Exploration and Development of Facile Strategies towards Quinoline Derivatives

by

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10CC18A39008

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

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9th November 2023

CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled, "***Exploration and Development of Facile Strategies towards Quinoline Derivative***", submitted by ***Mr. Rahul P.*** to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of ***Doctor of Philosophy in Sciences***, embodies original research work carried out by the student. We further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research materials obtained from other sources and used in this research work have been duly acknowledged in the thesis. Images, illustrations, figures, tables, etc., used in the thesis from other sources, have also been duly cited and acknowledged.

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ACKNOWLEDGEMENTS

It is with immense pleasure and utmost reverence that I place on record my deep sense of gratitude to my research supervisors, ***Dr. Jubi John*** *and* ***Dr. Praveen V. K.****, 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.Sunil Varughese, 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 would like to thank Dr. D. S. Reddy (Director,CSIR IICT. Former Seniour scientist in NCL Pune) who introduce me to the realm of research.

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. Sunil Varughese (CSIR-NIIST) for single crystal X-ray analysis, Mrs. Saumini Mathew for recording NMR spectra, Mrs. Viji for mass spectral analysis.

I am grateful to the present and former members of JJ family, Dr. Nitha P. R., Dr. Jagadeesh Krishnan, Dr. Vishnu K. Omanakuttan, Dr. Dipankar Paul, Ms. Sheba Ann Babu , Mr. Akhil Krishnan, Ms. Anjana S., Mrs. Reshma, Mrs. Uthara, Ms. Angel Jhony, Ms.

Nandhana, 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.Veena S, Mr.Arun Kumar T. K. Ms. Haritha Raveendran, Ms Seena Sebastian. for helping me to carry out some of my lab work.

I am grateful to Dr. Shandev P. P., Dr. Santhini P. V., Dr. Rahul Shingare, Dr. Vasudevan N., Dr. Ramya Ramesh, Dr. Shaiju, Mr. Vibhu Dharshan, Mr. Listo Varghese for their help and cooperation.

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 little brothers and sisters in NIIST, Ms. Anjana Sidharthan. Mrs. Reshmam, Mr. Harikrishnan,Ms. Aiswarya Siby, Mr. Gourab Mohanty, Ms Haritha S.,Ms. Simi for always being a source of happiness, love and support.

I would also like to thank Dr. S. Prathapan, Dr. Manoj N., and all other faculties at DAC CUSAT, Dr K. T. Radhamani and all other faculties at Payyanr College, Vasanthi teacher and all my teachers for their help and blessings.

I am forever grateful to my dear friends Dr. Neethu S., Mr. Shamjith, Ms. Ranjina, Ms. Suja Vasudevan, Ms. Krishnapriya, Ms. Anjali, Ms. Divya, Mr. Rishad Baig, Mrs. Priya, Ms. Drishya, Ms. Meera, Mr. Manikandan, Ms. Jebin, friends in CSIR NIIST, friends in DAC CUSAT, friends in Payyanur College for their help and support.

I would also like to thank HLS and Security Staffs at CSIR NIIST.

I am deeply indebted to my Achan, Amma, Ammamma, sister Ms. Rahitha, and other family members for their continued energy, unconditional love, and unerring support in my life.

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

Rahul P.

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LIST OF ABBREVIATIONS

Å	Angstrom
Ac	Acetyl
ACN	Acetonitrile
AcOH	Acetic acid
Ar	Argon
Ar-	Aryl
Aza-*o*-QM	Aza-ortho-quinone methide
BHT	Butylated hydroxytoluene
BIL	Basic Insulation Level
Bn	Benzyl
Calcd	Calculated
CCDC	Cambridge crystallographic data centre
°C	Degree celsius
CNS	central nervous system
CSA	Camphorsulfonic acid
Cu-MOF	Copper-Metal Organic Framework
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMF	N, N-Dimethylformamide
DMF.DMA	N, N-Dimethylformamide dimethyl acetal
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
d	Doublet

dd	Doublet of doublets
dr	Diastereomeric ratio
dt	Doublet of triplets
E1cb	Elimination unimolecular conjugate base
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
GC-MS	Gas chromatography–mass spectrometry
HMPT	Hexamethyl phosphoric triamide
h	Hour
HRMS	High resolution mass spectrometry
Hz	Hertz
^{i}Pr	Isopropyl
$^{i}PrOH$	Isopropyl alcohol
J	Coupling constant
LED	Light Emitting Diode
Me	Methyl
MeOH	Methanol
mCPBA	meta-Chloroperoxybenzoic acid
m	Multiplet

m	Meta
Me	Methyl
MeOH	Methanol
mg	Milligram
MHz	Mega hertz
min	Minutes
mL	Millilitre
mmol	Millimolar
mol%	Mole percent
Mp	Melting point
MPV	Meerwein–Ponndorf–Verley
MS	Molecular sieves
MW	Microwave
NHC	N-heterocyclic carbenes
NIS	N-iodosuccinimide
Na	Sodium
NMR	Nuclear magnetic resonance
o	Ortho
OLED	Organic Light Emitting Diode
p	Para
Pd	Palladium
Ph	Phenyl
*p*TsCl	*p*-Toluenesulfonyl chloride
q	Quartet
rt	Room temperature
Rh	Rhodium
Ru	Ruthenium

s	Singlet
t	Triplet
TBAB	Tetra-n-butylammonium bromide
tert	Tertiary
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
Tol	Tolyl
Ts	Tosyl
USD	United States Dollar
UV	Ultraviolet
δ	NMR chemical shift in parts per million

PREFACE

Heterocyclic compounds play a vital role in our daily life. A cyclic organic compound containing all carbon atoms in ring formation is designated as a carbocyclic compound, while the cyclic compounds consisting of at least one hetero (i.e., noncarbon) atom in the ring are known as heterocyclic compounds. Among these heterocyclic compounds, quinoline, also known as benzo[*b*]pyridine or 1-aza naphthalene, are privileged scaffolds because of their wide range of applications. Quinoline is a heterocyclic base and was first isolated in 1834 by Runge from coal tar and he named it Leukol. Later in 1842, Gerhardt isolated it by heating the alkaloid cinchonine extracted from the bark of Cinchona officinalis with an alkali and named as quinoline. The Peruvian stick insect, scientifically known as *Oreophoetes peruana* is the sole identified natural source of unsubstituted quinoline in the animal kingdom. When these insects feel threatened or disturbed, they release a defensive secretion that contains quinoline, emanating from a pair of thoracic glands. The biosynthesis of quinoline in nature typically occurs through a series of enzymatic reactions, starting from the amino acid L-tryptophan. The class of quinoline derivatives pose a continuous challenge to synthetic chemists in devising straightforward routes for accessing them. The profound interest invested in this heterocyclic moiety is due to its wide applicability in pharmaceuticals, materials and industry. Substituted quinolines exhibit promising biological activities such as antimalarial, antibacterial, antiviral, antitumor, analgesic, anticonvulsant, anti-inflammatory etc. These findings have resulted in the development of blockbuster drugs (of natural and synthetic origin) such as quinine, chloroquine, camptothecin, pitavastatin, bedaquiline, lenvatinib, tipifarnib and saquinavir which are being heavily used worldwide for the treatment of different ailments. Because of their relevance, various techniques for synthesizing quinolines have been documented. The synthesis of quinoline derivatives with substituents at specified positions is still a challenge.

We have seen that quinoline and its derivatives have found immense applications in medicine and related areas. There are a plethora of synthetic methodologies reported for the synthesis of quinoline derivatives. However, none of the methods described thus far are without drawbacks. Low efficiency, harsh reagents and reaction conditions, and functional group incompatibility are some of the common challenges of these well known classical reactions. Therefore, the quest to find new synthetic methodologies to address these inherent issues has been a recurring endeavour of numerous research groups. Through the work depicted in this thesis, we have tried to answer some of the issues by introducing

methodologies for accessing quinoline motifs wherein substituents can be introduced at various positions at will.

First we have developed a superbase-mediated indirect Friedländer reaction towards functionalized quinolines. The reaction was performed with *o*-aminobenzyl alcohol and ketones having an active methylene moiety in the presence of KOH and in DMSO. The reaction proceeds predominantly *via* the initial formation of an imine intermediate and subsequent oxidation of the benzyl alcohol functionality and condensation to afford substituted quinolines. We could also demonstrate that a minor fraction of the reaction proceeds via a chalcone intermediate. The transition metal-free oxidative annulation was found to be general affording 2-substituted, 2,3-disubstituted/fused or multi-substituted quinolines. The reaction was extended towards the functionalization of natural products and the applicability of the reaction for gram scale synthesis of quinolines was also demonstrated

In addition, we have featured a superbase mediated chemoselective reaction of tosylhydrazone with two aza-*ortho*-quinone methide precursors namely *o*-aminobenzyl alcohol and *N*-tosyl chloroarylamine. We observed the formation of substituted quinoline when tosylhydrazone was treated with *o*-aminobenzyl alcohol under superbasic conditions. In contrast, the reaction between *N*-tosyl chloroarylamine and tosylhydrazone results in the formation of sulfonamide derivatives.

Further, we designed an inverse electron demand Diels Alder cycloaddition between aza-*o*-quinone methide and enaminones for the synthesis of 3-aroyl quinolines. The reaction was found to be general with a range of substituted enaminones and aza-*o*-quinone methides and we could validate the applicability of the methodology in gram-scale. We also demonstrated a one-pot strategy towards 3-aroyl quinolines starting from the corresponding aliphatic ketones. Finally, we utilized the 3-aroyl quinolines for synthesizing indeno[1,2-*b*]quinolinones *via* a Pd-catalyzed dual C-H activation approach.

Chapter 1

Quinoline a Versatile *N*-Heterocycle - An Overview

1.1. Abstract

H*eterocyclic compounds play a crucial role in our everyday lives. Among these heterocyclic compounds, quinoline, also known as benzo[b]pyridine or 1-aza naphthalene, stands out as an exceptional scaffold for synthetic chemists due to its broad range of applications. Quinoline, a heterocyclic base, was initially extracted from coal tar by Runge in 1834 and named Leukol. Later, in 1842, Gerhardt isolated it by heating the alkaloid cinchonine obtained from the bark of Cinchona officinalis, with an alkali, thus coining the term "quinoline." The profound interest in this heterocyclic structure arises from its extensive utility in pharmaceuticals, materials, and various industries. Substituted quinolines demonstrate significant biological potential, showcasing a range of beneficial activities such as antimalarial, antibacterial, antiviral, antitumor, analgesic, anticonvulsant, and anti-inflammatory properties. These findings have driven the creation of widely used blockbuster drugs, whether derived from natural sources or synthesized, including medications like quinine, chloroquine, camptothecin, pitavastatin, bedaquiline, lenvatinib, tipifarnib, and saquinavir, employed globally to address diverse medical conditions. Given their significance, numerous techniques for synthesizing quinolines have been documented. However, the synthesis of quinoline derivatives with specific substituents in defined positions remains a challenging problem for organic chemists. In this chapter, we extensively covered the diverse natural sources, biosynthesis, recent methodologies concerning quinoline and its derivatives, and their position in the global market.*

1.2 Introduction

Heterocyclic chemistry holds a significant position within the realm of organic chemistry, contributing to approximately one-third of scientific publications. Heterocyclic compounds are cyclic organic compounds that contain at least one atom, aside from carbon, within the circular structure. The most prevalent heteroatoms found in these compounds include nitrogen (N), oxygen (O), and sulfur (S). Heterocyclic compounds are commonly present in plants and animal-derived substances, constituting a significant portion of nearly half of all known natural organic compounds. They play a crucial role in various natural substances, including alkaloids, natural dyes, drugs, proteins, enzymes, and more. Much study has been conducted into the applications of nitrogen-containing heterocyclic molecules.[1] Green chemical strategies[2] for organic compound synthesis are gaining popularity in organic chemistry research domains. Metal-free coupling processes have advanced significantly in recent years. They are ideal for selectively forming carbon-carbon and carbon-heteroatom bonds to synthesize natural products and functionalized compounds.[3]

The history of heterocyclic chemistry finds its roots in the 1800s, paralleling the growth of organic chemistry.[4] Several key milestones (Fig. 1.1) that mark its progression are the isolation of alloxan from uric acid by Brugnatelli in 1818, the production of furfural (a furan) by Dobereiner by treating starch with sulfuric acid, and the distillation of bones to isolate pyrrole (also known as "fiery oil") by Runge. In 1906, Friedlander's synthesis of indigo dye marked a pivotal moment, displacing the agricultural industry with synthetic chemistry. In 1936, Treibs made a breakthrough by isolating chlorophyll derivatives from crude oil, shedding light on the biological origin of petroleum. The year 1951 witnessed the description of Chargaff's rules, which underscored the significance of heterocyclic compounds, specifically purines and pyrimidines, in the genetic code. These historical events showcase the growth and significance of heterocyclic chemistry in the broader context of organic chemistry's development. *N*-heterocyclic chemistry occupies a central and vital position within the domain of heterocyclic chemistry. Its significance stems from the prevalence of nitrogen-containing ring structures in a wide array of natural products, pharmaceuticals, and biomolecules. *N*-heterocyclic chemistry is a fascinating and dynamic field of study within the realm of organic chemistry. It is dedicated to the exploration and understanding of compounds that contain one or more nitrogen atoms

incorporated within a heterocyclic ring structure. These compounds play a pivotal role in numerous aspects of science and technology, ranging from pharmaceuticals and agrochemicals to material science and catalysis. Variations in the structure and functionality of nitrogen-containing heterocyclic compounds stem from the presence and properties of the heteroatom, customizing the compound for specific purposes.

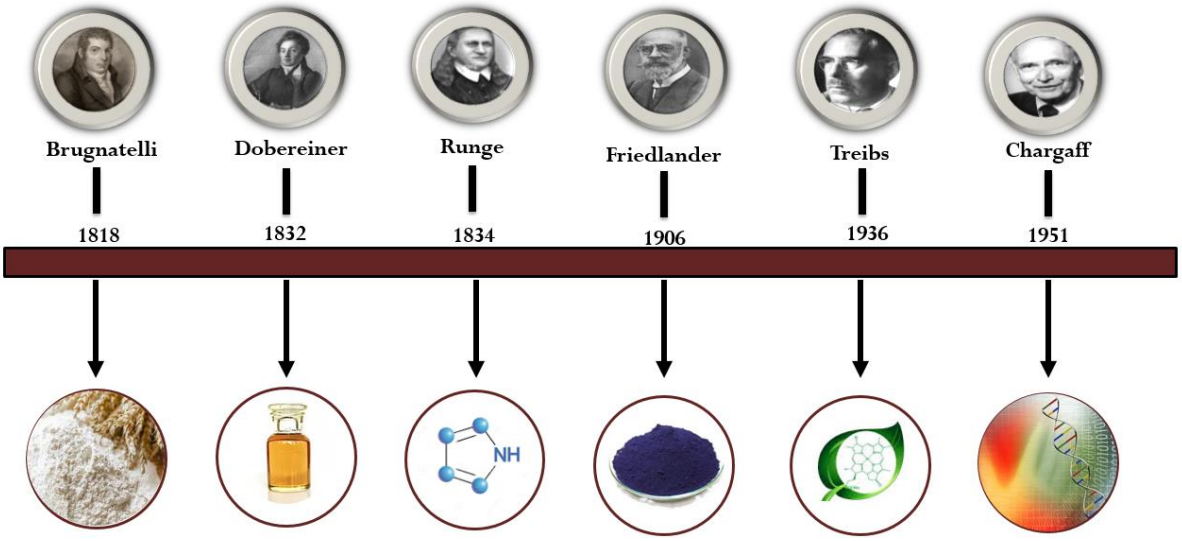


Fig. 1.1: History of Heterocyclic Chemistry

Even though *N*-heterocyclic chemistry has made significant contributions to various fields, there are still obstacles to overcome. The synthesis of complex *N*-heterocyclic compounds can be challenging due to the potential for side reactions and low yields. Moreover, there is an increasing demand for sustainable and environmentally friendly methods. Since the future of *N*-heterocyclic chemistry is promising, the ongoing research aims at developing novel synthetic strategies, exploring uncharted reactivity, and expanding the scope of applications.

Heterocyclic chemistry centered around nitrogen is a distinctive and vital category within the applied disciplines of organic chemistry. It garners considerable research attention aimed at creating innovative compounds and composite materials. Among these, quinoline and its derivatives hold a privileged status owing to their extensive range of applications. The profound interest invested in this heterocyclic moiety is due to its wide applicability in pharmaceuticals,[1] materials[2], and industry. Substituted quinolines exhibit promising biological activities such as antimalarial, antibacterial, antiviral, antitumor, analgesic, anticonvulsant,

anti-inflammatory, etc. These findings have resulted in the development of blockbuster drugs (of natural and synthetic origin) such as quinine, chloroquine, camptothecin, pitavastatin, bedaquiline, lenvatinib, tipifarnib, and saquinavir which are being heavily used worldwide for the treatment of different ailments. The initial discovery of quinoline is attributed to the English chemist F. Runge in 1834, who isolated it as a byproduct during the distillation of coal tar. Initially, Runge referred to this compound as " leukol " ("white oil" in Greek) and later renamed as quinoline. The pivotal breakthrough in deciphering the molecular structure of quinolone was in the year 1869, courtesy of the efforts of another English chemist, Sir William Henry Perkin. Perkin successfully synthesized quinoline from aniline and acrolein, a milestone that not only confirmed its structure but also significantly contributed to the enhanced understanding of this intriguing chemical entity.

1.3 Natural occurrence and isolation

Quinine, strychnine, and cinchonine (Fig. 1.2) are quinoline-based alkaloids present in the stembark of *Cinchona officinalis* (Fig. 1.3). Charles Gerhardt, a French chemist obtained a compound through the dry distillation of quinine, strychnine, or cinchonine with potassium hydroxide and named as Chinoilin or Chinolein in 1842. Apart from this, quinoline-based natural products are isolated from various plants such as Lycopodium, Lunasia, Papaver, Galipea, Cryptolepis, and Camptotheca etc.

Fig. 1.2: Quinoline based alkaloids

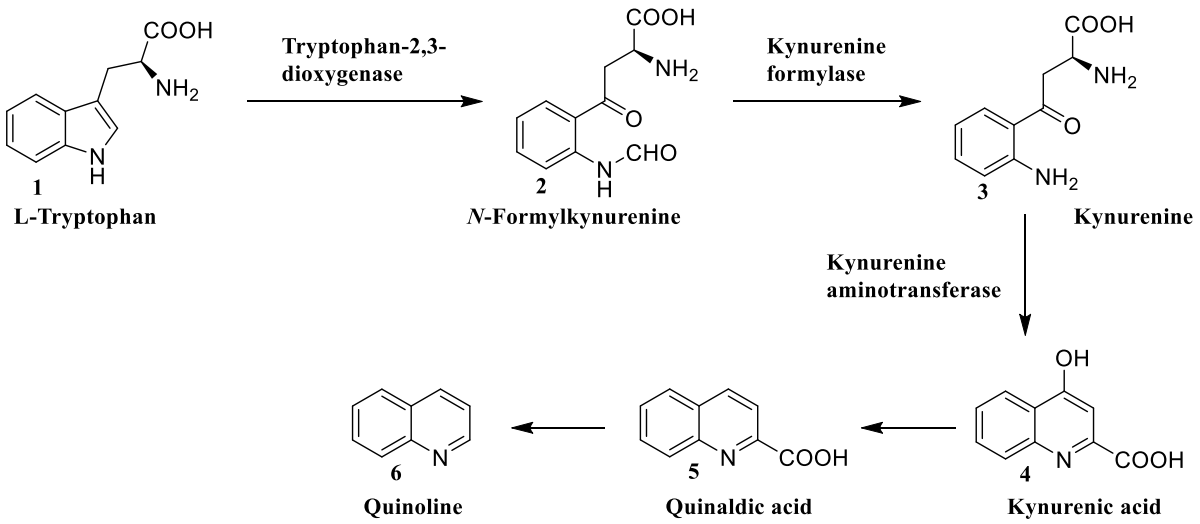
Fig. 1.3: *Cinchona officinalis*

1.4 Biosynthesis of quinoline

The Peruvian stick insect, scientifically known as *Oreophoetes peruana* (Fig.1.4), is the sole identified natural source of unsubstituted quinoline in the animal kingdom. When these insects feel threatened or disturbed, they release a defensive secretion that contains quinoline,

emanating from a pair of thoracic glands. The biosynthesis of quinoline in nature typically occurs through a series of enzymatic reactions (Scheme 1.1). Attygalle *et al.* comprehensively elucidated the biosynthesis of unsubstituted quinoline, starting from the amino acid L-tryptophan **1**.[5] The process commences with tryptophan 2,3-dioxygenase catalyzing the cleavage of the 2,3-double bond in the pyrrole ring of tryptophan, resulting in the production of *N*-formylkynurenine **2**. The elimination of the formyl group is carried out by a kynurenine formylase to produce kynurenine **3**. Subsequently, kynurenine aminotransferase catalyzes the cyclization of kynurenine into kynurenic acid **4**. Alternatively, prior to cyclization, the ketone group in kynurenine may undergo reduction. Ultimately, a deoxygenation step transforms kynurenic acid into quinaldic acid **5**. In the case of *O. peruana*, the species has evolved to decarboxylate quinaldic acid, leading to the production of quinoline **6** as the final product. Nevertheless, this marks the initial account of the biosynthetic source for the defensive allomones in any stick insects.

Fig. 1.4: *Oreophoetes peruana*



Scheme 1.1 Biosynthesis of quinoline

1.5 Quinoline in the global market

The Quinoline Market is projected to achieve a value of USD 545 billion by 2035, with an estimated growth rate of approximately 4% from 2023 to 2035. By 2022, the quinolone market

had surpassed USD 340 billion in size (Fig.1.5).[6] The propelling market growth in the foreseeable future is credited to the increasing global utilization of quinoline in drug synthesis, ranging from antimalarial, antibacterial, antifungal, cardiotonic, anti-inflammatory, analgesic, anticonvulsant, and anthelmintic (Fig. 1.6).

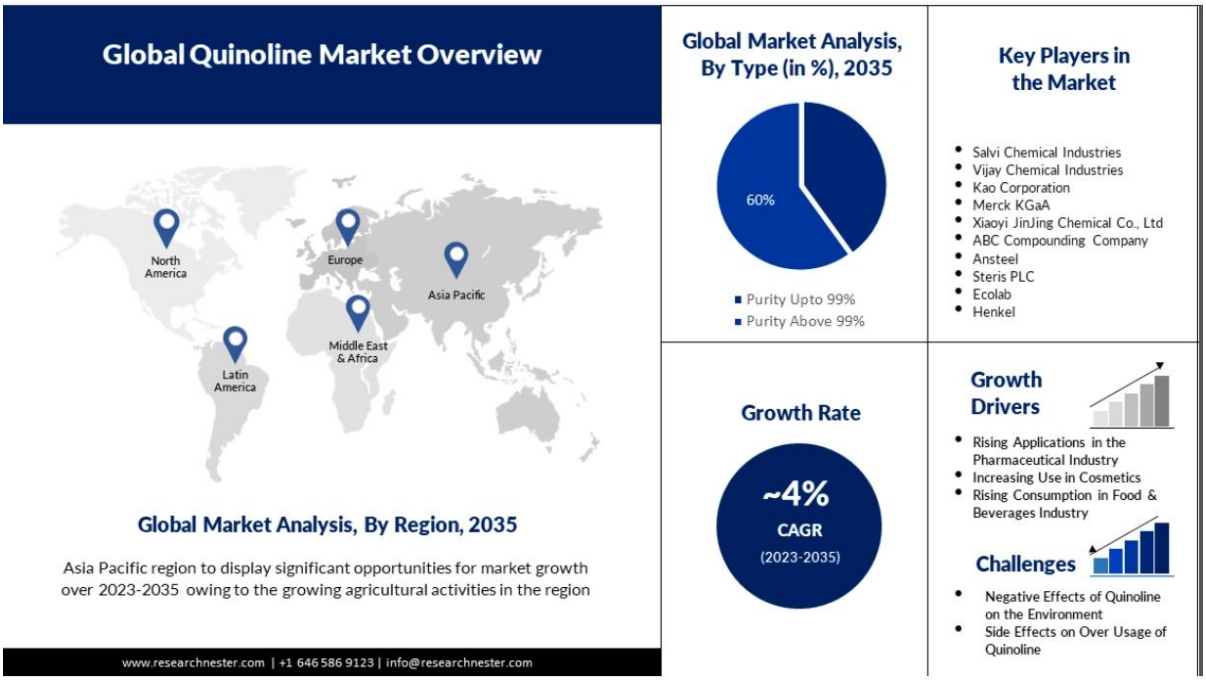


Fig. 1.5: Overview of global quinoline market[6]

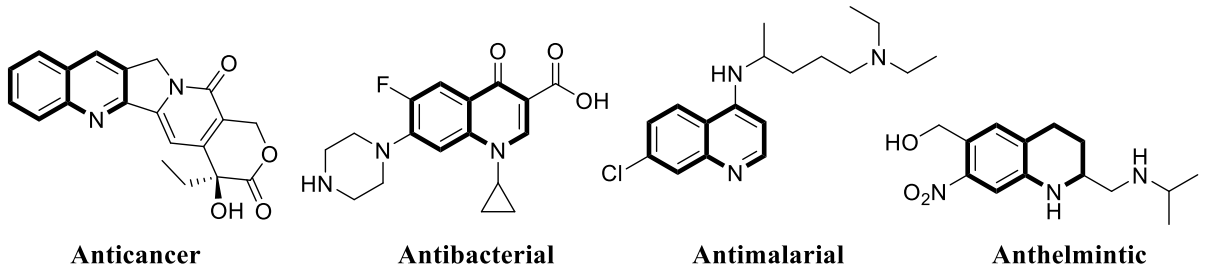


Fig. 1.6: Diverse pharmacological applications of quinoline derivatives

Apart from the diversified applications in the drug industry, quinoline finds application in the manufacturing of various personal care products including conditioners, shampoos, bath soaps, toothpaste, hair gels, lotions, etc. Furthermore, the food and beverage industry also use quinoline as a food additive or colorant, casting a yellow hue on various food products. Quinoline yellow, a synthetic lemon-yellow azo dye is used widely in the food industry. It has

been utilized particularly as a coloring agent in various food products such as desserts, beverages, snacks, and various processed foods which imparts a bright yellow hue. Also, studies have shown that quinoline derivatives serve as effective materials for the emission layer in organic light-emitting diodes (OLEDs) and are also utilized in transistors.

Fig. 1.7: Quinoline Yellow

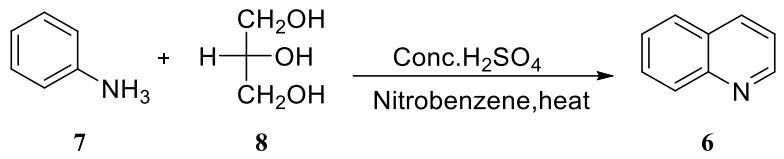
Quinoline has been detected at historical wood treatment sites and is frequently reported as an environmental pollutant connected to coal or oil shale processing plants, like other nitrogen heterocyclic compounds. Quinoline exhibits a notable degree of water solubility, rendering it highly mobile in the environment and potentially contributing to water contamination. If nature can generate these heterocyclic patterns, it also possesses mechanisms for breaking them down. For instance, Rhodococcus, a Gram-positive bacterium typically present in soil and the effluent of paper mills can effectively degrade quinoline.

1.6 Milestones in quinoline synthesis

The synthesis of quinoline has a rich history with several key milestones. Quinoline was first isolated by Friedlieb Ferdinand Runge from coal tar. This marked the discovery of the compound in a natural source, which later led to its synthesis. There is a plethora of classical reactions such as Gould–Jacob, Friedländer, Pfitzinger, Skraup, Doebner–von Miller, Conrad–Limpach, etc. for accessing quinoline and its derivatives.[4]

1.61 Skraup Synthesis

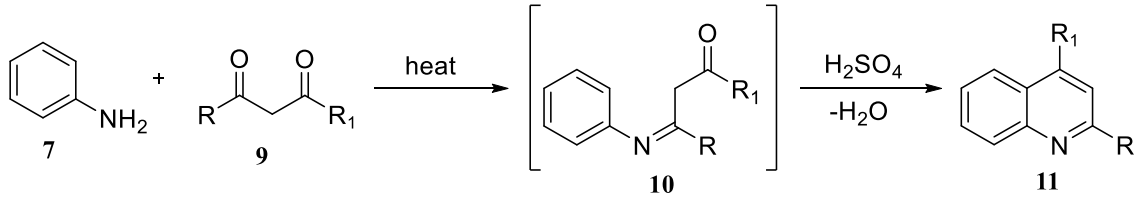
This was one of the earliest synthetic methods for quinoline, named after the Czech chemist Zdenko Hans Skraup (Scheme 1.2).[7] This synthetic process involves the formation of quinoline derivatives from aniline (or its derivatives), sulfuric acid, glycerol, and an oxidizing agent such as nitrobenzene. The reaction typically occurs at high temperatures. The Skraup synthesis typically involves the condensation of aniline (a primary aromatic amine) with a ketone, such as acetylacetone or methyl ethyl ketone, in the presence of a strong acid, usually concentrated sulfuric acid. The Skraup synthesis is a versatile method for the preparation of quinoline derivatives with various substituents.



Scheme 1.2 Skraup synthesis

1.62 Combes Quinoline Synthesis

The Combes quinoline synthesis, introduced by Combes in 1888, is a well-known method for producing the 2,4-substituted quinoline **11** structure (Scheme 1.3).[8] This process involves an acid-catalyzed condensation where an aromatic amine **7** such as aniline reacts with compounds like acetylacetone (a 1,3-diketone) **9**, a keto aldehyde, or a dialdehyde to create the quinoline framework.

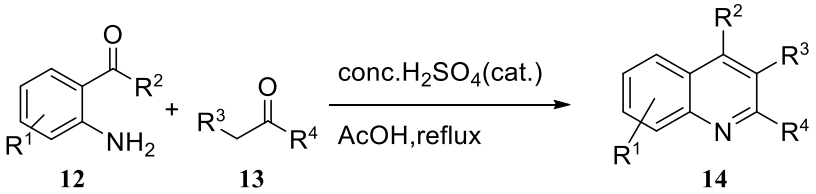


Scheme 1.3 Combes Quinoline Synthesis

Enamine formation occurs during the reaction, leading to cyclization. The presence of a strong electron-withdrawing group (-NO_2) inhibits this cyclization process. However, a rearrangement is noticeable when using ketoaldehyde during the cyclization step.

1.63 Friedländer Synthesis

Friedländer synthesis is one of the simplest approaches for the synthesis of quinolines. This method involves the reaction between *o*-aminoaryl aldehydes or ketones **12** and a ketone with an α-methylene group **13** (Scheme 1.4).[9] This reaction can be effectively catalyzed by either a base or an acid, including a Brønsted acid or a Lewis acid.

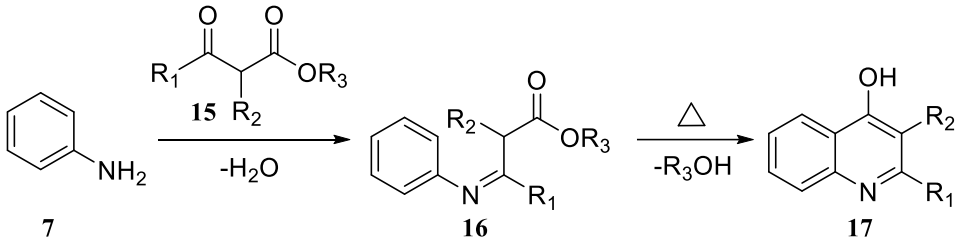


Scheme 1.4 Friedländer synthesis

Additionally, ionic liquids are also capable of effectively activating it. Moreover, it can efficiently advance without a catalyst by simply heating the reaction mixture. The advantage of this reaction lies in its broad substrate scope, accommodating diverse functional groups on both arylamine and ketone components.

1.64 Conrad–Limpach Synthesis

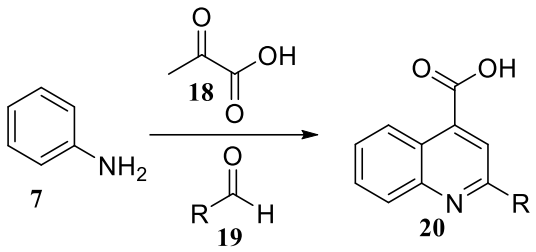
The Conrad–Limpach synthesis, unveiled by Max Conrad and Leonhard Limpach in 1887, includes the reaction of anilines **7** with β-ketoesters **15** to generate 4-hydroxyquinolines **17** *via* the formation of a Schiff base (Scheme 1.5).[10] The general reaction involves a combination of an addition and a rearrangement reaction. The choice of solvent and temperature significantly influences the yield of the 4-hydroxyquinoline **17** product. The nitrogen atom of the aniline can attack either at the less reactive ester group or the highly reactive keto group. Initially observed by Conrad and Limpach at room temperature, the reaction resulted in high yields of the kinetic product, β-aminoacrylate, followed by the formation of the stable product, 4-hydroxyquinoline.



Scheme 1.5 Conrad–Limpach synthesis

1.65 Doebner Reaction

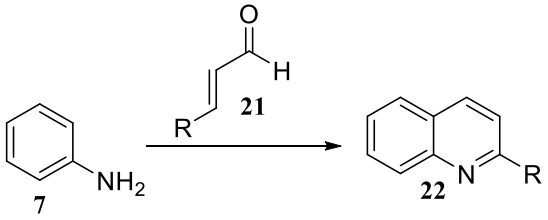
This reaction describes the synthesis of quinoline-4-carboxylic acids **20** *via* aniline **7** with aldehyde **19** and pyruvic acid **18**. This reaction serves as an alternative to the Pfitzinger reaction (Scheme 1.6).[11] While the exact mechanistic pathway remains uncertain, two proposed mechanisms have been suggested. One possibility includes an initial aldol condensation, followed by a Michael addition with aniline, cyclization at the benzene ring, and two proton shifts, ultimately resulting in the formation of quinoline-4-carboxylic acid through the elimination of water. An alternative mechanism focuses on the formation of a Schiff base between the aniline and the aldehyde. Subsequent reaction with the enol form of pyruvic acid leads to the creation of the previously mentioned aniline derivative, followed by a mechanism akin to the one mentioned earlier.



Scheme 1.6 Doebner reaction

1.66 Doebner–Miller Reaction

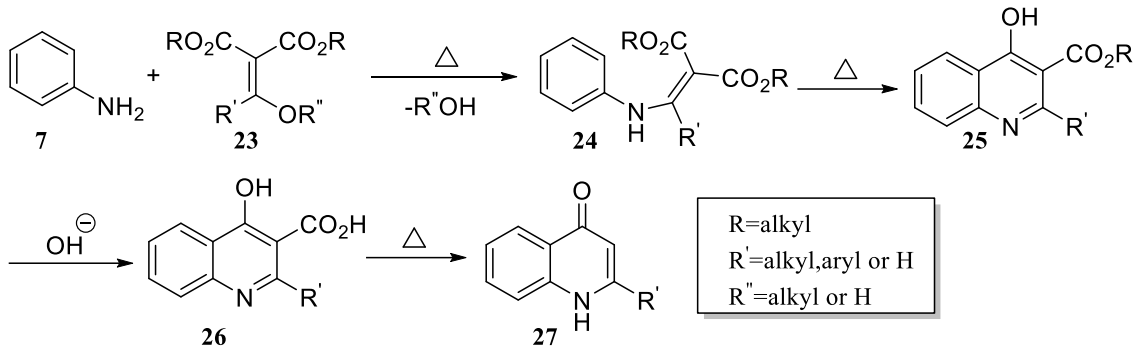
The Doebner-Miller reaction accounts another method for quinoline synthesis via the reaction of aniline **7** with α,β-unsaturated carbonyl compounds (Scheme 1.7).[12] Various Lewis acids, such as tin tetrachloride and scandium(III) triflate, and also Brønsted acids, including *p*-toluenesulfonic acid, perchloric acid, amberlite, and iodine facilitate this reaction. This chemical transformation is also known as **Skraup-Doebner-Von Miller** quinoline synthesis.



Scheme 1.7 Doebner–Miller reaction

1.67 Gould–Jacobs Reaction

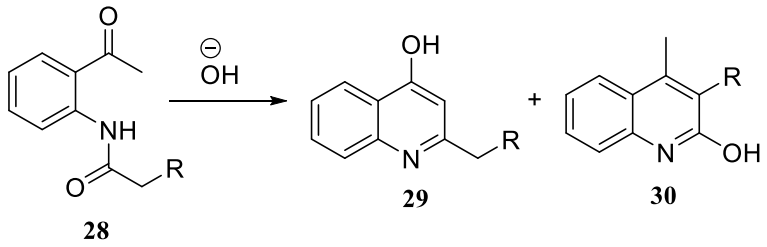
The process for creating 4-hydroxyquinoline derivatives involves the interaction of aniline **7** with an alkoxy methylenemalonic ester **23**, producing anilidomethylenemalonic ester **24** (Scheme 1.8).[13] Following this, a 6-electron cyclization resulting in the formation of 4-hydroxy-3-carboalkoxyquinoline **25**, famously known as the Gould–Jacobs reaction. This is succeeded by the decarboxylation yielding 4-hydroxyquinoline **26**. This reaction's effectiveness is remarkable for anilines that possess electron-donating groups positioned at the meta-position. The Gould-Jacobs approach can be extended to fabricate unsubstituted parent heterocycles characterized by a fused pyridine ring in the style of the Skraup type.



Scheme 1.8 Gould–Jacobs reaction

1.68 Camps Quinoline Synthesis

The Camps quinoline synthesis, or Camps cyclization, describes a chemical reaction where the conversion of an *o*-acylaminoacetophenone **28** results in the formation of two distinct hydroxyquinolines **29** and **30** in the presence of a hydroxide ion (Scheme 1.9).[14] The proportions of the two hydroxyquinolines produced are influenced by the reaction conditions and the initial compound's structure. Despite the common representation of the reaction product as a quinoline (in its enol form), it is widely accepted that the keto form is predominant, both in the solid state and in solution, classifying the compound as a quinolone.

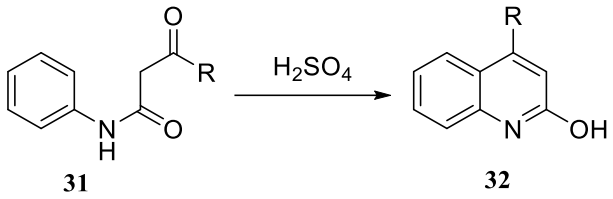


Scheme 1.9 Camps quinoline synthesis

1.69 Knorr Quinoline Synthesis

This intramolecular synthesis converts a β-ketoanilide **31** into a 2-hydroxyquinoline **32**, assisted by sulfuric acid. In specific reaction conditions, the competing formation of a 4-hydroxyquinoline is also observed (Scheme 1.10).[15] Ludwig Knorr initially reported this reaction in 1886. It involves an electrophilic aromatic substitution process accompanied by water elimination. A reaction mechanism identifies the presence of an N,O-dicationic intermediate in excess acid conditions, which aids in ring closure, and a monocationic intermediate that eventually disassembles to generate aniline and, ultimately, acetophenone. Aniline then reacts with another equivalent of benzoylacetanilide before yielding

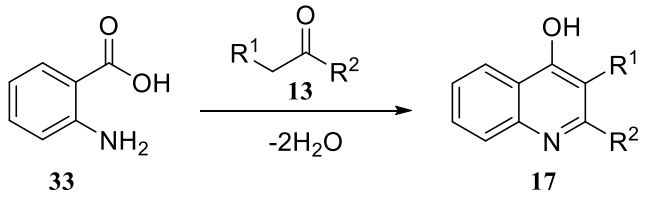
4-hydroxyquinoline. A later study revisited the reaction mechanism and proposed that a super electrophilic O,O-dicationic intermediate is more favorable than the N,O-dicationic intermediate.



Scheme 1.10 Knorr quinoline synthesis

1.610 Niementowski Quinoline Synthesis

In 1894, Niementowski reported the formation of 4-hydroxyquinoline **17** from the heating of anthranilic acid **33** and ketone **13** at temperatures ranging between 120 and 130 °C (Scheme 1.11).[16] This reaction is less common than other synthetic methods for quinoline because of the high-temperature requirements. However, variations have been proposed to make it a more pragmatic and useful reaction. The mechanism is only minimally different from that of the Friedländer synthesis. The process is believed to initiate by forming a Schiff base, followed by an intra-molecular condensation, resulting in an imine intermediate. Subsequently, the elimination of a water molecule induces ring closure, yielding the quinoline derivative. This mechanism is widely supported under standard conditions around 120–130 °C. Conversely, under acidic or basic conditions, an alternative mechanism starts with an intermolecular condensation, leading to the formation of the imine intermediate. It has been noted that the latter mechanism is more prominent in these specific acidic or basic environments.

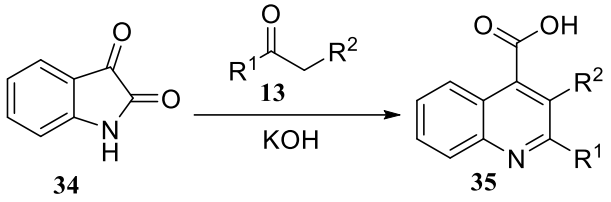


Scheme 1.11 Niementowski quinoline synthesis

1.611 Pfitzinger Reaction

This chemical transformation, also recognized as the Pfitzinger-Borsche reaction, entails the production of substituted quinoline-4-carboxylic acids through the interaction of isatin **34** with a base and a carbonyl compound **13** (Scheme 1.12).[17] When a ketone (or aldehyde) reacts

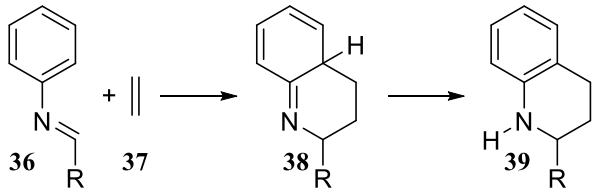
with the aniline, it forms both the imine and the enamine. The enamine undergoes cyclization and dehydration, resulting in the formation of the targeted quinoline.



Scheme 1.12 Pfitzinger reaction

1.612 Povarov Reaction

Povarov reaction is a multicomponent process that encompasses a formal cycloaddition between an aromatic imine **36** and an alkene **37** (Scheme 1.13).[18] The reaction product in the original Povarov reaction is quinoline. According to the mechanistic studies, in the first step, aniline and benzaldehyde react to form a Schiff base. In the Povarov reaction, the activation of the imine for electrophilic addition to the activated alkene is facilitated by a Lewis acid, such as boron trifluoride. This process results in the formation of an oxonium ion, which subsequently undergoes a classical electrophilic aromatic substitution with the aromatic ring. Two further elimination reactions lead to the formation of the quinoline ring structure.



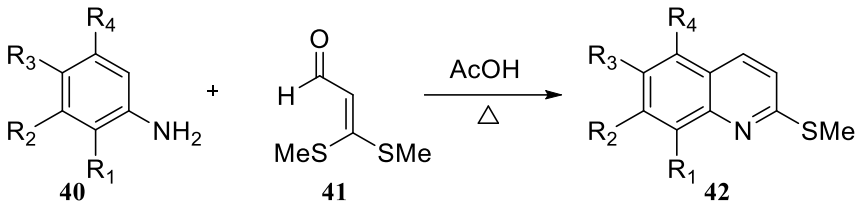
Scheme 1.13 Povarov reaction

These classical reactions reflect the evolution of quinoline synthesis starting from its initial discovery to the development of diverse and more efficient methods for accessing quinoline and its derivatives. Over time, these landmark synthesis methods have been modified, improved, and adapted to produce various quinoline derivatives for applications in pharmaceuticals, material science, and in other industries. These historic methodologies laid the groundwork for the development of numerous modern strategies for synthesizing quinoline and its derivatives.

1.7 Recent approaches towards the synthesis of quinoline

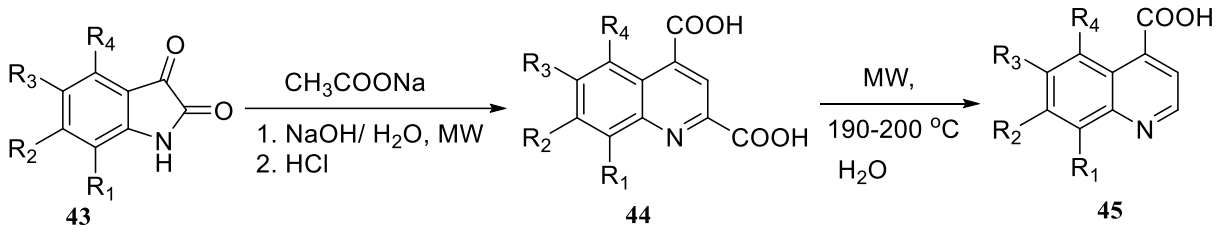
The development of new methodologies for quinoline synthesis remains an active area of research. Researchers continually explore innovative techniques to improve efficiency, selectivity, and sustainability in the synthesis of quinoline and its derivatives.

Panda *et al.* in 2004 devised a straightforward and effective method for synthesizing 2-(methylthio)quinolines **42** and their derivatives (Scheme 1.14).[19] This synthesis entailed an acid-catalyzed cyclocondensation process, wherein the corresponding anilines **40** were combined with 3,3-bis(methylthio)acrylaldehyde **41**.



Scheme 1.14 Acid-induced cyclocondensation of anilines with 3-bis(methylthio)acrolein

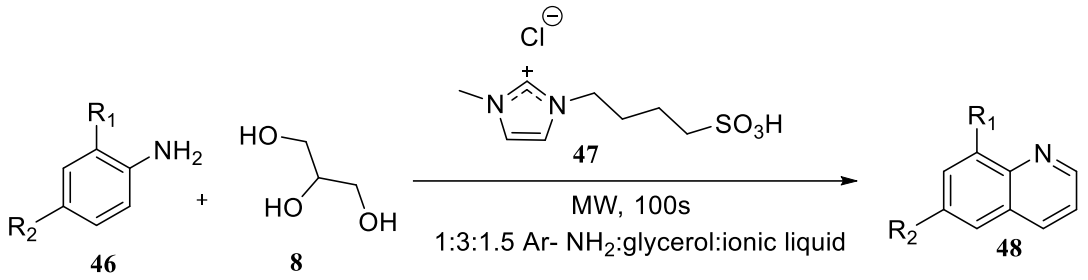
Over the past decade, the adoption of microwave irradiation as an alternative to traditional heat sources has gained popularity. Zhu *et al.* introduced a convenient microwave-assisted method in 2010 to synthesize a range of quinoline-4-carboxylic acids **45**.[20] The process involves the production of 2-non-substituted quinoline-4-carboxylic acids through the Pfitzinger reaction. This reaction occurs by combining isatins **43** with sodium pyruvate, followed by subsequent decarboxylation under microwave irradiation (Scheme 1.15).



Scheme 1.15 Microwave-assisted synthesis of quinoline-4-carboxylic acids

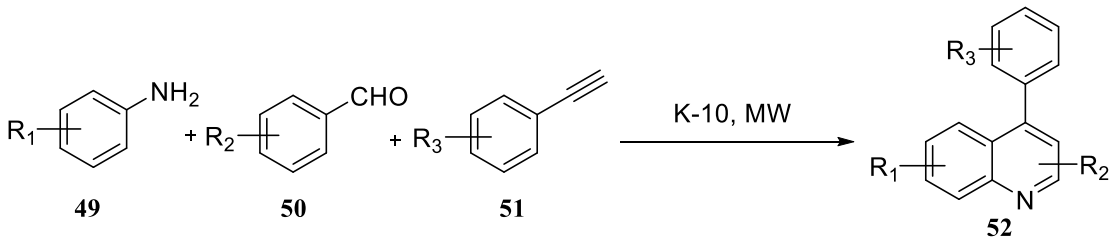
Based on this research, Amarasekara *et al.* utilized microwave heating for the Skraup synthesis, employing a 1:3 ratio of anilines **46** to glycerol **8** (Scheme 1.16).[21] Interestingly, by substituting concentrated sulfuric acid with an imidazolium cation-based sulfonic acid ionic liquid **47**, the reaction outcome notably improved. Moreover, it was observed that the addition

of an external oxidant was no longer required. With these improvisations, they achieved excellent yields of the quinoline product.



Scheme 1.16 Imidazolium cation-based sulfonic acid mediated Skraup synthesis

A solid acid-catalyzed microwave-assisted method for producing substituted quinolines is detailed by Kulkarni *et al.* in 2010 (Scheme 1.17).[22] The process involves a multicomponent domino reaction that combines anilines **49**, aldehydes **50**, and terminal aryl alkynes **51**. Initially, an imine is formed, followed by subsequent intermolecular addition of an alkyne to the imine. The resulting intermediate subsequently undergoes rapid ring closure and oxidative aromatization.

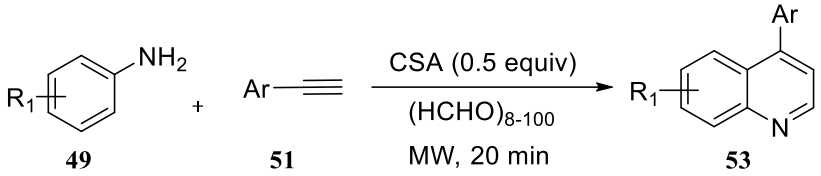


Scheme 1.17 Multicomponent domino reaction of anilines, aldehydes, and terminal aryl alkynes

This multi-component approach results in nearly 90% atom efficiency, yielding high product quantities in just minutes. Moreover, employing microwave activation substantially decreases the reaction duration.

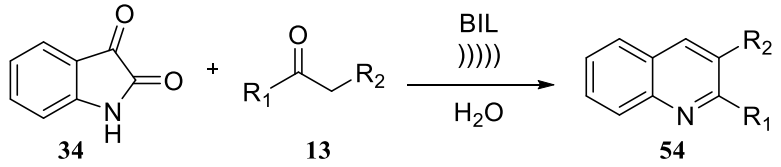
In 2019, Chandra and co-workers introduced a microwave-assisted multicomponent synthesis, reminiscent of the Povarov reaction, to produce 4-arylated quinolines using anilines **49**, paraformaldehyde, and alkynes **51** (Scheme 1.18).[23] This reaction involves the initial formation of an imine from aniline and paraformaldehyde, followed by a [4+2] cycloaddition between the imine and alkynes. The cycloaddition process is facilitated by camphor-10-

sulfonic acid (CSA), which activates the imine. The resulting products were acquired in yields ranging from moderate to excellent, showcasing adaptability with different anilines and alkynes.



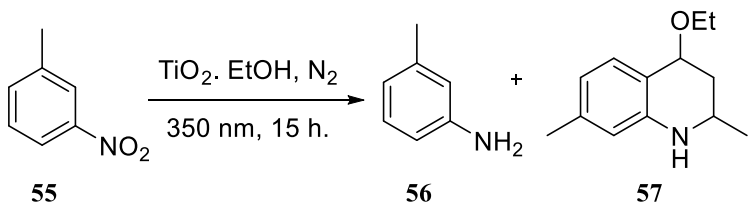
Scheme 1.18 Microwave-assisted Povarov-type multicomponent synthesis

Kowsari *et al.* introduced a method for synthesizing a quinoline derivative using ultrasound in combination with an ionic liquid (Scheme 1.19).[24] This process involves a two-component, one-pot condensation reaction between isatin **34** and an enolizable ketone **13**, resulting in the production of the quinoline derivative **54**. Notably, this method achieves high selectivity. Another advantage of this approach is the avoidance of secondary reactions, such as aldol condensation. In comparison to traditional methods, this procedure stands out for its eco-friendliness, milder reaction conditions, reduced reaction time, and higher yields with enhanced selectivity, all accomplished without the requirement for a transition metal catalyst.



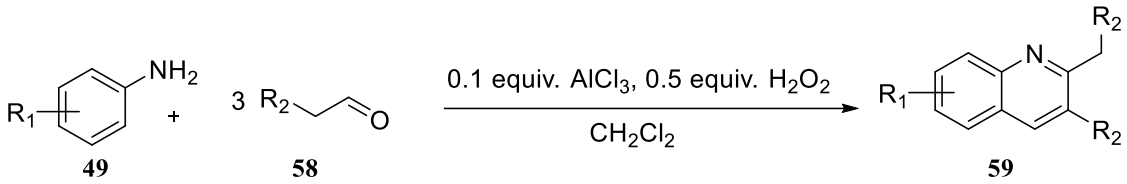
Scheme 1.19 Synthesis of quinoline derivative using ultrasound in combination with an ionic liquid

Park and co-workers described a one-step process to produce 4-ethoxy-1,2,3,4-tetrahydroquinoline **57**. This method involved a heterogeneous solution comprising nitroarene **55**, ethanol, and TiO_2 under UV light irradiation (Scheme 1.20).[25] Substrates containing oxygen or amino substituents, like *m*-nitroanisole, notably display slower reaction rates when compared to those with alkyl substituents under identical reaction conditions. An important benefit of this method is the direct synthesis of quinoline derivatives from nitroarenes instead of aminoarenes, achieved under environmentally friendly conditions.



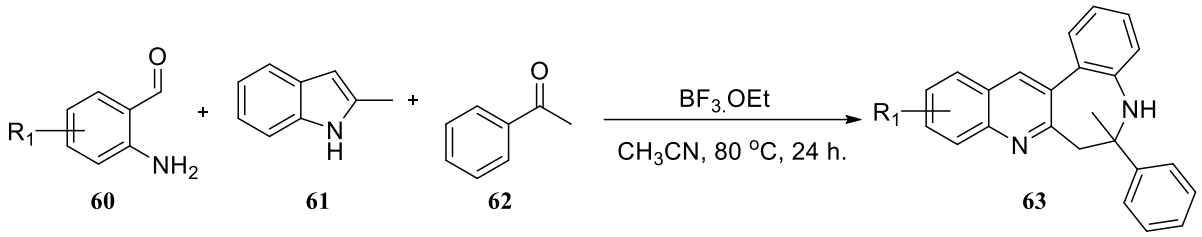
Scheme 1.20 One-pot method for synthesizing 4-ethoxy-1,2,3,4-tetrahydroquinoline

Guo *et al.* employed a Doebner-like approach for quinoline synthesis, initially condensing aniline **49** with an aldehyde **58** (Scheme 1.21).[26] Diverging from the conventional approach, they replaced the pyruvic acid component with an additional aldehyde molecule, leading to quinolines substituted at the 2- and 3-positions. Their study revealed that integrating a sub stoichiometric amount of H_2O_2 as an environmentally friendly oxidant alternative significantly enhanced the yield of the quinoline product when used alongside a catalytic quantity of aluminum chloride. The proposed mechanism for this annulation begins with the $AlCl_3$-mediated condensation of aniline with one aldehyde molecule, leading to the formation of the imine. The enol tautomer of a second aldehyde molecule subsequently adds to the imine, initiating cyclization to generate the tetrahydroquinoline. Elimination of one equivalent of H_2O forms the dihydroquinoline, which then undergoes aromatization through oxidation with hydrogen peroxide, ultimately resulting in the formation of the product.



Scheme 1.21 Synthesis of quinoline *via* condensation of aniline with an aldehyde

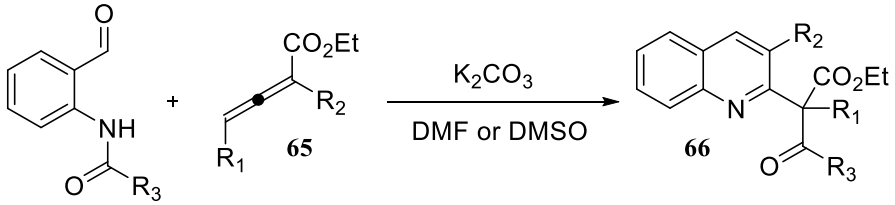
Gu and co-workers reported the Lewis acid-catalyzed synthesis, resulting in unexpected benzazepine-fused quinoline products from the combination of 2-aminobenzaldehydes **60**, 2-methylindole **61**, and acetophenone **62** (Scheme 1.22).[27] The proposed mechanism initiates with the union of 2-aminobenzaldehyde **60** and 2-methylindole **61** mediated by a Lewis acid. This intermediate undergoes nucleophilic cyclization, leading to the breaking of the C-N bond. The resulting arylamine then engages with acetophenone **62**, forming a compound that undergoes an enamine-activated Mannich-like cyclization. This process ultimately leads to the creation of benzazepine-fused quinolines **63**, with yields varying from fair to excellent.



60 61 62 63

Scheme 1.22 Lewis acid-catalyzed synthesis of quinoline

Taking advantage of the inherent electrophilic and nucleophilic properties of allenoates (α-allenic esters), Selig and Raven examined their application in generating quinolines (Scheme 1.23).[28] Initially, their attempts with *o*-aminobenzaldehyde did not yield the expected cyclization product. However, upon monoprotection of the amine, they observed successful cyclization. Interestingly, they noted the formation of both the desired quinoline product and a secondary product showcasing a protecting group migration leading to the creation of a new quaternary center. The suggested mechanism encompasses an aza-Michael addition, assisted by a Brønsted base-promoted amide anion of the 2-aminobenzaldehyde, targeting the β carbon of the allenoate. This particular step induces cyclization specifically from the γ position. The resulting intermediate, in its zwitterionic state, experiences a 1,3-shift of the protecting group, culminating in the production of the desired product. Through refined reaction conditions, they achieved the selective synthesis of rearrangement products featuring diverse protecting groups, resulting in high yields.

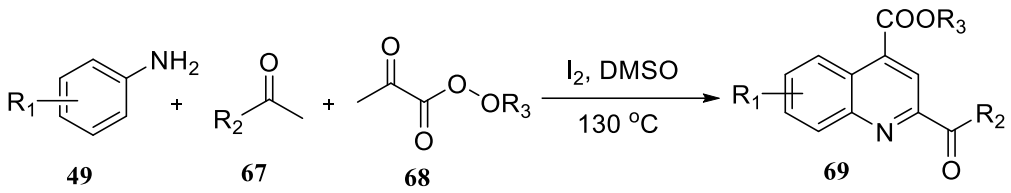


64 65 66

Scheme 1.23 Utilization of allenoates in quinoline synthesis

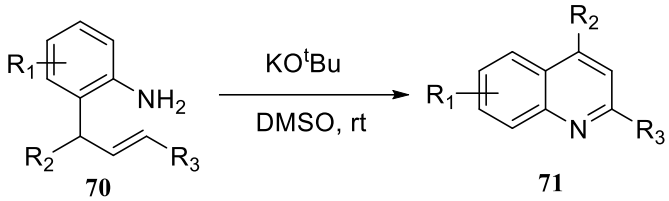
The synthesis of quinoline through a three-component reaction involving methyl ketones **67**, arylamines **49**, and α-ketoesters **68** is achieved in the presence of iodine and a catalytic quantity of hydroiodic acid (Scheme 1.24).[29] In this process, the co-produced HI serves as a promoter, displaying excellent functional compatibility. This straightforward procedure

introduces a novel facet of reactivity to the Povarov reaction, exhibiting remarkable compatibility with various functional groups.



Scheme 1.24 Synthesis of quinoline through a three-component reaction involving methyl ketones, arylamines, and α-ketoesters

Ghorai *et al.* devised a metal-free cycloisomerization approach for quinoline synthesis, replacing molecular oxygen with dimethyl sulfoxide (DMSO) for the oxidation step. By reacting ortho-allylanilines with a sub stoichiometric quantity of potassium *tert*-butoxide in DMSO, a series of quinoline products, notably 2-styryl derivatives, were successfully generated, providing a solution to the lack of synthetic alternatives. The proposed mechanism involves the oxidation of 2-allylaniline **70** *via t*-BuOK and DMSO, followed by a six-electron cyclization, resulting in the formation of dihydroquinoline (Scheme 1.25).[30] Subsequent oxidation transforms the dihydroquinoline into the final quinoline product **71**.



Scheme 1.25 Metal-free cycloisomerization of 2-allylaniline

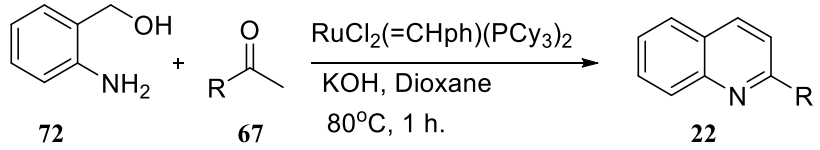
These diverse approaches in quinoline synthesis reflect an ongoing effort to develop more efficient, sustainable, and versatile methods while exploring a range of chemical and catalytic principles.

1.8 Recent advancements in the synthesis of quinolines from 2-aminobenzyl alcohol

Researchers have focused on developing innovative methodologies to construct quinoline derivatives using 2-aminobenzyl alcohol as a starting material. This compound serves as a valuable building block due to its structural versatility and potential for diverse chemical

transformations. Recent studies have explored various synthetic routes, including multicomponent reactions, metal-catalyzed processes, and novel catalytic strategies, aiming to streamline and enhance the efficiency of quinoline synthesis. These advancements not only contribute to expanding the repertoire of available synthetic routes but also hold promise for applications in medicinal chemistry, material science, and other scientific domains. Such progress highlights the continual exploration and refinement of methodologies in the quest for novel and efficient routes to quinoline derivatives.

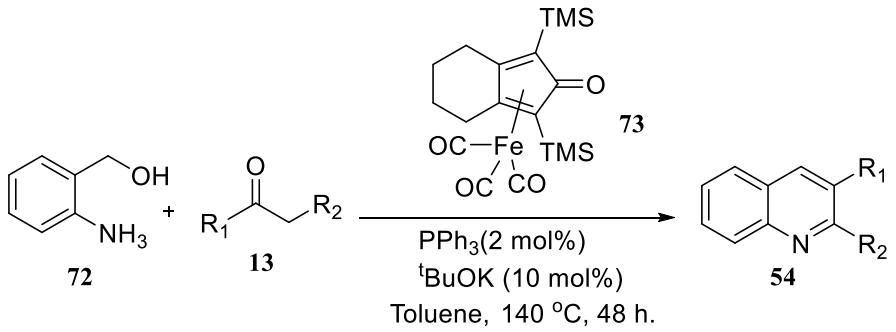
One such approach presents a variation of the Friedlaender quinoline synthesis, employing a ruthenium-catalyzed oxidative cyclization of 2-aminobenzyl alcohol **72** with ketones **67** (Scheme 1.26).[31] The product yield increased with an increase in reaction temperature up to 80°C. A range of ketones was systematically examined to explore the reaction's applicability, and key findings were summarized. Alkyl aryl ketones readily underwent cyclization with 2-aminobenzyl alcohol, yielding 2-arylquinolines **22** in high to satisfactory yields. The reaction pathway appears to initiate with the initial oxidative bonding of ruthenium to the O–H bond in 2-aminobenzyl alcohol, followed by a *β*-hydrogen elimination step that produces 2-aminobenzaldehyde. For this transformation, Cho *et al*. utilized a rhodium ($RhCl(PPh_3)_3$) catalyst instead of ruthenium.[32]



72 **67** **22**

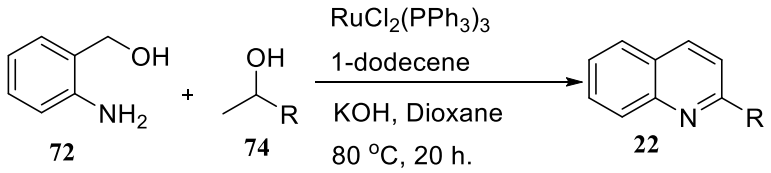
Scheme 1.26 Ruthenium-catalyzed oxidative cyclisation

Elangovan and co-workers introduced an iron-catalyzed approach to produce quinoline and its derivatives (Scheme 1.27).[33] Utilizing the comparatively stable 2-amino-benzyl alcohol **72** in the presence of a catalytic quantity of base under hydrogen-borrowing conditions offers significant advantages for this reaction compared to methods that require stoichiometric amounts of base.



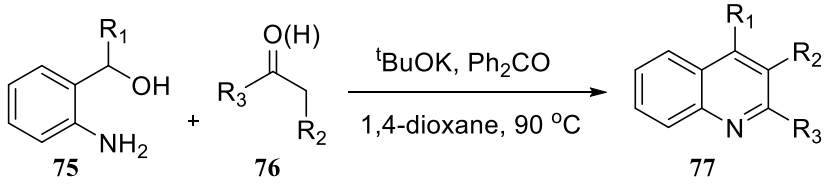
Scheme 1.27 Iron-catalyzed synthesis of quinoline and its derivatives

Cho and co-workers detailed ruthenium-catalyzed oxidative coupling followed by cyclization between 2-aminobenzyl alcohol **72** and secondary alcohol **74.** This process was facilitated by KOH and 1-dodecene to accomplish quinoline synthesis (Scheme 1.28).[34] This method employs a catalytic quantity of $RuCl_2(PPh_3)_3$ and KOH, with 1-dodecene serving as a hydrogen acceptor, enabling the synthesis of quinolines with satisfactory yields. The cyclization method is applicable to a wide range of alkyl(aryl) and alkyl(alkyl) carbinols. The catalytic process seems to begin with the initial oxidation of both substrates to create carbonyl compounds, followed by a cross-aldol reaction and cyclodehydration.



