu(OAc)_2{\cdot}H_2O$	DMF	60	Trace
18[d]	2,6-Lutidine, $Cu(OAc)_2{\cdot}H_2O$	DMF	60	Trace
19[e]	K_3PO_4	CH_3CN	60	20

[a] Reaction conditions: **5a** (1.0 equiv., 0.28 mmol), **2b** (1.5 equiv.), base (2.0 equiv.), solvent (1.0 mL), rt, 24 h. [b] Base (4.0 equiv.). [c] **2b** (3.0 equiv.). [d] Base (5.0 equiv.); $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv.). [e] Under an argon atmosphere.

Table 5 Generalization of 1,3-dipolar cycloaddition reaction of various isoquinolinium methylides with 3-nitro benzothiophene[a]



[a] Reaction conditions: **5** (1.0 equiv., 100 mg), **2** (1.5 equiv.), K_3PO_4 (2.0 equiv.), CH_3CN (0.28 M), 60 °C, 24 h.

With the optimized conditions in hand [1.0 equiv. of **5a**, 1.5 equiv. of **2b**, 2.0 equiv. of K_3PO_4, CH_3CN (1 ml), 60 °C], the scope of the reaction for the synthesis of bis-pyrrolo[2,1-*a*]isoquinoline was investigated (Table 5). The presence of a phenylethanone substitution on the isoquinolinium N-atom resulted in a better reaction, furnishing the corresponding S–S-bridged bis-pyrrolo[2,1-*a*]isoquinolines **6a–6c** in good to excellent yields. Reactions of isoquinolinium methylides **2e** with an ethoxycarbonyl group as the electron-withdrawing substituent afforded the corresponding products **6d** and **6e** in satisfactory yields. In all the reactions mentioned above, unreacted 3-nitrobenzothiophene **5a** was recovered.

Conclusions

In short, we have developed a domino reaction involving a 1,3-dipolar cycloaddition and a ring-opening between isoquinolinium ylides and electrophilic benzannulated heterocycles. This hitherto unknown methodology gives easy access to a series of highly functionalized pyrrolo[2,1-*a*] isoquinolines starting from different isoquinolinium methylides and 3-nitroindoles. In addition, we observed the formation of S–S-bridged bis-pyrrolo[2,1-*a*]isoquinolines from the reaction of 3-nitro benzothiophene and isoquinolinium methylides. We have also demonstrated the applicability of this cycloaddition reaction for the generation of pyrrolo[2,1-*a*] isoquinolines on the gram scale. Presently, we are currently looking at ways to synthesize pentacenes and dibenzazepines *via* site-selective C–H activation from the above obtained pyrrolo[2,1-*a*]isoquinolines, the details of which will be reported in due course.

Experimental

General experimental methods

All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the methods in the literature and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets pre-coated with silica gel containing a fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using neutral alumina, and mixtures of ethyl acetate hexanes were used for elution melting points which were determined using a calibrated digital melting point apparatus (Büchi 530 melting point apparatus). Infrared spectra were recorded on a Bruker FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker Avance-300 (300 MHz for ^{1}H NMR, 75 MHz for $^{13}C\{^1H\}$ NMR) and Bruker AMX-500 (500 MHz for ^{1}H NMR, 125 MHz for $^{13}C\{^1H\}$ NMR) instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were recorded with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with a JMS-T100GC spectrometer or with an ESI/HRMS at 60 000 resolution using a Thermo Scientific Exactive mass spectrometer with orbitrap analyzer. Gas chromatographic analysis was performed using GCMS-TQ8030 SHIMADZU.

Experimental procedure for the reaction between 3-nitro-*N*-tosyl indole and isoquinolinium salt

A mixture of 3-nitro-*N*-tosyl indole (1.0 equiv., 100 mg), isoquinolinium salt (1.5 equiv.) and KOH (4.0 equiv.) was weighed into a dry reaction tube. Dry DMF was added and the reaction mixture was stirred at room temperature. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer was extracted three times with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (neutral alumina, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and characterization of pyrrolo[2,1-*a*]isoquinolines (3a–3v)

***N*-(2-(3-Cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (3a).** The general procedure was followed using 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (118 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 1 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3a** as a pale yellow solid (122 mg, 88%). Mp: 147–150 °C. IR (neat) ν_{max}: 3884, 3822, 3732, 3485, 3010, 2356, 1546, 1493, 1452, 1334, 1161, 1091, 903, 762 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.09 (d, J = 7 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.50–7.44 (m, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.25–7.21 (m, 2H), 7.17–7.13 (m, 3H), 7.10 (d, J = 8 Hz, 2H), 6.44 (s, 1H), 6.38 (s, 1H), 2.37 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 144.0, 136.2, 135.6, 131.6, 130.1, 129.7, 129.6, 128.6, 128.4, 128.1, 127.5, 127.0, 126.8, 125.4, 124.9, 122.8, 122.7, 122.5, 121.7, 114.6, 113.0, 112.9, 98.0, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{26}H_{19}N_3NaO_2S$ 460.10902, found 460.11007.

***N*-(4-Bromo-2-(3-cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (3b).** The general procedure was followed using 5-bromo-3-nitro-*N*-tosyl indole **1b** (100 mg, 0.25 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (95 mg, 0.38 mmol) and KOH (57 mg, 1.01 mmol) at rt for 1 h. Chromatography (eluent: 25% ethyl acetate in hexane) afforded the desired product **3b** as a brown solid (98 mg, 75%). Mp: 208–210 °C. IR (neat) ν_{max}: 3837, 3747, 3534, 3463, 3273, 2959, 2205, 1721, 1451, 1269, 1116, 1069, 885, 740 cm^{-1}. ^{1}H NMR (500 MHz, $(CD_3)_2CO$, TMS): δ 8.20 (d, J = 7.5 Hz, 1H), 8.13 (s, 1H), 7.85 (d, J = 8 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.71 (dd, J_1 = 9 Hz, J_2 = 1.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.51 (d, J

= 1.5 Hz, 1H), 7.44 (d, J = 8 Hz, 2H), 7.35 (d, J = 7.5 Hz, 1H), 7.29–7.24 (m, 2H), 7.17 (d, J = 7.5 Hz, 2H), 6.73 (s, 1H), 2.36 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 143.7, 137.3, 136.1, 134.4, 132.2, 130.5, 130.4, 129.4, 128.6, 128.2, 127.9, 127.6, 126.8, 125.1, 124.9, 123.2, 122.8, 122.6, 117.5, 114.3, 112.6, 112.5, 97.8, 20.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{26}H_{18}BrN_3NaO_2S$ 538.01953, found 538.02063.

***N*-(4-Chloro-2-(3-cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (3c).** The general procedure was followed using 5-chloro-3-nitro-*N*-tosyl indole **1c** (100 mg, 0.28 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (106 mg, 0.42 mmol) and KOH (64 mg, 1.14 mmol) at rt for 1 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3c** as a yellow solid (96 mg, 72%). Mp: 190–192 °C. IR (neat) ν_{max}: 3839, 3751, 3570, 3481, 3265, 3239, 3142, 3048, 2952, 2207, 1595, 1490, 1327, 1160, 1087, 890, 778, 674 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.02 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 9 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.42–7.37 (m, 2H), 7.29 (d, J = 8 Hz, 2H), 7.16–7.05 (m, 6H), 6.32 (s, 1H), 6.25 (s, 1H), 2.32 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 144.4, 135.9, 134.3, 131.4, 130.7, 130.1, 129.8, 129.7, 128.8, 128.6, 128.5, 128.3, 127.7, 127.0, 124.7, 123.1, 122.7, 122.5, 114.8, 112.6, 111.6, 98.3, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{26}H_{18}ClN_3NaO_2S$ 494.07004, found 494.07205.

***N*-(2-(3-Cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)-4-fluorophenyl)-4-methylbenzenesulfonamide (3d).** The general procedure was followed using 5-flouro-3-nitro-*N*-tosyl-indole **1d** (100 mg, 0.29 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (111 mg, 0.44 mmol) and KOH (67 mg, 1.19 mmol) at rt for 1 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3d** as a brown solid (97 mg, 71%). Mp: 172–174 °C. IR (neat) ν_{max}: 3869, 3805, 3714, 3622, 3479, 3326, 3190, 2214, 1546, 1453, 1324, 1154, 1087, 784, 662 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.07 (d, J = 7 Hz, 1H), 7.85–7.82 (m, 1H), 7.69 (d, J = 8 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 8 Hz, 2H), 7.25–7.17 (m, 3H), 7.15 (d, J = 7.5 Hz, 1H), 7.10 (d, J = 7.5 Hz, 2H), 6.94 (d, J = 8 Hz, 1H), 6.27 (s, 1H), 6.26 (s, 1H), 2.38 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 161.0, 159.1, 144.2, 135.9, 131.6, 131.6, 129.9, 129.7, 129.6, 128.8, 128.5, 128.3, 127.7, 127.0, 125.0, 124.9, 124.6, 122.6, 122.5, 122.4, 118.3, 118.1, 116.8, 116.6, 114.8, 112.7, 112.0, 98.1, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{26}H_{18}FN_3NaO_2S$ 478.09960, found 478.10168.

***N*-(4-Cyano-2-(3-cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (3e).** The general procedure was followed using 5-cyano-3-nitro-*N*-tosyl-indole **1e** (100 mg, 0.29 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (110 mg, 0.44 mmol) and KOH (66 mg, 1.17 mmol) at rt for 1 h. Chromatography (eluent: 25% ethyl acetate in hexane) afforded the desired product **3e** as a yellow solid (71 mg, 52%). Mp: 217–220 °C. IR (neat) ν_{max}: 3920, 3870, 3815, 3750, 3674, 3535, 3463, 2906, 2209, 1523, 1490, 1334, 1163, 901 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.13 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 9 Hz, 1H), 7.72 (t, J = 7 Hz, 2H), 7.53–7.46 (m, 4H), 7.22–7.15 (m, 4H), 7.06 (d, J = 8.5 Hz, 1H), 6.76 (s, 1H), 6.69 (s, 1H), 2.40 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 144.8, 140.2, 135.6, 135.5, 133.6, 130.3, 129.9, 128.8, 128.6, 128.4, 127.8, 127.1, 126.4, 124.5, 124.1, 122.6, 122.6, 122.4, 122.0, 120.7, 119.8, 119.3, 118.0, 115.1, 112.4, 111.0, 110.0, 108.0, 102.7, 99.0, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{27}H_{18}N_4NaO_2S$ 485.10427, found 485.10656.

***tert*-Butyl(2-(3-cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl) carbamate (3g).** The general procedure was followed using 3-nitro-*N*-Boc indole **1g** (100 mg, 0.38 mmol), 2-(cyanomethyl) isoquinolin-2-ium-bromide **2a** (143 mg, 0.57 mmol) and KOH (85 mg, 1.53 mmol) at rt for 1 h. Chromatography (eluent: 10% ethyl acetate in hexane) afforded the desired product **3g** as a colourless solid (110 mg, 75%). Mp: 157–160 °C. IR (neat) ν_{max}: 3804, 3586, 3533, 3506, 3365, 2992, 2359, 2326, 2206, 1717, 1513, 1452, 1151, 1021, 829, 763, 739, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.14 (d, J = 8 Hz, 1H), 8.07(d, J = 7.5 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.42–7.39 (m, 2H), 7.26–7.22 (m, 2H), 7.19 (s, 1H), 7.17 (s, 1H), 7.10–7.07 (m, 2H), 6.22 (s, 1H), 1.23 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 152.7, 137.1, 131.3, 130.1, 129.4, 128.6, 128.4, 128.0, 127.2, 125.4, 124.2, 123.5, 123.4, 123.2, 122.7, 119.8, 114.5, 114.3, 113.3, 98.2, 80.6, 28.1 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{24}H_{21}N_3NaO_2$ 406.15260, found 406.15397.

***N*-(2-(3-Cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)methanesulfonamide (3h).** The general procedure was followed using 1-(methylsulfonyl)-3-nitro-1*H*-indole **1h** (100 mg, 0.42 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (155 mg, 0.62 mmol) and KOH (93 mg, 1.66 mmol) at rt for 1 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3h** as a colourless solid (78 mg, 52%). Mp: 167–169 °C. IR (neat) ν_{max}: 3884, 3769, 3688, 3546, 3478, 3269, 2903, 2206, 1569, 1485, 1385, 1326, 1157, 1101, 969, 768 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.08 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.24–7.19 (m, 2H), 7.12–7.10 (m, 2H), 6.22 (s, 1H), 2.78 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.0, 132.2, 130.2, 128.7, 128.6, 128.4, 127.8, 125.4, 125.0, 124.9, 122.9, 122.7, 122.7, 118.8, 114.9, 112.9, 112.8, 98.6, 39.9 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{20}H_{15}N_3NaO_2S$ 384.07772, found 384.07822.

***N*-(2-(3-Cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide (3i).** The general procedure was followed using 3-nitro-1-(phenylsulfonyl)-1*H*-indole **1i** (100 mg, 0.33 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (124 mg, 0.50 mmol) and KOH (74 mg, 1.32 mmol) at rt for 1 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3i** as a colourless solid (85 mg, 61%). Mp: 203–205 °C. IR (neat) ν_{max}: 3870, 3848, 3726, 3675, 3536, 3451, 3301, 3260, 2876, 2355, 2196, 1576, 1487, 1445, 1386, 1329, 1159, 1092, 896 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.02 (d, J = 7 Hz, 1H), 7.77 (d, J = 8 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 7.45–7.38 (m, 5H), 7.28–7.25 (m, 1H), 7.19–7.11 (m, 5H), 7.08 (d, J = 8 Hz, 1H), 6.31 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 139.0, 135.4, 133.1, 131.7, 130.1, 129.8,

129.0, 128.7, 128.4, 128.2, 127.6, 127.0, 126.9, 125.5, 124.9, 122.8, 122.6, 122.5, 121.7, 114.7, 112.9, 98.1 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{25}H_{17}N_3NaO_2S$ 446.09337, found 446.09430.

***N*-(2-(3-Cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-2,4,6-trimethylbenzenesulfonamide (3j).** The general procedure was followed using 1-(mesitylsulfonyl)-3-nitro-1*H*-indole **1j** (100 mg, 0.29 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (109 mg, 0.44 mmol) and KOH (65 mg, 1.16 mmol) at rt for 1 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3j** as a colourless solid (77 mg, 57%). Mp: 213–215 °C. IR (neat) ν_{max}: 3895, 3788, 3669, 3636, 3531, 3436, 3300, 3123, 2922, 2794, 2340, 2207, 1573, 1485, 1441, 1330, 1258, 1156, 1011, 791 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.02 (d, J = 7 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 7.41–7.38 (m, 2H), 7.19–7.18 (m, 2H), 7.15–7.13 (m, 2H), 7.07 (d, J = 7 Hz, 1H), 6.59 (s, 1H), 6.57 (s, 2H), 6.45 (s, 1H), 2.11 (s, 3H), 2.04 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 142.4, 138.8, 135.3, 133.9, 131.8, 131.6, 129.9, 129.5, 128.6, 128.4, 128.2, 128.0, 127.5, 125.9, 124.9, 123.8, 122.9, 122.6, 122.4, 114.6, 113.7, 112.9, 98.1, 22.8, 21.0 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{28}H_{23}N_3NaO_2S$ 488.14032, found 488.14207.

***N*-(2-(3-Cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide (3k).** The general procedure was followed using 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1*H*-indole **1k** (100 mg, 0.30 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (112 mg, 0.45 mmol) and KOH (68 mg, 1.20 mmol) at rt for 1 h. Chromatography (eluent: 25% ethyl acetate in hexane) afforded the desired product **3k** as a brown solid (125 mg, 91%). Mp: 183–185 °C. IR (neat) ν_{max}: 3838, 3728, 3675, 3644, 3459, 3217, 2319, 1700, 1543, 1402, 1324, 1153, 1091, 1019, 892, 836, 785, 660 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.02 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 7.43–7.34 (m, 4H), 7.17–7.15 (m, 2H), 7.10–7.06 (m, 3H), 6.68 (d, J = 8.5 Hz, 2H), 6.43 (s, 1H), 6.30 (s, 1H), 3.75 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.2, 135.6, 131.6, 130.6, 129.8, 129.2, 128.6, 128.4, 128.1, 127.5, 126.7, 125.3, 124.9, 122.9, 122.7, 122.5, 121.5, 114.7, 114.1, 113.0, 55.6 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{26}H_{19}N_3NaO_3S$ 476.10393, found 476.10366.

***N*-(2-(3-Cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-2-nitrobenzenesulfonamide (3l).** The general procedure was followed using 3-nitro-1-((2-nitrophenyl)sulfonyl)-1*H*-indole **1l** (100 mg, 0.29 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (108 mg, 0.43 mmol) and KOH (64 mg, 1.15 mmol) at rt for 1 h. Chromatography (eluent: 25% ethyl acetate in hexane) afforded the desired product **3l** as a yellow solid (66 mg, 49%). Mp: 132–135 °C. IR (neat) ν_{max}: 3865, 3803, 3680, 3605, 3453, 3112, 2203, 1635, 1582, 1532, 1400, 1349, 1173, 1121, 898, 850, 777, 733 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 7.94 (d, J = 7 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 8 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.45–7.38 (m, 3H), 7.36–7.33 (m, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.23–7.19 (m, 2H), 7.04–7.00 (m, 3H), 6.42 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 147.1, 135.0, 133.7, 132.9, 132.4, 131.5, 130.5, 130.2, 129.8, 129.0, 128.6, 128.5, 128.0, 127.7, 126.9, 125.5, 125.1, 124.9, 122.5, 122.2, 114.6, 113.5, 112.8 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{25}H_{16}N_4NaO_4S$ 491.07845, found 491.07918.

***N*-(2-(3-Cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-nitrobenzenesulfonamide (3m).** The general procedure was followed using 3-nitro-1-((4-nitrophenyl)sulfonyl)-1*H*-indole **1m** (100 mg, 0.29 mmol), 2-(cyanomethyl)isoquinolin-2-ium-bromide **2a** (108 mg, 0.43 mmol) and KOH (65 mg, 1.15 mmol) at rt for 1 h. Chromatography (eluent: 25% ethyl acetate in hexane) afforded the desired product **3m** as a yellow solid (54 mg, 40%). Mp: 209–212 °C. IR (neat) ν_{max}: 3825, 3711, 3630, 3484, 3187, 2364, 1562, 1520, 1338, 1156, 862, 754, 679 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.03 (d, J = 7.5 Hz, 1H), 7.80–7.76 (m, 3H), 7.55 (d, J = 7.5 Hz, 1H), 7.49–7.44 (m, 3H), 7.31 (t, J = 7.5 Hz, 1H), 7.24–7.19 (m, 2H), 7.05 (d, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.82 (s, 1H), 6.64 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 149.8, 144.8, 134.5, 132.0, 130.1, 130.0, 128.3, 128.2, 128.2, 127.9, 127.7, 127.3, 126.3, 124.7, 123.8, 122.6, 122.4, 122.3, 122.2, 114.8, 112.8, 112.6, 98.5 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{25}H_{16}N_4NaO_4S$ 491.07845, found 491.08002.

***N*-(2-(3-Benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (3n).** The general procedure was followed using 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **2b** (156 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 4 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3n** as a yellow solid (111 mg, 68%). Mp: 223–226 °C. IR (neat) ν_{max}: 3843, 3741, 3633, 3438, 3251, 2371, 1608, 1487, 1436, 1334, 1231, 1159, 905, 871, 807 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.59 (d, J = 7.5 Hz, 1H), 7.78–7.76 (m, 3H), 7.64 (d, J = 8 Hz, 1H), 7.54–7.52 (m, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.42–7.36 (m, 2H), 7.24 (s, 1H), 7.21–7.19 (m, 2H), 7.15–7.11 (m, 3H), 7.04 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 8 Hz, 2H), 6.65 (s, 1H), 6.46 (s, 1H), 2.07 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.4, 143.7, 140.2, 136.0, 135.7, 132.7, 131.7, 131.5, 129.6, 129.5, 129.3, 129.2, 128.4, 128.0, 127.8, 127.2, 127.0, 127.0, 126.8, 125.5, 125.0, 124.6, 124.0, 123.4, 120.5, 114.3, 113.1, 21.4 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + H)^+$ calcd for $C_{32}H_{25}N_2O_3S$ 517.15804, found 517.15996.

***N*-(2-(3-(4-Chlorobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (3o).** The general procedure was followed using 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(4-chlorophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2c** (172 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 1 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3o** as a yellow solid (127 mg, 73%). Mp: 215–218 °C. IR (neat) ν_{max}: 3837, 3750, 3478, 3247, 2360, 1606, 1433, 1365, 1331, 1155, 1084, 900, 804 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.54 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8 Hz, 1H), 7.43–7.36 (m, 4H), 7.26 (d, J = 8 Hz, 2H), 7.20–7.12 (m, 4H), 7.05 (t, J = 7.5 Hz, 1H), 6.74 (d, J = 7.5 Hz, 2H), 6.60 (s,

1H), 6.44 (s, 1H), 2.11 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 183.9, 143.8, 138.5, 137.8, 136.0, 135.7, 133.0, 131.7, 130.5, 129.6, 129.3, 128.7, 128.2, 127.9, 127.1, 127.0, 126.7, 125.4, 125.0, 124.5, 123.7, 123.4, 120.5, 114.5, 113.3, 21.4 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{32}H_{33}ClN_2NaO_3S$ 573.10101, found 573.10307.

4-Methyl-*N*-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide (3p). The general procedure was followed using 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2d** (177 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 1 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3p** as a bright yellow solid (134 mg, 75%). Mp: 199–203 °C. IR (neat) ν_{max}: 3876, 3831, 3798, 3717, 3573, 3463, 3404, 3229, 2348, 1740, 1650, 1587, 1523, 1440, 1333, 1161, 1086, 798, 704 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.61 (d, J = 7.5 Hz, 1H), 8.30 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8 Hz, 1H), 7.68 (d, J = 8 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 8 Hz, 2H), 7.20–7.19 (m, 2H), 7.16–7.11 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 8 Hz, 2H), 6.73 (s, 1H), 6.45 (s, 1H), 2.12 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 182.7, 149.3, 145.6, 143.8, 136.1, 135.7, 133.7, 131.7, 129.9, 129.8, 129.4, 128.5, 128.1, 127.3, 127.2, 127.0, 126.5, 125.4, 124.9, 124.4, 124.6, 123.6, 123.2, 120.1, 115.1, 114.0, 21.4 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{32}H_{23}N_3NaO_5S$ 584.12506, found 584.12785.

***N*-(4-Bromo-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4 methylbenzene sulfonamide (3q).** The general procedure was followed using 5-bromo-3-nitro-*N*-tosyl indole **1b** (100 mg, 0.25 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2d** (142 mg, 0.38 mmol) and KOH (57 mg, 1.01 mmol) at rt for 1 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3q** as a yellow solid (115 mg, 71%). Mp: 250–252 °C. IR (neat) ν_{max}: 3937, 3870, 3792, 3726, 3597, 3560, 3527, 3396, 3337, 3238, 3043, 2927, 1729, 1694, 1589, 1518, 1468, 1435, 1334, 1163, 802, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.59 (d, J = 7.5 Hz, 1H), 8.31 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8 Hz, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 9 Hz, 1H), 7.49–7.46 (m, 2H), 7.34 (s, 1H), 7.28 (s, 1H), 7.21–7.19 (m, 2H), 7.16–7.10 (m, 2H), 6.81 (d, J = 7.5 Hz, 2H), 6.69 (s, 1H), 6.42 (s, 1H), 2.14 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 182.8, 149.4, 145.4, 144.0, 135.9, 135.0, 134.3, 133.5, 132.7, 129.9, 129.8, 129.5, 128.7, 128.5, 128.3, 127.3, 127.1, 127.0, 125.4, 124.1, 123.6, 123.5, 123.4, 121.5, 117.6, 115.2, 112.4, 21.4 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{32}H_{22}BrN_3NaO_5S$ 662.03558, found 662.03709.

Ethyl 1-(2-(4-methylphenylsulfonamido)phenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (3r). The general procedure was followed using 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium-bromide **2e** (140 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 1 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3r** as a colourless solid (95 mg, 62%). Mp: 125–126 °C. IR (neat) ν_{max}: 3904, 3831, 3700, 3437, 3267, 2837, 1684, 1544, 1493, 1447, 1380, 1332, 1290, 1203, 1158, 1079, 954, 902, 790, 742 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.23 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 7.38–7.30 (m, 2H), 7.27 (d, J = 8 Hz, 2H), 7.18–7.10 (m, 2H), 7.04 (d, J = 8 Hz, 1H), 7.00–6.95 (m, 2H), 6.87–6.86 (m, 3H), 6.54 (s, 1H), 4.35 (q, J = 7 Hz, 2H,), 2.19 (s, 3H), 1.37 (t, J = 7 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 161.1, 143.6, 136.0, 135.5, 131.7, 131.1, 130.3, 129.4, 129.3, 128.5, 127.7, 127.6, 127.4, 127.0, 127.0, 127.0, 125.0, 125.0, 124.6, 122.9, 122.0, 120.8, 116.3, 113.5, 112.3, 60.3, 21.6, 14.6 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{28}H_{24}N_2NaO_4S$ 507.13490, found 507.13644.

***N*-(2-(7-Bromo-3-cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (3s).** The general procedure was followed using 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 5-bromo-2-(cyanomethyl)isoquinolin-2-ium-bromide **2f** (156 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 1 h. Chromatography (eluent: 10% ethyl acetate in hexane) afforded the desired product **3s** as a colourless solid (96 mg, 59%). Mp: 74–76 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.13 (d, J = 7.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 8 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.50–7.46 (m, 1H), 7.36 (d, J = 8 Hz, 2H), 7.24–7.14 (m, 3H), 7.08 (d, J = 8 Hz, 2H), 6.98 (t, J = 8 Hz, 1H), 6.50 (s, 1H), 6.40 (s, 1H), 2.37 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 144.1, 136.1, 135.5, 131.9, 131.5, 130.0, 129.6, 129.3, 129.0, 127.6, 127.0, 126.5, 126.4, 125.5, 123.7, 123.4, 122.5, 122.1, 121.8, 113.8, 113.2, 112.5, 98.3, 21.6 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{26}H_{18}BrN_3NaO_2S$ 538.01953, found 538.02089.

***N*-(2-(3-Benzoyl-7-bromopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (3t).** The general procedure was followed using 3 -nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 5-bromo-2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **2g** (192 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 4 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3t** as a yellow solid (98 mg, 52%). Mp: 243–247 °C. IR (neat) ν_{max}: 3916, 3877, 3804, 3670, 3529, 3444, 2957, 2450, 1727, 1673, 1618, 1334, 1162, 911, 867, 787 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.62 (d, J = 7.5 Hz, 1H), 7.79–7.75 (m, 3H), 7.64 (d, J = 7.5 Hz, 1H), 7.55–7.53 (m, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.40–7.37 (m,1H), 7.25 (d, J = 8 Hz, 2H), 7.17–7.11 (m, 3H), 6.86 (t, J = 8 Hz, 1H), 6.74 (d, J = 8 Hz, 2H), 6.71 (s, 1H), 6.42 (s, 1H), 2.08 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.5, 143.8, 139.9, 136.0, 135.6, 131.8, 131.8, 131.7, 131.6, 129.7, 129.3, 129.2, 128.6, 128.4, 128.2, 127.0, 127.0, 126.7, 126.1, 125.1, 124.0, 122.8, 122.0, 120.8, 113.7, 112.8, 21.4 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + H)^+$ calcd for 617.05050, found 617.05084.

***N*-(2-(6-Bromo-3-cyanopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (3u).** The general procedure was followed using 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 4-bromo-2-(cyanomethyl)isoquinolin-2-ium-bromide **2h** (156 mg, 0.47 mmol) and KOH (70 mg, 1.26 mmol) at rt for 1 h. Chromatography (eluent: 10% ethyl acetate in hexane) afforded the desired product **3u** as a yellow solid (88 mg, 54%). Mp: 167–170 °C. IR (neat) ν_{max}: 3917, 3847,

3803, 3619, 3448, 3227, 2204, 1591, 1489, 1434, 1331, 1159, 1086, 915, 811 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.37 (s, 1H), 8.04 (d, J = 8 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.56–7.53 (m, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.37 (d, J = 7.5 Hz, 2H), 7.28–7.21 (m, 4H), 7.09 (d, J = 7.5 Hz, 2H), 6.46 (s, 2H), 2.38 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 144.0, 136.2, 135.6, 131.5, 129.9, 129.5, 129.4, 128.6, 127.3, 127.2, 127.0, 126.4, 125.4, 125.0, 123.6, 123.1, 122.9, 121.8, 113.6, 112.4, 110.8, 98.0, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{26}H_{18}BrN_3NaO_2S$ 538.01953, found 538.02112.

***N*-(2-(3-Benzoyl-6-bromopyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (3v).** The general procedure was followed using 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 4-bromo-2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **2i** (192 mg, 0.47 mmol) and KOH (71 mg, 1.26 mmol) at rt for 4 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **3v** as a yellow solid (90 mg, 48%). Mp: 230–234 °C. IR (neat) ν_{max}: 3878, 3744, 3638, 3557, 3492, 3264, 3059, 1744, 1708, 1649, 1613, 1428, 1335, 1160, 1089, 980, 903, 814, 762, 727 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.92 (s, 1H), 8.02 (d, J = 8 Hz, 1H), 7.77–7.74 (m, 3H), 7.53 (t, J = 7 Hz, 1H), 7.50–7.43 (m, 3H), 7.38 (t, J = 7.5 Hz, 1H), 7.24 (d, J = 8 Hz, 2H), 7.19–7.12 (m, 3H), 7.08 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 8 Hz, 2H), 6.67 (s, 1H), 6.43 (s, 1H), 2.07 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.4, 143.8, 139.8, 136.0, 135.6, 131.8, 131.7, 131.6, 129.7, 129.3, 129.2, 128.7, 128.5, 128.2, 126.9, 126.9, 126.9, 126.6, 126.6, 125.2, 124.5, 123.8, 123.5, 120.9, 113.5, 110.6, 21.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for$C_{32}H_{23}BrN_2NaO_sS$ 617.05050, found 617.05255.

Phenyl(1-phenylpyrrolo[2,1-*a*]isoquinolin-3-yl)methanone (3w). The general procedure was followed using 3-nitro-*N*-methyl indole **1n** (100 mg, 0.57 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **2b** (279 mg, 0.85 mmol) and KOH (128 mg, 2.28 mmol) at rt for 1 h. Chromatography (eluent: 5% ethyl acetate in hexane) afforded the desired product **3w** as a yellow solid (65 mg, 33%). Mp: 183–185 °C. IR (neat) ν_{max}: 3700, 3643, 3531, 3557, 3358, 2328, 1911, 1764, 1730, 1598, 1566, 1443, 1393, 1364, 1331, 1282, 1195, 902, 790, 747, 718 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.30 (d, J = 8 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.59–7.55 (m, 2H), 7.52 (d, J = 8 Hz, 2H), 7.19 (t, J = 7 Hz, 1H), 7.15–7.13 (m, 3H), 7.09–7.04 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 187.6, 139.7, 138.1, 135.8, 134.8, 131.2, 130.1, 129.8, 128.9, 127.9, 127.7, 127.7, 127.5, 126.9, 126.6, 125.3, 124.7, 123.4, 122.0, 113.0, 103.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for$C_{25}H_{18}NO$ 348.13829, found 348.13923.

Synthesis and characterization of 4

The compound **3a** (100 mg, 0.23 mmol) was treated with concentrated H_2SO_4 (2.0 equiv.) at room temperature for 2 hours. After completion of the reaction as indicated from the TLC, the reaction mixture was cooled and quenched by drop-wise addition of saturated $NaHCO_3$ solution and the aqueous layer extracted three times with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (50% ethyl acetate in hexane) to afford the pyrrolo[2,1-*a*]isoquinoline **4** as a brown solid (49 mg, 71%). Analytical data of **4**: Mp: 118–120 °C. ^1H NMR (500 MHz, $(CD_3)_2CO$, TMS): δ 9.45 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.24 (s, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 6.60 (t, J = 7 Hz, 1H), 4.28 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 163.3, 146.7, 131.2, 129.0, 128.7, 128.1, 127.0, 126.6, 126.5, 126.0, 125.2, 123.4, 121.3, 118.7, 118.5, 116.8, 115.7, 115.1, 114.6, 112.0 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{19}H_{16}N_3O$ 302.12879, found 302.12991.

Experimental procedure for the reaction between 3-nitrobenzothiophene and isoquinolinium salt

A mixture of 3-nitrobenzothiophene (1.0 equiv., 100 mg), isoquinolinium salt (1.5 equiv.) and K_3PO_4 (2.0 equiv.) was weighed into a dry reaction tube. Dry CH_3CN was added and allowed to stir at 60 °C for 24 h. After completion of the reaction, the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and characterization of bis-pyrrolo[2,1-*a*] isoquinolines (6a–6e)

(1,1′-(Disulfanediylbis(2,1-phenylene))bis(pyrrolo[2,1-*a*]isoquinoline-3,1-diyl))bis(phenylmethanone) (6a). The general procedure was followed using 3-nitrobenzo[*b*]thiophene **5a** (100 mg, 0.56 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **2b** (275 mg, 0.84 mmol) and K_3PO_4 (237 mg, 1.12 mmol) at 60 °C for 24 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **6a** as a yellow solid (169 mg, 80%). Mp: 249–252 °C. IR (neat) ν_{max}: 3945, 3846, 3779, 3682, 3538, 2961, 2363, 1728, 1613, 1414, 1331, 1227, 1168, 1121, 1072, 1031, 965, 932, 871, 791, 756, 727, 688 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.61 (dd, J_1 = 7.5 Hz, J_2 = 1 Hz, 2H), 7.80–7.77 (m, 4H), 7.63 (t, J = 7 Hz, 2H), 7.47–7.42 (m, 5H), 7.41–7.37 (m, 7H), 7.25–7.20 (m, 3H), 7.17–7.14 (m, 3H), 7.12–7.05 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.6, 185.5, 140.5, 140.4, 137.1, 137.1, 134.4, 134.4, 132.8, 132.7, 131.3, 131.3, 129.7, 129.6, 129.2, 128.9, 128.9, 128.2, 127.9, 127.8, 127.8, 127.6, 127.5, 127.0, 126.9, 126.5, 126.4, 125.7, 125.7, 125.5, 125.4, 125.2, 125.1, 124.0, 123.7, 123.7, 116.4, 114.0 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{50}H_{33}N_2O_2S_2$ 757.19780, found 757.20007.

(1,1′-(Disulfanediylbis(2,1-phenylene))bis(pyrrolo[2,1-*a*]isoquinoline-3,1-diyl))bis((4-nitrophenyl)methanone) (6b). The general procedure was followed using 3-nitrobenzo[*b*]thiophene **5a** (100 mg, 0.56 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl) isoquinolin-2-ium-bromide **2d** (312 mg, 0.84 mmol) and K_3PO_4 (237 mg, 1.12 mmol) at 60 °C for 24 h. Chromatography (eluent: 20% ethyl acetate in hexane) afforded the desired product **6b** as a yellow solid (145 mg, 61%). Mp: 290–292 °C.

IR (neat) ν_{max}: 3900, 3822, 3722, 3650, 3430, 2959, 2918, 2336, 1727, 1616, 1519, 1334, 1282, 1119, 1072, 853, 798, 729, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.62 (d, J = 7.5 Hz, 2H), 8.26–8.24 (m, 4H), 7.93–7.90 (m, 4H), 7.69 (t, J = 7 Hz, 2H), 7.50–7.36 (m, 7H), 7.27–7.23 (m, 3H), 7.17–7.06 (m, 8H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 182.8, 182.7, 149.2, 145.9, 145.9, 137.0, 137.0, 134.0, 133.9, 133.8, 133.7, 131.3, 129.9, 129.1, 129.1, 128.5, 128.4, 127.9, 127.9, 127.8, 127.8, 127.2, 127.1, 126.7, 126.7, 125.6, 125.5, 125.0, 124.9, 124.1, 123.5, 123.1, 123.0, 117.2, 117.2, 114.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{25}H_{15}N_2O_3S$ 847.16795, found 847.16754.

