Exploration of Novel Organic Reactions Catalyzed by Nucleophilic Heterocyclic Carbenes (NHCs)

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November 2014

…..to my Brother Binu C. R. and my Parents

DECLARATION

I hereby declare that the Ph. D. thesis entitled "**Exploration of Novel Organic Reactions Catalyzed by Nucleophilic Heterocyclic Carbenes (NHCs)**" is an independent work carried out by me and it has not been submitted anywhere else for any other degree, diploma or title.

Sinu C. R.

Trivandrum
November, 2014

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CERTIFICATE

This is to certify that the work embodied in the thesis entitled "**Exploration of Novel Organic Reactions Catalyzed by Nucleophilic Heterocyclic Carbenes (NHCs)**" has been carried out by **Mr. Sinu C. R.** 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 **Mr. Sinu C. R.** have been incorporated in the thesis.

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PREFACE

Organocatalysis can be defined as the acceleration of chemical reactions by the addition of a substoichiometric quantity of organic compound which does not contain an inorganic element. Organocatalysis has several advantages over transition metal catalysis and enzymatic transformations. Presently organocatalysis is an area of great interest in synthetic organic chemistry. The catalysts are usually robust, inexpensive and readily available small organic molecules. In this scenario, *N*-heterocyclic carbenes (NHCs) have been studied for their ability to catalyze organic reactions. In recent years NHCs have assumed importance due to the progress made in umpolung reactivity of aldehydes and especially in generating homoenolates, a species containing anionic carbon β- to a carbonyl group. Several research groups including our own have employed this three carbon synthon in the synthesis of various carbo– and heterocycles.

In the context of our continuing interest in the chemistry of NHCs, we have carried out a detailed and systematic investigation of the reactivity of the homoenolate, generated in situ from enals and NHCs, towards various electrophiles. The results of our studies in this direction constitute the subject matter of the thesis entitled "**Exploration of Novel Organic Reactions Catalyzed by Nucleophilic Heterocyclic Carbenes (NHCs)**".

The thesis is composed of five chapters which are presented as independent units and therefore the structure formulae, schemes, figures and references are numbered chapterwise.

Exploration of the reactivity of NHC-bound homoenolate towards various electrophiles for the construction of novel carbon-carbon and carbon-heteroatom bonds was selected as the general theme of this thesis. To put things in perspective, an overview of the chemistry of NHCs and homoenolates is provided in the first chapter of the thesis and the definition of the present research problem is also provided in this chapter.

The second chapter presents the results of our investigations of the reaction of homoenolate, generated from enal by NHC, with various substituted

nitrostyrenes. General information on the experimental procedures is given in this chapter.

The reaction of NHC with chromene-3-carboxaldehye, which revealed a novel reactivity pattern, constitutes the subject matter of the third chapter of the thesis. Our original objective was to extend the homoenolate generation to endocyclic systems, but the reaction took an unexpected path leading to an efficient synthesis of 3-alkylcoumarins.

The results of our investigations on the intramolecular reaction of NHC-homoenolate with α,β-unsaturated esters, leading to the facile synthesis of 4-alkylcoumarin derivatives are disclosed in the fourth chapter.

The final chapter describes an unexpected transformation of 1,6-disubstituted hexa-1,5-diene-3,4-diones (Cinnamils) catalyzed by NHCs to vinylfulvenes and terphenyls.

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

ABBREVIATIONS

Ac : acetyl

Ad : adamantyl

Ar : argon

Ar- : aryl

atm : atmosphere

Bn : benzyl

calcd. : calculated

CCDC : cambridge crystallographic data centre

Cy : cyclohexyl

d : doublet

DABCO : 1,4-diazabicyclo[2.2.2]octane

DBU : 1,8-diazabicyclo[5.4.0]undec-7-ene

dd : doublet of doublets

ddd : doublet of doublets of doublets

DEAD : diethyl azodicarboxylate

dil : dilute

DMAP : 4-dimethylaminopyridine

DME : dimethoxyethane

DMF : dimethylformamide

DMSO : dimethyl sulfoxide

dr : diastereomeric ratio

ee : enantiomeric excess

EI : electron ionization

equiv : equivalent

ESI : electron spray ionization

Et : ethyl

Et_3N : triethylamine

EtOAc : ethyl acetate

FAB : fast atom bombardment

FT-IR : Fourier transform infrared spectroscopy

h : hour

HRMS : high-resolution mass spectrometry

Hz : Hertz

Imes : 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene

i-Pr : isopropyl

i-PrOH : isopropanol

IR : infrared

J : coupling constant

KHMDS : potassium hexamethyldisilazide

LiHMDS : lithium hexamethyldisilazide

LRMS : low resolution mass spectrometry

m : multiplet

M : molar

m : meta

m p : melting point

Me : methyl

MeCN : acetonitrile

MeOH : Methanol

Mes : 2,4,6-trimethylphenyl

mg : milligram

min : minute

mL : milliliter

mmol : millimolar

mol : mole

mol % : mole percent

MOM : methoxymethyl

MS : molecular sieves

MW : microwave

NHCs : *N*-heterocyclic carbenes

NMM : *N*-methylmorpholine

NMR : nuclear magnetic resonance

o : ortho

p : para

pet ether : petroleum ether

Ph : phenyl

PhMe : toluene

PMP : 4-Methoxyphenyl

PTSA : *p*-Toluenesulfonic acid

q : quartet

rt : room temperature

s : singlet (spectra), second (scheme)

t : triplet

TBAT : tetrabutylammonium triphenyldifluorosilicate

TBD : 1,5,7-Triazabicyclo[4.4.0]dec-5-ene

TBDPS : tert-butyldiphenylsilyl

t-Bu : tertiary butyl

TCT : 2,4,6-trichloro-1,3,5-triazine

TEA : triethylamine

tert : tertiary

THF : tetrahydrofuran

TLC : thin layer chromatography

TMEDA : tetramethyl ethylenediamine

tol : tolyl (4-methylphenyl)

δ : NMR chemical shift in parts per million

CHAPTER 1

Chemistry of *N*-Heterocyclic Carbenes and Homoenolates: An Introduction

1.1. Introduction

Carbenes are neutral divalent carbon species with six valence electrons. Investigations carried out by Staudinger on the decomposition of diazo compounds can be considered as the preliminary work in the field of methylenes (original name for carbenes).[1] The development in carbene chemistry began when Doering introduced carbenes to organic chemistry in 1950s.[2] Since then, these fascinating species have played a crucial role in many important synthetic organic reactions. Depending on the spin multiplicity, carbenes are classified into singlet and triplet states. Singlet carbenes feature a filled and a vacant orbital, thereby showing ambiphilic character while triplet carbenes have two singly occupied orbitals and are generally regarded as diradicals (Figure 1.1).

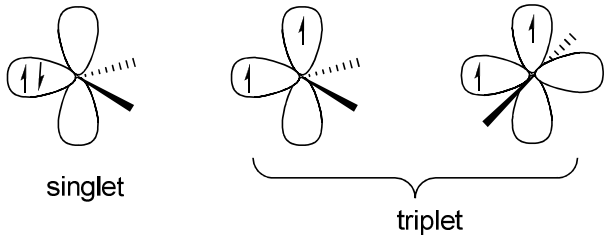
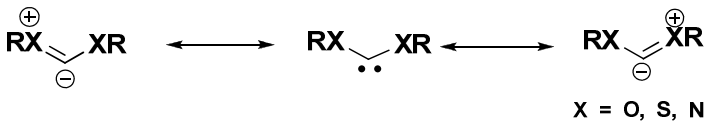


Figure 1.1. Spin multiplicity of carbenes

Nucleophilic carbenes are characterized by the presence of heteroatoms such as oxygen, nitrogen and sulfur. These heteroatoms are capable of donating their lone pair electrons to the vacant p-orbitals of carbene carbon. This lone pair electron donation brings nucleophilicity to the carbene species and strongly stabilizes the singlet state and imparts dipolar character (Scheme 1.1).



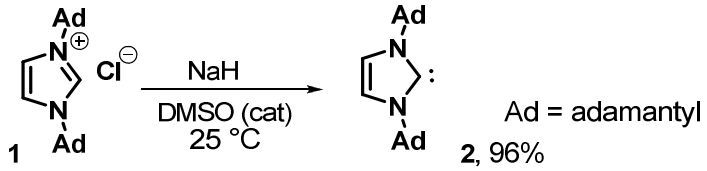
Scheme 1.1

Among various nucleophilic carbenes, *N*-heterocyclic carbenes (NHCs) are the most widely studied ones. Due to their steric and electronic properties, NHCs are a rapidly growing area of research in transition metal chemistry[3] and in synthetic organic

chemistry.[4] Due to the excellent σ-donating properties and their close resemblance to trialkyl phosphines, NHCs are well exploited as ligands for transition metals. The stability of the transition metal complexes of *N*-heterocyclic carbenes is often cited as one of the key advances of these ligands versus their phosphine counterparts. NHC-incorporated organometallic catalysts[5] are found to be much more effective than conventional catalysts in many reactions, including Heck reaction,[6] olefin metathesis,[7] and a number of coupling reactions.[8] This allows the constitution of organometallic catalysts of enormous utility in organic synthesis.[9] Recently, chemists are more interested in exploring the utility of NHCs as nucleophilic reagents and organocatalysts.[10] Presently NHCs occupy a distinguished position both as a reagent and catalyst in organic synthesis.[11] The focal theme of the present thesis is exploration of novel reactions catalyzed by NHCs. Therefore, in this introductory chapter, after a brief history of *N*-heterocyclic carbenes, an overview of NHC catalysis is presented.

1.2. History of *N*-Heterocyclic Carbenes (NHCs)

The origin of NHC catalysis can be traced to the preliminary experiments of Ugai as well as Mizuhara.[12,13] Ugai found that, instead of cyanide ions thiazolium salts can be used for the benzoin condensation. From his studies Mizuhara identified that, catalytic property of natural thiamine is based on the thiazolium unit present. In 1958, Breslow presented a mechanism for the thiamine action in benzoin condensation.[14] In his proposal he demonstrated that a thiazol-2-ylidene, a carbene is the catalytically active species. This thiazol-2-ylidene belongs to the class of *N*-heterocyclic carbene. Subsequently, several attempts were made to isolate stable carbenes. In the 1960s Wanzlick et al. made a deliberate attempt to isolate stable carbenes.[15] Although Wanzlick was unsuccessful in his objective, his recognition that a carbene center at the 2-position of the imidazole ring will be stable due to the electron donating effects of adjacent nitrogen atoms provided the conceptual framework for the development of the chemistry of these species.[16] The first stable carbenes coordinated to metal atoms were synthesized by Wanzlick and co-workers.[17] The isolation of a stable liquid dicarbene was reported in 1989 by Bertrand et al.[18] In 1991, Arduengo and co-workers isolated a stable, crystalline, *N*-adamantyl substituted carbene (Scheme 1.2).[19]



Scheme 1.2

The structure of the carbene isolated was unequivocally established by single crystal X-ray analysis. A number of factors viz., the large singlet-triplet energy gap in imidazol-2-ylidene (~336 kJ/mol), π-interactions in the imidazole ring, and electronegativity effect from the nitrogen contribute to the unusual stability of **2**. In addition to the electronic factors, it was believed initially that steric effects also play a major role in stabilizing the carbene **2**. Later, Arduengo demonstrated that stable NHCs could be prepared by the deprotonation of imidazolium salts bearing less bulky substituents at first and third positions.[20]

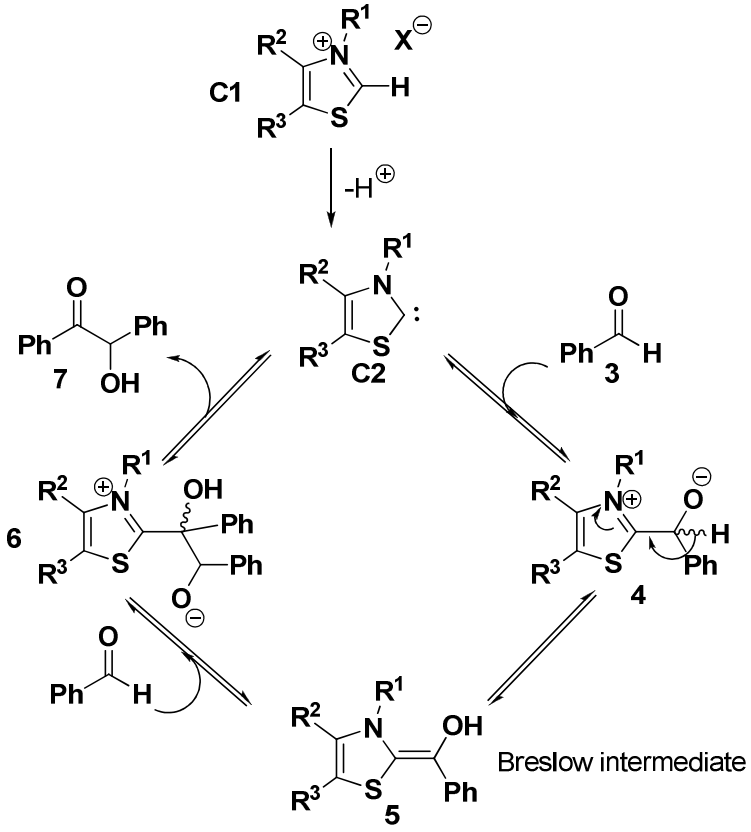
1.3. NHC as an Organocatalyst

Organocatalysis can be defined as the acceleration of chemical reactions by the addition of a substoichiometric quantity of an organic compound which does not contain an inorganic element.[21] Because of their lower cost and benign environmental impact; organocatalyzed reactions serve an attractive alternative to metal-catalyzed processes. The classical Knoevenagel condensation reported way back in 1894 can be considered as the first organocatalytic reaction.[22] Investigations by Langenbeck in the 1920s provided sufficient momentum to research in this area and the term "Organic Catalysts" ("Organische Katalysatoren") was coined by Langenbeck.[23] The catalysts are usually robust, inexpensive and readily available small organic molecules. Work in early 1970s signaled the onset of another era of intensive research activity called asymmetric organocatalysis.[24,25] The elegant work of List, MacMillan, Jacobsen and many other researchers in the 1990s and early 2000s, revisited asymmetric organocatalysis as a powerful strategy for the diastereoselective/ enantioselective construction of complex molecular skeletons.[26] In this scenario, the role of NHCs as organocatalyst received great attention.

1.3.1. Benzoin Reaction

Benzoin reaction is the cyanide mediated coupling reaction of aldehydes that leads to the formation of α-hydroxy ketones. This reaction was first reported by Wöhler and Leibig.[27] An acceptable mechanism for this reaction was proposed by Lapworth in

1903;[28] in which an intermediate aldehyde-cyanohydrin was deprotonated to generate an acyl anion equivalent with inverted reactivity (umpolung) at the carbonyl carbon. In 1943, Ugai et al. reported that the combination of thiazolium salt and a base could also effectively catalyze the benzoin condensation.[12] This work along with studies of reactions catalyzed by thiamine dependent enzymes indicated that, acyl anion equivalents are also likely intermediates in these thiazolium/base catalyzed processes. It was Breslow who proposed the pathbreaking mechanism for this transformation. In 1958, from his model studies he suggested that the catalytically active species is a thiazolin-2-ylidene **C2**, a carbene compound, which is formed in situ by the deprotonation of thiazolium salt **C1**. The catalytic process is demonstrated in scheme (Scheme 1.3).

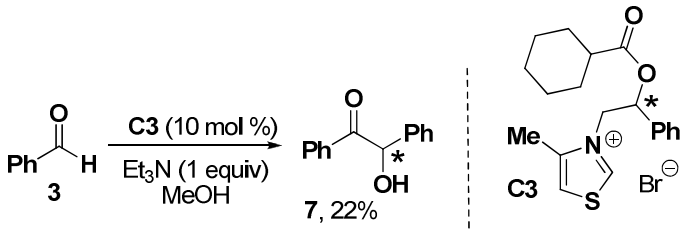


Scheme 1.3

In this mechanism it is assumed that the thiazolium salt **C1** is deprotonated at its most acidic position (C2-carbon) to form the thiazolium-2-ylidene **C2**, originally drawn as a mesomeric zwitterion. Nucleophilic addition of ylidene **C2** to the carbonyl group of an aldehyde **3** generates a thiazolium salt adduct **4**. Deprotonation at C-position and reprotonation at O leads to the active aldehyde in the form of the resonance-stabilized enaminol intermediate **5** (presently known as the Breslow intermediate). This nucleophilic acyloin reagent reacts again with an electrophilic substrate such as the carbonyl group of

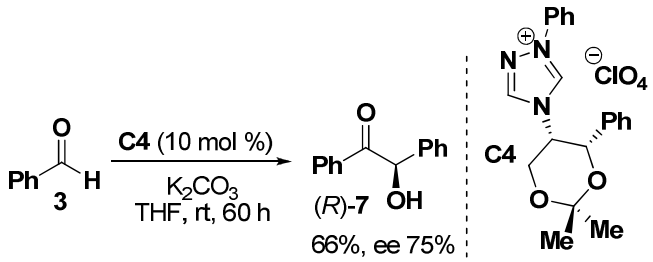
a second aldehyde molecule. The subsequent elimination of benzoin **7** regenerates the original carbene catalyst. NHCs derived from a number of azolium species viz., thiazolium, imidazolium and triazolium salts have been shown to catalyze the benzoin condensation analogous to the thiamine reaction under biochemical conditions.

In 1966, Sheehan and Hunneman reported the first asymmetric benzoin reaction using chiral thiazolium precatalyst **C3**. However, the observed enantiomeric excess of the benzoin was only 22% (Scheme 1.4).[29] Several groups have attempted to improve the enantioselectivity of thiazolium catalyzed benzoin reaction.



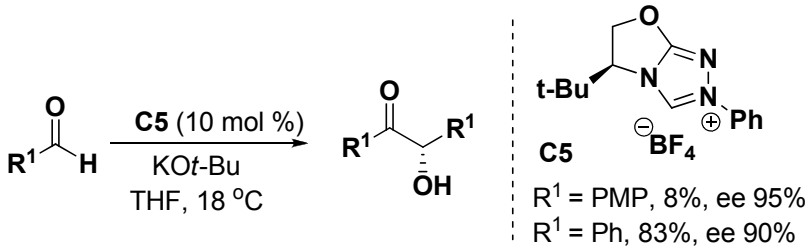
Scheme 1.4

A breakthrough in the asymmetric benzoin reaction was achieved in 1996 when Enders and co-workers introduced chiral triazolinylidene carbene instead of thiazolylidene carbene (Scheme 1.5).[30] They have utilized a variety of triazolium salts, which provided increased yield and enantioselectivities.



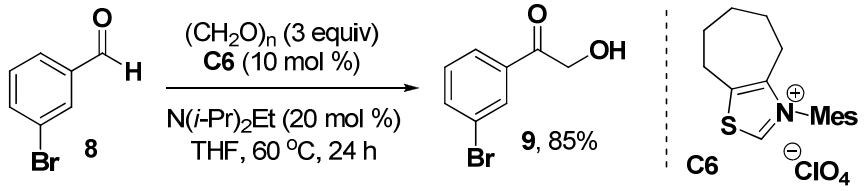
Scheme 1.5

In 1997 Leeper and co-workers developed a series of rigid bicyclic thiazolium salts for asymmetric benzoin condensation.[31] Rawal and Dvorak synthesized a bicyclic thiazolium salt and utilized it to increase the enantioselectivity of the benzoin reaction.[32] Later, Leeper and co-workers observed increased enantioselectivities up to 80% when they exchanged the thiazole frame-work of the carbene to more reactive triazole system.[33] In 2002, Enders and co-workers took the advantage of the bicyclic restriction introduced by Leeper and Rawal to develop catalyst **C5**. Use of this catalyst provided a number of benzoin derivatives with enantioselectivities up to 95% (Scheme 1.6).[34]



Scheme 1.6

In continuation of NHC-catalyzed addition of aldehydes to formaldehyde towards an efficient synthesis of hydroxymethyl ketones,[35] recently Khul and Glorius reported a mechanistic study of this *N*-heterocyclic carbene-catalyzed hydroxymethylation (Scheme 1.7).[36] Coupling of several aldehydes with paraformaldehyde directly provided the corresponding valuable hydroxymethyl ketones.

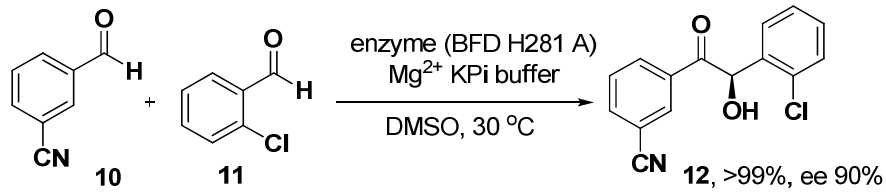


Scheme 1.7

1.3.2. Cross-Benzoin Reaction

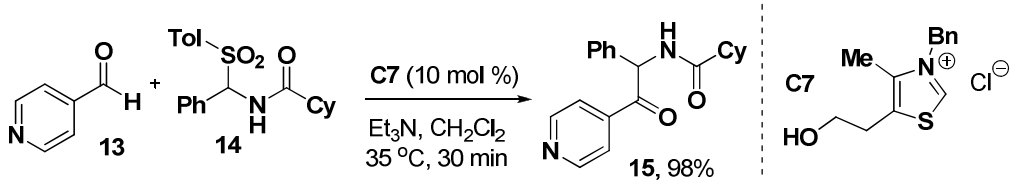
The benzoin reaction is typically a homocoupling of two aldehydes, which results in the formation of dimeric compounds; consequently, it limits the scope of this method. Recent developments in the benzoin condensation are the synthesis of non-symmetrical benzoins by cross coupling of two different aldehydes. This can provide four products viz., two homocoupled and two cross-benzoin products. To ensure the success, Breslow intermediate has to be formed predominantly on one aldehyde and it should add selectively to the second aldehyde. Several strategies have been employed to develop this method, including the use of donor acceptor aldehydes, acyl silanes and aryl imines; intramolecular reactions have also been exploited.

Müller and co-workers reported the first example of an enantioselective cross-benzoin reaction that takes the advantage of donor acceptor concept (Scheme 1.8).[37,38] The ortho-substitution on the aldehyde hinders the formation of Breslow intermediate and thereby facilitates selectivity.



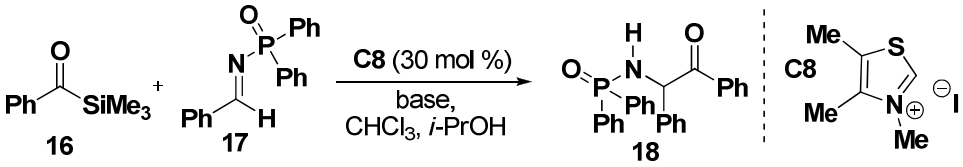
Scheme 1.8

In 2001, Murry et al. extended the scope of benzoin condensation to the in situ formed acyl imines (Scheme 1.9). Due to the stability and ease of formation of acyl imines, the authors used α-amido sulfones. This method is suitable for aryl aldehydes with electron-rich and electron-deficient aryl substituents. Reaction with acetaldehyde afforded the corresponding amido ketone in 62% yield.[39]



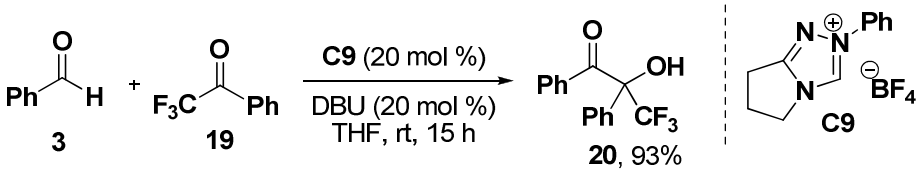
Scheme 1.9

Scheidt and co-workers utilized the acyl silanes and *N*-diphenylphosphinoylimines to form α-amino ketones (Scheme 1.10).[40] The asymmetric version of the aldehyde-imine cross-coupling was reported with thiazolylalanine-derived catalysts by Miller and co-workers.[41]



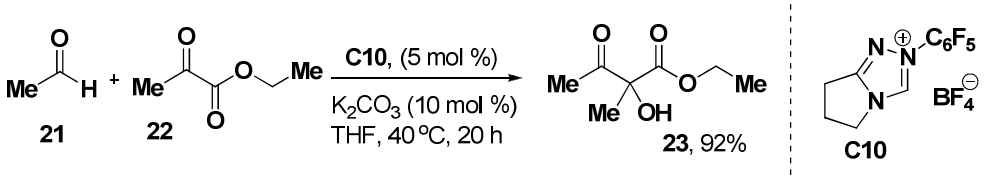
Scheme 1.10

Extension of NHC catalyzed cross-benzoin condensation to ketones offered only limited success; a few intramolecular examples can be found in the literature.[42] In 2009, a direct intermolecular cross-benzoin type condensation catalyzed by an *N*-heterocyclic carbene was developed.[43] The cross-coupling of commercially available aromatic aldehydes and trifluoromethyl ketones results in α-hydroxy-α-trifluoromethyl ketones bearing a quaternary stereocenter with excellent chemoselectivity and good to excellent yields (Scheme 1.11).



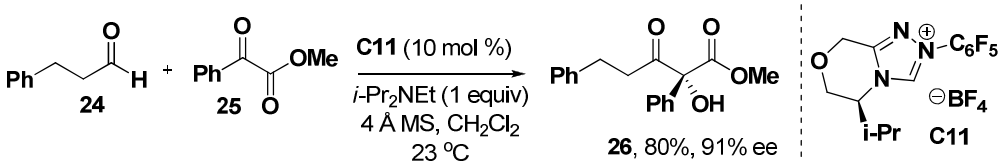
Scheme 1.11

Recently a significant improvement in this strategy was reported by the groups of Connon and Zeitler; they utilized α-ketoesters as the cross-coupling partner (Scheme 1.12).[44] Use of relatively electron deficient triazolium pre-catalysts avoided the un-desired hydroacylation pathways already reported with related substrates.[45]



Scheme 1.12

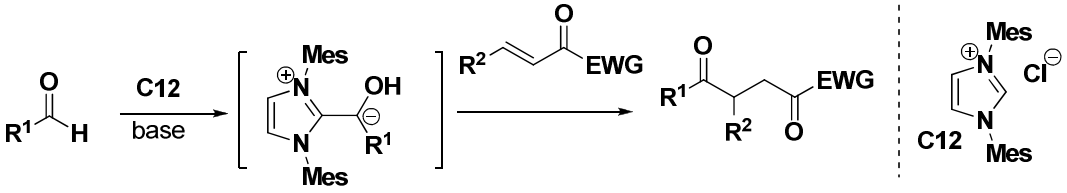
Very recently, Thai et al. showed that an electron-deficient, valine-derived triazolium salt catalyzed, highly chemo- and enantioselective cross-benzoin reaction between aliphatic aldehydes and α-ketoesters (Scheme 1.13).[46]



Scheme 1.13

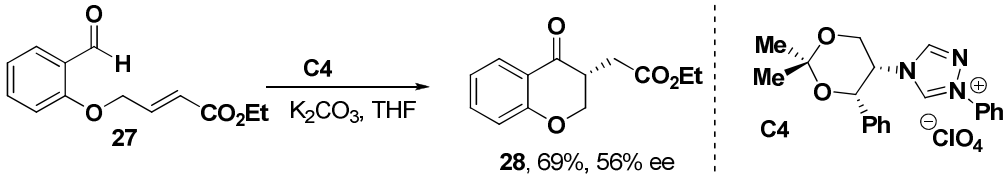
1.3.3. Stetter Reaction

In the 1970s Stetter reported the direct addition of aromatic aldehyde to α,β-unsaturated nitriles and ketones in the presence catalytic amount of sodium cyanide.[47] Later this method was successfully applied to aliphatic aldehydes by the use of catalytic amount of thiazolium salts in presence of bases. Several azolium salts such as imidazolium, thiazolium and triazolium salts are found to be effective as catalysts for this transformation.[48] When α,β-unsaturated ketones are employed, the reaction is often called Michael-Stetter reaction; a representative reaction involving an imidazolium salt, an α,β-unsaturated ketone and an aldehyde is shown in Scheme 1.14.



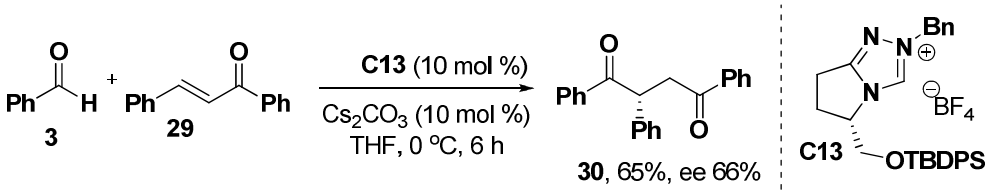
Scheme 1.14

The first asymmetric version of the Michael-Stetter reaction employing a chiral azolium salt for the synthesis of the benzopyran derivative **28** was reported by Enders and co-workers (Scheme 1.15).[49] Independently, Rovis and co-workers have shown that the use of a fused chiral triazolium salt leads to the product in higher yield and enantioselectivity.[50]



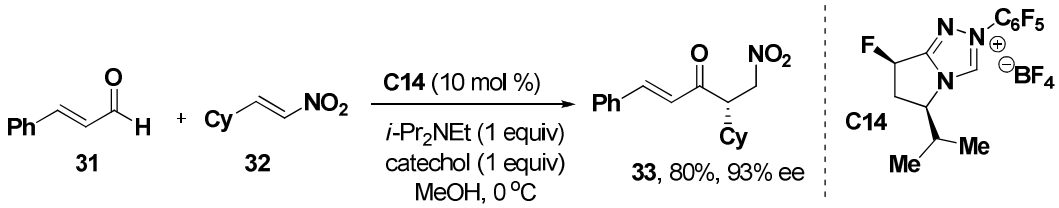
Scheme 1.15

In 2008, Enders et al. reported the first general NHC-catalyzed enantioselective intermolecular addition of aldehydes to chalcones (Scheme 1.16).[51]



Scheme 1.16

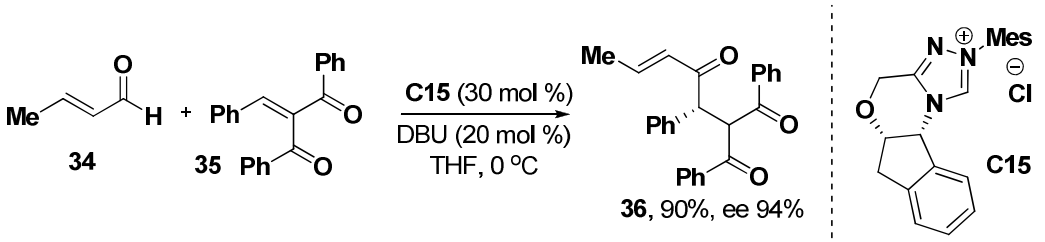
An asymmetric intermolecular Stetter reaction of enals with nitroalkenes catalyzed by chiral *N*-heterocyclic carbenes was developed Rovis and DiRocco (Scheme 1.17). The presence of catechol profoundly impacted the reaction rate and efficiency. The reaction proceeded with high selectivities and afforded good yield of the Stetter product. Internal redox products were not observed despite the protic conditions.[52]



Scheme 1.17

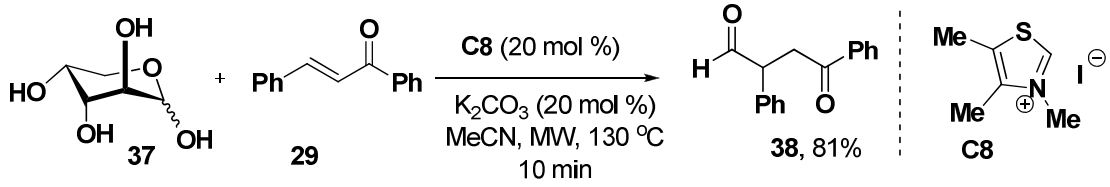
Chi and co-workers reported an *N*-heterocyclic carbene catalyzed enantioselective Stetter reactions of enals and modified chalcones (Scheme 1.18).[53] The selective

capturing of the enal acyl anion intermediates was realized by an alteration of the reaction partners and the proper choice of the NHC catalyst.



Scheme 1.18

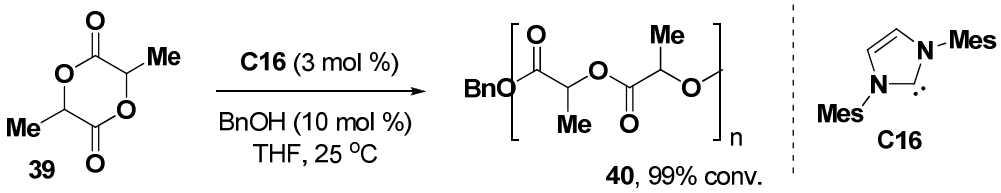
Recently, the authors disclosed a catalytic activation of carbohydrates as formaldehyde equivalents to generate acyl anions as one-carbon nucleophilic units for a Stetter reaction (Scheme 1.19).[54] This activation involves *N*-heterocyclic carbene-catalyzed carbon−carbon bond cleavage of carbohydrates via a retro-benzoin-type process to generate the acyl anion intermediates.



Scheme 1.19

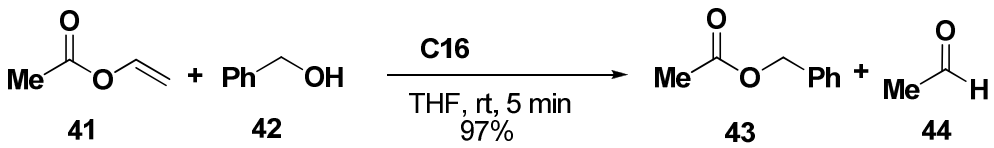
1.3.4. Transesterification Reactions

Stable NHCs have been found to be very efficient catalysts for transesterification and acylation reactions. The first example of an NHC catalyzed transesterification type reaction was reported by Hedrick et al. in 2002 (Scheme 1.20).[55]



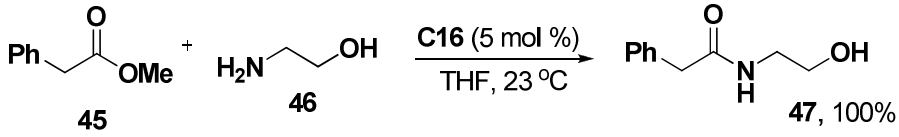
Scheme 1.20

Following these reports, the groups of Nolan, Hedrick and Waymouth independently reported the NHC catalyzed transesterification of a wide range of esters (Scheme 1.21).[56,57]



Scheme 1.21

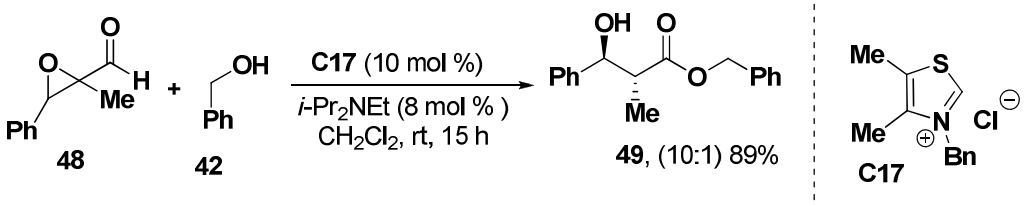
An NHC catalyzed amidation of unactivated esters with amino alcohols was reported by Movassaghi and Schmidt (Scheme 1.22).[58] In addition to the synthetic utility, these studies have thrown light on the mechanism of NHC catalyzed transesterifications.



Scheme 1.22

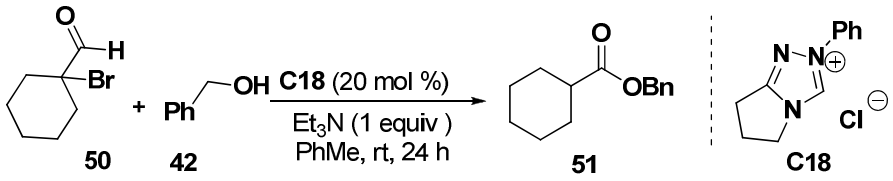
1.3.5. Internal Redox Reaction

Internal redox esterification reaction is another emerging area of research in NHC catalysis. The diastereoselective synthesis of β-hydroxy esters from 2,3-epoxyaldehydes by Chow et al. is an excellent illustration of this protocol (Scheme 1.23).[59] The proposed reaction mechanism involves NHC mediated epoxide ring opening.



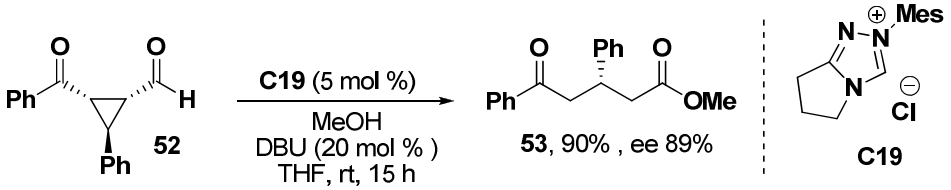
Scheme 1.23

In conjunction with the efforts to extend the utility of the umpolung reactivity, Rovis reported the conversion of α-haloaldehyde into an acylating agent catalyzed by NHCs.[60] In this process an activated carboxylate has been generated at the expense of a β-leaving group (Scheme 1.24).



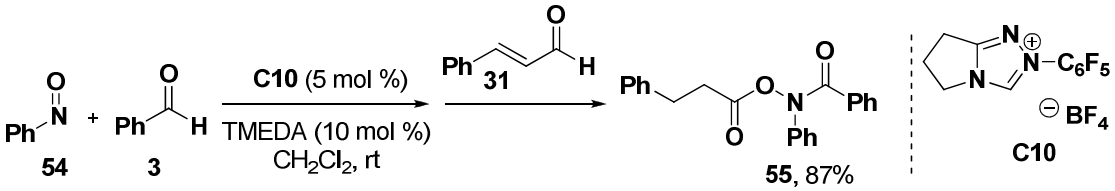
Scheme 1.24

Bode et al. have shown an efficient catalytic method for the redox esterification of formylcyclopropanes, which involves the ring opening of cyclopropane via carbon-carbon bond cleavage (Scheme 1.25).[61]



Scheme 1.25

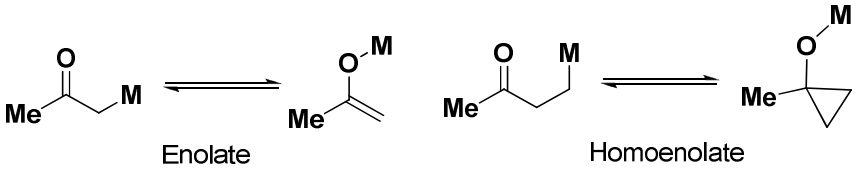
Recently, Enders and co-workers developed a new NHC-catalyzed one-pot reaction. Hydroxamic esters were formed by the reaction of nitroso benzenes, aldehydes and enals in a one-pot, two step reaction (Scheme 1.26).[62]Initially, an aza-benzoin-type condensation reaction between nitroso benzenes and aldehydes catalyzed by NHC took place. The resulting *N*-arylhydroxamic acids subsequently reacted with enals through an NHC catalyzed redox esterification reaction.



Scheme 1.26

1.4. Homoenolates

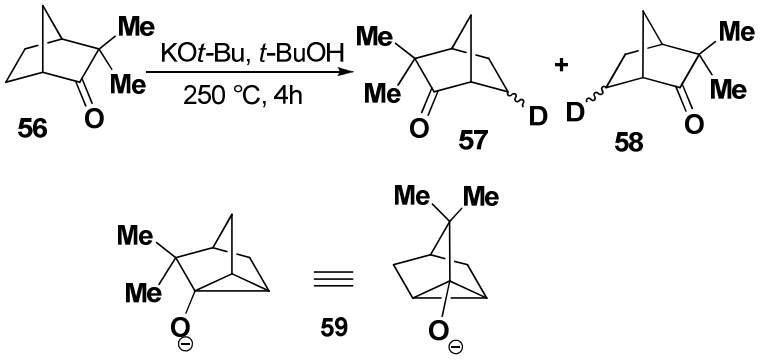
Carbon–carbon bond formation constitutes the central event in organic synthesis. The vast majority of carbon–carbon and carbon-heteroatom bond forming reactions occurring in Nature and in the laboratory are at the carbon adjoining the carbonyl group of ketones and aldehydes. Among the plethora of methods developed over the years, a large number of them take advantage of the activation of methyl/methylene, imparted by the electron withdrawing effect of an adjacent carbonyl group, and proceed via the intermediacy of enol/enolate or enamine. Enolate anion is a versatile reactive intermediate, and it is usually generated in the laboratory by the removal of the α-proton of a carbonyl compound, often with the aid of alkali metal reagents. Addition of a secondary amine to the carbonyl compound followed by the elimination of water affords enamines. Just as a carbonyl would facilitate the reaction of an electrophile at the α-carbon via enol/enolate, the reaction at the β carbon via a potentially reactive intermediate, a homoenolate is conceptually feasible. By analogy to enolate, homoenolate[63] is a species containing anionic carbon β to a carbonyl group or a moiety that can be transformed to a carbonyl group (Scheme 1.27).



Scheme 1.27

In 1962 Nickon introduced the concept of homoenolates to organic chemistry community,[64] and he proved the existence of such a species by demonstrating the

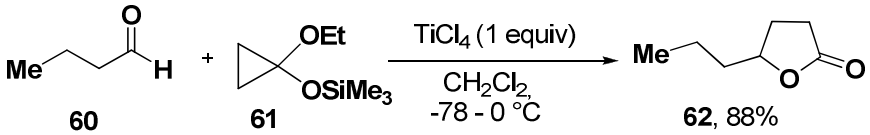
racemization of (+)-camphenilone **56** by alkaline treatment and its deuterium exchange to produce **57** and **58**, consistent with the symmetrical intermediate **59**. The racemization is attributed to the deprotonation of C6-H to form a non-classical anion, termed homoenolate anion whose charge is stabilized by delocalization to the carbonyl group (Scheme 1.28).



Scheme 1.28

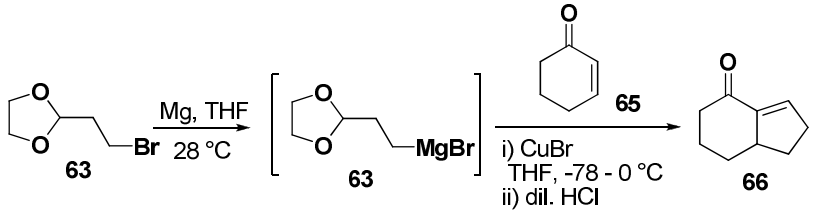
1.4.1. Metal Homoenolates

The application of homoenolates in organic synthesis was limited, presumably due to the difficulty in directly generating homoenolates. The use of homoenol silyl ether, in the form of cyclopropanone ketal **61**, was the simplest solution offered to this problem. It was Nakamura and Kuwajima who first described the potential utility of this homoenolate equivalent in carbon–carbon bond-formation (Scheme 1.29).[65] In their report, the addition of **61** to a carbonyl compound in the presence of $TiCl_4$ delivers γ-lactones in high yield. Presumably this is the first example of a homoaldol reaction.



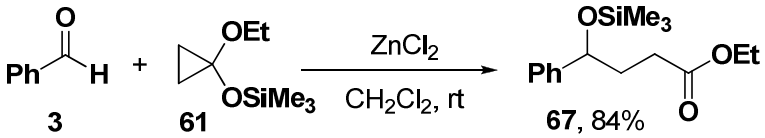
Scheme 1.29

An important innovation to circumvent the problem of chlorinated side-products associated with trichlorotitanium homoenolates was introduced by Helquist.[66] The acetal-embedded Grignard reagent **63** was used as homoenolate equivalent (Scheme 1.30). Copper catalyzed conjugate addition of **63** to cyclohexenone, followed by deprotection and subsequent intramolecular aldol condensation afforded bicyclic cyclopentene derivative **66** in good yield.



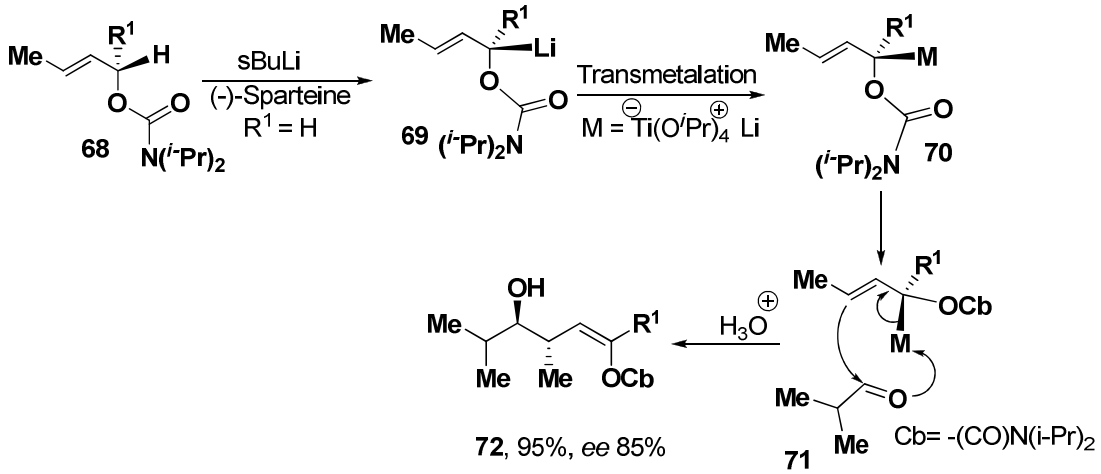
Scheme 1.30

Another important event in the area of homoenolate occurred when Nakamura et al. developed a method for the catalytic generation of homoenolate.[67] They showed that zinc homoenolate can be generated by the reaction of siloxycyclopropane **61** with catalytic amount of zinc chloride; synthetic utility of **61** was demonstrated by its participation in homoaldol reaction (Scheme 1.31).



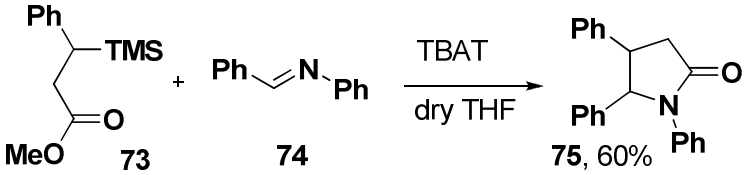
Scheme 1.31

Induction of chirality in homoenolate reaction was the main challenge to accomplish stereocontrolled homoaldol reactions. First example of a chiral homoenolate equivalent and its application in asymmetric reactions was reported by Albrecht and Enders.[68] The most advanced and synthetically useful chiral homoenolate equivalents are the 2-alkenyl-1-metallocarbamates introduced by Hoppe. In his elegant work, Hoppe has shown that these species react with aldehydes and ketones with virtually complete 1,3-transfer of chirality to form optically active homoaldol products.[69] An illustrative example is given in Scheme 1.32. Analogous work was subsequently reported by Whisler and Beak also.[70]



Scheme 1.32

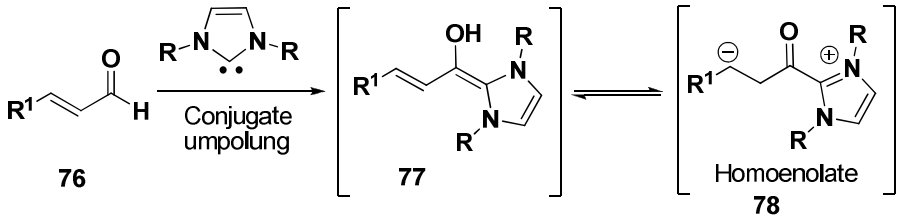
Fry et al. synthesized the first metal free homoenolate by the reaction of β-trimethylsilyl propionate with tetrabutylammonium triphenyldifluorosilicate (TBAT). It was found to be reactive enough to add to imines, aldehydes and ketones (Scheme 1.33).[71]



Scheme 1.33

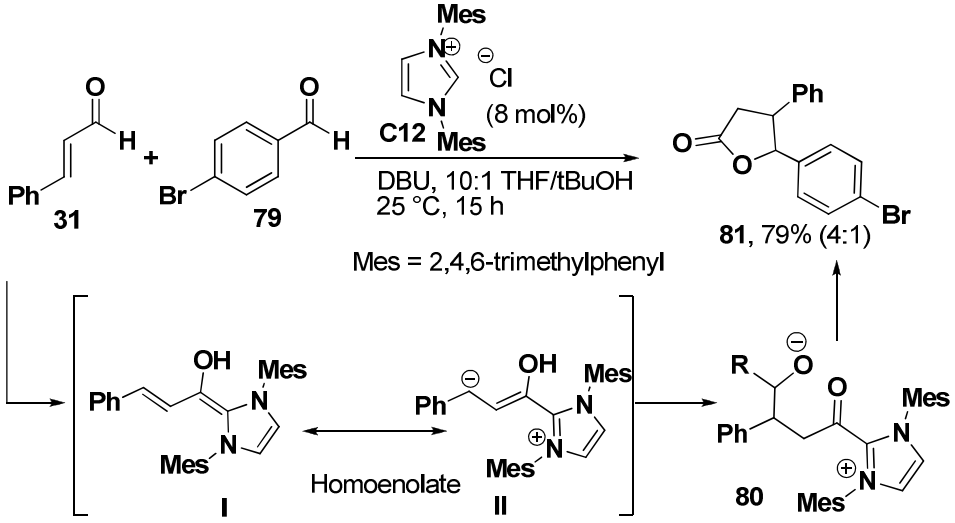
1.4.2. *N*-Heterocyclic Carbene (NHC) Derived Homoenolates

Based on the mechanistic pathways available to the "Breslow intermediate" two research groups led by Glorius[72] and Bode[73] independently and simultaneously reported a conceptually new approach to generate homoenolate from enal using *N*-heterocyclic carbene. They surmised that, just as the addition of NHC to aldehyde would generate an enol/enaminol (Breslow intermediate), the addition of NHC to α,β-unsaturated aldehyde can, in principle, generate a conjugated acyl anion, more appropriately called homoenolate (Scheme 1.34).



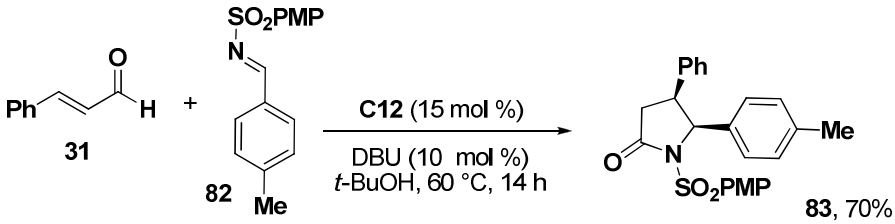
Scheme 1.34

The homoenolate intermediate **II** formed by NHC catalysis on reaction with an aldehyde culminated in the synthesis of γ-butyrolactones. The formation of γ-butyrolactones can be depicted as the addition of homoenolate to aldehyde to generate an alkoxide intermediate **80**, which undergoes an intramolecular lactonization with the activated carboxylate surrogate (Scheme 1.35). In the absence of other electrophiles, enal undergoes homodimerization.



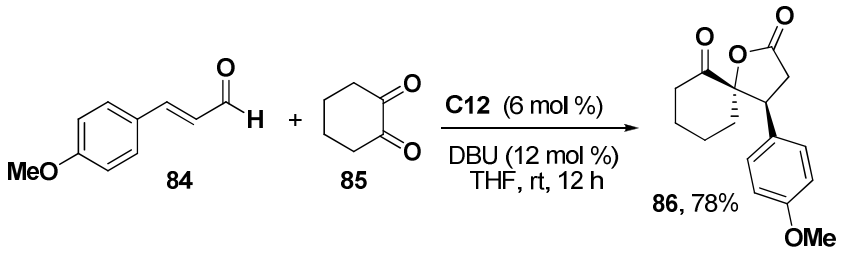
Scheme 1.35

Subsequent work by Bode has shown that this homoenolate annulation can be extended to the synthesis of γ-lactams (Scheme 1.36).[74]



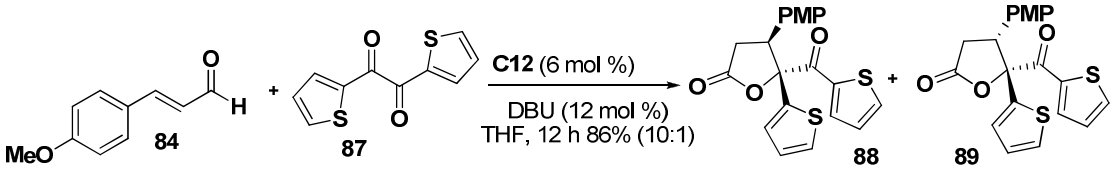
Scheme 1.36

In his original work, Glorius has reported that, with the exception of α,α,α-trifluoroacetophenone, ketones failed to undergo homoenolate annulations. Work from our laboratory has shown that homoenolate reactions proceed well with activated carbonyl compounds viz., 1, 2-diones, yielding spiro γ-butyrolactones in high yields and excellent diastereoselectivities (Scheme 1.37).[75] It was found that the spiroannulation strategy could be extended to isatins also, which afforded a diastereomeric mixture (1:1) of spiro γ-butyrolactone oxindole derivative. Spirooxindole derivatives are known to be important structural units of biologically active natural products such as the mycotoxin triptoquivaline.