Scheme 1.28 Ruthenium-catalyzed oxidative coupling reaction

Martínez *et al*. revealed a transition-metal-free indirect Friedländer synthesis method for quinolines derived from alcohols (Scheme 1.29).[35]

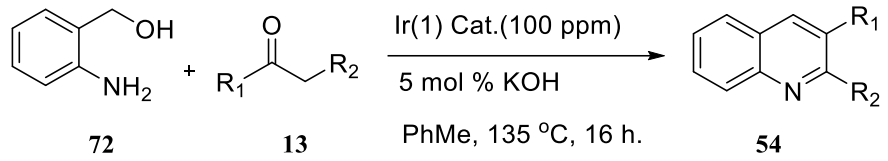


Scheme 1.29 Indirect Friedländer synthesis of quinolines derived from alcohols

The direct synthesis of polysubstituted quinolines was achieved by reacting 2-aminobenzylic alcohol with a ketone or alcohol in the presence of a base. This method

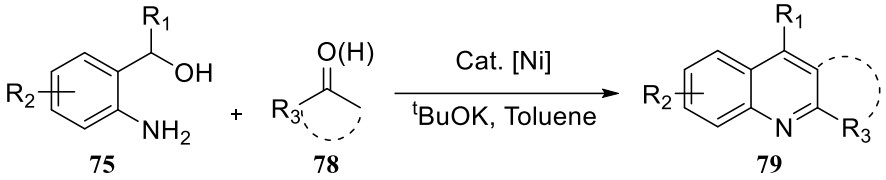
eliminates the necessity for a transition-metal catalyst, thus establishing a more environmentally friendly and simpler approach.

Genc *et al.* recently detailed an iridium-catalyzed process for quinoline synthesis (Scheme 1.30).[36] Iridium(I) complexes, incorporating an imidazol-2-ylidene ligand, efficiently facilitated this acceptor less dehydrogenative cyclization of 2-aminobenzyl alcohol with ketones via a borrowing hydrogen pathway. Employing a limited quantity of the catalyst in combination with a catalytic amount of NaOH or KOH in an air atmosphere resulted in the formation of products. In this process, water and H_2 were generated as byproducts.



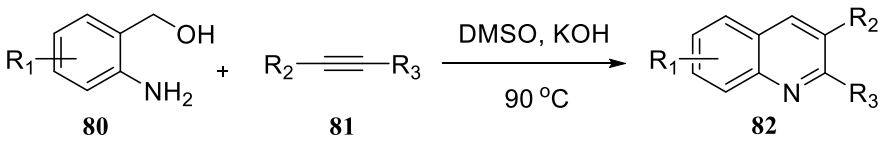
Scheme 1.30 Iridium-catalyzed quinoline synthesis

Das and co-workers detailed the production of diverse polysubstituted quinolines by employing commercially accessible aminoaryl alcohol in combination with acyclic/cyclic ketones or secondary alcohols (Scheme 1.31).[37] This synthesis process involves a successive dehydrogenation and condensation reaction. The advantage of employing this method is the utilization of a cost-effective and easy-to-manage nickel(II) catalyst.



Scheme 1.31 Nickel-catalyzed quinoline synthesis

Verma and co-workers outlined a chemo- and regioselective [4 + 2]-cycloaddition process involving alkynes and azadienes generated *in situ* (Scheme 1.32).[38] The process is believed to commence with the dehydration of 2-aminobenzyl alcohol **80** facilitated by DMSO/KOH, producing the azadiene, which was isolated in controlled experiments. Subsequently, this azadiene undergoes cyclization with the alkyne **81**, ultimately leading to the formation of quinoline upon oxidation.



Scheme 1.32 Chemo- and regioselective [4 + 2]-cycloaddition of alkynes with azadienes

So far, we detailed some of the recent approaches towards the synthesis of quinoline and its derivative. Overall, metal-free approaches to quinoline synthesis and its derivatives offer advantages in terms of environmental sustainability, cost-effectiveness, safety, and applicability, making them a valuable choice in various chemical and pharmaceutical research endeavors.

1.9 Superbase

Organic chemists frequently employ terms like 'strong' or 'super' to intensively express basic properties. Nevertheless, the criteria for such terms are vague and rely on the individual chemists who use them. Consequently, the use of expressions such as 'strong' or 'super' leads to ambiguity and confusion within the organic chemistry community. In an insightful review by Caubère,[39] a proposed definition of superbases is introduced. According to this definition, the term 'superbases' is used to describe bases formed by the combination of two or more individual bases, resulting in entirely new basic species with unique properties. It's important to note that the term 'superbase' does not necessarily imply that the base is thermodynamically or kinetically stronger than another; rather, it signifies the development of a basic reagent by incorporating attributes from different bases. An essential and advantageous characteristic of an organic base, particularly concerning environmental considerations, is its ability to be recycled for repeated reactions involving reversible proton transfers between the base and an acidic counterpart substrate. As a result, highly potent organic bases that can serve as effective base catalysts in various organic syntheses have garnered significant attention.

1.10 Conclusion

The future of quinoline chemistry holds promise and potential in various areas, building on its diverse properties and applications (Fig. 1.8). Some key aspects of its future trajectory include drug development, material science, electronics, agrochemicals, etc.

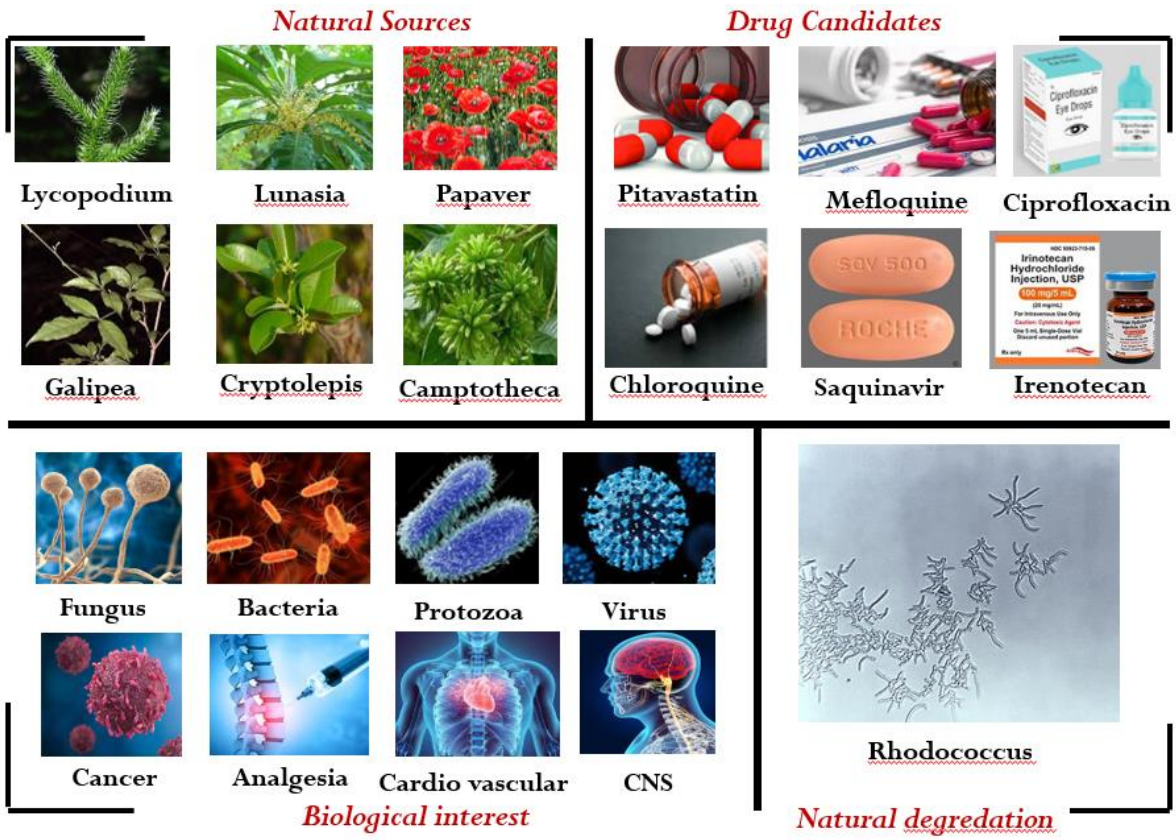


Fig. 1.8: An overview of quinoline sources and applications

Numerous synthetic methods have been documented for producing quinoline and its derivatives. However, their drawbacks include low efficiency, the use of harsh reagents, reaction conditions, and incompatibility with various functional groups. Consequently, the ongoing pursuit of discovering new synthetic methodologies aims to address these intrinsic challenges and has remained a consistent focus for numerous research groups. Through the work depicted in this thesis, we have tried to answer some of the issues by introducing methodologies for accessing quinoline motifs wherein substituents can be introduced at various positions at will.

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Chapter 2

Super Base Mediated Indirect Friedländer Reaction: A Metal-Free Oxidative Annulation toward Functionalized Quinolines

2.1. Abstract

A super base mediated indirect Friedländer reaction towards functionalized quinolines has been realized. The reaction was performed with o-aminobenzyl alcohol and ketones having an active methylene moiety in the presence of KOH and DMSO. The reaction proceeds predominantly via the initial formation of an imine intermediate and subsequent oxidation of the benzyl alcohol functionality and condensation to afford substituted quinolines. We could also demonstrate that a minor fraction of the reaction proceeds via a chalcone intermediate. The metal-free oxidative annulation was found to be generally affording 2-substituted, 2,3-disubstituted/fused, or multi-substituted quinolines. The reaction was extended toward the functionalization of natural products, and its applicability was demonstrated for the gram-scale synthesis of quinolines.

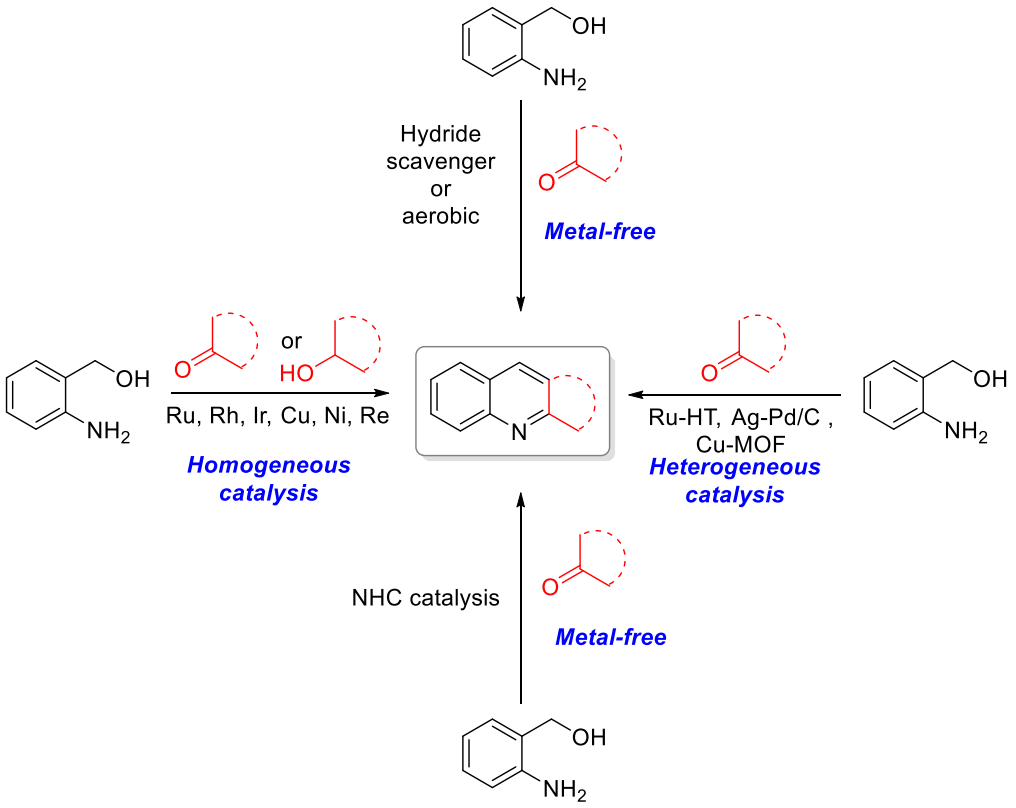
2.2 Introduction

The class of quinoline derivatives pose a continuous challenge in devising straightforward routes for accessing them. [1] The profound interest invested in this heterocyclic moiety is due to its wide applicability in pharmaceuticals,[2] materials,[3] and industry.[4] Substituted quinolines exhibit promising biological activities such as antimalarial, antibacterial, antiviral, antitumor, analgesic, anticonvulsant, anti-inflammatory, etc, are detailed in Chapter 1.

Several classical organic reactions exist that utilize arylamines as precursors for quinoline synthesis and its derivatives. Friedländer quinoline synthesis can still be considered one of the most direct routes for accessing this important heterocycle.[5] The traditional Friedländer reaction involves a base-promoted condensation of 2-amino-substituted carbonyl compound (aromatic) and an α-methylene group containing carbonyl derivative followed by

dehydration. The high reactivity and instability of 2-aminobenzaldehyde demand its *in-situ* generation. Such kind of reactions are termed indirect Friedländer quinoline synthesis.

Recently, modified or indirect Friedländer quinoline synthesis protocols with dehydrogenative cyclization of 2-aminobenzyl alcohol with carbonyl compounds (or alcohols) were developed in the presence of metal catalysts (Scheme 2.1).[6] Different complexes of metals such as Ru,[6b] Rh,[6c] Ir,[6d-f] Cu,[6g] Ni[6h-i], and Re[6j] were utilized as catalysts in indirect Friedländer quinoline synthesis. In addition, several heterogeneous catalysts, which include Ru-HT (ruthenium on hydrotalcite support), Pd/C, $Pd(OAc)_2$/PEG-2000, Ag-Pd alloy on carbon and a Cu-based MOF were also developed and used for synthesizing substituted quinolines (Scheme 2.1).[7]

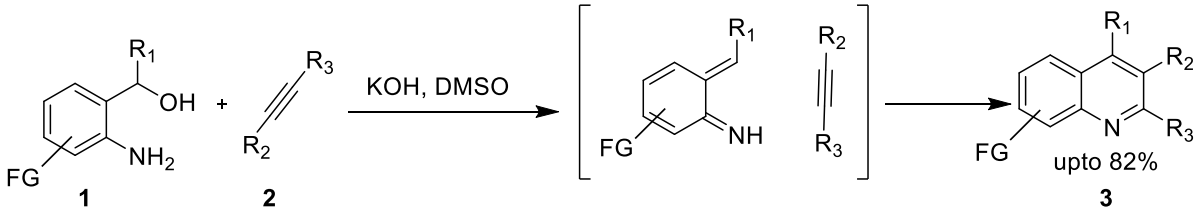


Scheme 2.1 Indirect Friedländer synthesis of quinolines from 2-aminobenzyl alcohol

In the middle of the 1970s, Trofimov began using the phrase "superbase media" frequently, which also appeared in monographs then. Superbase media of lithium dialkylamides in hexamethylphosphoric triamide (HMPT) also referred as "hyperbasic media" by Normant and his team, were utilized for the synthesis of nitriles *via*

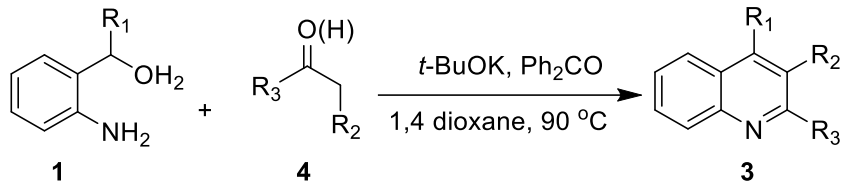
metalation of hydrazine. KOH/DMSO suspension is the best among the superbases and consists of two phases, namely alkali metal hydroxide and dipolar nonhydroxylic solvent, which are thought to be the most widely used, accessible, stable, and easy to handle. This is a two-phase equilibrium system is similar to phase-transfer catalytic processes in that it has a small amount of the superbase in the liquid phase that must be continuously supplied from the solid phase when it is spent. The ability of the water molecules held in the solid phase by excess KOH to progressively provide protons (strictly on "demand") to change the anions generated during the reaction into new stable molecules without diminishing the medium's basicity is crucial. Superbasic medium (mainly the combination of KOH and DMSO) have been utilized extensively for different organic transformations such as chalcogenation, cross-coupling, intramolecular cyclization, heterocyclic synthesis, styrylation, inter- and intramolecular hydroaminations, etc.[9]

Verma and co-workers made use of the KOH-DMSO system for the synthesis of functionalized quinolines from *o*-aminobenzyl alcohol and alkynes (Scheme 2.2).[10] The reaction proceeded *via* a [4+2] cycloaddition of alkyne with azadiene (in situ generated from *o*-aminobenzyl alcohol).



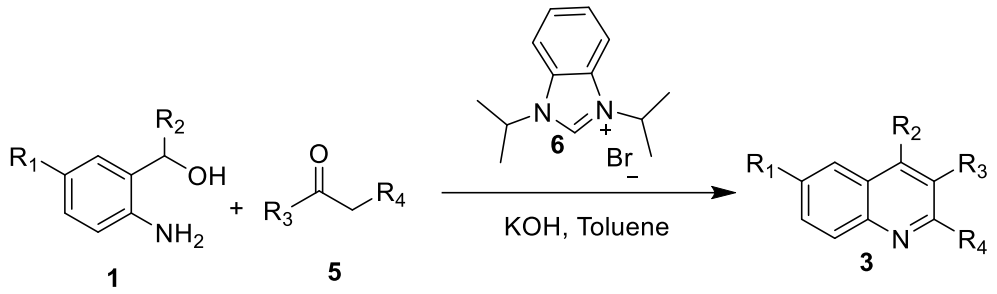
Scheme 2.2 Synthesis of quinolines from *o*-aminobenzyl alcohol and alkynes

Another advancement in the area of indirect Friedländer quinoline synthesis was the introduction of metal-free strategies.[8] The first among them was reported in 2008 by Ramón, Yus and co-workers which combined the Meerwein-Ponndorf-Verley reaction of 2-aminobenzyl alcohols with benzophenone and the Friedländer annulation to synthesize quinoline derivatives (Scheme 2.3).[8a]



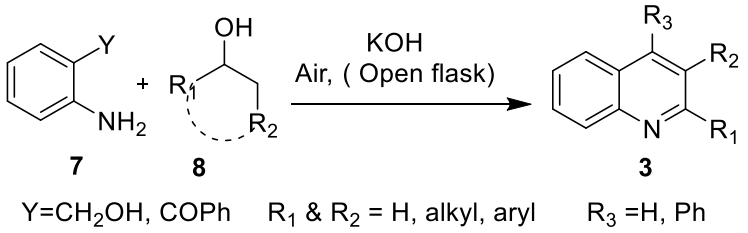
Scheme 2.3 Metal-free indirect Friedländer quinoline synthesis

Zhu and Cai recently disclosed an N-heterocyclic carbene-catalyzed indirect Friedländer quinoline synthesis by executing a reaction of 2-aminobenzyl alcohol with ketones (Scheme 2.4).[8b] The appropriate multi-substituted quinolines are produced *via* this tandem reaction, which involves alpha-alkylation followed by indirect Friedländer annulation in the presence of air.



Scheme 2.4 N-heterocyclic carbene-catalyzed indirect Friedländer quinoline synthesis

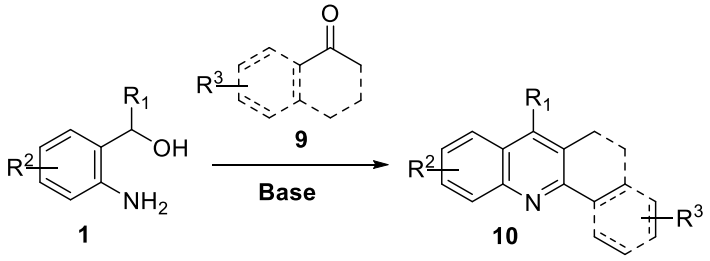
Singh *et al* reported a one-pot aerobic process for the synthesis of functionalized quinolines devised from 2-aminobenzyl alcohol or 2-aminobenzophenones with alkyl or aryl alcohols (Scheme 2.5).[8c] The process involves two sequential reactions, namely *in situ* aerial oxidation of alcohols to the corresponding aldehydes and ketones followed by Friedländer annulation. These reported metal-free methodologies required additional reagents (benzophenone) for the MPV reaction of 2-aminobenzyl alcohol[8a] or the presence of a catalyst.[8b] We were interested in developing a transition metal-free and additional reagent-free methodology for quinoline synthesis based on the indirect Friedländer reaction.



Scheme 2.5 One-pot aerobic process for the synthesis of functionalized quinolines

2.3 Statement of the problem

We have seen that quinoline and its derivatives are widely used both in medicine and materials, but the routes for synthesizing these motifs still pose a challenge to synthetic chemists. In the preceding section, we have covered a variety of ways to make quinoline moieties. These techniques can be used effectively to synthesize a wide variety of quinolines, from monosubstituted to highly functionalized or fused motifs. But all of the techniques that have been outlined so far have shortcomings. Low efficiency, costly reagents, harsh reaction conditions, and functional group incompatibility are common problems encountered in the reported methods. Therefore, several research groups have engaged in efforts to modify these reactions to address their underlying problems. These characteristics have sparked interest in creating more effective synthetic pathways to synthesize quinoline derivatives.



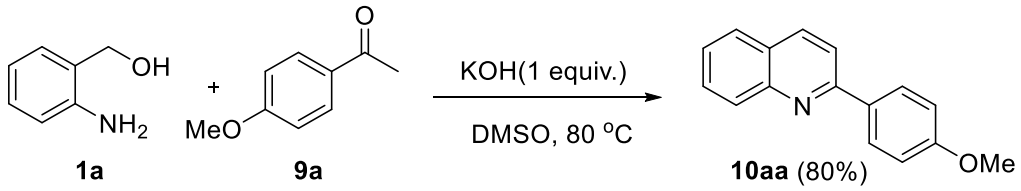
Scheme 2.6 Superbase mediated indirect Friedländer quinoline synthesis

An efficacious methodology for the oxidation of active methylenes and benzhydrols to corresponding carbonyl compounds mediated by a base-DMSO system was reported by Ravikumar *et al*.[11] Motivated by the above mentioned reports on the use of superbasic media and owing to our interest in heterocyclic synthesis,[12] we hypothesized that functionalized quinolines could be generated from *o*-aminobenzyl alcohol and an α-methylene group containing carbonyl derivatives *via* an oxidation-condensation sequence in the presence of a base-DMSO system and most importantly in the absence of any additional reagent or catalyst (Scheme 2.6).

2.4 Result and discussions

We commenced our investigations by selecting *o*-aminobenzyl alcohol **1a** and 4'-methoxy acetophenone **9a** as model substrates (Scheme 2.7). The initial reaction was performed with one equivalent each of **1a** and **9a** in the presence of KOH (1.0 equivalent)

and DMSO (1.0 mL) at 80 ^{o}C for 7 h. After completion of the reaction, 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. As expected, 2-(4-methoxyphenyl)quinoline **10aa** was isolated in 80% yield (Table 2.1, entry 1).



Scheme 2.7 Superbase mediated indirect Friedländer quinoline synthesis

The structural assignment of the product was done with the aid of various spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR, and HRMS analysis. In the ^{1}H NMR spectrum (Fig 2.1**)** the aromatic protons resonated between 8.18-7.04 ppm. The methoxy protons resonated at 3.89 ppm. In the ^{13}C NMR (Fig 2.2**)** the methoxy carbon resonated at 55.4 ppm. All other signals in the ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structure and literature. The high-resolution mass spectral analysis showed a peak at *m/z* 236.1078 $(M+H)^{+}$, which also supported the proposed structure.

Then we moved on with optimizing the reaction conditions starting with base screen. Different bases other than KOH such as ^{t}BuONa, ^{t}BuOK, NaOH, and K_2CO_3 were screened for the present indirect Friedländer quinoline synthesis (Table 2.1, entries 1-5). From the tested bases, KOH was found to be the best and the reaction failed to furnish any product in the presence of K_2CO_3. Increasing the equivalents of *o*-aminobenzyl alcohol had a beneficial effect on the outcome of the reaction. Thus, with 1.1 equivalents of **1a**, the substituted quinoline was isolated in 83% yield, and with 1.2 equivalents of **1a**, the substituted quinoline was isolated in 88% yield respectively (Table 2.1, entries 1, 6, and 7). It was found that both increasing (to 120 ^{o}C) and decreasing the temperature (to RT) considerably decreased the yield of **10aa** (Table 2.1, entries 7-9). A decrease in the equivalents of KOH (to 0.5 equivalents) was found to lower the yield of **10aa** to 72% (Table 2.1, entry 10) and the reaction failed to afford any product in the absence of KOH (Table 2.1, entry 11).

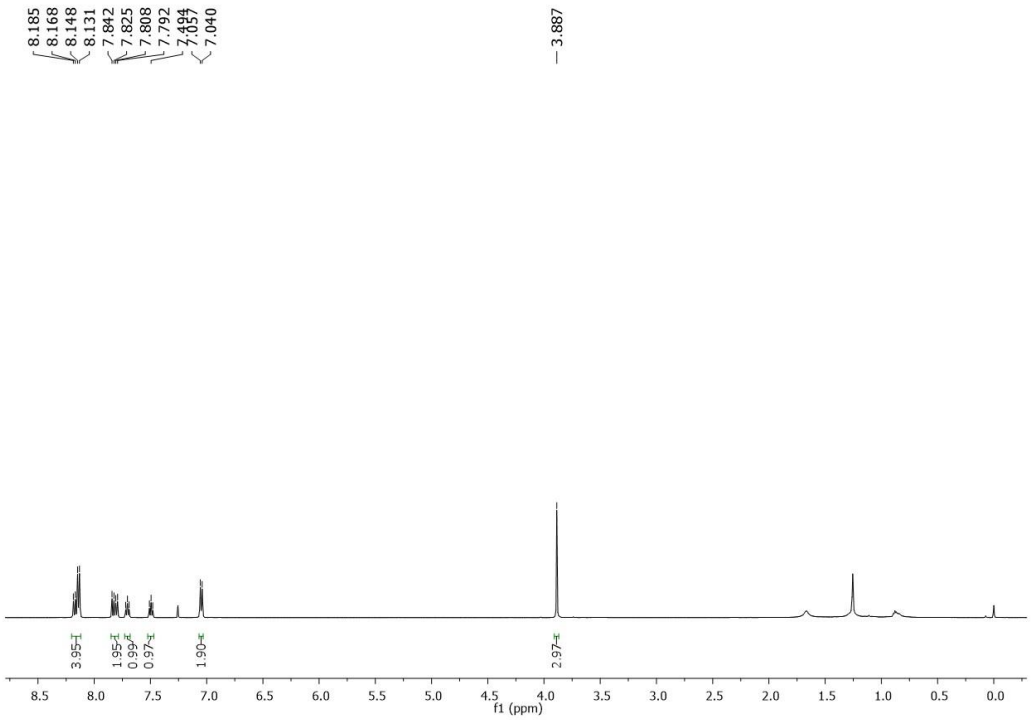


Figure 2.1 ^{1}H NMR (500 MHz) Spectra of **10aa**

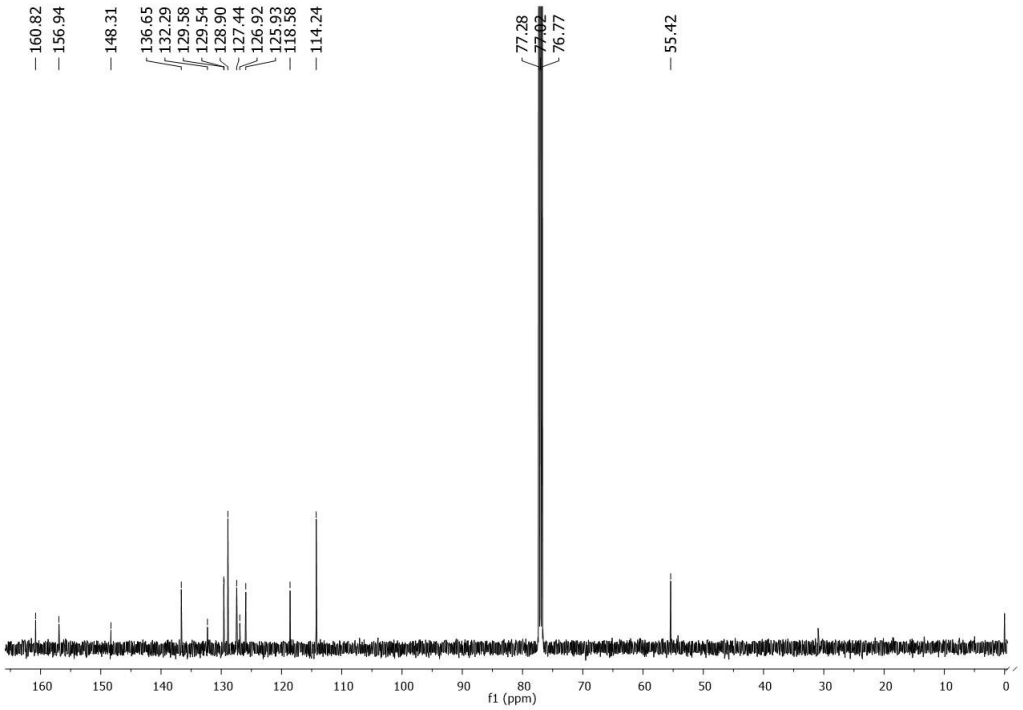


Figure 2.2 ^{13}C{^{1}H} NMR (125 MHz) Spectra of **10aa**

Finally, conducting the reaction under an inert atmosphere didn't significantly influence the outcome of the reaction proving that oxygen is not required for the oxidation step (Table 2.1, entry 12). In conclusion, the reaction holds best at one equivalent each of **1a** and **9a** in the presence of KOH (1.0 equivalent) and DMSO (1.0 mL) at 80 ^{o}C for 7h. False order during the reaction is due to the evolution of dimethyl sulfide (DMS).

Table 2.1 Optimization studies

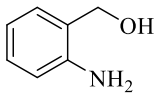
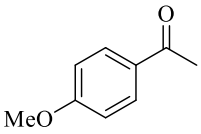
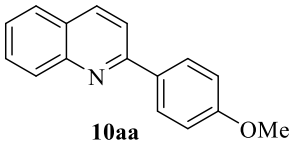
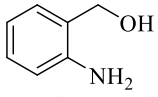
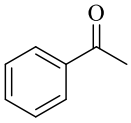
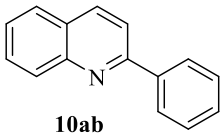
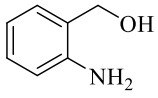
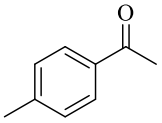
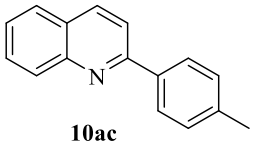
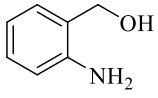
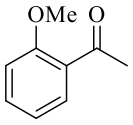
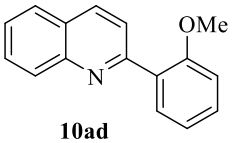
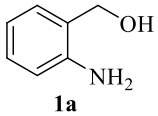
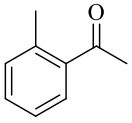
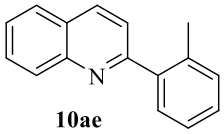
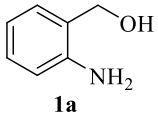
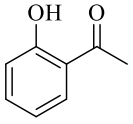
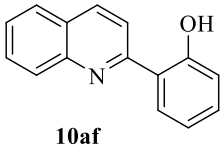
Entry	Base	Time (h)	T (^{o}C)	Yield of **10aa**[a] (%)
1	KOH	7	80	80
2	^{t}BuONa	7	80	48
3	^{t}BuOK	7	80	51
4	NaOH	7	80	61
5	K_2CO_3	7	80	-
6[b]	KOH	7	80	83
7[c]	**KOH**	**7**	**80**	**88**
8[c]	KOH	7	120	59
9[c]	KOH	48	RT	23
10[d]	KOH	7	80	72
11[c]	-	7	80	-
12[e]	KOH	7	80	86

Reaction conditions: [a] **1a** (1.0 equiv.), **9a** (1.0 equiv., 0.6 mmol), base (1.0 equiv.), DMSO (1.0 mL), 80 ^{o}C, 7 h. [b] **1a** (1.1 equiv.). [c] **1a** (1.2 equiv.). [d] **1a** (1.2 equiv.), KOH (0.5 equiv.). [e] **1a** (1.2 equiv.), argon atmosphere.

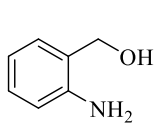
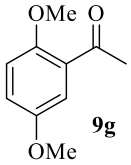
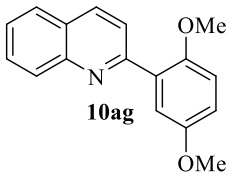
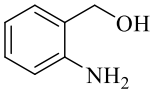
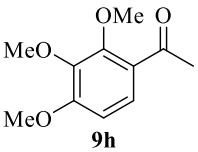
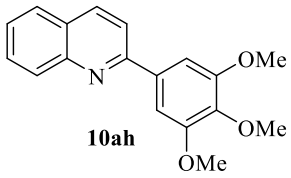
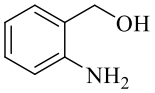
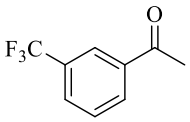
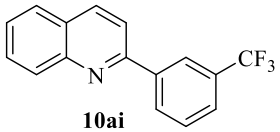
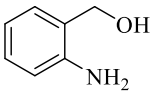
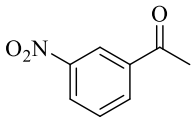
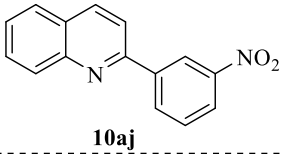
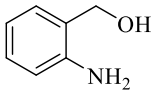
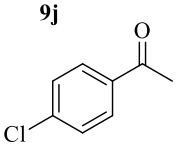
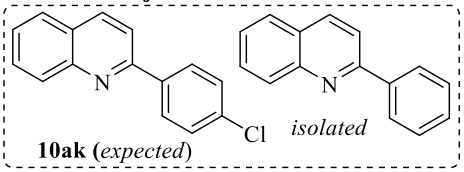
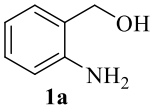
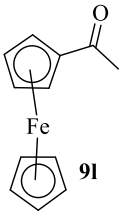
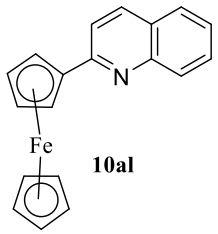
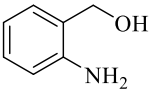
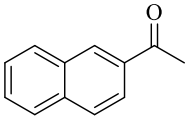
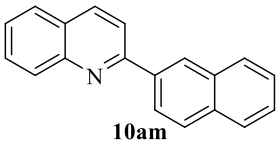
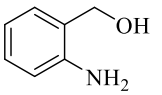
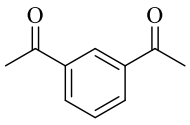
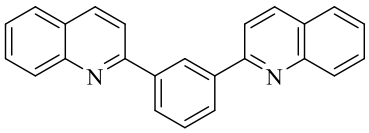
The scope and limitation of the indirect Friedländer quinoline synthesis were then studied (Table 2.2) under the optimized conditions [**1** (1.2 equiv.), **9** (1.0 equiv.), KOH (1.0 equiv.), DMSO (1.0 mL), 80 ^{o}C, 7 h]. Both acetophenone **9b** and 4'-methylacetophenone **9c** participated in the oxidative annulation with *o*-aminobenzyl alcohol **1a** affording the corresponding products **10ab** and **10ac** in 75 and 80% respectively. 2-Phenyl quinoline **10ab** was also synthesized in a gram scale and good yield (70%) by starting with 1.0 g of

acetophenone **9b.** A substituent on the *ortho*-position of the aryl ring of acetophenone did not affect the reaction yield and in this line, the reactions with 2'-methoxy (**9d**) and 2'-methylacetophenone (**9e**) afforded the products **10ad** and **10ae** in good yields, whereas the reaction with 2'-hydroxyacetophenone (**9f**) furnished the product **10af** only in 56% yield.

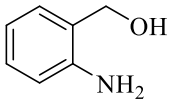
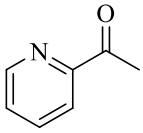
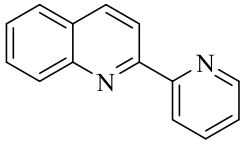
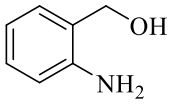
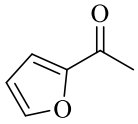
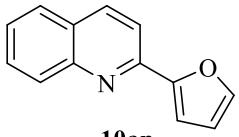
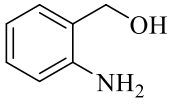
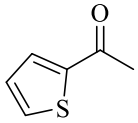
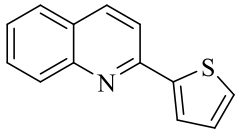
Table 2.2 Generality of indirect Friedländer reaction toward 2-substituted quinolines

Entry	*Ortho*- aminobenzyl alcohol	Ketones having active methylene moiety	Product	Yield (%)
1	 **1a**	 **9a**	 **10aa**	82
2	 **1a**	 **9b**	 **10ab**	75%, 70%[a]
3	 **1a**	 **9c**	 **10ac**	80%
4	 **1a**	 **9d**	 **10ad**	82%
5	 **1a**	 **9e**	 **10ae**	82%
6	 **1a**	 **9f**	 **10af**	56%

Reaction conditions: **1a** (1.2 equiv.), **9** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv.), DMSO (1.0 mL), 80 ^{o}C, 7 h.
[a] started with 1.0 g of **9b**. [b] 120 ^{o}C, 12 h. [c] 14 h.

Entry	*Ortho*- aminobenzyl alcohol	Ketones having active methylene moiety	Product	Yield (%)
7	 **1a**	 **9g**	 **10ag**	56%
8	 **1a**	 **9h**	 **10ah**	87%
9	 **1a**	 **9i**	 **10ai**	46%
10	 **1a**	 **9j**	 **10aj**	26%
11	 **1a**	 **9k**	 **10ak (*expected*)** *isolated*	
12	 **1a**	 **9l**	 **10al**	45%
13	 **1a**	 **9m**	 **10am**	79%
14	 **1a**	 **9n**	 **10an**	69%

Reaction conditions: **1a** (1.2 equiv.), **9** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv.), DMSO (1.0 mL), 80 ^{o}C, 7 h.
[a] started with 1.0 g of **9b**. [b] 120 ^{o}C, 12 h. [c] 14 h.

Entry	*Ortho*- aminobenzyl alcohol	Ketones having active methylene moiety	Product	Yield (%)
15	 **1a**	 **9o**	 **10ao**	75%
16	 **1a**	 **9p**	 **10ap**	69%
17	 **1a**	 **9q**	 **10aq**	65%

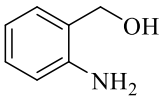
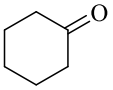
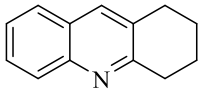
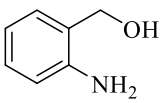
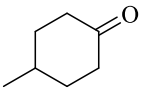
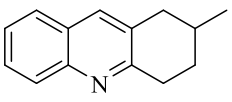
Reaction conditions: **1a** (1.2 equiv.), **9** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv.), DMSO (1.0 mL), 80 ^{o}C, 7 h. [a] started with 1.0 g of **9b**. [b] 120 ^{o}C, 12 h. [c] 14 h.

The superbase mediated oxidative annulation proceeded well with di- (**9g**) and tri-methoxy acetophenones (**9h**) affording the products **10ag** and **10ah** in excellent yields. The presence of electron-withdrawing groups were found to influence the reaction outcome as the reactions with both 3'-(trifluoromethyl)acetophenone (**9i**) and 3-nitroacetophenone (**9j**) could only furnish the corresponding 2-substituted quinolines **10ai** and **10aj** in poor yields. Another interesting observation that we came across was in the reaction with 4'-chloroacetophenone **(9k)** and *o*-aminobenzyl alcohol **1a**. Contrary to our expectation of 2-(4-chlorophenyl) quinoline **10ak**, we obtained a dehalogenated quinoline derivative (**10ab**). The dehalogenation of aromatic compounds with a DMSO-base combination was reported earlier which might be the reason for the present observation.[13] The oxidative annulation also worked with acetylferrocene affording 2-ferrocenylquinoline **10al** in 45% yield. 2-Naphthylquinoline **10am** was synthesized in excellent yield but after 14 h of reaction time. By starting with 1,3-dicetylbenzene we could synthesize 1,3-di-quinolylbenzene **10an** in 69% yield. Finally, the reactivity of different acetyl heteroarenes toward the present indirect

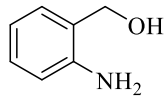
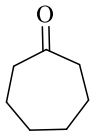
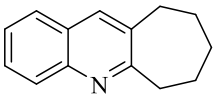
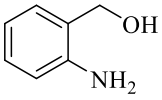
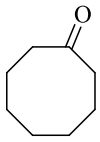
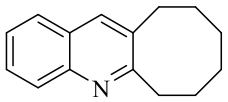
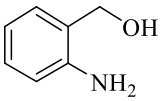
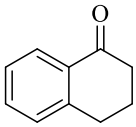
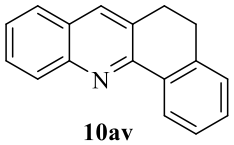
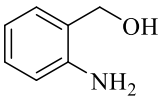
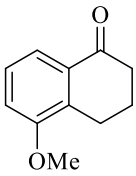
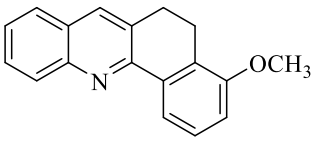
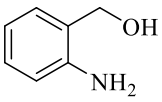
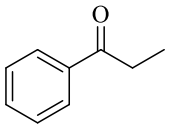
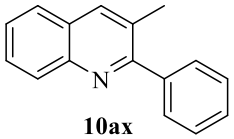
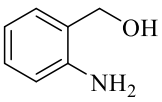
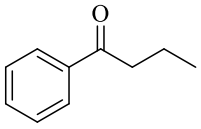
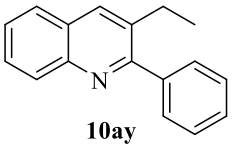
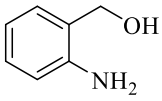
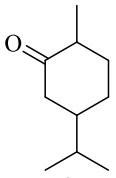
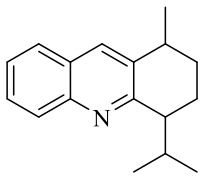
Friedländer reaction was examined and thus pyridyl (**10ao**), furyl (**10ap**), and thienyl (**10aq**) substituted quinolines were synthesized in good yields.

Next, we focused on synthesizing 2,3-disubstituted/fused quinolines *via* the developed superbase mediated oxidative annulation (Table 2.3). We commenced our investigations with *o*-aminobenzyl alcohol **1a** and cyclohexanone under the optimized conditions and 1,2,3,4-tetrahydroacridine **10ar** was isolated in 72% yield. The reaction with 4-methylcyclohexanone also afforded the corresponding substituted tetrahydroacridine derivative **10as** in 68% yield. Other cyclic ketones such as cycloheptanone and cyclooctanone afforded the 2,3-fused quinoline derivatives **10at** and **10au** in good yields. The indirect Friedländer reaction was also found to work well with tetralone **9v** and methoxytetralone **9w** from which the respective dihydrobenzo[*c*]acridine derivatives **10av** and **10aw** were isolated in excellent yields. We then checked the reactivity of propiophenone **9x** and butyrophenone **9y** and these ketones reacted well under the optimized conditions affording the corresponding 2,3-disubstitued quinolines **10ax** and **10ay** in good yields. We have also checked the reactivity of acyclic ketones such as acetone and 2-hexanone but to our dismay, after the required time an intractable reaction mixture was observed. The importance of the present oxidative annulation was exemplified by performing 'quinolization' of natural products containing an enolizable ketone moiety. Thus both menthone (mixture of isomers) and 5α-cholestan-3-one were treated with *o*-aminobenzyl alcohol **1a** under our optimized conditions and the corresponding annulated natural products **10az** and **10aaa** were isolated.

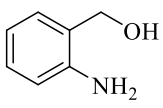
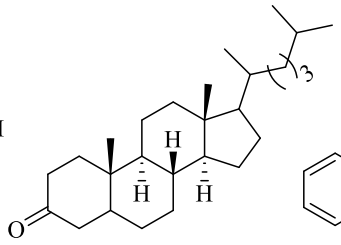
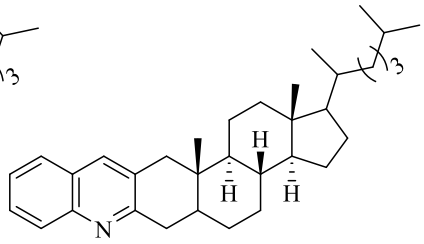
Table 2.3 Generality of indirect Friedländer reaction toward 2,3-disubstituted quinolines

Entry	*Ortho*- aminobenzyl alcohol	Ketones having active methylene moiety	Product	Yield (%)
1	 **1a**	 **9r**	 **10ar**	72%
2	 **1a**	 **9s**	 **10as**	68%

Reaction conditions: **1a** (1.2 equiv.), **9** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv.), DMSO (1.0 mL), 80 ^{o}C, 7 h.

Entry	*Ortho*- aminobenzyl alcohol	Ketones having active methylene moiety	Product	Yield (%)
3	 **1a**	 **9t**	 **10at**	64%
4	 **1a**	 **9u**	 **10au**	52%
5	 **1a**	 **9v**	 **10av**	89%
6	 **1a**	 **9w**	 **10aw**	90%
7	 **1a**	 **9x**	 **10ax**	61%
8	 **1a**	 **9y**	 **10ay**	62%
9	 **1a**	 **9z**	 **10az** isomeric mixture	68%

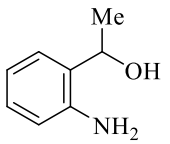
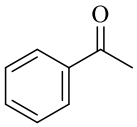
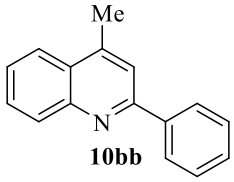
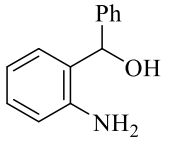
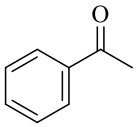
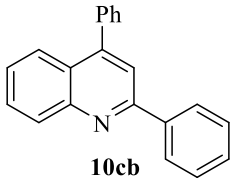
Reaction conditions: **1a** (1.2 equiv.), **9** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv.), DMSO (1.0 mL), 80 ^{o}C, 7 h.

Entry	*Ortho*- aminobenzyl alcohol	Ketones having active methylene moiety	Product	Yield (%)
10	 **1a**	 **9aa**	 **10aaa**	28%

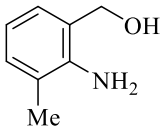
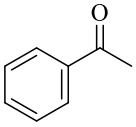
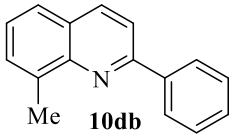
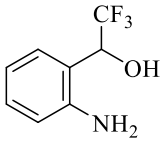
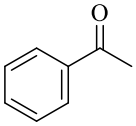
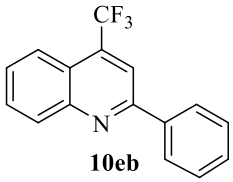
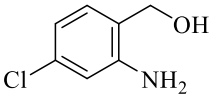
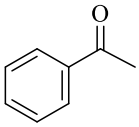
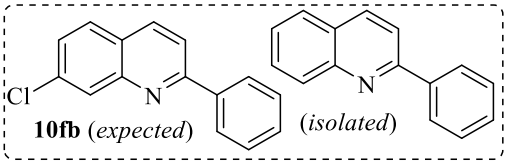
Reaction conditions: **1a** (1.2 equiv.), **9** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv.), DMSO (1.0 mL), 80 ^{o}C, 7 h.

Subsequently, we examined the effect of substituents on *o*-aminobenzyl alcohols on the outcome of the superbase mediated quinoline synthesis (Table 2.4). We commenced with the reaction of acetophenone **9b** with 1-(2-aminophenyl)ethan-1-ol **1b**. The reaction was complete in 7 h from which the 2,4-disubstituted quinoline **10bb** was isolated in 75% yield. 2-aminobenzhydrol **1c** also reacted with ease affording the 2,4-diphenylquinoline **10cb** in good yield. Next, we checked the reactivity of 2-amino-3-methylbenzyl alcohol **1d** under the optimized conditions, and the respective quinoline derivative **10db** was obtained in 86% yield.

Table 2.4 Generality of indirect Friedländer with substituted *o*-aminobenzyl alcohols

Entry	*Ortho*- aminobenzyl alcohol	Ketones having active methylene moiety	Product	Yield (%)
1	 **1b**	 **9b**	 **10bb**	75%
2	 **1c**	 **9b**	 **10cb**	72%

Reaction conditions: **1** (1.2 equiv.), **9b** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv.), DMSO (1.0 mL), 80 ^{o}C, 7 h.

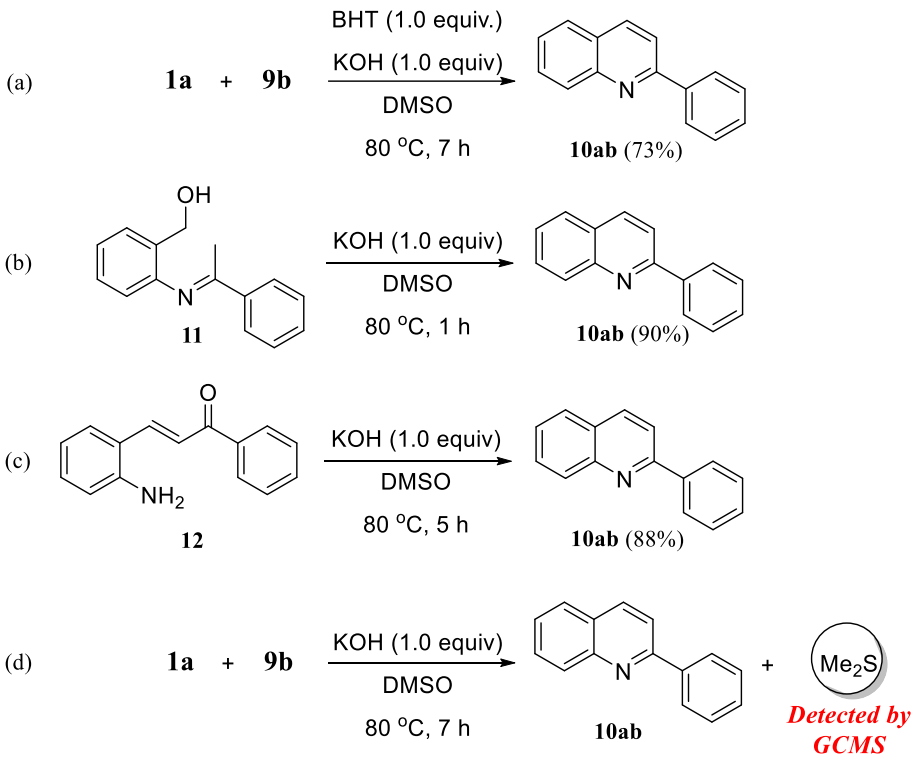
Entry	*Ortho*- aminobenzyl alcohol	Ketones having active methylene moiety	Product	Yield (%)
3	 **1d**	 **9b**	 **10db**	86%
4	 **1e**	 **9b**	 **10eb**	74%
5	 **1f**	 **9b**	 **10fb** (*expected*) (*isolated*)	

Reaction conditions: **1** (1.2 equiv.), **9b** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv.), DMSO (1.0 mL), 80 ^{o}C, 7 h.

The reaction of 1-(2-aminophenyl)-2,2,2-trifluoroethan-1-ol **1e** also proceeded well affording 2-phenyl-4-(trifluoromethyl)quinoline **10eb** in 74% yield. Lastly, we checked the reactivity of 2-amino-4-chlorobenzyl alcohol **1f** with acetophenone and as observed earlier (Table 2.2, compound **10ab**) we obtained the dehalogenated product (Table 2.4).

2.5 Mechanism

To prove the mechanism of the superbase mediated indirect Friedländer quinoline synthesis, we conducted several experiments with substrates **1a** and **9b** (Scheme 2.8). The possibility for a radical-mediated reaction was ruled out with the first reaction (Scheme 2.8 (a)) where **1a** and **9b** were allowed to react under the optimized conditions but in the presence of 1.0 equivalent of BHT from which 2-phenylquinoline **10ab** was isolated in 73% yield. The excellent yield, even in the presence of a radical scavenger like BHT, indicates that the reaction doesn't involve any radical mechanism.

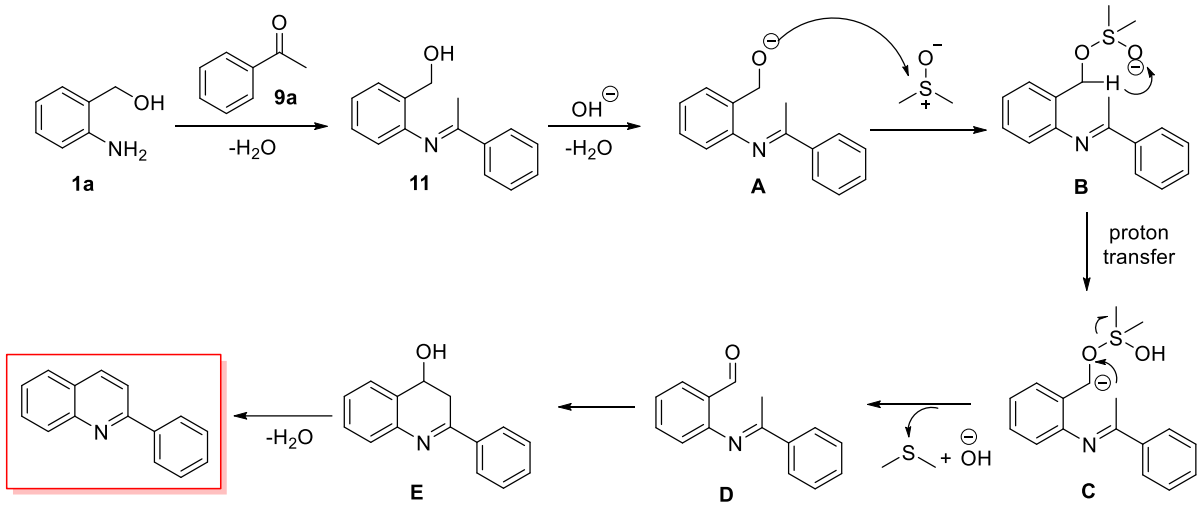


Scheme 2.8 Control experiments

It is reported that the classical Friedländer quinoline synthesis can proceed either *via* the imine **11** or *o*-amino chalcone **12** as intermediates.[5] So we synthesized the possible intermediates imine and *o*-amino chalcone with the reported procedure. When **11** was subjected to the optimized conditions, we isolated the expected product **10ab** in 90% yield after an hour (Scheme 2.8 (b)). On the other hand, when *o*-amino chalcone **12** was allowed to react at the optimized conditions, the reaction took 5 h to furnish 88% of **10ab** (Scheme 2.8 (c)). These results show that the present superbase mediated quinoline synthesis might be proceeding predominantly *via* the imine intermediate **11** rather than the chalcone **12** and that imine formation must be happening preferentially over the oxidation of the benzyl alcohol moiety. Finally, we detected the formation of Me_2S as a by-product by conducting a GCMS experiment (Scheme 2.8 (d)).[14] The false odour that evolved during the reaction is due to the formation of dimethylsulphide.

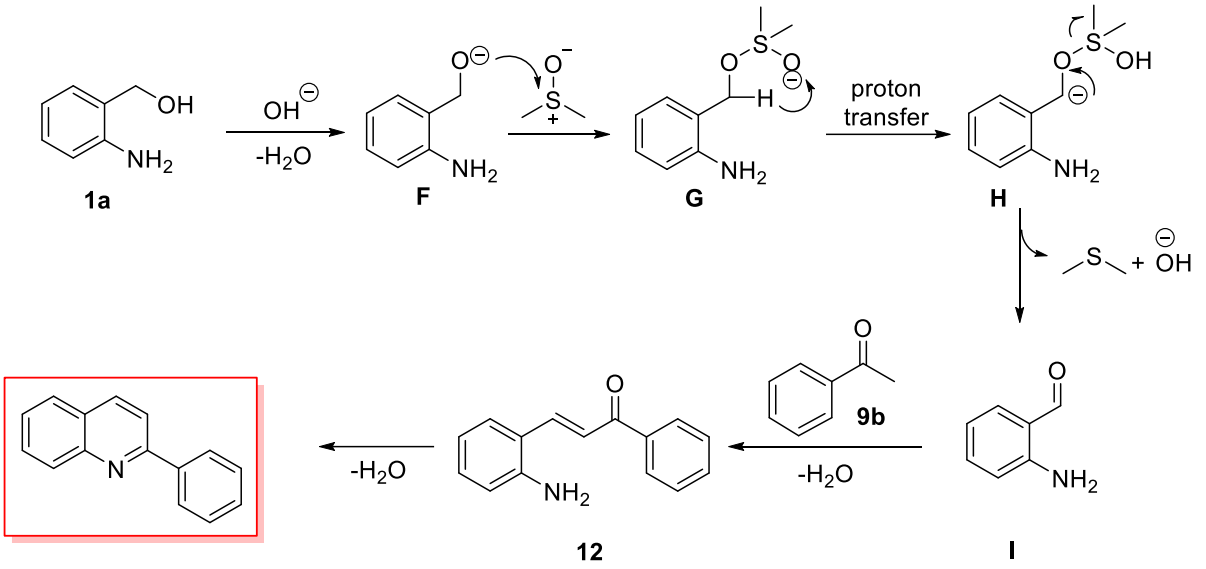
From the results obtained for the experiments depicted above, we believe that the first step of quinoline synthesis (predominant pathway) would be the condensation of the amino group of 2-aminobenzylalcohol and acetophenone to yield the imine **11** (Scheme 2.9). This will be

followed by the oxidation of the alcohol to the corresponding carbonyl group which proceeds *via* a mechanism analogous to the one proposed by Ravikumar *et al.*[11a] Initially, the base will generate the alkoxide intermediate **A** from **11** by eliminating a water molecule. The adduct **B** is then formed by the attack of the alkoxide to the electrophilic sulfur of DMSO.



Scheme 2.9 Predominant Pathway

Subsequently, proton transfer occurs from the benzylic carbon to the alkoxide generating the carbanion **C** which further undergoes an $E1_{cb}$ elimination furnishing the corresponding carbonyl compound **D** along with dimethylsulphide as a by-product. An intramolecular aldol addition occurs in intermediate **D** to furnish the dihydroquinoline **E** from which water is eliminated to finally afford the substituted quinoline derivative.[5] The secondary pathway will commence with the benzylic alcohol functionality to the *o*-amino benzaldehyde I by following a similar mechanism as shown before (Scheme 2.10). The base will generate the alkoxide intermediate **F** from 2-aminobenzylalcohol by the elimination of a water molecule. The adduct **G** is then formed by the attack of the alkoxide to the electrophilic sulfur of DMSO. Subsequently, proton transfer occurs from the benzylic carbon to the alkoxide generating the carbanion H which further undergoes an $E1_{cb}$ elimination furnishing the corresponding carbonyl compound **I** along with dimethylsulphide as a by-product. The *o*-amino chalcone **12** is then formed by the condensation of **I** with acetophenone. The intermediate **12** subsequently undergoes intramolecular annulation to furnish 2-substituted quinoline by the elimination of H_2O.



Scheme 2.10 Secondary Pathway

2.6 Conclusion

In conclusion, we have developed a mild, transition metal-free, and general methodology for the synthesis of functionalized quinolines. In contrast to the reported methods that required either metal catalysts (homogeneous or heterogeneous) or additional reagents (hydride scavenger or NHC catalyst) our strategy required only the combination of KOH in DMSO. In this superbasic medium, the reaction proceeds predominantly *via* the formation of an imine and successive oxidation of 2-aminobenzyl alcohol to the corresponding aldehyde followed by condensation with the enamine moiety. We could propose a mechanistic postulate by isolating the imine intermediate and subjecting it to oxidative annulation conditions. We could also show that a minor fraction of the reaction proceeds *via* a chalcone intermediate. This oxidative annulation worked well affording mono-, di- and poly-substituted quinolines in good yields. In the case of halogen substituted quinoline derivatives, dehalogenation was observed as reported earlier. It is noteworthy to mention that we could synthesize substituted quinoline by this methodology in gram scale thereby proving the applicability of the reaction. In addition, we also utilized this superbase mediated oxidative annulation to functionalize natural products.

2.7 Experimental section

2.71 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, and mixtures of ethyl acetate/ hexanes were used for elution. Melting points were determined using a calibrated digital melting point apparatus (Büchi 530 melting point apparatus). NMR spectra were recorded with 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 performed with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with an ESI/ HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer with orbitrap analyzer. Gas chromatographic analysis was performed using GCMS-TQ8030 SHIMADZU.

2.72 Detection of dimethylsulphide (DMS) by GCMS

Gas chromatographic analysis was performed using GCMS-TQ8030 SHIMADZU. Reaction (*o*-aminobenzyl alcohol **1a** (12 mg, 0.1 mmol), acetophenone **9b** (10 mg, 0.08 mmol), KOH (5 mg, 0.08 mmol) in DMSO (0.5 mL)) was incubated in Head Space reaction chamber (15 min at 60 ^{o}C). 1µL of the gaseous sample was injected onto a GC equipped with an MS and a medium polar capillary column Rxi-5Sil MS, (30m X 0.25mm I. D., 0.25µm), the oven program had an initial temperature of 30 ^{o}C for 1 min, increased to 60 ^{o}C for 2min at the rate of 5 ^{o}C /min followed by the temperature was increased to 220 ^{o}C for 1min at the rate of 5 ^{o}C /min. Finally, the temperature was increased to 250 ^{o}C at the rate of 2 ^{o}C /min for

8 min. The total run time was 47.75 min. The detector temperature and injection temperature were 250 ^{o}C, and helium was used as the carrier gas with a purity of 99.999% at a flow rate of 1mL/ min. The samples were injected in the splitless mode. The ion energy used for the electron impact ionization (EI) mode was 70eV. The mass range scanned was 50 - 1000 m/z. The formation of DMS was identified by comparing the mass spectra with the spectra of reference compound (DMS) in the mass spectral library of NIST and WILEY.

