Novel Synthesis of Carbocycles and Heterocycles Employing Zwitterions Derived from Allenic Esters

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By

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August 2014

.....To my parents and sister

DECLARATION

I hereby declare that the Ph.D. thesis entitled "**Novel Synthesis of Carbocycles and Heterocycles Employing Zwitterions Derived from Allenic Esters**" is an independent work carried out by me and it has not been submitted anywhere else for any other degree, diploma or title.

Anu Jose

Trivandrum
August, 2014

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CERTIFICATE

This is to certify that the work embodied in the thesis entitled "**Novel Synthesis of Carbocycles and Heterocycles Employing Zwitterions Derived from Allenic Esters**" has been carried out by **Ms. Anu Jose** under our supervision and guidance at the Organic Chemistry Section of National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Trivandrum and the same has not been submitted elsewhere for any other degree. All the relevant corrections, modifications and recommendations suggested by the audience and the doctoral committee members during the pre-synopsis seminar of **Ms. Anu Jose** have been incorporated in the thesis.

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Trivandrum
August, 2014

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Anu Jose

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CHAPTER 4B

PREFACE

Carbon-carbon and carbon-heteroatom bond formations constitute the central events in organic synthesis. In view of this, much of the research in organic synthesis has been focused on devising novel and efficient methods for such bond constructions. In general, polar, pericyclic and radical methodologies are employed for this purpose. The polar and radical reactions proceed *via* reactive intermediates such as carbanions, enols/enolates, enamines, carbocations, radical cations, radical anions, carbenes, zwitterions *etc*. In recent years, there has been enormous interest in the chemistry of zwitterionic species largely from the standpoint of their applications in multicomponent reactions (MCRs) and organocatalytic reactions. Zwitterions formed by the addition of nucleophiles to electrophilic π-systems such as acetylenic esters and azoesters have been the subject of extensive investigations; their synthetic utility, however, remained largely unexplored. Investigations in a number of laboratories, including our own, have shown that zwitterions of the type mentioned above on reaction with electrophiles give rise to carbo- and heterocyclic products by 1,3- or 1,4-dipolar cycloadditions. Recently, allenoates, another class of active π-systems were introduced to this field. Against this background, a systematic investigation of the reactions of various zwitterions derived from allenoates with different electrophiles especially 1,2-diones, were carried out. The results of these studies are embodied in the thesis entitled "**Novel Synthesis of Carbocycles and Heterocycles Employing Zwitterions Derived from Allenic Esters**".

The thesis is divided into four chapters which are presented as independent units and therefore the structural formulae, schemes, figures and references are numbered chapterwise.

The focal theme of this thesis is the reaction of zwitterionic intermediate derived from allenic esters and nucleophiles such as phosphine and amine with various electrophiles. In this regard, an overview of the chemistry of zwitterions with special emphasis on the reactions of allenoate-phosphine zwitterions as well as a general introduction to multicomponent reactions is provided in the first

chapter of the thesis. The definition of the research problem is provided at the end of this chapter.

Even though the design and development of MCRs has emerged as an important synthetic strategy, those involving allenoate was not extensively studied. In view of this, we studied the reaction of the zwitterion derived from allenoate and a primary amine, aniline, and the results constitute the subject matter of chapter 2.

In the context of our long term interest in the chemistry of zwitterions as well as 1,2-diones, it was of interest to explore the reactivity of allenoate-phosphine zwitterions towards the latter, a class of uniquely reactive compounds. The reaction of diaryl 1,2-diones with 3-alkyl allenoates in presence of triarylphosphine is described in Chapter3.

Chapter 4 has been divided in to two parts. Part A contains the reactions of allenoate-triphenylphosphine zwitterion with alicyclic 1,2-diones with varying ring size and *o*-quinones such as acenaphthene quinone. Part B deals with the reaction of this zwitterion with isatins, another class of 1,2-dicarbonyl compounds.

A summary of the work is given towards the end of the thesis.

ABBREVIATIONS

Ac	: acetyl
Ar	: argon
Ar-	: aryl
atm	: atmosphere
BINAP	: 2,2′-bis(diphenylphosphino)- 1,1′binaphthyl
BINOL	: 1,1′-Bi-2-naphthol
Bn	: benzyl
t-Bu	: tertiary butyl
CAN	: ceric ammonium nitrate
Cy	: cyclohexyl
d	: doublet
DABCO	: 1,4-diazabicyclo[2.2.2]octane
DBU	: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	: dichloroethane
DCM	: dichloromethane
dd	: double doublet
DDQ	: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	: diethyl azodicarboxylate
DMA	: dimethylacetamide
DMAD	: dimethyl acetylenedicarboxylate
DMAP	: 4-dimethylaminopyridine
DMDO	: dimethyldioxirane
DME	: dimethoxyethane
DMF	: dimethylformamide
DMSO	: dimethyl sulfoxide
dr	: diastereomeric ratio
ee	: enantiomeric excess
equiv	: equivalent
ESI	: electron spray ionization
Et	: ethyl
FAB	: fast atom bombardment
Hz	: hertz
IR	: infrared
J	: coupling constant
LRMS	: low resolution mass spectroscopy
m	: multiplet
Me	: methyl
Mes	: 2,4,6-trimethylphenyl
mg	: milligram
mL	: milliliter
mmol	: millimolar
mp	: melting point
MS	: molecular sieves
NMO	: 4-methylmorpholine N-oxide
NMR	: nuclear magnetic resonance
o	: ortho
p	: para
Ph	: phenyl
piv	: pivaloyl

i-Pr	: isopropyl
PTSA	: *p*-Toluenesulfonic acid
Py	: pyridine
q	: quartet
rt	: room temperature
(*R*)-SITCP	: (11aR)-(+)-,6,10,11,12,13- hexahydro-5-phenyl-4H-diindeno[7,1-cd:1′,7′-ef]phosphocin
s	: singlet
t	: triplet
TBDPS	: *tert*-butyldiphenyl silyl
tert	: tertiary
Tf	: triflyl (trifluoromethane- sulfonyl)
TFA	: trifluoroacetic Acid
TMEDA	: tetramethyl ethylenediamine
TMS	: trimethylsilyl
Tol	: tolyl
THF	: tetrahydrofuran
TLC	: thin layer chromatography
Ts	: *p*-toluene sulfonyl
Xphos	: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

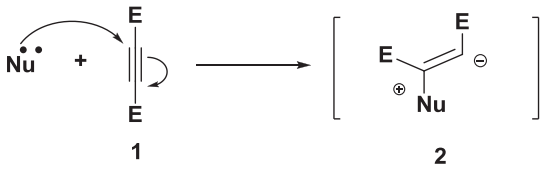
CHAPTER 1

Chemistry of Zwitterions: An Overview

1.1 Introduction

Carbon-carbon and carbon-heteroatom bond-forming reactions play pivotal role in organic synthesis. Generally polar, pericyclic and radical methodologies are employed for such bond constructions. Polar and radical processes rely on the use of various reactive intermediates like carbocations, carbanions, enols/enolates, radicals, and zwitterions. Among these, zwitterions received meager attention from the synthetic point of view, although they have been known in the literature for a long time. The focal theme of this thesis is the reaction of zwitterionic intermediate derived from allenic esters and nucleophiles such as phosphine and amine with various electrophiles. To put things in perspective, a brief overview of the chemistry of zwitterions in general and phosphine-mediated zwitterions in particular, is provided in the following sections.

Zwitterions are a class of dipolar species with formal charges on different atoms. The word zwitterion has its origin from the German word 'zwitter' which means hybrid and the Greek word 'ion'. As the name implies, it is a hybrid species with a positive charge and a negative charge. Typical examples of zwitterions include amino acids, natural products like psilocybin, lysergic acid etc. These are stable naturally occurring zwitterions. Another class of zwitterions includes transient zwitterions, resulting from the addition of nucleophiles to activated π-systems. Neutral nucleophiles like N-heterocycles, phosphines, nucleophilic carbenes, and isocyanides have been known to form 1:1 zwitterionic intermediates of the structure **2** by reaction with activated acetylenes (Scheme 1.1).[1]

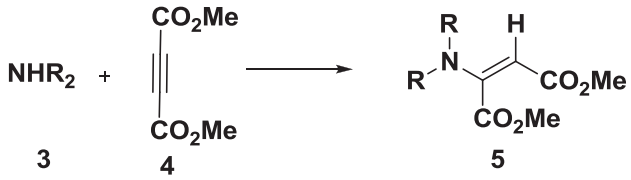


Nu = Phosphines, Isocyanides, *N*-Heterocycles, Nucleophilic Carbenes *etc.*

E = CO_2R, SO_2R, COR, CN *etc.*

Scheme 1.1

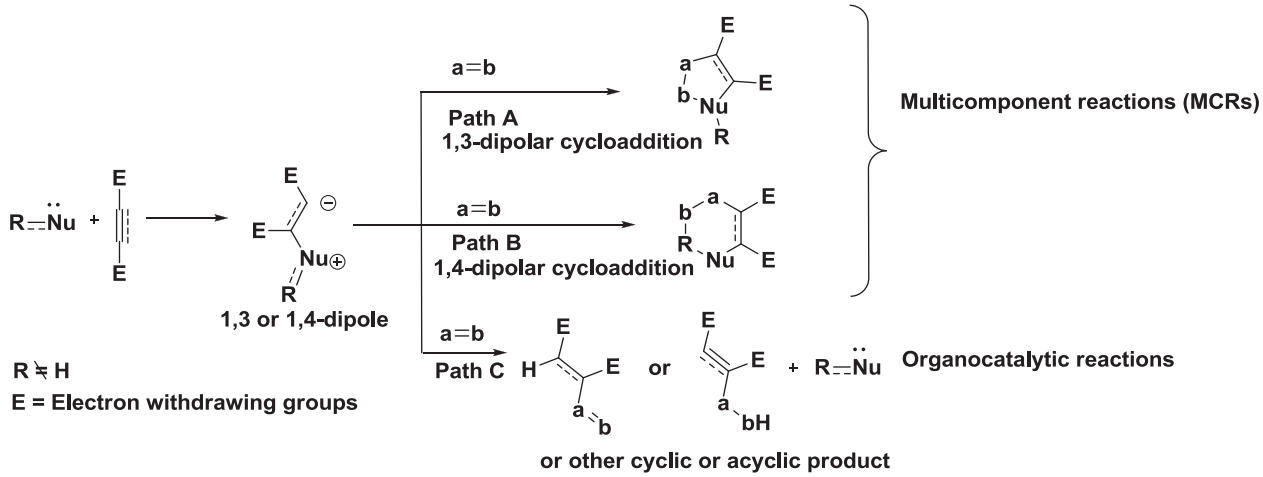
The nucleophiles are of two types, *i.e.*, those having active hydrogen atom and those without active hydrogen. Primary and secondary amines belong to the former category. The zwitterions formed by the addition of these nucleophiles to various π-systems are quenched by the active hydrogen (Scheme 1.2).



Scheme 1.2

The zwitterions generated from the nucleophiles without active hydrogen atom can be stabilized by internal cyclization, cycloaddition, rearrangement and addition reactions. Zwitterions include conventional dipoles such as 1,3-dipoles, which are basically a system of three atoms over which four π-electrons are distributed as in the allyl anion system. Another class of zwitterions *viz*., the 1,4-dipole is a system in which 4π-electrons are distributed among four atoms. These dipoles are successfully used as synthons for the construction of carbocyclic and heterocyclic systems by trapping them with various dipolarophiles. The nucleophile either incorporates with the product as in multicomponent reactions or it can help the union two electrophiles where the nucleophile plays the role of a catalyst.

A generalized and schematic representation of the above mentioned events is given below (Scheme 1.3).



Scheme 1.3

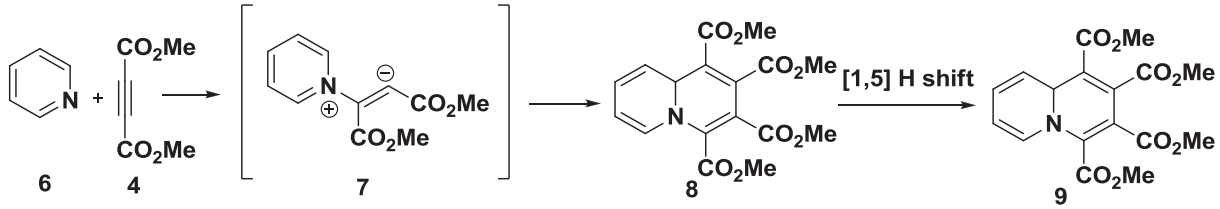
1.2 Reactions of Zwitterions

The reactions of zwitterions derived by the addition of nucleophiles without active hydrogen are described in the following section.

1.2.1 Reactions of Zwitterions Derived from N-Heterocycles

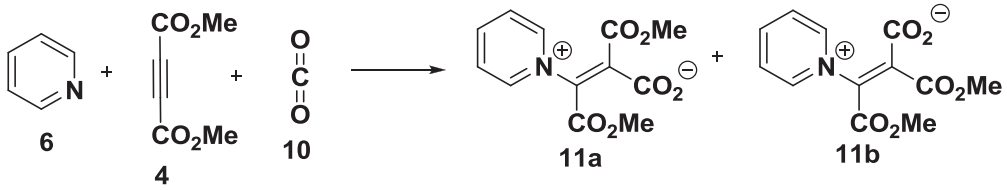
A large variety of N-heterocycles including pyridine, quinoline, isoquinoline, thiazole and imidazole form zwitterions by addition to activated π-systems. Among these, pyridine is the one that has been widely used to mediate different kinds of synthetic transformations.

In 1932 Diels and Alder isolated a 1:2 adduct from the reaction of pyridine and dimethyl acetylenedicarboxylate (DMAD).[2] The structure of this compound was conclusively established as **9** by the detailed investigations of Acheson[3] almost three decades later. Soon after, Huisgen[4] recognized this reaction as the 1,4-dipolar variant of the classical Diels-Alder reaction involving the intermediate **7** consequent to his postulation of the concept of dipolar cycloadditions. Thus, the addition of a second molecule of DMAD to the 1,4-dipole **7** followed by a [1,5] H-shift in the initial product **8** afforded the final product **9** as illustrated in Scheme 1.4.



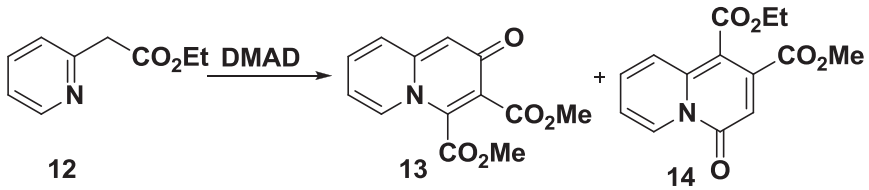
Scheme 1.4

More insight into the mechanistic details of 1,4-dipolar cycloaddition reactions was provided by Huisgen.[5] Later, the mechanistic studies by Acheson further confirmed the existence of the 1,4-dipole by its interception with carbon dioxide (Scheme 1.5).[6]



Scheme 1.5

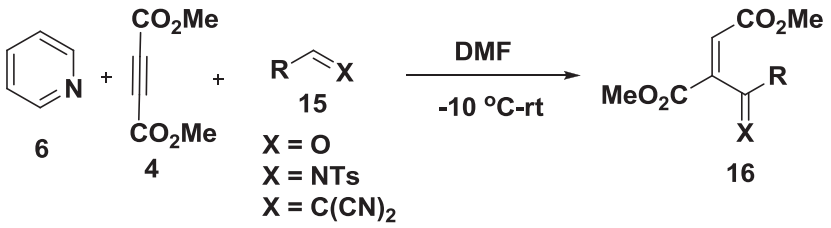
Intramolecular trapping of the prydine-DMAD zwitterion was reported by Winterfeldt. The reaction of ethyl pyridylacetate with DMAD afforded 2*H*-quinolizone **13** as the major product in polar solvents and 4*H*-quinolizone **14** in non-polar solvents (Scheme 1.6).[7]



Scheme 1.6

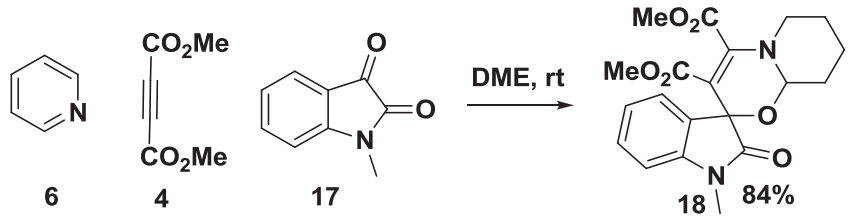
Independent investigations by Acheson and Winterfeldt in closely related areas provided further examples of similar reactions. However, the synthetic potential of the methodology remained untapped until recently.

Investigations in our laboratory have shown that the reaction of 1,4 dipole generated from pyridine and DMAD can be intercepted with aldehydes, N-tosylimines and activated styrenes leading to benzoyl fumarates, aza-dienes and 1,3-butadienes respectively (Scheme 1.7). In this case, pyridine acts as a catalyst (20 mol%) and the reaction proceeds with complete stereoselectivity affording only the *trans* product.[8,9]



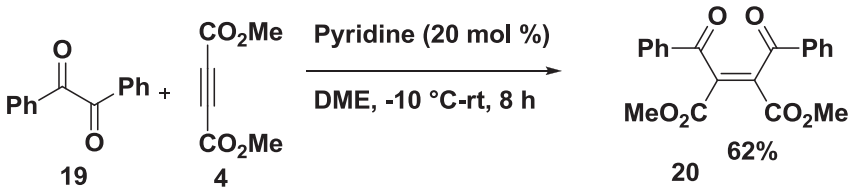
Scheme 1.7

The three component reaction involving pyridine, DMAD, and isatin resulted in the facile synthesis of spiro-pyridooxazino derivative **18**. Unlike the early reaction, in this case pyridine gets incorporated with the product (Scheme 1.8).[9]



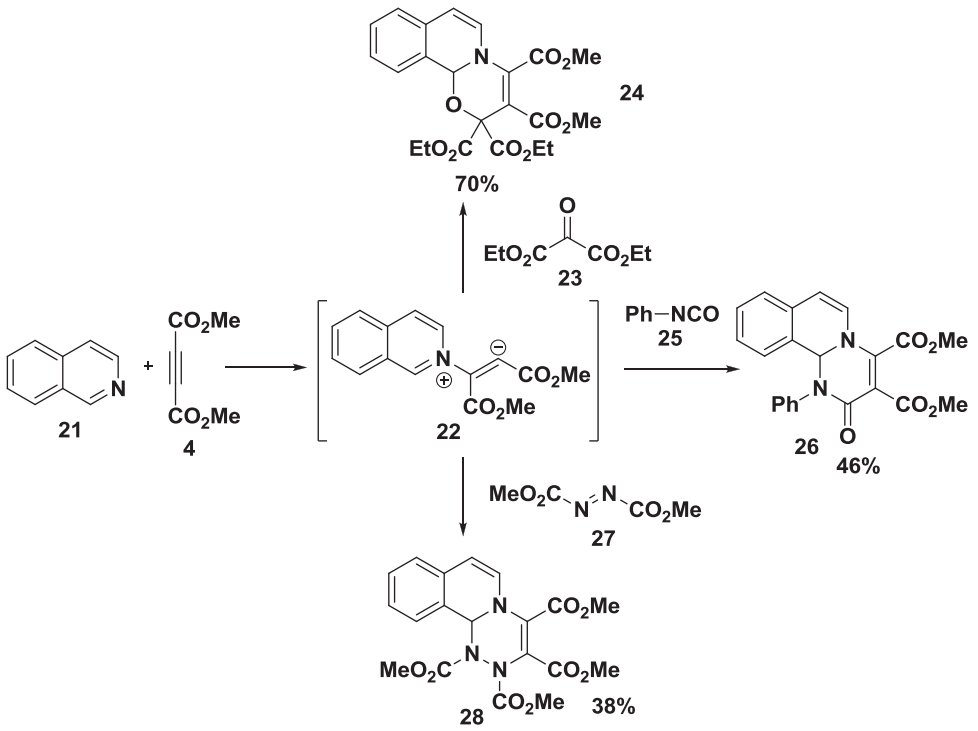
Scheme 1.8

It is noteworthy that the reaction of pyridine-DMAD zwitterion with diaryl 1,2-dione resulted in the stereoselective formation of dibenzoyl maleate **20** *via* an unprecedented rearrangement (Scheme 1.9).[10]



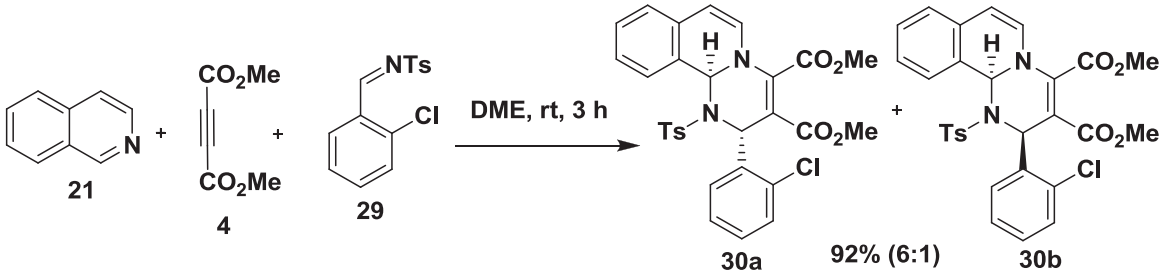
Scheme 1.9

In 1967, Huisgen, the pioneer of 1,3-dipolar cycloadditions, reported the formation of a 1,4-dipole by the reaction of isoquinoline with DMAD. He demonstrated the intermediacy of the zwitterion **22** in the reactions with various dipolarophiles to form isoquinoline-fused heterocycles (Scheme 1.10).[11]



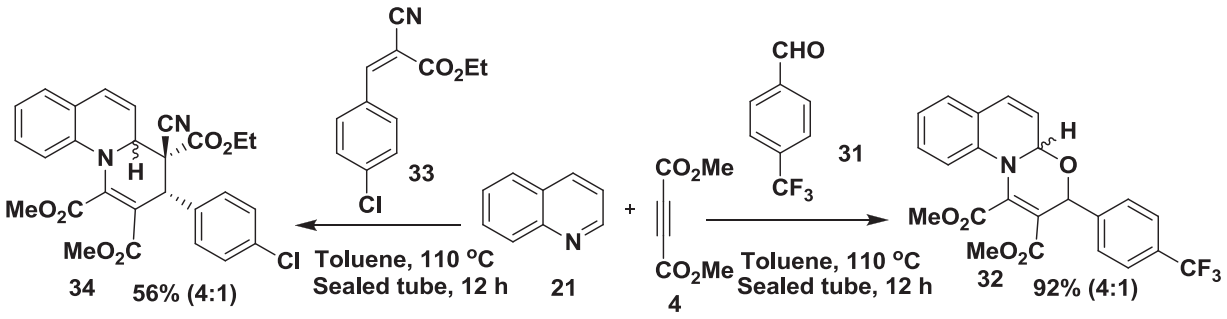
Scheme 1.10

From our group it was reported that the 1,4-dipolar zwitterion generated by the addition of isoquinoline to DMAD can be efficiently trapped with electrophiles such as aromatic aldehydes, *p*-quinones, 1,2-diones, dicyanostyrenes etc.[12] The 1,4-dipole derived from isoquinoline and DMAD reacts readily with N-tosylimine **29** resulting in the diastereoselective synthesis of 2*H*-pyrimido[2,1-a]isoquinoline derivatives (Scheme 1.11).[12a]



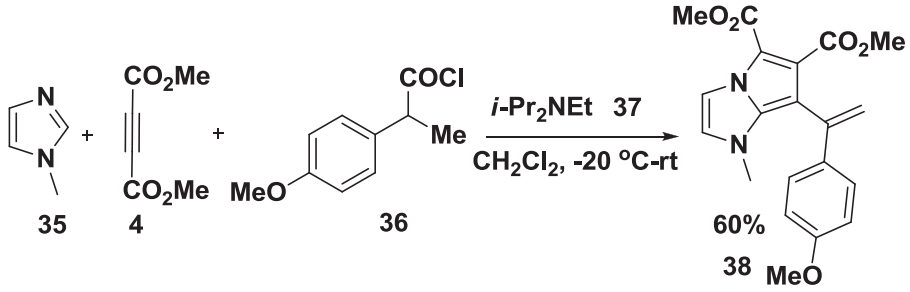
Scheme 1.11

Similarly, quinolone forms 1,4-dipolar zwitterion with dimethyl acetylenedicarboxyl- ate, which is trapped by various dipolarophiles to yield a variety of pyridoquinoline and oxazinoquinoline derivatives. An illustrative example is shown in Scheme 1.12.[13]



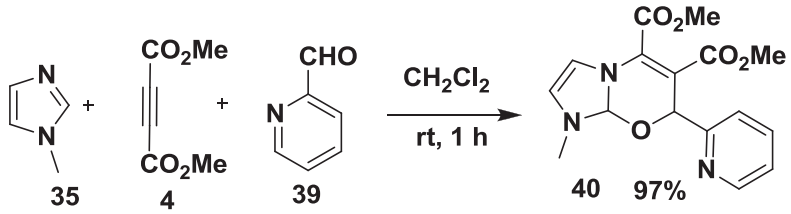
Scheme 1.12

In 2006, Ma *et al*. reported a novel three-component annulation reaction involving N-alkylimidazoles, dimethyl acetylenedicarboxylate, and *in situ* generated aryl methyl ketenes. The reaction led to the synthesis of 6-vinyl-1,3a-diazapentalene derivatives (Scheme 1.13).[14]



Scheme 1.13

The reaction of N-methyl imidazole with DMAD and pyridine-2-carboxaldehyde afforded 1,8a-dihydro-7*H*-imidazo[2,1-b][1,3]oxazine derivative **40** in 97% yield (Scheme 1.14).[15]

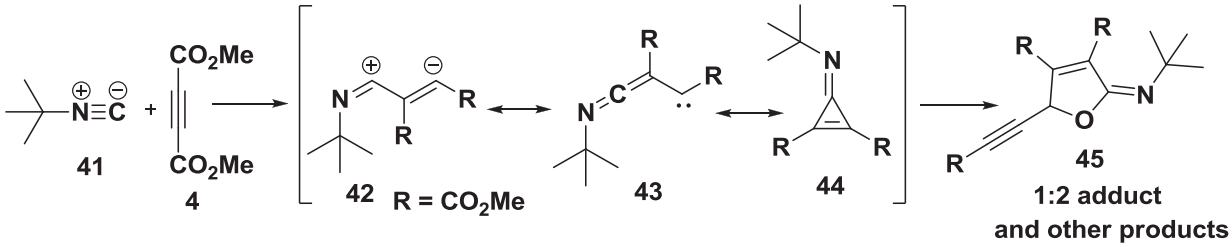


Scheme 1.14

1.2.2 Reactions of Zwitterions Derived from Isocyanide

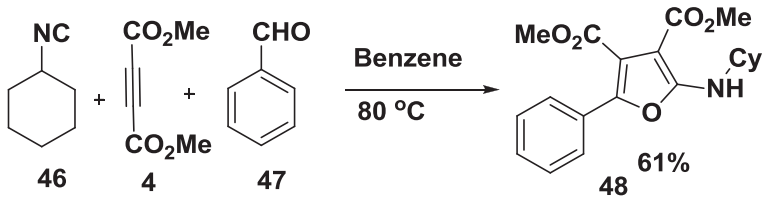
Isocyanides belong to a rare class of stable organic compounds with a formal divalent carbon. Gautier identified them as true homologues of hydrocyanic acid, since by hydrolysis they are converted into formic acid and amine.[16] Isocyanides are isoelectronic with carbon monoxide and have been shown to be of linear geometry by electron diffraction[17] and microwave studies.[18]

Isocyanides are known to form zwitterions with activated acetylenic compounds like dimethyl acetylenedicarboxylate (DMAD). The highly reactive zwitterionic intermediate undergoes further reaction with isocyanide or DMAD to yield a variety of complex heterocyclic compounds. Conceptually, the intermediate can be considered as a carbanion **42**, carbene **43** or even a cyclopropene imine **44** (Scheme 1.15).[19]



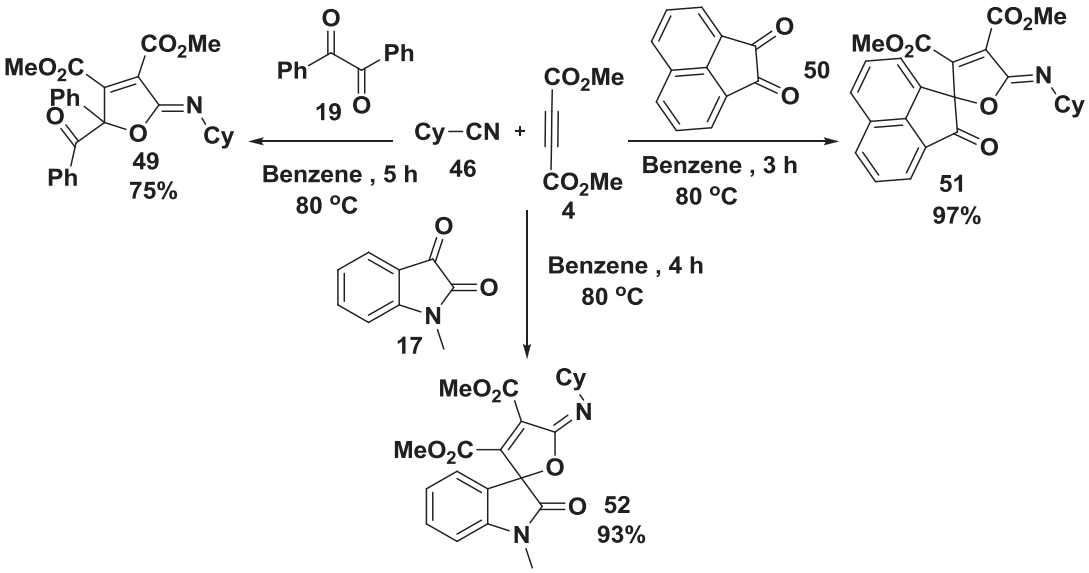
Scheme 1.15

The first report on the successful trapping of the zwitterion derived from isocyanide and DMAD with another electrophile was from our group. The reaction of this species with aldehydes led to the facile synthesis of aminofuran derivatives. (Scheme 1.16).[20]



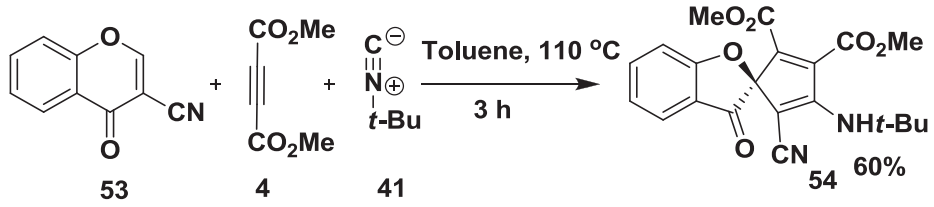
Scheme 1.16

Also it was found that the zwitterion reacted smoothly with various dipolarophiles such as 1,2 and 1,4-quinones, diaryl 1,2-diones and N-protected isatins to form iminolactones (Scheme 1.17).[21]



Scheme 1.17

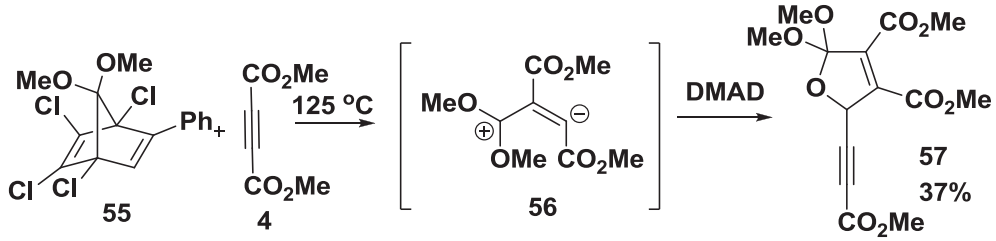
Recently, Zarganes-Tzitzikas *et al*. reported a one-pot synthesis of functionalized spiro-benzofuranone **54** by the reaction of isocyanide-DMAD zwitterion with 3-cyanochromone **53** (Scheme 1.18).[22]



Scheme 1.18

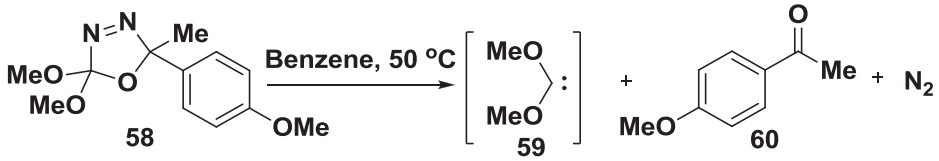
1.2.3 Reactions of Zwitterions Derived from Nucleophilic Carbenes

Nucleophilic carbenes also play key role in reactions analogous to those discussed above. Hoffman's earlier studies showed that dimethoxy carbene underwent addition to DMAD affording a 1:2 adduct in low yield. The carbene is generated *in situ* by the thermolysis of the norbornadiene ketal **55**. This method, however, is limited to the preparation of only a few alkoxycarbenes and is unsuitable for unsymmetrical carbenes (Scheme 1.19).[23]



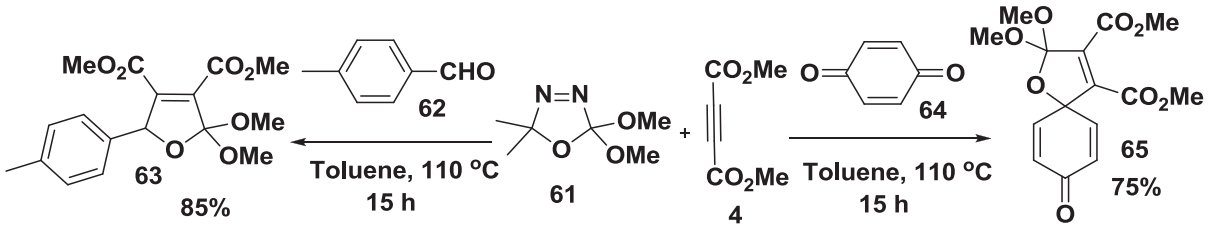
Scheme 1.19

Warkentin in 1992, identified 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline as a shelf stable, thermal source of dimethoxycarbene.[24] Since then, the Warkentin protocol is widely used for generating dimethoxy carbenes. Later he reported the generation of dimethoxycarbene **59** by the thermolysis of 2,5-dihydro-2,2-dimethoxy-5-methyl-5-(*p*-methoxy) phenyl-1,3,4-oxadiazole **58** at 40-50 °C (Scheme 1.20).[25] The lower temperature of this reaction permits the isolation of products that might not survive higher temperatures.



Scheme 1.20

Based on these findings we successfully trapped the zwitterionic species generated from dimethoxy carbene and DMAD with aldehydes and quinones. The reaction furnished dihydrofuran derivatives in good yields (Scheme 1.21).[26]

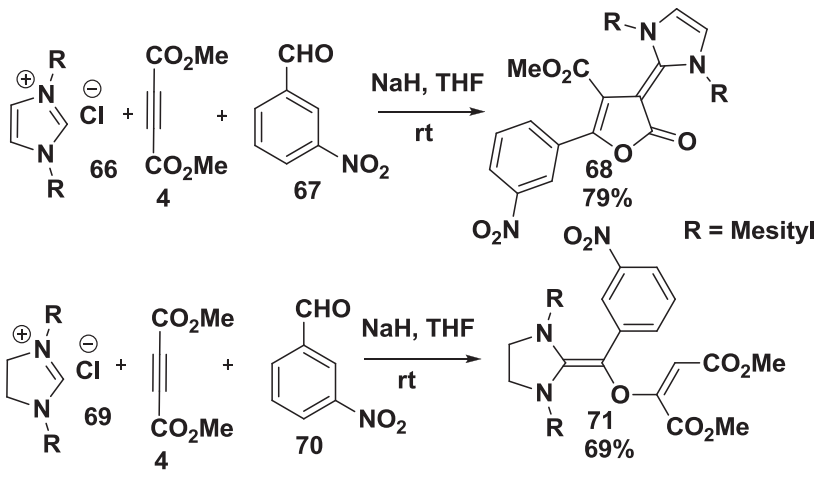


Scheme 1.21

Further investigations revealed that the zwitterion reacts readily with 1,2-diones such as benzils, isatins, cyclobutene 1,2-diones etc. to form the corresponding multicomponent reaction product in good yields.[27]

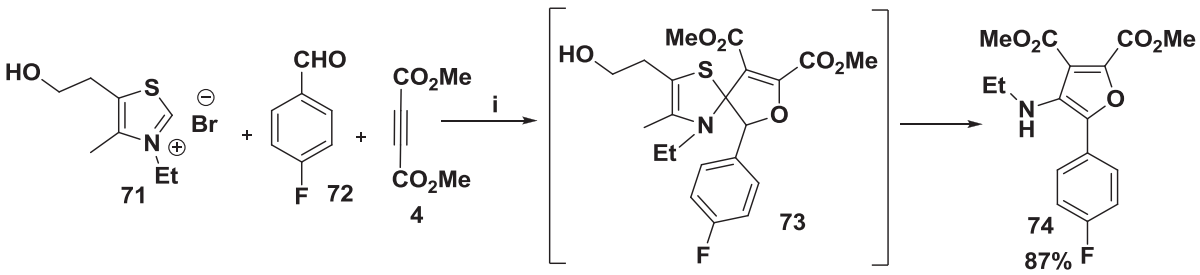
Nucleophilic heterocyclic carbenes (NHCs), which are widely used as organocatalysts and ligands for the synthesis of organoametallic reagents, owing to their σ-donating property, can form dipolar zwitterion with activated alkynes. It was reported from our laboratory that NHCs can undergo multicomponent reaction with DMAD and electrophiles such as aldehydes. By exploiting their nucleophilic property, we have synthesized furanones and oxymaleates from two NHCs, imidazol-2-ylidene and imidazolin-2-ylidene respectively, which follow different reaction pathways (Scheme 1.22).[28] In both cases, initial event is the generation of carbenes from the precatalysts **66** and **69**. The addition of imidazole-2-ylidene to aldehyde and DMAD afforded furanone

derivative while the addition of imidazolin-2-ylidene to DMAD and aldehyde furnished oxymaleate derivative.



Scheme 1.22

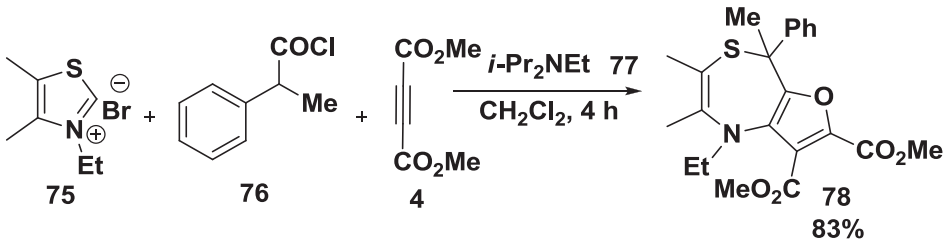
In 2005, Ma *et al.* reported an efficient synthesis of substituted 3-aminofurans by multicomponent reaction of thiazolium salts, aldehydes, and DMAD. The reaction proceeds *via* the *in situ* generation of thiazole-2-ylidene and its sequential nucleophlic addition to aldehyde **72** and DMAD (Scheme 1.23).[29]



i = (1) NaH (2 mmol), thiazolium salt (1 mmol), CH_2Cl_2, -78 °C, 15 min; then solution of aldehyde (0.5 mmol), DMAD (0.75 mmol), 2 h; 0 °C, 2 h; (2) $NaHCO_3$ (aq).

Scheme 1.23

An year later, the same group reported another three component reaction involving thiazole carbene, 1,1-disubstituted ketene and DMAD to form polysubstituted furan-fused 1,4-thiazepine derivatives. The thiazol-2-ylidene, first generated *in situ* from thiazolium salt **75**, would react with the 1,1-disubstituted ketene which is generated from the acid chloride **76** by the action of Hunig's base **77** to afford the zwitterion. The reaction of the zwitterion with DMAD yielded the furothiazepine **78** (Scheme 1.24).[30]



Scheme 1.24

1.2.4 Reactions of Zwitterions Derived from Phosphines

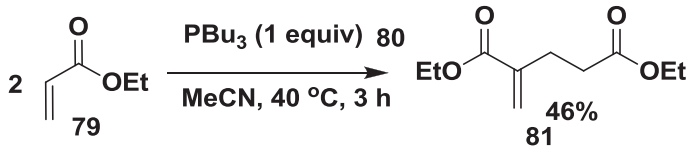
Organophosphorus compounds have enormous applications in synthetic organic chemistry.[31] The well-known applications include the use of (i) phosphonium ylides in Wittig reaction, (ii) phosphines in the Staudinger and Mitsunobu reactions and (iii) phosphines as ligands in transition metal mediated processes.[32] Phosphines readily undergo Michael type additions to activated π-systems such as alkenes, alkynes and can add to the carbonyl compounds in a 1,2 fashion. Nucleophilic phosphine organocatalysis has been emerging as a powerful tool for the synthesis of carbocycles and heterocycles. Phosphines are known to bring about transformations both catalytically and stoichiometrically. There are several attractive features related to phosphine catalysis. The chemistry of phosphines[33] is centered around the non-bonding lone pair of electrons on phosphorus atom that may be used to form new bonds between phosphorus and a variety of electrophiles. Relatively strong bonds can be formed by phosphorus to oxygen, sulfur, nitrogen, halogens and carbon, and P(III) to P(V) conversion is very easy. Phosphorus has 3d orbitals available for bonding and it can stabilize adjacent anions (Wittig ylide). Phosphine can be a leaving group as in organocatalytic reactions. They are weaker bases but stronger nucleophiles than nitrogen analogues and their nucleophilicity is readly tunable. As expected, trialkylphosphines are more nucleophilic compared to triarylphosphines. Phosphorus can be easily tailored to different moieties and the availability of chiral phosphines has made several synthetic transformations enantioselective. A brief overview of some important reactions of zwitterions derived from phosphine is provided in the following section.

1.2.4.1 Reactions of Phosphine-Alkene Zwitterion

1.2.4.1.1 Rauhut-Currier Reaction

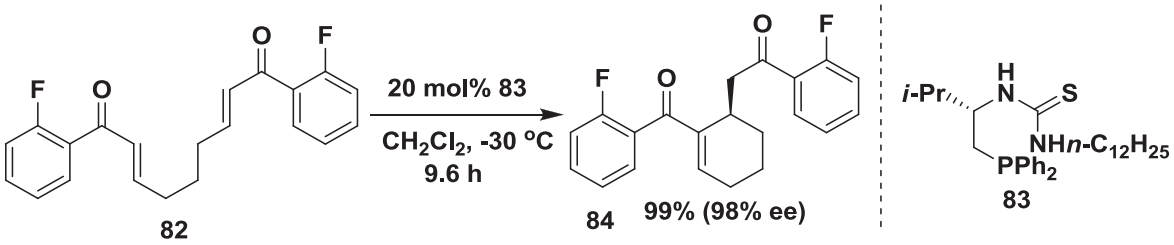
The original Rauhut–Currier reaction reported in 1963, describes the dimerization of the electron-deficient alkene ethyl acrylate **79** to the ethyl diester of 2-methylene-

glutaric acid **81** in presence of tributylphosphine in acetonitrile (Scheme 1.25).[34] The transformation involves a reversible conjugate addition of phosphine to the activated alkene followed by a Michael reaction of the enolate with the second molecule of the alkene. A proton shift followed by the elimination of phosphine forms the dimer.



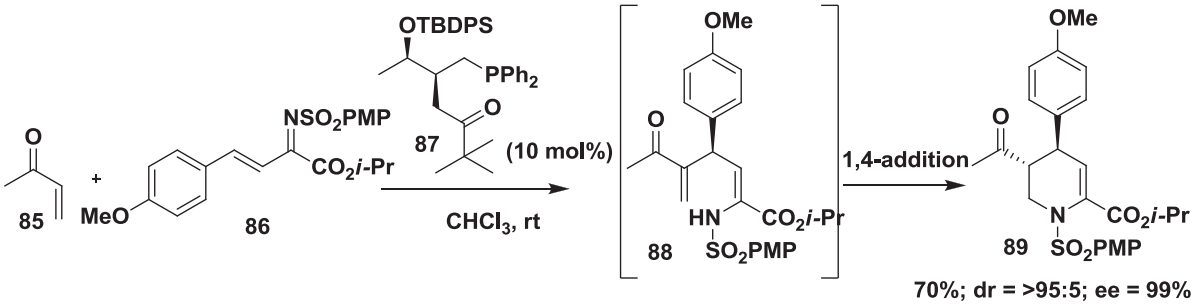
Scheme 1.25

A number of variants have been developed for this reaction. In 2011 Gong *et al*. reported chiral organophosphine-catalyzed enantioselective Rauhut–Currier reaction for the first time. Using L-valine-derived phosphinothiourea **83** as the chiral catalyst, the intramolecular Rauhut–Currier reaction of bis(enone) **82** was achieved in excellent yield and enantioselectivity (Scheme 1.26).[35]



Scheme 1.26

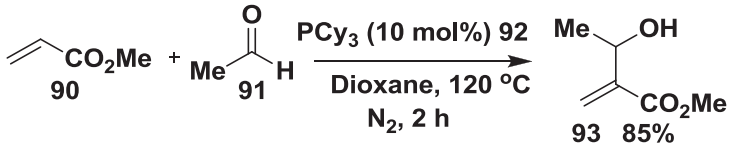
An unprecedented catalytic asymmetric [4+2] annulation initiated by an Aza-Rauhut–Currier reaction has been reported by Shi *et al*. in 2012. The [4+2] annulation of vinyl ketones with chalcone derived N-sulfonyl-1-aza-1,3-dienes in presence of amino phosphine catalyst afforded highly functionalized tetrahydropyridines, with high stereocontrol in good to excellent yields (Scheme 1.27).[36]



Scheme 1.27

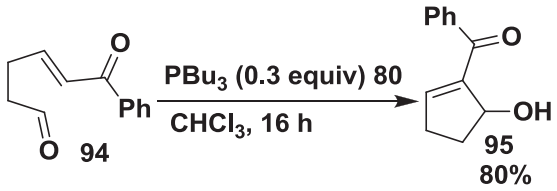
1.2.4.1.2 Morita-Baylis-Hillman Reaction

A carbon-carbon bond-forming reaction, which basically involves the reaction between an aldehyde and an activated alkene in the presence of a tertiary base, is known as Morita-Baylis-Hillman reaction. The reaction came in to existence in 1968, when H. Morita disclosed that the reaction of an aldehyde with an activated alkene in the presence of tricyclohexylphosphine (PCy_3) affords a densely functionalized product **93**, which can be further utilized in synthesis (Scheme 1.28).[37]



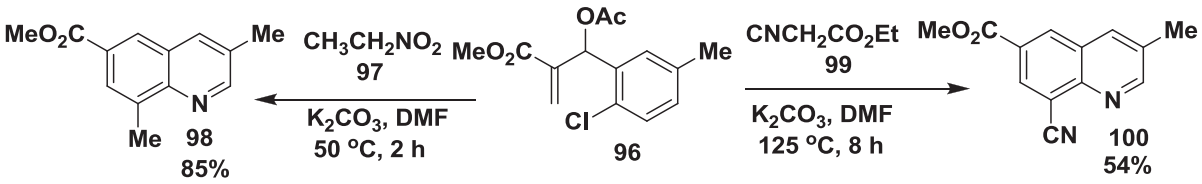
Scheme 1.28

Baylis and Hillman in 1972 used tertiary amines such as DABCO for the same reaction.[38] Since then research on tertiary amine catalyzed MBH reactions developed rapidly.[39] The first intramolecular variant of the MBH reaction was reported by Fráter in 1992 and investigated further by Murphy and also Keck (Scheme 1.29) [40]



Scheme 1.29

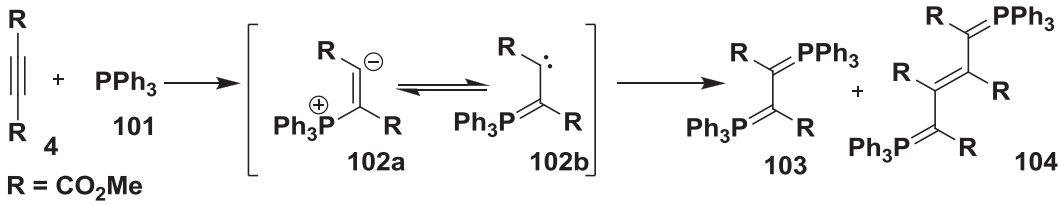
The MBH adducts incorporate three chemospecific groups, *viz*., a hydroxyl group, a double bond and an electron withdrawing group. These groups could be appropriately tailored to generate an array of cyclic compounds directly from the Morita-Baylis-Hillman adducts. The MBH adduct can be readily transformed in to the acetate *via* acetylation. The acetate undergoes a variety of reactions, leading to products, which could be efficiently exploited for the generation of cyclic scaffolds. For example, the acetyl derivatives of MBH adducts, derived from 2-chloronicotinaldehyde, were successfully utilized for the synthesis of 8-methyl- and 8-cyano-quinolines **98** & **100** (Scheme 1.30).[41]



Scheme 1.30

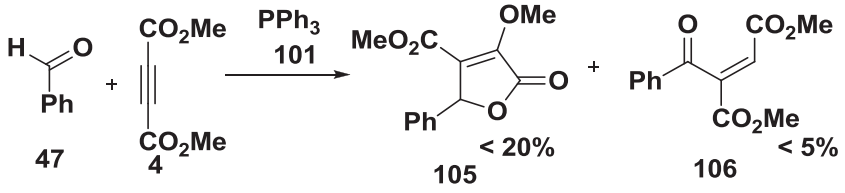
1.2.4.2 Phosphine-Activated Alkyne Zwitterion

Johnson and Tebby observed that addition of PPh_3 to various activated alkynes like DMAD, dicyanoacetylene, and dibenzoylacetylene generates zwitterionic intermediates and they studied the reactivity of the latter in detail.[42] They have shown that triarylphosphines react with DMAD to form a series of adducts of differing stoichiometry. The initial event is the formation of the 1,3-dipole **102a** which can be represented by a carbene structure **102b** also. In the presence of excess triphenylphosphine, the phosphorane **103** is obtained as the product while in presence of excess DMAD, the carbene **102b** dimerizes to form **104** (Scheme 1.31).



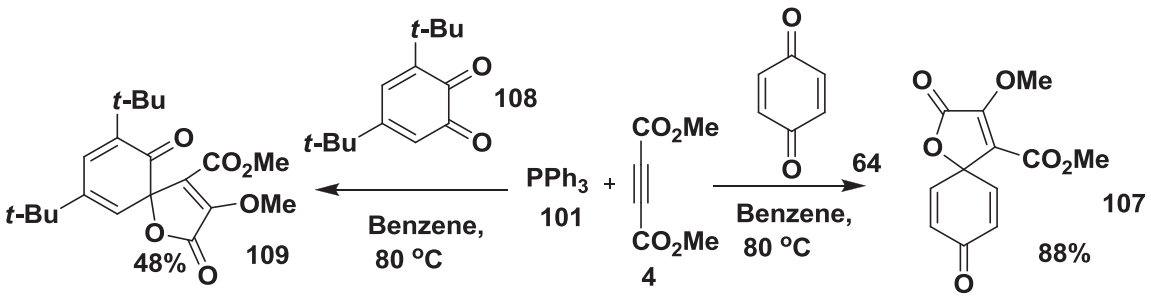
Scheme 1.31

Winterfeldt successfully trapped the phosphine-DMAD zwitterion with a third component *viz*., aldehyde. The reaction of zwitterion with benzaldehyde afforded two products; the lactone **105** and the benzyl fumarate **106** *albeit* in very low yield (Scheme 1.32).[43] Nozaki modified this protocol using activated carbonyl compounds such as α-ketoesters and α-ketonitriles to afford the unsaturated furan derivatives in 40-94% yields.[44]



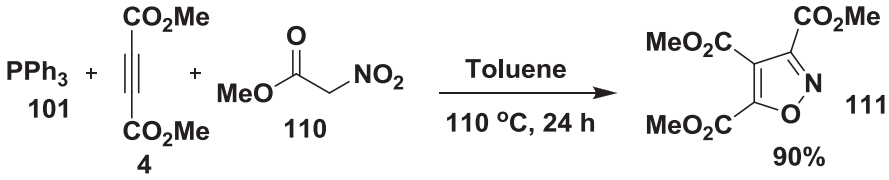
Scheme 1.32

It was reported from our group that the reaction of triphenylphosphine-DMAD zwitterion with *o*- and *p*-quinones furnished the corresponding substituted lactone derivatives in good yields (Scheme 1.33).[45]



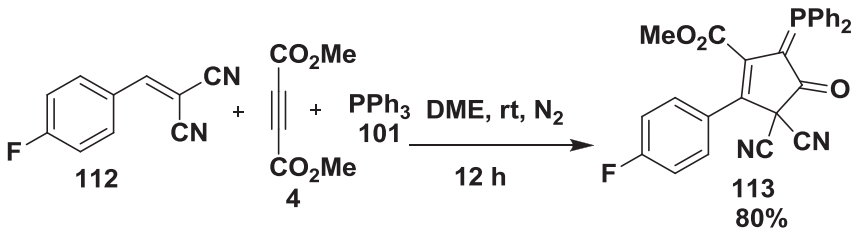
Scheme 1.33

In 2006, Yavari *et al*. reported the synthesis of isoxazole **111** by the reaction of activated acetylene and alkyl 2-nitroethanoate in the presence of triphenylphosphine (Scheme 1.34).[46]



Scheme 1.34

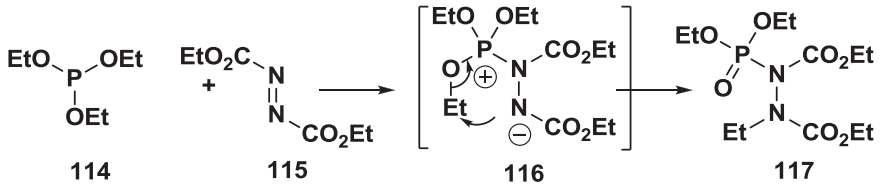
The reaction of triphenylphosphine, DMAD and electron deficient styrenes **112** results in a three-component reaction leading to the facile one-pot synthesis of highly substituted phosphorane **113**. This reaction is one of the rare examples in which the phosphine gets incorporated in the product (Scheme 1.35).[47]



Scheme 1.35

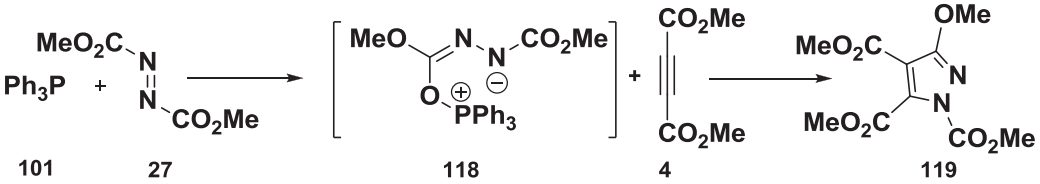
1.2.4.3 Phosphine-Azoester Zwitterion

Historically the reaction of P(III) compound with azoester was first reported by Morrison. He showed that the reaction of triethylphosphite with diethyl azodicarboxylate (DEAD) afforded **117**, an ethyl derivative of diethyl phosphoric acid-1,2-dicarboethoxy hydrazide (Scheme 1.36).[48]



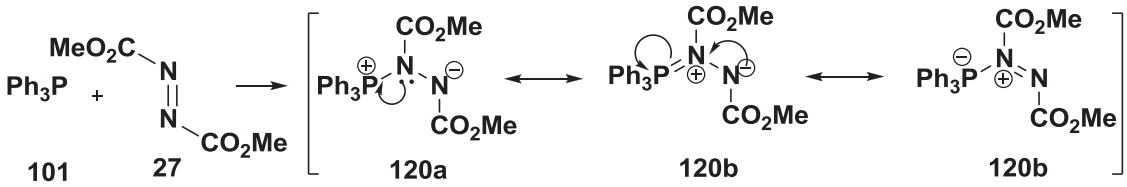
Scheme 1.36

Cookson and Locke reported that the reaction of triphenylphosphine and dimethyl azodicarboxylate with dimethyl acetylenedicarboxylate (DMAD) afforded trimethyl-3-methoxy-1,4,5-pyrazoledicarboxylate **119** and it was postulated to occur *via* the intermediate **118** (Scheme 1.37).[49]



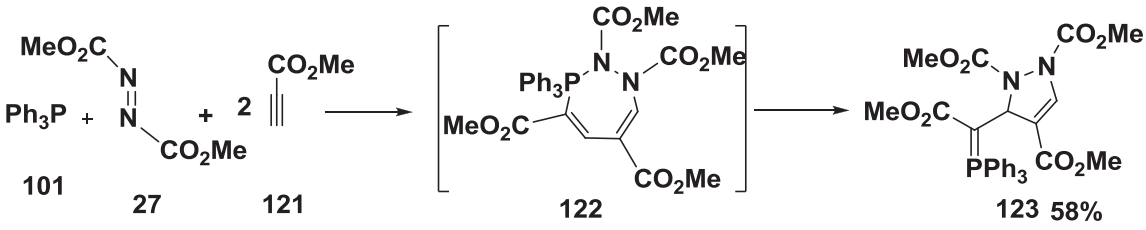
Scheme 1.37

The correct structure of the zwitterion formed in the above reaction was postulated by Huisgen and hence such species are known as Huisgen zwitterion. This zwitterion can be considered as a quasi 1,3-dipole as it does not contain an electronic sextet. It is best pictured as a resonance hybrid of three structures, the most significant contributor being **120b**. (Scheme 1.38).[50]



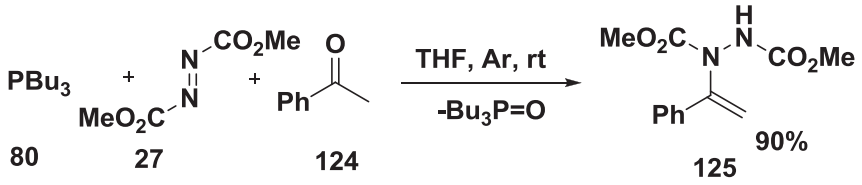
Scheme 1.38

The reaction of Huisgen zwitterion with two equivalents of methyl propiolate afforded the heterocyclic methylene phosphorane **123** in 58% yield. It is formed *via* ring contraction of the seven membered cycloadduct **122** (Scheme 1.39).[51]



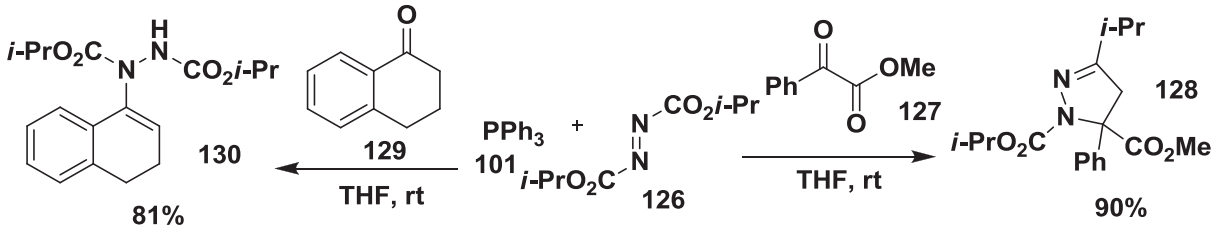
Scheme 1.39

The synthesis of vinyl hydrazine dicarboxylate from ketones was reported by Liu *et al*. For example, the reaction of tributylphosphine and dimethyl azodicarboxylate with acetophenone afforded the vinyl hydrazine dicarboxylate **125** in 90% yield (Scheme 1.40).[52]



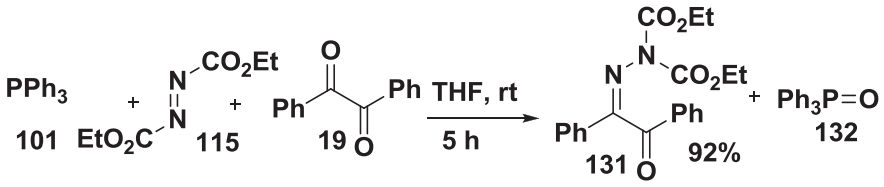
Scheme 1.40

Lee *et al*. reported the reactions of the Huisgen zwitterion with carbonyl compounds like α-ketoesters, dialkyl α-diketones, and aliphatic aldehydes to afford various products.[53] The reaction of Huisgen zwitterion with α-ketoester **127** afforded pyrazole derivative **128** while the reaction with ketone **129** afforded compound **130** as the product (Scheme 1.41).



