N-Heterocyclic Carbene-Organocatalyzed Umpolung of Aldehydes and Imines for New Synthetic Transformations

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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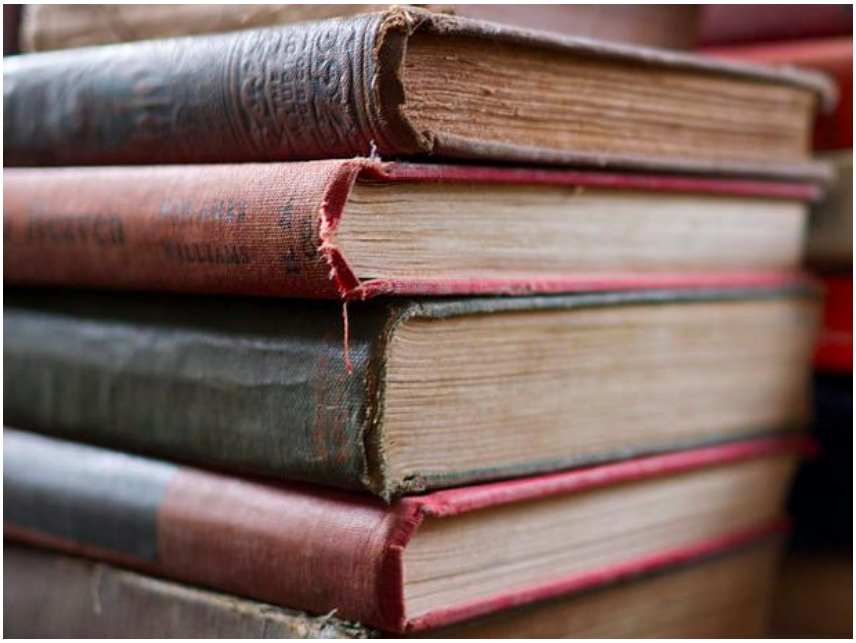
November 2017

Dedicated

To

My Beloved Parents

For their unconditional Love, Support, Pray and Encouragement….



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This is to certify that the work incorporated in this Ph.D. thesis entitled "**N-Heterocyclic Carbene-Organocatalyzed Umpolung of Aldehydes and Imines for New Synthetic Transformations**" submitted by **Mr. Atanu Patra** 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.

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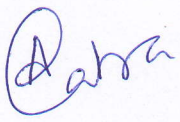
Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"N-Heterocyclic Carbene-Organocatalyzed Umpolung of Aldehydes and Imines for New Synthetic Transformations''** 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.



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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. Nemai Patra*** *and mother* ***Smt. Nilima Patra*** *and beloved brother* ***Santanu*** *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.

Atanu Patra

List of Abbreviations

Ac	:	Acetyl
acac	:	Acetylacetone
ACN	:	Acetonitrile
t-Am	:	Tertiary amyl
Ar	:	Aryl
Ad	:	Adamantyl
BIPHEP	:	2,2'-Bis(diphenylphosphino)biphenyl
Bn	:	Benzyl
Boc	:	Tertiary butyloxycarbonyl
bs	:	Broad singlet
t-Bu	:	Tertiary butyl
n-BuLi	:	*n*-Butyllithium
Cy	:	Cyclohexyl
Cat.	:	Catalytic
CDI	:	Carbonyldiimidazole
cod	:	1,5-Cyclooctadiene
Cp*	:	Pentamethylcyclopentadiene
m-CPBA	:	*meta*-Chloroperoxybenzoic acid
CPME	:	Cyclopentyl methyl ether
DABCO	:	1,4-Diazabicyclo[2.2.2]octane
DBU	:	1 8-Diazabicyclo 5.4.0 undec-7-ene
DCE	:	1,2-Dichloroethane
DCM	:	Dichloromethane
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 Dicarboxylate
DMSO	:	Dimethyl sulfoxide

dr	:	Diastereomer
E^+	:	Electrophile
ee	:	Enantiomeric excess
Et_3N	:	Triethyl amine
Et	:	Ethyl
g	:	gram(s)
h	:	hour(s)
HFIP	:	Hexafluoro-2-propanol
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
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
PBE	:	Perdue Burke Ernzerhof
Ph	:	Phenyl
i-Pr	:	Isopropyl
q	:	Quartet
rt	:	Room temperature
s	:	Singlet
t	:	Triplet
TBDPS	:	Tertiarybutyldiphenylsilyl
TBS	:	Tertiarybutylsilyl

TMEDA	:	Tetramethylethylenediamine
Tf	:	Trifluromethanesulfonyl
Tf_2O	:	Trifluoromethanesulfonic anhydride
THF	:	Tetrahydofuran
TLC	:	Thin layer chromatography
TMS	:	Trimethylsilyl
Ts	:	Tosyl
TZVP	:	Triple zeta for valence electrons plus polarzation

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	
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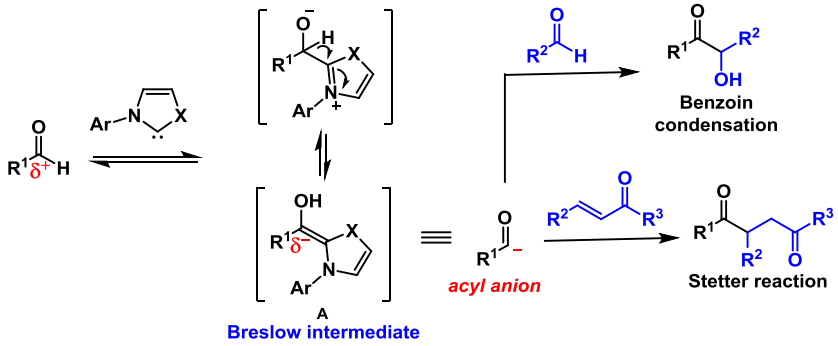
Research Supervisor	Dr. A. T. Biju (CSIR-NCL, Pune)

The proposed thesis is divided into five chapters. The first chapter deals with a brief introduction to N-heterocyclic carbene (NHC)-organocatalysis. The second chapter describes the facile synthesis of γ-ketophosphonates by an intermolecular Stetter reaction onto vinylphosphonates. A diastereoselective synthesis of cyclopentanone-fused spirooxindoles using NHC-catalyzed homoenolate annulation with isatilidenes forms the subject matter of the third chapter. In chapter four, the studies towards the development of NHC-catalyzed umpolung of imines for the synthesis of indole 3-acetic acid derivatives is presented. The focal theme of the fifth chapter is the synthesis of difluoromethylated quinoline derivatives using the NHC-catalyzed umpolung of imines strategy. The details are presented below.

Chapter 1: Introduction to NHC-organocatalysis

NHC-organocatalysis is one of the important synthetic strategies for the unconventional construction of various carbon-carbon and carbon-heteroatom bonds thereby leading to the synthesis of various carbocycles, heterocycles and acyclic molecules. In most cases, NHCs are employed to render aldehydes nucleophilic, thereby reversing their normal reactivity. This reversal of normal mode of reactivity is referred to as *umpolung*. Benzoin condensation and Stetter reaction are the two well-known transformations catalyzed by NHCs, which proceed via the generation of the key "Breslow intermediate" (Scheme 1).[1] The two important modes of NHC reactivity are formation of acyl-anion equivalents and generation of homoenolate equivalents.

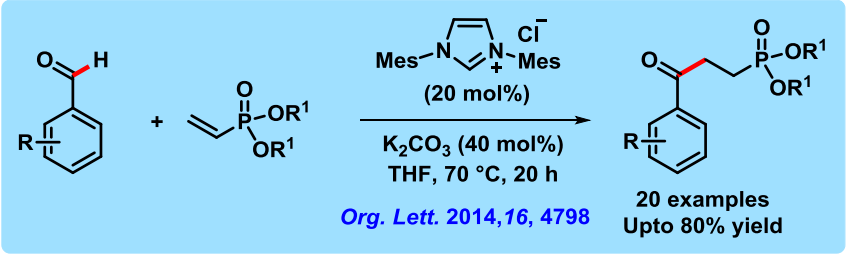


Scheme 1. NHC-Catalyzed Umpolung of Aldehydes

Chapter 2: Facile Synthesis of γ-Ketophosphonates by an Intermolecular Stetter Reaction Onto Vinylphosphonates

The NHC-catalyzed generation of the Breslow intermediate from aldehydes and its subsequent interception with a variety of Michael acceptors are well documented. Notably, the

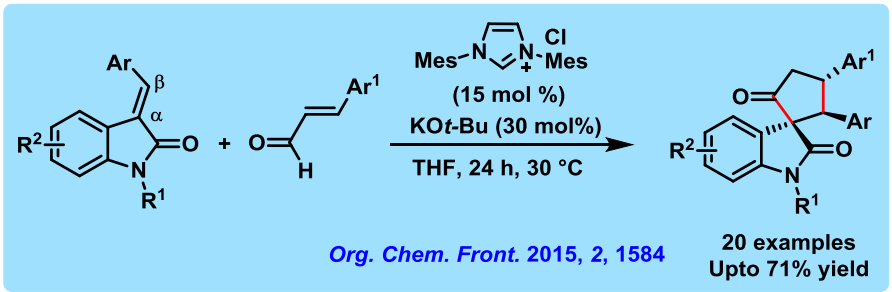
NHC-catalyzed addition of aldehydes to moderately electron-poor Michael acceptors have received only limited attention. In the course of our studies, we have developed the NHC-catalyzed intermolecular Stetter reaction onto α,β-unsaturated phosphonates, which are moderately electron-poor Michael acceptors. The carbene generated from the imidazolium salt (IMes.HCl) in the presence of K2CO3 was the key for the success of this transformation (Scheme 2).2 The reaction resulted in the efficient synthesis of γ-ketophosphonates in moderate to good yields. The reaction showed good tolerance with a wide variety of aldehydes. Further, this methodology was extended to α,α-disubstituted vinyl phosphonates under a modified reaction condition. Preliminary mechanistic studies indicated the low reactivity of vinyl phosphonates over acrylates thus demonstrating moderately electron poor C-C double bond of vinyl phosphonates.



Scheme 1. NHC-Catalyzed Umpolung of Aldehydes

Chapter 3: Diastereoselective Synthesis of Cyclopentanone-Fused Spirooxindoles Using NHC-Catalyzed Homoenolate Annulation with Isatilidenes

One of the interesting modes of NHC reactivity is the generation of homoenolate equivalents from α,β-unsaturated aldehydes. In this area, we have recently developed the NHC-catalyzed formal [3 + 2] annulation of α,β-unsaturated aldehydes with *N*-substituted isatilidenes resulting in the diastereoselective synthesis of cyclopentanone-fused spirooxindoles (Scheme 3).[3] Mechanistically, the reaction proceeds via the generation of homoenolate equivalent intermediates from NHC and enals. This nucleophilic homoenolates upon interception with isatilidenes afford spiroheterocyclic compounds bearing an all-carbon quaternary spiro-center in moderate to good yields, and generally with high diastereoselectivity. Moreover, the functionalization of the spirooxindoles has been performed. Furthermore, preliminary studies on the enantioselective version of this reaction afforded the chiral spiroheterocycle in up to 97% ee.

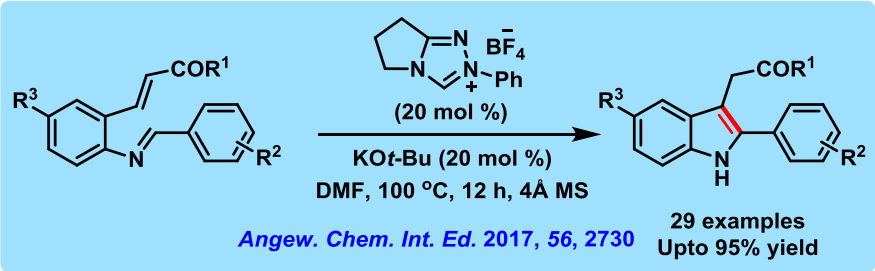


Scheme 3. Diastereoselective Homoenolate Annulation with Isatilidenes

Chapter 4: NHC-Catalyzed Umpolung of Imines for the Synthesis of Indole 3-Acetic Acid Derivatives

NHC-Catalysis has been widely used for the umpolung of aldehydes, and recently for the umpolung of Michael acceptors.[4] Interestingly, the umpolung of imines using NHCs, to the best of our knowledge was unknown. We have recently developed the umpolung of aldimines catalyzed by NHCs (aza-Stetter reaction), and the reaction likely proceeds via aza-Breslow intermediates. The NHC catalyzed intramolecular cyclization of aldimines bearing a Michael

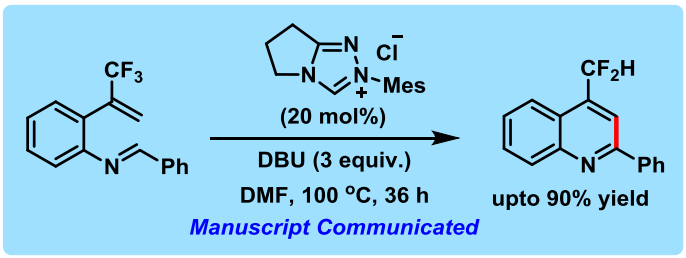
acceptor resulted in the formation of biologically important 2-(hetero)aryl indole 3-acetic-acid derivatives in moderate to good yields (Scheme 4).[5] The carbene generated from the bicyclic triazolium salt was found to be efficient for this transformation. The preliminary mechanistic experiments on this reaction shed light on the intermediacy of the aza-Breslow intermediate, which was supported by DFT studies.



Scheme 4. NHC-Catalyzed Umpolung of Aldimines

Chapter 5: Synthesis of Difluoromethylated Quinoline derivative using NHC-Catalyzed Umpolung of Imines

Quinoline derivatives are endowed with diverse biological properties. In an attempt to expand the scope of the NHC-catalyzed umpolung of imines, we have recently developed the NHC-catalyzed intramolecular cyclization of α-trifluoromethyl styrenes having an imine moiety for the synthesis of functionalized difluoromethyl quinolines (Scheme 5).[6] The carbene generated from the triazolium salt in the presence of excess DBU was the optimized reaction conditions used for this transformation. Mechanistically, the reaction proceeds via the umpolung of imines. This reaction works well with a wide variety of substrates having different substitution patterns.



Scheme 5. Synthesis of Difluoromethylated Quinolines via NHC-Catalyzed Umpolung of Imines

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5. Patra, A.; Mukherjee, S.; Das, T. K.; Jain, S.; Gonnade, R. G.; Biju, A. T. *Angew. Chem. Int. Ed.* **2017**, *56*, 2730.
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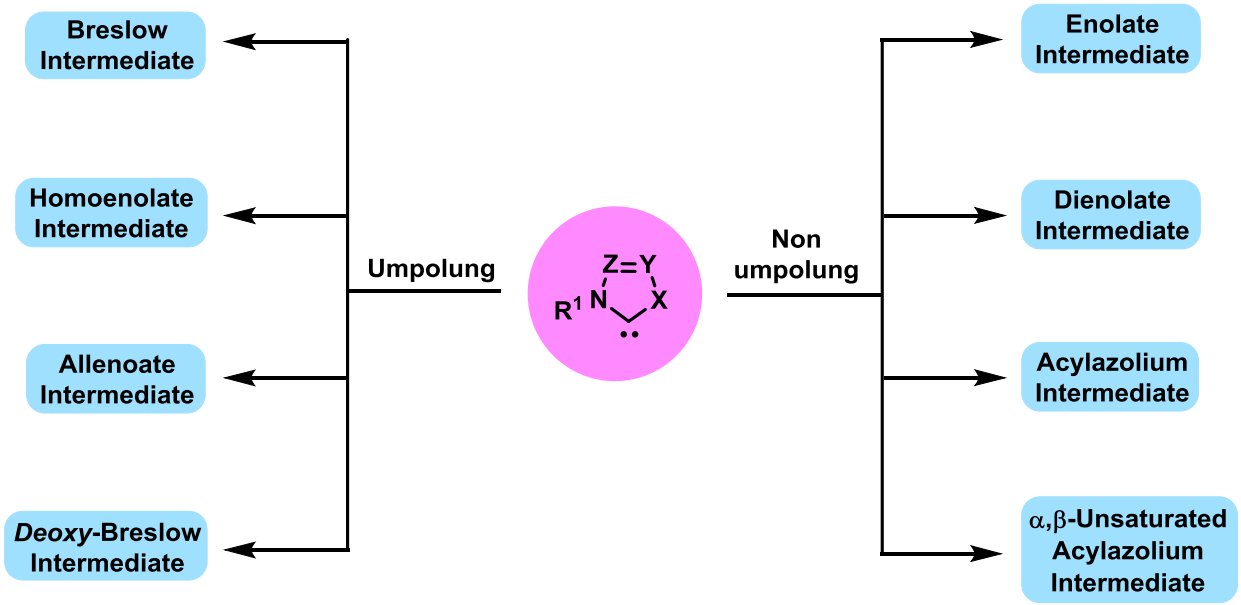
Chapter 1

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

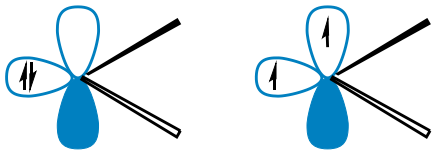
Carbenes are highly reactive and short lived species. Their reactivity comes mainly from their electronic unsaturation. Carbenes have been known as very unstable species for long, however recently developed N-heterocyclic carbene (NHC) derivatives proved to display higher stability making their handling much easier and allowing their use as efficient catalysts in various organic reactions. NHCs are considered as ligands in various metal-based catalytic reactions and also effective for the organocatalytic formation of carbon-carbon, carbon-heteroatom bonds and various carbocycles, heterocycles. In organocatalytic applications, NHCs-mainly catalyze the umpolung of aldehydes, alkyl halides and Michael acceptors which opened up new synthetic pathways. In this chapter, the chemistry of NHCs in synthetic organic chemistry as an organocatalyst has been presented.



1.1. Introduction

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

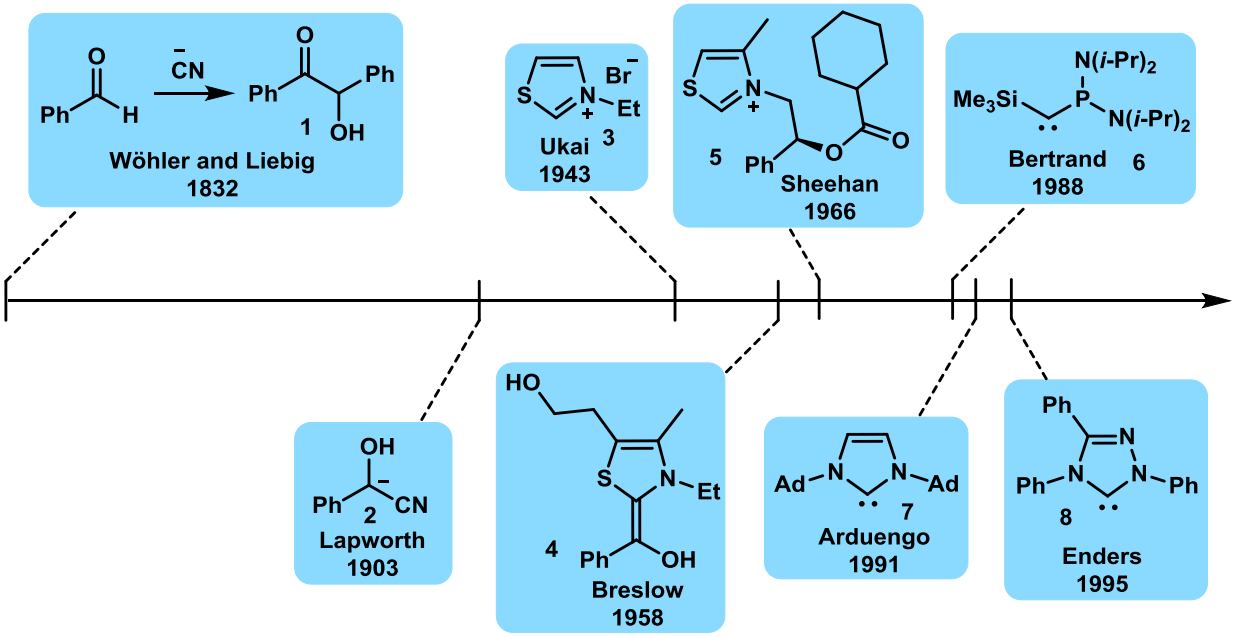


They have found widespread applications as versatile ligands in transition metal catalysis[1] and as organocatalyst in their own right. Their propensity to coordinate to carbon-electrophiles has led to a third major class of applications, in which NHCs act as organocatalyst. The majority of these processes are initiated by nucleophilic attack of the carbene onto carbonyl groups present in organic substrates. The electron-withdrawing nature of the cationic N-heterocyclic fragment generated upon nucleophilic attack has a key role in the subsequent reactivity of adduct. Usually, organocatalyzed reactions are divided into four major categories such as Lewis Base, Lewis acid, Brønsted base and Brønsted acid based transformations. Phosphines,[2] amines[3] and carbenes[4] are the common Lewis base catalysts, which are studied extremely in the last few decades. In this chapter, we will highlight the recent advances in NHC-organocatalysis for various organic transformations.

1.2. History of NHC-Organocatalysis

In 1832, Wöhler and Liebig described the self condensation of aromatic aldehyde in presence of cyanide to form benzoin **1**.[5] This Phenomenon is popularly known as benzoin condensation. Lapworth postulated a mechanism for this cyanide catalyzed reaction in early 19th century (Fig. 1.2).[6] The reaction proceeds via the formation of a carbinol intermediate **2** by hydrogen cyanide addition to benzaldehyde followed by protonation via the tetrahedral intermediate. 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.

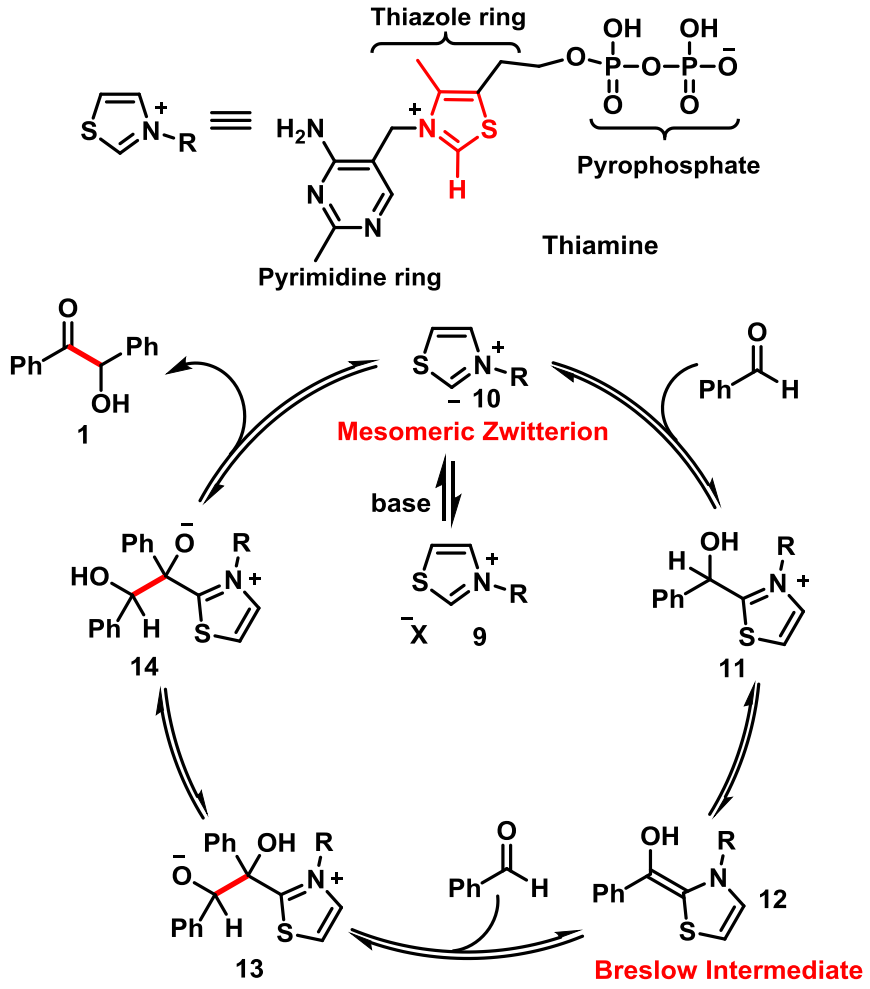
Fig. 1.2: Timeline of NHC-Organocatalysis



In 1943, Ukai and co-workers observed that the thiazolium moiety **3** embedded in coenzyme thiamine (Vitamin B1) could also catalyze the benzoin reaction.[7] Later in 1958, Breslow proposed a mechanistic explanation for the thiazolium salt-catalyzed benzoin condensation.[8] The key step in benzoin condensation is the nucleophilic attack of the in situ generated carbene **10** to the aldehyde, leading to the tetrahedral intermediate **11**, which undergoes proton transfer to the nucleophilic enaminol intermediate **12**. This acyl anion equivalent **12** reacts as a nucleophile with another molecule of aldehyde to furnish another tetrahedral intermediate **13,** which upon proton transfer followed by regeneration of NHC leads to the α-hydroxy ketone **1** as benzoin product (Scheme 1.1).

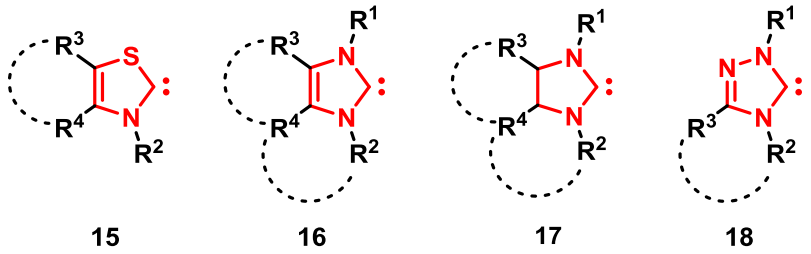
In this mechanism, the catalytically active species **10** was represented as mesomeric zwitterions, the resonance structure of NHC. Subsequently, Sheehan and Hunneman rendered the enantioselective benzoin reaction focusing on a chiral thiazolium precatalyst **5**. Initially NHC was mainly considered as a ligand in metal chemistry. Almost three decades later Bertrand and co-workers proved the existence of carbenes as catalytically active species in the benzoin reaction, with the synthesis of a stable phosphinocarbene **6**.[9a] Arduengo and co-workers isolated and characterized a stable NHC **7** in 1991.[9b] These two reports on the isolation of carbenes implied that they are more stable and robust than previously considered. Moreover, in 1995, Enders and co-workers reported the isolation of stable triazol-5-ylidene **8**.[10]

Scheme 1.1: Thiamine Catalyzed Benzoin Condensation



Generally, four types of NHCs are used of organocatalytic 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. The excellent σ-donor characteristics and moderate π-acidity are the reason behind facile generation of acyl anion equivalent.

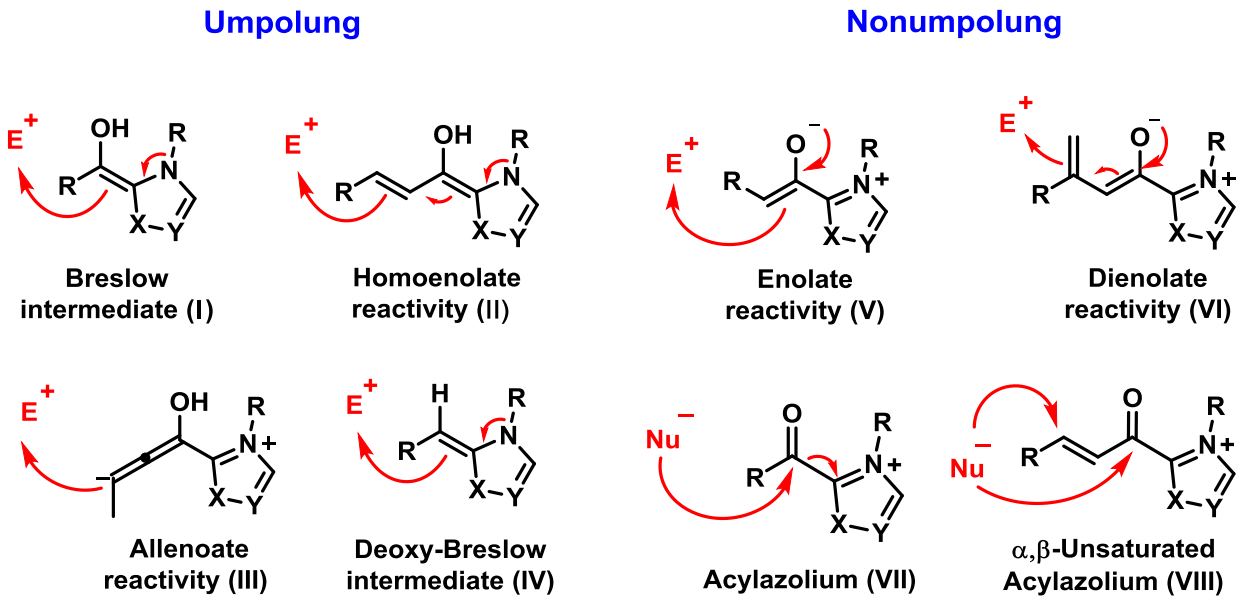
Fig. 1.3: Representative types of NHCs



1.3. Various Reactivity Modes of NHCs

The chemistry of NHC-catalysis is categorized according to the reaction mode and the intermediates formed in the reaction (Figure 1.4). This can be categorized based on two types of reactivity. One is umpolung reactivity and another one is non-umpolung reactivity. So, first we will classify umpolung reactivity. 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. The umpolung of ynals with NHC affords allenoate intermediate (**III**), 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 (**IV**).

Fig. 1.4: Various Reactivity Modes of NHC



The non-umpolung intermediates associate with reactions of α-halo aldehydes and ketenes with NHC affords the nucleophilic enolate intermediate (**V**) which is a two- carbon

synthon normally gives [4+2] and [3+2] annulations. Interestingly, an enolizable γ-proton of the α,β-unsaturated carbonyl compounds and enals with leaving groups generates NHC-bound dienolate intermediates (**VI**), which reacts in [4+2] and [2+2] cyclizations. A variety of NHC-catalyzed redox processes lead to the formation of acylazolium (**VII**) and α,β-unsaturated acylazolium (**VIII**) using external oxidant.

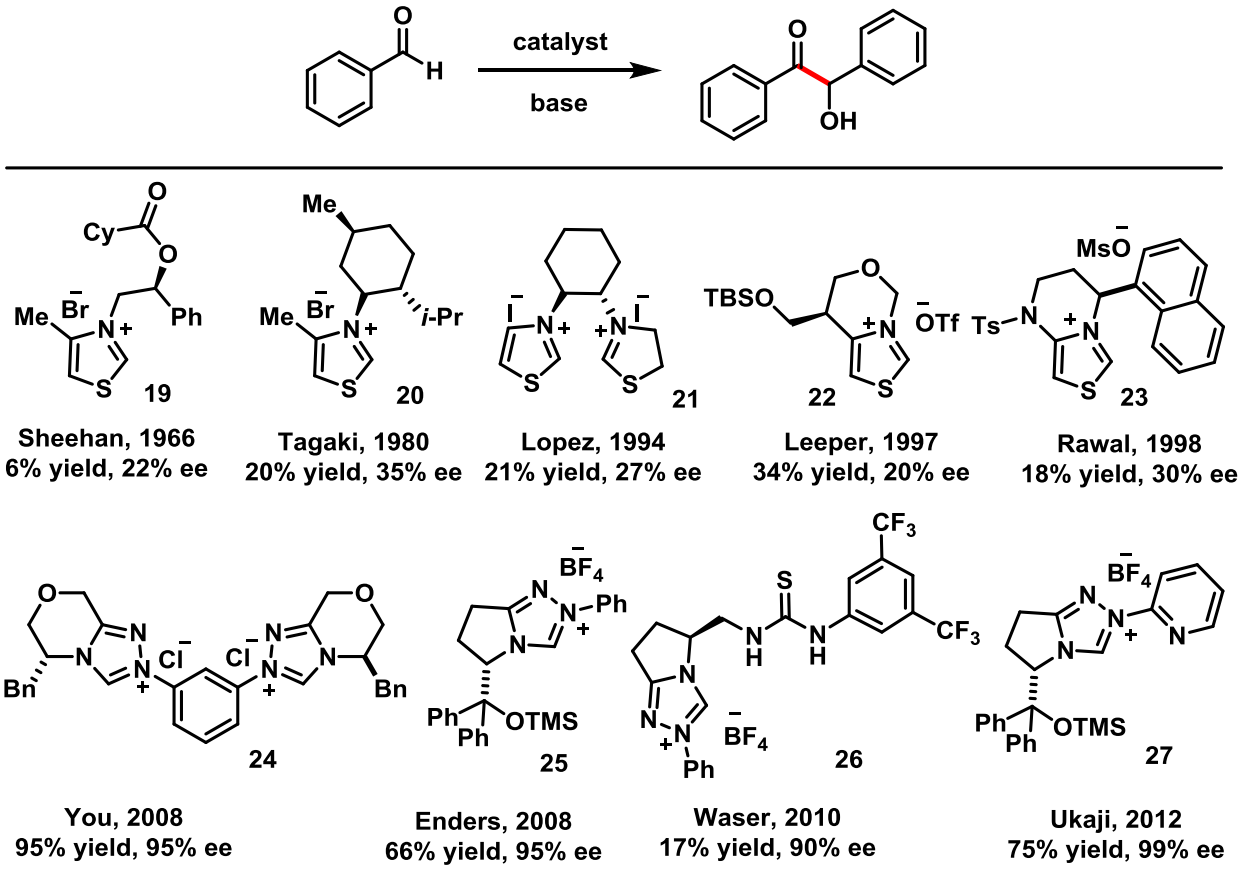
1.3.1. NHC-Catalyzed Reactions via Breslow Intermediate (I)

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. Benzoin reactions are divided in to two categories a) intermolecular benzoin and b) intramolecular benzoin reactions. The Stetter reactions are divided into two types such as c) Stetter reactions and d) hydroacylation reactions.

1.3.1.1. Intermolecular Benzoin Condensation

The benzoin reaction, coupling of two aldehydes, is one of the first transformations found

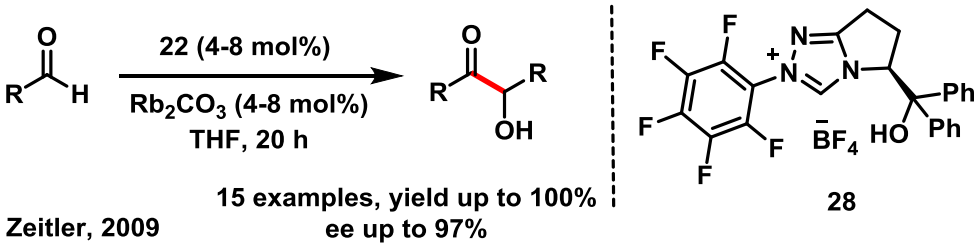
Scheme 1.2: List of Chiral NHC-Catalysts Used for Asymmetric Homobenzoin Condensation



to be catalyzed by NHCs.[7] Since the benzoin reaction is a valuable strategy to form new C-C bonds leading to the formation of α-functionalized carbonyl compounds, this unique process and its mechanism have been intensively studied.[11] Moreover, the effort to develop a highly asymmetric homobenzoin reaction led to the development of numerous chiral NHC precursors. A selected list of chiral-NHC catalysts has been presented in the Scheme 1.2. Thiazolium derived NHC-salts (**19-23**) provided the desired product in fewer yields and also the ee values are less. However, the catalyst generated from the triazolium salts (**24-27**) derived the benzoin product with moderate to good yields and with excellent ee values.[12]

Zeitler and co-workers reported pentafluorophenyltriazolium catalyst **28** most efficient asymmetric benzoin reaction of benzaldehyde at a low loading (4 mol %) to afford benzoin in 90% yield and >99% ee (Scheme 1.3).[13] A co-operative hydrogen bond assisted by triazole containing a chiral hydroxyl group assisted enantioselective benzoin condensation.

Scheme 1.3: Co-Operative Hydrogen Bond Assisted Enantioselective Benzoin Condensation

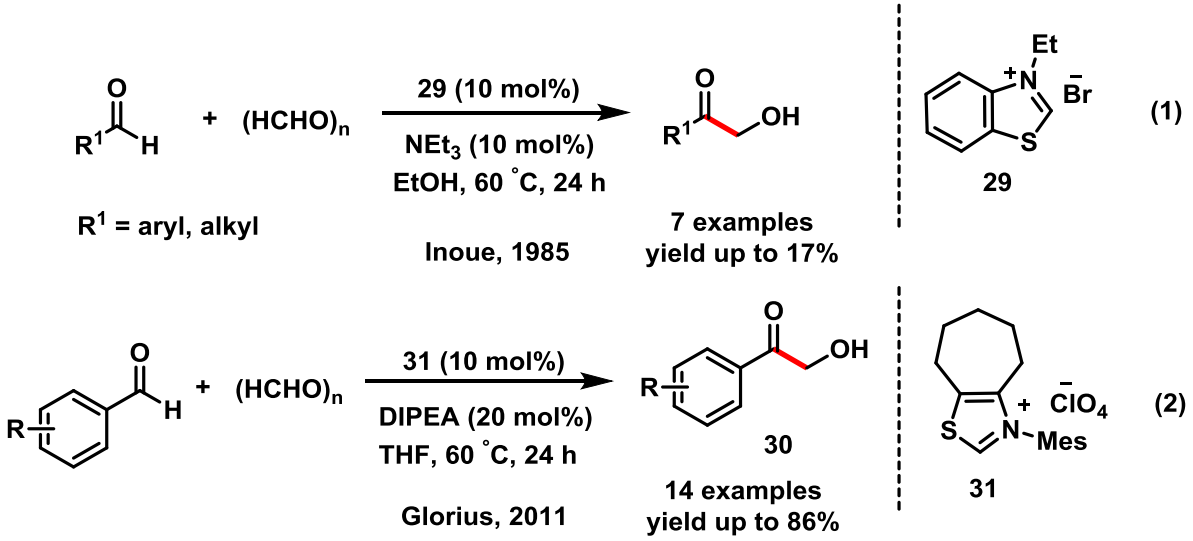


Intermolecular Cross-Benzoin Reaction

A cross-benzoin reaction unites two different aldehydes wherein one of them functions as the acyl anion equivalent. A total of four products are possible; a pair of homo-benzoin and cross-benzoin adducts each. A substrate-driven selectivity may be observed when one of the aldehydes is significantly less reactive due to electronic or steric reasons. The latter effect may be amplified by employing bulky NHCs.

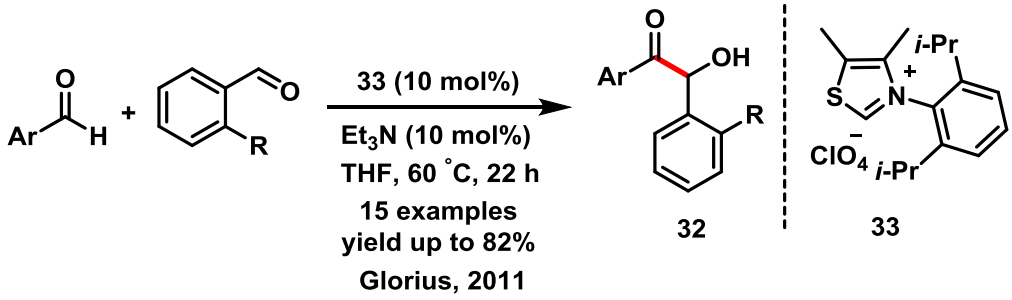
In 1985, Inoue and co-workers reported the NHC-catalyzed selective cross-benzoin reactions of aromatic and aliphatic aldehydes with formaldehyde leading to the formation of α-hydroxy ketones using thiazolium salt **29**. Although an excellent selectivity was observed for the cross-benzoin product, the yields were low (Scheme 1.4, Eq. 1).[14] Later Kuhl and Glorius demonstrated an NHC generated from the thiazolium salt **31** to synthesize α-hydroxyketones **30** in good yields (Scheme 1.4, Eq. 2).[15]

Scheme 1.4: Cross-Benzoin Reaction of Aldehydes and Formaldehydes



Glorius introduced a number of thiazolium NHC precatalyst having sterically bulky aryl groups on the nitrogen with varying backbone substitution. These NHCs exhibited high levels of reactivity and selectivity in intermolecular crossbenzoin reactions different aromatic aldehydes to afford a library of unsymmetrically substituted benzoins (Scheme 1.5).[16] The presence of an

Scheme 1.5: Cross-Benzoin Reaction of Aromatic Aldehydes Catalyzed by Bulky NHC

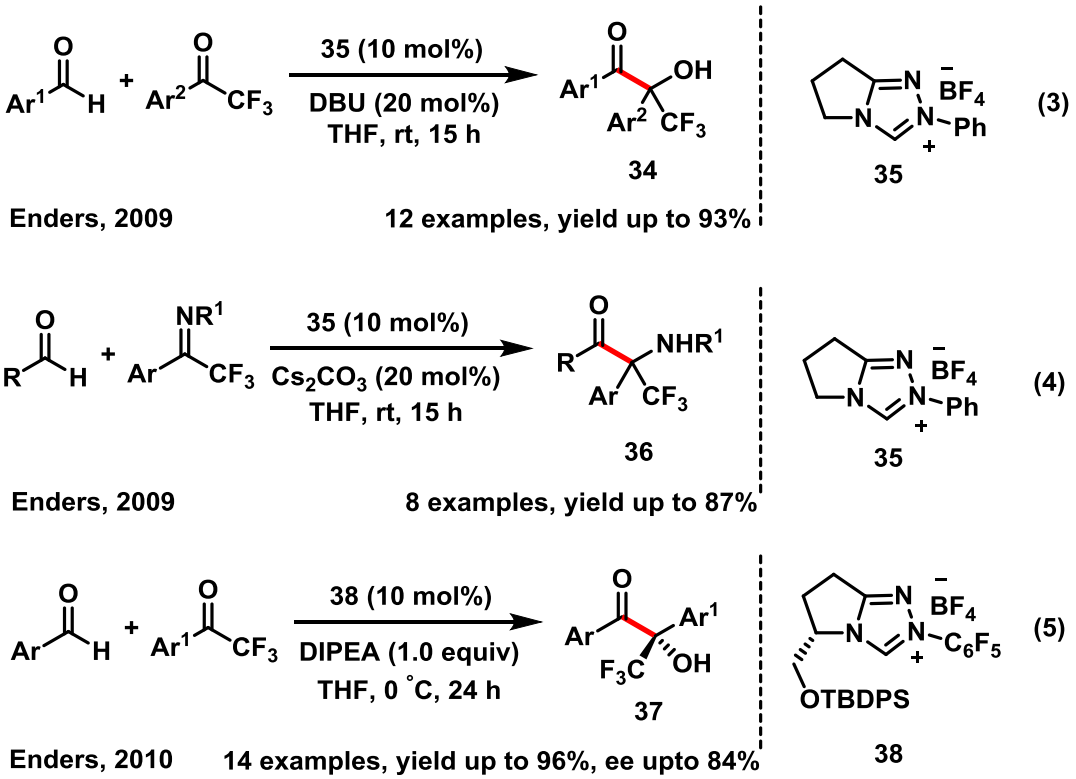


ortho-substituent on the electrophilic aromatic aldehyde (which presumably hinders the direct addition of NHC to these aldehydes) was necessary for the high levels of selectivity.

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.[17] The reaction furnished excellent yields of α-hydroxy-α-trifluoromethyl ketones **34** possessing a quaternary stereocentre using the carbene generated from triazolium salt **35**. Later they generalized the substrate scope with the use of trifluoromethyl ketimines (Scheme 1.6, Eq. 4).[18] Though initial attempts on chiral transformation were not

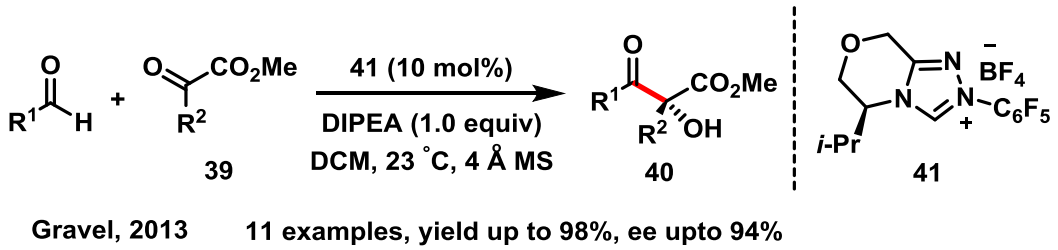
successful, later they found the use of heteroaromatic aldehydes in presence of the chiral NHC generated from **38** furnished the trifluoromethylated hydroxyl ketones **37** with good enantioselectivity (Scheme 1.6, Eq. 5).[19]

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



Gravel and co-workers reported a high yielding chemoselective and enantioselective intermolecular cross-benzoin reaction of aliphatic aldehydes and α-ketoesters **39**. Notably, the reaction affords enantiomerically enriched tertiary alcohols **40**. Excellent levels of enantioselection were obtained by using an electron deficient valine-derived triazolium salt precatalyst **41** (Scheme 1.7).[20]

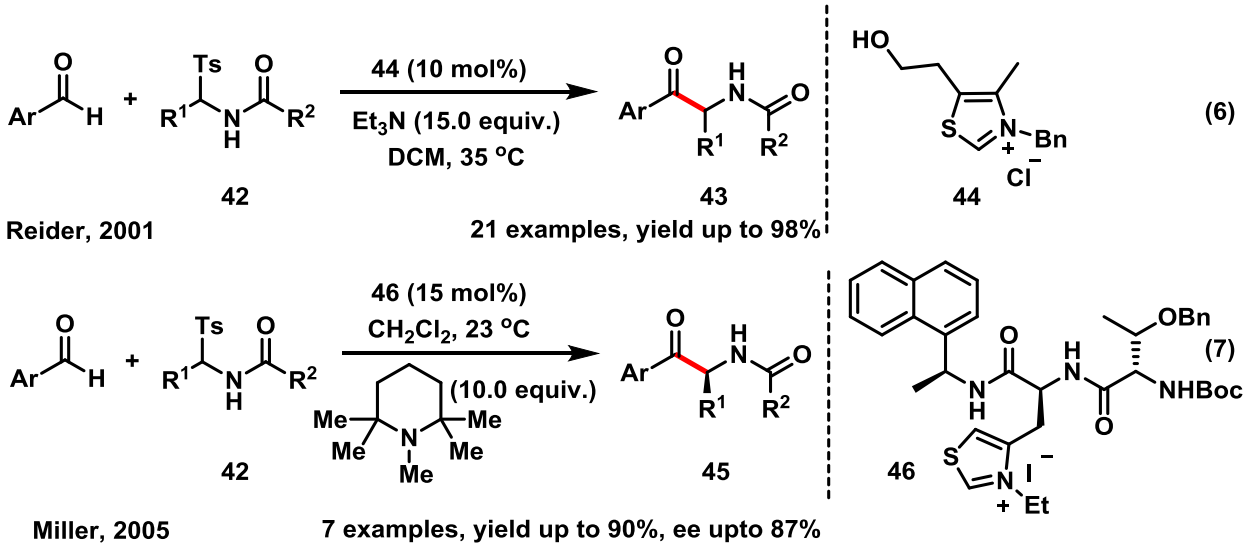
Scheme 1.7: Enantioselective Cross-Benzoin Reactions of Aliphatic Aldehydes and α-Ketoesters



Reider and coworkers used acylimines function as electrophiles in NHC-catalyzed azabenzoin reaction with aldehydes. The reactive masked imine is generated in situ by the action

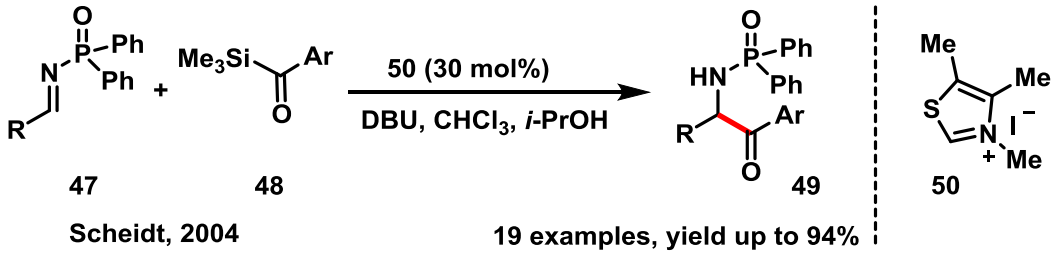
of base on the sulfonylamide derivative **42**.[21] Carbene generated from thiazolium salt **44** reacts with aldehyde to generate Breslow intermediate which intercepts with acylimine intermediates furnished α-amidoketones **43** in excellent yields (Scheme 1.8, Eq. 6). Later Miller and coworkers employed a chiral thiazolium salt **46** to demonstrate the enantioselective version of the cross-aza-benzoin reaction afforded the α-amino ketones **45** 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 (Scheme 1.8, Eq. 7).[22]

Scheme 1.8: Aza-Benzoin Reaction of Aldehydes and Masked Imines



Mattson and Scheidt developed a catalytic coupling reaction of acylsilanes with imines **47** for the synthesis of aminoketones **49** (Scheme 1.9). The reaction proceeds through the generation of the Breslow intermediate from the acylsilane **48** followed by a cross-coupling with the imine.[23] Carbene generated from thiazolium salt **50** was effective for this transformation.

Scheme 1.9: NHC-Catalyzed Coupling Reaction of Acylsilanes with Imines

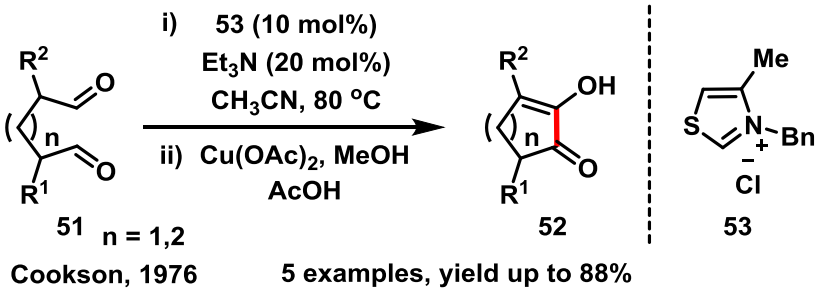


1.3.1.2. Intramolecular Benzoin Reaction

In 1976, Cookson and Lane found that the treatment of anhydrous glutaraldehyde with thiazolium salt **53** and triethylamine resulted in the formation of 2-hydroxycyclopentanone. The

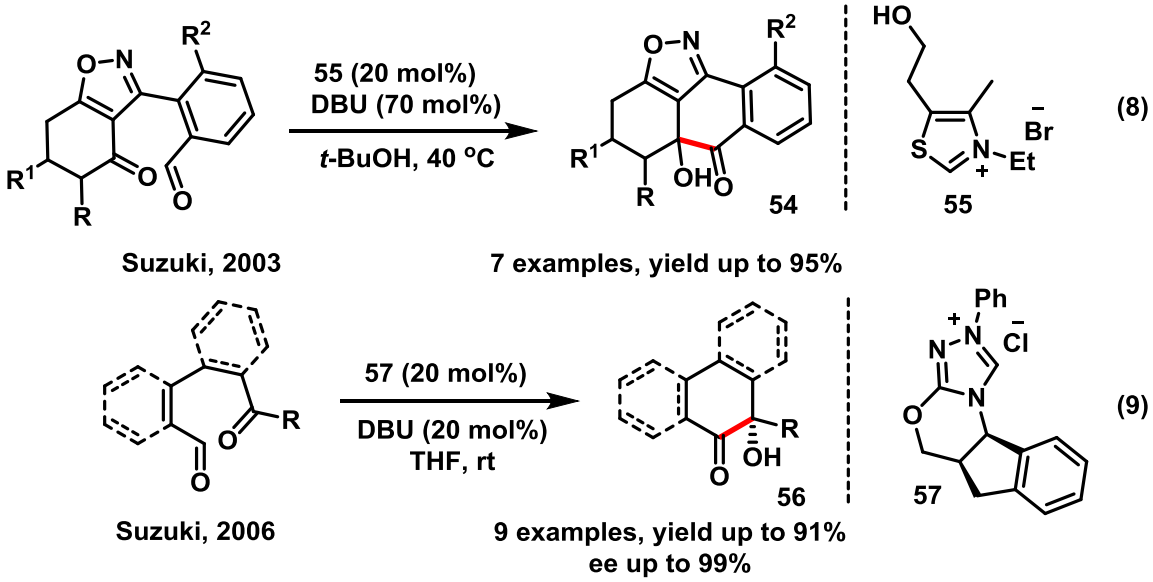
latter underwent oxidation to afford 2-hydroxycyclopent- 2-en-1-one **52** upon treatment with $Cu(OAc)_2$ (Scheme 1.10).[24]

Scheme 1.10: Intramolecular Benzoin Condensation of Alkanedial



In 2003, Suzuki and co-workers developed the first intramolecular cross benzoin

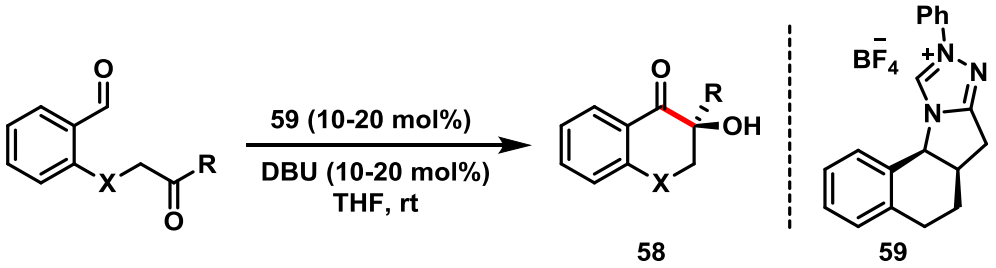
Scheme 1.11: Intramolecular Cross-Benzoin Reaction



condensation between aldehyde and ketone (Scheme 1.11, Eq. 8).[25a] 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 **54** with excellent yield. Later in 2006, they developed the enantioselective versions of the same reaction using an aminoindanol derived triazolium salt **57** for the intramolecular benzoin reaction leading to **56** in high ee values (Eq. 9).[25b]

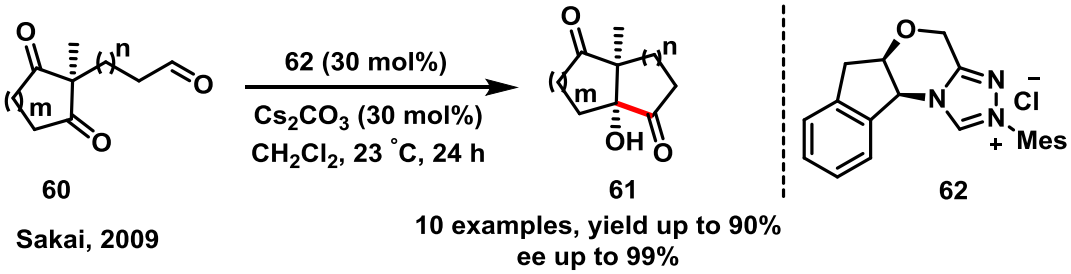
Enders and co-workers reported enantioselective NHC-catalyzed crossed aldehyde-ketone benzoin reaction for the synthesis of five- and six-membered cyclic acyloins **58**. NHC generated from the tetracyclic triazolium salt **59** gave the best results (Scheme 1.12).[26]

Scheme 1.12: Enantioselective Intramolecular Crossed Aldehyde-Ketone Benzoin Reaction



In 2009 Sakai and co-workers achieved synthesis of bicyclic tertiary alcohols possessing two quaternary stereocentres at the bridgehead positions via an asymmetric intramolecular crossed benzoin reaction. A relatively high loading of the NHC precatalyst **62** was necessary for efficient reactions (Scheme 1.13).[27]

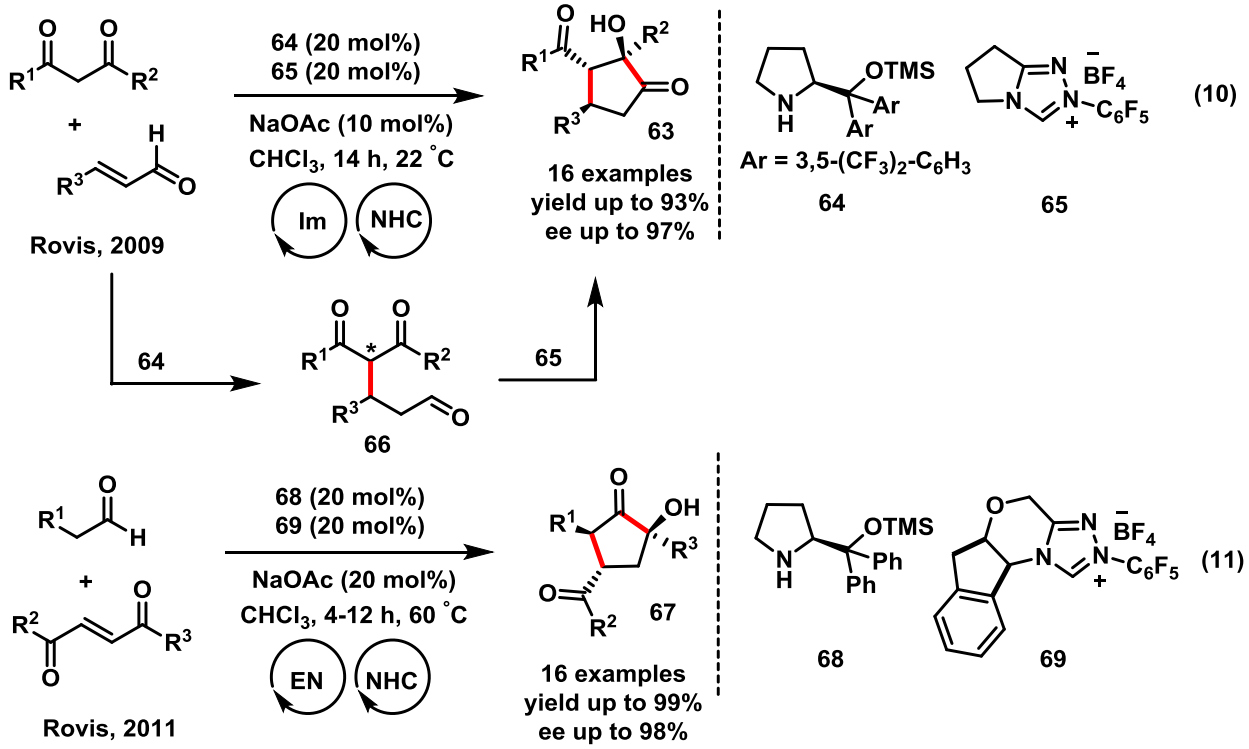
Scheme 1.13: Synthesis of Bicyclic Tertiary Alcohols by Intramolecular Benzoin Reaction



In 2009, Rovis and co-workers developed a Michael-benzoin cascade process to synthesize highly functionalized enantioenriched cyclopentanone derivatives **63** (Scheme 1.14, Eq. 10).[28] The reaction was initiated with an iminium generation from enal and catalyst **64** followed by conjugate addition of 1,3-diketone generating an intramolecular keto-aldehyde system **66**. Subsequently, the NHC generated from **65** catalyzed the keto-aldehyde cross benzoin reaction to furnish the observed product **63**.

Later, in 2011 they have demonstrated the generation of enamine from an enolizable aldehyde in presence of a secondary amine catalyst **68** followed by addition to a activated Michael acceptor (Scheme 1.14, Eq. 11).[29] The first process generates a keto-aldehyde system, which undergoes intramolecular cross-benzoin reaction in presence of a chiral carbene **69** to generate the enantioselective and highly functionalized cyclopentene derivatives **67**.

Scheme 1.14: Secondary Amine-NHC Dual-Catalytic, Michael–Benzoin Cascade Reaction



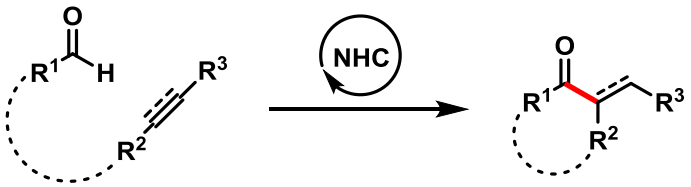
1.3.1.3. Stetter Reaction

Details on NHC-catalyzed Stetter reaction and related chemistry are described in Chapter 2. (For details, see page 33)

1.3.1.4. 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, addition of Breslow intermediate across unactivated carbon-carbon multiple bonds (known as hydroacylation reaction) are challenging and explored very recently (Scheme 1.15).

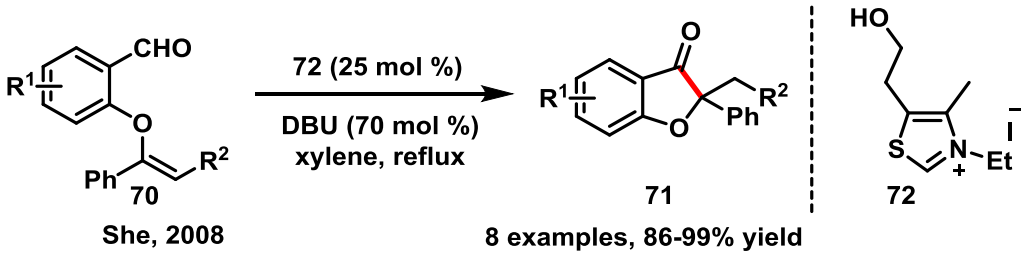
Scheme 1.15: Hydroacylation Reaction



She and co-workers developed intramolecular nucleophilic addition reaction of acyl anion equivalents to enol ethers **70** catalyzed by the NHC generated from readily available

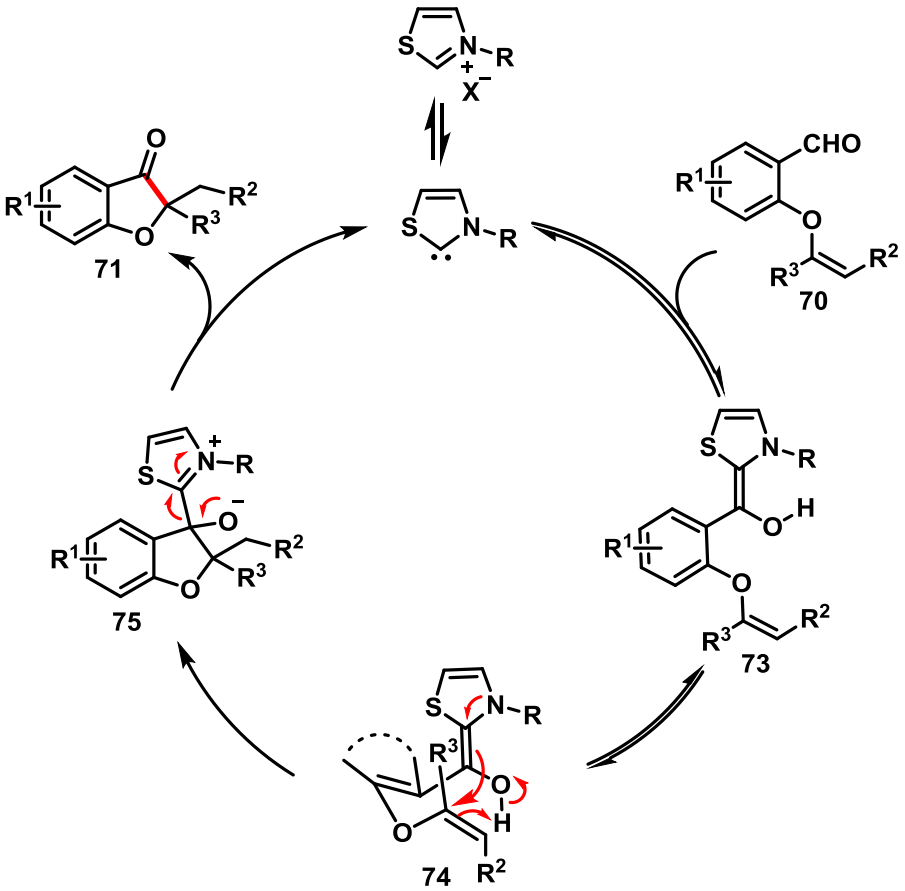
thiazolium salt **72** leading to the formation of benzofuranones **71** in excellent yield (Scheme 1.16).[30] Mechanistically, the reaction proceeds via the addition of the Breslow intermediate to the carbon-carbon double bond of enol ether, however, it was unclear whether the addition proceeds via a concerted pathway or involving an oxonium intermediate.

Scheme 1.16: NHC-Catalyzed Hydroacylation of Enol Ethers



The mechanism starts with the addition of NHC to the carbonyl group of 2-allyloxy benzaldehyde to form Breslow intermediate **73** (Scheme 1.17). In a concerted transition state **74**, this could add as a nucleophile to the olefin of the allyl moiety and the resulting zwitterionic

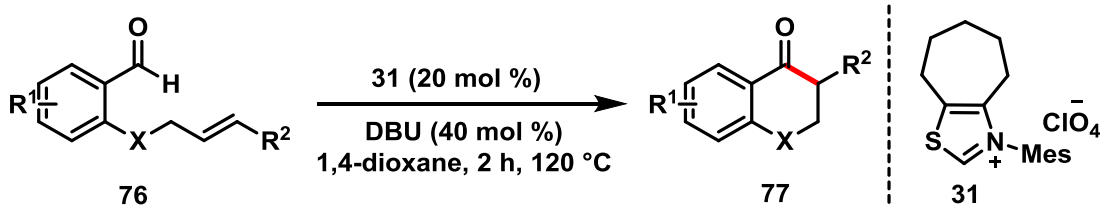
Scheme 1.17: Proposed Mechanism for the Hydroacylation of Unactivated Double Bonds



tetrahedral intermediate **75** liberates the desired product and the catalyst. The similarity to Conia-ene type transition states (same polarity of reacting olefins) and reverse-Cope elimination type ones as suggested by Rovis (five-membered transition state) is striking.[31,32] It should be noted in this context that the possibility of addition of Breslow intermediates[8] to Michael acceptors in a concerted manner analogous to the reverse Cope elimination was previously mentioned by Rovis and Read de Alaniz.[32] Furthermore, density functional theory calculations were performed by Grimme et al.[33] to get more insight into the crucial step of the reaction, that is, whether the proton migration or the C-C bond formation occurs first. These studies support a concerted but highly asynchronous transition state.

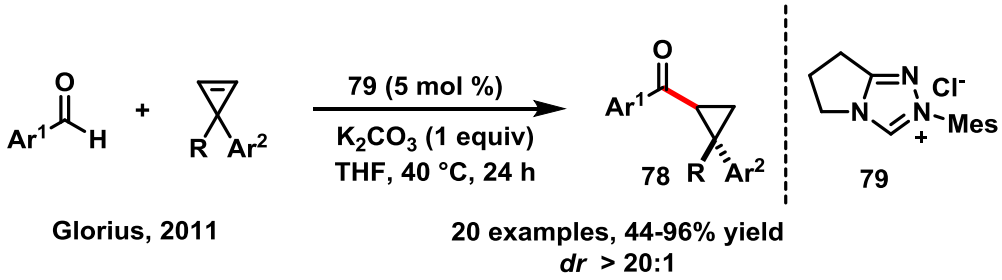
In 2009 Glorius and co-workers developed an intramolecular NHC-catalyzed hydroacylation of unactivated alkenes. The carbene generated from the thiazolium salt **31** catalyzed the intramolecular cyclization of 2-allyloxy benzaldehydes **76** to form the corresponding chromanones **77** (Scheme 1.18).[34] 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 1.18: NHC-Catalyzed Hydroacylation of Unactivated Double Bonds



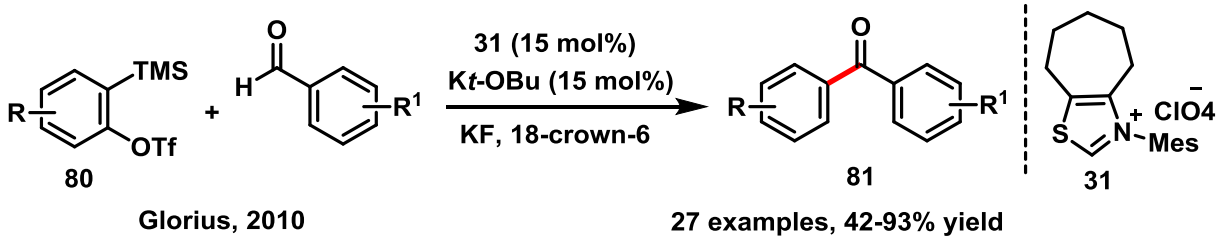
Very recently same group reported the first intermolecular hydroacylation of cyclopropenes.[35] The treatment of aromatic aldehydes with cyclopropenes under mild conditions using carbene generated from the triazolium salt **79** afforded the acyl cylopropanes **78** in excellent diastereoselectivity and good yield (Scheme 1.19). Experiments with deuterated substrates demonstrated that the hydroacylation is a syn addition process. Subsequently, they have developed the enantioselective hydroacylation of cyclopropenes using NHC generated from chiral *ortho, ortho'*-disubstituted electron-rich triazolium salts.[36]

Scheme 1.19: Intermolecular Hydroacylation of Cyclopropene



Additionally, Glorius and co-workers uncovered NHC-catalyzed intermolecular hydroacylation of arynes (Scheme 1.20).[37] 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 **80** using KF and 18-crown-6 in the presence of carbene generated from **31** by deprotonation using KO*t*-Bu resulted in the formation of the aryl ketones **81** in moderate to excellent yield.

Scheme 1.20: NHC-Catalyzed Hydroacylation of Arynes



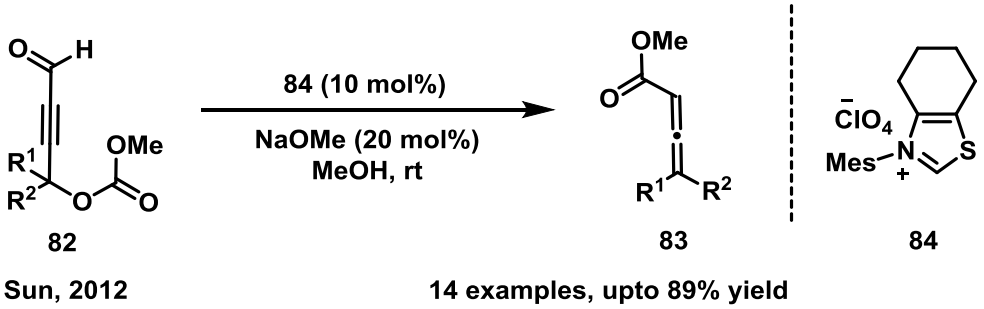
1.3.2. NHC-Catalyzed Reactions using Homoenolate Intermediate (II)

NHC-organocatalyzed generation of homoenolate equivalents and related chemistry is described in details in Chapter 3. (For details, see page 76)

1.3.3. NHC-Catalyzed Reactions using Allenoate Intermediate (III)

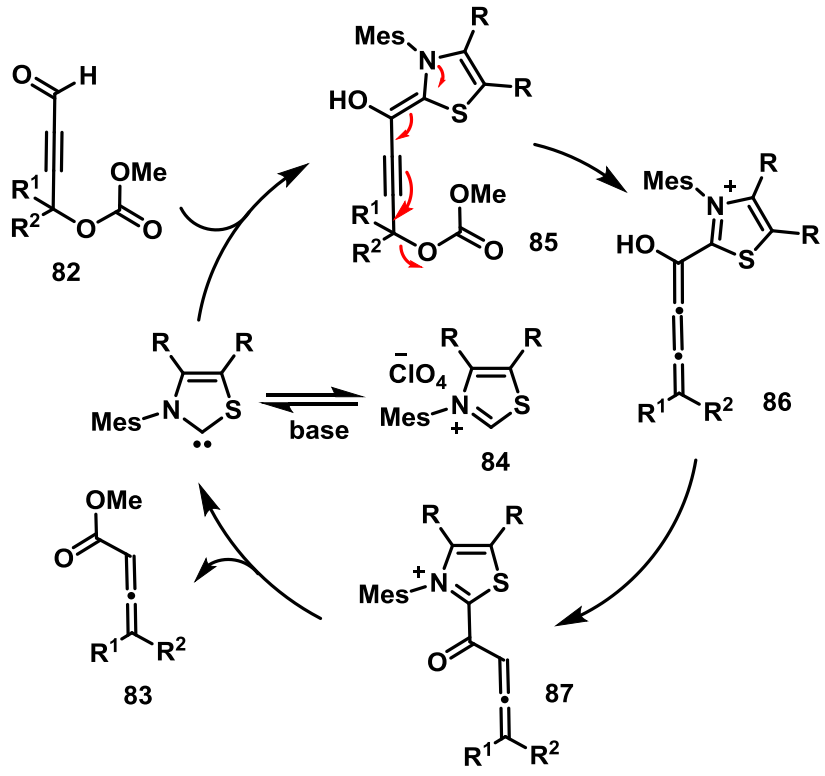
Sun and co-workers reported isomerization of ynals to allenoates by an NHC-catalyzed internal redox reaction (Scheme 1.21).[38] Alkynyl aldehydes **82** containing a methyl carbonate group at the γ-position, which acts as a leaving group, are used as the substrates, and the thiazolium salt **84** is 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 **83**. Preliminary experiments demonstrate that the enantioselective variant can also be achieved. A pilot experiment with the use of the chiral NHC precursor **69** provides low enantioselectivity (30% ee).