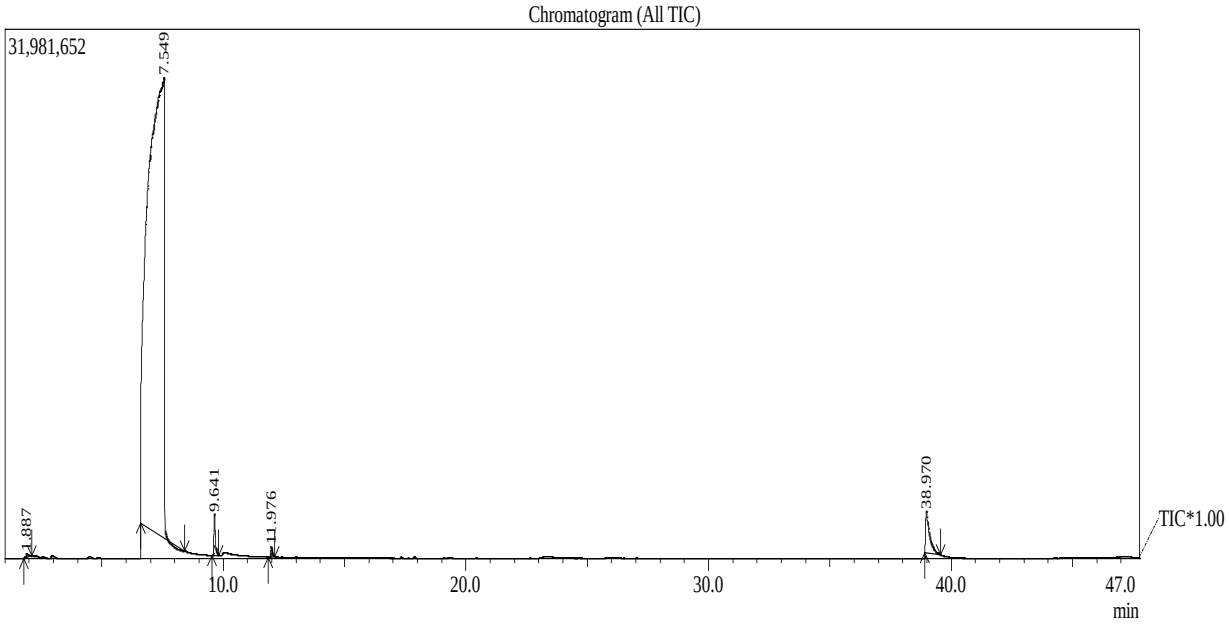


Figure 2.3: GC-MS Spectra 1

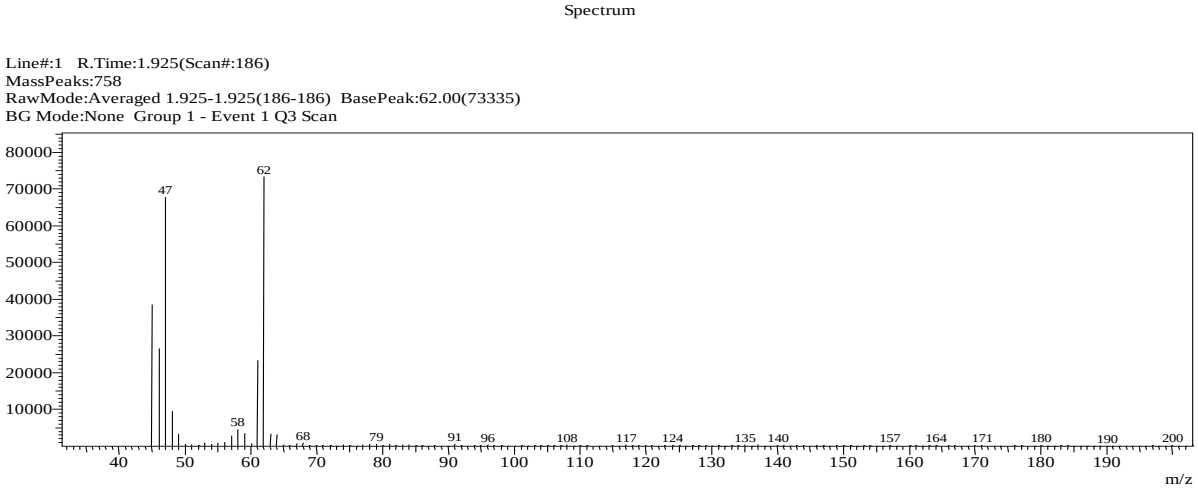


Figure 2.4: GC-MS Spectra 2

Peak#	Ret. Time	Start Tm	End Tm	m/z	Area	Area%	Height	Height%	A/H	Mark	Name
1	1.887	1.775	2.115	TIC	1558097	0.12	212043	0.63	7.35	MI	Dimethyl sulfide
2	7.549	6.590	8.420	TIC	1305250564	96.91	27739885	82.48	47.05	MI	Dimethylsulfoxonium formylmethylide
3	9.641	9.550	9.805	TIC	10845217	0.81	2511315	7.47	4.32	MI	Benzene, (1-methylethyl)-
4	11.976	11.865	12.130	TIC	2345489	0.17	630940	1.88	3.72	MI	Benzene, (1-methylethenyl)-
5	38.970	38.910	39.560	TIC	26868573	1.99	2535902	7.54	10.60	MI	Quinolinium, 1-methyl-2-phenyl-, iodide

Figure 2.5: GC-MS Spectra 3

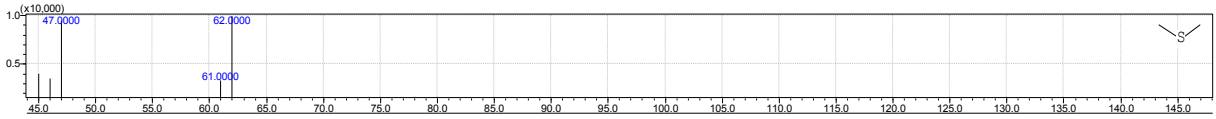


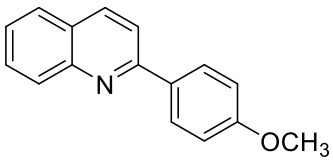
Figure 2.6: Mass spectral data of DMS (WILEY library)

2.73 Experimental procedure for the synthesis of substituted quinoline derivatives

To a reaction tube equipped with a magnetic stirring bar, acetophenone **9** (1.0 equiv.), *o*-aminobenzylalcohol **1** (1.2 equiv.) KOH (1 equiv.) and 1 mL of DMSO were added. The resultant reaction mixture was kept for stirring at 80°C for 7 h. After completion of the reaction, water was added and the aqueous layer was extracted thrice with ethylacetate. 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 ethylacetate/hexanes) to afford the corresponding 2-substituted quinolones.

2-(4-methoxyphenyl)quinoline (10aa)[6i,14a]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 4-methoxyacetophenone **9a** (100 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10aa** as a white solid (138mg, 88%).



Analytical data of 10aa

Mp: 125−126 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.18−8.13 (m, 4H), 7.84−7.79 (m, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 3.89 (s, 3H) ppm.

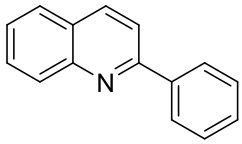
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.8, 156.9, 148.3, 136.6, 132.3, 129.6, 129.5, 128.9, 127.4,

126.9, 125.9, 118.6, 114.2, 55.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{14}NO$ 236.1070, found 236.1078.

2-phenylquinoline (10ab)[6i,14a]

Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), acetophenone **9b** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10ab** as a white solid (103 mg, 75%). For the gram-scale preparation of **10ab**, the yield was 70% (1.19 g**).**



Analytical data of 10ab

Mp: 84−87 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.20−8.15 (m, 4H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.73−7.70 (m, 1H), 7.53−7.49 (m, 3H), 7.47−7.44 (m, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, TMS): δ 157.4, 148.3, 139.7, 136.8, 129.8, 129.7, 129.3, 128.9, 127.6, 127.5, 127.2, 126.3, 119.1 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{12}N$ 206.0964, found 206.0975.

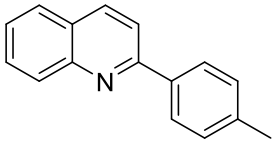
2-(*p*-tolyl)quinoline (10ac)[6i,14a]

Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80mmol), 4-methylacetophenone **9c** (90mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10ac** as a white solid (117 mg, 80%).

Analytical data of 10ac

Mp: 81−84 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.17 (t, *J* = 9 Hz, 2H), 8.07 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 8.5



Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.71 (t, *J* = 8 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.32 (d, J = 7.5 Hz, 2H), 2.43 (s, 3H) ppm.

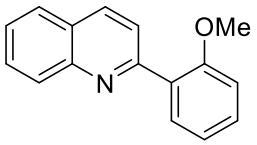
$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 157.4, 148.3, 139.4, 136.9, 136.7, 129.7, 129.6, 127.4, 127.1, 126.1, 118.9, 21.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{14}N$ 220.1121, found 220.1124.

2-(2-methoxyphenyl)quinoline (**10ad**)[6i,14a]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-methoxyacetophenone **9d** (100 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10ad** as a colourless liquid (129 mg, 82%).

Analytical data of 10ad



^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.18−8.13 (m, 2H), 7.89−7.82 (m, 3H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.13 (t, *J* = 7.5Hz, 1H), 7.03 (d, *J* = 8 Hz, 1H), 3.86 (s, 3H) ppm.

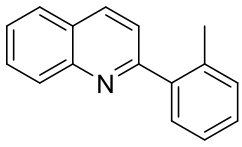
$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 157.2, 157.2, 148.3, 135.1, 131.5, 130.4, 129.8, 129.6, 129.2, 127.4, 127.1, 126.2, 123.5, 121.3, 111.4, 55.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{14}NO$ 236.1070, found 236.1072.

2-(*o*-tolyl)quinoline (**10ae**)[6i,14a]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-methylacetophenone **9e** (90 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by

neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10ae** as a white solid, 104 mg (71%).



Analytical data of 10ae:

Mp: 69−71°C

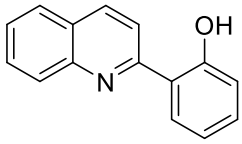
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.21 (d, *J* = 8 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8 Hz, 1H), 7.74 (t, *J* = 8 Hz, 1H), 7.58−7.53 (m, 2H), 7.50 (d, *J* = 7 Hz, 1H), 7.36−7.33 (m, 3H), 2.41 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.3, 147.9, 140.8, 136.1, 136.0, 130.9, 129.7, 129.6, 128.5, 127.5, 126.8, 126.4, 126.0, 122.4, 20.4 ppm.

HRMS (ESI-Orbitrap) *m/z*: $(M+H)^+$ calcd for $C_{16}H_{14}N$ 220.1121, found 220.1124

2-(quinolin-2-yl)phenol (10af)[14c]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-hydroxyacetophenone **9f** (92 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10af** as a white solid (83 mg, 56%).



Analytical data of 10af

Mp: 113−115 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 15.24 (s, 1H), 8.27 (d, *J* = 9 Hz, 1H), 8.06−8.03 (m, 2H), 7.95 (d, *J* = 8 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.74 (t, *J* = 8 Hz, 1H), 7.57−7.54 (m, 1H), 7.37 (t, *J* = 7. 5 Hz, 1H) 7.09 (d, *J* = 8.5 Hz, 1H), 6.96 (t, *J* = 7. 5 Hz, 1H) ppm.

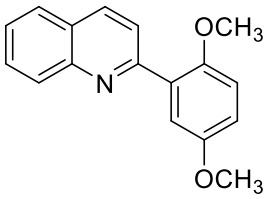
^{13}C{^{1}H} NMR (125 MHz, CDCl3): δ 161.0, 158.0, 144.8, 137.6, 130.5, 127.6, 127.5, 126.9,

126.7, 126.6, 119.0, 118.7, 118.7, 117.3 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{12}NO$ 222.0913, found 222.0924.

2-(2,5-dimethoxyphenyl)quinolone (**10ag**)

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2,5-dimethoxyacetophenone **9g** (121 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product of **10ag** as a white solid (138 mg, 78%).



Analytical data of 10ag

Mp: 141−143 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.16 (t, *J* = 9.5 Hz, 2H), 7.91 (d, *J* = 8 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.72−7.70 (m, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45 (s, 1H), 6.98 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.9, 154.1, 151.6, 148.3, 135.2, 130.4, 129.7, 129.3, 127.4, 127.1, 126.3, 123.4, 116.2, 116.1, 113.3, 56.6, 55.9 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{16}NO_2$ 266.1176, found 266.1181.

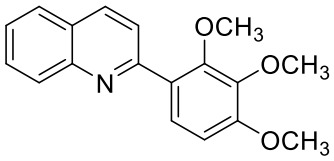
2-(2,3,4-trimethoxyphenyl)quinoline (**10ah**)

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2,3,4-trimethoxyacetophenone **9h** (141 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product of **10ah** a white solid (172 mg, 87%).

Analytical data of 10ah

Mp: 104−106 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.16−8.15



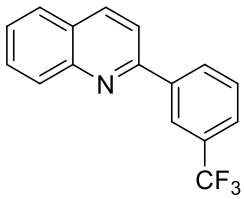
(m, 2H), 7.90 (d, *J* = 9 Hz, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.5Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.77 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, CDCl3): δ 156.6, 154.6, 152.3, 148.3, 142.4, 135.5, 129.6, 129.3, 127.6, 127.4, 127.0, 126.1, 125.8, 122.9, 108.1, 61.5, 61.1, 56.2 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{18}H_{18}NO_3$ 296.1281, found 296.1287.

2-(3-(trifluoromethyl)phenyl)quinoline (**10ai**)[14b]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 3-trifluoromethyl acetophenone **9i** (126 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexanes) to afford the desired product **10ai** as a white solid (84 mg, 46%).



Analytical data of 10ai

Mp: 51−53 °C.

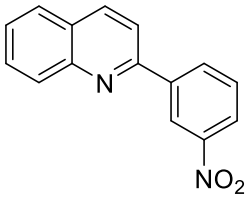
^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.47 (s, 1H), 8.36 (d, *J* = 7.5 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.78−7.72 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 155.6, 148.3, 140.4, 137.2, 131.3 (q, j = 32.5 Hz), 130.7, 130.0, 129.8, 129.3, 127.5, 127.4, 126.8, 125.9 (q, j = 3.8 Hz), 124.4 (q, j = 3.8 Hz), 118.6 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{11}F_3N$ 274.0844, found 274.0851.

2-(3-nitrophenyl)quinoline (**10aj**)[14a]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 1.2 0.80 mmol), 3-nitroacetophenone **9j** (110.6 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 120 °C and subsequent stirring for 12 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexanes) to afford the desired product **10aj** as a white solid (44 mg, 26%).



Analytical data of 10aj

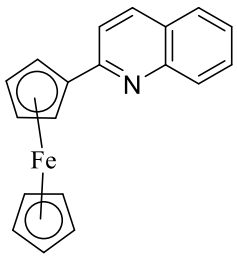
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.06 (s, 1H), 8.57 (d, *J* = 8 Hz, 1H), 8.33−8.31 (m, 2H), 8.20 (d, *J* = 8 Hz, 1H), 7.95 (d, *J* = 8.5Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.79 (t, *J* = 8 Hz, 1H), 7.72 (t, *J* = 8 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.3, 141.3, 137.4, 137.1, 133.3, 130.2, 129.9, 129.8, 127.6, 127.1, 123.9, 122.5, 118.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{11}N_2O_2$ 251.0815, found 251.0825.

2-Ferrocenylquinoline (**10al**)[14c]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), acetylferrocene **9l** (153 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10al** as red solid (94 mg, 45%).



Analytical data of 10l

Mp: 135−138 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.48–7.45 (m, 1H), 5.07 (s, 2H), 4.47 (s, 2H), 4.06 (s, 5H) ppm.

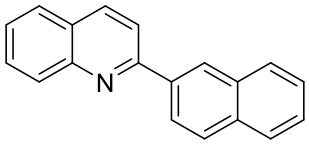
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.5,

148.3, 135.4, 129.4, 129.0, 127.5, 126.7, 125.4, 119.5, 84.0, 70.4, 69.7, 68.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{13}H_{10}NS$ 314.0627, found 314.0621.

2-(naphthalen-2-yl)quinoline (**10am**).[14c]

Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2-acetonaphthone **9m** (114 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 14 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10am** as a pale yellow solid (135 mg, 79%).



Analytical data of 10am

Mp: 136 −139 ^oC

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 8.63 (s, 1H), 8.39 (dd, J_1= 8.7 Hz, J2 = 1.8 Hz, 1H), 8.27–8.23 (m, 2H), 8.04–7.99 (m, 3H), 7.93–7.89 (m, 1H), 7.86–7.83 (m, 1H), 7.79−7.74 (m, 1H) 7.58−7.53 (m, 3H) ppm.

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 157.1, 148.3, 136.9, 136.8, 133.8, 133.5, 129.7, 129.7, 128.8, 128.6, 127.7, 127.5, 127.2, 127.1, 126.7, 126.3, 126.3, 125.0, 119.1 ppm.

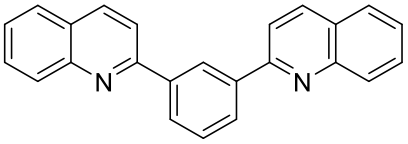
1,3-di(quinolin-2-yl)benzene (**10an**).[14d]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (197 mg, 1.6 mmol), 1,3-diacetylbenzene **9n** (109 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10an** as a white solid (153 mg, 69%).

Analytical data of 10an

Mp: 138-141 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.97 (s,



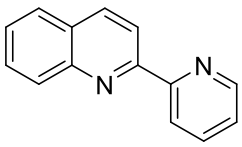
1H), 8.30–8.27 (m, 4H), 8.23 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 9 Hz, 2H), 7.86 (d, *J* = 8 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 8 Hz, 1H), 7.55 (t, *J* = 8 Hz, 2H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 157.2, 148.3, 140.3, 136.9, 129.8, 129.8, 129.5, 128.6, 127.5, 127.3, 126.8, 126.4, 119.2 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{24}N_2$ 333.1386, found 333.1395.

2-(pyridin-2-yl)quinoline (**10ao**)[14a]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-acetylpyridine **9o** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10ao** as a white solid (103 mg, 75%).



Analytical data of 10ao

Mp: 98−100°C.

^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.74−8.73 (1H, m), 8.65 (d, *J* = 8 Hz, 1H), 8.56 (d, *J* = 8.5 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.88-7.84 (m, 2H), 7.73 (t, *J* = 8 Hz, 1H) 7.55 (t, *J* = 7.5Hz, 1H), 7.35 (t, *J* = 6 Hz, 1H) ppm.

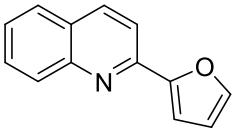
$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 156.4, 156.2, 149.2, 148.0, 137.0, 136.8, 129.8, 129.6, 128.3, 127.6, 126.8, 124.1, 121.9, 119.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{14}H_{11}N_2$ 207.0917, found 207.0922.

2-(furan-2-yl)quinoline (**10ap**)[14a]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-acetylfuran **9p** (74 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0

mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexanes) to afford the desired product **10ap** as a white solid (90 mg, 69%).



Analytical data of 10ap

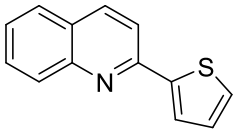
Mp: 87−89 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.17 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H), 7.72−7.69 (m, 1H), 7.63 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.22 (s, 1H), 6.60 (s, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.0, 144.2, 136.7, 129.9, 129.4, 127.6, 127.2, 126.2, 117.5, 112.2, 110.2 ppm.

2-(thiophen-2-yl)quinoline (10aq)[14a]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-acetylthiophene **9q** (85 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10aq** as a white solid (92 mg, 65%).



Analytical data of 10aq

Mp: 131−134 °C.

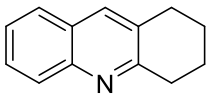
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.15 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.82−7.76 (m, 3H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.51−7.47 (m, 2H), 7.18−7.16 (m, 1H), ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.4, 148.1, 136.7, 129.8, 129.3, 128.6, 128.1, 127.5, 126.1, 125.9, 117.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{13}H_{10}NS$ 212.0528, found 212.0539.

1,2,3,4-tetrahydroacridine (**10ar**)[14c]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), cyclohexanone **9r** (66 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10ar** as a pale yellow solid (88 mg, 72%).



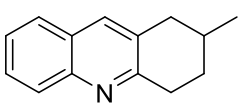
Analytical data of 10ar

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.77 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.62−7.56 (m, 1H), 7.44−7.39 (m, 1H), 3.13 (t, *J* = 6.6 Hz, 2H), 2.94 (t, *J* = 6.6 Hz, 2H), 2.02−1.93 (m, 2H), 1.88−1.83 (m, 2H) ppm.

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 159.2, 146.3, 135.1, 130.9, 128.5, 128.0, 127.1, 126.8, 125.5, 33.4, 29.1, 23.1, 22.8 ppm.

2-methyl-1,2,3,4-tetrahydroacridine (**10as**)[14f]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 4-methylcyclohexanone **9s** (75mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10as** as a white solid (90 mg, 68%).



Analytical data of 10as

Mp: 78−79°C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.97 (d, *J* = 8.5 Hz, 1H), 7.74 (s, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 3.23−3.20 (m, 1H), 3.12−3.05 (m, 1H), 3.00−2.96 (m, 1H), 2.59−2.53 (m, 1H), 2.06−1.95 (m, 2H), 1.62−1.54 (m, 1H), 1.11 (d, *J* = 7 Hz, 3H).

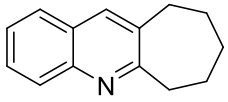
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.1,

146.7, 135.0, 130.6, 128.5, 128.3, 127.2, 126.9, 125.5, 37.8, 33.1, 31.4, 29.1, 21.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{14}H_{16}N$ 198.1277, found 198.1286.

7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline (10at)[14c]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), cycloheptanone **9t** (75 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10at** as a white solid (84 mg, 64%).



Analytical data of 10at

Mp: 92−94°C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.00 (d, *J* = 8.5 Hz, 1H), 7.79 (s, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.61 (t, *J* = 8 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 3.21−3.20 (m, 2H), 2.93−2.92 (m, 2H), 1.89−1.74 (m, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.7, 146.2, 136.5, 134.6, 128.5, 128.4, 127.4, 126.8, 125.8, 40.1, 35.5, 32.2, 28.9, 27.0 ppm.

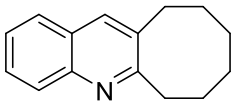
HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{14}H_{16}N$ 198.1277, found 198.1270.

6,7,8,9,10,11-hexahydrocycloocta[b]quinoline (10au)[14d]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), cyclooctanone **9u** (85mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10au** as a colorless liquid (74 mg, 52%).

Analytical data of 10au

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.03 (d, *J* =



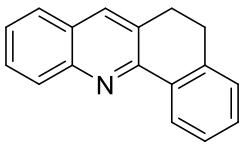
8.5 Hz, 1H), 7.84 (s, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 3.17 (t, *J* = 6.5 Hz, 2H), 2.96 (t, *J* = 6 Hz, 2H), 1.90 (s, 2H), 1.78 (s, 2H), 1.41 (s, 4H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.2, 147.0, 135.2, 135.0, 128.5, 128.4, 127.6, 126.9, 125.6, 35.3, 32.7, 32.1, 31.0, 26.0, 25.9 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{18}N$ 212.1434, found 212.1438.

5,6-dihydrobenzo[c]acridine (**10av**)[14a]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80), 1-tetralone **9v** (98 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80°C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10av** as a white solid (138 mg, 89%).



Analytical data of 10av

Mp: 59-62°C.

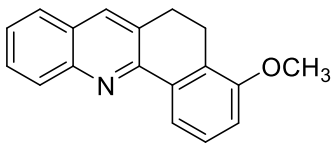
^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.57 (d, *J* = 8 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.66−7.63 (m, 1H), 7.48−7.41 (m, 2H), 7.37 (t, *J* = 7. 5 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 3.13 (t, *J* = 7 Hz, 2H), 3.01 (t, *J* = 7 Hz, 2H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 153.4, 147.7, 139.4, 134.7, 133.7, 130.6, 129.7, 129.4, 129.1, 128.7, 128.0, 127.9, 127.4, 126.9, 126.1, 28.9, 28.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{14}N$ 232.1121, found 232.1129.

4-methoxy-5,6-dihydrobenzo[c]acridine (**10aw**)

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 5-methoxy-1-tetralone **9w** (118 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10aw** as a white solid (157 mg, 90%).



Analytical data of 10aw

Mp: 120-123°C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.22 (d, *J* = 7.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.65−7.62 (m, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 8.5Hz, 1H), 6.96 (d, *J* = 8 Hz, 1H), 3.90 (s, 3H), 3.09 (t, *J* = 6.5 Hz, 2H), 3.02 (t, *J* = 6.5 Hz, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.3, 153.4, 147.6, 135.9, 133.6, 130.6, 129.5, 128.5, 128.2, 127.9, 127.4, 126.9, 126.1, 118.4, 111.4, 55.7, 28.3, 20.4 ppm.

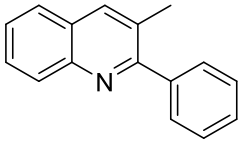
HRMS (ESI-Orbitrap) m/z: ($(M+H)^+$ calcd for $C_{18}H_{16}NO$ 262.1226, found 262.1236.

3-methyl-2-phenylquinoline (**10ax**)[14a]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), propiophenone **9x** (90 mg, 0.67 mmol), KOH (38 mg, 0.67 mg) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10ax** as a colourless liquid (89 mg, 61%).

Analytical data of 10ax

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.13 (d, *J* = 8 Hz, 1H), 8.00 (s, 1H), 7.76 (d, *J* = 8 Hz, 1H), 7.67−7.64 (m, 1H), 7.58 (d, *J* = 7 Hz, 2H), 7.52−7.47 (m, 3H), 7.44-7.41 (m, 1H), 2.45 (s,



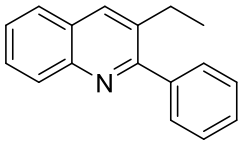
3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.6, 146.6, 140.9, 136.8, 129.3, 129.2, 128.9, 128.8, 128.3, 128.2, 127.6, 126.8, 126.4, 20.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{14}N$ 220.1121, found 220.1134.

3-ethyl-2-phenylquinoline (**10ay**)[14a]

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg,0.80 mmol), butyrophenone **9y** (99 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexanes) to afford the desired product **10ay** as a colourless liquid (90 mg, 58%).



Analytical data of 10ay

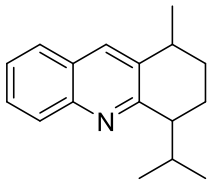
^1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.13 (d, *J* = 8.5 Hz, 1H), 8.06 (s, 1H), 7.82 (d, *J* = 8 Hz, 1H), 7.68−7.65 (m, 1H), 7.56−7.53 (m, 3H), 7.50−7.42 (m, 3H), 2.90 (q, *J* = 7.5 Hz,2H), 1.20 (t, *J* = 7.5Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.7, 146.4, 140.9, 135.3, 134.9, 129.3, 128.8, 128.7, 128.3, 128.1, 127.8, 127.0, 126.4, 26.0, 14.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{16}N$ 234.1277, found 234.1283.

4-isopropyl-1-methyl-1,2,3,4-tetrahydroacridine (**10az**)

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), menthone (isomeric mixture) **9z** (104 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexanes) to afford the desired product **10az** as a colourless liquid and as an isomeric mixture (ratio 2:1) (109 mg, 68%).



Analytical data of 10az

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.99 (d, *J* = 8.5 Hz,1.5 H), 7.94 (s, 0.53H), 7.85 (s, 1H), 7.72 (t, *J* = 8.5 Hz, 1.5H), 7.60 (t, *J* = 7Hz, 1.54H), 7.43 (t, *J* = 7 Hz, 1.54H), 3.13−3.07 (m, 1.62H), 3.02 – 2.95 (m, 3.17H), 2.06−2.04 (m, 1.2H), 1.94−1.85 (m, 3.30H), 1.76−1.74 (m, 1.63H), 1.41 (d, *J* = 6.5 Hz, 1.6H), 1.37 (d, *J* = 7 Hz, 3.08H), 1.11 (d, *J* = 6.5 Hz, 3.04H), 1.07 (d, *J* = 7 Hz, 1.70H), 0.75 (d, *J* = 6.5 Hz, 3.00H), 0.67 (d, *J* = 6.5 Hz, 1.63H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.0, 161.7, 146.7, 146.4, 137.1, 136.8, 134.2, 132.4, 128.7, 128.5, 128.3, 128.2, 127.1, 126.9, 126.8, 125.4, 47.6, 47.0, 33.3, 32.9, 31.4, 31.3, 30.5, 28.6, 23.1, 21.8, 21.2, 21.0, 20.8, 18.7, 17.5, 17.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{22}N$ 240.1747, found 240.1752.

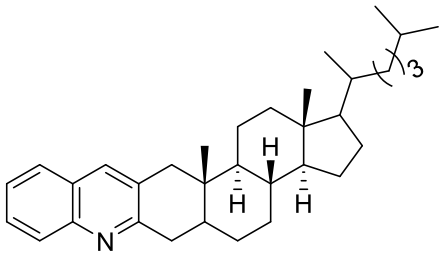
(3aS,3bR,13S,13bS,15aR)-13,15a-dimethyl-1-(6-methylheptan-2-yl)-2,3,3a,3b,4,5,5a,6, 13,13a,13b,14,15,15a-tetradecahydro-1*H*-cyclopenta[5,6]naphtho[1,2-*b*]acridine (**10aaa**)

Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), cholestan-3-one **9aa** (260 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10aaa** as a white solid (88 mg, 28%).

Analytical data of 10aaa

Mp: 183−186 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.97 (d, *J* = 8.5 Hz, 1H), 7.81 (s, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 3.08 (dd, J_1 = 18 Hz, J_2 = 5.0 Hz, 1H), 2.99 (d, *J* =



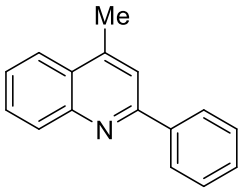
16 Hz, 2H), 2.79 (dd, J_1 = 18 Hz, J_2 = 13 Hz, 1H), 2.61 (d, J = 16.0 Hz, 1H), 2.06 (d, J = 12 Hz, 1H), 1.88−1.75 (m, 3H), 1.67−1.62 (m, 5H), 1.54−1.47 (m, 2H), 1.40−1.34 (m, 4H), 1.28−1.21 (m, 2H), 1.15−1.04 (m, 6H), 1.02−0.98(m, 2H), 0.94 (d, J = 6 Hz, 3H), 0.87 (d, J = 6 Hz, 6H), 0.80 (s, 3H), 0.70 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 158.6, 146.7, 135.7, 130.3, 128.5, 128.3, 127.3, 126.8, 125.4, 56.5, 56.4, 53.6, 43.6, 42.5, 42.3, 40.0, 39.5, 37.5, 36.2, 35.8, 35.6, 35.3, 31.7, 28.8, 28.3, 28.2, 24.3, 23.9, 22.8, 22.6, 21.4, 18.7, 12.0, 11.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{22}N$ 472.3938, found 472.3962.

4-methyl-2-phenylquinoline (**10bb**)[14g]

Following the general experimental procedure with 1-(2-aminophenyl)ethan-1-ol **1b** (110 mg, 80 mmol), acetophenone **9b** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10bb** as a pale yellow solid (110 mg, 75%).



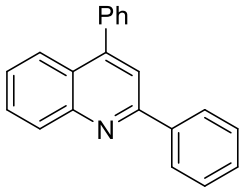
Analytical data of 10bb

^1H NMR (300 MHz, $CDCl_3$, TMS): δ 8.31 – 8.24 (m, 3H), 7.99 (d, J = 8.7 Hz, 1H), 7.80– 7.75 (m, 1H), 7.72 (s, 1H), 7.62 – 7.53 (m, 4H), 2.74 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 156.8, 147.9, 144.6, 139.6, 130.1, 129.1, 129.0, 128.6, 127.4, 127.0, 125.8, 123.4, 119.5, 18.8 ppm.

2,4-diphenylquinoline (**10cb**)[14g]

Following the general experimental procedure with (2-aminophenyl)(phenyl)methanol **1c** (159 mg, 0.80 mmol), acetophenone **9b** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10cb** as a pale yellow solid (135 mg, 72%).



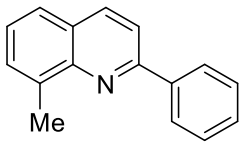
Analytical data of 3ae

^{1}H NMR (300 MHz, CDCl$_3$, TMS): δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.22 – 8.20 (m, 2H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.83 (s, 1H), 7.77 – 7.72 (m, 1H), 7.58 – 7.46 (m, 9H) ppm.

^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ 156.9, 149.2, 148.8, 139.6, 138.4, 130.1, 129.6, 129.4, 128.8, 128.6, 128.4, 127.6, 126.3, 125.8, 125.6, 119.4 ppm.

8-methyl-2-phenylquinoline (**10db**)[14a]

Following the general experimental procedure with (2-amino-3-methylphenyl)methanol **1d** (110 mg, 0.80 mmol), acetophenone **9b** (81 mg, 0.67 mmol), KOH (37.5 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **10db** as a pale yellow solid (126 mg, 86%).



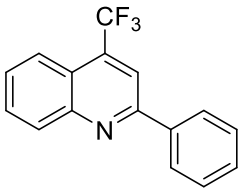
Analytical data of 10db

^{1}H NMR (300 MHz, CDCl$_3$, TMS): δ 8.29−8.26 (m, 2H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.59 – 7.56 (m, 1H), 7.54−7.51 (m, 2H), 7.49−7.45 (m, 1H) 7.44−7.39 (m, 1H), 2.92 (s, 3H) ppm.

^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ 155.5, 147.1, 139.8, 137.7, 137.0, 129.7, 129.2, 128.8, 127.5, 127.1, 126.0, 125.4, 118.2, 17.9 ppm.

2-phenyl-4-(trifluoromethyl)quinoline (**10eb**)

Following the general experimental procedure with 1-(2-aminophenyl)-2,2,2-trifluoroethan-1-ol **1e** (151 mg, 0.80 mmol), acetophenone **9b** (81 mg, 0.67 mmol), KOH (37.5 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (5% ethyl acetate in hexane) to afford the desired product **10eb** as a white solid, 135 mg (74%).



Analytical data of 10eb

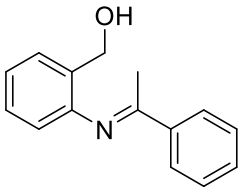
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.30 (d, *J* = 8 Hz, 1H), 8.23−8.20 (m, 3H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.85 (t, *J* = 7.5 Hz, 1H), 7.69 (t, *J* = 8 Hz, 1H), 7.60-7.52 (m, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.7, 149.2, 138.5, 130.7, 130.4, 130.0 129.0, 127.9, 127.5, 123.9 (q, *J* = 2.5 Hz), 116.0(q, *J* = 1.3Hz) ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{11}F_3N$ 274.0838, found 274.0842.

(2-((1-phenylethylidene)amino)phenyl)methanol (**11**)

The imine intermediate was synthesized by treating o-aminobenzylalcohol **1a** (200 mg, 1.62 mmol), acetophenone **9b** (194 mg, 1.62 mmol) in benzene (5.0 mL) at 100 °C during which water was removed by azeotropic distillation. After 12 h, the reaction mixture was allowed to cool and the precipitate formed was filtered and purified by washing with benzene to afford the desired product **11** as a white solid (218 mg, 60%).



Analytical data of 11

^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 8.22 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8. Hz, 2H), 7.62 (t, *J* = 7.5. Hz, 1H), 7.41 (t, *J* = 7.5. Hz, H), 6.97(d, *J* = 8 Hz, 2H), 3.76 (s, 2H), 1.92 (s, 3H) ppm.

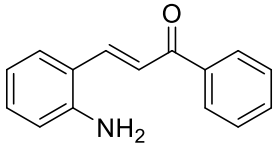
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 161.2,

156.3, 148.3, 136.7, 131.8,129.5, 129.3, 128.7, 127.6, 127.0, 125.9, 118.1, 114.1, 54.8, 29.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{15}H_{15}NNaO$ 248.1046, found 248.1055.

(*E*)-3-(2-aminophenyl)-1-phenylprop-2-en-1-one (**12**)[15]

To a mixture of 2-nitrobenzaldehyde (2g, 13.2 mmol) in ethanol (10 mL.) was added acetophenone **9b** (1.589 g, 13.24 mmol), NaOH (53 mg, 1.32mmol) and stirred at room temperature for 2h. After the complete consumption of 2-nitrobenzaldehyde, the reaction mixture was quenched with water. The crude product was filtered and recrystallized from ethanol. To a solution of the resulting (*E*)-2-nitrochalcone (1 mmol) in ethanol (15 mL) was added iron powder (183 mg, 3 mmol), followed by HCl (1.0 N, 1.3 mL). The reaction mixture was vigorously stirred at 80 ^oC. After the complete consumption of (*E*)-2-nitrochalcone, the reaction mixture was allowed to cool at room temperature and then extracted with ethyl acetate. The organic layer was washed with saturated Na_2CO_3 solution and brine dried over Na_2SO_4, and concentrated to afford the desired product **12** as a yellow solid, 116 mg (52%).



Analytical data of 12

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.04-8.02 (m, 2H), 8.00 (d, *J* = 15.5 Hz, 1H), 7.60−7.57 (m, 1H), 7.54-7.48(m, 4H), 7.23−7.20 (m, 1H), 6.81(t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8 Hz, 1H), 4.07 (s, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 190.3, 146.2, 140.1, 138.4, 132.8, 131.7, 128.6, 128.5, 128.2, 121.8, 120.3, 119.0, 116.8, ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{14}NO$ 224.1070, found 224.1072.

2.8 References

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Chapter 3

Investigations on Superbase Mediated Reactivity of *N*-Tosylhydrazones with Aza-*ortho*-Quinone Methide Precursors

3.1 Abstract

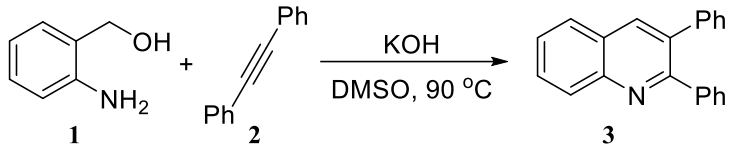
We have encountered a superbase-mediated chemoselective reaction of N-tosylhydrazones with aza-ortho-quinone methide precursors. When tosylhydrazone was treated with ortho-aminobenzyl alcohol in super basic conditions (KOH+DMSO), we observed the formation of 2-substituted quinoline. The reaction was found to be general, and by this method, mono-, di- and tri-substituted quinolines could be made. We could prove experimentally that the reaction proceeded via the formation of an azine from the basic decomposition of N-tosylhydrazones. Whereas the reaction of tosylhydrazone with N-(2-(chloromethyl)phenyl)-4-methylbenzene sulfonamide (aza-ortho-quinone methide precursor) under super basic conditions afforded hydrazine substituted sulphonamides.

3.2 Introduction

N-Tosylhydrazones have found a plethora of applications in synthetic organic chemistry as a source of diazo compounds, as a reagent in metal-free reactions, and as a coupling partner in metal-catalyzed reactions.[1] *N*-Tosylhydrazones are stable organic compounds that can be easily synthesized and purified, and the wide reactivity pattern exhibited by these was utilized for carbon-carbon and carbon-heteroatom bond formation towards synthesizing acyclic, carbocyclic, and heterocyclic compounds.[2] Organic chemists have utilized these nitrogenated compounds for generating alkenes (Bamford-Stevens & Shapiro), cyclopropanes, pyrazoles, triazoles, indazoles, benzofurans, indoles, pyridazines, thiadiazoles, phenanthridines to name a few.[1-2] In this Chapter, we disclose a chemoselective transformation of *N*-tosylhydrazones towards functionalized quinolines and hydrazine-substituted sulphonamides.

Over the years, several methods were developed to generate aza-*ortho*-quinone methides, and these reactive intermediates were utilized for accessing diverse families of *N*-heterocycles.[3-4] *Ortho*-aminobenzyl alcohol has been utilized to generate different *N*-heterocycles, especially quinolines, *via* metal-catalysed[5] and metal-free methodologies.[6]

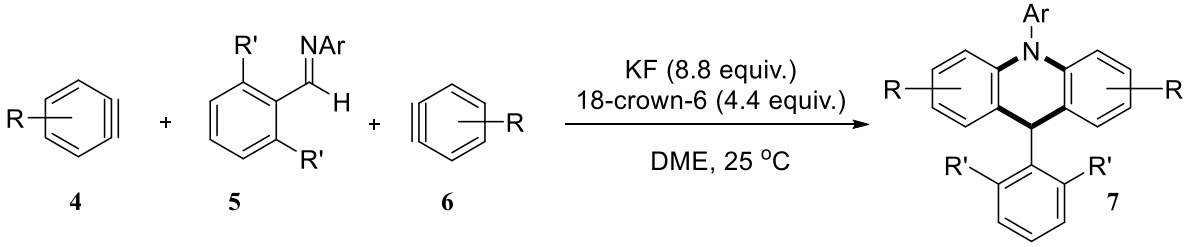
Verma and co-workers have shown that aza-*ortho*-quinone methides can be generated from *ortho*-aminobenzyl alcohol under super basic conditions, and they utilized these intermediates to generate substituted quinolines by reacting with alkynes (Scheme 3.1).[7]



Scheme 3.1 Superbase mediated synthesis of quinoline derivatives

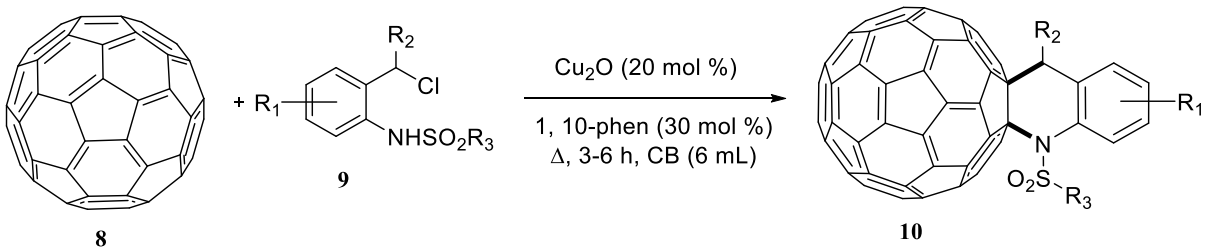
Since the first report by Steinhagen and Corey on the generation of aza-*ortho*-quinone methides from *N*-(*o*-chloromethyl)arylamides,[8] many groups have made use of this intermediate as a 4π component for the [4+2] cycloaddition towards *N*-heterocycles.[9]

In 2017, Takaki *et al.* created a direct approach for synthesizing acridane derivatives based on a 2:1 coupling reaction between arynes and imines (Scheme 3.2). As the arynes and imines undergo a net [2+2] cycloaddition, transitory aza-*ortho*-quinone methides are produced. An imine carbon requires the introduction of steric bulk to undergo this simple coupling.[10b]



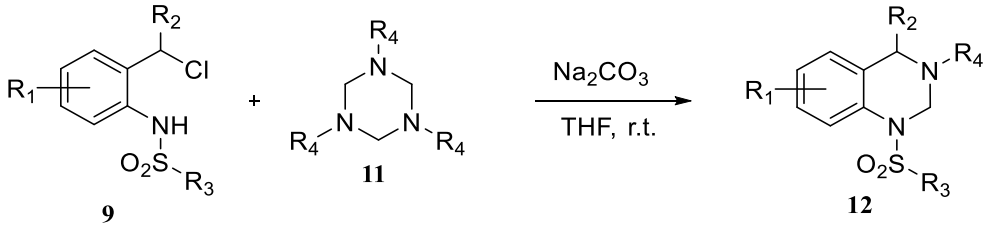
Scheme 3.2 [4+2] Cycloaddition of aza-*o*-quinone methides with arynes

Wang *et al.* (2018) successfully developed an effective and convenient method for synthesizing fullerotetrahydroquinolines from the hetero-Diels-Alder reaction of C_{60} with *in situ* generated aza-*o*-quinone methides from *N*-(*o*-chloromethyl)aryl sulfonamides using catalytic amounts of Cu_2O and 1,10-phenanthroline (Scheme 3.3).[10c] This approach is more efficient than those that use inorganic bases such as Cs_2CO_3, Na_2CO_3, and K_2CO_3. This is the first report of *in situ* aza-*o*-quinone methides generation *via* metal oxide mediation and this methodology offers a high functional group tolerance and a broad substrate range.



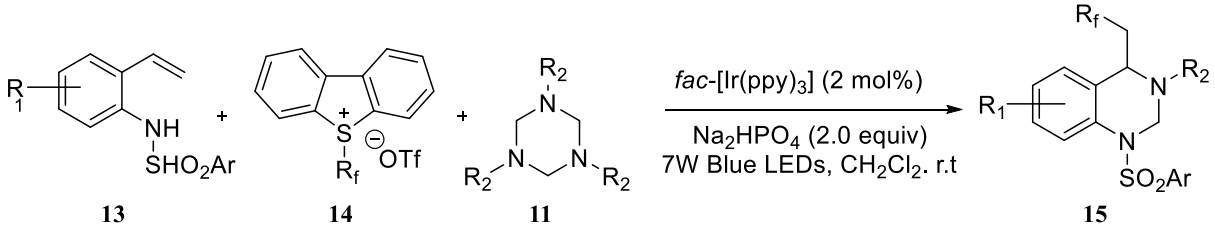
Scheme 3.3 [4+2] cycloaddition reaction of [60]fullerene with aza-*o*-quinone methides

In 2018, Liu and colleagues reported a moderate and catalyst-free inverse-electron-demand [4+2] cycloaddition process of *in situ* produced aza-*o*-quinone methides with 1,3,5-triazinanes (Scheme 3.4).[10d] This approach provides a simple and efficient way to obtain tetrahydroquinazolines with a high yield.



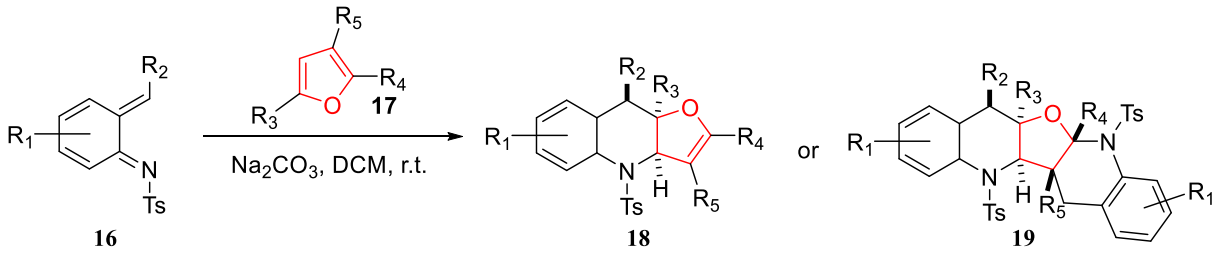
Scheme 3.4 Inverse-electron-demand [4+2]-cycloaddition for the synthesis of 1,3,5-triazinanes

In 2020, the first instance of [4+2] cycloaddition of photogenerated aza-*o*-QMs with 1,3,5-triazinane-derived formaldimines was disclosed by Chen and colleagues (Scheme 3.5). The formation of aza-*o*-QMs from 2-vinylanilines and perfluoroalkyl radical precursors through photocatalytic radicals, as well as the *in situ* release of formaldimines from 1,3,5-triazinanes, are essential to these three-component process.[10e] With the straightforward operation, easily accessible substrates, and strong functional group tolerance, this redox-neutral technique offers broadly applicable access to perfluoroalkylated tetrahydroquinazolines.



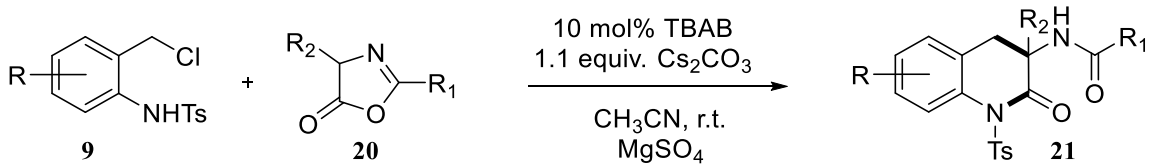
Scheme 3.5 Accessing perfluoroalkylated tetrahydroquinazolines *via* an inverse-electron-demand [4+2] cycloaddition

Mo and colleagues came up with a method for making furo[3,2-*b*]quinolines and furo[2,3-*b*:4,5-*b*′]tetrhydroquinoline in the year 2020. Diquinolines are produced through a metal-free [4+2] cycloaddition of readily accessible *in situ* produced aza-*o*-quinone methides and furans (Scheme 3.6).[10f] The reaction can produce the matching dihydro- or tetrahydrofuroquinolines in good to excellent yields with wide substrate scope. Mechanistic investigations have revealed that the reaction involves a coordinated [4+2] cycloaddition pathway and exhibits strong regioselectivity and diastereoselectivity for furans. The reaction conditions were mild, exhibited dearomatization of furans, and were also able to demonstrate gram-scalability.



Scheme 3.6 [4+2] cycloaddition of aza-*o*-quinone methides and furans yields furo[3,2-*b*]quinolines and furo[2,3-*b*:4,5-*b*′]diquinolines.

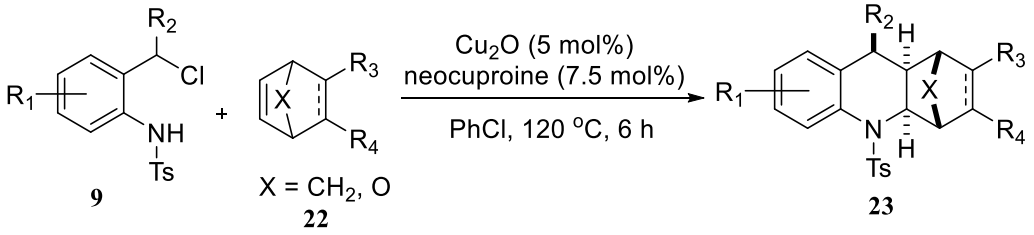
In 2021, using *N*-(*o*-chloromethyl)aryl amides as a template, aza-*o*-quinone methides (aza-*o*-QMs) underwent a base-mediated [4+2] cycloaddition (Scheme 3.7).[10g] With azlactones as a coupling partner, this method produced several dihydroquinolinone derivatives in good to excellent yields (up to 98%). This procedure has helped to increase the understanding of aza-*o*-QM-related reactions while also providing a helpful technique for creating physiologically significant dihydroquinolinone frameworks.



Scheme 3.7 [4+2] cyclization of aza-*o*-quinone methides with azlactones

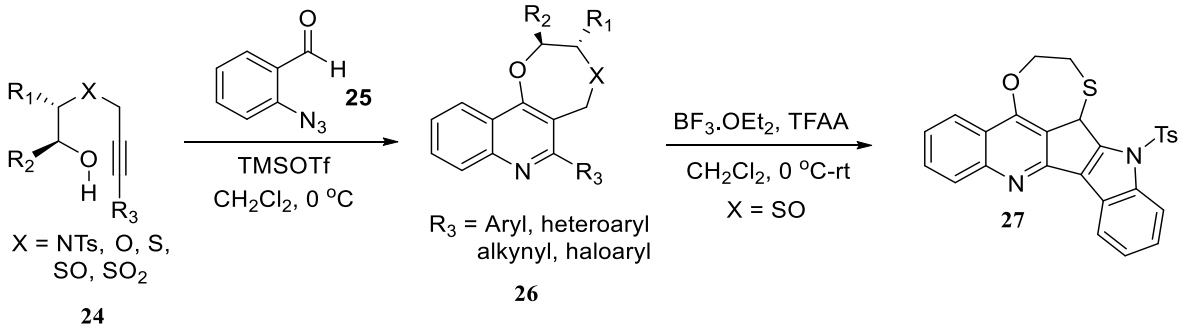
In the same year, using aza-*o*-quinone methides (aza-*o*-QMs) and bicyclic alkenes in a Cu_2O-catalyzed [4+2] cycloaddition, Mo *et al.* created a range of tetrahydroquinoline-fused bicycles carrying numerous stereocenters in excellent yields with great diastereoselectivity (Scheme 3.8).[10h] Mechanistic studies show that the Cu(I) catalyst expedites [4+2]

cycloaddition, as well as accelerates the radical process that leads to the formation of aza-*o*-QMs. The process is effortless to execute on a gram scale, and the resulting tetrahydroquinoline-fused bicycles can be utilized to create a variety of tetrahydroquinoline scaffolds.



Scheme 3.8 A copper(I)-catalyzed [4+2] cycloaddition of aza-*ortho*-quinone methides and bicyclic alkenes

Fartade *et al.* established a procedure employing intramolecular formal [4+2]-cycloaddition of *in situ-produced* aza-*o*-quinone methide for the simple synthesis of 1,4-heterocycle-fused quinoline motifs in 2021 (Scheme 3.9).[10i] A tandem C-O, C-C, and C-N bond formation was demonstrated, with a high degree of functional group tolerance. Enantiomerically enriched 1,4-oxazepino quinolines were produced utilizing alkynols generated from L-amino acids. Pummerer cyclization was used to convert the sulfoxide-embedded quinolines to pentacyclic 1,4-thiepino tethered indeno-quinoline scaffolds.

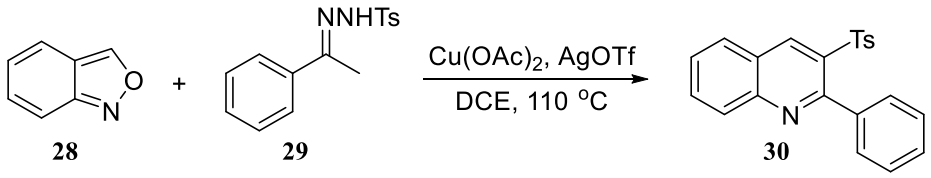


Scheme 3.9 1,4-heterocycle-fused quinolines synthesis through formal [4+2] cycloaddition

3.3 Statement of the problem

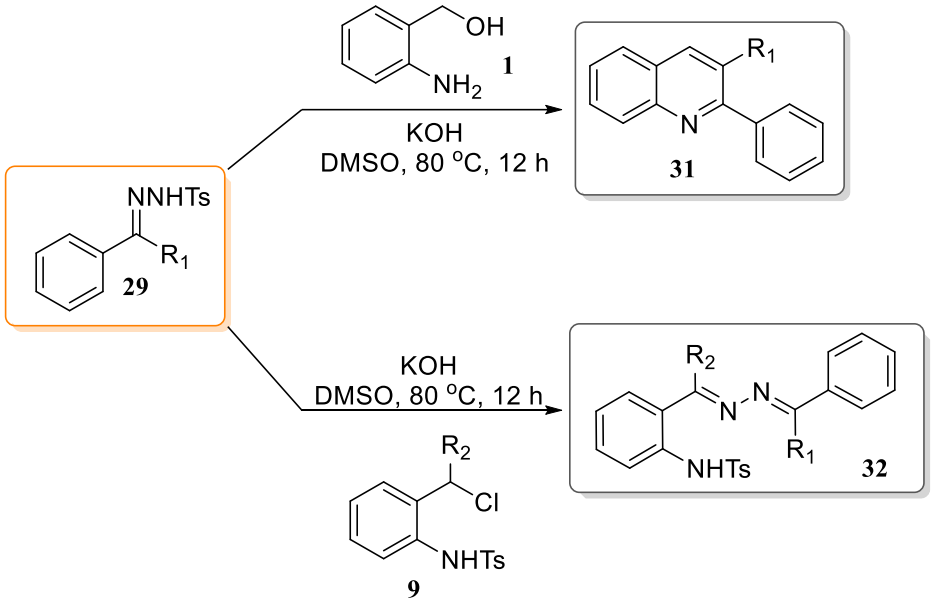
Different organic transformations such as styrylation, chalcogenation, cross-coupling, heterocyclic synthesis, inter- and intramolecular hydroaminations were effected in superbasic medium by Trofimov and others.[11-12] In most of the cases mentioned previously, a combination

of KOH and DMSO was used to create the superbasic medium. From *N*-tosylhydrazones, we could only find one report by Wang and Ji where the reaction of the former with anthranils furnished 2-aryl-3-sulfonyl substituted quinoline derivatives under Cu(II)/Ag(I) catalysis (Scheme 3.10).[13]



Scheme 3.10 Synthesis of quinoline derivatives from *N*-tosylhydrazones and anthranils

In light of the reports on the use of aza-*ortho*-quinone methides and *N*-tosylhydrazones for the generation of *N*-heterocycles and due to our continued interest in synthetic methodologies towards heterocycles,[14] we chose to study the reactivity difference of aza-*ortho*-quinone methide precursors such as *ortho*-aminobenzyl alcohol and *N*-(*o*-chloromethyl)arylamides with *N*-tosylhydrazones in super basic medium (Scheme 3.11).

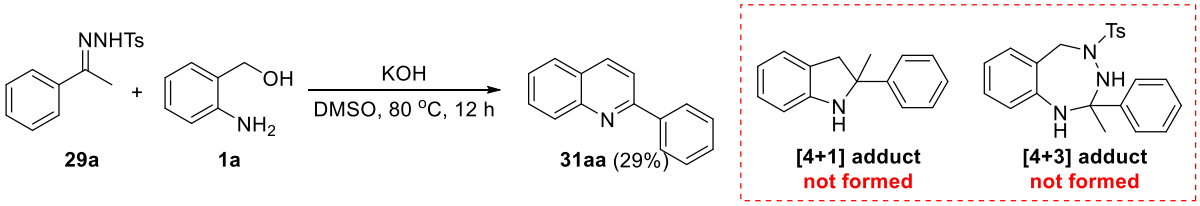


Scheme 3.11 Superbase mediated reactivity of *N*-tosylhydrazones with aza-*ortho*-quinone methide precursors

3.4 Results and discussion

We planned to initiate the investigations on chemoselectivity with *N*-tosylhydrazone and *ortho*-aminobenzyl alcohol under super basic conditions, and by following literature

precedents,[7, 15] we were expecting either [4+1] or [4+3] addition products from the aza-*ortho*-quinone methide and the hydrazine (Scheme 3.12). *N*-tosylhydrazone **29a** (1.0 equiv.) derived from acetophenone and *ortho*-aminobenzyl alcohol **1a** (1.0 equiv.) were taken as test substrates, and these were treated in the presence of KOH (1.0 equiv.) in DMSO at 80 °C for 12 h (Scheme 3.12). In contrast to our expectation, we isolated 2-phenyl quinoline **31aa** from the reaction mixture in 29% yield, and the product's structure was characterized by various spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR, and HRMS analysis, and compared with the literature.



Scheme 3.12 Reaction of *N*-tosylhydrazone and *ortho*-aminobenzyl alcohol

In the ^{1}H NMR spectrum (Fig 3.1**)** the aromatic protons were found to resonate between 8.25-7.46 ppm. In the ^{13}C NMR (Fig 3.2**)** carbon signals were found to appear between 157.4-119.1 ppm. All other signals in the ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structure and literature. The high-resolution mass spectral analysis showed a peak at *m/z* 206.0973 $(M+H)^{+}$, which also supported the proposed structure.

The reaction was then optimized with **29a** and **1a** as substrates, and first, the amount of base was increased to 2 and 3 equivalents (Table 3.1, entries 1-3), and it was found that for the present annulation, 2.0 equivalents of the base was optimal. Then, the investigations by increasing the amounts of *ortho*-aminobenzyl alcohol **1a** were carried out, and the reaction with 1.2 equivalents of **1a** furnished 2-phenyl quinoline **31aa** in 79% yield. Next, the effect of temperature on the reaction outcome was studied, and it was found that both increasing (100 °C) and decreasing (60 °C) the reaction temperature had a negative effect on the yield. Finally, the optimized condition was a combination of 1.0 equivalents of **29a**, 1.2 equivalents of **1a**, 2.0 equivalents of KOH in DMSO at 80 °C for 12 h.

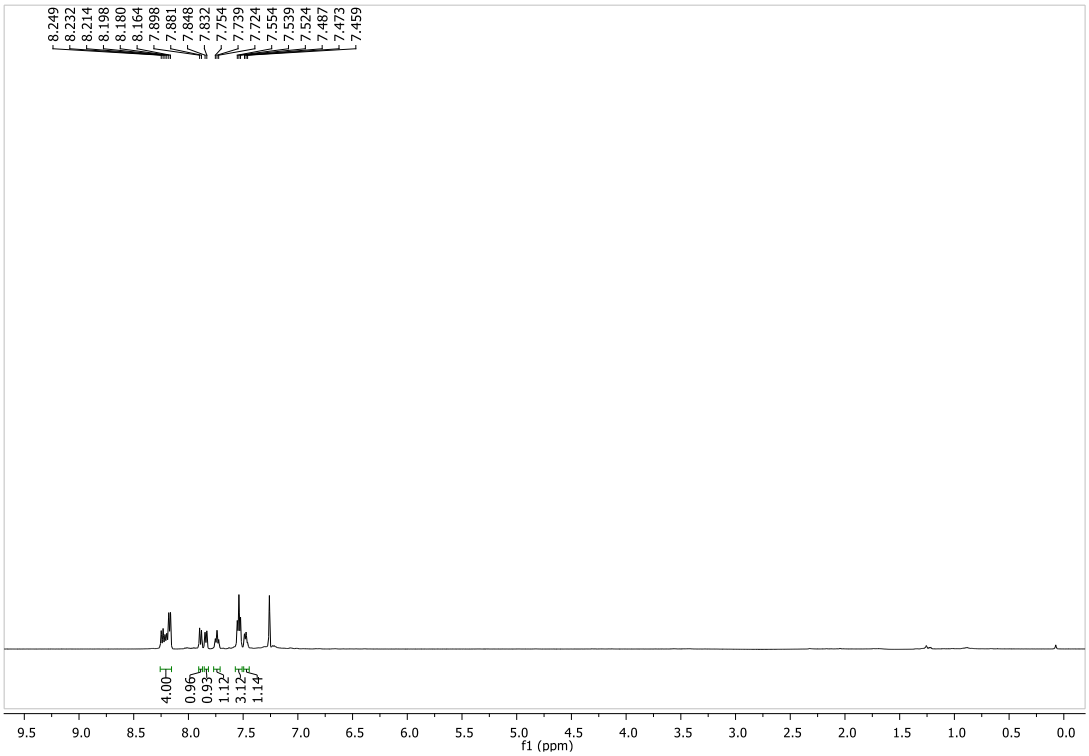


Fig. 3.1: ^{1}H NMR (500 MHz) Spectra of **31aa**

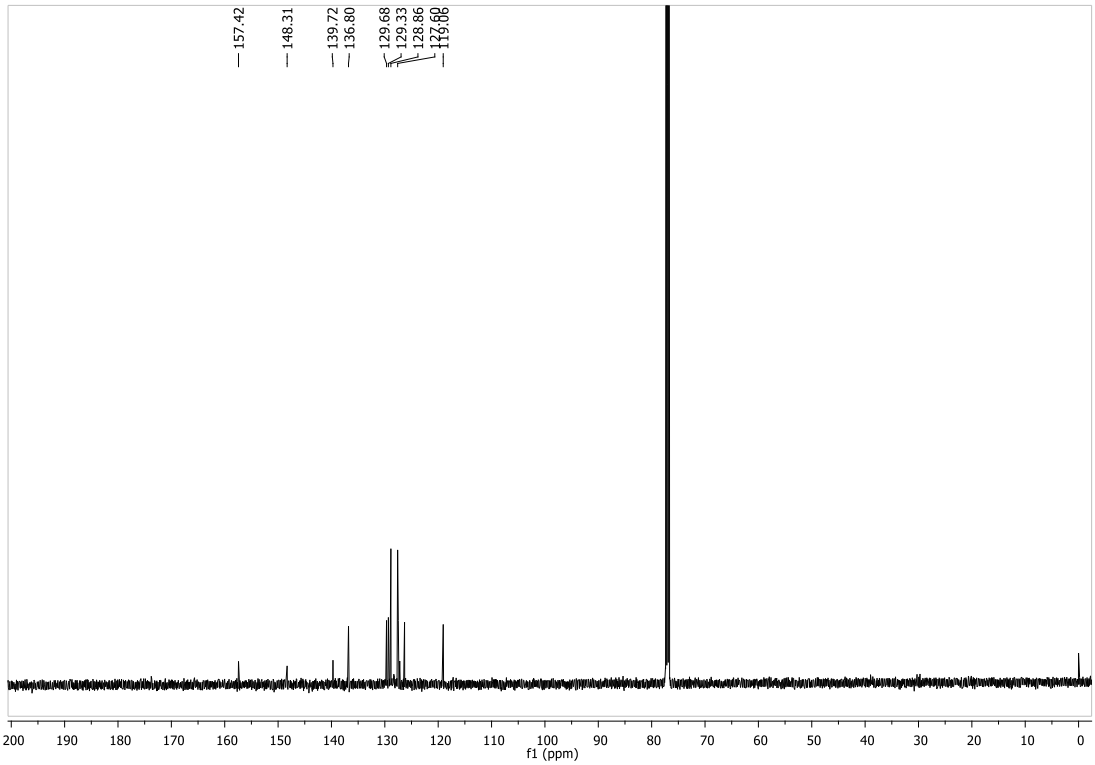
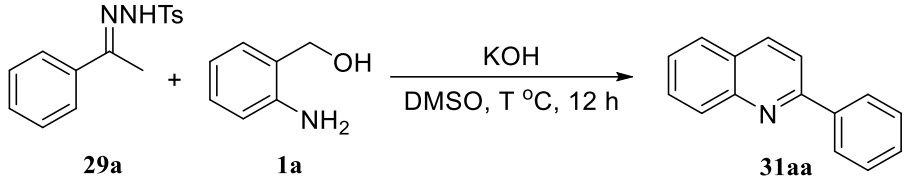


Fig. 3.2: ^{13}C{^{1}H} NMR (125 MHz) Spectra of **31aa**

Table 3.1 Optimisation studies

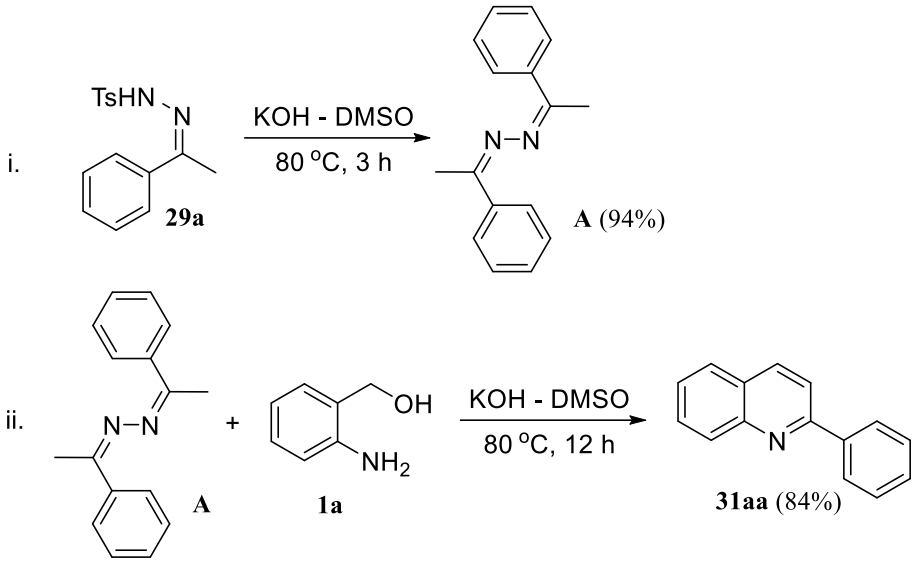


29a **1a** **31aa**

Entry	**1a** (equiv.)	KOH (equiv.)	T °C	Yield of **31aa** (%)[a]
1	1.0	1.0	80	29
2	1.0	2.0	80	48
3	1.0	3.0	80	49
4	1.1	2.0	80	65
5	**1.2**	**2.0**	**80**	**79**
6	1.3	2.0	80	78
7	1.2	2.0	60	66
8	1.2	2.0	100	70

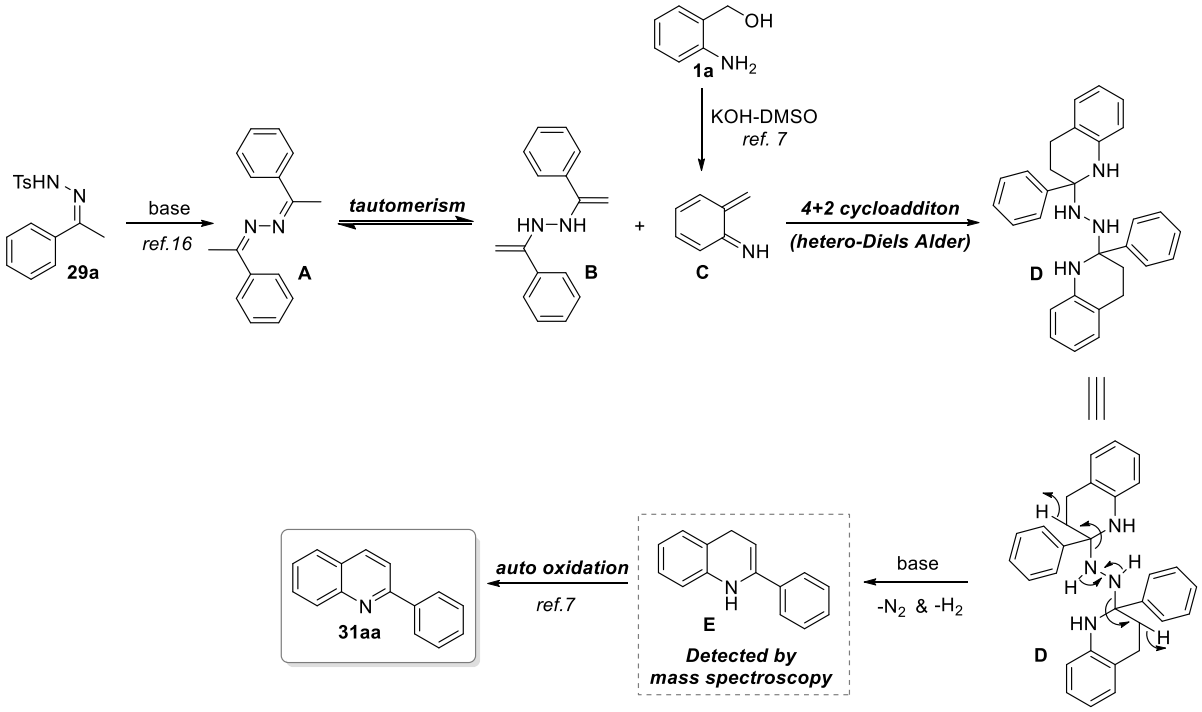
Reaction conditions: **29a** (1.0 equiv., 0.17 mmol), **1a**, KOH, DMSO (1.0 mL), 60-100 °C, 12 h.