(1,1′-(Disulfanediylbis(3-bromo-6,1phenylene))bis(pyrrolo[2,1-*a*]isoquinoline-3,1 diyl))bis(phenylmethanone) (6c). The general procedure was followed using 5-bromo-3-nitrobenzo[*b*]thiophene **5b** (100 mg, 0.39 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **2b** (191 mg, 0.58 mmol) and K_3PO_4 (165 mg, 0.78 mmol) at 60 °C for 24 h. Chromatography (eluent: 10% ethyl acetate in hexane) afforded the desired product **6c** as a light yellow solid (117 mg, 66%). Mp: 230–232 °C. IR (neat) ν_{max}: 3952, 3803, 3390, 3072, 2958, 2922, 2357, 1722, 1606, 1572, 1457, 1328, 1279, 1118, 1070, 938, 868, 791, 742, 687 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.60 (d, J = 7.5 Hz, 2H), 7.78 (t, J = 7 Hz, 4H), 7.70–7.66 (m, 2H), 7.50–7.46 (m, 3H), 7.44–7.39 (m, 8H), 7.33 (d, J = 8 Hz, 1H), 7.26–7.22 (m, 2H), 7.18–7.05 (m, 8H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.6, 185.6, 140.3, 140.2, 136.4, 136.4, 136.3, 133.9, 132.6, 132.4, 131.9, 131.8, 131.5, 129.7, 129.6, 129.2, 128.3, 128.3, 128.2, 128.2, 127.7, 127.6, 127.5, 127.5, 127.4, 127.3, 127.2, 127.1, 125.7, 125.6, 124.9, 124.8, 123.9, 123.8, 123.7, 120.4, 120.4, 114.9, 114.9, 114.2, 114.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{50}H_{31}Br_2N_2O_2S_2$ 915.01677, found 915.01770.

Diethyl1,1′-(disulfanediylbis(2,1-phenylene))bis(pyrrolo[2,1-*a*]isoquinoline-3-carboxylate)(6d). The general procedure was followed using 3-nitrobenzo[*b*]thiophene **5a** (100 mg, 0.56 mmol), 2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium-bromide **2e** (248 mg, 0.84 mmol) and K_3PO_4 (237 mg, 1.12 mmol) at 60 °C for 24 h. Chromatography (eluent: 5% ethyl acetate in hexane) afforded the desired product **6d** as a colourless solid (93 mg, 48%). Mp: 248–250 °C. IR (neat) ν_{max}: 3898, 3841, 3732, 3598, 3357, 2917, 2846, 2312, 1738, 1477, 1444, 1374, 1331, 1203, 1074, 693, 665 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.26 (d, J = 7.5 Hz, 2H), 7.60–7.58 (m, 2H), 7.48–7.46 (m, 1H), 7.42 (dd, J_1 = 8 Hz, J_2 = 1 Hz, 1H), 7.39–7.32 (m, 6H), 7.23–7.20 (m, 2H), 7.18–7.10 (m, 6H), 6.99 (d, J = 7.5 Hz, 2H), 4.36–4.29 (m, 4H), 1.36–1.32 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 161.4, 161.4, 137.1, 137.0, 134.6, 131.3, 131.2, 131.1, 128.8, 128.7, 128.6, 128.5, 127.5, 127.4, 127.2, 126.9, 126.8, 126.3, 126.3, 125.6, 125.6, 125.3, 125.2, 124.8, 124.8, 123.5, 122.6, 115.9, 115.9, 115.6, 115.6, 60.2, 14.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{42}H_{32}N_2NaO_4S_2$ 715.16957, found 715.17230.

Diethyl 1,1′-(disulfanediylbis(3-bromo-6,1-phenylene))bis(pyrrolo[2,1-a]isoquinoline-3-carboxylate) (6e). The general procedure was followed using 5-bromo-3-nitrobenzo[*b*]thiophene **5b** (100 mg, 0.39 mmol), 2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium-bromide **2e** (172 mg, 0.58 mmol) and K_3PO_4 (165 mg, 0.78 mmol) at 60 °C for 24 h. Chromatography (eluent: 10% ethyl acetate in hexane) afforded the desired product **6e** as a colourless solid (66 mg, 40%). Mp: 237–240 °C. IR (neat) ν_{max}: 3911, 3840, 3754, 3681, 3603, 3564, 3263, 3130, 2361, 1691, 1457, 1375, 1340, 1214, 1077, 801, 745, 691, 638 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.26 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 2H), 7.64–7.60 (m, 2H), 7.43–7.38 (m, 4H), 7.34–7.31 (m, 2H), 7.28–7.27 (m, 2H), 7.22–7.14 (m, 6H), 7.03–7.00 (m, 2H), 4.37–4.29 (m, 4H),1.36–1.32 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 161.3, 161.2, 136.7, 136.3, 136.3, 133.9, 133.9, 131.8, 131.7, 131.1, 130.9, 128.6, 128.6, 127.6, 127.6, 127.5, 127.5, 127.4, 127.1, 127.0, 125.3, 125.2, 124.8, 124.8, 123.2, 122.4, 122.3, 120.3, 120.3, 116.2, 116.1, 114.2, 114.1, 113.4, 113.4, 60.3, 60.3, 14.5, 14.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{42}H_{30}Br_2N_2NaO_4S_2$ 872.98855, found 872.98987.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

SAB, NPR, VKO and RP thank CSIR and UGC for research fellowship. JJ thanks CSIR (HCP-029) for financial assistance. The authors thank Prof. Mahesh Hariharan and Mr Alex Andrews of IISER-Thiruvananthapuram for single-crystal X-ray analysis. The authors also thank Mrs Saumini Mathew and Mrs Viji S. of CSIR-NIIST for recording the NMR and mass spectra, respectively.

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Copper-Catalyzed Annulation of Electrophilic Benzannulated Heterocycles with 2-Aminopyridine and 2-Aminoquinoline: Direct Access toward Polyring-Fused Imidazo[1,2-*a*]pyridines

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Cite This: *J. Org. Chem.* 2023, 88, 10027−10039 Read Online

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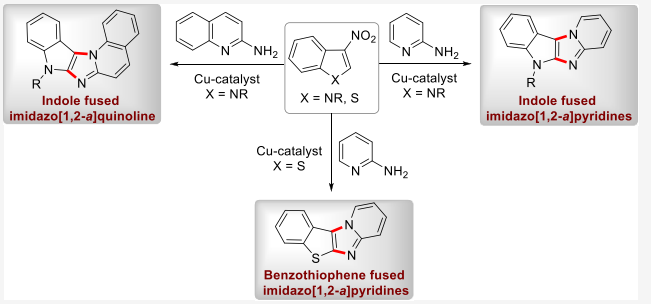
ABSTRACT: We have developed a direct method for the synthesis of polyring-fused imidazo[1,2-*a*]pyridines via a copper-catalyzed annulation of electrophilic benzannulated heterocycles with 2-aminopyridine and 2-aminoquinoline. From 3-nitroindoles and 2-aminopyridine, we could synthesize tetracenes, viz., indole-fused imidazo[1,2-*a*]pyridines, and by starting from 2-aminoquinoline, we could generate pentacenes, viz., indolo-imidazo[1,2-*a*]quinolines. In addition, we could also extend the methodology toward the synthesis of benzothieno-imidazo[1,2-*a*]pyridines starting from 3-nitrobenzothiophene. Furthermore, the basic photophysical properties of these synthesized heteroacenes were evaluated.



INTRODUCTION

Heteroacenes are considered as promising candidates in the field of organic semiconductors, light-emitting diodes, field-effect transistors, and photovoltaics.[1] The reason for the huge potential of heteroacenes can be attributed to the presence of heteroatoms and the possibility of variation of conjugation lengths, both of which have beneficial effects on their optoelectronic properties.[2] Because of them being the subject of extensive research in material applications, several groups have come up with versatile and efficient synthetic strategies toward polyring-fused heterocycles.[3] Inspired by the tremendous utilization of heteroacenes, we were interested in finding synthetic routes toward seldom-explored ones, and herein, we report a copper-catalyzed strategy toward the synthesis of polyring-fused imidazo[1,2-*a*]pyridines.

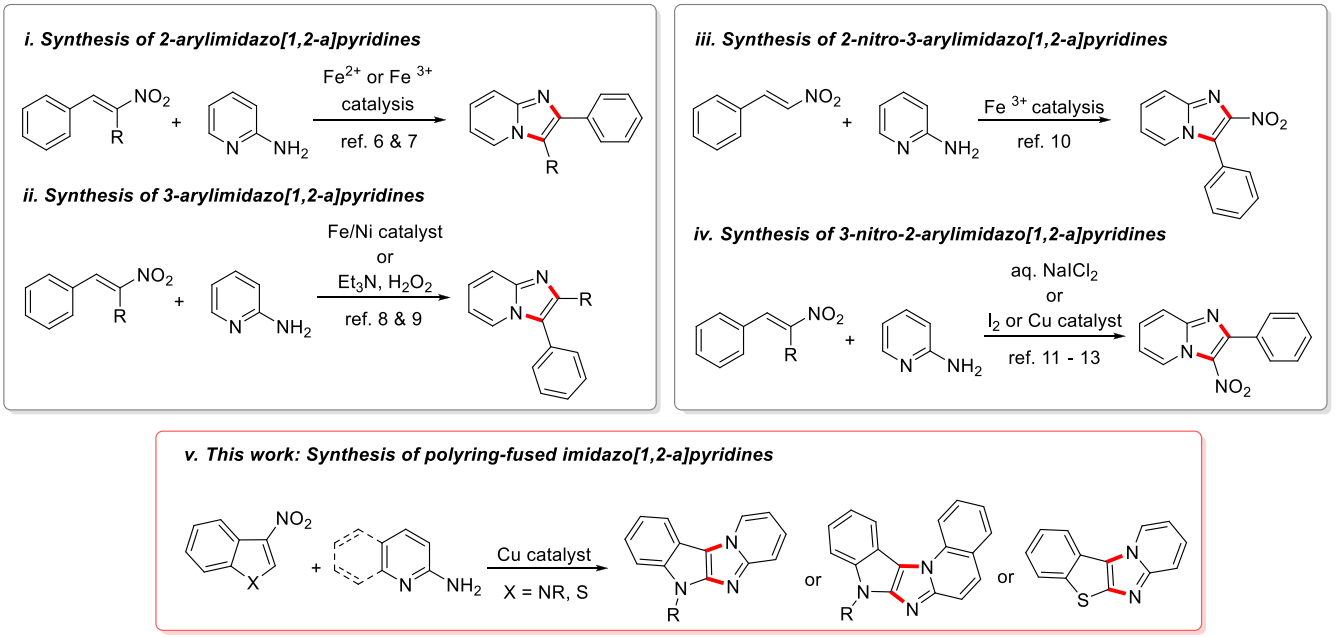
2-Aminopyridine, a pyridine ring with an *ortho*-substituted amine functionality, is a heavily utilized synthon in the field of pharmaceuticals.[4] Due to its binucleophilic nature, a plethora of heterocycles can be synthesized from this simple starting material, wherein the exocyclic amino group or endocyclic pyridinium nitrogen initiates the reaction. During the past decades, several methods were developed for deriving pharmacologically active heterocyclic compounds from 2-aminopyridine,[4] among which imidazo[1,2-*a*]pyridine[5] is recognized as the most important one. Synthesis of this moiety is desirable due to its tremendous use in the field of medicinal chemistry and materials science.[5] Accordingly, various synthetic strategies have been developed toward imidazo[1,2-*a*]pyridine derivatives, out of which the coupling between 2-aminopyridine and nitroolefins seems to be attractive. The first reports in this line came from the groups of Yan[6] and Hajra[7] wherein the synthesis of 2-arylimidazo[1,2-*a*]pyridine derivatives was described (Scheme 1i). Later, both metal-catalyzed and metal-free pathways toward 3-arylimidazo-[1,2-*a*]pyridines scaffolds[8,9] were reported (Scheme 1ii). It is interesting to note that in some cases, the nitro group of the olefin is retained as such, thereby leading to the synthesis of 2-nitro and 3-nitro-arylimidazo[1,2-*a*]pyridines[10−13] (Scheme 1(iii,iv). With these literature precedents in mind, we believed that a methodology could be developed for the annulation of electrophilic benzannulated heterocycles with 2-aminopyridine.

Recently, electrophilic benzannulated heterocycles, notably 3- and 2-nitroindoles have been disclosed as promising electron-deficient moieties.[14] By installing electron-withdrawing groups on the N-atom and C-2 or C-3 carbon atoms of indole, the intrinsic nucleophilic character of indole is reversed, making the system quite electrophilic.[15] Several groups have utilized this reactivity for the generation of different fused indoline/indole scaffolds via annulation reactions,[16] and an interesting nucleophilic aromatic substitution of 2-iodo-3-nitro-1-(phenylsulfonyl)indole with different amines was also reported by Roy and Gribble in 2007.[15a] Due to our continued interest in the chemistry of electrophilic benzannulated

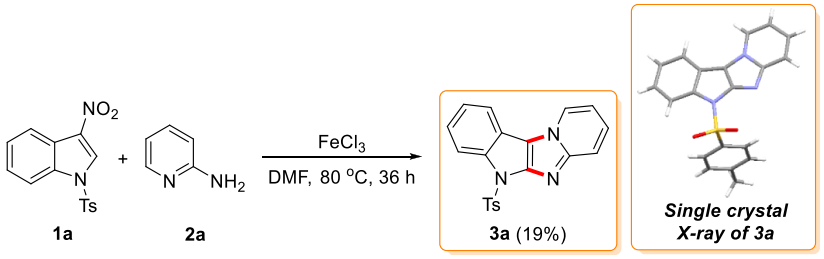
Received: April 18, 2023
Published: July 11, 2023

https://doi.org/10.1021/acs.joc.3c00849
J. Org. Chem. 2023, 88, 10027−10039

Scheme 1. Reactions of 2-Aminopyridine with Nitroolefins toward the Synthesis of Imidazo[1,2-*a*]pyridine Derivatives



Scheme 2. Synthesis of Indole-Fused Imidazo[1,2-*a*]pyridine via the Cu-Catalyzed Annulation of 3-Nitro-*N*-tosyl Indole with 2-Aminopyridine [X-ray of 3a (CCDC: 2237083), 50% Ellipsoid Contour Probability Level]



heterocycles[17] and also due to our search for novel heteroacenes for material applications,[18] we hypothesized that the reaction of 2-aminopyridine with electrophilic benzannulated heterocycles should result in an annulation process, and the results of the investigations in this line are disclosed in this article.

RESULTS AND DISCUSSION

Our investigations commenced with 3-nitro-*N*-tosyl indole **1a** and 2-aminopyridine **2a** as substrates. The initial reaction between **1a** (1.0 equiv) and **2a** (1.5 equiv) was carried out in the presence of $FeCl_3$ (10 mol %) as a catalyst in DMF at 80 °C. After 36 h, as expected, we could isolate indole-fused imidazo[1,2-*a*]pyridine **3a** in 19% yield (Scheme 2). The structure of **3a** established by various spectroscopic analyses was further confirmed from single-crystal X-ray crystallographic data. High-quality single crystals of **3a** in white color were obtained by slow vaporization of its saturated solution in CH_2Cl_2/hexane (1:2 vol/vol).

Inspired by this result, we went on with the optimization of the reaction conditions. First, we checked the efficacy of different metal salts such as $FeCl_3$, $FeCl_2$, CuBr, CuI, CuCl, $Cu(OAC)_2$, and $Cu(OTf)_2$, out of which the CuI-catalyzed reaction afforded indole-fused imidazo[1,2-*a*]pyridine **3a** in a 41% yield (Table 1, entries 1−7). To our delight, increasing the reaction temperature to 100 °C resulted in an improvement in the yield of **3a** to 60% (Table 1, entry 8). The screening of different solvents such as DMF, DMSO, DMA, DCE, NMP, MeCN, chlorobenzene, toluene, and ethanol showed that DMF was the best medium for the present annulation (Table 1, entries 8−16). Next, we turned our attention to checking the effect of concentration on the outcome of the reaction. Changing the concentration to 0.1 mmol as well as 0.3 mmol did not have a positive influence on the reaction yield (Table 1, entries 17 and 18). Our next attempt was to check the effect of increasing and decreasing the amount of **2a** used in the reaction (Table 1, entries 19 and 20). From these reactions, the one with 1.2 equivalents of **2a** afforded the indole-fused imidazo[1,2-*a*]pyridine in 70% yield. Next, on using PTSA as an acid catalyst, the reaction produced a yield of 50% (Table 1, entry 21). Finally, an increase in the catalyst loading led to a drop in the yield of **3a** to 42% and the reaction failed to proceed in the absence of the catalyst (Table 1, entries 22 and 23).

With the optimized conditions in hand [3-nitro-*N*-tosyl indole (1.0 equiv), 2-aminopyridine (1.2 equiv), CuI (10 mol %), DMF (0.15 mmol), 100 °C, 36 h], we examined the reactivity of a series of substituted 2-aminopyridines and 3-nitro-*N*-tosyl indoles to establish the generality of this annulation (Table 2). First, the Cu-catalyzed annulation of **1a** with **2a** was repeated by starting with 1.0 g of **1a**, from which indole-fused imidazo[1,2-*a*]pyridine **3a** was isolated in

https://doi.org/10.1021/acs.joc.3c00849
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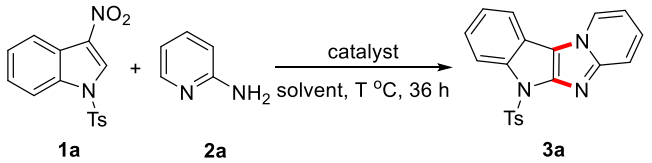
Table 1. Optimization Studies[a]



1a 2a 3a

entry	catalyst	solvent	temperature (°C)	yield of 3a (%)
1	$FeCl_3$	DMF	80	19
2	$FeCl_2$	DMF	80	NR
3	CuBr	DMF	80	23
4	CuI	DMF	80	41
5	CuCl	DMF	80	26
6	$Cu(oAc)_2$	DMF	80	22
7	$Cu(oTf)_2$	DMF	80	traces
8	CuI	DMF	100	60
9	CuI	DMSO	100	58
10	CuI	DMA	100	traces
11	CuI	DCE	100	41
12	CuI	NMP	100	48
13	CuI	MeCN	100	37
14	CuI	chlorobenzene	100	35
15	CuI	Toluene	100	traces
16	CuI	EtOH	100	55
17[b]	CuI	DMF	100	40
18[c]	CuI	DMF	100	25
19[d]	**CuI**	**DMF**	**100**	**70**
20[e]	CuI	DMF	100	66
21[f]	CuI	DMF	100	50
22[g]	CuI	DMF	100	42
23		DMF	100	NR

[a]Reaction conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), catalyst (10 mol %), solvent (0.15 mM), *T* °C, 36 h, isolated yields. [b]Solvent (0.1 mM). [c]Solvent (0.3 mM). [d]**2a** (1.2 equiv). [e]**2a** (2.0 equiv). [f]PTSA (1.2 equiv). [g]Catalyst (20 mol %); NR = no reaction.

61% yield. Then, we checked the reactivity of halogenated electrophilic indoles in the present annulation reaction. In this line, we could install halogens such as F, Cl, and Br at different positions of the indole moiety of the fused imidazo[1,2-*a*]pyridine as in **3b** to **3g**. In accordance with our previous observations, the presence of an electron-donating substituent (OMe) on the indole motif hindered the annulation process and **3h** was not obtained. Next, we tried the reaction by starting with electrophilic indoles having different aryl sulphonyl groups on the N-atom. The Cu-catalyzed annulation of these resulted in the formation of indole-fused imidazo[1,2-*a*]pyridines **3i** to **3l** in satisfactory yields. Further investigations were focused on evaluating the reactivity of different 2-aminopyridines, among which 3-methyl, 5-methyl, and 6-ethyl substituted 2-aminopyridine furnished the corresponding products **3m**, **3n**, and **3o** in poor yields.[19] The reason for the drop in the yield with substituted 2-aminopyridines is not properly understood at the moment. Surprisingly, by changing the electron-withdrawing substituent on the N-atom of indole to Boc, Ac, and benzoyl groups, we observed the formation of**3p** with the *N*-substituents cleaved probably by 2-aminopyridine after the annulation process.

After establishing the generality of the annulation of electrophilic indoles with 2-aminopyridine toward tetracene, we planned to utilize 2-aminoquinoline for the annulation with the idea of generating pentacene (Table 3). The Cu-catalyzed reaction of 3-nitro-*N*-tosyl indole **1a** with 2-aminoquinoline **4** under the optimized conditions afforded indolo-imidazo[1,2-*a*]quinoline **5a** in a 65% yield. The annulation of halogenated electrophilic indoles with 2-aminoquinoline also resulted in the formation of expected products **5b** to **5d** in moderate yields. We were also able to introduce CN-group to the indole part of **5e** by starting from appropriately substituted electrophilic indole. As observed earlier, we could see that with *N*-Boc-3-nitro-indole, the annulated product **5f** was obtained after the Boc-group cleavage. Finally, indole with the SO_2Ph-substituent on the N-atom (**4g**) also furnished the desired product **5g** in a 60% yield.

To further highlight the developed methodology, we attempted Ts-deprotection[17a] in the synthesized indole-fused imidazo[1,2-*a*]pyridine (Scheme 3). Upon subjecting **3a** to basic conditions in a mixture of THF and MeOH, the expected Ts-deprotected compound **3p** was obtained in an 85% yield. Then, **3p** was easily *N*-alkylated by treating with methyl iodide under basic conditions to give **3q** in an 80% yield. The *N*-alkylation of **5f** was also attempted in a similar manner as mentioned above, and the corresponding product **5h** was obtained in an 82% yield.

In order to get an insight into the mechanism of this Cu-catalyzed annulation, we carried out some control experiments (Scheme 4).

To our surprise, when the optimized reaction was carried out at room temperature, we obtained the annulated product (non-aromatic) **3a′**, which we believe is the intermediate of the present annulation reaction (Scheme 4i). Then, **3a′** was subjected to two reaction conditions (DMF, 100 °C, 6 h) in the presence and absence of CuI, and from both the reactions, the product **3a** was obtained in quantitative yields (Scheme 4(ii,iii). This observation proves that the Cu-catalyst is not required in the aromatization stage. Finally, in order to check whether the reaction is proceeding via a radical pathway, we repeated the optimized reaction in the presence of 1.0 equivalent of butyrated hydroxyl toluene (BHT) from which we could observe the formation of product **3a** (Scheme 4iv).

Based on the above observations and literature precedents,[20,21] we propose a mechanism for the annulation reaction, as shown in Scheme 5. The first step is the Michael addition of 2-aminopyridine to the C-2 of 3-nitroindole wherein the Cu-catalyst (acting as a Lewis acid) coordinates with the oxygen of the nitro group in **1a**.[20] This will make the C-2 of **1a** more electrophilic, thereby enabling Michael addition of **2a** to happen to furnish intermediate **A**. Then, the annulation is completed by the attack of lone pair on the pyridine N-atom to the C-3 of **1a** along with protodemetalation. This step affords the intermediate **3a′**, which we could isolate as depicted in Scheme 4i. This is followed by the elimination of nitrous acid and subsequent aromatization to furnish indole-fused imidazo[1,2-*a*]pyridine **3a**.[21]

In order to explore the material aspects of these heteroacenes, we investigated the preliminary photophysical properties of indole-fused imidazo[1,2-*a*]pyridine and indolo-imidazo[1,2-*a*]quinoline. The normalized UV−vis absorption and the steady-state photoluminescence (PL) spectra of these compounds recorded in chloroform (1×10^{-5} M) are shown in Figure 1, and the corresponding photophysical parameters are expressed in Table 4.

From Figure 1, it is clear that when compared to indole-fused imidazo[1,2-*a*]pyridines (**3a**, **3f**, **3n**, **3p**, and **3q**), the indolo-imidazo[1,2-*a*]quinolines derivatives (**5a**, **5d**, **5f**, **5g**, and **5h**) showed a redshifted absorption due to the extended π-

https://doi.org/10.1021/acs.joc.3c00849
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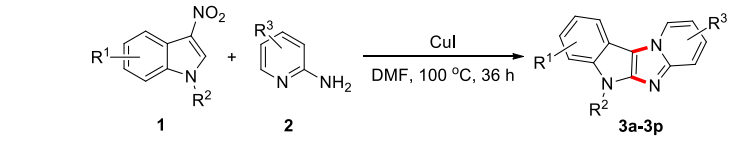
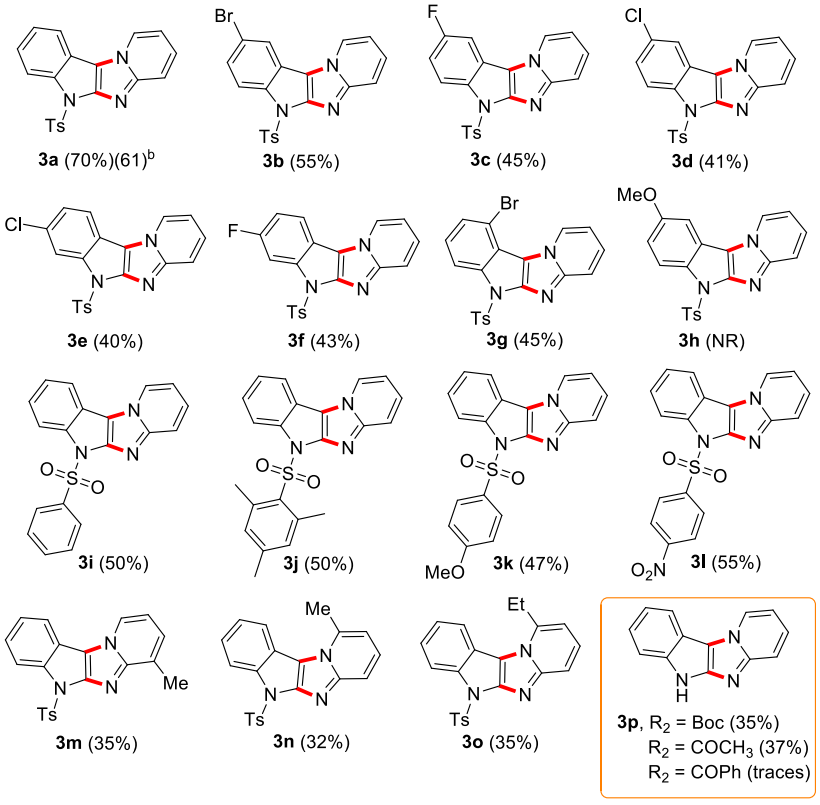
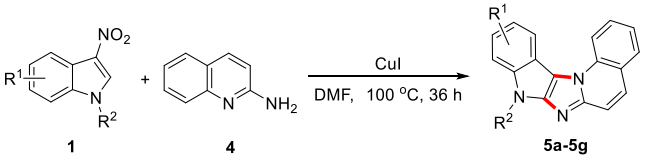
Table 2. Generality of Indole-Fused Imidazo[1,2-*a*]pyridine Synthesis[a]

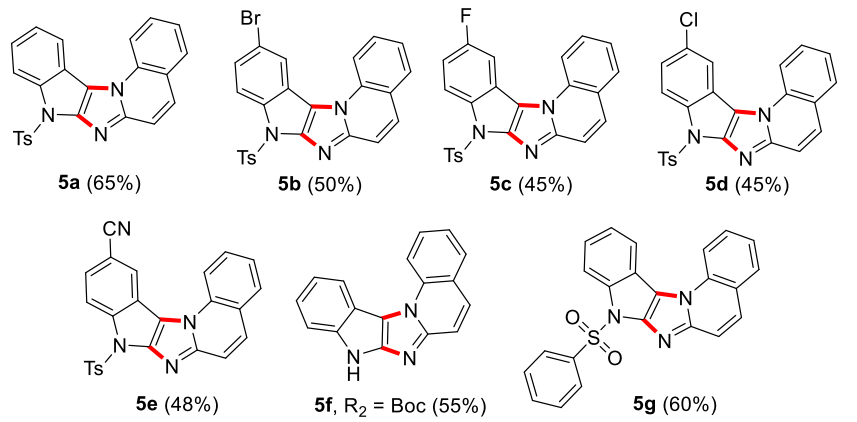




[a]Reaction conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), CuI (10 mol %), DMF (0.15 mM), 100 °C, 36 h. [b]Starting from 1.0 g of **1a**; NR = no reaction.

Table 3. Generality of Indolo-imidazo[1,2-*a*]quinoline Synthesis[a]

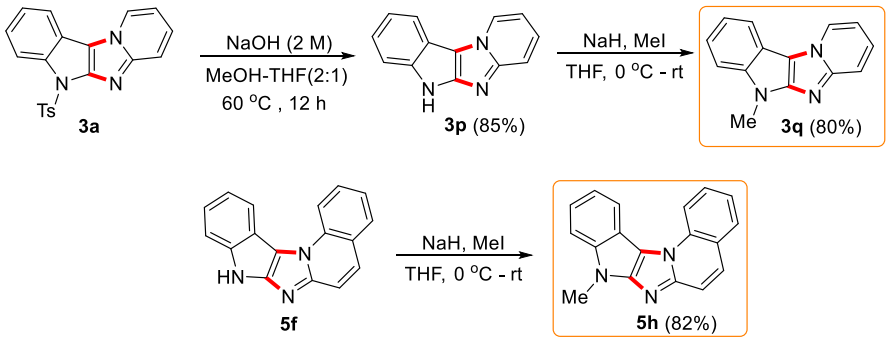




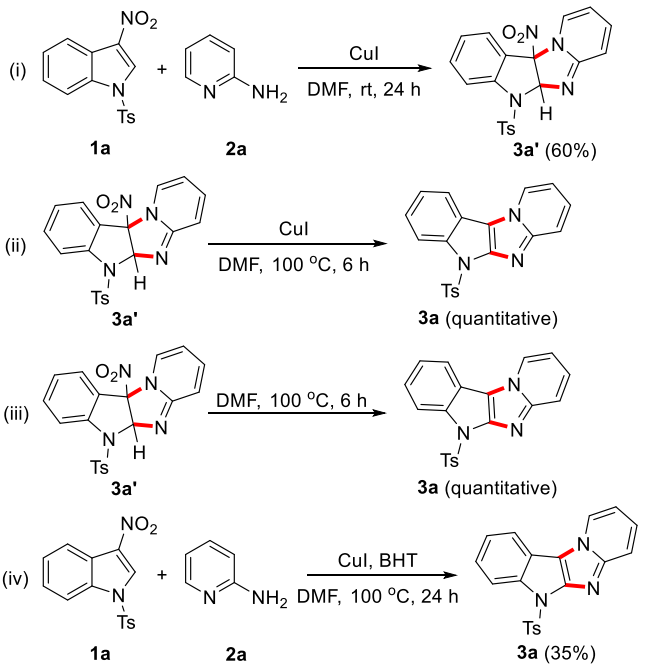
[a]Reaction conditions: **1a** (1.0 equiv), **4** (1.2 equiv), CuI (10 mol %), DMF (0.15 mM), 100 °C, 36 h.

https://doi.org/10.1021/acs.joc.3c00849
J. Org. Chem. 2023, 88, 10027−10039

Scheme 3. Synthetic Transformations of Pyrido-imidazo[4,5-*b*]indole and Indolo-imidazo[1,2-*a*]quinoline



Scheme 4. Control Experiments for Elucidating the Mechanism



conjugation in it. This is also reflected in the emission profile of the corresponding compounds with a redshifted emission maximum. The absorption and emission properties of all these compounds are summarized in Table 4. In addition, we have recorded the fluorescence quantum yield of compounds **3a**, **3q**, **5a**, and **5h** (Table 5). We observed higher fluorescence quantum yields for pentacenes (**5a** and **5h**) than for tetracenes (**3a** and **3q**). All these findings reveal the structure−property relationship of *N*-heterocyclic systems that would benefit the development of novel materials with advanced functionalities.

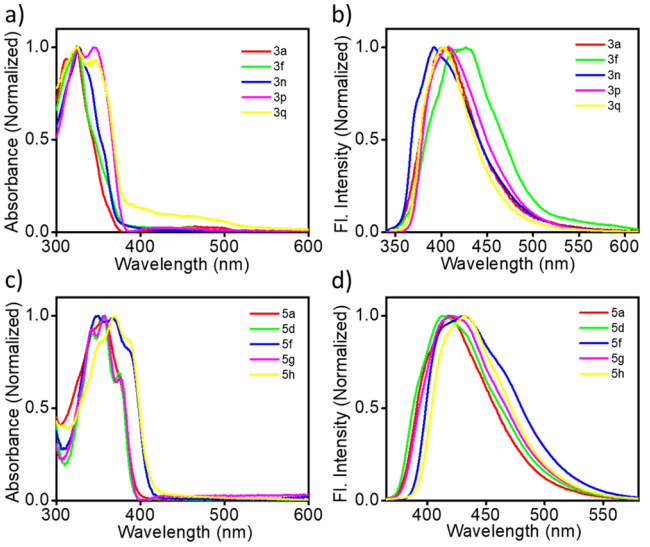
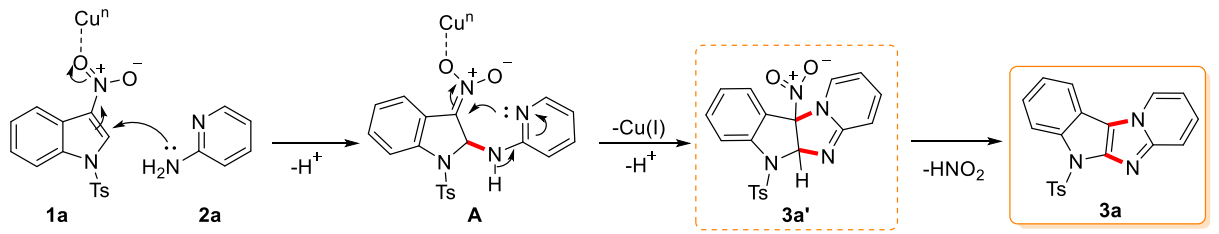


Figure 1. Normalized (a) absorption and (b) emission spectra of indole-fused imidazo[1,2-*a*]pyridines; normalized (c) absorption and (d) emission spectra of indolo-imidazo[1,2-*a*]quinolines in $CHCl_3$ [conc. = 1×10^{-5} M].

Table 4. Absorption Maximum, Extinction Coefficient (ε), and Emission Maximum in $CHCl_3$ (1×10^{-5} M)

compound	λ_{abs} (nm)	$\varepsilon \times 10^5$ (M^{-1} cm^{-1})	λ_{em} (nm)
3a	311, 324	0.13, 0.14	400
3f	325	0.30	421
3n	327	0.37	392
3p	325, 345	0.08, 0.08	408
3q	324, 345	0.06, 0.05	402
5a	342, 357	0.18, 0.19	419
5d	342, 356, 375	0.06, 0.07, 0.04	414
5f	348, 367, 388	0.04, 0.04, 0.03	432
5g	342, 357, 376	0.07, 0.08, 0.05	420
5h	352, 369, 386	0.11, 0.12, 0.11	433

Scheme 5. Mechanism for the Synthesis of Pyrido-imidazo[4,5-*b*]indoles



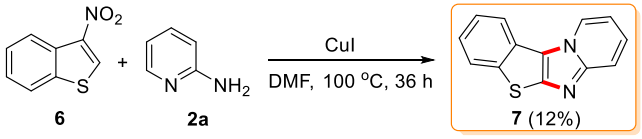
https://doi.org/10.1021/acs.joc.3c00849
J. Org. Chem. 2023, 88, 10027−10039

Table 5. Fluorescence Quantum Yield (Φ_f) in $CHCl_3$ (1×10^{-5} M)

3a Φ_f (%)	3q Φ_f (%)	5a Φ_f (%)	5h Φ_f (%)
2.15	1.63	10.59	26.89

Finally, we wanted to extend this annulation to electrophilic benzothiophene, and when 3-nitrobenzothiophene **6** was treated with 2-aminopyridine **2a** under the optimized conditions, the expected annulated product benzothiophene-fused imidazo[1,2-*a*]pyridine **7** was obtained in 12% yield (Scheme 6). From this reaction, we could isolate both the unreacted starting materials, which warrants further optimization and this will be done in due course.

