Transition-Metal-Free Carbon-Carbon and Carbon-Heteroatom Bond-Forming Reactions Using N-Heterocyclic Carbene Organocatalysis and Aryne Chemistry

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

BY

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Under the guidance of
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May 2016

Dedicated

To

My Beloved Parents

For their Love, Support and Encouragement….

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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Transition-Metal-Free Carbon-Carbon and Carbon-Heteroatom Bond-Forming Reactions Using N-Heterocyclic Carbene Organocatalysis and Aryne Chemistry"** submitted by **Mr. Anup Bhunia** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

Anup Bhunia
(Research Student)

Dr. A. T. Biju
(Research Supervisor)

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"Transition-Metal-Free Carbon-Carbon and Carbon-Heteroatom Bond-Forming Reactions Using N-Heterocyclic Carbene Organocatalysis and Aryne Chemistry"** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. A. T. Biju**, Senior Scientist, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

May 2016
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At this moment of submission of my thesis, I invariably feel short of words to express my sincere thanks to my father **Sri. Manoranjan Bhunia** and mother **Smt. Basanti Bhunia** and beloved sister **Anupama** and brother **Debu** and all my well-wishers whose continuous encouragement and support have been a source of inspiration in completion of this tough task.

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Many people have contributed towards the successful completion of this research work, it would be incomplete without giving due tribute to them. So I convey my heartfelt thanks to all those who directly or indirectly helped me in diverse ways that lead to completion of this doctoral thesis work.

Anup Bhunia

List of Abbreviations

Ac	:	Acetyl
ACN	:	Acetonitrile
Ar	:	Aryl
1-Ad	:	1-Adamantyl
bs	:	Broad singlet
Bn	:	Benzyl
t-Bu	:	tertiary Butyl
n-BuLi	:	*n*-Butyllithium
Cy	:	Cyclohexyl
Cat.	:	Catalytic
DABCO	:	1,4-Diazabicyclo[2.2.2]octane
DBU	:	1 8-Diazabicyclo 5.4.0 undec-7-ene
DCE	:	1,2-Dichloroethane
DCM	:	Dichloromethane
DDQ	:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT	:	Density functional theory
DIPEA	:	N,N-Diisopropylethylamine
Dipp	:	2,6-Diisopropylphenyl
DME	:	1,2-Dimethoxyethane
DMF	:	*N*,*N*-Dimethylformamide
DMAP	:	4-Dimethylaminopyridine
DMAD	:	Dimethyl Acetylene Dicarcoxylate
DMP	:	Dess-Martin Periodinane
DMSO	:	Dimethyl sulfoxide
dr	:	Diastereomer
E^+	:	Electrophile
ee	:	Enantiomeric excess
Et_3N	:	Triethyl amine
Et	:	Ethyl
g	:	gram(s)
h	:	hour(s)
HMDS	:	Bis(trimethylsilyl)amine

HPLC	:	High Performance Liquid Chromatography
HRMS	:	High-resolution mass spectrometry
Hz	:	Hertz
IMes.HCl	:	1,3-Dimesitylimidazoliumchloride
IR	:	Infra red
J	:	Coupling constant in NMR
LDA	:	Lithium diisopropyl amide
m	:	Multiplet
Me	:	Methyl
Mes	:	Mesityl
min	:	Minute(s)
mL	:	Milliliter(s)
mmol	:	Millimole(s)
MW	:	Microwave
NHC	:	N-Heterocyclic Carbene
NMR	:	Nuclear magnetic resonance
Nu^-	:	Nucleophile
ORTEP	:	Oak Ridge Thermal Ellipsoid Plot
Ph	:	Phenyl
i-Pr	:	Isopropyl
q	:	Quartet
rt	:	Room temperature
s	:	Singlet
t	:	Triplet
TBAF	:	Tetrabutylammonium fluoride
TBAT	:	Tetrabutylammonium difluorotriphenylsilicate
TBS	:	Tertiarybutylsilyl
TEMPO	:	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TMEDA	:	Tetramethylethylenediamine
Tf	:	Trifluromethanesulfonyl
Tf_2O	:	Trifluoromethanesulfonic anhydride
THF	:	Tetrahydofuran
TLC	:	Thin layer chromatography
TMS	:	Trimethylsilyl

Synopsis

Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	Mr. Anup Bhunia
Degree Enrolment No. & Date	Ph. D in Chemical Sciences (10CC11A26029); August 2011
Title of the Thesis	Transition-Metal-Free Carbon-Carbon and Carbon-Heteroatom Bond-Forming Reactions Using N-Heterocyclic Carbene Organocatalysis and Aryne Chemistry
Research Supervisor	Dr. Akkattu T. Biju (AcSIR, CSIR-NCL, Pune)

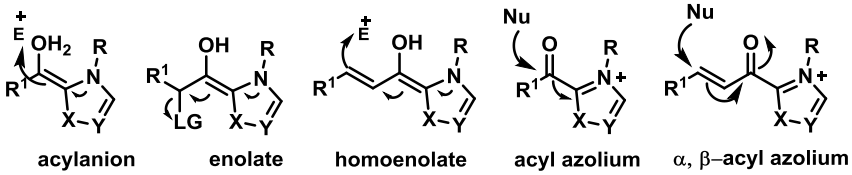
The proposed thesis is divided in two parts. The first part deals with the N-heterocyclic carbene (NHC)-organocatalyzed transformations, and the second part describes the transition-metal-free multicomponent reactions involving arynes.

Part 1: NHC-Organocatalysis

NHC-based organocatalysis is one of the important method for the unconventional construction of various carbon-carbon and carbon-heteroatom bonds. NHCs in organocatalysis are typically employed to render aldehydes nucleophilic, thereby reversing their normal reactivity. This reversal is referred to as *umpolung*. The usefulness of NHCs are demonstrated in nature itself. The presence of coenzyme thiamine is responsible for several biological transformations. On the other hand NHCs are useful as a successful ligand in various organometallic transformations.

Statement of the Problem

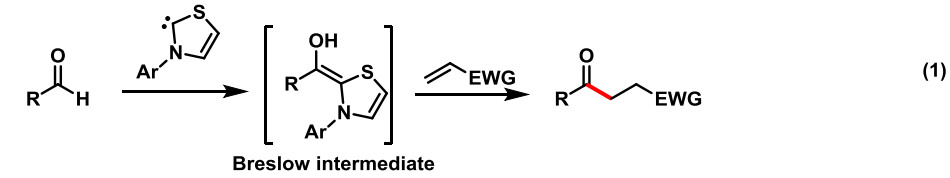
NHCs have a rich history in organic chemistry.[1] The benzoin condensation and Stetter reactions are the two most well-known transformations, which employ the Breslow intermediate as key intermediate. In the last few decades, several other modes of NHC-organocatalysis has been developed including the catalytic generation of NHC-bound enolates, homoenolates as well as acyl azolium intermediates.



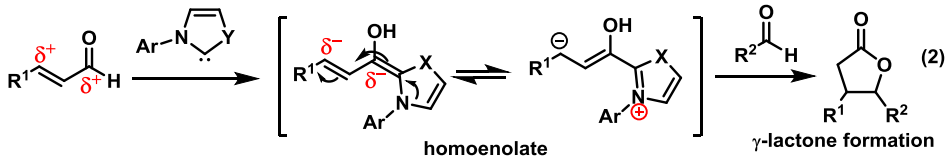
Methodology

In the last few decades, much focus have been on the Stetter reaction. These reactions proceed via the formation of nucleophilic acyl anion intermediates, which can react with various activated C-C double bonds. The NHC-catalyzed generation of the Breslow intermediate (**A**) and its subsequent interception with a variety of Michael acceptors are well documented (eq 1). The reaction of Breslow intermediates with unconventional reaction partners proves the unparalleled transformations of NHC catalyzed reactions over metal catalyzed reactions. The addition of NHC to α,β-unsaturated aldehyde could be converted into unique homoenolate nucleophiles. Addition of NHCs containing two bulkier group as a nitrogen substituents to an α,β-unsaturated aldehyde would generate a reactive dienamine (eq. 2). The unique nucleophilic character of the carbonyl carbon then extended to the β-position. In the present thesis, the focus is on the developments of new synthetic methodologies based on these key intermediates

Stetter reaction: coupling of aldehydes with Michael acceptors

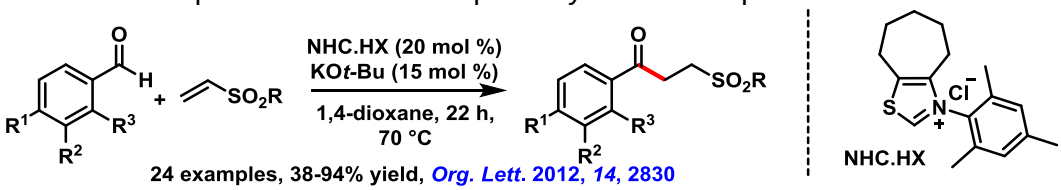


Conjugate Umpolung



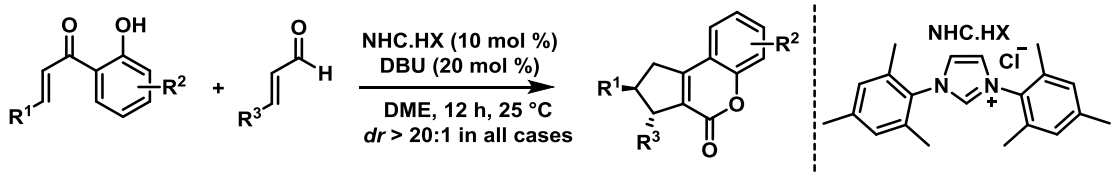
Noteworthy Findings

Intermolecular Stetter Reaction: In the course of our studies, we have developed the NHC-catalyzed intermolecular Stetter reaction of α,β-unsaturated sulfones leading to the efficient formation of γ-ketosulfones in good yields. The reaction shows good tolerance to a variety of substitution patterns. The product formation took place in spite of various selectivity issues under basic conditions. We have carried out several mechanistic studies to demonstrate the possible mechanistic pathways of this unique reaction.[2]



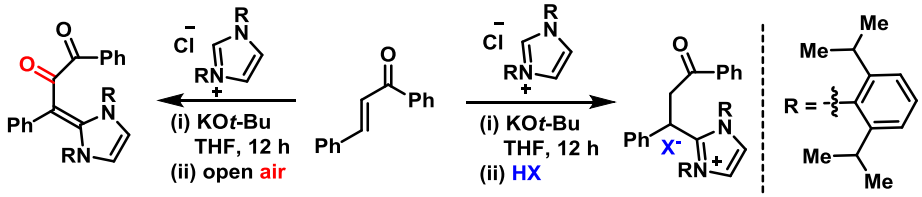
24 examples, 38-94% yield, *Org. Lett.* 2012, *14*, 2830

Conjugate Umpolung: A highly diastereoselective synthesis of cyclopentane-fused coumarins has been uncovered by an NHC catalyzed annulation of enals and hydroxyl chalcones. The reaction shows good tolerance to a variety of substitution patterns. Preliminary, mechanistic experiments shows that the presence of hydroxyl group in the chalcone starting material is essential for the coumarin formation. A plausible mechanism based on the initial mechanistic investigation has been proposed.[3]



25 examples, 74-98% yield, *Org. Lett.* 2013, *15*, 1756

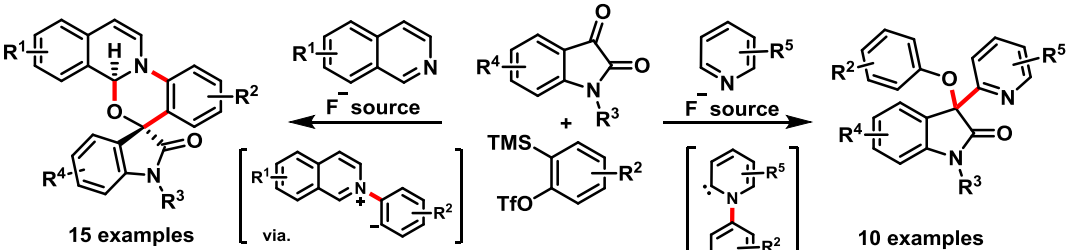
Chalcone-NHC Adducts: Recently, we have disclosed the umpolung of β-substituted Michael acceptors. The addition of NHCs to chalcones generated the *deoxy*-Breslow intermediates in their oxidized form. The reaction proceeds via an alkoxide intermediate which undergoes an unexpected oxidation in presence of air. Alternatively, use of Brønsted acid in the absence of air leads to the formation a tetrahedral intermediate. A series of experiments have been performed to shed light on the chalcone-NHC adduct formation.[4]



Chem. Commun.. 2015, *51*, 13690

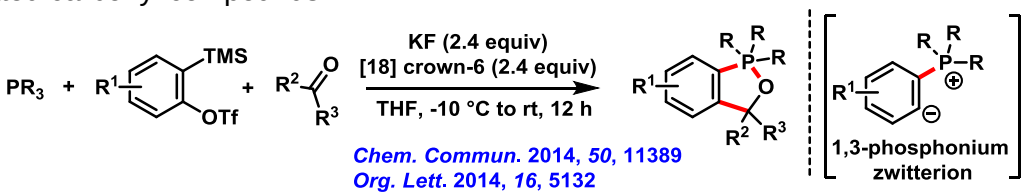
Part 2: Transition-Metal-Free Multicomponent Reactions (MCRs)

N-Heterocycle Triggered Aryne MCRs: Transition-metal-free aryne MCRs provides straightforward access to various heterocycles and carbocycles.[5,6] In the present work, we have utilized N-heterocycles such as pyridine and (iso)quinoline as the nucleophilic triggers. The important aspect of the present work is the divergent reactivity based on the nucleophilic trigger. When iso(quinoline) system was used as the nucleophilic source, the reaction proceeds via a 1,4-dipolar intermediate leading to the spirooxazino (iso)quinoline derivatives. Interestingly, use of pyridine as a nucleophile resulted in an unprecedented transformation. The reaction proceeds via a pyridylidene intermediate to generate the indolin-2-one derivative. Subsequently, we have expanded the scope of iso(quinoline) triggered aryne MCRs with activated acyclic carbonyls.[7]



Angew. Chem. Int. Ed. 2013, *52*, 10040
Org. Lett. 2013, *15*, 4620

Phosphine Triggered Aryne MCRs: Recently, we have expanded the scope of aryne MCRs by developing efficient transformations initiated by phosphines. The reaction proceeds via a formal [3+2] cycloaddition of 1,3-phosphonium zwitterion generated from phosphine and aryne with aldehydes. The method afforded diverse range of stable benzooxaphosphole derivatives in good to excellent yields. Subsequently, we developed an operationally simple MCR involving phosphines, arynes and various acyclic and cyclic activated carbonyl compounds.[8]



Chem. Commun. 2014, *50*, 11389
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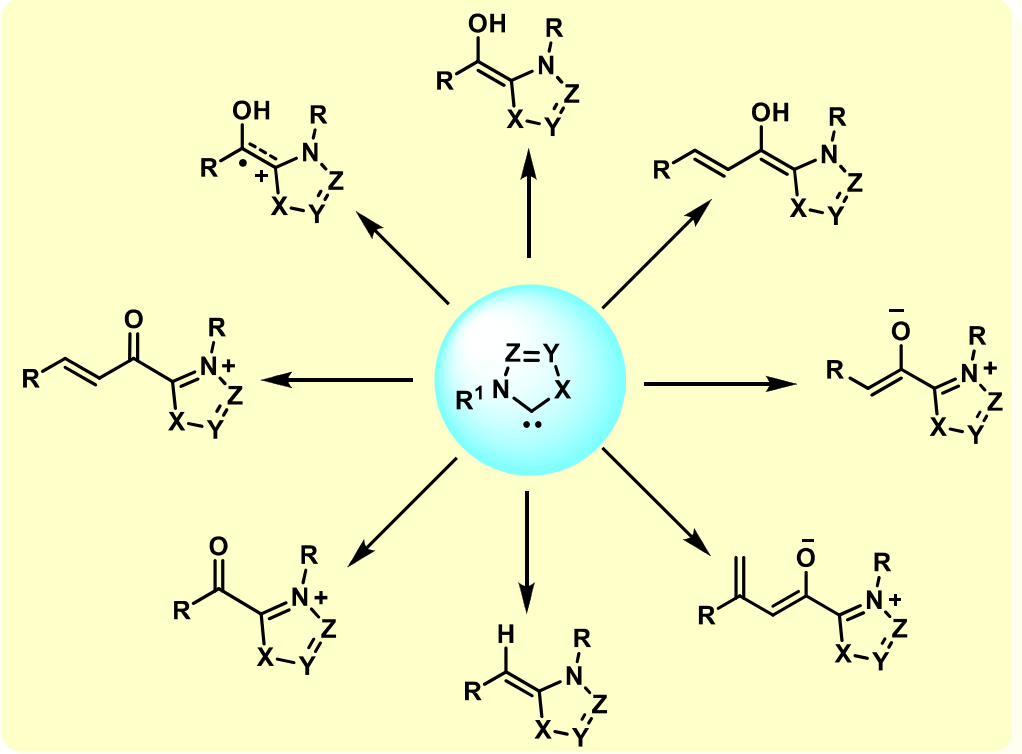
Chapter 1

A Brief Introduction to N-Heterocyclic Carbene (NHC)-Organocatalysis

Carbenes are highly reactive, short lived species and are inherently electrophilic in nature. However, there are a class of carbenes known to be nucleophilic, where the carbene centre is a part of the ring, which are called N-heterocyclic carbenes (NHCs). NHCs are long time known as ligands for organometallic transformations, but in the last two decades, these species are well employed as catalysts in various organic reactions. The benzoin reaction and the Stetter reaction are the two important reactions catalyzed by NHCs. NHCs are well-known for the umpolung of aldehydes, and for the generation of homoenolate equivalents from enals. In this chapter, the chemistry of NHCs highlighting the different modes of action in organocatalysis has been presented.

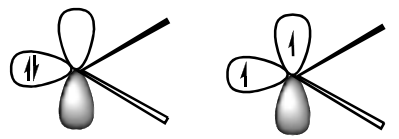


1.1. Introduction

The catalysis with small organic molecules is an important aspect in modern synthetic chemistry. Historically the word "Organiche Katalysatoren" or organic catalyst was used by Langenback in 1929.[1] Later MacMillan defined the term "Organocatalysis", where a small organic molecule catalyzed a reaction.[2] In view of the sustainable developments and green chemistry, organocatalytic methods are practically applicable for their low toxicity and atom-economy in contrast to the traditional transition-metal-based catalysis. In the last century, a large number of organocatalyzed reactions are reported in the literature. Usually, organocatalyzed reactions are divided into four major categories such as Lewis Base, Lewis acid, Brønsted base and Brønsted acid based transformations. Phosphines,[3] amines[4] and carbenes[5] are the common Lewis base catalysts, which are studied extremely in the last few decades. In this chapter, we will highlight on the recent advances made by N-heterocyclic carbene (NHC)-organocatalysis.

NHCs belong to one of the most investigated reactive species in the field of organic chemistry. They are highly reactive intermediates and possess a bivalent carbon atom with an electron sextet (Figure 1.1). According to the spin multiplicity, carbenes are divided into two categories, singlet (paired electrons) and triplet (unpaired electrons). NHCs have both nucleophilic and electrophilic character and it belongs to the singlet category.

Figure 1.1: Electronic Structure of Carbene

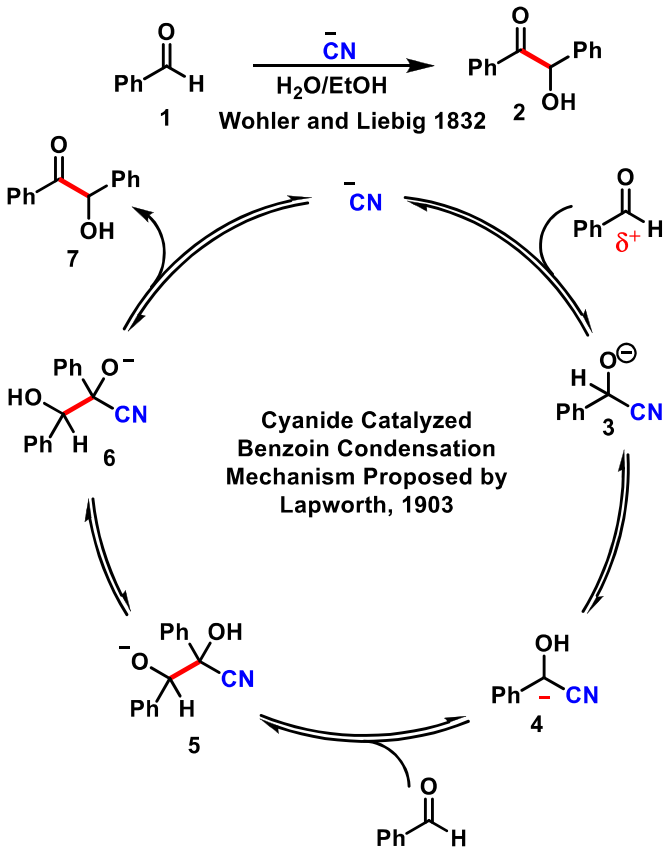


1.2: Evolution of NHC-Organocatalysis

In 1832, Wöhler and Liebig demonstrated the self condensation of aromatic aldehyde **1** in presence of cyanide to form benzoin **2**.[6] This transformation is popularly known as "Benzoin condensation". Later in 1903, Lapworth postulated a mechanism for this condensation reaction (Scheme 1.1).[7] Mechanistically, the reaction proceeds via the formation of a carbinol intermediate **4** by cyanide addition to benzaldehyde followed by protonation via the tetrahedral intermediate **3**. Notably, the electrophilic aldehyde carbon property was inverted to nucleophilic reactivity upon addition of cyanide. This reversal of

polarity is known as the "*Umpolung*" concept.

Scheme 1.1: Cyanide catalyzed Benzoin Condensation



In 1943, Ukai and co-workers found that the thiazolium moiety embedded in coenzyme thiamine (Vitamin B1; Scheme 1.2) could also catalyze the benzoin reaction.[8] Later in 1958, Breslow proposed a mechanistic explanation for the thiazolium salt-catalyzed benzoin condensation.[9] The key step in benzoin condensation is the nucleophilic attack of the in situ generated carbene **8** to the aldehyde, leading to the tetrahedral intermediate **9**, which undergoes proton transfer to the nucleophilic enaminol intermediate **10**. This acyl anion equivalent **10** reacts as a nucleophile with another molecule of aldehyde to furnish the final product, the α-hydroxy ketone **7** (Scheme 1.2).

In this mechanism, the catalytically active species **8** was represented as mesomeric zwitterions, the resonance structure of NHC (Scheme 1.2). However, the existence of NHC as catalytically active species in these processes was only realized almost three decades later when the Arduengo and co-workers reported the isolation and characterization of stable imidazolium NHC **B** in 1991 (Figure 1.2).[10a] Moreover, in 1995, Enders and co-workers reported the isolation of stable triazol-5-ylidene.[11] Triphenyl triazol-5-ylidene **C**

was the first commercially available NHC.

Scheme 1.2: Thiamine catalyzed Benzoin Condensation

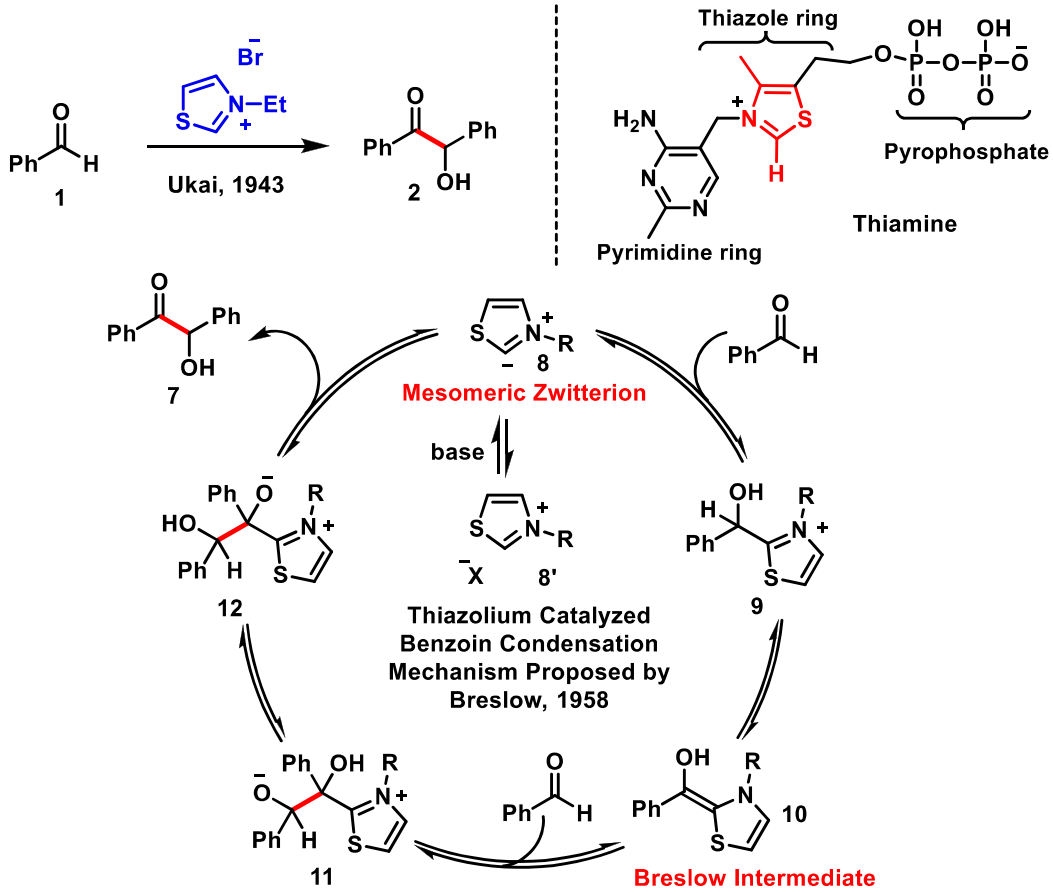
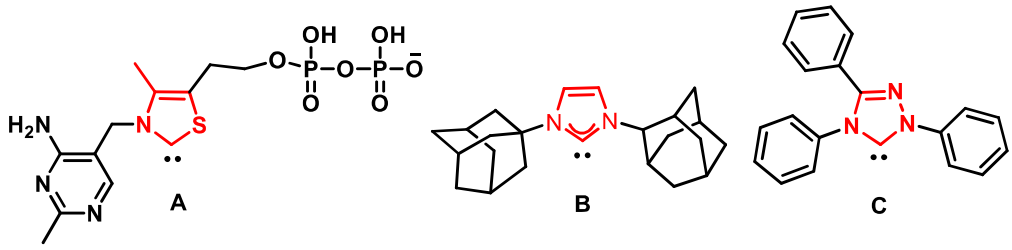


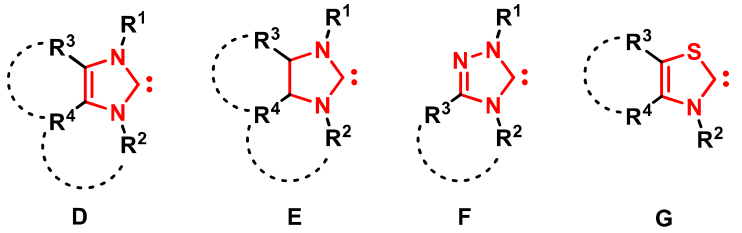
Figure 1.2: Early N-Heterocyclic Carbenes



Initially NHCs field experienced a sluggish growth and it was mainly considered as a ligand in metal chemistry. Since the isolation of stable nucleophilic carbenes by Arguendo[10a], Bertrand[10b] and Enders[11], the chemistry of NHCs has received a wide interest as highly selective catalysts. Generally, four types of NHCs are used of organocatalyzed transformations (Figure 1.3). The carbene carbon is stabilized by heteroatoms on either side, thereby the nucleophilicity of NHCs are increased substantially. The stability of NHCs

has been attributed to both electronic and steric effects.

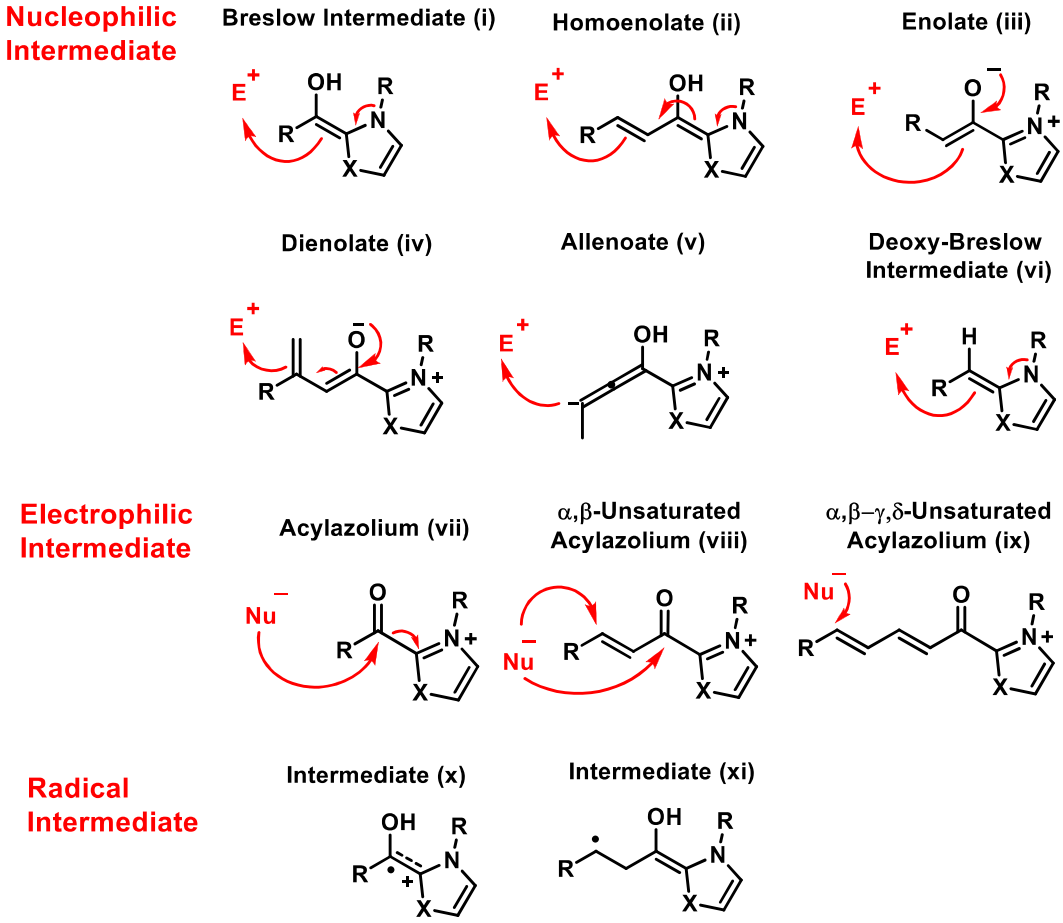
Figure 1.3: Representative types of NHCs



1.3: Important Reactivity Modes of NHC

The chemistry of NHC-catalysis is categorized according to the reaction mode and the intermediates formed in the reaction (Figure 1.4). The various reactions of Breslow intermediates (**i**) with unconventional reaction partners prove the unparalleled transformations of NHC catalyzed reactions over metal catalyzed reactions. The 1,2-addition of Breslow intermediate to another aldehyde is referred as the benzoin condensation, while the addition of the acyl anion to a Michael acceptor is known as the Stetter reaction. These reactions belong to the class of a^1–d^1 coupling, according to the terminology of Seebach. However, the addition of an NHC to α,β-unsaturated aldehydes can lead to a dienamine intermediate, rendering the β-carbon atom nucleophilic (**ii**). The homoenolate equivalents can be considered as a d^3–nucleophile and thus, constitutes an a^3–d^3 coupling. Moreover, reactions of α-halo aldehydes and ketenes with NHC affords the nucleophilic enolate intermediate (**iii**) which is a two- carbon synthon normally gives [4+2] and [3+2] annulations. Interestingly, a enolizable γ-proton of the α,β-unsaturated carbonyl compounds and enals with leaving groups generates NHC-bound dienolate intermediates (**iv**), which reacts in [4+2] and [2+2] cyclizations. The *umpolung* of ynals with NHC affords allenoate intermediate (**v**), which is a three-carbon synthon and normally participates in [3+2] annulations. Addition of NHCs to alkyl halides or Michael acceptors resulted in the formation of *deoxy*-Breslow intermediate (**vi**). A variety of NHC-catalyzed redox processes lead to the formation of acylazolium (**vii**), α,β-unsaturated acylazolium (**viii**) and α,β-γ,δ-unsaturated acylazolium intermediates (**ix**) using external oxidant. Recently, few reports on NHC-catalysis based on radical process have been reported (intermediate **x** and **xi**). The choice of the NHC catalyst, coupling partners and reaction conditions can allow selective formation of each of these reactive intermediates.

Figure 1.4: Important Reactivity Modes of NHC



1.3.1: NHC-Catalyzed Reaction via Breslow Intermediate (i)

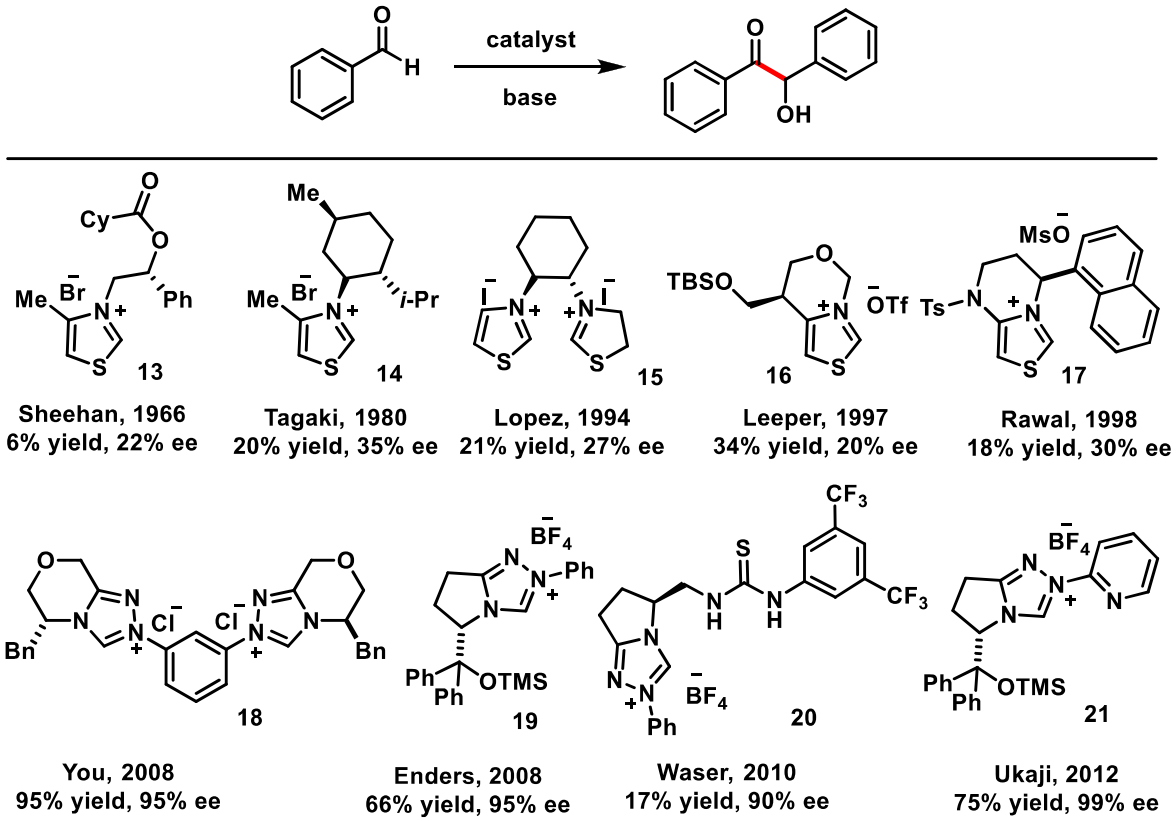
The NHC-catalyzed *umpolung* of aldehydes by means of formation of the nucleophilic Breslow intermediates (**i**) is probably the most important mode of action of NHC. The benzoin and Stetter reactions are the two prominent reactions in NHC-catalysis. Bonzoin reactions are divided in to two categories a) intermolecular benzoin and b) inramolecular benzoin reactions. The Stetter reactions are divided into two types such as c) Stetter reactions and d) hydroacylation reactions.

a) Intermolecular Benzoin Condensation

In 1943, Ukai and co-workers reported the thiazolium mediated homo-benzoin condensation (two same aldehyde molecules coupled). Later in 1976, Stetter developed the synthesis of benzoin in laboratory scale using commercially available thiazolium salt.[12] Subsequently, several chemists attempted to develop the asymmetric versions of the homo-

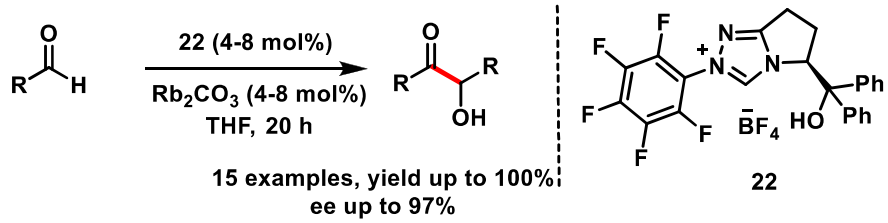
benzoin reaction using chiral NHCs. In 1966, Sheehan reported the first asymmetric benzoin condensation using the chiral thiazolium salt **13** and obtained the product with 22% ee and 6% yield.[13] Since then, various chiral thiazolium and triazolium salt has been developed to increase the efficiency of the homo-benzoin reaction. A selected list of chiral-NHC catalysts has been presented in the Scheme 1.3. Thiazolium derived NHC-salts (**13-17**) provided the desired product in fewer yields and also the ee values are less. However, the catalyst generated from the triazolium salts (**18-21**) derived the benzoin product with moderate to good yields and with excellent ee values.[14]

Scheme 1.3: Variation of Chiral-NHCs for Asymmetric Homo-Benzoin Condensarion



A co-operative hydrogen bond assisted enantioselective benzoin condensation was reported recently by Zeitler and Connon (Scheme 1.4). They have designed a rigid bicyclic triazole precatalyst **22** containing a chiral hydroxyl group and a pentafluoroarene substitution, which improves the enantioselectivity of the benzoin condensation reaction.[15]

Scheme 1.4: Co-operative Hydrogen Bond Assisted Enantioselective Benzoin Condensation

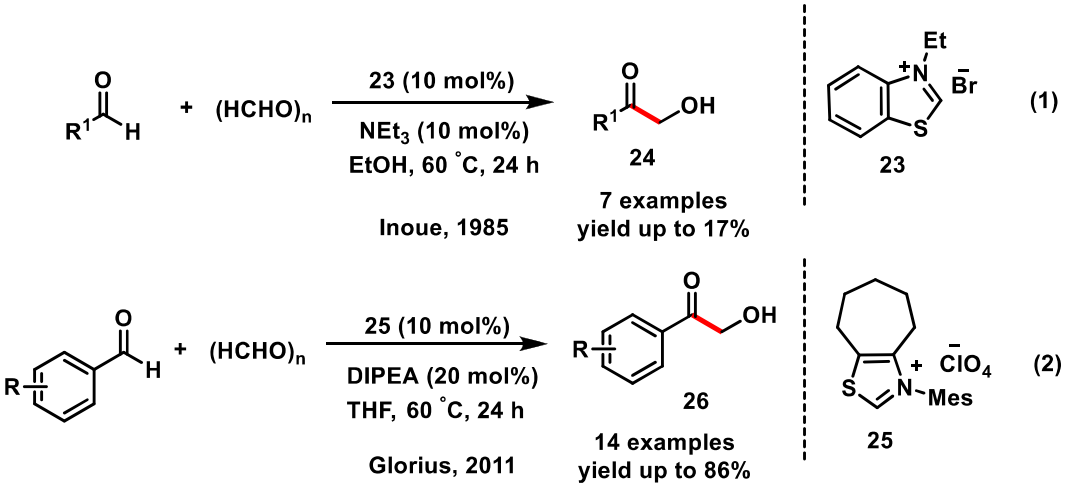


Zeitler and Connon, 2009

Intermolecular Cross-Benzoin Reaction

In 1985, Inoue and co-workers demonstrated the selective cross coupling of aromatic and aliphatic aldehydes with formaldehyde. The reaction proceeds via the umpolung of aldehyde followed by addition to formaldehyde to generate the hydroxyl ketone **24** in very low yield (Scheme 1.5, Eq. 1).[16] Later Kuhl and Glorius used NHC generated from the thiazolium salt **25** to synthesize the similar hydroxyl ketone in good yields with a very broad substrate scope (Scheme 1.5, Eq. 2).[17]

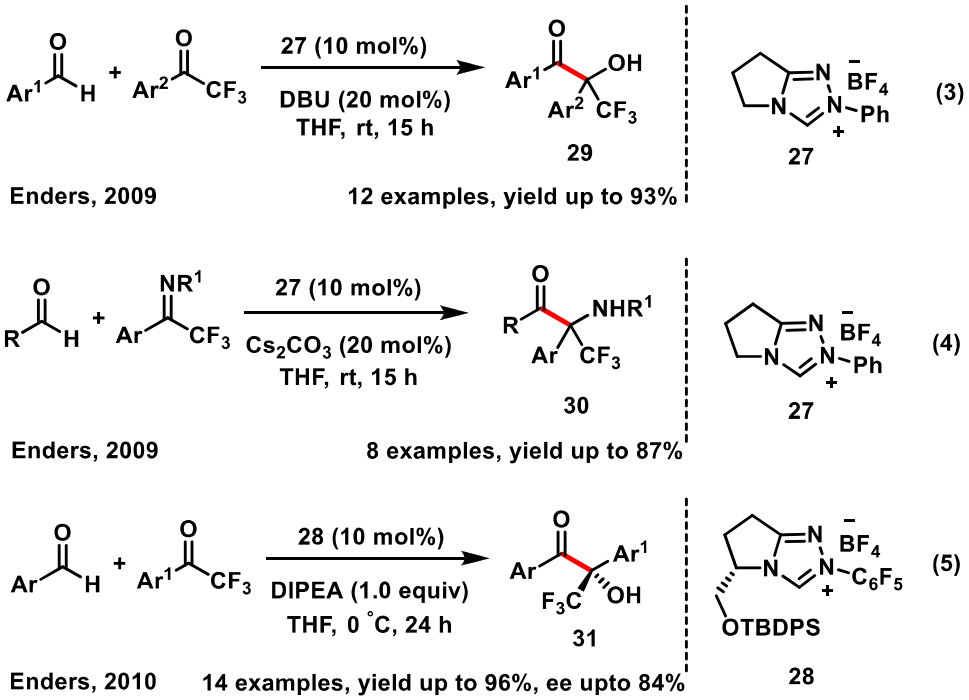
Scheme 1.5: Cross-Benzoin Reaction of Aldehydes and Formaldehydes



The cross-coupling reaction of aryl aldehydes with aryl trifluoromethyl ketones was disclosed by Enders and Henseler (Scheme 1.6; Eq. 3). The reaction proceeds with high yield and excellent chemoselectivity.[18] The reaction furnished excellent yields of α-hydroxy-α-trifluoromethyl ketones **29** possessing a quaternary stereocentre. Later they generalized the substrate scope with the use of Trifluoromethyl ketimines (Eq. 4).[19] Though initial attempts on chiral transformation were not successful later they found the use of

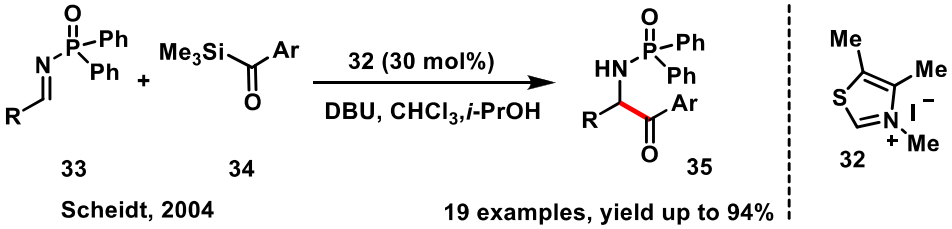
heteroaromatic aldehydes in presence of the chiral NHC generated from **28** furnished the trifluoromethylated hydroxyl ketones **31** with good enantioselectivity (Eq. 5).[20]

Scheme 1.6: Cross-Benzoin Reactions of Aldehydes and Trifluoromethyl Ketones



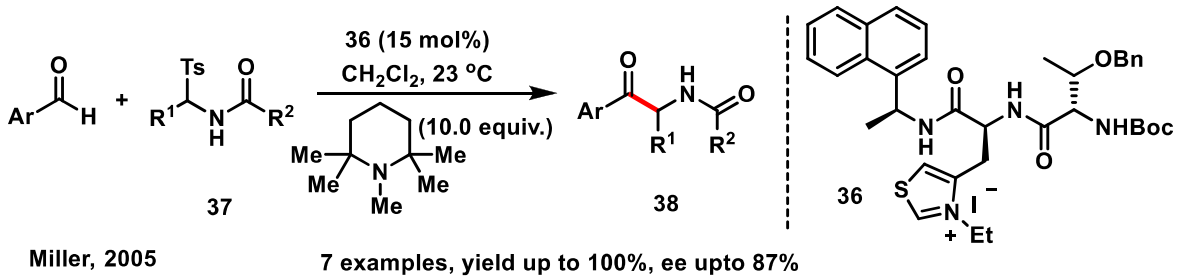
Mattson and Scheidt developed a catalytic cross-aza-benzoin coupling reaction between acylsilanes **34** and imines **33** for the synthesis of aminoketones **35** (Scheme 1.7).[21] The reaction proceeds via the generation of Breslow intermediate from the acylsilanes followed by a cross-coupling with the imine.

Scheme 1.7: *Umpolung* of Acylsilanes



In 2005, Miller and co-workers employed a chiral thiazolium salt **36** to demonstrate the enantioselective version of the cross-aza-benzoin reaction (Scheme 1.8).[22] The reaction of aldehydes with the masked imines **37** afforded the α-amino ketones **38** in high yield and good ee values. The reaction suffers a racemisation issue under the reaction conditions. The problem was suppressed by using a hindered base pentamethyl piperidine, which gives the maximum enantioselectivity.

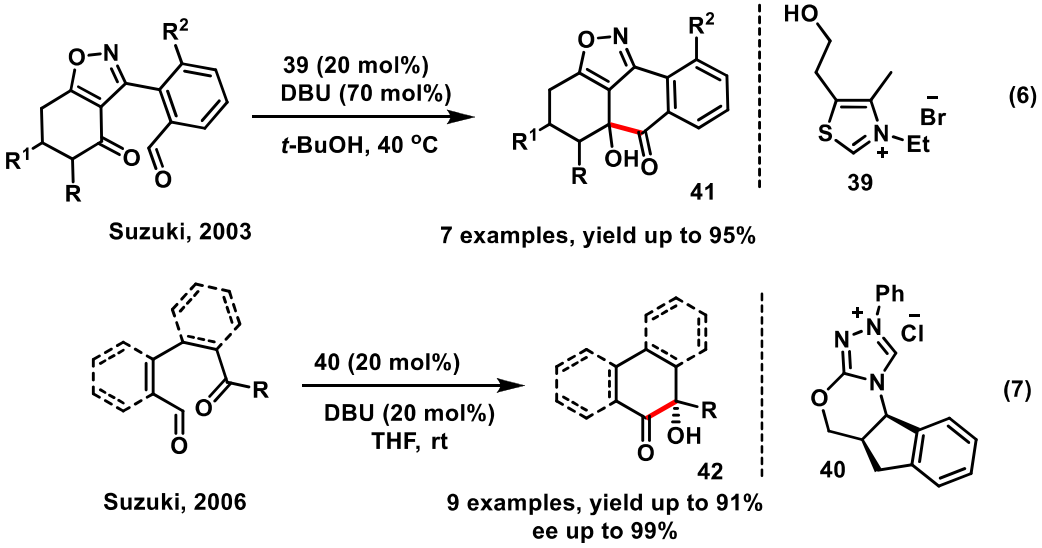
Scheme 1.8: Cross Aza-Benzoin Reaction



Intramolecular Benzoin Reaction

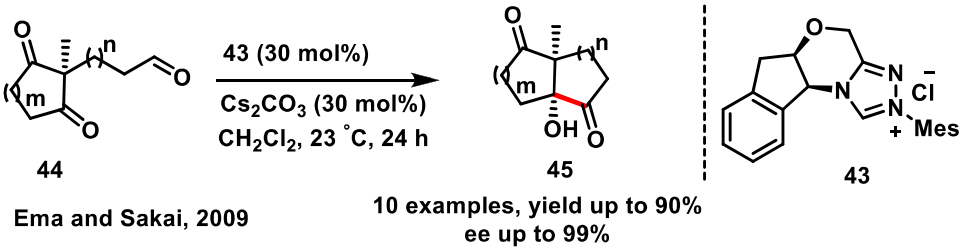
In 2003, Suzuki and co-workers developed the first intramolecular cross benzoin condensation between aldehyde and ketone (Scheme 1.9).[23a] This report demonstrated for the first time, the use of ketone as an electrophile in non-enzymatic benzoin reaction. Due to the highly rigid isoxazole building block, the reaction offered a very high stereo and regioselective polycyclic pre-anthraquinone derivatives **41** with excellent yield. Later in 2006, they developed the enantioselective versions of the same reaction using an aminoindanol derived triazolium salt **40** for the intramolecular benzoin reaction leading to **42** in high ee values (Eq. 7).[23c]

Scheme 1.9: Intramolecular Cross-benzoin Reaction



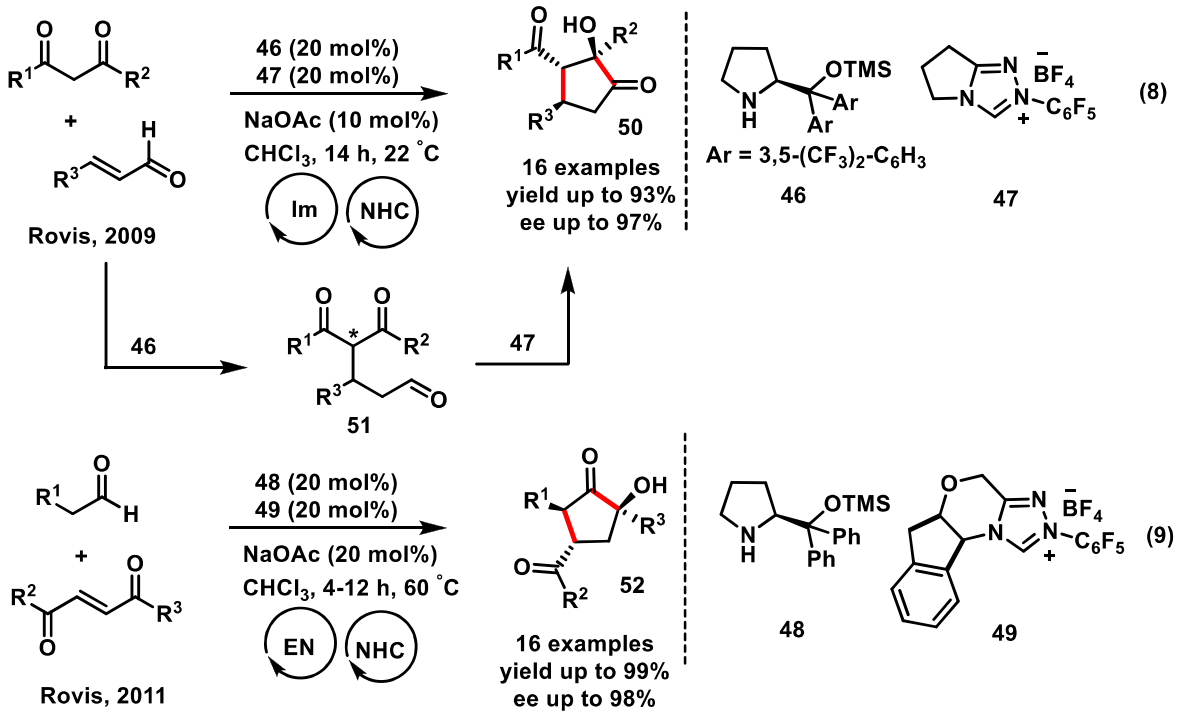
Ema, Sakai and co-workers reported the synthesis of bicyclic tertiary alcohol **45** possessing with two quaternary stereocenters at the bridgehead position by the intramolecular benzoin reaction of **44** using the NHC derived from **43** (Scheme 1.10).[24] The reaction needs a high loading (30 mol%) of catalyst for good enantioselectivity.

Scheme 1.10: Synthesis of Bicyclic Tertiary Alcohols by Intramolecular Benzoin Reaction



In 2009, Rovis and co-workers developed a Michael-benzoin cascade process to synthesize highly functionalized enantioenriched cyclopentanone derivatives **50** (Scheme 1.11, Eq. 8).[25] The reaction was initiated with an iminium generation from enal and catalyst **46** followed by conjugate addition of 1,3-diketone generating an intramolecular keto-aldehyde system **51**. Subsequently, the NHC generated from **47** catalyzed the keto-aldehyde cross benzoin reaction to furnish the observed product **50**.

Scheme 1.11: Secondary Amine-NHC Dual-Catalytic, Michael–Benzoin Cascade Reaction



Later, in 2011 they have demonstrated the generation of enamine from an enolizable aldehyde in presence of a secondary amine catalyst **48** followed by addition to an activated Michael acceptor (Scheme 1.11, Eq. 9).[26] The first process generates a keto-aldehyde system, which undergoes intramolecular cross-benzoin reaction in presence of a chiral

carbene **49** to generate the enantioselective and highly functionalized cyclopentene derivatives **52**.

Stetter Reaction

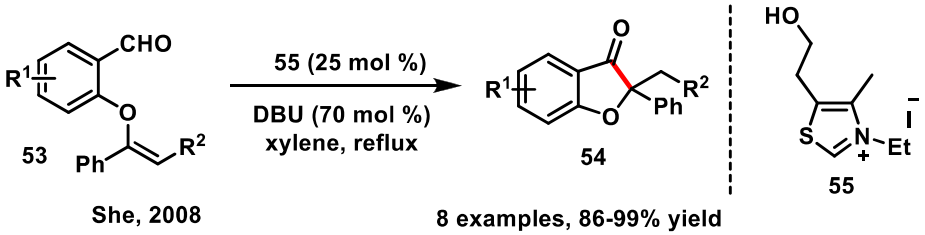
Details on NHC-catalyzed Stetter reaction and related chemistry are described in Chapter 2.

Hydroacylation Reaction

Stetter reaction represents the umpolung of aldehydes followed by the nucleophilic addition of the generated acyl anion equivalents to activated carbon-carbon multiple bonds (electron-poor). However, the umpolung of aldehydes followed by the addition across unactivated carbon-carbon multiple bonds, the NHC-catalyzed hydroacylation reactions are reported recently.

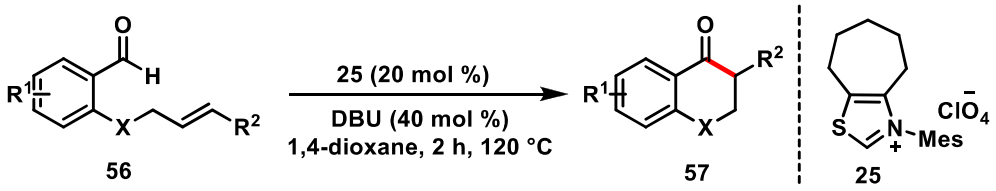
In 2008, She and co-workers developed the intramolecular nucleophilic addition reaction of acyl anion equivalents to enol ethers by the NHC generated from commercially available thiazolium salt **55**. The reaction resulted in the formation of the benzofuranones **54** in high yields (Scheme 1.12).[27] Mechanistically, the reaction proceeds via the addition of the Breslow intermediate to the carbon-carbon double bond of enol ether, however, it was unclear whether the addition proceeds via a concerted pathway or involving an oxonium intermediate.

Scheme 1.12: NHC-Catalyzed Hydroacylation of Enol Ethers



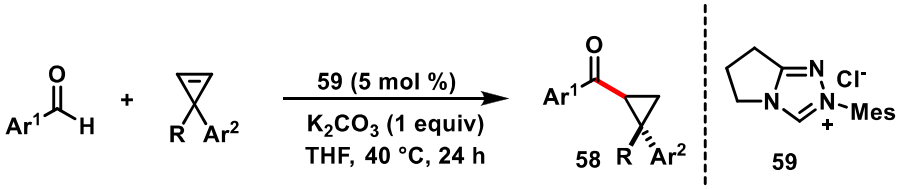
Intramolecular NHC-catalyzed hydroacylation of unactivated alkenes was developed by Glorius and co-workers in 2009. The carbene generated from the thiazolium salt **25** catalyzed the intramolecular cyclization of 2-allyloxy benzaldehydes **56** to form the corresponding chromanones **57** (Scheme 1.13).[28] This reaction tolerates a broad range of substrates, and in all cases, the desired chromanone was formed in moderate to good yields. These reactions represent the NHC-organocatalyzed hydroacylation of unactivated carbon-carbon double bonds.

Scheme 1.13: NHC-Catalyzed Hydroacylation of Unactivated Double Bonds



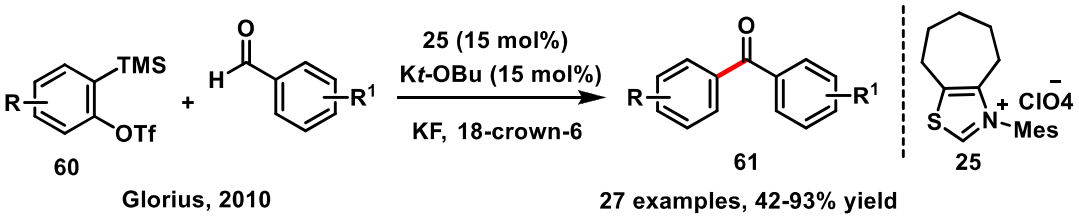
Glorius and co-workers reported the first intermolecular hydroacylation of unactivated double bonds. The treatment of aromatic aldehydes with cyclopropenes under mild conditions using carbene generated from the triazolium salt **59** afforded the acyl cylopropanes **58** in excellent diastereoselectivity and good yield (Scheme 1.14).[29] Subsequently, they have developed the enantioselective hydroacylation of cyclopropenes using NHC generated from chiral *ortho, ortho'*-disubstituted electron-rich triazolium salts.[30]

Scheme 1.14: Intermolecular Hydroacylation of Cyclopropene



Additionally, NHC-catalyzed intermolecular hydroacylation of arynes has been recently uncovered by Biju and Glorius (Scheme 1.15).[31] This method reveals the rare compatibility of nucleophilic carbenes with highly electrophilic arynes. The reaction of a wide variety of aldehydes with the aryne generated in situ from 2-trimethylsilylaryl triflate **60** using KF and 18-crown-6 in the presence of carbene generated from **25** by deprotonation using KO*t*-Bu resulted in the formation of the aryl ketones **61** in moderate to excellent yield.

Scheme 1.15: NHC-Catalyzed Hydroacylation of Arynes



1.3.2: NHC-Catalyzed Reaction using Homoenolate Intermediate (ii)

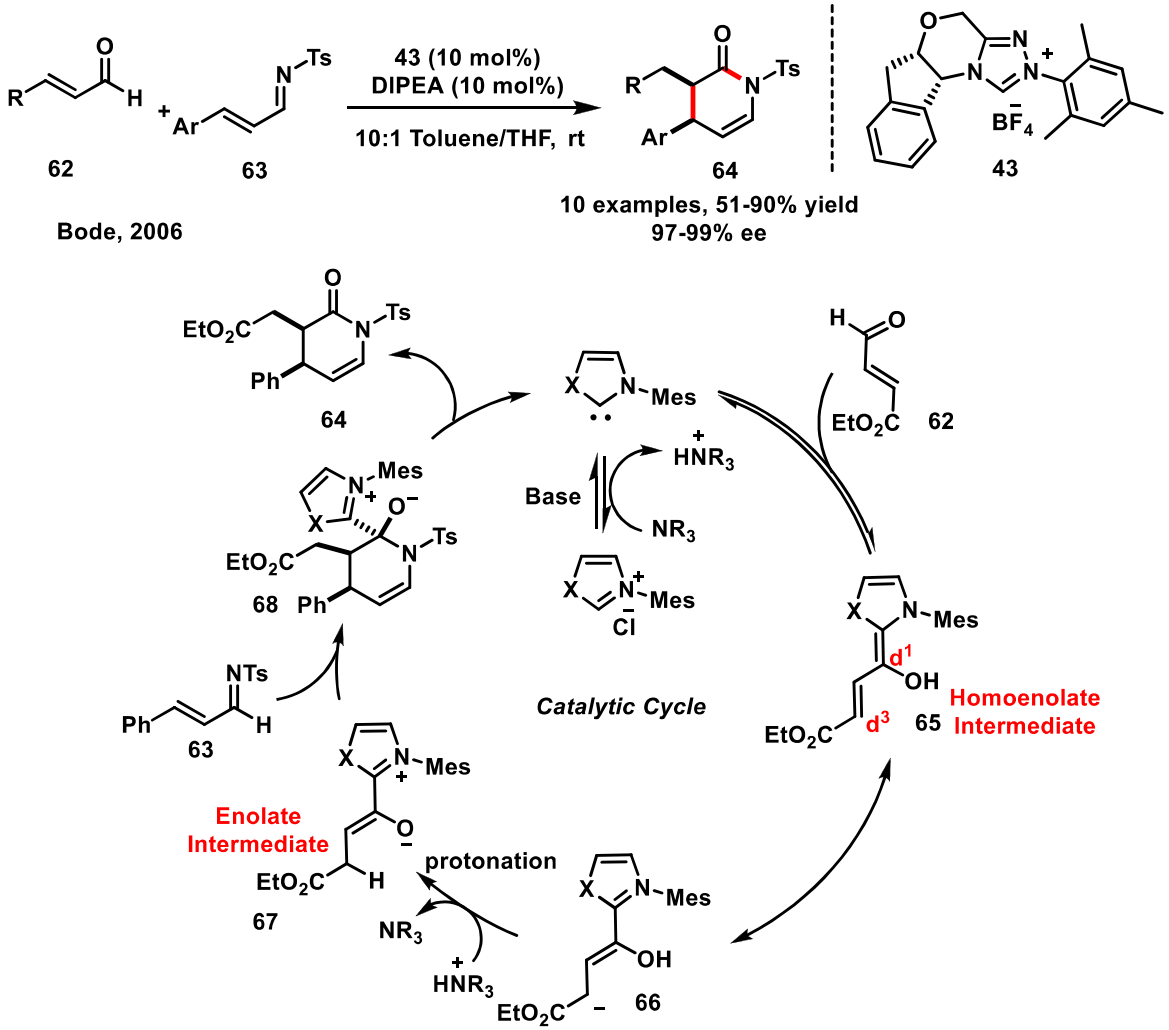
NHC-organocatalyzed generation of homoenolate equivalents and related chemistry is described in details in Chapter 3.

1.3.3: NHC-Catalyzed Reaction using Enolate Intermediate (iii)

In addition to generating nucleophilic homoenolate intermediate from an enal, NHC can generate nucleophilic enolate intermediate after protonation of the β-position of the homoenolate intermediate, which can trapped with electrophile or undergo a number of formal cycloadditions.

In 2006, Bode and co-workers reported the enantiopure synthesis of dihydropyridinone derivatives **64** by NHC-catalyzed formal hetero Diels-Alder reaction of enals **62** with α,β-unsaturated imines **63** (Scheme 1.16).[32]

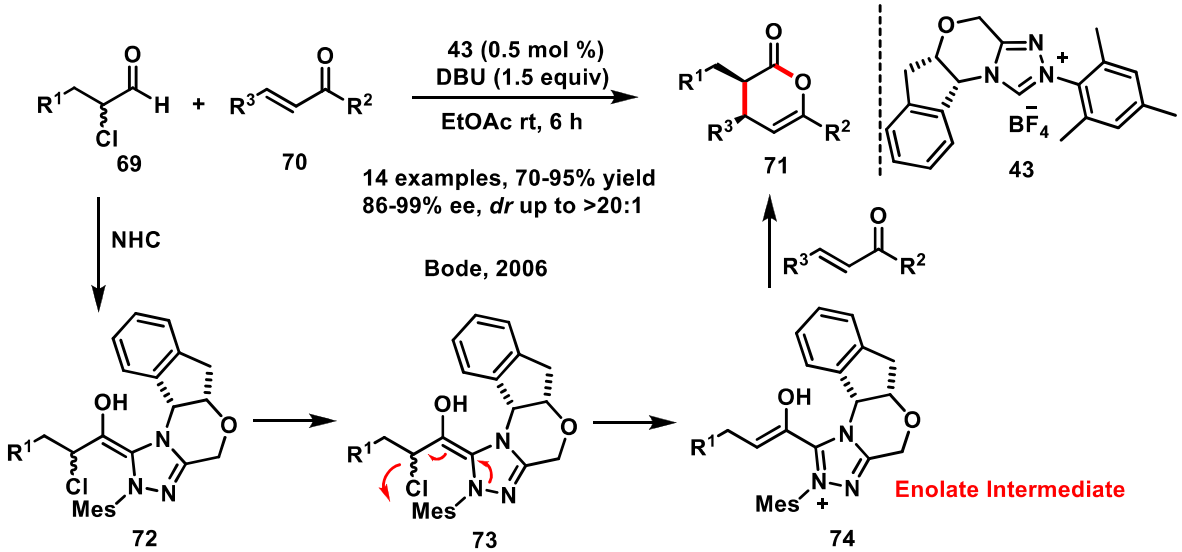
Scheme 1.16: NHC-Catalyzed Generation of Enolate Intermediate



As shown in the mechanism (Scheme 1.16; catalytic cycle), the NHC reacts with an enal **62** to form the homoenolate intermediate **65**. The key to success of these reactions are the use of catalytic amount of mild organic base. If the conjugate acid of the catalytic base, generated by deprotonation of the azolium salt, is acidic enough to protonate the conjugated Breslow intermediate at the β-position, the formation of enolate equivalent **67** occurs. The success of the reactions is therefore determined by the reactive intermediates and the protonation step. A [4+2] cycloaddition between **63** and the enolate **67** generates the alkoxide **68**, which releases free NHC to furnish **64**.

Subsequently, the same group reported the generation of enolate intermediate **74** from α-chloro aldehydes **69** for highly enantioselective inverse-electron demand Diels-Alder reactions with enones **70** to give enantiopure dihydropyranone product **71**.[33] Aromatic and aliphatic α-chloro aldehydes when treated with enones furnished the desired dihydropyranones products **71** under mild reaction conditions (Scheme 1.17). The reaction proceeds with low catalyst loading of NHC precursor **43** and provides the dihydropyranones **71** in good yield and excellent diastereo- and enantio-selectivity.

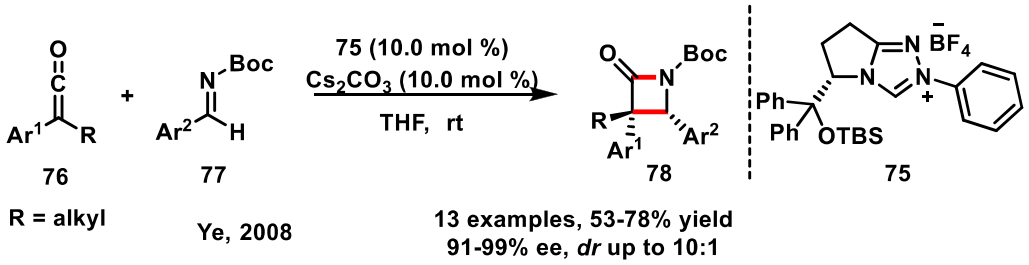
Scheme 1.17: Diels-Alder Reaction of α-Chloro aldehydes with Enones



In 2008, Ye and co-workers demonstrated the NHC-catalyzed Staudinger reaction of ketenes with *N*-benzyloxycarbonyl, or *N*-*tert*-butoxycarbonyl imines (Scheme 1.18).[34] Addition of the chiral NHC generated from **75** adds with ketenes **76** to form the enolate intermediate, which undergoes a formal [2+2] cycloaddition reaction with imines **77** to form the corresponding *cis*-β-lactams **78**. A wide variety of ketenes and imines reacted

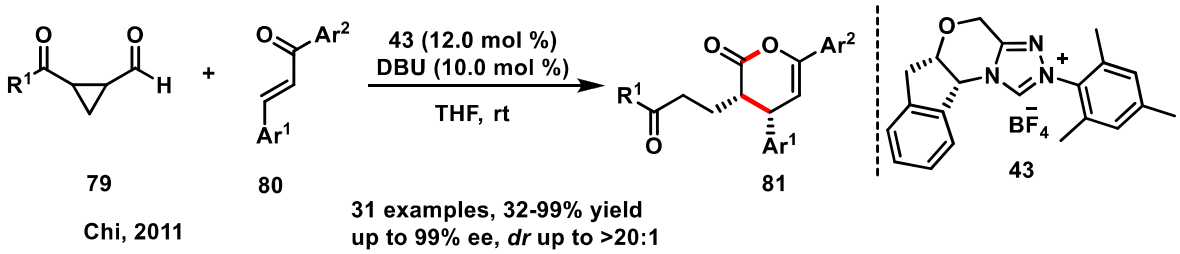
smoothly to afford corresponding β-lactams in good yields with high diastereoselectivities and excellent enantioselectivities.

Scheme 1.18: Staudinger Reaction of Ketenes with Imines



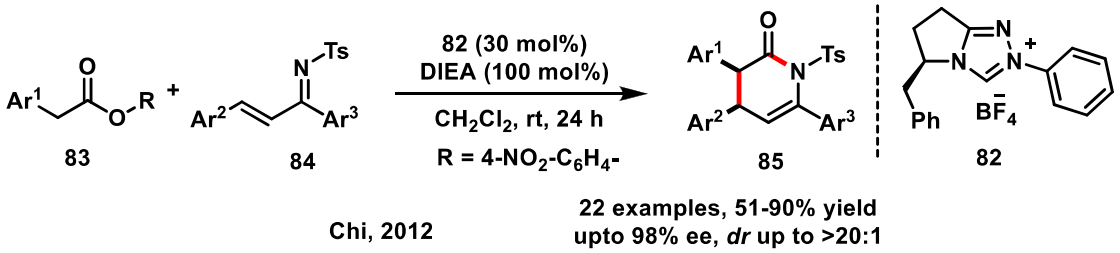
Chi and co-workers described the enantioselective synthesis of dihydropyranones via formal hetero Diels-Alder reactions of formyl cyclopropanes **79** and chalcones **80** (Scheme 1.19). In this work, the NHC-bound enolate intermediate generated from formyl cyclopropane was intercepted with chalcones. The dihydropyranone products **81** can easily be transformed to highly substituted cyclohexanes in good yields and excellent stereoselectivities.[35]

Scheme 1.19: Diels-Alder Reaction of Formylcyclopropanes with Chalcones



Further, they reported the activation of the carboxylic esters to generate the enolate intermediate (Scheme 1.20).[36] The catalytically generated arylacetic ester enolates from **83** using NHC precursor **82** undergo enantioselective inverse electron demand hetero Diels-Alder reactions with α,β-unsaturated imines **84** to form the desired dihydropyridinone derivatives **85** with good yield and moderate to good enantioselectivity.

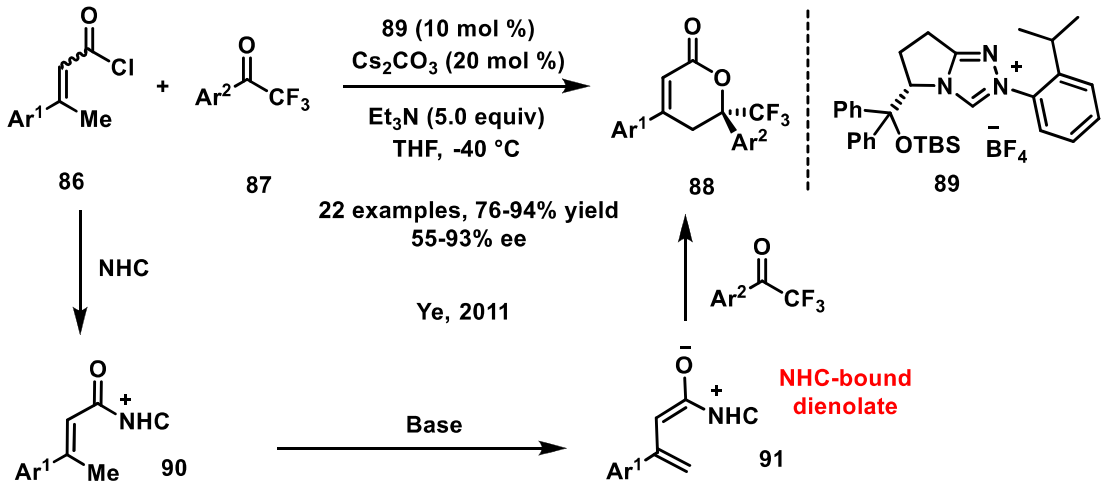
Scheme 1.20: NHC-Catalyzed Generation of Enolate Intermediate form Carboxylate Esters



1.3.4: NHC-Catalyzed Reaction using Dienolate Intermediate (iv)

A recent development in NHC-organocatalysis is the NHC-bound dienolates, which play a vital role in the construction of six-membered heterocycles and carbocycles via [4+2] cycloaddition reactions. In 2011, Ye and co-workers developed the catalytically generated NHC-bound dienolates **91** from unsaturated acylchlorides **86** (Scheme 1.21).[37] Interception of these intermediates with trifluoromethyl ketones **87** afforded the enantioselective synthesis of trifluoromethyl substituted δ-lactones **88** in good yields with high enantioselectivity. Best results were obtained with NHC generated from **89** and catalytic amounts of Cs_2CO_3 in excess Et_3N. The reactions are found to be quite general with other activated ketones such as isatins for the enantioselective synthesis of spirocyclic oxindole-δ-lactones.

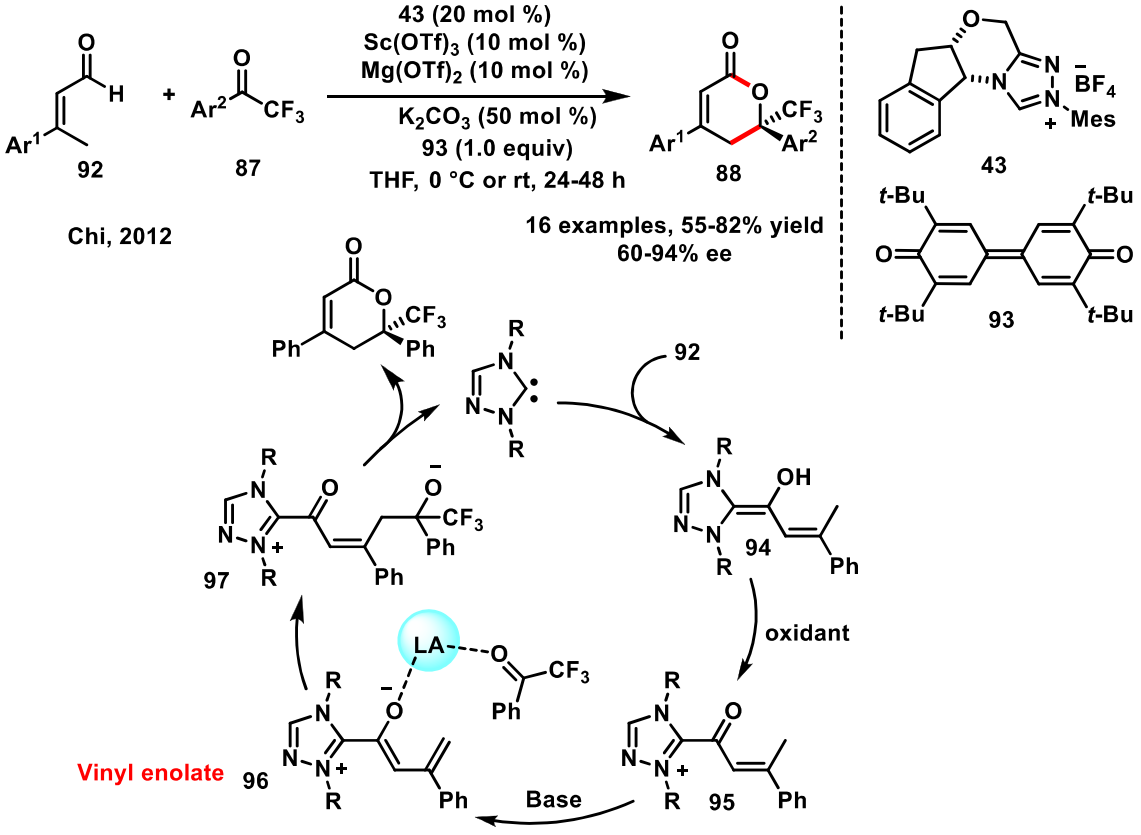
Scheme 1.21: Generation of NHC-bound Vinylenolates from Unsaturated Acylchlorides



Subsequently, Chi and co-workers reported the oxidative NHC-catalyzed [4 + 2] cycloaddition of β,β′-disubstituted enals **92** with trifluoromethyl ketones **87** (Scheme 1.22).[38] The dienolate intermediate **96** was generated under oxidative NHC-catalysis. Notably, introduction of an extra substituent at β-carbon of the enal suppressed the generally observed homoenolate reactivity in NHC-mediated enal reactions. The reaction affords a very broad substrate scope with the variation of both the enals and trifluoromethyl ketones. In all the cases, the desired lactones are obtained in moderate to good yields and high enantioselectivity. The high selectivity is attained with the carbene generated from the chiral triazolium precatalyst **43** in presence of Sc/Mg-based Lewis acid co-catalyst.

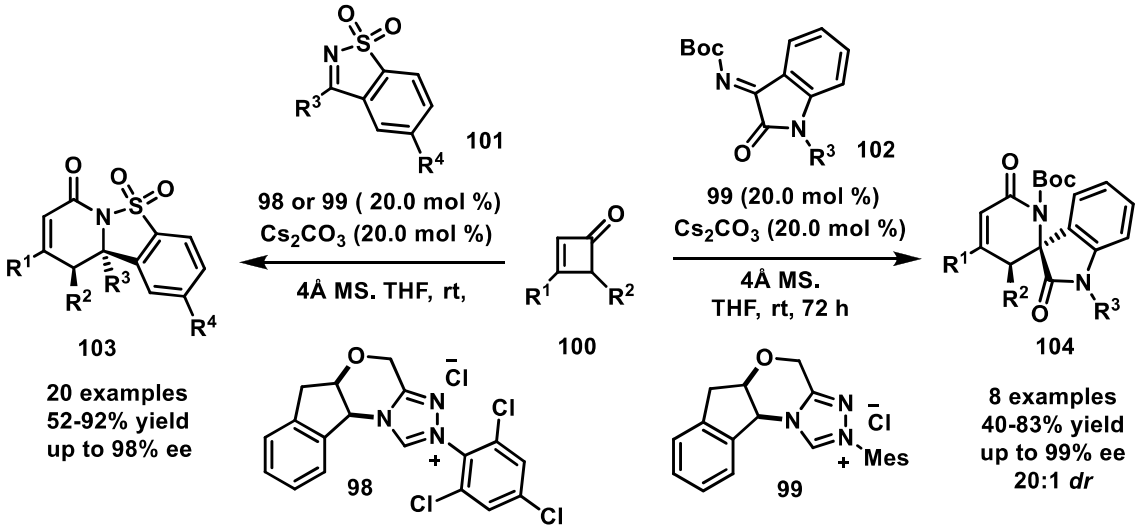
The proposed mechanism involves the 1,2-addition of the carbene to α,β-unsaturated aldehyde **92** followed by proton transfer to afford the extended Breslow intermediate **94**. Oxidation of **94** with oxidant **93** generates the α,β-unsaturated acylazolium intermediate **95**. γ-deprotonation of α,β-unsaturated acylazolium **95** forms the key dienolate intermediate **96**. Nucleophilic addition of dienolate **96** to the trifluoromethyl ketone leads to the product dihydropyranone **88** and regenerates the NHC catalyst.

Scheme 1.22: Generation of NHC-bound Vinylenolates from Unsaturated Aldehydes



Interestingly, cyclobutenones **100** were aslo used to generate the NHC-bound dienolate (Scheme 1.23).[39] The addition of NHC generated from the salt **98/99** to cyclobutenones **100** initiate a C-C single bond cleavage, which is the key step to generate the NHC-bound dienolate intermediate. The interception of this intermediate with sulfonyl imines **101** afforded cyclic lactams **103** in 52-92% yield with good enantioselectivities (up to 98%). With the same optimized conditions, isatin imines gave spirolactams **104** in moderate to good yields (40-83%) with good selectivities (up to 20:1 *dr*).

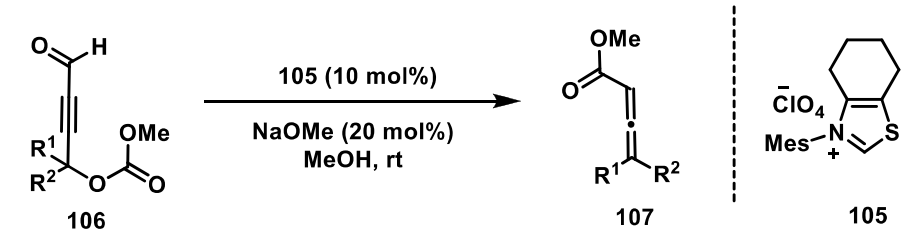
Scheme 1.23: Generation of NHC-bound Vinylenolates from Cyclobutenones



1.3.5: NHC-Catalyzed Reaction using Allenoate Intermediate (v)

Sun and co-workers carried out the isomerization of ynals to allenoates by an NHC-catalyzed internal redox reaction (Scheme 1.24).[40] Alkynyl aldehydes **106** containing a methyl carbonate group at the γ-position, which acts as a leaving group, are used as the substrates, and the thiazolium salt **105** is required for optimal reactivity. The reaction worked well with the variation of R^1 and R^2 with aryl and alkyl groups and affords good-to-excellent yields of the product allenoates **107**. Preliminary experiments demonstrate that the enantioselective variant can also be achieved. A pilot experiment with the use of the chiral NHC precursor **49** provides low enantioselectivity (30% ee).

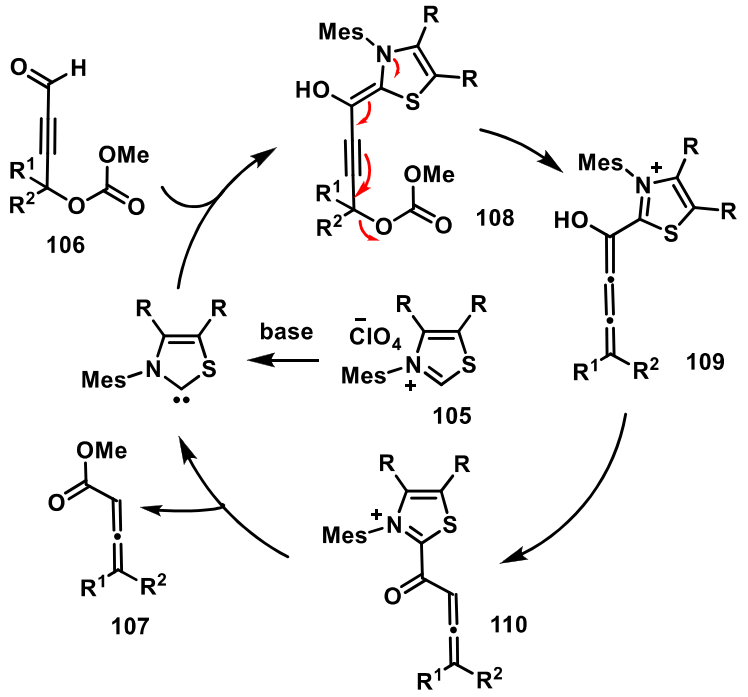
Scheme 1.24: NHC-Catalyzed Isomerization of Ynals to Allenoates



Sun, 2012

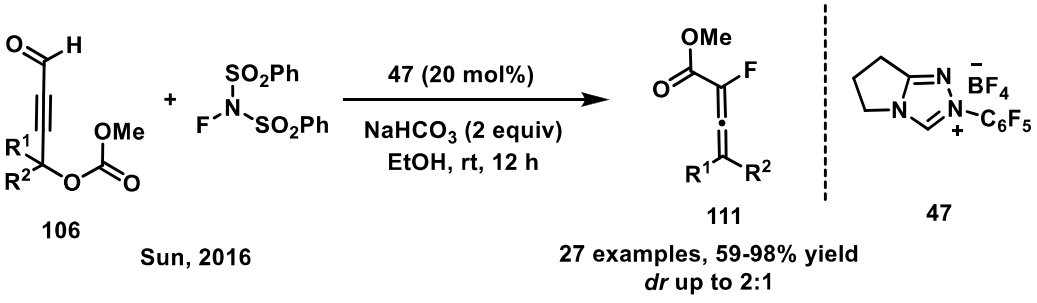
Mechanistically, the reaction proceeds through the generation of the Breslow intermediate **108** (formed by nucleophilic addition of carbene on to the ynal). After leaving the methyl carbonate group a cumulenol intermediate **109** formed (Scheme 1.25). The cumulenol intermediate **109** then tautomerizes to allenoyl azolium **110**, which is finally intercepted by methanol to form the desired product **107**.

Scheme 1.25: Catalytic Cycle for NHC-Catalyzed Isomerization of Ynals to Allenoates



Recently, Wang and co-workers reported NHC-catalyzed synthesis of α-fluoroallenoate (Scheme 1.26).[41] Alkynyl aldehydes **106** are used as the substrates and the NFSI is used as a fluorinating source. The reaction proceeds via a similar cumulenol intermediate **109**, which instead of tautomerization undergoes nucleophilic addition to NFSI and generates the desired α-fluoroallenoate **111**, with moderate to good yield and with excellent chemoselectivity.

Scheme 1.26: NHC-Catalyzed α-Fluorination of Alkynyl Aldehydes



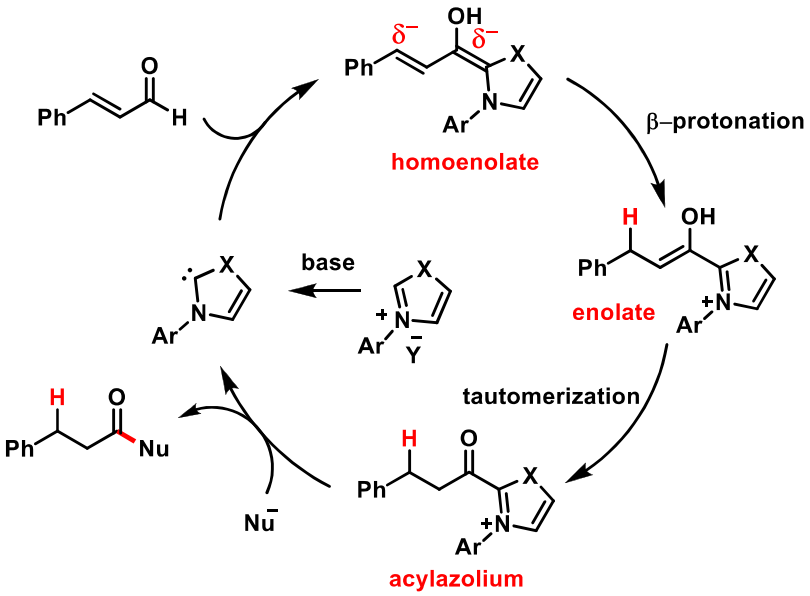
1.3.6: NHC-Catalyzed Reaction using *Deoxy*-Breslow Intermediate (vi)

The NHC-catalyzed generation of *deoxy*-Breslow intermediates and their subsequent reactivity are described in details in Chapter 4.

1.3.7: NHC-Catalyzed Reaction using Acylazolium Intermediate (vii)

In addition to the *umpolung* chemistry, NHCs have also been used in a variety of non-*umpolung* processes. Notably, NHC-bound acylazolium, α,β-unsaturated acylazolium, and azolium enolate intermediates have attracted considerable attention over the past decade. NHCs can generate acylazolium intermediates from α,β-unsaturated aldehydes (Scheme 1.27).[42] Mechanistically, the reaction proceeds in a similar manner to the enolate intermediates. In presence of extra proton source, the enolate intermediate undergoes tautomerization to form the acylazolium intermediate. The success of the reactions is therefore determined by the reactive intermediates and the protonation steps. This acylazolium is essentially an activated carboxylate. Addition of nucleophiles to these activated carboxylates proceeds smoothly. Addition of alcohols forms esters, thiols forms thioesters,[43] amines in presence of additive forms amides,[44] water forms carboxylic acid[45] and azides forms carbomyl azides or oxazolidinones.[46] Intramolecular redox esterifications of *ortho*-hydroxy cinnamaldehydes have been demonstrated to yield lactones.[47] Other aldehydes such as α-chloro aldehydes,[48] formyl cyclopropanes,[43] epoxy aldehydes,[49] aziridinyl aldehydes[50] have also been used for the acylazolium synthesis. Acylazolium can also be generated from simple aldehydes under oxidative conditions[51] or from ketenes.[52]

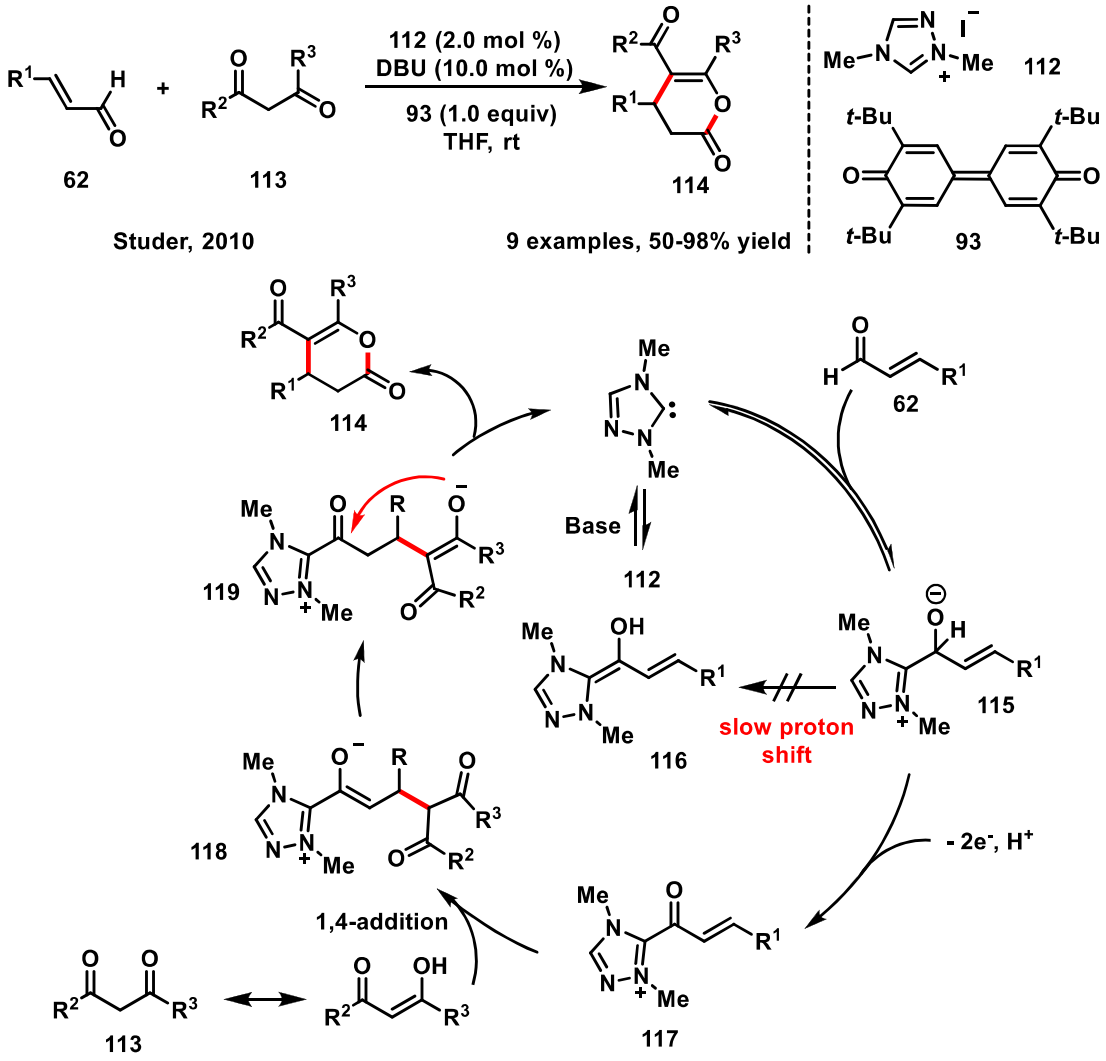
Scheme 1.27: NHC-Catalyzed Generation of Acylazolium Intermediate



1.3.8: NHC-Catalyzed Reaction using α,β-Unsaturated Acylazolium Intermediate (viii)

In 2010, Studer and co-workers reported the generation of catalytically active α,β-unsaturated acylazolium intermediates **117** from enals **62** and its subsequent interception with 1,3-dicarbonyl compounds to form the functionalized dihydropyranones **114** (Scheme 1.28).[53] Mechanistically, the reaction proceeds through the oxidation of in situ generated tetrahedral intermediate **115** to the corresponding α,β-unsaturated acylazolium species **117** in presence of mild organic oxidant **93.** Enals **62** with phenyl ring having electron-releasing and -withdrawing groups, heteroaryl, alkyl groups are well tolerated whereas 1,3-dicarbonyl compounds (**113**) such as β-diketones and β-keto esters were found to be efficient to afford the desired products in moderate to good yield.

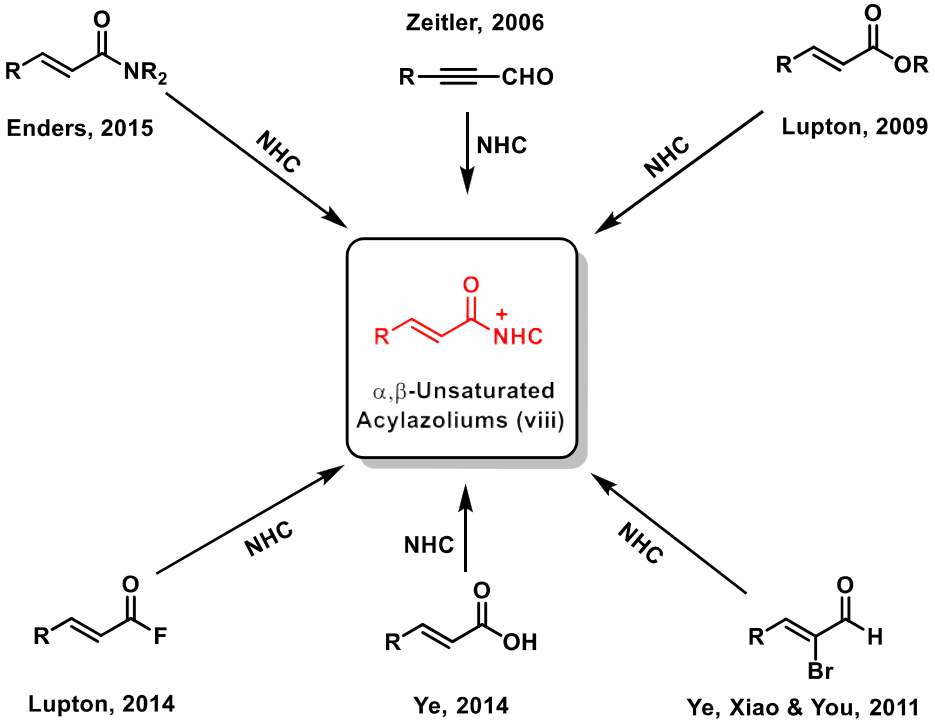
Scheme 1.28: NHC-Catalyzed Generation of α,β-Unsaturated Acylazoliums from Enals



Furthermore, they have performed experimental and DFT studies on mode of addition of nucleophiles to α,β-unsaturated acylazolium intermediate and found that 1,4-addition is more preferable than 1,2-addition.[54] They also proposed that under optimal conditions, this oxidation is faster than the proton transfer that would lead to the extended Breslow intermediate **116**. Later, You and Xiao groups independently reported the enantioselective reaction of enals with 1,3-dicarbonyl compounds under oxidative conditions to form the enantiorich dihydropyranones.[55]

Herein, few common routes to access NHC-bound α,β-unsaturated acylazolium intermediate has been presented. (a) Reaction of ynals with NHCs[56] (b) reaction of α,β-unsaturated esters with NHCs[57] (c) reaction of 2-bromoenals with NHCs[58] (d) from α,β-unsaturated acids with NHCs[59] (e)) reaction of α,β-unsaturated acyl fluorides with NHCs[60] (f) from α,β-unsaturated amides with NHCs[61] (Scheme 1.29).

Scheme 1.29: Access of α,β-Unsaturated Acylazoliums

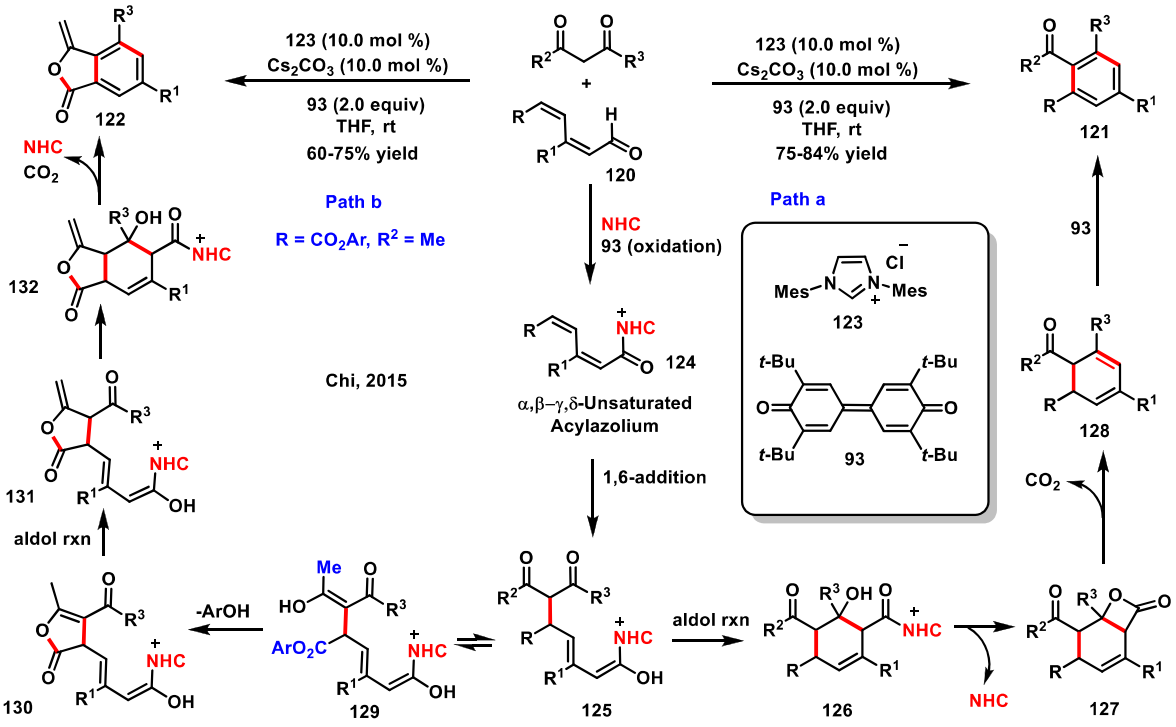


1.3.9: NHC-Catalyzed Reaction using α,β-γ,δ-Unsaturated Acylazolium Intermediate (ix)

In 2015, Chi and co-workers reported the activation of the δ-carbon of α,β-γ,δ-diunsaturated aldehydes **120** (Scheme 1.30).[62] The chemoselectivity issue between the β- and δ-carbons was addressed by introducing a substituent to block the reactivity of the β-

carbon. This δ-LUMO activated enals under oxidative conditions reacts with 1,3-carbonyls in formal [4+2] pathway to afford multi-substituted arenes **121**. The proposed catalytic cycle involves oxidative conversion of unsaturated aldehyde **120** to unsaturated acylazolium intermediate **124**. The 1,6-addition of 1,3-diketone to α,β-γ,δ-diunsaturated acyl azolium **124** leads to enol intermediate **125**, and a subsequent aldol reaction and lactonization affords bicyclic adduct **127**, with the regeneration of NHC catalyst. This can then undergo decarboxylation followed by spontaneous oxidative aromatization in presence of **93** to provide the multi-substituted benzene product **121**. Whereas, when R is a reactive aryl ester unit (Scheme 1.30, path b), intramolecular transesterification of enol intermediate generates **130**. Followed by isomerization (**130** to **131**) yields **131**, this can undergo further transformations to form the 3-ylidenephthalide product **122** via a process similar to the conversion of **127** to **121** (path a).

Scheme 1.30: NHC-Catalyzed Generation of α,β-γ,δ-Unsaturated Acylazolium Intermediate

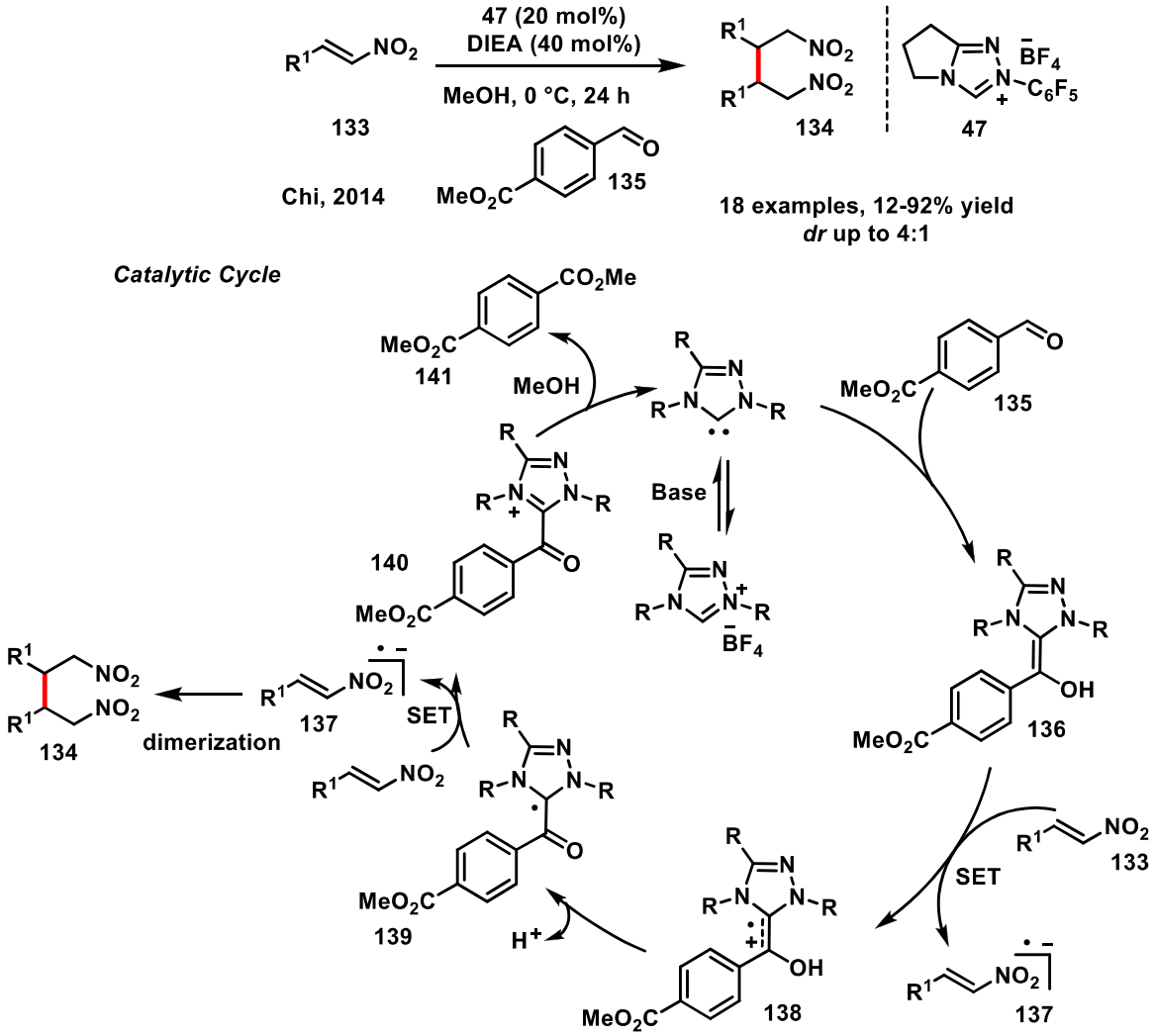


1.3.10: NHC-Catalyzed Single Electron Transfer Reaction (Intermediate x)

Recently, Chi and co-workers developed a NHC-catalyzed single electron strategy for the dimerization of nitroalkenes (Scheme 1.31), wherein it is proposed that the nitroalkene acts as a single-electron oxidant to generate radical anion **137** and radical cation

138.[63] Aryl aldehyde **135** is required as the electron donor in this reaction. The intermediate **138** undergoes a deprotonation to generate radical acylazolium intermetiate **139**, which in presence of nitro olefin releases another single electron to form the acylazolium intermediate **140**. The nitroalkene-derived radical anion couples with another equivalent of nitroalkene to generate the desired product **134**. This proposed mechanism is supported by EPR analysis of the nitroalkene centered radical anion. Electron-rich and electron-poor aryl and aliphatic nitroalkenes undergo the dimerization with moderate to good yields and *dr* ranging from 2:1 to 9:1. β,β-Disubstituted nitroalkenes also participate in this reaction.

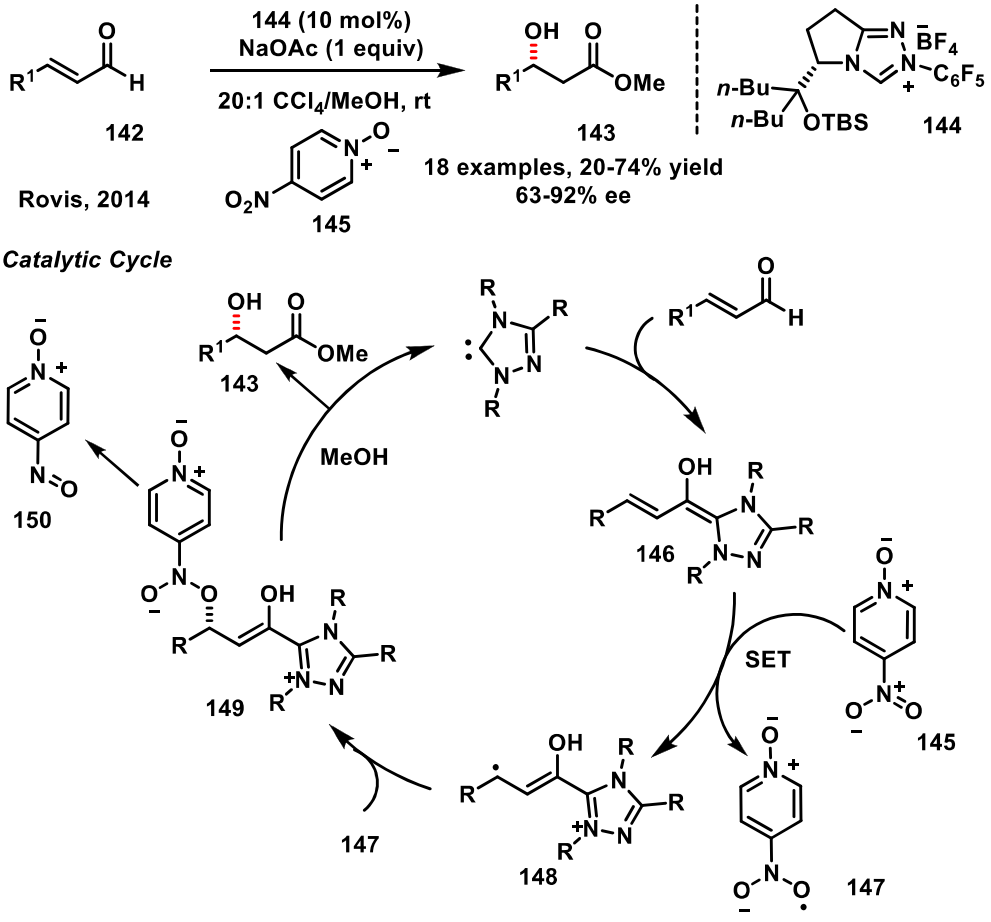
Scheme 1.31: NHC-Catalyzed Single Electron Transfer Reaction, Dimerization of Nitroalkenes.



1.3.11: NHC-Catalyzed Single Electron Transfer Reaction (Intermediate xi)

The β-hydroxylation of enals using the concept of single-electron oxidation of the Breslow intermediate was reported by White and Rovis (Scheme 1.32).[64] The electron deficient nitroarene **145** are used as the oxidant. β-Hydroxylated products **143** are isolated in moderate to good yields, with good enantioselectivity. Aliphatic enals provide the desired product in good yields, while aryl enals afford the desired product with lower yields. The reaction proceeds via the transfer of a single electron from the Breslow intermediate **146** to the electron-deficient nitroarene **145** to generate radical cation **148** and nitroarene centered radical anion **147**. This oxygen centered radical **147** combined at the β-position of the enal to generate intermediate **149**, which releases the nitroso compound **150** and affords acylazolium, which in situ trapped with methanol to provide the β-hydroxy ester **143** and regenerate the carbene catalyst. Isolation of nitroso derivatives **150** from the reaction medium indicates the nitro group as the source of oxygen in this reaction.