Scheme 1.41

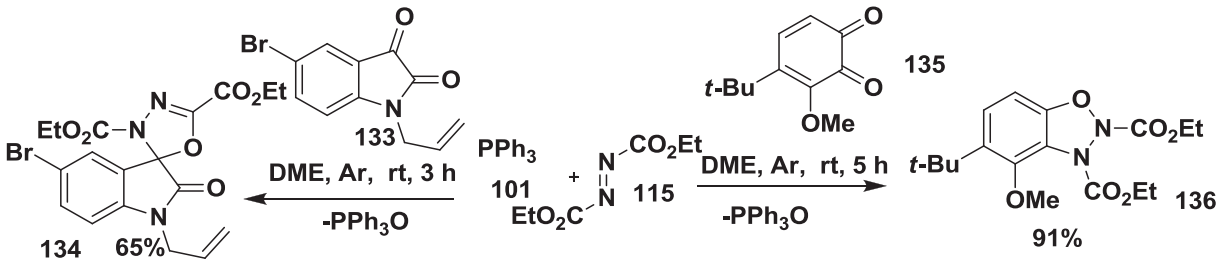
Our group has investigated the reactions of Huisgen zwitterions with a variety of carbonyl compounds in detail. The reaction of Huisgen zwitterion with diaryl-1,2-dione **19** proceeded with rearrangement to afford dicarboethoxy monohydrazone of the dione **131**.[54] This novel rearrangement involves a unique nitrogen-to-nitrogen migration of a carboethoxy group.



Scheme 1.42

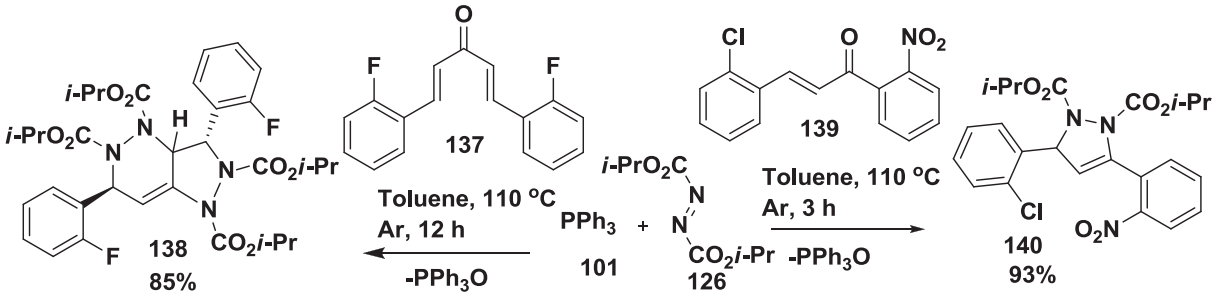
The reaction of Huisgen zwitterion with *o*-quinone **135** revealed some interesting reactivity patterns yielding dihydro-1,2,3-benzoxadiazole derivative **136** in good yields. Hydrogenolysis of the dihydro-1,2,3-benzoxadiazole using Pd-C afforded 2-(N,N'-

dicarboethoxyhydrazino)phenol. In a related study, the reaction of Huisgen Zwitterion with N-substituted isatin resulted in the formation of spiro-oxadiazoline **134** (Scheme 1.43).[55]



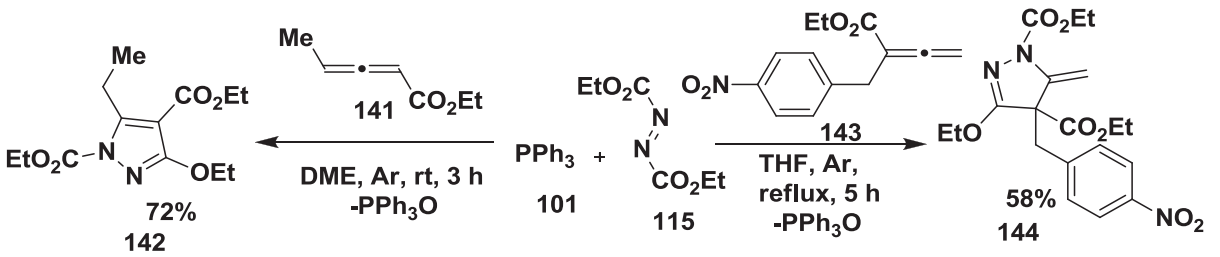
Scheme 1.43

Another interesting observation is that the reaction of Huisgen zwitterion with enone **139** and dienone **137** led to the efficient synthesis of pyrazoline **140** and pyrazolopyridazine **138** respectively (Scheme 1.44).[56]



Scheme 1.44

Subsequent studies showed that the reaction of Huisgen zwitterion with electron deficient allenes yielded highly functionalized pyrazolines **142** and **144** (Scheme 1.45).[57]

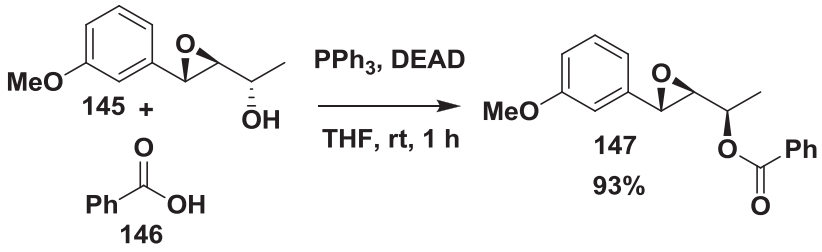


Scheme 1.45

1.2.4.3.1 Mitsunobu Reaction

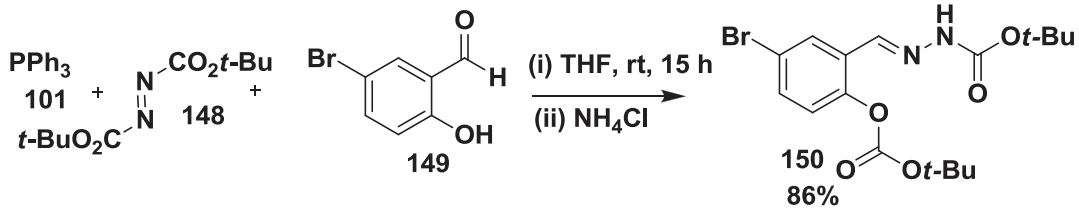
The phosphine-diethyl azodicarboxylate zwitterion was recognized as the key intermediate in the well-known Mitsunobu reaction. It is a versatile and widely used method for effecting a clean stereochemical inversion of chiral alcohols and was reported by Mitsunobu in 1971.[58] The reaction involves dehydrative coupling of an alcohol with

an acid or pronucleophile using a combination of an oxidizing azo reagent and a reducing phosphine under mild and neutral conditions (Scheme 1.46).[59] Diethyl azodicarboxylate (DEAD), is the commonly used azo reagent, triphenylphosphine (TPP) being the reducing phosphine. Carboxylic acids, phenols, diols, activated carbon acids, imides etc. can serve as the acid/pronucleophile reaction component.



Scheme 1.46

In 2005, Girard *et al*. observed the facile conversion of salicylaldehyde to protected hydrazone derivative **150** when it was exposed to triphenylphosphine-di-*tert*-butyl azodicarboxylate zwitterion. It is noteworthy that this is an exception to the normal Mitsunobu reaction in which phenols usually afford the alkyl aryl ethers whereas hydrazones are formed from salicylaldehyde (Scheme 1.47).[60]



Scheme 1.47

1.2.4.4 Phosphine-Allenoate Zwitterion

Allenes[61] are compounds characterized by a 1,2-diene group (Figure 1.1). Cumulated diene system of allenes has extraordinary properties, such as the axial chirality of the elongated tetrahedron and a higher reactivity than non-cumulated C-C double bonds. Naturally, these are very reactive molecules that can participate in a wide variety of reactions such as ionic and radical addition, cycloaddition, cyclization, transition metal catalyzed cycloisomerization, addition/cycloadddition, phosphine-catalyzed addition, cyclization etc.

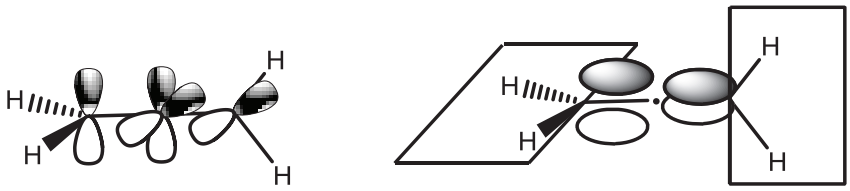
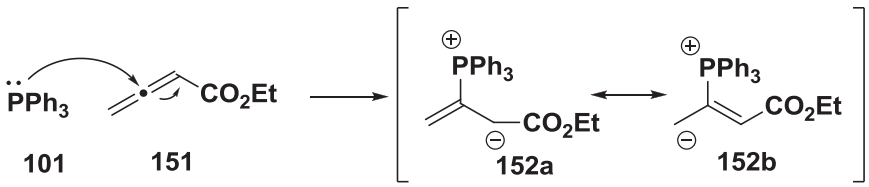


Figure 1.1 Pictorial representation of electronic structure of allene

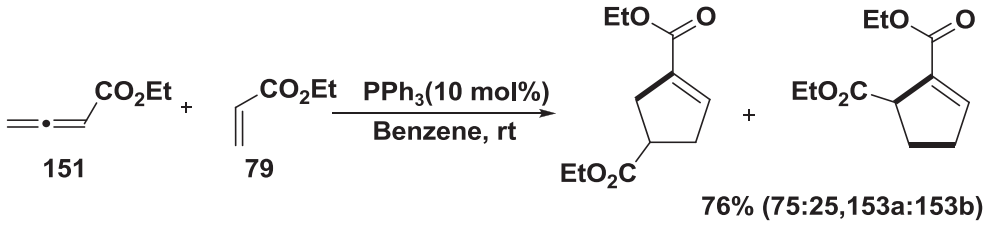
Allenoates can also form zwitterion as in the case of alkenes, alkynes and azoesters by the nucleophilic addition of phosphine (Scheme 1.48). The resultant zwitterionic intermediates can be trapped by various electrophiles to afford cyclic or acyclic compounds. Phosphine-allenoate zwitterions mainly undergo [3+2] and [4+2] cycloaddition reactions. The following section gives a brief description of these reactions.



Scheme 1.48

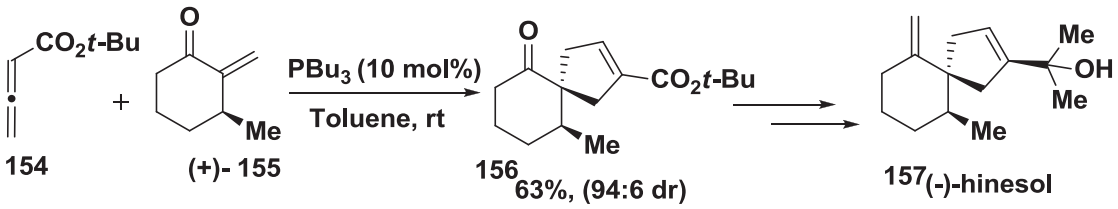
1.2.4.4.1 [3+2] Cycloaddition Reactions

Phosphine-catalyzed [3+2] cycloaddition of allenoates with α,β-unsaturated carbonyl compounds has been established as a promising method for the preparation of a variety of carbocycles from readily available starting materials. In 1995, α-allenoates were first utilized for phosphine-mediated coupling reactions in the pioneering work of Zhang and Lu.[62] Treatment of ethyl 2,3-butadienoate with electron-deficient olefins such as ethyl acrylate, in the presence of catalytic amount of triphenylphosphine, led to a formal [3+2] cycloaddition reaction (Scheme 1.49) to afford cyclopentenes **153a** and **153b** as regioisomers in a combined yield of 76%. It was found that in addition to acrylates, methyl vinyl ketone, acrylonitrile, diethyl fumarate and diethyl maleate were good substrates for this cycloaddition reaction.



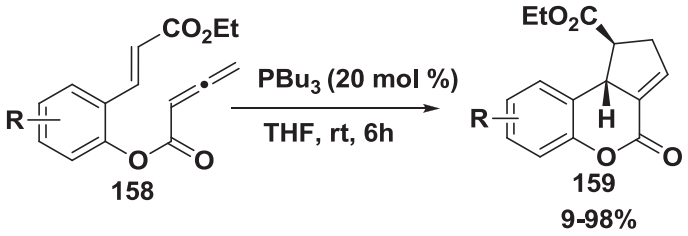
Scheme 1.49

Lu and co-workers then expanded the cycloaddition methodology to include exocyclic olefin substrates. The utility of this advance was demonstrated in the synthesis of (-)-hinesol **157** (Scheme 1.50) [63]



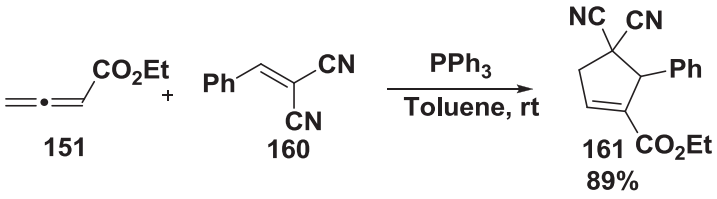
Scheme 1.50

Kwon *et al*. reported an intramolecular variant of this [3+2] cycloaddition, in which cyclopentene-fused dihydrocoumarins were formed in good to excellent yields, providing a simple and efficient approach to the synthesis of structurally complex coumarins **159** (Scheme 1.51).[64]



Scheme 1.51

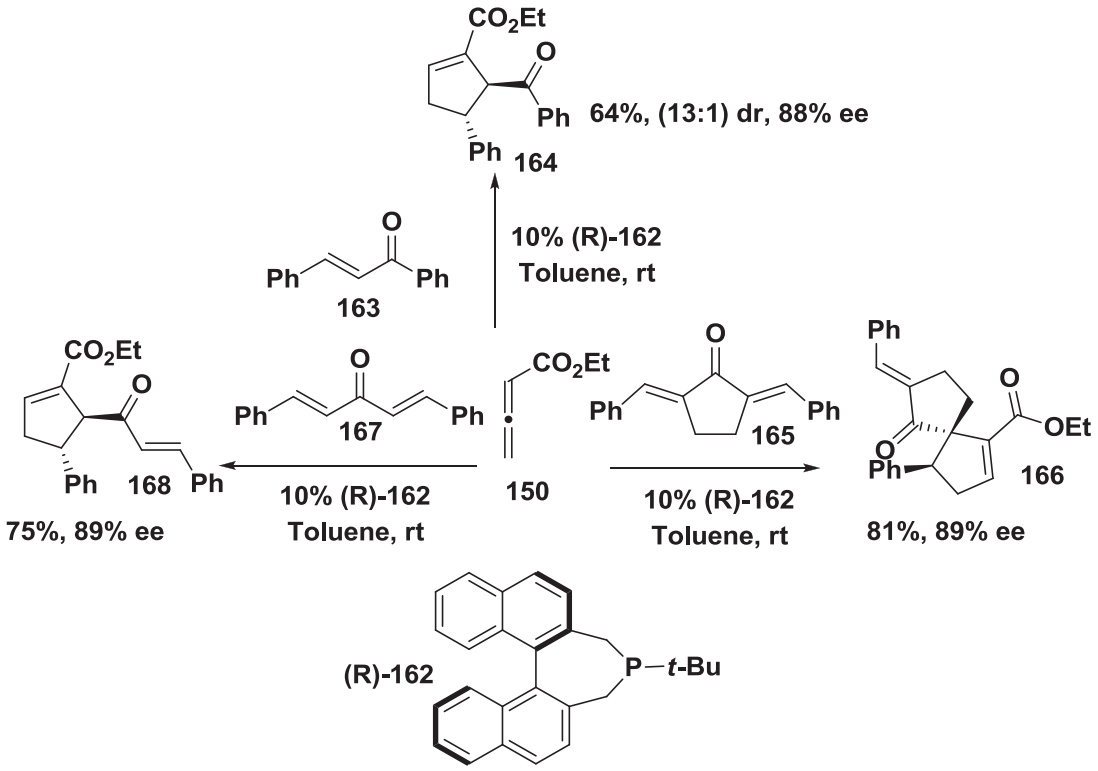
Lu *et al*. reported an intermolecular [3+2] cycloaddition of allenoate **151** with dicyanostyrene **160**. The reaction yielded single regioisomer of substituted cyclopentene derivative **161** (Scheme 1.52).[65]



Scheme 1.52

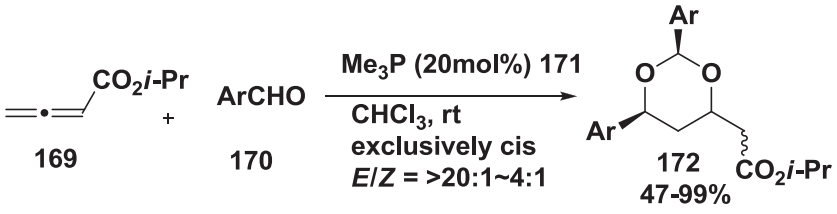
Asymmetric catalytic version of Lu's [3+2] cycloaddition of allenes with olefins was reported by Zhang and co-workers.[66] Here, the range of olefins is limited to unsubstituted acrylate esters and diethyl maleate, although good enantioselectivity is achieved. Fu and co-workers expanded the asymmetric [3+2] cycloaddition of allenes with olefins using chiral phosphine (R)-**162**. With the latter, the scope of activated

olefins was broadened to include α,β-unsaturated enones, dienones and tethered dienones to yield functionalized cyclopentenes with high enantioselectivity (Scheme 1.53).[67]



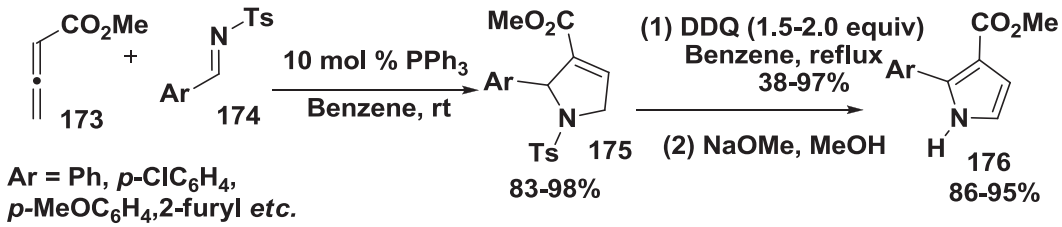
Scheme 1.53

It has been reported by Kwon and co-workers that the reaction of allenoate and aldehyde, in the presence of 20 mol% Me_3P, afforded the (2,6-diaryl[1,3]dioxan-4-ylidene)acetates **172** in moderate to excellent yields with complete diastereoselectivity and high *E*/*Z*-selectivities.[68]



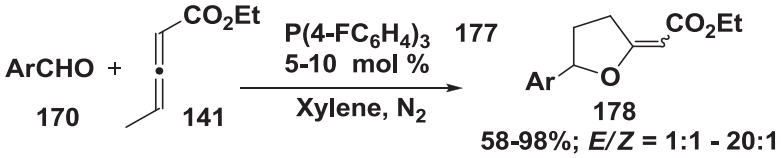
Scheme 1.54

Xu and Lu extended this [3+2] cycloaddition to tosylimines, and the reaction afforded various nitrogen heterocyles as single regioisomers (Scheme 55).[69]



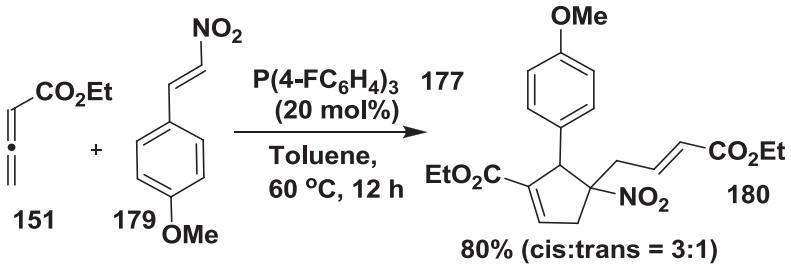
Scheme 1.55

In 2009 He *et al.* reported a [3+2] annulation of 3-methyl allenoate with aromatic aldehydes using tris(pentafluorophenyl)phosphine **177** to form 2-alkylidine tetrahydrofuran derivative **178** (Scheme 1.56).[70]



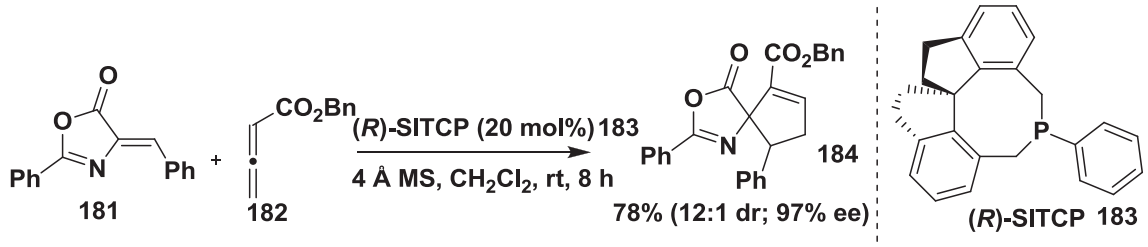
Scheme 1.56

It has been reported by Shi and co-workers that phosphine-catalyzed tandem reaction between ethyl 2,3-butadienoate and nitrostyrene **179** delivered cyclopentene derivative **180** in 80% yield. The transformation involves a [3+2] cycloaddition and a subsequent umpolung addition. The asymmetric version of this reaction has also been investigated using chiral phosphines (Scheme 1.57).[71]



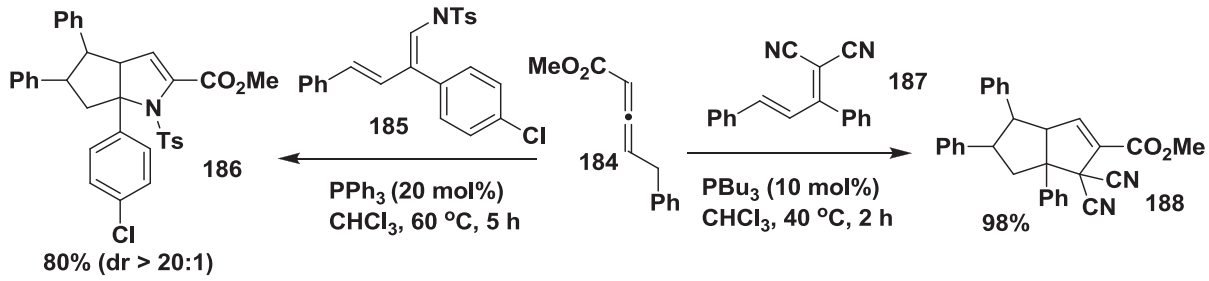
Scheme 1.57

A highly regio-, diastereo- and enantioselective [3+2] cycloaddition of alkylidene azlactones with various allenic esters has been developed by the same group using an axially chiral spiro-phosphine catalyst **183**. The reaction afforded the corresponding functionalized spirocyclic products in moderate to excellent yields under mild conditions (Scheme 1.58).[72]



Scheme 1.58

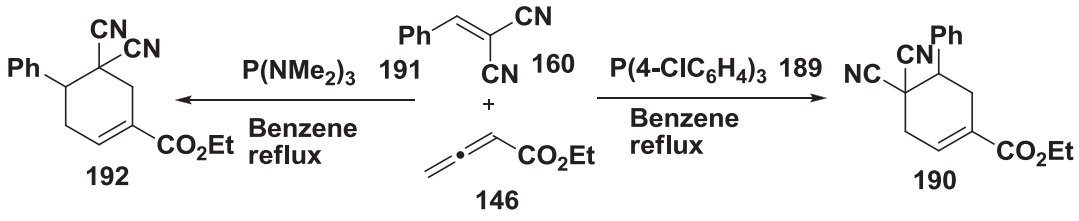
Very recently, Huang *et al*. reported a novel and efficient phosphine-catalyzed sequential [2+3] and [3+2] annulation domino reaction of γ-benzyl substituted allenoate. The reaction of the zwitterion with (*E*)-2-(1,3-diarylallylidene)malononitrile **187** and (*E*)-1-(3,4-diarylallylidene)-4-methylbenzenesulfonamide **185** proceeded smoothly to produce bicyclo[3.3.0]octene derivative **188** and aza-bicyclo[3.3.0]octene derivative **186** respectively in good yields (Scheme 1.59).[73]



Scheme 1.59

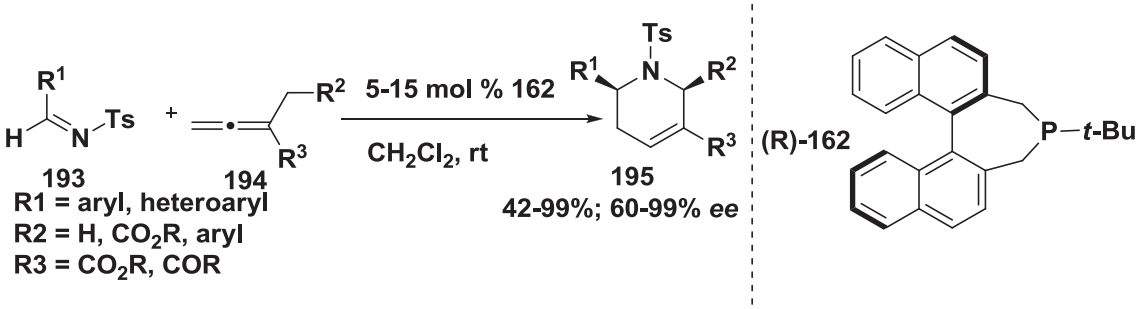
1.2.4.4.2 [4+2] Cycloaddition Reactions

Recently, the Kwon group successfully utilized nucleophilic phosphine catalysis for the highly regioselective synthesis of cyclohexenes from activated allenes and alkenes *via* intermolecular [4+2] annulations (Scheme 1.60).[74]



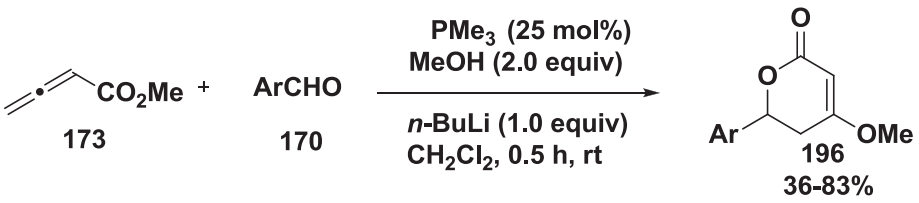
Scheme 1.60

Also, the [4+2] annulation of allenes with imines using chiral phosphine catalyst (R)-**162** afforded piperidine derivatives enantioselectively (Scheme 1.61).[75,76]



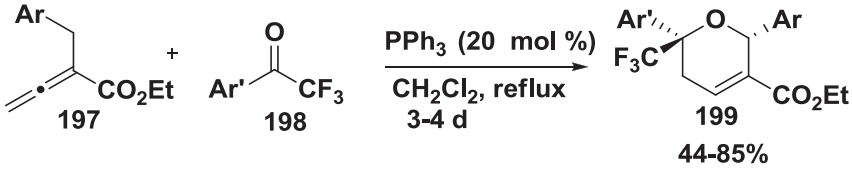
Scheme 1.61

The same group, in result of their research on phosphine-catalyzed annulation of allenoate with aldehydes, found that the addition of an alcohol to the reaction system can promote the formation of disubstituted dihydropyrones (Scheme 1.62).[77]



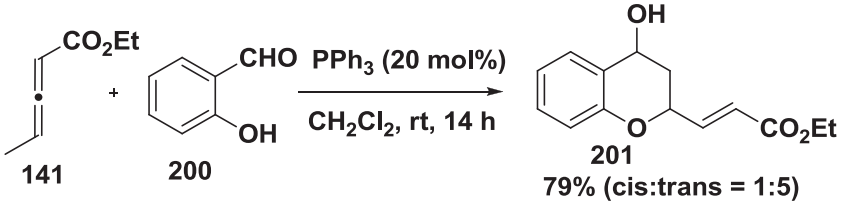
Scheme 1.62

Wang and Ye found that 6-trifluoromethyl-5,6-dihydropyran derivatives could be synthesized with high diastereoselectivity by the phosphine catalyzed [4+2] annulation of α-benzyl butadienoate and trifluoromethyl ketones (Scheme 1.63).[78]



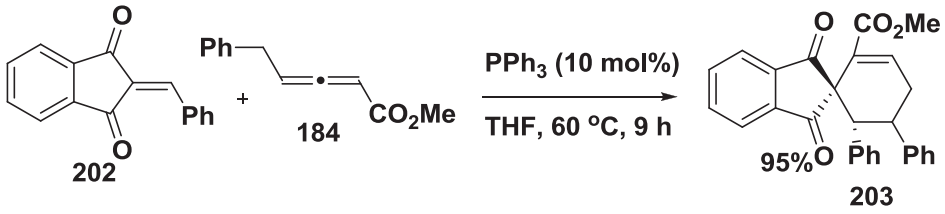
Scheme 1.63

Phosphine-catalyzed [4+2] annulation of γ-methyl allenoate **141** with salicylaldehyde was reported in 2011 by Ma *et al*. The reaction afforded highly functionalized chroman **201** (Scheme 1.64).[79]



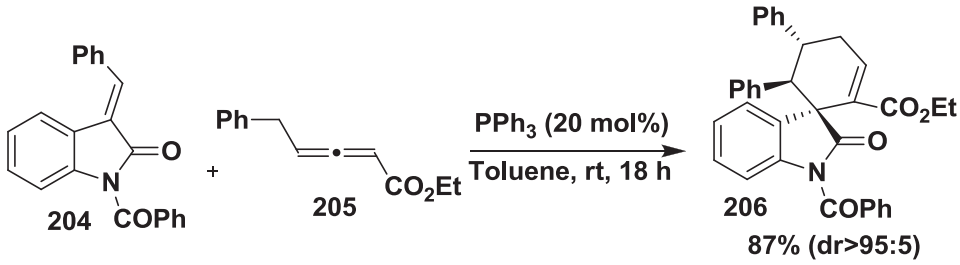
Scheme 1.64

The first phosphine-catalyzed [4+2] annulation of γ-substituted allenoates with 2-arylidene-1*H*-indene-1,3(2*H*)-diones has been reported by Li *et al.* In this case, the γ-benzyl allenoate **184** serves as a 1,4-dipolar synthon and the reaction led to the construction of highly substituted spiro[4.5]dec-6-ene skeleton **203** in excellent yields, and with complete regioselectivity and high diastereoselectivity (Sheme 65).[80]



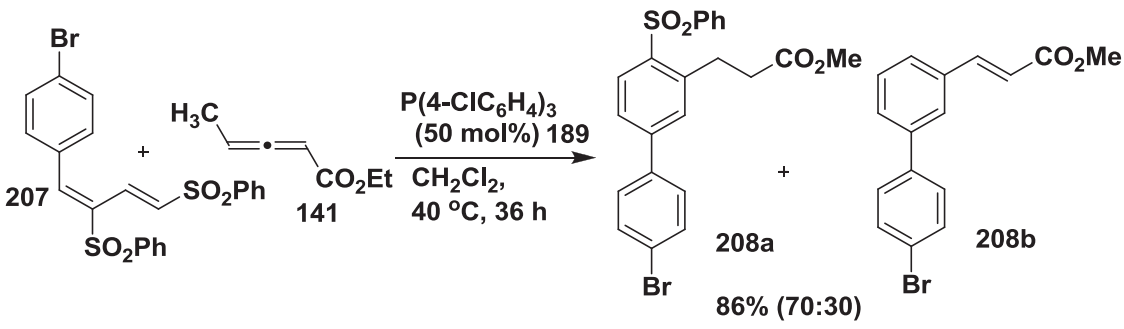
Scheme 1.65

Independently, the reaction of the same allenoate showing similar reactivity pattern was reported by Gicquel *et al*. The reaction of 3-arylidene oxindoles and γ-benzyl allenoate in presence of phosphine afforded spirocyclic oxindoles with functionalized six-membered rings (Scheme 1.66).[81]



Scheme 1.66

The first phosphine-catalyzed domino benzannulation of 1,3-bis(sulfonyl)butadiene and γ-methyl allenoate was reported from the group of Huang. The reaction furnished biaryl derivatives in good yields (Scheme 1.67).[82]

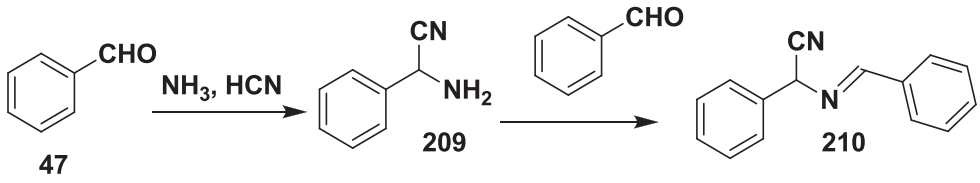


Scheme 1.67

1.3 Multicomponent reactions

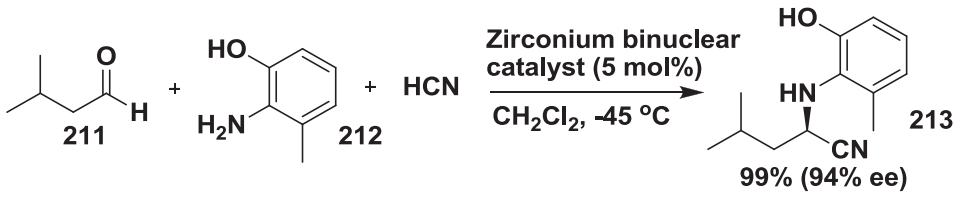
Multicomponent reactions (MCRs) are those reactions whereby more than two reactants combine in a sequential manner to give highly selective products that retain majority of the atoms of the starting material.[83] In other words, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. Multicomponent reactions (MCRs) have gained great importance in modern organic synthesis, due to their atom economy, environmental amiability and operational simplicity.

The history of MCRs began, when Laurent and Gerhardt prepared "benzoylazotid" from bitter almond oil and ammonia in 1838. In this reaction the cyanohydrin, derived from benzaldehyde **45** and hydrocyanic acid, reacts with ammonia giving amino benzyl cyanide **209** whose Schiff base with benzaldehyde was called "benzoyl azotid" **201** (Scheme 1.68).[84]



Scheme 1.68

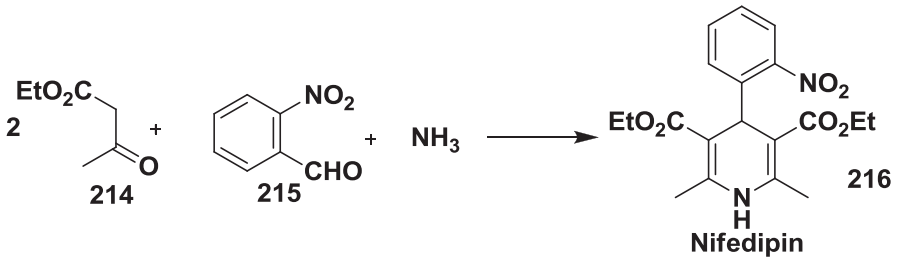
The Strecker α-amino acid synthesis, reported in 1850, is another important MCR that involves the three-component condensation of ammonia, aldehyde and hydrogen cyanide to afford α-amino nitrile, which on subsequent hydrolysis furnishes the α-amino acid.[85] Kobayashi and co-workers reported the first efficient three-component asymmetric version of the Strecker reaction by employing a chiral zirconium binuclear catalyst (Scheme 1.69).[86]



Scheme 1.69

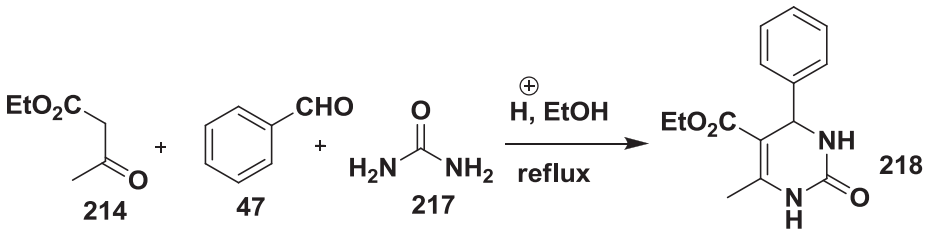
Hantzsch 1,4-dihydropyridine synthesis from ammonia, aldehyde and acetoacetic ester, reported in 1882 is another historically relevant MCR.[87] Dihydropyridines are biologically important compounds and this methodology has been applied to the

synthesis of Nifedipin® **216**, an important drug used in cardiovascular therapy (Scheme 1.70).[88]



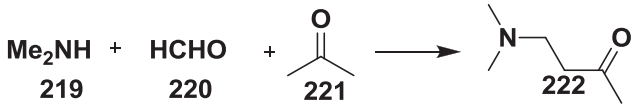
Scheme 1.70

The acid catalyzed three-component condensation of aldehydes, β-ketoesters and urea to afford dihydropyrimidines was reported by Biginelli in 1891 (Scheme 1.71).[89] Several variants of this reaction have been reported by changing all building blocks, allowing access to a large number of multifunctionalized pyrimidine derivatives with important biological properties.[90]



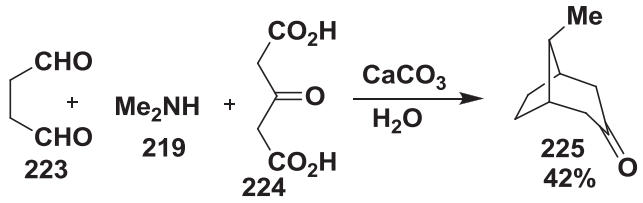
Scheme 1.71

The one-pot synthesis of aminomethylated carbonyl compounds from formaldehyde, secondary amine and ketones is a commonly used and important MCR achieved by Mannich in 1912 (Scheme 1.72).[91]



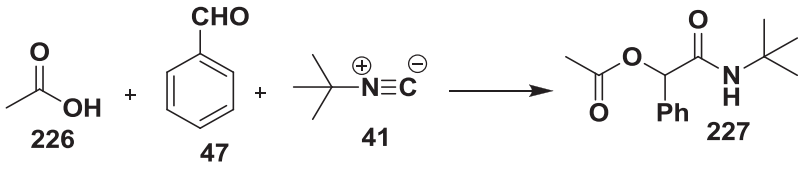
Scheme 1.72

It is worthy of note that Robinson's landmark synthesis of tropinone **225** — precursor for the alkaloid tropane—involves two successive Mannich reactions and provides a spectacular application of MCRs in natural product synthesis (Scheme 1.73).[92]



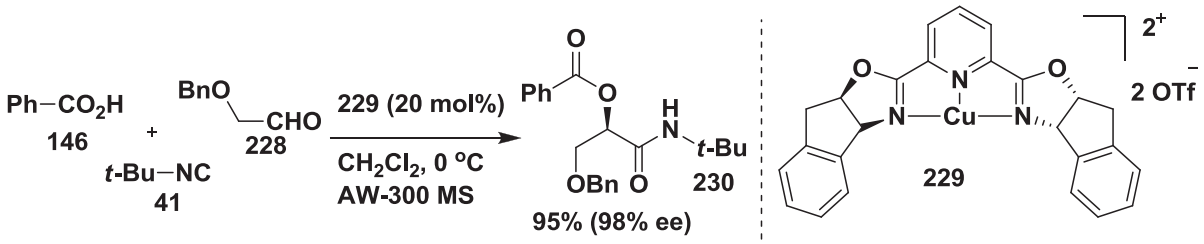
Scheme 1.73

Introduction of isocyanides in organic synthesis was a boon to the realm of multicomponent reactions. The great potential of isocyanides for the development of MCRs lies in the diversity of bond forming processes available, their functional group tolerance and the high levels of chemo-, regio- and stereoselectivity often observed. A large number of isocyanide based multicomponent reactions has been reported. In his seminal work in 1921, Passerini discovered the three-component reaction (P-3CR) of electrophilic ketones or aldehydes with isocyanides and carboxylic acids leading to α-acyloxy amides (Scheme 1.74).[93]



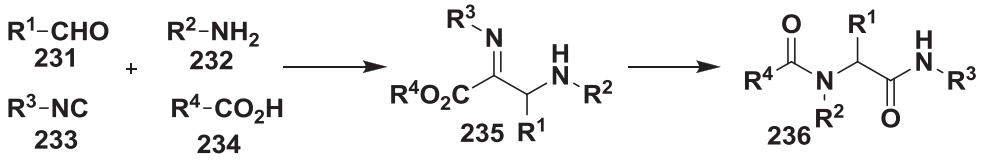
Scheme 1.74

Schreiber and co-workers reported a catalytic asymmetric Passerini reaction using tridentate indan (pybox) Cu(II) Lewis acid complex **229**. The reaction is found to be accelerated by the ligand of the catalyst (Scheme 1.75).[94]



Scheme 1.75

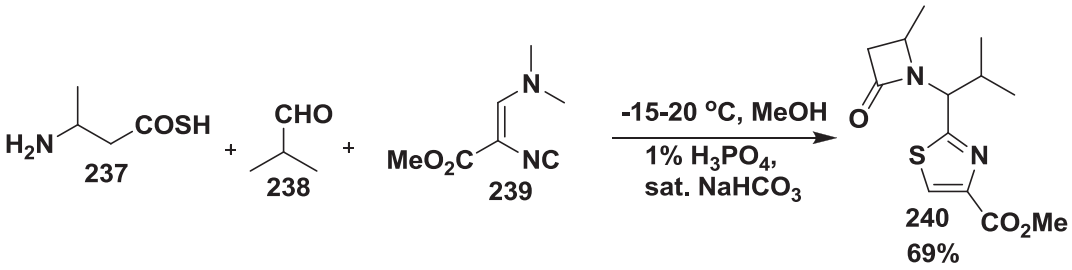
Another important isocyanide-based multicomponent reaction is the Ugi four-component reaction (U-4CR) discovered by Ivar Ugi in 1959. He showed that by exposing amines to carbonyl compounds, isocyanides and acids, high yields of α-aminocarboxamide derivatives can be obtained (Scheme 1.76).[95]



Scheme 1.76

The scope of the Ugi reaction has been extended considerably by changing the bulding blocks and reaction conditions. For example Dömling reported a novel three-

component reaction of β-aminothiocarboxylic acids, aldehydes, and 3-dimethylamino-2-isocyanoacylate under mild conditions. During the course of this reaction two heterocyclic moieties, a thiazole and a β-lactam ring, are formed simultaneously by the construction of two C–N, two C–S and one C–C bonds (Scheme 1.77).[96]



Scheme 1.77

1.4 Conclusion and Present Work

From the above discussion, it is clear that the zwitterions play a key role in organic synthesis, particularly in organocatalysis and in multicomponent reactions (See section **1.2.1.** to **1.2.3.**). The zwitterions can be generated by addition of nucleophiles to activated π-systems such as alkenes, alkynes and allenoates. The primary dipolar complex generated is stabilized by trapping with electrophilic π-systems which can lead to the formation of two kinds of products; one which retains all or most of the atoms of the starting materials including the nucleophile (Multicomponent reaction) and the other devoid of the nucleophile (Organocatalytic reaction).

The role of alkenes, alkynes and azoesters in zwitterion chemistry is well established several years ago. Allenoates were introduced to this field only recently. The following chapters discuss the reactions of various zwitterions derived from allenic esters. The second chapter describes a multicomponent reaction involving aniline-allenoate zwitterion. And the succeeding chapters deal with the phosphine-mediated reactions of 3-alkyl allenoates with various 1,2-dicarbonyl compounds, *viz*., diaryl 1,2-diones, alicyclic 1,2-diones, *o*-quinones, and isatins to furnish a variety of carbocycles and heterocycles.

1.5 References

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CHAPTER 2

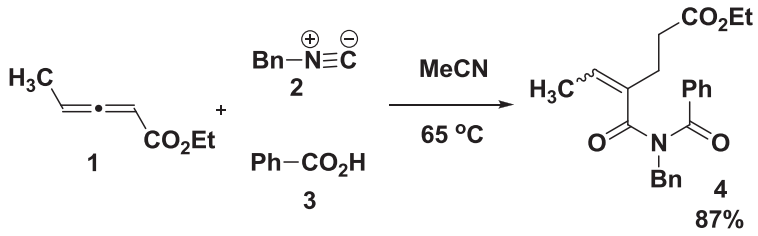
Synthesis of Dihydropyridine Derivatives *via* Multicomponent Reactions Involving Allenoate-Aniline Zwitterions

2.1 Introduction

Multicomponent reactions (MCRs) are important tools for the construction of a large variety of cyclic and acyclic compounds. They are well-known for their convergence, atom economy and high stereoselectivity and constitute relatively simple and benign procedures which often lead to biologically important and complex organic molecules in one pot. By definition, MCRs are reactions in which three or more reactants combine in a sequential manner to afford a product which retains all or most of the atoms of the starting materials. In the previous chapter we have discussed some historically important multicomponent reactions, *viz*., Strecker aminoacid synthesis,[1] Hantzsch dihydropyridine synthesis,[2] Beginelli reaction,[3] Mannich reaction,[4] Robinson's tropinone synthesis,[5] Passerini reaction[6] and Ugi reaction.[7] The emergence of zwitterion chemistry[8] has added a new dimension to multicomponent reactions. In this chapter, a novel MCR involving allenoate-aniline zwitterion for the facile synthesis of dihydropyridines is described. To put the present work in perspective, a brief survey of the multicomponent reactions involving allenic esters and various methods for the synthesis of dihydropyridines are given in the following section.

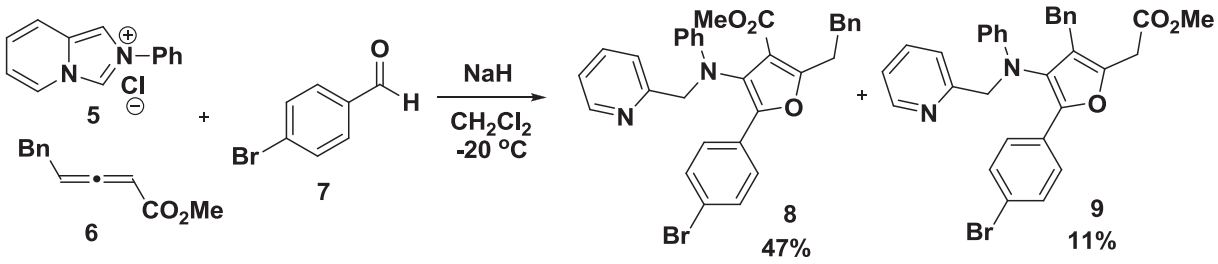
2.2 MCRs Involving Allenoates

Allenoates can participate as a component in multicomponent reactions. Huang and Sha reported the synthesis of highly substituted acrylimide exemplified by **4**, by the three-component reaction of allenoates, isocyanides, and carboxylic acids (Scheme 2.1).[9]



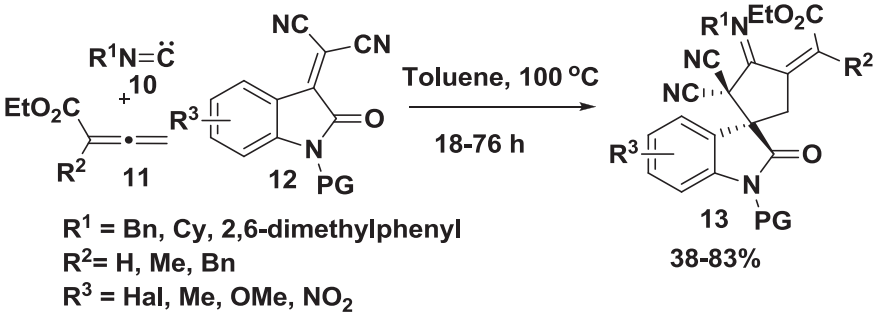
Scheme 2.1

A three-component reaction of N,N-substituted imidazo[1,5-a]pyridine carbenes, also called imidazo[1,5-a]pyridin-3-ylidenes, with aldehydes and allenoates leading to the synthesis of furan derivatives was reported by Cheng and co-workers (Scheme 2.2).[10]



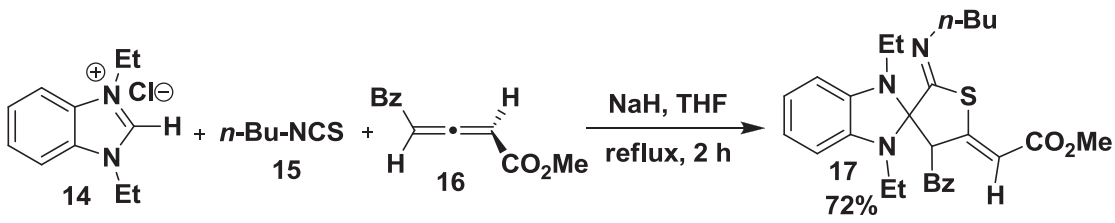
Scheme 2.2

Recently Li *et al*. reported a three component [2+2+1] cycloaddition reaction of isocyanide-allenoate zwitterion with isatilidene malononitriles to form spirocyclic oxindoles (Scheme 2.3).[11]



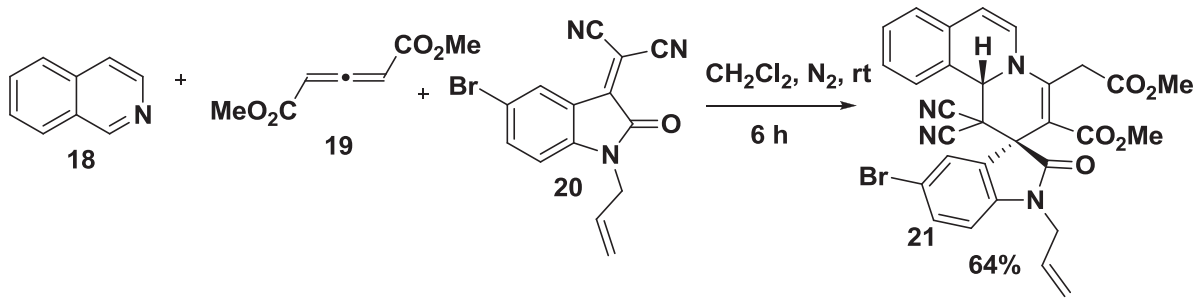
Scheme 2.3

A three-component reaction of benzimidazole carbene with isothiocyanate and allenoate proceeded efficiently in a highly site-, regio-, and stereoselective manner to afford predominantly spiro[benzimidazoline-2,3′-tetrahydrothiophene] derivative **17** (Scheme 2.4).[12] The reaction was proposed to occur *via* a tandem nucleophilic addition of carbene to isothiocyanate followed by an unusual [3+2] cycloaddition to the less activated carbon–carbon double bond of allenoate.



Scheme 2.4

Work in our laboratory has shown that the three component reaction of isoquinoline, allenoate and isatilidene furnished spiro-oxindole derivative **21** (Scheme 2.5)[13]



Scheme 2.5

2.3 Synthesis of Dihydropyridines *via* MCRs

Dihydropyridines are important structural frameworks present in many pharmacologically important compounds. These compounds are found to be calcium channel modulators, and were developed as cardiovascular and antihypertensive drugs, which include nifedipine, amlodipine and felodipine (Figure 2.1).