Scheme 6. Synthesis of Benzothiophene-Fused Imidazo[1,2-*a*]pyridine via the Cu-Catalyzed Annulation of 3-Nitrobenzothiophene with 2-Aminopyridine



CONCLUSIONS

To conclude, we have successfully developed a Cu-catalyzed methodology for the synthesis of heteroacenes. By the annulation of electrophilic indole with 2-aminopyridine, we could generate indole-fused imidazo[1,2-*a*]pyridine, an interesting seldom-explored tetracene. We could also synthesize pentacene from electrophilic indole by performing annulation with 2-aminoquinoline. The present annulation was found to be general as a range of indole-fused imidazo[1,2-*a*]pyridines and indolo-imidazo[1,2-*a*]quinolines could be synthesized in moderate to good yields. We have proposed a mechanism that involves a Cu-catalyzed Michael addition and ring-closing to furnish a non-aromatic intermediate, which was isolated. The basic photophysical properties of representative examples of the synthesized heteroacenes were evaluated in order to assess their suitability in material applications. Finally, we could also extend the Cu-catalyzed annulation for the synthesis of benzothiophene-fused imidazo[1,2-*a*]pyridine. The application of these heteroacenes as components of dyes for DSCs is currently progressing in our lab.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were conducted in oven-dried glassware. Solvents used for the experiments were distilled and degassed with argon. All other reagents were purchased from local suppliers. All reactions were monitored by TLC (Silica gel 60 F254, 0.25 mm, Merck); visualization was effected with UV and/or by staining with Enholm yellow solution. Gravity column chromatography was performed using 100−200 mesh silica gel and mixtures of hexane-ethyl acetate were used for elution. Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Fourier-transform infrared spectrometer. Nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C{^{1}H} NMR). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.25, singlet). Multiplicities were given as follows: s (singlet); d (doublet); t (triplet); q (quartet); dd (double doublet); and m (multiplet). Coupling constants are reported as *J* values in Hz. Carbon nuclear magnetic resonance spectra (^{13}C{^{1}H} NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.03, triplet). Mass spectra were recorded under ESI/HRMS at 60,000 resolution using a Thermo Scientific Exactive mass spectrometer. Absorption spectra were measured using a Shimadzu UV−visible 3101 PC NIR spectrophotometer using a quartz cell with a 1 cm path length. Fluorescence spectra were recorded using a SPEX-Fluorolog F112X spectrofluorometer equipped with a 450 W xenon arc lamp. The spectra were corrected using the program installed by the manufacturer. The fluorescence quantum yields in the solution state were determined relative to a standard compound, quinine sulfate (0.1 M H_2SO_4; ϕ_F = 0.546), using optically matching solutions. The diffraction data of single crystals were collected on a Bruker Apex-II diffractometer using graphite monochromated Mo Kα radiation. The data were processed with the SMART software suite. The structure solution was carried out by direct methods, and the refinements were performed by full-matrix least-squares on F2 using the SHELXTL suite of programs. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments.

All chemicals were purchased from TCI Chemicals, Sigma-Aldrich, or Spectrochem.

Procedure for the Synthesis of Electrophilic Benzannulated Heterocycles. 3-Nitroindoles (**1a−1n**) and 3-nitrobenzothiophene (**6a**) were prepared by following a literature report.[22]

Preformed acetyl nitrate was generated by the dropwise addition of neat yellow 90% HNO_3 (30.0 mmol, 1.35 mL) to cooled (0 °C) acetic anhydride (20 mL) followed by standing at r.t. for 10 min and was used immediately. To a stirred solution of indole 3 (10.0 mmol) in acetic anhydride (50 mL) at −70 °C was added a solution of the preformed acetyl nitrate dropwise via an addition funnel over 30 min. The mixture was kept at this temperature until the reaction was found to be complete by TLC. The mixture was then poured onto ice (50 g) and stirred for 1 h with external cooling. If a precipitate formed, it was collected by suction filtration. The aqueous solution was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), dried (Na_2SO_4), and concentrated in vacuo to give a crude solid. The crude was then purified by column chromatography (ethyl acetate/hexane) to give the desired 3-nitroindole (**1a−1n**) and 3-nitrobenzothiophene (**6a**).

*3-Nitro-1-tosyl-1H-indole (**1a**).*[22] Column chromatography (5% ethyl acetate/hexane) gave **1a** as a white solid (928 mg, 80%). Analytical data of **1a**: mp 135−136 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.59 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.49−7.48 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 146.8, 133.8, 133.6, 130.5, 127.9, 127.5, 126.8, 125.9, 121.8, 121.3, 113.6, 21.8 ppm.

*5-Bromo-3-nitro-1-tosyl-1H-indole (**1b**).*[22] Column chromatography (5% ethyl acetate/hexane) gave **1b** as a white solid (896 mg, 80%). Analytical data of **1b**: mp 230−232 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.46 (s, 1H), 8.32 (s, 1H), 7.80 (t, *J* = 9.0 Hz, 3H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H) 2.34 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 147.1, 133.5, 132.2, 130.7, 130.3, 130.0, 128.6, 127.5, 126.9, 124.0, 123.2, 119.9, 115.0, 21.8 ppm. HRMS (ESI-Orbitrap) *m*/*z*: $(M + Na)^+$ calcd for $C_{15}H_{11}BrN_2NaO_4S$, 416.9515; found, 416.9530.

*5-Fluoro-3-nitro-1-tosyl-1H-indole (**1c**).* Column chromatography (5% ethyl acetate/hexane) gave **1c** as a white solid (808 mg, 70%). Analytical data of **1c**: mp 199−201 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.60 (s, 1H), 8.00−7.97 (m, 1H), 7.93−7.91 (m, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.24−7.20 (m, 1H), 2.43 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.0, 160.0, 147.1, 133.6, 130.6, 129.9, 129.1, 127.5, 122.9 (d, *J* = 42.77 Hz), 115.4, 115.2 (d, *J* = 29.14 Hz), 115.0, 107.3 (d, *J* = 100.11 Hz), 21.8 ppm.

*5-Chloro-3-nitro-1-tosyl-1H-indole (**1d**).*[22] Column chromatography (5% ethyl acetate/hexane) gave **1d** as a white solid (573 mg, 50%). Analytical data of **1d**: mp 198−200 °C. ^{1}H NMR (500 MHz,

https://doi.org/10.1021/acs.joc.3c00849
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$CDCl_3$, TMS): δ 8.49 (s, 1H), 8.17 (s, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 2.34 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 147.1, 133.6, 132.3, 131.8, 130.7, 130.3, 128.8, 127.5, 127.3, 122.8, 121.0, 114.8, 21.8 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{15}H_{11}ClN_2NaO_4S$, 373.0020; found 373.0035.

*6-Chloro-3-nitro-1-tosyl-1H-indole (**1e**).*[22] Column chromatography (5% ethyl acetate/hexane) gave **1e** as a white solid (745 mg, 65%). Analytical data of **1e**: mp 190−192 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.45 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.96 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 147.2, 133.8, 133.6, 133.1, 130.7, 128.1, 127.5, 126.7, 122.2, 120.3, 113.8, 21.8 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{15}H_{11}ClN_2NaO_4S$, 373.0020; found, 373.0033.

*6-Fluoro-3-nitro-1-tosyl-1H-indole (**1f**).* Column chromatography (5% ethyl acetate/hexane) gave **1f** as a white solid (736 mg, 64%). Analytical data of **1f**: mp 196−198 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.55 (s, 1H), 8.23−8.20 (m, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.23 (t, J = 8.5 Hz, 1H), 2.44 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 162.7, 160.7, 147.1, 133.6, 130.7, 127.99, 127.96, 127.5, 122.7, 122.6, 114.8, 114.6, 101.2, 101.0, 21.8 ppm.

*4-Bromo-3-nitro-1-tosyl-1H-indole (**1g**).* Column chromatography (5% ethyl acetate/hexane) gave **1g** as a white solid (672 mg, 60%). Analytical data of **1g**: mp 188−190 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.42 (s, 1H), 7.94 (t, J = 8.5 Hz, 1H), 7.78 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 2.34 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 147.0, 134.7, 133.6, 131.1, 130.6, 130.4, 128.4, 127.5, 127.3, 120.7, 113.6, 112.8, 21.9 ppm.

*5-Cyano-3-nitro-1-tosyl-1H-indole (**1i**).*[22] Column chromatography (5% ethyl acetate/hexane) gave **1i** as a white solid (783 mg, 68%). Analytical data of **1i**: mp 220−222 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.58 (s, 1H), 8.54 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 7.5 Hz, 2H), 7.65 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 147.6, 134.9, 133.3, 130.9, 129.61, 129.55, 127.6, 126.4, 121.9, 118.2, 114.8, 110.0, 21.8 ppm.

*tert-Butyl 3-Nitro-1H-indole-1-carboxylate (**1j**).*[22] Column chromatography (5% ethyl acetate/hexane) gave **1j** as a yellow solid (600 mg, 50%). Analytical data of **1j**: mp 136−138 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.48 (s, 1H), 8.21−8.19 (m, 1H), 8.17−8.16 (m, 1H), 7.40−7.38 (m, 2H), 1.64 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 148.2, 127.9, 126.7, 125.5, 121.6, 120.8, 115.5, 86.7, 28.0 ppm.

*3-Nitro-1-(phenylsulfonyl)-1H-indole (**1k**).*[22] Column chromatography (10% ethyl acetate/hexane) gave **1k** as a white solid (587 mg, 50%). Analytical data of **1k**: mp 139−141 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.60 (s, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.05−8.02 (m, 3H), 7.69 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 7.5 Hz, 2H), 7.50−7.49 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.9, 135.2, 133.6, 129.9, 127.8, 127.4, 126.9, 126.0, 121.8, 121.3, 113.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{14}H_{10}N_2NaO_4S$, 325.0253; found, 325.0269.

*1-(Mesitylsulfonyl)-3-nitro-1H-indole (**1l**).* Column chromatography (5% ethyl acetate/hexane) gave **1l** as a white solid (862 mg, 75%). Analytical data of **1l**: mp 210−212 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.49 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.34−7.25 (m, 3H), 2.49 (s, 6H), 2.24 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 145.8, 140.7, 133.6, 133.0, 128.3, 126.5, 125.6, 121.4, 121.3, 112.8, 22.8, 21.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{17}H_{16}N_2NaO_4S$, 367.0723; found, 367.0741.

*1-((4-Methoxyphenyl)sulfonyl)-3-nitro-1H-indole (**1m**).* Column chromatography (10% ethyl acetate/hexane) gave **1m** as a white solid (810 mg, 70%). Analytical data of **1m**: mp 205−207 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.59 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.48−7.47 (m, 2H), 7.00 (d, J = 8.5 Hz, 2H), 3.86 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 164.9, 133.5, 129.9, 127.90, 127.87, 126.7, 125.8, 121.8, 121.2, 115.1, 113.6, 55.9 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{15}H_{12}N_2NaO_5S$, 355.0359; found, 355.0373.

*3-Nitro-1-((4-nitrophenyl)sulfonyl)-1H-indole (**1n**).* Column chromatography (10% ethyl acetate/hexane) gave **1n** as a white solid (459 mg, 40%). Analytical data of **1n**: mp 218−220 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.35 (d, J = 8.5 Hz, 2H), 8.20 (d, J = 9.0 Hz, 2H), 8.12 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.38 (t, J = 7.5 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 144.0, 132.7, 130.2, 128.9, 126.0, 125.8, 125.5, 125.0, 124.5, 124.4, 115.8, 114.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{14}H_9N_3NaO_6S$, 370.0104; found, 370.0111.

*3-Nitro-benzothiophene (**6a**).* Column chromatography (hexane) gave **6a** as a yellow solid (465 mg, 35%). Analytical data of **6a**: mp 130−132 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.62 (s, 1H), 8.55 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 142.7, 138.7, 132.7, 130.0, 127.1, 126.4, 124.0, 123.0 ppm.

Procedure for the Reaction of 3-Nitro-N-tosyl Indole and 2-Aminopyridine. A mixture of 3-nitro-*N*-tosyl indole (1.0 equiv), 2-aminopyridine (1.2 equiv), and copper iodide (10 mol %) was weighed into a dry reaction tube. Dry DMF (0.15 mmol) was added, and the mixture was allowed to stir at 100 °C in an oil bath for 36 h. After completion of the reaction as indicated by the TLC, water was added and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products. The copies of ^1H NMR and ^{13}C NMR spectra of all the examples are included in the Supporting Information (S3−S19).

*Synthesis and Characterization of Indole-Fused Imidazo[1,2-a]pyridines. 6-Tosyl-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3a**).* The reaction was performed according to the general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-aminopyridine **2a** (36 mg, 0.38 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3a** as a white solid in a 70% yield (81 mg). Analytical data of **3a**: mp 228−230 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.30 (d, J = 6.5 Hz, 1H), 8.26 (d, J = 7.5 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 9.0 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.30−7.25 (m, 3H), 7.06 (d, J = 8.0 Hz, 2H), 6.95 (t, J = 6.5 Hz, 1H), 2.20 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 148.8, 148.0, 144.9, 138.0, 135.2, 129.7, 127.0, 124.8, 124.6, 124.1, 123.7, 118.4, 118.2, 116.4, 115.6, 112.7, 21.6 ppm. IR (neat) ν_{max}: 2929, 1595, 1526, 1430, 1405, 1374, 1245, 1172, 1121, 1088, 1023, 933, 816, 738, 677, 568, 540, 421 cm^{-1}. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{20}H_{16}N_3O_2S$, 362.0957; found, 362.0969.

*9-Bromo-6-tosyl-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3b**).* The reaction was performed according to the general procedure with 5-bromo-3-nitro-*N*-tosyl indole **1b** (100 mg, 0.25 mmol), 2-aminopyridine **2a** (28 mg, 0.3 mmol), and copper iodide (5 mg, 0.025 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3b** as a white solid in a 55% yield (61 mg). Analytical data of **3b**: mp 203−205 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.27 (d, J = 6.5 Hz, 1H), 8.12 (d, J = 9 Hz, 1H), 7.85−7.80 (m, 3H), 7.71 (s, 1H), 7.37 (d, J = 8 Hz, 1H), 7.31 (t, J = 8 Hz, 1H), 7.08 (d, J = 8 Hz, 2H), 6.97 (t, J = 6.5 Hz, 1H), 2.21 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 148.5, 145.2, 136.6, 134.9, 129.8, 127.1, 126.3, 125.4, 124.9, 119.6, 119.1, 118.5, 117.5, 116.9, 113.0, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{20}H_{15}BrN_3O_2S$, 440.0063; found, 440.0067.

*9-Fluoro-6-tosyl-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3c**).* The reaction was performed according to the general procedure with 5-fluoro-3-nitro-*N*-tosyl indole **1c** (100 mg, 0.30 mmol), 2-aminopyridine **2a** (34 mg, 0.36 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3c** as a white solid in a 45%

https://doi.org/10.1021/acs.joc.3c00849
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yield (51 mg). Analytical data of **3c**: mp 235−237 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.24 (d, J = 6.5 Hz, 1H), 8.20−8.17 (m, 1H), 7.84−7.79 (m, 3H), 7.29 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 7.00−6.96 (m, 2H), 2.20 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.0, 149.8, 148.4, 145.1, 134.9, 134.0, 129.7, 127.0, 125.3, 124.9, 118.4, 116.65, 116.58, 113.0, (d, J = 24.5 Hz), 103.0 (d, J = 26.0 Hz), 21.6 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −117.6 (s) ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{20}H_{15}FN_3O_2S$, 380.0864; found, 380. 0860.

*9-Chloro-6-tosyl-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3d**).* The reaction was performed according to the general procedure with 5-chloro-3-nitro-*N*-tosyl indole **1d** (100 mg, 0.28 mmol), 2-amino-pyridine **2a** (32 mg, 0.34 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3d** as a brown solid in a 41% yield (46 mg). Analytical data of **3d**: mp 260−262 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.26 (d, J = 6.5 Hz, 1H), 8.16 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 1H), 7.54 (s, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 6.97 (t, J = 6.5 Hz, 1H), 2.21 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.4, 145.3, 136.2, 134.8, 130.0, 129.8, 127.0, 125.5, 125.0, 123.6, 119.2, 118.3, 116.5, 116.2, 113.1, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{20}H_{15}ClN_3O_2S$, 396.0568; found, 396.0570.

*8-Chloro-6-tosyl-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3e**).* The reaction was performed according to the general procedure with 6-chloro-3-nitro-*N*-tosyl indole **1e** (100 mg, 0.28 mmol), 2-amino-pyridine **2a** (32 mg, 0.34 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3e** as a white solid in a 40% yield (44 mg). Analytical data of **3e**: mp 238−240 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.24 (m, 2H), 7.87 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.28−7.25 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.95 (t, J = 6.5 Hz, 1H), 2.21 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.9, 148.1, 145.3, 138.1, 135.0, 129.8, 129.3, 127.1, 125.0, 124.8, 124.4, 118.4, 116.8, 116.5, 115.8, 113.0, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{20}H_{15}ClN_3O_2S$, 396.0568; found, 396.0581.

*8-Fluoro-6-tosyl-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3f**).* The reaction was performed according to the general procedure with 6-fluoro-3-nitro-*N*-tosyl indole **1f** (100 mg, 0.30 mmol), 2-aminopyridine **2a** (34 mg, 0.36 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C stirred for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3f** as a white solid in a 43% yield (49 mg). Analytical data of **3f**: mp 244−246 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.23 (d, J = 6.5 Hz, 1H), 7.99 (d, J = 10.5 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 1H), 7.48−7.46 (m, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H), 7.03 (t, J = 8.5 Hz, 1H), 6.94 (t, J = 6.5 Hz, 1H), 2.21 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.8 (d, J = 240.4 Hz), 148.8, 147.6, 145.2, 138.3, 138.2, 135.0, 129.8, 127.1, 124.6, 124.6, 118.3, 116.8, 116.7, 114.6, 112.8, 112.1, 111.7 (d, J = 23.8 Hz), 103.8 (d, J = 29.2 Hz), 29.7 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −115.8 (s) ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{20}H_{15}FN_3O_2S$, 380.0864; found, 380.0864.

*10-Bromo-6-tosyl-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3g**).* The reaction was performed according to the general procedure with 4-bromo-3-nitro-*N*-tosyl indole **1g** (100 mg, 0.25 mmol), 2-amino-pyridine **2a** (28 mg, 0.30 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3g** as a white solid in a 45% yield (50 mg). Analytical data of **3g**: mp 228−230 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.58 (d, J = 6.5 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.91 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.23−7.18 (m, 3H), 6.99 (t, J = 6.5 Hz, 1H), 2.31 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.2, 149.1, 138.6, 134.9, 129.8, 128.1, 127.9, 127.1, 125.6, 124.4, 120.7, 118.2, 114.2, 112.4, 111.8, 109.8, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{20}H_{14}BrN_3NaO_2S$, 461.9882; found, 461.9905.

*6-(Phenylsulfonyl)-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3i**).* The reaction was performed according to the general procedure with 3-nitro-1-(phenylsulfonyl)-1*H*-indole **1k** (100 mg, 0.33 mmol), 2-aminopyridine **2a** (37 mg, 0.39 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3i** as a white solid in a 50% yield (61 mg). Analytical data of **3i**: mp 170−172 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.28 (d, J = 7.0 Hz, 1H), 8.24 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.31−7.24 (m, 5H), 6.94 (t, J = 7.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.6, 148.0, 138.1, 137.9, 133.8, 129.1, 127.0, 124.84, 124.75, 124.2, 123.8, 118.3, 118.2, 116.4, 115.5, 112.8 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{19}H_{14}N_3O_2S$, 348.0801; found, 348.08087.

*6-(Mesitylsulfonyl)-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3j**).* The reaction was performed according to the general procedure with 1-(mesitylsulfonyl)-3-nitro-1*H*-indole **1l** (100 mg, 0.29 mmol), 2-aminopyridine **2a** (33 mg, 0.35 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3j** as a white solid in a 50% yield (57 mg). Analytical data of **3j**: mp 201−203 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): 8.32 (d, J = 6.5 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.21−7.14 (m, 2H), 6.91 (t, J = 6.5 Hz, 1H), 6.86 (s, 2H), 2.58 (s, 6H), 2.18 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.4, 147.9, 143.8, 140.8, 138.1, 133.7, 132.2, 124.8, 124.3, 123.3, 123.2, 118.2, 117.1, 116.4, 114.8, 112.5, 111.4, 22.9, 21.1 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{22}H_{20}N_3O_2S$, 390.1271; found, 390.1295.

*6-((4-Methoxyphenyl)sulfonyl)-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3k**).* The reaction was performed according to the general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1*H*-indole **1m** (100 mg, 0.30 mmol), 2-amino-pyridine **2a** (34 mg, 0.36 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3k** as a white solid in a 47% yield (53 mg). Analytical data of **3k**: mp 262−264 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.30 (d, J = 6.5 Hz, 1H), 8.25 (d, J = 7.5 Hz, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 9.5 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.31−7.25 (m, 3H), 6.95 (t, J = 6.5 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 3.65 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 183.8, 148.6, 147.9, 138.0, 129.7, 129.3, 124.8, 124.7, 124.1, 123.7, 118.3, 118.2, 116.4, 115.6, 114.2, 112.8, 55.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{20}H_{16}N_3O_3S$, 378.0907; found, 378.0921.

*6-((4-Nitrophenyl)sulfonyl)-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]-indole (**3l**).* The reaction was performed according to the general procedure with 3-nitro-1-((4-nitrophenyl)sulfonyl)-1*H*-indole **1n** (100 mg, 0.29 mmol), 2-amino-pyridine **2a** (33 mg, 0.35 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3l** as a white solid in a 55% yield (63 mg). Analytical data of **3l**: mp 210−212 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.31 (d, J = 6.5 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.17 (d, J = 9.0 Hz, 2H), 8.10 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.36−7.30 (m, 3H), 6.99 (t, J = 6.5 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 150.8, 148.1, 143.0, 128.4, 125.3, 125.0, 124.3, 124.2, 118.4, 116.7, 115.6, 113.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{19}H_{13}N_4O_4S$, 393.0652; found, 393.0653.

*4-Methyl-6-tosyl-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3m**).* The reaction was performed according to the general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-amino-3-methyl-pyridine **2b** (41 mg, 0.38 mmol), and copper iodide (6 mg, 0.03

https://doi.org/10.1021/acs.joc.3c00849
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mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3m** as a white solid in a 35% yield (42 mg). Analytical data of **3m**: mp 229−231 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.25 (d, J = 7.5 Hz, 1H), 8.17 (d, J = 6.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 7.0 Hz, 1H), 7.29−7.25 (m, 2H), 7.08−7.05 (m, 3H), 6.86 (t, J = 6.5 Hz, 1H), 2.70 (s, 3H), 2.21 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.3, 144.8, 138.1, 135.1, 129.6, 128.4, 127.1, 124.1, 123.9, 123.6, 122.6, 118.5, 116.2, 115.7, 112.6, 21.5, 17.6 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{21}H_{18}N_3O_2S$, 376.1114; found, 376.1148.

*1-Methyl-6-tosyl-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3n**).* The reaction was performed according to the general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-amino-6-methylpyridine **2c** (41 mg, 0.38 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3n** as a white solid in a 32% yield (38 mg). Analytical data of **3n**: mp 215−217 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.27 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 7.0 Hz, 1H), 7.27−7.24 (m, 3H), 7.08 (d, J = 7.5 Hz, 2H), 6.69 (d, J = 6.5 Hz, 1H), 3.09 (s, 3H), 2.21 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.3, 144.9, 137.9, 135.2, 134.8, 129.6, 127.1, 125.7, 124.0, 123.5, 118.9, 117.7, 115.7, 115.6, 112.1, 22.3, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{21}H_{18}N_3O_2S$, 376.1114; found, 376.1121.

*1-Ethyl-6-tosyl-6H-pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3o**).* The reaction was performed according to the general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-amino-6-ethylpyridine **2d** (46 mg, 0.38 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3o** as a white solid in a 35% yield (43 mg). Analytical data of **3o**: mp 220−222 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.30−8.28 (m, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.70−7.69 (m, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.25−7.23 (m, 3H), 7.06 (d, J = 8.5 Hz, 2H), 6.67 (d, J = 7.0 Hz, 1H), 3.38 (q, J = 7.5 Hz, 2H), 2.20 (s, 3H), 1.43 (t, J = 7.5 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.4, 144.9, 140.3, 137.9, 135.2, 129.6, 127.1, 125.8, 124.1, 123.4, 118.9, 117.8, 115.8, 115.5, 112.4, 109.8, 27.9, 21.6, 12.5 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{22}H_{20}N_3O_2S$, 390.1271; found, 390.1279.

*6H-Pyrido[1′,2′:1,2]imidazo[4,5-b]indole (**3p**).* The reaction was performed according to the general procedure with 3-nitro-*N*-Boc indole **1j** (100 mg, 0.38 mmol.), 2-aminopyridine **2a** (42 mg, 0.45 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford the desired product **3p** as a white solid in a 35% yield (28 mg). Analytical data of **3p**: mp 238−240 °C. ^{1}H NMR (500 MHz, acetone-d_6, TMS): δ 10.32 (s, 1H), 8.77 (d, J = 6.5 Hz, 1H), 7.89 (d, J = 7.0 Hz, 1H), 7.51 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.12−7.07 (m, 2H), 6.93 (t, J = 6.5 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, acetone-d_6): δ 139.3, 125.6, 123.4, 121.4, 119.4, 116.5, 116.3, 115.0, 112.0, 110.9 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{13}H_{10}N_3$, 208.0869; found, 208.0880.

*Procedure for the Scale-Up of **3a**.* A mixture of 3-nitro-*N*-tosyl indole **1a** (1.0 g, 3.16 mmol), 2-aminopyridine **2a** (356 mg, 3.79 mmol), and copper iodide (60 mg, 0.316 mmol) was weighed into a dry reaction tube. Dry DMF (0.15 mmol) was added, and the mixture was allowed to stir at 100 °C in an oil bath for 36 h. After completion of the reaction as indicated by TLC, water was added and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was then purified by silica gel column chromatography (30% ethyl acetate in hexane) to afford the desired product **3a** (695 mg, 61%).

*Procedure for the Deprotection of **3a**.* A solution of NaOH (2.0 M, 2.0 mL) in MeOH was added to a stirring solution of **3a** (100 mg, 0.28 mmol) in dry THF, and the resulting mixture was refluxed in an oil bath under nitrogen overnight. Upon completion, the reaction mixture was concentrated under reduced pressure, water was added, and the mixture was extracted with EtOAc. The organic layer was washed successively with brine, the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the residue on activated neutral alumina column chromatography (30% ethyl acetate in hexane) yielded the deprotected compound **3p** as a white solid (50 mg, 85%)

*Synthesis and Characterization of 6-Methyl-6H-pyrido[1′,2′:1,2]-imidazo[4,5-b]indole (**3q**).* To a stirred solution of **3p** (100 mg, 0.48 mmol) in dry THF, NaH (23 mg, 0.96 mmol) was added portion-wise under a nitrogen atmosphere at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 30 min. The reaction mixture was cooled again to 0 °C, and methyl iodide (135 mg, 0.96 mmol) was added dropwise and stirred at room temperature for 3 h. After completion of the reaction as indicated by TLC, water was added and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was then purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **3q** as a white solid in 80% yield (85 mg). Analytical data of **3q**: mp 200−210 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.44 (d, J = 6.5 Hz, 1H), 7.74 (t, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.31−7.26 (m, 2H), 7.22 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 6.5 Hz, 1H), 3.92 (s, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.2, 146.5, 139.9, 125.1, 124.7, 121.9, 119.9, 116.4, 116.1, 114.3, 112.4, 109.9, 109.3, 29.7 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{14}H_{12}N_3$, 222.1026; found, 222.1033.

Control Experiments. *Synthesis and Characterization of 10b-Nitro-6-tosyl-6,10b-dihydro-5aH-pyrido[1′,2′:1,2]imidazo[4,5-b]-indole (**3a′**).* A mixture of 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-amino-pyridine **2a** (36 mg, 0.38 mmol), and copper iodide (6 mg, 0.03 mmol) was weighed into a dry reaction tube. Dry DMF (0.15 mmol) was added, and the mixture was allowed to stir at room temperature for 24 h. After completion of the reaction as indicated by TLC, water was added and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by silica gel chromatography (20% ethyl acetate in hexane) to afford the desired product **3a′** as a brown solid in a 60% yield (79 mg). Analytical data of **3a′**: mp 140−142 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.74 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.5 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.04 (t, J = 7.5 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 6.68 (s, 1H), 6.54 (d, J = 9.0 Hz, 1H), 5.89 (t, J = 6.5 Hz, 1H), 2.31 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.0, 145.0, 144.6, 138.3, 134.2, 133.2, 130.5, 129.9, 127.8, 124.6, 123.9, 123.0, 116.5, 116.0, 106.7, 106.2, 93.5, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{20}H_{17}N_4O_4S$, 409.0965; found, 409.0979.

*Procedure for the Reaction of **1a** and **2a** in the Presence of BHT.* A mixture of 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-amino-pyridine **2a** (36 mg, 0.38 mmol), BHT (71 mg, 0.32 mmol), and copper iodide (6 mg, 0.03 mmol) was weighed into a dry reaction tube. Dry DMF (0.15 mmol) was added, and the mixture was allowed to stir at 100 °C in an oil bath. After 24 h, the reaction was stopped, water was added, and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by silica gel chromatography (30% ethyl acetate in hexane) to afford product **3a** as a white solid in a 35% yield (41 mg).

Procedure for the Reaction of 3-Nitro-N-tosyl Indole and 2-Aminoquinoline. A mixture of 3-nitro-*N*-tosyl indole (1.0 equiv), 2-aminoquinoline (1.2 equiv), and copper iodide (10 mol %) was weighed into a dry reaction tube. Anhydrous DMF (0.15 mmol) was added and allowed to stir at 100 °C in an oil bath for 36 h. After completion of the reaction as indicated by TLC, water was added and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was then purified by activated neutral

https://doi.org/10.1021/acs.joc.3c00849
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alumina column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products. The copies of ^{1}H NMR and ^{13}C NMR spectra of all the examples are included in the Supporting Information (S20−S27).

*Synthesis and Characterization of Indolo-imidazo[1,2-a]-quinolines. 8-Tosyl-8H-indolo[2′,3′:4,5]imidazo[1,2-a]quinoline (**5a**).* The reaction was performed according to the general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-aminoquinoline **4** (55 mg, 0.38 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **5a** as a white solid in a 65% yield (86 mg). Analytical data of **5a**: mp 248−250 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.32 (t, J = 7.0 Hz, 2H), 7.97 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 9.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.52 (d, J = 9.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.33−7.27 (m, 2H), 7.03 (d, J = 8.0 Hz, 2H), 2.15 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.1, 146.8, 145.0, 138.3, 135.0, 132.8, 129.7, 129.1, 128.5, 127.1, 127.0, 124.8, 124.1, 124.0, 123.6, 118.44, 118.37, 117.8, 116.8, 115.7, 114.7, 21.5 ppm. IR (neat) ν_{max}: 3051, 1595, 1539, 1483, 1436, 1413, 1369, 1300, 1215, 1178, 1132, 1090, 1026, 951, 812, 796, 671, 659, 614, 571, 538, 505, 432 cm^{-1}. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{24}H_{18}N_3O_2S$, 412.1114; found, 412.1129.

*11-Bromo-8-tosyl-8H-indolo[2′,3′:4,5]imidazo[1,2-a]quinoline (**5b**).* The reaction was performed according to the general procedure with 5-bromo-3-nitro-*N*-tosyl indole **1b** (100 mg, 0.25 mmol), 2-aminoquinoline **4** (43 mg, 0.30 mmol), and copper iodide (4 mg, 0.02 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **5b** as a white solid in a 50% yield (61 mg). Analytical data of **5b**: mp 282−284 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.32 (d, J = 8.5 Hz, 1H), 8.25 (d, J = 8.5 Hz, 1H), 8.15 (s, 1H), 7.85 (d, J = 7.5 Hz, 3H), 7.78−7.73 (m, 2H), 7.64 (d, J = 9.0 Hz, 1H), 7.50 (t, J = 7.0 Hz, 1H), 7.44 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H) 2.20 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 147.5, 145.3, 136.9, 134.8, 129.8, 129.4, 129.0, 127.7, 127.1, 126.6, 125.1, 123.7, 121.0, 120.0, 117.8, 117.5, 117.0, 116.7, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{24}H_{17}BrN_3O_2S$, 490.0219; found, 490.0235.

*11-Fluoro-8-tosyl-8H-indolo[2′,3′:4,5]imidazo[1,2-a]quinoline (**5c**).* The reaction was performed according to the general procedure with 5-fluoro-3-nitro-*N*-tosyl indole **1c** (100 mg, 0.30 mmol), 2-aminoquinoline **4** (52 mg, 0.36 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **5c** as a white solid in a 45% yield (58 mg). Analytical data of **5c**: mp 232−234 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.34−8.31 (m, 2H), 7.84 (d, J = 8.0 Hz, 3H), 7.74 (t, J = 8.5 Hz, 3H), 7.64 (d, J = 9.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.08−7.05 (m, 3H), 2.20 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.4, 147.4, 145.2, 134.8, 132.9, 129.7, 129.4, 128.9, 127.6, 127.1, 125.1, 124.1, 123.7, 119.4, 117.9, 116.8, 116.6, 111.1 (d, J = 24.0 Hz), 105.1 (d, J = 27.0 Hz), 21.6 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −117.0 (s) ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{24}H_{17}FN_3O_2S$, 430.1020; found, 430.1036.

*11-Chloro-8-tosyl-8H-indolo[2′,3′:4,5]imidazo[1,2-a]quinoline (**5d**).* The reaction was performed according to the general procedure with 5-chloro-3-nitro-*N*-tosyl-indole **1d** (100 mg, 0.29 mmol), 2-aminoquinoline **4** (50 mg, 0.34 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **5d** as a yellow solid in a 45% yield (58 mg). Analytical data of **5d**: mp 278−280 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.36 (d, J = 8.5 Hz, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.02 (s, 1H), 7.88−7.77 (m, 5H), 7.72−7.67 (m, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.09 (d, J = 7.5 Hz, 2H), 2.21 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 145.3, 136.5, 134.8, 132.9, 132.5, 129.8, 129.4, 129.0, 127.7, 127.1, 125.1, 123.8, 123.7, 119.6, 118.2, 117.8, 116.7, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{24}H_{17}ClN_3O_2S$, 446.0725; found, 446.0742.

*8-Tosyl-8H-indolo[2′,3′:4,5]imidazo[1,2-a]quinoline-11-carbonitrile (**5e**).* The reaction was performed according to the general procedure with 5-cyano-3-nitro-*N*-tosyl-indole **1i** (100 mg, 0.29 mmol), 2-aminoquinoline **4** (50 mg, 0.34 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **5e** as a white solid in a 48% yield (60 mg). Analytical data of **5e**: mp 220−222 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.48 (d, J = 8.5 Hz, 1H), 8.38 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.78 (d, J = 9.5 Hz, 1H), 7.71 (d, J = 9.5 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 2.23 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.4, 148.0, 145.8, 139.9, 134.8, 132.9, 130.0, 129.6, 129.3, 128.3, 127.2, 127.0, 125.4, 123.7, 122.2, 118.5, 117.8, 116.5, 116.1, 113.2, 107.4, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{25}H_{16}N_4NaO_2S$, 459.0886; found, 459.0899.

*8H-Indolo[2′,3′:4,5]imidazo[1,2-a]quinoline (**5f**).* The reaction was performed according to the general procedure with 3-nitro-*N*-Boc-indole **1j** (100 mg, 0.38 mmol), 2-aminoquinoline **4** (66 mg, 0.45 mmol), and copper iodide (8 mg, 0.04 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **5f** as a white solid in a 55% yield (54 mg). Analytical data of **5f**: mp 158−160 °C. ^{1}H NMR (500 MHz, dmso-d_6, TMS): δ 11.74 (s, 1H), 8.75 (d, J = 8.5 Hz, 1H), 8.40 (d, J = 6.5 Hz, 1H), 8.11 (d, J = 7.5 Hz, 1H), 7.99 (t, J = 7.0 Hz, 1H), 7.86 (d, J = 9.5 Hz, 1H), 7.71 (d, J = 9.5 Hz, 1H), 7.64−7.58 (m, 2H), 7.31−7.30 (m, 2H) ppm. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 150.2, 146.3, 139.7, 133.7, 132.9, 129.6, 126.3, 125.2, 124.6, 123.1, 122.1, 119.8, 118.5, 117.4, 113.5, 113.0, 111.1 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{17}H_{12}N_3$, 258.1026; found, 258.1037.

*8-(Phenylsulfonyl)-8H-indolo[2′,3′:4,5]imidazo[1,2-a]quinoline (**5g**).* The reaction was performed according to the general procedure with 3-nitro-1-(phenylsulfonyl)-1*H*-indole **1k** (100 mg, 0.35 mmol), 2-aminoquinoline **4** (60 mg, 0.42 mmol), and copper iodide (6 mg, 0.03 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by activated neutral alumina column chromatography (30% ethyl acetate in hexane) to afford the desired product **5g** as a white solid in a 60% yield (83 mg). Analytical data of **5g**: mp 190−192 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.50 (d, J = 8.5 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 7.5 Hz, 1H), 7.77−7.71 (m, 2H), 7.62 (d, J = 9.0 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.41−7.34 (m, 3H), 7.29 (t, J = 7.5 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.2, 147.0, 138.3, 138.0, 133.9, 129.2, 129.1, 128.6, 127.1, 127.0, 124.9, 124.2, 124.1, 123.7, 118.4, 117.9, 116.9, 115.8 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{23}H_{16}N_3O_2S$, 398.0958; found, 398.0970.