Scheme 1.21: NHC-Catalyzed Isomerization of Ynals to Allenoates



Mechanistically, the catalytic cycle begins with nucleophilic addition of the NHC generated from thiazolium salt **84** to the carbonyl group of alkynal **82**, to obtain Breslow intermediate **85** (Scheme 1.22). Next, electron-pushing from the nitrogen lone pair of the

Scheme 1.22: Catalytic Cycle for NHC-Catalyzed Isomerization of Ynals to Allenoates

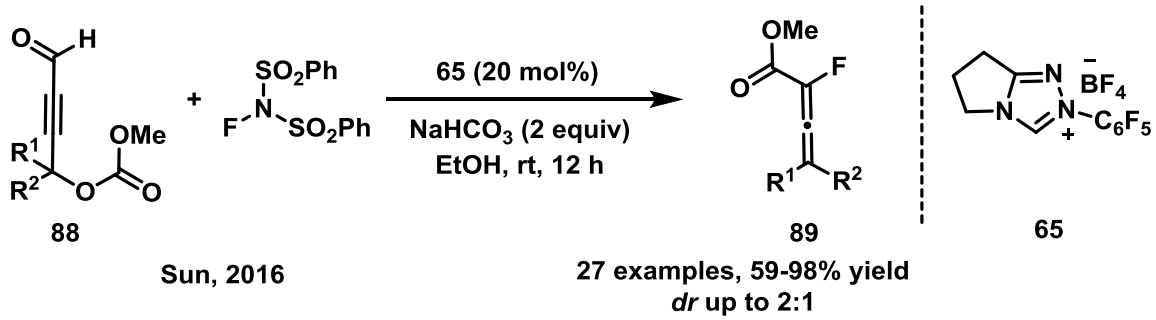


resulting Breslow intermediate 10, along the conjugated π- system, triggers the elimination of methyl carbonate group to form cumulative allenol **86**. Subsequent steps involve tautomerization to form allene **87** and then nucleophilic acyl substitution by methoxide anion to form the observed allenoate **83** and regenerate the NHC catalyst.

Very recently, Wang and co-workers described an efficient α-fluorination of azolium allenols that were generated from various γ-substituted alkynals **88** (Scheme 1.23).[39] With a

suitable combination of NHC precatalyst **65**, base, and fluorine reagent, the reaction proceeded smoothly to yield a wide range of α-fluoroallenoates with excellent chemoselectivity. NFSI serves as the fluorine source in the reactions.

Scheme 1.23: NHC-Catalyzed α-Fluorination of Alkynyl Aldehydes



1.3.4. NHC-Catalyzed Reactions using *Deoxy*-Breslow Intermediate (IV)

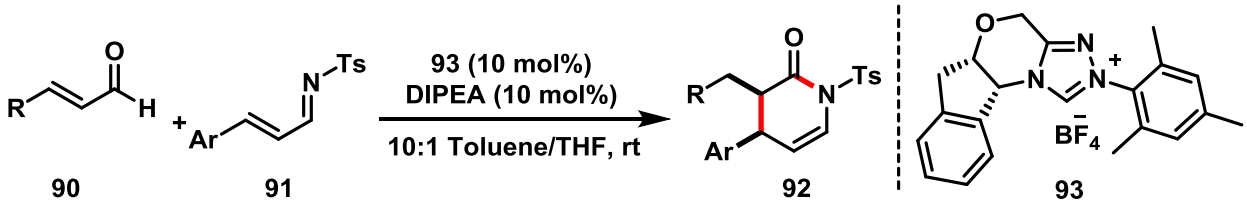
The NHC-catalyzed generation of *deoxy*-Breslow intermediates and their subsequent reactivity are described in details in Chapter 4. (For details, see page 115)

1.3.5. NHC-Catalyzed Reactions using Enolate Intermediate (V)

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 described a highly Enantioselective Azadiene Diels-Alder Reactions Catalyzed by Chiral N-Heterocyclic Carbene **93** for the synthesis of dihydropyridinone derivatives **92** (Scheme 1.24).[40] The chiral dihydropyridinone products are obtained in good yield and with remarkable enantioselectivities.

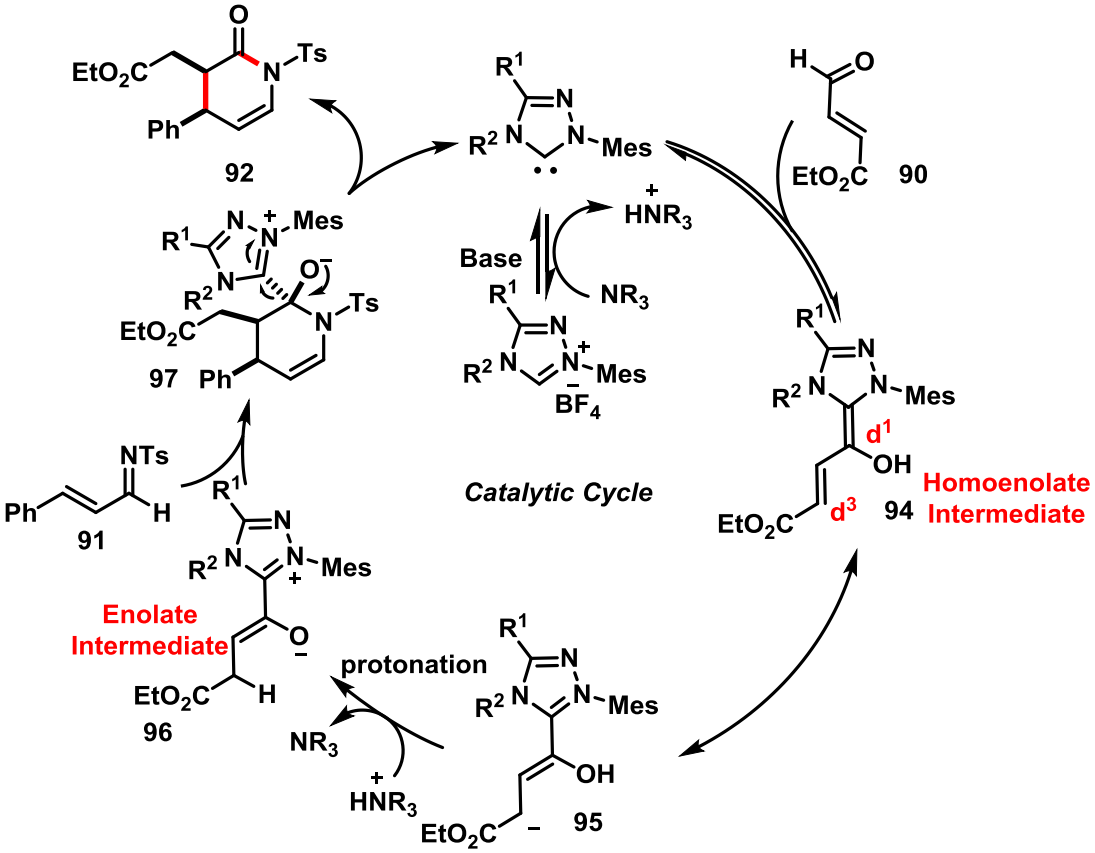
Scheme 1.24: Hetero Diels-Alder Reaction using NHC-Catalyzed Enolate Intermediate



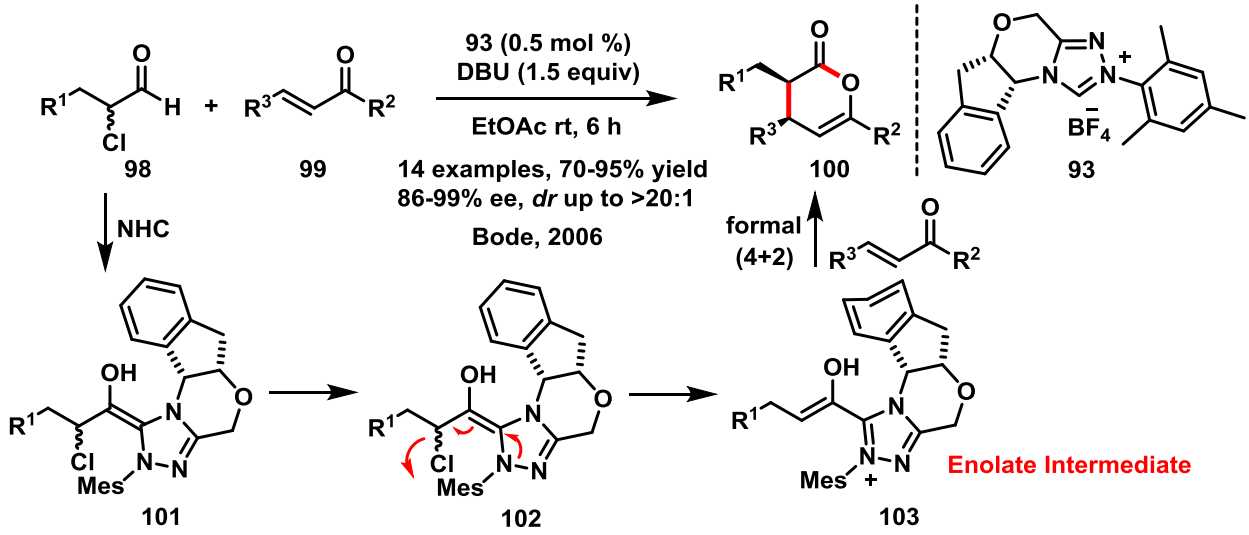
Mechanistically, the reaction proceeds via addition of free carbene towards enal **90** to obtain homoenolate intermediate **94** which is a resonance form with intermediate **95** (Scheme 1.25). The key to success of these reactions are the use of catalytic amount of mild organic base.

Intermediate **95** undergoes protonation to form enolate intermediate **96** which involves in a formal aza Diels-Alder reaction with **91** to produce enantiopure dihydropyridinone derivatives **92** after removal of NHC.

Scheme 1.25: Mechanism for Hetero Diels-Alder Reaction



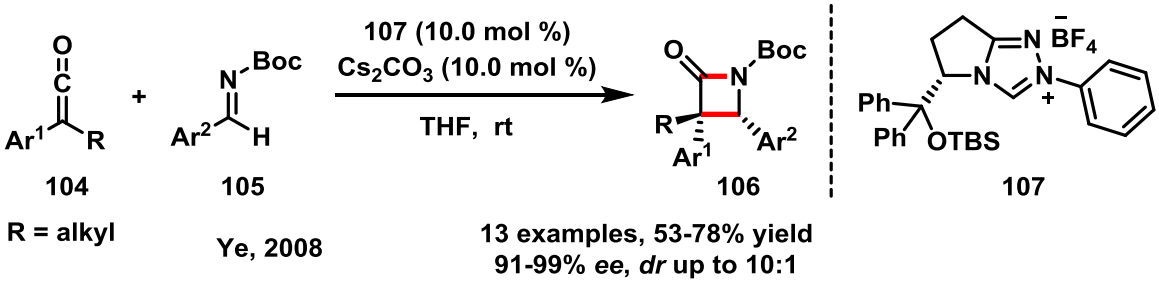
Scheme 1.26: Diels-Alder Reaction of α-Chloro aldehydes with Enones



Subsequently, the same group reported the generation of enolate intermediate **103** from α-chloro aldehydes **98** for highly enantioselective inverse-electron demand Diels-Alder reactions with enones **99** to give enantiopure dihydropyranone product **100** with good yields and excellent diastereo- and enantio-selectivity (Scheme 1.26).[41] Key features for this transformation was very low catalyst loading of triazolium based NHC precursor . The reaction was well tolerated with various aryl and alkyl R^1 substituents of α-chloro aldehydes.

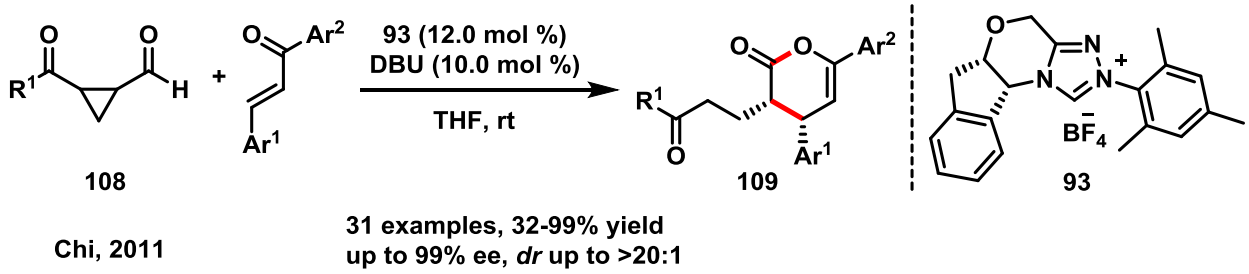
In 2008, Ye and co-workers demonstrated an efficient Staudinger reaction of ketenes **104** with N-tosyl, N-benzyloxycarbonyl, or N-tert-butoxycarbonyl imines **105**. Chiral NHC **107** derived from L-pyroglutamic acid catalyzed the reactions of arylalkylketenes with a variety of N-tert-butoxycarbonyl arylimines to give the corresponding cis-β-lactams in good yields with good diastereoselectivities and excellent enantioselectivities (Scheme 1.27).[42]

Scheme 1.27: Staudinger Reaction of Ketenes with Imines



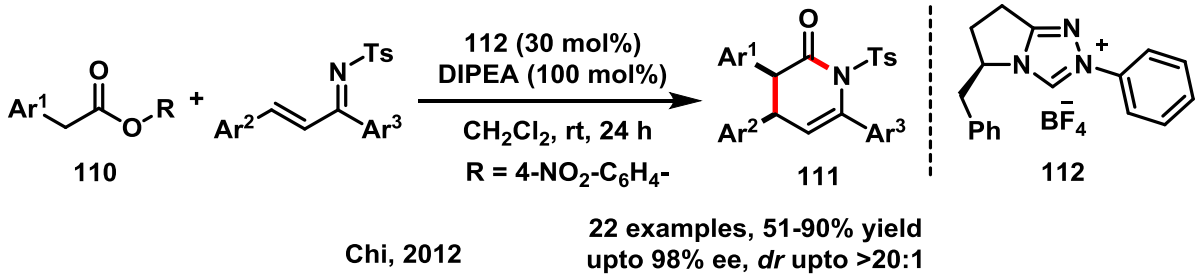
Later, Chi and co-workers disclosed highly enantioselective formal hetero Diels-Alder reactions between chalcones and formylcyclopropanes **108** using N-heterocyclic carbene (NHC)-bounded enolate intermediates generated from formylcyclopropanes. The reaction provided highly diastereo- and enantioselective functionalized δ-lactones **109** (Scheme 1.28).[43] The resulting functionalized δ-lactone products can be easily transformed to highly substituted cyclohexanes with good regio- and stereoselectivities.

Scheme 1.28: Diels-Alder Reaction of Formylcyclopropanes with Chalcones



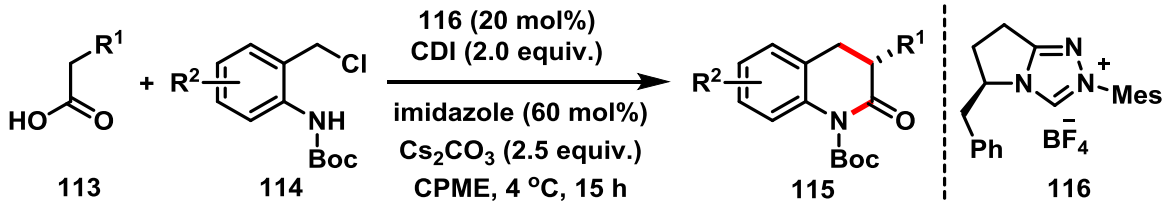
Subsequently, same group disclosed first N-Heterocyclic Carbene (NHC) mediated activation of stable carboxylate esters **110** to generate enolate intermediates. The catalytically generated aryl acetic ester enolates undergo enantioselective reactions with α,β-unsaturated imines (Scheme 1.29).[44] The catalytic process likely proceeds through a direct addition of NHC **112** to the ester substrate without involving a ketene intermediate.

Scheme 1.29: NHC-Catalyzed Generation of Enolate Intermediate form Carboxylate Esters



Recently, Scheidt and co-workers developed a convergent, catalytic asymmetric formal [4 + 2] annulation for the synthesis of dihydroquinolones **115** with moderate to good yields and good enantioselectivities (Scheme 1.30).[45] They employed carboxylic acids as precursors to NHC bound enolates through an in situ activation strategy. This transformation features a dual activation system focusing on combining a Lewis base (NHC) mediated generation of a reactive aza *o*-quinone methide and in situ generated active NHC bound enolates as nucleophile, intercepts to form enantioselective dihydroquinolones.

Scheme 1.30: NHC-Catalyzed Generation of Enolate Intermediate form Carboxylic Acids



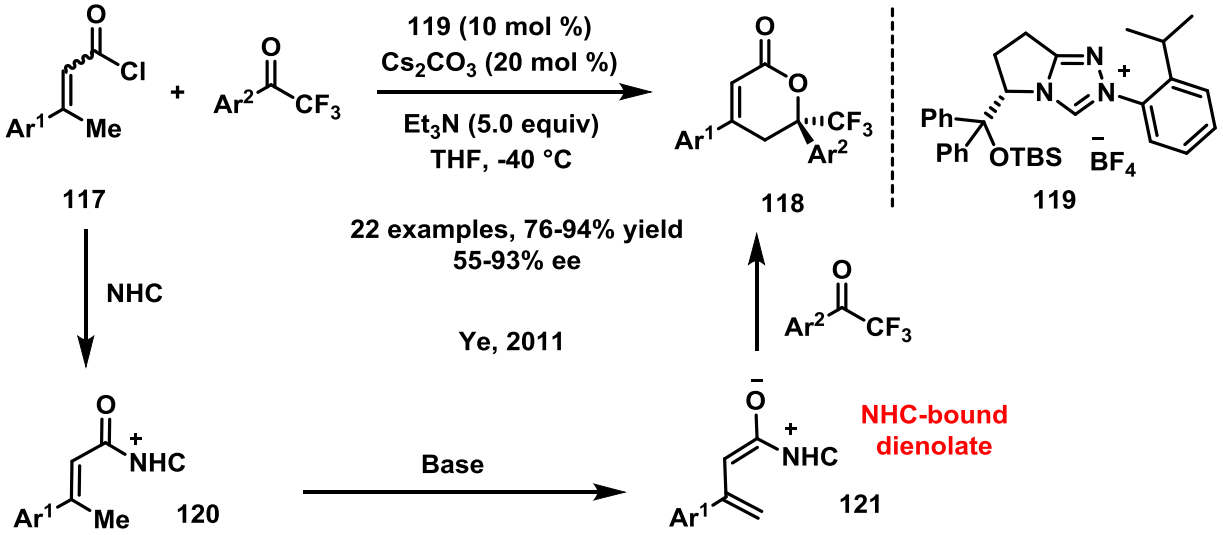
1.3.6. NHC-Catalyzed Reactions using Dienolate Intermediate (VI)

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 reported synthesis of 5,6-dihydropyran-2- ones **118** (α,β-unsaturated δ-lactones) using NHC-catalyzed cyclization reaction of α,β-unsaturated β-

methylacyl chloride **117** with activated ketones in good yield with good to high enantioselectivity (Scheme 1.31).[46] Two highly activated ketone system (trifluoromethyl ketones and N-substituted isatins) have been used for efficient synthesis of enantiopure δ-lactones.

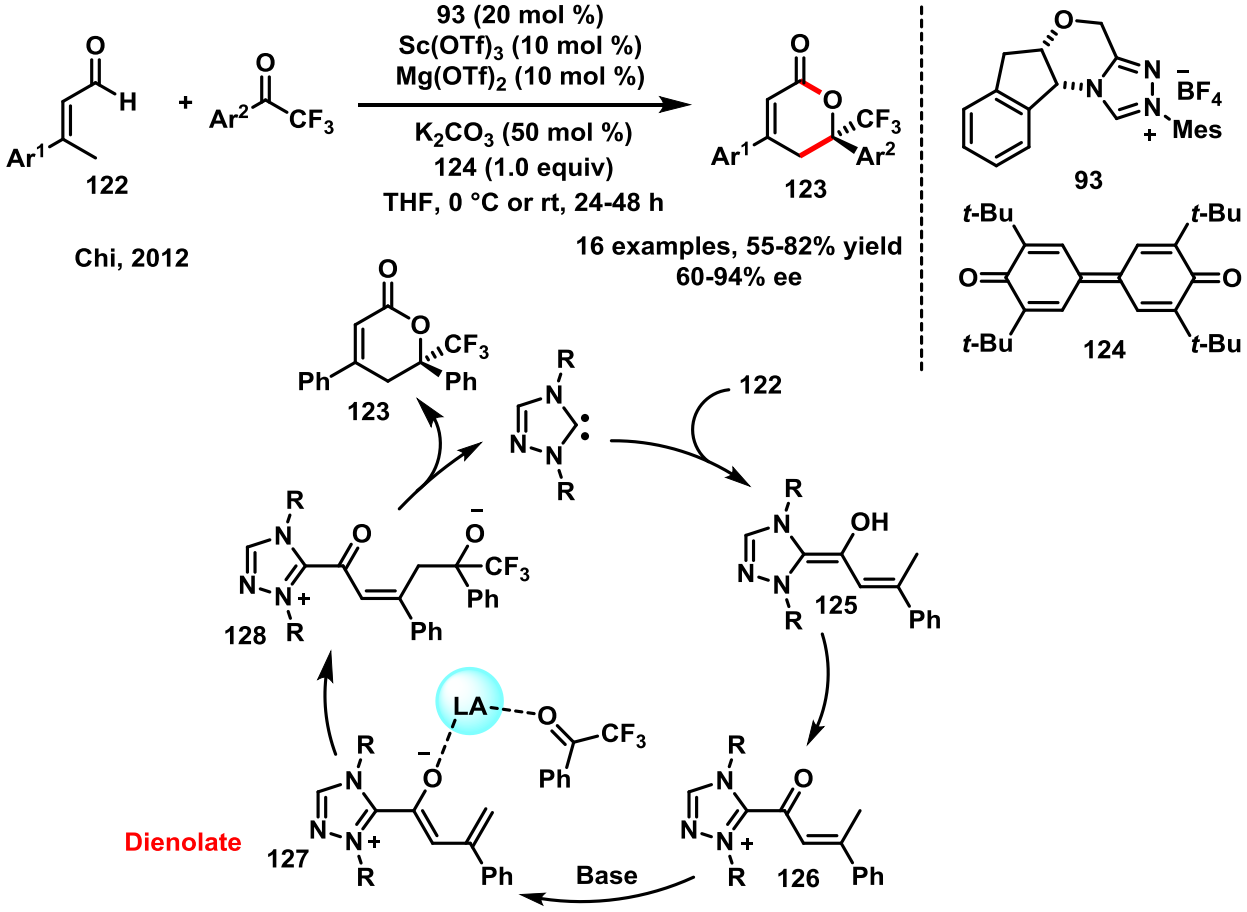
Scheme 1.31: Generation of NHC-Bound Dienolates from Unsaturated Acylchlorides



Subsequently, Chi and co-workers disclosed an oxidative γ-functionalization of enals under N-heterocyclic carbene (NHC) catalysis to give unsaturated δ-lactones **123** (Scheme 1.32).[47] 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. Enantioselectivity control involving the relatively remote enal γ-carbon was achieved via Lewis acid [$Sc(OTf)_3$ or combined $Sc(OTf)_3/Mg(OTf)_2$] and NHC cooperative catalysis.

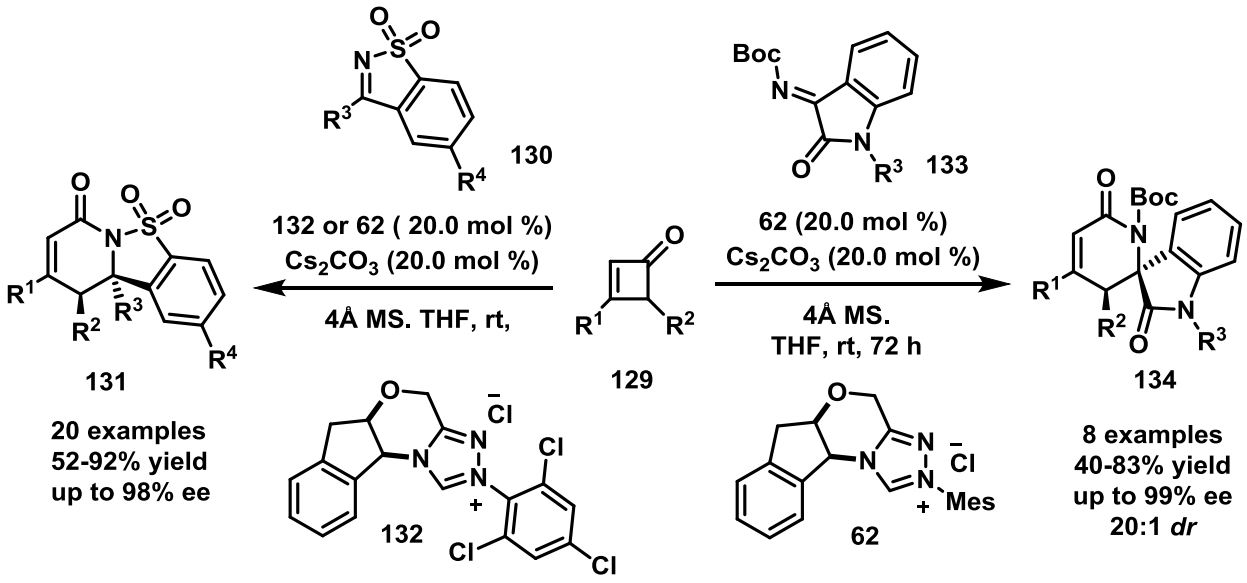
A probable reaction pathway is illustrated in Scheme 1.32. In situ generated NHC reacts with β,β′-disubstituted enals **122** to form Breslow intermediate **125**, which under oxidized condition generates β-methyl substituted α,β-unsaturated acyl azolium **126**. In presence of base **126** was converted to dienolate intermediate. The Sc(III) Lewis acid, which is known to have good affinities for carbonyl oxygens and carboxylates, likely is involved in multisite coordination to bring the ketone electrophile into close proximity with intermediate having chiral NHC bound, as illustrated in **127**. Nucleophilic addition of dienolate **127** to the trifluoromethyl ketone leads to the product dihydropyranone **123** and regenerates the NHC catalyst.

Scheme 1.32: Generation of NHC-Bound Dienolates from Unsaturated Aldehydes



Interestingly, cyclobutenones **129** were also used to generate the NHC-bound dienolate

Scheme 1.33: Generation of NHC-Bound Dienolates from Cyclobutenones

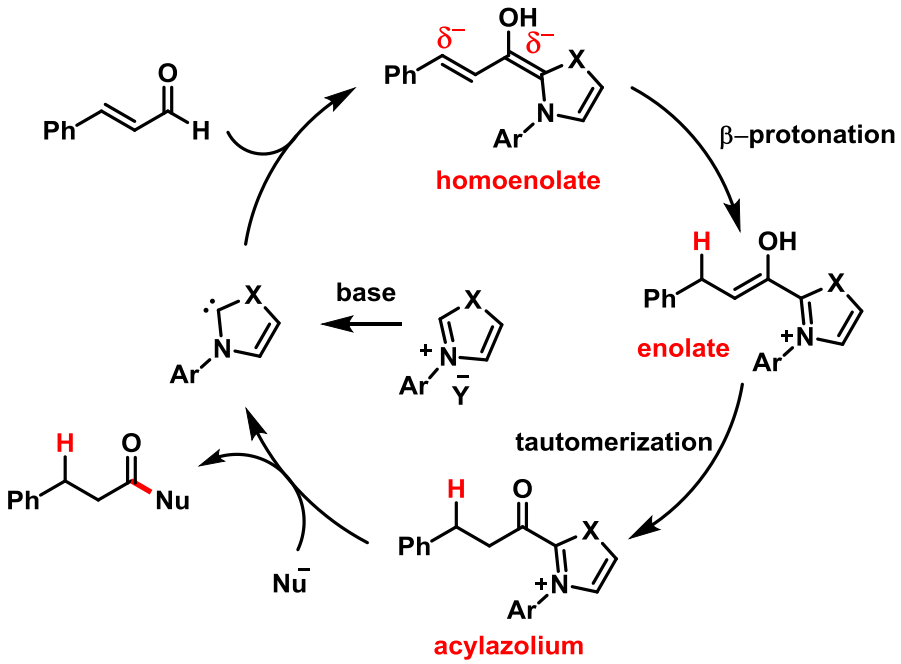


(Scheme 1.33).[48] The addition of NHC generated from the salt **132/62** to cyclobutenones **129** initiate a C-C single bond cleavage, which is the key step to generate the NHC-bound dienolate intermediate. The interception of this intermediate with sulfonyl imines **130** afforded cyclic lactams **131** in 52-92% yield with good enantioselectivities (up to 98%). With the same optimized conditions, isatin imines gave spirolactams **134** in moderate to good yields (40-83%) with good selectivities (up to 20:1 *dr*).

1.3.7. NHC-Catalyzed Reactions 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, intermediates have attracted considerable attention over the past decade. NHCs can generate acylazolium intermediates from α,β-unsaturated aldehydes (Scheme 1.34).[49] Mechanistically, the

Scheme 1.34: NHC-Catalyzed Generation of Acylazolium Intermediate



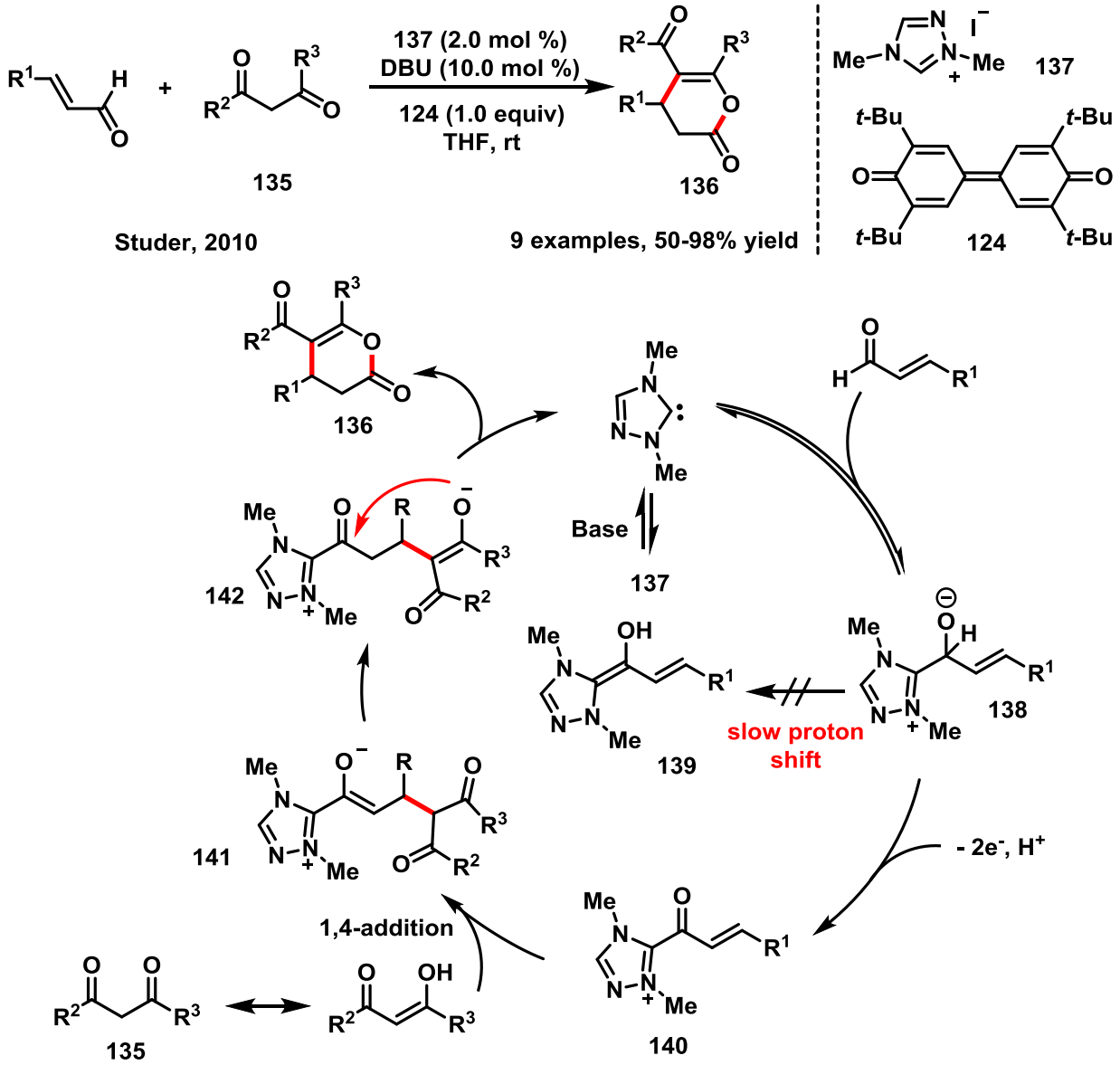
reaction proceeds in a similar manner to the enolate intermediates. In presence of extra proton source, the enolate intermediate undergoes tautomerization to form the acylazolium intermediate. The success of the reactions is therefore determined by the reactive intermediates and the protonation steps. This acylazolium is essentially an activated carboxylate. Addition of nucleophiles to these activated carboxylates proceeds smoothly. Addition of alcohols forms esters, thiols forms thioesters,[50] amines in presence of additive forms amides,[51] water forms carboxylic acid[52] and azides forms carbomyl azides or oxazolidinones.[53] Intramolecular redox

esterifications of *ortho*-hydroxy cinnamaldehydes have been demonstrated to yield lactones.[54] Other aldehydes such as α-chloro aldehydes,[55] formyl cyclopropanes,[50] epoxy aldehydes,[56] aziridinyl aldehydes[57] have also been used for the acylazolium synthesis. Acylazolium can also be generated from simple aldehydes under oxidative conditions[58] or from ketenes.[59]

1.3.8. NHC-Catalyzed Reactions using α,β-Unsaturated Acylazolium Intermediate (VIII)

In 2010, Studer and co-workers reported the generation of catalytically active α,β-unsaturated acylazolium intermediates **140** from enals and its subsequent interception with 1,3-

Scheme 1.35: NHC-Catalyzed Generation of α,β-Unsaturated Acylazoliums from Enals

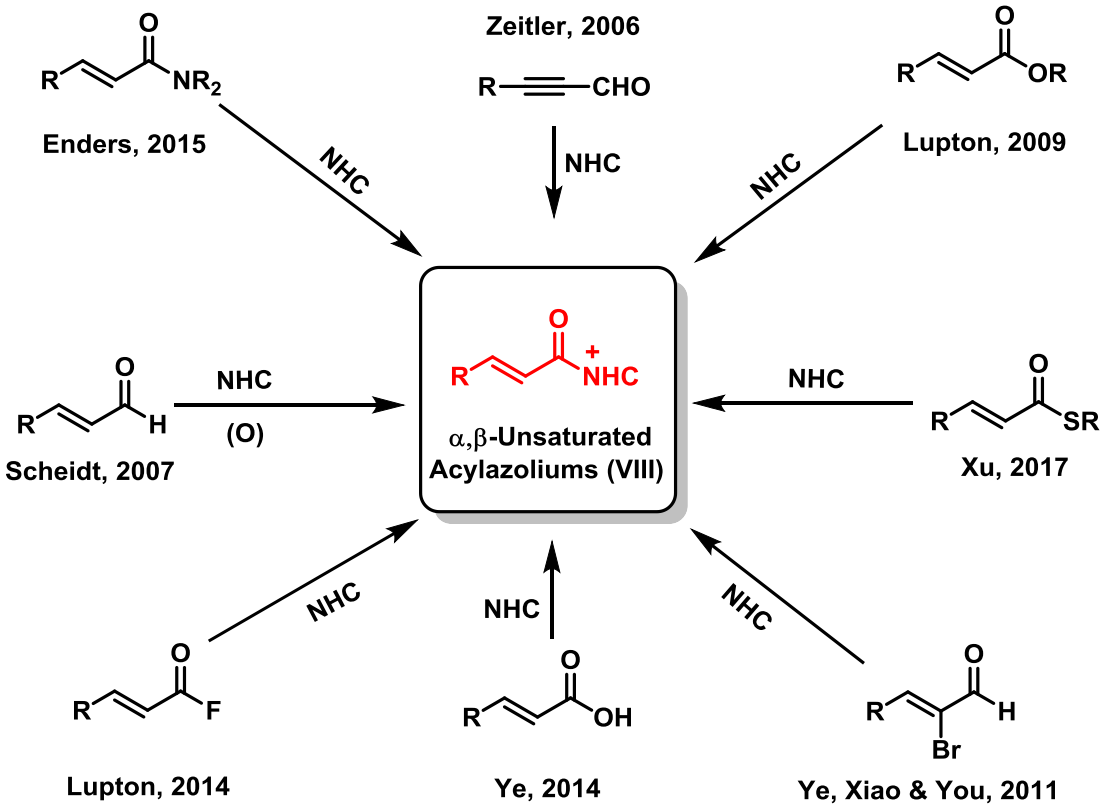


dicarbonyl compounds to form the functionalized dihydropyranones **136** (Scheme 1.35).[60]

Mechanistically, the reaction proceeds through the oxidation of in situ generated tetrahedral intermediate **138** to the corresponding α,β-unsaturated acylazolium species **140** in presence of mild organic oxidant **124.** Enals with phenyl ring having electron-releasing and -withdrawing groups, heteroaryl, alkyl groups are well tolerated whereas 1,3-dicarbonyl compounds (**135**) such as β-diketones and β-keto esters were found to be efficient to afford the desired products in moderate to good yield.

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.[61] They also proposed that under optimal conditions, this oxidation is faster than the proton transfer that would lead to the extended Breslow intermediate **139**. 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.[62]

Scheme 1.36: Various Ways to Access α,β-Unsaturated Acylazoliums



Herein, few common routes to access NHC bound α,β-unsaturated acylazolium intermediate has been presented. (a) Reaction of ynals with NHCs[63] (b) reaction of α,β-

unsaturated esters with NHCs[64] (c) reaction of α,β-unsaturated thioesters with NHCs (d) reaction of 2-bromoenals with NHCs[65] (e) from α,β-unsaturated acids with NHCs[66] (f) reaction of α,β-unsaturated acyl fluorides with NHCs[67] (g) reaction of enals with NHCs in oxidized condition (h) from α,β-unsaturated amides with NHCs[68] (Scheme 1.36).

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 vinylphosphonates. This Stetter reaction using moderately electron-poor Michael acceptor afforded biologically diverse γ-ketophosphonates in 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 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 isatilidenes to afford cyclopentanone-fused spirooxindoles bearing an all-carbon quaternary spiro-center in moderate to good yields and with high diatereoselectivity. The reaction is compatible with wide variety of enals as well as isatilidenes. Additionally, functionalization of the spirooxindoles resulted various spiro heterocycles. Moreover, preliminary studies on enantioselective version of this reaction is presented.

We have demonstrated the umpolung of aldimines catalyzed by NHCs, and the reaction likely proceeds via the *aza*-Breslow intermediates. The NHC-catalyzed intramolecular cyclization of aldimines bearing a Michael acceptor resulted in the formation of biologically important 2-(hetero)aryl indole 3-acetic acid derivatives in moderate to good yields. The carbene generated from the bicyclic triazolium salt was found to be efficient for this transformation. The reaction is compatible with respect a wide variety of aldimines. Investigations of these reactions are described in details in chapter 4 of the thesis.

In the fifth chapter, we have demonstrated the NHC-catalyzed umpolung of aldimines for the synthesis of 4-difluoromethyl quinoline derivatives. The NHC-catalyzed intramolecular cyclization of aldimines bearing a moderately electron-poor double bond due to the presence of

the $–CF_3$ group resulted in the formation of biologically relevant 4-difluoromethyl quinoline derivatives in moderate to good yields. The reaction tolerates a broad range of functional groups. Simple functionalization of the reaction products resulted in the synthesis of valuable heterocycles.

1.5. References

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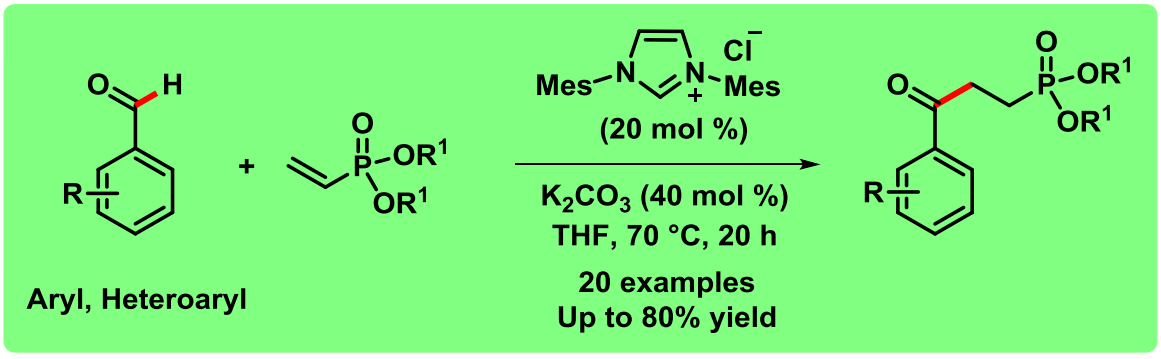
Chapter 2

Facile Synthesis of γ-Ketophosphonates by an Intermolecular Stetter Reaction Onto Vinylphosphonates

In this chapter, we have demonstrated the NHC-catalyzed cross-coupling of aromatic aldehydes with α,β-unsaturated phosphonates. This Stetter reaction using moderately electron-poor Michael acceptor afforded biologically diverse γ-ketophosphonates in 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 to a wide range of aldehydes as well as vinylphosphonates.



Org. Lett. **2014,** ***16,*** **4798**

2.1. Introduction

Organophosphorus compounds are an important class of molecules having potential application in various areas of chemistry including materials chemistry, pharmaceuticals, agrochemicals, and in catalysis.[1] Among the various organophosphorus compounds, phosphonates in general and γ-ketophosphonates in particular are associated with diverse biological properties.[2] For instance, the triazole-containing γ-ketophosphonate (**A**) is important due to its herbicide and fungicide activity,[3] and the pyrrole linked compound (**B**) is used in the treatment of osteoporosis (Fig 2.1).[4] Moreover, the biphenyl-derived γ-ketophosphonate (**C**) shows activity as inhibitors of matrix-metalloprotease (MMP-2),[5] and the amino acid-derived compound (**D**) exhibits 5-alanine levulinic acid dehydratase inhibitor activity.[6]

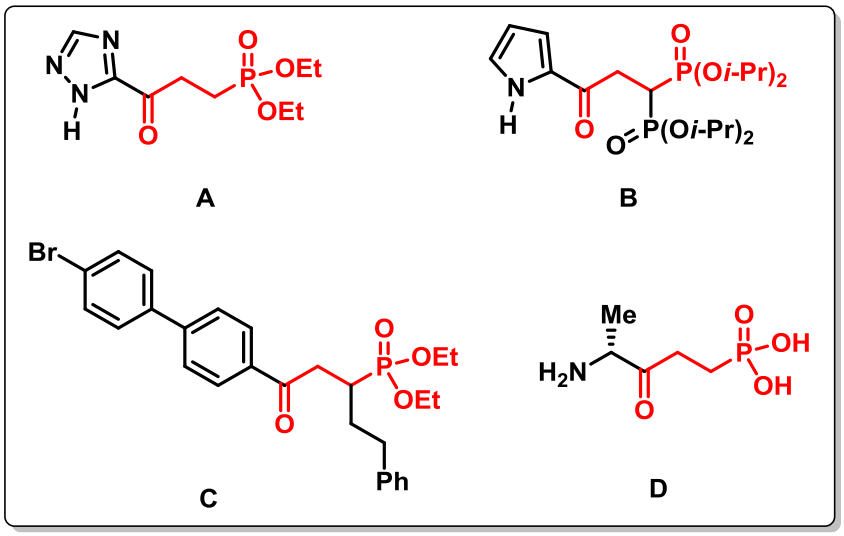


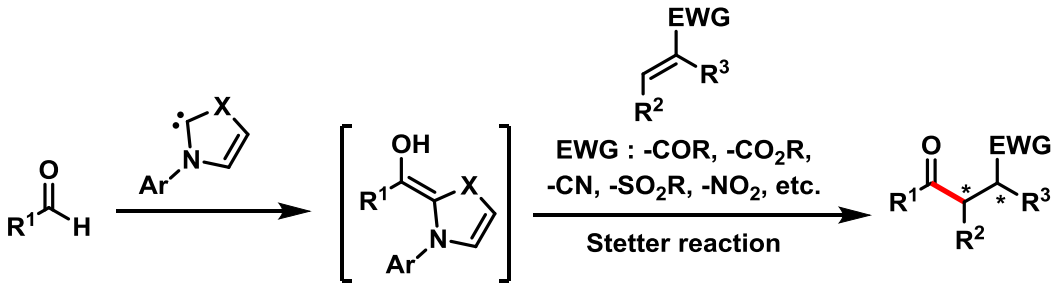
Fig 2.1: Selected Biologically Active γ-Ketophosphonates

However, flexible and efficient synthetic methods to modify these privileged organophosphorus structures are surprisingly underrepresented. Traditional strategies for the modification of organophosphorus compounds usually suffer from a limited substrate scope as well as nontrivial multistep reaction sequences.

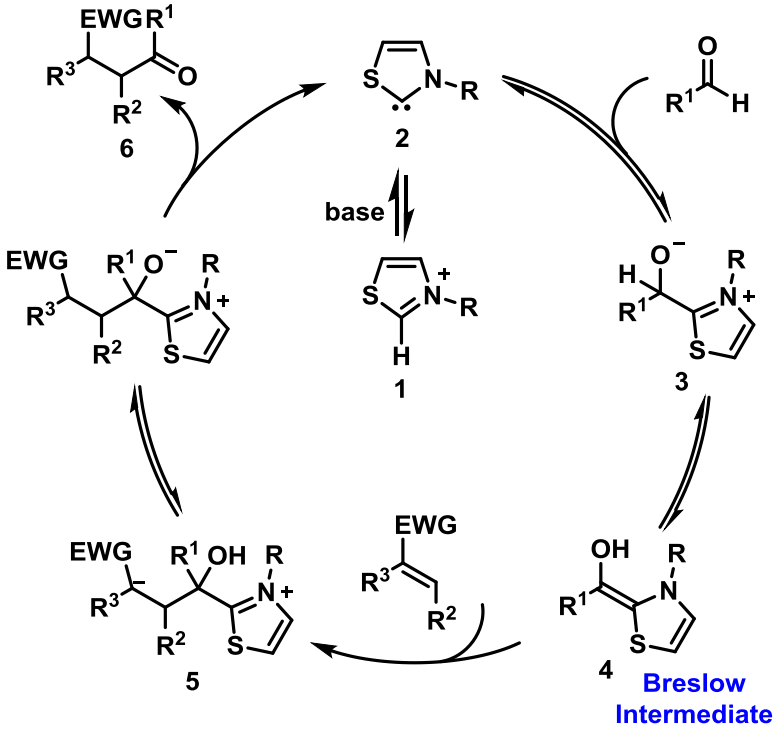
Since 1973, N-heterocyclic carbene (NHC)-catalysis became a powerful tool for the construction of several carbon-carbon and carbon-heteroatom bonds. The concept behind NHC-catalyzed reaction was reversing the polarity (also known as umpolung) and its interception towards electrophilic carbon-carbon and carbon-heteroatom double bonds (Michael acceptors, known as Stetter reaction).[7,8] 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 2.1). Now it is known that these reactions are catalyzed by NHCs and proceed via the formation of nucleophilic acyl anion equivalents (Breslow intermediates), which can react with various activated, polarized C-C double bonds.[9]

Scheme 2.1: NHC-Catalyzed Stetter Reaction



Scheme 2.2: Proposed Mechanism of Stetter Reaction



According to the proposed mechanism of NHC-catalyzed Stetter reaction (Scheme 2.2), the free carbene **2** is generated from the azolium precursor **1** upon treatment with base. The carbene **2** adds to aldehyde generating the nucleophilic Breslow intermediate **4**, via the tetrahedral intermediate **3**. Up to the generation of **4**, the steps are considered to be reversible. It should be noted in this context that Rovis and co-workers recently reported that the proton transfer from the tetrahedral intermediate **3** to Breslow intermediate **4** as the first irreversible step

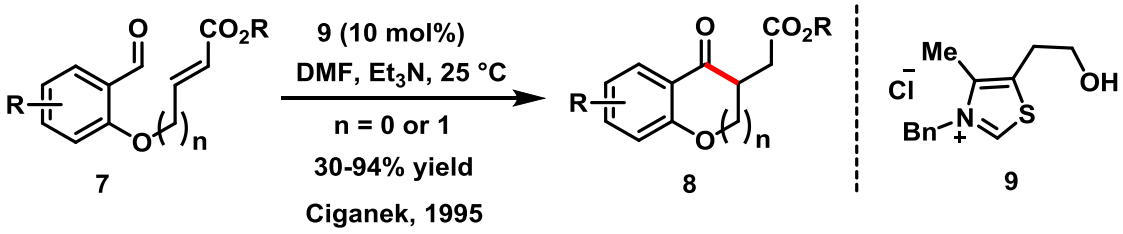
in the triazolinylidine carbene-catalyzed asymmetric intramolecular Stetter reaction.[10] The Breslow intermediate **4** then undergoes an irreversible addition to the Michael acceptor generating the intermediate **5**, which on proton transfer and subsequent release of free carbene affords 1,4-bifunctional Stetter product **6**. 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.

In this chapter, NHC-catalyzed intermolecular Stetter reaction of aldehydes onto vinyl phosphonates has been presented. The reaction furnished agro and medicinally important γ-ketophosphonates 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

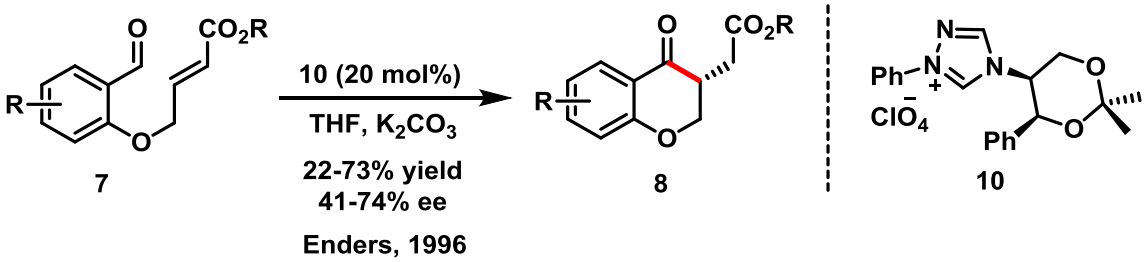
In 1995, Ciganek developed the first intramolecular Stetter reaction.[11] The NHC derived from the thiazolium salt **9** catalyzed intramolecular cyclization of 2-formyl aryloxy crotonates **7** and 2-formyl aryloxyacrylates to afford benzannulated pyranones and furanones **8** respectively (Scheme 2.3). The reaction was found to take place in the absence of base and in DMF under reflux conditions. Various newly developed carbene precursors have been examined for the successful demonstration of this reaction.

Scheme 2.3: First Intramolecular Stetter Reaction by Ciganek

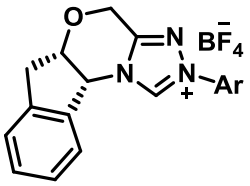


In an effort to induce stereoselectivity to the intramolecular Stetter reaction, Enders and co-workers developed the chiral triazolium salt **10** (Scheme 2.4).[12] A variety of aromatic aldehydes **7**, which are connected to the Michael acceptor through a tether (usually the oxygen tether) underwent NHC-catalyzed cyclization reaction to furnish the desired chromanones in moderate yield and enantioselectivity.

Scheme 2.4: First Asymmetric Intramolecular Stetter Reaction by Enders et al.

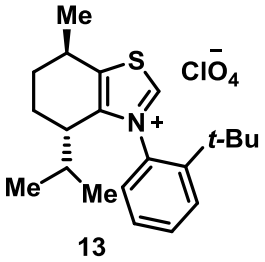


In 2002, Rovis and co-workers developed a highly enantioselective intramolecular Stetter reaction of substrate of the type **7** using the aminoindanol-derived chiral triazolium salt **11.**[13] The reaction was well tolerated with the variation of heteroatom linker to furnish the desired chromanones **8** with good yields and enantioselectivity (Fig 2.2). After that, Rovis and co-workers developed the aminoindanol-derived pentafluoroaryl substituted chiral triazolium salt **12** to obtain chromanones **8** with better reactivity and selectivity.[14] Subsequently, they reported a phenylalanine based triazolium salt **16**, which successfully catalyzed the aliphatic analogues of 2-formylaryloxy crotonates, to derive five- and six-membered carbocycles with good selectivity.[15] Moreover, Bach and co-workers developed an axially chiral thiazolium salt **13** with an N-aryl substituent, which afforded the Stetter adduct **8** in up to 94% yield and 94% ee.[16] Miller and co-workers developed the peptide backbone based chiral thiazolium salts **14** and **15** for the enantioselective synthesis of chromanones **8** from 2-formylaryloxy crotonates **7**.[17] Additionally, You and co-workers reported the diphenyl ethylenediamine (DPEN) derived chiral triazolium salt **17** and D-camphor derived chiral triazolium salt **18,** which furnished the chromanones derivative **8** in excellent yields and enatioselectivity.[18] Recently, Shibasaki and co-workers addressed bis(hydroxyaryl)diamide containing chiral thiazolium salt **19** as carbene precursor for the generation of chromanones **8**.[19] Subsequently, Rafińsky and co-workers came up with a new β-pinene-derived chiral triazolium salt **20** to get chromanones **8** with excellent yield and enantioselectivity.[20] Chiral triazolium based carbene precursor was found to be the most efficient catalysts for asymmetric intramolecular Stetter reaction.



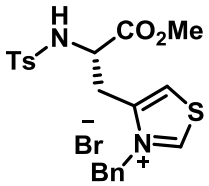
11, Ar = 4-OMeC$_6$H$_4$
Rovis, 2002
35-95% yield, 82-97% ee

12, Ar = C$_6$F$_5$
Rovis, 2004
55-96% yield, 89-99% ee



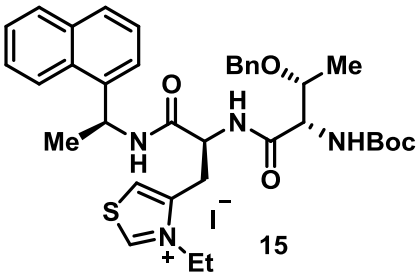
13

Bach, 2004
94% yield, 94% ee



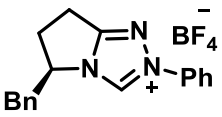
14

Miller, 2005
40% yield, 80% ee



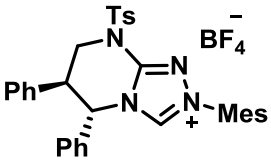
15

Miller, 2005
67% yield, 73% ee



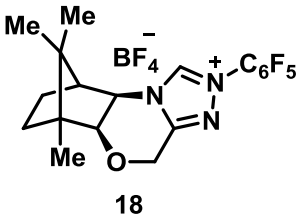
16

Rovis, 2005
56-98% yield, 78-97% ee



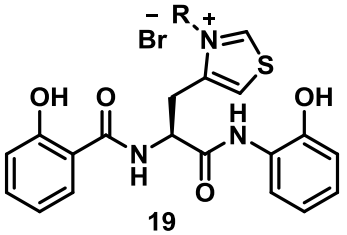
17

You, 2011
56-98% yield, 78-97% ee



18

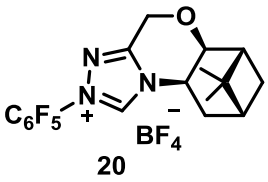
You, 2011
26-97% yield, 56-97% ee



19

R = CH$_2$C$_6$H$_4$-*p*-O*n*C$_{10}$H$_{21}$

Shibasaki, 2014
45-88% yield, 38-63% ee



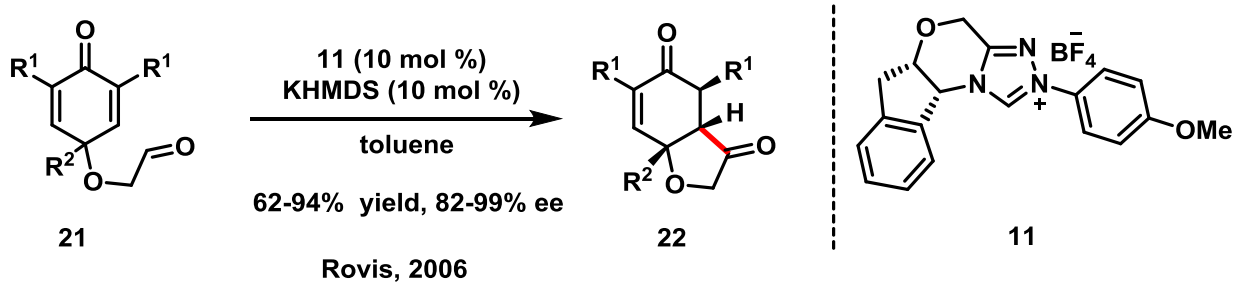
20

Rafinski, 2014
94-99% yield, 24-98% ee

Fig 2.2: Catalysts Developed for Asymmetric Intramolecular Stetter Reaction

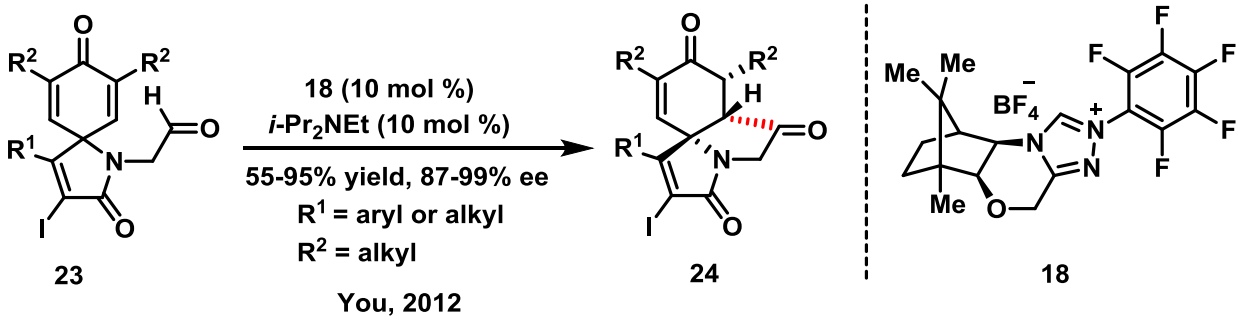
In 2006, Rovis and co-workers developed NHC-catalyzed desymmetrization of cyclohexadienones **21** via the intramolecular Stetter reaction. The carbene generated from the 4-methoxyaryl substituted triazolium salt **11** catalyzed the reaction efficiently to furnish the hydrobenzofurans **22** with good enantioselectivity and diastereoselectivity (Scheme 2.5).[21]

Scheme 2.5: Desymmetrization of Cyclohexadienones via Intramolecular Stetter Reaction by Rovis et al.

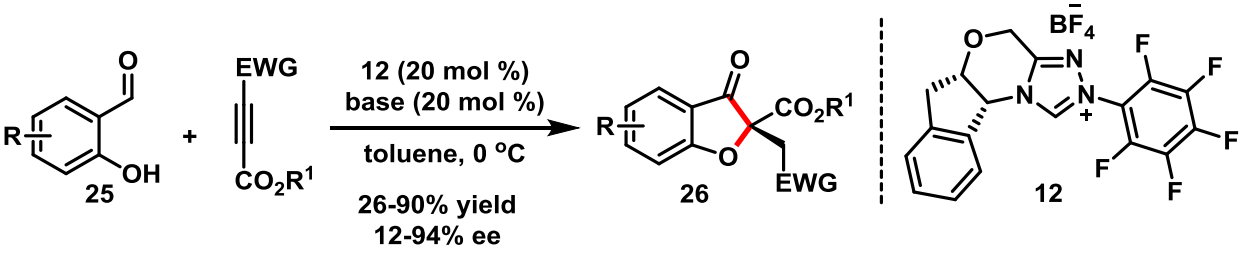


Subsequently, You and co-workers reported an analogous desymmetrization reaction of cyclohexadienone derivatives **11** using the camphor-derived triazolium salt **1j** leading to the formation of the tricyclic compound **12** in moderate to good yield and good enantioselectivity (Scheme 2.6).[22] They also applied this method for the enantioselective construction of tricyclic carbocycles possessing a quaternary stereocenter by the desymmetrization of cyclohexadienones using the camphor-derived NHC precatalyst **1j**.[23]

Scheme 2.6: Desymmetrization of Cyclohexadienones via Intramolecular Stetter Reaction by You et al.



Scheme 2.7: A One-pot Michael/ Intramolecular Stetter Reaction



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 **25** and electrophilic alkynes (Scheme 2.7).[24] The reaction furnished the

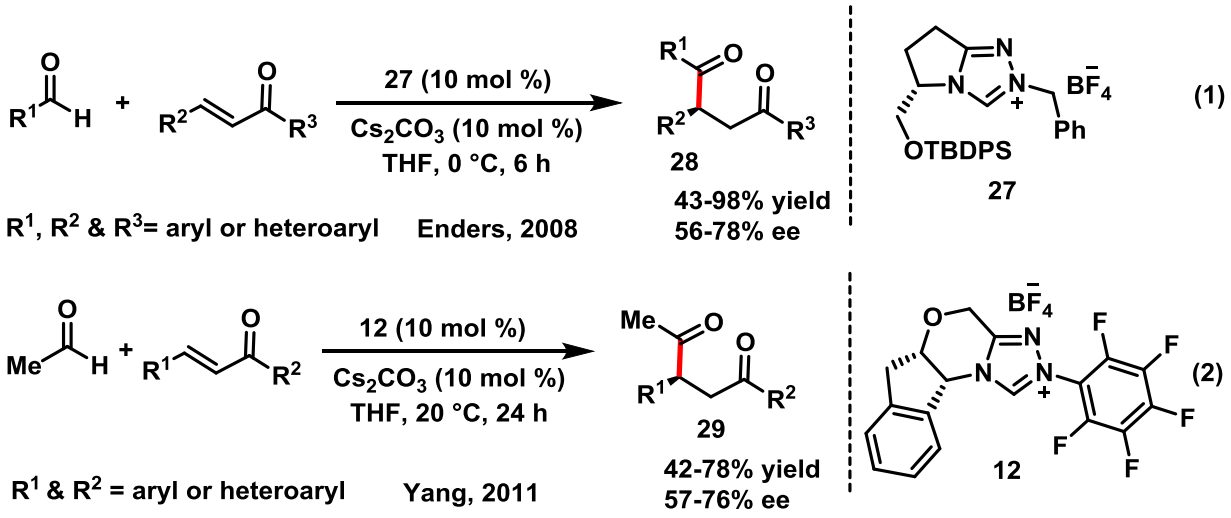
benzofuranone derivatives **26** with good yield and enantioselectivity.

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 intermolecular Stetter reaction, the catalysts development as well as reaction procedures for the enantioselective intramolecular Stetter reaction was well established. Moreover, the Michael acceptors with a β-substitution usually show lower reactivity in intermolecular Stetter reaction.

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.[25] Recently, they demonstrated the enantioselective intermolecular Stetter reaction of aromatic and hetero aromatic aldehydes with chalcones, using chiral triazolium salt **27**. The reaction afforded the 1,4-diketones **28** in moderate to good yields with moderate to good enantioselectivity (Scheme 2.8: Eq. 1).[26] Subsequently, Yang and co-workers reported the generation of acyl anion equivalent from acetaldehyde, which undergoes intermolecular Stetter reaction with chalcones to form the desired 1,4-diketones **29** with moderate yield and enantioselectivity (Scheme 2.8: Eq. 2).[27]

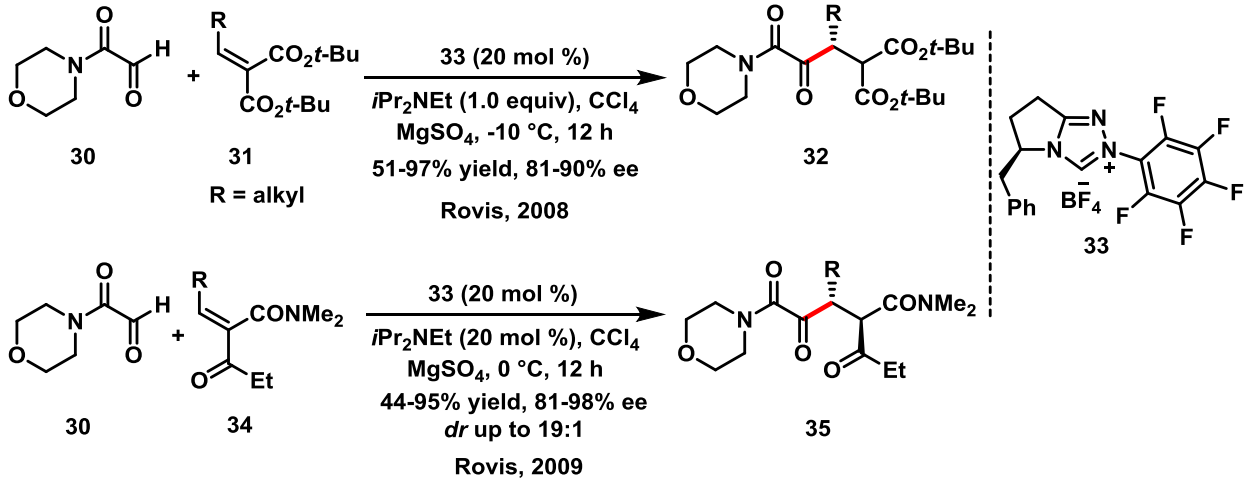
Scheme 2.8: Asymmetric Intermolecular Stetter Reaction



Independently, Rovis and co-workers reported the asymmetric intermolecular Stetter reaction between morpholine-derived glyoxamide derivative **30** and alkylidenemalonate **31**. The reaction afforded Stetter product **32** in good yield with high ee values in the presence of a phenylalanine-derived NHC catalyst **33** (Scheme 2.9).[28] Subsequently, the same group developed

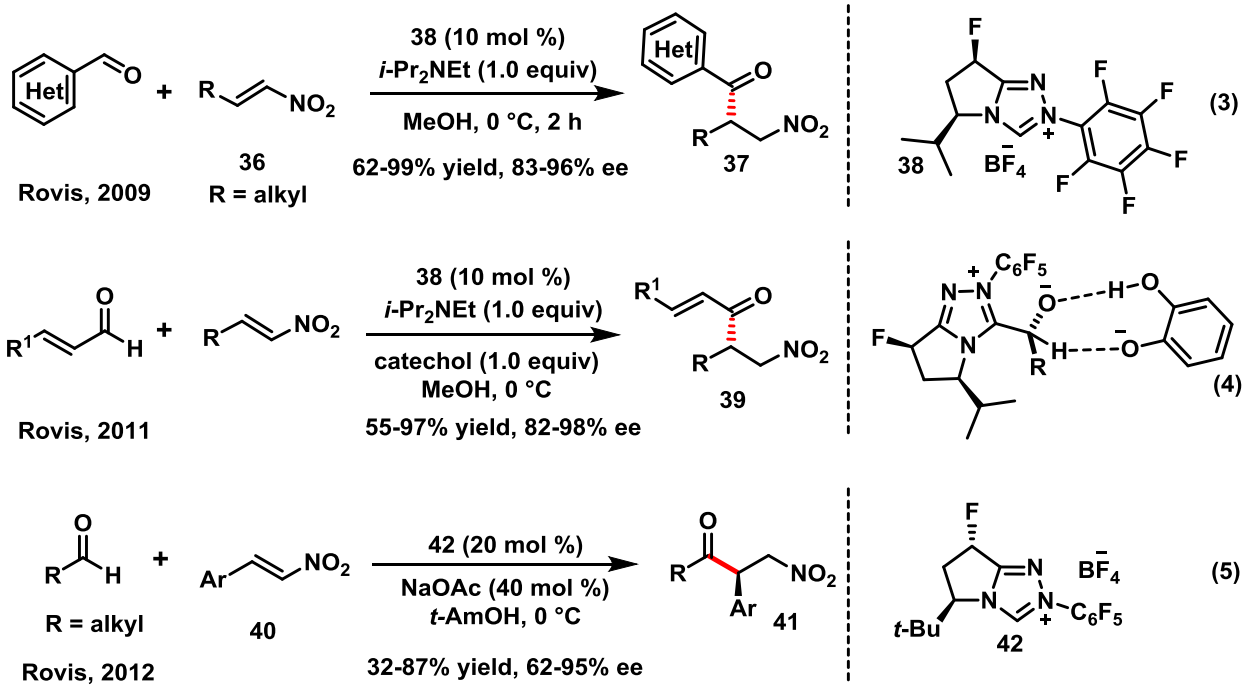
highly enantioselective and diastereoselective intermolecular Stetter reaction of the glyoxamide **30** and β-alkyl alkylidene ketoamides **34** in the presence of NHC precatalysts **33**, which afforded corresponding 1,4-dicarbonyl compounds **35**, in good to excellent yields.[29] Later, Johnson and co-workers used related intermolecular Stetter reaction strategy using ethyl glyoxylate as the aldehyde component and benzylidene malonates/enones as the Michael acceptors.[30]

Scheme 2.9: Asymmetric Intermolecular Stetter Reaction by Rovis et al.