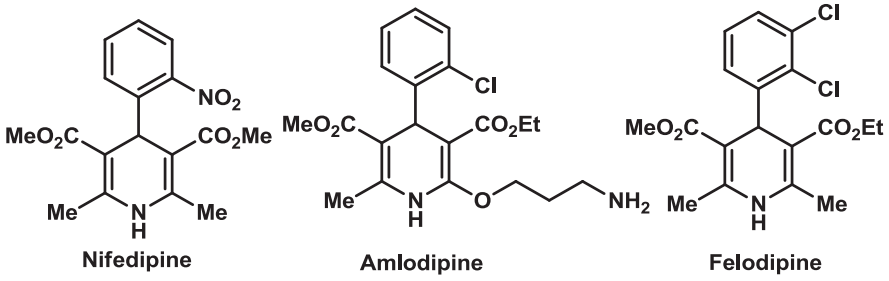
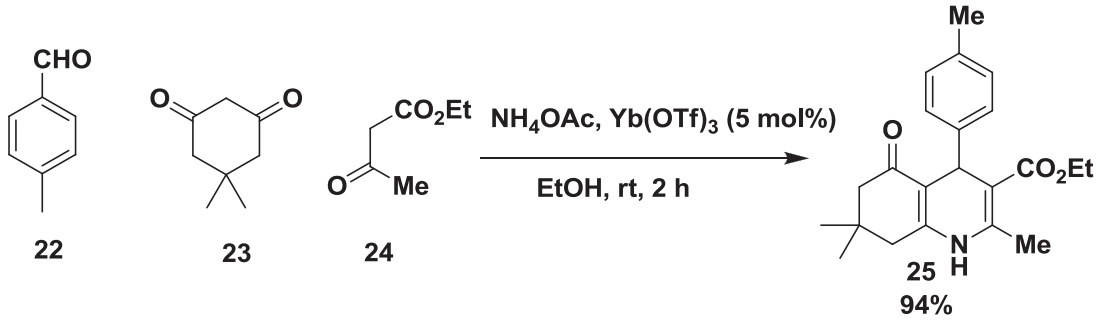


Figure 2.1. Dihydropyridine drugs

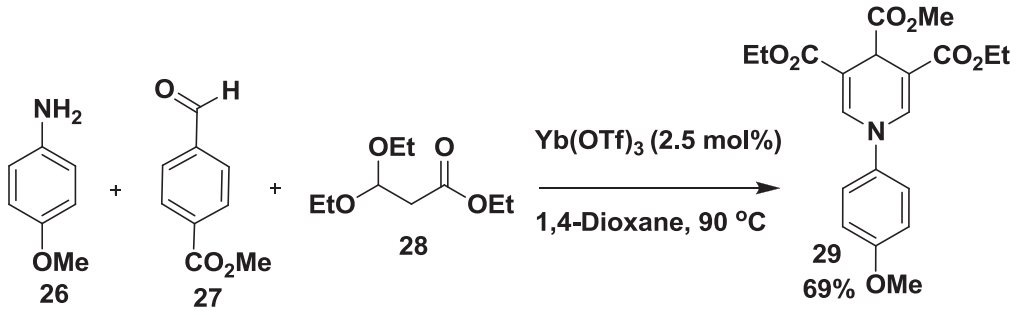
Hantzsch reaction is the best known method for the synthesis of dihydropyridine derivatives. Classical Hantzsch reaction involves the reaction of ammonia, aldehyde and acetoacetic ester to form 1,4-dihydropyridine derivatives. A number of modern varients of this strategy is available. In 2005, an efficient $Yb(OTf)_3$ catalyzed Hantzsch reaction was reported by Wang and co-workers. The reaction of aldehyde, dimedone, ethyl

acetoacetate and ammonium acetate under mild conditions afforded polyhydroquinoline derivative **25** (Scheme 2.6). [14]



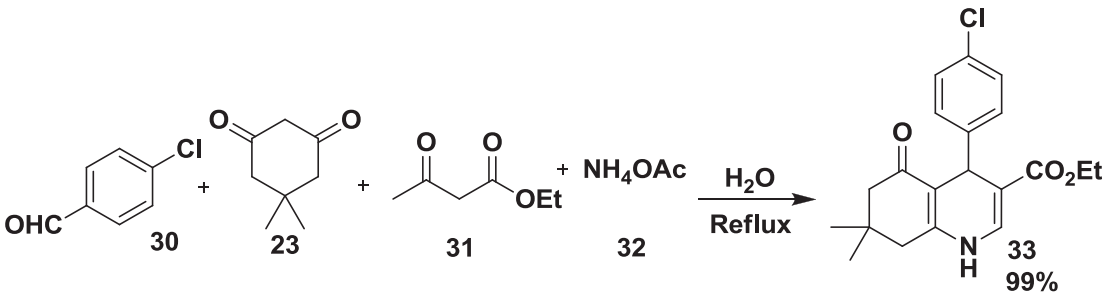
Scheme 2.6

One pot reaction of aniline, benzaldehyde, and ethyl 3,3-diethoxypropionate in the presence of $Yb(OTf)_3$ led to the synthesis of 1,4-dihydropyridine derivative **29** in good yields (Scheme 2.7).[15]



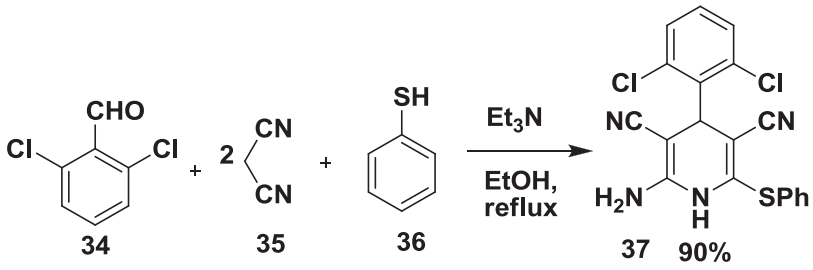
Scheme 2.7

Highly efficient and environmentally benign synthesis of polyhydroquinoline derivatives was recently reported *via* four component reaction of aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate in refluxing water. Polyhydroquinoline derivatives were obtained in excellent yield using this green protocol (Scheme 2.8).[16]



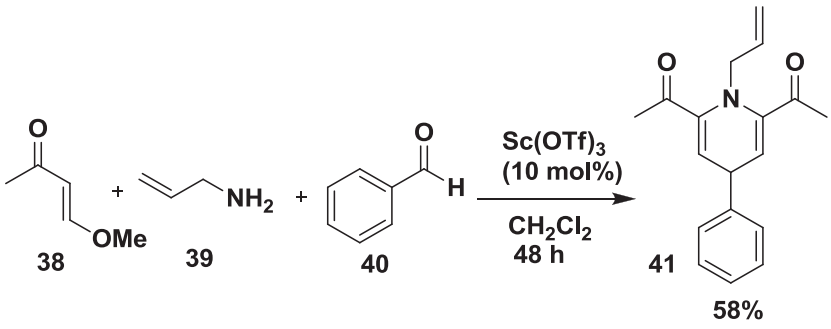
Scheme 2.8

One step, three-component synthesis of dihydropyridines was reported by the reaction of aldehydes with various thiols and malononitrile in presence of a base (Scheme 2.9).[17]



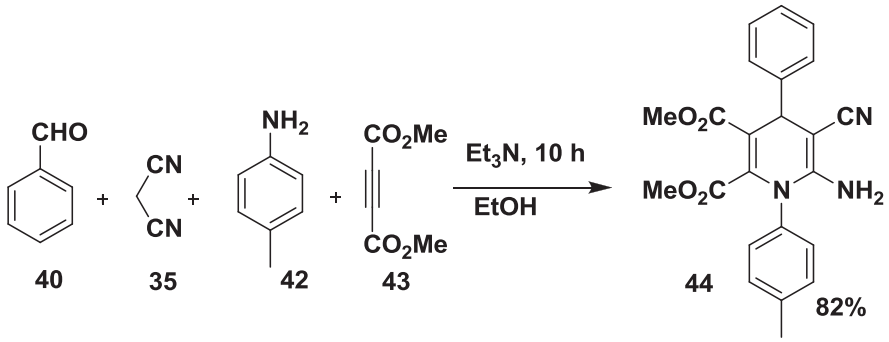
Scheme 2.9

Lewis acid catalyzed reaction of methoxy vinylmethylketone **38** with amine **39** and benzaldehyde resulted in a formal [1+2+1+2] cycloaddition to yield dihydropyridine derivative **41** (Scheme 2.10).[18]



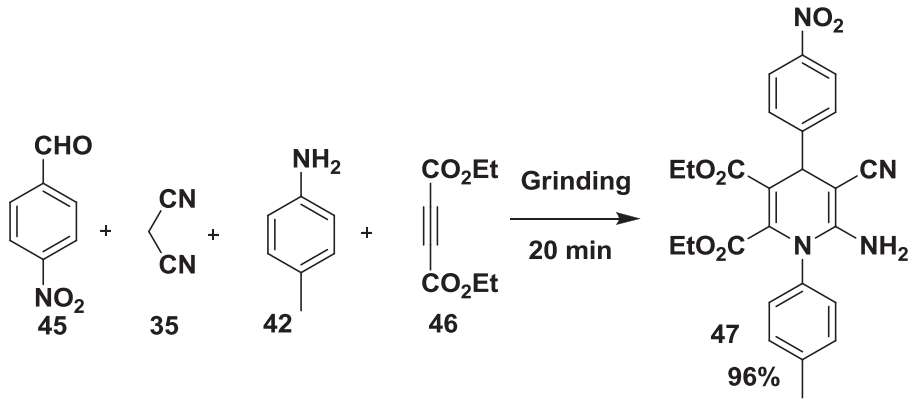
Scheme 2.10

Another efficient strategy for the preparation of polysubstituted dihydropyridines was developed through a four component reaction of aromatic aldehydes, malononitrile, arylamines and acetylenedicarboxylate in the presence of triethylamine as a base promoter (Scheme 2.11).[19]



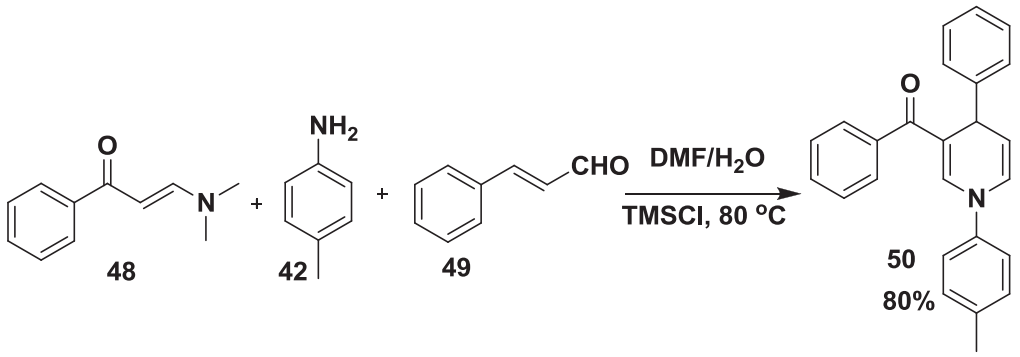
Scheme 2.11

A grinding-induced, catalyst and solvent free domino multicomponent reaction for the synthesis of 1,4-dihydropyridines was reported employing aldehydes, amines, diethyl acetylenedicarboxylate, and malononitrile or ethyl cyanoacetate. Mild conditions, high yields, environmental amiability and operational simplicity are the attractive features of this procedure (Scheme 2.12).[20]



Scheme 2.12

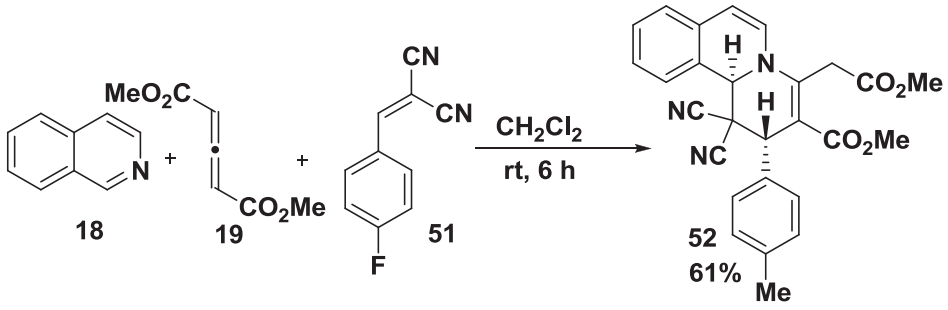
The synthesis of 1,3,4-trisubstituted 1,4-dihydropyridines was reported by Pan and co-workers in 2009. The three-component reaction of α,β-unsaturated aldehyde, amine, and enaminone in aqueous DMF proceeded smoothly to give 1,4-dihydropyridine **50**. Interestingly, the unexpected regioselective formation of 1,2-dihydropyridines was observed when anilines with bulky or strong electron withdrawing groups were used (Scheme 2.13).[21]



Scheme 2.13

2.4 Background to the Present Work

Recently, a novel three component reaction utilizing the transient zwitterion generated from allenoate **19** and isoquinoline was reported by our group. The allenoate–isoquinoline zwitterion was efficiently intercepted with cyanoacrylates and arylidenemalononitriles to form highly functionalized pyridoisoquinoline derivatives (Scheme 2.14).[22] Success of this reaction encouraged us to explore this area further, especially to investigate the chemistry of the zwitterion derived from allenoate and a primary amine, *viz*., aniline.

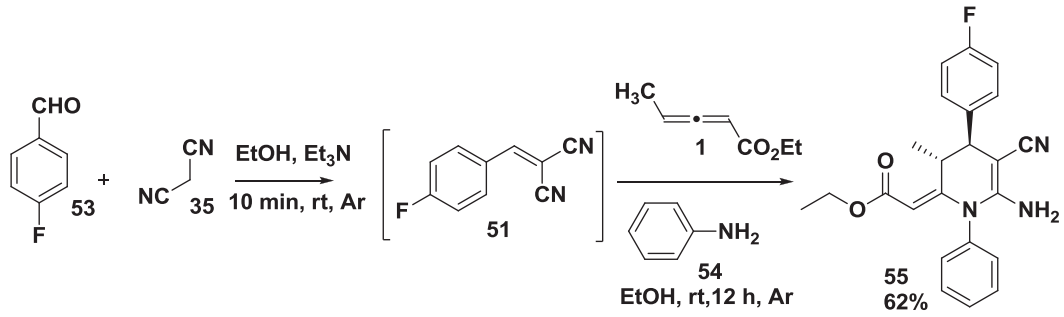


Scheme 2.14

2.5 Results and Discussion

2.5.1 Synthesis of Dihydropyridines

In a prototype experiment, a solution of 4-fluorobenzaldehyde, malononitrile and triethylamine was stirred under argon atmosphere in ethanol. After 10 minutes, a solution of aniline and ethyl penta-2, 3-dienoate in ethanol was added and the mixture was stirred for 12 h. The crude product on purification by column chromatography using silica gel and hexane: ethylacetate (70: 30) as the eluent afforded (*E*)-Ethyl2-(6-amino-5-cyano-4-(4-fluorophenyl)-3-methyl-1-phenyl-3,4-dihydropyridin-2(1*H*)-ylid- ene)acetate **55** as colourless crystalline solid (mp184-186 ^{o}C) in 62% yield (Scheme 2.15).



Scheme 2.15

The structure of the product was established using common spectroscopic analysis and elemental analysis. The IR spectrum showed characteristic –NH_2 absorptions at 3471, 3337 cm^{-1} and –CN absorption at 2179 cm^{-1}. Absorption at 1702 cm^{-1} corresponds to the ester carbonyl group. In the ^{1}H NMR spectrum the olefinic proton and the –NH_2 protons were discernible as singlets at δ 4.33 and 4.19 ppm respectively (Figure 2.2). In the ^{13}C NMR spectrum the ester carbonyl group displayed a resonance signal at δ 166.2 ppm (Figure 2.3). Final confirmation of the structure and relative stereochemistry was derived from single crystal X-ray analysis of the compound **55** (Figure 2.4).

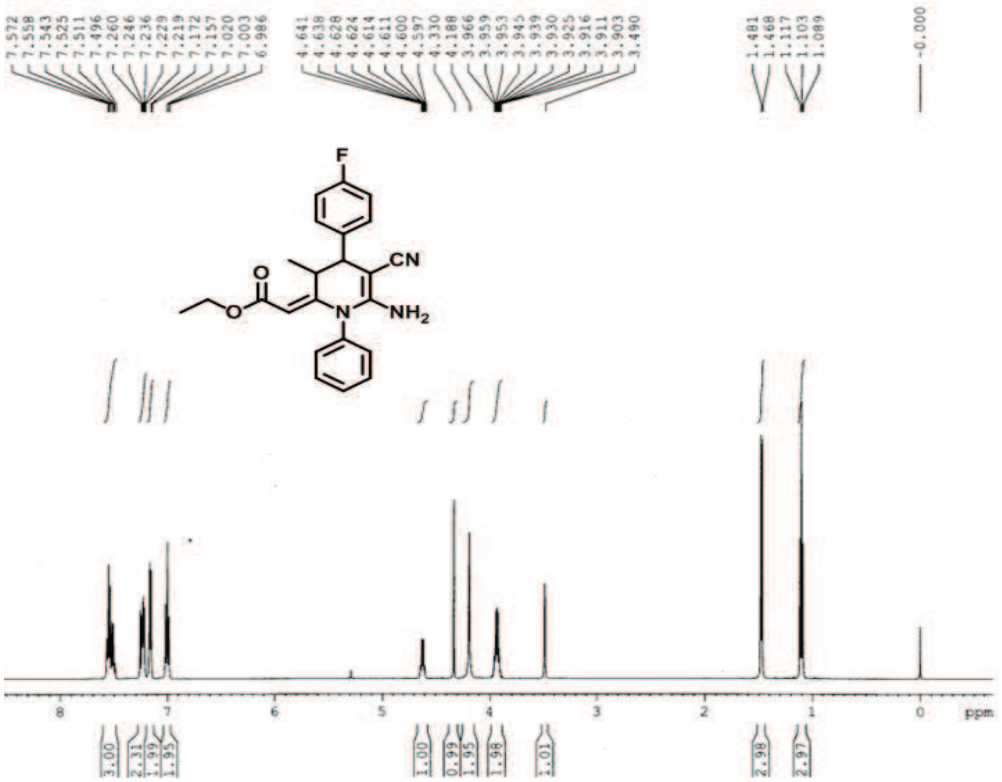


Figure 2.2 ^{1}H NMR spectrum of compound **55**

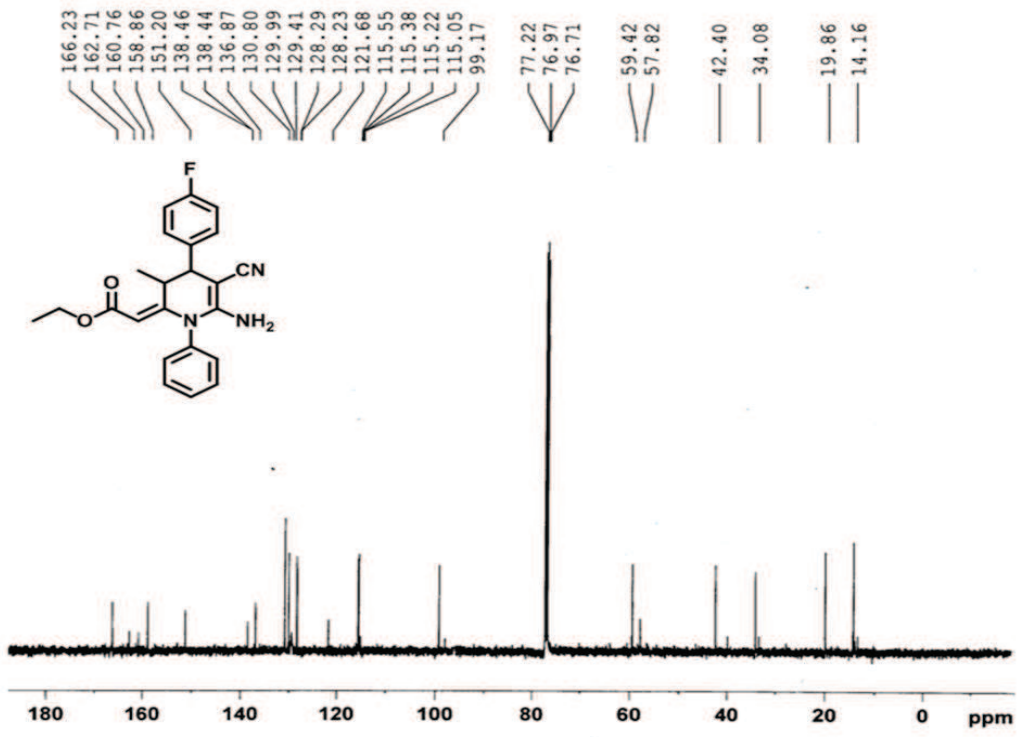


Figure 2.3 ^{13}C NMR spectrum of compound **55**

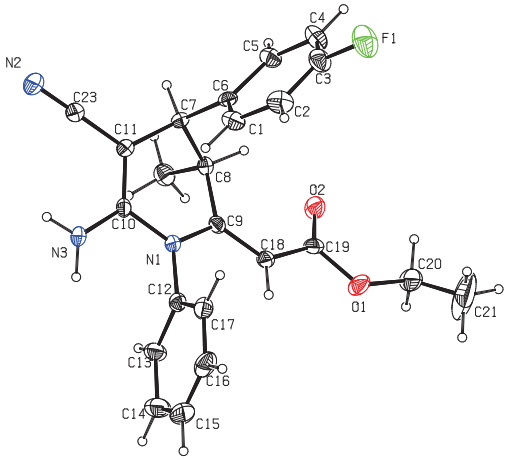


Figure 2.4 ORTEP diagram of **55**

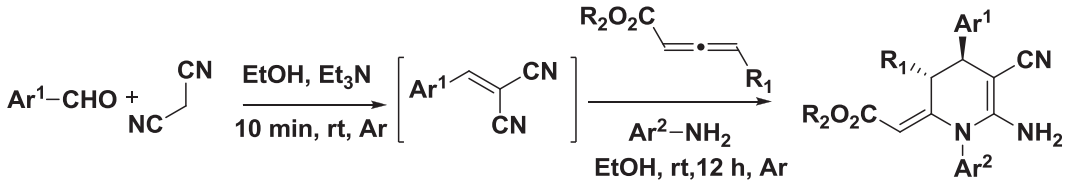
With a view to optimize the reaction conditions, experiments were conducted by varying solvent, base and temperature. However, no improvement in the yield was observed, and the results are depicted in Table 2.1.

Table 2.1 Condition optimization

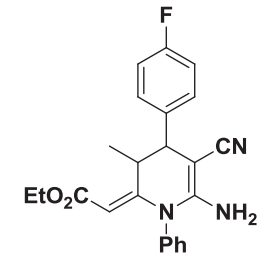
Entry	Base	Solvent	Temperature	Yield (%)
1	Et_3N	EtOH	rt	62
2	Et_3N	THF	rt	-
3	Et_3N	DCM	rt	-
4	Et_3N	EtOH	0 ^oC-rt	32
5	Et_3N	EtOH	80 ^oC	56
6	DBU	EtOH	rt	-
7	DMAP	EtOH	rt	-
8	DABCO	EtOH	rt	-
9	NaH	EtOH	rt	-

Analogous products were obtained when the reaction was carried out using dialkyl penta-2,3-dienedioates under the same conditions, and structure of the products was assigned using spectroscopic analysis. The reaction was found to be general with respect to different types of allenoates and aldehydes and the results are summarized in Table 2.2.

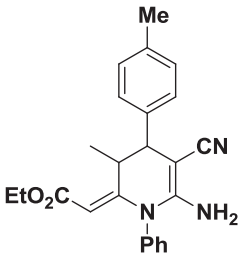
Table 2.2 Substrate scope



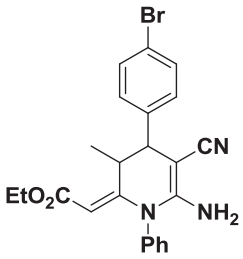
Ar^1 = aryl; Ar^2 = aryl; R^1 = Me, CO_2Et, CO_2t-Bu; R^2 = Me, Et



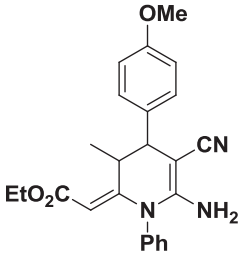
55 (62%)



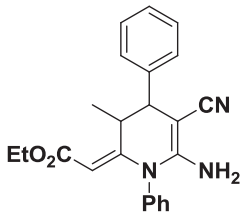
56 (56%)



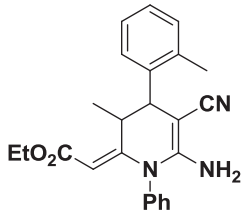
57 (49%)



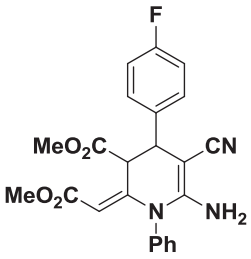
58 (45%)



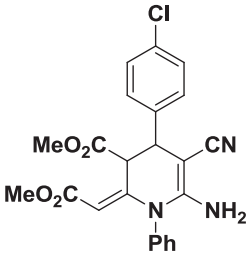
59 (42%)



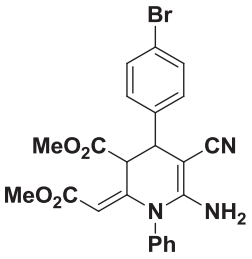
60 (46%)



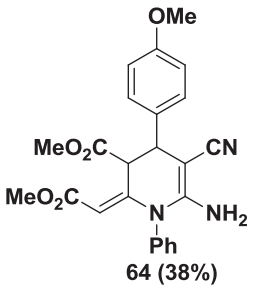
61 (56%)



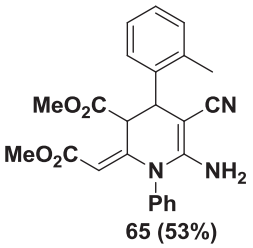
62 (58%)



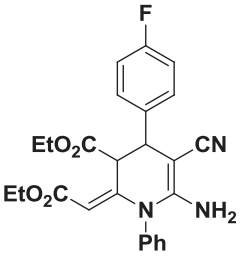
63 (42%)



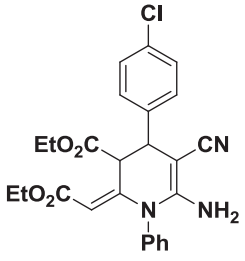
64 (38%)



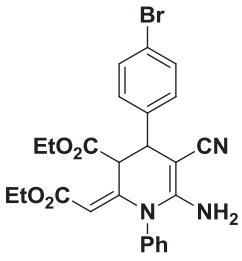
65 (53%)



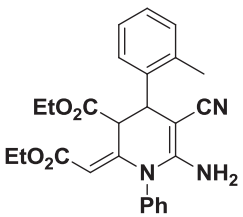
66 (71%)



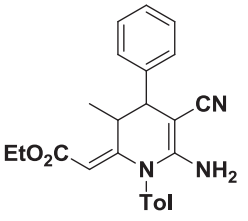
67 (65%)



68 (57%)



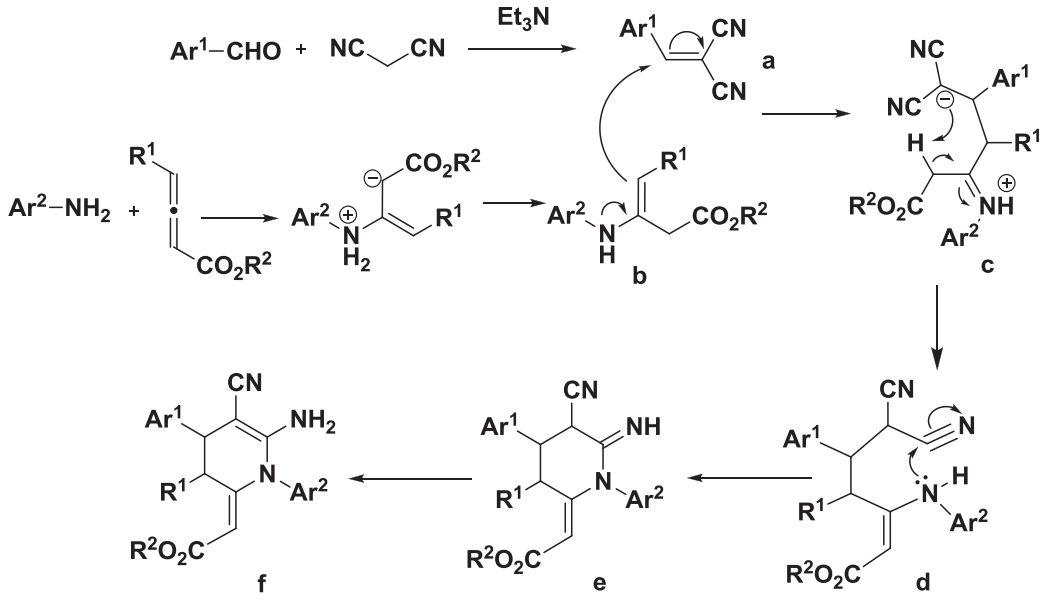
69 (48%)



70 (56%)

A mechanistic rationale for the formation of the dihydropyridine derivative may be outlined as follows. Addition of aniline to the allenoate affords a zwitterion which on proton transfer delivers the enamine **b**. The latter then adds to the dicyanostyrene **a**, which is formed by the *in situ* Knoevenagel condensation of aldehyde and malononitrile,

to form **c**. This intermediate after proton transfer yields **d** which then undergoes cyclization to an imine followed by isomerization to afford the product **f** (Scheme 2.16). The *anti* disposition of Ar^1 and R^1 is predicated by the Michael addition of the enamine **b** to the acceptor **a**; Michael reactions of this type are usually *anti* selective, presumably due to steric factors.



Scheme 2.16

2.6 Conclusion

In conclusion, a novel methodology for the synthesis of dihydropyridine derivatives in one pot was developed. Dihydropyridine derivatives are biologically important compounds. It is noteworthy that the enamine moiety makes them versatile intermediates for further synthetic transformations. It may also be mentioned that the involvement of allene-aniline zwitterion in MCR was explored for the first time.

2.7 Experimental Section

2.7.1 General

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300/500 (^{1}H) and 75/125 (^{13}C) MHz respectively on Bruker Avance DPX-300/500S MHz NMR spectrometers. Chemical shifts (δ) are reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constant (*J*) is reported in Hertz (Hz). Mass spectra were recorded under LRMS (FAB) using JEOL JMS 600H mass spectrometer. Elemental analysis was carried out on

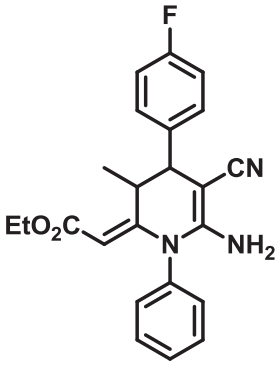
Perkin Elmer Series II CHNS Analyser 2400. IR spectra were recorded on a Bruker Alpha-T FT-IR spectrophotometer. Allenoates were prepared using known literature procedures.[23] Gravity column chromatography was performed using silica gel, and mixtures of petroleum ether–ethyl acetate were used for elution.

2.7.2 General procedure for the synthesis of dihydropyridines

The aldehyde (1 mmol) and malononitrile (1 mmol) in ethanol (3 ml) were taken in a round bottom flask under argon atmosphere. Triethylamine (1.2 mmol) was added and stirred for 10 min. To this reaction mass, mixture of aniline (1.2 mmol) and allenoate (1.2 mmol) was added as a solution in ethanol (3 ml) and stirred the reaction for 12 h at room temperature. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel (100–200 mesh) using hexane: ethylacetate (70: 30) as the eluent to afford the pure product as colourless solid.

(*E*)-Ethyl 2-(6-amino-5-cyano-4-(4-fluorophenyl)-3-methyl-1-phenyl-3,4-dihydropyridin -2(1*H*)-ylidene) acetate (55)

Following the general procedure, the reaction of 4-fluorobenzaldehyde (124 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121 mg, 1.2 mmol) with ethyl 3-methyl allenoate (151 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Ethyl2-(6-amino-5-cyano-4-(4-fluorophenyl)-3-methyl-1-phenyl-3,4-dihydropyridin-2(1*H*)-ylidene) acetate in 62% (242 mg, 0.62 mmol) yield as colourless solid.



Yield: 242 mg (0.62 mmol, 62%), colourless solid, mp 184-186 ^{o}C.

IR (film) ν_{max}: 3471, 3337, 2179, 1702, 1614, 1587, 1392, 1141 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.50 (m, 3H), 7.25 – 7.22 (m, 2H), 7.16 (d, 2H, *J*= 7.5 Hz), 7.00 (t, 2H, *J*= 8.5 Hz), 4.64-4.60 (m, 1H), 4.33 (s, 1H), 4.19 (s, 2H), 3.97-3.90 (m, 2H), 3.49 (s, 1H), 1.47 (d, 3H, *J*= 6.5 Hz), 1.10 (t, 3H, *J*= 7 Hz) ppm.

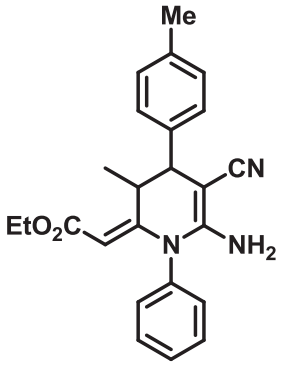
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 161.7 (d, $^{1}J_{CF}$= 243.8 Hz), 158.9, 151.2, 138.5 7 (d, $^{4}J_{CF}$= 2.5Hz), 136.9, 130.8, 130.0, 129.4, 128.3, (d,$^{3}J_{CF}$=7.5 Hz) 121.7, 115.5 (d,$^{2}J_{CF}$=21.3 Hz), 99.2, 59.4, 57.8, 42.4, 34.1, 19.9, 14.2 ppm.

LRMS (+FAB) m/z calcd for $C_{23}H_{22}FN_3O_2$ $(M+H)^+$ 392.17; Found: 392.69.

Anal. Calcd for $C_{23}H_{22}FN_3O_2$: C, 70.57; H, 5.66; N, 10.73. Found: C, 70.71; H, 5.83; N, 10.94.

(*E*)-Ethyl 2-(6-amino-5-cyano-3-methyl-1-phenyl-4-p-tolyl-3,4-dihydropyridin-2(1*H*)-ylidene)acetate (56)

Following the general procedure, the reaction of 4-methylbenzaldehyde (120 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with ethyl 3-methyl allenoate (151 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Ethyl 2-(6-amino-5-cyano-3-methyl-1-phenyl-4-p-tolyl-3,4-dihydropy- ridin-2(1*H*)-ylidene)acetate in 56% (217 mg, 0.56 mmol) yield as colourless solid.



Yield: 217 mg (0.56 mmol, 56%), colourless solid, mp176-178 ^oC

IR (film) ν_{max}: 3470, 3336, 2178, 1702, 1613, 1588, 1393, 1138 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.54 (m, 2H), 7.52-7.50 (m, 1H), 7.18-7.16 (m, 3H) 7.14-7.10 (m, 3H), 4.62 (m, 1H), 4.32 (s, 1H), 4.10 (s, 2H), 3.97-3.91 (m, 2H), 3.47 (s, 1H), 2.32 (s, 3H), 1.47 (d, 3H, *J*= 7 Hz), 1.10 (t, 3H, *J*= 7 Hz) ppm.

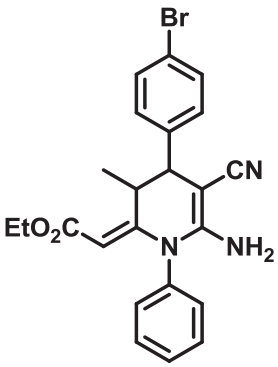
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 159.3, 150.9, 139.7, 137.1, 136.2, 130.7, 129.9, 129.4, 126.6, 98.8, 59.3, 58.5, 42.6, 34.1, 21.1, 20.0, 14.2 ppm.

LRMS (+FAB) m/z calcd for $C_{24}H_{25}N_2O_3$ $(M+H)^+$ 388.19; Found: 388.99.

Anal. Calcd for $C_{24}H_{25}N_2O_3$: C, 74.39; H, 6.50; N, 10.84. Found: C, 73.83; H, 6.85; N, 10.78.

(*E*)-Ethyl2-(6-amino-4-(4-bromophenyl)-5-cyano-3-methyl-1-phenyl-3,4-dihydropyridin -2(1H)-ylidene) acetate (57).

Following the general procedure, the reaction of 4-bromobenzaldehyde (185 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with ethyl 3-methyl allenoate (151 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Ethyl 2-(6-amino-4-(4-bromophenyl)-5-cyano-3-methyl-1-phenyl-3,4-dihydropyridin-2(1*H*)-ylidene) acetate 49% (222 mg, 0.49 mmol) yield as colourless solid.



Yield: 222 mg (0.49 mmol, 49%), colourless solid, mp 148-150 ^{o}C

IR (film) ν_{max}: 3463, 3333, 2178, 1699, 1615, 1586, 1389, 1139 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.51 (m, 3H), 7.45 (d, 2H, *J*= 8 Hz), 7.16 (d, 4H, *J*= 8.5 Hz), 4.64 (q, 1H, *J*= 7 Hz), 4.33 (s, 1H), 4.15 (s, 2H), 3.96-3.93 (m, 2H), 3.47 (s, 1H), 1.48 (d, 3H, *J*= 7 Hz), 1.11 (t, 3H, *J*= 7 Hz) ppm.

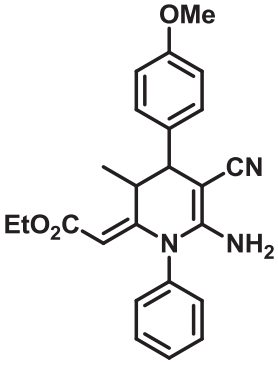
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 158.6, 151.1, 141.8, 131.7, 130.8, 130.7, 129.9, 129.3, 128.5, 120.7, 99.5, 59.5, 59.4, 42.8, 33.8, 19.8, 14.1ppm.

LRMS (+FAB) m/z calcd for $C_{23}H_{22}BrN_3O_2$ $(M+H)^+$ 453.09; Found: 452.89.

Anal. Calcd for $C_{23}H_{22}BrN_3O_2$: C, 61.07; H, 4.90; N, 9.29. Found: C, 61.38; H, 5.07; N, 9.00.

(*E*)-Ethyl 2-(6-amino-5-cyano-4-(4-methoxyphenyl)-3-methyl-1-phenyl-3,4-dihydropy- ridin-2(1H)-ylidene)acetate (58)

Following the general procedure, the reaction of 4-bromobenzaldehyde (136 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with ethyl 3-methyl allenoate (151 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Ethyl 2-(6-amino-4-(4-bromophenyl)-5-cyano-3-methyl-1-phenyl-3,4-dihydro- pyridin-2(1*H*)-ylidene) acetate 45% (182 mg, 0.45 mmol) yield as colourless solid.



Yield: 182 mg (0.45 mmol, 45%), colourless solid, mp 210-214 ^{o}C

IR (film) ν_{max}: 3458, 3354, 2177, 1700, 1610, 1586, 1391, 1139 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56-7.49 (m, 3H), 7.17 (d, 4H, *J*= 8 Hz), 6.83 (d, 2H, *J*= 8.5 Hz), 4.61 (q, 1H, *J*= 7 Hz), 4.30 (s, 1H), 4.11 (s, 2H), 3.98-3.89 (m, 2H), 3.78 (s, 3H), 3.45 (s, 1H), 1.46 (d, 3H, *J*= 6.5 Hz), 1.11 (t, 3H, *J*= 7 Hz) ppm.

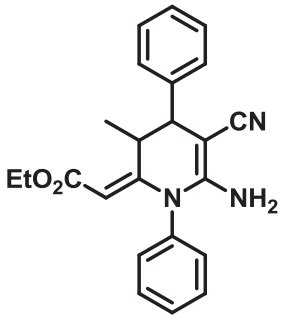
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 159.4, 158.4, 151.0, 137.1, 134.8, 130.7, 129.9, 129.44, 127.7, 121.8, 114.0, 98.8, 59.3, 58.5, 55.1, 42.3, 34.2, 19.9, 14.2 ppm.

LRMS (+FAB) m/z calcd for $C_{24}H_{25}N_3O_3$ $(M+H)^+$ 404.19; Found: 404.56.

Anal. Calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.41. Found: C, 71.40; H, 6.46; N, 10.46.

(*E*)-Ethyl 2-(6-amino-5-cyano-3-methyl-1,4-diphenyl-3,4-dihydropyridin-2(1H)-ylidene) acetate (59)

Following the general procedure, the reaction of benzaldehyde (106 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with ethyl 3-methyl allenoate (151 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Ethyl 2-(6-amino-5-cyano-3-methyl-1,4-diphenyl-3,4-dihydropyridin-2(1*H*)-ylidene) acetate 42% (157 mg, 0.42 mmol) yield as colourless solid.



Yield: 157 mg (0.42 mmol, 42%), colourless solid, mp 130-134 ^oC

IR (film) ν_{max}: 3469, 3335, 2178, 1701, 1614, 1587, 1392, 1139 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.51 (m, 3H), 7.34-7.31 (m, 2H), 7.27 (d, 2H, *J*= 7.5 Hz) 7.23-7.18 (m, 3H), 4.66-4.61 (m, 1H), 4.34 (s, 1H), 4.15 (s, 2H), 3.96-3.90 (m, 2H), 3.51 (s, 1H), 1.49 (d, 3H, *J*= 6.5 Hz), 1.09 (t, 3H, *J*= 7 Hz) ppm.

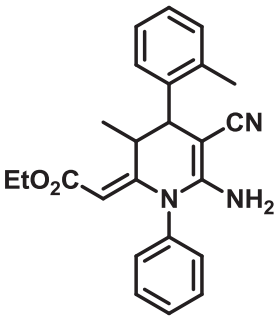
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 159.2, 151.0, 142.7, 137.0, 130.8, 129.9, 128.6, 126.8, 126.7, 98.9, 59.3, 58.3, 43.0, 34.1, 20.0, 14.2 ppm.

LRMS (+FAB) m/z calcd for $C_{23}H_{23}N_3O_2$ $(M+H)^+$ 374.19**;** Found: 374.34.

Anal. Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 73.62; H, 6.54; N, 10.92.

(*E*)-Ethyl 2-(6-amino-5-cyano-3-methyl-1-phenyl-4-o-tolyl-3,4-dihydropyridin-2(1H)-ylidene)acetate (60)

Following the general procedure, the reaction of 2-methylbenzaldehyde (120 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121 mg, 1.2 mmol) with ethyl 3-methyl allenoate (151 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Ethyl 2-(6-amino-5-cyano-3-methyl-1-phenyl-4-o-tolyl-3,4-dihydropyr- idin-2(1*H*)-ylidene)acetate 46% (178 mg, 0.46 mmol) yield as colourless solid.



Yield: 178 mg (0.46 mmol, 46%), colourless solid, mp 218-220 ^{o}C.

IR (film) ν_{max}: 3472, 3333, 2174, 1705, 1613, 1581, 1394, 1144 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.54 (m, 2H), 7.52-7.49 (m, 1H), 7.23 (s, 2H), 7.19-7.09 (m, 4H), 4.48 (q, 1H, *J*= 6 Hz), 4.30 (s, 1H), 4.22 (s, 2H), 3.93-3.84 (m, 2H), 3.67 (s, 1H), 2.43 (s, 3H), 1.49 (d, 3H, *J*= 6.5 Hz), 1.05 (t, 3H, *J*= 7.5 Hz) ppm.

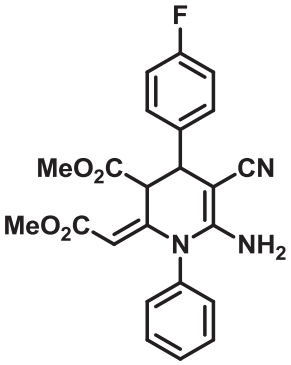
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 158.9, 151.6, 140.2, 137.1, 135.4, 131.0, 130.8, 129.9, 129.4, 126.8, 126.0, 125.7, 99.3, 59.3, 57.8, 40.1, 32.8, 20.1, 19.2, 14.1 ppm.

LRMS (+FAB) m/z calcd for $C_{24}H_{25}N_3O_2$ $(M+H)^+$ 388.19; Found: 388.94.

Anal. Calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.58; H, 6.45; N, 10.64.

(*E*)-Methyl 6-amino-5-cyano-4-(4-fluorophenyl)-2-(2-methoxy-2-oxoethylidene)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate (61)

Following the general procedure, the reaction of 4-fluorobenzaldehyde (124 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with dimethyl penta-2,3-dienedioate (187 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Methyl 6-amino-5-cyano-4-(4-fluorophenyl)-2-(2-methoxy-2-oxoethylidene)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate 56% (236 mg, 0.56 mmol) yield as colourless solid.



Yield: 236 mg (0.56 mmol, 56%), colourless solid, mp 178-180 ^{o}C

IR (film) ν_{max}: 3464, 3351, 2180, 1736, 1703, 1621, 1580, 1426, 1386, 1149 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (s, 4H), 7.29-7.27 (m, 3H), 7.06-7.01 (m, 2H), 5.65 (s, 1H), 4.59 (s, 1H), 4.31 (s, 1H), 4.27 (s, 2H), 3.88 (s, 3H), 3.48 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 166.7, 162.0 (d, $^{1}J_{CF}$=245 Hz), 152.2, 151.3, 136.8, 136.1, 130.2, 129.3, 128.4 (d, $^{3}J_{CF}$= 8.8Hz), 115.7 (d, $^{2}J_{CF}$= 21.3 Hz), 102.1, 57.6, 53.0,

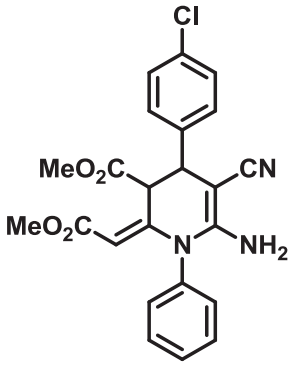
52.9, 50.9, 45.8, 38.4 ppm.

LRMS (+FAB) m/z calcd for $C_{23}H_{20}FN_3O_4$ $(M+H)^+$ 422.14; Found: 422.96.

Anal. Calcd for $C_{23}H_{20}FN_3O_4$: C, 65.55; H, 4.78; N, 9.97. Found: C, 65.47; H, 4.80; N, 10.05.

(*E*)-Methyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-(2-methoxy-2-oxoethylidene)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate (62)

Following the general procedure, the reaction of 4-chlorobenzaldehyde (141 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with dimethyl penta-2,3-dienedioate (187 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Methyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-(2-methoxy-2-oxoethylidene)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate 58% (254 mg, 0.58 mmol) yield as colourless solid.



Yield: 254 mg (0.58 mmol, 58%), colourless solid, mp 184-186 ^oC

IR (film) ν_{max}: 3466, 3351, 2180, 1736, 1620, 1581, 1491, 1385, 1151 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.54 (m, 4H), 7.34-7.26 (m, 5H), 5.66 (d, 1H, *J*= 2.1 Hz), 4.59 (s, 1H), 4.31 (s, 1H), 4.24 (s, 2H), 3.88 (s, 3H), 3.49 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 166.7, 152.3, 151.2, 139.0, 136.7, 133.1, 131.0, 130.2, 129.3, 129.0, 128.3, 120.7, 102.1, 57.0, 53.0, 50.9, 45.6, 38.5 ppm.

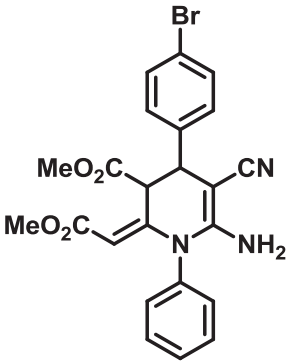
LRMS (+FAB) m/z calcd for $C_{23}H_{20}ClN_3O_4$ $(M+H)^+$ 438.11; Found: 438.61.

Anal. Calcd for $C_{23}H_{20}ClN_3O_4$: C, 63.09; H, 4.60; N, 9.60. Found: C, 62.73; H, 4.79; N, 9.76.

(*E*)-Methyl 6-amino-4-(4-bromophenyl)-5-cyano-2-(2-methoxy-2-oxoethylidene)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate (63)

Following the general procedure, the reaction of 4-bromobenzaldehyde (185 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with dimethyl penta-2,3-dienedioate (95 mg, 1.2 mmol) and aniline (332 mg, 1.2 mmol)

afforded (*E*)-Methyl 6-amino-4-(4-bromophenyl)-5-cyano-2-(2-methoxy-2-oxoethylidene)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate 42% (203 mg, 0.42 mmol) yield as colourless solid.



Yield: 203 mg (0.42 mmol, 42%), colourless solid, M.P**:** 177-179 ^{o}C

IR (film) ν_{max}: 3469, 3360, 2182, 1736, 1624, 1581, 1460, 1380, 1154 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57- 7.51 (m, 3H), 7.47 (d, 2H, *J*= 8.5 Hz), 7.21 (d, 3H, *J*= 8.5 Hz), 7.16 (s, 1H), 5.66 (d, 1H, *J*= 2 Hz), 4.58 (s, 1H), 4.29 (s, 1H), 4.22 (s, 2H), 3.88 (s, 3H), 3.49 (s, 3H) ppm.

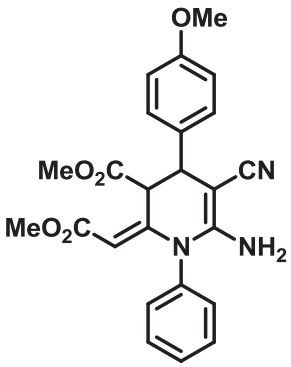
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 166.7, 152.5, 151.2, 139.6, 136.8, 131.9, 130.2, 129.3, 128.7, 121.3, 120.7, 102.1, 56.9, 53.0, 50.9, 45.6, 38.7 ppm.

LRMS (+FAB) m/z calcd for $C_{23}H_{20}BrN_3O_4$ $(M+H)^+$ 482.06; Found: 482.87.

Anal. Calcd for $C_{23}H_{20}BrN_3O_4$: C, 57.27; H, 4.18; N, 8.71. Found: C, 57.53; H, 4.33; N, 8.92.

(*E*)-Methyl 6-amino-5-cyano-2-(2-methoxy-2-oxoethylidene)-4-(4-methoxyphenyl)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate (64)

Following the general procedure, the reaction of 4-methoxybenzaldehyde (136 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with dimethyl penta-2,3-dienedioate (187 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Methyl 6-amino-5-cyano-2-(2-methoxy-2-oxoethylidene)-4-(4-methoxyphenyl)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate 38% (165 mg, 0.38 mmol) yield as colourless solid.



Yield: 165 mg (0.38 mmol, 38%), colourless solid, M.P**:** 167-169 ^{o}C

IR (film) ν_{max}: 3461, 3348, 2179, 1734, 1618, 1579, 1384, 1143 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56- 7.50 (m, 3H), 7.46 (s, 1H), 7.23 (d, 2H, *J*= 9 Hz), 7.19 (s, 1H), 6.86 (d, 2H, *J*= 8.5 Hz), 5.62 (d, 1H, *J*= 2.5 Hz), 4.57 (s, 1H), 4.27 (s, 1H), 4.17 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.48 (s, 3H) ppm.

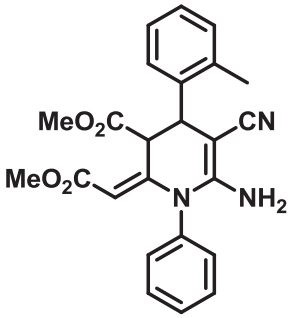
^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 166.8, 158.8, 152.0, 151.8, 137.0, 132.4, 130.0, 129.4, 127.9, 120.8, 114.2, 101.8, 58.3, 55.1, 52.8, 50.8, 46.1, 38.4 ppm.

LRMS (+FAB) m/z calcd for $C_{24}H_{23}N_3O_5$ $(M+H)^+$ 434.16; Found: 435.04.

Anal. Calcd for $C_{24}H_{23}N_3O_5$: C, 66.50; H, 5.35; N, 9.69. Found: C, 66.15; H, 5.35; N, 9.32.

(*E*)-Methyl 6-amino-5-cyano-2-(2-methoxy-2-oxoethylidene)-1-phenyl-4-o-tolyl-1,2,3,4-tetrahydropyridine-3-carboxylate (65)

Following the general procedure, the reaction of 2-methylbenzaldehyde (120 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with dimethyl penta-2,3-dienedioate (187 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Methyl 6-amino-5-cyano-2-(2-methoxy-2-oxoethylidene)-1-phenyl-4-o-tolyl-1,2,3,4-tetrahydropyridine-3-carboxylate 53% (221 mg, 0.53 mmol) yield as colourless solid.



Yield: 221 mg (0.53 mmol, 53%), colourless solid, M.P: 210-214 ^{o}C

IR (film) ν_{max}: 3466, 3355, 2180, 1735, 1620, 1585, 1386, 1148 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59-7.56 (m, 2H), 7.53-7.50 (m, 1H), 7.47 (s, 1H), 7.29 (s, 1H), 7.19-7.14 (m, 4H), 5.54 (d, 1H, *J*= 2 Hz), 4.54 (s, 1H), 4.47 (s, 1H), 4.26 (s, 2H), 3.90 (s, 3H), 3.42 (s, 3H), 2.53 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 166.7, 152.6, 151.4, 137.8, 137.0, 135.8, 131.2, 130.1, 129.4, 127.4, 126.1, 120.7, 102.0, 57.6, 53.0, 50.8, 44.2, 36.6, 19.0 ppm.

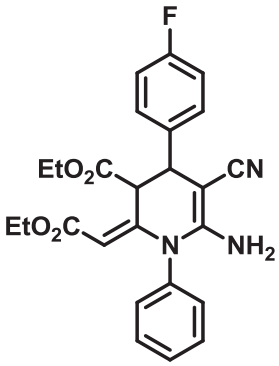
LRMS (+FAB) m/z calcd for $C_{24}H_{23}N_3O_4$ $(M+H)^+$ 418.17; Found:

419.03**.**

Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07. Found: C, 68.68; H, 5.72; N, 10.36.

(*E*)-Ethyl 6-amino-5-cyano-2-(2-ethoxy-2-oxoethylidene)-4-(4-fluorophenyl)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate (66)

Following the general procedure, the reaction of 4-fluorobenzaldehyde (124 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with diethyl penta-2,3-dienedioate (221 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Ethyl 2-(6-amino-4-(4-bromophenyl)-5-cyano-3-methyl-1-phenyl-3,4-dihydropyridin -2(1*H*)-ylidene) acetate 71% (319 mg, 0.71 mmol) yield as colourless solid.



Yield: 319 mg (0.71 mmol, 71%), light yellow solid, M.P**:** 156-160 ^{o}C

IR (film) ν_{max}: 3463, 3385, 2180, 1732, 1623, 1578, 1382, 1138 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57- 7.51 (m, 3H), 7.47 (s, 1H), 7.31-7.29 (m, 2H), 7.16 (s, 1H), 7.03 (t, 2H, *J*= 8.5 Hz), 5.64 (d, 1H, *J*= 2.5 Hz), 4.57 (s, 1H), 4.35-4.31 (m, 3H), 4.22 (s, 2H), 3.94 (q, 2H, *J*= 7 Hz), 1.39 (t, 3H, *J*= 7 Hz), 1.10 (t, 3H, *J*= 7 Hz) ppm.

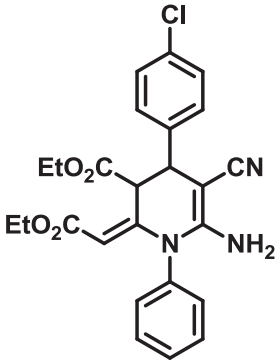
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 166.3, 161.9 (d, $^{1}J_{CF}$= 243.8 Hz), 152.4, 151.3, 136.9, 136.2, 130.4, 130.1, 129.3, 128.5 (d, $^{3}J_{CF}$=7.5 Hz), 120.8, 115.6 (d, $^{2}J_{CF}$=21.3 Hz), 102.4, 61.8, 59.7, 57.3, 45.9, 38.6, 14.3, 14.1 ppm.

LRMS (+FAB) m/z calcd for $C_{25}H_{24}FN_3O_4$ $(M+H)^+$ 450.18; Found: 451.05.

Anal. Calcd for $C_{25}H_{24}FN_3O_4$: C, 66.80; H, 5.38; N, 9.35. Found: C, 66.57; H, 5.77; N, 9.40.

(*E*)-Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-(2-ethoxy-2-oxoethylidene)-1-phenyl-1,2,3,4-tetrahydro-pyridine-3-carboxylate (67)

Following the general procedure, the reaction of 4-chlorobenzaldehyde (141 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with diethyl penta-2,3-dienedioate (221 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-(2-ethoxy-2-oxoethylide- ne)-1-phenyl-1,2,3,4-tetrahydro-pyridine-3-carboxylate 65% (303 mg, 0.65 mmol) yield as colourless solid.



Yield: 303 mg (0.65 mmol, 65%), colourless solid, M.P**:** 168-170 ^{o}C

IR (film) ν_{max}: 3460, 3358, 2180, 1731, 1618, 1588, 1385, 1143 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56- 7.50 (m, 3H), 7.47 (s, 1H), 7.32-7.26 (m, 4H), 7.15 (s, 1H), 5.65 (d, 1H, *J*= 2 Hz), 4.55 (s, 1H), 4.35-4.31 (m, 2H), 4.29 (s, 1H), 4.26 (s, 2H), 3.94 (q, 2H, *J*= 7 Hz), 1.39 (t, 3H, *J*= 7 Hz), 1.11 (t, 3H, *J*= 7 Hz) ppm.

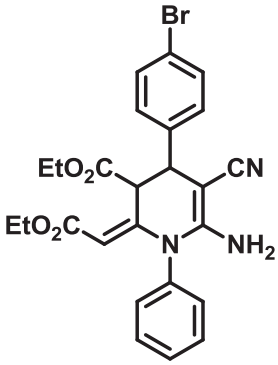
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 166.3, 152.4, 151.1, 139.0, 136.9, 133.1, 130.1, 129.4, 128.9, 128.3, 120.6, 102.5, 61.8, 59.7, 57.1, 45.7, 38.7, 14.3, 14.1 ppm.

LRMS (+FAB) m/z calcd for $C_{25}H_{24}ClN_3O_4$ $(M+H)^+$ 466.15; Found: 466.86.

Anal. Calcd for $C_{25}H_{24}ClN_3O_4$: C, 64.44; H, 5.19; N, 9.02. Found: C, 64.71; H, 5.11; N, 9.32.

(*E*)-Ethyl 6-amino-4-(4-bromophenyl)-5-cyano-2-(2-ethoxy-2-oxoethylidene)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate (68)

Following the general procedure, the reaction of 4-bromobenzaldehyde (185 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with diethyl penta-2,3-dienedioate (221 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Ethyl 6-amino-4-(4-bromophenyl)-5-cyano-2-(2-ethoxy-2-oxoethylid- ene)-1-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate 57% (291 mg, 0.57 mmol) yield as colourless solid.



Yield: 291 mg (0.57 mmol, 57%), light yellow solid, M.P: 190-192 ^{o}C

IR (film) ν_{max}: 3463, 3347, 2180, 1731, 1621, 1587, 1384, 1143 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.51 (m, 3H), 7.47 (d, 3H, *J*= 8 Hz), 7.22 (d, 2H, *J*= 8.5 Hz), 7.15 (s, 1H), 5.66 (d, 1H, *J*= 2 Hz), 4.56 (s, 1H), 4.36-4.30 (m, 2H), 4.28 (s, 1H), 4.22 (s, 2H), 3.94 (q, 2H, *J*= 7 Hz), 1.39 (t, 3H, *J*= 7 Hz), 1.11 (t, 3H, *J*= 7 Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 166.3, 152.6, 151.1, 139.6, 136.8, 131.9, 130.4, 130.1, 129.3, 128.7, 121.2, 120.8, 102.5, 61.9, 59.7, 56.8, 45.7, 38.8, 14.3, 14.1 ppm.

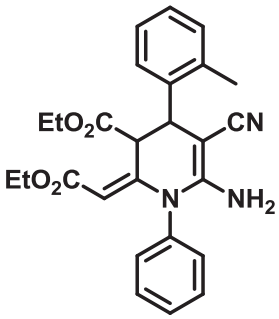
LRMS (+FAB) m/z calcd for $C_{25}H_{24}BrN_3O_4$ $(M+H)^+$ 510.10; Found:

510.82.

Anal. Calcd for $C_{25}H_{24}BrN_3O_4$: C, 58.83; H, 4.74; N, 8.23. Found: C, 59.03; H, 4.88; N, 8.64.

(*E*)-Ethyl 6-amino-5-cyano-2-(2-ethoxy-2-oxoethylidene)-1-phenyl-4-o-tolyl-1,2,3,4-tetrahydropyridine-3-carboxylate (69)

Following the general procedure, the reaction of 2-methylbenzaldehyde (120 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with diethyl penta-2,3-dienedioate (221 mg, 1.2 mmol) and aniline (112 mg, 1.2 mmol) afforded (*E*)-Ethyl 6-amino-5-cyano-2-(2-ethoxy-2-oxoethylidene)-1-phenyl-4-o-tolyl-1,2,3,4-tetrahydropyridine-3-carboxylate 48% (214 mg, 0.48 mmol) yield as light yellow solid.