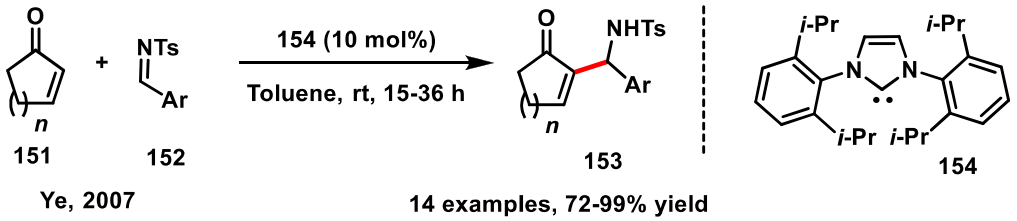
Scheme 1.32: NHC-Catalyzed β-Hydroxylation of Enals



1.3.12: Miscellaneous Reactions (xii)

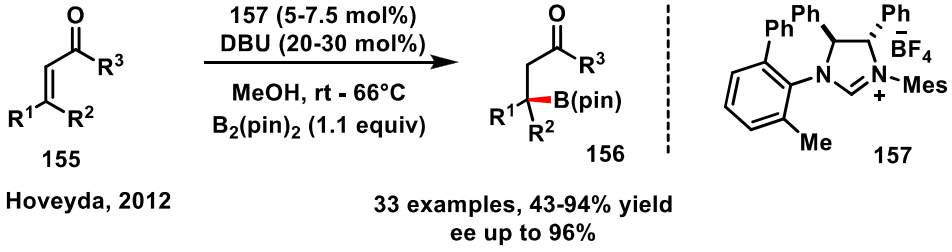
Ye and co-workers reported the use of NHCs as a Lewis base to promote the Morita−Baylis−Hillman (MBH) type reaction (Scheme 1.33).[65a] Intermolecular coupling of cyclic enones **151** with aryl N-tosyl imines **152** affords the corresponding MBH adduct **153** in presence of the NHC **154.** The reaction furnished the desired MBH adducts with good to excellent yields. The enantioselective variant was also reported, coupling cyclopent-2-enone with N-tosylphenylmethanimine in up to 44% ee.[65b]

Scheme 1.33: NHC-Catalyzed Morita−Baylis−Hillman Reaction



In 2009, Hoveyda and co-workers demonstrated the NHC-catalyzed conjugate addition of boranes to enones to form the β-boronsubstituted ketones.[66a] A wide variety of Michael acceptors, including enones, enals, enoates, and α,β-unsaturated amides, are tolerated in the reaction. Later, they developed the enantioselective variant of the reaction in presence of a chiral imidazolium precatalyst **157**. Yields in this reaction range from 43 to 94% and enantioselectivity ranges from 42 to 96% ee (Scheme 1.34).[66b]

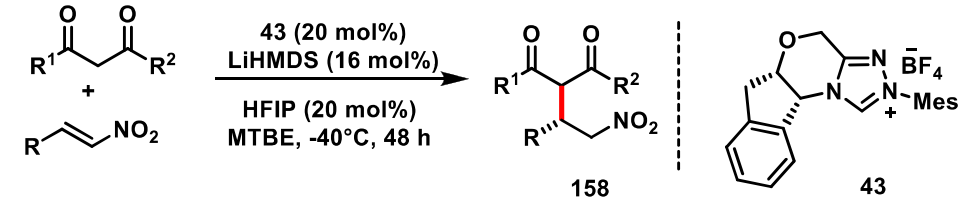
Scheme 1.34: NHC-Catalyzed Conjugate Addition of Boranes to Eenones

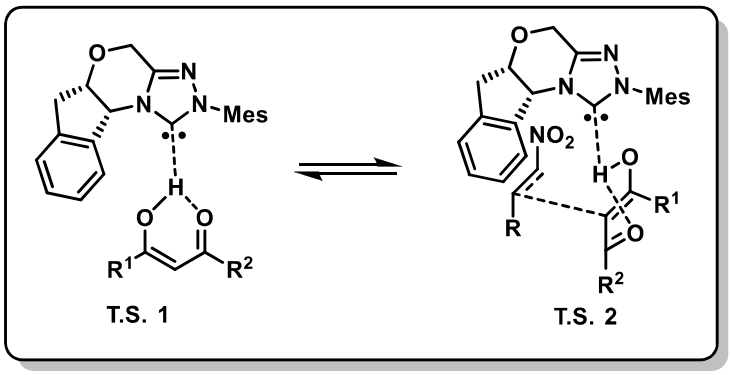


Chen and Huang reported the enantioselective conjugate addition of 1,3-dicarbonyl compounds to nitrostyrene derivatives (Scheme 1.35).[67] This reaction proceeds via complexation between the free NHC generated from the triazolium salt **43** and the cyclic enol form of the 1,3-dicarbonyl (T.S. 1). The activated complex reacts with nitrostyrene via an ene-type mechanism (T.S. 2) to afford the desired product **158**. The high stereoselectivity of this reaction comes from the strong co-ordiantion between free carbene,

olefins and 1,3-dicarbonyls (T.S. 2). A wide variety of electron-rich and electron-deficient nitrostyrenes are well tolerated as Michael acceptors. Symmetrical and unsymmetrical aliphatic and aryl 1,3-diketones including 1,3-dicarbonyls and β-/α-keto esters worked well in the reaction. Due to the high basic reaction conditions, products epimerize easily and the observed diastereoselectivity is low.

Scheme 1.35: NHC-Catalyzed Conjugate Addition of 1,3-Dicarbonyls to Nitro-Olefines





1.4. Conclusion and Focal Theme of the Present Work

This chapter has illustrated the wide variety of NHC-catalyzed carbon-carbon and carbon-heteroatom bond forming reactions. From the above discussion, it is clear that the successes of NHC-catalysis are attributed to the right choice of the NHC catalyst, coupling partners and reaction conditions.

We have recently uncovered the NHC-catalyzed intermolecular Stetter reaction of aldehydes with α,β-unsaturated sulfones, which allows the atom-economic and selective formation of γ-keto sulfones in good yields. Key to the success of this unique transition-metal-free carbon-carbon bond-forming reaction is the right choice of the NHC precursor and base. The reaction tolerates a broad range of different aldehydes. Investigations of these reactions are documented in the second chapter of the thesis.

In the third chapter, we investigated the NHC-catalyzed annulation of enals with 2′-hydroxy chalcones to afford cyclopentane-fused coumarin derivatives with an excellent level of diastereocontrol. The ease of δ-lactonization over the β-lactonization appears to be the key feature of this transformations. The reaction is compatible with wide range of enals as well as 2'-hydroxy chalcones. Preliminary mechanistic studies has been preformed to shed light on the mechanism of this reaction.

Moreover, we have studied the reaction of NHCs with chalcones. The addition of NHCs to chalcones generates the *deoxy*-Breslow intermediates in their oxidized form. The reaction proceeds via an alkoxide intermediate which undergoes an unexpected oxidation in presence of air. Alternatively, use of Brønsted acid in the absence of air leads to the formation a tetrahedral intermediate which upon treatment with base in open air generated the oxidized *deoxy*-Breslow intermediate. A series of experiments have been performed to establish the mechanism of this reaction. In addition, a catalyst-free intramolecular Rauhut-Currier type reaction was also developed during the investigation of the reaction mechanism. Investigations of these reactions are described in details in chapter 4 of this thesis.

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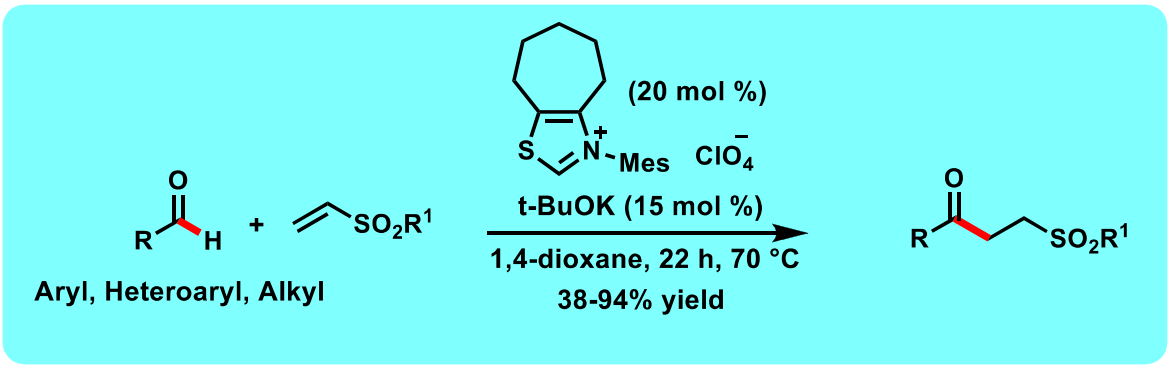
Chapter 2

NHC-Organocatalyzed Intermolecular Stetter Reaction onto Vinyl Sulfones

In this chapter, we have demonstrated the N-heterocyclic carbene (NHC)-organocatalyzed intermolecular Stetter reaction of aldehydes with α,β-unsaturated sulfones resulting in the selective synthesis of γ-keto sulfones with moderate to good yields. Key to the success for this unique transition-metal-free carbon-carbon bond-forming reaction is the right choice of the NHC precursor and the base. The reaction is compatible with respect a wide variety of aldehydes as well as unsaturated sufones. Additionally, we have performed mechanistic studies to set insight into the key intermediate and reaction pathways of this intermolecular Stetter reaction.

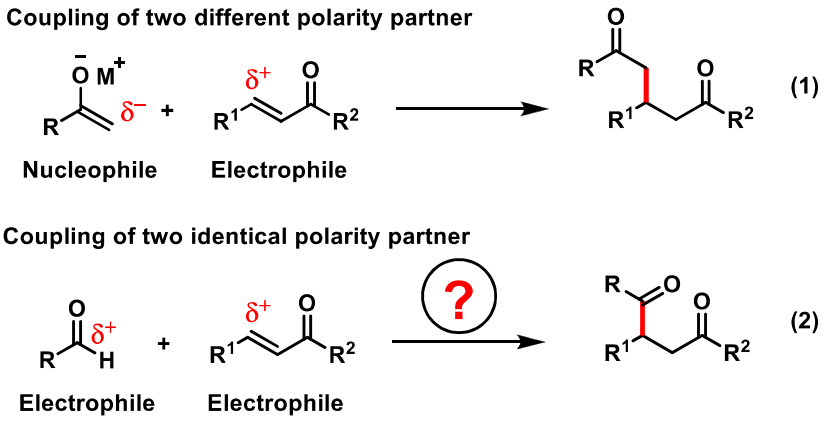


Org. Lett. **2012**, *14*, 2830-2833

2.1. Introduction

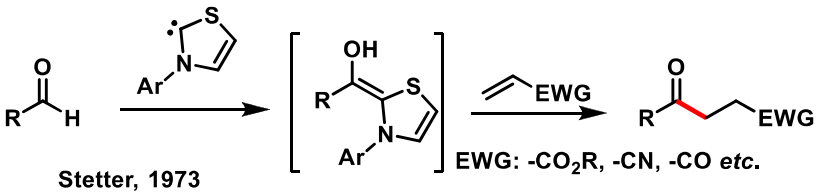
The reactivity in most of the chemical transformations arises due to the polar nature of the substrates where bonds are created from nucleophilic and electrophilic sites.[1] For instance, Michael addition also involves the coupling of a nucleophile (donor) with an electrophile (acceptor, activated double or triple bond). The conjugate addition of an enolate to a Michael acceptor results in the formation of a 1,5-bifunctional compound (Scheme 2.1; Eq. 1). During the last century, this area has been developed substantially. However, the synthesis of a 1,4-bifunctional compound remained challenging because it needs the coupling of two electrophilic partners (Scheme 2.1; Eq. 2).

Scheme 2.1: Michael Reaction



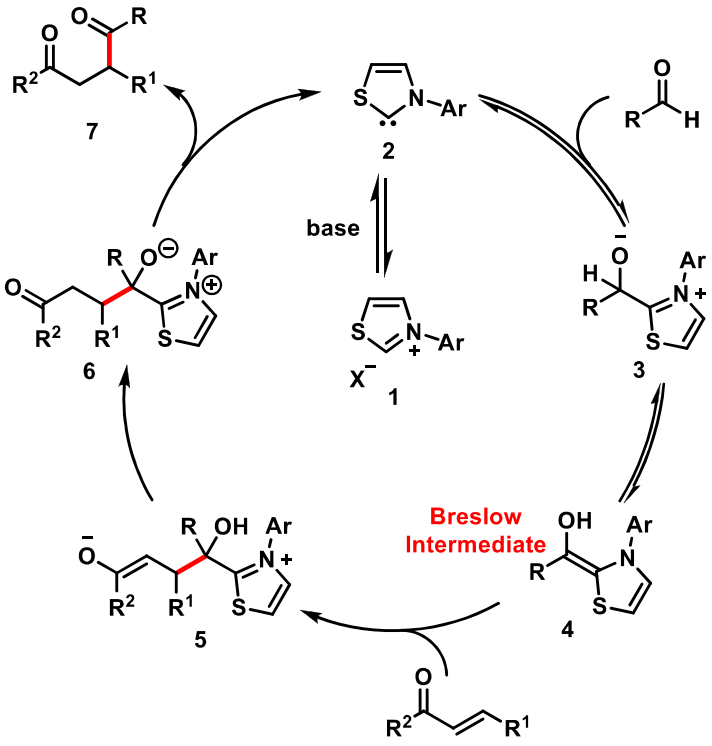
In 1973, Stetter and co-workers demonstrated the thiazolium salt catalyzed umpolung of aldehydes followed by their interception with α,β-unsaturated Michael acceptors.[2] It is established that aldehydes can add to a number of Michael acceptors *i.e.* α,β-unsaturated esters, nitriles, or ketones in the presence of thiazolium catalysts to form highly valuable 1,4-bifuntionalized products (Scheme 2.2). Now it is known that these reactions are catalyzed by N-heterocyclic carbene (NHCs) and proceed via the formation of nucleophilic acyl anion equivalents (Breslow intermediates), which can react with various activated, polarized C-C double bonds.[3]

Scheme 2.2: Stetter Reaction



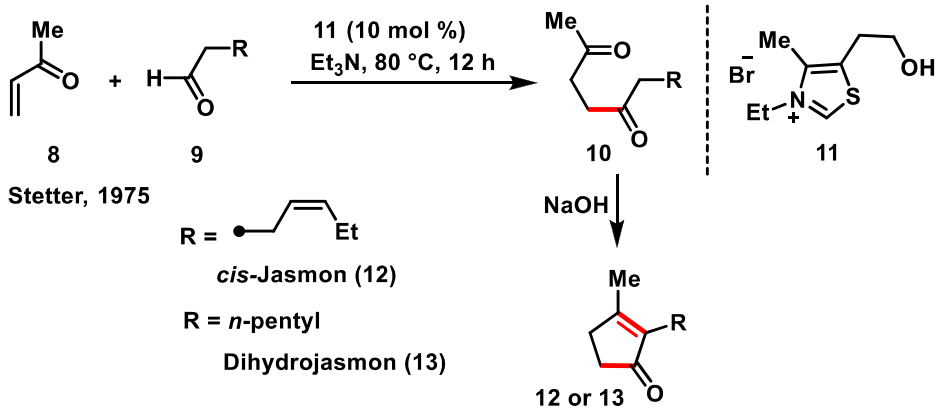
According to the proposed mechanism, the in situ generated NHC **2** undergoes the nucleophilic attack to the aldehyde, leading to the tetrahedral intermediate **3**, which undergoes proton transfer to provide the nucleophilic Breslow intermediate **4** in a reversible process. This acyl anion equivalent **4** reacts as a nucleophile with Michael acceptors in a irreversible process to furnish the alkoxide **5** followed by a proton transfer to give **6**, which releases NHC **2** and affords 1,4-bifunctional product **7** (Scheme 2.3).[4] Although a stepwise mechanism for the addition of Breslow intermediate to the Michael acceptor has been proposed, the possibility of Breslow intermediate addition to Michael acceptors in a concerted pathway is also possible.

Scheme 2.3: Catalytic Cycle of Stetter Reaction



The 1,4-diketones, in particular, are important synthons in the total synthesis of complex molecules. In 1975, Stetter and Kuhlmann applied NHC-organocatalysis for the synthesis of *cis*-jasmon (**12**) and dihydrojasmon (**13**).[5] The carbene generated from the thiazolium salt **11** was used for the Stetter reaction between methyl vinyl ketone and the aliphatic aldehyde, which was followed by aldol condensation reaction to afford the natural products **12** and **13** (Scheme 2.4). Moreover, the 1,4-diketones are important precursors for the synthesis of valuable heterocycles such as furans, pyrroles, and thiophenes.[6]

Scheme 2.4: Application of Stetter Reaction in Total Synthesis

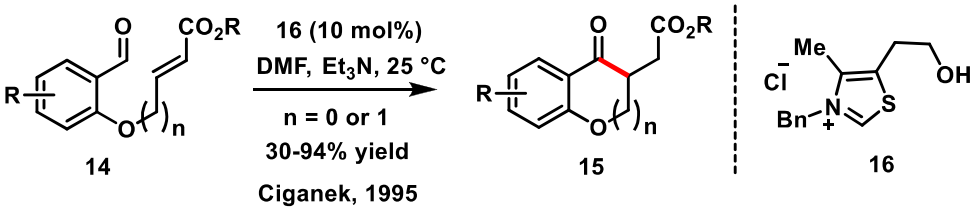


In this chapter, NHC-catalyzed intermolecular Stetter recation of aldehydes and α,β-unsaturated sulfone has been presented. The reaction proceeds under mild conditions to furnish the γ-keto sulfones in moderate to good yield. Before discussing the results, a brief overview of the recent developments on the intramolecular and intermolecular Stetter reaction is presented in the following sections.

2.2. Intramolecular Stetter Reaction

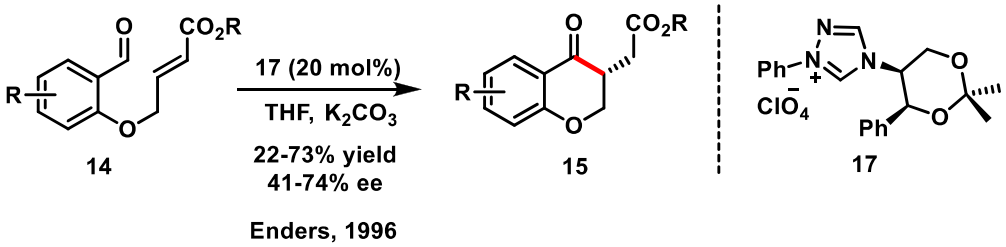
In 1995, Ciganek developed the first intramolecular Stetter reaction.[7] The NHC derived from the thiazolium salt **16** catalyzed the intramolecular cyclization of 2-formylaryloxy crotonates **14** to afford benzannulated pyranones (Scheme 2.5, n = 1). Interestingly, the reaction of 2-formyl aryloxyacrylates (n = 0) took place in the absence of base under reflux conditions to deliver the furanone derivatives in moderate to good yields. Subsequently, the formation of **15** from **14** under NHC-catalysis became a general process to examine the reactivity of newly developed carbene precursors.

Scheme 2.5: First Intramolecular Stetter Reaction by Ciganek



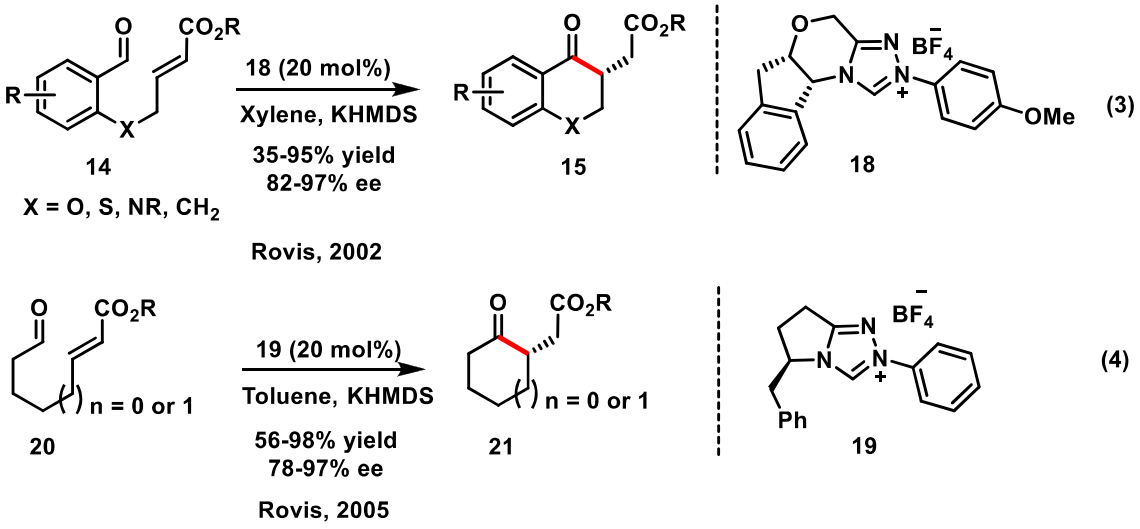
In an effort to impart stereoselectivity to the intramolecular Stetter reaction, Enders and co-workers developed the chiral triazolium salt **17** (Scheme 2.6).[8] Various 2-formylaryloxy crotonates **14** underwent NHC-catalyzed annulation reaction to furnish the desired chromanones in moderate yield and enantioselectivity.

Scheme 2.6: First Asymmetric Intramolecular Stetter Reaction by Enders et al.



Rovis and co-workers also undertook the challenge of inducing enantioselectivity in intramolecular Stetter reaction. They have developed an aminoindanol derived triazolium salt **18**, which significantly increased the selectivity of this reaction.[9] The reaction was well tolerated with various salicylaldehyde derivatives, as well as the variation of heteroatom linker was well tolerated to furnish the desired chromanones **15** with good yields and enantioselectivity (Scheme 2.7; Eq. 3). Furthermore, they have expanded the substrate scope with various types of Michael acceptors, such as vinylphosphonates, vinylphosphine oxides and alkylvinylphosphonates.[10] However, the reactivity was only limited to the aromatic aldehydes **14** due to their rigid conformational structure. Recently, they have developed a phenylalanine based triazolium salt **19**, which successfully catalyzed the aliphatic analogues **20**, to derive five- and six-membered carbocycles with good selectivity (Scheme 2.7; Eq. 4).[11]

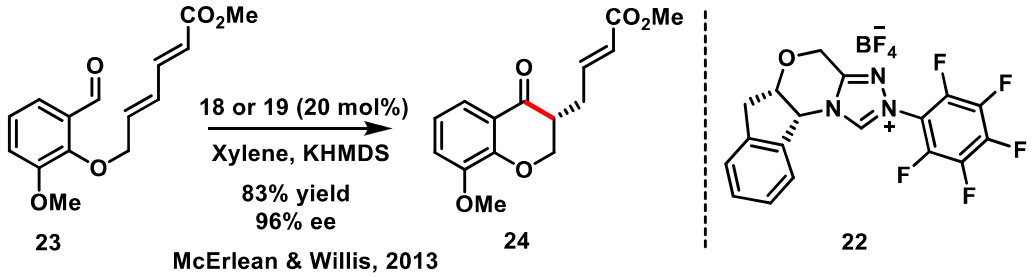
Scheme 2.7: Asymmetric Intramolecular Stetter Reaction by Rovis et al.



McErlean and Willis have further demonstrated the vinylogous version of the Stetter reaction.[12] The NHC-catalyzed intramolecular 1,6-addition of aldehyde **23** bearing a

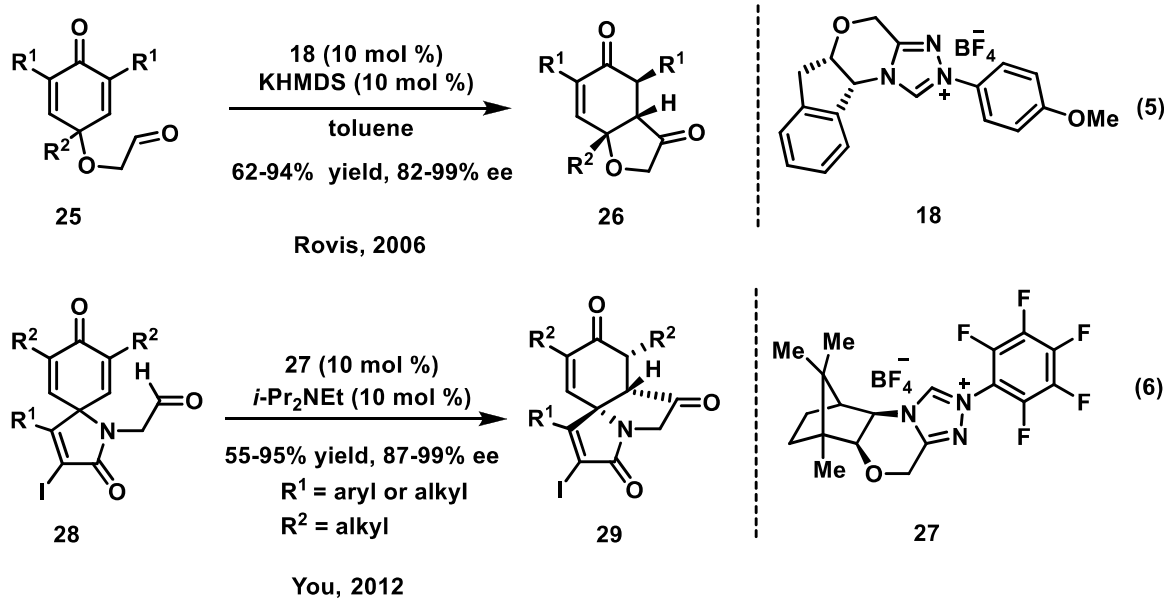
α,β,γ,δ-unsaturated carbonyl moiety afforded the desired product in 96% ee (Scheme 2.8).

Scheme 2.8: Intramolecular Stetter Reaction by McErlean and Willis.



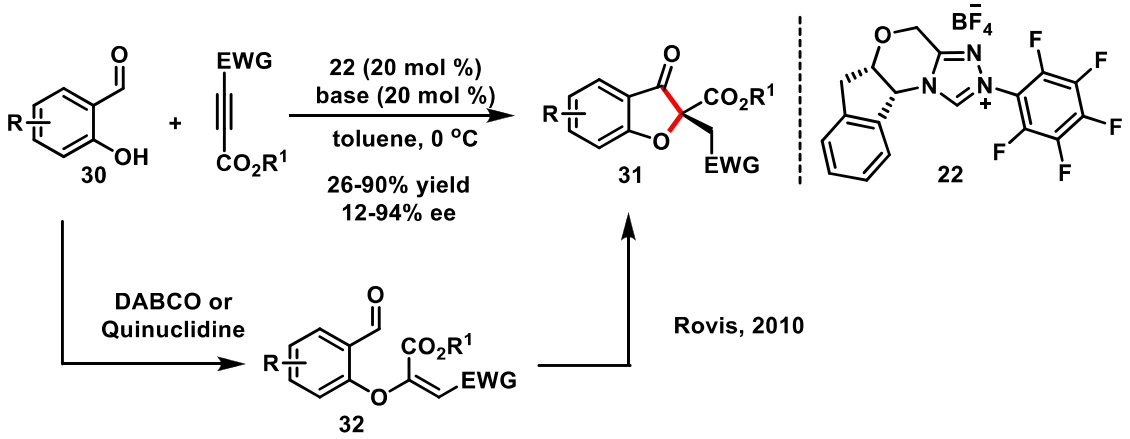
Rovis and Liu demonstrated the NHC-catalyzed desymmetrization of cyclohexadienones **25** via intramolecular Stetter reaction.[13] The carbene generated from the aminoindanol-derived chiral triazolium salt **18** catalyzed the reaction efficiently to furnish the hydrobenzofurans **26** with good enantioselectivity and diastereoselectivity (Scheme 2.8; Eq. 5). You and co-workers have developed a similar desymmetrization strategy for cyclohexadienone derivatives **28**.[14] The camphor-derived precatalyst **27** was found to be the best for this intramolecular Stetter reaction. The desymmetrization reaction proceeds to form a tricyclic carbocycles possessing three consecutive stereocenters with good yields and high ee values (Scheme 2.9; Eq. 6).

Scheme 2.9: Application of Intramolecular Stetter Reaction for Desymmetrization of Cyclohexadienone Derivatives.



Rovis and co-workers developed a one-pot sequential multicatalytic process, a base catalyzed oxa-Michael followed by NHC-catalyzed asymmetric intramolecular Stetter reaction between salicylaldehydes **30** and electrophilic alkynes (Scheme 2.10).[15] The reaction furnished the benzofuranone derivatives **31** with good yield and enantioselectivity.

Scheme 2.10: A Cascade Oxa-Michael/Intramolecular Stetter Reaction

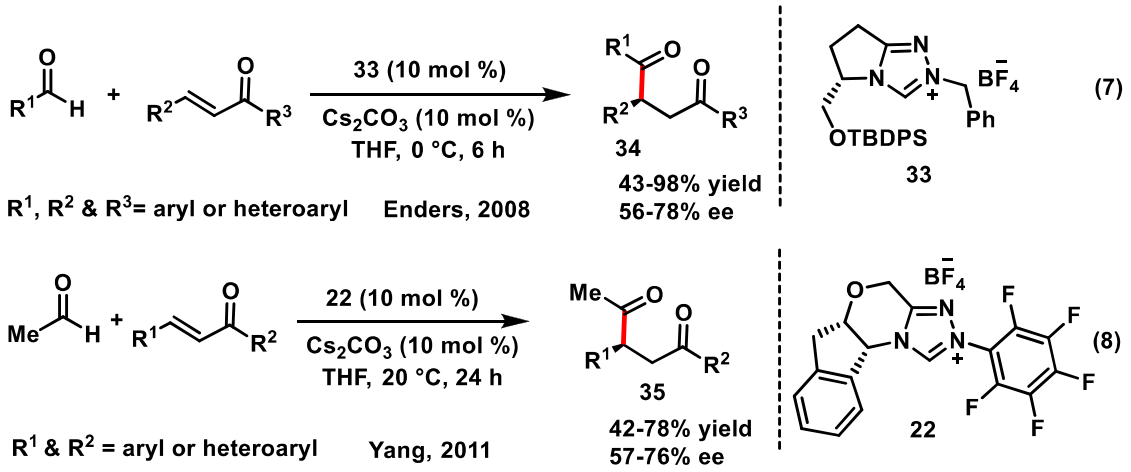


2.3. Intermolecular Stetter Reaction

Since the Stetter's own contribution in 1970's, a number of new coupling partners in Stetter reaction have been reported. Compared to the intramolecular Stetter reaction, the advancement on intermolecular Stetter is less due to the lower reactivity and selectivity. However, the recent developments on intermolecular Stetter reaction are mainly focused on the enantioselective transformations.

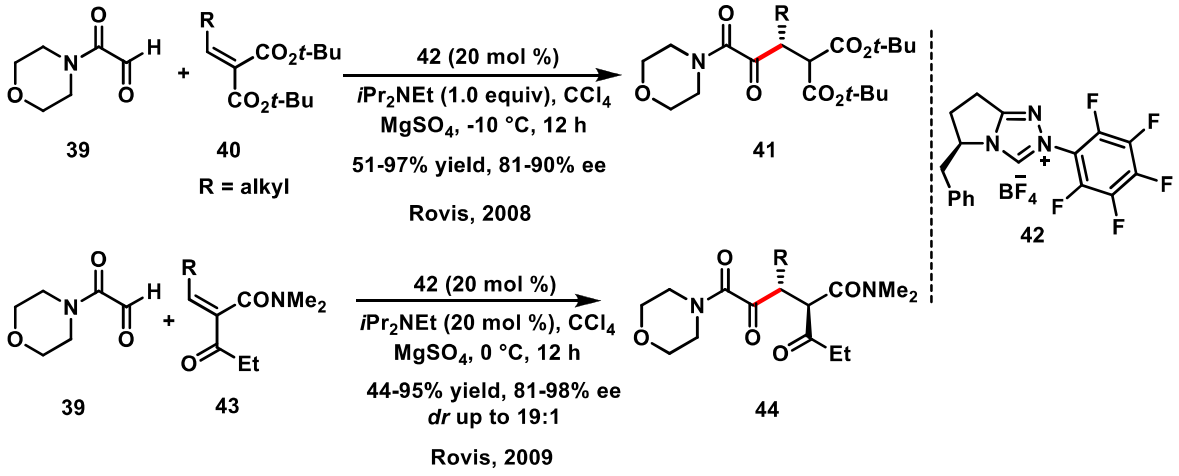
In 1989, Enders and co-workers reported the enantioselective intermolecular coupling of *n*-butanal with chalcone in presence of a chiral thiazolium precatalyst leading to the formation of the 1,4-diketone in low yield with 30% ee values.[16] Recently, they have developed a new carbene derived from the triazolium salt **33**, which catalyzed the intermolecular Stetter reaction of aryl aldehydes with chalcones affording the 1,4-diketones **34** in good yields and moderate to good enantioselectivity (Scheme 2.11; Eq. 7).[17] Subsequently, they have demonstrated the coupling of aldehydes with arylidene malonates using the newly derived carbene.[18] Recently, Yang and co-workers reported the generation of acyl anion equivalent from acetaldehyde, which undergoes intermolecular coupling with chalcones to form the desired 1,4-diketones **35** with moderate yield and enantioselectivity (Scheme 2.11; Eq. 8).[19]

Scheme 2.11: Asymmetric Intermolecular Stetter Reaction



Recently, Rovis and co-workers have made significant progress in the asymmetric intermoleculr Stetter Reaction. They have reported the NHC-catalyzed intermolecular coupling of morpholine-derived glyoxamide **39** and alkylidene malonate **40**.[20] The carbene generated from phenylalanine based triazolium salt **42** affords the desired Stetter product **41** in good yield with high enantioselectivity (Scheme 2.12). Subsequently, they have investigated the role of a α-substituation on the Michael acceptor using alkylidene ketoamides **43**.[21] The reaction furnished the Stetter product **44** with two stereocenters with moderate to good diastereoselectivity (Scheme 2.12).

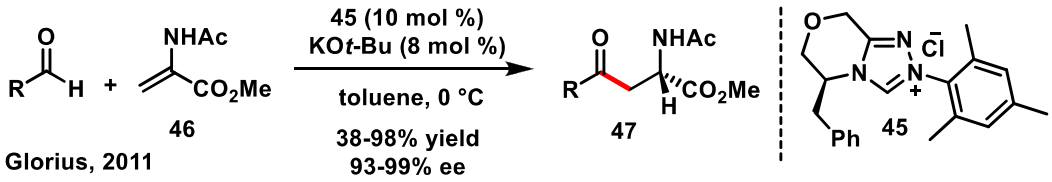
Scheme 2.12: Asymmetric Intermolecular Stetter Reaction by Rovis et al.



Glorius and co-workers reported an asymmetric intermolecular Stetter reaction of aldehydes with *N*-acylamido acrylate **46** leading to the formation of enantioriched amino acid derivatives **47** (Scheme 2.13).[22] The carbene generated from **45** was found to be the

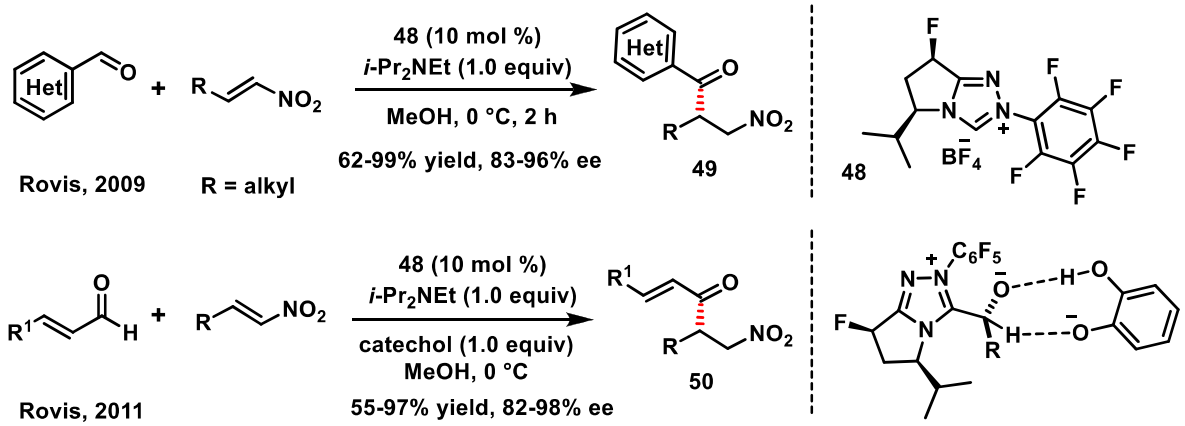
best catalyst and low amount of base compared to the NHC precursor was the key for excellent selectivity. Several aryl aldehydes afforded the α-amino acid derivatives **47** in the presence of NHC generated from L-phenyl alaninol derived triazolium salt **45** (Scheme 2.13). Interestingly, the enantioinduction occured due to the asymmetric protonation of the enolate formed after conjugate addition of the acyl anion to the Michael acceptor.

Scheme 2.13: Asymmetric Intermolecular Stetter Reaction by Glorius et al.



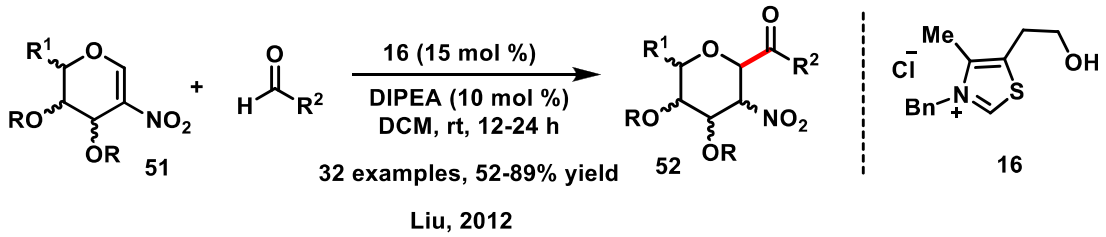
The scope of the asymmetric intermolecular Stetter reaction was further expanded by Rovis and co-workers by employing heteroaryl aldehydes and nitroalkenes.[23] Interestingly, the fluorinated NHC generated from the triazolium salt **48** increased the stereoselectivity of the Stetter product (Scheme 2.14). The fluorine effect on the reaction was studied by DFT calculations, which showed that fluorine increased the electrostatic interaction of the Breslow intermediate and the nitroalkene.[24] Notably, heterocyclic aldehydes are necessary for high level of selectivity. Furthermore, they have extended the reaction scope to α,β-unsaturated aldehydes.[25] The use of catechol as an additive enhanced the reactivity and selectivity, also allows low catalyst loadings without affecting the reactivity resulting in the formation of **50** in high ee values.

Scheme 2.14: Asymmetric Intermolecular Stetter Reaction by Rovis et al.



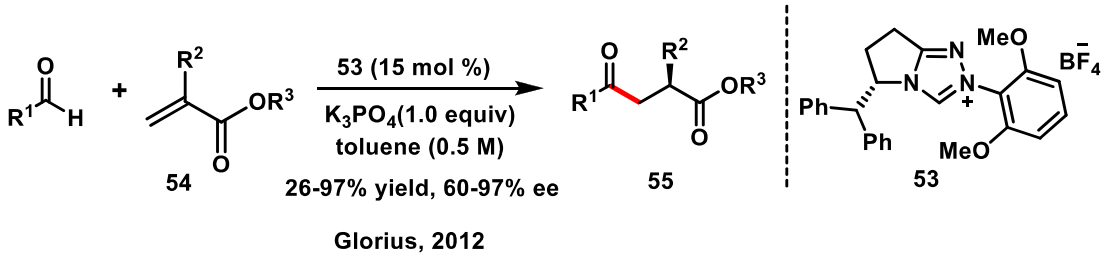
Recently, Liu and co-workers reported an intermolecular Stetter reaction of aldehydes and 2-nitroglucal.[26] The acyl anion added to the anomeric carbon of 2-nitroglucal leading to the formation of β-selective *C*-glycosides **52** in good yields. Various (hetero)aromatic aldehydes as well as aliphatic aldehydes underwent smooth Stetter reaction under the optimized reaction conditions (Scheme 2.15)

Scheme 2.15: Intermolecular Stetter Reaction by Liu et al.



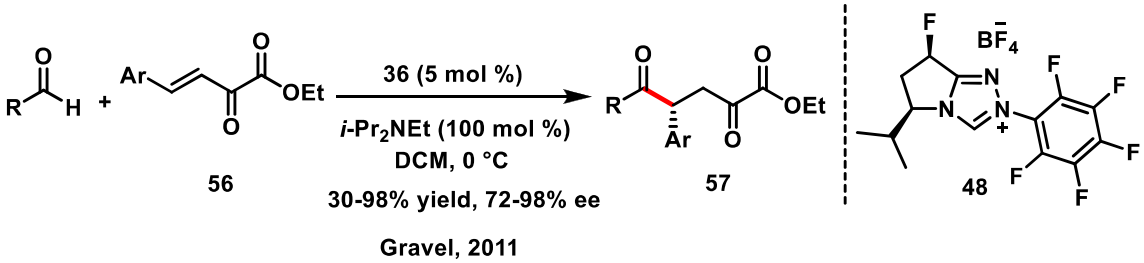
In 2012, Glorius and co-workers reported the enantioselective intermolecular Stetter reaction with a less electrophilic acrylates **54** resulting in the formation of α-chiral γ-ketoesters **55** (Scheme 2.16).[27] The carbene generated from 2,6-dimethoxyaryl substituted triazolium salt **53** was found to be an efficient catalyst for this transformation.

Scheme 2.16: Asymmetric Intermolecular Stetter Reaction by Glorius et al.



Gravel and co-workers devloped an asymmetric intermolecular Stetter reaction using β,γ-unsaturated α-ketoesters **56** as Michael acceptors in (Scheme 2.17).[28] The reaction furnished 1,2,5-tricarbonyl compounds **57** in high yields and ee values.

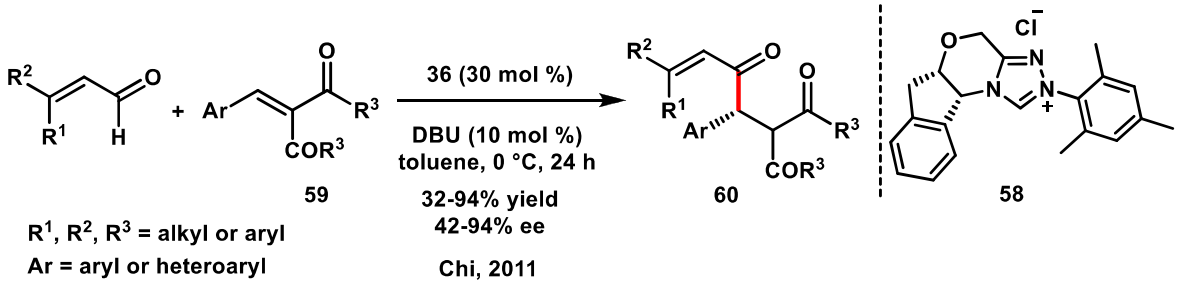
Scheme 2.17: Asymmetric Intermolecular Stetter Reaction by Gravel et al.



Interestingly, the α,β-unsaturated aldehyde showed the acyl anion type reactivity with α-acyl chalcones **59** in an NHC-catalyzed transformations developed by Chi and co-

workers (Scheme 2.18).[29] The chiral carbene derived from **58** was found to be the most efficient catalyst for intermolecular Stetter reaction, furnishing the tricarbonyl product **60** in reasonable yields and excellent ee values.

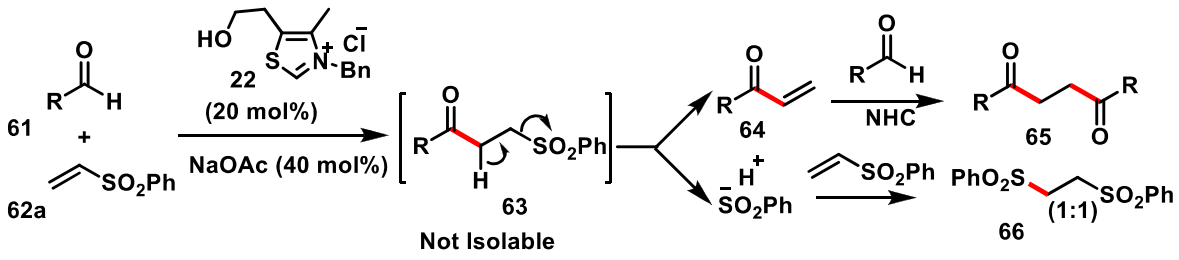
Scheme 2.18: Asymmetric Intermolecular Stetter Reaction α,β-Unsaturated Aldehydes with Modified Chalcones by Chi et al.



2.4. Statement of the Problem

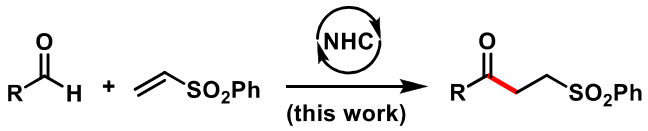
As mentioned in the previous section, the NHC-catalyzed generation of the acyl anion and its subsequent interception with a variety of electrophiles are well documented, however, the analogous reaction with α,β-unsaturated sulfones as Michael acceptor is extremely rare. In 1978, Stetter and Bender reported the first NHC-catalyzed addition of aldehydes to vinyl sulfone **62** (Scheme 2.19).[30] Surprisingly, however, the product was not the expected γ-keto sulfone **63** but was a 1:1 mixture of 1,4-diketone **65** and γ-disulfone **66**. The reaction proceeds through the formation of the desired keto sulfones **63**, which undergoes elimination of the sulfonyl group under the basic reaction condition to form the eneone **64**. Subsequently, the enone **64** participates in another Stetter reaction to form the 1,4-diketone **65**. In addition, the sulfonyl group generated from γ-keto sulfone **63** undergoes a Michael addition with phenyl vinyl sulfone **62** leading to the formation of γ-disulfone **66**. It is important to note that that keto sulfones are biogologically importent molecules, since they are potent and selective 11β-hydroxysteroid dehydrogenase type I inhibitors.[31]

Scheme 2.19: Intermolecular Stetter Reaction onto α,β-Unsaturated Sulfones



The NHC-catalyzed intermolecular Stetter reaction of aldehydes with vinyl sulfones leading to the formation of γ-keto sulfones is unknown to the best of our knowledge, (Scheme 2.20). A detailed study of the Intermolecular Stetter reaction of aldehydes with α,β-unsaturated sulfones was carried out and the results are presented in this chapter. This investigation revealed a high yielding method for the synthesis of γ-keto sulfone derivatives with broad substrate scope.

Scheme 2.20: Intermolecular Stetter of Aldehydes and α,β-Unsaturated Sulfones



2.5. Results and Discussion

2.5.1. Optimization Studies

Our optimization study commenced with the treatment of 4-chloroobenzaldehyde **61a** with phenyl vinyl sulfone **62a**. We started off by using the carbene generated from thiazolium salt **67**. Treatment of **61a** with **62a** in the presence of the carbene generated from **67** by deprotonation using KO*t*-Bu resulted in the formation of γ-keto sulfone **63a** in 56% yield along with the undesired side products **65a** and **66a** derived from the base-induced elimination of the sulfonyl group of **63a** were in low yields. (Table 2.1, entry 1, yield calculated based on ^{1}H NMR). Surprisingly, other NHCs derived from **68-71** are far less effective (entries 2-5). Other Bases such as K_2CO_3, Na_2CO_3, Et_3N and DBU furnished the desired product **63a** in reduced yields (entries 6-9), and solvents other than 1,4-dioxane resulted in inferior reactivity and/or selectivity (entries 10-12). The reaction is sluggish at 60 °C (entry 13), and the yield of **63a** was reduced considerably when the amount of **67** and KO*t*-Bu was varied (entries 14-16). The change of aldehyde amount to 1.4 equivalent substantially increased the product amount (entries 17-19). Interestingly, reducing the reaction time to 22 h, improved the reactivity, with **63a** obtained in 81% yield (entry 20). Under the optimized conditions, the symmetric 1,4-diketone **65a** was isolated in 8% yield and no disulfone **66a** was formed. The amount of KO*t*-Bu plays an important role for the synthesis of the desired stetter product (entries 22 & 23). The key to success of this reaction is the right choice of NHC precursor and the strong base (KO*t*-Bu), which is mostly protonated by the thiazolium salt (**67**) and the base induced elimination is less. Addition of

special additive such as 18-crown-6 or Molecular sieves has no special effect on selectivity (entries 24-26).

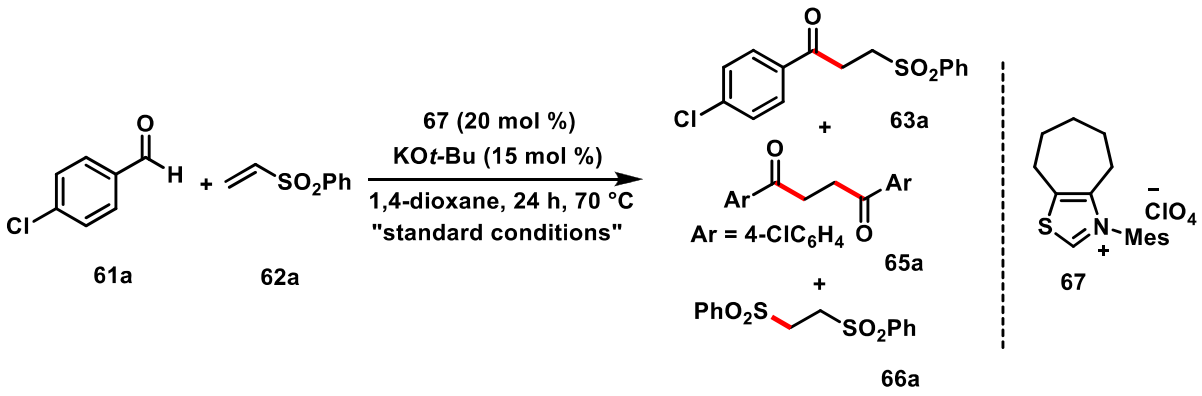
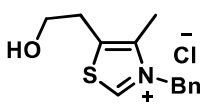


Table 2.1: Optimization Studies

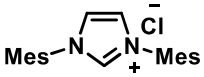
Entry	Variation of The Standard Conditions[a]	Yield of **63a** (%)[b]	Yield of **65a** (%)[b]	yield of **66a** (%)[b]
1	None	56	10	<1
2	**68** instead of **67**	9	3	<1
3	**69** instead of **67**	<1	50	44
4	**70** instead of **67**	<1	23	23
5	**71** instead of **67**	<1	20	2
6	K_2CO_3 instead of KO*t*-Bu	47	12	<1
7	Na_2CO_3 instead of KO*t*-Bu	<1	<1	<1
8	Et_3N instead of KO*t*-Bu	37	8	<1
9	DBU instead of KO*t*-Bu	<1	43	30
10	THF instead of 1,4-dioxane	34	19	18
11	Toluene instead of 1,4-dioxane	48	7	7
12	Ethanol instead of 1,4-dioxane	<1	29	17
13	Reaction run at 60 °C	35	3	<1
14	15 mol % of **6**, 10 mol % KO*t*-Bu	34	8	<1
15	20 mol% KO*t*-Bu instead of 15 mol% KO*t*-Bu	36	17	<1
16	25 mol% KO*t*-Bu instead of 15 mol% KO*t*-Bu	17	34	11
17	1.4 equiv of **61a**, reaction time: 24 h	70	17	<1
18	1.4 equiv of **61a**, reaction time: 16 h	60	7	<1
19	1.4 equiv of **61a**, reaction time: 20 h	69	8	<1
20	**1.4 equiv of 61a, reaction time: 22 h**	**80(81)**	**8(8)**	**<1**

21	2 ml of 1,4-dioxane instead of 1 ml 1,4-dioxane	33	7	0
22	1.2 equiv of **61a** & 20 mol% KO*t*-Bu	45	10	<1
23	1.4 equiv of **61a** & 20 mol% KO*t*-Bu	63	21	<1
24	1.4 equiv of **61a**, 15 mol% KO*t*-Bu & 15 mol% 18-crown-6	18	15	<1
25	15 mol% KF & 30 mol% 18-crown-6 instead of KO*t*-Bu	43	10	<1
26	1.4 equiv of **61a,** 15 mol% KO*t*-Bu & 100 mg 4 Å MS	22	11	<1

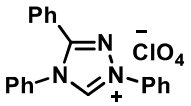
[a] Standard conditions: **61a** (0.25 mmol), **62a** (0.25 mmol), **NHC·HX** (20 mol %), KO*t*-Bu (15 mol %), 1,4-dioxane (1.0 mL), 70 °C and 24 h. [b] The yields were determined by ^{1}H-NMR analysis (DMSO-d_6) of crude products using CH_2Br_2 as the internal standard. Isolated yield in 1.0 mmol scale in parentheses.



68



69



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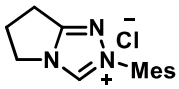
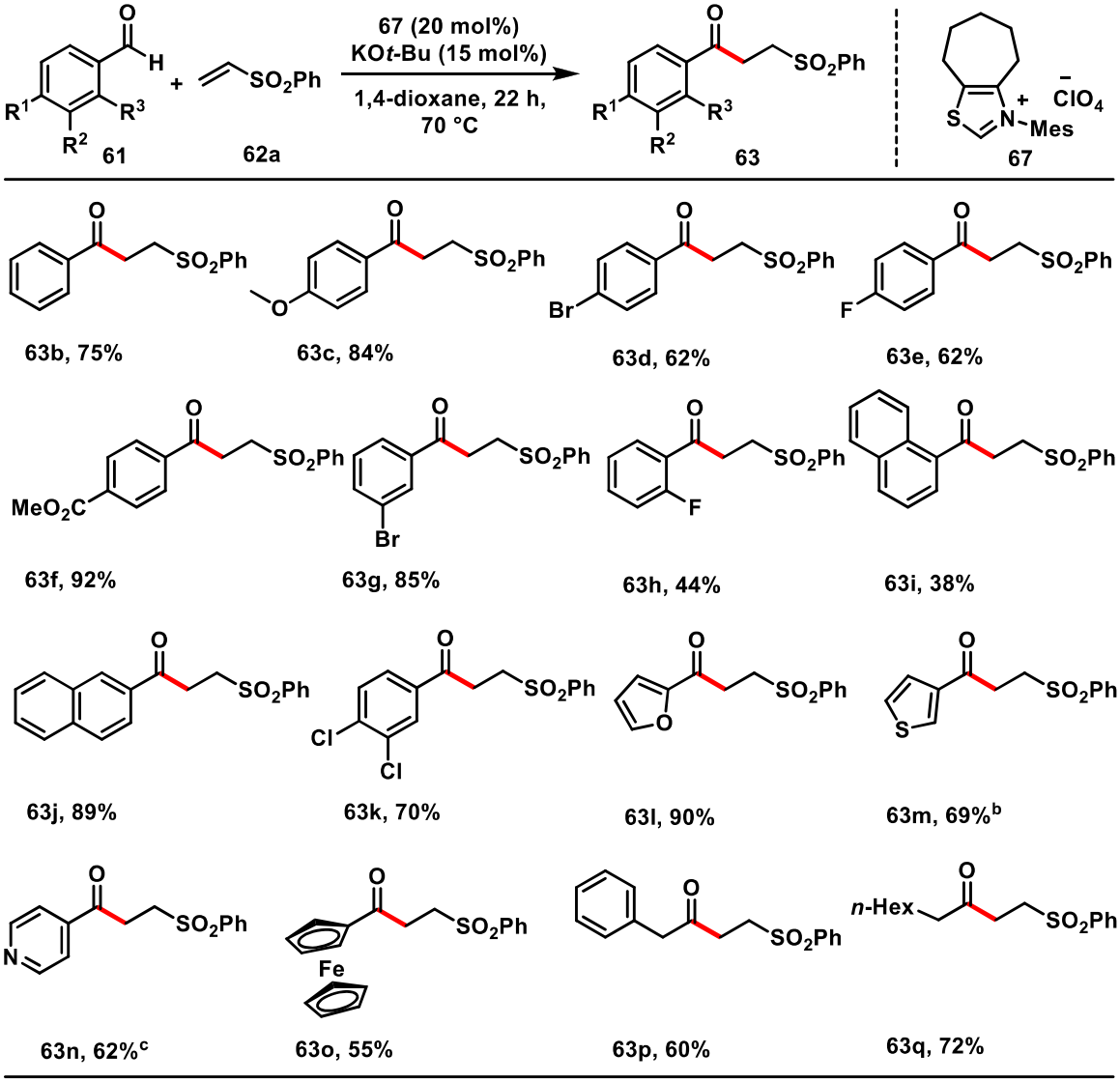


71

2.5.2. Intermolecular Stetter Reaction of Aldehydes and α,β-Unsaturated Sulfones: Substrate Scope

With these optimized reaction conditions in hand, we then examined the substrate scope of this unique intermolecular Stetter reaction (Scheme 2.21). A variety of electron-donating and electron-withdrawing groups at the 4-position of the aromatic ring were well tolerated, leading to γ-keto sulfones in good to excellent yields (62-92%, entries **63b–63f**). Moreover, the 3-bromo benzaldehyde underwent smooth coupling with phenyl vinyl sulfone to form the desired product in 85% yield (**63g**). *ortho*-Substituted aromatic aldehydes such as 2-fluorobenzaldehyde and 1-napthaldehyde furnished the desired products (**63h** & **63i)** in reduced yields (38-44%). However, 2-napthylbenzaldehyde and 3,4-dichlorobenzaldehyde afforded the Stetter product (**63j** & **63k**) in moderate to good yields (70-89%). Interestingly, heterocyclic aldehydes also furnished moderate to good yields of the desired products (**63l**-**63n**, 62-90%) Furthermore, challenging aldehydes such as ferrocenecarboxaldehyde was also well tolerated this intermolecular Stetter reaction (**63o**, 55%). Additionally, this novel hydroacylation reaction is not only limited to aromatic aldehydes. Gratifyingly, aliphatic aldehydes also worked well leading to the formation of the desired products (**63p** & **63q**) in moderate to good yields (60-72%).

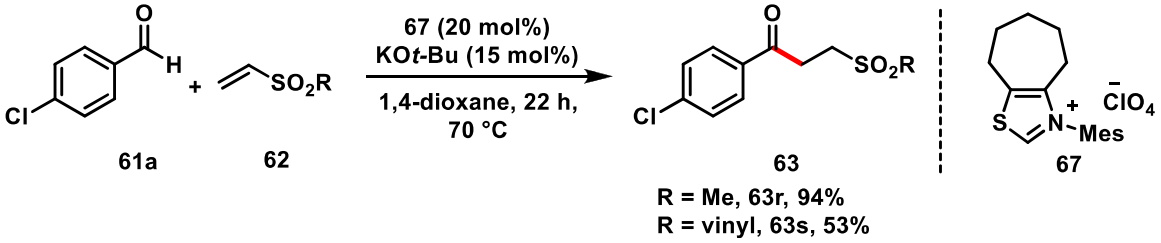
Scheme 2.21: Intermolecular Stetter of Aldehydes and α,β-Unsaturated Sulfones: Variation of Aldehydes[a]



[a] General conditions: **62a** (1.0 mmol), **61** (1.4 mmol), **67** (20 mol %), t-BuOK (15 mol %), 1,4-dioxane (2.0 mL), 70 °C and 22 h. Yields of isolated products are given. In the optimized conditions, the symmetric 1,4-diketone **65** were isolated in <10% yield and no disulfone **66a** was formed. [b] Reaction was run for 18 h. [c] Reaction was run for 15 h.

Next, we examined the effect of varying the α,β-unsaturated sulfones (Scheme 2.22). Interestingly, methyl and vinyl substituents at the unsaturated sulfone moiety are well tolerated leading to the formation of γ-keto sulfones (**63r** & **63s**) in moderate to excellent yields (the diketones were formed in <5% yield and no disulfones were formed). The preliminary studies on β-substituted α,β-unsaturated sulfones failed to undergo this transformation under the optimized reaction conditions.

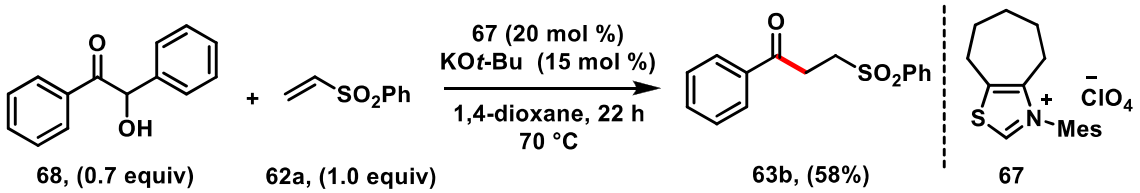
Scheme 2.22: Intermolecular Stetter of Aldehydes and α,β-Unsaturated Sulfones: Variation of Vinyl Sulfones [a]



2.5.3. Mechanistic Studies

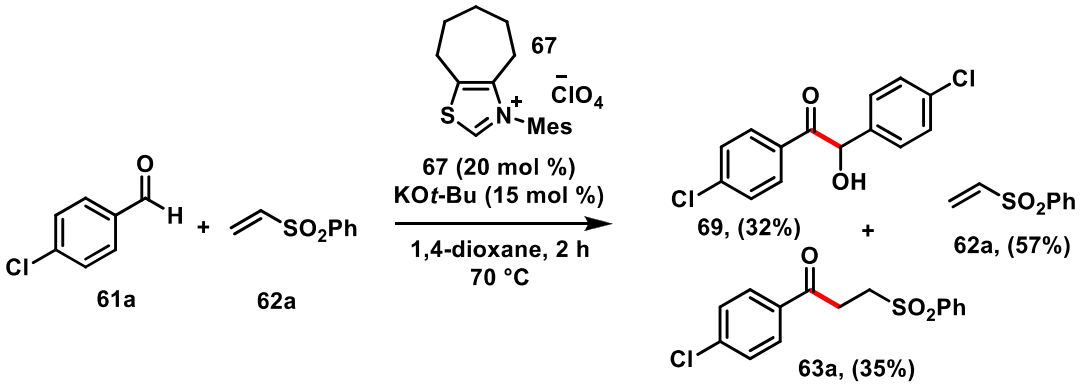
To gain mechanistic insight on this reaction, benzoin was subjected to the optimized reaction conditions. Interestingly, the desired γ-keto sulfone **63b** was formed in 58% yield (Scheme 2.23). This experiment reveals the reversibility of the formation of Breslow intermediate under the present reaction conditions.[32]

Scheme 2.23: Intermolecular Stetter Reaction of Benzoin and Phenyl Vinyl Sulfone



Moreover, to evaluate the generation of benzoin, the reaction was quenched after 2 h under optimized conditions. Interestingly, the 4-chlorobenzoin **69** was formed in 32% yield along with the desired Stetter product **63a** in 35 % yield (Scheme 2.24). This experiment indicates that the formation of benzoin is kinetically controlled and the γ-ketosulfone is the thermodynamically controlled product.

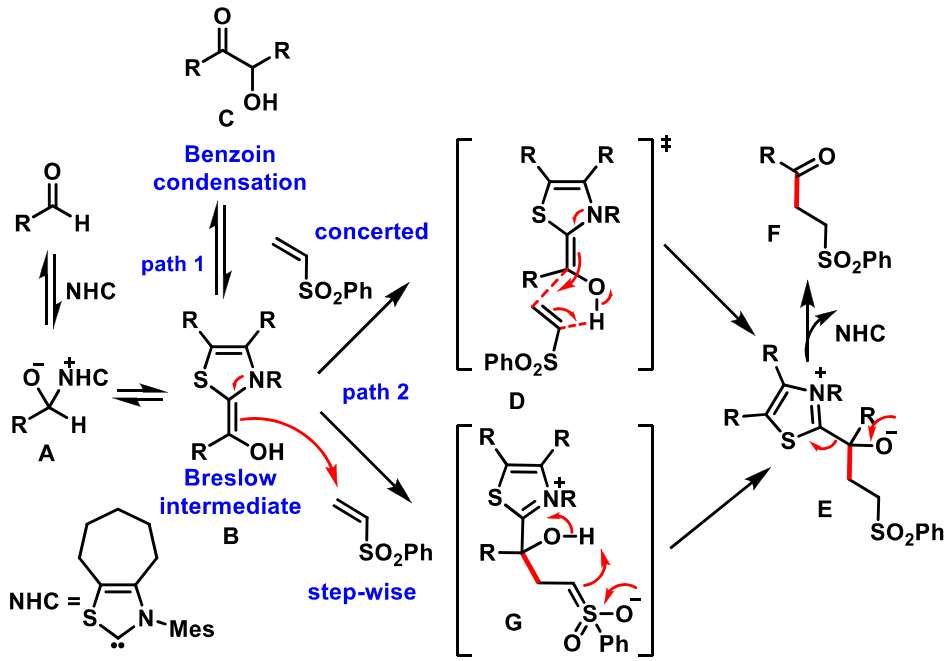
Scheme 2.24: Kinetic Studies



2.5.4. Reaction Mechanism

The plausible mechanism for this NHC-catalyzed annulation reaction is shown in Scheme 2.25. The reaction is initiated by the addition of NHC to aldehyde generating the terahedral intermediate (**A**), which undergoes proton transfer to form the nucleophilic Breslow intermediate (**B**). This acyl anion equivalent (**B**) can add to another one molecule of aldehyde in a reversible process to form the benzoin (**C**). Alternatively, it (**B**) can add to vinyl sulfone in a concerted pathway via the five-membered transition state **D** to furnish the alkoxide intermediate **E**.[33] On the other hand, a stepwise pathway involving the formation of the intermediate **G** can also be invoked. Elimination of NHC from **E** completes the catalytic cycle furnishing the γ-keto sulfones. The addition of acyl anion equivalent (B) to Michael acceptor is likely an irreversible process.

Scheme 2.25: Proposed Mechanistic Pathways

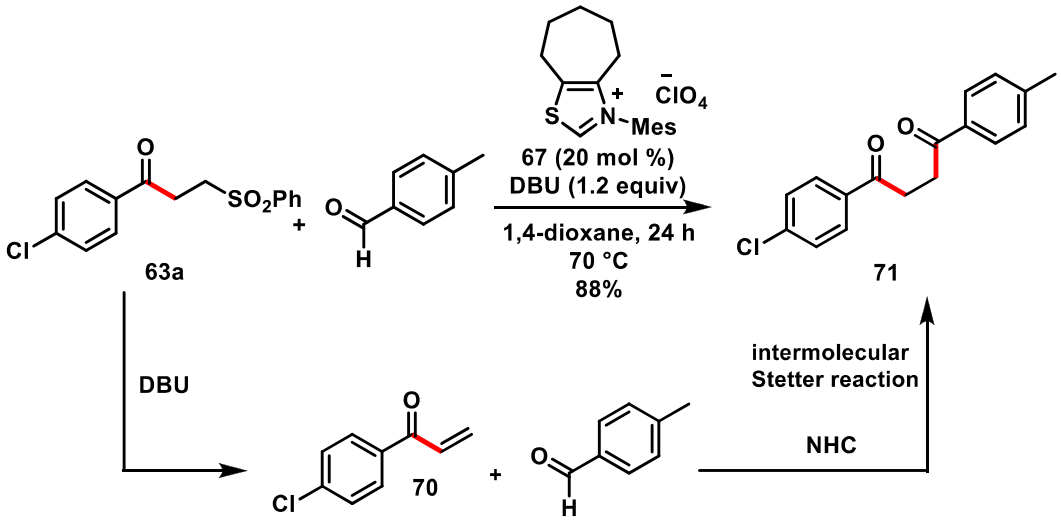


2.5.5. Synthesis of Unsymmetrical 1,4-Diketone

The synthetic utility of the γ-keto sulfones has been demonstrated by an efficient NHC-catalyzed synthesis of 2,3-unsubstituted unsymmetrical 1,4-diketones (Scheme 2.26).[34] Thus treatment of γ-keto sulfones **63a** with *para*-tolualdehyde in the presence of 20 mol% of **67** under basic conditions afforded the unsymmetrical 1,4-diketone **71** in 88% yield. The reaction proceeds via the DBU induced elimination of sulfonyl group from **63a**

generating the enone intermediate **70**, which undergoes an intermolecular Stetter reaction with *para*-tolualdehyde leading to the formation of **71**.

Scheme 2.26: NHC-Catalyzed Synthesis of Unsymmetrical 1,4-Diketones



2.6. Conclusion

In conclusion, we have developed a transition-metal-free NHC-organocatalyzed intermolecular Stetter reaction of aldehydes with α,β-unsaturated sulfones leading to the efficient formation of γ-keto sulfones in good yields. The product formation took place in spite of various selectivity issues under basic conditions. The key to success of this reaction is the careful selection of NHC precursor and a strong base, which will be mostly protonated by the thiazolium salt so that minimum amount of free base will be available for inducing elimination. High levels of functional group tolerance, mild reaction conditions, and high yields of products are the notable features of the present reaction.

2.7. Experimental Details

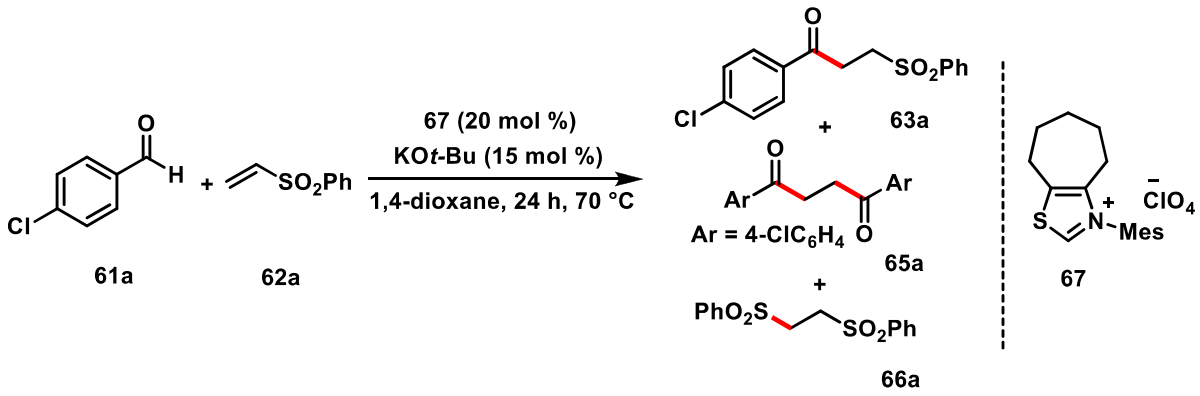
2.7.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. Dry 1,4-dioxane was purchased from commercial sources and stored under argon over 4 Å molecular sieves. The aldehydes were purchased from Aldrich or Acros and were purified either by distillation or washing with $NaHCO_3$ after dissolving in ether or dichloromethane, prior to use. The phenyl vinyl sulfone, methyl vinyl sulfone and divinyl sulfone were purchased

from Sigma Aldrich and used as received, without any further purification. KO*t*-Bu was dried by heating at 110 °C for 12 h and left to cool under argon. The thiazolium salt **67** was synthesized following the literature procedure.[35]

Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with solvents as indicated. All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400, AV 500 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm, DMSO-d_6 δH = 2.52 ppm). Infrared spectra were recorded on a Perkin-Elmer 1615 FT Infrared Spectrophotometer Model 60B. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

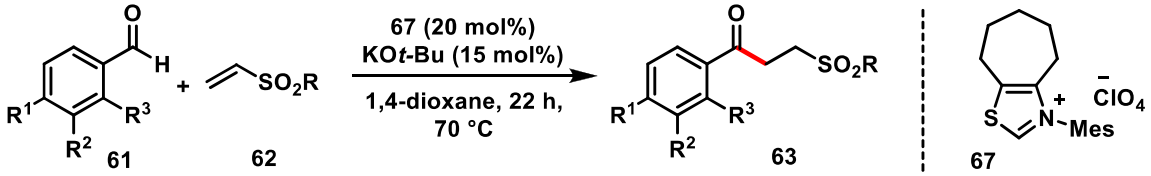
2.7.2. General Procedure for the Optimization of Reaction Conditions



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry KO*t*-Bu (4.2 mg, 0.037 mmol) and the thiazolium **67** (18.5 mg, 0.05 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in 1,4-dioxane under argon atmosphere (1.0 mL). The resultant reaction mixture was kept stirring at 30 °C (rt) for 45 min. To the stirring solution 4-chlorobenzaldehyde **61a** (35.1 mg, 0.25 mmol) and the phenyl vinyl sulfone **62a** (42.0 mg, 0.25 mmol) were successively added. Then the reaction mixture is placed in a preheated oil bath at 70° C for the indicated time. The reaction mixture was cooled and the mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0

mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard.

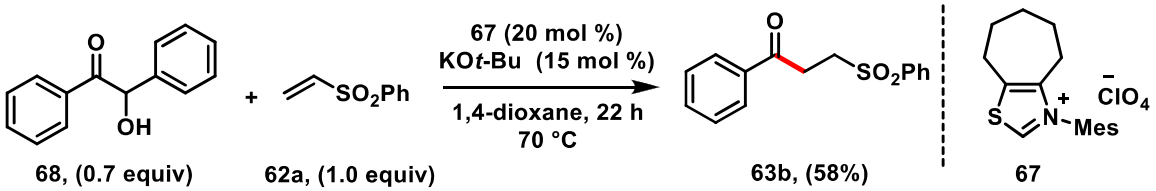
2.7.3. General Procedure for the NHC-Catalyzed Intermolecular Stetter Reaction



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken dry KO*t*-Bu (16.8 mg, 0.15 mmol) and the thiazolium salt **67** (74.4 mg, 0.20 mmol) was added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added 1,4-dioxane (4.00 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C (rt) for 45 min. To this mixture was added the aldehyde **61** (1.4 mmol) (*solid* aldehydes were weighed in air and transferred to the schlenk tube by closing the argon flow and *liquid* aldehydes were transferred via syringe with argon flow) and the vinyl sulfone **62** (1.0 mmol) were successively added. Then the reaction mixture was placed in preheated oil bath at 70° C. When TLC control showed the completion of the reaction (typically after 22 h), the mixture was diluted with CH_2Cl_2 (5.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2. The solvent was evaporated and the crude residue purified by flash column chromatography on silica gel to afford the corresponding γ-keto sulfones **63** in moderate to good yields.

2.7.4. Mechanistic Experiments

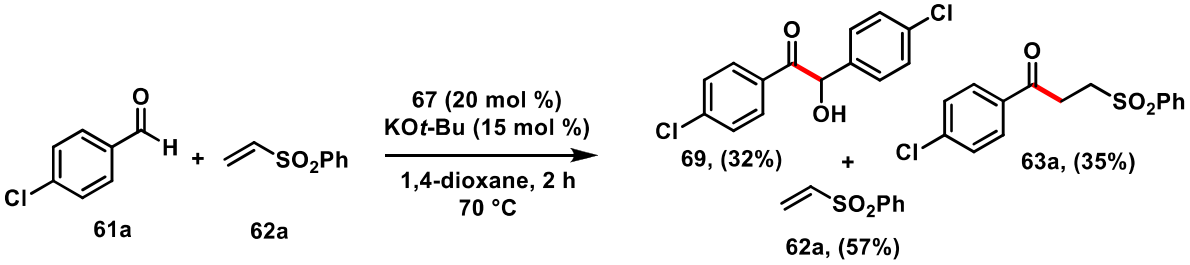
Reaction Employing Benzoin as Substrate



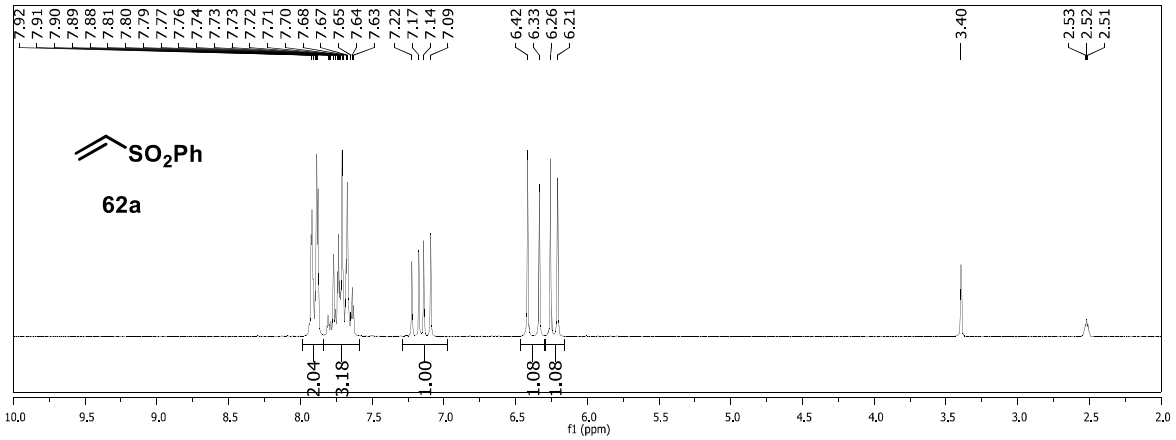
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry KO*t*-Bu (16.8 mg, 0.15 mmol) and the thiazolium salt **67** (74.4mg, 0.20 mmol) was added. Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in 1,4-dioxane under argon atmosphere (4.0 mL). The resultant reaction mixture was kept stirring at 30 °C (rt) for 45 min. To this mixture was added the benzoin **68** (149 mg, 0.7 mmol) and the phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) was

successively added. Then the reaction mixture is placed in a preheated oil bath at 70° C. After 22 h, the reaction mixture cooled and the mixture was diluted with CH_2Cl_2 (5 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2. The solvent was evaporated and the crude residue purified by flash column chromatography on silica gel to afford the corresponding γ-keto sulfone **63b** in 58% yield.

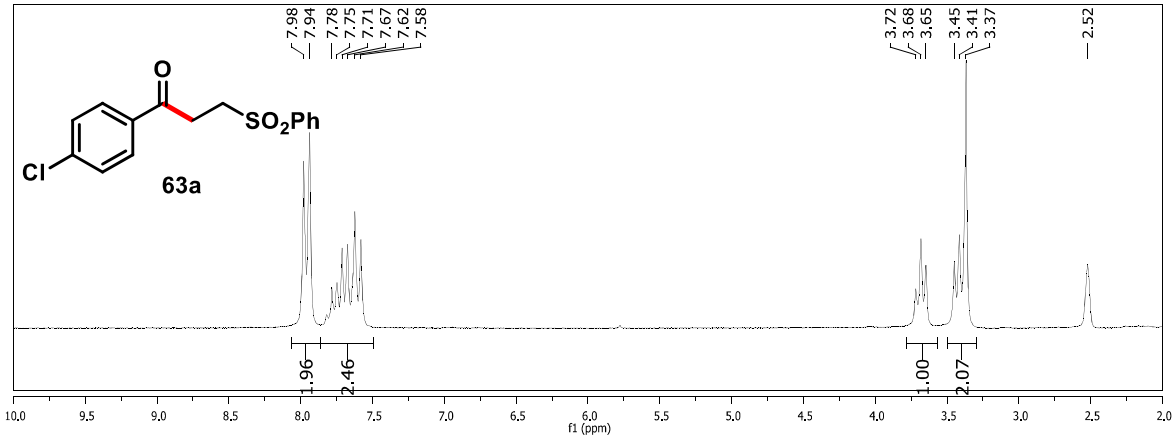
Experiment to Confirm the Formation of Benzoin under the Optimized Conditions



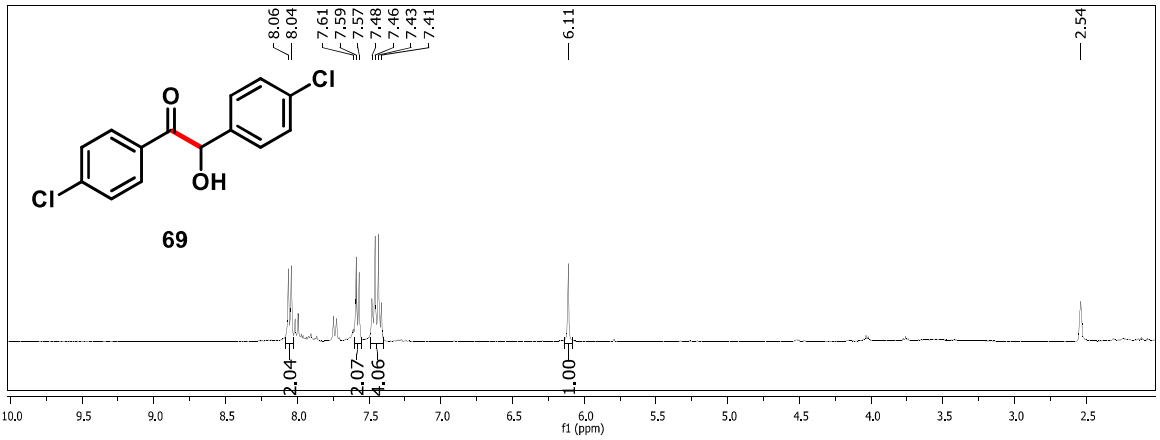
^{1}H-NMR Spectrum of Phenyl Vinyl Sulfone (DMSO-d_6)



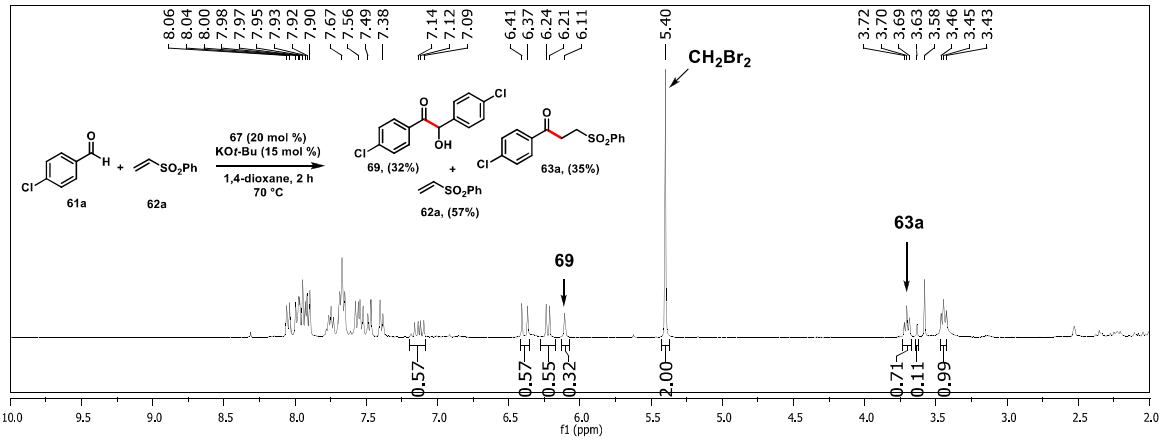
^{1}H-NMR Spectrum of 63a (DMSO-d_6)



^{1}H-NMR Spectrum of 4-Chlorobenzoin (DMSO-d_6)



^{1}H-NMR of Crude Reaction Mixture after 2 h (DMSO-d_6)

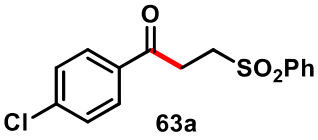


Reaction Procedure: To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry KO*t*-Bu (4.2 mg, 0.037 mmol) and the thiazolium **67** (18.5 mg, 0.05 mmol) was added. Then the screw-capped tube was evacuated and backfilled with argon. After that the mixture was dissolved in 1,4-dioxane under argon atmosphere (1.0 mL). The resultant reaction mixture was kept stirring at 30 °C (rt) for 45 min. To this stirring solution 4-chlorobenzaldehyde **61a** (49.1 mg, 0.35 mmol) and the phenyl vinyl sulfone **62a** (42.0 mg, 0.25 mmol) were successively added. Then the reaction mixture is placed in preheated oil bath at 70° C. After 2 hour heating the reaction is quenched and the mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^{1}H NMR using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard. ^{1}H NMR study

shows that the crude mixture contains 32% 4-chlorobenzoin **69**, 35% product and 57% unreacted **62a**.

2.7.5. Synthesis and Characterization of γ-Keto Sulfones

1-(4-Chlorophenyl)-3-(phenylsulfonyl)propan-1-one (63a)[36]



63a

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) and 4-chlorobenzaldehyde **61a** (0.197 g, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(4-chlorophenyl)-3-(phenylsulfonyl)propan-1-one **63a** as a white solid (0.247 g, 81%).

R_f (Pet. ether/EtOAc = 60/40): 0.72.

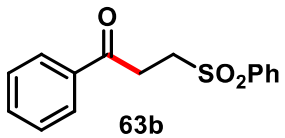
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 7.4 Hz, 2H, H_{ar}), 7.82 (d, *J* = 8.4 Hz, 2H, H_{ar}), 7.67 (t, *J* = 7.4 Hz, 1H, H_{ar}), 7.57 (t, *J* = 8.4, 2H, H_{ar}), 7.43 (d, *J* = 8.4 Hz, 2H, H_{ar}), 3.57-3.52 (m, 2H, CH_2), 3.48-3.44 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.37, 140.43, 139.12, 134.22, 134.11, 129.58, 129.25, 128.08, 51.00, 31.43.

HRMS: calculated $[M+Na]^+$ for $C_{15}H_{13}ClNaO_3S$: 331.0166, found: 331.0203.

FTIR (cm^{-1}): 3019, 2977, 1690, 1591, 1477, 1422, 1319, 1216, 1152, 1046, 1086, 928, 909, 849, 669.

1-Phenyl-3-(phenylsulfonyl)propan-1-one (63b)[37]



63b

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) and benzaldehyde **61b** (0.148 g, 142 μL, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-phenyl-3-(phenylsulfonyl)propan-1-one **63b** as a white solid (0.206 g, 75%).

R_f (Pet. ether /EtOAc = 60/40): 0.56.

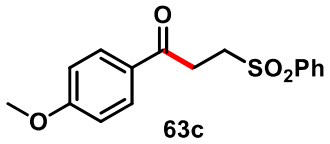
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (dd, J_1 = 7.9 Hz, J_2 = 16.0 Hz, 4H, H_{ar}), 7.67 (m, 1H, H_{ar}), 7.58 (m, 3H, H_{ar}), 7.47 (m, 2H, H_{ar}), 3.57-3.54 (m, 2H, CH_2), 3.50-3.46 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.49, 139.09, 133.87, 129.51, 128.87, 128.12, 128.06, 51.06, 31.46.

HRMS: calculated $[M+Na]^+$ for $C_{15}H_{14}NaO_3S$: 297.0561, found: 297.0591.

FTIR (cm^{-1}): 3020, 1686, 1448, 1319, 1216, 1151, 1087, 771, 687, 668.

1-(4-Methoxyphenyl)-3-(phenylsulfonyl)propan-1-one (63c)



63c

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) and 4-methoxybenzaldehyde **61c** (0.190 g, 170 μL, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 30 h followed by flash column chromatography afforded 1-(4-methoxyphenyl)-3-(phenylsulfonyl)propan-1-one **63d** as a white solid (0.255 g, 84%).

***R**f* (Pet. ether/EtOAc = 60/40): 0.46.

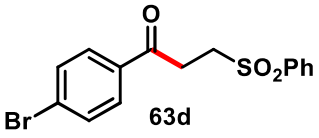
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.89 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.66 (t, *J* = 7.4 Hz, 1H, H_{ar}), 7.57 (t, *J* = 7.4 Hz, 2H, H_{ar}), 6.92 (d, *J* = 8.2 Hz, 2H, H_{ar}), 3.36 (s, 3H, CH_3), 3.56-3.51 (m, 2H, CH_2), 3.46-3.41 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.96, 164.10, 139.17, 134.03, 130.50, 129.52, 128.96, 128.09, 114.04, 55.65, 51.25, 31.03.

HRMS: calculated $[M+Na]^+$ for $C_{16}H_{16}NaO_4$: 327.0662, found: 327.0697.

FTIR (cm^{-1}): 3019, 2360, 1676, 1600, 1512, 1420, 1308, 1255, 1218, 1172, 1150, 1087, 1025, 977, 771.

1-(4-Bromophenyl)-3-(phenylsulfonyl)propan-1-one (63d)



63d

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) and 4-bromobenzaldehyde **61d** (0.259 g, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(4-bromophenyl)-3-(phenylsulfonyl)propan-1-one **63d** as a white solid (0.220 g, 62%).

***R**f* (Pet. ether /EtOAc = 60/40): 0.60.

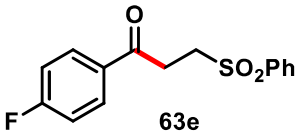
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 8 Hz, 2H, H_{ar}), 7.78 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.69-7.56 (m, 5H, H_{ar}), 3.56-3.53 (m, 2H, CH_2), 3.48-3.44 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.59, 139.12, 134.62, 134.13, 132.27, 129.59, 129.22, 128.09, 51.00, 31.42.

HRMS: calculated $[M+Na]^+$ for $C_{15}H_{13}NaBrO_3S$: 374.9666, found: 374.9707.

FTIR (cm^{-1}): 3065, 2974, 1687, 1630, 1579, 1529, 1486, 1399, 1360, 1289, 1266, 1216, 1172, 1129, 1089, 1009, 956, 914, 865, 821, 753, 715, 681.

1-(4-Fluorophenyl)-3-(phenylsulfonyl)propan-1-one (63e)



63e

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) and 4-fluorobenzaldehyde **61e** (0.174 g, 152 µL, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(4-fluorophenyl)-3-(phenylsulfonyl)propan-1-one **63e** as a white solid (0.182 g, 62%).

***R**f* (Pet. ether/EtOAc = 60/40): 0.64.

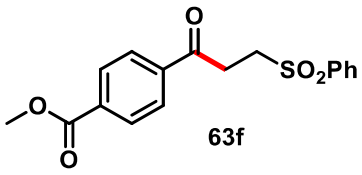
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95-7.92 (m, 4H, H_{ar}), 7.65 (t, *J* = 8.2 Hz, 1H, H_{ar}), 7.56 (t, *J* = 7.5 Hz, 2H, H_{ar}), 7.11 (t, *J* = 9.3 Hz, 2H, H_{ar}), 3.56-3.52 (m, 2H, CH_2), 3.46-3.43 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.92, 166.13 (d, J_{C-F} = 258.15 Hz), 139.09, 134.05, 132.34 (d, J_{C-F} = 2.8 Hz), 130.85 (d, J_{C-F} = 9.9 Hz), 129.52, 128.04, 116.03 (d, J_{C-F} = 22.1 Hz), 51.00, 31.34.

HRMS: calculated $[M+Na]^+$ for $C_{15}H_{13}FNaO_3S$: 315.0462, found: 315.0497.

FTIR (cm^{-1}): 3021, 2401, 1683, 1601, 1509, 1448, 1309, 1217, 1152, 1088, 979, 929, 842.

Methyl 4-(3-(phenylsulfonyl)propanoyl)benzoate (63f)



63f

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) and methyl 4-formylbenzoate **61f** (0.250 g, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded methyl 4-(3-(phenylsulfonyl)propanoyl)benzoate **63f** as a white solid (0.305 g, 92%).

***R**f* (Pet. ether/EtOAc = 60/40): 0.46.

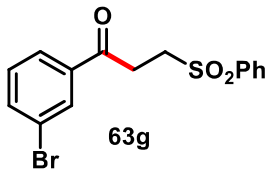
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, *J* = 7.3 Hz, 2H, H_{ar}), 7.96 (t, *J* = 7.7 Hz, 4H, H_{ar}), 7.67 (t, *J* = 7.7 Hz, 1H, H_{ar}), 7.58 (t, *J* = 7.7 Hz, 2H, H_{ar}), 3.94 (s, 3H, CH_3), 3.59-3.50 (m, 4H, $2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.14, 166.11, 139.10, 139.01, 134.63, 134.15, 130.11, 129.60, 128.12, 52.67, 50.97, 31.85.

HRMS: calculated $[M+Na]^+$ for $C_{17}H_{16}NaO_5S$: 355.0611, found: 355.0648.

FTIR (cm^{-1}): 3418, 3019, 2400, 1724, 1694, 1437, 1285, 1216, 1152, 1111, 1046, 768.

1-(3-Bromophenyl)-3-(phenylsulfonyl)propan-1-one (63g)



63g

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.084 g, 0.5 mmol) and 3-bromobenzaldehyde **61g** (0.130 g, 82 μL, 0.7 mmol) with thiazolium salt **67** (37.2 mg, 0.10 mmol) and KO*t*-Bu (8.4 mg, 0.075 mmol) in 1,4-dioxane (2.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(3-bromophenyl)-3-(phenylsulfonyl) propan-1-one **63g** as a white solid (0.150 g, 85%).

***R*$_f$** (Pet. ether/EtOAc = 60/40): 0.62.

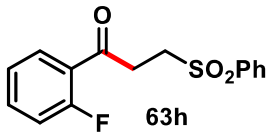
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (s, 1H, H_{ar}) 7.94 (d, *J* = 7.8 Hz, 2H, H_{ar}), 7.83 (d, *J* = 8.2 Hz, 1H, H_{ar}), 7.69-7.65 (m, 2H, H_{ar}), 7.57 (t, *J* = 7.8 Hz, 2H, H_{ar}), 7.34 (t, *J* = 7.8 Hz, 1H, H_{ar}), 3.56-3.52 (m, 2H, CH_2), 3.47-3.43 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.27, 138.99, 137.51, 136.71, 134.13, 131.15, 130.49, 129.57, 128.06, 126.70, 123.73, 50.89, 31.53.

HRMS: calculated $[M+Na]^+$ for $C_{15}H_{13}BrNaO_3S$: 374.9661, found: 374.9708.

FTIR (cm^{-1}): 3054, 2305, 2254, 1694, 1568, 1448, 1421, 1318, 1264, 1152, 911, 669, 651.

1-(2-Fluorophenyl)-3-(phenylsulfonyl)propan-1-one (63h)



63h

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) and 2-fluorobenzaldehyde **61h** (0.174 g, 149 μL, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(2-fluorophenyl)-3-(phenylsulfonyl)propan-1-one **63h** as a white solid (0.128 g, 44%, yield based on recovered **62**a is 68%)

***R*$_f$** (Pet. ether/EtOAc = 60/40): 0.59.

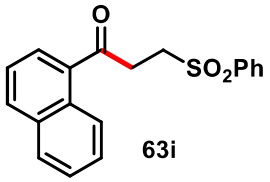
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95-7.93 (m, 2H, H_{ar}), 7.85-7.78 (m, 1H, H_{ar}), 7.68-7.65 (m, 1H, H_{ar}), 7.59-7.51 (m, 3H, H_{ar}), 7.24-7.20 (m, 1H, H_{ar}), 7.16-7.11 (m, 1H, H_{ar}), 3.58-3.53 (m, 2H, CH_2), 3.49-3.43 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.68 (d, *J*(C-F) = 4.3 Hz), 162.24 (d, *J*(C-F) = 255.0 Hz), 139.05, 135.53(d, $J_{(C-F)}$ = 9.1 Hz), 134.03, 130.73(d, $J_{(C-F)}$ = 2.6 Hz), 129.51, 128.20, 124.75 (d, *J*(C-F) = 3.9 Hz), 124.45 (d, *J*(C-F) = 12.2 Hz), 116.90 (d, *J*(C-F) = 24.2 Hz), 50.96 (d, $J_{(C-F)}$ = 2.4 Hz), 36.49 (d, $J_{(C-F)}$ = 9.7 Hz).

HRMS: calculated $[M+Na]^+$ for $C_{15}H_{13}FNaO_3S$: 315.0462, found: 315.0498.

FTIR (cm^{-1}): 3020, 2928, 1685, 1610, 1481, 1453, 1319, 1278, 1217, 1087, 980, 687.

1-(Naphthalen-1-yl)-3-(phenylsulfonyl)propan-1-one (63i)



63i

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) and 1-naphthaldehyde **61i** (0.218 g, 190 µL, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(naphthalen-1-yl)-3-(phenylsulfonyl) propan-1-one **63i** as a white solid (0.123 g, 38%, yield based on recovered **62a** is 75%)

***R*$_f$** (Pet-ether/EtOAc = 60/40): 0.64.

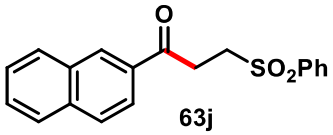
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, *J* = 8.4 Hz, 1H, H_{ar}), 8.00 (d, *J* = 8.4 Hz, 1H, H_{ar}), 7.96 (d, *J* = 7.2 Hz, 2H, H_{ar}), 7.90 (d, *J* = 7.2 Hz, 1H, H_{ar}), 7.86 (d, *J* = 8.4 Hz, 1H, H_{ar}), 7.64 (t, *J* = 7.2 Hz, 1H, Har), 7.57-7.64 (m, 5H, H_{ar}) 3.67-3.64 (m, 2H, CH_2), 3.59-3.55 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.77, 139.10, 134.04, 134.00, 133.74, 130.09, 129.50, 128.57, 128.46, 128.36, 128.06, 126.70, 125.65, 124.39, 51.29, 34.33.

HRMS: calculated $[M+Na]^+$ for $C_{19}H_{16}NaO_3S$: 347.0712, found: 347.0754.

FTIR (cm^{-1}): 3019, 2400, 1683, 1509, 1422, 1309, 1217, 1151, 1086, 1046, 928, 669.

1-(Naphthalen-2-yl)-3-(phenylsulfonyl)propan-1-one (63j)



63j

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.84 g, 0.5 mmol) and 2-naphthaldehyde **61j** (0.109 g, 0.7 mmol) with thiazolium salt **67** (37.2 mg, 0.10 mmol) and KO*t*-Bu (8.4 mg, 0.075 mmol) in 1,4-dioxane (2.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(Naphthalen-2-yl)-3-(phenylsulfonyl)propan-1-one **63j** as a white solid (0.145 g, 89%).

***R*$_f$** (Pet. ether/EtOAc = 60/40): 0.64.

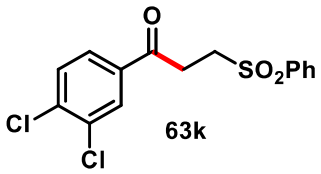
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45 (s, 1H, H_{ar}), 7.99-7.94 (m, 4H, H_{ar}), 7.89-7.86 (m, 2H, H_{ar}), 7.67 (t, *J* = 7.2 Hz, 1H, H_{ar}), 7.63-7.55 (m, 4H, H_{ar}), 3.65-3.63 (m, 4H, $2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.42, 139.16, 135.89, 134.06, 133.17, 132.46, 130.15, 129.54, 128.99, 128.79, 128.09, 127.89, 127.13, 123.52, 51.23, 31.43.

HRMS: calculated $[M+Na]^+$ for $C_{19}H_{16}NaO_3S$: 347.0712, found: 347.0751.

FTIR (cm^{-1}): 3060, 2302, 1678, 1446, 1310, 1266, 1146, 1087, 911.

1-(3,4-dichlorophenyl)-3-(phenylsulfonyl)propan-1-one (63k)



63k

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g. 1.0 mmol) and 3,4-dichlorobenzaldehyde **61k** (0.245 g, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(3,4-dichlorophenyl)-3-(phenylsulfonyl)propan-1-one **63k** as a white solid (0.241 g, 70%).

R_f (Pet. ether/EtOAc = 60/40): 0.64.

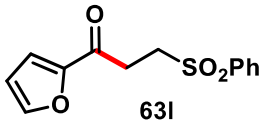
^{1}H NMR (400 MHz, CDCl3) δ: 7.99(d, *J*=1.7Hz, 1H, H_{ar}), 7.95 (d, *J*=7.4 Hz, 2H, H_{ar}), 7.76-7.74 (m, 1H, H_{ar}), 7.69 (t, *J*=7.4 Hz, 1H, H_{ar}), 7.61-7.55 (m, 3H, H_{ar}), 3.56-3.53(m, 2H, CH_2), 3.48-3.44 (m, 2H, CH_2) .

^{13}C NMR (100 MHz, CDCl3): δ: 193.51, 139.04, 138.64, 135.38, 134.22, 133.76, 131.09, 130.18, 129.64, 128.10, 127.19, 50.90, 31.51.

HRMS: calculated $[M+Na]^+$ for $C_{15}H_{12}Cl_2O_3SNa$: 364.9776, found: 364.9771.

FTIR (cm^{-1}): 3412, 2923, 1697, 1446, 1389, 1309, 1279, 1143, 1086, 1027, 783, 750, 693.

1-(Furan-2-yl)-3-(phenylsulfonyl)propan-1-one (63l)



63l

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) and furan-2-carbaldehyde **61l** (0.134 g, 116 μL, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(furan-2-yl)-3-(phenylsulfonyl)propan-1-one **63l** as a white solid (0.259g, 98%).

R_f (Pet ether/EtOAc = 60/40): 0.47.

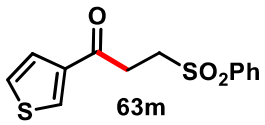
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.93 (d, *J* = 7.5 Hz, 2H, H_{ar}), 7.66 (t, *J* = 7.5 Hz, 1H, H_{ar}), 7.59-7.55 (m, 3H, H_{ar}), 7.21 (d, *J* = 3.6 Hz, 1H, H_{ar}), 6.55-6.54 (m, 1H, H_{ar}), 3.54-3.51 (m, 2H, CH_2), 3.35-3.32 (m, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 184.48, 151.86, 147.05, 139.02, 134.08, 129.52, 128.17, 117.96, 112.70, 50.60, 31.30.

HRMS: calculated $[M+Na]^+$ for $C_{13}H_{12}NaO_4S$: 287.0349, found: 287.0380.

FTIR (cm^{-1}): 3019, 2977. 3444, 3020, 2400, 1634, 1319, 1217, 1025, 928, 771, 669.

3-(Phenylsulfonyl)-1-(thiophen-3-yl)propan-1-one (63m)



63m

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1 mmol) and thiophene-3-carbaldehyde **61m** (0.157 g, 123 μL, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 18 h followed by flash column chromatography afforded 3-(phenylsulfonyl)-1-(thiophen-2-yl)propan-1-one **63m** as a white solid (0.193 g, 69%).

***R**$_f$* (Pet. ether/EtOAc = 60/40): 0.60.

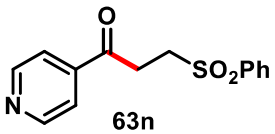
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (dd, J_1 = 1.2 Hz, J_2 = 2.8 Hz, 1H, H_{ar}), 7.95-7.93 (m, 2H, H_{ar}), 7.67 (t, *J* = 7.4 Hz, 1H, H_{ar}), 7.58 (t, *J* = 8.0 Hz, 2H, H_{ar}), 7.50 (dd, J_1 = 1.2 Hz, J_2 = 5.0 Hz, 1H, H_{ar}), 7.34-7.32 (m, 1H, H_{ar}), 3.55-3.52 (m, 2H, CH_2), 3.42-3.39 (m, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 189.71, 141.15, 139.21, 134.09, 132.82, 129.56, 128.13, 126.98, 126.80, 50.97, 32.46.

HRMS: calculated $[M+Na]^+$ for $C_{13}H_{12}NaO_3S2$: 303.0120, found: 303.0153.

FTIR (cm^{-1}): 3446, 3019, 2977, 2400, 1680, 1512, 1417, 1309, 1265, 1216, 1151, 1087, 1046, 928, 849, 771, 669, 626.

3-(Phenylsulfonyl)-1-(pyridin-4-yl) propan-1-one (63n)



63n

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1 mmol) and pyridine 4-carbaxaldehyde **61n** (0.150 g, 132 μL, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 15 h followed by flash column chromatography afforded 3-(phenylsulfonyl)-1-(pyridin-4-yl)propan-1-one **63n** as a white solid (0.171 g, 62%).

***R*$_f$** (Pet. ether/EtOAc = 60/40): 0.35.

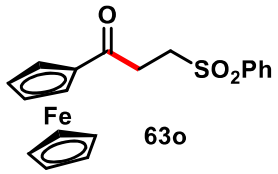
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.84 (d, *J* = 5.7 Hz, 2H, H$_{ar}$), 7.95 (d, *J* = 8.0 Hz, 2H, H$_{ar}$), 7.75 (d, *J* = 5.7 Hz, 2H, H$_{ar}$), 7.71-7.67 (m, 1H, H$_{ar}$), 7.59 (t, *J* = 8.0 Hz, 2H, H$_{ar}$), 3.59-3.55 (m, 2H, CH$_2$), 3.53-3.49 (m, 2H, CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 195.11, 150.67, 142.18, 139.00, 134.29, 129.69, 128.12, 121.32, 50.71, 31.91.

HRMS: calculated [M+Na]$^+$ for $C_{14}H_{13}NNaO_3S$: 298.0508, found: 298.0545.

FTIR (cm^{-1}): 3445, 3054, 1634, 1421, 1265, 896, 739.

1-(2-Ferrocenyl)-3-(phenylsulfonyl)propan-1-one (63o)



63o

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1.0 mmol) and ferreocene carboxaldehyde **61o** (0.300 g, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(2-ferrocenyl)-3-(phenylsulfonyl) propan-1-one **63o** as a red solid (0.211 g, 55%).

***R*$_f$** (Pet. ether/EtOAc = 60/40): 0.53.

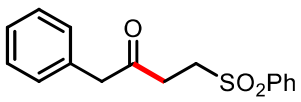
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.97 (d, *J* = 7.1 Hz, 2H, H$_{ar}$), 7.08-7.59 (m, 3H, H$_{ar}$), 4.87 (bs, 2H, H$_{ar}$), 4.54 (bs, 2H, H$_{ar}$), 3.55-3.48 (m, 2H, CH$_2$), 3.27-3.20 (m, 2H, CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 199.60, 139.23, 134.04, 129.54, 128.08, 73.16, 69.64, 50.87, 31.99.

HRMS: calculated [M+Na]$^+$ for $C_{19}H_{18}FeNaO_3S$: 405.0218, found: 405.0267.

FTIR (cm^{-1}): 3413, 3020, 2400, 1669, 1455, 1380, 1308, 1215, 1151, 1086, 1029, 756, 668.

1-Phenyl-4-(phenylsulfonyl)butan-2-one (63p)



63p

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g. 1 mmol) and phenyl acetaldehyde **61p** (0.168 g, 163 μL, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-phenyl-4-(phenylsulfonyl)butan-2-one **63p** as a white solid (0.173 g, 60%).

***R*$_f$** (Pet. ether/EtOAc = 60/40): 0.43.

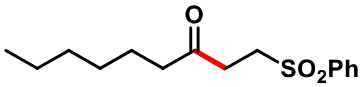
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, *J*=7.6Hz, 2H, H_{ar}), 7.65 (t, *J*=7.4Hz, 1H, H_{ar}), 7.54 (t, *J*=7.6 Hz, 2H, H_{ar}), 7.34-7.27 (m, 2H, H_{ar}), 7.16 (d, *J*=7.2 Hz, 1H, H_{ar}), 3.70 (s, 2H, CH_2), 3.38-3.55 (m, 2H, CH_2), 2.96-2.93 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.61, 138.77, 133.87, 133.21, 129.34, 128.79, 127.85, 127.27, 50.42, 49.77, 34.27.

HRMS: calculated $[M+Na]^+$ for $C_{16}H_{16}O_3SNa$: 311.0712, found: 311.0745.

FTIR (cm^{-1}): 3022, 2931, 1721, 1603, 1586, 1480, 1496, 1447, 1413, 1353, 1309, 1216, 1150, 1086, 1031, 1000, 928, 755, 699, 668.

1-(Phenylsulfonyl)nonan-3-one (63q)



63q

Following the general procedure, treatment of phenyl vinyl sulfone **62a** (0.168 g, 1 mmol) and heptanal **61q** (0.160 g, 195 μL, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(phenylsulfonyl)nonan-3-one **63q** as a white solid (0.225 g, 79%).

***R**$_f$* (Pet. ether/EtOAc = 60/40): 0.72.

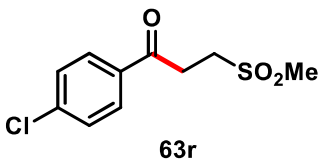
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.90 (d, *J* = 7.6 Hz, 2H, H_{ar}), 7.66 (t, *J* = 7.6 Hz, 1H, H_{ar}), 7.57 (t, *J* = 7.6 Hz, 2H, H_{ar}), 3.36 (t, *J* = 7.8 Hz, 2H, CH_2), 2.89 (t, *J* = 7.8 Hz, 2H, CH_2), 2.41 (t, *J* = 7.5 Hz, 2H, CH_2), 1.54-1.51 (m, 2H, CH_2), 1.29-1.24 (m, 6H, $3CH_2$), 0.86 (t, *J* = 6.9 Hz, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.42, 139.18, 134.04, 129.53, 128.10, 50.70, 43.01, 34.99, 31.61, 28.87, 23.77, 22.56, 14.11.

HRMS: calculated $[M+Na]^+$ for $C_{15}H_{22}NaO_3S$: 305.1182, found: 305.1215.

FTIR (cm^{-1}): 3445, 3020, 2254, 1716, 1644, 1448, 1380, 1265, 1216, 1151, 1087, 911, 741, 669, 650.

1-(4-Chlorophenyl)-3-(methylsulfonyl)propan-1-one (63r)



63r

Following the general procedure, treatment of methyl vinyl sulfone **62b** (0.106 g, 88 μL, 1.0 mmol) and 4-chloro benzaldehyde **61a** (0.197 g, 1.4 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in

1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(4-chlorophenyl)-3-(methylsulfonyl)propan-1-one **63r** as a white solid (0.232 g, 94%).

***R*$_f$** (Pet. ether/EtOAc = 60/40): 0.031.

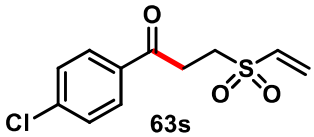
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.93 (d, *J* = 8.5 Hz, 2H, H$_{ar}$), 7.47 (d, *J* = 8.5 Hz, 2H, H$_{ar}$), 3.57-3.50 (m, 4H, 2CH$_2$), 3.00 (s, 3H, CH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 194.64, 140.70, 134.15, 129.69, 129.38, 49.37, 41.90, 31.23.

HRMS: calculated [M+Na]$^+$ for $C_{10}H_{11}ClNaO_3S$: 269.0010, found: 269.0042.

FTIR (cm^{-1}): 3414, 3020, 2400, 1690, 1420, 1314, 1216, 1123, 1093, 1045, 929, 770, 669.

1-(4-Chlorophenyl)-3-(vinylsulfonyl)propan-1-one (63s)



63s

Following the general procedure, treatment of (vinylsulfonyl) ethene **62c** (0.120 g, 116 μL, 1 mmol) and 4-chlorobenzaldehyde **61a** (0.141 g, 1.0 mmol) with thiazolium salt **67** (74.4 mg, 0.20 mmol) and KO*t*-Bu (16.8 mg, 0.15 mmol) in 1,4-dioxane (4.0 mL) at 70 °C for 22 h followed by flash column chromatography afforded 1-(4-chlorophenyl)-3-(vinylsulfonyl)propan-1-one **63s** as a white solid (0.137 g, 53%).

***R*$_f$** (Pet. ether/EtOAc = 60/40): 0.53.

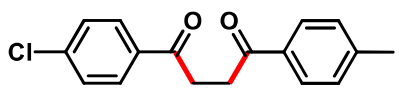
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.90 (d, *J* = 8.8 Hz, 2H, H$_{ar}$), 7.46 (d, *J* = 8.8 Hz, 2H, H$_{ar}$), 6.70 (dd, J_1 = 10.14 Hz, J_2 = 16.8 Hz, 1H, H$_{ar}$), 6.46 (d, *J* = 16.8 Hz, 1H, H$_{ar}$), 6.18 (d, *J* = 9.8 Hz, 1H, H$_{ar}$), 3.51-3.44 (m, 4H, 2CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 194.43, 140.59, 136.37, 134.20, 130.91, 129.64, 129.34, 48.84, 31.23.

HRMS: calculated [M+Na]$^+$ for $C_{11}H_{11}ClNaO_3S$: 281.0010, found: 281.0047.