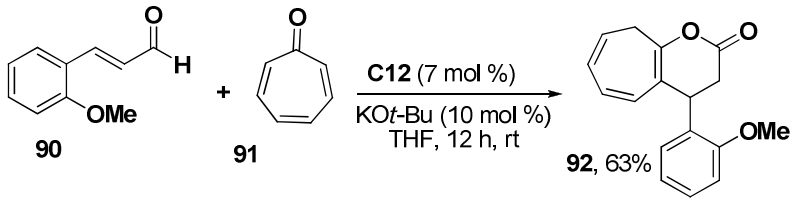
Scheme 1.37

Further investigations in our laboratory have shown that acyclic 1,2-diones also undergo this NHC catalyzed homoenolate annulation to yield γ-butyrolactones in high yields (Scheme 1.38).[76]



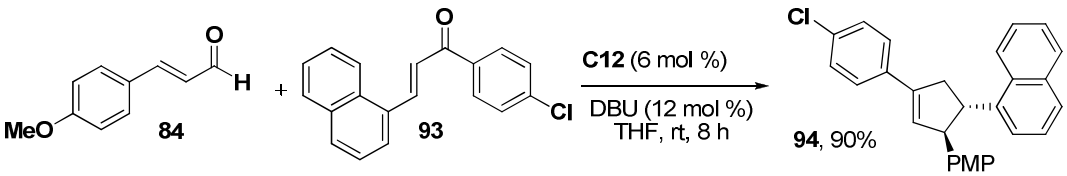
Scheme 1.38

In a related study, the reaction of homoenolate from **90** underwent an uncommon [8+3] annulation with tropone to afford bicyclic δ-lactone derivative **92** (Scheme 1.39). Interestingly, aliphatic enals could also be converted to the corresponding δ-lactones by this method.[77]



Scheme 1.39

Inspired by the homoenolate annulation to an activated carbonyl to afford a lactone, we were intrigued by the possibility of homoenolate annulation with an activated carbon–carbon double bond such as that of a chalcone. An attempted synthesis of cyclopentanone from chalcone and enal resulted in the serendipitous synthesis of 3,4-trans-disubstituted-1-aryl cyclopentene (Scheme 1.40).[78]

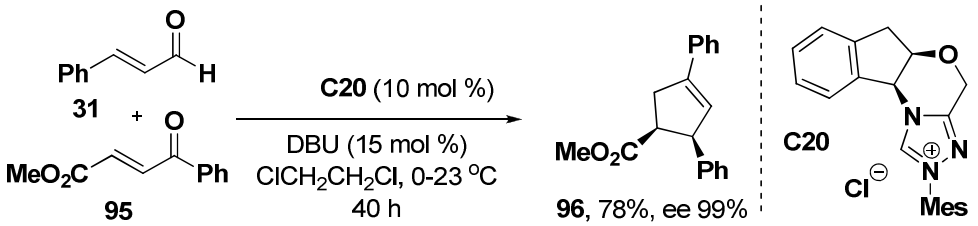


Scheme 1.40

Mechanistic rationale for the cyclopentene formation can considered as occurring via the initial Michael addition of homoenolate to the enone. Subsequent intramolecular aldol reaction set the stage for the formation of a β-lactone. This β-lactone is unstable and it undergoes a retro [2+2] process to yield the cyclopentenes.

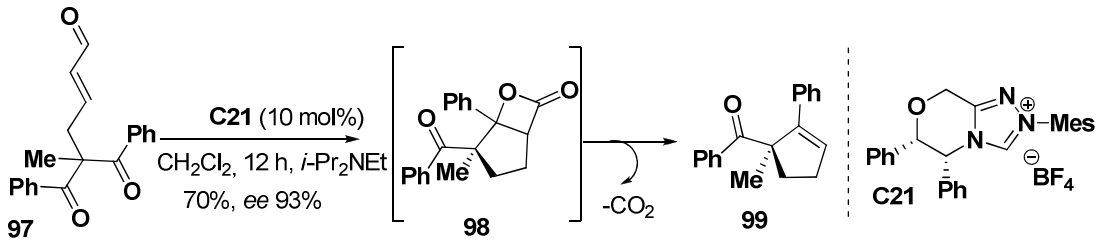
Subsequently, an asymmetric version of cyclopentene annulation using *N*-mesityl-substituted chiral triazole carbene was reported by Bode and coworkers (Scheme 1.41).[79]

They attributed the cis-cyclopentene formation to an NHC-catalyzed oxy-Cope rearrangement.



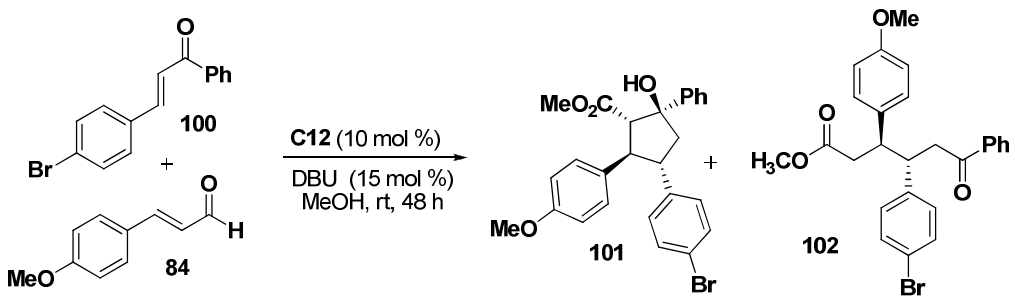
Scheme 1.41

Interestingly, β-lactone intermediate invoked in our cyclopentannulation has accrued additional support from the work of Scheidt; who isolated a bicyclic β-lactone from an intramolecular variant of this reaction.[80] The enantioselective formation of α,α-disubstituted cyclopentene **99** was interpreted by invoking the intramolecular aldol reaction of achiral tricarbonyl compound **97** catalyzed by chiral *N*-heterocyclic carbene (Scheme 1.42).



Scheme 1.42

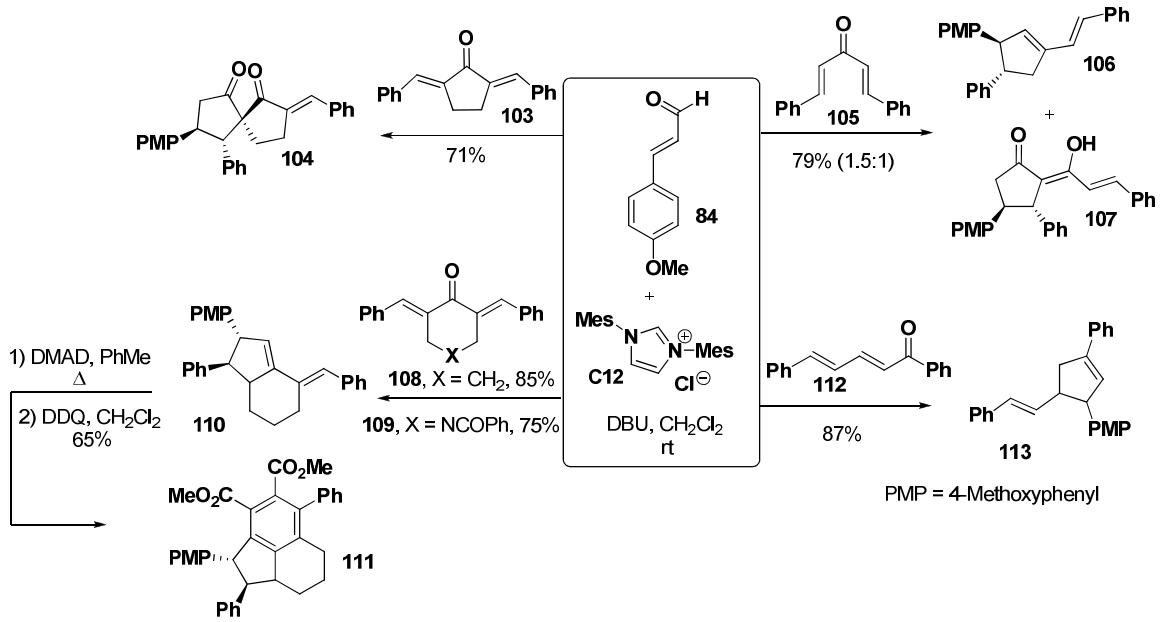
When the annulation reaction of homoenolates and chalcones was conducted in a protic solvent, a new facet of homoenolate reactivity was revealed.[81] The annulation of homoenolates with chalcones catalyzed by imidazolium salt **C12** in methanol proceeded to afford β-hydroxycyclopentane carboxylate **101** as the major product along with acyclic δ-ketoester **102** as minor product. It is noteworthy that the cyclopentane product **101** possesses four contiguous stereocenters including a quaternary one (Scheme 1.43).



Scheme 1.43

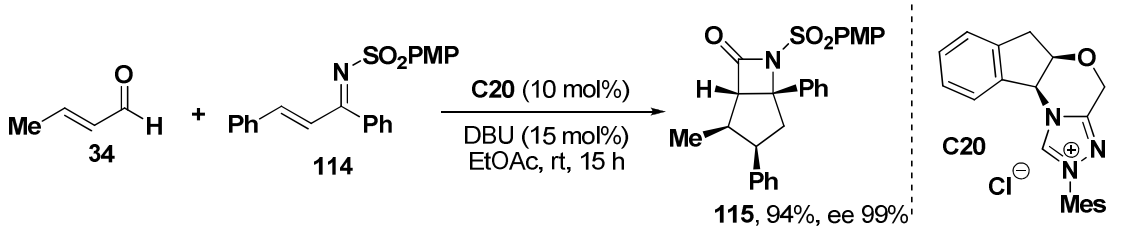
Recent work in our group on the reactions of homoenolates with different kinds of cross-conjugated dienones demonstrated that subtle changes in the structure of the

reactants would lead to reactive intermediates that may differ considerably in stability and thus alter the outcome of the reaction completely (Scheme 1.44). For example, stereoselective formation of spirocyclopentanone products was observed when dibenzylidine cyclopentanones **103** were employed as dienone components. However, homoenolate annulation of acyclic dienones resulted in the formation of separable mixtures of cyclopentenes **106** and cyclopentanones **107**.[82] On the other hand, under similar reaction conditions dibenzylidine cyclohexanones **108** afforded cyclopentene derivatives **110** as the only product with exclusive diastereoselectivity.[83] A facile Diels–Alder reaction of **110** with dimethylacetylene dicarboxylate (DMAD) and subsequent oxidation of the Diels–Alder adduct delivered a hexasubstituted benzene derivative **111**. NHC mediated annulation of enals to 2,4-dien-1-ones led to efficient diastereoselective synthesis of 1,3-diaryl-4-styrenyl cyclopentenes.[84]



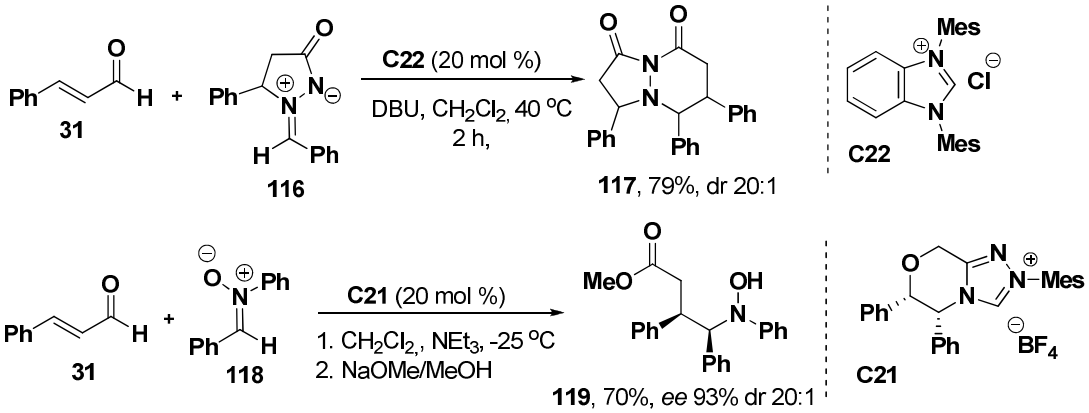
Scheme 1.44

In an extension of their previous work, Bode and co-workers synthesized bicyclic β-lactams from enals and unsaturated *N*-sulfonyl ketimines.[85] They invoked a tandem, or possibly concerted, crossed-benzoin/oxy-Cope reaction to explain the cis-relative configuration of the cyclopentane substituents. The high preference for this process was due to the slow β-protonation of unactivated enals to generate the corresponding enolate (Scheme 1.45).



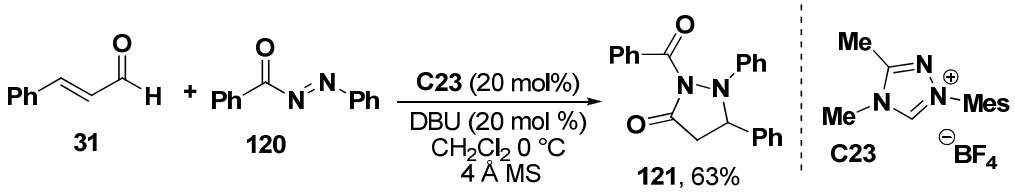
Scheme 1.45

1,3-dipoles such as azomethine imines and nitrones take part in formal [3+3] cycloaddition reactions with NHC-homoenolate. Synthesis of pyridazinones[86] and γ-amino esters[87] by the addition of azomethine imines and nitrones respectively to enals catalyzed by NHC was reported (Scheme 1.46).



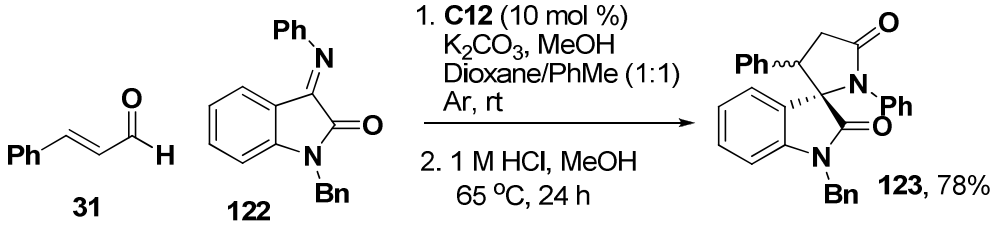
Scheme 1.46

A direct electrophilic amination of homoenolates catalyzed by *N*-heterocyclic carbenes was developed by Scheidt and co-workers.[88] The addition of a carbene derived from triazolium salt **C23** to an α,β-unsaturated aldehyde generates a homoenolate intermediate which undergoes a formal [3+2] cycloaddition with an 1-acyl-2-aryldiazene to afford pyrazolidinone as a single regioisomer (Scheme 1.47).



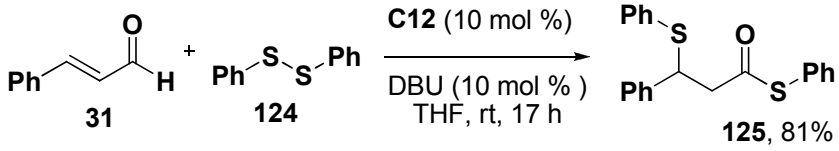
Scheme 1.47

In 2012 Jiao et al. demonstrated that *N*-aryl isatin imines can be used as stable and useful electrophiles in the NHC-catalyzed addition of enals to imines.[89] They have developed an efficient one-pot protocol for the synthesis of spirocyclic γ-lactam oxindoles by a synthetically challenging addition of homoenolate equivalents to *N*-aryl isatin imines and subsequent acid hydrolysis (Scheme 1.48).



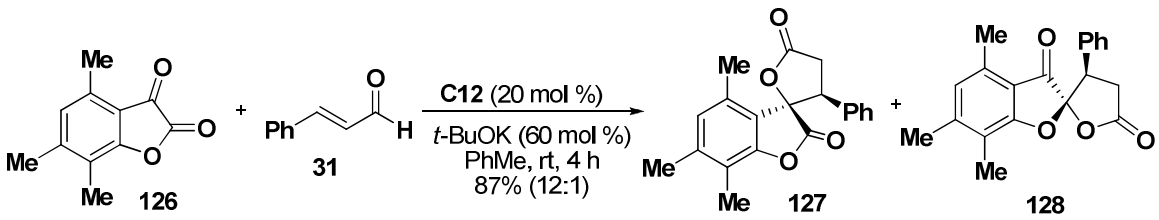
Scheme 1.48

Yadav and Santhosh reported a novel *N*-heterocyclic carbene catalyzed direct dithiolation of enals with organic disulfides (Scheme 1.49).[90] In this catalytic method thioesterification take place in a one-pot operation.



Scheme 1.49

Recently, Cheng's group and our group reported an *N*-heterocyclic carbene catalyzed spirobislactone synthesis by the annulation of benzofuran-2,3-diones and enals via homoenolate intermediate (Scheme 1.50).[91] The ketone-carbonyl group annulated products and the ester-carbonyl group annulated products can be obtained as major products with good yields by convenient catalyst regulation. Furthermore, commercially available thiazolium salt can also catalyze this reaction with modest yield.

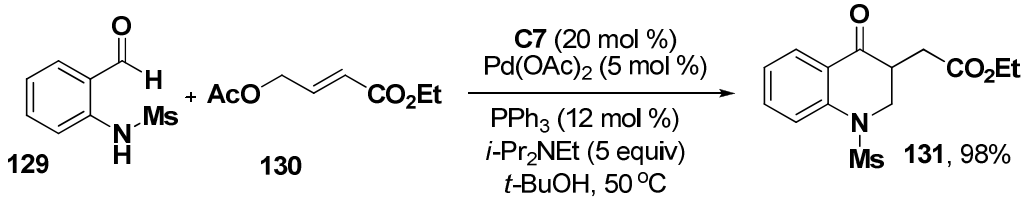


Scheme 1.50

1.4.3. Dual Activation in *N*-Heterocyclic Carbene Organocatalysis

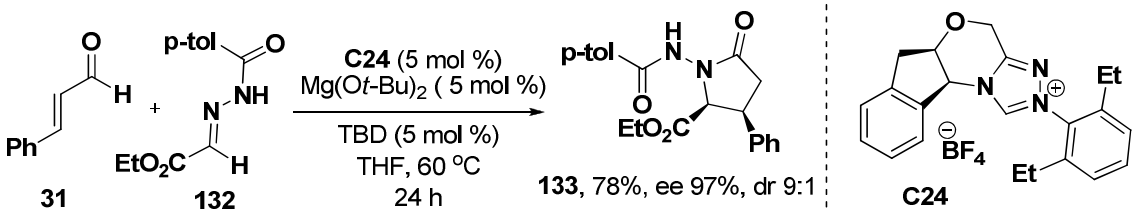
Recently, NHC-involving dual catalytic approaches have received much attention. In such cases, typically, combination of *N*-heterocyclic carbene with a second catalyst that may be another organocatalyst, or a metal-based catalyst or another NHC is used. The appropriate combination of catalysts allows two compatible yet independent catalytic systems in one-pot to undergo tandem processes. Furthermore, simultaneous action of two activators in a bond-forming event enables new reactivity, which often cannot be achieved by mono catalytic approaches.

Hamada and co-workers effectively utilized this strategy for the first time in the synthesis of dihydroquinolinones by a one-pot sequential Pd-catalyzed allylic amination and thiazolylidene-catalyzed Stetter reaction (Scheme 1.51).[92]



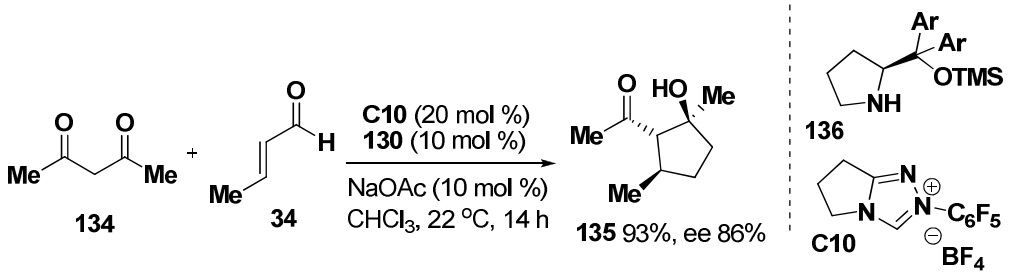
Scheme 1.51

In the area of NHC catalysis, Scheidt group has made a number of important contributions, demonstrating the simultaneous catalytic activation of two reaction partners in the same step using NHC and metal catalyst. These include the cooperative catalysis[93] by carbenes and Lewis acids in a highly stereoselective route to γ-lactams from acyl hydrazones and enals (Scheme 1.52).[94] In this reaction NHC activates the enal and co-catalyst [Mg(Ot-Bu)$_2$] activates the acyl hydrazine.



Scheme 1.52

The continuous quest for new types of NHC-catalyzed processes has found some important synergetic actions of NHC-and other organocatalysts. Vora and Rovis reported an orthogonal amide formation by NHC- and 1-hydroxy-7-azabenzotriazole (HOAt) relay catalysis.[95] Lathrop and Rovis reported an NHC-catalysis in combination with iminium catalysis, culminating in the enantioselective synthesis of functionalized cyclopentanols (Scheme 1.53).[96]



Scheme 1.53

1.5. Definition of the Problem

Introduction of NHC mediated generation of homoenolate, a three carbon synthon directly from enals has made it possible to explore the synthetic utility of this unique reactive intermediate.[10] Work from different research groups including our own has revealed the versatility and usefulness of NHC-bound homoenolate annulation with a wide range of electrophiles leading to various carbocycles and hetrocycles. Homoenolates have also been shown to add efficiently to sulfonimines leading to precursors of novel γ-aminobutyric acid (GABA) derivatives. However, NHC-catalysis is an emerging area and it will be very interesting to explore the potentiality of homoenolates in the construction of novel carbon–carbon and carbon-heteroatom bonds, ultimately leading to viable routes for carbo- and heterocycles.

In the initial phase of our study we undertook a systematic investigation of the reactivity of homoenolate, generated from enals by NHC catalysis, towards various β-nitrostyrenes, powerful Michael acceptors. These results comprise the subject matter of second chapter. Third chapter deals with an NHC-catalyzed transformation leading to the synthesis of 3-alkyl coumarins. The next chapter describes an efficient intramolecular homoenolate reaction of 2-O-alkenoate appended cinnamaldehydes. In the fifth and final chapter, transformation of cinnamils to vinylfulvenes and *o*-terphenyls is described.

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CHAPTER 2

N-Heterocyclic Carbene Catalyzed Reaction of Enals with Nitroalkenes via Homoenolate: Stereoselective Synthesis of δ-Nitro Esters

2.1. Introduction

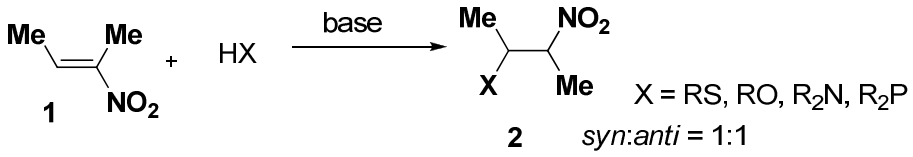
Carbon-carbon bond forming reactions constitute a challenging area in organic chemistry; hence, the discovery of new, efficient synthetic methods for the construction of C-C bond remains a topic of great interest. From the literature, it is evident that most of the carbon-carbon bond forming reactions proceeds via the intermediacy of enol/enolate or enamine. The versatile reactive intermediate enolate anion is generated by the removal of alpha proton of carbonyl compounds, often with the aid of alkali metal reagents. As we have already discussed in the introductory chapter (Chapter 1), it is possible to facilitate the reaction of an electrophile at the β-position of a carbonyl group by the intermediacy of homoenolate. The introduction of NHC for the generation of homoenolate from enals made it possible to explore the synthetic utility of this uniquely reactive intermediate. Since the subject matter of this chapter is the *N*-heterocyclic carbene catalyzed conjugate addition of homoenolate to nitroalkenes, a brief overview of Michael additions to nitroalkenes is presented first.

2.1.1. Michael Addition to Nitroalkenes

Conjugate addition of nucleophiles to electron deficient alkenes, generally called Michael addition, is an important tool for the creation of carbon-carbon and carbon-heteroatom bonds. These reactions proceed under very mild reaction conditions and tolerate various functional groups. Nitroalkenes are powerful Michael acceptors, due to the presence of a strong electron withdrawing nitro group. Because of the ease of conversion of nitro group to various functional groups, nitro compounds have been used extensively in organic synthesis.[1]

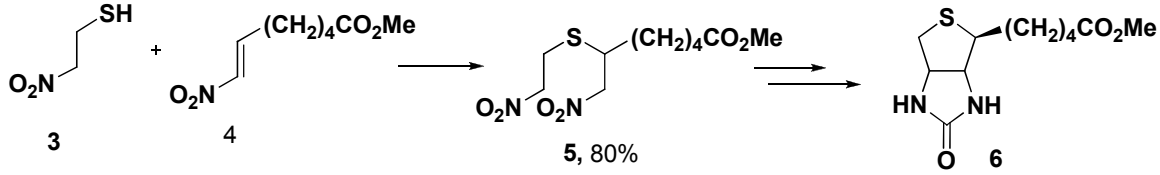
Oxygen, sulfur, nitrogen and phosphorous anions are good heteroatom-centered nucleophiles for the Michael addition to nitroalkenes. Use of such nucleophiles renders a useful method for the introduction of two heteroatoms at vicinal positions. The addition

of thiols and alcohols has frequently found use in organic synthesis because of the stability of the addition product. For example, the reaction of thiols with nitroalkenes readily proceeds in the presence of catalytic amount of base to give β-nitro sulphides in quantitative yields.[2] The stereoselectivity of this type of reactions is low and the diastereomers are formed in 1:1 ratio (Scheme 2.1).



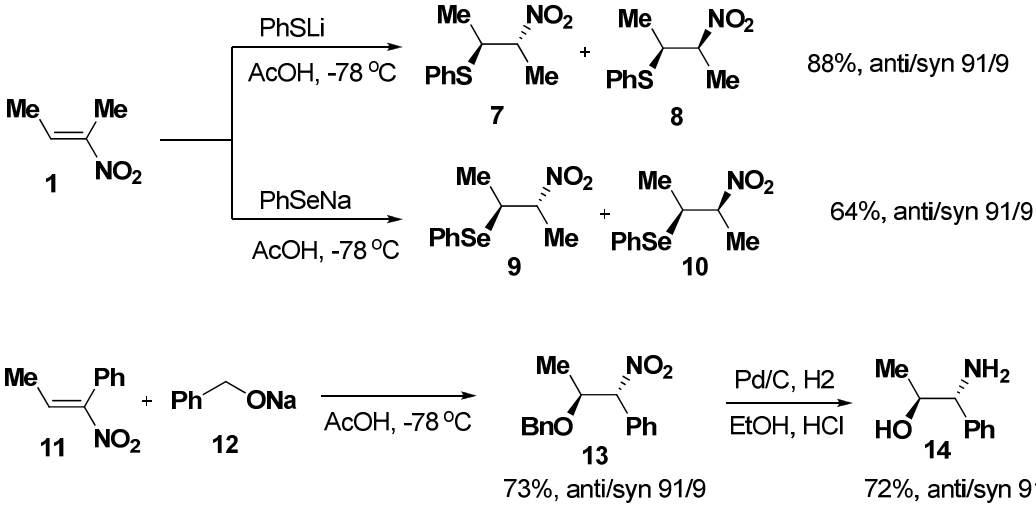
Scheme 2.1

β-nitrosulphides are useful intermediates for the preparation of various heterocycles containing sulphur atoms. Clark and co-workers reported the synthetic application of conjugate addition of thiols to nitroalkenes in a stereospecific total synthesis of biotin **6** (Scheme 2.2).[3]



Scheme 2.2

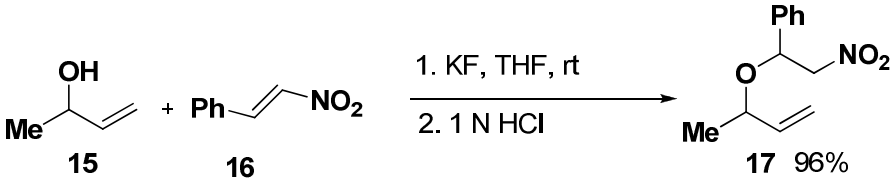
Kamimura et al. reported a very simple method for the stereo-control of the Michael addition of thiols, selenols and alcohols. The Michael addition of thiols to nitroalkenes followed by protonation at -78 ^{o}C gives anti β-nitrosulphides.[2] This process was then extended to anti β-nitro selenides and anti β-nitro ethers (Scheme 2.3).[4]



Scheme 2.3

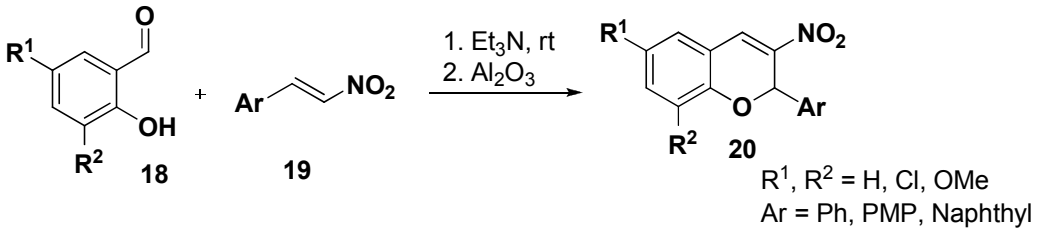
The Michael addition of alkoxide to nitroalkenes generally gives a complex mixture of products due to the polymerization of nitroalkenes.[5] The effect of alkoxides

has been examined carefully and it was found that potassium and sodium alkoxides give pure β-nitroethers in excellent yields (Scheme 2.4).[6]



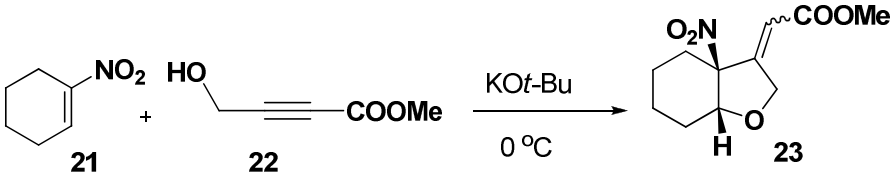
Scheme 2.4

The Michael addition of oxygen nucleophiles to nitroalkenes and subsequent cyclization or cycloaddition of adducts provides an important method for the preparation of oxygen-heterocycles. For example, various substituted 3-nitro-2*H*-chromenes have synthesized by the reaction of salicylaldehydes with nitroalkenes (Scheme 2.5).[7]



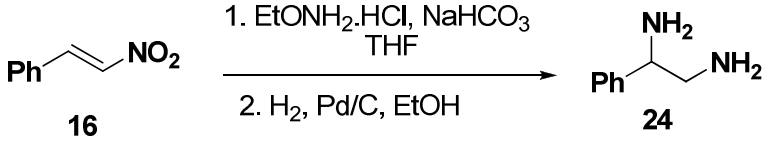
Scheme 2.5

Tandem Michael addition of oxygen nucleophiles has received much attention for the construction of octahydro benzo[b] furans. Treatment of 1-nitro-1-cyclohexene with methyl 4-hydroxy-2-butynoate in the presence of potassium tert-butoxide gave 3a-nitrooctahydrobenzo[b]furan in excellent yield through a tandem conjugate addition initiated by the oxygen nucleophile (Scheme 2.6).[8]



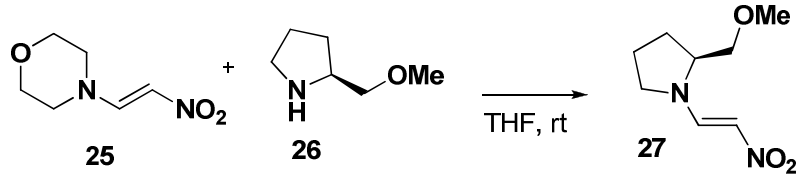
Scheme 2.6

A Convenient method for the preparation of 1,2-diamine from the corresponding nitroalkene was accomplished by Imagawa, by successive reactions of Michael addition of ethoxyamine to nitroalkene and reduction with hydrogen (Scheme 2.7). This preparative method is applicable to various nitroalkenes in one-pot procedure.[9]



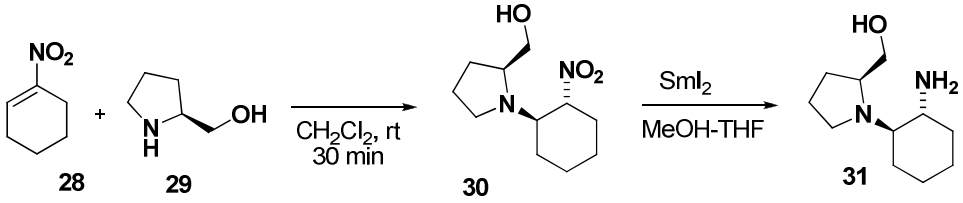
Scheme 2.7

Conjugate addition of chiral nitrogen nucleophiles to nitro alkenes provides access to chiral compounds having nitrogen functionalities at vicinal positions (Scheme 2.8).[9]



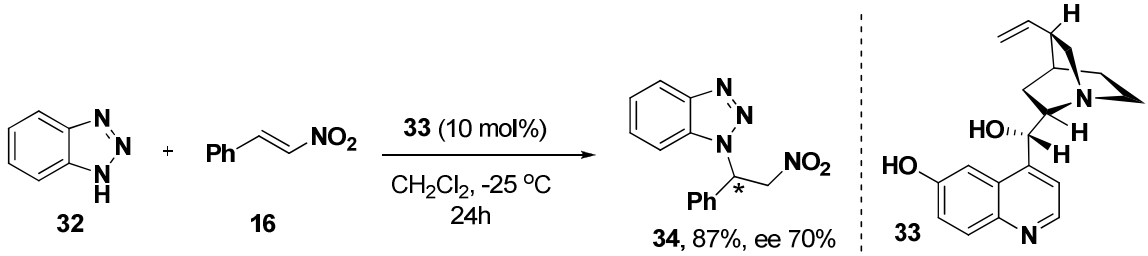
Scheme 2.8

Amino alcohols like (s)–prolinols react with nitroalkenes very rapidly with very high facial selectivity. Rapid and stereoselective reduction of nitro group is essential for the conversion of products to 1,2-diamine derivatives with retention of configuration. SmI_2 is utilized in the stereoselective reduction of the thermally unstable 2-amino nitroalkenes to give a range of useful 1,2-diamines (Scheme 2.9).[10]



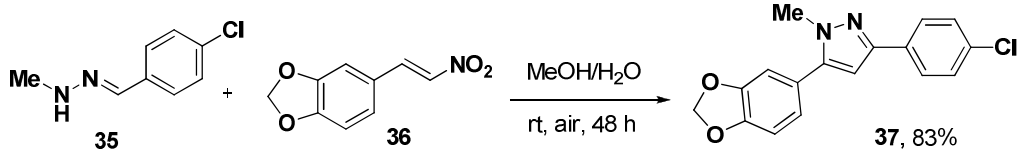
Scheme 2.9

In 2006, Won et al. reported a cinchona alkaloid promoted Michael addition of *N*-heterocycles to nitro alkenes, with moderate to high enantioselectivities (Scheme 2.10).[11]



Scheme 2.10

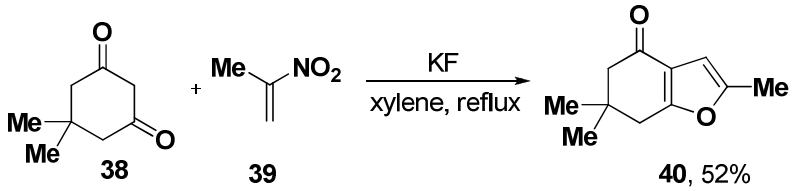
Substituted pyrazoles are important synthetic targets in the pharmaceutical industry because numerous biologically active compounds possess the pyrazole motif. A regio and stereoselctive synthesis of 1,3,5-tri- and 1,3,4,5-tetra substituted pyrazoles by the reaction of *N*-aryl hydrazones and nitroalkens has been reported. The reaction mechanism involves a stepwise cycloaddtion pathway (Scheme 2.11).[12]



Scheme 2.11

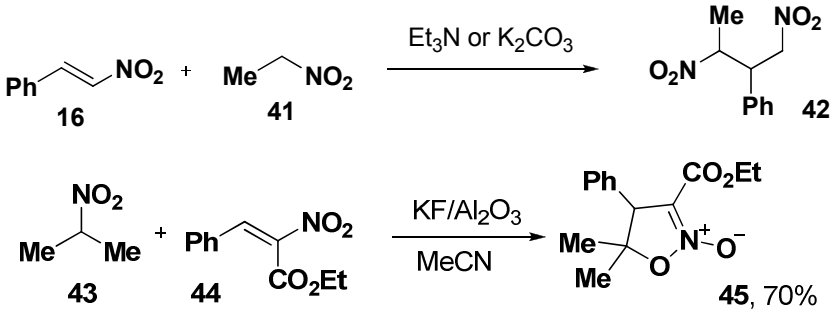
2.1.2. Michael Addition of Carbon Centered Nucleophiles

Classically, the reaction of nitroalkenes with carbon centered nucleophiles has been limited to reactions carried out under mild basic condition using relatively acidic reaction partners such as malonate derivatives and 1,3-diketones.[13] For example, the reaction of acetylacetone or ethyl acetate with nitrostyrene proceeds in the presence of triethylamine at room temperature to give adduct in high yield. Yoshikoshi and co-workers have found that the potassium fluoride catalyzed addition of 1,3-diketones to nitroalkenes leads to the formation of furans or Michal adducts and their Nef products (Scheme 2.12).[14]



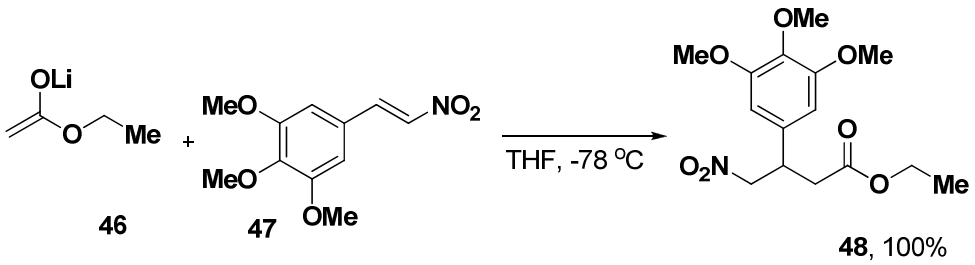
Scheme 2.12

Michael addition of nitroalkanes to nitroalkenes is catalyzed by triehylamine to give 1,3-dinitrocompounds. In some cases intramolecular displacement of nitro group take place to give cyclic nitronates (Scheme 2.13).[15]



Scheme 2.13

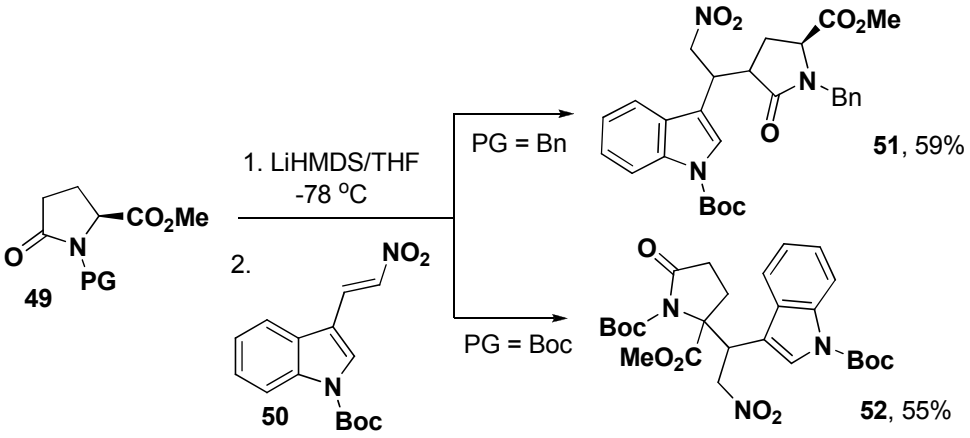
Seebach and co-workers have developed the Michael type addition of lithium enolates to nitroalkenes (Scheme 2.14).[16]



Scheme 2.14

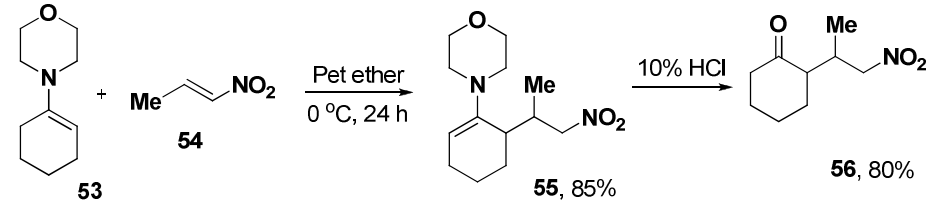
Pyroglutamic acid is a useful starting material for the synthesis of several natural products, such as pyrrolidine alkaloids, kainoids and other unnatural amino acids.

Interesting chemoselective Michael addition of pyroglutamate anions to indole-derived nitroalkenes was reported by Braña et al.[17] By choosing appropriate amide protecting groups, the reaction can be carried out either at C2 or C4 position (Scheme 2.15).



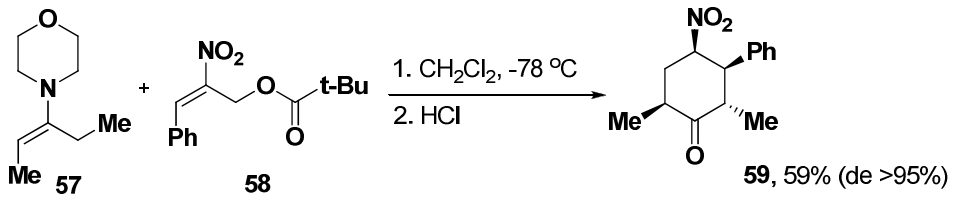
Scheme 2.15

Valentine and co-workers have extensively studied the reaction of enamines with nitroalkenes.[18] The reaction of morpholino-cyclohexene with nitropropenes proceed under mild conditions to give γ-nitroketones (Scheme 2.16).[19] The morpholine-enamine of monoprotected butane-2,3-dione reacts with cyclic and acyclic conjugated nitroalkenes in a Michael-type reaction to yield nitro-substituted α-diketones, after acidic hydrolysis of the mononitroalkylated enamine adducts. Cyclopentanone, hexahydro-1*H*-pentalen-2-one and octahydro-2*H*-inden-2-one derivatives are readily obtained by base-catalyzed intramolecular nitroaldol reaction of the acyclic hydrolysis products.[20]



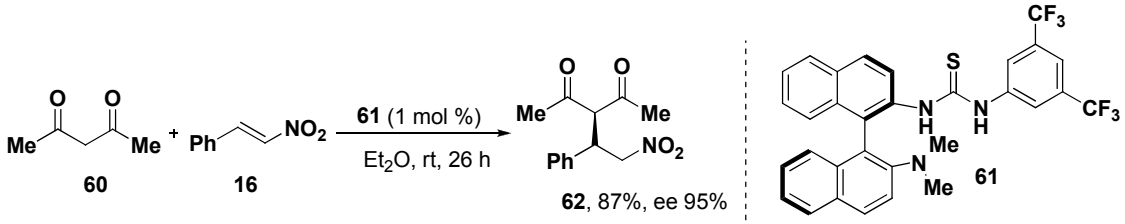
Scheme 2.16

The reaction of enamine **57** with 2-nitro-2-propen-1-yl pivaloates gives 4-nitro cyclohexenone **59** via route that can be regarded as formal [3+3] carbocyclization.[21] With proper substitution of reactants, up to five stereogenic centers can be installed in this reaction (Scheme 2.17).



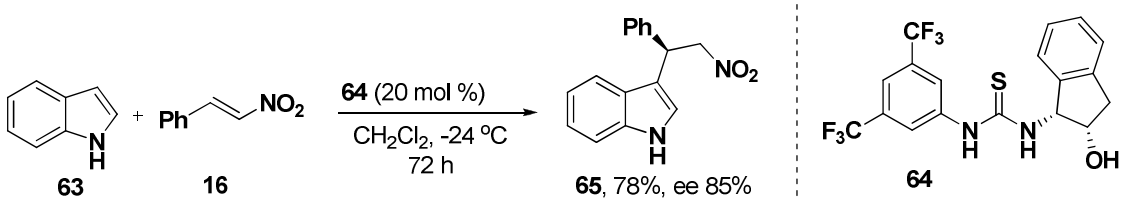
Scheme 2.17

A binaphthyl-derived amine thiourea catalyzed Michael addition reaction of diketones to nitroalkenes with high enantioselectivity was developed by Wang and co-workers. Because of high catalytic activity, utilization of the catalyst in an amount as low as 1 mol % is sufficient for the process (Scheme 2.18).[22]



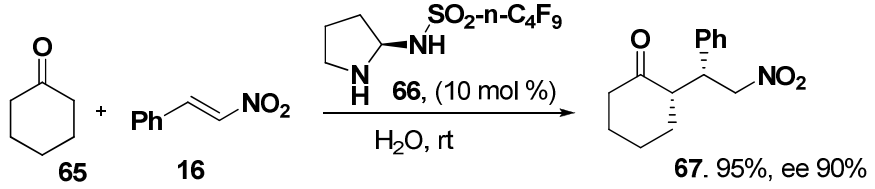
Scheme 2.18

Optically active 2-indolyl-1-nitro derivatives in good yield and enantioselectivity can be synthesized by a novel catalytic enantioselective Friedel–Crafts alkylation of indoles with nitroalkenes using a simple thiourea organocatalyst (Scheme 2.19).[23] The high synthetic versatility of the products render this new approach highly appealing for the synthesis of optically active target compounds such as tryptamines and 1,2,3,4-tetrahydro-β-carbolines.



Scheme 2.19

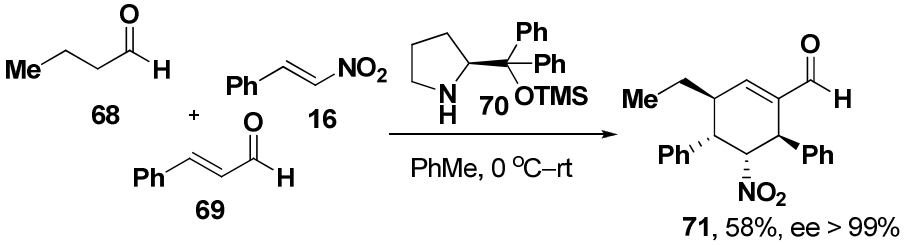
Highly enantio- and diastereoselective Michael addition reactions of ketones and aldehydes with nitroalkenes in water has been achieved by the reusable fluorous (S)-pyrrolidine sulfonamide organocatalyst (Scheme 2.20). The catalyst is conveniently recovered from the reaction mixture by fluorous solid-phase extraction and can be subsequently reused (up to six cycles) without significant loss of catalytic activity and stereoselectivity.[24]



Scheme 2.20

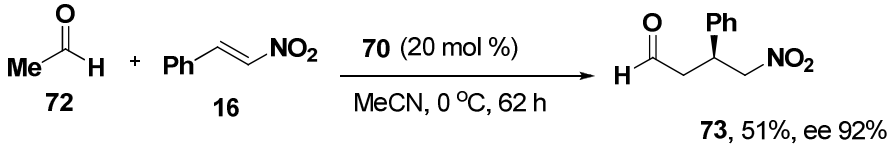
Enders and co-workers reported a chemo-, diastereo- and enantioselective three-component domino reaction of nitroalkene and aldehydes. This proline derived

organocatalytic reaction afforded tetra-substituted cyclohexene carbaldehydes in moderate yield. The four stereogenic centers are generated in three consecutive carbon–carbon bond formations with high diastereo- and complete enantiocontrol (Scheme 2.21).[25]



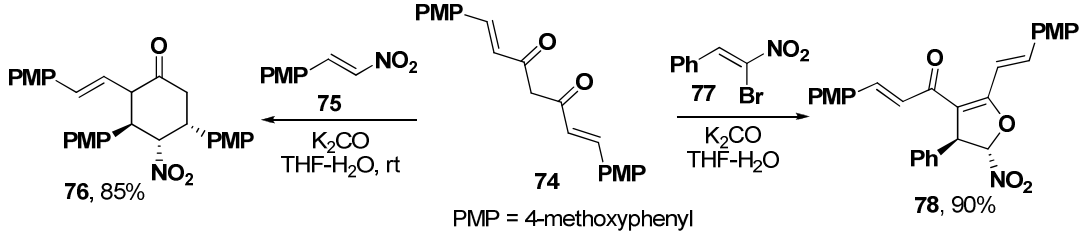
Scheme 2.21

Prolinol silyl ether catalyzed highly enantioselective Michael reaction of acetaldehyde with nitroalkenes was reported by List et al (Scheme 2.22).[26]



Scheme 2.22

Recently, Namboothiri et al. reported a novel reaction of curcumins with nitroalkenes (Scheme 2.23).[27] Highly functionalized cyclohexanones possessing three contiguous chiral centers with complete diastereoselectivity have been synthesized through an inter–intramolecular double Michael reaction involving curcumin and nitroalkene under extremely simple experimental conditions (K_2CO_3 in aqueous THF). Under identical conditions, curcumins react with α-bromonitroalkenes to afford dihydrofurans through an intermolecular Michael addition-intramolecular nucleophilic substitution (O-alkylation), which is analogous to an 'interrupted' Feist–Benary reaction. Later the authors have reported the asymmetric version of this reaction by a combination of a dihydrocinchonine-thiourea organocatalyst and K_2CO_3.[28]



Scheme 2.23

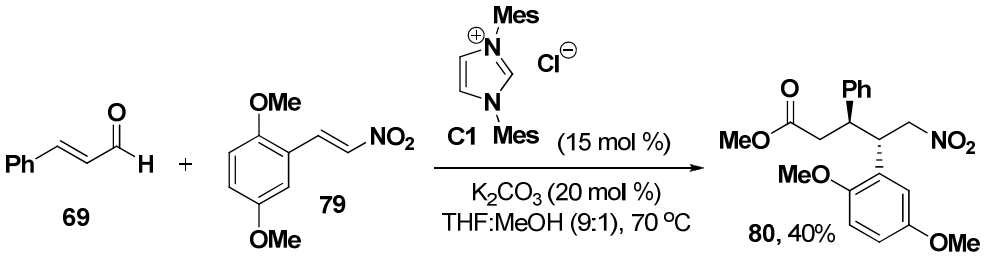
2.2. Background to the Present Work

In the context of our recent discovery of synthetic routes for cyclopentanones and related organic compounds by the reaction of homoenolates with chalcones in methanol

(see Chapter 1), it was of interest to investigate the prospect of homoenolate addition to nitroalkenes. Evidently, the nitroalkenes are unique Michael accepters endowed with the powerful electron-withdrawing group (EWG), which is amenable to a variety of synthetic transformations. A successful Michael addition of homoenolate to β-nitroalkene as envisioned above would provide access to functionalized five-carbon synthons potentially useful in the synthesis of δ-amino acid derivatives and related compounds of therapeutic value. The results of our work constituting the novel synthesis of δ-nitro esters are presented in the following sections.

2.3. Results and Discussion

Against the above backdrop, in a pilot experiment, cinnamaldehyde **69** and 2,5-dimethoxy-β-nitrostyrene **79** were exposed to imidazolin-2-ylidene, generated from catalytic amount of imidazolium chloride, by potassium carbonate in THF–methanol. The reaction mixture was processed after 24 h and the crude product on purification by chromatography afforded a crystalline solid **80** as the major product (Scheme 2.24).



Scheme 2.24

The structure of the product was assigned on the basis of spectroscopic data. ^{1}H NMR spectrum showed two sets of methoxy proton signals at δ 3.75 and δ 3.57 respectively. The methylene protons appeared as doublet of doublets. The benzylic protons were found to resonate as multiplets. The ester group displayed ^{13}C resonance signal at δ 172 and it was supported by the carbonyl absorption at 1730 cm^{-1} in the IR spectrum. The nitro group showed its characteristic absorption 1552 cm^{-1}. The mass spectrum obtained was in good agreement with the proposed structure.