This unforeseen observation made us examine the mechanism and perform some control experiments. First, we treated *N*-tosylhydrazone **29a** with KOH in DMSO at 80 °C, and this reaction resulted in the formation of the azine **A** in 94% yield**,** as shown in scheme 3.13(i). The formation of azines from *N*-tosylhydrazones under basic conditions was reported earlier.[16] By considering the azine **A** as the stable intermediate formed from *N*-tosylhydrazone **29a**, we treated the former with twice the amount of *ortho*-aminobenzyl alcohol **1a**, and this reaction resulted in the formation of 2-phenyl quinoline **31aa** in 94% yield (Scheme 3.13(ii)). The next intermediate, i.e. aza-*ortho*-quinone, the generation of which was proved by Verma and co-workers, methides from *ortho*-aminobenzyl alcohol under super basic conditions.[7]



Scheme 3.13 Control experiments

Based on the control experiments and the literature precedents,[7,16] we have postulated a mechanism, as shown in scheme 3.14.



Scheme 3.14 Mechanistic postulate for the formation of 2-aryl quinoline from the reaction of *N*-tosylhydrazone and *ortho*-aminobenzyl alcohol under super basic conditions

The azine **A** formed from *N*-tosylhydrazone **29a** will undergo tautomerism to form intermediate **B,** which will undergo a hetero Diels-Alder reaction with aza-*ortho*-quinone methide **C** to form **D**. From the intermediate **D**, the formation of 2-phenyl-1,4-dihydroquinoline **E** can occur by eliminating N_2. From the intermediate **E**, 2-phenyl quinoline **31aa** is formed by auto oxidation as reported by Verma *et al*.[7] We tried to detect the proposed intermediates by mass spectroscopy, and from the data, we could confirm the presence of 2-phenyl-1,4-dihydroquinoline **E,** and we believe that all other intermediates must be having extremely short half-lives.

The regioselectivity of the reaction can also be explained by the enamine addition, as shown in Figure 3.3 The carbon end of the enamine **B** will add to the methide end of **C,** followed by the cyclization from the *N*-end of **C** to the quaternary carbon of **B**, leading to the regioselective formation of 2-aryl quinoline.

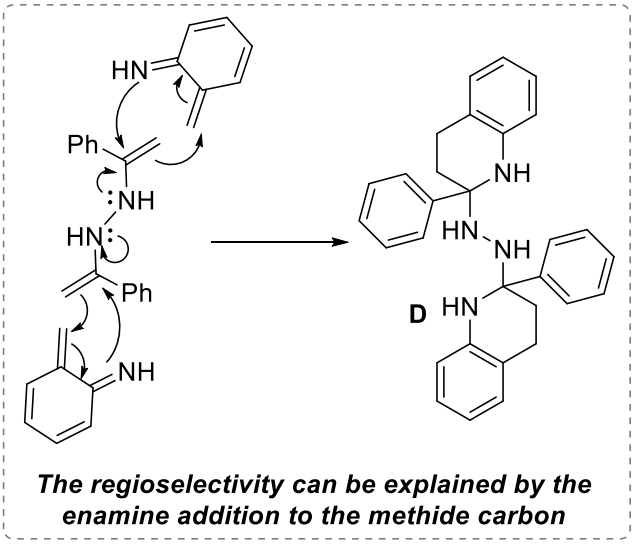
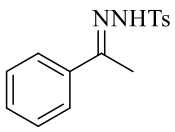
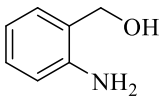
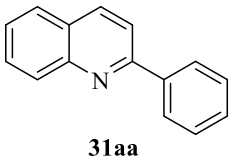
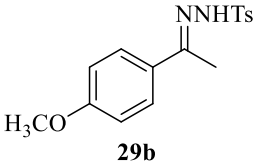
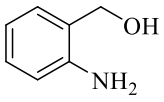
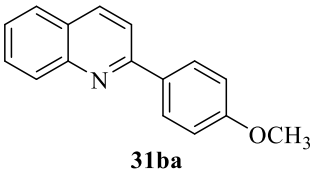
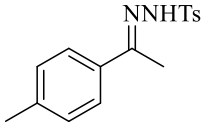
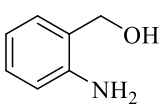
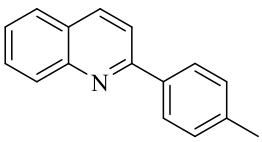


Fig. 3.3: Addition of enamine to azine

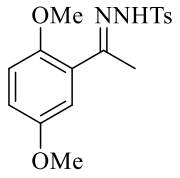
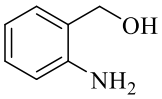
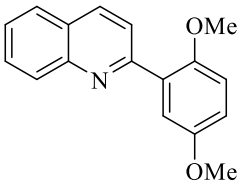
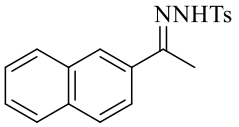
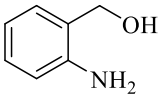
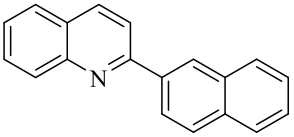
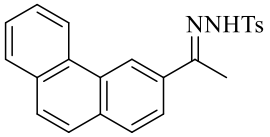
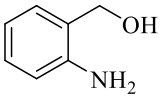
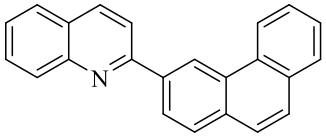
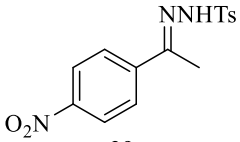
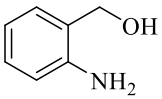
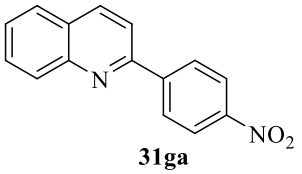
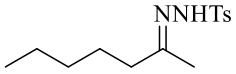
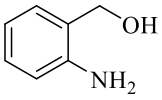
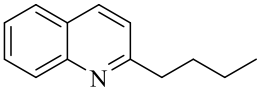
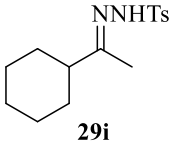
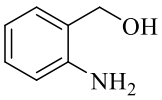
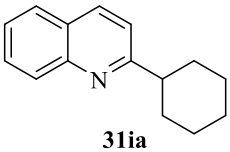
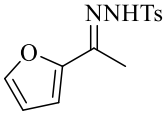
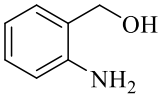
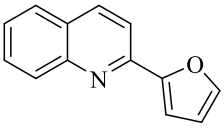
We then planned to study the generality of this reaction by varying *N*-tosylhydrazones and *ortho*-aminobenzyl alcohols (Table 3.2). Under the optimized conditions, *N*-tosylhydrazone derived from acetophenones bearing electron-donating substituents on the aryl ring reacted well with *ortho*-aminobenzyl alcohol **1a**, affording the products **31ba**, **31ca**, and **31da** in excellent yields. 2-Naphthyl quinoline **31ea** and 2-phenanthrenyl quinoline **31fa** were also formed in good yields from the reactions of corresponding *N*-tosylhydrazones and *ortho*-aminobenzyl alcohol **1a**. The reaction yield decreased with acetophenones bearing electron-

withdrawing substituents on the aryl ring, and thus **31ga** was obtained in 58% yield. *N*-tosylhydrazone derived from 2-hexanone and acetyl cyclohexane also participated in the reaction with **1a** under superbasic medium, affording the products 2-butylquinoline **31ha** and 2-cyclohexylquinoline **31ia** in good yields. By this methodology, we could synthesize 2-heteroayl quinolines such as 2-(furan-2-yl)quinoline **31ja** and 2-(thiophen-2-yl)quinoline **31ka** in excellent yields. 1,2,3,4-tetrahydroacridine **31la** was synthesized in good yield by starting from the *N*-tosylhydrazone derived from cyclohexanone and *ortho*-aminobenzyl alcohol **1a**. The present reaction was extended from *N*-tosylhydrazone derived from acetophenone to the one derived from propiophenone, whereby we could synthesize 3-methyl-2-phenylquinoline **31ma** in a 73% yield. By using *ortho*-aminobenzyl alcohols **1b**-**1d** with different substituents on the methylene unit and aryl ring, we could synthesize 2,4-diphenylquinoline **31ab**, 4-methyl-2-phenylquinoline **31ac,** and 7-chloro-2-phenylquinoline **31ad** in good to excellent yields. We could also synthesize 2,3,4-trisubstituted quinolines **31mb** and **31mc** by starting from appropriately functionalized *N*-tosylhydrazone and *ortho*-aminobenzyl alcohol. Finally, we utilized the *N*-tosylhydrazone derived from the natural product vanillin to synthesize **31na** in a 66% yield.

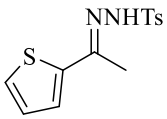
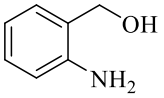
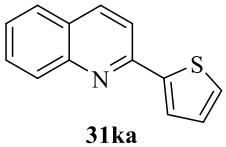
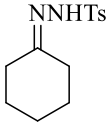
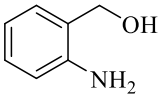
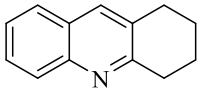
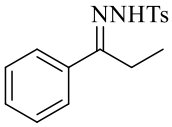
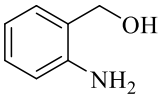
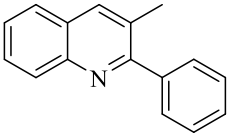
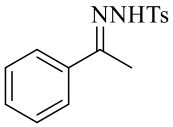
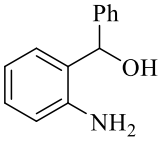
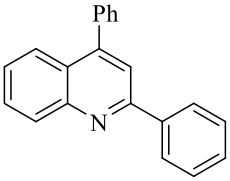
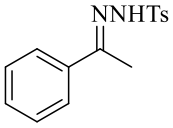
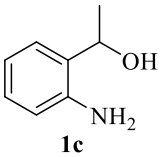
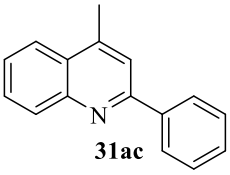
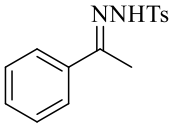
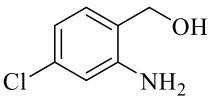
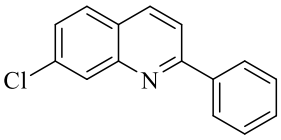
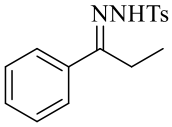
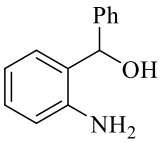
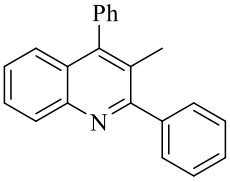
Table 3.2 The generality of the reaction between *N*-tosylhydrazone and *ortho*-aminobenzyl alcohol under super basic conditions

Entry	Tosylhydrazone	*Ortho*- aminobenzyl alcohol	Product	Yield (%)
1	 **29a**	 **1a**	 **31aa**	79%
2	 **29b**	 **1a**	 **31ba**	86%
3	 **29c**	 **1a**	 **31ca**	83%

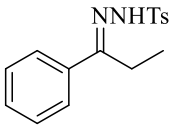
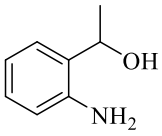
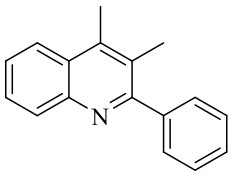
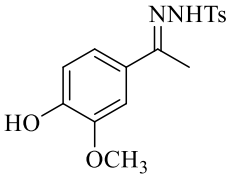
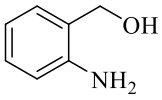
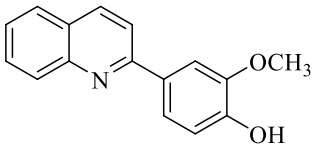
Reaction conditions: **29** (1.0 equiv., 0.35 mmol), **1a** (1.2 equiv.), KOH (2.0 equiv.), DMSO (2.0mL), 80 ^{o}C, 12 h

Entry	Tosylhydrazone	*Ortho*- aminobenzyl alcohol	Product	Yield (%)
4	 **29d**	 **1a**	 **31da**	82%
5	 **29e**	 **1a**	 **31ea**	71%
6	 **29f**	 **1a**	 **31fa**	78%
7	 **29g**	 **1a**	 **31ga**	58%
8	 **29h**	 **1a**	 **31ha**	62%
9	 **29i**	 **1a**	 **31ia**	77%
10	 **29j**	 **1a**	 **31ja**	90%

Reaction conditions: **29** (1.0 equiv., 0.35 mmol), **1a** (1.2 equiv.), KOH (2.0 equiv.), DMSO (2.0 mL), 80 ^{o}C, 12 h.

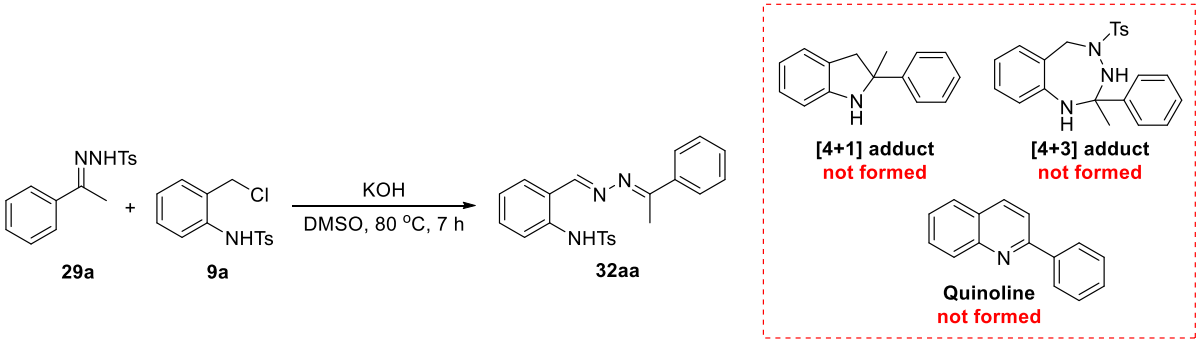
Entry	Tosylhydrazone	*Ortho*- aminobenzyl alcohol	Product	Yield (%)
11	 **29k**	 **1a**	 **31ka**	88%
12	 **29l**	 **1a**	 **31la**	66%
13	 **29m**	 **1a**	 **31ma**	73%
14	 **29a**	 **1b**	 **31ab**	81%
15	 **29a**	 **1c**	 **31ac**	83%
16	 **29a**	 **1d**	 **31ad**	76%
17	 **29m**	 **1b**	 **31mb**	71%

Reaction conditions: **29** (1.0 equiv., 0.35 mmol), **1** (1.2 equiv.), KOH (2.0 equiv.), DMSO (2.0 mL),80 ^{o}C, 12 h.

Entry	Tosylhydrazone	*Ortho*- aminobenzyl alcohol	Product	Yield (%)
18	 **29m**	 **1c**	 **31mc**	74%
19	 **29n**	 **1a**	 **31na**	66%

Reaction conditions: **29** (1.0 equiv., 0.35 mmol), **1** (1.2 equiv.), KOH (2.0 equiv.), DMSO (2.0 mL), 80 ^{o}C, 12 h.

Next, we planned to study the reactivity of aza-*ortho*-quinone methides generated from *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide with *N*-tosylhydrazones under super basic conditions. The initial reaction was set up with *N*-tosylhydrazone **29a** (1.0 equiv.) derived from acetophenone and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** in the presence of KOH and DMSO at 80 ^{o}C (Scheme 3.15). Contrary to our expectations of [4+1] or [4+3] addition products or quinoline derivatives as shown before,[7,15] we observed the formation of an azine sulphonamide **32aa** in 49% yield. The structure of the compound was characterized by various spectroscopic techniques and then confirmed by single-crystal X-ray analysis.



Scheme 3.15 Reaction of *N*-tosylhydrazone and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide under super basic conditions

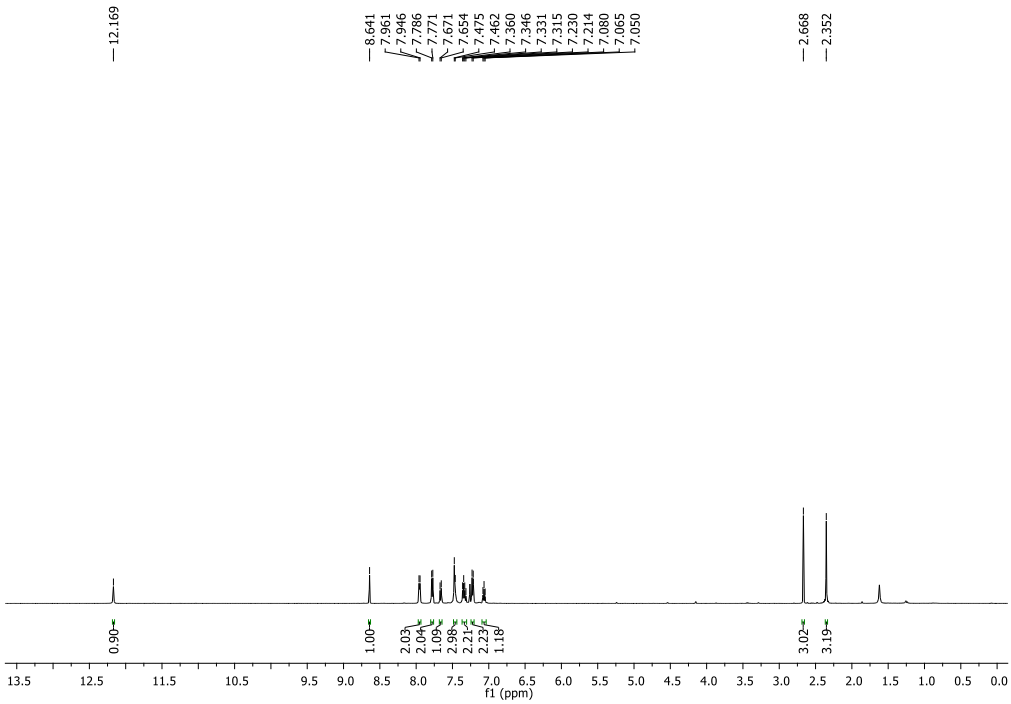


Fig. 3.4: ^{1}H NMR (500 MHz) Spectra of **32aa**

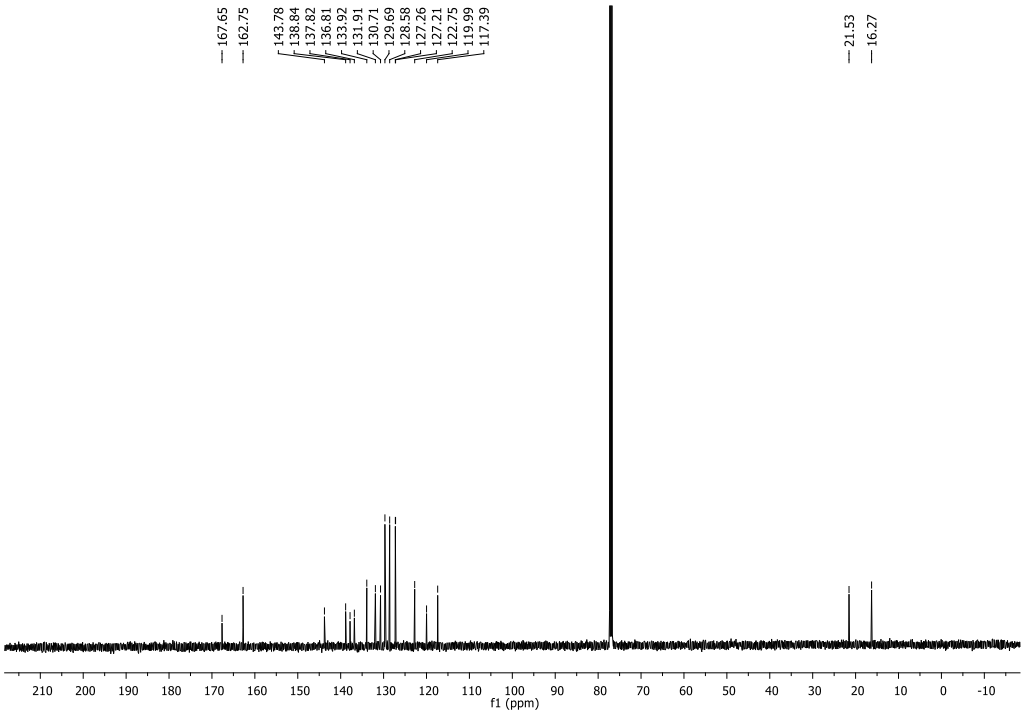


Fig. 3.5: ^{13}C{^{1}H} NMR (125 MHz) Spectra of **32aa**

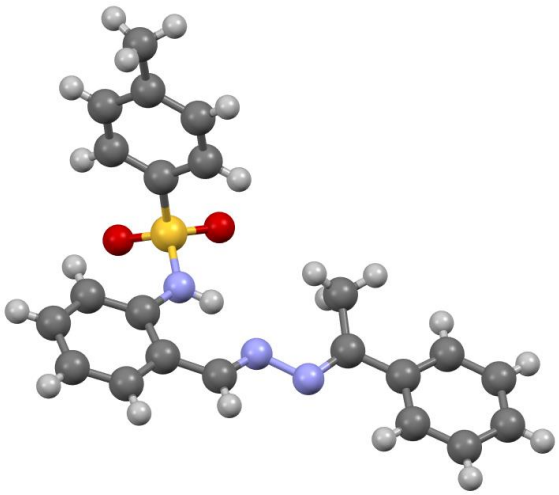
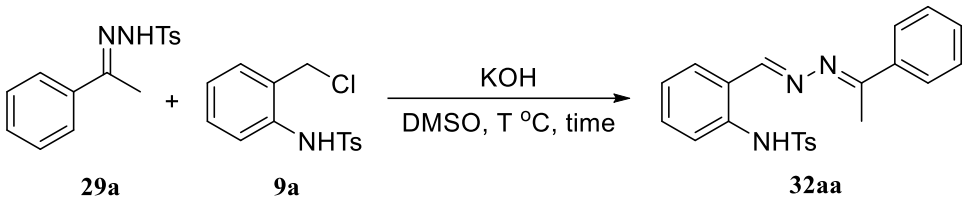


Fig. 3.6: Single crystal X-ray structure of **32aa** (CCDC No. 2298825)

In the ^{1}H NMR spectrum (Fig 3.4**)** the aromatic protons resonated between 8.64-7.05 ppm. The proton attached to the nitrogen atom resonated at 12.17 ppm. The methyl protons resonated at 2.67 ppm and the tosylmethyl protons resonated at 2.35 ppm. In the ^{13}C NMR (Fig 3.5), methyl carbon appears at 21.5 ppm and the tosyl methyl carbon appears at 16.3 ppm. All other signals in the ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structure. The high-resolution mass spectral analysis showed a peak at *m/z* 237.1395 $(M+H)^{+}$, which also supported the proposed structure.

From the literature, we found that the synthesis of azine sulphonamide was reported by Li and co-workers, where they describe a Rh-catalyzed C-H amidation of azines with sulphonamides.[17] As sulphonamides are considered privileged scaffolds in medicinal chemistry mainly due to sulpha drugs,[18] we thought of studying the reaction in detail. By taking *N*-tosylhydrazone **29a** and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** as substrates for optimisation, we tried a few reactions by changing the time and equivalents of **9a**. Increasing the reaction time from 7 h to 12 h did not influence the yield of the azine sulphonamide (Table 3.3, entries 1-2). Then, we tried increasing the equivalents of **9a** from 1.0 to 2.0, and the best yield for **32aa** of 68% was obtained with 1.5 equivalents of **9a**. The optimized condition for the azine sulphonamide synthesis was found to be a combination of 1.0 equivalents of **29a**, 1.5 equivalents of **9a**, and 2.0 equivalents of KOH in DMSO at 80 ^{o}C for 12 h.

Table 3.3 Optimisation studies



29a **9a** **32aa**

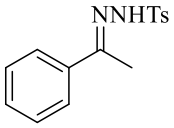
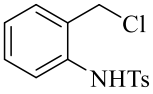
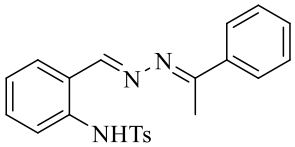
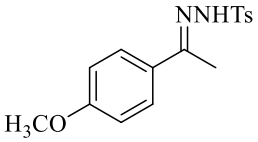
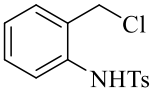
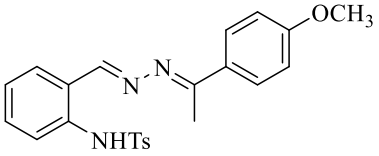
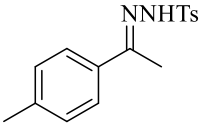
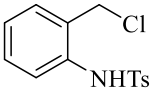
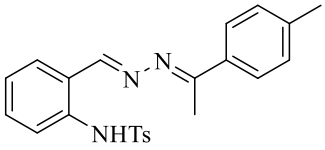
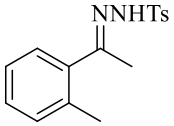
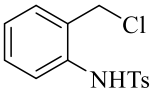
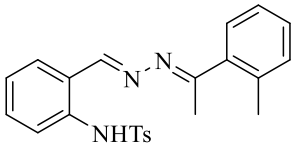
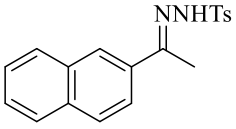
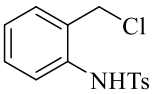
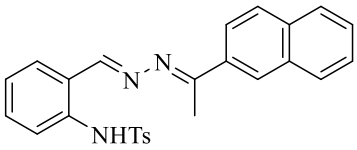
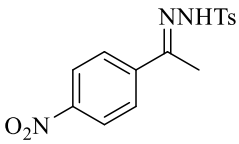
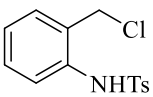
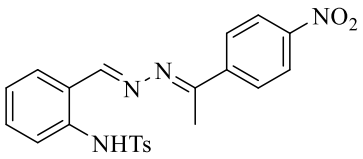
Entry	**9a** (equiv.)	Time (h)	Yield of **32aa** (%)[a]
1	1.0	7	49
2	1.0	12	50
3	1.2	12	54
4	**1.5**	**12**	**68**
5	2.0	12	68

Reaction conditions: **29a** (1.0 equiv., 0.17 mmol), **9a**, KOH (2.0 equiv.), DMSO (1.0 mL), 80 °C, time.

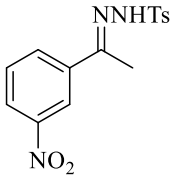
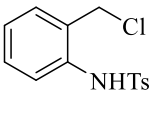
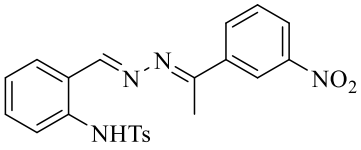
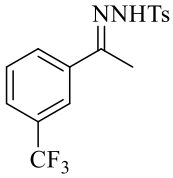
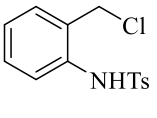
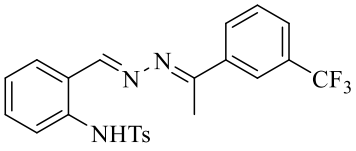
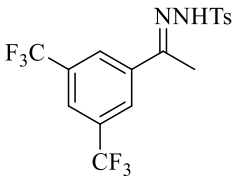
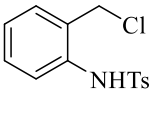
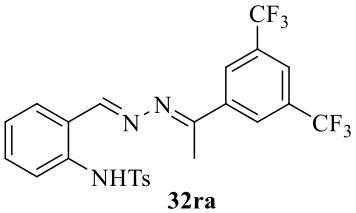
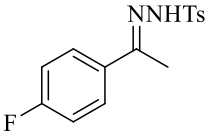
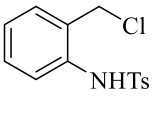
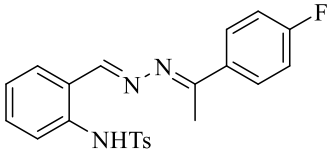
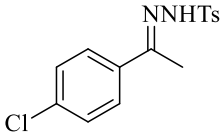
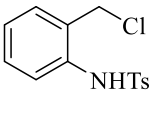
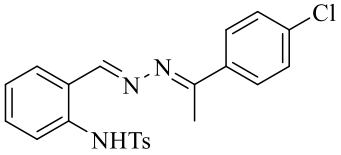
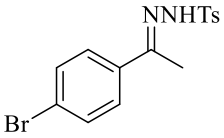
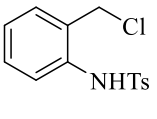
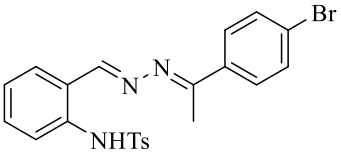
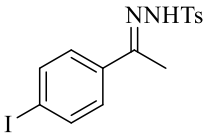
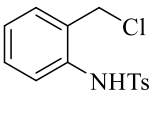
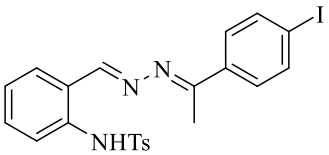
Under the optimized conditions, we planned to study the generality of the azine sulphonamide synthesis (Table 3.4). The electron-donating substituent on *N*-tosylhydrazone had a detrimental effect on the reaction, and when OMe and Me- substituents were present, the corresponding products **32ba**, **32ca**, and **32oa** were obtained in moderate yields. The *N*-tosylhydrazone derived from 2-acetyl naphthalene, when reacted with **9a**, afforded the corresponding azine sulphonamide **32ea** in 61% yield. The presence of electron-withdrawing substituents on *N*-tosylhydrazone had a positive effect on the reaction, and by this methodology, we could synthesize four azine sulphonamides **32ga**, **32pa**, **32qa**, and **32ra** (bearing NO_2, CF_3 groups) in excellent yields. We could also synthesize halogen (F, Cl, Br & I) bearing azine sulphonamides **32sa**-**32va** in moderate to good yields starting from the corresponding halogen containing *N*-tosylhydrazone. Acetylated heterocycle derived *N*-tosylhydrazones also reacted with **9a** under super basic medium, producing **32ja**, **32ka,** and **32wa** in good yields where we could introduce furan, thiophene, and pyridine rings

respectively. Finally, by starting from *N*-(5-chloro-2-(chloromethyl)phenyl)-4-methylbenzene sulfonamide **9d** and *N*-(2-(chloromethyl)phenyl)-2,4,6-triisopropylbenzene sulfonamide **9e**, we could synthesize **32ad** and **32ae** in 60% and 48% yields.

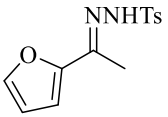
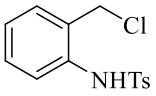
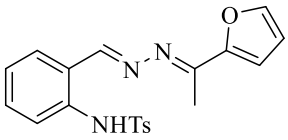
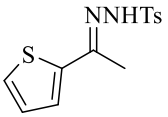
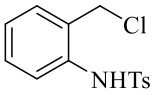
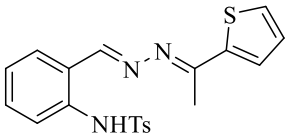
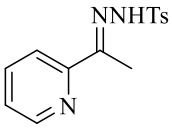
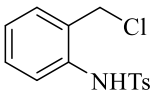
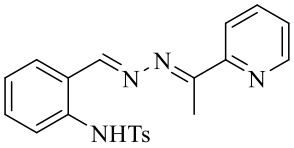
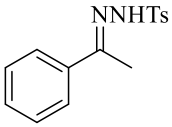
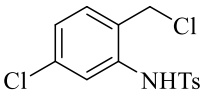
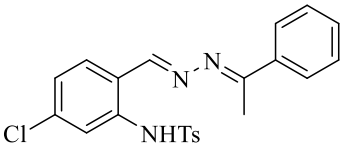
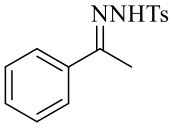
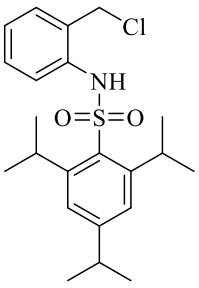
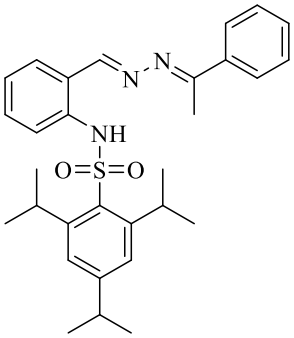
Table 3.4 The generality of the reaction between *N*-tosylhydrazone and *N*-(2-(chloromethyl) phenyl)-4-methylarenesulfonamide under super basic conditions

Entry	Tosylhydrazone	aza-*ortho*-quinone methide precursor	Product	Yield (%)
1	 **29a**	 **9a**	 **32aa**	68%
2	 **29b**	 **9a**	 **32ba**	45%
3	 **29c**	 **9a**	 **32ca**	51%
4	 **29o**	 **9a**	 **32oa**	42%
5	 **29e**	 **9a**	 **32ea**	61%
6	 **29g**	 **9a**	 **32ga**	78%

Reaction conditions: **29** (1.0 equiv., 0.35 mmol), **9a** (1.5 equiv.), KOH (2.0 equiv.), DMSO (2.0 mL), 80 ^{o}C, 12 h.

Entry	Tosylhydrazone	aza-*ortho*-quinone methide precursor	Product	Yield (%)
7	 **29p**	 **9a**	 **32pa**	82%
8	 **29q**	 **9a**	 **32qa**	75%
9	 **29r**	 **9a**	 **32ra**	88%
10	 **29s**	 **9a**	 **32sa**	70%
11	 **29t**	 **9a**	 **32ta**	61%
12	 **29u**	 **9a**	 **32ua**	58%
13	 **29v**	 **9a**	 **32va**	52%

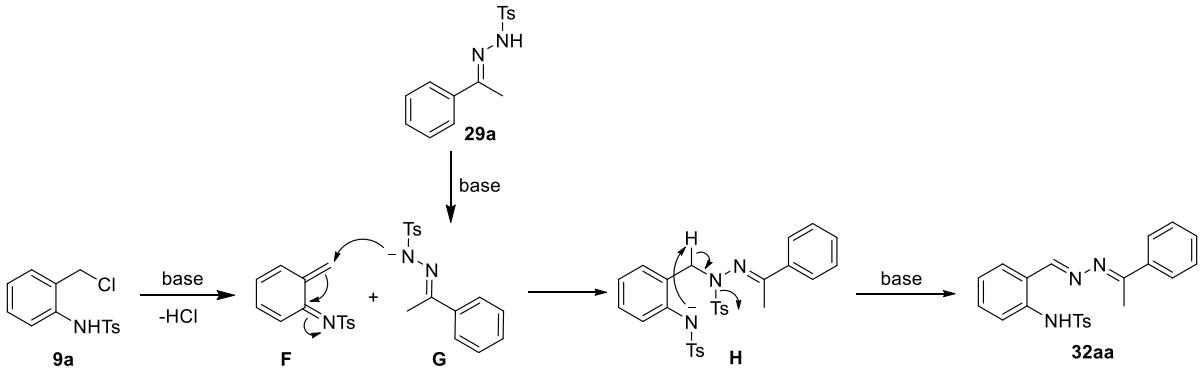
Reaction conditions: **29** (1.0 equiv., 0.35 mmol), **9a** (1.5 equiv.), KOH (2.0 equiv.), DMSO (2.0 mL),80 ^{o}C, 12 h
.

Entry	Tosylhydrazone	aza-*ortho*-quinone methide precursor	Product	Yield (%)
14	 **29j**	 **9a**	 **32ja**	62%
15	 **29k**	 **9a**	 **32ka**	62%
16	 **29w**	 **9a**	 **32wa**	58%
17	 **29a**	 **9c**	 **32ac**	60%
18	 **29a**	 **9e**	 **32ae**	48%

Reaction conditions: **29** (1.0 equiv., 0.35 mmol), **9** (1.5 equiv.), KOH (2.0 equiv.), DMSO (2.0 mL), 80 ^{o}C, 12 h.

We propose a mechanism for the formation of azine sulphonamides from the reaction between *N*-tosylhydrazone and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide under super basic conditions as shown in Scheme 3.16. We believe that the reaction is initiated by the base-mediated formation of aza-*ortho*-quinone methide **F** from **9a**. At the same time, an anionic species **G** is formed from **29a**,[16,19] which then adds to the carbon end of the aza-

ortho-quinone methide **F**, resulting in the intermediate **H**. Then, one benzylic proton is abstracted, followed by the elimination of the Ts-group to afford the azine sulphonamide **32aa**.



Scheme 3.16 Mechanistic postulate for the formation of azine sulphonamide

3.5 Conclusion

In conclusion, we have investigated chemoselectivity in superbase-mediated reactions of *N*-tosylhydrazones with aza-*ortho*-quinone methide precursors. We have observed the regioselective formation of 2-substituted quinoline from the reaction of tosylhydrazone with *ortho*-aminobenzyl alcohol under super basic conditions (KOH+DMSO). It was revealed that the reaction was universal and that mono-, di-, and tri-substituted quinolines could be produced using this methodology. We demonstrated experimentally that the reaction was carried out by the basic decomposition of *N*-tosylhydrazones, which created an azine. Finally, we could generate a series of azine sulphonamides from the reaction of tosylhydrazone and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide under super basic conditions. We believe that the determining factor of chemoselectivity is the formation speed of aza-*ortho*-quinone methide intermediates from the precursors.

3.6 Experimental section

3.61 General experimental methods

All reactions were performed in oven-dried glassware with magnetic stirring. All chemicals used were of analytical quality, were of the best grade, were 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 silica gel, and ethyl acetate and hexane mixtures were used 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 {^{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 OrbitrapVelos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with an ESI/ HRMS at a resolution of 60,000, using Thermo Scientific Exactive mass spectrometer with orbitrap analyzer. 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.

3.62 General procedure for the preparation of *N*-tosylhydrazones

The *N*-tosylhydrazones were prepared according to the literature procedure.[20] To a round bottom flask (100 mL), a solution of *p*-toluene sulfonylhydrazide (16 mmol) in anhydrous methanol, aryl ketone (16 mmol) was added dropwise under refluxing. The reaction mixture was stirred at 60 ^{o}C for 3 h, and the complete consumption of aryl ketone was confirmed by TLC. The solution was cooled until a solid precipitate was formed. The product aryl sulfonylhydrazone **29** was obtained by filtering, washing with petroleum ether, and drying in a vacuum.

3.63 General procedure for the preparation of sulfonaminobenzyl chlorides

The sulfonaminobenzyl chlorides were synthesized according to the reported literature.[21] To a solution of substituted 2-aminobenzyl alcohol (1g, 8.12 mmol) in $CHCl_3$ (40 mL) was added pyridine (720 μL, 8.93mmol). The reaction was stirred for 25 min, and a solution of *p*-TsCl (1.703g, 8.93 mmol) in $CHCl_3$ was added dropwise over 20 min. After 12 h, the reaction was quenched with sat. aq. NH_4Cl. The layers were separated, and the aqueous layer was

extracted with $CHCl_3$. The combined organic layers were then washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude *N*-protected 2-aminobenzyl alcohol, which was used in the subsequent transformation without further purification. To a solution of *N*-protected 2-aminobenzyl alcohol (2.1g, 7.58 mmol) in $CHCl_3$ (40 mL), was added a solution of thionyl chloride (764 μL, 9.10mmol 9.10 mmol) in $CHCl_3$ (5mL) over 1 min. The reaction was heated to 40 ^oC overnight, cooled to room temperature, and poured into ice water (30 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 x 40 mL). The combined organic layers were washed with brine (30mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded crude sulfonaminobenzylchloride as a brown solid and was used without further purification.

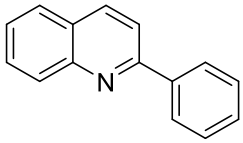
3.64 General procedure for the [4+2] cycloaddition reaction of 2- aminobenzyl alcohol with *N*- tosylhydrazones

A mixture of *N*-tosylhydrazone **29** (0.35 mol, 1 equiv.), 2- aminobenzyl alcohol **1** (0.42 mmol, 1.2 equiv.) and KOH (0.70 mmol, 2.0 equiv.) were weighed into a dry reaction tube. Dimethyl sulphoxide (2 mL) was added using a micropipette and allowed to stir at 80 ^oC on a reaction block for 12 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: ethyl acetate/hexane (1:9) to afford the corresponding products **31**.

3.65 Synthesis and characterization of quinoline derivatives

2-phenylquinoline (31aa)[22]

The reaction was performed according to the general procedure. (*E*)-4-methyl-*N*'-(1-phenylethylidene)benzenesulfonohydrazide **29a** (100 mg, 0.35 mmol), 2-aminobenzyl alcohol **1a** (52 mg. 0.42 mmol), and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^oC for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31aa** as a white solid (57 mg, 79%).



Analytical data of 31aa

Mp: 85−87 ºC.

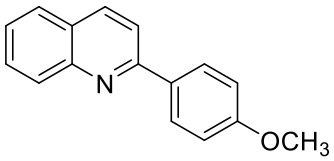
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.25 – 8.16 (m, 4H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 3H), 7.47 (t, *J* = 7.0 Hz, 1H) ppm.

^{13}C {^{1}H} (125 MHz, $CDCl_3$, TMS): δ 157.4, 148.3, 139.7, 136.8, 129.8, 129.7, 129.3, 128.9, 127.6, 127.5, 127.2, 126.3, 119.1 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{12}N$ 206.0964, found 206.0973.

2-(4-methoxyphenyl)quinoline (31ba)[22]

The reaction was performed according to the general procedure. *(E)-N'*-(1-(4-methoxy phenyl)ethylidene)-4-methylbenzenesulfonohydrazide **29b** (0.35 mmol, 112 mg), 2-aminobenzyl alcohol **1a (**52mg, 0.42 mmol), and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ºC for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ba** as a white solid (71 mg, 86%).



Analytical data of 31ba

Mp: 123−125 °C.

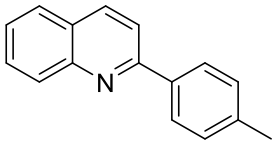
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.21– 8.14 (m, 4H), 7.85– 7.80 (m, 2H), 7.72 (t, *J* = 8 Hz, 1H), 7.51 (t, *J* = 8 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 2H), 3.89 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.9, 156.9, 136.9, 129.7, 129.3, 129.0, 127.4, 126.9, 126.0, 118.6, 114.3, 55.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{14}NO$ 236.1070, found 236.1078.

2-(*p*-tolyl)quinoline (31ca)[22]

The reaction was performed according to the general procedure. 4-methyl-*N*'-(1-(*p*-tolyl)ethylidene)benzenesulfonohydrazide **29c** (106 mg, 0.35 mmol), 2- aminobenzyl alcohol **1a** (52 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 ml) was added and allowed to stir at 80 ^{o}C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ca** as a white solid (64 mg, 83%).



Analytical data of 31ca

Mp: 82−84 ^{o}C.

^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 8.20 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 157.4, 148.3, 139.4, 136.9, 136.7, 129.7, 129.6, 127.4, 127.1, 126.1, 118.9, 21.4 ppm.

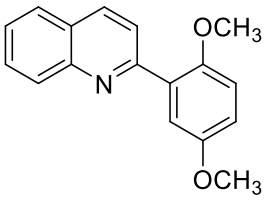
HRMS (ESI-Orbitrap) *m/z*: $(M+H)^+$ calcd for $C_{16}H_{14}N$ 220.1121, found 220.1124.

2-(2,5-dimethoxyphenyl)quinoline (31da)[24]

The reaction was performed according to the general procedure. (*E*)-*N*'-(1-(2,5-dimethoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide **29d** (122mg, 0.35 mmol), 2-aminobenzyl alcohol **1a** (52 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^{o}C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31da** as a white solid (76 mg, 82%).

Analytical data of 31da

Mp: 140 −142 ^{o}C.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.16 (t, *J* = 10.0 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45 (s, 1H), 6.98 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H) ppm.

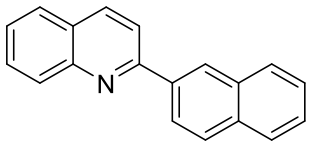
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.9, 154.1, 151.6, 148.3, 135.2, 130.4, 129.6, 129.3, 127.4, 127.1, 126.3, 123.4, 116.2, 116.1, 113.3, 56.5, 55.9 ppm.

HRMS (ESI-Orbitrap) *m/z*: $(M+H)^+$ calcd for $C_{17}H_{16}NO_2$ 266.1176, found 266.1181.

2-(naphthalen-2-yl)quinoline (31ea)[25]

The reaction was performed according to the general procedure. 4-methyl-*N*'-(1-(naphthalen-2-yl)ethylidene)benzenesulfonohydrazide **29e** (0.35 mol, 118 mg), 2-aminobenzyl alcohol **1a** (52 mg0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^{o}C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the product **31ea** as a pale yellow solid (64 mg, 71%).

Analytical data of 31ea



Mp: 136 −139 ^{o}C.

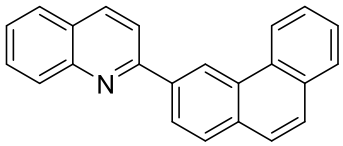
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.62 (s, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.90 – 7.85 (m, 2H), 7.76 (t, *J* = 8.0 Hz, 1H), 7.56 – 7.54 (m, 3H).

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 157.2, 148.4, 137.0, 136.8, 133.9, 133.5, 129.8, 128.8, 128.6, 127.8, 127.5, 127.3, 127.2 126.7, 126.4, 126.4, 125.1, 119.2 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{19}H_{14}N$ 256.1121, found 256.1124.

2-(phenanthren-3-yl)quinoline (31fa)[22]

The reaction was performed according to the general procedure. (*E*)-4-methyl-*N*'-(1-(phenanthren-3-yl)ethylidene)benzenesulfonohydrazide **29f** (136 mg, 0.35 mmol), 2-aminobenzyl alcohol **1a** (52 mg. 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^oC for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31fa** as a yellow solid (83 mg, 78%).



Analytical data of 31fa

Mp: 136 −139 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.53 (s, 1H), 8.92 (d, *J* = 8.5 Hz, 1H), 8.42 (d, *J* = 8.5 Hz, 1H), 8.29 (t, *J* = 7.0 Hz, 2H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.81 – 7.77 (m, 3H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H).

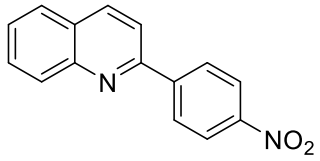
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 157.5, 148.5, 137.6, 136.9, 132.7, 132.3, 130.7, 130.6, 129.8, 129.8, 129.2, 128.7, 127.9 127.5, 127.3, 126.8, 126.8, 126.6, 126.4, 125.8, 123.0, 122.1, 119.3 ppm.

HRMS (ESI-Orbitrap) *m/z*: $(M+H)^+$ calcd for $C_{23}H_{16}N$ 306.1277, found 306.1286.

2-(4-nitrophenyl)quinoline (31ga)[22]

The reaction was performed according to the general procedure. (*(E)*-4-methyl-*N*'-(1-(4-nitrophenyl)ethylidene)benzenesulfonohydrazide **29g** (117 mg, 0.35 mmol), 2- aminobenzyl alcohol **1a** (52 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^oC for 12 h. After solvent removal,

the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ga** as a white solid (51 mg, 58%).



Analytical data of 31ga

Mp: 122−125 °C.

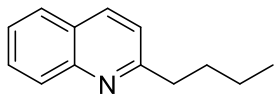
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.16 - 8.13 (m, 2H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.82 - 7.78 (m, 2H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 2H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 157.2, 147.9, 136.6, 129.6, 129.2, 128.9, 127.4, 126.8, 125.7, 118.4, 115.1 ppm.

HRMS (ESI-Orbitrap) *m/z*: $(M+H)^+$ calcd for $C_{15}H_{11}N_2O_2$ 251.0815, found 251.0821.

2-butylquinoline (31ha)[23]

The reaction was performed according to the general procedure. (*E*)-*N*'-(hexan-2-ylidene)-4-methylbenzenesulfonohydrazide **29h** (94 mg, 0.35 mmol), 2- aminobenzyl alcohol **1a** (52 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 °C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ha** as a colourless liquid (40 mg, 62%).



Analytical data of 31ha

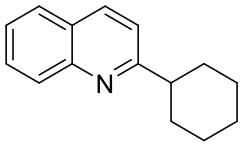
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.05 (t, *J* = 7.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 2.98 (t, *J* = 8.0 Hz, 2H), 1.83 – 1.77 (m, 2H), 1.47 – 1.42 (m, 2H), 0.96 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.1, 147.9, 136.2, 129.3, 128.8, 127.5, 126.7, 125.6, 121.4, 39.1, 32.2, 22.7, 14.0 ppm.

HRMS (ESI-Orbitrap) *m/z*: $(M+H)^+$ calcd for $C_{13}H_{16}N$ 186.1277, found 186.1283.

2-cyclohexylquinoline (31ia)[24]

The reaction was performed according to the general procedure. (*E*)-*N*'-(1-cyclohexylethylidene)-4-methylbenzenesulfonohydrazide **29i** (103 mg, 0.35 mmol), 2-aminobenzyl alcohol **1a** (52 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^oC for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ia** as a colourless liquid (57 mg, 77%).



Analytical data of 31ia

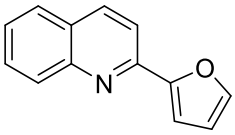
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.09 – 8.04 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 2.92 (t, *J* = 12.0 Hz, 1H), 2.03 (d, *J* = 13.0 Hz, 2H), 1.90 (d, *J* = 12.5 Hz, 2H), 1.80 – 1.76 (m, 2H), 1.63 (q, *J* = 12.5 Hz, 2H), 1.47 (q, *J* = 13.0 Hz, 2H).

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): 166.9, 147.8, 136.3, 136.3, 129.2, 129.2, 129.0, 127.4, 127.0, 125.6, 119.6, 47.7, 32.9, 26.6, 26.1ppm.

HRMS (ESI-Orbitrap) *m/z*: $(M+H)^+$ calcd for $C_{15}H_{18}N$ 212.1434, found 212.1439.

2-(furan-2-yl)quinoline (31ja)[24]

The reaction was performed according to the general procedure. (*E*)-*N*'-(1-(furan-2-yl)ethylidene)-4-methylbenzenesulfonohydrazide **29j** (97 mg, 0.35 mmol), 2-aminobenzyl alcohol **1a** (52 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^oC for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ja** as a white solid (62 mg, 90%).



Analytical data of 31ja

Mp: 87−89 °C.

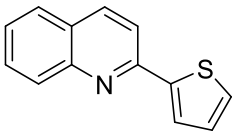
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.17 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.22 (s, 1H), 6.59 (s, 1H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.0, 144.2, 136.7, 129.9, 129.4, 127.6, 127.2, 126.2, 117.5, 112.2, 110.2 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{13}H_{10}NO$ 196.0757, found 196.0762.

2-(thiophen-2-yl)quinoline (31ka)[4]

The reaction was performed according to the general procedure. (*E*)-4-methyl-*N*'-(1-(thiophen-2-yl)ethylidene)benzenesulfonohydrazide **29k** (103 mg, 0.35 mmol), 2-aminobenzyl alcohol **1a** (52 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 °C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ka** as a white solid (65 mg, 88%).



Analytical data of 31ka

Mp: 131−134 °C.

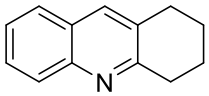
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.15 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.74 (d, *J* = 2.5 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.51– 7.47 (m, 2H), 7.17 (t, *J* = 4.5 Hz, 1H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.4, 136.6, 129.8, 129.3, 128.6, 128.1, 127.5, 126.1, 125.9, 117.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{13}H_{10}NS$ 212.0528, found 212.0536.

1, 2, 3, 4-tetrahydroacridine (31la)[24]

The reaction was performed according to the general procedure. *N*'-cyclohexylidene-4-methylbenzenesulfonohydrazide **29l** (0.35 mmol, 93 mg), 2- aminobenzyl alcohol **1a** (52 mg. 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 °C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31la** as a colourless liquid (42 mg, 66%).



Analytical data of 31la

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.97 (d, *J* = 8.5 Hz, 1H), 7.81 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 3.13 (t, *J* = 6.5 Hz, 2H), 2.98 (t, *J* = 6.5 Hz, 2H), 2.00 – 1.99 (m, 2H), 1.92– 1.90 (m, 2H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.4, 146.6, 135.0, 131.0, 128.5, 128.3, 127.2, 126.9, 125.6, 33.6, 29.3, 23.2, 22.9 ppm.

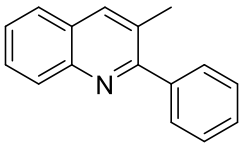
HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{13}H_{14}N$ 184.1121, found 184.1124.

3-methyl-2-phenylquinoline (31ma)[24]

The reaction was performed according to the general procedure. (*E*)-4-methyl-*N*'-(1-phenyl propylidene)benzenesulfonohydrazide **29m** (106 mg, 0.35 mmol), 2-aminobenzyl alcohol **1a** (52 mg, 0.42 mmol) and KOH (0.70 mmol, 39 mg) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 °C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ma** as a colourless liquid (56 mg, 73%).

Analytical data of 31ma

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.14 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 7.78 (d, *J* = 8 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.60 (d,



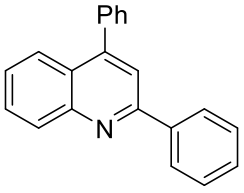
J = 7 Hz, 2H), 7.53– 7.48 (m, 3H), 7.46 – 7.43 (m, 1H), 2.47 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 160.6, 146.6, 140.9, 136.8, 129.3, 129.2, 128.9, 128.8, 128.3, 128.2, 127.6, 126.8, 126.4, 20.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{14}N$ 220.1121, found 220.1123.

2,4-diphenylquinoline (31ab)[24]

The reaction was performed according to the general procedure. (*E*)-4-methyl-*N*'-(1-phenylethylidene)benzenesulfonohydrazide **29a** (100 mg, 0.35 mmol), (2-aminophenyl)(phenyl)methanol **1b** (84 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^{o}C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ab** as a pale yellow solid (80 mg, 81%).



Analytical data of 31ab

Mp: 104−106 ^{o}C.

^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 8.25 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 2H), 7.92 (d, *J* = 8 Hz, 1H), 7.83 (s, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.57 – 7.47 (m, 9H) ppm.

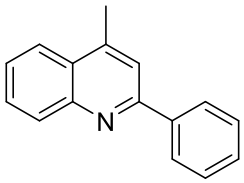
^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 157.0, 149.2, 139.7, 138.4, 130.1, 129.6, 129.6, 129.4, 128.9, 128.6, 128.4, 127.6, 126.4, 125.8, 125.7, 119.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+ H)^+$ calcd for $C_{21}H_{16}N$ 282.1277, found 282.1282.

4-methyl-2-phenylquinoline (3ac)[24]

The reaction was performed according to the general procedure. (*E*)-4-methyl-*N*'-(1-phenyl ethylidene)benzenesulfonohydrazide **29a** (100 mg, 0.35 mmol), 1-(2-aminophenyl) ethan-1-ol **1c** (58 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube.

DMSO (2 mL) was added and allowed to stir at 80 ^{o}C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ac** as a colourless liquid (64 mg, 83%).

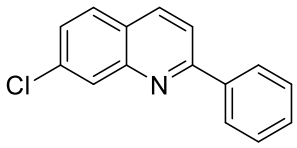


Analytical data of 31ac

^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 8.27 (d, *J* = 7.5 Hz, 2H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 6.5 Hz, 1H), 7.54 (t, *J* = 7.0 Hz, 2H), 7.48 – 7.45 (m, 1H), 7.43 – 7.40 (m, 1H), 2.91 (s, 3H) ppm. **^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$):** δ 154.5, 146.1, 138.8, 136.6, 135.9, 128.6, 128.2, 127.8, 126.4, 126.1, 125.0, 124.4, 117.2, 16.9 ppm. **HRMS (ESI-Orbitrap) m/z:** (M+ H)$^{+}$ calcd for $C_{16}H_{14}N$ 220.1121, found 220.1126.

7-chloro-2-phenylquinoline (31ad)[24]

The reaction was performed according to the general procedure. (*E*)-4-methyl-*N*'-(1-phenyl ethylidene)benzenesulfonohydrazide **29a** (100 mg, 0.35 mmol), (2-amino-5-chloro phenyl) methanol **1d** (66 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^{o}C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31ad** as a pale yellow solid (64 mg, 76%).



Analytical data of 31ad

Mp: 107−109 ^{o}C.

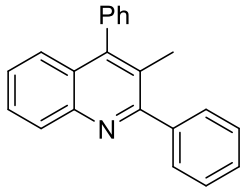
^{1}H NMR (500 MHz, CDCl$_3$, δ 8.24 (d, *J* = 8.5 Hz, 1H), 8.19 – 8.16 (m, 2H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.0 Hz, 3 H), 7.48 (t, *J* = 7.5 Hz, 1H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 157.4, 139.7, 136.8, 129.8, 129.7, 129.3, 128.9, 127.6, 127.5, 127.2, 126.3, 119.1 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{11}ClN$ 240.0575, found 240.0586.

3-methyl-2,4-diphenylquinoline (31mb)[24]

The reaction was performed according to the general procedure. (*E*)-4-methyl-*N*'-(1-phenylpropylidene)benzenesulfonohydrazide **29m** (106 mg, 0.35 mmol), (2-aminophenyl)(phenyl)methanol **1b** (84 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 °C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31mb** as a pale yellow solid (73 mg, 71%).



Analytical data of 31mb

Mp: 130 − 132 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.16 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.61 (m, 3H), 7.55 (t, *J* = 7.0 Hz, 2H), 7.50 – 7.49 (m, 3H), 7.45 (d, *J* = 7 Hz, 1H), 7.39 (s, 2H), 7.32 (d, *J* = 7.0 Hz, 2H), 2.15 (s, 3H) ppm.

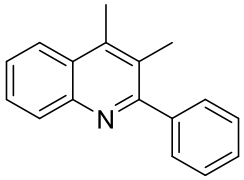
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.9, 147.8, 146.2, 141.5, 137.8, 129.4, 129.4, 128.9, 128.7, 128.6, 128.3, 128.1, 127.8, 127.1, 126.8, 126.3, 126.0, 18.6 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{22}H_{18}N$ 296.1434, found 296.1432.

3,4-dimethyl-2-phenylquinoline (31mc)[24]

The reaction was performed according to the general procedure. (*E*)-4-methyl-*N*'-(1-phenylpropylidene)benzenesulfonohydrazide **29m** (106 mg, 0.35 mmol), 1-(2-aminophenyl)ethan-1-ol **1c** (58 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 °C for 12 h. After

solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31mc** as a colourless liquid (61 mg, 74%).



Analytical data of 31mc

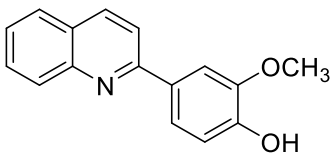
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.98 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.48 (m, 3H), 7.45 (d, *J* = 7.0 Hz, 1H), 7.40 (t, *J* = 8 Hz, 1H), 2.81 (s, 3H), 2.51 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 141.3, 137.1, 129.4, 128.7, 128.7, 128.1, 127.4, 126.1, 124.6, 20.8, 18.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{16}N$ 234.1277, found 234.1284.

2-methoxy-4-(quinolin-2-yl)phenol (31na)

The reaction was performed according to the general procedure. (*E*)-*N*'-(1-(4-hydroxy-3-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide **29n** (117mg, 0.35 mmol,), 2-aminobenzyl alcohol **1a** (52 mg, 0.42 mmol) and KOH (39 mg, 0.70 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^{o}C for 12 h. After solvent removal, the residue was then purified by silica gel column chromatography (10% EtOAc/ Hexane) to afford the desired product **31na** as a colourless liquid (58 mg, 66%).



Analytical data of 31na

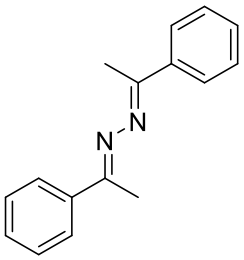
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.19 (d, *J* = 9.0 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 7.85 - 7.80 (m, 2H), 7.71 (t, *J* = 7.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 5.84 (s, 1H), 4.06 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 157.0, 153.0 147.2, 136.7, 132.1, 129.6, 129.4, 127.5, 127.0, 126.0, 120.9, 118.6, 114.5, 109.9, 56.1 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{14}NO_2$ 252.1019 found 252.1027.

3.66 Synthesis and characterization data for (1*E*,2*E*)-1,2-bis(1-phenylethylidene) hydrazine (A)

A mixture of (*E*)-4-methyl-*N*'-(1-phenylethylidene)benzenesulfonohydrazide **29a** (100 mg, 0.35 mmol) and KOH (19 mg, 0.35 mmol) were weighed into a dry reaction tube. DMSO (2 mL) was added and allowed to stir at 80 ^oC for 12 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 silica gel column chromatography (5% EtOAc/ Hexane) to afford the desired product **A** as a yellow solid (39 mg, 94%).