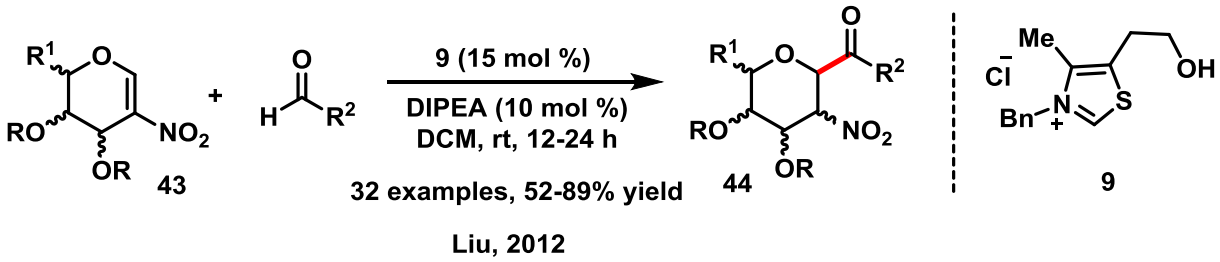
As part of their efforts to develop a general and broad scope enantioselective intermolecular Stetter reaction, Rovis and co-workers employed nitroalkenes **36** as feasible Michael acceptors using a new fluorinated chiral NHC pre-catalyst **38** (Scheme 2.10; Eq. 3). The fluorine effect and isopropyl substituents in **37** was studied by DFT calculations, which showed that electrostatic interaction of fluorine in the Breslow intermediate with nitroalkene and steric effect of isopropyl group was essential for a facile and efficient intermolecular enantioselective Stetter reaction.[31] Notably, heterocyclic aldehydes are necessary for high level of selectivity. Furthermore, they have extended the reaction scope to α,β-unsaturated aldehydes (Scheme 2.10; Eq. 4).[32] 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 **39** in high ee values. Moreover, Houk, Rovis and co-workers used enolizable aldehydes as the coupling partner for β-nitrostyrenes.[33] The carbene generated from chiral triazolium salt **42** was found to be effective one (Scheme 2.10; Eq. 5). Interestingly, the *trans* fluorinated geometry in the pyrrolidine ring of **42** was essential for high reactivity and selectivity.

Scheme 2.10: Asymmetric Intermolecular Stetter Reaction by Rovis et al.



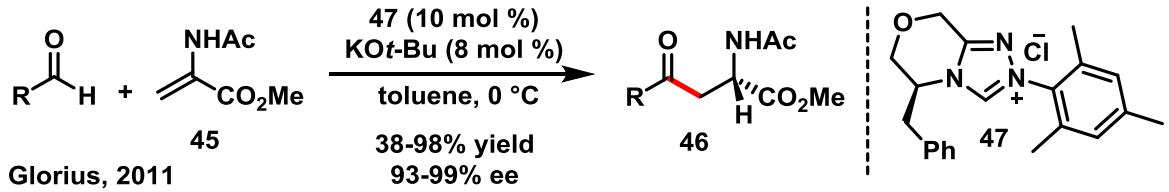
Additionally, Liu and co-workers reported the NHC-catalyzed acyl anion addition to the anomeric carbon of 2-nitroglucal leading to the formation of β-selective *C*-glycosides **44** in good yields using thiazolium salt **9** as carbene precursor (Scheme 2.11).[34] However, when the reaction was performed using Cs_2CO_3 as the base, the nitro-eliminated *C*-glycosides were obtained.

Scheme 2.11: NHC-Catalyzed *C*-Glycosylation Using Stetter Reaction



Glorius and co-workers developed an intermolecular Stetter reaction using *N*-acylamido acrylate **45** as the Michael acceptor for the synthesis of enantioenriched α-amino acid derivatives (Scheme 2.12).[35] Carbene generated from L-phenyl alaninol derived triazolium salt **47** was the key for excellent selectivity. Interestingly, the enantioinduction occured due to the asymmetric protonation of the enolate formed after conjugate addition of the acyl anion to the Michael acceptor (Fig. 2.3).

Scheme 2.12: Asymmetric Intermolecular Stetter Reaction of *N*-Acylamido Acrylate



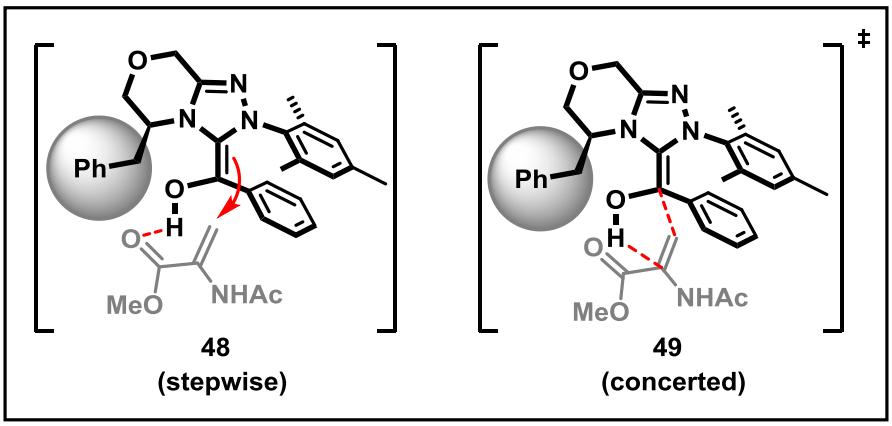
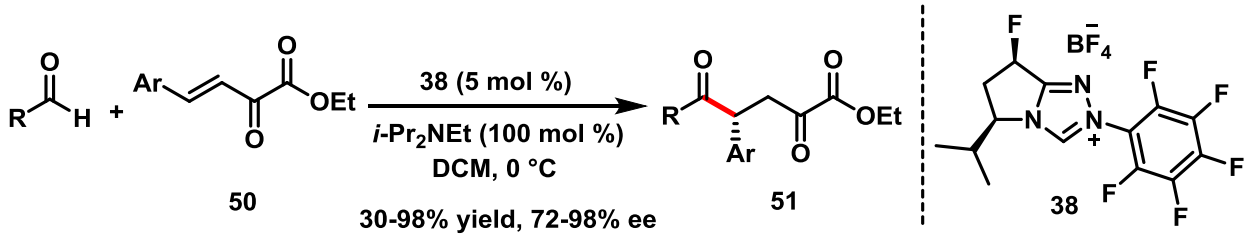


Fig. 2.3: Stepwise and Concerted Pathways in Enantioselective Intermolecular Stetter Reaction Involving *N*-Acylamido Acrylate

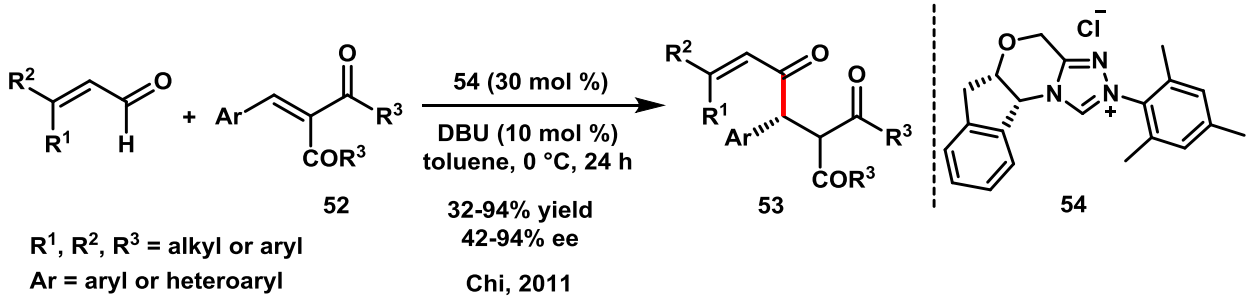
Gravel and co-workers further demonstrated the synthetic utility of the fluorinated triazolium salt **38** by using α,β-unsaturated α-ketoesters **50** as Michael acceptors in asymmetric intermolecular Stetter reaction (Scheme 2.13).[36] The reaction furnished 1,2,5-tricarbonyl compounds **51** in high yields and ee values.

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



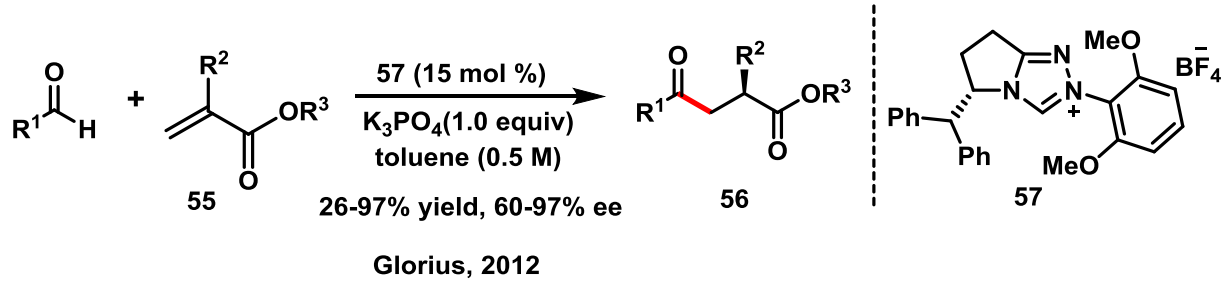
Chi and co-workers uncovered enantioselective Stetter reaction of α,β-unsaturated aldehydes with α-acyl chalcones **52** using sterically demanding aminoindanol-derived triazolium salt **54** (Scheme 2.14).[37] The reaction resulted in the synthesis of triketones **53** in good yields and excellent ee by a selective acyl anion addition to modified chalcones. Notably, various β-alkyl, β-aryl, and β,β-disubstituted enals worked well under the present reaction conditions.

Scheme 2.14: Asymmetric Intermolecular Stetter Reaction α,β-Unsaturated Aldehydes with Modified Chalcones by Chi et al.



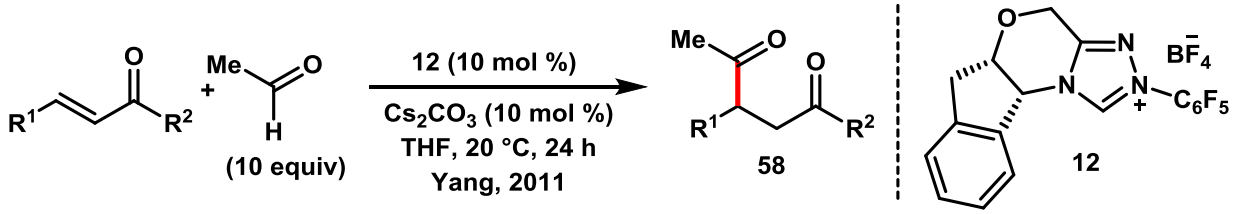
Glorius and co-workers reported an asymmetric intermolecular Stetter reaction using simple acrylates **55** resulting in the formation of α-chiral γ-ketoesters **56** (Scheme 2.15).[38] The carbene generated from 2,6-dimethoxyaryl substituted triazolium salt **57** was found to be an efficient catalyst for this transformation.

Scheme 2.15: Asymmetric Intermolecular Stetter Reaction by Glorius et al.



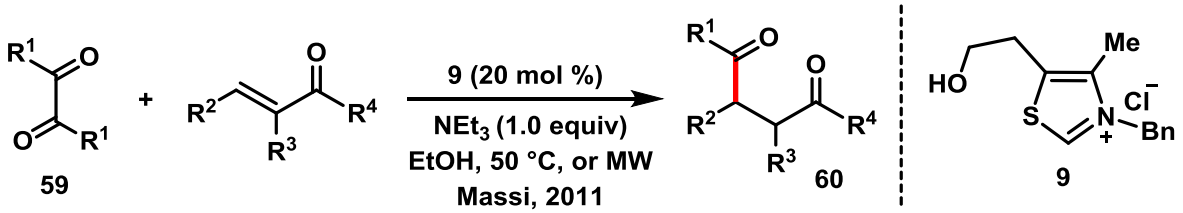
Ryu, Yang and co-workers developed an enantioselective Stetter reaction using acetaldehyde and chalcones catalyzed by the carbene generated from **12** resulting in the formation of the 1,4-diketone **58** in moderate enantioselectivity values (Scheme 2.16).[39]

Scheme 2.16: Synthetic Utility of Acetaldehyde in Stetter Reaction



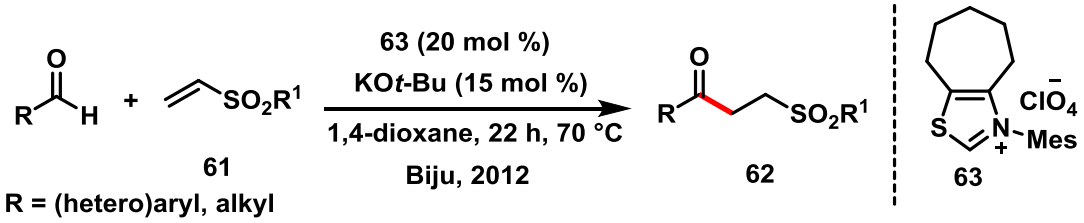
Moreover, Massi and co-workers uncovered the use of 2,3-butanedione (biacetyl) **59** as an effective, bench-stable, and inexpensive alternative surrogate of acetaldehyde for acyl anion generation. The carbene generated from the thiazolium salt **9** catalyzed the reaction and it proceeds under hot condition as well as using microwave conditions (Scheme 2.17).[40]

Scheme 2.17: Use of Biacetyl for Acyl Anion Generation in Stetter Reaction by Massi et al.



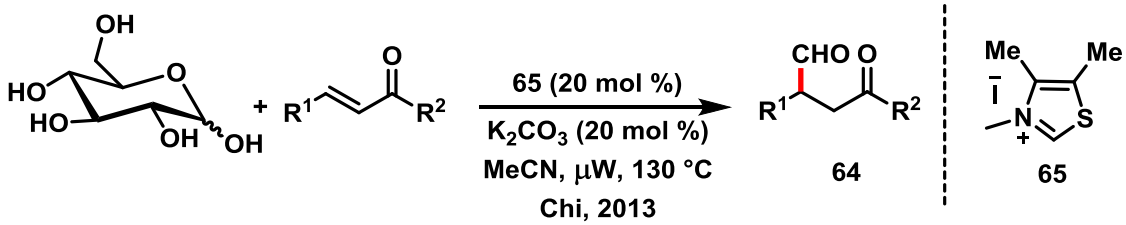
Recently, Biju and co-workers reported the highly selective and efficient NHC-catalyzed intermolecular Stetter reaction of aldehydes with α,β-unsaturated sulfones **61** for the synthesis of γ-ketosulfones **62** in moderate to excellent yields (Scheme 2.18).[41] Carbene generated from the thiazolium salt **63** was efficient in catalyzing this transformation.

Scheme 2.18: Intermolecular Stetter Reaction Using Vinylsulfones by Biju et al.



In 2013, Chi and coworkers disclosed the biomass-based carbohydrates as formal formaldehyde equivalents to generate acyl anion intermediates in Stetter reaction. This one-carbon nucleophile added to various chalcones leading to the formation of β-formyl ketones **64** in good yields under microwave conditions (Scheme 2.19).[42] The reaction involves the NHC-catalyzed carbon-carbon bond cleavage of carbohydrates via a retro-benzoin type reaction to generate the acyl anion intermediates.

Scheme 2.19: Use of Carbohydrates as Formaldehyde Equivalents in Stetter Reaction by Chi et al.

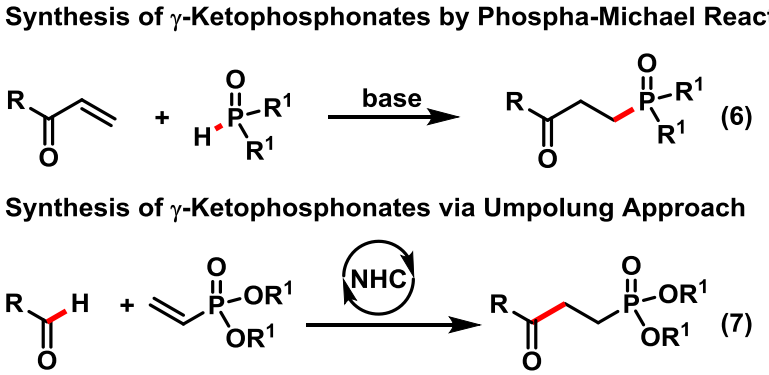


2.4. Statement of the Problem

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 vinylphosphonates as Michael acceptor is unknown. If the reaction works, it will lead to the formation of γ-ketophosphonates. Notably, the intramolecular Stetter reaction of vinylphosphine oxides and vinylphosphonates has been demonstrated by Rovis and co-workers.[43] Previously, reported methods for the synthesis of γ-ketophosphonates are via the phospha-Michael reaction by the addition of phosphorus nucleophiles to α,β-unsaturated ketones (Scheme 2.20; Eq. 6).[44] It is important to note that γ-ketophosphonates are associated with diverse properties such as in crop protection and medicinal chemistry.

Scheme 2.20: Synthesis of γ-Ketophosphonates



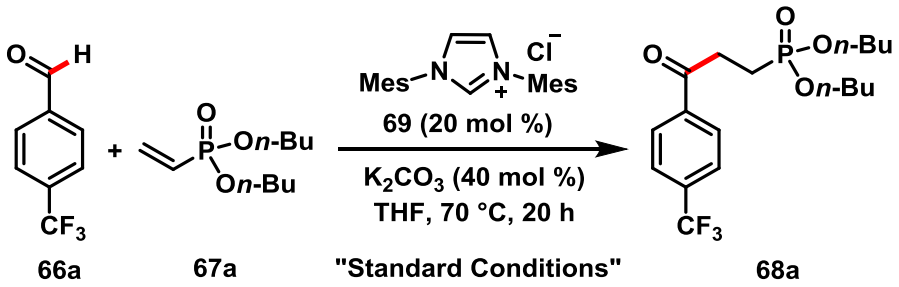
We demonstrate the NHC-organocatalyzed reaction of aromatic aldehydes with vinyl phosphonates can lead to the synthesis of biologically important γ-ketophosphonates (Scheme 2.20; Eq. 7).[45] The present reaction can be considered as a hydroacylation to moderately electron-poor C-C double bond of vinylphosphonates. A detailed study of the intermolecular Stetter reaction of aldehydes with vinyl phosphonates was carried out and the results are presented in this chapter. This investigation revealed the synthesis of γ-ketophosphonate derivatives with broad substrate scope.

2.5. Results and Discussion

2.5.1. Optimization Studies

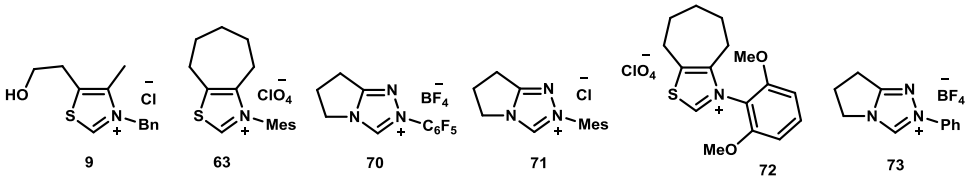
Our optimization study commenced with treatment of 4-trifluoromethyl benzaldehyde **66a** with the vinylphosphonate **67a** in the presence of the imidazolium salt **69** and K_2CO_3 in THF as the solvent. Interestingly, under these conditions, a facile reaction occurred leading to the formation of the γ-ketophosphonate **68a** in 80% isolated yield (Table 2.1, entry 1). In comparison to carbene generated from **69**, other carbene precursors **(9, 63, 70, 71, 72, 73)** are far less reactive in this case (entries 2-7). Screening of different bases for the generation of free carbenes indicated that K_2CO_3 is the optimal base for this transformation, and reactions carried out using

Table 2.1: Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions[a]	yield of **68a** (%)[b,c]
1	None	82 (80)[c]
2	**9** instead of **69**	<5
3	**63** instead of **69**	<5
4	**70** instead of **69**	19
5	**71** instead of **69**	<5
6	**72** instead of **69**	15
7	**73** instead of **69**	<5
8	DBU instead of K_2CO_3	14
9	Et_3N instead of K_2CO_3	<5
10	KO*t*-Bu instead of K_2CO_3	39
11	1,4-dioxane instead of THF	21
12	DME instead of THF	24
13	toluene instead of THF	44
14	CH_2Cl_2 instead of THF	19
15	Reaction run at 50 °C	42
16	1.0 equiv of **66a** instead of 1.5 equiv	49
17	10 mol % of **69** instead of 20 mol %	50

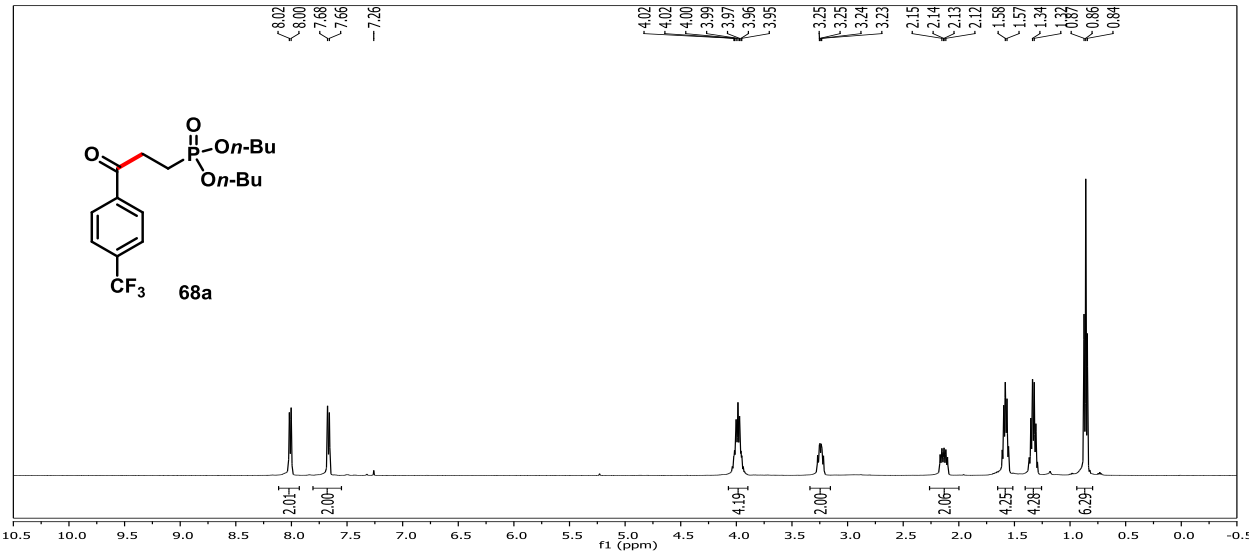
[a] Standard conditions: **66a** (0.38 mmol), **67a** (0.25 mmol), NHC·HX (20 mol %), K_2CO_3 (40 mol %), THF (1.5 mL), 70 °C and 20 h. [b] The yields were determined by ^{1}H-NMR analysis (in $CDCl_3$) of crude products using CH_2Br_2 as the internal standard. [c] Isolated yield in parentheses.



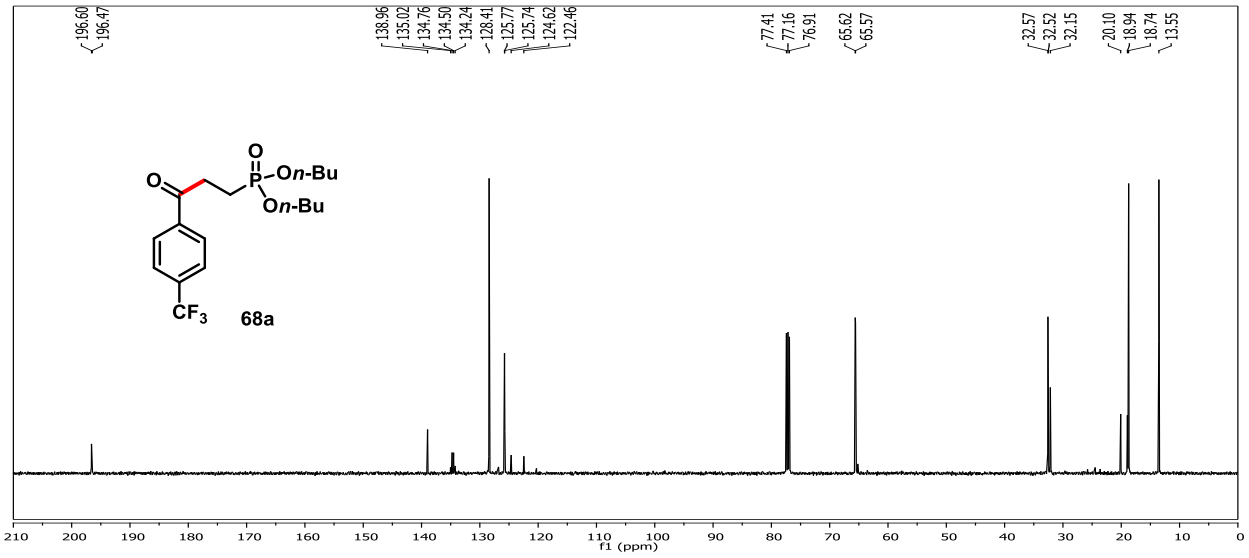
other bases such as DBU, Et_3N, and KO*t*-Bu furnished inferior results (entries 8-10). We also tested the effect of solvent in this Stetter reaction, which indicated that THF is the solvent of choice and the reactions performed in other solvents afforded the γ-ketophosphonate **68a** in low yields (entries 11-14). The reaction returned only 42% of **69a** when the temperature was lowered to 50 °C indicating the role of 70 °C for this Stetter reaction (entry 15). Moreover, decreasing the amount of either the aldehyde **66a** or the carbene precursor **69** resulted in reduced yield of the product (entries 16, 17). So standard condition was optimized condition (entry 1).

2.5.2. Spectral Data of 68a

^{1}H NMR Spectrum of 68a ($CDCl_3$)



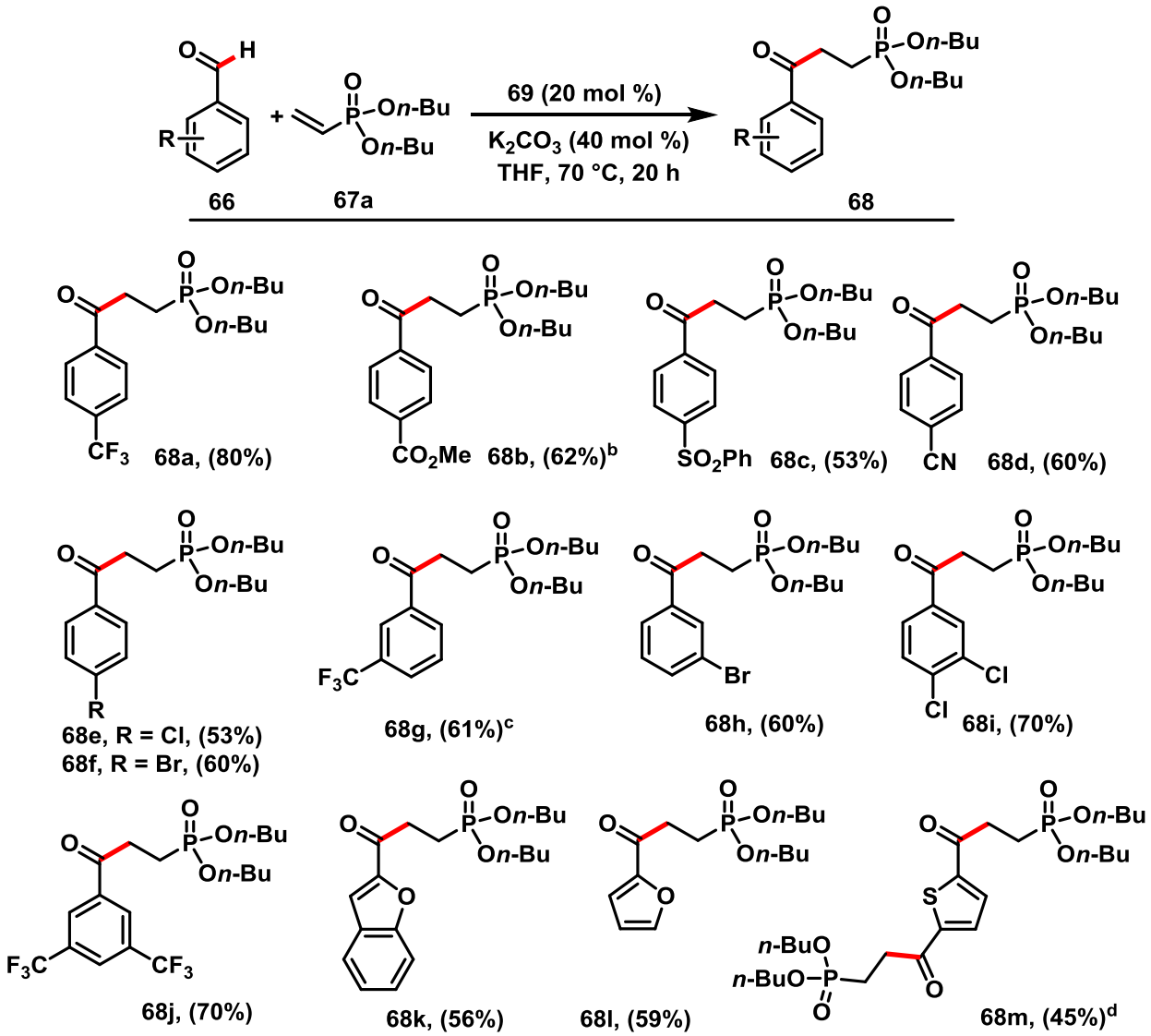
^{13}C NMR Spectrum of 68a ($CDCl_3$)



2.5.3. Substrate Scope

We examined the scope and limitations of the present NHC-catalyzed Stetter reaction for the synthesis of γ-ketophosphonates (Scheme 2.21). A series of aromatic aldehydes with electron-withdrawing groups at the 4-position of the ring underwent smooth coupling reaction leading to the formation of the expected γ-ketophosphonates in moderate to good yields (**68a-68e**).[46] Moreover, 4-bromo substitution is well-tolerated, and the corresponding

Scheme 2.21: NHC-Catalyzed Synthesis of γ-Ketophosphonates, Variation of the Aldehydes[a]

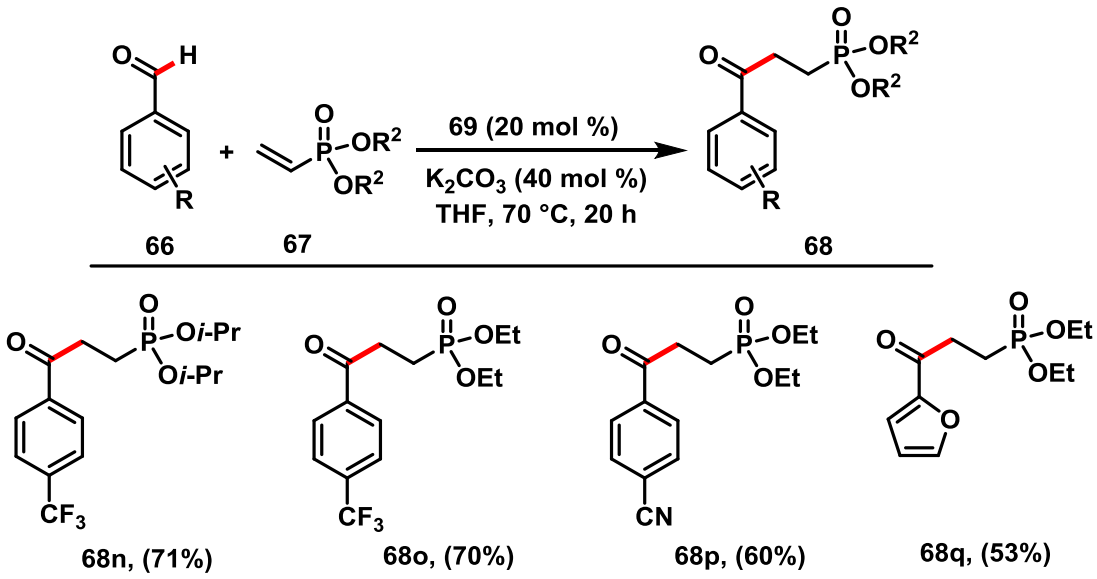


[a] General conditions: **67a** (0.50 mmol), **66** (0.75 mmol), **69** (20 mol %), K_2CO_3 (40 mol %), THF (3.0 mL), 70 °C, and 20 h. Yields of isolated products are given. [b] Reaction was run for 36 h. [c] Reaction was run for 24 h. [d] Reaction was run for 30 h using **67a** (1.25 mmol), the dialdehyde (0.50 mmol), **69** (40 mol %), K_2CO_3 (80 mol %).

-bromophosphonate **68f** was isolated in 60% yield. Disappointingly, the parent benzaldehyde and aldehydes containing electron-releasing group at 4-position of the ring afforded only traces of the desired γ-ketophosphonates. Additionally, 3-substituted benzaldehydes as well as disubstituted benzaldehydes worked well to furnish the target product in good yields (**68g-68j**). Furthermore, heteroaromatic aldehydes can also be used as the aldehyde component in this umpolung approach providing access to various heterocyclic γ-ketophosphonates in moderate yields (**68k-68l**). Interestingly, thiophene-2,5-dicarbaldehyde underwent double Stetter reaction with excess of vinylphosphonate to form the phosphonate **68m** in 45% yield. It may be mentioned that our preliminary studies showed that aliphatic aldehydes and α,β-unsaturated aldehydes[47] did not afford the desired γ-ketophosphonates under the optimized reaction conditions.

We further examined the scope of this reaction using various vinylphosphonate derivatives (Scheme 2.22). The reaction of 4-trifluoromethyl benzaldehyde **66a** with diisopropyl

Scheme 2.22: Variation of the Vinylphosphonate Moiety[a]

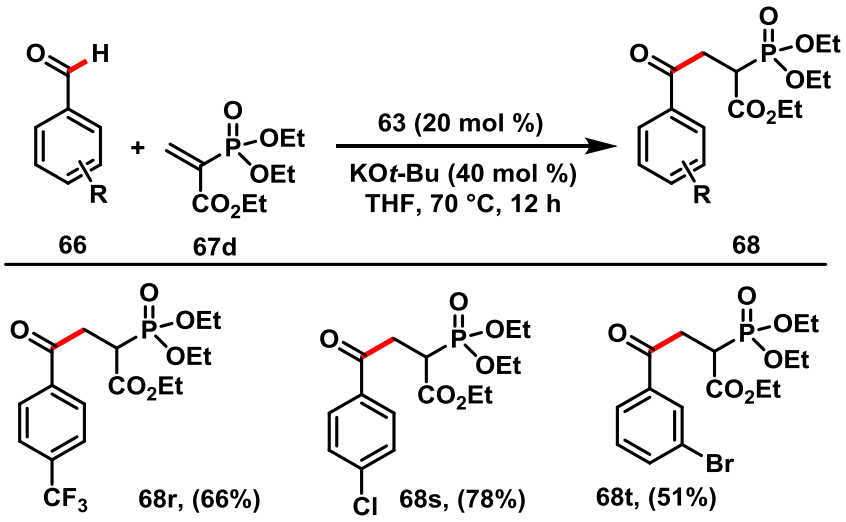


[a] General conditions: **67** (0.50 mmol), **66** (0.75 mmol), **69** (20 mol %), K_2CO_3 (40 mol %), THF (3.0 mL), 70 °C, and 20 h. Yields of isolated products are given.

vinylphosphonate afforded the expected γ-ketophosphonate **68n** in 71% yield. Moreover, diethyl vinylphosphonate also furnished the desired product in moderate to good yield (**68o-68q**). Disappointingly, preliminary experiments revealed that β-substituted α,β-unsaturated phosphonates failed to undergo this transformation under the optimized reaction conditions.

We also tested the feasibility of this reaction with α,α-disubstituted olefins (Scheme 2.23). The reaction of **66a** with ethyl 2-(diethoxyphosphoryl)acrylate **67d** using carbene derived from **69** afforded only reduced yield of the γ-ketophosphonate **68r**. Interestingly, when the reaction was performed using the carbene generated from **63**,[48] an efficient reaction occurred leading to the formation of **68r** in 66% yield. Analogous reactivity was achieved using halogenated aldehydes, and the desired product was isolated in moderate to good yields (**68s-68t**).

Scheme 2.23: Stetter Reaction Using Phosphoryl Acrylate[a]

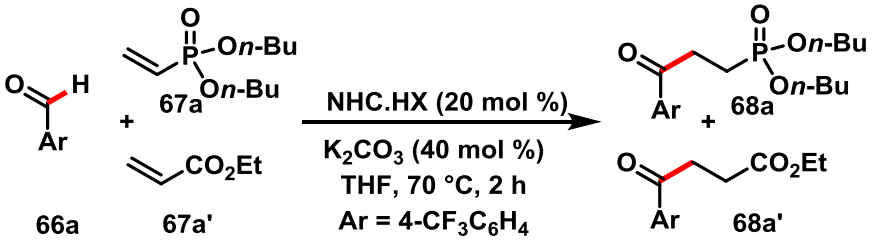


[a] General conditions: **2d** (0.50 mmol), **1** (0.75 mmol), **6** (20 mol %), KO*t*-Bu (40 mol %), THF (2.0 mL), 70 °C, and 12 h. Yields of isolated products are given.

2.5.4. Competition Study

To get insight into the relatively poor reactivity of vinylphosphonate compared to other Michael acceptors, we carried out intermolecular competition experiments using **67a** and the acrylate **67a'**. Interestingly, upon performing the reaction under optimized conditions and quenching after 2 h, the acrylate-derived Stetter product **68a'** was isolated in 27% yield, whereas the phosphonate derived product **68a** was isolated in 10% only (Scheme 2.24). Moreover, executing the reaction using carbene derived from **63**, **68a'** was isolated in 44% yield, only a trace of **68a** was observed. When this reaction was run for 20 h, **68a'** was observed in 95% and **68a** in 10% yield. These experiments shed light on the moderately electron-poor carbon-carbon double bond in vinylphosphonates.

Scheme 2.24: Competition Experiment between Vinylphosphonate and Acrylate

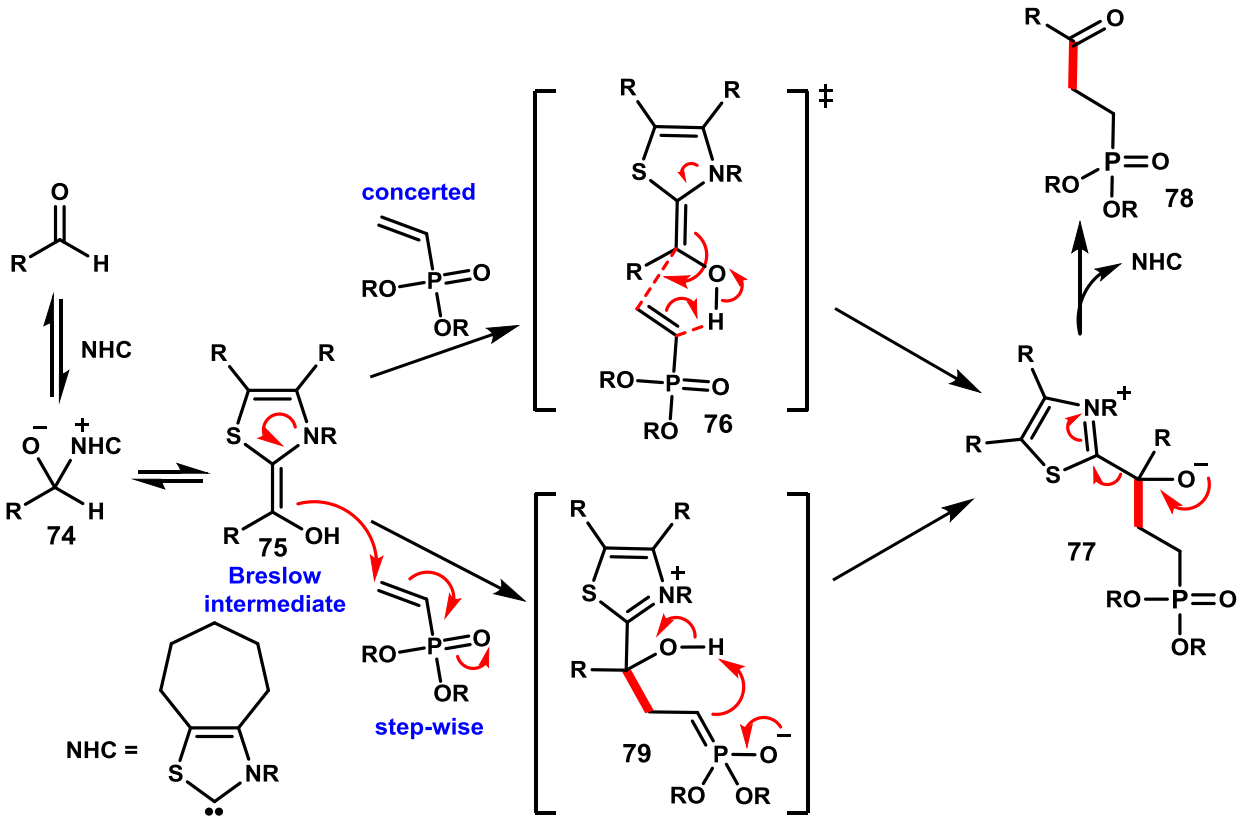


When NHC.HX = 69, 68a (10%), 68a' (27%)
When NHC.HX = 63, 68a (<5%), 68a' (44%)

2.5.5. Reaction Mechanism

A tentative 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 tetrahedral intermediate (**74**), which undergoes proton transfer to form the nucleophilic Breslow intermediate (**75**). This acyl anion equivalent (**75**) can add to vinylphophonate in a concerted pathway via the five-membered transition state **76** to furnish the alkoxide intermediate **77**.[49] On the other hand, a stepwise pathway involving the formation of the intermediate **79** can also be

Scheme 2.25: Tentative Mechanistic Pathways

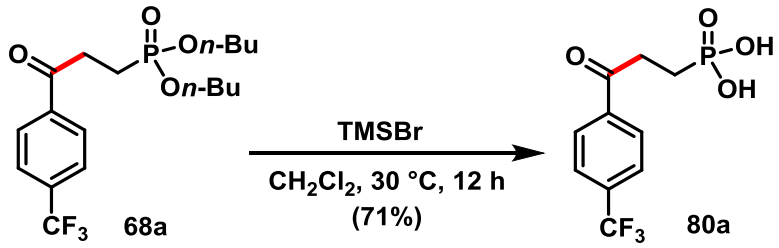


invoked. Elimination of NHC from **77** completes the catalytic cycle furnishing the γ-ketophosphonates **78**. The addition of acyl anion equivalent (**75**) to Michael acceptor is likely an irreversible process.

2.5.6. Synthesis of γ-Ketophosphonic acid

The γ-ketophosphonate **68a** can easily be converted into the free γ-ketophosphonic acid derivative. Bromotrimethylsilane-mediated hydrolysis of **68a** followed by quenching with methanol resulted in the formation of the phosphonic acid **80a** in 71% yield (Scheme 2.26).

Scheme 2.26: NHC-Catalyzed Synthesis of γ-Ketophosphonic Acid



2.6. Conclusion

In conclusion, we have developed the NHC-catalyzed cross-coupling of aromatic aldehydes with α,β-unsaturated phosphonates. This Stetter reaction using moderately electron-poor Michael acceptor afforded the γ-ketophosphonates in moderate to good yields. Given the importance of γ -ketophosphonates in crop-protection and medicinal chemistry, the protocol demonstrated herein is likely a practical method for accessing these compounds.

2.7. Experimental Details

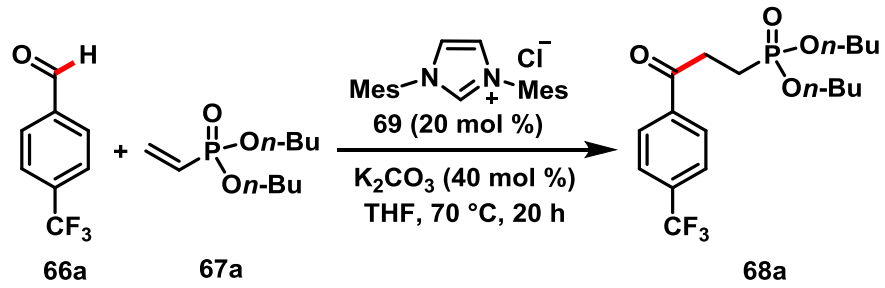
2.7.1. General Information

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. THF was freshly purified by distillation over Na-benzophenone and was transferred under argon. 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 vinylphosphonates and ethyl 2-(dimethoxyphosphoryl)acrylate were synthesized following the modified literature procedure.[50] K_2CO_3 and KO*t*-Bu were dried by heating at 110 °C for 12 h and left to cool under argon. The imidazolium salt **69** and the thiazolium salt **63** were synthesized following the literature procedure.[51,52]

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.

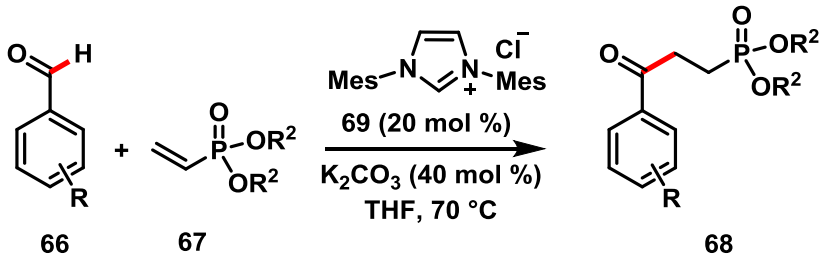
All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400, AV 500 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Infra-red spectra were recorded on a Bruker FT-IR (ATR mode) Infra-red Spectrophotometer. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS (ESI) data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

2.7.2. Procedure for the Optimization of Reaction Conditions



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry K_2CO_3 (14 mg, 0.10 mmol) and the imidazolium salt **69** (17 mg, 0.05 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF under argon atmosphere (1.5 mL). The resultant reaction mixture was kept stirring at 30 °C (rt) for 15 min. To the stirring solution 4-(trifluoromethyl)benzaldehyde **66a** (65.3 mg, 51 µL, 0.375 mmol) and the dibutyl vinylphosphonate **67a** (55.0 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. Subsequently, 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 ^1H NMR analysis using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard.

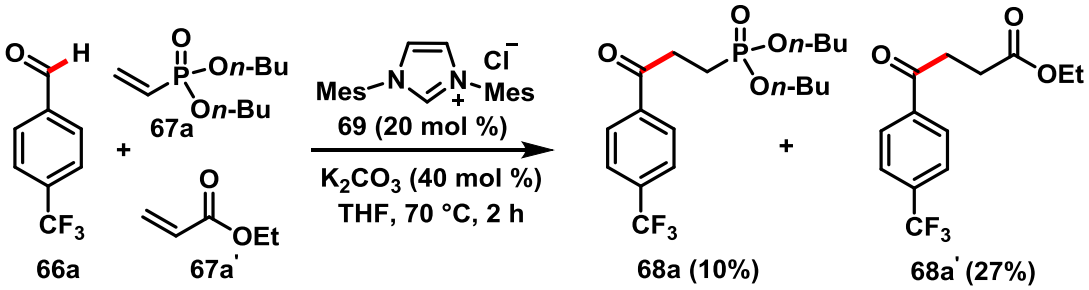
2.7.3. General Procedure for the NHC-Catalyzed Intermolecular Stetter Reaction



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry K_2CO_3 (28.0 mg, 0.20 mmol) and the imidazolium salt **69** (34.0 mg, 0.10 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF under argon atmosphere (3.0 mL). The resultant reaction mixture was kept stirring at 30 °C (rt) for 15 min. To the stirring solution aromatic aldehyde **66** (130.6 mg, 102 µL, 0.75 mmol) vinylphosphonate **67** (110.0 mg, 0.50 mmol) were successively added. Then the reaction mixture is placed in a preheated oil bath at 70° C for the indicated time. When TLC control showed the completion of the reaction (typically after 20 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-ketophosphonates **68** in moderate to good yields.

2.7.4. Competition Experiments

Reaction Carried out Using Carbene Precursor 69

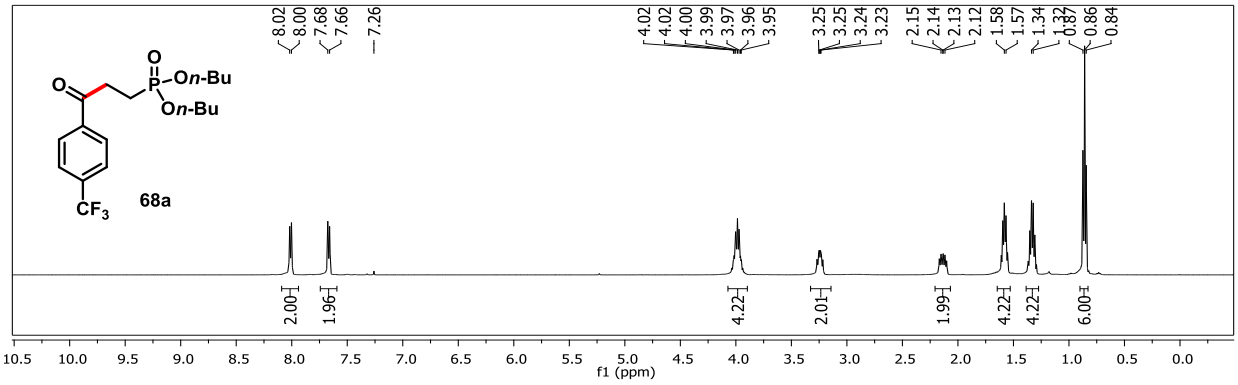


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the imidazolium salt **69** (17.0 mg, 0.05 mmol) and K_2CO_3 (14.0 mg, 0.10 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C for 10 minutes. To this mixture was added the 4-(trifluoromethyl)benzaldehyde **66a** (65.3 mg, 51 µL, 0.375 mmol) followed by dibutyl vinylphosphonate (28.0 mg, 0.125 mmol) and ethyl acrylate

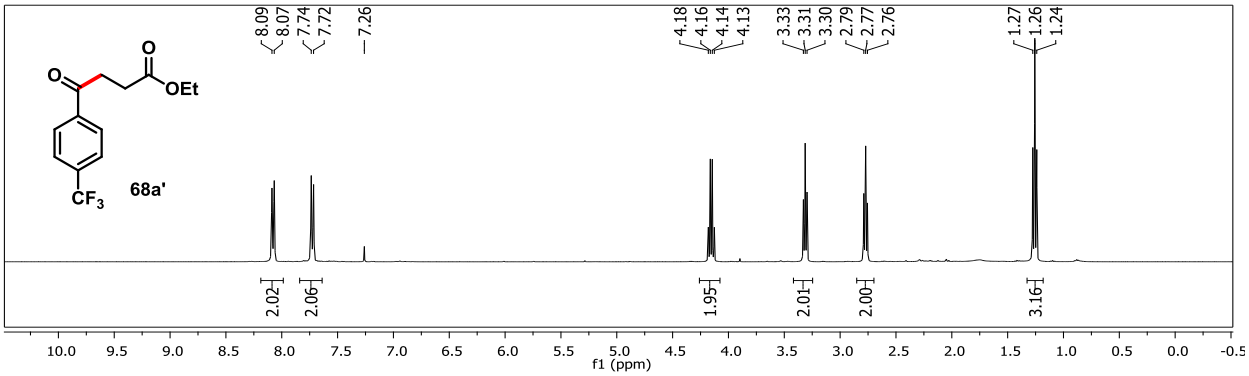
(12.5 mg, 14µL, 0.125 mmol). Then the resultant reaction mixture was kept in stirring at 70 ^{o}C. After 2 h stirring, the reaction is quenched and the mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^{1}H NMR using CH_2Br_2 (9.0 µL, 0.125 mmol) as the internal standard. ^{1}H NMR analysis shows that the crude mixture contains 11% dibutyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate **68a** and 28% ethyl 4-oxo-4-(4-(trifluoromethyl)phenyl)butanoate **68a'**. Moreover, the same reaction was performed in a 0.25 mmol scale and the products were purified by column chromatography. The product **68a** obtained: 10 mg (10% yield), and **68a**' obtained: 19 mg (27% yield)

*The relatively less reactivity of vinylphosphonate **67a** over acrylate **67a'** sheds light on the moderately electron-poor carbon-carbon double bond in vinylphosphonates.*

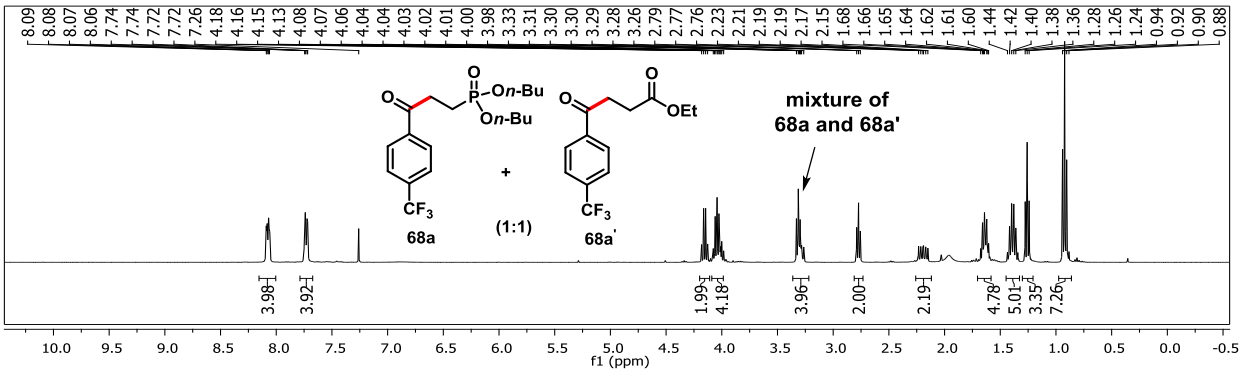
Dibutyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate (68a)



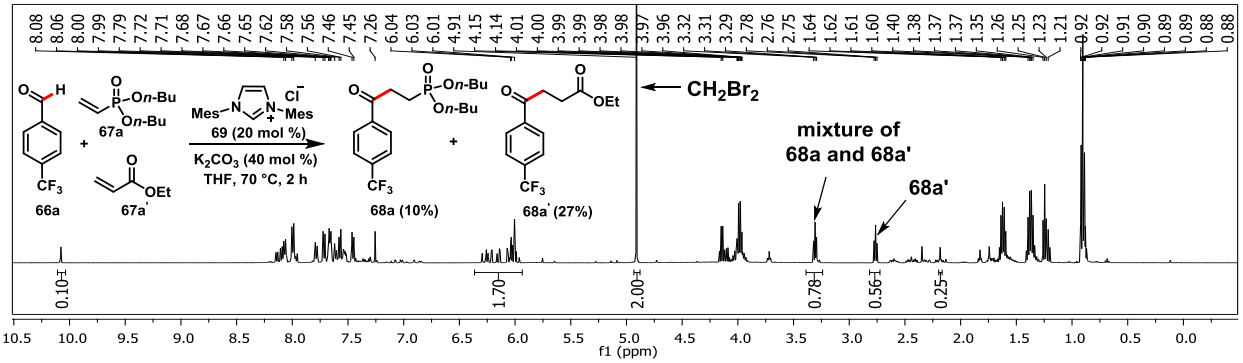
Ethyl 4-oxo-4-(4-(trifluoromethyl)phenyl)butanoate (68a')



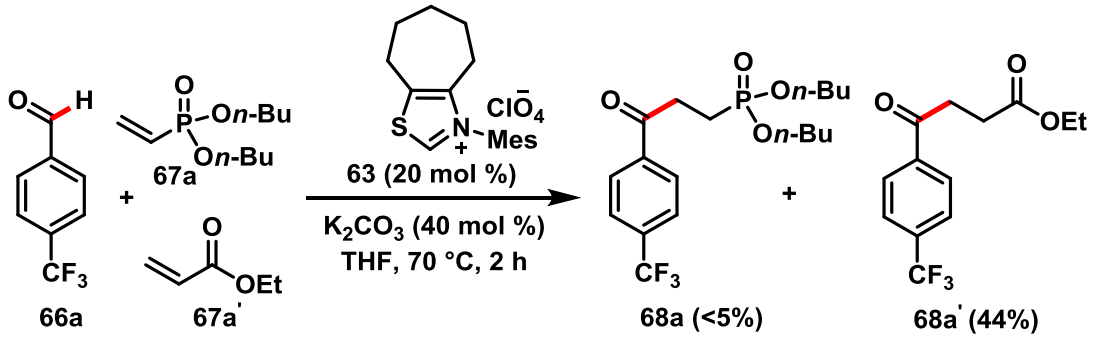
^{1}H-NMR of 1:1 Mixture of 68a and 68a' ($CDCl_3$)



^{1}H-NMR of Crude Reaction Mixture after 2 h ($CDCl_3$)



Reaction Carried out Using Carbene Precursor 63

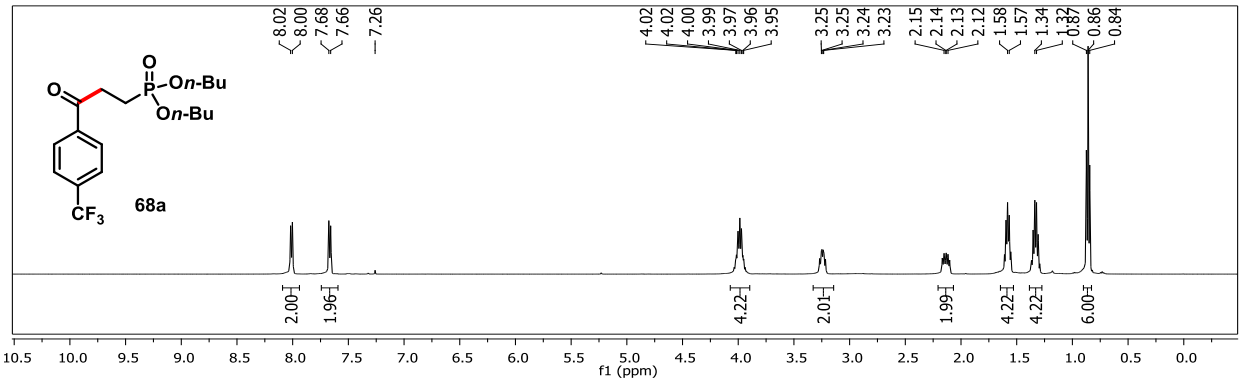


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the imidazolium salt **63** (19.0 mg, 0.05 mmol) and K_2CO_3 (14.0 mg, 0.10 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C for 10 minutes. To this mixture was added the 4-(trifluoromethyl)benzaldehyde **66a** (53.0 mg, 51 µL, 0.375 mmol) followed by dibutyl vinylphosphonate (28.0 mg, 0.125 mmol) and ethyl acrylate (12.5 mg, 14µL, 0.125 mmol). Then the resultant reaction mixture was kept in stirring in a 70 °C.

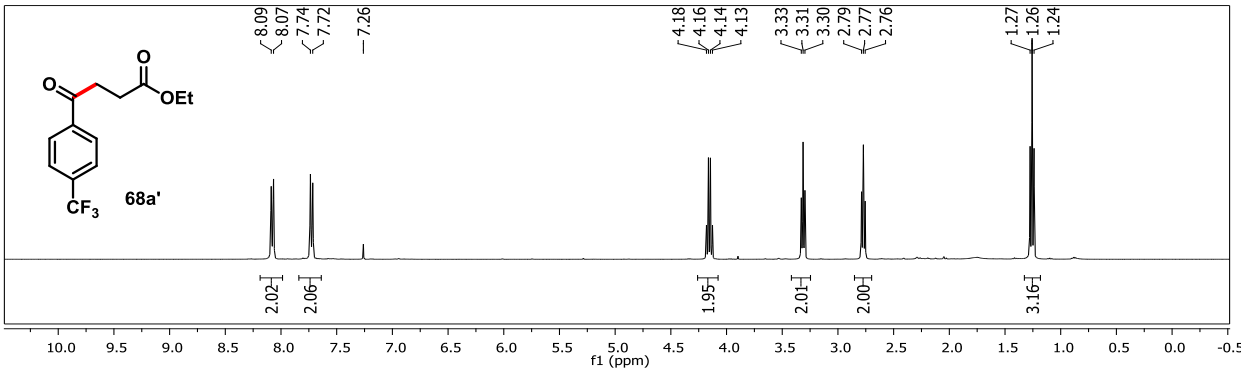
After 2 h stirring, the reaction is quenched and the mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^1H NMR using CH_2Br_2 (9.0 µL, 0.125 mmol) as the internal standard. ^1H NMR analysis shows that the crude mixture contains only traces (<5%) dibutyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate **68a** and 44% ethyl 4-oxo-4-(4-(trifluoromethyl)phenyl)butanoate **68a'**. The same yield was obtained after purification by column chromatography.

Moreover, another reaction carried out under the same conditions was quenched after 20 h, 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 (9.0 µL, 0.125 mmol) as the internal standard. ^1H NMR analysis shows that the crude mixture contains 10% dibutyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate **68a** and 95% ethyl 4-oxo-4-(4-(trifluoromethyl) phenyl)butanoate **68a'**.

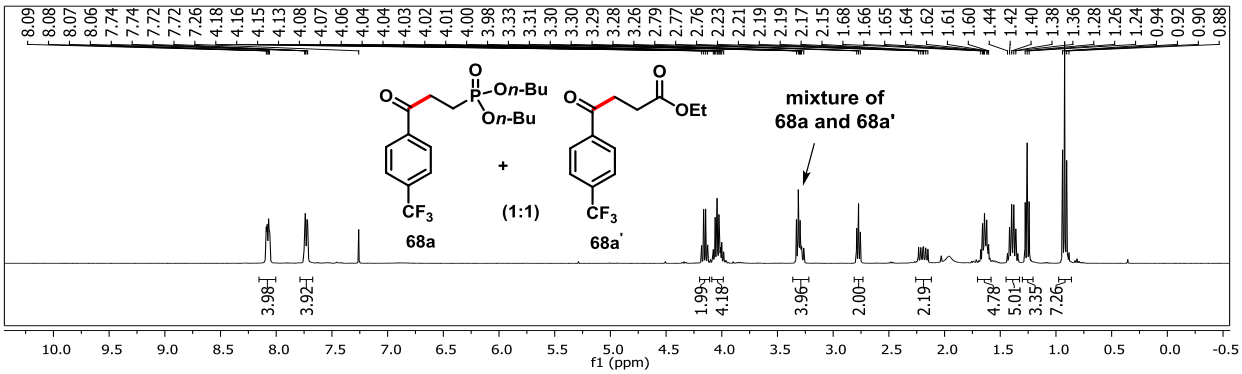
Dibutyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate (68a)



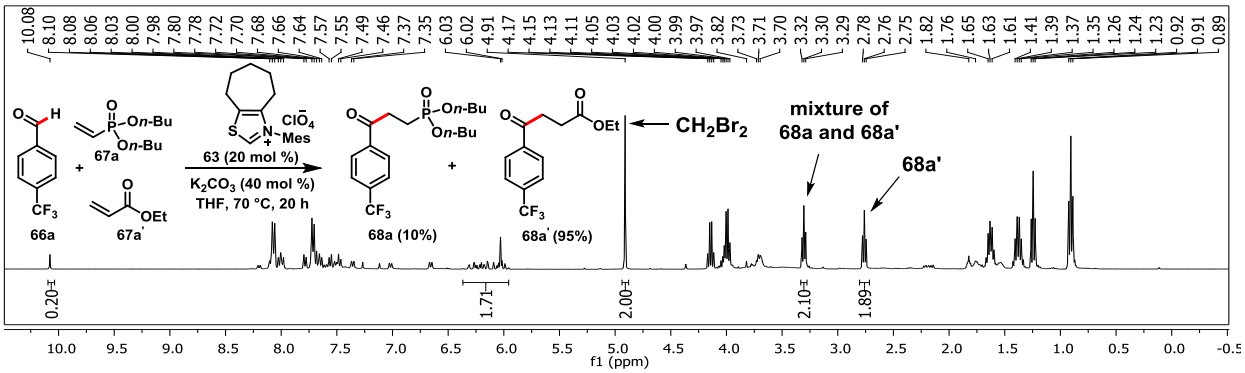
Ethyl 4-oxo-4-(4-(trifluoromethyl)phenyl)butanoate (68a')



^{1}H-NMR of 1:1 Mixture of 68a and 68a' ($CDCl_3$)

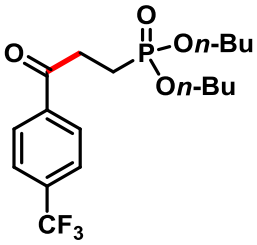


^{1}H-NMR of Crude Reaction Mixture after 20 h ($CDCl_3$)



2.7.5. Synthesis and Characterization of γ-Ketophosphonates

Dibutyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate (68a)



68a

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and 4-(trifluoromethyl) benzaldehyde **66a** (0.131 g, 102 µL, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded dibutyl (3-oxo-3-(4-(trifluoromethylphenyl) propyl)phosphonate **68a** as a colourless oil (0.156 g, 80%).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.34.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 2H, H_{ar}), 7.67 (d, *J* = 8.1 Hz, 2H, H_{ar}), 4.02-3.95 (m, 4H), 3.27-3.22 (m, 2H), 2.17-2.10 (m, 2H), 1.61-1.55 (m, 4H), 1.37-1.29 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 6H, $2CH_3$).

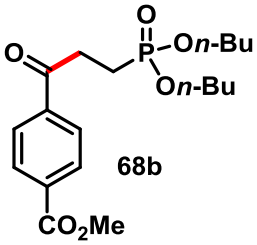
^{13}C NMR (100 MHz, $CDCl_3$) δ 196.54 (d, J_{C-P} = 15.5 Hz), 138.96, 134.63 (q, $J_{1\ C-F}$ = 33.0 Hz, $J_{2\ C-F}$ = 65.8 Hz), 128.41, 125.75 (d, J_{C-P} = 3.4 Hz), 124.62, 122.46, 65.60 (d, J_{C-P} = 6.6 Hz), 32.55 (d, J_{C-P} = 6.1 Hz), 32.15 (d, J_{C-P} = 2.3 Hz), 19.52 (d, J_{C-P} = 145.1 Hz), 18.74, 18.35.

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.16.

HRMS calculated $[M+Na]^+$ for $C_{18}H_{26}F_3O_4PNa$: 417.1413, found: 417.1395.

FTIR (cm^{-1}) 2961, 2875, 1695, 1411, 1323, 1234, 1168, 1129, 1064, 1020, 977, 900, 839, 800, 730.

Methyl 4-(3-(dibutoxyphosphoryl)propanoyl)benzoate (68b)



Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and methyl 4-formylbenzoate **66b** (0.123 g, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 36 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded methyl 4-(3-(dibutoxyphosphoryl)propanoyl)benzoate **68b** as a colourless oil (0.119 g, 62%).

R_f (Pet. ether /EtOAc = 70/30): 0.27.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.5 Hz, 2H, H_{ar}), 7.99 (d, J = 8.5 Hz, 2H, H_{ar}), 4.08-3.98 (m, 4H), 3.92 (s, 3H, CH_3), 3.31-3.25 (m, 2H), 2.21-2.13 (m, 2H), 1.66-1.59 (m, 4H), 1.42-1.33 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H, $2CH_3$).

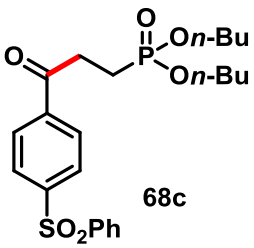
^{13}C NMR (100 MHz, $CDCl_3$) δ 197.12 (d, J_{C-P} = 15.6 Hz), 166.22, 139.54, 134.24, 130.57, 130.01, 128.69, 128.07, 65.74 (d, J_{C-P} = 6.7 Hz), 52.58, 32.64 (d, J_{C-P} = 6.1 Hz), 32.27 (d, J_{C-P} = 2.6 Hz), 20.33, 18.84, 13.69.

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.45.

HRMS calculated $[M+Na]^+$ for $C_{19}H_{29}O_6PNa$: 407.1594, found: 407.1583.

FTIR (cm^{-1}) 2962, 1727, 1694, 1282, 1245, 1112, 1067, 1025, 980, 745.

Dibutyl (3-oxo-3-(4-(phenylsulfonyl)phenyl)propyl)phosphonate (68c)



Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and 4-(phenylsulfonyl)benzaldehyde **66c** (0.184 g, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction

mixture afforded dibutyl (3-oxo-3-(4-(phenylsulfonyl)phenyl)propyl)phosphonate **68c** as a colourless oil (0.124 g, 53%).

R_f (Pet. ether /EtOAc = 70/30): 0.26.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (q, J_1 = 7.5 Hz, J_2 = 15.4 Hz 4H, H_{ar}), 7.94 (d, J = 7.5 Hz, 2H, H_{ar}), 7.59 (t, J = 7.2 Hz, 1H, H_{ar}), 7.52 (t, J = 7.2 Hz, 2H, H_{ar}), 4.07-3.97 (m, 4H), 3.28-3.23 (m, 2H), 2.19-2.13 (m, 2H), 1.65-1.59 (m, 4H), 1.40-1.34 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H, $2CH_3$).

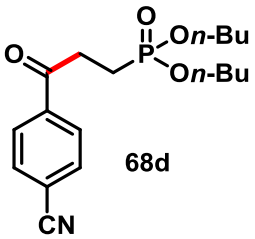
^{13}C NMR (125 MHz, $CDCl_3$) δ 196.47 (d, J_{C-P} = 15.4 Hz), 145.84, 140.84, 139.72, 133.81, 129.61, 128.97, 128.19, 128.00, 65.78 (d, J_{C-P} = 6.6 Hz), 32.64 (d, J_{C-P} = 5.9 Hz), 32.42, 19.60 (d, J_{C-P} = 144.8 Hz), 18.85, 13.70.

^{31}P NMR (203 MHz, $CDCl_3$) δ 31.07.

HRMS calculated $[M+Na]^+$ for $C_{23}H_{31}SO_6PNa$: 489.1471, found: 489.1458.

FTIR (cm^{-1}) 2961, 1693, 1319, 1299, 1229, 1157, 1066, 1022, 977, 725.

Dibutyl (3-(4-cyanophenyl)-3-oxopropyl)phosphonate (68d)



68d

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and 4-formylbenzonitrile **66d** (0.098 g, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded dibutyl (3-(4-cyanophenyl)-3-oxopropyl)phosphonate **68d** as a yellowish oil (0.106 g, 60%).

R_f (Pet. ether /EtOAc = 70/30): 0.32.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.3 Hz, 2H, H_{ar}), 7.75 (d, J = 8.3 Hz, 2H, H_{ar}), 4.04-3.97 (m, 4H), 3.29-3.23 (m, 2H), 2.20-2.11 (m, 2H), 1.64-1.57 (m, 4H), 1.40-1.31 (m, 4H), 0.89 (t, J = 7.3 Hz, 6H, $2CH_3$).

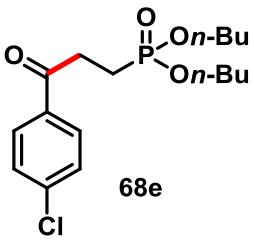
^{13}C NMR (100 MHz, $CDCl_3$) δ 196.28 (d, J_{C-P} = 15.4 Hz), 139.23, 132.64, 128.53, 117.84, 116.70, 65.70 (d, J_{C-P} = 6.6 Hz), 32.57 (d, J_{C-P} = 6.0 Hz), 32.26, 20.22, 18.77, 13.63.

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.01.

HRMS calculated $[M+Na]^+$ for $C_{18}H_{26}NO_4PNa$: 374.1492, found: 374.1483.

FTIR (cm^{-1}) 2961, 2874, 2232, 1695, 1464, 1408, 1234, 1066, 1024, 980, 902, 839, 802, 745.

Dibutyl (3-(4-chlorophenyl)-3-oxopropyl)phosphonate (68e)



68e

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and 4-chlorobenzaldehyde **66e** (0.106 g, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded dibutyl (3-(4-chlorophenyl)-3-oxopropyl)phosphonate **68e** as a yellowish oil (0.096 g, 53%).

***R**f* (Pet. ether /EtOAc = 70/30): 0.36.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 2H, H_{ar}), 7.44 (d, *J* = 8.3 Hz, 2H, H_{ar}), 4.08-4.00 (m, 4H), 3.28-3.21 (m, 2H), 2.21-2.13 (m, 2H), 1.67-1.60 (m, 4H), 1.44-1.34 (m, 4H), 0.92 (t, *J* = 7.3 Hz, 6H, $2CH_3$).