*Synthesis and Characterization of 8-Methyl-8H-indolo[2′,3′:4,5]-imidazo[1,2-a]quinoline (**5h**).* To a stirred solution of **5f** (100 mg, 0.39 mmol) in dry THF, NaH (19 mg, 0.78 mmol) was added portion-wise under a nitrogen atmosphere at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 30 min. The reaction mixture was cooled again to 0 °C, and methyl iodide (109 mg, 0.78 mmol) was added dropwise and stirred at room temperature for 3 h. After completion of the reaction as indicated by TLC, water was added and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was then purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **5h** as a white solid in an 82% yield (87 mg). Analytical data of **5h**: mp 200−220 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.70 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.0 Hz,

https://doi.org/10.1021/acs.joc.3c00849
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1H), 7.87 (d, J = 8.0 Hz, 1H), 7.79 (t, J = 7.5 Hz, 1H), 7.67 (d, J = 9.5 Hz, 1H), 7.63 (d, J = 9.5 Hz, 1H), 7.51−7.46 (m, 2H), 7.36−7.29 (m, 2H), 3.99 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 140.2, 129.0, 128.6, 124.4, 123.4, 122.0, 119.7, 118.3, 117.1, 110.1, 29.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{18}H_{14}N_3$, 272.1182; found, 272.1195.

*Synthesis and Characterization of Benzo[4′,5′]thieno[2′,3′:4,5]-imidazo[1,2-a]pyridine (**7**).* The reaction was performed according to the general procedure with 3-nitro-benzothiophene **6** (100 mg, 0.56 mmol), 2-aminopyridine **2** (63 mg, 0.67 mmol), and copper iodide (11 mg, 0.06 mmol) in DMF (0.15 mmol) at 100 °C for 36 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product as a white solid in a 12% yield (15 mg). Analytical data of **7**: mp 200−202 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.54 (d, J = 6.5 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 9.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.34−7.29 (m, 2H), 7.00 (t, J = 6.5 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 149.3, 139.6, 125.3, 125.13, 125.08, 124.74, 124.66, 123.8, 118.1, 117.4, 112.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{13}H_9N_2S$, 225.0481; found, 225.0489.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c00849.

NMR spectra of all newly synthesized compounds and crystallographic data for **3a** (PDF)

Accession Codes

CCDC 2237083 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.A.B. and S.P. thank the CSIR and UGC for the research fellowship. J.J. thanks the CSIR (HCP-029 & OLP-162539) and AICTE (GAP-161939) for financial assistance. The authors also thank Saumini Mathew and Viji S. of the CSIR-NIIST for recording NMR and mass spectra, respectively.

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Discovery of Oxygen Induced Chemoselectivity in Pd-Catalyzed C−H Functionalization: Cross-Dehydrogenative Coupling vs C−H Amination

Sheba Ann Babu, Sunil Varughese, Jomon Mathew,* and Jubi John*

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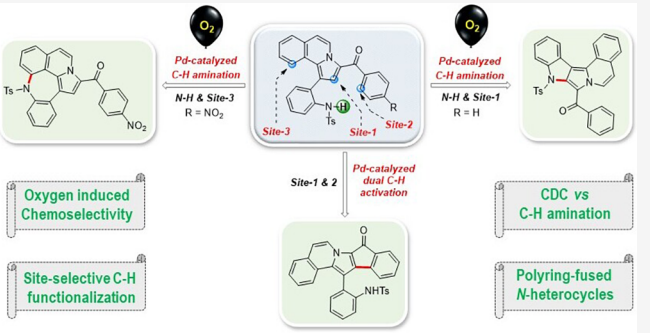
ABSTRACT: We have come across a substrate namely, 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline in which three different functionalizable C−H bonds were identified that could be judiciously transformed site selectively for the generation of complex polyring fused *N*-heterocycles. A Pd-catalyzed cross-dehydrogenative coupling of 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline afforded 8*H*-indeno-pyrrolo[2,1-*a*]isoquinolinone and an oxygen induced palladium catalyzed selective C−H amination in the same substrate provided a pentacene viz., 9*H*-indolo-pyrrolo[2,1-*a*]-isoquinoline. We also observed the formation of a multiring fused benzazepine scaffold by the site selective C−H amination in 5-(4-nitro benzoyl)-pyrrolo[2,1-*a*]isoquinoline.



INTRODUCTION

Organic synthesis has taken a huge stride with the advancements in the functionalization of unactivated C−H bonds directly to carbon−carbon or carbon−heteroatom bonds.[1] The initial reports on selective C−H functionalization relied on free radical transformations,[2] and this was followed by the development of metal complexes that could activate C−H bonds.[3] For the past two decades, organic chemists have taken up the challenge of designing substrates or environments that would enable selective functionalization of unactivated C−H bonds.[4] These developments have indeed shortened the way that retrosynthetic approaches are planned toward complex organic molecules thereby improving step and atom economy.

Cross-dehydrogenative coupling (CDC) or dual C−H activation is presently considered as an inevitable tool for the generation of carbon−carbon bonds both in intermolecular and intramolecular fashion.[5] This powerful methodology which does not require any preactivation of reaction centers has been utilized for the synthesis of carbocycles and heterocycles under both transition metal catalyzed and metal-free conditions.[6] Another equally important transformation is C−H amination which also is a heavily relied strategy for generating substituted amines or *N*-heterocycles.[7] The initial reports in this line came from the groups of Stahl and Buchwald wherein the former reported Pd-cataylzed oxidative amination of unactivated alkenes toward substituted amines[8] and the latter reported Pd-catalyzed intramolecular C−H amination toward carbazoles.[9]

Achieving high position selectivity in C−H functionalization among similar reactive sites is still a challenging task for chemists.[10] Site selective C−H functionalization is currently effected either by utilizing the stereoelectronic differences in reactive centers or by installing appropriate directing groups that can limit the reactivity to particular centers of interest.[11] In this article, we report our observations on site-selective C−H functionalization between three different reactive centers toward polyring fused *N*-heterocycles. In continuation of our interest in the chemistry of electrophilic benzannulated heterocycles,[12] we recently reported an unexpected observation of pyrrolo[2,1-*a*]isoquinoline **3a** formation from the reaction of electrophilic indoles and isoquinolinium methylides (Scheme 1).[13]

In the substrate 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline **3a** (Scheme 1), we identified two functionalizable C−H centers, at site-1 and site-2. Under Pd-catalyzed cross-dehydrogenative coupling conditions, we hypothesized that an intramolecular cyclization will happen between site-1 and site-2 affording 8*H*-indeno-pyrrolo[2,1-*a*]isoquinolinone moiety **4a**. In addition, by tuning the reaction conditions, we postulated that a C−H amination could be effected between N−H and site-1 for the synthesis of 9-tosyl-9*H*-indolo-pyrrolo[2,1-*a*]isoquinoline **5a**. These investigations resulted in unraveling an oxygen induced chemoselectivity which to the best of our knowledge is unknown thus far. Finally, during the investigations on the generality of C−H amination reaction, we came across an unprecedented

Received: March 25, 2023
Published: July 12, 2023

https://doi.org/10.1021/acs.joc.3c00651
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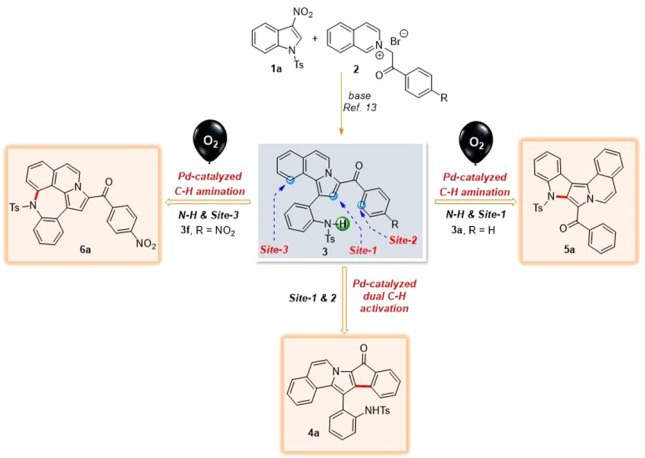
Scheme 1. Pd-Catalyzed Site Selective C−H Functionalization in 5-Benzoyl-pyrrolo[2,1-*a*]isoquinoline towards Polyring Fused *N*-Heterocycles

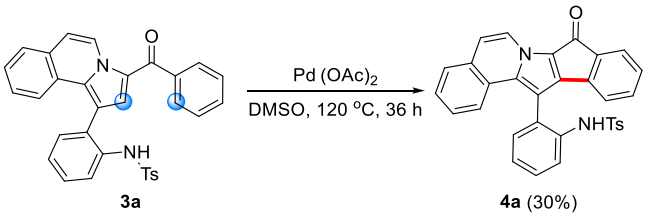


observation of formation of a polyring fused azepine **6a** by the C−H amination between N−H and site-3. In this article, we describe in detail our examinations on Pd-catalyzed cross-dehydrogenative coupling and C−H aminations toward polyring fused *N*-heterocycles.

RESULTS AND DISCUSSION

We initiated our investigations by synthesizing 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline **3a** from 3-nitro-*N*-tosyl indole **1a** and 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **2a** (Scheme 1).[13] By keeping **3a** as a substrate, we planned to examine the possibility of Pd-catalyzed cross-dehydrogenative coupling for activating C−H bonds at sites 1 and 2 as shown in Scheme 1. The test reaction was set up with **3a** in the presence of 10 mol % of $Pd(OAc)_2$ in DMSO at 120 °C for 36 h (Scheme 2).

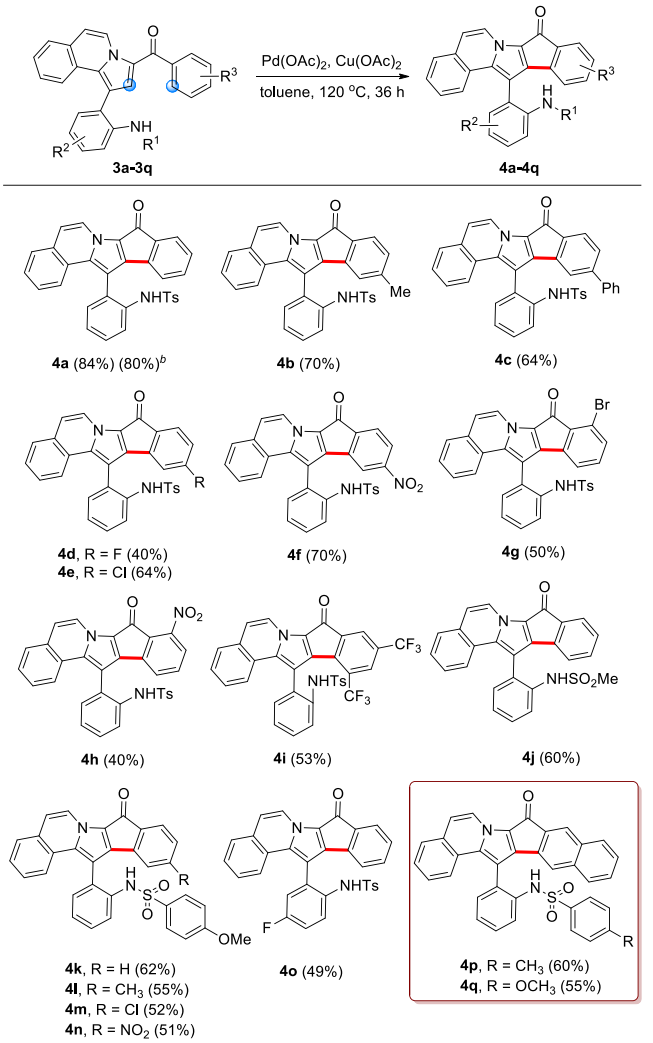
Scheme 2. Pd(II) Mediated Cross-Dehydrogenative Coupling of Pyrrolo[2,1-*a*]isoquinolines



As expected, we could isolate the product 8*H*-indenopyrrolo-[2,1-*a*]isoquinolin-8-one **4a** formed by dual C−H activation in 30% yield. The structure of **4a** was established with various spectroscopic methods and single crystal X-ray analysis.[14]

The optimization of Pd(II) mediated cross-dehydrogenative coupling toward functionalized 8*H*-indenopyrrolo[2,1-*a*]-isoquinolin-8-one was carried out with **3a** as the substrate.[14] Under the optimized conditions [$Pd(OAc)_2$ (20 mol %), $Cu(OAc)_2$ (1.0 equiv), toluene, 120 °C, 36 h] for the Pd-catalyzed cross-dehydrogenative coupling toward functionalized 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-one, we explored the scope of the reaction using different 5-benzoyl pyrrolo[2,1-*a*]isoquinolines, the results of which are summarized in Table 1. Different starting substrates **3** for this study were synthesized by following our methodology from a series of electrophilic indoles and isoquinolinium salts.[13]

Table 1. Generality of Pd-Catalyzed Cross-Dehydrogenative Coupling[a]



[a]Reaction conditions: **3** (1.0 equiv, 0.20 mmol), $Pd(OAc)_2$ (20 mol %), $Cu(OAc)_2$ (1.0 equiv), toluene (2.0 mL), 120 °C, 36 h; starting material was recovered in the cases where yields were moderate. [b]From 1.0 g of **3a**.

We initiated the studies (Table 1) by using 5-benzoyl pyrrolo[2,1-*a*]isoquinolines with substituents on the benzoyl moiety. In this line, we could introduce methyl (in **4b**) and phenyl (in **4c**) substituents on the indanone ring. Next, we were able to synthesize 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-ones **4d** and **4e** with halogen substitutions (F and Cl) on the indanone ring. The Pd-catalyzed cross-dehydrogenative coupling conditions also worked well with a NO_2-group on the benzoyl moiety thereby furnishing **4f** in 70% yield. By the synthesis of **4g**, **4h**, and **4i**, we could demonstrate that substituents can be introduced at any position of the indanone ring by starting with the appropriately functionalized 5-benzoyl pyrrolo[2,1-*a*]isoquinolines. We also tried reactions with substrates having different *N*-substituents such as $-SO_2Me$ and $-SO_2Ph$-4OMe, and all these afforded the corresponding products **4j** to **4n** in moderate to good yields. We could

https://doi.org/10.1021/acs.joc.3c00651
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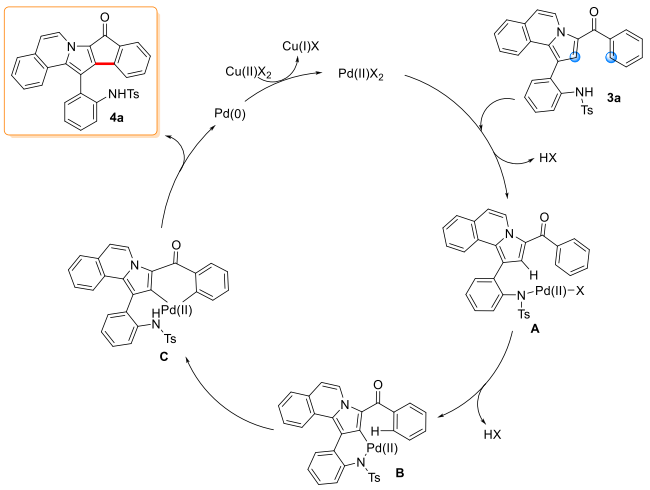
synthesize **4o** in 49% yield with a F-substituent on the aryl group attached to the pyrrole ring. Finally, the methodology could be extended for the synthesis of six-ring fused heteroacenes **4p** and **4q** by starting from suitably substituted 5-naphthoyl pyrrolo-[2,1-*a*]isoquinolines. The reaction of 1.0 g of **3a** afforded the product 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-one **4a** in 80% yield.

Based on our observations and by following reported literature, we propose a mechanism for the Pd-catalyzed cross-dehydrogenative coupling toward indenopyrrolo[2,1-*a*]-isoquinolinones (Scheme 3).[5,6,15] The first step of the catalytic

Scheme 3. Plausible Mechanism for the Synthesis of Indenopyrrolo[2,1-*a*]isoquinolinones [X = OAc]

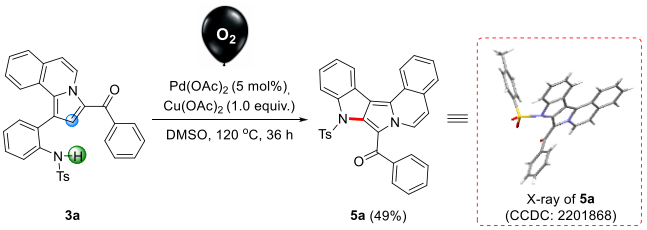


cycle will be the formation of the N−Pd bond as in intermediate **A** from **3a** and the Pd-catalyst.[7,8] Next, a selective activation of the C−H bond in pyrrole ring takes place to form a six-membered palladacycle **B**.[9] A Fujiwara−Moritani type process is then believed to occur in intermediate **B** via a C−H bond activation in the benzoyl moiety to furnish the new six-membered cyclic Pd(II) intermediate **C**.[15,17] Subsequently, the reductive elimination occurs in **C** affording the product **4a** and Pd(0). Finally, the Pd(II) species is regenerated by the oxidation with $Cu(OAc)_2$ to complete the catalytic cycle.

The metal-catalyzed intramolecular C−H amination provides a straightforward approach for the synthesis of *N*-containing heterocycles such as carbazoles, benzimidazoles, indazoles, indolines, etc.[18] In this line, we targeted the C−H amination between the N−H and site-1 of pyrrolo[2,1-*a*]isoquinolines (Scheme 1) toward the synthesis of indolo-pyrrolo[2,1-*a*]isoquinoline. During our optimization studies on Pd-catalyzed cross-dehydrogenative coupling with **3a**, we came across a combination of $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (1.0 equiv) under an O_2 atmosphere in DMSO. The reaction at 120 °C was allowed to continue for 36 h after which we could isolate indolo-pyrrolo[2,1-*a*]isoquinoline **5a** in 49% yield along with **4a** in minor amounts (Scheme 4). Interestingly, in the present observation, the presence of oxygen has changed the course of the reaction furnishing the C−H amination product in major quantity and such an oxygen induced chemoselective transformation is rare.

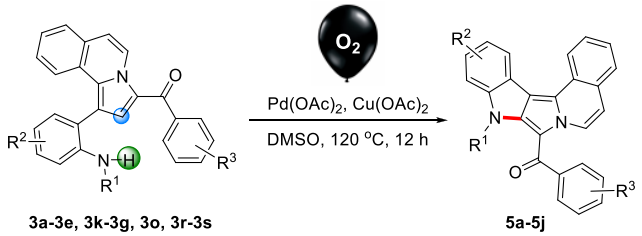
A systematic investigation was then carried out to find the best conditions for Pd-catalyzed site selective C−H amination with **3a** as the substrate.[14] With the optimized conditions in hand [$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (1.0 equiv), DMSO, O_2, 120

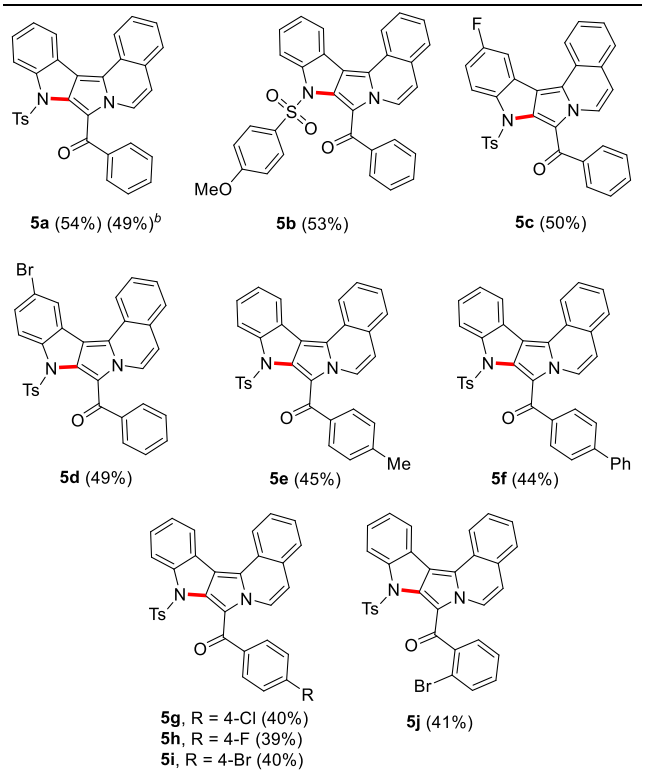
Scheme 4. Pd(II) Catalyzed Site-Selective C−H Activation towards Indolo[3′,2′:3,4]pyrrolo[2,1-*a*]isoquinoline



°C, 12 h], we explored the scope of the reaction using different pyrrolo[2,1-*a*]isoquinolines, the results of which are summarized in Table 2. First, we repeated the Pd-catalyzed C−H amination with **3a** from which the product **5a** was obtained in 54% yield. Then, we changed the substituent at the *N*-atom from Ts- to 4-OMe-C_6H_4-SO_2-, and from the reaction the corresponding indolo-pyrrolo[2,1-*a*]isoquinoline **5b** was iso-

Table 2. Pd-Catalyzed C−H Amination of Pyrrolo[2,1-*a*]isoquinolines towards Indolopyrrolo[2,1-*a*]isoquinolines[a]





[a]Reaction conditions: **3** (1.0 equiv., 100 mg), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (1.0 equiv), O_2 (1.0 atm), DMSO (0.1 M), 120 °C, 12 h, formation of indenopyrrolo[2,1-*a*]isoquinolinones **4** in trace amounts detected in all cases. [b]From 1.0 g of **3a**.

https://doi.org/10.1021/acs.joc.3c00651
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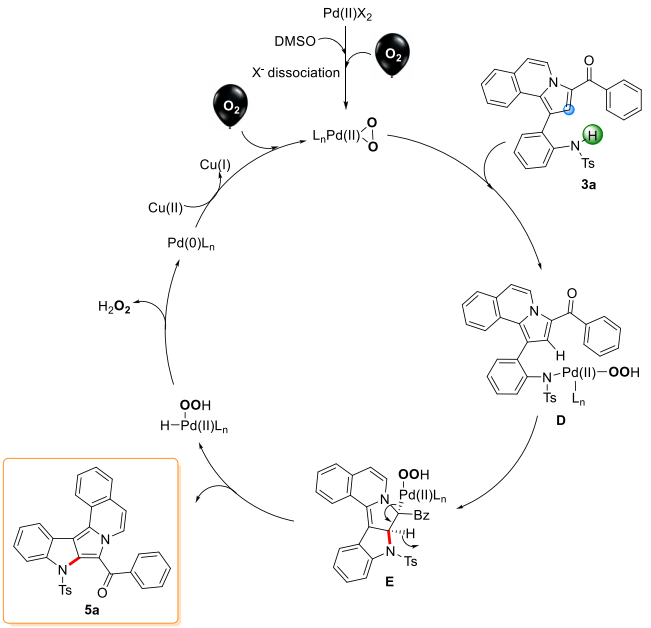
lated in 53% yield. We could synthesize indole fused pyrrolo[2,1-*a*]isoquinolines **5c** and **5d** with halogens such as F and Br on the indole ring in satisfactory yields. Next, we evaluated the variations in substitutions on the benzoyl group attached to the pyrrole ring. The reaction was found to be compatible with electronically diverse functionalities at the para position, including electron donating methyl (**5e**) and phenyl groups (**5f**). In addition, halogens such as F, Cl, and Br on different positions of the benzoyl group were also tolerated under these reaction conditions affording the products **5g** to **5j**. In all the above cases, we could observe the formation of indenopyrrolo[2,1-*a*]isoquinolines in trace amounts. The reaction of 1.0 g of **3a** afforded the product indolo-pyrrolo-[2,1-*a*]isoquinoline **5a** in 49% yield.

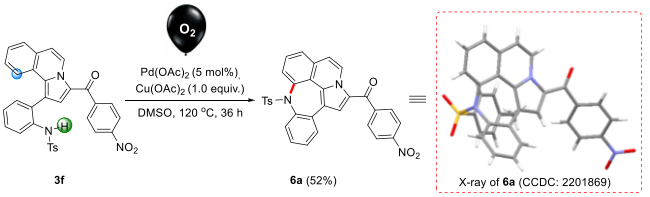
This oxygen-induced chemoselective synthesis of indolo-pyrrolo[2,1-*a*]isoquinoline **5** made us believe that oxygen might be involved from the start of the catalytic cycle. We hypothesize that initially DMSO interacts with the catalyst $Pd(OAc)_2$ to form a $Pd(0)(DMSO)_n$ species as per the theoretical investigations carried out by Zierkiewicz and Privalov.[16] Stahl and co-workers have investigated in detail on the Pd-catalyzed aerobic oxidations promoted by ligands.[19] By following the literature precedents,[20] we believe that $Pd(0)(DMSO)_n$ is then oxidized by oxygen to form the active η^2-peroxo-Pd(II) species. We consider that the presence of oxygen forces the reaction to take a Wacker-like pathway as proposed by Buchwald and Monguchi for the oxygen promoted Pd-catalyzed synthesis of carbazoles.[9,21] In this line, the complexation of η^2-peroxo-Pd(II) intermediate to the *N*-center in **3a** takes place generating the amide **D**. Next, a Wacker-like addition of the Pd-species across the pyrrole double bond will give rise to the intermediate **E**. A β-hydride elimination then happens in **E** releasing the indolo-pyrrolo[2,1-*a*]isoquinoline **5** and H-Pd(II)Ln-OOH moiety. Reductive elimination happens in H-Pd(II)Ln-OOH releasing the $Pd(0)L_n$ and H_2O_2. The $Pd(0)L_n$ is then reoxidized by $Cu(OAc)_2$ and O_2 to continue the catalytic cycle (Scheme 5).

Scheme 5. Plausible Mechanism for the O_2 Induced Pd-Catalyzed C−H Amination for Synthesis of *N*-Ts-Indolopyrrolo[2,1-*a*]isoquinolines [X = OAc, L = DMSO]



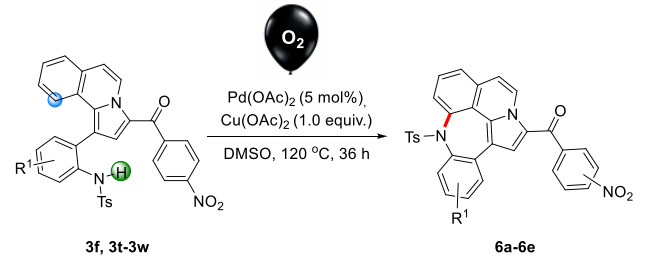
We came across a serendipitous observation of the activation of C−H bond in the isoquinoline ring (site-3, Scheme 1) in **3f** during the generality studies of Pd-catalyzed C−H amination. The reaction of appropriately functionalized 5-(4-nitro benzoyl)-pyrrolo[2,1-*a*]isoquinolines **3f** under the optimized conditions for O_2 promoted Pd-catalyzed C−H amination furnished tetra-ring-fused azepine **6a** in 52% yield. The structure of **6a** was established by various spectroscopic analysis and further confirmed by single crystal X-ray analysis (Scheme 6). We observed that the reaction does not proceed further after 36 h and from this reaction mixture we could recover unreacted **3f**.

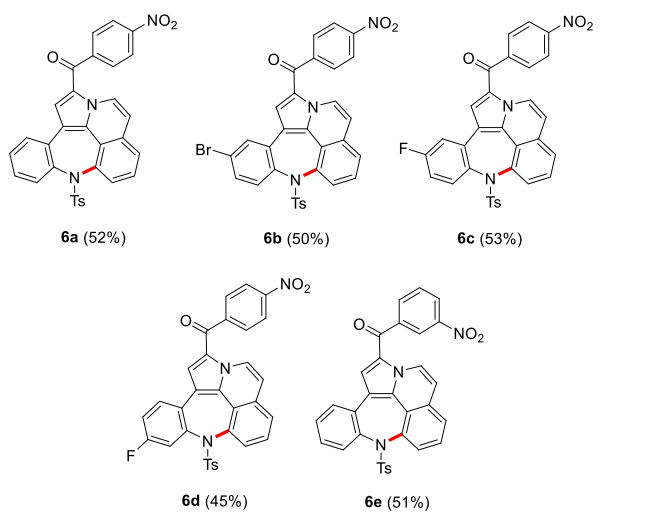
Scheme 6. Pd-Catalyzed Site-Selective C−H Activation towards Tetra-Ring-Fused Azepine 6a



We were excited to observe the formation of this multiring fused azepine scaffold, and we went on in exploring the scope of the reaction by starting from different 5-benzoyl-pyrrolo[2,1-*a*]isoquinolines with the NO_2-group on the phenyl ring (Table 3). With this methodology, we could introduce halogens such as Br and F on the fused benzene ring thereby generating multiring

Table 3. Pd-Catalyzed C−H Amination of Pyrrolo[2,1-*a*]isoquinolines towards Multiring Fused Azepines[a]





[a]Reaction conditions: **3** (1.0 equiv, 100 mg), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (1.0 equiv), O_2 (1.0 atm), DMSO (0.1 M), 120 °C, 36 h; unreacted starting compounds were recovered in all cases.

https://doi.org/10.1021/acs.joc.3c00651
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fused azepines **6b**, **6c**, and **6d** in moderate yields. Moreover, changing the nitro group to meta position of the benzene ring in the benzoyl substituent also gave a positive result and we isolated the corresponding product **6e** in 51% yield. As mentioned above, we could recover unreacted starting compounds in all cases.

The factors influencing the site selective C−H functionalization toward different fused *N*-heterocycles were then analyzed. The single crystal X-ray structures of **3a** and **3f** (Figure 1) and

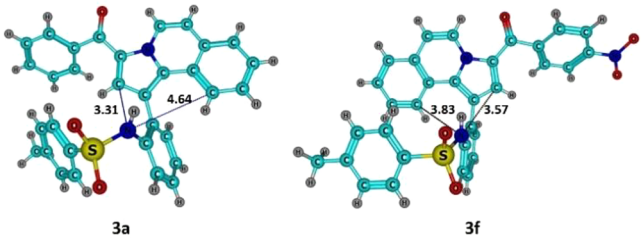

Figure 1. X-ray structures of **3a** (CCDC: 2201867) and **3f** (CCDC: 2174937) [N−C distances are given in Å].

density functional theory calculations at the B3LYP-D3/6-31G(d,p)[22] level showed that the orientation of the tosylamine group, C−H bond electron density at the sites 1 and 3, and the thermodynamic stability of possible products will be decisive in the site selective C−H amination.

The X-ray structure of **3a** shows the closeness of the *N*-center to site-1 (3.31 Å) compared to site-3 (4.64 Å). Therefore, the binding of $Pd(OAc)_2$ to nitrogen would lead to the C−H activation at site-1. It can further proceed to the C−H activation of phenyl ring (site-2) forming **4a** which is thermodynamically more stable than the possible C−H aminated products (Figure 2).

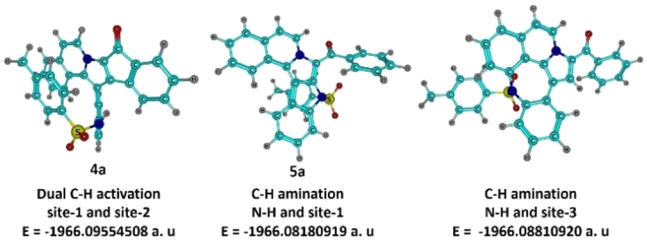

Figure 2. Optimized structures of the possible C−H activation products of **3a** along with energy values.

Binding of oxygen to $Pd(OAc)_2$ would hinder the phenyl C−H activation and results in C−H amination to form **5a**. In the case of **3f**, dual C−H activation product is thermodynamically more stable than the possible C−H amination products and therefore **4f** forms (Figure 3). Binding of oxygen to Pd center hinders the activation of phenyl C−H (site-2), and the isoquinoline C−H undergoes activation to form **6a** albeit N is slightly closer to site-1 (3.57 Å) than site-3 (3.83 Å). This can be attributed to the higher electron density at site-3 and the stability of **6a** (more stable than site-1 C−H aminated product by 3 kcal/mol). The molecular electrostatic potential at the carbon nucleus on site-1 is −14.74153 a.u. while that at site-3 is −14.74500 a.u., suggesting a higher electron density at site-3 than site-1.[23]

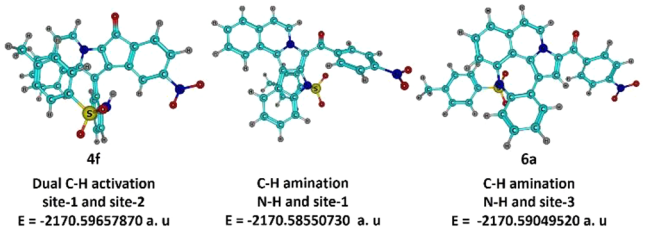

Figure 3. Optimized structures of the possible C−H activation products of **3f** along with energy values.

CONCLUSIONS

To conclude, we have unraveled an interesting Pd-catalyzed site selective C−H functionalization toward multiring fused *N*-heterocycles. These observations were made on the 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline scaffold, where we could identify three sites for C−H functionalization and a *N*-center which could participate in C−H amination. The experimental and theoretical investigations have shown that there is a preference for Pd-catalyzed cross-dehydrogenative coupling toward 8*H*-indeno-pyrrolo[2,1-*a*]isoquinolinone derivatives. Then during our attempts for selective C−H amination, we came across a unique and previously unknown O_2 induced chemoselectivity forcing the formation of the 9*H*-indolo-pyrrolo[2,1-*a*]-isoquinoline scaffold over the CDC product. We believe that this selectivity is induced by O_2 which gets incorporated in the active Pd-species driving the reaction to take a Wacker-type pathway leading to C−H amination. When we tried the Pd-catalyzed C−H amination with a substrate bearing a NO_2-group on the benzoyl moiety of the starting substrate, we found that the C−H amination was taking place preferentially at the isoquinoline ring. This result can be attributed to the higher electron density at the reactive center on the isoquinoline ring and also to the stability of multiring fused benzazepine in comparison with the pentacene regioisomer. Currently we are investigating the reaction pathway in detail both experimentally and theoretically and also are trying to apply the site selectivity in similar scaffolds.

EXPERIMENTAL SECTION

General Experimental Methods. All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets precoated with silica gel containing fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using neutral alumina, silica gel, and mixtures of ethyl acetate−hexanes for elution. Melting points were determined using a calibrated digital melting point apparatus (Büchi 530 melting point apparatus). NMR spectra were recorded with Bruker AMX-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C{1H} NMR) instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (J) are reported in hertz (Hz), and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were performed with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with a JMS-T100GC spectrometer or with an ESI/HRMS at 60,000 resolution using a ThermoScientificExactive mass spectrometer with an orbitrap analyzer. The diffraction data of single crystals were collected on a Bruker Apex-II diffractometer using

https://doi.org/10.1021/acs.joc.3c00651
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graphite monochromated Mo−Kα radiation. The data were processed with the SMART software suite. The structure solution was carried out by direct methods, and the refinements were performed by full-matrix least-squares on F2 using the SHELXTL suite of programs.

Procedure for the Synthesis of Electrophilic Benzannulated Heterocycles. 3-Nitroindoles (**1a−1f**)[14] were prepared by following a literature report.[24]

Procedure for the Synthesis of Isoquinolinium Salts. All isoquinolinium salts (**2a−2l**)[14] were prepared by following a previously reported procedure.[25] To isoquinoline dissolved in acetone at 0 °C, the α-halocarbonyl compound was added and the mixture was stirred at room temperature for a period of time. After the completion of the reaction, the precipitate formed was filtered and washed with diethyl ether to get the pure product.

Experimental Procedure for the Reaction between 3-Nitro-*N*-tosyl Indole and Isoquinolinium Salt. A mixture of 3-nitro-*N*-tosyl indole (100 mg, 1.0 equiv), isoquinolinium salt (1.5 equiv), and KOH (4.0 equiv) was weighed into a dry reaction tube. Dry DMF was added, and the reaction mixture was allowed to stir at room temperature. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was then purified by column chromatography (neutral alumina, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and Characterization of Pyrrolo[2,1-*a*]-isoquinolines. *N-(2-(3-Benzoylpyrrolo[2,1-a]isoquinolin-1-yl)-phenyl)-4-methylbenzenesulfonamide (**3a**).* The reaction was performed according to the general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **2a** (156 mg, 0.47 mmol), and KOH (71 mg, 1.26 mmol) at rt for 4 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3a** as a yellow solid (111 mg, 68%). Analytical data of **3a**: Mp: 223−226 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.59 (d, J = 7.5 Hz, 1H), 7.78−7.76 (m, 3H), 7.64 (d, J = 8 Hz, 1H), 7.54−7.52 (m, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.42−7.36 (m, 2H), 7.24 (s, 1H), 7.21−7.19 (m, 2H), 7.15−7.11 (m, 3H), 7.04 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 8 Hz, 2H), 6.65 (s, 1H), 6.46 (s, 1H), 2.07 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.4, 143.7, 140.2, 136.0, 135.7, 132.7, 131.7, 131.5, 129.6, 129.5, 129.3, 129.2, 128.4, 128.0, 127.8, 127.2, 127.0, 127.0, 126.8, 125.5, 125.0, 124.6, 124.0, 123.4, 120.5, 114.3, 113.1, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{32}H_{25}N_2O_3S$ 517.1580, found 517.1599.