Analytical data of A

Mp: 126−129 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.92 (d, *J* = 6 Hz, 4H), 7.42 (s, 6H), 2.32 (s, 6H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, TMS): δ 157.7, 138.4, 129.6, 128.4, 126.6, 15.1 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{17}N_2$ 237.1386, found 237.1395.

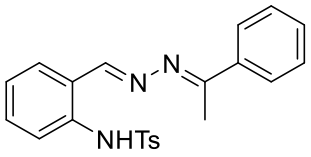
3.67 General procedure for the reaction of aza-*o*-quinone methides with *N*-tosylhydrazones

To a mixture of *N*-tosylhydrazone **29** (0.35 mmol, 1 equiv.), aza-*o*-QM precursor **9** (0.52 mmol, 1.5 equiv.), and KOH (0.70 mmol, 2.0 equiv.) were weighed into a dry reaction tube. Dry DMSO (2 mL) was added *via* a syringe and allowed to stir at 80 ^oC on a reaction block for 12 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: ethyl acetate/hexane (1:9) to afford the corresponding product **32**.

3.68 Synthesis and characterization data for Sulfonamide derivaives 32

4-methyl-*N*-(2-((*E*)-(((*E*)-1-phenylethylidene)hydrazineylidene)methyl)phenyl) benzenesulfonamide (32aa)

The reaction was performed according to the general procedure. (*E*)-4-methyl-*N*'-(1-phenylethylidene)benzenesulfonohydrazide **29a** (100 mg, 0.35 mmol), *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol), and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32aa** as a yellow solid (93 mg, 68%).



Analytical data of 32aa

Mp: 102 –105 ^{o}C.

^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 12.17 (s, 1H), 8.64 (s, 1H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 6.5 Hz, 3H), 7.36 – 7.32 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 2.67 (s, 3H), 2.35 (s, 3H) ppm.

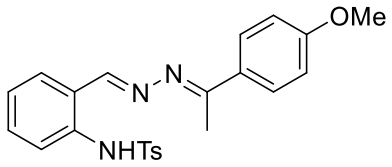
^{13}C {^{1}H} NMR (125 MHz, CDCl3): δ 167.6, 162.8, 143.8, 138.8, 137.8, 136.8, 133.9, 131.9, 130.7, 129.7, 128.6, 127.3, 127.2, 122.8, 120.0, 117.4, 21.5, 16.3 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{22}H_{22}N_3O_2S$ 392.1427, found 392.1428.

4-methyl-*N*-(2-((*E*)-(((*E*)-1-(4-methoxyphenyl)ethylidene)hydrazineylidene)methyl)phenyl)-4-methylbenzenesulfonamide (32ba)

The reaction was performed according to the general procedure with (*E*)-*N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide **29b** (111 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol,) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica

gel column chromatography (10% EtOAc/hexane) to afford the desired product **32ba** as a pale yellow solid (66 mg, 45%).



Analytical data of 32ba

Mp: 88-90 ^{o}C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 12.22 (s, 1H), 8.62 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.35 - 7.30 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 3H), 2.64 (s, 3H), 2.35 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.1, 162.1, 161.8, 143.7, 138.8, 136.8, 133.8, 131.7, 130.2, 129.7, 128.9, 127.2, 122.7, 120.2, 117.4, 113.9, 113.6, 55.4, 21.5, 16.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{23}H_{24}N_3O_3S$ 422.1533, found 422.1544.

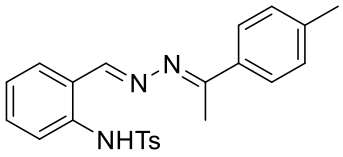
4-methyl-*N*-(2-((*E*)-(((*E*)-1-(*p*-tolyl)ethylidene)hydrazineylidene)methyl)phenyl) benzenesulfonamide (32ca)

The reaction was performed according to the general procedure with 4-methyl-*N*'-(1-(p-tolyl)ethylidene)benzenesulfonohydrazide **29c** (104 mg, 0.35 mmol), *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32ca** as a pale-yellow solid (72 mg, 51%).

Analytical data of 32ca

Mp: 125-128 ^{o}C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 12.13 (s, 1H), 8.56 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.20



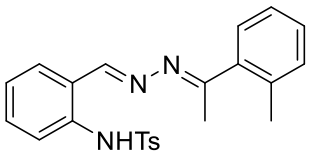
(d, *J* = 7.0 Hz, 3H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 2.58 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 167.6, 162.4, 143.7, 141.1, 138.8, 136.8, 135.0, 133.8, 131.8, 129.7, 129.3, 122.7, 120.1, 117.4, 21.53, 21.46, 16.2 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{23}H_{24}N_3O_2S$ 406.1584, found 406.1588.

4-methyl-*N*-(2-((*E*)-(((*E*)-1-(*o*-tolyl)ethylidene)hydrazineylidene)methyl)phenyl) benzenesulfonamide (32oa)

The reaction was performed according to the general procedure with (*E*)-4-methyl-*N*'-(1-(*o*-tolyl)ethylidene)benzenesulfonohydrazide, **29o** (104 mg, 0.35 mmol), *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32oa** as a pale yellow solid (60 mg, 42%).



Analytical data of 32oa

Mp: 87-88 ^{o}C.

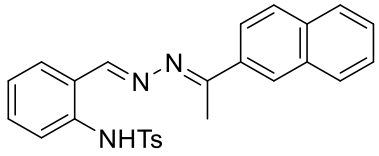
^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 12.07 (s, 1H), 8.52 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.31 – 7.23 (m, 4H), 7.20 – 7.17 (m, 4H), 6.99 (t, *J* = 7.5 Hz, 1H), 2.53 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 171.4, 163.0, 143.8, 139.3, 138.9, 137.0, 135.5, 134.0, 132.0, 131.0, 129.7, 129.1, 127.8, 127.2, 126.0, 122.7, 119.8, 117.4, 21.5, 20.4, 20.2 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{23}H_{24}N_3O_2S$ 406.1584, found 406.1588.

4-methyl-*N*-(2-((*E*)-(((*E*)-1-(naphthalen-2-yl)ethylidene)hydrazineylidene) methyl)phenyl)benzenesulfonamide (32ea)

The reaction was performed according to the general procedure with (*E*)-4-methyl-*N*'-(1-(naphthalen-2-yl)ethylidene)benzenesulfonohydrazide **29e** (118mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32ea** as a pale yellow solid (94 mg, 61%).



Analytical data of 32ea

Mp: 195-198 ^{o}C.

^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 12.22 (s, 1H), 8.70 (s, 1H), 8.34 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.96 – 7.94 (m, 1H), 7.91 – 7.87 (m, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.54 (m, 2H), 7.38– 7.33 (m, 2H) 7.23 (d, *J* = 8.0 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 2.78 (s, 3H), 2.35 (s, 3H) ppm.

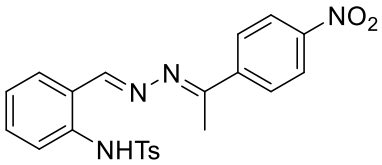
^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 165.3, 157.7, 144.0, 138.9, 136.6, 135.9, 134.5, 134.1, 133.1, 132.7, 129.7, 128.7, 128.0, 127.7, 127.2, 126.8, 126.7, 126.3, 124.0, 123.2, 119.3, 118.1, 21.6, 15.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{26}H_{24}N_3O_2S$ 442.1584, found 442.1602.

4-methyl-*N*-(2-((*E*)-(((*E*)-1-(4-nitrophenyl)ethylidene)hydrazineylidene)methyl) phenyl)benzenesulfonamide (32ga)

The reaction was performed according to the general procedure with (*E*)-4-methyl-*N*'-(1-(4-nitrophenyl)ethylidene)benzenesulfonohydrazide **29g** (117 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel

column chromatography (10% EtOAc/hexane) to afford the desired product **32ga** as a yellow solid (119 mg, 78%).



Analytical data of 32ga

Mp: 211-213 ^{o}C.

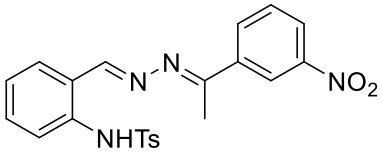
^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 11.99 (s, 1H), 8.66 (s, 1H), 8.31 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 2.69 (s, 3H), 2.36 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 165.2, 164.1, 149.0, 143.9, 143.6, 139.1, 136.8, 134.3, 132.5, 129.7, 128.1, 127.3, 123.7, 122.8, 119.6, 117.4, 21.5, 16.2 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{22}H_{21}N_4O_4S$ 437.1278, found 437.1290.

4-methyl-*N*-(2-((*E*)-(((*E*)-1-(3-nitrophenyl)ethylidene)hydrazineylidene)methyl)phenyl) benzenesulfonamide (32pa)

The reaction was performed according to the general procedure with (*E*)-4-methyl-*N*'-(1-(3-nitrophenyl)ethylidene)benzenesulfonohydrazide **29p** (117 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32pa** as a yellow solid (125 mg, 82%).



Analytical data of 32pa

Mp: 127-130 ^{o}C.

^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 12.01 (s, 1H), 8.85 (s, 1H), 8.68 (s, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.67 - 7.64 (m, 2H), 7.40 - 7.35 (m, 2H),

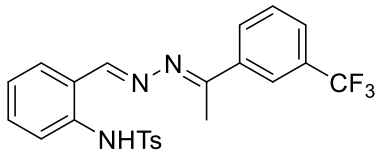
7.24 (d, *J* = 8.5 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 2.70 (s, 3H), 2.36 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.9, 164.1, 143.9, 139.5, 139.0, 136.7, 134.3, 132.9, 132.4, 129.8, 129.6, 127.3, 125.0, 122.8, 122.2, 119.6, 117.4, 21.6, 16.1 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{22}H_{21}N_4O_4S$ 437.1278, found 437.1296.

4-methyl-*N*-(2-((*E*)-(((*E*)-1-(3-(trifluoromethyl)phenyl)ethylidene)hydrazineylidene) methyl)phenyl)benzenesulfonamide (32qa)

The reaction was performed according to the general procedure with (*E*)-4-methyl-*N*'-(1-(3-(trifluoromethyl)phenyl)ethylidene)benzenesulfonohydrazide **29q** (125 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32qa** as a pale-yellow solid (121 mg, 75%).



Analytical data of 32qa

Mp: 110-112 ^{o}C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 12.06 (s, 1H), 8.66 (s, 1H), 8.26 (s, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.38 - 7.33 (m ,2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 2.68 (s, 3H), 2.36 (s, 3H) ppm.

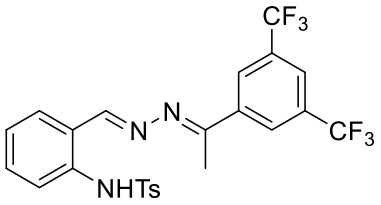
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 165.9, 163.6, 143.9, 139.0, 138.6, 136.8, 134.1, 132.2, 131.1(q, *J* = 244.0 Hz, 121.5 Hz), 130.4, 129.7, 129.1, 127.2, 127.1 (d, *J* = 13.2 Hz), 124.0 (d, *J* = 14.2Hz), 122.8, 119.8, 117.4, 21.5, 16.1 ppm.

^{19}F NMR (471 MHz, $CDCl_3$): δ -62.69 (s, 3F) ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{23}H_{21}F_3N_3O_2S$ 460.1301, found 460.1314.

***N*-(2-((*E*)-(((*E*)-1-(3,5-bis(trifluoromethyl)phenyl)ethylidene)hydrazineylidene)methyl) phenyl)-4-methylbenzenesulfonamide (32ra)**

The reaction was performed according to the general procedure with (*E*)-*N*'-(1-(3,5-bis(trifluoromethyl)phenyl)ethylidene)-4-methylbenzenesulfonohydrazide **29r** (149 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^oC for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32ra** as a pale yellow solid (162 mg, 88%).



Analytical data of 32ra

Mp: 147-149 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 11.96 (s, 1H), 8.69 (s, 1H), 8.41 (s, 2H), 7.98 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 2.70 (s, 3H), 2.36 (s, 3H) ppm.

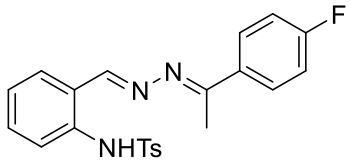
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.4, 164.2, 144.0, 139.8, 139.1, 136.7, 134.3, 132.6, 132.0 (q, *J* = 254.8 Hz, 125.8 Hz), 129.8, 127.25, 127.2 (d, *J* = 11.3 Hz), 122.9, 119.5, 117.4, 21.5, 15.9 ppm.

^{19}F NMR (471 MHz, $CDCl_3$): δ -62.87 (s, 6F) ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{24}H_{20}F_6N_3O_2S$ 528.1175, found 528.1168.

_N_-(2-((_E_)-(((_E_)-1-(4-fluorophenyl)ethylidene)hydrazineylidene)methyl)phenyl)-4-methylbenzenesulfonamide (32sa)

The reaction was performed according to the general procedure with (*E*)-*N*'-(1-(4-fluorophenyl)ethylidene)-4-methylbenzenesulfonohydrazide **29s** (107 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol)at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32sa** as a pale yellow solid (100 mg, 70%).



Analytical data of 32sa

Mp: 123-125 ^{o}C.

^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 12.13 (s, 1H), 8.63 (s, 1H), 7.98 – 7.95 (m, 2H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 2.65 (s, 3H), 2.35 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 166.4, 162.8, 143.8, 138.8, 136.8, 133.9, 132.0, 129.7, 129.3 (d, *J* = 32.5 Hz), 127.2, 122.8, 119.9, 117.4, 115.6 (d, *J* = 81 Hz), 21.5, 16.2 ppm.

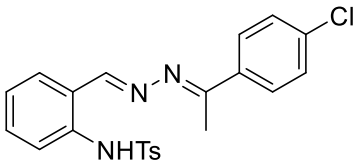
^{19}F NMR (471 MHz, CDCl$_3$): δ -109.65 (s, 1F) ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{22}H_{21}FN_3O_2S$ 410.1333, found 410.1346.

_N_-(2-((_E_)-(((_E_)-1-(4-chlorophenyl)ethylidene)hydrazineylidene)methyl)phenyl)-4-methyl benzenesulfonamide (32ta)

The reaction was performed according to the general procedure with *(E)-N'-(*1-(4-chlorophenyl)ethylidene)-4-methylbenzenesulfonohydrazide **29t** (113 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel

column chromatography (10% EtOAc/hexane) to afford the desired product **32ta** as a pale yellow solid (91 mg, 61%).



Analytical data of 32ta

Mp: 135-138 ^{o}C.

^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 12.11 (s, 1H), 8.63 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.36 - 7.32 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 2.64 (s, 3H), 2.36 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 166.3, 163.0, 143.8, 138.9, 136.85, 136.77, 136.2, 134.0, 132.1, 129.74, 129.71, 128.8, 128.5, 127.3, 122.8, 119.8, 117.3, 21.5, 16.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{22}H_{21}ClN_3O_2S$ 426.1038, found 426.1033.

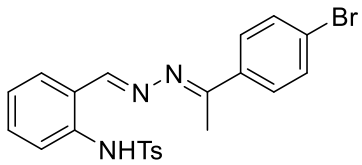
***N*-(2-((*E*)-(((*E*)-1-(4-bromophenyl)ethylidene)hydrazineylidene)methyl)phenyl)-4-methylbenzenesulfonamide (32ua)**

The reaction was performed according to the general procedure with (*E*)-*N'*-(1-(4-bromophenyl)ethylidene)-4-methylbenzenesulfonohydrazide **29u** (129 mg, 0.35 mmol) *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ºC for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32ua** as a pale yellow solid (95 mg, 58%).

Analytical data of 32ua

Mp: 118-120 ^{o}C.

^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 12.03 (s, 1H), 8.56 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.25 (m, 2H), 7.15 (d,



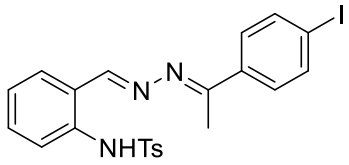
J = 8.0 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 2.56 (s, 3H), 2.28 (s, 3H).

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 166.4, 163.1, 143.8, 138.9, 136.8, 136.6, 134.0, 132.1, 131.8, 129.7, 128.7, 127.3, 125.3, 122.8, 119.8, 117.4, 21.5, 16.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{22}H_{21}BrN_3O_2S$ 470.0532, found 470.0540.

***N*-(2-((*E*)-(((*E*)-1-(4-iodophenyl)ethylidene)hydrazineylidene)methyl)phenyl)-4-methyl benzenesulfonamide (32va)**

The reaction was performed according to the general procedure with (*E*)-*N*'-(1-(4-iodophenyl)ethylidene)-4-methylbenzenesulfonohydrazide **29v** (145 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32va** as a yellow solid (94 mg, 52%).



Analytical data of 32va

Mp: 130-132 ^{o}C.

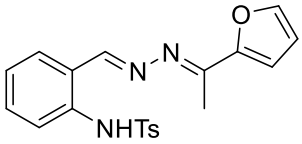
^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 12.09 (s, 1H), 8.62 (s, 1H), 7.81- 7.76 (m, 4H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.36 - 7.32 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 2.62 (s, 3H), 2.35 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 166.5, 163.0, 143.8, 138.9, 137.8, 137.3, 136.9, 134.0, 132.1, 129.7, 128.8, 127.2, 122.8, 119.9, 117.4, 97.4, 21.5, 15.9 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{22}H_{21}IN_3O_2S$ 518.0394, found 518.0391.

***N*-(2-((*E*)-(((*E*)-1-(furan-2-yl)ethylidene)hydrazineylidene)methyl)phenyl)-4-methyl benzenesulfonamide (32ja)**

The reaction was performed according to the general procedure with (*E*)-*N*'-(1-(furan-2-yl)ethylidene)-4-methylbenzenesulfonohydrazide **29j** (97 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32ja** as a pale yellow solid (88 mg, 66%).



Analytical data of 32ja

Mp: 137-139 ^{o}C.

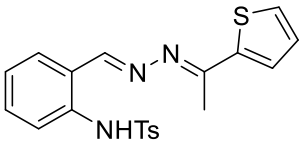
^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 12.09 (s, 1H), 8.69 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.66 – 7.62 (m, 2H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.07 – 7.04 (m, 2H), 6.57 (s, 1H), 2.59 (s, 3H), 2.34 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 163.0, 158.6, 151.7, 145.6, 143.8, 138.8, 136.7, 134.0, 132.0, 129.7, 127.2, 122.8, 120.0, 117.5, 114.9, 112.2, 21.5, 15.4 ppm.

HRMS (ESI-Orbitrap) m/z: (M+H) $^{+}$ calcd for $C_{20}H_{20}N_3O_3S$ 382.1220, found 382.1237.

4-methyl-*N*-(2-((*E*)-(((*E*)-1-(thiophen-2-yl)ethylidene)hydrazineylidene)methyl) phenyl)benzenesulfonamide (32ka)

The reaction was performed according to the general procedure with (*E*)-4-methyl-*N*'-(1-(thiophen-2-yl)ethylidene)benzenesulfonohydrazide **29k** (103 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzene sulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32ka** as a pale yellow solid (86 mg, 62%).



Analytical data of 32ka

Mp: 134-136 ^{o}C.

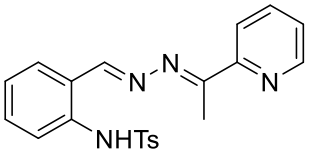
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 12.11 (s, 1H), 8.62 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 5.0 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.21 (d, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 4.0 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 2.68 (s, 3H), 2.35 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.0, 162.5, 143.8, 143.1, 138.8, 136.8, 133.9, 131.9, 130.2, 129.70, 129.67, 127.8, 127.2, 122.8, 120.1, 117.5, 21.5, 16.2 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{20}H_{20}N_3O_2S_2$ 398.0991, found 398.1003.

4-methyl-*N*-(2-((*E*)-(((*E*)-1-(pyridin-2-yl)ethylidene)hydrazineylidene)methyl)phenyl) benzenesulfonamide (32wa)

The reaction was performed according to the general procedure with (*E*)-4-methyl-*N*'-(1-(pyridin-2-yl)ethylidene)benzenesulfonohydrazide **29w** (101 mg, 0.35 mmol), *N*-(2(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9a** (154 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32wa** as a pale yellow solid (80 mg, 58%).



Analytical data of 32wa

Mp: 185-188 ^{o}C.

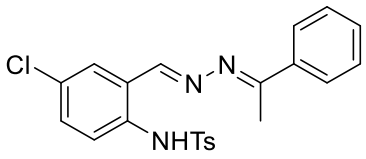
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 12.06 (s, 1H), 8.71 (d, *J* = 3.5 Hz, 1H), 8.63 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.80 - 7.77 (m, 3H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 2.74 (s, 3H), 2.35 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.2, 165.3, 163.2, 155.3, 149.1, 143.8, 139.0, 136.9, 136.4, 134.0, 132.2, 129.7, 127.2, 124.8, 123.2, 122.8, 121.7, 119.8, 117.5, 21.5, 14.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_2S$ 393.1380, found 398.1382.

***N*-(4-chloro-2-((*E*)-(((*E*)-1-phenylethylidene)hydrazineylidene)methyl)phenyl)-4-methylbenzenesulfonamide (32ad)**

The reaction was performed according to the general procedure with (*E*)-4-methyl-*N*'-(1-phenylethylidene)benzenesulfonohydrazide **29a** (0.35 mmol, 100 mg), *N*-(5-chloro-2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **9d** (172 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ºC for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32ad** as a pale yellow solid (89 mg, 60%).



Analytical data of 32ad

Mp: 205-208 ºC.

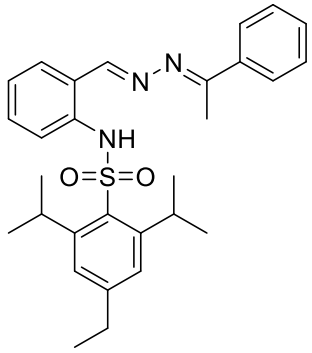
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 12.06 (s, 1H), 8.55 (s, 1H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 3H), 7.38 (d, *J* = 4.0 Hz, 1H), 7.31(s,1H), 7.23 (d, *J* = 8.0 Hz, 2H), 2.66 (s, 3H), 2.37 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.3, 161.4, 144.1, 137.6, 137.3, 136.5, 133.0, 131.6, 130.9, 129.8, 129.6, 128.7, 128.6, 128.3, 128.0, 127.3, 127.2, 126.5, 124.9, 121.4, 118.9, 21.6, 16.3 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{22}H_{21}ClN_3O_2S$ 426.1038, found 426.1048.

2,4,6-triisopropyl-*N*-(2-((*E*)-(((*E*)-1-phenylethylidene)hydrazineylidene)methyl) phenyl)benzenesulfonamide (32ae)

The reaction was performed according to the general procedure with (*E*)-4-methyl-*N*'-(1-phenylethylidene)benzenesulfonohydrazide **29a** (100 mg, 0.35 mmol), *N*-(2-(chloromethyl)phenyl)-2,4,6-triisopropylbenzenesulfonamide **9e** (212 mg, 0.52 mmol) and KOH (39 mg, 0.70 mmol) at 80 ^{o}C for 12 h. After solvent removal, the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford the desired product **32ae** as a pale yellow solid (125 mg, 48%).



Analytical data of 32ae

Mp: 151-153 ^{o}C.

^{1}H NMR (500 MHz, CDCl$_3$, TMS): δ 12.19 (s, 1H), 8.64 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.39 (d, *J* = 6.5 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.19 (s, 2H), 7.08 (s, 2H), 6.95 (t, *J* = 7.5 Hz, 1H), 4.40 – 4.35 (m, 2H), 2.83– 2.78 (m,1H), 2.44 (s, 3H), 1.16 (d, *J* = 6.5 Hz, 18H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 167.1, 163.3, 153.3, 150.7, 139.5, 137.8, 134.0, 132.6, 131.9, 130.6, 128.6, 127.2, 124.0, 121.8, 119.0, 115.8, 34.1, 29.5, 24.7, 23.5, 15.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{30}H_{38}N_3O_2S$ 504.2679, found 504.2696.

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Chapter 4

Inverse Electron Demand Diels Alder Reaction of Aza-*o*-Quinone Methides and Enaminones: Accessing 3-Aroyl Quinolines and Indeno[1,2-*b*]quinolinones

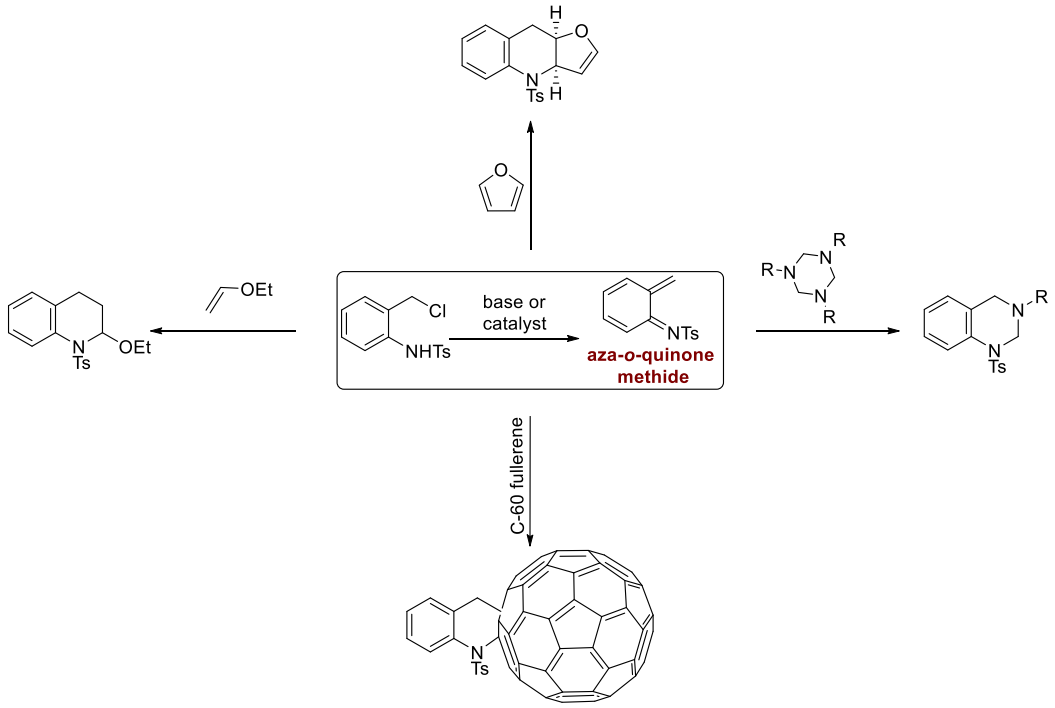
4.1. Abstract

We have developed a Diels Alder cycloaddition route towards 3-aroyl quinolines from enaminones and in situ generated aza-o-quinone methides. The reaction was found to be general with a range of substituted enaminones and aza-o-quinone methides, and we could validate the applicability of the methodology in a gram-scale. We also demonstrated a one-pot strategy towards 3-acyl quinolines starting from the corresponding aliphatic ketones. Finally, we utilized the 3-aroyl quinolines for synthesizing indeno[1,2-b]quinolinones via a Pd-catalyzed dual C-H activation approach.

4.2 Introduction

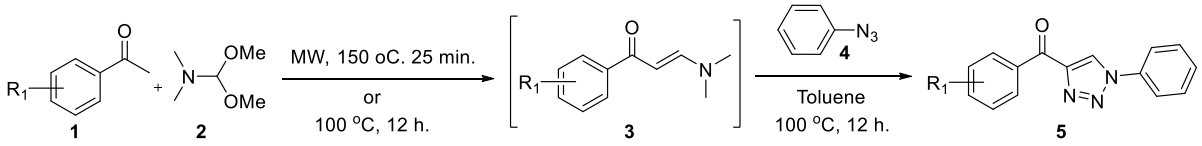
Quinolines are a class of heterocycles of utmost importance in medicinal chemistry and industry.[1] The need for new methods for the synthesis of quinolines is driven by the demand for diverse and tailor-made compounds for pharmaceuticals, materials, and other applications, as well as the desire to make the synthesis process more efficient, cost-effective, and sustainable. This Chapter describes a new approach to synthesize 3-aroyl/acyl quinolines. Organic chemists have exploited the reactivity of aza-*o*-quinone methides for the generation of different classes of *N*-heterocycles.[6] Several groups have utilised this reactive intermediate as an aza-diene for the Diels Alder cycloaddition.[7] Steinhagen and Corey reported the use of *N*-(*o*-chloromethyl)arylamides for the first time as the precursor of aza-*o*-quinone methides (for [4+2] cycloaddition with electron-rich olefins) after which it has become the most common approach for the generation of these reactive intermediates (Scheme 4.1).[8] An inverse-electron-demand [4+2]-cycloaddition of 1,3,5-triazinanes with aza-*o*-quinone methides towards tetrahydroquinazolines was reported by Liu and co-workers.[9] Another report on the use of aza-*o*-quinone methide as a diene came recently for the synthesis of furo[3,2-*b*]quinolines.[10] Utilization of [60]fullerene as a dienophile in the [4+2]-cycloaddition with aza-*o*-quinone methide for the generation of fullerotetrahydro

quinolines was reported by Wang and co-workers.[11] It's noteworthy to mention that in all the above mentioned reports, the product obtained was tetrahydro quin(az)olines wherein we observed aromatization of the cycloadduct towards the formation of substituted quinolines.



Scheme 4.1 [4+2] cycloaddition of aza-*o*-quinone methides with dienophiles

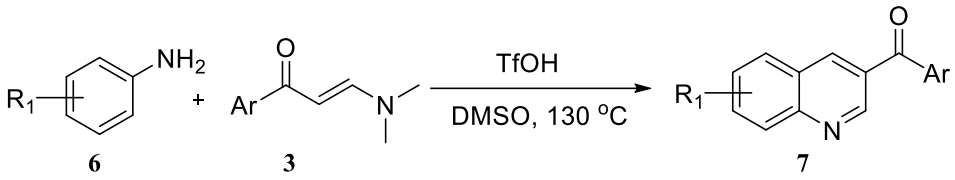
Enaminones are a class of electron-rich olefins that were exploited to generate a wide variety of heterocycles such as pyrroles, pyrazoles, isoxazoles, imidazoles, oxadiazoles, aziridines, 1,2,4-triazoles, etc.[12] They are considered as a synthetic equivalent to ynones. In 2016, an elegant report on the use of enaminones as a dipolarophile in the dipolar cycloaddition with azides towards 4-acyl-1*H*-1,2,3-triazoles came from the group of Dehaen (Scheme 4.2).[13]



Scheme 4.2 Dipolar cycloaddition reaction of enaminones with azides

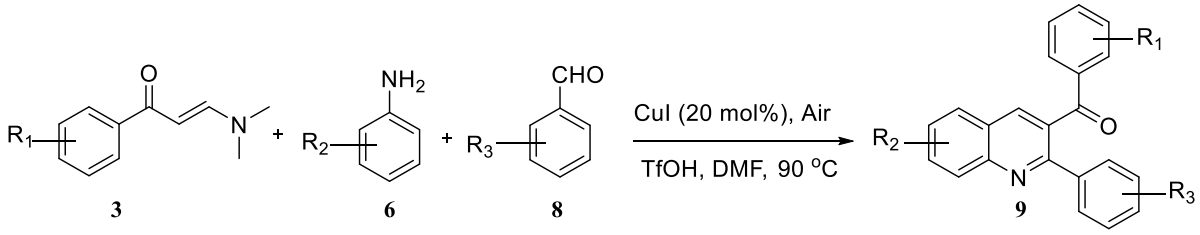
Later, Wan and co-workers reported the synthesis of 3-acyl quinolines by an acid-mediated reaction of enaminones and anilines (Scheme 4.3).[14a] The synthesis of quinolines involves breaking the branched C=C and C=N bonds in enaminones to yield C2-C3 and C4

fragments, respectively. This process results in the formation of two new C-C bonds and a new C-N bond as part of the product formation.



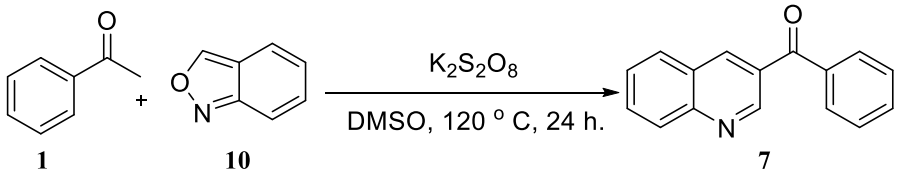
Scheme 4.3 Acid-mediated reaction of enaminones and anilines

At the same time, the same group reported the synthesis of 2,3-disubstituted quinolines *via* a three-component reaction involving enaminones, aldehydes, and anilines (Scheme 4.4).[14b] The current approach enables the rapid and selective generation of 2,3-disubstituted quinolines, representing an enhanced and updated iteration of the Povarov reaction.



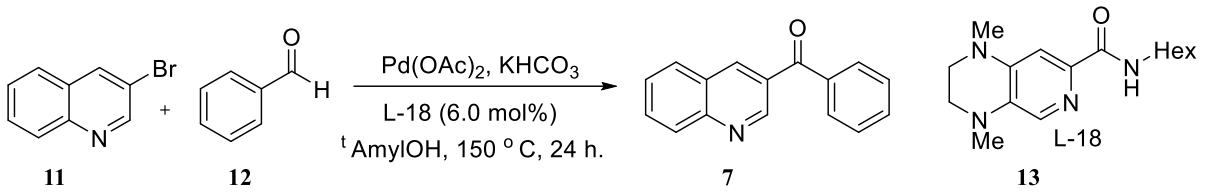
Scheme 4.4 Transition metal-free synthesis of quinolines from acetophenones and anthranils

A transition metal-free synthesis of functionalized quinolines from readily available acetophenones and anthranils was disclosed by Wakade *et al.* in 2017 (Scheme 4.5).[14c] This one-pot reaction entails the aza-Michael addition of anthranils, annulation, and one-carbon homologation by DMSO, which produces α,β-unsaturated ketones *in situ* from the acetophenone.



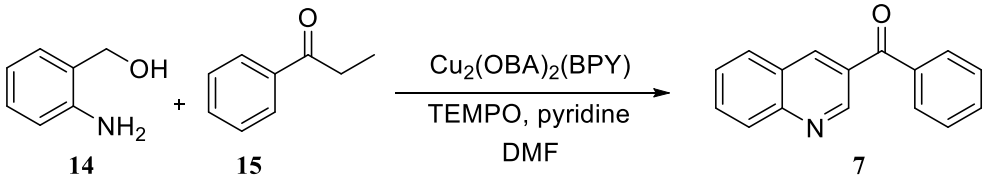
Scheme 4.5 Transition metal-free synthesis of quinolines from acetophenones and anthranils

Another synthesis of 3-acyl quinoline was achieved by a palladium-catalyzed C−H transformation from aldehydes and (hetero)aryl halides by Wakaki *et al.* in 2018 (Scheme 4.6).[14d] Picolinamide ligands were used for this transformation.



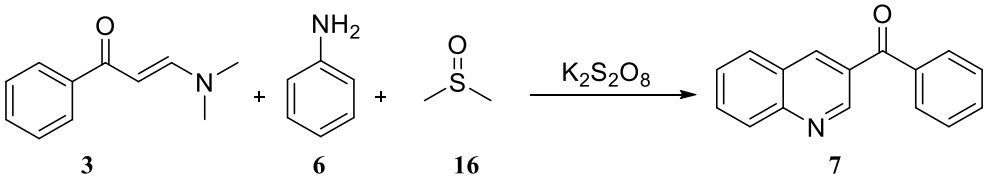
Scheme 4.6 Palladium catalyzed C−H transformation from aldehydes and aryl halides

Dang *et al.* utilized a copper metal–organic framework (Cu-MOF) for the synthesis of 3-aroyl quinolines via one-pot domino reactions of 2-aminobenzylalcohols with propiophenones (Scheme 4.7).[14e]



Scheme 4.7 One-pot domino reactions of 2-aminobenzylalcohols with propiophenones

In 2019, Wakade and co-workers reported an alternative transition metal-free method for synthesizing functionalized 3-acyl quinolines (Scheme 4.8).[14f] This process utilizes readily accessible anilines, enaminones, and dimethyl sulfoxide (DMSO) in the presence of potassium persulfate ($K_2S_2O_8$). The reaction involves a tandem process that proceeds through a [3+2+1] cycloaddition reaction, where DMSO, enaminones, and amines play pivotal roles in the formation of these quinolines.

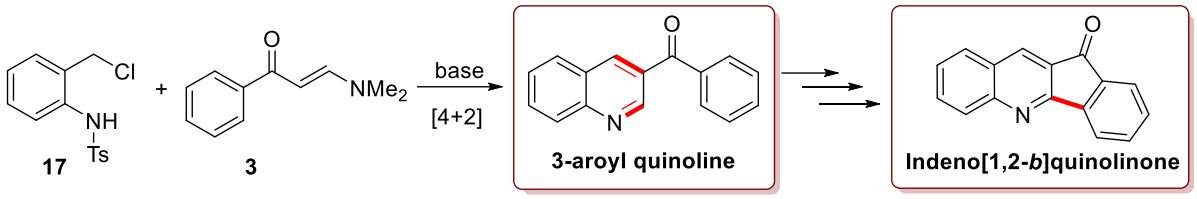


Scheme 4.8 [3+2+1] cycloaddition reaction for the synthesis of 3-acyl quinolines

4.3 Statement of the problem

There is a plethora of classical reactions such as Gould–Jacob, Friedländer, Pfitzinger, Skraup, Doebner–von Miller, and Conrad–Limpach for accessing quinoline and its derivatives.[4] Apart from these methods, several transition metal-catalyzed approaches and green protocols were also developed. Many of these methods have drawbacks, such as intricate reaction systems, stringent reaction conditions, and the generation of complex

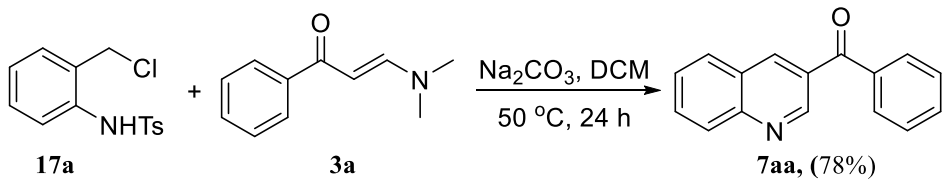
by-products. The transition metal-free approaches for the synthesis of quinoline and its derivative are particularly appealing from a synthetic standpoint. In line with our interest in the chemistry of heterocycles[15] and based on the reactivity of aza-*o*-quinone methide and enaminone, we envisaged whether these two would react to generate acyl quinoline derivatives. We also hypothesized that *via* a Pd-catalyzed dual C-H activation in the synthesized acyl quinoline motifs, indeno[1,2-*b*]quinolinones could be generated (Scheme 4.9).



Scheme 4.9 Inverse Electron Demand Diels Alder Reaction of Aza-*o*- Quinone Methides and Enaminones and a Pd-catalyzed dual C-H activation

4.4 Result and discussions

To test our hypothesis, we chose to work with *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **17a** and 3-(dimethylamino)-1-phenylprop-2-en-1-one **3a** as substrates (Scheme 4.10). Our first attempt to react both **17a** and **3a** in the presence of 2.0 equiv. of Na_2CO_3 at room temperature in DCM (1mL) turned out to be futile (Table 4.1, entry 1). When the same reaction was kept at 50 ^oC, we could isolate the expected phenyl(quinolin-3-yl)methanone **7aa** after 24 h of reaction time (Table 4.1, entry 2). After completion of the reaction, as indicated by the TLC, the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: Ethyl acetate/hexane (1:4)) to afford the corresponding product phenyl(quinolin-3-yl)methanone **7aa** in 78% yield.



Scheme 4.10 3 acyl quinoline synthesis from aza-*o*- quinone methides and enaminones

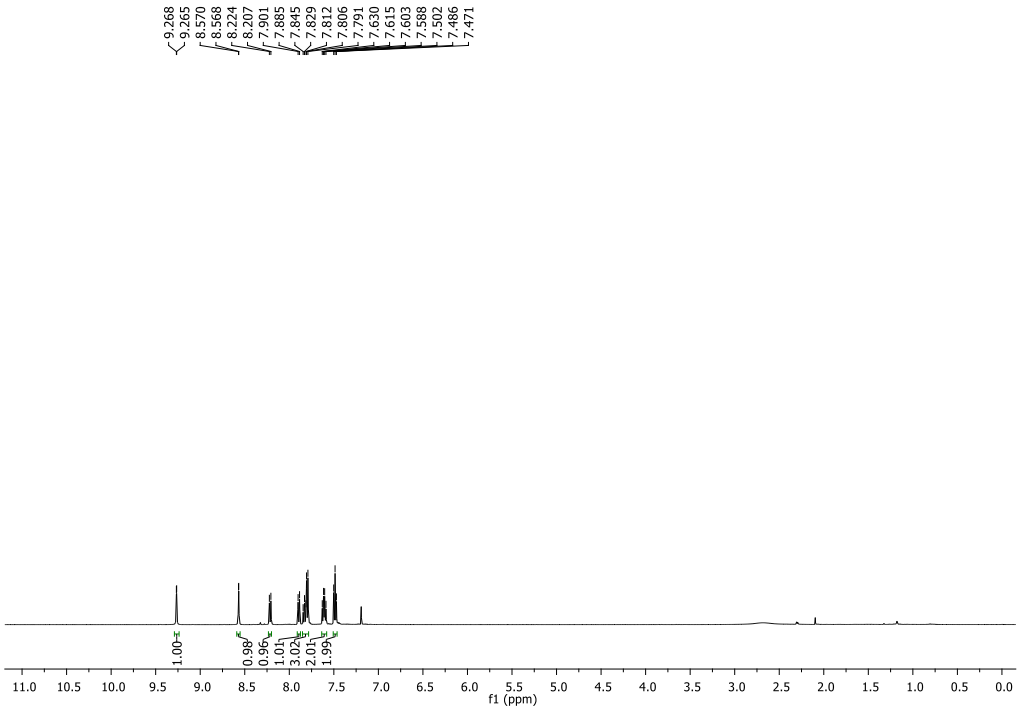


Figure 4.1: ^{1}H NMR (500 MHz) Spectra of **7aa**

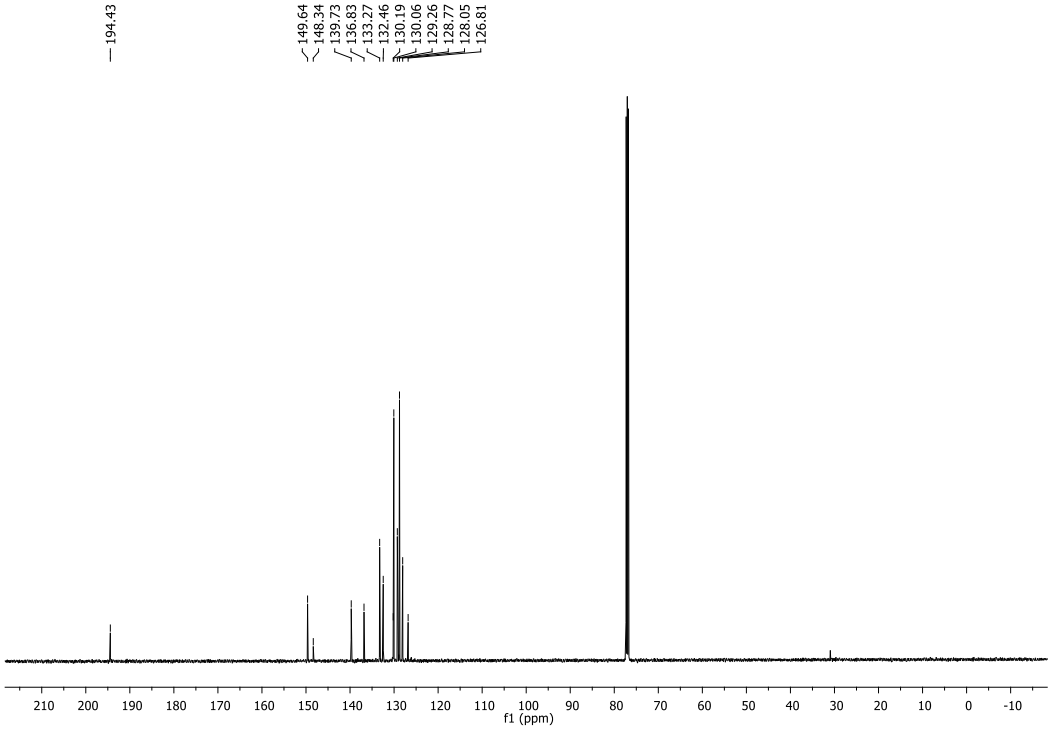


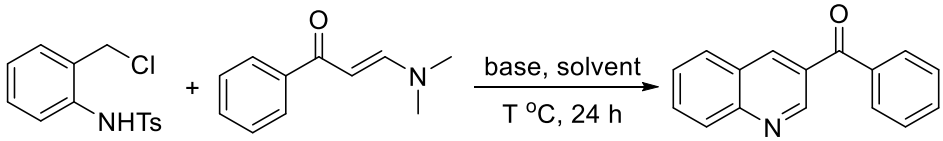
Figure 4.2: ^{13}C{^{1}H} NMR (125 MHz) Spectra of **7aa**

The structure of the product was assigned based on various spectral analyses such as ^{1}H NMR, ^{13}C NMR, and HRMS analysis. In the ^{1}H NMR spectrum (Fig 4.1**)** the aromatic protons resonated between 9.27-7.47 ppm. The proton attached to C4 carbon resonated at 9.27 ppm.

In the ^{13}C NMR (Fig 4.2**)** the carbonyl carbon resonated at 194.4 ppm. All other signals in the ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structure and literature. The high-resolution mass spectral analysis showed a peak at *m/z* 234.0918 $(M+H)^{+}$, which also supported the proposed structure.

Then we moved on with optimizing the reaction conditions starting with the solvent screen. Among the different solvents such as DCM, Acetonitrile, THF, 1,4-dioxane, toluene, 1,2-DCE, DMF, and $CHCl_3$, the best medium for the reaction was found to be DCM (Table 4.1, entries 2-9). Next, a base screen was carried out among Na_2CO_3, K_2CO_3, Cs_2CO_3, NaOAc, KOH, and $NaHCO_3$ (Table 4.1, entries 2, 10-14). The reaction mediated by NaOAc was found to be the best affording **7aa** in 81% yield. Finally, we observed an increase in yield by increasing the amount of *N*-(2-(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (Table 4.1, entries 15-16). In this line, we found that the reaction with 1.3 equiv. of **1a** resulted in a yield of 89% for **7aa**.

Table 4.1 Optimization studies for the synthesis of 7aa[a]



17a **3a** **7aa**

Entry	Base	Solvent	Temp.	Yield of 7aa
1	Na_2CO_3	DCM	rt	NR
2	Na_2CO_3	DCM	50 °C	78%
3	Na_2CO_3	ACN	50 °C	66 %
4	Na_2CO_3	THF	50 °C	51%
5	Na_2CO_3	1,4-Dioxane	50 °C	46%

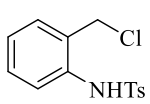
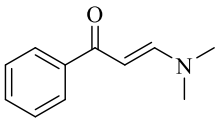
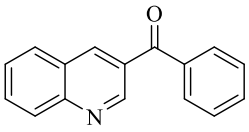
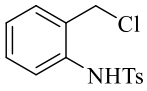
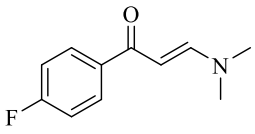
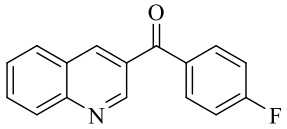
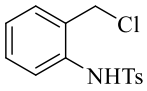
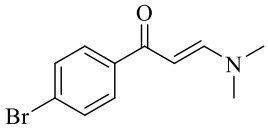
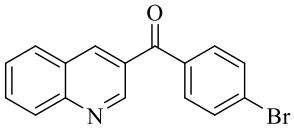
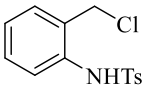
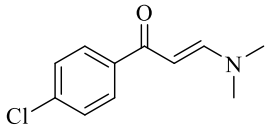
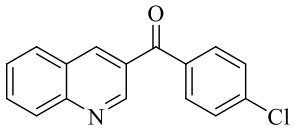
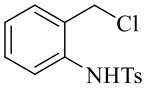
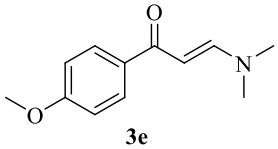
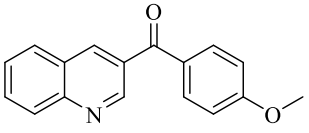
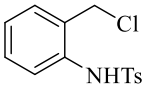
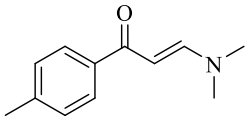
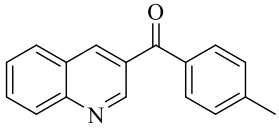
6	Na_2CO_3	Toluene	50 °C	53%
7	Na_2CO_3	1,2-DCE	50 °C	71%
8	Na_2CO_3	DMF	50 °C	trace
9	Na_2CO_3	$CHCl_3$	50 °C	73%
10	K_2CO_3	DCM	50 °C	68%
11	Cs_2CO_3	DCM	50 °C	76%
12	NaOAc	DCM	50 °C	81%
13	KOH	DCM	50 °C	56%
14	$NaHCO_3$	DCM	50 °C	56%
15[b]	NaOAc	DCM	50 °C	84%
16[c]	**NaOAc**	**DCM**	**50 °C**	**89%**

Reaction conditions: [a] **17a** (1.0 equiv., 0.17 mmol), **3a** (1.0 equiv., 0.17 mmol), base (2.0 equiv.), solvent (1.0 mL), 24 h, isolated yields; [b] **17a** (1.2 equiv.); [c] **17a** (1.3 equiv.); NR – No reaction

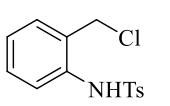
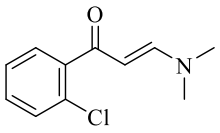
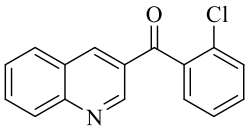
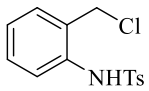
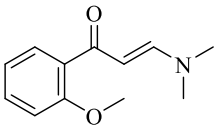
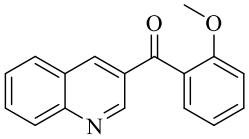
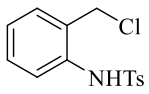
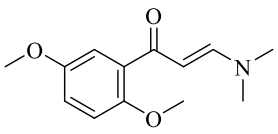
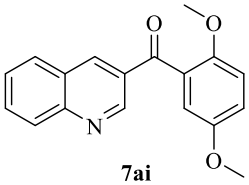
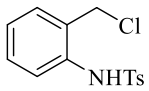
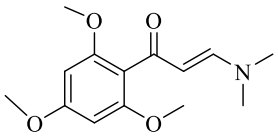
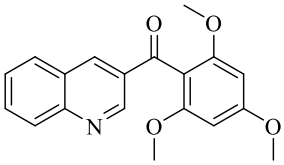
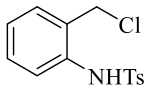
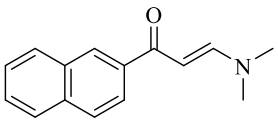
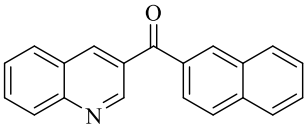
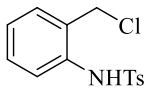
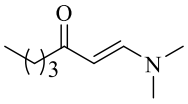
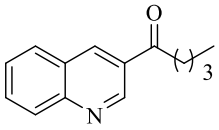
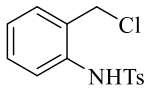
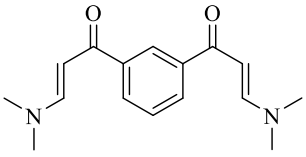
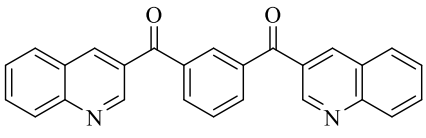
We then concentrated our efforts towards studying the generality of 3-acyl quinoline synthesis under the optimized conditions (Table 4.2). We first tried the gram-scale synthesis of **7aa** starting from 1 gram of **17a** which resulted in a yield of 84%. The reactivity of different enaminones **3b**-**3f** derived from 4-substituted acetophenones (substituents were F, Br, Cl, OMe, and Me) was then tested. From these reactions, we could isolate the corresponding functionalized 3-acyl quinolines **7ab** to **7af** in good to excellent yields. We then checked the reactivity of enaminones **3g**-**3h** derived from 2-substituted acetophenones (substituents were Cl and OMe) and the respective reactions yielded the products **7ag** and **7ah** in 84% and 87% yields respectively. Enaminones **3i** & **3j** synthesized from dimethoxy and trimethoxy acetophenones also underwent the base-mediated tandem Diels Alder reaction-aromatization affording the products **7ai** and **7aj** in excellent yields. Naphthyl quinolinyl ketone **7ak** was obtained in 94% yield from the reaction between 3-(dimethylamino)-1-(naphthalen-2-yl)prop-2-en-1-one **3k** and aza-*o*-quinone methide derived from **17a**. By this methodology, we could also synthesize 1-(naphthalen-2-yl)pentan-1-one **7al** in 81% yield starting from 2-hexanone derived enaminone **3l**. Interestingly, our attempt

to synthesize 1,3-phenylene bis(quinolin-3-ylmethanone) **7am** was successful starting from the corresponding di-enaminone **3m**. Finally, we could introduce the Cl-substituent to the quinoline ring in product **7ba** (89%) by starting from the appropriately substituted **17b**.

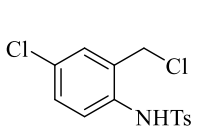
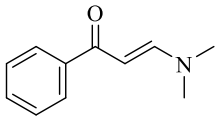
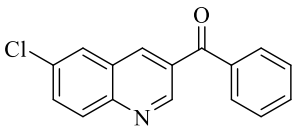
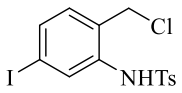
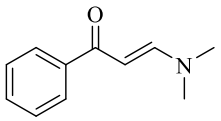
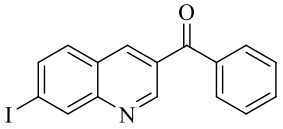
Table 4.2 Generality of 3-acyl quinoline synthesis[a]

Entry	aza-*o*-quinone methide precursor	enaminone	Product	Yield (%)
1	 **17a**	 **3a**	 **7aa**	89%,84%[b]
2	 **17a**	 **3b**	 **7ab**	74%
3	 **17a**	 **3c**	 **7ac**	92%
4	 **17a**	 **3d**	 **7ad**	93%
5	 **17a**	 **3e**	 **7ae**	91%
6	 **17a**	 **3f**	 **7af**	88%

Reaction conditions: [a] **17** (1.3 equiv., 0.44 mmol), **3** (1.0 equiv., 0.34 mmol), NaOAc (2.0 equiv.), DCM (2.0 mL), 50 °C, 24 h, isolated yields. [b] from 1 gram of **3a**.

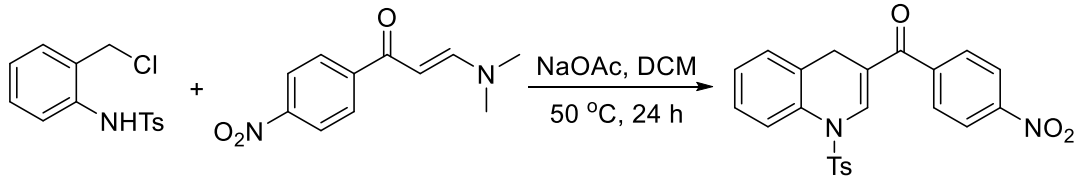
Entry	aza-*o*-quinone methide precursor	enaminone	Product	Yield (%)
7	 **17a**	 **3g**	 **7ag**	84%
8	 **17a**	 **3h**	 **7ah**	87%
9	 **17a**	 **3i**	 **7ai**	84%
10	 **17a**	 **3j**	 **7aj**	89%
11	 **17a**	 **3k**	 **7ak**	94%
12	 **17a**	 **3l**	 **7al**	81%
13	 **17a**	 **3m**	 **7am**	85%

Reaction conditions: [a] **17** (1.3 equiv., 0.44 mmol), **3** (1.0 equiv., 0.34 mmol), NaOAc (2.0 equiv.), DCM (2.0 mL), 50 °C, 24 h, isolated yields. [b] from 1 gram of **3a.**

Entry	aza-*o*-quinone methide precursor	enaminone	Product	Yield (%)
14	 **17b**	 **3a**	 **7ba**	89%
15	 **17c**	 **3a**	 **7ca**	86%

Reaction conditions: [a] **17** (1.3 equiv., 0.44 mmol), **3** (1.0 equiv., 0.34 mmol), NaOAc (2.0 equiv.), DCM (2.0 mL), 50 °C, 24 h, isolated yields. [b] from 1 gram of **3a.**

During our investigations on the generality of this tandem quinoline synthesis, we treated *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **17a** with 3-(dimethylamino)-1-(4-nitrophenyl)prop-2-en-1-one **3n** under optimized conditions and found that **7an'** was forming exclusively (38%) which we believed this to be the intermediate of this tandem transformation (Scheme 4.11).



17a **3n** **7an'** (38%)

Scheme 4.11 Base mediated reaction of **17a** with **3n**

The structure of this intermediate was confirmed by ^{1}H NMR and ^{13}C NMR analysis. In the ^{1}H NMR spectrum (Fig 4.3**)** the aromatic protons resonated between 8.29-7.06 ppm. The benzylic proton appears at 3.50 ppm, and the methyl protons of the tosyl ring resonate at 2.33 ppm. In the ^{13}C NMR (Fig 4.4**)** the benzylic carbon resonated at 25.8 ppm, and methyl carbon resonated at 21.7 ppm. All other signals in the ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structure. We then optimized the reaction conditions including an oxidizing agent in order to obtain the 3-aroyl quioline derivative exclusively.[16]

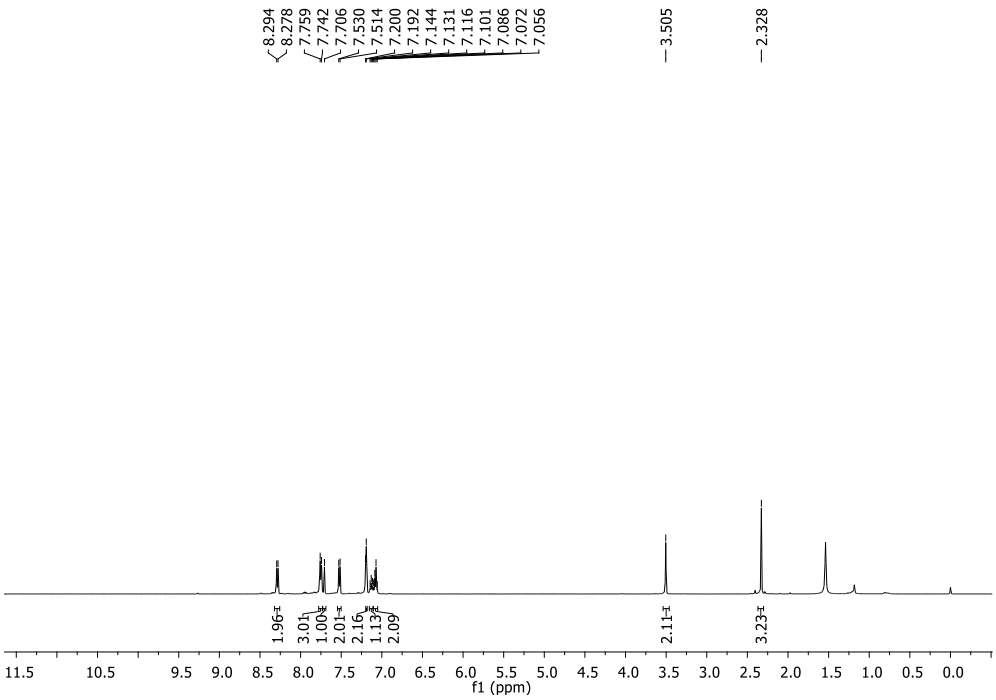


Figure 4.3: ^{1}H NMR (500 MHz) Spectra of **7an'**

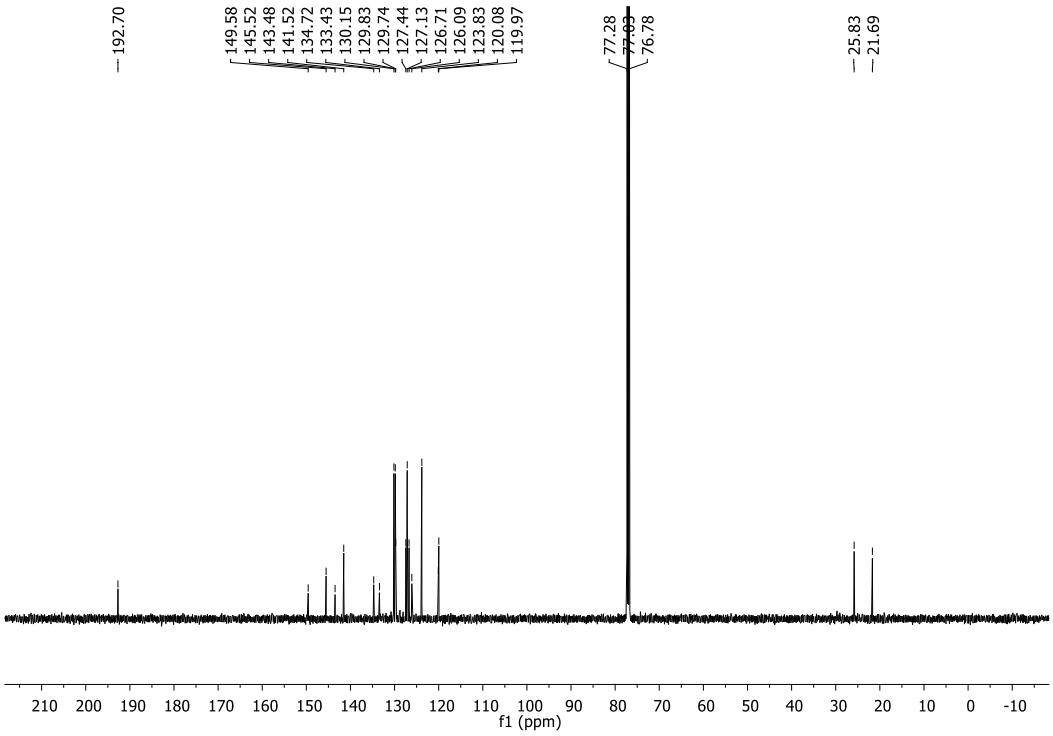
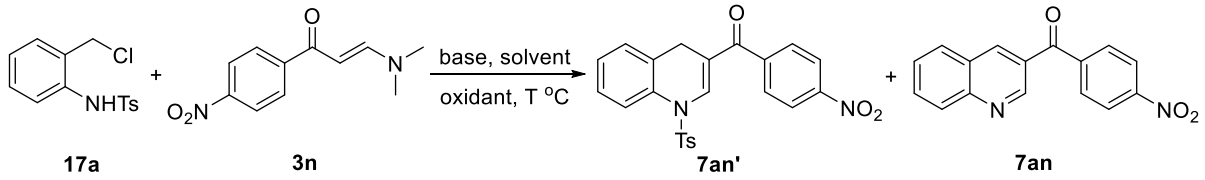


Figure 4.4: ^{13}C{^{1}H} NMR (125 MHz) Spectra of **7an'**

The Table 4.3 shows the optimization of the reaction using **17a** and **3n** as substrates. First, we checked the effect of oxidizing agents DDQ and chloranil on the previously optimized

conditions. These two reactions also furnished the intermediate **7an'** as the sole product. Then, we changed the solvent to toluene and increased the reaction temperature to 120 °C by using DDQ as the oxidant. To our dismay, this reaction gave an intractable reaction mixture. Finally, our attempt with chloranil as the oxidizing agent furnished the full aromatized 3-aroyl quinoline **7an** in 66% yield.