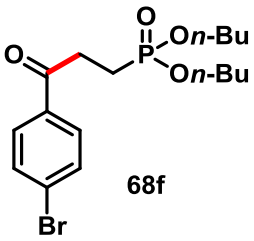
^{13}C NMR (100 MHz, $CDCl_3$) δ 196.44 (d, J_{C-P} = 15.7 Hz), 140.01, 134.74, 129.60, 129.16, 65.72 (d, J_{C-P} = 6.6 Hz), 32.68 (d, J_{C-P} = 6.0 Hz), 31.90 (d, J_{C-P} = 2.3 Hz), 19.71 (d, J_{C-P} = 144.9Hz), 18.88, 13.73.

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.48.

HRMS calculated $[M+Na]^+$ for $C_{17}H_{26}ClO_4PNa$: 383.1149, found: 383.1139.

FTIR (cm^{-1}) 2960, 1689, 1589, 1233, 1065, 1020, 975, 826, 797.

Dibutyl (3-(4-bromophenyl)-3-oxopropyl)phosphonate (68f)



68f

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and 4-bromobenzaldehyde **66f** (0.138 g, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded dibutyl (3-(4-bromophenyl)-3-oxopropyl)phosphonate **68f** as a yellowish oil (0.122 g, 60%).

***R**f* (Pet. ether /EtOAc = 70/30): 0.31.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.6 Hz, 2H, H_{ar}), 7.60 (d, *J* = 8.6 Hz, 2H, H_{ar}), 4.09-3.99 (m, 4H), 3.26-3.21 (m, 2H), 2.20-2.14 (m, 2H), 1.66-1.61 (m, 4H), 1.42-1.35 (m, 4H), 0.92 (t, *J* = 7.4 Hz, 6H, $2CH_3$).

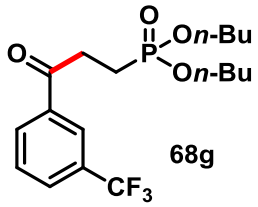
^{13}C NMR (125 MHz, $CDCl_3$) δ 196.61 (d, J_{C-P} = 15.9 Hz), 135.11, 132.15, 129.70, 128.73, 65.76 (d, J_{C-P} = 6.6 Hz), 33.66 (d, J_{C-P} = 6.0 Hz), 31.87, 19.64 (d, J_{C-P} = 144.8 Hz), 18.87, 13.73.

^{31}P NMR (203 MHz, $CDCl_3$) δ 31.55.

HRMS calculated $[M+Na]^+$ for $C_{17}H_{26}BrO_4PNa$: 427.0644, found: 427.0632.

FTIR (cm^{-1}) 2691, 1690, 1585, 1244, 1068, 1022, 978.

Dibutyl (3-oxo-3-(3-(trifluoromethyl)phenyl)propyl)phosphonate (68g)



68g

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and 3-(trifluoromethyl)benzaldehyde **66g** (0.131 g, 100 µL, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded dibutyl (3-oxo-3-(3-(trifluoromethyl)phenyl)propyl)phosphonate **68g** as a yellowish oil (0.120 g, 61%).

R_f (Pet. ether /EtOAc = 70/30): 0.37.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H, H_{ar}), 8.16 (d, J = 7.8 Hz, 1H, H_{ar}), 7.83-7.79 (m, 1H, H_{ar}), 7.63-7.57 (m, 1H, H_{ar}), 4.12-4.02 (m, 4H), 3.36-3.31 (m, 2H), 2.27-2.20 (m, 2H), 1.68-1.63 (m, 4H), 1.43-1.36 (m, 4H), 0.92 (t, J = 7.4 Hz, 6H, $2CH_3$).

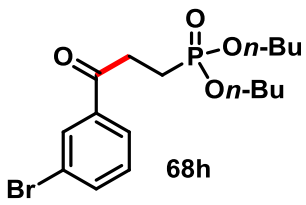
^{13}C NMR (125 MHz, $CDCl_3$) δ 196.25 (d, J_{C-P} = 15.5 Hz), 136.88, 133.10, 131.45 (q, $J_{1\ C-F}$ = 33.5 Hz, $J_{2\ C-F}$ = 66.1 Hz), 131.32, 129.85 (d, J_{C-P} = 3.1 Hz), 129.50, 128.94, 124.99 (d, J_{C-P} = 3.5 Hz) 65.88 (d, J_{C-P} = 6.6 Hz), 32.60 (d, J_{C-P} = 6.1 Hz), 32.00, 19.54 (d, J_{C-P} = 145.2 Hz), 18.82, 13.63.

^{31}P NMR (203 MHz, $CDCl_3$) δ 31.48.

HRMS calculated $[M+Na]^+$ for $C_{18}H_{26}F_3O_4PNa$: 417.1413, found: 417.1396.

FTIR (cm^{-1}) 2962, 2875, 1696, 1612, 1464, 1412, 1361, 1327, 1238, 1170, 1127, 1067, 1022, 979, 899, 805, 745, 695, 670.

Dibutyl (3-(3-bromophenyl)-3-oxopropyl)phosphonate (68h)



68h

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and 3-bromobenzaldehyde **66h** (0.139 g, 88 µL, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70

°C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded dibutyl (3-(3-bromophenyl)-3-oxopropyl)phosphonate **68h** as a colourless oil (0.121 g, 60%).

R_f (Pet. ether /EtOAc = 70/30): 0.33.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 1.7 Hz, 1H, H_{ar}), 7.88-7.86 (m, 1H, H_{ar}), 7.68-7.67 (m, 1H, H_{ar}), 7.35-7.31 (m, 1H, H_{ar}), 4.06-3.97 (m, 4H), 3.26-3.19 (m, 2H), 2.26-2.21 (m, 2H), 1.66-1.59 (m, 4H), 1.42-1.33 (m, 4H), 0.93-0.89 (m, 6H, $2CH_3$).

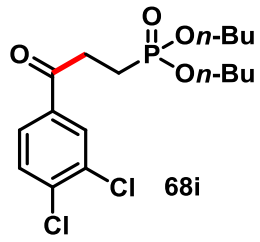
^{13}C NMR (100 MHz, $CDCl_3$) δ 196.23 (d, J_{C-P} = 15.7 Hz), 138.09, 136.30, 131.21, 130.39, 126.68, 123.16, 65.76 (d, J_{C-P} = 6.6 Hz), 32.63 (d, J_{C-P} = 6.1 Hz), 31.97 (d, J_{C-P} = 2.8 Hz), 20.33, 18.86 (d, J_{C-P} = 4.7 Hz), 13.68.

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.39.

HRMS calculated $[M+Na]^+$ for $C_{17}H_{26}BrO_4PNa$: 427.0644, found: 427.0635.

FTIR (cm^{-1}) 2960, 2873, 1692, 1566, 1466, 1418, 1239, 1066, 1023, 980, 899, 792, 750, 681.

Dibutyl (3-(3,4-dichlorophenyl)-3-oxopropyl)phosphonate (68i)



68i

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and 3,4-dichlorobenzaldehyde **66i** (0.132 g, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded dibutyl (3-(3,4-dichlorophenyl)-3-oxopropyl)phosphonate **68i** as a yellowish oil (0.141 g, 70%).

R_f (Pet. ether /EtOAc = 70/30): 0.34.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.9 Hz, 1H, H_{ar}), 7.73 (dd, J_1 = 1.9 Hz, J_2 = 8.4 Hz, 1H, H_{ar}), 7.49 (d, *J* = 8.4 Hz, 1H, H_{ar}), 4.06-3.93 (m, 4H), 3.21-3.14 (m, 2H), 2.16-2.08 (m, 2H), 1.63-1.56 (m, 4H), 1.39-1.29 (m, 4H), 0.87 (t, *J* = 7.4 Hz, 6H, $2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.30 (d, J_{C-P} = 15.5 Hz), 137.96, 135.83, 133.44, 130.84, 130.06, 127.09, 65.65 (d, J_{C-P} = 6.6 Hz), 32.55 (d, J_{C-P} = 6.0 Hz), 31.89 (d, J_{C-P} = 2.6 Hz), 19.51 (d, J_{C-P} = 145.5 Hz), 18.76, 13.60.

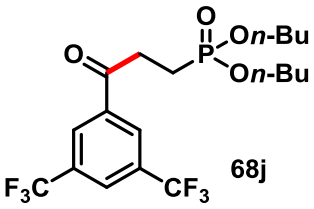
^{31}P NMR (162 MHz, $CDCl_3$) δ 31.12.

HRMS calculated $[M+Na]^+$ for $C_{17}H_{25}Cl_2O_4PNa$: 417.0760, found: 417.0746.

FTIR (cm^{-1}) 2959, 1692, 1464, 1386, 1230, 1064, 1024, 982. 898, 816.

Dibutyl (3-(3,5-bis(trifluoromethyl)phenyl)-3-oxopropyl)phosphonate (68j)

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde **66j** (0.182 g, 124 µL, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded dibutyl (3-(3,5-bis(trifluoromethyl)phenyl)-3-oxopropyl)phosphonate **68j** as a yellowish oil (0.162 g, 70%).



68j

***R**f* (Pet. ether /EtOAc = 70/30): 0.29.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 2H, H_{ar}), 8.06 (s, 1H, H_{ar}), 4.10-3.98 (m, 4H), 3.35-3.28 (m, 2H), 2.25-2.16 (m, 2H), 1.67-1.60 (m, 4H), 1.42-1.33 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 6H, $2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.95 (d, $J_{C\text{-}P}$ = 15.1 Hz), 137.89, 132.65 (q, $J_{1\ C\text{-}F}$ = 34.0 Hz, $J_{2\ C\text{-}F}$ = 67.8 Hz), 128.21, 126.63, 124.30, 121.59, 65.87 (d, $J_{C\text{-}P}$ = 6.1 Hz), 32.65 (d, $J_{C\text{-}P}$ = 5.7 Hz), 32.33, 20.32, 18.85, 13.64.

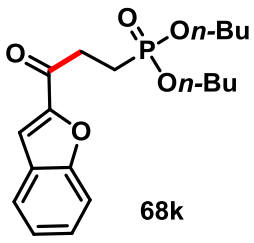
^{31}P NMR (162 MHz, $CDCl_3$) δ 30.70.

HRMS calculated $[M+Na]^+$ for $C_{19}H_{25}F_6O_4PNa$: 485.1287, found: 485.1274.

FTIR (cm^{-1}) 2963, 1703, 1278, 1237, 1176, 1136, 1111, 1065, 1024, 981, 900, 840, 700, 682.

Dibutyl (3-(benzofuran-2-yl)-3-oxopropyl)phosphonate (68k)

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and benzofuran-2-carbaldehyde **66k** (0.110 g, 90 µL, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded dibutyl (3-(benzofuran-2-yl)-3-oxopropyl)phosphonate **68k** as a yellowish oil (0.102 g, 56%).



68k

***R**f* (Pet. ether /EtOAc = 70/30): 0.29.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.7 Hz, 1H, H_{ar}), 7.59-7.55 (m, 2H, H_{ar}), 7.48 (t, *J* = 7.4 Hz, 1H, H_{ar}), 7.33-7.30 (m, 1H, H_{ar}), 4.09-4.01 (m, 4H), 3.31-3.25 (m, 2H), 2.25-2.17 (m, 2H), 1.66-1.63 (m, 4H), 1.42-1.37 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 6H, $2CH_3$).

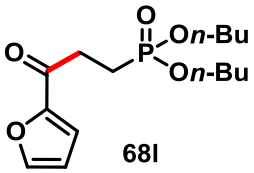
^{13}C NMR (100 MHz, $CDCl_3$) δ 188.83 (d, J_{C-P} = 15.9 Hz), 155.81, 152.11, 128.57, 127.08, 124.14, 123.50, 113.22, 112.61, 65.79 (d, J_{C-P} = 6.7 Hz), 32.68 (d, J_{C-P} = 6.1 Hz), 32.14, 19.44 (d, J_{C-P} = 145.5 Hz), 18.88, 13.73.

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.08.

HRMS calculated $[M+Na]^+$ for $C_{19}H_{27}O_5PNa$: 389.1488, found: 389.1478.

FTIR (cm^{-1}) 2961, 1685, 1558, 1240, 1066, 1025, 992, 752.

Dibutyl (3-(furan-2-yl)-3-oxopropyl)phosphonate (68l)



68l

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.110 g, 0.5 mmol) and furan-2-carbaldehyde **67l** (0.072 g, 62 µL, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded dibutyl (3-(furan-2-yl)-3-oxopropyl)phosphonate **68l** as a yellowish oil (0.095 g, 59%).

R_f (Pet. ether /EtOAc = 70/30): 0.30.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.58 (m, 1H, H_{ar}), 7.22- (d, J = 3.4 Hz, 1H, H_{ar}), 6.54-6.52 (m, 1H, H_{ar}), 4.09-3.96 (m, 4H), 3.16-3.10 (m, 2H), 2.19-2.12 (m, 2H), 1.67-1.61 (m, 4H), 1.43-1.34 (m, 4H), 0.92 (t, J = 7.4 Hz, 6H, $2CH_3$).

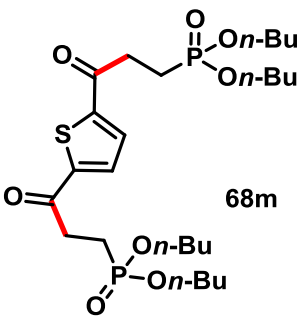
^{13}C NMR (100 MHz, $CDCl_3$) δ 186.83 (d, J_{C-P} = 16.3 Hz), 146.70, 117.48, 112.46, 65.71 (d, J_{C-P} = 6.5 Hz), 32.67 (d, J_{C-P} = 6.1 Hz), 31.55 (d, J_{C-P} = 3.1 Hz), 19.38 (d, J_{C-P} = 145.2 Hz), 18.86, 13.73.

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.23.

HRMS calculated $[M+Na]^+$ for $C_{15}H_{25}O_5PNa$: 339.1332, found: 339.1322.

FTIR (cm^{-1}) 2960, 2935, 2874, 1678, 1570, 1468, 1395, 1269, 1233, 1165, 1066, 1022, 979, 901, 884, 768.

Tetrabutyl (thiophene-2,5-diylbis(3-oxopropane-3,1-diyl))bis(phosphonate) (68m)



68m

Following the general procedure, treatment of dibutyl vinylphosphonate **67a** (0.275 g, 1.25 mmol) and thiophene-2,5-dicarbaldehyde **66m** (0.070 g, 0.50 mmol) with imidazolium salt **69** (0.068g, 0.40 mmol) and K_2CO_3 (0.056 g, 0.80 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded

tetrabutyl (thiophene-2,5-diylbis(3-oxopropane-3,1-diyl))bis(phosphonate) **68m** as a yellowish oil (0.131 g, 45%).

R_f (Pet. ether /EtOAc = 70/30): 0.20.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 2H, H_{ar}), 4.09-3.97 (m, 8H), 3.26-3.19 (m, 4H), 2.21-2.13 (m, 4H), 1.67-1.60 (m, 8H), 1.43-1.33 (m, 8H), 0.92 (t, J = 7.4 Hz, 12H, $4CH_3$).

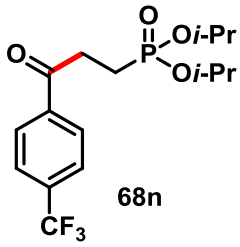
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.84 (d, J_{C-P} = 15.7 Hz), 148.34, 131.95, 65.85 (d, J_{C-P} = 6.6 Hz), 32.76, 32.64 (d, J_{C-P} = 6.1 Hz), 20.33, 18.86, 13.71.

^{31}P NMR (162 MHz, $CDCl_3$) δ 30.73.

HRMS calculated $[M+Na]^+$ for $C_{26}H_{46}SO_8P_2Na$: 603.2281, found: 603.2260.

FTIR (cm^{-1}) 2963, 2875, 1678, 1246, 1188, 1067, 1027, 985, 901, 852, 806.

Diisopropyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate (68n)



68n

Following the general procedure, treatment of diisopropyl vinylphosphonate **67b** (0.960 g, 0.5 mmol) and 4-(trifluoromethyl) benzaldehyde **66a** (0.131 g, 102 µL, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded diisopropyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate **68n** as a colourless oil (0.130 g, 71%).

R_f (Pet. ether /EtOAc = 70/30): 0.31.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.2 Hz, 2H, H_{ar}), 7.69 (d, J = 8.2 Hz, 2H, H_{ar}), 4.74-4.63 (m, 2H), 3.28-3.22 (m, 2H), 2.15-2.07 (m, 2H), 1.29 (d, J = 6.2 Hz, 12H, $4CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.81 (d, J_{C-P} = 16.4 Hz), 139.08, 134.66 (q, $J_{1\ C-F}$ = 32.7 Hz, $J_{2\ C-F}$ = 65.1 Hz), 128.47, 125.84, 125.81, 70.49 (d, J_{C-P} = 6.5 Hz), 32.42 (d, J_{C-P} = 2.4 Hz), 24.09 (d, J_{C-P} = 4.5 Hz), 21.12 (d, J_{C-P} = 145.6 Hz).

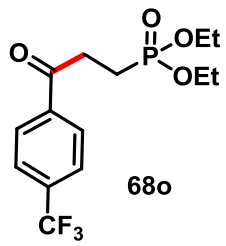
^{31}P NMR (162 MHz, $CDCl_3$) δ 29.03.

HRMS calculated $[M+Na]^+$ for $C_{16}H_{22}F_3O_4PNa$: 389.1100, found: 389.1089.

FTIR (cm^{-1}) 2983, 2936, 1696, 1461, 1413, 1383, 1327, 1232, 1172, 1133, 1067, 987, 844, 780.

Diethyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate (68o)

Following the general procedure, treatment of diethyl vinylphosphonate **67c** (0.082 g, 0.5 mmol) and 4-(trifluoromethyl)benzaldehyde **66a** (0.131 g, 102 µL, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h



68o

followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded Diethyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate **68o** as a yellowish oil (0.117 g, 70%).

R_f (Pet. ether /EtOAc = 70/30): 0.30.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H, H_{ar}), 7.67 (d, *J* = 8.0 Hz, 2H, H_{ar}), 4.12-4.05 (m, 4H), 3.30-3.22 (m, 2H), 2.19-2.11 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 6H, $2CH_3$).

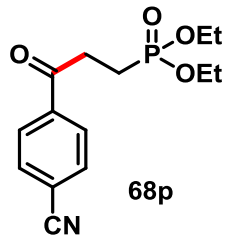
^{13}C NMR (100 MHz, $CDCl_3$) δ 196.56 (d, J_{C-P} = 15.5 Hz), 138.97, 134.64 (q, J_{1C-F} = 33.1 Hz, J_{2C-F} = 64.9 Hz), 130.18, 128.44, 125.78 (d, J_{C-P} = 3.6 Hz), 61.94(d, J_{C-P} = 6.4 Hz), 32.15 (d, J_{C-P} = 2.6 Hz),19.65 (d, J_{C-P} = 145.2Hz), 16.42 (d, J_{C-P} = 5.9 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.29.

HRMS calculated $[M+Na]^+$ for $C_{14}H_{18}F_3O_4PNa$: 361.0787, found: 361.0777.

FTIR (cm^{-1}) 2987, 1697, 1447, 1412, 1327, 1248, 1170, 1132, 1063, 1027, 973, 845, 795, 671.

Diethyl (3-(4-cyanophenyl)-3-oxopropyl)phosphonate (68p)



68p

Following the general procedure, treatment of diethyl vinylphosphonate **67c** (0.082 g, 0.5 mmol) and 4-formylbenzonitrile **66d** (0.100 g, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded Diethyl (3-(4-cyanophenyl)-3-oxopropyl)phosphonate **68p** as a yellowish oil (0.089 g, 60%).

R_f (Pet. ether /EtOAc = 70/30): 0.32.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 2H, H_{ar}), 7.76 (d, *J* = 8.3 Hz, 2H, H_{ar}), 4.15-4.06 (m, 4H), 3.31-3.25 (m, 2H), 2.21-2.13 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 6H, $2CH_3$).

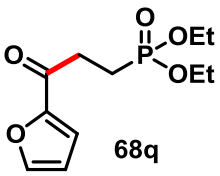
^{13}C NMR (100 MHz, $CDCl_3$) δ 196.32 (d, J_{C-P} = 15.9 Hz), 139.28, 132.70, 128.59, 117.90, 116.77, 62.01 (d, J_{C-P} = 6.6 Hz), 32.31 (d, J_{C-P} = 2.7 Hz), 19.70 (d, J_{C-P} = 145.5 Hz), 16.52 (d, J_{C-P} = 6.0 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.05.

HRMS calculated $[M+Na]^+$ for $C_{14}H_{18}O_4NPNa$: 318.0866, found: 318.0858.

FTIR (cm^{-1}) 2985, 2916, 2231, 1694, 1405, 1230, 1027, 970, 844, 795, 672.

Diethyl (3-(furan-2-yl)-3-oxopropyl)phosphonate (68q)



68q

Following the general procedure, treatment of diethyl vinylphosphonate **67c** (0.082 g, 0.5 mmol) and furan-2-carbaldehyde **66l** (0.072 g, 62 µL, 0.75 mmol) with imidazolium salt **69** (0.034 g, 0.10 mmol) and K_2CO_3 (0.028 g, 0.20 mmol) in THF (3.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded Diethyl (3-(furan-2-yl)-3-oxopropyl)phosphonate **68q** as a yellowish oil (0.069 g, 53%).

***R**f* (Pet. ether /EtOAc = 70/30): 0.30.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.58 (m, 1H, H_{ar}), 7.23-7.21 (m, 1H, H_{ar}), 6.55-6.52 (m, 1H, H_{ar}), 4.18-4.03 (m, 4H), 3.20-3.07 (m, 2H), 2.23-2.06 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 6H, $2CH_3$).

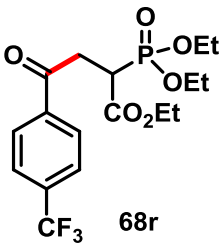
^{13}C NMR (100 MHz, $CDCl_3$) δ 186.79 (d, $J_{C\text{-}P}$ = 16.2 Hz), 152.25, 146.70, 117.50, 112.46, 61.99(d, $J_{C\text{-}P}$ = 6.5 Hz), 31.51, 19.50 (d, $J_{C\text{-}P}$ = 144.8 Hz), 16.52 (d, $J_{C\text{-}P}$ = 5.9 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 31.35.

HRMS calculated $[M+Na]^+$ for $C_{11}H_{17}O_5PNa$: 283.0706, found: 283.0699.

FTIR (cm^{-1}) 2959, 2938, 2144, 1677, 1639, 1468, 1230, 1024, 679.

Ethyl 2-(diethoxyphosphoryl)-4-oxo-4-(4-(trifluoromethyl)phenyl)butanoate (68r)



68r

Following the general procedure, treatment of ethyl 2-(diethoxyphosphoryl) acrylate **67d** (0.118 g, 0.5 mmol) and 4-(trifluoromethyl) benzaldehyde **66a** (0.131 g, 102 µL, 0.75 mmol) with thiazolium salt **63** (0.038 g, 0.10 mmol) and KO*t*-Bu (0.022 g, 0.20 mmol) in THF (2.0 mL) at 70 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded ethyl 2-(diethoxyphosphoryl)-4-oxo-4-(4-(trifluoromethyl) phenyl)butanoate **68r** as a yellow oil (0.135 g, 66%). *Product **3r** contained small amounts of an impurity.*

***R**f* (Pet. ether /EtOAc = 70/30): 0.28.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2H, H_{ar}), 7.72 (d, *J* = 8.4 Hz, 2H), 4.27-4.13 (m, 6H, $3CH_2$), 3.86-3.77 (m, 1H), 3.71-3.61 (m, 1H), 3.46-3.39 (m, 1H), 1.37-1.26 (m, 9H, $3CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.81 (d, $J_{C\text{-}P}$ = 15.6 Hz), 168.35 (d, $J_{C\text{-}P}$ = 5.6 Hz), 138.77, 134.85 (q, $J_{1\ C\text{-}F}$ = 32.6 Hz, $J_{2\ C\text{-}F}$ = 65.4 Hz), 128.61, 128.35, 125.89-125.79 (m), 124.96-124.85

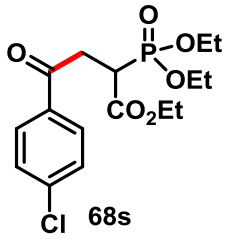
(m), 63.17 (d, J_{C-P} = 7.1 Hz), 61.91, 40.30 (d, J_{C-P} = 131.8 Hz), 36.38, 29.76, 16.41 (t, J_{C-P} = 5.4 Hz), 14.13.

^{31}P NMR (162 MHz, $CDCl_3$) δ 23.77.

HRMS calculated $[M+Na]^+$ for $C_{17}H_{22}F_3O_6PNa$: 433.0998, found: 433.0996.

FTIR (cm^{-1}) 2986, 2933, 1725, 1639, 1447, 1410, 1372, 1324, 1246, 1167, 1126, 1062, 1021, 971, 845, 755, 685.

Ethyl 4-(4-chlorophenyl)-2-(diethoxyphosphoryl)-4-oxobutanoate (68s)



68s

Following the general procedure, treatment of ethyl 2-(diethoxyphosphoryl)acrylate **67d** (0.118 g, 0.5 mmol) and 4-chlorobenzaldehyde **66e** (0.105 g, 0.75 mmol) with thiazolium salt **63** (0.038 g, 0.10 mmol) and KO*t*-Bu (0.022 g, 0.20 mmol) in THF (2.0 mL) at 70 °C for 20 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded ethyl 4-(4-chlorophenyl)-2-(diethoxyphosphoryl)-4-oxobutanoate **68s** as a colorless oil (0.147 g, 78%).

R_f (Pet. ether /EtOAc = 70/30): 0.31.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.88 (m, 2H, H_{ar}), 7.45-7.40 (m, 2H), 4.26-4.09 (m, 6H, $3CH_2$), 3.86-3.54 (m, 2H), 3.45-3.31 (m, 1H), 1.38-1.23 (m, 9H, $3CH_3$).

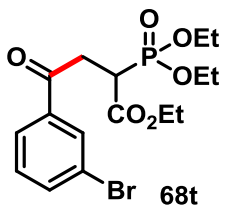
^{13}C NMR (100 MHz, $CDCl_3$) δ 195.45 (d, J_{C-P} = 16.6 Hz), 166.44 (d, J_{C-P} = 5.3 Hz), 140.08, 134.42, 129.66, 129.08, 63.12 (d, J_{C-P} = 6.4 Hz), 61.85, 40.29 (d, J_{C-P} = 132.2 Hz), 36.04 (d, J_{C-P} = 6.1 Hz), 16.42 (t, J_{C-P} = 5.9 Hz), 14.13.

^{31}P NMR (162 MHz, $CDCl_3$) δ 22.52.

HRMS calculated $[M+Na]^+$ for $C_{16}H_{22}ClO_6PNa$: 399.0735, found: 399.0726.

FTIR (cm^{-1}) 2984, 1732, 1688, 1590, 1398, 1366, 1319, 1246, 1224, 1160, 1091, 1022, 982, 825, 793.

Ethyl 4-(3-bromophenyl)-2-(diethoxyphosphoryl)-4-oxobutanoate (68t)



68t

Following the general procedure, treatment of ethyl 2-(diethoxyphosphoryl)acrylate **67d** (0.118 g, 0.5 mmol) and 3-bromobenzaldehyde **66h** (0.139 g, 87 µL, 0.75 mmol) with thiazolium salt **63** (0.038 g, 0.10 mmol) and KO*t*-Bu (0.022 g, 0.20 mmol) in THF (2.0 mL) at 70 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded ethyl 4-(3-bromophenyl)-2-(diethoxyphosphoryl)-4-

oxobutanoate **68t** as a colourless oil (0.105 g, 51%).

R_f (Pet. ether /EtOAc = 70/30): 0.35.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (t, *J* = 1.6 Hz, 1H, H_{ar}), 7.89 (d, *J* = 7.9 Hz, 1H, H_{ar}), 7.68 (d, *J* = 8.8 Hz, 1H, H_{ar}), 7.34 (t, *J* = 7.9 Hz, 1H, H_{ar}), 4.24-4.14 (m, 6H, $3CH_2$), 3.81-3.72 (m, 1H), 3.68-3.59 (m, 1H), 3.41-3.34 (m, 1H), 1.37-1.25 (m, 9H, $3CH_3$).

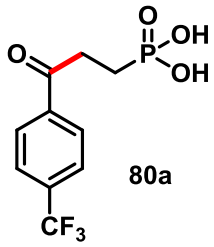
^{13}C NMR (100 MHz, $CDCl_3$) δ 195.38 (d, J_{C-P} = 15.7 Hz), 168.39 (d, J_{C-P} = 5.5 Hz), 137.82, 136.46, 131.30, 130.38, 126.79, 123.13, 63.14 (d, J_{C-P} = 6.7 Hz), 61.89, 40.95, 39.64, 36.19, 16.45 (t, J_{C-P} = 5.3 Hz), 14.16.

^{31}P NMR (162 MHz, $CDCl_3$) δ 22.38.

HRMS calculated $[M+Na]^+$ for $C_{16}H_{22}BrO_6PNa$: 443.0230, found: 443.0220.

FTIR (cm^{-1}) 2960, 1730, 1689, 1634, 735, 670.

(3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonic acid (80a)



80a

To a flame dried screw cap test tube was charged with dibutyl (3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)phosphonate **68a** (0.197 g, 0.50 mmol) and dissolved with dichloromethane (3.0 mL) in argon atmosphere, followed by addition of bromotrimethylsilane (0.153 g, 132 µL, 1.0 mmol) and continued stirring at 30 °C for 12 h. After consumption of total starting materials (followed by TLC), solvent was evaporated and MeOH (2.5 mL) and water mixture (0.20 mL) were added and continued stirring for 1 h. Further evaporation of the solvent followed by crystallization (Pet.ether:DCM) to get the (3-oxo-3-(4-(trifluoromethyl)phenyl) propyl)phosphonic acid as white solid **80a** (100 mg, yield 71%)

R_f (Pet. ether /EtOAc = 70/30): 0.15.

^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, *J* = 8.1 Hz, 2H, H_{ar}), 7.81 (d, *J* = 8.1 Hz, 2H, H_{ar}), 3.39-3.34 (m, 2H), 2.17-2.08 (m, 2H).

^{13}C NMR (100 MHz, CD_3OD) δ 198.84 (d, J_{C-P} = 15.6 Hz), 141.00, 135.45 (q, $J_{1\ C-F}$ = 31.7 Hz, $J_{2\ C-F}$ = 64.6 Hz), 129.88, 126.92 (d, J_{C-P} = 3.6 Hz), 123.99, 33.60, 22.30 (d, J_{C-P} = 142.5 Hz).

^{31}P NMR (162 MHz, CD_3OD) δ 29.03.

HRMS calculated $[M+Na]^+$ for $C_{10}H_{10}F_3O_4PNa$: 305.0161, found: 305.0153.

FTIR (cm^{-1}) 3352, 2970, 1689, 1330, 1170, 1132, 1068, 986.

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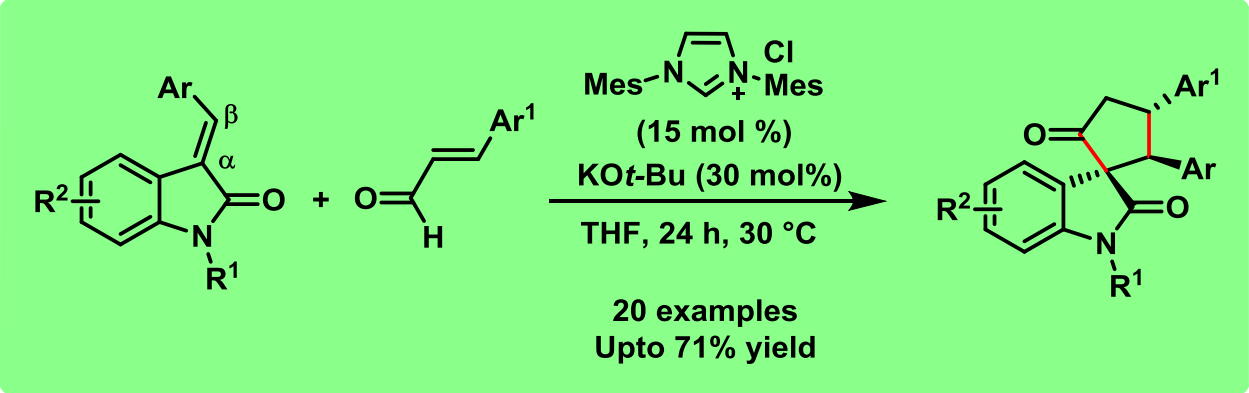
51. (a) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523. (b) Cooke, J.; Lightbody, O. C. *J. Chem. Educ.* **2009**, *86*, 610.

52. (a) Piel, I.; Pawelczyk, M. D.; Hirano, K.; Fröhlich, R.; Glorius, F. *Eur. J. Org. Chem.* **2011**, 5475. (b) Lebeuf, R.; Hirano, K.; Glorius, F. *Org. Lett.* **2008**, *10*, 4243.

Chapter 3

NHC-Catalyzed Annulation of Enals and Isatilidenes

In this chapter, an NHC-organocatalyzed homoenolate annulation of enals with isatilidenes is demonstrated. The reaction afforded cyclopentanone-fused spirooxindoles bearing an all-carbon quaternary spiro-center in moderate to good yields and with high diatereoselectivity. The reaction is compatible with wide variety of enals as well as isatilidenes. Additionally, we have carried out functionalization of the spirooxindoles as well as the initial studies on the enantioselective version of this reaction.

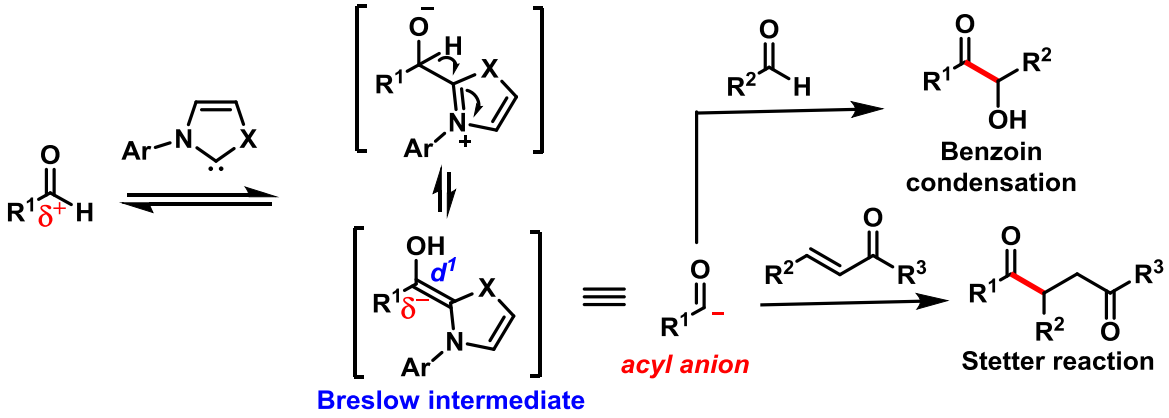


Org. Chem. Front. **2015**, *2*, 1584-1588

3.1. Introduction

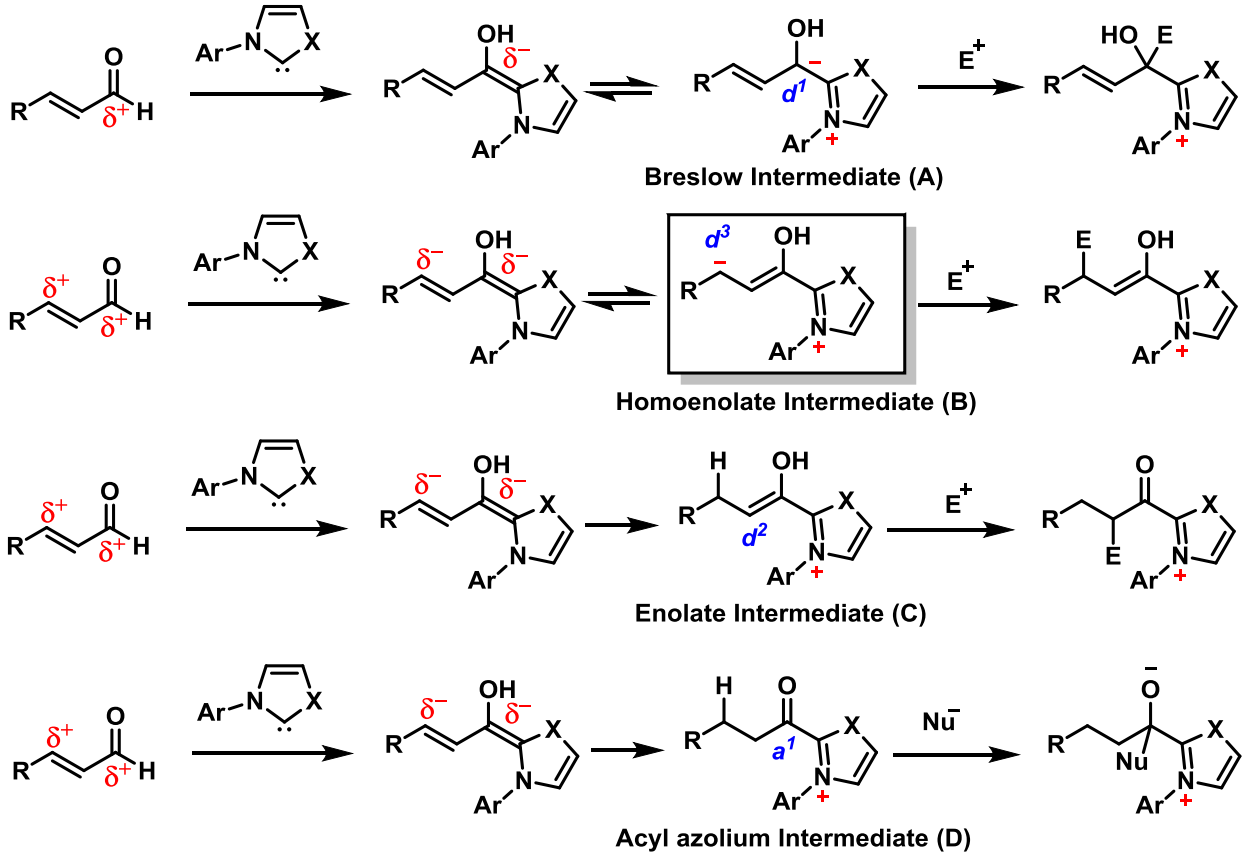
In recent years, N-heteocyclic carbene (NHC)–organocatalysis have attracted considerable interest, which arise due to their new catalytic bond forming abilities that enhances the efficiency and offers a broad range of unconventional transformations. The chemistry of NHC has witnessed rapid development 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 another molecule 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, 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

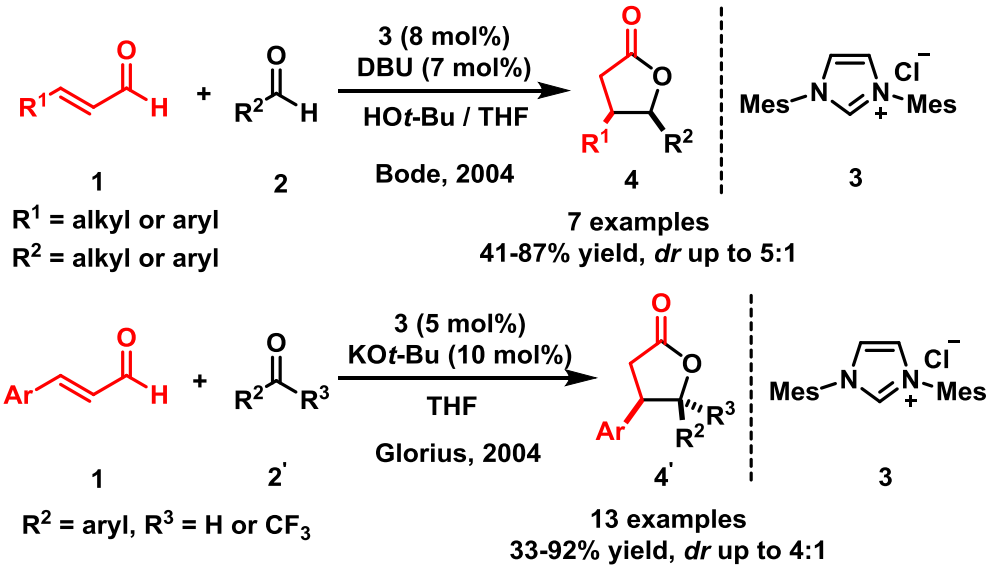


The focal theme of this chapter is the NHC-catalyzed annulation of enals with isatilidenes. The reaction afforded cyclopentanone-fused spirooxindoles bearing an all-carbon quaternary spiro-center in moderate to good yields and generally with high diastereoselectivity. Before discussing the results, a brief overview of the recent developments on the NHC-catalyzed construction of several carbocycles, heterocycles, and even spiroheterocycles using homoenolate concept are presented in the following section.

3.2. NHC-Catalyzed Construction of Carbocycles, Heterocycles, and Spiroheterocycles using Homoenolate Concept

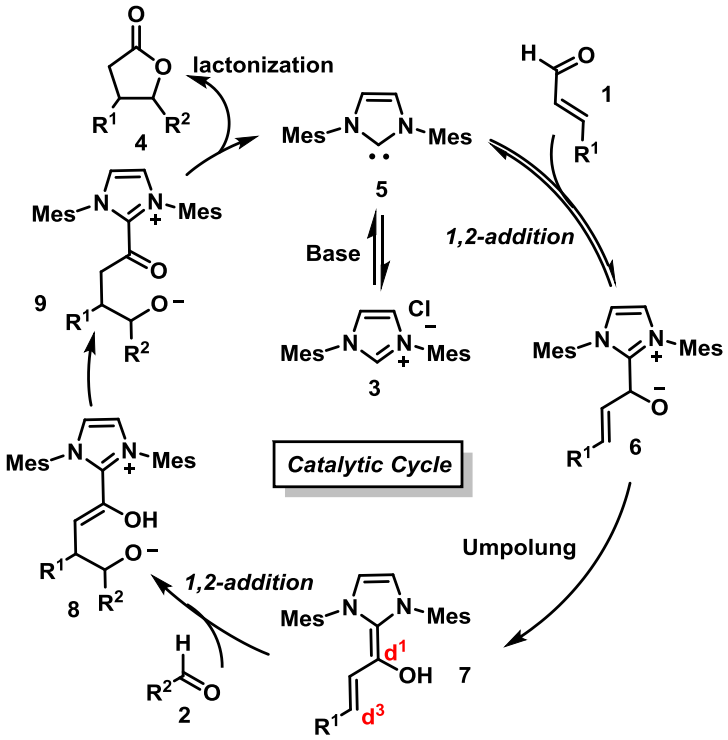
In 2004, the Glorius group[4] and the Bode group[5] independently developed NHC (generated from bismesityl imidazolium precatalyst **3)**-catalyzed generation of homoenolate equivalents from α,β-unsaturated aldehydes followed by the formal [3+2] annulation with aldehydes leading to γ-butyrolactones **4** in good yields and good diastereoselectivity (Scheme 3.3). An enantioselective transformation using trifluoromethyl ketones as electrophile was demonstrated by Glorius and co-workers.

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–Butyrolactone 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 (Fig. 3.1). 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.

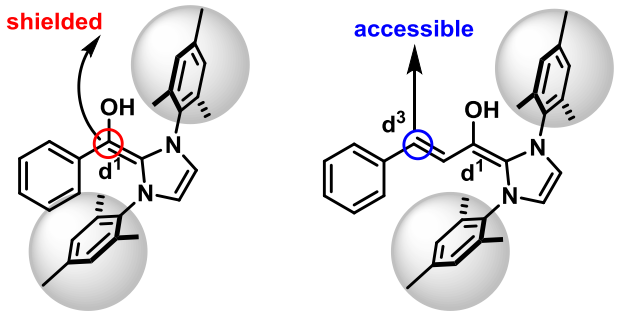
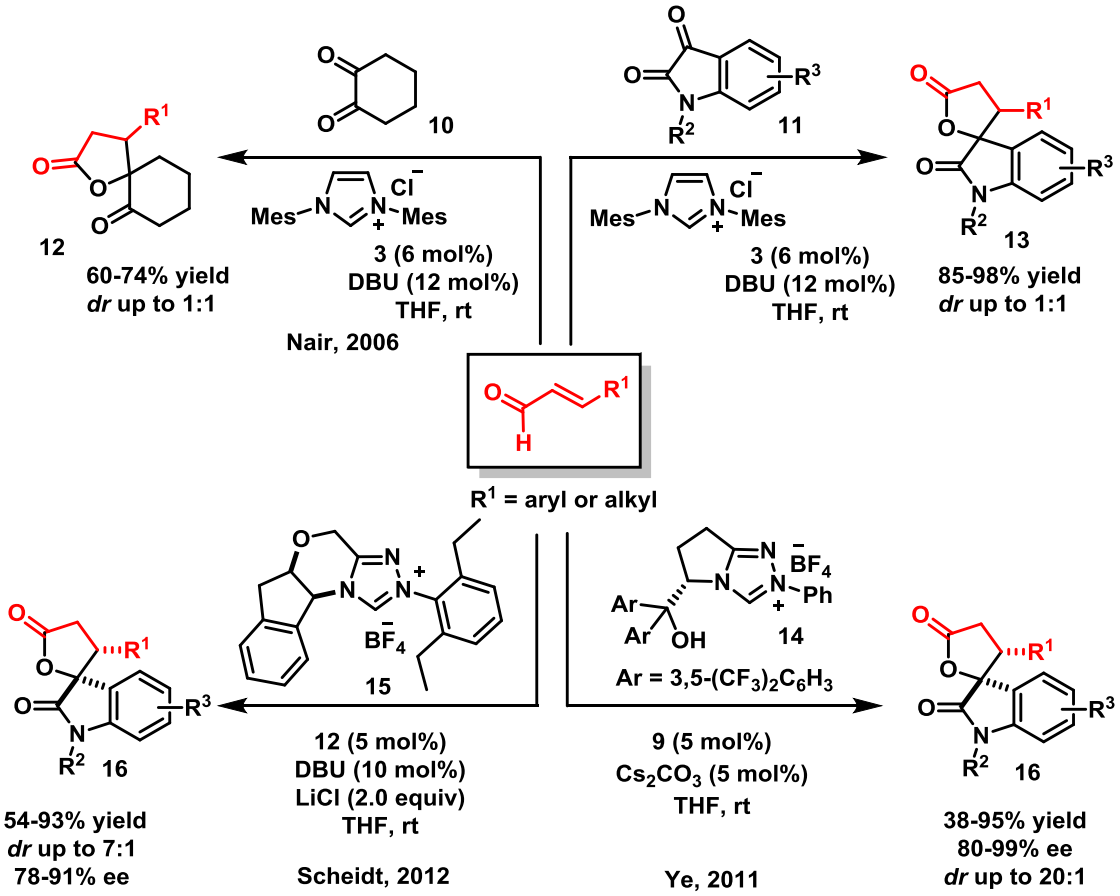


Fig. 3.1: Bulkiness or Electron Richness Demotes the Reactivity

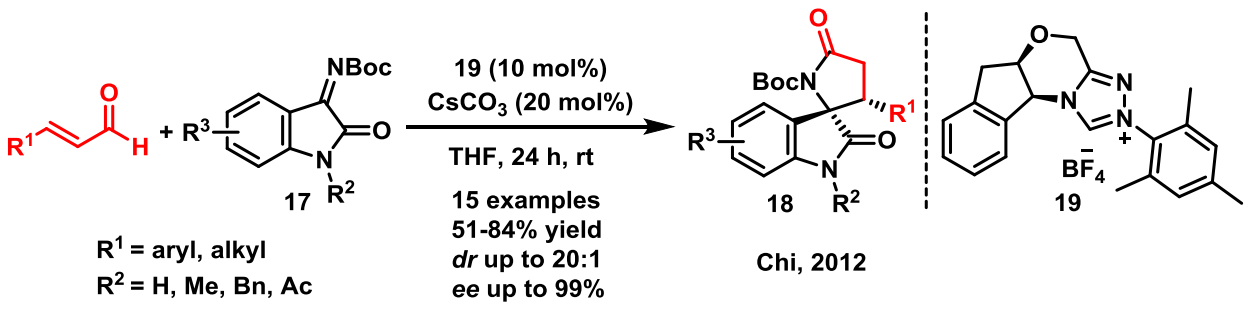
Scheme 3.5: NHC-Catalyzed Homoenolate Annulation of Enals and Activated Ketones



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 triazolium 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]

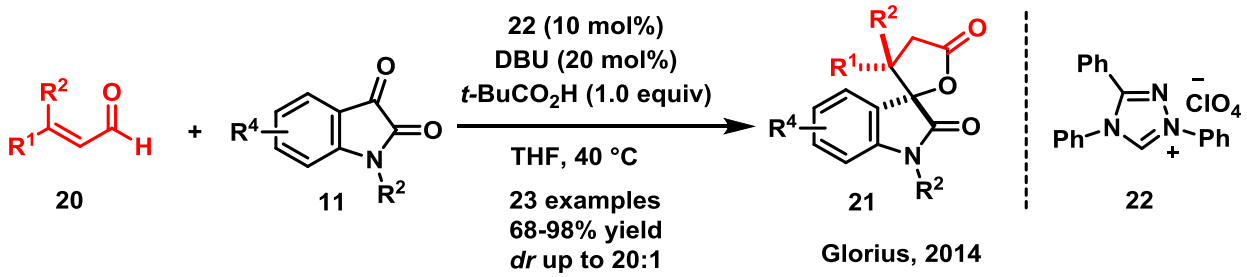
In 2012, Chi and co-workers developed NHC-catalyzed annulation reaction of isatin N-Boc ketimines **17** and enals for the synthesis of spirocyclic oxindole-γ-lactams bearing one quaternary chiral center in good yields and excellent stereoselectivities (Scheme 3.6).[10] Chiral amino indanol derived mesityl triazolium salt **19** was found to be best precatalyst for this transformation.

Scheme 3.6: NHC-Catalyzed Homoenolate Annulation of Enals and Isatin N-Boc Ketimines



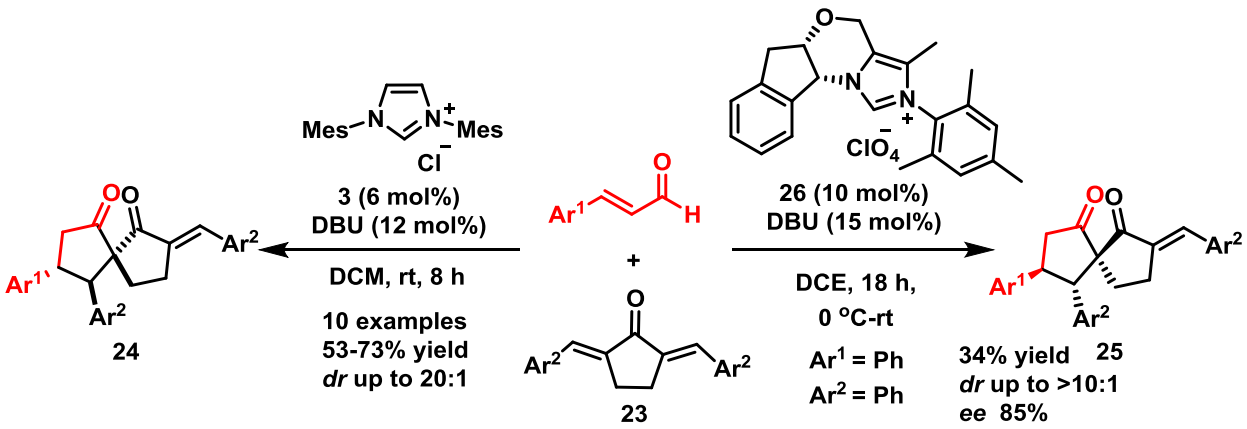
Recently, Glorius and co-workers studied the annulation of isatins with sterically hindered β,β-disubstituted enals **20** in a dual catalytic (NHC/ Brønsted acid) process (Scheme 3.7).[11] Notably, the use of Brønsted acid has substantially increased the yield as well as the diastereoselectivity. The reaction tolerates a broad range of aryl and aliphatic substituted enals.

Scheme 3.7: NHC-Catalyzed Annulation of β,β-Disubstituted Enals with Isatins



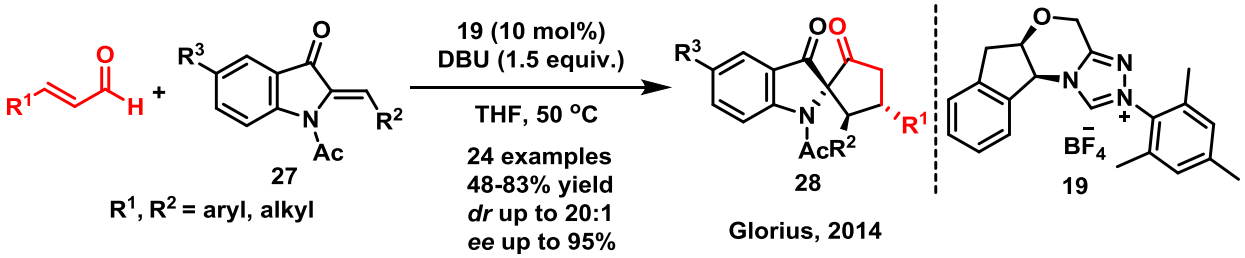
In 2008, Nair and co-workers demonstrated a formal [3+2] annulation route to spirocyclopentanones **24** by the NHC-catalyzed reaction of enals with cyclic dienones in moderate to good yields with single diastereomer (Scheme 3.8).[12] An enantioselective version of this reaction was achieved by Bode and co-workers using chiral imidazolium precatalyst **26.**[13]

Scheme 3.8: NHC-Catalyzed Annulation of Enals with Cyclic Dienones



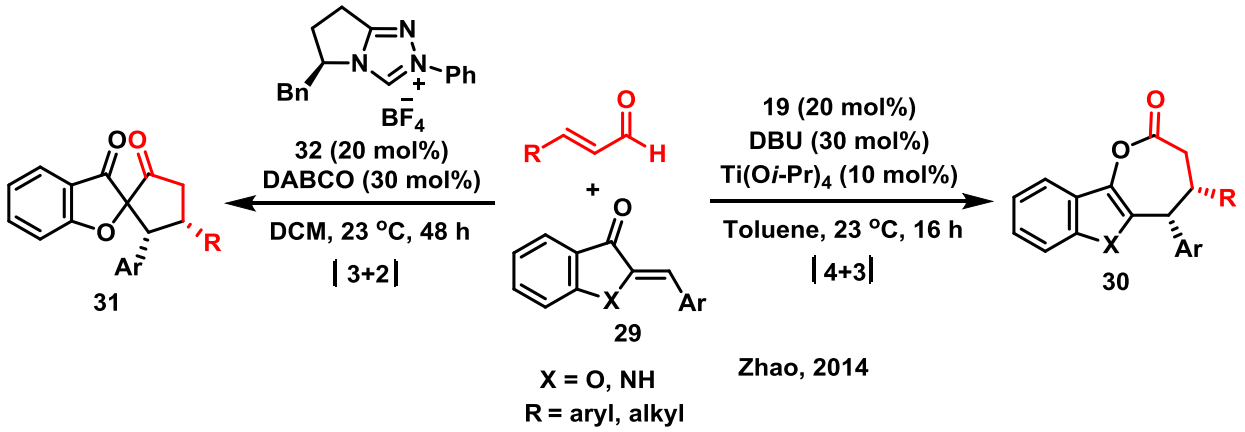
Later, Glorius and co-workers developed an asymmetric, NHC-catalyzed formal [3+2] annulation of α,β-unsaturated aldehydes with azaaurones **27** (Scheme 3.9).[14] This approach formed spiroheterocyclic derivatives bearing a quaternary stereogenic center in moderate to good yields with excellent enantioselectivity. The reaction proceeded probably through the conjugate addition of an NHC–homoenolate to the azaaurone, followed by C-acylation to regenerate the NHC catalyst and provide the spiroheterocyclic product **28**. This structural unit is difficult to prepare by traditional strategies.

Scheme 3.9: NHC-Catalyzed Annulation of Enals with Azaaurones



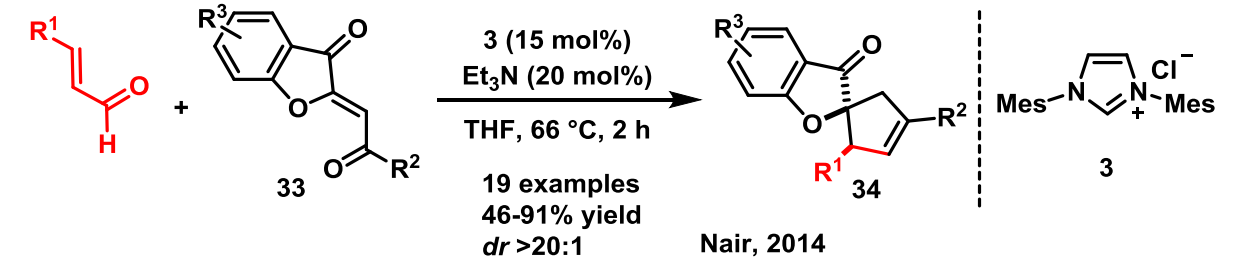
In the same year, Zhao and co-workers reported NHC-catalyzed divergent annulation of enals with heterocyclic enones to produce benzofuran/indole-containing e-lactones **30** or spiro-heterocycles **31** in a highly diastereo- and enantioselective fashion (Scheme 3.10).[15] The chemo-selectivity controlled by the chiral catalyst backbone was particularly noteworthy.

Scheme 3.10: NHC-Catalyzed Divergent Annulation of Enals with Heterocyclic Enones



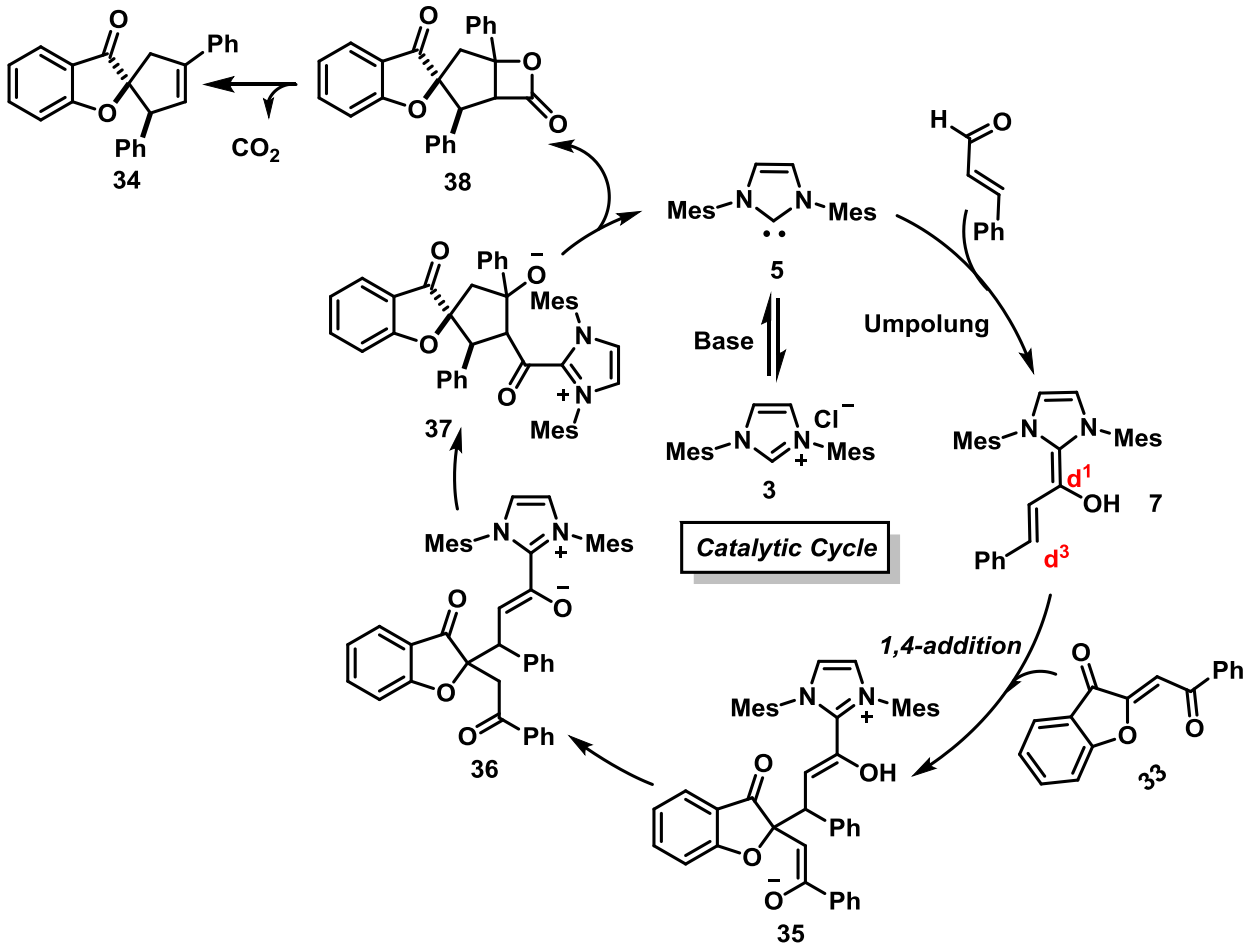
Recently, Nair and co-workers reported the homoenolate annulation of enals with 2-aroylidene benzofuran-ones **33** (Scheme 3.11).[16] The reaction afforded highly diastereoselective cyclopentene-fused spirobenzofuran-3-ones **34** with moderate to excellent yields. The formation of cyclopentene-fused spirobenzofuran-3-one in higher yield was facilitated by the combination of imidazolium carbene precursor **3** and Et_3N in THF as the solvent under reflux conditions.

Scheme 3.11: NHC-Catalyzed Annulation of Enals with Aurone Analogs



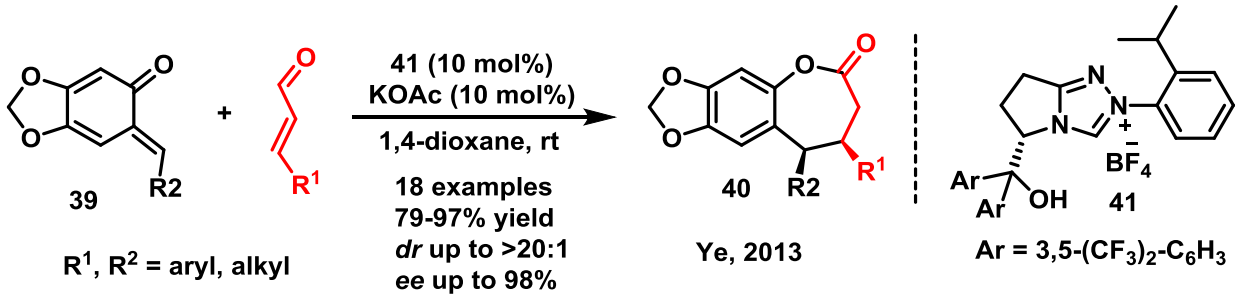
A plausible mechanism is presented in Scheme 3.12. The 1,2–addition of NHC to *trans*-cinnamaldehyde gives rise to the extended Breslow intermediate **7**, which undergoes the 1,4-addition to the 2-benzoylidene benzofuran-3-one to produce the enolate **35** and consequent to a proton transfer generates the enolate **36**, which then undergoes an intramolecular aldol reaction followed by β-lactonization generates **38**. The β-lactone **38** releases a molecule of CO_2 to form the cyclopentene-fused spirobenzofuran-3-one **34**.

Scheme 3.12: Proposed Mechanism for Cyclopentenes Formation



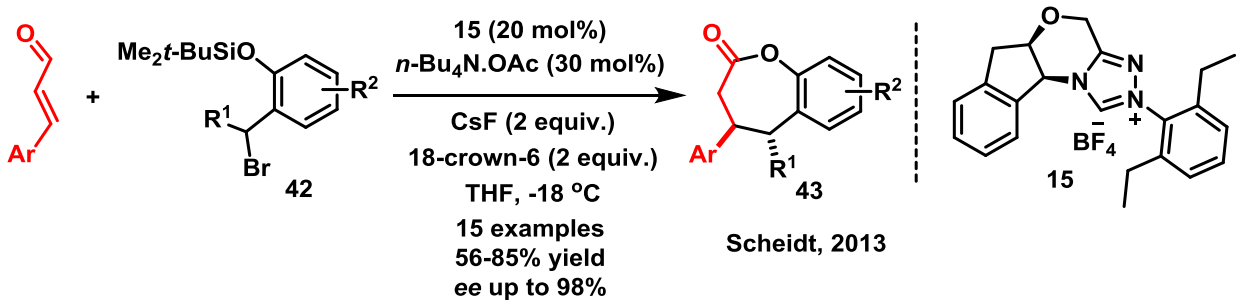
Ye and co-workers established an unprecedented NHC-catalyzed [4+3] annulation of enals with *o*-quinone methides **39** (Scheme 3.13).[17] This approach provided benzo-ε-lactones **40** in high yields with moderate (for β-aryl enals) to excellent (for β-alkyl enals) diastereoselectivties. High to excellent enantioselectivities (81–98% ee) were achieved by using a chiral triazolium NHC precursor **41** with a free hydroxy group.

Scheme 3.13: NHC-Catalyzed Annulation of Enals with *o*-Quinone Methides



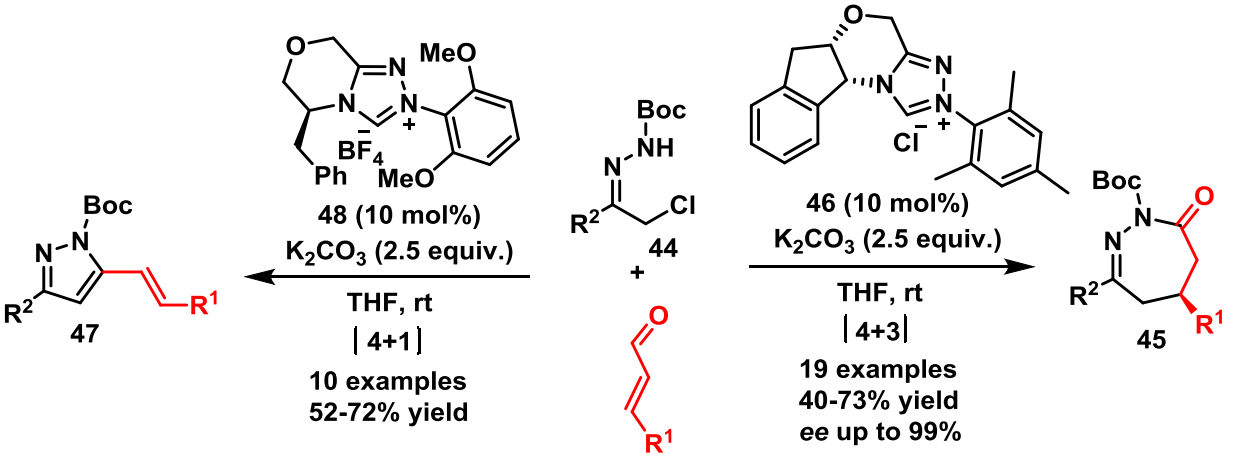
Scheidt and co-workers reported a dual activation strategy integrating N-heterocyclic carbene (NHC) catalysis and a second Lewis base. NHC-bound homoenolate equivalents derived from α,β-unsaturated aldehydes combine with transient reactive o-quinone methides provided 2-benzoxopinones in an enantioselective formal [4 + 3] fashion with moderate to good yield and excellent enantioselectivity(Scheme 3.14).[18]

Scheme 3.14: NHC-Catalyzed Annulation of Enals with Transient *o*-Quinone Methides



In 2014, Glorius and co-workers developed a regio- and enantioselective formal [4 + 3] annulation reaction between enals and in situ formed azoalkenes leads to form a diverse set of 1,2-diazepine derivatives **45** in good yields with excellent enantioselectivities. Furthermore, a

Scheme 3.15: NHC-Catalyzed Annulation of Enals with Transient Azoalkenes

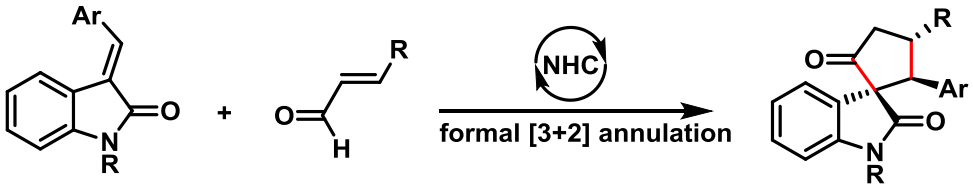


switch in NHC catalyst also allowed a controlled formal [4 + 1] reaction pathway, generating synthetically useful pyrazoles **47**.

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. NHC-catalyzed formation of spiro-heterocycles are studied by various groups, however 3-position cyclopentanone fused spiro-heterocycle of isatin derivatives are not explored. Hence, these spirooxindoles are associated with interesting biological properties and this core structure can be found in various natural products and medicinally relevant molecules.[20] We envisaged that if the reaction is carried out using N-substituted isatilidenes, it can lead to form cyclopentanone-fused spirooxindole derivatives (Scheme 3.16).

Scheme 3.16: Proposed Methodology



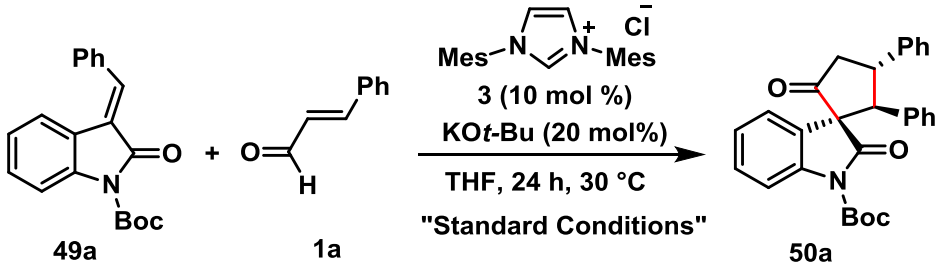
A detailed study of the intermolecular homoenolate reaction of enals with N-substituted isatilidenes is carried out and the details are presented in this chapter.[21] This investigation revealed for the synthesis of cyclopentanone-fused spirooxindole derivatives in moderate to good yield with an excellent level of diastereoselectivity. Moreover, functionalization of the spirooxindoles as well as the initial studies on the enantioselective version of this reaction are reported.