FTIR (cm^{-1}): 3020, 2935, 2400, 1688, 1591, 1401, 1317, 1215, 1124, 1138, 1094, 1014, 979, 953, 835.770,668.

1-(4-Chlorophenyl)-4-(*p*-tolyl)butane-1,4-dione (71)[38]



71

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken 1-(4-chlorophenyl)-3-(phenylsulfonyl) propan-1-one **63a** (0.077 g, 0.25 mmol) and 4-methyl benzaldehyde (0.030 g, 30 μL, 0.25 mmol) and thiazolium salt **67** (18.6 mg, 0.05 mmol). To this mixture was added 1,4-dioxane (1.0 mL) followed by DBU (45.6 mg,

45 μL, 0.30 mmol). The resulting mixture was stirred in a pre-heated oil bath at 70 °C for 22 h. After the reaction was complete, the reaction mixture was cooled to room temperature, and the crude mixture was purified by flash column chromatography on silica gel to afford 1-(4-chlorophenyl)-4-(*p*-tolyl)butane-1,4-dione **71** as a white solid (63 mg, 88%).

R_f (Pet. ether/EtOAc = 60/40): 0.84.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.98 (d, *J* = 8.4 Hz, 2H, H_{ar}), 7.93 (d, *J* = 8.4 Hz, 2H, H_{ar}), 7.45 (d, *J* = 8.4 Hz, 2H, H_{ar}), 7.27 (d, *J* = 8.4 Hz, 2H, H_{ar}), 3.46-3.43 (m, 2H, CH_2), 3.41-3.39 (m, 2H, CH_2), 2.42 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 193.27, 197.77, 144.18, 139.70, 135.32, 134.36, 129.70, 129.44, 129.06, 128.38, 32.69, 32.59, 21.08.

HRMS: calculated $[M+Na]^+$ for $C_{17}H_{15}ClNaO_2$: 309.0653, found: 309.0692.

FTIR (cm^{-1}): 3053, 2685, 2305, 2254, 1681, 1606, 1422, 1265, 1216, 1180, 1094, 991, 742, 669.

6.12. References

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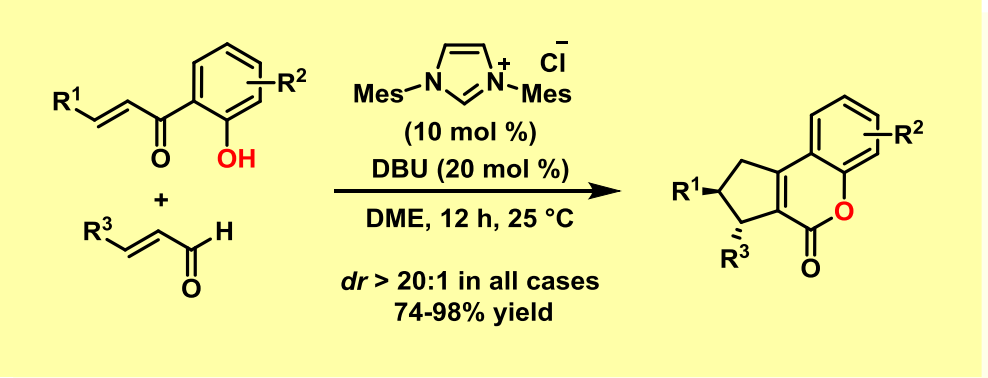
Chapter 3

NHC-Catalyzed Annulation of Enals and 2'-Hydroxy Chalcones

In this chapter, an NHC-organocatalyzed homoenolate annulation of enals with 2'-hydroxy chalcones is demonstrated. The reaction afforded highly functionalized cyclopentane fused coumarins with an excellent level of diastereoselectivity. The reaction is compatible with wide variety of enals as well as 2'-hydroxy chalcones. Additionally, we have carried out preliminary mechanistic studies to to shed light on the mechanism of this transformations.

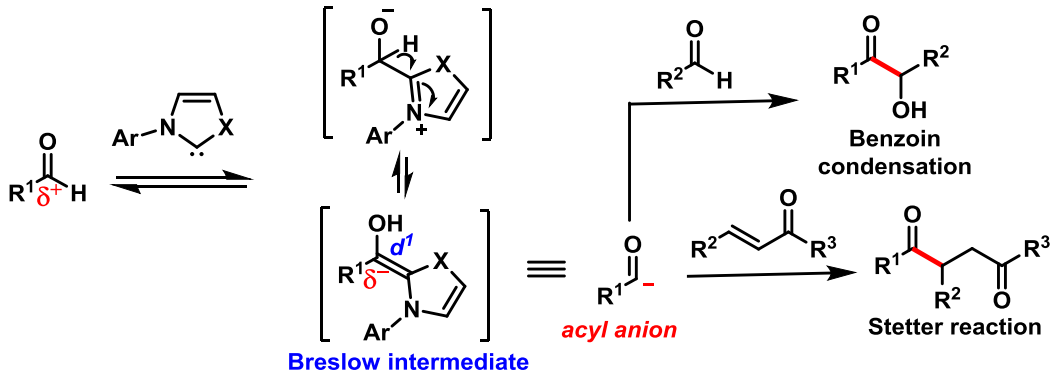


Org. Lett. **2013**, *15*, 1756-1759

3.1. Introduction

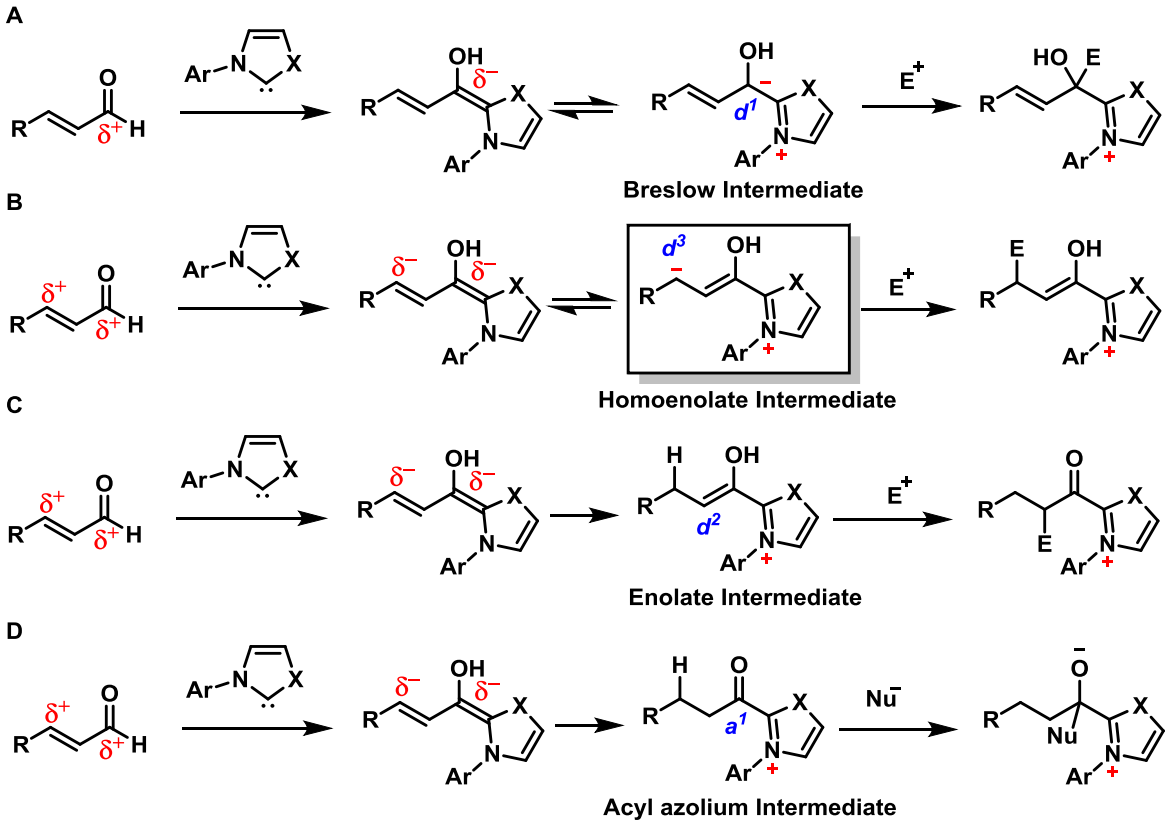
In recent years, N-heteocyclic carbene (NHC)–organocatalysis have attracted considerable interest, which arise due to their new catalytic bond forming abilities that enhances the efficiency and offers a broad range of unconventional transformations. The chemistry of NHC has witnessed rapid development primarily by exploiting the concept of polarity reversal (*umpolung*).[1] Their ability to access the acyl anion intermediates and their synthetic applications have been discussed in the previous Chapter. The 1,2-addition of Breslow intermediate to anothermolecule of aldehyde is referred as the benzoin condensation, while the addition of the acyl anion to a Michael acceptor is known as the Stetter reaction. These reactions belong to the class of a^1-d^1 coupling, according to the terminology of Seebach.[2]

Scheme 3.1: Generation and Reaction of Breslow Intermediate



For a long time (1943-2004), NHC-organocatalysis field remain limited with this acyl anion equivalent intermediate based reactivity. However, this development has urged researchers to objectively examine the other modes of reactivity. The innovation of new catalyst has derived new modes of reactivity. According to the catalytic activation modes of NHCs, a rationalizations of the umpolung of aldehydes are classified into four categories. NHCs can activate aldehyde or their synthetic equivalents to generate nucleophilic Breslow intermediate (A), homoenolate (B), enolate (C) or electrophilic acyl azolium intermediate (D), each of which show different type of reactivities (Scheme 3.2). The choice of the catalyst and reaction conditions can result in the selective formation of each of these reactive intermediates. In this chapter, we will focus on the NHC-derived homoenolate intermediate.[3] The homoenolate equivalents can be considered as a d^3-nucleophile and thus, constitutes an a^3-d^3 coupling.

Scheme 3.2: Reaction Modes in NHC-Catalysis

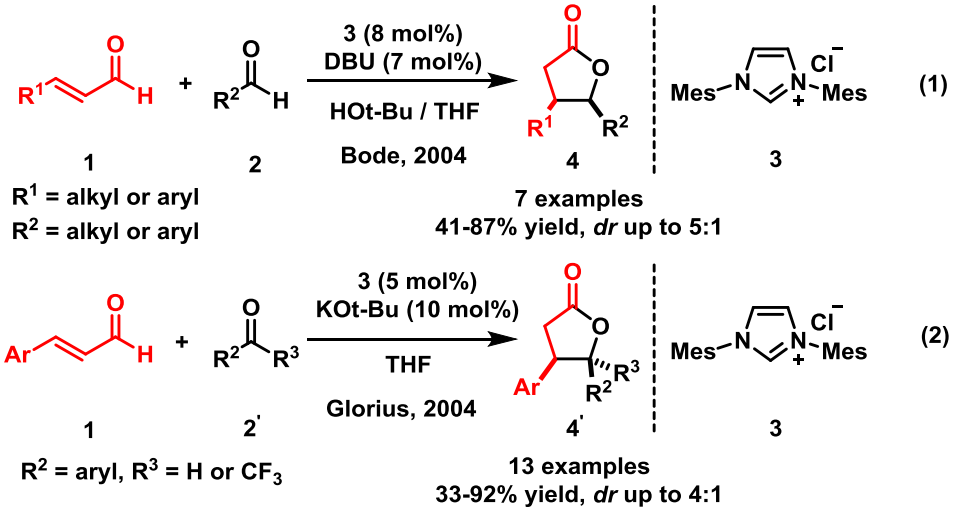


The focal theme of this chapter is the NHC-catalyzed annulation of enals with 2'-hydroxy chalcones. The reaction offered highly functionalized cyclopentane fused coumarins derivatives with good yield and excellent diastereoselectivity. Before discussing the results, a brief overview of the recent developments on the NHC-catalyzed homoenolate reactions are presented in the following section.

3.2. NHC-Catalyzed Homoenolate Reactions

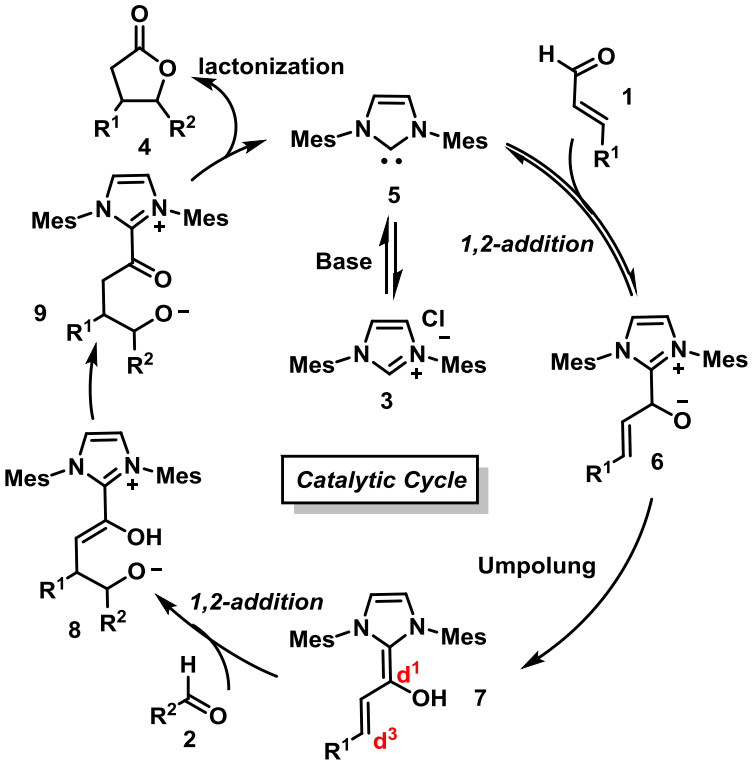
In 2004, the Glorius group[4] and the Bode group[5] independently developed a conceptually new approach for the generation of homoenolate equivalents from α,β–unsaturated aldehydes **1** using bismesityl imidazolium precatalyst **3** (Scheme 3.3). In the presence of aldehydes **2**, the catalytic generation of homoenolate equivalents led to the synthesis of γ-butyrolactones **4** in good yields and good diastereoselectivity. An enantioselective transformation using trifluoromethyl ketones as electrophile was demonstrated by Glorius and co-workers. However the homoenolate annulation with other ketones remains elusive.

Scheme 3.3: Annulation of Enals and Aldehydes/Activated Ketones by NHC

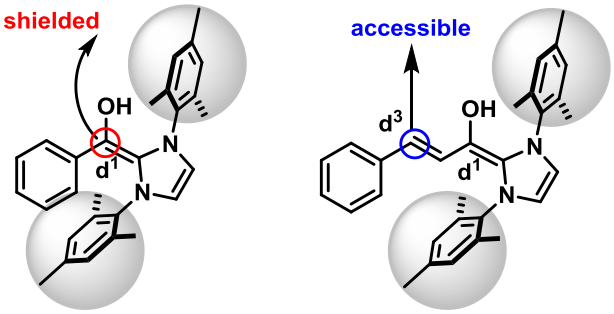


A plausible mechanism is presented in Scheme 3.4. The 1,2-addition of NHC to enal gives rise to the tetrahedral intermediate **6**, which undergoes proton transfer to generate the conjugate enaminol **7**. The d^3-nucleophile **7** adds to electrophile **2** to form the intermediate **8** followed by tautomerization giving alkoxide intermediate **9**, which upon intramolecular cyclization leads to the γ-butyrolactone **4** and regenerates the NHC **5**.

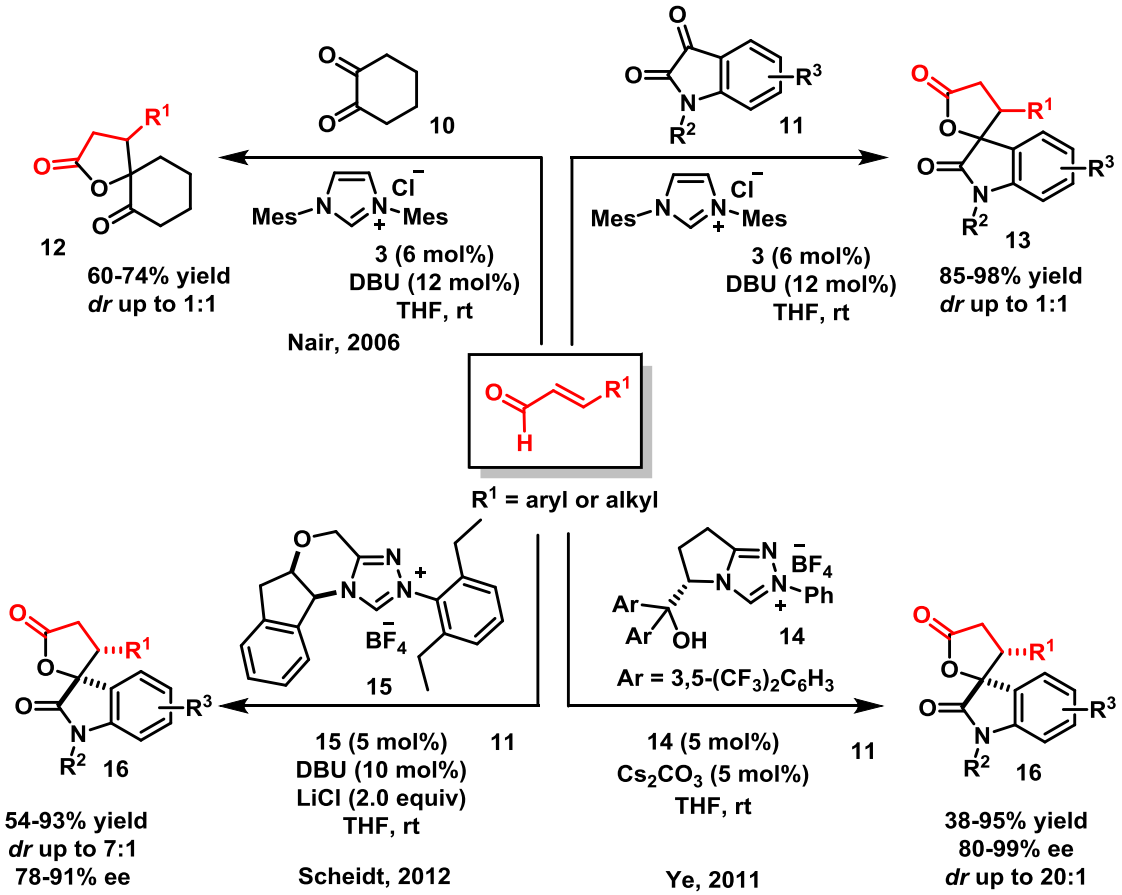
Scheme 3.4: Proposed Mechanism for γ-Lactone Formation



In both works, bismesityl imidazolium precatalyst **3** was used. The use of bulky substitutions on the N-centre of NHC facilitates reaction at the β-position (d^3-centre) by shielding the nucleophilic d^1-centre. The use of catalyst with inappropriate bulkiness or electron richness demotes the reactivity. These two reports have widely expanded the application of NHC-organocatalysis. Subsequently, a number of γ-lactone forming reactions were reported using this unique concept.



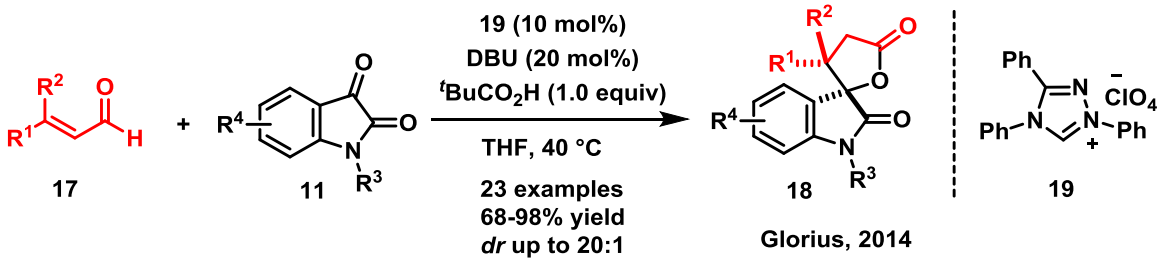
Scheme 3.5: NHC-Catalyzed Homoenolate Annulation of Enals and Activated Ketones



In 2006, Nair and co-workers reported the annulation of enals and 1,2-carbonyls to synthesize spiro γ-lactone in the presence of a catalytic amount of 1,3-dimesitylimidazol-2-ylidene (IMes) **5**.[6] 1,2-Cyclohexanedione **10** afforded the spirocyclohexanone derivatives **12** with moderate yields (60-74% yield) while isatins **11** furnished spirooxindole γ-lactone **13** with moderate to good yields (85-98%). In both cases, the diastereoselectivity remained low (1:1) (Scheme 3.5). Moreover, they have expanded the substrate scope of this reaction using diaryl 1,2-diones.[7] In further investigations, Ye and co-workers also used this concept to synthesize enantioriched spirooxindole γ-lactone **16** by using the sterically demanding chiral triazolum precatalyst **14**.[8] It is noteworthy that, in most cases, excellent diastereo- and enantio-selectivity was obtained. Subsequently, Scheidt and co-workers reported the stereoselective synthesis of spirooxindole γ-lactone **16** using the aminoindanol derived triazolium salt **15** and LiCl as Lewis acid.[9]

Recently, Glorius and co-workers studied the annulation of isatins with sterically hindered β,β-disubstituted enals in a dual catalytic (NHC/ Brønstead acid) process (Scheme 3.6).[10] Notably, the use of Brønstead acid has substantially increased the yield as well as the diastereoselectivity. The reaction tolerates a broad range of aryl and aliphatic substituted enals.

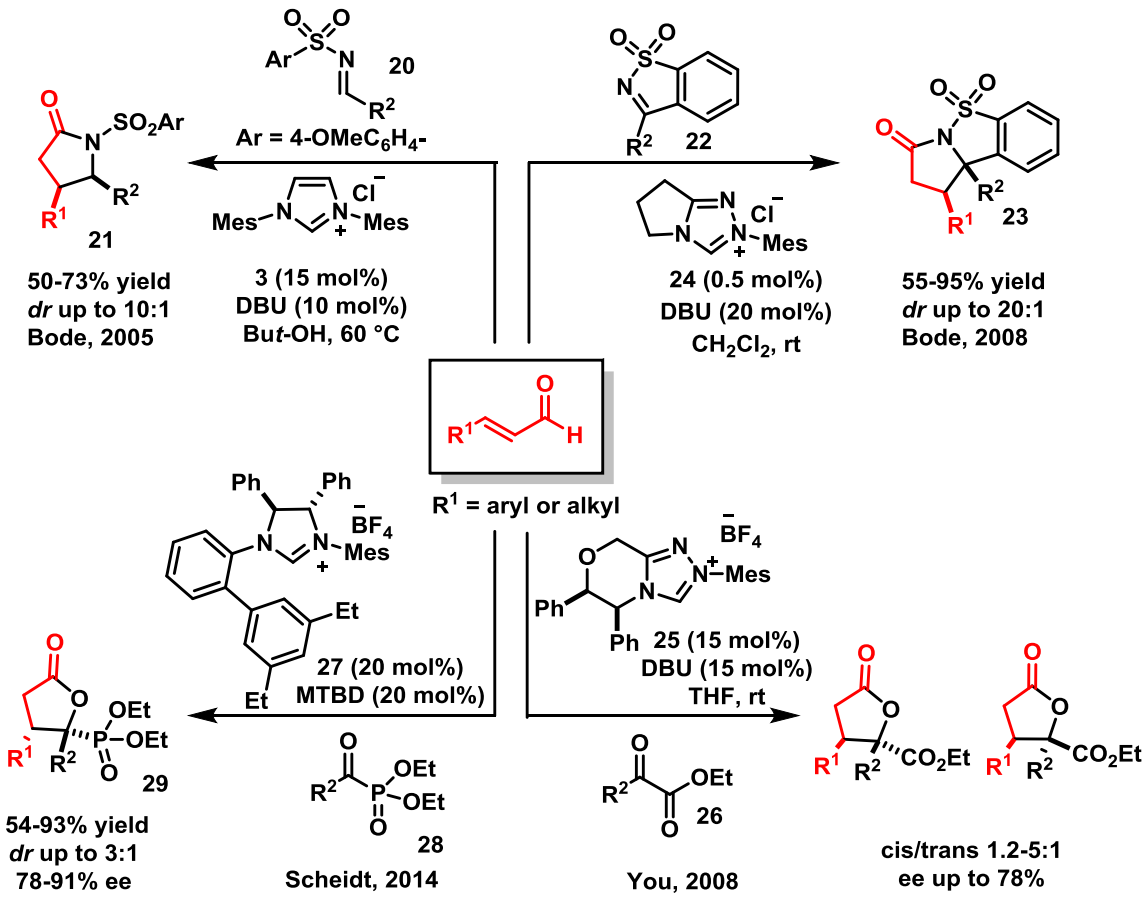
Scheme 3.6: NHC-Catalyzed Annulation of β,β-Disubstituted Enals with Isatins



In 2005, Bode and He reported the synthesis of γ-lactams **21** (Scheme 3.7).[11] The use of acyclic sulfonylketimines showed fruitful results in this annulation reaction leading to the synthesis of γ-lactams **21** with good yields and modest diastereoselectivity. The reaction tolerates a broad range of aromatic enals. However, the variation of imines **20** is limited. In many cases, imines undergo irreversible binding with the catalyst and thereby terminating the catalytic process. Subsequently, they have demonstrated the coupling of enals with cyclic sulfonylketimines **22**.[12] The reaction needs very less catalyst loading and favors the formation of *cis*-isomers with excellent diastereoselectivity. The irreversible

binding of imines-catalyst was overcame with this cyclic sulfonylketimines **22**. Mechanistically, this reaction proceeds through the same catalytic cycle (Scheme 3.4) proposed by Glorius and Bode. Later, You and co-workers showed that ethyl glyoxalate derivatives **26** also underwent the homoenolate annulation reaction to derive the γ-lactones in presence of a chiral triazolium precatalyst **25**.[13] Recently, Scheidt and co-workers demonstrated enantioselective homoenolate annulation of enals with acyl phosphonates **28**.[14] The reaction afforded the enantioriched γ-lactone derivatives **29** in presence of a chiral imidazolidinium carbene generated from the precatalyst **27**.

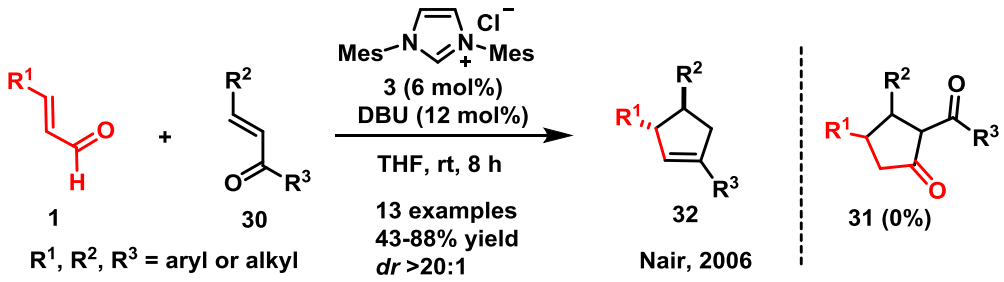
Scheme 3.7: NHC-Catalyzed Annulation of Enals with Imines or Activated Carbonyls



In addition to the generation of lactones and lactams, the NHC-catalyzed homoenolate generation has been utilized to form the carbocycles as well. In 2006, Nair and co-workers developed an elegant procedure for the synthesis of 3,4-*trans*-disubstituted-1-aryl cyclopentene **32** through the annulation of enals **1** with an α,β-unsaturated ketones **30** (Scheme 3.8).[15] The reaction results in the serendipitous formation of cyclopentenes **32** instead of the expected cyclopentanones **31**. This observation has led to the development of

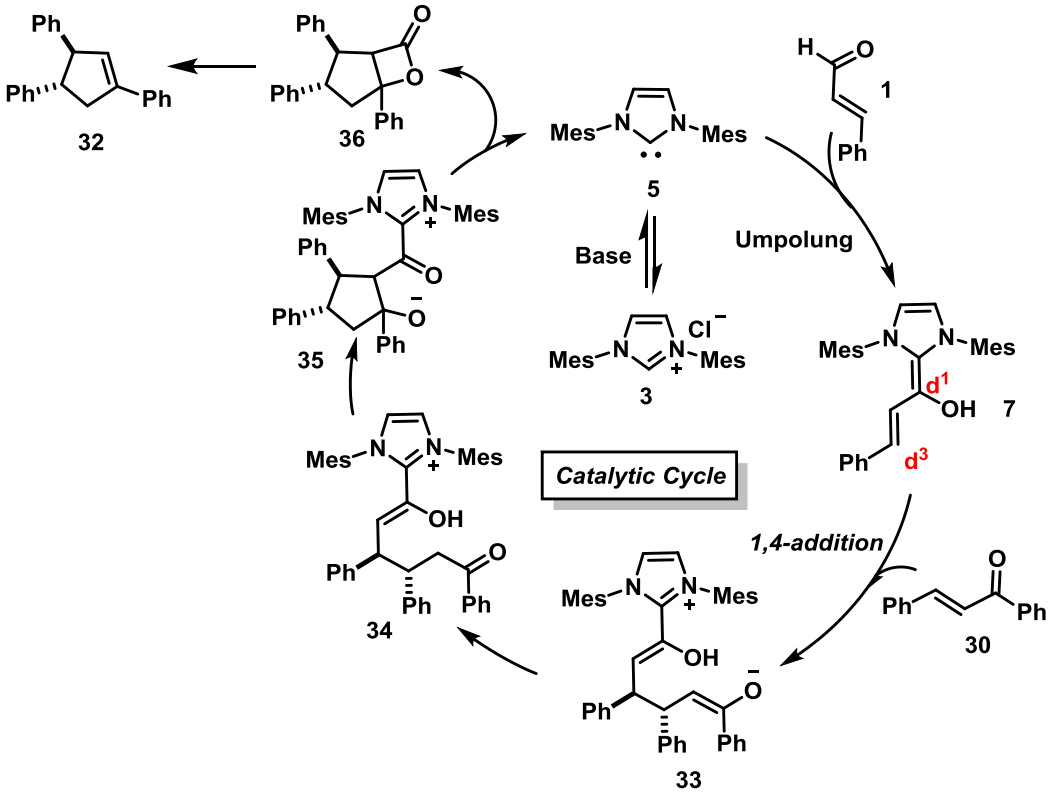
a new NHC-catalyzed homoenolate annulation method. Interestingly, the reaction afforded a single diastereomer with *trans* selectivity.

Scheme 3.8: NHC-Catalyzed Annulation of Enals and Chalcones



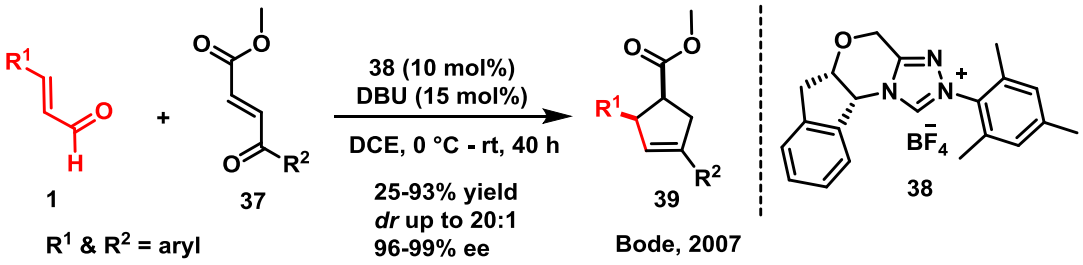
A plausible mechanism is presented in Scheme 3.9. The 1,2-addition of NHC to *trans*-cinnamaldehyde gives rise to the extended Breslow intermedite **7**, which undergoes the 1,4-addition to the chalcone to produce the enolate **33**. Tautomerization of **33** leads to the ketone **34**, which then undergoes an intramolecular aldol reaction followed by β-lactonization generates **36**. The β-lactone **36** releases a molecule of CO_2 to form the 3,4-*trans*-disubstituted-1-aryl cyclopentene **32**. Notably, the loss of CO_2 from β-lactone **36** was supported by IR studies.

Scheme 3.9: Proposed Mechanism for Cyclopentenes Formation



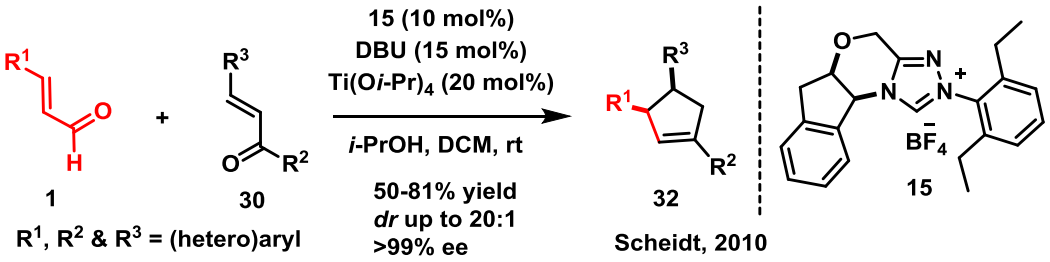
Subsequently, Bode and co-workers developed the enantioselective synthesis of cyclopentenes from enals and 4-oxoenoates **37** in presence of the chiral aminoindanol derived triazolium precatalyst **38** (Scheme 3.10).[16] The reaction afforded the desired product **39** with high enantio- and diastereo-selectivity. Interestingly, this method provides *cis*-isomer, in contrast to the Nair's protocol, which delivered the *trans*-isomer.

Scheme 3.10: NHC-Catalyzed Annulation of Enals and 4-Oxoenoates



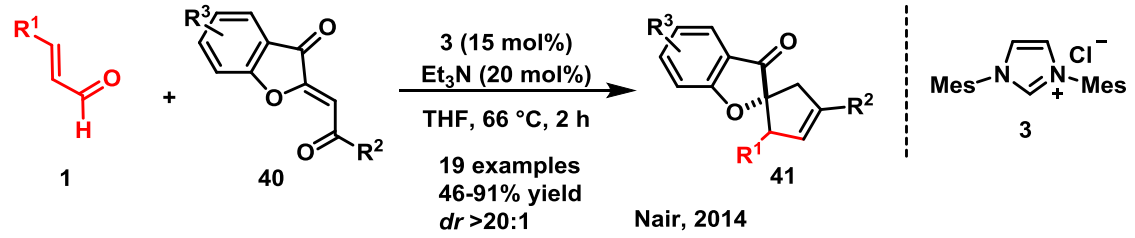
Scheidt and co-workers also reported the enantioselective synthesis of *cis*-cyclopentenes (Scheme 3.11).[17] They started off with the Nair's starting materials. The use of titanium isopropoxide as an additive with a chiral NHC derived from precatalyst **15**, delivered the product **32** with moderate to good yields and with high enantioselectivity.

Scheme 3.11: Lewis Acid/NHC-Catalyzed Enantioselective Annulation of Enals and Chalcones

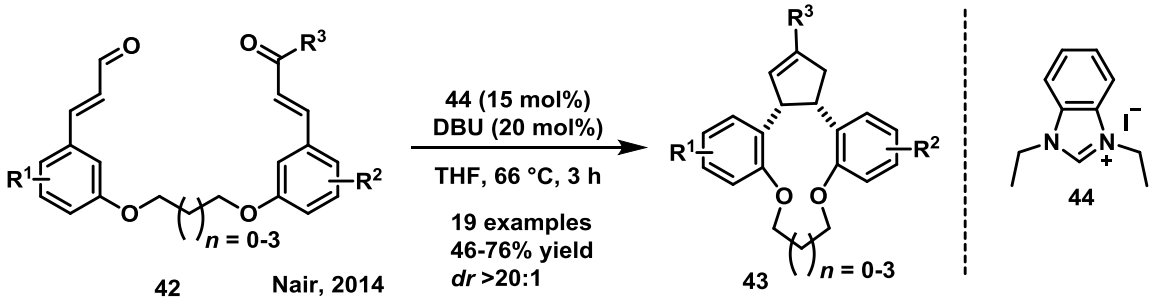


Recently, Nair and co-workers reported the homoenolate annulation of enals with 2-aroylidene benzofuran-ones **40** (Scheme 3.12).[18] The reaction afforded highly diastereoselective cyclopentene-fused spirobenzofuran-3-ones **41** with moderate to excellent yields. The mechanism is similar to the enal-chalcone annulation, while the first nucleophilc homoenolate addition happened with the endocyclic double bond. Recently, the same group employed tethered enal-chalcone substrates **42** in the cyclopentene reation to form the cyclopentene fused macrocyclic ethers **43** (Scheme 3.13).[19] The process allows the synthesis of 10-13 membered heterocycles with moderate to good yields and with excellent diastereoselectivity.

Scheme 3.12: NHC-Catalyzed Annulation of Enals with Aurone Derivatives

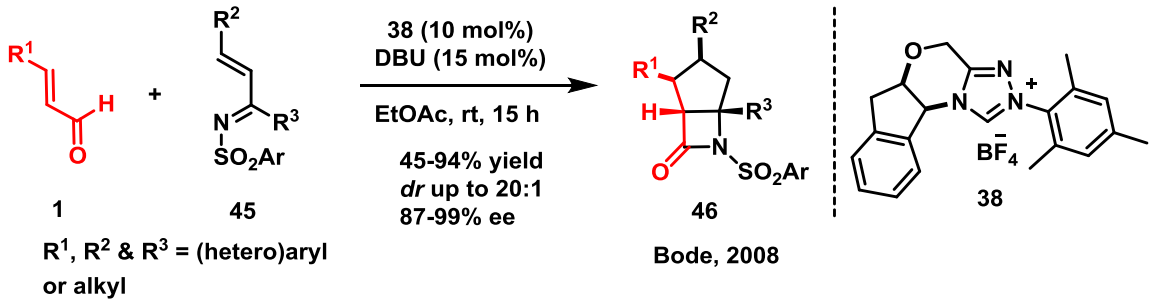


Scheme 3.13: NHC-Catalyzed Macrocycle Synthesis



Bode and He reported the conjugate addition of homoenolate to α,β-unsaturated N-sulfonyl ketimines **45** to form the cyclopentane fused β-lactams **46** (Scheme 3.14).[20] The reaction of sulfonyl ketimines **45** favours the strained β-lactam formation, in contract to the chalcone system (Scheme 3.8), which delivers the cyclopentenes through decarboxylation. The substrate scope of this reaction is good with respect to enals and imines. Yields are moderate to excellent, enantioselectivity is high and diastereoselectivity is moderate to excellent (5:1 to 20:1).

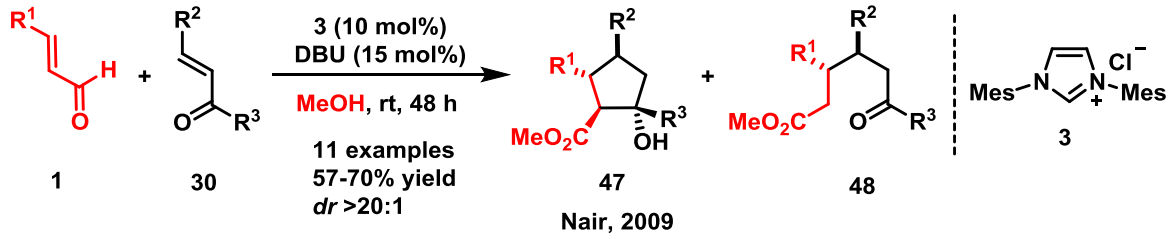
Scheme 3.14: NHC-Catalyzed Annulation of Enals and Ketimines



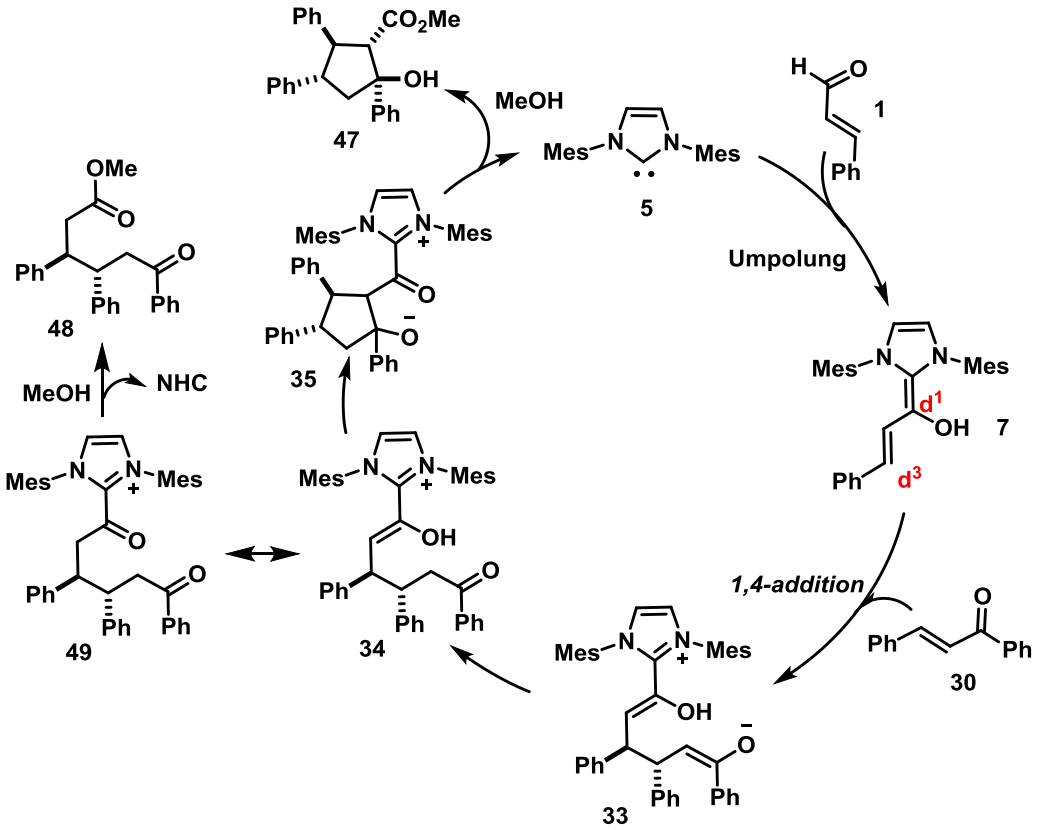
In 2009, Nair and co-workers demonstrated the synthesis of highly functionalized cyclopentanes **47** and the linear ester **48** (Scheme 3.15).[21] Mechanistically, the reaction proceeds in a similar pathway to the cyclopentene formation (Scheme 3.9). The product **47** arises from the acylation of the intermediate **35** (Scheme 3.16). Alternatively, intermediate **35** undergoes tautomerization to form the acyl-azolium **49**, which in presence of methanol

formed the linear ester **48**. The combined yield of this reaction is moderate to good (57-70%) and diastereoselectivity is high (>20:1). The product ratio varies from 2:1 to 5:1. Notably, the cyclopentane product **47** contains four contiguous stereocentres including a quaternary one.

Scheme 3.15: NHC-Catalyzed Annulation of Enals and Chalcones in Presence of MeOH

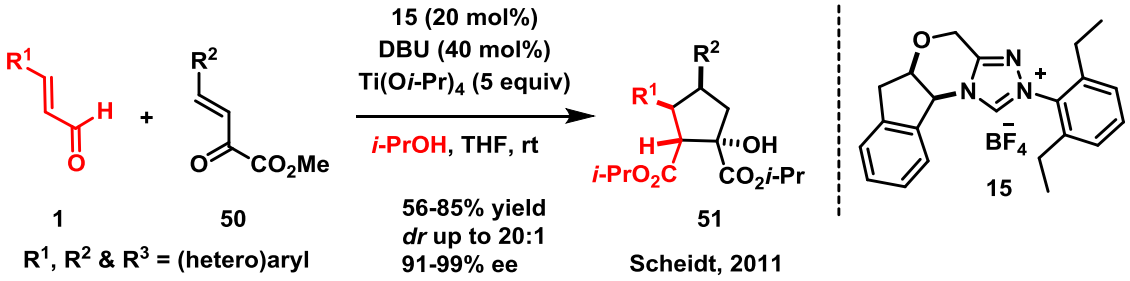


Scheme 3.16: Catalytic Cycle



Later, Scheidt and co-workers developed a NHC/Lewis acid catalyzed annulation of enals and α-keto β,γ-unsaturated esters **50** (Scheme 3.17).[22] The reaction afforded highly enantio- and diastereo-selective cyclopentane derivatives **51** in moderate to good yield. Notably, the linear ester did not form in this method. The enals with aromatic and aliphatic substitutions were well tolerated, but requires the use of aryl keto esters.

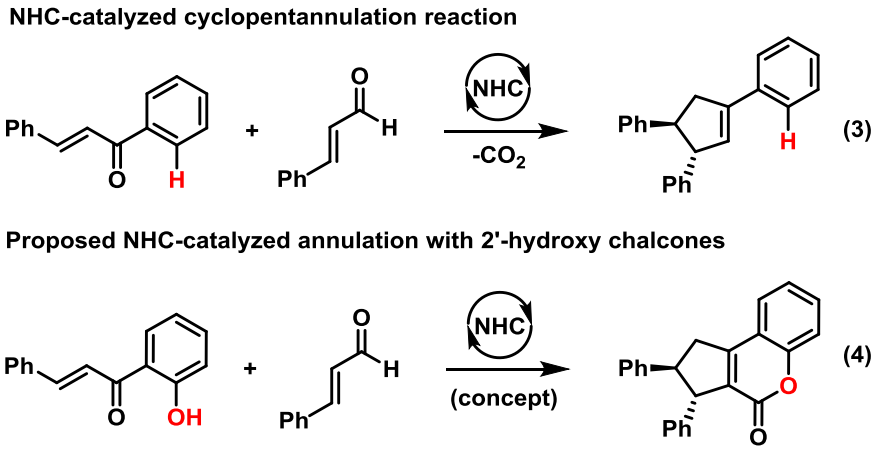
Scheme 3.17: NHC-Catalyzed Annulation of Enals and α-Keto β,γ-Unsaturated Esters by Scheidt et al.



3.3. Statement of the Problem

As mentioned in the previous section, the NHC-catalyzed generation of the homoenolate and its subsequent interception with a variety of electrophiles are well documented. The annulation of enals with chalcones are studied by several groups, however all the methods furnished 1,3,4-trisubstituted cyclopentenes (Scheme 3.8-3.13). We envisaged that if the reaction is carried out using hydroxy chalcones, there is a possibility of δ-lactonization to furnish functionalized coumarin derivatives (Scheme 3.18).

Scheme 3.18: Proposed Methodology



A detailed study of the intermolecular homoenolate reaction of enals with 2'-hydroxy chalcones is carried out and the details are presented in this chapter.[23] This investigation revealed a high yielding method for the synthesis of cyclopentane-fused coumarin derivatives with an excellent level of diastereoselectivity. Moreover, we have carried out priliminary mechanistic studies to confirm the reaction pathways. Notably, functionalized coumarin derivatives are biologically important and some of them have fluorescent properties.[24]

3.4. Results and Discussion

3.4.1. Optimization Studies

To validate our assumption, we started a preliminary study with the treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** with *trans*-cinnamaldehyde **1a** (Scheme 3.19). Treatment of **52a** with **1a** in the presence of the carbene generated from **3** by deprotonation using DBU resulted in the formation of functionalized coumarin derivative **53a** in 88% yield with a diastereoselectivity of >20:1 (based on ^{1}H NMR spectroscopy). Interestingly, the corresponding cyclopentene **54** did not form under the present conditions. The redox esterification was largely suppressed under the present reaction conditions.[25] The structure and stereochemistry of **53a** was unequivocally confirmed by single-crystal X-ray analysis (Figure 3.2).

Scheme 3.19: Intermolecular Homoenolate Annulation of Enals with 2'-Hydroxy Chalcones: Preliminary Results

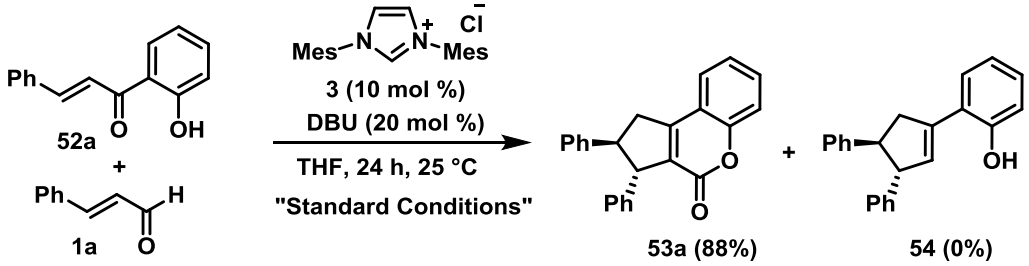
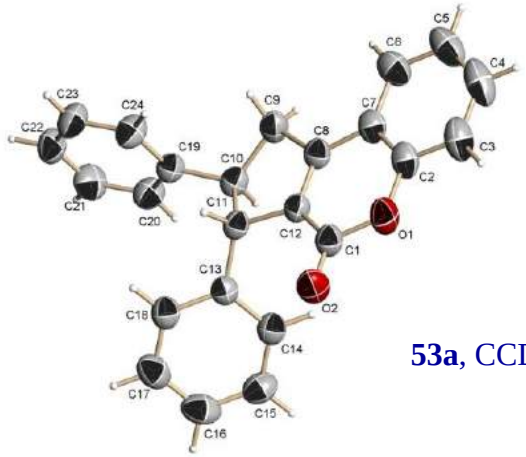


Figure 3.2: ORTEP diagram of one of the molecules of **53a** drawn at 50 % probability.



53a, CCDC-918307

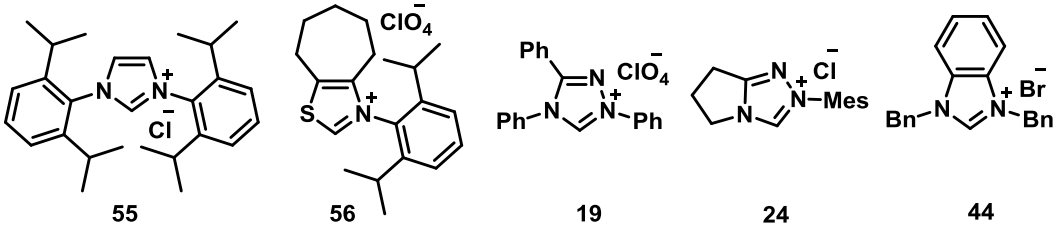
Surprisingly, in contrast to this NHC, other common NHCs are less effective (Table 1, entries 2-5). Other bases such as NaOAc, KO*t*-Bu, NEt_3, and DMAP furnished the desired product in reduced yields (entries 6-10). Among the various solvents screened, THF and

1,4-dioxane resulted in comparable result (entries 1 and 11) whereas the reaction carried out in other solvents such as toluene and CH_2Cl_2 resulted in inferior yields of **53a** (entries 12,13). Delightfully, reaction carried out in DME showed excellent reactivity with a selectivity of >20:1 (entry 14). Additionally, reaction carried out using 7 mol % of **3** and 14 mol % loading of DBU, resulted in reduced the yield of **53a** (entry 15).

Table 2.1: Optimization Studies [a]

entry	variation of the standard conditions[a]	*dr*[b]	yield of **53a** (%)[c]
1	None	>20:1	88(86)
2	**55** instead of **3**	n.d	<1
3	**56** instead of **3**	n.d	<1
4	**19** instead of **3**	n.d	<1
5	**24** instead of **3**	>20:1	67
6	**44** instead of **3**	n.d	<1
7	NaOAc instead of DBU	>20:1	46
8	KOt-Bu instead of DBU	>20:1	86
9	Et_3N instead of DBU	>20:1	10
10	DMAP instead of DBU	>20:1	6
11	1,4-dioxane instead of THF	>20:1	89
12	Toluene instead of THF	>20:1	49
13	CH_2Cl_2 instead of THF	>20:1	50
14	DME instead of THF	>20:1	99(98)[d]
15	7 mol % of **3**, 14 mol % DBU in DME	>20:1	72

[a]Standard conditions: **52a** (0.25 mmol), **1a** (0.25 mmol), NHC·HX (10 mol %), DBU (20 mol %), THF (1.0 mL), 25 °C and 24 h. [b] *dr* determined by ^{1}H-NMR analysis of crude products. [c] The yields were determined by ^{1}H-NMR analysis of crude products using CH_2Br_2 as the internal standard, Isolated yield in 1.0 mmol scale in parentheses. [d] The reaction was completed in 12 h.



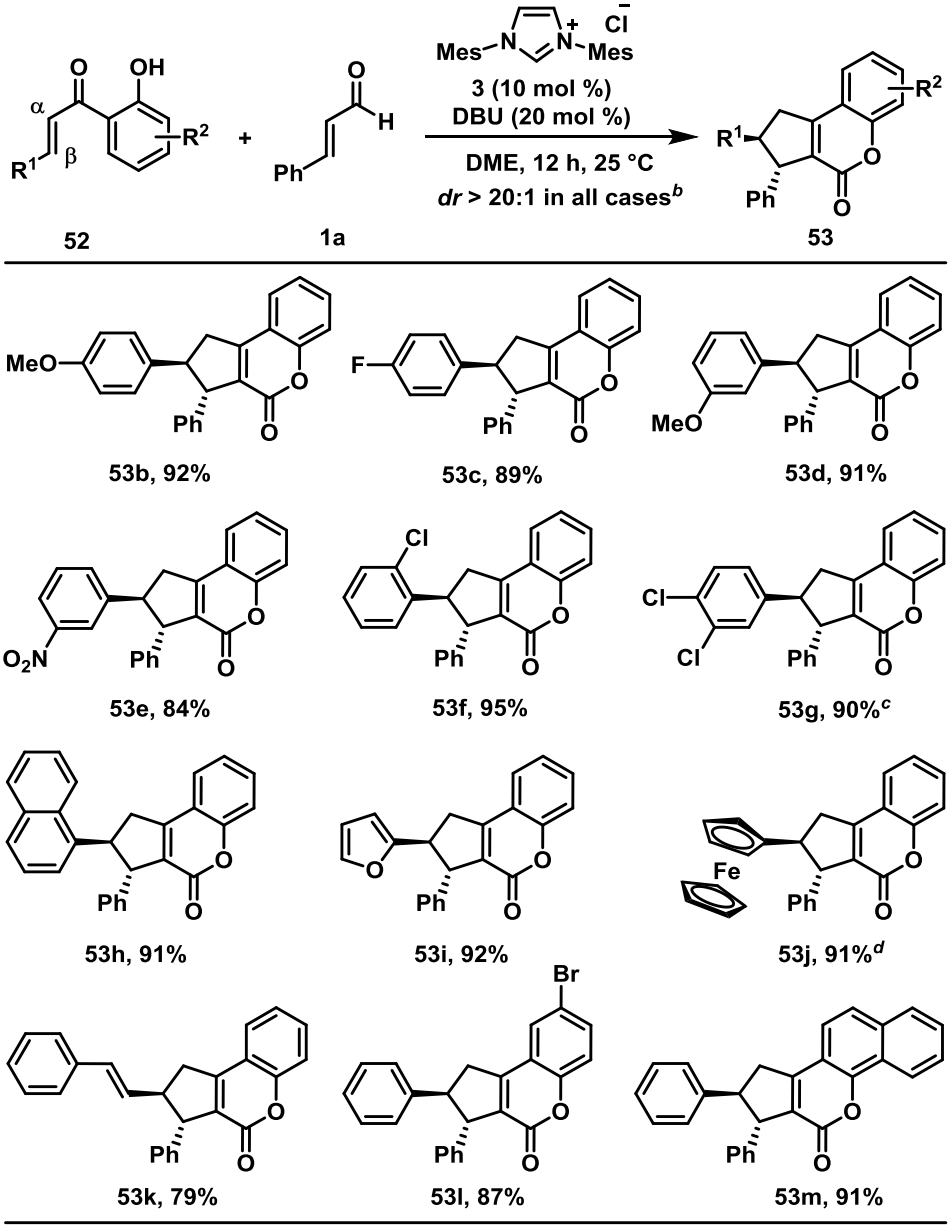
55 56 19 24 44

3.4.2. Annulation of Enals and 2'-Hydroxy Chalcones: Substrate Scope

With this reaction conditions in hand, first we evaluated the substrate scope of this unique homoenolate annulation reaction (Scheme 3.20). Electron donating and -withdrawing groups at the 4-position of the aromatic ring at β-position of **52** are well tolerated leading to the formation of cyclopentane-fused coumarin derivatives in 89-92%

yields and excellent diastereoselectivity of >20:1 in all cases (**53b** & **53c**). Moreover, substitution at 3-position and 2-position of β-aromatic ring resulted in a smooth conversion to the product (**53d-53f**). Additionally, disubstitution and the naphthyl moiety at β-position of **52** afforded the desired product in excellent yield (**53g** & **53h**). Furthermore, heteroaromatic group and ferrocenyl moiety at β-position also derived the coumarins with

Scheme 3.20: Substrate Scope for the Synthesis of Functionalized Coumarins: Variation of the 2'-Hydroxy Chalcones Moiety [a]

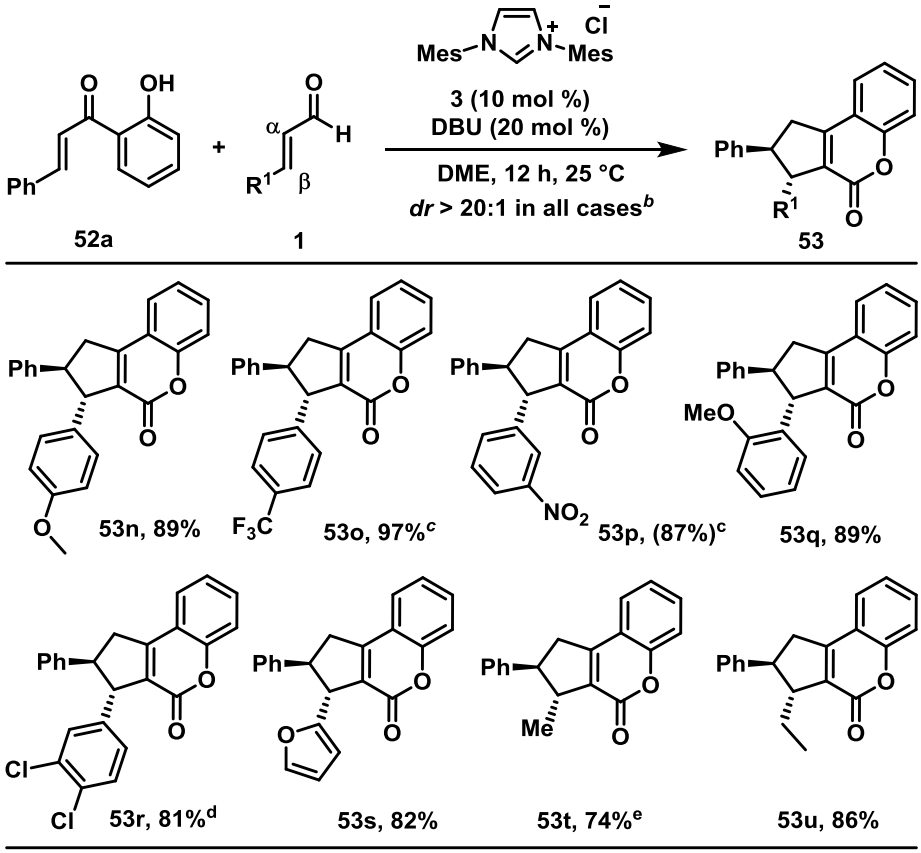


[a] General reaction conditions: **52** (1.0 mmol), **1a** (1.0 mmol), **3** (10.0 mol %), DBU (20.0 mol %) in DME (4.0 mL) at 25 °C for 12 h. [b] Determined by ^{1}H-NMR analysis of crude products. [c] Reaction run on 0.50 mmol scale. [d] Reaction run on 0.25 mmol scale.

excellent yields (**53i** & **53j**). Interestingly, it was observed that additional conjugation at β-position has no effect in the course of the reaction and the corresponding product **53k** was formed in 79% yield. Finally, the substitution at the benzoyl moiety of **52** was well tolerated leading to the formation of the desired products (**53l** & **53m**) in good yields.

In view of these interesting results, we further investigated the tolerance of this reaction with various α,β-unsaturated aldehydes **1** (Scheme 3.21). Electron donating and -withdrawing groups at the *para*-position of the β-aryl ring of **1** were well tolerated, leading to synthesis of coumarins in good yields and with excellent *dr* values (**53n** & **53o**).Various electronically different substituents at the *meta*-position and *ortho*-position of the aromatic ring at β-position of **1** are well tolerated affording the desired products in high yields (**53p** & **53q**). Moreover, disubstitution at the β-position of **1** afforded the product in good yield

Scheme 3.21: Substrate Scope for the Synthesis of Functionalized Coumarins: Variation of the Enals [a]



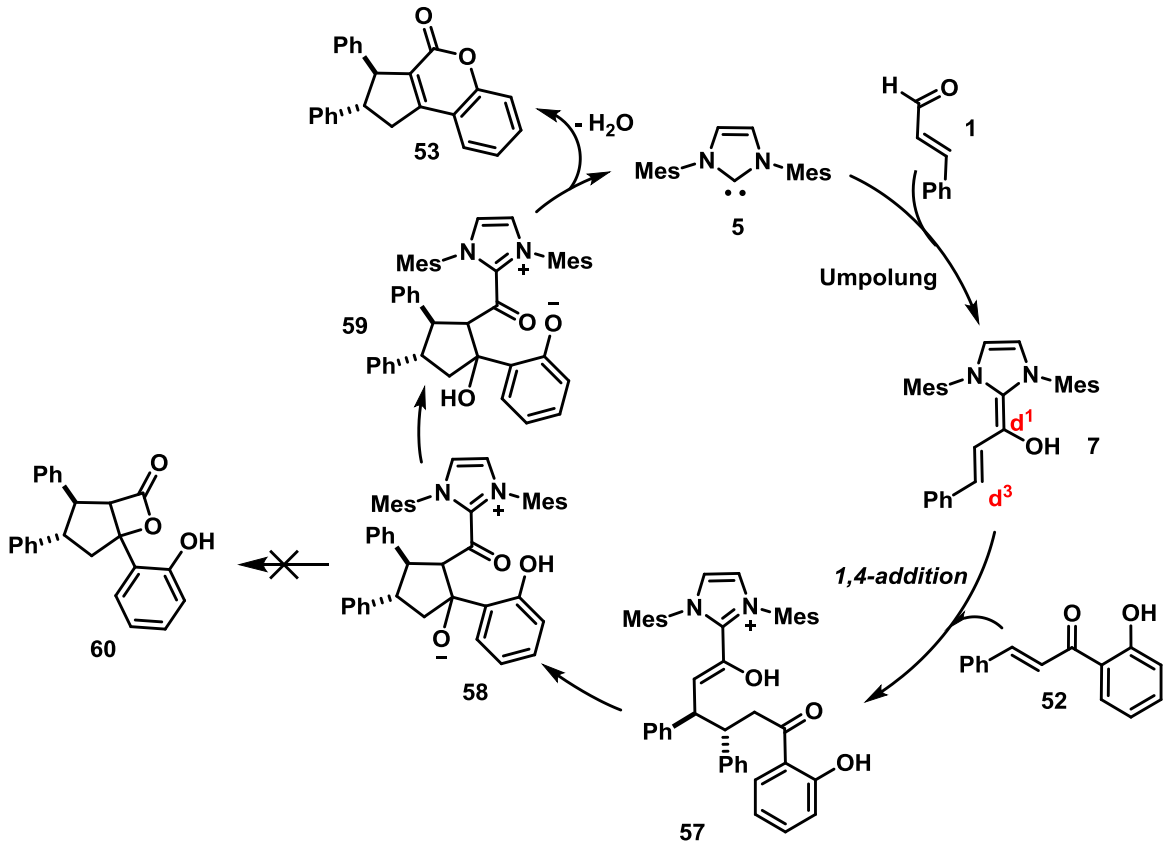
[a] General reaction conditions: **52a** (1.0 mmol), **1** (1.0 mmol), **3** (10.0 mol %), DBU (20.0 mol %) in DME (4.0 mL) at 25 °C for 12 h. [b] Determined by ^{1}H-NMR analysis of crude products. [c] Reaction run on 0.50 mmol scale. [d] Reaction run on 0.25 mmol scale. [e] 2-phenylchroman-4-one (54) was isolated in 22% yield.

(**53r**). Additionally, heterocyclic α,β-unsaturated aldehyde as well as aliphatic enals resulted in the formation of the cyclopentane-fused coumarin derivatives (**53s-53u**) maintaining the diastereoselectivity. Notably, in case of crotonaldehyde, the 2-phenyl chroman-4-one (**54**) was also isolated in 22% yield.

3.4.3. Reaction Mechanism

The reaction proceeds via the generation of homoenolate intermediate **7** from the enal **1** and the NHC **5**. The conjugate addition of **7** to the 2'-hydroxy chalcone **52** followed by the proton transfer generates the enolate **57**, which undergoes intramolecular aldol reaction generating intermediate **58**. The intermediate **58** undergoes an intramolecular proton transfer to afford phenoxide **59** followed by δ-lactonization and dehydration to furnish the coumarin derivative **53**. Due to the presence of the second nucleophilic site in **52**, the alkoxide intermediate **58** avoids the high energy β-lactonization and hence the β-lactone **60** is not formed in this case.

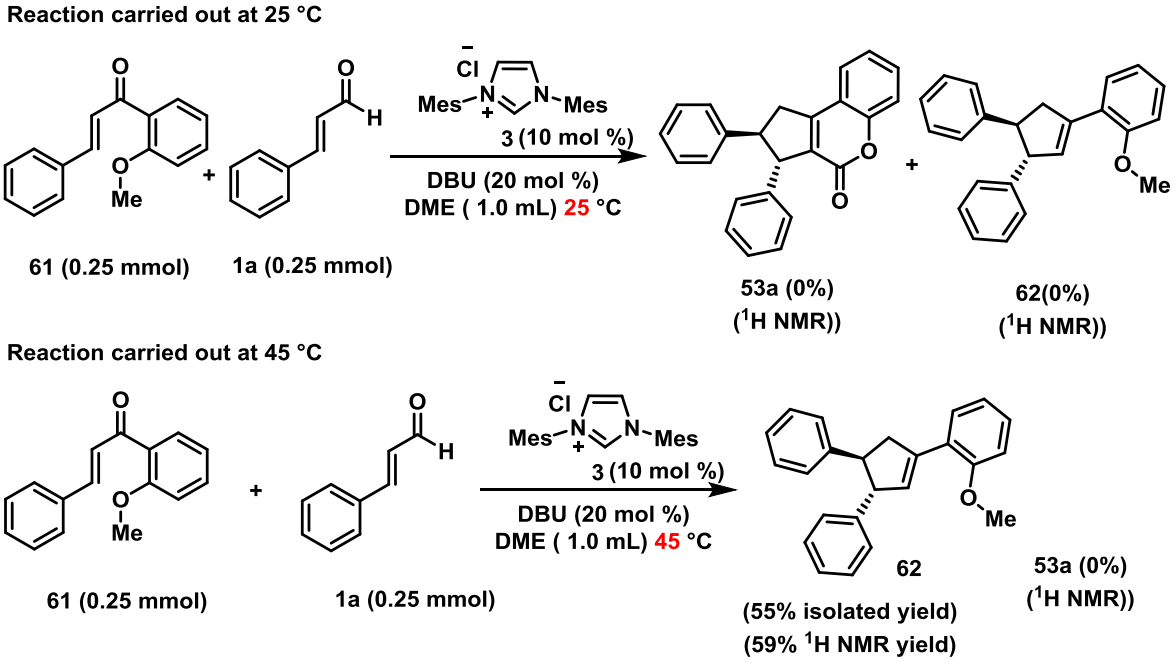
Scheme 3.22: Proposed Mechanistic Pathways



3.4.4. Mechanistic Studies

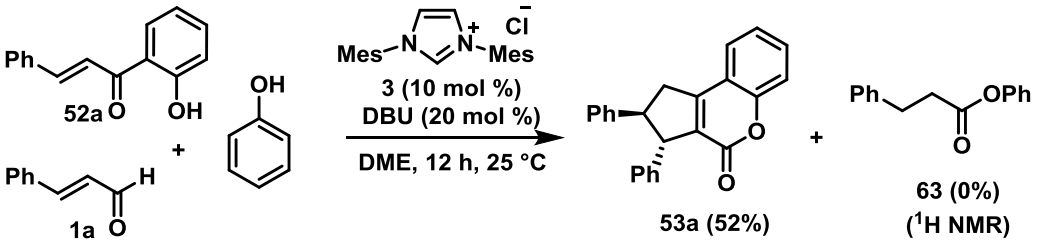
To gain mechanistic insight on this reaction, the -OH group at 2'-position was protected (substrate **61**). Interestingly, the reaction did not work under the optimized conditions. When the reaction was carried out at 45 °C, the cyclopentene derivative **62** was formed in 55% yield (Scheme 3.23). No detectable formation of **53a** was observed and this indicates the importance of free -OH group at 2'-position for the δ-lactonization. NMR data has been provided in the experimental section.

Scheme 3.23: Reaction with Protected –OH Group



An additional experiment was performed in presence of external proton source, the reaction was carried out with stoichiometric amounts of phenol. Gratifyingly, even in the presence of additional proton source, the desired product **53a** was formed in 52% yield and no detectable amounts of the redox esterification product **63** was observed (Scheme 3.24).[25]

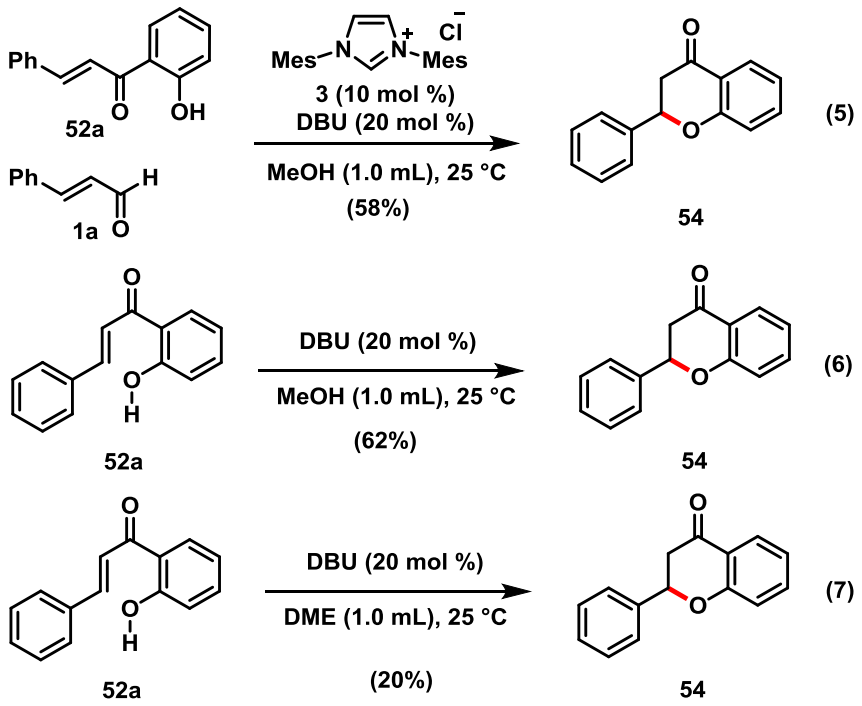
Scheme 3.24: Controlled Experiment in Presence of Extra Proton Source



This result tends to indicate that the proton transfer events are *intramolecular* (Scheme 3.22) and the nucleophilic attack of homoenolate equivalent **7** onto **52** is energetically favourable than its protonation (leading to redox-esterification product).

To shed more light on the reaction mechanism, a reaction was performed using methanol as a solvent under the optimized reaction conditions (Scheme 3.25).[21] The 2'-hydroxy chalcone **52a** undergoes intramolecular cyclization to form 2-phenyl chroman-4-one **54**. No participation of *trans*-cinnamaldehyde **1a** was observed (Scheme 3.25; Eq. 5). Interestingly, just stirring **52a** in methanol in the presence of 20 mol % DBU for 12 h afforded **54** in 62% yield. This indicates that in methanol, **52a** undergoes intramolecular cyclization catalyzed by DBU leading to the formation of **54** (Scheme 3.25; Eq. 6). Moreover, in DME, the blank reaction afforded 20% of **54** in presence of 20 mol% of DBU (Scheme 3.25; Eq. 7).

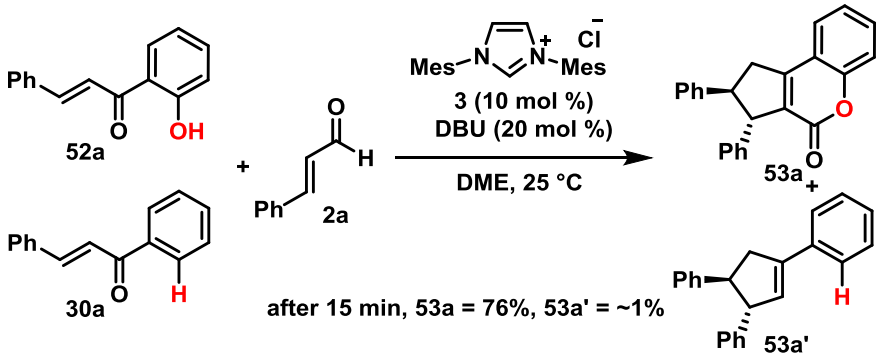
Scheme 3.25: Controlled Experiment in Presence of Protic Solvent



A kinetics study has been preformed to investigate the ease of δ-lactonization over β-lactonization. Intermolecular competition experiments carried out between 2'-hydroxy chalcone **52a** and chalcone **30a** revealed that **52a** reacted ~75 times faster than **30a** indicating the preferential formation of **53a** (Scheme 3.26). The low rate of formation of

53a' may be due to the fact that this reaction proceeds via the high energy β-lactone intermediate. These observations indicate that the thermodynamically more feasible δ-lactonization proceeds over the high energy β-lactonization. Alternatively, the H-bonding interaction in **52** can also enhance its reactivity with homoenolate equivalent **7** (Scheme 3.22).

Scheme 3.26: Competition Experiment between Chalcone and 2'-Hydroxy Chalcone



3.5. Conclusion

In conclusion, we have developed a metal-free and scalable NHC-organocatalyzed homoenolate annulation with hydroxy chalcones to furnish functionalized coumarin derivatives in good to excellent yields. The key to success of the present reaction is the ease of δ-lactonization over the β-lactonization. Moreover, broad substrate scope, high yields of products, and mild reaction conditions are the notable features of the present reaction.

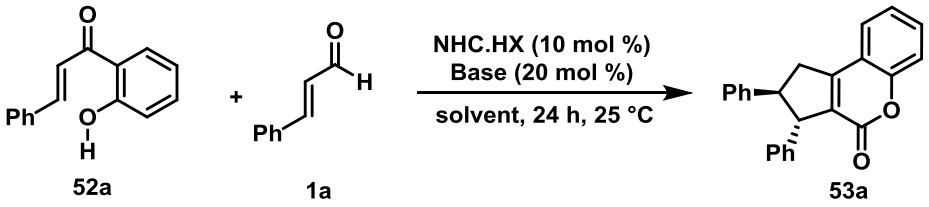
3.6. Experimental Details

3.6.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw cap. Dry DME was purchased from commercial sources and stored under argon over 4 Å molecular sieves. The 2'-hydroxy acetophenone derivatives were purchased from commercial sources and they were used without any further purification. The α,β-unsaturated aldehydes **1** were synthesized from corresponding aldehydes following the literature procedure.[26] DBU was purchased from Sigma Aldrich and was distilled, prior to use. The imidazolium salt **3** was synthesized following the literature procedure.[27] The 2'-hydroxy chalcones **52** used in the present study were prepared following the procedure by Bai and coworkers.[28]

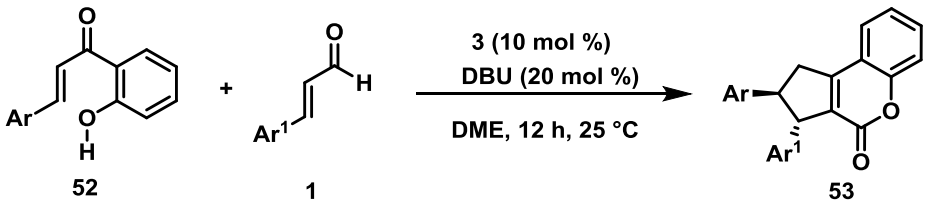
Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or KMnO4 staining solutions followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with solvents as indicated. All compounds were fully characterized. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400, AV 500, and JEOL 400 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Infrared spectra were recorded on a Perkin-Elmer 1615 FT Infrared Spectrophotometer Model 60B. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

3.6.2. General Procedure for the Optimization of Reaction Conditions



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the azolium salt NHC.HX (0.025 mmol) and (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (56 mg, 0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in DME (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 25 °C. To this mixture was added the *trans* cinnamaldehyde **1a** (33 mg, 31 μL, 0.25 mmol) followed by the addition of DBU (7.6 mg, 7.5 μL, 0.05 mmol). After 24 hour stirring, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^{1}H NMR using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard.

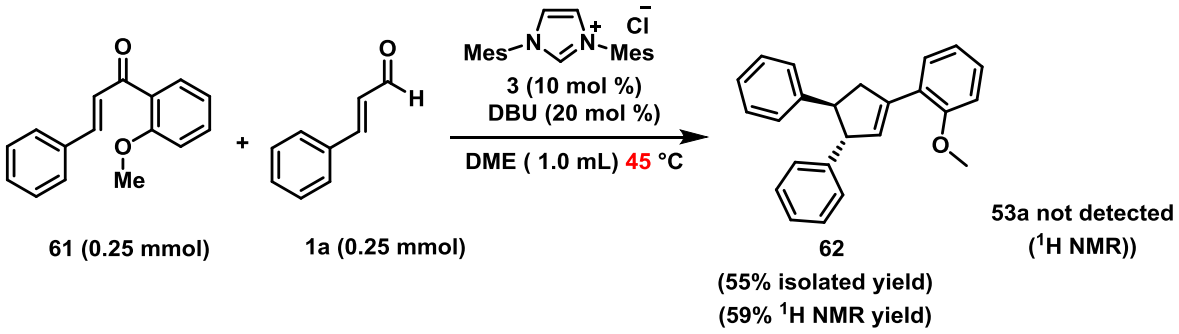
3.6.3. General Procedure for the NHC-Catalyzed Annulation Reaction



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the imidazolium salt **3** (0.034 g, 0.1 mmol) and the 2'-hydroxychalcone **52** (1.0 mmol) was added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added DME (4.00 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 25 °C. To this mixture was added the aldehyde **1** (1.0 mmol) (*solid* aldehydes were transferred to the screw-capped tube by closing the argon flow and *liquid* aldehydes were transferred via syringe under argon flow) and the DBU (0.030 gm, 30 μL, 0.20 mmol) were successively added. Then the reaction mixture was stirred at 25° C for 12 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding functionalized coumarin derivatives **53**.

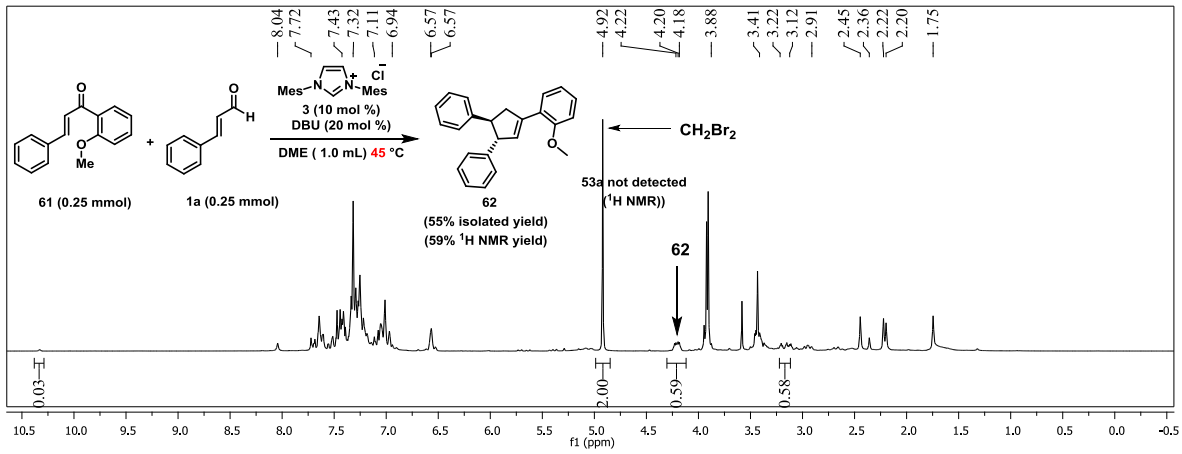
3.6.4. Mechanistic Experiments

a) Reaction Employing 2'-Methoxy Chalcone as Substrate

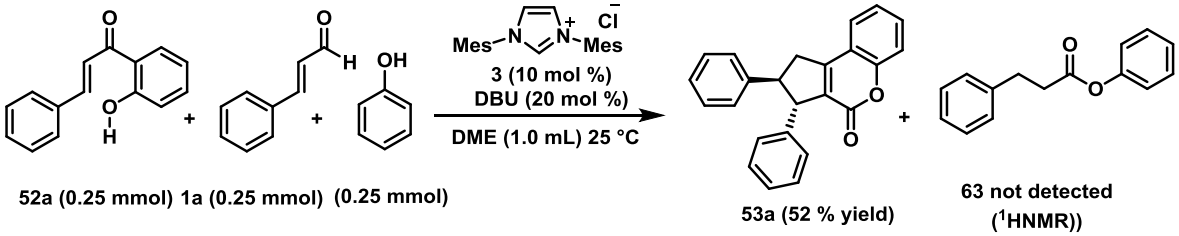


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the imidazolium salt **3** (8.5 mg, 0.025 mmol) was added. Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in DME (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 25 °C. To this mixture was added the (*E*)-1-(2-methoxyphenyl)-3-phenylprop-2-en-1-one **61** (60 mg, 0.25 mmol) and the *trans*-cinnamaldehyde **1a** (33 mg, 31 μL, 0.25 mmol) was successively added followed by DBU (7.6 mg, 7.5 μL, 0.05 mmol). Then the reaction mixture is placed in a preheated oil bath at 45 °C. After 12 h, the reaction mixture cooled and the mixture was diluted with CH_2Cl_2 (5.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2. The solvent was evaporated and the crude residue purified by flash column chromatography on silica gel to afford (4-(2-methoxyphenyl)cyclopent-3-ene-1,2-diyl)dibenzene **62** (45 mg, 55%).

^{1}H-NMR of Crude Reaction Mixture after 12 h at 45 °C ($CDCl_3$)

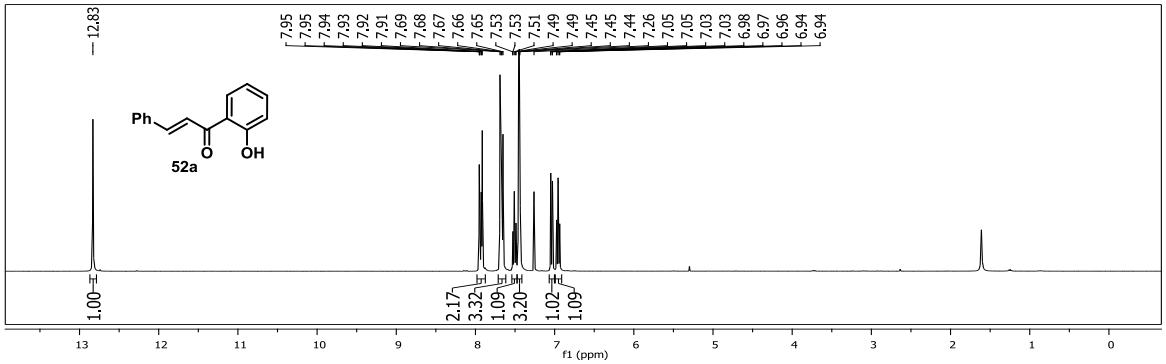


b) Reaction in the Presence of Phenol

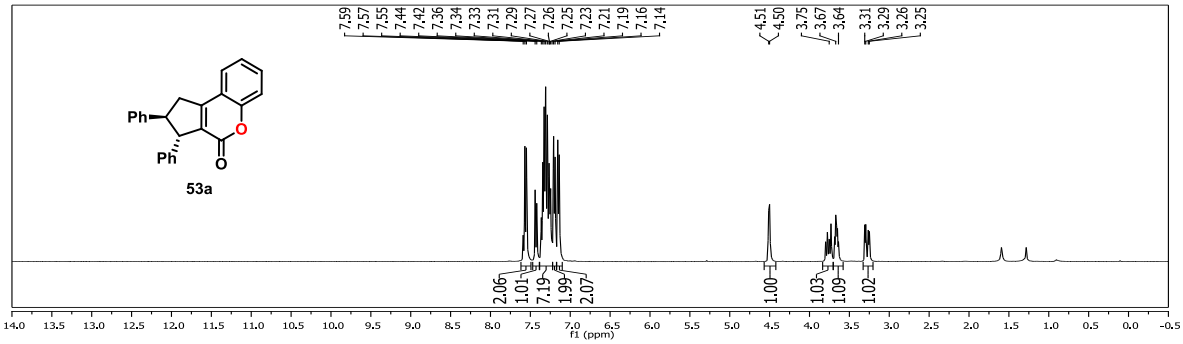


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the imidazolium salt **3** (8.5 mg, 0.025 mmol), (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (56 mg, 0.25 mmol) and phenol (23.6 mg, 0.25 mmol) was added. Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in DME (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 25 °C. To this mixture was added the *trans*-cinnamaldehyde **1a** (33 mg, 31 μL, 0.25 mmol) followed by DBU (7.6 mg, 7.5 μL, 0.05 mmol). After 12 hour stirring the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^{1}H NMR using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard. ^{1}H NMR analaysis shows that the crude mixture contains 52% product, 33% unreacted hydroxyl chalcone **52a,** and 30% unreacted *trans* cinnamaldehyde **1a**, but there is no detectable amounts of phenyl 3-phenylpropanoate **63**.

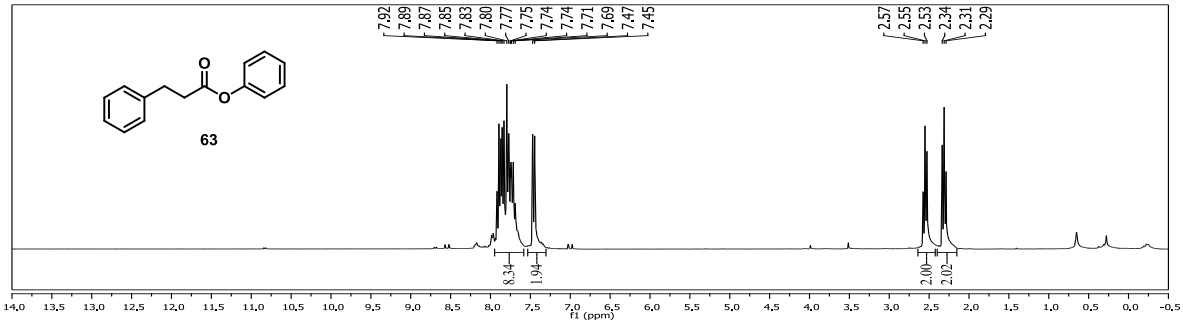
^{1}H-NMR Spectrum of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (52a)



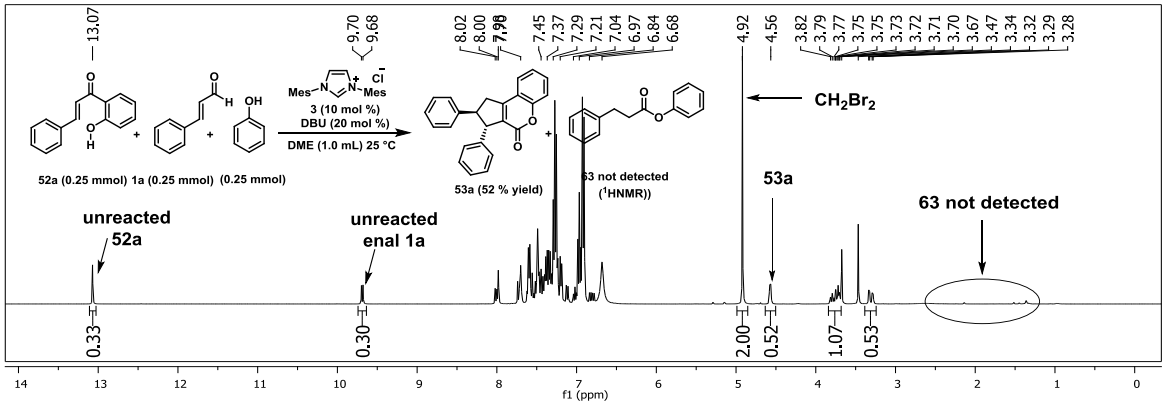
^{1}H-NMR Spectrum of 2,3-diphenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53a)



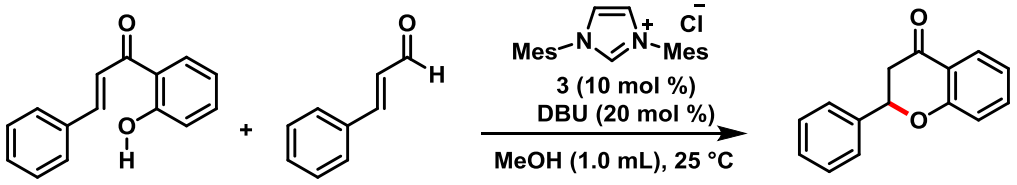
^{1}H-NMR of phenyl 3-phenylpropanoate (63)



^{1}H-NMR of Crude Reaction Mixture after 12 h ($CDCl_3$)



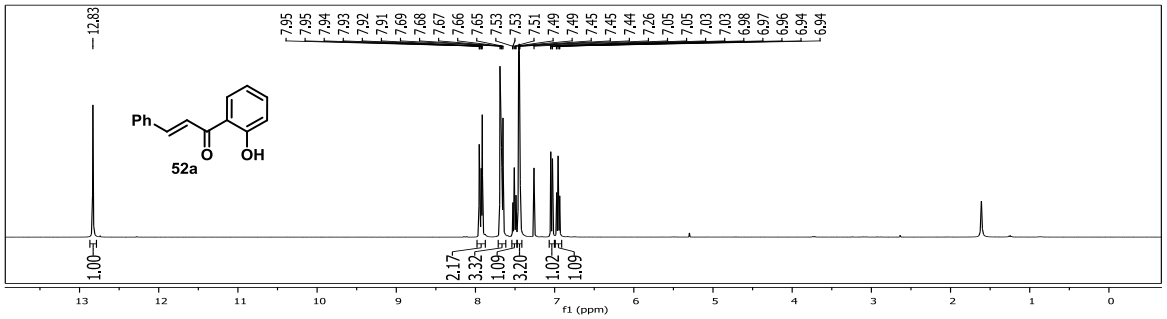
c) Reaction Employing Methanol as the Solvent



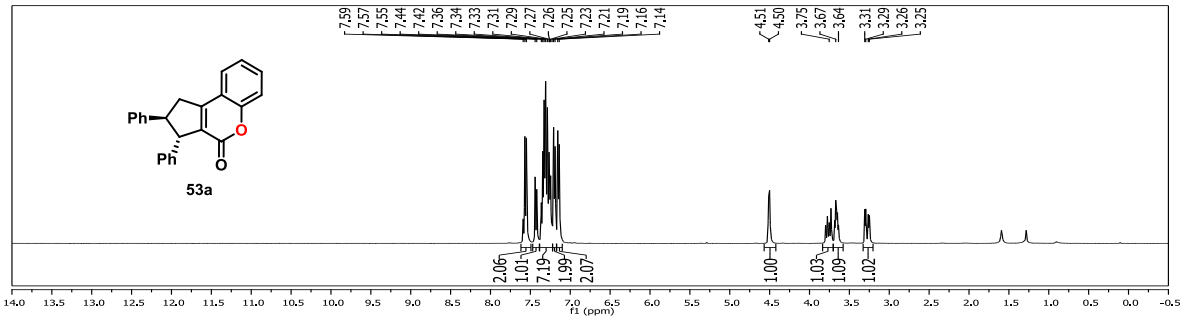
52a (0.25 mmol) **1a (0.25 mmol)** **54 (58%)**

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the imidazolium salt **3** (8.5 mg, 0.025 mmol) and (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (56 mg, 0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in MeOH (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 25 °C. To this mixture was added the *trans*-cinnamaldehyde **1a** (33 mg, 31 µL, 0.25 mmol) followed by DBU (7.6 mg, 7.5 µL, 0.05 mmol). After 12 hour stirring, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^{1}H NMR using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. ^{1}H NMR analysis shows that the crude mixture contains 58% of 2-phenylchroman-4-one **54**.

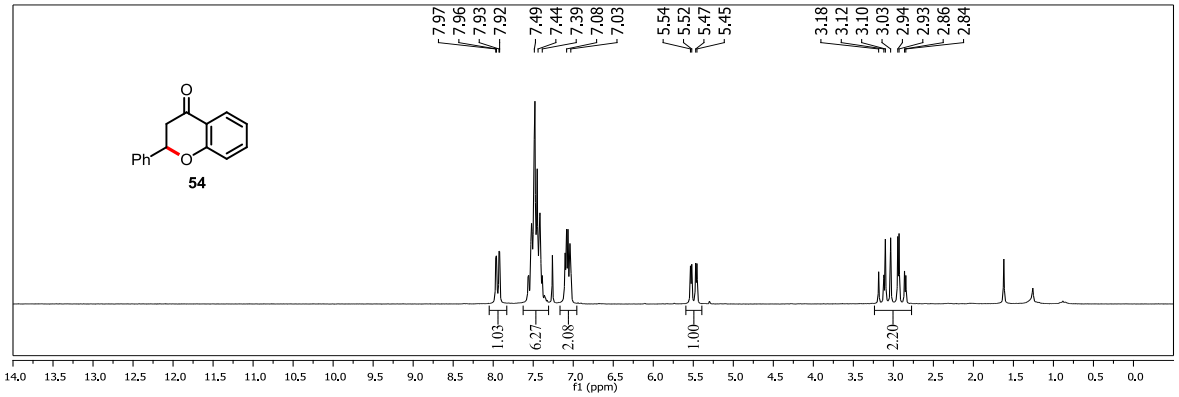
^{1}H-NMR Spectrum of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (52a)



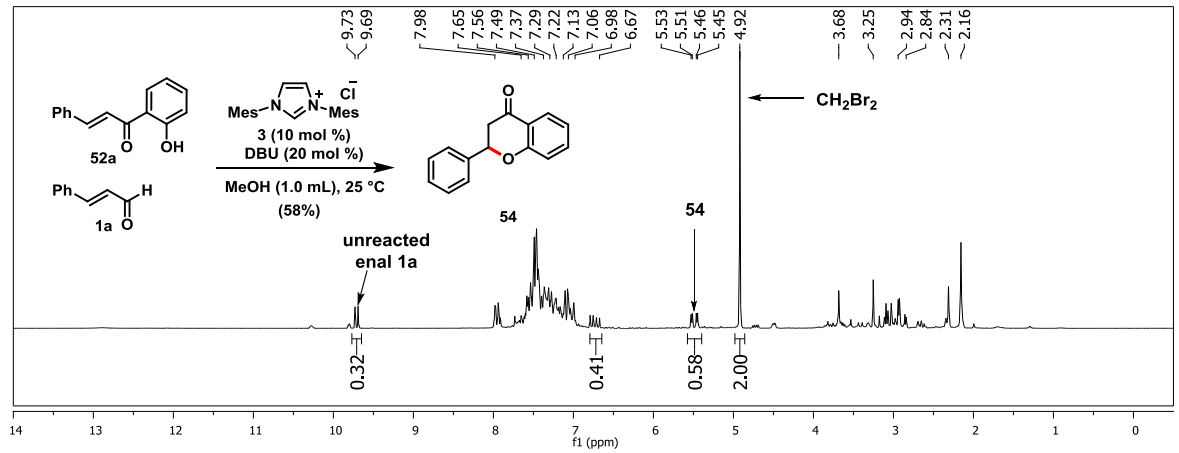
^{1}H-NMR Spectrum of 2,3-diphenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53a)



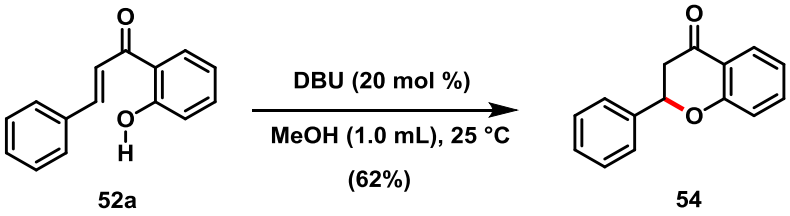
^{1}H-NMR Spectrum of 2-phenylchroman-4-one (54)



^{1}H-NMR of Crude Reaction Mixture after 12 h ($CDCl_3$)



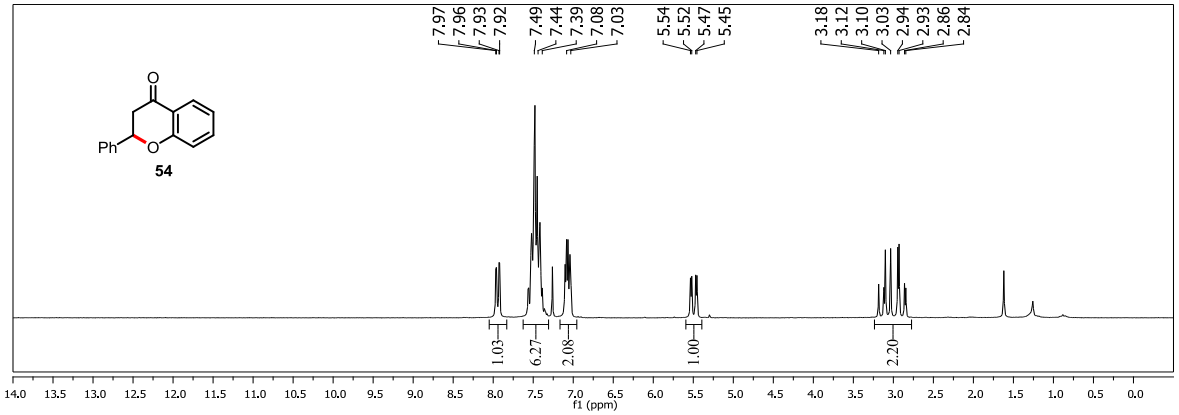
d) Blank Reaction in Methanol as the Solvent and DBU as the Catalyst



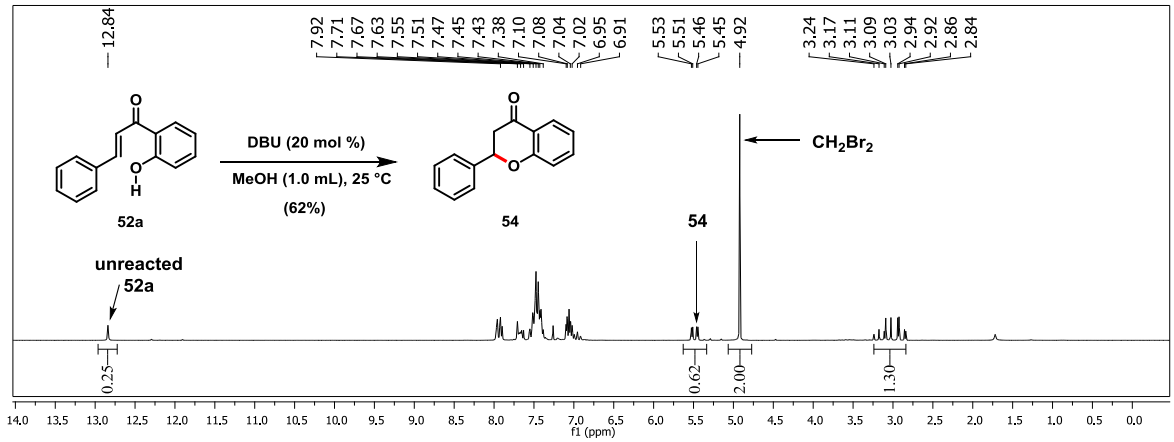
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (56 mg, 0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in MeOH (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 25 °C. To this mixture was added DBU (7.6 mg, 7.5 µL, 0.05 mmol). After 12 hour stirring the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the

crude product, which was analyzed using ^{1}H NMR using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard. ^{1}H NMR analaysis shows that the crude mixture contains 62% 2-phenylchroman-4-one **54**.

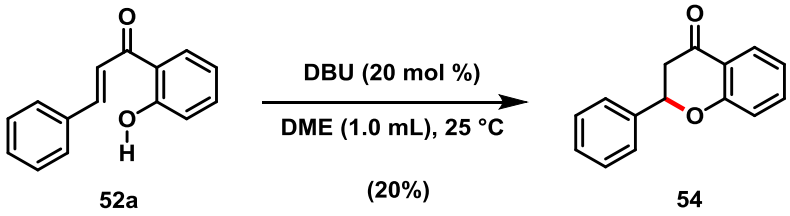
1H-NMR Spectrum of 2-phenylchroman-4-one (54)



^{1}H-NMR of Crude Reaction Mixture after 12 h ($CDCl_3$)



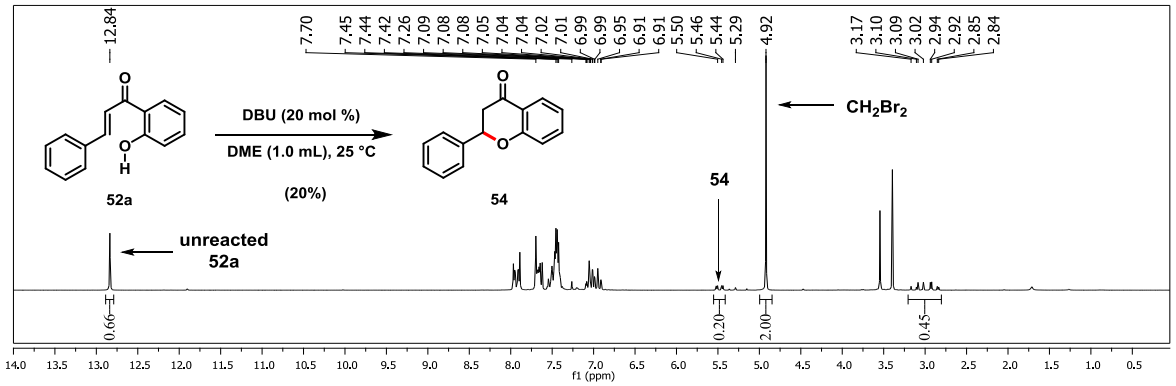
e) Blank Reaction in DME as the Solvent



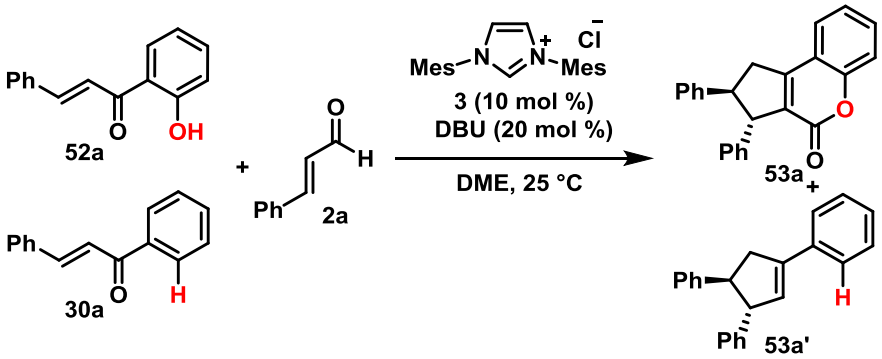
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (56 mg, 0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in DME (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 25 °C. To this mixture was added DBU (7.6 mg, 7.5 μL, 0.05 mmol). After 12 hour stirring the

reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^1H NMR using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. ^1H NMR study shows that the crude mixture contains 20% 2-phenylchroman-4-one **54**.

^1H-NMR of Crude Reaction Mixture after 12 h ($CDCl_3$)



f) Competition Experiments between 2'-Hydroxy Chalcone (52a) and Chalcone (30a)



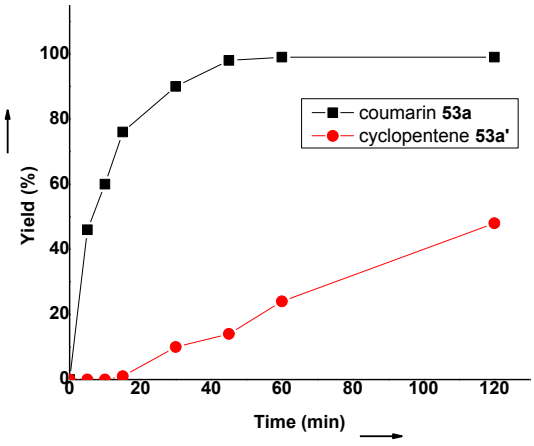
Seven reactions were carried out parallel. To each of the flame-dried screw-capped test tube equipped with a magnetic stir bar was added the imidazolium salt **3** (8.5 mg, 0.025 mmol) (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (28 mg, 0.125 mmol) and (*E*)-chalcone **30a** (26 mg, 0.125 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in DME (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 25 °C. To this mixture was added the *trans*-cinnamaldehyde **1a** (33 mg, 31 µL, 0.25 mmol) followed by DBU (7.6 mg, 7.5 µL, 0.05 mmol). After 5 minutes stirring the reaction is quenched and the mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with

CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^1H NMR using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. The same procedure is followed for other six reactions and they were quenched at 10 min, 15 min, 30 min, 45 min, 60 min, and 120 min respectively. The yields were determined by ^1H-NMR analysis of crude products using CH_2Br_2 as the internal standard.