Table 4.3 Optimization studies



17a **3n** **7an'** **7an**

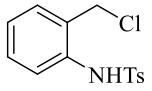
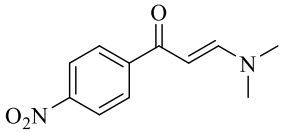
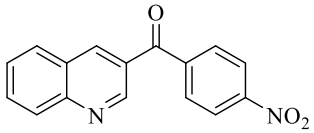
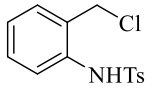
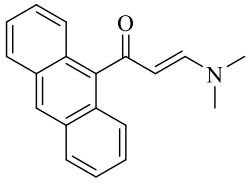
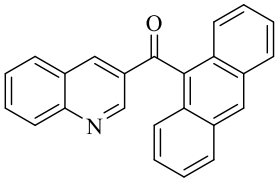
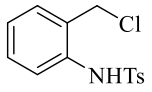
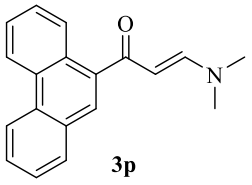
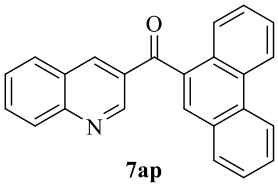
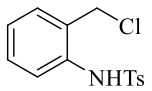
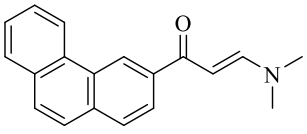
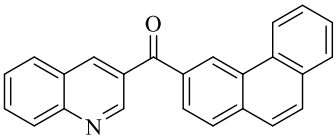
Sovent	Base	Oxidant	T °C	Yield(%)	
				7an'	7an
Dichloromethane[a]	NaOAc	—	50	38%	—
Dichloromethane[b]	NaOAc	DDQ	50	37%	
Dichloromethane[b]	NaOAc	Chloranil	50	35%	
Toluene[b]	NaOAc	DDQ	120	—	—
Toluene[b]	NaOAc	Chloranil	120	—	66%

Reaction conditions: [a] (i) **17a** (1.3 equiv., 0.22 mmol), **3n** (1.0 equiv., 0.17 mmol), NaOAc (2.0 equiv.),solvent (1.0 mL), T °C, 24 h; [b](ii) oxidant (2.0 equiv.), T °C, 12 h, isolated yields.

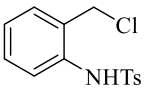
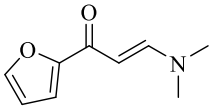
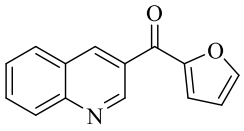
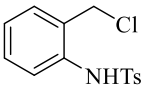
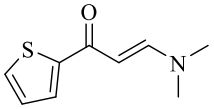
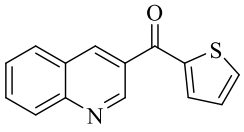
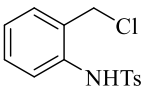
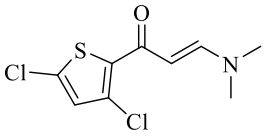
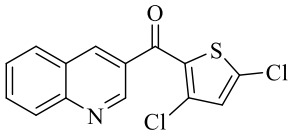
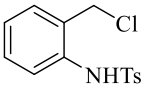
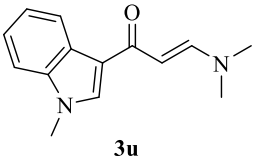
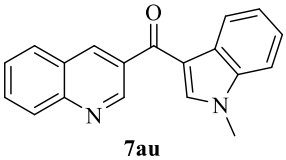
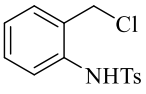
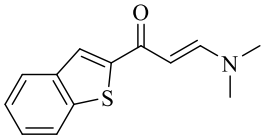
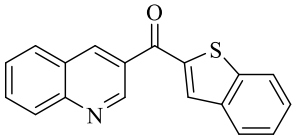
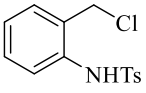
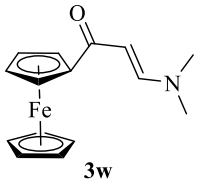
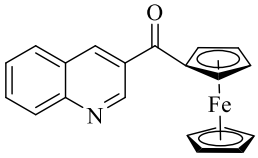
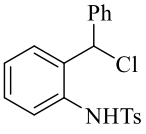
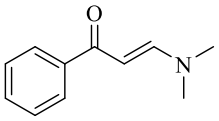
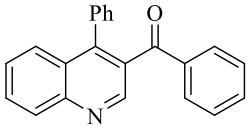
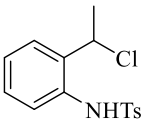
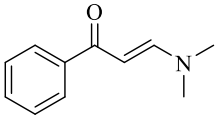
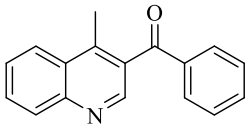
All the substrates that failed to afford 3-aroyl quinolines under the conditions depicted in Table 4.1 were allowed to react under the newly optimized condition (Table 4.4). We started with the reaction of **17a** and **3n** from which the corresponding 3-aroyl quinoline derivative **7an** was isolated in 66% yield. Enaminones derived from acyl ketones of tricyclic aromatic hydrocarbons such as anthracene and phenanthrene **3o-3q** were then treated with **17a** and these reactions also furnished the respective products **7ao-7aq** in good yields. Our efforts to check the reactivity of different enaminones **3r-3v** derived from heterocyclic acyl ketones

also were successful and the corresponding bis-heterocyclic ketones **7ar**-**3av** were isolated in excellent yields. With this methodology, we could introduce heterocycles such as furan, thiophene, indole, and benzothiophene as heteroaryl functionalities. The enaminone **3w** derived from acetyl ferrocene also underwent the one-pot quinoline synthesis with **17a** affording the product **7aw** in 95% yield. Finally, we could introduce phenyl (**7da**, 44%) and methyl (**7ea**, 62%) groups to the 4th position of the quinoline ring by starting from the corresponding aza-*o*-quinone methide precursors **17d** and **17e**.

Table 4.4 Generality of 3-acyl quinoline synthesis[a]

Entry	aza-*o*-quinone methide precursor	Enaminone	Product	Yield (%)
1	 **17a**	 **3n**	 **7an**	66%
2	 **17a**	 **3o**	 **7ao**	66%
3	 **17a**	 **3p**	 **7ap**	59%
4	 **17a**	 **3q**	 **7aq**	63%

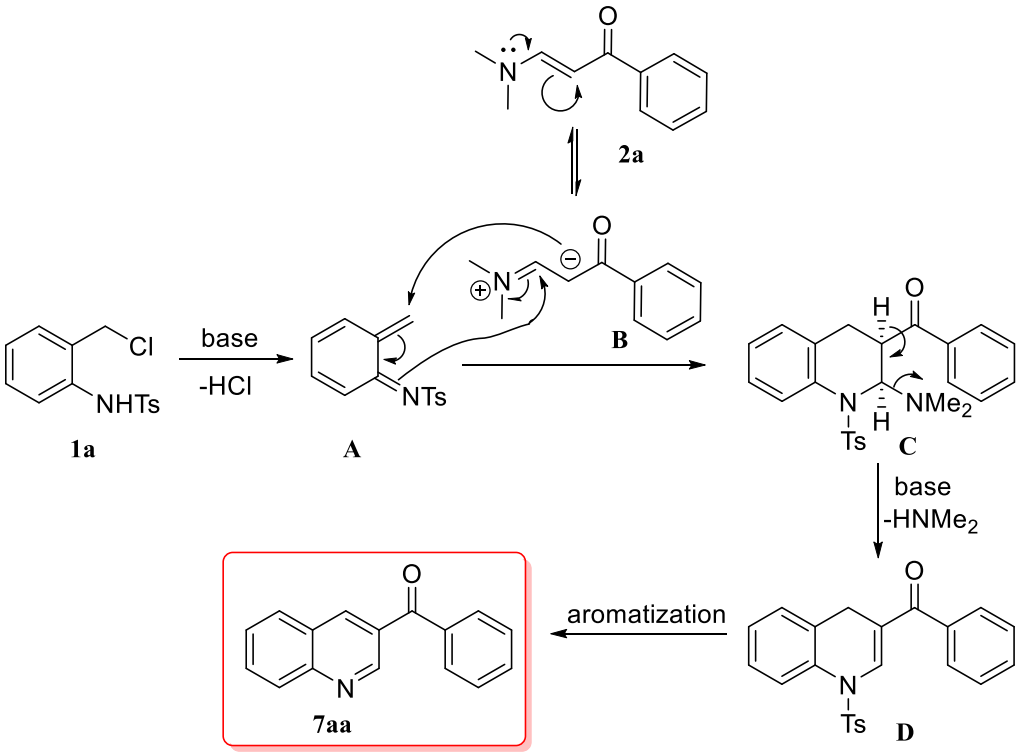
Reaction conditions: [a] (i) **17** (1.3 equiv., 0.44 mmol), **3** (1.0 equiv., 0.34 mmol), NaOAc (2.0 equiv.), toluene (2.0 mL), 120 °C, 24 h; (ii) oxidant (2.0 equiv.), 120 °C, 12 h, isolated yields.

Entry	aza-*o*-quinone methide precursor	Enaminone	Product	Yield (%)
5	 **17a**	 **3r**	 **7ar**	87%
6	 **17a**	 **3s**	 **7as**	83%
7	 **17a**	 **3t**	 **7at**	83%
8	 **17a**	 **3u**	 **7au**	86%
9	 **17a**	 **3v**	 **7av**	76%
10	 **17a**	 **3w**	 **7aw**	95%
11	 **17d**	 **3a**	 **7da**	44%
12	 **17e**	 **3a**	 **7ea**	62%

Reaction conditions: [a] (i) **17** (1.3 equiv., 0.44 mmol), **3** (1.0 equiv., 0.34 mmol), NaOAc (2.0 equiv.), toluene (2.0 mL), 120 ^{o}C, 24 h; (ii) oxidant (2.0 equiv.), 120 ^{o}C, 12 h, isolated yields.

4.5 Mechanism for inverse electron demand Diels Alder reaction of aza-*o*-quinone methides and enaminones

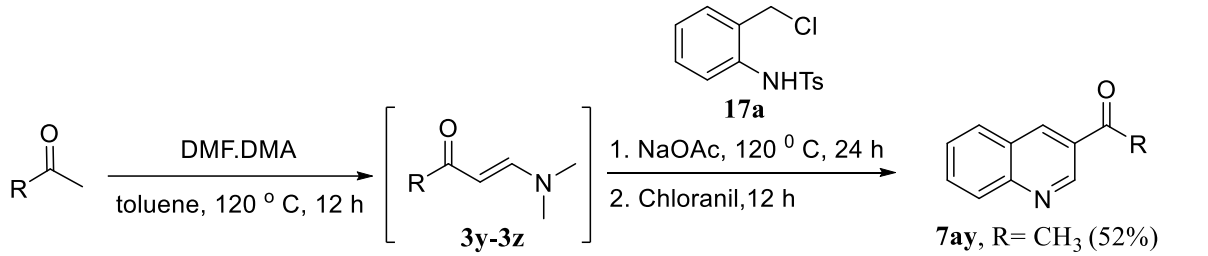
In scheme 4.12, we propose a mechanism for the 3-aroyl quinoline synthesis from aza-*o*-quinone methide and enaminone based on literature reports[7, 12-13] and our own observations. The first step of the mechanism starts with the base-mediated generation of aza-*o*-quinone methide **A** from **17a**. The enaminone **3a** tautomerizes to **B** from which the anionic center attacks the terminal carbon of the methide functionality in **A** leading to the formation of the cycloadduct **C** after ring closure from the *N*-end. A quick elimination of $HNMe_2$ from intermediate **C** affords **D**, the formation of which was proved by the isolation of **7an'** as depicted in scheme 4.11. Finally, a base/oxidizing agent-mediated aromatization affords 3-aroyl quinoline.



Scheme 4.12 Proposed mechanism for the synthesis of 3-aroyl quinoline from aza-*o*-quinone methide and enaminone

In order to formulate a one pot synthetic protocol for the syntheses of 3-substituted quinolines, we started from the ketone rather than enaminone (Scheme 4.13). Here aliphatic ketones (acetone and 2-octanone; 1.0 equiv.) were chosen as substrates and were refluxed

with DMF.DMA (1.2 equiv.) in toluene to form the corresponding enaminones. For this, we started by treating acetone **3y′** and 2-octanone **3z′** with DMF.DMA in refluxing toluene to furnish the corresponding enaminones **3y** & **3z**. Upon completion of enaminone formation, to the same pot, **17a** was added along with the base. After 24 h, chloranil was added and refluxed for 12 more hours after which the corresponding substituted quinolines **7ay** and **7az** were isolated in 52% and 31% overall yields respectively.



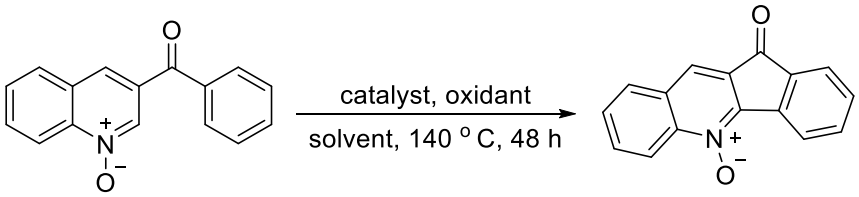
Scheme 4.13 One-pot reaction for the synthesis of 3-substituted quinolines starting from ketones

4.6 Pd-catalyzed dual C−H activation

Due to our continued interest in devising methodologies towards heteroarenes[17] and inspired by the report on Pd-catalyzed dual C−H activation of 3-phenoxypyridine-1-oxides,[18] we planned to utilize 3-aroyl quinolines to synthesize rarely known indeno[1,2-*b*]quinoline-11-ones.[19] We started with the *N*-oxidation of 3-aroyl quinolines with mCPBA and the obtained quinolinyl-*N*-oxides were directly taken for the Pd-catalyzed dual C-H activation after optimization[16] (Table 4.5). We commenced our investigations by selecting 3-benzoylquinoline 1-oxide as the model substrate. The initial reaction was performed with 1.5 equivalents of Ag_2O as oxidant and 10 mol% of $PdCl_2$ as the catalyst in acetic acid. As expected, 11-oxo-11*H*-indeno[1,2-*b*]quinoline 5-oxide **19aa** was isolated in a 69% yield (Table 4.5, entry 1). Different Pd-catalysts other than $PdCl_2$ such as $Pd(OAc)_2$, $Pd(CF_3COO)_2$, $Pd(CH_3CN)_2Cl_2$, and $Pd(PPh_3)_2Cl_2$ were screened for the present Pd(II)-catalyzed dehydrogenative cyclization (Table 4.5, entries 1-5). Among the Pd-catalysts tested, $PdCl_2$, $Pd(CH_3CN)_2Cl_2$, and $Pd(PPh_3)_2Cl_2$ were found to catalyze the reaction equally (Table 4.5, entries 1, 4-5). An increase in the catalyst loading from 10 mol% to 20 mol% had a beneficial effect on the outcome of the reaction and $Pd(CH_3CN)_2Cl_2$ showed better

catalysis (Table 4.5, entries 6-8). Among the solvents screened, acetic acid was found to be the best medium for the Pd-catalyzed dual C-H activation. Thus the expected product, 11-oxo-11*H*-indeno[1,2-*b*]quinoline 5-oxide **19aa** was isolated in 76% yield with 1.5 equivalents of Ag_2O, and 20 mol% $Pd(CH_3CN)_2Cl_2$ in acetic acid at 140 ^oC.

Table 4.5 Optimization studies



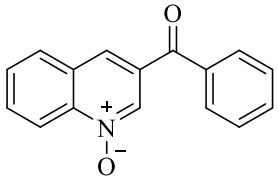
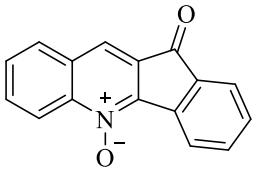
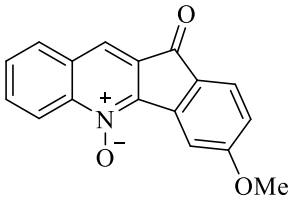
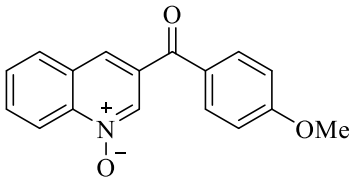
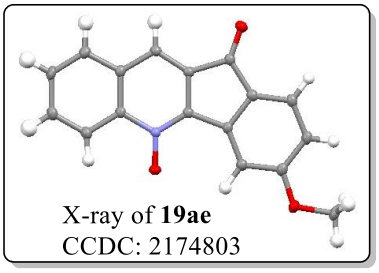
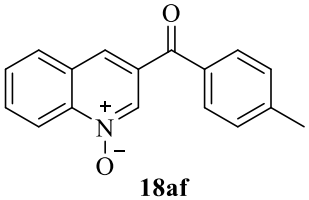
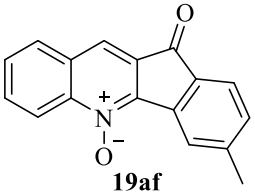
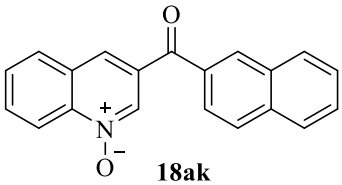
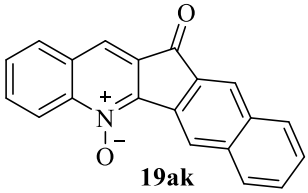
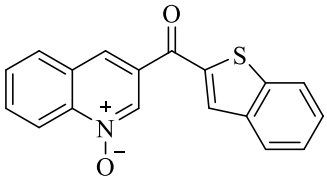
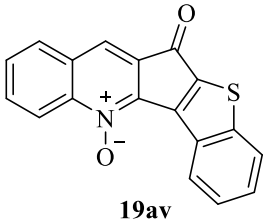
18aa **19aa**

Sl No.	Solvent	Catalyst	Catalyst loading	Oxidant	Yield
1	CH_3COOH	$PdCl_2$	10 mol%	Ag_2O	69%
2	CH_3COOH	$Pd(OAc)_2$	10 mol%	Ag_2O	44%
3	CH_3COOH	$Pd(CF_3COO)_2$	10 mol%	Ag_2O	32%
4	CH_3COOH	$Pd(CH_3CN)_2Cl_2$	10 mol%	Ag_2O	69%
5	CH_3COOH	$Pd(PPh_3)_2Cl_2$	10 mol%	Ag_2O	69%
6	CH_3COOH	$PdCl_2$	20 mol%	Ag_2O	69%
7	CH_3COOH	$Pd(PPh_3)_2Cl_2$	20 mol%	Ag_2O	73%
8	**CH_3COOH**	**$Pd(CH_3CN)_2Cl_2$**	**20 mol%**	**Ag_2O**	**76%**
9	DMSO	$Pd(CH_3CN)_2Cl_2$	20 mol%	Ag_2O	36%
10	CF_3COOH	$Pd(CH_3CN)_2Cl_2$	20 mol%	Ag_2O	20%
11	PivOH	$Pd(CH_3CN)_2Cl_2$	20 mol%	Ag_2O	-

Reaction conditions: (i) **18aa** (0.10 mmol, 1.0 equiv.), oxidant (1.5 equiv.) solvent (1.0 mL), 140 ^oC, 48 h, isolated yields.

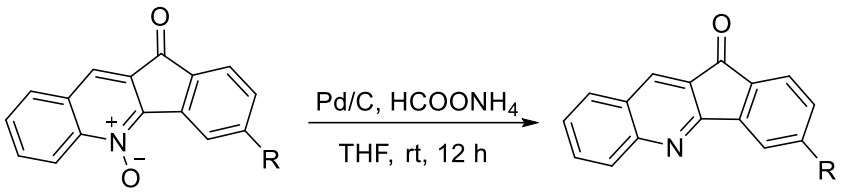
The quinolinyl-*N*-oxides **19** upon treatment with $Pd(CH_3CN)_2Cl_2$ (20 mol%) and Ag_2O (1.5 equiv.) in HOAc at 140 ^oC for 48 h afforded the corresponding indeno[1,2-*b*]quinolinone-*N*-oxides in good yields (Table 4.6). We could also confirm the structure of the heteroacene with a single crystal X-ray of **19ae**.

Table 4.6 The generality of Pd-catalyzed dual C-H activation[a]

Entry	Quinoline *N*-oxide	Product	Yield (%)
1	 **18aa**	 **19aa**	74%
		 **19ae**	
2	 **18ae**	 X-ray of **19ae** CCDC: 2174803	53%
3	 **18af**	 **19af**	76%
4	 **18ak**	 **19ak**	68%
5	 **18av**	 **19av**	33%

Reaction conditions: [a] **18** (0.10 mmol), Pd(CH3CN)2Cl2 (20 mol%), Ag2O (1.5 equiv.), AcOH (1.0 mL), 140 °C, 48 h; isolated yields.

It's noteworthy to mention that we could extend the method for the synthesis of five-ring fused systems **19ak** and **19aw** by starting from appropriately functionalized quinolinyl-*N*-oxides**.** We then subjected 11-oxo-indeno[1,2-*b*]quinoline-*N*-oxide **19aa** and **19af** to reduction with $HCOONH_4$ in the presence of Pd/C in THF at rt to synthesise the corresponding indeno[1,2-*b*]quinolinones **20aa** and **20af** in good yields (Scheme 4.14).



19aa, R = H
19af, R = Me

20aa, R = H (82%)
20af, R = Me (85%)

Scheme 4.14 Reduction of indeno[1,2-*b*]quinolinone-*N*-oxides to indeno[1,2-*b*]quinolinones

4.7 Conclusion

To conclude, we have developed a methodology for the synthesis of 3-aroyl/acyl quinolines by the inverse electron demand [4+2] cycloaddition of *in situ* generated aza-*o*-quinone methides and enaminones. The reaction was found to be general with a range of enaminones and aza-*o*-quinone methides affording the corresponding quinoline derivatives in good to excellent yields. We have proposed a mechanism that involves two stages; [4+2] cycloaddition and aromatization. The applicability of the developed methodology in the gram-scale synthesis of 3-aroyl quinolines was validated. We have also demonstrated a one-pot method starting from ketones to generate enaminones and have utilized it to synthesize alkyl quinolinyl ketones. Lastly, we have employed the synthesized 3-aroyl quinolines for accessing indeno[1,2-*b*]quinolinones *via* a Pd-catalyzed dual C-H activation route.

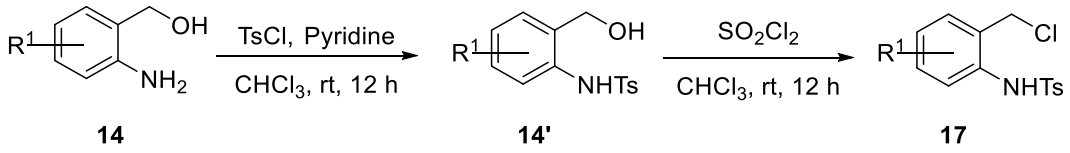
4.8Experimental section

4.81 General experimental methods

All chemicals used were of analytical quality 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 silica gel, and mixtures of ethyl acetate and hexane were used 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{^{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 an ESI/ HRMS at a resolution of 60,000, using ThermoScientific Exactive mass spectrometer with orbitrap analyzer.

4.82 General procedure for the preparation of sulfonaminobenzyl chlorides

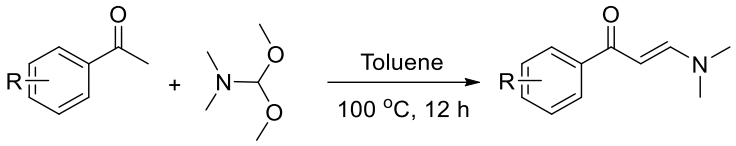


Scheme 4.15 Synthesis of sulfonaminobenzyl chlorides

The sulfonaminobenzyl chlorides were synthesized according to the reported literature.[16a] To a solution of 2-aminobenzyl alcohol (1g, 8.12 mmol) in $CHCl_3$ (40 mL) was added pyridine (720 μL, 8.93mmol). The reaction was stirred for 25 min, and a solution of TsCl (1.703g, 8.93 mmol) in $CHCl_3$ was added dropwise over 20 min. After 12 h, the reaction was quenched with sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were then washed with brine, and dried over Na_2SO_4. Evaporation of solvent under reduced pressure afforded the crude *N*-protected 2-aminobenzyl alcohol, which was used in the subsequent transformation without further purification. To a solution of *N*-protected 2-aminobenzyl alcohol (2.1g 7.58 mmol) in $CHCl_3$ (40 mL), was added a solution of thionyl chloride (764 μL, 9.10mmol) in $CHCl_3$ (5mL) over 1 min. The reaction was heated to 40 °C overnight, cooled to rt, and then poured into ice water (30 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$

(3 x 40 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded crude sulfonaminobenzyl chloride as a brown solid, and is used without further purification.

4.83 General procedure for the preparation of enaminones



Scheme 4.16 Synthesis of enaminones

The enaminones were synthesized by following the reported procedures.[13] A mixture of acetophenone (1.0 equiv.) and *N, N*-dimethylformamide dimethyl acetal (2.4 equiv.) in dry toluene was taken in a round bottom flask. The reaction mixture was then stirred at 100°C for 12 h. After completion of the reaction, as indicated by the TLC, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated to obtain the crude product which was then purified by column chromatography using silica gel.

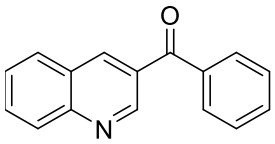
4.84 Optimized procedure for the synthesis of 3-acyl quinolines

A mixture of sulfonaminobenzyl chloride **17** (1.3 equiv., 0.44 mmol), enaminone **3** (1.0 equiv., 0.34 mmol), and NaOAc (2.0 equiv.) was weighed into a dry reaction tube. Dry DCM (2.0 ml) was added and allowed to stir at 50 ^oC for 24 h. After completion of the reaction, as indicated by the TLC, the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: Ethyl acetate/hexane (1:4)) to afford the corresponding products.

4.85 Synthesis and characterization of 3-acyl quinolines 7aa-7ca

phenyl(quinolin-3-yl)methanone (7aa)[16b]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-phenyl prop-2-en-1-one **3a** (60 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ^oC for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7aa** as a colourless solid (70 mg, 89%).



Analytical data of 7aa

Mp: 74-76 °C.

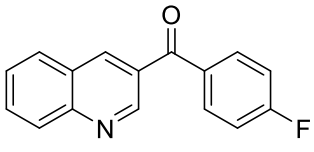
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.27 (d, *J* = 1.5 Hz, 1H), 8.57 (d, *J* = 1.5 Hz, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8 Hz, 1H), 7.84 – 7.79 (m, 3H), 7.61 (dd, *J* = 13.5, 7 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 194.4, 149.6, 148.3, 139.7, 136.8, 133.3, 132.5, 130.2, 130.1, 129.3, 128.8, 128.0, 126.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{12}NO$ 234.0913, found 234.0918.

(4-fluorophenyl)(quinolin-3-yl)methanone (7ab) [16c]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(4-fluorophenyl)prop-2-en-1-one **3b** (66 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ^oC for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ab** as a colourless solid (64 mg, 74%).



Analytical data of 7ab

Mp: 104-106 °C.

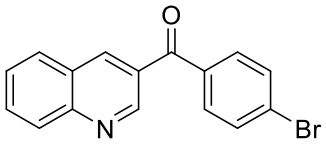
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.22 (s, 1H), 8.47 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.87 – 7.78 (m, 4H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 8 Hz, 2H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.2, 165.8 (d, *J* = 255 Hz), 149.8, 149.7, 148.9, 139.1, 133.2 (d, *J* = 3.75 Hz), 132.7 (d, *J* = 8.75 Hz), 132.3, 130.1, 129.2, 129.1(d, *J* = 3.75 Hz),128.0, 126.7, 116.0 (d, *J* = 21.25 Hz) ppm. ^{19}F NMR ($CDCl_3$, 471 MHz) δ -104.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{11}FNO$ 252.0819, found 252.0819.

(4-bromophenyl)(quinolin-3-yl)methanone (7ac)[16b]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-1-(4-bromophenyl)-3-(dimethylamino)prop-2-en-1-one **3c** (86 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ºC for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ac** as a colourless solid (98 mg, 92%).



Analytical data of 7ac

Mp: 108-110 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.22 (d, *J* = 2Hz, 1H), 8.46 (d, *J* = 2Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8 Hz, 1H), 7.80 (t, *J* = 7 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.63 – 7.57 (m, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.8, 150.1, 149.5, 138.8, 135.8, 132.1, 132.0, 131.5, 129.7, 129.5, 129.2, 128.3, 127.8, 126.6 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{11}BrNO$ 312.0019, found 312.0036.

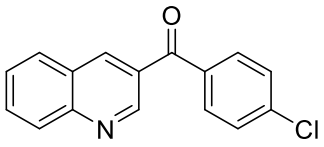
(4-chlorophenyl)(quinolin-3-yl)methanone (7ad)[16d]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-1-(4-chlorophenyl)-3-(dimethylamino)prop-2-en-1-one **3d** (72 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ºC for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ad** as a colourless solid (84 mg, 93%).

Analytical data of 7ad

Mp: 104-106 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (d, *J* =



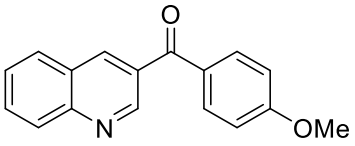
1.5 Hz, 1H), 8.48 (d, *J* = 1Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.81 (t, *J* = 7 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 193.7, 150.1, 149.5, 139.7, 138.8, 135.3, 132.1, 131.4, 129.8, 129.5, 129.2, 129.1, 127.8, 126.6 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{11}ClNO$ 268.0524, found 268.0532.

(4-methoxyphenyl)(quinolin-3-yl)methanone (7ae)[16e]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(4-methoxyphenyl)prop-2-en-1-one **3e** (70 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50^{o}C for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ae** as a colourless liquid (82 mg, 91%).



Analytical data of 7ae

^{1}H NMR (500 MHz, CDCl$_3$): δ 9.20 (s, 1H), 8.46 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.86 – 7.76 (m, 4H), 7.57 (t, *J* = 7 Hz, 1H), 6.95 (d, *J* = 8 Hz, 2H), 3.84 (s, 3H) ppm.

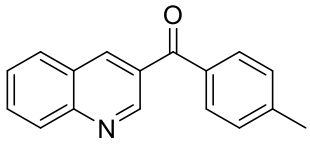
^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 193.5, 163.8, 150.3, 149.2, 138.3, 132.6, 131.6, 130.8, 129.7, 129.4, 129.0, 127.6, 126.7, 114.0, 55.6 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{14}NO_2$ 264.1019, found 264.1007.

quinolin-3-yl(p-tolyl)methanone (7af)[16d]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(p-tolyl)prop-2-en-1-one **3f** (64 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ^{o}C for

24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7af** as a liquid (74 mg, 88%).



Analytical data of 7af

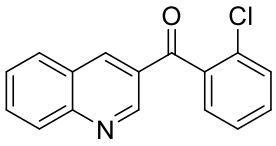
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (s, 1H), 8.62 (s, 1H), 8.30 (d, *J* = 8 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.86 (t, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 8 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8 Hz, 2H), 2.42 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.5, 148.8, 144.6, 140.6, 133.9, 133.0, 130.7, 130.3, 129.6, 129.3, 128.5, 127.8, 127.1, 21.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{14}NO$ 248.1070, found 248.1075.

(2-chlorophenyl)(quinolin-3-yl)methanone (7ag)[16f]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(2-chlorophenyl)prop-2-en-1-one **3g** (72 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ^{o}C for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ag** as a liquid (76 mg, 84%).



Analytical data of 7ag

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.27 (d, *J* = 2 Hz, 1H), 8.41 (d, *J* = 1.5 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 – 7.35 (m, 4H) ppm.

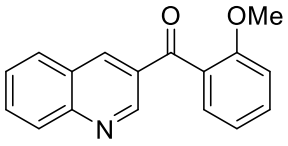
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.9, 149.9, 139.6, 132.5, 131.9, 131.5, 130.4, 129.5, 129.5, 129.4, 129.1, 127.7,

127.1, 126.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{11}ClNO$ 268.0524, found 268.0531.

(2-methoxyphenyl)(quinolin-3-yl)methanone (7ah)[16f]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(2-methoxyphenyl)prop-2-en-1-one **3h** (70 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ^oC for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ah** as a liquid (78 mg, 87%).



Analytical data of 7ah

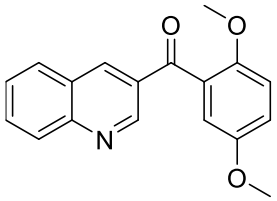
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.17 (s, 1H), 8.48 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.74 (t, *J* = 7 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8 Hz, 1H), 3.61 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 194.8, 157.6, 150.5, 149.5, 138.6, 133.1, 131.8, 130.6, 130.2, 129.4, 129.3, 127.8, 127.4, 127.0, 121.0 111.5, 55.6 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{14}NO_2$ 264.1019, found 264.1007.

2, 5-dimethoxyphenyl(quinolin-3-yl)methanone (7ai)

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-1-(2,5-dimethoxyphenyl)-3-(dimethylamino)prop-2-en-1-one **3i** (80 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ^oC for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ai** as a liquid (84 mg, 84%).



Analytical data of 7ai

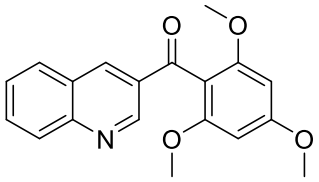
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.17 (d, *J* = 2 Hz, 1H), 8.50 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.75 (t, *J* = 7 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.04 – 6.99 (m, 2H), 6.89 (d, *J* = 9 Hz, 1H), 3.75(s, 3H), 3.56 (s, 3H) ppm.

^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 194.5, 153.8, 151.7, 150.4, 149.4, 138.7, 131.9, 130.5, 129.5, 129.2, 128.2, 127.4, 127.0, 118.8, 114.7, 113.1, 56.1, 55.9 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{18}H_{16}NO_3$ 294.1125, found 294.1130.

quinolin-3-yl(2,4,6-trimethoxyphenyl)methanone (7aj)

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(2,4, 6 -trimethoxyphenyl)prop-2-en-1-one **3j** (91 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ^{o}C for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7aj** as a colourless solid (98 mg, 89%).



Analytical data of 7aj

Mp: 127-129 °C.

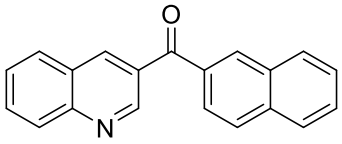
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.31 (s, 1H), 8.60 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.84 (t, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 6.24 (s, 2H), 3.92 (s, 3H), 3.72 (s, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.2, 163.1, 159.2, 150.5, 149.6, 138.5, 131.7, 130.8, 129.5, 129.2, 127.2, 109.9, 90.8, 55.8, 55.6 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{19}H_{18}NO_4$ 324.1230, found 324.1239.

naphthalen-2-yl(quinolin-3-yl)methanone (7ak)[16c]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(naphthalen-2-yl)prop-2-en-1-one **3k** (76 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ºC for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ak** as a colourless solid (90 mg, 94%).



Analytical data of 7ak

Mp: 102-104 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.29 (d, *J* = 2 Hz, 1H), 8.53 (d, *J* = 1 Hz, 1H), 8.23 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.91 (s, 2H), 7.85 – 7.83 (m, 3H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.48 (t, *J* = 7.5 Hz, 1H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 194.9, 150.4, 149.4, 138.8, 135.5, 134.3, 132.3, 132.1, 131.9, 130.5, 129.5, 129.5, 129.2, 128.8, 128.8, 127.9, 127.7, 127.1, 126.7, 125.4 ppm.

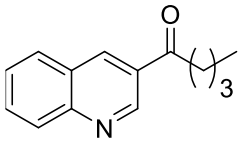
HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{20}H_{14}NO$ 284.1070, found 284.1065.

1-(quinolin-3-yl)pentan-1-one (7al)

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-1-(dimethylamino)hept-1-en-3-one **3l** (53 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ºC for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7al** as a liquid (59 mg, 81%).

Analytical data of 7al

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.37 (d, *J* = 2.0 Hz, 1H), 8.65 (d, *J* = 2 Hz, 1H), 8.09 (d,



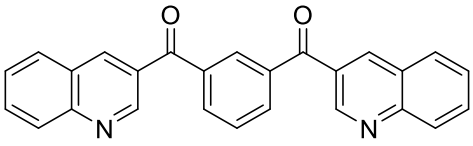
J = 8.5 Hz, 1H), 7.89 (d, *J* = 8 Hz, 1H), 7.79 – 7.76 (m, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 3.04 (t, *J* = 7.5 Hz, 2H), 1.74 – 1.70 (m, 2H), 1.43 – 1.36 (m, 2H), 0.92 (t, *J* = 7 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 199.3, 149.7, 149.2, 137.0, 131.9, 129.4, 129.4, 129.2, 127.6, 126.9, 38.7, 26.3, 22.5, 14.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{14}H_{16}NO$ 214.1226, found 214.1235.

1,3-phenylenebis(quinolin-3-ylmethanone) (7am)

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (260 mg, 0.88mmol), (2*E*,2'*E*)1,1'(1,3phenylene) bis(3-(dimethylamino)prop-2-en-1-one) **3m** (93 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 °C for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7am** as a yellow solid (112 mg, 85%).



Analytical data of 7am

Mp: 168-170 °C.

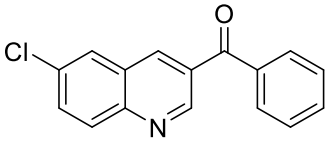
^1H NMR (500 MHz, $CDCl_3$): δ 9.28 (s, 2H), 8.53 (s, 2H), 8.25 (s, 1H), 8.11 (dd, *J* = 17.5, 8 Hz, 4H), 7.89 (d, *J* = 8 Hz, 2H), 7.80 (t, *J* = 7.5 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 2H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.9, 150.1, 149.6, 139.1, 137.7, 134.0, 132.3, 131.0, 129.5, 129.4, 129.3, 127.8, 126.6 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{26}H_{17}N_2O_2$ 389.1285, found 389.1286.

(6-chloroquinolin-3-yl)(phenyl)methanone (7ba)[16g]

The reaction was performed according to the general procedure with *N*-(4-chloro-2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide**17b** (148 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-phenyl prop-2-en-1-one **3a** (62 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ^{o}C for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ba** as a liquid (81 mg, 89%).



Analytical data of 7ba

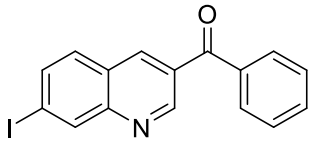
^{1}H NMR (500 MHz, CDCl$_3$): δ 9.25 (s, 1H), 8.51 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.90 (s, 1H), 7.78 (t, *J* = 8 Hz, 3H), 7.63 (t, *J* = 7 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 194.5, 150.5, 147.8, 137.6, 136.8, 133.5, 133.3, 132.7, 131.1, 130.9, 130.0, 128.7, 127.6, 127.3 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^{+}$ calcd for $C_{16}H_{11}ClNO$ 268.0524, found 268.0532

(7-iodoquinolin-3-yl)(phenyl)methanone (7ca)

The reaction was performed according to the general procedure with N-(2-(chloromethyl)-5- iodophenyl)-4-methylbenzenesulfonamide **17c** (186 mg, 0.44 mmol), (E)-3-(dimethylamino)-1- phenyl prop-2-en-1-one **3a** (62 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ^{o}C for 24 h. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product 3ca as a liquid (105 mg, 86%).



Analytical data of 7ca

^{1}H NMR (500 MHz, CDCl3): δ 9.24 (d, J = 1.0 Hz, 1H), 8.35 (s, 1H), 8.24 (s, 1H), 8.00 (d, J = 9 Hz, 1H), 7.85 (d, J = 9 Hz, 1H), 7.78 (d, J = 8 Hz, 2H), 7.60 (d, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H) ppm.

^{13}C {1H} NMR (125 MHz, CDCl3): δ 194.5,

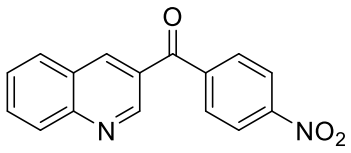
150.8, 148.3, 140.5, 137.7, 137.4, 136.7, 133.3, 131.0, 130.6, 130.1, 128.8, 128.3, 93.3. ppm. **HRMS (ESI-Orbitrap) m/z:** (M+H) + calcd for C16H11INO 359.9880, found 359.9895.

4.86 Procedure for the synthesis and characterization of 3-acyl quinolines 7an-7ea

A mixture of sulfonaminobenzyl chloride **17** (1.3 equiv., 0.44 mmol), enaminone **3** (1.0 equiv., 0.34 mmol), and NaOAc (2.0 equiv. 0.68 mmol) was weighed into a dry reaction tube. Toluene (2.0 ml) was added and allowed to stir at 120 ^{o}C for 24 hours, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. 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: Ethyl acetate/hexane (1:4)) to afford the corresponding products.

(4-nitrophenyl)(quinolin-3-yl)methanone (7an)[16d]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(4-nitrophenyl)prop-2-en-1-one **3n** (75 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 120 ^{o}C for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7an** as a colourless solid (63 mg, 66%).



Analytical data of 7an

Mp: 135-137°C.

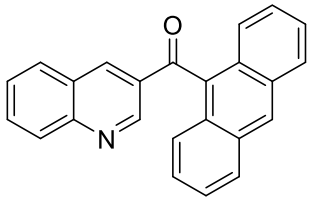
^{1}H NMR (500 MHz, CDCl$_3$): δ 9.26 (s, 1H), 8.49 (s, 1H), 8.34 (d, *J* = 8.5 Hz, 2H), 8.15 (d, *J* = 8.5Hz, 1H), 7.95 (d, *J* = 8.5Hz, 2H), 7.88 – 7.82 (m, 2H), 7.62 (t, *J* = 7.5 Hz, 1H) ppm.

^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 193.2, 150.2, 149.8, 149.8, 142.1, 139.3, 132.6, 130.8, 129.6, 129.3, 128.8, 128.1, 126.5, 123.9 ppm.

HRMS (ESI-Orbitrap) m/z: (M+H) $^{+}$ calcd for $C_{16}H_{11}N_2O_3$ 279.0764, found 279.0774.

anthracen-9-yl(quinolin-3-yl)methanone (7ao)[16h]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(4-nitrophenyl)prop-2-en-1-one **3o** (94 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ^{o}C for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ao** as a solid (75 mg, 66%).



Analytical data of 7ao

Mp: 112-114 °C.

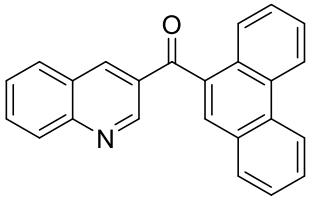
^{1}H NMR (500 MHz, CDCl$_3$): δ 9.36 (s, 1H), 9.14 (s, 1H), 8.58 (t, *J* = 8.5 Hz, 2H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.98 (dd, *J* = 21.0, 7.5 Hz, 2H), 7.88 – 7.80 (m, 4H), 7.75 (d, *J* = 9 Hz, 1H), 7.61 – 7.58 (m, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 195.0, 150.4, 149.5, 139.0, 135.0, 134.7, 132.3, 131.9, 130.6, 130.5, 130.0, 129.8, 129.5, 129.2, 129.1, 128.9, 127.7, 127.4, 127.4, 127.0, 126.8, 126.3, 125.9, 122.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{24}H_{16}NO$ 334.1226, found 334.1236.

phenanthren-9-yl(quinolin-3-yl)methanone (7ap)

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(159uinoline159ne-9-yl)prop-2-en-1-one **3p** (94 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 120 ^{o}C for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ap** as a colourless solid (67 mg, 59%).



Analytical data of 7ap

Mp: 108-110 °C.

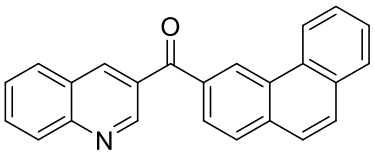
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.42 (d, *J* = 2 Hz, 1H), 8.73 (d, *J* = 8.5 Hz, 1H), 8.69 (d, *J* = 8 Hz, 1H), 8.54 (d, *J* = 2 Hz, 1H), 8.14 (d, *J* = 8 Hz, 2H), 7.86 (s, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.80 – 7.76 (m, 2H), 7.74 – 7.70 (m, 1H), 7.68 – 7.65 (m, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.56 – 7.52 (m, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.4, 150.5, 149.9, 139.8, 134.4, 132.3, 131.6, 130.8, 130.8, 130.2, 129.9, 129.7, 129.5, 129.5, 129.1, 128.8, 127.7, 127.5, 127.5, 127.3, 126.8, 126.5, 123.1, 122.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{24}H_{16}NO$ 334.1226, found 334.1236.

phenanthren-3-yl(quinolin-3-yl)methanone (7aq)

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(160uinoline160ne-3-yl)prop-2-en-1-one **3q** (62 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 120 °C for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7aq** as a colourless solid (72 mg, 63%).



Analytical data of 7aq

Mp: 106-108 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.48 (s, 1H), 8.65 (s, 1H), 8.34 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 7.83 (t, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 9 Hz, 2H), 7.71 (d, *J* = 8 Hz, 1H), 7.56 – 7.49 (m, 3H), 7.43 – 7.40 (m, 2H)

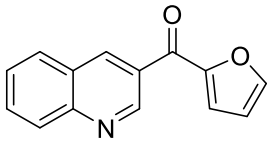
ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 199.0, 150.2, 149.9, 140.0, 132.7, 132.5, 131.1, 130.5, 129.6, 129.5, 129.1, 128.9, 128.7, 127.6, 127.0, 126.9, 125.7, 125.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{24}H_{16}NO$ 334.1226, found 334.1236.

furan-2-yl(quinolin-3-yl)methanone (7ar)[16b]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(furan-2-yl)prop-2-en-1-one **3r** (56 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 120 ^oC for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ar** as a liquid (66 mg, 87%).



Analytical data of 7ar

^1H NMR (500 MHz, $CDCl_3$): δ 9.40 (s, 1H), 8.78 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8 Hz, 1H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.71 (s, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 2.5 Hz, 1H), 6.61 (s, 1H) ppm.

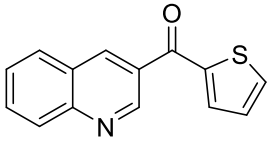
$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 180.4, 152.4, 149.8, 149.6, 147.5, 138.4, 131.9, 129.7, 129.5, 129.3, 127.6, 126.8, 120.8, 112.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{14}H_{10}NO_2$ 224.0706, found 224.0735.

quinoline-3-yl(thiophen-2-yl)methanone (7as)[16f]

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(thiophen-2-yl)prop-2-en-1-one **3s** (62 mg, 0.34 mmol) and NaOAc (28 mg, 0.68 mmol) at 120 ^oC for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed

for 12 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7as** as a liquid (68 mg, 83%).



Analytical data of 7as

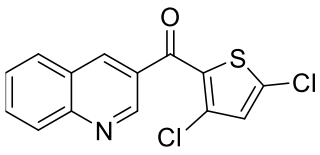
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.59 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8 Hz, 1H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 4.5 Hz, 1H), 7.65 (d, *J* = 2.5 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.15 (s, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.2, 149.6, 149.4, 143.2, 137.8, 135.1, 135.1, 131.8, 130.7, 129.4, 129.1, 128.4, 127.7, 126.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{14}H_{10}NOS$ 240.0478, found 240.0475

(3,5-dichlorothiophen-2-yl)(quinolin-3-yl)methanone (7at)

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-1-(3,5-dichlorothiophen-2-yl)-3-(dimethylamino)prop-2-en-1-one **3t** (85 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 120 ^{o}C for 24 h after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7at** as a liquid (87 mg, 83%).



Analytical data of 7at

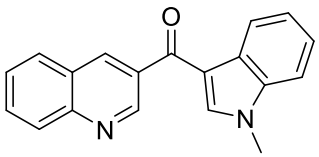
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (s, 1H), 8.51 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8 Hz, 1H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.02 (s, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.0, 148.8, 148.6, 138.0, 135.0, 131.4, 130.6, 128.9, 128.5, 128.5, 128.4, 127.6, 126.8, 126.8, 126.30, 125.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{14}H_8Cl_2NOS$ 307.9698, found 307.9696.

(1-methyl-1*H*-indol-3-yl)(quinolin-3-yl)methanone (7au)

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-(1-methyl-1H-indol-3-yl)prop-2-en-1-one **3u** (78 mg, 0.34 mmol) and NaOAc (28 mg, 0.68 mmol) at 120 ºC for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7au** as a colourless solid (84 mg, 86%).



Analytical data of 7au

Mp:172-174 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.27 (d, *J* = 1.5 Hz, 1H), 8.53 (s, 1H), 8.38 (dd, *J* = 6, 2.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8 Hz, 1H), 7.77 (t, *J* = 8 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.53 (s, 1H), 7.36 – 7.30 (m, 3H), 3.82 (s, 3H) ppm.

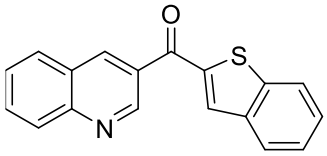
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 188.3, 149.9, 149.1, 138.0, 137.7, 136.7, 133.4, 131.1, 129.4, 128.9, 127.4, 127.1, 127.0, 124.1, 123.2, 122.7, 115.8, 109.8, 33.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{19}H_{15}N_2O^+$ 287.1179, found 287.1184.

benzo[*b*]thiophen-2-yl(quinolin-3-yl)methanone (7av)

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-1-(benzo[b]thiophen-2-yl)-3-(dimethylamino)prop-2-en-1-one **3v** (79 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 50 ºC for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. After solvent removal, the residue was purified by silica gel column

chromatography (Ethyl acetate/hexane) to afford the desired product **7av** as a colourless solid (75 mg, 76%).



Analytical data of 7av

Mp: 132-134 °C.

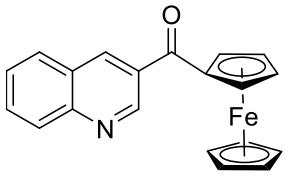
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.32 (d, *J* = 1.5 Hz, 1H), 8.64 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8 Hz, 1H), 7.87 – 7.78 (m, 4H), 7.60 (t, *J* = 8 Hz, 1H), 7.44 (t, *J* = 8 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 187.7, 149.6, 149.6, 142.9, 142.7, 139.0, 138.0, 132.7, 132.0, 130.5, 129.6, 129.2, 127.9, 127.8, 126.7, 126.3, 125.4, 123.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{18}H_{12}NOS^+$ 290.0634, found 290.0642.

ferrocene-2-yl(quinolin-3-yl)methanone (7aw)

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (130 mg, 0.44 mmol), (*E*)-1-(ferrocene-2-yl)-3-(dimethylamino)prop-2-en-1-one **3w** (96 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 120 ^{o}C for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7aw** as a red solid (110 mg, 95%).



Analytical data of 7aw

Mp: 138-140 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.45 (s, 1H), 8.70 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 8 Hz, 1H), 7.85 (t, *J* = 8 Hz, 1H), 7.67 – 7.61 (m, 1H), 4.97 (d, *J* = 1 Hz, 2H), 4.68 (d, *J* = 8Hz, 2H), 4.27 (s, 5H) ppm.

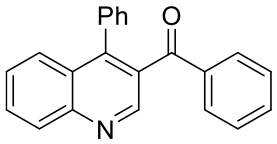
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.0,

149.3, 136.4,132.3, 131.4, 129.7, 129.4, 129.0, 127.5, 127.5, 127.0, 73.2, 71.5, 70.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{20}H_{16}FeNO^+$ 342.0576, found 342.0587.

phenyl(4-phenylquinolin-3-yl)methanone (7da)[16b]

Then reaction was performed according to the general procedure with *N*-(2-(chloro(phenyl)methyl)phenyl)-4-methylbenzenesulfonamide **17d** (163 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one **3a** (60 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 120 ^oC for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 24 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7da** as a colourless solid (46 mg, 44%).



Analytical data of 7da

Mp: 156 -158 °C.

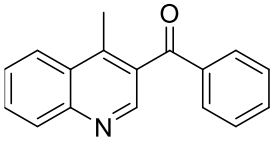
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.31 (d, *J* = 8 Hz, 1H), 7.82 – 7.75 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 3H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.24 – 7.22 (m, 7H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 196.0, 147.2, 137.0, 134.5, 133.5, 132.0, 131.5, 130.0, 129.8, 128.9, 128.4, 128.2, 127.0, 126.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{22}H_{16}NO^+$ 310.1226, found 310.1237.

(4-methylquinolin-3-yl)(phenyl)methanone (7ea)[16b]

The reaction was performed according to the general procedure with *N*-(2-(1-chloroethyl)phenyl)-4-methylbenzenesulfonamide **17e** (136 mg, 0.44 mmol), (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one **3a** (60 mg, 0.34 mmol) and NaOAc (56 mg, 0.68 mmol) at 120 ^oC for 24 h, after which chloranil (167 mg, 0.68 mmol) was added and further refluxed for 12 h more. After solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane) to afford the desired product **7ea** as a liquid (84 mg, 62%).



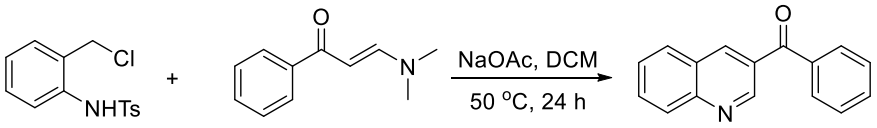
Analytical data of 7ea

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (s, 1H), 8.46 (s, 1H), 7.79 (d, *J* = 8 Hz, 2H), 7.68 (d, *J* = 8 Hz, 1H), 7.61 (d, *J* = 7 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45 (dd, *J* = 14.5, 7 Hz, 3H), 2.78 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.0, 149.2, 148.5, 139.0, 137.5, 137.2, 133.0, 132.0, 130.1, 129.8, 128.6, 127.3, 127.2, 126.7, 18.04 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{14}NO^+$ 248.1070, found 248.1078.

4.87 Procedure for gram-scale synthesis of 7aa



17a, 1.3 g **3a**, 620 mg **7aa** (84%, 862 mg)

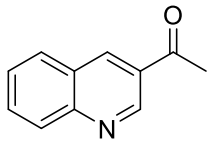
Scheme 4.17 Gram-scale synthesis

The reaction was performed according to the general procedure with *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (1.30 g, 4.4 mmol), (*E*)-3-(dimethylamino)-1-phenyl prop-2-en-1-one **3a** (620 mg, 3.4 mmol) and NaOAc (560 mg, 6.8 mmol) in DCM (20 mL) at 50 °C for 24 h. Upon completion of the reaction, the solvent was removed and the residue was purified by silica gel column chromatography (eluent: a mixture of ethyl acetate/hexane) to afford the desired product **7aa** as a colourless solid (862 mg, 84%).

(1-(quinolin-3-yl)ethanone (7ay)

The reaction was performed according to the general procedure with acetone (25 mg, 0.43 mmol) and DMF.DMA (62 mg, 0.52 mmol) in toluene (1.0 mL) which was refluxed for 12 h to furnish the corresponding enaminone. Subsequently *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (165 mg, 0.56 mmol) and NaOAc (71 mg, 0.86 mmol) were added to the same pot and refluxed at 120 °C for 24 h, after which chloranil (211 mg, 0.86

mmol) was added and further refluxed for 12 h more. Upon completion of the reaction, the solvent was removed and the residue was purified by silica gel column chromatography (eluent: a mixture of ethyl acetate/hexane) to afford the desired product **7ay** as a liquid (38 mg, 52%).



Analytical data of 7ay

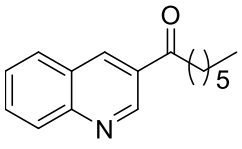
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (s, 1H), 8.66 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 2.68 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.6, 149.6, 149.1, 137.5, 132.1, 129.4, 129.3, 127.7, 126.9, 26.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{11}H_{10}NO^+$ 172.0757, found 172.0763.

1-(quinolin-3-yl)heptan-1-one (7az)

The reaction was performed according to the general procedure with octanone (55 mg, 0.43 mmol) and DMF.DMA (62 mg, 0.52 mmol) in toluene (1.0 mL) which was refluxed for 12 h to furnish the corresponding enaminone. Subsequently *N*-(2(chloromethyl) phenyl)-4-methylbenzenesulfonamide **17a** (165 mg, 0.56 mmol) and NaOAc (71 mg, 0.86 mmol) were added to the same pot and refluxed at 120 ºC for 24 h after which chloranil (211 mg, 0.86 mmol) was added and further refluxed for 12 h more. Upon completion of the reaction, the solvent was removed and the residue was purified by silica gel column chromatography (eluent: mixture of ethyl acetate/hexane) to afford the desired product **7az** as a liquid (32 mg, 31%).



Analytical data of 7az

^{1}H NMR (500 MHz, CDCl3): δ 9.37 (s, 1H), 8.67 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8 Hz, 1H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 3.07– 3.02 (m, 2H), 1.77 – 1.71 (m, 2H), 1.38 – 1.18 (m, 6H), 0.84 (t, *J* = 6 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 199.2,

149.1, 137.1, 132.0, 129.4, 129.3, 129.3, 127.6, 127.0, 39.0, 31.7, 29.0, 24.2, 22.5, 14.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{20}NO$ 242.1539, found 242.1544.

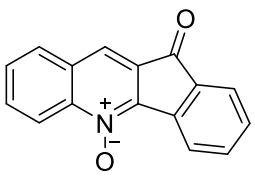
4.88 Procedure for Pd(II)-catalyzed dehydrogenative cyclization

The Pd(II)-catalyzed dehydrogenative cyclization was carried out using quinolinyl-*N*-oxides. Quinolinyl-*N*-oxides were synthesized according to reported literature,[11] and were used without further purification. The quinolinyl-*N*-oxides upon treatment with $Pd(CH_3CN)_2Cl_2$ (20 mol%) and Ag_2O (1.5 equiv.) in acetic acid at 140 ^oC for 48 h afforded the corresponding cyclized intermediates. After completion of the reaction, as indicated by the TLC, the mixture was cooled to room temperature and neutralized with saturated K_2CO_3 solution, extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. The residue was then purified by column chromatography (silica gel, eluent: Ethyl acetate/hexane) to afford the corresponding products.

4.89 Synthesis and characterization of indeno[1,2-*b*]quinoline 5-oxides

11-oxo-11*H*-indeno[1,2-b]quinoline 5-oxide (19aa)

The dehydrogenative cyclization was carried out by heating the 3-benzoylquinoline 1-oxide **18aa** (25 mg, 0.10 mmol) in a sealable reaction tube charged with $Pd(CH_3CN)_2Cl_2$ (20 mol%) and Ag_2O (35 mg, 0.15 mmol) in AcOH at 140 ^oC for 48 h. After the reaction was completed, the mixture was cooled to room temperature and neutralized with saturated K_2CO_3 solution, extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. After the solvent removal, the residue was purified by silica gel column chromatography (Ethyl acetate/hexane (3:7)) to afford the desired product **19aa** as a yellow solid (18 mg, 74%).



Analytical data of 19aa

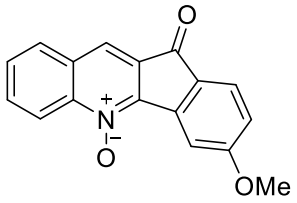
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 (d, *J* = 7.5 Hz, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.02 (s, 1H), 7.92 (d, *J* = 8 Hz, 1H), 7.82 (d, *J* = 5.5 Hz, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7 Hz, 1H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 187.7, 144.2, 143.2, 137,5, 134.9, 134.5, 131.6, 130.7, 130.1, 128.5, 128.3, 127.8, 125.2, 123.4, 121.2, 119.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M/Z)^+$ calcd for $C_{16}H_{10}NO_2$ 248.0706, found 248.0714.

3-methoxy-11-oxo-11*H*-indeno[1,2-b]quinoline 5-oxide (19ea)

The dehydrogenative cyclization was carried out by heating 3-(4-methoxybenzoyl) quinoline 1-oxide **18ea** (28 mg, 0.10 mmol) in a sealable reaction tube charged with $Pd(CH_3CN)_2Cl_2$ (20 mol%) and Ag_2O (35 mg, 0.15mmol) in AcOH at 140 ºC for 48 h. After the reaction was completed, the mixture was cooled to room temperature and neutralized with saturated K_2CO_3 solution, extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. After the solvent removal, the obtained residue was purified by silica gel column chromatography (Ethyl acetate/hexane (3:7)) to afford the desired product **19ea** as a yellow solid (15 mg, 53%).



Analytical data of 19ea

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (d, *J* = 8.5 Hz, 1H), 8.36 (s, 1H), 7.93 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 3.95 (s, 3H) ppm.

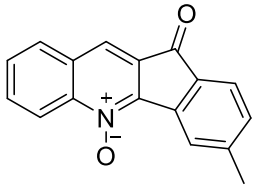
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 187.1, 166.1, 141.3, 132.4, 130.9, 130.0, 129.7, 129.4, 128.7, 126.4, 121.8, 119.8, 118.5, 110.4, 56.2 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{12}NO$ 278.0812, found 278.0821.

3-methyl-11-oxo-11*H*-indeno[1,2-b]quinoline 5-oxide (19af)

The dehydrogenative cyclization was carried out by heating 3-(4-methylbenzoyl)quinoline 1-oxide **18af** (26 mg, 0.10 mmol) in a sealable reaction tube charged with $Pd(CH_3CN)_2Cl_2$ (20 mol%) and Ag_2O (35 mg, 0.15mmol) in AcOH at 140 ºC for 48. After the reaction was

completed, the mixture was cooled to room temperature and neutralized with saturated K_2CO_3 solution, extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. After the solvent removal, the obtained residue was purified by silica gel column chromatography (Ethyl acetate/hexane (3:7)) to afford the desired product **19af** as a yellow solid (20 mg, 76%).



Analytical data of 19af

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, *J* = 9 Hz, 1H), 8.63 (s, 1H), 7.95 (s, 1H), 7.89 (d, J = 8 Hz, 1H), 7.78 (t, J = 7.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 2.47 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 188.3, 147.6, 145.1, 138.8, 133.4, 132.5, 132.4, 131.0, 129.6, 129.4, 129.3, 126.9, 124.5, 122.1, 120.0, 22.4 ppm.

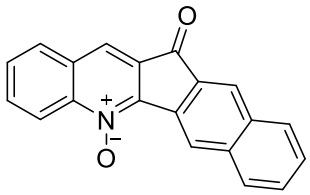
HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{12}NO_2$ 262.0863, found 262.0870.

12-oxo-12*H*-benzo[5,6]indeno[1,2-b]quinoline 5-oxide (19ak)

The dehydrogenative cyclization was carried out by heating 3-(2-naphthoyl)quinoline 1-oxide **18ak** (31 mg, 0.10 mmol) in a sealable reaction tube charged with $Pd(CH_3CN)_2Cl_2$ (20 mol%) and Ag_2O (35 mg, 0.15mmol) in AcOH at 140 ^oC for 48 h. After the reaction was completed, the mixture was cooled to room temperature and neutralized with saturated K_2CO_3 solution, extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. After the solvent removal, the obtained residue was purified by silica gel column chromatography (Ethyl acetate/hexane (3:7)) to afford the desired product **19ak** as a red solid (20 mg, 68%).

Analytical data of 19ak

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.48 (d, *J* = 8.5 Hz, 1H), 8.82 (d, *J* = 8.5 Hz, 1H), 7.99 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8 Hz, 1H), 7.82 – 7.77 (m, 3H), 7.66 – 7.58 (m, 3H)



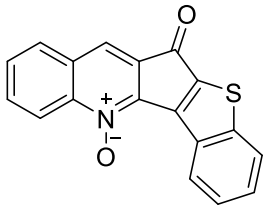
ppm.

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{20}H_{12}NO_2$ 298.0863, found 298.0860.

We faced difficulty in solubilizing the compounds **19ak** in deuterated solvents and hence only ^1H NMR spectra are reported.

11-oxo-11*H*-benzo[4',5']thieno[2',3':4,5]cyclopenta[1,2-*b*]quinoline 5-oxide (19aw)

The dehydrogenative cyclization was carried out by heating 3-(benzo[*b*]thiophene-2-carbonyl)quinoline 1-oxide **18aw** (31 mg, 0.10 mmol) in a sealable reaction tube charged with $Pd(CH_3CN)_2Cl_2$ (20 mol%) and Ag_2O (35 mg, 0.15mmol) in AcOH at 140 ^oC for 48 h to afford 3-(benzo[b]thiophene-2-carbonyl)quinoline 1-oxide. After the reaction was completed, the mixture was cooled to room temperature and neutralized with saturated K_2CO_3 solution, extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4. After the solvent removal, the obtained residue was purified by silica gel column chromatography (Ethyl acetate/hexane (3:7)) to afford the desired product **19aw** as a red solid (10 mg, 33%).



Analytical data of 19aw

^1H NMR (500 MHz, $CDCl_3$): δ 9.49 (d, *J* = 7.5 Hz, 1H), 8.71 (d, *J* = 8.5 Hz, 1H), 7.83 – 7.82(m, 3H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.52 – 7.46 (m, 2H) ppm.

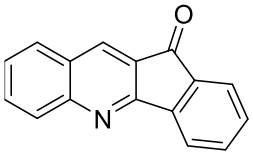
HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{18}H_{10}NO_2$ 304.0427, found 304.0436.

We faced difficulty in solubilizing the compounds **19aw** in deuterated solvents and hence only ^1H NMR spectra are reported.