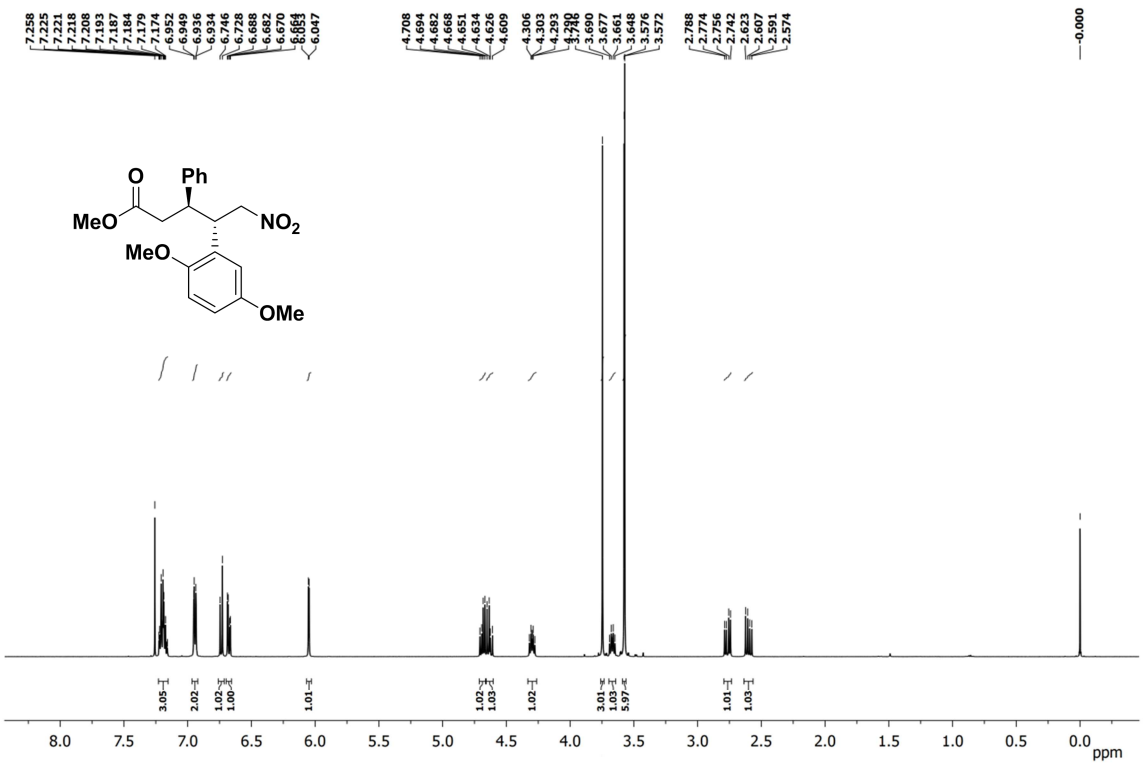


Figure 2.1. ^{1}H NMR spectrum of **80**

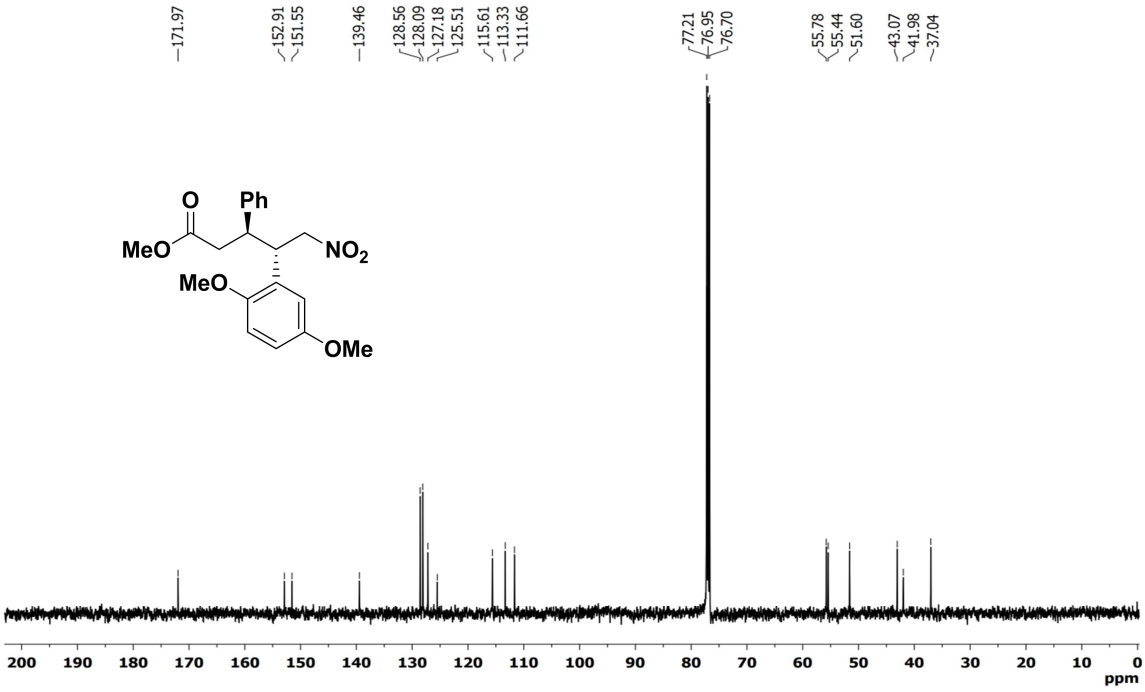


Figure 2.2. ^{13}C NMR spectrum of **80**

The final confirmation of the structure and relative stereochemistry of **80** was obtained from single crystal X-ray analysis.

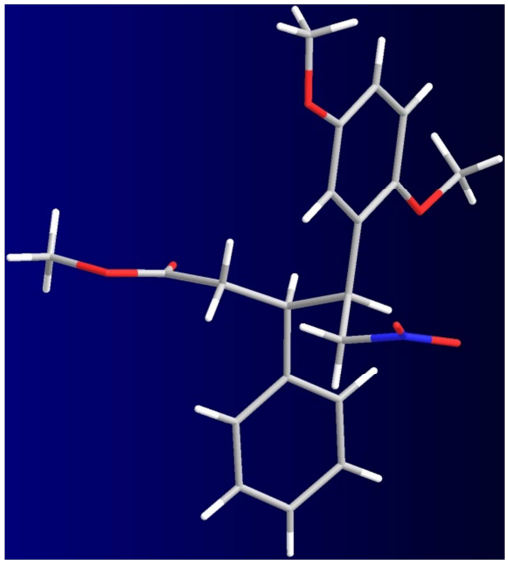
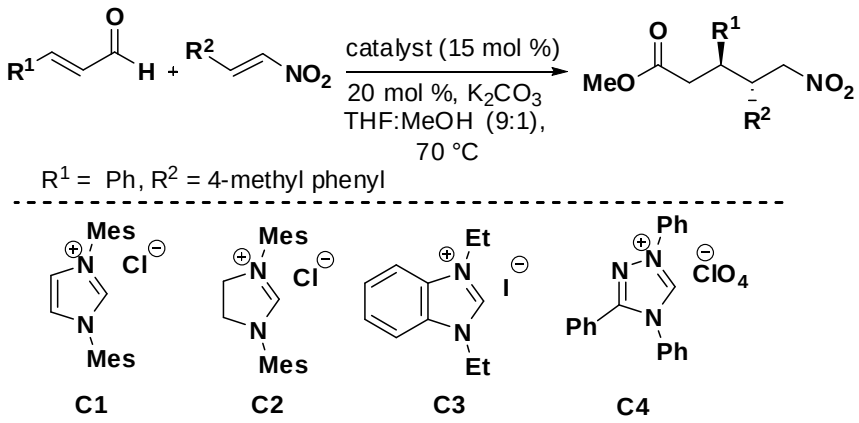


Figure 2.3. Single crystal X-ray structure of **80. CCDC** number: **743837.**

In view of the success of the reaction, it was obligatory to assess the usefulness of other commonly available NHC catalysts in this reaction. A number of experiments were conducted, and the results are summarized in Table 1.

Table 2.1. Catalyst Screening



Entry	Catalyst	Condition	Yield(%)[a]
1	**C1**	THF:MeOH(9:1), 70 °C, 24 h	56
2	**C2**	THF:MeOH(9:1), 70 °C, 24 h	70
3	**C3**	THF:MeOH(9:1), 70 °C, 24 h	20
4	**C4**	THF:MeOH(9:1), 70 °C, 36 h	-

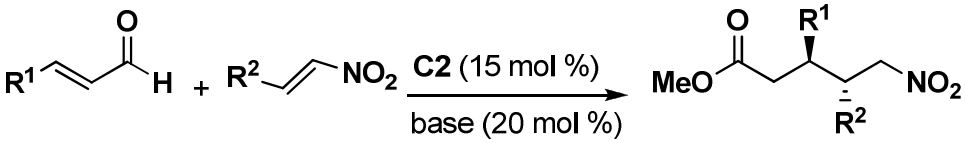
[a] isolated yield

Among the four catalysts investigated, imidazolinium catalyst **C2** gave the best result. The benzimidazolium catalyst **C3** gave low yield of the product, while the triazolium catalyst, **C4**, was completely ineffective. Although it is not possible to rationalize the superior performance of **C2** vis à vis other catalysts, it is noteworthy that

C2 is the most nucleophilic one in this group.

With a view to optimize the yield of the product, we studied the influence of different bases in generating the NHC catalyst and the results are shown in Table 2. Interestingly the best results were obtained with potassium carbonate in THF/MeOH (9:1).

Table 2.2. Condition optimization



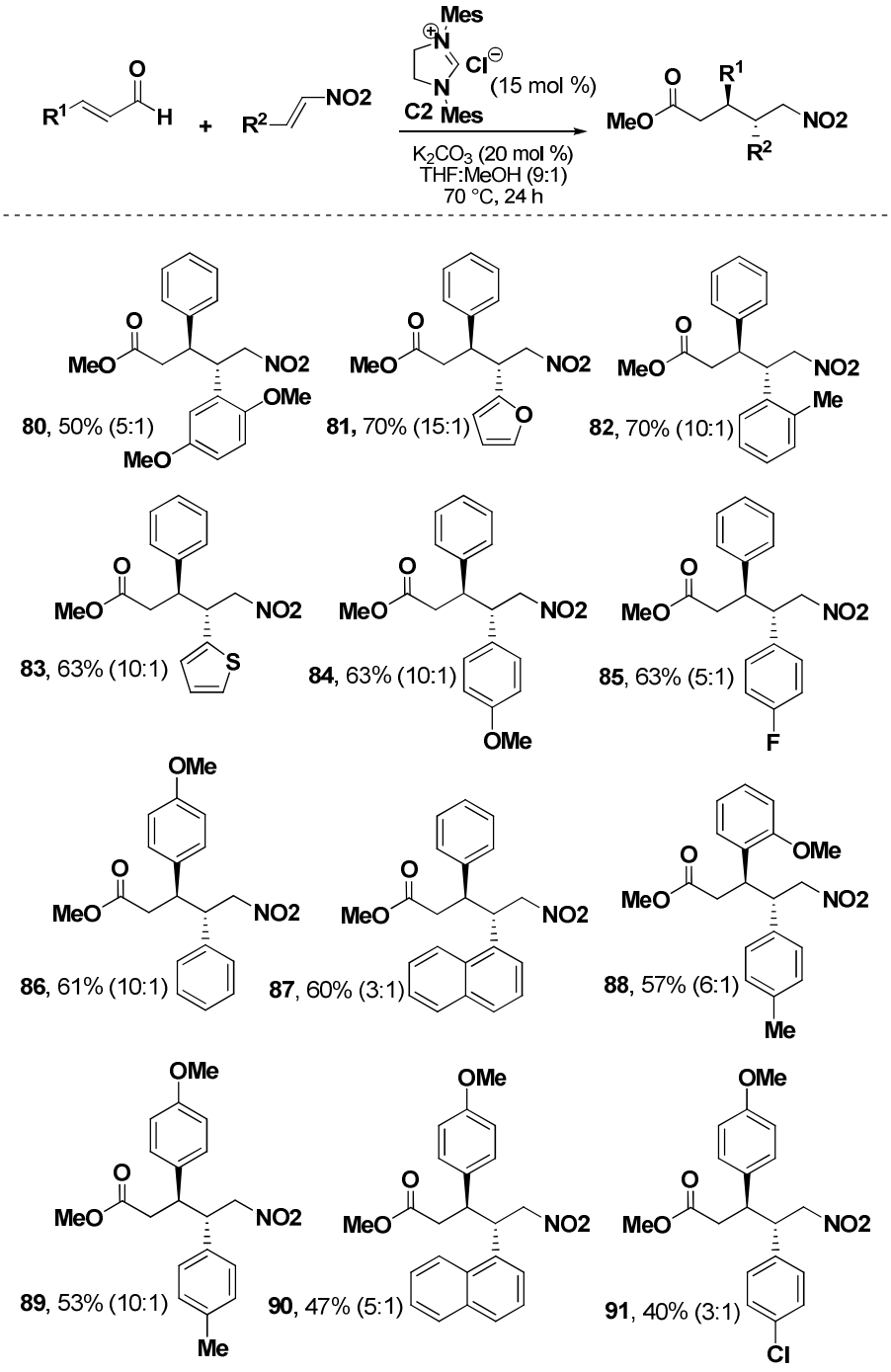
R^1 = Ph, R^2 = 4-methylphenyl

Entry	Base	Condition	Yield[a] %
1.	DBU	THF:MeOH (9:1), 70 °C, 24 h	-
2.	K_2CO_3	THF:MeOH (9:1), 70 °C, 24 h	70
3.	$CsCO_3$	THF:MeOH (9:1), 70 °C, 24 h	34
4.	Na_2CO_3	THF:MeOH (9:1), 70 °C, 24 h	37
5.	$BaCO_3$	THF:MeOH (9:1), 70 °C, 24 h	-
6.	Li_2CO_3	THF:MeOH (9:1), 70 °C, 24 h	-
7.	K_2CO_3	THF:MeOH (7:2), 70 °C, 24 h	56
8.	K_2CO_3	THF:MeOH (1:1), 70 °C, 24 h	34
9.	K_2CO_3	THF:MeOH (1:1), rt, Ar, 24 h	-
10.	K_2CO_3	THF , 70 °C, 24 h	-
11.	K_2CO_3	MeOH , 70 °C, 24 h	-
12.	K_2CO_3	PhMe:MeOH (7:2), 70 °C, 24 h	15

[a] isolated yield

After having reasonably established the optimum parameters, the reaction was extended to a number of nitroalkenes and the results are summarized in Scheme 2.25. Inevitable polymerization of nitroalkenes may be the reason for a substantial decrease in the product formation. In our studies, useful yields of products were obtained only with aryl substituted enals and β- nitrostyrenes.

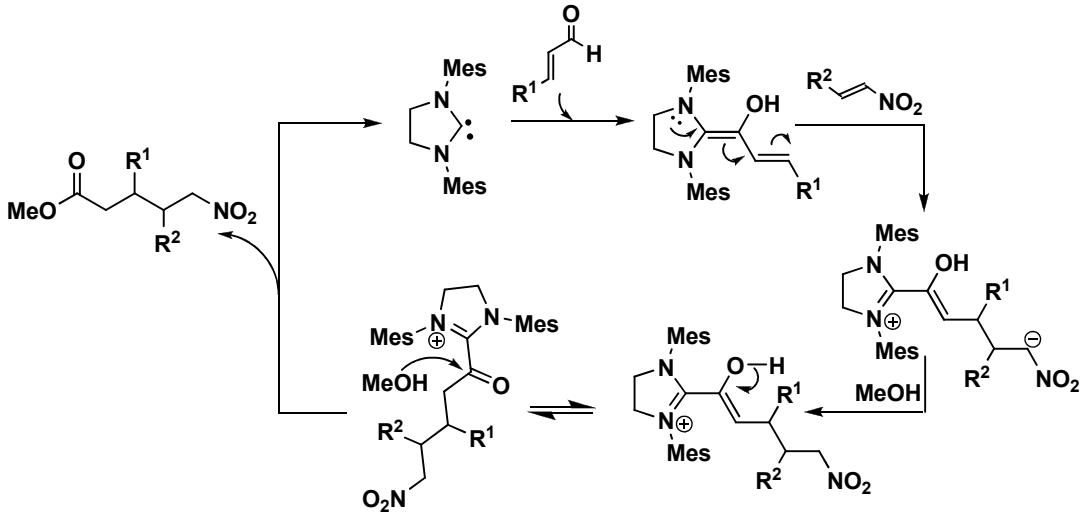
Scheme 2.25. Substrate scope[a,b]



[a] isolated yield, [b]dr is determined by ^{1}H NMR analysis

2.4. Mechanism

Mechanistically the reaction may be viewed as involving the initial formation of homoenolate by the reaction of NHC with the enal followed by its Michael addition to β-nitrostyrene. The stereoselectivity observed in the product formation may be attributed to the trans-selective Michael addition (Scheme 2.26).



Scheme 2.26. Proposed mechanism

2.5. Conclusion

In conclusion, the first report on the efficient, NHC catalyzed stereoselective Michael addition of enals to β-nitrostyrenes *via* the intermediacy homoenolate is developed. The saturated imidazolinium chloride is used as a catalyst for the first time to generate homoenolate from enals. It is reasonable to assume that since the products are doubly functionalized five carbon synthons; this reaction will find application in organic synthesis,[29] especially in the synthesis of biologically active piperidinone and δ-amino acid derivatives.

2.6. Experimental Details

NMR spectra were recorded at 500 (^{1}H) or 300 (^{1}H) and 126 (^{13}C) or 75 (^{13}C) MHz respectively on Brucker Avance DPX - 500 or 300 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 EI/HRMS or FAB using JEOL JMS 600H mass spectrometer. IR spectra were recorded on Brucker Alpha-T or E FT-IR spectrophotometer; absorbencies are reported in cm^{-1}. Commercially available enals were purchased from Aldrich Chemical Co. and others were synthesized by Wittig reaction between (triphosphoranylidene)acetaldehyde and the corresponding aldehydes.[30] The nitrostyrenes were easily prepared by the condensation of corresponding aldehydes with nitromethane (Henry reaction). The carbene precursor 1,3-dimesityl-imidazolinium chloride was also prepared according to known literature procedure.[31] Commercial grade solvents were distilled prior to use. All reactions were carried out in oven-dried glassware. Progress of reactions was monitored

by Thin Layer Chromatography. Gravity column chromatography was performed using 60-120/100-200 mesh silica gel, and mixtures of petroleum ether-ethyl acetate were used for elution. Melting points were recorded on a Büchi melting point apparatus and are uncorrected.

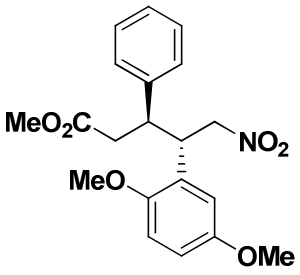
2.6.1. General Experimental Procedure

Synthesis of methyl 4-(2, 5-dimethoxyphenyl)-5-nitro-3-phenylpentanoate ***80***:- K_2CO_3 (13.8 mg, 20 mol %) was added to a solution of 1,3-dimesityl imidazolinium chloride **C2** (26 mg, 15 mol %), cinnamaldehyde (132 mg, 1 mmol) and 2,5-dimethoxy-β-nitrostyrene (104.5 mg, 0.5 mmol) in 9:1 dry THF: methanol, this solution was stirred for 24 h at 70 ^{o}C under reflux condition. After the completion of the reaction, the reaction mixture was acidified by 1:1 HCl. After the removal of the solvent, the residue was extracted with ethyl acetate and organic layer was dried with anhydrous Na_2SO_4. The concentrated residue was subjected to column chromatography on a silica gel (100-200 mesh) column using 93:7 hexane: ethyl acetate solvent mixture as eluent to afford **80** (50% yield)**.**

2.6.2. Characterization Data of Compounds

Methyl-4-(2,5-dimethoxyphenyl)-5-nitro-3-phenylpentanoate (80)

Following the general procedure, the reaction of 2,5-dimethoxy-β-nitrostyrene (104.5 mg, 0.5 mmol), cinnamaldehyde (132 mg, 2 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 4-(2,5-dimethoxyphenyl)-5-nitro-3-phenylpentanoate in 50% (93 mg) yield as white crystalline solid.



Chemical Formula: $C_{20}H_{23}NO_6$

m p 112-114 °C.

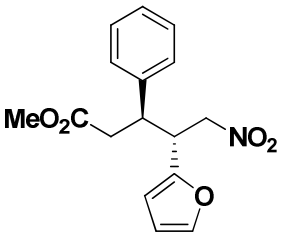
IR (film) ν_{max} 1730,1552,1377,1265, 1046 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.22-7.15 (m, 3H) 6.95-6.93 (m, 2H) 6.73 (d, *J* = 9 Hz, 1H) 6.66-6.68 (m, 1H) 6.05 (d, *J* = 3 Hz, 1H) 4.68 (dd, *J* =13 Hz, 7 Hz, 1H) 4.63 (dd, *J* = 13 Hz, 8.5 Hz, 1H) 4.277-4.319 (m, 1H) 3.746 (s, 3H) 3.64-3.69 (m, 1H) 3.57(s, 3H) 3.57(s, 3H) 2.76(dd, *J* = 16 Hz, 7 Hz, 1H) 2.60 (dd, *J* = 16.5 Hz, 8.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.9, 152.9, 151.5, 139.4, 128.5, 128.0,

127.1, 125.5, 115.6, 113.3, 111.6, 55.7, 55.4, 51.6, 43.0, 41.9, 37.0. **HRMS-EI** Calculated for $C_{20}H_{23}NO_6$: 373.1525, Found: 373.1528.

Methyl-4-(furan-2-yl)-5-nitro-3-phenylpentanoate (81)

Following the general procedure, the reaction of 2-(2-nitrovinyl)furan (69.5 mg, 0.5 mmol), cinnamaldehyde (132 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 4-(furan-2-yl)-5-nitro-3-phenylpentanoate in 70% (106 mg) yield as yellow viscous liquid.



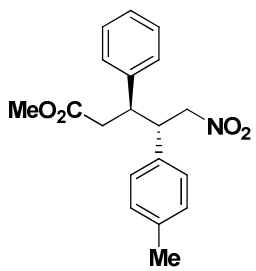
Chemical Formula: $C_{16}H_{17}NO_5$

IR (film) ν_{max} 1738,1557,1377,1261,1013 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33-7.3 (m, 1H) 7.24-7.25 (m, 3H) 6.87-6.89 (m, 2H) 6.29-6.30 (m, 1H) 5.99 (d, *J* = 3.5 Hz, 1H) 4.56(dd, *J* = 13.5 Hz, 7 Hz, 1H) 4.51 (dd, *J* = 13 Hz, 8.5 Hz, 1H) 4.07-4.11 (m, 1H) 3.63 (s, 3H) 3.53-3.58 (m, 1H) 2.87 (dd, *J* = 16 Hz, 7.5 Hz, 1H) 2.72 (dd, *J*= 16 Hz, 8Hz, 1H). **^{13}C (126 MHz, $CDCl_3$)** δ = 171.6, 150.0, 142.1, 138.4, 128.3, 128.2, 127.5, 110.4, 108.6, 75.7, 51.7, 43.3, 41.5, 37.4. **HRMS-EI** Calculated for $C_{16}H_{17}NO_5$: 303.1107, Found: 303.1128.

Methyl-5-nitro-3-phenyl-4-p-tolylpentanoate (82)

Following the general procedure, the reaction of 1-methyl-4-(2-nitrovinyl)benzene (81.5 mg, 0.5 mmol), cinnamaldehyde (132 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 5-nitro-3-phenyl-4-p-tolylpentanoate in 70% (114.5 mg) yield as white solid.



Chemical Formula: $C_{19}H_{21}NO_4$

m p 79-81 ^oC.

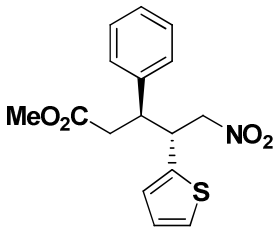
IR (film) ν_{max} 1732, 1557, 1379, 1263, 1021 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.19-7.21 (m, 3H) 7.00 (d, *J* = 8 Hz, 2H) 6.83-6.85 (m, 2H) 6.68 (d, *J* = 8 Hz, 2H) 4.67 (dd, *J* = 13 Hz, 7 Hz, 1H) 4.51 (dd, *J* = 13 Hz, 8.5 Hz, 1H) 3.83-3.85 (m, 1H) 3.60 (s, 3H) 3.52-3.54 (m, 1H) 2.72 (dd, *J*

= 15.5 Hz, 7.5 Hz, 1H) 2.59 (dd, *J* = 15.5 Hz, 7.5 Hz, 1H) 2.29 (s, 3H). **^{13}C NMR (125MHz, $CDCl_3$)** δ = 171.8, 138.5, 137.3, 132.4, 128.9, 128.8, 128.8, 128.1, 127.3, 77.9, 51.7, 47.3, 43.8, 37.5, 21.0. **HRMS-EI** Calculated for $C_{19}H_{21}NO_4$: 327.1471, Found 327.1479.

Methyl-5-nitro-3-phenyl-4-(thiophen-2-yl)pentanoate (83)

Following the general procedure, the reaction of 2-(2-nitrovinyl)thiophene (77.6 mg, 0.5 mmol), cinnamaldehyde (132 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 5-nitro-3-phenyl-4-(thiophen-2-yl)pentanoate in 63% (100.5 mg) yield as white solid.



Chemical Formula: $C_{16}H_{17}NO_4S$

m p 61-63 ^oC.

IR (film) ν_{max} 1736,1556,1379,1258,1018 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.25-7.27 (m, 3H) 7.18-7.19 (m, 1H) 6.94-9.96 (m, 2H) 6.89-6.91 (m, 1H) 6.55-6.56 (m, 1H) 4.68 (dd, *J* = 13 Hz, 7 Hz, 1H) 4.51 (dd, *J* = 13 Hz, 8.5 Hz, 1H) 4.25-4.27 (m, 1H) 3.64 (s, 3H) 3.57-3.59 (m, 1H) 2.85 (dd, *J* = 16 Hz, 7.5 Hz, 1H) 2.72 (dd, *J* = 16 Hz, 7.5 Hz, 1H). **^{13}C (126 MHz, $CDCl_3$)** δ = 171.6, 138.1, 137.9, 128.7, 128.3, 127.6, 126.7, 126.7, 124.8, 78.2, 51.8, 44.1, 43.1, 37.4. **HRMS-EI** Calculated for $C_{16}H_{17}NO_4S$: 319.0878, Found: 319.0868.

Methyl-4-(4-methoxyphenyl)-5-nitro-3-phenylpentanoate (84)

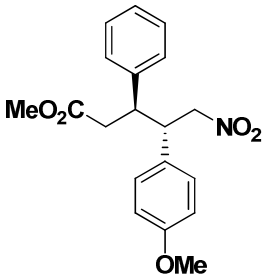
Following the general procedure, the reaction of 1-methoxy-4-(2-nitrovinyl)benzene (89.5 mg, 0.5 mmol), cinnamaldehyde (132 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 4-(4-methoxyphenyl)-5-nitro-3-phenylpentanoate in 63% (108 mg) yield as white solid.

Chemical Formula: $C_{19}H_{21}NO_5$

m p 67-69 ^oC.

IR (film) ν_{max} 1732,1556,1379,1252,1032 cm^-1.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.22-7.23 (m, 3H) 6.84-



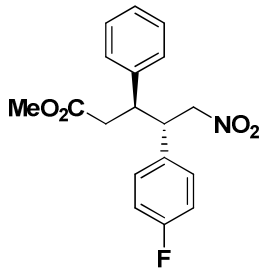
6.86 (m, 2H) 6.72-6.76 (m, 4H) 4.7 (dd, *J* = 13 Hz, 7 Hz, 1H) 4.52 (dd, *J* = 12.5 Hz, 9 Hz, 1H) 3.83-3.87 (m, 1H) 3.77 (s, 3H) 3.63 (s, 3H) 3.51-3.55 (m, 1H) 2.75 (dd, *J* = 15.5 Hz, 7.5 Hz, 1H) 2.62 (dd, *J* = 16 Hz, 7.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.8, 159.0, 138.5, 130.0, 129.1, 128.8, 128.1, 127.3, 113.6, 78.0, 55.0, 51.7, 46.9, 43.9, 37.6. **HRMS-EI** Calculated for $C_{19}H_{21}NO_5$: 343.1420, Found: 343.1405.

Methyl-4-(4-fluorophenyl)-5-nitro-3-phenylpentanoate (85)

Following the general procedure, the reaction of 1-fluoro-4-(2-nitrovinyl)benzene (83.6 mg, 0.5 mmol), cinnamaldehyde (132 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 4-(4-fluorophenyl)-5-nitro-3-phenylpentanoate in 63% (104 mg) yield as yellow viscous liquid.

Chemical Formula: $C_{18}H_{18}FNO_4$

IR (film) ν_{max} 1738,1556,1379,1228,1015 cm^{-1}.



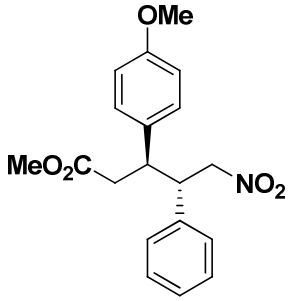
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.19-7.213 (m, 3H) 6.87-6.91 (m, 2H) 6.76-6.82 (m, 4H) 4.71 (dd, *J* = 13 Hz, 7 Hz, 1H) 4.53 (dd, *J* = 13 Hz, 9 Hz, 1H) 3.85-3.89 (m, 1H) 3.62 (s, 3H) 3.51-3.52 (m, 1H) 2.72 (dd, *J* = 15.5 Hz, 7.5 Hz, 1H) 2.61 (dd, *J* = 15.5 Hz, 7.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ =171.9, 152.9, 151.5, 139.4, 128.5, 128.0, 127.1, 125.5, 115.6, 113.3, 111.6, 77.9, 55.7, 55.4, 51.6, 43.0, 41.9, 37.0. **HRMS-EI** Calculated for $C_{18}H_{18}FNO_4$: 331.1220, Found: 331.1237.

Methyl-3-(4-methoxyphenyl)-5-nitro-4-phenylpentanoate (86)

Following the general procedure, the reaction of (2-nitrovinyl)benzene (74.6 mg, 0.5 mmol), 4-methoxycinnamaldehyde (162 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 3-(4-methoxyphenyl)-5-nitro-4-phenylpentanoate in 60% (104.6 mg) yield as yellow viscous liquid.

Chemical Formula: $C_{19}H_{21}NO_5$

IR (film) ν_{max} 1732, 1556, 1379,1251, 1033 cm^{-1}**.**



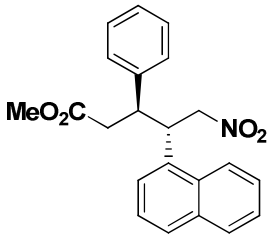
1H NMR (500 MHz, $CDCl_3$) δ = 7.20-7.21 (m, 3H) 6.79 - 6.81 (m, 2H) 6.72 (m, 4H) 4.6 (dd, *J* = 13 Hz, 7.5 Hz, 1H) 4.53 (dd, *J* = 12.5 Hz, 8.5 Hz, 1H) 3.32-3.86 (m, 1H) 3.75 (s, 3H) 3.60 (s, 3H) 3.48-3.52 (m, 1H) 2.69 (dd, *J* = 15.5 Hz, 7 Hz, 1H) 2.55 (dd, *J* = 15.5 Hz, 8 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.8, 158.7, 135.6, 130.1, 129.8, 129.0, 128.2, 127.79, 113.5, 77.8, 55.0, 51.7, 47.7, 43.0, 37.8. **HRMS-EI** Calculated for $C_{19}H_{21}NO_5$: 343.1420, Found: 343.1425.

Methyl-4-(naphthalen-1-yl)-5-nitro-3-phenylpentanoate (87)

Following the general procedure, the reaction of 1-(2-nitrovinyl)naphthalene (99.6 mg, 0.5 mmol), cinnamaldehyde (132 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 4-(naphthalen-1-yl)-5-nitro-3-phenylpentanoate in 60% (109 mg) yield as brown viscous liquid.

Chemical Formula: $C_{22}H_{21}NO_4$

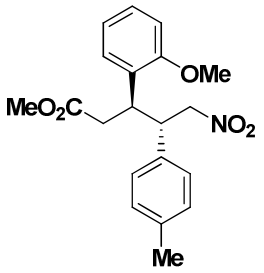
IR (film) ν_{max} 1732, 1553, 1377, 1259, 1017 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.1 (d, *J* = 10 Hz, 1H) 7.81(d, *J* = 10 Hz, 1H) 7.71 (d, *J* = 10 Hz, 1H) 7.56-7.53 (m, 1H) 7.48-7.45 (m, 1H) 7.37-7.38 (m, 1H) 7.16-7.20 (m, 3H) 6.995 (d, *J* = 5 Hz, 2H) 6.83-6.85 (m, 1H) 4.94 (bs, 1H) 4.80-4.73 (m, 2H) 3.84-3.81 (m, 1H) 3.49 (s, 3H) 2.69-2.66 (m, 1H) 2.63-2.60 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.9, 140.4, 134.0, 132.6, 129.2, 128.4, 128.3, 127.9, 127.4, 126.6, 125.8, 124.6, 122.6, 77.5, 51.6, 44.1, 39.0, 36.5. **HRMS-EI** Calculated for $C_{22}H_{21}NO_4$: 363.1471, Found: 363.1472.

Methyl 3-(2-methoxyphenyl)-5-nitro-4-p-tolylpentanoate (88)

Following the general procedure, the reaction of 1-methyl-4-(2-nitrovinyl)benzene (81.5 mg, 0.5 mmol), 2-methoxycinnamaldehyde (162 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 3-(2-methoxyphenyl)-5-nitro-4-p-tolylpentanoate in 57% (101.8 mg) yield as yellow viscous liquid.



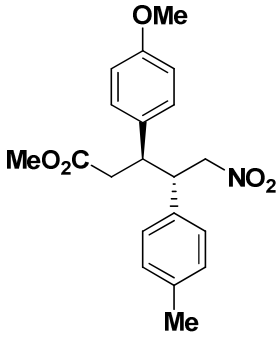
Chemical Formula: $C_{20}H_{23}NO_5$

IR(film) ν_{max} 1732, 1557,1379,1244,1026 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.19-7.21 (m, 1H) 7.02 (d, *J* = 7.5 Hz, 2H) 6.87 (d, *J* = 7.5 Hz, 1H) 6.74-6.79 (m, 3H) 6.50-6.6.51 (m, 1H) 4.72 (dd, *J* = 13.5 Hz, 6.5 Hz, 1H) 4.51 (dd, *J* = 13.5 Hz, 9.5 Hz, 1H) 4.10 (m, 1H) 3.95 (m, 1H) 3.86 (s, 3H) 3.63 (s, 3H) 2.69 (dd, *J* = 16 Hz, 8 Hz, 1H) 2.54 (dd, *J* = 15.5 Hz, 7.5 Hz, 1H) 2.31 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 172.2, 157.0, 137.0, 133.1, 129.7, 129.4, 128.8, 128.2, 127.1, 120.1, 110.4, 77.3, 55.2, 51.6, 46.3, 36.8, 36.5, 21.0. **HRMS-EI** Calculated for $C_{20}H_{23}NO_5$: 357.1576, Found: 357.1524.

Methyl-3-(4-methoxyphenyl)-5-nitro-4-p-tolylpentanoate (89)

Following the general procedure, the reaction of 1-methyl-4-(2-nitrovinyl)benzene (81.5 mg, 0.5 mmol), 4-methoxycinnamaldehyde (162 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 3-(4-methoxyphenyl)-5-nitro-4-p-tolylpentanoate in 53% (94.6 mg) yield as yellow viscous liquid.



Chemical Formula: $C_{20}H_{23}NO_5$

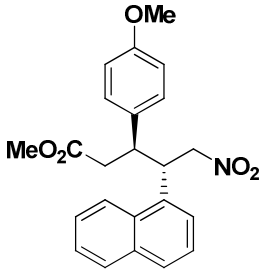
IR (film) ν_{max} 1737,1603,1556,1378,1251,1033 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.03 (d, *J* = 8 Hz, 2H) 6.78-6.74 (m, 4H) 6.71 (d, *J* = 8 Hz, 2H) 4.68 (dd, *J* = 13 Hz, 7.5 Hz, 1H) 4.52 (dd, *J* = 12.5 Hz, 8.5 Hz, 1H) 3.80-3.84 (m, 1H) 3.79 (s, 3H) 3.62 (s, 3H) 3.52-3.48 (m, 1H) 2.71 (dd, *J* = 15.5 Hz, 7 Hz, 1H) 2.56 (dd, *J* = 16 Hz, 8 Hz, 1H) 2.32 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.9, 158.7, 137.3, 132.4, 130.2, 130.2, 129.9, 128.9, 114.5, 113.4, 77.9, 55.0, 51.7, 47.3, 43.0, 37.8, 21.0. **HRMS-EI** Calculated for $C_{20}H_{23}NO_5$: 357.1576, Found: 357.1581.

Methyl-3-(4-methoxyphenyl)-4-(naphthalen-1-yl)-5-nitropentanoate (90)

Following the general procedure, the reaction of 1-(2-nitrovinyl)naphthalene (99.6 mg, 0.5 mmol), 4-methoxycinnamaldehyde (162 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1

THF:MeOH solvent mixture afforded methyl 3-(4-methoxyphenyl)-4-(naphthalen-1-yl)-5-nitropentanoate in 47% (92.3 mg) yield as yellow viscous liquid.



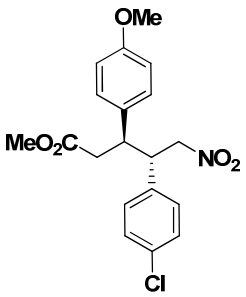
Chemical Formula: $C_{23}H_{23}NO_5$

IR (film) ν_{max} 1732, 1553, 1377, 1252, 1032 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.20 (d, *J* = 8.5 Hz, 1H) 7.86 (d, *J* = 7.5 Hz, 1H) 7.75 (d, *J* = 8.5 Hz, 1H) 7.57-7.6 (m, 1H) 7.49-7.54 (m, 1H) 7.30-7.33 (m, 1H) 7.31 (t, *J* = 8.5 Hz, 1H) 6.93 (d, *J* = 7 Hz, 2H) 6.84 (d, *J* = *7* Hz, 1H) 6.77 (d, *J* = 7 Hz, 2H) 4.95 (m, 1H) 4.72-4.78 (m, 1H) 3.79-3.84 (m, 1H) 3.77 (s, 3H) 3.53 (s, 3H) 2.65-2.70 (m, 1H) 2.54-2.59 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.9, 158.7, 134.0, 132.6, 132.1, 131.0, 129.5, 129.2, 128.9, 128.4, 126.5, 125.7, 124.5, 122.6, 114.5, 113.7, 77.6, 55.0, 51.6, 43.2, 36.8. **HRMS-EI** Calculated for $C_{23}H_{23}NO_5$: 393.1576, Found: 393.1560.

Methyl-4-(4-chlorophenyl)-3-(4-methoxyphenyl)-5-nitropentanoate (91)

Following the general procedure, the reaction of 1-chloro-4-(2-nitrovinyl)benzene (91.5 mg, 0.5 mmol), 4-methoxycinnamaldehyde (162 mg, 1 mmol), 1,3-dimesityl imidazolinium chloride (26 mg, 15 mol %) and K_2CO_3 (13.8 mg, 20 mol %) in 9:1 THF:MeOH solvent mixture afforded methyl 4-(4-chlorophenyl)-3-(4-methoxyphenyl)-5-nitropentanoate in 40% (75.4 mg) yield as yellow viscous liquid.



Chemical Formula: $C_{19}H_{20}ClNO_5$

IR (film) ν_{max} 1732,1556,1378,1251,1033 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.16 (d, *J* = 8.5 Hz, 1H) 7.12 (d, *J* = 8.5 Hz, 2H) 6.67-6.69 (m, 5H) 4.62 (dd, *J* = 13 Hz, 7 Hz, 1H) 4.43 (dd, *J* = 13 Hz, 9 Hz, 1H) 3.75-3.78 (m, 1H) 3.70 (s, 3H) 3.55 (s, 3H) 3.40-3.42 (m, 1H) 2.6 (dd, *J* = 16 Hz, 8 Hz, 1H) 2.48 (dd, *J* = 15.5 Hz, 7.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.6, 159.1, 158.8, 134.1, 133.8, 130.2, 129.8, 129.7, 129.4, 128.4, 114.6, 113.6, 77.9, 55.0, 51.8, 47.1, 43.0, 37.8. **HRMS-EI** Calculated for $C_{19}H_{20}ClNO_5$: 377.1030, Found: 377.1020.

2.7. References

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CHAPTER 3

Novel Transformation of 2*H*-Chromene-3-carboxaldehydes to 3-Methyl-2*H*-chromen-2-ones Catalyzed by *N*-Heterocyclic Carbenes

3.1. Introduction

Coumarin (2*H*-chromen-2-one or 2*H*-1-benzopyran-2-one) belongs to a group of benzopyrones, which consists of a benzene ring fused to a pyrone nucleus. Coumarins possess a number of biological activities like anticoagulant, antimicrobial, anti-inflammatory, analgesic, antioxidant, anticancer, antiviral, antimalarial etc.[1] In addition to biological activities, they have found use as additives to food and cosmetics,[1c] as dyes[2] and optical brightening agents.[3] The potent antibiotics like novobiocin, clorobiocin and coumermycin are coumarin derivatives.[4] Some examples of naturally occurring biologically active coumarin derivatives are shown in figure 3.1.

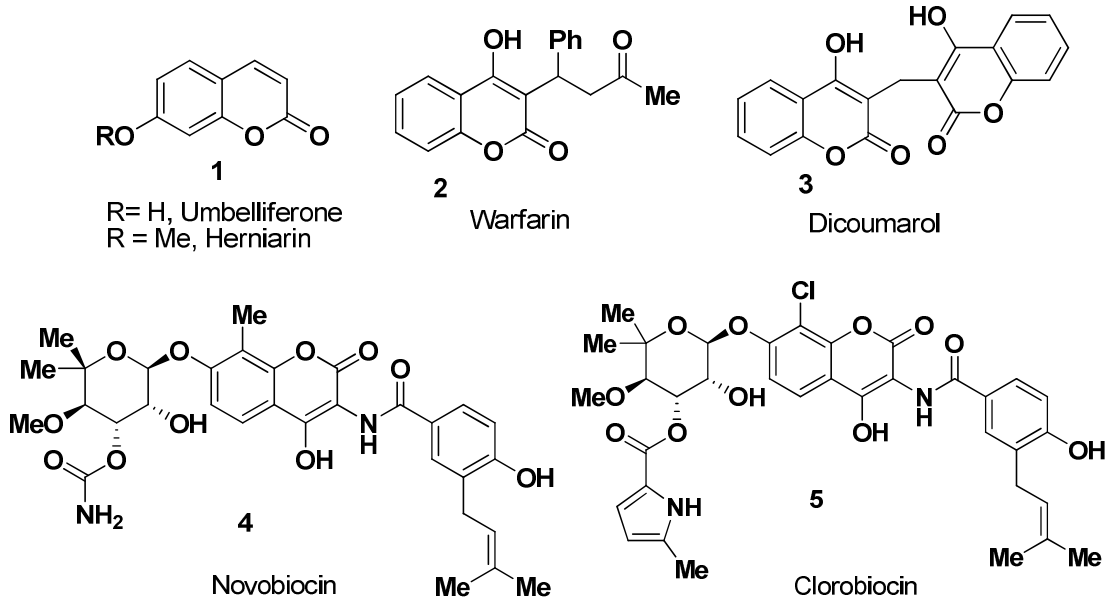


Figure 3.1. Biologically active coumarin derivatives

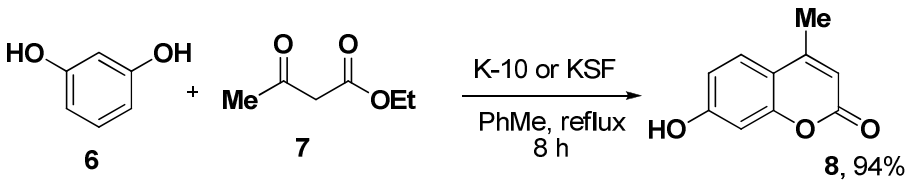
3.2. Methods of Coumarin Synthesis

A number of synthetic routes to the coumarins have been developed. These include use of the Pechmann, Claisen, Perkin, Knoevenagel, Reformatsky, and Wittig reactions; some of them are discussed in the following section.

3.2.1. Pechmann Reaction

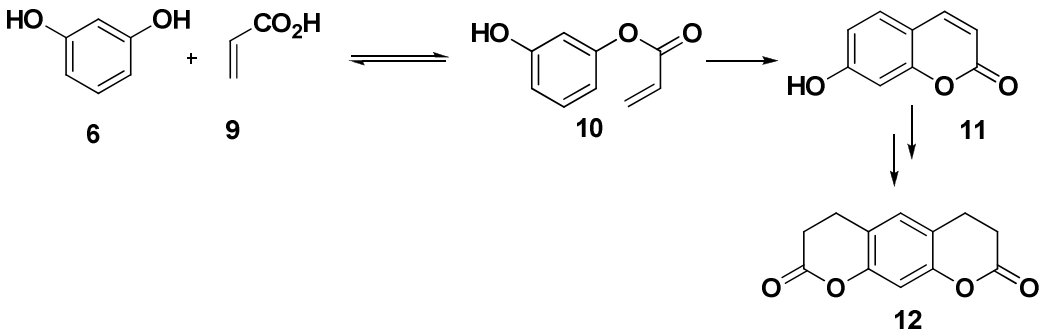
This reaction was first reported by Pechmann and Duisberg in 1883.[5] It is an acid-promoted synthesis of coumarin derivatives by the condensation of phenols and β-ketoesters or β-keto carboxylic acids. Pechmann reaction is a widely used method for preparing coumarins in good yield. This reaction can be done with homogeneous[6] and heterogeneous catalysts.[7] The use of microwave irradiation has also been applied to accelerate this reaction.[8]

Zhang et al.[9] reported the synthesis of coumarins via the Pechmann reaction catalyzed by montmorillonite K-10 or KSF in high yields (Scheme 3.1). This procedure is environmentally friendly and inexpensive compared to previous methods. They reported that K-10 worked better than KSF in terms of reaction time and yield. Furthermore, this method has the advantages of easy separation of the product and recyclability of the catalyst.



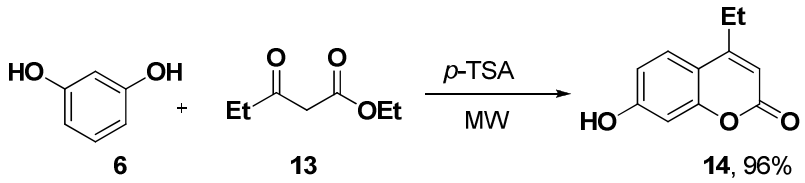
Scheme 3.1

Bekkum et al. have reported the synthesis of 7-hydroxycoumarin in good yield using a solid-acid catalyzed reaction of phenols with carboxylic acids.[7a] Equimolar amounts of resorcinol and acrylic acid, in the presence of zeolite H beta or Amberlyst-15, undergo esterification followed by ring closure (Scheme 3.2) to give both 7-hydroxy-3,4-dihydrocoumarin **11** and 3,4,6,7-tetrahydropyrano[3,2-g]chromene-2,8-dione **12**.



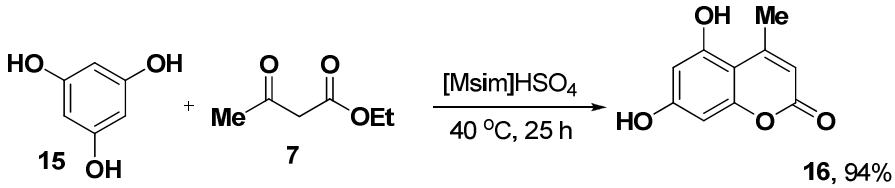
Scheme 3.2

Microwave initiated energy-efficient protocol has been developed for solvent-free Pechmann coumarin synthesis (Scheme 3.3).[8b]



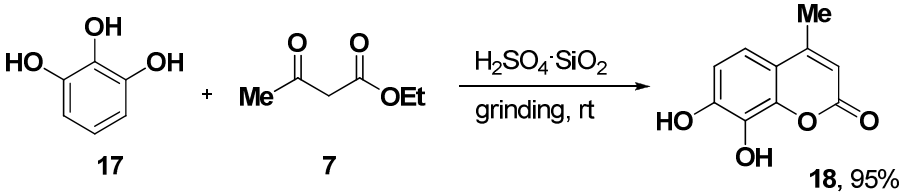
Scheme 3.3

Recently, Khaligh reported the synthesis of coumarins via Pechmann reaction catalyzed by 3-methyl-1-sulfonic acid imidazolium hydrogen sulfate as an efficient, halogen-free and reusable acidic ionic liquid (Scheme 3.4).[10]



Scheme 3.4

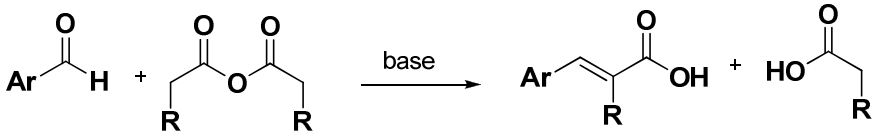
In 2013, a simple and highly efficient grinding procedure for the synthesis of coumarins via Pechmann condensation was reported (Scheme 3.5).[11] Different phenols and β -ketoesters in the presence of silica supported sulphuric acid at room temperature, under solvent free conditions afforded coumarin derivatives.



Scheme 3.5

3.2.2. Perkin Reaction

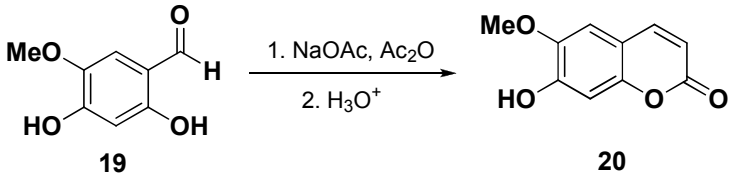
Perkin reaction is the direct preparation of cinnamic acid derivatives by the thermal condensation between aromatic aldehydes and aliphatic carboxylic acid anhydrides or carboxylic derivatives in the presence of a base catalyst (Scheme 3.6). This reaction was first reported by Perkin in 1868.[12]



Scheme 3.6

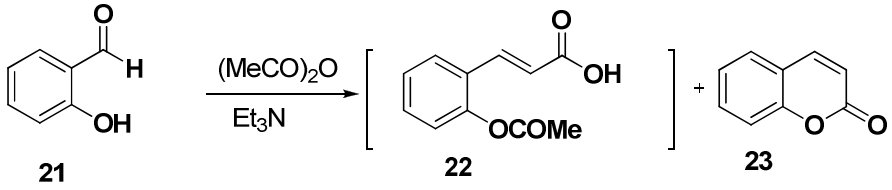
When the reaction is applied to salicylaldehydes, coumarins are obtained (Scheme 3.7). The disadvantage of this approach is the generally poor yield of the coumarins

obtained, due to the production of tarry materials under the severe reaction conditions of the Perkin synthesis.[13]



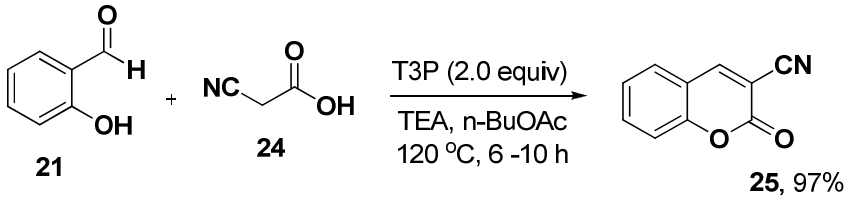
Scheme 3.7

Coumarin is also formed in the reaction of acetic anhydride and salicylaldehyde in presence of trimethylamine as the catalyst (Scheme 3.8).[14]



Scheme 3.8

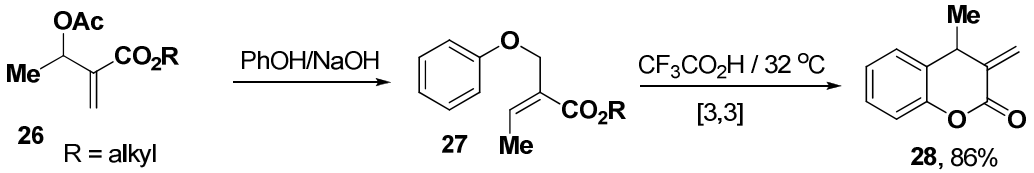
Recently, Augustine et al. reported an efficient coumarin synthesis via the Perkin condensation.[15] This one-pot synthesis was mediated by propylphosphonic anhydride (T3P), a mild and low toxic peptide coupling agent (Scheme 3.9).



Scheme 3.9

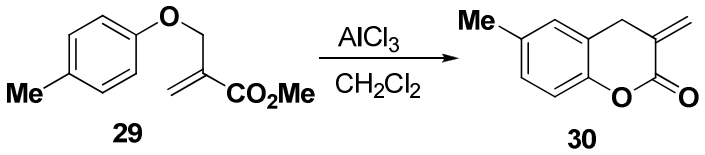
3.2.3. Claisen Rearrangement

Drewes et al.[16] reported the synthesis of 4-methyl-3-methylene-3,4-dihydrocoumarin **28** via the intramolecular Claisen-rearrangement of the aryl ether **27** in the presence of trifluoroacetic acid (Scheme 3.10). Drewes method is more efficient than earlier synthetic methods, because the precursor alkyl 3-acetoxy-2-methylene butanoate is readily prepared via acetylation of a Baylis-Hillman product and cyclization may be effected in the presence of trifluoroacetic acid to afford the coumarin **28** in 86% yield in a one-pot procedure.



Scheme 3.10

Previously, a similar approach to 3-methylenecoumarin was reported, which involves Lewis-acid catalyzed Claisen rearrangement of an α-aryloxy methyl acrylate ester **29** (Scheme 3.11).[17] A small amount of a dimer is also produced, which is assumed to form via an ene reaction of the highly reactive methylenecoumarin **30**.

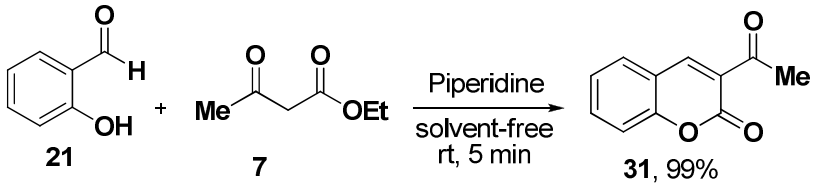


Scheme 3.11

3.2.4. Knoevenagel Condensation

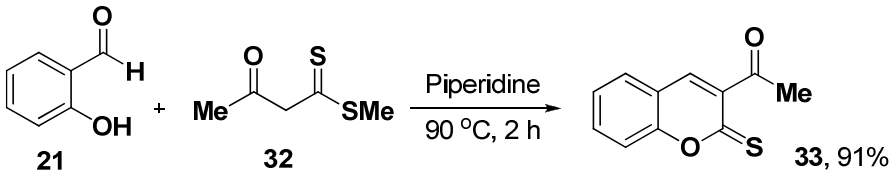
The Knoevenagel reaction[18] involves the condensation of benzaldehydes with activated methylene compounds in the presence of an amine. Knoevenagel condensation is one of the most important methods of coumarin synthesis in organic chemistry.