3.4. Results and Discussion

3.4.1. Optimization Studies

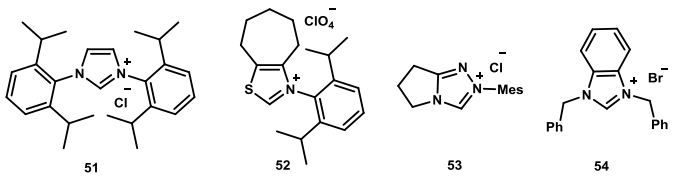
Our optimization study commenced with treatment of *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** with *trans* cinnamaldehyde **1a**. Treatment of **49a** with **1a** in the presence of the carbene generated from **3** by deprotonation using KO*t*-Bu resulted in the formation of cyclopentanone-fused spirooxindoles derivative **50a** in 51% yield (isolated yield). Notably, in contrast to this NHC, other common NHCs derived from precursors **51-54** are less effective (entries 2-4). NHC derived from precursor **54** resulted with increasing reactivity but *dr*

Table 3.1: Optimization of the Reaction Conditions[a]



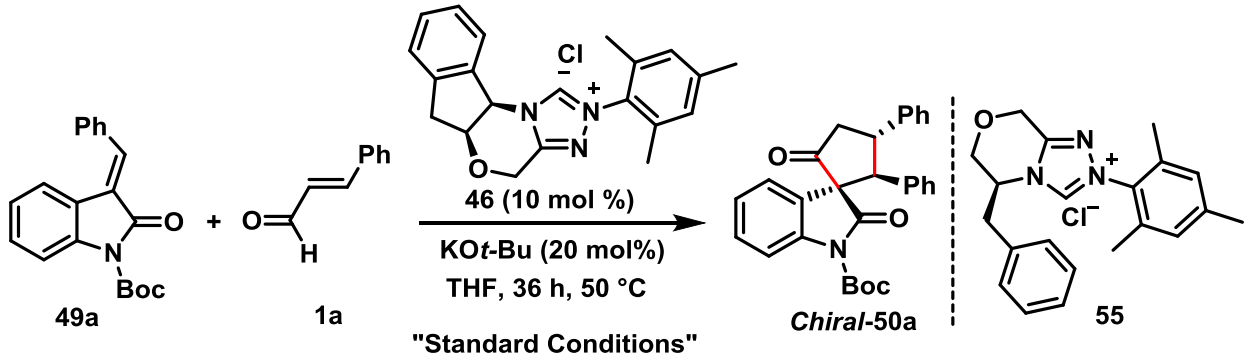
entry	variation of the standard conditions[a]	yield of **50a** (%)[b,c]
1	none	51
2	**51** instead of **3**	<5
3	**52** instead of **3**	21
4	**53** instead of **3**	<5
5	**54** instead of **3**	59[d]
6	50 °C instead of 30 °C	41
7	DBU instead of KO*t*-Bu	29
8	K_2CO_3 instead of KO*t*-Bu	23
9	Et_3N instead of KO*t*-Bu	<5
10	Cs_2CO_3 instead of KO*t*-Bu	<5
11	KOAc instead of KO*t*-Bu	<5
12	DMAP instead of KO*t*-Bu	<5
13	K_3PO_4 instead of KO*t*-Bu	<5
14	DME instead of THF	<5
15	1,4-dioxane instead of THF	11
16	CH_2Cl_2 instead of THF	<5
17	toluene instead of THF	26
18	15 mol % of **3** and 30 mol % of KO*t*-Bu	59
19	15 mol % of **3**, 30 mol % of KO*t*-Bu and 1.5 equiv of **1a**	71
20	AcOH as a additive	54
21	Benzoic acid as a additive	48
22	LiCl as a additive	62
23	LiO*t*-Bu as a additive	51

[a] Standard conditions: **49a** (0.25 mmol), **1a** (0.25 mmol), **3** (10 mol %), KO*t*-Bu (20 mol %), THF (1.0 mL), 30 °C and 40 h. [b] Isolated yield of the product. [c] The diastereoselectivity observed by ^{1}H NMR of crude products was >20:1 unless indicated. [d] The dr of 3:1 was observed.



decreased (entry 5). With increase in temperature to 50 °C instead of 30 °C reactivity decreases, resulted 41% yield (entry 6). Other bases such as DBU, K_2CO_3, NEt_3, Cs_2CO_3, KOAc, DMAP, and K_3PO_4 furnished the desired product in reduced yields (Table 1, entries 7-13). Among the various solvents screened, DME, 1,4-dioxane, DCM, and Toluene resulted in very less reactivity (entries 14-17). Gratifyingly, when the reaction was performed using 15 mol % of **3** and 30 mol % of KO*t*-Bu, the yield of **50a** was improved to 59% maintaining the excellent diastereoselectivity (entry 18). Interestingly, use of 1.5 equiv of enal **1a** afforded **50a** in 71% yield and >20:1 diastereoselectivity (entry 19). Additionally, use of Lewis acids and Brønstead acids to improve the yield of **50a** were unsuccessful (entries 20-23).

3.4.2. Optimization Studies for the Enantioselective Synthesis of Cyclopentanone-Fused Spirooxindole (*chiral*-50a)

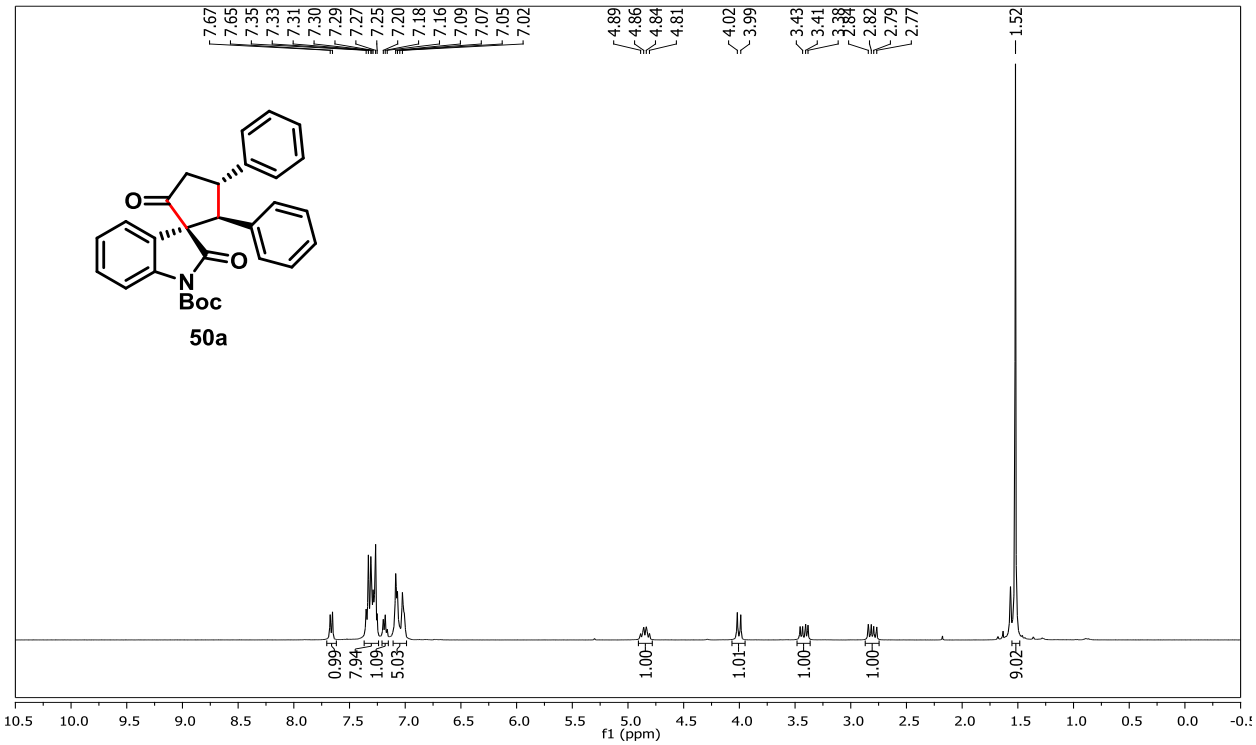


entry	variation of standard conditions[a]	yield of ***Chiral* 50a** (%)[b]	ee of ***Chiral* 50a** (%)[c,d]
1	none	22	97
2	**55** instead of **46**	<5	N.D.
3	DBU instead of KO*t*-Bu	<5	N.D.
4	DABCO instead of KO*t*-Bu	<5	N.D.
5	Et_3N instead of KO*t*-Bu	<5	N.D.
6	DMAP instead of KO*t*-Bu	<5	N.D.
7	K_2CO_3 instead of KO*t*-Bu	<5	N.D.
8	Cs_2CO_3 instead of KO*t*-Bu	<5	N.D.

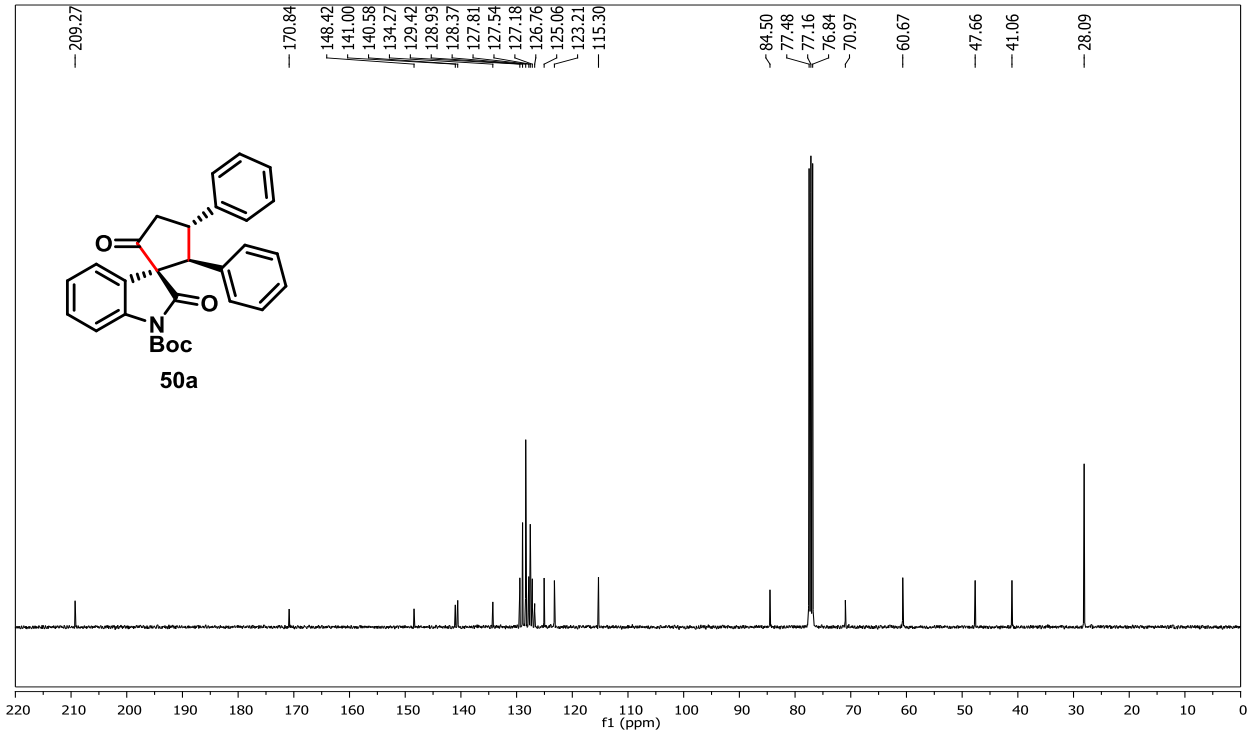
[a] Standard conditions: **49a** (0.25 mmol), **1a** (0.38 mmol), **46** (10 mol %), KO*t*-Bu (20 mol %), THF (1.0 mL), 50 °C and 36 h. [b] The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard. [c] Determined by HPLC analysis on a chiral column. [d] dr > 20:1

3.4.3. Spectral Data of 50a

^{1}H NMR Spectrum of 50a ($CDCl_3$)



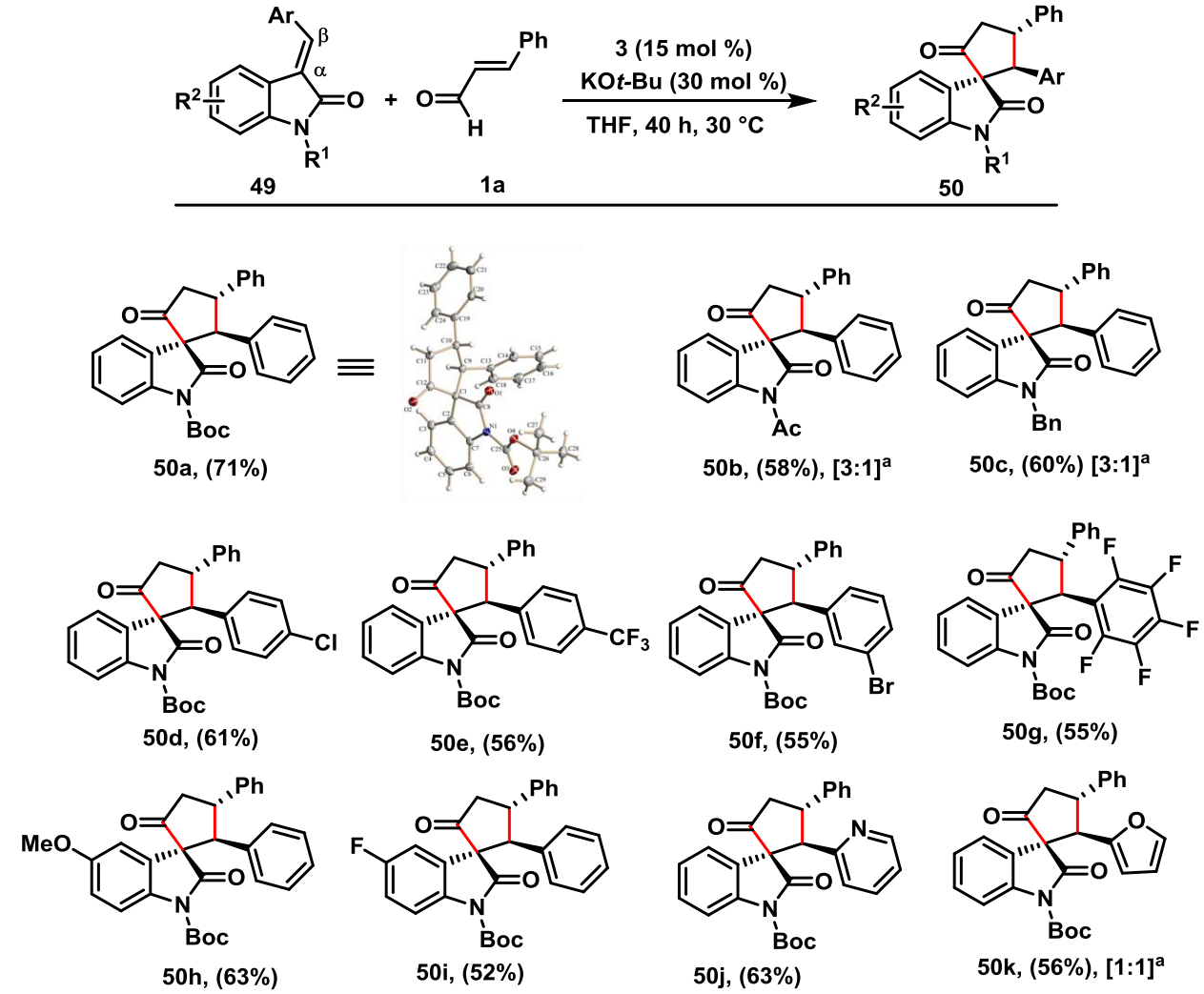
^{13}C NMR Spectrum of 50a ($CDCl_3$)



3.4.4. Substrate Scope

With the reaction conditions for the diastereoselective synthesis of cyclopentanone-fused

Scheme 3.17: Synthesis of Cyclopentanone-Fused Spirooxindoles, Variation of Isatilidenes

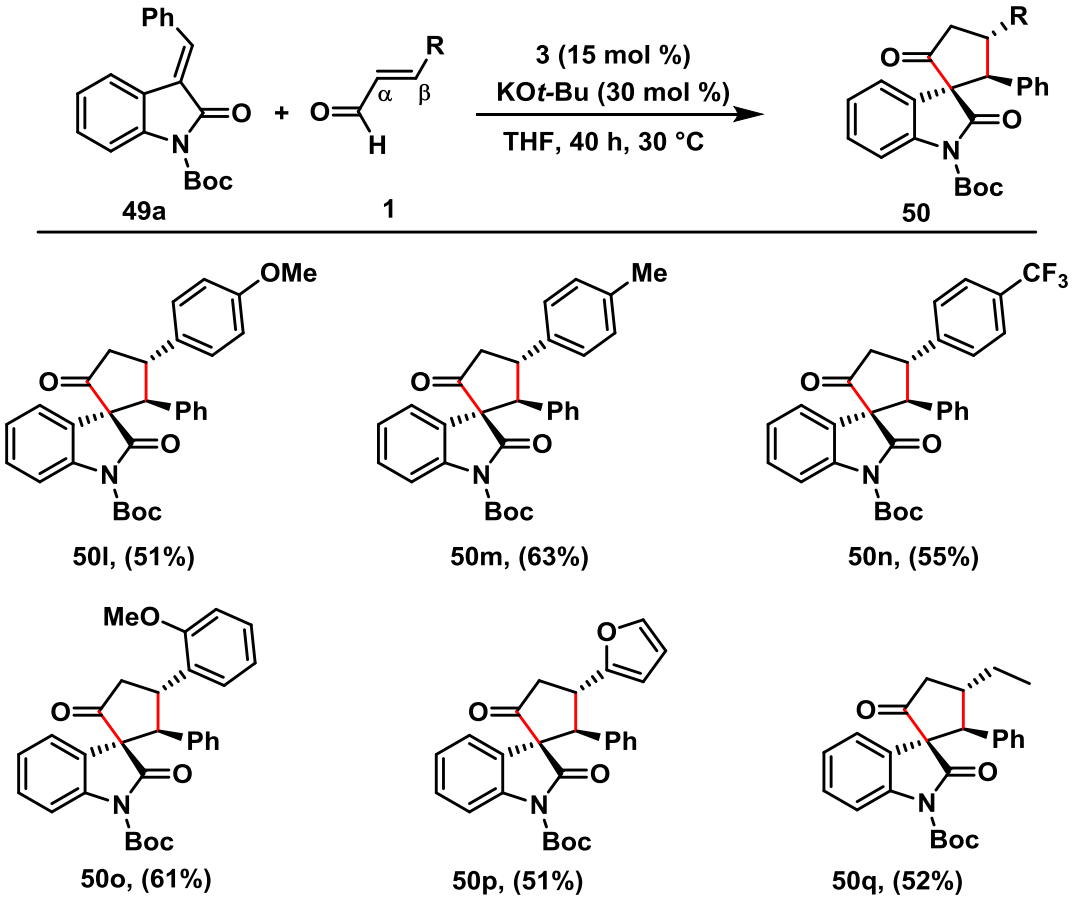


General reaction conditions: **49** (0.50 mmol), **1a** (0.75 mmol), **3** (15 mol %), KOt-Bu (30 mol %), THF (2.0 mL) at 30 °C for 40 h. Isolated yields of products after flash column chromatography are provided and dr is >20:1 unless indicated. [a]The diastereomeric ratio determined by ^{1}H NMR of the crude reaction mixture.

spirooxindoles, we then examined the scope and limitations of this annulation reaction. First, we studied the variation of the isatilidene moiety (Scheme 3.17). When acetyl protection on nitrogen was used, the product **50b** was formed in 58% yield, but with reduced diastereoselectivity of 3:1. However, *N*-benzyl protection afforded the desired product **50c** in 60% yield in >20:1 *dr*. A series of isatilidenes with different substitution on the β-aryl ring underwent smooth annulation reaction resulting in the formation of the spirooxindoles in moderate to good yields (**50d-50g**). It

is noteworthy that the pentafluoroaryl substitution on the β-aryl ring furnished the expected product **50g** in 55% yield. Moreover, electron-releasing and -withdrawing substituents are tolerated at the carbocyclic ring of isatilidenes, and the desired products are formed in moderate to good yields (**50h, 50i**). In addition, β-heteroaryl substituted isatilidenes also afforded the spiroheterocycles in moderate to good yields (**50j, 50k**). Notably, in the case of β-furyl substrate, the product **50k** was formed in 56% yield and 1:1 *dr*. Disappointingly, β-alkyl substituted isatilidenes did not undergo the present homoenolate annulation reaction under the optimized reaction conditions.

Scheme 3.18: Synthesis of Cyclopentanone-Fused Spirooxindoles: Variation of Enals



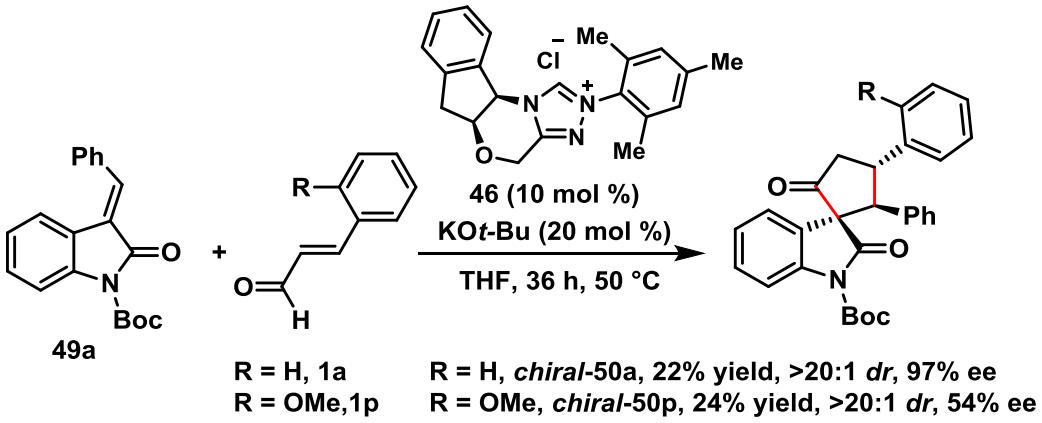
General reaction conditions: **49a** (0.50 mmol), **1** (0.75 mmol), **3** (15 mol %), KO*t*-Bu (30 mol %), THF (2.0 mL) at 30 °C for 40 h. Isolated yields of products are provided and *dr* is >20:1 in all cases.

Next, we evaluated the scope of the reaction with various α,β-unsaturated aldehyde derivatives. Interestingly, electron-releasing and -withdrawing groups at the 4-position of β-aryl ring are well- tolerated and the corresponding cyclopentanone-fused spiroheterocycles are formed in moderate yields (**50l-50n**). Moreover, 2-methoxy cinnamaldehyde afforded the desired

product **50o** in 61% yield. Additionally, β-furyl enal afforded the desired spiroheterocycle **50p** in 51% yield. Gratifyingly, an alkyl substituent at the β-position of the enal was also tolerated and the target product **50q** was isolated in 52% yield. In all cases, the cyclopentanone-fused spiroheterocycles were formed in high diastereoselectivity of >20:1 (Scheme 3.18).

Furthermore, we performed experiments on the enantioselective version of this reaction.[22] Reaction of *N*-Boc isatilidene **49a** with enal **1a** in the presence NHC generated from the chiral amino indanol-derived triazolium salt **46** using KO*t*-Bu as the base resulted in the enantioselective synthesis of the cyclopentanone-fused spirooxindole ***chiral*-50a** in 22% yield, and excellent diastereoselectivity of >20:1 and in 97% ee (Scheme 3.19). Although the yield of ***chiral*-50a** is less, the high diastereoselectivity and enantioselectivity observed in this reaction is noteworthy. Notably, when the reaction of **49a** was performed with 2-methoxy cinnamaldehyde **1p** under the present reaction conditions, the desired product ***chiral*-50p** was isolated in 24% yield and in high diastereoselectivity of >20:1, but the ee value dropped to 54%.

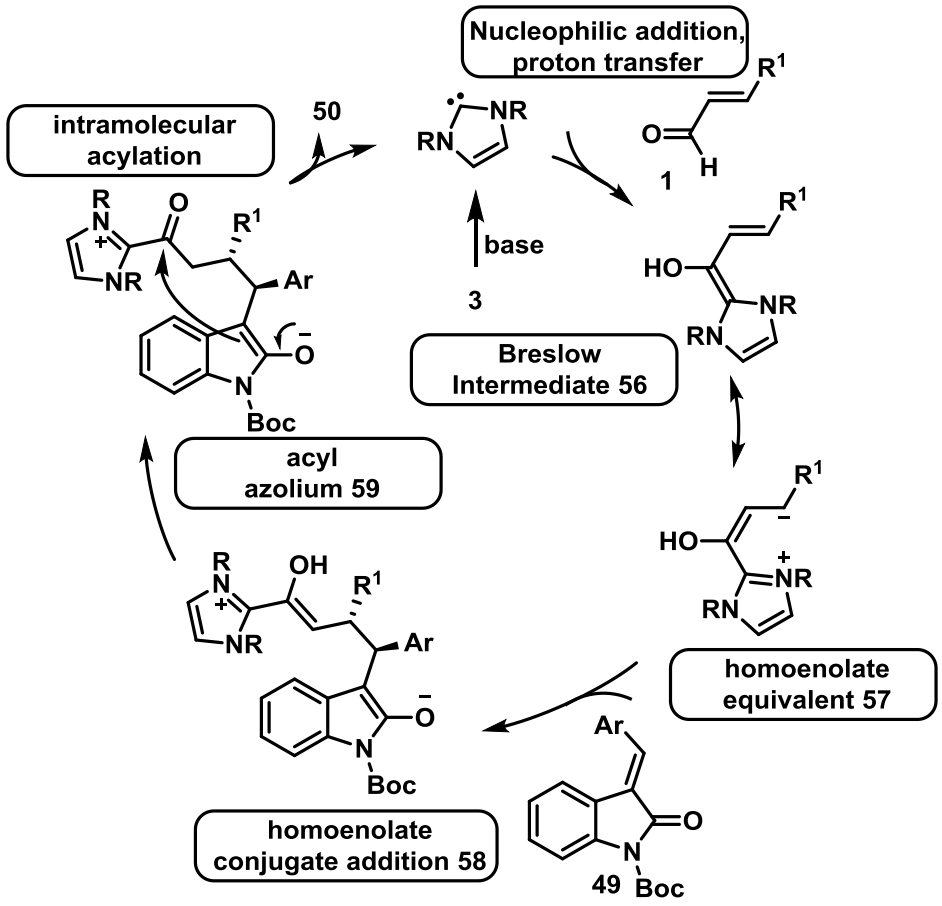
Scheme 3.19: Enantioselective synthesis of the cyclopentanone-fused spirooxindole



3.4.5. Proposed Mechanism

The tentative mechanism of this transformation is shown in Scheme 3.20. The free carbene generated from the imidazolium salt **3** undergoes nucleophilic addition to the enal followed by a proton transfer allows the formation of the nucleophilic Breslow intermediate **56**.[22] This is in resonance with the homoenolate equivalent **57**. The selective conjugate addition of homoenolate equivalent to isatilidene **49** generates the enol intermediate **58**, which on tautomerization forms the acyl azolium intermediate **59**. An intramolecular C-acylation can result in the formation of the spirocyclic compound **50** regenerating the free carbene.

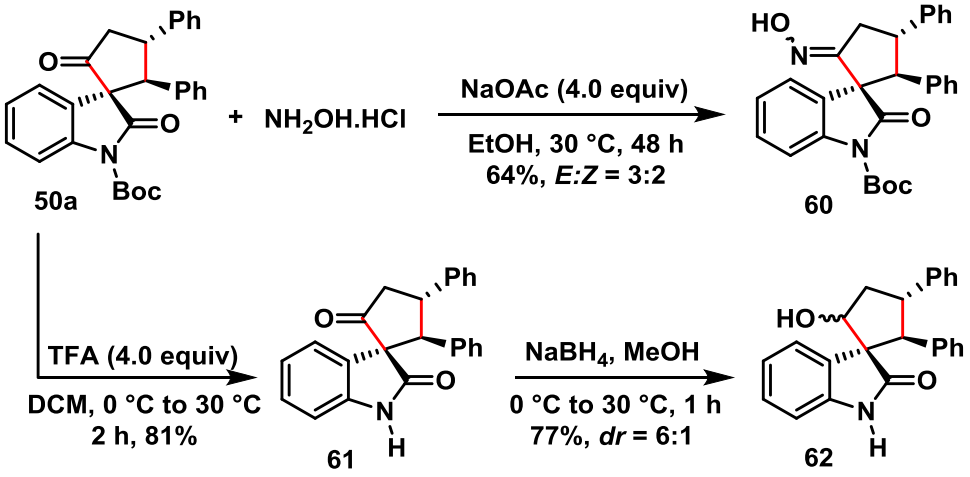
Scheme 3.20: Proposed Mechanism of the Reaction



3.4.6. Synthetic Transformation

We also carried out functionalization of the cyclopentanone-fused spirooxindole **50a**. Treatment of **50a** with hydroxylamine hydrochloride under basic conditions afforded the corresponding spirooxindole oxime **60** in 64% yield and in *E:Z* ratio of 3:2 (Scheme 3.21). The product **60** could be a substrate for the Beckmann rearrangement leading to the spiro δ-lactams. Moreover, N-Boc deprotection under trifluoroacetic acid (TFA) conditions furnished *N*-unprotected spirooxindole derivative **61** in 81% yield. Selective reduction of the keto group in **61** using $NaBH_4$ resulted in the formation of the cyclopentanol-fused spirooxindole **62** in 77% yield and a moderate *dr* of 6:1.

Scheme 3.21: Functionalization of Cyclopentanone-Fused Spirooxindoles



3.5. Conclusion

In conclusion, we have developed the NHC-catalyzed reaction of α,β-unsaturated aldehydes with isatilidene derivatives resulting in the diastereoselective synthesis of cyclopentanone-fused spirooxindoles bearing an all-carbon quaternary spiro-stereogenic center. The reaction proceeds via the generation of homoenolate intermediates, which underwent a formal [3+2] annulation reaction to afford the desired products. In view of the interesting biological properties of spirooxindoles, and their ubiquity in various natural products and medicinally important molecules, it is anticipated that the cyclopentanone-fused spirooxindoles synthesized herein may have potential biological properties.

3.6. Experimental Details

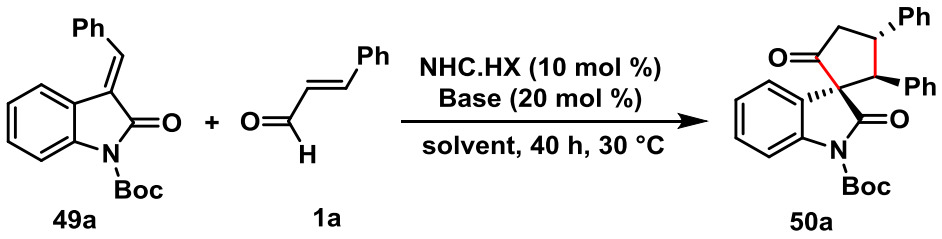
3.6.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw cap. 30 °C corresponds to the room temperature of the lab when experiments were performed. Dry THF was purchased from commercial sources and stored under argon over 4 Å molecular sieves. The isatin derivatives and aldehydes were purchased from commercial sources, and used without any further purification. The α,β-unsaturated aldehydes[23] and isatilidenes[24] were synthesized from corresponding aldehydes following the literature procedure. KO*t*-Bu was purchased from Sigma Aldrich and was handled inside glove box. The imidazolium salt **3** was synthesized following the literature procedure.[25]

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.

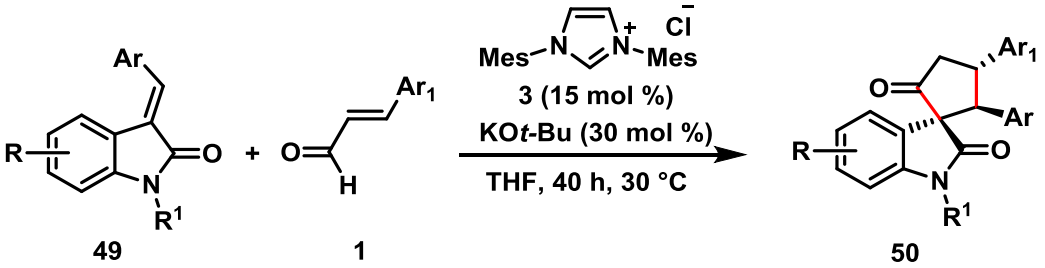
All compounds were fully characterized. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker AV 400 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, 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. HPLC analysis was performed on either a Shimadzu Class-VP V6.12 SP5 with UV detector or Agilent Technologies 1260 Infinity with UV detector.

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 *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (80 mg, 0.25 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. To this mixture was added the *trans* cinnamaldehyde **1a** (33 mg, 31 μL, 0.25 mmol) followed by the addition of KO*t*-Bu (8.5 mg, 0.05 mmol). After 40 hours stirring, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding cyclopentanone-fused spirooxindoles. The diastereoselectivity was determined by ^{1}H NMR of crude products (obtained by filtration of the crude reaction mixture through a pad of silica gel and eluting using EtOAc).

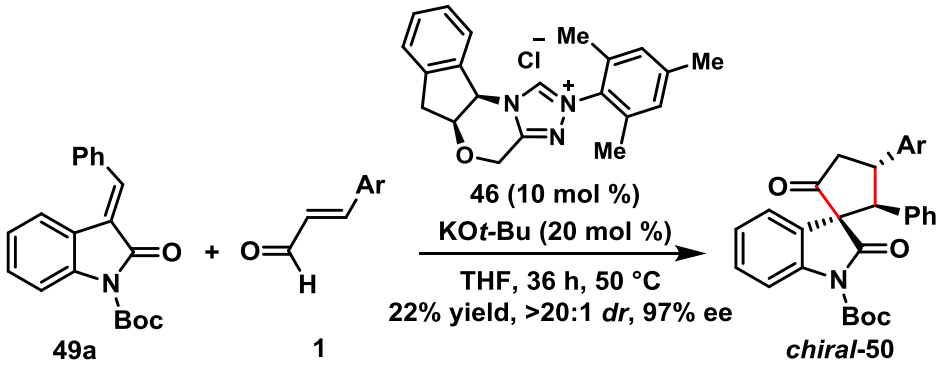
3.6.3. General Procedure for the NHC-Catalyzed Annulation Reaction



49 1 50

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the imidazolium salt **3** (0.027 g, 0.075 mmol) and the (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49** (0.5 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C. To this mixture was added the aldehyde **1** (0.75 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 KO*t*-Bu (0.017 gm, 0.15 mmol) was successively added. Then the reaction mixture was stirred at 30° C for 40 h. After 40 h the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding functionalized cyclopentanone-fused spirooxindoles derivatives **50**.

3.6.4. Procedure for the Enantioselective Synthesis of Cyclopentanone-fused Spirooxindoles (*chiral*-50)



49a 1 *chiral*-50

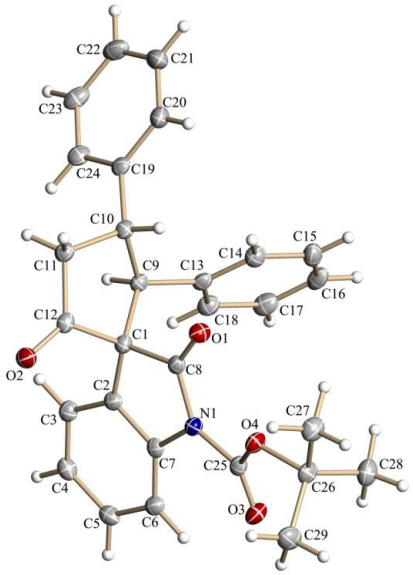
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the triazolium salt **46** (0.008 g, 0.025 mmol) and the *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added THF (1.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C. To this mixture was added the aldehyde **1** (0.375 mmol) and

the KO*t*-Bu (0.006 gm, 0.05 mmol) was successively added. Then the reaction mixture was stirred at 50° C for 36 h. After 36 h, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding cyclopentanone-fused spirooxindoles in high enantioselectivity.

3.6.5. X-ray Crystal Structure Analysis of 50a

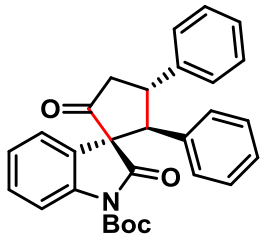
X-ray intensity data measurements of compound **50a** was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation at 90(2) K. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 10 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[26] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[26b] All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. An *ORTEP* III[26c] view of both compounds were drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii. The crystals belog to triclinic P-1 space group containing two molecules in the asymmetric unit. The detail crystallography data is gievn below.

Crystal data of **50a** $C_{29}H_{27}NO_4$, M = 453.51, colorless block, 0.47 x 0.44 x 0.13 mm^3, triclinic, space group P-1, a = 10.7670(9) Å, b = 11.4830(9) Å, c = 19.2866(15) Å, α = 88.719(3)°, β = 87.476(3)°, γ = 80.292(3)°, V = 2347.8(3) $Å^3$, Z = 4, T = 90(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.283, F(000) = 960, μ (mm^{-1}) = 0.085, 35150 reflections collected, 9223 unique reflections (R_{int}=0.0300), 8423 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.961, T_{max} = 0.989, 619 refined parameters, S = 1.031, $R1$ = 0.0393, $wR2$ = 0.0876 (all data R = 0.0357, $wR2$ = 0.0906), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.33, $\Delta\rho_{min}$ = -0.21 ($eÅ^{-3}$).



3.6.6. Synthesis and Characterization Cyclopentanone-fused Spirooxindoles

***tert*-Butyl -2',5-dioxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50a)**



50a

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 µL, 0.75 mmol) and *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (0.160 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.075 mmol) and KO*t*-Bu (0.017 g, 0.15 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -2',5-dioxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50a** as a white solid (0.161 g, 71% yield).

R_f (Pet. ether /EtOAc = 80/20): 0.61.

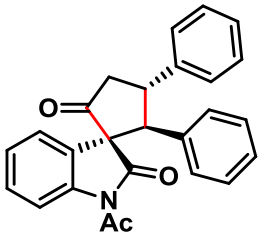
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 1H), 7.35-7.25 (m, 7H), 7.20-7.16 (m, 1H), 7.09-7.02 (m, 5H), 4.89-4.81 (m, 1H), 4.01 (d, *J* = 12.3 Hz, 1H), 3.45-3.38 (m, 1H), 2.84-2.77 (m, 1H), 1.52 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.27, 170.84, 148.42, 141.00, 140.58, 134.27, 129.42, 128.93, 128.37, 127.81, 127.54, 127.18, 126.76, 125.06, 123.21, 115.30, 84.50, 70.97, 60.67, 47.66, 41.06, 28.09.

HRMS calculated $[M+Na]^+$ for $C_{29}H_{27}O_4NNa$: 476.1832, found: 476.1833.

FTIR (cm^{-1}): 3023, 2403, 1742, 1661, 1607, 1482, 1354, 1258, 1216, 1150, 1092, 1026, 928, 842, 767, 670.

1'-Acetyl-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-2',5-dione (50b)



50b

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 μL, 0.75 mmol) and (*E*)-1-acetyl-3-benzylideneindolin-2-one **49b** (0.132 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.075 mmol) and KO*t*-Bu (0.017 g, 0.15 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded 1'-acetyl-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-2',5-dione **50b** as a white solid (0.115 g, 58%, dr determined by ^{1}H NMR analysis of crude reaction mixture is 3:1).

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

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.03 (m, 1H), 7.35-7.25 (m, 7H), 7.20-7.16 (m, 1H), 7.09-7.02 (m, 5H), 4.89-4.81 (m, 1H), 4.01 (d, *J* = 12.3 Hz, 1H), 3.45-3.38 (m, 1H), 2.84-2.77 (m, 1H), 1.52 (s, 9H).

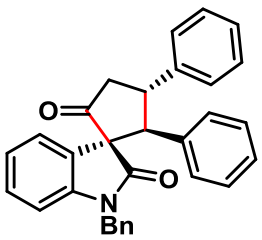
^{13}C NMR (100 MHz, $CDCl_3$) δ 209.14, 173.60, 170.03, 141.35, 140.17, 139.86, 138.35, 137.65, 134.37, 134.05, 131.06, 130.83, 130.75, 129.89, 129.63, 129.01, 128.44, 128.10, 128.06, 127.89, 127.79, 127.50, 127.31, 125.88, 122.98, 116.72, 70.85, 60.44, 48.02, 40.93, 26.32. Representative Peaks of Minor Isomer: **^{1}H NMR** δ 7.93 (m), 6.59 (d, *J* = 7.6 Hz), 5.03-5.00 (m), 4.32 (d, *J* = 9.4 Hz), 2.72-2.65 (m), 1.52 (s**).**

^{13}C NMR δ 201.53, 174.42, 170.43, 141.10, 133.93, 129.26, 128.89, 127.96, 125.69, 122.37, 116.51, 68.04, 59.19, 26.55.

HRMS calculated $[M+Na]^+$ for $C_{26}H_{21}O_3NNa$: 418.1414, found: 418.1410.

FTIR (cm^{-1}): 3023, 2403, 1710, 1650, 1612, 1482, 1422, 1378, 1269, 1216, 1158, 1095, 1026, 922, 767, 670.

1'-Benzyl-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-2',5-dione (50c)



50c

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 μL, 0.75 mmol) and (*E*)-1-benzyl-3-benzylideneindolin-2-one **49c** (0.156 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded 1'-benzyl-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-2',5-dione **50c** as a white solid (0.133 g, 60% dr determined by ^{1}H NMR analysis of crude reaction mixture is 3:1).

***R**f* (Pet. ether /EtOAc = 80/20): 0.51.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 4H), 7.32-7.27 (m, 4H), 7.21-7.05 (m, 12H), 6.45-6.43 (m, 2H), 5.08-4.99 (m, 2H), 4.32 (d, *J* = 16.3 Hz, 1H), 4.18 (d, *J* = 12.5 Hz, 1H), 3.47-3.40 (m, 1H), 2.87-2.79 (m, 1H).

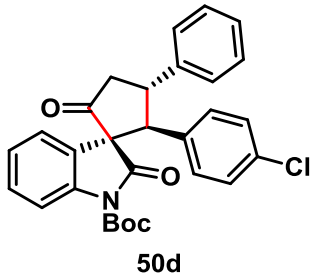
^{13}C NMR (100 MHz, $CDCl_3$) δ 210.26, 172.14, 143.88, 140.81, 134.94, 134.73, 133.98, 129.28, 129.23, 128.91, 128.81, 128.73, 128.69, 128.50, 128.14, 128.03, 127.61, 127.41, 127.27, 127.10, 126.89, 126.41, 124.81, 123.38, 123.37, 109.71, 86.87, 58.83, 48.02, 43.55, 41.00. Representative Peaks of Minor Isomer: **^{1}H NMR** δ 6.62-6.58 (m)**,** 6.26-6.20 (m)**,** 3.57-3.50 (m), 3.06-3.00 (m).

^{13}C NMR δ 70.70, 48.47, 36.79, 31.08.

HRMS calculated $[M+Na]^+$ for $C_{31}H_{25}O_2NNa$: 466.1778, found: 466.1768.

FTIR (cm^{-1}): 3023, 2926, 2334, 1745, 1687, 1648, 1609, 1483, 1459, 1368, 1216, 1142, 1103, 1026, 758, 700, 665.

***tert*-Butyl -2-(4-chlorophenyl)-2',5-dioxo-3-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50d)**



50d

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 µL, 0.75 mmol) and *tert*-butyl (*E*)-3-(4-chlorobenzylidene)-2-oxoindoline-1-carboxylate **49d** (0.178 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -2-(4-chlorophenyl)-2',5-dioxo-3-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50d** as a white solid (0.149 g, 61% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.57.

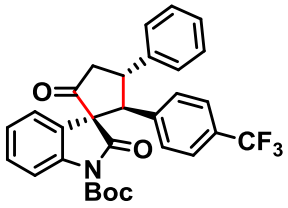
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.35-7.29 (m, 7H), 7.22-7.21 (m, 1H), 7.07-7.06 (m, 2H), 6.98-6.96 (m, 2H), 4.84-4.76 (m, 1H), 3.99 (d, *J* = 12.3 Hz, 1H), 3.45-3.38 (m, 1H), 2.85-2.77 (m, 1H), 1.55 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.69, 170.67, 148.27, 140.94, 140.30, 133.71, 132.88, 129.70, 129.59, 129.01, 128.59, 127.44, 127.35, 126.43, 125.15, 123.10, 115.40, 84.78, 70.74, 59.82, 47.90, 41.21, 28.06.

HRMS calculated $[M+Na]^+$ for $C_{29}H_{26}O_4NClNa$: 510.1443, found: 510.1433.

FTIR (cm^{-1}): 3022, 2976, 2358, 1783, 1723, 1654, 1611, 1526, 1482, 1423, 1355, 1297, 1254, 1217, 1154, 1094, 1031, 751, 670.

***tert*-Butyl -2',5-dioxo-3-phenyl-2-(4-(trifluoromethyl)phenyl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50e)**



50e

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 µL, 0.75 mmol) and *(E)-tert*-butyl *(E)*-3-(4-(trifluoromethyl)benzylidene)-2-oxoindoline-1-carboxylate **49e** (0.194 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -2',5-dioxo-3-phenyl-2-(4-(trifluoromethyl)phenyl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50e** as a white solid (0.146 g, 56% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.51.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.44-7.37 (m, 10H), 7.22-7.20 (m, 2H), 4.96-4.88 (m, 1H), 4.35 (d, *J* = 12.4 Hz, 1H), 3.53-3.46 (m, 1H), 2.93-2.86 (m, 1H), 1.59 (s, 9H).

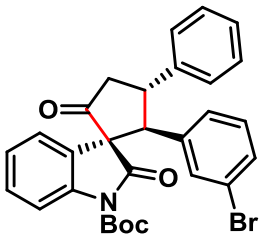
^{13}C NMR (100 MHz, CDCl$_3$) δ 208.38, 170.57, 148.21, 140.96, 139.92, 138.51, 129.76, 129.13, 129.06, 128.77, 128.69, 128.08, 127.49, 127.43, 127.06, 126.84, 126.35, 125.35, 125.26, 123.12, 115.48, 88.48, 70.69, 59.94, 47.58, 43.11, 28.02.

^{19}F NMR (376 MHz, CDCl$_3$) δ: -62.58.

HRMS calculated $[M+Na]^+$ for $C_{30}H_{26}O_4NF_3Na$: 544.1706, found: 544.1708.

FTIR (cm^1) 3356, 3023, 2977, 2403, 1784, 1737, 1660, 1611, 1480, 1323, 1216, 1159, 1062, 1028, 929, 842, 766, 671.

***tert*-Butyl -2-(3-bromophenyl)-2',5-dioxo-3-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50f)**



50f

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 µL, 0.75 mmol) and *tert*-butyl (*E*)- (3-bromobenzylidene)-2-oxoindoline-1-carboxylate **49f** (0.200 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -2-(3-bromophenyl)-2',5-dioxo-3-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50f** as a white solid (0.146 g, 55% yield).

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

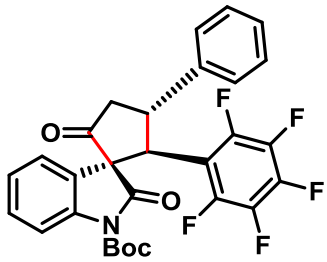
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71 (d, *J* = 8.0 Hz, 1H), 7.37-7.29 (m, 7H), 7.24-7.20 (m, 3H), 6.96-6.92(m, 2H), 4.81-4.73 (m, 1H), 3.94 (d, *J* = 12.3 Hz, 1H), 3.45-3.38 (m, 1H), 2.84-2.76 (m, 1H), 1.55 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 208.71, 170.61, 148.41, 140.94, 140.06, 136.74, 131.21, 131.05, 129.93, 129.68, 129.07, 127.46, 127.40, 127.23, 126.24, 125.22, 123.11, 115.41, 84.78, 70.75, 60.20, 47.47, 41.16, 28.07.

HRMS calculated $[M+Na]^+$ for $C_{29}H_{26}O_4NBrNa$: 554.0937, found: 554.0930.

FTIR (cm^{-1}): 3024, 1781, 1718, 1661, 1608, 1481, 1358, 1303, 1263, 1215, 1154, 1090, 1026, 841, 759, 667.

***tert*-Butyl -2',5-dioxo-2-(perfluorophenyl)-3-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50g)**



50g

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 μL, 0.75 mmol) and *tert*-butyl 2-oxo- (*E*)-3-(perfluorobenzylidene)indoline-1-carboxylate **49g** (0.206 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -2',5-dioxo-2-(perfluorophenyl)-3-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50g** as a white solid (0.152 g, 56% yield).

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

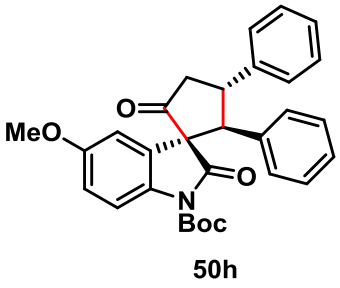
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H),7.46-7.42 (m, 1H), 7.31-7.16 (m, 6H), 4.79-4.71 (m, 1H), 4.64 (d, *J* = 8.9 Hz, 1H), 3.55-3.43 (m, 1H), 3.16-3.06 (m, 1H), 1.60 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 207.89, 169.07, 148.34, 139.40, 136.77, 129.83, 128.87, 128.71, 127.75, 126.88, 125.22, 122.06, 116.03, 85.32, 66.91, 47.16, 43.06, 38.59, 28.12.

HRMS calculated $[M+Na]^+$ for $C_{29}H_{22}O_4NF_5Na$: 566.1361, found: 566.1364.

FTIR (cm^{-1}): 3023, 2403, 1791, 1743, 1659, 1606, 1510, 1424, 1305, 1216, 1147, 1096, 1012, 925, 767, 670.

***tert*-Butyl -5'-methoxy-2',5-dioxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50h)**



50h

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 μL, 0.75 mmol) and *tert*-butyl (*E*)- 3-benzylidene-5-methoxy-2-oxoindoline-1-carboxylate **49h** (0.176 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -5'-methoxy-2',5-dioxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50h** as a white solid (0.152 g, 63% yield).

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

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 1H), 7.34-7.26 (m, 5H), 7.11-7.05(m, 5H), 6.90-6.85 (m, 2H), 4.90-4.82 (m, 1H), 4.00 (d, *J* = 12.3 Hz, 1H), 3.88 (s, 3H), 3.47-3.40 (m, 1H), 2.86-2.78 (m, 1H), 1.53 (s, 9H).

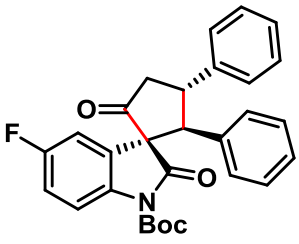
^{13}C NMR (100 MHz, $CDCl_3$) δ 209.24, 170.83, 157.26, 148.46, 140.55, 134.35, 134.25, 128.91, 128.37, 127.90, 127.79, 127.53, 127.16, 116.23, 113.94, 109.60, 84.29, 71.20, 60.64, 55.88, 47.63, 41.04, 28.09.

HRMS calculated $[M+Na]^+$ for $C_{30}H_{29}O_5NNa$: 506.1938, found: 506.1928.

FTIR (cm^{-1}): 3022, 2403, 1779, 1724, 1664, 1606, 1486, 1437, 1262, 1216, 1159, 1109, 1040, 927, 766, 670.

***tert*-Butyl -5'-fluoro-2',5-dioxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50i)**

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 μL, 0.75 mmol) and *tert*-butyl (E)-3-benzylidene-5-fluoro-2-oxoindoline-1-carboxylate **49i**(0.160 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-Butyl -5'-fluoro-2',5-dioxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50i** as a white solid (0.122 g, 52% yield).



50i

***R**f* (Pet. ether /EtOAc = 80/20): 0.51.

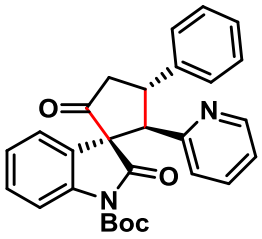
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.34-7.28 (m, 4H), 7.13-7.11 (m, 3H), 7.07-7.04 (m, 3H), 6.84 (d, *J* = 7.4 Hz, 1H), 4.90-4.82 (m, 1H), 3.98 (d, *J* = 12.0 Hz, 1H), 3.48-3.41 (m, 1H), 2.86-2.79 (m, 1H), 1.54 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.55, 170.40, 160.17 (d, J_{C-F} = 243.3 Hz), 158.95, 148.32, 140.26, 133.94, 131.90 (d, J_{C-F} = 24.5 Hz), 131.03 (d, J_{C-F} = 19.2 Hz), 129.85, 128.96, 128.83, 128.70, 128.45, 128.32, 128.07, 127.97, 127.81, 127.49, 127.26, 116.73, 116.00 (d, J_{C-F} = 23.0 Hz), 110.78 (d, J_{C-F} = 24.6 Hz), 84.73, 71.11, 60.79, 47.47, 41.08, 28.05.

HRMS calculated $[M+Na]^+$ for $C_{29}H_{26}O_4NFNa$: 494.1738, found: 494.1727.

FTIR (cm^{-1}): 2978, 2104, 1782, 1648, 1623, 1485, 1403, 1307, 1266, 1213, 1153, 1027, 838, 764, 667.

***tert*-Butyl -2',5-dioxo-3-phenyl-2-(pyridin-2-yl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50j)**



50j

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 μL, 0.75 mmol) and *tert-butyl* 2-oxo (*E*)-3-((pyridin-2-yl)methylene)indoline-1-carboxylate **49j** (0.161 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -2',5-dioxo-3-phenyl-2-(pyridin-2-yl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50j** as a brownish solid (0.143 g, 63% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.48.

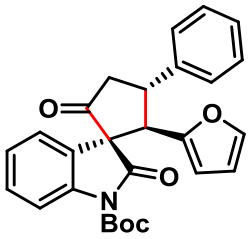
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.7 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H),7.27-7.18 (m, 3H), 7.09-7.08 (m, 4H), 7.04-7.01 (m, 2H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 6.17 (d, *J* = 7.6 Hz, 1H), 5.20-5.13 (m, 1H), 4.13 (d, *J* = 7.1 Hz, 1H), 3.88-3.81 (m, 1H), 3.09-3.02 (m, 1H), 1.68 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.28, 172.57, 158.03, 148.94, 148.70, 140.75, 139.21, 136.33, 128.97, 128.04, 127.98, 126.39, 126.33, 125.53, 124.32, 122.54, 114.58, 85.08, 69.78, 59.22, 42.75, 40.24, 28.22.

HRMS calculated $[M+H]^+$ for $C_{28}H_{27}O_4N_2$: 455.1965, found: 455.1954.

FTIR (cm^{-1}): 3024, 2951, 1821, 1781, 1662, 1607, 1484, 1308, 1264, 1215, 1155, 1027, 840, 761, 699.

***tert*-Butyl -2-(furan-2-yl)-2',5-dioxo-3-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50k)**



50k

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.099 g, 94 µL, 0.75 mmol) and *tert*-butyl (*E*)-3-((furan-2-yl)methylene)-2-oxoindoline-1-carboxylate **49k** (0.156 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -2-(furan-2-yl)-2',5-dioxo-3-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50k** as a brownish solid (0.124 g, 56%, dr determined by ^{1}H NMR analysis of crude reaction mixture is 1:1).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.58.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 (d, *J* = 8.2 Hz, 1H), 7.45-7.43 (m, 2H), 7.39-7.34 (m, 7H), 7.28-7.25 (m, 5H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.10-7.02 (m, 3H), 6.13-6.11 (m, 1H), 6.01-6.00 (m, 2H), 5.97-5.96 (m, 1H), 4.68-4.60 (m, 2H), 3.40-3.33 (m, 1H), 3.00-2.92 (m, 1H), 1.68 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 208.50, 172.99, 150.32, 149.90, 148.87, 142.09, 140.97, 140.55, 129.44, 128.97, 127.65, 127.30, 126.70, 125.06, 124.30, 123.96, 84.91, 69.33, 53.99, 47.39, 43.66, 28.18.

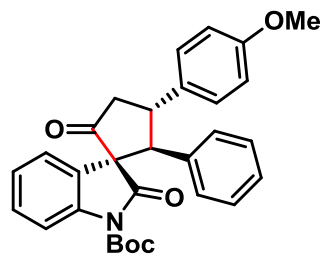
Representative Peaks of Other Isomer: **^{1}H NMR** δ 7.80 (d, *J* = 8.2 Hz, 1H), 4.17-4.08 (m, 2H), 3.18-3.11 (m, 1H), 2.83-2.76 (m, 1H), 1.61 (s, 9H).

^{13}C NMR δ 207.78, 170.45, 148.68, 140.61, 140.03, 129.08, 127.39, 123.02, 84.67, 68.97, 51.79, 46.86, 42.01, 28.13.

HRMS calculated $[M+Na]^+$ for $C_{27}H_{25}O_5NNa$: 466.1625, found: 466.1620.

FTIR (cm^{-1}): 3023, 2403, 1782, 1720, 1608, 1480, 1424, 1356, 1257, 1216, 1155, 1090, 1043, 925, 843, 766, 670.

***tert*-Butyl -3-(4-methoxyphenyl)-2',5-dioxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50l)**



50l

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **1l** (0.122 g, 0.75 mmol) and *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (0.160 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by

flash column chromatography afforded *tert*-butyl -3-(4-methoxyphenyl)-2',5-dioxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50l** as a white solid (0.116 g, 51% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.52.

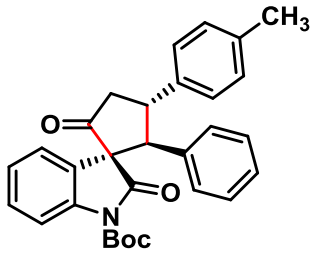
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.34-7.21 (m, 2H), 7.23-7.21 (m, 2H), 7.09-7.05 (m, 3H), 7.01-6.99 (m, 2H), 6.81-6.78 (m, 2H),4.83-4.75 (m, 1H), 3.94 (d, *J* = 12.6 Hz, 1H), 3.73 (s, 3H), 3.41-3.34 (m, 1H), 2.79-2.72 (m, 1H), 1.51 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 209.44, 170.86, 158.61, 148.42, 140.97, 134.36, 132.44, 132.15, 129.38, 128.47, 128.39, 128.34, 127.77, 126.81, 125.03, 123.19, 115.27, 114.32, 84.48, 70.99, 60.94, 55.33, 47.72, 40.31, 28.08.

HRMS calculated $[M+Na]^+$ for $C_{30}H_{29}O_5NNa$: 506.1938, found: 506.1940.

FTIR (cm^{-1}): 3020, 1737, 1643, 1611, 1514, 1482, 1467, 1371, 1348, 1310, 1256, 1218, 1148, 1095, 1043, 1016, 835, 772, 669.

***tert*-Butyl -2',5-dioxo-2-phenyl-3-(p-tolyl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50m)**



50m

Following the general procedure, treatment of *(E)*-3-*p*-tolylacrylaldehyde **1m** (0.110 g, 0.75 mmol) and *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (0.160 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -2',5-dioxo-2-phenyl-3-(p-tolyl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50m** as a white solid (0.147 g, 63% yield).

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

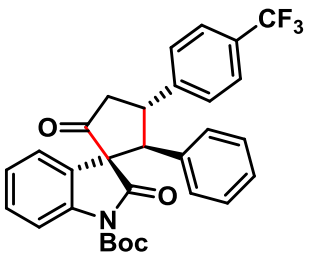
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.37-7.30 (m, 3H), 7.24-7.22 (m, 2H), 7.11-7.09 (m, 5H), 7.04-7.02 (m, 2H), 4.87-4.79 (m, 1H), 4.01 (d, *J* = 12.4 Hz, 1H), 3.45-3.38 (m, 1H), 2.84-2.77 (m, 1H), 2.29 (s, 3H), 1.54 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 209.45, 170.83, 148.40, 140.96, 137.44, 136.76, 134.32, 129.60, 129.37, 128.35, 128.32, 127.74, 127.37, 126.80, 125.03, 123.19, 115.26, 84.46, 70.97, 60.68, 47.75, 40.64, 28.06, 21.10.

HRMS calculated $[M+Na]^+$ for $C_{30}H_{29}O_4NNa$: 490.1989, found: 490.1975.

FTIR (cm^{-1}): 3024, 1781, 1725, 1665, 1608, 1479, 1424, 1355, 1301, 1261, 1216, 1153, 1096, 1030, 839, 759, 669.

***tert*-Butyl -2',5-dioxo-2-phenyl-3-(4-(trifluoromethyl)phenyl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50n)**



50n

Following the general procedure, treatment of (*E*)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde **1n** (0.150 g, 0.75 mmol) and *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (0.160 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -2',5-dioxo-2 phenyl-3-(4-(trifluoromethyl)phenyl)spiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50n** as a white solid (0.143 g, 55% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.51.

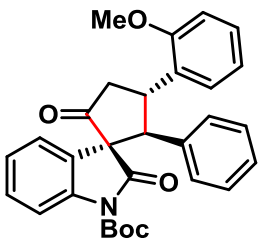
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63-7.40 (m, 6H), 7.35-7.31 (m, 2H), 7.21-7.20 (m, 1H), 7.11-7.08 (m, 2H), 7.04-7.00 (m, 2H), 5.01-4.90 (m, 1H), 3.98 (d, *J* = 12.3 Hz, 1H), 3.50-3.36 (m, 1H), 2.85-2.77 (m, 1H), 1.52 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 207.96, 172.99, 153.20, 148.65, 142.14, 141.98, 135.03, 129.15, 128.37, 128.04, 127.59, 125.22, 124.14 (d, $J_{C\text{-}F}$ = 35.71Hz), 115.72, 110.46, 106.74, 84.93, 70.41, 56.03, 44.53, 36.94, 28.18.

HRMS calculated $[M+Na]^+$ for $C_{30}H_{26}O_4NF_3Na$: 544.1706, found: 544.1707.

FTIR (cm^{-1}): 3022, 2971, 2403, 1782, 1736, 1665, 1611, 1482, 1426, 1322, 1216, 1138, 1025, 928, 766, 671.

***tert*-Butyl -3-(2-methoxyphenyl)-2',5-dioxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50o)**



50o

Following the general procedure, treatment of (*E*)-3-(2-methoxyphenyl)acrylaldehyde **1o** (0.122 g, 0.75 mmol) and *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (0.160 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -3-(2-methoxyphenyl)-2',5-dioxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50o** as a white solid (0.150 g, 62% yield).

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

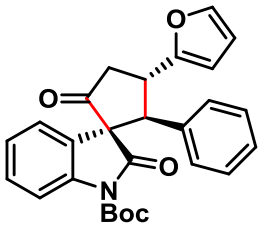
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 1H), 7.37-7.28 (m, 3H), 7.20-7.17 (m, 2H), 7.09-7.02 (m, 5H), 6.90-6.82 (m, 2H), 5.02-4.94 (m, 1H), 4.36 (d, *J* = 12.1 Hz, 1H), 3.92 (s, 3H), 3.49-3.41 (m, 1H), 2.93-2.85 (m, 1H), 1.53 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.14, 170.77, 157.84, 148.47, 141.01, 135.02, 129.24, 128.83, 128.64, 128.31, 128.21, 127.55, 127.22, 124.98, 123.35, 120.81, 115.21, 111.02, 84.34, 70.79, 57.87, 55.38, 45.41, 37.31, 28.06.

HRMS calculated $[M+Na]^+$ for $C_{30}H_{29}O_5NNa$: 506.1938, found: 506.1923.

FTIR (cm^{-1}): 3022, 2403, 1780, 1739, 1666, 1605, 1482, 1355, 1216, 1153, 1096, 1034, 921, 843, 766, 670.

***t*ert-Butyl -3-(furan-2-yl)-2',5-dioxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50p)**



50p

Following the general procedure, treatment of (*E)*-3-(furan-2-yl)acrylaldehyde **1p** (0.092 g, 0.75 mmol) and *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (0.160 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *t*ert-butyl -3-(furan-2-yl)-2',5-dioxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50p** as a white solid (0.113 g, 51% yield). Compound having unknown impurity.

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

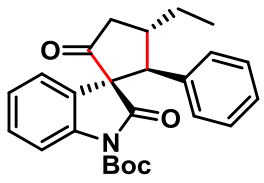
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 1H), 7.34-7.31 (m, 2H), 7.19-7.16 (m, 2H), 7.08-7.05 (m, 4H), 6.30-6.19 (m, 2H), 6.08-6.04 (m, 1H), 4.59 (d, *J* = 12.6 Hz, 1H), 4.40-4.32 (m, 1H), 3.75-3.57 (m, 1H), 3.23-3.17 (m, 1H), 3.07-2.99 (m, 1H), 1.62 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.96, 172.99, 153.20, 141.98, 140.39, 135.03, 129.15, 128.37, 128.04, 127.99, 125.22, 124.31, 123.96, 115.72, 110.46, 106.74, 84.93, 70.41, 56.03, 44.53, 36.94, 28.18.

LCMS calculated $[M+Na]^+$ for $C_{27}H_{25}O_5NNa$: 466.1625, found: 466.1.

FTIR (cm^{-1}): 3024, 2403, 1780, 1651, 1617, 1483, 1308, 1264, 1216, 1155, 1022, 926, 842, 764, 669.

***tert*-Butyl -3-ethyl-2',5-dioxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (50q)**



50q

Following the general procedure, treatment of (*E*)-pent-2-enal **1q** (0.063 g, 73 µL, 0.75 mmol) and *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (0.160 g, 0.5 mmol) with imidazolium salt **3** (0.027 g, 0.15 mmol) and KO*t*-Bu (0.017 g, 0.30 mmol) in THF (2.0 mL) at 30 °C for 40 h followed by flash column chromatography afforded *tert*-butyl -3-ethyl-2',5-dioxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50q** as a white solid (0.085 g, 42% yield).

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

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.28-7.15 (m, 6H), 7.04-7.02 (m, 2H), 3.51-3.46 (m, 1H), 3.39 (d, *J* = 12.1 Hz, 1H), 3.19-3.12 (m, 1H), 2.34-2.27 (m, 1H), 1.50 (s, 9H), 1.29-1.21(m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H) .

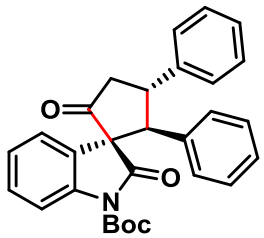
^{13}C NMR (100 MHz, $CDCl_3$) δ 210.39, 170.82, 148.47, 140.89, 135.15, 131.27, 129.48, 129.16, 128.46, 128.40, 127.79, 124.90, 123.08, 115.14, 84.36, 71.06, 60.77, 44.76, 37.61, 28.07, 26.76, 12.52.

HRMS calculated $[M+Na]^+$ for $C_{25}H_{27}O_4NNa$: 428.1832, found: 428.1821.

FTIR (cm^{-1}): 3023, 2975, 2403, 1779, 1739, 1660, 1609, 1522, 1481, 1427, 1355, 1216, 1154, 1035, 928, 768, 671.

3.6.7. Synthesis and Characterization of Chiral Cyclopentanone-fused Spirooxindoles

***tert*-Butyl -2',5-dioxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (*Chiral*-50a)**



***Chiral*-50a**

Following the general procedure, treatment of *trans* cinnamaldehyde **1a** (0.049 g, 47 µL, 0.375 mmol) and *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (0.080 g, 0.25 mmol) with chiral triazolium salt **46** (0.008 g, 0.025 mmol) and KO*t*-Bu (0.006 g, 0.05 mmol) in THF (1.0 mL) at 50 °C for 36 h followed by flash column chromatography afforded *tert*-butyl -2',5-dioxo-2,3- diphenylspiro [cyclopentane-1,3'-indoline]-1'-carboxylate **(*Chiral*-50a)** as a white solid (0.024 g, 21% yield).

***R**f* (Pet. ether /EtOAc = 60/40): 0.61; 97% ee, $[\alpha]_D^{25}$ = -5.76 (c 0.1, $CHCl_3$).

HPLC (Kromasil-5-Amycoat, 15:85 IPA / n-Hexane, 0.7 mL/min.) Major: 7.56 min, Minor: 8.89 min.

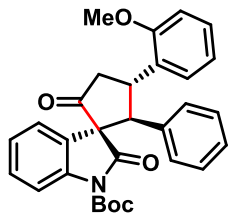
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 1H), 7.35-7.25 (m, 7H), 7.20-7.16 (m, 1H), 7.09-7.02 (m, 5H), 4.89-4.81 (m, 1H), 4.01 (d, *J* = 12.3 Hz, 1H), 3.45-3.38 (m, 1H), 2.84-2.77 (m, 1H), 1.52 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.27, 170.84, 148.42, 141.00, 140.58, 134.27, 129.42, 128.93, 128.37, 127.81, 127.54, 127.18, 126.76, 125.06, 123.21, 115.30, 84.50, 70.97, 60.67, 47.66, 41.06, 28.09.

HRMS calculated $[M+Na]^+$ for $C_{29}H_{27}O_4NNa$: 476.1832, found: 476.1833.

FTIR (cm^{-1}): 3023, 2403, 1742, 1661, 1607, 1482, 1354, 1258, 1216, 1150, 1092, 1026, 928, 842, 767, 670.

***tert*-Butyl -3-(2-methoxyphenyl)-2',5-dioxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (*Chiral*-50p)**



Chiral-3p

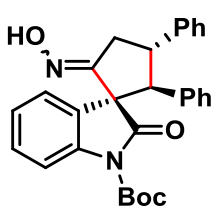
Following the general procedure, treatment of (*E*)-3-(2-methoxyphenyl)acrylaldehyde **1p** (0.030 g, 0.187 mmol) and *tert*-butyl (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **49a** (0.040 g, 0.125 mmol) with chiral triazolium salt **46** (0.004 g, 0.0125 mmol) and KO*t*-Bu (0.003 g, 0.025 mmol) in THF (0.5 mL) at 50 °C for 36 h followed by flash column chromatography afforded *tert*-Butyl -3-(2-methoxyphenyl)-2',5-dioxo-2-phenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **(*Chiral*-50p)** as a white solid (0.015 g, 24% yield; the absolute stereochemistry of ***Chiral*-50p** was not determined).

Rf (Pet. ether /EtOAc = 60/40): 0.56; 54% ee, $[\alpha]_D^{25}$ = -4.52 (c 0.1, $CHCl_3$).

HPLC (Chiralpak AD, 10:90 IPA / n-Hexane, 1.0 mL/min.) Major: 9.46 min, Minor: 10.67 min.

3.7. Synthesis and Characterization of Functionalized Spirooxindoles

***tert*-Butyl -5-(hydroxyimino)-2'-oxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate (60)**



60

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was charged with hydroxylamine hydrochloride (0.052 g, 0.75 mmol, 5.0 equiv.) and sodium acetate (0.049 g, 0.60 mmol, 4.0 equiv.). The resultant mixture was dissolved in ethanol (2.0 mL) followed by addition of *tert*-butyl -2',5-dioxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50a**

(0.068 g, 0.15 mmol) and the resulting reaction mixture was stirred at rt for 48 h. 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.[27] The crude reaction mixture was purified by flash column chromatography through silica gel (petroleum ether: ethyl acetate 60:40) to afford *tert*-butyl -5-(hydroxyimino)-2'-oxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **60** inseparable mixture of diastereomers as a white solid (0.045 g, 64% yield).

***R**f* (Pet. ether /EtOAc = 60/40): 0.31.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 1H), 7.42-7.38 (m, 1H), 7.22-7.19 (m, 1H), 7.12-7.09 (m, 1H), 7.05-7.01 (m, 5H), 6.88-6.85 (m, 1H), 6.81-5.78 (m, 3H), 6.52 (d, *J* = 7.5 Hz, 1H), 4.33-4.24 (m, 1H), 4.07-4.00 (m, 1H), 3.84-3.76 (m, 1H), 3.02-2.87 (m, 1H), 2.59 (bs, 1H), 1.47 (s, 9H).

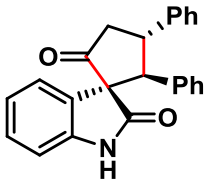
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.18, 169.50, 145.50, 140.98, 140.72, 136.26, 129.24, 128.69, 128.38, 128.32, 127.34, 126.85, 126.64, 125.36, 124.56, 124.00, 114.98, 84.27, 53.31, 48.77, 43.14, 38.39, 28.04.

Representative Peaks of Minor Isomer: **^{1}H NMR** δ 7.63 (d, *J* = 7.1 Hz), 7.30-7.26 (m), 6.93 (m), 6.76-6.75 (m), 2.83-2.79 (m), 1.59 (s).

^{13}C NMR δ 175.86, 169.81, 148.85, 141.50, 139.74, 137.58, 128.65, 128.49, 128.26, 128.02, 127.56, 126.95, 126.72, 125.20, 124.31, 114.70, 84.43, 52.76, 47.98, 43.53, 38.06, 28.21.

FTIR (cm^{-1}): 3427, 3023, 2403, 2105, 1781, 1652, 1524, 1482, 1357, 1301, 1252, 1217, 1155, 1087, 1043, 924, 843, 767, 671.