Yield: 214 mg (0.48 mmol, 48%), light yellow solid, M.P: 138-140 ^{o}C

IR (film) ν_{max}: 3467, 3366, 2180, 1733, 1623, 1590, 1394, 1148 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60-7.57 (m, 2H), 7.54-7.49 (m, 2H), 7.30 (s, 1H), 7.20-7.13 (m, 4H), 5.51 (d, 1H, *J*= 2 Hz), 4.53 (s, 1H), 4.47 (d, 1H, *J*= 2 Hz), 4.37-4.30 (m, 2H), 4.22 (s, 2H), 3.93-3.82 (m, 2H), 2.53 (s, 3H), 1.40 (t, 3H, *J*= 7 Hz), 1.05 (t, 3H, *J*= 7 Hz) ppm.

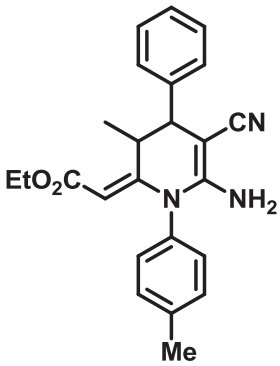
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 166.3, 152.8, 151.3, 137.9, 137.0, 135.7, 131.1, 130.5, 130.0, 129.4, 127.3, 126.2, 126.1, 120.9, 102.4, 61.7, 59.6, 57.2, 44.4, 36.8, 18.9, 14.3, 14.1 ppm.

LRMS (+FAB) m/z calcd for $C_{26}H_{27}N_3O_4$ $(M+H)^+$ 446.20; Found: 446.85.

Anal. Calcd for $C_{26}H_{27}N_3O_4$: C, 70.09; H, 6.11; N, 9.43. Found: C, 69.78; H, 6.17; N, 9.62.

(*E*)-Ethyl 2-(6-amino-5-cyano-4-(4-fluorophenyl)-3-methyl-1-p-tolyl-3,4-dihydropyridin-2(1H)-ylidene) acetate (70)

Following the general procedure, the reaction of 4-fluorobenzaldehyde (124 mg, 1 mmol), malononitrile (66 mg, 1 mmol) and triethylamine (121, 1.2 mmol) with diethyl penta-2,3-dienedioate (151 mg, 1.2 mmol) and 4-methylaniline (128 mg, 1.2 mmol) afforded (*E*)-Ethyl 2-(6-amino-5-cyano-4-(4-fluorophenyl)-3-methyl-1-p-tolyl-3,4-dihydropyridin-2(1H)-ylidene) acetate 56% (227 mg, 0.56 mmol) yield as colourless solid.



Yield: 227 mg (0.56 mmol, 56%), colourless solid, M.P: 150-152°C

IR (film) ν_{max}: 3471, 3345, 2177, 1701, 1600, 1581, 1501, 1385, 1139 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, 2H, *J*= 8 Hz), 7.24 – 7.21 (m, 2H), 7.04-6.98 (m, 4H), 4.61 (q, 1H, *J*= 6.5 Hz), 4.37 (s, 1H), 4.16 (s, 2H), 3.97-3.92 (m, 2H), 3.48 (s, 1H), 2.44 (s, 3H), 1.46 (d, 3H, *J*= 6.5 Hz), 1.11 (t, 3H, *J*= 7 Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 161.7 (d, $^1J_{CF}$= 243 Hz), 159.0, 151.6, 140.2, 138.7 (d, $^4J_{CF}$= 3 Hz) , 134.2, 131.4, 129.1, 128.3 (d, $^3J_{CF}$=7.5 Hz), 121.9, 115.4 (d, $^2J_{CF}$=21 Hz), 99.0, 59.3, 57.3, 42.5, 34.1, 21.3, 19.9, 14.2 ppm.

LRMS (+FAB) m/z calcd for $C_{24}H_{24}FN_3O_2$ $(M+H)^+$ 406.19; Found: 406.38.

Anal. Calcd for $C_{24}H_{24}FN_3O_2$: C, 71.09; H, 5.97; N, 10.36. Found: C, 70.40; H, 5.83; N, 10.54.

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CHAPTER 3

Phosphine-Mediated Reactions of 3-Alkyl Allenoates and Diaryl 1,2-Diones: Efficient Diastereoselective Synthesis of Fully Substituted Cyclopentenones

3.1 Introduction

Cyclopentenones are important structural motifs because they form the building blocks for a large variety of natural products and many important biologically active compounds such as prostaglandins,[1] jasmonoids,[2] rethrolones,[3] and methylenomycins[4] (Figure 3.1). They are also useful synthons for the construction of complex organic molecules. In general, 2-cyclopentenones can be synthesized by the Pauson-Khand reaction, Nazarov cyclization of dienones, metal-mediated reactions and other miscellaneous transformations. The importance of cyclopentenones in organic synthesis continues to inspire the development of simple and efficient methods for their stereoselective preparation. The present chapter describes the reaction of acyclic 1,2-diones with 3-alkyl allenoate leading to fully substituted cyclopentenones. In this regard, a brief discussion on the synthesis of cyclopentenones using conventional methods is given in the following section.

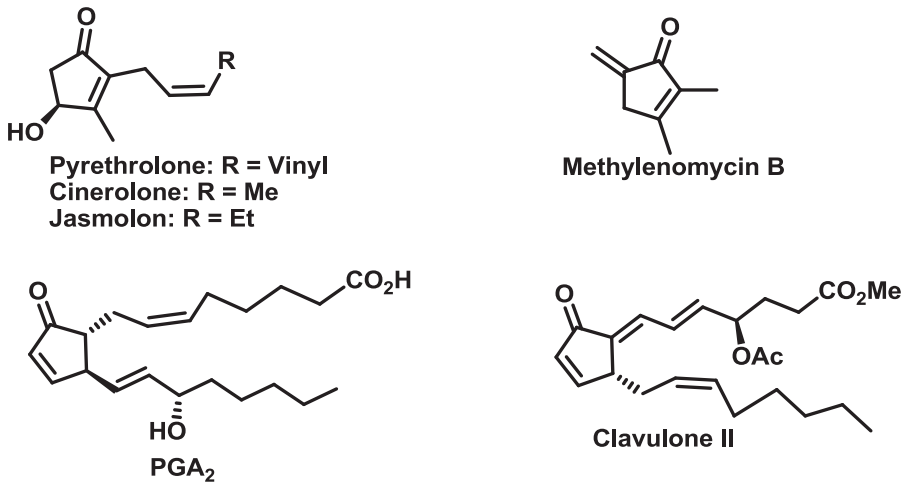
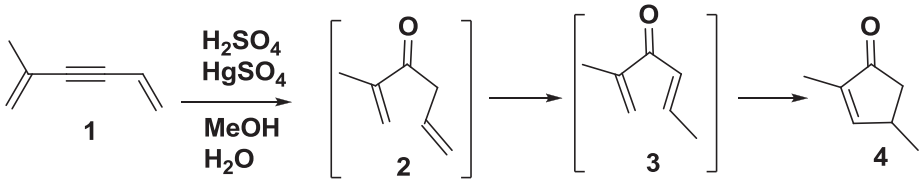


Figure 3.1 Some important biologically active and naturally occurring cyclopentenones

3.2 Synthesis of cyclopentenones

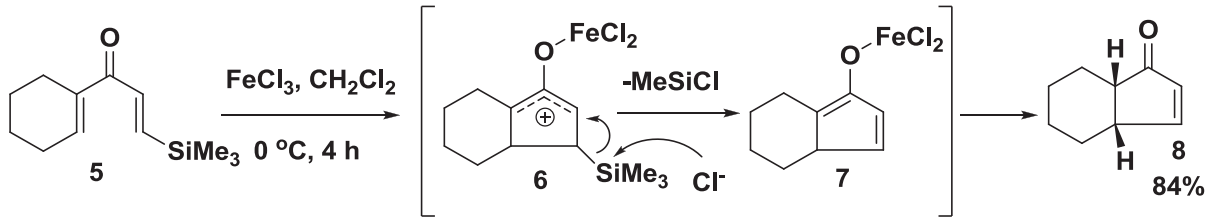
3.2.1 Nazarov Cyclization

The classical Nazarov cyclization is the process that converts a divinyl ketone to 2-cyclopentenone.[5] The reaction is catalyzed by Brønsted or Lewis acids and is named after the eminent Russian chemist I. N. Nazarov who discovered the reaction in 1941. It involves the acid induced cationic 4π conrotatory electrocyclic ring closure reaction of divinyl ketone to furnish cyclopentenone (Scheme 3.1). There are a number of modern variants of this reaction involving substrates other than divinyl ketones and promoters other than Lewis acids which follow the same mechanistic pathway.



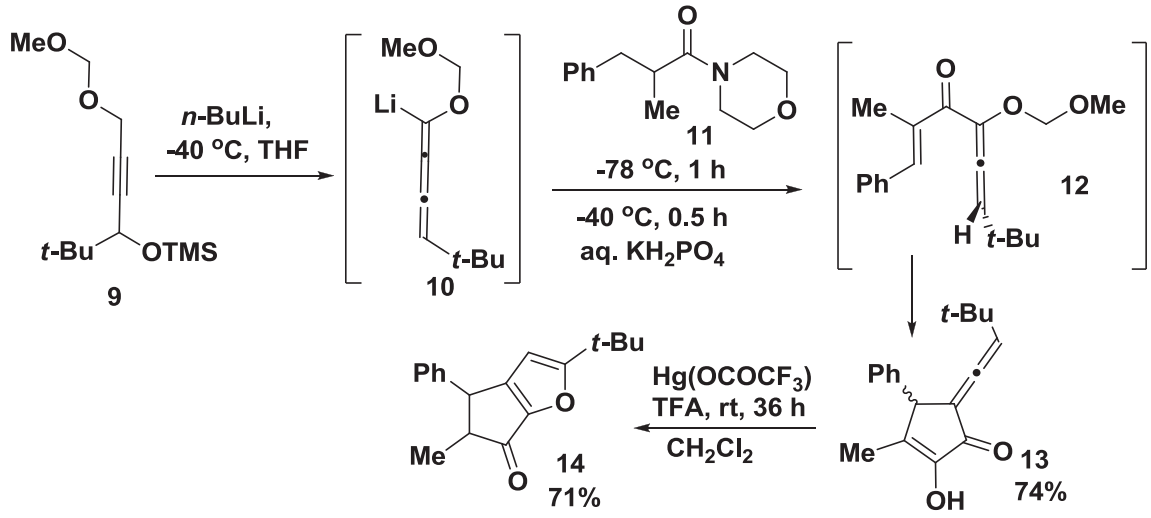
Scheme 3.1

With a view to overcome the lack of control over the position of the double bond in the cyclopentenone moiety, —a major disadvantage associated with classical Nazarov cyclization—Denmark *et al.* reported a silicon directed Nazarov cyclization reaction. The key to this modification lies in the ability of silicon to control the regio- and stereochemical outcome of certain carbonium ion processes and this property is known as β-effect (Scheme 3.2).[6] Thus this method constitutes a general methodology for the construction of 4,5-annulated 2-cyclopentenones.



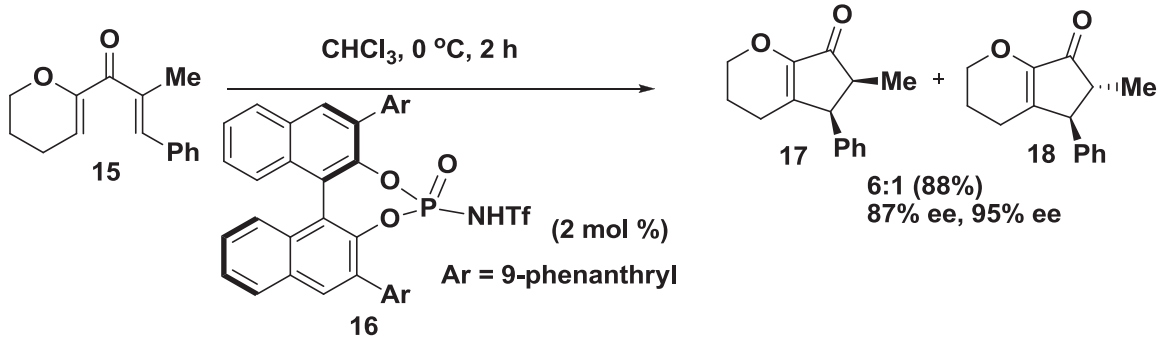
Scheme 3.2

In 2003, Tius and co-workers reported the first Nazarov reaction of vinyl cumulenyl ketone.[7] α-Lithio cumulenyl ether **10** was generated *in situ* and converted to α-allenyl cyclopentenone. Isomerization of α-allenyl cyclopentenone afforded furanyl cyclopentenone **14**, the core structure of nakadomarin A.



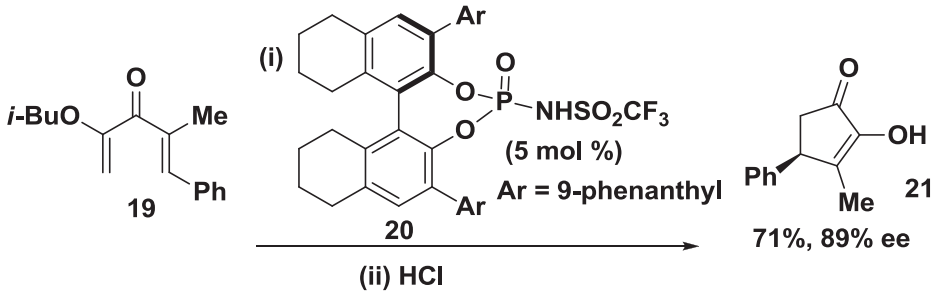
Scheme 3.3

The first enantioselective organocatalytic Nazarov reaction was developed by the group of Rueping in 2007.[8] In the presence of chiral Brønsted acid (R)-BINOL-derived N-triflylphosphoramide **16** the dienone **15** yielded a 6:1 mixture of *cis* and *trans* cyclopentenones **17** (87% ee) and **18** (95% ee), respectively (Scheme 3.4).



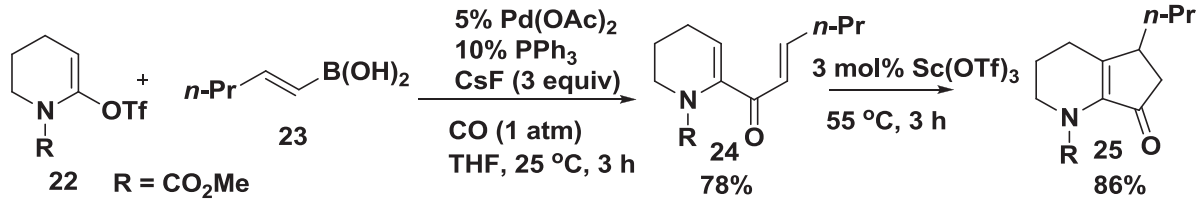
Scheme 3.4

The same group recently reported the Brønsted acid-catalyzed asymmetric Nazarov cyclization of acyclic alkoxy dienones to furnish chiral cyclopentenone **21** in a highly enantioselective manner (Scheme 3.5).[9]



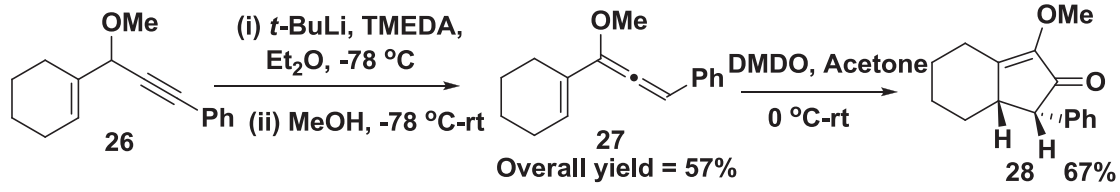
Scheme 3.5

Lewis acid-catalyzed Nazarov reaction of 2-(N-Methoxycarbonylamino)-1,4-pentadien-3-one **25** was reported by Occhiato and co-workers.[10] This substrate in turn was synthesized by the carbonylative Suzuki-Miyaura coupling reaction of lactam-derived vinyl triflates and alkenylboronic acids. The overall methodology constitutes a concise and efficient route to [1] pyrindine systems (Scheme 3.6).



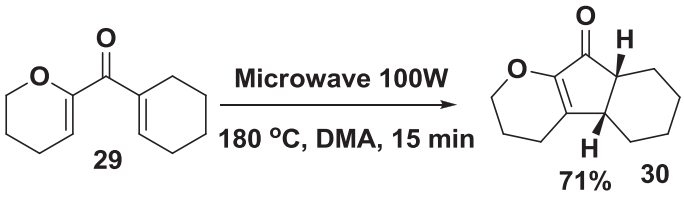
Scheme 3.6

A diastereoselective formation of 4,5-disubstituted cyclopentenone **28** has been developed by the oxidation-initiated Nazarov cyclization of vinyl alkoxyallenes (Scheme 3.7).[11] The use of vinyl alkoxyallenes controls the regioselectivity of oxidation, which occurs on the more electron-rich internal allene double bond.



Scheme 3.7

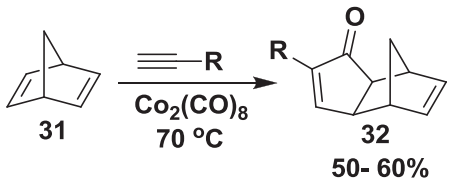
A reagent free Nazarov cyclization was introduced in 2005. Simple heating of the dienone under microwave condition furnished the cyclopentenone product **30** in good yield (Scheme 3.8).[12]



Scheme 3.8

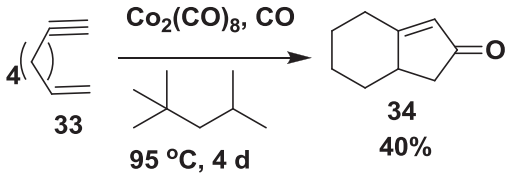
3.2.2 Pauson-Khand Reaction

The Pauson-Khand reaction (PKR) is another widely utilized method for synthesizing cyclopentenones. Cyclopentenone is formed by cyclization of an alkyne, olefin, and carbon monoxide in the presence of $Co_2(CO)_8$ in a formal [2+2+1] cycloaddition reaction. The reaction was first reported in 1973 by P. L. Pauson and I. U. Khand.[13] In their initial study of intermolecular reaction, symmetrical and active alkenes such as ethylene and norbornene **31** were used because four regioisomers, which are often difficult to separate, could be obtained when unsymmetrical alkynes and alkenes were used (Scheme 3.9). Poor regioselectivity, harsh reaction conditions and the use of superstoichiometric amount of the metal complex were the major draw backs of this classical protocol.



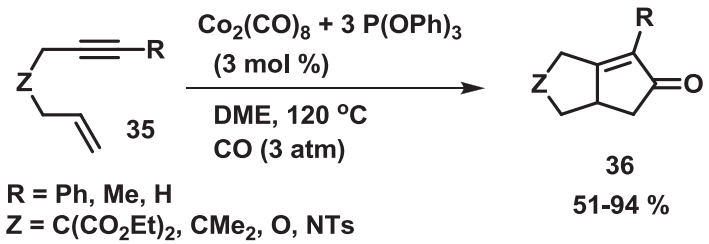
Scheme 3.9

Schore introduced the intramolecular version of Pauson-Khand reaction in 1981.[14] The inherent regiocontrol of the intramolecular PKR of enyne to form bicyclic cyclopentenone **34** makes this variant appealing and it has been actively investigated since its inception (Scheme 3.10).



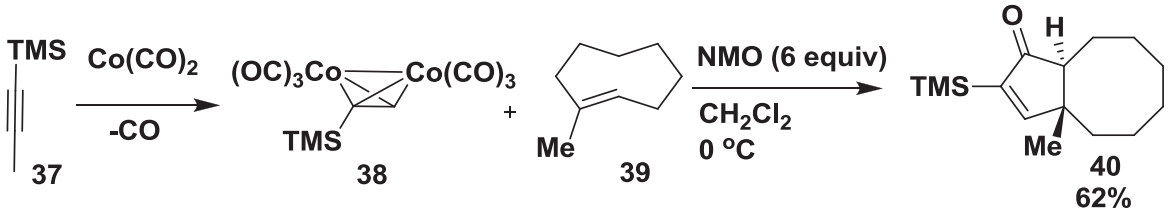
Scheme 3.10

The first catalytic intramolecular PKR was reported in 1994 when Jeong disclosed a catalytic carbonylative coupling of enynes using $Co_2(CO)_8$ with triphenyl phosphite under pressurized carbon monoxide to yield bicyclic cyclopentenones (Scheme 3.11).[15]



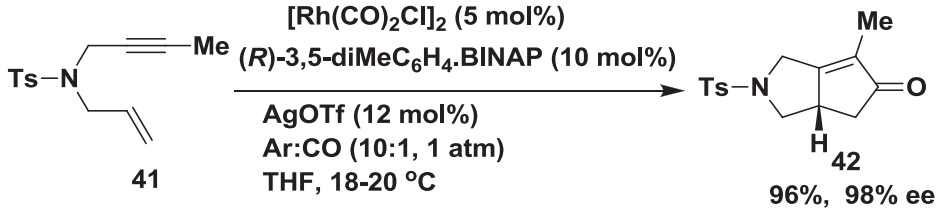
Scheme 3.11

Very recently, the Pauson-Khand reaction of medium sized *trans*-cycloalkenes was reported by Lledó *et al*. *Trans*-cycloalkenes are found unusually reactive in the intermolecular Pauson–Khand reaction (PKR) with respect to typical monocyclic alkenes owing to the ring strain imparted by the *E* stereochemistry. Exploiting this property, bicyclic structures were constructed using 8, 9, and 10 membered *trans*-cycloalkenes with high regio and stereoselectivity (Scheme 3.12).[16]



Scheme 3.12

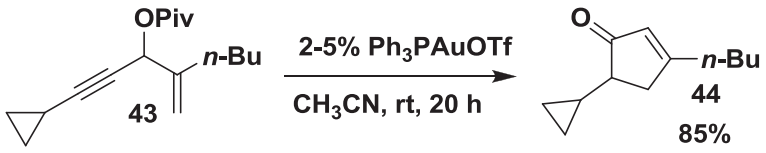
Rhodium-catalyzed enantioselective Pauson–Khand type reaction of enynes was reported in 2008. The reaction utilizing a Rh(I) catalyst bearing a (*R*)-3,5-diMeC_4H_4-BINAP ligand and enyne **41** at 18-20 °C under a reduced partial pressure of CO (0.1 atm) afforded PKR product **42** in high yield as well as high enantioselectivity (Scheme 3.13).[17]



Scheme 3.13

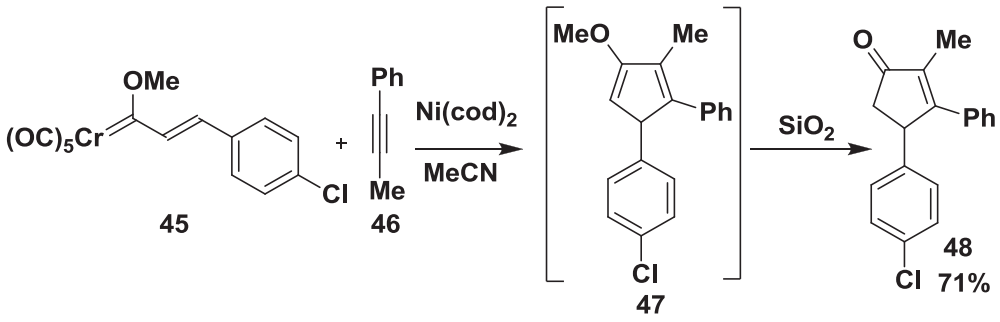
3.2.3 Metal-Mediated Transformations

Au(I) catalyzed rearrangement of 1-ethynyl-2-propenyl pivaloates to cyclopentenones under mild conditions was reported by Toste and co-workers (Scheme 3.14).[18] Enantioenriched cyclopentenones can also be prepared from enantioenriched propargyl alcohols by this method since the mechanism involves C-C bond formation prior to the scission of stereogenic C–O bond.



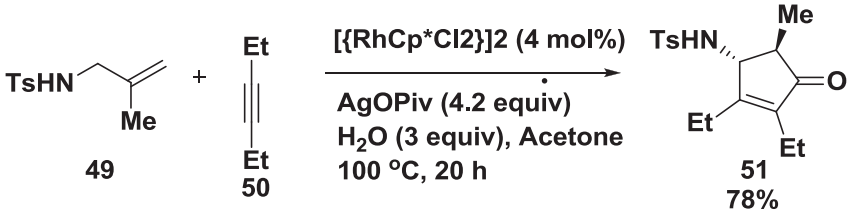
Scheme 3.14

Cyclopentenone derivatives were synthesized through Nickel(0)-mediated [3 + 2] cyclization of alkenyl Fischer carbene complexes and internal alkynes. The reaction takes place with complete regioselectivity with both unactivated alkynes and activated alkynes (Scheme 3.15).[19]



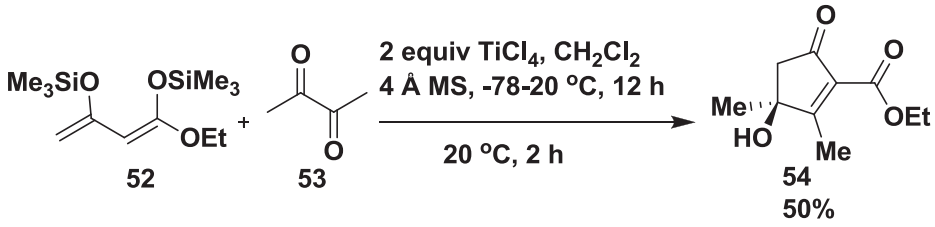
Scheme 3.15

Recently, Wang *et al*. reported Rhodium(III)-catalyzed oxidative coupling of N-allyl arenesulfonamides **49** with alkynes to form cyclopentenones **51** (Scheme 3.16).[20]



Scheme 3.16

Langer and co-workers reported a convenient access to functionalized 4-hydroxycyclopent-2-en-1-ones by the cyclization of 1,3-bis(silyl) enol ethers and 1,3-dicarbonyl dianions with 1,2-diketones (Scheme 3.17).[21]



Scheme 3.17

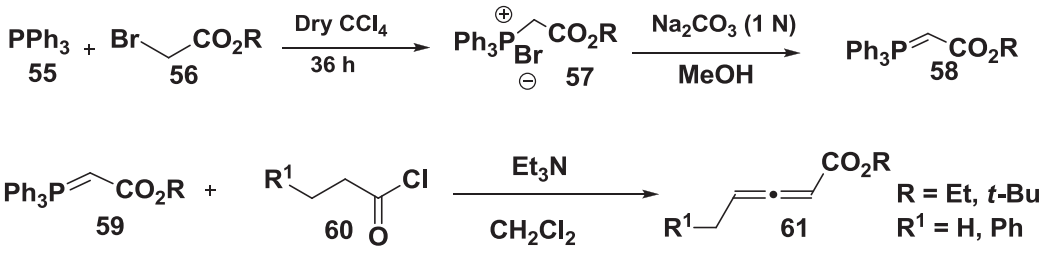
3.3 Background to the Present Work

In recent years our research group has explored the synthetic potential of phosphine-azoester and phosphine-dialkyl acetylene dicarboxylate zwitterions *via* 1,3-or 1,4-dipolar cycloaddition reactions by trapping them with different electrophiles such as aromatic aldehydes, ketones, chalcones, dienones, diaryl 1,2-diones, quinones, isatins, allenes etc.[22] In the context of our general interest in the chemistry of zwitterions and 1,2-diones[23] we initiated a study of reactivity of triphenylphosphine-allenoate zwitterion toward acyclic 1,2-diones, especially benzils. It is noteworthy that although annulation of allenoate-phosphine zwitterions with aldehydes has been reported by various groups,[24] their reactivity toward 1,2-diones remained unexplored.

3.4 Results and Discussion

3.4.1 Synthesis of 3-alkyl allenoates

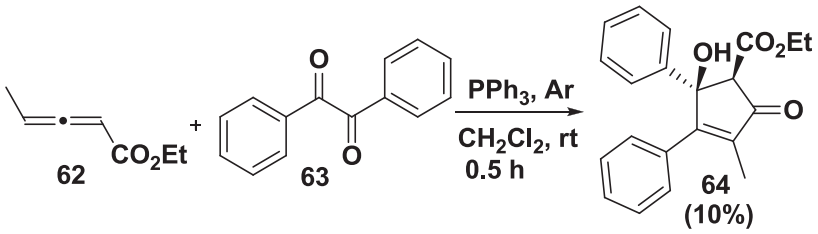
3-Alkyl allenoates used in the present study were prepared by the reported procedures.[25] Carboalkoxymethylene triphenylphosphoranes were prepared from triphenylphosphine and the corresponding alkyl bromoacetate. Reaction of the phosphorane with acid chloride and triethylamine afforded the respective allenoate as colourless oil (Scheme 3.18).



Scheme 3.18

3.4.2 Synthesis of Cyclopentenones

In a pilot experiment, triphenylphosphine was added to a solution of allenoate **62** and benzil **63** in DCM under argon atmosphere and the mixture was stirred for 30 minutes. The reaction mixture after column chromatography afforded a product, ethyl 2-hydroxy-4-methyl-5-oxo-2,3-diphenylcyclopent-3-enecarboxylate **64**, in 10% yield (Scheme 3.19).



Scheme 3.19

The structure of the product was established using common spectroscopic methods. The IR spectrum showed the keto and ester carbonyl absorption around 1698 cm^{-1} as a broad band. In the ^{1}H NMR spectrum the -OH proton resonated as singlet at δ 4.75 ppm. The compound showed multiplet resonance signal at δ 4.29-4.24 ppm due to methylene protons of ester group, and methyl protons of ester group were discernible as a triplet at δ 1.32 ppm (Figure 3.2). In ^{13}C NMR the keto carbon resonated at δ 199.2 ppm. The ester carbonyl group exhibited resonance signal at δ 170.1 ppm (Figure 3.3). The HRMS was also in good agreement with the proposed structure. Conclusive evidence for the structure and relative stereochemistry was derived from single crystal X-ray analysis of the analogous compound **66** (*vide infra*) (Figure 3.4).

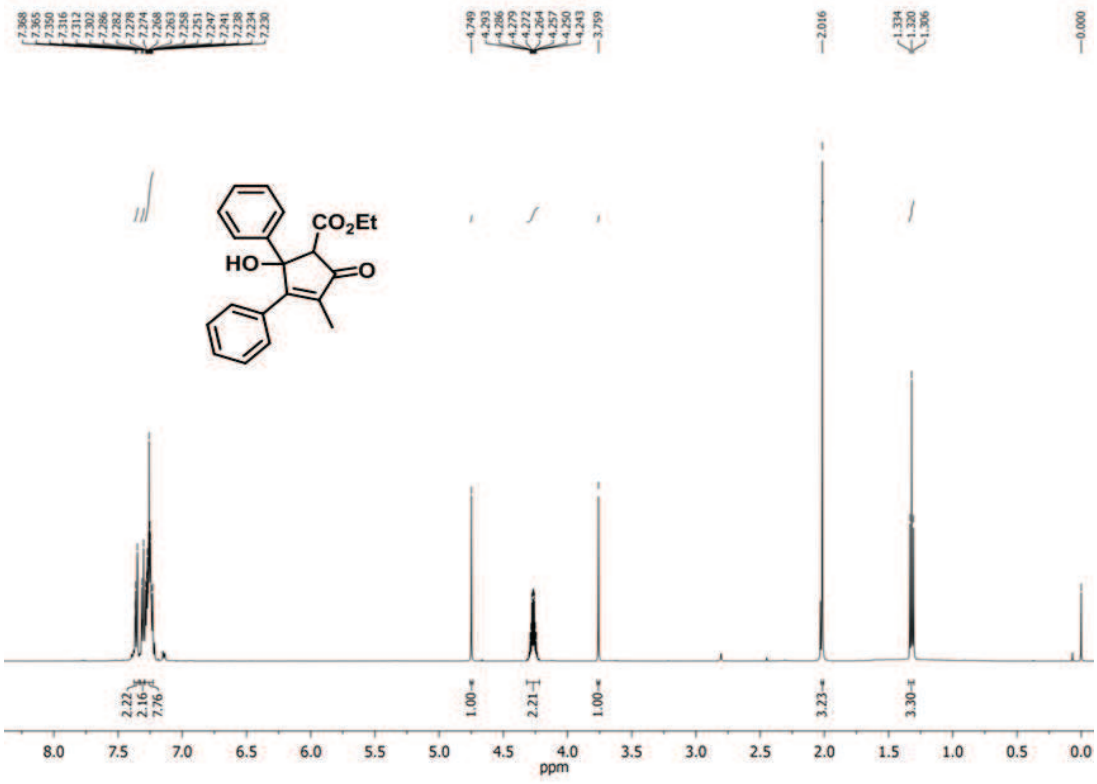


Figure 3.2 ^{1}H NMR spectrum of compound **64**

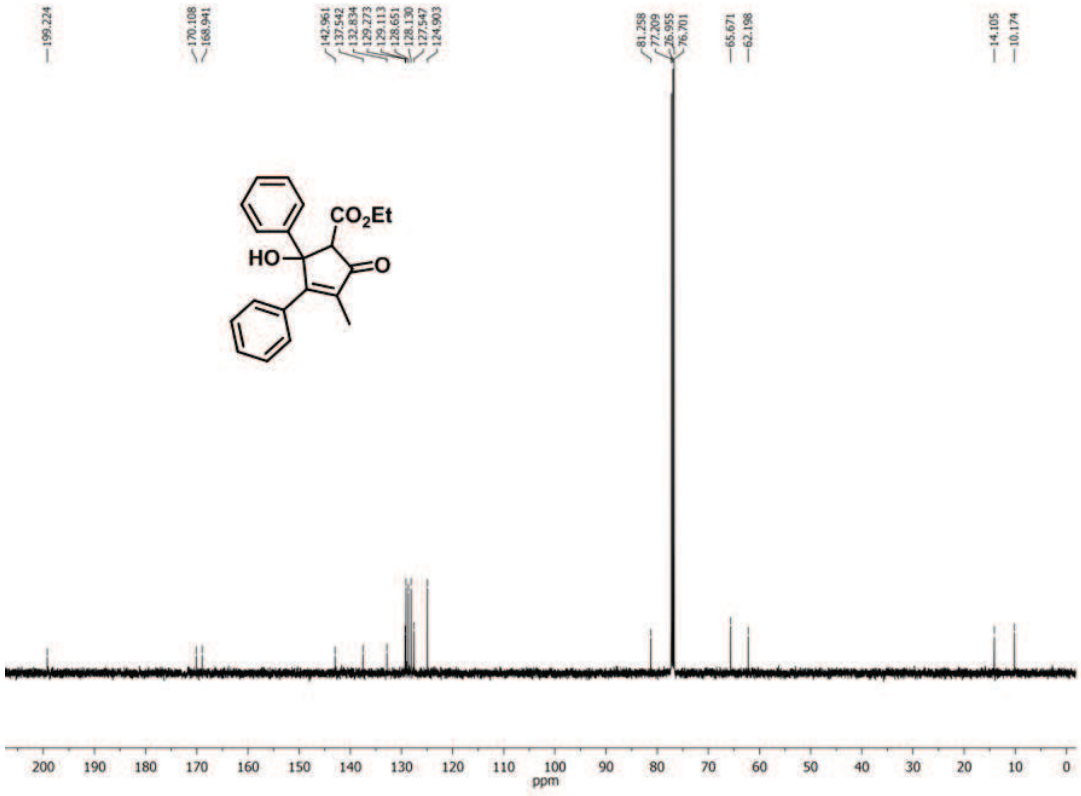
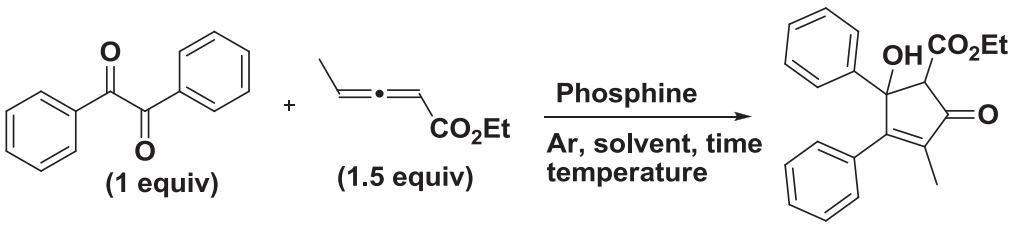


Figure 3.3 ^{13}C NMR spectrum of compound **64**

In view of the surprising result and the fact that cyclopentenones are important compounds, it was obligatory to pursue the reaction in some detail. The reaction was optimized by varying solvent, phosphine, temperature, and time; the results are presented in Table 3.1.

Table 3.1. Condition optimization

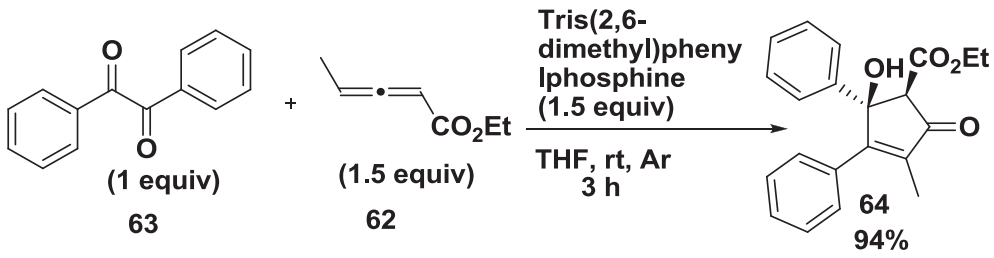


Entry	Solvent	Phosphine[a]	Temp (^{o}C)	Time (h)	Yield (%)
1	DCM	PPh_3	rt	0.5	10
2	DCM	PPh_3 (0.5 equiv)	rt	0.5	trace
3	DCM	PPh_3	50 ^{o}C	0.5	5
4	DCM	PPh_3	0 ^{o}C-rt	0.5	8
5	DCE	PPh_3	rt	0.5	5

6	$CHCl_3$	PPh_3	rt	1	trace
7	DCM	PMe_3	rt	12	-
8	DCM	PBu_3	rt	0.5	25
9	DCM	$P(2\text{-}CH_3C_6H_4)_3$	rt	24	-
10	DCM	TDMPP[b]	rt	4	45
11	DCM	$P(Cy)_3$	rt	4	33
12	DCM	$P(C_6F_5)_3$	rt	24	-
13	THF	TDMPP[b]	rt	3	94
14	Toluene	TDMPP[b]	rt	16	20

[a]1.5 equiv of phosphine is used unless otherwise specified; [b]TDMPP = tris(2,6-dimethoxyphenyl)phosphine.

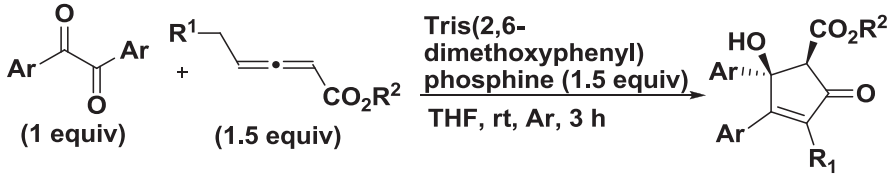
From the optimization studies it is clear that the best result is obtained when the reaction is carried out in THF using 1.5 equiv of allenoate and tris(2,6-dimethoxyphenyl)phosphine under argon atmosphere. The catalytic reaction is very slow, and it suffers from side reactions. Under optimized conditions, the reaction was completed in 3 h. The reaction mixture after column chromatography, using 100-200 mesh silica gel and hexane: ethyl acetate (85:15) as the eluent, afforded the compound **64** in 94% yield (Scheme 3.20).

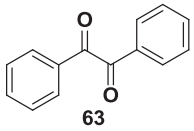
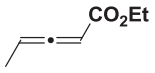
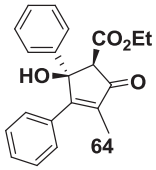
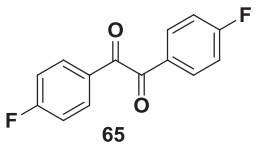
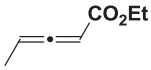
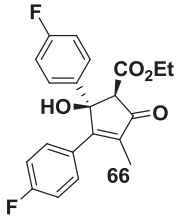
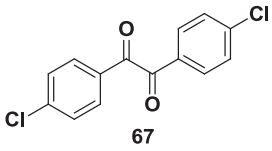
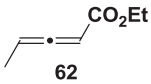
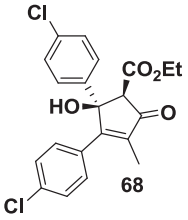
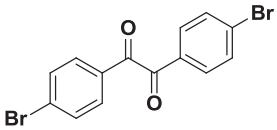
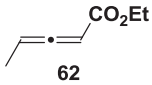
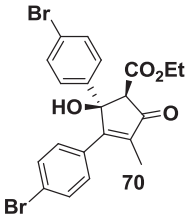
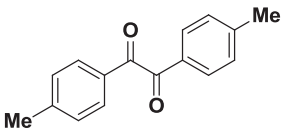
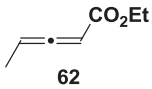
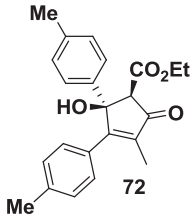
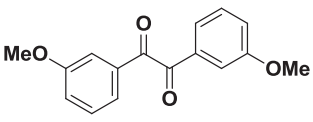
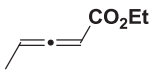
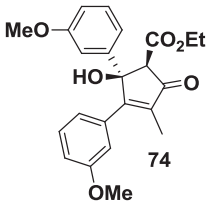
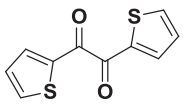
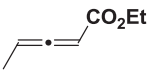
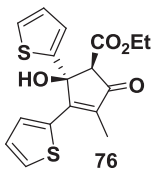


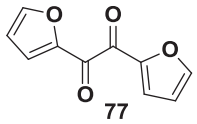
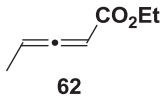
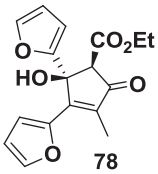
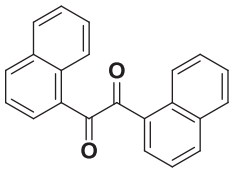
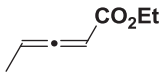
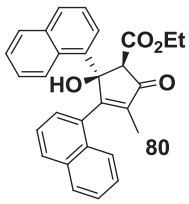
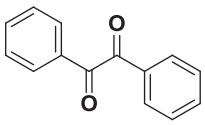
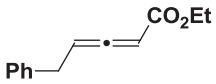
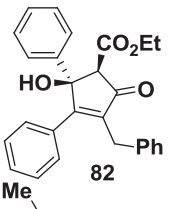
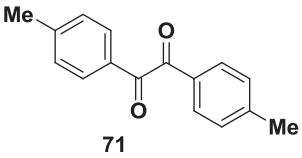
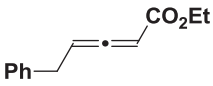
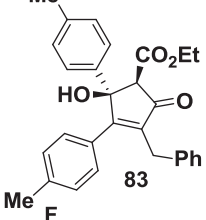
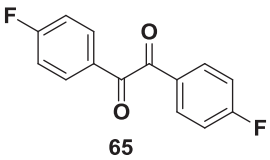
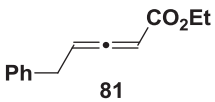
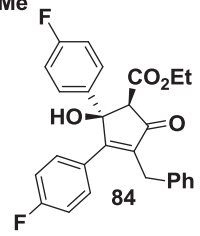
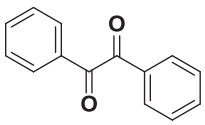
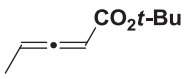
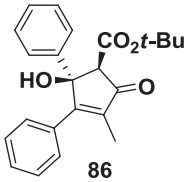
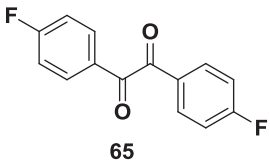
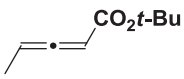
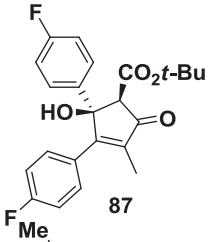
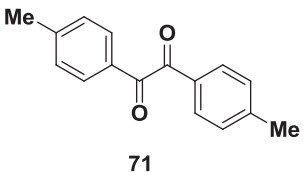
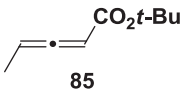
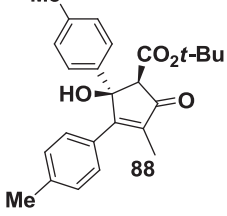
Scheme 3.20

The generality of the reaction was tested with various diaryl 1,2-diones and 3-alkyl allenoates. In all cases the reaction afforded the cyclopentenone derivatives in very good yields and the results are summarized in Table 3.2

Table 3.2 Substrate scope



Entry	Dione	Allenoate	Product	Yield (%)
1	 63	 62	 64	94
2	 65	 62	 66	96
3	 67	 62	 68	93
4	 69	 62	 70	90
5	 71	 62	 72	92
6	 73	 62	 74	88
7	 75	 62	 76	81

8	 77	 62	 78	65
9	 79	 62	 80	93
10	 63	 81	 82	81
11	 71	 81	 83	92
12	 65	 81	 84	94
13	 63	 85	 86	82
14	 65	 85	 87	83
15	 71	 85	 88	78

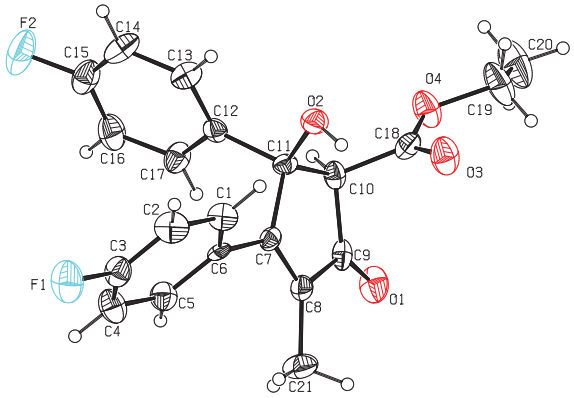
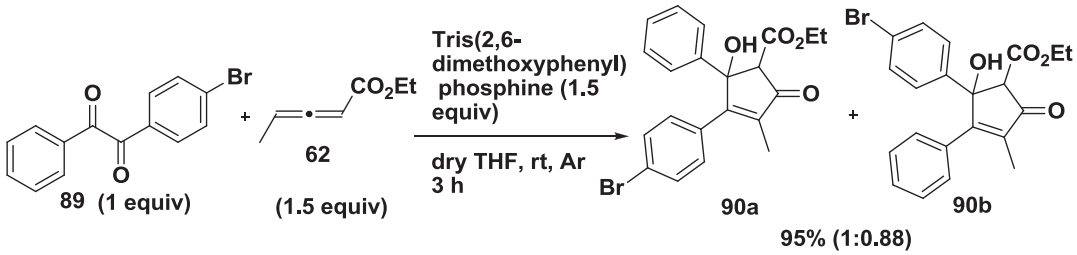


Figure 3.4 ORTEP of compound **66**

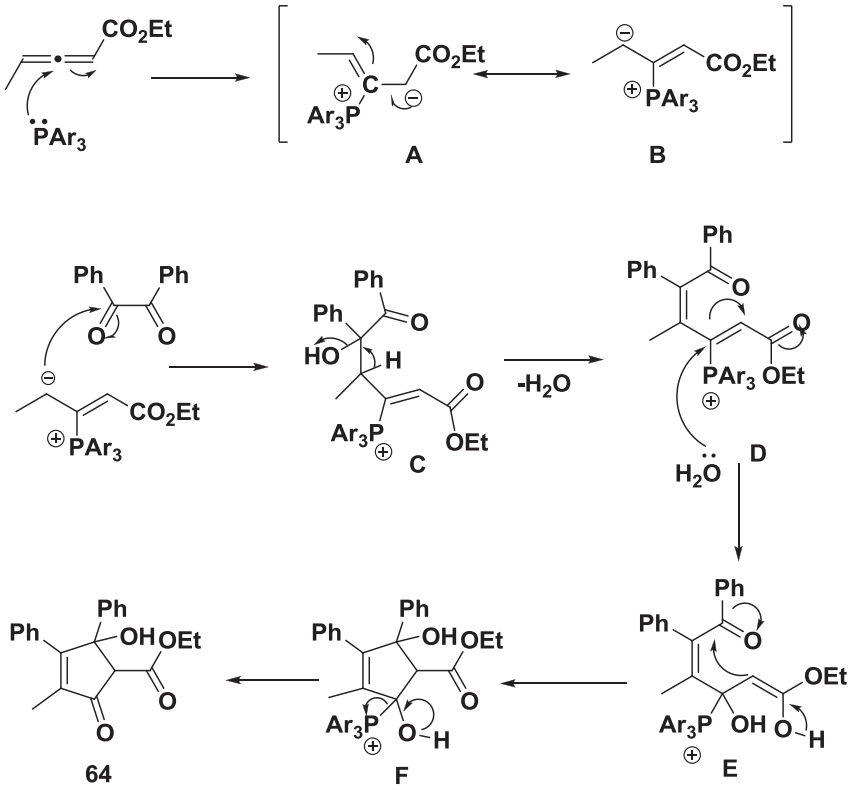
The reaction appears to work well with unsymmetrical diaryl 1,2-diones, and an example using 1-(4-bromophenyl)-2-phenylethane-1,2-dione is shown in Scheme 3.21. However, as expected, the reaction yielded two regioisomers as inseparable mixture in 1:0.88 ratio.



Scheme 3.21

3.5 Mechanism

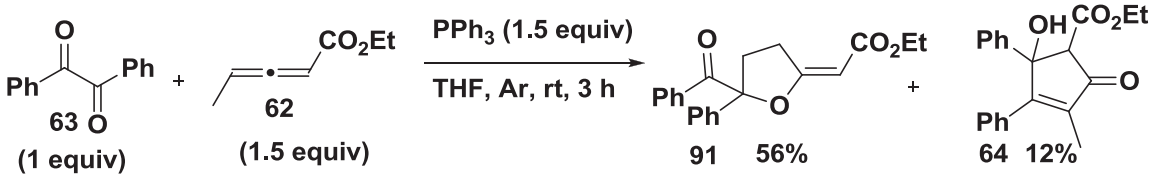
The reaction may be rationalized by the following mechanistic postulate. Conceivably, the first step is the nucleophilic addition of triarylphosphine to allene ester resulting in the formation of a 1,3-dipolar zwitterion. The latter then attacks a carbonyl group of the dione forming **C**. This species loses a molecule of water to afford the cationic intermediate **D**. Addition of water to the latter followed by cyclization and elimination of phosphine delivers **64**.



Scheme 3.22

3.6 Synthesis of Tetrahydrofuran Derivatives

Our subsequent studies showed that the reaction afforded 2-alkylidenetetrahydrofuran **91** as the major product, when triphenylphosphine was used as the catalyst with THF as solvent at room temperature. Purification of the crude mixture by column chromatography afforded the compound as colourless oil. When the reaction was conducted in solvents such as toluene, dioxane or xylene, the same product was obtained in low yield.



Scheme 3.23

The compound was characterized using various spectroscopic techniques. The IR spectrum showed the keto carbonyl absorption at 1708 cm^{-1} and the conjugated ester at 1683 cm^{-1}. The -C=C- stretching was observed around 1650 cm^{-1}. In the ^{1}H NMR spectrum, the characteristic olefin proton resonated as triplet at δ 5.43 ppm. The compound showed quartet resonance signal at δ 4.04 ppm due to methylene protons of ester group, and methyl protons of ester group were discernible as triplet at δ 1.18 ppm

(Figure 3.5). In ^{13}C NMR the keto carbon resonated at δ 195.9 ppm and the furan carbon attached to the alkylidene group was discernible at δ 174.5 ppm. The ester carbonyl group exhibited resonance signal at δ 167.8 ppm (Figure 3.6). The structure was further confirmed using high resolution mass spectrometry.

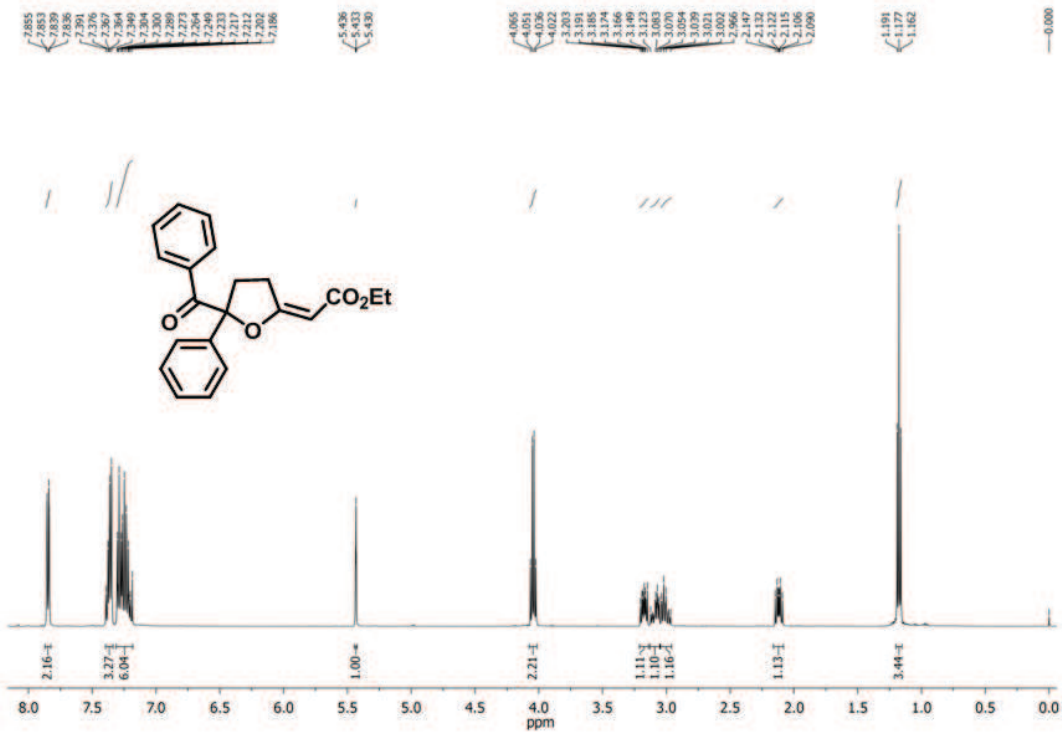


Figure 3.5 ^{1}H NMR spectrum of compound **91**

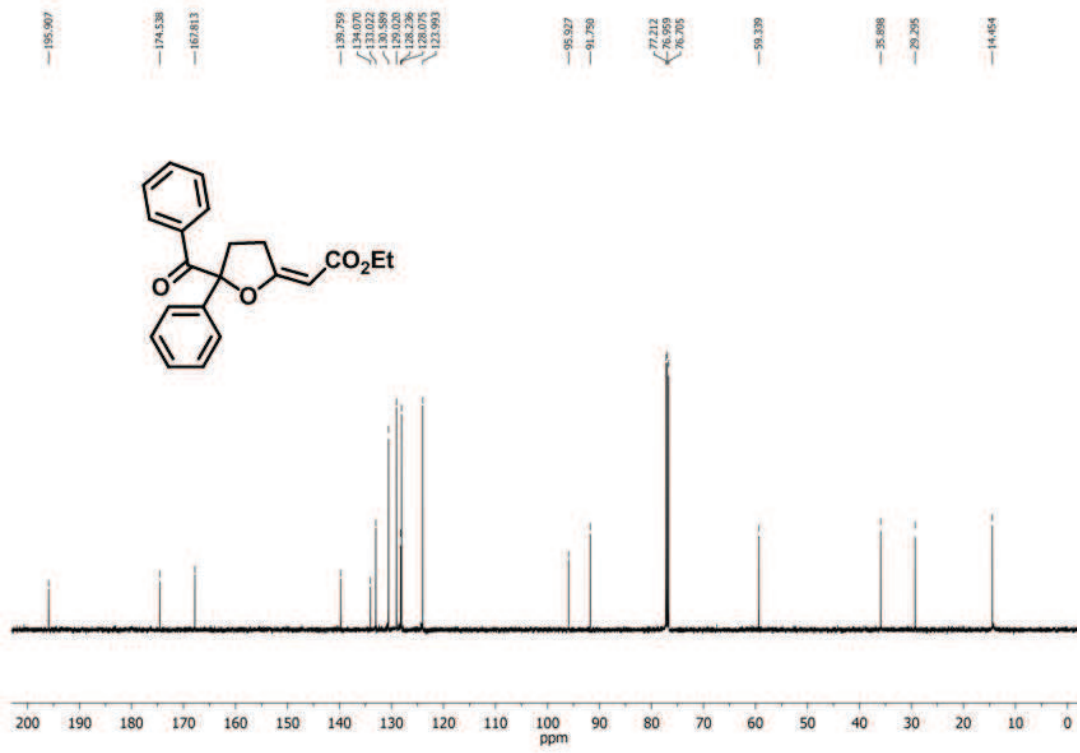


Figure 3.6 ^{13}C NMR spectrum of compound **91**

In this context, it may be recalled that He and coworkers have reported the annulation of phosphine-γ-alkyl allenoate zwitterion to aldehydes to afford 2-alkylidenetetrahydrofurans.[24f] The *E* geometry of the double bond in 2-alkylidenetetrahydrofurans obtained was ascertained by nOe studies of compound **94**. The selective irradiation of H_a produced only feeble enhancement in the signals corresponding to H_b (Figure 3.7). Further support for the assignment was accrued by comparing the chemical shift values of analogous compounds reported.[24f]

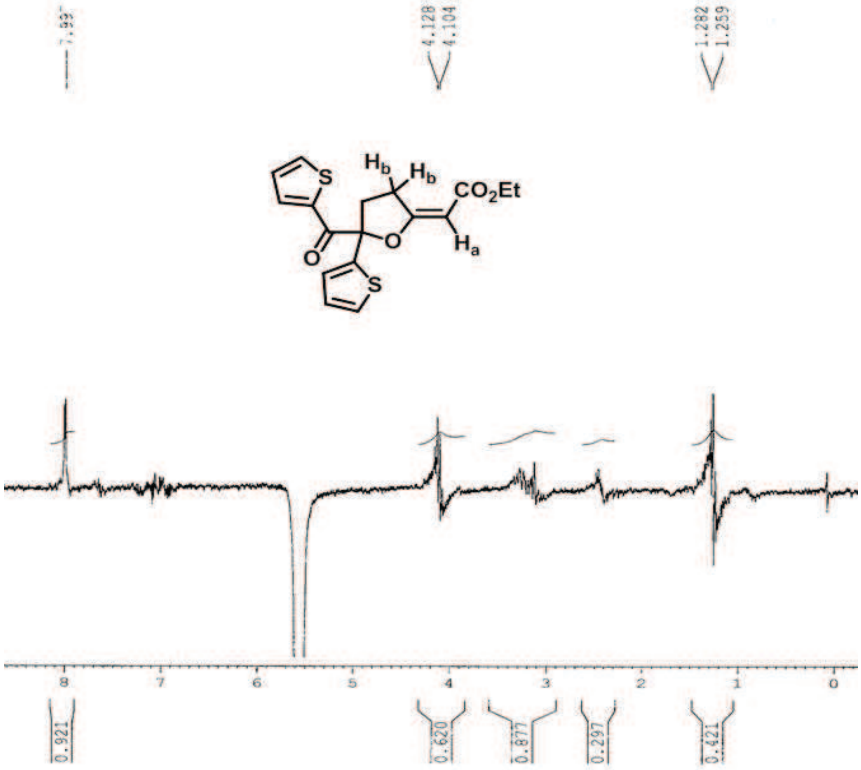
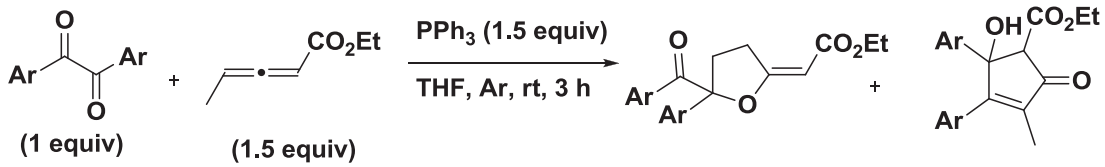
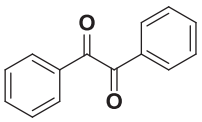
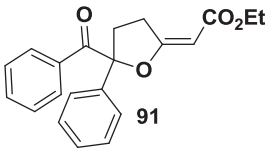
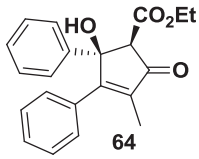
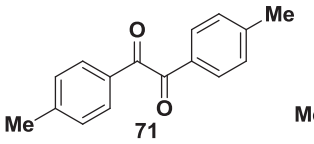
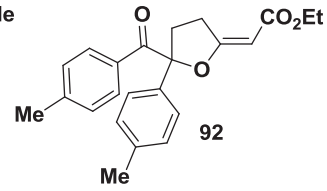
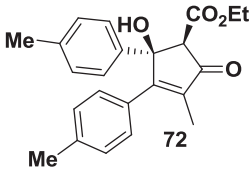
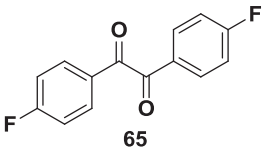
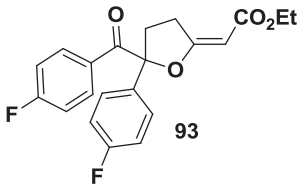
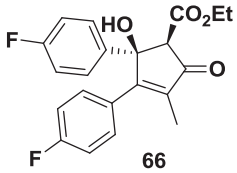
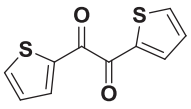
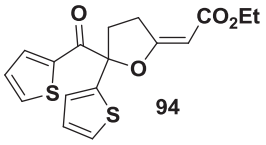
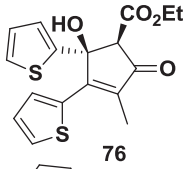
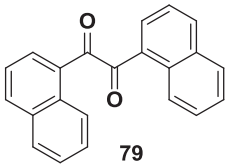
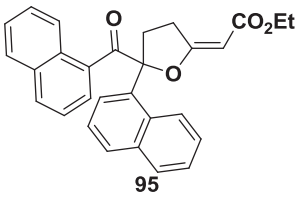
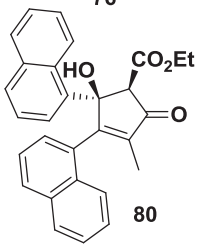


Figure 3.7 nOe spectrum of compound **94**

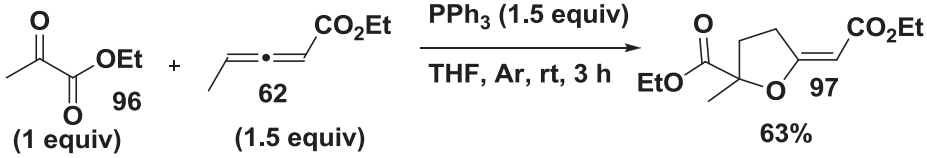
The reaction was found to be general with respect to various diones and the results obtained using representative 1,2-diones and ethyl penta 2,3-dienoate are given in Table 3.3.