In 2001 Sugino and Tanaka reported a simple and efficient synthesis of coumarins via the Pechmann and Knoevenagel condensation reactions under solvent-free conditions (Scheme 3.12).[19]



Scheme 3.12

A facile synthesis of 3-alkanoyl/aroyl/heteroaroyl-2*H*-chromene-2-thiones has been developed by Singh and co-workers (Scheme 3.13).[20] The reaction was carried out by condensation of easily accessible β-oxodithioesters and salicylaldehyde under solvent-free conditions. The newly synthesized compounds exhibited profound antioxidant activities.

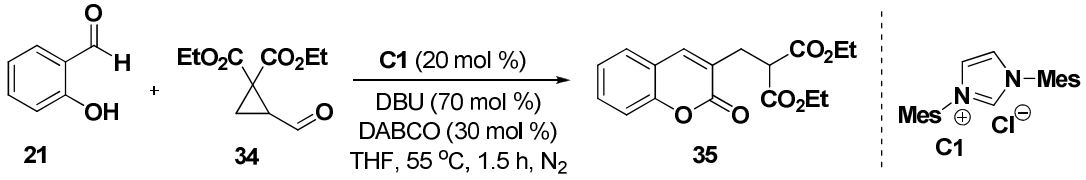


Scheme 3.13

3.2.5. NHC Catalyzed Coumarin Synthesis

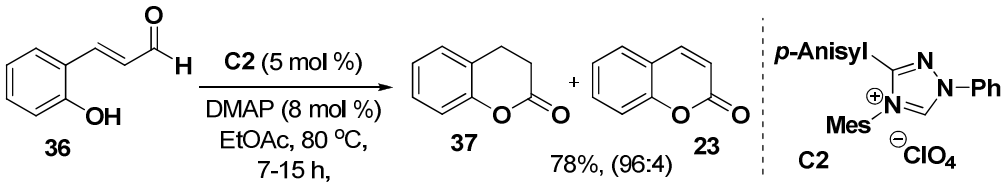
In 2008 Wang and Du reported an *N*-heterocyclic carbene (NHC) catalyzed reaction of formylcyclopropane 1,1-diesters with salicylaldehydes.[21] This domino redox

esterification/cyclization reaction afforded coumarins in good to excellent yields (Scheme 3.14).



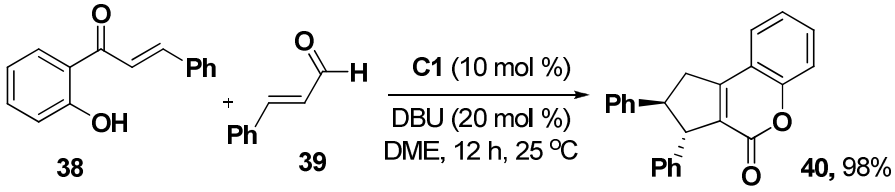
Scheme 3.14

Zeitler and Rose reported;[22] a mild, atom-economic, *N*-heterocyclic carbene-catalyzed redox lactonization of cinnamaldehydes to 3,4-dihydrocoumarins in a one-pot domino procedure in the presence of oxidants (Scheme 3.15).



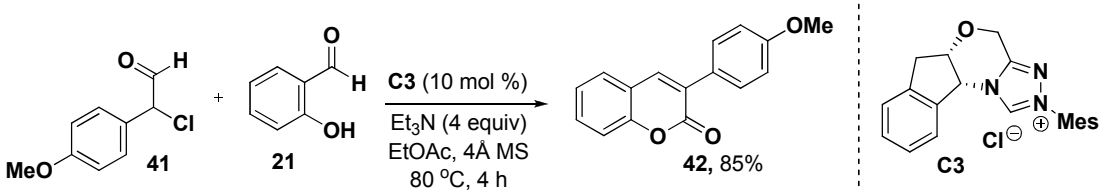
Scheme 3.15

Recently, it was reported that NHC-catalyzed annulation of enals with *o*-hydroxy chalcones afforded cyclopentane-fused coumarin derivatives with an excellent level of diastereocontrol (Scheme 3.16).[23] The reaction tolerates a broad range of functional groups.



Scheme 3.16

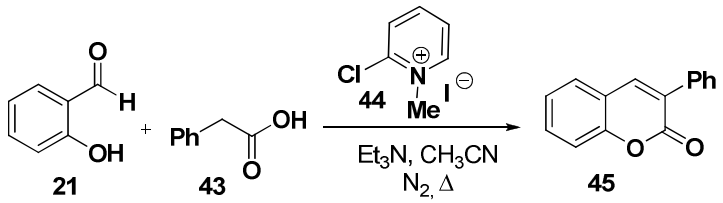
A facile and experimentally simple and mild reaction of 2-chloro-2-arylacetaldehyde with salicylaldehyde catalyzed by NHC leading to 3-arylcoumarin was reported.[24] A number of 3-arylcoumarin derivatives were obtained in good to excellent yields via this umpolung reaction (Scheme 3.17).



Scheme 3.17

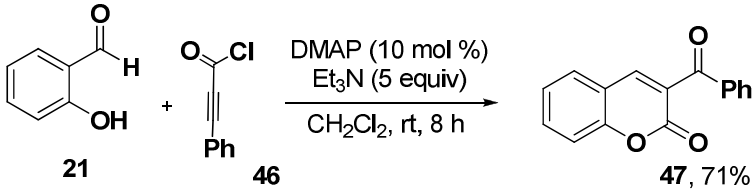
3.2.6. Miscellaneous Reactions

The Mukaiyama esterification protocol has been successfully exploited to provide rapid access to a variety of 3-substituted coumarins in satisfactory yields using 2-chloro-1-methylpyridinium iodide-triethylamine reagent (Scheme 3.18).[25]



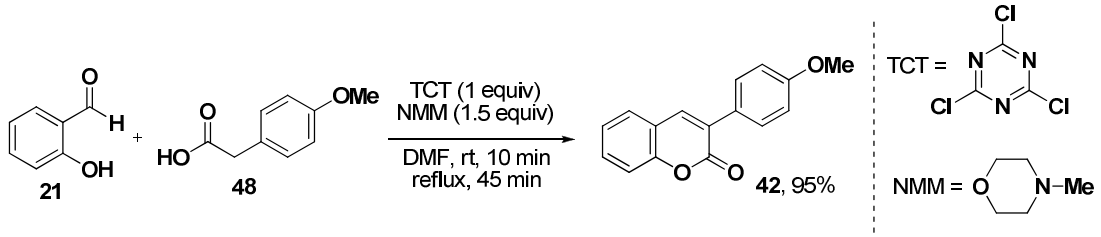
Scheme 3.18

An unusual one-pot synthesis of 3-benzoylcoumarins and coumarin-3-carbaldehydes was reported by the reaction of easily available 2-hydroxybenzaldehydes and phenylpropiolyl chloride/propiolyl chloride under esterification condition (Scheme 3.19).[26]



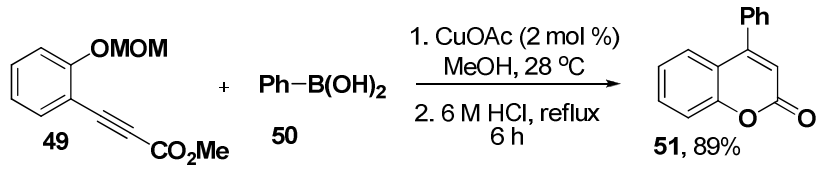
Scheme 3.19

The use of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) and *N*-methyl morpholine enables an efficient and general protocol for a rapid synthesis of substituted 3-aryl coumarins. A series of substituted phenyl acetic acids have been successfully reacted with substituted 2-hydroxy benzaldehydes to afford 3-aryl coumarins in excellent yield (Scheme 3.20).[27]



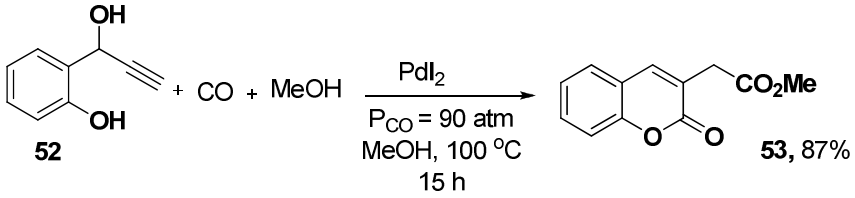
Scheme 3.20

2-Hydroxy (MOM-protected) arylpropiolic acid methyl esters underwent hydroarylation with various arylboronic acids in MeOH at ambient temperature in the presence of a catalytic amount of CuOAc, to afford 4-arylcoumarins in high yields after the acidic workup (Scheme 3.21).[28]



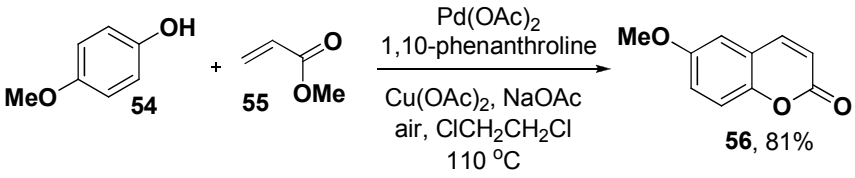
Scheme 3.21

A novel approach to coumarin derivatives starting from readily available 2-(1-hydroxyprop-2-ynyl) phenols was reported.[29] The reaction was based on an unprecedented palladium-catalyzed dicarbonylation process (Scheme 3.22).



Scheme 3.22

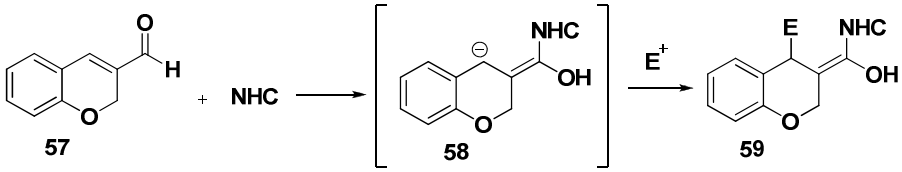
A versatile catalytic method for the synthesis of 2-substituted benzofuran and various substituted coumarins through palladium-catalyzed intermolecular annulation of phenols and olefins has been reported recently (Scheme 3.23).[30]



Scheme 3.23

3.3. Present Work

In the context of our persistent interest in the chemistry of homoenolates, and with a view to extend the scope of the latter, we sought to generate endocyclic homoenolate and examine its reactivity towards electrophiles (Scheme 3.24).

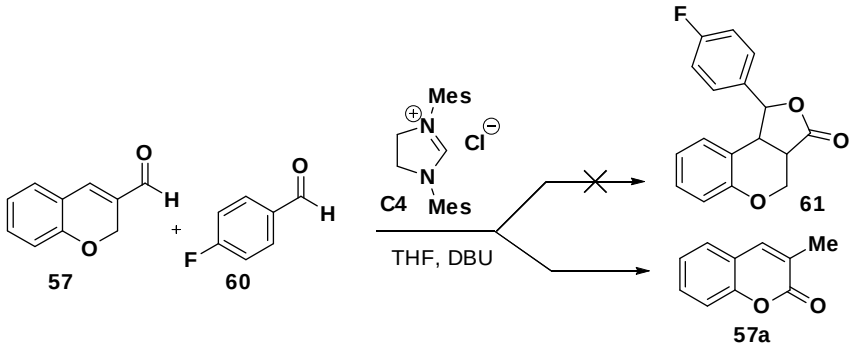


Scheme 3.24

3.4. Results and Discussion

In a prototype experiment, 2*H*-chromene-3-carboxaldehyde **57** was exposed to saturated imidazole carbene (SIMes), generated from the chloride salt **C4** by DBU, in the presence of 4-flourobenzaldehyde in THF. It was surmised that the homoenolate formed from **57** would be trapped by the latter to form a γ-lactone consistent with the known

chemistry of homoenolate. In the event, the reaction yielded none of the expected product, but surprisingly 3-methyl-2*H*-chromen-2-one (3-methyl coumarin) **57a** was formed in 25 % yield (Scheme 3.25).



Scheme 3.25

The structure of the compound was obtained from common spectroscopic data. In the ^{1}H NMR spectrum a signal at δ 2.13 showed the presence of methyl proton. The methyl group was confirmed from the ^{13}C NMR spectrum and a signal at δ 161.9 can be attributed to an ester carbonyl carbon. In the IR spectrum an absorption signal at 1709 cm^{-1} confirmed the presence of a carbonyl group. The mass spectrum was also in agreement with the proposed structure.

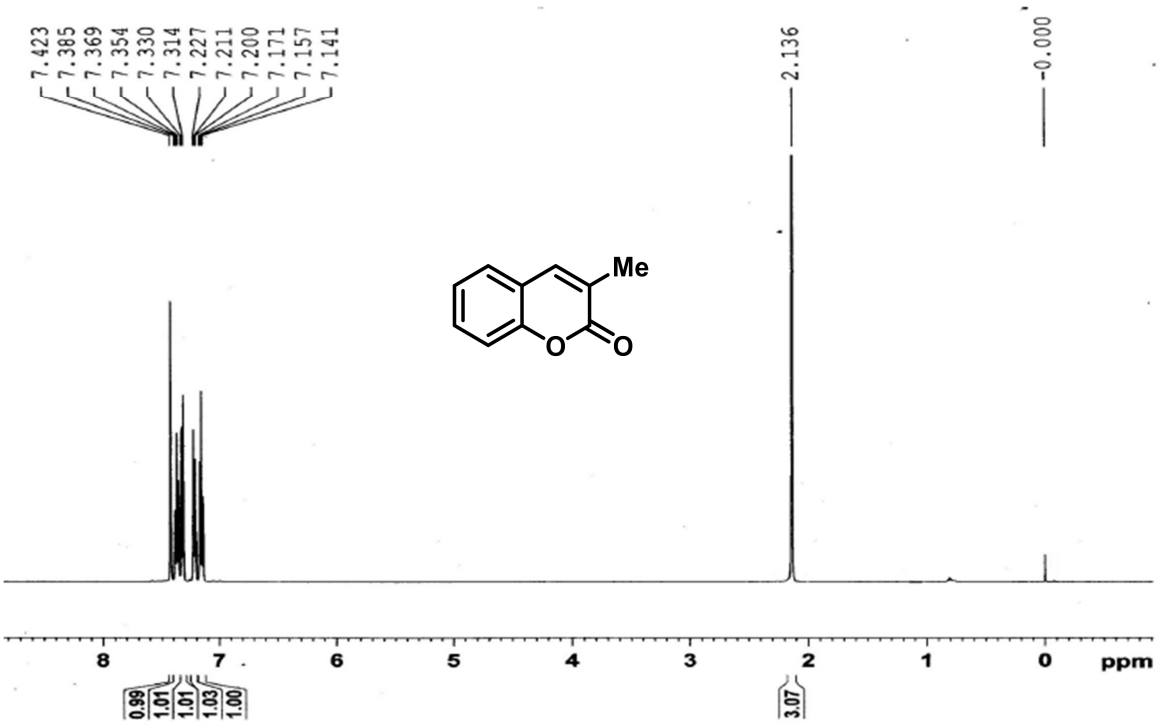


Figure 3.2. ^{1}H NMR Spectrum of **57a**

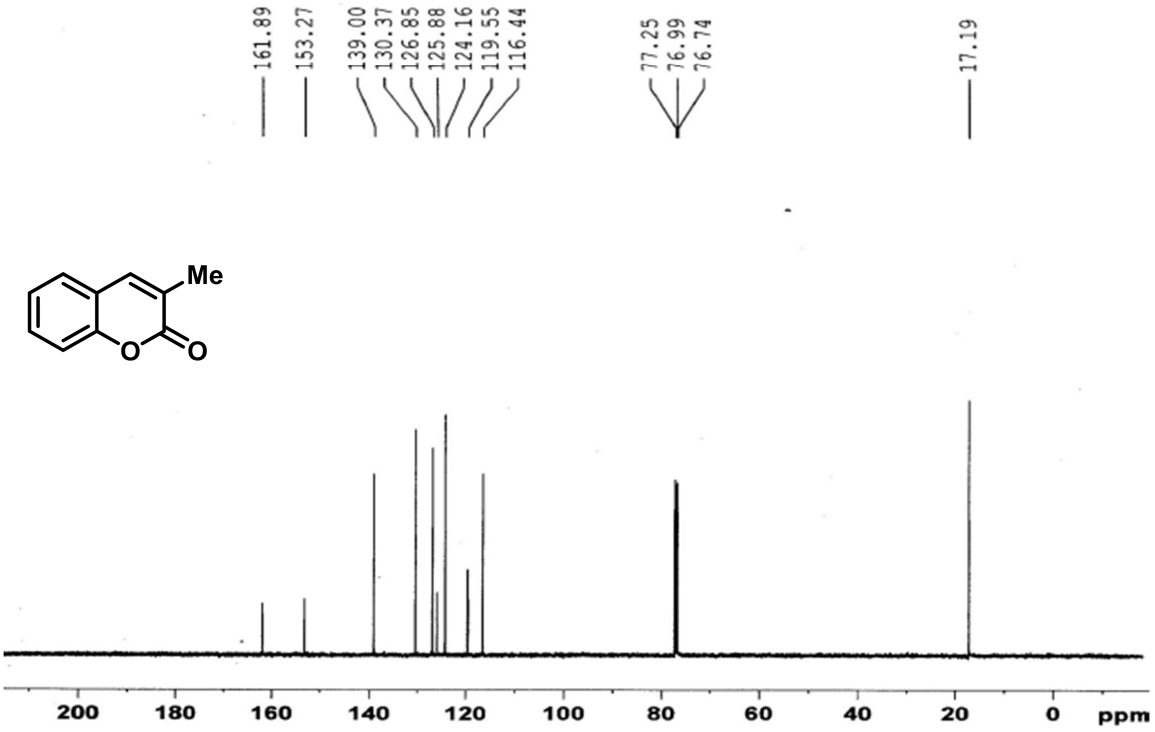


Figure 3.3. ^{13}C NMR Spectrum of **57a**

The final confirmation of the structure of the compound was ascertained from the single crystal X-ray analysis of an analogous compound **67a**, derived from 6-methyl chromene-3-carboxaldehyde (Figure 3.4).

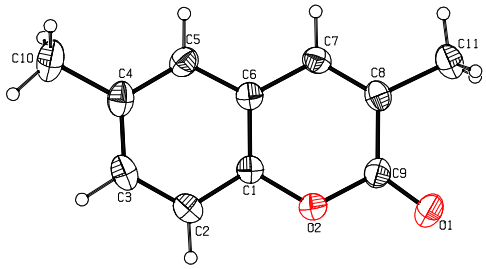
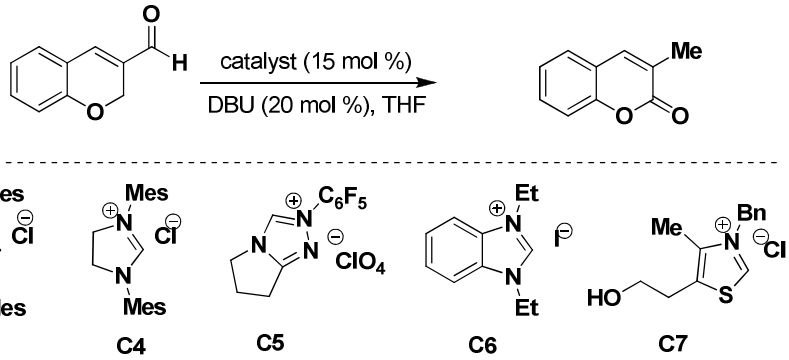


Figure 3.4. Single crystal X-ray Structure of **67a**, **CCDC** number: **813059.**

Although the expected reaction did not occur, intrigued by the novelty of the reaction, we decided to pursue it in some detail. Additional incentive for our studies was accrued from the well documented and important biological properties of coumarin derivatives.

In an experiment in which the aldehyde **57** was exposed to the catalyst **C4**, in the absence of 4-fluorobenzaldehyde, in CH_2Cl_2, the product **57a** was formed in 30 % yield. Subsequent studies aimed at catalyst screening revealed that the best result was obtained with **C4**; the results are summarized in Table 1

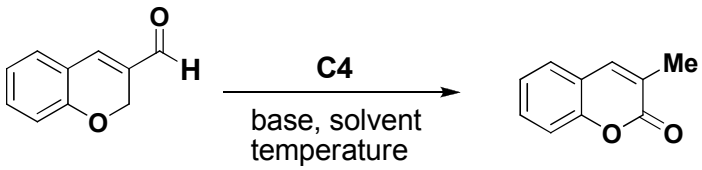
Table 3.1. Catalyst Screening



Entry	Catalyst	Condition	Yield (%)
1	**C1**	THF, rt, 8h	27
2	**C4**	THF, rt, 8h	94
3	**C5**	THF, rt, 8h	-
4	**C6**	THF, rt, 8h	50
5	**C7**	THF, rt, 24h	-

The reaction conditions were optimized by varying the solvents, base and temperature; results are summarized in Table 2.

Table 3.2. Condition Optimization

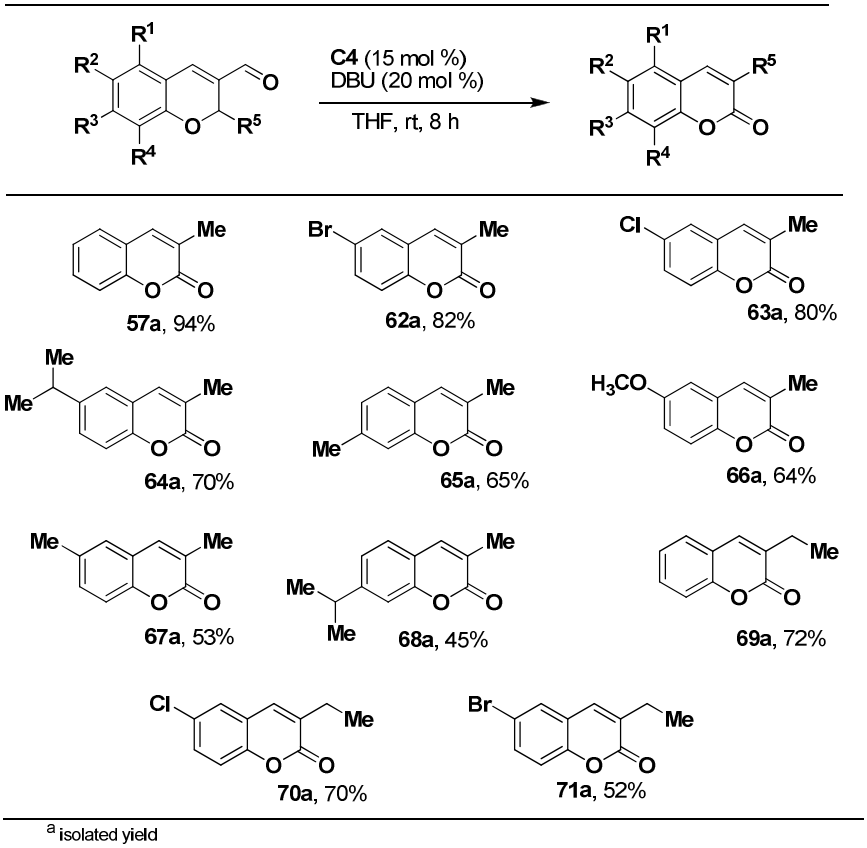


Entry	Base	Solvent	Temp.	Time (h)	Yield[a] (%)
1	DBU	CH_2Cl_2	rt	24	30
2	DBU	THF	rt	8	94
3	DBU	PhMe	rt	24	38
4	DBU	CH_3CN	rt	24	-
5	K_2CO_3	CH_3CN	82 ^oC	12	-
6	DMAP	THF	rt	24	-
7	K_2CO_3	THF	rt	24	-

[a] isolated yield

In order to explore the generality of the reaction, a number of substituted chromene aldehydes were treated with the catalyst, and the results are presented in Scheme 3.26

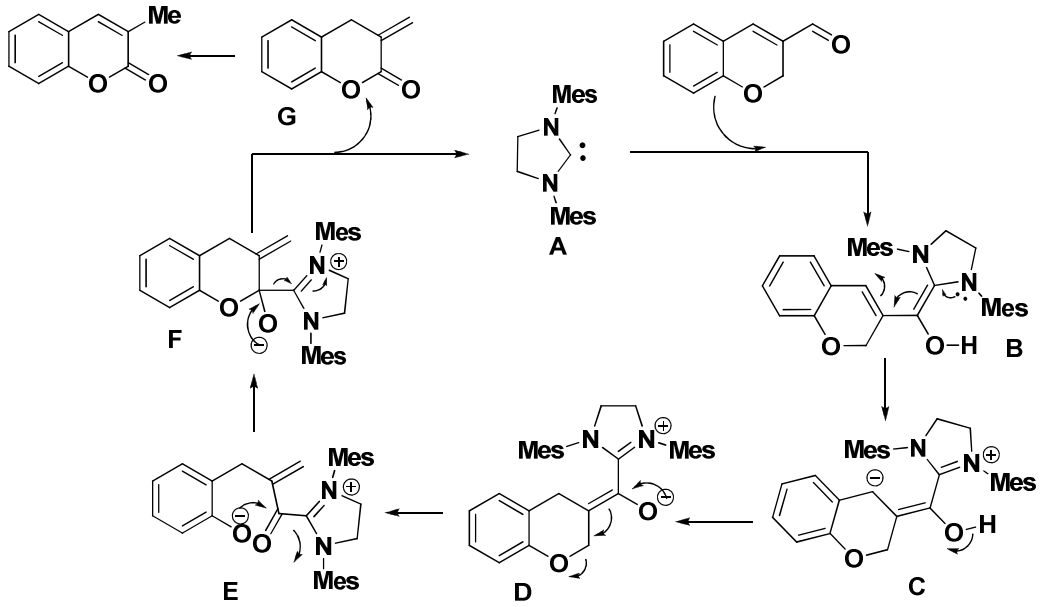
Scheme 3.26. Substrate Scope[a]



[a] isolated yield

3.5. Mechanism

A mechanistic rationalization for the transformation reported herein may be postulated as follows (Scheme 3.27).



Scheme 3.27

Conceivably the initially formed Breslow intermediate **B** transforms to the homoenolate equivalent **C** which on proton transfer followed by a 'Grob type' fragmentation affords **E**. The latter undergoes cyclization to provide **F**; elimination of the carbene followed by isomerization of the exo-enone delivers the 3-methyl coumarin derivative.

3.6. Conclusion

In conclusion, we have uncovered a novel NHC catalyzed rearrangement of chromene-3-carboxaldehydes to 3-alkyl coumarins. It is conceivable that the process will find application in the synthesis of biologically active coumarin derivatives.

3.7. Experimental Section

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 a Bruker DPX-500 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 EI/HRMS or FAB using JEOL JMS 600H mass spectrometer. IR spectra were recorded on a Bruker Alpha-T FT-IR spectrophotometer. Gravity column chromatography was performed using 100-200 mesh silica gel and mixtures of petroleum ether-ethyl acetate were used for elution.

3.7.1. General Experimental Procedures

3.7.1.1. Synthesis of 2*H*-chromene-3-carbaldehydes[31]

To a solution of salicylaldehyde (10 mmol) in dioxane (20 mL) taken in a round bottom flask was added K_2CO_3 (10 mmol) and acrolein (16 mmol). The mixture was refluxed for 2 h, and then poured into water (100 mL). The solution was extracted with diethylether (30 mL × 3). The combined organic layers were washed with NaOH (0.1 N, 30 mL) and water (30 mL) successively. Then the organic layer was dried over anhydrous Na_2SO_4 and evaporated. Silica gel chromatography of the crude material using 95:5 petolium ether: ethyl acetate mixtures gave 2*H*-chromene-3-carbaldehydes as a yellow solid.

3.7.1.2. Synthesis of 3-alkyl coumarins

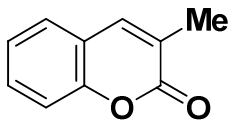
DBU (20 mol %) was added to a suspension of the carbene precursor 1,3-dimesityl imidazolinium chloride (15 mol %) and 2*H*-chromene-3-carboxaldehyde (0.50

mmol) in dry THF (5 mL) and the resulting solution was stirred at room temperature for 8–12 h. After the removal of the solvent by distillation in vacuum using a rotary evaporator, the residue was subjected to column chromatography on a silica gel (100-200 mesh) column using 95:5 petroleum ether: ethyl acetate solvent mixtures to afford the 3-alkyl coumarin derivatives.

3.7.2. Characterization Data of Compounds

3-methyl-2*H*-chromen-2-one (57a)

Following the general procedure, reaction of 2*H*-chromene-3-carbaldehyde (80 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 3-methyl-2*H*-chromen-2-one in 94% (75.3 mg) yield as white solid.



Chemical Formula: $C_{10}H_8O_2$

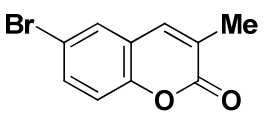
m p 90-92 ^oC.

IR (film) ν_{max} 1709, 1638, 1447, 918 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (s, 1H) 7.39-7.35 (m, 1H) 7.32 (d, *J* = 8 Hz, 1H) 7.2 (d, *J* = 8 Hz, 1H) 7.17-7.14 (m, 1H) 2.14 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 161.9, 153.3, 139.0, 130.4, 126.8, 125.9, 124.1, 119.5, 116.4, 17.2 ppm. **LRMS-FAB** calcd. for $C_{10}H_9O_2$ $[M+H]^+$: 161.06, found: 161.09.

6-bromo-3-methyl-2*H*-chromen-2-one (62a)

Following the general procedure, reaction of 6-bromo-2*H*-chromene-3-carbaldehyde (119.5 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 6-bromo-3-methyl-2*H*-chromen-2-one in 82% (98.0 mg) yield as yellow solid.



Chemical Formula: $C_{10}H_7BrO_2$

m p 152-153 ^oC.

IR (film) ν_{max} 1726, 1599, 1478, 1248, 922, 815 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55-7.53 (m, 2H) 7.41 (s, 1H) 7.19 (d, *J* = 9.5 Hz, 1H) 2.23 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 161.2, 152.1, 137.6, 133.2, 129.2, 127.3, 121.1, 118.2, 116.8, 17.3 ppm. **LRMS-FAB** calcd. for

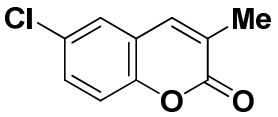
$C_{10}H_8BrO_2$ $[M+H]^+$: 238.97, found 239.11.

6-chloro-3-methyl-2*H*-chromen-2-one (63a)

Following the general procedure, reaction of 6-chloro-2*H*-chromene-3-carbaldehyde (97.3 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 6-chloro-3-methyl-2*H*-chromen-2-one in 80% (77.8 mg) yield as yellow solid.

Chemical Formula: $C_{10}H_7ClO_2$

m p 152-154 ^oC.



IR (film) ν_{max} 1726, 1602, 1410, 1479, 925, 815 cm^{-1}.

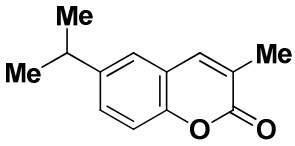
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (s, 1H) 7.41-7.38 (m, 2H) 7.25 (s, 1H) 2.23 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 161.2, 151.6, 137.7, 130.4, 129.5, 127.4, 126.1, 120.6, 117.9, 17.3 ppm. **LRMS-FAB** calcd. for $C_{10}H_8ClO_2$ $[M+H]^+$: 195.02, found:195.01.

6-isopropyl-3-methyl-2*H*-chromen-2-one (64a)

Following the general procedure, reaction of 6-isopropyl-2*H*-chromene-3-carbaldehyde (101.1 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 6-isopropyl-3-methyl-2*H*-chromen-2-one in 70% (70.8 mg) yield as colourless liquid.

Chemical Formula: $C_{13}H_{14}O_2$

IR (film) ν_{max} 1724, 1619, 1428 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.48 (s, 1H) 7.32-7.29 (m, 1H) 7.22-7.20 (m, 2H) 2.98-2.93 (m, 1H) 2.20 (s, 3H) 1.27 (d, *J* = 7 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 162.2, 151.5, 144.8, 139.2, 128.9, 125.5, 124.1, 119.3, 116.2, 33.5, 24.1, 17.2 ppm. **LRMS-FAB** calcd. for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.11, found 203.21.

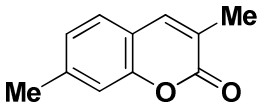
3,7-dimethyl-2*H*-chromen-2-one (65a)

Following the general procedure, reaction of 7-methyl-2*H*-chromene-3-carbaldehyde (87 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 3,7-dimethyl-2*H*-chromen-2-one in 65% (56.6 mg) yield as white solid.

Chemical Formula: $C_{11}H_{10}O_2$

m p 104-106 °C.

IR (film) ν_{max} 1710, 1623, 1437 cm^{-1}.



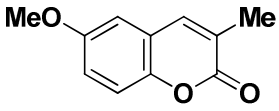
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.69 (s, 1H) 7.33 (d, *J* = 8 Hz, 1H) 7.15 (d, *J* = 8 Hz, 1H) 7.11 (s, 1H) 2.52 (s, 3H) 2.24 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 161.8, 153.8, 138.9, 135.9, 130.1, 126.5, 124.6, 117.1, 114.6, 21.7, 17.2 ppm. **LRMS-FAB** calcd. For $C_{11}H_{11}O_2$ $[M+H]^+$: 175.07, found 175.20.

6-methoxy-3-methyl-2*H*-chromen-2-one (66a)

Following the general procedure, reaction of 6-methoxy-2*H*-chromene-3-carbaldehyde (95 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 6-methoxy-3-methyl-2*H*-chromen-2-one in 64% (60.9 mg) yield as white solid.

Chemical Formula: $C_{11}H_{10}O_3$

m p 114–116 °C.



IR (film) ν_{max} 1704, 1630, 1538 cm^{-1}.

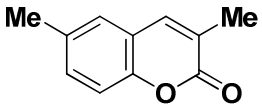
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45 (s, 1H) 7.23 (d, *J* = 9 Hz, 1H) 7.03-7.00 (m, 1H) 6.82 (s, 1H) 3.83 (s, 3H) 2.21 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 162.0, 155.9, 147.7, 138.8, 126.3, 119.9, 117.8, 117.4, 109.2, 55.6, 17.3 ppm. **LRMS-FAB** calcd. for $C_{11}H_{11}O_3$ $[M+H]^+$: 191.07, found 191.27.

3,6-dimethyl-2*H*-chromen-2-one (67a)

Following the general procedure, reaction of 6-methyl-2*H*-chromene-3-carbaldehyde (87 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 3,6-dimethyl-2H-chromen-2-one in 53% (46.2 mg) yield as white solid.

Chemical Formula: $C_{11}H_{10}O_2$

m p 114–116 °C.



IR (film) ν_{max} 1711, 1600 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43 (s, 1H) 7.24-7.23 (m, 1H) 7.19-7.17 (m, 2H) 2.39 (s, 3H) 2.19 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 162.1, 151.4, 138.9, 133.7, 131.3,

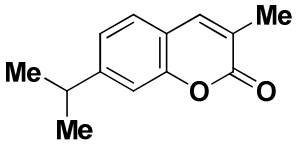
126.7, 125.7, 119.3, 116.2, 20.8, 17.2 ppm. **LRMS-FAB** calcd. For $C_{11}H_{11}O_2$ $[M+H]^+$: 175.07, found 175.23.

7-isopropyl-3-methyl-2*H*-chromen-2-one (68a)

Following the general procedure, reaction of 7-isopropyl-2*H*-chromene-3-carbaldehyde (101.1 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 7-isopropyl-3-methyl-2*H*-chromen-2-one in 45% (45.5 mg) yield as colourless liquid.

Chemical Formula: $C_{13}H_{14}O_2$

IR (film) ν_{max} 1706, 1627, 1533 cm^{-1}.



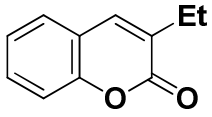
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47 (s, 1H) 7.30 (d, *J* = 8 Hz, 1H) 7.17-7.15 (m, 1H) 7.11-7.09 (m, 1H) 3.02-2.94 (m, 1H) 2.20 (s, 3H) 1.28 (d, *J* = 7 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 162.3, 152.3, 138.9, 135.3, 130.4, 126.6, 125.1, 117.5, 114.1, 34.2, 23.7, 23.6, 17.2 ppm. **LRMS-FAB** calcd. For $C_{13}H_{15}O_2$ $[M+H]^+$: 203.11, found 203.13.

3-ethyl-2*H*-chromen-2-one (68a)

Following the general procedure, reaction of 2-methyl-2*H*-chromene-3-carbaldehyde (87 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 3-ethyl-2*H*-chromen-2-one 72% (67.2 mg) yield as white solid.

Chemical Formula: $C_{11}H_{10}O_2$

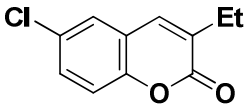
IR (film) ν_{max} 1719, 1628, 1599 cm^{-1}.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.47-7.42 (m, 2H) 7.32-7.22 (m, 2H) 7.18 (s, 1H) 2.61 (q, *J* = 7.5 Hz, 2H) 1.27 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 160.9, 153.2, 139.0, 130.4, 126.8, 125.9, 124.1, 119.5, 116.4, 23.8, 11.9. **LRMS-FAB** calcd. For $C_{11}H_{10}ClO_2$ $[M+H]^+$: 175.07 found 175.09.

6-chloro-3-ethyl-2*H*-chromen-2-one (70a)

Following the general procedure, reaction of 6-chloro-2-methyl-2H-chromene-3-carbaldehyde (104.3 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 6-chloro-3-ethyl-2*H*-chromen-2-one 70% (73.0 mg) yield as white solid.



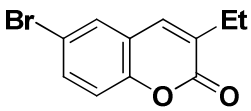
Chemical Formula: $C_{11}H_9ClO_2$

IR (film) ν_{max} 1716, 1675, 1479 cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$) δ = 7.42-7.26 (m, 3H) 7.24-7.14 (m, 1H) 2.61 (q, *J* = 7.5 Hz, 2H) 1.26 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 160.8, 151.4, 135.9, 132.8, 130.3, 129.4, 126.3, 120.6, 117.8, 24.0, 12.2 ppm. **LRMS-FAB** calcd. For $C_{11}H_{10}ClO_2$ $[M+H]^+$: 209.03 found 209.60.

6-bromo-3-ethyl-2*H*-chromen-2-one (71a)

Following the general procedure, reaction of 6-bromo-2-methyl-2*H*-chromene-3-carbaldehyde (126.5 mg, 0.5 mmol), 1,3-dimesityl imidazolinium chloride (27.5 mg, 15 mol%) and DBU (15.2 mg, 15 µL, 20 mol%) afforded 6-bromo-3-ethyl-2*H*-chromen-2-one 52% (65.8 mg) yield as white solid.



Chemical Formula: $C_{11}H_9BrO_2$

m p 110–112 ^oC

IR (film) ν_{max} 1719, 1628, 1599 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.50 (d, *J* = 2 Hz, 1H) 7.48-7.46 (m, 1H) 7.31 (s, 1H) 7.13 (d, *J* = 8.5 Hz, 1H) 2.57-2.52 (m, 2H) 1.19 (t, *J* = 7 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 159.7, 150.9, 134.8, 132.1, 131.7, 128.4, 120.1, 117.1, 115.7, 22.9, 11.1 ppm. **LRMS-FAB** calcd. For $C_{11}H_{10}BrO_2$ $[M+H]^+$: 252.99, found 253.28.

3.7. References

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CHAPTER 4

Intramolecular Homoenolate Reaction of Enals with α,β-Unsaturated Esters: Efficient Synthesis of Coumarin Derivatives

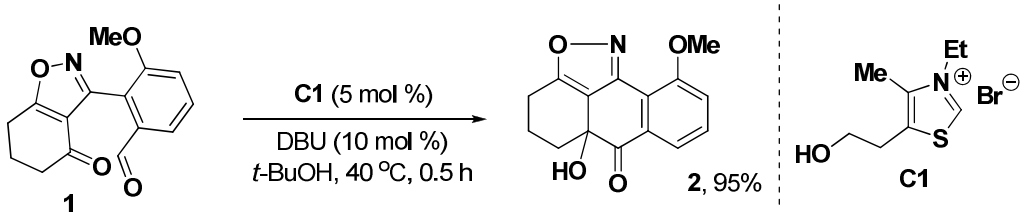
4.1. Introduction

Discovery of novel and efficient synthetic methods is essential for the development of sustainable chemical transformations, especially for carbon-carbon bond formation. Hence, carbon-carbon bond formation has been an area of constant interest and remains a great challenge. During the past two decades, organocatalysis became an important tool in synthetic organic chemistry. Along with this, *N*-heterocyclic carbenes (NHCs) have assumed a significant role. Following the general trend, most of the NHC catalyzed reactions are also intermolecular, i.e., the reaction sites belong to two or more molecules. This chapter presents a novel NHC catalyzed intramolecular homoenolate reaction for the efficient synthesis of coumarin derivatives. In this context, a brief survey of *N*-heterocyclic carbene catalyzed intramolecular reactions is essential and is given in the following section. Since coumarin derivatives constitute the target molecules of the work described in this chapter, inclusion of review of the existing methods of coumarin synthesis would be customary. However, a review of coumarin synthesis is already available in the previous chapter (Chapter 3). Therefore to avoid duplication; a review of coumarin synthesis is excluded.

4.2. NHC Catalyzed Intramolecular Reactions

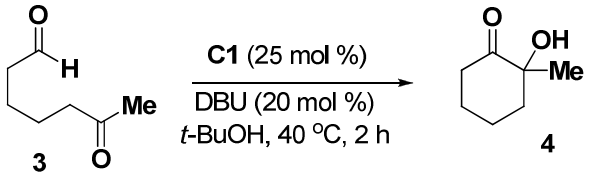
4.2.1. Intramolecular Benzoin Reactions

In 2003, Hachisu et al. reported a catalytic intramolecular crossed aldehyde ketone benzoin reaction for the synthesis of functionalized preanthraquinones (Scheme 4.1).[1] This process offers a simple and remarkably mild entry to useful, orthogonally protected polycyclic quinones with a high degree of regio- and stereoselectivity.



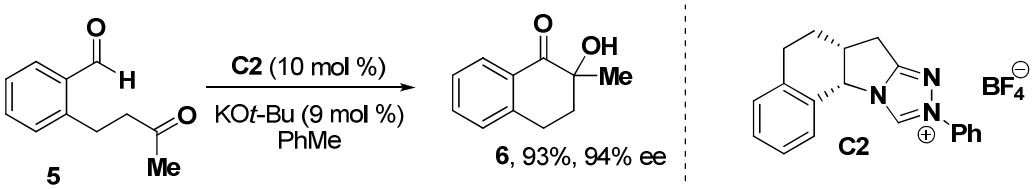
Scheme 4.1

The same group extended the scope of this reaction to aliphatic substrates.[2] After the optimization of reaction conditions, it was found that the five and six membered cyclic acyloins were formed in good to excellent yields and the competing intramolecular aldol reactions were suppressed (Scheme 4.2). Not surprisingly, the analogous formation of seven membered rings was found difficult.



Scheme 4.2

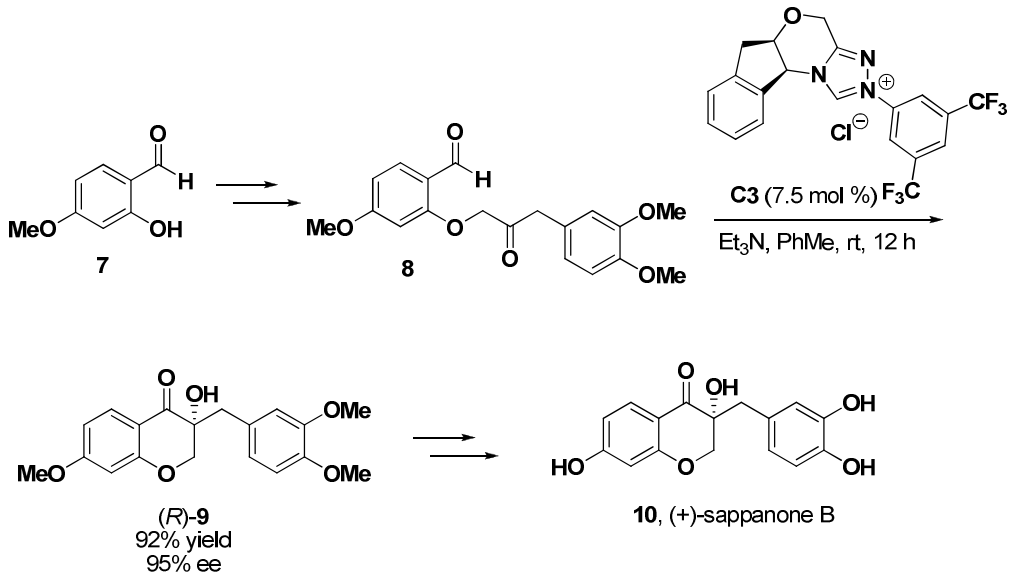
First enantioselective intramolecular crossed benzoin reaction catalyzed by *N*-heterocyclic carbene was reported by Enders and co-workers.[3] The tetracyclic triazole carbene catalyzed cyclization afforded the α-ketol with a quaternary stereocenter in high yield and excellent enantioselectivity (Scheme 4.3).



Scheme 4.3

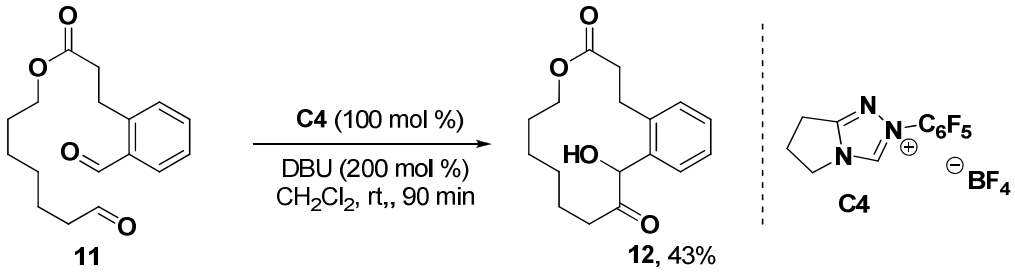
Another triazole carbene catalyzed enantioselective crossed aldehyde ketone benzoin cyclization was reported by Takikawa and co-workers.[4] Both aromatic and aliphatic substrates underwent highly enantioselective cyclization; excellent selectivity was observed for the formation of six membered rings compared to the five membered ones.

In 2007, Takikawa and Suzuki utilized this methodology for the synthesis of (+)-Sappanone B (Scheme 4.4).[5] Commercially available 2-hydroxy-4-methoxybenzaldehyde **7** was transformed into aldehyde **8**, which upon treatment with triazolium salt in presence of base afforded (*R*)-**9** in 92% yield and 95% ee. Subsequently the latter was transformed to (+)-Sappanone B.



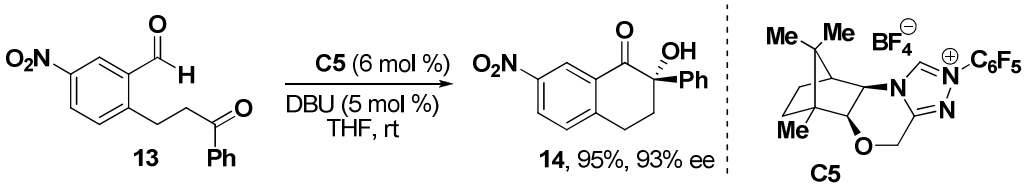
Scheme 4.4

Later, a bio-inspired acyl-anion equivalent macrocyclization and synthesis of a trans-resorcylide precursor was reported (Scheme 4.5).[6] The electron-deficient triazolium salts served as precatalysts for the cyclization, the N-pentafluorophenyl triazole carbene derived from **C4** led to cyclization at room temperature within a short time.



Scheme 4.5

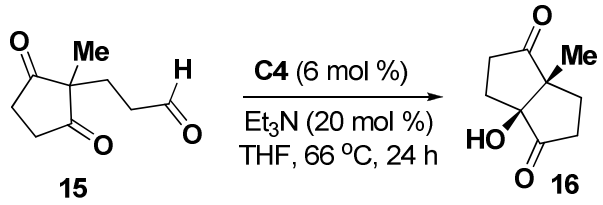
In 2008, You and co-workers showed that the efficiency of intramolecular crossed benzoin reaction can be improved by using D-camphor derived triazolium salt (Scheme 4.6).[7] The NHC catalyst derived from **C5** and DBU is found to be efficient for intramolecular crossed aldehyde–ketone benzoin reaction, and α-ketol containing a quaternary stereocenter was formed in excellent yield with up to 93% ee.



Scheme 4.6

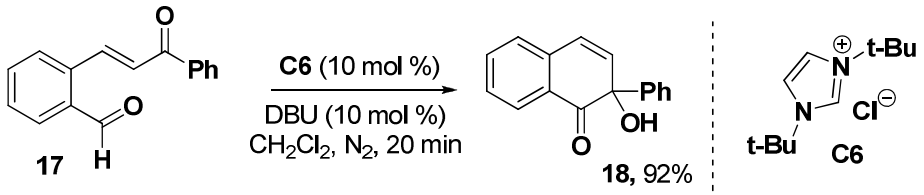
A stereoselective synthesis of bicyclic tertiary alcohols with quaternary stereocenter was developed via *N*-heterocyclic carbene catalyzed intramolecular crossed

benzoin reaction (Scheme 4.7).[8] Later the scope of the reaction was explored with chiral catalysts.[9]



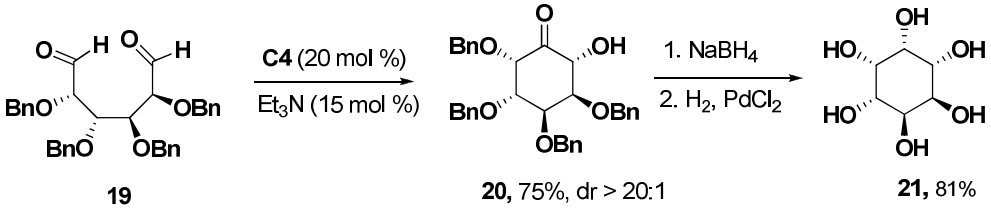
Scheme 4.7

A facile one-pot synthetic route to naphthalenone based bicyclic tertiary alcohol from chalcone **17** via intramolecular aldehyde–ketone crossed benzoin condensation reaction catalyzed by NHC was reported (Scheme 4.8).[10]



Scheme 4.8

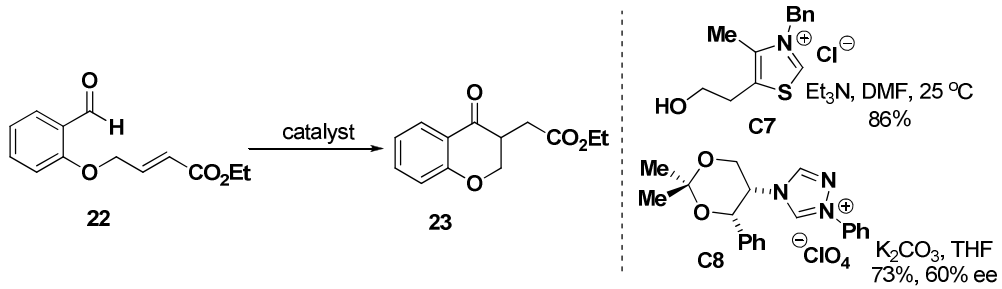
Recently, Greatrex et al. reported NHC-catalyzed carbocyclization of carbohydrate-derived dialdehydes for the synthesis of allo- and epi-inositol. The inososes were stereospecifically reduced using sodium borohydride and then deprotected to give inositol in good yield (Scheme 4.9).[11]



Scheme 4.9

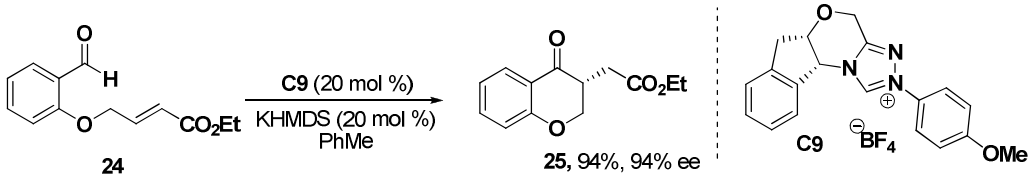
4.2.2. Intramolecular Stetter Reaction

Almost 20 years after the initial report of the Stetter reaction,[12] Ciganek reported an intramolecular variant of this reaction in 1995 with thiazolium precatalyst **C7** providing chromanone **23** in 86% yield (Scheme 4.10).[13] In 1996, Enders and co-workers illustrated the first asymmetric variant of the intramolecular Stetter reaction utilizing chiral triazolinylidene derived from **C8**.[14]



Scheme 4.10

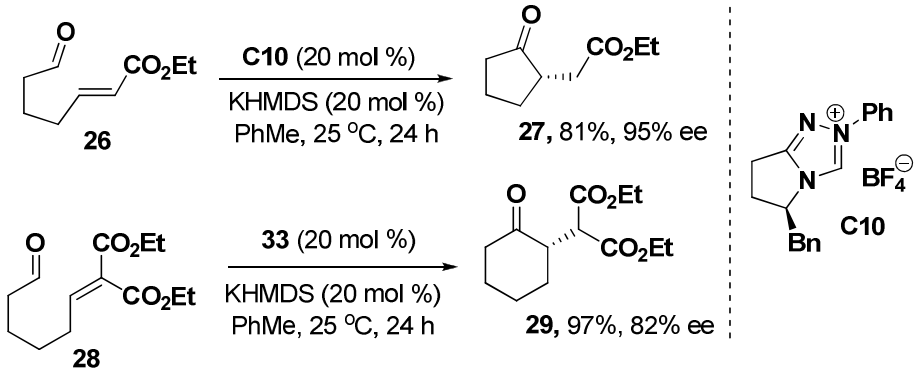
In 2002 Rovis and co-workers synthesized a series of triazolium precatalysts, e.g., **C9** and these were utilized for the intramolecular Stetter reaction of variety of substrates. The products were obtained in good yields with high enantioselectivities (Scheme 4.11).[15] Among those catalysts, the tetracyclic structure of the catalyst **C9** provided sufficient steric bulk on reaction centre.