2,3-Diphenylspiro[cyclopentane-1,3'-indoline]-2',5-dione (61)



61

To a stirred solution of *tert*-butyl -2',5-dioxo-2,3-diphenylspiro[cyclopentane-1,3'-indoline]-1'-carboxylate **50a** (0.068 g, 0.15 mmol) in 2.0 mL of dry CH_2Cl_2 was added trifluoroacetic acid (0.068 g, 0.60 mmol, 45 µL) under argon atmosphere. After stirring for 2 h at 0 ^oC to rt, the mixture was concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography through silica gel (petroleum ether: ethyl acetate 40:60) to afford 2,3-diphenylspiro[cyclopentane-1,3'-indoline]-2',5-dione **61** as a white solid (0.043 g, 81% yield).

***R**f* (Pet. ether /EtOAc = 40/60): 0.47.

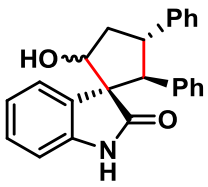
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H, NH), 7.55 (d, *J* = 7.2 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 2H), 7.07-7.03 (m, 3H), 6.95 (d, *J* = 7.1 Hz, 1H), 6.87-6.95 (m, 3H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.1 Hz, 2H), 4.11 (d, *J* = 3.8 Hz, 1H), 3.95 (d, *J* = 8.9 Hz, 1H), 3.68 (dd, J_1 = 4.2 Hz, J_2 = 11.8 Hz, 1H), 2.73 (dd, J_1 = 4.2 Hz, J_2 = 11.6 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 177.58, 173.36, 143.20, 142.22, 138.39, 128.97, 128.48, 128.18, 127.82, 127.31, 127.21, 127.06, 126.27, 126.09, 124.92, 121.31, 109.44, 51.01, 47.99, 44.04, 39.65.

HRMS calculated $[M+Na]^+$ for $C_{24}H_{19}O_2NNa$: 376.1308, found: 376.1313.

FTIR (cm^{-1}): 3410, 3063, 3025, 2942, 1960, 1890, 1715, 1637, 1592, 1493, 1450, 1375, 1315, 1269, 1166, 1039, 984, 870, 760, 697.

5-Hydroxy-2,3-diphenylspiro[cyclopentane-1,3'-indolin]-2'-one (62)



62

To a stirred solution of 2,3-diphenylspiro[cyclopentane-1,3'-indoline]-2',5-dione **61** (0.040 g, 0.11 mmol) in 2.0 mL of dry MeOH was added $NaBH_4$ (0.007 g, 0.17 mmol) under argon atmosphere. After stirring for 1 h at 0 ^oC 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 5-hydroxy-2,3-diphenylspiro[cyclopentane-1,3'-indolin]-2'-one **62** inseparable mixture of diastereomers as a white solid (0.031 g, 77% yield).

R$_f$ (Pet. ether /EtOAc = 40/60): 0.38.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H, NH, proton exchangeable with D_2O), 7.89 (d, *J* = 7.4 Hz, 1H), 7.70-7.65 (m, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.54-7.48 (m, 4H), 7.47-7.43 (m, 1H), 7.42-7.40 (m, 2H), 7.35-7.31 (m, 2H), 6.95 (d, *J* = 7.5 Hz, 1H), 4.75-4.70 (m, 1H), 4.65-4.53 (m, 1H), 4.22 (d, *J* = 11.9 Hz, 1H), 3.54-3.46 (m, 1H), 2.50-2.33 (m, 2H, OH peak is merged, one of the proton is exchangeable with D_2O);

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.59, 143.54, 141.23, 136.54, 128.60, 128.52, 128.48, 128.36, 128.10, 127.95, 127.88, 126.99, 126.34, 126.07, 122.42, 109.62, 75.94, 60.74, 46.37, 43.40.

Representative Peaks of Minor Isomer: **^{1}H NMR** δ 8.58 (s), 3.89 (d, *J* = 11.6 Hz), 2.89-2.82 (m), 2.70-2.62 (m).

^{13}C NMR δ 143.81, 140.28, 128.80, 128.64, 128.26, 128.04, 127.48, 124.98, 122.67, 110.26, 78.21, 66.61, 46.88, 43.58.

HRMS calculated $[M+H]^+$ for $C_{24}H_{22}O_2N$: 365.1645, found: 356.1643.

FTIR (cm^{-1}): 3442, 3039, 2975, 2935, 2728, 1950, 1682, 1600, 1485, 1380, 1260, 1162, 1111, 1024, 915, 858, 744, 704, 664.

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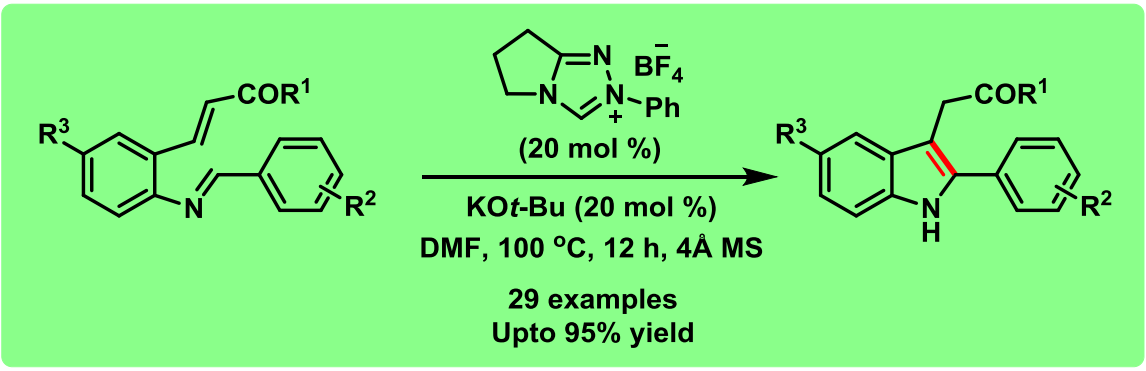
Chapter 4

NHC-Catalyzed Umpolung of Imines for the Synthesis of Indole 3-Acetic Acid Derivatives

In this chapter, we have demonstrated the umpolung of aldimines catalyzed by NHCs, and the reaction likely proceeds via the aza-Breslow intermediates. The NHC-catalyzed intramolecular cyclization of aldimines bearing a Michael acceptor resulted in the formation of biologically important indole 3-acetic acid derivatives in moderate to good yields. The carbene generated from the bicyclic triazolium salt was found to be efficient for this transformation. The reaction is compatible with respect to a wide variety of aldimines. Preliminary computational study indicates that the reaction proceeds via the umpolung of imines in preference to the umpolung of Michael acceptors.



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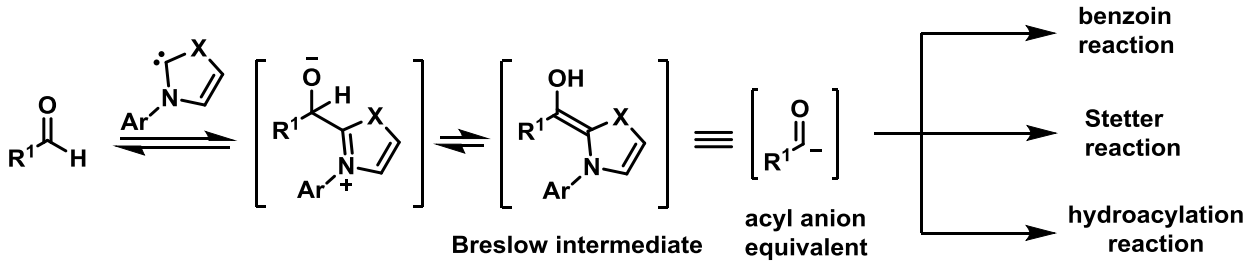
4.1. Introduction

The organocatalytic transformations catalyzed by N-heterocyclic carbenes (NHCs) have been widely used for the access of various carbocycles, heterocycles and acyclic compounds.[1] The underlying principle behind many of the NHC-organocatalytic reactions are based on the umpolung of aldehydes.[2] The nucleophilic acyl anion equivalents (Breslow intermediate)[3] generated by the addition of NHCs to aldehydes can add to a variety of carbonyl compounds (benzoin reaction), Michael acceptors (Stetter reaction), and even to unpolarized, electron-neutral carbon-carbon multiple bonds (hydroacylation reactions) (Scheme 4.1). Moreover, NHCs are employed for the conjugate umpolung of enals for the generation of homoenolate equivalents. In majority cases, the umpolung using NHCs is limited to aldehydes.

Scheme 4.1: Umpolung of Aldehyde (Breslow Intermediate)



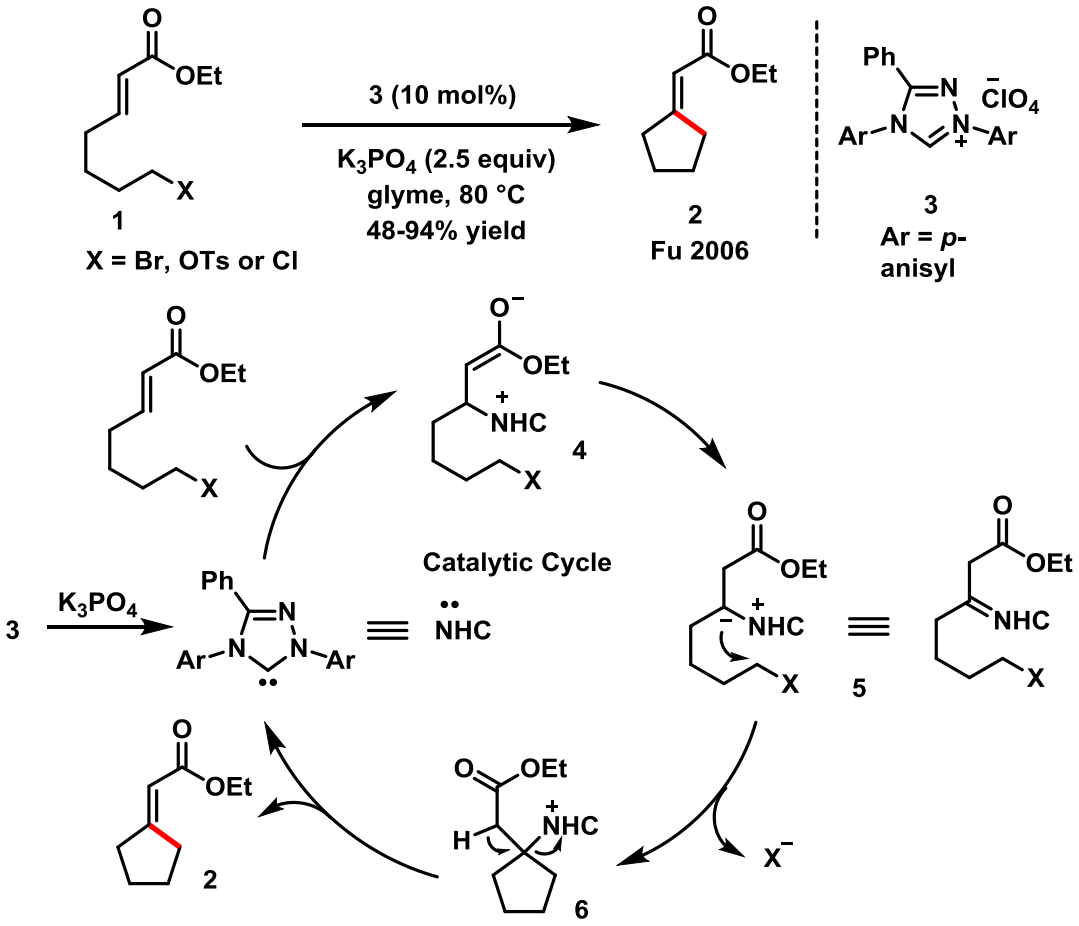
Moreover, NHCs are employed for the conjugate umpolung of enals for the generation of homoenolate equivalents. In majority cases, the umpolung using NHCs is limited to aldehydes.

4.2. Recent Developments on *Deoxy*-Breslow Intermediates

4.2.1. Umpolung of Michael Acceptors

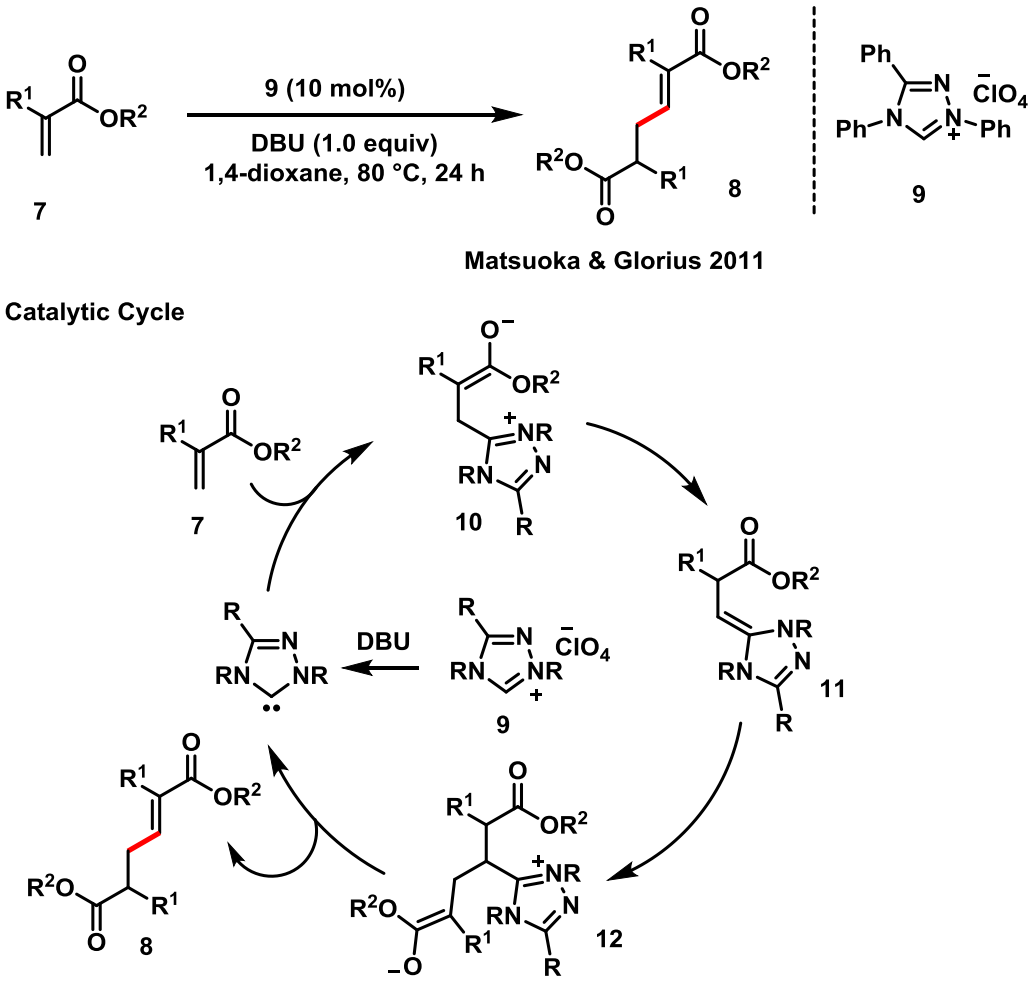
In view of these developments of aldehyde umpolung using NHCs, significant efforts have been directed towards different coupling partners (Michael acceptors). In 2006, Fu and coworkers extended the umpolung concept to Michael acceptors for the synthesis of cyclic α,β-unsaturated esters **2** from α,β-unsaturated esters **1** with good to excellent yields (Scheme 4.2).[4] This reaction proceeds through the formal *deoxy*-Breslow intermediate **5** generated from enolate **4**, which transforms the electrophilic β-carbon to nucleophilic. It can be considered as a NHC-catalyzed intramolecular Heck-type reaction. The reaction works with a broad range of Michael acceptors such as α,β-unsaturated esters, amides and nitriles.

Scheme 4.2: Umpolung of Michael Acceptors: β-Alkylation of α,β-Unsaturated Esters



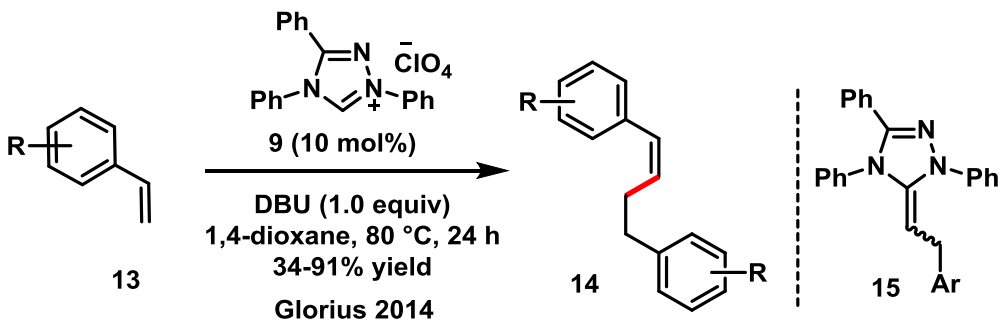
Later the Matsuoka[5] and Glorius[6] groups independently reported efficient tail to tail dimerization of methacrylates via the NHC-catalyzed umpolung of Michael acceptors (Scheme 4.3). Mechanistically, the reaction proceeds through the conjugate addition of NHC to the methacrylate **7** followed by proton transfer leading to the generation of *deoxy*-Breslow intermediate **11**. The Michael addition of **11** to the another molecule of methacrylate **7** forms the ester enolate **12**, which undergoes proton transfer followed by release of NHC to form the observed dimerized product **8** 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.[7] Subsequently, this chemistry have been reported for the β-coupling of methacrylates to form trimers, tetramers as well as polymers.[8] Interestingly, Zhang and Chen very recently uncovered the isolation of *deoxy*-Breslow intermediates formed from NHC-methacrylate reaction.[9]

Scheme 4.3: Umpolung of Methacrylates



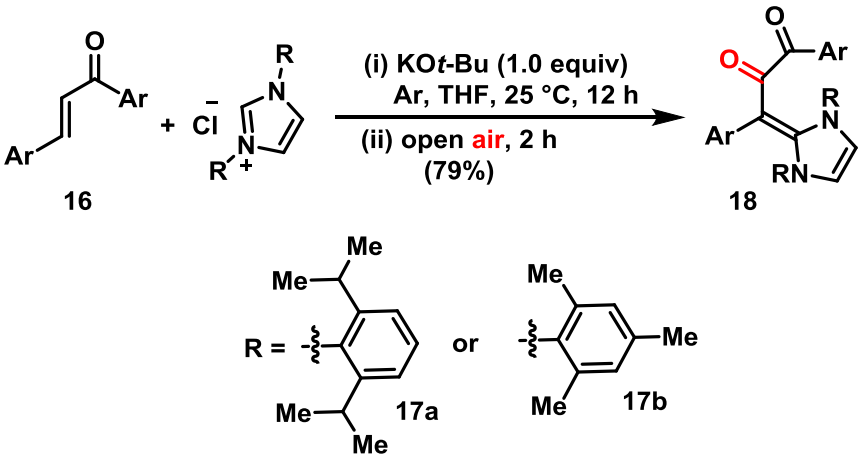
Glorius and co-workers developed the selective tail to tail dimerization of activated styrenes **13** (Scheme 4.4).[10] The reaction proceeds through the *deoxy*-Breslow intermediate **15**, which was isolated and characterized. Styrenes incorporating electron-withdrawing groups at the *para*-position of the aromatic ring and the vinyl pyridines worked efficiently to form the desired product **14**.

Scheme 4.4: Umpolung of Styrenes



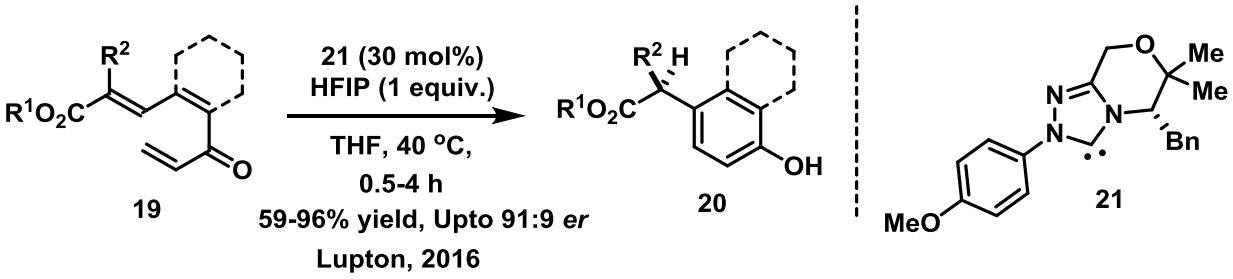
In 2015, Biju and co-workers developed the reaction of NHCs with chalcones **16** resulting in the synthesis of the oxidized form of the *deoxy*-Breslow intermediates **18** (Scheme 4.5).[11] Moreover, the tetrahedral intermediate formed from the initial addition of NHCs to chalcones has been isolated. However, catalysis using these intermediates, to the best of our knowledge is unknown.

Scheme 4.5: Synthesis of Oxidized *Deoxy*-Breslow Intermediate



Later Lupton and co-workers reported the NHC-catalyzed formation of β-anionic intermediates from enones **19** for the enantioselective synthesis of 2-aryl propionates **20** (Scheme 4.6).[12] Homochiral morpholinone derived triazolidine **21** found to be responsible for this transformation. This was the first example of enantioselective catalysis by umpolung of α,β-unsaturated ketones.

Scheme 4.6: Umpolung of α,β-Unsaturated Ketones

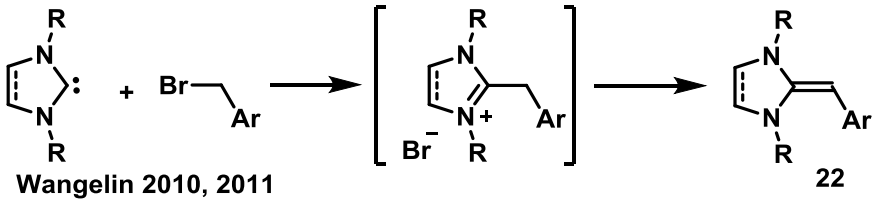


4.2.2. Umpolung of Alkyl Halides

However, the umpolung triggered by NHCs is mostly limited to aldehydes, and the use of other electrophiles has received only limited attention. Recently, Wangelin and co-workers reported the umpolung of alkyl halides leading to the isolation of *deoxy*-Breslow intermediates **22** (Scheme 4.7).[13] This work constitutes the first systematic study of the synthesis and stereo-

electronic properties of such enediamines that contain exocyclic alkene, diene, enyne, and styryl moieties and further unsaturation in the side chain (e.g., keto, cyclopropyl, epoxy, ester, nitrile functions). Furthermore, they performed a combined synthetic and theoretical study of the consequences of basicity, nucleophilicity, and sterics of N-heterocyclic carbenes in substitution reactions with benzyl bromides.[14] Subtle changes in the substitution pattern of the NHC can have a dramatic influence on reaction selectivity and stability of the resultant enediamines. Subsequently, Mayr and co-workers investigated the nucleophilic reactivties of these *deoxy*-Breslow intermediates through kinetic measurements.[15]

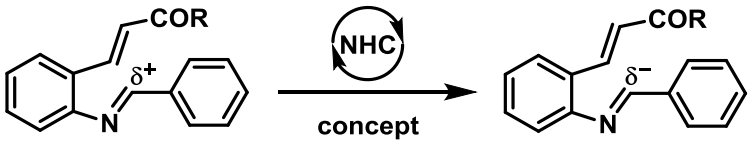
Scheme 4.7: Umpolung of Alkyl Halides (*Deoxy*-Breslow Intermediate)



4.3. Statement of the Problem

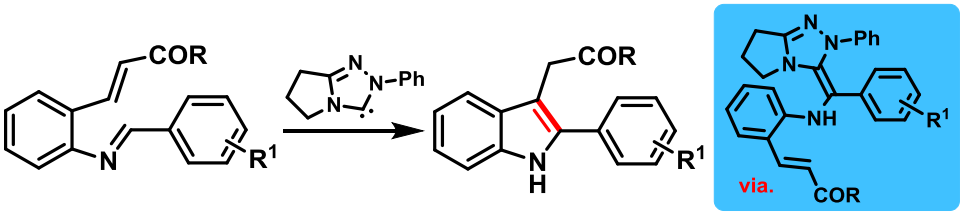
From the above mentioned literature, it is clear that the NHC-catalyzed umpolung is limited to aldehydes, Michael acceptors and alkyl halides. Notably, the reaction of NHCs with iminium salts resulting in the isolation of *aza*-Breslow intermediates was uncovered by Rovis and co-workers.[16] However, catalysis using these intermediates, to the best of our knowledge is unknown. We envisaged that if the reaction is carried out using proper imine substrate, there is a possibility of NHC-catalyzed umpolung of imine (Scheme 4.8).

Scheme 4.8: Proposed Methodology



A detailed study of the reaction of aldimines with NHCs is carried out in the present chapter.[17] NHC-catalyzed umpolung of aldimines likely proceeds via the aza-Breslow intermediates leading to the formation of biologically important 2-(hetero)aryl indole 3-acetic acid derivatives in moderate to good yields (Scheme 4.9). The carbene generated from the bicyclic triazolium salt was found to be efficient for this transformation. These results are being presented in the following sections.

Scheme 4.9: Umpolung of Imines

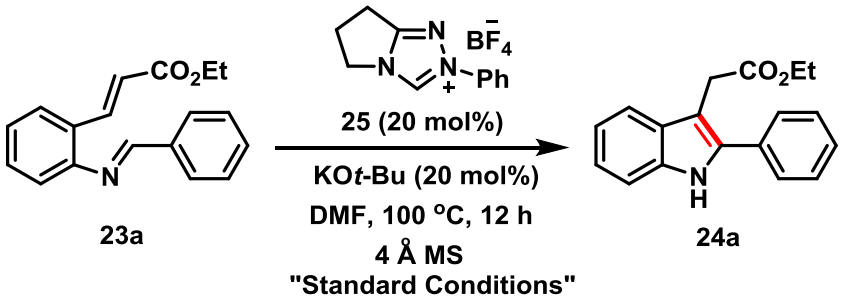


4.4. Results and Discussion

4.4.1. Optimization Studies

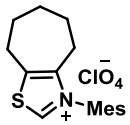
Our optimization study commenced with treatment of ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate **23a** in the presence of the carbene generated from **25** by deprotonation using KO*t*-Bu resulted in the formation of 2-aryl indole 3-acetic acid derivative **24a** in 82% yield (Table 4.1, entry 1, isolated yield). Notably, in contrast to this NHC, other common NHCs derived from precursors (**26, 17b, 9, 27, 28, 17a, 29**) are less effective (entries 2-8), and NHC derived from precursor 2**7** furnished **24a** in 52% yield (entry 5). Other bases such as K_2CO_3, DBU, and Et_3N furnished the desired product in reduced yields (entries 9-11). Among the various solvents screened, DMSO, 1,4-dioxane and Toluene resulted the desired product in reduced yields (entries 12-14). With decrease in temperature to 80 °C and RT reactivity decreases abruptly (entry 15 and 16). With increase or decrease the reaction time reactivity decreases (entry 17 and 18). Gratifyingly, when the reaction was performed using 1 mL of DMF instead of 2 mL of DMF furnished the desired product in reduced yield (entry 19). Additionally, decrease in catalyst loading to 15 mol% and 10 mol% reactivity decreases (entry 20 and 21).

Table 4.1: Optimization of the Reaction Conditions[a]



Entry	variation of the standard conditions	yield of **24a** (%)[b]
1	None	82(82)
2	**26** instead of **25**	<5
3	**17b** instead of **25**	<5
4	**9** instead of **25**	<5
5	**27** instead of **25**	52
6	**28** instead of **25**	<5
7	**17a** instead of **25**	<5
8	**29** instead of **25**	<5
9	K_2CO_3 instead of KO*t*-Bu	73
10	DBU instead of KO*t*-Bu	78
11	Et_3N instead of KO*t*-Bu	29
12	DMSO instead of DMF	72
13	1,4-dioxane instead of DMF	41
14	Toluene instead of DMF	<5
15	80 °C instead of 100 °C	38
16	30 °C instead of 100 °C	15
17	24 h instead of 12 h	71
18	6 h instead of 12 h	75
19	1 mL of DMF instead of 2 mL	52
20	15 mol% of **25** instead of 20 mol%	73
21	10 mol% of **25** instead of 20 mol%	71

[a] Standard conditions: **23a** (0.25 mmol.), **25** (0.05 mmol.), KO*t*-Bu (0.05 mmol.), DMF (2.0 mL), 4Å MS (50 mg), 100 °C, 12 h. [b] The yields were determined by ^{1}H-NMR analysis ($CDCl_3$) of crude products using CH_2Br_2 as the internal standard. Isolated yield in parentheses.



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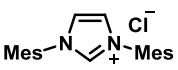
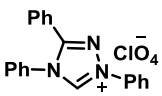


17b



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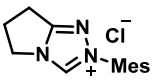

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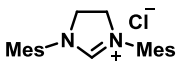

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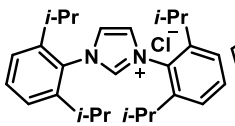
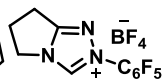


17a



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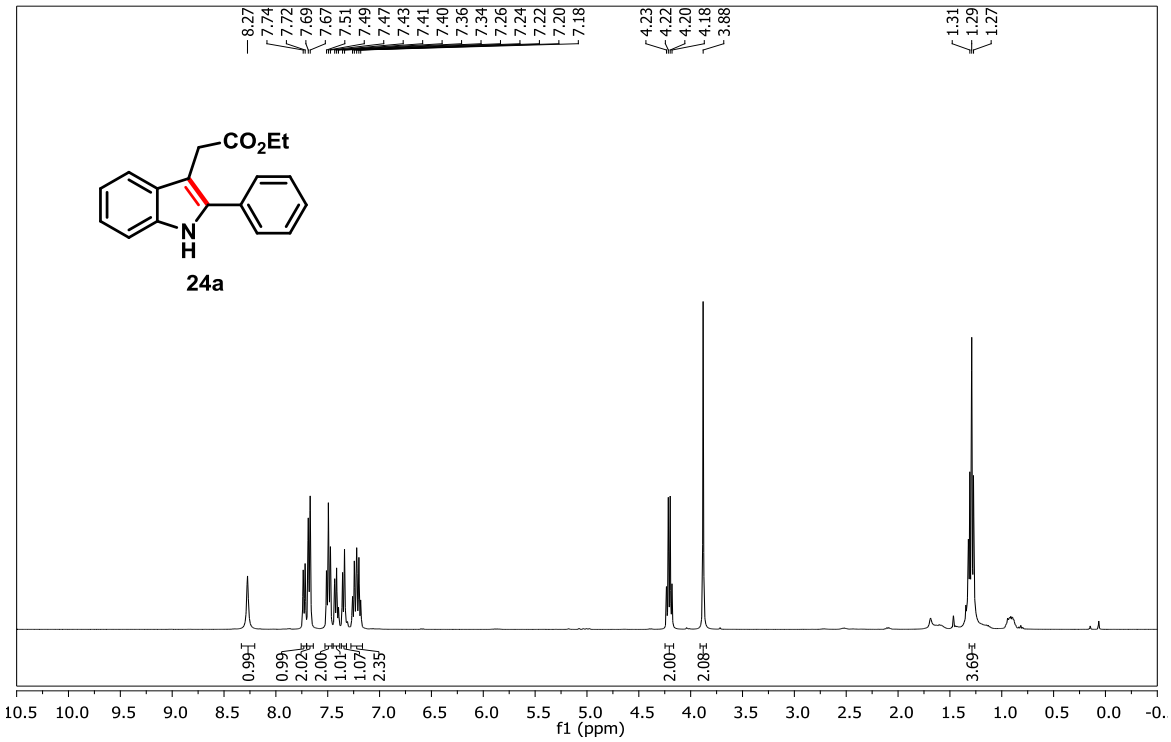
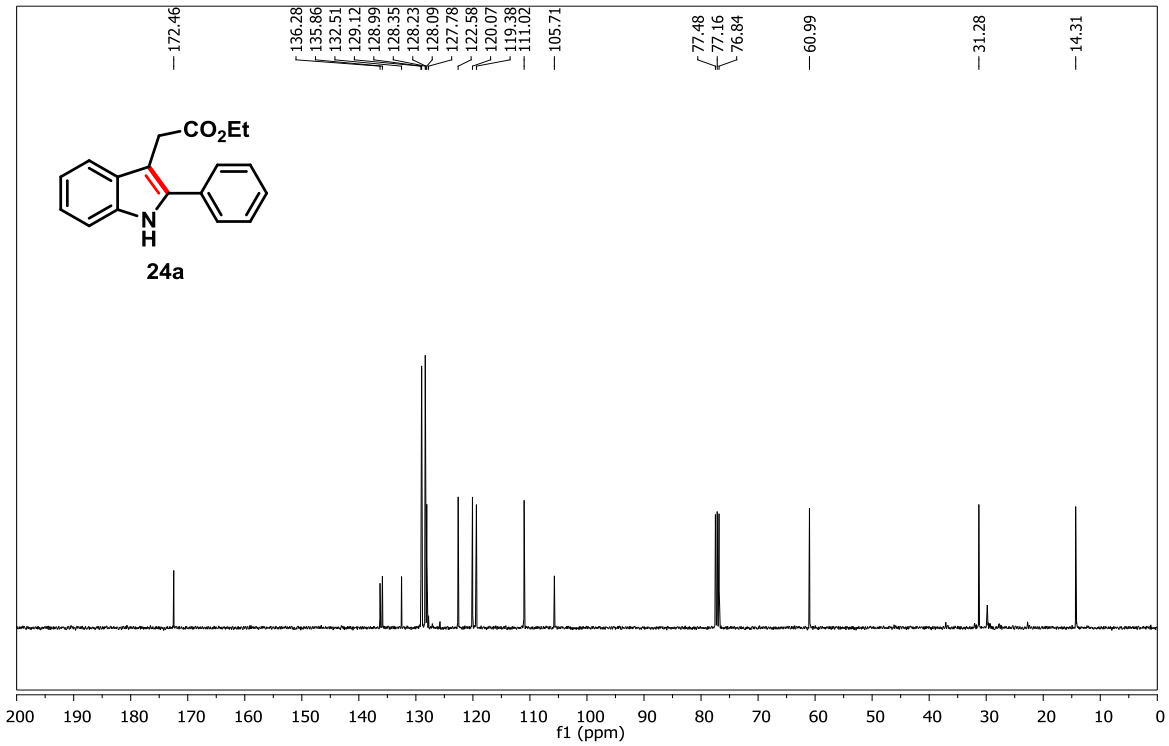
4.4.2. Spectral Data of 24a

^{1}H NMR Spectrum of 24a ($CDCl_3$)



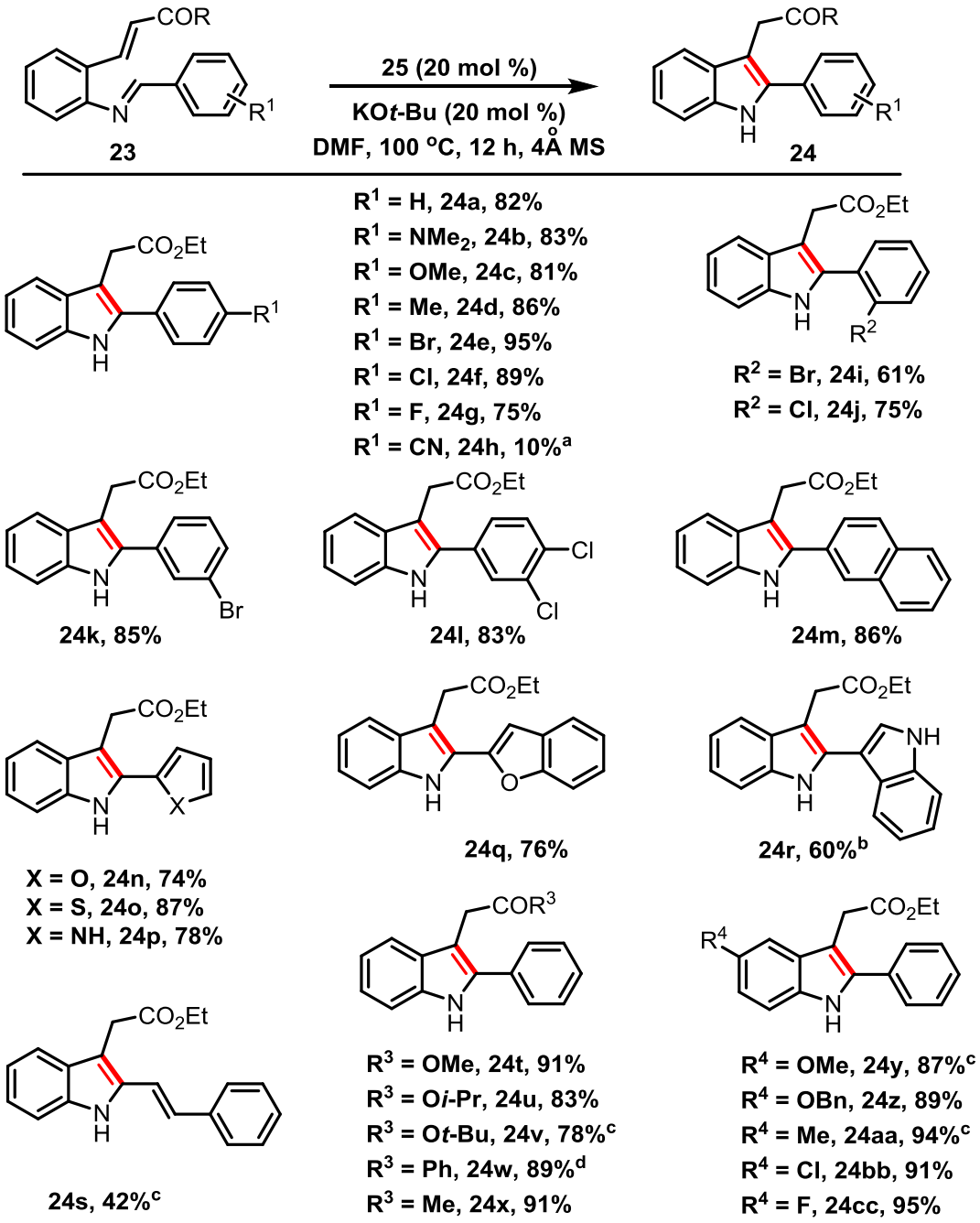
^{13}C NMR Spectrum of 24a ($CDCl_3$)



4.4.3. Substrate Scope

After deriving at the optimized reaction conditions, the scope of the reaction has been examined. A series of aldimines synthesized by the condensation of aromatic amines with the

Scheme 4.10: Scope of the NHC-Catalyzed Umpolung of Imines for the Synthesis of Indoles.



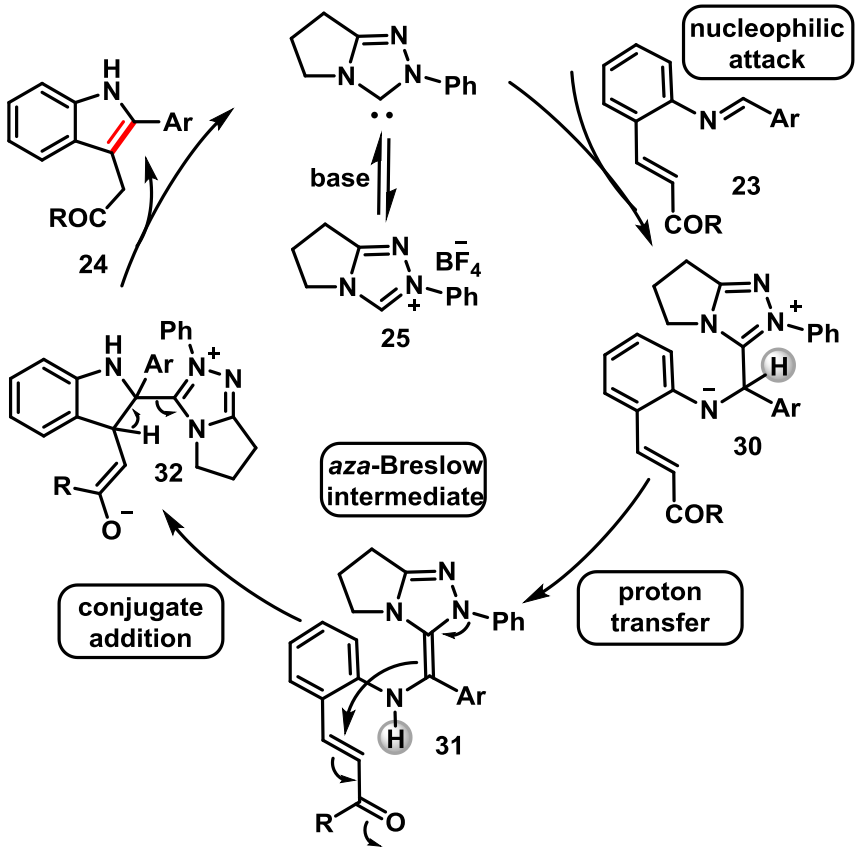
General conditions: **23** (0.5 mmol), **25** (0.1 mmol), KOt-Bu (0.1 mmol), DMF (4.0 mL), 4Å MS (100 mg), 100 °C, 12 h. Yields of the isolated products are given. [a] Reaction run for 36 h. [b] Run for 48 h. [c] Reaction run on 0.25 mmol Scale. [d] Structure confirmed by X-ray analysis.

aromatic aldehydes having electron-releasing, -neutral and moderately electron-poor groups at 4-position of the ring is well tolerated in the cyclization reaction to furnish the functionalized indoles in 75-95% yields (**24a-42g**). Disappointingly, imines formed from aldehydes having electron-withdrawing groups such as -CN at the 4-position furnished reduced yield of the indole product **24h** (Scheme 4.10). Moreover, substrates having 2-substitution, 3-substitution as well as disubstitution on the aryl ring of imine carbon underwent smooth umpolung using NHCs leading to the formation of the desired product in good yields (**24i-24m**). Additionally, various heterocyclic aldehyde-derived aldimines furnished the desired 2-heteroaryl indole derivatives in good yields (**24n-24r**). Interestingly, the α,β-unsaturated aldimine **23s** afforded the expected indole **24s** in 42% yield. Besides, sterically different alkoxycarbonyl groups at the Michael acceptor moiety were well tolerated and in all cases, the target product was formed in good yields (**24t-24v**). Furthermore, this reaction is not limited to α,β-unsaturated esters as Michael acceptor, but instead α,β-unsaturated ketones can also be used as the Michael acceptors providing the indole functionalized ketones in high yields (**24w-24x**). In the case of indole derivative **2w**, the structure was confirmed using single-crystal X-ray analysis. Finally, a series of aldimines with electron-releasing and -withdrawing groups at the N-aryl ring furnished the indoles in high yields (**24y-24cc**).

4.4.4. Tentative Mechanism

A proposed mechanism of this transformation is shown in Scheme 4.11. The free carbene generated from the precursor **25** undergoes a nucleophilic attack on the imine moiety of **23** generating the tetrahedral intermediate **30**, which on proton transfer forms the key *aza*-Breslow intermediate **31**. Disappointingly, all attempts to isolate the NHC-imine adduct failed in our hands.[18] The nucleophilic intermediate **31** then undergoes an intramolecular 1,4-addition (aza version of Stetter reaction) to form the ester/keto enolate **32**. The intermediate **32** upon proton transfer and elimination of NHC forms the desired product **24**. Preliminary computational results with density functional theory (DFT) at the TZVP/PBE level of theory indicate that the reaction proceeds via the umpolung of imines, as the more stable intermediate is found to be the one that lead to the imine umpolung.

Scheme 4.11: Tentative Mechanism of the Reaction

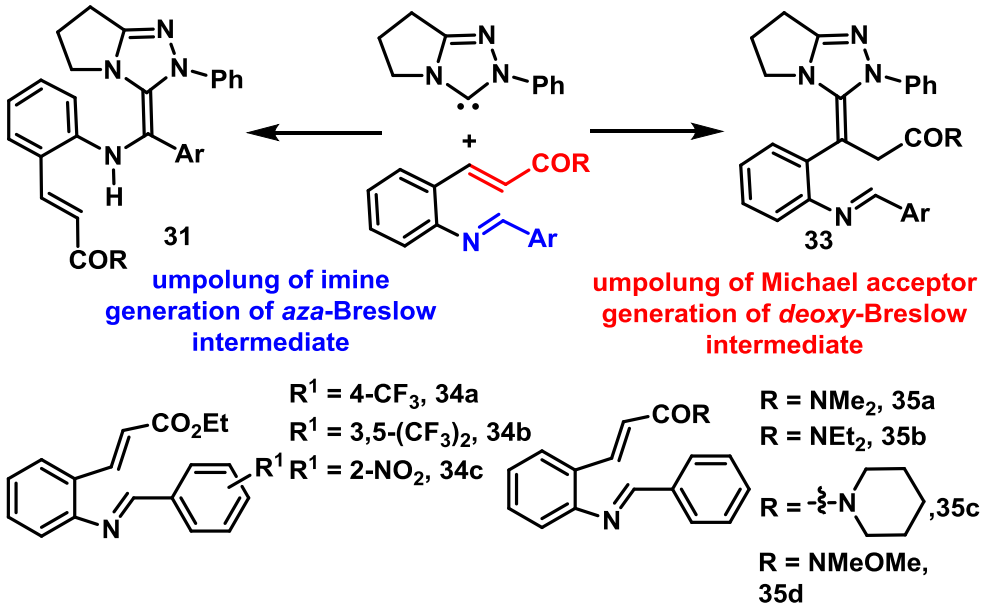


4.4.5. Mechanistic Studies

To get insight into the mechanism of this transformation, we performed several mechanistic experiments. The reaction likely proceeds via the umpolung of imine generating the *aza*-Breslow intermediate **31**. However, the indole product **24** can also be envisioned by the umpolung of Michael acceptor generating the deoxy-Breslow intermediate **33** followed by its interception with the imine and a subsequent release of carbene (Scheme 4.12). To get information on the mode of action in the present case, the NHC-catalyzed reaction has been performed with imines (**34a-34c**) derived from aromatic aldehydes having strongly electron-withdrawing groups. These reactions did not afford the expected indole derivative. It is reasonable to believe that the generated aza-Breslow intermediate in these cases will be less nucleophilic for the conjugate addition. Given the priority of umpolung of α,β-unsaturated esters bearing a β-substituent,[4] the absence of indole formation indicates that the umpolung of Michael acceptors is not operating in this case. This was again confirmed by the NHC-catalyzed reactions of various α,β-unsaturated amides (**35a-35d**). In this case also, the desired indole was not

formed. Naturally, the generated aza-Breslow intermediate cannot add to the weakly electrophilic α,β-unsaturated amides. It is noteworthy that umpolung of α,β-unsaturated amides are known by Fu and co-workers as early as 2006[4] and the absence of indole formation indicates that umpolung of Michael acceptors is not operating in the present case.

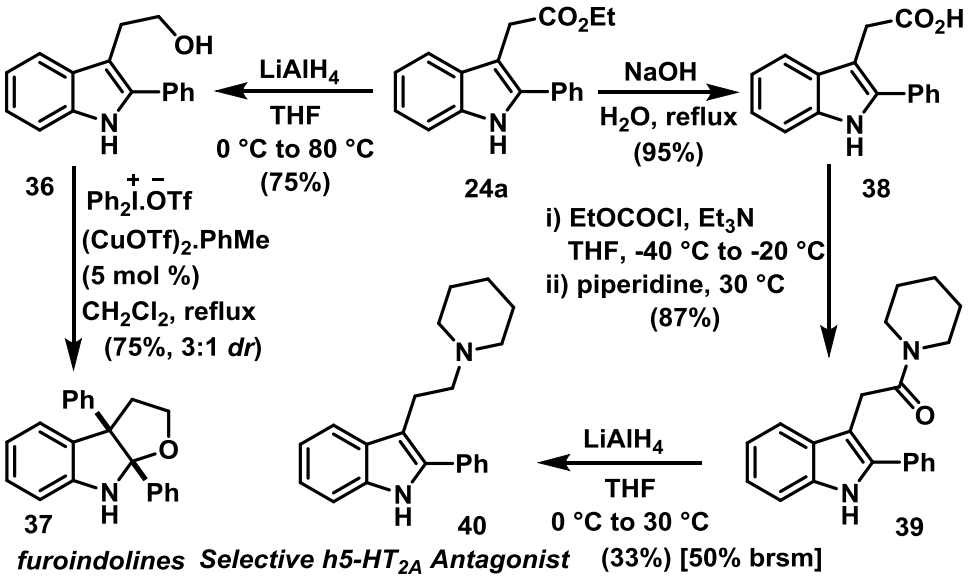
Scheme 4.12: Studies towards the Mechanism of this Reaction



4.4.7. Synthetic Transformation

We also performed the functionalization of indole 3-acetic acid derivative **24a**. Reduction of **24a** using $LiAlH_4$ afforded the alcohol **36** in 75% yield (Scheme 4.14). Cu-catalyzed arylation

Scheme 4.14: Functionalization of Indole 3-Acetic Acid Derivatives

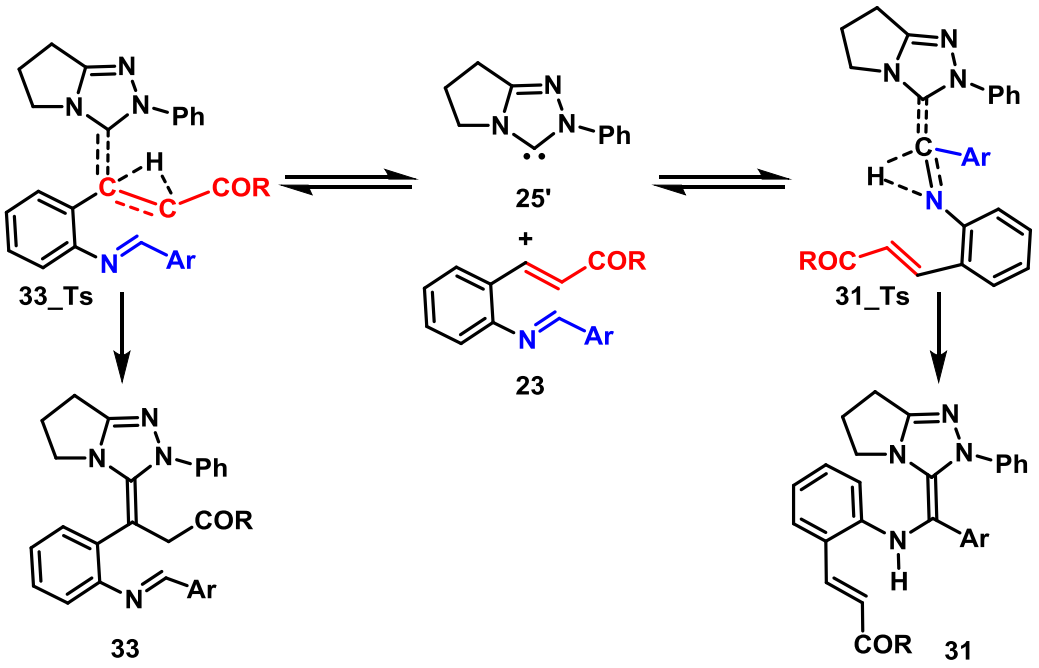


of **36**via dearomatization furnished furoindoline **37** having two quaternary carbon centres in 75% yield.[19] Moreover, basic hydrolysis of ester moiety in **24a** allowed the synthesis of acid **38** in 95% yield. Amidation of **38** using piperidine gave the amide **39** in 87% yield. The reduction of **39** under $LiAlH_4$ conditions afforded the tryptamine **40**, which is a high-affinity, selective h5-HT_{2A} antagonist.[20]

4.5. Computational Studies

All the DFT calculations were carried out using the Turbomole 7.0 suite of programs.[24] Geometry optimizations were performed using the Perdew, Burke, and Erzenhof density functional (PBE)[25] the electronic configuration of the atoms was described by a triple-ζ basis set augmented by a polarization function (Turbomole basis set TZVP).[26] The resolution of identity (ri)[27] along with the multipole accelerated resolution of identity (marij)[28] approximations were employed for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations. The real system has been employed for all the calculations. Care was taken to ensure that the obtained transition state structures possessed only one imaginary frequency corresponding to the correct normal mode. In order to obtain more reliable energy values for the investigated potential energy surface, solvent effects introduce by using the COSMO model,[29] with ε = 36.7, for dimethyl formamide (DMF). The values reported in

Scheme 4.15: Two possibility of formation of intermediates **31** and **33**



manuscript are ΔG values,with zero point energy ,internal energy and entropic contribution with the tempreture taken to be 373K. We have performed preliminary computational studies to shed light on the mechanism of this reaction. The obtained free energy profile for both intermediate **31** (derived from the umpolung of imines) and **33** (derived from the umpolung of Michael acceptors) is shown in Figure 1 and Figure 2. All ΔG values calculated in kcal/mol at 373 K.

Fig. 4.1 and Fig. 4.2 suggest that, formation of intermediate **31** is more exergonic (ΔG= -5.8 kcal/mol) than formation of intermediate **33** (ΔG= -3.4 kcal/mol). Kinetic study suggests that free energy barrier is almost same for both **31** ($\Delta G^{\#}$ = 41.1 kcal/mol) and **33** ($\Delta G^{\#}$ = 41.3 kcal/mol). This indicates C-Ts and B-Ts are in equilibrium with **23** and **25'**. But thermodynamic study suggests that the formation of intermediate **31** is stable by 2.4 kcal/mol than intermediate **33**. Hence, for the reaction performed for a sufficient period of time (12 h, at 100 °C), the thermodynamic product will prevail, and hence intermediate **31** would be the one preferred. Therefore, the results corroborate the experimental observation.

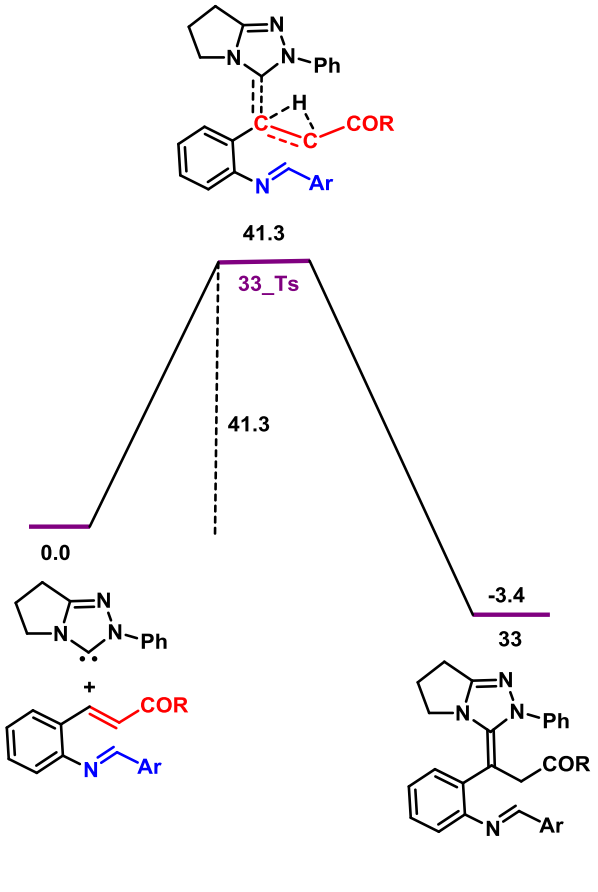


Fig. 4.1: Free energy profile (ΔG in kcal/mol) for formation of intermediate **31**

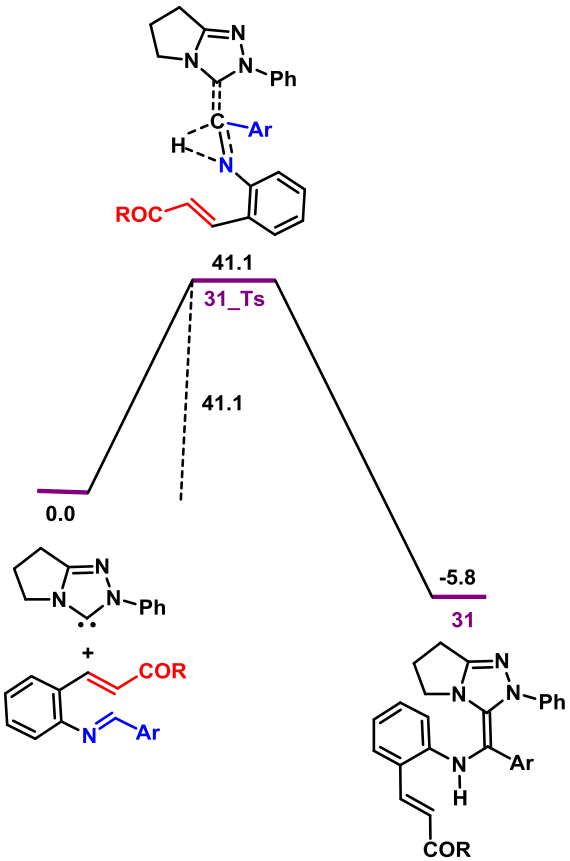


Fig. 4.2: Free energy profile (ΔG in kcal/mol) for formation of intermediate **33**

4.6. Conclusion

In conclusion, we have developed the NHC-catalyzed umpolung of imines for intramolecular reactions, and the reaction proceeds via the *aza*-Breslow intermediates. The reaction of aldimines having a Michael acceptor moiety under NHC-catalysis resulted in the formation of 2-(hetero)aryl indole 3-acetic acid derivatives in an *aza*-Stetter reaction. A preliminary computational study indicates that the reaction proceeds via the umpolung of imines in preference to the umpolung of Michael acceptors. Given the importance of indole scafold in medicine and natural products, the indole derivatives synthesized herein in high yields is expected to make the methodology important.

4.7. Experimental Details

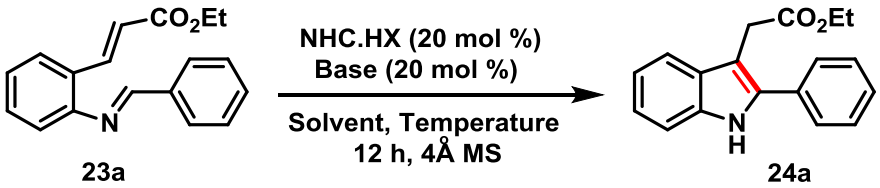
4.7.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw cap. Dry DMF was purchased from commercial sources and stored under argon over 4 Å molecular sieves. The 2-nitro benzaldehyde and aldehydes were purchased from commercial sources and were used without any further purification. The aldimines[21,22] were synthesized from corresponding aldehydes following the literature procedure. KOt-Bu was purchased from Sigma Aldrich and was used inside glove box. The triazolium salt **25** was synthesized following the literature procedure.[23]

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.

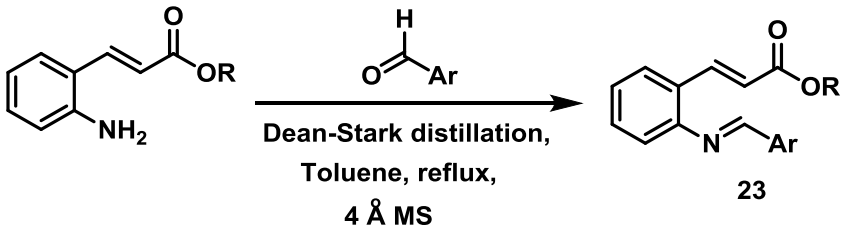
All compounds were fully characterized. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 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.

4.7.2. General Procedure for the Optimization of Reaction Conditions



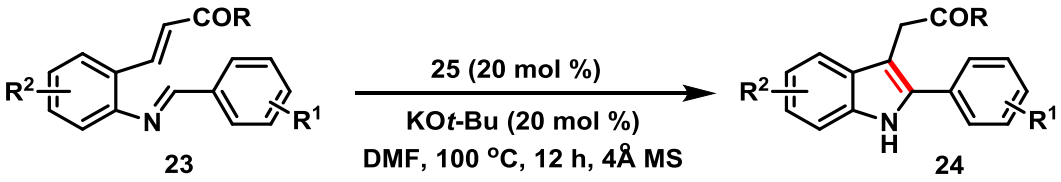
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the triazolium salt **25** (0.013 g, 0.05 mmol) and KO*t*-Bu base (0.006 g, 0.05 mmol) was added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added DMF (2.00 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at ambient temperature (25°C) for 10 min. To this mixture was added the aldimine **23a** (0.25 mmol) (solid aldimines were transferred to the screw-capped tube by closing the argon flow and liquid aldimines were transferred via syringe under argon flow) and 4 Å molecular sieves. Then the reaction mixture was stirred at 100° C for 12 h. After 12 hour stirring, work-up of the reaction mixture was done using EtOAc (2 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.

4.7.3. General Procedure for the Synthesis of Aldimines



To a 50 mL round-bottom flask equipped with Dean-Stark distillation were added (*E*)-2-aminocinnamic acid derivatives (1.0 equiv.) and toluene (15 mL). To the above solution were added aldehydes (1.0 equiv.) and 4 Å molecular sieves. The mixture was refluxed, after the complete conversion of starting material; the reaction mixture was concentrated in vacuo to furnish the crude product of compound **23** as yellow oil. The crude product was recrystallized in a mixture of diethyl ether and hexanes to afford the corresponding aldimines **23**.[21]

4.7.4. General Procedure for the Synthesis of 2-Aryl Indole 3-Acetic Acid Derivatives

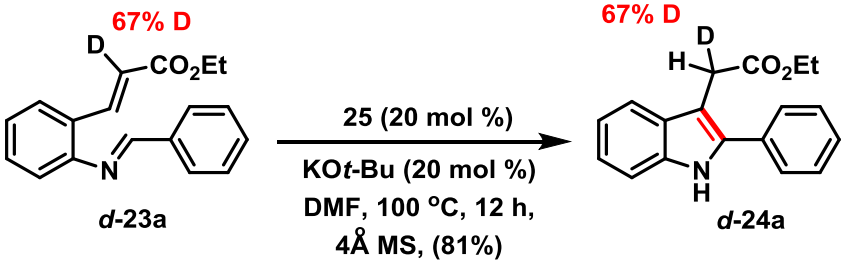


To a flame-dried screw-capped test tube equipped with a magnetic stir bar the triazolium salt **25** (0.027 g, 0.10 mmol) and KO*t*-Bu base (0.011 g, 0.10 mmol) was added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added DMF (4.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at ambient temperature (25°C) for 10 min. To this mixture was added the aldimine **23** (0.5 mmol) (solid aldimines were transferred to the screw-capped tube by closing the argon flow and liquid aldimines were transferred via syringe under argon flow) and 4 Å molecular sieves (100 mg). Then the reaction mixture was stirred at 100° C for 12 h. When the reaction is complete, work-up of the reaction mixture was done using EtOAc and organic fractions were dried with Na_2SO_4, solvent was evaporated. The crude residue was purified by flash column chromatography on silica gel to afford the corresponding 2-aryl indole 3-acetic acid derivative **24**.

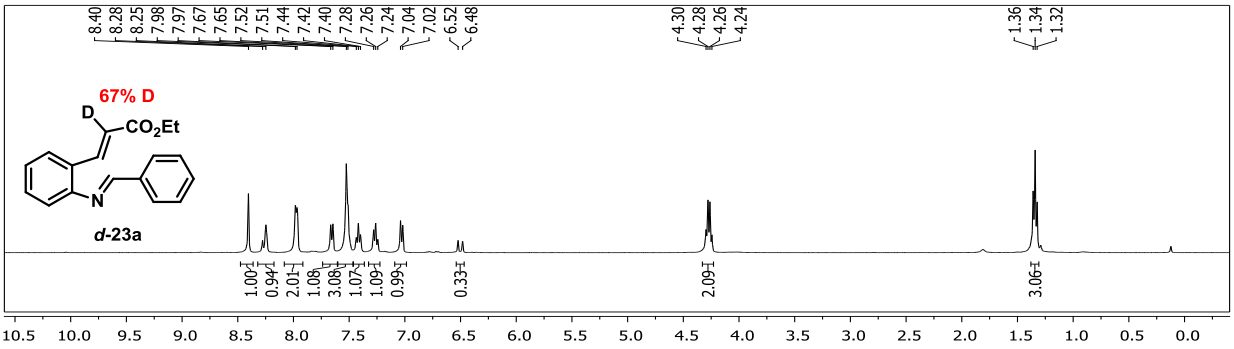
4.7.5. Mechanistic Experiments

Reactions Using Deuterium Labelled Imine Substrates

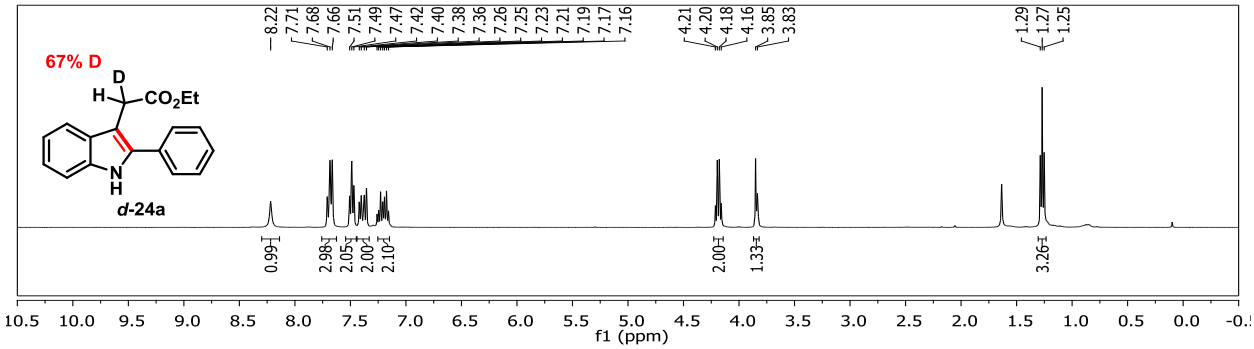
In first experiment, compound ***d*-23a** (having 67% Deuterium at the α-position of ester) was treated under the optimized reaction conditions. This reaction afforded the indole ***d*-24a** in 81% yield with 100% deuterium incorporation in the product.



^{1}H-NMR Spectrum of Ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate-2-*d* (*d*-23a)

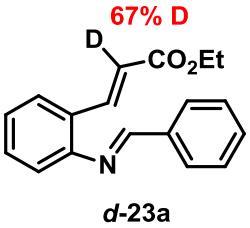


^{1}H-NMR Spectrum of Ethyl 2-(2-phenyl-1*H*-indol-3-yl)acetate-2-*d* (*d*-24a)



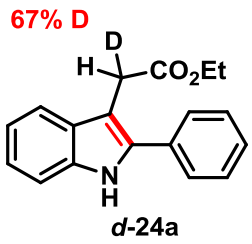
Ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate-2-*d* (*d*-23a)

Following the general known procedure,[21] treatment of ethyl (*E*)-3-(2-aminophenyl)acrylate-2-*d* (2.614 mmol.), benzaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate-2-*d* ***d*-23a** (0.432 g**,** 59 % yield) as a yellow solid.



***R**f* (Pet. ether /EtOAc = 90/10): 0.50; **^{1}H NMR (CDCl$_3$, 400 MHz)** δ 8.40 (s, 1H), 8.28-7.25 (m, 2H), 7.98 (d, J = 5.8 Hz, 2H), 7.66 (d, J = 7.7 Hz, 1H), 7.52-7.51 (m, 3H), 7.42 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 6.50 (d, J = 16.2 Hz, 1H (0.33H, 0.67D)), 4.27 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). **^{13}C NMR (CDCl$_3$, 100 MHz)** δ 167.24, 160.85, 151.38, 141.40, 131.78, 131.20, 129.15, 128.90, 128.48, 127.43, 126.10, 119.26, 118.86, 60.41, 14.39. **HRMS**: calculated $[M+H]^+$ for $C_{18}H_{17}DNO_2$: 281.1397, found: 281.1384. **FTIR (cm^{-1}):** 3061, 2981, 2895, 1954, 1705, 1624, 1587, 1478, 1449, 1366, 1308, 1248, 1189, 1101, 1041, 982, 884, 759, 692, 648.

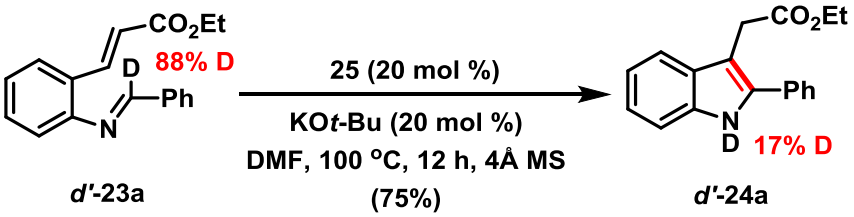
Ethyl 2-(2-phenyl-1*H*-indol-3-yl)acetate-2-*d* (*d*-24a)



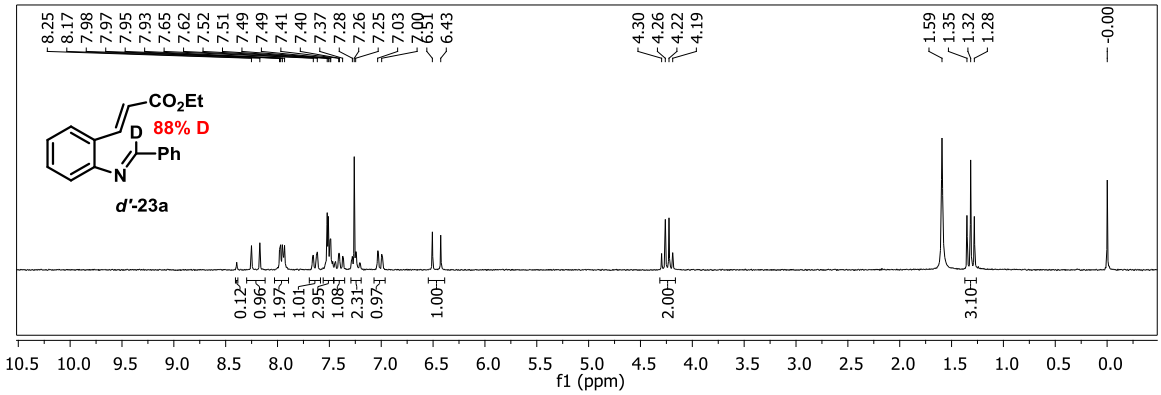
Following the general procedure, treatment of ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl) acrylate ***d*-23a** (140.2 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-phenyl-1*H*-indol-3-yl)acetate-2-*d* ***d*-24a** as a yellow solid (0.113 g, 81%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.40; **^{1}H NMR (CDCl$_3$, 400 MHz)** δ 8.22 (s, 1H), 7.71 – 7.76 (m, 3H), 7.49 (t, J = 7.5 Hz, 2H), 7.39 (dd, J = 18.4, 7.7 Hz, 2H), 7.20 (dt, J = 14.6, 7.1 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.85-3.83 (m, 2H (1.33H, 0.67D)) , 1.27 (t, J = 7.1 Hz, 3H). **^{13}C NMR (CDCl$_3$, 100 MHz)** δ 172.42, 136.30, 135.88, 132.55, 129.17, 129.04, 128.38, 128.15, 122.65, 120.13, 119.46, 110.99, 105.82, 60.99, 31.30, 14.34. **HRMS**: calculated $[M+H]^+$ for $C_{18}H_{17}DNO_2$: 281.1397, found: 281.1384. **FTIR (cm^{-1}):** 3396, 3058, 2982, 1720, 1603, 1489, 1454, 1369, 1308, 1245, 1185, 1107, 1029, 968, 921, 847, 744, 699.