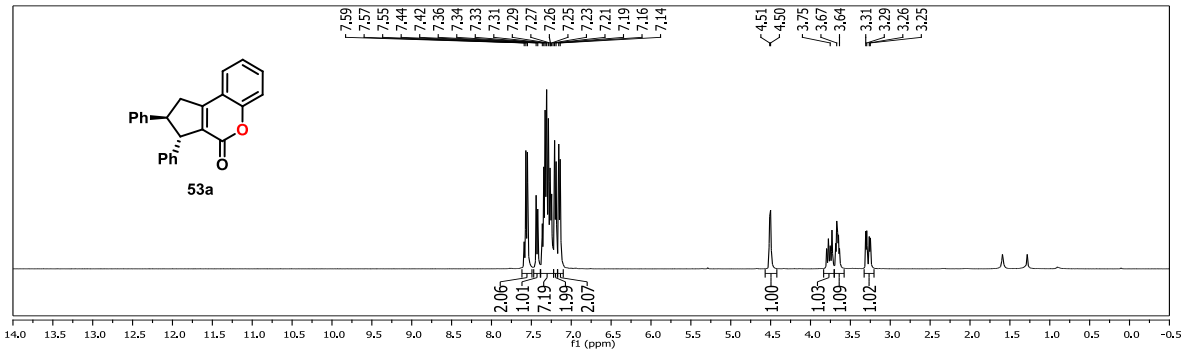
Table 3.2: Competition Experiments between 2'-hydroxy Chalcone and Chalcone

entry	Time (min)	Yield of **53a** (%)	Yield of **53a'** (%)
1	5	46	not detected
2	10	60	not detected
3	15	76	~1
4	30	90	10
5	45	98	14
6	60	>99	24
7	120	>99	48

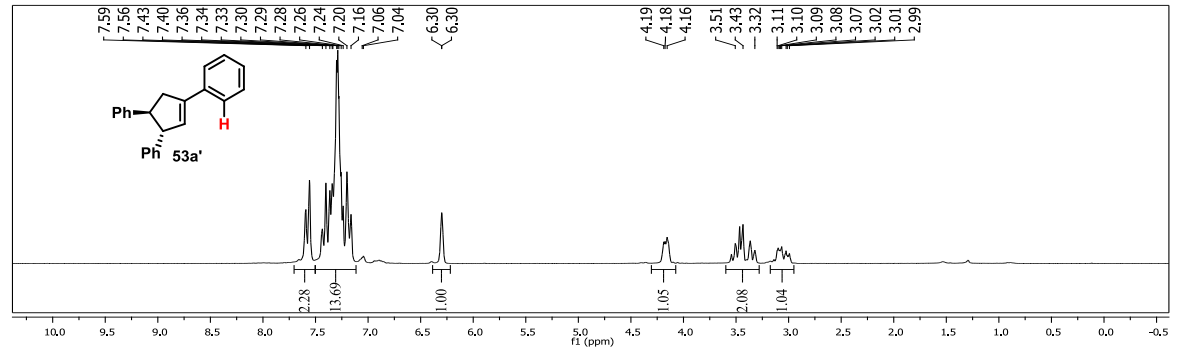
Figure 3.2. Intermolecular competition experiments between 2'-hydroxy chalcone **53a** and chalcone **53a'**



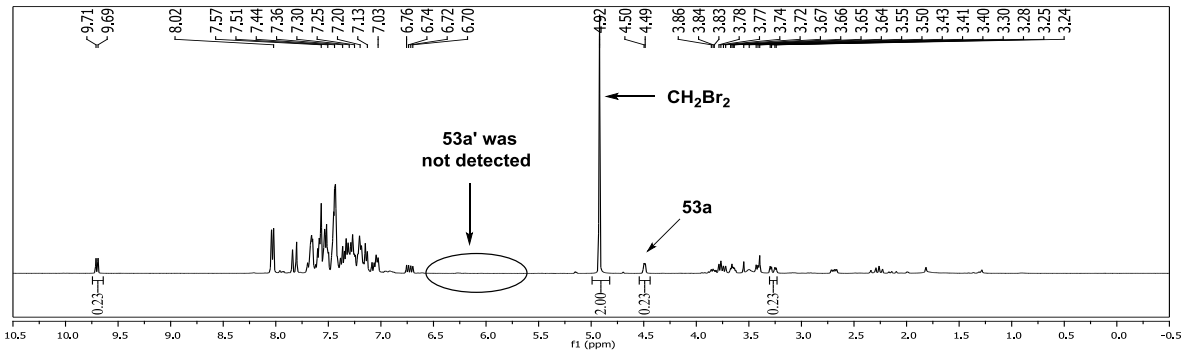
^{1}H-NMR Spectrum of 2,3-diphenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53a)



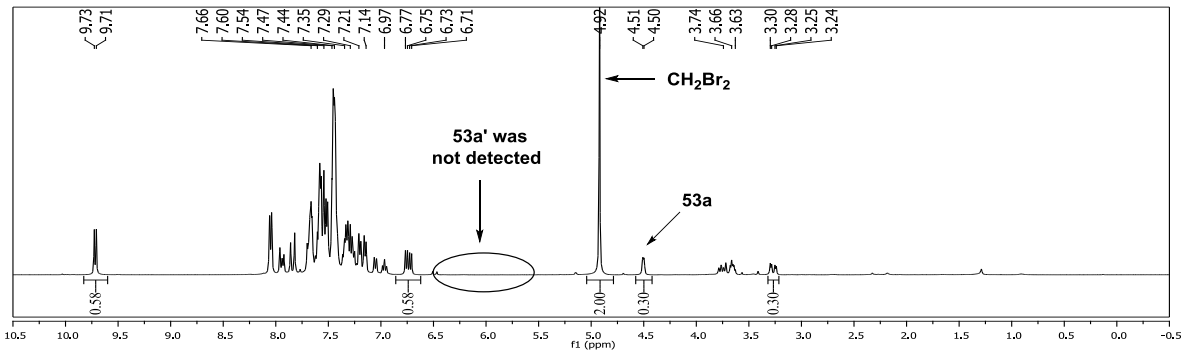
^{1}H-NMR Spectrum of cyclopent-3-ene-1,2,4-triyltribenzene (53a')



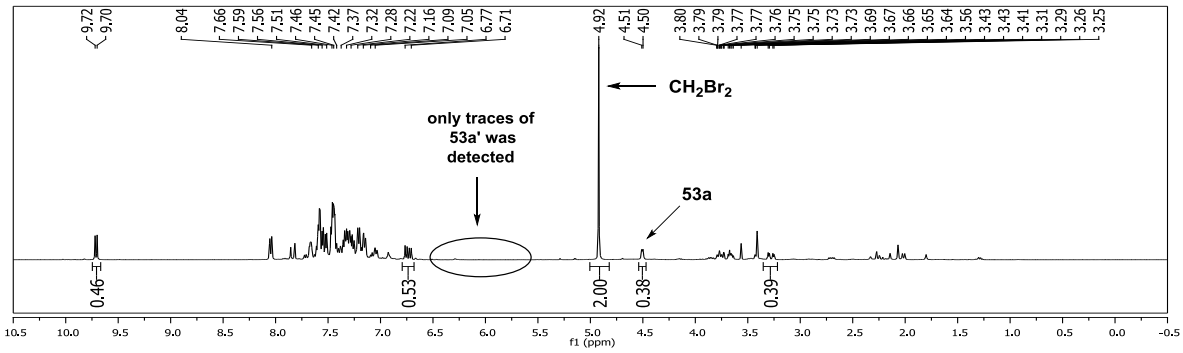
^{1}H-NMR of Crude Reaction Mixture after 5 minutes ($CDCl_3$)



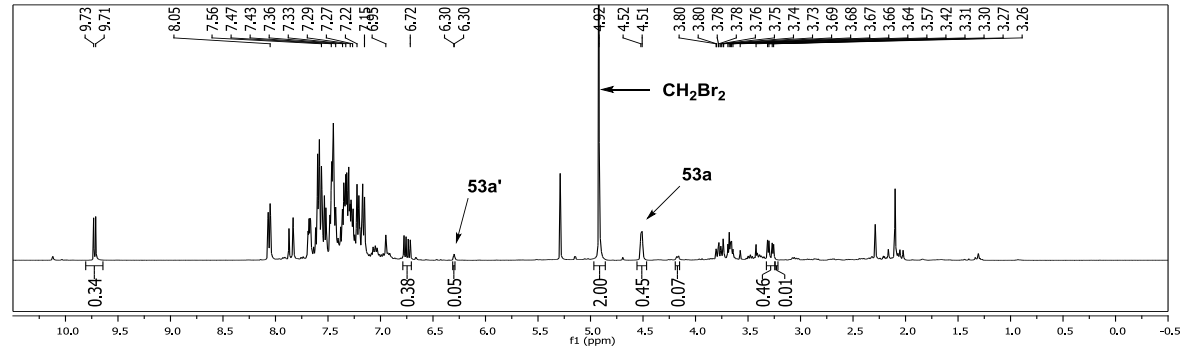
^{1}H-NMR of Crude Reaction Mixture after 10 minutes ($CDCl_3$)



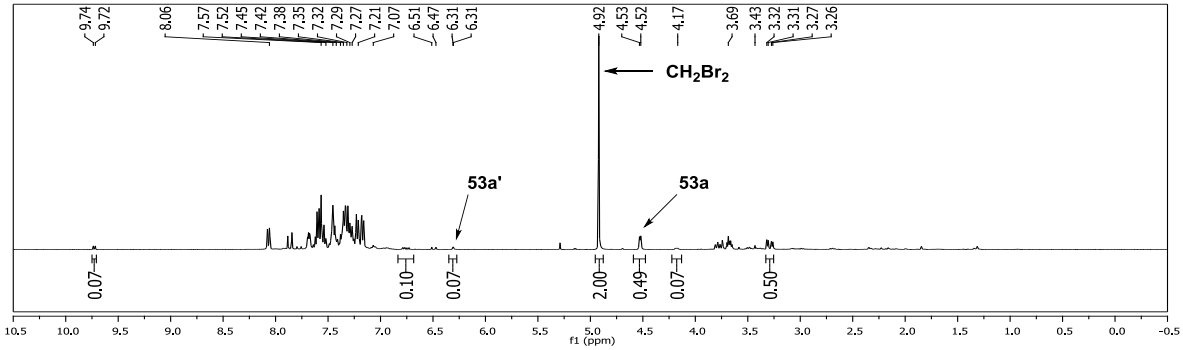
^{1}H-NMR of Crude Reaction Mixture after 15 minutes ($CDCl_3$)



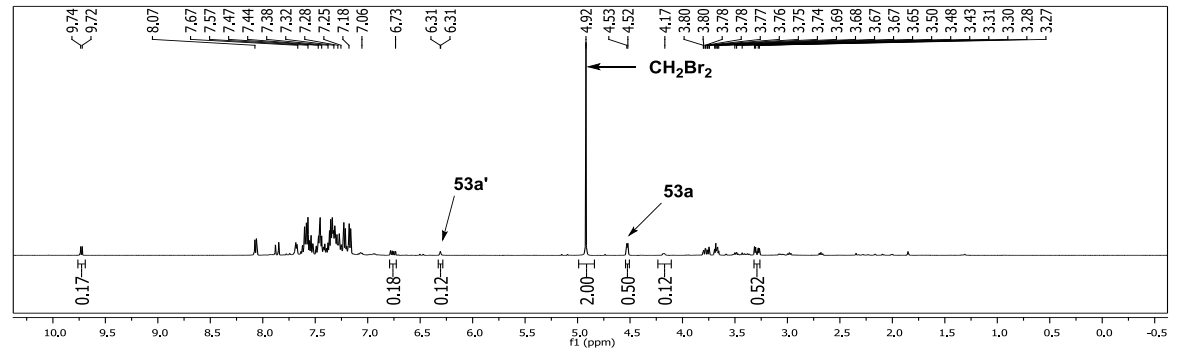
^{1}H-NMR of Crude Reaction Mixture after 30 minutes ($CDCl_3$)



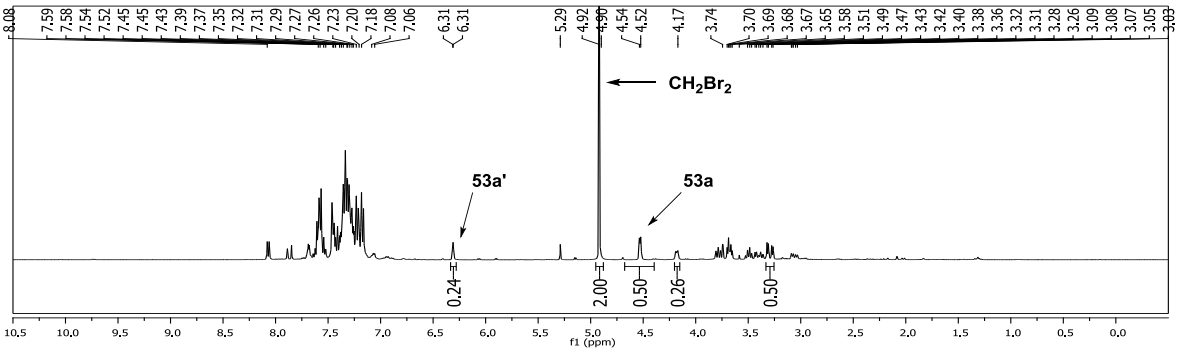
^{1}H-NMR of Crude Reaction Mixture after 45 minutes ($CDCl_3$)



^{1}H-NMR of Crude Reaction Mixture after 60 minutes ($CDCl_3$)

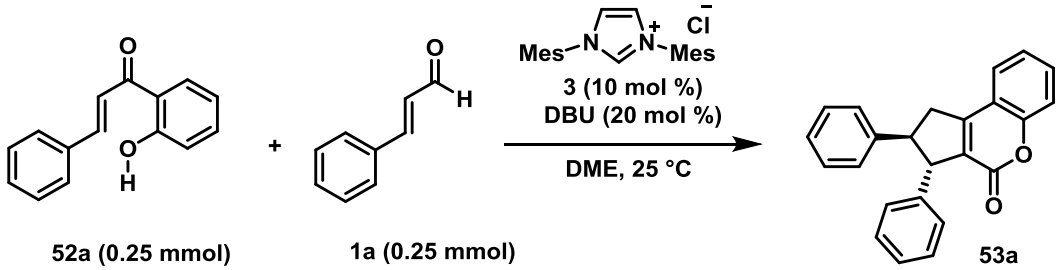


^{1}H-NMR of Crude Reaction Mixture after 120 minutes ($CDCl_3$)



*It is interesting to note, that the formation of **53a** proceeds first and the formation of cyclopentene **53a'** begins when most of **52a** has been consumed. Thus, it is reasonable to assume that the thermodynamically more feasible δ-lactonization proceeds over the β-lactonization.*

g) Kinetics Study of the Reaction

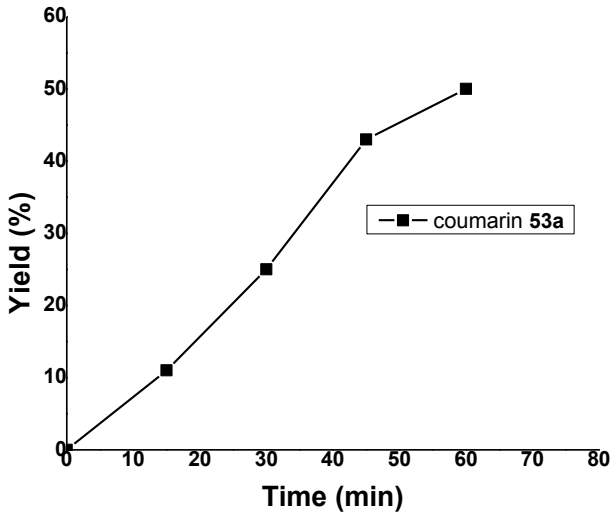


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the imidazolium salt **3** (8.5 mg, 0.025 mmol) and (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (56 mg, 0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in DME (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 25 °C. To this mixture was added the *trans*-cinnamaldehyde **1a** (33 mg, 31 μL, 0.25 mmol) followed by DBU (7.6 mg, 7.5 μL, 0.05 mmol). After 15 minutes stirring the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^{1}H NMR using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard. Similar procedure followed for other three reactions, which were analyzed after 30 min, 45 min, and 60 min respectively. The yields were determined by ^{1}H-NMR analysis of crude products using CH_2Br_2 as the internal standard.

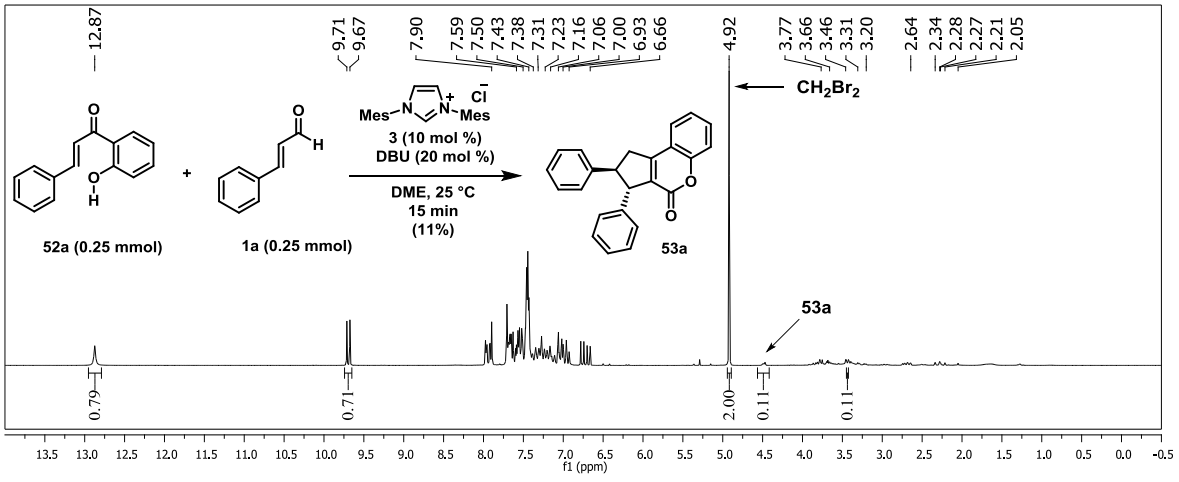
Table 3.3: Kinetics Study of the Reaction

entry	Time (min)	Yield of **53a** (%)
1	15	11
2	30	25
3	45	43
4	60	50

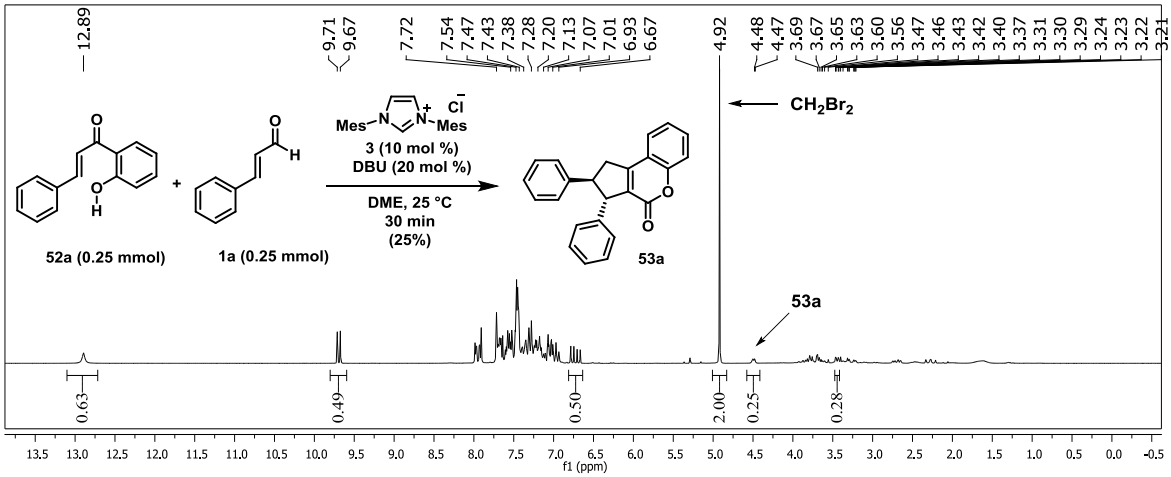
Figure 3.3. Kinetics study



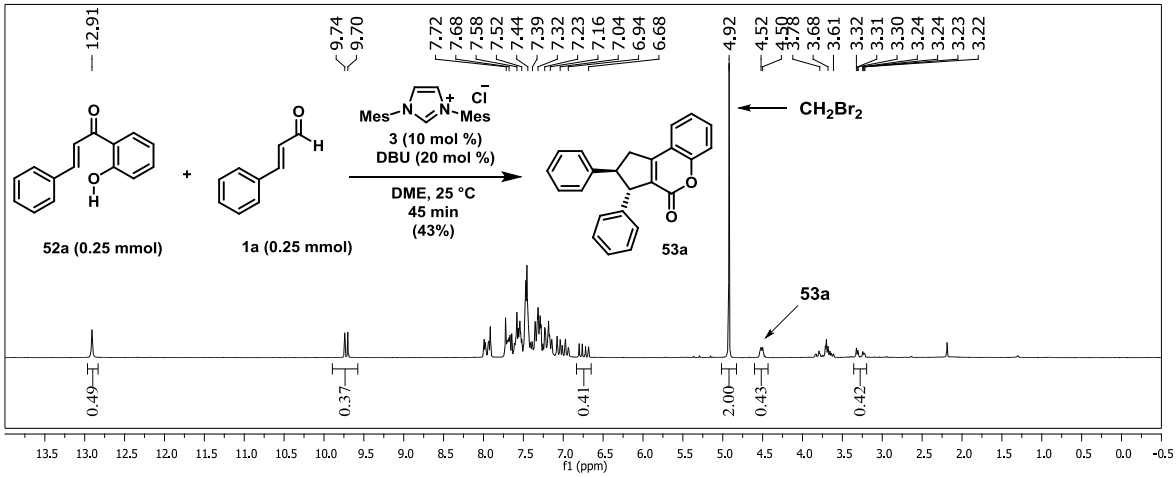
^{1}H-NMR of Crude Reaction Mixture after 15 minutes ($CDCl_3$)



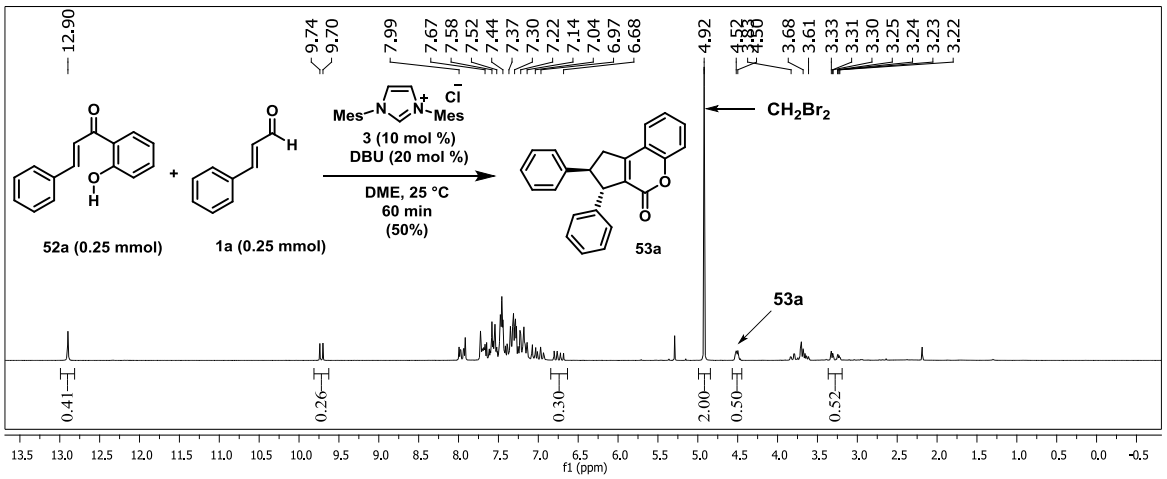
^{1}H-NMR of Crude Reaction Mixture after 30 minutes ($CDCl_3$)



^{1}H-NMR of Crude Reaction Mixture after 45 minutes ($CDCl_3$)

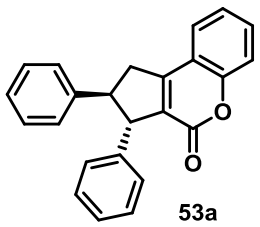


^{1}H-NMR of Crude Reaction Mixture after 60 minutes ($CDCl_3$)



3.7. Synthesis and Characterization of Functionalized Coumarins

2,3-Diphenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53a)



53a

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (0.224 g 1.0 mmol) and *trans*-cinnamaldehyde **1a** (0.132 g, 126 μL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 2,3 diphenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53a** as a white solid (0.336 g, 98%).

R_f (Pet. ether /EtOAc = 80/20): 0.62.

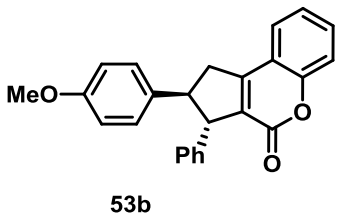
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59-7.55 (m, 2H, H_{ar}), 7.43 (d, *J* = 8.2 Hz, 1H, H_{ar}), 7.36-7.25 (m, 7H, H_{ar}), 7.20 (d, *J* = 7.6 Hz, 2H, H_{ar}), 7.15 (d, *J* = 7.4 Hz, 2H, H_{ar}) 4.51 (d, *J* = 4.6 Hz, 1H, CH), 3.80-3.75 (m, 1H, CH), 3.68-3.64 (m, 1H, CH), 3.27 (dd, J_1 = 5.0 Hz, J_2 = 17.8 Hz, 1H, CH).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.96, 155.65, 154.92, 144.69, 142.50, 131.61, 129.01, 128.86, 128.76, 127.19, 127.08, 126.96, 125.17, 124.39, 118.47, 117.11, 59.29, 53.52, 39.63.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{19}O_2$: 339.1380, found: 339.1380.

FTIR (cm^{-1}): 3063, 3028, 2927, 2853, 1728, 1627, 1607, 1568, 1494, 1453, 1432, 1388, 1322, 1274, 1250, 1218, 1134, 1078, 1059, 1037, 925, 883, 754, 700.

2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53b)



53b

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one **52b** (0.255 g 1.0 mmol) and *trans* cinnamaldehyde **1a** (0.132 g, 126 μL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 2-(4-methoxyphenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53b** as a white solid (0.339 g, 92%).

R_f (Pet. ether /EtOAc = 80/20): 0.56.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61-7.57 (m, 2H, H_{ar}), 7.45 (d, *J* = 7.8 Hz, 1H, H_{ar}), 7.39-7.25 (m, 4H, H_{ar}), 7.18-7.11 (m, 4H, H_{ar}), 6.89 (d, *J* = 8.6 Hz, 2H, H_{ar}), 4.49 (d, *J* = 4.9 Hz,

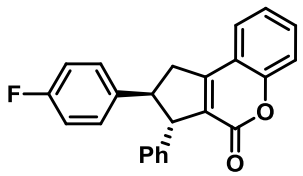
1H, CH), 3.84-3.74 (m, 4H, CH), 3.66-3.61 (m, 1H, CH), 3.26 (dd, J_1 = 5.6 Hz, J_2 = 17.9 Hz, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.88, 158.56, 155.64, 154.83, 142.48, 136.53, 131.51, 128.74, 128.62, 127.93, 127.14, 126.94, 125.14, 124.32, 118.43, 116.98, 114.24, 59.35, 55.33, 52.91, 39.62.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{21}O_3$: 369.1485, found: 369.1485.

FTIR (cm^{-1}): 3438, 3060, 3027, 2934, 2836, 1729, 1625, 1607, 1584, 1492, 1453, 1388, 1320, 1288, 1263, 1215, 1156, 1078, 1038, 1001, 924, 887, 761.

2-(4-Fluorophenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53c)



53c

Following the general procedure, treatment of (*E*)-3-(4-fluorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one **52c** (0.121 g 0.5 mmol) and *trans* cinnamaldehyde **1a** (0.066 g, 63 μL, 0.5 mmol) with imidazolium salt **3** (0.017 g, 0.05 mmol) and DBU (0.015 g, 15 μL, 0.1 mmol) in DME (2.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 2-(4-fluorophenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53c** as a white solid (0.159 g, 89%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.55.

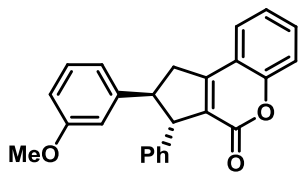
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18-8.11 (m, 2H, H_{ar}), 7.96 (d, J = 10.4 Hz, 1H, H_{ar}), 7.89-7.71 (m, 4H, H_{ar}), 7.64-7.56 (m, 4H, H_{ar}), 7.47-7.41 (m, 2H, H_{ar}), 4.21 (d, J = 6.4 Hz, 1H, CH), 3.44-3.33 (m, 1H, CH), 3.26-3.19 (m, 1H, CH), 2.76-2.68 (m 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.89 (d, J = 244.8 Hz), 158.88, 155.48, 154.92, 142.22, 140.26 (d, J = 3.0 Hz), 131.71, 128.90, 128.58, 128.48 (d, J = 8.1 Hz), 127.18, 127.15, 125.15, 124.44, 118.38, 117.14, 115.80 (d, J = 21.7 Hz), 59.45, 52.94, 39.66.

HRMS: calculated $[M+Na]^+$ for $C_{24}H_{17}O_2FNa$: 379.1105, found: 379.1099.

FTIR (cm^{-1}): 3062, 3018, 2928, 2855, 1725, 1608, 1569, 1511, 1496, 1454, 1388, 1301, 1248, 1217, 1178, 1158, 1064, 1038, 923, 909, 831, 756, 701.

2-(3-Methoxyphenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53d)



53d

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-(3-methoxyphenyl)prop-2-en-1-one **52d** (0.255 g 1.0 mmol) and *trans* cinnamaldehyde **1a** (0.132 g, 126 μL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU

(0.030 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 2-(3-methoxyphenyl)-3-phenyl-2,3-dihydrocyclopenta [*c*]chromen-4(1*H*)-one **53d** as a white solid (0.335 g, 91%)

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.53.

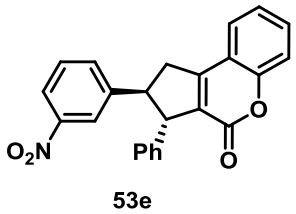
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.55 (d, *J* = 6.9 Hz, 2H, Har), 7.41 (d, *J* = 8.4 Hz, 1H, H$_{ar}$), 7.35-7.23 (m, 5H, H$_{ar}$), 7.16 (d, *J* = 6.6.Hz, 2H, H$_{ar}$), 6.83-6.75 (m, 3H, H$_{ar}$), 4.51 (bs, 1H, CH), 3.77-3.71 (m, 4H, CH), 3.64-3.63 (m, 1H, CH), 3.27 (dd, J_1 = 4.5 Hz, J_2 = 17.8 Hz, 1H, CH).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 159.90, 158.82, 155.57, 154.78, 146.16, 142.45, 131.52, 129.95, 128.74, 128.55, 127.12, 126.97, 125.12, 124.32, 119.13, 118.34, 116.92, 113.03, 111.83, 59.07, 55.22, 53.45, 39.42.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{21}O_3$: 369.1485, found: 369.1478.

FTIR (cm^{-1}): 2935, 2837, 1725, 1607, 1492, 1388, 1263, 1217, 1078, 1039, 888, 704.

2-(3-Nitrophenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53e)



53e

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one **52e** (0.269 g 1.0 mmol) and *trans*-cinnamaldehyde **1a** (0.132 g, 126 μL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.0304 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 2-(3-nitrophenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53e** as a white solid (0.322 g, 84%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.53.

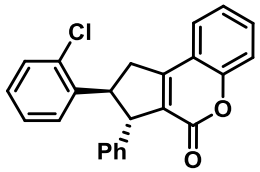
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.15-8.12 (m, 1H, H$_{ar}$), 8.09 (s, 1H, H$_{ar}$), 7.61-7.55 (m, 2H, H$_{ar}$), 7.51-7.50 (m, 2H, H$_{ar}$), 7.44 (d, *J* = 8.3 Hz, 1H, H$_{ar}$), 7.38-7.28 (m, 4H, H$_{ar}$), 7.13-7.11 (m, 2H, H$_{ar}$), 4.47 (d, *J* = 4.2 Hz, 1H, CH), 3.84-3.75 (m, 2H, CH), 3.31-3.26 (m, 1H, CH).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 158.68, 154.98, 148.68, 146.39, 141.61, 133.31, 131.97, 130.12, 129.11, 128.35, 127.53, 127.15, 125.12, 124.58, 122.32, 122.06, 118.16, 117.27, 59.32, 53.27, 39.35.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{18}O_4N$: 384.1230, found: 384.1226.

FTIR (cm^{-1}): 3028, 2926, 1727, 1626, 1607, 1528, 1495, 1453, 1388, 1349, 1218, 1038, 925, 889, 754, 700.

2-(2-Chlorophenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53f)



53f

Following the general procedure, treatment of (*E*)-3-(2-chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one **52f** (0.259 g 1.0 mmol) and *trans* cinnamaldehyde **1a** (0.132 g, 126 µL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 µL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded2-(2-chlorophenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*] chromen-4(1*H*)-one **53f** as a white solid (0.356 g, 95%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.56.

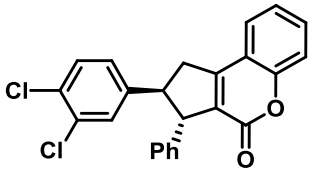
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.60-7.56 (m, 2H, H$_{ar}$), 7.45-7.41 (m, 2H, H$_{ar}$), 7.38-7.30 (m, 3H, H$_{ar}$), 7.27-7.19 (m, 6H, H$_{ar}$), 4.64 (d, J = 3.6 Hz, 1H, CH), 4.20-4.16 (m, 1H, CH), 3.85-3.78 (m, 1H, CH), 3.25 (dd, J_1 = 4.6 Hz, J_2 = 18.3 Hz, 1H, CH).

^{13}C NMR (125 MHz, CDCl$_3$) δ: 158.93, 155.40, 154.91, 142.08, 141.74, 133.74, 131.66, 130.12, 128.90, 128.83, 128.23, 127.76, 127.44, 127.22, 127.16, 125.18, 124.42, 118.38, 117.09, 57.29, 49.51, 38.45.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{18}O_2Cl$: 373.0990, found: 373.0988.

FTIR (cm^{-1}): 3019, 2928, 2401, 1951, 1725, 1628, 1608, 1570, 1494, 1475, 1454, 1389, 1276, 1216, 1134, 1038, 926, 754, 700, 668, 482.

3,4-(Dichlorophenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53g)



53g

Following the general procedure, treatment of (*E*)-3-(3,4-dichlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one **52g** (0.147 g 0.5 mmol) and *trans* cinnamaldehyde **1a** (0.066 g, 63 µL, 0.5 mmol) with imidazolium salt **3** (0.017 g, 0.05 mmol) and DBU (0.015 g, 15 µL, 0.1mmol) in DME (2.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 3,4-(dichlorophenyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53g** as a white solid (0.183 g, 90%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.54.

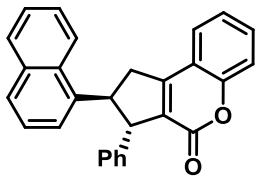
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.61-7.53 (m, 2H, H$_{ar}$), 7.43 (d, J = 8.3 Hz, 1H, H$_{ar}$), 7.38 (d, J = 8.3 Hz, 1H, H$_{ar}$), 7.35-7.31 (m, 2H, H$_{ar}$), 7.29-7.24 (m, 3H, H$_{ar}$), 7.13-7.11 (m, 2H, H$_{ar}$), 7.01 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H, H$_{ar}$), 4.43 (d, J = 5.2 Hz, 1H, CH), 3.80-3.73 (m, 1H, CH), 3.62-3.57 (m, 1H, CH), 3.24-3.18 (m, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.70, 155.09, 154.93, 144.72, 141.84, 132.93, 131.85, 131.10, 130.97, 129.01, 128.41, 127.38, 127.12, 126.47, 125.13, 124.51, 118.21, 117.18, 59.20, 52.77, 39.45.

HRMS: calculated $[M+Na]^+$ for $C_{24}H_{17}O_2Cl_2Na$: 429.0420, found: 429.0419.

FTIR (cm^{-1}): 3063, 3019, 2936, 1727, 1628, 1608, 1493, 1468, 1454, 1389, 1216, 1133, 1079, 1133, 1079, 1038, 886, 820, 756, 701.

2-(Naphthalen-1-yl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53h)



53h

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52h** (0.275 g 1.0 mmol) and *trans* cinnamaldehyde **1a** (0.132 g, 126 μL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 2-(naphthalen-1-yl)-3-phenyl-2,3-dihydrocyclopenta [*c*]chromen-4(1*H*)-one **53h** as a white solid (0.353 g, 91%).

R_f (Pet. ether /EtOAc = 80/20): 0.50.

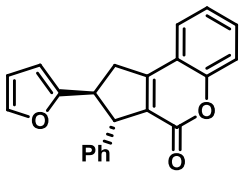
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (d, J = 8.4 Hz, 2H, H_{ar}), 7.83 (d, J = 8.3 Hz, 1H, H_{ar}), 7.62-7.44 (m, 6H, H_{ar}), 7.40-7.35 (m, 4H, H_{ar}), 7.33-7.28 (m, 3H, H_{ar}), 4.79 (bs, 1H, CH), 4.51 (bs, 1H, CH), 3.98-3.93 (m, 1H, CH), 3.46 (dd, J_1 = 3.7 Hz, J_2 = 18.2 Hz, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.45, 175.16, 174.27, 158.99, 159.19, 148.50, 145.18, 144.63, 142.24, 142.14, 141.84, 140.25, 139.71, 139.61, 138.55, 137.95, 137.73, 137.17, 136.16, 134.93, 134.76, 128.73, 126.98, 77.41, 53.13, 29.63.

HRMS: calculated $[M+H]^+$ for $C_{28}H_{21}O_2$: 389.1536, found: 389.1526.

FTIR (cm^{-1}): 3059, 2928, 1728, 1628, 1607, 1493, 1453, 1388, 1322, 1225, 1078, 1058, 1036, 925, 884, 797, 778, 760, 737, 700, 561, 473.

2-(Furan-2-yl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53i)



53i

Following the general procedure, treatment of (*E*)-3-(furan-2-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one **52i** (0.215 g 1.0 mmol) and *trans* cinnamaldehyde **1a** (0.132 g, 126 μL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography

afforded 2-(Furan-2-yl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53i** as a gray solid (0.303 g, 92%).

R_f (Pet. ether /EtOAc = 80/20): 0.65.

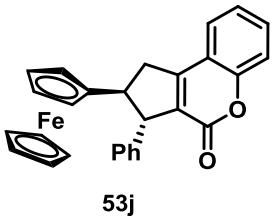
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57-7.53 (m, 2H, H_{ar}), 7.41-7.37 (m, 2H, H_{ar}), 7.35-7.30 (m, 3H, H_{ar}), 7.26-7.23 (m, 1H, H_{ar}), 7.20-7.18 (m, 1H, H_{ar}), 6.32-6.30 (m, 1H, H_{ar}), 6.10 (d, J = 3.2 Hz), 4.61 (d, J = 5.2 Hz, 1H, CH), 3.76-3.71 (m, 1H, CH), 3.68-3.60 (m, 1H, CH), 3.36 (dd, J_1 = 5.4 Hz, J_2 = 17.7 Hz, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.92, 156.20, 155.25, 154.81, 142.20, 141.98, 131.58, 128.80, 128.35, 127.24, 127.18, 125.09, 124.37, 118.43, 117.04, 110.35, 105.38, 55.93, 46.71, 36.58.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{17}O_3$: 329.1172, found: 329.1167.

FTIR (cm^{-1}): 3113, 3063, 3019, 2927, 2854, 1725, 1630, 1608, 1570, 1494, 1454, 1390, 1321, 1276, 1217, 1148, 1135, 1078, 1063, 1039, 1013, 927, 894, 753, 700, 667.

2-(Ferroceniyl)-3-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53j)



53j

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-(ferroceniyl)prop-2-en-1-one **52j** (0.083 g 0.25 mmol) and *trans* cinnamaldehyde **1a** (0.033 g, 31 μL, 0.25 mmol) with imidazolium salt **3** (0.0085 mg, 0.025 mmol) and DBU (0.0076 mg, 7.5 μL, 0.05 mmol) in DME (1.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 2-(ferroceniyl)-3-phenyl-2,3-dihydrocyclop enta[*c*]chromen-4(1*H*)-one **53j** as a yellow solid (0.101 g, 91%).

R_f (Pet. ether /EtOAc = 80/20): 0.53.

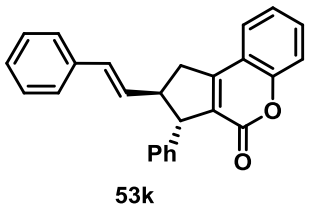
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63-7.55 (m, 2H, H_{ar}), 7.42-7.34 (m, 4H, H_{ar}), 7.29-7.26 (m, 3H, H_{ar}), 4.42 (d, J = 3.6 Hz, 1H, CH), 4.16-4.05 (m, 9H), 3.76-3.69 (m, 1H, CH), 3.54-3.50 (m, 1H, CH), 3.27 (dd, J_1 = 4.8 Hz, J_2 = 17.7 Hz, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.02, 155.14, 154.74, 142.78, 131.43, 129.09, 128.82, 127.41, 127.02, 125.12, 124.29, 118.52, 117.00, 92.30, 68.56, 67.99, 67.88, 67.25, 65.90, 58.52, 47.47, 38.91.

HRMS: calculated $[M]^+$ for $C_{28}H_{22}O_2Fe$: 446.0964, found: 446.0962.

FTIR (cm^{-1}): 3025, 2923, 2841, 1718, 1628, 1607, 1492, 1452, 1388, 1214, 1134, 1033, 964, 924, 754, 697.

3-Phenyl-2-((*E*)-styryl)-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53k)



53k

Following the general procedure, treatment of (2*E*,4*E*)-1-(2-hydroxyphenyl)-5-phenylpenta-2,4-dien-1-one **52k** (0.251 g 1.0 mmol) and *trans* cinnamaldehyde **1a** (0.132 g, 126 μL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 3-phenyl-2-((*E*)-styryl)-2,3-dihydrocyclopenta[c]chromen-4(1H)-one **53k** as a yellow solid (0.289 g, 79%).

***R**_f* (Pet. ether /EtOAc = 80/20): 0.50.

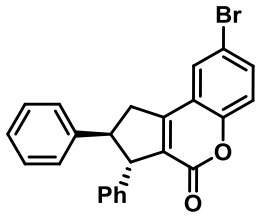
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62-7.58 (m, 2H, H_{ar}), 7.46-7.44 (m, 1H, H_{ar}), 7.42-7.34 (m, 7H, H_{ar}), 7.32-7.25 (m, 4H, H_{ar}), 6.44 (d, *J* = 5.6 Hz, 2H, H_{ar}), 4.36 (d, *J* = 5.6 Hz, 1H, CH), 3.65-3.58 (m, 1H, CH), 3.36-3.29 (m, 1H, CH), 3.14-3.08 (m, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.89, 155.61, 154.67, 141.85, 136.87, 131.46, 131.42, 130.56, 128.72, 128.62, 128.47, 127.53, 127.29, 126.95, 126.25, 125.10, 124.27, 118.43, 116.87, 56.86, 51.71, 37.44.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{21}O_2$: 365.1536, found: 365.1535.

FTIR (cm^{-1}): 2928, 1735, 1651, 1608, 1493, 1429, 1322, 1216, 1078, 1039, 1001, 925, 888, 753, 699.

8-bromo-2,3-diphenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53l)



53l

Following the general procedure, treatment of (*E*)-1-(5-bromo-2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52l** (0.303 g 1.0 mmol) and *trans*-cinnamaldehyde **1a** (0.132 g, 126 μL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.0304 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 8-bromo-2,3-diphenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53l** as a white solid (0.363 g, 87%).

***R**_f* (Pet. ether /EtOAc = 60/40): 0.54.

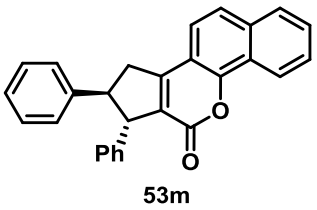
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69-7.66 (m, 2H, H_{ar}), 7.36-7.27 (m, 8H, H_{ar}), 7.21-7.20 (m, 1H, H_{ar}), 7.14 (d, *J* = 7.1 Hz, 2H, H_{ar}), 4.51-4.50 (m, 1H, CH), 3.78-3.67 (m, 2H, CH), 3.29-3.24 (m, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.25, 154.35, 153.76, 144.35, 142.13, 134.32, 129.99, 129.07, 128.93, 127.75, 127.23, 127.19, 126.90, 120.12, 118.81, 117.06, 59.32, 53.39, 39.51.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{18}O_2Br$: 417.0485, found: 417.0479.

FTIR (cm^{-1}): 3027, 2923, 1729, 1601, 1492, 1453, 1414, 1373, 1265, 1218, 1078, 1029, 932, 818, 761, 698.

7,8-Diphenyl-8,9-dihydrobenzo[*h*]cyclopenta[*c*]chromen-6(7*H*)-one (53m)



53m

Following the general procedure, treatment of (*E*)-1-(1-hydroxynaphthalen-2-yl)-3-phenylprop-2-en-1-one **52m** (0.274 g 1.0 mmol) and *trans* cinnamaldehyde **1a** (0.132 g, 126 μL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.0304 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 7,8-diphenyl-8,9-dihydrobenzo[*h*]cyclopenta[*c*]chromen-6(7*H*)-one **53m** as a white solid (0.354 g, 91%).

R_f (Pet. ether /EtOAc = 60/40): 0.56.

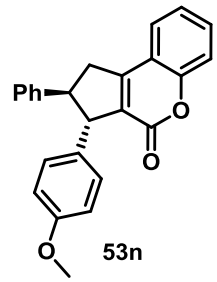
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57- 8.54 (m, 1H, H_{ar}), 7.69 (d, J = 8.7 Hz,1H, H_{ar}), 7.61-7.59 (m, 2H, H_{ar}), 7.49 (d, J = 8.6 Hz, 1H, H_{ar}), 7.29-7.11 (m, 10H, H_{ar}), 4.51-4.50 (m, 1H, CH), 3.81-3.74 (m, 1H, CH), 3.65-3.61 (m, 1H, CH), 3.29 (dd, J_1 = 5.3 Hz, J_2 = 18.0 Hz, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.99, 156.77, 152.07, 144.73, 142.55, 134.82, 129.02, 128.86, 128.63, 127.99, 127.92, 127.35, 127.23, 127.07, 127.02, 124.50, 123.37, 122.92, 121.11, 113.73, 59.15, 53.71, 39.97.

HRMS: calculated $[M+H]^+$ for $C_{28}H_{21}O_2$: 389.1536, found: 389.1536.

FTIR (cm^{-1}): 3019, 2400, 1722, 1611, 1565, 1531, 1495, 1370, 1353, 1216, 1080, 1030, 962, 929, 768, 668.

3-(4-methoxyphenyl)-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53n)



53n

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (0.224 g 1.0 mmol) and (*E*)-3-(4-methoxyphenyl)acrylaldehyde **1b** (0.162 g, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography

afforded 3-(4-methoxyphenyl)-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53n** as a white solid (0.327 g, 89%).

R_f (Pet. ether /EtOAc = 80/20): 0.51.

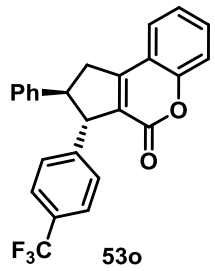
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22-8.17 (m, 2H, H_{ar}), 8.02 (d, *J* = 10.8 Hz, 1H, H_{ar}), 7.94-7.89 (m, 3H, H_{ar}), 7.85-7.81 (m, 1H, H_{ar}), 7.75 (d, *J* = 9.3 Hz, 2H, H_{ar}), 7.59 (d, *J* = 10.3 Hz, 2H, H_{ar}), 7.30 (d, *J* = 10.3 Hz, 2H, H_{ar}), 4.33 (d, *J* = 6.0 Hz, 1H, CH), 3.47-3.39 (m, 4H, CH), 3.32-3.26 (m, 1H, CH), 2.83 (dd, J_1 = 6.7 Hz, J_2 = 22.4 Hz, 1H, CH).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.18, 178.13, 174.79, 174.03, 161.21, 148.79, 144.93, 141.69, 141.50, 140.76, 139.24, 137.01, 136.00, 128.59, 126.69, 123.26, 53.70, 49.63, 47.68, 29.80.

HRMS: calculated $[M+Na]^+$ for $C_{25}H_{20}O_3Na$: 391.1305, found: 391.1299.

FTIR (cm^{-1}): 3062, 3016, 2935, 2837, 1727, 1608, 1585, 1568, 1512, 1495, 1454, 1388, 1322, 1302, 1249, 1217, 1134, 1065, 1038, 923, 908, 831, 755, 701, 667, 556.

3-(4-(Trifluromethyl)phenyl)-2,3-dihydro-2-phenylcyclopenta[*c*]chromen-4(1*H*)-one (53o)



53o

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (0.112 g 0.5 mmol) and (*E*)-3-(4-(trifluromethyl) phenyl)acrylaldehyde **1c** (0.100 g, 0.5 mmol) with imidazolium salt **3** (0.017 g, 0.05 mmol) and DBU (0.0152 g, 15 μL, 0.1 mmol) in DME (2.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 3-(4-(trifluromethyl)phenyl)-2,3-dihydro-2-phenylcyclopenta[*c*]chromen-4(1H)-one **53o** as a white solid (0.197 g, 97%).

R_f (Pet. ether /EtOAc = 60/40): 0.58.

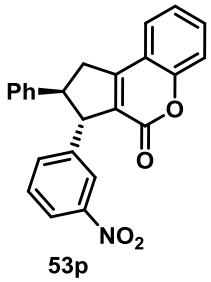
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61-7.54 (m, 4H, H_{ar}), 7.44 (d, *J* = 8.2 Hz, 1H, H_{ar}), 7.37-7.33 (m, 3H, H_{ar}), 7.30-7.29 (m, 1H, H_{ar}), 7.23 (d, *J* = 7.9 Hz, 2H, H_{ar}), 7.18 (d, *J* = 7.2 Hz, 2H, H_{ar}), 4.55-4.54 (m, 1H, CH), 3.80-3.74 (m, 1H, CH), 3.63-3.60 (m, 1H, CH), 3.31 (dd, J_1 = 6.2 Hz, J_2 = 18.2 Hz, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.84, 156.26, 154.98, 146.42, 143.70, 131.94, 129.14, 127.82, 127.59, 127.37, 127.06, 125.86, 125.83, 125.24, 124.56, 118.29, 117.20, 59.08, 53.81, 39.75.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{18}O_2F_3$: 407.1253, found: 407.1249.

FTIR (cm^{-1}): 3029, 2029, 1726, 1620, 1607, 1496, 1454, 1420, 1389, 1326, 1218, 1164, 1110, 1064, 1018, 925, 842, 757.

3-(3-Nitrophenyl)-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53p)



53p

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (0.112 g 0.5 mmol) and (*E*)-3-(3-nitrophenyl)acrylaldehyde **1d** (0.088 g, 0.5 mmol) with imidazolium salt **3** (0.017 g, 0.05 mmol) and DBU (0.015 g, 15 μL, 0.1 mmol) in DME (2.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 3-(3-nitrophenyl)-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53p** as a white solid (0.167 g, 87%).

***R**_f* (Pet. ether /EtOAc = 60/40): 0.61.

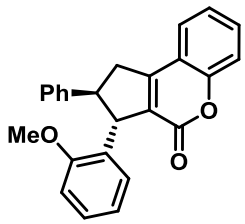
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12-8.09 (m, 1H, H_{ar}), 7.98 (bs, 1H, H_{ar}), 7.62-7.56 (m, 2H, H_{ar}), 7.47-7.42 (m, 3H, H_{ar}), 7.39-7.29 (m, 4H, H_{ar}), 7.20-7.18 (m, 2H, H_{ar}), 4.60-4.58 (m, 1H, CH), 3.84-3.77 (m, 1H, CH), 3.66-3.61 (m, 1H, CH), 3.37-3.30 (m, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.78, 156.58, 154.97, 148.69, 144.47, 143.01, 134.01, 132.12, 129.71, 129.21, 127.52, 127.29, 127.06, 125.30, 124.65, 122.29, 122.00, 118.18, 117.22, 58.85, 54.04, 39.75.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{18}O_4N$: 384.1230, found: 384.1229.

FTIR(cm^{-1}): 3020, 2930, 2401, 1957, 1723, 1627, 1608, 1530, 1496, 1454, 1389, 1352, 1216, 1065, 1046, 942, 883, 805, 757, 701, 668.

3-(2-Methoxyphenyl)-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53q)



53q

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (0.224 g 1.0 mmol) and (*E*)-3-(2-methoxyphenyl)acrylaldehyde **1e** (0.162 g, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography 3-(2-methoxyphenyl)-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53q** as a white solid (0.331 g, 89%).

***R**_f* (Pet. ether /EtOAc = 80/20): 0.59.

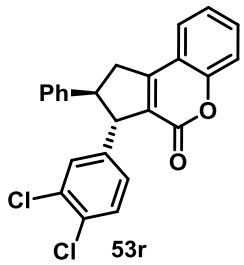
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60-7.56 (m, 2H, H_{ar}), 7.46 (d, *J* = 8.5 Hz, 1H, H_{ar}), 7.38-7.30 (m, 3H, H_{ar}), 7.27-7.22 (m, 4H, H_{ar}), 6.95-6.86 (m, 3H, H_{ar}), 4.84 (d, *J* = 2.7 Hz, 1H, CH), 3.73-3.64 (m, 5H), 3.29-3.23 (m, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.86, 157.28, 156.05, 154.84, 145.65, 131.34, 130.24, 128.66, 128.47, 128.15, 127.55, 126.87, 126.69, 125.07, 124.29, 120.64, 118.59, 117.04, 111.06, 55.35, 53.60, 51.85, 39.04.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{21}O_3$: 369.1485, found: 369.1482.

FTIR (cm^{-1}): 2936, 1725, 1626, 1607, 1493, 1439, 1272, 1246, 1110, 1092, 974, 926, 754.

3-(3,4-Dichlorophenyl)-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53r)



53r

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (0.056 g 0.25 mmol) and (*E*)-3-(3,4-dichlorophenyl)acrylaldehyde **1f** (0.050 g, 0.25 mmol) with imidazolium salt **3** (0.0085 g, 0.025 mmol) and DBU (0.0076 g, 7.5 μL, 0.050 mmol) in DME (1.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 3-(3,4-Dichlorophenyl)-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53r** as a white solid (0.082 g, 81% after crystalisation in Pet. ether).

R_f (Pet. ether /EtOAc = 80/20): 0.49.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62-7.60 (m, 2H, H_{ar}), 7.44-7.26 (m, 7H, H_{ar}), 7.15 (d, *J* = 6.9 Hz, 2H, H_{ar}), 7.05 (dd, J_1 = 2.0 Hz, J_2 = 8.3 Hz, 1H, H_{ar}) 4.45 (d, *J* = 5.1 Hz, 1H, CH), 3.82-3.75 (m, 1H, CH), 3.65-3.60 (m, 1H, CH), 3.23 (dd, J_1 = 5.7 Hz, J_2 = 18.1 Hz, 1H, CH).

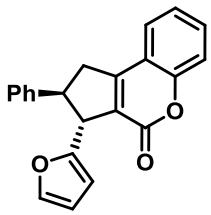
^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.58, 155.08, 154.81, 144.60, 141.78, 132.77, 131.75, 130.94, 130.86, 128.96, 128.89, 128.22, 127.26, 127.06, 126.45, 125.10, 124.43, 118.12, 117.00, 59.09, 52.72, 39.30.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{17}O_2Cl_2$: 407.0600, found: 407.0601.

FTIR (cm^{-1}): 3029, 1726, 1683, 1625, 1607, 1568, 1494, 1470, 1454, 1400, 1288, 1217, 1133, 1066, 1030, 935, 819, 757, 719.

3-(Furan-2-yl)-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53s)

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (0.224 g 1.0 mmol) and (*E*)-3-(furan-2-yl)acrylaldehyde **1g** (0.122 g, 1.0 mmol)



53s

with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 3-(furan-2-yl)-2-phenyl-2,3-dihydrocyclo penta[*c*]chromen-4(1*H*)-one **53s** as a white solid (0.271 g, 82%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.62.

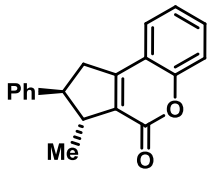
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.59-7.53 (m, 2H, H$_{ar}$), 7.42 (d, *J* = 8.2 Hz, 1H, H$_{ar}$), 7.35-7.31 (m, 4H, H$_{ar}$), 7.26 (d, *J* = 6.8 Hz, 1H, H$_{ar}$), 7.25-7.21 (m, 2H, H$_{ar}$), 6.33-6.32 (m, 1H, H$_{ar}$), 6.15 (d, *J* = 3.2 Hz, 1H, H$_{ar}$), 4.59 (d, *J* = 4.7 Hz, 1H, CH), 3.92-3.87 (m, 1H, CH), 3.80-3.73 (m, 1H, CH), 3.26 (dd, J_1 = 4.8 Hz, J_2 = 17.8 Hz, 1H, CH).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 158.84, 155.91, 154.82, 154.14, 144.19, 141.87, 131.74, 129.00, 127.13, 126.81, 126.42, 125.21, 124.40, 118.41, 117.07, 110.60, 106.42, 51.99, 49.63, 39.05.

HRMS: calculated [M+H]$^+$ for $C_{22}H_{17}O_3$: 329.1172, found: 329.1165.

FTIR (cm^{-1}): 3165, 3004, 2943, 2628, 2411, 2293, 2253, 1726, 1625, 1602, 1452, 1416, 1376, 1147, 1070, 1039, 1007, 918, 758.

3-Methyl-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53t)



53t

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (0.224 g 1.0 mmol) and (*E*)-but-2-enal **1h** (0.0702 g, 82 μL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 μL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 3-methyl-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **53t** as a white solid (0.205 g, 74%) along with 2-phenylchroman-4-one **54** as a white solid (0.050 g, 22%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.61.

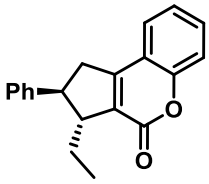
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.55-7.51 (m, 1H, H$_{ar}$), 7.47-7.45 (m, 1H, H$_{ar}$), 7.41-7.32 (m, 3H, H$_{ar}$), 7.32-7.25 (m, 4H, H$_{ar}$), 3.57 (dq, J_1 = 1.9 Hz, J_2 = 18.7 Hz, J_3 = 17.7 Hz, J_4 = 26.5, Hz, 1H, CH), 3.43-3.38 (m, 1H, CH), 3.29-3.23 (m, 1H, CH), 3.15-3.09 (m, 1H, CH), 1.46 (d, *J* = 6.9 Hz, 3H, CH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 159.58, 154.51, 154.09, 144.23, 131.13, 130.29, 128.86, 127.27, 126.90, 124.87, 124.22, 118.60, 116.84, 52.26, 47.90, 39.19, 18.47.

HRMS: calculated [M+H]$^+$ for $C_{19}H_{16}O_2Na$: 299.1043, found: 299.1041.

FTIR (cm^{-1}): 3062, 3020, 2960, 2871, 1950, 1720, 1625, 1608, 1584, 1571, 1430, 1453, 1389, 1373, 1320, 1288, 1217, 1135, 1033, 1019, 976, 948, 884, 756, 702.

3-Ethyl-2-phenyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one (53u)



53u

Following the general procedure, treatment of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **52a** (0.224 g 1.0 mmol) and (*E*)-pent-2-enal **1i** (0.132 g, 126 µL, 1.0 mmol) with imidazolium salt **3** (0.034 g, 0.1 mmol) and DBU (0.030 g, 30 µL, 0.2 mmol) in DME (4.0 mL) at 25 °C for 12 h followed by flash column chromatography afforded 3-ethyl-2-phenyl-2,3-dihydrocyclopenta [*c*]chromen-4(1*H*)-one **53u** as a white solid (0.251 g, 86% yield).

***R**$_f$* (Pet. ether /EtOAc = 80/20): 0.56.

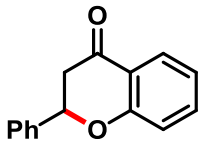
^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.54-7.51 (m, 1H, H$_{ar}$), 7.45 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz , 1H, H$_{ar}$), 7.41 (d, J = 7.9 Hz, 1H, H$_{ar}$), 7.32-7.28 (m, 3H, H$_{ar}$), 7.24-7.21 (m, 3H, H$_{ar}$), 3.59 (qd, J_1 = 2.3Hz, J_2 = 9.2 Hz, J_3 = 18.2 Hz, 1H, CH), 3.48-3.45 (m, 1H, CH), 3.39-3.38 (m, 1H, CH), 3.13-3.08 (m, 1H, CH), 2.07-2.02 (m, 1H, CH), 1.78-1.72 (m, 1H, CH), 0.98 (t, J = 7.7 Hz, 3H, CH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$) δ: 159.65, 154.59, 146.25, 131.19, 129.53, 128.94, 126.94, 126.72, 124.92, 124.27, 118.62, 116.93, 54.62, 47.59, 39.91, 25.44, 11.12.

HRMS: calculated [M+H]$^+$ for $C_{20}H_{19}O_2$: 291.1380, found: 291.1378.

FTIR (cm^{-1}): 3062, 3029, 2963, 2252, 1719, 1630, 1607, 1577, 1494, 1454, 1389, 1321, 1305, 1282, 1268, 1227, 1198, 1156, 1100, 1076, 1065, 1036, 1020, 910, 886, 756, 735.

2-Phenylchroman-4-one (54)[29]



54

***R**$_f$* (Pet. ether /EtOAc = 80/20): 0.65.

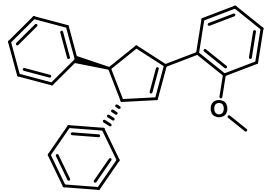
^{1}H NMR (200 MHz, CDCl$_3$) δ: 7.95 (dd, J_1 = 1.8 Hz, J_2 = 8.2 Hz, 1H, H$_{ar}$), 7.57-7.36 (m, 6H, H$_{ar}$), 7.10-7.03 (m, 2H, H$_{ar}$), 5.50 (dd, J_1 = 3.3 Hz, J_2 = 13.0 Hz, 1H, CH), 3.19-2.85 (m, 2H, CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 192.16, 161.70, 138.86, 136.37, 129.00, 128.93, 127.20, 126.29, 121.77, 121.05, 118.28, 79.75, 44.82.

HRMS: calculated [M+H]$^+$ for $C_{15}H_{13}O_2$: 225.0910, found: 225.0910.

FTIR (cm^{-1}): 3066, 3035, 1692, 1606, 1577, 1498, 1472, 1463, 1371, 1321, 1304, 1228, 1149, 1116, 1066, 1027, 988, 906, 760, 699.

4-(2-Methoxyphenyl)cyclopent-3-ene-1,2-diyl)dibenzene (62)



62

R_f (Pet. ether /EtOAc = 80/20): 0.85.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44-7.41 (m, 1H, H_{ar}), 7.35-7.28 (m, 7H, H_{ar}), 7.27-7.22 (m, 4H, H_{ar}), 7.03-6.98 (m, 2H, H_{ar}), 6.57 (bs, 1H, CH), 4.21-4.19 (m, 1H, CH), 3.91 (s, 3H, CH_3), 3.46-3.39 (m, 2H), 3.18-3.09 (m, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.97, 145.68, 145.40, 139.17, 132.68, 129.00, 128.54, 128.51, 128.36, 127.66, 127.57, 126.40, 126.27, 125.47, 120.58, 111.03, 61.27, 55.37, 54.19, 44.07.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{23}O$: 327.1743, found: 327.1735.

FTIR (cm^{-1}): 3060, 3026, 2925, 2852, 1600, 1576, 1492, 1454, 1435, 1295, 1251, 1181, 1161, 1125, 1077, 1057, 1028, 992, 868, 751, 700.

3.8. References

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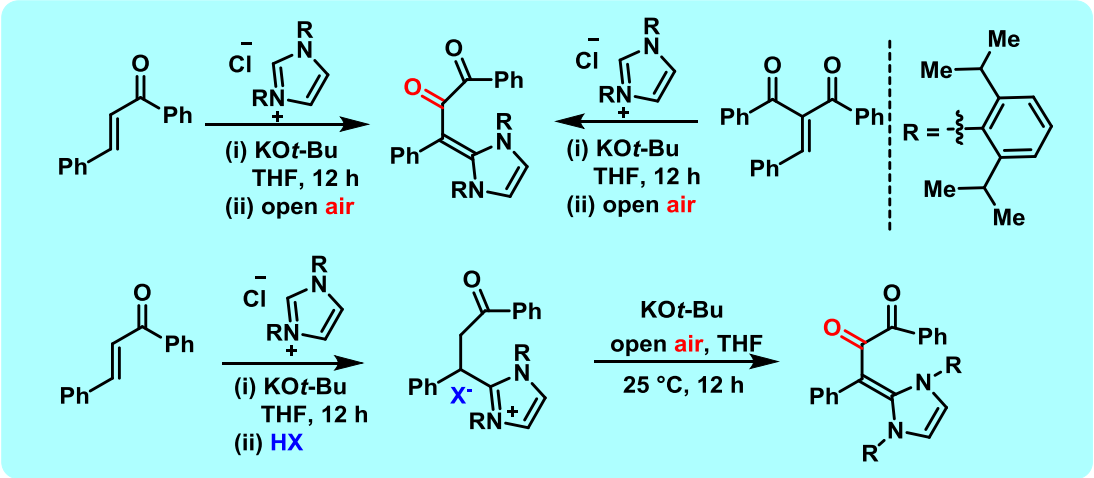
30. CCDC-918307 (**53a**) contains the supplementary crystallographic data for this chapter.

Chapter 4

Reaction of N-Heterocyclic Carbenes (NHCs) with Chalcones: Isolation of Oxidized *Deoxy*-Breslow Intermediates

In this chapter, we report the reaction of NHCs with chalcones leading to the synthesis of *deoxy*-Breslow intermediate in their oxidized form. The reaction proceeds via an enolate intermediate, which undergoes an unexpected oxidation in presence of air. Alternatively, use of Brønsted acid in the absence of air leads to the formation a tetrahedral intermediate, which upon treatment with base in open air generated the oxidized *deoxy*-Breslow intermediate. A series of experiments have been performed to establish the mechanism of this reaction. In addition, a catalyst-free intramolecular Rauhut-Currier type reaction is also developed during the investigation of the reaction mechanism.



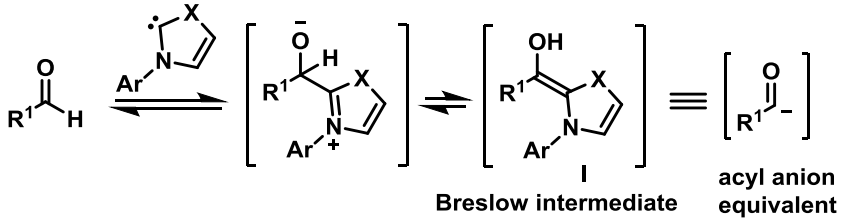
Chem. Commun. **2015**, *51*, 13690-13693

Org. Biomol. Chem. **2016**, ***DOI:*** *10.1039/C6OB00654J*

4.1. Introduction

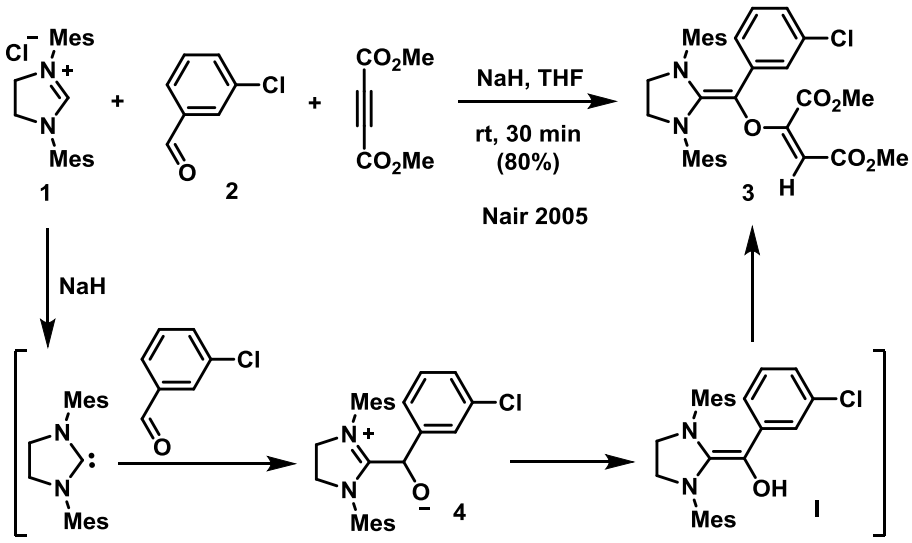
NHC-catalyzed *umpolung* or polarity reversal of aldehyde is an important concept in the design of new synthetic strategies. NHCs have found various applications as versatile catalysts in several organic transformations.[1] The Breslow intermediates[2] formed from the 1:1 addition of aldehyde and NHC can add to electrophiles including aldehydes and ketones (benzoin reaction), imines (aza-benzoin reaction), Michael acceptors (Stetter reaction) and even unactivated C-C multiple bonds (Scheme 4.1).

Scheme 4.1: *Umpolung* of aldehyde (Breslow Intermediate)



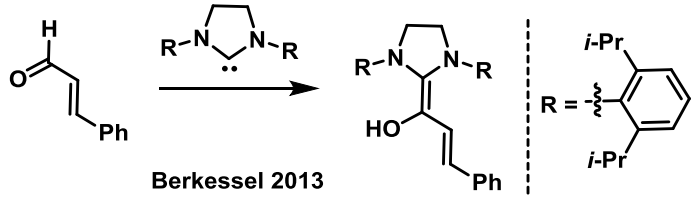
In view of these developments, significant efforts have been directed towards the mechanistic studies, kinetics, analysis and isolation of intermediates. These fundamental studies have advanced the recent developments of NHC-catalysis. In 2005, Nair and co-workers suggested the existence of Breslow intermediate **l** by the isolation of the protected enaminol **3** by the reaction of azolium salt **1** with aldehyde **2** in presence of activated alkyne (Scheme 4.2).[3] The in situ generated unstable Breslow intermediate **l** underwent an oxa-Michael reaction with dimethyl acetylene dicarboxylate (DMAD) to form the **3**.

Scheme 4.2: Isolation of Protected Breslow Intermediate



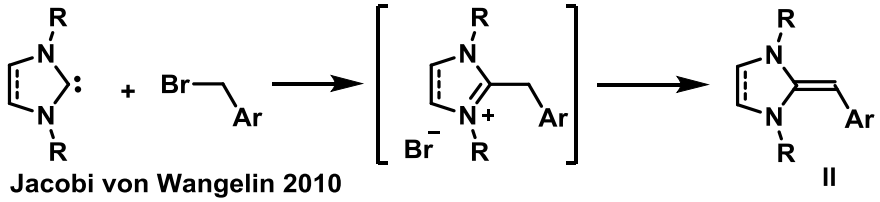
Subsequently, *O*-methylated enaminols were isolated by the groups of Mayr and Berkessel.[4] Later Berkessel and co-workers reported the selective generation and characterization of the Breslow intermediates (Scheme 4.3).[5] The isolation and characterization of this intermediate provides the most direct evidence for the role of Breslow intermediates in NHC catalysis.

Scheme 4.3: Isolation of Breslow Intermediate



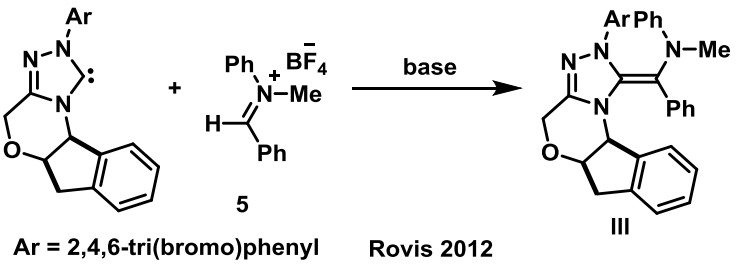
Surprisingly, however, the *umpolung* triggered by NHCs is mostly limited to aldehydes, and the use of other electrophiles has received only limited attention. Recently, the umpolung of alkyl halides leading to the isolation of *deoxy*-Breslow intermediates **II** was reported by the group of Jacobi von Wangelin (Scheme 4.4).[6] Subsequently, Mayr and co-workers investigated the nucleophilic reactivties of these *deoxy*-Breslow intermediates through kinetic measurements.[7]

Scheme 4.4: *Umpolung* of Alkyl Halides (*deoxy*-Breslow Intermediate)



Recently, Rovis and co-workers disclosed the isolation of stable *aza*-Breslow intermediate **III** by the reaction of chiral triazolylidene carbene and iminium salt **5** (Scheme 4.5).[8] The nucleophilic reactivities of this *aza*-Breslow intermediate is not known in NHC-catalysis.

Scheme 4.5: *Umpolung* of Imines *(aza*-Breslow intermediates)

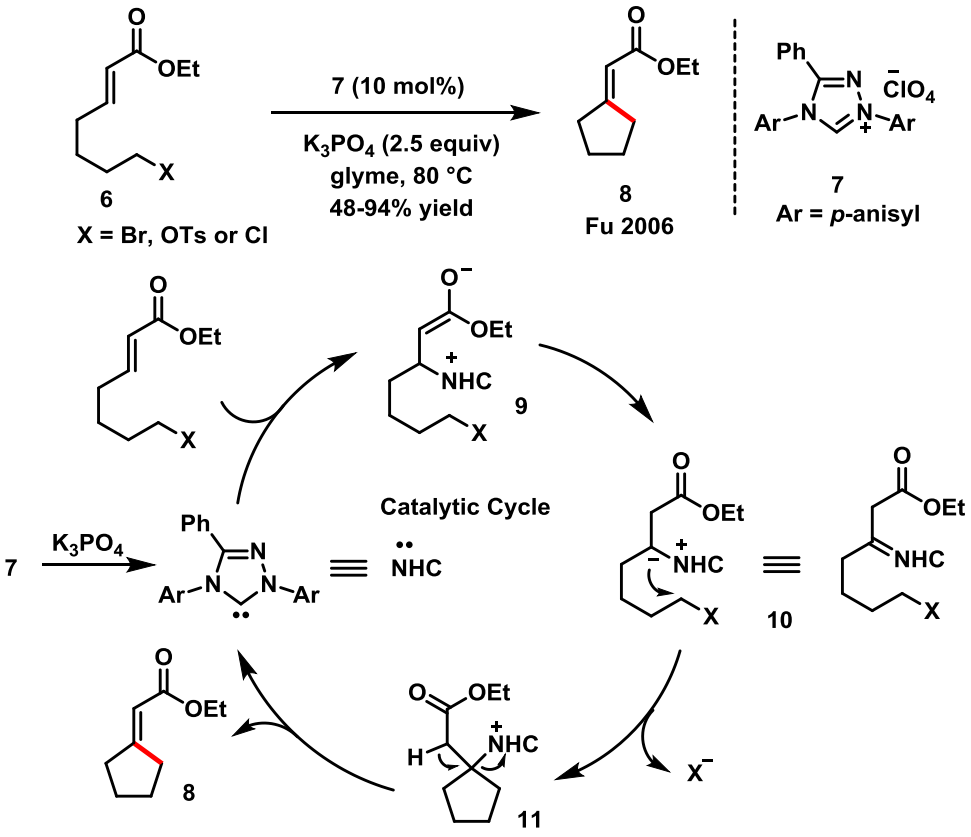


In this chapter, we will focus on the *deoxy*-Breslow intermediates. The work involves the isolation and characterization of the oxidized *deoxy*-Breslow intermediates formed from NHCs and chalcones. In addition, an unprecedented catalyst free intramolecular Rauhut-Currier type reaction is also developed during the investigation of the reaction mechanism. Before discussing the results, a brief overview of the recent developments on the *deoxy*-Breslow intermediates is presented in the following sections.

4.2. Recent Developments on *deoxy*-Breslow Intermediates

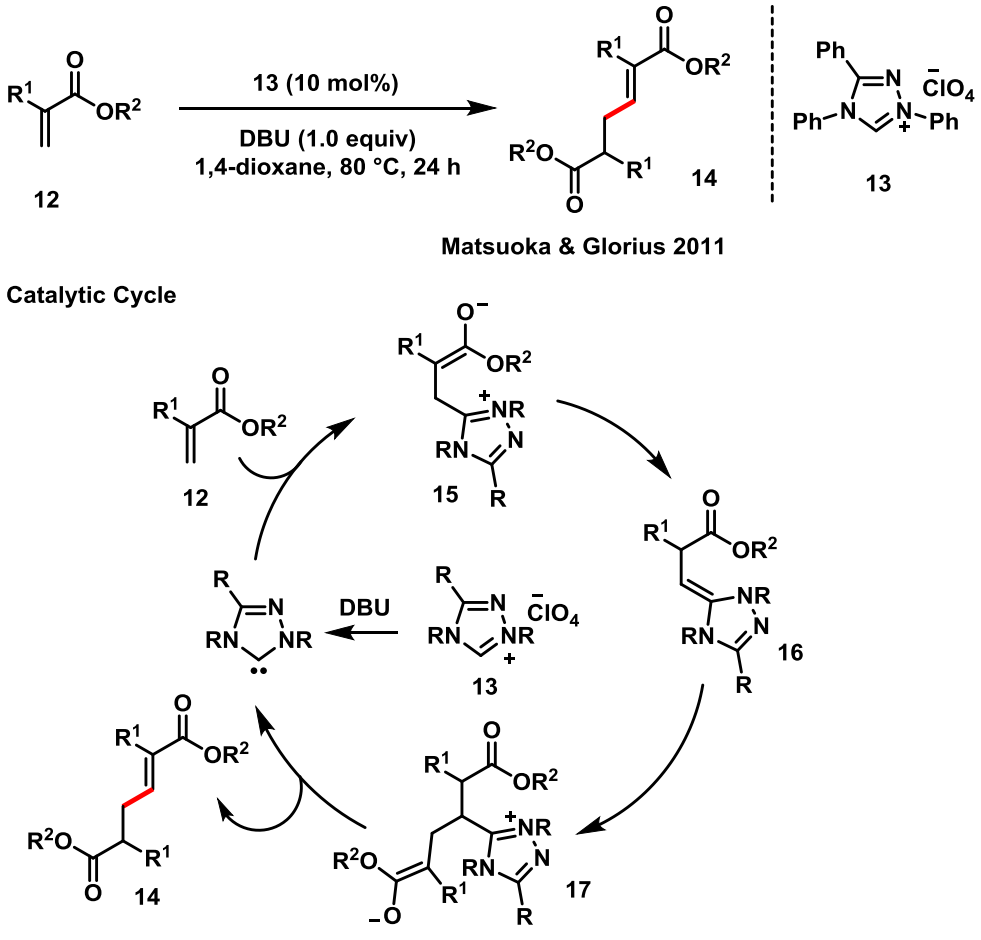
The *umpolung* of Michael acceptors using NHCs for the intramolecular β-alkylation of α,β-unsaturated esters **6** to form cyclopentenes **8** was demonstrated by Fu and co-workers in 2006 (Scheme 4.6).[9] This reaction proceeds through the formal *deoxy*-Breslow intermediate **10** generated from enolate **9**, which transforms the electrophilic β-carbon to nucleophilic. It can be considered as a NHC-catalyzed intramolecular Heck reaction. The reaction works with a broad range of Michael acceptors such as α,β-unsaturated esters, amides and nitriles.

Scheme 4.6: *Umpolung* of Michael Acceptors: β-alkylation of α,β-Unsaturated esters



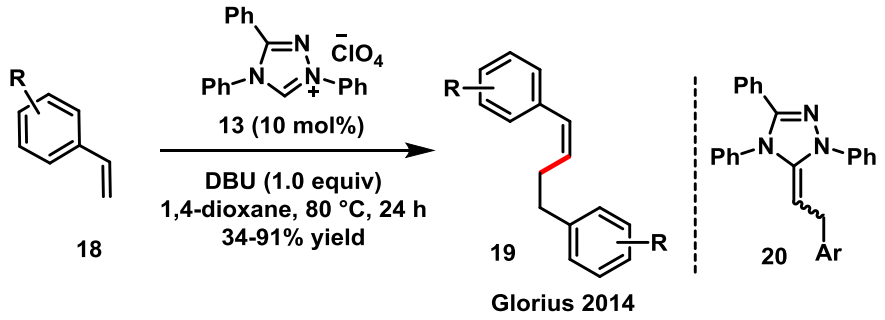
Matsuoka[10] and Glorius[11] groups independently reported the tail to tail dimerization of methacrylates using NHCs (Scheme 4.7). Mechanistically, the reaction proceeds through the conjugate addition of NHC to the methacrylate **12** followed by proton transfer leading to the generation of *deoxy*-Breslow intermediate **16**. The Michael addition of **16** to the another molecule of methacrylate **12** forms the ester enolate **17**, which undergoes proton transfer followed by release of NHC to form the observed dimerized product **14** with moderate to good yield and excellent *E*/*Z* ratio (up to 98:2). The initial results showed that, the reaction preferred homo-coupling in contrast to the cross-coupling. Later Matsuoka and co-workers expanded the scope of this reaction with various other Michael acceptors such as methacrylonitrile, acrylonitrile *etc*.[12] Subsequently, this chemistry have been reported for the β-coupling of methacrylates to form trimers, tetramers as well as polymers.[13] Interestingly, Zhang and Chen very recently uncovered the isolation of *deoxy*-Breslow intermediates formed from NHC-methacrylate reaction.[14]

Scheme 4.7: *Umpolung* of Methacrylates



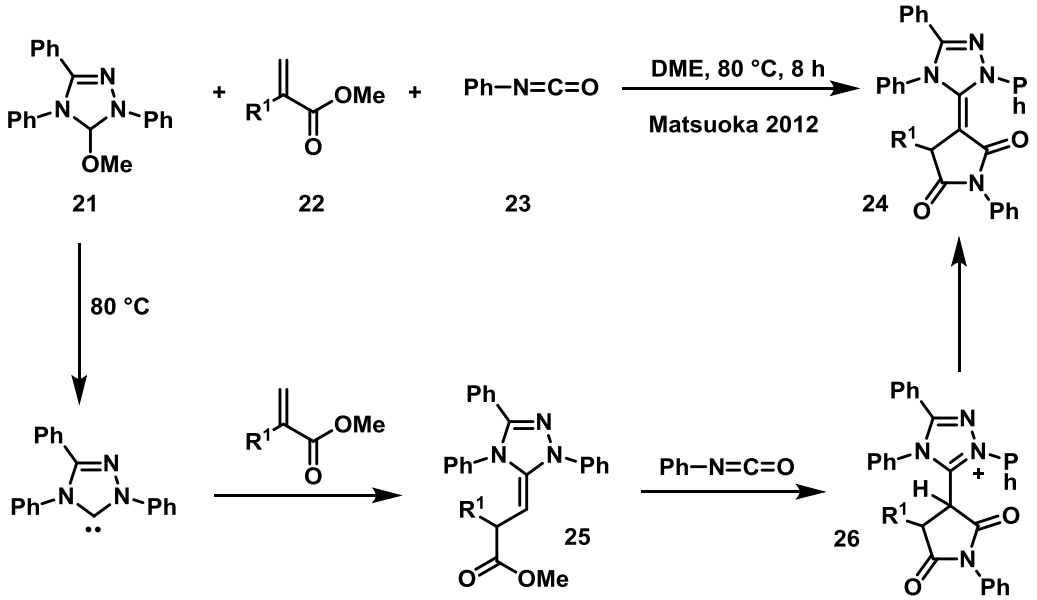
Glorius and co-workers developed the selective tail to tail dimerization of activated styrenes **18** (Scheme 4.8).[15] Mechanistically, the reaction proceeds through the *deoxy*-Breslow intermediate **20**, which was isolated and characterized. Styrenes incorporating electron withdrawing groups at the *para*-position of the aromatic ring and the vinyl pyridines worked efficiently to form the desired product **19**. Later, Nair and co-workers demonstrated the reaction of unsaturated cinnamils to give vinylfulvene derivatives.[16]

Scheme 4.8: *Umpolung* of Styrenes



A tandem one pot three component reaction has been developed by Matsuoka and co-workers.[17] The *deoxy*-Breslow intermediates **25** generated from methacrylates **22** and NHC underwent annulation with isocyanates **23** to give urea derivatives **24** in good yields (Scheme 4.9).

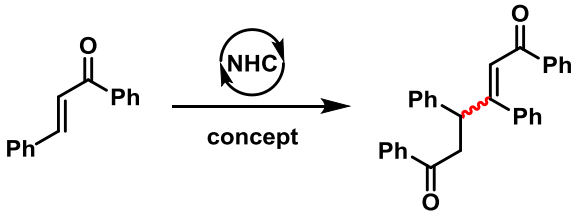
Scheme 4.9: Multicomponent Reaction by *Umpolung*/Cyclization Cascade



4.3. Statement of the Problem

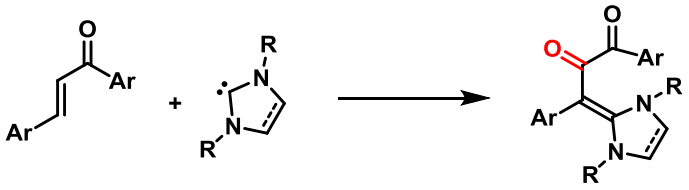
From the above mentioned literature it is clear that, the NHC-catalyzed generation of the *deoxy*-Breslow intermediates and their subsequent catalysis is in the primary stage of development. The umpolung of α,β-unsaturated ketones having β-substitution are underexplored,[18] and the umpolung of chalcones, to the best of our knowledge is unknown. We envisaged that if the reaction is carried out using chalcones, there is a possibility of tail to tail coupling to furnish highly functionalized olefins (Scheme 4.10).

Scheme 4.10: Proposed Methodology



A detailed study of the eaction of chalcones with NHCs is carried out in the present chapter.[19] This investigation resulted in a 1:1 adduct of chalcones with NHC leading to the formation of stable oxidized *deoxy*-Breslow intermediates (Scheme 4.11). We have carried out priliminary mechanistic studies to confirm the reaction pathways. It is important to note that chalcones are widely used Michael acceptors for acyl anions[19] and homoenolates[20] in NHC-organocatalysis.

Scheme 4.11: *Umpolung* of Chalcones: Isolation of Oxidized *deoxy*-Breslow Intermediate



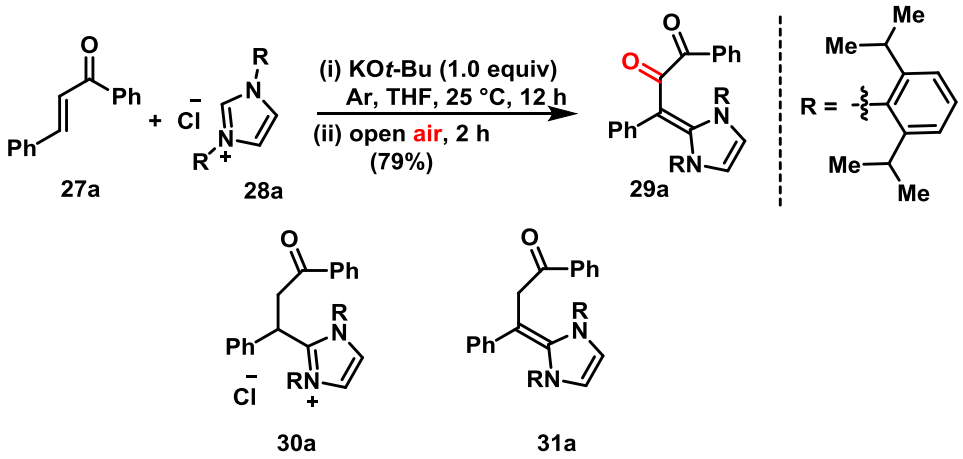
4.4. Results and Discussion

4.4.1. Optimization Studies

Against the literature backdrop and considering the ready availability and potential applications of chalcones, the present study was commenced by the treatment of chalcone **27a** with the imidazolium salt **28a** in the presence of KO*t*-Bu as base in THF at 25 °C. Stirring the reaction mixture under argon for 12 h followed by 2 h stirring in open atmosphere afforded the oxidized form of the *deoxy* Breslow intermediate **29a** in 79% yield (Scheme 4.12). Performing the reaction in air afforded **29a** in ~10% yield. However,

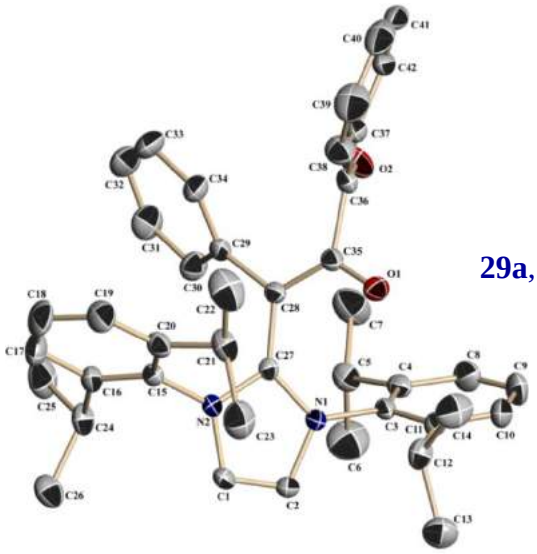
generation of carbene from **28a** under argon followed by stirring in open air improved the yield of **29** to 31%. The diketone **29a** was possibly formed by the aerobic oxidation of the NHC-chalcone adduct under basic conditions.

Scheme 4.12: Synthesis of Oxidized *deoxy*-Breslow Intermediate



The formation of the oxidized form of the *deoxy*-Breslow intermediate **29a** depends on several parameters. KO*t*-Bu was found to be the optimal base for this transformation and other common bases including DBU, Et_3N, Cs_2CO_3 and K_2CO_3 showed inferior reactivity for the formation of **29a**. Surprisingly, under these conditions, the tetrahedral intermediate **30a** or the *deoxy*-Breslow intermediate **31a** (formed from the conjugate addition of NHC derived from **28a** to **27a**) was not isolated. The structure of **29a** was confirmed by single crystal X-ray analysis (Figure 4.1).

Figure 4.1: ORTEP diagram of **29a** drawn at 30% probability displacement ellipsoids

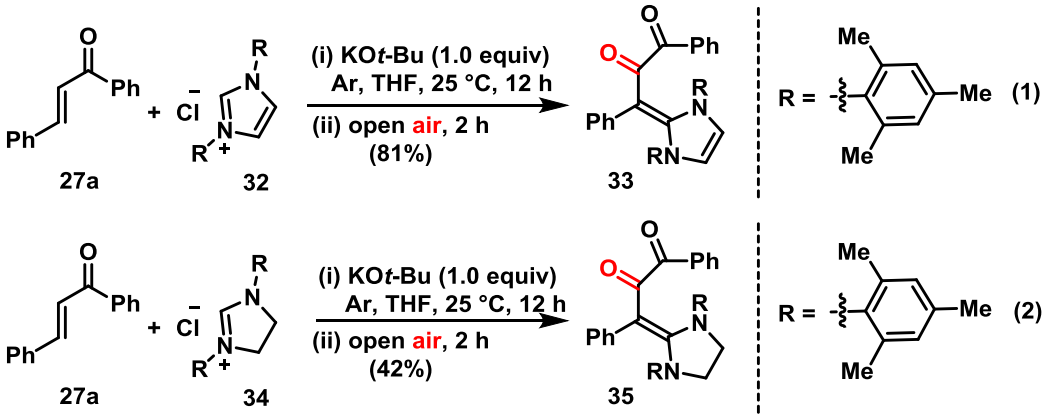


29a, CCDC-1061964

4.4.2. Substrate Scope

In addition to this preliminary result, the reaction worked well with other sterically demanding imidazolium salts. The reaction of chalcone **27a** with the carbene generated from *N*-mesityl imidazolium salt **32** (IMes.HCl) afforded the diketone derivative **33** in 81% yield (Scheme 4.13; Eq. 1). Moreover, the carbene generated from the imidazolinium salt (SIMes.HCl) **34** in this reaction furnished the oxidized form of the *deoxy*-Breslow intermediate **35** in 42% yield (Scheme 4.13; Eq. 2). The structure of **33** and **35** were confirmed by single crystal X-ray analysis (Figure 4.2 & 4.3).

Scheme 4.13: Attempted Azolium Salts and Enones in this Reaction



Interestingly, the reaction works with imidazolium salts with sterically demanding *N*-substituents only. The performed reactions using the thiazolium salt **36a**, the triazolium salt **36b**, and the imidazolium salts **36c-36f** were found to be unsuccessful (Scheme 4.14). Additionally, at present the reaction is limited to chalcones as the enone component. The reactions carried out using other enones **37a-37e** did not afford the desired product under the present conditions.

Scheme 4.14: Attempted Azolium Salts and Enones in this Reaction

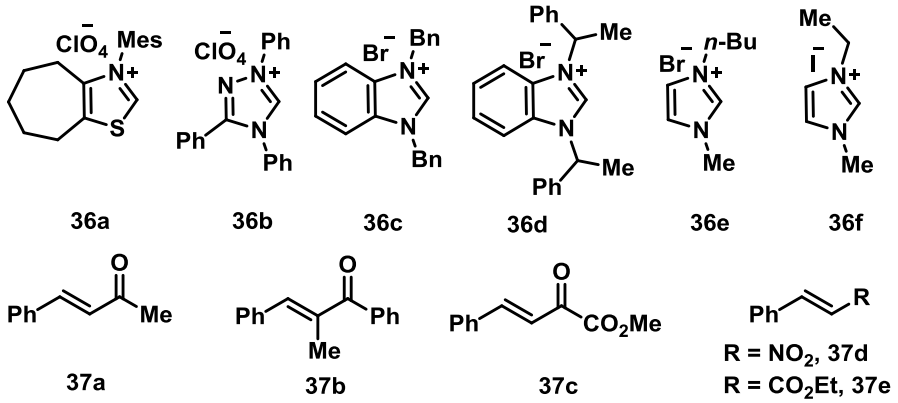
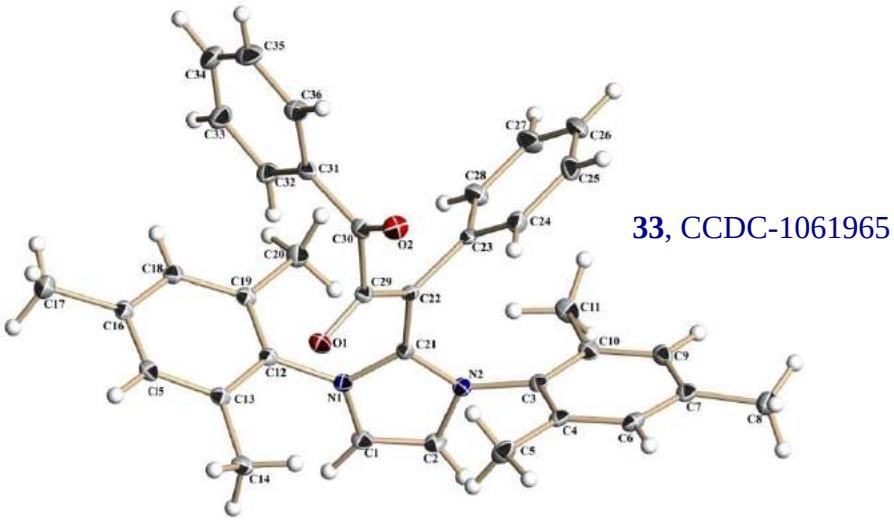
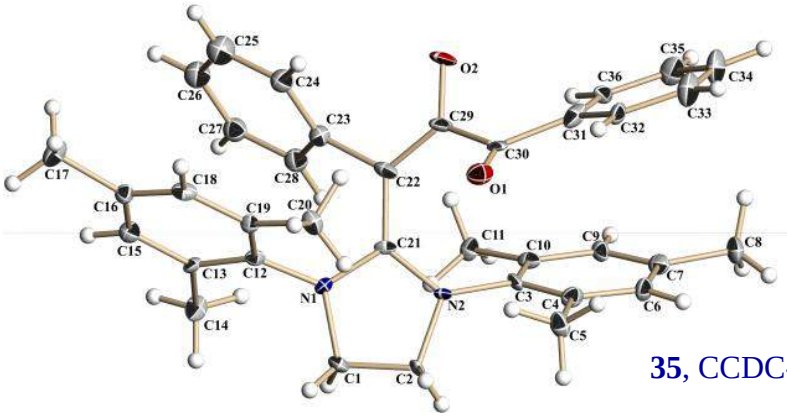


Figure 4.2: ORTEP diagram of **33** drawn at 30% probability displacement ellipsoids



33, CCDC-1061965

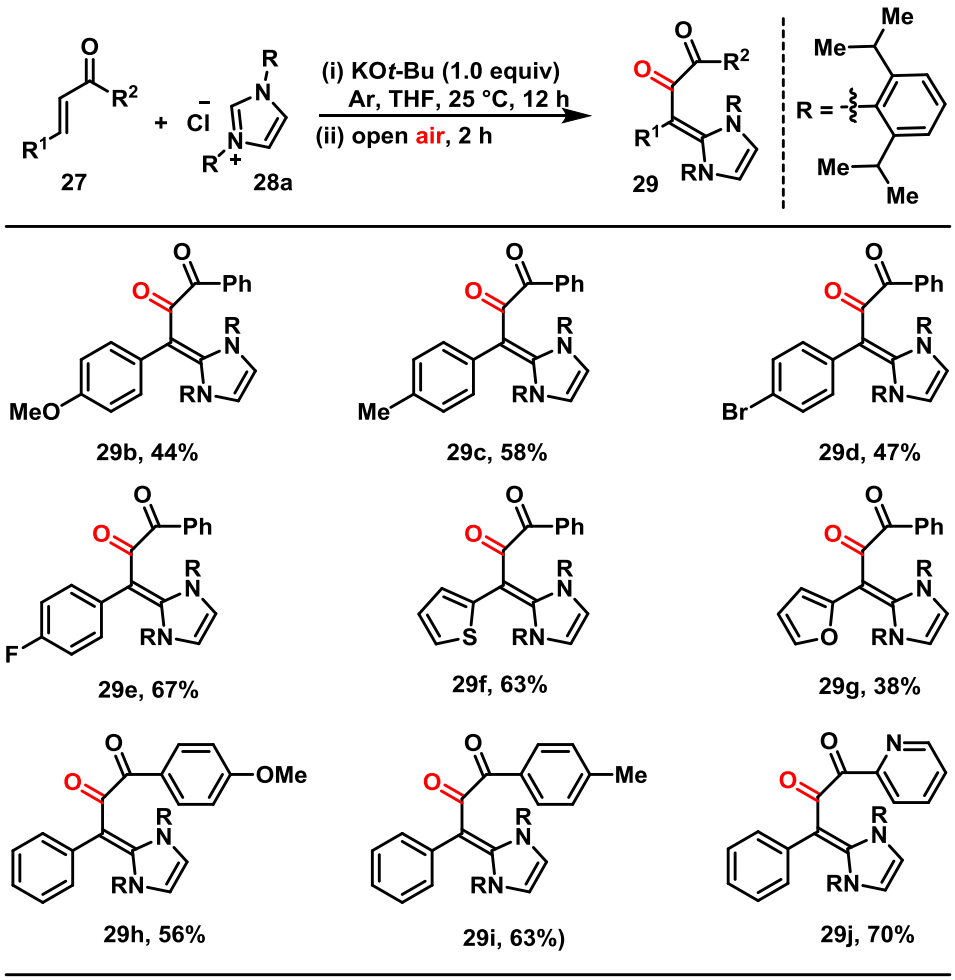
Figure 4.3: ORTEP diagram of **35** drawn at 30% probability displacement ellipsoids



35, CCDC-1061966

With the reaction of chalcone **27a** with the imidazolium salts for the isolation of the oxidized form of the *deoxy*-Breslow intermediate, we then examined the generality of this reaction with substituted chalcones (Scheme 4.15). Chalcones bearing electron-releasing and -withdrawing groups at the 4-position of the β-aryl ring are tolerated well in the reaction with NHC generated from **28a**, and in all cases the oxidized form of the deoxy-Breslow intermediate was isolated in moderate to good yields (**29b-29e**). Moreover, chalcones possessing heteroaryl substitution at the β-position furnished the corresponding diketones in moderate yields (**29f, 29g**). Additionally, various substitutions at the benzoyl moiety of chalcone, and even a pyridine moiety did not create any problems with the reactivity. In all cases, the desired product was synthesized in moderate to good yields (**29h-29j**).

Scheme 4.15: Scope of the Synthesis of Oxidized *deoxy*-Breslow Intermediates[a]



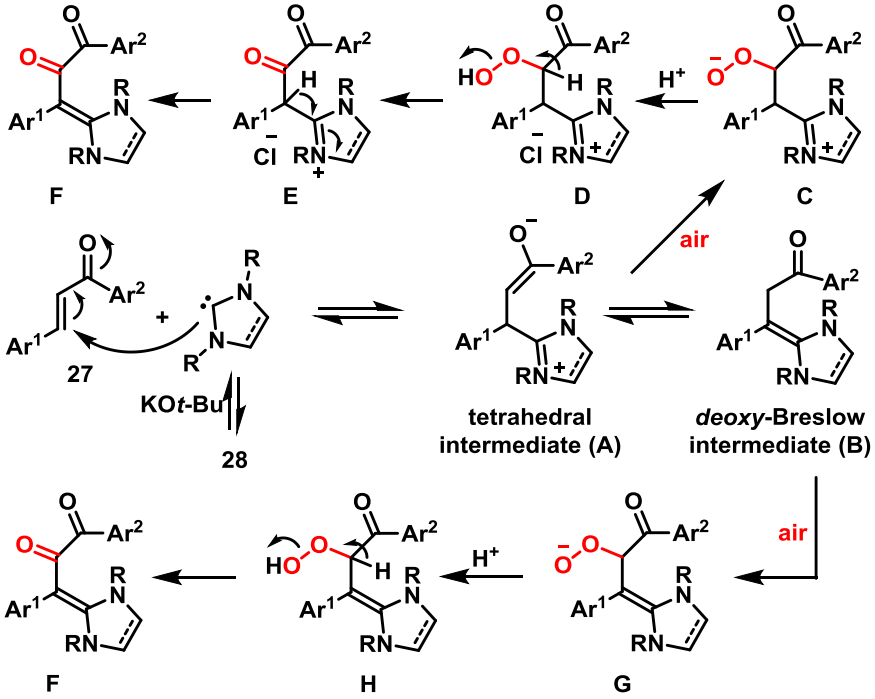
[a] General conditions: **27** (0.5 mmol), **28a** (0.5 mmol), KO*t*-Bu (0.5 mmol), THF (3.0 mL), 25 °C, 12 h stirring under argon atmosphere followed by 2 h stirring in open air, Yields of isolated product are given.

4.4.3. Proposed Mechanism

A tentative mechanism for the formation of the oxidized form of *deoxy*-Breslow intermediate is shown in Scheme 4.16. Likely, the reaction began with the conjugate addition of the NHC generated from **28a/32/34** to the chalcone **27** to generate the azolium enolate **A** (tetrahedral intermediate). This intermediate undergoes a proton transfer to form the enamine intermediate **B** (the *deoxy*-Breslow intermediate). The steps leading to the generation of **A** and **B** appear to be reversible. Notably, analogous enamines of the type **B** have been isolated in the reaction of NHC generated from **36b** (Enders carbene) with activated alkenes such as fumaric dinitrile, dimethyl fumarate and *N*-substituted maleic imides.[18] Moreover, the enamine derivative obtained by the 1:1 addition of **32** with methyl

methacrylate was recently isolated.[14] In an irreversible step, the tetrahedral intermediate **A** captures a molecule of oxygen to generate the α-hydroperoxy ketone anion **C**, which is subsequently protonated to generate the α-hydroperoxy ketone **D**. The intermediate **D** undergoes an elimination of a molecule of water under basic conditions to form the azolium diketone **E**. Deprotonation of the intermediate **E** results in the formation of the oxidized form of *deoxy*-Breslow intermediate **F**. Alternatively, the intermediate **B** under basic conditions can react with molecular oxygen to form the α-hydroperoxy ketone anion **G**, which on protonation generates the α-hydroperoxy ketone **H**. Elimination of a molecule of water from intermediate **H** delivers **F**. It may be mentioned in this context that the aerobic oxidation of ketones at the α-position leading to the synthesis of diketones using air as the sole oxidant under basic conditions is well demonstrated in the literature.[22]

Scheme 4.16: Proposed Mechanism of the Reaction



4.4.4. Mechanistic Studies

To shed light on this unique transformation, we have carried out a series of mechanistic experiments. First we attempted the isolation of the keto form of the tetrahedral intermediate (**A**) or the *deoxy*-Breslow intermediate (**B**). Either the keto form of **A** or the intermediate **B** were not isolable in our hands by the purification of the reaction mixture obtained by mixing **27a** with NHC generated from **28a** using KO*t*-Bu (the reaction mixture

was not exposed to air for 2 h). Moreover, given the importance of the basic medium in the aerobic oxidation to form the diketone **29**, experiments were performed using Brønsted acid quenching instead of exposure to air. Thus, the reaction of **27** with NHC generated from **28** using KO*t*-Bu for 12 h followed by quenching the reaction mixture using HBF_4 resulted in the formation of the salt **38a** in 63% yield (Scheme 4.17). Similar results were obtained by quenching the reaction with TfOH leading to the isolation of the triflate salt **38b** in 51% yield. The salts **38a** and **38b** correspond to the keto form of the tetrahedral intermediate (**A**) formed by the addition of NHC to chalcone. Notably, similar tetrahedral intermediates have been isolated by the 1:1 addition of NHC generated from **36b** to butyl methacrylate.[11] The structure of **38a** was confirmed by single crystal X-ray analysis (Figure 4.4).

Scheme 4.17: Brønsted Acid Quenching Experiments

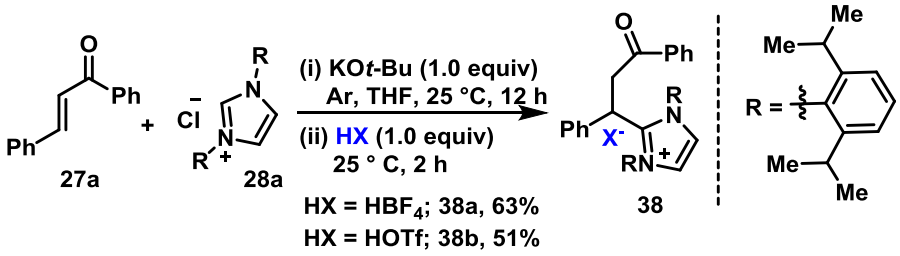
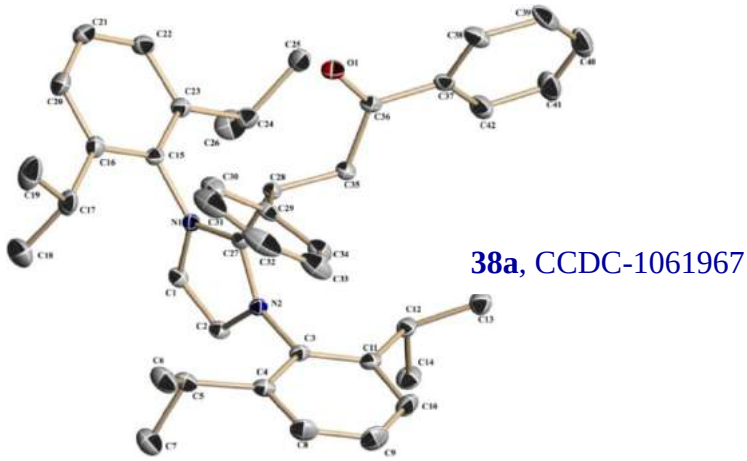
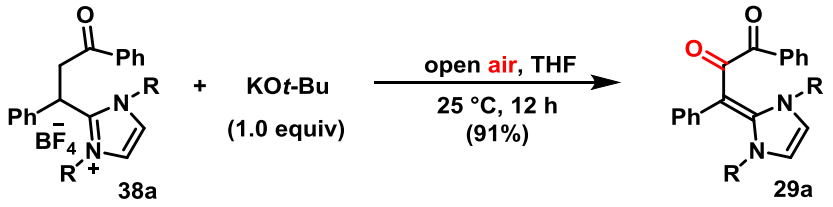


Figure 4.4: ORTEP diagram of **38a** drawn at 30% probability displacement ellipsoids



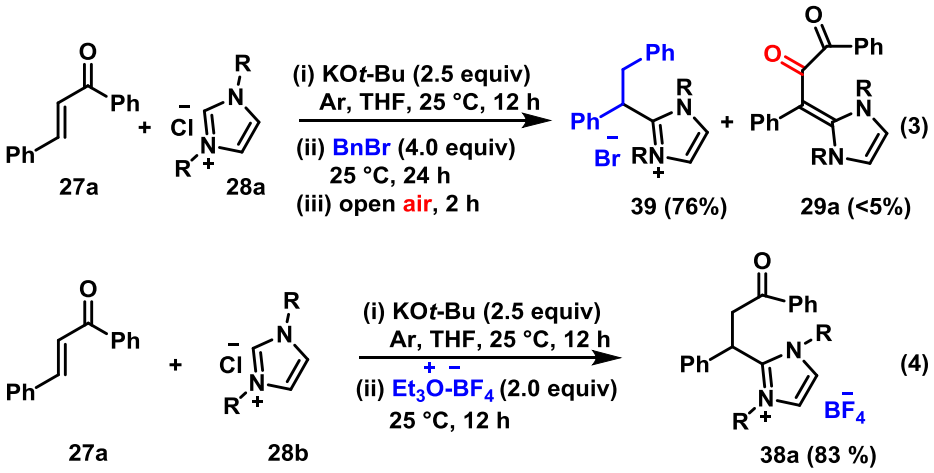
Interestingly, treatment of the salt **38a** with KO*t*-Bu in open air resulted in the formation of the oxidized form of *deoxy*-Breslow intermediate **29a** in 91% yield (Scheme 4.18). These studies indicate the intermediacy of the tetrahedral intermediate **38** in the formation of the diketone **29a**. This also sheds light on the reversible nature of the generation of the tetrahedral intermediate **A** and *deoxy*-Breslow intermediate **B** (Scheme 4.16).

Scheme 4.18: Treatment of Salts with Base in Presence of Air



Given the nucleophilic nature of the enolate intermediate **A** (the tetrahedral intermediate), and the *deoxy*-Breslow intermediate **B** (both enolate reactivity and enamine reactivity possible) formed by the initial addition of NHC to chalcones (Scheme 4.16), we have performed experiments using external electrophiles. Treatment of chalcone **27a** with the imidazolium salt **28a** in the presence of KO*t*-Bu and stirring the reaction mixture under argon for 12 h followed by addition of benzyl bromide and 12 h stirring under argon and an additional 2 h stirring in open atmosphere afforded the imidazolium salt **39** in 76% yield along with traces of **29a** (Scheme 4.19, Eq 3). The formation of products related to **39** was observed by Jacobi von Wangelin in the umpolung of alkyl halides.[6a] The isolation of **39** under the present conditions sheds light on the reversibility of the formation of intermediates **A** and **B** from chalcones and NHCs.Moreover, we have performed the reaction in the presence of Meerwein's reagent anticipating the alkylation of the tetrahedral intermediate **A**. Surprisingly, this reaction furnished the imidazolium salt **38a** in 83% yield (Eq. 4).

Scheme 4.19: Electrophile Trapping Experiments



Gratifyingly, when the reaction of NHC generated from **28a** was carried out using 2'-aminochalcone derivative **27k**, the initially formed oxidized form of the deoxy-Breslow intermediate (**41**) underwent an intramolecular cyclization reaction leading to the formation of 2-benzylidene 1-methylindoline 3-one derivative having an imidazolium salt (**40a**) in 72% yield (Scheme 8). Moreover, the reaction worked well with NHC generated from **32** affording the corresponding product **40b** in 63% yield. These reactions proceed via the generation of diketone **41** followed by the intramolecular nucleophilic attack of the amine moiety on the carbonyl to afford the desired product via the carbinol intermediate **42**. It may be noted that the related reaction of NHCs with 2'-hydroxy chalcones under the present conditions did not afford the expected cyclized product. The structure of **40a** was confirmed by single crystal X-ray analysis (Figure 4.5).

Scheme 4.20: Reaction of NHCs with 2'-Aminochalcones

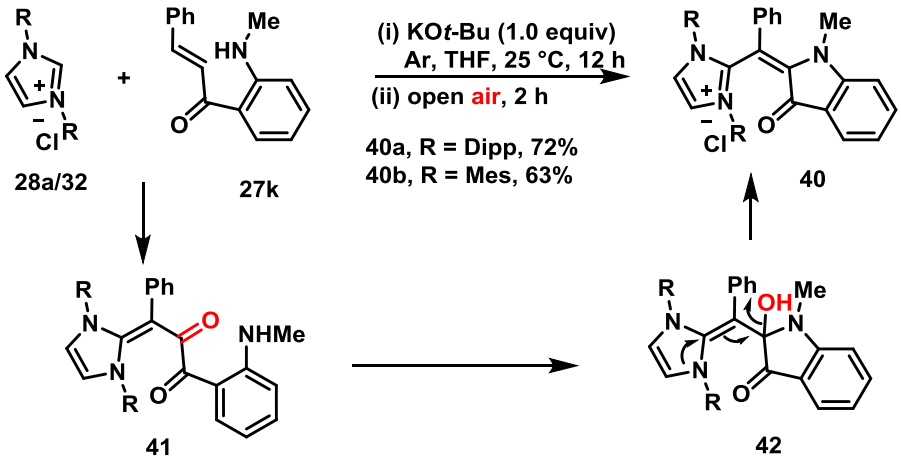
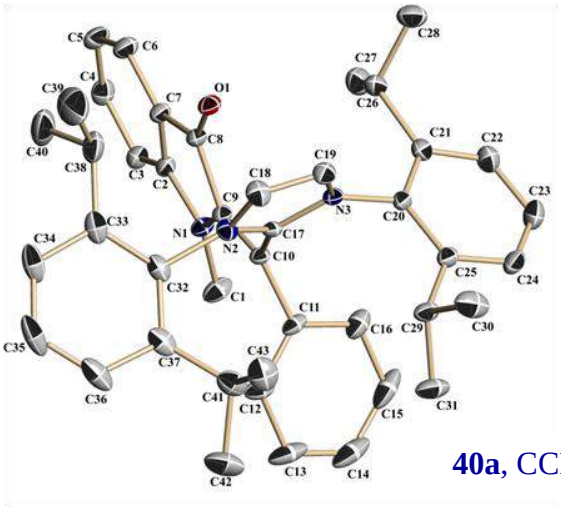


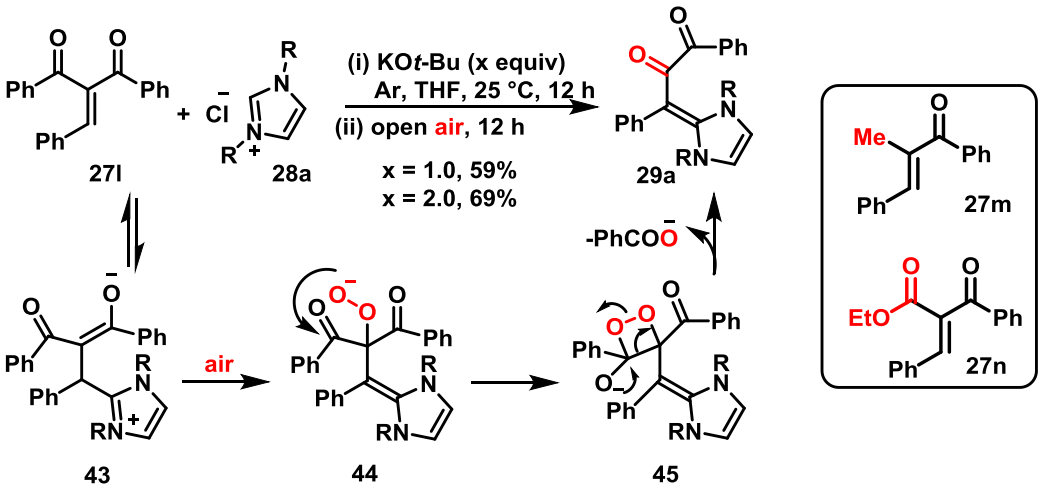
Figure 4.5: ORTEP diagram of **40a** drawn at 30% probability displacement ellipsoids



40a, CCDC-1061968

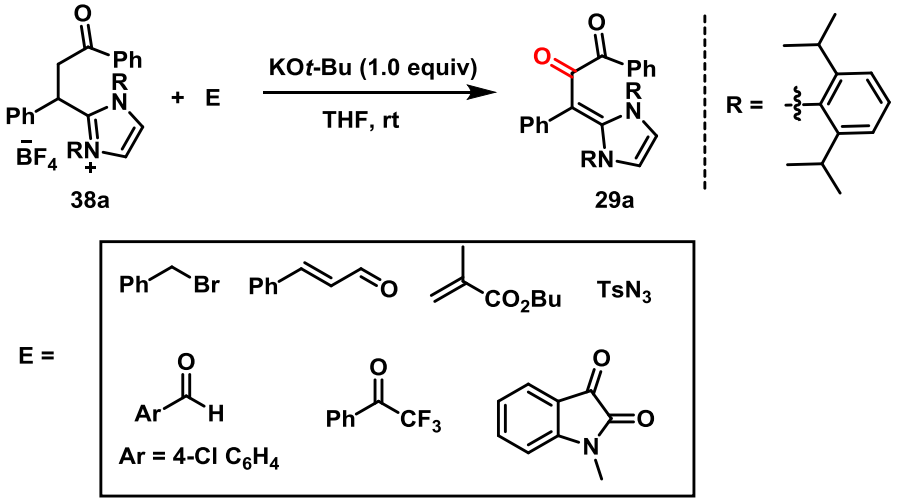
We also examined the reaction of NHCs with α-substituted electron deficient chalcones. Interestingly, the reaction of α-benzoyl chalcone **27l** with NHC derived from **28a** using KO*t*-Bu as the base resulted in the formation of the oxidized form of *deoxy*-Breslow intermediate **29a** in 59% yield under the standard conditions (Scheme 4.21). With 2.0 equiv of KO*t*-Bu the yield was improved to 69%. Notably, one of the benzoyl moiety was cleaved under the reaction conditions. Mechanistically, the reaction proceeds via the generation of the tetrahedral intermediate **43**, which on exposure to air under basic conditions forms the α-hydroperoxy diketone anion **44**. The intermediate **44** cyclizes to form the 1,2-dioxetane intermediate **45**, which on carbon-carbon bond cleavage results in the formation of **29a**. Alternatively, the enolate intermediate **43** can be transformed to the corresponding *deoxy*-Breslow intermediate, which can also oxidize to afford **29a** (analogous to the mechanism proposed in Scheme 4.16). Closely related carbon-carbon bond scission proceeding via the intermediacy of 1,2-dioxetane under basic medium using air as the oxidant is known in the literature.[22b,22c] It may be mentioned that both benzoyl moieties are necessary for this transformation, and the attempted reaction of α-methyl chalcone (**27m**) or α-ester chalcone (**27n**) with NHCs under the present reaction conditions were unsuccessful.