Scheme 4.11

The reaction works well with a number of acceptors such as α,β-unsaturated esters, amides, alkyl ketones, and phosphine oxides under suitable reaction conditions to afford products in more than 90% ee.[16]

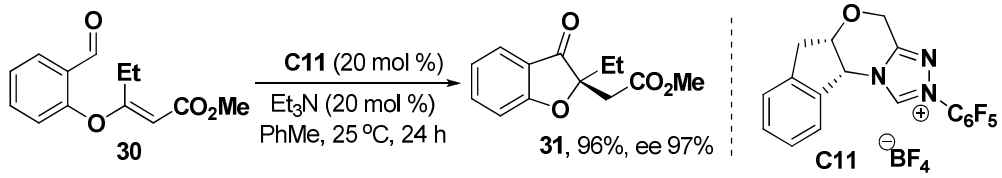
Aliphatic substrates also performed well for the construction of five membered rings in good yield and high enantioselectivity. The corresponding six membered cyclization product was formed from substrate endowed with the more electrophilic Michael acceptor, alkylidene malonate (Scheme 4.12).[17]



Scheme 4.12

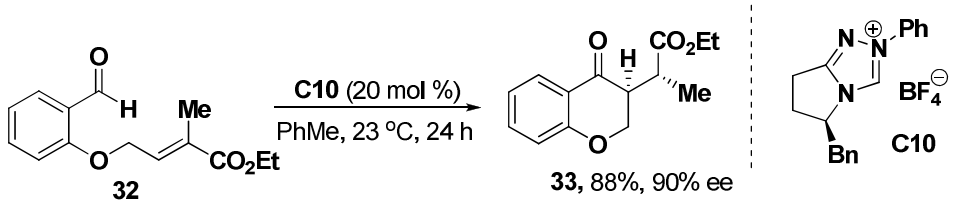
The scope of this strategy was expanded to enantioselective formation of quaternary stereocenters by inducing the intramolecular addition of aromatic as well as

aliphatic aldehydes to β,β-disubstituted Michael acceptors (Scheme 4.13).[18] They also demonstrated sensitivity of intramolecular Stetter reaction to the nature and geometry of the Michael acceptor.[17]



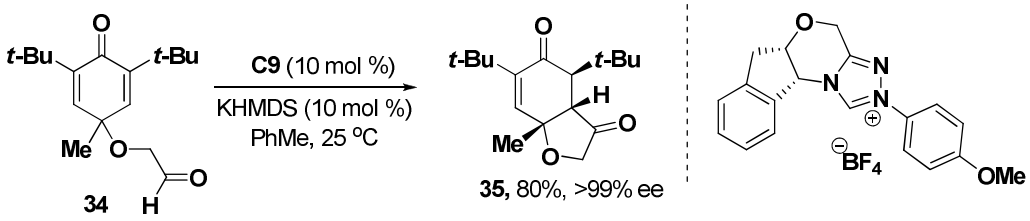
Scheme 4.13

Utilizing prochiral α,α-disubstituted Michael acceptors, the Stetter reaction catalyzed by **C10** has proven to be both enantio- and diastereoselective, allowing control of the formation of contiguous stereocenters (Scheme 4.14).[19]



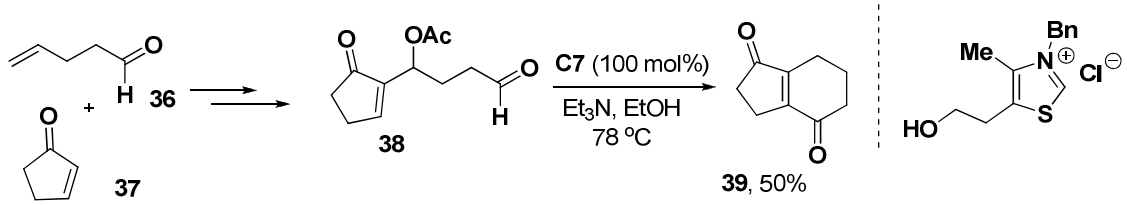
Scheme 4.14

Rovis and Liu have accomplished the desymmetrization of cyclohexadienones by using triazolinylidene carbene generated from **C9** (Scheme 4.15).[20] Multiple hydrobenzofuranones were synthesized in good yield with excellent enantio- and diastereoselectivity. Up to three stereocenters as well as a quaternary stereocenter were formed from polysubstituted substrates.



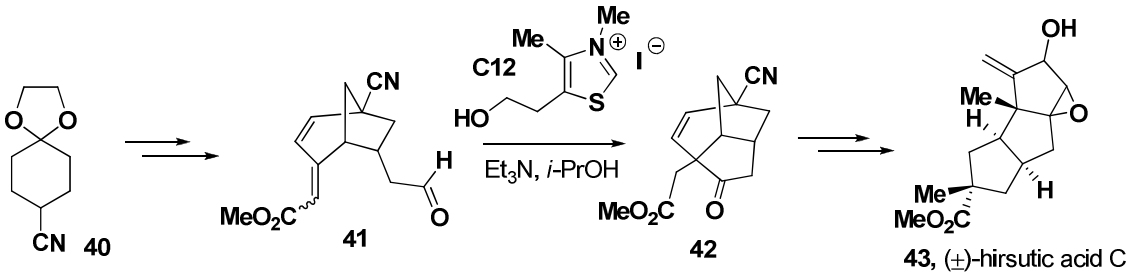
Scheme 4.15

Markó and co-workers utilized the Stetter reaction in the synthesis of bicycloenediones, proceeding in moderate yields using stoichiometric thiazolium pre-catalyst **C7** (Scheme 4.16).[21] Morita-Baylis-Hillman adduct **38** was formed in three steps from commercially available starting materials, 4-pentenal **36** and the corresponding cyclic enone **37**. The carbene induced Stetter reaction followed by acetate elimination and alkene isomerization delivered bicyclic enedione **39**.



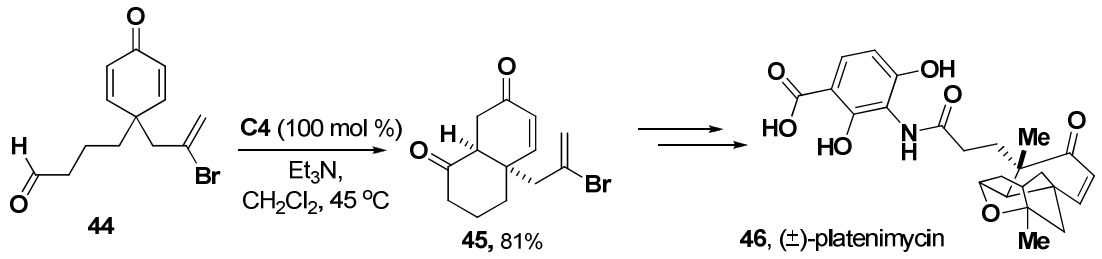
Scheme 4.16

Trost and co-workers relied on Stetter reaction to set the relative stereochemistry for the core of hirsutic acid C (Scheme 4.17).[22]



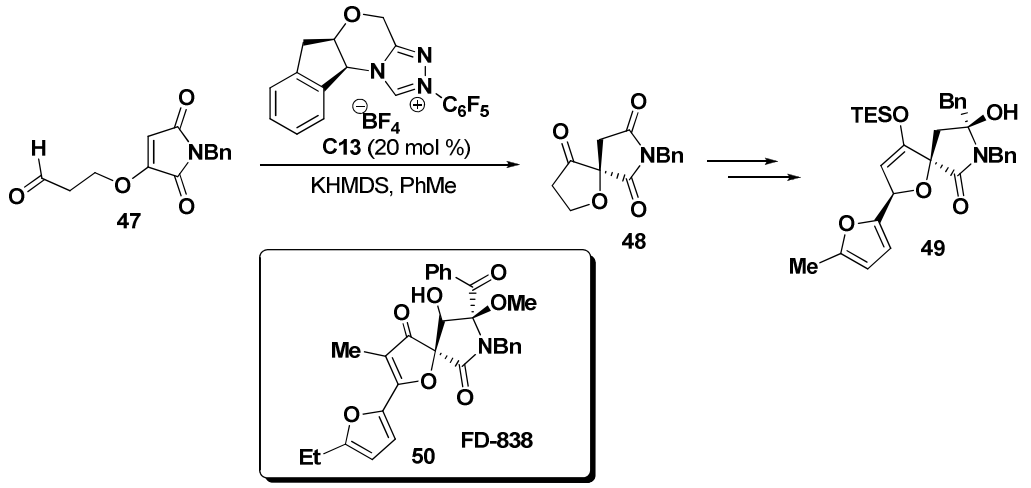
Scheme 4.17

Nicolaou and co-workers reported a formal synthesis of (±)-platensimycin utilizing Stetter methodology (Scheme 4.18).[23] Aldehyde **44** when treated with achiral *N*-pentafluorophenyl pre-catalyst **C4** readily underwent cyclization to yield **45** as a single diastereomer.



Scheme 4.18

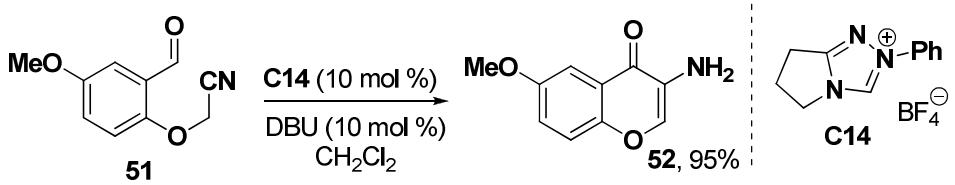
Rovis and Orellana have reported the progress toward the synthesis of FD-838.[24] In four steps, the Stetter substrate **47** was obtained, and it endured cyclization under the influence of aminoindanol derived pre-catalyst **C13** to produce spirocycle **48** in good yield and 99% ee (Scheme 4.19).



Scheme 4.19

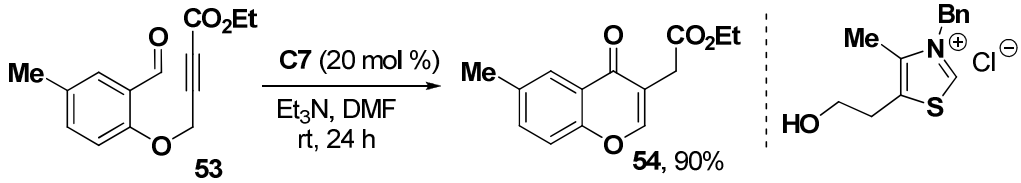
4.2.3. Intramolecular Hydroacylation Reactions

In 2010, Liu and co-workers reported an NHC catalyzed intramolecular aldehyde-nitrile cross coupling reaction for the synthesis of 3-aminochromenones (Scheme 4.20).[25]



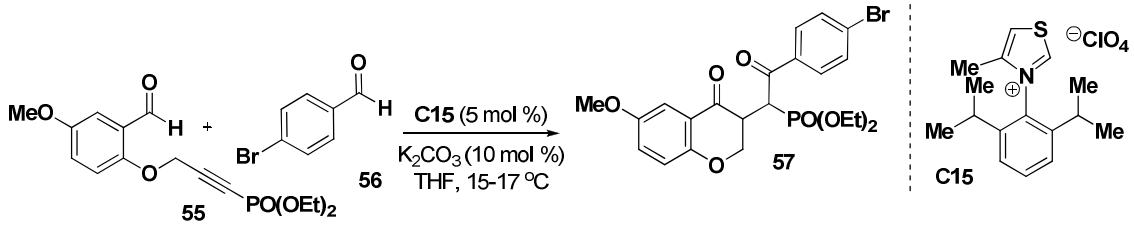
Scheme 4.20

The authors extended this strategy to an intramolecular Stetter type hydroacylation reaction between an aldehyde and activated alkyne (Scheme 4.21).[26]



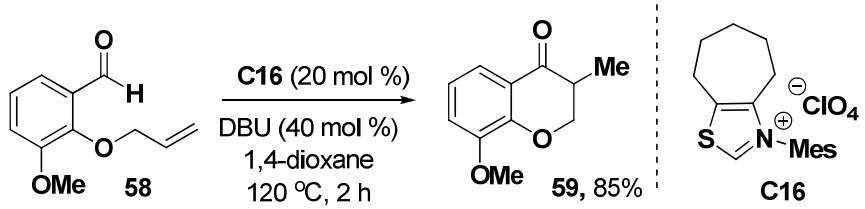
Scheme 4.21

A 1,4-dicarbonyl compound carrying a phosphonate group was synthesised by utilizing a dually NHC-catalyzed domino hydroacylation of salicyl alkynylphosphonates (Scheme 4.22).[27]



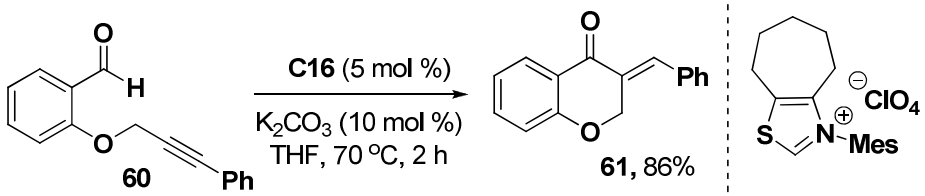
Scheme 4.22

Glorius et al. reported an unprecedented reactivity of acyl anion generated via *N*-heterocyclic carbenes, towards hydroacylation of unactivated double bonds (Scheme 4.23).[28]



Scheme 4.23

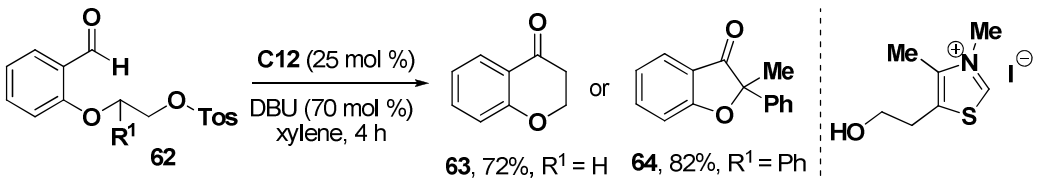
In 2010 this methodology was extended to the hydroacylation of unactivated alkynes to provide α, β-unsaturated ketone products (Scheme 4.24).[29] In addition, these authors and Zeitler et al. reported a rare case of an efficient and selective dually NHC-catalyzed cascade reaction involving the hydroacylation of alkynes and a subsequent intermolecular Stetter reaction.[30]



Scheme 4.24

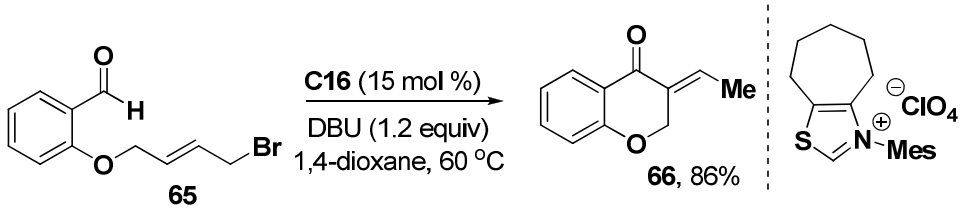
4.2.4. Nucleophilic Substitution Reaction

A novel intramolecular nucleophilic substitution reaction catalyzed by NHC leading to the synthesis of benzopyrones was reported by He et al. (Scheme 4.25). When R^1 was a phenyl group, the cyclization product underwent isomerization, resulting in the benzofuranone. A variety of substrates underwent the reaction in good yields. The formation of benzopyrone was achieved by a direct nucleophilic substitution reaction of NHC-aldehyde umpolung. Mechanism of benzofuranone formation was explained by invoking rearrangement of the intermediate cation followed by intramolecular cyclization.[31]



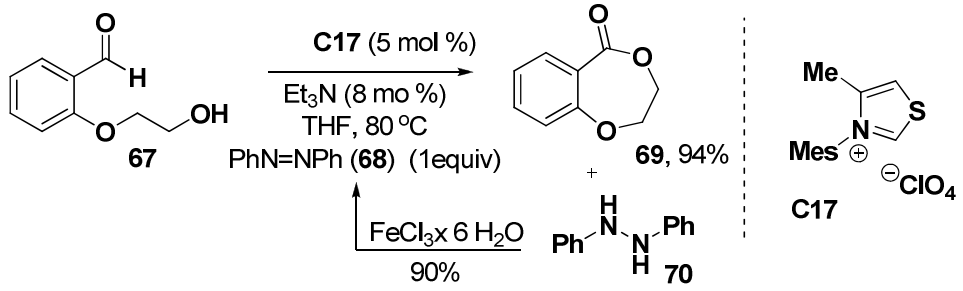
Scheme 4.25

Recently Zhao et al. reported the first NHC-catalyzed intramolecular S_N2' substitution reaction of aldehydes with allylic electrophiles (Scheme 4.26). The reaction exhibited excellent functional group tolerance and afforded good yield of products.[32]



Scheme 4.26

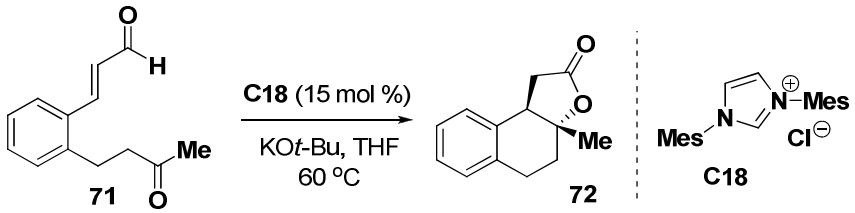
A variety of benzodioxepinone products were synthesised by an efficient, oxidative carbene-catalyzed lactonization reaction (Scheme 4.27).[33] The thiazole carbene catalyzed reaction afforded products in good to excellent yield. The selective oxidation was done by azobenzene, which can easily be recovered and reused after applying inexpensive $FeCl_3$ as a formal terminal oxidant.



Scheme 4.27

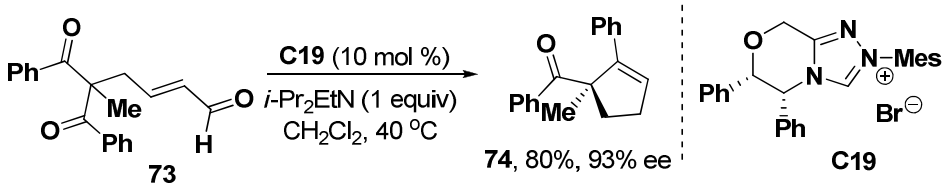
4.2.5. Homoenolate Reactions

Glorius and co-workers extended the NHC mediated homoenolate reaction to intramolecular homoenolate addition in modest yield (Scheme 4.28).[34]



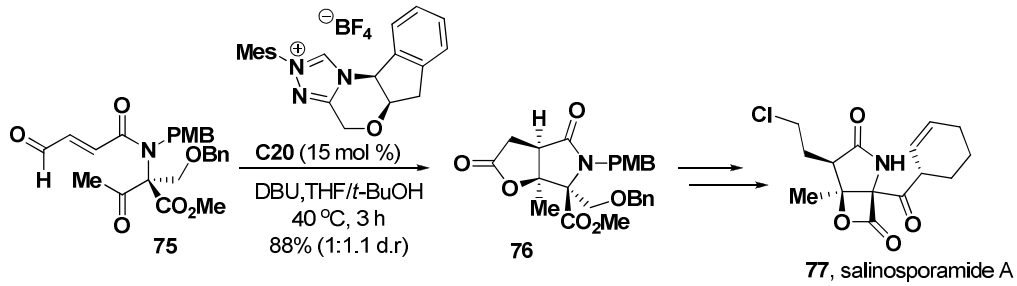
Scheme 4.28

In 2007, Scheidt and co-workers reported the intramolecular desymmetrization of 1,3-diketones utilizing triazolium precatalyst (Scheme 4.29).[35] The formation of α,α-disubstituted cyclopentenes was rationalized by invoking the initial formation of homoenolate followed by β-protonation and aldol reaction, and subsequent loss of carbon dioxide, along the lines suggested by us previously.[36]



Scheme 4.29

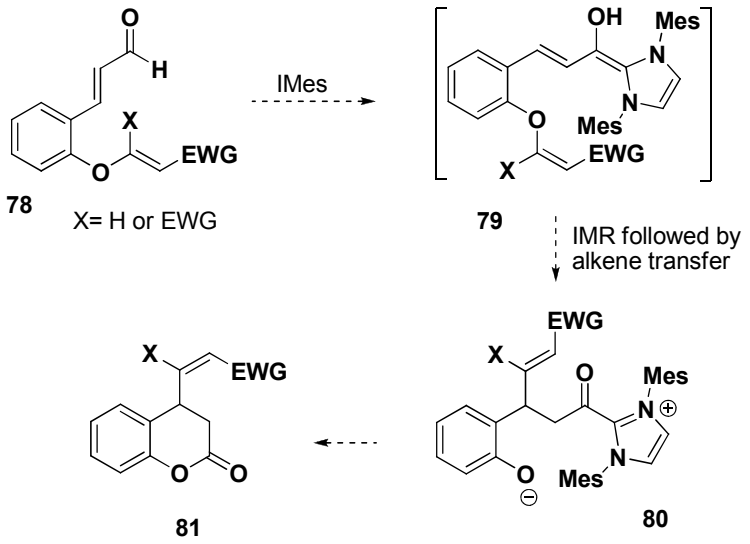
NHC-catalyzed intramolecular cyclization–lactonization of enals to ketones tethered by an amide bond, produced densely functionalized γ-lactam-γ-lactone adducts.[37] To demonstrate the utility of this method, the authors accomplished a formal synthesis of salinosporamide A, a potent 20S proteasome inhibitor and anti-cancer therapeutic (Scheme 4.30).



Scheme 4.30

4.3. Present Work

The above discussion makes it clear that, in spite of the enormous progress in the area of NHC mediated intermolecular homoenolate chemistry, there are only a few intramolecular homoenolate reactions known in the literature. In view of this, intrigued by the possibility of designing an intramolecular reaction, it was conceptualized that cinnamaldehyde appended with 2-O-alkenoate, on treatment with NHC, was likely to undergo a cascade reaction triggered by the initial formation of homoenolate and its intramolecular Michael addition, and a series of events culminating in the formation of a coumarin derivative (Scheme 4.31).

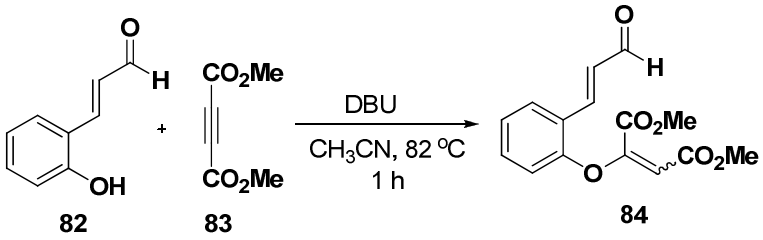


78 79 80 81

Scheme 4.31

4.4. Results and Discussion

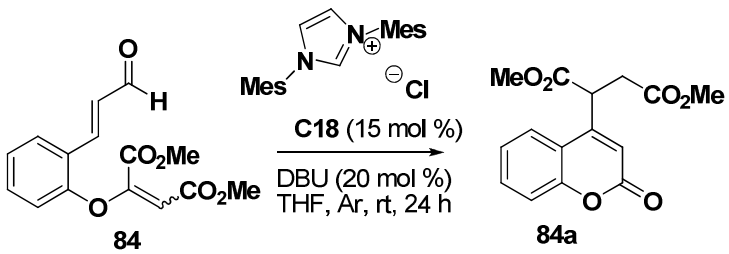
The present studies were initiated by synthesizing 2-O-alkenoate substituted cinnamaldehydes by the reaction of 2-hydroxycinnamaldehyde and dimethyl acetylenedicarboxylate (DMAD) (Scheme 4.32).



82 83 84

Scheme 4.32

In a preliminary experiment, the 2-substituted cinnamaldehyde **84** was treated with the imidazolium precatalyst **C18** and DBU in dry THF under an argon atmosphere (Scheme 4.33). After 24 hours the solvent was removed and the crude product when subjected to column chromatography on silica gel afforded 15% of the product, 4-alkyl substituted coumarin **84a**.



84 84a

Scheme 4.33

The structure of the product was established by common spectroscopic techniques. The proton NMR spectrum showed singlet at δ 6.27 corresponding to the alkenyl proton. The final confirmation was obtained from single crystal X-ray analysis.

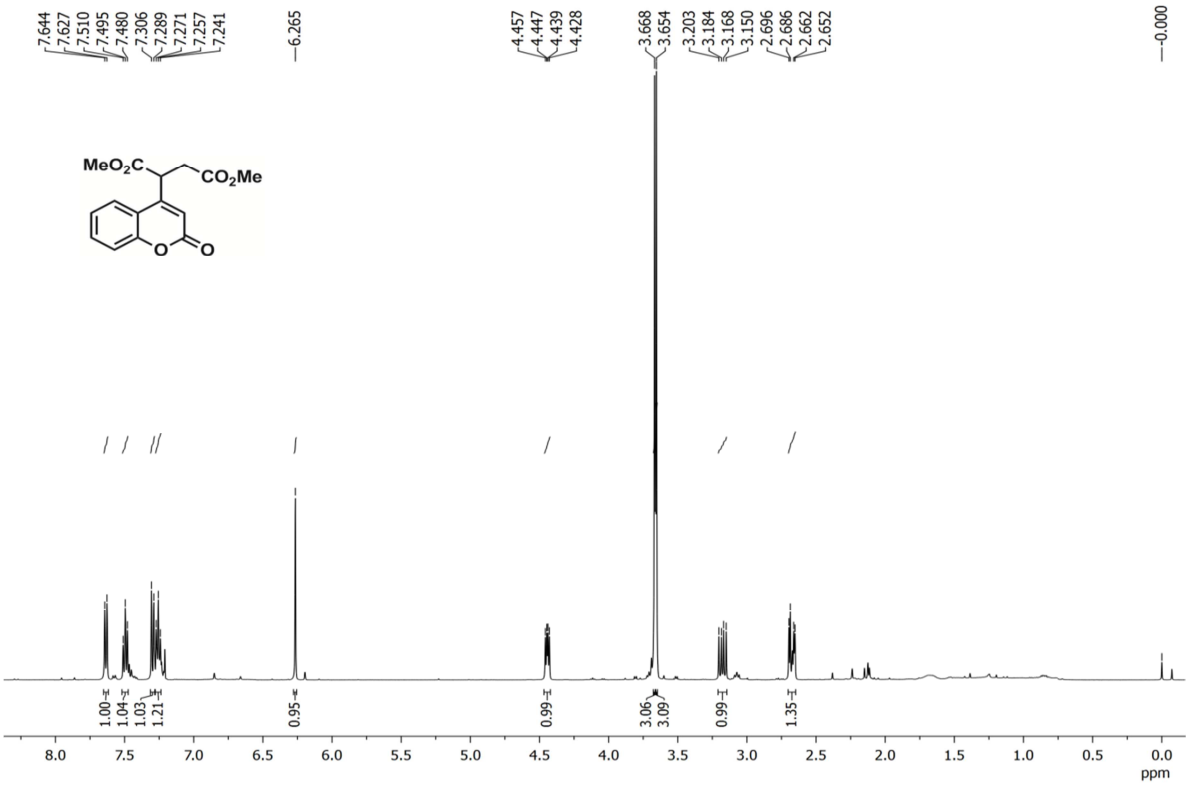


Figure 4.1. ^{1}H NMR Spectrum of **84a**

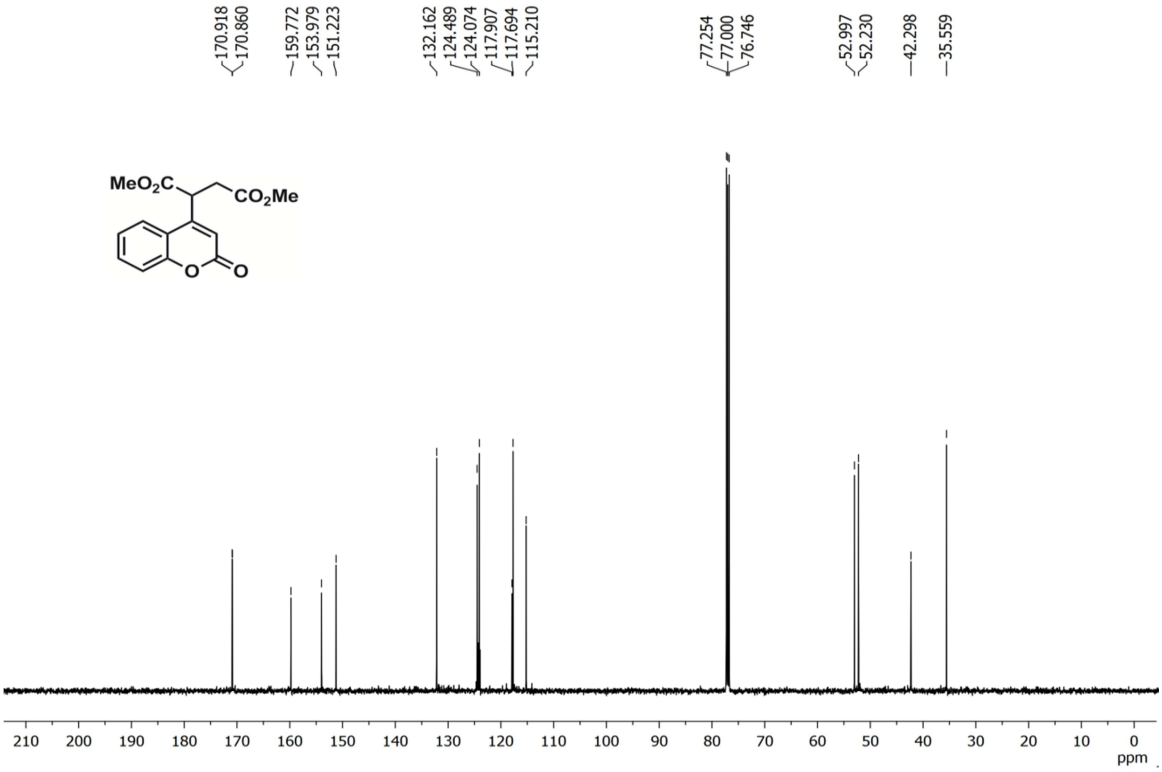


Figure 4.2. ^{13}C NMR Spectrum of **84a**

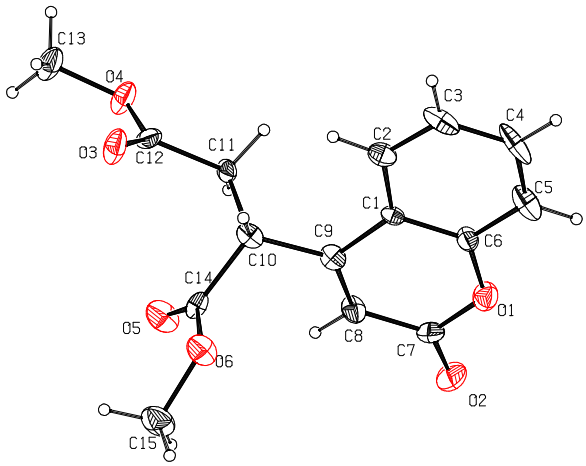
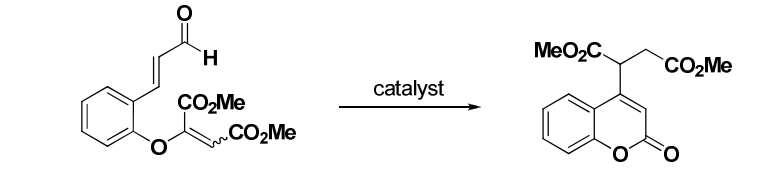
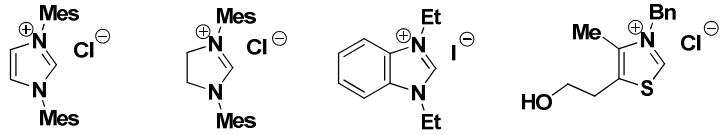


Figure 4.3 Single crystal X-ray Structure of **84a**, CCDC number: **903579**

In view of the success of the reaction, we examined the usefulness of other commonly available NHC catalysts in this reaction. A number of experiments were conducted, and the results are summarised in Table 1. Among the four catalysts investigated, imidazolinium catalyst **C21** gave the best result (table 1, entry 7).

Table 4.1. Condition optimization





C18 C21 C22 C7

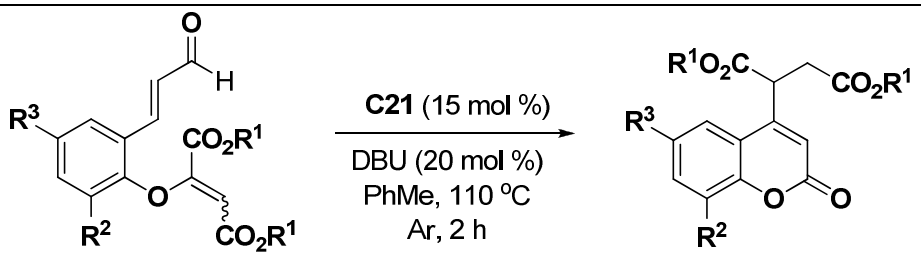
Entry	Catalyst	Base	Solvent, temp (^{o}C)	Time (h)	Yield[a] (%)
1	**C18**	DBU	THF, rt	24	15
2	**C18**	DBU	THF, 65 ^{o}C	24	45
3	**C18**	DBU	PhMe, 110 ^{o}C	24	56
4	**C21**	DBU	THF, rt	24	20
5	**C21**	DBU	THF, 65 ^{o}C	24	68
6	**C21**	DBU	PhMe, rt	24	48
7	**C21**	DBU	PhMe, 110 ^{o}C	2	93
8	**C21**	DMAP	PhMe, 110 ^{o}C	24	40
9	**C21**	K_2CO_3	PhMe, rt	24	-

10	**C21**	Et_3N	PhMe, rt	24	-
11	**C22**	DBU	PhMe, 110 ^oC	24	42
12	**C7**	DBU	PhMe, 110 ^oC	24	50
13	-	DBU	PhMe, 110 ^oC	24	-
14	**C21**	DBU	CH_2Cl_2, rt	24	-

[a] isolated yield

After having reasonably well established the optimum parameters, the reaction was extended to other substituted cinnamaldehyde derivatives, Table 2.

Table 4.2. Reaction of mixture of *E* & *Z* isomers



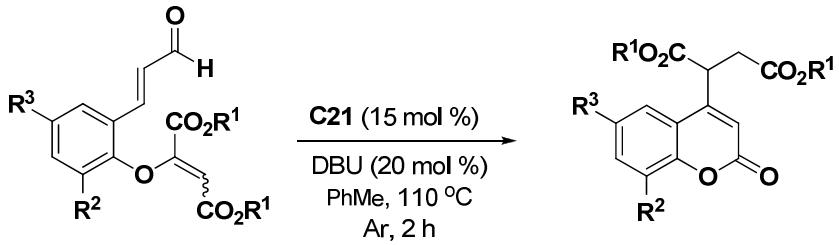
Entry	*E: Z* isomer ratio[a]	R^1	R^2	R^3	Product	Yield[b] (%)
1	1: 1	Me	H	H	**84a**	93
2	0.65: 1	Me	H	Br	**85a**	78
3	0.88: 1	Me	H	*t*-Bu	**86a**	70
4	0.65: 1	Me	H	*i*-Pr	**87a**	66
5	1: 1	Me	OMe	H	**88a**	60
6	0.75: 1	Me	H	OMe	**89a**	60
7	1: 0.68	Me	H	Cl	**90a**	55
8	1: 1	Me	Me	H	**91a**	47
9	1: 1	Me	H	Me	**92a**	46
10	1: 1	Me	I	H	**93a**	46
11	0.6: 1	Me	H	NO_2	**94a**	-
12	1: 0.61	*t*-Bu	H	Br	**95a**	21
13	1: 1	Et	H	H	**96a**	81

[a] *E: Z* ratio calculated from ^1H NMR, [b] isolated yield

In order to establish advantages, if any, in subjecting the *E* and *Z* isomers separately to the cascade process, we prepared them in pure form. When these were

subjected to the reaction conditions identical to those experienced by *E*-*Z* mixtures, the same products were obtained in comparable yields. The results are summarised in table 3.

Table 4.3. Reaction of *E* & *Z* isomers

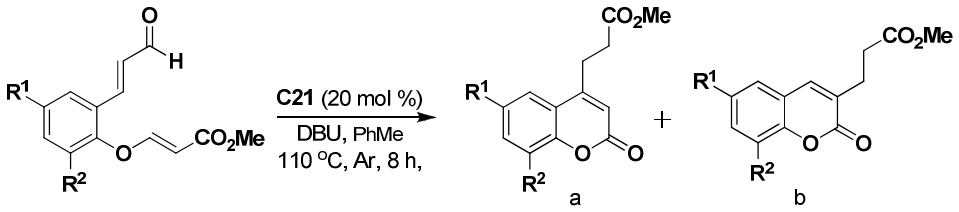


Entry	R^1	R^2	R^3	Product	Yield (%)	
					Z [a]	***E*** [b]
1	Me	H	H	**84a**	83	66
2	Me	OMe	H	**88a**	63	81
3	Me	H	Cl	**92a**	69	60
4	Me	H	Br	**85a**	75	69
5	Me	H	OMe	**89a**	65	78
6	Et	H	H	**96a**	68	72
7	Et	H	Cl	**97a**	65	58
8	Et	H	Br	**98a**	85	89
9	Et	H	OMe	**99a**	62	76
10	Et	OMe	H	**100a**	67	74

[a] isolated yield from (*Z*) isomer, [b] isolated yield from (*E*) isomer.

In order to explore the scope of the coumarin synthesis, we conducted the reaction with substrates derived from other acetylenic esters; the results are presented in Table 4.

Table 4.4. Reaction of acetylenic esters

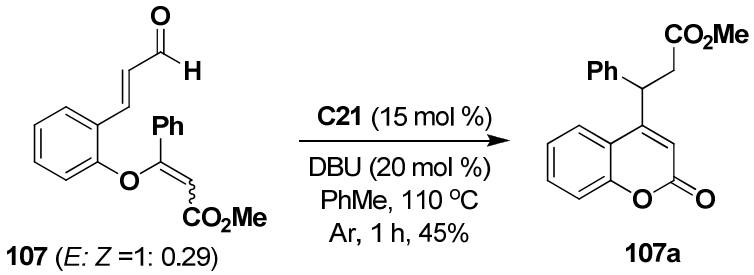


Entry	R^1	R^2	Product	Yield[a] (%)	
				a	**b**
1	H	H	**101**	30	50
2	Me	H	**102**	21	14
3	Cl	H	**103**	60	35

4	Br	H	**104**	39	41
5	H	Me	**105**	19	32
6	*t*-Bu	H	**106**	14	04

[a] isolated yield

When the reaction was carried out with 2-O-phenylacrylate substituted cinnamaldehyde **107**, methyl 3-(2-oxo-2*H*-chromen-4-yl)-3-phenylpropanoate **107a** was obtained (Scheme 4.34).



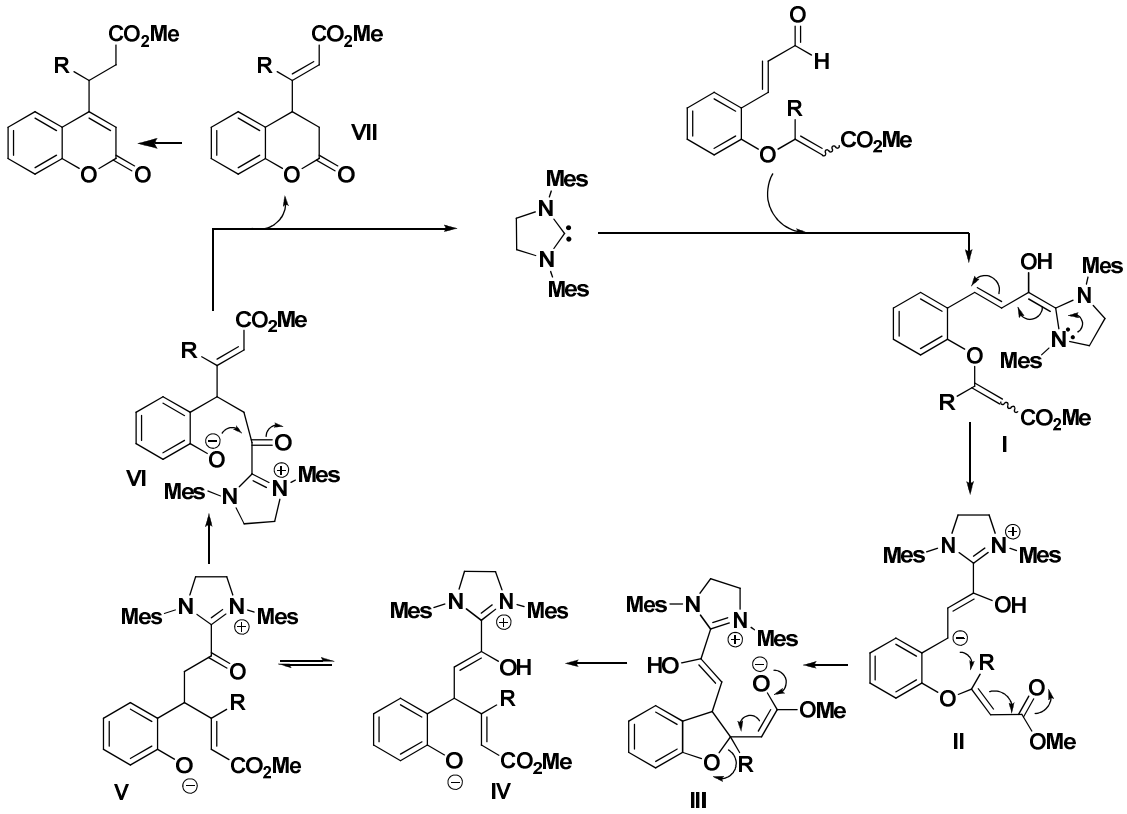
107 (*E: Z* =1: 0.29) **107a**

Scheme 4.34

The above results suggest that 1,2-substitution of the acetylenic esters is crucial to the selective formation of the homoenolate product over the enolate product.

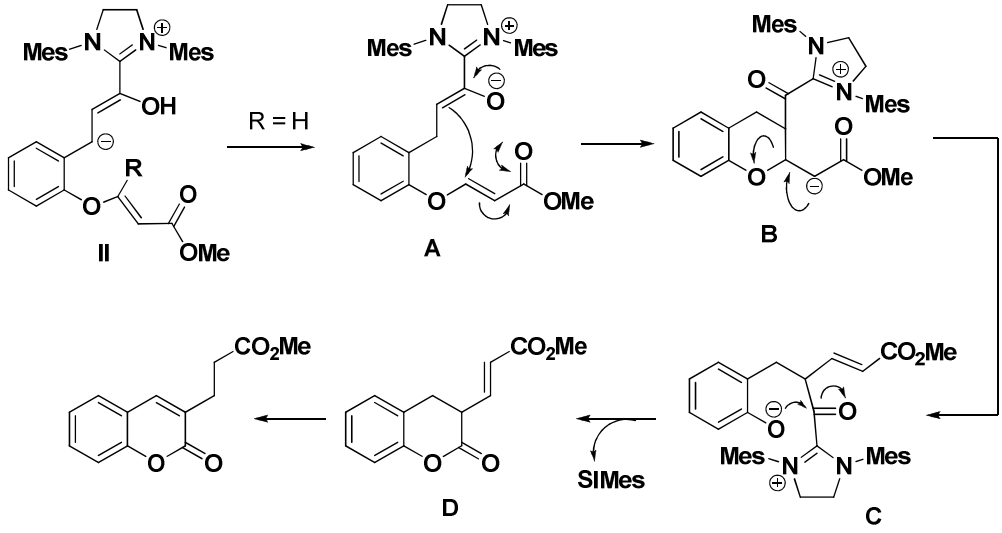
4.5. Mechanism

The proposed catalytic cycle begins with the initial addition of NHC to the aldehyde leading to the generation of the homoenolate species **II**. The latter is suitably positioned for a Michael addition to the olefinic ester resulting in a five-membered intermediate **III** which on fragmentation renders the phenoxide ion **IV**. The formation of this phenoxide ion may provide the driving force for this reaction. Conceivably **V** can endure σ-bond rotation and subsequent cyclization concomitant with the ejection of the catalyst to deliver **VII**; the latter on isomerization affords the final product (Scheme 4.35).



Scheme 4.35

The formation of 3-alkylsubstituted coumarins can be explained as follows; the homoenolate **II** undergoes a β-protonation leading to the enolate **A**, which on Michael addition forms a chromane type intermediate **B**. The phenoxide ion **C**, formed by the ring fragmentation of **B** undergoes an intramolecular acylation. Subsequent elimination of carbene followed an isomerization delivers the final product (Scheme 4.36).



Scheme 4.36

4.6. Conclusion

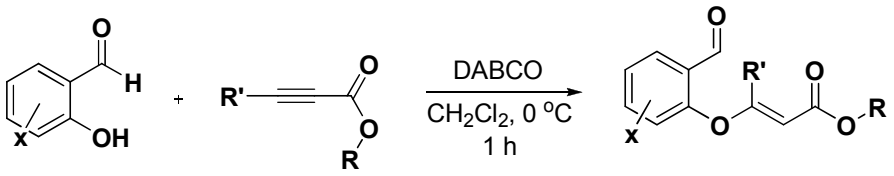
The coumarin synthesis reported herein is noteworthy for its efficiency, novel cascading process involving an intramolecular Michael addition of homoenolate, alkene transfer via Grob type fragmentation, and intramolecular cyclization. It may also be mentioned that the coumarins obtained are endowed with a functionalized carbon chain, thus allowing their further transformation to diverse products of potential value.

4.7. Experimental Section

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 a Bruker DPX-500 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 EI/HRMS or FAB using JEOL JMS 600H mass spectrometer. IR spectra were recorded on a Bruker Alpha-T FT-IR spectrophotometer. Gravity column chromatography was performed using 100-200 mesh silica gel and mixtures of petroleum ether-ethyl acetate were used for elution.

4.7.1. General Experimental Procedures

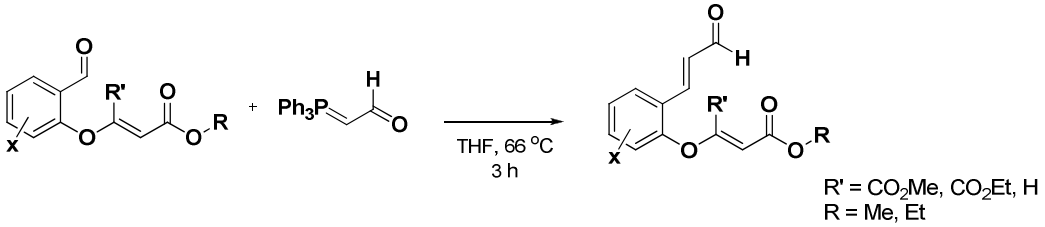
4.7.1.1. Syntheses of Methyl 3-(2-formylphenoxy) acrylates, dialkyl 2-(2-formyl-phenoxy)maleate



R' = H, R= Me
R' = CO_2Me, CO_2Et, R = Me, Et

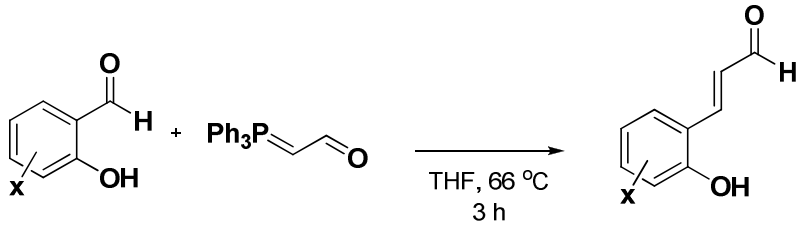
Methyl propiolate/dialkyl acetylenedicarboxylate (4.1 mmol, 1 equiv.) was added to a solution of salicylaldehyde (0.5 g, 4.1 mmol, 1 equiv.) in 5mL dichloromethane. Then a solution of DABCO (0.459 g, 4.1 mmol, 1 equiv.) in 5 mL dichloromethane was added to the above solution drop wise with stirring in an ice bath for 1 h. After the completion of the reaction, water was added to the mixture and swirled, and the aqueous layer was extracted with dichloromethane (3x5 mL). The organic layer was separated and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue obtained was subjected to column chromatography on a silica gel (60-120 mesh) column using 95:5 hexane: ethyl acetate solvent mixture to afford the product.

4.7.1.2. Syntheses of Methyl 3-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylates, dialkyl 2-(2-((*E*)-3-oxoprop-1-enyl) phenoxy)maleate



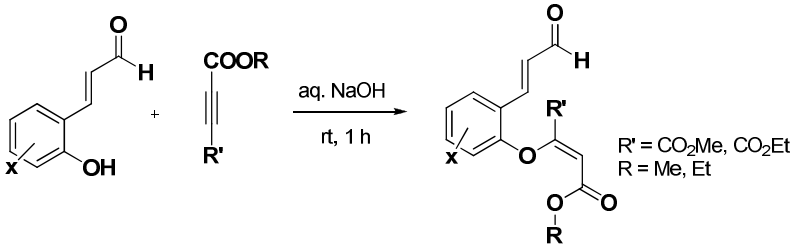
In a 50 mL round bottom flask, methyl 3-(2-formylphenoxy)acrylate (0.983 g, 4.7 mmol) and (Triphenylphosphoranylidene)-acetaldehyde (1.466 g, 4.8 mmol) were taken. Into this was added 10 mL dry THF and refluxed for 3 h. After the completion of the reaction monitored by TLC, solvent was removed and the residue on purification by column chromatography (using 100-200 mesh silica gel and 10: 90 ethyl acetate: hexane mixtures) gave the corresponding phenoxy acrylates/maleates.

4.7.1.3. Synthesis of 3-(2-Hydroxyphenyl) acrylaldehyde (2-hydroxy cinnamaldehyde)



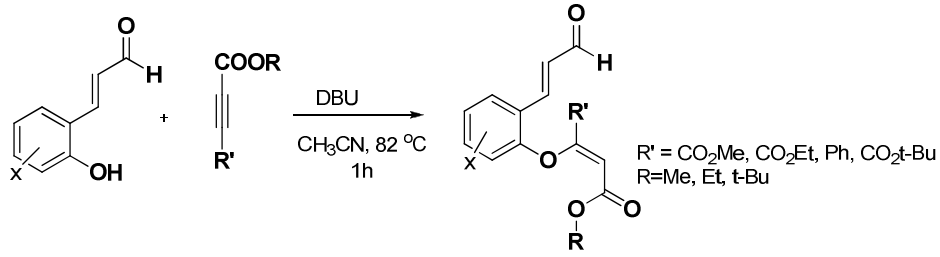
In a round bottom flask, salicylaldehyde (4.7 mmol,) and (Triphenyl–phosphoranylidene)-acetaldehyde (4.8 mmol) were taken. Into this was added 10 mL dry THF and refluxed for 3 h. After the completion of the reaction monitored by TLC, solvent was removed and the residue on purification by column chromatography (using 100-200 mesh silica gel and 90:10 hexane: ethyl acetate mixture) afforded the corresponding 2-hydroxy cinnamaldehydes.

4.7.1.4. Syntheses of Dialkyl 2-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarates



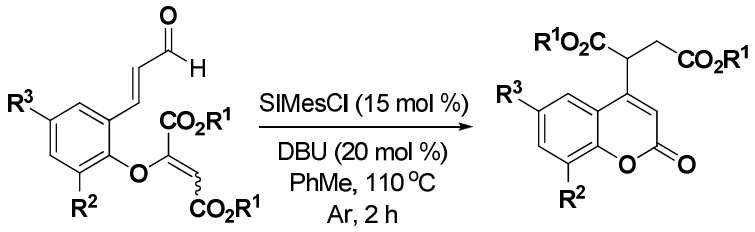
2-hydroxycinnamaldehyde (2 mmol) was dissolved in aqueous solution of NaOH (2.5 mmol) in a round bottom flask and DMAD (0.284 g, 2 mmol) was added. The reaction mixture was stirred vigorously at room temperature for 1 h. After the completion of the reaction, the solid product formed was separated by vacuum filtration. In the case of liquid products, the reaction mixture was extracted with dichloromethane (3x5 mL) and washed with water. The organic layer was dried over anhydrous sodium sulfate. After the removal of the solvent, the crude product was purified by column chromatography on 60–120 mesh silica gel using 90:10 hexane: ethyl acetate mixture.