*4-Methyl-N-(2-(3-(4-methylbenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)benzenesulfonamide (**3b**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-oxo-2-(p-tolyl)ethyl)isoquinolin-2-ium bromide **2g** (164 mg, 0.48 mmol), and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3b** as a pale yellow solid (128 mg, 75%). Analytical data of **3b**: Mp: 230−232 °C. 1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.56 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 7.5 Hz, 1H), 7.41−7.36 (m, 2H), 7.26−7.24 (m, 4H), 7.21 (brs, 1H), 7.15−7.10 (m, 3H), 7.04 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 8.0 Hz, 2H), 6.62 (s, 1H), 6.45 (s, 1H), 2.40 (s, 3H), 2.06 (s, 3H) ppm. 13C{1H} NMR (125 MHz, $CDCl_3$): δ 185.3, 143.7, 142.2, 137.4, 135.9, 135.6, 132.5, 131.7, 129.5, 129.4, 129.3, 129.1, 128.0, 127.8, 127.4, 127.0, 126.6, 125.5, 125.0, 124.1, 123.3, 120.6, 114.2, 112.9, 21.6, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{33}H_{27}N2O_3S$ 531.1737, found 531.1750.

*N-(2-(3-([1,1′-Biphenyl]-4-carbonyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (**3c**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-([1,1′-biphenyl]-4-yl)-2-oxoethyl)-isoquinolin-2-ium bromide **2f** (192 mg, 0.48 mmol), and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3c** as a pale yellow solid (142 mg, 75%). Analytical data of **3c**: Mp: 138−140 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.59 (d, J = 7.5 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.5 Hz, 1H), 7.69−7.64 (m, 3H), 7.60 (d, J = 7.5 Hz, 2H), 7.44−7.33 (m, 5H), 7.26 (d, J = 8.5 Hz, 2H), 7.23−7.21 (m, 1H), 7.16−7.12 (m, 3H), 7.05 (t, J = 7.5 Hz, 1H), 6.74 (d, J = 8.0 Hz, 2H), 6.70 (s, 1H), 6.47 (s, 1H), 2.00 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.0, 144.4, 143.8, 140.0, 138.9, 135.7, 131.7, 129.8, 129.3, 129.0, 128.1, 127.2, 127.1, 127.04, 127.02, 126.8, 125.5, 125.0, 124.6, 124.1, 123.4, 120.6, 114.4, 113.2, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$ calcd for $C_{38}H_{28}N_2NaO_3S$ 615.1713, found 615.1743.

*N-(2-(3-(4-Fluorobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (**3d**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(4-fluorophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2c** (164 mg, 0.48 mmol), and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3d** as a pale yellow solid (116 mg, 68%). Analytical data of **3d**: Mp: 210−212 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.54 (d, J = 7.5 Hz, 1H), 7.82−7.79 (m, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.42−7.36 (m, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.21−7.19 (m, 1H), 7.14 (t, J = 7.0 Hz, 5H), 7.04 (t, J = 7.5 Hz, 1H), 6.76 (d, J = 8.0 Hz, 2H), 6.64 (s, 1H), 6.46 (s, 1H), 2.10 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 183.8, 143.7, 136.3, 136.0, 135.7, 132.8, 131.7, 131.6 (d, J = 32.9 Hz), 129.6 (d, J = 23.5 Hz), 129.3, 128.1, 127.9, 127.0 (d, J = 37.6 Hz), 126.6, 125.4, 125.0, 124.6, 123.8, 123.4, 120.5, 115.5 (d, J = 84.6 Hz), 114.4, 113.2, 21.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −107.6 (s) ppm. HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$ calcd for $C_{32}H_{23}FN_2NaO_3S$ 557.1306, found 557.1329.

*N-(2-(3-(4-Chlorobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (**3e**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(4-chlorophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2b** (172 mg, 0.47 mmol), and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3e** as a yellow solid (127 mg, 73%). Analytical data of **3e**: Mp: 215−218 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.54 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8 Hz, 1H), 7.43−7.36 (m, 4H), 7.26 (d, J = 8 Hz, 2H), 7.20−7.12 (m, 4H), 7.05 (t, J = 7.5 Hz, 1H), 6.74 (d, J = 7.5 Hz, 2H), 6.60 (s, 1H), 6.44 (s, 1H), 2.11 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 183.9, 143.8, 138.5, 137.8, 136.0, 135.7, 133.0, 131.7, 130.5, 129.6, 129.3, 128.7, 128.2, 127.9, 127.1, 127.0, 126.7, 125.4, 125.0, 124.5, 123.7, 123.4, 120.5, 114.5, 113.3, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$ calcd for $C_{32}H_{23}ClN_2NaO_3S$ 573.1010, found 573.1030.

*4-Methyl-N-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)-phenyl)benzenesulfonamide (**3f**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2e** (177 mg, 0.47 mmol), and KOH (71 mg, 1.26 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3f** as a bright yellow solid (134 mg, 75%). Analytical data of **3f**: Mp: 199−203 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.61 (d, J = 7.5 Hz, 1H), 8.30 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8 Hz, 1H), 7.68 (d, J = 8 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 8 Hz, 2H), 7.20−7.19 (m, 2H), 7.16−7.11 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 8 Hz, 2H), 6.73 (s, 1H), 6.45 (s, 1H), 2.12 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 182.7, 149.3, 145.6, 143.8, 136.1, 135.7, 133.7, 131.7, 129.9, 129.8, 129.4, 128.5, 128.1, 127.3, 127.2, 127.0, 126.5, 125.4, 124.9, 124.4, 124.6, 123.6, 123.2, 120.1, 115.1, 114.0, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$ calcd for $C_{32}H_{23}N_3NaO_5S$ 584.1250, found 584.1278.

*N-(2-(3-(2-Bromobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (**3g**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(2-bromophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2i** (193 mg, 0.48 mmol), and KOH (71 mg, 1.28 mmol) at rt for 1

https://doi.org/10.1021/acs.joc.3c00651
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h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3g** as a pale yellow solid (137 mg, 72%). Analytical data of **3g**: Mp: 205−206 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.80 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.77−7.73 (m, 2H), 7.53−7.50 (m, 2H), 7.48−7.38 (m, 5H), 7.29−7.28 (m, 1H), 7.25−7.13 (m, 4H), 6.86 (d, J = 8.0 Hz, 2H), 6.64 (s, 1H), 6.58 (s, 1H), 2.19 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 184.2, 143.6, 141.6, 135.9, 135.6, 133.3, 131.7, 130.9, 129.6, 129.3, 129.2, 127.9, 127.4, 127.2, 127.1, 127.0, 125.6, 124.8, 124.5, 123.6, 120.3, 114.9, 113.8, 21.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{24}BrN_2O_3S$ 595.0686, found 595.0702.

*4-Methyl-N-(2-(3-(2-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)-phenyl)benzenesulfonamide (**3h**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(2-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2h** (177 mg, 0.48 mmol), and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3h** as a yellow solid (129 mg, 72%). Analytical data of **3h**: Mp: 140−142 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.63 (d, J = 7.5 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.73−7.60 (m, 6H), 7.43−7.40 (m, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.14−7.13(d, J = 7.0 Hz, 1H), 7.09 (d, J = 7.5 Hz, 2H), 7.02 (t, J = 7.5 Hz, 1H), 6.74 (d, J = 8.0 Hz, 2H), 6.52 (s, 1H), 6.47 (s, 1H), 2.10 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 181.6, 147.2, 143.5, 135.2, 136.1, 135.5, 133.7, 133.5, 131.8, 130.5, 129.7, 129.61, 129.57, 129.3, 128.3, 127.9, 127.1, 127.0, 126.7, 125.6, 125.4, 124.9, 124.6, 124.4, 123.6, 123.5, 120.6, 115.0, 113.9, 21.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{23}N_3NaO_5S$ 584.1251, found 584.1271.

*N-(2-(3-(3,5-Bis(trifluoromethyl)benzoyl)pyrrolo[2,1-a]-isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (**3i**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(3,5-bis(trifluoromethyl)-phenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2k** (220 mg, 0.48 mmol), and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3i** as a yellow solid (146 mg, 70%). Analytical data of **3i**: Mp: 125−128 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.57 (d, J = 7.5 Hz, 1H), 8.21 (s, 2H), 8.01 (s, 1H), 7.68 (t, J = 8.5 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.21−7.19 (m, 2H), 7.15−7.13 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 6.70 (s, 1H), 6.45 (s, 1H), 2.09 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 181.5, 143.7, 142.1, 136.1, 135.7, 133.9, 132.1, 131.8 (d, J = 32.9 Hz), 129.8, 129.3, 129.0, 128.6, 128.2, 127.2, 127.0 (d, J = 47.0 Hz), 126.3, 125.3, 124.9, 124.7, 124.3, 123.6, 123.0, 120.1, 115.2, 114.3, 21.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −62.8 (s) ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{34}H_{23}F_6N_2O_3S$ 653.1328, found 653.1355.

*N-(2-(3-Benzoylpyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-methanesulfonamide (**3j**).* The reaction was performed according to general procedure with 1-(methylsulfonyl)-3-nitro-1*H*-indole **1e** (100 mg, 0.42 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **2a** (207 mg, 0.63 mmol), and KOH (94 mg, 1.68 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3j** as a pale yellow solid (126 mg, 68%). Analytical data of **3j**: Mp: 179−181 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.69 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 7.0 Hz, 2H), 7.79−7.74 (m, 2H), 7.58−7.48 (m, 6H), 7.43−7.41 (m, 1H), 7.31−7.27 (m, 2H), 7.23 (d, J = 7.5 Hz, 1H), 7.19 (s, 1H), 6.40 (s, 1H), 2.82 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.6, 140.1, 136.0, 132.2, 131.5, 129.8, 129.1, 128.3, 127.9, 127.3, 127.0, 125.7, 124.8, 124.4, 123.2, 118.6, 114.4, 113.0, 39.9 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{26}H_{21}N_2O_3S$ 441.1267, found 441.1278.

*N-(2-(3-Benzoylpyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide (**3k**).* The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1*H*-indole **1f** (100 mg, 0.30 mmol), 2-(2-oxo-2-phenylethyl)-isoquinolin-2-ium bromide **2a** (148 mg, 0.45 mmol), and KOH (67 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3k** as a pale yellow solid (83 mg, 52%). Analytical data of **3k**: Mp: 228−230 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.59 (d, J = 8.0 Hz, 1H), 7.78−7.74 (m, 3H), 7.64 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 7.0 Hz, 1H), 7.46−7.43 (m, 2H), 7.41−7.35 (m, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.21 (brs, 1H), 7.13−7.10 (m, 3H), 7.03 (t, J = 7.5 Hz, 1H), 6.78 (s, 1H), 6.50 (s, 1H), 6.42 (d, J = 8.5 Hz, 2H), 3.60 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.5, 162.3, 140.1, 135.7, 131.8, 131.5, 130.5, 129.5, 129.1, 128.5, 128.4, 128.0, 127.8, 127.0, 126.9, 125.5, 124.9, 123.4, 120.3, 114.4, 113.8, 113.2, 55.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{25}N_2O_4S$ 533.1530, found 533.1559.

*4-Methoxy-N-(2-(3-(4-methylbenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)benzenesulfonamide (**3l**).* The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1*H*-indole **1f** (100 mg, 0.30 mmol), 2-(2-oxo-2-(*p*-tolyl)ethyl)-isoquinolin-2-ium bromide **2g** (155 mg, 0.45 mmol), and KOH (68 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3l** as a pale yellow solid (115 mg, 70%). Analytical data of **3l**: Mp: 200−202 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.65 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 7.5 Hz, 1H), 7.49−7.45 (m, 2H), 7.40 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.30−7.28 (m, 1H), 7.23−7.19 (m, 3H), 7.14−7.11 (m, 1H), 6.85 (s, 1H), 6.58 (s, 1H), 6.51 (d, J = 9.0 Hz, 2H), 3.70 (s, 3H), 2.06 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.3, 162.9, 142.2, 137.4, 135.7, 132.4, 131.8, 130.5, 129.4, 129.3, 129.1, 129.0, 127.9, 127.8, 127.2, 127.0, 126.6, 125.5, 124.9, 124.6, 123.3, 120.4, 114.2, 113.8, 113.0, 55.3, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{33}H_{26}N_2NaO_4S$ 569.1505, found 569.1522.

*N-(2-(3-(4-Chlorobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide (**3m**).* The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1*H*-indole **1f** (100 mg, 0.30 mmol), 2-(2-(4-chlorophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2b** (164 mg, 0.45 mmol), and KOH (68 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3m** as a yellow solid (122 mg, 72%). Analytical data of **3m**: Mp: 145−147 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.55 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.44−7.37 (m, 4H), 7.30 (d, J = 9.0 Hz, 2H), 7.21−7.19 (m, 1H), 7.15−7.13 (m, 3H), 7.07−7.04 (m, 1H), 6.67 (s, 1H), 6.44 (d, J = 9.0 Hz, 3H), 3.63 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 183.9, 163.0, 138.4, 137.8, 135.7, 131.7, 130.5, 129.6, 129.1, 128.6, 128.2, 127.9, 127.1, 126.7, 125.4, 125.0, 124.5, 123.4, 120.6, 114.5, 113.8, 113.4, 55.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{24}ClN_2O_4S$ 567.1140, found 567.1167.

*4-Methoxy-N-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)benzenesulfonamide (**3n**).* The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1*H*-indole **1f** (100 mg, 0.30 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2e** (168 mg, 0.45 mmol), and KOH (68 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3n** as a yellow solid (130 mg, 75%). Analytical data of **3n**: Mp: 140−142 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.61 (d, J = 7.5 Hz, 1H), 8.30 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.46−7.38 (m, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.21−7.19 (m, 2H), 7.16−7.13 (m, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.63 (s, 1H), 6.43 (d, J = 8.5 Hz, 2H), 6.38 (s, 1H), 3.63 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 182.8, 162.9, 149.4, 145.6, 135.7, 131.7, 130.6, 129.9, 129.8, 129.1, 128.6, 128.2, 127.3, 127.2, 125.4, 125.1, 124.4, 123.6, 123.5, 120.6, 115.1, 114.1, 113.8, 55.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{23}N_3NaO_6S$ 600.1200, found 600.1225.

https://doi.org/10.1021/acs.joc.3c00651
J. Org. Chem. 2023, 88, 9877−9892

*N-(2-(3-Benzoylpyrrolo[2,1-a]isoquinolin-1-yl)-4-fluorophenyl)-4-methylbenzenesulfonamide (**3o**).* The reaction was performed according to general procedure with 5-Fluoro-3-nitro-*N*-tosyl indole **1c** (100 mg, 0.30 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **2a** (148 mg, 0.45 mmol), and KOH (67 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3r** as a pale yellow solid (83 mg, 52%). Analytical data of **3r**: Mp: 200−202 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.56 (d, J = 7.5 Hz, 1H), 7.77−7.74 (m, 3H), 7.66 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.48−7.42 (m, 3H), 7.18−7.10 (m, 6H), 6.95−6.93 (m, 1H), 6.70 (d, J = 8.0 Hz, 2H), 6.52 (s, 1H), 6.34 (s, 1H), 2.02 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.4, 143.8, 140.0, 135.6, 132.4, 131.7, 130.0, 129.6, 129.2 (d, J = 42.3 Hz), 128.5, 128.3, 128.0, 127.2, 127.0, 126.4, 125.4, 124.3, 124.0, 123.5 (d, J = 28.2 Hz), 123.1, 118.4 (d, J = 84.6 Hz), 116.4 (d, J = 84.6 Hz), 114.5, 21.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −116.6 (s) ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{32}H_{24}FN_2O_3S$ 535.1486, found 535.1488.

*N-(2-(3-(2-Naphthoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (**3p**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(naphthalen-2-yl)-2-oxoethyl)isoquinolin-2-ium bromide **2l** (181 mg, 0.48 mmol), and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3p** as a yellow solid (132 mg, 73%). Analytical data of **3p**: Mp: 215−217 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.60 (d, J = 7.5 Hz, 1H), 8.24 (s, 1H), 7.92−7.86 (m, 4H), 7.75 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.54−7.48 (m, 2H), 7.41−7.34 (m, 2H), 7.22 (d, J = 8.0 Hz, 3H), 7.18 (d, J = 7.5 Hz, 1H), 7.14−7.12 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.64 (s, 1H), 6.56 (d, J = 8.0 Hz, 2H), 6.49 (s 1H), 1.76 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.3, 143.7, 137.5, 135.8, 135.7, 134.9, 132.8, 132.4, 131.8, 129.9, 129.6, 129.5, 129.3, 129.2, 128.3, 128.1, 128.0, 127.8, 127.1, 127.0, 126.9, 125.8, 125.5, 125.0, 124.6, 124.2, 123.4, 120.6, 114.4, 113.2, 21.0 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{36}H_{27}N_2O_3S$ 567.1737, found 567.1751.

*N-(2-(3-(2-Naphthoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide (**3q**).* The reaction was performed according to general procedure with 1-((4-methoxyphenyl)sulfonyl)-3-nitro-1*H*-indole **1f** (100 mg, 0.30 mmol), 2-(2-(naphthalen-2-yl)-2-oxoethyl)isoquinolin-2-ium bromide **2l** (171 mg, 0.45 mmol), and KOH (68 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3q** as a yellow solid (129 mg, 74%). Analytical data of **3q**: Mp: 185−187 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.71 (d, J = 7.5 Hz, 1H), 8.37 (s, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.98−7.96 (m, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.65−7.59 (m, 2H), 7.52−7.45 (m, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.26−7.21 (m, 3H), 7.16 (t, J = 7.5 Hz, 1H), 6.86 (s, 1H), 6.58 (s, 1H), 6.41 (d, J = 8.5 Hz, 2H), 3.45 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.4, 162.9, 137.4, 135.7, 134.9, 132.7, 132.4, 131.8, 130.4, 129.9, 129.6, 129.5, 129.3, 129.1, 128.3, 128.1, 127.9, 127.8, 127.1, 126.8, 125.6, 125.5, 124.9, 124.6, 124.3, 123.4, 120.5, 114.4, 113.8, 111.3, 55.1 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{36}H_{27}N_2O_4S$ 583.1686, found 583.1713.

*N-(2-(3-Benzoylpyrrolo[2,1-a]isoquinolin-1-yl)-4-bromophenyl)-4-methylbenzenesulfonamide (**3r**).* The reaction was performed according to general procedure with 5-Bromo-3-nitro-*N*-tosyl indole **1b** (100 mg, 0.25 mmol), 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **2a** (125 mg, 0.38 mmol), and KOH (56 mg, 1.00 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3r** as a pale yellow solid (101 mg, 68%). Analytical data of **3r**: Mp: 265−267 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.57 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.67−7.65 (m, 2H), 7.54−7.49 (m, 1H), 7.48−7.42 (m, 4H), 7.36 (s, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.16−7.09 (m, 3H), 6.75 (d, J = 8.0 Hz, 2H), 6.59 (s, 1H), 6.41 (s, 1H), 2.08 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 185.4, 144.0, 140.0, 135.6, 135.0, 134.3, 132.6, 132.4, 131.7, 129.6, 129.4, 129.3, 129.2, 129.0, 128.4, 128.3, 128.1, 127.2, 127.0, 126.7, 125.5, 124.3, 124.1, 123.2, 122.0, 117.8, 114.5, 111.5, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{32}H_{24}BrN_2O_3S$ 595.0686, found 595.0656.

*N-(2-(3-(4-Bromobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide (**3s**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(4-bromophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2d** (195 mg, 0.48 mmol), and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3s** as a pale yellow solid (137 mg, 72%). Analytical data of **3s**: Mp: 235−237 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.55 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 8.0 Hz, 3H), 7.59 (d, J = 8.0 Hz, 2H), 7.43−7.37 (m, 3H), 7.26 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.0 Hz, 3H), 7.06 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 8.0 Hz, 2H), 6.59 (s, 1H), 6.43 (s, 1H), 2.12 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 184.0, 143.8, 139.0, 135.9, 135.7, 133.1, 131.7, 131.6, 130.7, 129.6, 129.6, 129.3, 128.2, 127.9, 127.1, 127.0, 126.8, 126.3, 125.4, 125.0, 124.5, 123.6, 123.4, 120.5, 114.6, 113.3, 21.5 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{32}H_{24}BrN_2O_3S$ 595.0686, found 595.0673.

*N-(4-Bromo-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)-phenyl)-4 methylbenzenesulfonamide (**3t**).* The reaction was performed according to general procedure with 5-bromo-3-nitro-*N*-tosyl indole **1b** (100 mg, 0.25 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2e** (142 mg, 0.38 mmol), and KOH (57 mg, 1.01 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3t** as a yellow solid (115 mg, 71%). Analytical data of **3t**: Mp: 250−252 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.59 (d, J = 7.5 Hz, 1H), 8.31 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8 Hz, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 9 Hz, 1H), 7.49−7.46 (m, 2H), 7.34 (s, 1H), 7.28 (s, 1H), 7.21−7.19 (m, 2H), 7.16−7.10 (m, 2H), 6.81 (d, J = 7.5 Hz, 2H), 6.69 (s, 1H), 6.42 (s, 1H), 2.14 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 182.8, 149.4, 145.4, 144.0, 135.9, 135.0, 134.3, 133.5, 132.7, 129.9, 129.8, 129.5, 128.7, 128.5, 128.3, 127.3, 127.1, 127.0, 125.4, 124.1, 123.6, 123.5, 123.4, 121.5, 117.6, 115.2, 112.4, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$ calcd for $C_{32}H_{22}BrN_3NaO_5S$ 662.0355, found 662.0370.

*N-(4-Fluoro-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)-phenyl)-4-methylbenzenesulfonamide (**3u**).* The reaction was performed according to general procedure with 5-Fluoro-3-nitro-*N*-tosyl indole **1c** (100 mg, 0.30 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2e** (168 mg, 0.45 mmol), and KOH (67 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3u** as a pale yellow solid (122 mg, 70%). Analytical data of **3u**: Mp: 198−200 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.60 (d, J = 7.5 Hz, 1H), 8.32 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 7.24−7.21 (m, 3H), 7.17−7.11 (m, 3H), 6.95−6.93 (m, 1H), 6.77 (d, J = 8.0 Hz, 2H), 6.65 (s, 1H), 6.30 (s, 1H), 2.08 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 182.8, 149.5, 145.4, 143.8, 136.1, 133.4, 129.9, 129.3, 128.7, 128.3, 127.3, 126.9 (d, J = 61.1 Hz), 125.3, 124.1, 123.6, 123.4,123.1, 118.4 (d, J = 84.6 Hz), 116.6 (d, J = 79.9 Hz), 115.2, 21.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −116.5 (s) ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{32}H_{23}FN_3O_5S$ 580.1337, found 580.1316.

*N-(5-Fluoro-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)-phenyl)-4-methylbenzenesulfonamide (**3v**).* The reaction was performed according to general procedure with 6-Fluoro-3-nitro-*N*-tosyl indole **1d** (100 mg, 0.30 mmol), 2-(2-(4-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2e** (168 mg, 0.45 mmol), and KOH (67 mg, 1.20 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3v** as a pale yellow

https://doi.org/10.1021/acs.joc.3c00651
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solid (125 mg, 72%). Analytical data of **3v**: Mp: 205−207 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.62 (d, J = 7.5 Hz, 1H), 8.31 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.49−7.44 (m, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.22−7.21 (m, 2H), 7.16−7.12 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 8.0 Hz, 2H), 6.76 (s, 1H), 6.49 (s, 1H), 2.17 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 182.8, 149.4, 145.6, 144.2, 137.3, 137.2, 135.8, 133.8, 133.0, 132.9, 129.9 (d, J = 155.1 Hz), 128.6, 128.2, 127.4 (d, J = 89.3 Hz), 127.0, 125.4, 124.2, 123.6, 123.4, 121.5, 115.2, 112.8, 111.6 (d, J = 79.9 Hz), 106.9 (d, J = 103.4 Hz), 21.5 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −109.4 (s) ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{32}H_{23}FN_3O_5S$ 580.1337, found 580.1328.

*4-Methyl-N-(2-(3-(3-nitrobenzoyl)pyrrolo[2,1-a]isoquinolin-1-yl)-phenyl)benzenesulfonamide (**3w**).* The reaction was performed according to general procedure with 3-nitro-*N*-tosyl indole **1a** (100 mg, 0.32 mmol), 2-(2-(3-nitrophenyl)-2-oxoethyl)isoquinolin-2-ium bromide **2j** (179 mg, 0.48 mmol), and KOH (71 mg, 1.28 mmol) at rt for 1 h. After workup, the residue was purified by activated neutral alumina column chromatography (20% ethyl acetate in hexane) to afford the desired product **3w** as a pale yellow solid (117 mg, 65%). Analytical data of **3w**: Mp: 190−192 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.60 (d, J = 7.5 Hz, 1H), 8.61 (s, 1H), 8.37 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.71−7.65 (m, 3H), 7.46−7.43 (m, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.29 (d, J = 7.5 Hz, 2H), 7.22−7.21 (m, 2H), 7.16−7.12 (m, 2H), 7.07−7.04 (m, 1H), 6.79 (d, J = 7.5 Hz, 2H), 6.77 (s, 1H), 6.45 (s, 1H), 2.11 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 182.2, 148.1, 143.7, 141.7, 136.1, 135.6, 134.7, 131.8, 129.7, 129.6, 129.4, 128.5, 128.1, 127.2, 127.0, 126.4, 125.8, 125.4, 124.9, 123.9, 123.6, 123.2, 120.1, 115.0, 114.0, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{32}H_{24}N_3O_5S$ 562.1431, found 562.1436.

Experimental Procedure for the Pd-Catalyzed Cross-Dehydrogenative Coupling of Pyrrolo[2,1-*a*]isoquinolines. A mixture of pyrrolo[2,1-*a*]isoquinoline **3** (1.0 equiv), $Pd(OAc)_2$ (20 mol %), and $Cu(OAc)_2$ (1.0 equiv) was weighed into a dry reaction tube. Dry toluene was added, and the reaction mixture was allowed to stir at 120 °C in an oil bath for 36 h. After completion of the reaction as indicated from the TLC, the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and Characterization of Indenopyrrolo[2,1-*a*]-isoquinolinones (4a−4q). *4-Methyl-N-(2-(8-oxo-8H-indeno-[1′,2′:4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzene-sulfonamide (**4a**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)-phenyl)-4-methylbenzenesulfonamide **3a** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.036 mmol), and $Cu(OAc)_2$ (35 mg, 0.19 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4a** as an orange solid (84 mg, 84%). Analytical data of **4a**: Mp: 264−268 °C. IR (neat) ν_{max}: 3253, 2922, 1686, 1612, 1489, 1385, 1332, 1158, 1097, 896, 792, 722, 660, 565, 538 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.29 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 7.0 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.0 Hz, 1H), 7.32−7.29 (m, 2H), 7.26 (d, J = 7.5 Hz, 2H), 7.22−7.19 (m, 1H), 7.13−7.09 (m, 2H), 7.04 (d, J = 7.0 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 7.5 Hz, 2H), 6.65 (s, 1H), 6.15 (d, J = 7.0 Hz, 1H), 2.05 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 179.4, 143.7, 143.3, 139.6, 137.2, 136.1, 135.3, 132.7, 131.4, 129.8, 129.4, 129.1, 128.6, 128.3, 128.1, 127.7, 126.8, 125.9, 125.6, 123.7, 123.5, 122.7, 121.9, 120.1, 115.4, 108.5, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{32}H_{23}N_2O_3S$ 515.1424, found 515.1447.

*4-Methyl-N-(2-(11-methyl-8-oxo-8H-indeno[1′,2′:4,5]pyrrolo-[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**4b**).* The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-methylbenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-benzenesulfonamide **3b** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.038 mmol), and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4b** as an orange solid (70 mg, 70%). Analytical data of **4b**: Mp: 216−220 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.27 (d, J = 7.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 7.0 Hz, 1H), 7.36−7.33 (m, 1H), 7.30−7.26 (m, 3H), 7.22−7.19 (m, 3H), 7.09−7.04 (m, 1H), 7.01 (d, J = 7.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.72−6.69 (m, 3H), 5.98 (s, 1H), 2.07 (s, 3H), 2.04 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 179.6, 143.6, 143.5, 142.9, 137.6, 137.0, 136.2, 135.4, 135.3, 131.4, 129.8, 129.3, 129.0, 128.5, 128.3, 127.9, 127.7, 126.8, 126.0, 125.5, 123.7, 123.5, 122.7, 121.9, 121.4, 115.2, 108.4, 21.9, 21.5 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{33}H_{25}N_2O_3S$ 529.1580, found 529.1589.

*4-Methyl-N-(2-(8-oxo-11-phenyl-8H-indeno[1′,2′:4,5]pyrrolo-[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**4c**).* The reaction was performed according to general procedure with *N*-(2-(3-([1,1′-biphenyl]-4-carbonyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3c** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (8 mg, 0.034 mmol) and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4c** as a pale orange solid (64 mg, 64%). Analytical data of **4c**: Mp: 255−257 °C. IR (neat) ν_{max}: 3079, 2930, 2843, 1682, 1603, 1489, 1394, 1341, 1150, 1080, 904, 792, 747, 660, 565, 538 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.31 (d, J = 7.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.39−7.37 (m, 2H), 7.34−7.32 (m, 3H), 7.30−7.27 (m, 5H), 7.23−7.20 (m, 2H), 7.18−7.16 (m, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.72 (s, 1H), 6.66 (d, J = 8.0 Hz, 2H), 6.43 (s, 1H), 1.89 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 179.2, 145.6, 143.8, 142.7, 139.9, 138.4, 138.2, 136.2, 135.7, 135.3, 131.4, 129.9, 129.4, 129.1, 128.9, 128.7, 128.2, 127.7, 126.83, 126.76, 126.7, 125.5, 123.9, 123.7, 122.7, 121.9, 118.9, 115.4, 108.7, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: (M + H)$^+$ calcd for $C_{38}H_{27}N_2O_3S$ 591.1737, found 591.1759.

*N-(2-(11-Fluoro-8-oxo-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]-isoquinolin-13-yl)phenyl)-4-methylbenzenesulfonamide (**4d**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-fluorobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3d** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.038 mmol), and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4d** as an orange solid (40 mg, 40%). Analytical data of **4d**: Mp: 290−292 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.27 (d, J = 7.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.39 (t, J = 7.0 Hz, 1H), 7.31−7.26 (m, 4H), 7.22−7.21 (m, 2H), 7.17−7.14 (m, 2H), 7.07 (d, J = 7.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 2H), 6.60 (s, 1H), 5.70 (d, J = 8.0 Hz, 1H), 2.10 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 178.2, 144.0, 136.0, 135.5 (d, J = 211.5 Hz), 131.2, 130.1, 129.6, 129.0, 128.9, 128.3, 127.8, 126.9, 125.6, 125.5, 125.4, 125.2, 125.02, 124.94, 123.6, 122.7, 121.5, 115.8, 109.0, 108.7 (d, J = 108.1 Hz), 21.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −105.6 (s) ppm. HRMS (ESI-Orbitrap) m/z: (M - H) calcd for $C_{32}H_{20}FN_2O_3S$ 531.1173, found 531.1176.

*N-(2-(11-Chloro-8-oxo-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]-isoquinolin-13-yl)phenyl)-4-methylbenzenesulfonamide (**4e**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-chlorobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3e** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.36 mmol), and $Cu(OAc)_2$ (33 mg, 0.18 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4e** as an orange solid (64 mg, 64%). Analytical data of **4e**: Mp: 295−298 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.28 (d, J = 7.0 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.49−7.45 (m, 1H), 7.41−7.38 (m, 1H), 7.30−7.27 (m, 3H), 7.23−7.19 (m, 2H), 7.17−7.14 (m, 2H), 7.07 (d, J = 7.0 Hz, 1H), 6.97−6.95 (m, 1H), 6.81 (d, J = 8.0 Hz, 2H), 6.59 (s, 1H), 5.98 (d, J = 1.5 Hz, 1H), 2.10 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 178.1, 143.9, 141.8, 139.0, 138.6, 137.7, 136.0, 135.4, 131.2, 130.2, 129.4, 129.1, 128.9, 128.4, 127.8, 126.9, 125.6, 125.4, 125.2, 124.2, 123.6, 122.7, 121.6,

https://doi.org/10.1021/acs.joc.3c00651
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120.6, 115.8, 108.8, 21.5 ppm. HRMS (ESI-Orbitrap) m/z: (M - H) calcd for $C_{32}H_{20}ClN_2O_3S$ 547.0877, found 547.0881.

*4-Methyl-N-(2-(11-nitro-8-oxo-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**4f**).* The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide **3f** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.035 mmol), and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4f** as an orange solid (70 mg, 70%). Analytical data of **4f**: Mp: 260−262 °C. IR (neat) ν_{max}: 2922, 2852, 1673, 1498, 1402, 1324, 1272, 1158, 1080, 904, 809, 722, 660, 556, 538 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.30 (d, J = 7.0 Hz, 1H), 7.90−7.86 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.45−7.41 (m, 2H), 7.31−7.25 (m, 5H), 7.12 (d, J = 7.0 Hz, 1H), 6.77−6.74 (m, 3H), 6.62 (s, 1H), 2.04 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 176.0, 150.8, 144.9, 141.3, 136.2, 131.1, 130.6, 129.5, 129.4, 129.2, 128.9, 127.9, 127.0, 125.8, 125.3, 124.4, 123.7, 123.2, 123.0, 121.4, 116.4, 114.2, 109.6, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{21}N_3NaO_5S$ 582.1094, found 582.1100.

*N-(2-(9-Bromo-8-oxo-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)-4-methylbenzenesulfonamide (**4g**).* The reaction was performed according to general procedure with *N*-(2-(3-(2-bromobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3g** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (8 mg, 0.034 mmol), and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4g** as an orange solid (50 mg, 50%). Analytical data of **4g**: Mp: 255−258 °C. IR (neat) ν_{max}: 3245, 2922, 2852, 1673, 1603, 1498, 1402, 1158, 1088, 887, 800, 757, 669, 565, 530 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.28 (d, J = 7.0 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.46−7.42 (m, 1H), 7.38−7.35 (m, 1H), 7.32−7.29 (m, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.21−7.20 (m, 1H), 7.13−7.09 (m, 2H), 7.03 (d, J = 7.0 Hz, 1H), 6.99 (t, J = 8.0 Hz, 1H), 6.90 (t, J = 8.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 2H), 6.65 (s, 1H), 6.15 (d, J = 7.5 Hz, 1H), 2.05 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 179.4, 143.7, 143.3, 139.5, 137.2, 136.1, 135.7, 135.3, 132.7, 131.4, 129.8, 129.4, 129.1, 128.6, 128.3, 128.1, 127.7, 126.8, 125.9, 125.5, 125.4, 123.7, 123.4, 122.8, 121.9, 120.1, 115.4, 108.6, 21.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{22}BrN_2O_3S$ 593.0529, found 593.0536.

*4-Methyl-N-(2-(9-nitro-8-oxo-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**4h**).* The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(2-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide **3h** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.036 mmol), and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4h** as an orange solid (40 mg, 40%). Analytical data of **4h**: Mp: 238−240 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.28 (d, J = 7.5 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.29−7.27 (m, 3H), 7.24−7.21 (m, 3H), 7.15−7.13 (m, 2H), 7.09 (d, J = 7.0 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 6.63 (s, 1H), 6.30 (d, J = 7.0 Hz, 1H), 2.10 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.1, 154.1, 153.7, 153.0, 143.8, 136.9, 133.7, 133.3, 131.3, 130.2, 129.4, 129.0, 128.7, 127.9, 126.8, 125.7, 125.4, 125.3, 123.6,122.8, 122.6, 122.1, 116.3, 21.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{22}N_3O_5S$ 560.1275, found 560.1288.