Scheme 4.21: Reaction of NHCs with α-Substituted Chalcones



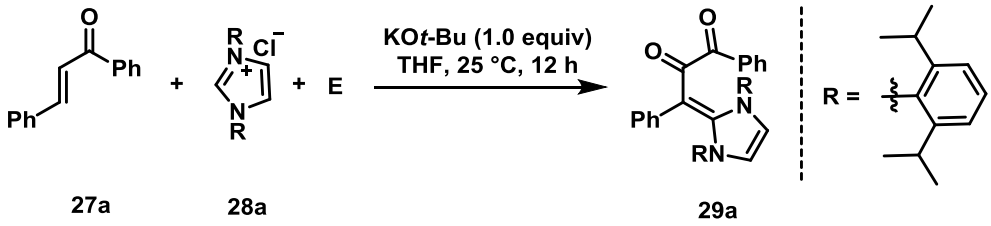
Furthermore, we have carried out cross coupling reaction utilizing the salt **38a** with different type of electrophiles (Scheme 4.22). Unfortunately, we could not able to get any kind of coupled product. In most of the cases quantitative amount of oxidized product was isolated. The reaction under degassed condition has no promising result.

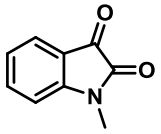
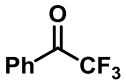
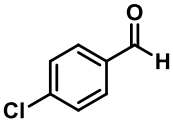
Scheme 4.22: Electrophile Trapping Experiments



The parent reaction was then repeated in presence of various electrophilic systems and the yield of the product **29a** was determined (Scheme 4.23). Notably, in all the cases, no electrophile coupled product was observed. Catalysis using this concept was not successful because of the irreversible binding between chalcone and NHC.

Scheme 4.23: Attempted Intermolecular Cross-Coupling



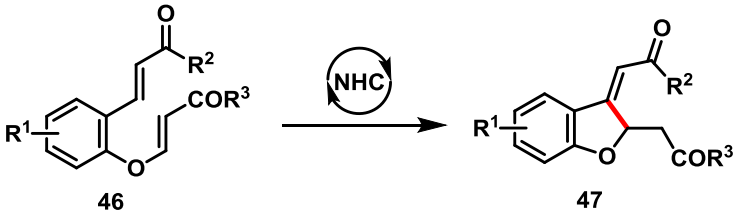
Electrophile (E)	Yield of **29a** (%)[a]
	65
	71
	44

[a] General Conditions: **27a** (0.25 mmol), **28a** (0.25 mmol), KO*t*-Bu (0.25 mmol), THF (1.5 mL mmol), 25 °C, 12 h, Yields of isolate product are given.

4.5. Attempted Intramolecular Cross-Coupling

In this context, we envisaged that a chalcone having an enoate moiety (**46**) may help to develop the NHC-catalyzed intramolecular cross-coupling (Scheme 4.24). If successful, this will constitute the synthesis of benzofuran derivatives via *deoxy*-Breslow intermediate.

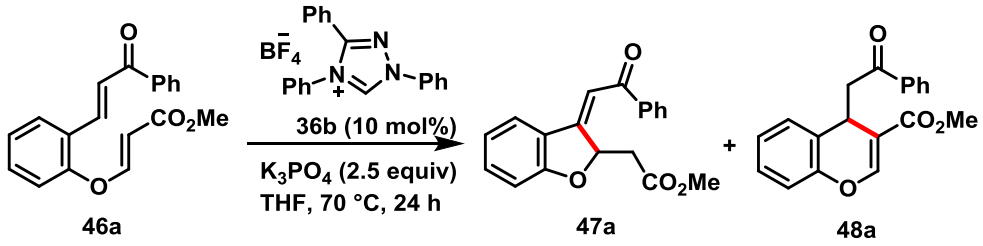
Scheme 4.24: Proposed Intramolecular Cross-Coupling by NHC-Catalysis



46 47

Based on this background, the present study was initiated by treating **46a** with the triazolium salt **36b** and excess of K_3PO_4 (Scheme 4.25). Surprisingly, the functionalized benzofuran product **47a** derived from the umpolung of α,β-unsaturated ketone was not observed. However, the reaction afforded the 4*H*-chromene derivative **48a** in 48% yield. Interestingly, **48a** was formed even in the absence of the triazolium salt **36b** under basic conditions.

Scheme 4.25: Attempted Intramolecular Cross-Coupling by NHC-Catalysis



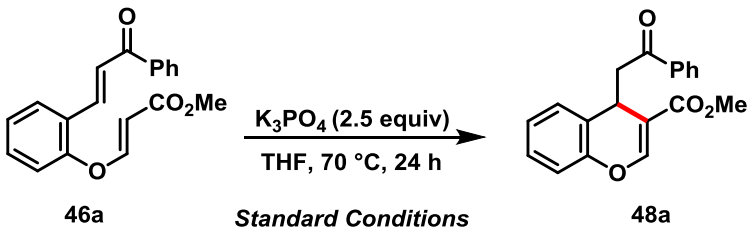
46a 47a 48a

with 10 mol % of 36b, 47a was not formed and 48a was isolated in 48% yield
In the absence of 36b, 47a was not formed and 48a was isolated in 48% yield

The 4*H*-chromene **48a** was likely formed by the intramolecular Rauhut-Currier type reaction in the absence of a nucleophilic catalyst, where the enol ether moiety functions as the nucleophilic trigger under basic conditions.[23] Although intramolecular Rauhut Currier reaction of unsymmetrical enone-enoate systems are known under nucleophilic catalysis,[24, 25] related cyclization reactions using enol ethers as enoate components under basic conditions leading to the formation of 4*H*-chromenes, to the best of our knowledge is unknown. Even though the catalysis using NHCs was not working, we visualized the importance of chromene derivatives[26] and performed the optimization studies.

4.5.1. Optimization Studies

Table 4.1: Optimization of the Reaction Conditions [a]



46a — *Standard Conditions* — 48a

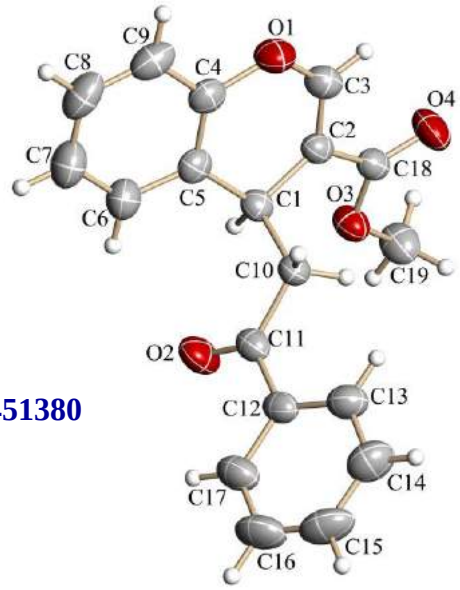
entry	variation from the standard conditions	yield of **48a** (%)[b]
1	None	50 (48)
2[c]	No K_3PO_4	<5
3[c]	DBU instead of K_3PO_4	<5
4[c]	DABCO instead of K_3PO_4	<5
5[c]	PPh_3 instead of K_3PO_4	<5
6[c]	P*n*-Bu_3 instead of K_3PO_4	<5
7[d]	KO*t*-Bu instead of K_3PO_4	<5
8[d]	NaO*t*-Bu instead of K_3PO_4	<5
9[d]	LiO*t*-Bu instead of K_3PO_4	<5
10[c]	K_2CO_3 instead of K_3PO_4	<5
11	Cs_2CO_3 instead of K_3PO_4	28
12	CsF instead of K_3PO_4	20
13[c]	HCl in dioxane instead of K_3PO_4	<5
14[c]	H_3PO_4 instead of K_3PO_4	<5
15[c]	$Sc(OTf)_3$ instead of K_3PO_4	<5
16[c]	$Sc(OTf)_2$ instead of K_3PO_4	<5
17[c]	$Zn(OTf)_2$ instead of K_3PO_4	<5
18[c]	I_2 instead of K_3PO_4	<5
19	DME instead of THF	50
20[c]	MeOH instead of THF	<5
21	Run at 60 °C	49
22	Run at 50 °C	23
23	60 °C, 1.0 equiv of K_3PO_4	52
24	60 °C, 1.0 equiv of K_3PO_4, 48 h	78
25	**60 °C, 1.0 equiv of K_3PO_4, 72 h**	**92 (88)**

[a] Standard conditions: **46a** (0.25 mmol), K_3PO_4 (2.5 equiv), THF (2.0 mL), 70 °C and 24 h. [b] The yields were determined by ^{1}H-NMR analysis (in $CDCl_3$) of crude products using CH_2Br_2 as the internal standard; Isolated yield in parentheses. [c] No reaction was observed and **46a** was recovered. [d] Decomposition of **46a** was observed.

With the initial result on K_3PO_4-mediated intramolecular cyclization of enone-enoate **46a** to form the 4*H*-chromene **47a**, a systematic optimization study was carried out (Table 1). The reaction did not work at all in the absence of K_3PO_4 (entry 2). The conversion of **46a** to **48a** did not take place when the reaction was performed using

nucleophilic bases such as DBU and DABCO (entries 3,4). Moreover, **46a** to **48a** transformation was not effective in the presence of phosphines such as PPh_3 and P*n*-Bu_3 (entries 5,6). These studies indicate that the present cyclization reaction takes place in the absence of nucleophilic catalysts. Other Inorganic bases were not efficient in this intramolecular cyclization to 4*H*-chromemes (entries 7-12). The use of Brønsted acid and Lewis acid was not beneficial in this reaction (entries 13-18). A quick solvent screening indicated that reaction tried in DME returned the 4*H*-chromene in same yield as in THF (entry 19), but the reaction carried out in MeOH did not work at all (entry 20). The reaction was found to be equally efficient at 60 °C (entry 21), but when the temperature was further lowered to 50 °C, the yield of **48a** dropped to 23% (entry 22). Interestingly, reducing the amount of K_3PO_4 at 60 °C improved the yield of **48a** (entry 23), and increasing the reaction time further enhanced the amount of **48a** (entry 24). Finally, performing the reaction at 60 °C using 1.0 equiv K_3PO_4 for 72 h afforded the 4*H*-chromeme **48a** in 88% isolated yield (entry 25). The structure of **48a** was confirmed by single crystal X-ray analysis (Figure 4.6).

Figure 4.6: ORTEP diagram of **48a** drawn at 30% probability displacement ellipsoids



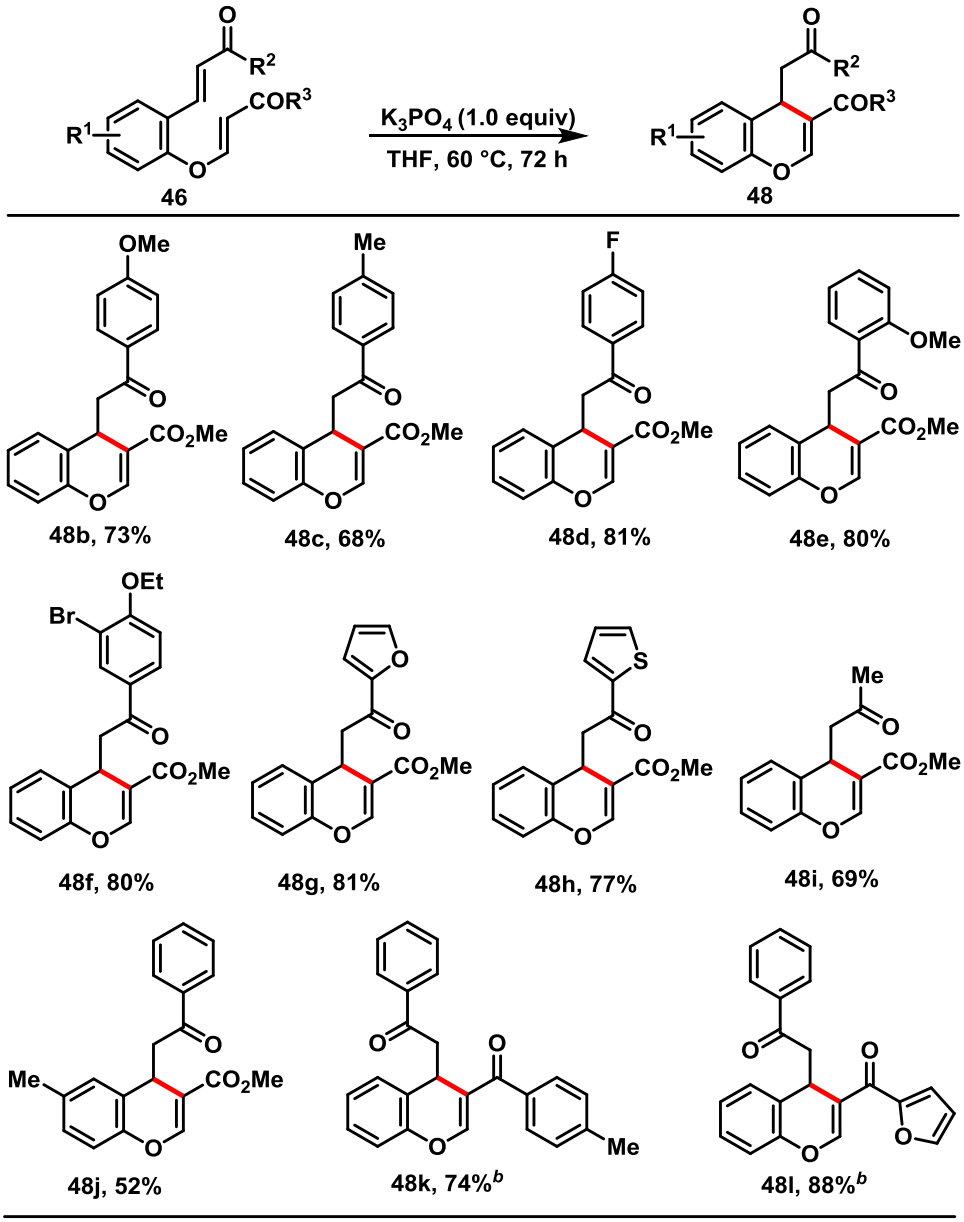
48a, CCDC-**1451380**

4.5.2. Substrate Scope

After establishing the optimized reaction conditions for the K_3PO_4-mediated intramolecular Rauhut-Currier type reaction of the enone-enoate system, we then examined the scope and limitations of this transformation (Scheme 4.26). A series of substituents on

the aroyl moiety of **46** are well tolerated. Substrates having substituents such as OMe, Me, halides at the 4-position and 2-position of the aroyl moiety readily underwent smooth intramolecular Rauhut-Currier type reaction to furnish the functionalized 4*H*-chromones in good yields (**48b**-**48f**).

Scheme 4.26: Substrate Scope of the Synthesis of 4*H*-Chromones

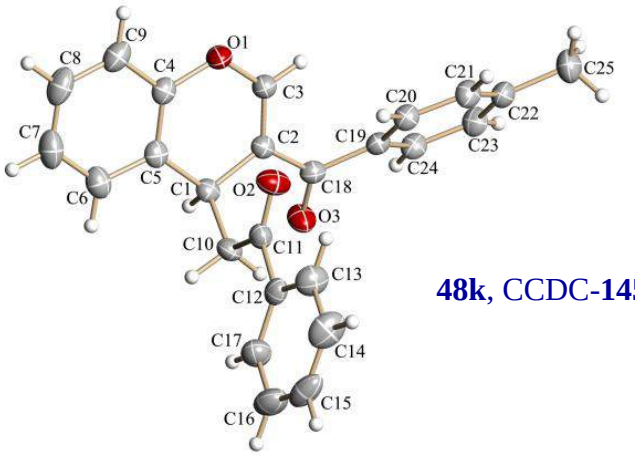


[a] General conditions: **46** (0.50 mmol), K_3PO_4 (0.5 mmol), THF (4.0 mL), 60 °C, reaction time 72 h. Yields of isolated products are given. [b] Reaction was run for 60 h.

Moreover, the heteroaryl group at the aroyl terminus did not affect the outcome of this intramolecular cyclization reaction and the corresponding products are formed in good yields (**48g, 48h**). Interestingly, the benzylidene acetone derivative **46i** afforded the

cyclized product **48i** in 69% yield. In addition, substituent on the β-aryl ring of the enone **46** was tolerated well under the basic condition (**48j**). Furthermore, instead of the enone-enoate system, bis(enones) can also be used as the precursor for the present cyclization reaction. In this case, the 4*H*-chromene having a 1,5-diketone moiety was formed in good yields (**48k-48l**). The structure of **48k** was confirmed by single crystal X-ray analysis (Figure 4.7).

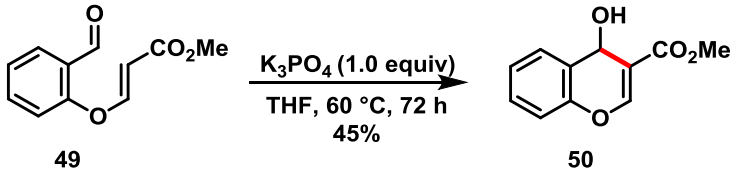
Figure 4.7: ORTEP diagram of **48k** drawn at 30% probability displacement ellipsoids



48k, CCDC-**1451381**

Interestingly, this cyclization reaction is not limited to chalcone derivatives. treatment of 2-vinyloxy benzaldehyde **49** in the presence of K_3PO_4 afforded the 4-hydroxy-4*H*-chromene-3-carboxylate **50** in 45% yield (Scheme 4.27). This reaction is analogous to the intramolecular Baylis-Hillman reaction[27] with the enol ether moiety as the nucleophilic trigger for the reaction without the aid of nucleophilic catalysts.

Scheme 4.27: Intramolecular Cyclization of 2-Vinyloxy Benzaldehyde



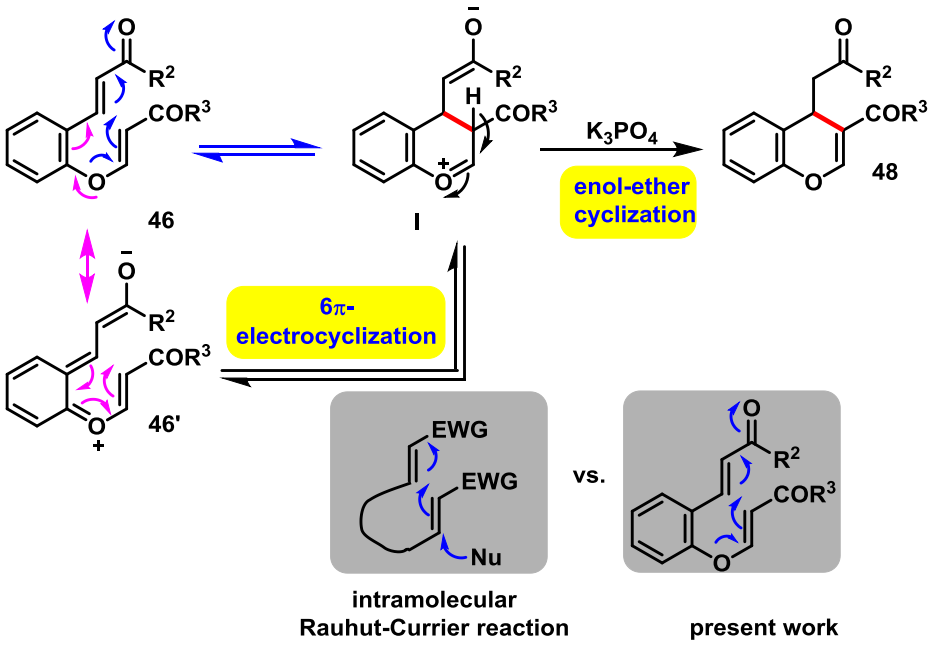
49 **50**

4.5.3. Proposed Mechanism

A plausible mechanism of this reaction is shown in Scheme 4.28. The enol ether assisted intramolecular cyclization of **46** can result in the formation of the oxonium enolate **I**, which under basic conditions can result in the formation of the 4*H*-chromene **48**. The conversion of **46** to **I** may be reversible and **I** to **48** under basic conditions might be irreversible. This also explains the observation of no product formation when **46** was stirred

at 60 °C in the absence of K_3PO_4. It is also probable that, the mesomeric form of **46** (the quinonemethide form **46'**) can undergo a 6π-electrocyclization resulting in the generation of the intermediate **I**. It is interesting to note the similarity of the present transformation with the intramolecular Rauhut-Currier reaction. In Rauhut-Currier reaction, an external nucleophilic catalyst triggers the addition of α-position of first Michael acceptor to the β-position of the second Michael acceptor (head to tail coupling). In the present case, a nucleophilic site within the substrate (enol ether oxygen) initiates the reaction, which is finally incorporated in the product.

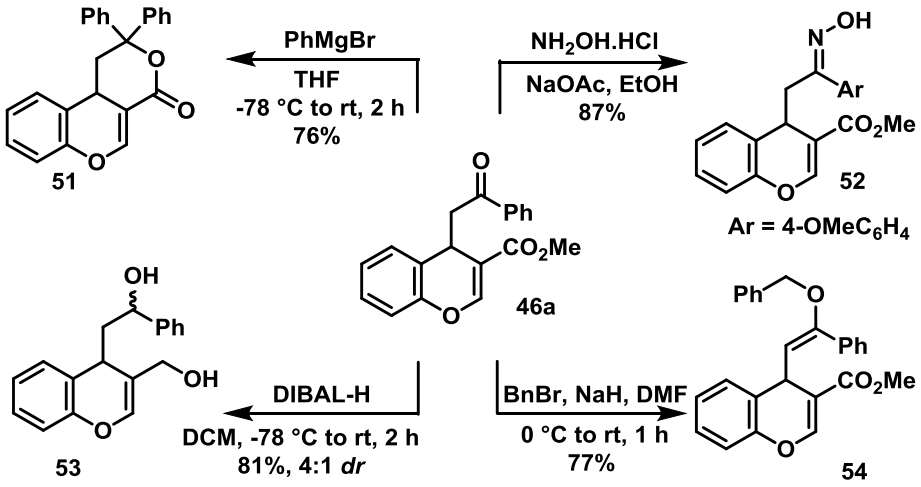
Scheme 4.28: Tentative Mechanism of the Reaction



4.5.4. Product Functionalization

The 4*H*-chromenes synthesized herein features valuable functional groups such as ester and ketone, which allow further functional group manipulations (Scheme 4.29). Treatment of **46a** with PhMgBr afforded the chromene-fused tricyclic δ-lactone **51** in 76% yield. Moreover, the keto group in **46** was efficiently converted into the oxime by reaction with hydroxylamine. Reduction of both the ketone and ester groups in 4*H*-chromene **46a** was demonstrated using DIBAL-H to afford the diol derivative **53** in 81% yield and in 4:1 *dr*. Furthermore, selective *O*-benzylation was achieved by the treatment of **46a** with benzyl bromide in the presence of NaH as base. The enol ether product **54** was formed in 77% yield.

Scheme 4.29: Synthetic Transformations of 4*H*-Chromones



4.6. Conclusion

In conclusion, we have developed a method for the reaction of chalcones with NHCs. The resultant oxidized form of the *deoxy*-Breslow intermediates are well characterized, and the generality of this reaction using various chalcones and NHCs have been examined. Moreover, the tetrahedral intermediate formed from the initial addition of NHC to chalcone has been isolated. It is reasonable to assume that the results of the present study provide a deeper understanding of the umpolung of Michael acceptors in general and umpolung of chalcones in particular. In addition, a K_3PO_4-mediated synthesis of functionalized 4*H*-chromenes by the intramolecular Rauhut-Currier type reaction of chalcones bearing an enoate moiety has been developed. The desired product was formed in an unexpected reaction when the umpolung of α,β-unsaturated ketones under NHC-catalysis was envisioned. The use of stoichiometric amounts of K_3PO_4 was found to be the key for the success of this reaction. Given the importance of chromenes in natural products synthesis, the present method is likely to find application for the synthesis of 3,4-disubstituted chromenes.

4.7. Experimental Details

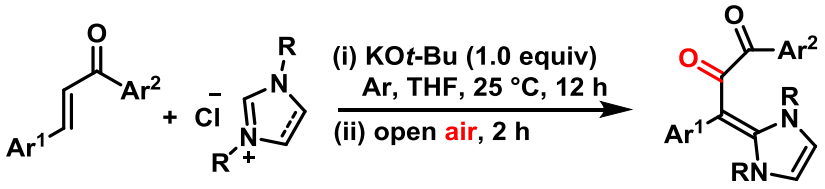
4.7.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. 25 °C corresponds to the room temperature of the lab when the experiments were carried out. THF was freshly

purified by distillation over Na-benzophenone and was transferred under argon. The (*E*)-chalcone **27a** and the other chalcone derivatives were synthesized following the literature procedure.[28] KO*t*-Bu was purchased from Sigma Aldrich and was stored in glove-box. The imidazolium salt **28a/32** and imidazolinium salt **34** were synthesized following the literature procedure.[29] The enone-enoate **46a** and the other enone-enoate derivatives were synthesized following literature procedure.[30] Salicylaldehyde and acetophenone derivatives were purchased from commercial source and used directly without any further purification. K_3PO_4 was purchased from Sigma Aldrich and was stored in glove-box.

Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with solvents as indicated. All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400, AV 500 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm and DMSO-d_6: δH = 2.51 ppm, δC = 39.51 ppm). Infrared spectra were recorded on a Bruker Alpha-E Infrared Spectrophotometer. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

4.7.2. General Procedure for the Synthesis of Oxidized *deoxy*-Breslow Intermediate



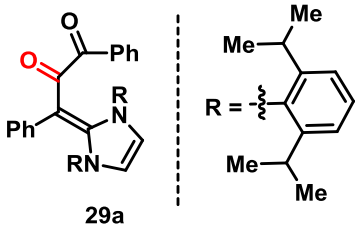
27 **28/32/34** **29/33/35**

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added KO*t*-Bu (0.5 mmol) inside the glove-box. To this was added the azolium salt **28/32/34** (0.5 mmol) outside the glove-box followed by addition of THF (3.0 mL) under a positive pressure of argon and the resultant reaction mixture was kept stirring at 25 °C for 10 minutes. To this mixture was added the (*E*)-chalcone **27** (0.5 mmol). The resulting mixture was then stirred at 25° C for 12 h under argon atmosphere followed by open air

stirring for another 2 h. Then the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding oxidized *deoxy*-Breslow intermediate derivatives (**29/33/35**).

4.7.3. Synthesis and Characterization of Oxidized *Deoxy*-Breslow Intermediates

3-(1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-1,3-diphenylpropane -1,2-dione (29a)



29a

Following the general procedure, treatment of (*E*)-chalcone **27a** (0.104 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-1,3-diphenylpropane-1,2-dione **29a** as a red solid (0.241 g, 79% yield).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.64.

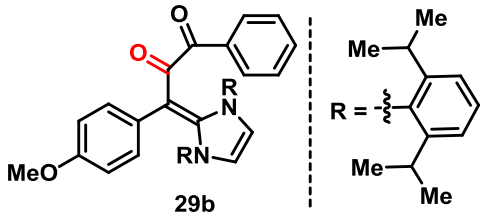
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.37 (t, *J* = 5.5 Hz, 4H), 7.28 (t, *J* = 6.1 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 4H), 7.11 (t, *J* = 7.6 Hz, 2H), 7.02 (s, 2H), 6.74-6.69 (m, 3H), 6.62-6.61 (m, 2H), 3.04-2.97 (m, 4H), 1.38 (d, *J* = 6.7 Hz, 12H), 1.19 (d, *J* = 6.8 Hz, 12H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 196.78, 179.10, 155.01, 145.69, 137.14, 136.09, 134.06, 132.83, 131.70, 129.92, 129.35, 127.60, 127.41, 124.91, 124.05, 121.57, 86.24, 29.02, 26.20, 22.68.

HRMS: calculated $[M+H]^+$ for $C_{42}H_{47}N_2O_2$: 611.3632, found: 611.3643.

FTIR (cm^{-1}): 3366, 3020, 2967, 1670, 1598, 1533, 1450, 1218, 1024, 924, 854, 766, 668.

3-(1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-(4-methoxyphenyl) -1-phenylpropane-1,2-dione (29b)



29b

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **27b** (0.119 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under

argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-(4-methoxyphenyl)-1-phenylpropane-1,2-dione **29b** as a red solid (0.141 g, 44% yield).

***R**_f* (Pet. ether /EtOAc = 50/50): 0.59.

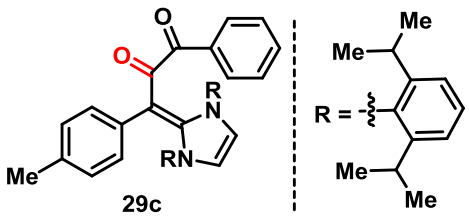
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.30 (m, 4H), 7.26-7.25 (m, 1H), 7.20 (d, *J* = 7.7 Hz, 4H), 7.08 (t, *J* = 7.5 Hz, 2H), 6.96 (s, 2H), 6.46 (d, *J* = 8.6 Hz, 2H), 6.22 (d, *J* = 8.6 Hz, 2H), 3.55 (s, 3H), 2.97-2.90 (m, 4H), 1.34 (d, *J* = 6.7 Hz, 12H), 1.15 (d, *J* = 6.8 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.98, 179.05, 157.09, 155.03, 145.70, 136.01, 134.56, 134.15, 131.68, 129.92, 129.33, 128.99, 127.57, 124.06, 121.50, 112.87, 85.10, 55.05, 29.00, 26.15, 22.67.

HRMS: calculated $[M+H]^+$ for $C_{43}H_{49}N_2O_3$: 641.3738, found: 641.3736.

FTIR (cm^{-1}): 3146, 3065, 3015, 2966, 2874, 1676, 1599, 1519, 1456, 1358, 1226, 1174, 1040, 928, 761, 657.

3-(1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-1-phenyl-3-(*p*-tolyl) propane-1,2-dione (29c)



Following the general procedure, treatment of (*E*)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one **27c** (0.111 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and in 2 h in open air followed by flash column chromatography afforded 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-1-phenyl-3-(*p*-tolyl)propane-1,2-dione **29c** as a red solid (0.181 g, 58% yield).

***R**_f* (Pet. ether /EtOAc = 50/50): 0.54.

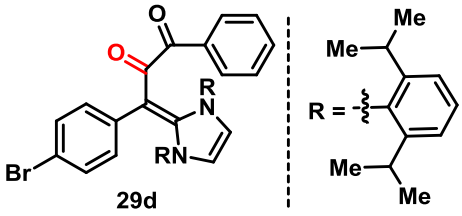
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (t, *J* = 8.0 Hz, 4H), 7.26-7.23 (m, 1H), 7.19 (d, *J* = 7.8 Hz, 4H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.96 (s, 2H), 6.46 (q, *J* = 8.2 Hz, 4H), 2.98-2.92 (m, 4H), 2.01 (s, 3H), 1.33 (d, *J* = 6.7 Hz, 12H), 1.15 (d, *J* = 6.8 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.68, 179.01, 155.33, 145.74, 136.11, 134.24, 134.20, 133.85, 132.90, 131.68, 129.89, 129.49, 128.20, 127.59, 124.06, 121.52, 85.89, 29.01, 26.20, 22.67, 20.94.

HRMS: calculated $[M+H]^+$ for $C_{43}H_{49}N_2O_2$: 625.3789, found: 625.3786.

FTIR (cm^{-1}): 3349, 2964, 2928, 1661, 1595, 1453, 1369, 1219, 930, 770.

3-(1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-(4-bromophenyl)-1-phenylpropane-1,2-dione (29d)



Following the general procedure, treatment of (*E*)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one **27d** (0.144 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-(4-bromophenyl)-1-phenylpropane-1,2-dione **29d** as a red solid (0.162 g, 47% yield).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.62.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.39-7.30 (m, 4H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 4H), 7.10 (t, *J* = 7.5 Hz, 2H), 7.01 (s, 2H), 6.80 (d, *J* = 8.3 Hz, 2H), 6.45 (d, *J* = 8.3 Hz, 2H), 2.93-2.87 (m, 4H), 1.34 (d, *J* = 6.7 Hz, 12H), 1.16 (d, *J* = 6.8 Hz, 12H).

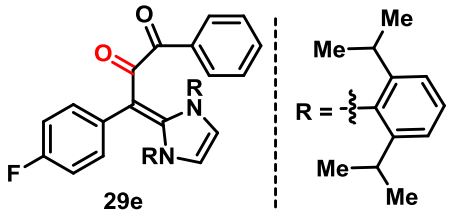
^{13}C NMR (100 MHz, CDCl$_3$) δ: 196.49, 178.93, 155.03, 145.70, 136.47, 135.80, 134.25, 133.86, 132.02, 130.48, 130.16, 129.47, 127.77, 124.20, 121.70, 119.00, 84.96, 29.08, 26.28, 22.67.

HRMS: calculated $[M+H]^+$ for $C_{42}H_{46}{}^{81}BrN_2O_2$: 691.2717, found: 691.2717.

FTIR (cm^{-1}): 3345, 3167, 3067, 3016, 2966, 2872, 1667, 1535, 1452, 1362, 1220, 1009, 927, 808, 755, 699.

3-(1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-(4-fluorophenyl)-1-phenylpropane-1,2-dione (29e)

Following the general procedure, treatment of (*E*)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one **27e** (0.113 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-(4-fluorophenyl)-1-phenylpropane-1,2-dione **29e** as a red solid (0.210 g, 67% yield).



***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.60.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.40 (t, *J* = 7.8 Hz, 2H), 7.31-7.23 (m, 7H), 7.12-7.05 (m, 4H), 6.56-6.52 (m, 2H), 6.40 (t, *J* = 8.8 Hz, 2H), 2.97-2.90 (m, 4H), 1.35 (d, *J* = 6.7 Hz, 12H), 1.18 (d, *J* = 6.8 Hz, 12H).

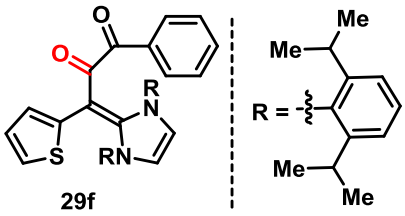
^{13}C NMR (100 MHz, CDCl$_3$) δ: 196.81, 178.73, 160.70 (d, *J* = 243.4 Hz), 154.59, 145.67, 135.80, 134.80 (d, *J* = 8.0 Hz), 133.85, 132.74, 131.88, 130.08, 129.23, 127.65, 124.09, 121.71, 114.04 (d, *J* = 20.9 Hz), 84.64, 28.98, 26.15, 22.56.

^{19}F NMR (376 MHz, CDCl$_3$) δ: -117.80.

HRMS: calculated $[M+H]^+$ for $C_{42}H_{46}FN_2O_2$: 629.3538, found: 629.3535.

FTIR (cm^{-1}): 3665, 3066, 3015, 2967, 2875, 1671, 1590, 1539, 1455, 1393, 1359, 1222, 1164, 1057, 1008, 928, 811, 759.

3-(1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-1-phenyl-3-(thiophen-2-yl)propane-1,2-dione (29f)



Following the general procedure, treatment of (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one **29f** (0.107 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-1-phenyl-3-(thiophen-2-yl)propane-1,2-dione **29f** as a red solid (0.194 g, 63% yield).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.49.

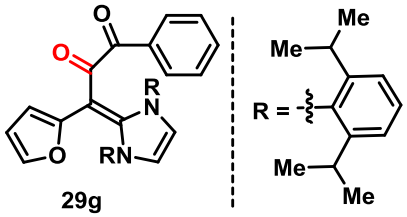
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.39 (t, *J* = 7.9 Hz, 2H), 7.27-7.23 (m, 7H), 7.07 (t, *J* = 8.0 Hz, 2H), 7.03 (s, 2H), 6.71-6.70 (m, 1H), 6.31-6.29 (m, 1H), 5.84-5.83 (m, 1H), 2.99-2.93 (m, 4H), 1.35 (d, *J* = 6.7 Hz, 12H), 1.14 (d, *J* = 6.8 Hz, 12H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 197.14, 179.73, 153.92, 145.82, 138.97, 135.66, 133.79, 132.00, 131.84, 130.12, 129.23, 127.62, 126.14, 125.48, 124.13, 121.66, 76.08, 29.08, 26.13, 22.73.

HRMS: calculated $[M+H]^+$ for $C_{40}H_{45}N_2O_2S$: 617.3196, found: 617.3193.

FTIR (cm^{-1}): 3165, 3068, 2967, 2874, 1671, 1547, 1456, 1370, 1220, 1138, 1053, 1011, 973, 938, 888, 758.

3-(1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-(furan-2-yl)-1-phenylpropane-1,2-dione (29g)



Following the general procedure, treatment of (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one **27g** (0.099 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-(furan-2-yl)-1-phenylpropane-1,2-dione **29g** as a red solid (0.114 g, 38% yield).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.55.

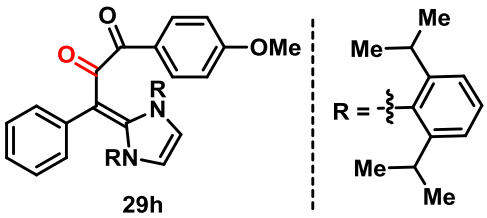
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (t, *J* = 7.8 Hz, 2H), 7.27-7.24 (m, 5H), 7.19 (d, *J* = 7.2 Hz, 2H), 7.08-7.04 (m, 4H), 6.73 (d, *J* = 1.3 Hz, 1H), 5.68-5.67 (m, 1H), 5.30 (d, *J* = 3.1 Hz, 1H), 3.05-2.98 (m, 4H), 1.36 (d, *J* = 6.7 Hz, 12H), 1.15 (d, *J* = 6.9 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.71, 179.60, 153.19, 150.63, 146.03, 140.57, 135.44, 133.14, 131.87, 130.07, 129.25, 127.62, 124.13, 121.60, 111.59, 110.26, 76.53, 28.91, 26.22, 22.71.

HRMS: calculated $[M+H]^+$ for $C_{40}H_{45}N_2O_3$: 601.3425, found: 601.3423.

FTIR (cm^{-1}): 3067, 3016, 2967, 1671, 1580, 1541, 1461, 1334, 1221, 1589, 939, 875.

3-(1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-1-(4-methoxy phenyl)-3-phenylpropane-1,2-dione (29h)



Following the general procedure, treatment of (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one **27h** (0.119 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-1-(4-methoxyphenyl)-3-phenylpropane-1,2-dione **29h** as a red solid (0.180 g, 56% yield).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.58.

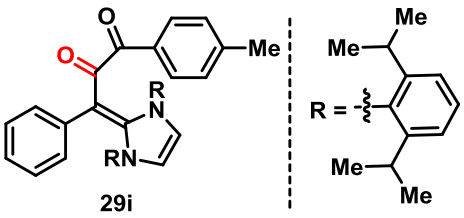
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39-7.35 (m, 4H), 7.22 (d, *J* = 7.7 Hz, 4H), 7.02 (s, 2H), 6.75-6.70 (m, 3H), 6.64-6.61 (m, 4H), 3.76 (s, 3H), 3.04-2.99 (m, 4H), 1.39 (d, *J* = 6.7 Hz, 12H), 1.20 (d, *J* = 6.8 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.50, 179.49, 162.44, 155.16, 145.68, 137.37, 134.12, 132.74, 131.61, 129.86, 129.38, 127.36, 124.81, 124.02, 121.49, 112.85, 86.30, 55.26, 29.00, 26.19, 22.70.

HRMS: calculated $[M+H]^+$ for $C_{43}H_{49}N_2O_3$: 641.3738, found: 641.3762.

FTIR (cm^{-1}): 3014, 2966, 2875, 1662, 1594, 1540, 1460, 1361, 1314, 1224, 1165, 931.

3-(1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-phenyl-1-(*p*-tolyl)propane-1,2-dione (29i)



Following the general procedure, treatment of (*E*)-3-phenyl-1-(*p*-tolyl)prop-2-en-1-one **27i** (0.111 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-phenyl-1-(*p*-tolyl)propane-1,2-dione **29i** as a red solid (0.197 g, 63% yield).

***R**$_f$* (Pet. ether /EtOAc = 50/50): 0.53.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (t, *J* = 7.4 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 4H), 7.07 (s, 2H), 6.96 (d, *J* = 7.7 Hz, 2H), 6.77-6.76 (m, 3H), 6.68 (s, 2H), 3.07-3.04 (m, 4H), 2.31 (s, 3H), 1.43 (d, *J* = 6.6 Hz, 12H), 1.24 (d, *J* = 6.7 Hz, 12H).

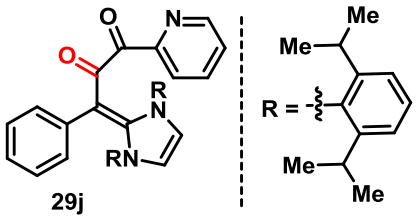
^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.38, 179.27, 155.00, 145.63, 142.06, 137.22, 134.04, 133.55, 132.74, 129.81, 129.46, 128.27, 127.31, 124.74, 123.95, 121.52, 86.11, 28.93, 26.14, 22.63, 21.61.

HRMS: calculated $[M+H]^+$ for $C_{43}H_{49}N_2O_2$: 625.3789, found: 625.3787.

FTIR (cm^{-1}): 3065, 3020, 2968, 2874, 1663, 1602, 1529, 1462, 1284, 1220, 1121, 930.

3-(1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-phenyl-1-(pyridin-2-yl)propane-1,2-dione (29j)

Following the general procedure, treatment of (*E*)-3-phenyl-1-(pyridin-2-yl)prop-2-en-1-one **27j** (0.105 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu



29j

(0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-3-phenyl-1-(pyridin-2-yl)propane-1,2-dione **29j** as a red solid (0.214 g, 70% yield).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.40.

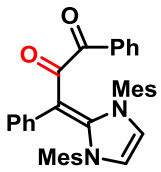
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.45 (d, *J* = 4.2 Hz, 1H), 7.45-7.40 (m, 1H), 7.34-7.38 (m, 3H), 7.16 (d, *J* = 7.8 Hz, 4H), 7.13-7.10 (m, 1H), 6.95 (s, 2H), 6.70-6.62 (m, 5H), 3.01-2.94 (m, 4H), 1.38 (d, *J* = 6.6 Hz, 12H), 1.16 (d, *J* = 6.9 Hz, 12H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 195.47, 179.33, 154.66, 153.51, 148.84, 145.57, 137.42, 135.78, 134.23, 132.53, 129.74, 127.49, 125.40, 124.89, 124.00, 121.39, 86.43, 29.02, 26.18, 22.67.

HRMS: calculated $[M+H]^+$ for $C_{41}H_{46}N_3O_2$: 612.3585, found: 612.3587.

FTIR (cm^{-1}): 3018, 2967, 2874, 1683, 1551, 1458, 1357, 1259, 1217, 1055, 1031, 929, 761, 666.

3-(1,3-Dimesityl-1,3-dihydro-2*H*-imidazol-2-ylidene)-1,3-diphenylpropane-1,2-dione (33)



33

Following the general procedure, treatment of (*E*)-chalcone **27a** (0.104 g, 0.5 mmol) with imidazolium salt **32** (0.170 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-dimesityl-1,3-dihydro-2*H*-imidazol-2-ylidene)-1,3-diphenylpropane-1,2-dione **33** as a red solid (0.213 g, 81% yield).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.31.

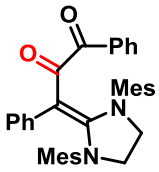
^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 7.66 (s, 2H), 7.47-7.43 (m, 1H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 6.89 (s, 4H), 6.68 (s, 5H), 2.22 (s, 6H), 2.19 (s, 12H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ: 196.13, 177.20, 152.08, 137.80, 137.61, 135.65, 134.47, 133.45, 132.32, 129.93, 128.73, 127.95, 126.65, 123.79, 121.68, 86.44, 20.49, 18.15.

HRMS: calculated $[M+H]^+$ for $C_{36}H_{35}N_2O_2$: 527.2693, found: 527.2693.

FTIR (cm^{-1}): 2966, 1670, 1596, 1540, 1457, 1359, 1283, 1231, 1173, 1116, 1043, 927.

3-(1,3-Dimesitylimidazolidin-2-ylidene)-1,3-diphenylpropane-1,2-dione (35)



35

Following the general procedure, treatment of (*E*)-chalcone **27a** (0.104 g, 0.5 mmol) with imidazolinium salt **34** (0.171 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded 3-(1,3-dimesitylimidazolidin-2-ylidene)-1,3-diphenylpropane-1,2-dione **35** as a red solid (0.111 g, 42% yield).

***R**$_f$* (Pet. ether /EtOAc = 50/50): 0.26.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.32-7.27 (m, 3H), 7.13 (t, *J* = 7.6 Hz, 2H), 6.79-6.63 (m, 9H), 3.95 (s, 4H), 2.38 (s, 12H), 2.17 (s, 6H).

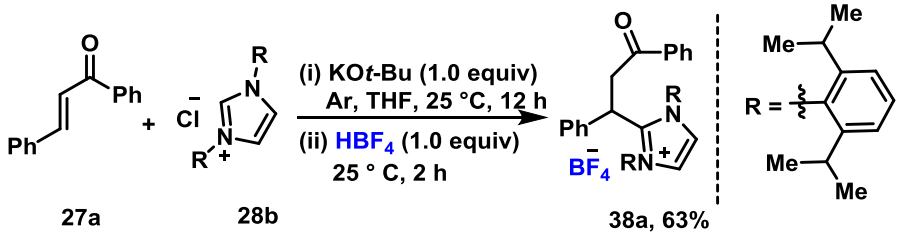
^{13}C NMR (100 MHz, CDCl$_3$) δ: 184.56, 164.26, 137.35, 136.69, 135.29, 132.60, 131.97, 129.44, 129.12, 127.65, 126.66, 125.38, 73.72, 50.31, 20.93, 18.87.

HRMS: calculated $[M+H]^+$ for $C_{36}H_{37}N_2O_2$: 529.2850, found: 529.2856.

FTIR (cm^{-1}): 3025, 2922, 1707, 1583, 1490, 1370, 1308, 1281, 1219, 1049, 904.

4.7.4. Procedure for Mechanistic Experiments

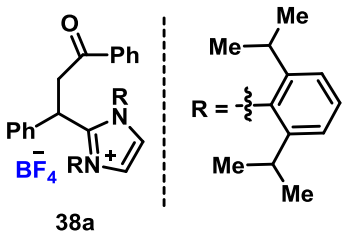
(a) Isolation of the Tetrahedral Intermediate: Quenching of the Reaction Mixture with Brønsted Acid.



27a 28b 38a, 63%

Following the general procedure, treatment of (*E*)-chalcone **27a** (0.104 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere followed by addition of HBF_4 (0.044 mg, 32 µL, 0.50 mmol) and continued stirring for another 2 h followed by flash column chromatography and crystallization (using CH_2Cl_2-Petroleum ether) afforded 1,3-bis(2,6-diisopropylphenyl)-2-(3-oxo-1,3-diphenylpropyl)-1*H*-imidazol-3-ium tetrafluoro borate **38a** as a white solid (0.216 g, 63% yield).

1,3-Bis(2,6-diisopropylphenyl)-2-(3-oxo-1,3-diphenylpropyl)-1*H*-imidazol-3-ium tetrafluoro borate (38a)



38a

***R**f* (DCM /MeOH = 90/10): 0.74.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 1.9 Hz, 2H), 7.68 (t, *J* = 7.8 Hz, 2H), 7.54-7.46 (m, 5H), 7.39-7.33 (m, 4H), 7.11 (t, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.7 Hz, 2H), 6.44 (d, *J* = 7.7 Hz, 2H), 5.04 (d, *J* = 10.1 Hz, 1H), 3.70-3.63 (m, 1H), 3.08 (d, *J* = 16.6 Hz, 1H), 2.49-2.42 (m, 2H), 2.24-2.18 (m, 2H), 1.37 (d, *J* = 6.7 Hz, 6H), 1.25 (d, *J* = 6.5 Hz, 6H), 1.16 (d, *J* = 6.5 Hz, 6H), 0.98 (d, *J* = 6.8 Hz, 6H).

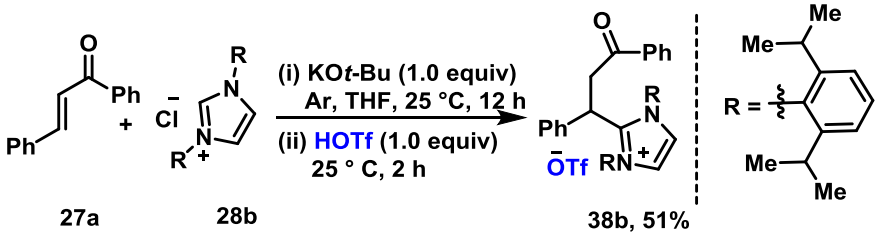
^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.47, 147.18, 145.80, 145.40, 135.48, 134.24, 133.49, 132.91, 130.16, 129.16, 129.03, 128.86, 128.60, 127.75, 127.13, 125.44, 125.26, 40.11, 37.97, 29.80, 26.68, 26.26, 22.07, 21.69.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -153.01.

HRMS: calculated $[M]^+$ for $C_{42}H_{49}N_2O$: 597.3839, found: 597.3840.

FTIR (cm^{-1}): 3130, 3029, 2968, 2926, 2877, 1731, 1629, 1593, 1458, 1400, 1324, 1216, 1046, 967, 760, 670.

1,3-Bis(2,6-diisopropylphenyl)-2-(3-oxo-1,3-diphenylpropyl)-1*H*-imidazol-3-ium trifluoro methanesulfonate (38b)



27a 28b 38b, 51%

Following the general procedure, treatment of (*E*)-chalcone **27a** (0.052 g, 0.25 mmol) with imidazolium salt **28a** (0.106 g, 0.25 mmol) and KO*t*-Bu (0.028 g, 0.25 mmol) in THF (1.5 mL) at 25 °C for 12 h under argon atmosphere followed by addition of HOTf (0.045 mg, 27 µL, 0.30 mmol) and continued stirring for another 2 h followed by flash column chromatography afforded 1,3-bis(2,6-diisopropylphenyl)-2-(3-oxo-1,3-diphenylpropyl)-1*H*-imidazol-3-ium trifluoromethanesulfonate **38b** as a white solid (0.095 g, 51% yield).

***R**f* (DCM /MeOH = 90/10): 0.59.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36-8.32 (m, 2H), 7.66-7.62 (m, 2H), 7.51-7.41 (m, 5H), 7.35-7.29 (m, 4H), 7.07-7.04 (m, 1H), 6.99-6.94 (m, 2H), 6.40-6.37 (m, 2H), 5.00 (d, *J* = 11.6 Hz, 1H), 3.65-3.56 (m, 1H), 3.03-2.98 (m, 1H), 2.42-2.38 (m, 2H), 2.19-2.13 (m, 2H), 1.31 (t, *J* = 4.7 Hz, 6H), 1.24 (t, *J* = 6.5 Hz, 6H), 1.15 (t, *J* = 6.5 Hz, 6H), 0.96 -0.93(m, 6H).

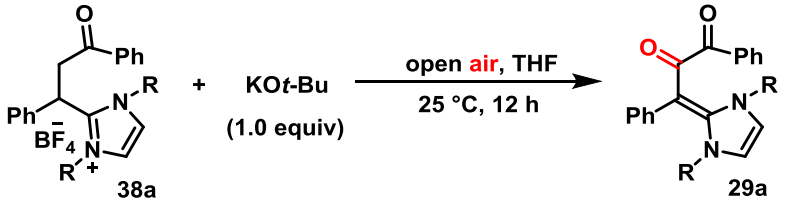
^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.34, 146.95, 145.69, 145.32, 135.44, 134.20, 133.50, 132.80, 130.15, 129.12, 128.96, 128.81, 128.54, 127.82, 127.76, 127.66, 125.36, 125.16, 40.05, 37.90, 29.80, 26.91, 26.47, 22.06, 21.67.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -78.72.

HRMS: calculated $[M]^+$ for $C_{42}H_{49}N_2O$: 597.3839, found: 597.3831.

FTIR (cm^{-1}): 3129, 3042, 2969, 2925, 2876, 1735, 1685, 1630, 1592, 1540, 1458, 1374, 1330, 1239, 1207, 1045, 749.

(b) Reaction of Salt 38a in Presence of Base

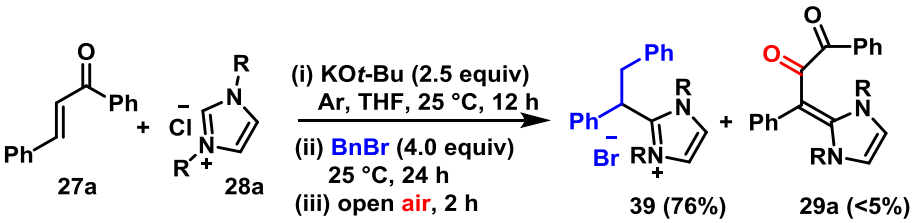


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was charged with KO*t*-Bu (0.028 g, 0.25 mmol), inside the glove-box. To this was added the salt **38a** (0.171 g, 0.25 mmol) followed by addition of dry THF (3.0 mL) and the resultant reaction mixture was kept stirring at 25 °C for 12 h in open air. Then the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the 3-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)-1,3-diphenylpropane-1,2-dione **29a** as a red solid (0.138 g, 91% yield).

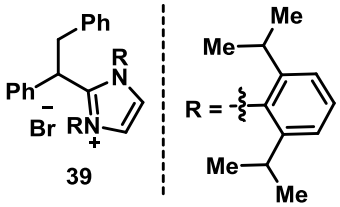
(c) Study on Reversible Nature of Tetrahedral Intermediate

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was charged with KO*t*-Bu (0.070 g, 0.63 mmol), inside the glove-box. To this was added the imidazolium salt **28a** (0.106 g, 0.25 mmol) followed by addition of THF (1.5 mL) under a positive pressure of argon and the resultant reaction mixture was kept stirring at 25 °C for 10 minutes. To this mixture was added the (*E*)-chalcone **27a** (0.052 g, 0.25 mmol). The resulting mixture was then stirred at 25° C for 12 h at argon atmosphere followed by

addition of benzyl bromide (0.172 g, 120 µL, 1.0 mmol) to the reaction mixture and continued stirring for another 24 h. Subsequently, the reaction mixture was stirred in air for 2 h. Then the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the 1,3-bis(2,6-diisopropylphenyl)-2-(1,2-diphenylethyl)-1*H*-imidazol-3-ium bromide **39** as a white solid (0.124 g, 76% yield). It may be noted that the oxidized form of *deoxy*-Breslow intermediate **29a** was formed in <5% yield under this condition.



1,3-Bis(2,6-diisopropylphenyl)-2-(1,2-diphenylethyl)-1*H*-imidazol-3-ium bromide (39)



***R**f* (DCM /MeOH = 90/10): 0.61.

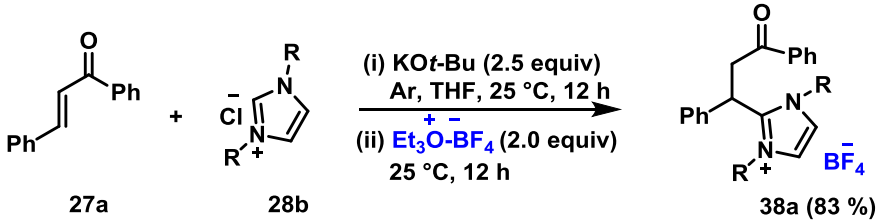
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.41-8.40 (m, 2H), 7.65 (t, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.95-6.88 (m, 5H), 6.30 (d, *J* = 6.7 Hz, 2H), 6.25 (d, *J* = 7.5 Hz, 2H), 4.24 (dd, J_1 = 2.1 Hz, J_2 = 12.3 Hz, 1H), 3.01-2.89 (m, 2H), 2.46-2.41 (m, 2H), 2.23-2.18 (m, 2H), 1.34 (d, *J* = 6.7 Hz, 6H), 1.26-11.21 (m, 12H), 1.01 (d, *J* = 6.5 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 147.12, 145.16, 144.69, 134.74, 132.52, 131.17, 129.78, 128.84, 128.44, 128.21, 127.68, 127.12, 126.78, 125.00, 124.83, 44.88, 37.58, 29.42, 29.35, 26.36, 26.24, 21.54, 21.40.

HRMS: calculated $[M]^+$ for $C_{41}H_{49}N_2$: 569.3890, found: 569.3896.

FTIR (cm^{-1}): 3409, 3163, 2969, 2931, 2451, 1732, 1675, 1624, 1558, 1482, 1372, 1244, 1218, 1048, 929, 756, 664.

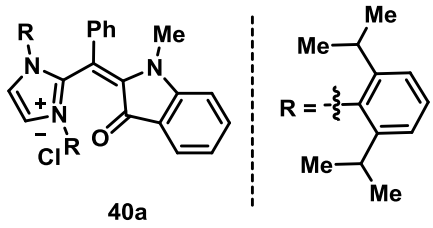
(d) Electrophilic Trapping Experiment with Meerwein's Reagent



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was charged with KO*t*-Bu (0.056 g, 0.50 mmol), inside the glove-box. To this was added the imidazolium salt **28a** (0.212 g, 0.50 mmol) followed by addition of THF (3.0 mL) under a positive pressure of argon and the resultant reaction mixture was kept stirring at 25 °C for 10 minutes. To this mixture was added the (*E*)-chalcone **27a** (0.104 g, 0.50 mmol). The resulting mixture was then stirred at 25° C for 12 h at argon atmosphere followed by addition of Meerwein's reagent (0.190 g, 1.0 mmol) to the reaction mixture and continued stirring for another 12 h. Subsequently, the reaction mixture was stirred in air for 2 h. Then the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel and crystallization (CH_2Cl_2: Petroleum ether) to afford the 1,3-bis(2,6-diisopropylphenyl)-2-(3-oxo-1,3-diphenylpropyl)-1*H*-imidazol-3-ium tetrafluoroborate **38a** as a white solid (0.284 g, 83% yield).

(e) Reactionof NHCs with 2'-Aminochalcone

(*E*)-1,3-Bis(2,6-diisopropylphenyl)-2-((1-methyl-3-oxoindolin-2 ylidene)(phenyl) methyl)-1*H*-imidazol-3-ium chloride (40a)



40a

Following the general procedure, treatment of (*E*)-1-(2-(methylamino)phenyl)-3-phenylprop-2-en-1-one **27k** (0.119 g, 0.5 mmol) with imidazolium salt **28a** (0.212 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h in open air followed by flash column chromatography afforded (*E*)-1,3-bis(2,6-diisopropylphenyl)-2-((1-methyl-3-oxoindolin-2-ylidene)(phenyl)methyl)-1*H*-imidazol-3-ium chloride **40a** as a red solid (0.237 g, 72% yield).

R_f (DCM /MeOH = 90/10): 0.41.

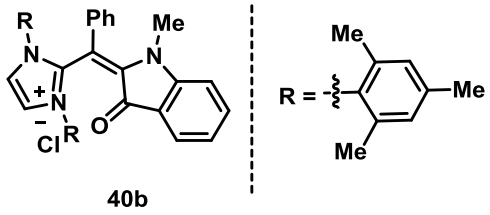
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (s, 2H), 7.58-7.50 (m, 4H), 7.34-7.28 (m, 3H), 7.19-7.14 (m, 4H), 7.00 (t, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.34 (d, *J* = 7.6 Hz, 2H), 3.23-3.19 (m, 2H), 2.20 (s, 3H), 2.12-2.09 (m, 2H), 1.22 (d, *J* = 5.4 Hz, 6H), 1.04 (d, *J* = 5.6 Hz, 6H), 0.95 (d, *J* = 5.9 Hz, 6H), 0.66 (d, *J* = 5.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 184.26, 154.90, 147.44, 145.62, 144.80, 143.60, 138.31, 132.01, 131.39, 131.09, 130.91, 129.94, 128.80, 127.40, 125.86, 124.95, 124.21, 122.27, 119.18, 110.33, 100.97, 32.22, 29.60, 28.14, 26.86, 26.25, 23.53, 21.19.

HRMS: calculated $[M]^+$ for $C_{43}H_{48}N_3O$: 622.3792, found: 622.3789.

FTIR (cm^{-1}): 3032, 2927, 2869, 1688, 1598, 1563, 1495, 1450, 1360, 1267, 1232, 1217, 1059, 857, 755.

(*E*)-1,3-Dimesityl-2-((1-methyl-3-oxoindolin-2-ylidene)(phenyl)methyl)-1*H*-imidazol-3-ium chloride (40b)



Following the general procedure, treatment of (*E*)-1-(2-(methylamino)phenyl)-3-phenylprop-2-en-1-one **27k** (0.119 g, 0.5 mmol) with imidazolium salt **32** (0.170 g, 0.5 mmol) and KO*t*-Bu (0.056 g, 0.5 mmol) in THF (3.0 mL) at 25 °C for 12 h under argon atmosphere and 2 h open air followed by flash column chromatography afforded (*E*)-1,3-dimesityl-2-((1-methyl-3-oxoindolin-2-ylidene)(phenyl)methyl)-1*H*-imidazol-3-ium chloride **40b** as a red solid (0.181 g, 63% yield).

***R*$_f$** (DCM /MeOH = 90/10): 0.38.

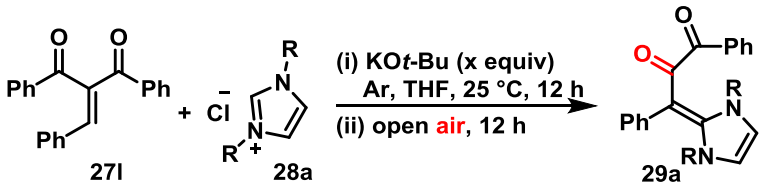
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.17 (s, 2H), 7.51-7.47 (m, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.18-7.09 (m, 3H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.90-6.88 (m, 2H), 6.84-6.82 (m, 3H), 6.64 (s, 2H), 2.59 (s, 3H), 2.23 (s, 6H), 2.12-2.11 (m, 12H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 182.94, 153.86, 144.51, 143.28, 140.42, 137.47, 135.87, 132.95, 132.90, 130.91, 130.38, 130.19, 129.57, 128.65, 126.74, 124.87, 122.39, 119.66, 110.33, 101.43, 33.28, 20.84, 19.74, 19.08.

HRMS: calculated $[M]^+$ for $C_{37}H_{36}N_3O$: 538.2853, found: 538.2854.

FTIR (cm^{-1}): 3153, 2923, 1703, 1619, 1568, 1485, 1365, 1324, 1230, 1167, 1116, 1034, 874, 757.

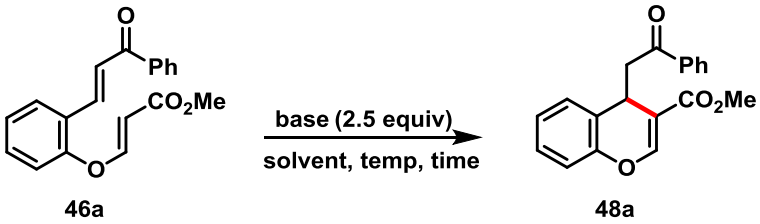
(f) The Reaction of NHC with α-Benzoyl Chalcone



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was charged with KO*t*-Bu (0.056 g, 0.5 mmol), inside the glove-box. To this was added the imidazolium salt **28a** (0.212 g, 0.5 mmol) followed by addition of THF (3.00 mL) under a

positive pressure of argon and the resultant reaction mixture was kept stirring at 25 °C for 10 minutes. To this mixture was added the 2-benzylidene-1,3-diphenylpropane-1,3-dione **27l** (0.156 g, 0.5 mmol). The resulting mixture was then stirred at 25° C for 12 h at argon atmosphere followed by open air stirring for another 12 h. Then the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the oxidized *deoxy*-Breslow intermediate **29a** in 59% yield (0.181 g). Notably, when the reaction was performed with 2.0 equivalents of KO*t*-Bu (0.112 g, 0.5 mmol) the yield of **3a** increased to 69% (0.210 g).

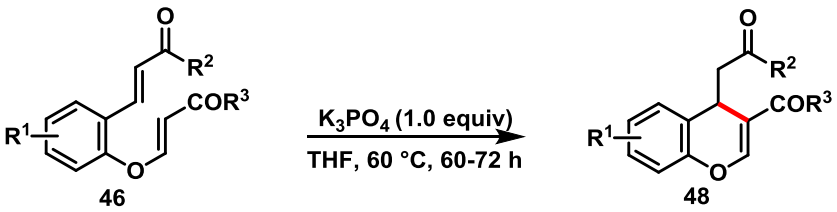
4.7.5. General Procedure for the Optimization of Intramolecular Rauhut-Currier Reaction



46a 48a

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was charged with base (0.625 mmol). To this was added the methyl (*E*)-3-(2-((*E*)-3-oxo-3-phenylprop-1-en-1-yl)phenoxy)acrylate **46a** (0.25 mmol) outside the glovebox followed by addition of solvent (2.0 mL) under a positive pressure of argon, and the reaction mixture was placed in a preheated oil bath at the indicated temperature for the indicated time. Then the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^1H NMR using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard.

4.7.6. General Procedure for the Intramolecular Rauhut-Currier Reaction



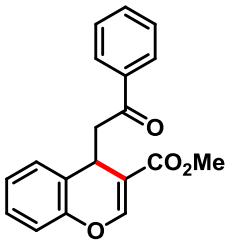
46 48

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was charged with K_3PO_4 (0.50 mmol), inside the glovebox. To this was added the enone-enoate

46 (0.50 mmol) outside the glovebox followed by addition of THF (4.0 mL) under a positive pressure of argon, and the reaction mixture was placed in a preheated oil bath at 60 °C for the 60/72 h. When TLC control showed the completion of the reaction (typically after 72 h), the solvent was evaporated and the crude residue purified by flash column chromatography on silica gel to afford the corresponding 4*H*-chromenes **48** in moderate to good yields.

4.7.7. Synthesis and Characterization of 4*H*-Chromenes

Methyl-4-(2-oxo-2-phenylethyl)-4*H*-chromene-3-carboxylate (48a)



48a

Following the general procedure, treatment of methyl (*E*)-3-(2-((*E*)-3-oxo-3-phenylprop-1-en-1-yl)phenoxy)acrylate **46a** (0.154 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded methyl-4-(2-oxo-2-phenylethyl)-4*H*-chromene-3-carboxylate as white solid **48a** (0.135 g, 88% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.56.

Melting point: 97-99 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.93– 7.91 (m, 2H), 7.74 (s, 1H), 7.54– 7.50 (m, 1H), 7.44 – 7.40 (m, 2H), 7.21 (dd, J_1 = 1.5 Hz, J_2 = 7.6 Hz, 1H), 7.15 (td, J_1 = 1.6 Hz, J_2 = 7.8 Hz, 1H), 7.04 – 6.98 (m, 2H), 4.53 (dd, J_1 = 4.1 Hz, J_2 = 7.0 Hz, 1H), 3.74 (s, 3H), 3.40 – 3.29 (m, 2H).

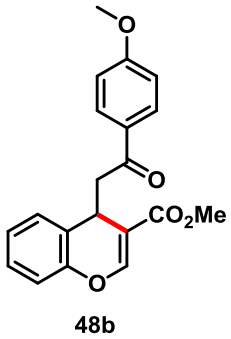
^{13}C NMR (100 MHz, CDCl$_3$) δ: 197.98, 166.94, 152.04, 150.14, 137.03, 133.14, 129.30, 128.65, 128.27, 128.05, 125.00, 123.96, 116.60, 109.24, 51.65, 47.49, 29.82.

HRMS: calculated $[M+Na]^+$ for $C_{19}H_{16}O_4Na$: 331.0941, found: 331.0953.

FTIR (cm^{-1}): 2922, 2855, 1705, 1650, 1586, 1487, 1446, 1389, 1294, 1230, 1195, 1088, 1035, 914, 828, 759, 691.

Methyl 4-(2-(4-methoxyphenyl)-2-oxoethyl)-4*H*-chromene-3-carboxylate (48b)

Following the general procedure, treatment of methyl (*E*)-3-(2-((*E*)-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)phenoxy)acrylate **46b** (0.169 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction



48b

mixture using silica gel afforded methyl 4-(2-(4-methoxyphenyl)-2-oxoethyl)-4*H*-chromene-3-carboxylate as white solid **48b** (0.124 g, 73% yield).

***R*f** (Pet. ether /EtOAc = 80/20): 0.41.

Melting point: 96-98 °C.

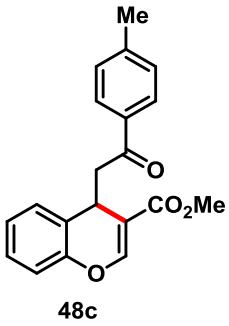
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.973– 7.9 (m, 2H), 7.74 (s, 1H), 7.169-7.13(m, 2H), 7.03 – 6.97 (m, 2H), 6.91 – 6.89 (m, 2H), 4.50 (dd, J_1 = 3.6 Hz, J_2 = 7.7 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.28 (dd, J_1 = 5.7 Hz, J_2 = 18.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.61, 167.05, 163.57, 152.04, 150.15, 130.64, 130.19, 129.38, 128.04, 124.99, 124.04, 116.60, 113.82, 109.40, 55.58, 51.71, 47.29, 30.08.

HRMS:calculated $[M+Na]^+$ for $C_{20}H_{18}O_5Na$: 361.1046, found: 361.1043.

FTIR (cm^{-1}): 3017, 2952, 2844, 1708, 1662, 1593, 1449, 1299, 1227, 1180, 1091, 1032, 982, 833, 758.

Methyl-4-(2-oxo-2-(*p*-tolyl)ethyl)-4*H*-chromene-3-carboxylate (48c)



48c

Following the general procedure, treatment of methyl (*E*)-3-(2-((*E*)-3-oxo-3-(*p*-tolyl)prop-1-en-1-yl)phenoxy)acrylate **46c** (0.161 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded methyl-4-(2-oxo-2-(*p*-tolyl)ethyl)-4*H*-chromene-3-carboxylate as white solid **48c** (0.110 g, 68% yield).

***R*f** (Pet. ether /EtOAc = 80/20): 0.45.

Melting point: 104-106 °C.

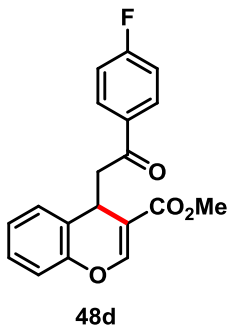
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, J = 8.0 Hz, 2H), 7.76 (s, 1H), 7.24 – 7.15 (m, 4H), 7.02 (dd, J_1 = 14.5 Hz, J_2 = 7.7 Hz, 2H), 4.54 (dd, J_1 = 7.1 Hz, J_2 = 3.8 Hz, 1H), 3.76 (s, 3H), 3.38 – 3.27 (m, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.60, 166.93, 151.97, 150.12, 143.90, 134.59, 129.31, 128.39, 127.99, 124.95, 124.03, 116.56, 109.34, 51.62, 47.45, 29.87, 21.68.

HRMS: calculated $[M+Na]^+$ for $C_{20}H_{18}O_4Na$: 345.1097, found: 345.1090.

FTIR (cm^{-1}): 3349, 3022, 2954, 2402, 1918, 1708, 1610, 1487, 1447, 1397, 1294, 1230, 1194, 1092, 1045, 983, 917, 758, 667, 624.

Methyl 4-(2-(4-fluorophenyl)-2-oxoethyl)-4*H*-chromene-3-carboxylate (48d)



48d

Following the general procedure, treatment of methyl (*E*)-3-(2-((*E*)-3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)phenoxy)acrylate **46d** (0.163 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded methyl 4-(2-(4-fluorophenyl)-2-oxoethyl)-4*H*-chromene-3-carboxylate as white solid **48d** (0.133 g, 81% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.61.

Melting point: 79-81 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.96 – 7.93 (m, 2H), 7.73 (s, 1H), 7.219– 7.13 (m, 2H), 7.10-7.06 (m, 2H), 7.04 – 6.97 (m, 2H), 4.49 (dd, J_1 = 3.7 Hz, J_2 = 7.3 Hz, 1H), 3.74 (s, 3H), 3.31 (qd, J_1 = 5.6 Hz, J_2 = 16.2, Hz, 2H).

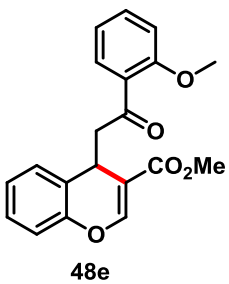
^{13}C NMR (100 MHz, CDCl$_3$) δ: 196.46, 166.94, 165.79 (d, *J* = 255.1 Hz), 152.09, 150.11, 133.46, 130.96 (d, *J* = 9.3 Hz), 129.22, 128.13, 125.02, 123.76, 116.64, 115.73 (d, *J* = 21.79 Hz), 109.08, 51.69, 47.33, 29.95.

^{19}F NMR (376 MHz, CDCl$_3$) δ: -105.18.

HRMS: calculated $[M+Na]^+$ for $C_{19}H_{15}O_4FNa$: 349.0847, found: 349.0841.

FTIR (cm^{-1}): 3022, 2953, 1704, 1646, 1595, 1496, 1447, 1401, 1294, 1225, 1092, 1042, 838, 759, 668.

Methyl-4-(2-(2-methoxyphenyl)-2-oxoethyl)-4*H*-chromene-3-carboxylate (48e)



48e

Following the general procedure, treatment of methyl (*E*)-3-(2-((*E*)-3-(2-methoxyphenyl)-3-oxoprop-1-en-1-yl)phenoxy)acrylate **46e** (0.169 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded methyl-4-(2-(2-methoxyphenyl)-2-oxoethyl)-4*H*-chromene-3-carboxylate as white solid **48e** (0.135 g, 80% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.32.

Melting point: 89-91 °C.

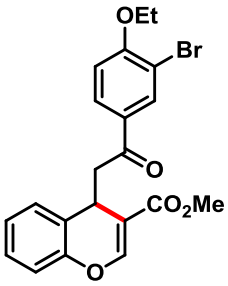
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.68 (s, 1H), 7.59 (dd, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.28 – 7.26 (m, 1H), 7.14 – 7.10 (m, 1H), 7.01 (t, J = 10.8 Hz, 1H), 6.94-6.90 (m, 2H), 6.84 (d, J = 8.4 Hz, 1H), 4.51 (dd, J_1 = 7.0 Hz, J_2 = 3.9 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.42 (dd, J_1 = 16.9 Hz, J_2 = 7.1 Hz, 1H), 3.31 (dd, J_1 = 16.9 Hz, J_2 = 3.9 Hz, 1H).

^{13}C NMR (100 MHz, CDCl3) δ: 200.07, 166.86, 158.43, 151.58, 150.05, 133.46, 130.32, 129.30, 128.37, 127.67, 124.74, 124.48, 120.50, 116.30, 111.36, 109.57, 55.32, 52.26, 51.45, 29.57.

HRMS: calculated $[M+Na]^+$ for $C_{20}H_{18}O_5Na$: 361.1046, found: 361.1041.

FTIR (cm^{-1}): 3402, 3015, 2951, 2844, 1709, 1661, 1592, 1476, 1449, 1390, 1295, 1240, 1194, 1088, 1026, 955, 821, 758, 663, 624.

Methyl-4-(2-(3-bromo-4-ethoxyphenyl)-2-oxoethyl)-4*H*-chromene-3-carboxylate (48f)



48f

Following the general procedure, treatment of methyl (*E*)-3-(2-((*E*)-3-(3-bromo-4-ethoxyphenyl)-3-oxoprop-1-en-1-yl)phenoxy)acrylate **46f** (0.216 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded methyl-4-(2-(3-bromo-4-ethoxyphenyl)-2-oxoethyl)-4*H*-chromene-3-carboxylate as white semisolid **48f** (0.174 g, 80% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.44.

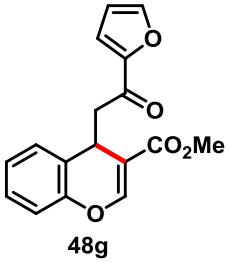
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.11 (d, J = 2.1 Hz, 1H), 7.86 (dd, J_1 = 8.6 Hz, J_2 = 2.2 Hz, 1H), 7.72 (s, 1H), 7.18 – 7.0 (m, 2H), 7.05 – 6.94 (m, 2H), 6.85 (d, J = 8.7 Hz, 1H), 4.47 (dd, J = 6.9, 4.2 Hz, 1H), 4.13 (q, J_1 = 7.0 Hz, J_2 = 14.0 Hz, 2H), 3.75 (s, 3H), 3.38 – 3.15 (m, 2H), 1.47 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 195.54, 166.96, 159.16, 152.08, 150.14, 133.88, 130.83, 129.46, 129.28, 128.13, 125.03, 123.80, 116.63, 112.27, 111.97, 109.17, 65.15, 51.73, 47.13, 30.06, 14.61.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{19}O_5BrNa$: 453.0308, found: 453.0302.

FTIR (cm^{-1}): 3347, 2989, 2945, 2587, 1914, 1707, 1589, 1488, 1445, 1396, 1262, 1232, 1092, 1044, 918, 806, 758, 677, 624.

Methyl 4-(2-(furan-2-yl)-2-oxoethyl)-4*H*-chromene-3-carboxylate (48g)



48g

Following the general procedure, treatment of methyl (*E*)-3-(2-((*E*)-3-(furan-2-yl)-3-oxoprop-1-en-1-yl)phenoxy)acrylate **46g** (0.149 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded methyl 4-(2-(furan-2-yl)-2-oxoethyl)-4*H*-chromene-3-carboxylate as brown solid **48g** (0.121 g, 81% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.38.

Melting point: 101-103 °C.

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.72 (s, 1H), 7.52 (s, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.15 (m, 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.50 – 6.47 (m, 1H), 4.47 (t, *J* = 5.8 Hz, 1H), 3.74 (s, 3H), 3.17 (d, *J* = 5.9 Hz, 2H).

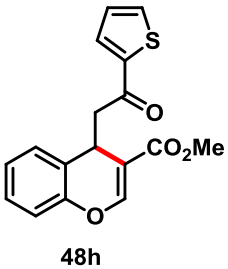
^{13}C NMR (125 MHz, CDCl$_3$) δ: 187.02, 166.92, 152.80, 152.06, 150.11, 146.58, 129.37, 128.14, 125.07, 123.62, 117.60, 116.64, 112.34, 109.09, 51.71, 47.46, 30.07.

HRMS: calculated $[M+Na]^+$ for $C_{17}H_{14}O_5Na$: 321.0733, found: 321.0732.

FTIR (cm^{-1}): 3137, 3021, 2956, 1711, 1653, 1575, 1454, 1392, 1297, 1228, 1092, 1024, 915, 758.

Methyl-4-(2-oxo-2-(thiophen-2-yl)ethyl)-4*H*-chromene-3-carboxylate (48h)

Following the general procedure, treatment of methyl (*E*)-3-(2-((*E*)-3-oxo-3-(thiophen-2-yl)prop-1-en-1-yl)phenoxy)acrylate **46h** (0.157 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded methyl-4-(2-oxo-2-(thiophen-2-yl)ethyl)-4*H*-chromene-3-carboxylate as white solid **48h** (0.121 g, 77% yield).



48h

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.34.

Melting point: 99-101 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.73 (s, 1H), 7.67 (d, *J* = 3.4 Hz, 1H),

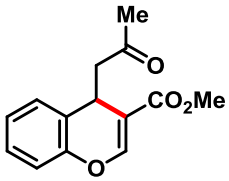
7.58 (d, J = 4.8 Hz, 1H), 7.21 – 7.13 (m, 2H), 7.07 – 6.96 (m, 3H), 4.48 (dd, J_1 = 7.6 Hz, J_2 = 3.6 Hz, 1H), 3.74 (s, 3H), 3.30 (dd, J_1 = 15.5 Hz, J_2 = 3.6 Hz, 1H), 3.20 (dd, J_1 = 15.5 Hz, J_2 = 7.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.85, 166.85, 152.04, 150.07, 144.51, 133.86, 132.35, 129.29, 128.20, 128.12, 125.02, 123.54, 116.60, 109.03, 51.65, 48.15, 30.44.

HRMS: calculated $[M+Na]^+$ for $C_{17}H_{14}O_4SNa$: 337.0505, found: 337.0500.

FTIR (cm^{-1}): 3348, 3095, 2948, 1707, 1654, 1588, 1477, 1447, 1297, 1227, 1090, 757.

Methyl 4-(2-oxopropyl)-4*H*-chromene-3-carboxylate (48i)



48i

Following the general procedure, treatment of methyl (*E*)-3-(2-((*E*)-3-oxobut-1-en-1-yl)phenoxy)acrylate **46i** (0.123 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded methyl 4-(2-oxopropyl)-4*H*-chromene-3-carboxylate as white semisolid **48i** (0.085 g, 69% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.32.

Melting point: 97-99 °C.

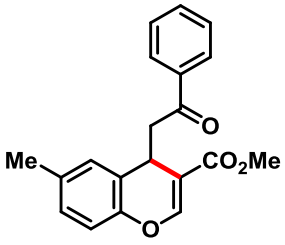
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (s, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 4.32 (t, J = 5.4 Hz, 1H), 3.76 (s, 3H), 2.79 (d, J = 5.5 Hz, 2H), 2.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.60, 166.89, 151.83, 149.99, 129.17, 128.08, 125.12, 124.07, 116.66, 109.05, 52.32, 51.68, 30.72, 29.14.

HRMS: calculated $[M+Na]^+$ for $C_{14}H_{14}O_4Na$: 269.0784, found: 269.0783.

FTIR (cm^{-1}): 2951, 1712, 1646, 1486, 1444, 1358, 1299, 1233, 1190, 1087, 1036, 950, 759, 624.

Methyl 6-methyl-4-(2-oxo-2-phenylethyl)-4*H*-chromene-3-carboxylate (48j)



48j

Following the general procedure, treatment of methyl (*E*)-3-(4-methyl-2-((*E*)-3-oxo-3-phenylprop-1-en-1-yl)phenoxy)acrylate **46j** (0.161 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10)

of the crude reaction mixture using silica gel afforded methyl 6-methyl-4-(2-oxo-2-phenylethyl)-4*H*-chromene-3-carboxylate as yellow solid **48j** (0.083 g, 52% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.32.

Melting point: 109-111 °C.

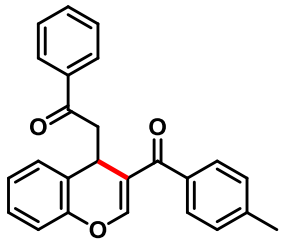
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.95 – 7.91 (m, 2H), 7.74 (s, 1H), 7.54 – 7.39 (m, 3H), 7.00 – 6.86 (m, 3H), 4.48 (t, *J* = 5.5 Hz, 1H), 3.74 (s, 3H), 3.45 – 3.24 (m, 2H), 2.23 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 198.08, 167.10, 152.20, 148.07, 137.16, 134.57, 133.12, 129.49, 128.65, 128.29, 123.65, 116.32, 108.96, 51.63, 47.56, 29.83, 20.88.

HRMS: calculated $[M+Na]^+$ for $C_{20}H_{18}O_4Na$: 345.1097, found: 345.1094.

FTIR (cm^{-1}): 3021, 2949, 1719, 1638, 1638, 1587, 1493, 1443, 1372, 1252, 1216, 1089, 1040, 815, 756, 701.

2-(3-(4-Methylbenzoyl)-4*H*-chromen-4-yl)-1-phenylethan-1-one (48k)



48k

Following the general procedure, treatment of (*E*)-3-(2-(((*E*)-3-oxo-3-(p-tolyl)prop-1-en-1-yl)oxy)phenyl)-1-phenylprop-2-en-1-one **46k** (0.184 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 60 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded 2-(3-(4-methylbenzoyl)-4*H*-chromen-4-yl)-1-phenylethan-1-one as white solid **48k** (0.136 g, 74% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.40.

Melting point: 129-131 °C.

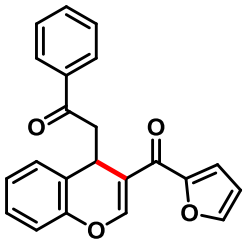
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.97 – 7.95 (m, 2H), 7.55– 7.51 (m, 3H), 7.47 (s, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.23 (m, 3H), 7.19 (td, J_1 = 1.5 Hz, J_2 = 7.9 Hz, 1H), 7.07 (td, J_1 = 1.2 Hz, J_2 = 7.5 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 4.73 (dd, J_1 = 3.8 Hz, J_2 = 7.1 Hz, 1H), 3.52 (dd, J_1 = 3.8 Hz, J_2 = 16.1 Hz, 1H), 3.41 (dd, J_1 = 7.2 Hz, J_2 = 16.1 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 198.32, 194.98, 156.24, 150.37, 142.25, 137.14, 136.10, 133.13, 129.29, 129.14, 128.69, 128.38, 128.07, 125.14, 124.18, 118.34, 116.54, 46.28, 30.08, 21.65.

HRMS: calculated $[M+Na]^+$ for $C_{25}H_{20}O_3Na$: 391.1305, found: 391.1303.

FTIR (cm^{-1}): 3022, 2923, 1681, 1630, 1487, 1452, 1395, 1301, 1226, 1189, 1112, 1035, 982, 755, 693.

2-(3-(Furan-2-carbonyl)-4*H*-chromen-4-yl)-1-phenylethan-1-one (48l)



48l

Following the general procedure, treatment of (*E*)-1-(furan-2-yl)-3-(2-((*E*)-3-oxo-3-phenylprop-1-en-1-yl)phenoxy)prop-2-en-1-one **46l** (0.172 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 60 h followed by flash column chromatography using (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded 2-(3-(furan-2-carbonyl)-4*H*-chromen-4-yl)-1-phenylethan-1-one as yellow solid **48l** (0.151 g, 88% yield).

***R*f** (Pet. ether /EtOAc = 80/20): 0.35.

Melting point: 93-95 °C.

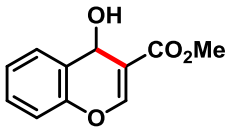
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (s 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.60 (s, 1H), 7.54 – 7.51 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.18 (m, 3H), 7.07 (t, *J* = 7.4 Hz, 2H), 6.55 (s, 1H), 4.72 (dd, J_1 = 3.1 Hz, J_2 = 7.3 Hz, 1H), 3.49 (dd, J_1 = 3.3 Hz, J_2 = 16.2 Hz, 1H), 3.35 (dd, J_1 = 7.7 Hz, J_2 = 16.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.11, 179.80, 155.08, 152.73, 150.20, 145.88, 137.02, 133.10, 129.31, 128.65, 128.35, 128.05, 125.15, 124.21, 118.16, 117.87, 116.47, 112.05, 46.88, 29.76.

HRMS: calculated $[M+Na]^+$ for $C_{22}H_{16}O_4Na$: 367.0941, found: 367.0933.

FTIR (cm^{-1}): 3019, 2922, 1681, 1627, 1574, 1467, 1395, 1310, 1269, 1225, 1020, 856, 758, 679.

Methyl 4-hydroxy-4*H*-chromene-3-carboxylate (49)



50

Following the general procedure, treatment of methyl (E)-3-(2-formylphenoxy)acrylate **49** (0.103 g, 0.5 mmol) with anhydrous tribasic potassium phosphate (0.106 g, 0.5 mmol) in THF (4.0 mL) at 60 °C for 72 h followed by flash column chromatography using (Pet. ether/EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl 4-hydroxy-4*H*-chromene-3-carboxylate as white solid **50** (0.046 g, 45% yield).

***R*f** (Pet. ether /EtOAc = 80/20): 0.30.

Melting point: 104-106 °C.

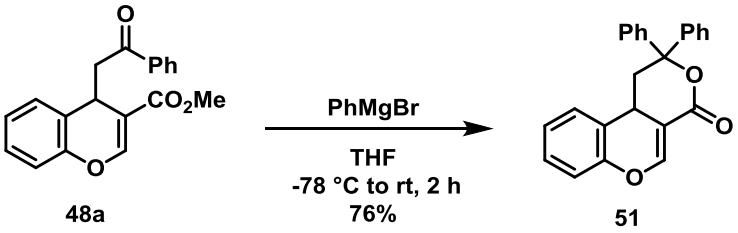
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (s, 1H), 7.38 – 7.31 (m, 2H), 7.07 – 7.02 (m, 2H), 6.40 (d, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 3.73 – 3.54 (bs, 1H, OH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.41, 152.10, 134.39, 132.48, 129.31, 122.38, 122.31, 119.09, 117.46, 88.79, 52.30.

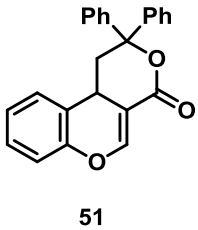
HRMS: calculated $[M+Na]^+$ for $C_{11}H_{10}O_4Na$: 229.0471, found: 229.0471.

FTIR (cm^{-1}): 3366, 3021, 2924, 2856, 1719, 1609, 1447, 1298, 1251, 1218, 1128, 1041, 756.

2,2-Diphenyl-1,10b-dihydro-2*H*,4*H*-pyrano[3,4-*c*]chromen-4-one (51)



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added methyl-4-(2-oxo-2-phenylethyl)-4*H*-chromene-3-carboxylate **48a** (0.077 g, 0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) undera positive pressure of argon atmosphere. The resultant reaction mixture was kept stirring at -78 °C. To this mixture was added the 1 (M) solution of phenyl magnesium bromide (PhMgBr) in THF (0.4 mL, 0.4 mmol, 1.6 equiv) and continued stirring at -78 °C to rt. After 2 h stirring, water (2 mL) was added to quench the reaction. The organic layer was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography through silica gel (petroleum ether: ethyl acetate 80:20) to afford 2,2-diphenyl-1,10b-dihydro-2*H*,4*H*-pyrano[3,4-*c*]chromen-4-one **51** as a white solid (0.067 g, 76% yield).



51

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.17.

Melting point: 87-89 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 6.5 Hz, 2H), 7.21 - 7.17 (m, 3H), 7.12 - 7.10 (m, 1H), 7.02 (s, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.81 (t, *J* = 7.3 Hz, 1H), 6.61

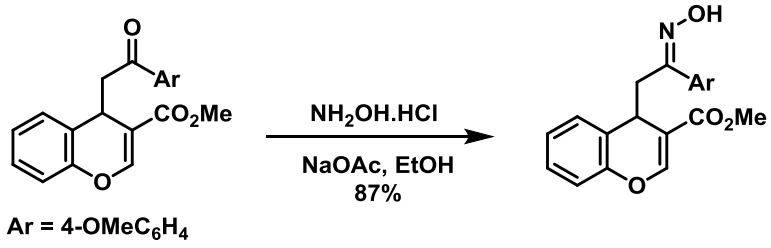
(d, J = 7.9 Hz, 1H), 6.50 (s, 1H), 4.12 – 4.07 (m, 1H), 3.16 (dd, J_1 = 7.6 Hz, J_2 = 14.6 Hz, 1H), 2.85 - 2.78 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.04, 154.00, 144.32, 142.00, 141.32, 135.05, 130.20, 130.15, 129.27, 128.94, 128.46, 128.33, 128.26, 127.94, 127.59, 126.46, 125.65, 119.87, 116.64, 86.82, 41.83, 39.57.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{19}O_3$: 355.1329, found: 355.1320.

FTIR (cm^{-1}): 3062, 2954, 1704, 1599, 1497, 1452, 1375, 1218, 1128, 1101, 1058, 990, 909, 737, 708, 652.

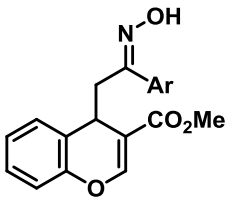
Methyl (*Z*)-4-(2-(hydroxyimino)-2-(4-methoxyphenyl)ethyl)-4*H*-chromene-3 carboxylate (12)



Ar = 4-OMeC$_6$H$_4$

48b 52

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was charged with hydroxylamine hydrochloride (0.045 g, 0.65 mmol, 5.0 equiv.) and sodium acetate (0.043 g, 0.52 mmol, 4.0 equiv.). The resultant mixture was dissolved in ethanol (2.0 mL) followed by addition of methyl 4-(2-(4-methoxyphenyl)-2-oxoethyl)-4*H*-chromene-3-carboxylate **48b** (0.045 g, 0.13 mmol) and the resulting reaction mixture was stirred at rt for 48 h. Water (2.0 mL) was added to quench the reaction. The organic layer was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography through silica gel (petroleum ether: ethyl acetate 80:20) to afford methyl (*Z*)-4-(2-(hydroxyimino)-2-(4-methoxyphenyl)ethyl)-4*H*-chromene-3-carboxylate **52** as a white semisolid (0.040 g, 87% yield).



52

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.30.

^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.65 (s, 1H), 7.57 – 7.54 (m, 2H), 7.33 – 7.31 (m, 3H), 6.84 (d, J = 8.9 Hz, 1H), 6.64 (dd, J_1 = 2.8 Hz, J_2 = 8.9 Hz, 1H), 6.52 (d, J = 2.7 Hz, 1H), 4.21 (dd, J_1 = 4.9 Hz, J_2 = 8.3 Hz,

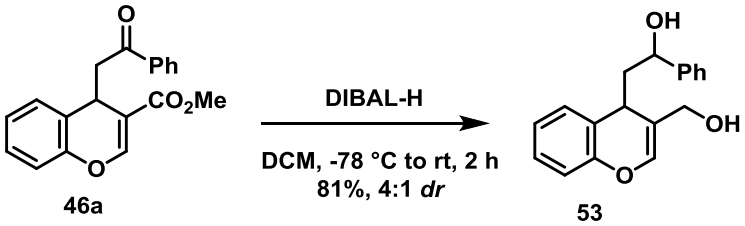
1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.30 (dd, J_1 = 8.5 Hz, J_2 = 13.2 Hz, 1H), 3.11 (dd, J_1 = 4.9 Hz, J_2 = 13.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.27, 157.27, 156.42, 152.03, 144.45, 135.56, 129.29, 128.54, 126.57, 124.12, 117.14, 114.27, 113.14, 109.03, 77.48, 77.16, 76.84, 55.76, 51.64, 34.29, 31.97.

HRMS: calculated $[M+Na]^+$ for $C_{20}H_{19}O_5NNa$: 376.1155, found: 376.1150.

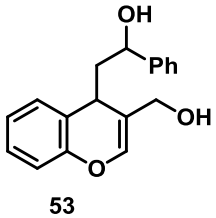
FTIR (cm^{-1}): 3358, 2948, 2851, 1706, 1641, 1493, 1439, 1374, 1300, 1215, 1096, 1033, 922, 759.

2-(3-(Hydroxymethyl)-4*H*-chromen-4-yl)-1-phenylethan-1-ol (53)



46a 53

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added methyl 4-(2-oxo-2-phenylethyl)-4*H*-chromene-3-carboxylate **48a** (0.077 g, 0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon followed by addition of 2.0 mL dry DCM and the resultant reaction mixture was kept stirring at -78 °C. To this mixture 1 (M) solution DIBAL-H in cyclohexane (0.6 mL, 0.60 mmol, 2.4 equiv.) was added under argon atmosphere. After stirring for 2 h at -78 °C to rt, the reaction was quenched with water. The organic layer was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography through silica gel (petroleum ether: ethyl acetate 60:40) to afford 2-(3-(hydroxymethyl)-4*H*-chromen-4-yl)-1-phenylethan-1-ol **53** inseparable mixture of diastereomers as a sticky colourless liquid (0.057 g, 81% yield, 4:1 dr detected by ^{1}H NMR).



53

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.25.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 – 7.16 (m, 7H), 7.11 - 7.02 (m, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.63 (s, 1H), 4.81 – 4.75 (m, 1H), 4.32 – 4.25 (m, 1H), 4.15 – 4.05 (m, 1H), 3.89 – 3.80 (m, 1H), 3.09 – 2.70 (bs, 2H, 2OH), 2.25 – 2.15 (m, 1H), 1.86 – 1.81 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.58, 144.74, 139.28, 129.24, 128.57, 127.69, 127.61, 125.80, 125.62, 124.66, 123.64, 117.36, 116.57, 72.07, 61.99, 46.81, 32.30.

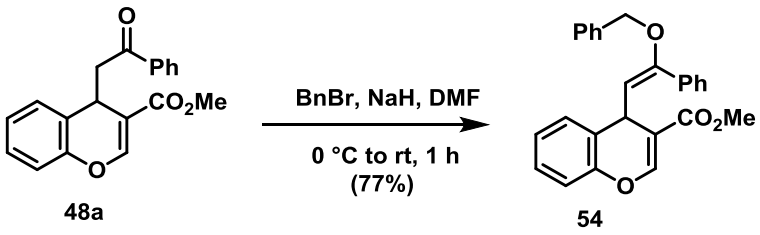
Representative peak for minor isomer **^{1}H NMR** δ: 6.74 (s), 4.14 (d, *J* = 11.5 Hz), 3.83 – 3.80 (m), 2.44 – 2.37 (m), 2.11 – 2.06 (m).

^{13}C NMR δ: 145.00, 140.17, 128.65, 127.50, 123.96, 116.39, 71.70, 63.66, 47.08, 34.13.

HRMS: calculated $[M+Na]^+$ for $C_{18}H_{18}O_3Na$: 305.1148, found: 305.1145.

FTIR (cm^{-1}): 3386, 2925, 2860, 1671, 1583, 1454, 1230, 1190, 1114, 1050, 909, 806, 734.

Methyl (*E*)-4-(2-(benzyloxy)-2-phenylvinyl)-4*H*-chromene-3-carboxylate (54)



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added methyl-4-(2-oxo-2-phenylethyl)-4*H*-chromene-3-carboxylate **48a** (0.077 g, 0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in DMF (2.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 0 °C. To this mixture was added the NaH (55% in mineral oil) (16 mg, 0.375 mmol, 1.5 equiv.) followed by the addition of benzyl bromide (43 mg, 30 µL, 0.25 mmol). After 1 h stirring, water (2.0 mL) was added to quench the reaction. The organic layer was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography through silica gel (petroleum ether: ethyl acetate 80:20) to afford methyl (*E*)-4-(2-(benzyloxy)-2-phenylvinyl)-4*H*-chromene-3-carboxylate **54** as a white solid (0.077 g, 77% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.27.

Melting point: 100-102 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (s, 1H), 7.52 (bs, 4H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.38 – 7.33 (m, 4H), 7.28 – 7.18 (m, 2H), 6.99 – 6.96 (m, 2H), 5.68 (d, *J* = 3.9 Hz, 1H), 5.20 (s, 2H), 5.07 (d, *J* = 4.1 Hz, 1H), 3.67 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.23, 155.54, 151.85, 146.63, 137.47, 133.71, 133.28, 129.11, 128.69, 128.62, 128.40, 127.96, 127.83, 127.46, 125.91, 124.53, 121.50, 112.37, 108.39, 103.02, 70.48, 51.54, 30.50.

HRMS: calculated $[M+Na]^+$ for $C_{26}H_{22}O_4Na$: 421.1410, found: 421.1405.

FTIR (cm^{-1}): 3023, 2926, 2859, 1712, 1633, 1596, 1489, 1450, 1377, 1298, 1247, 1098, 1201, 756, 698.

4.8. References

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Chapter 5

A Brief Introduction to Transition-Metal-Free Aryne Multicomponent Reactions

Arynes are one of the most important class of reactive intermediates due to their electron-deficient nature, and they have been widely used for the synthesis of 1,2-disubstituted benzenes and benzo-fused heterocycles and carbocycles of structural complexity and diversity. The application of arynes to any synthetic effort must exploit the highly reactive intermediate under controlled conditions. Recently, various type of aryne based methodology has been developed under transition-metal-catalyzed or metal-free conditions, because the functionalized products are much more interesting from a synthetic perspective. In this chapter, the application of arynes in transition-metal-free multicomponent reactions has been presented.

Chem. Soc. Rev. **2012**, *41*, 3140-3152

Synlett. **2014**, *25*, 608-614

5.1. Introduction

Multicomponent Reactions (MCRs) have emerged as an active and potential area of research for organic chemist in recent decades.[1] MCR has made a significant advancement by generating structurally complex molecules in a single step from three or more reactants. It has been widely accepted by the synthetic chemists due to adventages such as atom-economy, selectivity (minimizing the by-product), efficiency (high yield), easily available starting materials and less time consuming (tandem process to form two or more bonds simultaneously) process. Since the discovery of Strecker reaction, endless developments happened in this field.[2] The celebrated MCRs in the last two century include Hantzsch,[3] Biginelli,[4] Mannich,[5] Passerini,[6] Ugi[7] *etc*. The application of MCRs had an important role in the exploration of a very high chemical space with exceptional synthetic utility and in drug development before the advent of diversity oriented synthesis or combinatorial technologies. The efficiency of these processes depends on the careful selection of the suitable coupling partners. In recent years, transition-metal-free MCRs became a practical and straightforward process for organic synthesis. The literature on MCRs has been broadened by using the transient intermediate "aryne" as one of the component. The appropriate employment of nucleophiles and electrophiles to the polarized triple bond of aryne can lead to the facile transformation leading to the synthesis of 1,2-disubstituted arene product. The focal theme of this chapter is to summarize the recent developments on transition-metal-free MCR based on arynes. In order to put things on perspective, a brief introduction to arynes and their application in transition-metal-free MCRs is given in the following sections.

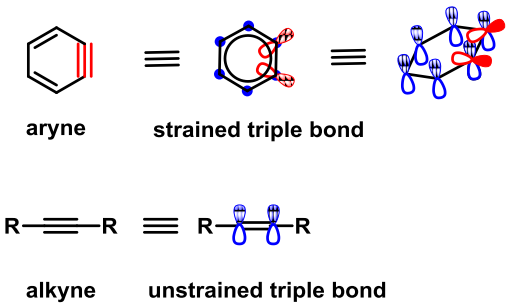
5.2. A Brief Introduction to Arynes

5.2.1. Historical Perspective

Benzyne or aryne or 1,2-dehydroarene is an uncharged intermediate formally contained a highly strained C-C triple bond generated from an aromatic system by removal of two *ortho*-substituents.[8] Due to the geometric constraints on the C-C triple bond in a six-membered ring, the *p*-orbitals overlap is reduced and they are no longer parallel to each other as in normal alkynes (Figure 5.1). The reduced *p*-orbital overlap also results in significant lowering of the LUMO energy. Thus the energy gap between HOMO and LUMO is decreased substantially. This strain created by the distorted triple bond in the ring

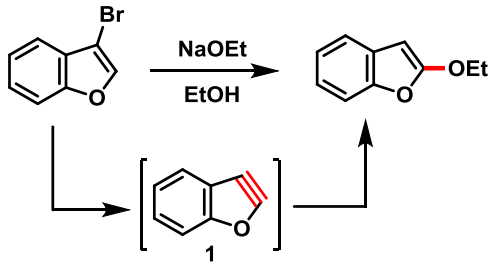
makes them highly reactive. Hence, a wide variety of anionic as well as uncharged nucleophiles can add to this kinetically unstable intermediate.[9]

Figure 5.1: Geometry of Aryne



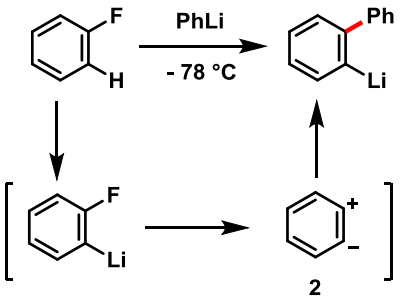
The existence of aryne intermediate was documented in 1902 by Stoermer and Kahlert.[10] They observed the formation of 2-ethoxybenzofuran upon treatment of 3-bromobenzofuran with sodium ethoxide in ethanol (Scheme 5.1). But there was no direct experimental evidence about the intermediate **1**.

Scheme 5.1: Stoermer and Kahlert Experiment



Later in 1942, Wittig reported the synthesis of biphenyl from fluorobenzene and phenyllithium. It was proposed that the reaction proceeds through a zwitterionic intermediate **2** (Scheme 5.2).[11]

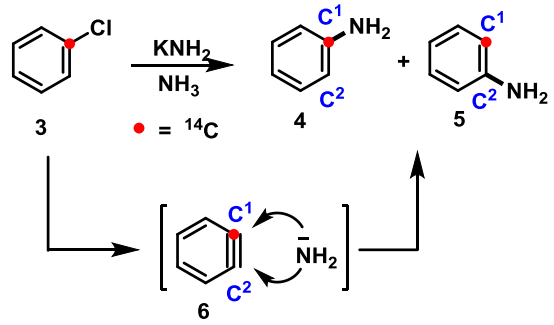
Scheme 5.2: Wittig's Experiment



In 1953, Roberts and co-workers performed a seminal ^{14}C labelling experiment, which provided the structure of the intermediate "benzyne".[12] The treatment of isotopically

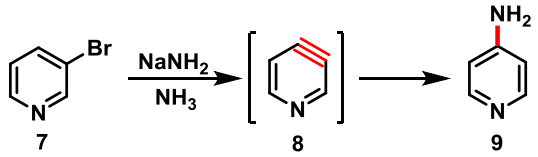
labelled chlorobenzene-1-^{14}C (**3**) with amine proceeded to give a mixture of labelled isomers, of aniline-1 (**4**) and aniline-2 (**5**) in 43% yield. The observed mixture of product strongly indicates that the $\mathbf{C^1}$ and $\mathbf{C^2}$ are equivalent in the intermediate **6** (Scheme 5.3).

Scheme 5.3: Roberts's Experiment



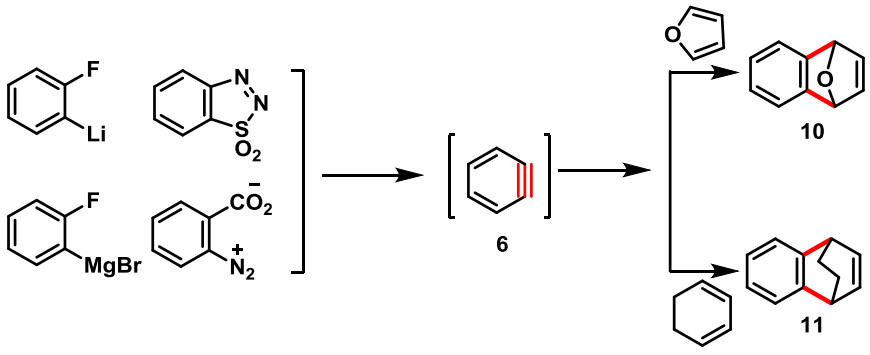
Levine and co-workers reported the generation of heteroaryne from pyridine (Scheme 5.4).[13] The reaction of 3-bromopyridine **7** with sodamide resulted the formation of pyridyne **8**, which upon treatment with excess sodamide delivered 4-amino pyridine **9**.