Table 3.3. Scope of the reaction



Entry	Dione	Product a	Yield (%)	Product b	Yield (%)
1	 63	 91	56	 64	12
2	 71	 92	77	 72	2
3	 65	 93	35	 66	20
4	 75	 94	63	 76	trace
5	 79	 95	40	 80	9

It is worthy of note that the reaction with ethyl pyruvate under the same conditions afforded 2-alkylidenetetrahydrofuran derivative exclusively (Scheme 3.24).

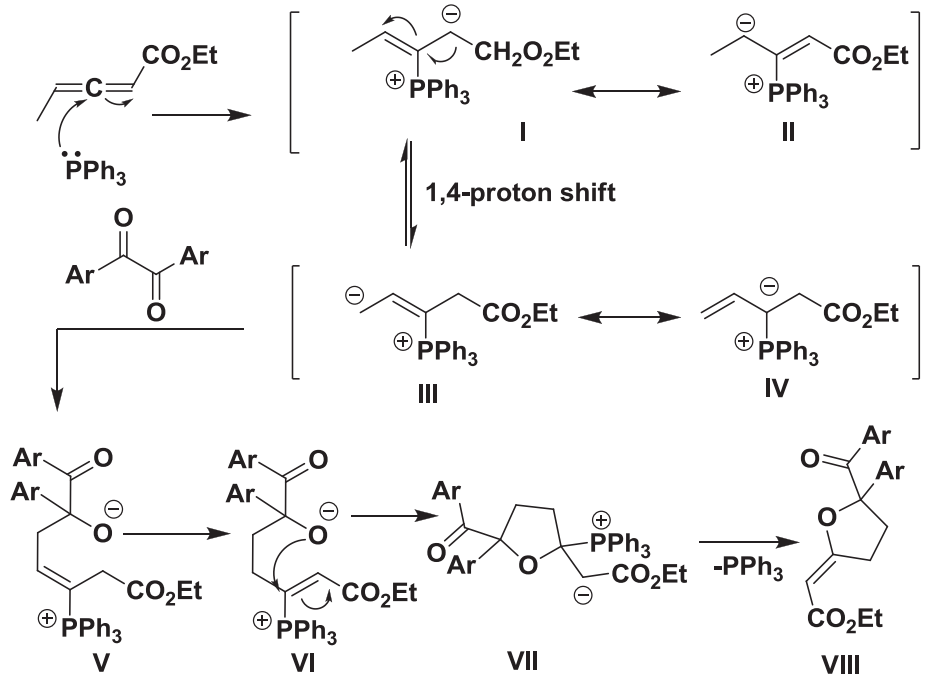


Scheme 3.24

3.7 Mechanism

A mechanistic postulate for the formation of 2-alkylidene terahydrofuran can be invoked as follows. Initial event can be construed as the formation of zwitterion by the addition of phosphine to the allenoate. The zwitterionic form I undergoes a [1,4] H- shift to form intermediate III. The latter adds to the carbonyl of benzil to form V. This

intermediate after proton transfer and cyclization yields the 2-alkylidene tetrahydrofuran derivative VIII (Scheme 3.25).



Scheme 3.25

3.8 Conclusion

In conclusion, we have encountered a novel annulation of allenoate-phosphine zwitterion with acyclic 1,2-diones resulting in the formation of substituted cyclopentenone derivatives and 2-alkylidenetetrahydrofuran derivatives. 2-Cyclopentenones are of pharmacological importance and are embedded in natural products such as prostaglandins.[1] In addition, a number of natural and synthetic 4-hydroxy cyclopentene-1-ones are useful crop protection agents.[1c,26] It may also be mentioned that cyclopentenones have found use in the construction of polysubstituted aromatic hydrocarbons,[27] isotruxenones,[28] and diquinanes.[29] It is noteworthy that the reactivity of acyclic 1,2-diones towards the allenoate-phosphine zwitterions is explored for the first time.

3.9 Experimental Section

3.9.1 General

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300/500 (^{1}H) and 75/126(^{13}C) MHz respectively on Bruker Avance DPX-500S MHz NMR spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling

constant (*J*) is reported in Hertz (Hz). Mass spectra were recorded under HRMS (ESI) using Thermo Scientific Exactive Orbitrap mass spectrometer. IR spectra were recorded on a Bruker Alpha-T FT-IR spectrophotometer. Allenoates were prepared using known literature procedures.[25] Gravity column chromatography was performed using silica gel and mixtures of petroleum ether-ethyl acetate were used for elution.

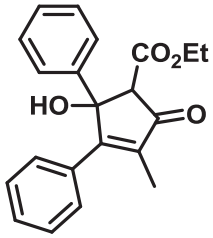
3.9.2 General experimental procedures

3.9.2.1 General procedure for the synthesis of cyclopentenone derivatives

The dione (0.5 mmol) and the allenoate (0.75 mmol) were taken in an R.B. flask as a solution in dry THF (5 ml) under argon atmosphere. To this solution, tris(2,6-dimethoxyphenyl) phosphine (0.75 mmol) was added and stirred for 3 h. The crude product, on removal of the solvent and purification by column chromatography using 100-200 silica gel and 85:15 hexane: ethyl acetate as the eluent afforded the product as a cyclopentenone derivative.

Ethyl 2-hydroxy-4-methyl-5-oxo-2,3-diphenylcyclopent-3-enecarboxylate (64)

Following the general procedure, the reaction of benzil (105 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 2-hydroxy-4-methyl-5-oxo-2,3-diphenylcyclopent-3-enecarboxylate in 94% (158 mg, 0.47 mmol) yield as colourless solid.



Yield: 158 mg (0.47 mmol, 94%), colourless solid, mp 94-98 ^{o}C

IR (film) ν_{max}: 3454, 1697 (broad), 1621 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.35 (m, 2H), 7.32 -7.30 (m, 2H), 7.29 - 7.23 (m, 6H), 4.75 (s, 1H), 4.29-4.24 (m, 2H), 3.76 (s, 1H), 2.02 (s, 3H), 1.32 (t, 3H, *J* = 7.0 Hz) ppm.

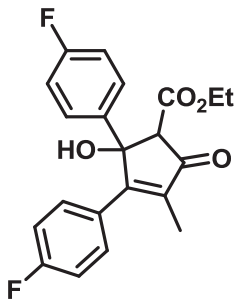
^{13}C NMR (126 MHz, $CDCl_3$): δ 199.2, 170.1, 168.9, 143.0, 137.5, 132.8, 129.3, 129.1, 128.7, 128.1, 127.6, 124.9, 81.3, 65.7, 62.2, 14.1, 10.2 ppm.

HRMS (ESI-MS) calcd for $C_{21}H_{20}O_4$ Na^+ 359.1259; Found: 359.1255.

Ethyl 2,3-bis(4-fluorophenyl)-2-hydroxy-4-methyl-5-oxocyclopent-3-enecarboxylate (66)

Following the general procedure, the reaction of 4,4′-difluorobenzil (123 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 2,3-bis(4-

fluorophenyl)-2-hydroxy-4-methyl-5-oxocyclopent-3-enecarboxylate in 96% (179 mg, 0.48 mmol) yield as colourless solid.



Yield: 179 mg (0.48 mmol, 96%), colourless solid, mp 108-110 ^{o}C

IR (film) ν_{max}: 3451, 1737, 1702, 1603, 1509 cm^{-1}.

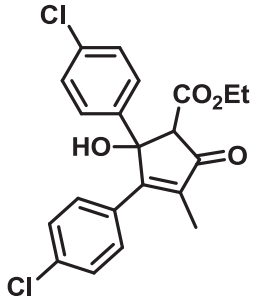
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.22 (m, 4H), 6.91 (t, 4H, J = 8.0 Hz), 4.93 (s, 1H), 4.26-4.16 (m, 2H), 3.62 (s, 1H), 1.94 (s, 3H), 1.26 (t, 3H, J = 7.5 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 198.8, 168.9, 168.4, 163.0 (d, $^{1}J_{CF}$ = 251.8 Hz), 162.0 (d, $^{1}J_{CF}$ = 247.8 Hz), 138.7 (d, $^{4}J_{CF}$ = 2.9 Hz), 137.5, 131.3 (d, $^{3}J_{CF}$ = 8.3 Hz), 128.8 (d, $^{4}J_{CF}$ = 3.4 Hz), 126.7 (d, $^{3}J_{CF}$ = 8.2 Hz), 115.5 (d, $^{2}J_{CF}$ = 21.5 Hz), 115.4 (d, $^{2}J_{CF}$ = 21.5 Hz), 80.9, 65.2, 62.2, 14.1, 10.1 ppm.

HRMS (ESI-MS) calcd for $C_{21}H_{18}F_2O_4Na^+$ 395.1071; Found: 395.1068.

Ethyl 2,3-bis(4-chlorophenyl)-2-hydroxy-4-methyl-5-oxocyclopent-3-enecarboxylate (68)

Following the general procedure, the reaction of 4,4′-dichlorobenzil (140 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 2,3-bis(4-chlorophenyl)-2-hydroxy-4-methyl-5-oxocyclopent-3-enecarboxylate in 93% (188 mg, 0.46 mmol) yield as colourless solid.



Yield: 188 mg (0.46 mmol, 93%), colourless solid, mp 115-117 ^{o}C

IR (film) ν_{max}: 3448, 1735, 1701, 1602, 1504 cm^{-1}.

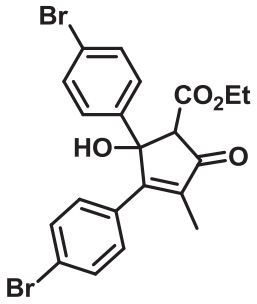
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, 8H, J = 1.5 Hz), 5.07 (s, 1H), 4.33 - 4.23 (m, 2H), 3.67 (s, 1H), 2.00 (s, 3H), 1.33 (t, 3H, J = 7.0 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 198.5, 168.9, 168.2, 141.4, 137.9, 135.7, 133.7, 131.0, 130.4, 128.9, 128.6, 126.4, 80.9, 64.9, 62.4, 14.1, 10.2 ppm.

HRMS (ESI-MS): calcd for $C_{21}H_{18}Cl_2O_4Na^+$ 427.0480; Found: 427.0473.

Ethyl 2,3-bis(4-bromophenyl)-2-hydroxy-4-methyl-5-oxocyclopent-3-enecarboxylate (70)

Following the general procedure, the reaction of 4,4′-dibromobenzil (184 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 2,3-bis(4-bromophenyl)-2-hydroxy-4-methyl-5-oxocyclopent-3-enecarboxylate in 90% (222 mg, 0.45 mmol) yield as colourless solid.



Yield: 222 mg (0.45 mmol, 90%), pale yellow solid, mp 126-130 ^{o}C

IR (film) ν_{max}: 3439, 1699 (broad), 1487, 1333 cm^{-1}

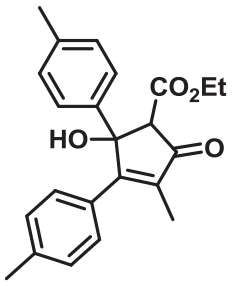
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 - 7.41 (m, 4H), 7.21 - 7.17 (m, 4H), 5.07 (s, 1H), 4.31 - 4.24 (m, 2H), 3.67 (s, 1H), 1.99 (s, 3H), 1.33 (t, 3H, J = 7.0 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 198.5, 169.0, 168.3, 142.0, 138.0, 132.0, 131.7, 131.6, 130.7, 126.8, 124.2, 122.0, 81.0, 64.9, 62.5, 14.2, 10.3 ppm.

HRMS (ESI-MS) calcd for $C_{21}H_{18}Br_2O_4Na^+$ 514.9470; Found: 514.9463.

Ethyl 2-hydroxy-4-methyl-5-oxo-2,3-dip-tolylcyclopent-3-enecarboxylate (72)

Following the general procedure, the reaction of 4,4′-dimethylbenzil (119 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 2-hydroxy-4-methyl-5-oxo-2,3-dip-tolylcyclopent-3-enecarboxylate in 92% (167 mg, 0.46 mmol) yield as colourless solid.



Yield: 167 mg (0.46 mmol, 92%), colourless solid, mp: 130-134 ^{o}C

IR (film) ν_{max}: 3448, 1696 (broad), 1610, 1511 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 - 7.12 (m, 4H), 7.00 (t, 4H, J = 8.5 Hz), 4.59 (s, 1H), 4.20 - 4.15 (m, 2H), 3.62 (s, 1H), 2.23 (d, 6H, J = 3.5 Hz), 1.95 (s, 3H), 1.23 (t, 3H, J = 7.0 Hz) ppm.

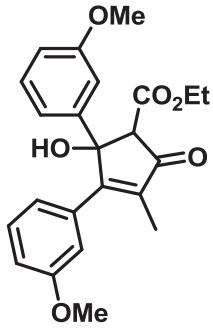
^{13}C NMR (126 MHz, $CDCl_3$): δ 198.2, 168.9, 167.9, 139.2, 138.2, 135.9, 135.8, 128.9, 128.2, 128.2, 127.8, 123.7, 80.2, 64.8, 60.9,

20.3, 20.0, 13.0, 9.2 ppm.

HRMS (ESI-MS) calcd for $C_{23}H_{24}O_4Na^+$ 387.1572; Found: 387.1569.

Ethyl 2-hydroxy-2,3-bis(3-methoxyphenyl)-4-methyl-5-oxocyclopent-3-enecarboxylate (74)

Following the general procedure, the reaction of 3,3′-dimethoxybenzil (135 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 2-hydroxy-2,3-bis(3-methoxyphenyl)-4-methyl-5-oxocyclopent-3-enecarboxylate in 88% (174 mg, 0.44 mmol) yield as colourless solid.



Yield: 174 mg (0.44 mmol, 88%), colourless solid, mp 118-120 ^oC

IR (film) ν_{max}: 3459, 1696 (broad), 1598, 1576, 1251, 1170 cm^{-1}.

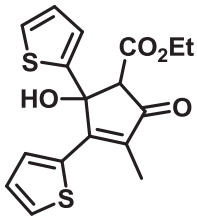
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 - 7.16 (m, 2H), 7.00 (s, 1H), 6.87 - 6.74 (m, 5H), 4.77 (s, 1H), 4.27 - 4.22 (m, 2H), 3.75 (s, 4H), 3.64 (s, 3H), 2.01 (s, 3H), 1.31 (t, 3H, J = 7.0 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 199.3, 169.7, 168.9, 159.9, 159.1, 144.8, 137.7, 134.0, 129.7, 129.1, 121.6, 117.1, 115.2, 114.2, 113.00, 110.9, 81.2, 65.5, 62.1, 55.1, 54.9, 14.1, 10.2 ppm.

HRMS (ESI-MS) calcd for $C_{23}H_{24}O_6Na^+$419.1471; Found: 419.1468.

Ethyl 2-hydroxy-4-methyl-5-oxo-2,3-di(thiophen-2-yl)cyclopent-3-enecarboxylate (76)

Following the general procedure, the reaction of 2,2′-thenil (111 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 2-hydroxy-4-methyl-5-oxo-2,3-di(thiophen-2-yl)cyclopent-3-enecarboxylate in 81% (141 mg, 0.41 mmol) yield as yellow solid.



Yield: 141 mg (0.41 mmol, 81%), yellow solid, mp 63-65 ^oC

IR (film) ν_{max}**:** 3439, 1731, 1688, 1598 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, 1H, J = 4.0 Hz), 7.48 (d, 1H, J = 5.0 Hz), 7.14 - 7.13 (m, 1H), 7.02 - 7.00 (m, 1H), 6.80 - 6.78

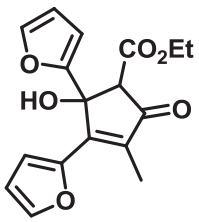
(m, 1H), 6.67 - 6.66 (m, 1H), 5.08 (s, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.73 (s, 1H), 2.13 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ: 196.5, 168.7, 161.00, 148.8, 134.5, 134.2, 133.2, 131.1, 127.6, 127.1, 125.3, 123.3, 80.1, 65.5, 62.4, 14.1, 10.6 ppm.

HRMS (ESI-MS) calcd for $C_{17}H_{16}O_4S_2Na^+$ 371.0388; Found: 371.0384.

Ethyl 2,3-di(furan-2-yl)-2-hydroxy-4-methyl-5-oxocyclopent-3-enecarboxylate (78)

Following the general procedure, the reaction of 2,2′-furil (95 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 2,3-di(furan-2-yl)-2-hydroxy-4-methyl-5-oxocyclopent-3-enecarboxylate in 65% (103mg, 0.33 mmol) yield as yellow solid.



Yield: 103 mg (0.33 mmol, 65%), yellow solid, mp 80-84 ^oC

IR (film) ν_{max}: 3450, 1733, 1694, 1618 cm^{-1}.

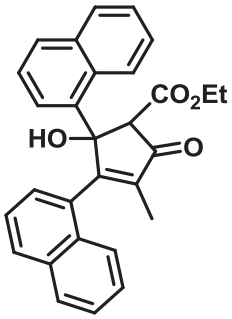
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.28 (s, 1H), 6.95 (d, 1H, *J* = 3.5 Hz), 6.48 - 6.47 (m, 1H), 6.43 (d, 1H, *J* = 3.5 Hz), 6.32 (s, 1H), 4.83 (s, 1H), 4.27 (q, 2H, *J* = 7.0 Hz), 3.83 (s, 1H), 2.22 (s, 3H), 1.33 (t, 3H, *J* = 7.0 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 196.7, 168.6, 154.9, 153.5, 148.8, 145.3, 142.3, 134.3, 117.6, 112.3, 110.5, 106.7, 76.8, 62.2, 61.3, 14.1, 9.9 ppm.

HRMS (ESI-MS) calcd for $C_{17}H_{16}O_6Na^+$ 339.0845; Found: 39.0839.

Ethyl 2-hydroxy-4-methyl-2,3-di(naphthalen-1-yl)-5-oxocyclopent-3-enecarboxylate (80)

Following the general procedure, the reaction of 1,2-di(naphthalen-1-yl)ethane-1,2-dione (155 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 2-hydroxy-4-methyl-2,3-di(naphthalen-1-yl)-5-oxocyclopent-3-enecarboxylate in 93% (203 mg, 0.47 mmol) yield as colourless solid.



Yield: 203 mg (0.47 mmol, 93%), colourless solid, mp 160-162 ^{o}C

IR (film) ν_{max}: 3450, 1698 (broad), 1326 cm^{-1}.

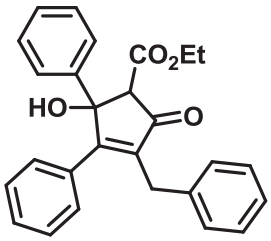
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.85 (s, 1H), 7.79 - 7.74 (m, 3H), 7.70 - 7.64 (m, 3H), 7.45 - 7.33 (m, 6H), 5.07 (s, 1H), 4.31 - 4.24 (m, 2H), 3.87 (s, 1H), 2.13 (s, 3H), 1.31 (t, 3H, J = 7.0 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 199.3, 170.0, 169.1, 140.3, 138.0, 133.3, 133.2, 132.7, 132.6, 130.5, 129.5, 128.8, 128.6, 128.4, 127.8, 127.6, 127.1, 126.4, 126.3, 126.2, 126.00, 124.3, 122.7, 81.7, 65.4, 62.3, 14.1, 10.4 ppm.

HRMS (ESI-MS) calcd for $C_{29}H_{24}O_4$ Na^+ 459.1572; Found: 459.1573.

Ethyl 4-benzyl-2-hydroxy-5-oxo-2,3-diphenylcyclopent-3-enecarboxylate (82)

Following the general procedure, the reaction of benzil (105 mg, 0.5 mmol) with ethyl 3-benzyl allenoate (152 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 2-hydroxy-4-methyl-5-oxo-2,3-dip-tolylcyclopent-3-enecarboxylate in 81% (167 mg, 0.41 mmol) yield as colourless solid.



Yield: 167 mg (0.41 mmol, 81%), colourless solid, mp 64-66 ^{o}C

IR (film) ν_{max}: 3448, 1698 (broad), 1313 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 - 7.32 (m, 2H), 7.30 - 7.16 (m, 9H), 7.13 - 7.09 (m, 4H), 4.77 (s, 1H), 4.28 - 4.21 (m, 2H), 3.82 (s, 1H), 3.73 (d, 2H, J = 5.0 Hz), 1.28 (t, 3H, J = 7.0 Hz) ppm.

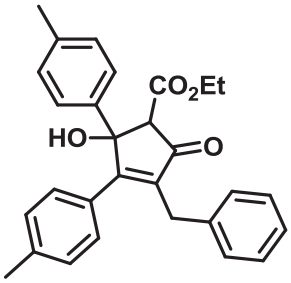
^{13}C NMR (126 MHz, $CDCl_3$): δ 198.7, 171.8, 168.8, 142.7, 140.1, 138.3, 132.6, 129.4, 128.7, 128.6, 128.3, 128.2, 127.6, 126.4, 125.0, 81.3, 66.0, 62.2, 30.1, 14.1 ppm.

HRMS (ESI-MS) calcd for $C_{27}H_{24}O_4$ Na^+ 435.1572; Found: 435.1568.

Ethyl 4-benzyl-2-hydroxy-5-oxo-2,3-dip-tolylcyclopent-3-enecarboxylate (83)

Following the general procedure, the reaction of 4,4′-dimethylbenzil (119 mg, 0.5 mmol) with ethyl 3-benzyll allenoate (152 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl) phosphine (332 mg, 0.75 mmol) afforded ethyl 4-benzyl-2-hydroxy-5-

oxo-2,3-dip-tolylcyclopent-3-enecarboxylate in 92% (203 mg, 0.46 mmol) yield as pale yellow solid.



Yield: 203 mg (0.46 mmol, 92%), pale yellow solid, mp 62-64 ^{o}C

IR (film) ν_{max}: 3470, 1697 (broad), 1311 cm^{-1}.

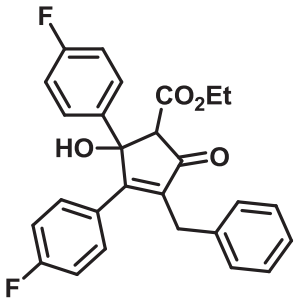
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 - 7.20 (m, 4H), 7.18 -7.13 (m, 4H), 7.08 - 7.00 (m, 5H), 4.67 (s, 1H), 4.25 - 4.19 (m, 2H), 3.77-3.73 (m, 3H), 2.28 (d, 6H, *J* = 15.0 Hz), 1.26 (t, 3H, *J* = 7.5 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 198.9, 171.9, 168.8, 140.0, 139.6, 139.5, 138.5, 137.2, 129.7, 129.4, 129.00, 128.9, 128.6, 128.5, 128.3, 126.3, 124.9, 81.3, 66.3, 62.1, 30.2, 21.4, 21.1, 14.1 ppm.

HRMS (ESI-MS) calcd for $C_{29}H_{28}O_4Na^+$ 463.1885; Found: 463.1881.

Ethyl 4-benzyl-2,3-bis(4-fluorophenyl)-2-hydroxy-5-oxocyclopent-3-enecarboxylate (84)

Following the general procedure, the reaction of 4,4′-difluorobenzil (123 mg, 0.5 mmol) with ethyl 3-benzyl allenoate (152 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded ethyl 4-benzyl-2,3-bis(4-fluorophenyl)-2-hydroxy-5-oxocyclopent-3-enecarboxylate in 94% (211 mg, 0.47 mmol) yield as pale yellow solid.



Yield: 211 mg (0.47 mmol, 94%), pale yellow solid, mp 72-74 ^{o}C

IR (film) ν_{max}: 3457, 1698 (broad), 1506, 1225, 1157 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 - 7.23 (m, 4H), 7.20 - 7.17 (m, 1H), 7.16 - 7.13 (m, 2H), 7.09 (d, 2H, *J* = 8.0 Hz), 6.99 - 6.90 (m, 4H), 5.02 (s, 1H), 4.30 - 4.22 (m, 2H), 3.77 (s, 1H), 3.72 (d, 2H, *J* = 6.5 Hz), 1.30 (t, 3H, *J* = 7.5 Hz) ppm.

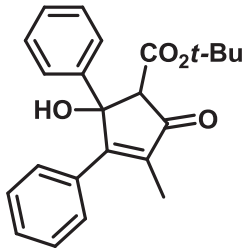
^{13}C NMR (126 MHz, $CDCl_3$): δ 198.4, 170.4, 168.8, 163.2 (d, $^{1}J_{CF}$ = 251.6 Hz), 162.1(d, $^{1}J_{CF}$ = 248.1 Hz), 140.2, 138.3 (d, $^{4}J_{CF}$ = 2.8 Hz), 138.0, 130.9 (d, $^{3}J_{CF}$ = 8.3 Hz), 128.7,

128.3,128.1, 126.8 (d, $^{3}J_{CF}$ = 8.2 Hz), 126.5, 115.7 (d, $^{2}J_{CF}$ = 21.7 Hz),115.5 (d, $^{2}J_{CF}$ = 21.5 Hz), 81.0, 65.6, 62.4, 30.0, 14.0 ppm.

HRMS (ESI-MS) calcd for $C_{27}H_{22}F_2O_4Na^+$ 471.1384; Found: 471.1378.

***Tert*-butyl 2-hydroxy-4-methyl-5-oxo-2,3-diphenylcyclopent-3-enecarboxylate (86)**

Following the general procedure, the reaction of benzil (105 mg, 0.5 mmol) with *tert*-butyl 3-methyl allenoate (116 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded *tert*-butyl 2-hydroxy-4-methyl-5-oxo-2,3-diphenylcyclopent-3-enecarboxylate in 82% (149 mg, 0.41 mmol) yield as colourless solid.



Yield: 149 mg (0.41 mmol, 82%), colourless solid, mp 91-93 ^{o}C

IR (film) ν_{max}: 3464, 1692 (broad), 1332, 1150 cm^{-1}.

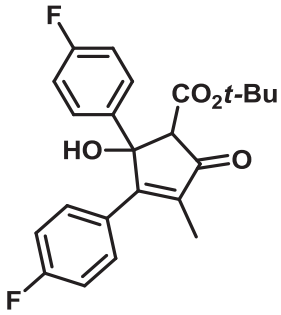
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, 2H, *J* = 7.5 Hz), 7.29 (d, 2H, *J* = 7.5 Hz), 7.27 - 7.20 (m, 6H), 4.92 (s, 1H), 3.65 (s, 1H), 2.00 (s, 3H), 1.50 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 199.6, 170.1, 168.3, 143.3, 137.5, 133.0, 129.1, 128.6, 128.1, 127.4, 125.00, 83.6, 81.2, 66.3, 28.1, 10.1 ppm.

HRMS (ESI-MS) calcd for $C_{23}H_{24}O_4Na^+$ 387.1572; Found: 387.1569.

***Tert*-butyl 2,3-bis(4-fluorophenyl)-2-hydroxy-4-methyl-5-oxocyclopent-3-necarboxylate (87)**

Following the general procedure, the reaction of 4,4′-fluorobenzil (123 mg, 0.5 mmol) with *tert*-butyl 3-methyl allenoate (116 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded *tert*-butyl 2,3-bis(4-fluorophenyl)-2-hydroxy-4-methyl-5-oxocyclopent-3-necarboxylate in 83% (186mg, 0.41 mmol) yield as colourless solid.



Yield: 186 mg (0.41 mmol, 83%), colourless solid, mp 88-90 ^{o}C

IR (film) ν_{max}: 3452, 1693 (broad), 1507, 1225, 1156 cm^{-1}.

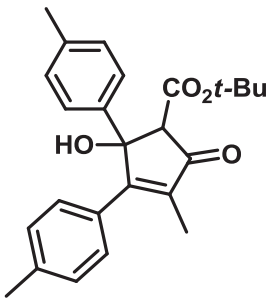
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 - 7.28 (m, 4H), 6.97 (t, 4H, J = 8.5 Hz), 5.18 (s, 1H), 3.58 (s, 1H), 1.99 (s, 3H), 1.50 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 199.1, 168.4, 168.3, 163.0 (d, $^{1}J_{CF}$ = 251.5 Hz), 162.0 (d, $^{1}J_{CF}$ = 247.6 Hz), 138.9 (d, $^{4}J_{CF}$ = 2.9 Hz), 137.4, 131.2 (d, $^{3}J_{CF}$ = 8.3 Hz), 128.9 (d, $^{4}J_{CF}$ = 3.5 Hz) , 126.7 (d, $^{3}J_{CF}$ = 8.1 Hz), 115.5 (d, $^{2}J_{CF}$ = 21.4 Hz), 115.3 (d, $^{2}J_{CF}$ = 21.5 Hz), 83.8, 80.9, 65.7, 28.0, 10.1 ppm.

HRMS (ESI-MS) calcd for $C_{23}H_{22}F_2O_4$ Na^{+}423.1384; Found: 423.1380.

***Tert*-butyl 2-hydroxy-4-methyl-5-oxo-2,3-dip-tolylcyclopent-3-enecarboxylate (88)**

Following the general procedure, the reaction of 4,4′-dimethylbenzil (119 mg, 0.5 mmol) with *tert*-butyl 3-methyl allenoate (116 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded *tert*-butyl 2-hydroxy-4-methyl-5-oxo-2,3-dip-tolylcyclopent-3-enecarboxylate in 78% (172 mg, 0.39 mmol) yield as colourless solid.



Yield: 172 mg (0.39 mmol, 78%), colourless solid, mp 75-76 ^{o}C

IR (film) ν_{max}: 3457, 1692 (broad), 1332, 1152 cm^{-1}.

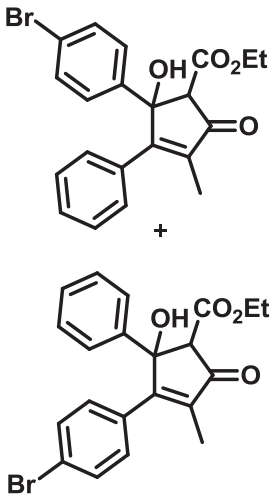
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (dd, 4H, J_1 = 17.5 Hz, J_2 = 8.0 Hz), 7.06 (t, 4H, J = 9.0 Hz), 4.82 (s, 1H), 3.59 (s, 1H), 2.29 (d, 6H, J = 4.0 Hz), 2.00 (s, 3H), 1.49 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 199.7, 170.0, 168.4, 140.6, 139.2, 136.9, 136.8, 130.2, 129.3, 129.1, 128.8, 124.9, 83.4, 81.2, 66.5, 28.1, 21.4, 21.1, 10.3 ppm.

HRMS (ESI-MS) calcd for $C_{25}H_{28}O_4Na^{+}$ 415.1885; Found: 415.1877.

Ethyl 3-(4-bromophenyl)-2-hydroxy-4-methyl-5-oxo-2-phenylcyclopent-3-enecarboxy- late (90a) & ethyl 2-(4-bromophenyl)-2-hydroxy-4-methyl-5-oxo-3-phenylcyclopent-3-enecarboxylate (90b)

Following the general procedure, the reaction of 1-(4-bromophenyl)-2-phenylethane-1,2-dione (145 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and tris(2,6-dimethoxyphenyl)phosphine (332 mg, 0.75 mmol) afforded mixture of regioisomers ethyl 3-(4-bromophenyl)-2-hydroxy-4-methyl-5-oxo-2-phenylcyclopent-3-enecarboxy- late (5a) and ethyl 2-(4-bromophenyl)-2-hydroxy-4-methyl-5-oxo-3-phenylcyclopent-3-enecarboxylate (5b) in 95% (197 mg, 0.46 mmol) yield as yellow oil.



Combined yield of two regioisomers with ratio (1:0.88): 197 mg (0.48 mmol, 95%), yellow oil.

IR (film) ν_{max}: 3460, 1696 (broad), 1333, 1316, 1181, 1010 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 - 7.36 (m, 4H), 7.31 - 7.30 (m, 3H), 7.28 - 7.26 (m, 5H), 7.23 - 7.18 (m, 3H), 7.15 (d, 2H, J = 8.5 Hz), 4.95 (s, 1.88H), 4.26 - 4.19 (m, 3.76H), 3.70 (s, 1H), 3.64 (s, 0.88H), 1.99 (s, 2.64H), 1.97 (s, 3H), 1.31 - 1.28 (m, 5.64H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 198.7, 198.7, 169.3, 168.9, 168.8, 168.5, 142.8, 142.3, 137.7, 137.7, 132.7, 131.8, 131.7, 131.4, 130.7, 129.4, 129.1, 128.7, 128.2, 127.6, 126.8, 124.9, 123.8, 121.7, 81.1, 81.0, 65.2, 65.1, 62.1, 14.1, 10.2, 10.1 ppm.

HRMS (ESI-MS) calcd for $C_{21}H_{19}BrO_4Na^+$ 437.0364; Found: 437.0347.

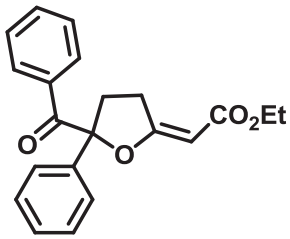
3.9.2.2 General procedure for the synthesis of tetrahydrofuran derivatives

The dione (0.5 mmol) and the alleneoate (0.75 mmol) were taken in an R.B. as a solution in dry THF (5 ml) under argon atmosphere. To this solution triphenylphosphine (0.75 mmol) was added and stirred for 3 h. The crude product after removal of the solvent was purified by column chromatography using 100-200 silica gel and 95:5 hexane: ethyl acetate as the eluent afforded the product as a tetrahydrofuran derivative.

(*E*)-Ethyl 2-(5-benzoyl-5-phenyldihydrofuran-2(3H)-ylidene)acetate (91)

Following the general procedure, the reaction of benzil (105 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and triphenylphosphine (197 mg, 0.75

mmol) afforded (*E*)-ethyl 2-(5-benzoyl-5-phenyldihydrofuran-2(3*H*)-ylidene)acetate in 56% (94 mg, 0.28 mmol) yield as colourless oil.



Yield: 94 mg (0.28 mmol, 56%), colourless oil.

IR (film) ν_{max}: 1708, 1683, 1650, 1120 cm^{-1}.

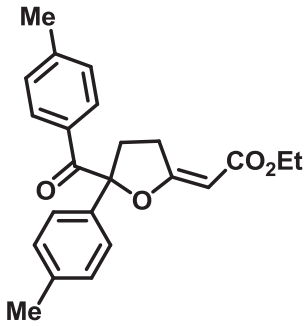
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, 2H, J_1 = 8.3 Hz, J_2 = 1.0 Hz), 7.39 - 7.35 (m, 3H), 7.30 - 7.19 (m, 5H), 5.43 (t, 1H, *J* = 1.5 Hz)), 4.04 (q, 2H, *J* = 7.0 Hz), 3.20 - 3.15 (m, 1H), 3.12 - 2.97 (m, 2H), 2.15 - 2.09 (m, 1H), 1.18 (t, 3H, *J* = 7.0 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 195.9, 174.5, 167.8, 139.8, 134.1, 133.0, 130.6, 129.0, 128.2, 128.1, 124.0, 95.9, 91.8, 59.3, 35.9, 29.3, 14.5 ppm.

HRMS (ESI-MS): calcd for $C_{21}H_{20}O_4Na^+$ 359.1259; Found 359.1247.

(*E*)-Ethyl 2-(5-(4-methylbenzoyl)-5-p-tolyldihydrofuran-2(3H)-ylidene)acetate (92)

Following the general procedure, the reaction of 4,4′-dimethylbenzil (119 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(5-(4-methylbenzoyl)-5-*p*-tolyldihydrofuran-2(3*H*)-ylidene)acetate in 77% (140 mg, 0.39 mmol) yield as colourless oil.



Yield: 140 mg (0.39 mmol, 77%), colourless oil.

IR (film) ν_{max}: 1708, 1679, 1650, 1119 cm^{-1}.

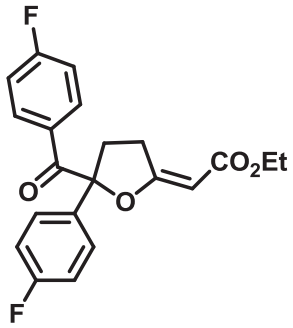
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, 2H, *J* = 8.5 Hz), 7.28 (d, 2H, *J* = 8.5 Hz), 7.13 (dd, 4H, J_1 = 16.0 Hz, J_2 = 8.0 Hz), 5.48 (s, 1H)), 4.11 (q, 2H, *J* = 7.5 Hz), 3.24 - 3.18 (m, 1H), 3.17 - 3.02 (m, 2H), 2.33 (d, 6H, *J* = 9.5 Hz), 2.18 - 2.12 (m, 1H), 1.25 (t, 3H, *J* = 7.0 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 195.5, 174.8, 167.9, 143.8 137.9, 137.0, 131.5, 130.8, 129.6, 128.8, 124.0, 96.0, 91.5, 59.3, 35.8, 29.3, 21.6, 21.1, 14.5 ppm.

HRMS (ESI-MS): calcd for $C_{23}H_{24}O_4Na^+$ 387.1572; Found 387.1568.

(*E*)-Ethyl 2-(5-(4-fluorobenzoyl)-5-(4-fluorophenyl)dihydrofuran-2(3H)-ylidene)acetate (93)

Following the general procedure, the reaction of 4,4′-difluorobenzil (123 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(5-(4-fluorobenzoyl)-5-(4-fluorophenyl)dihydrofuran-2(3*H*)-ylidene)acetate in 35% (65 mg, 0.17 mmol) yield as colourless oil.



Yield: 65 mg (0.17 mmol, 35%), colourless oil.

IR (film) ν_{max}: 1706, 1680, 1652, 1115 cm^{-1}.

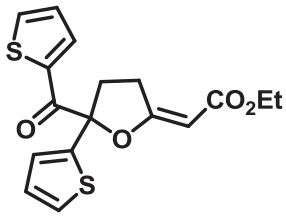
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (dd, 2H, J_1 = 8.5 Hz, J_2 = 5.5 Hz), 7.39 (dd, 2H, J_1 = 8.5 Hz, J_2 = 5.0 Hz), 7.03 (dt, 4H, J_1 = 22.5 Hz, J_2 = 8.5 Hz), 5.50 (s, 1H)), 4.12 (q, 2H, J = 7.0 Hz), 3.27 - 3.21 (m, 1H), 3.19 - 3.13 (m, 1H), 3.09 - 3.03 (m, 1H), 2.17 - 2.11(m, 1H), 1.25 (t, 3H, J = 7.5 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 194.2, 174.0, 167.6, 165.6 (d, $^{1}J_{CF}$ = 245.6 Hz), 162.6 (d, $^{1}J_{CF}$ = 249.0 Hz), 135.3 (d, $^{4}J_{CF}$ = 3.3 Hz), 133.4 (d, $^{3}J_{CF}$ = 9.3 Hz), 130.1 (d, $^{3}J_{CF}$ = 3.2 Hz), 125.9 (d, $^{3}J_{CF}$ = 8.2 Hz), 116.1 (d, $^{2}J_{CF}$ = 21.8 Hz), 115.4 (d, $^{2}J_{CF}$ = 21.8 Hz), 95.4, 92.1, 59.5, 36.0, 29.2, 14.4 ppm.

HRMS (ESI-MS): calcd for $C_{21}H_{18}F_2O_4\,Na^+$ 395.1071; Found 395.1066.

(*E*)-Ethyl 2-(5-(thiophen-2-yl)-5-(thiophene-2-carbonyl)dihydrofuran-2(3H)-ylidene)acetate (94)

Following the general procedure, the reaction of thenil (111 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(5-(thiophen-2-yl)-5-(thiophene-2-carbonyl)dihydrofuran-2(3*H*)-ylidene)acetate in 63% (110 mg, 0.32 mmol) yield as pale yellow oil.



Yield: 110 mg (0.32 mmol, 63%), pale yellow oil.

IR (film) ν_{max}: 1705, 1681, 1650, 1118 cm^{-1}.

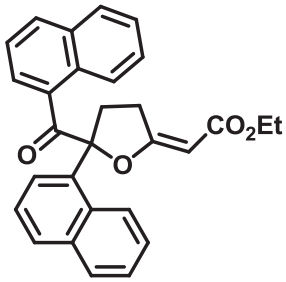
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, 1H, *J* = 3.9 Hz), 7.57 (d, 1H, *J* = 4.8 Hz), 7.17 (d, 1H, *J* = 4.8 Hz), 7.01 (t, 1H, *J* = 4.2 Hz), 6.94 (d, 1H, *J* = 3.3 Hz), 6.85 (t, 1H, *J* = 4.5 Hz), 5.49 (s, 1H)), 4.04 (q, 2H, *J* = 6.9 Hz), 3.26 - 2.96 (m, 3H), 2.40 - 2.34 (m, 1H), 1.18 (t, 3H, *J* = 6.9 Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 188.4, 173.3, 167.4, 142.1, 139.1, 135.8, 135.3, 128.1, 127.2, 126.0, 125.2, 93.8, 92.5, 59.4, 36.2, 29.4, 14.5 ppm.

HRMS (ESI-MS): calcd for $C_{17}H_{16}O_4S_2Na^+$ 371.0388; Found 371.0380.

(*E*)-Ethyl 2-(5-(1-naphthoyl)-5-(naphthalen-1-yl)dihydrofuran-2(3H)-lidene) acetate (95)

Following the general procedure, the reaction of 1,2-di(naphthalen-1-yl)ethane-1,2-dione (155 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(5-(1-naphthoyl)-5-(naphthalen-1-yl)dihydrofuran-2(3*H*)-ylidene)acetate in 40% (87 mg, 0.20 mmol) yield as colourless oil.



Yield: 87 mg (0.20 mmol, 40%), colourless oil.

IR (film) ν_{max}: 1704, 1677, 1650, 1114 cm^{-1}.

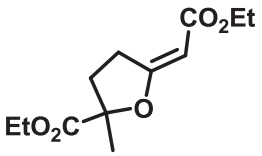
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.00 - 7.95 (m, 2H), 7.86 - 7.78 (m, 4H), 7.73 (t, 2H, *J* = 10.0 Hz), 7.57 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.5 Hz), 7.52 - 7.42 (m, 4H), 5.59 (s, 1H), 4.12 (q, 2H, *J* = 7.0 Hz), 3.42 - 3.37 (m, 1H), 3.27 - 3.13 (m, 2H), 2.23 - 2.27 (m, 1H), 1.25 (t, 3H, *J* = 7.0 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 195.8, 174.6, 167.8, 137.3, 135.4, 133.2, 133.0, 132.2, 131.4, 129.9, 129.2, 128.6, 128.2, 127.8, 127.7, 127.5, 126.7, 126.6, 126.5, 125.8, 123.1, 121.7, 96.3, 92.0, 59.4, 36.0, 29.4, 14.5 ppm.

HRMS (ESI-MS): calcd for $C_{29}H_{24}O_4Na^+$ 459.1572; Found 459.1563.

(*E*)-Ethyl 5-(2-ethoxy-2-oxoethylidene)-2-methyltetrahydrofuran-2-carboxylate (97)

Following the general procedure, the reaction of ethyl pyruvate (58 mg, 0.5 mmol) with ethyl 3-methyl allenoate (95 mg, 0.75 mmol) and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 5-(2-ethoxy-2-oxoethylidene)-2-methyltetrahydrofuran-2-carboxylate in 63% (76 mg, 0.31 mmol) yield as colourless oil.



Yield: 76 mg (0.31 mmol, 63%), colourless oil.

IR (film) ν_{max}: 1738, 1704, 1648, 1372, 1182, 1107, 1093, 1021 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.35 (t, 1H, J = 1,5 Hz), 4.22 (dq, 2H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 4.12 (q, 2H, J = 7.0 Hz), 3.31 (dddd, 1H, J_1 = 18.5 Hz, J_2 = 9.3 Hz, J_3 = 3.5 Hz, J_4 = 1.5 Hz), 3.06 - 2.98 (m, 1H), 2.45 (ddd, 1H, J_1 = 13.0 Hz, J_2 = 9.3 Hz, J_3 = 4.0 Hz), 2.00 - 1.94 (m, 1H), 1.61 (s, 3H), 1.29 (t, 3H, J = 7.0 Hz), 1.26 (t, 3H, J = 7.0 Hz) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.9, 172.0, 168.1, 90.8, 87.1, 61.7, 59.2, 34.5, 30.0, 23.2, 14.4, 14.1 ppm.

HRMS (ESI-MS): calcd for $C_{12}H_{18}O_5Na^+$ 265.1052; Found 265.1036.

3.10 References

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CHAPTER 4A

Phosphine-Mediated Reactions of Cyclic 1,2-Diones and 3-Alkyl Allenoates: An Efficient Protocol for Benzannulation Applicable to the Synthesis of Polycyclic Aromatic Hydrocarbons

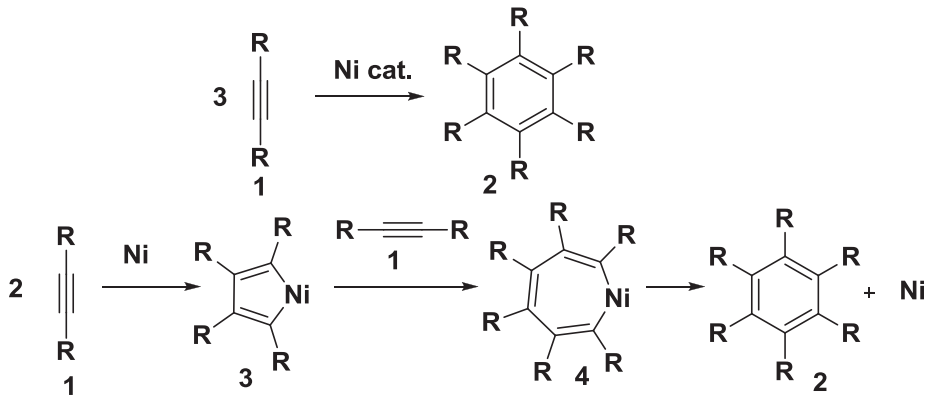
4a.1 Introduction

Benzene derivatives and benzenoid aromatics occupy a central place in organic chemistry.[1] Various polycyclic aromatics have been used in functional organic materials such as liquid crystals, organic light emitting and semiconducting materials, and other electronic devices.[2] Many of them are biologically active and used as medicines or pesticides. Thus functionalized aromatic hydrocarbons are important building blocks in synthetic organic chemistry and in medicinal chemistry. Earlier methods for their synthesis mainly relied on electrophilic substitution reaction on preformed aromatic ring and further functional group transformations. Low regioselectivity and limited substitution modes are the drawbacks of this strategy. In this regard, the synthesis of functionalized benzene derivatives and the benzannulation reactions which append an aromatic ring to the pre-existing polycyclic moiety have been pursued vigorously. The present chapter contains the results of a detailed study of a novel triphenylphosphine mediated benzannulation reaction of cyclic 1,2-diones and 3-alkyl allenoate, and the photophysical properties of the representative compounds synthesized by this method. In this regard, a brief description of various benzannultion reactions is presented in the following section.

4a.2 Benzannulation Reactions

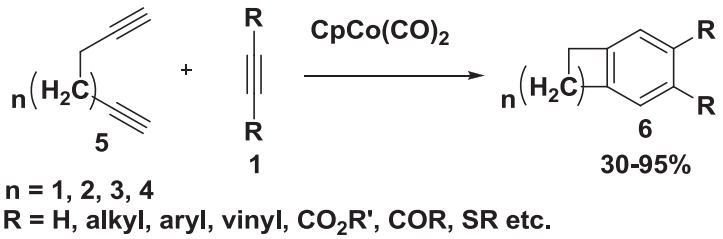
Benzannulation reaction involves the construction of a new benzene ring on another molecule; often on another ring. Consequent to the prominent place occupied by benzene derivatives and benzenoid aromatics in organic chemistry, a plethora of benzannulation protocols[3] have been developed during the last century. *Inter alia*, these include Diels-Alder reaction, Reppe-Vollhardt cyclotrimerization of alkynes,[4] Bergman cyclization,[5] ring closing metathesis,[6] Dötz reaction,[7] Danheiser annulations,[8] benzyne mediated reactions,[9] and assorted transformations.[10]

A useful synthetic approach which provides polysubstituted aromatic compounds much efficiently would involve the cyclization of unsaturated acyclic compounds. Bertholet *et al*. in 1866 reported that benzene was formed as a minor product by the thermal cyclotrimerization of acetylene.[11] The first efficient example for the above mentioned strategy was reported in 1948 by Reppe *et al.*[12] which involves nickel complex catalyzed cyclotrimerization of alkynes **1**. The reaction involves a metallacyclopentadiene intermediate **3** which undergoes alkyne insertion, followed by reductive elimination of the metal to afford the cyclized product **2** (Scheme 4a.1). Poor regiocontrol was the mojor problem associated with this annulation.



Scheme 4a.1

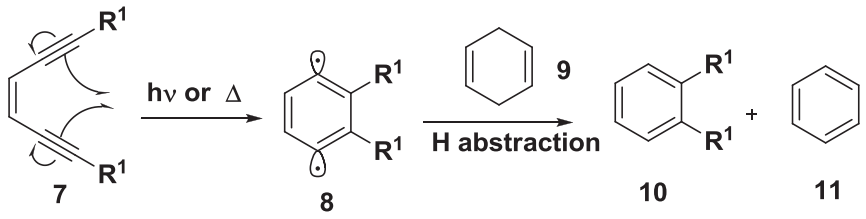
Vollhardt successfully synthesized benzenoid systems using γ^5-cyclopentadienyldicarbonyl cobalt [$CpCo(CO)_2$] ($Cp=C_5H_5$) by the cyclotrimerization of α,ω-diynes **5** (Scheme 4a.2).[4]



Scheme 4a.2

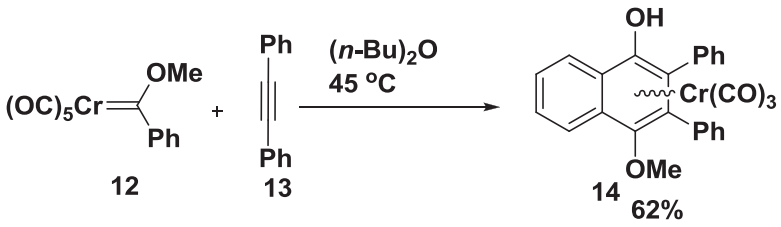
Among all the available catalysts, [$CpCo(CO)_2$] has proved to be the most popular and versatile reagent for the [2+2+2] cyclotrimerization of alkynes. Vollhardt's group has reported numerous applications of cobalt-catalyzed reactions including total syntheses of different natural products and compounds of theoretical interest.

Bergman cyclotrimerization is another strategy which involves the formation of aromatic compounds from (*Z*)-enediynes *via* a 1,4-biradical intermediate **8**. Although this reaction can be traced back to 1940–1950s,[13] it is Bergman who first proposed and proved the existence of the 1,4-aryldiradical intermediate in the gas phase for the thermal rearrangement of substituted 3-hexene-1,5-diynes in 1972 (Scheme 4a.3).[5] The most potent antibiotic antitumor agents such as calicheamicin, esperamicin, dynemicin and kedarcidin contain enediyne moiety. Their reactivity is believed to be due to the action of enediyne moiety, which undergoes a Bergman cyclization to generate a reactive diradical that can abstract hydrogen atoms from the backbone of DNA, thus cleaving the DNA.[14]



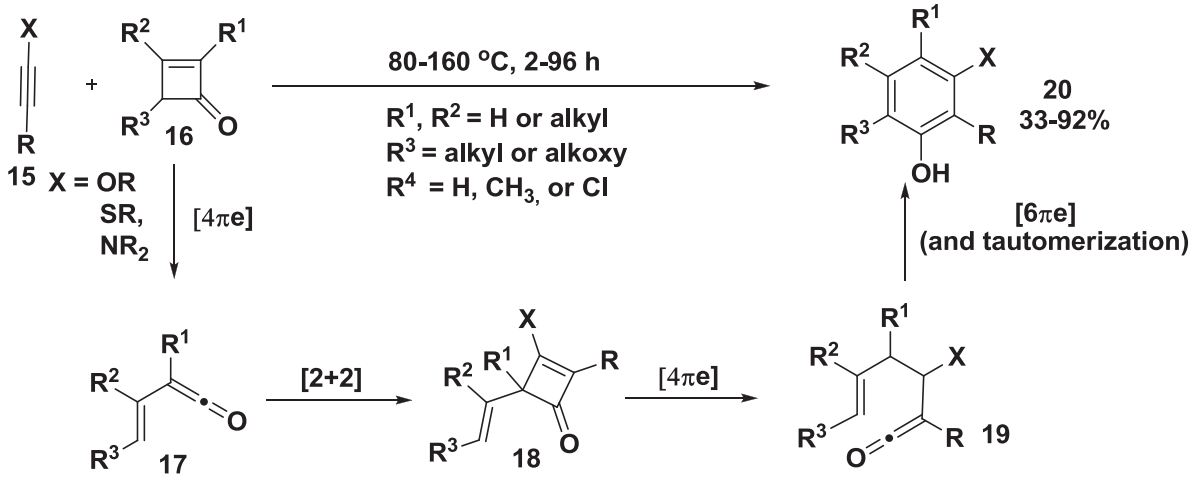
Scheme 4a.3

Another protocol employing a Fischer carbene complex was invented in 1975 by Dötz and it is named Dötz benzannulation reaction. It is the thermal [3+2+1] reaction of an aromatic or vinylic alkoxy pentacarbonyl chromium carbene complex **12** with an alkyne and carbon monoxide to give a $Cr(CO)_3$-coordinated substituted phenol **14** (Scheme 4a.4)[7].