11*H*-indeno[1,2-*b*]quinolin-11-one (20aa)[16b]

The reduction of indeno[1,2-*b*]quinolinone-*N*-oxides was performed according to the reported literature.[12] To a stirring solution of 11-oxo-indeno[1,2-*b*]quinoline-5-oxide **19aa** (15 mg, 0.06 mmol) in THF, $HCOONH_4$ (57 mg, 0.91mmol) and Pd/C (10 mol%) were added and allowed to stir at ambient temperature. Upon completion of the reaction, the

solvent was removed and the residue was purified by silica gel column chromatography (Ethyl acetate/hexane (3:7)) to afford the desired product **20aa** as a yellow solid (11 mg, 82%).



Analytical data of 20aa

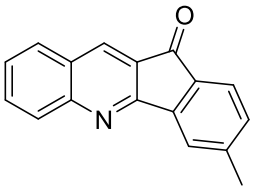
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, *J* = 7.5 Hz, 1H), 8.74 (d, *J* = 8.5 Hz, 1H), 7.98 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 7.5 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 188.7, 145.2, 138.5, 136.0, 135.6, 132.6, 131.7, 131.1, 129.6, 129.4, 128.9, 126.2, 124.5, 122.2, 120.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M/Z)^+$ calcd for $C_{16}H_9NO$ 231.0684, found 231.0679.

3-methyl-11*H*-indeno[1,2-*b*]quinolin-11-one (20af)

The reduction of indeno[1,2-*b*]quinolinone-*N*-oxides was performed according to the reported literature. To a stirring solution of 3-methyl-11-oxo-11*H*-indeno[1,2-*b*]quinoline 5-oxide **19af** (20 mg, 0.08 mmol) in THF, $HCOONH_4$ (73 mg, 1.15mmol) and Pd/C (10 mol%) were added and allowed to stir at ambient temperature. Upon completion of the reaction, the solvent was removed and the residue was purified by silica gel column chromatography (Ethyl acetate/hexane (3:7)) to afford the desired product **20af** as a yellow solid (17 mg, 85%).



Analytical data of 20af

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (d, *J* = 8.5 Hz, 1H), 8.64 (s, 1H), 7.96 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 2.47 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 188.3, 147.6, 138.8, 133.4, 132.5, 132.4, 131.0, 129.3,

126.9, 124.5, 122.1, 120.0, 22.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M/Z)^+$ calcd for $C_{17}H_{11}NO$ 245.0841, found 245.0834.

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ABSTRACT

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AcSIR academic center/CSIR Lab**: CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST)**
Name of the Supervisors**: Dr. Jubi John & Dr. Praveen V. K.**
Title of the thesis: **Exploration and Development of Facile Strategies towards Quinoline Derivatives**

Heterocyclic compounds play a crucial role in our everyday lives. The significance of heterocyclic chemistry is multifaceted, impacting various fields such as drug discovery, material science, and agriculture. Among these, Quinolines are privileged scaffolds, the inherent properties render it a compound of substantial interest and value across a multitude of scientific and industrial applications. Substituted quinolines demonstrate remarkable medicinal properties such as antimalarial, antibacterial, antiviral, antitumor, analgesic, anticonvulsant, and anti-inflammatory etc. These findings have driven the creation of widely used blockbuster drugs, whether derived from natural sources or synthesized, including medications like quinine, chloroquine, camptothecin, pitavastatin, bedaquiline, lenvatinib, tipifarnib, and saquinavir, employed globally to address diverse medical conditions. There are a plethora of synthetic methodologies reported for the synthesis of quinoline derivatives. However, none of these methods described thus far are without drawbacks. Low efficiency, harsh reagents and reaction conditions, and functional group incompatibility are some of the common challenges of these well known classical reactions. Therefore, the quest to find new synthetic methodologies to address these inherent issues has been a recurring endeavor of numerous research groups. Through the work depicted in this thesis, we have tried to answer some of the issues by introducing methodologies for accessing quinoline motifs wherein substituents can be introduced at various positions at will.

Chapter 1, begins with a quick introduction of heterocycles, especially quinoline *N*-heterocycles, and we extensively covered the diverse natural sources, biosynthesis, and its position in the global market. The chapter also encompasses the rich history of the synthesis of quinolines, starting from the classical milestone reactions to recent methodologies towards quinoline and its derivatives.

In Chapter 2, a superbase-mediated indirect Friedländer reaction applied to the synthesis of functionalized quinolines is described. The process involved the use of *o*-aminobenzyl alcohol and ketones containing an active methylene group in the presence of KOH and DMSO. This transition metal-free oxidative annulation was found to be generally applicable, producing 2-substituted, 2,3-disubstituted/fused, or multi-substituted quinolines. The research extended to the functionalization of natural products and showcased the feasibility of gram-scale synthesis of quinolines.

In Chapter 3, we tried to account the superbase-mediated reactivity of tosylhaydrazones with aza-*ortho*-quinone methide precursors, namely *o*-aminobenzyl alcohol and *N*-tosyl chloroarylamine. This chapter is divided into two sections. In Part A, we delve into the reaction of tosylhydrazone with *o*-aminobenzyl alcohol, focusing on the regioselective synthesis of 2-substituted quinoline derivatives. Part B unveils our findings related to the reaction between *N*-tosyl chloroarylamine and tosylhydrazone, leading to the synthesis of sulfonamide derivatives.

Chapter 4, illustrates a Diels Alder cycloaddition route towards 3-aroyl quinolines from enaminones and in situ generated aza-*o*-quinone methides. The reaction was found to be general with a range of substituted enaminones and aza-*o*-quinone methides and we could validate the applicability of the methodology in gram-scale. We also demonstrated a one-pot strategy towards 3-aroyl quinolines starting from the corresponding aliphatic ketones. Finally, we utilized the 3-aroyl quinolines for synthesizing indeno[1,2-*b*]quinolinones *via* a Pd-catalyzed dual C-H activation approach.

List of Publications Emanating from the Thesis

1. **Rahul P.**, Nitha P. Ravi, Vishnu. K. Omanakuttan, Sheba A. Babu, Sasikumar Parameswaran, Vakayil. K. Praveen, Henning Hopf and Jubi John, Superbase-Mediated Indirect Friedländer Reaction: A Transition Metal-Free Oxidative Annulation toward Functionalized Quinolines. *Eur. J. Org. Chem.*, **2020**, 3081–3089.

2. **Rahul P.**, Veena S. and Jubi John, Inverse Electron Demand Diels Alder Reaction of Aza-*o*-Quinone Methides and Enaminones: Accessing 3-Aroyl Quinolines and Indeno[1,2-*b*]quinolinones. *J. Org. Chem.* **2022**, *87*, 13708–13714.

3. **Rahul P.**, Arunkumar T. K., Haritha Raveendran, Seena Sebastian, Jomon Mathew, Sunil varughese, Praveen V. K., Jubi John, Investigations on Superbase Mediated Reactivity of *N*-Tosylhydrazones with Aza-*ortho*-Quinone Methide Precursors. *Eur. J. Org. Chem.* **2024**, e202400151.

List of Publications not Related to Thesis Work

1. **Rahul P**., Joice Thomas, Wim Dehaen and Jubi John, Advances in the Synthesis of Fused 1,2,3-Triazoles *via* an MCR-Intramolecular Azide-Alkyne Cycloaddition Approach, *Molecules*, **2023**, *28*, 308.

2. Sheba A. Babu, A. R. Rajaleksshmi, P. R. Nitha, Vishnu. K. Omanakuttan, **Rahul P.**, Sunil Varughese and Jubi John, Unprecedented Access of Functionalized Pyrrolo[2,1-*a*]isoquinolines from the Domino Reaction of Isoquinolinium Ylides and Electrophilic Benzannulated Heterocycles. *Org. Biomol. Chem*., **2021**, *19*, 1807- 1817.

3. Nandana S. K., **Rahul P**., Sheba Ann Babu, Jubi John, Henning Hopf, A Review on the Synthetic Methods towards Benzothienobenzothiophenes. *Chem. Rec.* **2024**, e202400019

4. Suja P., **Rahul P**., Vidha Bhasin, S. N. Jha, D. Bhattacharya, Rajan T. P. D, Jubi John, U. S. Hareesh, Atomically dispersed high density copper on graphitic carbon nitride as heterogeneous catalysts for high yield conversions in azide-alkyne cycloadditions. (Manuscript submitted in Journal of Materials Chemistry A - manuscript ID is: **TA-ART-02-2024-001412**).

List of Papers/Posters Presented in Conference

1. Inverse Electron Demand Diels Alder Reaction towards 3-Aroyl Quinolines (Poster) **Rahul P.** and Jubi John, 30th CRSI-NSC and 16th CRSI-RSC Research Conference on Chemistry organized by Jawaharlal Nehru University (JNU), Delhi, on February 02-05, 2023.

2. Superbase-Mediated Oxidative Annulation Toward Functionalised Quinolines. (Oral) **Rahul P.**, V.K. Praveen and Jubi John, International Conference on Current Trends in Chemistry- CTriC 2022 organized by Department of Applied Chemistry, CUSAT during March 11-12, 2022.

3. Superbase-Mediated Oxidative Annulation Toward Functionalised Quinolines. (Poster) **Rahul P.**, V.K. Praveen 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 16 – 18, 2021.

EurJOC
European Journal of Organic Chemistry

Full Paper
doi.org/10.1002/ejoc.202000365

Chemistry Europe
European Chemical Societies Publishing

Indirect Friedländer Reaction

Superbase-Mediated Indirect Friedländer Reaction: A Transition Metal-Free Oxidative Annulation toward Functionalized Quinolines

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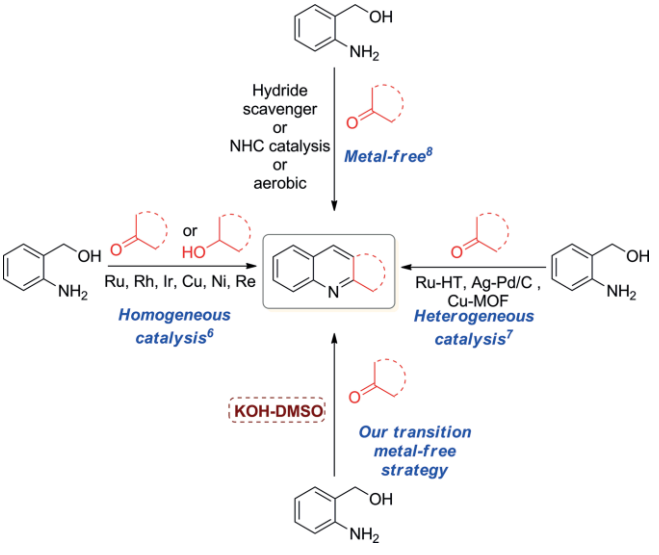
Abstract: A superbase mediated indirect Friedländer reaction towards functionalized quinolines has been realized. The reaction was performed with o-aminobenzyl alcohol and ketones having an active methylene moiety in the presence of KOH and in DMSO. The reaction proceeds predominantly via initial formation of an imine intermediate and subsequent oxidation of the benzyl alcohol functionality and condensation to afford substituted quinolines. We could also demonstrate that a minor fraction of the reaction proceeds via a chalcone intermediate. The transition metal-free oxidative annulation was found to be general affording 2-substituted, 2,3-disubstituted/fused or multi-substituted quinolines. The reaction was extended towards the functionalization of natural products and the applicability of the reaction for gram-scale synthesis of quinolines was also demonstrated.

Introduction

The class of quinoline derivatives pose a continuous challenge to synthetic chemists in devising straightforward routes for accessing them.[1] The profound interest invested in this heterocyclic moiety is due to its wide applicability in pharmaceuticals,[2] materials[3] and industry.[4] Substituted quinolines exhibit promising biological activities such as antimalarial, antibacterial, antiviral, antitumor, analgesic, anticonvulsant, anti-inflammatory etc.[2] These findings have resulted in the development of blockbuster drugs (of natural and synthetic origin) such as quinine, chloroquine, camptothecin, pitavastatin, bedaquiline, lenvatinib, tipifarnib and saquinavir which are being heavily used worldwide for the treatment of different ailments.

Several classical organic reactions exist which utilize arylamines as precursors for the synthesis of quinoline and its derivatives and out of which Friedländer quinoline synthesis can still be considered as one of the most direct routes for accessing this important heterocycle.[5] The traditional Friedländer reaction involves a base promoted condensation of a 2-amino-substituted carbonyl compound (aromatic) and an α-methylene group containing carbonyl derivative followed by dehydration. Recently, modified or indirect Friedländer quinoline synthesis protocols with dehydrogenative cyclization of 2-aminobenzyl alcohol with carbonyl compounds (or alcohols) were developed in the presence of metal catalysts (Scheme 1).[6] Different complexes of metals such as Ru,[6b] Rh,[6c] Ir,[6d–6f] Cu,[6g] Ni[6h–6i] and Re[6j] were utilized as catalysts in indirect Friedländer quinoline synthesis. In addition, several heterogeneous catalysts including Ru-HT (ruthenium on hydrotalcite support), Pd/C, $Pd(OAc)_2$/PEG-2000, Ag-Pd alloy on carbon and a Cu based MOF were also developed and used for synthesizing substituted quinolines (Scheme 1).[7]



Scheme 1. Indirect Friedländer synthesis of quinolines from 2-aminobenzyl alcohol.

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Another advancement in the area of indirect Friedländer quinoline synthesis was the introduction of metal-free strategies.[8] The first among them was reported in 2008 by Ramón, Yus, and co-workers which combined the Meerwein-Ponndorf-Verley reaction of 2-aminobenzyl alcohols with benzophenone and the Friedländer annulation to synthesize quinoline derivatives.[8a] Recently, an *N*-heterocyclic carbene-catalyzed indirect Friedländer quinoline synthesis was reported by Zhu and Cai.[8b] and an aerobic one-pot synthesis by Singh et al. (Scheme 1).[8c] These reported metal-free methodologies required additional reagents (benzophenone for the MPV reaction of 2-aminobenzyl alcohol[8a] or the presence of a catalyst.[8b] We were interested in developing a transition metal-free and additional reagent-free methodology for quinoline synthesis based on the indirect Friedländer reaction.

Superbasic media (mainly the combination of KOH and DMSO) have been utilized extensively by Trofimov and others for effecting different organic transformations such as chalcogenation, cross-coupling, intramolecular cyclization, heterocyclic synthesis, styrylation, inter- and intramolecular hydroaminations, etc.[9] Verma and co-workers made use of the KOH-DMSO system for the synthesis of functionalized quinolines from *o*-aminobenzyl alcohol and alkynes.[10] The reaction proceeded via a [4 + 2] cycloadditions of alkyne with azadiene (in situ generated from *o*-aminobenzyl alcohol). An efficacious methodology for the oxidation of active methylenes and benzhydrols to corresponding carbonyl compounds mediated by a base-DMSO system was reported by Ravikumar et al.[11] Motivated by the above-mentioned reports on the use of superbasic media and owing to our interest in heterocyclic synthesis,[12] we hypothesized that functionalized quinolines could be generated from *o*-aminobenzyl alcohol and α-methylene group containing carbonyl derivatives via an oxidation-condensation sequence in the presence of a base-DMSO system and most importantly in the absence of any additional reagent or catalyst.

Result and Discussions

We commenced our investigations by selecting *o*-aminobenzyl alcohol **1a** and 4′-methoxy acetophenone **2a** as model substrates. The initial reaction was performed with one equivalent each of **1a** and **2a** in the presence of KOH (1.0 equivalent) and DMSO (1.0 mL) at 80 °C for 7 h. As expected, 2-(4-methoxyphenyl)quinoline **3a** was isolated in 80 % yield (Table 1, entry 1). Different bases other than KOH such as *t*BuONa, *t*BuOK, NaOH and K_2CO_3 were screened for the present indirect Friedländer quinoline synthesis (Table 1, entries 1–5). From the tested bases, KOH was found to be the best and the reaction failed to furnish any product in the presence of K_2CO_3. Increasing the equivalents of *o*-aminobenzyl alcohol had a beneficial effect on the outcome of the reaction. Thus, with 1.2 equivalents of **1a**, the substituted quinoline was isolated in 88 % yield (Table 1, entries 1, 6 and 7). Next, we checked the effect of change in temperature on the yield of the reaction. It was found that both increasing (to 120 °C) and decreasing the temperature (to r.t.) considerably decreased the yield of **3a** (Table 1, entries 7–9). A decrease in the equivalents of KOH (to 0.5 equivalents) was found to lower the yield of **3a** to 72 % (Table 1, entry 10) and the reaction failed to afford any product in the absence of KOH (Table 1, entry 11). Finally, conducting the reaction under inert atmosphere didn't significantly influence the outcome of the reaction proving that oxygen is not required for the oxidation step (Table 1, entry 12).

Table 1. Optimization studies.

Entry	Base	Time	T [°C]	Yield of **3a**[a] [%]
1	KOH	7	80	80
2	*t*BuONa	7	80	48
3	*t*BuOK	7	80	51
4	NaOH	7	80	61
5	K_2CO_3	7	80	–
6[b]	KOH	7	80	83
7[c]	**KOH**	**7**	**80**	**88**
8[c]	KOH	7	120	59
9[c]	KOH	48	r.t.	23
10[d]	KOH	7	80	72
11[c]	–	7	80	–
12[e]	KOH	7	80	86

[a] Reaction conditions: **1a** (1.0 equiv.), **2a** (1.0 equiv., 0.6 mmol), base (1.0 equiv.), DMSO (1.0 mL), 80 °C, 7 h. [b] Reaction conditions: **1a** (1.1 equiv.). [c] Reaction conditions: **1a** (1.2 equiv.). [d] Reaction conditions: **1a** (1.2 equiv.), KOH (0.5 equiv.). [e] Reaction conditions: **1a** (1.2 equiv.), argon atmosphere.

The scope and limitation of the indirect Friedländer quinoline synthesis were then studied (Table 2) under the optimized conditions [**1** (1.2 equiv.), **2** (1.0 equiv.), KOH (1.0 equiv.), DMSO (1.0 mL), 80 °C, 7 h]. Both acetophenone **2b** and 4′-methylacetophenone **2c** participated in the oxidative annulation with *o*-aminobenzyl alcohol **1a** affording the corresponding products **3b** and **3c** in 75 and 80 % respectively. 2-Phenyl quinoline **3b** was also synthesized in gram scale and good yield (70 %) by starting with 1.0 g of acetophenone **2b.** A substituent on the *ortho*-position of the aryl ring of acetophenone did not affect the reaction yield and in this line, the reactions with 2′-methoxy (**2d**) and 2′-methylacetophenone (**2e**) afforded the products **3d** and **3e** in good yields, whereas the reaction with 2′-hydroxyacetophenone (**2f**) furnished the product **3f** only in 56 % yield.

The superbase mediated oxidative annulation proceeded well with di- (**2g**) and tri-methoxy acetophenones (**2h**) affording the products **3g** and **3h** in excellent yields. The presence of electron-withdrawing groups was found to influence the reaction outcome as the reactions with both 3′-(trifluoromethyl)-acetophenone (**2i**) and 3-nitroacetophenone (**2j**) could only furnish the corresponding 2-substituted quinolines **3i** and **3j** in poor yields. Another interesting observation that we came across was in the reaction with 4′-chloroacetophenone and *o*-aminobenzyl alcohol **1a**. Contrary to our expectation of 2-(4-chlorophenyl)quinoline **3k**, we obtained a dehalogenated quinoline derivative. The dehalogenation of aromatic compounds with a DMSO-base combination was reported earlier which might be the reason for the present observation.[13] The oxidative annulation also worked with acetylferrocene affording 2-ferrocenylquinoline **3l** in 45 % yield. 2-Naphthylquinole **3m** was synthesized in excellent yield but after 14 h of reaction time. By starting with 1,3-dicetylbenzene we could synthesize 1,3-diquinolylbenzene **3n** in 69 % yield. Finally, the reactivity of differ-

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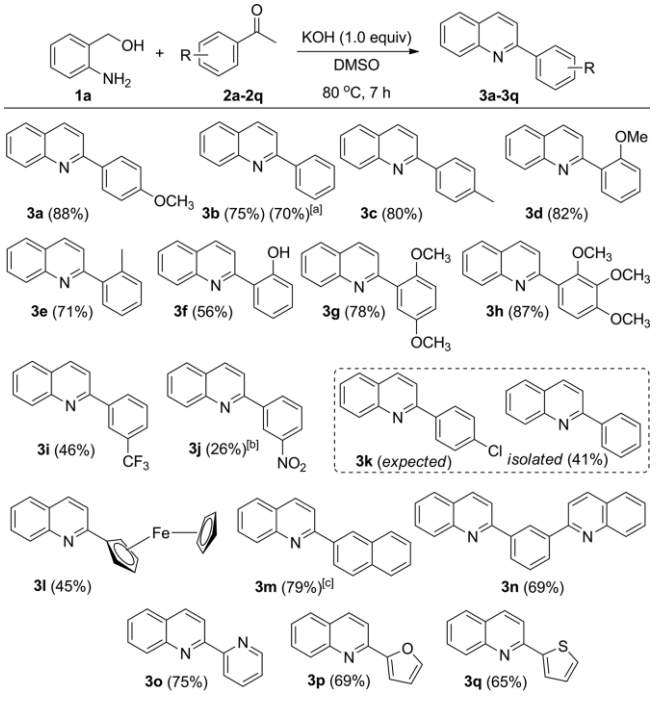
Table 2. Generality of indirect Friedländer reaction toward 2-substituted quinolines. (Reaction conditions: **1a** (1.2 equiv.), **2** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv., 0.6 mmol), DMSO (1.0 mL), 80 °C, 7 h).

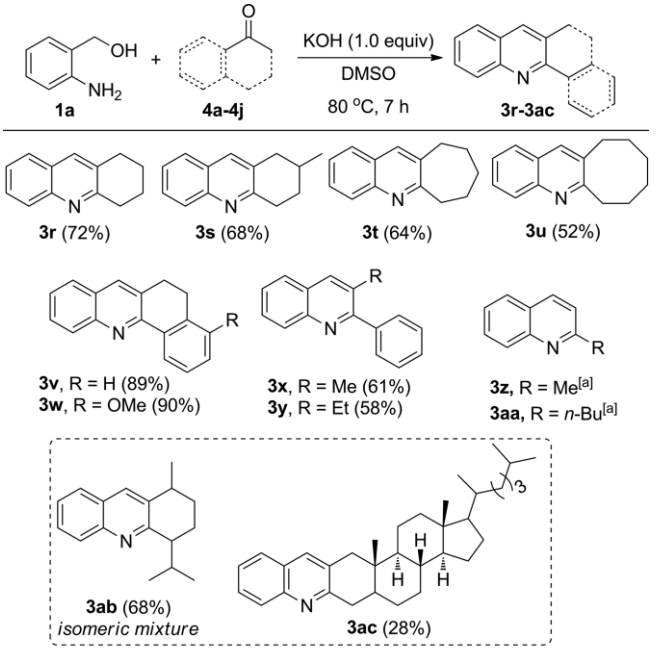


[a] Started with 1.0 g of **2b**. [b] 120 °C, 12 h. [c] 14 h.

ent acetylheteroarenes toward the present indirect Friedländer reaction was examined and thus pyridyl (**3o**), furyl (**3q**) and thienyl (**3r**) substituted quinolines were synthesized in good yields.

Next, we turned our attention in synthesizing 2,3-disubstituted/fused quinolines via the developed superbase mediated oxidative annulation (Table 3). We commenced our investigations with *o*-aminobenzyl alcohol **1a** and cyclohexanone under the optimized conditions and 1,2,3,4-tetrahydroacridine **3r** was isolated in 72 % yield. The reaction with 4-methylcyclohexanone also afforded the corresponding substituted tetrahydroacridine derivative **3s** in 68 % yield. Other cyclic ketones such as cycloheptanone and cyclooctanone afforded the 2,3-fused quinoline derivatives **3t** and **3u** in good yields. The indirect Friedländer reaction was also found to work well with tetralone **4e** and methoxytetralone **4f** from which the respective dihydrobenzo[c]acridine derivatives **3v** and **3w** were isolated in excellent yields. We then checked the reactivity of propiophenone **4g** and butyrophenone **4h** and these ketones reacted well under the optimized conditions affording the corresponding 2,3-disubstituted quinolines **3x** and **3y** in good yields. We have also checked the reactivity of acyclic ketones such as acetone and 2-hexanone but to our dismay, after the required time an intractable reaction mixture was observed. The importance of the present oxidative annulation was exemplified by performing "quinolization" of natural products containing an enolizable ketone moiety. Thus both menthone (mixture of isomers) and 5α-cholestan-3-one were treated with *o*-aminobenzyl alcohol **1a** under our optimized conditions and the corresponding annulated natural products **3ab** and **3ac** were isolated.

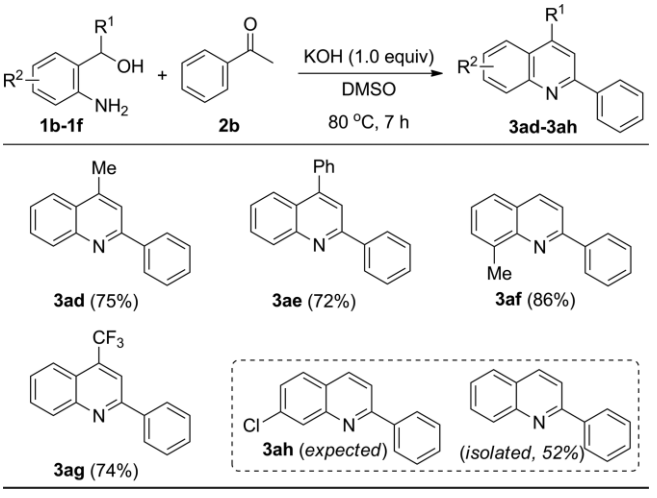
Table 3. Generality of indirect Friedländer reaction toward 2,3- disubstituted/fused quinolines. (Reaction conditions: **1a** (1.2 equiv.), **4** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv., 0.6 mmol), DMSO (1.0 mL), 80 °C, 7 h).



[a] Intractable reaction mixture.

Subsequently, we examined the effect of substituents on *o*-aminobenzyl alcohols on the outcome of the superbase mediated quinoline synthesis (Table 4). We commenced with the reaction of acetophenone **2b** with 1-(2-aminophenyl)ethan-1-ol **1b**. The reaction was complete in 7 h and from which the 2,4-disubstituted quinoline **3ad** was isolated in 75 % yield. 2-aminobenzhydrol **1c** also reacted with ease affording the 2,4-diphenylquinoline **3ae** in good yield.

Table 4. Generality of indirect Friedländer with substituted *o*-aminobenzyl alcohol.[a]



[a] Reaction conditions: **1a** (1.2 equiv.), **2** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv., 0.6 mmol), DMSO (1.0 mL), 80 °C, 7 h.

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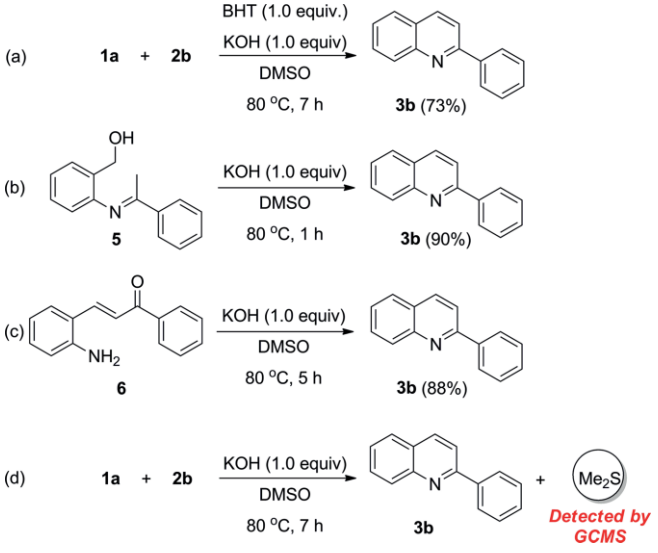
Next, we checked the reactivity of 2-amino-3-methylbenzyl alcohol **1d** under the optimized conditions and the respective quinoline derivative **3af** was obtained in 86 % yield (Table 4). The reaction of 1-(2-aminophenyl)-2,2,2-trifluoroethan-1-ol **1e** also proceeded well affording 2-phenyl-4-(trifluoromethyl)-quinoline **3ag** in 74 % yield. Lastly, we checked the reactivity of 2-amino-4-chlorobenzyl alcohol **1f** with acetophenone and as observed earlier (Table 2, compound **3k**) we obtained the dehalogenated product.

To prove the mechanism of the superbase mediated indirect Friedländer quinoline synthesis we carried out several experiments with substrates **1a** and **2b** (Scheme 2). The possibility for a radical-mediated reaction was ruled out with the first reaction (Scheme 2a) where **1a** and **2b** were allowed to react under the optimized conditions but in the presence of 1.0 equivalent of BHT from which 2-phenylquinoline **3b** was isolated in 73 % yield. It is reported that the classical Friedländer quinoline synthesis can proceed either via the imine **5** or *o*-amino chalcone **6** as intermediates.[5] When **5** was subjected to the optimized conditions, we were able to isolate the expected product **3b** in 90 % yield after an hour (Scheme 2b). On the other hand, when *o*-amino chalcone **6** was allowed to react at the optimized conditions, the reaction took 5 h to furnish 88 % of **3b** (Scheme 2c). These results show that the present superbase mediated quinoline synthesis might be proceeding predominantly via the imine intermediate **5** rather than the chalcone **6** and that imine formation must be happening preferentially over the oxidation of the benzyl alcohol moiety. Finally, we were able to detect the formation of Me_2S as a by-product by conducting a GC–MS experiment (Scheme 2d).[14]

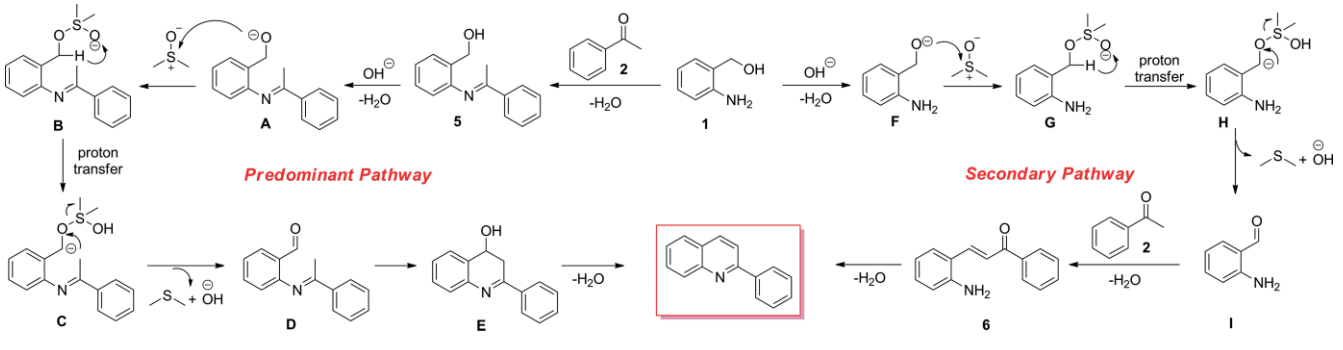


Scheme 2. Reactions to support the mechanism of superbase mediated indirect Friedländer quinoline synthesis.

From the results obtained for the experiments depicted above, we believe that the first step of quinoline synthesis (predominant pathway) would be the condensation of amino group of 2-aminobenzyl alcohol and acetophenone to yield the imine **5** (Scheme 3). This will be followed by the oxidation of the alcohol to the corresponding carbonyl group which proceeds via a mechanism analogous to the one proposed by Ravikumar et al.[11a] Initially the base will generate the alkoxide intermediate **A** from **5**. The adduct **B** is then formed by the attack of the alkoxide to the electrophilic sulfur of DMSO. Subsequently, proton transfer occurs from the benzylic carbon to the alkoxide generating the carbanion **C** which further undergoes an $E1_{cb}$ elimination furnishing the corresponding carbonyl compound **D**. An intramolecular aldol addition occurs in intermediate **D** to furnish the dihydroquinoline **E** from which water is eliminated to finally afford the substituted quinoline derivative.[5] The secondary pathway will commence with the benzylic alcohol functionality to the *o*-amino benzaldehyde I by following a similar mechanism as shown before. The *o*-amino chalcone **6** is then formed by the condensation of **I** with acetophenone. The intermediate **6** subsequently undergoes intramolecular annulation to furnish 2-substituted quinoline by the elimination of H_2O.

Conclusion

In conclusion, we have developed a mild, transition metal-free and general methodology for the synthesis of functionalized quinolines. In contrast to the reported methods that required either metal catalysts (homogeneous or heterogeneous) or additional reagents (hydride scavenger or NHC catalyst) our strategy required only the combination of KOH in DMSO. In this superbasic medium, the reaction proceeds predominantly via the formation of an imine and successive oxidation of 2-aminobenzyl alcohol to the corresponding aldehyde followed by condensation with the enamine moiety. We could propose a mechanistic postulate by isolating the imine intermediate and by subjecting it to oxidative annulation conditions. We could also show that a minor fraction of the reaction proceeds via a chalc-



Scheme 3. Mechanism of superbase mediated indirect Friedländer quinoline synthesis.

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one intermediate. This oxidative annulation worked well-affording mono-, di- and poly-substituted quinolines in good yields. In the case of halogen-substituted quinoline derivatives, dehalogenation was observed as reported earlier. It is noteworthy to mention that we could synthesize substituted quinoline by this methodology in gram scale thereby proving the applicability of the reaction. In addition, we also utilized this superbase mediated oxidative annulation to functionalize natural products. We are currently focusing on other superbase mediated reactions of 2-aminobenzyl alcohol and the results will be published.

Experimental Section

General

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, and mixtures of ethyl acetate/hexanes were used for elution. Melting points were determined using a calibrated digital melting point apparatus (Büchi 530 melting point apparatus). NMR spectra were recorded with 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. 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 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 Thermo Scientific Exactive mass spectrometer with orbitrap analyzer. Gas chromatographic analysis was performed using GC–MS-TQ8030 SHIMADZU.

Experimental procedure for the synthesis of substituted quinoline derivatives: To a reaction tube equipped with a magnetic stirring bar, acetophenone **2** (1.0 equiv.), *o*-aminobenzyl alcohol **1** (1.2 equiv.) and KOH (1 equiv.) and 1 mL of DMSO were added. The resultant reaction mixture was kept for stirring at 80 °C for 7 h. After completion of the reaction, water was added and the aqueous layer extracted thrice with ethyl acetate. The organic layer was dried with 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 2-substituted quinolines.

2-(4-Methoxyphenyl)quinoline (**3a**).[6i,14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 4-methoxyacetophenone **2a** (100 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3a** as white solid (138 mg, 88 %). Analytical data of **3a**: Mp: 125–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 8.18–8.13 (m, 4H), 7.84–7.79 (m, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 3.89 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 160.8, 156.9, 148.3, 136.6, 132.3, 129.6, 129.5, 128.9, 127.4, 126.9, 125.9, 118.6, 114.2, 55.4 ppm. HRMS (ESI-Orbitrap) *m/z*: $(M+H)^+$ calcd. for $C_{16}H_{14}NO$ 236.1070, found 236.1078.

2-Phenylquinoline (**3b**).[6i,14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), acetophenone **2b** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3b** as white solid (103 mg, 75 %). For the gram-scale preparation of **3b**, the yield was 70 % (1.19 g). Analytical data of **3b**: Mp: 84–87 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.20–8.15 (m, 4H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.73–7.70 (m, 1H), 7.53–7.49 (m, 3H), 7.47–7.44 (m, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, TMS) δ = 157.4, 148.3, 139.7, 136.8, 129.8, 129.7, 129.3, 128.9, 127.6, 127.5, 127.2, 126.3, 119.1 ppm. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{12}N$ 206.0964, found 206.0975.

2-(*p*-Tolyl)quinoline (**3c**).[6i,14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 4-methylacetophenone **2c** (90 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3c** as white solid (117 mg, 80 %). Analytical data of **3c**: Mp: 81–84 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.17 (t, *J* = 9 Hz, 2H), 8.07 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.71 (t, *J* = 8 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 2H), 2.43 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 157.4, 148.3, 139.4, 136.9, 136.7, 129.7, 129.6, 127.4, 127.1, 126.1, 118.9, 21.4 ppm. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{14}N$ 220.1121, found 220.1124.

2-(2-Methoxyphenyl)quinoline (**3d**).[6i,14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2-methoxyacetophenone **2d** (100 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3d** as colorless liquid (129 mg, 82 %). Analytical data of **3d**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.18–8.13 (m, 2H), 7.89–7.82 (m, 3H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.13 (t, *J* = 7.5Hz, 1H), 7.03 (d, *J* = 8 Hz, 1H), 3.86 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 157.2, 157.2, 148.3, 135.1, 131.5, 130.4, 129.8, 129.6, 129.2, 127.4, 127.1, 126.2, 123.5, 121.3, 111.4, 55.7 ppm. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{14}NO$ 236.1070, found 236.1072.

2-(o-Tolyl)quinoline (**3e**).[6i,14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2-methylacetophenone **2e** (90 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3e** as white solid, 104 mg (71 %). Analytical data of **3e**: Mp: 69–71 °C ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.21 (d, *J* = 8 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8 Hz, 1H), 7.74 (t, *J* = 8 Hz, 1H), 7.58–7.53 (m, 2H), 7.50 (d, *J* = 7 Hz, 1H), 7.36–7.33 (m, 3H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 160.3, 147.9, 140.8, 136.1, 136.0, 130.9, 129.7, 129.6, 128.5, 127.5, 126.8, 126.4, 126.0, 122.4, 20.4 ppm. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^{+}$.[calcd] for $C_{16}H_{14}N$ 220.1121, found 220.1124.

2-(Quinolin-2-yl)phenol (**3f**).[14c] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2-hydroxyacetophenone **2f** (92 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3f** as white solid (83 mg, 56 %). Analytical data of **3f**: Mp: 113–115 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 15.24 (s, 1H), 8.27 (d, *J* = 9 Hz, 1H), 8.06–8.03 (m, 2H), 7.95 (d, *J* = 8 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.74 (t, *J* = 8 Hz, 1H), 7.57–7.54 (m, 1H), 7.37 (t, *J* = 7. 5 Hz, 1H) 7.09 (d, *J* = 8.5 Hz, 1H), 6.96 (t, *J* = 7. 5 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, CDCl3) δ = 161.0, 158.0, 144.8, 137.6, 130.5, 127.6, 127.5, 126.9, 126.7, 126.6, 119.0, 118.7, 118.7, 117.3 ppm. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ calcd. for $C_{15}H_{12}NO$ 222.0913, found 222.0924.

2-(2,5-Dimethoxyphenyl)quinolone (**3g**). Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2,5-dimethoxyacetophenone **2g** (121 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3g** as white solid (138 mg, 78 %). Analytical data of **3g**: Mp: 141–143 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.16 (t, *J* = 9.5 Hz, 2H), 7.91 (d, *J* = 8 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.72–7.70 (m, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45 (s, 1H), 6.98 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 156.9, 154.1, 151.6, 148.3, 135.2, 130.4, 129.7, 129.3, 127.4, 127.1, 126.3, 123.4, 116.2, 116.1, 113.3, 56.6, 55.9 ppm. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ calcd. for $C_{17}H_{16}NO_2$ 266.1176, found 266.1181.

2-(2,3,4-Trimethoxyphenyl)quinoline (**3h**). Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2,3,4-trimethoxyacetophenone **2h** (141 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3h** as white solid (172 mg, 87 %). Analytical data of **3h**: Mp: 104–106 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.16–8.15 (m, 2H), 7.90 (d, *J* = 9 Hz, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.5Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.77 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, CDCl3) δ = 156.6, 154.6, 152.3, 148.3, 142.4, 135.5, 129.6, 129.3, 127.6, 127.4, 127.0, 126.1, 125.8, 122.9, 108.1, 61.5, 61.1, 56.2 ppm. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ calcd. for $C_{18}H_{18}NO_3$ 296.1281, found 296.1287.

2-(3-(Trifluoromethyl)phenyl)quinoline (**3i**).[14b] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 3-trifluoromethylacetophenone **2i** (126 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexanes) to afford the desired product **3i** as white solid (84 mg, 46 %). Analytical data of **3i**: Mp: 51–53 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.47 (s, 1H), 8.36 (d, *J* = 7.5 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.78–7.72 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 155.6, 148.3, 140.4, 137.2, 131.3 (q, j = 32.5 Hz), 130.7, 130.0, 129.8, 129.3, 127.5, 127.4, 126.8, 125.9 (q, j = 3.8 Hz), 124.4 (q, j = 3.8 Hz), 118.6 ppm. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ calcd. for $C_{16}H_{11}F_3N$ 274.0844, found 274.0851.

2-(3-Nitrophenyl)quinoline (**3j**).[14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 1.2 0.80 mmol), 3-nitroacetophenone **2j** (110.6 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 120 °C and subsequent stirring for 12 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexanes) to afford the desired product **3j** as white solid (44 mg, 26 %). Analytical data of **3j**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 9.06 (s, 1H), 8.57 (d, *J* = 8 Hz, 1H), 8.33–8.31 (m, 2H), 8.20 (d, *J* = 8 Hz, 1H), 7.95 (d, *J* = 8.5Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.79 (t, *J* = 8 Hz, 1H), 7.72 (t, *J* = 8 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 148.3, 141.3, 137.4, 137.1, 133.3, 130.2, 129.9, 129.8, 127.6, 127.1, 123.9, 122.5, 118.4 ppm. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ calcd. for $C_{15}H_{11}N_2O_2$ 251.0815, found 251.0825.

2-Ferrocenylquinoline (**3l**).[14c] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), acetylferrocene **2l** (153 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3l** as red solid (94 mg, 45 %). Analytical data of **3l**: Mp: 135–138 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.04 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.48– 7.45 (m, 1H), 5.07 (s, 2H), 4.47 (s, 2H), 4.06 (s, 5H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 159.5, 148.3, 135.4, 129.4, 129.0, 127.5, 126.7, 125.4, 119.5, 84.0, 70.4, 69.7, 68.0 ppm. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ calcd. for $C_{13}H_{10}NS$ 314.0627, found 314.0621.

2-(Naphthalen-2-yl)quinoline (**3m**).[14c] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2-acetonaphthone **2m** (114 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 14 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3m** as a pale yellow solid (135 mg, 79 %). Analytical data of **3m**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 8.63 (s, 1H), 8.39 (dd, J_1= 8.7 Hz, J2 = 1.8 Hz, 1H), 8.27– 8.23 (m, 2H), 8.04–7.99 (m, 3H), 7.93–7.89 (m, 1H), 7.86–7.83 (m, 1H), 7.79–7.74 (m, 1H) 7.58–7.53 (m, 3H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ = 157.1, 148.3, 136.9, 136.8, 133.8, 133.5, 129.7, 129.7, 128.8, 128.6, 127.7, 127.5, 127.2, 127.1, 126.7, 126.3, 126.3, 125.0, 119.1 ppm.

1,3-Di(quinolin-2-yl)benzene (**3n**).[14d] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (197 mg, 1.6 mmol), 1,3-diacetylbenzene **2n** (109 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3n** as white solid (153 mg, 69 %). Analytical data of **3n**: Mp: 138–141 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.97 (s, 1H), 8.30–8.27 (m, 4H), 8.23 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 9 Hz, 2H), 7.86 (d, *J* = 8 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 8 Hz, 1H), 7.55 (t, *J* = 8 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 157.2, 148.3, 140.3, 136.9, 129.8, 129.8, 129.5, 128.6, 127.5, 127.3, 126.8, 126.4, 119.2 ppm. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ calcd. for $C_{17}H_{24}N_2$ 333.1386, found 333.1395.

2-(Pyridin-2-yl)quinoline (**3o**).[14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2-acetylpyridine **2o** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3o** as white solid (103 mg, 75 %). Analytical data of **3o**: Mp: 98–100 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.74–8.73 (1H, m), 8.65 (d, *J* = 8 Hz, 1H), 8.56 (d, *J* = 8.5 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.88–7.84 (m, 2H), 7.73 (t, *J* =

8 Hz, 1H) 7.55 (t, *J* = 7.5Hz, 1H), 7.35 (t, *J* = 6 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 156.4, 156.2, 149.2, 148.0, 137.0, 136.8, 129.8, 129.6, 128.3, 127.6, 126.8, 124.1, 121.9, 119.0 ppm. HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ calcd. for $C_{14}H_{11}N_2$ 207.0917, found 207.0922.

2-(Furan-2-yl)quinoline (**3p**).[14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2-acetylfuran **2p** (74 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexanes) to afford the desired product **3p** as white solid (90 mg, 69 %). Analytical data of **3p**: Mp: 87–89 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.17 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H), 7.72–7.69 (m, 1H), 7.63 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.22 (s, 1H), 6.60 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 149.0, 144.2, 136.7, 129.9, 129.4, 127.6, 127.2, 126.2, 117.5, 112.2, 110.2 ppm.

2-(Thiophen-2-yl)quinoline (**3q**).[14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2-acetylthiophene **2q** (85 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3q** as white solid (92 mg, 65 %). Analytical data of **3q**: Mp: 131–134 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.15 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.82–7.76 (m, 3H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.51–7.47 (m, 2H), 7.18–7.16 (m, 1H), ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 152.4, 148.1, 136.7, 129.8, 129.3, 128.6, 128.1, 127.5, 126.1, 125.9, 117.7 ppm. HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ calcd. for $C_{13}H_{10}NS$ 212.0528, found 212.0539.

1,2,3,4-Tetrahydroacridine (**3r**).[14c] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), cyclohexanone **4a** (66 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3r** as pale yellow solid (88 mg, 72 %). Analytical data of **3r**: ^1H NMR (300 MHz, $CDCl_3$, TMS) δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.77 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.62–7.56 (m, 1H), 7.44–7.39 (m, 1H), 3.13 (t, *J* = 6.6 Hz, 2H), 2.94 (t, *J* = 6.6 Hz, 2H), 2.02–1.93 (m, 2H), 1.88–1.83 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ = 159.2, 146.3, 135.1, 130.9, 128.5, 128.0, 127.1, 126.8, 125.5, 33.4, 29.1, 23.1, 22.8 ppm.

2-Methyl-1,2,3,4-tetrahydroacridine (**3s**).[14f] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 4-methylcyclohexanone **4b** (75 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3s** as white solid (90 mg, 68 %). Analytical data of **3s**: Mp: 78–79 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ = 7.97 (d, *J* = 8.5 Hz, 1H), 7.74 (s, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 3.23–3.20 (m, 1H), 3.12–3.05 (m, 1H), 3.00–2.96 (m, 1H), 2.59–2.53 (m, 1H), 2.06–1.95 (m, 2H), 1.62–1.54 (m, 1H), 1.11 (d, *J* = 7 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 159.1, 146.7, 135.0, 130.6, 128.5, 128.3, 127.2, 126.9, 125.5, 37.8, 33.1, 31.4, 29.1, 21.7 ppm. HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ calcd. for $C_{14}H_{16}N$ 198.1277, found 198.1286.

7,8,9,10-Tetrahydro-6H-cyclohepta[b]quinoline (**3t**).[14c] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), cycloheptanone **4c** (75 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3t** as white solid (84 mg, 64 %). Analytical data of **3t**: Mp: 92–94 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.00 (d, *J* = 8.5 Hz, 1H), 7.79 (s, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.61 (t, *J* = 8 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 3.21–3.20 (m, 2H), 2.93–2.92 (m, 2H), 1.89–1.74 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 164.7, 146.2, 136.5, 134.6, 128.5, 128.4, 127.4, 126.8, 125.8, 40.1, 35.5, 32.2, 28.9, 27.0 ppm. HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ calcd. for $C_{14}H_{16}N$ 198.1277, found 198.1270.

6,7,8,9,10,11-Hexahydrocycloocta[b]quinoline (**3u**).[14d] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), cyclooctanone **4d** (85 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3u** as colorless liquid (74 mg, 52 %). Analytical data of **3u**: ^1H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.03 (d, *J* = 8.5 Hz, 1H), 7.84 (s, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 3.17 (t, *J* = 6.5 Hz, 2H), 2.96 (t, *J* = 6 Hz, 2H), 1.90 (s, 2H), 1.78 (s, 2H), 1.41 (s, 4H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 163.2, 147.0, 135.2, 135.0, 128.5, 128.4, 127.6, 126.9, 125.6, 35.3, 32.7, 32.1, 31.0, 26.0, 25.9 ppm. HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{18}N$ 212.1434, found 212.1438.

5,6-Dihydrobenzo[c]acridine (**3v**).[14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80), 1-tetralone **4e** (98 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3v** as white solid (138 mg, 89 %). Analytical data of **3v**: Mp: 59–62 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.57 (d, *J* = 8 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.66–7.63 (m, 1H), 7.48–7.41 (m, 2H), 7.37 (t, *J* = 7. 5 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 3.13 (t, *J* = 7 Hz, 2H), 3.01 (t, *J* = 7 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 153.4, 147.7, 139.4, 134.7, 133.7, 130.6, 129.7, 129.4, 129.1, 128.7, 128.0, 127.9, 127.4, 126.9, 126.1, 28.9, 28.4 ppm. HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ calcd. for $C_{17}H_{14}N$ 232.1121, found 232.1129.

4-Methoxy-5,6-dihydrobenzo[c]acridine (**3w**). Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 5-methoxy-1-tetralone **4f** (118 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3o** as white solid (157 mg, 90 %). Analytical data of **3w**: Mp: 120–123 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.22 (d, *J* = 7.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.65–7.62 (m, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 8.5Hz, 1H), 6.96 (d, *J* = 8 Hz, 1H), 3.90 (s, 3H), 3.09 (t, *J* = 6.5 Hz, 2H), 3.02 (t, *J* = 6.5 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 156.3, 153.4, 147.6, 135.9, 133.6, 130.6, 129.5, 128.5, 128.2, 127.9, 127.4, 126.9, 126.1, 118.4, 111.4, 55.7, 28.3, 20.4 ppm. HRMS (ESI-Orbitrap) *m/z*:$[M + H]^+$ calcd. for $C_{18}H_{16}NO$ 262.1226, found 262.1236.

3-Methyl-2-phenylquinoline (**3x**).[14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), propiophenone **4g** (90 mg, 0.67 mmol), KOH (38 mg, 0.67 mg) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the de-

sired product **3x** as colourless liquid (89 mg, 61 %). Analytical data of **3x**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.13 (d, J = 8 Hz, 1H), 8.00 (s, 1H), 7.76 (d, J = 8 Hz, 1H), 7.67–7.64 (m, 1H), 7.58 (d, J = 7 Hz, 2H), 7.52–7.47 (m, 3H), 7.44–7.41 (m, 1H), 2.45 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 160.6, 146.6, 140.9, 136.8, 129.3, 129.2, 128.9, 128.8, 128.3, 128.2, 127.6, 126.8, 126.4, 20.7 ppm. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd. for $C_{16}H_{14}N$ 220.1121, found 220.1134.

3-Ethyl-2-phenylquinoline (**3y**).[14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), butyrophenone **4h** (99 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexanes) to afford the desired product **3y** as colourless liquid (90 mg, 58 %). Analytical data of **3y**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.13 (d, J = 8.5 Hz, 1H), 8.06 (s, 1H), 7.82 (d, J = 8 Hz, 1H), 7.68–7.65 (m, 1H), 7.56–7.53 (m, 3H), 7.50–7.42 (m, 3H), 2.90 (q, J = 7.5 Hz,2H), 1.20 (t, J = 7.5Hz, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 160.7, 146.4, 140.9, 135.3, 134.9, 129.3, 128.8, 128.7, 128.3, 128.1, 127.8, 127.0, 126.4, 26.0, 14.7 ppm. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd. for $C_{17}H_{16}N$ 234.1277, found 234.1283.

4-Isopropyl-1-methyl-1,2,3,4-tetrahydroacridine (**3ab**). Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), menthone (isomeric mixture) **4i** (104 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexanes) to afford the desired product **3ab** as a colourless liquid and as an isomeric mixture (ratio 2:1) (109 mg, 68 %). Analytical data of **3ab**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 7.99 (d, J = 8.5 Hz,1.5 H), 7.94 (s, 0.53H), 7.85 (s, 1H), 7.72 (t, J = 8.5 Hz, 1.5H), 7.60 (t, J = 7Hz, 1.54H), 7.43 (t, J = 7 Hz, 1.54H), 3.13–3.07 (m, 1.62H), 3.02–2.95 (m, 3.17H), 2.06–2.04 (m, 1.2H), 1.94–1.85 (m, 3.30H), 1.76–1.74 (m, 1.63H), 1.41 (d, J = 6.5 Hz, 1.6H), 1.37 (d, J = 7 Hz, 3.08H), 1.11 (d, J = 6.5 Hz, 3.04H), 1.07 (d, J = 7 Hz, 1.70H), 0.75 (d, J = 6.5 Hz, 3.00H), 0.67 (d, J = 6.5 Hz, 1.63H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 162.0, 161.7, 146.7, 146.4, 137.1, 136.8, 134.2, 132.4, 128.7, 128.5, 128.3, 128.2, 127.1, 126.9, 126.8, 125.4, 47.6, 47.0, 33.3, 32.9, 31.4, 31.3, 30.5, 28.6, 23.1, 21.8, 21.2, 21.0, 20.8, 18.7, 17.5, 17.0 ppm. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd. for $C_{17}H_{22}N$ 240.1747, found 240.1752.

(3aS,3bR,13S,13bS,15aR)-13,15a-Dimethyl-1-(6-methylheptan-2-yl)-2,3,3a,3b,4,5,5a,6,13,13a,13b,14,15,15a-tetradecahydro-1H-cyclopenta[5,6]naphtho[1,2-b]acridine (3ac). Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), cholestan-3-one **4j** (260 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3ac** as white solid (88 mg, 28 %). Analytical data of **3ac**: Mp: 183–186 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 7.97 (d, J = 8.5 Hz, 1H), 7.81 (s, 1H), 7.70 (d, J = 8 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 3.08 (dd, J_1 = 18 Hz, J_2 = 5.0 Hz, 1H), 2.99 (d, J = 16 Hz, 2H), 2.79 (dd, J_1 = 18 Hz, J_2 = 13 Hz, 1H), 2.61 (d, J = 16.0 Hz, 1H), 2.06 (d, J = 12 Hz, 1H), 1.88–1.75 (m, 3H), 1.67–1.62 (m, 5H), 1.54–1.47 (m, 2H), 1.40–1.34 (m, 4H), 1.28–1.21 (m, 2H), 1.15–1.04 (m, 6H), 1.02–0.98(m, 2H), 0.94 (d, J = 6 Hz, 3H), 0.87 (d, J = 6 Hz, 6H), 0.80 (s, 3H), 0.70 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 158.6, 146.7, 135.7, 130.3, 128.5, 128.3, 127.3, 126.8, 125.4, 56.5, 56.4, 53.6, 43.6, 42.5, 42.3, 40.0, 39.5, 37.5, 36.2, 35.8, 35.6, 35.3, 31.7, 28.8, 28.3, 28.2, 24.3, 23.9, 22.8, 22.6, 21.4, 18.7, 12.0, 11.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd. for $C_{17}H_{22}N$ 472.3938, found 472.3962.

4-Methyl-2-phenylquinoline (**3ad**).[14g] Following the general experimental procedure with 1-(2-aminophenyl)ethan-1-ol **1b** (110 mg, 80 mmol), acetophenone **2b** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3ad** as a pale yellow solid (110 mg, 75 %). Analytical data of **3ad**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 8.31–8.24 (m, 3H), 7.99 (d, J = 8.7 Hz, 1H), 7.80– 7.75 (m, 1H), 7.72 (s, 1H), 7.62–7.53 (m, 4H), 2.74 (s, 3H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ = 156.8, 147.9, 144.6, 139.6, 130.1, 129.1, 129.0, 128.6, 127.4, 127.0, 125.8, 123.4, 119.5, 18.8 ppm.

2,4-Diphenylquinoline (**3ae**).[14g] Following the general experimental procedure with (2-aminophenyl)(phenyl)methanol **1c** (159 mg, 0.80 mmol), acetophenone **2b** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3ae** as a pale yellow solid (135 mg, 72 %). Analytical data of **3ae**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 8.27 (d, J = 8.4 Hz, 1H), 8.22–8.20 (m, 2H), 7.92 (d, J = 8.7 Hz, 1H), 7.83 (s, 1H), 7.77–7.72 (m, 1H), 7.58–7.46 (m, 9H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ = 156.9, 149.2, 148.8, 139.6, 138.4, 130.1, 129.6, 129.4, 128.8, 128.6, 128.4, 127.6, 126.3, 125.8, 125.6, 119.4 ppm.

8-Methyl-2-phenylquinoline (**3af**).[14a] Following the general experimental procedure with (2-amino-3-methylphenyl)methanol **1d** (110 mg, 0.80 mmol), acetophenone **2b** (81 mg, 0.67 mmol), KOH (37.5 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10 % ethyl acetate in hexane) to afford the desired product **3af** as a pale yellow solid (126 mg, 86 %). Analytical data of **3af**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 8.29–8.26 (m, 2H), 8.19 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.59–7.56 (m, 1H), 7.54–7.51 (m, 2H), 7.49–7.45 (m, 1H) 7.44–7.39 (m, 1H), 2.92 (s, 3H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ = 155.5, 147.1, 139.8, 137.7, 137.0, 129.7, 129.2, 128.8, 127.5, 127.1, 126.0, 125.4, 118.2, 17.9 ppm.

2-Phenyl-4-(trifluoromethyl)quinoline (**3ag**). Following the general experimental procedure with 1-(2-aminophenyl)-2,2,2-trifluoroethan-1-ol **1e** (151 mg, 0.80 mmol), acetophenone **2b** (81 mg, 0.67 mmol), KOH (37.5 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (5 % ethyl acetate in hexane) to afford the desired product **3ag** as a white solid, 135 mg (74 %). Analytical data of **3ag**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ = 8.30 (d, J = 8 Hz, 1H), 8.23–8.20 (m, 3H), 8.17 (d, J = 8.5 Hz, 1H), 7.85 (t, J = 7.5 Hz, 1H), 7.69 (t, J = 8 Hz, 1H), 7.60–7.52 (m, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 156.7, 149.2, 138.5, 130.7, 130.4, 130.0 129.0, 127.9, 127.5, 123.9 (q, J = 2.5 Hz), 116.0(q, J = 1.3Hz) ppm. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd. for $C_{16}H_{11}F_3N$ 274.0838, found 274.0842.

(2-((1-Phenylethylidene)amino)phenyl)methanol (**5**). The imine intermediate was synthesized by treating o-aminobenzyl alcohol **1a** (200 mg, 1.62 mmol), acetophenone **2b** (194 mg, 1.62 mmol) in benzene (5.0 mL) at 100 °C during which water was removed by azeotropic distillation. After 12 h, the reaction mixture was cooled and the precipitate formed was filtered and purified by washing with benzene to afford the desired product **5** as a white solid (218 mg, 60 %). Analytical data of **5**: ^{1}H NMR (500 MHz, [D_6]Acetone,

TMS) δ = 8.22 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8. Hz, 2H), 7.62 (t, J = 7.5. Hz, 1H), 7.41 (t, J = 7.5. Hz, H), 6.97(d, J = 8 Hz, 2H), 3.76 (s, 2H), 1.92 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 161.2, 156.3, 148.3, 136.7, 131.8,129.5, 129.3, 128.7, 127.6, 127.0, 125.9, 118.1, 114.1, 54.8, 29.4 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd. for $C_{15}H_{15}NNaO$ 248.1046, found 248.1055.

(E)-3-(2-Aminophenyl)-1-phenylprop-2-en-1-one (**6**).[15] To a mixture of 2-nitrobenzaldehyde (2 g, 13.2 mmol) in ethanol (10 mL.) was added acetophenone **2b** (1.589 g, 13.24 mmol), NaOH (53 mg, 1.32 mmol) and stirred at room temperature for 2 h. After the complete consumption of 2-nitrobenzaldehyde, the reaction mixture was quenched with water. The crude product was filtered and recrystallized from ethanol. To a solution of the resulting (*E*)-2-nitrochalcone (1 mmol) in ethanol (15 mL) was added iron powder (183 mg, 3 mmol), followed by HCl (1.0 N, 1.3 mL.). The reaction mixture was vigorously stirred at 80 °C. After the complete consumption of (*E*)-2-nitrochalcone, the reaction mixture was cooled at room temperature and then extracted with ethyl acetate. The organic layer was washed with saturated Na_2CO_3 solution and brine, dried with Na_2SO_4, and concentrated to afford the desired product **6** as yellow solid, 116 mg (52 %). Analytical data of **6**: ^1H NMR (500 MHz, $CDCl_3$, TMS, δ = 8.04–8.02 (m, 2H), 8.00 (d, J = 15.5 Hz, 1H), 7.60–7.57 (m, 1H), 7.54–7.48(m, 4H), 7.23–7.20 (m, 1H), 6.81(t, J = 7.5 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 4.07 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 190.3, 146.2, 140.1, 138.4, 132.8, 131.7, 128.6, 128.5, 128.2, 121.8, 120.3, 119.0, 116.8, ppm. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd. for $C_{15}H_{14}NO$ 224.1070, found 224.1072.

Acknowledgements

The authors thank Dr. K. V. Radhakrishnan, Principal Scientist, CSIR-NIIST for the constructive discussions. RP, NPR and SAB thanks CSIR and VKO thanks UGC for research fellowship. J. J. and V. K. P. thanks the Director of CSIR-NIIST for the support and JJ thanks Alexander von Humboldt Foundation for an experienced research grant. The authors also thank Mrs. Saumini Mathew and Mrs. Viji S. of CSIR-NIIST for recording NMR and mass spectra, respectively.

Keywords: Annulation · Nitrogen heterocycles · Quinolines · Superbases · Synthetic methods

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Received: March 18, 2020

JOC The Journal of Organic Chemistry

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Inverse Electron Demand Diels Alder Reaction of Aza-*o*-Quinone Methides and Enaminones: Accessing 3-Aroyl Quinolines and Indeno[1,2-*b*]quinolinones

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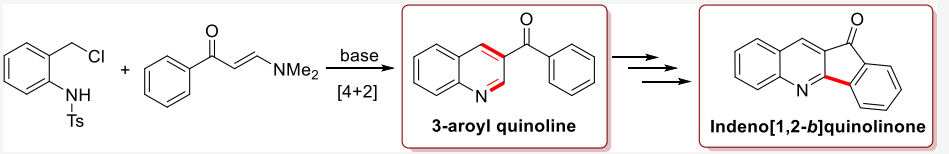


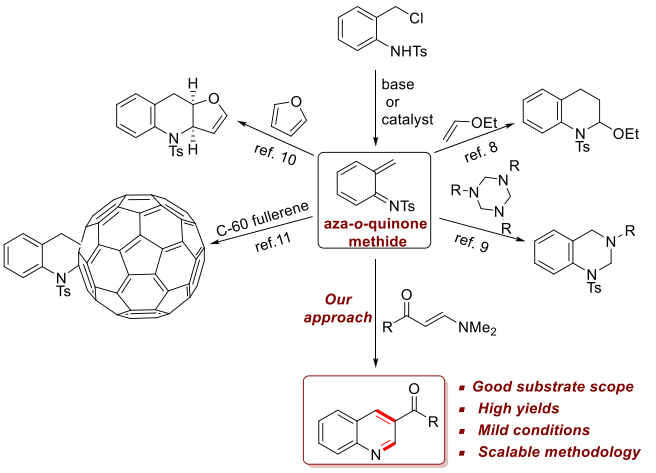
ABSTRACT: We have developed a Diels Alder cycloaddition route toward 3-aroyl quinolines from enaminones and in situ generated aza-*o*-quinone methides. The reaction was found to be general with a range of substituted enaminones and aza-*o*-quinone methides, and we could validate the applicability of the methodology in gram scale. We also demonstrated a one-pot strategy toward 3-acyl quinolines starting from the corresponding aliphatic ketones. Finally, we utilized the 3-aroyl quinolines for synthesizing indeno[1,2-*b*]quinolinones via a Pd-catalyzed dual C−H activation approach.

INTRODUCTION

Quinolines are a class of heterocycles which are of utmost importance in medicinal chemistry and industry.[1] Quinoline derivatives exhibit a wide range of biological activities such as antibacterial, antioxidant, anticancer, anti-inflammatory, antifungal, and antileishmanial.[2] The excellent antimalarial activity of these heterocycles have indeed resulted in the development of blockbuster drugs like pamaquine, chloroquine, tafenoquine, bulaquine, quinine, and mefloquine.[3] There is a plethora of classical reactions such as Gould−Jacob, Friedländer, Pfitzinger, Skraup, Doebner−von Miller, and Conrad−Limpach for accessing quinoline and its derivatives.[4] Apart from these methods, a number of transition metal catalyzed approaches and green protocols were also developed.[5] In this letter, we describe a new approach to synthesize 3-aroyl/acyl quinolines.