Scheme 5.4: Reactions of Heteroaryne



Later, Wittig and Pohmer successfully trapped the aryne intermediate **6** with furan via a [4+2] cycloaddition reaction, resulting in the formation of epoxynaphthalene derivative **10** (Scheme 5.5).[14] Here, the aryne intermediate **6** was used as an electrophilic dienophile. Independently, Huisgen and Knorr have demonstrated the generation of aryne from different precursors and subsequent interception of the intermediate with furan or cyclohexadine.[15]

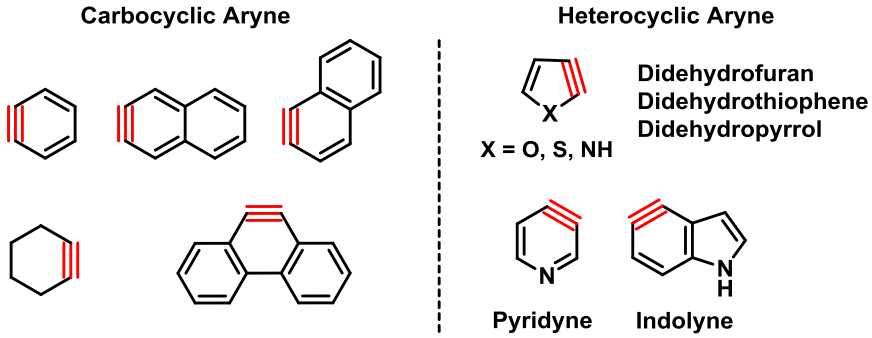
Scheme 5.5: Wittig and Huisgen's Experiment



5.2.2. Different Class of Arynes

Arynes have found growing applications in various carbon-carbon and carbon-heteroatom bond-forming reactions. In the last few decades, several new arynes have been reported. Few popular aryne intermediates, which are generally used for synthetic transformations are shown below (Scheme 5.6).[16]

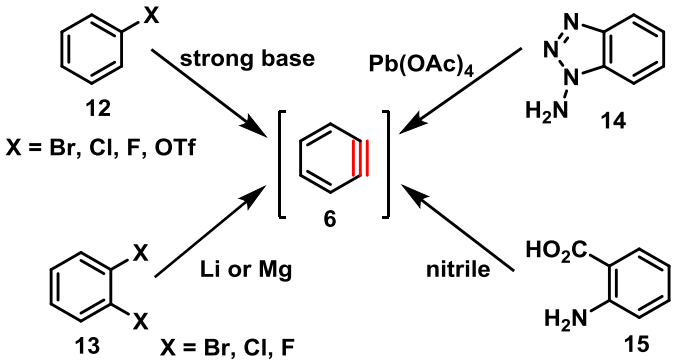
Scheme 5.6: Aryne Derivatives



5.2.3. Methods for the Generation of Arynes

Arynes are formally derived from aromatic rings by abstraction of two *o*-substituents. In view of its transient intermediate character, it has to be generated *in situ* in the reaction vessel. In 1942, Wittig reported the generation of aryne from fluororobenzene using Grignard reagent. Since then there are numerous methods reported to generate aryne *in situ.* An organic chemist now has access to a variety of methods for the generation of arynes, all of which have both pros and cons in their use. Some of the more popular classical methods for generating arynes are detailed in Scheme 5.7.

Scheme 5.7: Methods of Aryne Generation

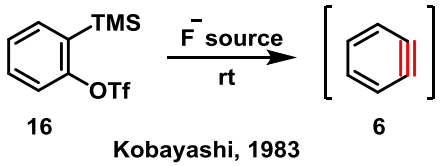


All of the methods described are well known and are taught in most undergraduate courses and textbooks.[17] However, all of the conditions have major drawbacks which have restricted the development of aryne chemistry in the past. The requirement of strong bases,

oxidants, stoichiometric amounts of metals or explosive intermediates are either harsh or intolerable to different functional groups.

In 1983, Kobayashi and co-workers developed a facile and efficient method for the generation of aryne **6** by the fluoride-induced 1,2- elimination of 2-(trimethylsilyl)aryl triflates **16** (Scheme 5.8).[18] The mild reaction conditions involved in this procedure are compatible with a variety of reagents, substrates, functional groups and even transition metal catalysts. Recently, this method is widely used for *in situ* generation of aryne in the reaction vessel.

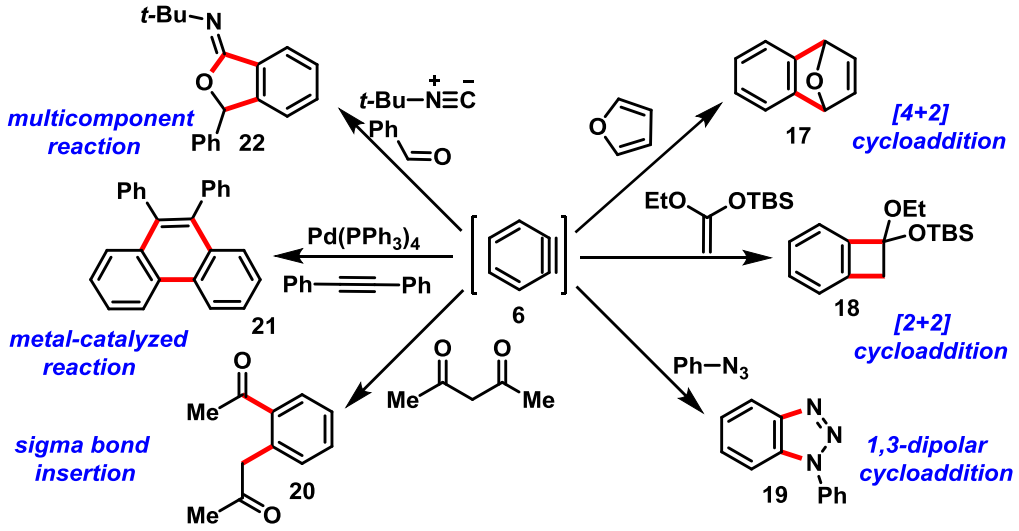
Scheme 5.8: The generation of benzyne from ortho-trimethylsilylphenyl triflate



5.2.4 Different Modes of Reactivity of Arynes

The application of arynes to any synthetic effort must exploit the reactivity of this highly energetic intermediate under controlled circumstances. Over the past 30 years, numerous methods have been developed using Kobayashi's *ortho*-silyl aryl triflate as an aryne precursor. The phenomenal success of arynes in organic synthesis can be attributed primarily to their electron deficient nature leading to different modes of action in various carbon-carbon and carbon-heteroatom bond forming reactions (Scheme 5.9) including pericyclic reactions ([4+2], [2+2] and 1,3-dipolar cycloaddition), insertion reactions,

Scheme 5.9: Different modes of Reactivity of Arynes

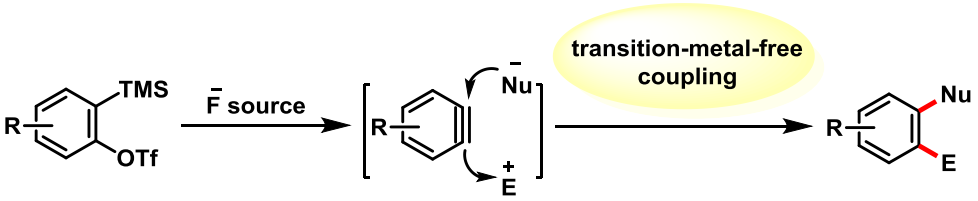


transition-metal catalyzed reactions and multicomponent reactions (MCRs).[19] In the following sections, we focus exclusively on arynes that are used in transition-metal-free MCRs uncovered in the last decade.

5.3. Transition-Metal-Free Multi-Component Reactions (MCRs)

The design and development of new benzannulated heterocycles via aryne-based MCRs makes this methodology exceedingly appealing. Aryne is ideally suited for multicomponent synthesis because it functions as a neutral agent to transfer charge between nucleophiles and electrophiles, leading to the dual functionalization of the strained triple bond (Scheme 5.10). Recently, various type of MCRs has been developed under metal-catalyzed or metal-free conditions, because the functionalized products are much more interesting from a synthetic view point. In this section, we will highlight only the recent developments carried out under transition-metal-free conditions.[20]

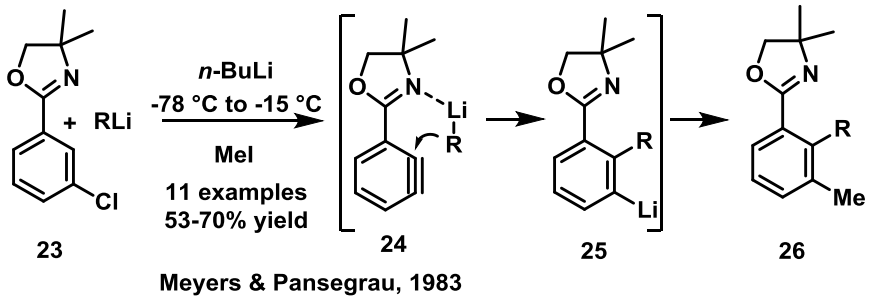
Scheme 5.10: Transition-Metal-Free MCRs Involving Arynes



5.3.1. Aryne MCRs Initiated by Anionic Nucleophiles

In 1983, Meyers and Pansegrau reported the first MCR based on aryne.[21] The treatment of 2- (3-chlorophenyl) 2-oxazoline **23** with butyl lithium resulted in the formation of aryne **24**, which upon addition of organolithium reagents followed by the trapping of the arylanion intermediate **25** using MeI leading to the formation of 2-substituted 3-methyl phenyl 2-oxazoline derivative **26** (Scheme 5.11). The reaction was found to be working with various organolithium and organomagnesium reagents.

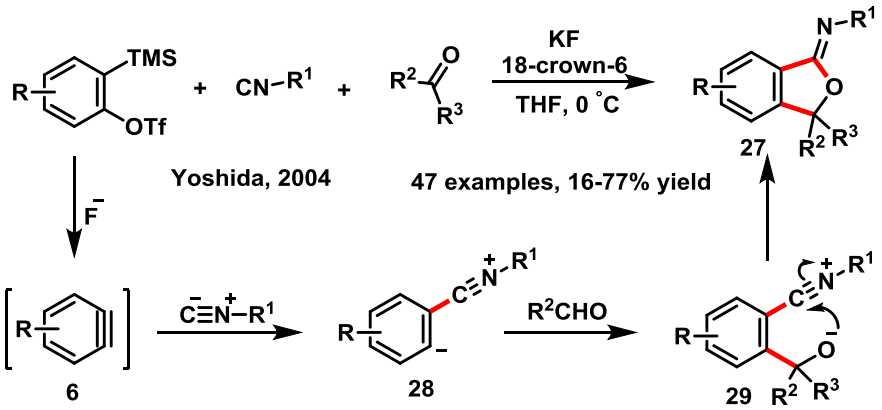
Scheme 5.11: Aryne MCR Initiated by Anionic Nucleophile



5.3.2. Aryne MCRs Initiated by Isocyanides

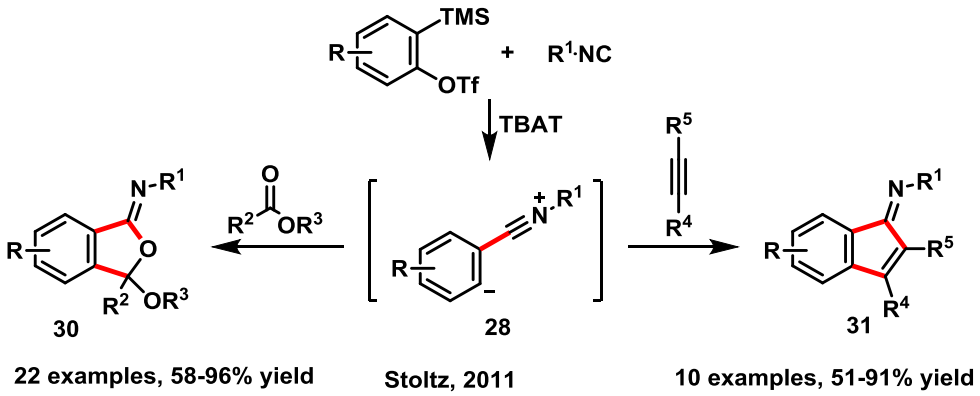
In 2004 Yoshida and co-workers reported an elegant way to synthesize iminoisobenzofurans by the association of aryne, isocyanides and aldehydes.[22] The isocyanide acts as a nucleophile and the aldehyde acts as the electrophile (Scheme 5.12). Addition of the isocyanide to the aryne generates zwitterion **28**. The *ortho*-anionic aryl species **28** adds to the carbonyl component followed by intramolecular cyclization gives the iminoisobenzofurans **27**. Though aryl aldehydes were used as the third-component in most of the cases, aliphatic aldehydes also participate in this unique MCR to form alkyl-substituted iminoisobenzofurans. Moreover, use of ketones and benzoquinones as the third-components were beneficial. Further studies revealed that imines can be used as the electrophile leading to the formation of the desired iminoisoindolines in good to excellent yields.[23]

Scheme 5.12: MCR of Arynes, Isocyanides with either Aldehydes or Activated Ketones



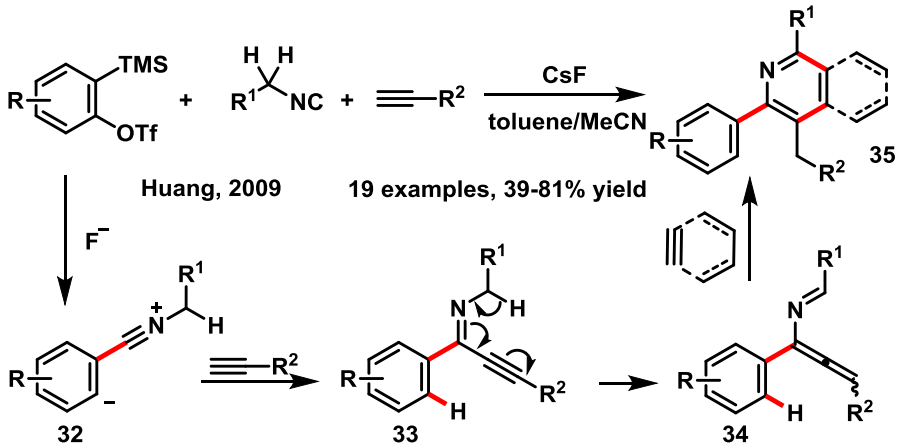
Stoltz and co-workers uncovered a similar three-component reaction of arynes, isocyanides and phenyl esters that provided the phenoxy iminoisobenzofuran derivatives **30** in good yields (Scheme 5.13).[24] This reaction may proceed through the similar sequence as described in Scheme 5.12 or a formal [3+2] cycloaddition can happen with the third-component to form the desired product. It is noteworthy to mention that the product **30** can afford *o*-keto benzamides in one-pot acidic hydrolysis. Additionally, when the ester component of this MCR was replaced by an electron deficient alkyne, the reaction afforded carbocyclic iminoindenones **31**.

Scheme 5.13: MCR of Arynes and Isocyanides with either Phenyl Ester or Electrophilic Alkynes



Recently, Sha and Huang demonstrated an easy access to polysubstituted pyridines and isoquinolines by the three-component reaction involving arynes, isocyanides and terminal alkynes(Scheme 5.14).[25] The key to success for the observed selectivity arose from the appropriate reaction conditions: with excess of terminal alkynes, pyridines were formed and with excess of arynes, isoquinoline were formed. The reaction proceeds with the formation of 1,3-zwitterionic intermediate **32** from aryne and isocyanide, which is intercepted by the terminal alkyne to generate the allenyl imine intermediate **34**. The successive cycloaddition of **34** with another molecule of terminal alkyne or aryne afforded either pyridine or isoquinoline derivatives respectively.

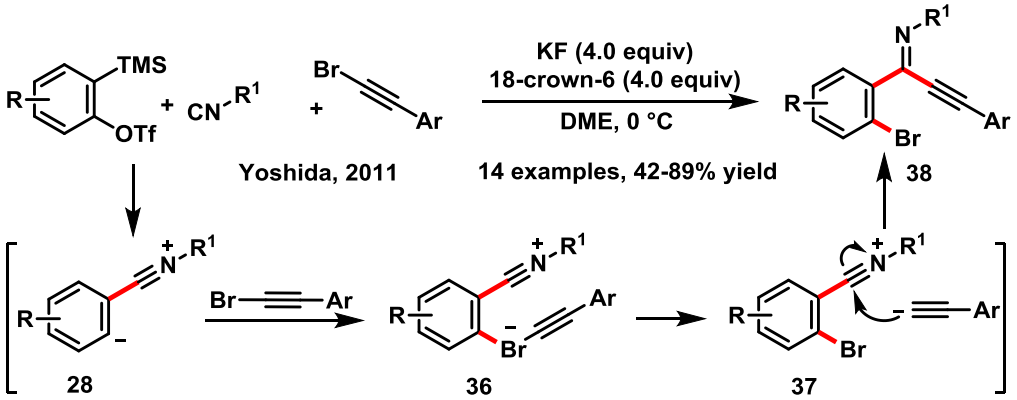
Scheme 5.14: MCR of Arynes, Isocyanides and Terminal Alkynes



The Yoshida group has recently disclosed a unique coupling of isocyanides, alkynyl bromides and arynes to form bromoarenes **38** (Scheme 5.15).[26] The 1,3-zwitterionic intermediate **28** generated from isocyanide and aryne reacts with alkynyl bromides involves

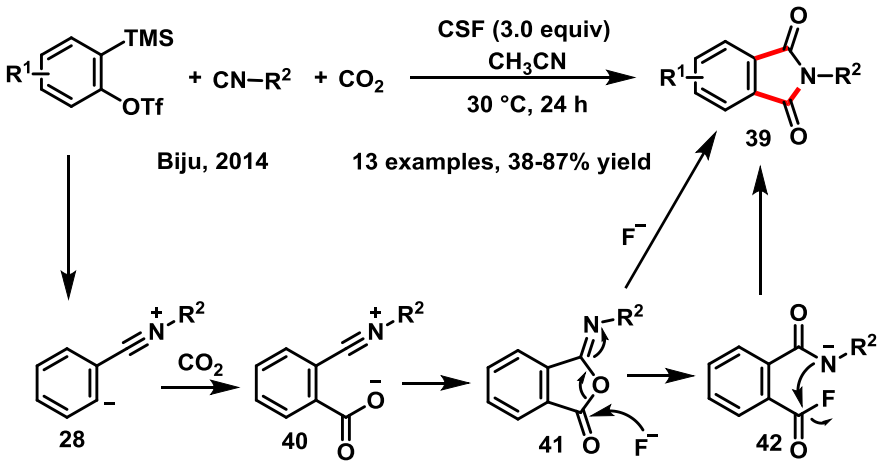
ortho-bromination followed by addition of acetylide to nitriniumcation **37** to generate **38**.

Scheme 5.15: MCR of Arynes and Isocyanides with Organic Bromides



Recently, our laboratory has reported an isocyanide triggered aryne MCR using CO_2 as the third-coupling partner leading to phthalimide derivatives **39** with the formation of two C-C and one C-N bond in a unique fashion (scheme 5.16).[27] Mechanistically, this reaction proceeds via the generation of 1,3-dipolar intermediate **28** followed by trapping of aryl anion with CO_2 and subsequent cyclization leading to the formation of intermediate iminoisobenzofuranone **41**, which undergoes a fluoride induced rearrangement to form the desired product **39**. In a control experiment, the transformation of the intermediate **41** to the desired product **39** in presence of same fluoride source has been established (Scheme 5.16).

Scheme 5.16: MCR of Arynes, Isocyanides and CO_2

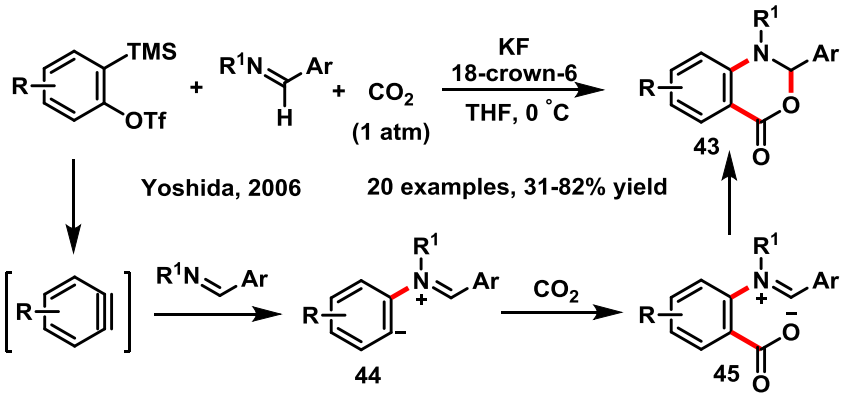


5.3.3. Aryne MCRs Initiated by Imines

Yoshida, Kunai and co-workers developed a unique three-component coupling of aryne, imine and CO_2.[28] The 1,3-zwitterionic intermediate **44** generated by the addition of imines to arynes were trapped using CO_2 to form the carboxylate **45**, which undergoes

cyclization leading to the formation of benzoxazinone derivatives **43** (Scheme 5.16).

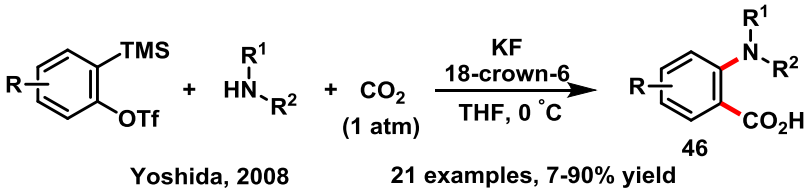
Scheme 5.16: MCR of arynes, Imines and CO_2



5.3.4. Aryne MCRs Initiated by Amines

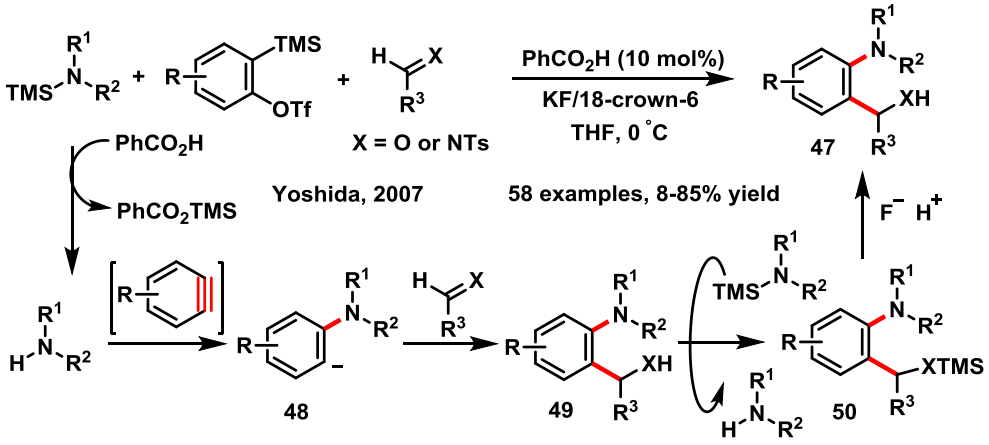
Subsequently, the Yoshida group has reported the use of secondary amine as the nucleophilic trigger instead of imine in a three-component coupling reaction generating anthranilic acid derivatives **46** (Scheme 5.17).[29]

Scheme 5.17: MCR of Arynes, Amines and CO_2



Recently the same group has developed a MCR process of arynes, aminosilanes and aldehydes in presence of catalytic amount of benzoic acid, which is responsible for the generation of free amine leading to the formation of 2-amino benzhydrol derivatives **49** (Scheme 5.18).[30] Subsequently, **49** reacts with aminosilane to give silyl ether **50** with the

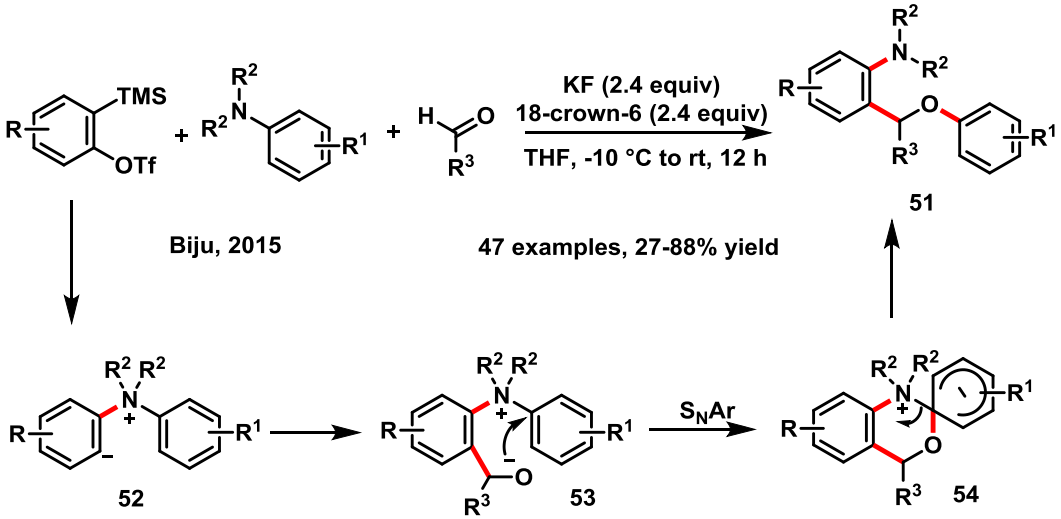
Scheme 5.18: MCR of Arynes, Aminosilanes and Aldehydes or Imines or Ketones



regeneration of the unprotected amine. The resulting silyl ether **50** would be transformed into benzhydrol derivatives **47** via a work up process. This reaction is not only limited to aldehyde as a third coupling partner. Imines as well as activated ketones also have shown excellent reactivity (Scheme 5.18).

Recently, our group has developed a three-component coupling of arynes, aldehydes and aromatic tertiary amines leading to the synthesis of *o*-functionalized tertiary amines **51** in moderate to good yields (Scheme 5.19).[31] The reaction proceeds with the formation of 1,3-zwitterionic intermediate **52** from aryne and aromatic tertiary amines, which is intercepted by the carbonyl to generate the alkoxide intermediate **53**. Subsequently, **53** undergoes an intramolecular aromatic nucleophilic substitution to form the intermediate **54**, followed by a Smiles type rearrangement to form the corresponding product **51**. Notably, the product formation took place via the migration of NMe_2 group from the amino aryl moiety to the aryne. Moreover, activated ketones can also be used as the aldehyde component in this reaction.

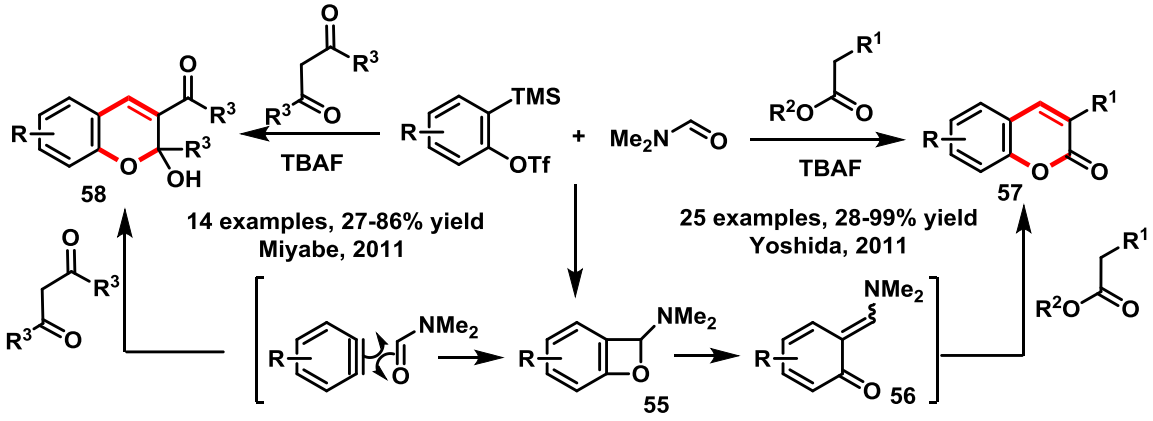
Scheme 5.19: MCR of Arynes, Amines and Carbonyls



5.3.5. Aryne MCRs Initiated by DMF

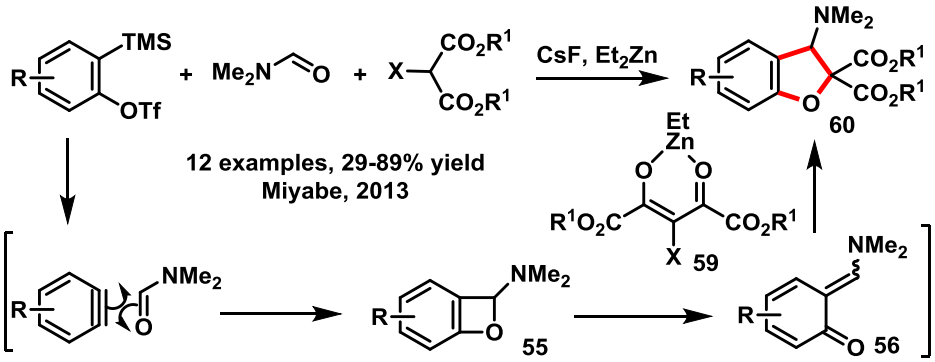
Yoshida and Miyabe independently demonstrated the DMF triggered aryne MCR with enolizable carbonyls (Scheme 5.20).[32] DMF was added to aryne in a formal [2 + 2] cycloaddition, generating a strained cyclic aminal **55**, which rapidly undergoes a 4π-retrocyclization to form the *ortho*-quinonemethide **56**. At this point, a 1,3-diketone or β-ketoester derivative adds to the reactive quinonemethide in a formal [4+2] cycloaddition to furnish coumarins **57** or 2*H*-chromenes **58**, respectively.

Scheme 5.20: MCR of Arynes and DMF with Active Methylene Compounds



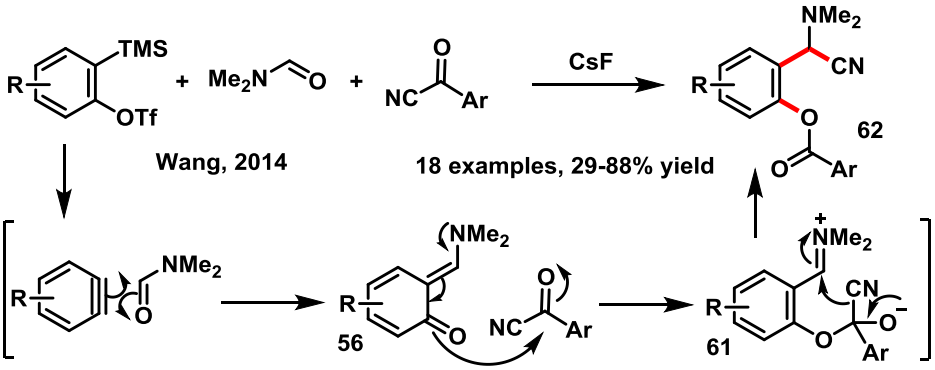
Recently, Miyabe and co-workers reported that the *ortho*-quinonemethides **56** can also be intercepted with a zinc enolate **59** of α-halo methines to provide dihydrobenzofurans **60** in moderate to excellent yield.[33] This reaction can be viewed as a formal [4+1] cyclization of *ortho*-quinonemethides with zinc enolate (Scheme 5.21).

Scheme 5.21: MCR of Arynes and DMF with Zinc-Enolate



Wang and co-workers reported an efficient synthesis of α-amino-α-aryl carbonitriles from the multicomponent coupling of aryne, DMF and benzoyl cyanides (Scheme 5.22).[34]

Scheme 5.22: MCR of Arynes and DMF with Carbonitriles

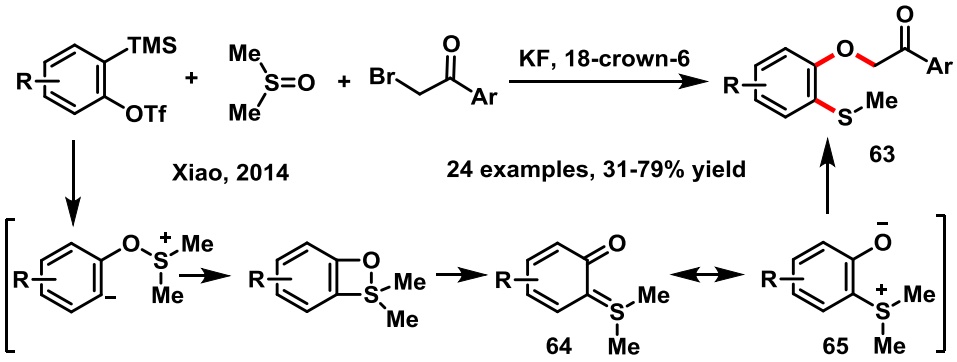


The reaction proceeds through a similar *ortho*-quinonemethide intermediate **56**, which undergoes a nucleophilic attack to aryl cyanides to generate the intermediate **61** followed by the cyanide migration resulting in the formation of the desired product (Scheme 5.22).

5.3.6. Aryne MCRs Initiated by DMSO

Xiao and the co-workers disclosed the use of DMSO as a solvent as well as the coupling partner.[35] DMSO in presence of aryne formed the *ortho*-quinone methide type intermediate **64**, which can also exist in the mesomeric form **65**. The nucleophilic addition of **65** to α-bromo carbonyl afforded arylmethyl thioethers **63** in good yields. DMSO acts both as a methyl thiolating agent as well as an oxygen source (Scheme 5.23).

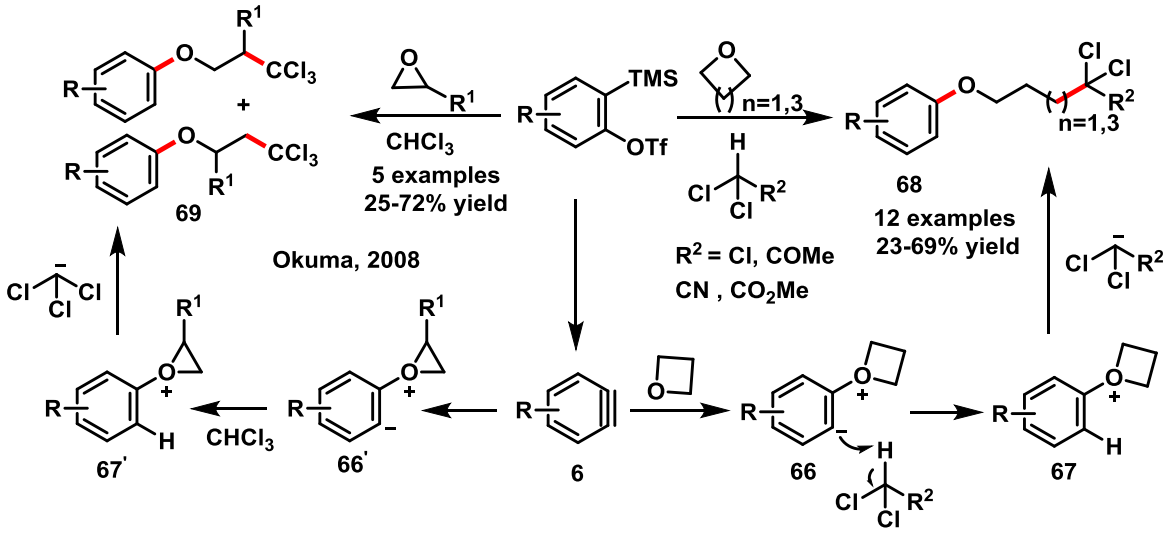
Scheme 5.23: MCR of Aryne, DMSO and α-Bromo Carbonyl Compound



5.3.7. Aryne MCRs Initiated by Cyclic Ethers

Okuma and co-workers reported the cyclic ether triggered aryne MCR (Scheme 5.24).[36] Cyclic ether can undergo nucleophilic attack to the aryne **6** and the resulting

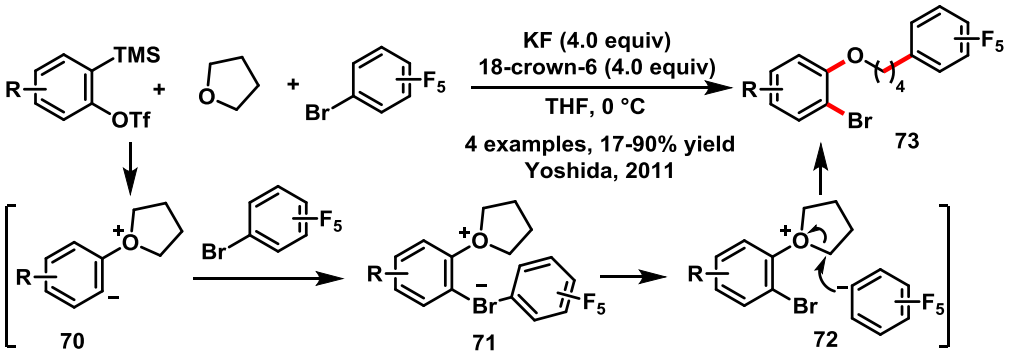
Scheme 5.24: MCR of Aryne, Cyclic Ether and Active Methines



zwitterion **66** was generated, which abstract proton from active methines to form the oxonium **67**. The resulting anion generated from active methines open-up the oxonium ring of **67** leading to the formation of chlorinated alkyl phenyl ether **68** with good yields. In case of unsymetrically substituted epoxide, regioisomeric mixture of the product **69** was obtained (Scheme 5.24).

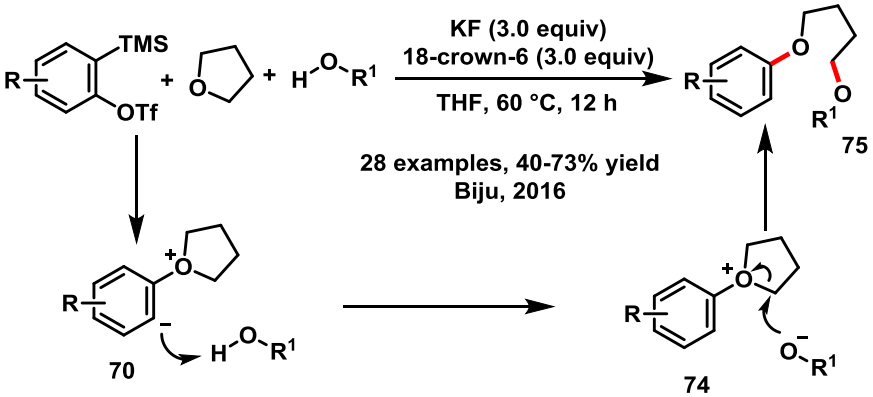
Subsequent report from Yoshida group has shown yet another interesting MCR involving aryne, THF and perfluoroaryl (or alkynyl) bromides.[26] The 1,3-dipole **70** generated from aryne and THF can be intercepted with perfluoroaryl (or alkynyl) bromides with good functional group compatibility (Scheme 5.26).

Scheme 5.26: MCR of Arynes and Cyclic Ethers with Organic Bromides



Recently, our group has reported a related work on the cyclic ether trigger aryne MCR, where aliphatic alcohols were used as the third-component.[37] The zwitterionic intermediate **70** abstracted a proton from alcohol to form the oxonium **71**, which undergoes the ring-opening by the alkoxide nucleophilic attack (Scheme 5.25).

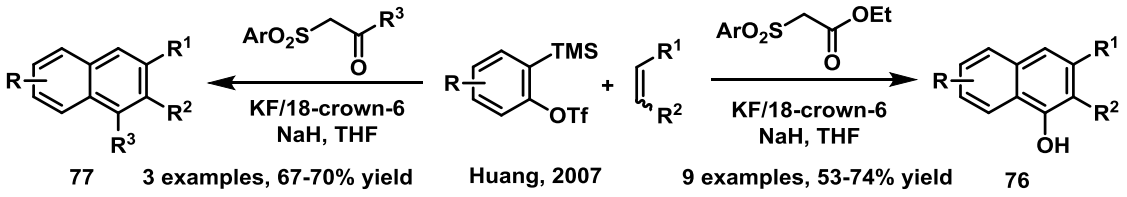
Scheme 5.25: MCR of Arynes and Cyclic Ethers with Aliphatic Alcohol



5.3.8. Miscellaneous

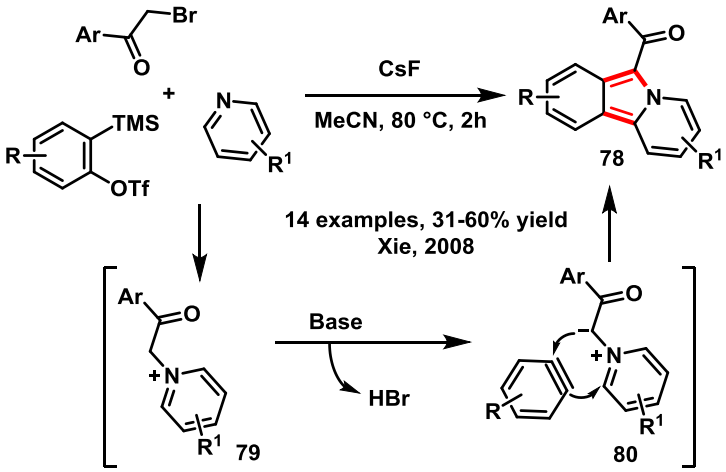
Huang reported the synthesis of α-naphthol derivatives **76** by a unique three-component reaction involving arynes, β-sulfonyl acetates and Michael acceptors (Scheme 5.27).[38] The reaction proceeds via aryne C-C insertion on β-sulfonyl compound followed by Michael addition. Moreover, β-ketosulfones instead of β-sulfonyl acetates afforded naphthalene derivatives **77**.

Scheme 5.27: MCR of Arynes, β-Sulfonyl Acetates (or β-Ketosulfones) and Michael acceptors



Xie and co-workers disclosed a three-component reaction of arynes with pyridine and α-bromo carbonyl compound leading to the formation of pyrido[2,1-a]isoindoles **78**.[39] The reaction proceeds with the formation of the pyridinium salt **79**, which generates the azomethine ylide **80** by the release of HBr. The ylide **80** undergoes a [3+2] cycloaddition with aryne followed by aromatization affording the product (Scheme 5.28).

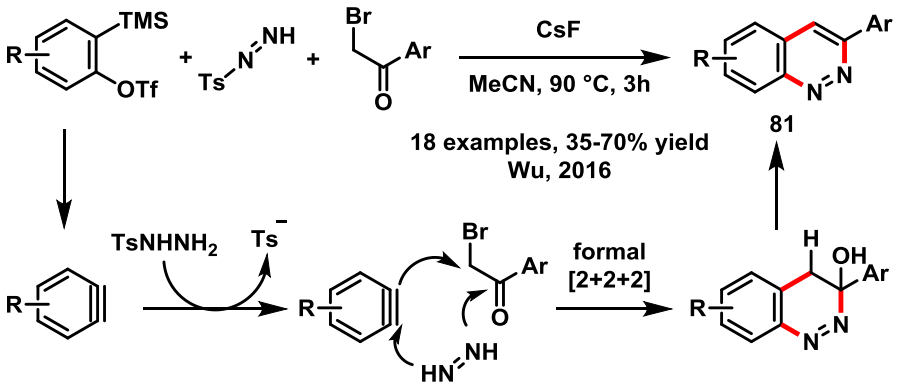
Scheme 5.28: MCR Involving Arynes, Pyridine and α-Bromo Carbonyls



Very recently, Wu and co-workers reported a MCR of aryne, tosylhydrazine and α-bromo ketones.[40] The reaction proceeds via a fluoride induced generation of diazene from tosylhydrazine followed by a formal [2+2+2] cycloaddition with aryne and α-bromo

ketones, resulting to the formation of cinnoline derivatives **81** with moderate to good yields (Scheme 5.29).

Scheme 5.28: MCR involving arynes, Hydrazines and α-bromo carbonyls



5.4. Conclusion and Focal Theme of the Present Work

This chapter has illustrated the wide variety of transition-metal-free aryne multicomponent couplings and their synthetic potential for constructing highly functionalized aromatic compounds. From the above discussion, it is clear that the successes of aryne MCR is attributed to the use of Kobayashi's 2-(trimethylsilyl)aryl triflates **16** as aryne precursors, which allows the generation of arynes under extremely mild conditions. In view of the usefulness of biologically important aromatic compounds, development of new aryne MCRs is considered to be an important area in synthetic organic chemistry. Even though, various nucleophile initiated aryne MCRs are well established, the usefulness of N-heterocycles and phosphines as nucleophilic triggers remains unexplored. In view of this, we turned our attention to the development of new heterocyclic systems by multicomponent aryne reactions.

In this context, N-heterocycles as a nucleophilic trigger in aryne MCRs was investigated. When iso(quinoline) system was used as a nucleophilic source, the reaction proceeds via a 1,4-dipolar intermediate leading to the spirooxazino (iso)quinoline derivatives. Interestingly, use of pyridine as a nucleophile resulted in a very unprecedented outcome. The reaction proceeds through a pyridylidene intermediate to generate the indolin-2-one derivative. Investigations of these reactions are documented in the 6th chapter of the thesis.

We have shown the usefulness of phosphines as a nucleophilic trigger for transition-metal-free aryne MCRs. The reaction proceeds via a formal [3+2] cycloaddition of 1,3-phosphonium zwitterions generated from phosphine and aryne with aldehydes. The method gives a diverse range of stable benzooxaphosphole derivatives with good to excellent yields. Subsequently, the methodology has been expanded with various acyclic and cyclic activated carbonyl compounds. The reaction resulted in a convenient synthesis of (spiro)benzoxaphospholes in moderate to good yields. These details form the subject matter of the 7th chapter of the thesis.

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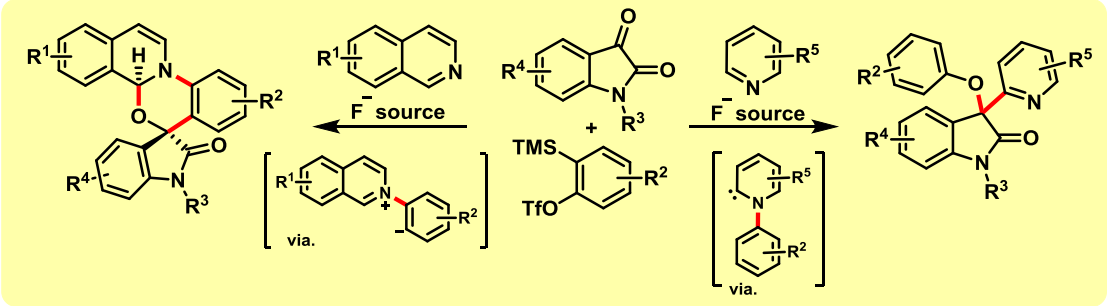
Chapter 6

N-Heterocycles Triggered Aryne Multicomponent Reactions

In this chapter, the use of N-heterocycles as a nucleophilic trigger in aryne MCRs has been demonstrated. The important aspect of the present work is the divergent reactivity of the nucleophilic triggers. When iso(quinoline) system was used as a nucleophilic source, the reaction proceeds via a 1,4-dipolar intermediate leading to the formation of spirooxazino (iso)quinoline derivatives. The reaction provides a broad substrate scope with respect to the variation of all the three coupling partners. Interestingly, use of pyridine as the nucleophile resulted in an unprecedented outcome. The reaction proceeds through a pyridylidene intermediate to generate the indolin-2-one derivatives. A series of mechanistic experiments were preformed to establish the mechanism of this transformation. Subsequently, the scope of iso(quinoline) triggered aryne MCRs with activated acyclic carbonyls has been investigated.



Angew. Chem. Int. Ed. **2013**, *52*, 10040-10043

Patent No. (**2014**) WO 2014162319-A2; 2014162319-A3

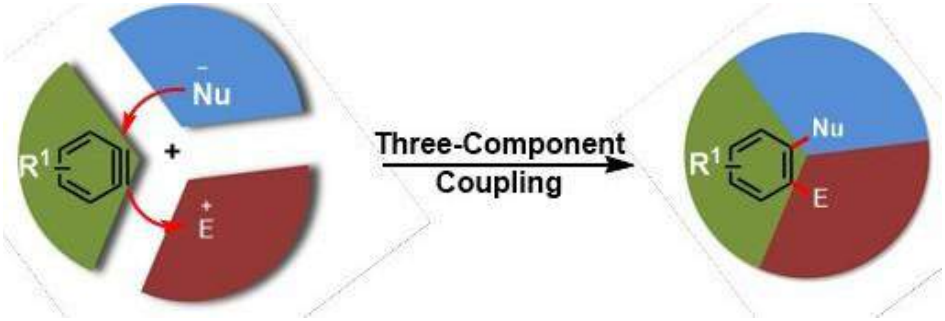
Org. Lett. **2013**, *15*, 4620-4623

US Patent No. (**2015**) US9206196-B1

6.1. Introduction

Arynes are highly electrophilic reactive intermediate, which has been extensively used in various carbon-carbon and carbon-heteroatom bond forming reactions. Recent developments in aryne chemistry are mainly focused on the transition-metal-free reactions.[1] The development of mild condition, i.e. the fluoride induced 1,2-elimination of *ortho*-silyl aryl triflate to aryne, has led to a broad expansion of aryne participation in synthetic organic chemistry.[2] Aryne is well suited for multicomponent synthesis because it functions as a neutral agent to transfer charge between nucleophiles and electrophiles in majority of its known applications. The simplest aryne multicomponent reactions (MCRs) would initiate by addition of a nucleophilic species into aryne followed by subsequent trapping of the aryl anion with external electrophiles (Figure 6.1).

Figure 6.1: Aryne Multicomponent Reactions



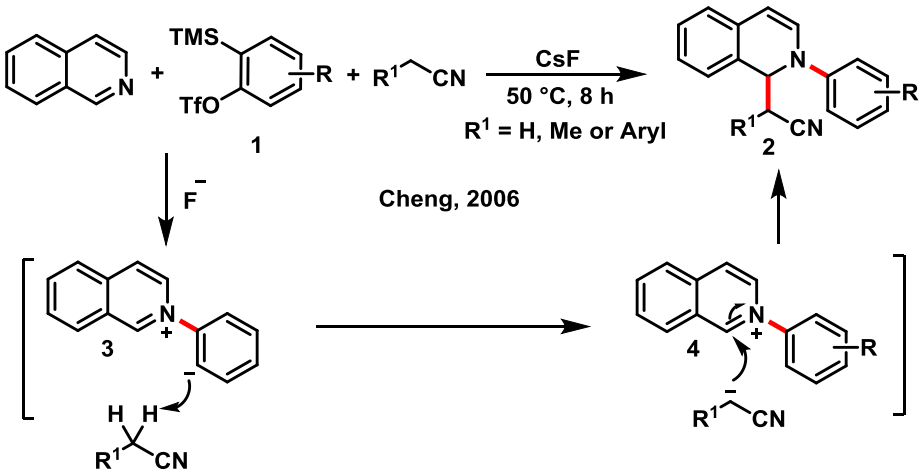
The synthetic utility of arynes in MCRs is significant now a day, as this method allows a straightforward access to various multisubstituted arenes of structural complexity and diversity.[3] The success of these reactions depend on the careful selection of coupling partners capable of reacting in a specific sequence under controlled conditions. Arising from the low-lying LUMO of arynes, a number of nucleophiles such as isocyanides,[4] amines,[5] imines,[6] amides,[7] DMF,[8] DMSO,[9] cyclic-ethers,[10] alcohols[11] as well as aldehydes[12] can add to the strained triple bond of aryne. In the last two decades, several report appeared on the developments of transition-metal-free aryne MCRs. However the utility of N-heterocycles such as isoquinoline, quinoline, pyridine, aziridine, azirine as the nucleophilic trigger are very rare in the realm of aryne MCRs.

6.2. N-Heteroaromatics as a Nucleophilic Trigger in Aryne MCRs

In 2006, Jeganmohan and Cheng reported a pseudo multicomponent reaction of arynes, N-heteroaromatic compounds and nitriles having an acidic α-hydrogen.[13] In this

case, nitrile works as a solvent as well as the third-component for the MCR and the reaction resulted in the construction of new C-C and C-N bonds in one pot (Scheme 6.1). The reaction proceeds through the N-arylation of isoquinoline with aryne generated from **1**, resulting in the formation of isoquinolium species **4** after deprotonation of the nitrile. Addition of the nitrile anion to the iminium **4** then yields the desired product **2**. The key intermediate of this reaction is the 1,4-zwitterionic intermediate **3**. Other N-heteroaromatic compounds such as quinolines and pyridines are successfully applied for the N-arylation purpose. Subsequently, they have reported similar reactivity where terminal alkynes and ketones having α-hydrogen acts as the third component.[14]

Scheme 6.1: Three-Component Reaction of Arynes, N-Heteroaromatics and Nitriles.

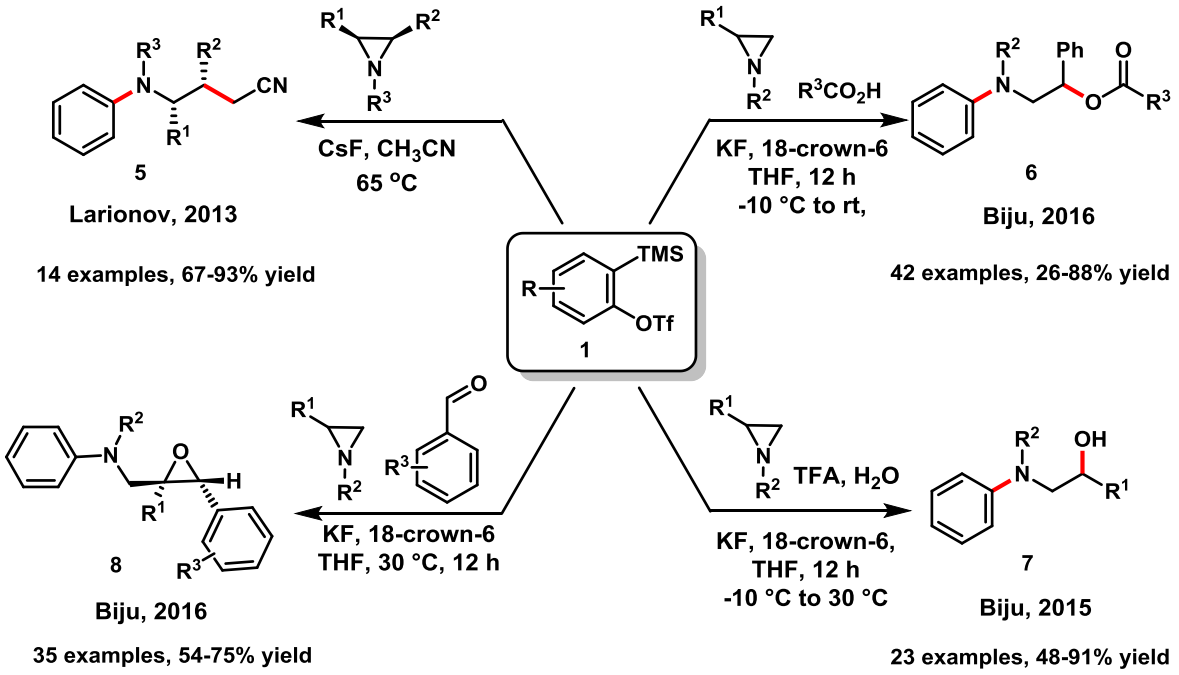


6.3. Aziridine as a Nucleophilic Trigger in Aryne MCRs

Larionov and co-workers developed a three-component reaction using arynes N-substituted aziridines and nitriles by exploiting the above mechanism to form the aminonitriles **5** in good yields.[15] In this case, the aziridines are used as a nucleophilic source and solvent CH_3CN as the third-component (Scheme 6.2). Recently, our group has also developed an aziridine triggered three component reactions where carboxylic acids are used as the third component to form the β-amino esters **6** in moderate to good yields.[16] In addition, an efficient method has been developed for the synthesis of *N*-aryl β-amino alcohols **7** in presence of trfluoroacetic acid and water.[17] Very recently, our group reported the MCRs of arynes, aziridines and aldehydes leading to the formation of *N*-aryl α-amino epoxides **8** in moderate to good yields and diastereoselectivity (Scheme 6.2).[18] It may be noted that, Nair and Kim reported the synthesis of indole from azirine and aryne generated

by the thermal decompositiom of benzenediazonium 2-carboxylate as early as 1975.[19] Apart from these reports, the utility of N-heterocycles in aryne MCRs has not been well-studied.

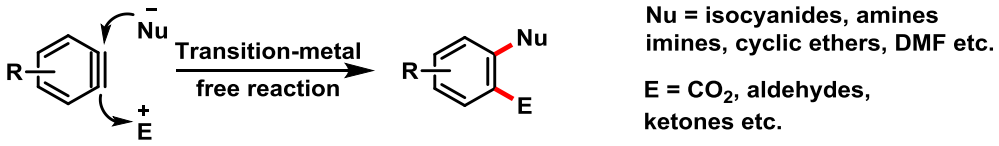
Scheme 6.2: Aziridine Triggered Aryne MCRs.



6.4. Statement of the Problem

In aryne MCRs, isocyanides are the commonly used nucleophilic trigger. In addition, amines, imines, cyclic ethers, DMF and DMSo are also used as the nucleophiles. Usually, the trapping agents used are carbonyl compounds including CO_2. However, the synthetic utility of N-heterocycles such as (iso)quinolines, pyridines are not well studied in aryne MCRs. In this context, we have carried out a systematic study on the reaction of N-heterocycles with arynes and suitable third-component (such as aldehydes, activated ketones, N-sunstituted isatins etc.). These results are presented in the following sections. It may be noted that the formation of a zwitterion from pyridine/isoquinoline and activated alkynes and its interception with third-components are already known in the literature.[20-23]

Scheme 6.3: MCRs Employing Arynes

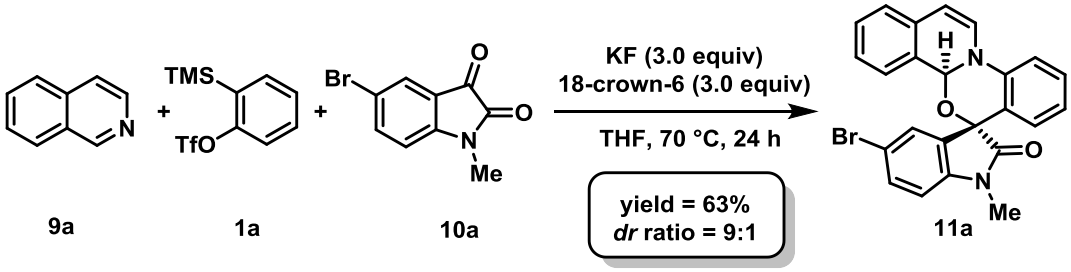


6.5. Results and Discussion

6.5.1. MCR Involving Isoquinoline, Arynes and N-Substituted Isatins

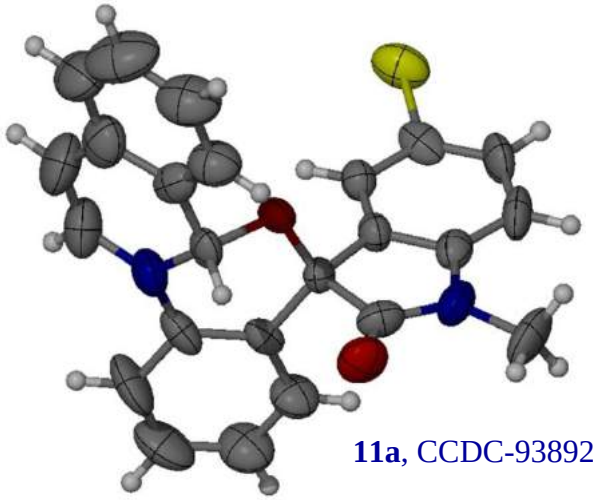
In a pilot experiment, isoquinoline **9a** and N-substituted isatin **10a** was treated with the aryne generated in situ from 2-(trimethylsilyl)aryl triflate **1a** using KF and 18-crown-6. Pleasingly, a facile reaction occurred resulting in the formation of the spirooxazino isoquinoline derivative **11a** in 63% yield with a moderate diastereoselectivity of 9:1 (Scheme 6.4). The optimization studies revealed that the use of other fluoride sources such as tetrabutylammonium fluoride (TBAF) and CsF were not beneficial, and reaction temperature below 70 °C was not efficient.

Scheme 6.4: Application of 1,4-Zwitterions in Multicomponent Synthesis.



The major diastereomer **11a** was separated by crystallization and its structure and stereochemistry was unequivocally confirmed by single-crystal X-ray analysis.

Figure 6.2: The ORTEP Diagram of **11a**

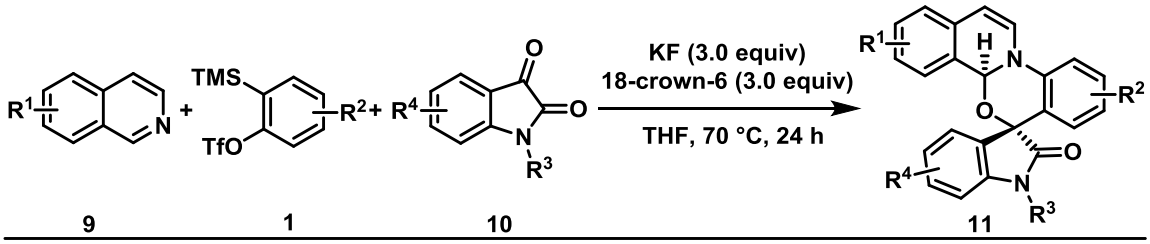


11a, CCDC-938921

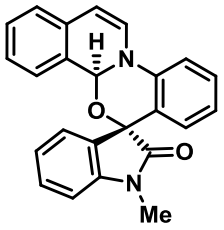
6.5.2. MCR Involving Isoquinoline, Arynes and Isatins: Substrate Scope

With this optimized reaction condition in hand, first we evaluated the substrate scope (Scheme 6.5) of this isoquinoline triggered aryne MCR.

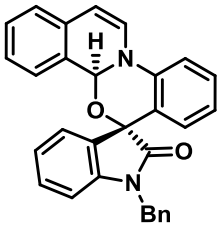
Scheme 6.5: MCR Involving Isoquinoline, Arynes and Isatins: Substrate Scope [a]



9 1 10 11

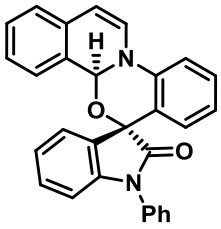


11b, 71%, (4:1)

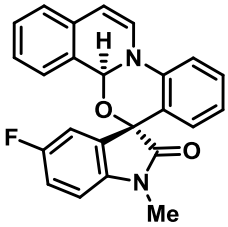


11c, 77%, (6:1)

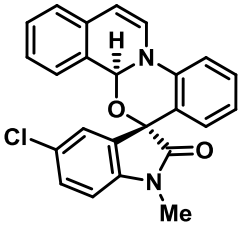
11d, 60%, (6:1)



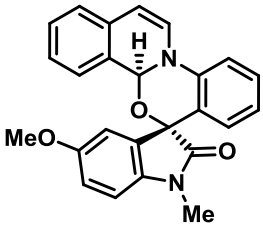
11e, 69%, (4:1)



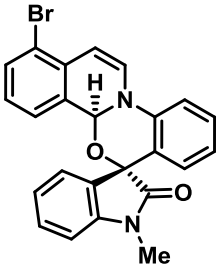
11f, 69%, (6:1)



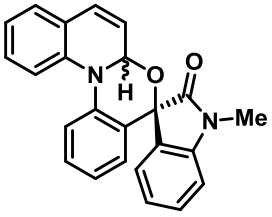
11g, 81%, (5:1)



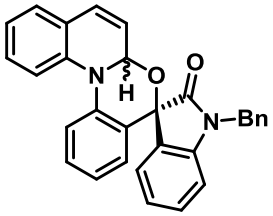
11h, 72%, (5:1)



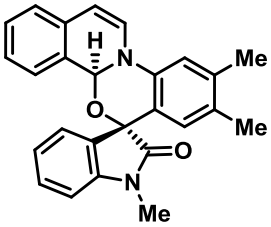
11i, 90%, (>20:1)



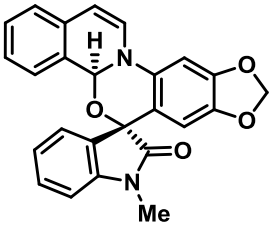
11j, 49%, (>20:1)



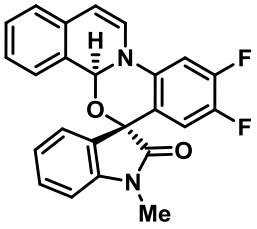
11k, 63%, (>20:1)[b]



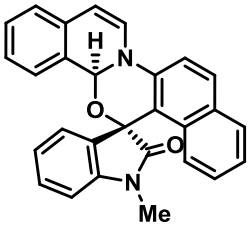
11l, 74%, (6:1)



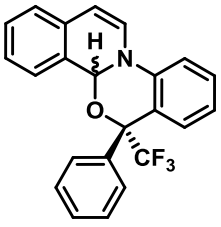
11m, 67%, (10:1)



11n, 70%, (12:1)



11o, 76%, (6:1)



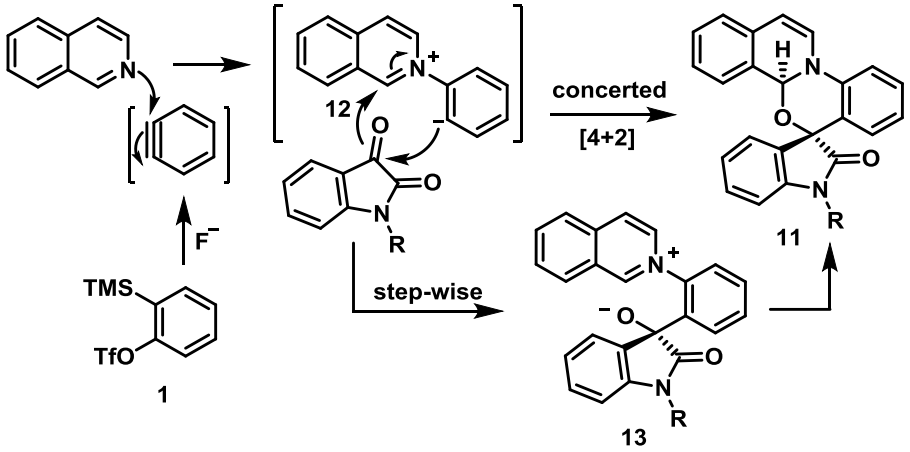
11p, 74%, (5:1)

[a] General conditions: **9** (0.5 mmol), **1** (0.75 mmol), **10** (0.5 mmol) KF (1.5 mmol), 18-crown-6 (1.5 mmol), THF (2.0 mL), 70 °C, 24 h. Yields of isolated products are given. Diastereomeric ratio determined by ^{1}H NMR analysis of crude reaction mixture was given in parentheses. [b] Reaction using 2.0 equiv of quinoline and 2.0 equiv of **1a**.

The reaction was well tolerated by various substituents on the nitrogen atom of isatin leading to inseparable mixture of oxazino isoquinoline derivatives in 60-77% yield and moderate diastereoselectivity (**11b-11e**). Moreover, electron withdrawing and -releasing groups at the carbocyclic ring of isatin resulted in the smooth conversion to the product (**11f-11h**). Interestingly, 5-bromoisoquinoline worked well leading to the formation of the desired products **11i** in good yield with excellent diastereoselectivity. Furthermore, this unique MCR is not limited to isoquinoline. Quinoline also worked well leading to the formation of the corresponding products in moderate yields and excellent diastereoselectivity thus demonstrating the versatility of the present reaction (**11j** & **11k**). Moreover, electronically different 4,5-disubstituted symmetrical arynes readily afforded the oxazino isoquinoline derivatives in good yields and diastereoselectivities (**11l-11n**). Interestingly, an unsymmetric aryne generated from 1-(trimethylsilyl)-2-naphthyltriflate furnished the desired product in 76% yield in a 6:1 ratio (**11o**). In this case, the observed regioselectivity may be due to the addition of isoquinoline to the least hindered position of naphthalyne. Additionally, the isatin component of the reaction can be replaced with an activated acyclic ketone leading to good yield of the desired product thereby significantly expanding the scope of the MCR (**11p**).

6.5.3. Proposed Reaction Mechanism of Isoquinoline Triggered MCR

Scheme 6.6: Plausible Reaction Mechanism of MCR Involving Isoquinoline, Arynes and N-Substituted Isatins.



The plausible mechanism for this reaction is shown in Scheme 6.6. The reaction proceeds via the initial generation of the 1,4-dipolar intermediate **12** from isoquinoline and

aryne, followed by its trapping with electrophilic carbonyl group of isatin in a concerted [4+2] cycloaddition mode to give the corresponding spiro[1,3]oxazino isoquinolines **11**. Alternatively, in a step-wise pathway, the 1,4-dipolar intermediate **12** can add to isatin, generating the alkoxide intermediate **13**, which undergoes intramolecular cyclization to generate the desired product **11**. The observed diastereoselectivity in this process suggest a step-wise path.

6.6. MCR Involving Pyridine, Arynes and N-Substituted Isatins

Inspired by the interesting results on the MCR of isoquinoline, arynes and N-substituted isatins, we then focused our efforts on pyridine derivatives as the nucleophilic source for the aryne MCRs with a perception that the reaction would offer the analogous pyridooxazino derivatives **16** (Scheme 6.7). Surprisingly, however, treating pyridine **14a** and N-substituted isatin **10b** with the aryne generated insitu from **1a** using KF and 18-crown-6 furnished the indolin 2-one derivative **15a** in 79% isolated yield (Scheme 6.7). The structure of **15a** was unequivocally confirmed by single-crystal X-ray analysis (Figure 6.3).

Scheme 6.7: Pyridine Triggered Aryne MCR.

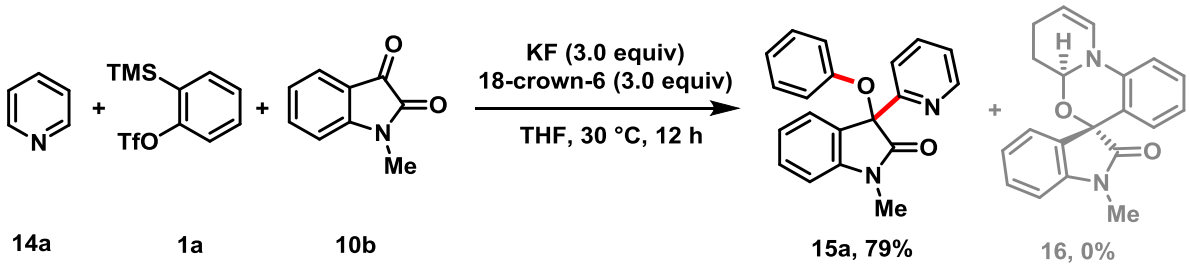
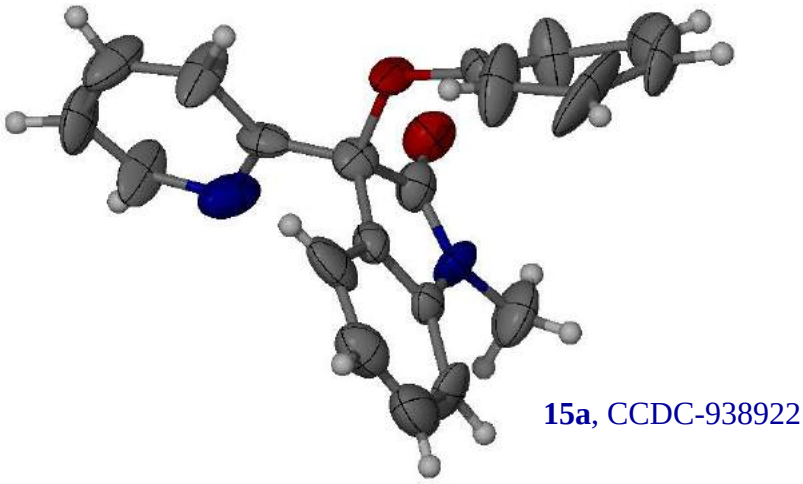


Figure 6.3: The ORTEP Diagram of **15a**



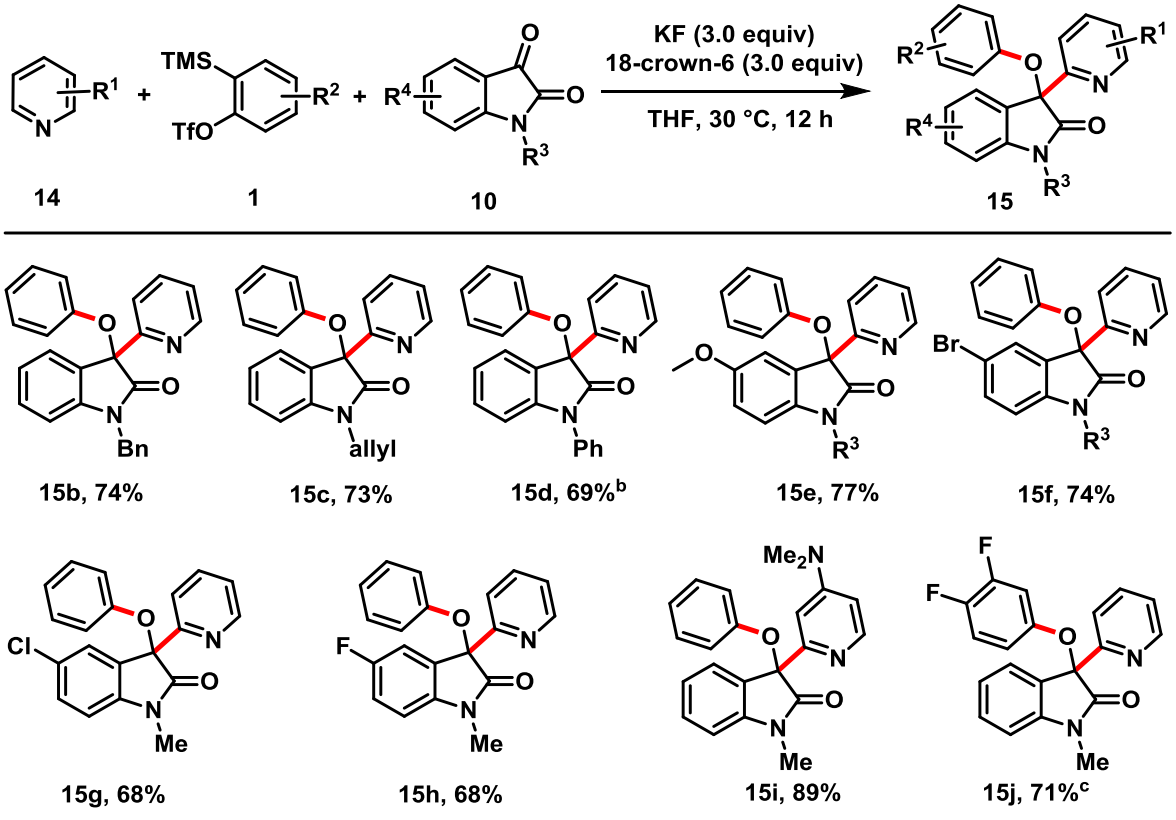
15a, CCDC-938922

The reaction proceeds via an unusual C–H bond functionalization of pyridine and the reaction resulted in the construction of new C-C and C-O bonds in one pot. Interestingly, no product derived from the initial generation of 1,4-dipolar intermediate from pyridine and aryne (analogous to **11**) and its interception with isatin was observed.[23] It is noteworthy that the use of other fluoride sources such as TBAF and CsF were not beneficial and the reaction at higher temperature (70 °C) reduced the yield of **15a**.

6.6.1. MCR Involving Pyridine, Arynes and Isatins: Substrate Scope

Though the reaction path of this pyridine triggered MCR was unclear, we examined the substrate scope of this unprecedented aryne MCR (Scheme 6.8). Various substituents on isatin nitrogen resulted in the smooth conversion to the indolin 2-one derivatives (**15b-15d**). In addition, electron releasing and -withdrawing groups at the carbocyclic ring of isatin are well tolerated leading to the desired products in moderate to good yields (**15e-15h**). Interestingly, 4-dimethylamino pyridine (DMAP) also worked well, furnishing the

Scheme 6.8: MCR Involving Pyridine, Arynes and N-Substituted Isatins: Substrate Scope [a]



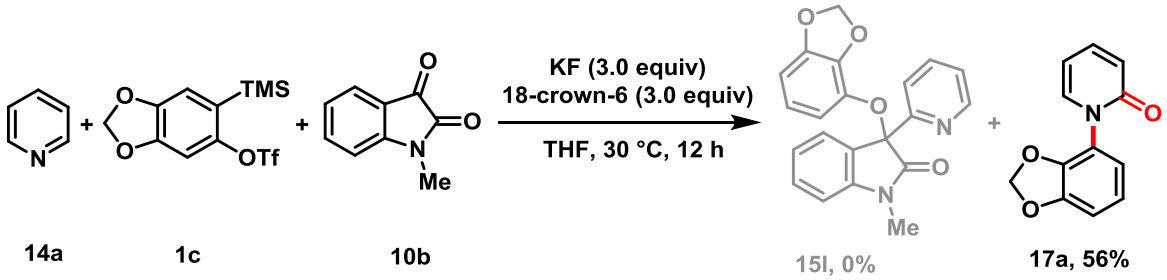
[a] General conditions: **14** (0.75 mmol), **1** (0.75 mmol), **10** (0.5 mmol) KF (1.5 mmol), 18-crown-6 (1.5 mmol), THF (2.0 mL), 30 °C, 12 h. Yields of isolated products are given. [b] Yield determined by ^{1}H NMR spectroscopy. [c] Reaction run on 0.25 mmol scale.

desired product **15i** in 89% yield. Moreover, symmetrical 4,5-difluorobenzyne derived the corresponding product **15j** in 71% yield.

6.6.2. Pyridine Triggered Aryne MCR: Mechanistic Experiments

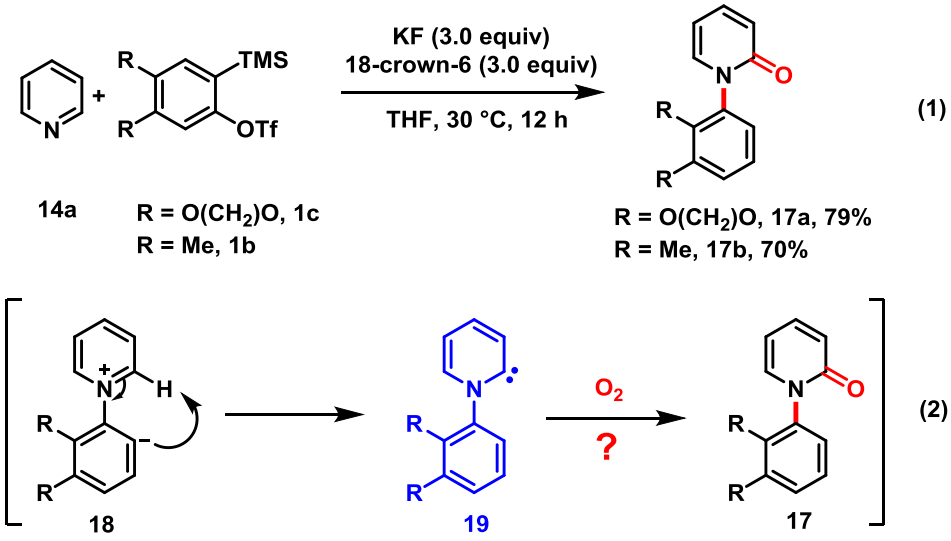
Interestingly, the reaction carried out using electron-rich 4,5-disubstituted symmetrical aryne precursors **1c** did not afford the expected indolin 2-one derivatives (**15l**), but instead furnished the N-aryl pyridin-2-one derivatives **17a** in 56% yield (Scheme 6.9).[24]

Scheme 6.9: MCR Involving Pyridine, Isatins and Electron-rich Aryne



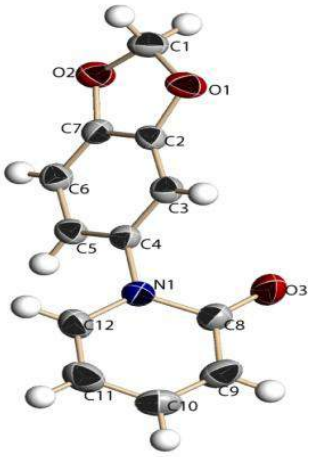
Since **17a** was formed from pyridine and aryne derived from **1c** without incorporating isatin **10b**, an additional experiment was performed without adding isatin under the optimized conditions (Scheme 6.10, eq. 1). As expected, a two component reaction of pyridine and the aryne generated from the precursor **1c** afforded **17a** in 79% yield. Similarly, aryne precursor **1b** furnished the corresponding product **17b** in 70% yiled (eq. 1). The structure of **17a** was confirmed by single-crystal X-ray analysis (Figure 6.4).

Scheme 6.10: Reaction of Pyridine and Electron rich Aryne in Optimized Conditions



These results indicates that the initially formed 1,4-dipolar intermediate **18** between pyridine and aryne (Scheme 6.10, eq. 2) undergoes an intramolecular proton transfer to form highly nucleophilic pyridylidene intermediate **19**, which was quenched by molecular oxygen to form the pyridine-2-one derivatives **17**.[25]

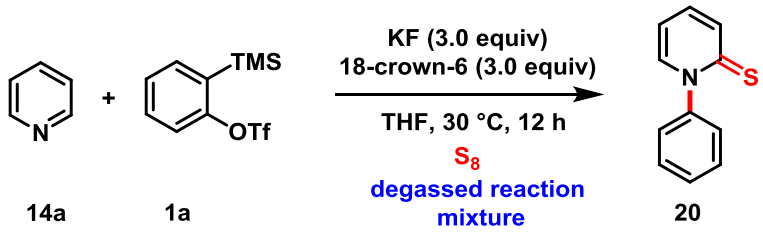
Figure 6.4: The ORTEP Diagram of **17a.**



17a, CCDC-938923

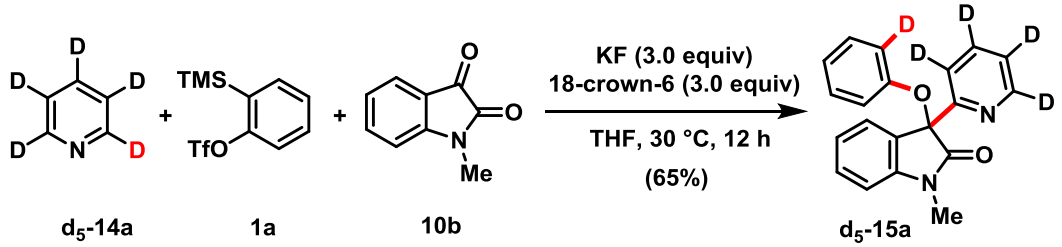
To get further insight on the proposed pyridylidene intermediate **19**, an experiment was conducted between aryne generated from **1a** and pyridine under degassed condition in presence of elemental sulphur (Scheme 6.11). Delightfully, the reaction furnished the desired 1-phenylpyridine-2(1*H*)-thione derivative[26] **20** in 16% yield. Although the yield of sulphur incorporated product **20** is less, this experiment strongly suggest the generation of a nucleophilic carbene intermediate.

Scheme 6.11: Sulphur Quenching Experiment of Pyridylidene Intermediate.



Furthermore, an experiment was performed using d_5-pyridine ***d*$_5$-14a** under the optimization conditions, and delightfully, the reaction furnished the ***d*$_5$-15a** in 65% yield with incorporation of deuterium at the *ortho*-position of the phenoxyl group (Scheme 6.12). This experiment is an indication of the intramolecular proton transfer to generate **19** (Scheme 6.10; Eq. 2)

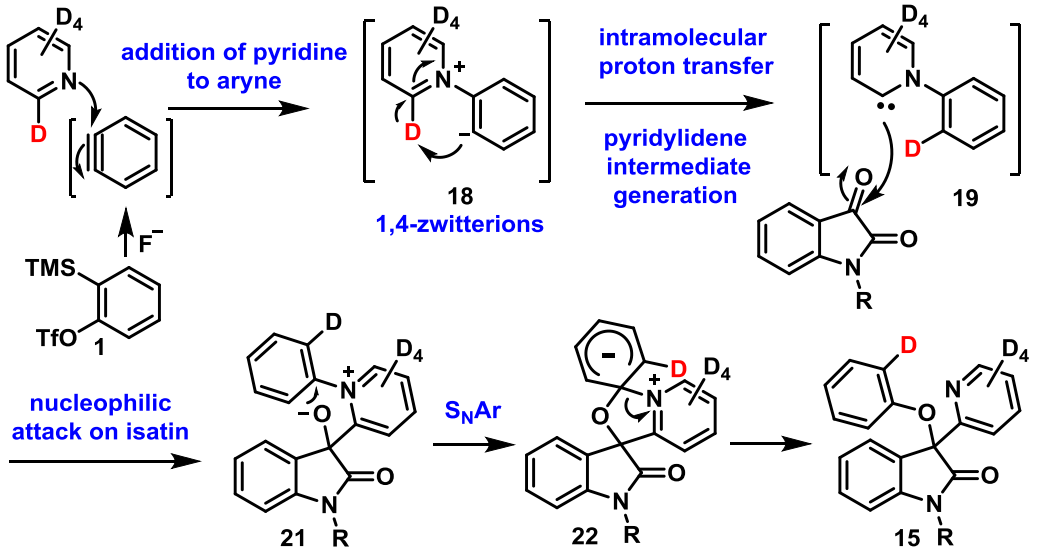
Scheme 6.12: Deuterium Labelling Experiment.



6.6.3. Pyridine Triggered Aryne MCR: Proposed Reaction Mechanism

Based on the results of our preliminary mechanistic investigation, we propose a plausible mechanism of this unprecedented aryne MCR as outlined in Scheme 6.13. First, the nucleophilic attack of pyridine on aryne generates the 1,4-dipolar intermediate **18**. In the absence of external proton source, **18** undergo an intramolecular proton transfer to generate the pyridylidene intermediate **19**. The nucleophilic intermediate **19** adds to isatin generating the tetrahedral intermediate **21**, which on intramolecular nucleophilic aromatic substitution generates the σ-complex **22** followed by ring opening rearrangement furnished the indolin 2-one **15**. In the case of electronically different aryne precursors **1b** and **1c**, the electron richness of the aryl ring (intermediate **21**) may hamper the formation of σ-complex **22** from **21** and hence corresponding indolin 2-ones were not formed in these cases. In addition, the generated pyridylidene intermediate was quenched by atmospheric oxygen to furnish **17a**.

Scheme 6.13: Possible Reaction Mechanism.



6.7. MCR Involving Quinolines, Arynes and Aldehydes

In view of the aryne MCRs triggered by pyridine and isoquinoline using N-substituted isatins as third-component, we then expanded the scope of this reaction using different third-component. The trapping agents planned aldehydes, benzil, thenil, phenzophenone, benzoquinone, acetophenone etc.

6.7.1. Optimization Studies

Initially we focused on aldehydes as third-component. The optimization study for the aryne MCR using aldehydes as the third-component began by the treatment of quinoline **23a**, 4-chlorobenzaldehyde **24a** and aryne generated in situ from 2-(trimethylsilyl)aryl triflate **1a** using 2.4 equiv of KF and 18-crown-6 in THF as a solvent at 30 ℃. Interestingly, under these mild reaction conditions oxazinoquinoline derivatives **25a** was formed in 43% yield with a 10:1 diastereoselectivity (Table 2.1, entry 1). The use of TBAF as fluoride source proved to be futile (entry 2). When the reaction was carried out using CsF as the fluoride source in PhCN solvent furnished the oxazinoquinoline in 22% yield with 10:1 *dr* (entry 3). Lowering the temperature to 0 °C increased the yield of the product but it decreased the *dr* (entry 4). Finally, performing the reaction at -10 °C to rt the *dr* increased to 10:1 (entry 5).

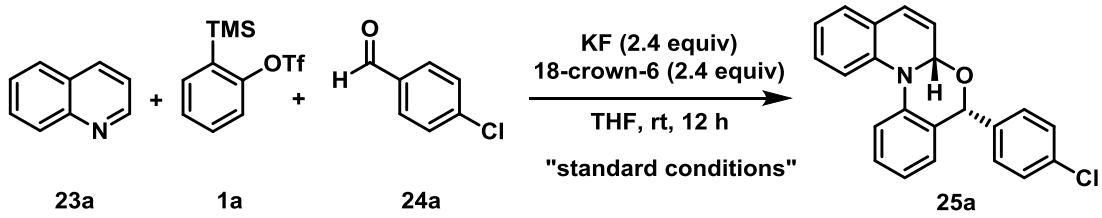


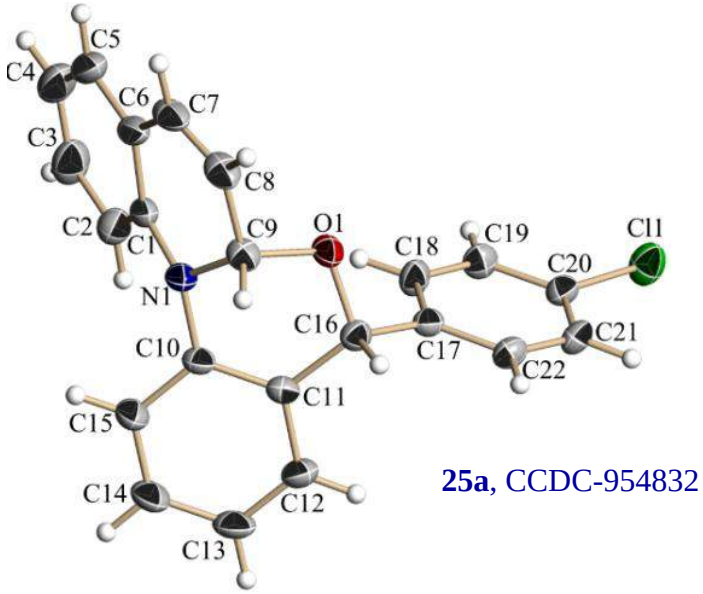
Table 6. 1: Optimization Studies on Quinoline Triggered MCRs of Arynes with Aldehydes

Entry	Variation of the standard conditions [a]	Yield of **25a** (%) [b]	*dr* [c]
1	None	43	10:1
2	TBAF instead of 18-crown-6 and KF	<5	nd
3[d]	CsF instead of 18-crown-6 and KF	22	10:1
4	Reaction at 0 °C to rt	70	6:1
5	**Reaction at -10 °C to rt**	**70(68)[e]**	**10:1**

[a] General conditions: **23a** (0.25 mmol), **1a** (0.30 mmol), **24a** (0.375 mmol) KF (0.60 mmol), 18-crown-6 (0.60 mmol), THF (1.0 mL), rt, 12 h. [b] The yields was determined by ^{1}H-NMR analysis of crude products using CH_2Br_2 as the internal standard. [c] Determined by ^{1}H-NMR analysis of crude mixture. [d] The reaction was carried out in benzonitrile as the solvent. [e] Isolated yield in 0.5 mmol scale in parentheses.

The major diastereomer **25a** was separated by crystallization and its structure and stereochemistry was unequivocally confirmed by single-crystal X-ray analysis (Figure 6.5).

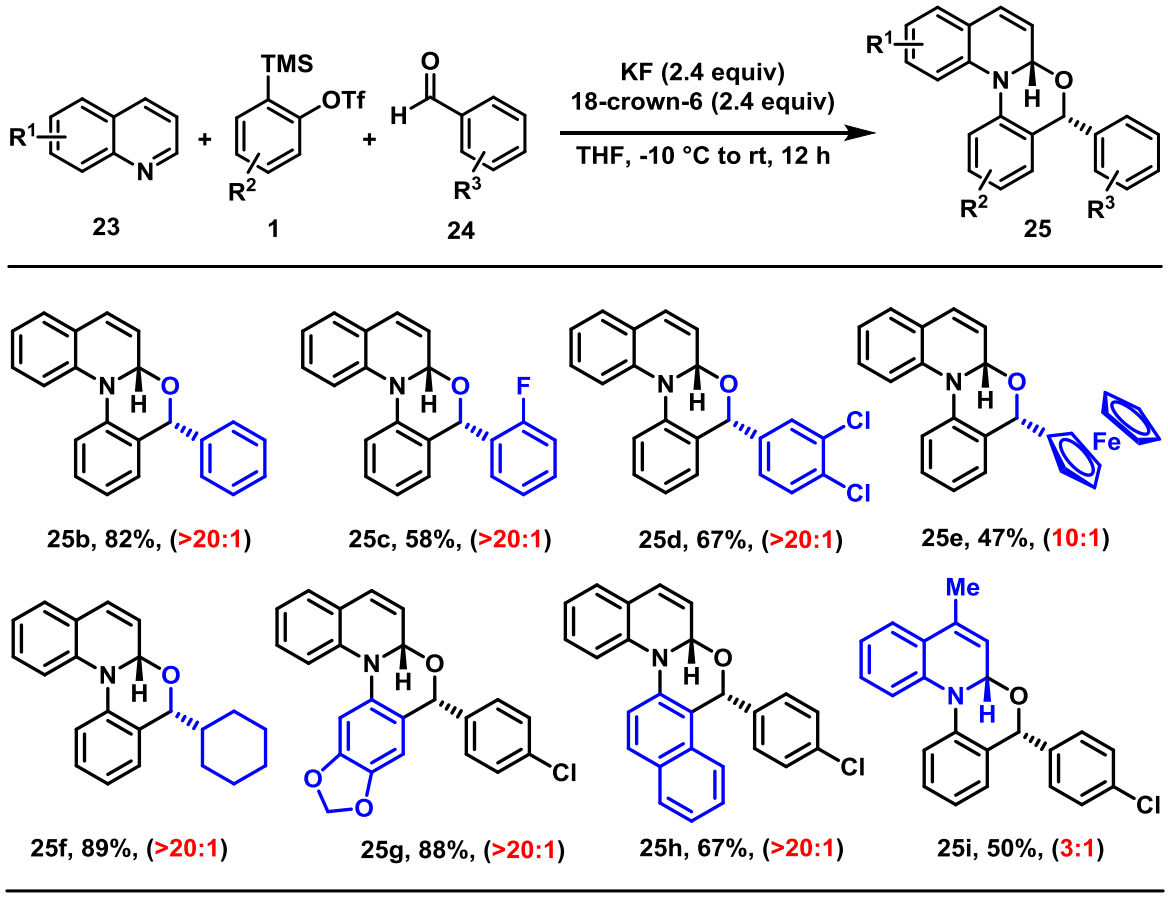
Figure 6.5: The ORTEP Diagram of **25a.**



6.7.2. MCR Involving Quinolines, Arynes and Aldehydes: Substrate Scope

With this reaction condition in hand, we then examined the substrate scope of this quinoline initiated aryne MCR (Scheme 6.14). First, we evaluated various aldehydes. Benzaldehyde was well tolerated, leading to benzooxazino quinoline derivatives in good yield and excellent diastereoselectivity (**25b**). Moreover, a fluoro substitution is tolerated at the 2-position of the aromatic ring of **24** resulting in the smooth conversion to the product with excellent diastereoselectivity (**25c**). Furthermore, disubstituted aldehyde worked well (**25d**). Interestingly, challenging aldehydes such as ferrocenecarboxaldehyde as well as aliphatic aldehydes also furnished moderate to good yields of the desired products, with excellent diastereoselectivity (**25e, 25f**). Moreover, the sesamol derived aryne afforded the corresponding product (Scheme 6.14) with good yields and excellent diastereoselectivity (**25g)**. Interestingly, the unsymmetrical naphthalyne underwent efficient MCR to deliver a single regioisomer, in 67% yield with >20:1 *dr* (**25h**). Furthermore, 4-methylquinoline furnished the desired product in moderate yield (**25i**).

Scheme 6.14: Substrate Scope: MCR Involving Isoquinoline Arynes with Aldehydes [a]

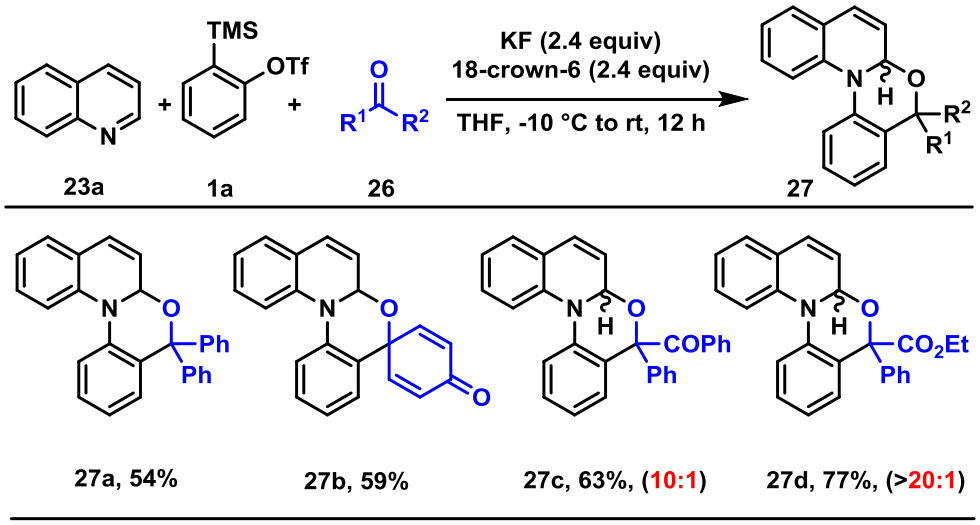


[a] General conditions: **23** (0.5 mmol), **1** (0.6 mmol), **24** (0.75 mmol) KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), -10 °C to rt, 12 h. Total yields of both diastereomers are given and the major diastereomer is shown. Diastereomeric ratio is given in parentheses and was determined by ^{1}H NMR analysis of crude reaction mixture.

6.8. MCR Involving Quinolines, Arynes and Ketones

Next, we evaluated the scope of activated ketones in this unique MCR (Scheme 6.15). Delightfully, benzophenone underwent efficient cyclization with quinoline and arynes leading to the formation of the 5,5-diphenyl benzooxazino quinoline derivative **27a** in 54% yield. Moreover, *p*-benzoquinone can be used as an effective carbonyl surrogate in this reaction, and the reaction afforded the spirobenzooxazino quinoline derivative **27b** in 59% yield. Additionally, benzil as well as ethylphenyl glyoxylate can also be used as the third-component in this MCR furnishing the desired products in moderate yield (**27c, 27d**).

Scheme 6.15: Substrate Scope: MCR Involving Quinoline, Aryne, and Ketones [a]

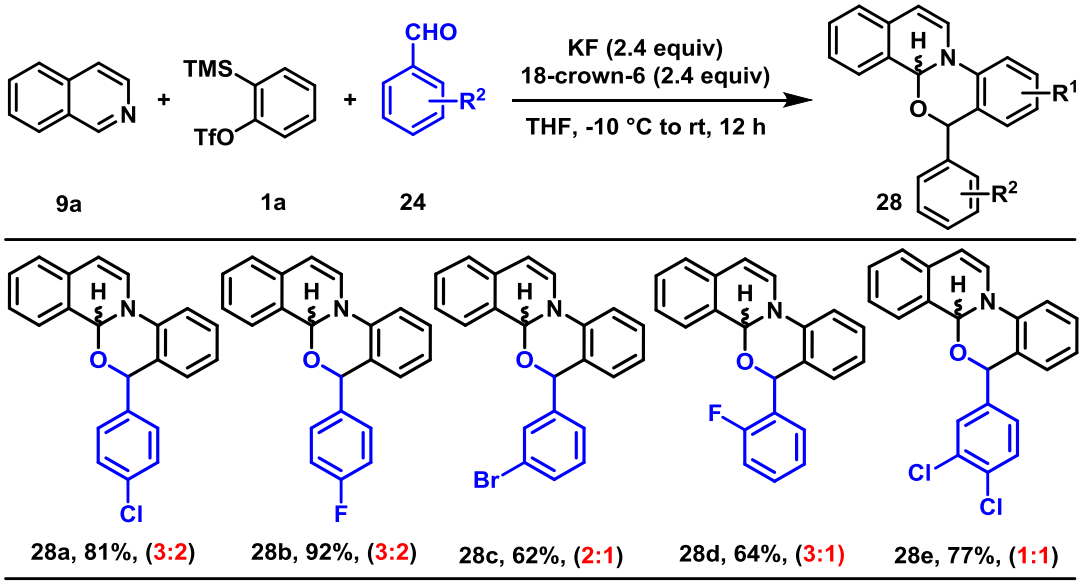


[a] General conditions: **23a** (0.5 mmol), **1a** (0.6 mmol), ketone **26** (0.75 mmol) KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), -10 °C to rt, 12 h. Diastereomeric ratio is given in parentheses and was determined by ^{1}H NMR analysis of crude reaction mixture

6.9. MCR Involving Isoquinolines, Arynes and Aldehydes

We also focused our attention on isoquinoline as the nucleophile for the aryne MCRs anticipating that the reaction would afford the analogous benzoxazino isoquinoline derivatives (Scheme 6.16). In an initial experiment, treatment of isoquinoline **9a** and 4-

Scheme 6.16: Substrate Scope: MCR Involving Isoquinoline, Aryne, and Aldehyde [a]



[a] General conditions: **9a** (0.5 mmol), **1a** (0.6 mmol), **24** (0.75 mmol) KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), -10 °C to rt, 12 h. Total yields of mixture of diastereomers are given. Diastereomeric ratio is given in parentheses and was determined by ^{1}H NMR analysis of crude reaction mixture.

chloro benzaldehyde with aryne precursor **1a** in the presence of the fluoride source afforded the benzoxazino isoquinoline derivatives as an inseparable mixture of diastereomers **28a** in 81% yield and 3:2 diastereomeric ratio. A variety of aromatic aldehydes with mono and disubstitution on the aromatic ring were well tolerated, leading to the desired heterocycle in good yields and diastereoselectivity up to 3:1(**28b-28e**).

6.10. Conclusion

In conclusion, we have developed a conceptually new MCR involving arynes, N-heterocycles and N-substituted isatins. When iso(quinoline) was used as the nucleophile, the reaction furnished the spirooxazino derivatives and the reaction proceeds via 1,4-dipolar intermediates. Interestingly, when pyridine was used as nucleophilic trigger, the reaction afforded indolin 2-one derivatives and the reaction is likely to proceed through a pyridylidene intermediate.[27] It is noteworthy to mention that the mechanistic difference in the reactivity of isoquinoline and pyridine towards aryne and isatin may be due to the less aromatic nature of the heterocyclic ring of isoquinoline, which facilitates the formation of spirooxazino derivatives (Scheme 6.4). Due to the relatively high aromaticity of pyridine, the corresponding spirocyclization is less favoured in this case.[28] We also developed a high yielding, practical and scalable MCRs of (iso)quinolines, arynes and aldehydes or activated ketones. Present protocol offers straightforward access to various benzoxazino (iso)quinoline derivatives, and the reaction proceeds via 1,4-dipolar intermediates.[29,30] The desired product was formed in moderate to good yields with good diastereoselectivity. High levels of functional group tolerance, mild reaction conditions, and high yields of products are the significant features of the present reaction. It is reasonable to assume that the protocol presented in this chapter is likely to find application in organic synthesis.

6.11. Experimental Details

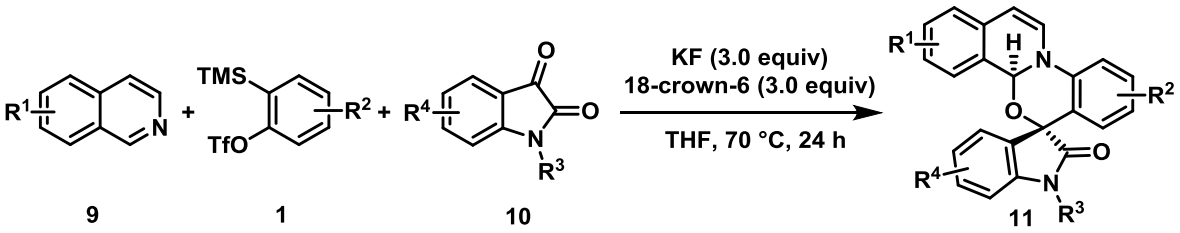
6.11.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. 30 °C corresponds to the room temperature of the lab when the experiments were carried out. THF was freshly purified by distillation over Na-benzophenone and was transferred under argon. 18-Crown-

6 was recrystallized from dry CH_3CN and KF was dried by heating at 110 °C for 12 h and left to cool under argon. The isatin derivatives were purchased from Sigma Aldrich or Acros and the N-alkylation was carried out by treating with the corresponding alkyl halides under basic condition following the known procedure.[31] Isoquinoline and quinoline were purchased from Aldrich and was purified by distillation prior to use. Dry pyridine was purchased from local sources and was purified by distillation and was stored under KOH. The 2(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** and the other symmetric and unsymmetric aryne precursors were synthesized following literature procedure.[32]

Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with solvents as indicated. All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400, 500 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm, DMSO-d_6: δH = 2.51 ppm, δC = 39.51 ppm). Infrared spectra were recorded on a Perkin-Elmer 1615 FT Infrared Spectrophotometer Model 60B. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

6.11.2. General Procedure for the MCR involving Isoquinoline, Aryne and Isatin

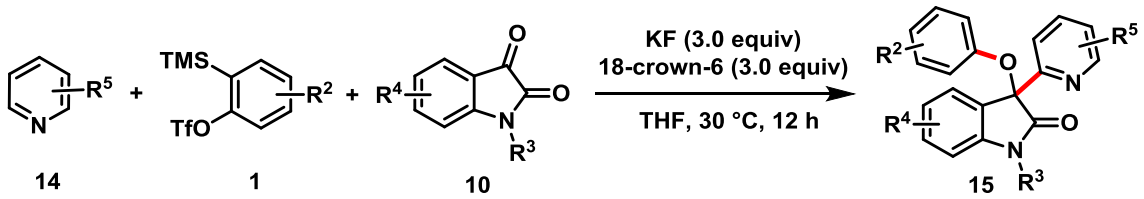


9 1 10 11

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.396 g, 1.5 mmol), KF (0.087 g, 1.5 mmol) and 1-methylindoline-2,3-dione **10** (0.50 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C for 5 min. To the stirring solution was then added isoquinoline **9** (0.50 mmol) and the aryne precursor **1** (0.75 mmol). Then the reaction mixture was placed in preheated oil bath at 70° C. When TLC control showed the

completion of the reaction (typically after 24 h), the reaction mixture cooled to room temperature and the solvent was evaporated and the crude residue was subsequently purified by flash column chromatography on silica gel to afford the corresponding spirooxazino isoquinoline derivatives **11** as an inseparable mixture of diastereomers in moderate to good yields. The dr was determined by ^{1}H NMR analysis of crude reaction mixture.

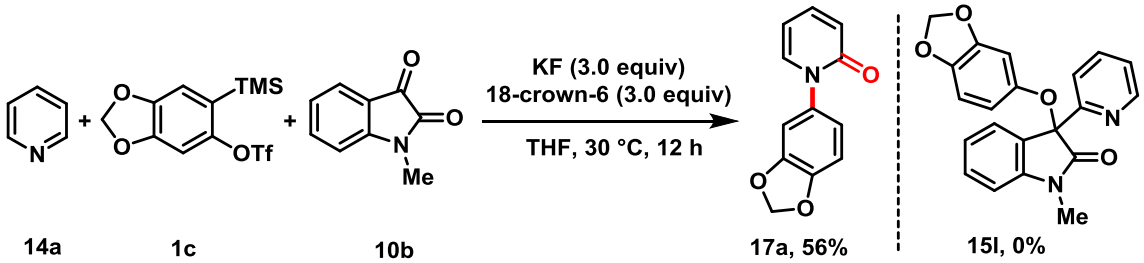
6.11.3. General Procedure for the MCR involving Pyridine, Aryne and Isatin



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.396 g, 1.5 mmol), KF (0.087 g, 1.5 mmol) and 1-methylindoline-2,3-dione **10** (0.50 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C for 5 min. To the stirring solution was added pyridine **14** (0.75 mmol) and the aryne precursor **1** (0.75 mmol). When TLC control showed the completion of the reaction (typically after 12 h), the reaction stopped and the crude reaction mixture was purified by column chromatography on silica gel to afford the corresponding indolin 2-one derivatives **15** in good yields.

6.11.4. Mechanistic Experiments

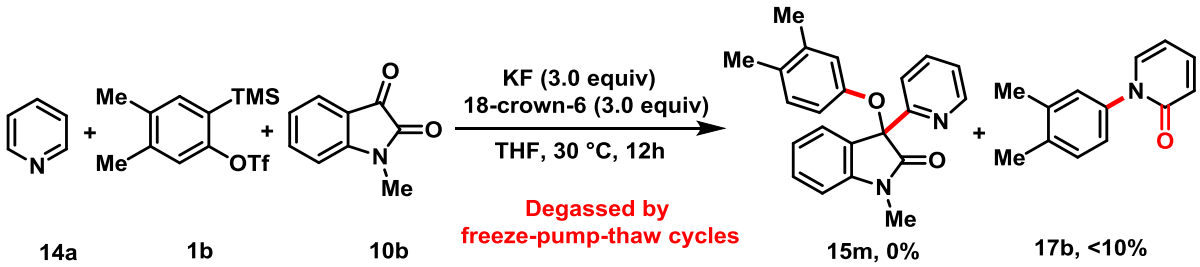
Attempted Multicomponent Reaction of Pyridine with Electronically Different Aryne Precursor and Isatin



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.396 g, 1.5 mmol), KF (0.087 g, 1.5 mmol) and 1-methylindoline-2,3-dione **10b** (0.50 mmol). Then the screw-capped tube was evacuated and backfilled with

argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C for 05 min. To the stirring solution was added pyridine **14a** (0.75 mmol) and 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate **1c** (0.75 mmol) and the reaction mixture was stirred for 12h. The crude reaction mixture was then purified by column chromatography on silica gel to afford the 1-(benzo[*d*][1,3]dioxol-4-yl)pyridin-2(1*H*)-one **17a** in 56% yield. Interestingly, under the reaction conditions, the multicomponent product **15l** was not observed.

Attempted Multicomponent Reaction of Pyridine with Aryne Precursor (2b) and Isatin under Degassing Condition

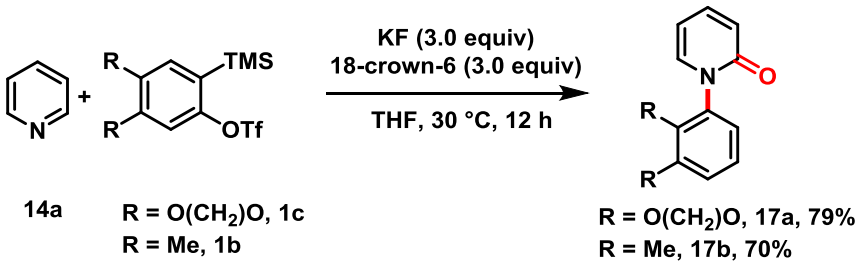


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18- crown-6 (0.396 g, 1.5 mmol) KF (0.087 g, 1.5 mmol) and 1-methylindoline-2,3-dione **10b** (0.080 g, 0.50 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere followed by the addition of pyridine **14a** (0.060 mg, 60 µL, 0.75 mmol). Then the resultant reaction mixture was subjected to degassing (freeze-pump-thaw cycles). The resultant reaction mixture was kept stirring at 30 °C for 5 min. To the stirring solution was 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1b** (0.244 g, 0.75 mmol) and the reaction mixture was stirred at 30 °C for 12h. The crude reaction mixture was then purified by flash column chromatography on silica gel to afford the 1-(3,4-dimethylphenyl)pyridin-2(1*H*)-one **17b** in <10% yield and 89% of the isatin derivative **10b** was recovered. Interestingly, under the reaction conditions, the multicomponent product **15m** was not observed.