*4-Methyl-N-(2-(8-oxo-10,12-bis(trifluoromethyl)-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**4i**).* The reaction was performed according to general procedure with *N*-(2-(3-(3,5-bis(trifluoromethyl)benzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3i** (100 mg, 0.15 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), and $Cu(OAc)_2$ (28 mg, 0.15 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4i** as a pale orange solid (53 mg, 53%). Analytical data of **4i**: Mp: 290−292 °C. IR (neat) ν_{max}: 3253, 3061, 2922, 2852, 1690, 1595, 1498, 1398, 1332, 1280, 1158, 1131, 1080, 914, 782, 757, 695, 561, 538 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.44 (d, J = 7.0 Hz, 1H), 7.74−7.71 (m, 2H), 7.56−7.54 (m, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.34−7.32 (m, 3H), 7.17−7.15 (m, 1H), 7.13−7.11 (m, 2H), 6.88 (t, J = 7.5 Hz, 1H), 6.76 (d, J = 8.0 Hz, 2H), 6.57−6.56 (m, 2H), 2.17 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 175.6, 143.5, 142.2, 138.3, 137.5, 136.5, 132.2, 130.3, 129.5, 129.2, 128.6 (d, J = 263.2 Hz), 127.7, 127.0, 125.4, 124.4, 123.4, 123.3, 122.9, 122.4, 118.6 (d, J = 37.6 Hz), 117.4, 112.5, 21.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −62.5 (s), −63.5 (s) ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{34}H_{21}F_6N_2O_3S$ 651.1172, found 651.1183.

*N-(2-(8-Oxo-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)methanesulfonamide (**4j**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)methanesulfonamide **3j** (100 mg, 0.22 mmol), $Pd(OAc)_2$ (10 mg, 0.045 mmol), and $Cu(OAc)_2$ (41 mg, 0.22 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4j** as an orange solid (60 mg, 60%). Analytical data of **4j**: Mp: 250−252 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.27 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 6.5 Hz, 1H), 7.39−7.35 (m, 2H), 7.29−7.21 (m, 3H), 7.01−6.97 (m, 3H), 6.60 (s, 1H), 6.48 (d, J = 6.5 Hz, 1H), 2.76 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 179.4, 143.4, 139.6, 137.4, 136.0, 132.9, 131.9, 130.2, 129.2, 128.6, 128.3, 127.9, 125.5, 125.2, 124.9, 123.8, 123.7, 122.7, 119.9, 119.5, 115.5, 108.09, 39.8 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{26}H_{19}N_2O_3S$ 439.1111, found 439.1115.

*4-Methoxy-N-(2-(8-oxo-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**4k**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide **3k** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.038 mmol), and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4k** as an orange solid (62 mg, 62%). Analytical data of **4k**: Mp: 150−152 °C. IR (neat) ν_{max}: 2930, 2852, 1686, 1603, 1498, 1402, 1262, 1167, 1088, 1028, 887, 722, 652, 565, 535 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.29 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.46−7.35 (m, 4H), 7.33−7.29 (m, 4H), 7.11−7.08 (m, 2H), 7.04 (d, J = 7.0 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.91−6.88 (m, 1H), 6.63 (s, 1H), 6.38 (d, J = 9.0 Hz, 1H), 6.13 (d, J = 7.0 Hz, 1H), 3.56 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 179.4, 162.8, 139.5, 137.2, 135.4, 132.8, 131.4, 129.8, 129.1, 129.0, 128.8, 128.3, 128.1, 127.7, 125.5, 123.7, 123.4, 122.8, 121.8, 120.0, 115.4, 113.8, 55.3 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{23}N_2O_4S$ 531.1373, found 531.1383.

*4-Methoxy-N-(2-(11-methyl-8-oxo-8H-indeno[1′,2′:4,5]pyrrolo-[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**4l**).* The reaction was performed according to general procedure with 4-methoxy-N-(2-(3-(4-methylbenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-benzenesulfonamide **3l** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.036 mmol), and $Cu(OAc)_2$ (33 mg, 0.18 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4l** as an orange solid (55 mg, 55%). Analytical data of **4l**: Mp: 260−262 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.26 (d, J = 7.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.0 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.33−7.31 (m, 2H), 7.29 (d, J = 7.5 Hz, 1H), 7.21−7.16 (m, 3H), 7.08−7.07 (m, 2H), 7.00 (d, J = 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 6.68 (s, 1H), 6.37 (d, J = 7.5 Hz, 2H), 5.92 (s, 1H), 3.54 (s, 3H), 2.05 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 179.6, 162.8, 143.6, 142.9, 137.6, 136.9, 135.5, 135.4, 131.4, 130.6, 129.8, 129.0, 128.6, 128.3, 127.9, 127.6, 125.9, 125.5, 125.4, 123.7, 123.4, 122.7, 121.7, 121.3, 115.3, 113.7, 108.4, 55.2, 21.9 ppm. HRMS (ESI-

https://doi.org/10.1021/acs.joc.3c00651
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Orbitrap) m/z: $(M + H)^+$ calcd for $C_{33}H_{25}N_2O_4S$ 545.1530, found 545.1541.

*N-(2-(11-Chloro-8-oxo-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]-isoquinolin-13-yl)phenyl)-4-methoxybenzenesulfonamide (**4m**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-chlorobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide **3m** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.036 mmol), and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4m** as an orange solid (52 mg, 52%). Analytical data of **4m**: Mp: 230−232 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.23 (d, J = 7.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.37−7.33 (m, 3H), 7.26 (d, J = 7.0 Hz, 1H), 7.24 (d, J = 7.0 Hz, 1H), 7.16−7.11 (m, 3H), 7.01 (d, J = 6.5 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.71 (s, 1H), 6.44 (d, J = 9.0 Hz, 2H), 5.99 (s, 1H), 3.60 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 178.0, 162.9, 141.8, 139.0, 138.6, 137.6, 136.1, 135.5, 131.2, 130.5, 130.1, 129.1, 129.0, 128.9, 128.3, 127.73, 127.72, 125.5, 125.4, 25.2, 125.2, 124.2, 123.6, 122.7, 121.4, 120.5, 115.8, 113.8, 108.9, 55.3 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{21}ClN_2NaO_4S$ 587.0803, found 587.0822.

*4-Methoxy-N-(2-(11-nitro-8-oxo-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]isoquinolin-13-yl)phenyl)benzenesulfonamide (**4n**).* The reaction was performed according to general procedure with 4-methoxy-*N*-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl) benzenesulfonamide **3n** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (8 mg, 0.035 mmol), and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4n** as an orange solid (51 mg, 51%). Analytical data of **4n**: Mp: 255−258 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.32 (d, J = 7.0 Hz, 1H), 7.95−7.91 (m, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.56−7.52 (m, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.35−7.33 (m, 2H), 7.28−7.21 (m, 5H), 7.15 (d, J = 7.0 Hz, 1H), 6.62 (d, J = 2.0 Hz, 1H), 6.50 (s, 1H), 6.39−6.37 (m, 2H), 3.53 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 178.3, 162.9, 150.7, 144.8, 141.3, 138.6, 135.5, 131.0, 130.6, 129.0, 127.9, 125.8, 125.3, 124.4, 123.7, 123.2, 122.9, 121.7, 116.5, 114.1, 113.8, 55.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{22}N_3O_6S$ 576.1224, found 576.1224.

*N-(4-Fluoro-2-(8-oxo-8H-indeno[1′,2′:4,5]pyrrolo[2,1-a]-isoquinolin-13-yl)phenyl)-4-methylbenzenesulfonamide (**4o**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)-4-fluorophenyl)-4-methylbenzenesulfonamide **3o** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.38 mmol), and $Cu(OAc)_2$ (35 mg, 0.19 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4o** as an orange solid (49 mg, 49%). Analytical data of **4o**: Mp: 249−251 °C. IR (neat) ν_{max}: 2956, 2922, 2843, 1682, 1595, 1481, 1402, 1341, 1258, 1163, 1088, 1018, 887, 792, 722, 669, 547, 512 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.28 (d, J = 7.0 Hz, 1H), 7.85−7.82 (m, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.0 Hz, 1H), 7.32 (d, J = 7.0 Hz, 1H), 7.18−7.11 (m, 5H), 7.06−7.03 (m, 2H), 7.01 (d, J = 7.0 Hz, 1H), 6.95 (t, J = 7.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 2H), 6.52 (s, 1H), 6.20 (d, J = 7.0 Hz, 1H), 2.01 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 179.4, 143.8, 142.9, 139.4, 137.0, 136.0, 132.9, 131.2, 129.4, 129.1, 128.8, 128.4 (d, J = 70.5 Hz), 127.9, 126.6, 125.4, 125.3, 125.2, 125.1, 123.6 (d, J = 32.9 Hz), 122.4, 120.0, 117.9 (d, J = 79.9 Hz), 116.7 (d, J = 79.9 Hz), 116.1, 115.5, 21.5 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −115.5 (s) ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{22}FN_2O_3S$ 533.1330, found 533.1342.

*4-Methyl-N-(2-(8-oxo-8H-benzo[5′,6′]indeno[1′,2′:4,5]pyrrolo-[2,1-a]isoquinolin-15-yl)phenyl)benzenesulfonamide (**4p**).* The reaction was performed according to general procedure with N-(2-(3-(2-naphthoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3p** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (8 mg, 0.035 mmol), and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4p** as a yellow solid (60 mg, 60%). Analytical data of **4p**: Mp: 240−242 °C. IR (neat) ν_{max}: 3069, 2930, 2860, 1673, 1621, 1489, 1406, 1332, 1167, 1088, 904, 800, 765, 669, 565, 547 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.37 (d, J = 7.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.37−7.36 (m, 1H), 7.32−7.31 (m, 3H), 728−7.26 (m, 3H), 7.24−7.21 (m, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.72 (s, 1H), 6.62 (d, J = 8.0 Hz, 2H), 6.37 (s, 1H), 1.71 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 178.1, 143.7, 143.2, 138.8, 136.7, 136.1, 135.8, 135.5, 133.4, 132.0, 131.5, 130.3, 129.9, 129.3, 128.8, 128.5, 127.8, 126.9, 126.7, 125.3, 124.3, 123.8, 123.1, 121.7, 118.9, 115.1, 108.1, 21.0 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{36}H_{25}N_2O_3S$ 565.1580, found 565.1583.

*4-Methoxy-N-(2-(8-oxo-8H-benzo[5′,6′]indeno[1′,2′:4,5]pyrrolo-[2,1-a]isoquinolin-15-yl)phenyl)benzenesulfonamide (**4q**).* The reaction was performed according to general procedure with *N*-(2-(3-(2-naphthoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide **3q** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (8 mg, 0.34 mmol), and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in toluene at 120 °C for 36 h. After solvent removal, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **4q** as an orange solid (55 mg, 55%). Analytical data of **4q**: Mp: 254−256 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.27 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.56−7.49 (m, 3H), 7.39−7.36 (m, 4H), 7.32−7.31 (m, 2H), 7.29−7.21 (m, 3H), 7.13 (t, J = 7.5 Hz, 1H), 6.96 (s, 1H), 6.87 (d, J = 7.0 Hz, 1H), 6.40 (s, 1H), 6.30 (d, J = 9.0 Hz, 2H), 3.22 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 178.0, 162.7, 143.2, 138.7, 134.8, 135.7, 133.4, 131.5, 130.7, 130.2, 129.9, 129.4, 129.0, 128.7, 128.6, 128.3, 128.3, 127.7, 126.6, 125.8, 125.4, 125.3, 124.3, 123.7, 123.1, 121.4, 118.8, 115.0, 113.7, 108.2, 54.9 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{36}H_{24}N_2NaO_4S$ 603.1349, found 603.1358.

Procedure for scale up of 4a. A mixture of *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3a** (1.0 g, 1.9 mmol), $Pd(OAc)_2$ (90 mg, 0.36 mmol), and $Cu(OAc)_2$ (350 mg, 1.9 mmol) was weighed into a dry reaction tube. Dry toluene was added, and the reaction mixture was allowed to stir at 120 °C in an oil bath for 36 h. After completion of the reaction as indicated from the TLC, the solvent was removed under vacuum. The residue was then purified by column chromatography (20% ethyl acetate in hexane) to afford the desired product **4a** as an orange solid (800 mg, 80%).

Experimental Procedure for the Pd-Catalyzed CH Amination of Pyrrolo[2,1-*a*]isoquinolines toward Indolopyrrolo[2,1-*a*]-isoquinolines. A mixture of pyrrolo[2,1-*a*]isoquinoline **3** (1.0 equiv), $Pd(OAc)_2$ (5 mol %) and $Cu(OAc)_2$ (1.0 equiv) was weighed into a dry Schlenk tube. Dry DMSO was added, and the reaction mixture was stirred at 120 °C in an oil bath for 12 h under an O_2 atmosphere. After completion of the reaction as indicated from the TLC, water was added, and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and Characterization of Indolo[3′,2′:3,4]pyrrolo-[2,1-*a*]isoquinolines (5a−5j). *Phenyl(9-tosyl-9H-indolo[3′,2′:3,4]-pyrrolo[2,1-a]isoquinolin-8-yl)methanone (**5a**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3a** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (9 mg, 0.038 mmol), and $Cu(OAc)_2$ (35 mg, 0.19 mmol) in DMSO under O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **5a** as a pale yellow solid (54 mg, 54%). Analytical data of **5a**: Mp: 220−222 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.96 (d, J = 7.5 Hz, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.09−8.05 (m, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.0 Hz, 1H), 7.53−7.51 (m, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.36−7.29 (m, 2H), 7.08−7.05 (m, 3H), 6.77 (d, J = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. ^{13}C{^{1}H} NMR

https://doi.org/10.1021/acs.joc.3c00651
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(125 MHz, $CDCl_3$): δ 187.3, 144.6, 139.8, 132.6, 129.6, 129.0, 128.5, 127.6, 127.1, 125.5, 125.1, 125.0, 124.8, 121.1, 118.5, 113.2, 21.4 ppm. HRMS (ESI-Orbitrap) *m/z*: $(M + Na)^+$ calcd for $C_{32}H_{22}N_2NaO_3S$ 537.1243, found 537.1270.

*(9-((4-Methoxyphenyl)sulfonyl)-9H-indolo[3′,2′:3,4]pyrrolo[2,1-a]isoquinolin-8-yl)(phenyl)methanone (**5b**).* The reaction was performed according to general procedure with N-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methoxybenzenesulfonamide **3k** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and $Cu(OAc)_2$ (34 mg, 0.18 mmol) in DMSO under an O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **5b** as a yellow solid (53 mg, 53%). Analytical data of **5b**: Mp: 125−128 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.95 (d, *J* = 7.5 Hz, 1H), 8.52 (d, *J* = 8.0 Hz, 1H), 8.10−8.06 (m, 2H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.53−7.51 (m, 2H), 7.44−7.42 (m, 2H), 7.37−7.29 (m, 2H), 7.13 (d, *J* = 9.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 9.0 Hz, 2H), 3.54 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 187.3, 163.5, 144.1, 139.8, 136.4, 132.6, 129.6, 129.3, 129.1, 128.5, 127.6, 127.1, 126.0, 125.5, 125.1, 125.0, 124.8, 121.1, 118.5, 113.5, 113.2, 55.3 ppm. HRMS (ESI-Orbitrap) *m/z*: $(M + H)^+$ calcd for $C_{32}H_{23}N_2O_4S$ 531.1373, found 531.1388.

*(12-Fluoro-9-tosyl-9H-indolo[3′,2′:3,4]pyrrolo[2,1-a]isoquinolin-8-yl)(phenyl)methanone (**5c**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)-4-fluorophenyl)-4-methylbenzenesulfonamide **3o** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (2 mg, 0.0095 mmol), and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in DMSO under O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **5c** as a yellow solid (50 mg, 50%). Analytical data of **5c**: Mp: 282−284 °C. IR (neat) ν_{max}: 3069, 2982, 2912, 1690, 1630, 1577, 1394, 1332, 1158, 1088, 957, 792, 660, 590, 538 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.95 (d, *J* = 7.5 Hz, 1H), 8.36 (d, *J* = 8.5 Hz, 1H), 8.04−8.01 (m, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.72−7.70 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.10−7.03 (m, 3H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 2.08 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 187.2, 144.8, 139.6, 137.2, 132.7, 131.8, 129.6, 129.1, 128.6, 127.8 (d, *J* = 42.3 Hz), 127.2, 127.1, 125.0, 124.9, 124.6, 119.4 (d, *J* = 32.9 Hz), 113.6, 111.8, 111.6, 111.2, 108.0 (d, *J* = 51.7 Hz), 21.5 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −116.2 (s) ppm. HRMS (ESI-Orbitrap) *m/z*: $(M + H)^+$ calcd for $C_{32}H_{22}FN_2O_3S$ 533.1330, found 533.1342.

*(12-Bromo-9-tosyl-9H-indolo[3′,2′:3,4]pyrrolo[2,1-a]isoquinolin-8-yl)(phenyl)methanone (**5d**).* The reaction was performed according to general procedure with *N*-(2-(3-benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl)-4-bromophenyl)-4-methylbenzenesulfonamide **3r** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085 mmol), and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **5d** as a yellow solid (49 mg, 49%). Analytical data of **5d**: Mp: 215−218 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.93 (d, *J* = 7.0 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 8.14 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 7.0 Hz, 1H), 7.56−7.52 (m, 2H), 7.47−7.40 (m, 4H), 7.09 (t, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 2.10 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 187.2, 144.9, 142.7, 139.6, 132.8, 132.0, 129.6, 129.2, 128.6, 127.9, 127.6, 127.3, 127.1, 125.0, 124.6, 123.9, 119.5, 118.9, 113.6, 21.5 ppm. HRMS (ESI-Orbitrap) *m/z*: $(M + H)^+$ calcd for $C_{32}H_{22}BrN_2O_3S$ 593.0529, found 593.0549.

*p-Tolyl(9-tosyl-9H-indolo[3′,2′:3,4]pyrrolo[2,1-a]isoquinolin-8-yl)methanone (**5e**).* The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-methylbenzoyl)pyrrolo[2,1-*a*]-isoquinolin-1-yl)phenyl)benzenesulfonamide **3b** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in DMSO under O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **5e** as a yellow solid (45 mg, 45%). Analytical data of **5e**: Mp: 203−205 °C. IR (neat) ν_{max}: 2974, 2922, 2860, 1700, 1586, 1376, 1332, 1254, 1167, 1088, 1036, 809, 757, 669, 565, 538 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.87 (d, *J* = 7.5 Hz, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.0 Hz, 1H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.36−7.29 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H), 2.06 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 187.1, 144.5, 144.1, 143.9, 143.9, 143.4, 137.2, 135.9, 132.2, 129.8, 129.3, 129.3, 129.0, 129.0, 127.5, 127.5, 127.5, 127.4, 127.1, 125.9, 125.4, 125.4, 125.1, 125.0, 124.7, 121.11, 121.10, 118.4, 113.1, 113.0, 112.0, 21.8, 21.4 ppm. HRMS (ESI-Orbitrap) *m/z*: $(M + H)^+$ calcd for $C_{33}H_{25}N_2O_3S$ 529.1580, found 529.1580.

*[1,1′-Biphenyl]-4-yl(9-tosyl-9H-indolo[3′,2′:3,4]pyrrolo[2,1-a]-isoquinolin-8-yl)methanone (**5f**).* The reaction was performed according to general procedure with *N*-(2-(3-([1,1′-biphenyl]-4-carbonyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3c** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085 mmol), and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under an O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **5f** as a yellow solid (44 mg, 44%). Analytical data of **5f**: Mp: 205−207 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.92 (d, *J* = 7.5 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 7.5 Hz, 3H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.41−7.38 (m, 2H), 7.36−7.30 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H) 2.06 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 186.9, 144.6, 144.0, 140.3, 138.6, 136.1, 132.2, 130.2, 129.0, 128.8, 128.0, 127.6, 127.4, 127.2, 127.1, 125.9, 125.5, 125.1, 125.14, 125.07, 124.8, 121.2, 118.5, 113.2, 112.1, 111.1, 21.4 ppm. HRMS (ESI-Orbitrap) *m/z*: $(M + H)^+$ calcd for $C_{38}H_{27}N_2O_3S$ 591.1737, found 591.1740.

*(4-Chlorophenyl)(9-tosyl-9H-indolo[3′,2′:3,4]pyrrolo[2,1-a]-isoquinolin-8-yl)methanone (**5g**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-chlorobenzoyl)-pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3e** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and $Cu(OAc)_2$ (33 mg, 0.18 mmol) in DMSO under an O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **5g** as a yellow solid (40 mg, 40%). Analytical data of **5g**: Mp: 198−200 °C. IR (neat) ν_{max}: 2974, 2930, 2843, 1682, 1638, 1586, 1372, 1324, 1158, 1088, 809, 739, 660, 573, 538 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.97 (d, *J* = 7.5 Hz, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.54−7.59 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.36−7.30 (m, 2H), 7.06 (t, *J* = 8.5 Hz, 3H), 6.77 (d, *J* = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.8, 144.7, 144.0, 138.8, 136.6, 132.0, 131.0, 130.3, 129.2, 129.0, 128.9, 127.8, 127.7, 127.2, 127.1, 125.8, 125.6, 125.1, 125.0, 125.0, 125.0, 124.8, 121.2, 118.6, 113.4, 112.3, 110.8, 21.5 ppm. HRMS (ESI-Orbitrap) *m/z*: $(M + H)^+$ calcd for $C_{32}H_{22}ClN_2O_3S$ 549.1034, found 549.1032.

*(4-Fluorophenyl)(9-tosyl-9H-indolo[3′,2′:3,4]pyrrolo[2,1-a]-isoquinolin-8-yl)methanone (**5h**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-fluorobenzoyl)-pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3d** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and $Cu(OAc)_2$ (34 mg, 0.19 mmol) in DMSO under an O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **5h** as a pale yellow solid (39 mg, 39%). Analytical data of **5h**: Mp: 250−252 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.95 (d, *J* = 7.5 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 7.95−7.92 (m, 2H), 7.77−7.75 (m, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.55−7.51 (m, 1H), 7.37−7.30 (m, 2H), 7.11−7.06 (m, 4H), 6.77 (d, *J* = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 185.7, 144.6, 144.0, 136.3

https://doi.org/10.1021/acs.joc.3c00651
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(d, J = 84.6 Hz), 132.1 (d, J = 37.6 Hz), 130.3, 129.0, 127.7, 127.6, 127.1, 125.9, 125.6, 125.1, 125.0, 124.8, 121.1, 118.60, 118.56, 115.7 (d, J = 79.9 Hz), 113.3, 112.2, 110.8, 21.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −106.2 (s) ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{22}FN_2O_3S$ 533.1330, found 533.1343.

*(4-Bromophenyl)(9-tosyl-9H-indolo[3′,2′:3,4]pyrrolo[2,1-a]-isoquinolin-8-yl)methanone (**5i**).* The reaction was performed according to general procedure with *N*-(2-(3-(4-bromobenzoyl)-pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3s** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085 mmol), and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under an O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **5i** as a pale yellow solid (40 mg, 40%). Analytical data of **5i**: Mp: 210−212 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.97 (d, J = 7.5 Hz, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.56−7.51 (m, 3H), 7.37−7.30 (m, 2H), 7.08−7.05 (m, 3H), 6.77 (d, J = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.0, 144.7, 144.0, 138.8, 136.6, 131.8, 131.1, 129.0, 127.8, 127.7, 127.2, 127.1, 125.1, 125.0, 124.8, 121.2, 118.6, 113.4, 112.3, 110.7, 21.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{22}BrN_2O_3S$ 593.0529, found 593.0549.

*(2-Bromophenyl)(9-tosyl-9H-indolo[3′,2′:3,4]pyrrolo[2,1-a]-isoquinolin-8-yl)methanone (**5j**).* The reaction was performed according to general procedure with *N*-(2-(3-(2-bromobenzoyl)-pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3g** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085), and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under an O_2 atmosphere at 120 °C for 12 h. After workup, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the desired product **5j** as a yellow solid (41 mg, 41%). Analytical data of **5j**: Mp: 244−248 °C. IR (neat) ν_{max}: 2969, 2912, 2852, 1690, 1630, 1577, 1394, 1376, 1336, 1167, 1088, 800, 739, 660, 573, 530 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.96 (d, J = 7.5 Hz, 1H), 8.51 (d, J = 8.5 Hz, 1H), 8.09−8.05 (m, 2H), 7.92 (d, J = 7.5 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.52 (d, J = 6.5 Hz, 2H), 7.43−7.41 (m, 2H), 7.34−7.29 (m, 2H), 7.08−7.05 (m, 2H), 6.77 (d, J = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 187.3, 144.6, 143.9, 139.8, 136.4, 132.6, 132.2, 129.6, 129.1, 129.0, 128.5, 127.6, 127.6, 127.1, 125.9, 125.5, 125.1, 125.0, 124.8, 124.7, 121.1, 118.5, 113.2, 112.1, 111.0, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{22}BrN_2O_3S$ 593.0529, found 593.0542.

Experimental Procedure for the Pd-Catalyzed C−H Activation of Pyrrolo[2,1-*a*]isoquinolines toward Multiring Fused Azepines. A mixture of pyrrolo[2,1-*a*]isoquinoline **3** (1.0 equiv), $Pd(OAc)_2$ (5 mol %), and $Cu(OAc)_2$ (1.0 equiv) was weighed into a dry Schlenk tube. Dry DMSO was added, and the reaction mixture was stirred at 120 °C in an oil bath for 36 h under an O_2 atmosphere. After completion of the reaction as indicated from the TLC, water was added, and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the corresponding products.

Synthesis and Characterization of Fused Azepines (6a−6e). *(4-Nitrophenyl)(6-tosyl-6H-6,12a-diazacyclopenta[gh]pleiaden-12-yl)methanone (**6a**).* The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]-isoquinolin-1-yl)phenyl)benzenesulfonamide **3f** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in DMSO under an O_2 atmosphere at 120 °C for 36 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **6a** as a yellow solid (52 mg, 52%). Analytical data of **6a**: Mp: 260−262 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.25 (d, J = 7.5 Hz, 1H), 8.37 (d, J = 9.0 Hz, 2H), 7.91−7.88 (m, 3H), 7.73−7.70 (m, 3H), 7.41−7.32 (m, 3H), 7.10 (s, 1H), 7.07 (d, J = 7.5 Hz, 1H), 6.71 (d, J = 8.0 Hz, 2H), 6.61 (d, J = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 182.9, 145.3, 143.2, 136.0, 135.5, 135.2, 132.5, 132.4, 131.6, 130.2, 129.8, 128.4, 127.9, 127.5, 127.4, 126.3, 125.2, 123.8, 121.4, 119.4, 113.8, 21.3 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{21}N_3NaO_5S$ 582.1094, found 582.1088.

*(9-Bromo-6-tosyl-6H-6,12a-diazacyclopenta[gh]pleiaden-12-yl)(4-nitrophenyl)methanone (**6b**).* The reaction was performed according to general procedure with *N*-(4-bromo-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3t** (100 mg, 0.16 mmol), $Pd(OAc)_2$ (2 mg, 0.008 mmol), and $Cu(OAc)_2$ (29 mg, 0.16 mmol) in DMSO under an O_2 atmosphere at 120 °C for 36 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **6b** as a yellow solid (50 mg, 50%). Analytical data of **6b**: Mp: 257−259 °C. IR (neat) ν_{max}: 2912, 1708, 1621, 1481, 1341, 1237, 1158, 1088, 939, 809, 757, 669, 573, 530 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.25 (d, J = 7.5 Hz, 1H), 8.39 (d, J = 8.0 Hz, 2H), 7.90−7.86 (m, 3H), 7.75−7.74 (m, 2H), 7.56 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.43 (s, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.06 (s, 1H), 6.71 (d, J = 8.0 Hz, 2H), 6.63 (d, J = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 182.6, 145.2, 143.2, 136.9, 135.0, 131.2, 130.4, 130.0, 128.0, 127.4, 125.2, 123.9, 121.6, 121.3, 118.5, 117.9, 113.9, 21.3 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{32}H_{21}BrN_3O_5S$ 638.0380, found 638.0377.

*(9-Fluoro-6-tosyl-6H-6,12a-diazacyclopenta[gh]pleiaden-12-yl)(4-nitrophenyl)methanone (**6c**).* The reaction was performed according to general procedure with *N*-(4-fluoro-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3u** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085 mmol), and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under an O_2 atmosphere at 120 °C for 36 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **6c** as a yellow solid (53 mg, 53%). Analytical data of **6c**: Mp: 279−281 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.25 (d, J = 7.5 Hz, 1H), 8.38 (d, J = 8.0 Hz, 2H), 7.90−7.87 (m, 3H), 7.75−7.74 (m, 2H), 7.69−7.66 (m, 1H), 7.10−7.06 (m, 2H), 7.04 (s, 1H), 6.97 (d, J = 7.0 Hz, 1H), 6.71(d, J = 7.5 Hz, 2H), 6.63 (d, J = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 183.0, 149.7, 145.1, 143.4, 136.0, 135.4, 135.3, 135.1, 131.6, 130.4 (d, J = 61.1 Hz), 129.8, 128.0, 127.4, 126.4, 125.2, 123.8, 121.4, 115.4, 115.2 (d, J = 84.6 Hz), 114.0, 21.3 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −112.0 (s) ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{21}FN_3O_5S$ 578.1180, found 578.1176.

*(8-Fluoro-6-tosyl-6H-6,12a-diazacyclopenta[gh]pleiaden-12-yl)(4-nitrophenyl)methanone (**6d**).* The reaction was performed according to general procedure with *N*-(5-fluoro-2-(3-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl)phenyl)-4-methylbenzenesulfonamide **3v** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.0085 mmol), and $Cu(OAc)_2$ (31 mg, 0.17 mmol) in DMSO under an O_2 atmosphere at 120 °C for 36 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **6d** as a yellow solid (45 mg, 45%). Analytical data of **6d**: Mp: 180−182 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.25 (d, J = 7.5 Hz, 1H), 8.37 (d, J = 7.5 Hz, 2H), 7.89 (d, J = 7.5 Hz, 2H), 7.86−7.85 (m, 1H), 7.74−7.73 (m, 2H), 7.45 (d, J = 9.5 Hz, 1H), 7.29−7.26 (m, 1H), 7.10−7.07 (m, 2H), 7.04 (s, 1H), 6.72 (d, J = 7.5 Hz, 2H), 6.62 (d, J = 7.5 Hz, 2H), 2.06 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 182.9, 145.2, 143.5, 135.8, 131.8, 130.4, 130.2, 129.8, 128.0, 127.4, 126.5, 125.2, 123.8, 123.3, 121.1, 120.3, 118.6, 117.1, 113.8, 21.3 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ −113.4 (s) ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{20}FN_3NaO_5S$ 600.1000, found 600.1005.

*(3-Nitrophenyl)(6-tosyl-6H-6,12a-diazacyclopenta[gh]pleiaden-12-yl)methanone (**6e**).* The reaction was performed according to general procedure with 4-methyl-*N*-(2-(3-(3-nitrobenzoyl)pyrrolo-[2,1-*a*]isoquinolin-1-yl)phenyl)benzenesulfonamide **3w** (100 mg, 0.18 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and $Cu(OAc)_2$ (32 mg, 0.18 mmol) in DMSO under an O_2 atmosphere at 120 °C for 36 h. After workup, the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford the desired product **6e** as a yellow solid (51 mg, 51%). Analytical data of **6e**: Mp: 295−298 °C. IR (neat) ν_{max}: 2956, 2912, 2852, 1725, 1682, 1612, 1533, 1472, 1341,

https://doi.org/10.1021/acs.joc.3c00651
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1254, 1158, 1088, 817, 747, 660, 565, 530 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 9.25 (d, J = 7.5 Hz, 1H), 8.58 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 6.5 Hz, 1H), 7.74−7.71 (m, 4H), 7.41−7.32 (m, 3H), 7.13 (s, 1H), 7.07 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 8.0 Hz, 2H), 6.67 (d, J = 8.0 Hz, 2H), 2.05 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 182.3, 143.4, 141.4, 136.1, 135.2, 134.6, 133.5, 132.4, 131.6, 130.3, 130.1, 129.4, 128.4, 128.0, 127.5, 127.4, 126.3, 126.2, 125.2, 123.8, 121.3, 121.2, 119.5, 113.7, 22.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{21}N_3NaO_5S$ 582.1094, found 582.1107.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c00651.

Optimization studies, spectral data and crystallographic data (PDF)

Accession Codes

CCDC 2174937 and 2201867−2201869 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

SAB thank CSIR for research fellowship. JJ thanks CSIR (OLP-162539, HCP-029, MLP-064) and AICTE (GAP-161939) for financial assistance. The authors thank Prof. Mahesh Hariharan and Mr. Alex Andrews of IISER-Thiruvananthapuram for single crystal X-ray analysis. The authors also thank Mrs. Saumini Mathew and Mrs. Viji S. of CSIR-NIIST for recording NMR and mass spectra, respectively.

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Cite this: *Chem. Commun.*, 2024, **60**, 1674

Annulation reactions of electrophilic benzannulated heterocycles towards heteroacenes

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The current review describes different annulation strategies reported with electrophilic benzannulated heterocycles for accessing heteroacenes. For the past two decades, the chemistry of electrophilic benzannulated heterocycles was extensively investigated, and several dipolar cycloadditions, metal and organo-catalyzed transformations were introduced for the generation of fused heterocycles. In this review, we have collected all the reports where the annulation of electrophilic benzannulated heterocycles results in a fully aromatic system, *viz.* heteroacenes with tri-, tetra-, and pentacyclic rings. We reviewed every paper on the synthesis of fused heterocycles that was accessible and categorized the review into several parts based on the electrophilic benzannulated heterocycle used in the heteroacene synthesis such as electrophilic indole, electrophilic benzothiophene, and so forth. The generality and mechanistic postulates of each methodology are highlighted. In addition, we have also tried to feature the advantages or shortcomings of each method and have mentioned the possible applications of these methodologies for accessing heteroacenes for material applications.

Received 5th November 2023,
Accepted 16th January 2024

DOI: 10.1039/d3cc05449g

rsc.li/chemcomm

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Introduction

The creation of materials for organic semiconductors, light-emitting diodes, field-effect transistors, and photovoltaics has resulted from significant developments in the study of polycyclic aromatic hydrocarbons during recent decades.[1–4] When

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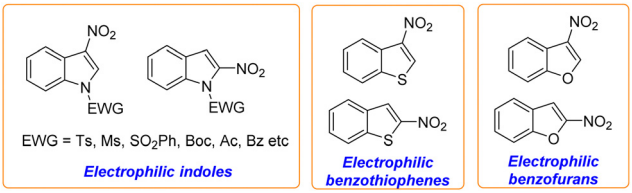
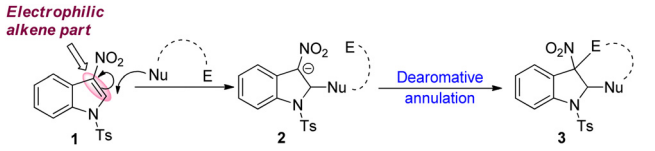


Fig. 1 Electrophilic benzannulated heterocycles.

one or more of the C–H bonds in an acene (polycyclic aromatic compound) is substituted by a heteroatom such as N, S, O, *etc.*, it becomes a heteroacene. Recent research has uncovered various heteroacenes containing S- or N-atoms that exhibit intriguing properties that could be used as functional materials.[5–7] These heteroacenes have several advantages over conventional polycyclic aromatic hydrocarbons, such as electron-richness, stability, and tunable properties.[8–11] This has led to the quest for simple synthetic methods for accessing conjugated heteroacenes.[12–14] In this review, we have attempted to collate all the reports from 1988 to date available on the synthesis of heteroacenes from electrophilic benzannulated heterocycles. The present review considers electrophilic benzannulated heterocycles such as indole, benzothiophene, and benzofuran, which are substituted with a nitro-group at the C-2 or C-3 position (Fig. 1).

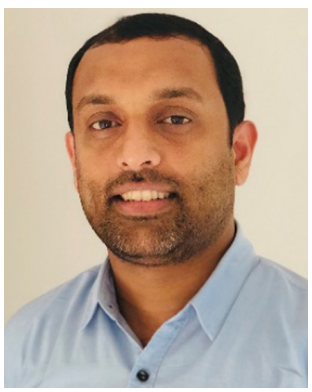
Indole is generally considered an electron-rich species due to the characteristic nucleophilicity at the 3rd position.[15] But, if the N-atom and the C-2 or C-3 position of indole are substituted with electron-withdrawing substituents, the nucleophilic character is overturned.[16] This is the case also with benzothiophene or benzofuran; the installation of electron-withdrawing groups on the C-2 or C-3 position will make them electrophilic. For example, if *N*-Ts-3-nitro-indole is considered, the C2=C3–NO_2 moiety acts as an electron-deficient alkene which can participate in annulation reactions (Scheme 1). When a reagent with both nucleophilic and electrophilic centres is allowed to react with *N*-Ts-3-nitro-indole, the nucleophilic end of a bis-reactive species will add to the C-2 position of electrophilic indole. The nucleophilic centre, thus formed at the C-3 position, will react with the electrophilic end of the bis-reactive species, leading to a dearomative annulation.