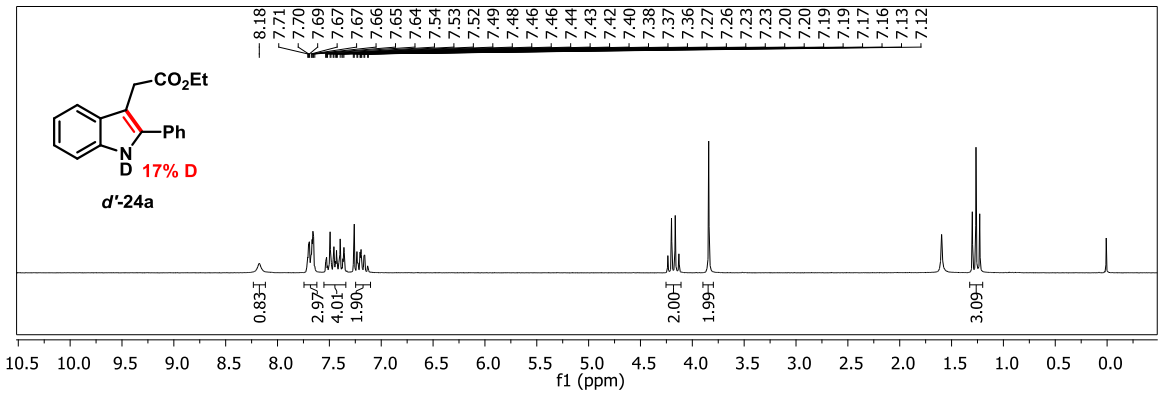
In another experiment, compound ***d'*-23a** (having 88% Deuterium at the imine carbon) was treated under our optimized reaction conditions. This reaction furnished indole ***d'*-24a** in 75% yield with 17% deuterium incorporation at the indole nitrogen in the product. This experiment is an indication that the tetrahedral intermediate generated by nucleophilic addition of free carbene on imine moiety ***d'*-23a** undergoes 1,2 deuterium shift to form aza- Breslow intermediate.



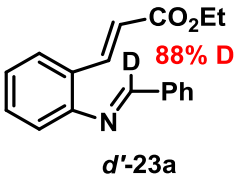
^{1}H-NMR Spectrum of Ethyl (*E*)-3-(2-(((*E*)-phenylmethylene-*d*)amino)phenyl)acrylate (*d'*-23a)



^{1}H-NMR Spectrum of Ethyl 2-(2-phenyl-1*H*-indol-3-yl-1-*d*)acetate (*d'*-24a)



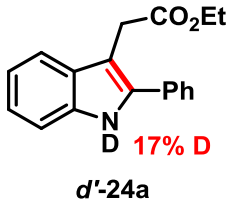
Ethyl (*E*)-3-(2-(((*E*)-phenylmethylene-*d*)amino)phenyl)acrylate (*d'*-23a)



Following the general known procedure,[21] treatment of ethyl (E)-3-(2-aminophenyl)acrylate (2.614 mmol.), benzaldehyde-α-*d* (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-phenylmethylene-*d*)amino)phenyl)acrylate ***d'*-23a** (0.418 g**,** 57 % yield) as a yellow solid.

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.50; **^{1}H NMR** (200 MHz, CDCl3) δ 8.39 (s, 1H (0.88D, 0.12H)), 8.21 (d, J = 16.2 Hz, 1H), 7.98-7.93 (m, 2H), 7.65-7.62 (m, 1H), 7.52 – 7.47 (m, 3H), 7.44 – 7.36 (m, 1H), 7.28 – 7.21 (m, 2H), 7.03-6.99 (m, 1H), 6.47 (d, J = 16.2 Hz, 1H), 4.24 (q, J = 7.1 Hz, 16H), 1.32 (t, J = 7.1 Hz, 25H). **HRMS**: calculated $[M+H]^+$ for $C_{18}H_{17}DNO_2$: 281.1395, found: 281.1387. **FTIR (cm^{-1}):** 3410, 3020, 2926, 2401, 2162, 1703, 1631, 1452, 1421, 1368, 1316, 1269, 1216, 1180, 1096, 1041, 928, 856, 756, 668.

Ethyl 2-(2-phenyl-1*H*-indol-3-yl-1-*d*)acetate (*d'*-24a)



d'-24a

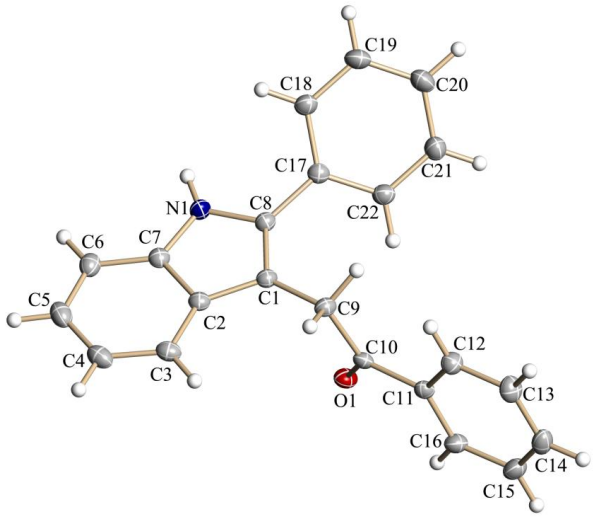
Following the general procedure, treatment of ethyl (*E*)-3-(2-(((*E*)-phenylmethylene-*d*)amino)phenyl)acrylate ***d'*-23a** (140.2 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-phenyl-1*H*-indol-3-yl-1-*d*)acetate ***d'*-24a** as a yellow solid (0.105 g, 75%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.41; **^{1}H NMR (CDCl$_3$, 400 MHz)** δ 8.18 (s, 1H (0.83H, 0.17D)), 7.71-7.64 (m, 3H), 7.54 – 7.36 (m, 4H), 7.27 – 7.12 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.84 (s, 2H), 1.26 (t, J = 7.1 Hz, 3H). **HRMS**: calculated $[M+H]^+$ for $C_{18}H_{17}DNO_2$: 281.1395, found: 281.1389. **FTIR (cm^{-1}):** 3465, 3020, 2980, 2401, 1726, 1604, 1526, 1456, 1425, 1370, 1307, 1216, 1032, 928, 877, 851, 772, 669.

4.7.6. X-ray Crystal Structure Analysis of 24w

X-ray intensity data measurement of compound **24w** was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with micro-focus sealed tube diffraction source (MoKα= 0.71073Å) at 100(2) K temperature. The X-ray generator was operated at 50 kV and 1.4 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 15 secs keeping the sample-to-detector distance fixed at 4.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[30] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[31] All the hydrogen atoms were placed in a geometrically idealized position and constrained to ride on their parent atoms.. The molecules of **24w** crystallized in triclinic P-1 space group containing two symmetry independednt moleucles in the asymmetriuc unit along with a molecule of dichloromethane as guest. An *ORTEP* III[32] view of unprimed molecule was drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

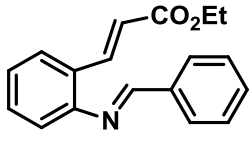
Crystal data of **24w**: $(C_{22}H_{17}N_2O_2)_2$ CH_2Cl_2, M = 707.66, colorless plate, 0.35 x 0.26 x 0.19 mm^3, triclinic, space group *P*-1, a = 11.6053(7) Å, b = 11.7949(6) Å, c = 15.3626(8) Å, α = 67.535(2)°, β = 68.697(2)°, γ = 71.831(3)°, V = 1773.60(17) $Å^3$, Z = 2, T = 100(2) K, $2\theta_{max}$ = 61.07°, D_{calc} (g cm–3) = 1.325, *F*(000) = 740, μ (mm^{-1}) = 0.226, 121686 reflections collected, 10823 unique reflections (R_{int}=0.0511), 9229 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.925, T_{max} = 0.958, 469 refined parameters, *S* = 1.043, *R*1 = 0.0367, w*R*2 = 0.0926 (all data *R* = 0.0451, w*R*2 = 0.0969), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.37, $\Delta\rho_{min}$ = -0.42 ($eÅ^{-3}$). **CCDC 1511141** This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



4.7.7. Synthesis and Characterization of Aldimines

Ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate (23a)

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (9.256 mmol.), benzaldehyde (9.256 mmol.) and 4 Å molecular sieves in toluene (50 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate **23a** (1.50 g**,** 58 % yield) as a yellow solid.



23a

***R**f* (Pet. ether /EtOAc = 90/10): 0.50.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (s, 1H), 8.27 (d, *J* = 16.2 Hz, 1H), 7.99-7.97 (m, 2H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.53-7.51 (m, 3H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.03

(d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 16.2 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.35 (t, J=7.1Hz, 3H).

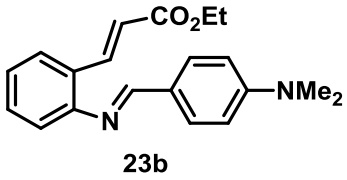
^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.24, 160.85, 151.38, 141.40, 131.78, 131.20, 129.15, 128.90, 128.48, 127.43, 126.10, 119.26, 118.86, 60.41, 14.39.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{18}O_2N$: 280.1332, found: 280.1332.

FTIR (cm^{-1}): 3068, 3020, 2401, 1703, 1631, 1594, 1479, 1452, 1369, 1315, 1270, 1217, 1181, 1095, 1041, 989, 886, 772, 691, 668.

Ethyl (*E*)-3-(2-(((*E*)-4-(dimethylamino)benzylidene)amino)phenyl)acrylate (23b)

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.614 mmol.), 4-(dimethylamino)benzaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-4-(dimethylamino)benzylidene)amino)phenyl)acrylate **23b** (0.550 g**,** 65 % yield) as a yellow solid.



23b

***R**f* (Pet. ether /EtOAc = 90/10): 0.35.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27-8.24 (m, 2H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.49 (d, *J* = 16.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.06 (s, 6H), 1.32 (t, *J* = 7.1 Hz, 3H);

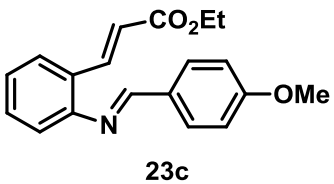
^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.47, 160.45, 152.79, 152.52, 142.01, 131.17, 130.86, 128.34, 127.53, 125.11, 124.44, 119.24, 118.85, 111.64, 60.34, 40.34, 14.46.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{23}O_2N_2$: 323.1754, found: 323.1748.

FTIR (cm^{-1}): 3019, 2903, 1702, 1629, 1602, 1588, 1555, 1529, 1479, 1447, 1367, 1315, 1269, 1216, 1171, 1125, 1095, 1042, 989, 946, 889, 819, 772, 668.

Ethyl (*E*)-3-(2-(((*E*)-4-methoxybenzylidene)amino)phenyl)acrylate (23c)

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.614 mmol.), benzaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-4-methoxybenzylidene)amino)phenyl)acrylate **23c** (0.30 g**,** 37 % yield) as a yellow solid.



23c

***R**f* (Pet. ether /EtOAc = 90/10): 0.47.

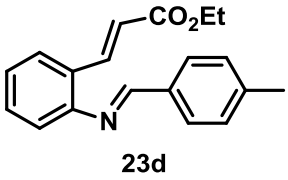
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (s, 1H), 8.23 (d, J = 16.1 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 7.7 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.6 Hz, 3H), 6.47 (d, J = 16.1 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.33, 162.59, 160.05, 151.75, 141.61, 131.20, 130.90, 129.22, 128.40, 127.44, 125.71, 119.05, 118.99, 114.32, 60.39, 55.52, 14.41.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{20}O_2N$: 310.1438, found: 310.1439.

FTIR (cm^{-1}): 3408, 3067, 3019, 2984, 1702, 1658, 1629, 1604, 1576, 1513, 1479, 1462, 1446, 1424, 1368, 1314, 1257, 1216, 1180, 1164, 1032, 988, 834, 772, 668.

Ethyl (*E*)-3-(2-(((*E*)-4-methylbenzylidene)amino)phenyl)acrylate (23d):



23d

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.614 mmol.), 4-methylbenzaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-4-methylbenzylidene)amino)phenyl)acrylate **23d** (0.314 g **,** 41% yield) as a orange red oil.

***R**$_f$* (Pet. ether /EtOAc = 90/10): 0.49.

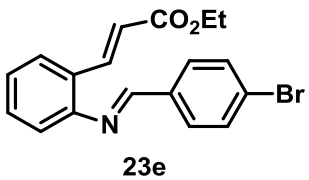
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (s, 1H), 8.24 (d, *J* = 16.2 Hz, 1H), 7.85 (d, *J* = 7.9Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.5Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 16.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.26, 160.72, 151.58, 142.32, 141.50, 133.60, 131.18, 129.63, 129.15, 128.42, 127.44, 125.89, 119.17, 118.93, 60.38, 21.72, 14.39.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{20}O_2N$: 294.1489, found: 294.1488.

FTIR (cm^{-1}): 3063, 3020, 2984, 2928, 1703, 1629, 1592, 1568, 1513, 1480, 1450, 1392, 1368, 1315, 1269, 1216, 1176, 1095, 1039, 986, 888, 867, 816, 770, 668.

2*E*)-Ethyl 3-((*E*)-2-(4-bromobenzylideneamino)phenyl)acrylate (23e):



23e

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.614 mmol.), 4-bromobenzaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl

ether and hexanes to afford the corresponding aldimine (2*E*)-ethyl 3-((*E*)-2-(4-bromobenzylideneamino)phenyl)acrylate **23e** (0.40 g **,** 42.7 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.45.

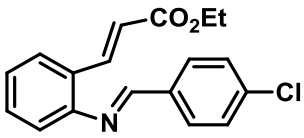
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (s, 1H),8.22 (d, *J* = 16.0 Hz, 1H), 7.81 (d, J=8.3Hz, 2H), 7.64 (t, *J* = 8.3 Hz, 3H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.18, 159.41, 150.89, 141.20, 134.96, 132.16, 131.20, 130.43, 128.57, 127.44, 126.37, 119.34, 118.67, 60.46, 14.40.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}O_2NBr$: 358.0437, found: 358.0440.

FTIR (cm^{-1}): 3063, 2982, 2901, 1705, 1629, 1589, 1564, 1487, 1448, 1367, 1316, 1268, 1176, 1095, 1068, 1037, 1010, 988, 886, 865, 822, 757.

(2*E*)-Ethyl 3-((*E*)-2-(4-chlorobenzylideneamino)phenyl)acrylate (23f)



23f

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.614 mmol.), 4-chlorobenzaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine (2*E*)-Ethyl 3-((*E*)-2-(4-chlorobenzylideneamino)phenyl)acrylate **23f** (0.38 g**,** 57.9 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.48.

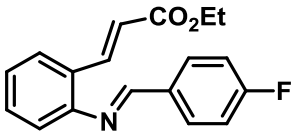
^{1}H NMR ($CDCl_3$, 400 MHz) 8.35 (s, 1H),8.20 (d, *J* = 16.2 Hz, 1H), 7.78 (d, *J* = 8.4, 2H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 16.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.27, 159.40, 151.02, 141.29, 131.26, 130.33, 129.29, 128.64, 127.50, 126.40, 119.40, 118.77, 60.52, 14.45.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}O_2NCl$: 314.0942, found: 314.0942.

FTIR (cm^{-1}): 3019, 2400, 1702, 1630, 1491, 1368, 1316, 1217, 1181, 1090, 1039, 771, 668.

(*E*)-Ethyl 3-(2-((*E*)-4-fluorobenzylideneamino)phenyl)acrylate (23g)



23g

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.614 mmol.), 4-fluorobenzaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition

for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine (*E*)-ethyl 3-(2-((*E*)-4-fluorobenzylideneamino)phenyl)acrylate **23g** (0.357 g**,** 46 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.42.

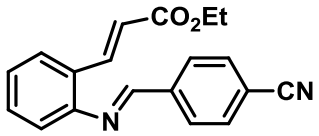
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (s, 1H), 8.25 (d, *J* = 16.2 Hz, 1H), 7.98 – 7.93 (m, 2H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 16.2 Hz, 1H), 4.27 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.21, 164.95 (d, JC-F = 252.6 Hz), 159.25, 151.09, 141.29, 132.46 (d, JC-F = 2.9 Hz), 131.20, 131.18, 131.09, 128.49, 127.38, 126.16, 119.21, 118.76, 116.06 (d, JC-F = 22.0 Hz), 60.43, 14.37.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}O_2NF$: 298.1238, found: 298.1235.

FTIR (cm^{-1}): 3447, 2982, 1708, 1629, 1599, 1568, 1509, 1479, 1450, 1416, 1367, 1316, 1267, 1237, 1221, 1178, 1094, 1037, 988, 837, 758.

Ethyl (*E*)-3-(2-(((*E*)-4-cyanobenzylidene)amino)phenyl)acrylate (23h)



23h

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.615 mmol.), 4-formylbenzonitrile (2.615 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-4-cyanobenzylidene)amino)phenyl)acrylate **23h** (469 mg**,** 59 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.35.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (s, 1H), 8.20 (d, *J* = 16.2 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.45 (d, *J* = 16.1 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

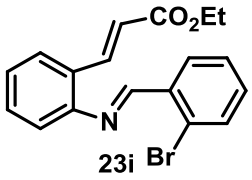
^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.17, 158.60, 150.28, 140.94, 139.77, 132.76, 131.30, 129.48, 128.98, 127.52, 127.12, 119.68, 118.48, 114.89, 60.61, 14.45.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{17}O_2N_2$: 305.1276, found: 305.1285.

FTIR (cm^{-1}): 3062, 2980, 2901, 2227, 1702, 1626, 1591, 1562, 1503, 1479, 1447, 1409, 1390, 1365, 1314, 1266, 1173, 1094, 1033, 986, 886, 866, 834, 759, 722, 645.

Ethyl (*E*)-3-(2-(((*E*)-2-bromobenzylidene)amino)phenyl)acrylate (23i)

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.61 mmol.), 2-bromobenzaldehyde (2.61 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-2-bromobenzylidene)amino)phenyl)acrylate **23i** (0.53 g**,** 54 % yield) as a yellow solid.



23i

***R**f* (Pet. ether /EtOAc = 90/10): 0.45.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.80 (s, 1H), 8.32 (d, *J* = 7.7 Hz, 1H), 8.23 (d, *J* = 16.1 Hz, 1H), 7.65 (t, *J* = 8.3 Hz, 2H), 7.46-7.41 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.47 (d, *J* = 16.1 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.33 (t, J=7.1Hz, 3H).

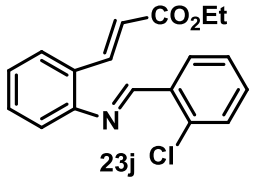
^{13}C NMR (CDCl$_3$, 100 MHz) δ 167.27, 159.88, 151.03, 141.29, 134.42, 133.40, 132.87, 131.33, 129.54, 128.81, 128.00, 127.39, 126.61, 119.41, 119.09, 60.53, 14.45.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}BrO_2N$: 358.0437, found: 358.0435.

FTIR (cm^{-1}): 3411, 3020, 2400, 1633, 1481, 1439, 1216, 928, 771.

Ethyl (*E*)-3-(2-(((*E*)-2-chlorobenzylidene)amino)phenyl)acrylate (23j)

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.61mmol.), 2-chlorobenzaldehyde (2.61mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-2-chlorobenzylidene)amino)phenyl)acrylate **23j** (0.37 g**,** 43 %yield) as a yellow solid.



23j

***R**f* (Pet. ether /EtOAc = 90/10): 0.48.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.87 (s, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 8.23 (d, *J* = 16.2 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.44-7.40 (m, 4H), 7.30-7.27 (m, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 16.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.33 (t, J=7.2Hz, 3H).

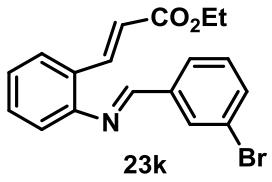
^{13}C NMR (CDCl$_3$, 100 MHz) δ 167.28, 157.54, 151.19, 141.30, 136.37, 133.11, 132.63, 131.32, 130.13, 129.07, 128.80, 128.15, 127.66, 127.40, 126.59, 123.25, 119.40, 119.04, 115.40, 60.53, 14.45.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}ClO_2N$: 314.0942, found: 314.0937.

FTIR (cm^{-1}): 3466, 3019, 2400, 1639, 1452, 1369, 1216, 1042, 928, 772, 669.

Ethyl (*E*)-3-(2-(((*E*)-3-bromobenzylidene)amino)phenyl)acrylate (23k)

Following the general known procedure,[21] treatment of ethyl (E)-3-(2-aminophenyl)acrylate



23k

(2.61 mmol.), 3-bromobenzaldehyde (2.61 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-3-bromobenzylidene)amino) phenyl)acrylate **23k** (421 mg**,** 45 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.45.

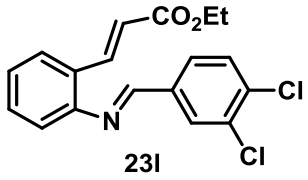
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.17 (d, *J* = 16.2 Hz, 1H), 8.08 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.0 Hz, 2H), 7.43 – 7.30 (m, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 16.2 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.23, 159.21, 150.82, 141.14, 138.09, 134.66, 131.81, 131.26, 130.50, 128.68, 127.83, 127.46, 126.57, 123.22, 119.52, 118.75, 60.56, 14.44.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}O_2NBr$: 358.0437, found: 358.0437.

FTIR (cm^{-1}): 3063, 3020 2982, 2901, 1705, 1630, 1592, 1563, 1480, 1448, 1427, 1390, 1366, 1316, 1268, 1216, 1180, 1094, 1066, 1038, 990, 892, 873,785, 762, 681, 592, 501, 469, 438.

Ethyl (*E*)-3-(2-(((*E*)-3,4-dichlorobenzylidene)amino)phenyl)acrylate (23l)



23l

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.614 mmol.), 3,4-dichlorobenzaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-3,4-dichlorobenzylidene)amino)phenyl)acrylate **23l** (0.437 g**,** 48 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.44.

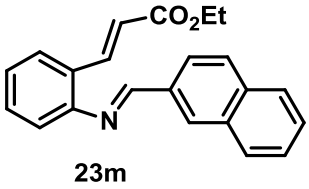
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (s, 1H), 8.03 (d, J = 16.1 Hz, 1H), 7.85 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.29 (d, J = 16.2 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.16, 158.06, 150.44, 141.00, 135.98, 135.88, 133.45, 131.26, 131.00, 130.57, 128.72, 127.99, 127.42, 126.73, 119.50, 118.60, 60.55, 14.41.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{15}O_2NCl_2$: 370.0372, found: 370.0373.

FTIR (cm^{-1}): 3408, 3020, 1708, 1631, 1438, 1368, 1315, 1282, 1216, 1113, 1042, 772, 668.

Ethyl (*E*)-3-(2-(((*E*)-naphthalen-2-ylmethylene)amino)phenyl)acrylate (23m)



23m

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.615 mmol.), 2-naphthaldehyde (2.615 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-naphthalen-2-ylmethylene)amino)phenyl)acrylate **23m** (422.0 mg**,** 49 % yield) as a yellow solid.

***R**f* (Pet. ether /EtOAc = 90/10): 0.40.

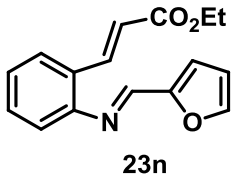
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.57 (s, 1H), 8.27 (dd, J_1 = 22.3, J_2 = 10.4 Hz, 3H), 7.94 (dd, J_1 = 17.0, J_2 = 8.0 Hz, 3H), 7.68 (d, J = 7.7 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.52 (d, J = 16.1 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.35, 160.92, 151.52, 141.50, 135.34, 133.98, 133.19, 131.89, 131.29, 129.00, 128.95, 128.66, 128.13, 127.89, 127.55, 126.82, 126.21, 124.11, 119.38, 118.95, 60.50, 14.47**.**

HRMS: calculated $[M+H]^+$ for $C_{22}H_{20}O_2N$: 330.1486, found: 330.1489.

FTIR (cm^{-1}): 3439, 3019, 1693, 1628, 1447, 1367, 1315, 1268, 1216, 1176, 1120, 1041, 859, 821, 771, 667, 502, 438, 415.

(*E*)-Ethyl 3-(2-((*E*)-furan-2-ylmethyleneamino)phenyl)acrylate (23n)



23n

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.614 mmol.), furan-2-carbaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine (*E*)-ethyl 3-(2-((*E*)-furan-2-ylmethyleneamino)phenyl)acrylate **23n** (0.36 g**,** 52 % yield) as a yellow solid.

***R**f* (Pet. ether /EtOAc = 90/10): 0.42.

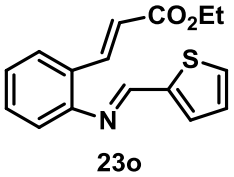
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18-8.15 (m, 2H), 7.64-7.61 (m, 2H), 7.38 (d, J = 7.7 Hz, 1H), 7.24-7.21 (m, 1H), 7.03-7.02 (m, 1H), 6.97 (d, J = 7.7 Hz, 1H), 6.58-6.57 (m, 1H), 6.46 (d, J = 15.9 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.31 (t, J=7.1Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.25, 152.28, 151.32, 148.80, 146.10, 141.31, 131.19, 128.54, 127.55, 126.22, 119.54, 118.95, 116.50, 112.43, 60.48, 14.45.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{16}O_3N$: 270.1125, found: 270.1122.

FTIR (cm^{-1}): 2984, 2094, 1705, 1630, 1469, 1393, 1367, 1316, 1266, 1219, 1177, 1095, 1036, 988, 934, 882, 833, 771.

Ethyl (*E*)-3-(2-(((*E*)-thiophen-2-ylmethylene)amino)phenyl)acrylate (23o):



23o

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.61 mmol.), thiophene-2-carbaldehyde (2.61 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine Ethyl (*E*)-3-(2-(((*E*)-thiophen-2-ylmethylene)amino)phenyl)acrylate **23o** (0.36 g**,** 46 % yield) as a yellow solid.

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.43.

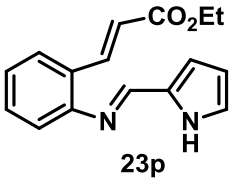
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 (s, 1H), 8.23 (d, *J* = 16.2 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 5.0 Hz, 1H), 7.52 (d, *J* = 3.4 Hz, 1H), 7.39 (t, *J* = 7.4 4Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.16-7.14 (m, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.35 (t, J=7.1Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.18, 153.38, 150.65, 142.86, 141.32, 132.57, 131.12, 131.07, 128.52, 127.93, 127.86, 127.62, 126.10, 119.42, 118.80, 60.35, 14.35.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{16}O_2NS$: 286.0896, found: 286.0894.

FTIR (cm^{-1}): 3066, 2979, 2901, 1702, 1629, 1590, 1479, 1365, 1267, 1174, 1042, 988, 878, 652.

Ethyl (*E*)-3-(2-(((*E*)-(1*H*-pyrrol-2-yl)methylene)amino)phenyl)acrylate (23p)



23p

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (5.229 mmol.), 1*H*-pyrrole-2-carbaldehyde (5.229 mmol.) and 4 Å molecular sieves in toluene (50 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-(1*H*-pyrrol-2-yl)methylene) amino) phenyl)acrylate **23p** (0.720 g**,** 51 % yield) as a yellow solid.

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.30.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.69 (bs, 1H), 8.26 (d, *J* = 16.1 Hz, 1H), 8.19 (s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.02-7.00 (m, 2H), 6.71 (d, *J* =

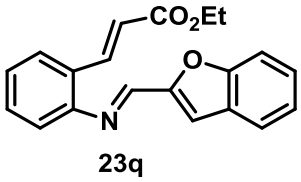
2.3 Hz, 1H), 6.44 (d, *J* = 16.2 Hz, 1H), 6.33 (bs, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.54, 151.36, 150.05, 141.72, 131.37, 131.07, 128.62, 127.23, 125.62, 123.57, 119.03, 118.70, 117.02, 110.76, 60.54, 14.48.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{17}O_2N_2$: 269.1285, found: 269.1283.

FTIR (cm^{-1}): 3453, 3020, 2979, 2401, 1670, 1617, 1592, 1526, 1479, 1420, 1369, 1317, 1267, 1216, 1082, 1035, 929, 881, 772, 669.

Ethyl (*E*)-3-(2-(((*E*)-benzofuran-2-ylmethylene)amino)phenyl)acrylate (23q)



23q

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.61 mmol.), benzofuran-2-carbaldehyde (2.61 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-benzofuran-2-ylmethylene)amino)phenyl) acrylate **23q** (0.61 g**,** 70 % yield) as a yellow solid.

***R**f* (Pet. ether /EtOAc = 90/10): 0.38.

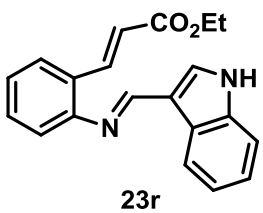
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (s, 1H), 8.23 (d, *J* = 16.2 Hz, 1H), 7.70-7.63 (m, 3H), 7.46-7.40 (m, 2H), 7.34-7.26 (m, 3H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 16.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.32 (t, J=7.2Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.21, 156.14, 153.09, 151.04, 149.55, 141.17, 131.21, 128.73, 127.85, 127.60, 127.41, 126.69, 123.78, 122.50, 119.79, 118.89, 113.37, 112.36, 60.54, 14.47.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{18}O_3N$: 320.1281, found: 320.1278.

FTIR (cm^{-1}): 3062, 2900, 1913, 1702, 1623, 1561, 1448, 1314, 1212, 1094, 989, 837, 650.

Ethyl (*E*)-3-(2-(((*E*)-(1*H*-indol-3-yl)methylene)amino)phenyl)acrylate (23r)



23r

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.614 mmol.), 1H-indole-3-carbaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-(1*H*-indol-3-yl)methylene)amino)phenyl)acrylate **23r** (0.34 g **,** 41.12 % yield) as a yellow solid.

***R**f* (Pet. ether /EtOAc = 90/10): 0.19.

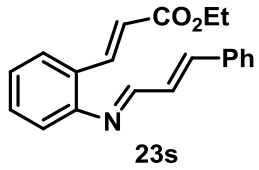
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.42 (s, 1H), 8.69-8.61 (m, 2H), 8.50 (s, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.57-7.52 (m, 2H), 7.37-7.35 (m, 4H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 16.4 Hz, 1H), 4.42 (d, *J* = 6.5 Hz, 2H), 1.48 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.15, 155.46, 153.16, 142.53, 137.03, 131.79, 131.57, 128.02, 127.11, 125.04, 123.55, 122.24, 121.87, 119.20, 118.15, 116.27, 111.60, 60.68, 14.44.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{19}O_2N_2$: 319.1441, found: 319.1438.

FTIR (cm^{-1}): 3020, 2983, 2937, 2402, 1694, 1657, 1620, 1591, 1565, 1535, 1478, 1423, 1394, 1369, 1318, 1295, 1270, 1245, 1216, 1186, 1104, 1043, 833, 777, 669.

Ethyl (*E*)-3-(2-(((*1E,2E*)-3-phenylallylidene)amino)phenyl)acrylate (23s)



23s

Following the general known procedure,[21] treatment of (*E*)-3-(2-aminophenyl)acrylate (2.614 mmol.), cinnamaldehyde (2.614 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*1E,2E*)-3-phenylallylidene)amino)phenyl)acrylate **23s** (0.41 g **,** 51.4 % yield) as a yellow solid.

***R**f* (Pet. ether /EtOAc = 90/10): 0.38.

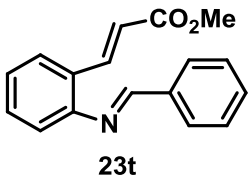
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19-8.15 (m, 2H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.0 Hz, 2H), 7.43-7.36 (m, 4H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.18-7.17 (m, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 16.1 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.26, 162.58, 151.58, 144.77, 141.36, 135.58, 131.17, 129.90, 129.08, 128.75, 128.44, 127.75, 127.43, 126.12, 119.39, 118.92, 60.51, 14.50.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{20}O_2N$: 306.1489, found: 306.1489.

FTIR (cm^{-1}): 2897, 2112, 1704, 1630, 1447, 1368, 1316, 1268, 1219, 1177, 1039, 988, 772.

Methyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate (23t)



23t

Following the general known procedure,[21] treatment of methyl (*E*)-3-(2-aminophenyl)acrylate (3.95 mmol.), benzaldehyde (3.95 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine methyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate **23t** (0.67 g**,** 57 % yield) as a yellow solid.

***R**f* (Pet. ether /EtOAc = 90/10): 0.48.

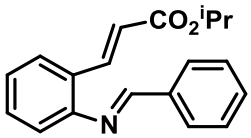
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (s, 1H), 8.22 (d, *J* = 16.2 Hz, 1H), 7.97-7.95 (m, 2H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.55-7.51 (m, 3H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 16.3 Hz, 1H), 3.79 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.75, 160.98, 151.55, 141.74, 136.14, 131.87, 131.32, 129.23, 128.99, 128.44, 127.64, 126.15, 118.97, 51.73.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{16}O_2N$: 266.1176, found: 266.1173.

FTIR (cm^{-1}): 3430, 3066, 3020, 2951, 2401, 1704, 1630, 1593, 1452, 1369, 1217, 1172, 1041, 988, 866, 668.

Isopropyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate (23u)



23u

Following the general known procedure,[21] treatment of isopropyl (E)-3-(2-aminophenyl)acrylate (1.5 mmol.), benzaldehyde (1.5 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine isopropyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate **23u** (257.8 mg**,** 41 % yield) as a yellow solid.

***R**$_f$* (Pet. ether /EtOAc = 90/10): 0.47.

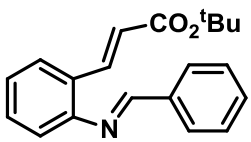
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (s, 1H), 8.22 (d, *J* = 16.2 Hz, 1H), 8.01 – 7.91 (m, 2H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 5.9 Hz, 3H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.45 (d, *J* = 16.2 Hz, 1H), 5.12 (dt, *J* = 12.4, 6.2 Hz, 1H), 1.30 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.83, 160.88, 151.40, 141.17, 136.19, 131.83, 131.18, 129.21, 128.96, 128.63, 127.38, 126.14, 119.77, 118.88, 67.75, 22.06.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{20}O_2N$: 294.1484, found: 294.1489.

FTIR (cm^{-1}): 3426, 3020, 2982, 2400, 1693, 1632, 1451, 1312, 1216, 1107, 1045, 772, 669, 494, 457, 439, 419.

***Tert*-butyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate (23v)**



23v

Following the general known procedure,[21] treatment of *tert*-butyl (E)-3-(2-aminophenyl)acrylate (3.42 mmol.), benzaldehyde (3.42 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the

corresponding aldimine *tert*-butyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate **23v** (0.76 g**,** 70 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.46.

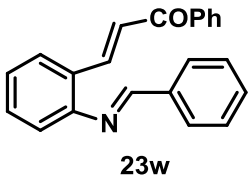
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (s, 1H), 8.16 (d, *J* = 16.1 Hz, 1H), 7.97-7.95 (m, 2H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.55-7.47 (m, 3H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 16.1 Hz, 1H), 1.52 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.64, 160.80, 151.32, 140.31, 136.22, 131.80, 131.03, 129.89, 129.20, 128.95, 128.71, 127.21, 126.12, 121.01, 118.83, 80.37, 28.33.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{22}O_2N$: 308.1645, found: 308.1640.

FTIR (cm^{-1}): 3440, 3020, 2980, 2400, 1697, 1631, 1453, 1368, 1216, 1152, 1044, 987, 772, 668.

(*E*)-3-(2-((*E*)-benzylideneamino)phenyl)-1-phenylprop-2-en-1-one (23w)



23w

Following the general known procedure,[22] treatment of (*E*)-3-(2-aminophenyl)-1-phenylprop-2-en-1-one (2.24 mmol.), benzaldehyde (2.24 mmol.) and magnesium sulphate (2.5 g) in DCM (12 mL) at rt for 12 h followed by recrystallisation in ethanol to afford the corresponding aldimine (*E*)-3-(2-((*E*)-benzylideneamino)phenyl)-1-phenylprop-2-en-1-one **23w** (0.200 g**,** 29 % yield) as a green solid.

R_f (Pet. ether /EtOAc = 90/10): 0.48.

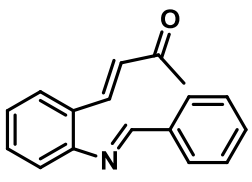
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (s, 1H), 8.27 (d, *J* = 15.9 Hz, 1H), 7.99-7.97 (m, 4H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 15.9 Hz, 1H), 7.57-7.49 (m, 4H), 7.44 (t, *J* = 7.6 Hz, 3H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.16, 160.83, 152.02, 142.25, 138.49, 136.11, 132.66, 131.95, 131.47, 129.22, 129.00, 128.84, 128.76, 128.71, 128.61, 126.19, 124.23, 119.01.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{18}ON$: 312.1383, found: 312.1379.

FTIR (cm^{-1}): 3018, 2400, 1657, 1631, 1490, 1450, 1333, 1268, 1215, 1017, 980, 770, 692.

(*E*)-4-(2-(((*E*)-benzylidene)amino)phenyl)but-3-en-2-one (23x)



23x

Following the general known procedure,[21] treatment of (*E*)-4-(2-aminophenyl)but-3-en-2-one (5.87 mmol.), benzaldehyde (5.87 mmol.) and 4 Å molecular sieves in toluene (15 mL) at reflux condition for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-4-(2-(((*E*)-

benzylidene)amino)phenyl)but-3-en-2-one **23x** (0.99 g**,** 64 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.45.

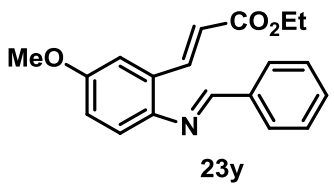
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (s, 1H), 8.11 (d, *J* = 16.7 Hz, 1H), 7.96-7.94 (m, 2H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.53-7.51 (m, 3H),7.43 (t, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.72 (d, *J* = 16.6 Hz, 1H), 2.83 (S, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.11, 161.05, 151.46, 140.49, 136.13, 131.98, 131.61, 129.13, 129.07, 128.63, 128.42, 127.27, 126.36, 118.90, 27.14.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{16}ON$: 250.1226, found: 250.1223.

FTIR (cm^{-1}): 3059, 2881, 1953, 1822, 1686, 1591, 1478, 1357, 1312, 1291, 1172, 1022, 977, 885, 737, 691.

Ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-methoxyphenyl)acrylate (23y)



23y

Following the known procedure,[22] treatment of ethyl (*E*)-3-(2-amino-5-methoxyphenyl)acrylate (1.36 mmol.), benzaldehyde (1.36 mmol.) and magnesium sulphate (1.5 g) in DCM (10 mL) at rt for 12 h followed by recrystallisation in ethanol to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-methoxyphenyl)acrylate **23y** (0.175 g**,** 42 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.25.

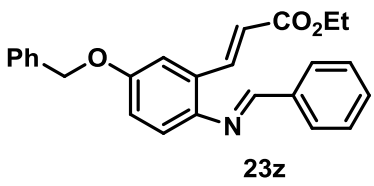
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (s, 1H), 8.34 (d, *J* = 16.2 Hz, 1H), 7.96 – 7.94 (m, 2H), 7.50 – 7.49 (m, 3H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.99 – 6.96 (m, 1H), 6.48 (d, *J* = 16.2 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 1H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.17, 159.20, 158.10, 144.53, 141.42, 136.36, 131.47, 130.02, 128.97, 128.86, 119.54, 119.27, 117.50, 111.25, 60.47, 55.61, 14.41.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{20}O_3N$: 310.1438, found: 310.1439.

FTIR (cm^{-1}): 3359, 2945, 2833, 2523, 2046, 1706, 1695, 1630, 1451, 1420, 1291, 1189, 1110, 1030, 816, 756.

Ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-(benzyloxy)phenyl)acrylate (23z)



23z

Following the known procedure,[22] treatment of ethyl (*E*)-3-(2-amino-5-(benzyloxy)phenyl)acrylate (3.36 mmol.), benzaldehyde (3.36 mmol.) and magnesium sulphate (3.5 g) in DCM (25 mL) at rt for 12 h followed by recrystallisation in ethanol to afford the

corresponding aldimine Ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-(benzyloxy)phenyl)acrylate **23z** (0.430 g**,** 33 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.23.

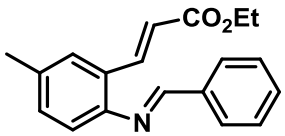
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (s, 1H), 8.31 (d, *J* = 16.2 Hz, 1H), 7.95 – 7.93 (m, 2H), 7.49 – 7.34 (m, 9H), 7.25 (s, 1H), 7.04 (s, 2H), 6.45 (d, *J* = 16.2 Hz, 1H), 5.11 (s, 2H), 4.26 (q, *J* = 7.0 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.22, 159.39, 157.32, 144.84, 141.40, 136.75, 136.38, 131.55, 130.09, 129.03, 128.92, 128.79, 128.26, 127.65, 119.62, 119.42, 118.32, 112.56, 70.49, 60.53, 14.45.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{24}O_3N$: 386.1751, found: 386.1752.

FTIR (cm^{-1}): 2945, 2833, 2523, 2048, 1705, 1659, 1452, 1114, 1030, 913, 745.

Ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-methylphenyl)acrylate (23aa)



23aa

Following the known procedure,[22] treatment of ethyl (*E*)-3-(2-amino-5-methylphenyl)acrylate (3.89 mmol.), benzaldehyde (3.89 mmol.) and $MgSO_4$ in DCM (20 mL) for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-methylphenyl)acrylate **23aa** (0.82 g**,** 68 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.45.

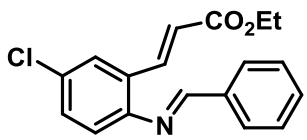
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (s, 1H), 8.26 (d, *J* = 16.2 Hz, 1H), 7.95-7.94 (m, 2H), 7.49-7.45 (m, 4H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 16.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.38 (S, 3H), 1.33 (t, J=7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.32, 160.17, 148.91, 141.55, 136.24, 135.83, 132.00, 131.61, 129.81, 129.07, 128.87, 128.45, 127.86, 118.97, 118.58, 60.38, 21.05, 14.41.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{20}O_2N$: 294.1489, found: 294.1490.

FTIR (cm^{-1}): 3413, 2979, 2868, 1705, 1629, 1579, 1484, 1452, 1391, 1367, 1314, 1263, 1219, 1174, 1099, 1049, 1034, 816, 751.

Ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-chlorophenyl)acrylate (23bb):



23bb

Following the known procedure,[21] treatment of ethyl (*E*)-3-(2-amino-5-chlorophenyl)acrylate (2.437 mmol.), benzaldehyde (2.437 mmol.) and 4 Å molecular sieves in toluene (10 mL) at reflux condition for 12

h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-chlorophenyl)acrylate **23bb** (0.290 g**,** 38 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.21.

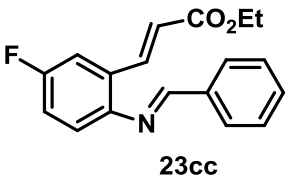
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (s, 1H), 8.14 (d, *J* = 16.2 Hz, 1H), 7.94 (d, *J* = 7.0 Hz, 2H), 7.60 (bs, 1H), 7.53-7.48 (m, 3H), 7.36-7.34 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.45 (d, *J* = 16.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.91, 161.29, 149.74, 140.05, 135.92, 132.10, 131.74, 130.97, 130.15, 129.30, 129.03, 127.11, 120.45, 120.18, 60.66, 14.42.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{18}O_2NCl$: 314.0942, found: 314.0944.

FTIR (cm^{-1}): 3385, 2952, 2842, 2515, 2124, 1703, 1648, 1635, 1453, 1408, 1312, 1164, 1112, 1053, 1030, 1017, 915, 813, 747.

Ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-fluorophenyl)acrylate (23cc)



23cc

Following the general known procedure,[22] treatment of ethyl (*E*)-3-(2-amino-5-methylphenyl)acrylate (6.73 mmol.), benzaldehyde (6.73 mmol.) and $MgSO_4$ in DCM (40 mL) for 12 h followed by recrystallisation in a mixture of diethyl ether and hexanes to afford the corresponding aldimine ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-fluorophenyl)acrylate **23cc** (1.20 g**,** 60 % yield) as a yellow solid.

R_f (Pet. ether /EtOAc = 90/10): 0.39.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.38 (s, 1H), 8.20 (dd, *J* = 16.2, 1.4 Hz, 1H), 7.97-7.92 (m, 2H), 7.52-7.49 (m, 3H), 7.33 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.16-7.98 (m, 2H), 6.43 (d, *J* = 16.1 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

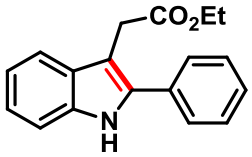
^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.93, 161.13 (d, $J_{C\text{-}F}$ = 244.0 Hz), 160.89, 147.49, 140.32, 136.06, 131.94, 130.41, 130.35, 129.21, 129.00, 120.34, 120.15 (d, $J_{C\text{-}F}$ = 8.1 Hz), 118.03 (d, $J_{C\text{-}F}$ = 22.9 Hz), 113.42 (d, $J_{C\text{-}F}$ = 22.8 Hz) 60.65.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}O_2NF$: 298.1238, found: 298.1239.

FTIR (cm^{-1}): 3383, 2948, 2840, 1705, 1628, 1578, 1479, 1450, 1425, 1367, 1317, 1272, 1238, 1211, 1156, 1097, 1030, 913, 815, 745.

4.7.8. Synthesis and Characterization of 2-Aryl Indole 3-Acetic Acid Derivatives

Ethyl 2-(2-phenyl-1*H*-indol-3-yl)acetate (24a)[21b]



24a

Following the general procedure, treatment of ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate **23a** (139.6 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-phenyl-1*H*-indol-3-yl)acetate **24a** as a yellow solid (0.115 g, 82%).

***R**f* (Pet. ether /EtOAc = 80/20): 0.40.

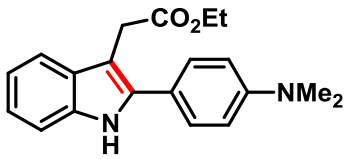
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.27 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.6, 2H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.43-7.40 (m, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.26-7.18 (m, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 2H), 1.29 (t, *J* = 7.1Hz, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 172.46, 136.28, 135.86, 132.51, 129.12, 128.99, 128.35, 128.09, 122.58, 120.07, 119.38, 111.02, 105.71, 60.99, 31.28, 14.31.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{18}O_2N$: 280.1332, found: 280.1332.

FTIR (cm^{-1}): 3465, 3019, 2983, 2932, 2401, 1726, 1605, 1457, 1426, 1370, 1308, 1216, 1179, 1114, 1031, 927, 772, 700, 669.

Ethyl 2-(2-(4-(dimethylamino)phenyl)-1*H*-indol-3-yl)acetate (24b)



24b

Following the general procedure, treatment of (*E*)-ethyl 3-(2-((*E*)-4-(dimethylamino)benzylideneamino)phenyl)acrylate **23b** (139.6 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-(4-(dimethylamino)phenyl)-1*H*-indol-3-yl)acetate **24b** as a yellow solid (0.139 g, 83%).

***R**f* (Pet. ether /EtOAc = 80/20): 0.25.

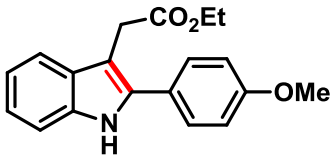
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.14 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 8.6, 2H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.20-7.15 (m, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 2H), 3.02 (s, 6H), 1.28 (t, J=7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.69, 150.27, 137.10, 135.63, 129.44, 129.22, 121.88, 120.34, 119.83, 119.01, 112.61, 110.71, 104.18, 60.87, 40.51, 31.44, 14.37.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{23}O_2N_2$: 323.1754, found: 323.1740.

FTIR (cm^{-1}): 3019, 2982, 2901, 2807, 2401, 1725, 1658, 1614, 1552, 1517, 1485, 1460, 1443, 1366, 1312, 1216, 1171, 1031, 944, 823, 773, 669.

Ethyl 2-(2-(4-methoxyphenyl)-1*H*-indol-3-yl)acetate (24c)[21b]



24c

Following the general procedure, treatment of (*E*)-ethyl 3-(2-((*E*)-4-methoxybenzylideneamino)phenyl)acrylate **23c** (77.3 mg, 0.25 mmol) with the triazolium salt **25** (13.6 mg, 0.05 mmol), KO*t*-Bu (5.5 mg, 0.05 mmol) and 4 Å molecular sieves in DMF (2.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-(4-methoxyphenyl)-1*H*-indol-3-yl)acetate **24c** as a white solid (0.125 g, 81%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.35.

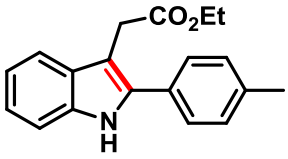
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (s, 1H), 7.67-7.59 (m, 3H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.22-7.13 (m, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.50, 159.69, 136.31, 135.72, 129.69, 129.25, 125.05, 122.37, 120.08, 119.29, 114.52, 110.85, 105.15, 60.97, 55.51, 31.34, 14.38.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{20}O_3N$: 310.1438, found: 310.1428.

FTIR (cm^{-1}): 3020, 2978, 2401, 2350, 1726, 1644, 1511, 1461, 1439, 1250, 1216, 1178, 1033, 909, 772, 669.

Ethyl 2-(2-p-tolyl-1*H*-indol-3-yl)acetate (24d)[21b]



24d

Following the general procedure, treatment of ethyl (*E*)-3-(2-(((*E*)-4-methylbenzylidene)amino)phenyl)acrylate **23d** (146.0 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-p-tolyl-1*H*-indol-3-yl)acetate **24d** as a yellow solid (0.126 g, 86%).

***R**f* (Pet. ether /EtOAc = 80/20): 0.39.

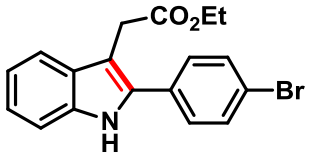
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.23-7.14 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 2H), 2.42 (s, 3H), 1.27 (t, *J*=7.1Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.46, 138.09, 136.43, 135.78, 129.75, 129.66, 129.23, 128.26, 122.48, 120.07, 119.36, 110.91, 105.46, 60.96, 31.33, 21.41, 14.36.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{20}O_2N$: 294.1489, found: 294.1487.

FTIR (cm^{-1}): 3018, 2983, 2925, 2400, 1722, 1622, 1508, 1489, 1459, 1369, 1306, 1217, 1177, 1113, 1030, 927, 824, 771.

Ethyl 2-(2-(4-bromophenyl)-1*H*-indol-3-yl)acetate (24e)



24e

Following the general procedure, treatment of (*E*)-ethyl 3-(2-((*E*)-4-bromobenzylideneamino)phenyl)acrylate **23e** (179.0 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-(4-bromophenyl)-1*H*-indol-3-yl)acetate **24e** as a yellow solid (0.170 g, 95%).

***R**f* (Pet. ether /EtOAc = 80/20): 0.38.

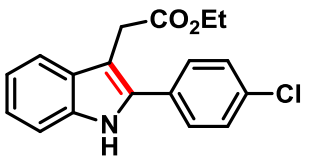
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.24-7.15 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 2H), 1.28 (t, J=7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.32, 135.95, 135.07, 132.17, 131.37, 129.78, 129.03, 122.94, 122.32, 120.29, 119.42, 111.08, 106.23, 61.12, 31.21, 14.34.

HRMS: calculated $[M+Na]^+$ for $C_{18}H_{16}O_2NBrNa$: 380.0257, found: 380.0255.

FTIR (cm^{-1}): 3463, 3019, 1725, 1486, 1458, 1370, 1312, 1216, 1074, 1029, 1011, 929, 831, 772, 669.

Ethyl 2-(2-(4-chlorophenyl)-1*H*-indol-3-yl)acetate (24f)[21b]



24f

Following the general procedure, treatment of ethyl (*E*)-ethyl 3-(2-((*E*)-4-chlorobenzylideneamino)phenyl)acrylate **23f** (156.8 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C

for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-(4-chlorophenyl)-1*H*-indol-3-yl)acetate **24f** as a yellow solid (0.140 g, 89%).

***R*$_f$** (Pet. ether / EtOAc = 80/20): 0.40.

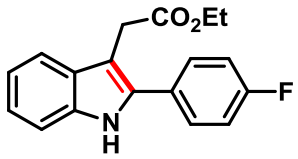
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.25 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.58-7.55 (m, 2H), 7.43-7.40 (m, 2H), 7.31-7.28 (m, 1H), 7.23-7.16 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 172.38, 135.93, 135.08, 134.11, 130.92, 129.51, 129.21, 129.02, 122.90, 120.26, 119.40, 111.08, 106.16, 61.12, 31.21, 14.33.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}O_2NCl$: 314.0942, found: 314.0942.

FTIR (cm^{-1}): 3462, 3020, 2982, 2401, 1725, 1643, 1487, 1458, 1370, 1312, 1216, 1180, 1094, 1030, 927, 835, 773, 669.

Ethyl 2-(2-(4-fluorophenyl)-1*H*-indol-3-yl)acetate (24g)[21b]



24g

Following the general procedure, treatment of ethyl (*E*)-3-(2-(((*E*)-4-fluorobenzylidene)amino)phenyl)acrylate **23g** (148.7 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-(4-fluorophenyl)-1*H*-indol-3-yl)acetate **24g** as a yellow solid (0.111 g, 75%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.35.

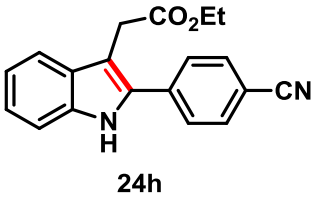
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.19 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.62 (dd, J_1 = 8.3, J_2 =5.5 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.24 – 7.13 (m, 4H), 4.18 (t, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 172.39, 162.73 (d, $J_{C\text{-}F}$ = 248.4 Hz), 135.84, 135.38, 130.16 (d, $J_{C\text{-}F}$ = 8.1 Hz), 129.04, 128.66, 122.73, 120.23, 119.40, 116.04 (d, $J_{C\text{-}F}$ = 21.6 Hz), 111.01, 105.85, 61.07, 31.23, 14.34.

HRMS: calculated $[M+Na]^+$ for $C_{18}H_{16}O_2NFNa$: 320.1057, found: 320.1052.

FTIR (cm^{-1}): 3464, 3020, 2980, 2401, 1726, 1601, 1507, 1459, 1437, 1370, 1310, 1216, 1158, 1031, 928, 877, 843, 772, 669.

Ethyl 2-(2-(4-cyanophenyl)-1*H*-indol-3-yl)acetate (24h)



24h

Following the general procedure, treatment of Ethyl (E)-3-(2-(((E)-4-cyanobenzylidene)amino)phenyl)acrylate **23h** (152.2 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-(4-cyanophenyl)-1*H*-indol-3-yl)acetate **24h** as a yellow solid (15.0 mg, 10 %).

***R**_f* (Pet. ether /EtOAc = 80/20): 0.21.

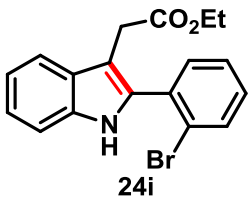
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.75 – 7.66 (m, 3H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.03, 136.96, 136.38, 134.04, 132.80, 129.02, 128.56, 123.77, 120.65, 119.79, 118.87, 111.28, 108.00, 61.30, 31.25, 14.35.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{17}O_2N_2$: 305.1276, found: 305.1285.

FTIR (cm^{-1}): 3459, 3020, 2983, 2400, 2253, 2229, 1724, 1644, 1609, 1493, 1454, 1370, 1316, 1265, 1216, 1182, 1029, 909, 845, 772, 668, 649, 502, 454, 440, 412.

Ethyl 2-(2-(2-bromophenyl)-1*H*-indol-3-yl)acetate (24i)[21b]



24i

Following the general procedure, treatment of Ethyl (*E*)-3-(2-(((*E*)-2-bromobenzylidene)amino)phenyl)acrylate **23i** (179.0 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded Ethyl 2-(2-(2-bromophenyl)-1*H*-indol-3-yl)acetate **24i** as a yellow solid (0.109 g, 61%).

***R**_f* (Pet. ether /EtOAc = 80/20): 0.39.

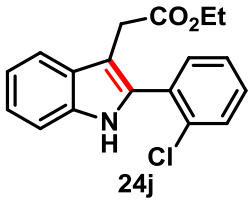
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (s, 1H), 7.73-7.70 (m, 2H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.41 (dd, J_1 = 17.5 Hz, J_2 = 7.9 Hz, 2H),7.33-7.24 (m, 2H), 7.19 (t, *J*=7.4 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 2H), 1.23 (t, *J*=7.1Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.02, 135.59, 134.74, 133.33, 133.26, 133.17, 130.27, 127.92, 127.48, 123.99, 122.76, 120.01, 119.54, 111.12, 107.45, 60.86, 31.20, 14.30.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}BrO_2N$: 358.0437, found: 358.0431.

FTIR (cm^{-1}): 3466, 3400, 3019, 2936, 2400, 1726, 1598, 1564, 1476, 1369, 1267, 1180, 1026, 771, 694, 668.

Ethyl 2-(2-(2-chlorophenyl)-1*H*-indol-3-yl)acetate (24j)



24j

Following the general procedure, treatment of Ethyl (*E*)-3-(2-(((*E*)-2-chlorobenzylidene)amino)phenyl)acrylate **23j** (159.0 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded Ethyl 2-(2-(2-chlorophenyl)-1*H*-indol-3-yl)acetate **24j** as a yellow solid (0.120 g, 75%).

***R*$_f$** (Pet. Ether /EtOAc = 80/20): 0.40.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.65-7.63 (m, 1H), 7.56-7.54 (m, 1H), 7.41-7.36 (m, 3H), 7.23 (t, *J*=7.0 Hz, 1H), 7.21 (t, J=7.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 2H), 1.26 (t, *J*=7.1Hz, 3H).

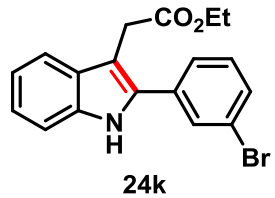
^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.08, 135.71, 133.86, 133.24, 132.90, 131.12, 130.15, 129.94, 127.93, 126.94, 122.72, 119.92, 119.45, 111.10, 107.55, 60.85, 31.20, 14.24.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}ClO_2N$: 314.0942, found: 314.0936.

FTIR (cm^{-1}): 3466, 3020, 2400, 1725, 1644, 1451, 1311, 770, 668, 501.

Ethyl 2-(2-(3-bromophenyl)-1*H*-indol-3-yl)acetate (24k)

Following the general procedure, treatment of ethyl ethyl (E)-3-(2-(((E)-3-bromobenzylidene)amino)phenyl)acrylate **23k** (179.0 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-(3-bromophenyl)-1*H*-indol-3-yl)acetate **24k** as a yellow solid (153.0 mg, 85%).



24k

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.38.

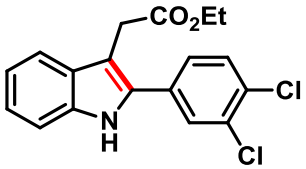
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (s, 1H), 7.83 (s, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.20 (dt, J_1 = 14.7, J_2 = 7.1 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.18, 136.00, 134.60, 134.56, 131.15, 131.04, 130.53, 129.00, 126.91, 123.09, 120.34, 119.57, 111.12, 106.66, 61.16, 31.25, 14.35.

HRMS: calculated $[M+Na]^+$ for $C_{18}H_{16}O_2NBrNa$: 380.0251, found: 380.0257.

FTIR (cm^{-1}): 3459, 3019, 1724, 1599, 1454, 1369, 1311, 1217, 1180, 1029, 771, 668, 499, 478, 461, 447, 424, 412.

Ethyl 2-(2-(3,4-dichlorophenyl)-1*H*-indol-3-yl)acetate (24l)



24l

Following the general procedure, treatment of ethyl (*E*)-ethyl 3-(2-((*E*)-3,4-dichlorobenzylideneamino)phenyl)acrylate **23l** (174.0 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture using silica gel afforded ethyl 2-(2-(3,4-dichlorophenyl)-1*H*-indol-3-yl)acetate **24l** as a yellow solid (0.145 g, 83%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.35.

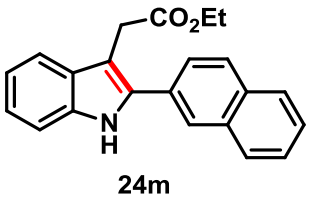
^{1}H NMR ($CDCl_3$, 400 MHz) δ δ 8.19 (s, 1H), 7.80 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.53 (s, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.80 (s, 2H), 1.29 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.04, 136.06, 133.75, 133.27, 132.50, 132.31, 131.05, 129.97, 128.99, 127.47, 123.37, 120.54, 119.65, 111.14, 107.10, 61.24, 31.23, 14.36.

HRMS: calculated $[M+Na]^+$ for $C_{18}H_{15}O_2NCl_2Na$: 370.0372, found: 370.0373.

FTIR (cm^{-1}): 3020, 2977, 2400, 1720, 1641, 1526, 1425, 1216, 1046, 928, 751, 669.

Ethyl 2-(2-(naphthalen-2-yl)-1*H*-indol-3-yl)acetate (24m)[21b]



24m

Following the general procedure, treatment of ethyl (E)-3-(2-(((E)-naphthalen-2-ylmethylene)amino)phenyl)acrylate **23m** (139.6 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash

column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl ethyl 2-(2-(naphthalen-2-yl)-1*H*-indol-3-yl)acetate **24m** (0.142 g, 86%).

***R**_f* (Pet. ether /EtOAc = 80/20): 0.29.

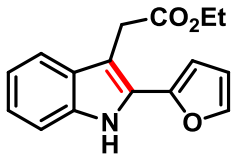
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.35 (s, 1H), 8.17 (s, 1H), 7.92 (dd, J_1 = 17.8, J_2 = 8.9 Hz, 3H), 7.77 (dd, J_1 = 11.2, J_2 = 8.6 Hz, 2H), 7.62 – 7.50 (m, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.24 (dt, J_1 = 14.7, J_2 = 6.8 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.94 (s, 2H), 1.32 (t, J = 7.1 Hz, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 172.44, 136.31, 136.07, 133.56, 132.91, 129.90, 129.26, 128.73, 128.34, 127.90, 127.49, 126.74, 126.55, 126.05, 122.76, 120.21, 119.49, 111.04, 106.26, 61.05, 31.42, 14.39**.**

HRMS: calculated $[M+H]^+$ for $C_{22}H_{20}O_2N$: 330.1484, found: 330.1489.

FTIR (cm^{-1}): 3462, 3019, 2400, 1724, 1603, 1454, 1369, 1306, 1216, 1177, 1030, 769, 668, 498, 438, 414.

Ethyl 2-(2-(furan-2-yl)-1*H*-indol-3-yl)acetate (24n)[21b]



24n

Following the general procedure, treatment of (*E*)-ethyl 3-(2-((*E*)-furan-2-ylmethyleneamino)phenyl)acrylate **23n** (139.6 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-(furan-2-yl)-1*H*-indol-3-yl)acetate **24n** as a dark red solid (0.099 g, 74%).

***R**_f* (Pet. ether /EtOAc = 80/20): 0.29.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.47 (s, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.50 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.80-6.79 (m, 1H), 6.54-6.53 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.94 (s, 2H), 1.23 (t, J=7.1 Hz, 3H).

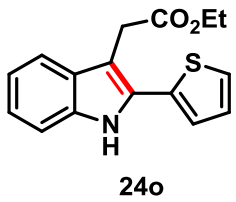
^{13}C NMR (CDCl$_3$, 100 MHz) δ 171.71, 147.01, 142.03, 135.64, 128.95, 126.96, 123.01, 120.28, 119.19, 112.09, 110.98, 107.51, 105.40, 61.01, 31.27, 14.35.

HRMS: calculated $[M+Na]^+$ for $C_{16}H_{15}O_3NNa$: 292.0944, found: 292.0941.

FTIR (cm^{-1}): 3017, 1723, 1448, 1368, 1305, 1220, 1159, 1017, 772, 741.

Ethyl 2-(2-(thiophen-2-yl)-1*H*-indol-3-yl)acetate (24o)[21b]

Following the general procedure, treatment of Ethyl (*E*)-3-(2-(((*E*)-thiophen-2-ylmethylene)amino)phenyl)acrylate **23o** (142.0 mg, 0.50 mmol) with the triazolium salt **25** (27.0



24o

mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded Ethyl 2-(2-(thiophen-2-yl)-1*H*-indol-3-yl)acetate **24o** as a yellow solid (0.123 g, 87%).

***R**f* (Pet. ether /EtOAc = 80/20): 0.30.

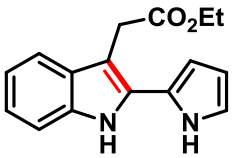
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.29 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.40-7.31 (m, 3H), 7.23-7.14 (m, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 2H), 1.26 (t, *J*=7.0Hz, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 172.01, 135.88, 134.05, 130.10, 129.13, 128.07, 126.02, 125.81, 122.99, 120.31, 119.31, 110.95, 106.47, 61.06, 31.38, 14.33.

HRMS: calculated $[M+Na]^+$ for $C_{16}H_{15}O_2NS$: 308.0716, found: 308.0711.

FTIR (cm^{-1}): 3360, 2981, 1721, 1549, 1459, 1369, 1304, 1216, 1033, 850, 753, 699.

Ethyl 2-(2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl)acetate (24p)



24p

Following the general procedure, treatment of ethyl (*E*)-3-(2-(((*E*)-(1*H*-pyrrol-2-yl)methylene)amino)phenyl)acrylate **23p** (134.1 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded ethyl 2-(2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl)acetate **24p** as a yellowish solid (0.105 g, 78%).

***R**f* (Pet. ether /EtOAc = 80/20): 0.45.

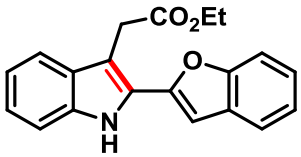
^{1}H NMR (CDCl$_3$, 400 MHz) δ 10.78 (s, 1H), 8.21 (s, 1H), 7.71 (d, *J* = 6.2 Hz, 1H), 7.45 – 7.18 (m, 3H), 7.03 (s, 1H), 6.49 (s, 1H), 6.41 (s, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 2H), 1.33 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 174.71, 135.46, 130.58, 128.97, 124.48, 122.21, 120.07, 120.03, 118.25, 110.79, 109.69, 106.78, 102.71, 61.82, 31.13, 14.18.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{17}O_2N_2$: 269.1285, found: 269.1278.

FTIR (cm^{-1}): 3465, 3019, 2983, 2932, 2401, 1726, 1605, 1457, 1426, 1370, 1308, 1216, 1179, 1114, 1031, 927, 772, 700, 669.

Ethyl 2-(2-(benzofuran-2-yl)-1*H*-indol-3-yl)acetate (24q)



24q

Following the general procedure, treatment of Ethyl (*E*)-3-(2-(((*E*)-benzofuran-2-ylmethylene)amino)phenyl)acrylate **23q** (160.0 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded Ethyl 2-(2-(benzofuran-2-yl)-1*H*-indol-3-yl)acetate **24q** as a yellow solid (0.121 g, 76%).

***R**_f* (Pet. ether /EtOAc = 80/20): 0.25.

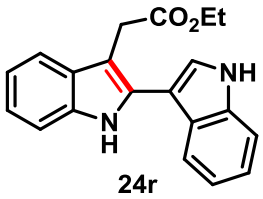
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (s, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.5, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.35-7.28 (m, 3H), 7.24-7.17 (m, 2H), 7.10 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.09 (s, 2H), 1.31 (t, J=7.2Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.86, 154.34, 148.65, 135.99, 129.10, 128.83, 126.30, 124.56, 123.50, 123.31, 121.22, 120.36, 119.16, 111.22, 110.99, 107.58, 103.42, 61.16, 31.34, 14.36.

HRMS: calculated $[M+Na]^+$ for $C_{20}H_{17}O_3NNa$: 342.1101, found: 320.1096.

FTIR (cm^{-1}): 3466, 3019, 2400, 1725, 1642, 1516, 1451, 1294, 1030, 881, 771, 668.

Ethyl 2-(1*H*,1'*H*-[2,3'-biindol]-3-yl)acetate (24r)



24r

Following the general procedure, treatment of ethyl (E)-3-(2-(((E)-(1H-indol-3-yl)methylene)amino)phenyl)acrylate **23r** (159.2 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 48 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 80/20) of the crude reaction mixture using silica gel afforded ethyl 2-(1*H*,1'*H*-[2,3'-biindol]-3-yl)acetate **24r** as a yellow solid (95.0 mg, 60%).

***R**_f* (Pet. ether /EtOAc = 70/30): 0.53.

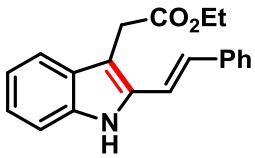
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.47 (s, 1H), 8.36 (s, 1H), 7.76 – 7.65 (m, 2H), 7.42 (s, 1H), 7.33 (dd, J_1 = 10.0, J_2 = 7.7 Hz, 2H), 7.26 – 7.09 (m, 4H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.44, 136.31, 136.07, 133.56, 132.91, 129.90, 129.26, 128.73, 128.34, 127.90, 127.49, 126.74, 126.55, 126.05, 122.76, 120.21, 119.49, 111.04, 106.26, 61.05, 31.42, 14.39.

HRMS: calculated $[M+Na]^+$ for $C_{20}H_{18}O_2N_2Na$: 341.1256, found: 341.1260.

FTIR (cm^{-1}): 3396, 3060, 3011, 2944, 2835, 2401, 2034, 1713, 1622, 1553, 1459, 1371, 1318, 1243, 1216, 1099, 1025, 935, 767, 667, 503, 456, 442, 434, 417.

(*E*)-Ethyl 2-(2-styryl-1*H*-indol-3-yl)acetate (24s)



24s

Following the general procedure, treatment of (*E*)-ethyl 3-(2-((*E*)-((*E*)-3-phenylallylidene)amino)phenyl)acrylate **23s** (76.3 mg, 0.25 mmol) with the triazolium salt **25** (13.5 mg, 0.05 mmol), KO*t*-Bu (5.5 mg, 0.05 mmol) and 4 Å molecular sieves in DMF (2.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture using silica gel afforded (*E*)-ethyl 2-(2-styryl-1*H*-indol-3-yl)acetate **24s** as a yellow solid (0.032 g, 42%).

***R**$_f$* (Pet. ether /EtOAc = 80/20): 0.22.

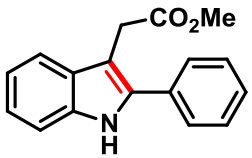
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.34-7.28 (m, 3H), 7.24-7.19 (m, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 16.4 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.61, 137.01, 133.73, 128.95, 127.98, 127.46, 126.61, 126.53, 123.50, 120.20, 119.26, 116.89, 110.69, 61.08, 30.73, 14.36.

HRMS: calculated $[M+H]^+$ for $C_{20}H_0O_2N$: 306.1489, found: 306.1480.

FTIR (cm^{-1}): 3017, 2112, 1704, 1630, 1447, 1368, 1316, 1268, 1219, 1177, 1039, 988, 772.

Methyl 2-(2-phenyl-1*H*-indol-3-yl)acetate (24t)



24t

Following the general procedure, treatment of methyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate **23t** (133.0 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.1 mmol), KO*t*-Bu (11.0 mg, 0.1 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded methyl 2-(2-phenyl-1*H*-indol-3-yl)acetate **24t** as a yellow solid (0.121 g, 91%).

***R**$_f$* (Pet. ether /EtOAc = 80/20): 0.38.

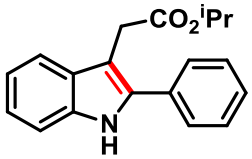
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (s, 1H), 7.73 (d, *J*=7.1 Hz, 1H), 7.66 (d, *J*=7.5 Hz, 2H), 7.50 (t, *J*=7.4 Hz, 2H), 7.44-7.41 (m, 1H), 7.33 (d, *J*=7.4 Hz, 1H), 7.28-7.21 (m, 2H), 3.91 (s, 2H), 3.75 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.96, 136.28, 135.83, 132.41, 129.01, 128.96, 128.30, 128.08, 122.58, 120.09, 119.22, 111.06, 105.41, 52.13, 30.99.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{16}O_2N$: 266.1176, found: 266.1169.

FTIR (cm^{-1}): 3374, 3057, 2950, 1717, 1604, 1488, 1370, 1268, 1169, 1061, 919, 766, 698.