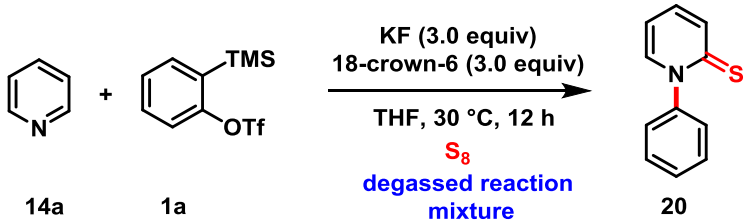
Reaction of arynes with pyridine

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.198 g, 0.75 mmol) and KF (0.043 g, 0.75 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C

for 05 min. To the stirring solution was added pyridine **14a** (0.75 mmol) and aryne precursors **1c** or **1b** (0.75 mmol) and stirred the reaction mixture for 12h. The reaction stopped after 12 h and the crude reaction mixture was purified by column chromatography on silica gel to afford pyridin-2(1*H*)-one **17a** and **17b**.



Attempted Reaction of Pyridine with Aryne Precursor in the Presence of Sulphur



1-Phenylpyridine-2(1*H*)-thione

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18- crown-6 (0.396 g, 1.5 mmol) and KF (0.087 g, 1.5 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere followed by the addition of pyridine **14a** (0.040 mg, 54 µL, 0.50 mmol). Then the resultant reaction mixture was subjected for degassing (freeze-pump-thaw cycles). The resultant reaction mixture was kept stirring at 30 °C for 5 min. To the stirring solution was added 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) and the reaction mixture was stirred at 30 °C for 2h followed by the addition of sulphur (0.032 g, 1.0 mmol) and stirred the reaction mixture for 12h. The crude reaction mixture was then purified by flash column chromatography (Pet. ether /EtOAc = 75/25) on silica gel to afford the 1-phenylpyridine-2(1*H*)-thione **20** as a yellow solid (0.015 g, 16 % yield).

***R*$_f$** (Pet. ether /EtOAc = 30/70): 0.32.

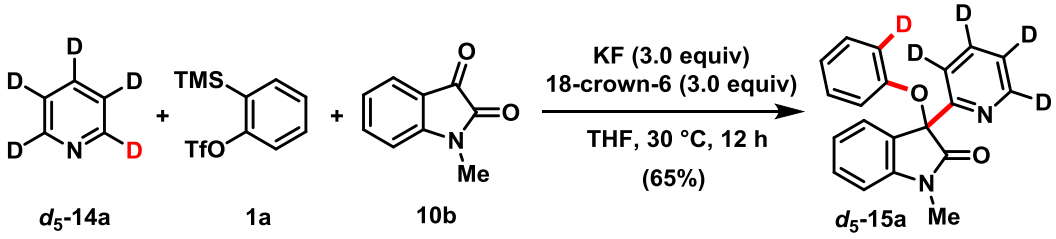
^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.76 (d, *J* = 8.8 Hz, 1H), 7.61 (bs, 1H), 7.54 (t, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.28-7.26(m, 1H), 6.70 (bs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 181.38, 143.83, 139.75, 135.71, 133.39, 128.74, 128.28, 125.59, 111.75.

HRMS: calculated $[M+H]^+$ for $C_{11}H_{10}SN$: 188.0528, found: 188.0529.

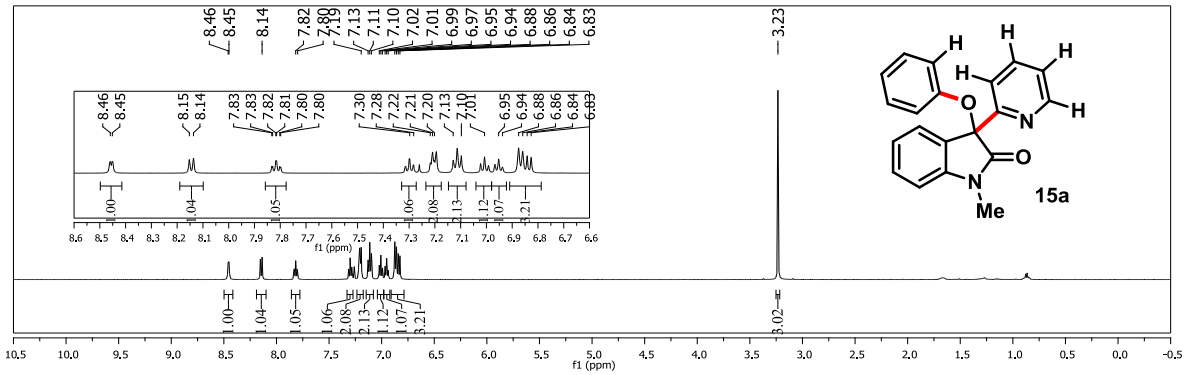
FTIR (cm^{-1}): 3061, 3016, 1715, 1635, 1612, 1567, 1488, 1471, 1421, 1369, 1347, 1300, 1251, 1217, 1130, 1091, 1025, 1001, 977, 953, 752, 691, 666.

Reaction of pyridine-d_5 with aryne and isatin

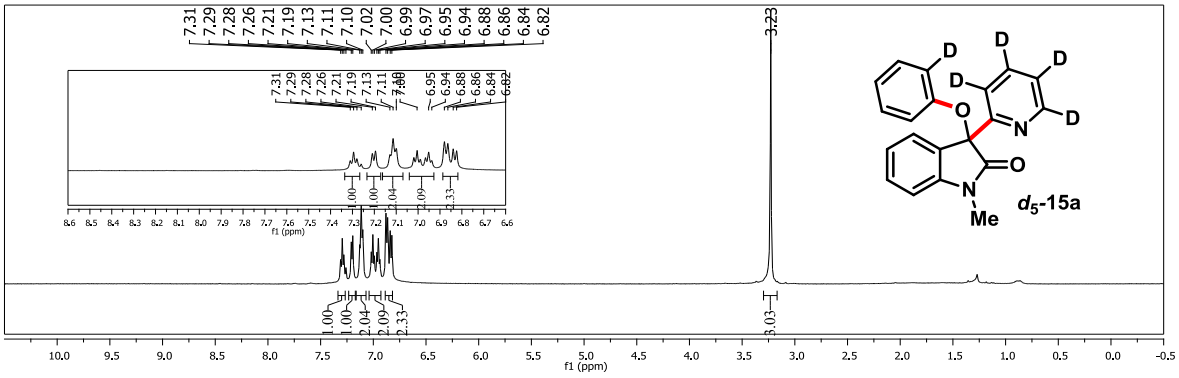


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.396 g, 1.5 mmol), KF (0.087 g, 1.5 mmol) and 1-methylindoline-2,3-dione **10b** (0.080 g, 0.50 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C for 5 min. To the stirring solution was added d_5-pyridine ***d*$_5$-14a** (0.063 g, 60 µL, 0.75 mmol) and the aryne precursor **1a** (0.223 g, 182 µL, 0.75 mmol). When TLC control showed the completion of the reaction (typically after 12 h), the reaction stopped and the crude reaction mixture was purified by column chromatography on silica gel to afford the corresponding indolin 2-one derivatives ***d*$_5$-15a** in 65% yield.

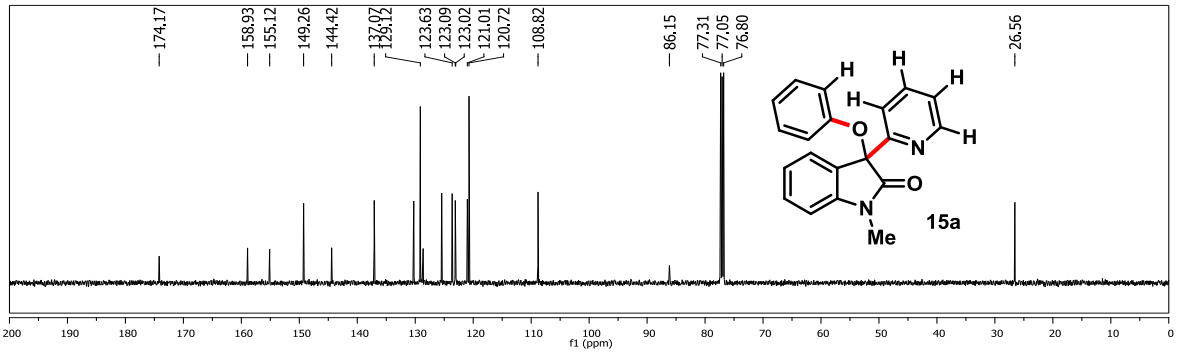
^{1}H NMR Spectrum of 15a



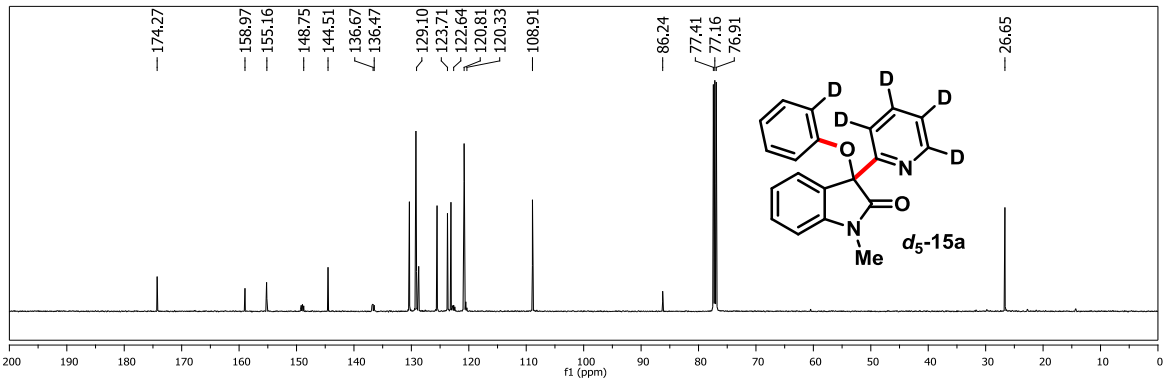
^{1}H NMR Spectrum of d_5-15a



^{13}C NMR Spectrum of 15a

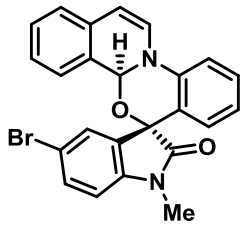


^{13}C NMR Spectrum of d_5-15a



6.11.5. Synthesis and Characterization of Spirooxazino Isoquinolines

5'-bromo-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11a)



11a

Following the general procedure, treatment of isoquinoline **9a** (0.129 g, 118 µL, 1.0 mmol) and 5-bromo-1-methylindoline-2,3-dione (0.240 g, 1.0 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.447 g, 364 µL, 1.5 mmol) in the presence of KF (0.174 g, 3.0 mmol) and 18-crown-6 (0.793 g, 3.0 mmol) in THF (4.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 5'-bromo-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one as inseparable mixture of diastereomers as a white solid (0.281 g, 63%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 9:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.63

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.45-7.39 (m, 3H), 7.35-7.29 (m, 3H), 7.21-7.11 (m, 3H), 7.00-6.96 (m, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.83 (d, *J* = 7.6 Hz, 1H), 3.29 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 175.62, 143.35, 141.62, 133.65, 132.99, 131.62, 129.56, 129.06, 128.90, 128.04, 126.54, 126.17, 125.43, 124.94, 124.73, 124.43, 123.73, 118.79, 116.11, 110.07, 100.70, 80.91, 79.62, 26.57.

Representative Peaks of Minor Isomer:

^{1}H NMR δ: 7.63-7.54 (m), 6.80 (d, *J* = 8.4 Hz), 3.14 (s).

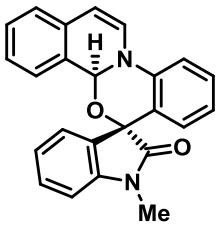
^{13}C NMR δ: 143.15, 142.14, 136.12, 134.05, 133.25, 129.29, 128.69, 128.20, 126.74, 110.27, 100.85, 81.74, 80.31, 26.79.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{18}O_2N_2Br$: 445.0546, found: 445.0563.

FTIR (cm^{-1}): 3015, 2939, 1851, 1788, 1774, 1716, 1637, 1608, 1568, 1488, 1463, 1424, 1358, 1342, 1257, 1217, 1141, 1101, 1057, 1026, 954, 899, 812, 756, 713.

1'-Methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11b)

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 1-methylindoline-2,3-dione (0.080 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087



11b

g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one as inseparable mixture of diastereomers as a white solid (0.130 g, 71%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 4:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.57.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.50-7.47 (m, 2H), 7.43-7.35 (m, 3H), 7.32-7.30 (m, 1H), 7.28-7.27 (m, 1H), 7.24-7.16 (m, 2H), 7.08-6.90 (m, 3H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 5.87 (d, *J* = 7.6 Hz, 1H), 3.33 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 176.11, 144.22, 141.60, 131.69, 131.61, 130.09, 129.30, 129.11, 128.89, 128.64, 126.62, 126.19, 125.09, 124.98, 124.81, 124.19, 123.61, 123.43, 118.45, 108.42, 100.57, 80.64, 79.76, 26.37.

Representative Peaks of Minor Isomer:

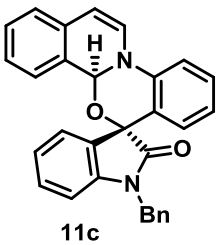
^{1}H NMR δ: 7.54-7.53 (m), 6.65-6.60 (m), 5.89 (d, *J* = 7.3 Hz), 3.18 (s).

^{13}C NMR δ: 174.94, 130.32, 126.89, 126.74, 125.72, 124.49, 123.49, 118.28, 108.60, 100.44, 81.47, 26.60.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{19}O_2N_2$: 367.1441, found: 367.1438.

FTIR (cm^{-1}): 3062, 3011, 2961, 2933, 1949, 1719, 1659, 1630, 1613, 1567, 1488, 1471, 1458, 1418, 1433, 1369, 1345, 1300, 1274, 1250, 1216, 1170, 1157, 1130, 1025, 1001, 976, 953, 905, 877, 861, 753, 695, 665, 650, 623, 570.

1'-Benzyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11c)



11c

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 1-benzylindoline-2,3-dione (0.119 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 1'-benzyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-

a]isoquinoline-6,3'-indolin]-2'-one as inseparable mixture of diastereomers as a white solid (0.172 g, 77%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 6:1).

R_f (Pet. ether /EtOAc = 70/30): 0.61.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.43-7.36 (m, 4H), 7.33-7.29 (m, 4H), 7.23-7.19 (m, 1H), 7.17-7.14 (m, 2H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.99-6.95 (m, 1H), 6.94-6.89 (m, 2H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 5.82 (d, *J* = 7.6 Hz, 1H), 5.16 (d, *J* = 15.7 Hz, 1H), 4.85 (d, *J* = 15.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.29, 143.44, 141.76, 135.81, 131.73, 130.16, 129.47, 129.20, 129.07, 129.02, 128.83, 127.95, 127.48, 126.75, 126.26, 126.14, 125.06, 125.03, 124.33, 123.74, 123.61, 118.62, 109.56, 100.68, 80.69, 79.83, 43.96.

Representative Peaks of Minor Isomer:

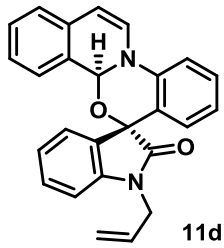
^{1}H NMR δ: 7.51(s), 7.11(s), 7.06(s), 6.82 (d, *J* = 7.9 Hz), 6.66(m), 5.87 (d, *J* = 7.6 Hz), 5.04 (d, *J* = 15.7 Hz), 4.66 (d, *J* = 15.6 Hz).

^{13}C NMR δ: 175.28, 143.09, 142.13, 130.27, 128.94, 128.66, 127.84, 127.57, 125.83, 124.64, 118.50, 109.78, 81.67, 44.24.

HRMS: calculated $[M+H]^+$ for $C_{30}H_{23}O_2N_2$: 443.1754, found: 443.1756.

FTIR (cm^{-1}): 3065, 3018, 2927, 2401, 1715, 1614, 1489, 1468, 1434, 1346, 1291, 1216, 1174, 1102, 1078, 1044, 1029, 1009, 977, 756, 698, 668.

1'-Allyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11d)



11d

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 1-allylindoline-2,3-dione (0.080 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 1'-allyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one as inseparable mixture of diastereomers as a white solid (0.119 g, 60%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 6:1).

R_f (Pet. ether /EtOAc = 70/30): 0.65.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H),7.38-7.32 (m, 3H), 7.30-7.15 (m, 3H), 7.05 (d, *J* = 7.4 Hz, 1H), 7.02-6.93 (m, 3H), 6.90 (d, *J* = 7.9 Hz, 1H),

6.72 (d, *J* = 8.1 Hz, 1H), 6.03-5.93 (m, 1H), 5.84 (d, *J* = 7.6 Hz, 1H), 5.43-5.33 (m, 2H), 4.57-4.51 (m, 1H), 4.43-4.35 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.99, 143.52, 141.72, 131.76, 131.71, 131.29, 130.07, 129.41, 129.17, 128.96, 128.77, 126.69, 126.09, 125.08, 125.01, 124.60, 124.29, 123.64, 123.55, 118.54, 118.05, 109.41, 100.66, 80.68, 79.77, 42.49.

Representative Peaks of Minor Isomer:

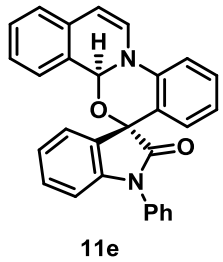
^{1}H NMR δ: 7.55 (d, *J* = 7.6 Hz), 7.44-7.40 (m), 6.68 (d, *J* = 8.2 Hz), 5.29-5.25 (m), 4.26-4.20 (m).

^{13}C NMR δ: 175.89, 143.24, 130.26, 128.69, 126.24, 125.79, 118.43, 109.64, 100.56, 81.61, 42.78.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{21}O_2N_2$: 393.1598, found: 393.1596.

FTIR (cm^{-1}): 2925, 2856, 1716, 1612, 1488, 1466, 1354, 1285, 1196, 1175, 1101, 1023, 999, 933, 750, 692, 598.

1'-Phenyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11e)



11e

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 1-phenylindoline-2,3-dione (0.112 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 1'-phenyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one as inseparable mixture of diastereomers as a white solid (0.147 g, 69%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 4:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.71.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63-7.45 (m, 8H), 7.40-7.34 (m, 3H), 7.29-7.19 (m, 3H), 7.13 (d, *J* = 7.1 Hz, 1H), 7.06-6.98 (m, 3H), 6.92 (d, *J* = 5.5 Hz, 1H), 5.88 (d, *J* = 7.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.47, 144.16, 141.65, 134.13, 131.66, 131.54, 130.01, 129.80, 129.43, 129.22, 128.95, 128.83, 128.35, 126.93, 126.69, 126.54, 126.47, 126.10, 125.25, 124.99, 124.28, 124.12, 123.67, 118.68, 109.83, 100.74, 80.85, 79.79.

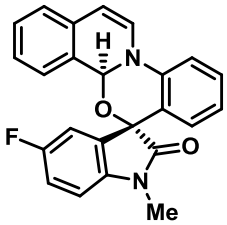
Representative Peaks of Minor Isomer:

^{13}C NMR δ: 174.17, 143.93, 142.20, 129.55, 129.47, 129.35, 128.74, 126.63, 126.05, 125.80, 124.63, 124.06, 123.73, 118.57, 109.98, 100.57, 81.71, 81.41.

HRMS: calculated $[M+H]^+$ for $C_{29}H_{21}O_2N_2$: 429.1598, found: 429.1607.

FTIR (cm^{-1}): 2928, 1728, 1657, 1629, 1481, 1454, 1429, 1363, 1303, 1248, 1201, 1168, 1100, 1026, 932, 746, 696.

5'-fluoro-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11f)



11f

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 5-fluoro-1-methylindoline-2,3-dione (0.090 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 5'-fluoro-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one as inseparable mixture of diastereomers as a white solid (0.134 g, 69%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 6:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.59.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.48-7.45 (m, 2H), 7.38-7.21 (m, 3H), 7.24-7.11 (m, 2H), 7.04-6.90 (m, 3H), 6.83-6.75 (m, 2H), 6.67 (d, *J* = 7.6 Hz, 1H), 5.83 (d, *J* = 7.6 Hz, 1H), 3.31 (s, 3H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) δ 176.70, 159.75 (d, *J* = 244.0 Hz), 141.63, 140.21, 136.12, 133.33 (d, *J* = 8.3 Hz), 131.66, 129.53, 129.14, 129.01, 126.54, 126.17, 125.7 (d, *J* = 15.2 Hz), 124.83, 124.40, 123.68, 118.74, 116.44 (d, *J* = 23.8 Hz), 112.98 (d, *J* = 25.3 Hz), 109.2 (d, *J* = 8.1 Hz), 100.88, 80.92, 79.88, 26.51.

Representative Peaks of Minor Isomer:

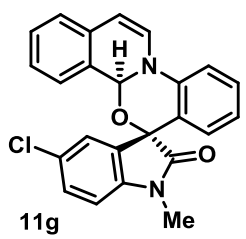
^{1}H NMR δ: 6.63-6.56 (m), 5.88-5.85 (m), 3.16 (s).

^{13}C NMR δ: 175.97, 160.01, 129.24, 128.90, 128.70, 126.09, 26.82.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{18}O_2N_2F$: 385.1347, found: 385.1347.

FTIR (cm^{-1}): 2926, 2729, 1735, 1604, 1460, 1377, 1353, 1299, 1251, 1269, 1215, 1123, 1038, 990, 950, 760, 723.

5'-Chloro-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11g)



11g

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 5-chloro-1-methylindoline-2,3-dione (0.098 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 5'-chloro-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one as inseparable mixture of diastereomers as a white solid (0.162 g, 81%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 5:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.58.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45-7.42 (m, 2H), 7.33-7.30 (m, 2H), 7.27-7.25 (m, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.19-7.11 (m, 2H), 7.04-6.85 (m, 3H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 5.82 (d, *J* = 7.7 Hz, 1H), 3.28 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.72, 142.83, 141.60, 133.31, 131.62, 130.08, 129.54, 129.10, 129.04, 128.98, 128.89, 126.51, 126.16, 125.45, 125.32, 124.74, 124.41, 123.71, 118.77, 109.58, 100.85, 80.90, 79.67, 26.59.

Representative Peaks of Minor Isomer:

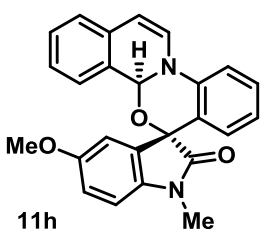
^{1}H NMR δ: 7.50-7.49 (m), 7.38-7.36 (m), 6.63-6.55 (m), 5.84 (d, *J* = 7.3 Hz), 3.13 (s).

^{13}C NMR δ: 174.60, 142.64, 142.13, 136.11, 133.67, 130.32, 129.27, 128.67, 126.67, 125.96, 125.77, 124.96, 109.73, 81.72, 80.35, 26.80.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{18}O_2N_2Cl$: 401.1051, found: 401.1051.

FTIR (cm^{-1}): 2956, 2933, 2873, 1723, 1637, 1610, 1488, 1460, 1432, 1360, 1340, 1312, 1251, 1103, 1025, 955, 812, 769, 725, 692.

5'-Methoxy-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11h)



Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 μL, 0.50 mmol) and 5-methoxy-1-methylindoline-2,3-dione (0.096 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 μL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 5'-methoxy-1'-methyl-4b*H*-spiro [benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one as inseparable mixture of diastereomers as a white solid (0.143 g, 72%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 5:1).

R_f (Pet. ether /EtOAc = 70/30): 0.46.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53-7.49 (m, 2H), 7.33 (s, 3H), 7.22-7.17 (m, 2H), 6.98-6.94 (m, 2H), 6.82 (d, *J* = 11.3 Hz, 2H), 6.71-6.64 (m, 2H), 5.83 (d, *J* = 6.8 Hz, 1H), 3.68 (s, 3H, CH_3), 3.31 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.03, 156.75, 141.57, 137.63, 132.81, 131.69, 129.39, 129.20, 128.90, 128.73, 126.71, 126.18, 126.06, 125.06, 124.26, 123.51, 118.45, 115.11, 111.58, 109.05, 100.59, 80.74, 80.21, 55.87, 26.51.

Representative Peaks of Minor Isomer:

^{1}H NMR δ: 3.85 (s), 3.17(s).

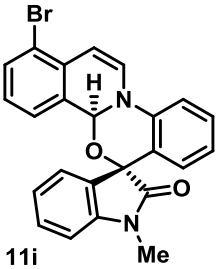
^{13}C NMR δ: 174.79, 156.69, 142.07, 137.50, 133.51, 131.93, 129.96, 126.83, 129.79, 125.69, 124.70, 124.57, 123.58, 118.35, 114.19, 112.74, 109.00, 100.50, 81.54, 80.92, 56.01, 26.75.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{21}O_3N_2$: 397.1547, found: 397.1554.

FTIR (cm^{-1}): 2868, 1695, 1637, 1602, 1490, 1451, 1349, 1286, 1206, 1163, 1105, 1031, 949, 837, 754, 702.

1-Bromo-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11i)

Following the general procedure, treatment of 5-bromoisoquinoline **9m** (0.104 g, 0.5 mmol) and 1-methylindoline-2,3-dione (0.080 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl



11i

trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded 1-bromo-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one as a white solid (0.201 g, 90%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.53.

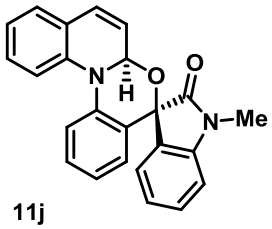
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.54 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.35-7.25 (m, 3H), 7.09-6.93 (m, 5H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.16 (d, *J* = 7.7 Hz, 1H), 3.32 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 176.01, 144.23, 141.06, 133.32, 131.40, 131.34, 130.84, 130.33, 128.89, 128.60, 126.74, 126.71, 126.62, 126.41, 124.85, 124.02, 123.80, 119.41, 118.69, 108.61, 98.98, 80.30, 79.87, 26.48.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{18}O_2N_2Br$: 445.0546, found: 445.0546.

FTIR (cm^{-1}): 2867, 1956, 1716, 1634, 1611, 1566, 1488, 1470, 1352, 1299, 1251, 1112, 991, 946, 755, 692.

1'-Methyl-6a*H*-spiro[benzo[4,5][1,3]oxazino[3,2-a]quinoline-5,3'-indolin]-2'-one (11j)



11j

Following the general procedure, treatment of quinoline (0.064 g, 59 µL, 0.50 mmol) and 1-methylindoline-2,3-dione (0.080 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixture afforded 1'-methyl-6a*H*-spiro[benzo[4,5][1,3]oxazino[3,2-a]quinoline-5,3'-indolin]-2'-one as as a red solid (0.089 g, 49%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.31.

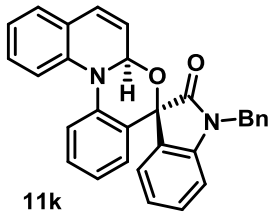
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.62 (d, *J* = 8.2 Hz, 1H), 7.39-7.34 (m, 2H), 7.30-7.24 (m, 3H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.98-6.81 (m, 6H), 6.59 (d, *J* = 5.0 Hz, 1H), 6.05-6.02 (m, 1H), 3.30 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.95, 144.10, 140.30, 139.59, 131.66, 130.28, 130.16, 129.94, 129.46, 128.50, 127.49, 126.95, 125.65, 125.59, 124.63, 123.72, 121.28, 120.08, 117.84, 112.84, 108.63, 80.07, 79.32, 26.43.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{19}O_2N_2$: 367.1441, found: 367.1441.

FTIR (cm^{-1}): 2959, 2872, 1716, 1636, 1611, 1567, 1488, 1466, 1359, 1251, 1102, 1024, 814, 754.

1'-Benzyl-6a*H*-spiro[benzo[4,5][1,3]oxazino[3,2-a]quinoline-5,3'-indolin]-2'-one (11k)



11k

Following the general procedure, treatment of quinoline (0.129 g, 118 µL, 1.0 mmol) and 1-benzylindoline-2,3-dione (0.119 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.298 g, 239 µL, 1.0 mmol) in the presence of KF (0.116 g, 2.0 mmol) and 18-crown-6 (0.528 g, 2.0 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixture afforded 1'-benzyl-6a*H*-spiro[benzo[4,5] [1,3]oxazino[3,2-a]quinoline-5,3'-indolin]-2'-one as a yellow solid (0.139 g, 63% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.36.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 8.0 Hz, 1H), 7.56-7.45 (m, 6H), 7.42-7.38 (m, 3H), 7.30-7.24 (m, 2H), 7.12-7.06 (m, 2H), 6.99-6.96 (m, 3H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 5.1 Hz, 1H), 6.24-6.21 (m, 1H), 5.24 (d, *J* = 15.5 Hz, 1H), 4.99 (d, *J* = 15.5 Hz, 1H).

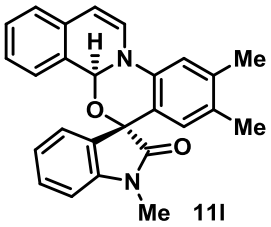
^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.11, 143.24, 140.37, 139.65, 135.76, 131.77, 130.45, 130.04, 130.00, 129.48, 129.07, 128.52, 127.96, 127.56, 127.54, 126.93, 125.77, 125.69, 124.72, 123.74, 121.34, 120.14, 117.91, 112.89, 109.69, 80.05, 79.45, 44.05.

HRMS: calculated $[M+H]^+$ for $C_{30}H_{23}O_2N_2$: 443.1754, found: 443.1757.

FTIR (cm^{-1}): 3058, 2855, 1728, 1644, 1610, 1489, 1466, 1433, 1356, 1241, 1210, 1176, 1105, 1026, 992, 929, 751, 694.

1',8,9-Trimethyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11l)

Following the general procedure, treatment of isoquinoline **9a** (0.032 g, 30 µL, 0.25 mmol) and 1-methylindoline-2,3-dione (0.040 g, 0.25 mmol) with 4,5-dimethyl-2-



11l

(trimethylsilyl)phenyl trifluoromethane sulfonate **1b** (0.122 g, 0.375 mmol) in the presence of KF (0.043 g, 0.75 mmol) and 18-crown-6 (0.198 g, 0.75 mmol) in THF (1.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 1',8,9-trimethyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one as inseparable mixture of diastereomers as a white solid (0.074 g, 74%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 6:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.55.

^{1}H NMR (200 MHz, CDCl$_3$) δ: 7.51-7.47 (m, 2H), 7.37-7.24 (m, 2H), 7.21-7.13 (m, 3H), 7.09-6.98 (m, 2H), 6.95-6.89 (m, 2H), 6.43 (s, 1H), 5.81 (d, *J* = 7.7 Hz, 1H), 3.35 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.13 (s, 3H, CH_3).

^{13}C NMR (50 MHz, CDCl$_3$) δ: 176.39, 144.37, 139.62, 137.64, 132.29, 131.97, 131.89, 130.03, 129.51, 129.29, 129.22, 127.02, 125.89, 125.06, 124.91, 124.18, 123.63, 119.67, 108.44, 100.08, 80.75, 79.65, 26.44, 19.97, 19.28.

Representative Peaks of Minor Isomer:

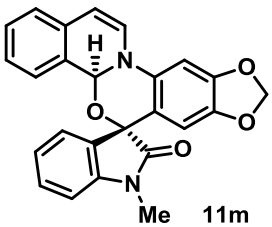
^{1}H NMR δ: 7.55 (d, *J* = 7.5 Hz), 7.44-7.43 (m), 6.66 (s), 5.87-5.79 (m), 3.22 (s).

^{13}C NMR δ: 175.31, 144.13, 140.02, 137.96, 132.60, 130.26, 128.70, 127.22, 125.63, 124.47, 123.51, 119.35, 108.62, 81.56, 80.48, 26.06.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{23}O_2N_2$: 395.1754, found: 395.1758.

FTIR (cm^{-1}): 2869, 1719, 1612, 1565, 1492, 1470, 1352, 1298, 1252, 1119, 1043, 947.

1-Methyl-4b'*H*-spiro[indoline-3,6'-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5] [1,3]oxazino[2,3-a]isoquinolin]-2-one (11m)



11m

Following the general procedure, treatment of isoquinoline **9a** (0.032 g, 30 µL, 0.25mmol) and 1-methylindoline-2,3-dione (0.040 g, 0.25 mmol) with 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl trifluoromethane sulfonate **1c** (0.128 g, 0.375 mmol) in the presence of KF (0.043g, 0.75 mmol) and 18-crown-6 (0.198 g, 0.75 mmol) in THF (1.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded 1-methyl-4b'*H*-spiro[indoline-3,6'-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5][1,3]oxazino[2,3-a]isoquinolin]-2-one as inseparable

mixture of diastereomers as a yellow solid (0.069 g, 67%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 10:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.48.

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.45 (d, *J* = 7.7 Hz, 1H), 7.37 (s, 1H), 7.32-7.29 (m, 2H), 7.20 (t, *J* = 7.0 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 7.0 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.81-6.79 (m, 2H), 6.09 (s, 1H), 5.92 (d, *J* = 9.6 Hz, 2H), 5.82 (d, *J* = 7.6 Hz, 1H), 3.31 (s, 3H, CH_3).

^{13}C NMR (1125 MHz, CDCl$_3$) δ: 176.01, 148.15, 144.46, 144.10, 136.51, 131.79, 130.11, 129.42, 129.29, 129.11, 125.97, 124.85, 124.68, 124.18, 123.60, 118.83, 108.48, 105.35, 101.47, 100.63, 100.14, 80.81, 79.51, 26.34.

Representative Peaks of Minor Isomer:

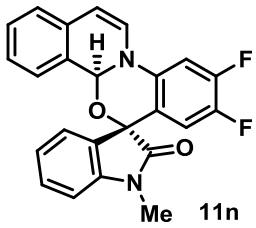
^{1}H NMR δ: 7.55-7.54 (m), 6.93-6.91 (m), 6.07-6.06 (m), 5.87-5.86 (m), 3.17 (s).

^{13}C NMR δ: 131.53, 130.35, 129.50, 129.36, 129.22, 128.57, 125.69, 124.75, 124.51, 123.53, 108.61, 106.50, 100.05, 26.56.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{19}O_2N_2$: 411.1339, found: 411.1339.

FTIR (cm^{-1}): 2926, 1778, 1716, 1614, 1492, 1470, 1369, 1349, 1292, 1215, 1091, 1026, 977, 954, 900, 752, 667.

8,9-Difluoro-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one (11n)



11n

Following the general procedure, treatment of isoquinoline **9a** (0.032 g, 30 µL, 0.25 mmol) and 1-methylindoline-2,3-dione (0.040 g, 0.25 mmol) with 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoro methanesulfonate **1d** (0.125 g, 0.375 mmol) in the presence of KF (0.043g, 0.75 mmol) and 18-crown-6 (0.198 g, 0.75 mmol) in THF (1.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 8,9-difluoro-1'-methyl-4b*H*-spiro[benzo[4,5][1,3]oxazino[2,3-a]isoquinoline-6,3'-indolin]-2'-one as inseparable mixture of diastereomers as a yellow solid (0.070 g, 70%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 12:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.59.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (t, *J* = 8.8 Hz, 2H), 7.33-7.28 (m, 3H), 7.21-7.11 (m, 3H), 6.99-6.96 (m, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 5.83 (d, *J* = 7.6 Hz, 1H), 3.29 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.70, 159.75 (dd, J_1 = 12.1 Hz, J_2 = 244.0 Hz), 159.64 (dd, J_1 = 11.0 Hz, J_2 = 240.7 Hz), 141.63, 140.21, 136.12, 133.33 (d, *J* = 8.3 Hz), 131.66, 129.53, 129.01 (m), 126.54, 126.17, 125.7 (d, *J* = 15.2 Hz), 124.83, 124.40, 123.68, 118.74, 116.44 (d, *J* = 23.8 Hz), 112.98 (d, *J* = 25.3 Hz), 109.2 (d, *J* = 8.1 Hz), 100.88, 80.92, 79.88, 26.51.

Representative Peaks of Minor Isomer:

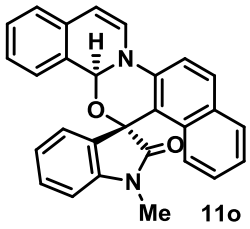
^{1}H NMR δ: 7.62-7.55 (m), 6.81-6.79 (m), 3.14 (s).

^{13}C NMR δ: 174.94, 130.32, 126.89, 126.74, 125.72, 124.49, 123.49, 118.28, 108.60, 100.44, 81.47, 26.60.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{17}O_2N_2F_2$: 403.1253, found: 403.1253.

FTIR (cm^{-1}): 1722, 1636, 1607, 1585, 1488, 1460, 1428, 1358, 1339, 1056, 1025, 953.

1-Methyl-13b'*H*-spiro[indoline-3,15'-naphtho[2',1':4,5][1,3]oxazino[2,3-a]isoquinolin]-2-one (11o)



11o

Following the general procedure, treatment of isoquinoline **9a** (0.032 g, 30 µL, 0.25 mmol) and 1-methylindoline-2,3-dione (0.040 g, 0.25 mmol) with 2-(trimethylsilyl)naphthalen-1-yl trifluoromethanesulfonate **1e** (0.131 g, 0.375 mmol) in the presence of KF (0.043 g, 0.75 mmol) and 18-crown-6 (0.198 g, 0.75 mmol) in THF (1.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded 1-methyl-13b'*H*-spiro[indoline-3,15'-naphtho[2',1':4,5][1,3]oxazino[2,3-a]isoquinolin]-2-one as inseparable mixture of diastereomers as a white solid (0.079 g, 76%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 6:1).

R_f (Pet. ether /EtOAc = 70/30): 0.50.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 9.1 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.9 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.31-7.26 (m, 2H), 7.24 (m, 1H), 7.20 (t, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 2H), 6.83-6.79 (m, 2H), 5.86 (d, *J* = 7.7 Hz, 1H), 3.45 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.00, 144.51, 140.72, 131.55, 131.19, 130.91, 130.60, 130.48, 130.34, 129.31, 129.17, 127.63, 126.98, 124.60, 124.19, 123.77, 122.50, 118.30, 112.16, 108.93, 98.32, 79.37, 78.14, 26.66.

Representative Peaks of Minor Isomer:

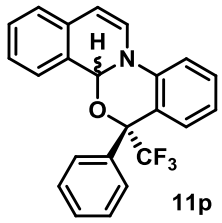
^{1}H NMR δ: 7.97 (t, *J* = 7.8 Hz), 7.83 (d, *J* = 7.8 Hz), 7.51-7.48 (m), 7.04-7.02 (m), 6.88-6.85 (m), 6.02 (d, *J* = 7.7 Hz), 3.31 (s).

^{13}C NMR δ: 129.79, 127.34, 123.28, 118.54, 111.71, 109.11, 78.96, 77.37, 26.92.

HRMS: calculated $[M+H]^+$ for $C_{28}H_{21}O_2N_2$: 417.1598, found: 417.1603.

FTIR (cm^{-1}): 2925, 2859, 1722, 1611, 1563, 1490, 1471, 1420, 1368, 1351, 1296, 1253, 1113, 1091, 1022, 992, 941, 814, 753, 665.

6-Phenyl-6-(trifluoromethyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline (11p)



11p

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 2,2,2-trifluoro-1-phenylethan-1-one (0.087g, 70 µL, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 97/03) of the crude reaction mixture afforded 6-phenyl-6-(trifluoromethyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline as inseparable mixture of diastereomers as a white solid (0.140 g, 74%, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 5:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.85.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 7.7 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.56-7.49 (m, 3H), 7.38-7.33 (m, 2H), 7.29-7.19 (m, 3H), 7.14 (t, *J* = 7.4 Hz, 2H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.05 (s, 1H), 5.80 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.38, 137.77, 131.72, 129.88, 129.64, 129.49, 129.38, 129.10, 128.86, 128.65, 128.37, 127.10-127.03 (m), 124.65, 124.48, 122.41, 122.08, 118.37, 101.01, 82.96-82.10 (m), 79.60.

Representative Peaks of Minor Isomer:

^{1}H NMR δ: 7.62 (d, *J* = 8.7 Hz), 7.56-7.54 (m, 2H), 7.44-7.40 (m), 6.83 (d, *J* = 7.6 Hz), 6.08 (s), 5.85 (d, *J* = 7.6 Hz).

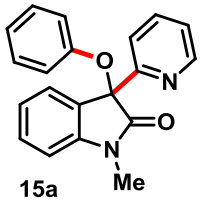
^{13}C NMR δ: 141.89, 139.42, 131.44, 129.22, 128.94, 128.81, 124.74, 123.84, 123.45, 119.44, 100.89, 81.50.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{17}ONF_3$: 380.1257, found380.1262.

FTIR (cm^{-1}): 3016, 2871, 1700, 1646, 1599, 1490, 1454, 1355, 1287, 1248, 1171, 1117, 1039, 952, 756.

6.11.6. Synthesis and Characterization of Indolin 2-ones

1-Methyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one (15a)



15a

Following the general procedure, treatment of pyridine **14a** (0.060 g, 60 µL, 0.75 mmol) and 1-methylindoline-2,3-dione (0.080 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 65/35) of the crude reaction mixture afforded 1-methyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one **15a** as a yellow solid (0.124 g, 79%).

R$_f$ (Pet. ether /EtOAc = 50/50): 0.61.

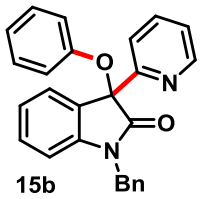
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.49-8.47 (m, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.84 (dt, J_1 = 1.7 Hz, J_2 = 7.8 Hz, J_3 = 15.6 Hz, 1H), 7.34-7.29 (m, 1H), 7.24-7.22 (m, 2H), 7.16-7.11 (m, 2H), 7.05-6.96 (m, 2H), 6.90-6.85 (m, 3H), 3.26 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 174.27, 159.00, 155.18, 149.34, 144.47, 137.18, 130.35, 129.21, 128.68, 125.50, 123.71, 123.19, 123.11, 121.07, 120.78, 108.93, 86.22, 26.65.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{17}O_2N_2$: 317.1285, found: 317.1282.

FTIR (cm^{-1}): 1729, 1611, 1588, 1434, 1348, 1302, 1239, 1214, 1131, 1108, 1091, 993.

1-Benzyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one (15b)



15b

Following the general procedure, treatment of pyridine **14a** (0.060 g, 60 µL, 0.75 mmol) and 1-benzylindoline-2,3-dione (0.119 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixture afforded benzyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one **15b** as a yellow solid (0.145 g, 74%).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.65.

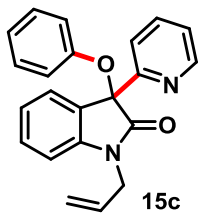
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.51-8.50 (m, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.87 (dt, J_1 = 1.7 Hz, J_2 = 7.9 Hz, J_3 = 15.6 Hz, 1H), 7.29-7.18 (m, 6H), 7.17-7.12 (m, 2H), 7.07-6.99 (m, 4H), 6.93 (d, *J* = 7.9 Hz, 2H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.13 (d, *J* = 15.9 Hz, 1H), 4.80 (d, *J* = 15.9 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 174.02, 159.19, 155.06, 149.36, 143.60, 137.26, 135.10, 130.26, 129.34, 128.96, 128.75, 127.52, 127.26, 125.49, 124.10, 123.13, 123.12, 121.77, 120.95, 110.12, 86.71, 44.04.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{21}O_2N_2$: 393.1598, found: 393.1592.

FTIR (cm^{-1}): 3059, 2923, 2854, 1730, 1611, 1588, 1489, 1467, 1434, 1359, 1210, 1173, 1077, 1050, 1028, 993, 965, 783, 751, 695, 550.

1-Allyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one (15c)



15c

Following the general procedure, treatment of pyridine **14a** (0.060 g, 60 µL, 0.75 mmol) and 1-allylindoline-2,3-dione (0.094 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 75/25) of the crude reaction mixture afforded 1-allyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one **15c** as a yellow solid (0.126 g, 73%).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.67.

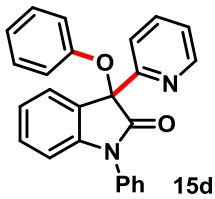
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.53-8.52 (m, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.89 (dt, J_1 = 1.7 Hz, J_2 = 7.8 Hz, J_3 = 15.6 Hz, 1H), 7.35-7.26 (m, 3H), 7.19 (t, *J* = 7.7 Hz, 2H), 7.10-7.02 (m, 2H), 6.99-6.97 (m, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 5.79-5.69 (m, 1H), 5.16 (d, *J* = 10.7 Hz, 1H), 5.08 (d, *J* = 17.2 Hz, 1H), 4.55-4.50 (m, 1H), 4.35-4.29 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 173.84, 159.05, 155.07, 149.37, 143.75, 137.19, 130.61, 130.23, 129.20, 128.88, 125.59, 124.05, 123.18, 123.04, 121.64, 121.00, 117.65, 109.89, 86.59, 42.51.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{19}O_2N_2$: 343.1441, found: 343.1440.

FTIR (cm^{-1}): 3057, 3010, 2924, 2855, 1731, 1612, 1588, 1490, 1466, 1435, 1376, 1356, 1241, 1215, 1176, 1151, 1115, 755, 666.

3-Phenoxy-1-phenyl-3-(pyridin-2-yl)indolin-2-one (15d)



15d

Following the general procedure, treatment of pyridine **14a** (0.060 g, 60 µL, 0.75 mmol) and 1-phenylindoline-2,3-dione (0.112 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 80/20) of the crude reaction mixture afforded 3-phenoxy-1-phenyl-3-(pyridin-2-yl)indolin-2-one **15d** as a red solid (0.075 g, ^{1}H NMR yield 69%).

***R**$_f$* (Pet. ether /EtOAc = 50/50): 0.75.

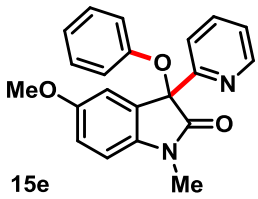
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.55-8.54 (m, 1H), 8.23 (d, *J* = 7.9 Hz, 1H), 7.87 (dt, J_1 = 1.8 Hz, J_2 = 7.8 Hz, J_3 = 15.6 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 3H), 7.28-7.25 (m, 2H), 7.22-7.18 (m, 2H), 7.10-7.02 (m, 4H), 6.79 (d, *J* = 7.9 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 173.55, 159.02, 155.16, 149.44, 144.79, 137.17, 134.25, 130.25, 129.71, 129.23, 128.75, 128.57, 128.37, 126.72, 125.91, 124.07, 123.51, 123.24, 121.44, 121.12, 110.10, 86.44.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{19}O_2N_2$: 379.1441, found: 379.1445.

FTIR (cm^{-1}): 2824, 1682, 1602, 1492, 1454, 1407, 1353, 1284, 1253, 1169, 1112, 955.

5-methoxy-1-methyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one (15e)



15e

Following the general procedure, treatment of pyridine **14a** (0.060 g, 60 µL, 0.75 mmol) and 5-methoxy-1-methylindoline-2,3-dione (0.096 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 60/40) of the crude reaction mixture afforded 5-methoxy-1-methyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one **15e** as a yellow solid (0.133 g, 77%).

***R**$_f$* (Pet. ether /EtOAc = 50/50): 0.48.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.47-8.46 (m, 1H), 8.13-8.11 (m, 1H), 7.81 (dt, J_1 = 1.7 Hz, J_2 = 7.7 Hz, J_3 = 15.7 Hz, 1H), 7.23-7.20 (m, 1H), 7.12 (t, *J* = 7.3 Hz, 2H), 6.96 (t, *J* =

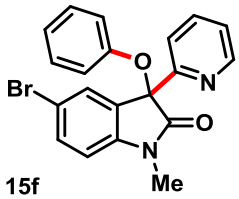
7.3 Hz, 1H), 6.87-6.81 (m, 4H), 6.75 (d, *J* = 8.4 Hz, 1H), 3.71 (s, 3H, CH_3), 3.21 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.16, 158.98, 156.30, 155.28, 149.42, 137.93, 137.21, 130.04, 129.28, 126.68, 123.67, 123.23, 121.10, 120.61, 114.73, 112.72, 109.36, 106.01, 86.41, 55.86, 26.77.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{19}O_3N_2$: 347.1390, found: 347.1393.

FTIR (cm^{-1}): 3006, 2873, 1698, 1638, 1599, 1492, 1449, 1350, 1289, 1253, 1163, 1034, 900, 952, 845, 755, 702, 661.

5-Bromo-1-methyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one (15f)



15f

Following the general procedure, treatment of pyridine **14a** (0.060 g, 60 µL, 0.75 mmol) and 5-bromo-1-methylindoline-2,3-dione (0.120 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixture afforded 5-bromo-1-methyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one **15f** as a yellow solid (0.146 g, 74%).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.65.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (d, *J* = 4.4 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.83 (dt, J_1 = 1.3 Hz, J_2 = 7.8 Hz, J_3 = 15.5 Hz, 1H), 7.41 (dd, J_1 = 1.7 Hz, J_2 = 8.3 Hz, 1H), 7.31 (m, 1H), 7.24-7.21 (m, 1H), 7.15(t, *J* = 7.7 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 3.20 (s, 3H, CH_3).

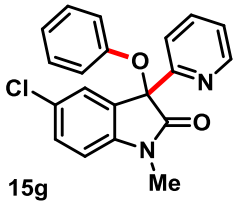
^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.68, 158.36, 154.90, 149.39, 143.51, 137.38, 133.15, 130.79, 129.39, 128.53, 124.00, 123.47, 121.01, 120.65, 115.74, 110.43, 85.90, 26.74.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{16}O_2N_2Br$: 395.0390, found: 395.0393.

FTIR (cm^{-1}): 3061, 2926, 1732, 1607, 1588, 1489, 1466, 1434, 1358, 1340, 1237, 1213, 1100, 1053, 1032, 994, 971, 752, 694.

5-Chloro-1-methyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one (15g)

Following the general procedure, treatment of pyridine **14a** (0.060 g, 60 µL, 0.75 mmol) and 5-chloro-1-methylindoline-2,3-dione (0.098 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the



15g

presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixture afforded 5-chloro-1-methyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one **15g** as a yellow solid (0.120 g, 68% yield).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.65.

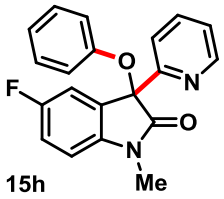
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.47-8.46 (m, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.85 (dt, J_1 = 1.8 Hz, J_2 = 7.8 Hz, J_3 = 15.5 Hz, 1H), 7.30-7.23 (m, 2H), 7.20-7.14 (m, 3H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 1H), 3.23 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 173.81, 158.40, 154.96, 149.39, 143.07, 137.36, 130.46, 130.27, 129.38, 128.48, 125.87, 124.00, 123.45, 121.05, 120.70, 109.91, 85.99, 26.75.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{16}O_2N_2Cl$: 351.0895, found: 351.0894.

FTIR (cm^{-1}): 2926, 2855, 1723, 1635, 1584, 1539, 1410, 1377, 1351, 1302, 1279, 1257, 1229, 1159, 1085, 997, 769, 746, 712, 657.

5-Fluoro-1-methyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one (15h)



15h

Following the general procedure, treatment of pyridine **14a** (0.060 g, 60 µL, 0.75 mmol) and 5-fluoro-1-methylindoline-2,3-dione (0.090 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 75/25) of the crude reaction mixture afforded 5-fluoro-1-methyl-3-phenoxy-3-(pyridin-2-yl)indolin-2-one **15h** as a yellow solid (0.114 g, 68%).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.68.

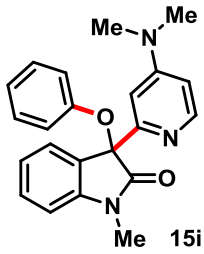
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.48 (d, *J* = 4.7 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.86 (dt, J_1 = 1.6 Hz, J_2 = 7.8 Hz, J_3 = 15.6 Hz, 1H), 7.29-7.25 (m, 1H), 7.17(t, *J* = 7.7 Hz, 2H), 7.06-6.98 (m, 3H), 6.91-6.89 (m, 2H), 6.79 (dd, J_1 = 4.0 Hz, J_2 = 8.5 Hz, 1H), 3.25 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 174.03, 159.52 (d, *J* = 219.2 Hz), 158.20, 155.02, 149.40, 140.49, 137.36, 130.32 (d, *J* = 7.6 Hz), 129.37, 123.73 (d, *J* = 55.0 Hz), 121.16, 120.78, 116.70 (d, *J* = 23.4 Hz), 113.64 (d, *J* = 25.5 Hz), 109.54 (d, *J* = 7.8 Hz), 86.20, 26.81.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{16}O_2N_2F$: 335.1190, found: 335.1183.

FTIR (cm^{-1}): 3060, 2937, 1732, 1618, 1588, 1492, 1469, 1435, 1347, 1270, 1237, 1213, 1152, 1129, 1106, 1051, 1032, 995, 971, 870, 813, 762, 694, 621.

3-(4-(Dimethylamino)pyridin-2-yl)-1-methyl-3-phenoxyindolin-2-one (15i)



15i

Following the general procedure, treatment of N,N-dimethylpyridin-4-amine **14i** (0.092 g, 0.75 mmol) and 1-methylindoline-2,3-dione (0.080 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 30/70) of the crude reaction mixture afforded 3-(4-(dimethylamino)pyridin-2-yl)-1-methyl-3-phenoxyindolin-2-one **15i** as a white solid (0.160 g, 89%).

R_f (Pet. ether /EtOAc = 50/50): 0.32.

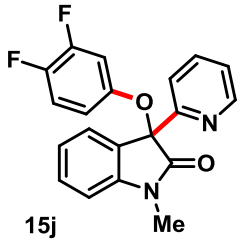
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 5.9 Hz, 1H), 7.40 (d, *J* = 2.5 Hz, 1H), 7.30-7.25 (m, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 2H), 7.02-6.93 (m, 2H), 6.89-6.87 (m, 2H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.39 (dd, J_1 = 2.5 Hz, J_2 = 5.9 Hz , 1H), 3.22 (s, 3H, CH_3), 3.22 (s, 6H, $2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.60, 158.84, 155.33, 155.25, 149.59, 144.63, 130.14, 129.11, 125.38, 123.73, 122.97, 121.30, 108.85, 105.96, 103.57, 86.41, 39.39, 26.64.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{22}O_2N_3$: 360.1707, found: 360.1704.

FTIR (cm^{-1}): 3054, 2865, 1959, 1729, 1599, 1542, 1489, 1469, 1451, 1352, 1296, 1251, 1123, 1036, 984, 948, 859, 756, 696.

3-(3,4-Difluorophenoxy)-1-methyl-3-(pyridin-2-yl)indolin-2-one (15j)



15j

Following the general procedure, treatment of pyridine **14a** (0.030 g, 30 µL, 0.375 mmol) and 1-methylindoline-2,3-dione (0.040 g, 0.25 mmol) with 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1d** (0.125 g, 0.375 mmol) in the presence of KF (0.043 g, 0.75 mmol) and 18-crown-6 (0.198 g, 0.75 mmol) in THF (1.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 80/20) of the crude reaction mixture afforded 3-(3,4-difluorophenoxy)-1-methyl-3-(pyridin-2-yl)indolin-2-one **15j** as a yellow solid (0.63 g, 71%).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.71.

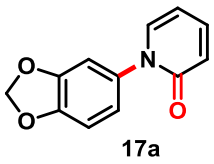
^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.46 (d, *J* = 4.2 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.81 (dt, J_1 = 1.8 Hz, J_2 = 7.7 Hz, J_3 = 15.5 Hz, 1H), 7.35-7.32 (m, 1H), 7.22 (t, *J* = 5.6 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.93-6.84 (m, 2H), 6.76-6.70 (m, 1H), 6.64-6.61 (m, 1H), 3.23 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 173.65, 158.27, 151.10(m), 149.49, 147.28 (dd, J_1 = 7.8 Hz, J_2 = 252.1 Hz), 147.18 (dd, J_1 = 7.5 Hz, J_2 = 256.0 Hz), 144.49, 137.27, 130.81, 127.99, 125.58, 123.40, 121.01, 127.29(m), 116.94 (d, *J* = 19.0 Hz), 111.15 (d, *J* = 19.2 Hz), 109.18, 86.90, 26.70.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{15}O_2N_2F_2$: 353.1096, found: 353.1096.

FTIR (cm^{-1}): 2926, 1742, 1685, 1611, 1512, 1492, 1472, 1430, 1369, 1328, 1252, 1214, 1159, 1117, 1093, 865, 754.

1-(Benzo[*d*][1,3]dioxol-5-yl)pyridin-2(1*H*)-one (17a)



17a

Following the general procedure, treatment of pyridine **14a** (0.020 g, 20 µL, 0.25 mmol) with 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate **1c** (0.086 g, 0.25 mmol) in the presence of KF (0.029 g, 0.50 mmol) and 18-crown-6 (0.132 g, 0.50 mmol) in THF (1.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 30/70) of the crude reaction mixture afforded 1-(benzo[*d*][1,3]dioxol-5-yl)pyridin-2(1*H*)-one **17a** as a brown solid (0.043 g, 79%).

***R*$_f$** (Pet. ether /EtOAc = 30/70): 0.30.

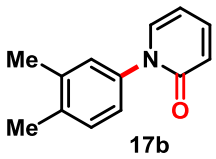
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.39-7.34 (m, 1H), 7.29-7.28 (m, 1H), 6.87-6.85 (m, 2H), 6.76 (dd, J_1 = 1.8 Hz, J_2 = 8.2 Hz, 1H), 6.62 (d, *J* = 9.3 Hz, 1H), 6.20 (t, *J* = 6.7 Hz, 1H), 6.01 (s, 2H, CH_2).

^{13}C NMR (100 MHz, CDCl$_3$) δ 162.71, 148.15, 147.82, 139.96, 138.36, 134.90, 121.84, 119.91, 108.48, 105.91, 101.98.

HRMS: calculated $[M+H]^+$ for $C_{12}H_{10}O_3N$: 216.0655, found: 216.0652.

FTIR (cm^{-1}): 2901, 1716, 1667, 1611, 1593, 1533, 1504, 1456, 1444, 1355, 1250, 1193, 1141, 1104, 1037, 1004, 933, 902, 841, 810, 761, 735, 639.

1-(3,4-Dimethylphenyl)pyridin-2(1*H*)-one (17b)



17b

Following the general procedure, treatment of pyridine **14a** (0.020 g, 20 µL, 0.25 mmol) with 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1b** (0.082 g, 0.25 mmol) in the presence of KF (0.029 g, 0.50 mmol) and 18-crown-6 (0.132 g, 0.50 mmol) in THF (1.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture afforded 1-(3,4-dimethylphenyl)pyridin-2(1*H*)-one **17b** as a yellow solid (0.035 g, 70%).

***R**_f* (Pet. ether /EtOAc = 30/70): 0.38.

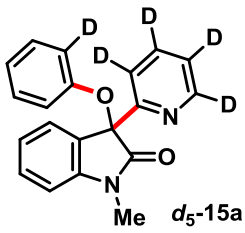
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40-7.35 (m, 1H), 7.30 (dd, J_1 = 1.8 Hz, J_2 = 6.8 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 1.8 Hz, 1H), 7.08 (dd, J_1 = 2.0 Hz, J_2 = 7.9 Hz, 1H), 6.63 (d, J = 9.3 Hz, 1H), 6.21 (t, J = 6.7 Hz, 1H), 2.29 (s, 6H, $2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.75, 139.85, 138.75, 138.33, 137.94, 137.32, 130.51, 127.55, 123.74, 121.85, 105.78, 19.96, 19.59.

HRMS: calculated $[M+H]^+$ for $C_{13}H_{14}ON$: 200.1070, found: 200.1067.

FTIR (cm^{-1}): 2922, 1668, 1594, 1534, 1504, 1471, 1453, 1384, 1373, 1347, 1295, 1277, 1141, 1121, 1021, 990, 838, 761, 730, 611.

1-Methyl-3-(phenoxy-2-*d*)-3-(pyridin-2-yl-d_4)indolin-2-one (*d*$_5$-15a)



d$_5$-15a

Following the general procedure, treatment of d_5-pyridine ***d*$_5$-14a** (0.063 g, 60 µL, 0.75 mmol) and 1-methylindoline-2,3-dione (0.080 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.223 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 65/35) of the crude reaction mixture afforded 1-methyl-3-(phenoxy-2-d)-3-(pyridin-2-yl-d4)indolin-2-one ***d*$_5$-15a** as a yellow solid (0.105 g, 65% yield).

***R**_f* (Pet. ether /EtOAc = 50/50): 0.61.

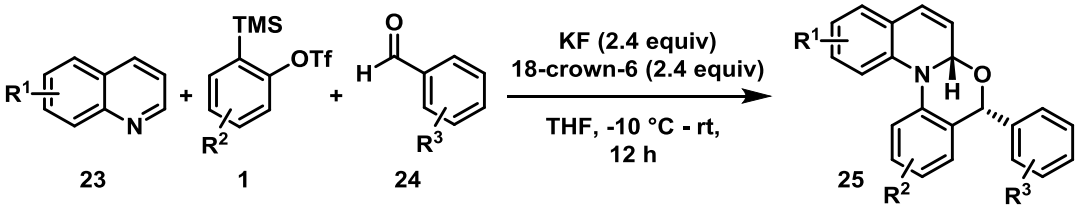
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (dt, J_1 = 1.4 Hz, J_2 = 7.8 Hz, J_3 = 15.6 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.13-7.10 (m, 2H), 7.01 (d, J = 7.7 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.88-6.86 (m, 1H), 6.83 (d, J = 7.8 Hz, 1H), 3.23 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.27, 158.97, 155.21, 155.16, 144.51, 130.34, 129.21, 129.10, 128.72, 125.53, 123.71, 123.11, 120.81, 108.91, 86.24, 26.65.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{10}{}^2H_5O_2N_2Na$: 343.1340, found: 343.1348.

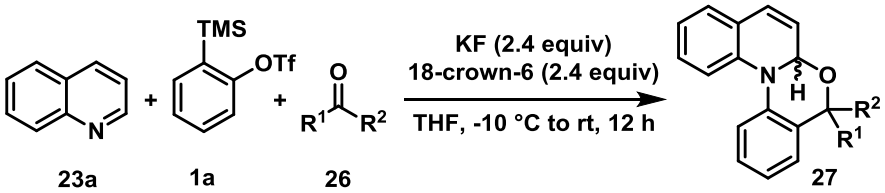
FTIR (cm^{-1}): 2925, 2854, 1728, 1611, 1491, 1470, 1422, 1372, 1348, 1329, 1302, 1231, 1211, 1168, 1091, 1028, 972, 752.

6.11.7. General Procedure for the MCR involving Quinoline, Aryne and Aldehydes



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.317 g, 1.2 mmol), KF (0.070 g, 1.2 mmol) and aldehyde **24** (0.75 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was cooled to -10 °C and kept stirring for 5 min. To the cooled stirring solution was then added quinoline **23** (0.50 mmol) and the aryne precursor **1** (0.60 mmol). Then the reaction mixture was gradually warmed to rt and kept for stirring at rt for 12 h. When TLC control showed the completion of the reaction (typically after 12 h), the reaction was stopped and the crude reaction mixture was purified by column chromatography on silica gel to afford the corresponding benzoxazino quinoline derivatives **25** as an inseparable mixture of diastereomers in moderate to good yields. The *dr* was determined by ^{1}H NMR analysis of crude reaction mixture.

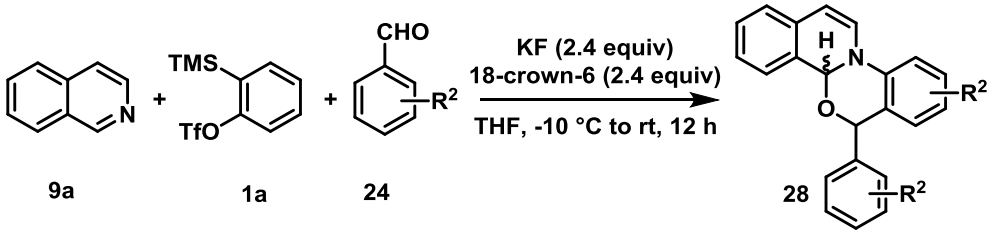
6.11.8. General Procedure for the MCR involving Quinoline, Aryne and Activated Ketones



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.317 g, 1.2 mmol), KF (0.070 g, 1.2 mmol) and ketone **26** (0.75 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture

was dissolved in THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was cooled to -10 °C and kept stirring for 5 min. To the cooled stirring solution was then added quinoline **23a** (0.50 mmol) and the aryne precursor **1a** (0.60 mmol). Then the reaction mixture was gradually warmed to rt kept for stirring at rt for 12 h. When TLC control showed the completion of the reaction (typically after 12 h), the reaction was stopped and the crude reaction mixture was purified by column chromatography on silica gel to afford the corresponding benzoxazino quinoline derivatives **27** as single product (in the case of **27a, 27b** & **27d**) or inseparable mixture of diastereomers (in the case of **27c**) in moderate to good yields. The *dr* (in the case of **27c**) was determined by ^{1}H NMR analysis of crude reaction mixture.

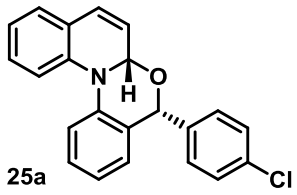
6.11.9. General Procedure for the MCR involving Isouinoline, Aryne and Aldehydes



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.317 g, 1.2 mmol), KF (0.070 g, 1.2 mmol) and aldehyde **24** (0.75 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was cooled to -10 °C and kept stirring for 5 min. To the cooled stirring solution was then added isoquinoline **9a** (0.064g, 59 µL, 0.50 mmol) and the aryne precursor **1a** (0.60 mmol). Then the reaction mixture was gradually warmed to rt and kept for stirring at rt for 12 h. When TLC control showed the completion of the reaction (typically after 12 h), the reaction was stopped and the crude reaction mixture was purified by column chromatography on silica gel to afford the corresponding benzoxazino isoquinoline derivatives **28** as an inseparable mixture of diastereomers in moderate to good yields. The *dr* was determined by ^{1}H NMR analysis of crude reaction mixture.

6.11.10. Synthesis and Characterization of Benzoxazino Quinolines

5-(4-Chlorophenyl)-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline (25a)



25a

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and 4-chlorobenzaldehyde (0.105 g, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 75/25) of the crude reaction mixture afforded 5-(4-chlorophenyl)-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline as inseparable mixture of diastereomers as a white solid (0.118 g, 68% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 10:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.49.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 7.53 (d, *J* = 7.8 Hz, 1H), 7.40-7.30 (m, 4H), 7.25-7.16 (m, 5H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 2H), 6.23 (s, 1H), 6.01-5.98 (m, 1H), 5.75 (d, *J* = 4.6 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ: 141.25, 139.46, 138.87, 133.48, 132.52, 129.37 (two signals overlapping), 128.55, 128.38, 128.07, 127.99, 126.54, 125.02, 124.75, 120.66, 119.49, 118.43, 112.11, 79.99, 78.77.

Representative Peaks of Minor Isomer:

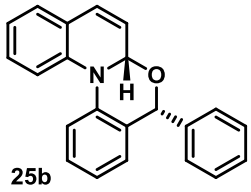
^{1}H NMR δ: 7.62 (d, *J* = 7.6 Hz), 7.49-7.40 (m), 5.88 (m), 5.68 (m).

^{13}C NMR δ: 141.68, 135.92, 132.76, 131.31, 130.49, 129.12, 126.76, 124.55, 124.50, 121.38, 118.56, 114.34, 76.16, 75.52.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{17}ONCl$: 346.0993, found: 346.0998.

FTIR (cm^{-1}): 1682, 1654, 1593, 1487, 1456, 1404, 1336, 1285, 1112, 1010, 974, 930.

5-Phenyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline (25b)



25b

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and benzaldehyde (0.080 g, 80µL, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 75/25) of the crude reaction mixture afforded

5-phenyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline as a yellow solid (0.128 g, 82% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.53.

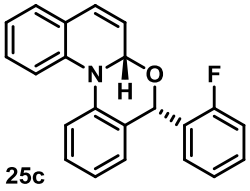
^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 7.52 (d, *J* = 8.0 Hz, 1H), 7.35-7.29 (m, 2H), 7.26-7.23 (m, 5H), 7.17-7.15 (m, 3H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.20 (s, 1H), 6.01-5.98 (m, 1H), 5.74 (d, *J* = 5.0 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 142.33, 139.65, 138.91, 134.03, 129.38, 128.53, 128.37, 128.11, 128.08, 127.95, 127.69, 126.42, 125.00, 124.77, 120.74, 119.47, 118.60, 112.19, 79.94, 79.63.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{18}ON$: 312.1383, found: 312.1393.

FTIR (cm^{-1}): 3744, 3014, 1651, 1594, 1492, 1452, 1420, 1287, 1216, 1120, 1011, 956.

5-(2-Fluorophenyl)-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline (25c)



25c

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and 2-fluorobenzaldehyde (0.095 g, 79 µL, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 75/25) of the crude reaction mixture afforded 5-(2-fluorophenyl)-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline as inseparable mixture of diastereomers as a white solid (0.118 g, 58% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.44.

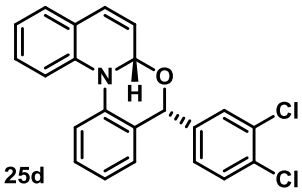
^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 7.54 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.31-7.26 (m, 3H), 7.24-7.15 (m, 3H), 7.11 (t, *J* = 9.6 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.93-6.89 (m, 2H), 6.48 (s, 1H), 6.01-5.98 (m, 1H), 5.80 (d, *J* = 4.7 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 160.28 (d, *J* = 248.1 Hz), 139.42 (d, *J* = 23.4 Hz), 133.09, 130.15 (d, *J* = 8.3 Hz), 129.69 (d, *J* = 3.7 Hz), 129.30, 129.04, 128.94, 128.66, 128.02, 127.39, 126.57, 125.09, 124.74, 124.44 (d, *J* = 3.7 Hz), 120.65, 119.44, 118.32, 115.71 (d, *J* = 21.2 Hz), 112.28, 80.16, 73.91.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{17}ONF$: 330.1289, found: 330.1297.

FTIR (cm^{-1}): 3747, 3015, 1651, 1592, 1491, 1453, 1419, 1288, 1216, 1104, 1045, 1013.

5-(3,4-Dichlorophenyl)-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline (25d)



25d

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and 3,4-dichlorobenzaldehyde (0.130 g, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 75/25) of the crude reaction mixture afforded 5-(3,4-dichlorophenyl)-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline as a yellow solid (0.127 g, 67% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.58.

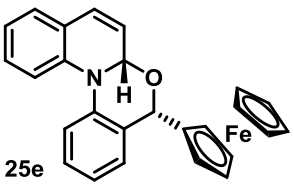
^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 7.53-7.46 (m, 2H), 7.43-7.40 (m, 1H), 7.36-7.29 (m, 2H), 7.21 (d, *J* = 3.8 Hz, 2H), 7.20-7.09 (m, 3H), 6.93-6.89 (m, 2H), 6.24 (s, 1H), 6.01-5.97 (m, 1H), 5.71 (d, *J* = 5.0 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ: 143.54, 139.39, 138.86, 133.04, 130.95, 130.70, 130.50, 129.39, 129.36, 128.68, 128.14, 127.97, 127.52, 126.80, 125.24, 124.91, 120.64, 119.63, 118.35, 112.11, 79.92, 77.88.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{16}ONCl_2$: 380.0603, found: 380.0609.

FTIR (cm^{-1}): 3016, 1652, 1593, 1491, 1456, 1394, 1292, 1214, 1125, 1034, 998, 915, 825.

5-Ferrocineyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline (25e)



25e

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and ferrociene carboxaldehyde (0.161 g, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixture afforded 5-ferrocineyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline as inseparable mixture of diastereomers as a red solid (0.099 g, 47% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 10:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.71.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 7.45 (d, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.33-7.28 (m, 2H), 7.23-7.21 (m, 1H), 7.14 (s, 2H), 6.93 (d, *J* = 9.4 Hz, 1H), 6.87-6.86 (m, 1H), 6.06 (bs, 1H), 5.94 (s, 1H), 5.62 (s, 1H), 4.24 (s, 2H), 4.11 (s, 5H), 3.98 (s, 1H), 3.78 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ: 139.34, 138.62, 134.35, 129.10, 128.28, 127.97, 127.77, 126.25, 124.62, 124.31, 120.47, 119.16, 118.82, 111.99, 90.96, 79.67, 75.05, 68.63, 67.49, 67.34, 66.92, 65.64.

Representative Peaks of Minor Isomer:

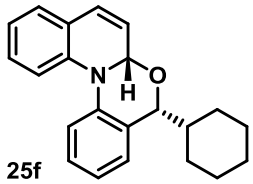
^{1}H NMR δ: 5.65 (s), 5.55 (s), 4.36 (s), 4.29 (s), 4.04 (s).

^{13}C NMR δ: 139.03, 138.15, 132.82, 129.04, 128.47, 128.20, 124.20, 120.65, 119.44, 112.13, 91.25, 76.79, 72.90, 68.74, 68.20, 65.92.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{22}FeON$: 420.1045, found: 420.1051.

FTIR (cm^{-1}): 1647, 1594, 1490, 1451, 1416, 1288, 1215, 1106, 1002, 925, 819, 744.

5-Cyclohexyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline (25f)



25f

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and cyclohexanecarbaldehyde (0.084 g, 91µL, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 75/25) of the crude reaction mixture afforded 5-cyclohexyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline as a yellow solid (0.141 g, 89% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.63.

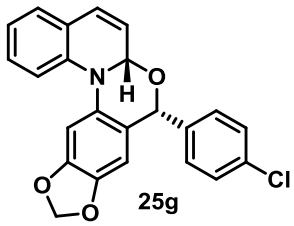
^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 7.44 (d, *J* = 8.0 Hz, 1H), 7.33-7.28 (m, 2H), 7.24 (d, *J* = 7.4 Hz, 2H), 7.13 (bs, 2H), 6.86-6.82 (m, 2H), 5.97-5.94 (m, 1H), 5.43 (d, *J* = 4.6 Hz, 1H), 5.03 (s, 1H), 1.70-1.63 (m, 3H), 1.48 (d, *J* = 10.7 Hz, 1H), 1.40 (d, *J* = 10.6 Hz, 1H), 1.24-1.15 (m, 2H), 1.00 (d, *J* = 13.1 Hz, 1H), 0.95-0.88 (m, 2H), 0.76-0.69 (m, 1H).

^{13}C NMR (125 MHz, DMSO-d_6) δ: 140.00, 139.40, 133.59, 129.08, 128.25, 127.91, 126.67, 125.98, 124.84, 124.02, 120.30, 118.96, 118.88, 111.95, 80.36, 79.13, 44.36, 29.30, 26.11, 25.82, 25.64, 24.54.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{24}ON$: 318.1852, found: 318.1859.

FTIR (cm^{-1}): 3748, 3014, 2929, 2855, 1651, 1593, 1492, 1451, 1420, 1294, 1216, 1041, 990, 768, 741, 667.

8-(4-Chlorophenyl)-6a*H*,8*H*-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5] [1,3]oxazino[3,2-a]quinoline (25g)



25g

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and 4-chlorobenzaldehyde (0.105 g, 0.75 mmol) with 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethane sulfonate **1c** (0.205 g, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixture afforded 8-(4-chlorophenyl)-6a*H*,8*H*-[1,3]dioxolo[4",5":4',5']benzo[1',2':4,5][1,3]oxazino[3,2-a]quinoline as inseparable mixture of diastereomers as a white solid (0.171 g, 88% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.38.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.29-7.27 (m, 3H), 7.25-7.20 (m, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.08 (s, 1H), 6.91-6.88 (m, 2H), 6.55 (s, 1H), 6.09-6.07 (m, 1H), 6.03 (d, *J* = 9.4 Hz, 2H), 5.99-5.96 (m, 1H), 5.64 (d, *J* = 5.0 Hz, 1H).

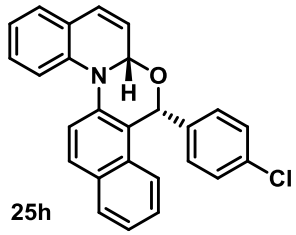
^{13}C NMR (125 MHz, DMSO-d_6) δ: 146.05, 145.10, 141.43, 139.90, 132.49, 129.39, 129.24, 128.52, 128.36, 127.99, 126.59, 120.77, 119.39, 118.61, 112.54, 106.54, 105.36, 101.48, 80.02, 78.42.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{17}O_3NCl$: 390.0891, found: 390.0899.

FTIR (cm^{-1}): 3395, 2998, 2895, 1648, 1599, 1481, 1430, 1295, 1243, 1215, 1190, 1119, 1089, 1031, 935, 824, 741, 664, 629.

5-Phenyl-5*H*,6a*H*-naphtho[2',1':4,5][1,3]oxazino[3,2-a]quinoline (25h)

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and 4-chlorobenzaldehyde (0.105 g, 0.75 mmol) with 2-(trimethylsilyl)naphthalen-1-yl



25h

trifluoromethanesulfonate **1e** (0.209 g, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 75/25) of the crude reaction mixture afforded 5-phenyl-5*H*,6a*H*-naphtho[2',1':4,5][1,3]oxazino[3,2-a]quinoline as a yellow solid (0.133 g, 67% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

R_f (Pet. ether /EtOAc = 60/40): 0.49.

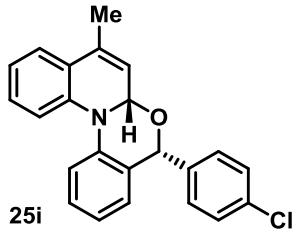
^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.01-7.96 (m, 2H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.42-7.36 (m, 3H), 7.30-7.20 (m, 5H), 7.14 (d, *J* = 2.5 Hz, 2H), 6.88 (d, *J* = 9.7 Hz, 2H), 6.46 (s, 1H), 5.72-5.68 (m, 1H), 5.58 (d, *J* = 4.4 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ: 141.45, 139.37, 137.64, 132.68, 130.75, 130.67, 130.56, 129.11, 128.87, 128.63, 128.58, 127.96, 127.64, 126.41, 125.10, 124.24, 124.03, 123.73, 121.09, 120.10, 118.63, 112.76, 74.50.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{19}ONCl$: 396.1150, found: 396.1163.

FTIR (cm^{-1}): 3390, 3012, 2962, 1647, 1597, 1570, 1490, 1459, 1415, 1347, 1287, 1214, 1176, 1090, 1005, 955, 829, 741, 662, 630.

5-(4-Chlorophenyl)-8-methyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline (25i)



25i

Following the general procedure, treatment of 4-methylquinoline **23m** (0.073 g, 66 µL, 0.50 mmol) and 4-chlorobenzaldehyde (0.105 g, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded 5-(4-chlorophenyl)-8-methyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline as inseparable mixture of diastereomers as a white solid (0.090 g, 50% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 3:1).

R_f (Pet. ether /EtOAc = 60/40): 0.20.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.49 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.36-7.30 (m, 2H), 7.27-7.23 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 3H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.99-6.95 (m, 1H), 6.20 (s, 1H), 5.86 (m, 1H), 5.66 (d, *J* = 5.0 Hz, 1H), 2.18 (s, 3H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6) δ: 141.33, 139.69, 139.13, 138.41, 133.72, 133.52, 132.51, 129.41, 129.19, 128.41, 128.04, 126.57, 125.10, 124.77, 121.86, 119.42, 116.48, 112.40, 79.98, 78.51, 18.32.

Representative Peaks of Minor Isomer:

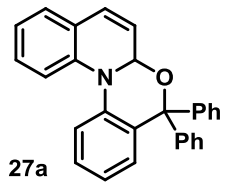
^{1}H NMR δ: 7.69-7.68 (m), 7.76-7.75 (m), 5.58-5.57 (m), 2.16 (s).

^{13}C NMR δ: 141.80, 133.68, 132.01, 130.50, 129.15, 128.52, 116.54, 76.07, 73.54.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{19}ONCl$: 360.1150, found: 360.1158.

FTIR (cm^{-1}): 3013, 1650, 1592, 1484, 1398, 1303, 1265, 1217, 1169, 1086, 985, 937, 812.

5,5-Diphenyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline (27a)



27a

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and benzophenone **26a** (0.136 g, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 5,5-diphenyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline as a yellow solid (0.105 g, 54% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.85.

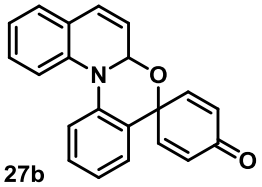
^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.55 (d, *J* = 7.7 Hz, 1H), 7.42-7.38 (m, 4H), 7.29-7.28 (m, 3H), 7.23-7.11 (m, 7H), 7.04-7.03 (m, 2H), 6.92-6.89 (m, 2H), 5.81-5.77 (m, 1H), 5.33 (d, *J* = 4.4 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d_6) δ: 146.46, 144.81, 139.37, 138.88, 134.36, 130.69, 129.30, 128.86, 128.77, 128.05, 127.78, 127.34, 127.08, 126.83, 125.52, 124.24, 120.76, 119.69, 118.40, 112.13, 84.65, 77.18.

HRMS: calculated $[M+H]^+$ for $C_{28}H_{22}ON$: 388.1696, found: 388.1701.

FTIR (cm^{-1}): 3012, 1656, 1599, 1489, 1457, 1369, 1215, 1029, 859, 817, 741, 665, 626.

6a*H*-Spiro[benzo[4,5][1,3]oxazino[3,2-a]quinoline-5,1'-cyclohexane]-2',5'-dien-4'-one (27b)



27b

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and benzoquinone **26b** (0.082 g, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 6a*H*-spiro[benzo[4,5][1,3]oxazino[3,2-a]quinoline-5,1'-cyclohexane]-2',5'-dien-4'-one as a white solid (0.124 g, 59% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.73.

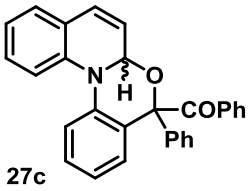
^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 7.62 (d, *J* = 7.9 Hz, 1H), 7.52-7.50 (m, 1H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.28-7.22 (m, 3H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 9.4 Hz, 1H), 6.93 (t, *J* = 6.7 Hz, 1H), 6.50-6.48 (m, 1H), 6.26 (d, *J* = 10.0 Hz, 1H), 6.09 (d, *J* = 9.9 Hz, 1H), 6.02-6.00 (m, 1H), 5.95 (d, *J* = 4.5 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 185.05, 150.78, 147.20, 139.68, 138.60, 129.53, 129.07, 128.20, 127.98, 127.92, 127.79, 126.51, 125.75, 125.57, 125.49, 120.58, 119.97, 117.98, 112.34, 77.36, 74.08.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{16}O_2N$: 314.1176, found: 314.1184.

FTIR (cm^{-1}): 3748, 3020, 1652, 1593, 1490, 1451, 1414, 1287, 1214, 1090, 1008, 928.

Phenyl(5-phenyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinolin-5-yl)methanone (27c)



27c

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and benzil **26c** (0.158 g, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded phenyl(5-phenyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinolin-5-yl)methanone as inseparable mixture of diastereomers as a yellow solid (0.131 g, 63% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.83.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.81 (d, *J* = 7.4 Hz, 2H), 7.55-7.49 (m, 2H), 7.41-7.32 (m, 5H), 7.29-7.16 (m, 8H), 7.00-6.91 (m, 2H), 5.65-5.55(m, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ: 197.06, 142.49, 139.05, 137.83, 134.08, 132.76, 131.84, 131.74, 130.59, 129.59, 129.55, 129.46, 128.74, 128.24, 128.02, 126.78, 125.49, 124.72, 124.08, 120.70, 120.02, 117.56, 112.42, 86.99, 79.05.

Representative Peaks of Minor Isomer:

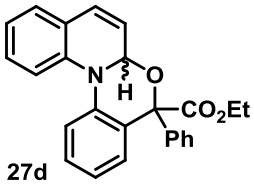
^{1}H NMR δ 7.67 (d, *J* = 8.1 Hz), 7.45-7.43 (m), 6.86 (d, *J* = 9.6 Hz), 5.89-5.85 (m).

^{13}C NMR δ: 198.60, 142.07, 139.35, 138.55, 135.04, 132.38, 130.00, 129.94, 127.75, 127.44, 129.41, 129.38, 128.88, 128.09, 125.20, 124.77, 120.24, 119.88, 111.75, 88.62, 78.32.

HRMS: calculated $[M+H]^+$ for $C_{29}H_{22}O_2N$: 416.1645, found: 416.1653.

FTIR (cm^{-1}): 1733, 1653, 1620, 1595, 1573, 1499, 1428, 1370, 1314, 1257, 1090, 1034.

5-Phenyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline-5-carboxylate (27d)



27d

Following the general procedure, treatment of quinoline **23a** (0.064 g, 59 µL, 0.50 mmol) and ethyl 2-oxo-2-phenylacetate **26d** (0.134 g, 119µL, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded ethyl 5-phenyl-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-a]quinoline-5-carboxylate as a white solid (0.147 g, 77% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is >20:1).

R_f (Pet. ether /EtOAc = 80/20): 0.80.

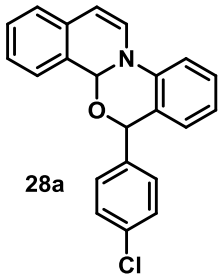
^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.59-7.55 (m, 2H), 7.49-7.45 (m, 1H), 7.30-7.20 (m, 7H), 7.06-7,04 (m, 2H), 6.95 (d, *J* = 9.6 Hz, 1H), 6.91-6.87 (m, 1H), 6.06-6.02 (m, 1H), 5.83 (t, *J* = 5.1 Hz, 1H), 4.31 (q, J_1 = 6.8 Hz, J_2 = 13.3 Hz, J_3 = 20.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, DMSO-d_6) δ: 171.33, 141.67, 139.58, 138.99, 130.22, 130.14, 129.42, 128.99, 128.22, 127.65, 126.79, 125.07, 124.64, 120.75, 119.86, 117.97, 112.18, 83.96, 79.29, 61.90, 13.89.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{22}O_3N$: 384.1594, found: 384.1599.

FTIR (cm^{-1}): 1732, 1651, 1593, 1487, 1446, 1280, 1217, 1118, 1052, 1027, 962, 896, 824.

6-(4-Chlorophenyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline (28a)



28a

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 4-chlorobenzaldehyde (0.105 g, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 6-(4-chlorophenyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline as inseparable mixture of diastereomers as a yellow solid (0.140 g, 81% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 3:2).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.71.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 7.43 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 3H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.28-7.25 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.15-7.13 (m, 1H), 7.11-7.08 (m, 2H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.49 (s, 1H), 6.43 (s, 1H), 5.75 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 140.87, 140.32, 132.60, 131.39, 130.81, 129.91, 1229.15, 128.56, 128.47, 128.40, 127.83, 127.24, 125.35, 125.29, 123.65, 122.80, 117.65, 99.24, 82.68, 74.93.

Representative Peaks of Minor Isomer:

^{1}H NMR δ: 7.52 (d, *J* = 78.4 Hz), 7.48 (d, *J* = 8.2 Hz), 7.04 (d, *J* = 7.2 Hz), 6.83 (d, *J* = 7.5 Hz), 6.05 (s), 5.99 (s), 5.70 (d, *J* = 7.6 Hz).

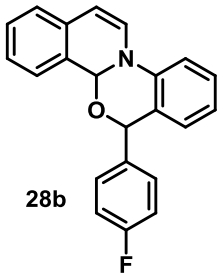
^{13}C NMR δ: 141.17, 140.16, 132.83, 129.80, 129.48, 128.99, 128.78, 128.28, 128.14, 127.72, 124.81, 123.71, 121.89, 116.80, 99.13, 77.44, 75.26.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{17}ONCl$: 346.0993, found: 346.0872.

FTIR (cm^{-1}): 3736, 3019, 1730, 1854, 1601, 1506, 1456, 1373, 1216, 1156, 1043, 931.

6-(4-Fluorophenyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline (28b)

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 4-fluorobenzaldehyde (0.093 g, 80µL, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g,



28b

1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 6-(4-fluorophenyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline as inseparable mixture of diastereomers as a yellow solid (0.151 g, 92% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 3:2).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.63.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 7.19-7.43 (m, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.34-7.32 (m, 2H), 7.28-7.26 (m, 1H), 7.19-7.13 (m, 2H), 7.12-7.07 (m, 3H), 7.00-6.96 (m, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.50 (s, 1H), 6.43 (s, 1H), 5.74 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 161.75 (d, *J* = 243.8 Hz), 140.35, 138.13 (d, *J* = 2.7 Hz), 131.40, 131.10 (d, *J* = 8.5 Hz), 130.18, 130.10, 129.14, 128.54, 127.78, 127.28, 125.41, 125.28, 123.62, 122.77, 117.62, 116.75, 115.18 (d, *J* = 21.5 Hz), 99.20, 82.68, 79.47.

Representative Peaks of Minor Isomer:

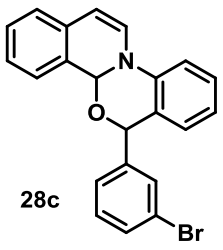
^{1}H NMR δ: 7.58-7.55 (m), 7.05-7.03 (m), 6.82(d, *J* = 7.5 Hz), 6.06 (s), 6.00 (s), 5.70 (d, *J* = 7.6 Hz).

^{13}C NMR δ: 140.14, 138.66 (d, *J* = 2.9 Hz), 131.42, 129.86, 129.78, 129.47, 128.97, 128.81, 128.18 (d, *J* = 8.2 Hz), 127.66, 125.45, 125.37, 125.13, 123.70, 121.86, 115.25 (d, *J* = 21.2 Hz), 99.10, 77.24, 75.30.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{17}ONF$: 330.1289, found: 330.1297.

FTIR (cm^{-1}): 3014, 1653, 1593, 1491, 1451, 1417, 1285, 1216, 1119, 1046, 1001, 922.

6-(3-Bromophenyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline (28c)



28c

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 3-bromobenzaldehyde (0.139 g, 88µL, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 6-(3-bromophenyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-

a]isoquinoline as inseparable mixture of diastereomers as a yellow solid (0.121 g, 62% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 3:2).

R_f (Pet. ether /EtOAc = 80/20): 0.61.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.62-7.59 (m, 1H), 7.49-7.43 (m, 2H), 7.41-7.35 (m, 2H), 7.33-7.31 (m, 2H), 7.29-7.25 (m, 1H), 7.19-7.16 (m, 1H), 7.14-7.08 (m, 2H), 6.99 (d, *J* = 7.1 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.48 (s, 1H), 6.43 (s, 1H), 5.76 (d, *J* = 7.4 Hz, 1H).

^{13}C NMR (100F MHz, DMSO-d_6) δ: 144.60, 140.32, 131.37, 130.95, 130.65, 130.53, 129.23, 129.18, 128.57, 127.90, 127.60, 127.23, 125.32, 125.28, 123.68, 122.89, 121.52, 117.78, 99,28, 82.65, 79.36.

Representative Peaks of Minor Isomer:

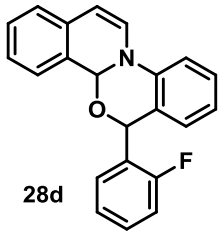
^{1}H NMR δ: 7.06-7.04 (m), 6.84 (d, *J* = 7.9 Hz), 6.08 (s), 6.00 (s), 5.71 (d, *J* = 7.7 Hz).

^{13}C NMR δ: 144.86, 140.17, 131.64, 131.40, 130.73, 129.80, 129.02, 128.75, 128.35, 128.12, 127.99, 125.40, 124.57, 123.75, 121.94, 121.83, 116.84, 99.18, 77.63, and 75.26.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{17}ONBr$: 390.0488, found: 390.0499.

FTIR (cm^{-1}): 3865, 3748, 3019, 1730, 1600, 1489, 1455, 1372, 1218, 1043, 934, 769, 741, 666, 631.

6-(2-Fluorophenyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline (28d)



28d

Following the general procedure, treatment of 1soquinoline **9a** (00.064 g, 59 µL, 0.50 mmol) and 2-fluorobenzaldehyde (0.095 g, 79µL, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded 6-(2-fluorophenyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline as inseparable mixture of diastereomers as a yellow solid (0.105 g, 64% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 3:1).

R_f (Pet. ether /EtOAc = 80/20): 0.65.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.48-7.46 (m, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.37-7.34 (m, 1H), 7.32-7.31 (m, 1H), 7.29-7.26 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 8.2

Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.07-7.06 (m, 1H), 7.01-6.97 (m, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.73 (s, 1H), 6.53 (s, 1H), 5.77 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 160.29 (d, *J* = 247.3 Hz), 140.63, 131.42, 130.09 (d, *J* = 8.5 Hz), 129.85, 129.81, 129.08 (d, *J* = 4.2 Hz), 128.62, 128.57, 127.79, 127.75, 126.46, 125.27 (d, *J* = 9.1 Hz), 124.42 (d, *J* = 3.9 Hz), 123.60, 122.85, 117.57, 115.56 (d, *J* = 21.6 Hz), 99.22, 82.89, 74.32.

Representative Peaks of Minor Isomer:

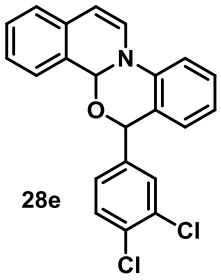
^{1}H NMR δ: 7.24-7.21 (m), 6.29 (s), 6.16 (s), 5.74 (d, *J* = 7.6 Hz).

^{13}C NMR δ: 160.44 (d, *J* = 248.7 Hz), 140.50, 131.32 (d, *J* = 3.6 Hz), 130.49 (d, *J* = 8.2 Hz), 129.88, 128.99, 128.92, 128.75, 128.25, 127.67, 123.97 (d, *J* = 2.7 Hz), 123.71, 122.03, 116.72, 115.70 (d, *J* = 21.4 Hz), 99.13, 77.56, 70.56.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{17}ONF$: 330.1289, found: 330.1300.

FTIR (cm^{-1}): 3015, 1654, 1601, 1490, 1456, 1216, 1029, 934, 740, 666, 629.

6-(3,4-Dichlorophenyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline (28e)



28e

Following the general procedure, treatment of isoquinoline **9a** (0.064 g, 59 µL, 0.50 mmol) and 3**,**4-dichlorobenzaldehyde (0.130 g, 0.75 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded **6**-(3,4-dichlorophenyl)-4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline as inseparable mixture of diastereomers as a yellow solid (0.146 g, 77% yield, *dr* determined by ^{1}H NMR analysis of crude reaction mixture is 1:1).

R$_f$ (Pet. ether /EtOAc = 80/20): 0.73.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 7.56-7.54 (m, 2H), 7.41-7.34 (m, 2H), 7.32-7.24 (m, 3H), 7.18-7.15 (m, 1H), 7.13-7.08 (m, 2H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.47 (s, 1H), 6.44 (s, 1H), 5.76 (d, *J* = 7.5 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 142.96, 140.30, 131.37, 131.04, 130.71, 129.87, 129.72, 129.22, 128.87, 128.60, 128.25, 128.01, 127.22, 125.34, 125.20, 123.72, 122.93, 117.82, 99.33, 82.69, 78.77.

Representative Peaks of Minor Isomer:

^{1}H NMR δ: 7.70 (d, *J* = 8.4 Hz), 7.62 (d, *J* = 1.8 Hz), 7.47 (d, *J* = 8.3 Hz), 7.04 (d, *J* = 7.2 Hz), 6.86 (d, *J* = 7.6 Hz), 6.08 (s), 5.99 (s), 5.71 (d, *J* = 7.5 Hz).

^{13}C NMR δ: 143.15, 140.24, 131.25, 130.95, 130.90, 129.16, 129.04, 128.74, 128.44, 128.10, 127.86, 125.40, 124.32, 122.03, 116.98, 99.20, 77.70, 74.69.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{16}ONCl_2$: 380.0603, found: 380.0611.

FTIR (cm^{-1}): 3744, 3017, 1653, 1593, 1491, 1456, 1290, 1216, 1033, 928, 768, 741, 667.

6.12. References

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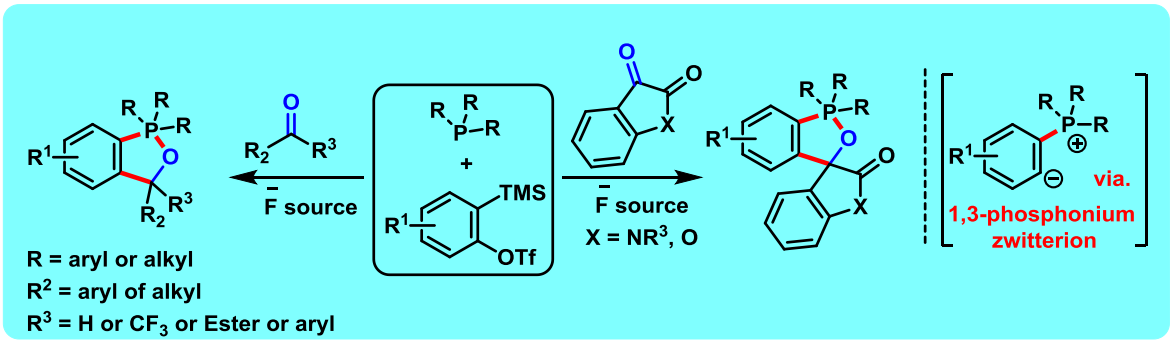
Chapter 7

Phosphines Triggered Aryne Multicomponent Reactions

The synthetic utilities of phosphines as a nucleophilic trigger in transition-metal-free aryne multicomponent reactions are demonstrated in this chapter. The reaction proceeds via a formal [3+2] cycloaddition of 1,3-phosphonium zwitterions generated from phosphine and aryne with aldehydes. This method gives a diverse range of stable benzooxaphosphole derivatives with good to excellent yields. The reaction is compatible with all the three components. Additionally, we have carried out mechanistic studies to get insight into the key intermediate, and the reaction pathways of this annulation reaction. Subsequently, we uncovered an operationally simple MCR involving phosphines, arynes and various acyclic and cyclic activated carbonyl compounds. The reaction resulted in a convenient synthesis of (spiro)benzoxaphospholes in moderate to good yields



Chem. Commun. **2014**, *50*, 11389-11392

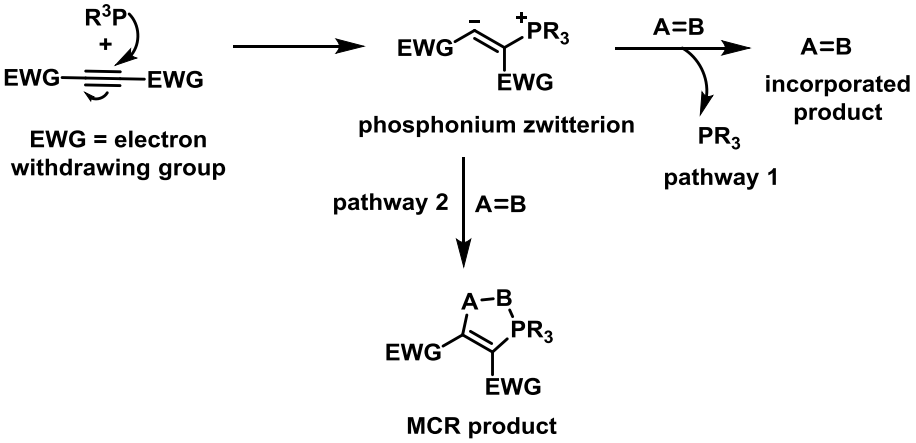
Org. Lett. **2014,** *16*, 5132-5135

PCT Int. Appl. (**2015**) WO 2015128878 A1 20150903

7.1. Introduction

Organophosphorous compounds contain a direct carbon-phosphorous bond, are synthetic target of interest because of their biological and industrial applications.[1] Moreover, phosphorous compounds are important for metal-mediated and organo-mediated processes.[2] Since the development of Wittig's olefination reaction using phosphonium ylides,[3] a number of phosphine mediated/catalyzed processes have been reported.[4] The non-basic nature of tri-substituted phosphine makes it a good nucleophilic species. Phosphines prove to be an important catalyst for many organic transformations such as Morita-Baylis-Hillman reaction, and its aza version, Rauhut-Currier reactions. The underlying principle of these reactions is the initial generation of the phosphonium zwitterion by the nucleophilic addition of phosphines to activated olefins (alkenes, alkynes, and allenes), which is subsequently intercepted with diverse electrophiles for the synthesis of various cyclic and acyclic products (Scheme 7.1 pathway 1). Apart from the phosphine catalyzed reactions, there are examples where phosphines are used in stoitiometric amounts such as the Staudinger and Mitsunobu reactions.[4b] In such reactions, the nucleophilic trigger is ejected out in the end as phosphine oxide. In comparison, the utility of phosphine as a substrate, which is incorporated in the final product thus leading to organophosphorous compounds are not well-explored (Scheme 7.1 pathway 2).

Scheme 7.1: Addition of Phospines to Activated Olefines

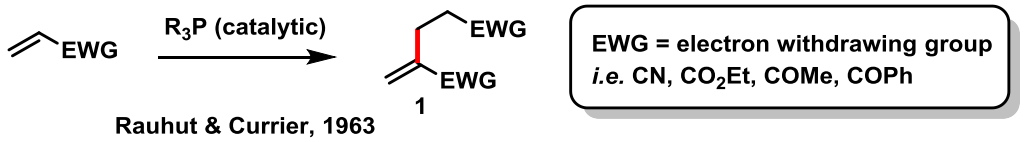


In this chapter, a unique MCR based on arynes, phosphine, and aldehydes are presented. Before discussing the results, a brief overview of phosphine mediated reaction is presented in the following sections.

7.2. Rauhut-Currier Reaction

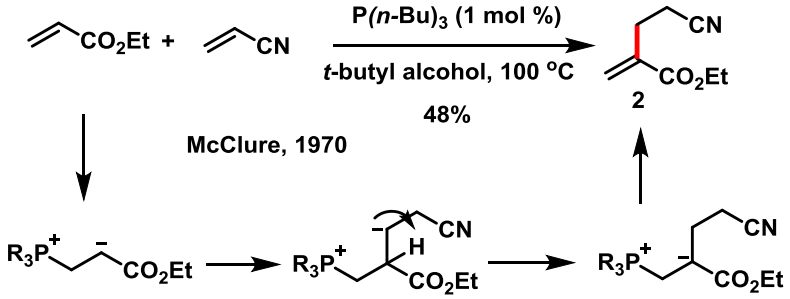
In the early 1960s, Rauhut and Currier established an elegant way of dimerization of activated alkenes mediated by phosphines to form the head-tail dimer **1** (Scheme 7.2).[5] Simultaneously, McClure and Anderson groups independently developed the homo-coupling of activated olefins.[6]

Scheme 7.2: Rauhut-Currier Reaction



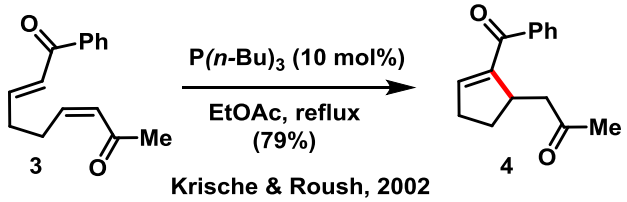
In 1970, McClure group reported the cross-coupling of ethyl acrylate and acrylonitrile. The reaction proceeds through a conjugate addition of phosphines to acrylate followed by a Michael addition to acrylonitrile. A proton shift followed by removal of phosphines resulted in cross-coupled products **2** (Scheme 7.3). However, the lack of selectivity in this cross-coupling reaction remains a primary issue.[7] After that there have been only few reports on the intermolecular Rauhut-Currier reactions.[8]

Scheme 7.3: Intermolecular Cross-Rauhut-Currier Reaction



Recently, Krische and Roush groups independently developed an intramolecular Rauhut-Currier reaction, in which the nucleophilic phosphines underwent a chemoselective addition to the more electrophilic olefin leading to the formation of cyclopentene derivatives **4** from the enone-enoate **3** (Scheme 7.4).[9]

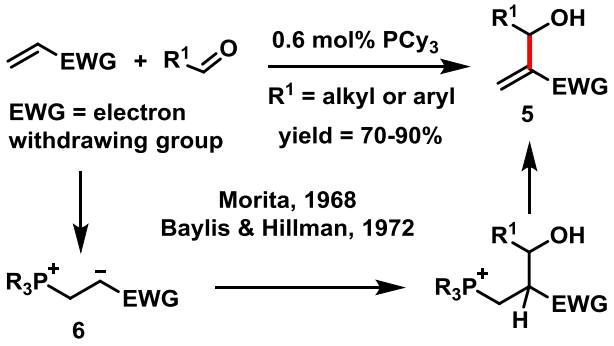
Scheme 7.4: Intramolecular Cross-Rauhut-Currier Reaction



7.3. Morita-Baylis-Hillman Reaction

Morita developed a phosphine-catalyzed cross-coupling reaction of aldehydes and activated olefins.[10] The phosphonium zwitterionic intermediate **6** undergoes a nucleophilic addition to aldehydes leading to the formation of α–alkylidene–β–hydroxy carbonyl derivatives **5** (Scheme 7.5). In 1972, Baylis and Hillman reported the same reactivity using DABCO as a catalyst instead of phosphine.[11] Recently Shi and co-workers developed the *aza*-MBH reaction by replacing the aldehydes with electrophilic imines.[12]

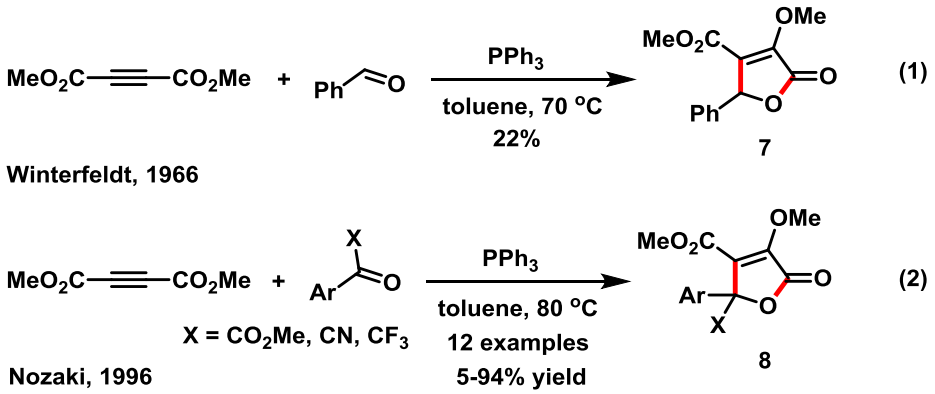
Scheme 7.5: Morita-Baylis-Hillman Reaction



7.4. Phosphonium Zwitterion from DMAD

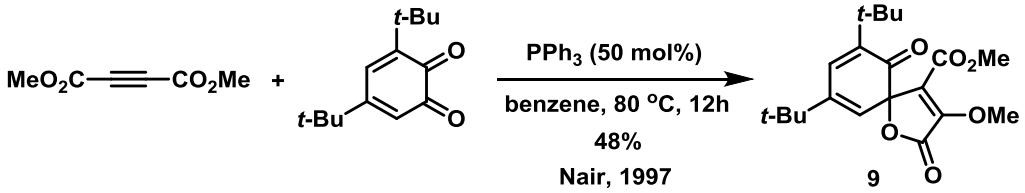
In 1966, Winterfeldt reported that the zwitterions generated from tri-phenyl phosphine and dimethyl acetylenedicarboxylate (DMAD) can react with benzaldehyde to give γ-butyrolactone derivative **7** in low yield (Scheme 7.6, eq. 1).[13] Later Nozaki modified the Winterfeldt's protocol using activated carbonyls such as α-ketoesters, α-ketonitriles *etc*. to achieve the γ-butyrolactone derivatives **8** in moderate to good yields (Scheme 7.6, eq. 2).[14] Lu and co-workers also reported similar annulation of phosphonium zwitterions with N-tosylimines to generate the pyrrolidone derivatives.[15]

Scheme 7.6: Trapping of Phosphonium Zwitterions with Aldehyde



In 1997, Nair and co-workers developed the synthesis of highly functionalized γ-spirolactones **9** by phosphine-mediated annulation of 1,2- and 1,4-benzoquinones and DMAD (Scheme 7.7).[16]

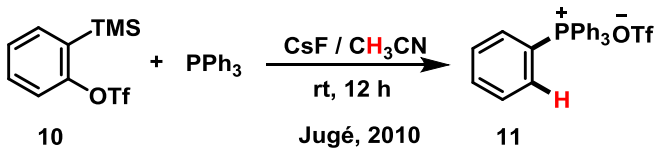
Scheme 7.7: Trapping of Phosphonium Zwitterions with Benzoquinones



7.5. Statement of the Problem

As already indicated, the phosphonium zwitterions generated from phosphines and activated olefins can be intercepted with diverse range of electrophiles to form various cyclic and acyclic products. However, the incorporation of phosphines as a third-component in the final product thereby constituting multicomponent reaction is not well developed.[17] In the previous chapter, we have demonstrated a novel MCR involving N-heterocycles, arynes and N-substituted isatins. With (iso)quinoline as the nucleophilic trigger, the reaction furnished spirooxazino (iso)quinoline derivatives and the reaction proceeded via 1,4-zwitterionic intermediates. Interestingly, when pyridine was used as the nucleophile, the reaction afforded indolin-2-one derivatives, and the reaction proceeded via a pyridylidene intermediate.[18] With this background information, we envisaged the MCR involving phosphines, arynes and electrophiles. Notably, the addition of phosphines to arynes leading to the formation of the phosphonium salt **11** via the phosphine-aryne zwitterion was first uncovered by Wittig in 1971,[19] and the scope of this reaction was expanded by Jugé and co-workers recently[20] by generating arynes from 2-(trimethylsilyl)aryl triflates **10** by the fluoride-induced 1,2-elimination (Scheme 7.8).[21]

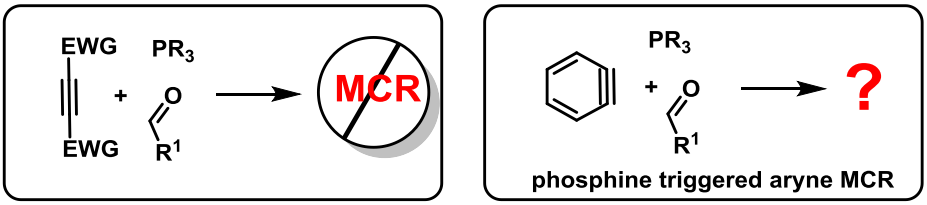
Scheme 7.8: Formation of Tetraphenyl Phosphonium Salt from PPh_3 and Aryne



However, the synthetic potential of phosphine-aryne zwitterion in MCRs is unexplored. We envisaged the generation of 1,3-zwitterionic system from highly electrophilic arynes.[22,23] However, the challenges include the compatibility of aryne

generation under the reaction conditions and the formation of the undesired adducts from phosphines and arynes. Notably, related MCRs are not reported using activated alkynes using phosphines. The successful application of aryne chemistry may extend this method to the synthesis of a variety of phosphine-heterocycles, where zwitterionic intermediates are generated by the addition of nucleophile to activated C-C multiple bonds followed by their interception with a third component (Figure 7.1).