4.7.1.5. Syntheses of mixture of *E* & *Z* isomers (dialkyl 2-(2-((*E*)-3-oxoprop-1-enyl)phenoxy) fumarate/maleate)



2-hydroxycinnamaldehyde (2 mmol) was dissolved in 7 mL acetonitrile in a round bottom flask. To this was added DBU (0.20 mmol) followed by DMAD (0.284 g, 2 mmol). The reaction mixture was refluxed for 1 h. After the completion of the reaction, crude mixture was purified by column chromatography on 60-120 mesh silica gel using 90:10 hexane: ethyl acetate mixture.

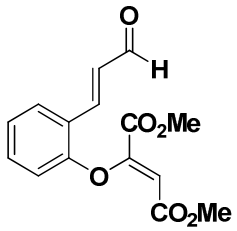
4.7.1.6. Synthesis of Coumarin Derivatives



Methyl 3-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (100 mg) and the carbene precursor-1,3-dimesityl imidazolinium chloride (15 mol %) were taken in a round bottom flask; into this was added 7 mL dry toluene followed by DBU (20 mol %) and the reaction mixture refluxed for 2 h under argon atmosphere. The completion of the reaction was monitored by TLC, and the reaction mixture was subjected to column chromatography on silica gel (100-200 mesh) using 90:10 hexane- ethyl acetate mixture.

4.7.2. Characterization Data of Compounds

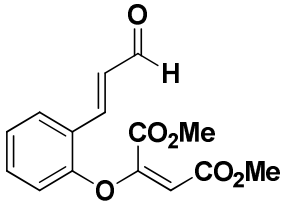
Dimethyl 2-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarate (84*E*)



Chemical Formula: $C_{15}H_{14}O_6$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.73 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 16.1 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.79 (dd, *J* = 16.5 Hz, 7.9 Hz, 2H), 6.69 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H).

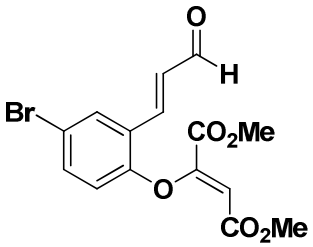
Dimethyl 2-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)maleate (84*Z*)



Chemical Formula: $C_{15}H_{14}O_6$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.64 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 16.1 Hz, 1H), 7.42 (t, *J* = 7.7, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.67 (dd, *J* = 16.1 Hz, 7.6 Hz, 1H), 5.01 (s, 1H), 3.87 (s, 3H), 3.60 (s, 3H).

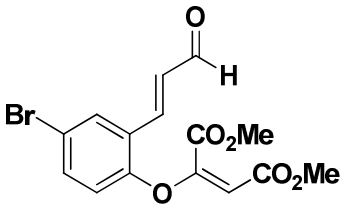
Dimethyl 2-(4-bromo-2-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarate (85*E*)



Chemical Formula: $C_{15}H_{13}BrO_6$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 16.2 Hz, 1H), 7.75 (d, *J* = 2.2 Hz, 1H), 7.41 (dd, *J* = 8.7 Hz, 2.3 Hz, 1H), 6.76 (dd, *J* = 16.2 Hz, 7.7 Hz, 1H), 6.71 (s, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H).

Dimethyl 2-(4-bromo-2-((*E*)-3-oxoprop-1-enyl)phenoxy)maleate (85*Z*)

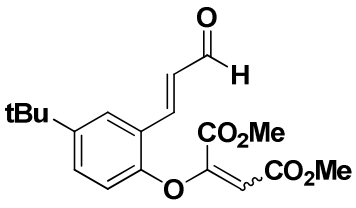


Chemical Formula: $C_{15}H_{13}BrO_6$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 1.9 Hz, 1H), 7.59 (dd, *J* = 8.7 Hz, 2.2 Hz, 1H), 7.54 (d, *J* = 16.2 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.73 (dd, *J* = 11.2 Hz, 4.9 Hz, 1H), 5.15 (s, 1H), 3.94 (s, 3H), 3.70 (s, 3H).

Dimethyl 2-(4-tert-butyl-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (86)

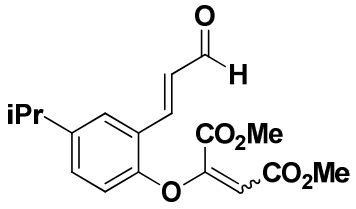
Chemical Formula: $C_{19}H_{22}O_6$.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (dd, *J* = 7.7 Hz, 6.0 Hz, 1.9H), 7.91 (d, *J* = 16.1 Hz, 0.98H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.61 (t, *J* = 9.5 Hz, 2H), 7.50 (dd, *J* = 8.6 Hz, 2.3 Hz, 1H), 7.34 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 6.81 (dd, *J* = 16.1 Hz, 7.8 Hz, 0.98H), 6.76 (dd, *J* = 16.1 Hz, 7.7 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 0.94H), 6.67 (s, 0.88H), 5.05 (s, 1H), 3.96 (s, 3H), 3.77 (s, 2.67H), 3.72 (s, 3H), 3.68 (s, 2.82H), 1.36 (s, 9H), 1.32 (s, 8H).

Dimethyl 2-(4-isopropyl-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (87)

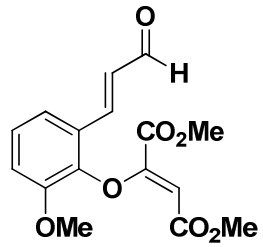
Chemical Formula: $C_{18}H_{20}O_6$.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (dd, *J* = 7.7 Hz, 5.6 Hz, 1.64H), 7.91 (d, *J* = 16.1 Hz, 0.62H), 7.60 (d, *J* = 16.1 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 0.63H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.35 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.18 (dd, *J* = 8.4 Hz, 2.1 Hz, 0.64H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.78 (ddd, *J* = 23.6 Hz, 16.1 Hz, 7.7 Hz, 1.7H), 6.70 (d, *J* = 8.4 Hz, 0.64H), 6.67 (s, 0.57H), 5.05 (s, 1H), 3.96 (s, 3H), 3.77 (s, 1.98H), 3.72 (s, 2.09H), 3.68 (s, 3H), 2.96 (dt, *J* = 13.8 Hz, 6.9 Hz, 0.72H), 2.90 (dt, *J* = 13.8 Hz, 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.25 (d, *J* = 6.8 Hz, 3.9H).

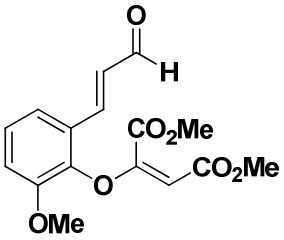
Dimethyl 2-(2-methoxy-6-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarate (88*E*)

Chemical Formula: $C_{16}H_{16}O_7$.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 16.1 Hz, 1H), 7.26 (d, *J* = 4.6 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.73 (dd, *J* = 16.1 Hz, 7.8, 1H), 6.23 (s, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H).

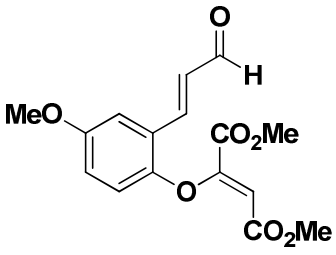
Dimethyl 2-(2-methoxy-6-((*E*)-3-oxoprop-1-enyl)phenoxy)maleate (88*Z*)



Chemical Formula: $C_{16}H_{16}O_7$.

^{1}H NMR **(500 MHz, $CDCl_3$)** δ = 9.72 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 16.1 Hz, 1H), 7.30 – 7.28 (m, 1H), 7.26 (d, *J* = 4.3 Hz, 1H), 7.10 – 7.05 (m, 1H), 6.72 (dd, *J* = 16.1 Hz, 7.6 Hz, 1H), 4.93 (s, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.67 (s, 3H).

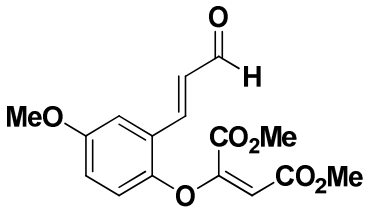
Dimethyl 2-(4-methoxy-2-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarate (89*E*)



Chemical Formula: $C_{16}H_{16}O_7$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.73 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 16.1 Hz, 1H), 7.12 (d, *J* = 2.9 Hz, 1H), 6.87 (dd, *J* = 8.9 Hz, 2.9 Hz, 1H), 6.81 – 6.70 (m, 2H), 6.61 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H).

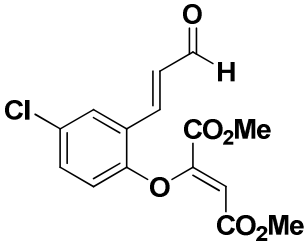
Dimethyl 2-(4-methoxy-2-((*E*)-3-oxoprop-1-enyl)phenoxy)maleate (89*Z*)



Chemical Formula: $C_{16}H_{16}O_7$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.71 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 16.1 Hz, 1H), 7.16 (d, *J* = 2.9 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 1H), 7.02 (dd, *J* = 8.9 Hz, 2.9 Hz, 1H), 6.71 (dd, *J* = 16.1 Hz, 7.6 Hz, 1H), 5.01 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.67 (s, 3H).

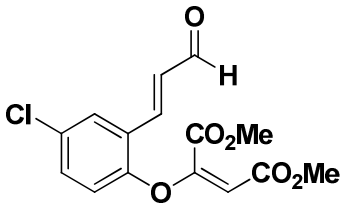
Dimethyl 2-(4-chloro-2-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarate (90*E*)



Chemical Formula: $C_{15}H_{13}ClO_6$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.73 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 16.2 Hz, 1H), 7.60 (d, *J* = 2.5 Hz, 1H), 7.28 (dd, *J* = 8.8 Hz, 2.5 Hz, 1H), 6.80 – 6.76 (m, 1H), 6.73 (t, *J* = 4.3 Hz, 2H), 3.78 (s, 3H), 3.73 (s, 3H).

Dimethyl 2-(4-chloro-2-((*E*)-3-oxoprop-1-enyl)phenoxy)maleate (90*Z*)

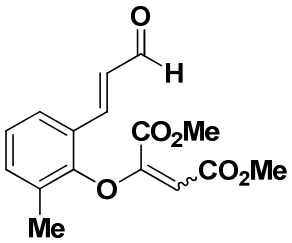


Chemical Formula: $C_{15}H_{13}ClO_6$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 16.2 Hz, 1H), 7.44 (dd, *J* = 8.7 Hz, 2.3 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.73 (dd, *J* = 16.2 Hz, 7.6, 1H), 5.14 (s, 1H), 3.94

(s, 3H), 3.70 (s, 3H).

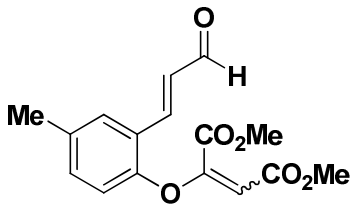
Dimethyl 2-(2-methyl-6-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (91)



Chemical Formula: $C_{16}H_{16}O_{6.}$

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.69 (dd, *J* = 11.5 Hz, 7.8 Hz, 2H), 7.80 (d, *J* = 16.1 Hz, 0.56H), 7.62 – 7.54 (m, 1.2H), 7.45 (d, *J* = 7.0 Hz, 0.57H), 7.36 (d, *J* = 7.0 Hz, 1.53H), 7.31 – 7.20 (m, 1.54H), 7.11 (d, *J* = 7.6 Hz, 0.53H), 7.08 – 6.98 (m, 2.68H), 6.76 – 6.62 (m, 1.16H), 6.22 (s, 1H), 4.80 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 2.29 (s, 6H).

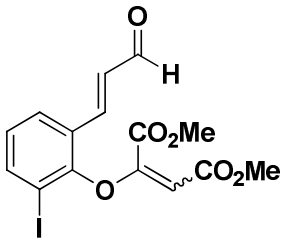
Dimethyl 2-(4-methyl-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (92)



Chemical Formula: $C_{16}H_{16}O_{6.}$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.71 (dd, *J* = 7.3 Hz, 6.0, 2H), 7.89 (d, *J* = 16.1 Hz, 1H), 7.58 (d, *J* = 16.1 Hz, 1H), 7.51 (s, 1H), 7.44 (s, 1H), 7.30 – 7.26 (m, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.80 – 6.69 (m, 2H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.65 (s, 1H), 5.05 (s, 1H), 3.95 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.67 (s, 2H), 2.41 (s, 3H), 2.34 (s, 3H).

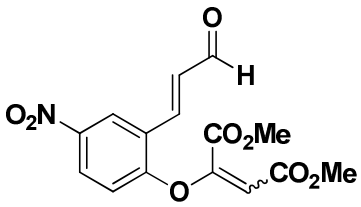
Dimethyl 2-(2-iodo-6-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (93)



Chemical Formula: $C_{15}H_{13}IO_{6.}$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.7 Hz, 1H), 9.67 (d, *J* = 7.7 Hz, 0.4H), 7.95 (dd, *J* = 7.9 Hz, 1.3 Hz, 1.20H), 7.83 (dd, *J* = 7.9 Hz, 1.4 Hz, 0.42H), 7.75 (d, *J* = 16.1 Hz, 0.45H), 7.71 – 7.66 (m, 3.12H), 7.61 (s, 0.57H), 7.59 (d, *J* = 1.4 Hz, 0.25H), 7.57 (s, 0.86H), 7.21 (dd, *J* = 7.6 Hz, 0.9 Hz, 1.93H), 7.12 (t, *J* = 7.9 Hz, 1.32H), 6.98 (t, *J* = 7.8 Hz, 0.47H), 6.86 (t, *J* = 7.8 Hz, 1.87H), 6.68 (ddd, *J* = 21.5 Hz, 16.1 Hz, 7.6 Hz, 1.88H), 6.34 (s, 0.33H), 4.81 (s, 1H), 4.01 (s, 3H), 3.76 (s, 1.35H), 3.71 (s, 1.34H), 3.68 (s, 3H).

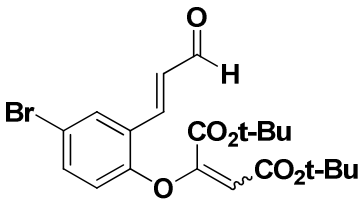
Dimethyl 2-(4-nitro-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (94)



Chemical Formula: $C_{15}H_{13}NO_{8.}$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.78 (d, *J* = 7.3 Hz, 1.58H), 8.57 (d, *J* = 2.3 Hz, 1H), 8.54 (d, *J* = 2.4 Hz, 0.50H), 8.31 (dd, *J* = 9.0 Hz, 2.5 Hz, 1H), 8.21 (dd, *J* = 9.0 Hz, 2.5 Hz, 0.52H), 7.85 (d, *J* = 16.2 Hz, 0.52H), 7.68 (d, *J* = 16.2 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.26 (s, 0.87H), 6.94 – 6.86 (m, 1.68H), 6.86 (s, 1H), 5.58 (s, 1H), 3.90 (s, 3H), 3.84 (s, 1.4H), 3.76 (s, 3H), 3.74 (s, 1.46H).

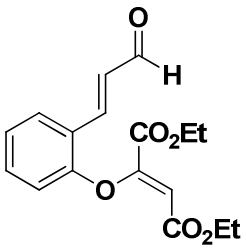
Di-tert-butyl 2-(4-bromo-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (95)



Chemical Formula: $C_{21}H_{25}BrO_{6.}$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.65 (dd, *J* = 7.6 Hz, 4.8 Hz, 1.6H), 7.77 (s, 0.59H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.67 (d, *J* = 2.3 Hz, 1H), 7.53 (d, *J* = 16.2 Hz, 0.69H), 7.48 (dd, *J* = 8.6 Hz, 2.3 Hz, 0.69H), 7.36 (dd, *J* = 8.7 Hz, 2.3 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 0.68H), 6.70 (d, *J* = 7.7 Hz, 0.62H), 6.68 (dd, *J* = 7.6 Hz, 3.4 Hz, 1H), 6.64 (dd, *J* = 8.1 Hz, 2.8 Hz, 1H), 6.48 (s, 1H), 5.11 (s, 0.58H), 1.43 (s, 5.7H), 1.38 (s, 5.8H), 1.33 (s, 9H), 1.29 (s, 9H).

Diethyl 2-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarate (96*E*)

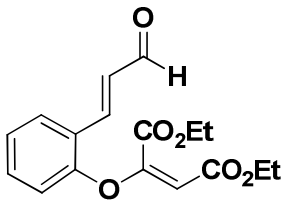


Chemical Formula: $C_{17}H_{18}O_{6.}$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.73 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 16.1 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.85 – 6.72 (m, 2H), 6.68 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 4H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

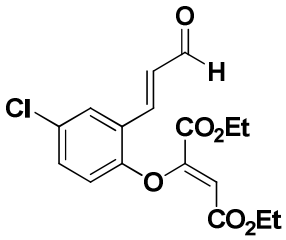
Diethyl 2-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)maleate (96*Z*)

Chemical Formula: $C_{17}H_{18}O_{6.}$



^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 16.1 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 6.75 (dd, *J* = 16.1 Hz, 7.7, 1H), 5.08 (s, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 4.14 (q, *J* = 7 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

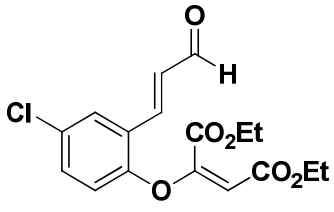
Diethyl 2-(4-chloro-2-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarate (97*E*)



Chemical Formula: $C_{17}H_{17}ClO_{6.}$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.7 Hz, 1H), 7.84 (d, *J* = 16.2 Hz, 1H), 7.60 (d, *J* = 2.5 Hz, 1H), 7.28 (dd, *J* = 8.7 Hz, 2.5 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.71 (s, 1H), 4.23-4.16 (m, 4H), 1.24-1.20 (m, 6H).

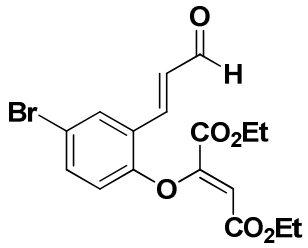
Diethyl 2-(4-chloro-2-((*E*)-3-oxoprop-1-enyl)phenoxy)maleate (97*Z*)



Chemical Formula: $C_{17}H_{17}ClO_{6.}$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.57 (d, *J* = 16.2 Hz, 1H), 7.44 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.73 (dd, *J* = 16.4 Hz, 7.8 Hz, 1H), 5.13 (s, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).

Diethyl 2-(4-bromo-2-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarate (98*E*)



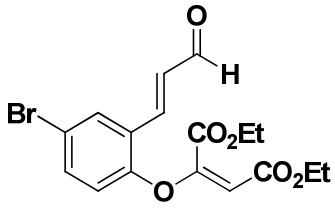
Chemical Formula: $C_{17}H_{17}BrO_{6.}$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.7 Hz, 1H), 7.82 (d, *J* = 16.2 Hz, 1H), 7.74 (d, *J* = 2.1 Hz, 1H), 7.42 (dd, *J* = 8.7 Hz, 2.2, 1H), 6.76 (dd, *J* = 16.2 Hz, 7.7 Hz, 1H), 6.71 (s, 1H), 6.69 (d, *J* = 8.7 Hz, 1H), 4.24-4.16 (m, 4H), 1.23 (m, 6H).

Diethyl 2-(4-bromo-2-((*E*)-3-oxoprop-1-enyl)phenoxy)maleate (98*Z*)

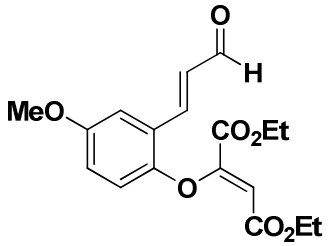
Chemical Formula: $C_{17}H_{17}BrO_{6.}$

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.58 (dd, *J* = 16.5 Hz, 9.0



Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.73 (dd, *J* = 16.0 Hz, 7.5 Hz, 1H), 5.14 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.15 (dd, *J* = 14.3 Hz, 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H).

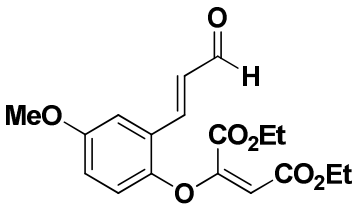
Diethyl 2-(4-methoxy-2-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarate (99*E*)



Chemical Formula: $C_{18}H_{20}O_7$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.73 (d, *J* = 7.7 Hz, 1H), 7.91 (d, *J* = 16.1 Hz, 1H), 7.11 (d, *J* = 3.0 Hz, 1H), 6.87 (dd, *J* = 8.9 Hz, 3.0, 1H), 6.78 – 6.72 (m, 2H), 6.60 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

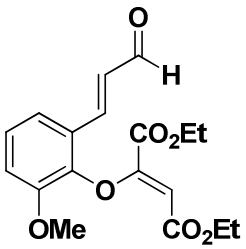
Diethyl 2-(4-methoxy-2-((*E*)-3-oxoprop-1-enyl)phenoxy)maleate (99*Z*)



Chemical Formula: $C_{18}H_{20}O_7$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.71 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 16.1 Hz, 1H), 7.15 (d, *J* = 2.9 Hz, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 7.01 (dd, *J* = 8.9 Hz, 2.9 Hz, 1H), 6.71 (dd, *J* = 16.1 Hz, 7.7 Hz, 1H), 5.00 (s, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H).

Diethyl 2-(2-methoxy-6-((*E*)-3-oxoprop-1-enyl)phenoxy)fumarate (100*E*)

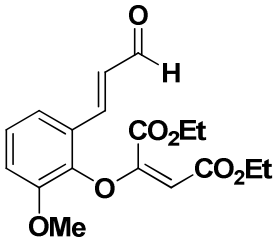


Chemical Formula: $C_{18}H_{20}O_7$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 16.1 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.74 (dd, *J* = 16.1 Hz, 7.8 Hz, 1H), 6.21 (s, 1H), 4.19-4.12 (m, 4H), 3.76 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

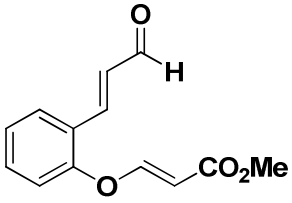
Diethyl 2-(2-methoxy-6-((*E*)-3-oxoprop-1-enyl)phenoxy)maleate (100*Z*)

Chemical Formula: $C_{18}H_{20}O_7$.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 16.1 Hz, 1H), 7.29 – 7.27 (m, 2H), 7.07 (dd, *J* = 6.5 Hz, 2.9 Hz, 1H), 6.73 (dd, *J* = 16.1 Hz, 7.6 Hz, 1H), 4.92 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 1.41 (t, *J* = 7.3 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H).

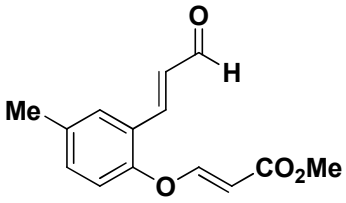
_(E)_-Methyl 3-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (101)



Chemical Formula: $C_{13}H_{12}O_4$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 12.2 Hz, 1H), 7.68 (dd, *J* = 16.3 Hz, 12.0 Hz, 2H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.27 (dd, *J* = 9.0 Hz, 6.2 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 6.74 (dd, *J* = 16.1 Hz, 7.6 Hz, 1H), 5.61 (d, *J* = 12.2 Hz, 1H), 3.74 (s, 3H).

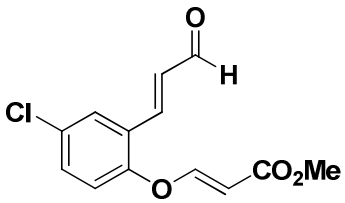
Methyl 3-(4-methyl-2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (102)



Chemical Formula: $C_{14}H_{14}O_4$

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.70 (d, 1H, *J* = 8 Hz), 7.75 (d, 1H, *J* = 12.5 Hz), 7.64 (d, 1H, *J* = 16 Hz), 7.44 (s, 1H), 7.27-7.24 (m, 1H), 7.0 (d, 1H *J* = 8.3), 6.72 (dd, 1H, *J* = 16.1, 7.7 Hz), 5.54 (d, 1H, *J* = 12 Hz), 3.73 (s, 3H), 2.39 (s,3H).

Methyl 3-(4-chloro-2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (103)



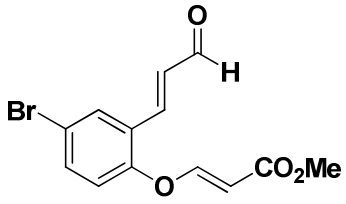
Chemical Formula: $C_{13}H_{11}O_4Cl$

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.72 (d, 1H, *J* = 7.5 Hz), 7.73 (d, 1H, *J* =12 Hz), 7.62 (d, 1H, *J* =2 Hz) 7.42 (dd, 1H, *J* = 8.5 Hz, 9Hz), 7.08 (d, 1H, *J* = 8.7Hz), 6.72 (dd, 1H, *J* = 16.2, 7.5 Hz), 5.61 (d, 1H, *J* = 12Hz), 3.75 (s, 3H)

Methyl 3-(4-bromo-2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (104)

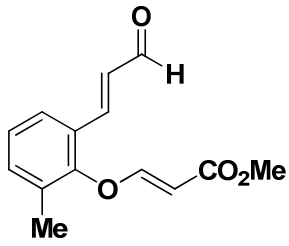
Chemical Formula: $C_{13}H_{11}O_4Br$

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.71 (d, 1H, *J* = 7.5



Hz), 7.77 (d, 1H, *J* = 2 Hz), 7.73 (d, 1H, *J* = 12 Hz), 7.62 (s, 1H), 7.59-7.57 (m, 1H), 7.03-7.01 (m, 1H), 6.72 (dd, 1H, *J* = 16.2 , 7.5 Hz), 5.63 (d, 1H, *J* =12 Hz), 3.75 (s, 3H).

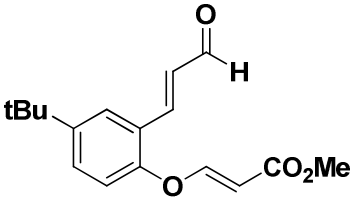
Methyl 3-(2-methyl-6-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (105)



Chemical Formula: $C_{14}H_{14}O_4$

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.61 (d, 1H, *J* = 8 Hz), 7.69 (d, 1H, *J* = 12.5 Hz), 7.45 (d, 1H, *J* = 5 Hz), 7.27 (d, 1H, *J* = 7.5 Hz), 7.16 (t, 1H, *J* = 1H), 6.63 (dd, 1H, J_1 = 16.1, J_2 = 7.7 Hz), 4.96 (d, 1H, *J* = 12.5 Hz), 3.62 (s, 3H), 2.18 (s, 3H).

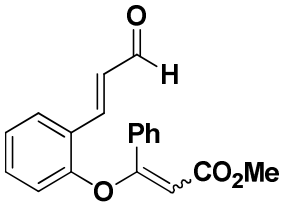
Methyl 3-(4-tert-butyl-2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (106)



Chemical Formula: $C_{17}H_{20}O_4$

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.7 (d, 1H, *J* = 7.5 Hz), 7.79 (d, 1H, *J* = 12 Hz), 7.70 (s, 1H), 7.65 (d, 1H, *J* = 15.5 Hz), 7.50-7.48 (m, 1H), 7.05 (d, 1H, *J* = 8.5 Hz), 6.77 (q, 1H, *J* = 16 Hz), 5.57 (d, 1H, *J* = 12.5 Hz), 3.74(s, 3H), 1.35 (s, 9H).

Methyl 3-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)-3-phenylacrylate (107)

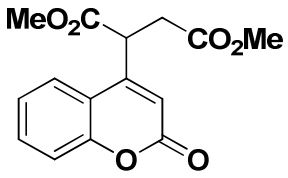


Chemical Formula: $C_{19}H_{16}O_4$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.78 (d, *J* = 7.8 Hz, 1H), 9.69 (d, *J* = 7.6 Hz, 0.29H), 8.06 (d, *J* = 16.1 Hz, 1H), 7.71 (dd, *J* = 7.8 Hz, 1.1 Hz, 0.33H), 7.67 – 7.62 (m, 2H), 7.60 – 7.56 (m, 2H), 7.49 – 7.43 (m, 1.47H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 0.33H), 7.23 – 7.18 (m, 1H), 7.17 (d, *J* = 8.0 Hz, 0.33H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.87 (dd, *J* = 16.1 Hz, 7.8 Hz, 0.25H), 6.80 – 6.74 (m, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.24 (s, 1H), 5.12 (s, 0.28H), 3.63 (s, 3H), 3.56 (s, 0.85H).

Dimethyl 2-(2-oxo-2*H*-chromen-4-yl)succinate (84a)

Following the general procedure, reaction of dimethyl 2-(2-((*E)*-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded dimethyl 2-(2-oxo-2*H*-chromen-4-yl)succinate as white solid.



Chemical Formula: $C_{15}H_{14}O_{6.}$

m p 86–88 ^{o}C.

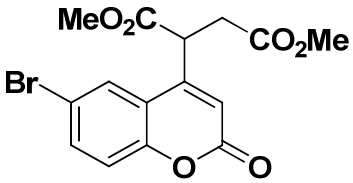
Yield: 93 mg (93%); For *Z*: 83 mg (83%); For *E:* 66 mg (66%).

IR (film) ν_{max} 2954, 2921, 1723, 1712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 8.1 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 6.27 (s, 1H), 4.44 (dd, *J* = 9.3 Hz, 5.2 Hz, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 3.18 (dd, *J* = 17.2 Hz, 9.3, 1H), 2.67 (dd, *J* = 17.3 Hz, 5.1 Hz, 1H). **^{13}C NMR (126 MHz, CDCl3)** δ = 170.9, 170.8, 159.8, 153.9, 151.2, 132.2, 124.5, 124.1, 117.9, 117.7, 115.2, 53.0, 52.2, 42.3, 35.6. **HRMS** (FAB) calcd for $[M+H]^{+}$: 291.0860; found: 291.0873.

Dimethyl 2-(6-bromo-2-oxo-2*H*-chromen-4-yl)succinate (85a)

Following the general procedure, reaction of dimethyl 2-(4-bromo-2-((*E)*-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded dimethyl 2-(6-bromo-2-oxo-2*H*-chromen-4-yl)succinate as white solid.



Chemical Formula: $C_{15}H_{13}BrO_{6}$.

m p 90–92 ^{o}C.

Yield: 78 mg (78%); For *Z*: 75 mg (75%); For *E:* 69 mg (69%).

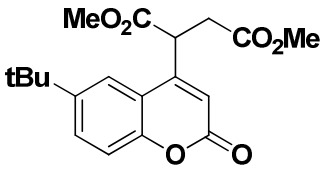
IR (film) ν_{max} 2954, 1721 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.77 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.29 (s, 1H), 4.37 (dd, *J* = 9.0 Hz, 5.6, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.17 (dd, *J* = 17.2 Hz, 9.1 Hz, 1H), 2.69 (dd, *J* = 17.3 Hz,

5.5 Hz, 1H). **^{13}C NMR (126 MHz, CDCl3)** δ = 170.7, 170.4, 159.0, 152.8, 150.2, 135.0, 126.8, 119.6, 119.3, 117.4, 116.0, 53.1, 52.3, 41.9, 35.5. **HRMS** (FAB) calcd for $[M+H]^{+:}$ 368.9966; found: 369.5410.

Dimethyl 2-(6-tert-butyl-2-oxo-2*H*-chromen-4-yl)succinate (86a)

Following the general procedure, reaction of dimethyl 2-(4-tert-butyl-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded dimethyl 2-(6-tert-butyl-2-oxo-2*H*-chromen-4-yl)succinate as viscous liquid..



Chemical Formula: $C_{19}H_{22}O_{6.}$

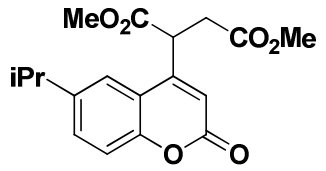
Yield: 70 mg (70%).

IR (film) ν_{max} 2956, 1720 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.32 (s, 1H), 4.52 (dd, *J* = 8.3 Hz, 5.7 Hz, 1H), 3.74 (s, 6H), 3.28 (dd, *J* = 17.1 Hz, 9.1 Hz, 1H), 2.74 (dd, *J* = 17.1 Hz, 5.1 Hz, 1H), 1.37 (s, 9H). **^{13}C NMR (126 MHz, CDCl3)** δ = 171.0, 170.9, 160.0, 151.9, 151.4, 147.5, 129.7, 120.4, 117.2, 115.2, 52.9, 52.2, 42.7, 35.5, 34.7, 31.4. **HRMS** (FAB) calcd for $[M+H]^{+}$: 347.1495, found: 347.1519.

Dimethyl 2-(6-isopropyl-2-oxo-2*H*-chromen-4-yl)succinate (87a)

Following the general procedure, reaction of dimethyl 2-(4-isopropyl-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded dimethyl 2-(6-isopropyl-2-oxo-2H-chromen-4-yl)succinate as viscous liquid.



Chemical Formula: $C_{18}H_{20}O_{6}$.

Yield: 66 mg (66%).

IR (film) ν_{max} 2956, 2917, 2850, 1736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 1.5 Hz, 1H), 7.36 (dd, *J* = 8.4 Hz, 1.9 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 6.25 (s, 1H), 4.44 (dd, *J* = 9.4 Hz, 5.1 Hz, 1H), 3.67 (s, 6H), 3.18 (dd, *J* = 17.2 Hz, 9.4 Hz, 1H), 2.97 –

2.89 (m, 1H), 2.66 (dd, *J* = 17.1 Hz, 5.2 Hz, 1H), 1.22 (dd, *J* = 6.9 Hz, 1.4 Hz, 6H). **^{13}C NMR (126 MHz, CDCl3)** δ = 171.03, 171.0, 160.1, 152.3, 151.3, 145.2, 130.6, 130.58, 121.4, 117.6, 115.1, 52.9, 52.2, 42.4, 35.6, 33.8, 24.2, 24.1. HRMS (FAB) calcd for [M+H]+: 333.1330; Found: 333.1351.

Dimethyl 2-(8-methoxy-2-oxo-2*H*-chromen-4-yl)succinate (88a)

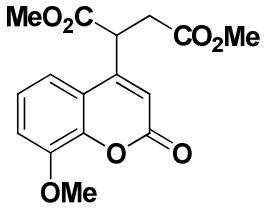
Following the general procedure, reaction of dimethyl 2-(2-methoxy-6-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded dimethyl 2-(8-methoxy-2-oxo-2*H*-chromen-4-yl)succinate as white solid.

Chemical Formula: $C_{16}H_{16}O_{7.}$

m p 85-87 ^{o}C.

Yield: 60 mg (60%); For *Z*: 63 mg (63%); For *E:* 81 mg (81%).

IR (film) ν_{max} 2954, 1720 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.17 (d, *J* = 6.5 Hz, 2H), 7.03 (dd, *J* = 6.5 Hz, 2.9, 1H), 6.26 (s, 1H), 4.41 (dd, *J* = 9.3 Hz, 5.1 Hz, 1H), 3.89 (s, 3H), 3.66 (s, 3H), 3.65 (s, 3H), 3.15 (dd, *J* = 17.2 Hz, 9.4 Hz, 1H), 2.67 (dd, *J* = 17.2 Hz, 5.2 Hz, 1H). **^{13}C NMR (126 MHz, CDCl3)** δ = 170.9, 159.2, 151.4, 147.9, 143.9, 124.1, 118.6, 115.4, 115.3, 113.9, 56.2, 52.9, 52.2, 42.6, 35.6. **HRMS** (FAB) calcd for [M+H]$^{+}$: 321.0966, found:321.0987.

Dimethyl 2-(6-methoxy-2-oxo-2*H*-chromen-4-yl)succinate (89a)

Following the general procedure, reaction of dimethyl 2-(4-methoxy-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded dimethyl 2-(6-methoxy-2-oxo-2*H*-chromen-4-yl)succinate as white solid.

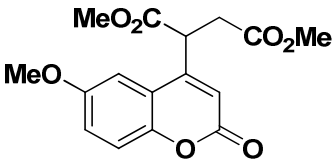
Chemical Formula: $C_{16}H_{16}O_{7.}$

m p 83-85 ^{o}C.

Yield: 60 mg (60%); For *Z*: 65 mg (65%); For *E:* 78 mg

(78%).

IR (film) ν_{max} 2958, 2917, 2849, 1736, 1721 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 12.6 Hz, 1H), 7.07 (s, 2H), 6.27 (s, 1H), 4.39 (dd, *J* = 9.1 Hz, 5.2 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 3.19 (dd, *J* = 17.2 Hz, 9.2 Hz, 1H), 2.67 (dd, *J* = 17.4 Hz, 4.9 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 170.9, 170.8, 160.0, 156.2, 150.9, 148.3, 119.4, 118.6, 118.3, 115.6, 107.0, 55.8, 53.0, 52.3, 42.6, 35.5. **HRMS** (FAB) calcd for $[M+H]^+$: 321.0966, found: 321.0977.

Dimethyl 2-(6-chloro-2-oxo-2*H*-chromen-4-yl)succinate (90a)

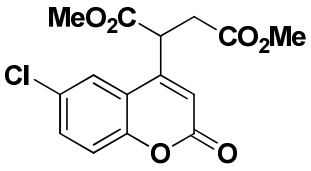
Following the general procedure, reaction of dimethyl 2-(4-chloro-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded dimethyl 2-(6-chloro-2-oxo-2*H*-chromen-4-yl)succinate as white solid.

Chemical Formula: $C_{15}H_{13}ClO_6$.

m p 89-91 ^oC.

Yield: 55 mg (55%); For *Z*: 69 mg (69%); For *E:* 60 mg (60%).

IR (film) ν_{max} 2955, 2917, 1726 cm^{-1}.

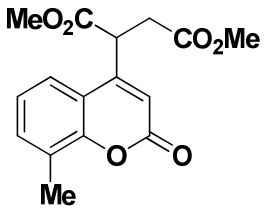


^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 2.1 Hz, 1H), 7.52 (dd, *J* = 8.8 Hz, 2.2 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 6.37 (s, 1H), 4.43 (dd, *J* = 9.0 Hz, 5.6 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.24 (dd, *J* = 17.2 Hz, 9.1 Hz, 1H), 2.75 (dd, *J* = 16.9 Hz, 5.6 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 170.7, 170.4, 159.0, 152.4, 150.3, 132.2, 130.1, 123.8, 119.2, 119.0, 116.1, 53.2, 52.3, 42.0, 35.5. **HRMS** (FAB) calcd for $[M+H]^+$: 325.0471, found: 325.0439.

Dimethyl 2-(8-methyl-2-oxo-2*H*-chromen-4-yl)succinate (91a)

Following the general procedure, reaction of dimethyl 2-(2-methyl-6-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol

%) and DBU (20 mol %) afforded dimethyl 2-(8-methyl-2-oxo-2*H*-chromen-4-yl)succinate as viscous liquid.



Chemical Formula: $C_{16}H_{16}O_{6.}$

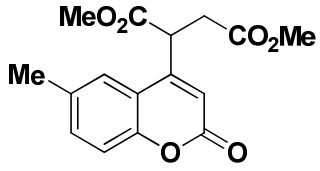
Yield: 47 mg (47%).

IR (film) ν_{max} 2955, 2918, 1721 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 6.32 (s, 1H), 4.50 (dd, *J* = 9.3 Hz, 5.2 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.23 (dd, *J* = 17.2 Hz, 9.4 Hz, 1H), 2.73 (dd, *J* = 17.2 Hz, 5.2 Hz, 1H), 2.47 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.0, 170.9, 159.9, 152.3, 151.6, 133.5, 127.1, 123.9, 121.7, 117.6, 114.9, 52.9, 52.2, 42.5, 35.7, 15.8. **HRMS** (FAB) calcd for $[M+H]^+$: 305.1017, found: 305.1091.

Dimethyl 2-(6-methyl-2-oxo-2*H*-chromen-4-yl)succinate (92a)

Following the general procedure, reaction of dimethyl 2-(4-methyl-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded dimethyl 2-(6-methyl-2-oxo-2*H*-chromen-4-yl)succinate as yellow solid.



Chemical Formula: $C_{16}H_{16}O_{6.}$

m p 87-89 ^{o}C.

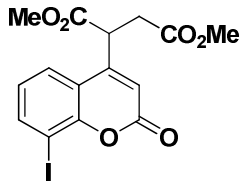
Yield: 46 mg (46%).

IR (film) ν_{max} 2951, 2922, 2854, 1736, 1720 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 (s, 1H), 7.36 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.27 (s, 1H), 6.30 (s, 1H), 4.50 (dd, *J* = 9.5 Hz, 5.1 Hz, 1H), 3.74 (s, 3H), 3.74 (s, 3H), 3.23 (dd, *J* = 17.2 Hz, 9.6 Hz, 1H), 2.73 (dd, *J* = 17.2 Hz, 5.1 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.0, 170.9, 159.9, 152.2, 151.1, 134.2, 133.2, 123.8, 117.6, 117.5, 115.0, 52.9, 52.2, 42.1, 35.7, 21.1. HRMS (FAB) calcd for [M+H]+: 305.1017, found: 305.1046.

Dimethyl 2-(8-iodo-2-oxo-2*H*-chromen-4-yl)succinate (93a)

Following the general procedure, reaction of dimethyl 2-(2-iodo-6-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded dimethyl 2-(8-iodo-2-oxo-2*H*-chromen-4-yl)succinate as viscous liquid.



Chemical Formula: $C_{15}H_{13}IO_6$.

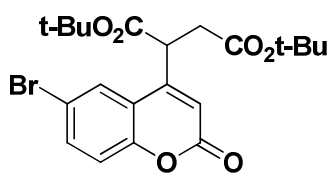
Yield: 46 mg (46%).

IR (film) ν_{max} 2955, 2917, 2850, 1734 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 7.9 Hz, 1H), 6.28 (s, 1H), 4.42 (dd, *J* = 8.9 Hz, 5.6 Hz, 1H), 3.66 (s, 3H), 3.66 (s, 3H), 3.18 (dd, *J* = 17.2 Hz, 9.0 Hz, 1H), 2.67 (dd, *J* = 17.2 Hz, 5.6 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 170.8, 170.6, 158.8, 153.1, 150.9, 142.1, 125.7, 124.4, 118.8, 115.9, 85.2, 53.1, 52.3, 42.2, 35.5. **HRMS** (FAB) calcd for $[M+H]^+$: 416.9827; found: 416.9880.

Di-tert-butyl 2-(6-bromo-2-oxo-2*H*-chromen-4-yl)succinate (95a)

Following the general procedure, reaction of di-tert-butyl 2-(4-bromo-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded di-tert-butyl 2-(6-bromo-2-oxo-2*H*-chromen-4-yl)succinate as white solid.



Chemical Formula: $C_{21}H_{25}BrO_6$.

m p 89-91 ^oC.

Yield: 21 mg (21%).

IR (film) ν_{max} 2957, 2923, 1731 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.90 (d, *J* = 2.1 Hz, 1H), 7.64 (dd, *J* = 8.8 Hz, 2.2 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 6.36 (s, 1H), 4.28 (dd, *J* = 8.9 Hz, 5.9, 1H), 3.08 (dd, *J* = 16.8 Hz, 9.0 Hz, 1H), 2.63 (dd, *J* = 16.8 Hz, 5.8 Hz, 1H), 1.45 (s, 9H), 1.42 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 169.5, 168.9, 159.2, 152.7, 151.0, 134.7, 127.4, 119.9, 119.2, 117.1, 115.6, 82.8, 81.7, 43.6, 36.6,

28.0, 27.8. **HRMS** (FAB) calcd for $[M+H]^+$: 453.0905; found: 454.4665.

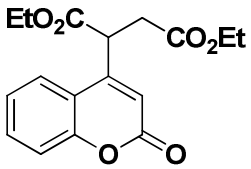
Diethyl 2-(2-oxo-2*H*-chromen-4-yl)succinate (96a)

Following the general procedure, reaction of diethyl 2-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded diethyl 2-(2-oxo-2*H*-chromen-4-yl)succinate as viscous liquid.

Chemical Formula: $C_{17}H_{18}O_{6.}$

Yield: 81 mg (81%); For *Z*: 68 mg (68%); For *E*: 72 mg (72%).

IR (film) ν_{max} 2917, 2850, 1729 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 7.9 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 6.28 (s, 1H), 4.41 (dd, *J* = 9.3 Hz, 5.3 Hz, 1H), 4.17 – 4.06 (m, 4H), 3.15 (dd, *J* = 17.1 Hz, 9.4 Hz, 1H), 2.65 (dd, *J* = 17.1 Hz, 5.3 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 170.5, 170.4, 159.9, 153.9, 151.5, 132.1, 124.4, 124.2, 117.9, 117.7, 115.1, 62.0, 61.2, 42.6, 35.8, 14.1, 13.9. **HRMS** (FAB) calcd for $[M+H]^+$: 319.1173; Found: 319.1127.

Diethyl 2-(6-chloro-2-oxo-2*H*-chromen-4-yl)succinate (97a)

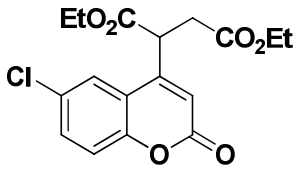
Following the general procedure, reaction of diethyl 2-(4-chloro-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded diethyl 2-(6-chloro-2-oxo-2*H*-chromen-4-yl)succinate as viscous liquid.

Chemical Formula: $C_{17}H_{17}ClO_{6.}$

Yield: For *Z*: 65 mg (65%); For *E:* 58 mg (58%).

IR (film) ν_{max} 2919, 2851, 1731 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.72 (s, 1H), 7.53 – 7.49 (m, 1H), 7.31 (dd, *J* = 8.8 Hz, 1.4 Hz, 1H), 6.38 (s, 1H), 4.41 (dd, *J* = 8.6 Hz, 5.9 Hz, 1H), 4.19 (ddt, *J* =



14.2 Hz, 12.7 Hz, 7.2 Hz, 4H), 3.21 (ddd, *J* = 17.1 Hz, 9.1 Hz, 1.1 Hz, 1H), 2.74 (ddd, *J* = 17.2 Hz, 5.6 Hz, 1.0 Hz, 1H), 1.26 (ddd, *J* = 23.6 Hz, 7.1 Hz, 1.4 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 170.2, 169.9, 159.2, 152.3, 150.5, 132.1, 130.0, 123.9, 119.2, 118.9, 116.0, 62.2, 61.3, 42.4, 35.7, 14.1, 13.9. **HRMS** (FAB) calcd for $[M+H]^+$: 353.0784; Found: 353.0763.

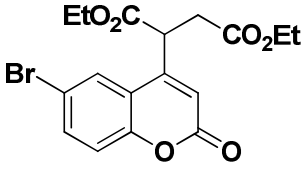
Diethyl 2-(6-bromo-2-oxo-2*H*-chromen-4-yl)succinate (98a)

Following the general procedure, reaction of diethyl 2-(4-bromo-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded diethyl 2-(6-bromo-2-oxo-2*H*-chromen-4-yl)succinate as viscous liquid.

Chemical Formula: $C_{17}H_{17}BrO_6$.

Yield: For *Z*: 85 mg (85%); For *E:* 89 mg (89%).

IR (film) ν_{max} 2981, 2936, 1730 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 2.0 Hz, 1H), 7.57 (dd, *J* = 8.8 Hz, 2.1 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.29 (s, 1H), 4.33 (dd, *J* = 9.1 Hz, 5.6 Hz, 1H), 4.16 – 4.08 (m, 4H), 3.13 (dd, *J* = 17.1 Hz, 9.1 Hz, 1H), 2.66 (dd, *J* = 17.1 Hz, 5.6 Hz, 1H), 1.19 (dt, *J* = 14.5 Hz, 7.1 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ= 170.2, 169.9, 158.9, 152.8, 150.3, 134.8, 126.9, 119.7, 119.2, 117.2, 116.0, 62.2, 61.3, 42.3, 35.7, 14.2, 13.9. **HRMS** (FAB) calcd for $[M+H]^+$: 397.0279; Found: 397.8125.

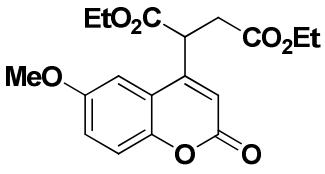
Diethyl 2-(6-methoxy-2-oxo-2*H*-chromen-4-yl)succinate (99a)

Following the general procedure, reaction of diethyl 2-(4-methoxy-2-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded diethyl 2-(6-methoxy-2-oxo-2*H*-chromen-4-yl)succinate as viscous liquid

Chemical Formula: $C_{18}H_{20}O_7$

Yield: For Z: 62 mg (62%); For E: 76 mg (76%).

IR (film) ν_{max} 2918, 2850, 1735, 1719 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.32 – 7.23 (m, 1H), 7.18 – 7.10 (m, 2H), 6.34 (s, 1H), 4.42 (dd, *J* = 9.2 Hz, 5.3 Hz, 1H), 4.25 – 4.14 (m, 4H), 3.86 (s, 3H), 3.22 (dd, *J* = 17.1 Hz, 9.2 Hz, 1H), 2.72 (dd, *J* = 17.1 Hz, 5.2 Hz, 1H), 1.25 (dt, *J* = 18.8 Hz, 7.1 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 170.5, 170.3, 160.0, 156.1, 151.1, 148.3, 119.4, 118.5, 118.4, 115.5, 107.1, 62.0, 61.2, 55.8, 42.8, 35.7, 14.1, 14.0. **HRMS** (FAB) calcd for [M+H]+: 349.1279; Found: 349.1214.

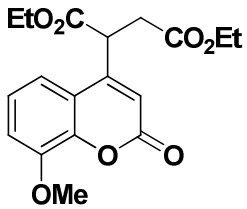
Diethyl 2-(8-methoxy-2-oxo-2*H*-chromen-4-yl)succinate (100a)

Following the general procedure, reaction of diethyl 2-(2-methoxy-6-((*E*)-3-oxoprop-1-enyl)phenoxy)but-2-enedioate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded diethyl 2-(8-methoxy-2-oxo-2*H*-chromen-4-yl)succinate as viscous liquid.

Chemical Formula: $C_{18}H_{20}O_7$

Yield: For *Z*: 67 mg (67%); For *E:* 74 mg (74%).

IR (film) ν_{max} 2916, 2849, 1729 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.30 – 7.24 (m, 2H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.35 (s, 1H), 4.46 (dd, *J* = 9.3 Hz, 5.2 Hz, 1H), 4.21 – 4.13 (m, 4H), 3.97 (s, 3H), 3.20 (dd, *J* = 17.1 Hz, 9.4 Hz, 1H), 2.72 (dd, *J* = 17.1 Hz, 5.2 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 170.5, 170.4, 159.3, 151.7, 147.9, 143.9, 124.1, 118.6, 115.4, 115.3, 113.9, 61.9, 61.2, 56.2, 42.9, 35.9, 14.1, 13.9. **HRMS** (FAB) calcd for [M+H]+: 349.1279; Found: 349.1210.

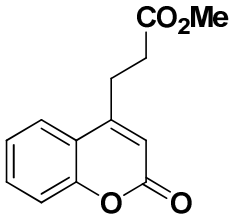
Methyl 3-(2-oxo-2*H*-chromen-4-yl)propanoate (101a)

Following the general procedure, reaction of (*E*)-Methyl 3-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded methyl 3-(2-oxo-2*H*-chromen-4-yl)propanoate **101a** as white solid in 60% (60 mg) and methyl 3-(2-oxo-2*H*-chromen-3-yl)propanoate **101b** as viscous liquid in 30% (30 mg).

Chemical Formula: $C_{13}H_{12}O_4$

m p 64-66 ^oC.

IR (film) ν_{max} 2917, 1721 cm^{-1}.



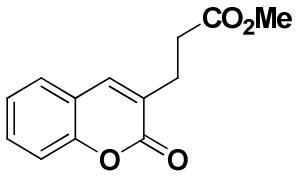
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 7.9 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 6.26 (s, 1H), 3.73 (s, 3H), 3.13 (t, *J* = 7.6 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H,). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.7, 159.9, 153.8, 153.4, 131.7, 124.1, 123.9, 118.9, 117.5, 114.2, 51.9, 3.8, 26.5. **HRMS** (FAB) calcd for $[M+H]^+$: 233.0806; Found: 233.0845.

Methyl 3-(2-oxo-2*H*-chromen-3-yl)propanoate (101b)

Chemical Formula: $C_{13}H_{12}O_4$

Yield: 30 mg (30%).

IR (film) ν_{max} 2917, 1713 cm^{-1}.



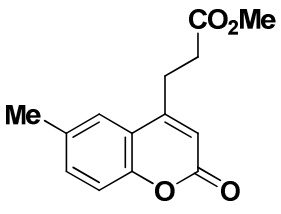
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.60 (s, 1H), 7.50 – 7.43 (m, 2H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 1H), 3.67 (s, 3H), 2.89 (t, *J* = 7.1 Hz, 2H), 2.72 (t, *J* = 7.1 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 172.9, 161.3, 153.4, 139.9, 130.8, 127.8, 127.4, 124.3, 119.4, 116.5, 51.6, 31.9, 26.6. **HRMS** (FAB) calcd for $[M+H]^+$: 233.0806; Found: 233.0828.

Methyl 3-(6-methyl-2-oxo-2*H*-chromen-4-yl)propanoate (102a)

Following the general procedure, reaction of methyl 3-(4-methyl-2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded methyl 3-(6-methyl-2-oxo-2*H*-chromen-4-yl)propanoate **102a** as white powder in 21**%** (21 mg) and methyl 3-(6-methyl-2-oxo-2*H*-chromen-3-yl)propanoate **102b** as viscous liquid in 14% (14 mg).