Organic chemists have exploited the reactivity of aza-*o*-quinone methides for the generation of different classes of *N*-heterocycles.[6] This reactive intermediate has been utilized as an aza-diene by several groups for the Diels Alder cycloaddition.[7] Steinhagen and Corey reported the use of *N*-(*o*-chloromethyl)arylamides for the first time as the precursor of aza-*o*-quinone methides (for [4 + 2] cycloaddition with electron rich olefins) after which it has become the most common approach for the generation of these reactive intermediates (Scheme 1).[8] An inverse-electron-demand [4 + 2]-cycloaddition of 1,3,5-triazinanes with aza-*o*-quinone methides toward tetrahydroquinazolines was reported by Liu and co-workers.[9] Another report on the use of aza-*o*-quinone methide as a diene came recently for the synthesis of furo[3,2-*b*]quinolines.[10] Utilization of [60] fullerene as dienophile in the [4 + 2]-cycloaddition with aza-*o*-quinone methide for the generation of fullerotetrahydroquinolines was reported by Wang and co-workers.[11] It is noteworthy to mention that in all of the above mentioned reports, the product obtained was tetrahydroquin(az)olines wherein we observed aromatization

Scheme 1. [4 + 2] Cycloaddition of Aza-*o*-Quinone Methides With Dienophiles



Received: June 9, 2022
Published: September 30, 2022

https://doi.org/10.1021/acs.joc.2c01361
J. Org. Chem. 2022, 87, 13708−13714

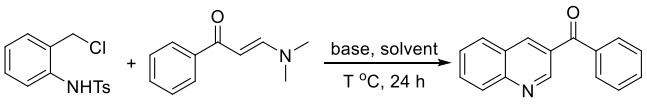
of the cycloadduct toward the formation of substituted quinolines.

Enaminones are a class of electron-rich olefins that were exploited to generate a wide variety of heterocycles such as pyrroles, pyrazoles, isoxazoles, imidazoles, oxadiazoles, aziridines, 1,2,4-triazoles, and so forth.[12] In 2016, an elegant report on the use of enaminones as a dipolarophile in the dipolar cycloaddition with azides toward 4-acyl-1*H*-1,2,3-triazoles came from the group of Dehaen.[13] Later, Wan and co-workers reported the synthesis of 3-acyl quinolines by an acid-mediated reaction of enaminones and anilines.[14a] At the same time, the same group reported the synthesis of 2,3-disubstituted quinolines via a three-component reaction involving enaminones, aldehydes, and anilines.[14b] In line with our interest in the chemistry of heterocycles[15] and based on the reactivity of aza-*o*-quinone methide and enaminone, we envisaged that these two would react to generate quinoline derivatives.

RESULTS AND DISCUSSION

To test our hypothesis, we chose to work with *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **1a** and 3-(dimethylamino)-1-phenylprop-2-en-1-one **2a** as substrates. Our first attempt to react both **1a** and **2a** in the presence of 2.0 equiv. of Na_2CO_3 at room temperature turned out to be futile (Table 1, entry 1). When the same reaction was kept at 50 °C, we could isolate the expected phenyl(quinolin-3-yl)methanone **3aa** in 78% yield after 24 h of reaction time (Table 1, entry 2).

Table 1. Optimization Studies for the Synthesis of 3aa[a]

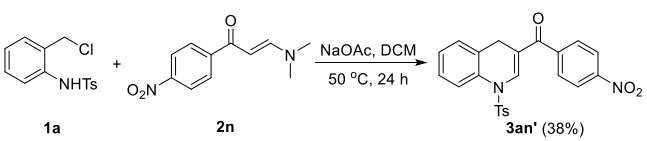


1a **2a** **3aa**

entry	base	solvent	temp.	yield of 3aa
1	Na_2CO_3	DCM	Rt	NR
2	Na_2CO_3	DCM	50 °C	78%
3	Na_2CO_3	ACN	50 °C	66%
4	Na_2CO_3	THF	50 °C	51%
5	Na_2CO_3	1,4-dioxane	50 °C	46%
6	Na_2CO_3	toluene	50 °C	53%
7	Na_2CO_3	1,2-DCE	50 °C	71%
8	Na_2CO_3	DMF	50 °C	trace
9	Na_2CO_3	$CHCl_3$	50 °C	73%
10	K_2CO_3	DCM	50 °C	68%
11	Cs_2CO_3	DCM	50 °C	76%
12	NaOAc	DCM	50 °C	81%
13	KOH	DCM	50 °C	56%
14	$NaHCO_3$	DCM	50 °C	56%
15[b]	NaOAc	DCM	50 °C	84%
16[c]	NaOAc	DCM	50 °C	89%

[a]Reaction conditions: **1a** (1.0 equiv., 0.17 mmol), **2a** (1.0 equiv., 0.17 mmol), base (2.0 equiv), solvent (1.0 mL), 24 h, isolated yields. [b]**1a** (1.2 equiv.). [c]**1a** (1.3 equiv); NR—No reaction.

Scheme 2. Base-Mediated Reaction of 1a with 2n



1a **2n** **3an'** (38%)

Among the different solvents such as DCM, acetonitrile, THF, 1,4-dioxane, toluene, 1,2-DCE, DMF, and $CHCl_3$, the best medium for the reaction was found to be DCM (Table 1, entries 2−9). Next, a base screen was carried out among Na_2CO_3, K_2CO_3, Cs_2CO_3, NaOAc, KOH, and $NaHCO_3$ (Table 1, entries 2, 10−14). The reaction mediated by NaOAc was found to be the best affording **3aa** in 81% yield. We observed an increase in yield by increasing the amount of *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **1a** (Table 1, entries 15−16). In this line, we found that the reaction with 1.3 equiv. of **1a** resulted in a yield of 89% for **3aa**. Finally, the reaction does not proceed in the absence of a base.

We, then concentrated our efforts toward studying the generality of 3-acyl quinoline synthesis under the optimized conditions (Table 2). We first tried the gram-scale synthesis of **3aa** starting from 1 gram of **1a** which resulted in a yield of 84%. The reactivity of different enaminones **2b−2f** derived from 4-substituted acetophenones (substituents were F, Br, Cl, OMe, and Me) were then tested. From these reactions, we could isolate the corresponding functionalized 3-acyl quinolines **3ab−3af** in good to excellent yields. We then checked the reactivity of enaminones **2g−2h** derived from 2-substituted acetophenones (substituents were Cl and OMe), and the respective reactions yielded the products **3ag** and **3ah** in 84 and 87% yields, respectively. Enaminones **2i** and **2j** synthesized from dimethoxy and trimethoxy acetophenones also underwent the base-mediated tandem Diels Alder reaction-aromatization affording the products **3ai** and **3aj** in excellent yields. Naphthyl quinolinyl ketone **3ak** was obtained in 94% yield from the reaction between 3-(dimethylamino)-1-(naphthalen-2-yl)prop-2-en-1-one **2k** and aza-*o*-quinone methide derived from **1a**. By this methodology, we could also synthesize 1-(naphthalen-2-yl)pentan-1-one **3al** in 81% yield starting from 2-hexanone-derived enaminone **2l**. Interestingly, our attempt to synthesize 1,3-phenylenebis(quinolin-3-ylmethanone) **3am** was successful starting from the corresponding di-enaminone **2m**. Finally, we could introduce Cl- and I-substituents to the quinoline ring in products **3ba** (89%) and **3ca** (86%) by starting from the appropriately substituted **1b** and **1c**.

During our investigations on the generality of this tandem quinoline synthesis, we treated *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **1a** with 3-(dimethylamino)-1-(4-nitrophenyl)prop-2-en-1-one **2n** under optimized conditions and found that **3an'** was forming exclusively (38%) which we believe is the intermediate of this tandem transformation (Scheme 2).

We then optimized the reaction conditions including an oxidizing agent in order to obtain the 3-aroyl quinoline derivative exclusively.[16] All substrates that failed to afford 3-aroyl quinolines under the conditions depicted in Table 1 were allowed to react under the newly optimized condition. We started with the reaction of **1a** and **2n** from which the corresponding 3-aroyl quinoline derivative **3an** was isolated in 66% yield (Table 3). Enaminones derived from acyl ketones of tricyclic aromatic hydrocarbons such as anthracene and phenanthrene **2n−2q** were then treated with **1a,** and these reactions also furnished the respective products **3ap−3ar** in good yields. Our efforts to check the reactivity of different enaminones **2r−2v** derived from heterocyclic acyl ketones also were successful, and the corresponding bis-heterocyclic ketones **3as−3aw** were isolated in excellent yields. With this methodology, we could introduce heterocycles such as furan,

https://doi.org/10.1021/acs.joc.2c01361
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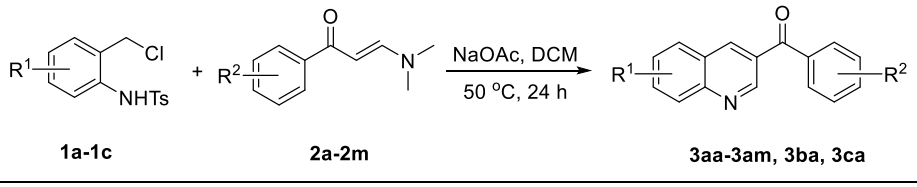
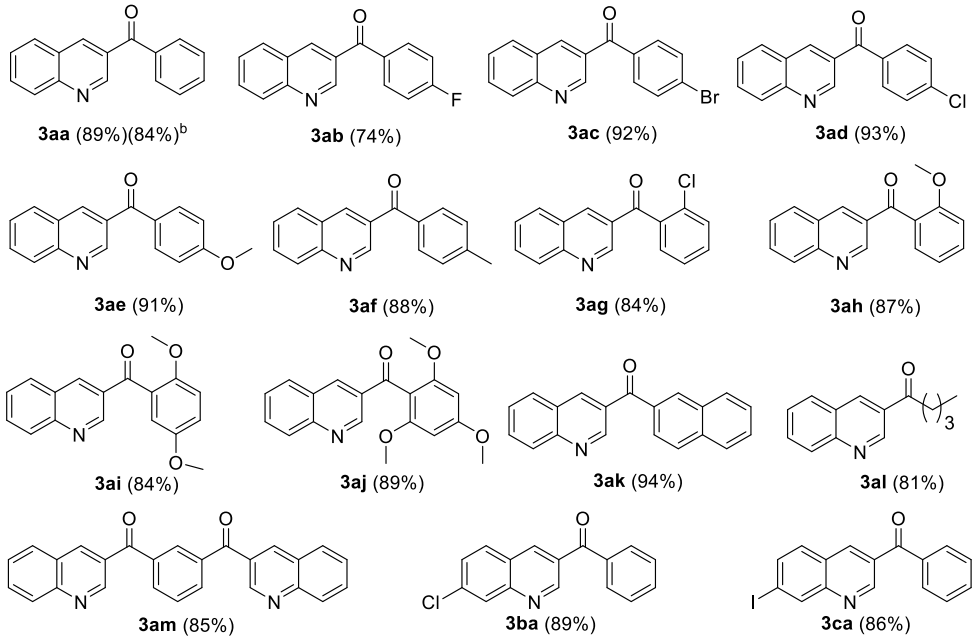
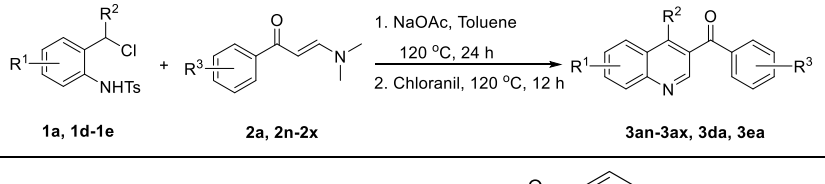
Table 2. Generality of 3-Acyl Quinoline synthesis[a]

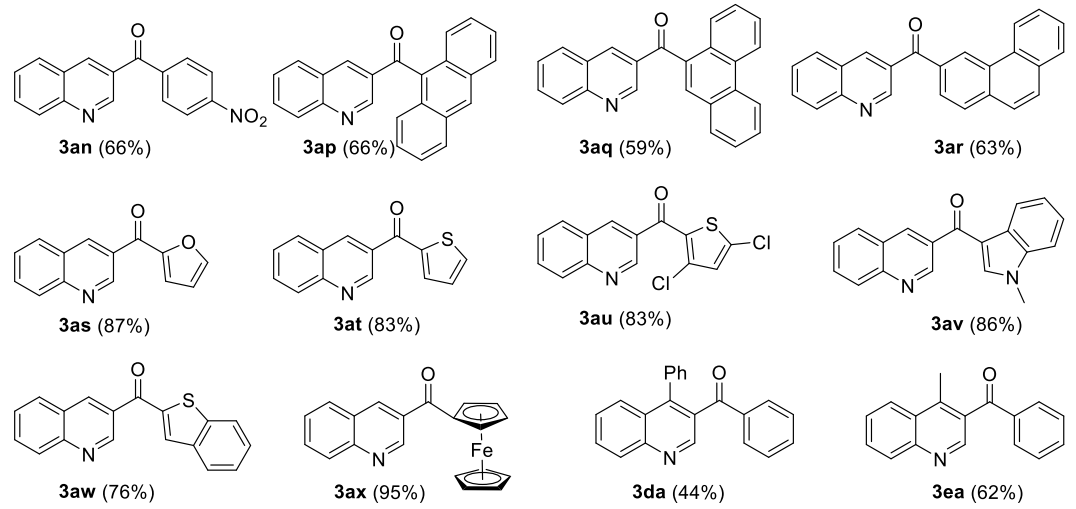




[a]Reaction conditions: **1a** (1.3 equiv., 0.44 mmol), **2a** (1.0 equiv., 0.34 mmol), NaOAc (2.0 equiv), DCM (2.0 mL), 50 °C, 24 h, isolated yields. [b]From 1 gram of **1a**.

Table 3. Generality of 3-Acyl Quinoline synthesis[a]





[a]Reaction conditions: (i) **1a** (1.3 equiv., 0.44 mmol), **2a** (1.0 equiv., 0.34 mmol), NaOAc (2.0 equiv), toluene (2.0 mL), 120 °C, 24 h; (ii) oxidant (2.0 equiv), 120 °C, 12 h, isolated yields.

https://doi.org/10.1021/acs.joc.2c01361
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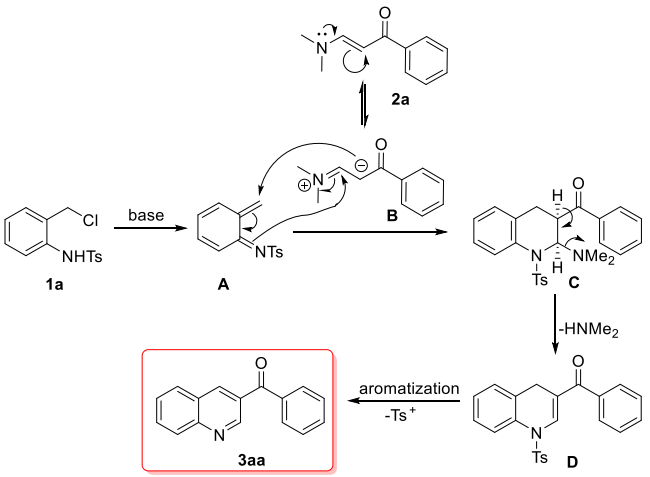
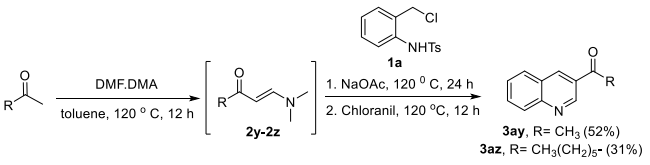
Scheme 3. Proposed Mechanism for the Synthesis of 3-Aroyl Quinoline From Aza-o-Quinone Methide and Enaminone

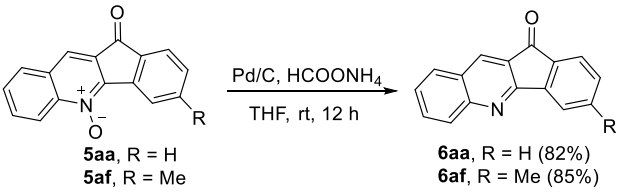


Scheme 4. One-Pot Reaction for the Synthesis of 3-Substituted Quinolines Starting From Ketones



thiophene, indole, and benzothiophene as heteroaryl functionalities. Enaminone **2x** derived from acetyl ferrocene also underwent the one-pot quinoline synthesis with **1a** affording the product **3ax** in 95% yield. Finally, we could introduce phenyl (**3da**, 44%) and methyl (**3ea**, 62%) groups to the fourth position of the quinoline ring by starting from the corresponding aza-*o*-quinone methide precursors **1c** and **1d**.

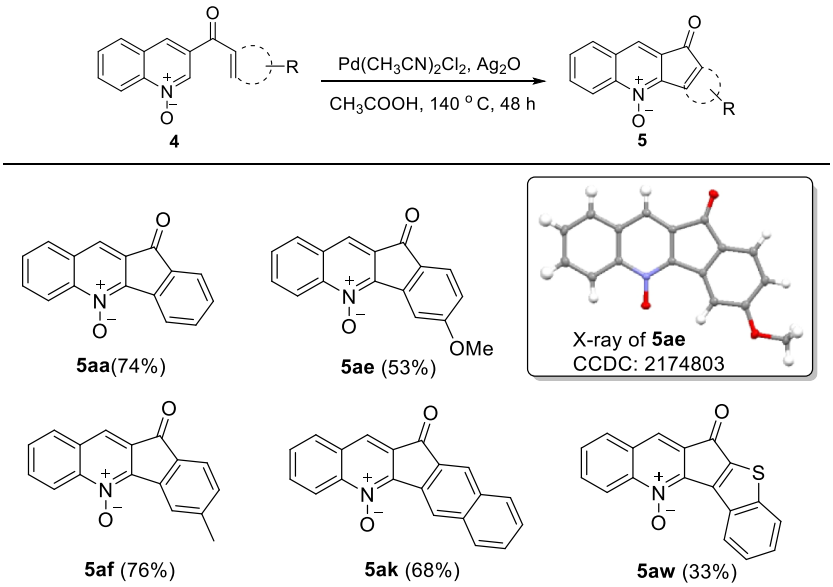
Scheme 5. Reduction of indeno[1,2-*b*]Quinolinone-*N*-Oxides to indeno[1,2-*b*]Quinolinones



In Scheme 3, we propose a mechanism for the 3-aroyl quinoline synthesis from aza-*o*-quinone methide and enaminone based on literature reports[7,12,13] and our own observations. The first step of the mechanism starts with the base-mediated generation of aza-*o*-quinone methide **A** from **1a**. Enaminone **2a** tautomerizes to **B** from which the anionic center attacks the terminal carbon of the methide functionality in **A** leading to the formation of the cycloadduct **C** after ring closure from the *N*-end. A quick elimination of $HNMe_2$ from intermediate **C** affords **D**, the formation of which was proved by the isolation of **3an′** as depicted in Scheme 2. Finally, a base/oxidizing agent-mediated aromatization affords 3-aroyl quinoline. The oxidation of intermediate **D** is promoted by chloranil as it gets reduced by the attack of the hydride from the methylene part of **D**.

We then concentrated on devising a one-pot process to synthesize 3-substituted quinolines starting from the ketone, rather than the enaminone (Scheme 4). For this, we started by treating acetone **2y′** and 2-octanone **2z′** with DMF.DMA in refluxing toluene to furnish the corresponding enaminones **2y** and **2z**. Upon completion of enaminone formation, to the same pot, **1a** was added along with the base. After 24 h, chloranil was added and refluxed for 12 more hours after which the corresponding substituted quinolines **3ay** and **3az** were isolated in 52 and 31% overall yields, respectively. These experiments were then repeated after isolating the enaminones **2y** and **2z** which furnished **3ay** and **3az** in 71 and 62% yields, respectively.

Table 4. Generality of Pd-Catalyzed Dual C−H activation[a]



[a]Reaction conditions: **4** (0.10 mmol), $Pd(CH_3CN)_2Cl_2$ (20 mol %), Ag_2O (1.5 equiv), AcOH (1.0 mL), 140 °C, 48 h; isolated yields.

https://doi.org/10.1021/acs.joc.2c01361
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Due to our continued interest in devising methodologies toward heteroarenes[17] and inspired from the report on Pd-catalyzed dual C−H activation of 3-phenoxypyridine-1-oxides,[18] we planned to utilize 3-aroyl quinolines to synthesize rarely known indeno[1,2-*b*]quinoline-11-ones.[19] We started with the *N*-oxidation of 3-aroyl quinolines with mCPBA, and the obtained quinolinyl-*N*-oxides were directly taken for the Pd-catalyzed dual C−H activation after optimization[16] (Table 4).

Quinolinyl-*N*-oxides **4** upon treatment with Pd-$(CH_3CN)_2Cl_2$ (20 mol %) and Ag_2O (1.5 equiv.) in HOAc at 140 °C for 48 h afforded the corresponding indeno[1,2-*b*]quinolinone-*N*-oxides in good yields. We could also confirm the structure of the heteroacene with the single-crystal X-ray of **5ae**. It is noteworthy to mention that we could extend the method for the synthesis of five-ring fused systems **5ak** and **5aw** by starting from appropriately functionalized quinolinyl-*N*-oxides.

We then subjected 11-oxo-indeno[1,2-*b*]quinoline-*N*-oxide **5aa** and **5af** to reduction with $HCOONH_4$ in the presence of Pd/C in THF at rt to synthesize the corresponding indeno[1,2-*b*]quinolinones **6aa** and **6af** in good yields (Scheme 5).

CONCLUSIONS

To conclude, we have developed a methodology for the synthesis of 3-aroyl/acyl quinolines by the inverse electron demand [4 + 2] cycloaddition of in situ generated aza-*o*-quinone methides and enaminones. The reaction was found to be general with a range of enaminones and aza-*o*-quinone methides affording the corresponding quinoline derivatives in good to excellent yields. We have proposed a mechanism which involves two stages; [4 + 2] cycloaddition and aromatization. The applicability of the developed methodology in the gram-scale synthesis of 3-aroyl quinolines was validated. We have also demonstrated a one-pot method starting from ketones for the generation of enaminones and have utilized it for the synthesis of alkyl quinolinyl ketones. Last, we have employed the synthesized 3-aroyl quinolines for accessing indeno[1,2-*b*]quinolinones via a Pd-catalyzed dual C−H activation route.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01361.

Synthetic procedures, analytical details, NMR spectra for all compounds, and X-ray of **5e** (PDF)

Accession Codes

CCDC 2174803 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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Author Contributions

The manuscript was written through the contributions of all authors.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

R.P. thanks the CSIR for research fellowship. J.J. thanks the AICTE [GAP-161939] and CSIR (OLP-162539 & MLP-064), Government of India, for funding. The authors thank Dr. Sunil Varughese for solving the single-crystal X-ray. The authors also thank Saumini Mathew and Viji V.S. of CSIR-NIIST for recording NMR and mass spectra, respectively.

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Accepted Article

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To be cited as: *Eur. J. Org. Chem.* **2024**, e202400151

Link to VoR: https://doi.org/10.1002/ejoc.202400151

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10.1002/ejoc.202400151

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Investigations on Superbase Mediated Reactivity of *N*-Tosylhydrazones with Aza-*ortho*-Quinone Methide Precursors

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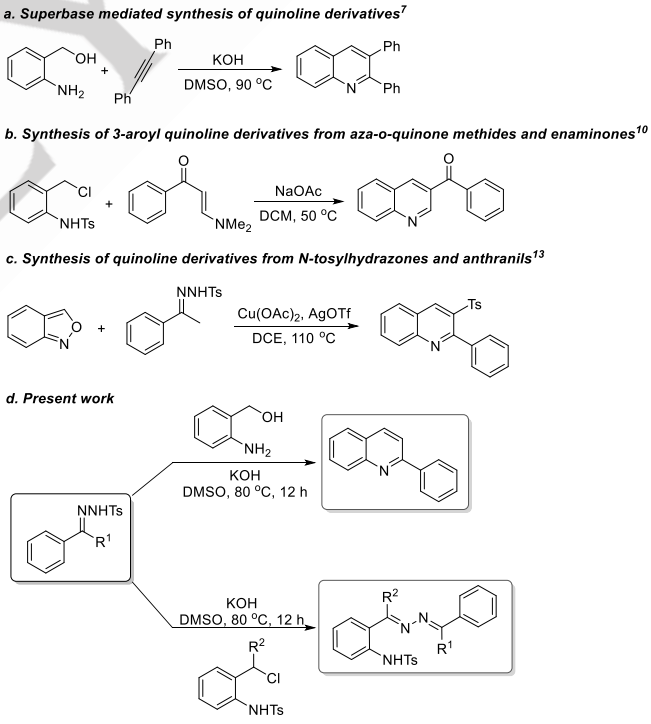
Supporting information for this article is given via a link at the end of the document.

Abstract: We have encountered a superbase-mediated chemoselective reaction of *N*-tosylhydrazones with aza-*ortho*-quinone methide precursors. When tosylhydrazone was treated with *ortho*-aminobenzyl alcohol in super basic conditions (KOH+DMSO), we observed the formation of 2-substituted quinoline. The reaction was found to be general, and by this method, mono-, di- and tri-substituted quinolines could be made. We could prove experimentally and theoretically that the reaction proceeded *via* the formation of an azine from the basic decomposition of *N*-tosylhydrazones. Finally, the reaction of tosylhydrazone with *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide (aza-*ortho*-quinone methide precursor) under super basic conditions afforded hydrazine substituted sulfonamides.

Introduction

N-Tosylhydrazones have found a plethora of applications in synthetic organic chemistry as a source of diazo compounds, as a reagent in metal-free reactions, and as a coupling partner in metal-catalysed reactions.[1] *N*-Tosylhydrazones are stable organic compounds that can be easily synthesized and purified, and the wide reactivity pattern exhibited by these was utilized for carbon-carbon and carbon-heteroatom bond formation towards synthesizing acyclic, carbocyclic and heterocyclic compounds.[2] Organic chemists have utilized these nitrogenated compounds for generating alkenes (Bamford-Stevens & Shapiro), cyclopropanes, pyrazoles, triazoles, indazoles, benzofurans, indoles, pyridazines, thiadiazoles, phenanthridines to name a few.[1-2] In this report, we disclose a chemoselective transformation of *N*-tosylhydrazones towards functionalized quinolines and hydrazine-substituted sulfonamides.

Over the years, several methods were developed to generate aza-*ortho*-quinone methides and these reactive intermediates were utilized for accessing diverse families of *N*-heterocycles.[3-4] *Ortho*-aminobenzyl alcohol has been utilized to generate different *N*-heterocycles, especially quinolines, *via* metal-catalysed[5] and metal-free methodologies.[6] Verma and co-workers have shown that aza-*ortho*-quinone methides can be generated from *ortho*-aminobenzyl alcohol under super basic conditions, and they utilized these intermediates to generate substituted quinolines by reacting with alkynes (Scheme 1a).[7] Since the first report by Steinhagen and Corey on the generation of aza-*ortho*-quinone methides from *N*-(*o*-chloromethyl)arylamides,[8] many groups have made use of this intermediate as a 4π component for the [4+2] cycloaddition towards *N*-heterocycles.[9] Recently, we found out that the aza-*ortho*-quinone methides generated from *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide easily reacted with enaminones to furnish 3-aroyl quinolines (Scheme 1b).[10]



Scheme 1. Synthesis of quinoline derivatives by different synthetic routes.

Different organic transformations such as styrylation, chalcogenation, cross-coupling, heterocyclic synthesis, inter- and intramolecular hydroaminations were effected in superbasic medium by Trofimov and others.[11-12] In most of the cases mentioned previously, a combination of KOH and DMSO was

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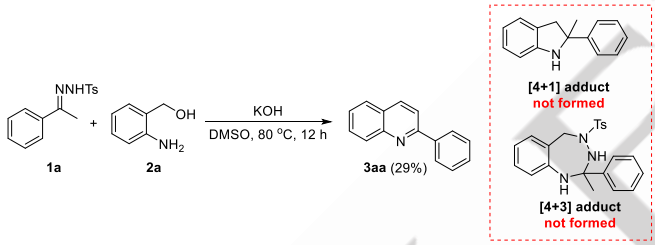
used to create the superbasic medium. From *N*-tosylhydrazones, we could only find one report by Wang and Ji where the reaction of the former with anthranils furnished 2-aryl-3-sulfonyl substituted quinoline derivatives under Cu(II)/Ag(I) catalysis (Scheme 1c).[13] In light of the reports on the use of aza-*ortho*-quinone methides and *N*-tosylhydrazones for the generation of *N*-heterocycles and due to our continued interest in synthetic methodologies towards heterocycles,[14] we chose to study the reactivity difference of aza-*ortho*-quinone methide precursors such as *ortho*-aminobenzyl alcohol and *N*-(*o*-chloromethyl)arylamides with *N*-tosylhydrazones (Scheme 1d).

Results and Discussion

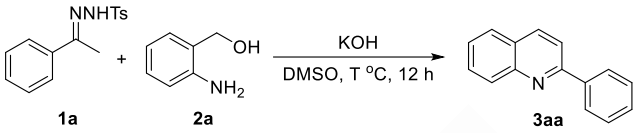
We planned to initiate the investigations on chemoselectivity with *N*-tosylhydrazone and *ortho* aminobenzyl alcohol under super basic conditions, and by following literature precedents,[7,15] we were expecting either [4+1] or [4+3] addition products from the aza-*ortho*-quinone methide and the hydrazine (Scheme 2). *N*-tosylhydrazone **1a** (1.0 equiv.) derived from acetophenone and *ortho*-aminobenzyl alcohol **2a** (1.0 equiv.) were taken as test substrates, and these were treated in the presence of KOH (1.0 equiv.) in DMSO at 80 °C for 12 h. In contrast to our expectation, we isolated 2-phenyl quinoline **3aa** from the reaction mixture in 29% yield, and the product's structure was characterized by various spectroscopic techniques and compared with the literature.



Scheme 2. Reaction of *N*-tosylhydrazone and *ortho*-aminobenzyl alcohol under super basic conditions.

The reaction was then optimized with **1a** and **2a** as substrates, and first, the amount of base was increased to 2 and 3 equivalents (Table 1, entries 1-3), and it was found that for the present annulation, 2.0 equivalents of the base was optimal. Then, the investigations by increasing the amounts of *ortho*-aminobenzyl alcohol **2a** were carried out and the reaction with 1.2 equivalents of **2a** furnished 2-phenyl quinoline **3aa** in 79% yield. Next, the effect of temperature on the reaction outcome was studied, and it was found that both increasing (100 °C) and decreasing (60 °C) the reaction temperature had a negative effect on the yield. Finally, the optimized condition was a combination of 1.0 equivalents of **1a**, 1.2 equivalents of **2a**, 2.0 equivalents of KOH in DMSO at 80 °C for 12 h.

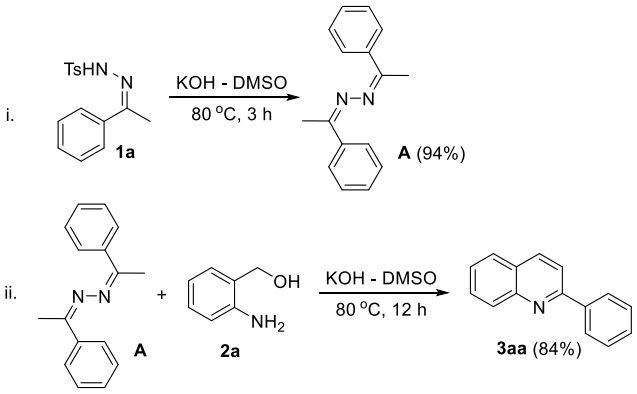
Table 1. Optimization studies.



Entry	**2a** (equiv.)	KOH (equiv.)	T °C	Yield of **3aa** (%)[a]
1	1.0	1.0	80	29
2	1.0	2.0	80	48
3	1.0	3.0	80	49
4	1.1	2.0	80	65
5	**1.2**	**2.0**	**80**	**79**
6	1.3	2.0	80	78
7	1.2	2.0	60	66
8	1.2	2.0	100	70

Reaction conditions: **1a** (1.0 equiv.), 0.17 mmol), **2a**, KOH, DMSO (1.0 mL), 60-100 °C, 12 h.

This unforeseen observation made us examine the mechanism and perform some control experiments. First, we treated *N*-tosylhydrazone **1a** with KOH in DMSO at 80 °C, and this reaction resulted in the formation of the azine **A** in 94% yield, as shown in scheme 3(i). The formation of azines from *N*-tosylhydrazones under basic conditions was reported earlier.[16] By considering the azine **A** as the stable intermediate formed from *N*-tosylhydrazone **1a**, we treated the former with twice the amount of *ortho*-aminobenzyl alcohol **2a**, and this reaction resulted in the formation of 2-phenyl quinoline **3aa** in 84% yield (Scheme 3(ii)). The next intermediate, i.e. aza-*ortho*-quinone methides **C**, the generation of which was proven by Verma and co-workers from *ortho*-aminobenzyl alcohol under super basic conditions.[7]



Scheme 3. Control experiments.

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To investigate the mechanism of the reaction, density functional theory calculations have been performed using Gaussian 16 suite of programs.[17] All the calculation were carried out at the M06-2X/6-311G(dp)[18] level and the solvent effects (DMSO) were incorporated using SMD model.[19] From the literature and control experiments, we believe that the azine **A** formed from *N*-tosylhydrazone **1a** will undergo tautomerism to form the intermediate **B**, which will react with aza-*ortho*-quinone methide **C**[7] to form 2-phenyl-1,4-dihydroquinoline **D**, which subsequently undergoes autooxidation yielding **3aa**.[7] The overall reaction is exothermic by 99 kcal/mol, which provides the driving force for the reaction.

The reaction initiates with the hetero Diels-Alder reaction between **B** and **C**. Two possible cycloaddition pathways, *viz*., the addition of the carbon end of the enamine **B** to the methide end of **C**, followed by the cyclization from the N-end of **C** to the quaternary carbon of **B**, and vice versa, can be observed, and the calculated free energy profile diagrams for both reaction pathways are depicted in Figure 1. Because of the lower activation barrier (16.55 kcal/mol) and higher exothemcity (43.92 kcal/mol), **INT1a**—which is produced via the former reaction pathway—is favored over **INT1b.**

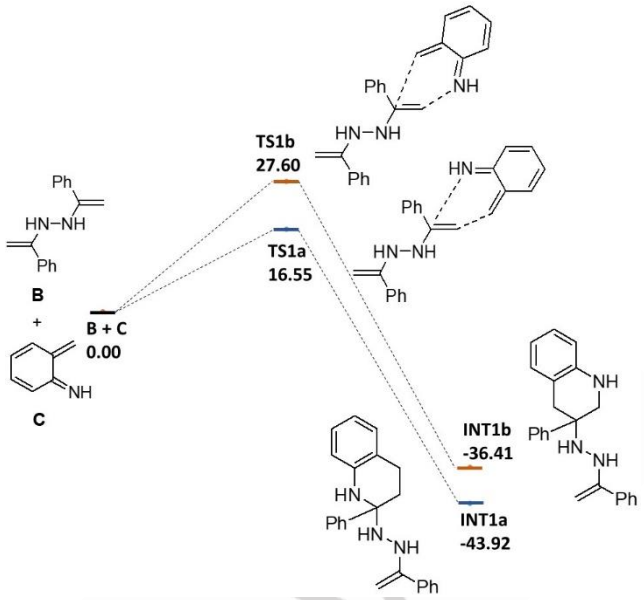

Figure 1. Free energy profile for the two possible hetero Diels-Alder reaction pathways for **B** and **C**. Relative free energy values are in kcal/mol.

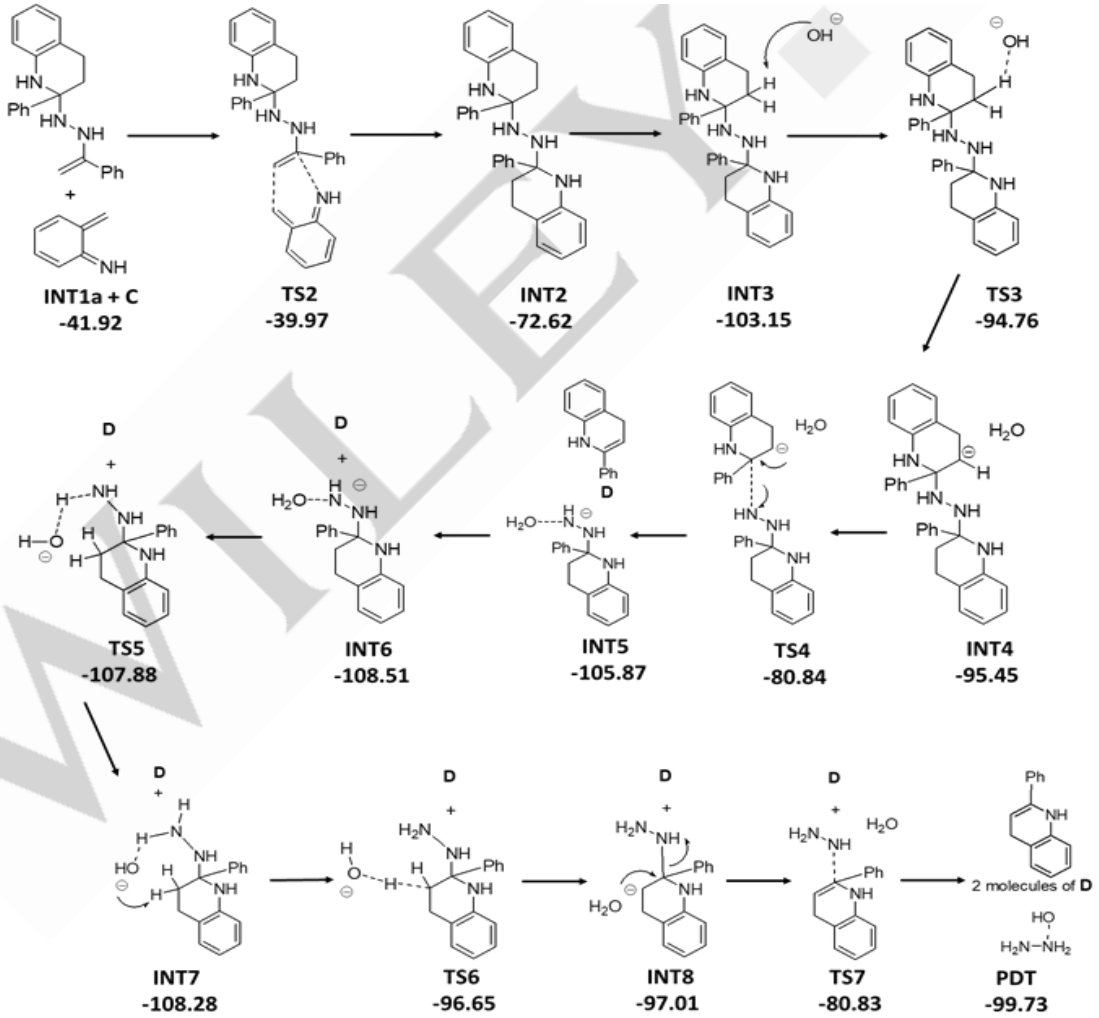

Figure 2. Summary of the structural changes involved in the formation of **D** from **INT1a**. Relative free energy values in kcal/mol.

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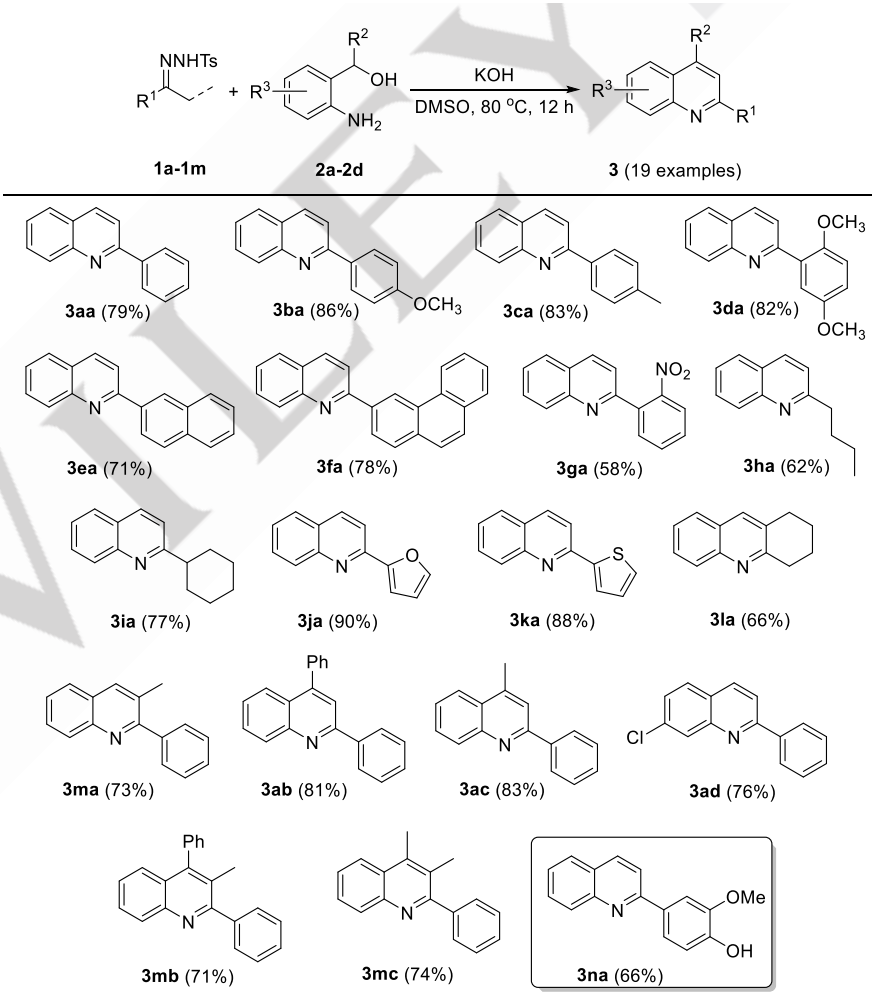
The intermediates and transition states involved in the formation of 2-phenyl-1,4-dihydroquinoline **D** from the intermediate **INT1a** are presented in Figure 2. (All the transition states are depicted in Figure S1 in the Supporting Information). The hetero Diels-Alder reaction of a second molecule of **C** with **INT1a** occurs *via* the transition state **TS2** (similar to that of **TS1a**) to form the second intermediate **INT2**. The activation barrier for the cycloaddition between **INT1a** and **C** is 1.95 kcal/mol and the formation of **INT2** is exothermic by 30.7 kcal/mol. (A transition state for the simultaneous addition of two molecules of **C** with **B** could not be located.). The abstraction of a $–CH_2$ proton in **INT3** by a hydroxide ion *via* the transition state **TS3** leads to **INT4** and the conversion from **INT2** to **INT4** is exothermic by 22.83 kcal/mol. **INT4** represents a carbanionic structure stabilized by nearby H_2O. The shifting of the negative charge to the C-C bond leads to the dissociation of the C-N bond in the transition state **TS4**, which produces one molecule of **D** (represented by **INT5**). We could detect the presence of intermediate **D** from mass spectroscopy as a $(M+H)^+$ peak at 237.1395. The activation barrier for the C-N bond dissociation is 14.61 kcal/mol. The C-N bond breaking shifts the negative charge to the terminal nitrogen (-NH-), which leads to the abstraction of a proton from H_2O to form $–NH_2$. The transition state **TS5** represents the proton abstraction by -NH- from H_2O, which generates a hydroxide ion (**INT7**). The activation barrier for the proton abstraction is only 0.63 kcal/mol (the relative free energy of **TS5** is -107.88 kcal/mol), and the relative energy of -108.28 kcal/mol for **INT7** indicates a shallow minimum in the potential energy surface. The hydroxide ion in **INT7** abstracts a $–CH_2$ proton and forms **INT8** *via* the transition state **TS6**. The transformation of **INT7** to **INT8** is endothermic by 11.27 kcal/mol, and the activation barrier for the proton abstraction is 11.63 kcal/mol. The C-N bond in **INT8** dissociates in the transition state **TS7** as a result of the shifting of the negative charge to the C-C bond and releases the second molecule of **D**. The final step is exothermic by 2.72 kcal/mol and the activation barrier is 16.18 kcal/mol. The high exothermicity and the low activation barriers (> 18 kcal/mol) well demonstrate the formation of **D** by the reaction of **B** and **C**. In a synthetic and mechanistic point of view, the reaction of **1a** under super basic conditions is interesting as the intermediate azine **A** could be judicioulsy utilized for generating heterocyclic or carbocyclic motifs with appropriate reaction partners.

An alternate pathway towards **3aa** from **1a** and **2a** can be *via* the formation of acetophenone. Under super basic conditions, the slow hydrolysis of *N*-tosylhydrazone **1a** can give rise to

Table 2. The generality of the reaction between *N*-tosylhydrazone and *ortho*-aminobenzyl alcohol under super basic conditions.



Reaction conditions: **1a** (1.0 equiv., 0.35 mmol), **2a** (1.2 equiv.), KOH (2.0 equiv.), DMSO (2.0 mL), 80 °C, 12 h.

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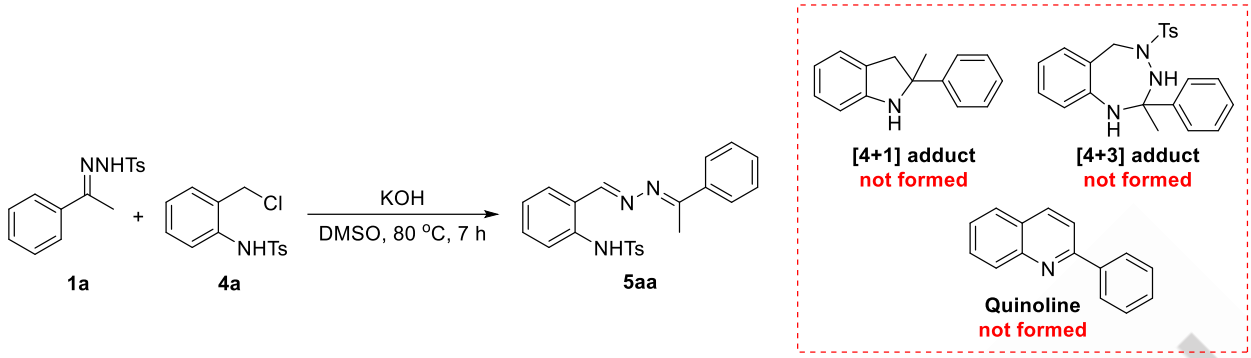


Scheme 4. Reaction of *N*-tosylhydrazone and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide under super basic conditions.

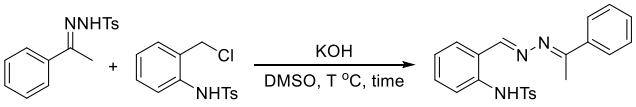
acetophenone which can react with *ortho*-aminobenzyl alcohol **2a** to afford 2-phenyl quinoline **3aa** in the way that we have reported earlier.[6g]

We then planned to study the generality of this reaction by varying *N*-tosylhydrazones and *ortho*-aminobenzyl alcohols. Under the optimized conditions, *N*-tosylhydrazone derived from acetophenones bearing electron-donating substituents on the aryl ring reacted well with *ortho*-aminobenzyl alcohol **2a**, affording the products **3ba**, **3ca**, and **3da** in excellent yields. 2-Naphthyl quinoline **3ea** and 2-phenanthrenyl quinoline **3fa** were also formed in good yields from the reactions of corresponding *N*-tosylhydrazones and *ortho*-aminobenzyl alcohol **2a**. The reaction yield decreased with acetophenones bearing electron-withdrawing substituents on the aryl ring, and thus **3ga** was obtained in 58% yield. *N*-tosylhydrazone derived from 2-hexanone and acetyl cyclohexane also participated in the reaction with **2a** under super medium, affording the products 2-butylquinoline **3ha** and 2-cyclohexylquinoline **3ia** in good yields. By this methodology, we could synthesize 2-heteroayl quinolines such as 2-(furan-2-yl)quinoline **3ja** and 2-(thiophen-2-yl)quinoline **3ka** in excellent yields. 1,2,3,4-tetrahydroacridine **3la** was synthesized in good yield by starting from the *N*-tosylhydrazone derived from cyclohexanone and *ortho*-aminobenzyl alcohol **2a**. The present reaction was extended from *N*-tosylhydrazone derived from acetophenone to the one derived from propiophenone, whereby we could synthesize 3-methyl-2-phenylquinoline **3ma** in 73% yield. By using *ortho*-aminobenzyl alcohols **2b**-**2d** with different substituents on the methylene unit and aryl ring, we could synthesize 2,4-diphenylquinoline **3ab**, 4-methyl-2-phenylquinoline **3ac**, and 7-chloro-2-phenylquinoline **3ad** in good to excellent yields. We could also synthesize 2,3,4-trisubstituted quinolines **3mb** and **3mc** by starting from appropriately functionalized *N*-tosylhydrazone and *ortho*-aminobenzyl alcohol. Finally, we utilized the *N*-tosylhydrazone derived from the natural product vanillin to synthesize **3na** in 66% yield.

Next, we planned to study the reactivity of aza-*ortho*-quinone methides generated from *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide with *N*-tosylhydrazones under super basic conditions. The initial reaction was set up with *N*-tosylhydrazone **1a** (1.0 equiv.) derived from acetophenone and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **4a** in the presence of KOH and in DMSO at 80 °C (Scheme 4). Contrary to our expectations of [4+1] or [4+3] addition products or quinoline derivatives as shown before, [7,15] we observed the formation of an azine sulfonamide **5aa** in 49% yield. The structure of the compound was characterized by various spectroscopic techniques and then confirmed by single-crystal X-ray analysis (see supporting information). From the literature, we found that the synthesis of azine sulfonamide was reported by Li and co-workers, where they describe a Rh-catalyzed C-H amidation of azines with sulfonamides.[20]

As sulfonamides are considered privileged scaffolds in medicinal chemistry mainly due to sulpha drugs,[21] we thought of studying the reaction in detail. By taking *N*-tosylhydrazone **1a** and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **4a** as substrates for optimisation, we tried a few reactions by changing the time and equivalents of **4a**. Increasing the reaction time from 7 h to 12 h did not influence the yield of the azine sulfonamide (Table 3, entries 1-2). Then, we tried increasing the equivalents of **4a** from 1.0 to 2.0, and the best yield for **5aa** of 68% was obtained with 1.5 equivalents of **4a**. The optimized condition for the azine sulfonamide synthesis was found to be a combination of 1.0 equivalents of **1a**, 1.5 equivalents of **4a**, 2.0 equivalents of KOH in DMSO at 80 °C for 12 h.

Table 3. Optimization studies.



Entry	4a (equiv.)	Time (h)	Yield of 5aa (%)[a]
1	1.0	7	49
2	1.0	12	50
3	1.2	12	54
4	1.5	12	68
5	2.0	12	68

Reaction conditions: **1a** (1.0 equiv., 0.17 mmol), **4a**, KOH (2.0 equiv.), DMSO (1.0 mL), 80 °C, time.

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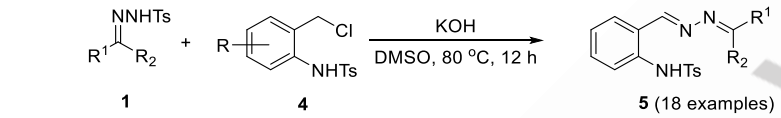
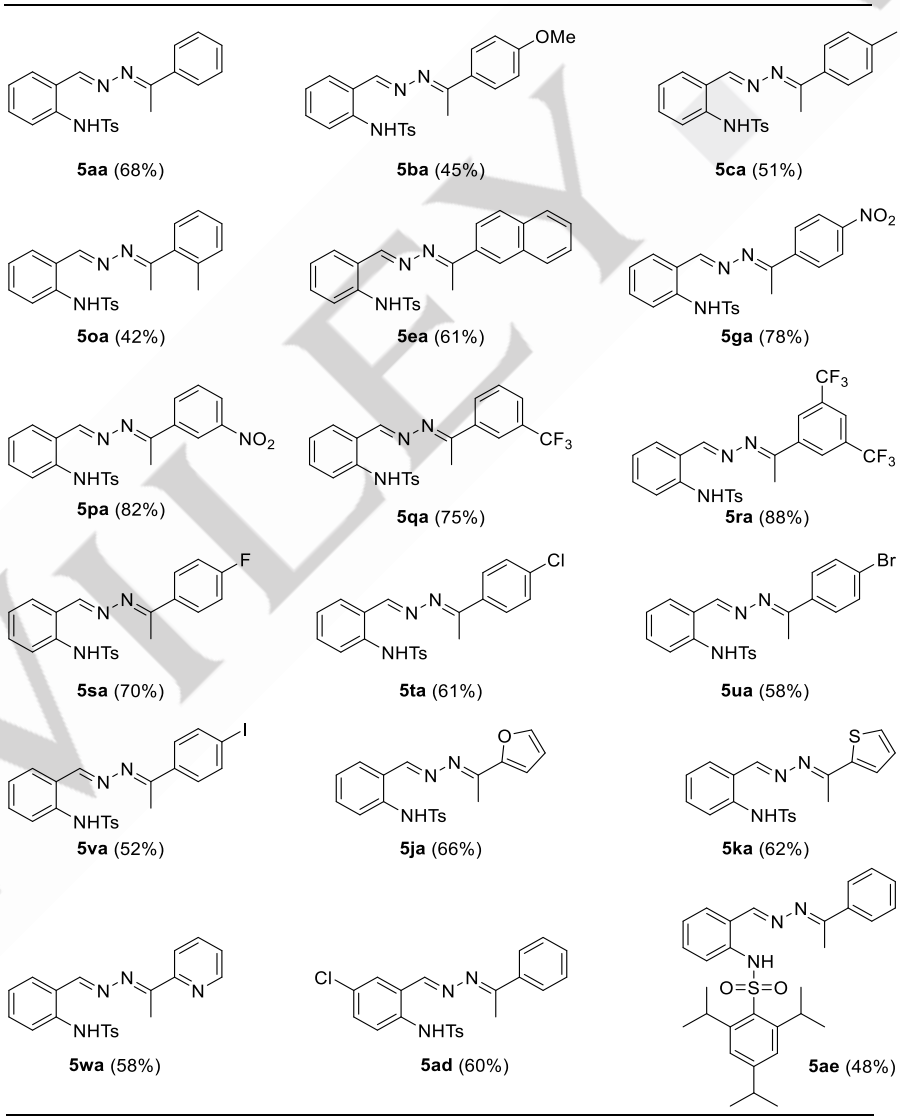
Under the optimized conditions, we planned to study the generality of the azine sulfonamide synthesis (Table 4). The electron-donating substituent on *N*-tosylhydrazone had a detrimental effect on the reaction, and when OMe and Me-substituents were present, the corresponding products **5ba**, **5ca** and **5oa** were obtained in moderate yields. The *N*-tosylhydrazone derived from 2-acetyl naphthalene, when reacted with **4a,** afforded the corresponding azine sulfonamide **5ea** in 61% yield. The presence of electron-withdrawing substituents on *N*-tosylhydrazone had a positive effect on the reaction, and by this methodology, we could synthesize four azine sulfonamides **5ga**, **5pa**, **5qa** and **5ra** (bearing NO_2, CF_3 groups) in excellent yields. We could also synthesize halogen (F, Cl, Br & I) bearing azine sulfonamides **5sa**-**5va** in moderate to good yields starting from the corresponding halogen containing *N*-tosylhydrazone. Acetylated heterocycle derived *N*-tosylhydrazones also reacted with **4a** under super basic medium, producing **5ja**, **5ka** and **5wa** in good yields where we could introduce furan, thiophene and pyridine rings respectively. Finally, by starting from *N*-(5-chloro-2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **4d** and *N*-(2-(chloromethyl)phenyl)-2,4,6-triisopropylbenzene sulfonamide **4e,** we could synthesize **5ad** and **5ae** in 60% and 48% yields.

Table 4. The generality of the reaction between *N*-tosylhydrazone and *N*-(2-(chloromethyl)phenyl)-4-methyl arenesulfonamide under super basic conditions.



1 **4** **5** (18 examples)



5aa (68%) **5ba** (45%) **5ca** (51%)

5oa (42%) **5ea** (61%) **5ga** (78%)

5pa (82%) **5qa** (75%) **5ra** (88%)

5sa (70%) **5ta** (61%) **5ua** (58%)

5va (52%) **5ja** (66%) **5ka** (62%)

5wa (58%) **5ad** (60%) **5ae** (48%)

Reaction conditions: **1a** (1.0 equiv., 0.35 mmol), **4a** (1.5 equiv.), KOH (2.0 equiv.), DMSO (2.0 mL), 80 °C, 12 h.

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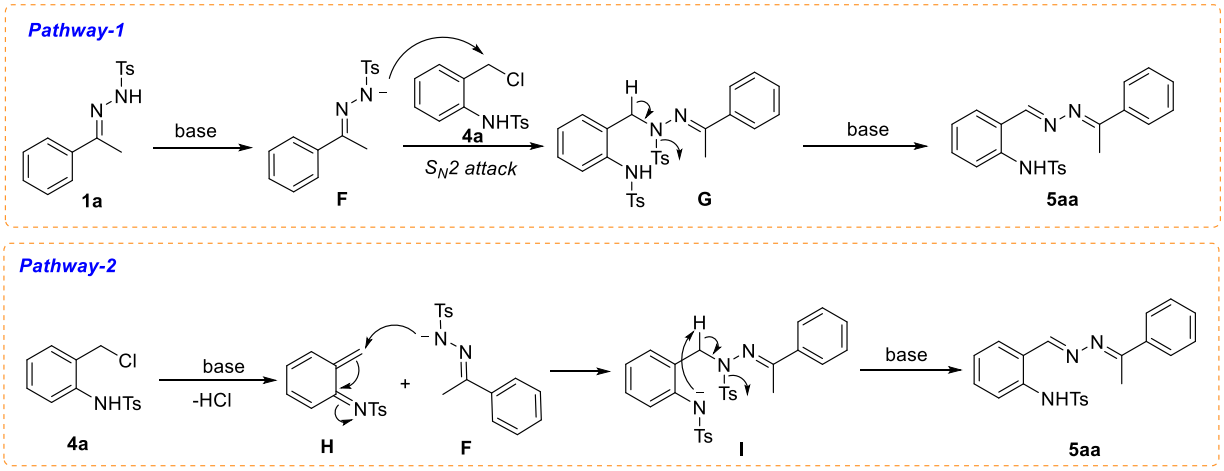

Scheme 5. Mechanistic postulate for the formation of azine sulfonamides from the reaction of *N*-tosylhydrazone and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide under super basic conditions.

We propose two mechanistic pathways for the formation of azine sulfonamides from the reaction between *N*-tosylhydrazone and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide under super basic conditions (Scheme 5). Both the pathways are believed to commence with the generation of the anionic species **F** from **1a**.[16,22] Then, in pathway-1, an S_N2 attack of the anionic species **F** on the benzylic carbon of **4a**, furnishes the intermediate **G**. The alternate pathway may involve the base-mediated formation of aza-*ortho*-quinone methide **H** from **4a**.[3] The anionic species **F** then reacts with the carbon end of the aza-*ortho*-quinone methide **H**, forming intermediate **I**. Subsequently, abstraction of a benzylic proton from either intermediate **G** or **I** occur, followed by the elimination of the Ts-group, ultimately leading to the formation of azine sulfonamides **5aa**.

Conclusion

In conclusion, we have investigated chemoselectivity in superbase-mediated reactions of *N*-tosylhydrazones with aza-*ortho*-quinone methide precursors. We have observed the regioselective formation of 2-substituted quinoline from the reaction of tosylhydrazone with *ortho*-aminobenzyl alcohol under super basic conditions (KOH+DMSO). It was revealed that the reaction was universal and that mono-, di-, and tri-substituted quinolines could be produced using this methodology. We demonstrated experimentally and theoretically that the reaction was carried out by the basic decomposition of *N*-tosylhydrazones, which created an azine. Finally, we could generate a series of azine sulfonamides from the reaction of tosylhydrazone and *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide under super basic conditions. We believe that the determining factor of chemoselectivity is the formation speed of aza-*ortho*-quinone methide intermediates from the precursors. Currently, efforts are underway to extend this observation of the chemoselectivity of aza-*ortho*-quinone methides with different reaction partners, and the results will be communicated in due course.

Experimental Section

General Experimental Methods. All reactions were performed in oven-dried glassware with magnetic stirring. All chemicals used were of analytical quality, were of the best grade, were 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. Gravity column chromatography was performed using silica gel, and ethyl acetate and hexane mixtures were used 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 {^{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 OrbitrapVelos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with an ESI/ HRMS at a resolution of 60,000, using Thermo Scientific Exactive mass spectrometer with orbitrap analyzer. 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.

General procedure for the preparation of *N*-Tosylhydrazones: The *N*-tosylhydrazones were prepared according to the literature procedure. [23] To a round bottom flask (100 mL), a solution of *p*-toluene sulfonylhydrazide (16 mmol) in anhydrous methanol, aryl ketone (16 mmol) was added dropwise under refluxing. The reaction mixture was stirred at 60 °C for 3 h, and the complete consumption of aryl ketone was confirmed by TLC. The solution was cooled until a solid precipitate was formed. The product aryl sulfonylhydrazone **1** was obtained by filtering, washing with petroleum ether, and drying in vacuum.

General procedure for the preparation of sulfonamino-benzyl chlorides: The sulfonaminobenzyl chlorides were synthesized according to the reported literature. [24] To a solution

of substituted 2-aminobenzyl alcohol (1g, 8.12 mmol) in $CHCl_3$ (40 mL) was added pyridine (720 µL, 8.93 mmol). The reaction was stirred for 25 min, and a solution of *p*-TsCl (1.703g, 8.93 mmol) in $CHCl_3$ was added dropwise over 20 min. After 12 h, the reaction was quenched with sat. aq. NH_4Cl. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were then washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude *N*-protected 2-aminobenzyl alcohol, which was used in the subsequent transformation without further purification. To a solution of *N*-protected 2-aminobenzyl alcohol (2.1g, 7.58 mmol) in $CHCl_3$ (40 mL), was added a solution of thionyl chloride (764 µL, 9.10 mmol) in $CHCl_3$ (5mL) over 1 min. The reaction was heated to 40 °C overnight, cooled to room temperature, and poured into ice water (30 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 x 40 mL). The combined organic layers were washed with brine (30mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded crude sulfonaminobenzyl chloride as a brown solid and was used without further purification.

General Procedure for the [4+2] Cycloaddition Reaction of 2-aminobenzyl alcohol with *N*- Tosyl hydrazones: A mixture of *N*-tosylhydrazone **1** (0.35 mol, 1 equiv.), 2- aminobenzyl alcohol **2** (0.42 mmol, 1.2 equiv.) and KOH (0.70 mmol, 2.0 equiv.) were weighed into a dry reaction tube. Dimethyl sulphoxide (1 mL) was added using a micropipette and allowed to stir at 80 °C on a reaction block for 12 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: ethyl acetate/hexane (1:9) to afford the corresponding products **3.**

General Procedure for the Reaction of aza-*o*-Quinone Methides with *N*-Tosylhydrazones: To a mixture of *N*-tosylhydrazone **1** (0.35 mmol, 1 equiv.), aza-*o*-QM precursor **4** (0.52 mmol, 1.5 equiv.), and KOH (0.70 mmol, 2.0 equiv.) were weighed into a dry reaction tube. Dry DMSO (2 mL) was added via a syringe and allowed to stir at 80 °C on a reaction block for 12 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: ethyl acetate/hexane (1:9) to afford the corresponding product **5**.

Supporting Information

Full experimental details and characterization data are included in the supporting information. The authors have cited additional references within the supporting information. [28- 31]

Acknowledgments

RP thanks CSIR for the research fellowship. JJ thank CSIR (HCP-41, HCP-49 & HCP-50) and DST-SERB (CRG/2023/001162) for financial assistance. The authors also thank Mrs. Saumini Mathew and Mrs. Viji S. of CSIR-NIIST for recording NMR and mass spectra, respectively. We also thank the reviewers for their constructive suggestions.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Superbase • *N*-Tosylhydrazones • Aza-*ortho*-Quinone Methide • Quinolines • Hydrazine-substituted sulfonamides

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[32] CCDC No for **5aa : 2298825**.

10.1002/ejoc.202400151

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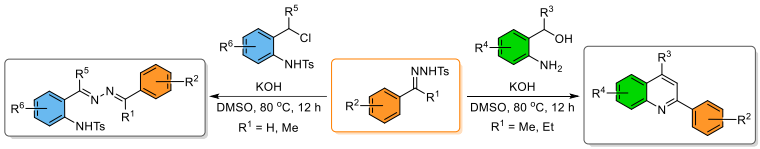

Investigations were made on the chemoselectivity in superbase-mediated reactions of *N*-tosylhydrazones with aza-*ortho*-quinone methide precursors. Under super basic conditions, the reaction of *N*-tosylhydrazone with *ortho*-aminobenzyl afforded 2-substituted quinoline while the reaction of former with *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide furnished azine sulphonamides.