Scheme 1 Dearomative annulation of electrophilic benzannulated heterocycles.

One of the first reports on utilizing the reactivity of electrophilic benzannulated heterocycles came from Wenkert and co-workers, wherein these were treated as dienophiles in Diels Alder cycloadditions.[17] Later, Gribble, Chataigner, and others have extensively investigated the reactivity of electrophilic benzannulated heterocycles in dipolar cycloadditions,[18,19,21,25] tandem transformations,[20] metal-catalyzed reactions,[22–24,26] *etc.*, for generating fused non-aromatic heterocyclic moieties. In 2021, Chataigner and co-workers reviewed the reactions of 3-nitroindoles with electron-rich species from which fused indoline derivatives were generated *via* dearomative processes.[16]

Owing to the importance of heteroacenes, as mentioned previously, and also due to the presence of several reports on



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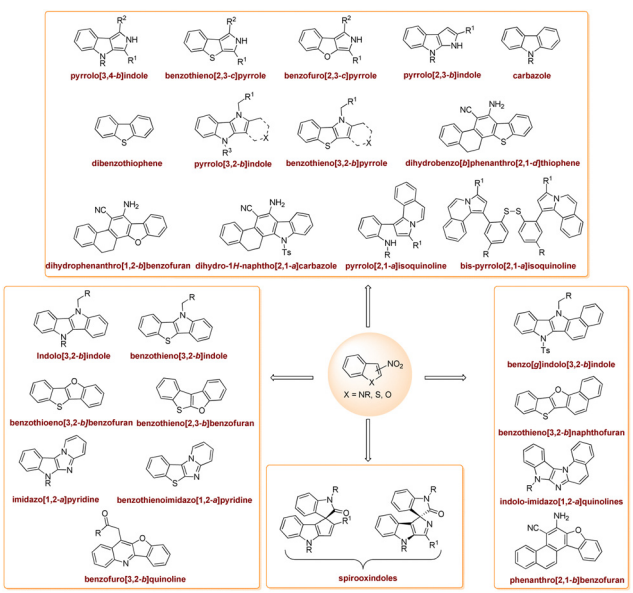


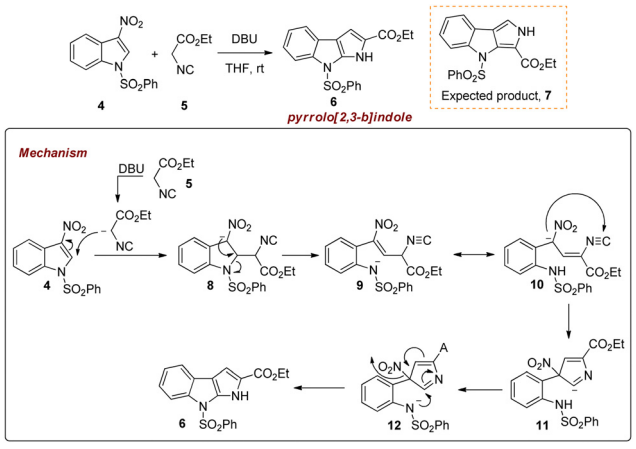
Fig. 2 Polyring fused heterocyclic moieties synthesized from electrophilic benzannulated heterocycles.

their synthesis from electrophilic benzannulated heterocycles since 1996, we have attempted to collect them in this review. Several groups, including ours, have carried out extensive research on finding annulation reactions of electrophilic benzannulated heterocycles towards polyring fused heteroaromatic systems. These include Barton–Zard reaction, 1,3-dipolar cycloaddition, [4+2] cycloadditions, multicomponent reactions, annulation processes, and several other tandem transformations. From these reactions, a number of polyring fused heterocyclic moieties, such as pyrroloindole, benzothienopyrrole, benzofuropyrrole, carbazoles, dibenzothiophene, pyrrolo[2,1-*a*]-isoquinoline, bis-pyrrolo[2,1-*a*]isoquinoline, dihydro-1*H*-naphtho-[2,1-*a*]carbazole, dihydrobenzo[*b*]phenanthro[2,1-*d*]thiophene, indoloindole, benzothienoindole, benzothienobenzofuran, benzofuroindole, benzofuro[3,2-*b*]quinoline, imidazo[1,2-*a*]pyridine, benzothienoimidazo[1,2-*a*]pyridine, spiroxindoles, phenanthro[2,1-*b*]benzofuran, *etc.* were synthesized (Fig. 2).

We have divided this review into different sections based on the starting electrophilic benzannulated heterocycle *i.e.* electrophilic indole, electrophilic benzothiophene and electrophilic benzofuran, leading to fused indole, benzothiophene, and benzofuran motifs, respectively. We have tried to analyze each reaction in detail and highlight the advantages and disadvantages.

Synthesis of fused indole heteroacenes starting from electrophilic indoles

The first publication on the synthesis of heteroacenes from electrophilic indoles came in 1996 when Gribble and coworkers reported the synthesis of pyrrolo[2,3-*b*]indole from electrophilic indole *via* an abnormal Barton–Zard reaction (Scheme 2).[27] The reagents, 3-nitro-*N*-(phenylsulfonyl)indole **4** was treated with ethyl isocyanoacetate **5** in the presence of DBU as base. In contrast to the expectation of product **7** [ethyl 4-(phenylsulfonyl)-2,4-dihydro-pyrrolo[3,4-*b*]indole-3-carboxylate], the authors isolated ethyl-8-(phenylsulfonyl)-1,8-dihydro-pyrrolo[2,3-*b*]indole-2-carboxylate **6** in 85% yield. The reaction starts with the addition of the anion of **5** to the C-2 of electrophilic indole. The anionic center at the C-3 of intermediate **8** then migrates resulting in the ring opening to form **9**. A rearrangement of the anionic center takes place in **9** forming **10** which then undergoes an intramolecular cyclization by the addition of the anionic center to the carbon end of the cyano-group forming **11**. A proton transfer takes place in **11** generating **12** in which the anionic N-atom attacks the C-2 of pyrrole ring resulting in the elimination of NO_2-group and formation of pyrrolo[2,3-*b*]indole **6**.

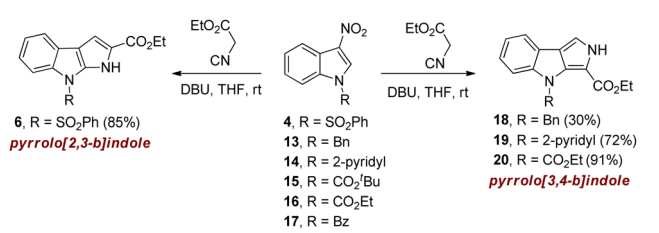


Scheme 2 Synthesis of pyrrolo[2,3-*b*]indole from electrophilic indole.

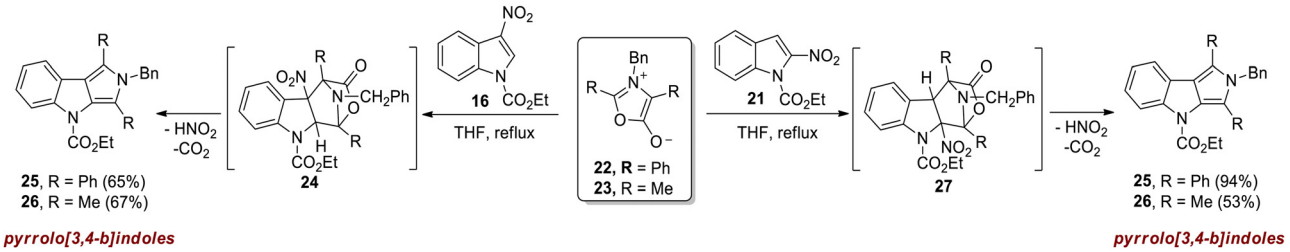
The unprecedented observation of formation of pyrrolo[2,3-*b*]indole from the reaction of electrophilic indole and ethyl isocyanoacetate in the presence of a base was later investigated in detail by the same group.[28] They hypothesized that the ring-opening observed in the Michael adduct **8** was due to the presence of a highly electron-withdrawing substituent such as phenylsulfonyl. In order to study the effect of the substituent on the *N*-atom of indole, they synthesized a variety of electrophilic indoles **4**, **13**–**17** with substituents such as SO_2Ph, Bn, 2-pyridyl, $CO_2{}^tBu$, CO_2Et and Bz. The electrophilic nitroindoles were then treated with ethyl isocyanoacetate in the presence of DBU as the base (Scheme 3). It was found that the electrophilic indoles with Bn, 2-pyridyl and CO_2Et as N-substituents furnished pyrrolo[3,4-*b*]indoles in satisfactory to good yields. The low yield of 30% for **18** was attributed to the decrease in electrophilicity of the starting electrophilic indole. In the case of *N*-benzoylindole **17**, the deprotection of the Bz-group was observed and the reaction with *N*-butoxycarbonylindole **15** failed to afford any product.

Later in 1998, the same group reported the synthesis of pyrrolo[3,4-*b*]indoles *via* a 1,3-dipolar cycloaddition reaction of Münchnones **22** and **23** (1,3-oxazolium-5-olates) with electrophilic indoles **16** and **21**.[29] The reaction occurs by the initial formation of the cycloadducts **24** and **27** from which HNO_2 and CO_2 is eliminated thereby resulting in aromatization (Scheme 4).

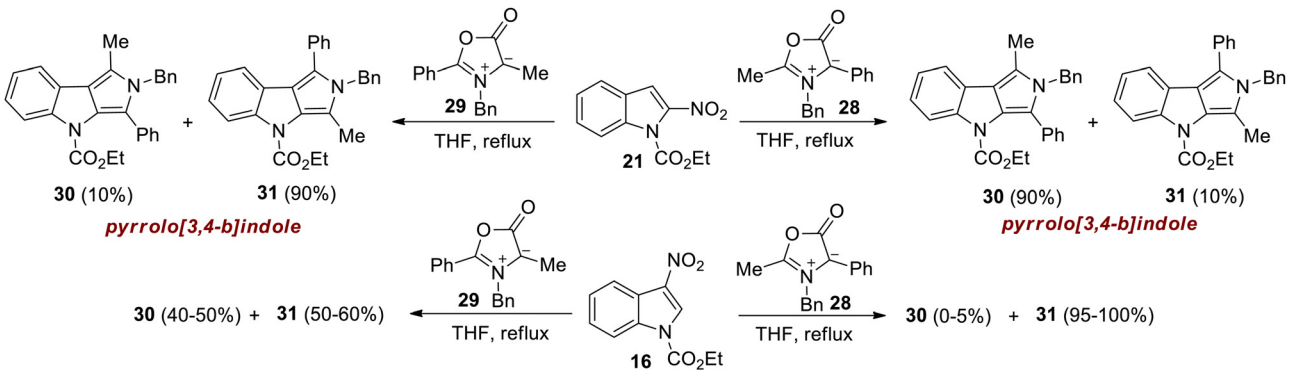
Unsymmetrical Münchnones were then utilized by the same group for the synthesis of pyrrolo[3,4-*b*]indoles from electrophilic indoles.[30] The reaction was carried out by treating various *N*-protected 2- and 3-nitroindoles with unsymmetrical mesoionic Münchnones **28** and **29** in THF at reflux conditions (Scheme 5). The reaction gave the corresponding products in good to excellent yields. The regioselectivity of the dipolar cycloaddition was found to be high, leading to even a single pyrrolo[3,4-*b*]indole isomer. Another interesting point was that the observed regioselectivity was opposite to that predicted by



Scheme 3 Synthesis of pyrrolo[2,3-*b*]indoles and pyrrolo[3,4-*b*]indoles from electrophilic indole.



Scheme 4 Synthesis of pyrrolo[3,4-*b*]indoles from the reaction of electrophilic benzannulated heterocycles with Münchnones.

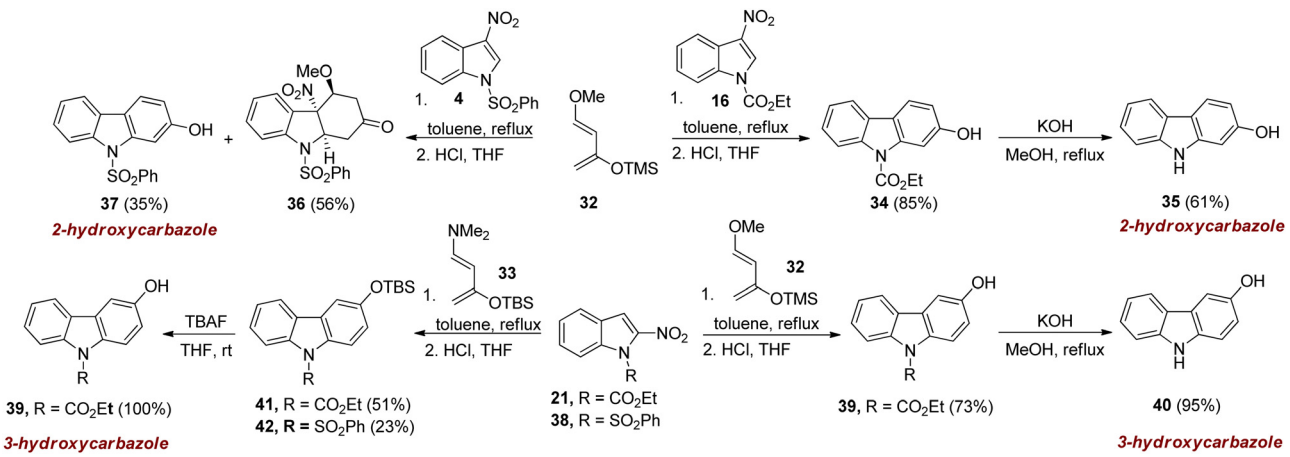


Scheme 5 Synthesis of pyrrolo[3,4-*b*]indoles from unsymmetrical Münchnones and electrophilic indoles.

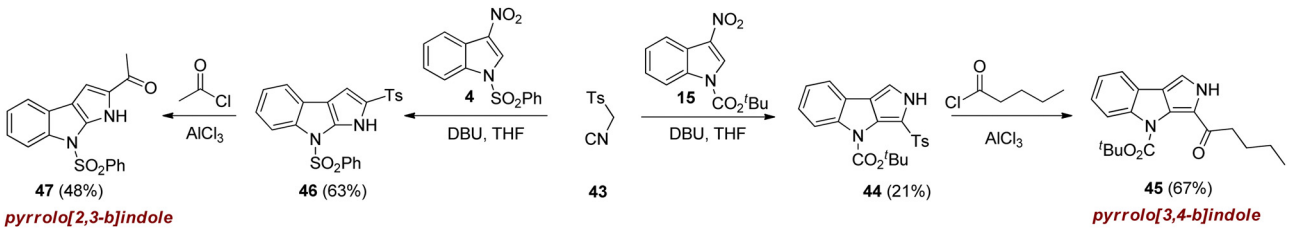
simple FMO theory. This observation was attributed to the favourable transition state π-interaction between the phenyl ring/enolate oxygen of the münchnone and the nitro group of the indole.

Another facile method for the synthesis of hydroxycarbazole was introduced in 2001 by Gribble and co-workers from electrophilic indole. The methodology utilized Diels–Alder reactions of 2- and 3-nitroindoles with Danishefsky's dienes[31] **32** and **33**. *N*-Ts-3-nitroindole **4** when treated with diene **32** in toluene followed by acid hydrolysis furnished a mixture of *exo* adduct **36** (56%) and carbazole **37** (35%). In the case of electrophilic indole **16**, only carbazole **34** (85%) was obtained without the isolation of any cycloadduct. Again, the cycloaddition of 2-nitroindole **21** with diene **32** gave carbazole **39** in 73% after acid hydrolysis. The reaction of diene **33** with *N*-carboxyethyl-2-nitroindole **21** afforded the carbazole **41** in 51%. Comparing the reactivity of 2-nitro-1-(phenylsulfonyl)indole **38** with either diene **32** or **33** showed that only the use of diene **33** permitted access to carbazole **42**, albeit in low yield (23%) (Scheme 6).

Gribble and co-workers extended their methodology for synthesizing pyrroloindoles for accessing further functionalized moieties. The dipolar cycloaddition of *N*-Boc-substituted-3-nitro-indole with TosMIC yielded pyrrolo[3,4-*b*]indole. The



Scheme 6 Diels–Alder cycloaddition of electrophilic indoles with Danishefsky's diene.



Scheme 7 Synthesis of acyl-substituted pyrroloindoles *via ipso*-acylation–detosylation reaction.

treatment of **44** with valeryl chloride resulted in an *ipso*-acylation–detosylation reaction furnishing acyl-substituted pyrrolo[3,4-*b*]indole **45**.[32] In the same way, acyl-substituted pyrrolo[2,3-*b*]indole **47** was synthesized from **46** which was obtained from the dipolar cycloaddition of *N*-SO_2Ph-substituted-3-nitro-indole with TosMIC (Scheme 7).

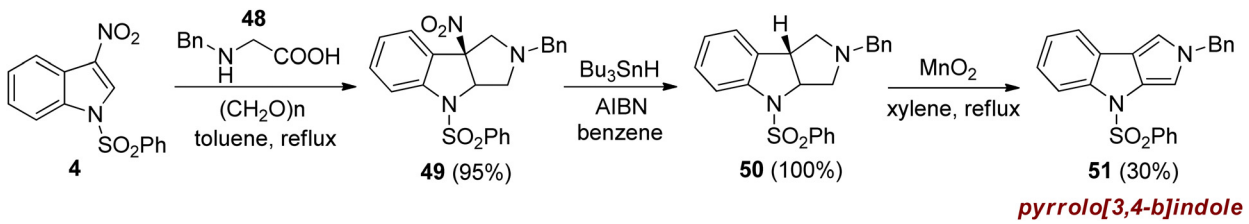
Another method was adopted by Gribble and coworkers for the synthesis of pyrrolo[3,4-*b*]indoles which involved a 1,3-dipolar cycloaddition of 3-nitroindoles with azomethine ylides.[33] The reaction of 3-nitro-indole **4** with the azomethine ylide (generated *in situ* from substituted glycine and paraformaldehyde) went smoothly, thereby affording the cycloadduct **49** in excellent yield (Scheme 8). The NO_2 group present in the cycloadduct was eliminated by treatment with Bu_3SnH/AIBN in benzene. Finally, pyrrolo[3,4-*b*]indole **51** was generated by MnO_2 mediated oxidation of **50** in refluxing xylene.

The above mentioned Schemes 2–8 depict the synthesis of pyrrolo[2,3-*b*]indole and pyrrolo[3,4-*b*]indole motifs which were seldom mentioned in literature prior to these reports. Most of the reactions gave the pyrroloindoles in satisfactory to good yields, and there is scope for utilizing these methodologies for accessing appropriately functionalized heteroacenes of choice for material applications.

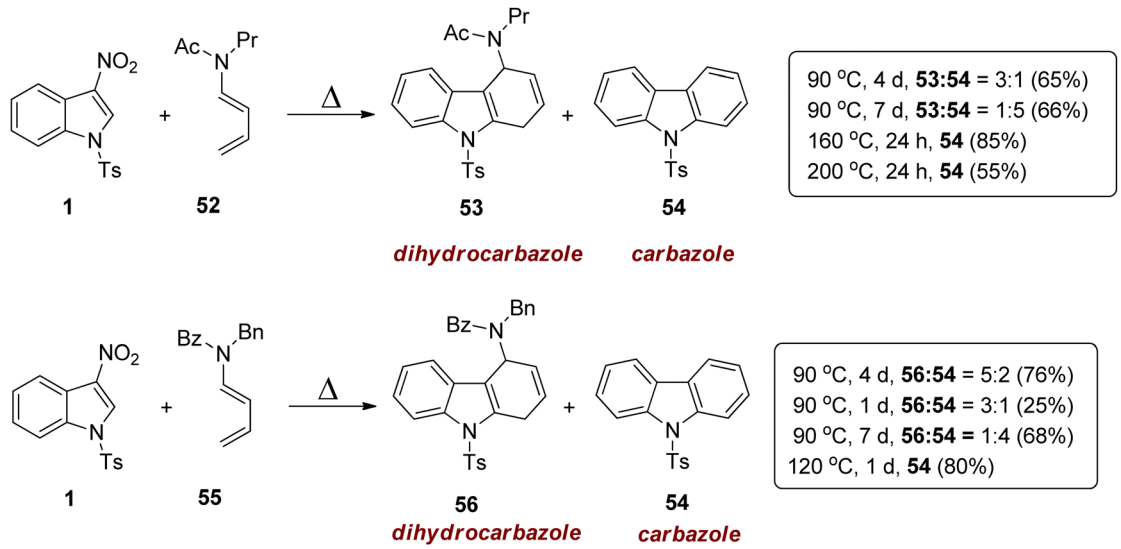
Mancini and coworkers reported the synthesis of intermediates of aspidosermine alkaloids *via* Diels–Alder reactions of electrophilic indole and dienamides.[34] They carried out reactions by treating 1-(*N*-acyl-*N*-alkylamino)-dienes **52** and **55** with *N*-Ts-3-nitroindole. When the diene **52** was treated with electrophilic indole **1** at 90 °C for 4 days, a mixture of *N*-Ts-dihydrocarbazole **53** and *N*-Ts-carbazole **54** was obtained in a ratio of 3 : 1 and in 65% total yield. On increasing the reaction time to 7 days, the product ratio of *N*-Ts-dihydrocarbazole **53**: *N*-Ts-carbazole **54** turned out to be 1 : 5 with overall 66% yield. The highest yield of 85% was obtained for *N*-tosyl carbazole **54** when the temperature was increased to 160 °C for 24 h. On further increasing the temperature to 200 °C, the yield of **54** was found to decrease to 55% due to detosylation of the *N*-tosyl carbazole (Scheme 9). Also, on treating diene **55** with 3-nitro-*N*-tosyl indole **1**, a mixture of *N*-Ts-dihydrocarbazole **56** and *N*-Ts-carbazole **54** was obtained. The excellent regioselectivity observed in the reaction was attributed to the alkylamino substituent in the diene and the powerful electron-withdrawing nitro group in the dienophile. Even if this methodology furnished the carbazole intermediate in the total synthesis of aspidosermine alkaloid, we believe that this synthetic route could also be utilized for the synthesis of substituted carbazoles by starting from suitably substituted electrophilic indoles, but this information is lacking in the report.

In 2009, Gómez *et al.* reported the reaction of nitroheterocycles such as 3-nitro-1-(*p*-toluenesulfonyl)indole **1** for the construction of carbazole derivatives by a tandem hetero Diels–Alder/[3,3] sigmatropic shift followed by elimination of the nitro group and *in situ* aromatization, as explained by computational studies (Scheme 10).[35a] The reaction between indole **1** and dienes **57–60** takes place efficiently under microwave irradiation in solvent-free conditions. Among this, a 65 : 35 mixture of 1-methoxy-1,3-cyclohexadiene **59** and 2-methoxy-1,3-cyclohexadiene **60** afforded carbazoles **61** and **62** in 61% yield exclusively, showing that the cycloaddition is regioselective. The authors have given an explanation for the formation of carbazoles from cyclohexadienes through a retro-Diels–Alder reaction[35b] or *in situ* elimination in the initially formed cycloadducts. For this explanation, the authors have not provided any theoretical support.

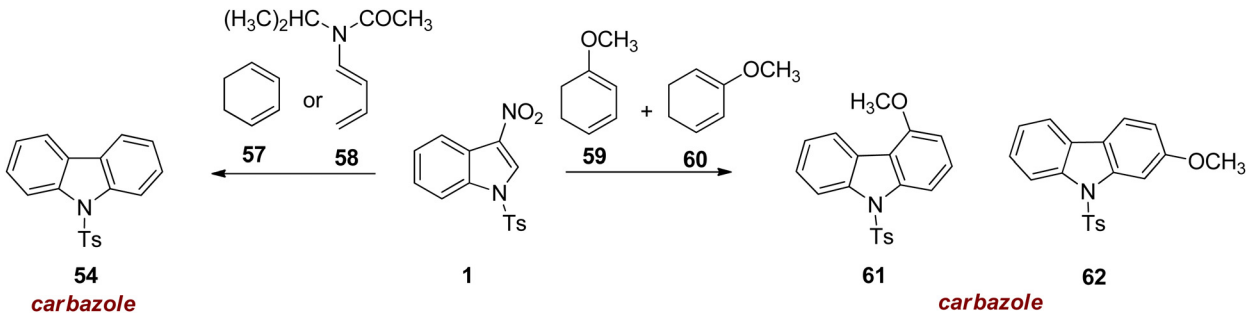
In 2015, Yuan and coworkers reported that the aminothiocarbamate catalyst **64** smoothly promoted the asymmetric Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles and 3-nitroindoles.[36] This reaction provides a method for the preparation of diverse and enantioenriched polycyclic spirooxindoles in high yields and excellent diastereo- and enantioselectivities. The potential utility of the developed



Scheme 8 Synthesis of pyrrolo[3,4-*b*]indole.



Scheme 9 Diels–Alder reactions of *N*-tosyl-3-nitroindole and dienamides.

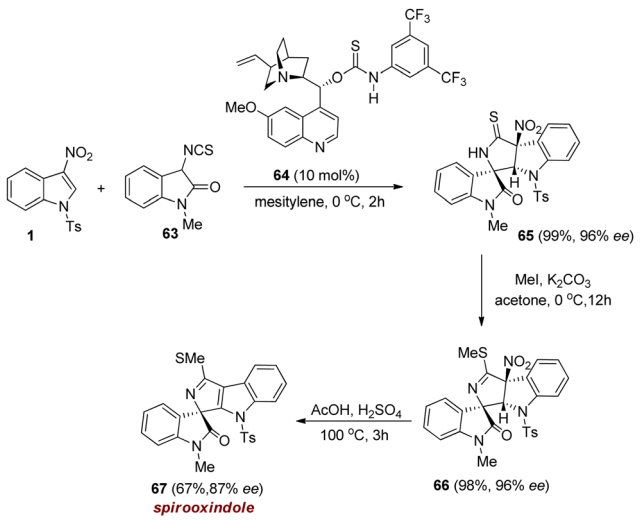


Scheme 10 Microwave-assisted reactions of nitroindoles with dienes.

method was shown by performing the reaction on a gram scale and the synthetic transformations of the products into other spirocyclic oxindoles (Scheme 11).

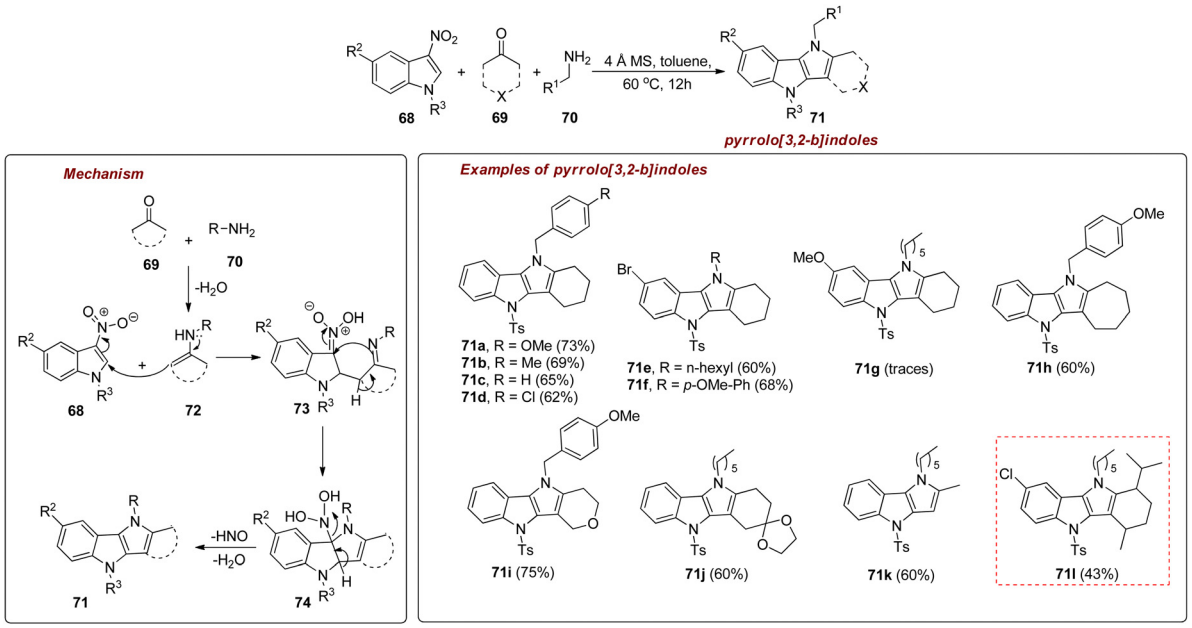
Multicomponent reactions have gained widespread attention for the stereoselective formation of several bonds in one pot.[37,38] These reactions have found useful applications in the construction of valuable organic molecules as well as in the construction and functionalization of indoles.

In 2017, we came across a multicomponent reaction involving an enolizable ketone, a primary amine and an *N*-protected 3-nitroindole for the synthesis of pyrrolo[3,2-*b*]indole.[39] Under the optimized conditions which consisted of 4 Å M.S., toluene as the solvent at 60 °C, the reaction was found to be general for a range of amines (aliphatic and aromatic), cyclic and acyclic ketones and electrophilic indoles affording the corresponding pyrroloindoles in moderate to good yields (60–89%) (Scheme 12). In this methodology, we could also use natural products containing an enolizable ketone part or an amine for accessing the corresponding heteroacene **71**. The first step of the reaction involves the Michael addition of enamine **72** to the C-2 position of the 3-nitroindole **68** to form intermediate **73**, which is then followed by cyclization to furnish pyrroline



Scheme 11 Reaction of 3-isothiocyanato oxindoles with 3-nitroindoles *via* asymmetric Michael/cyclization cascade reaction.

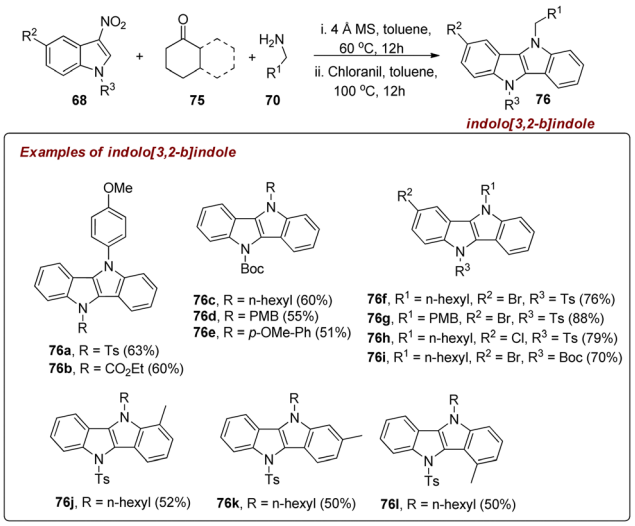
intermediate **74**. Subsequent elimination of hyponitrous acid and water resulted in the final compound **71** (Scheme 12).



Scheme 12 A multicomponent reaction towards pyrrolization of indoles.

Despite creating an extensive library of functionalized pyrrolo[3,2-*b*]indoles, a drawback of this method is its necessity to use an excess of both amine and ketone (2 equiv.).

Then, we introduced a sequential multicomponent reaction-oxidation approach towards the synthesis of indolo[3,2-*b*]indole motifs.[40d] The reaction was planned in such a way that the intermediate pyrrolo[3,2-*b*]indole formed from the multicomponent reaction could be oxidized *in situ* using chloranil (Scheme 13). The synthesized indoloindoles were also subjected to synthetic modifications in order to evaluate their photophysical properties. By using this strategy, we could make unsymmetrical indolo[3,2-*b*]indoles, a class of compound for which methods were found to be scarce prior to this report.[40a–c]

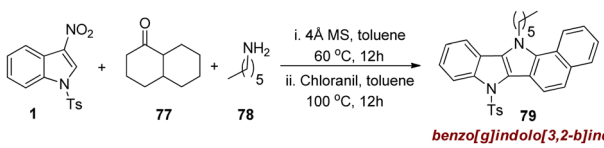


Scheme 13 A one-pot approach towards the synthesis of indolo[3,2-*b*]indole.

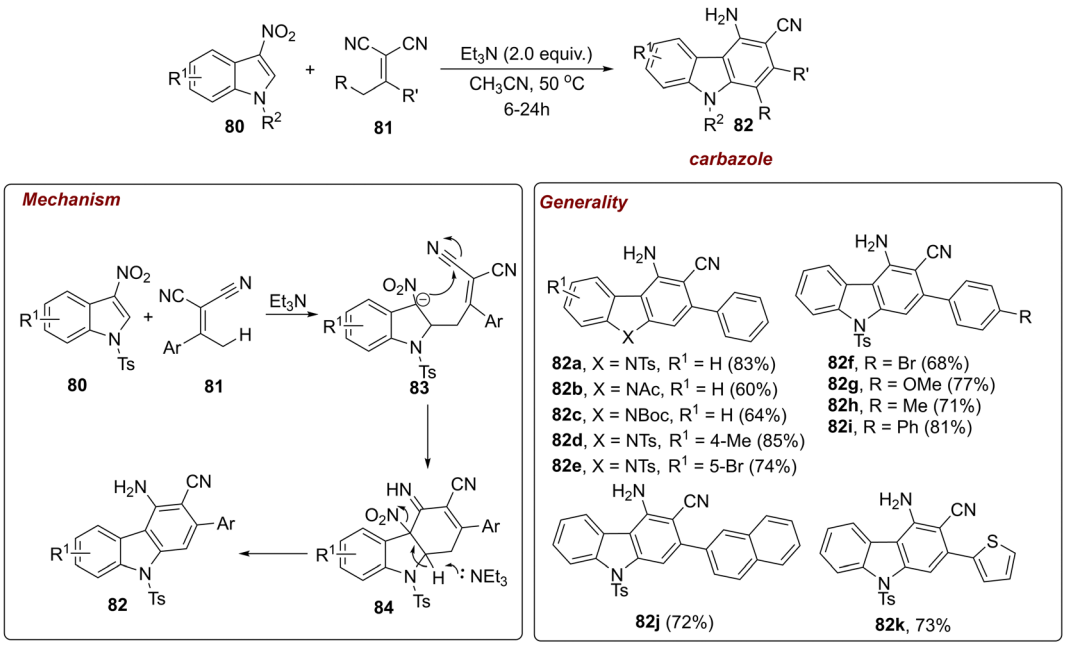
In addition, we could also synthesize halogenated indolo[3,2-*b*]indole moieties, which were further functionalized for dye-sensitized cell (DSC) applications.[41]

Under the same reaction conditions, benzo[*g*]indolo[3,2-*b*]indole was also synthesized using 1-decalone as the enolizable ketone (Scheme 14).

Yang and co-workers showed that carbazole-4-amine derivatives could be synthesized *via* a [4+2] annulation between 3-nitroindoles and alkylidene malononitriles.[42] Best results were obtained when Et_3N (2.0 equiv.) was used as the base in acetonitrile at 50 °C for 24 h (Scheme 15). The reaction was found to be general with a variety of substituted alkylidene malononitriles with aryl and heteroaryl substituents. The reaction was found to be inferior with alkylidene malononitriles derived from non-aromatic ketones such as acetone and cyclohexanone. A plausible mechanism was proposed for the reaction, which involves three main steps: deprotonation of alkylidine malononitrile, Michael addition/cyclization of the resulting anion with 3-nitroindole and isomerization of the resulting intermediate as shown above (Scheme 15). One main advantage of this methodology is that electrophilic indoles with electron-donating substituents also furnished the products in good yields which is seldom observed in the reports in this review.



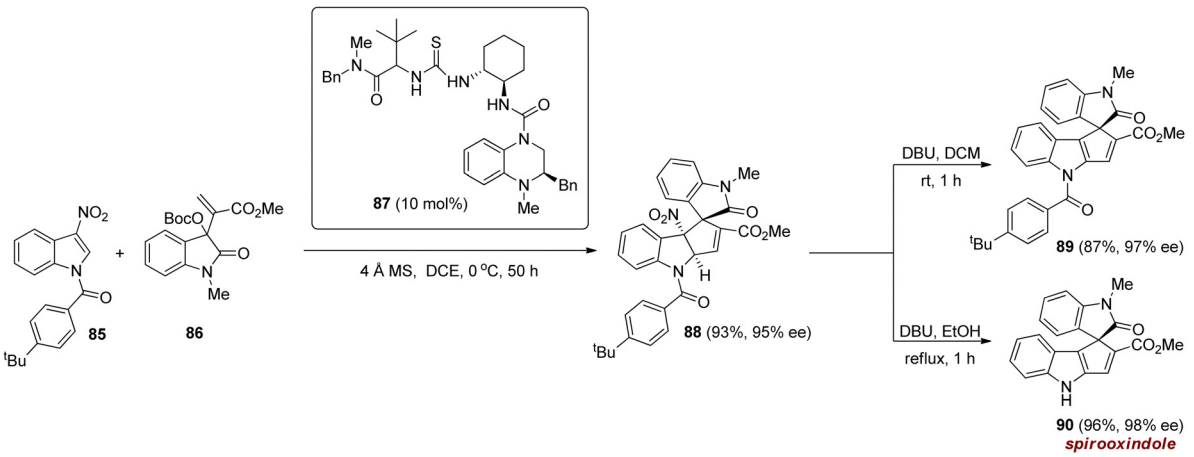
Scheme 14 A one-pot approach towards the synthesis of benzo[*g*]indolo[3,2-*b*]indole.