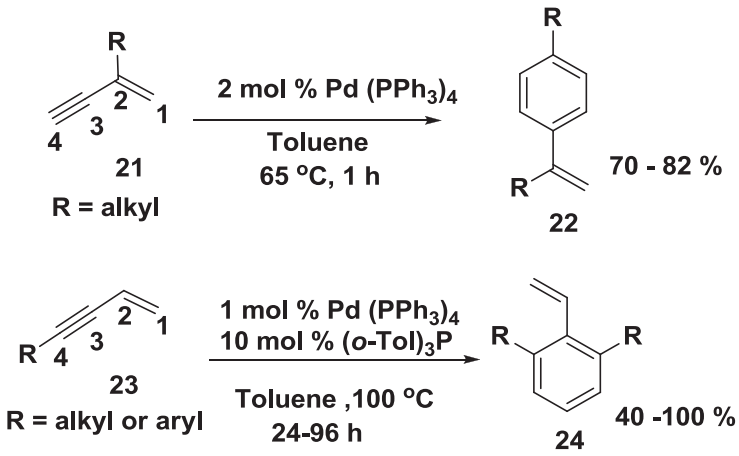
Scheme 4a.4

In 1984, Danheiser *et al.* reported the synthesis of polysubstituted phenol **20** with high regioselectivity. This annulation proceeds *via* a cascade of four pericyclic reactions. The regioselectivity of this reaction is due to the regiospecific [2+2] cycloaddition between a ketene **17**, generated upon heating the cyclobutenone, and the acetylene derivative (Scheme 4a.5).[8]



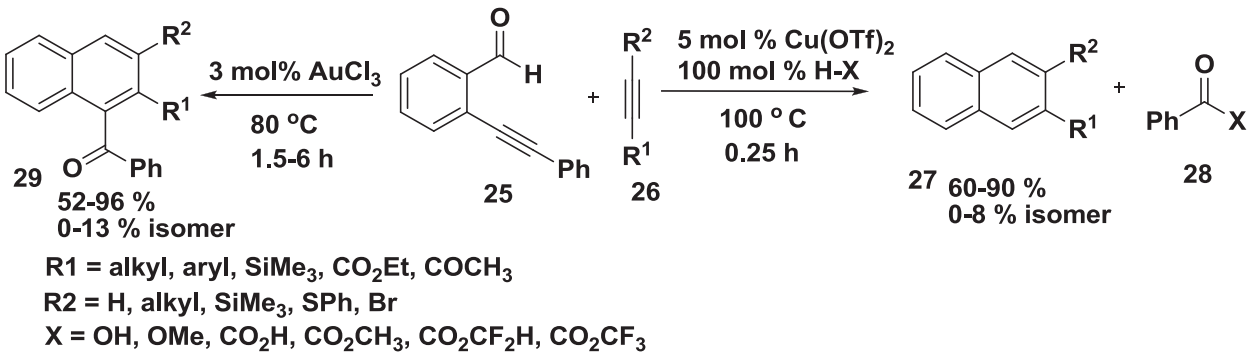
Scheme 4a.5

Yamamoto *et al.* first demonstrated the formation of aromatic compounds by dimerization of enynes (Scheme 4a.6).[15] In the presence of Pd (0) catalyst, the 2-substituted enyne **21** and the 4-substituted enyne **23** dimerize to give the corresponding benzene derivatives **22** and **24** with complete regioselectivity.



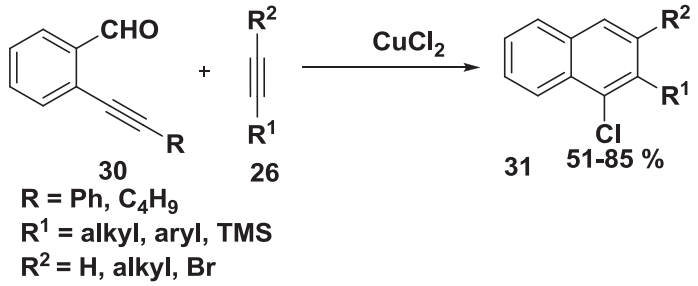
Scheme 4a.6

The same group developed another type of [4+2] benzannulation, utilizing an ortho alkynyl aromatic aldehyde as the 4-carbon component. In the presence of a catalytic amount of $AuCl_3$, the naphthyl ketone derivatives **29** were obtained with high regioselectivity starting from the aldehyde **25** and the alkyne **26**. When $Cu(OTf)_2$ is used as a catalyst in the presence of a stoichiometric amount of a Brønsted acid H-X, debenzoylated naphthalene **27** was obtained with high regioselectivity (Scheme 4a.7).[16]



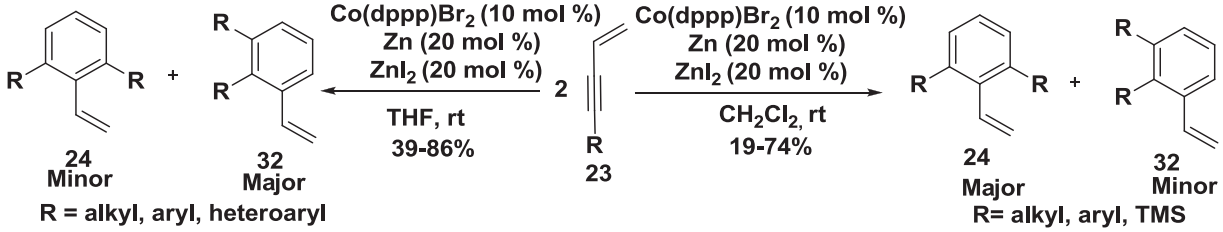
Scheme 4a.7

In 2009, Isogai *et al*. reported a $CuCl_2$ mediated [4+2] benzannulation of *ortho*-a lkynylbenzaldehydes with alkynes for the regioselective construction of haloaromatic compounds **31** (Scheme 4a.8).[17] Binaphthyl skeletons are also readily prepared by the reaction of *ortho*-alkynylbenzaldehydes and diynes.



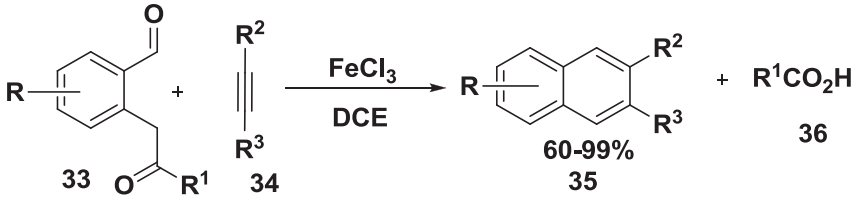
Scheme 4a.8

A cobalt catalysed regioselective solvent-dependent benzannulation of conjugated enynes was reported in 2012 from the group of Hilt. The transformation of enynes under cobalt-catalysis yielded symmetrical benzannulation products **24** in dichloromethane. In tetrahydrofuran the cobalt-catalyzed reactions afforded the unsymmetrical benzannulation products **32** in moderate to good yields and good regioselectivities. (Scheme 4a.9).[18]



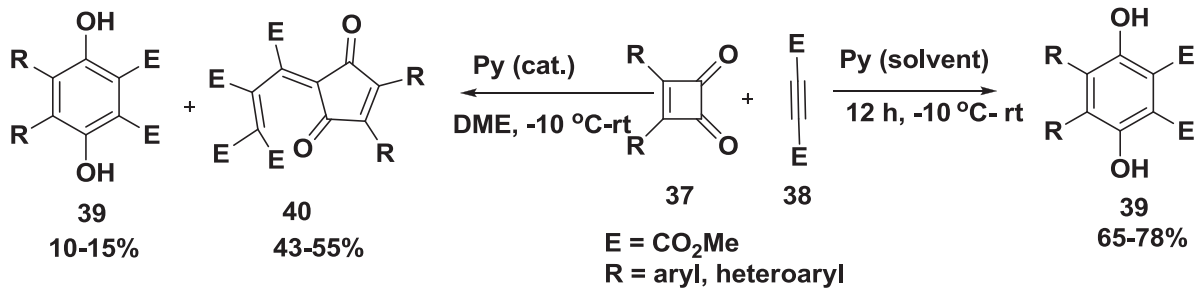
Scheme 4a.9

Recently, an iron-catalyzed benzannulation reaction of 2-alkylbenzaldehydes and alkynes was reported by Zhu *et al*. The reaction led to the synthesis of naphthalene derivatives **35** (Scheme 4a.10).[19]



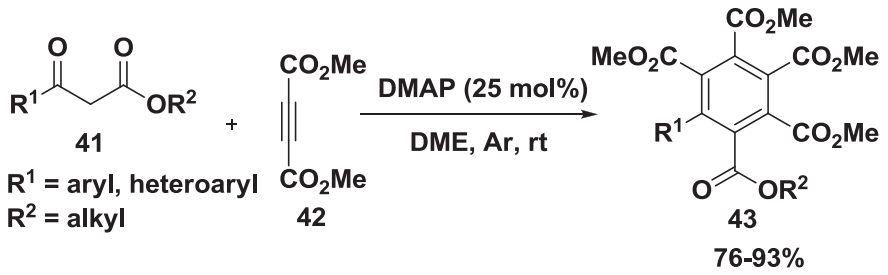
Scheme 4a.10

A pyridine-mediated reaction of dimethyl acetylenedicarboxylate and cyclobutene-1,2-diones to afford either hexasubstituted benzene derivatives **39** or cyclopentenedione derivatives **40** was reported from our group in 2005 (Scheme 4a.11).[20]



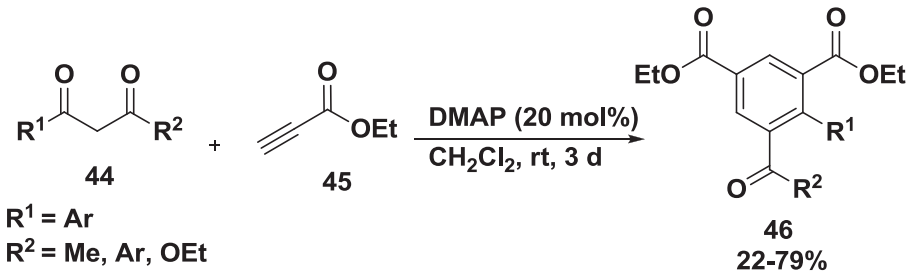
Scheme 4a.11

In 2006, our group reported another benzannulation reaction involving β-keto esters and dimethyl acetylenedicarboxylate, catalyzed by DMAP to yield polysubstituted benzenes and biaryls (Scheme 4a.12).[21]



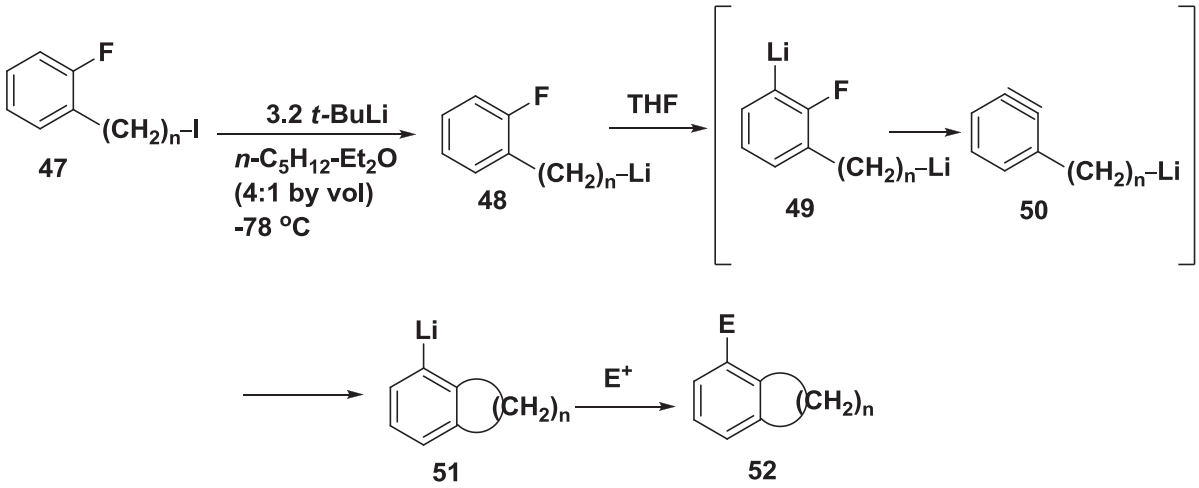
Scheme 4a.12

Soon after, a DMAP catalyzed reaction of ethyl propiolate with 1,3-dicarbonyl compounds was reported by Zhou *et al*. The reaction afforded substituted benzene derivatives in good yields. (Scheme 4a.13).[22]



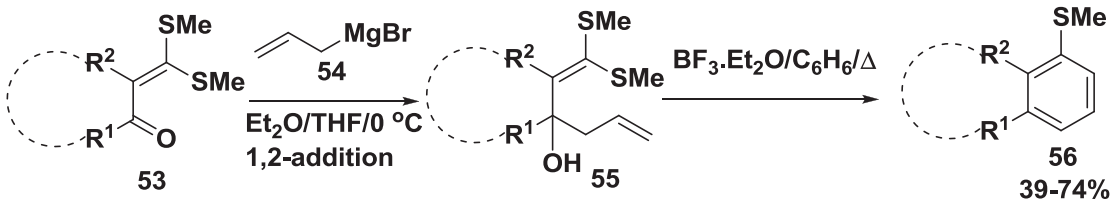
Scheme 4a.13

Baily *et al*. reported a five-step, one-pot preparation of isomerically pure 4-substituted indanes by the *5-exo* cyclization of benzyne-tethered propyl lithium generated from 2-fluoro-1-(3-iodopropyl)benzene.[23] Later this strategy was extended to synthesize 3-substituted benzocyclobutenes and 5-substituted tetralins from the appropriate 2-fluoro-1-(3-iodoalkyl)benzene, involving generation and subsequent *4-* or *6-exo* cyclization of a benzyne-tethered alkyl lithium (Scheme 4a.14).[24]



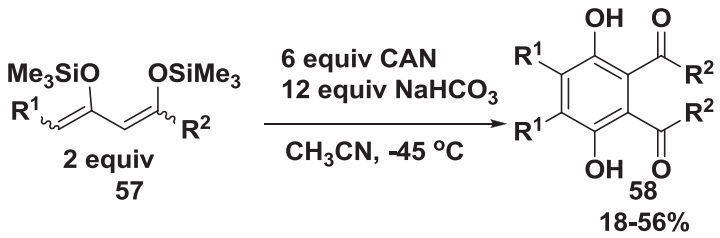
Scheme 4a.14

In 1984, Ila and Junjappa have shown that α-oxoketendithioacetals can be used as intermediates for benzannulation of α-methylene ketones by reaction with allylmagnesium bromide followed by cationic cyclization of the resulting carbinolacetals (Scheme 4a.15).[25]



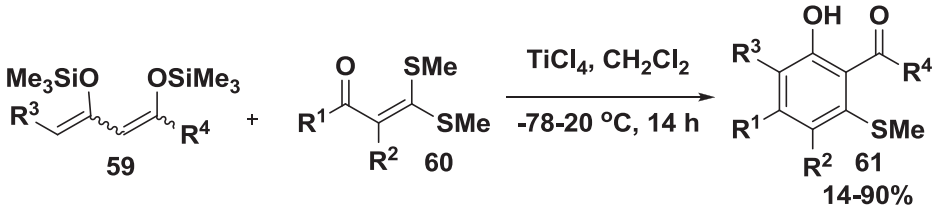
Scheme 4a.15

The first oxidative cyclization of 1,3-bis(trimethylsilyloxy)-buta-1,3-dienes, electroneutral 1,3-dicarbonyl dianion synthons, was developed by Langer and co-workers in the year 2000. The reaction resulted in the regioselective formation of functionalized 1,4-dihydroquinones (Scheme 4a.16).[26]



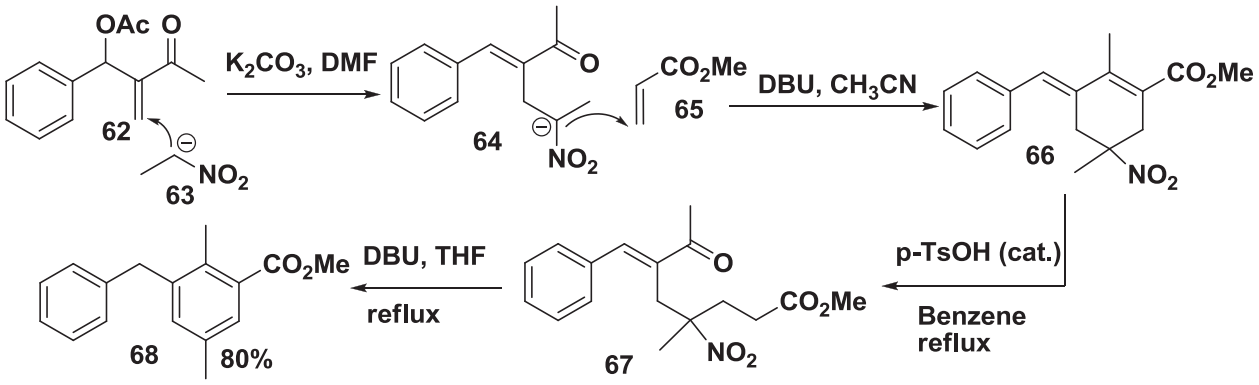
Scheme 4a.16

Very recently, a regioselective synthesis of 3-(methylthio)phenols was reported by the formal [3+3] cyclocondensations of 3-oxo-bis(methylthio)ketenacetals with 1,3-bis(trimethylsilyloxy)-1,3-butadienes and 1,3-dicarbonyl dianions (Scheme 4a.17).[27]



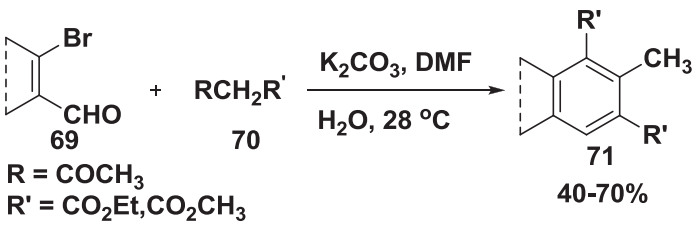
Scheme 4a.17

An efficient synthesis of polysubstituted benzene derivatives starting from Baylis–Hillman adducts *via* a regioselective [4+2] benzannulation protocol was developed by Lee and co-workers. In this reaction the nitroalkane derivative **64**, which was prepared from Baylis–Hillman adduct **62**, served as the four carbon unit and a Michael acceptor **65** as a two-carbon unit (Scheme 4a.18).[28]



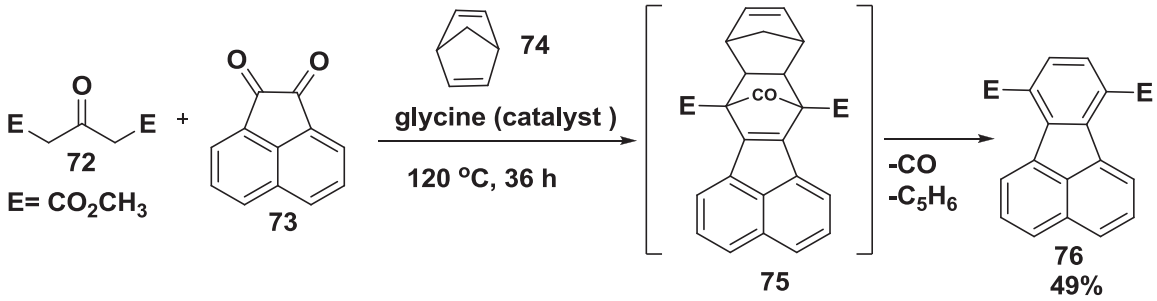
Scheme 4a.18

Ray *et al.* reported a simple and efficient one-pot protocol for the synthesis of cycloalkylfused benzene derivatives *via* a base catalysed water mediated condensation and aromatization of various β-bromoaldehydes with active methylene compounds (Scheme 4a.19).[29] Employing this methodology they have synthesized various fluoranthene derivatives and benzo-fused cycloalkane derivatives in good yields.



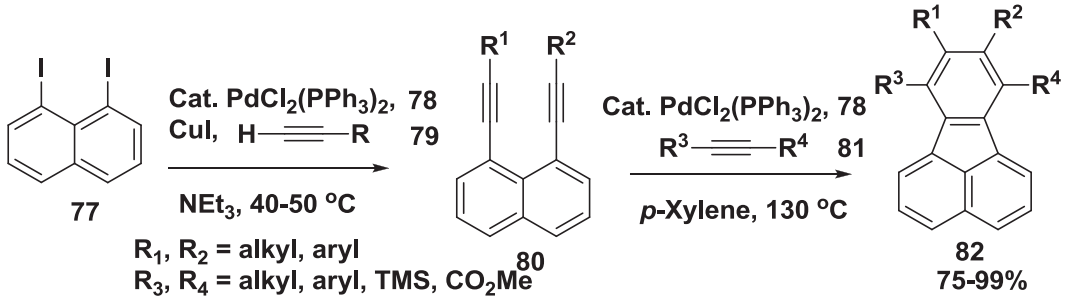
Scheme 4a.19

Meyer *et al.* designed a one pot synthesis of fluoranthene derivative by a double Knoevenagel condensation of acenaphthene quinone and a substituted acetone to form a cyclopentadienone, followed by an inverse electron demand Diels-Alder cycloaddition of norbornadiene with this cyclopentadienone to form a heptacyclic intermediate. The unstable heptacyclic intermediate **75** then loses carbon monoxide and cyclopentadiene to yield a fluoranthene ring system in 49% overall yield (Scheme 4a.20).[30]



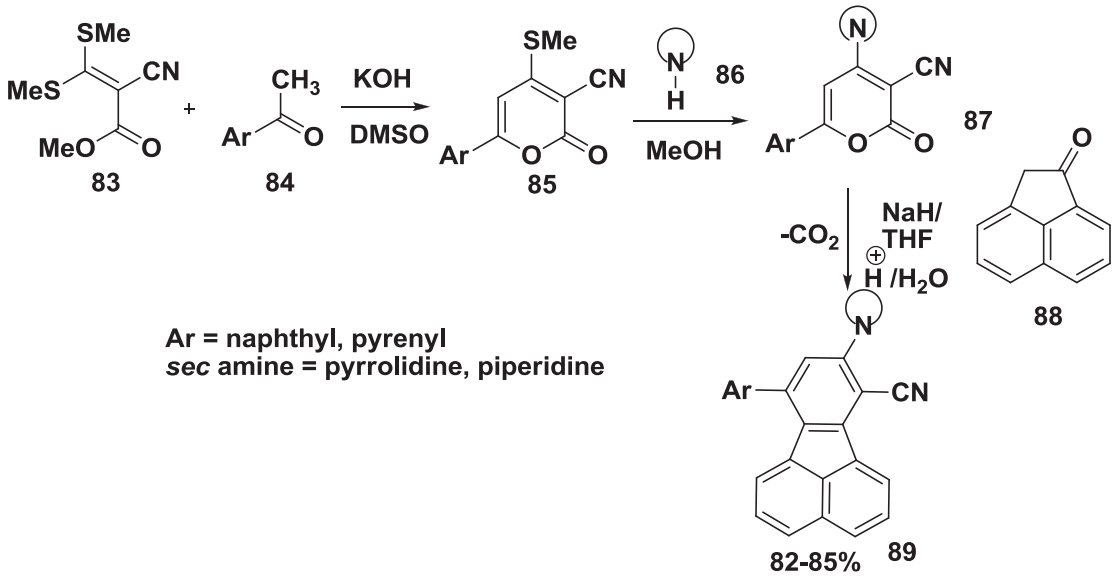
Scheme 4a.20

Fluoranthenes are easily accessible in good to excellent yields from the formal [(2+2)+2] cycloaddition reaction of peridiynes and alkynes in the presence of Wilkinson's catalyst (Scheme 4a.21).[31]



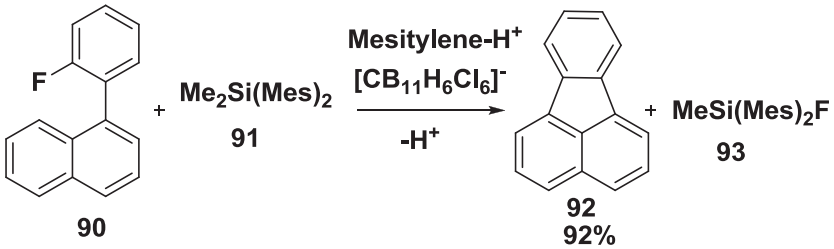
Scheme 4a.21

Novel synthesis of thermally stable yellow light emitting fluoranthenes substituted with an amine donor and a nitrile acceptor was reported by Goel *et al*. in 2010.[32] The methodology involves the Diels- Alder reaction of 2*H*-acenaphthylen-1-one **88** and 2*H*-pyran-2-ones **87** prepared from a ketene-*S*,*S*-acetal under mild conditions without using an organometal catalyst. They have successfully fabricated highly efficient nondoped fluoranthene-based yellow OLEDs, which exhibited bright yellow fluorescence, high quantum efficiency, and good thermal stability (Scheme 4a.22).



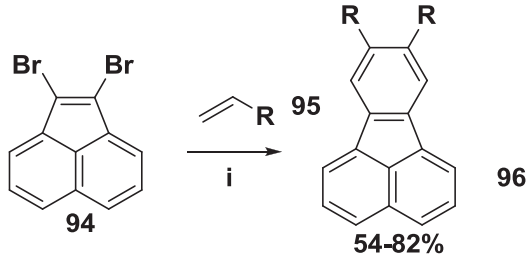
Scheme 4a.22

In 2011, Siegel and co-workers reported the Friedel-Crafts coupling of fluoroarenes for the synthesis of polyaromatic hydrocarbons. The phenyl cation equivalents, generated from aryl fluorides, allow intramolecular aryl coupling. The enabling feature of this reaction is the exchange of carbon-fluorine for silicon-fluorine bond enthalpies (Scheme 4a.23).[33]



Scheme 4a.23

Langer and co-workers reported the synthesis of fluoranthenes by domino two-fold Heck/electrocyclization/dehydrogenation reactions of 1,2-dibromoacenaphthylene (Scheme 4a.24).[34]

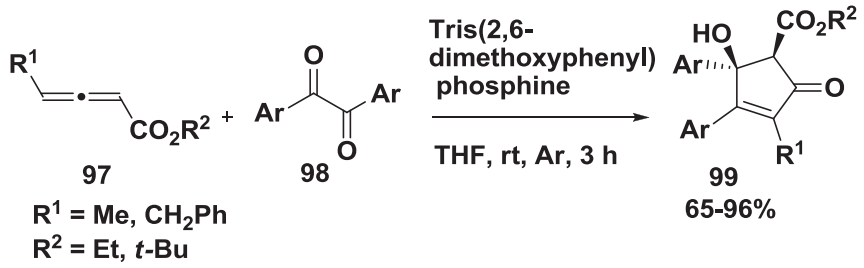


(i) $Pd(OAc)_2$ (5 mol%), X-Phos (10 mol%), NEt_3, DMF, 90 or 110 °C, 12 h

Scheme 4a.24

4a.3 Present Work

It may be recalled that the previous chapter described the reaction of phosphine-allenoate zwitterion with acyclic 1,2-diones to afford polysubstituted cyclopentenones (Scheme 4a.25).[35]

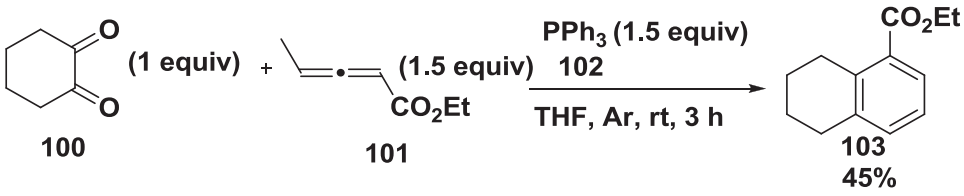


Scheme 4a.25

Against this background, it was of interest to explore the reactivity of allenoate-phosphine zwitterions towards cyclic 1,2-diones. When cyclohexane-1,2-dione was exposed to ethyl 3-methyl allenoate and triphenylphosphine, a completely different reaction manifested and the resulting product was characterized as ethyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate. We have investigated this reaction in detail using various cyclic 1,2-diones and the results constitute the subject matter of this chapter.

4a.4 Results and Discussion

In our prototype experiment, cyclohexane-1,2-dione **100** (1 equiv) and alleneoate **101** (1.5 equiv) were taken in an R.B flask with dry THF as solvent under argon atmosphere. To this mixture triphenylphosphine (1.5 equiv) was added and stirred for 3 h. The crude reaction mixture after removal of solvent and purification by column chromatography afforded the product ethyl 5,6,7,8-tetrahydronaphthalene-1-carboxylate **103** as a colourless oil in 45% yield (Scheme 4a.26).



Scheme 4a.26

The compound was characterized using conventional spectroscopic methods. The IR spectrum of **103** showed the characteristic ester carbonyl absorption at 1718 cm^{-1}. In the ^{1}H NMR spectrum (Figure 4a.1), signals due to the aromatic protons were resonated as doublets at δ 7.62 and δ 7.18 ppm and triplet at δ 7.10 ppm. The compound displayed a quartet resonance signal at δ 4.32 ppm due to methylene protons of ester group; the methyl protons of ester group were discernible as triplet at δ 1.38 ppm. In ^{13}C NMR spectrum (Figure 4a.2), the ester carbonyl group displayed resonance signal at δ 167.9 ppm. Further corroboration of the structure was obtained using high resolution mass spectroscopy.

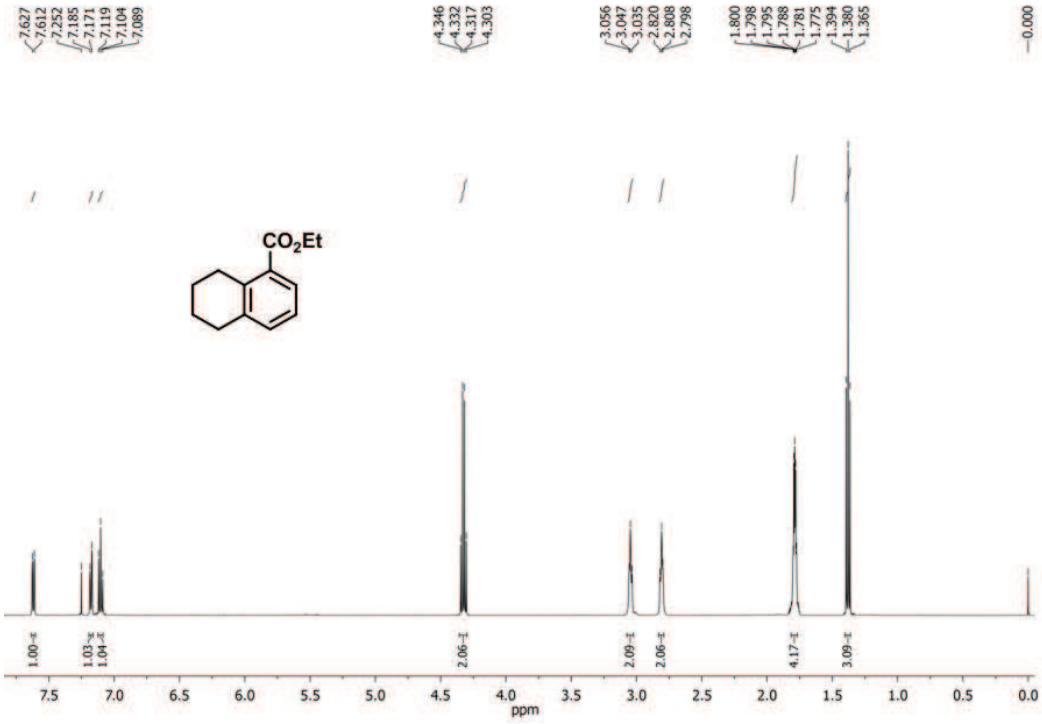


Figure 4a.1 ^{1}H NMR spectrum of compound **103**

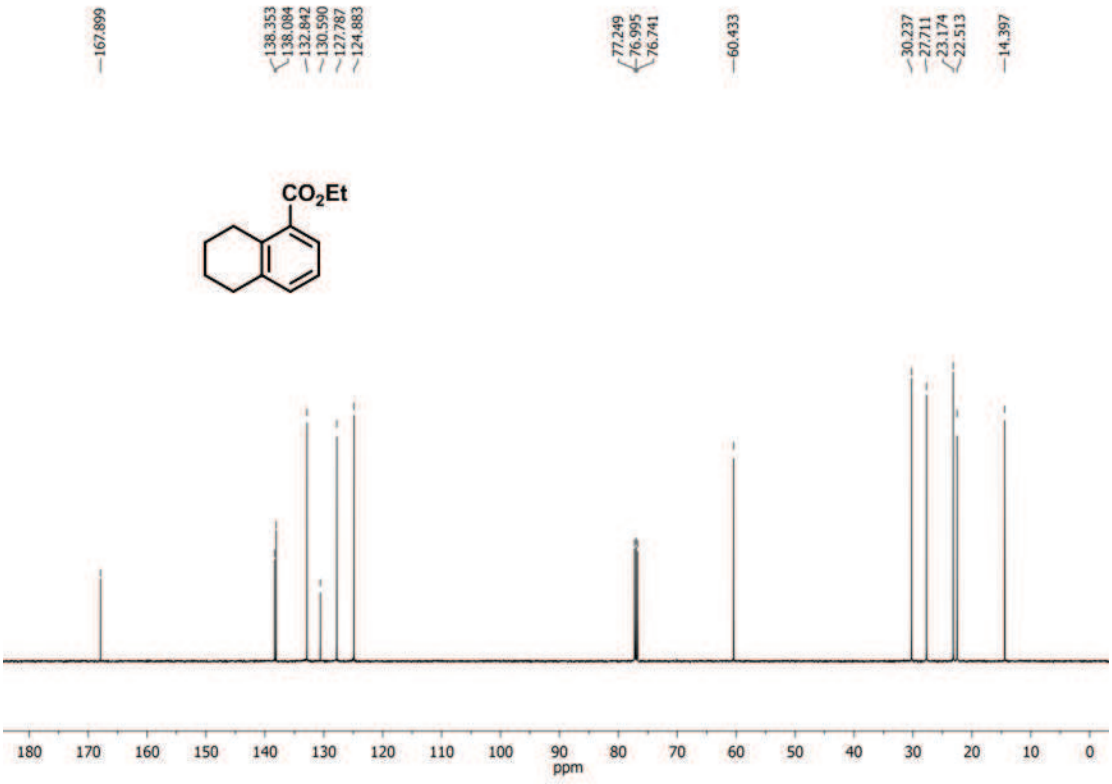


Figure 4a.2 ^{13}C NMR spectrum of compound **103**

Since the product **103** was formed in relatively low yield in our preliminary experiment (Scheme 4a.26), a detailed investigation on the optimization of reaction conditions was carried out. The results obtained by varying solvent, catalyst, temperature and stoichiometry of the reagents are summarized in Table 4a.1.

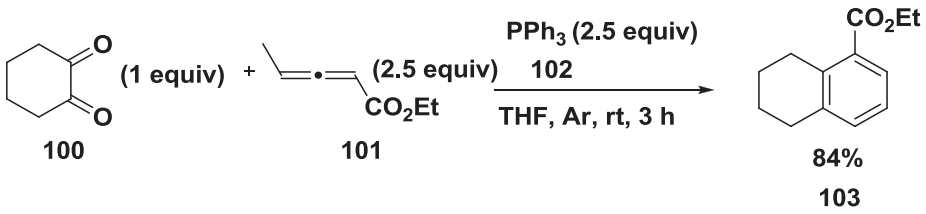
Table 4a.1 Condition optimization for the benzannulation of cycloalkane1,2-dione

Entry	Phosphine	Allenoate (equiv)	Solvent	Temp (^{o}C)	Time (h)	Yield (%)
1	PPh_3(1.5 equiv)	1.5	THF	rt	3	41
2	PPh_3 (0.5 equiv)	1.5	THF	rt	12	12
3	PPh_3 (1.5 equiv)	1.5	THF	65	2	18
4	PPh_3 (1.5 equiv)	1.5	DCM	rt	3	31
5	PPh_3 (1.5 equiv)	1.5	Toluene	rt	3	33
6	PPh_3 (1.5 equiv)	1.5	CH_3CN	rt	5	14

7	PPh_3(1.5 equiv)	1.5	THF	rt	3	76[a]
8	PPh_3 (2.5 equiv)	2.5	THF	rt	3	84
9	PBu_3 (2.5 equiv)	2.5	THF	rt	24	trace
10	$P(2\text{-}CH_3C_6H_4)_3$ (2.5 equiv)	2.5	THF	rt	24	-
11	TDMPP[b] (2.5 equiv)	2.5	THF	rt	24	-
12	$P(C_6F_5)_3$ (2.5 equiv)	2.5	THF	rt	24	-
13	$P(Cy)_3$ (2.5 equiv)	2.5	THF	rt	24	<5

[a]Isolated yield of **103** when both reagents were simultaneously added dropwise. [b]TDMPP = tris(2,6-dimethoxyphenyl)phosphine.

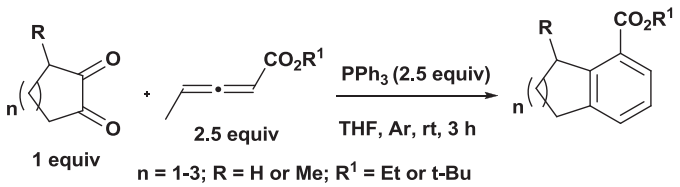
It was evident from our studies that the best results were obtained when 2.5 equivalents of allenoate-phosphine zwitterion was employed. In a typical experiment, triphenylphosphine (2.5 equiv) was added to a solution of dione (1 equiv) and the allenoate (2.5 equiv) in dry THF under argon atmosphere, and the mixture was stirred at room temperature. The reaction was completed in 3 h, and the crude product was purified by column chromatography on silica gel. The pure product was obtained in 84% yield (Scheme 4a.27). The use of catalytic amount of phosphine in the reaction yielded only small amount of the desired product along with unidentified impurities. It is noteworthy that the simultaneous dropwise addition of 1.5 equivalents of both the allenoate and phosphine over a period of 15 minutes followed by 3 h stirring furnished the product in 78% yield. Conceivably, this may be the ideal protocol in large scale experiments.

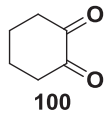
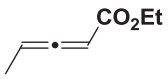
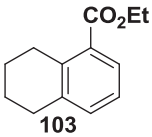
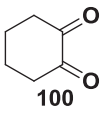
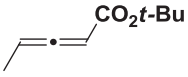
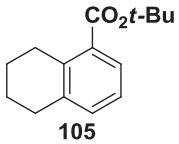
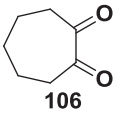
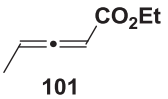
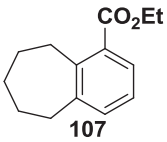
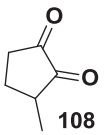
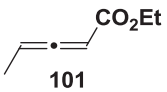
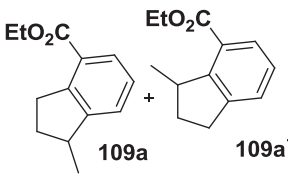


Scheme 4a.27

Encouraged by the experimental results, we probed the scope of the annulation with different 1,2-diones. Cycloheptane-1,2-dione and 3-methyl cyclopentane dione also afforded the benzannulated products *albeit* in low yields (Table 4a.2).

Table 4a.2. Scope of the reaction

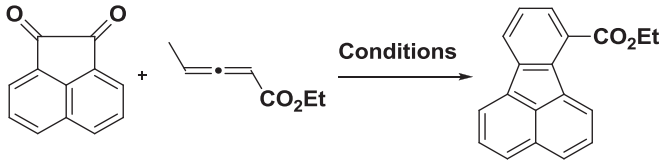


Entry	Dione	Allenoate	Product	Yield (%)
1	 100	 101	 103	84
2	 100	 104	 105	82
3	 106	 101	 107	38
4	 108	 101	 109a 109a[1]	30†

†overall yield of the inseparable regioisomers

With a view to probe the effectiveness of the reaction towards the synthesis of polyaromatic systems of practical value, we investigated the reactivity of the same zwitterion with *o*-quinones. For simple *o*-quinones the reaction yielded only trace amount of the benzannulated product mixed with impurities. But with acenaphthene quinone, the reaction proceeded well to afford the corresponding benzannulated product in good yields. Acenaphthenequinone reacted faster than cyclohexane-1,2-dione and the preferred solvent was dry dichloromethane. The optimization studies are presented in Table 4a.3.

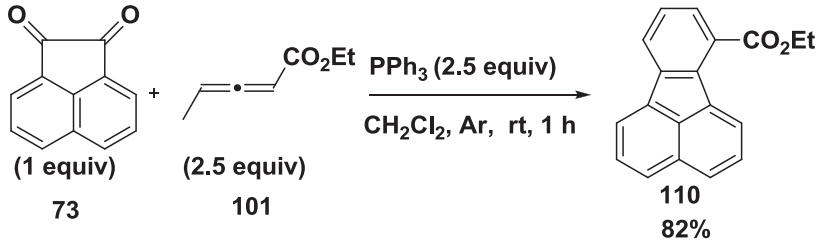
Table 4a.3 Condition optimization for the benzannulation of quinones



Entry	Phosphine	Allenoate (equiv)	Solvent	Time (h)	Temp	Yield (%)
1	PPh_3 (1.5 equiv)	1.5	THF	3	rt	29
2	PPh_3 (1.5 equiv)	1.5	Toluene	5	rt	34
3	PPh_3 (1.5 equiv)	1.5	DCM	3	rt	41
4	PPh_3 (2.5 equiv)	2.5	DCM	1	rt	82
5	TDMPP (2.5 equiv)	2.5	DCM	24	rt	-
6	$P(Cy)_3$ (2.5 equiv)	2.5	DCM	24	rt	<5

DMPP = tris(2,6-dimethoxyphenyl)phosphine

In a standard experiment, acenaphthene quinone **73** was treated with ethyl 2,3-pentadienoate **101** and triphenylphosphine in dry dichloromethane at room temperature under argon atmosphere for 1 h to yield ethyl fluoranthene-7-carboxylate **110** as a pale yellow solid in 82% yield (Scheme 4a.28).



Scheme 4a.28

The product was characterized by conventional spectroscopic analysis. In the IR spectrum the ester carbonyl absorption was observed at 1721 cm^{-1}. In ^1H NMR (Figure 4a.3) ester methylene groups displayed resonance signal at δ 4.52 ppm as quartet and methyl protons were discernible as triplet signals at δ 1.50 ppm. In ^{13}C NMR (Figure 4a.4) the characteristic ester carbonyl group resonated at δ 167.3 ppm. Mass spectrum was also in good agreement with the proposed structure. The final confirmation of the structure was ascertained by single crystal X-ray analysis of the analogous compound, ethyl 10-phenylfluoranthene-7-carboxylate **113** (vide infra) (Figure 4a.5).

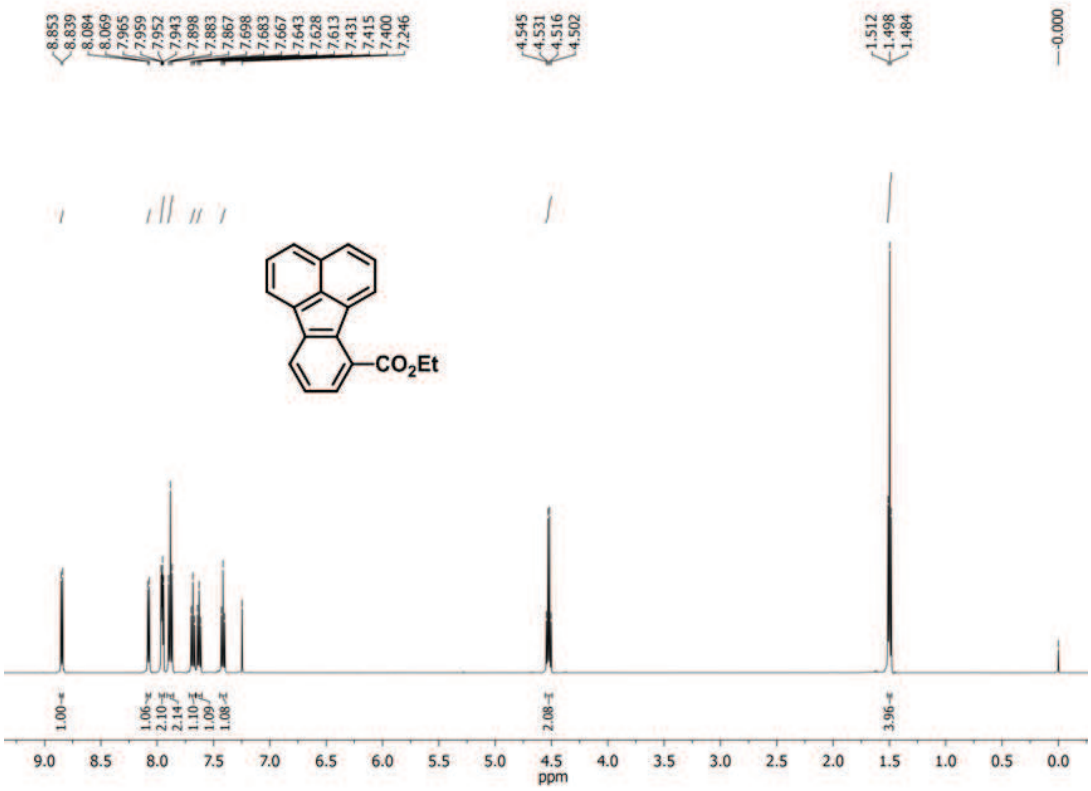


Figure 4a.3 ^{1}H NMR spectrum of compound **110**

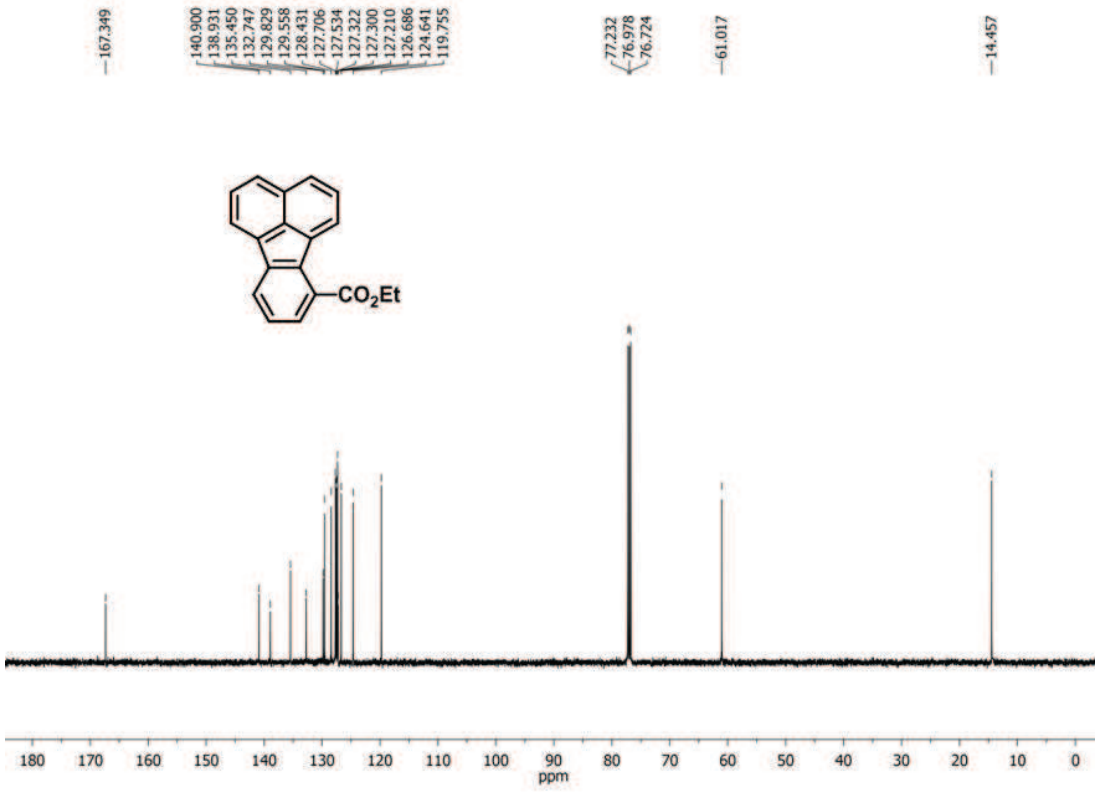
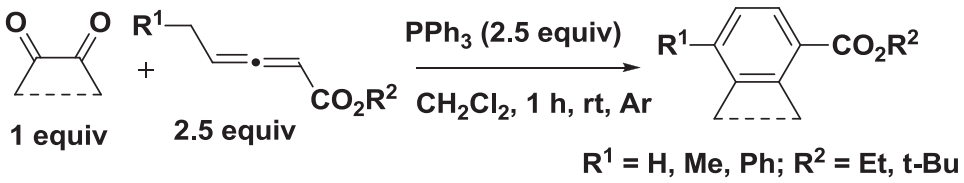
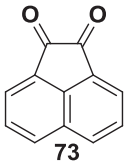
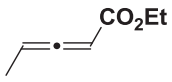
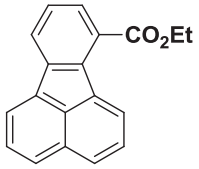
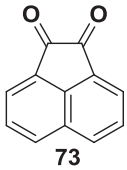
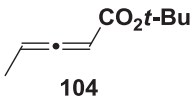
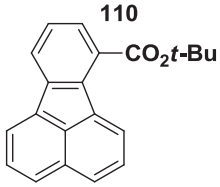
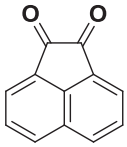
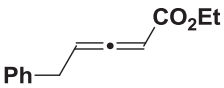
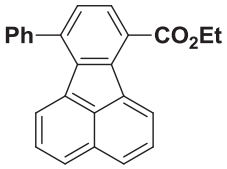
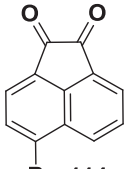
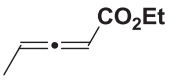
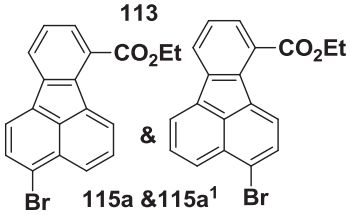
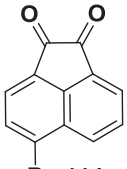
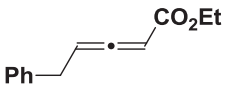
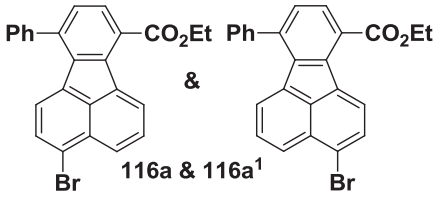
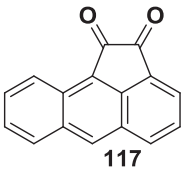
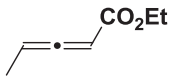
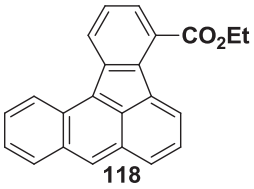
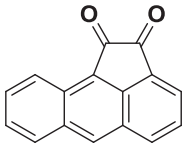
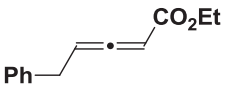
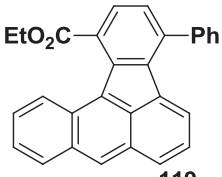
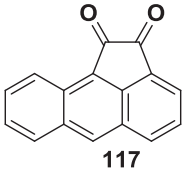
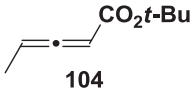
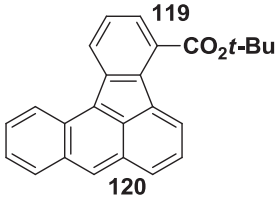


Figure 4a.4 ^{13}C NMR spectrum of compound **110**

The scope of the annulation was further explored with different acenaphthene quinones and allenoates. In all cases the reaction afforded the corresponding fluoranthene derivatives in acceptable yields (Table 4a.4). For the products of aceanthrene quinone, the regiochemistry was confirmed by single crystal X-ray analysis of ethyl 4-phenylbenzo[a]aceanthrylene-1-carboxylate **119** and *tert*-butyl benzo[a]aceanthrylene-4-carboxylate **120** (Figure 4a.5).

Table 4a.4 Scope of the reaction



Entry	Dione	Allenoate	Product	Yield (%)
1	 73	 101	 110	82
2	 73	 104	 111	65
3	 73	 112	 113	98
4	 Br 114	 101	 Br 115a &115a[1] Br	70†
5	 Br 114	 112	 Br 116a & 116a[1] Br	71†
6	 117	 101	 118	51
7	 117	 112	 119	38
8	 117	 104	 120	46

†overall yield of the inseparable regioisomers

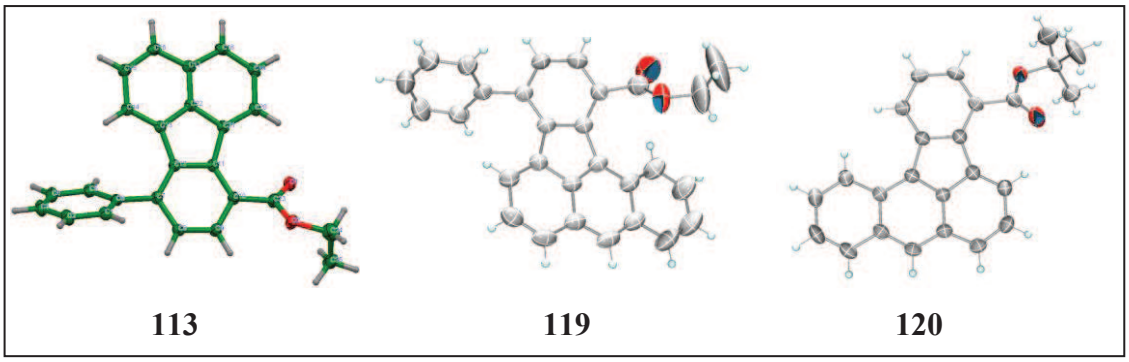
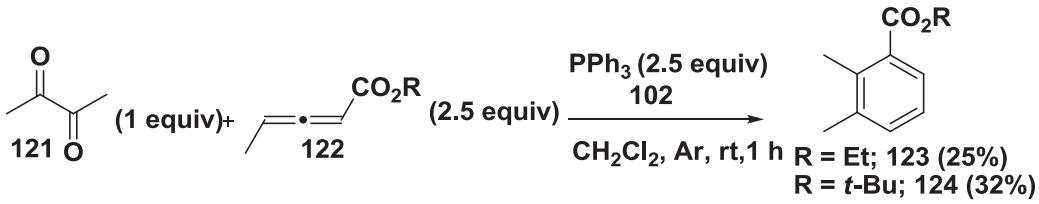


Figure 4a.5 ORTEP of (a) **113**; (b) **119** and (c) **120** (50% probability for the thermal ellipsoid)

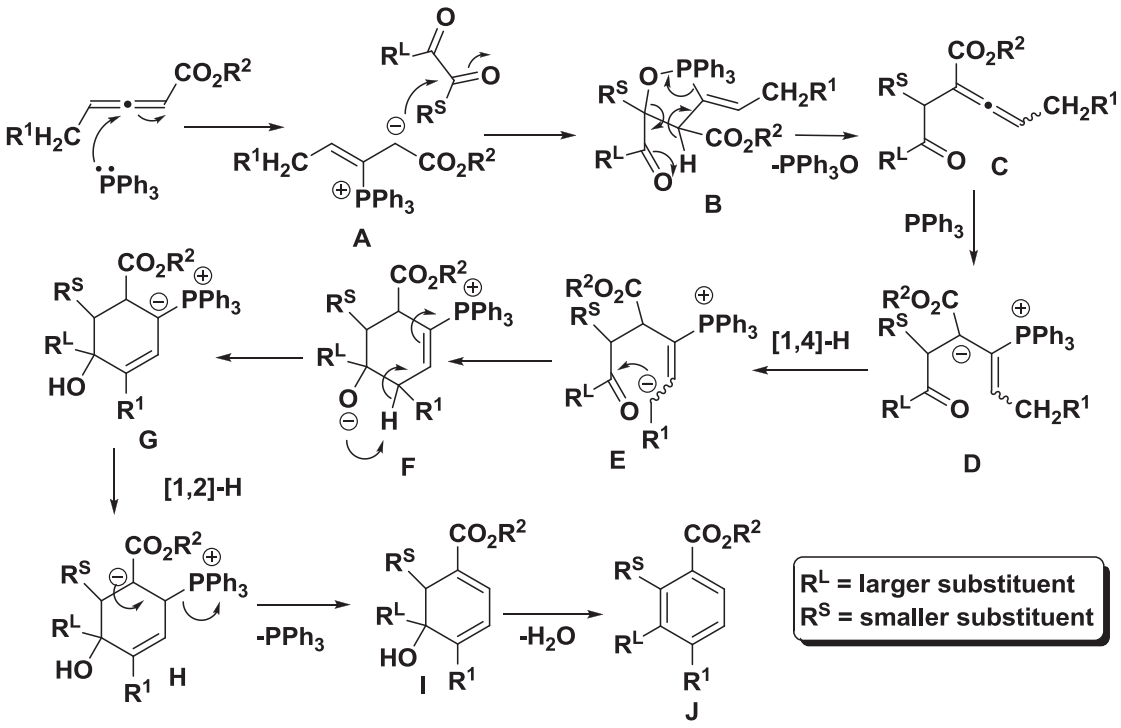
It is interesting to note that aliphatic 1,2-dione biacetyl yielded the benzannulated product under the standard conditions *albeit* in low yield (Scheme 4a.29).