Chemical Formula: $C_{14}H_{14}O_4$

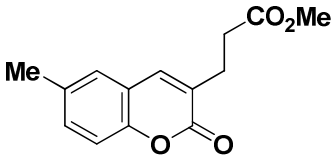
IR (film) ν_{max} 2953, 1724 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (s, 1H), 7.33 (d, *J* =8.4, 1H), 7.23 (d, 1H, *J* = 8.4 Hz), 6.23 (s, 1H), 3.74 (s, 3H), 3.10 (t, 2H, *J* = 7.7 Hz), 2.76 – 2.70 (m, 2H), 2.44 (s,

3H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 171.9, 160.4, 153.5, 151.9, 133.8, 132.7, 123.7, 118.6, 117.2, 114.1, 52.0, 31.8, 26.4, 21.1.

Methyl 3-(6-methyl-2-oxo-2*H*-chromen-3-yl)propanoate (102b)



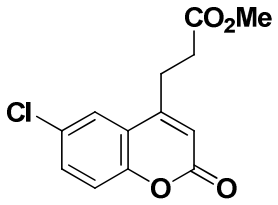
Chemical Formula: $C_{14}H_{14}O_4$

IR (film) ν_{max} 2920, 1717 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.26 (s, 1H), 7.23 – 7.18 (m, 2H), 3.66 (s, 3H), 2.87 (t, 2H, *J* = 7.1 Hz), 2.70 (t, 2H, *J* = 7.1Hz), 2.40 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 172.8, 147.2, 140.4, 128.4, 123.6, 116.1, 51.5, 34.5, 32.0, 31.4, 26.7.

Methyl 3-(6-chloro-2-oxo-2*H*-chromen-4-yl)propanoate (103a)

Following the general procedure, reaction of methyl 3-(4-chloro-2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded methyl 3-(6-chloro-2-oxo-2*H*-chromen-4-yl)propanoate **103a** as white powder in 60% (60 mg) and methyl 3-(6-chloro-2-oxo-2*H*-chromen-3-yl)propanoate **103b** as white powder in 35% (35 mg).

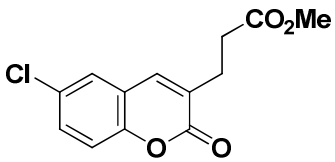


Chemical Formula: $C_{13}H_{11}O_4Cl$

IR (film) ν_{max} 2921, 1724 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, 1H, *J* = 2.2Hz), 7.63 (dd, 1H, *J* = 8.8, J_2 = 2.2 Hz), 7.24 (d, 1H, *J* = 8.8 Hz), 6.29 (s, 1H), 3.74 (s, 1H), 3.09 (t, 1H, *J* = 7.5 Hz), 2.74 (t, 1H, *J* = 7.5 Hz). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 171.7, 152.6, 131.8, 130.7, 129.9, 128.8, 123.6, 118.8, 115.1, 52.0, 32.0, 29.4, 22.7.

Methyl 3-(6-chloro-2-oxo-2*H*-chromen-3-yl)propanoate (103b)



Chemical Formula: $C_{13}H_{11}O_4Cl$

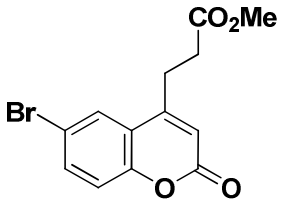
IR (film) ν_{max} 2920, 1739, 1718 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58 (d, 1H, *J* = 2.2 Hz), 7.56 (dd, 1H, *J* = 8.7, 2.3 Hz), 7.52 (s, 1H), 7.20 (d, 1H, *J* = 8.7 Hz), 3.67 (s, 3H), 2.88 (t, 2H, *J* = 7.0 Hz),

2.71 (t, 2H, *J* = 7.0 Hz). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 172.7, 151.7, 138.7, 130.8, 126.7, 125.4, 117.9, 51.7, 32.0, 22.7.

Methyl 3-(6-bromo-2-oxo-2*H*-chromen-4-yl)propanoate (104a)

Following the general procedure, reaction of methyl 3-(4-bromo-2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded methyl 3-(6-bromo-2-oxo-2*H*-chromen-4-yl)propanoate **104a** as white powder in 39% (39 mg) and methyl 3-(6-bromo-2-oxo-2*H*-chromen-3-yl)propanoate **104b** as white powder in 41% (41 mg).

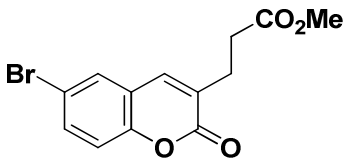


Chemical Formula: $C_{13}H_{11}O_4Br$

IR (film) ν_{max} 2919, 1735 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75(d, 1H, *J* = 2.5 Hz), 7.64-7.62(m, 1H), 7.24(d, 1H, *J* = 9 Hz), 2.29(s, 1H), 3.74(s, 3H), 3.11-3.08(m, 2H), 2.74(t, 2H, *J* = 7.5 Hz). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ 189.7, 152.6, 134.7, 129.9, 126.7, 123.1, 120.6, 119.1, 117.2, 115.0, 52.1, 31.5, 26.3.

Methyl 3-(6-bromo-2-oxo-2*H*-chromen-3-yl)propanoate (104b)



Chemical Formula: $C_{13}H_{11}O_4Br$

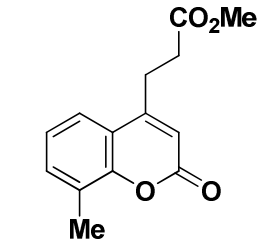
IR (film) ν_{max} 2916, 1713 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58 (d, 1H, *J* = 2 Hz), 7.55(d, 1H, *J* = 2.5 Hz), 7.52(s, 1H), 7.20(d, 1H, *J* = 9 Hz), 3.67(s, 3H), 2.89-2.87(m, 2H), 2.71(t, 2H, *J* = 7 Hz). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 172.7, 159.7, 138.6, 133.6, 132.1, 129.7, 118.2, 51.7, 31.8, 26.9

Methyl 3-(8-methyl-2-oxo-2*H*-chromen-4-yl)propanoate (105a)

Following the general procedure, reaction of methyl 3-(2-methyl-6-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded methyl 3-(8-methyl-2-oxo-2*H*-chromen-4-yl)propanoate **105a** as white powder in 19% (19 mg) and methyl 3-(8-methyl-2-oxo-2*H*-chromen-3-yl)propanoate **105b** as viscous liquid in 32% (32 mg).

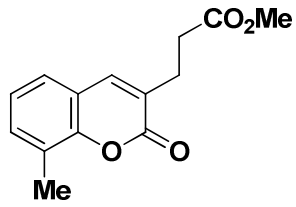
Chemical Formula: $C_{14}H_{14}O_4$



IR (film) ν_{max} 2918, 1720 cm^{-1}.

^{1}H NMR (126 MHz, $CDCl_3$): δ = 7.48 (d, 1H, *J* = 7.9 Hz), 7.38 (d, 1H, *J* = 7.3 Hz), 6.26 (s, 1H), 3.73 (s, 3H), 3.15 – 3.09 (m, 2H), 2.75 – 2.70 (m, 2H), 2.47 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 172.0, 160.5, 154.1, 152.1, 136.4, 133.1, 129.7, 129.5, 129.0, 126.9, 123.8, 121.6, 118.6, 113.9, 52.0, 32.0, 31.6, 26.7, 22.7, 15.8.

Methyl 3-(8-methyl-2-oxo-2*H*-chromen-3-yl)propanoate (105b)



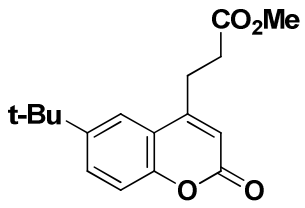
Chemical Formula: $C_{14}H_{14}O_4$

IR (film) ν_{max} 2918, 1725 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 7.48 (d, 2H, *J* = 8.1 Hz), 7.38 (d, 2H, *J* = 7.4 Hz), 7.19 (t, 2H, *J* = 7.7 Hz), 3.78 (s, 3H), 3.13 (dd, , 5H, *J* = 15.3, 8.0 Hz), 2.76 – 2.71 (m, 3H), 2.47 (s, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 164.0, 137.0, 136.4, 133.1, 129.7, 129.5, 129.3, 126.9, 123.8, 121.6, 113.9, 52.0, 47.2, 46.7, 44.2, 32.0, 26.7, 15.8.

Methyl 3-(6-tert-butyl-2-oxo-2*H*-chromen-4-yl)propanoate (106a)

Following the general procedure, reaction of methyl 3-(4-tert-butyl-2-((*E*)-3-oxoprop-1-enyl)phenoxy)acrylate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded methyl 3-(6-tert-butyl-2-oxo-2*H*-chromen-4-yl)propanoate **106a** as viscous liquid in 14% (14 mg) and methyl 3-(6-tert-butyl-2-oxo-2*H*-chromen-3-yl)propanoate **106b** as viscous liquid in 4% (4 mg).

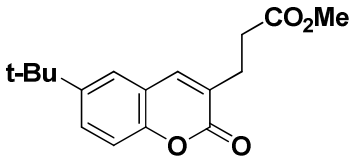


Chemical Formula: $C_{17}H_{20}O_4$

IR (film) ν_{max} 2956, 2869, 1736, 1724 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58 (s, 1H), 7.56 (d, 1H, *J* = 2 Hz), 7.29-7.26 (m, 1H), 6.24 (s, 1H), 3.74 (s, 3H), 3.16-3.13 (m, 2H), 2.74 (t, 2H, *J* = 7.5 Hz), 1.37 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 171.9, 153.9, 151.8, 147.2, 129.4, 119.9, 118.2, 117.0, 113.9, 52.0, 34.7, 31.8, 31.5, 26.4.

Methyl 3-(6-tert-butyl-2-oxo-2*H*-chromen-3-yl)propanoate (106b)



Chemical Formula: $C_{17}H_{20}O_4$

IR (film) ν_{max} 2957, 1717cm^{-1}.

^{1}H NMR (126 MHz, $CDCl_3$): δ = 7.58 (s, 1H), 7.5 (dd, 1H, *J* = 8.5 Hz), 7.39 (d, 1H, *J* = 2.5 Hz), 7.26-7.23 (m, 1H), 3.67 (s, 3H), 2.87 (t, 2H, *J* = 7 Hz), 2.70 (t, 2H, *J* = 7 Hz), 1.35 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ = 172.8, 147.2, 140.4, 128.4, 123.6, 116.1, 51.5, 34.5, 32.0, 31.4, 26.7.

Methyl 3-(2-oxo-2*H*-chromen-4-yl)-3-phenylpropanoate (107a)

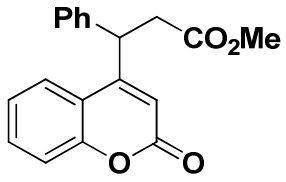
Following the general procedure, reaction of methyl 3-(2-((*E*)-3-oxoprop-1-enyl)phenoxy)-3-phenylacrylate (100 mg), 1,3-dimesityl imidazolinium chloride (15 mol %) and DBU (20 mol %) afforded methyl 3-(2-oxo-2*H*-chromen-4-yl)-3-phenylpropanoate as white solid.

Chemical Formula: $C_{19}H_{16}O_4$

m p: 112-114 ^{o}C.

Yield: 45 mg (45%).

IR (film) ν_{max} 2954, 2919, 1725 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 7.4 Hz, 1H), 7.48 – 7.43 (m, 1H), 7.34 – 7.26 (m, 5H), 7.23 (dd, *J* = 9.6 Hz, 4.4 Hz, 1H), 7.18 (dd, *J* = 11.2 Hz, 4.0 Hz, 1H), 6.37 (s, 1H), 4.90 (t, *J* = 7.6 Hz, 1H), 3.65 (s, 3H), 3.06 (dd, *J* = 16.2 Hz, 7.5 Hz, 1H), 2.96 (dd, *J* = 16.2 Hz, 7.7 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 170.9, 160.3, 155.7, 153.9, 139.6, 131.6, 129.3, 129.2, 127.76, 127.6, 124.8, 124.2, 118.6, 117.4, 113.6, 51.9, 42.3, 39.7. **HRMS** (FAB) calcd for $[M+H]^+$: 309.1119, found: 309.0998.

4.8. References

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CHAPTER 5

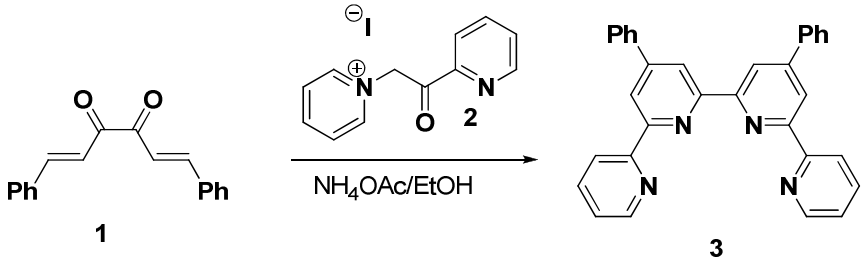
An Uncommon Transformation of Cinnamils to Vinylfulvenes Catalyzed by *N*-Heterocyclic Carbene

5.1. Introduction

Fulvenes represent a class of organic compounds with a unique π electron system and are superior models of cyclic cross-conjugated systems.[1] According to the size of the ring skeleton; they are named as triafulvenes, pentafulvenes, heptafulvenes etc. As a class of trienes, pentafulvenes have evoked great interest from both theoretical and synthetic perspectives. In particular, their propensity to undergo multiple modes of cycloadditions has been liberally exploited in synthesis.[2]

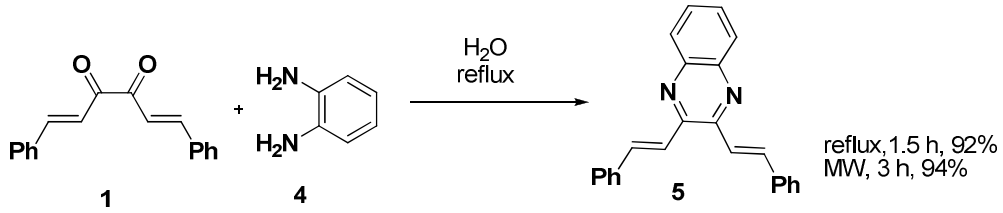
Fulvene synthesis has been the subject of a large number of studies; the classical approach to fulvenes involves the condensation of a carbonyl compound with cyclopentadiene.[3] In contrast, pentafulvenes with multiple substitution and conjugation have not received much attention presumably due to the difficulty in accessing them, and there are very few 6-vinylfulvenes reported in the literature.[4] The current chapter describes a serendipitous *N*-heterocyclic carbene (NHC) catalyzed transformation of 1,6-diarylhexa-1,5-diene-3,4-diones (cinnamils) to substituted vinylfulvenes. As an introduction to the present work, a brief review of the general reactions of cinnamils is presented.

Cinnamils can be converted to oligopyridine precursors[5] via the reaction sequence originally reported by Kröhnke.[6] A series of functionalized quaterpyridines were synthesized by this methodology.[7] Constable et al. utilized this protocol for the construction of quaterpyridines bearing phenyl rings on the central pyridines from cinnamils (Scheme 5.1).[8]



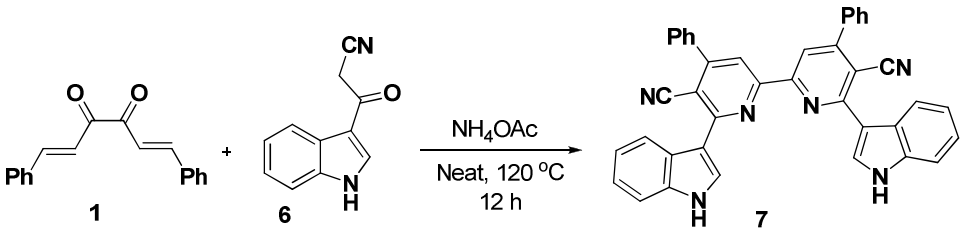
Scheme 5.1

A simple and efficient method for the synthesis of quinoxaline and pyridopyrazine was reported by Perumal and co-workers.[9] Condensation of cinnamils with 1,2-diaminobenzene and 2,3-diaminopyridine in water using conventional heating or microwave irradiation afforded high yields of aryl vinylquinoxalines and arylvinyl-pyrido pyrazines (Scheme 5.2). The photophysical studies revealed that pyridopyrazine derivatives exhibit halochromism.



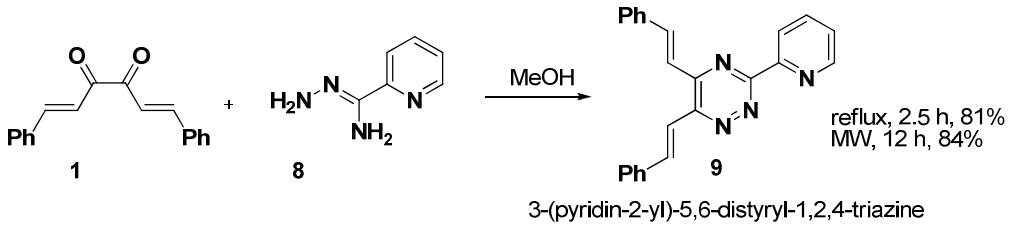
Scheme 5.2

A series of bipyridine dicarbonitrile derivatives **7** was synthesized using cinnamils, 3-(cyanoacetyl)indole and ammonium acetate (Scheme 5.3).[10]



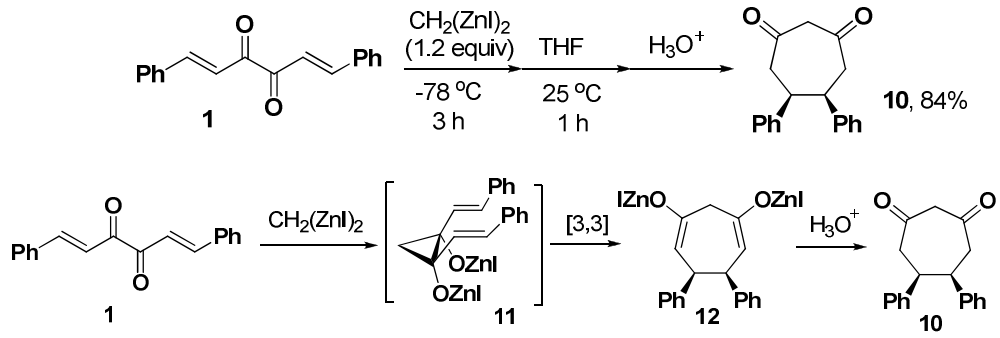
Scheme 5.3

An efficient synthesis of bis-aryl-3-pyridinyl-1,2,4-triazine derivatives was reported via condensation of cinnamils with picolinamide hydrazine **8** in methanol under both conventional heating as well as microwave irradiation in high yield (Scheme 5.4).[11]Photophysical studies revealed that the derivatives displayed good fluorescent properties. It was also found that the bis-aryl-3-pyrazine-1,2,4-triazine derivatives selectively bound Fe(III) ions.



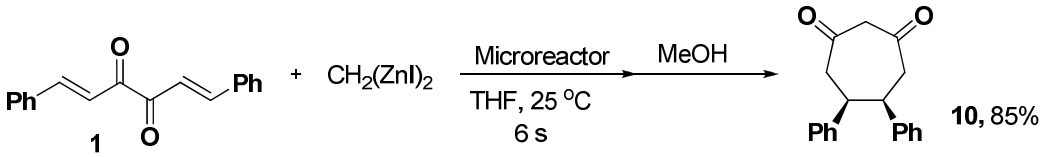
Scheme 5.4

In 2010, Matsubara and co-workers reported a stereoselective synthesis of cycloheptane derivatives (Scheme 5.5).[12] Treatment of 1,6-dialkylhexa-1,5-diene-3,4-diones with bis(iodozincio)methane gave zinc alkoxides of cis-5,6-dialkylcyclohepta-3,7-diene-1,3-diol in good yields and with high stereospecificity at room temperature.



Scheme 5.5

The authors improved the above method of cycloheptane ring synthesis using a microflow system (Scheme 5.6).[13] It was found that a careful temperature control is essential to suppress the side reaction between the product and the starting substrate. When the reaction was performed using a microflow system, the two-step reaction occurred in a few seconds at room temperature.



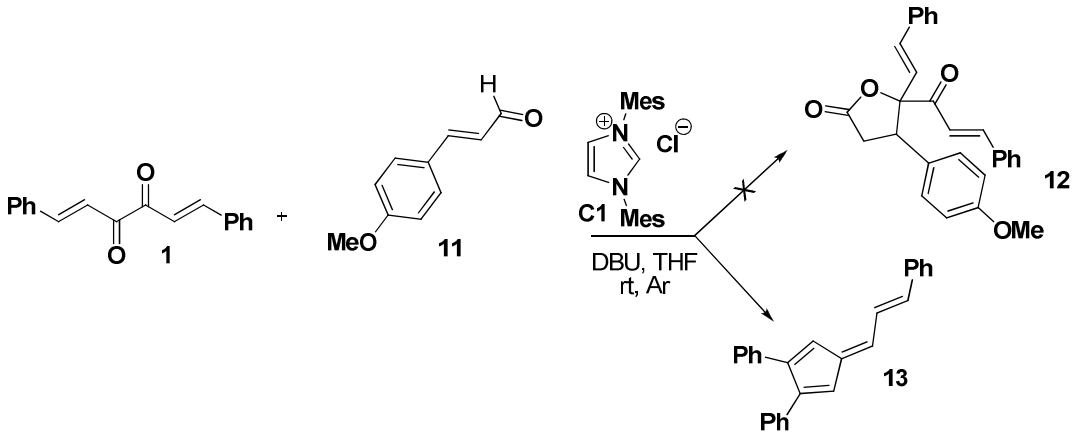
Scheme 5.6

5.2. Present work

The literature survey presented above has revealed some interesting reactivity patterns of 1,6-disubstituted hexa-1,5-diene-3,4-diones. As already stated (see Chapter 1) our studies on the homoenolate annulations of enals with α,β-unsaturated ketones led to the synthesis of substituted cyclopentenes[14] and dihydropyranones,[15] whereas the reaction carried out with cyclic as well as acyclic 1,2-diones afforded γ-lactones.[16] These results prompted us to investigate the reactivity of cinnamils towards homoenolates generated from α,β-unsaturated aldehydes by NHC catalysis.

5.3. Results and Discussion

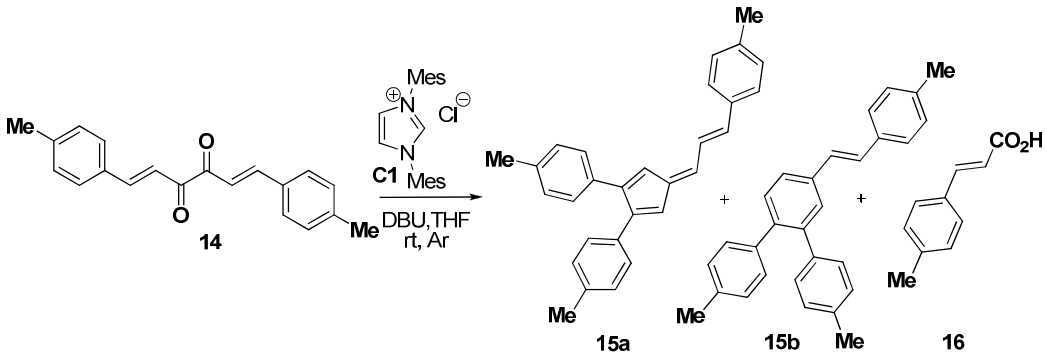
In a prototype experiment, cinnamil **1** (1,6-diphenylhexa-1,5-diene-3,4-dione) was exposed to 4-methoxycinnamaldehyde in the presence of 1,3-dimesityl imidazole carbene (IMes) in THF. A facile reaction occurred, and from the known reactivity of homoenolates the expected product was a lactone **12**. Surprisingly, however, the isolated product was a vinylfulvene **13** (Scheme 5.7).



Scheme 5.7

Evidently, the enal was not a participant in the reaction; the product **13** was formed by the interaction of two molecules of cinnamil under the influence of NHC. Naturally, the serendipitous formation of a vinylfulvene and the intriguing mechanistic aspects of the reaction fuelled our interest to pursue this uncommon reaction.

A systematic investigation of the reaction was initiated by stirring a solution of 1,6-bis(*p*-tolyl)-1,5-hexadiene-3,4-dione **14** and carbene, generated from IMesCl (**C1**) and DBU in THF. Conventional workup of the reaction mixture afforded **15a** and a trace of an isomeric product (later identified as the *o*-terphenyl derivative **15b**) along with 4-methylcinnamic acid **16** (Scheme 5.8).



Scheme 5.8

The products were characterized by standard spectroscopic and analytical methods. In the proton NMR spectrum, singlets due to three sets of methyl protons at δ 2.34, 2.35 and 2.37 ppm confirmed the presence of three tolyl groups. The proof for the structures was obtained from single crystal X-ray determination of **20a** and **15b** (Figure 5.5).

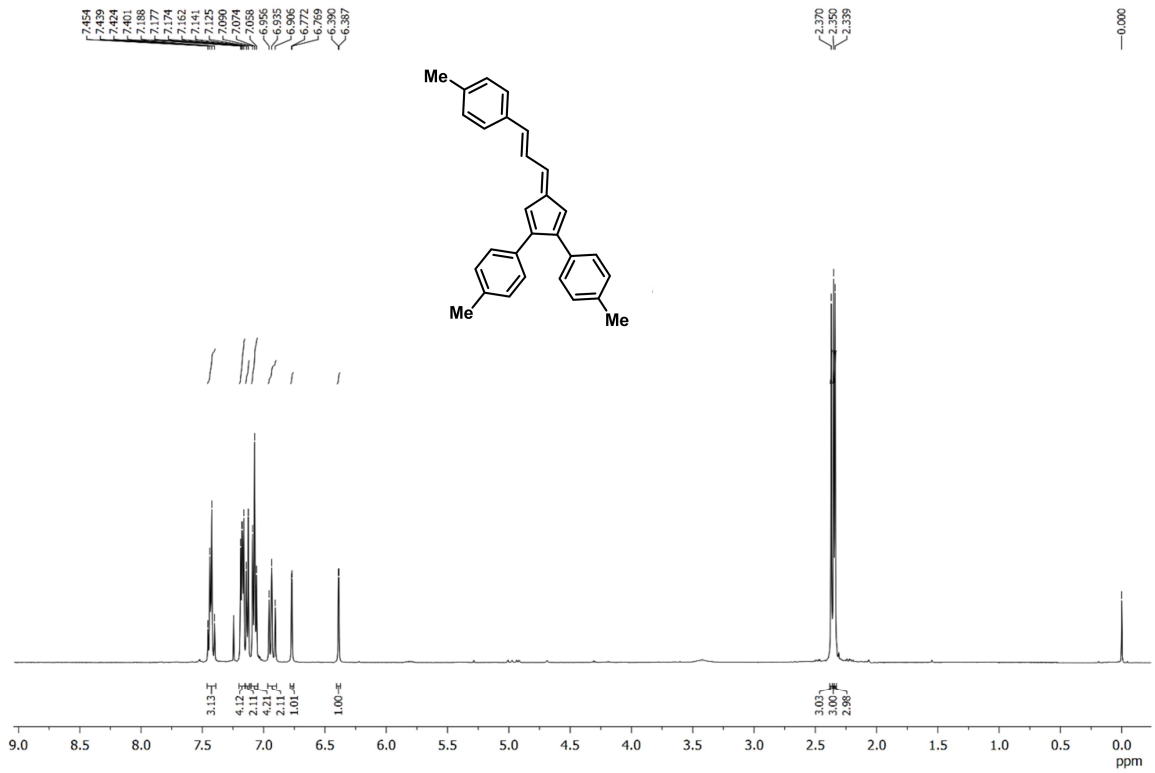


Figure 5.1 ^{1}H NMR Spectrum of **15a**

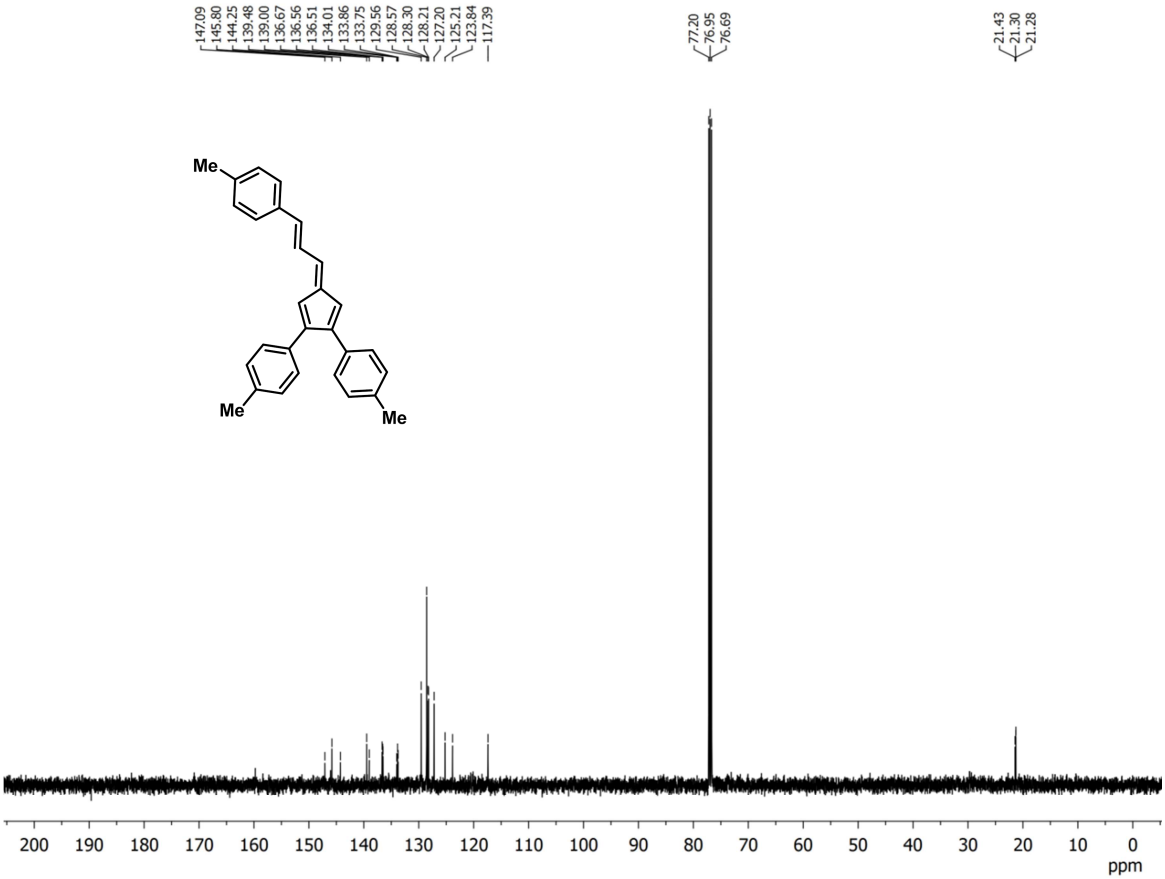


Figure 5.2 ^{13}C NMR Spectrum of **15a**

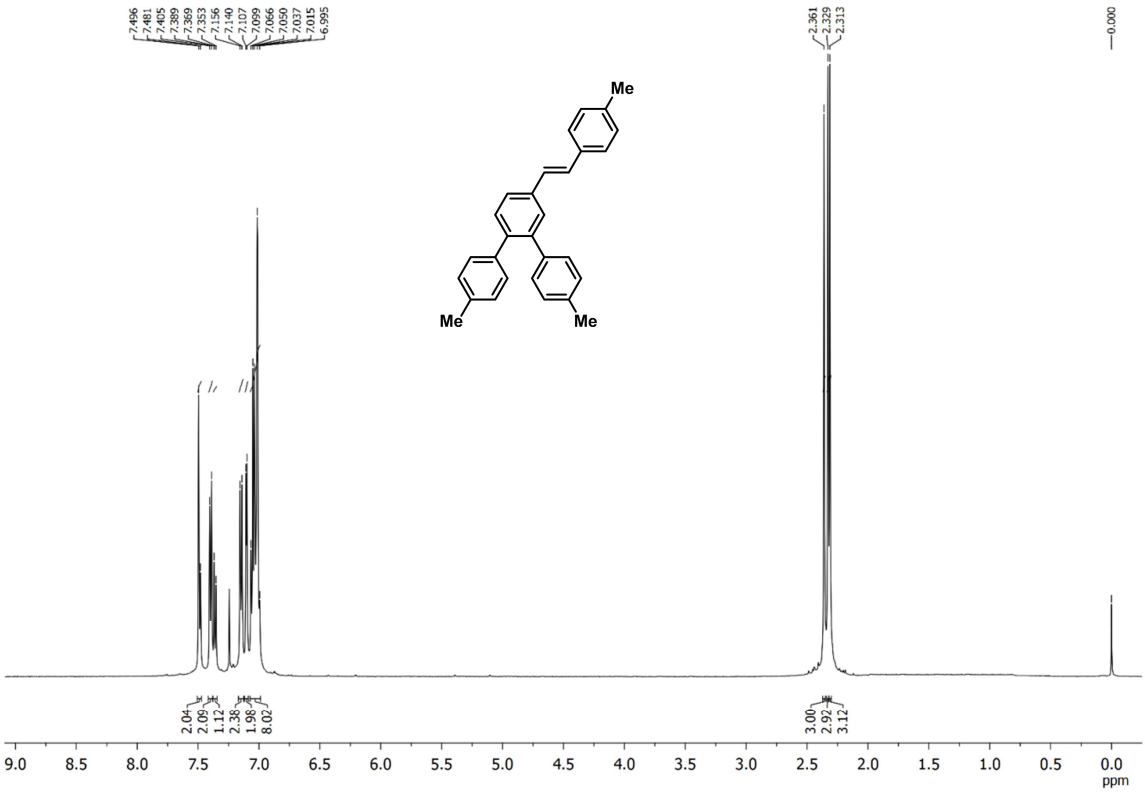


Figure 5.3 ^{1}H NMR Spectrum of **15b**

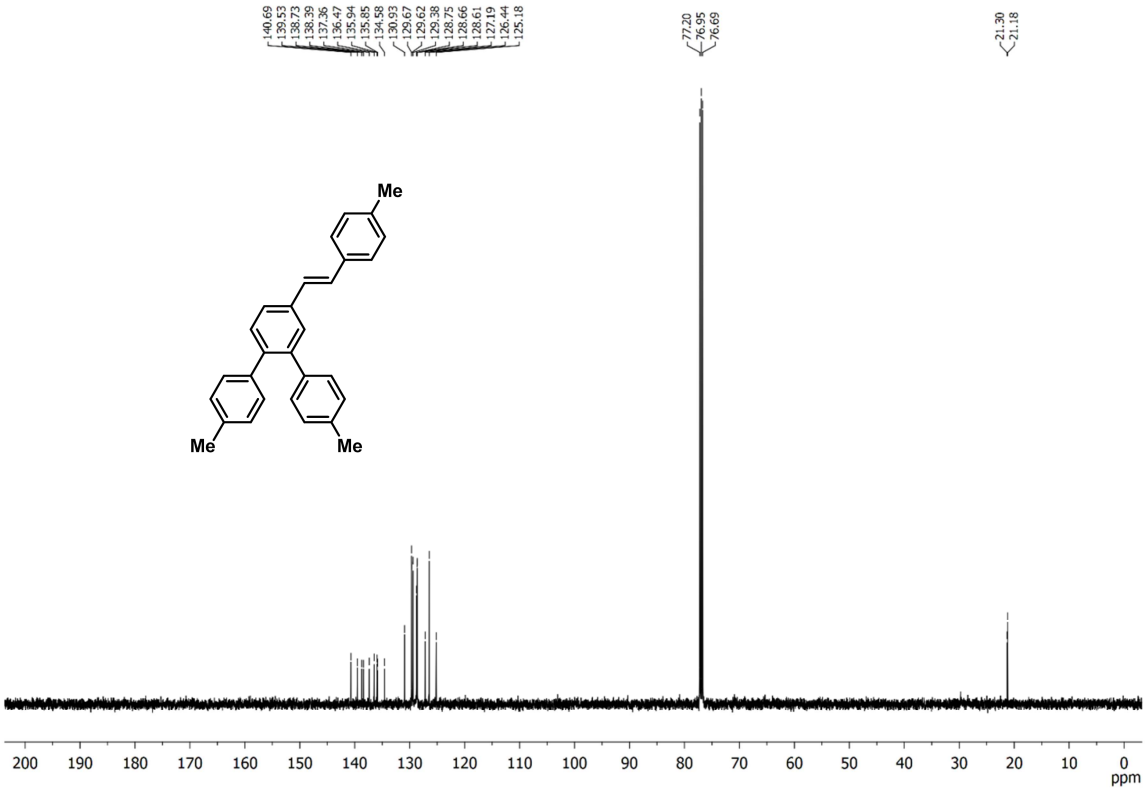
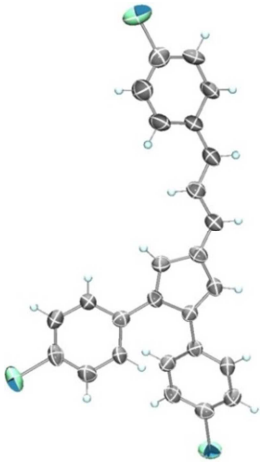
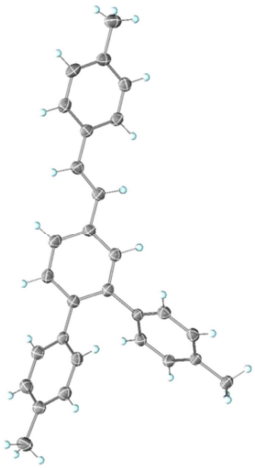


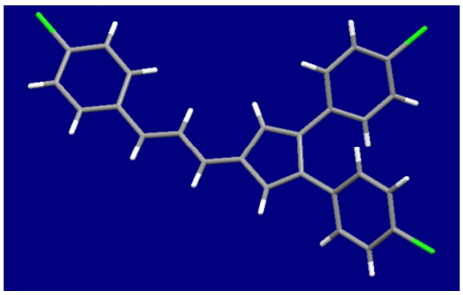
Figure 5.4 ^{13}C NMR Spectrum of **15b**



CCDC number: 965117.



CCDC number: 965118.



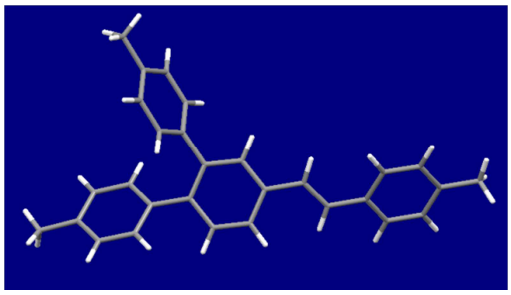
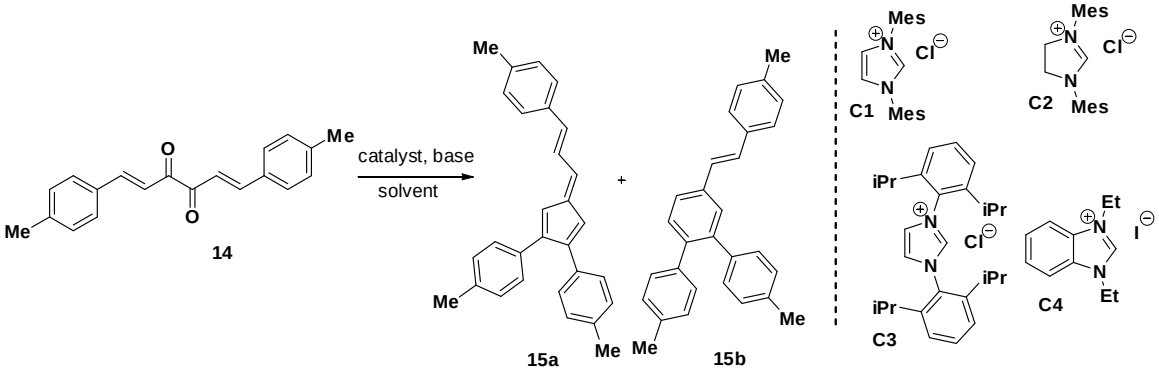


Figure 5.5 Single crystal X-ray structure of compounds **20a** and **15b**.

The reaction was optimized with 1,6-bis(*p*-tolyl)-1,5-hexadiene-3,4-dione **14** by varying the catalyst, base, solvent and temperature. The results are summarized in table 1.

Table 5.1. Optimization reactions



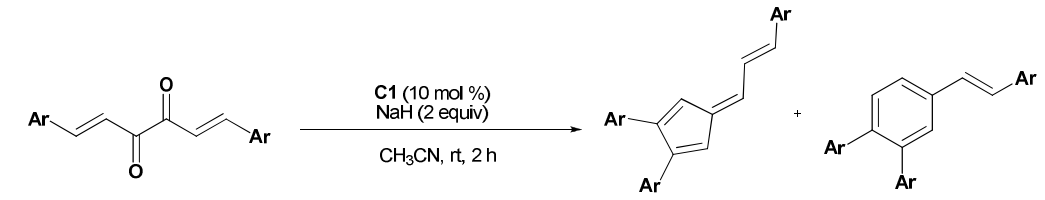
Entry	Catalyst	Condition	Time (h)	Yield (%)[c]
1	**C1**	DBU (0.50 equiv), THF,0-rt	12	16
2	**C1**	DBU (0.5 equiv), DMF, rt	5	64
3	**C1**	DBU (1equiv), DMF, rt	5	62
4	**C1**	K_2CO_3 (1 equiv), CH_3CN, rt	24	50
5	**C2**	K_2CO_3 (1equiv), CH_3CN,0-rt	24	-
6	**C3**	K_2CO_3 (1 equiv), CH_3CN,0-rt	24	35
7	**C4**	K_2CO_3 (1 equiv), CH_3CN,0-rt	24	19
8	**C1**	K_2CO_3 (1 equiv), DCM,0-rt	24	40

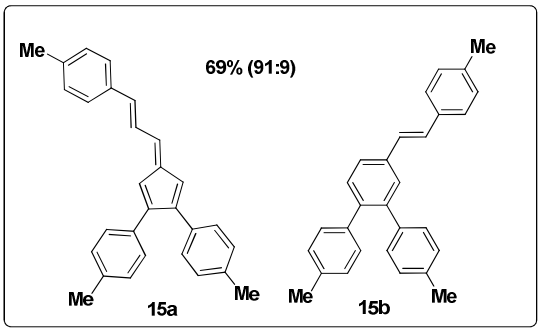
9	**C1**	K_2CO_3 (1 equiv), Toluene,0-rt	24	44
10	**C1**	DBU (0.5 equiv), DCM, 0-rt	10	56
11	**C1**	DBU (1equiv), DCM, 0-rt	7	45
12	**C1**	KO^tBu (1equiv), CH_3CN, rt	20	25
13	**C1**	DBU (1equiv), CH_3CN, rt	7	56
14	**C1**	NaH (1equiv), CH_3CN, rt	6	60
15	**C1**	NaH (1equiv), CH_3CN, 0-rt	12	50
16	**C1**	NaH (2 equiv), CH_3CN, rt	2	69
17	**C1**	K_2CO_3 (1 equiv), Hexane,0-rt	24	16
18	-	K_2CO_3 (1 equiv), CH_3CN,0-rt	24	-
19	-	DBU (1equiv), CH_3CN,0-rt	24	-

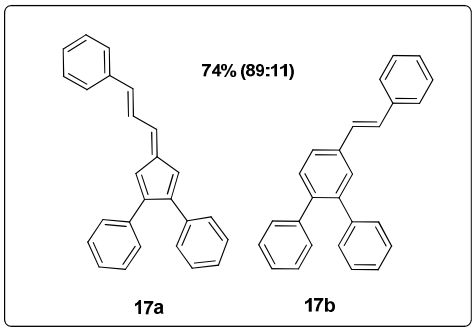
[c] overall yield of a and b

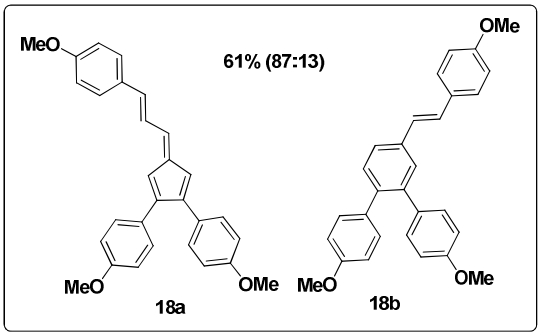
The scope of the reaction was examined under the optimized conditions, and the results are summarized in scheme 5.9.

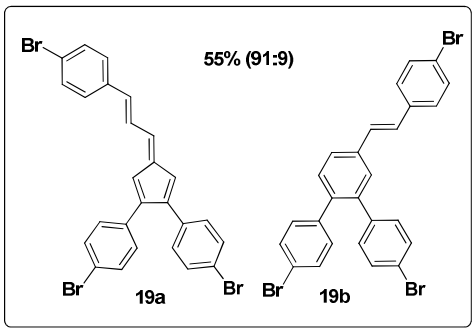
Scheme 5.9. Substrate scope

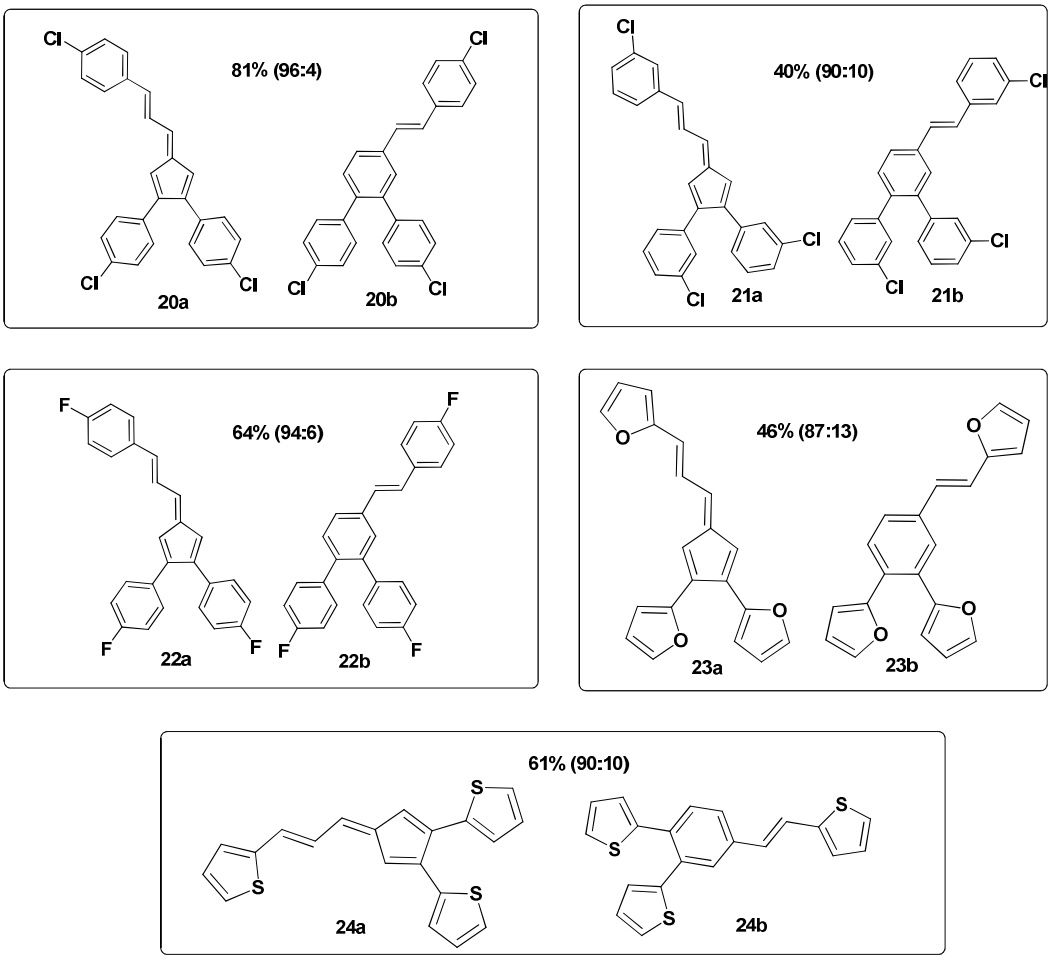




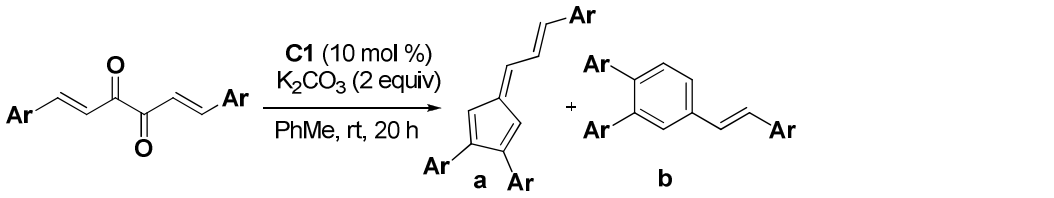








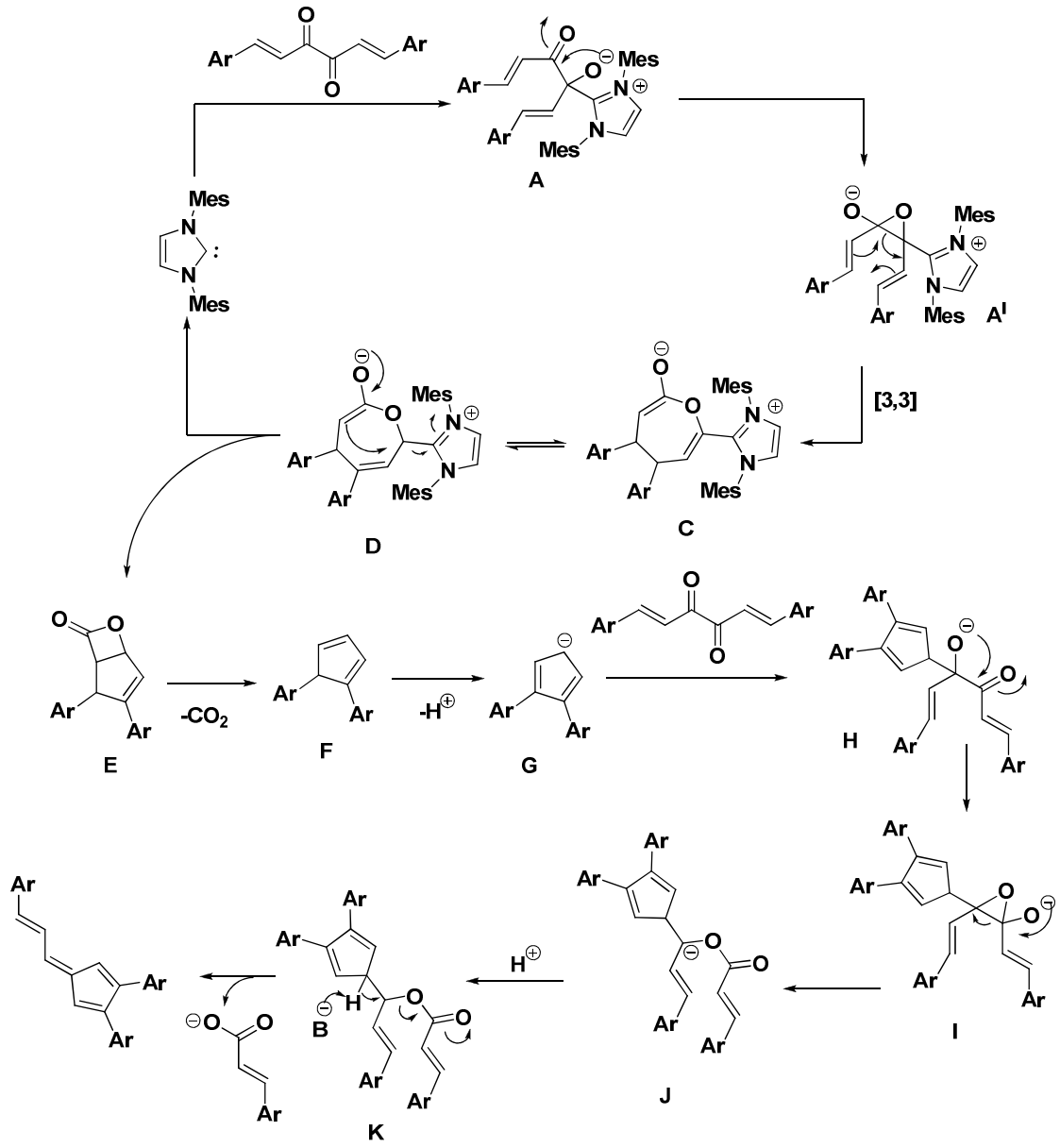
In subsequent experiments it was found that higher amount of *o*-terphenyl compound could be obtained by varying the reaction conditions from acetonitrile-sodium hydride to toluene-potassium carbonate (Scheme 5.10).