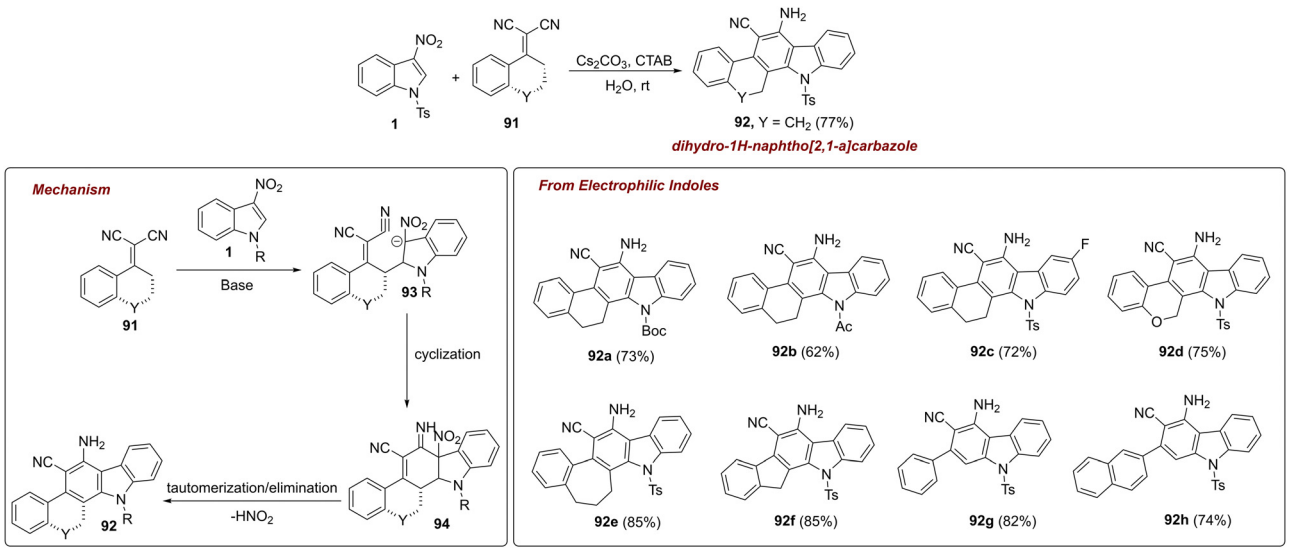
Scheme 15 [4+2] annulation of electrophilic 3-nitroindoles with alkylidene malononitrile.

In 2020, Mei *et al.* reported the synthesis of polycyclic spirooxindoles *via* [3+2] annulations of isatin-derived Morita–Baylis–Hillman (MBH)-carbonates and 3-nitroindoles.[43] Efforts were made to improve the stereoselectivity of the reaction using novel chiral DMAP-thiourea bifunctional catalyst **87**. Furthermore, Tian and coworkers reported a single example where the spirooxindole **88** upon treatment with DBU in DCM at room temperature, led to the formation of **89**, with the elimination of HNO_2 in 87% yield and 97% ee. When the reaction was conducted with DBU in EtOH at reflux, the acyl group was removed to give **90** with 96% yield and 98% ee (Scheme 16).

Yuan and coworkers developed an eco-friendly method for the synthesis of dibenzoheterocyclic compounds *via* a Michael addition process of electrophilic 3-nitroindoles with α,α-dicyanoalkenes.[44] This [4+2] annulation reaction took place in the presence of 1 equiv. of Cs_2CO_3 and 5 mol% of CTAB in water at room temperature (Scheme 17). A plausible mechanism was proposed in which the first step involves the deprotonation of α,α-dicyanoalkene in presence of a base to form a vinylogous carbanion, which is then followed by the Michael addition of this vinylogous carbanion onto the *N*-tosyl-3-nitroindole to form the corresponding intermediate **93**, which then undergoes cyclization by the attack of the carbanion present in it to one of the cyano groups affording the [4+2] annulation product **94**. Finally, the molecular tautomerization and subsequent elimination of nitrous acid in intermediate **94** furnished the desired carbazole derivatives. The scope of the reaction was expanded to different 3-nitroindoles bearing various substituents on the N-atom as well as with halogen-substituted ones. The reaction was also found to be compatible



Scheme 16 [3+2] annulations of 3-nitroindoles with isatin-derived MBH-carbonates.

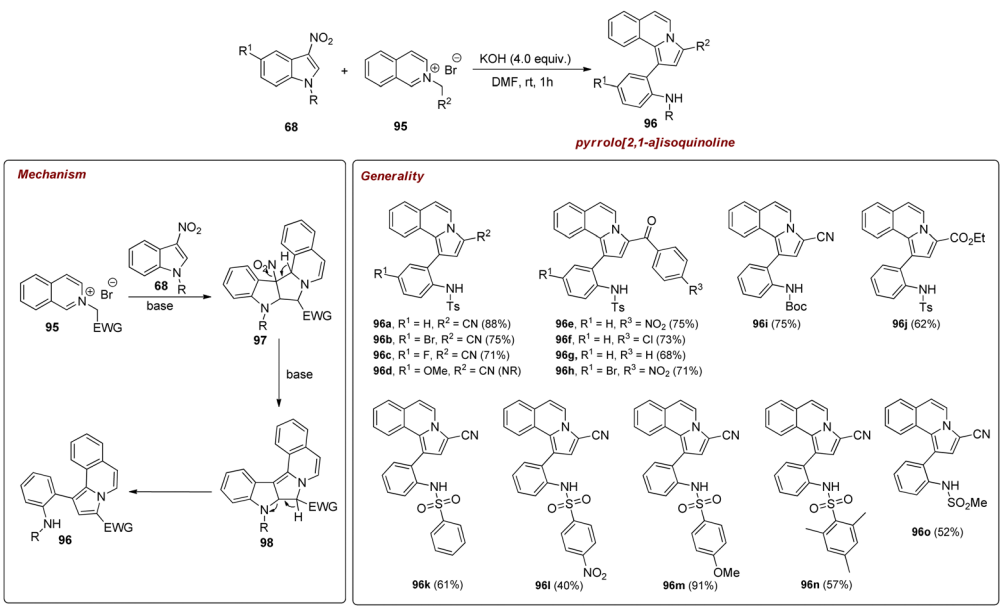


Scheme 17 [4+2] annulation of 3-nitroindoles with α,α-dicyanoalkenes.

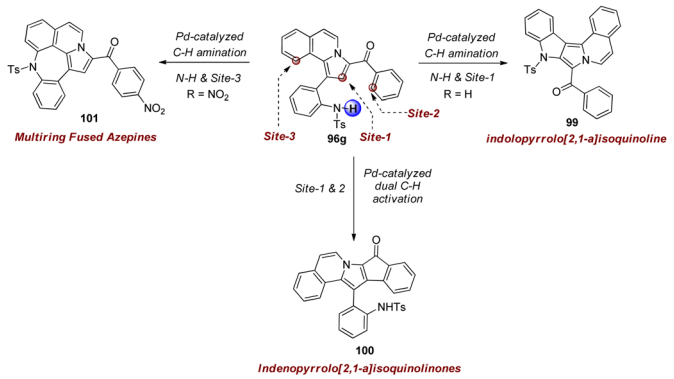
with various cyclic and acyclic α,α-dicyanoalkenes affording the corresponding carbazole derivatives.

Our attempt to perform 1,3-dipolar cycloaddition of isoquinolinium ylides with electrophilic indoles resulted in the unprecedented formation of pyrrolo[2,1-*a*]isoquinolines.[45] The reaction of 3-nitroindole **68** with 2-(cyanomethyl)isoqunolin-2-ium bromide **95** in the presence of base in DMF at room temperature delivered pyrrolo[2,1-*a*]isoquinoline **96** through a domino dipolar cycloaddition – ring opening process. The mechanism of the reaction involves the deprotonation of the activated methylene group by base to generate the *N*-ylide which then undergoes 1,3-dipolar cycloaddition with the electrophilic indole counterpart to give cycloadduct **97**. Elimination of HNO_2 from **97** followed by aromatization leading to a strain induced C–N bond cleavage furnishes pyrrolo[2,1-*a*]isoquinolines **96** (Scheme 18). The scope of this domino strategy was tested using various substituted 3-nitroindoles and also by changing the electron withdrawing group on the Nitrogen atom of the isoquinolinium salt. A slight variation in the yield of the products was observed by changing the substituent on the sulfonyl group. A library of pyrrolo[2,1-*a*]isoquinolines also was synthesized by employing different isoquinolinium bromides in the reaction, and in all cases, products were obtained in good yields (Scheme 18).

Later, we looked into the possibility of synthesizing complex polyring fused *N*-heterocycles *via* a palladium-catalyzed site-selective C–H functionalization of the above obtained pyrrolo[2,1-*a*]isoquinolines (Scheme 19).[46] We could identify



Scheme 18 Synthesis of pyrrolo[2,1-*a*]isoquinolines from electrophilic indoles.



Scheme 19 Pd-catalyzed site selective C–H functionalization towards polyring fused *N*-heterocycles.

three sites for C–H functionalization and a *N*-center on the 5-benzoylpyrrolo[2,1-*a*]isoquinoline scaffold **96g**. At first, the activation of C–H bonds at site-1 and site-2 of **96g** was effected by a Pd-catalyzed cross-dehydrogenative coupling [$Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv.), toluene, 120 °C, 36 h] to synthesize 8*H*-indeno-pyrrolo[2,1-*a*]isoquinolinone **100**. An oxygen induced palladium catalyzed selective C–H amination [$Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv.), DMSO, O_2, 120 °C, 12 h] in the same substrate **96g** furnished a pentacene, 9*H*-indolo-pyrrolo[2,1-*a*]isoquinoline **99**. Finally, the site selective C–H amination in 5-(4-nitrobenzoyl)pyrrolo[2,1-*a*]isoquinoline led to the formation of a multiring fused benzazepine scaffold **101**. A broad substrate scope further establishes the potential of this method for accessing complex polyring fused heterocycles.

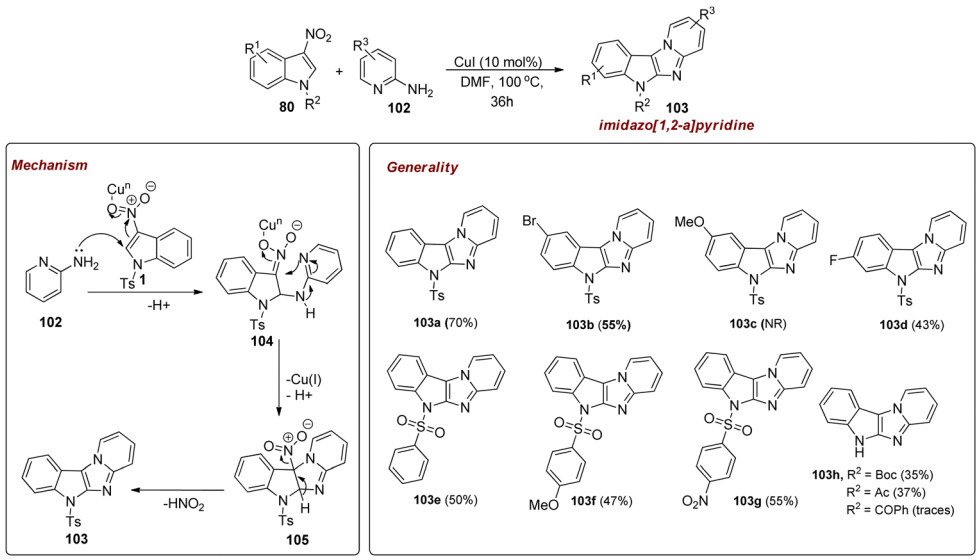
Recently, as a continuation of our work on the synthesis of novel heteroacenes, we reported a copper-catalyzed annulation of electrophilic benzannulated heterocycles with 2-aminopyridines and 2-aminoisoquinolines. The reaction of *N*-protected 3-nitroindoles with 2-aminopyridines in the presence of CuI afforded indole-fused imidazo[1,2-*a*]pyridines.[47]

The reaction proceeds through Michael addition of aminopyridines to the C-2 of the Cu-coordinated 3-nitroindoles and then the attack of pyridine nitrogen to C-3 along with protodemetallation to give **105**. Elimination of HNO_2 and subsequent aromatization leads to the product (Scheme 20). Halogenated electrophilic indoles and various other electron-withdrawing groups on the N-atom of indole successfully tolerated the reaction conditions. It was observed that Boc, Ac and benzoyl groups on N-atom of indole led to the formation of corresponding indolo-imidazo[1,2-*a*]quinolines in which *N*-substituents were cleaved. We could prove the suggested mechanism by isolating the annulated intermediate **105**, and we also demonstrated the applicability of the method in a gram scale.

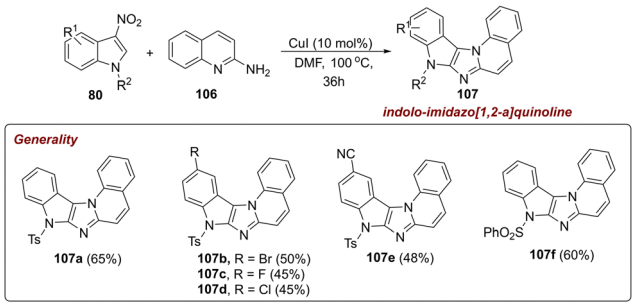
The copper catalyzed annulation protocol could also be extended to obtain pentacenes.[47] Electrophilic indoles on treatment with 2-aminoquinoline in the presence of CuI in DMF proceeded to afford indolo-imidazo[1,2-*a*]quinolines (Scheme 21). Finally, we also evaluated basic photophysical properties of these heteroacenes to assess their suitability in material applications.

Synthesis of benzothiophene fused heteroacenes starting from electrophilic benzothiophene

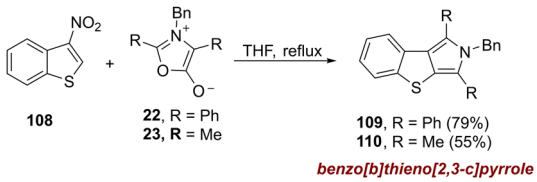
By following the same approach for the 1,3-dipolar cycloaddition reaction of electrophilic indoles with munchnones reported in 1998, Gribble and coworkers[29] synthesized other heteroacenes such as benzo[*b*]thieno[2,3-*c*]pyrroles[14c] **109** from 3-nitrobenzothiophene **108** (Scheme 22). In literature, the methods to access heteroacenes of this kind are rare and this



Scheme 20 Synthesis of indole-fused imidazo[1,2-*a*]pyridines from electrophilic indoles.



Scheme 21 Synthesis of indole-fused imidazo[1,2-*a*]quinolines from electrophilic indoles.

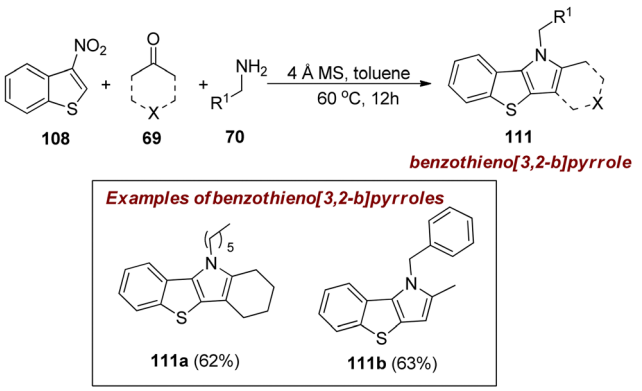


Scheme 22 Synthesis of benzo[*b*]thieno[2,3-*c*]pyrroles from the reaction of 3-nitrobenzothiophene and Münchnones.

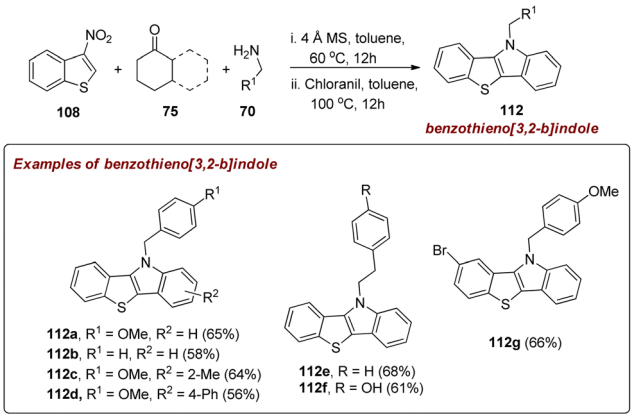
can be used for designing materials with benzothiophene fused heteroacenes.

In 2017, as discussed earlier, the multicomponent reaction of other electrophilic benzannulated heterocycles[39] such as 3-nitrobenzothiophene was carried out using the same conditions with an enolizable ketone and a primary amine towards the synthesis of benzothieno[3,2-*b*]pyrroles (Scheme 23). The generality of this method is limited and the applicability in gram scale was not demonstrated.

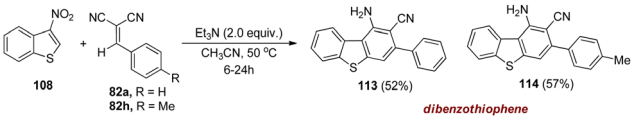
Later, the methodology was also extended to the synthesis of benzothieno[3,2-*b*]indole when starting from 3-nitrobenzothiophene *via* a one-pot multicomponent approach[40] using chloranil as the oxidizing agent, as discussed in the previous section for 3-nitroindoles (Scheme 24). The one-pot process worked well with different substituted cyclohexanones as well as with various anilines. The reactivity of



Scheme 23 A multicomponent reaction towards pyrrolization of benzothiophenes.



Scheme 24 A one-pot approach towards the synthesis of benzothieno[3,2-*b*]indole.

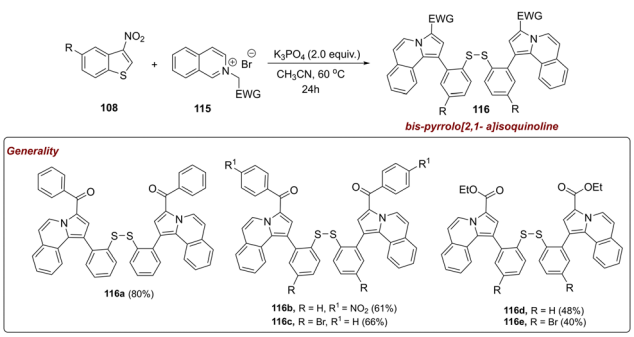


Scheme 25 [4+2] annulation of electrophilic 3-nitrobenzothiophene with alkylidene malononitrile.

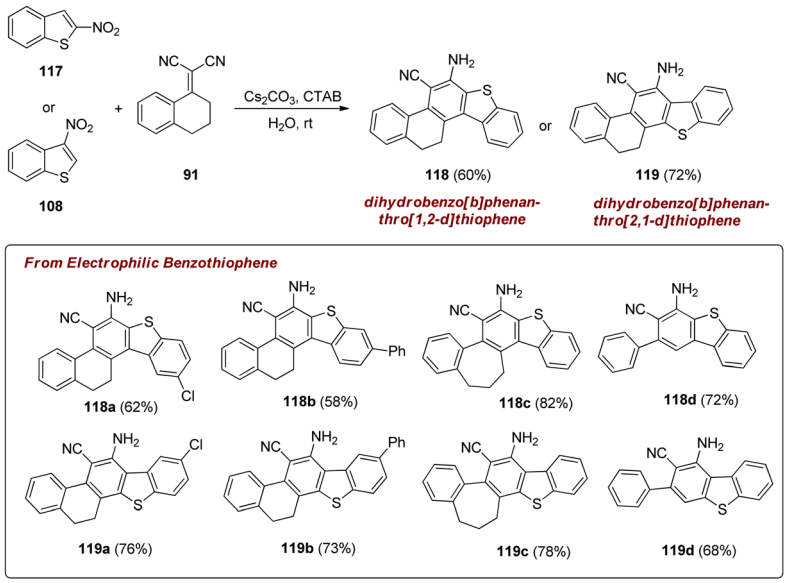
naturally available amines such as tyramine was also checked toward the annulation reaction with the aim of synthesizing biologically active benzothienoindoles **112**. By following this developed methodology, we synthesized several dyes based on the benzothieno[3,2-*b*]indole core for dye sensitized solar cell applications and the best dye gave a power conversion efficiency of 4.11%.[41]

Yang *et al.* also synthesized dibenzothiophenes **113–114** *via* a [4+2] annulation between 3-nitrobenzothiophene and alkylidene malononitriles (Scheme 25).[42] The mechanism for the reaction is discussed in detail in the above section (Scheme 15).

In 2021, in our work, electrophilic benzothiophenes were also applied as substrates in the domino dipolar cycloaddition reaction with isoquinolinium salts.[45] In this case, formation of bis-pyrrolo[2,1-*a*]isoquinolines linked with an S–S bond were observed which was formed *via* the *in situ* oxidation of the thiol intermediate (Scheme 26). The scope of the reaction was



Scheme 26 1,3 dipolar cycloaddition of electrophilic benzothiophenes with isoquinolinium bromides.



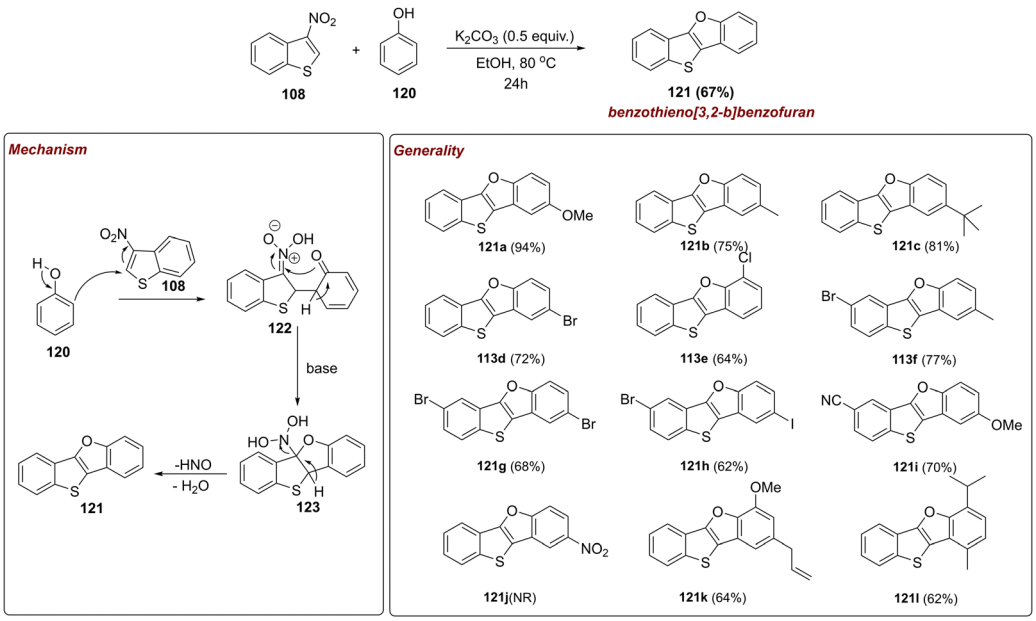
Scheme 27 [4+2] annulation of 3-nitrobenzothiophene with α,α-dicyanoalkenes.

explored with phenylethanone and ethoxycarbonyl group substituents on the isoquinolinium *N*-atom affording the corresponding bis-pyrrolo[2,1-*a*]isoquinolines **116a–116e** in good yields.

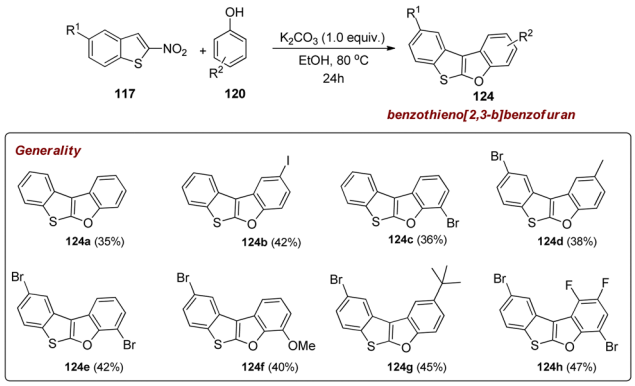
As discussed earlier by Yuan and coworkers,[44] the Michael addition process of electrophilic benzannulated heterocycle with α,α-dicyanoalkenes also worked well with both 2-nitro and 3-nitrobenzothiophenes leading to the synthesis of dibenzoheterocyclic compounds (Scheme 27).

Under the standard conditions, both these benzothiophenes substituted with electron-donating and electron-withdrawing groups reacted smoothly with α,α-dicyanoalkenes **91** affording the corresponding products. Also various α,α-dicyanoalkenes derived from cyclic aryl ketones were able to react well with both 2- and 3-nitrobenzothiophenes furnishing the pentacyclic heterocyclic compounds.

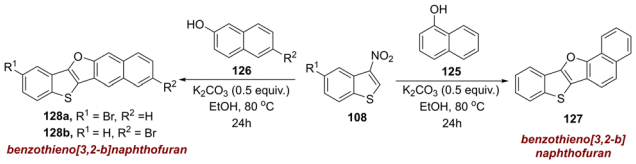
Ensuing the potential of benzothienobenzofurans in the field of materials and lack of easy routes to access them, led us to explore the reaction of electrophilic benzothiophenes with phenols.[48] As expected, reaction of 3-nitrobenzothiophene **108** with phenol in the presence of KOH as base delivered benzothieno[3,2-*b*]benzofuran. The methodology was found to be general for a range of substituted phenols and 3-nitrobenzothiophenes.



Scheme 28 Synthesis of benzothieno[3,2-*b*]benzofurans from electrophilic benzothiophenes.



Scheme 29 Synthesis of benzothieno[2,3-*b*]benzofurans from electrophilic benzothiophenes.



Scheme 30 Synthesis of benzothieno[3,2-*b*]naphthofurans from electrophilic benzothiophenes.

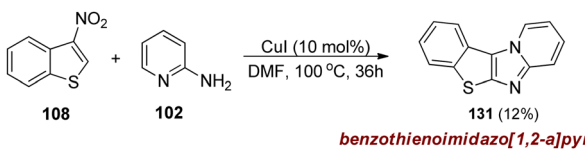
Amongst various benzothieno[3,2-*b*]benzofurans synthesized, the bis-halogenated ones **121g–121h** stand out as they could be further functionalized for tuning the properties for material application (Scheme 28). It was also found that electron releasing substituents on phenol had a positive influence on the reaction, whereas electron withdrawing substituents like $-NO_2$ failed to furnish the product. The annulation reaction is initiated by the addition of phenol to C-2 of 3-nitrobenzothiophene to give intermediate **122** which then undergoes an intramolecular cyclization followed by elimination of hyponitrous acid and water to deliver the desired product **121** (Scheme 28).

The easy access of benzothiophene[3,2-*b*]benzofurans prompted us to check the reactivity of 2-nitrobenzothiophenes as well in the base mediated annulation strategy. Reaction of 2-nitrobenzothiophenes with phenols under the developed conditions rendered benzothieno[2,3-*b*]benzofurans (Scheme 29).[49] The reactivity of 2-nitrobenzothiophene was checked with different substituted phenols and we were also able to introduce various halogens on the benzothieno[2,3-*b*]benzofuran core. Here, we could observe a decrease in the yield, which might be due to the lower nucleophilicity of the *ortho*-carbon of the phenoxy ion (compared to naphthol).

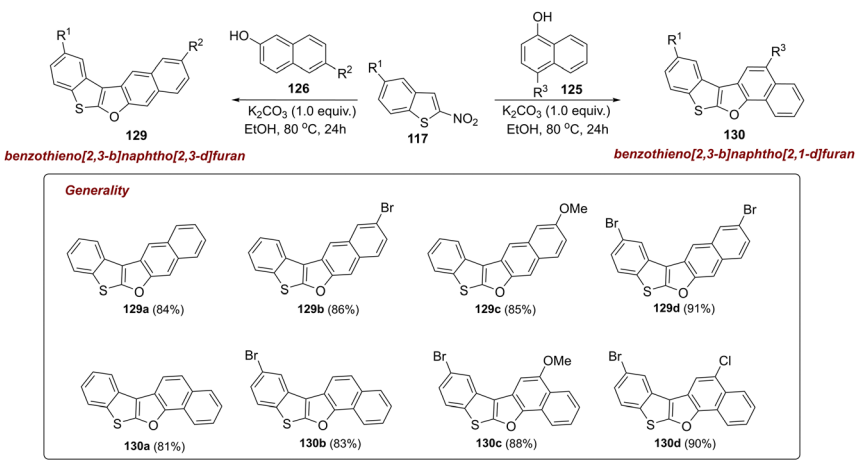
We also found that pentacenes such as benzothiophene [3,2-*b*]naphthofurans could be synthesized using the developed methodology[48] by choosing naphthol as the nucleophilic substrate in the annulation. Both 1- and 2-naphthols reacted well with electrophilic 3-nitrobenzothiophene to give the corresponding benzothieno[3,2-*b*]naphthofurans (Scheme 30).

2-Nitrobenzothiophenes also reacted with 1- and 2-naphthols in a similar way in the presence of K_2CO_3 base in EtOH to deliver benzothieno[2,3-*b*]naphtho[2,1-*d*]furan and benzothieno[2,3-*b*]naphtho[2,3-*d*]furan respectively[49] (Scheme 31). The reaction proceeded smoothly with different functionalized 1- and 2-naphthols alongwith substituted 2-nitrobenzothiophenes. We believe that the simple annulation methodology developed for accessing benzothienobenzofurans and benzothienonaphthofurans would enable researchers to design new materials incorporating these heteroacenes.

We also used copper catalyzed annulation reaction of 2-aminopyridine for the synthesis of benzothiophene-fused imidazo[1,2-*a*]pyridine by using 3-nitrobenzothiophene as substrate (Scheme 32).[47] From this reaction, we could observe only a trace amount of the product.



Scheme 32 Synthesis of benzothiophene-fused imidazo[1,2-*a*]pyridines from electrophilic 3-nitrobenzothiophene.



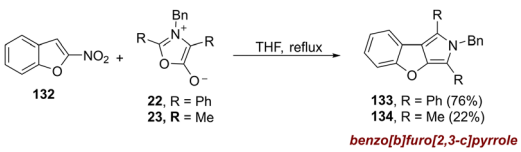
Scheme 31 Synthesis of benzothieno[2,3-*b*]naphthofurans from 2-nitrobenzothiophenes and naphthols.

Synthesis of benzofuran fused heteroacenes starting from electrophilic benzofuran

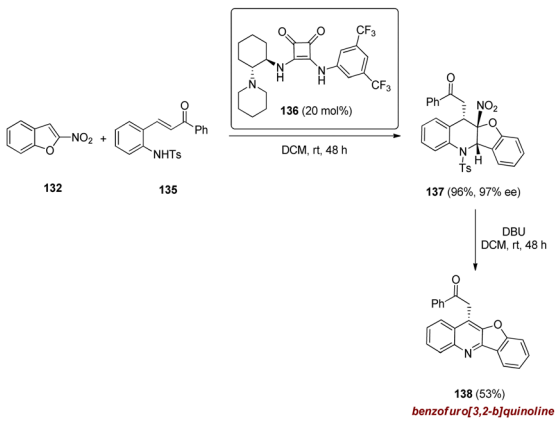
In continuation of the work done by Gribble and coworkers in 1998,[29] the 1,3-dipolar cycloaddition reaction of 2-nitrobenzofuran with unsymmetrical munchnones also led to the formation of another heteroacene, benzo[*b*]furo[2,3-*c*]pyrroles **133–134** (Scheme 33).

In 2019, Yuan *et al.* put forward the first dearomative aza-Michael/Michael addition of 2-nitrobenzofurans with 2-aminochalcones, thereby affording a series of optically active tetrahydrobenzofuro[3,2-*b*]quinolines (all cases >20 : 1 dr, up to 99% ee).[50] Afterwards, they decided to conduct some derivatisations on **137** among which benzofuro[3,2-*b*]quinoline **138** was obtained in 53% yield in the presence of DBU in DCM at room temperature (Scheme 34).

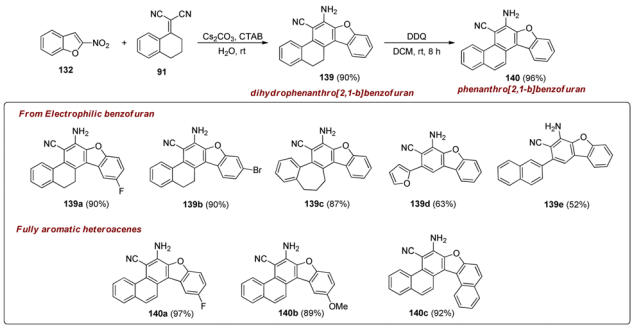
Being intrigued by the importance of fused polycyclic heteroaromatic compounds, Yuan *et al.* first synthesized dibenzoheterocyclic compounds *via* a Michael addition process of electrophilic benzannulated heterocycles such as 2-nitrobenzofurans with α,α-dicyanoalkenes,[44] which then further underwent an oxidative dehydrogenation reaction using 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) to afford the corresponding polycyclic heteroaromatic compounds **140a–140c** in excellent yields (Scheme 35). The reaction was found to be compatible with various substituted 2-nitrobenzofurans and also proceeded smoothly with diverse α,α-dicyanoalkenes, furnishing the corresponding products **139a–139e** in good yields. For the oxidized products **140a–c**, an increase in fluorescence emission intensity was observed due to the extended π-conjugation, thereby revealing their importance in photoluminescence materials.



Scheme 33 Synthesis of benzo[*b*]furo[2,3-*c*]pyrroles from the reaction of 2-nitrobenzofuran with Münchnones.



Scheme 34 Dearomative aza-Michael/Michael addition of 2-nitrobenzofurans with 2-aminochalcones.



Scheme 35 [4+2] annulation of 2-nitro-benzofuran with α,α-dicyanoalkenes.

Conclusions

Recent research in the field of organic chemistry has revealed a fascinating array of heteroacenes—polycyclic aromatic compounds that incorporate heteroatoms like sulfur (S), nitrogen (N) or oxygen (O) into their structures. These compounds have exhibited intriguing properties that have the potential for a wide range of applications in functional materials. As research in this field continues, it is likely to lead to even more innovative applications and discoveries.

In the present review, we focus on electrophilic benzannulated heterocycles, which are heterocyclic compounds such as indole, benzothiophene, or benzofuran, substituted with a nitro group at the C-2 or C-3 position. Their use as an electrophile with different nucleophiles has been well documented in various reactions, which includes [3+2], [4+2], 1,3-dipolar cycloadditions, and multicomponent reactions. Metal catalysed and non-catalyzed reactions also utilized these heterocycles for the synthesis of various substituted carbazoles, benzothienopyrrole, benzofuropyrrole, indoloindole, benzothienoindole, benzothienobenzofuran, benzofuroindole, *etc.* The versatility of electrophilic benzannulated heterocycles has been confirmed by numerous aromative cascade reactions. Research in this area has shown tremendous progress and continues to reveal novel synthetic routes towards fused indole heterocyclic moieties.

This review focusses on heteroacenes consisting of tri-, tetra-, and pentacyclic ring systems. The methodology outlined in these reports offers a valuable framework that can be extended to synthesize a wide range of molecules with diverse properties and applications in the fields of electronics, optoelectronics, and renewable energy. By utilizing the methodologies developed in our group, we have made dyes based on indolo[3,2-*b*]indole[4] and benzothieno[3,2-*b*]indole[4] for dye sensitized solar cell application. In a similar way, we have confidence that researchers will investigate the chemistry of these electrophilic benzannulated heterocycles and design new annulation

reactions with suitable dipoles or appropriately synthesized bis-reactive species, for accessing materials for different applications. Still, there is a huge scope for synthetic chemists for the synthesis and exploration of even more complex and diverse heteroacenes which might be revealed in the years to come.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

SAB thank CSIR for research fellowship. JE thank SERB for the TARE program (TAR/2022/000071). JJ thank CSIR (HCP-41, HCP-49 & HCP-50) and AICTE (GAP-161939) for financial assistance.

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