Scheme 4a.29

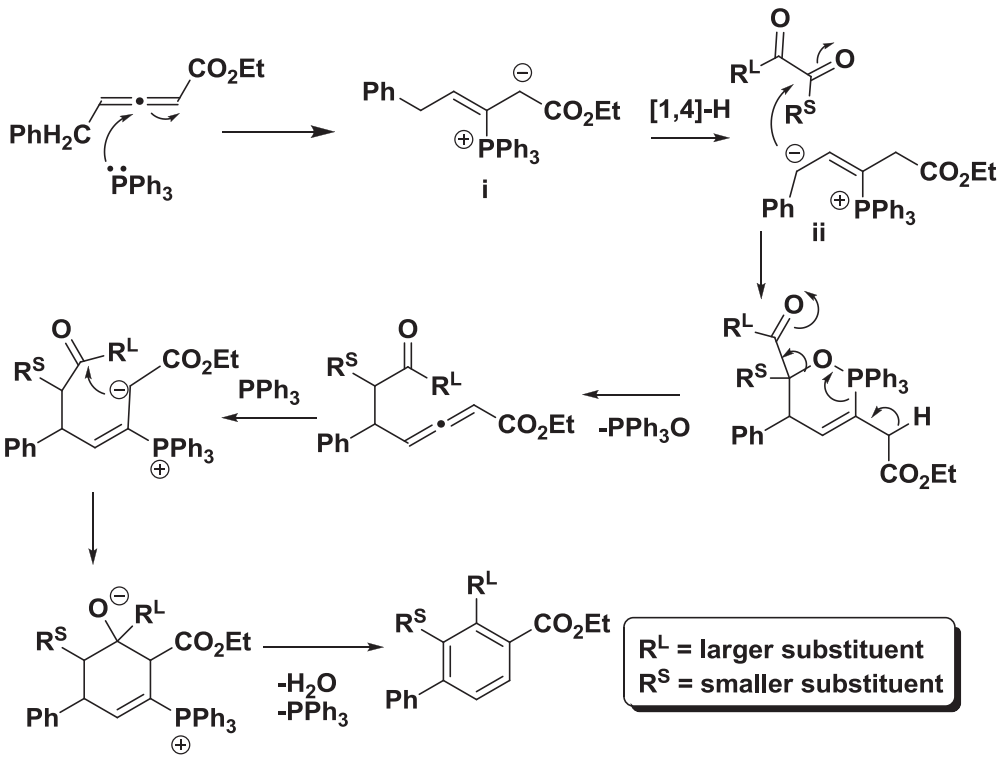
4a.5 Mechanism

A mechanistic postulate for the benzannulation may be advanced as follows (Scheme 4a.30). Presumably, the initial event is the generation of zwitterion by the nucleophilic addition of triphenylphosphine to allenoate. The zwitterion **A** can easily add to the dione to form the intermediate oxaphospholane **B**, which on triphenylphosphine oxide elimination will generate an allenoate **C**. Conceivably, the latter undergoes triphenylphosphine catalyzed cyclization followed by dehydration to afford the benzannulated product **J** *via* intermediates **D-I**.



Scheme 4a.30

The regiochemical preference exhibited by unsymmetrical dione **117** (entries 6 and 8, Table 4a.4) is presumably a result of addition of the zwitterion **i** to the less hindered carbonyl of dione **117** (*cf.* formation of **B** in Scheme 4a.30). Interestingly, the reaction of dione **117** with benzyl bearing allenoate (entry 7, Table 4a.4) selectively affords the other regioisomer **119**. This switch of regiochemical outcome may be attributed to the initial conversion of zwitterion **i** *via* a 1,4-H shift (analogous to the **D**-**E** conversion in Scheme 4a.30) to an isomeric zwitterion **ii** in which the benzylic position bears a negative charge. This isomeric zwitterion engages in a similar sequence of events as depicted in Scheme 4a.30 to afford the product **119** (Scheme 4a.31).



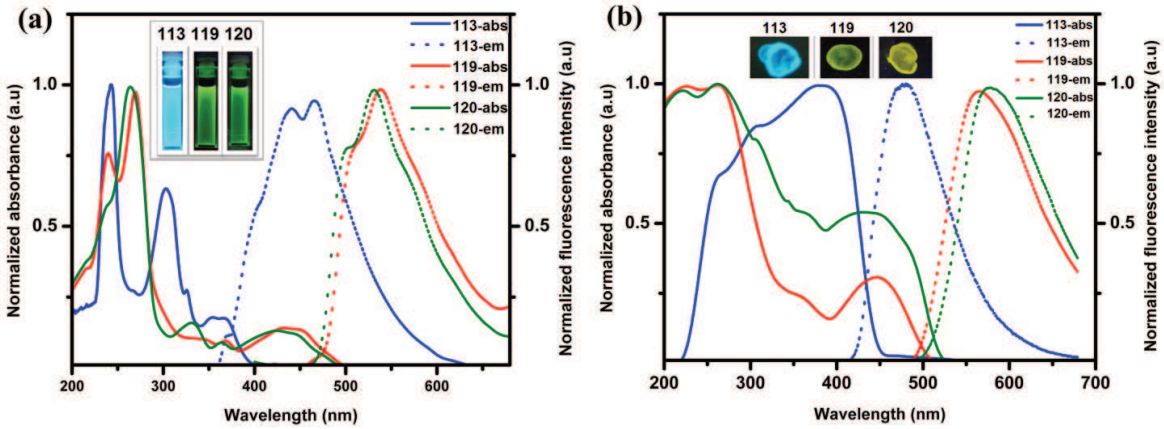
Scheme 4a.31

In addition to its intriguing mechanistic features, to the best of our knowledge, the present reaction constitutes the first example of the phosphine-3-alkyl allenoate zwitterion playing the role of four carbon synthon in benzannulation. In this context it may be recalled that there are two recent examples in which the zwitterion displays such reactivity in spiroannulation to afford six membered carbocycles.[36]

It is worthy of note that fluoranthene and related polycyclic aromatic hydrocarbons (PAHs) are important compounds since they can provide the framework for the preparation of organic light emitting diodes (OLEDs), field effect transistors, solar cells and chemosensors.[32, 37-40]

4a.6 Photophysical Studies

In view of the well-known fluorescent properties and the potential applications of fluoranthenes in OLEDs we have carried out some preliminary studies on photophysical properties of the compounds **113**, **119** and **120** as illustrative examples. The absorption and emission spectra of these compounds in solid and solution states are given in Figure 4a.6.



(C)

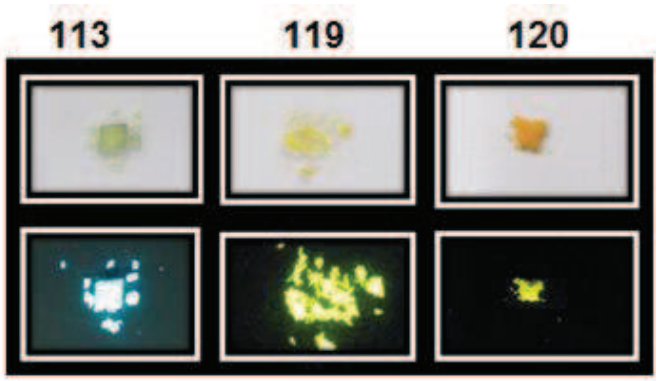


Figure 4a.6 Normalized absorption and fluorescence spectra of **113**, **119**& **120** in solution (a) and in film (b); Corresponding material images under UV (365 nm) are provided as insets; (c) Photographs of **113**, **119**& **120** in solid state under day light and UV(365 nm). Note: abs – absorption; em – emission.

Fluorescence was measured using IBH (FluoroCube) time-correlated picosecond single photon counting (TCSPC) system and the fluorescence decay profile is given below (Figure 4a.7).

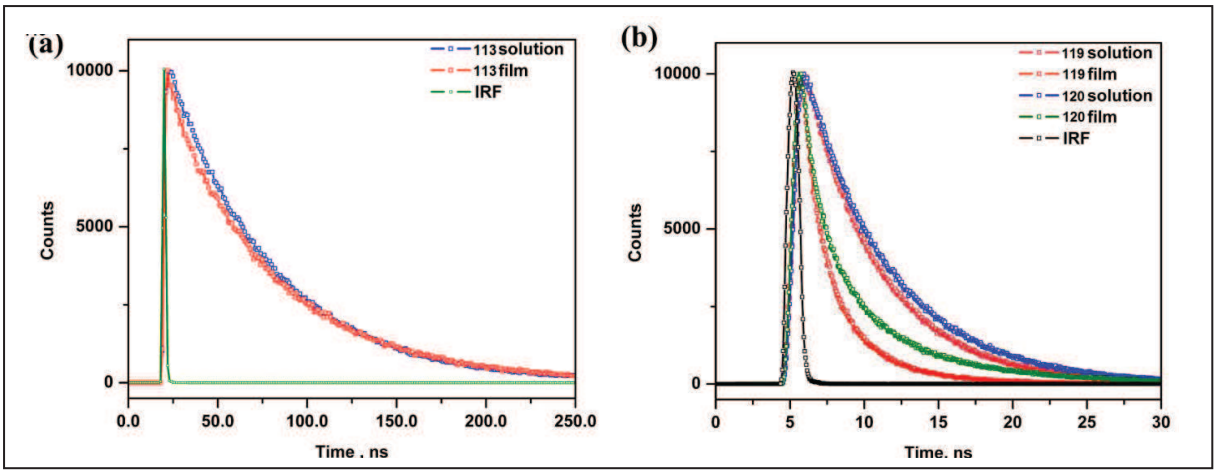


Figure 4a.7 Fluorescence decay profile of (a) **113** (at 450 nm) and (b) **119** and **120** (at 535 nm) with excitation wavelength of 335 nm

Relative fluorescence quantum yields (±5% error) were determined using quinine sulphate (ϕ_f = 0.546 in 0.1M H_2SO_4) and fluorescein (ϕ_f = 0.79 in 0.1M NaOH) as standards. The photophysical data are summarized in Table 4a.5.

Table 4a.5 Photophysical data

Compound	$\lambda_{max;abs}$ (nm)		$\lambda_{max;em}$ (nm)		Lifetime (ns)		Relative quantum yield[c]
	Solution ($CHCl_3$)	Film	Solution ($CHCl_3$)	Film	Solution ($CHCl_3$)	Film	
113	243, 303, 361[a]	(250-450)[b]	404,[a] 439, 465	480	27.9	28.5	0.88
119	239, 267, 440	239, 267, 440	503,[a] 538, 572[a]	563	4.9	0.63 (18.65%), 2.2 (59.08%), 5.1 (22.26%)	0.63
120	237[a] 262, 430	220, 265, 430	501,[a] 528, 562[a]	578	5.1	2.77 (41.85%), 7.7 (46.88%), 0.46 (11.27%)	0.66

[a]Shoulder peaks, [b]broad band, [c]fluorescence quantum yields in chloroform (Φ_s) relative to quinine sulphate (ϕ_f = 0.546 in 0.1 M H_2SO_4) and fluorescein (ϕ_f = 0.79 in 0.1 M NaOH) for **113**, **119**, and **120** respectively.

Packing motifs of compounds **113**, **119**, **120** were studied using single crystal X-ray analysis and are given in Figure 4a.8.

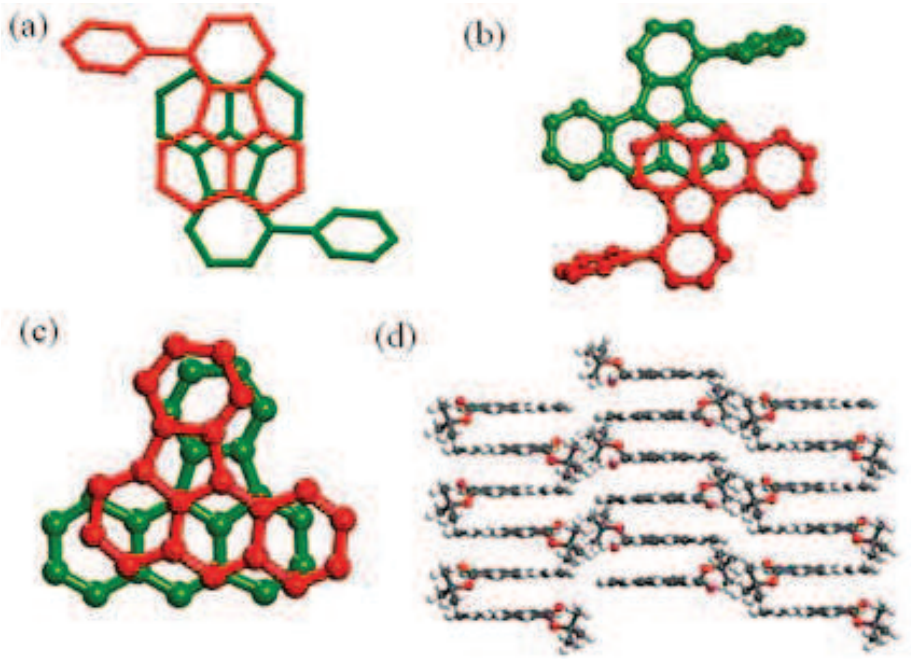


Figure 4a.8 Observed ring overlap from crystal structure information in (a) **113** (b) **119** and (c) **120**; (d) Extended 1D-π-stacking in **120** with an average π-π-distance of 3.5 Å.

4a.6.1 Discussion

Solution state absorption spectrum of **113** displays two maxima (λ_{max} = 243 and 303 nm) and a less resolved shoulder at 361 nm. In solid state (film), the absorption peaks show a marginal red-shift along with broadening (Figure 4a.6). The structured nature of emission peaks in solution however appears less resolved in film. The observed spectral characteristics can be understood in the context of crystal packing. Fluoranthene **113** shows the formation of a weak π-dimer motif with an average inter-aromatic plane distance of 3.73 Å. The dimers are further connected through C–H$\cdots\pi$ interactions (Figure 4a.8). Compared to the solution state, the fluorescence lifetime of **113** is slightly longer (27.9 vs 28.5 ns) and this may be attributed to the formation of the weak π-dimer in the solid state.

In the solid state, planar benzo[a]aceanthrylene moiety in **119** enhances the extended conjugation while the phenyl substituent at C4 adopts a twisted conformation. Edge-to-

edge π-overlap (π-π distance 3.38 Å) makes the intermolecular electron conjugation less effective (Figure 4a.8). However, the increased intramolecular effective conjugation length (ECL) due to the melding of more aromatic rings leads to redder emission (λ_{max} = 538 nm) with respect to **113** (Figure 4a.6). Interestingly, the effective emission color in solid state as well as in solution is green with only $\Delta\lambda_{em}$ = 25 nm; this corroborates well with the structural observations wherein the structure shows only weak edge-to-edge π interaction (3.38 Å). Because of this less efficient stacking, the lifetime of the transient species is comparable to that of solution. The multiple contributing factors in this decay curve may be attributed to the restricted intramolecular rotations induced by the constrained environment in solid state. However, **120** with more effective face-to-face extended stacking (1D-π-stacking and with an average π-π distance of 3.50 Å) exhibits longer lifetime in solid state. Rest of the spectral features are akin to **119**.

Notably, the emission wavelength in all the aforementioned compounds in solid state showed only marginal red-shift as compared to the solution state, and hence it can be assumed that emission characteristics is mainly determined by the intramolecular electronic conjugation rather than the stacking effect. The bulky substituents in the periphery of the aromatic core apparently deter the close stacking of the planar aromatics; this steric effect also avoids aggregation caused quenching (ACQ) and leads to comparable emission behavior of the compounds both in solution as well as aggregated states. However, the weak π-stacking in solid state enables the formation of possible transient species with longer lifetime, as evident from the lifetime studies (Figure 4a.7).

4a.7 Conclusion

In conclusion, we have uncovered a novel one pot benzannulation of 1,2-diones and allenoates that was found useful in the synthesis of benzo-fused cycloalkanes and PAHs with potential applications as OLEDs. Evidently, the presence of the carboxyl group on the fluoranthene will make it amenable for further synthetic modifications. It is also noteworthy that this work constitutes the first example of phosphine-3-alkyl allenoate zwitterions serving as four carbon synthon in benzannulation.

4a.8 Experimental Section

4a.8.1 General

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 500 (^{1}H) and 126(^{13}C) MHz respectively on Bruker Avance DPX-500S MHz NMR spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constant (*J*) is reported in Hertz (Hz). Mass spectra were recorded under HRMS (ESI) using Thermo Scientific Exactive Orbitrap mass spectrometer. IR spectra were recorded on a Bruker Alpha-T FT-IR spectrophotometer. Electronic absorption spectra were recorded on a Shimadzu UV-3101 PC NIR scanning spectrophotometer and the emission spectra on a SPEX-Fluorolog F112X spectrofluorimeter. Allenoates,[41] cycloheptane 1,2-dione,[42] and 3-bromoacenaphthene[43] were prepared using known literature procedures. Gravity column chromatography was performed using silica gel and mixtures of petroleum ether-ethyl acetate were used for elution.

4a.8.2 Flourescence Quantum Yield in the Solution State

Relative fluorescence quantum yields (±5% error) were determined using quinine sulphate (ϕ_f = 0.546 in 0.1M H_2SO_4) and fluorescein (ϕ_f = 0.79 in 0.1M NaOH) as standards. For fluorescence quantum yield measurement the absorbance at the excitation wavelength was adjusted at 0.1. Fluorescence decay profile of **113** (monitored at 450 nm), **119** and **120** (monitored at 535 nm) in chloroform with excitation wavelength of 335 nm. The experiments were done using optically matching solutions and the quantum yield is calculated using the following equation,

$$\Phi_s = \Phi_r \, (A_r F_s / A_s F_r) \, (\eta_s^2 / \eta_r^2)$$

where, A_s and A_r are the absorbance of the sample and reference solutions respectively at the same excitation wavelength, F_s and F_r are the corresponding relative integrated fluorescence intensities and η is the refractive index of the solvents used.

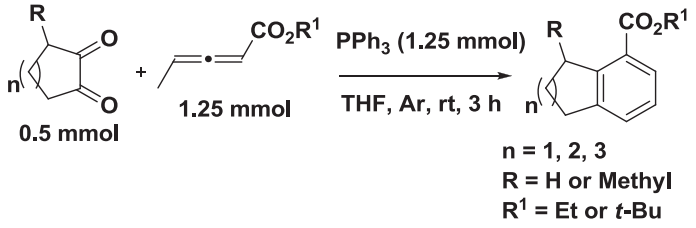
4a.8.3 Time Correlated Single Photon Counting (TCSPC)

Fluorescence was measured using IBH (FluoroCube) time-correlated picosecond single photon counting (TCSPC) system. Solutions were excited with a pulsed diode laser (<100 ps pulse duration) at a wavelength of 335 nm (NanoLED-11) with a repetition rate of 1 MHz. The detection system consists of a microchannel plate

photomultiplier (5000U-09B, Hamamatsu) with a 38.6 ps response time coupled to a monochromator (5000M) and TCSPC electronics (Data Station Hub including Hub-NL, NanoLED controller and preinstalled Fluorescence Measurement and Analysis Studio (FMAS) software). The fluorescence lifetime values were determined by deconvoluting the instrument response function with mono and triexponential decay using DAS6 decay analysis software. The quality of the fit has been judged by the fitting parameters such as $\chi 2$ (<1.2) as well as the visual inspection of the residuals. All measurements were carried out in a 1 mm cuvette using a front face sample holder (5000U-04).

4a.8.4 General procedure for the Benzannulation Reaction

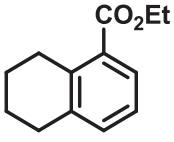
4a.8.4.1 General procedure for the benzannulation of cycloalkane1,2-diones



The dione (0.5 mmol) and the allenoate (1.25 mmol) in dry THF (5 ml) were taken in a round bottom flask under argon atmosphere. Triphenylphosphine (1.25 mmol) was added to this mixture and stirred at room temperature for 3 h. After the completion of the reaction, as indicated by TLC, the crude mixture was concentrated and purified by column chromatography on 100-200 mesh silica gel using hexane: ethyl acetate (98:2) as the eluent to afford the benzannulated product.

Ethyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate (103)

Following the general procedure, reaction of cyclohexane-1,2-dione (56 mg, 0.5 mmol) with ethyl 3-methyl allenoate (157 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded ethyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate in 84% (86 mg, 0.42 mmol) yield as colourless oil.



Yield: 86 mg (84%), colourless oil.

IR (film) ν_{max}: 1719, 1259, 1135 cm^{-1}.

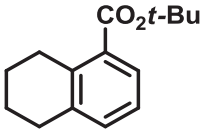
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 4.32 (q, *J* = 7.0 Hz, 2H), 3.06 – 3.04 (m, 2H), 2-82 – 2.80 (m, 2H), 1.80 – 1.78 (m, 4H), 1.38 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.9, 138.4, 138.1, 132.8, 130.6, 127.8, 124.9, 60.4, 30.2, 27.7, 23.2, 22.5, 14.4 ppm.

HRMS (ESI-MS) calcd for $C_{13}H_{16}O_2Na^+$ 227.1048; Found: 227.1050.

***tert*-Butyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate (105)**

Following the general procedure, reaction of cyclohexane-1,2-dione (56 mg, 0.5 mmol) with *tert*-butyl 3-methyl allenoate (192 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded *tert*-butyl -5,6,7,8-tetrahydronaphthalene-1-carboxylate in 82% (95 mg, 0.41 mmol) yield as colourless oil.



Yield: 95 mg (82%), colourless oil.

IR (film) ν_{max}: 1711, 1279, 1133 cm^{-1}.

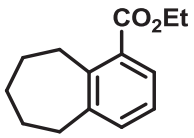
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 3.02 – 3.00 (m, 2H), 2.80 – 2.78 (m, 2H), 1.79-1.77 (m, 4H), 1.58 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.9, 138.4, 138.1, 132.8, 130.59, 127.8, 124.9, 60.4, 30.2, 27.7, 23.2, 22.5, 14.4 ppm.

HRMS (ESI-MS) calcd for $C_{15}H_{20}O_2Na^+$ 255.1361; Found: 255.1353.

Ethyl 6,7,8,9-tetrahydro-5H-benzo[7]annulene-1-carboxylate (107)

Following the general procedure, reaction of cycloheptane-1,2-dione (63 mg, 0.5 mmol) with ethyl 3-methyl allenoate (157 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded ethyl 6,7,8,9-tetrahydro-5H-benzo[7]annulene-1-carboxylate in 38% (41 mg, 0.19 mmol) yield as colourless oil.



Yield: 41 mg (38%), colourless oil.

IR (film) ν_{max}: 1715, 1293, 1131 cm^{-1}.

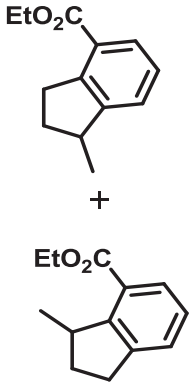
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.19 (d, J = 6.5 Hz1H), 7.08 (t, J = 7.5 Hz, 1H), 4.34 (q, J = 7.0 Hz, 2H), 3.02 – 3.00 (m, 2H), 2.86 – 2.84 (m, 2H), 1.86 – 1.81 (m, 2H), 1.71 – 1.63 (m, 4H), 1.38 (t, J = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.1, 144.8, 143.1, 131.6, 131.5, 127.0, 125.3, 60.7, 36.2, 32.1, 30.9, 27.9, 27.2, 14.3 ppm.

HRMS (ESI-MS) calcd for $C_{14}H_{18}O_2Na^+$ 241.1205; Found: 241.1198.

Ethyl 1-methyl-2,3-dihydro-1H-indene-4-carboxylate & Ethyl 3-methyl-2,3-dihydro-1H-indene-4-carboxylate (109a& 109a[1])

Following the general procedure, reaction of cycloheptane-1,2-dione (56 mg, 0.5 mmol) with ethyl 3-methyl allenoate (157 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded mixture of ethyl 1-methyl-2,3-dihydro-1H-indene-4-carboxylate and ethyl 3-methyl-2,3-dihydro-1H-indene-4-carboxylate in 30% (31 mg, 0.15 mmol) yield as colourless oil.



Yield: 31 mg (30%), colourless oil.

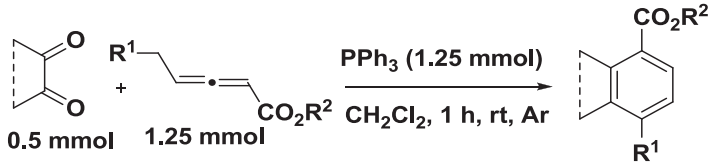
IR (film) ν_{max}: 1719, 1262, 1131 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 – 7.78 (m, 1.64H), 7.34 (m, 1.64H), 7.22 (t, *J* = 7.5 Hz, 0.64H), 7.18 (t, *J* = 7.5 Hz, 1H), 4.38 – 4.33 (m, 3.28H), 3.92 – 3.89 (m, 1H), 3.36 (ddd, J_1 = 17.5 Hz, J_2 = 8.8 Hz, J_3 = 4.0 Hz, 0.64H), 3.21 – 3.01 (m, 2.28H), 2.81 (dd, J_1 = 16.0 Hz, J_2 = 9.0 Hz, 1H), 2.37 – 2.29 (m, 0.64H), 2.25 – 2.18 (m, 1H), 1.82 (ddt, J_1 = 12.3, J_2 = 7.8, J_3 = 1.5 Hz, 1H), 1.65 – 1.57 (m, 0.64H), 1.42 – 1.38 (m, 4.92H), 1.29 (d, *J* = 7.0 Hz, 1.92H), 1.19 (d, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.0, 166.8, 151.4, 150.2, 146.2, 144.6, 128.7, 128.4, 128.1, 127.2, 126.7, 126.4, 126.2, 126.2, 60.4, 60.4, 39.6, 39.0, 34.2, 33.4, 32.4, 30.2, 20.1, 20.1, 14.4, 14.3 ppm.

HRMS (ESI-MS) calcd for $C_{13}H_{16}O_2Na^+$ 227.1048; Found: 227.1051.

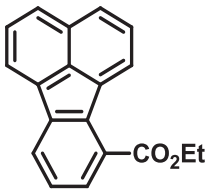
4a.8.4.2 General procedure for the benzannulation of quinones and biacetyl



The quinone (0.5 mmol) and the allenoate (1.25 mmol) in dry DCM (5 ml) were taken in a round bottom flask under argon atmosphere. Triphenylphosphine (1.25 mmol) was added to this mixture and stirred at room temperature for 1 h. After the completion of the reaction, as indicated by TLC, the crude mixture was concentrated and purified by column chromatography on 100-200 mesh silica gel using hexane: ethyl acetate (98:2) as the eluent to afford the benzannulated product.

Ethyl fluoranthene-7-carboxylate (110)

Following the general procedure, reaction of acenaphthenequinone (91 mg, 0.5 mmol) with ethyl 3-methyl allenoate (157 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded ethyl fluoranthene-7-carboxylate in 82% (112 mg, 0.41 mmol) yield as pale yellow solid.



Yield: 112 mg (82%), pale yellow solid. mp 60-62 ^{o}C.

IR (film) ν_{max}: 1721, 1263 cm^{-1}.

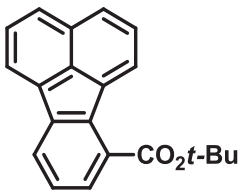
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (d, *J* = 7.0 Hz, 1H), 8.08 (d, *J* = 7.5 Hz, 1H), 7.97 - 7.94 (m, 2H), 7.88 (t, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 4.52 (q, *J* = 7.0 Hz, 2H), 1.50 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.4, 140.9, 138.9, 135.5, 132.8, 129.8, 129.6, 128.4, 127.7, 127.5, 127.3, 127.3, 127.2, 126.7, 124.6, 119.8, 61.0, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{19}H_{14}O_2Na^+$: 297.0892; Found: 297.0895.

***tert*-Butyl fluoranthene-7-carboxylate (111)**

Following the general procedure, reaction of acenaphthenequinone (91 mg, 0.5 mmol) with *tert*-butyl 3-methyl allenoate (192 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded *tert*-butyl fluoranthene-7-carboxylate in 65% (98 mg, 0.32 mmol) yield as pale yellow oil.



Yield: 98 mg (65%), pale yellow oil.

IR (film) ν_{max}: 1709, 1277, 1126 cm^{-1}.

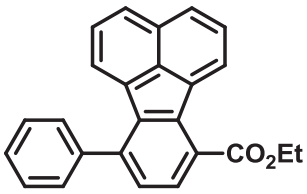
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 (d, *J* = 7.5 Hz, 1H), 8.02 (d, *J* = 7.0 Hz, 1H), 7.92 (d, *J* = 7.0 Hz, 1H), 7.87 - 7.83 (m, 3H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.0 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 1.71 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.8, 140.8, 138.6, 135.6, 135.6, 132.8, 129.8, 129.4, 129.1, 128.4, 127.5, 127.3, 127.3, 127.2, 126.6, 124.2, 119.7, 81.3, 28.4 ppm.

HRMS (ESI-MS) calcd for $C_{21}H_{18}O_2Na^+$: 325.1205; Found: 325.1198.

Ethyl-10-phenylfluoranthene-7-carboxylate (113)

Following the general procedure, reaction of acenaphthenequinone (91 mg, 0.5 mmol) with ethyl 3-benzyl allenoate (252 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded ethyl-10-phenylfluoranthene-7-carboxylate in 98% (172 mg, 0.49 mmol) yield as pale yellow solid.



Yield: 172 mg (98%), yellow solid, mp 94-96 ^{o}C

IR (film) ν_{max}: 1718, 1234, 1116 cm^{-1}.

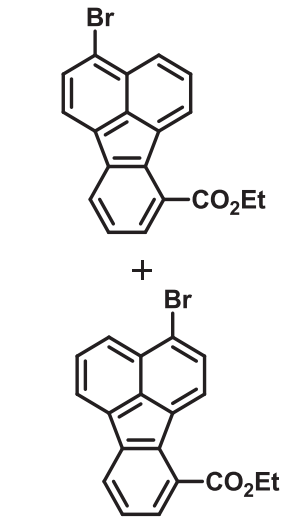
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (d, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.50 (m, 5H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.0 Hz, 1H), 4.55 (q, *J* = 7.0 Hz, 2H), 1.51 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.6, 142.2, 140.5, 139.2, 138.0, 135.3, 134.9, 132.9, 129.7, 129.0, 128.8, 128.7, 128.7, 128.1, 127.9, 127.2, 126.3, 123.2, 61.1, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{25}H_{18}O_2Na^+$: 373.1205; Found: 373.1187.

Ethyl 3-bromofluoranthene-7-carboxylate & Ethyl 4-bromofluoranthene-7-carboxylate (115a & 115a[1])

Following the general procedure, reaction of 5-bromoacenaphthylene-1,2-dione (130 mg, 0.5 mmol) with ethyl 3-methyl allenoate (157 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded mixture of ethyl 3-bromofluoranthene-7-carboxylate and ethyl 4-bromofluoranthene-7-carboxylate in 70% (124 mg, 0.35 mmol) yield as yellow solid.



Yield: 124 mg (70%), yellow solid

IR (film) ν_{max}: 1719, 1435, 1260, 1118 cm^{-1}.

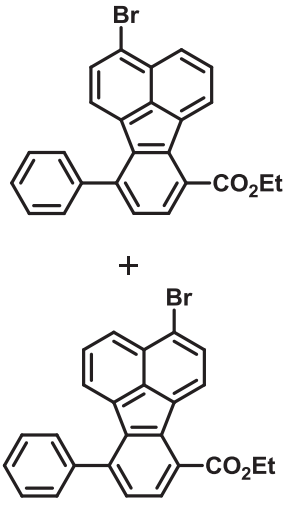
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, *J* = 7.0 Hz, 0.74H), 8.63 (d, *J* = 7.5 Hz, 1H), 8.01-7.97 (m, 1.74H), 7.95 – 7.91 (m, 3.48H), 7.85 (d, *J* = 7.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.0 Hz, 0.74H), 7.68 (t, *J* = 7.5 Hz, 0.74H), 7.64 – 7.60 (m, 1.74H), 7.38 – 7.33 (m, 1.74H), 4.52 – 4.47 (m, 3.48H), 1.51 – 1.48 (m, 5.22H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.8, 166.8, 140.5, 140.1, 138.6, 138.4, 135.7, 135.6, 135.1, 135.1, 133.8, 133.7, 131.6, 130.5, 129.9, 129.9, 129.5, 129.5, 128.4, 128.3, 128.2, 127.2, 127.0, 126.9, 126.9, 126.6, 124.7, 124.5, 123.3, 122.6, 120.3, 120.1, 61.0, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{19}H_{13}BrO_2Na^+$ 374.9997; Found: 375.0003 $(M+Na)^+$, 376.9982 $(M+2+Na)^+$

Ethyl 3-bromo-10-phenylfluoranthene-7-carboxylate & Ethyl 4-bromo-10-phenylfluoranthene-7-carboxylate (116a & 116a[1])

Following the general procedure, reaction of 5-bromoacenaphthylene-1,2-dione (130 mg, 0.5 mmol) with ethyl 3-benzyl allenoate (252 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded ethyl 3-bromo-10-phenylfluoranthene-7-carboxylate and ethyl 4-bromo-10-phenylfluoranthene-7-carboxylate in 71% (152 mg, 0.35 mmol) yield as yellow solid.



Yield: 152 mg, (71%), yellow solid.

IR (film) ν_{max}: 1719, 1422, 1249, 1122 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (d, *J* = 7.5 Hz, 0.84H), 8.69 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 0.84H), 7.96 – 7.92 (m, 2.84H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 0.84H), 7.54 – 7.48 (m, 9. 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.27 – 7.22 (m, 2.68H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 0.84H), 4.55 – 4.50 (m, 3.68H), 1.51 – 1.48 (m, 5.52H) ppm.

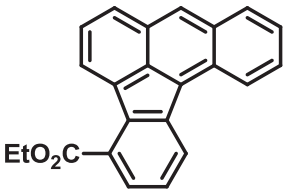
^{13}C NMR (126 MHz, $CDCl_3$): δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 167.2, 142.4, 142.2, 140.2, 140.1, 138.8, 138.7, 137.6, 137.3,

135.6, 135.2, 135.0, 134.7, 134.1, 134.1, 131.4, 130.5, 129.5, 129.4, 129.4, 129.4, 129.3, 129.0, 129.0, 128.8, 128.7, 128.7, 128.3, 128.2, 128.0, 127.9, 127.2, 126.4, 126.3, 123.8, 123.6, 123.5, 122.6, 61.2, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{25}H_{17}BrO_2Na^+$ 451.0310; Found: 451.0304 $(M+Na)^+$, $(M+2+Na)^+$ 453.0284.

Ethyl benzo[a]aceanthrylene-4-carboxylate (118)

Following the general procedure, reaction of aceanthrylene-1,2-dione (116 mg, 0.5 mmol) with ethyl 3-methyl allenoate (157 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded ethyl benzo[a]aceanthrylene-4-carboxylate in 51% (83 mg, 0.26 mmol) yield as orange solid.



Yield: 83 mg (51%), orange solid, mp 96-100 ^oC

IR (film) ν_{max}: 1719, 1248, 1126 cm^{-1}.

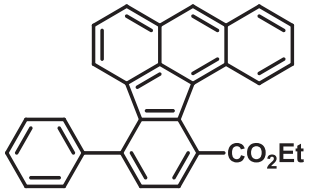
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.92 (d, *J* = 7.0 Hz, 1H), 8.81 (d, *J* = 8.5 Hz, 1H), 8.63 (d, *J* = 7.5 Hz, 1H), 8.52 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.73– 7.67 (m, 2H), 7.52 (t, *J* = 7.5 Hz, 2H), 4.56 (q, *J* = 7.0 Hz, 2H), 1.52 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.7, 141.9, 138.1, 135.0, 134.0, 131.1, 130.7, 129.3, 128.8, 128.3, 128.2, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 126.9, 126.8, 124.7, 123.8, 61.1, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{23}H_{16}O_2Na^+$: 347.1048; Found: 347.1050.

Ethyl 4-phenylbenzo[a]aceanthrylene-1-carboxylate (119)

Following the general procedure, reaction of aceanthrylene-1,2-dione (116 mg, 0.5 mmol) with ethyl 3-benzyl allenoate (252 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded ethyl 4-phenylbenzo[a]aceanthrylene-1-carboxylate in 38% (76 mg, 0.19 mmol) yield as orange yellow solid.



Yield: 76 mg (38%), orange yellow solid, mp 145-150 ^{o}C

IR (film) ν_{max}: 1712, 1244, 1101 cm^{-1}.

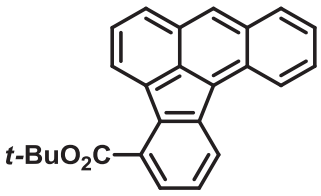
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.13 (t, *J* = 10.0 Hz, 2H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.58 – 7.52 (m, 4H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 6.5 Hz, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 1.03 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.5, 141.4, 140.5, 138.5, 137.2, 135.4, 134.5, 131.7, 131.0, 130.3, 129.9, 129.4, 128.9, 128.9, 128.7, 128.3, 128.1, 128.1, 127.6, 127.4, 127.0, 126.5, 125.8, 124.8, 124.1, 61.4, 13.7 ppm.

HRMS (ESI-MS) calcd for $C_{29}H_{20}O_2Na^+$: 423.1361; Found: 423.1366.

***tert*-Butyl benzo[a]aceanthrylene-4-carboxylate (120)**

Following the general procedure, reaction of aceanthrylene-1,2-dione (116 mg, 0.5 mmol) with *tert*-butyl 3-methyl allenoate (192 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded *tert*-Butyl benzo[a]aceanthrylene-4-carboxylate in 46% (81 mg, 0.23 mmol) yield as orange solid.



Yield: 81 mg (46%), orange solid, mp 125-130 ^{o}C

IR (film) ν_{max}: 1713, 1277, 1128 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (d, *J* = 7.0 Hz, 1H), 8.82 (d, *J* = 9.0 Hz, 1H), 8.60 (d, *J* = 7.5 Hz, 1H), 8.53 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.74 – 7.69 (m, 2H), 7.55 – 7.50 (m, 2H), 1.74 (s, 9H) ppm.

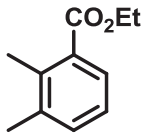
^{13}C NMR (126 MHz, $CDCl_3$): δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 141.8, 137.6, 135.2, 134.1, 131.2, 130.7, 129.6, 129.4, 128.8, 128.2, 128.1, 128.0, 127.8, 127.8, 127.7, 127.5, 127.0, 126.4, 124.8, 123.9, 81.6, 28.4 ppm.

HRMS (ESI-MS) calcd for $C_{25}H_{20}O_2$+Na^+: 375.1361; Found: 375.1356.

Ethyl 2,3-dimethylbenzoate (123)

Following the general procedure, reaction of biacetyl (43 mg, 0.5 mmol) with ethyl 3-methyl allenoate (157 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25

mmol) afforded ethyl 2,3-dimethylbenzoate in 25% (22 mg, 0.12 mmol) yield as colourless oil.



Yield: 22mg (25%), colourless oil.

IR (film) ν_{max}: 1717, 1247, 1146 cm^{-1}.

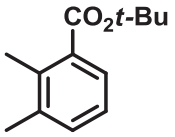
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 4.35 (q, *J* = 7.0 Hz, 2H), 2.45 (s, 3H), 2.32 (s, 3H), 1.39 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.7, 136.8, 136.2, 131.9, 130.4, 126.5, 124.1, 59.7, 19.5, 15.6, 13.3 ppm.

HRMS (ESI-MS) calcd for $C_{11}H_{14}O_2Na^+$:201.0892;Found: 201.0880.

***tert*-Butyl 2,3-dimethylbenzoate (124)**

Following the general procedure, reaction of biacetyl (43 mg, 0.5 mmol) with tert-butyl 3-methyl allenoate (192 mg, 1.25 mmol) and triphenylphosphine (327 mg, 1.25 mmol) afforded *tert*-butyl 2,3-dimethylbenzoate in 32% (33 mg, 0.16 mmol) yield as colourless oil.



Yield: 33 mg (32%), colourless oil.

IR (film) ν_{max}: 1714, 1299, 1144 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 2.41 (s, 3H), 2.30 (s, 3H), 1.59 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.2, 137.5, 136.4, 133.3, 132.31, 127.2, 125.1, 80.8, 28.3, 20.5, 16.6 ppm.

HRMS (ESI-MS) calcd for $C_{13}H_{18}O_2Na^+$:229.1205; Found: 229. 1193.

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CHAPTER 4B

Reactions of Phosphine-3-Alkyl Allenoate Zwitterions with Isatins: A Facile Entry to Spiro Tetrahydrofuran Oxindoles

4b.1 Introduction

Synthesis of spiro oxindoles has been a favourite task for synthetic and medicinal chemists since they are well-known for their bioactivities and pharmaceutical applications, and their presence in many natural products. They occur in natural products such as spirotryprostatins,[1] horsfiline,[2] gelsemine,[3] coerulescine,[4] rhynchophylline,[5] and elacomine[6] (Figure 4b.1) that are endowed with various types of bioactivities, *viz*., anti-HIV, anticancer, antitubercular and antimalarial activities.

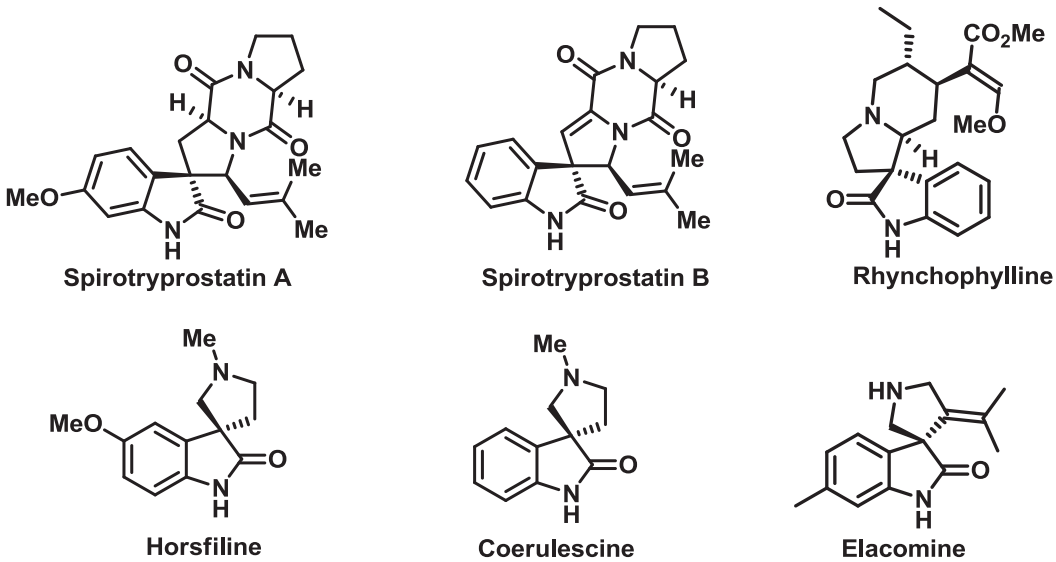


Figure 4b.1 Some naturally occuring spirooxindoles

Although a number of spiro-carbocyclic and spiro-heterocyclic oxindoles have been synthesized from isatins or isatin derivatives using multicomponent reactions, organocatalysis, cyclocondensation etc., their potential applications make them synthetic

targets of sustained interest. Specifically, spiro furan oxindoles are known to have antibacterial, anticancer, and growth inhibitory activities (Figure 4b.2).[7]

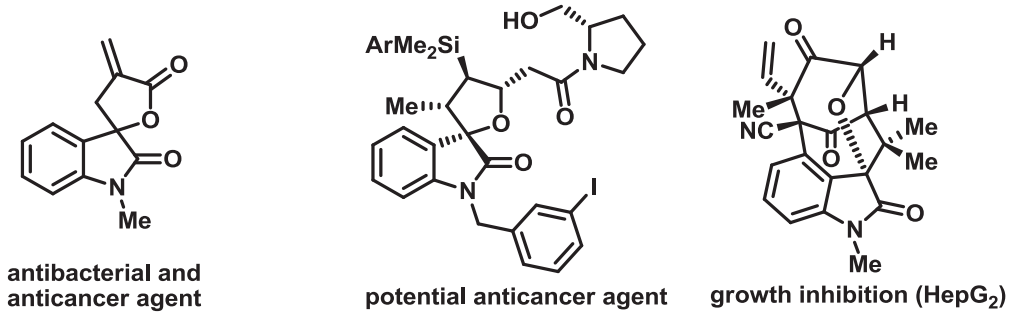


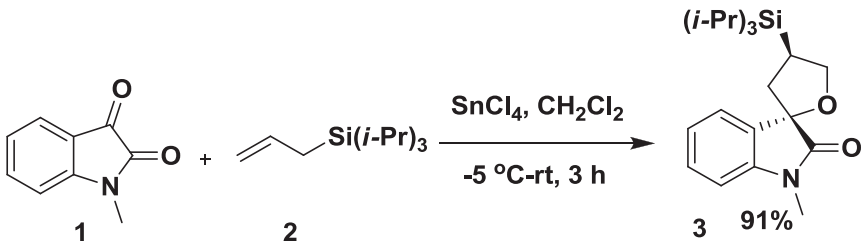
Figure 4b.2 Biologically active spiro furan oxindoles

In view of the results described in previous chapters it was of interest to investigate the reactivity of phosphine-3-alkyl allenoate zwitterion towards another type of 1,2-dicarbonyl compound *viz*., isatin. The results constitute the present chapter. Before going in to the details of the present work, a brief survey on the synthesis of spirofuran oxindole derivatives from isatin is provided in the following section.

4b.2. Synthesis of Spirofuran Oxindoles

4b.2.1. Synthesis of Spirofuran Oxindoles from Isatins

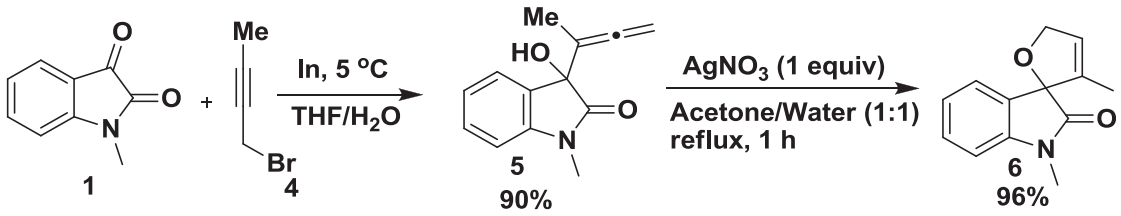
In 2002, it was reported from our group that a formal [3+2] dipolar cycloaddition of allylsilane **2** with keto carbonyl of isatin yielded spiro-oxindole derivative **3**. The reaction can be viewed as a two-step process involving initial addition of the allylsilane to the Lewis acid complexed isatin and subsequent quenching of the the silyl cation by cyclization (Scheme 4b.1).[8]



Scheme 4b.1

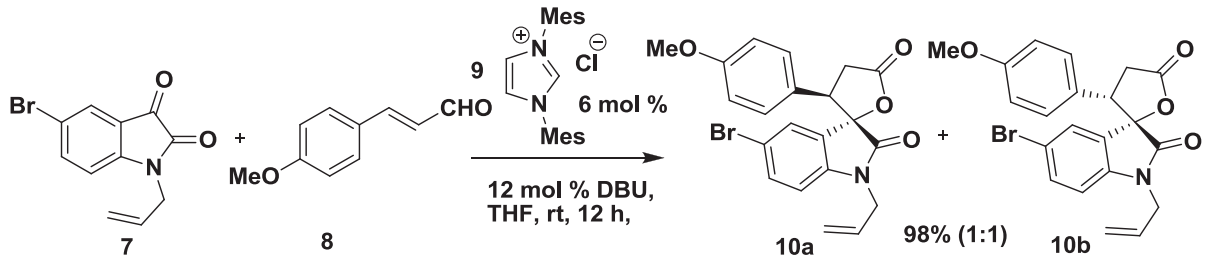
Almendros *et al*. reported the synthesis of a variety of oxaspiro oxindoles from precursors, 2-indolinone-tethered homoallylic alcohols, (buta-1,3-dien-2-yl)methanols, and α-allenols which in turn were prepared by the regioselective addition of the

respective stabilized organoindium reagents to isatins in aqueous environment. An example using α-allenol **5** is shown in scheme 2. Silver-catalyzed reaction of the unsaturated alcohol derivative yielded spiro furan oxindole **6**.[9]



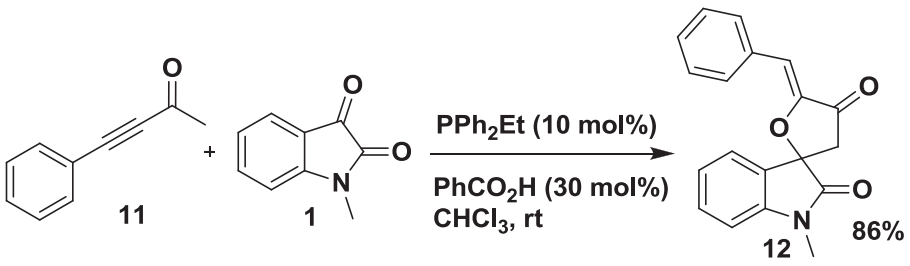
Scheme 4b.2

Investigations in our laboratory have shown that nucleophilic heterocyclic carbene (NHC) catalyzed annulation of enals and cyclic 1,2-dicarbonyl compounds yielded γ-spiro lactones. The addition of homoenolate generated from cinnamaldehyde **8** and NHC to the keto carbonyl of isatin followed by cyclization led to the facile synthesis of spirofuranone oxindole derivative **10a** and **10b** as 1:1 diastereometic mixture in almost quantitative yield (Scheme 4b.3).[10]



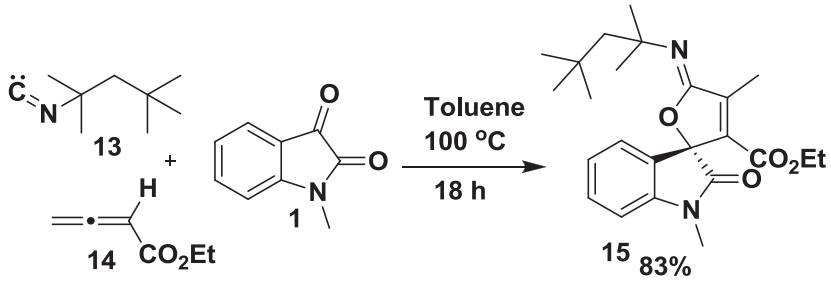
Scheme 4b.3

Huang and co-workers recently reported a novel phosphine-catalyzed intermolecular [3+2] cycloaddition of ynones and N-substituted isatins. In this reaction, substituted ynones, serving as a C3 synthon, were successfully applied to intermolecular annulation reactions to furnish a number of functionalized spirooxindoles in high yields and stereoselectivity (Scheme 4b.4).[11]



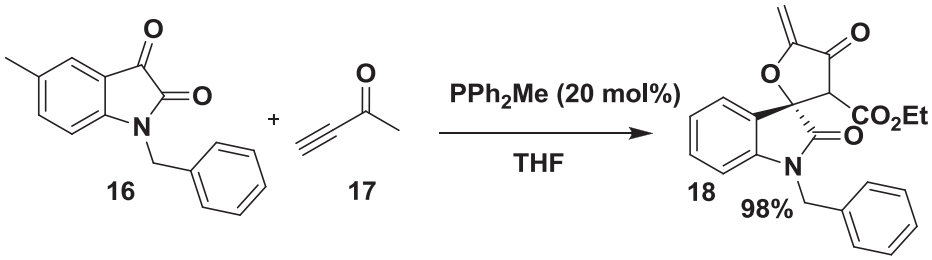
Scheme 4b.4

Synthesis of spirocyclic oxindole-butenolides was reported by the three component [2+2+1] cycloadditions of isocyanides, allenoates, and isatins. The zwitterionic species generated from isocyanide **13** and allenoate **14**, is trapped by the keto carbonyl group of isatin, and subsequent intramolecular annulation afforded the product **15** in 83% yield (Scheme 4b.5).[12]



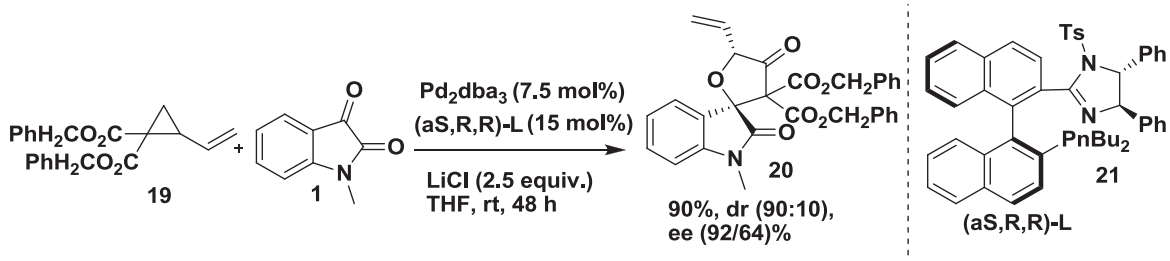
Scheme 4b.5

Phosphine catalysed [3+2] annulation of isatin with but-3-yn-2-one proceeded smoothly under mild conditions to give the spiro[furan-2,3′-indoline]-2′,4(5*H*)-dione **18** in excellent yield (Scheme 4b.6).[13]



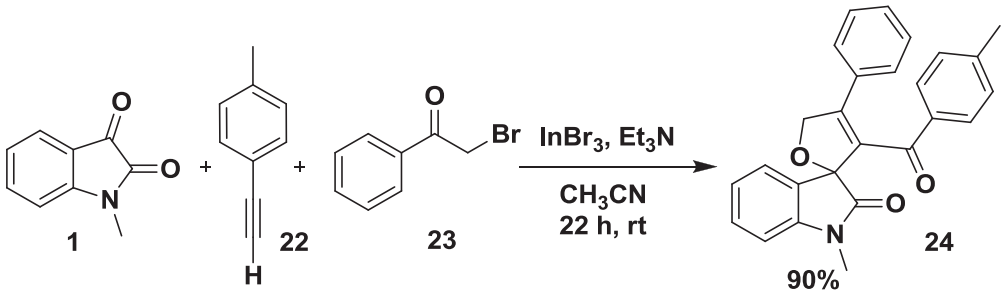
Scheme 4b.6

Vinyl cyclopropanes bearing electron-withdrawing groups have been demonstrated as a new family of three carbon synthons for the construction of cyclic compounds. It is well known in the literature that the ring-opening of vinyl cyclopropanes in the presence of Pd(0) catalysts, easily leads to 1,3-dipolar species and trapping the latter with olefins, isocyanates, aldehydes, azlactones, and β,γ-unsaturated α- keto esters directly afford different substituted five-membered ring compounds.[14] Recently, a novel asymmetric formal [3+2] cycloaddition of vinyl cyclopropanes and isatins in the presence of $Pd_2(dba)_3$ and the chiral imidazoline-phosphine ligand (aS,R,R)-L has been reported by Mei *et al*. The reaction, under mild conditions, afforded the corresponding highly functionalized oxindole-fused spirotetrahydrofuran frameworks in high yields and high diastereo- and enantioselectivities (Scheme 4b.7).[15]



Scheme 4b.7

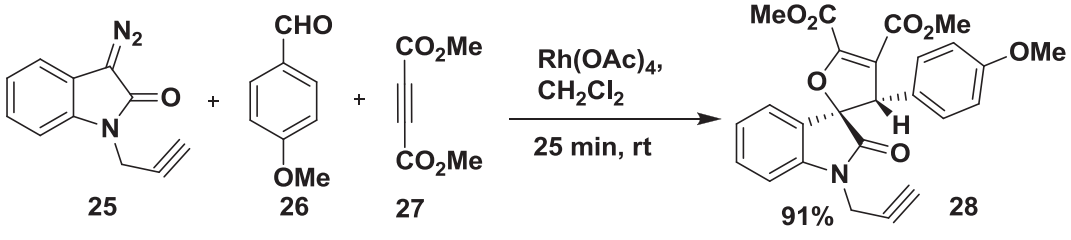
It has been repoted by Siddiqui and co-workers that indium bromide catalyzed, convenient one-pot reaction of N-methyl isatin, alkynes and phenacyl bromides under ambient conditions selectively afforded spiro dihydrofuran oxindole derivatives. The significant advantages of this protocol are highlighted by excellent yields, cleaner reaction profiles and avoidance of expensive catalysts (Scheme 4b.8).[16]



Scheme 4b.8

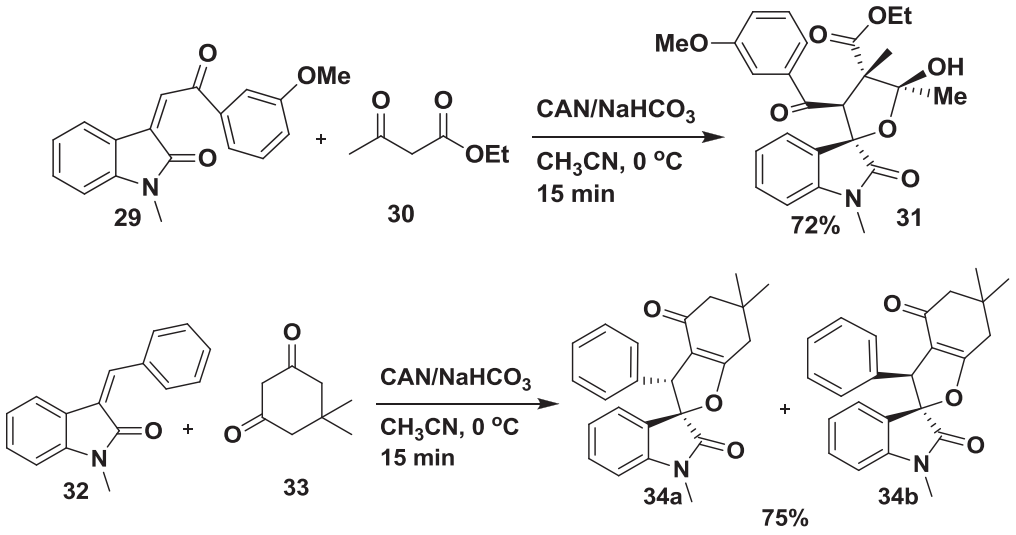
4b.2.2 Synthesis of Spirofuran Oxindoles from Isatin Derivatives

Spirofuran oxindole derivatives were efficiently prepared from various isatin derivatives. In 2004 Muthusamy *et al.* reported the first diastereoselective synthesis of spiro dihydrofurooxindoles through the multicomponent reactions of cyclic diazoamides. The reaction involves the intermolecular generation of carbonyl ylides by dirhodium(II) tetraacetate catalyzed reaction of 3-diazoindol-2-ones in the presence of aryl and heteroaryl aldehydes. These carbonyl ylides were subsequently trapped with dipolarophiles such as dimethyl acetylenedicarboxylate, maleic anhydride and ethyl acrylate to afford spiro furooxindoles (Scheme 4b.9).[17]



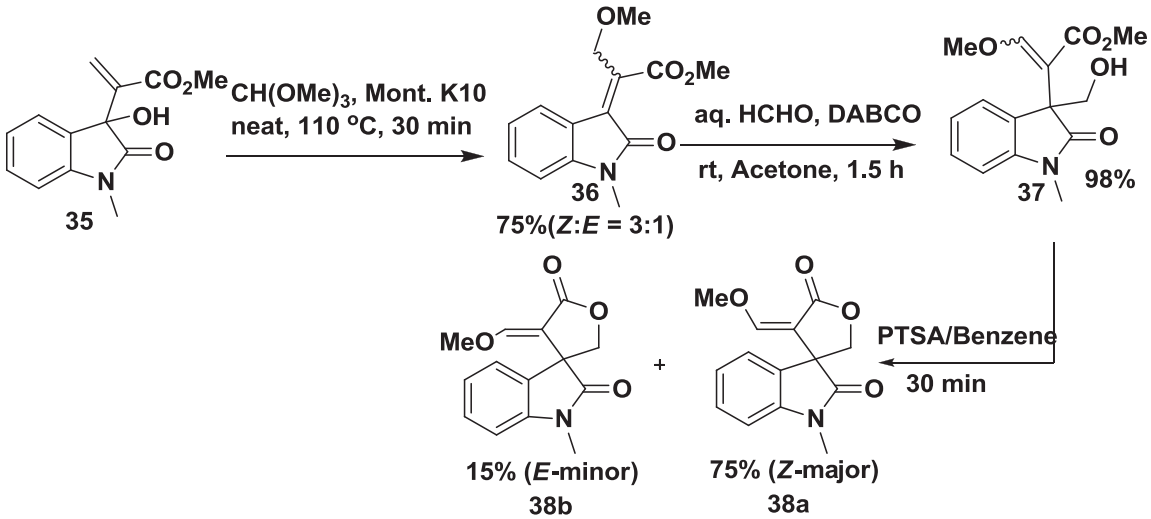
Scheme 4b.9

Ceric ammonium nitrate (CAN) mediated oxidative [3+2] cycloaddtion of 1,3-dicarbonyl compounds to 3-(phenyl-2-oxoethylidene)-1-methyloxindole and 3-benzylidene-1-methyloxindole derivatives led to the efficient one–pot synthesis of spirofuran oxindole derivatives (Scheme 4b.10).[18]



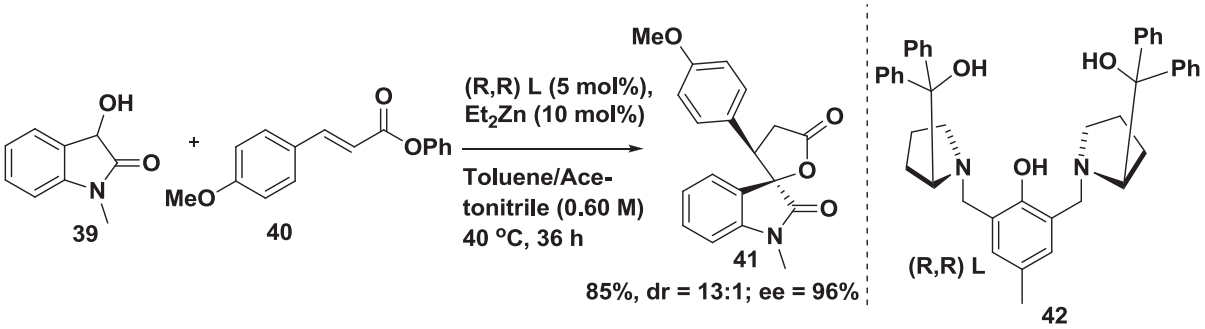
Scheme 4b.10

Stereoselective synthesis of spirofuranone oxindoles was accomplished from Morita-Baylis-Hillman adducts of isatin in a three step sequence. The reaction proceeds *via* the isomerisation of the Morita-Baylis-Hillman adducts of isatin, a second Morita-Baylis-Hillman reaction with formaldehyde, and an acid catalysed lactonization. In the given example, the reaction afforded the spirofuran oxindoles **38a** and **38b** (Scheme 4b.11).[19]



Scheme 4b.11

Trost *et al*. reported a highly diastereo- and enantioselective formal [3+2] cycloaddition of α,β-unsaturated ester and 3-hydroxyoxindole to yield spirocyclic δ-lactone **41**. The reaction is catalyzed by a dinuclear zinc-ProPhenol complex and involves stereoselective Michael addition of 3-hydroxyoxindole and subsequent transesterification. This represents a rare example of 3-hydroxyoxindole serving as an isatinic anion equivalent in a catalytic enantioselective reaction (Scheme 4b.12).[20]



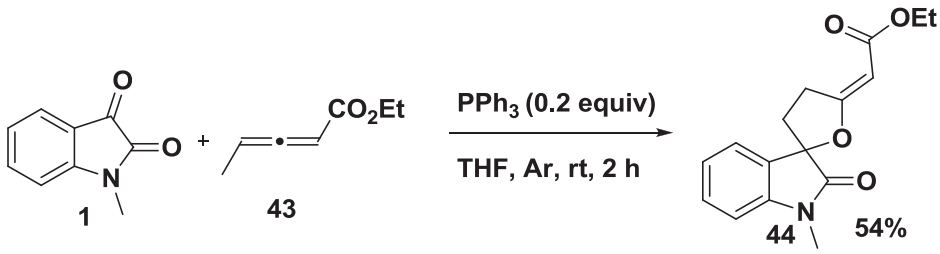
Scheme 4b.12

4b.3 Background to the Present Work

As a part of our continuing interest in the chemistry of zwitterions and 1,2-diones, we treated phosphine-3-alkyl allenoate zwitterions with diaryl 1,2-diones. The reaction afforded substituted cyclopentenones and alkylidene tetrahydrofuran derivatives under different conditions (See chapter 3). Interestingly, the reaction of alicyclic 1,2-diones and acenaphthene quinones afforded the corresponding benzannulated products. Although several groups have investigated the reactivity of isatilidenes and isatin oximes toward allenoates under different conditions,[12,21] the reactivity of isatin towards the latter remained under-explored. The exception being Min Shi's report in which a DMAP catalysed Morita-Baylis-Hillman reaction of isatins with α-substituted allenoates afforded allenoate appended oxindoles.[22] In this context, we were intrigued by the possibility of trapping the phosphine-3-alkyl allenoate zwitterion with isatins.