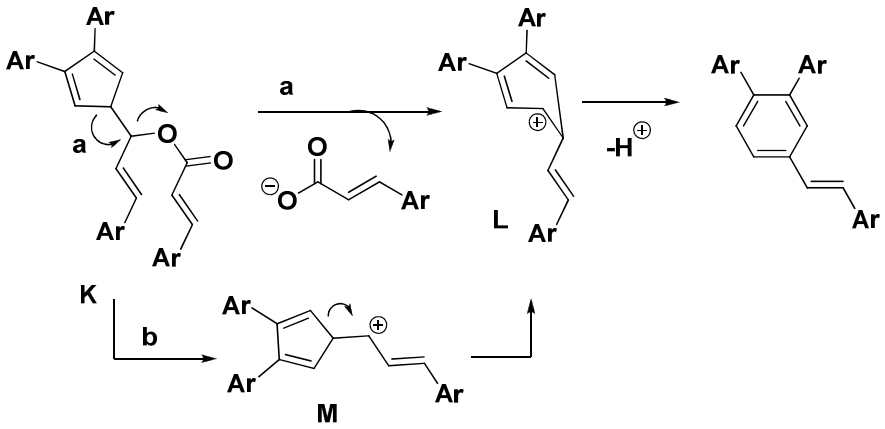
Scheme 5.10

5.4. Mechanism

Although the mechanistic underpinnings of the uncommon reaction reported herein are not known, a rationalization for the formation of the vinylfulvene as well as the *o*-terphenyl derivative may be advanced as follows (Scheme 5.11 and Scheme 5.12).



Scheme 5.11

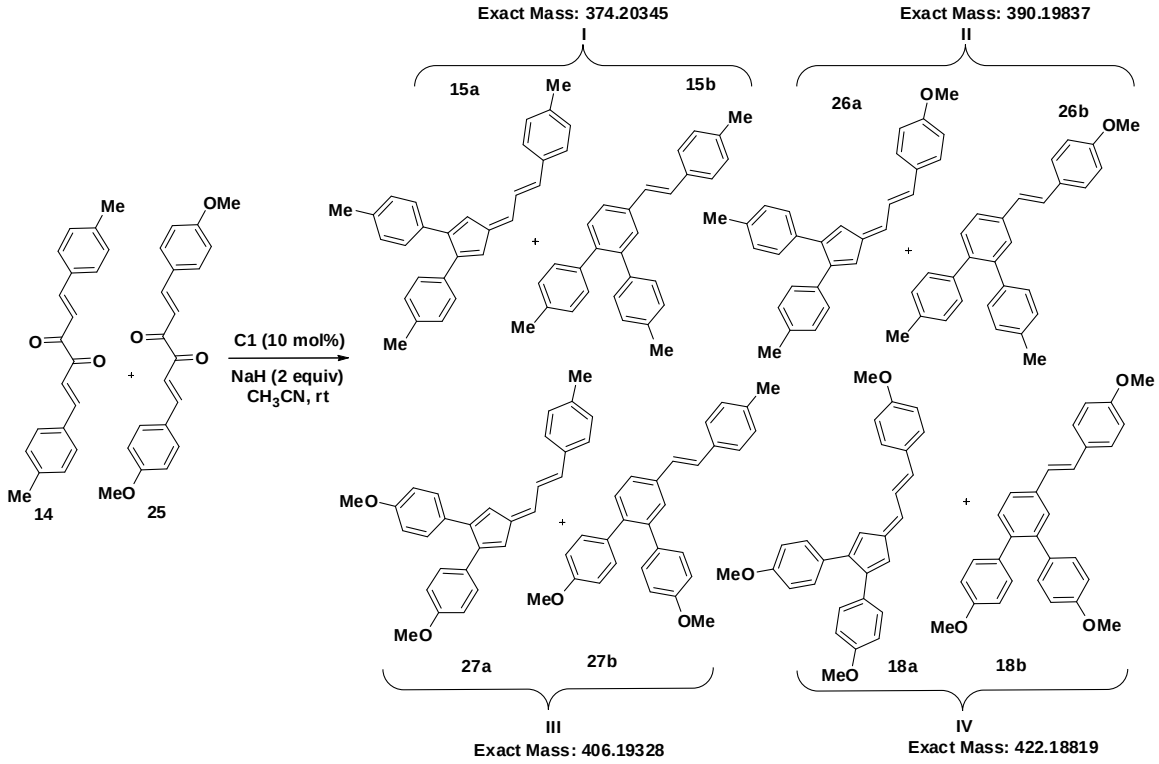


Scheme 5.12

It is conceivable that the addition of IMes to one of the carbonyls of cinnamil will be followed by the formation of the epoxy derivative $\mathbf{A^1}$, by a process analogous to the one reported previously.[17] Clearly $\mathbf{A^1}$ is set up for a [3,3] sigmatropic rearrangement to afford the oxepine derivative **C**. Isomerization of **C** followed by intramolecular elimination/displacement of IMes can lead to transient bicyclic β-lactone **E**, and the latter can afford the diaryl cyclopentadiene **F** by a retro [2+2] process. Parenthetically it may be added that such a retro [2+2] process leading to the formation of cyclopentene is supported experimentally[14a] and by computational studies.[18] The anion of **F** (**G**) presumably can undergo addition to a second molecule of cinnamil and subsequently afford the transient epoxide **I**. Fragmentation of **I** followed by protonation of the intermediate **J** will lead to **K**. The latter is set up to deliver the vinylfulvene or the *o*-terphenyl derivative by a concerted or stepwise process. In the concerted process, base **B** can eliminate cinnamate from **K** to afford the vinylfulvene (Scheme 5.10), whereas elimination of cinnamate by anchimeric assistance from the cyclopentadienyl moiety will lead to cyclohexadienyl cation **L** (path a) and subsequently the o-terphenyl derivative (Scheme 5.11). Alternatively **K** can undergo ionization to deliver a cation **M** (path b), which on proton loss can afford the fulvene, whereas it can undergo ring expansion to afford the cyclohexadienyl cation **L**. In this context, it is interesting to note that fulvene to benzene rearrangement has been observed previously by irradiation[19] or by gas phase pyrolysis.[20] The reaction has also been rationalized by invoking diradical intermediate. Very recently Diederich has observed a novel, thermal pentafulvene to benzene rearrangement in which anionic "ring-walk" mechanism has been suggested.[21]

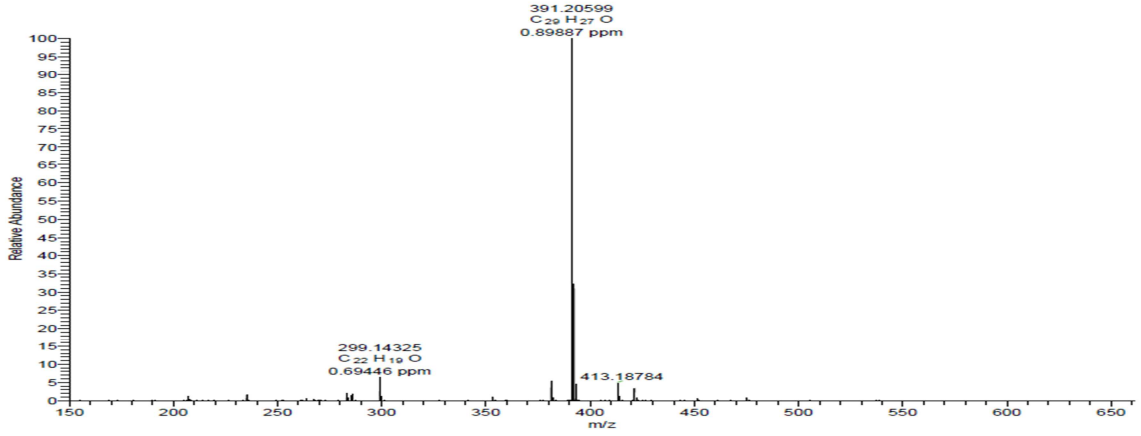
5.5. Mechanistic Study

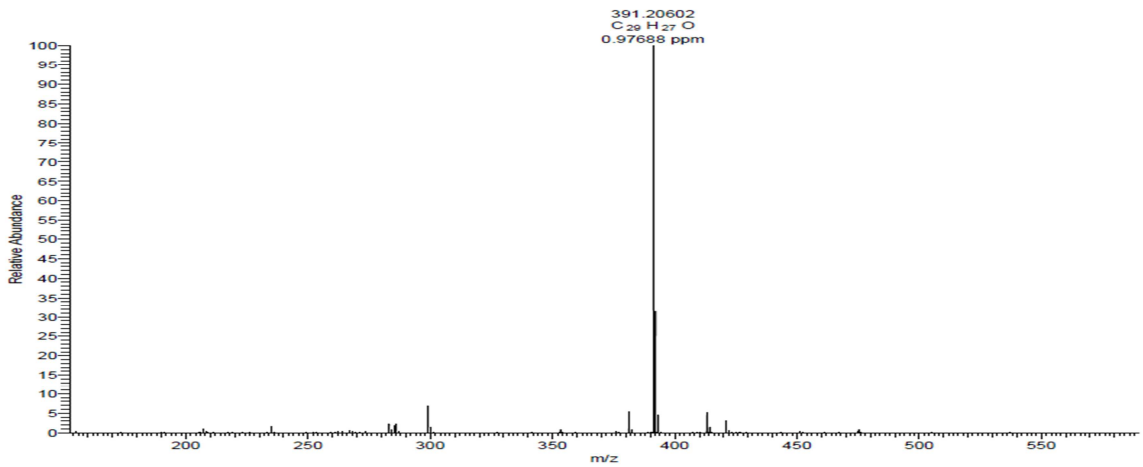
To shed some light on the mechanism of the reaction a crossover experiment was conducted between 1,6-bis(p-tolyl)-1,5-hexadiene-3,4-dione **14** and 1,6-bis(p-methoxyphenyl)-1,5-hexadiene-3,4-dione **25**, and the formation of hybrid products was confirmed by mass spectroscopy (Scheme 5.13). Arguably, these results provide indirect support for the formation of 2,3-diaryl cyclopentadiene **G**, and other intermediates invoked in the mechanistic postulate.



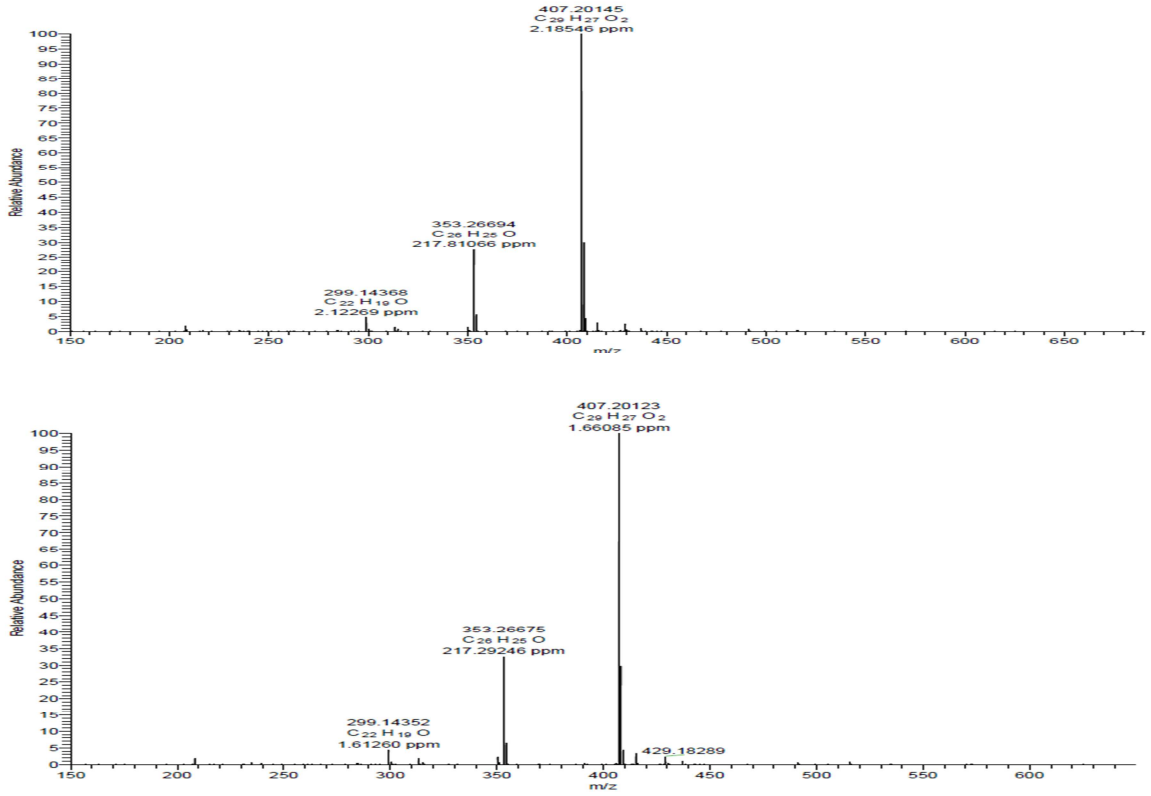
Scheme 5.13

Mass Spectrum of **II**

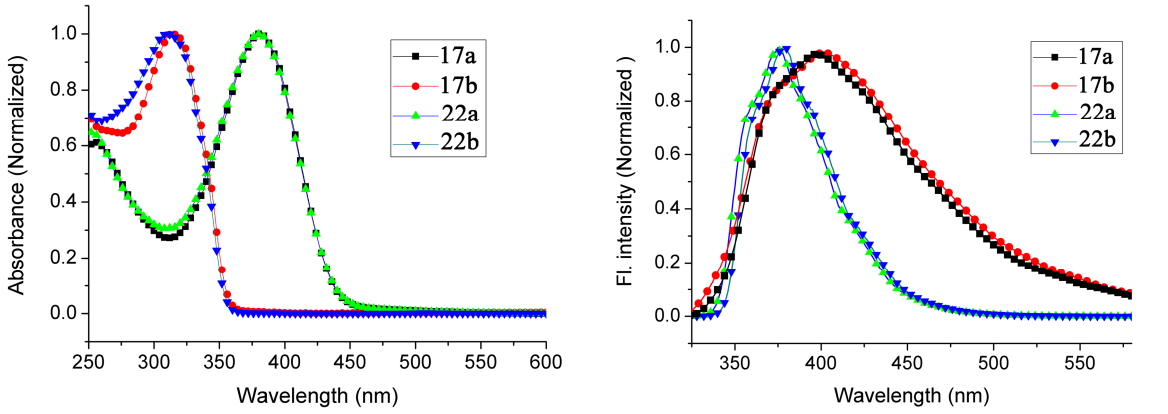




Mass Spectrum of **III**.



5.6. Absorption and Emission Spectra of Selected Compounds (in chloroform)**.**



Compounds	Absorption maximum (nm)	Emission maximum (nm)
17a	381	464
17b	313	375
22a	380	470
22b	311	378

5.7. Conclusion

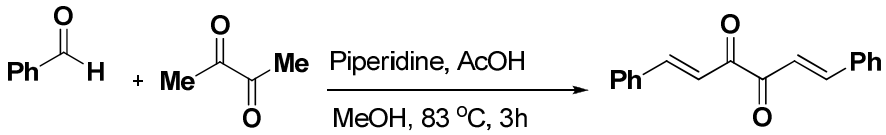
In conclusion, we have come across an uncommon cascade reaction involving two molecules of 1,2-diones that affords vinylfulvenes and *o*-terphenyl derivatives. The experimental conditions are simple and the products are obtained in good yields, thus adding preparative value to the reaction. In addition to its synthetic utility, the intriguing mechanistic steps of the process described here are also noteworthy.

5.8. Experimental Details

NMR spectra were recorded at 500 (^{1}H) and 126 (^{13}C) MHz respectively on a Bruker DPX-500 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 on Thermo Scientific™ Exactive mass Spectrometer for ESI and AXIMA-CFR™ plus for MALDI-TOF. Absorption spectra were measured on Shimadzu UV-2401PC UV-VIS recording spectrophotometer and fluorescent measurements done on Spex Fluorolog 112X spectrofluorimeter.

5.8.1. General Experimental Procedures

5.8.1.1. Preparation of cinnamils



Cinnamils were prepared according to the known literature procedure.[22] Biacetyl (2.15 g, 25 mmol) and 10 mL methanol were taken in a 100 mL round bottom flask; into this was added benzaldehyde (100 mmol, 4 equiv), acetic acid (0.03 equiv) and piperidine (0.03 equiv). The reaction mixture was refluxed at 83 °C for 3 h with stirring. The mixture was cooled to room temperature, solvent was removed and cooled in an ice bath and the precipitate formed was filtered, washed with cold methanol and dried.

5.8.1.2. Synthesis of vinylfulvenes and 3,4-Diphenylstilbenes.

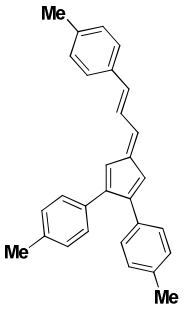
1,6-bis(*p*-tolyl)-1,5-hexadiene-3,4-dione (100 mg, 0.38 mmol) and 1,3-dimesityl imidazolium chloride (13 mg, 10 mol %) were taken in a round bottom flask. In to this was added 10 mL acetonitrile followed by 60% suspension of sodium hydride in mineral oil (30 mg, 200 mol %, 2 equiv) and the reaction mixture stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. After completion of the

reaction, solvent was evaporated off and the crude product was purified by column chromatography on neutral alumina using petroleum ether as eluant.

5.8.2. Characterization Data of Compounds

6-[(*E*)-2-(*p*-Tolyl)ethenyl]-2,3-bis(*p*-tolyl)fulvene (15a)

Following the general procedure, reaction of 1,6-dip-tolylhexa-1,5-diene-3,4-dione (145 mg, 0.5 mmol), 1,3-dimesityl imidazolium chloride (17 mg, 10 mol %) and sodium hydride 60 % dispersion in mineral oil (40 mg, 200 mol %, 2 equiv) afforded 6-[(*E*)-2-(p-tolyl)ethenyl]-2,3-bis(*p*-tolyl)fulvene **15a** in 63% (58.9 mg) and **15b** in 8% (5.6 mg).

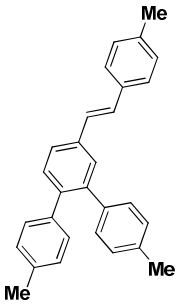


Chemical Formula: $C_{29}H_{26}$.

Dark solid

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 – 7.39 (m, 3H), 7.18 (dd, *J* = 7.3, 5.6 Hz, 4H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 4H), 6.93 (t, *J* = 12.6 Hz, 2H), 6.77 (d, *J* = 1.5 Hz, 1H), 6.39 (d, *J* = 1.8 Hz, 1H), 2.37 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 147.1, 145.8, 144.3, 139.5, 139.0, 136.7, 136.6, 136.5, 134.1, 133.86, 133.6, 129.6, 128.6, 128.3, 128.2, 127.2, 125.2, 123.8, 117.4, 21.4, 21.3, 21.2. **HRMS**: m/z (ESI) calcd. for 375.2112 $(M+H)^+$ found 375.2116.

(*E*)-7-Methyl-3,4-bis(*p*-tolyl)stilbene (15b)



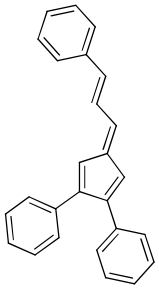
Chemical Formula: $C_{29}H_{26}$.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 4.0 Hz, 2H), 7.08 – 6.99 (m, 8H), 2.36 (s, 3H), 2.33 (s, 3H), 2.31 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 140.7, 139.5, 138.4, 138.4, 137.4, 136.5, 135.9, 135.8, 134.6, 130.9, 129.7, 129.6, 129.4, 128.8, 128.7, 128.6, 127.2, 126.4, 125.2, 21.3, 21.2. **HRMS:** m/z (ESI) calcd. for 375.2112 $(M+H)^+$ found 375.2117.

6-[(*E*)-2-Phenylethenyl]-2,3-diphenylfulvene (**17a**)

Following the general procedure, reaction of 1,6-diphenylhexa-1,5-diene-3,4-dione (131 mg, 0.5 mmol), 1,3-dimesityl imidazolium chloride (17 mg, 10 mol %) and sodium hydride 60 % dispersion in mineral oil (40 mg, 200 mol %, 2 equiv) afforded

6-[(*E*)-2-phenylethenyl]-2,3-diphenylfulvene **17a** in 66% (54.8 mg) and **17b** 8% (6.6 mg).

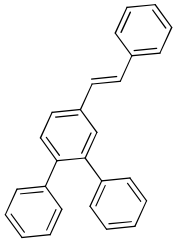


Chemical Formula: $C_{26}H_{20}$.

Dark solid

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.52 (d, *J* =7.5, 2H), 7.46 (dd, *J* =15.4, 11.6, 1H), 7.36 (t, *J* =7.5, 2H), 7.29 (t, *J* =7.3, 1H), 7.26 – 7.19 (m, 10H), 6.96 (d, *J* =3.8, 1H), 6.93 (d, *J* =7.7, 1H), 6.79 (d, *J* =2.1, 1H), 6.41 (d, *J* =2.2, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 147.3, 146.0, 144.6, 139.8, 136.9, 136.6, 136.6, 136.4, 128.9, 128.8, 128.4, 128.3, 127.9, 127.3, 127.2, 127.0, 126.0, 124.4, 118.0. **HRMS**: m/z (ESI) calcd. for $C_{26}H_{21}$ $(M+H)^+$ 333.1643, found 333.1647.

(*E*)-3,4-Diphenylstilbene (17b)



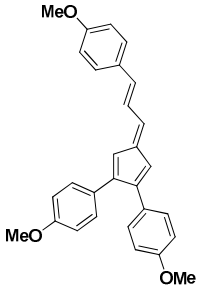
Chemical Formula: $C_{26}H_{20}$.

Off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 – 7.49 (m, 4H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.14 (m, 11H), 7.13 – 7.10 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 140.4, 140.1, 139.8, 138.8, 136.2, 135.5, 129.9, 128.8, 128.7, 128.0, 127.7, 127.6, 126.9, 126.8, 126.8, 126.6, 125.5, 125.5, 125.4, 124.4. **HRMS**: m/z (ESI) calcd. for $C_{26}H_{21}$ $(M+H)^+$ 333.1643, found 333.1648.

6-[(*E*)-2-(*p*-Methoxyphenyl)ethenyl]-2,3-bis(*p*-methoxyphenyl)fulvene (18a)

Following the general procedure, reaction of 1,6-bis(4-methoxyphenyl)hexa-1,5-diene-3,4-dione (161 mg, 0.5 mmol), 1,3-dimesityl imidazolium chloride (17 mg, 10 mol %) and sodium hydride 60 % dispersion in mineral oil (40 mg, 200 mol %, 2 equiv) afforded 6-[(*E*)-2-(*p*-methoxyphenyl)ethenyl]-2,3-bis(*p*-methoxyphenyl)fulvene **18a** in 53% (55.9 mg) and **18b** 8% (8.4 mg).

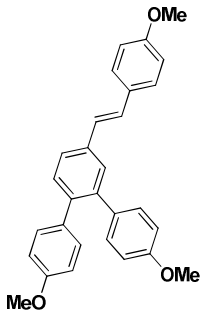


Chemical Formula: $C_{29}H_{26}O_3$.

Dark solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 (d, *J*=8.7, 2H), 7.33 (dd, *J*=15.3, 11.6, 1H), 7.19 (d, *J*=8.7, 2H), 7.15 (d, *J*=8.6, 2H), 6.91 – 6.84 (m, 4H), 6.79 (t, *J*=8.1, 4H), 6.70 (d, *J*=1.8, 1H), 6.32 (d, *J*=2.1, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 160.3, 158.8, 158.7, 146.5, 145.1, 143.7, 138.9, 136.4, 129.6, 129.5, 129.42, 129.3, 128.7, 124.2, 123.2, 116.8, 114.3, 113.3, 55.3, 55.1. **HRMS:** m/z (ESI) calcd. for $(M+H)^+$ 423.1960 found 423.2041.

(*E*)-7-Methoxy-3,4-bis(*p*-methoxyphenyl)stilbene (18b)



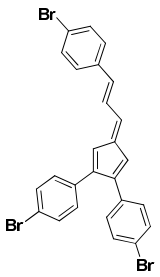
Chemical Formula: $C_{29}H_{26}O_3$.

Off-white solid.

^{1}H NMR (500 MHz, CDCl3) δ = 7.44 (dd, *J* = 10.6, 8.0 Hz, 4H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.11 – 6.97 (m, 6H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.75 (dd, *J* = 12.4, 8.7 Hz, 4H), 3.82 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H). **^{13}C NMR (126 MHz, CDCl3)** δ = 159.3, 158.3, 158.2, 140.3, 138.9, 136.5, 134.1, 133.8, 130.8, 130.8, 130.2, 128.5, 128.3, 127.7, 126.1, 124.9, 114.1, 113.4, 113.4, 55.1, 54.9, 54.9. **HRMS**: m/z (ESI) calcd.. for (M+H)+ 423.1960 found 423.2041.

6-[(*E*)-2-(*p*-Bromophenyl)ethenyl]-2,3-bis(*p*-bromophenyl)fulvene (19a)

Following the general procedure, reaction of 1,6-bis(4-bromophenyl)hexa-1,5-diene-3,4-dione (210 mg, 0.5 mmol), 1,3-dimesityl imidazolium chloride (17 mg, 10 mol %) and sodium hydride 60 % dispersion in mineral oil (40 mg, 200 mol %, 2 equiv) afforded 6-[(*E*)-2-(*p*-bromophenyl)ethenyl]-2,3-bis(*p*-bromophenyl)fulvene **19a** in 50% (70.7 mg) and **19b** 5% (7.1 mg).



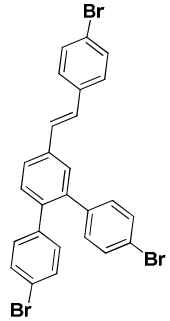
Chemical Formula: $C_{26}H_{17}Br_3$.

Dark solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.50 (d, *J* = 8.3 Hz, 2H), 7.39 (dd, *J* = 9.4, 7.4 Hz, 7H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 11.6 Hz, 1H), 6.90 (d, *J* = 15.4 Hz, 1H), 6.75 (d, *J* = 1.3 Hz, 1H), 6.38 (d, *J* = 1.7 Hz, 1H). **^{13}C NMR (126**

MHz, $CDCl_3$) δ = 145.9, 144.6, 139.0, 137.2, 135.3, 135.0, 134.9, 132.1, 131.2, 129.8, 129.7, 128.6, 126.3, 124.8, 123.3, 121.6, 121.5, 118.3. **HRMS**: m/z (MALDI-TOF) calcd. for $(M+H)^+$ 566.8958 found 567.3962.

(*E*)-7-Bromo-3,4-bis(*p*-bromophenyl)stilbene (19b)



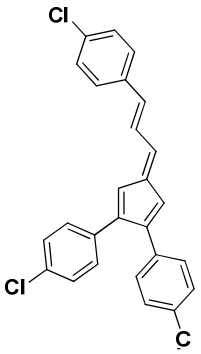
Chemical Formula: $C_{26}H_{17}Br_3$.

Off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53 (dd, *J* = 8.0, 1.8, 1H), 7.48 (d, *J* = 8.5, 3H), 7.40 – 7.34 (m, 7H), 7.10 (d, *J* = 5.8, 2H), 7.02 (d, *J* = 8.4, 2H), 6.98 (d, *J* = 8.4, 2H). **^{13}C NMR (126 MHz, CDCl3)** δ = 141.2, 139.9, 139.6, 138.6, 136.7, 136.0, 131.9, 131.4, 131.3, 130.9, 128.7, 128.4, 128.3, 128.0, 125.9, 121.7, 121.3, 121.2. **HRMS**: m/z (MALDI-TOF) calcd. for $(M+H)^+$ 566.8958 found 567.4069.

6-[(*E*)-2-(*p*-Chlorophenyl)ethenyl]-2,3-bis(*p*-chlorophenyl)fulvene (20a)

Following the general procedure, reaction of 1,6-bis(4-chlorophenyl)hexa-1,5-diene-3,4-dione (166 mg, 0.5 mmol), 1,3-dimesityl imidazolium chloride (17 mg, 10 mol %) and sodium hydride 60 % dispersion in mineral oil (40 mg, 200 mol %, 2 equiv) afforded 6-[(*E*)-2-(*p*-chlorophenyl)ethenyl]-2,3-bis(*p*-chlorophenyl)fulvene **20a** in 78% (84.6 mg) and **20b** 3% (3.3 mg).



Chemical Formula: $C_{26}H_{17}Cl_3$.

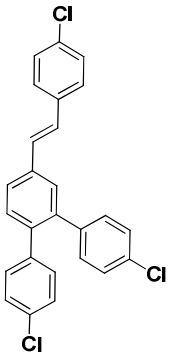
Dark solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 (d, *J* = 8.3, 2H), 7.39 (dd, *J* = 15.4, 11.7, 1H), 7.34 (d, *J* = 8.2, 2H), 7.24 (t, *J* = 7.7, 4H), 7.14 (d, *J* = 8.2, 2H), 7.11 (d, *J* = 8.2, 2H), 6.97 – 6.87 (m, 2H), 6.75 (s, 1H), 6.38 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 144.8, 143.6, 143.7, 137.8, 136.1, 133.9, 133.8, 133.6, 133.4, 132.3, 132.2, 128.4, 128.3, 128.1, 127.3, 127.2, 125.1, 123.7, 117.2. **HRMS:** m/z (MALDI-TOF) calcd. for $C_{26}H_{18}Cl_3$ $(M+H)^+$ 435.0474 found 435.5722.

(*E*)-7-Chloro-3,4-bis(*p*-chlorophenyl)stilbene (20b)

Chemical Formula: $C_{26}H_{17}Cl_3$.

Off-white solid.

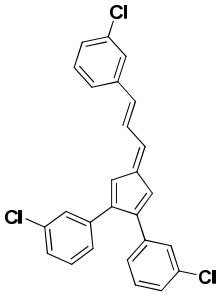


^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 8.0, 1H), 7.48 (s, 1H), 7.44 (d, *J* = 8.3, 2H), 7.36 (d, *J* = 7.9, 1H), 7.32 (d, *J* = 8.3, 2H), 7.24 (s, 1H), 7.22 (d, *J* = 4.6, 2H), 7.20 (s, 1H), 7.10 (s, 2H), 7.08 (d, *J* = 8.3, 2H), 7.04 (d, *J* = 8.3, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 139.7, 139.4, 139.1, 138.7, 136.7, 135.5, 133.9, 133.1, 133.0, 131.0, 130.9, 130.9, 128.9, 128.7, 128.4, 128.3, 128.3, 128.2, 127.7, 125.9. **HRMS:** m/z (MALDI-TOF) calcd.. for $C_{26}H_{18}Cl_3$ $(M+H)^+$ 435.04741 found 435.5722.

6-[(*E*)-2-(*m*-Chlorophenyl) ethenyl]-2,3-bis(*m*-chlorophenyl)fulvene (21a)

Following the general procedure, reaction of 1,6-bis(3-chlorophenyl)hexa-1,5-diene-3,4-dione (166 mg, 0.5 mmol), 1,3-dimesityl imidazolium chloride (17 mg, 10 mol %) and sodium hydride 60 % dispersion in mineral oil (40 mg, 200 mol %, 2 equiv) afforded 6-[(*E*)-2-(*m*-chlorophenyl) ethenyl]-2,3-bis(*m*-chlorophenyl)fulvene **21a** in 36% (39.1 mg) and **21b** 4% (4.3 mg).

Chemical Formula: $C_{26}H_{17}Cl_3$.

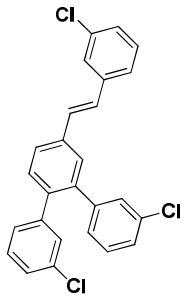


Dark solid.

^{1}H NMR (500 MHz, CDCl3) δ = 7.53 (s, 1H), 7.47 – 7.38 (m, 2H), 7.33 (d, *J* = 5.3, 1H), 7.29 (dd, *J* = 10.0, 8.1, 3H), 7.23 (d, *J* = 8.9, 2H), 7.17 (dd, *J* = 14.2, 7.7, 2H), 7.01 – 6.95 (m, 3H), 6.92 (d, *J* = 15.4, 1H), 6.81 (d, *J* = 2.0, 1H), 6.43 (d, *J* = 2.1, 1H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ = 145.7, 144.8, 144.5, 138.86, 138.2, 137.8, 137.7, 137.4, 135.1, 134.2, 134.1, 130.0, 129.0, 128.1, 128.0, 127.5, 127.3, 126.9, 126.8, 126.6, 126.4, 125.5, 125.2, 118.8. **HRMS:** m/z (MALDI-TOF) calcd. for $C_{26}H_{18}Cl_3$ $(M+H)^+$ 435.0474 found 435.5722.

(*E*)-13-Chloro-3,4-bis(*m*-chlorophenyl)stilbene (21b)

Chemical Formula: $C_{26}H_{17}Cl_3$.



Off-white solid.

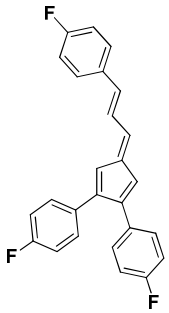
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 2H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.26 – 7.18 (m, 5H), 7.17 – 7.08 (m, 4H), 6.93 (dd, *J* = 13.3, 7.6 Hz, 2H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ = 142.7, 142.4, 139.6, 138.9, 138.7, 134.8, 134.2, 130.9, 129.9, 129.6,

129.6, 129.2, 129.1, 129.0, 128.7, 128.2, 128.1, 127.8, 127.1, 127.0, 126.4, 126.2, 124.8. **HRMS:** m/z (MALDI-TOF) calcd.. for $C_{26}H_{18}Cl_3$ $(M+H)^+$ 435.04741 found 435.5722.

6-[(*E*)-2-(*p*-Fluorophenyl)ethenyl]-2,3-bis(*p*-fluorophenyl)fulvene (22a)

Following the general procedure, reaction of 1,6-bis(4-fluorophenyl)hexa-1,5-diene-3,4-dione (149 mg, 0.5 mmol), 1,3-dimesityl imidazolium chloride (17 mg, 10 mol %) and sodium hydride 60 % dispersion in mineral oil (40 mg, 200 mol %, 2 equiv) afforded 6-[(*E*)-2-(*p*-fluorophenyl)ethenyl]-2,3-bis(*p*-fluorophenyl)fulvene **22a** in 60% (57.9 mg) and **22b** 4% (3.9 mg).

Chemical Formula: $C_{26}H_{17}F_3$.

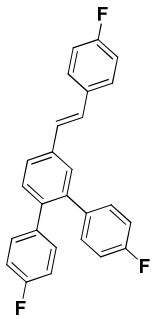


Dark solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.52 (dd, *J* = 8.3, 5.6, 2H), 7.37 (dd, *J* = 15.4, 11.6, 1H), 7.20 (dd, *J* = 8.4, 5.7, 2H), 7.16 (dd, *J* = 8.4, 5.7, 2H), 7.08 (t, *J* = 8.5, 2H), 7.00 – 6.92 (m, 6H), 6.76 (d, *J* = 1.1, 1H), 6.39 (d, *J* = 1.7, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 164.1, 163.2, 163.1, 162.1, 161.2, 161.1, 146.0, 144.8, 144.3, 138.5, 136.7, 132.8, 132.7, 132.4, 132.3, 132.3, 132.2, 129.9, 129.9, 129.8, 129.7, 128.9, 128.8, 125.6, 125.6, 124.2, 117.8, 116.1, 115.9, 115.1, 114.9. **HRMS**: m/z (ESI) calcd.. for $C_{26}H_{18}F_3$ $(M+H)^+$ 387.1360 found 387.1364.

(*E*)-7-Fluoro-3,4-bis(*p*-fluorophenyl)stilbene (22b)

Chemical Formula: $C_{26}H_{17}F_3$.



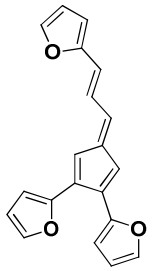
Off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.51 (dd, *J* = 8.0, 1.8, 1H), 7.49 – 7.46 (m, 3H), 7.36 (d, *J* = 7.9, 1H), 7.14 – 7.01 (m, 8H), 6.96 – 6.89 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 163.4, 162.8, 162.8, 161.5, 160.9, 160.8, 139.9, 138.8, 137.2, 136.8, 136.6, 133.3, 131.3, 131.3, 131.2, 130.9, 128.6, 128.1, 128.0, 127.9, 127.6, 125.6, 115.8, 115.6, 115.1, 115.1, 114.9, 114.9. **HRMS**: m/z (ESI) calcd.. for $C_{26}H_{18}F_3$ $(M+H)^+$ 375.1360 found 387.1365.

(*E*)-1-[2,3-Bis(2-furyl)-6-fulvenyl]-2-(2-furyl)ethane (23a)

Following the general procedure, reaction of 1,6-di(furan-2-yl)hexa-1,5-diene-3,4-dione (121 mg, 0.5 mmol), 1,3-dimesityl imidazolium chloride (17 mg, 10 mol %) and

sodium hydride 60 % dispersion in mineral oil (40 mg, 200 mol %, 2 equiv) afforded (*E*)-1-[2,3-bis(2-furyl)-6-fulvenyl]-2-(2-furyl)ethane **23a** in 40% (30.2 mg) and **23b** 6% (4.5 mg).

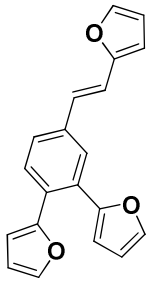


Chemical Formula: $C_{20}H_{14}O_3$.

Dark solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 5.0 Hz, 1H), 7.24 (d, *J* = 4.4 Hz, 1H), 7.21 (d, *J* = 4.9 Hz, 1H), 7.19 – 7.13 (m, 2H), 7.08 – 7.01 (m, 2H), 6.99 – 6.94 (m, 2H), 6.92 (d, *J* = 3.3 Hz, 1H), 6.88 (d, *J* = 3.4 Hz, 1H), 6.84 (d, *J* = 11.6 Hz, 1H), 6.79 (d, *J* = 1.2 Hz, 1H), 6.43 (d, *J* = 1.7 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 143.6, 142.3, 139.1, 138.5, 137.9, 136.8, 132.6, 128.5, 128.1, 127.3, 127.3, 127.0, 126.9, 126.6, 125.6, 125.1, 124.9, 124.4, 118.2.**HRMS**: m/z (MALDI_TOF) calcd. for $C_{20}H_{15}O_3$ $(M+H)^+$ 303.1021 found 303.2314.

(*E*)-2-[3,4-Bis(2-furyl)phenyl]-1-(2-furyl)ethane (23b)



Chemical Formula: $C_{20}H_{14}O_3$.

White solid.

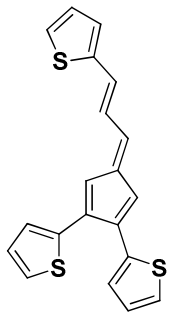
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.56 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.23 (d, *J* = 5.0 Hz, 1H), 7.19 (d, *J* = 5.0 Hz, 1H), 7.06 (d, *J* = 3.4 Hz, 1H), 7.01 – 6.98 (m, 1H), 6.97 – 6.95 (m, 1H), 6.94 – 6.88 (m, 3H), 6.85 (d, *J* = 3.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 142.7, 142.4, 136.5, 133.9, 133.0, 131.1, 129.9, 129.1, 127.6, 127.2, 126.9, 126.4, 125.9, 125.8, 125.6, 124.6, 122.6. **HRMS**: m/z (MALDI_TOF) calcd. for $C_{20}H_{15}O_3$ $(M+H)^+$ 303.1021 found 303.2443.

(*E*)-1-[2,3-Bis(2-thienyl)-6-fulvenyl]-2-(2-thienyl)ethane (24a)

Following the general procedure, reaction of 1,6-di(thiophen-2-yl)hexa-1,5-diene-3,4-dione (137 mg, 0.5 mmol), 1,3-dimesityl imidazolium chloride (17 mg, 10 mol %) and sodium hydride 60 % dispersion in mineral oil (40 mg, 200 mol %, 2 equiv) afforded (*E*)-1-[2,3-bis(2-thienyl)-6-fulvenyl]-2-(2-thienyl)ethane **24a** in 55% (48.1 mg) and **24b** 6% (5.3 mg).

Chemical Formula: $C_{20}H_{14}S_3$.

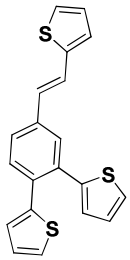


Dark solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 5.0, 1H), 7.27 (d, *J* = 5.1, 1H), 7.24 (d, *J* = 5.1, 1H), 7.21 – 7.16 (m, 2H), 7.08 (d, *J* = 15.1, 1H), 7.04 (t, *J* = 4.3, 1H), 7.01 – 6.97 (m, 2H), 6.94 (d, *J* = 3.5, 1H), 6.91 (d, *J* = 3.5, 1H), 6.88 (d, *J* = 11.6, 1H), 6.82 (s, 1H), 6.46 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 143.5, 142.3, 139.1, 138.5, 137.9, 137.0, 132.8, 128.7, 128.2, 127.4, 127.3, 127.2, 126.0, 126.7, 125.5, 125.1, 124.9, 124.5, 118.2. **HRMS**: m/z (MALDI-TOF) calcd. for $C_{20}H_{15}S_3$ $(M+H)^+$ 351.0335 found 351.2221.

(*E*)-2-[3,4-Bis(2-thienyl)phenyl]-1-(2-thienyl)ethane (24b)

Chemical Formula: $C_{20}H_{14}S_3$.



Yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.56 (d, *J* = 1.7 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.24 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.19 (d, *J* = 5.0 Hz, 1H), 7.07 (d, *J* = 3.4 Hz, 1H), 7.00 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.93 (dd, *J* = 5.2, 3.7 Hz, 2H), 6.92 – 6.89 (m, 1H), 6.86 (dd, *J* = 3.5, 1.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 141.6, 141.4, 135.4, 132.8, 132.0, 130.0, 128.1, 126.5, 126.1, 126.1, 125.8, 125.3, 124.9, 124.8, 124.6, 123.7, 121.8. **HRMS**: m/z (MALDI-TOF) calcd. for $C_{20}H_{15}S_3$ $(M+H)^+$ 351.0335 found 351.2221.

5.9. References

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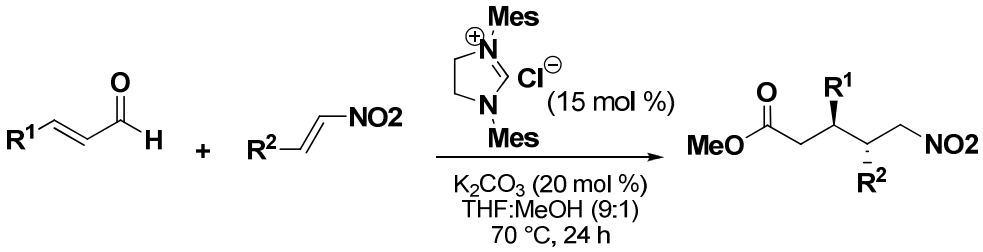
SUMMARY

The thesis entitled "**Exploration of Novel Organic Reactions Catalyzed by Nucleophilic Heterocyclic Carbenes (NHCs)"** embodies the results of the investigations carried out to explore the synthetic potential of *N*–heterocyclic carbenes (NHCs) as organocatalyst towards various electrophiles for the synthesis of heterocyclic and carbocyclic systems. Recent investigations in the generation of homoenolates by the addition of NHCs to conjugated aldehydes have made it possible to study the reactivity of this unique three carbon synthon.

As the thesis mainly focus on the reactions of NHC-bound homoenolates towards various electrophiles, an overview of the chemistry of NHCs and homoenolates is presented in Chapter 1. A definition of the present work is also incorporated in this chapter.

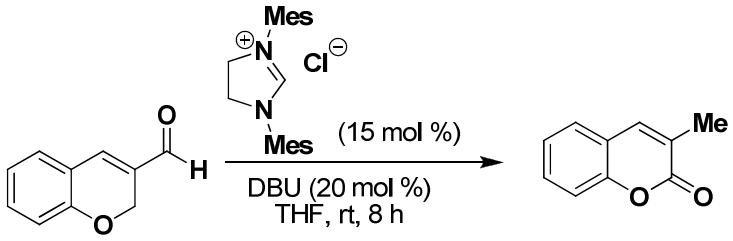
The second chapter describes an efficient NHC catalyzed Michael addition of homoenolates to β-nitrostyrenes (Scheme 1). This reaction afforded 3,4-disubstituted 5-nitro pentanoates in good yield. A number of substituted β-nitrostyrenes underwent this reaction smoothly. Since the products obtained are doubly functionalized five carbon synthons, this reaction will find application in organic synthesis. Moreover, this unprecedented reaction revealed the use of 1,3-dimesityl substituted saturated imidazole carbene (SIMes) in homoenolate generation for first time.



Scheme 1

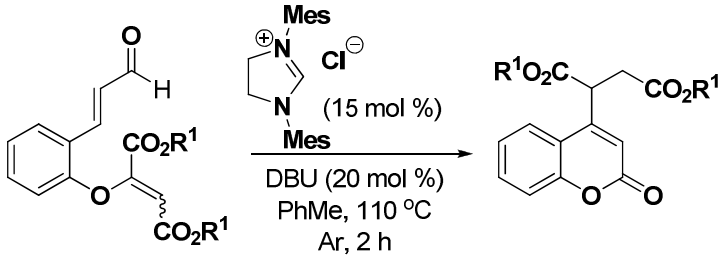
With a view to extend the scope of NHC-catalyzed homoenolate reaction to endocyclic systems; we further extended this protocol to chromene-3-carboxaldehydes, another class of α,β-unsaturated aldehyde. The reaction of the SIMes with chromene-3-carboxaldehyde revealed a serendipitous reactivity pattern, which constitutes the subject matter of the third chapter of the thesis. In contrast to the expected reaction, product obtained was 3-methyl coumarins. Mechanistically the reaction can be viewed to occur

via the β–protonation of the initially formed homoenolate, followed by an intramolecular rearrangement (Scheme 2).



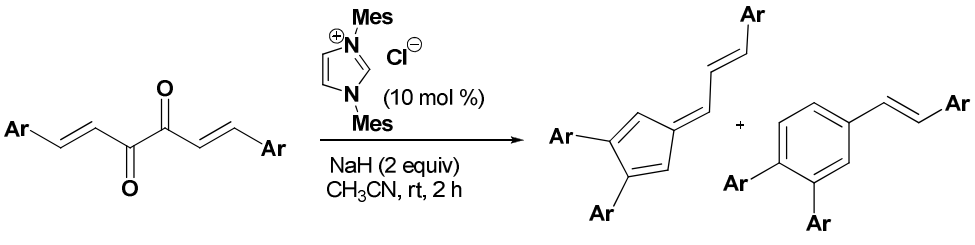
Scheme 2

This pleasing result obtained from a novel rearrangement triggered by a transient endocyclic homoenolate prompted us to study the reaction of NHC bound homoenolate in typical intramolecular reactions. In the event, when 2-O-alkenoate embedded cinnamaldehydes were exposed to NHCs, a cascading process, triggered by an intramolecular homoenolate reaction occurred, resulting in 4-alkyl coumarin synthesis.. The results of these investigations are embodied in the fourth chapter of the thesis. A typical example of this reaction is shown below (Scheme 3).



Scheme 3

Our continuing interest in the reactivity pattern of NHC bound homoenolate towards carbonyl compounds– especially to enones– resulted in an unprecedented NHC catalyzed reaction (Scheme 4). The fifth and final chapter describes this uncommon reaction observed with NHC and cinnamils for the synthesis of vinylfulvenes and *o*-terphenyls. Mechanistic as well as synthetic novelty is the hallmark of this reaction.



Scheme 4

In conclusion, these investigations enabled us to explore the synthetic potential of *N*-heterocyclic carbenes in intramolecular homoenolate reactions, intramolecular rearrangements, and in intermolecular transformations. It is conceivable that these novel reactions will find application in the synthesis of a variety of potentially useful carbo- and heterocycles.

List of Publications

1. *N*-Heterocyclic Carbene Catalyzed Reaction of Cinnamils Leading to the Formation of 2,3,8-Triaryl Vinyl Fulvenes: An Uncommon Transformation. **Sinu, C. R**.; Suresh, E.; Nair, V. *Org. Lett.* **2013**, *15*, 6230–6233.
2. A Cascade Reaction Actuated by Nucleophilic Heterocyclic Carbene Catalyzed Intramolecular Addition of Enals via Homoenolate to α,β-Unsaturated Esters: Efficient Synthesis of Coumarin Derivatives. **Sinu, C. R**.; Padmaja, D. V. M.; Ranjini, U. P.; Seetha Lakshmi, K. C.; Suresh, E.; Nair, V. *Org. Lett.* **2013**, *15*, 68–71.
3. A Novel NHC-Catalyzed Transformation of 2*H*-Chromene-3-Carboxaldehydes to 3-Methyl-2H-Chromen-2-Ones. Nair, V.; **Sinu, C. R**.; Rejithamol, R.; Seetha Lakshmi, K. C.; Suresh, E. *Org. Biomol. Chem.* **2011**, *9*, 5511–5514.
4. 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*, 5570–5573.

Publications not Included in Thesis

5. A Novel Intramolecular Homoenolate Annulation Leading to the Formation of Cyclopentene-Fused Macrocycles. Seetha Lakshmi, K. C.; **Sinu, C. R**.; Padmaja, D. V. M.; Gopinathan, A.; Suresh, E.; Nair, V. *Org. Lett.* **2014**. DOI: 10.1021/ol5023239.
6. NHC-Catalyzed Annulation of Enals to 2,4-Dien-1-Ones: Efficient Diastereoselective Synthesis of 1,3-Diaryl-4-Styrenyl Cyclopentenes. **Sinu, C. R**.; Padmaja, D. V. M.; Jini, P.; Seetha Lakshmi, K. C.; Nair, V. *Synlett* **2013**, *24*, 1671–1674.
7. A facile multicomponent reaction involving isoquinoline, dimethyl allenedicarboxylate, and 2-oxo-1 *H* -indol-3-ylidenes. Rejithamol, R., Beneesh P. B., Amit, K., Paul, R.R., **Sinu, C. R.**, Nair, V., Suresh, E. *Synthesis*, **2012**, *44*, 417 – 422.
8. 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.

9. *N*-Heterocyclic carbene (NHC) catalyzed annulation of enals and vinyl ketones: A novel synthesis of [2*H*]-pyranones. Nair, V., Paul, R.R., Seetha Lakshmi, K.C., Menon, R.S., Jose, A., **Sinu, C. R.** *Tetrahedron Lett.* **2011**, *52*, 5992-5994.
10. 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*, 5336-5346.
11. 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*, 2653-2655.
12. Nitrone cycloaddition to quinones: A novel strategy for the synthesis of benzisoxazolidenes. Paul, R.R., Varghese, V., Beneesh, P.B., **Sinu, C.R.**, Suresh, E., Anabha, E.R. *J. Heterocycl. Chem.* **2010**, *47*, 396-399.
13. A novel pseudo four component reaction involving homoenolate for the synthesis of γ-aminobutyric acid (GABA) derivatives. Nair, V., Varghese, V., Babu, B.P., **Sinu, C. R.**, Suresh, E. *Org. Biomol. Chem.* **2010**, *8*, 761-764.
14. A novel multicomponent reaction involving isoquinoline, allenoate and cyanoacrylates. Nair, V., Beneesh P. B, Vimal Varghese, **Sinu, C. R.,** Rony Rajan Paul, E.R. Anabha and Eringathodi Suresh. *Tetrahedron Lett*. **2009**, *50*, 3716-3718.
15. Insight into the Electron Delocalization in Phenylacetylenes and Phenylvinylenes: An NBO Analysis. Chaitanya, G. K.; Thomas, A.; **Sinu, C. R**.; Francis, B.; Subhashchandran, K. P.; Ramakrishna, K.; Bhanuprakash, K. *Indian J. Chem., Sect. A: Inorg., Bio-inorg., Phys., Theor. Anal. Chem.* **2008**, *47A*, 1171–1180.

Contributions to Academic Conferences

1. *N*-Heterocyclic Carbene Mediated Transformation of Cinnamils to Vinylfulvenes. **Sinu, C. R.;** Nair, V. 15th Tetrahedron Conference. London, United Kingdom, June, 2014.
2. NHC-Catalysed Inter and Intramolecular Reactions for Heterocyclic Constructions. **Sinu, C. R.;** Paul, R. R.; Nair, V. 15th CRSI Symposium in Chemistry, Banaras Hindu University, Varanasi, February 2013.
3. A Novel NHC-Catalyzed Intramolecular Homoenolate Reaction **Sinu C. R.** in 8th J-NOST Conference, IIT Guwahati, Assam, December 15-17, 2012. (Oral presentation).
4. NHC Catalyzed Homoenolate Reactions: A Promising Strategy for C-C Bond Formation. Paul, R. R.; **Sinu, C. R**.; Jose, A.; Seetha Lakshmi, K. C.; Padmaja,

D.V.M.; Nair, V. 14th CRSI Symposium in Chemistry, CSIR-NIIST, Thiruvananthapuram, February 2012.

5. A Novel NHC-Catalyzed Transformation of 2*H*-Chromene-3-carboxaldehydes to 3-Methyl-2*H*-chromen-2-ones. **Sinu, C. R.;** Nair, V. 3rd International conference on Heterocyclic Chemistry (*ICHC-2011*) Department of Chemistry, University of Rajasthan, Jaipur, December, 2011.
6. Novel Nucleophilic Heterocyclic Carbene Mediated Stereoselective Conjugate Addition of Enals to Nitrostyrenes via Homoenolate. **Sinu, C. R.;** Nair, V. National Conference on Recent Trends in Organic Synthesis (*RTOS-2011*), Bharathidasan University, Tiruchirappalli, February 2011.