Figure 7.1: Proposed MCR of Aryne, phosphine and aldehyde

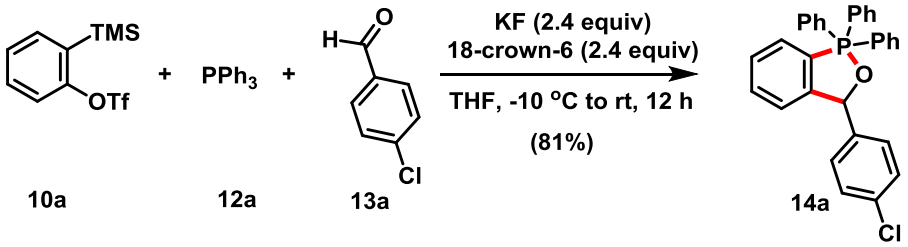


7.6. Results and Discussion

7.6.1. MCR Involving Phosphines, Arynes and Aldehydes

The present study commenced by treating triphenylphosphine **12a** and 4-chlorobenzaldehyde **13a** with the aryne generated from 2-(trimethylsilyl)aryl triflate **10a** using KF and 18-crown-6. Delightfully, a facile reaction took place resulting in the formation of benzooxaphosphole derivative **14a** in 81% yield (Scheme 7.9). The product **14a** was characterized using the common spectroscopic techniques and finally the structure of **14a** was unequivocally confirmed by single-crystal X-ray analysis (Figure 7.2). The optimization studies revealed that the use of other fluoride sources such as tetrabutylammonium fluoride (TBAF) and CsF were not beneficial, and reaction temperature above - 10 °C was not efficient.

Scheme 7.9: MCR Involving Phosphines, Arynes and Aldehydes

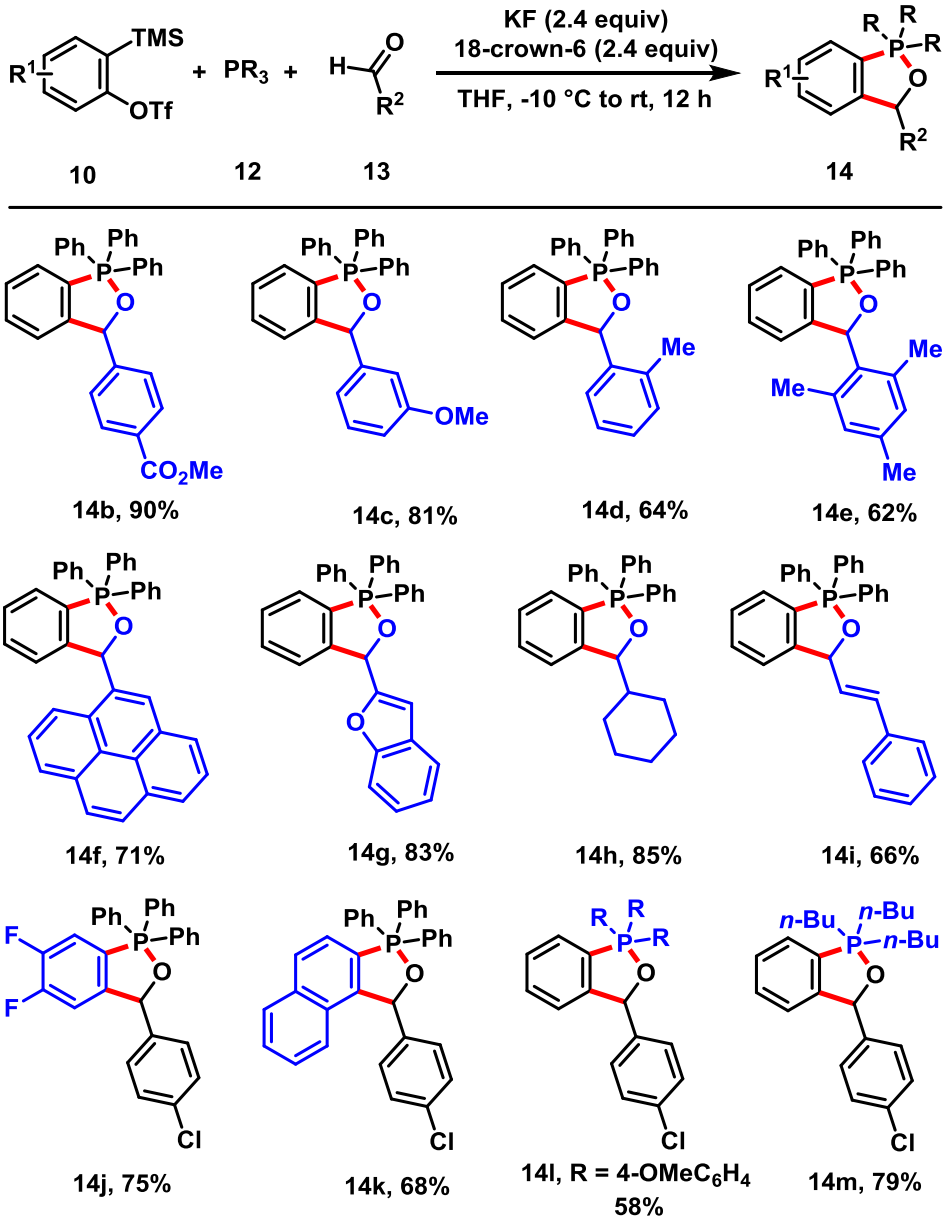


7.6.2. MCR Involving Phosphines, Arynes and Aldehydes: Substrate Scope

With the optimized reaction conditions in hand, we then examined the scope of this unique MCR (Scheme 7.10). First we evaluated various aldehydes. The reaction was well

tolerated with an ester group at the 4-position of the aromatic aldehyde, leading to the formation of corresponding benzoxaphosphole derivatives **14b** with 90% yield. Moreover, substitution at 3-position and 2-position of aromatic ring resulted in a smooth conversion to the product (**14c** & **14d**). Interestingly, sterically hindered 2,4,6-trimethylbenzaldehyde was well-tolerated leading to the formation of the desired product **14e** in 62% yield. Furthermore, pyrene-1-carbaldehyde worked efficiently, and the corresponding benzoxa-

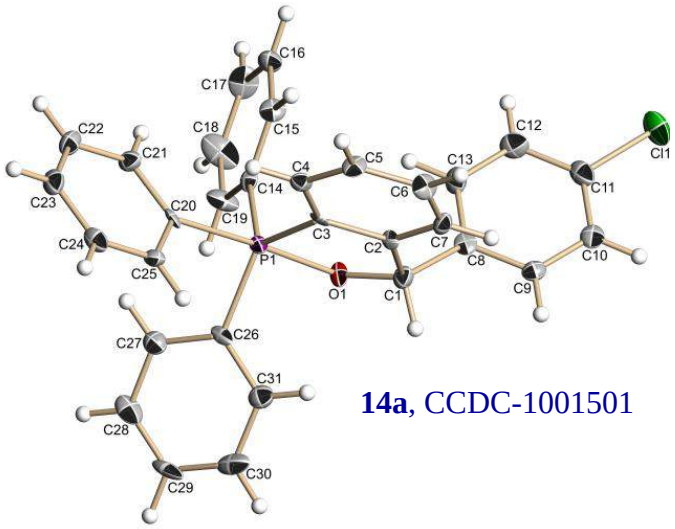
Scheme 7.10: MCR of Phosphines, Arynes and Aldehydes: Substrate Scope [a]



[a] General conditions: **10** (0.6 mmol), **12** (0.5 mmol), 1**3** (0.75 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (3.0 mL) at -10 °C to rt for 12 h. Yields of isolated products are given.

phosphole **14f** was formed in 71% yield. Additionally, benzofuran-2-carbaldehyde furnished the desired product **14g** in good yield. Furthermore, aliphatic aldehydes such as cyclohexyl carboxaldehyde and *trans*-cinnamaldehyde resulted in the formation of the desired products in moderate to good yields (**14h** & **14i**). The reaction of 4,5-difluoro substituted aryne readily furnished the benzooxaphosphole **14j** in 75% yield. Moreover, the reaction of unsymmetrical naphthalyne afforded single regioisomers **14k** in 68% yield. Furthermore, 4-methoxy substituted aromatic phosphine was well tolerated under the present reaction conditions furnishing the corresponding benzooxaphospholes in 58% yield (**14l**). Interestingly, aliphatic phosphine also underwent smooth annulation reaction producing the product **14m** in 79% yield.

Figure 7.2: The ORTEP Diagram of **14a**.

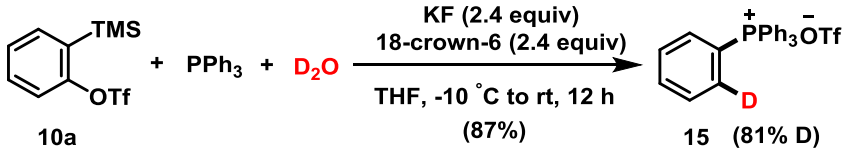


14a, CCDC-1001501

7.6.3. Deuterium Labelling Experiment

To get insight into the mechanism of this reaction, we performed several mechanistic experiments. To shed light on the generation of the phosphonium salt from aryne and phosphine, the reaction was carried out in presence of D_2O. Interestingly, the reaction of PPh_3 and aryne in the presence of D_2O afforded the phosphonium salt **15** in 87% yield with 81% deuterium incorporation at the 2-position of the ring (Scheme 7.11). The incorporation of 81% deuterium at the 2-position of the ring indicates the initial formation of the zwitterionic intermediate from PPh_3 and aryne, which is subsequently quenched by D_2O leading to **15**.

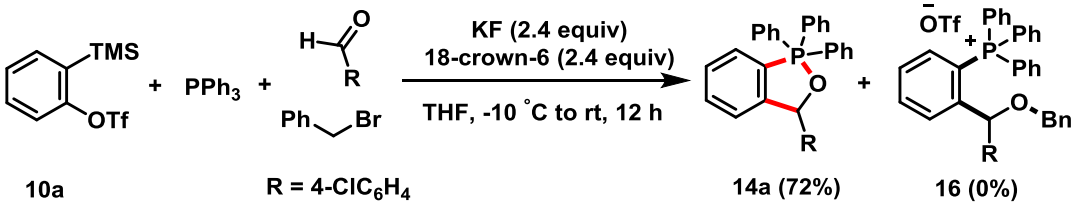
Scheme 7.11: Deuterium Labelling Experiment.



7.6.4. Zwitterion Trapping Experiment

To get further insight on the mechanism of this annulation reaction, an experiment was conducted in the presence of benzyl bromide under optimized conditions. The reaction resulted in the formation of the MCR product **14a** in 72% yield. No benzyl incorporated product **16** was observed, which indicates the concerted nature of this annulation reaction (92% benzyl bromide was recovered).

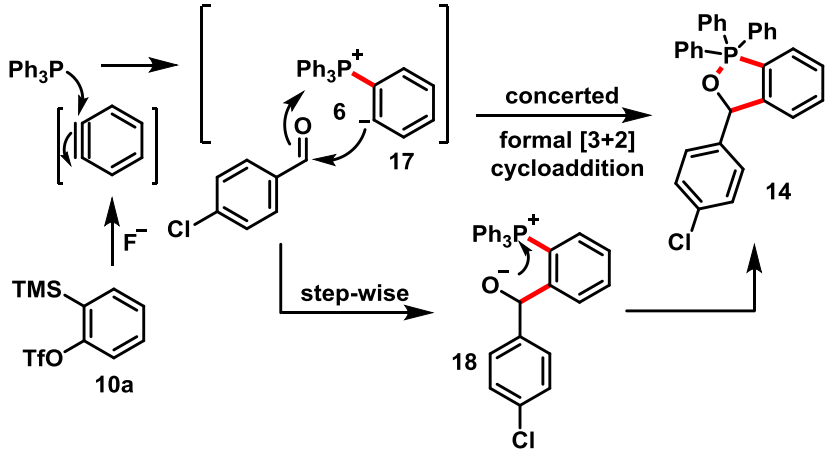
Scheme 7.12: Zwitterions Trapping Experiment.



7.6.5. Proposed Reaction Mechanism

Based on the results of our preliminary mechanistic investigation, we propose a plausible mechanism of this unprecedented aryne MCR as outlined in Scheme 7.13. The reaction can be considered to proceed via the initial generation of the 1,3-dipolar intermediate **17** from triphenylphosphine and aryne (generated from **10a**). The zwitterion **17** can undergo a concerted [3+2] cycloaddition reaction with electrophilic carbonyl group

Scheme 7.13: Plausible Mechanism of the Reaction



of aldehyde resulting in the formation of the benzooxaphosphole **14**. Alternatively, the desired product formation can also be rationalized by a step-wise mechanism proceeding through the tetrahedral intermediate **18**, which cyclizes to afford **14**. Since no alkylation of **18** was observed in the reaction using benzyl bromide (leading to **16**, Scheme 7.12), it is reasonable to believe that the present reaction proceeds via a concerted pathway.

7.6.6. Reaction using Triphenylarsine as a Nucleophilic Trigger

Next, we have studied the use of triphenylarsine **19** as the nucleophilic trigger instead of PPh_3. Interestingly; the expected annulation reaction did not take place in this case. But instead, the reaction afforded the arsonium triflate **20** in 52% yield (Scheme 7.14). The structure of the triflate salt **20** was confirmed by single crystal X-ray analysis (Figure 7.3).

Scheme 7.14: Triphenylarsine Triggered MCR

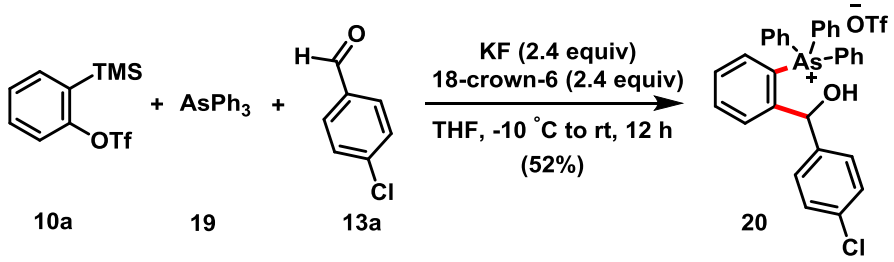
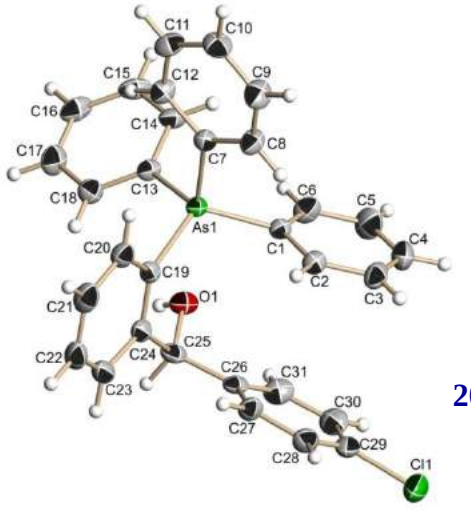


Figure 7.3: The ORTEP Diagram of **20**.



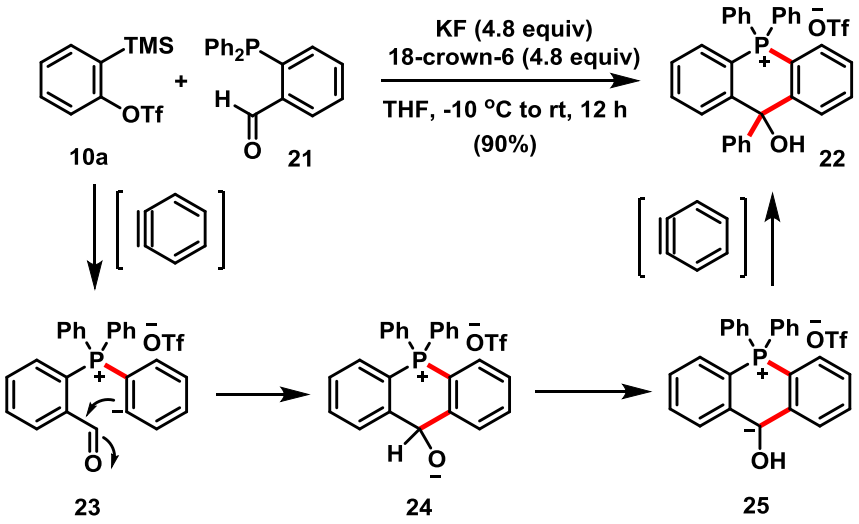
20, CCDC-1001503

7.6.7. Intramolecular Reaction

Furthermore, we have studied the intramolecular version of this reaction. Treatment of phosphanyl benzaldehyde **21** with aryne resulted in the formation of the phosphonium

salt **22** in 90% (Scheme 7.15). The reaction proceeds via the generation of alkoxide intermediate **24** followed by a proton exchange to generate the intermediate **25**. In addition, the formation of **22** sheds light on a rather non-concerted nature of the aryne annulation reactions triggered by phosphines. It may be mentioned that the expected bicyclic benzooxaphosphole derivative was not formed in this case may be due to the ring strain involved in the formation of the bicyclic system, which makes the intermediate alkoxide intermediate **24** to undergo *C*-arylation with excess aryne.

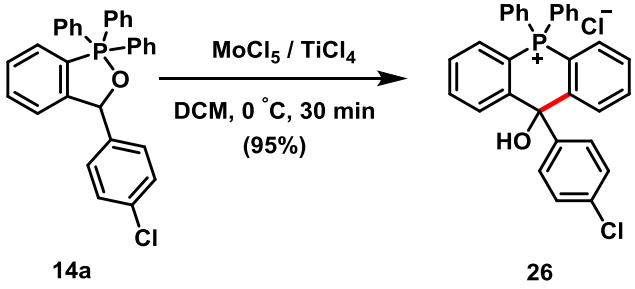
Scheme 7.15: Intramolecular Reaction

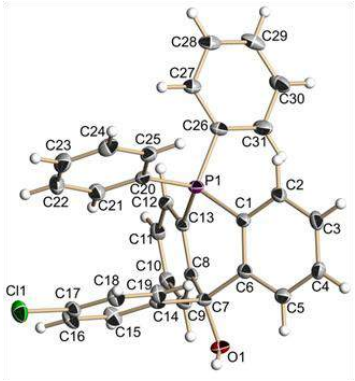


7.6.8. Mo-Mediated Oxidative Coupling

A synthetic transformation of the benzooxaphosphole derivative was performed using Mo-reagent.

Scheme 7.16: Mo-Mediated Oxidative Coupling





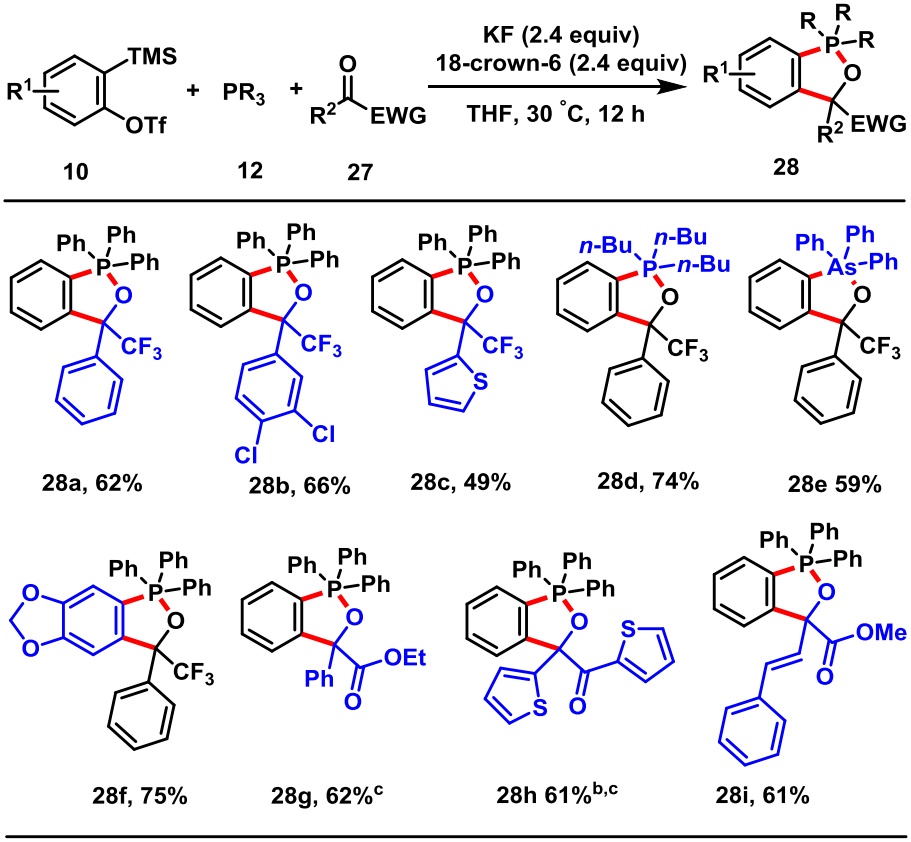
ORTEP Diagram of 26
CCDC-1001504

Treatment of **14a** with $MoCl_5/TiCl_4$ resulted in the formation of diphenyl dihydroacridophosphonium salt **26** in 95% yield (Scheme 7.16).[24] The reaction proceeds via the P-O bond-cleavage of benzooxaphosphole **14a** followed by a formal Csp^3-Csp^2 oxidative coupling mediated by Mo leading to the formation of **26**. The structure of **26** was confirmed by single crystal X-ray analysis.

7.6.9. MCR Involving Phosphines, Arynes and Activated Acyclic Carbonyls

In view of the interesting result obtained in MCR involving phosphines, arynes and aldehydes, we then focused our attention on various cyclic and acyclic carbonyl compounds. Initially, this mild and efficient phosphine-triggered aryne MCR has been expanded to activated acyclic ketones **27** as the third component resulting in the formation of functionalized benzoxaphospholes **28** in moderate to good yields (Scheme 7.17).

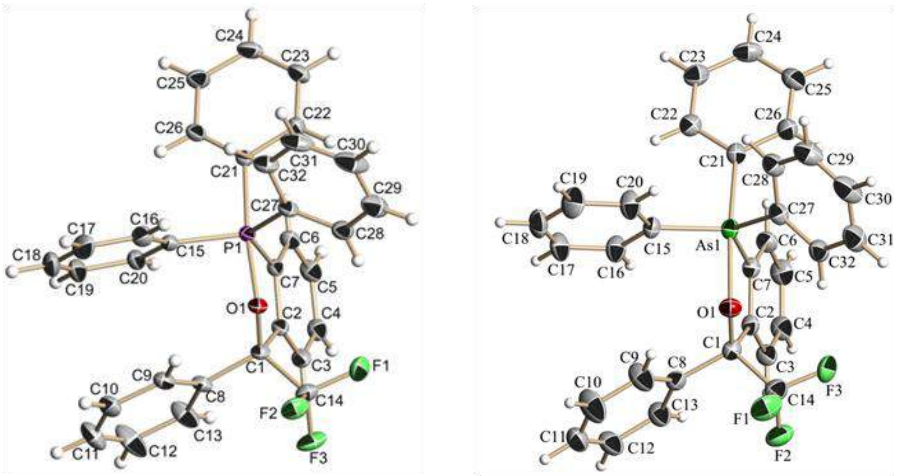
Scheme 7.17: MCR Involving Phosphines, Arynes and Activated Acyclic Carbonyls: Substrate Scope [a]



[a] General conditions: **10** (0.60 mmol), **12** (0.50 mmol), **27** (0.75 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (3.0 mL) at 30 °C for 12 h. Yields of isolated products are given. [b] The reaction was run on 0.25 mmol scale. [c] The reaction was performed using 1.0 mmol of **10**, 2.0 mmol of KF and 18-crown-6.

We initiated our study by treating triphenylphosphine **12a** and 2,2,2-trifluoro-1-phenylethan-1-one **27a** with the aryne generated from 2-(trimethylsilyl)aryl triflate **10a** using KF and 18-crown-6. Under these conditions, a facile reaction occurred leading to the formation of the benzoxaphosphole derivative **28a** in 68% yield. In addition, substituted aromatic trifluoroacetophenones and heterocyclic trifluoromethyl ketones were well-tolerated affording the benzoxaphosphole derivatives in good yields (**28b** & **28c**). Moreover, tributylphosphine and triphenylarsine can be used as the nucleophilic trigger providing the desired product in good yields (**28d** & **28e**). Symmetrically substituted aryne generated from 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate underwent smooth cyclization reaction to afford the **28f**. Interestingly, α-ketoester such as ethyl benzoylformate, and 2,2'-thenil furnished the corresponding benzoxaphosphole derivatives in moderate to good yields (**28g** & **28h**). Furthermore, α-keto β,γ-unsaturated ester can also be used as the activated carbonyl component, and the target benzoxaphosphole **28i** was isolated in 61% yield. The structure of **28a** and **28e** were confirmed by single crystal X-ray analysis (Figure 7.4).

Figure 7.4: ORTEP Diagram of **28a** and **28e**.

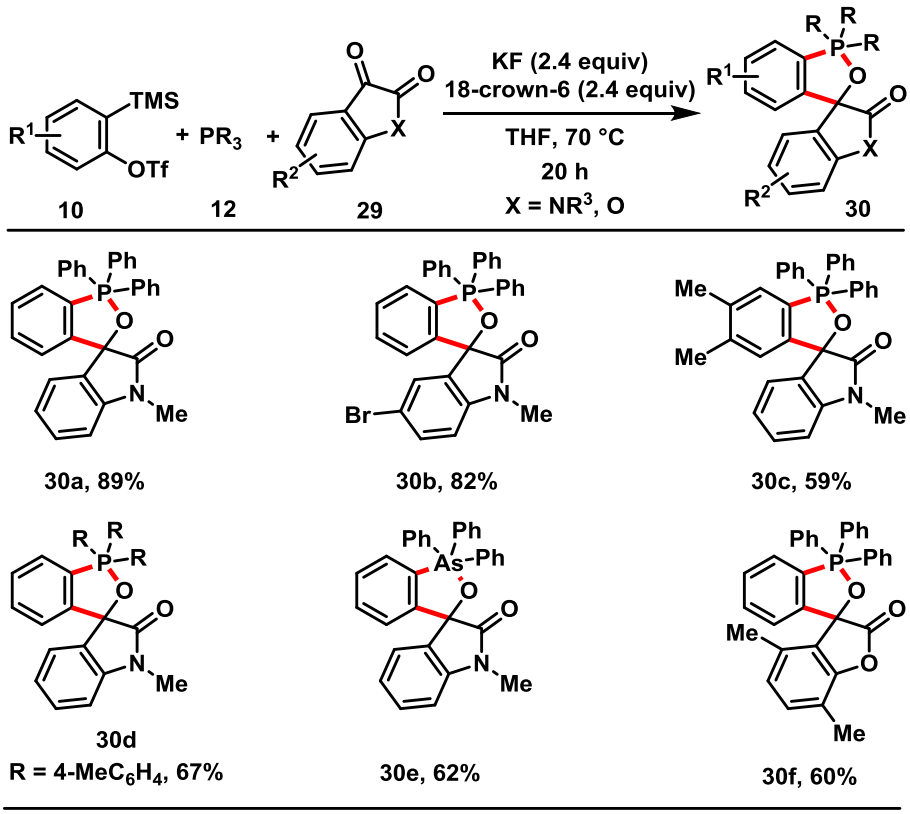


7.6.10. MCR Involving Phosphines, Arynes and Activated Cyclic Carbonyls

Next, we then focused our attention on activated cyclic carbonyl compounds. We began our studies using N-substituted isatins as the third-component. In a pilot experiment, treatment of **12a** with N-methyl isatin **29a** and aryne generated from **10a** using KF and 18-

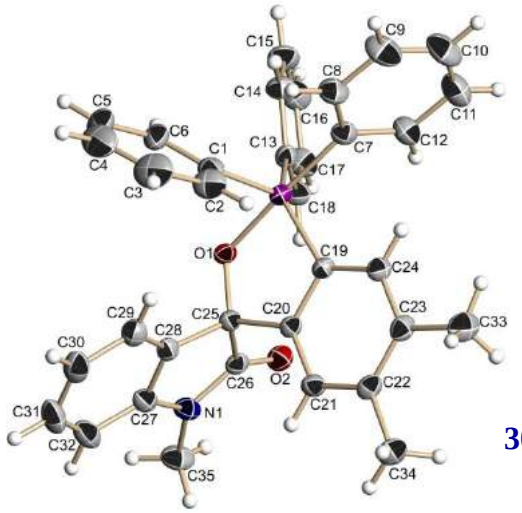
crown-6 resulted in the formation of the spirobenzoxaphosphole derivative **30a** in 89% yield (Scheme 7.18). Notably, this reaction proceeds at a high temperature (70 °C), and a longer reaction time of 20 h. Regarding the scope of this reaction, a substitution on the carbocyclic ring of isatin afforded the corresponding product **30b** in 82% yield. In addition, symmetrical aryne derived from its precursor afforded the corresponding product **30c** in 58% yield. Furthermore, tri *p*-tolyl phosphine is useful as nucleophilic trigger in the present annulation reaction to form the product **30d** in 67% yield, and triphenylarsine can also be used as the initiator in the present aryne MCR affording the desired product **30e** in 62% yield. Interestingly, the use of 4,7-dimethylbenzofuran-2,3-dione as a third-component was successful and the corresponding product **30f** was isolated in 60% yield. The structure of **30c** finally conformed by single crystal X-ray analysis (Figure 7.5).

Scheme 7.18: MCR Involving Phosphines, Arynes and Activated Cyclic Carbonyls: Substrate Scope [a]



[a] General conditions: **10** (0.75 mmol), **12** (0.50 mmol), **29** (0.75 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (4.0 mL) at 70 °C for 20 h. Yields of isolated products are given.

Figure 7.5: ORTEP Diagram of **30c**.



30c, CCDC-1020395

7.7. Conclusion

In conclusion, we have developed the transition-metal-free MCR involving phosphines, arynes and aldehydes leading to the synthesis of benzooxaphosphole system with pentacovalent phosphoranes. Subsequently, we uncovered the usefulness of various acyclic and cyclic activated carbonyl compounds as the third-components instead of aldehydes. The reaction resulted in a convenient synthesis of (spiro)benzoxaphospholes in moderate to good yields. Mechanistically, this reaction proceeds via the initial generation of a 1,3-zwitterionic intermediate from phosphine and aryne, which undergoes a formal [3+2] cycloaddition with carbonyls allowing the synthesis of phosphorus heterocycles. The compatibility with wide range of functional groups, ease of variation of all the three components, mild reaction conditions, and high yield of products are the noteworthy features of this reaction.

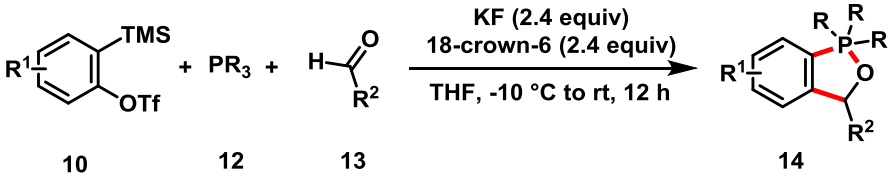
7.8 Experimental Details

7.8.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. 30 °C corresponds to the room temperature of the lab when the experiments were carried out. THF was freshly purified by distillation over Na-benzophenone and was transferred under argon. 18-Crown-6 was recrystallized from dry CH_3CN and KF was dried by heating at 110 °C for 12 h and left to cool under argon. The aldehydes and 2,2,2-trifluoro-1-phenylethan-1-one and ethyl

2-oxo-2-phenylacetate was purchased from Acros or Alfa Aesar and other trifluoro-ketone derivatives,[25] β,γ-unsaturated α-ketoesters[26] and furanone[27] were synthesized following the literature procedure. Aldehydes were purified before use. Phosphines and triphenylarsine were purchased from Sigma Aldrich or Alfa Aesar and used as received. The 2(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** and the other symmetric and unsymmetric aryne precursors were synthesized following literature procedure.[28] Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or Iodine vapor. Chromatography was performed on silica gel (100-200 mesh) by standard techniques eluting with solvents as indicated. All compounds were fully characterized. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400, 500 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Infrared spectra were recorded on a Bruker Alpha-E Infrared Spectrophotometer. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS data were recorded on either Thermo Scientific Q-Exactive, Accela 1250. X-ray intensity data measurements were carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation.

7.8.2. General Procedure for the MCR Involving Phosphine, Aryne and Aldehyde

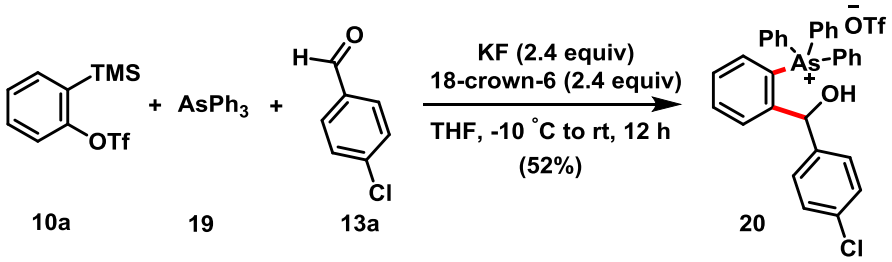


10 12 13 14

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the phosphine **12** (0.50 mmol), KF (70 mg, 1.20 mmol) and 18-crown-6 (0.317 mg, 1.20 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (3.0 mL) under argon atmosphere and subsequently cooled the reaction mixture to -10 °C and kept stirring for five minutes. To the stirring solution aryne precursor **10** (0.60 mmol) was added and continued stirring for another five minutes followed by addition of the aldehyde **13** (0.75 mmol). Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. When TLC control showed the completion of the reaction (typically after 12 h), the reaction stopped and the solvent was evaporated and the

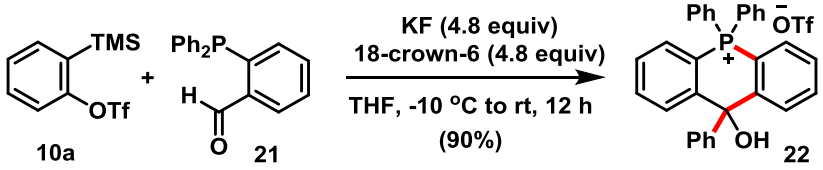
crude residue was purified by column chromatography on silica gel (100-200 mesh) (Petroleum ether/EtOAc = 40/60) to afford the corresponding benzooxaphosphole derivatives **4** in moderate to good yields.

7.8.3. Procedure for the MCR Involving Triphenylarsine, Aryne and Aldehyde



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the triphenylarsine **19** (0.153 g, 0.50 mmol), KF (70 mg, 1.20 mmol) and 18-crown-6 (0.317 mg, 1.20 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (3.0 mL) under argon atmosphere and subsequently cooled the reaction mixture to -10 °C and kept stirring for five minutes. To the stirring solution 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) was added and continued stirring for another five minutes followed by addition of the 4-chlorobenzaldehyde **13a** (0.105 g, 0.75 mmol). Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. After 12 h the reaction stopped and the solvent was evaporated and the crude residue was purified by column chromatography on silica gel (EtOAc) followed by crystallization with EtOAc/Petroleum ether afforded the (2-((4-chlorophenyl)(hydroxy)methyl)phenyl) triphenylarsonium trifluoromethanesulfonate **20** in 52% yield.

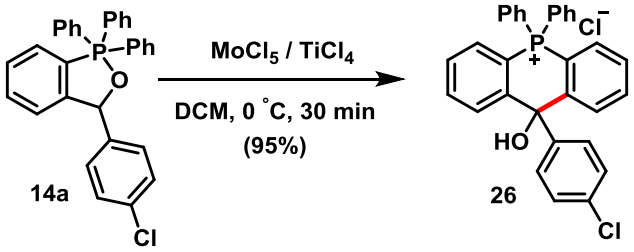
7.8.4. Procedure for the Intramolecular Reaction



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the 2-(diphenylphosphanyl)benzaldehyde **21** (0.073 g, 0.25 mmol), KF (70 mg, 1.20 mmol) and 18-crown-6 (0.317 mg, 1.20 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (3.0 mL) under argon

atmosphere and subsequently cooled the reaction mixture to -10 °C and kept stirring for five minutes. To the stirring solution 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) was added and continued stirring at 25° C for 12 h. After 12 h the reaction stopped and the solvent was evaporated and the crude residue was purified by column chromatography on silica gel (EtOAc) followed by crystallization with EtOAc/Petroleum ether afforded the (2-((4-chlorophenyl) (hydroxy)methyl)phenyl) triphenylarsonium trifluoromethanesulfonate **22** in 90% yield.

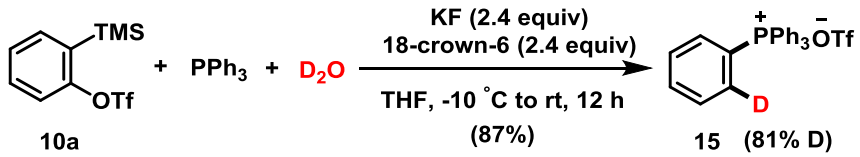
7.8.5. Procedure for the Mo-Mediated C-C Coupling Reaction



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the **14a** (120 mg, 0.25 mmol) in dichloromethane (5.0 mL) and the mixture was cooled to 0 °C. To the cold solution was added a solution of $TiCl_4$ in dichloromethane (0.5 mL, 1.0 M, 0.50 mmol) at 0 °C and stirred for five minutes at this temperature under argon atmosphere. Then $MoCl_5$ (137 mg, 0.50 mmol) was added and the mixture was stirred for 30 min at 0 °C. Subsequently, a saturated solution of sodium bicarbonate (10 mL) was added and it was stirred for further 5 minutes. The mixture was extracted with dichloromethane (3×50 mL), dried over sodium sulfate and the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel (DCM/MeOH = 90/10) afforded the 10-(4-chlorophenyl)-10-hydroxy-5,5-diphenyl-5,10-dihydroacridophosphin-5-ium chloride **26** in 95% yield.

7.8.6. Mechanistic Experiments

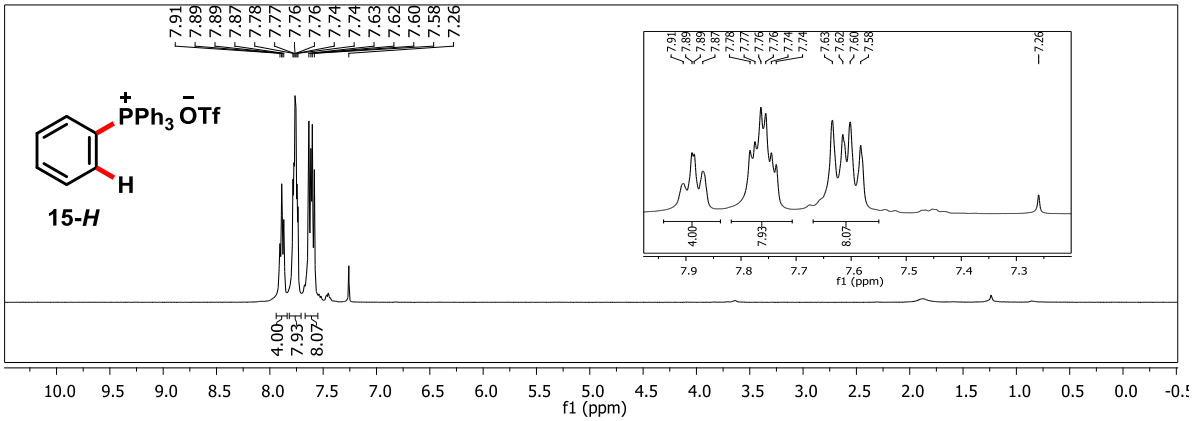
Deuterium Labeling Experiment



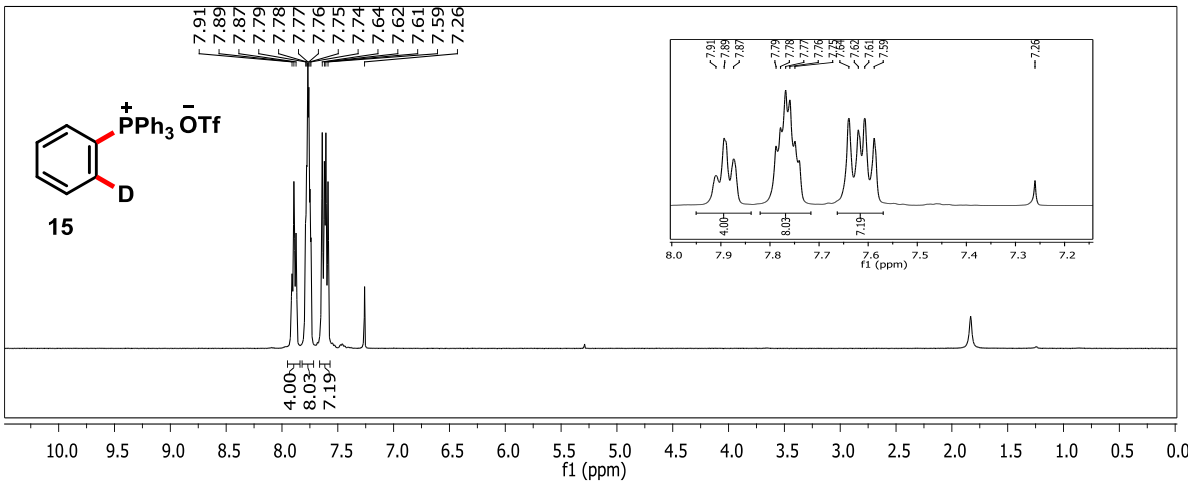
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the triphenylphosphine (131 mg, 0.50 mmol) KF (70 mg, 1.20 mmol) and 18-crown-

6 (0.317 mg, 1.20 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (3.0 mL) under argon atmosphere and subsequently cooled the reaction mixture to -10 °C and kept stirring for five minutes. To the stirring solution 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (179 mg, 146 µL, 0.60 mmol) was added and continued stirring for another five minutes followed by addition of the Deuterium Oxide (20 mg, 18 µL, 1.00 mmol). Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. When the reaction was complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel (MeOH/DCM = 05/95) to afford the triphenyl(phenyl-2-*d*)phosphonium trifluoromethanesulfonate **15** as a white solid (213 mg, 87% yield).

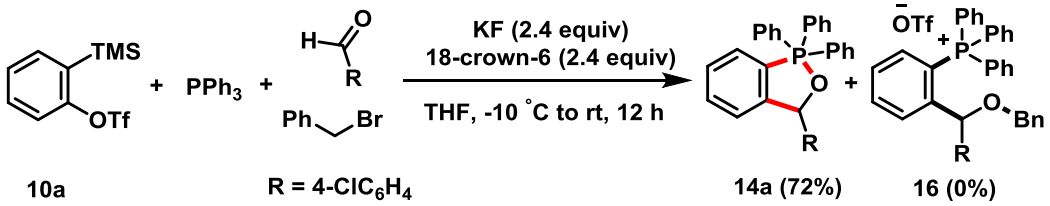
^{1}H-NMR Spectrum of Tetraphenylphosphonium Trifluoromethanesulfonate ($CDCl_3$) (15-*H*)



^{1}H-NMR of Triphenyl(phenyl-2-*d*)phosphonium Trifluoromethanesulfonate ($CDCl_3$) (15)

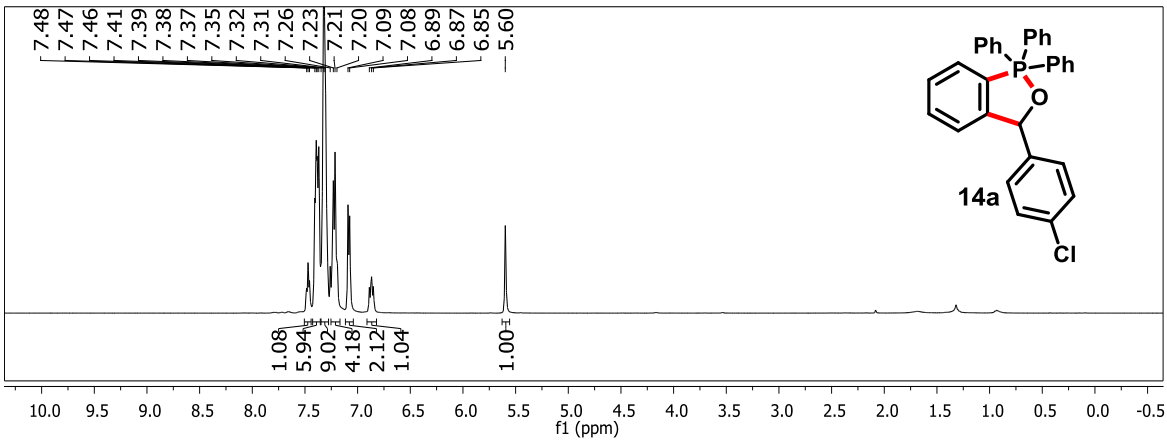


7.8.7. Zwitterion Trapping Experiments

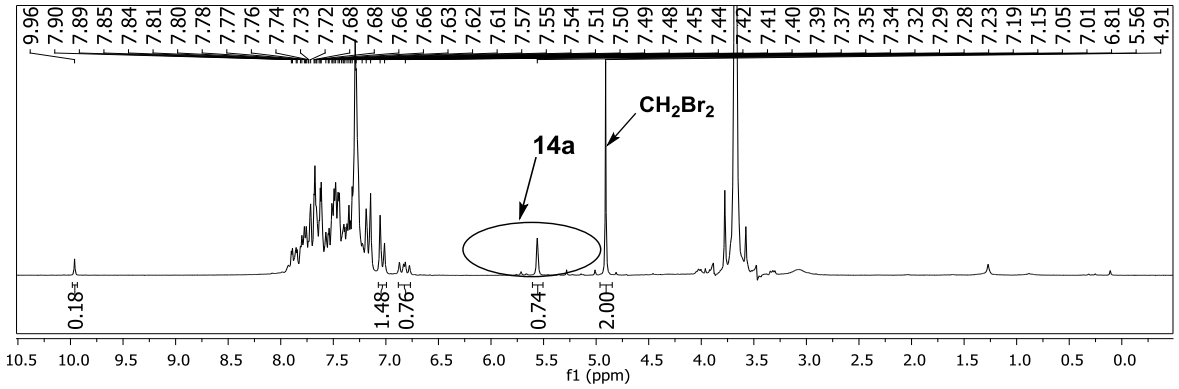


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the triphenylphosphine (131 mg, 0.50 mmol) KF (70 mg, 1.2 mmol) and 18-crown-6 (0.317 mg, 1.2 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere and subsequently cooled the reaction mixture to -10 °C and kept stirring for five minutes. To the stirring solution 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (179 mg, 146 µL, 0.60 mmol) was added and continued stirring for another five minutes followed by addition of the mixture of 4-chlorobenzaldehyde (105 mg, 0.75 mmol) and benzyl bromide (257 mg, 179 µL, 1.50 mmol) in 1.0 ml THF. Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. After 12 h the reaction stopped and the solvent was evaporated and the crude residue was purified by column chromatography on silica gel to afford the 3-(4-chlorophenyl)-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14a** as a white solid (0.171 g, 72% yield) and recovery of 236 mg (92%) benzyl bromide. Interestingly, no detectable amounts of (2-((benzyloxy)(4-chlorophenyl)methyl)phenyl)triphenyl phosphonium trifluoromethanesulfonate **16** was observed.

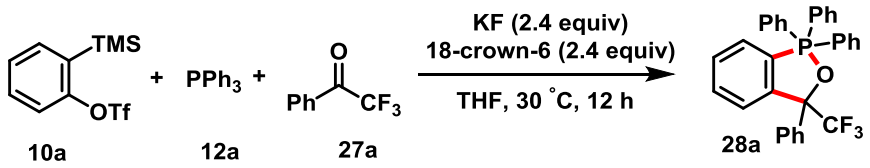
^{1}H-NMR Spectrum of 14a



^{1}H-NMR of Crude Reaction Mixture after 12 h

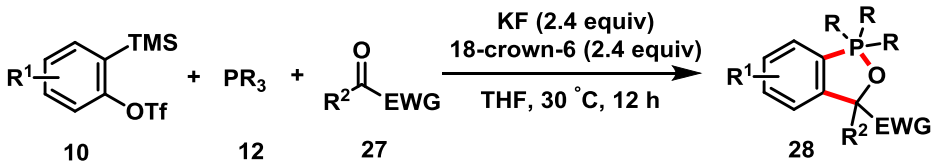


7.8.8. Procedure for the MCR involving Phosphine, Aryne and Trifluoroacetophenone



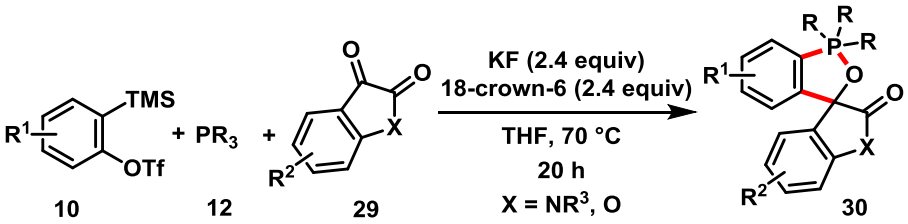
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the triphenylphosphine **12a** (0.131 g, 0.50 mmol), KF (70 mg, 1.20 mmol) and 18-crown-6 (0.317 mg, 1.20 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (3.0 mL) under argon atmosphere and continued stirring for five minutes at 30 °C. After five minutes of stirring, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) was added and continued stirring for another five minutes followed by addition of the 4-2,2,2-trifluoro-1-phenylethan-1-one **27a** (0.131 g, 105 µL, 0.75 mmol). Then the reaction mixture was stirred at 30 °C for 12 h. After 12 h the reaction was stopped, the solvent was evaporated and the crude residue was purified by column chromatography on silica gel (Pet. ether /EtOAc = 95/05) to afford the 1,1,1,3-tetraphenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **28a** in 68% yield.

7.8.9. General Procedure for the MCR involving Phosphine, Aryne and Activated Acyclic Ketones



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the phosphine **12** (0.05 mmol), KF (70 mg, 1.20 mmol) and 18-crown-6 (0.317 mg, 1.20 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (3.0 mL) under argon atmosphere and continued stirring for five minutes at 30 °C. After five minutes of stirring aryne precursor **10** (0.60 mmol) was added and continued stirring for another five minutes followed by addition of the ketones **27** (0.75 mmol). Then the reaction mixture was stirred at 30 °C for 12 h. When TLC control showed the completion of the reaction (typically after 12 h), the reaction stopped and the solvent was evaporated and the crude residue was purified by column chromatography on silica gel (100-200 mesh) (Pet. ether/EtOAc = 90/10) to afford the corresponding benzoxaphosphole derivatives **28** in moderate to good yields.

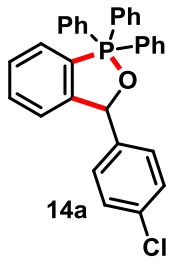
7.8.10. General Procedure for the MCR involving phosphines, Arynes and Isatins



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the phosphine **12** (0.05 mmol), KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (4.0 mL) under argon atmosphere and continued stirring for five minutes at 30 °C. After five minutes of stirring aryne precursor **10** (0.75 mmol) was added and continued stirring for another five minutes followed by addition of the Isatin **29** (0.75 mmol). Then the reaction mixture is placed in a preheated oil bath at 70 °C for the indicated time. The reaction mixture was cooled and the solvent was evaporated on rotary evaporator and the crude residue was purified by column chromatography on silica gel (100-200 mesh) (Pet. ether/EtOAc = 50/50) to afford the corresponding spirobenzoxaphosphole derivatives **30** in moderate to good yields.

7.9. Synthesis and Characterization of Benzooxaphospholes

3-(4-Chlorophenyl)-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (14a)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.358 g, 292 µL, 1.20 mmol) and 4-chlorobenzaldehyde **13a** (0.211 g, 1.50 mmol) with triphenylphosphine **12a** (0.262 g, 1.0 mmol) in the presence of KF (0.140 g, 2.40 mmol) and 18-crown-6 (0.634 g, 2.40 mmol) in THF (6.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 3-(4-chlorophenyl)-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2] oxaphosphole **14a** as a white solid (0.389 g, 81% yield).

***R*$_f$** (EtOAc): 0.41.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47 (t, *J* = 6.6 Hz, 1H), 7.41-7.37 (m, 6H), 7.35-7.31 (m, 9H), 7.23-7.20 (m, 4H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.87 (t, *J* = 10.7 Hz, 1H), 5.60 (s, 1H).

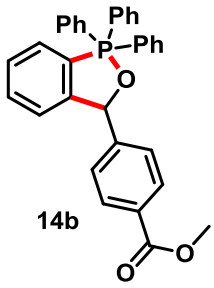
^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.92 (d, *J* = 21.5 Hz), 143.72, 142.93, 136.56 (d, *J* = 21.5 Hz), 132.95, 132.31 (d, *J* = 2.4 Hz), 131.42 (d, *J* = 8.8 Hz), 129.16, 129.02, 128.38, 128.13, 127.96, 127.53, 127.43, 127.36, 124.77 (d, *J* = 15.4 Hz), 76.25.

^{31}P NMR (203 MHz, $CDCl_3$) δ: -51.41.

HRMS: calculated $[M+H]^+$ for $C_{31}H_{25}ClOP$: 479.1326, found: 479.1327.

FTIR (cm^{-1}): 3829, 3743, 3618, 3058, 3005, 1897, 1588, 1485, 1437, 1406, 1257, 1229, 1183, 1112, 1078, 1020, 886, 847, 745, 695, 663.

Methyl-4-(1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphol-3-yl)benzoate (14b)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and methyl 4-formylbenzoate **13b** (0.123 g, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 120 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded methyl-4-(1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphol-3-yl)benzoate **14b** as a white solid (0.227 g, 90% yield).

***R*$_f$** (EtOAc): 0.47.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.93 (d, *J* = 6.9 Hz, 2H), 7.48 (t, *J* = 6.5 Hz, 1H), 7.40-7.37 (m, 6H), 7.33-7.29 (m, 9H), 7.27-7.24 (m, 1H), 7.21 (d, *J* = 7.2 Hz, 3H), 6.87 (t, *J* = 9.2 Hz, 1H), 5.70 (s, 1H), 3.90 (s, 3H).

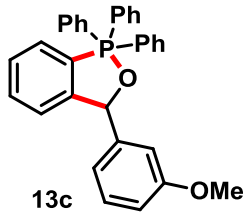
^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.19, 153.56 (d, *J* = 21.5 Hz), 149.72, 143.72, 142.88, 136.71 (d, *J* = 14.6 Hz), 132.39 (d, *J* = 2.5 Hz), 131.43 (d, *J* = 8.7 Hz), 129.68, 129.06, 128.83, 128.19, 127.70, 127.58, 127.48, 124.75 (d, *J* = 15.2 Hz), 76.70, 52.09.

^{31}P NMR (203 MHz, $CDCl_3$) δ: -50.75.

HRMS: calculated $[M+H]^+$ for $C_{33}H_{28}O_3P$: 503.1771, found: 503.1788.

FTIR (cm^{-1}): 3829, 3744, 3678, 3649, 3008, 2319, 1712, 1647, 1614. 1469. 1369. 1279, 1217, 1112, 1041, 986, 872, 834.

3-(3-Methoxyphenyl)-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (13c)



13c

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.6 mmol) and 3-methoxybenzaldehyde **13c** (0.102 g, 91 µL, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.5 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 3-(3-methoxyphenyl)-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14c** as a white solid (0.192 g, 81% yield).

***R*$_f$** (EtOAc): 0.50.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.46 (t, *J* = 7.2 Hz, 1H), 7.40-7.38 (m, 6H), 7.33-7.26 (m, 10H), 7.23-7.16 (m, 2H), 6.85-6.81 (m, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 1H), 5.66 (s, 1H), 3.58 (s, 3H).

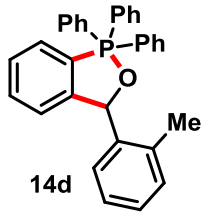
^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.76, 154.33 (d, *J* = 21.9 Hz), 146.01, 144.10, 143.26, 136.55 (d, *J* = 14.5 Hz), 132.36, 131.43 (d, *J* = 8.8 Hz), 129.10, 128.05, 127.50 (d, *J* = 12.2 Hz), 127.27(d, *J* = 14.2 Hz), 124.86 (d, *J* = 15.4 Hz), 120.12, 113.83, 112.05, 77.23, 55.20.

^{31}P NMR (203 MHz, $CDCl_3$) δ: -51.37.

HRMS: calculated $[M+H]^+$ for $C_{32}H_{28}O_2P$: 475.1821, found: 475.1852.

FTIR (cm^{-1}): 3678, 3015, 2361, 1647, 1462, 1215, 1052, 741, 667.

1,1,1-Triphenyl-3-(*o*-tolyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (14d)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.6 mmol) and 2-methylbenzaldehyde **13d** (0.090 g, 87 µL, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.5 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 1,1,1-triphenyl-3-(*o*-tolyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14d** as a white solid (0.147 g, 64% yield).

***R*$_f$** (EtOAc): 0.42.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45-7.37 (m, 7H), 7.30-7.26 (m, 9H), 7.24-7.20 (m, 1H), 7.12-7.09 (m, 3H), 7.06-7.03 (m, 1H), 6.96 (d, J = 7.36 Hz, 1H), 6.89 (dd, J_1 = 8.3 Hz, J_2 = 10.8 Hz, 1H), 5.32 (s, 1H), 2.31 (s, 3H).

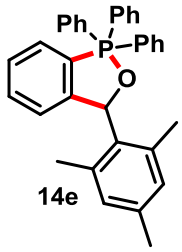
^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.74 (d, J = 20.1 Hz), 141.98, 136.49 (d, J = 14.3 Hz), 136.0, 132.18 (d, J = 2.6 Hz), 131.64 (d, J = 9.1 Hz), 130.28, 128.30, 128.14, 127.47 (d, J = 12.3 Hz), 127.21, 127.14, 127.10, 126.23, 124.77 (d, J = 15.0 Hz), 72.40, 19.74.

^{31}P NMR (203 MHz, $CDCl_3$) δ: -52.37.

HRMS: calculated $[M+H]^+$ for $C_{32}H_{28}OP$: 459.1872, found: 459.1873.

FTIR (cm^{-1}): 3828, 3060, 2361, 1835, 1741, 1484, 1264, 1050, 742, 665.

3-Mesityl-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (14e)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and 2,4,6-trimethylbenzaldehyde **13e** (0.111 g, 111 µL, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 3-mesityl-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14e** as a white solid (0.151 g, 62% yield).

***R*$_f$** (EtOAc): 0.29.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49-7.41 (m, 7H), 7.32 (bs, 9H), 7.27-7.17 (m, 1H), 7.07-7.03 (m, 2H), 6.76 (bs, 2H), 5.62 (s, 1H), 2.23 (s, 3H), 2.09 (s, 3H), 1.86 (s, 3H).

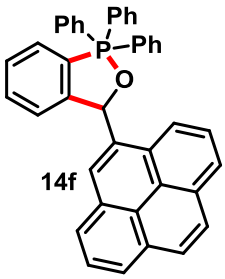
^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.41 (d, *J* = 19.4 Hz), 141.84, 140.79, 138.04, 137.38, 136.90, 136.49 (d, *J* = 13.8 Hz), 134.05, 132.10, 131.71 (d, *J* = 8.7 Hz), 130.76, 128.87, 128.33, 127.52 (d, *J* = 12.3 Hz), 126.81 (d, *J* = 14.3 Hz), 123.47 (d, *J* = 14.6 Hz), 70.45, 21.13, 20.96, 20.53.

^{31}P NMR (162 MHz, $CDCl_3$) δ: -49.31.

HRMS: calculated $[M+H]^+$ for $C_{34}H_{32}OP$: 487.2185, found: 487.2185.

FTIR (cm^{-1}): 3759, 3672, 3063, 3013, 2926, 2855, 1891, 1626, 1517, 1438, 1342, 1273, 1071, 987, 839, 744.

1,1,1-Triphenyl-3-(pyren-4-yl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (14f)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and pyrene-4-carbaldehyde **13f** (0.173 g, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 1,1,1-triphenyl-3-(pyren-4-yl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14f** as a yellow solid (0.201 g, 71% yield).

***R*$_f$** (EtOAc): 0.53.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 (d, *J* = 9.4 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 2H), 8.11 (d, *J* = 9.4 Hz, 1H), 8.07-8.04 (m, 3H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.60-7.50 (m, 6H), 7.40-7.34 (m, 10H), 7.29-7.22 (m, 2H), 7.04 (dd, J_1 = 8.3 Hz, J_2 = 11.2 Hz, 1H), 6.77 (s, 1H).

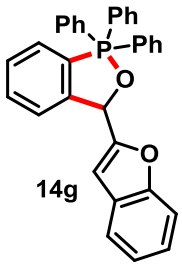
^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.84 (d, *J* = 21.0 Hz), 143.60, 142.55, 137.94, 136.72 (d, *J* = 14.4 Hz), 132.33 (d, *J* = 2.7 Hz), 132.22, 132.12, 131.62 (d, *J* = 8.9 Hz), 131.46, 130.80, 130.57, 129.46, 128.93, 128.66, 128.54, 128.25, 127.56 (d, *J* = 12.6 Hz), 127.44, 127.04, 125.96, 125.82, 125.23 (d, *J* = 15.9 Hz), 124.92 (d, *J* = 16.8 Hz), 123.60, 73.01.

^{31}P NMR (162 MHz, $CDCl_3$) δ: -50.44.

HRMS: calculated $[M+H]^+$ for $C_{41}H_{30}OP$: 569.2029, found: 569.2029.

FTIR (cm^{-1}): 2985, 1733, 1438, 1372, 1241, 1194, 1045, 939, 847, 754, 696, 654, 639.

3-(Benzofuran-2-yl)-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (14g)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and benzofuran-2-carbaldehyde **13g** (0.110 g, 91 µL, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 3-(benzofuran-2-yl)-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphos phole **14g** as a white solid (0.203 g, 83% yield).

***R*$_f$** (EtOAc): 0.36.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.65-7.63 (m, 1H), 7.60-7.56 (m, 1H), 7.52-7.43 (m, 8H), 7.39-7.31 (m, 9H), 7.29-7.25 (m, 2H), 7.23-7.20 (m, 1H), 6.83 (dd, J_1 = 8.0 Hz, J_2 = 11.3 Hz), 6.35 (s, 1H), 5.92 (s, 1H).

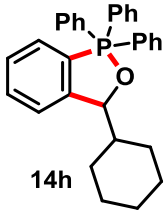
^{13}C NMR (100 MHz, CDCl$_3$) δ: 159.23, 155.21, 150.81 (d, *J* = 20.4 Hz), 143.66, 142.60, 136.88 (d, *J* = 14.3 Hz), 132.52 (d, *J* = 3.0 Hz), 131.69 (d, *J* = 9.0 Hz), 128.43, 128.26 (d, *J* = 2.2 Hz), 127.99 (d, *J* = 14.2 Hz), 127.46 (d, *J* = 12.5 Hz), 124.82 (d, *J* = 15.1 Hz), 123.70, 122.47, 120.92, 111.91, 103.94, 70.49.

^{31}P NMR (162 MHz, CDCl$_3$) δ: -43.56.

HRMS: calculated $[M+H]^+$ for $C_{33}H_{26}OP$: 485.1665, found: 485.1674.

FTIR (cm^{-1}): 3893, 3843, 3743, 3678, 3648, 3619, 3015, 2396, 1741, 1693, 1647, 1516, 1461, 1216, 1117, 741, 668.

3-Cyclohexyl-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (14h)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and cyclohexanecarbaldehyde **13h** (0.084 g, 91 µL, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 3-cyclohexyl-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14h** as a white solid (0.191 g, 85% yield).

***R*f** (EtOAc): 0.33.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.55 (s, 2H), 7.38-7.36 (m, 6H), 7.30-7.26 (m, 9H), 7.24 (bs, 1H), 6.91-6.89 (m, 1H), 4.64 (s, 1H), 1.75 (bs, 2H), 1.63 (bs, 3H), 1.38-1.25 (m, 3H), 1.10-1.06 (m, 2H), 0.84-0.83 (m, 1H).

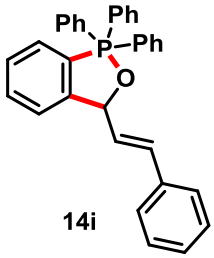
^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.05 (d, *J* = 24.2 Hz), 144.80, 143.96, 136.61 (d, *J* = 14.5 Hz), 131.59 (d, *J* = 8.8 Hz), 129.95, 127.64, 127.10 (d, *J* = 12.1 Hz), 126.77 (d, *J* = 14.1 Hz), 123.38 (d, *J* = 15.7 Hz), 77.84, 44.07, 30.69, 27.18, 26.87, 26.65, 26.54.

^{31}P NMR (203 MHz, $CDCl_3$) δ: -52.53.

HRMS: calculated $[M+H]^+$ for $C_{31}H_{32}OP$: 451.2185, found: 451.2185.

FTIR (cm^{-1}): 3840, 3861, 3743, 3678, 3619, 3059, 3007. 2929, 2854, 2361, 1693, 1647, 1515, 1482, 1437, 1261, 1218, 1107, 1023, 860, 812, 743, 698.

1,1,1-Triphenyl-3-styryl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (14i)



14i

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and *trans* cinnamaldehyde **13i** (0.099 g, 94 µL, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at -10 °C to rt for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 1,1,1-triphenyl-3-styryl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14i** as a yellow solid (0.156 g, 66% yield).

***R*f** (EtOAc): 0.30.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60-7.53 (m, 2H), 7.40-7.37 (m, 4H), 7.53-7.29 (m, 15H), 7.27-7.24 (m, 2H), 6.75 (dd, J_1 = 8.2 Hz, J_2 = 10.8 Hz, 1H), 6.49 (d, *J* = 15.6 Hz, 1H), 6.23 (dd, J_1 = 7.0 Hz, J_2 = 15.7 Hz, 1H), 5.35 (s, 1H).

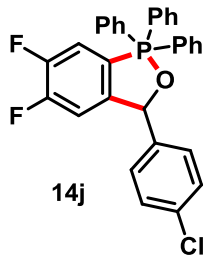
^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.17 (d, *J* = 22.4 Hz), 144.59, 143.53, 137.23, 136.84 (d, *J* = 14.6 Hz), 132.28 (d, *J* = 2.9 Hz), 131.59 (d, *J* = 8.9 Hz), 131.18 (d, *J* = 9.9 Hz), 129.00, 128.45, 128.03, (d, *J* = 2.0 Hz), 127.66, 127.58, 127.39 (d, *J* = 12.3 Hz), 126.62, 124.45 (d, *J* = 15.4 Hz), 75.35.

^{31}P NMR (162 MHz, $CDCl_3$) δ: -51.56.

HRMS: calculated $[M+H]^+$ for $C_{33}H_{28}OP$: 471.1872, found: 471.1896.

FTIR (cm^{-1}): 3829. 3743, 3678, 3648. 3061. 2980, 2320. 1738, 1647, 1609, 1469. 1433, 1370, 1250, 1195, 1112, 1039, 986, 872, 801, 742.

3-(4-Chlorophenyl)-5,6-difluoro-1,1,1-triphenyl-1,3-dihydro-1λ^5 benzo[*c*][1,2]oxaphosphole (14j)



14j

Following the general procedure, treatment of 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10b** (0.201 g, 0.60 mmol) and 4-chlorobenzaldehyde **13a** (0.105 g, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 3-(4-chlorophenyl)-5,6-difluoro-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14j** as a white solid (0.193 g, 75% yield).

***R*$_f$** (EtOAc): 0.48.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.37-7.32 (m, 15H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.93 (t, *J* = 6.9 Hz, 1H), 6.62-6.55 (m, 1H), 5.43 (s, 1H).

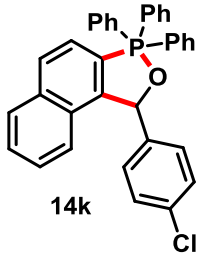
^{13}C NMR (100 MHz, CDCl$_3$) δ: 153.33 (d, *J* = 259.8 Hz), 153.20 (d, *J* = 257.5 Hz), 151.16-150.81 (m), 150.62 (d, *J* = 5.4 Hz), 148.51 (d, J_1 = 12.9 Hz, J_2 = 22.0 Hz), 142.99, 141.78, 133.46, 131.39 (d, *J* = 9.0 Hz), 129.03, 128.62 (d, *J* = 7.2 Hz), 127.93, 127.70 (d, *J* = 12.5 Hz), 124.57 (t, *J* = 18.7 Hz), 113.13 (t, *J* = 18.4 Hz), 75.45.

^{31}P NMR (162 MHz, CDCl$_3$) δ: -51.78.

HRMS: calculated $[M+H]^+$ for $C_{31}H_{23}ClF_2OP$: 515.1138, found: 515.1165.

FTIR (cm^{-1}): 3894, 3861, 3744, 3678, 2928, 2361, 1741, 1693, 1647, 1614, 1516, 1488, 1430, 1293, 1215, 1084, 1006, 898, 742.

1-(4-Chlorophenyl)-3,3,3-triphenyl-1,3-dihydro-3λ^5-naphtho[2,1-*c*][1,2]oxaphosphole (14k)



14k

Following the general procedure, treatment of 2-(trimethylsilyl)naphthalen-1-yl trifluoromethanesulfonate **10b** (0.209 g, 0.60 mmol) and 4-chlorobenzaldehyde **13a** (0.105 g, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0

mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 1-(4-chlorophenyl)-3,3,3-triphenyl-1,3-dihydro-3λ^5-naphtho[2,1-c][1,2]oxaphosphole **14k** as a white solid (0.181 g, 68% yield).

***R*$_f$** (EtOAc): 0.45.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.81 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.50-7.42 (m, 8H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.27-7.22 (m, 10H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.23 (d, *J* = 8.2 Hz, 1H).

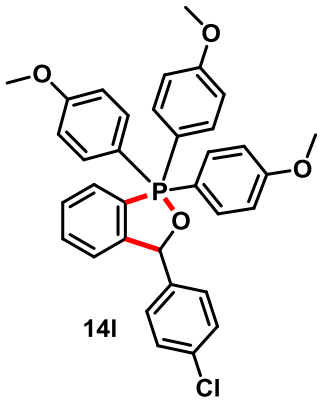
^{13}C NMR (100 MHz, CDCl$_3$) δ: 147.85, 147.00, 142.93, 141.47 (d, *J* = 2.0 Hz), 134.05 (d, *J* = 8.0 Hz), 133.55, 132.21 (d, *J* = 11.3 Hz), 131.83 (d, *J* = 9.9 Hz), 131.46, 128.79, 128.56, 128.32, 127.47 (d, *J* = 12.1 Hz), 125.29, 124.81, 121.00, 74.08.

^{31}P NMR (162 MHz, CDCl$_3$) δ: -49.36.

HRMS: calculated $[M+H]^+$ for $C_{35}H_{27}ClOP$: 529.1483, found: 529.1483.

FTIR (cm^{-1}): 3894, 3648, 3619, 3011, 2362, 1836, 1707, 1648, 1646, 1467, 1429, 1282, 1217, 1009, 743, 668.

3-(4-Chlorophenyl)-1,1,1-tris(4-methoxyphenyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosph-ole (14l)



14l

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 μL, 0.60 mmol) and 4-chlorobenzaldehyde **13a** (0.105 g, 0.75 mmol) with tris(4-methoxyphenyl)phosphane **12b** (0.176 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (EtOAc) of the crude reaction mixture using silica gel afforded 3-(4-chlorophenyl)-1,1,1-tris(4-methoxyphenyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14l** as a white solid (0.166 g, 58% yield).

***R*$_f$** (EtOAc): 0.23.

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.65 (t, *J* = 7.0 Hz, 2H), 7.35-7.31 (m, 7H), 7.03-6.99 (m, 3H), 6.92-6.91 (m, 6H), 6.76 (bs, 2H), 5.57 (s, 1H), 3.82 (s, 9H).

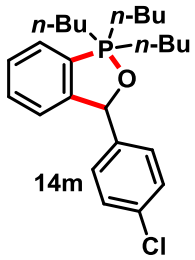
^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.34 (d, *J* = 8.8 Hz), 150.63, 141.46, 135.99 (d, *J* = 13.3 Hz), 134.89 (d, *J* = 7.3 Hz), 133.88, 132.73, 129.10, 128.40, 128.29, 128.04, 114.60, 73.86, 55.61.

^{31}P NMR (203 MHz, $CDCl_3$) δ: -40.79.

HRMS: calculated $[M+H]^+$ for $C_{34}H_{31}ClO_4P$: 569.1643, found: 569.1646.

FTIR (cm^{-1}): 3894, 3678, 3619, 3018, 2362, 1741, 1693, 1596, 1464, 1264, 1267, 1217, 1110, 1027, 740, 667.

1,1,1-Tributyl-3-(4-chlorophenyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (14m)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and 4-chlorobenzaldehyde **13a** (0.105 g, 0.75 mmol) with tri-*n*-butylphosphine **12c** (0.101 g, 125 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 40/60) of the crude reaction mixture using silica gel afforded 1,1,1-tributyl-3-(4-chlorophenyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14m** as a white solid (0.167 g, 79% yield).

***R*$_f$** (EtOAc): 0.21.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (dd, J_1 = 7.6 Hz, J_2 = 13.4 Hz, 1H), 7.59-7.50 (m, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 3H), 6.05 (s, 1H), 2.47-2.44 (m, 6H), 1.50-1.21 (m, 12H), 0.84 (t, *J* = 6.5 Hz, 9H).

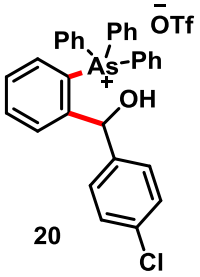
^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.38 (d, *J* = 6.4 Hz), 141.37, 134.33 (d, *J* = 8.8 Hz), 133.95 (d, *J* = 2.2 Hz), 133.75, 131.52 (d, *J* = 10.4 Hz), 128.85, 128.68 (d, *J* = 12.7 Hz), 115.78, 115.00, 73.47 (d, *J* = 1.8 Hz), 24.25 (d, *J* = 4.1 Hz), 23.63 (d, *J* = 16.3 Hz), 21.65 (d, *J* = 50.3 Hz), 13.36.

^{31}P NMR (162 MHz, $CDCl_3$) δ: 32.97.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{37}ClOP$: 419.2265, found: 419.2265.

FTIR (cm^{-1}): 3843, 3648, 3619, 3010, 2873, 2361, 1817, 1741, 1647, 1463, 1351, 1251, 1222, 1030, 949, 854, 742, 637.

(2-((4-Chlorophenyl)(hydroxy)methyl)phenyl)triphenylarsonium trifluoromethane sulfonate (20)



20

Treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and 4-chlorobenzaldehyde **13a** (0.105 g, 0.75 mmol) with triphenylarsane **19** (0.153 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (EtOAc) of the crude reaction mixture using silica gel afforded (2-((4-chlorophenyl)(hydroxy)methyl)phenyl)triphenylarsonium trifluoro methanesulfonate **20** as a white solid (0.172 g, 52% yield).

***R*f** (EtOAc): 0.13.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69-7.64 (m, 4H), 7.57 (t, *J* = 7.8 Hz, 6H), 7.52-7.50 (m, 6H), 7.44-7.37 (m, 2H), 7.29-7.26 (m, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.46 (bs, 1H), 6.07 (s, 1H).

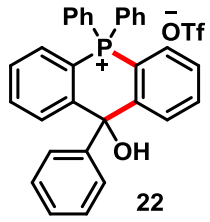
^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.64, 140.88, 135.39, 133.90, 133.40, 133.15, 132.57, 132.45, 131.41, 130.96, 130.40, 129.11, 128.83, 128.39, 126.64, 117.85, 73.29.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.04.

HRMS: calculated $[M]^+$ for $C_{31}H_{25}ClOAs$: 523.0804, found: 523.0801.

FTIR (cm^{-1}): 3843, 3744, 3638, 3619, 3013, 2361, 1741, 1693, 1647, 1516, 1495, 1444, 1270, 1161, 1030, 837, 665.

10-Hydroxy-5,5,10-triphenyl-5,10-dihydroacridophosphin-5-ium trifluoromethane-sulfonate (22)



22

Treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and 2-(diphenylphosphanyl)benzaldehyde **21** (0.073 g, 0.25 mmol) in the presence of KF (0.70 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (DCM /MeOH = 90/10) of the crude reaction mixture using silica gel afforded 10-hydroxy-5,5,10-triphenyl-5,10-dihydroacridophosphin-5-ium trifluoromethanesulfonate **22** as a white solid (0.134 g, 90% yield).

***R*f** (DCM/MeOH = 95/05): 0.23.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48-8.44 (m, 2H), 7.86 (t, *J* = 7.7 Hz, 2H), 7.79-7.76 (m, 1H), 7.60-7.54 (m, 5H), 7.49-7.40 (m, 4H), 7.37-7.33 (m, 2H), 7.22-7.17 (m, 2H), 6.81-6.78 (m, 1H), 6.70 (t, *J* = 7.8 Hz, 2H), 6.51 (d, *J* = 7.9 Hz, 2H), 5.95 (bs, 1H, OH) [exchangeable with D_2O].

^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.75 (d, *J* = 6.3 Hz), 143.52, 135.75 (d, *J* = 2.7 Hz), 135.47 (d, *J* = 1.8 Hz), 135.07 (d, *J* = 11.4 Hz), 134.59 (d, *J* = 2.7 Hz), 133.09 (d, *J* = 8.9 Hz), 132.89 (d, *J* = 10.7 Hz), 130.54 (d, *J* = 13.4 Hz), 130.15 (d, *J* = 13.1 Hz), 129.64 (d, *J* = 9.8 Hz), 129.14 (d, *J* = 12.5 Hz), 128.03, 127.86, 127.57, 122.21, 119.62, 118.70, 116.96 (d, *J* = 90.4 Hz), 113.60 (d, *J* = 88.1 Hz), 76.92.

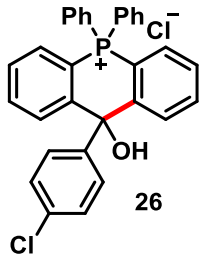
^{31}P NMR (162 MHz, $CDCl_3$) δ: 10.30.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.00.

HRMS: calculated $[M]^+$ for $C_{31}H_{24}OP$: 443.1559, found: 443.1554.

FTIR (cm^{-1}): 3534, 2871, 1974, 1695, 1644, 1471, 1454, 1439, 1350, 1272, 1257, 1224, 1202, 1148, 1098, 1029, 993, 960, 836, 766, 754, 721, 706.

10-(4-Chlorophenyl)-10-hydroxy-5,5-diphenyl-5,10-dihydroacridophosphin-5-ium chloride (26)



26

Treatment of 3-(4-chlorophenyl)-1,1,1-triphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **14a** (120 mg, 0.25 mmol) with 1.0 (M) $TiCl_4$ in dichloromethane (0.5 ml, 1M, 0.5 mmol) and $MoCl_5$ (137 mg, 0.5 mmol) in dichloromethane (5 mL) at 0 °C for 30 min followed by flash column chromatography on silica gel (DCM/MeOH = 90/10) afforded the 10-(4-chlorophenyl)-10-hydroxy-5,5-diphenyl-5,10-dihydroacridophosphin-5-ium chloride **26** as a yellow solid (122 mg, 95% yield).

***R*$_f$** (DCM/MeOH = 95/05): 0.17.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67-8.63 (m, 2H), 7.87 (t, *J* = 7.6 Hz, 2H), 7.79 (t, *J* = 7.2 Hz, 1H), 7.64-7.55 (m, 6H), 7.45-7.34 (m, 6H), 7.16-7.11 (m, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 6.41 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.23 (d, *J* = 6.2 Hz), 142.76, 135.81 (d, *J* = 2.2 Hz), 135.52, 135.07 (d, *J* = 11.4 Hz), 134.24 (d, *J* = 2.3 Hz), 133.39, 132.85, 132.79, 132.74, 130.51 (d, *J* = 13.2 Hz), 130.19 (d, *J* = 12.3 Hz), 129.47, 128.94 (d, *J* = 12.8 Hz), 127.81,

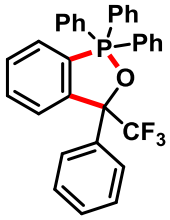
119.03 (d, *J* = 91.4 Hz), 116.95 (d, *J* = 89.3 Hz), 113.52 (d, *J* = 87.2 Hz), 76.54 (d, *J* = 8.5 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ:17.56.

HRMS: calculated $[M]^+$ for $C_{31}H_{23}ClOP$: 477.1170, found: 477.1167.

FTIR (cm^{-1}): 3058, 2954, 2922, 2853, 1731, 1667, 1586, 1486, 1463, 1437, 1398, 1373, 1268, 1236, 1162, 1139, 1106, 1092, 1044, 1012, 997, 925, 828, 739, 723, 686.

1,1,1,3-Tetraphenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (28a)



28a

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 μL, 0.60 mmol) and 4-2,2,2-trifluoro-1-phenylethan-1-one **27a** (0.131 g, 105 μL, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at 30 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 1,1,1,3-tetraphenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **28a** as a white solid (0.174 g, 68% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.61.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 6.4 Hz, 1H), 7.76 (t, *J* = 6.7 Hz, 1H), 7.14 (q, J_1 = 7.2 Hz, J_2 = 12.6 Hz, 1H), 7.28-7.23 (m, 11H), 7.17-7.16 (m, 6H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 2H), 6.89-6.87 (m, 1H).

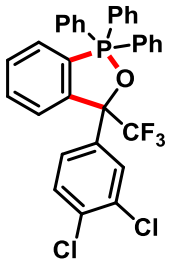
^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.48 (d, *J* = 19.4 Hz), 143.19, 142.12, 137.77 (d, *J* = 14.6 Hz), 137.24, 132.21 (d, *J* = 2.9 Hz), 131.98 (d, *J* = 9.2 Hz), 130.90, 129.55, 128.86 (d, *J* = 14.6 Hz), 128.20, 128.18, 128.14, 127.28, 127.18 (d, *J* = 4.6 Hz), 126.68 (d, *J* = 15.2 Hz), 124.28, 80.54-79.70 (m).

^{31}P NMR (162 MHz, $CDCl_3$) δ: -47.48.

HRMS: calculated $[M+H]^+$ for $C_{32}H_{25}F_3OP$: 513.1590, found: 513.1610.

FTIR (cm^{-1}): 3836, 3675, 3616, 3061, 2978, 2856, 2321, 1684, 1638, 1486, 1283, 1179, 999, 746, 691.

3-(3,4-dichlorophenyl)-1,1,1-triphenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*] [1,2] oxaphosphole (28b)



28b

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and 1-(3,4-dichlorophenyl)-2,2,2-trifluoroethan-1-one **27b** (0.182 g, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at 30 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 3-(3,4-dichlorophenyl)-1,1,1-triphenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphos phole **28b** as a white solid (0.193 g, 66% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.56.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.98 (d, *J* = 5.8 Hz, 1H), 7.69 (t, *J* = 6.6 Hz, 1H), 7.36-7.32 (m, 1H), 7.16-7.09 (m, 15H), 6.94-6.92 (m, 3H), 6.85-6.81 (m, 1H).

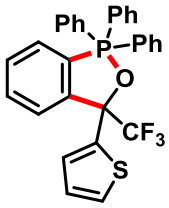
^{13}C NMR (125 MHz, $CDCl_3$) δ: 146.30 (d, *J* = 18.2 Hz), 140.80, 138.08 (d, *J* = 14.6 Hz), 133.82, 132.74, 131.91 (d, *J* = 8.7 Hz), 129.32 (d, *J* = 14.6 Hz), 128.84, 128.73, 127.63, 127.38 (d, *J* = 12.7 Hz), 126.87, 126.39 (d, *J* = 12.0 Hz), 79.67-79.25 (m).

^{31}P NMR (203 MHz, $CDCl_3$) δ: -47.59.

HRMS: calculated $[M+H]^+$ for $C_{32}H_{23}F_3OPCl_2$: 581.0810, found: 581.0805.

FTIR (cm^{-1}): 3376, 3066, 2928, 2860, 1964, 1893, 1817, 1729, 1600, 1572, 1478, 1432, 1388, 1264, 1180, 1069, 996, 965, 800, 695.

1,1,1-Triphenyl-3-(thiophen-2-yl)-3-(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2] oxaphosphole (28c)



28c

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and 2,2,2-trifluoro-1-(thiophen-2-yl)ethan-1-one **27c** (0.135 g, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at 30 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 1,1,1-triphenyl-3-(thiophen-2-yl)-3-

(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **28c** as a white solid (0.127 g, 49% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.51.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.09 (d, *J* = 7.4 Hz, 1H), 7.73 (d, *J* = 6.3 Hz, 1H), 7.42-7.37 (m, 1H), 7.26-7.15 (m, 15H), 7.02 (d, *J* = 4.9 Hz, 1H), 6.90-6.85 (m, 1H), 6.70-6.69 (m, 1H), 6.64 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 147.24 (d, *J* = 18.8 Hz), 142.46, 141.54, 137.57 (d, *J* = 14.6 Hz), 132.71 (d, *J* = 3.0 Hz), 131.80 (d, *J* = 9.1 Hz), 129.09 (d, *J* = 14.6 Hz), 128.18, 127.27, 127.15, 125.88, 125.78, 125.64.

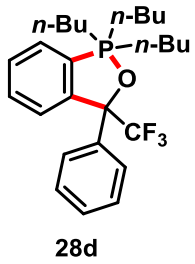
^{19}F NMR (376 MHz, CDCl$_3$) δ: -76.08.

^{31}P NMR (162 MHz, CDCl$_3$) δ: -49.44.

HRMS: calculated $[M+H]^+$ for $C_{30}H_{23}F_3OPS$: 519.1154, found: 519.1151.

FTIR (cm^{-1}): 3035, 2993, 2325, 1421, 1265, 892, 808, 788, 688, 640.

1,1,1-Tributyl-3-phenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole (28d)



28d

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and 4-2,2,2-trifluoro-1-phenylethan-1-one **27a** (0.131 g, 105 µL, 0.75 mmol) with tributylphosphane **12c** (0.101 g, 125 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at 30 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture using silica gel afforded 1,1,1-tributyl-3-phenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole **28d** as a colourless liquid (0.167 g, 74% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.21.

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.99 (d, *J* = 7.3 Hz, 1H), 7.83 (t, *J* = 8.8 Hz, 1H), 7.73 (q, *J* = 7.3 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.54-7.51 (m, 1H), 7.34-7.28 (m, 3H), 1.95-1.86 (m, 6H), 1.61-1.56 (m, 3H), 1.46-1.39 (m, 3H), 1.35-1.29 (m, 6H), 0.88 (t, *J* = 7.3 Hz, 9H).

^{13}C NMR (125 MHz, CDCl$_3$) δ: 147.42 (d, *J* = 14.2 Hz), 141.73, 134.41 (d, *J* = 12.6 Hz), 131.32 (d, *J* = 2.4 Hz), 130.02, 129.00, 128.29, 128.18, 127.70 (d, *J* = 5.6 Hz), 127.23 (d, *J*

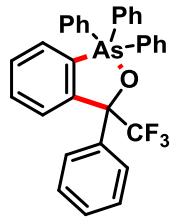
= 13.7 Hz), 125.37, 80.45-79.79 (m), 34.94 (d, *J* = 72.3 Hz), 26.83 (d, *J* = 4.8 Hz), 24.88 (d, *J* = 16.8 Hz), 13.85.

^{31}P NMR (203 MHz, $CDCl_3$) δ: -50.16.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{37}F_3OP$: 453.2529, found: 453.2525.

FTIR (cm^{-1}): 3434, 3065, 2960, 2931, 2868, 1954, 1700, 1638, 1591, 1458, 1377, 1260, 1215, 1159, 1076, 1002, 960, 929, 758, 701, 660.

1,1,1,3-Tetraphenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxarsole (28e)



28e

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.179 g, 146 µL, 0.60 mmol) and 4-2,2,2-trifluoro-1-phenylethan-1-one **27a** (0.131 g, 105 µL, 0.75 mmol) with triphenylarsane **19** (0.153 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at 30 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 1,1,1,3-tetraphenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxarsole **28e** as a white solid (0.164 g, 59% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.29.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, *J* = 7.7 Hz, 1H), 7.74 (t, *J* = 7.3 Hz, 1H), 7.42-7.35 (m, 10H), 7.28-7.25 (m, 8H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.02-6.96 (m, 3H).

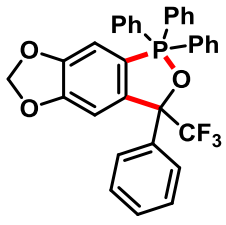
^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.54, 140.80, 140.04, 134.35, 132.27, 131.83, 129.34, 128.65, 128.22, 128.12, 128.02, 127.73, 127.10, 126.81, 80.17-79.75 (m).

^{19} F NMR (376 MHz, $CDCl_3$) δ:-73.94.

HRMS: calculated $[M+H]^+$ for $C_{32}H_{25}F_3OAs$: 557.1068, found: 557.1065.

FTIR (cm^{-1}): 3018, 2397, 1672, 1537, 1480, 1382, 1239, 1211, 858, 806, 779, 761.

1,1,1,3-Tetraphenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-[1,3]dioxolo[4',5':4,5]benzo [1,2-*c*][1,2]oxaphosphole (28f)



28f

Following the general procedure, treatment of 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate **10c** (0.205 g, 0.60 mmol) and 4-2,2,2-trifluoro-1-phenylethan-1-one **27a** (0.131 g, 105 µL, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (3.0 mL) at 30 °C to rt for 12 h followed

by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 1,1,1,3-tetraphenyl-3-(trifluoromethyl)-1,3-dihydro-1λ^5-[1,3]dioxolo[4',5':4,5] benzo[1,2-*c*][1,2] oxaphosphole **28f** as a white solid (0.209 g, 75% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.41.

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.51 (s, 1H), 7.24-7.18 (m, 11H), 7.15-7.13 (m, 6H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 2H), 6.19 (d, *J* = 11.9 Hz, 1H), 6.11 (s, 2H).

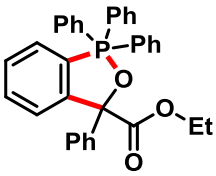
^{13}C NMR (125 MHz, CDCl$_3$) δ 151.77, 148.83 (d, *J* = 22.9 Hz), 143.43, 143.26, 142.39, 137.32, 131.89 (d, *J* = 9.0 Hz), 128.11 (d, *J* = 21.8 Hz), 127.26 (d, *J* = 4.8 Hz), 127.18, 115.78 (d, *J* = 19.3 Hz), 106.73 (d, *J* = 19.2 Hz), 102.80, 80.09-79.73 (m).

^{31}P NMR (203 MHz, CDCl$_3$) δ -50.80.

HRMS: calculated [M+H]$^+$ for $C_{33}H_{25}F_3O_3P$: 557.1488, found: 557.1481.

FTIR (cm^{-1}): 3441, 3128, 3068, 3019, 2911, 2627, 2401, 2078, 1960, 1902, 1814, 1615, 1499, 1474, 1435, 1364, 1261, 1218, 1076, 1036, 1001, 906, 755, 694.

Ethyl-1,1,1,3-tetraphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole-3-carboxylate (28g)



28g

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.298 g, 242 µL, 1.0 mmol) and ethyl 2-oxo-2-phenylacetate **27d** (0.134 g, 119 µL, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.116 g, 2.0 mmol) and 18-crown-6 (0.528 g, 2.0 mmol) in THF (3.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 80/20) of the crude reaction mixture using silica gel afforded ethyl-1,1,1,3-tetraphenyl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole-3-carboxylate **28g** as a yellow solid (0.161 g, 62% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.56.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.92 (d, *J* = 5.5 Hz, 1H), 7.61 (t, *J* = 6.0 Hz, 1H), 7.31-7.12 (m, 21H), 6.97 (bs, 1H), 4.04-3.98 (m, 1H), 3.79-3.75 (m, 1H), 1.09 (t, *J* = 7.1, 3H).

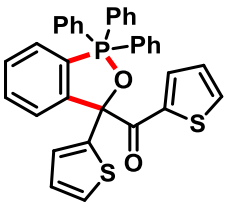
^{13}C NMR (400 MHz, CDCl$_3$) δ: 173.64, 151.02 (d, *J* = 20.1 Hz), 143.69, 143.43, 142.62, 136.67 (d, *J* = 14.6 Hz), 132.21 (d, *J* = 2.8 Hz), 131.75 (d, *J* = 8.9 Hz), 128.20, 128.05, 127.99, 127.98, 127.86, 127.35 (d, *J* = 12.7 Hz), 127.10, 126.59, 83.10, 61.46, 14.06.

^{31}P NMR (162 MHz, $CDCl_3$) δ: - 49.91.

HRMS: calculated $[M+H]^+$ for $C_{34}H_{30}O_3P$: 517.1927, found: 517.1921.

FTIR (cm^{-1}): 3783, 3695, 3004, 2362, 1718, 1592, 1474, 1440, 1220, 1071, 1029, 772, 743, 695, 664.

Thiophen-2-yl(1,1,1-triphenyl-3-(thiophen-2-yl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphol-3-yl)methanone (28h)



28h

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.149 g, 121 μL, 0.50 mmol) and 1,2-di(thiophen-2-yl)ethane-1,2-dione **27e** (0.091 g, 0.375 mmol) with triphenylphosphine **12a** (0.066 g, 0.25 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (3.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 80/20) of the crude reaction mixture using silica gel afforded thiophen-2-yl(1,1,1-triphenyl-3-(thiophen-2-yl)-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphol-3-yl)methanone **28h** as a yellow solid (0.086 g, 61% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.61.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (dd, J_1 = 7.5 Hz, J_2 = 2.31 Hz, 1H), 7.84 (d, *J* = 3.1, Hz, 1H), 7.76 (t, *J* = 7.3 Hz, 1H), 7.43-7.37 (m, 8H), 7.32-7.26 (m, 9H), 7.18 (d, *J* = 4.6 Hz, 1H), 7.06-7.00 (m, 2H), 6.94-6.91 (m, 1H), 6.81 (t, *J* = 4.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.14, 151.35 (d, *J* = 19.0 Hz), 150.79, 142.99, 141.92, 140.38, 136.42 (d, *J* = 14.8 Hz), 136.12, 133.25, 132.22 (d, *J* = 2.8 Hz), 131.54 (d, *J* = 8.9), 128.88 (d, *J* =15.3 Hz), 128.14, 128.03 (d, *J* = 1.9 Hz), 127.32 (d, *J* = 12.5), 126.81 (d, *J* = 17.1), 125.55, 124.78, 124.02, 84.99.

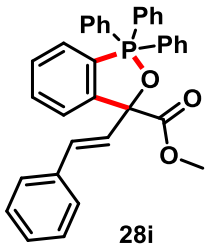
^{31}P NMR (162 MHz, $CDCl_3$) δ: - 48.64.

HRMS: calculated $[M+H]^+$ for $C_{34}H_{26}O_2PS_2$: 561.1106, found: 561.1097.

FTIR (cm^{-1}): 3743, 3067, 1822, 1650, 1582, 1434, 1350, 1279, 908, 793, 713, 693.

Methyl (*E*)-1,1,1-triphenyl-3-styryl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole-3-carboxyl zate (28i)

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.178 g, 150 μL, 0.60 mmol) and methyl (*E*)-2-oxo-4-phenylbut-3-enoate **27f** (0.142 g, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.5



28i

mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at 30 °C for 12 h followed by silica gel flash column chromatography (Pet. ether/EtOAc = 70/30) of the crude reaction mixture afforded methyl (*E*)-1,1,1-triphenyl-3-styryl-1,3-dihydro-1λ^5-benzo[*c*][1,2]oxaphosphole-3-carboxylate **28i** as a white solid (0.190g, 72%).

***R**$_f$* (Pet. ether /EtOAc = 70/30): 0.54.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.02-8.00(m, 1H), 7.67-7.64 (m, 1H), 7.37-7.20 (m, 18H), 7.17-7.12 (m, 3H), 6.79-6.74 (m, 1H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.13 (d, *J* = 15.7 Hz, 1H), 3.46 (s, 3H).

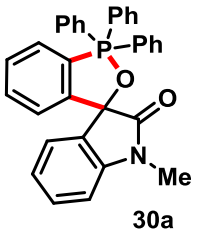
^{13}C NMR (100 MHz, CDCl$_3$) δ: 173.92, 150.69, 150.49, 143.64, 142.57, 137.05, 136.90, 136.81, 132.81, 131.77, (d, *J* = 8.9 Hz), 130.78, 129.69, 128.36, 128.19, 127.54, 127.42, 126.81, 126.54, 81.54, 52.4.

^{31}P NMR (162 MHz) δ: -48.14.

HRMS: calculated [M+H]$^+$ for $C_{35}H_{30}O_3P$: 529.1927, found: 529.1926.

FTIR (cm^{-1}): 3781, 3428, 3059, 2923, 2852, 2519, 2249, 2026, 1724, 1626, 1435, 1161, 1118, 766, 696.

1'-Methyl-1,1,1-triphenyl-1*H*-1λ^5-spiro[benzo[*c*][1,2]oxaphosphole-3,3'-indolin]-2'-one (30a)



30a

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.223 g, 182 μL, 0.75 mmol) and 1-methylindoline-2,3-dione **29a** (0.121 g, 0.75 mmol) with triphenylphosphine **12a** (0.132 g, 0.5 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 70 °C for 20 h followed by silica gel flash column chromatography (Pet. ether/EtOAc = 50/50) of the crude reaction mixture afforded 1'-methyl-1,1,1-triphenyl-1*H*-1λ^5-spiro[benzo[*c*][1,2]oxaphosphole-3,3'-indolin]-2'-one **30a** as a yellow solid (0.222 g, 89%).

***R**$_f$* (Pet. ether /EtOAc = 50/50): 0.63.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61-7.58 (m, 6H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.33-7.28 (m, 10H), 7.13-7.03 (m, 2H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.57 (t, *J* = 7.3 Hz, 1H), 5.54 (s, 1H), 3.24 (s, 3H).

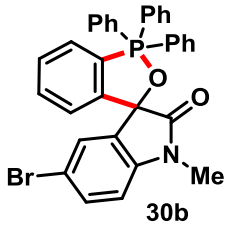
^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.04, 149.43 (d, *J* = 20.3 Hz), 144.07, 136.88 (d, *J* = 14.5 Hz), 133.30, 133.02, 132.44 (d, *J* = 9.1 Hz), 128.85, 128.30, 128.16, 127.59 (d, *J* = 12.6 Hz, 124.31, 122.96, 108.02, 81.04, 26.56.

^{31}P NMR (162 MHz, $CDCl_3$) δ: -47.21.

HRMS: calculated $[M+H]^+$ for $C_{33}H_{27}NO_2P$: 500.1774, found: 500.1774.

FTIR (cm^{-1}): 3784, 3704, 3010, 2361, 1718, 1610, 1473, 1440, 1370, 1221, 1195, 1111, 1040, 959, 911, 772, 697.

5'-Bromo-1'-methyl-1,1,1-triphenyl-1*H*-1λ^5-spiro[benzo[*c*][1,2]oxaphosphole-3,3' indolin]-2'-one (30b)



30b

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.223 g, 182 μL, 0.75 mmol) and 5-bromo-1-methylindoline-2,3-dione (0.180 g, 0.75 mmol) **29b** with triphenylphosphine **12a** (0.131 g, 0.5 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 70 °C for 20 h followed by silica gel flash column chromatography (Pet. ether/EtOAc = 50/50) of the crude reaction mixture afforded 5'-bromo-1'-methyl-1,1,1-triphenyl-1*H*-1λ^5-spiro[benzo[*c*][1,2]oxaphosphole-3,3' indolin]-2'-one **30b** as a yellow solid (0.237 g, 82%).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.49.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 -7.53 (m, 6H), 7.48-7.43 (m, 1H), 7.36-7.32 (m, 10H), 7.19 (dd, J_1 = 1.9 Hz, J_2 = 8.2 Hz, 1H), 7.09-7.04 (m, 1H), 6.96 (dd, J_1 = 2.1 Hz, J_2 = 7.4 Hz, 1H), 6.60 (d, *J* = 8.26 Hz, 1H), 5.43 (s, 1H), 3.19 (s, 3H).

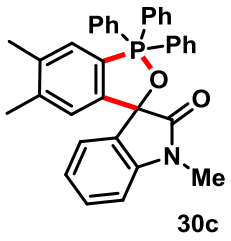
^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.69, 148.56 (d, *J* = 19.9 Hz), 143.08, 136.97 (d, *J* = 14.6 Hz), 135.35, 133.11 (d, *J* = 2.5 Hz), 132.39 (d, *J* = 9.1 Hz), 128.57, 128.43, 127.73, 127.66, 127.61, 124.22 (d, *J* = 19.6 Hz), 115.69, 109.42, 80.75, 26.65.

^{31}P NMR (162 MHz, $CDCl_3$) δ: -46.15.

HRMS: calculated $[M+H]^+$ for $C_{33}H_{26}BrNO_2P$: 578.0879, found: 578.0887.

FTIR (cm^{-1}): 3383, 3065, 2362, 1721, 1608, 1479, 1433, 1352, 1190, 1104, 960, 888, 697.

1',5,6-Trimethyl-1,1,1-triphenyl-1*H*-1λ^5-spiro[benzo[*c*][1,2]oxaphosphole-3,3'-indolin]-2'-one (30c)



30c

Following the general procedure, treatment of 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10d** (0.245 g, 0.75 mmol) and 1-methylindoline-2,3-dione **29a** (0.120 g, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.50 mmol) in the presence of KF (0.087 g, 1.50 mmol) and 18-crown-6 (0.396 g, 1.50 mmol) in THF (4.0 mL) at 70 °C for 20 h followed by silica gel flash column chromatography (Pet. ether/EtOAc = 50/50) of the crude reaction mixture afforded 1',5,6-trimethyl-1,1,1-triphenyl-1*H*-1λ^5-spiro[benzo[*c*][1,2]oxaphosphole-3,3'-indolin]-2'-one **30c** as a yellow solid (0.155 g, 59%).

***R*$_f$** (Pet. ether/EtOAc = 50/50): 0.57.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.62-7.60 (m, 6H), 7.33 (s, 10H), 7.13 (t, *J* =7.66 Hz 1H), 6.77 (t, *J* = 8.56 Hz, 2H), 6.59 (t, *J* = 7.43 Hz, 1H), 5.58 (d, *J* = 7.42, 1H), 3.26 (s, 3H), 2.23 (s, 3H), 2.15 (s, 3H).

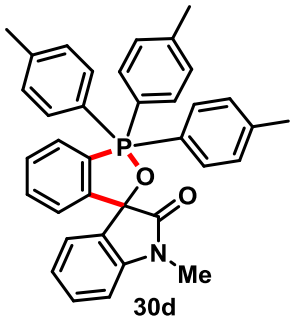
^{13}C NMR (100 MHz, CDCl$_3$) δ: 178.39, 147.36 (d, *J* = 20.35 Hz), 144.15, 144.10, 143.10, 142.78 (d, *J* = 3.20 Hz), 143.50 (d, *J* = 14.81 Hz), 136.99 (d, *J* = 14.88 Hz), 133.61, 132.40 (d, *J* = 9.11 Hz), 128.63, 128.05 (d, *J* = 1.71 Hz), 127.43 (d, *J* = 12.60 Hz), 126.13, 125.00 (d, *J* = 16.30 Hz), 124.74, 124.35, 122.87, 107.91, 80.86, 26.54, 20.35, 20.08.

^{31}P NMR (162 MHz, CDCl$_3$) δ: -51.65.

HRMS: calculated $[M+H]^+$ for $C_{35}H_{31}NO_2P$: 528.2087, found: 528.2096.

FTIR (cm^{-1}): 3663, 2927, 2361, 1718, 1608, 1473, 1440, 1355, 1219, 1112, 771, 740, 696.

1'-Methyl-1,1,1-tri-p-tolyl-1*H*-1λ^5-spiro[benzo[*c*][1,2]oxaphosphole-3,3'-indolin]-2'-one (30d)



30d

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.223 g, 182 μL, 0.75 mmol) and 1-methylindoline-2,3-dione **29a** (0.121 g, 0.75 mmol) with tristri-p-tolylphosphine **12d** (0.152 g, 0.5 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 70 °C for 20 h followed by silica gel flash column chromatography (Pet. ether/EtOAc = 50/50) of

the crude reaction mixture afforded 1'-methyl-1,1,1-tri-p-tolyl-1*H*-1λ^5-spiro[benzo[*c*][1,2]oxaphosphole-3,3'-indolin]-2'-one **30d** as a yellow solid (0.181 g, 67%).

R_f (Pet. ether /EtOAc = 50/50): 0.55.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49-7.38 (m, 7H), 7.28-7.25 (m, 1H), 7.12-7.03 (m, 8H), 6.95 (dd, J_1=1.85, J_2=7.3, 1H),), 6.74 (d, *J* = 7.7 Hz, 1H), 6.55 (t, *J* = 7.5 Hz, 1H), 5.54 (d, *J* = 7.3 Hz, 1H), 3.22 (s, 3H), 2.35 (s, 9H).

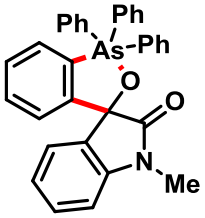
^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.27, 149.33 (d, *J* = 20.4 Hz), 144.04, 140.85, 139.80, 137.82, 136.79 (d, *J* = 14.71 Hz), 133.65, 132.70 (d, *J* = 2.8 Hz), 132.42 (d, *J* = 9.58 Hz), 128.59, 128.09 (d, *J* = 13.0 Hz), 127.92, 124.39, 124.05 (d, *J* = 15.3 Hz), 122.73, 107.83, 80.91, 26.47, 21.36.

^{31}P NMR (162 MHz) δ: -47.23.

HRMS: calculated $[M+H]^+$ for $C_{36}H_{33}NO_2P$: 542.2243, found: 542.2239.

FTIR (cm^{-1}): 2919, 1716, 1609, 1468, 1344, 1222, 1190, 1042, 743, 735, 689, 659, 615.

1'-Methyl-1,1,1-triphenyl-1*H*-1λ^5-spiro[benzo[*c*][1,2]oxarsole-3,3'-indolin]-2'-one (30e)



30e

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.223 g, 182 µL, 0.75 mmol) and 1-methylindoline-2,3-dione **29a** (0.121 g, 0.75 mmol) with triphenylarsine **19** (0.153 g, 0.5 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 70 °C for 20 h followed by silica gel flash column chromatography (Pet. ether/EtOAc = 30/70) of the crude reaction mixture afforded 1'-methyl-1,1,1-triphenyl-1*H*-1λ^5-spiro[benzo[*c*][1,2]oxarsole-3,3'-indolin]-2'-one **30e** as a yellow solid (0.167 g, 62%).

R_f (EtOAc): 0.42.

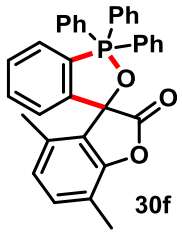
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 5.3 Hz, 6H), 7.43-7.36 (m, 10H), 7.29-7.25 (m, 1H), 7.10-7.07 (m, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 5.88 (d, *J* = 7.4 Hz, 1H), 3.22 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.44, 147.91, 144.13, 140.99, 136.38, 133.64, 132.75, 132.53, 129.38, 128.45, 128.23, 128.20, 126.56, 125.81, 123.98, 122.81, 107.86, 80.85, 26.48.

HRMS: calculated $[M+H]^+$ for $C_{33}H_{27}AsNO_2$: 544.1252, found: 544.1256.

FTIR (cm^{-1}): 3743, 3589, 3564, 2921, 2853, 1707, 11463, 1363, 1280, 1110, 745, 684.

4,7-Dimethyl-1',1',1'-triphenyl-1'*H*,2*H*-1'λ^5-spiro[benzofuran-3,3' benzo[*c*][1,2]oxaphosphol]-2-one (30f)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10a** (0.223 g, 182 μL, 0.75 mmol) and 4,7-dimethylbenzofuran-2,3-dione **29c** (0.132 g, 0.75 mmol) with triphenylphosphine **12a** (0.131 g, 0.5 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 70 °C for 20 h followed by silica gel flash column chromatography (Pet. ether/EtOAc = 50/50) of the crude reaction mixture afforded 4,7-Dimethyl-1',1',1'-triphenyl-1'*H*,2*H*-1'λ^5-spiro[benzofuran-3,3' benzo[*c*][1,2]oxaphosphol]-2-one **30f** as a yellow solid (0.154 g, 60%).

***R*$_f$** (Pet. ether/EtOAc = 50/50): 0.40.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.62-7.56 (m , 7H), 7.43-7.28 (m, 11H), 6.18 (d, *J* = 7.4 Hz, 1H), 6.75-6.70 (m, 1H), 6.61 (d, *J* = 7.4 Hz, 1H), 2.50 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ: 202.32, 171.02, 147.45, (d, *J* = 17.2 Hz), 138.12, 137.11, 137.02, 136.97, 133.81, 133.78, 132.59, 132.50, 129.66, 129.51, 129.09, 127.57 (d, *J* = 12.9 Hz), 124.90 (d, *J* =14.4 Hz), 121.97, 120.04, 117.56, 106.21, 17.71, 14.02.

^{31}P NMR (162 MHz) δ: -39.14.

HRMS: calculated $[M+H]^+$ for $C_{34}H_{28}O_3P$: 515.1771, found: 515.1768.

FTIR (cm^{-1}): 3106, 2397, 1719, 1500, 1413, 1220, 871, 811, 761, 680.

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List of Publications

1. **Bhunia, A.**, Yetra, S. R., Gonnade R. G., Biju A. T., Synthesis of 4H-chromenes by an unexpected, K_3PO_4-mediated intramolecular Rauhut-Currier type reaction, *Org. Biomol. Chem.* **2016,** DOI:*10.1039/C6OB00654J*.
2. Patra, A., **Bhunia, A.**, Yetra, S. R., Gonnade R. G., Biju A. T., Diastereoselective Synthesis of Cyclopentanone-Fused Spirooxindoles by N-Heterocyclic Carbene-Catalyzed Homoenolate Annulation with Isatilidenes, *Org. Chem. Front*. **2015**, *02*, 1584.
3. **Bhunia, A.**;Thorat, S.; Gonnade R. G.; Biju A. T., Reaction of N-Heterocyclic Carbenes with Chalcones leading to the Synthesis of *deoxy*-Breslow Intermediates in their Oxidized form, *Chem. Commun*. **2015,** *51*, 13690.
4. Patra, A.; **Bhunia, A.**; Biju, A. T. Facile Synthesis of γ-Ketophosphonates by an Intermolecular Stetter Reaction Onto Vinylphosphonates, *Org. Lett*. **2014,** *16*, 4798.
5. **Bhunia, A.**; Roy T.; Gonnade R. G.; Biju A. T., Rapid Access to Benzoxaphospholes and Their Spiro Analogues by a Three-Component Coupling Involving Arynes, Phosphines, and Activated Ketones, *Org. Lett*. **2014,** *16*, 5132.
6. **Bhunia, A.**; Kaicharla, T.; Porwal, D.; Gonnade, R. G.; Biju, A. T., Multicomponent Reactions Involving Phosphines, Arynes and Aldehydes, *Chem. Commun*. **2014,** *50*, 11389.
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