4b.4 Results and Discussions

In an initial experiment, ethyl 3-methylallenoate was treated with N-methylisatin in presence of catalytic amount of triphenylphosphine. The crude product after purification by column chromatography afforded (*E*)-ethyl 2-(1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate **44** (Scheme 4b.13) in 54% yield.



Scheme 4b.13

The structure of the compound **44** was assigned using conventional spectroscopic techniques. In the IR spectrum, the amide carbonyl absorption was observed at 1721 cm^{-1} and the conjugated ester carbonyl absorption at 1701 cm^{-1}. In ^{1}H NMR spectrum, the olefinic proton was discernible as singlet signal at δ 5.41 ppm. The methylene protons and the methyl protons of the ester group resonated as quartet and triplet at δ 4.14 and δ 1.27 ppm respectively (Figure 4b.3). In ^{13}C NMR spectrum the amide carbonyl was observed at δ 174.1 ppm and the ester carbonyl at δ 167.8 ppm (Figure 4b.4). Conclusive evidence for the structure and relative stereochemistry was derived from single-crystal X-ray analysis of (*E*)-Ethyl 2-(1'-benzyl-5'-bromo-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate **51** (*vide infra*) (Figure 4b.5).

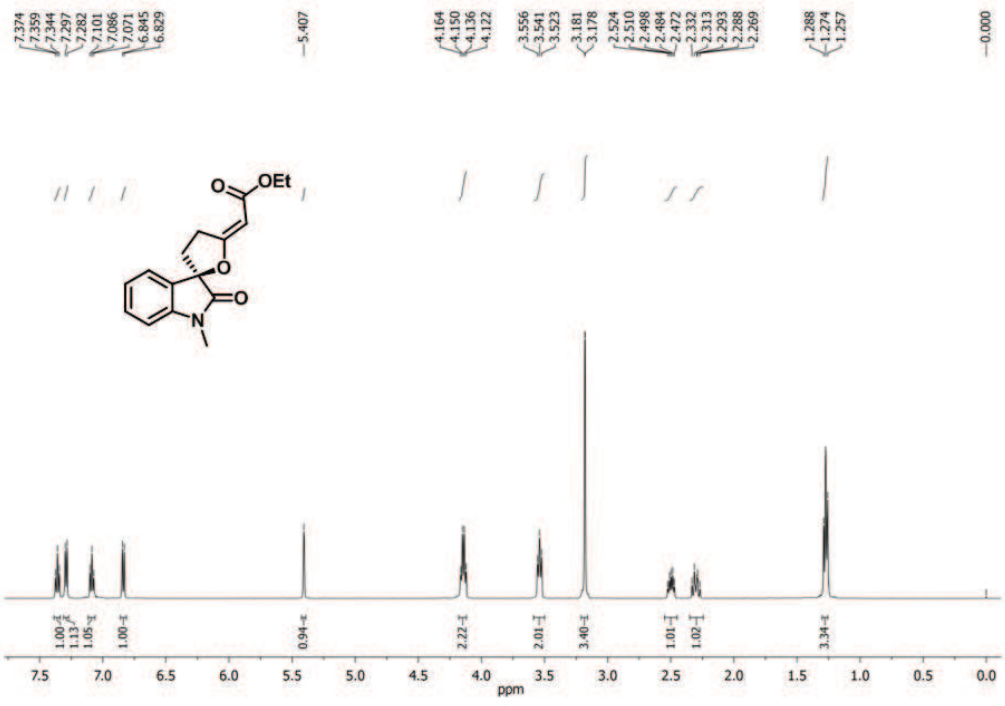


Figure 4b.3 ^{1}H NMR spectrum of compound 44

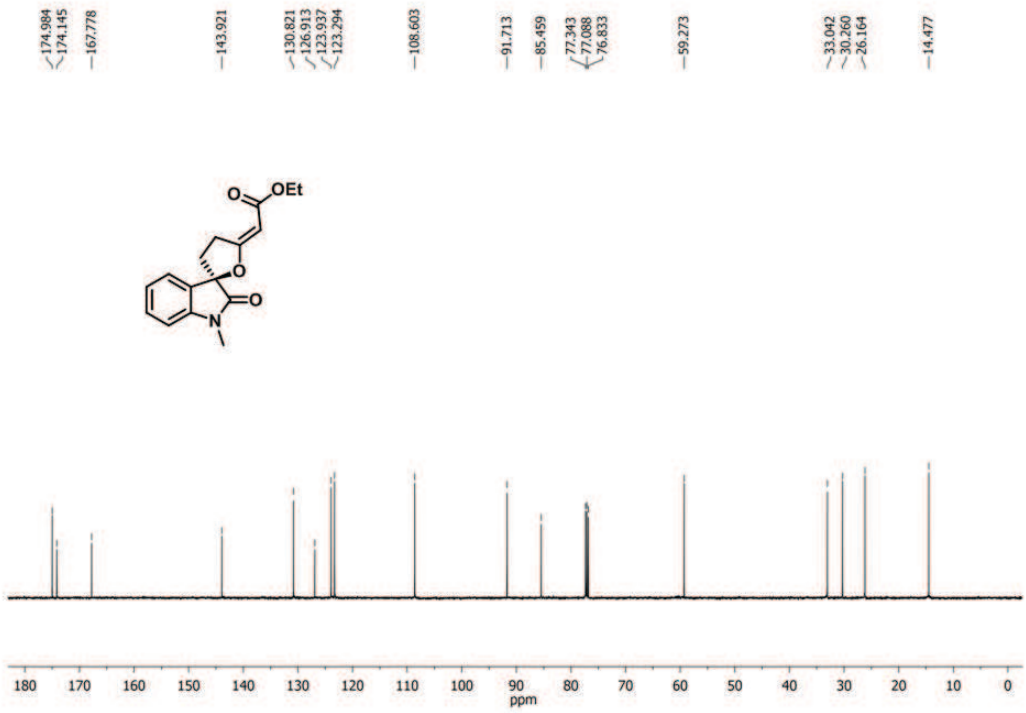
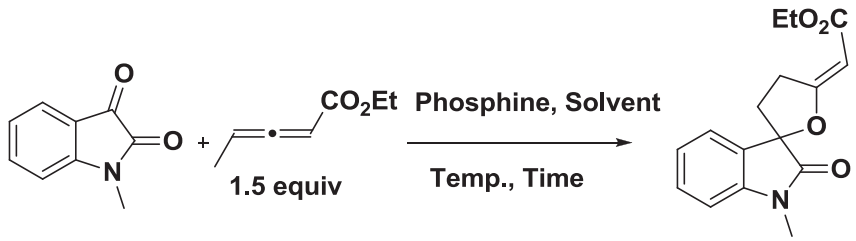


Figure 4b.4 ^{13}C NMR spectrum of compound 44

The facile synthesis of spirotetrahydrofuran under mild condition prompted us to study the reaction in some detail. The results of the optimization studies by varying different parameters are summarized in Table 4b.1.

Table 4b.1 Condition optimization



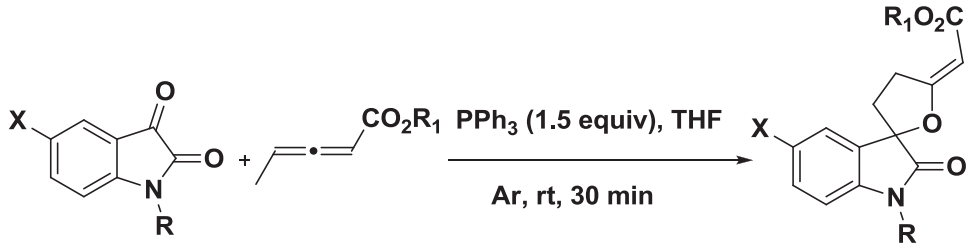
Entry	Phosphine	Solvent	Temp	Time (h)	Yield (%)
1	PPh_3(0.2 equiv)	THF	rt	2	54
2	PPh_3(0.5 equiv)	THF	rt	0.75	66
3	PPh_3(0.5 equiv)	THF	65 ^oC	0.5	78
4	PPh_3(1.5 equiv)	THF	rt	0.5	88
5	PPh_3(1.5 equiv)	DCM	rt	0.5	22
6	PPh_3(1.5 equiv)	Toluene	rt	0.5	32
7	PBu_3(1.5 equiv)	THF	rt	0.5	28
8	P(*o*-Tolyl)$_3$(1.5 equiv)	THF	rt	24	-

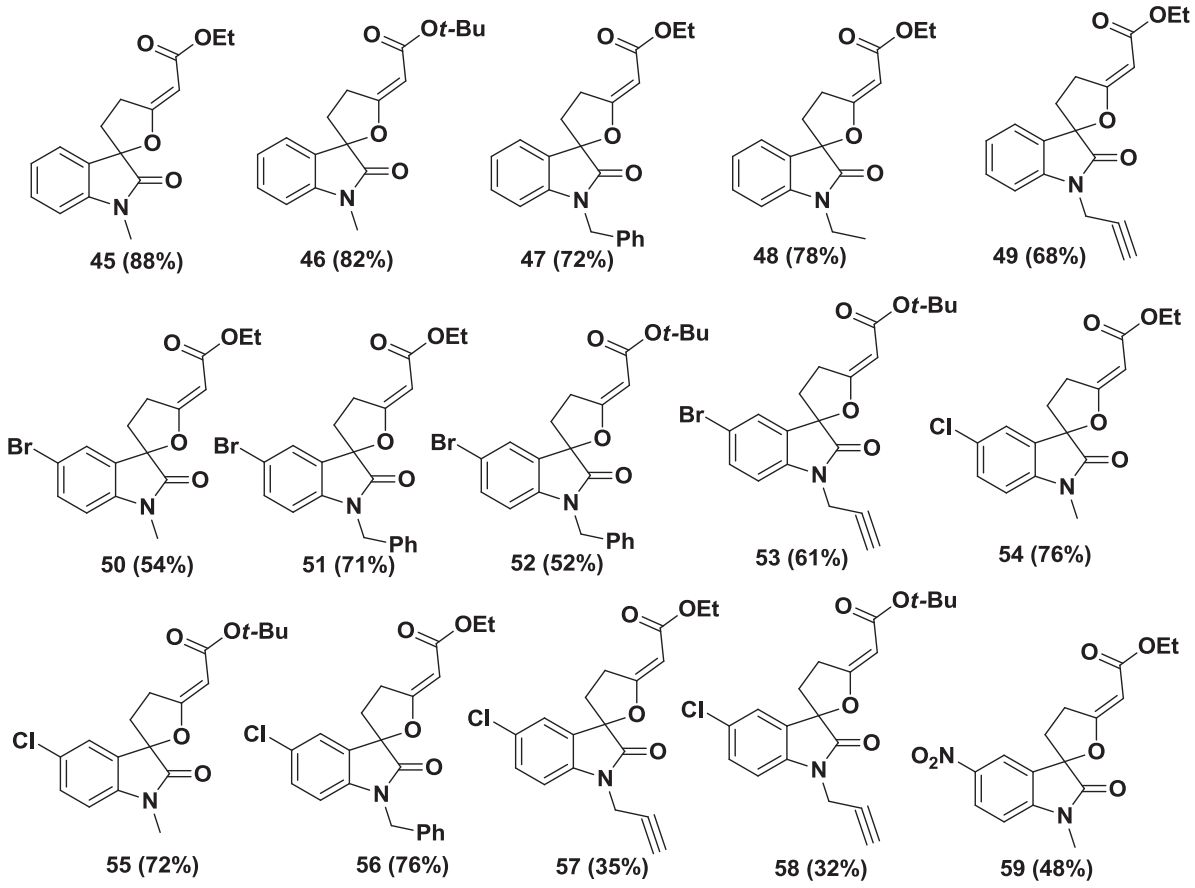
9	TDMPP(1.5 equiv)	THF	rt	24	-
10	$P(C_6F_5)_3$(1.5 equiv)	THF	rt	24	-
11	$P(Cy)_3$(1.5 equiv)	THF	rt	24	-

TDMPP = tris(2,6-dimethoxyphenyl)phosphine

From the above results, it is clear that the use of 1.5 equivalent of the allenoate and triphenyl phosphine furnished the product in 88% yield. After having optimized the reaction conditions, we examined the substrate scope using various isatins and allenoates and the results are presented in Table 2.

Table 4b.2 Scope of the reaction





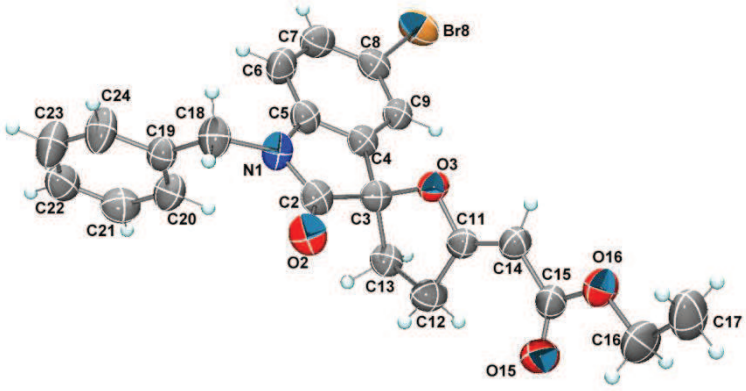
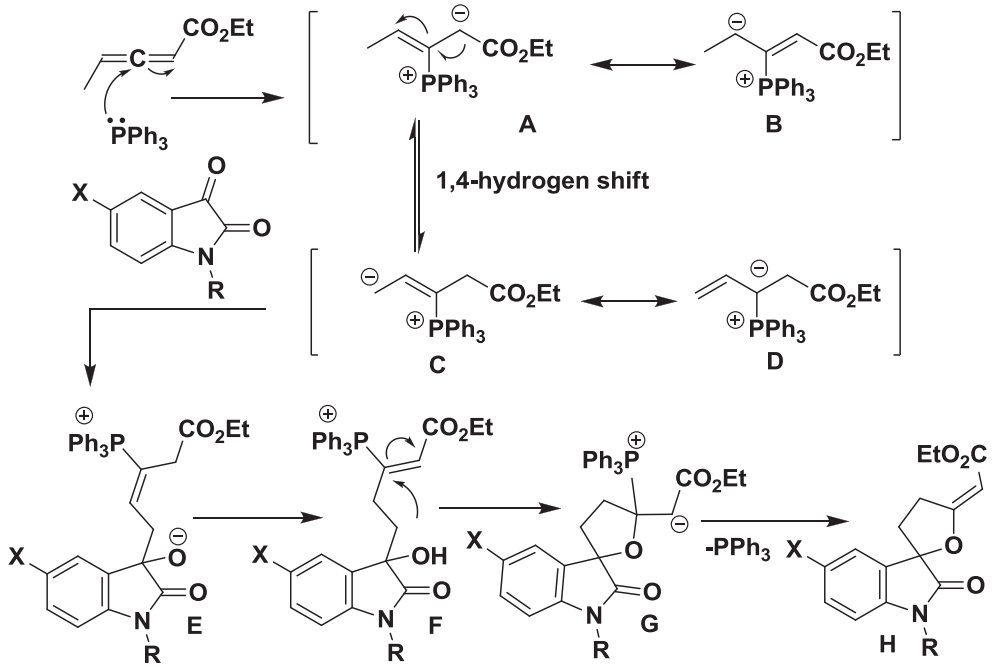


Figure 4b.5 ORTEP of compound **51**

4b.5 Mechanism

A mechanistic postulate invoked for the tetrahydrofuran synthesis described in chapter 3 (section 3.6) can be advanced here also. Conceivably, the initial event is the generation of zwitterion by the addition of triphenylphosphine to the 3-alkyl allenoate. The zwitterionic form **A** undergoes a [1,4] H-shift to form intermediate **C**. The latter then adds to the keto carbonyl of isatin to form **E**. This intermediate after proton transfer and cyclization yields the spiro tetrahydrofuran oxindole derivative **H** (Scheme 4b.14).



Scheme 4b.14

4b.6 Conclusion

In conclusion, a facile synthesis of spiro tetrahydrofuran oxindoles was developed by the reaction of allenoate-phosphine zwitterions with isatins. It is noteworthy that the spiro-oxindole motif is present in many biologically active natural and unnatural molecules and have potential pharmaceutical applications.

4b.7 Experimental Section

4b.7.1 General

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300/500 (^{1}H) and 75/126 (^{13}C) MHz respectively on Bruker Avance DPX-500S MHz NMR spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constant (*J*) is reported in Hertz (Hz). Mass spectra were recorded under HRMS (ESI) using Thermo Scientific Exactive Orbitrap mass spectrometer. IR spectra were recorded on a Bruker Alpha-T FT-IR spectrophotometer. Allenoates were prepared using known literature procedures.[23] Isatins were purchased from Sigma-Aldrich and the N-protection was carried out using known procedures.[24] Gravity column chromatography was performed using silica gel and mixtures of petroleum ether-ethyl acetate were used for elution.

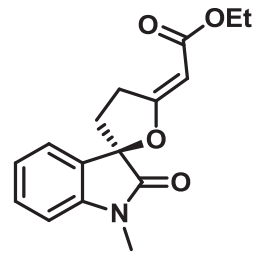
4b.7.2 General experimental procedure

4b.7.2.1 General procedure for the synthesis of spirotetrahydrofuran oxindole derivatives

A solution of the isatin (0.5 mmol) and the allenoate (0.75 mmol) in dry THF (5 ml) was taken in an R.B flask under argon atmosphere. To this solution triphenylphosphine (0.75 mmol) was added and stirred for 30 min. The crude product after removal of the solvent was purified by column chromatography using 100-200 silica gel and 85:15 hexane: ethyl acetate as the eluent afforded spirotetrahydrofuran oxindole derivative.

(*E*)-Ethyl 2-(1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)aceta te (45)

Following the general procedure, the reaction of N-methyl isatin (81 mg, 0.5 mmol), ethyl 3-methyl allenoate (95 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 88% (126 mg, 0.44 mmol) yield as pale yellow oil.



Yield: 126 mg (88%), pale yellow oil.

IR (film) ν_{max}: 1721, 1701, 1643, 1614, 1112, 1054 cm^{-1}.

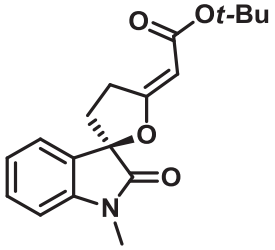
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.41 (s, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.56 – 3.52 (m, 2H), 3.18 (d, *J* = 1.5 Hz, 3H), 2.52 – 2.47 (m, 1H), 2.33 – 2.27 (m, 1H), 1.27 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.0, 174.1, 167.8, 143.9, 130.8, 126.9, 123.9, 123.3, 108.6, 91.7, 85.5, 59.3, 33.0, 30.3, 26.2, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{16}H_{17}NO_4Na^+$310.10553; Found: 310.10452.

(*E*)-*Tert*-butyl 2-(1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4H)-ylidene)acetate (46)

Following the general procedure, the reaction of N-methyl isatin (81 mg, 0.5 mmol), *tert*-butyl 3-methyl allenoate (116 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-*tert*-butyl 2-(1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 82% (129 mg, 0.41 mmol) yield as pale yellow oil.



Yield: 129 mg (82%), pale yellow oil.

IR (film) ν_{max}: 1726, 1698, 1644, 1615, 1109, 1057 cm^{-1}.

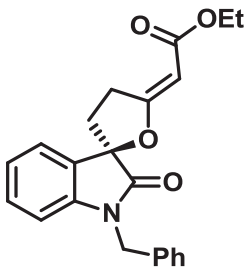
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.35 (s, 1H), 3.53 – 3.49 (m, 2H),3.19 (s, 3H), 2.52 – 2.46 (m, 1H), 2.32 – 2.25 (m, 1H), 1.48 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3, 173.9, 167.3, 143.9, 130.8, 127.1, 123.9, 123.3, 108.6, 93.5, 85.1, 79.1, 33.15, 30.0, 28.4, 26.2 ppm.

HRMS (ESI-MS) calcd for $C_{18}H_{21}NO_4Na^+$338.13683; Found: 338.13568.

(*E*)-Ethyl 2-(1'-benzyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate (47)

Following the general procedure, the reaction of N-benzyl isatin (119 mg, 0.5 mmol), ethyl 3-methyl allenoate (95 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(1'-benzyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 72% (131 mg, 0.36 mmol) yield as pale yellow oil.



Yield: 131 mg (72%), pale yellow oil.

IR (film) ν_{max}: 1718 (broad), 1647, 1614, 1113, 1053 cm^{-1}.

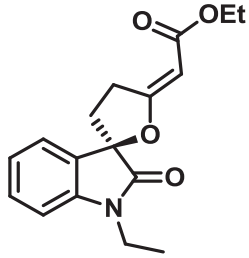
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.20 (m, 7H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.45 (s, 1H), 4.84 (q, *J* = 16.0 Hz, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.58 (t, *J* = 7.5 Hz, 2H), 2.58 – 2.53 (m, 1H), 2.36 – 2.30 (m, 1H), 1.27 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.0, 174.4, 167.8, 143.1, 135.1, 130.7, 128.9, 127.8, 127.2, 127.0, 124.1, 123.4, 109.7, 91.9, 85.5, 59.3, 43.8, 33.4, 30.3, 14.5ppm.

HRMS (ESI-MS) calcd for $C_{22}H_{21}NO_4Na^+$386.13683; Found: 386.13594.

(*E*)-Ethyl 2-(1'-ethyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate (48)

Following the general procedure, the reaction of N-ethyl isatin (88 mg, 0.5 mmol), ethyl 3-methyl allenoate (95 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(1'-ethyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetatein 78% (117 mg, 0.39 mmol) yield as pale yellow oil.



Yield: 117 mg (78%), pale yellow oil.

IR (film) ν_{max}: 1722 (broad), 1648, 1615, 1117, 1059 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.42 (s, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.73 (q, *J* = 7.0 Hz, 2H), 3.56 – 3.53 (m, 2H), 2.53 – 2.48 (m, 1H), 2.32 – 2.26 (m, 1H), 1.30 – 1.25 (m, 6H) ppm.

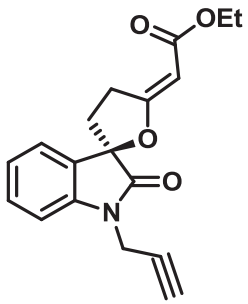
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.0, 173.8, 167.8, 143.0, 130.7, 127.2, 124.2, 123.1, 108.7, 91.7, 85.4, 59.2, 34.8,

33.1, 30.3, 14.5, 12.5 ppm.

HRMS (ESI-MS) calcd for $C_{17}H_{19}NO_4Na^+$324.12118; Found: 324.11960.

(*E*)-Ethyl 2-(2'-oxo-1'-(prop-2-ynyl)-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate (49)

Following the general procedure, the reaction of N-propargyl isatin (93 mg, 0.5 mmol), ethyl 3-methyl allenoate (95 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(2'-oxo-1'-(prop-2-ynyl)-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 68% (106 mg, 0.34 mmol) yield as pale yellow oil.



Yield: 106 mg (68%), colourless oil.

IR (film) ν_{max}: 1719 (broad), 1648, 1614, 1112, 1055 cm^{-1}.

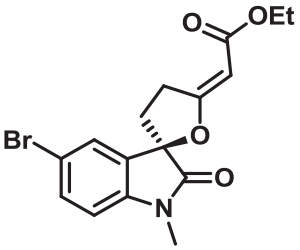
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 5.35 (s, 1H), 4.55 (dd, J_1 = 17.5 Hz, J_2 = 1.5 Hz, 1H), 4.36 (dd, J_1 = 18.0 Hz, J_2 = 2.0 Hz, 1H), 3.52 – 3.49 (m, 2H), 2.54 – 2.49 (m, 1H), 2.33 – 2.23 (m, 2H), 1.48 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$):δ 173.7, 173.4, 167.2, 142.0, 130.7, 127.1, 124.0, 123.7, 109.7, 93.7, 85.1, 79.1, 76.3, 72.9, 33.4, 29.9, 29.3, 28.4 ppm.

HRMS (ESI-MS) calcd for$C_{18}H_{17}NO_4Na^+$334.10553; Found: 334.10498

(*E*)-Ethyl 2-(5'-bromo-1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene) acetate (50)

Following the general procedure, the reaction of N-methyl 5-bromoisatin (120 mg, 0.5 mmol), ethyl 3-methyl allenoate (95 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(5'-bromo-1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 54% (99 mg, 0.27 mmol) yield as pale yellow oil.



Yield: 99 mg (54%), pale yellow oil.

IR (film) ν_{max}: 1729, 1705, 1650, 1612, 1118, 1059 cm^{-1}.

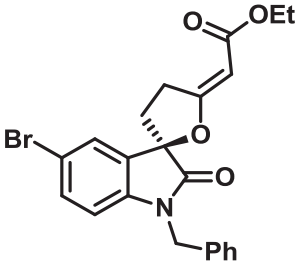
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.5 Hz, 1H), 7.40 (s, 1H), 6.71 (t, *J* = 8.0 Hz, 1H), 5.41 (s, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.55 – 3.52 (m, 2H), 3.18 (s, 3H), 2.53 – 2.48 (m, 1H), 2.32 – 2.26 (m, 1H), 1.29 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 173.6, 167.6, 142.9, 133.5, 129.1, 127.3, 115.9, 109.9, 92.2, 84.9, 59.4, 33.2, 30.1, 26.3, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{16}H_{16}BrNO_4Na^+$388.01604; Found: 388.01486.

(*E*)-Ethyl 2-(1'-benzyl-5'-bromo-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene) acetate (51)

Following the general procedure, the reaction of N-benzyl 5-bromoisatin (158 mg, 0.5 mmol), ethyl 3-methyl allenoate (95 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(1'-benzyl-5'-bromo-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 71% (157 mg, 0.36 mmol) yield as colourless solid.



Yield: 157 mg (71%), colourless solid (mp 132-133 ^oC).

IR (film) ν_{max}: 1734 (broad), 1651, 1265, 1118 cm^{-1}.

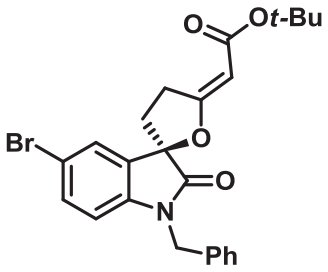
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.20 (m, 7H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.45 (s, 1H), 4.89 – 4.81 (m, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.59 – 3.56 (m, 2H), 2.58 – 2.53 (m, 1H), 2.36 – 2.30 (m, 1H), 1.27 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$):δ 174.4, 173.9, 167.7, 142.0, 134.6, 133.5, 129.0, 128.0, 127.4, 127.2, 116.1, 111.2, 92.3, 85.1, 59.5, 43.9, 33.5, 30.1, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{22}H_{20}BrNO_4Na^+$464.04734; Found: 464.04697.

(*E*)-*Tert*-butyl 2-(1'-benzyl-5'-bromo-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate (52)

Following the general procedure, the reaction of N-benzyl 5-bromoisatin (158 mg, 0.5 mmol), *tert*-butyl 3-methyl allenoate (116 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-*tert*-butyl 2-(1'-benzyl-5'-bromo-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetatein 52% (122 mg, 0.26 mmol) yield as colourless solid.



Yield: 122 mg (52%), pale yellow solid (mp 40-42^{o}C).

IR (film) ν_{max}: 1734 (broad), 1651, 1265, 1114 cm^{-1}.

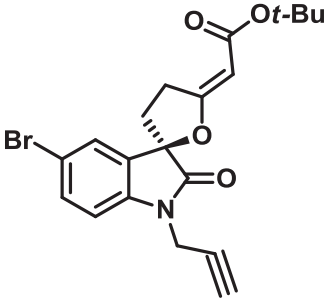
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, J = 7.0 Hz, 1H), 7.36 – 7.31 (m, 3H), 7.29 – 7.27 (m, 1H), 7.25 – 7.23 (m, 2H), 6.57 (d, J = 8.5 Hz, 1H), 5.39 (t, J = 1.5 Hz, 1H), 4.88 – 4.80 (m, 2H), 3.56 – 3.52 (m, 2H), 2.59 – 2.54 (m, 1H), 2.35 – 2.29 (m, 1H), 1.49 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 173.4, 167.2, 142.0, 134.6, 133.4, 129.3 129.0, 128.0, 127.4, 127.2, 116.1, 111.1, 94.1, 84.8, 79.3, 43.9, 33.6, 29.9, 28.4ppm.

HRMS (ESI-MS) calcd for $C_{24}H_{24}BrNO_4Na^+$ 492.07864; Found: 492.07806

(*E*)-*Tert*-butyl 2-(5'-bromo-2'-oxo-1'-(prop-2-ynyl)-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate (53)

Following the general procedure, the reaction of N-propargyl 5-bromoisatin (132 mg, 0.5 mmol), *tert*-butyl 3-methyl allenoate (116 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-*tert*-butyl 2-(5'-bromo-2'-oxo-1'-(prop-2-ynyl)-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetatein 61% (127 mg, 0.31 mmol) yield as yellow solid.



Yield: 127 mg (61%), yellow solid (mp 55-57^{o}C).

IR (film) ν_{max}: 1737, 1702, 1649, 1265, 1114 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 5.36 (t, J = 1.5 Hz, 1H), 4.54 (dd, J_1 = 17.5 Hz, J_2 = 2.5 Hz, 1H), 4.36 (dd, J_1 = 18.0 Hz, J_2 = 2.5 Hz, 1H), 3.52

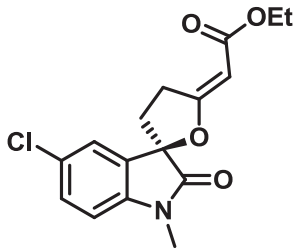
– 3.48 (m, 2H), 2.55 – 2.50 (m, 1H), 2.32 – 2.25 (m, 1H), 1.49 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.2, 173.0, 167.1, 141.0, 133.5, 129.1, 127.4, 116.4, 111.3, 94.1, 84.7, 79.4, 75.85, 73.28, 33.5, 29.8, 29.5, 28.4ppm.

HRMS (ESI-MS) calcd for $C_{20}H_{20}BrNO_4Na^+$440.04734; Found: 440.04630.

(*E*)-Ethyl 2-(5'-chloro-1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene) acetate (54)

Following the general procedure, the reaction of N-methyl 5-chloroisatin (98 mg, 0.5 mmol), ethyl 3-methyl allenoate (95 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(5'-chloro-1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 76% (122 mg, 0.38 mmol) yield as colourless oil.



Yield: 122 mg (76%), colourless oil.

IR (film) ν_{max}: 1726, 1701, 1646, 1613, 1113, 1056 cm^{-1}.

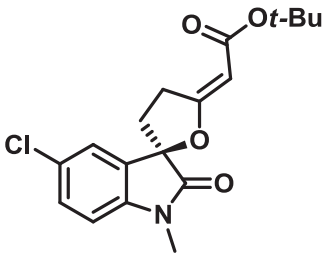
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.5 Hz, 1H), 7.28 (s, 1H), 6.77 (t, *J* = 8.0 Hz, 1H), 5.42 (s, 1H), 4.16 (q, *J* = 8.0 Hz, 2H), 3.55 – 3.52 (m, 2H), 3.18 (s, 3H), 2.54 – 2.49 (m, 1H), 2.33 – 2.26 (m, 1H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 173.8, 167.7, 142.4, 130.7, 128.8, 128.6, 124.6, 109.6, 92.2, 85.1, 59.4, 33.2, 30.1, 26.4, 14.5ppm.

HRMS (ESI-MS) calcd for $C_{16}H_{16}ClNO_4Na^+$344.06656; Found: 344.06512.

(*E*)-*Tert*-butyl 2-(5'-chloro-1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate (55)

Following the general procedure, the reaction of N-methyl 5-chloroisatin (98 mg, 0.5 mmol), *tert*-butyl 3-methyl allenoate (116 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-*tert*-butyl 2-(5'-chloro-1'-methyl-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 72% (126 mg, 0.36 mmol) yield as colourless oil.



Yield: 126 mg (72%), colourless oil.

IR (film) ν_{max}: 1728, 1702, 1648, 1613, 1110, 1059 cm^{-1}.

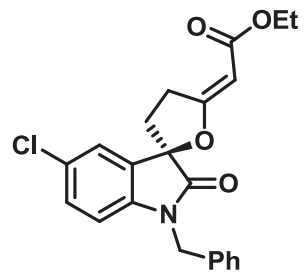
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 7.26 (s, 1H), 6.76 (d, J = 8.5 Hz, 1H), 5.34 (s, 1H), 3.52 – 3.48 (m, 2H),3.18 (s, 3H), 2.52 – 2.47 (m, 1H), 2.30 – 2.24 (m, 1H), 1.48 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 173.4, 167.1, 142.4, 130.5, 129.0, 128.8, 124.6, 109.5, 93.9, 84.7, 79.2, 33.3, 29.8, 28.4, 26.3ppm.

HRMS (ESI-MS) calcd for $C_{18}H_{20}ClNO_4Na^+$372.09786; Found: 372.09601.

(*E*)-Ethyl 2-(1'-benzyl-5'-chloro-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate (56)

Following the general procedure, the reaction of N-benzyl 5-chloroisatin (136 mg, 0.5 mmol), ethyl 3-methyl allenoate (95 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(1'-benzyl-5'-chloro-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 76% (151 mg, 0.38 mmol) yield as yellow solid.



Yield: 151 mg (76%), yellow solid (mp123-125^{o}C).

IR (film) ν_{max}: 1732, 1708, 1650, 1264, 1117 cm^{-1}.

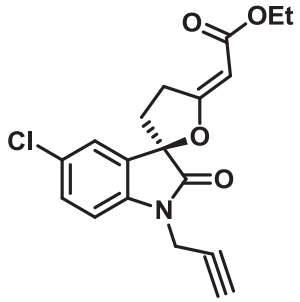
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.31 (m, 2H), 7.29 – 7.28 (m, 2H), 7.21 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 5.47(t, J = 2.0 Hz, 1H),4.89 – 4.81 (m, 2H), 4.17 (dq, J_1 = 7.0 Hz, J_2 = 2.0 Hz, 1H), 3.60 – 3.56 (m, 2H),2.61 – 2.56 (m, 1H), 2.37 – 2.31 (m, 1H), 1.29 (t, J = 7.0 Hz, 3H)ppm.

^{13}C NMR (126 MHz, $CDCl_3$):^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 174.0, 167.7, 141.5, 134.7, 130.6, 129.0, 128.90, 128.7, 128.0, 127.2, 124.7, 110.7, 92.3, 85.1, 59.4, 43.9, 33.5, 30.1, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{22}H_{20}ClNO_4Na^+$420.09786;Found: 420.09720.

(*E*)-Ethyl 2-(5'-chloro-2'-oxo-1'-(prop-2-ynyl)-3H-spiro[furan-2,3'-indoline]-5(4H)-ylidene)acetate (57)

Following the general procedure, the reaction of N-propargyl 5-chloroisatin (110 mg, 0.5 mmol), ethyl 3-methyl allenoate (95 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(5'-chloro-2'-oxo-1'-(prop-2-ynyl)-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 35% (61 mg, 0.18 mmol) yield as colourless oil.



Yield: 61 mg (35%), colourless oil.

IR (film) ν_{max}: 1731, 1703, 1649, 1262, 1115 cm^{-1}.

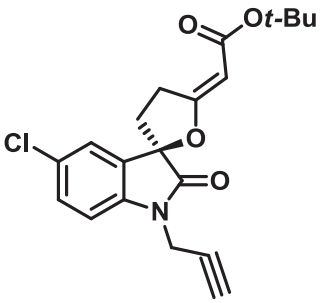
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, J_1 = 8.3 Hz, J_2 = 2.5 Hz, 1H),7.31 (d, J = 2.0 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 5.44 (t, J = 1.5 Hz, 1H), 4.54 (dd, J_1 = 18.0 Hz, J_2 = 2.5 Hz, 1H),4.37 (dd, J_1 = 17.5 Hz, J_2 = 2.5 Hz, 1H), 4.16 (dq, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 2H), 3.56 – 3.52 (m, 2H),2.57 – 2.52 (m, 1H),2.34 – 2.27 (m, 2H), 1.29 (t, J = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3, 172.9, 167.7, 140.5, 130.7, 129.3, 128.5, 124.7, 110.8, 92.4, 85.0, 75.9, 73.3, 59.5, 33.4, 30.00, 29.5, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{18}H_{16}ClNO_4Na^+$ 368.06656; Found: 368.06601.

(*E*)-*Tert*-butyl 2-(5'-chloro-2'-oxo-1'-(prop-2-ynyl)-3H-spiro[furan-2,3'-indoline]-5(4H)-ylidene)acetate (58)

Following the general procedure, the reaction of N-propargyl 5-chloroisatin (110 mg, 0.5 mmol), *tert*-butyl 3-methyl allenoate (116 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-*tert*-butyl 2-(5'-chloro-2'-oxo-1'-(prop-2-ynyl)-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 32% (60 mg, 0.16 mmol) yield as colourless oil.



Yield: 60 mg (32%), colourless oil.

IR (film) ν_{max}: 1732, 1699, 1649, 1255, 1111 cm^{-1}.

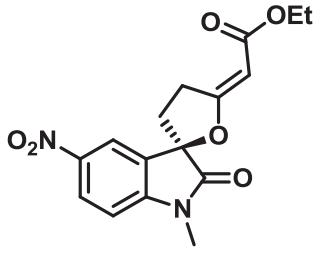
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H),7.29 (d, J = 2.0 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 5.36 (t, J = 1.5 Hz, 1H), 4.54 (dd, J_1 = 17.5 Hz, J_2 = 2.5 Hz, 1H),4.36 (dd, J_1 = 17.5 Hz, J_2 = 2.5 Hz, 1H), 3.52 – 3.48 (m, 2H),2.55 – 2.50 (m, 1H),2.32 – 2.25 (m, 2H), 1.49 (s, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ173.2, 173.0, 167.1, 140.4, 130.6, 129.3, 128.8, 124.6, 110.8, 94.1, 84.7, 79.3, 75.9, 73.3, 33.5, 29.7, 29.5, 28.4.

HRMS (ESI-MS) calcd for $C_{20}H_{20}ClNO_4Na^+$ 396.09786; Found: 396.09694.

(*E*)-Ethyl 2-(1'-methyl-5'-nitro-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate (59)

Following the general procedure, the reaction of N-methyl 5-nitroisatin (115 mg, 0.5 mmol), ethyl 3-methyl allenoate (95 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) afforded (*E*)-ethyl 2-(1'-methyl-5'-nitro-2'-oxo-3*H*-spiro[furan-2,3'-indoline]-5(4*H*)-ylidene)acetate in 48% (80 mg, 0.24 mmol) yield as colourless oil.



Yield: 80 mg (48%), colourless oil.

IR (film) ν_{max}: 1740, 1707, 1656, 1618, 1115, 1064 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 8.19 (d, J = 1.0 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 5.43 (s, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.62 – 3.51 (m, 2H),3.28 (s, 3H), 2.58 – 2.52 (m, 1H), 2.41 – 2.35 (m, 1H), 1.29 (t, J = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3, 173.8, 167.4, 149.3, 144.0, 127.9, 127.7, 120.1, 108.2, 92.7, 84.2, 59.5, 33.2, 29.9, 26.7, 14.5 ppm.

HRMS (ESI-MS) calcd for $C_{16}H_{16}N_2O_6Na^+$355.09061; Found: 355.08923.

4b.8 References

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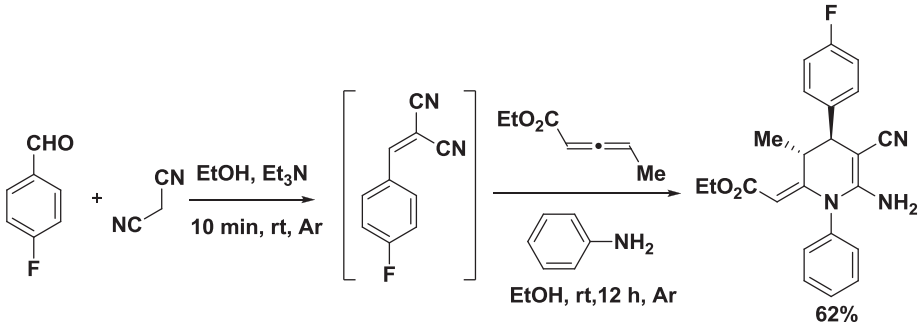
SUMMARY

The thesis entitled "**Novel Synthesis of Carbocycles and Heterocycles Employing Zwitterions Derived from Allenic Esters**" embodies the results of the investigations carried out to explore the reactivity of the transient zwitterions generated *in situ* from allenic esters and nucleophiles such as amine and phosphine toward various electrophiles. In this regard, an overview of the chemistry of zwitterions with special emphasis on the reactions of allenoate-phosphine zwitterions and a general introduction to multicomponent reactions are provided in the first chapter of the thesis.

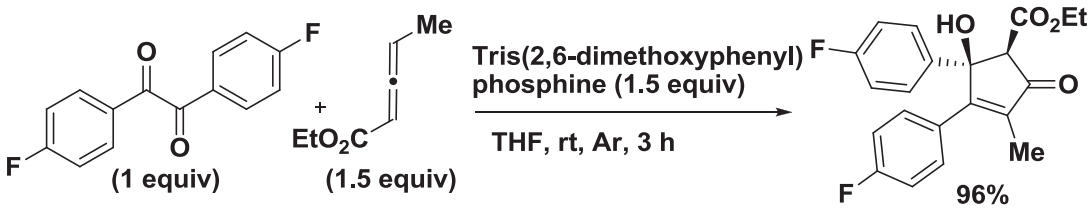
Even though the design and development of multicomponent reactions (MCRs) has emerged as an important synthetic strategy, those involving allenoate was not extensively studied. In view of this, we studied the reaction of the zwitterion derived from allenoate and a primary amine, aniline, and the results constitute the subject matter of chapter 2. The allenoate-aniline zwitterion adds to the dicyanostyrene, generated *in situ* by the condensation of aldehyde and malononitrile in presence of triethylamine. The reaction yielded dihydropyridine derivatives in good yields. An illustrative example is shown in Scheme 1.



Scheme 1

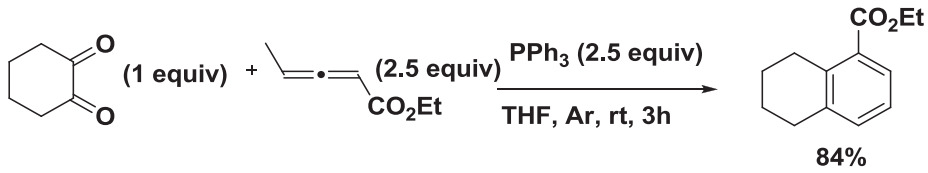
In the context of our long term interest in the chemistry of zwitterions as well as 1,2-diones, it was of interest to explore the reactivity of allenoate-phosphine zwitterions towards the latter, a class of uniquely reactive compounds. The reaction of 4,4′-difluorobenzil with 3-alkyl allenoates in presence of tris(2,6-dimethoxyphenyl)phosphine afforded fully substituted cyclopentenone in 96%

yield (Scheme 2). The results of the detailed invetigations are described in chapter 3.



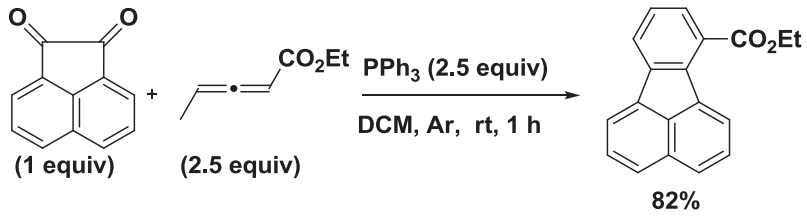
Scheme 2

Against this background, it was of interest to explore the reactivity of phosphine-3-alkyl allenoate-zwitterion towards cyclic 1,2-diones including *o*-quinones and the results are included in the first part of fourth chapter. When cyclohexane-1,2-dione was exposed to ethyl 3-methyl allenoate and triphenylphosphine, a completely different reaction manifested and the resulting product was characterized as ethyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate (Scheme 3).



Scheme 3

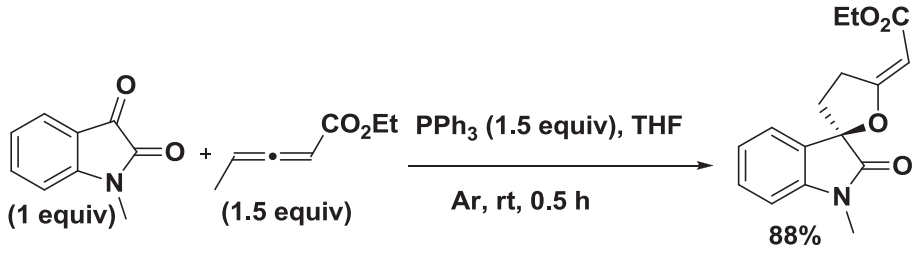
With a view to understand the effectiveness of this benzannulation reaction towards the synthesis of polyaromatic systems of practical value, we investigated the reactivity of the same zwitterion with *o*-quinones. With acenaphthene quinones, the reaction proceeded well to afford the respective benzannulated products in good yields. The reaction of acenaphthene quinone with 3-methyl allenoate in presence of triphenyl phosphine furnished fluoranthene-7-carboxylate in 82% yield (Scheme 4).



Scheme 4

This reaction constitutes the first example of the phosphine-3-alkyl allenoate zwitterion playing the role of four carbon synthon in benzannulation. In view of the well-known fluorescent properties and the potential applications of fluoranthenes in OLEDs, some preliminary studies on photophysical properties of the representative compounds were carried out and the results are included in the thesis.

The interesting results obtained with *o*-quinones prompted us to investigate the reaction of phosphine-3-alkyl allenoate zwitterion with other cyclic 1,2-dicarbonyl compounds. Second part of chapter 4 deals with the reaction of 3-methyl allenoate-triphenylphosphine zwitterions with N-protected isatins. The reaction led to the facile synthesis of spirotetrahydrofuran oxindole derivatives in moderate to good yields (Scheme 5).



Scheme 5

List of Publications

1. Reactions of Morita-Baylis-Hilman acetates with Huisgen Zwitterions-A novel strategy for the synthesis of β-aminoacid derivatives. **Jose, A**.; Paul, R. R.; Mohan, R; Mathew, S. C.; Biju, A.T.; Suresh, E.; Nair, V. *Synthesis* **2009**, 1829.
2. Novel Nucleophilic Heterocyclic Carbene Mediated Stereoselective Conjugate Addition of Enals to Nitrostyrenes via Homoenolate. Nair, V.; Sinu, C. R.; Babu, B. P.; Varghese, V.; **Jose, A**., Suresh, E. *Org. lett*. **2009**, *11*, 5570.
3. NHC Catalyzed Transformation of Aromatic Aldehydes to Acids by Carbon Dioxide: An Unexpected Reaction. Nair, V.; Varghese, V.; Paul, R. R.; **Jose, A**.; Sinu, C.R.; Menon, R. S. *Org. Lett.* **2010**, *12*, 2653.
4. Employing homoenolates generated by NHC catalysis in carbon-carbon bond-forming reactions: State of the art. Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; **Jose, A**.; Sreekumar, V. *Chem. Soc. Rev*. **2011**, *40*, 5336.
5. N-Heterocyclic carbene (NHC) catalyzed annulation of enals and vinyl ketones: A novel synthesis of [2H]-pyranones. Nair, V.; Paul, R.R.; Seetha Lakshmi, K.C.; Menon, R.S.; **Jose, A**.; Sinu, C.R. *Tetrahedron Letters.* **2011**, *52*, 5992.
6. NHC-catalyzed annulation of enals and chalcones: Further explorations on the novel synthesis of 1,3,4-trisubstituted cyclopentenes. Nair, V.; Paul, R. R.; Padmaja, D.V.M.; Aiswarya, N.; Sinu, C.R.; **Jose, A.** *Tetrahedron* **2011**, *67*, 9885-9889.
7. A Facile Four-Component Protocol for the Synthesis of Dihydropyridine Derivatives. Nair, V., **Jose, A**.; Seetha Lakshmi, K. C.; Rajan, R.; Suresh, E. *Org. Biomol. Chem.* **2012**, *10*, 7747.
8. Phosphine-Mediated Reaction of 3−Alkyl Allenoates and Diaryl 1,2-diones: Efficient Diastereoselective Synthesis of Fully Substituted Cyclopentenones. **Jose, A**.; Seetha Lakshmi, K. C.; Suresh E.; Nair, V. *Org. Lett.* **2013**, *15*, 1858.
9. Phosphine Mediated Reaction of Cyclic 1,2-Diones and 3-Alkyl Allenoates: An Efficient Protocol for Benzannulation Applicable to the Synthesis of Polycyclic Aromatic Hydrocarbons. **Jose, A**.; Jayakrishnan, A. J.; Vedhanarayanan, B.; Menon, R. S.; Varughese, S.; Suresh E.; Nair V. *Chem. Comm*. **2014**, 4616.
10. Reactions of Phosphine-3-Alkyl Allenoate Zwitterions with Isatins : A Facile Entry to Spiro Tetrahydrofuran Oxindoles. **Jose, A**.; Jayakrishnan, A. J.; Seetha Lakshmi, K. C.; Varughese, S.; Nair V. (To be communicated to *J. Org. Chem*.)

Posters presented at symposia

1. NHC Catalyzed Transformation of Aromatic Aldehydes to Acids by Carbon Dioxide. **Jose**, **A.**; Varghese, V.; Nair, V. *Recent Trends in Organic Synthesis (RTOS 2011),* Bharathidasan University, Tiruchirappalli, February 24-26, 2011, P #52.
2. A Facile Four Component Protocol for the Synthesis of Dihydropyridine Derivatives. **Jose**, **A.**; Rejithamol R., Nair, V.; *International Conference on Heterocyclic Chemistry (ICHC 2011),* Jaipur, December 10-13**,** 2011, P #24.
3. A Novel Multicomponent Reaction for the Synthesis of Dihydropyridine Derivatives, **Jose, A.**; K. C. Seetha Lakshmi, Nair, V. *Current Trends in Drug Discovery Research (CTDDR-2013)*, CSIR-CDRI, Lucknow, February 26-28, 2013, P #7.