Isopropyl 2-(2-phenyl-1*H*-indol-3-yl)acetate (24u)



24u

Following the general procedure, treatment of Isopropyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate **23u** (146.7 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded isopropyl 2-(2-phenyl-1*H*-indol-3-yl)acetate **24u** as a yellow solid (121.0 mg, 83%).

***R*$_f$** (Pet. ether /EtOAc = 95/5): 0.38.

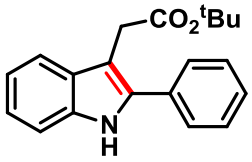
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (s, 1H), 7.70 (dd, J_1 = 15.8, J_2 = 7.5 Hz, 3H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.25 – 7.14 (m, 2H), 5.07 (dt, J_1 = 12.4, J_2 = 6.2 Hz, 1H), 3.84 (s, 2H), 1.26 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.02, 136.27, 135.90, 132.59, 129.18, 128.96, 128.36, 128.05, 122.54, 120.00, 119.43, 111.00, 105.91, 68.42, 31.58, 21.92.

HRMS: calculated $[M+Na]^+$ for $C_{19}H_{19}O_2NNa$: 316.1307, found: 316.1308.

FTIR (cm^{-1}): 3464, 3370, 3061, 3019, 2982, 2937, 1719, 1606, 1489, 1456, 1426, 1373, 1340, 1309, 1274, 1216, 1178, 1142, 1105, 1029, 968, 772, 700, 668, 499, 485, 473, 447, 430, 416.

***tert*-Butyl 2-(2-phenyl-1*H*-indol-3-yl)acetate (24v)**



24v

Following the general procedure, treatment of *tert*-butyl (*E*)-3-(2-(((*E*)-benzylidene)amino)phenyl)acrylate **23v** (77.0 mg, 0.25 mmol) with the triazolium salt **25** (14.0 mg, 0.05 mmol), KO*t*-Bu (5.5 mg, 0.05 mmol) and 4 Å molecular sieves in DMF (2.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column

chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded *tert*-butyl 2-(2-phenyl-1*H*-indol-3-yl)acetate **24v** as a yellow solid (0.06 g, 78%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.35.

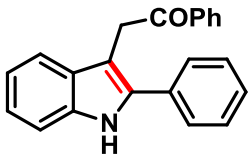
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.23 (s, 1H), 7.72 (dd, J_1 = 16.4 Hz, J_2 = 7.5 Hz, 3H), 7.49 (t, *J*=7.6 Hz, 2H), 7.40 (t, *J*=7.1 Hz, 1H), 7.35 (d, *J*=7.8 Hz, 1H),7.25-7.17 (m, 2H), 3.79 (s, 2H), 1.18 (s, 9H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 171.75, 136.14, 135.93, 132.67, 129.28, 128.96, 128.35, 128.01, 122.51, 119.96, 119.57, 110.95, 106.39, 80.98, 32.61, 28.20.

HRMS: calculated $[M+Na]^+$ for $C_{20}H_{21}O_2NNa$: 330.1465, found: 330.1458.

FTIR (cm^{-1}): 3395, 1708, 1644, 1454, 1368, 1310, 1219, 1139, 772, 502, 461.

1-Phenyl-2-(2-phenyl-1*H*-indol-3-yl)ethanone (24w)



24w

Following the general procedure, treatment of (*E*)-3-(2-((*E*)-benzylideneamino)phenyl)-1-phenylprop-2-en-1-one **23w** (155.7 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture using silica gel afforded 1-phenyl-2-(2-phenyl-1*H*-indol-3-yl)ethanone **24w** as a yellow solid (0.138 g, 89%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.37.

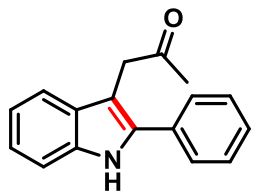
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.25 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.56-7.50 (m, 4H), 7.47-7.39 (m, 4H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 4.54 (s, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 198.15, 136.80, 136.36, 136.05, 133.12, 132.83, 129.27, 129.08, 128.63, 128.54, 128.31, 128.14, 122.59, 120.14, 119.31, 111.10, 106.08, 35.56.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{18}ON$: 312.1383, found: 312.1375.

FTIR (cm^{-1}): 3020, 2400, 1710, 1679, 1448, 1216, 1045, 928, 773, 669.

1-(2-phenyl-1*H*-indol-3-yl)propan-2-one (24x)



24x

Following the general procedure, treatment of (*E*)-4-(2-(((*E*)-benzylidene)amino)phenyl)but-3-en-2-one **23x** (125.0 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h

followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 1-(2-phenyl-1*H*-indol-3-yl)propan-2-one **24x** as a yellow solid (0.114 g, 91%).

***R**_f* (Pet. ether /EtOAc = 80/20): 0.30.

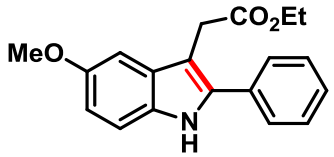
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.63 (s, 1H), 7.58-7.35 (m, 7H), 7.26-7.19 (m, 2H), 3.95 (s, 2H), 2.15 (s, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 208.49, 136.19, 135.94, 132.42, 128.96, 128.03, 122.54, 120.08, 118.78, 111.22, 105.63, 40.55, 29.10.

HRMS: calculated $[M+Na]^+$ for $C_{17}H_{15}ONNa$: 272.1046, found: 272.1042.

FTIR (cm^{-1}): 3404, 1697, 1644, 1454, 1356, 1218, 1075, 771, 494.

Ethyl 2-(5-methoxy-2-phenyl-1*H*-indol-3-yl)acetate (24y)



24y

Following the general procedure, treatment of ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-methoxyphenyl)acrylate **23y** (77.0 mg, 0.25 mmol) with the triazolium salt **25** (13.6 mg, 0.05 mmol), KO*t*-Bu (5.6 mg, 0.05 mmol) and 4 Å molecular sieves in DMF (2.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture using silica gel afforded ethyl 2-(5-methoxy-2-phenyl-1*H*-indol-3-yl)acetate **24y** as a yellow solid (0.067 g, 87%).

***R**_f* (Pet. ether /EtOAc = 80/20): 0.20.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.07 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.14 (bs, 1H), 6.88 (dd, *J* = 8.7, 1.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.81 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

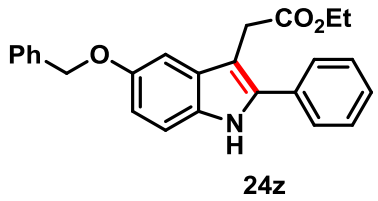
^{13}C NMR (CDCl$_3$, 100 MHz) δ 172.37, 154.52, 137.11, 132.61, 131.00, 129.65, 129.06, 128.31, 128.12, 112.91, 111.78, 105.68, 101.20, 60.99, 56.01, 31.42, 14.42.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{20}O_3N$: 310.1438, found: 310.1436.

FTIR (cm^{-1}): 3383, 2946, 2834, 2523, 2362, 2220, 2042, 1723, 1658, 1592, 1451, 1415, 1218, 1179, 1115, 1029, 921, 771.

Ethyl 2-(5-(benzyloxy)-2-phenyl-1*H*-indol-3-yl)acetate (24z)

Following the general procedure, treatment of ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-(benzyloxy)phenyl)acrylate **23z** (192.7 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100



24z

°C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture using silica gel afforded ethyl 2-(5-(benzyloxy)-2-phenyl-1*H*-indol-3-yl)acetate **24z** as a yellow solid (0.171 g, 89%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.15.

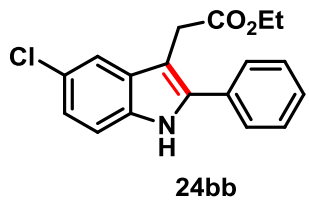
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.08 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 2H), 7.50 (dd, *J* = 14.6, 7.4 Hz, 4H), 7.45 – 7.37 (m, 3H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.29 – 7.23 (m, 2H), 6.97 (dd, *J* = 8.7, 1.6 Hz, 1H), 5.15 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 172.37, 153.71, 137.76, 137.16, 132.57, 131.19, 129.63, 129.05, 128.64, 128.30, 128.12, 127.91, 127.76, 113.55, 111.78, 105.68, 102.82, 70.99, 60.98, 31.39, 14.42.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{24}O_3N$: 386.1751, found: 386.1750.

FTIR (cm^{-1}): 3359, 2945, 2866, 2832, 2051, 1721, 1654, 1453, 1112, 1031, 913, 745.

Ethyl 2-(5-chloro-2-phenyl-1*H*-indol-3-yl)acetate (24bb)



24bb

Following the general procedure, treatment of ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-chlorophenyl)acrylate **23bb** (156.9 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture using silica gel afforded ethyl 2-(5-chloro-2-phenyl-1*H*-indol-3-yl)acetate **24bb** as a yellow solid (0.143 g, 91%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.22.

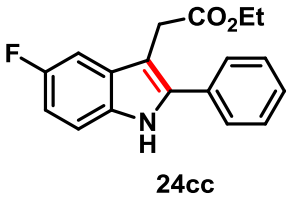
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.30 (s, 1H), 7.63-7.58 (m, 3H), 7.47-7.37 (m, 3H), 7.21-7.17 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 172.26, 137.72, 134.19, 131.97, 130.19, 129.08, 128.43, 128.29, 125.72, 122.81, 118.82, 112.06, 105.36, 61.18, 31.08, 14.32.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}O_2NCl$: 314.0942, found: 314.0943.

FTIR (cm^{-1}): 3381, 2948, 2865, 2840, 2522, 2362, 2153, 1723, 1653, 1453, 1412, 1112, 1052, 1030, 1019, 902, 797, 768.

Ethyl 2-(5-fluoro-2-phenyl-1*H*-indol-3-yl)acetate (24cc)



24cc

Following the general procedure, treatment of ethyl (*E*)-3-(2-(((*E*)-benzylidene)amino)-5-fluorophenyl)acrylate **23cc** (148.7 mg, 0.50 mmol) with the triazolium salt **25** (27.0 mg, 0.10 mmol), KO*t*-Bu (11.0 mg, 0.10 mmol) and 4 Å molecular sieves in DMF (4.0 mL) at 100 °C for 12 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture using silica gel afforded ethyl 2-(5-fluoro-2-phenyl-1*H*-indol-3-yl)acetate **24cc** as a yellow solid (0.142 g, 95%).

***R**f* (Pet. Ether /EtOAc = 80/20): 0.27.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 9.1 Hz, 1H), 7.23-7.20 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

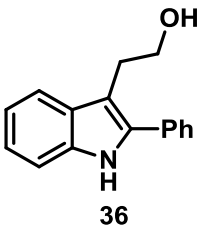
^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.30, 158.15 (d, $J_{C\text{-}F}$ = 234.6 Hz) , 138.13, 132.35, 132.16, 129.60, 129.50, 129.07, 128.37, 128.31, 111.70 (d, $J_{C\text{-}F}$ = 9.6 Hz), 110.88 (d, $J_{C\text{-}F}$ = 26.3 Hz), 105.85, 104.33 (d, $J_{C\text{-}F}$ = 23.8 Hz), 61.13, 31.21, 14.33.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{17}O_2NF$: 298.1238, found: 298.1235.

FTIR (cm^{-1}): 3345, 2945, 2832, 2523, 2048, 1723, 1452, 1112, 1030, 913, 745.

4.7.9. Functionalization of Indole 3-Acetic Acid Derivatives

2-(2-phenyl-1*H*-indol-3-yl)ethanol (36)[19]



36

Ethyl 2-(2-phenyl-1*H*-indol-3-yl)acetate **24a** (0.316 g, 1.13 mmol.) was taken in a flame dried round bottom flask were dissolved with argon inlet. Dry THF (5 mL) was added and cooled to 0 °C. To this stirring solution lithium aluminium hydride (0.051 g, 5.65 mmol., 5.0 equiv.) was added portion wise. The reaction mixture was stirred for 2 h at 80 °C. The reaction was quenched by 2N NaOH (2 mL) followed by addition of H_20 (5 mL) at 0°C, and the resulting mixture was extracted with EtOAc (10 mL). The organic extracts were washed successively with aqueous 5 % HCl (5 mL) and saturated brine and dried over Na_2SO_4. The crude alcohol was obtained by removing the solvent under reduced pressure. The crude residue was purified by flash column chromatography (Pet. ether /EtOAc = 85/15) on silica gel to afford the corresponding 2-(2-phenyl-1*H*-indol-3-yl)ethanol **36** (0.201 g, 75% yield)**.**

***R**f* (Pet. ether /EtOAc = 80/20): 0.24.

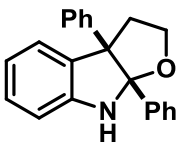
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (s, 1H), 7.65 (dd, *J* = 15.8, 7.8 Hz, 3H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.40 – 7.38 (m, 2H), 7.26 – 7.22 (m, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 3.97 (t, *J* = 6.6 Hz, 2H), 3.19 (t, *J* = 6.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.04, 133.00, 129.32, 129.06, 128.30, 128.02, 122.62, 119.99, 119.28, 111.04, 109.04, 63.14, 28.19.

HRMS: calculated $[M+Na]^+$ for $C_{16}H_{15}ONNa$: 260.1046, found: 260.1044.

FTIR (cm^{-1}): 3464, 3061, 3017, 2958, 2885, 2401, 1605, 1487, 1456, 1426, 1388, 1340, 1307, 1216, 1073, 1043, 1011, 773, 700, 668.

3a,8a-Diphenyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-b]indole (37)[19]



37

In a glove box, $(CuOTf)_2$.PhMe (11.0 mg, 0.021 mmol, 0.05 mmol) were added to an oven dried Schlenk tube. The Schlenk tube was then sealed and taken out from the glove-box and diphenyliodonium trifluoromethanesulfonate (218.0 mg, 0.508 mmol), 2-(2-phenyl-1*H*-indol-3-yl)ethan-1-ol (100 mg, 0.423 mmol) and DCM (4.0 mL) were added under argon. The reaction mixture was allowed to stir at reflux condition. After 48 h the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The crude product was then purified by silica gel column chromatography (PE: EA = 1:7) to afford the desired product as inseparable diastereomers 3a,8a-diphenyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-b]indole **37** (0.099 g**,** 75 % yield) as a white solid with 3:1 *dr*.

***R**$_f$* (Pet. ether /EtOAc = 80/20): 0.35.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83-7.73 (m, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.39-7.35 (m, 1H), 7.28-7.26 (m, 2H), 7.20-7.18 (m, 1H), 7.06-7.05 (m, 2H), 7.00-6.96 (m, 3H), 6.88-6.79 (m, 3H), 4.71 (s, 1H), 4.46-4.40 (m, 1H), 3.97-3.85 (m, 1H), 3.12-3.04 (m, 1H), 2.48 (dd, *J* = 12.1Hz and 4.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.91, 141.19, 140.81, 132.88, 129.40, 128.80, 128.66, 128.60, 127.32, 126.55, 126.40, 126.34, 125.68, 125.20, 123.97, 122.23, 119.76, 108.93, 107.57, 68.57, 66.28, 38.36.

Representative peaks of minor isomer

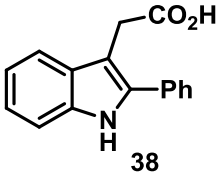
^{1}H NMR δ 7.47 (d, *J* = 7.9 Hz, 1H), 4.78 (s, 1H), 2.54 (dd, *J* = 12.1Hz and 4.4 Hz, 1H).

^{13}C NMR δ 128.06**,** 127.35, 109.03, 68.53, 38.62.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{20}ON$: 314.1539, found: 314.1542

FTIR (cm^{-1}): 3359, 2945, 2833, 2523, 2044, 1658, 1450, 1108, 1029, 699.

2-(2-phenyl-1*H*-indol-3-yl)acetic acid (38)[33]



38

Ethyl 2-(2-phenyl-1*H*-indol-3-yl)acetate **24a** (0.10 g, 0.358 mmol.) was taken in round bottom flask and distilled H_2O (2.0 mL) was added to the reaction vessel. The reaction mixture was stirred at 30 °C, then 3N NaOH (0.15 g) was added to it. The stirring solution was allowed to reflux and stirring was continued for 3 h. The reaction mixture was cooled to RT and the resulting mixture was made acidic by using 6 N HCl (3 mL) solutions. Then workup was done using Et_2O. The ethereal extracts were dried over Na_2SO_4. The crude acid **38** was obtained by removing the solvent under reduced pressure. The crude residue was purified by flash column chromatography (Pet. ether /EtOAc = 80/20) on silica gel to afford 2-(2-phenyl-1*H*-indol-3-yl)acetic acid **38** (0.085 g, 95% yield).

R_f (Pet. ether /EtOAc = 70/30): 0.25.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (s, 1H), 7.65 (dd, *J* = 16.1, 7.6 Hz, 3H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.26 – 7.22 (m, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 3.88 (s, 2H).

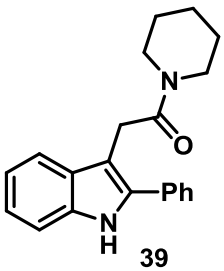
^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.58, 136.60, 135.85, 132.33, 129.18, 129.01, 128.41, 128.37, 122.90, 120.40, 119.38, 111.09, 105.02, 30.84.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{14}O_2N$: 252.1019, found: 252.1015.

FTIR (cm^{-1}): 3399, 3056, 2923, 2853, 2680, 1703, 1605, 1487, 1456, 1410, 1371, 1340, 1308, 1288, 1236, 1186, 1155, 1140, 1075, 1029, 1009, 925, 822, 794, 742, 699, 672.

2-(2-phenyl-1*H*-indol-3-yl)-1-(piperidin-1-yl)ethanone (39)[33]

2-(2-phenyl-1*H*-indol-3-yl)acetic acid **38** (0.065g, 0.258 mmol) and triethylamine (0.2 mL, 1.293 mmol) were taken in a flame dried round bottom flask with N_2 inlet. Dry THF (8 mL) was added to it and cooled it to -40 °C. To this stirring solution ethylchloroformate was added dropwise. The reaction suspension was stirred for 30 min at -20 °C before the addition of piperidine (26 µL, 0.258 mmol). The suspension was allowed to warm to room temperature, and stirring was continued for another 1 h. The reaction was quenched by H_20 (5 mL), and the resulting mixture was extracted with ether (20 mL). The ethereal extracts were washed successively with aqueous 5 % HCl (10 mL) and saturated brine and dried



39

over Na_2SO_4. The crude amide **39** was obtained by removing the solvent under reduced pressure. The crude residue was purified by flash column chromatography (Pet. ether /EtOAc = 93/07) on silica gel to afford the corresponding 2-(2-phenyl-1*H*-indol-3-yl)-1-(piperidin-1-yl)ethanone **39** (0.071 g, 87% yield)**.**

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.35.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (s, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.3 Hz, 2H), 7.46 (t, J = 7.4 Hz, 2H), 7.40-7.33 (m, 2H), 7.19 (t, J = 7.4 Hz, 1H), 7.12 (t, J = 7.3 Hz, 1H), 3.92 (s, 2H), 3.50 (bs, 2H), 3.16 (bs, 2H), 1.47 – 1.39 (m, 4H), 1.14 (bs, 2H).

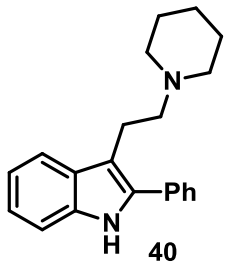
^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.57, 136.11, 135.40, 132.86, 129.15, 129.03, 128.41, 128.10, 122.58, 120.12, 119.92, 110.89, 107.01, 47.09, 43.20, 31.42, 26.15, 25.74, 24.57.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{23}ON_2$: 319.1805, found: 319.1799.

FTIR (cm^{-1}): 3246, 3055, 2928, 2851, 1630, 1491, 1475, 1460, 1445, 1410, 1342, 1306, 1258, 1245, 1223, 1162, 1138, 1122, 1076, 1025, 1010, 953, 909, 890, 853, 835, 818, 767, 736, 694, 659.

2-Phenyl-3-(2-(piperidin-1-yl)ethyl)-1*H*-indole (40)

Following the procedure of Tsoungas,[34] 2-(2-Phenyl-1*H*-indol-3-yl)-1-(piperidin-1-yl)ethan-1-one **39** (0.213g, 0.669 mmol) was taken in a flame dried round bottom flask with N_2 inlet. Dry THF (12 mL) was added to it and cooled it to 0°C. To this stirring solution $LiAlH_4$ (0.127 g, 3.345 mmol.) in THF (25 mL) was added dropwise at 0°C. The suspension was allowed to warm to room temperature, and stirring was continued for another 3 h. The reaction was quenched by H_20 (5 mL), 15% aq. NaOH (5 mL). The resulting mixture was extracted with Et_2O (50 mL). The ethereal extracts were dried over Na_2SO_4. The crude amine **40** was obtained by removing the solvent under reduced pressure. The crude residue was purified by flash column chromatography (Pet. ether /EtOAc = 75/25) on silica gel to afford the corresponding 2-phenyl-3-(2-(piperidin-1-yl)ethyl)-1*H*-indole **40** (0.067 g, 33% yield) [50% based on recovered **39**]**.**



40

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.25

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 3.15 – 3.11 (m, 2H), 2.72-2.68 (m, 2H), 2.54 (bs, 4H), 1.66 – 1.63 (m, 4H), 1.47 (bs, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.03, 134.81, 133.26, 129.31, 129.00, 128.03, 127.79, 122.41, 119.74, 119.24, 111.20, 110.97, 60.12, 54.71, 25.97, 24.50, 22.19.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{25}N_2$: 305.2012, found: 305.2008.

FTIR (cm^{-1}): 3386, 3020, 2977, 2401, 1594, 1422, 1216, 1121, 1044, 929, 878, 757, 699.

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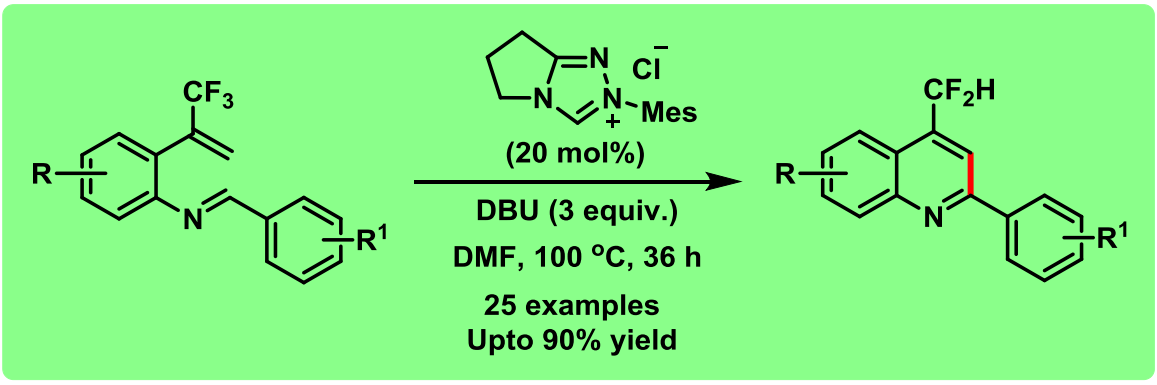
Chapter 5

Synthesis of Difluoromethylated Quinoline Derivative using NHC-Catalyzed Umpolung of Imines

In this chapter, we have demonstrated the N-heterocyclic carbene (NHC)-catalyzed umpolung of aldimines for the synthesis of 4-difluoromethyl quinoline derivatives. The NHC-catalyzed intramolecular cyclization of aldimines bearing a moderately electron-poor double bond due to the presence of the $-CF_3$ group resulted in the formation of biologically relevant 4-difluoromethyl quinoline derivatives in moderate to good yields. The NHC generated from the bicyclic triazolium salt using DBU as base was effective for this transformation. The reaction tolerates a broad range of functional groups. Simple functionalization of the reaction products resulted in the synthesis of valuable heterocycles.



manuscript communicated

5.1. Introduction

Quinolines are one of the most important N-based heterocyclic aromatic compounds. Quinolines recently have been caught the attention of researchers because of their broad range of activities and of course for their wide application too. Quinoline derivatives in general are known to have a broad range of applications in medicinal, bioorganic, and industrial chemistry as well as in the field of synthetic organic chemistry. Their derivatives have been found to possess various biological activity like anti-malarial, anti-bacterial, anti-fungal, anti-asthmatic, anti-hypertensive, anti-inflammatory and anti-platelet activity.[1] They also exhibit anti-tubercular and immune depressing[2] activities. Specially, 2-aryl quinoline derivatives were associated with diverse biological properties.

The 2-arylquinoline derivatives **1** and **2** show selectivity in binding to the estrogen receptor β (ER β), which plays an important role in the development, maintenance, and function of the mammalian reproductive system, as well as in non-sexual tissues.[3] 4-[2-(Diethylamino) ethylamino] quinolin-7-ol (**3**) containing nitrogen at position 4 exhibits antiplasmodial activity.[4] Polysubstituted quinoline derivatives such as 8-hydroxyquinoline and quinoline-8-thiol have been used to produce metal complexes which emit light.[5] 2-(4-Bromo-5-ethylnylthiophen-2- yl)-6-ethynyl-4-phenylquinoline (**4**) has been applied in sensors and light emitting diodes.[6] Some quinoline derivatives such as quinalidine (**5**) and quinaldic acid (**6**) show activity as corrosion inhibitors for mild steel in hydrochloric acid (Fig. 5.1).[2]

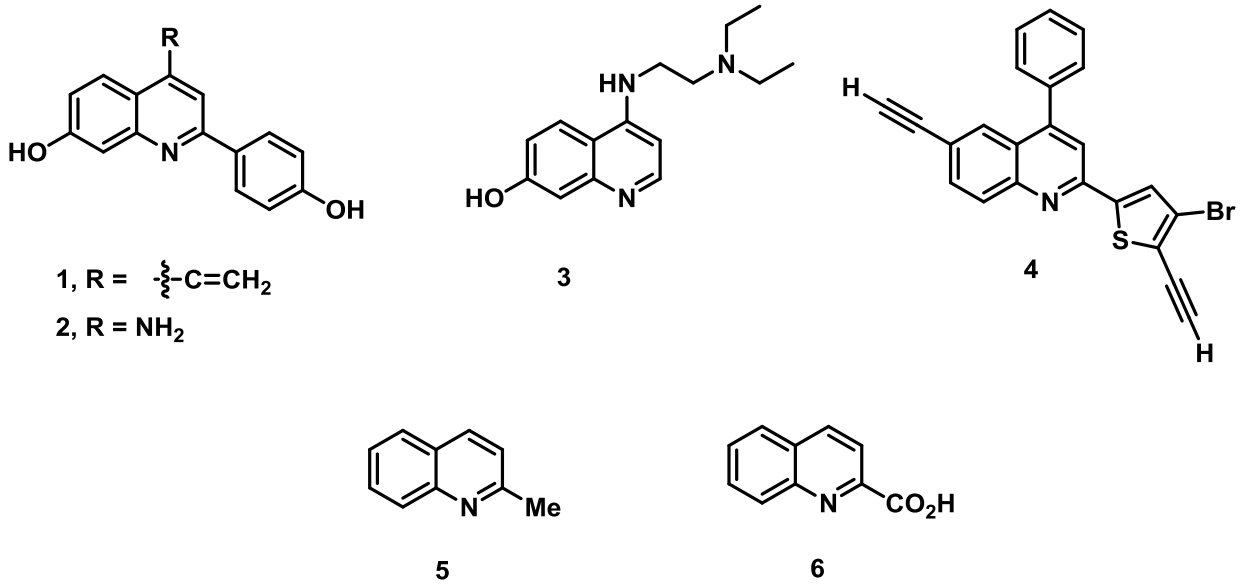


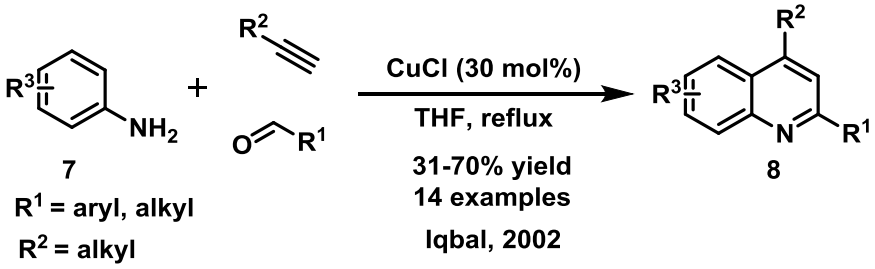
Fig. 5.1: Biologically Important Quinoline Derivatives

5.2. Synthesis of 2-Aryl Substituted Quinoline Derivatives

A number of methods have been known for the synthesis of quinoline and its derivatives. Generally, structural core of quinoline has been synthesized by various conventional named reactions such as Skraup, Doebner-von Miller, Friedlander, Pfitzinger, Conrad-Limpach, Combes synthesis.[7] Selected methods for the synthesis of 2,4-disubstituted quinolines are presented in the following section.

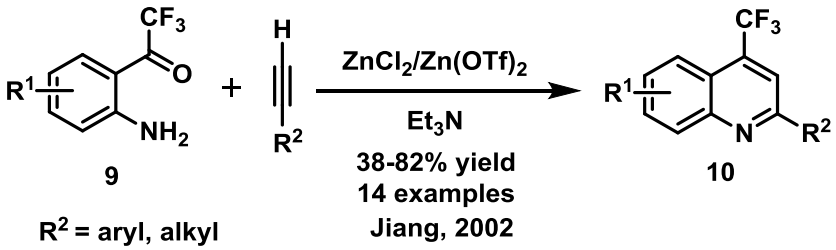
In 2002 Iqbal and co-workers developed an efficient and general route to 2,4-disubstituted quinolines **8** in a one-pot synthesis from an aryl amine, an aldehyde and a terminal alkyne using CuCl as a catalyst (Scheme 5.1).[8]

Scheme 5.1: Synthesis of 2,4-Disubstituted Quinolines using CuCl as a Catalyst



Subsequently, Jiang and co-workers reported a regioselective and efficient route to 4-trifluoromethyl substituted quinoline derivatives **10** via the reaction of o-trifluoro-acetyl aniline **9** using zinc(II) salt and triethylamine (Scheme 5.2).[9] The reaction proceeds via Zn(II)-mediated alkynylation-cyclization of o-trifluoroacetyl anilines.

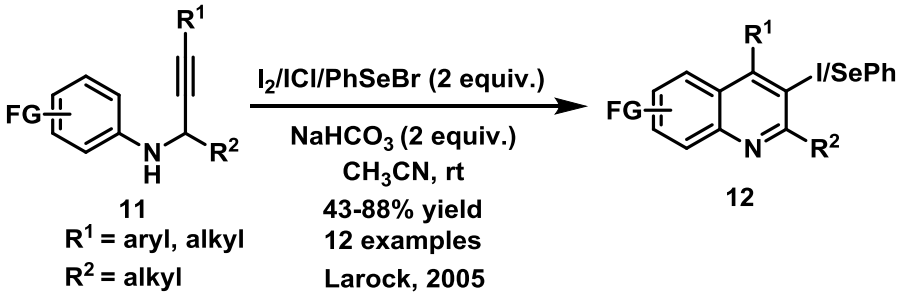
Scheme 5.2: Zn(II)-Mediated Synthesis of 4-Trifluoromethyl Substituted Quinoline



In 2005, Larock and co-workers developed a new approach to 3-iodo or phenylseleno substituted quinolines **12** in good to excellent yields by the reaction of propargylic anilines **11** with appropriate electrophiles under mild reaction conditions, which are difficult to prepare using previous methods (Scheme 5.3).[10] The reaction proceeds via coordination of the carbon-carbon triple bond of the propargylic aniline to the proper electrophile, generating an three membered cationic intermediate, intramolecular nucleophilic attack of the aromatic ring of the

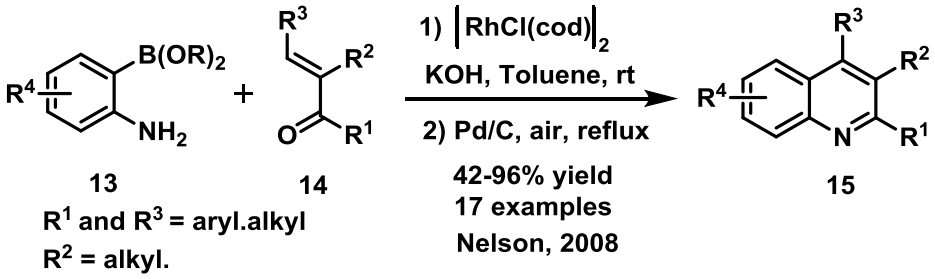
aniline on the activated triple bond to form dihydroquinoline followed by oxidation of the dihydroquinoline to the corresponding quinoline in the presence of I_2 or air.

Scheme 5.3: Synthesis of Quinolines by Electrophilic Cyclization of N-(2-Alkynyl)anilines



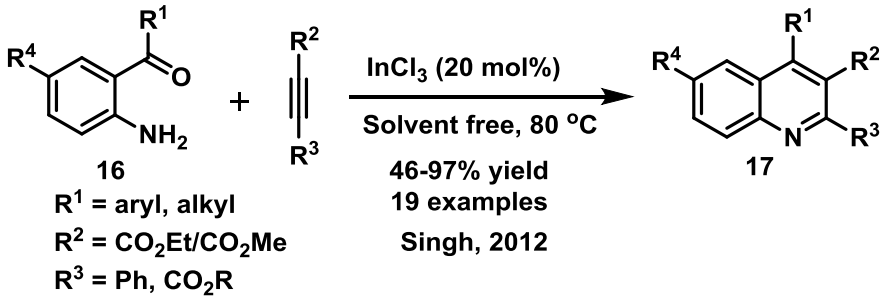
Later in 2008, Nelson and co-workers reported a direct convergent, two-component, regiospecific synthesis of quinolines **15** in moderate to good yields from α,β-unsaturated ketones **14** and o-aminophenylboronic acid derivatives **13** (Scheme 5.4).[11] The reaction based upon the rhodium-catalyzed conjugate addition, then cyclisation and followed by oxidation using Pd/C.

Scheme 5.4: Synthesis of Substituted Quinolines from Aminobenzenepincacolboronates.



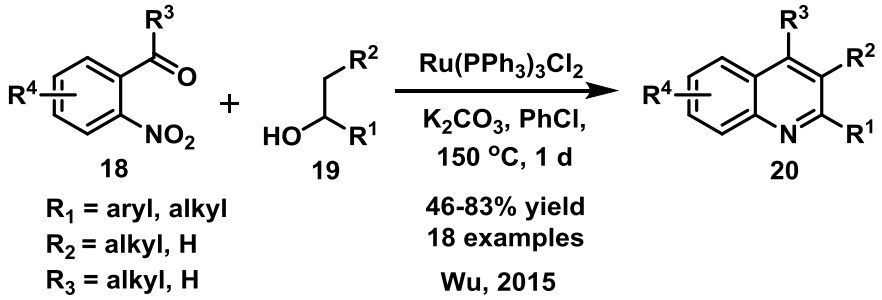
Singh and co-workers achieved an efficient, regioselective synthesis of functionalized/annulated quinolines **17** by the coupling of 2-aminoaryl ketones with alkynes promoted by $InCl_3$ in solvent-free conditions with excellent yields (Scheme 5.5).[12] This transformation proceeded through the hydroamination–hydroarylation of alkynes. The reaction avoids the use of hazardous acids or bases and harsh reaction conditions.

Scheme 5.5: Synthesis of Quinolines using $InCl_3$ as Catalyst



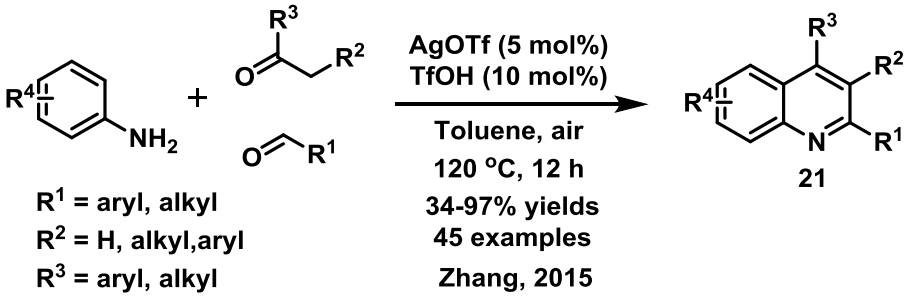
Wu and co-workers reported synthesis of quinolines **20** from alcohols **19** and 2-nitrobenzaldehydes **18** in good yields (Scheme 5.6).[13] Unreactive alcohols and 2-nitrobenzaldehydes were converted to the reactive substrates for a Friedlander annulation via a hydrogen transfer. It was found that tris(triphenylphosphine)ruthenium(II) dichloride [$Ru(PPh_3)_3Cl_2$] appeared to serve the dual role of an efficient hydrogen transfer catalyst and a suitable Friedlander annulation catalyst.

Scheme 5.6: Synthesis of Quinolines using Ru(II)-Catalyzed Annulation



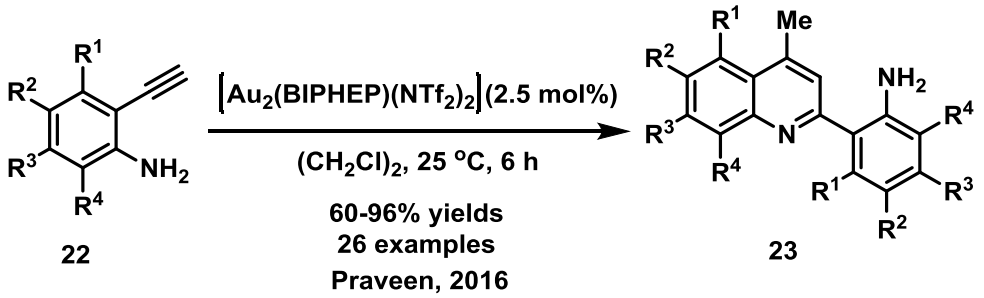
Consequently, Zhang and co-workers reported an efficient and regioselective synthesis of multiply substituted quinolines **21** from aldehyde, aniline, and carbonyl compounds using a silver-catalyzed formation of C–C bond for the construction (Scheme 5.7).[14] Additionally, they reported condensation of arylamine and 1,3-diketone leading to the formation of quinolines.

Scheme 5.7: Synthesis of Quinolines using AgOTf as Catalyst



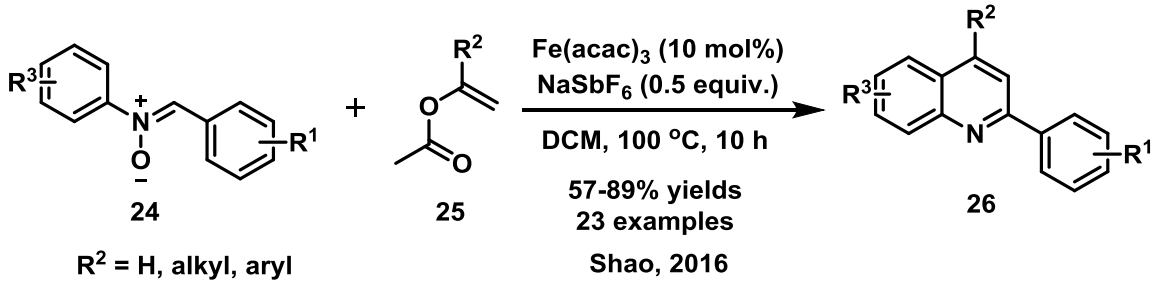
Later in 2016 Praveen and co-workers developed synthesis 2,4-disubstituted quinolines **23** by dimerization of 2-ethynylanilines **22** under dinuclear gold catalyst (Scheme 5.8).[15] This protocol offered broad substrate scope with good to excellent yields. The reaction was readily applied to other heterocycles also as exemplified by the preparation of naphthyridines. However, control experiments with substrates possessing internal alkynes resulted in cycloisomerization instead of expected dimerization, which is indicative of possible steric influence of the alkyne terminus in the reaction outcome.

Scheme 5.8: Synthesis of Quinolines using Au-Catalyzed Dimerization



Shao and co-workers reported an iron-catalyzed intermolecular [4 + 2] cyclization of arylnitrones **24** with geminal-substituted vinyl acetates **25** for the synthesis of 2,4-disubstituted quinolines **26** in moderate to good yields (Scheme 5.9).[16] A preliminary mechanistic study suggested iron-catalyzed C−H activation process under external-oxidant-free conditions.

Scheme 5.9: Fe-Catalyzed Synthesis of Quinolines using Arylnitrones and Vinyl Acetates

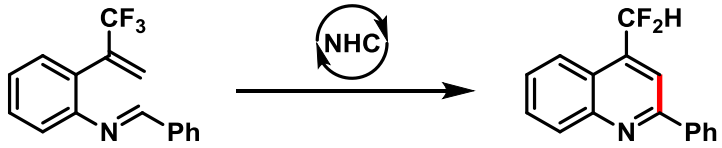


5.3. Statement of the Problem

From the above mentioned literature, it is clear that one can synthesize 2,4-disubstituted quinoline derivatives in various way. Extensively, proposed way to obtain quinolines by using metal as a catalyst or strong inorganic acids. Driven by our recent synthesis of indole derivatives by NHC-catalyzed umpolung of imines, we are interested in extending the scope of NHC-catalyzed umpolung of imines for the generation of biologically important 2,4-disubstituted quinolines. We envisaged that if the reaction is carried out using aldimine having *o*-substituted α-trifluoromethyl olefin, it can result in the synthesis of biologically relevant 2-aryl 4-difluoromethylated quinolines (Scheme 5.10). The results of our studies leading to an efficient synthesis of 2-aryl 4-difluoromethylated quinolines are presented in the following sections.[17] In the presence of NHCs, the intramolecular cyclization of aldimines bearing a moderately electron-poor double bond due to the presence of the $–CF_3$ group resulted corresponding quinoline

derivatives with moderate to good yields (Scheme 5.10). The NHC generated from the bicyclic triazolium salt using DBU as a base was effective for this transformation.

Scheme 5.10: Proposed Methodology

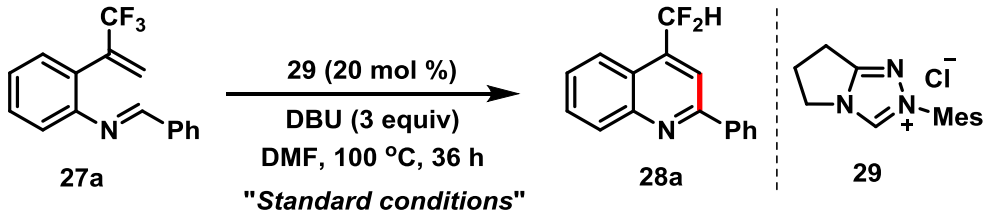


5.4. Results and Discussion

5.4.1. Optimization Studies

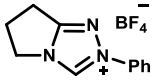
Our optimization study commenced with treatment of (*E*)-1-phenyl-N-(2-(3,3,3- trifluoro prop-1-en-2-yl)phenyl)methanimine **27a** in the presence of the carbene generated from **29** by deprotonation using KO*t*-Bu leading to the formation of difluoromethylated quinoline derivative **28a** in 75% yield (Table 5.1, entry 1, isolated yield). The NHCs generated from other triazolium salts **30** and **31** furnished **28a** in reasonable yield (entries 2, 3) whereas the carbenes derived from the common thiazolium salt **32** and imidazolium salt **33** are not found to be reactive for this imine umpolung (entries 4, 5). Other bases such as DMAP, DABCO, KO*t*-Bu, and K_2CO_3 furnished the desired product in reduced yields (entries 6-9). Among the various solvents screened such as DMSO, chlorobenzene, 1,4-dioxane and Toluene, toluene was found to give comparable yield of the desired product (entries 10-13). With decrease in temperature to 80 °C reactivity decreases abruptly (entry 14). The reaction afforded reduced yield of **28a** when the reaction time was reduced to 24 h (entry 15). Moreover, an excess of DBU was required for good conversion to **28a** (entries 16-19). Additionally, decrease in catalyst loading to 15 mol% reactivity decreases to 51% (entry 20).

Table 5.1: Optimization Table

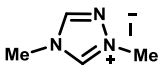


Entry	variation of the standard conditions[a]	yield of **28a** (%)[b]
1	None	75
2	**30** instead of **29**	70
3	**31** instead of **29**	59
4	**32** instead of **29**	<5
5	**33** instead of **29**	<5
6	DMAP instead of DBU	26
7	DABCO instead of DBU	19
8	KO*t*-Bu instead of DBU	21
9	K_2CO_3 instead of DBU	34
10	DMSO instead of DMF	48
11	chlorobenzene instead of DMF	41
12	1,4-dioxane instead of DMF	63
13	toluene instead of DMF	<5
14	80 °C instead of 100 °C	41
15	run for 24 h instead of 36 h	53
16	2.0 equiv of DBU instead of 3.0 equiv	44
17	1.5 equiv of DBU instead of 3.0 equiv	32
18	1.0 equiv of DBU instead of 3.0 equiv	21
19	40 mol% of DBU instead of 3.0 equiv	14
20	15 mol% of **29** instead of 20 mol%	51

[a] Standard conditions: **27a** (0.25 mmol), **29** (0.05 mmol), DBU (0.75 mmol), DMF (2.0 mL), 100 °C, 36 h. [b] Isolated yield after column chromatography.

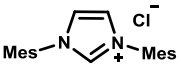


30



31

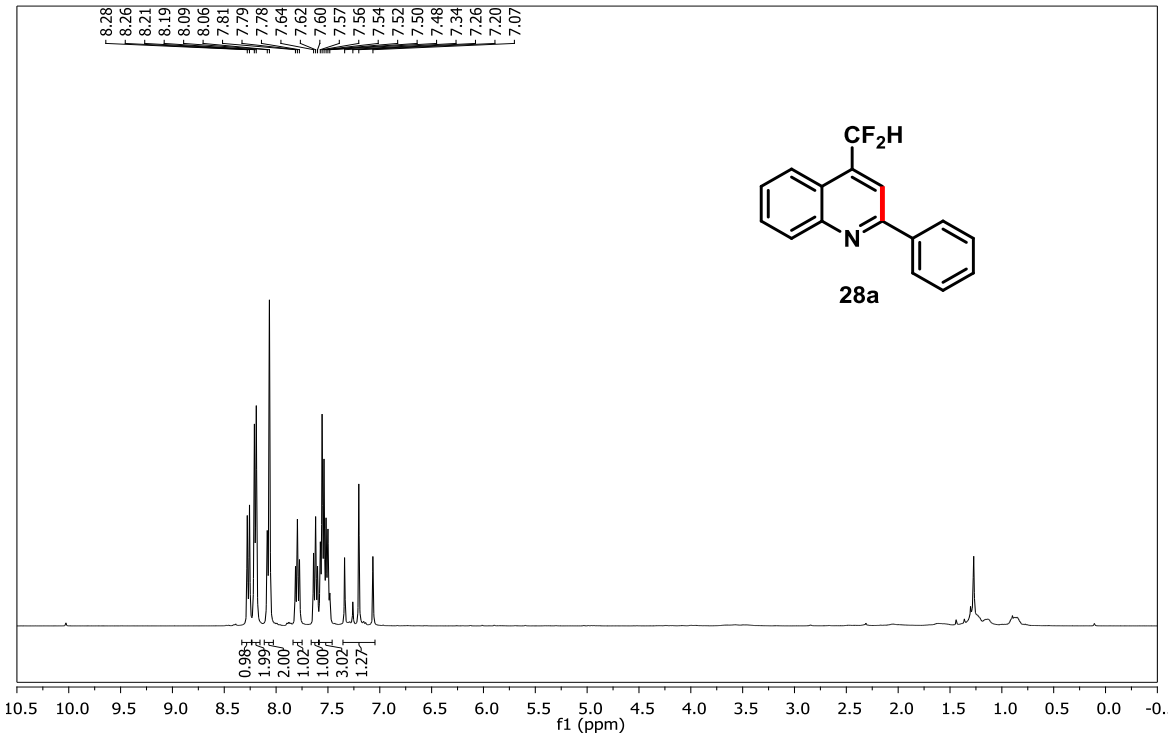
32



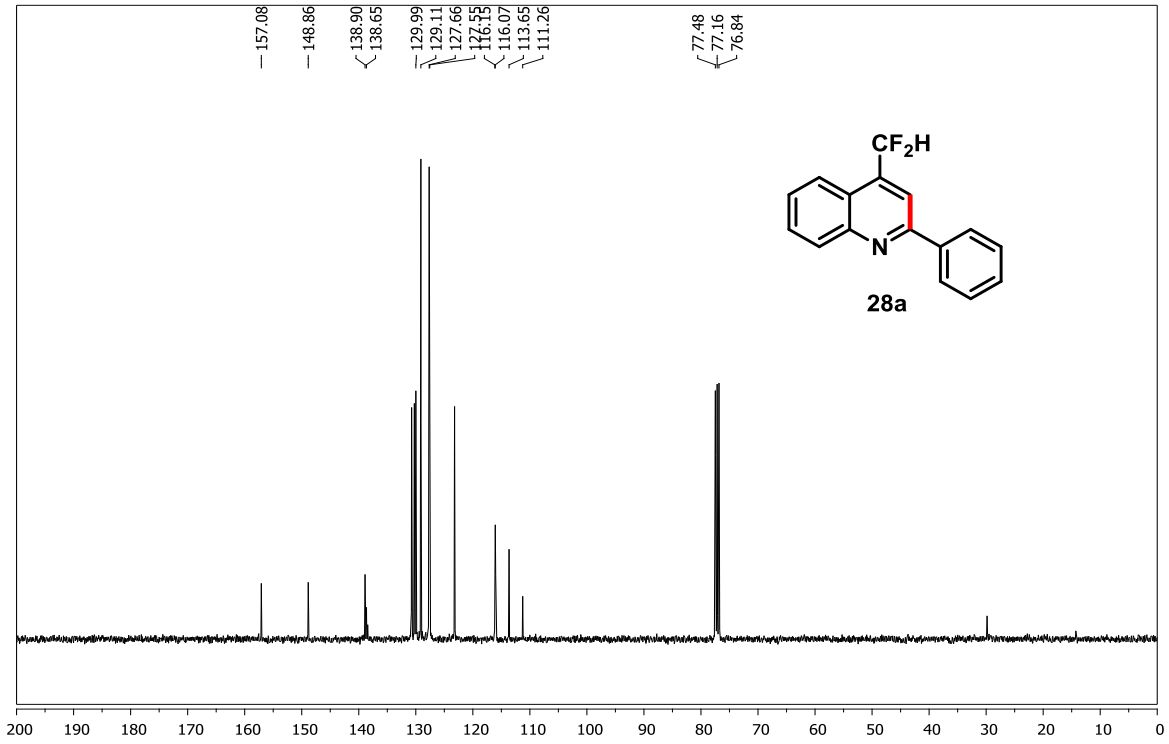
33

5.4.2. Spectral Data of 28a

^{1}H NMR Spectrum of 28a ($CDCl_3$)



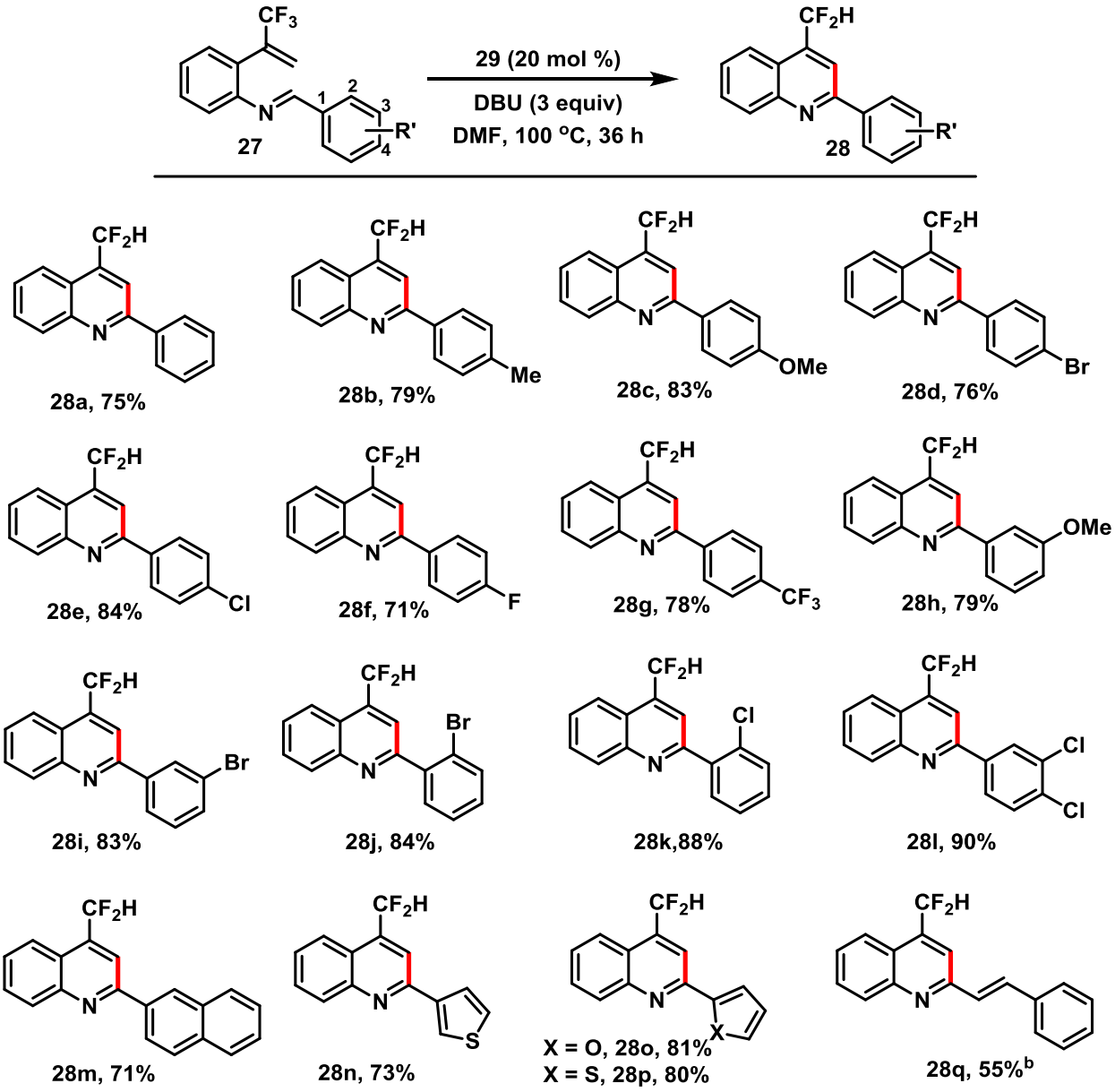
^{13}C NMR Spectrum of 28a ($CDCl_3$)



5.4.3. Substrate Scope

With the optimized reaction conditions in hand, we then examined the substrate scope of this quinoline synthesis via the NHC-catalyzed umpolung of imines (Scheme 5.11). A series of trifluoromethylated aldimines synthesized from the corresponding aromatic amines and aromatic

Scheme 5.11: Substrate Scope of the NHC-Catalyzed Umpolung for the Synthesis of Functionalized Quinolines[a]

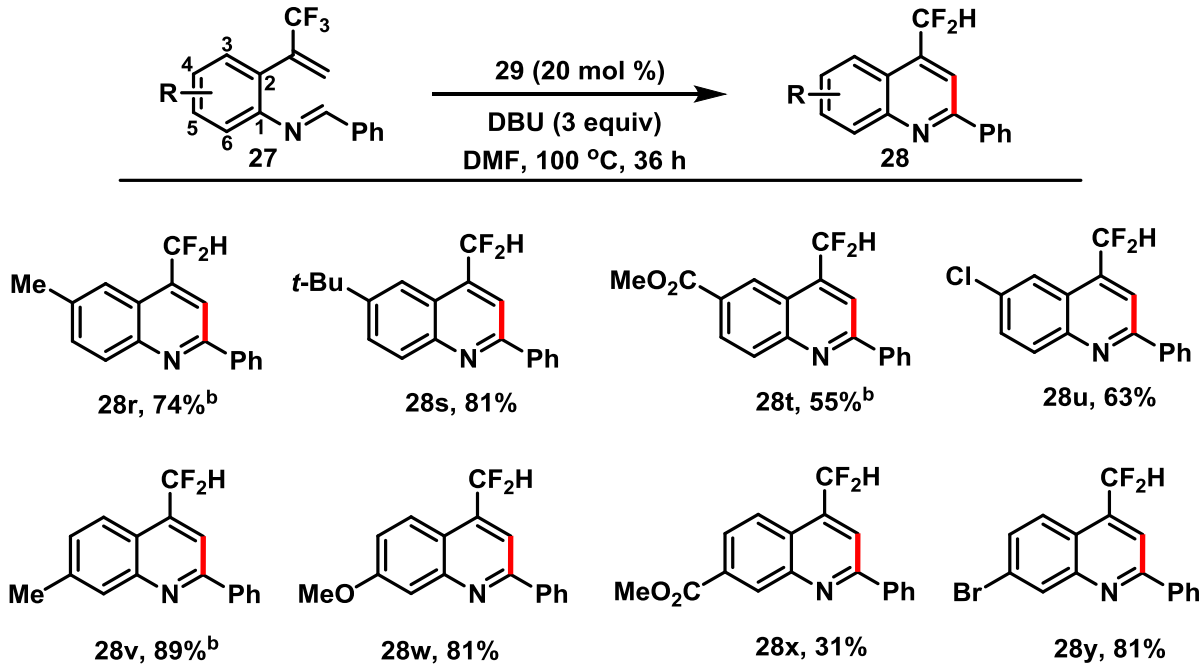


[a] General conditions: **27** (0.5 mmol), **29** (0.1 mmol), DBU (1.5 mmol), DMF (4.0 mL), 100 °C, 36 h. Yields of the isolated products are given. [b] Reaction was run for 48 h.

-aldehydes having electron-neutral, -releasing and -withdrawing groups at the 4-position of the ring underwent smooth annulation via the NHC-catalyzed umpolung leading to the synthesis of 2-aryl 4-difluoromethyl quinolines in good yields (**28a-28g**). Moreover, aldimines derived from aromatic aldehydes having substitution at the 3-position, 2-position as well as the disubstitution (3 and 4 positions) are well tolerated and the corresponding quinolines were formed in generally high yields (**28h-28m**). In addition, aldimines derived from heteroaromatic aldehydes worked well under the present conditions and the 2-heteroaryl functionalized quinolines are formed in good yields (**28n-28p**) thereby expanding the scope of the present quinoline synthesis. Furthermore, aldimine synthesized from cinnamaldehyde afforded the 2-vinyl quinoline derivative **28q** in 55% yield after running the reaction for 48 h. Disappointingly, preliminary studies using aldimines synthesized from linear and branched aliphatic aldehydes failed to give the corresponding quinolines under the present reaction conditions.

Next, we examined the scope of the reaction with aldimines synthesized from differently substituted aromatic amines and benzaldehyde (Scheme 5.12). Aldimines synthesized from

Scheme 5.12: Substrate Scope with Imines Derived from Differently Substituted Aromatic Amines[a]



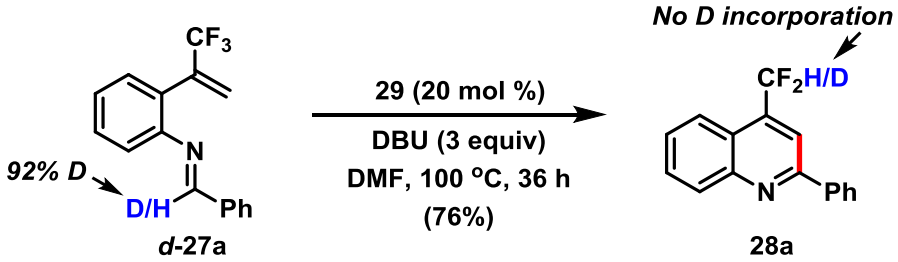
[a] General conditions: **27** (0.5 mmol), **29** (0.1 mmol), DBU (1.5 mmol), DMF (4.0 mL), 100 °C, 36 h. Yields of the isolated products are given. [b] Reaction was run on 0.25 mmol scale.

-anilines having alkyl, ester and chloro substitution at the 4-position underwent smooth annulation under the present reaction conditions resulting in the synthesis of functionalized quinolines (**28r-28u**) in good yields. Moreover, substitution is well tolerated with substrates derived from anilines having substituent at the 5-position of the ring. In all cases, the desired product was formed in moderate to good yield thus demonstrating the versatility of the present method.

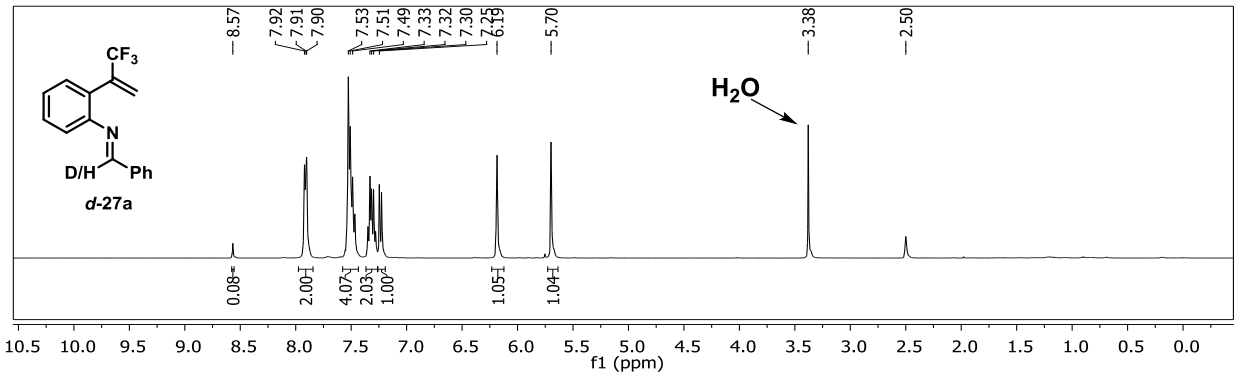
5.4.4. Mechanistic Studies

Reactions Using Deuterium Labelled Imine Substrate

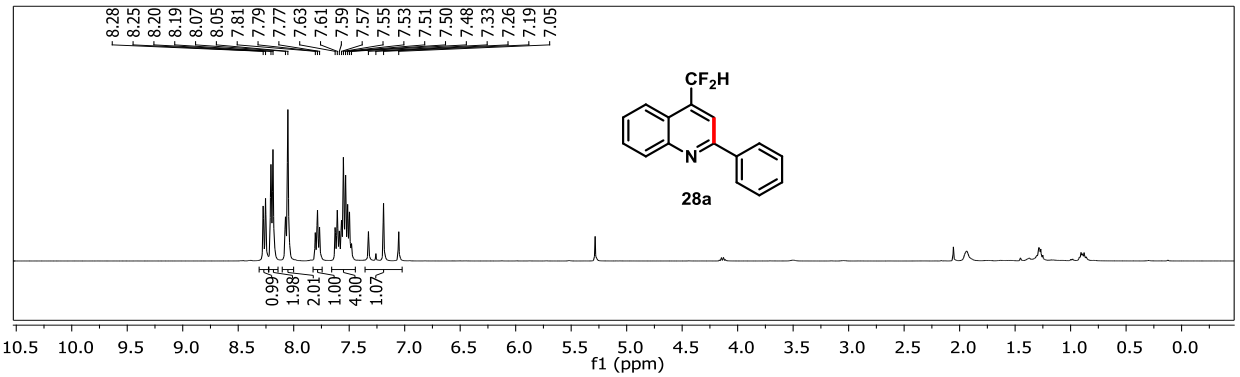
To get insight into the mechanism, compound ***d*-27a** (having 92% Deuterium at the imine carbon) was treated under our optimized reaction conditions. This reaction furnished quinoline **28a** in 76% yield and without deuterium incorporation in the final product **28a**. This experiment sheds light on the involvement of base in the isomerization to quinoline, and the formation of difluoromethyl moiety proceeds via 1,3-H shift instead of 1,5-H shift.



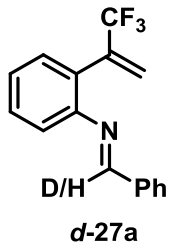
^{1}H-NMR Spectrum of (*E*)-1-Phenyl-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl) methanimine-*d* (*d*-27a)



^{1}H-NMR Spectrum of 4-(difluoromethyl)-2-phenylquinoline (28a)



(*E*)-1-Phenyl-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine-*d* (*d*-27a)



***d*-27a**

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.40 g, 2.115 mmol.), benzaldehyde-α-*d* (0.226 g, 2.115 mmol.), $MgSO_4$ (0.636 g, 5.287 mmol.) and Na_2SO_4 (0.751 g, 5.287 mmol.) in DCM (30 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-phenyl-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine-*d* ***d*-27a** (0.304 g, 52 % yield) as a yellow liquid.

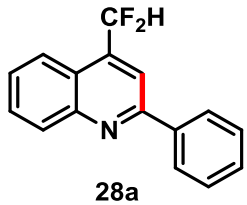
***R**f* (Pet. ether /EtOAc = 95/05): 0.45.

^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.57 (s, 1H (0.92 D, 0.08 H)), 7.92-7.90 (m, 2H), 7.53-7.47 (m, 4H), 7.35-7.28 (m, 2H), 7.24 (d, *J* = 7.9 Hz, 1H), 6.19 (s, 1H), 5.70 (s, 1H).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}DNF_3$: 277.1057, found: 277.1057.

FTIR (cm^{-1}): 3443, 3068, 2980, 2475, 2250, 2122, 1823, 1623, 1492, 1444, 1406, 1346, 1251, 1228, 1177, 1123, 1041, 821, 766.

4-(difluoromethyl)-2-phenylquinoline (28a)



28a

Following the general procedure, treatment of (*E*)-1-phenyl-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine-*d* ***d*-27a** (137.6 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-phenylquinoline **28a** as a yellowish liquid (0.097 g, 76%).

***R**f* (Pet. ether /EtOAc = 90/10): 0.40.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 7.4 Hz, 2H), 8.07-8.05 (m, 2H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.63-7.48 (m, 4H), 7.19 (t, *J* = 54.6 Hz, 1H).

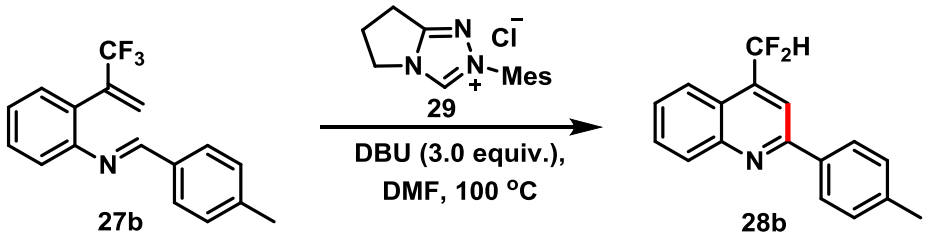
HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}NF_2$: 256.0932, found: 256.0932.

FTIR (cm^{-1}): 3407, 3021, 2976, 2403, 1609, 1372, 1216, 1117, 1047, 928, 887, 767, 669.

Kinetics studies

To get insight into the rate of the reaction, we have monitored the kinetics of the reaction (Table 5.2). The reactions performed using 7**2b** with 10 mol % of **29** and 20 mol % **29** have been analyzed at various time intervals and the results are presented Fig. 5.2. The results indicate that irrespective of the catalyst loading, the initial rate of the reaction is comparable (till ~3 h) and with the increase in the time, the experiment with more catalyst loading afforded more amount of the corresponding quinoline product **28b**.

Table 5.2: Reaction Kinetics with Respect to Time



Sl. no	Time (h)	Yield of **28b** 20 mol% **29**	Yield of **28b**10 mol% **29**
1	2	27	23
2	6	53	35
3	12	62	46
4	18	67	54
5	24	72	61
6	30	76	67
7	36	79	69

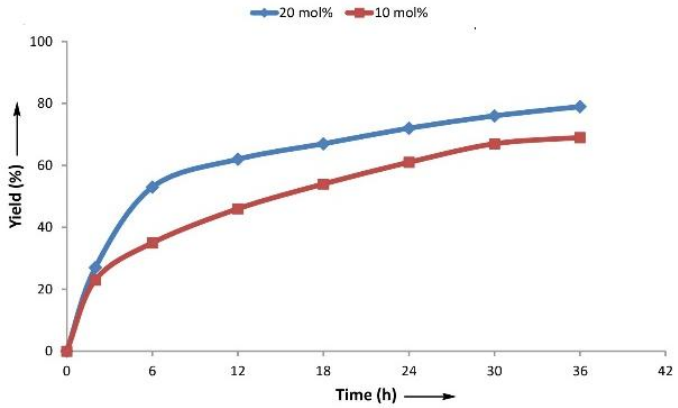
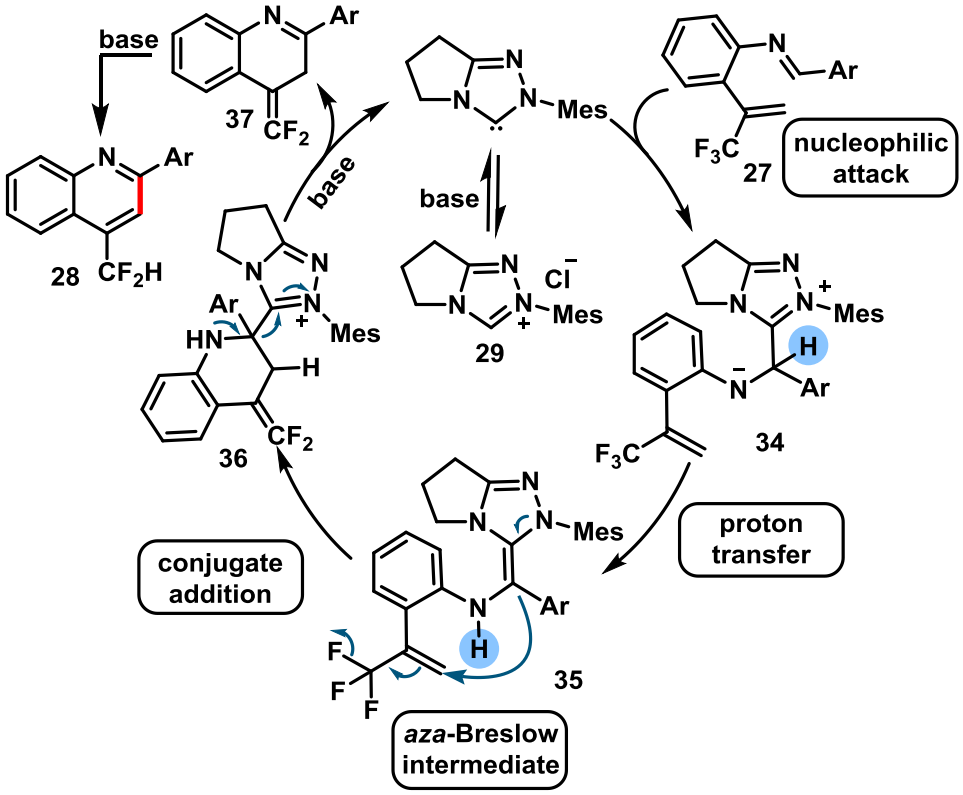


Fig. 5.2: Kinetics of the Reaction

5.4.5. Reaction Mechanism

Mechanistically, the reaction proceeds via the generation of free NHC using the base (Scheme 5.13). Addition of NHC to the aldimines **27** could form the tetrahedral intermediate **34**, which undergoes a rapid proton transfer to generate the key aza-Breslow intermediate **35**. The intermediate **35** is not isolable under the reaction conditions, and could intercept the moderately electron-poor double bond in an intramolecular fashion forming NHC-bound intermediate **36**. In the presence of excess base, elimination of carbene takes place to form the intermediate **37**, which on 1,3-H shift could result in the formation of quinoline **28**. Since the carbon-carbon double bond in **27** is moderately electron-poor, the initial NHC addition to the double bond (generating the deoxy-Breslow intermediate) followed by the interception with the imine moiety may not be taking place in the present case.

Scheme 5.13: Tentative Mechanism of the Reaction

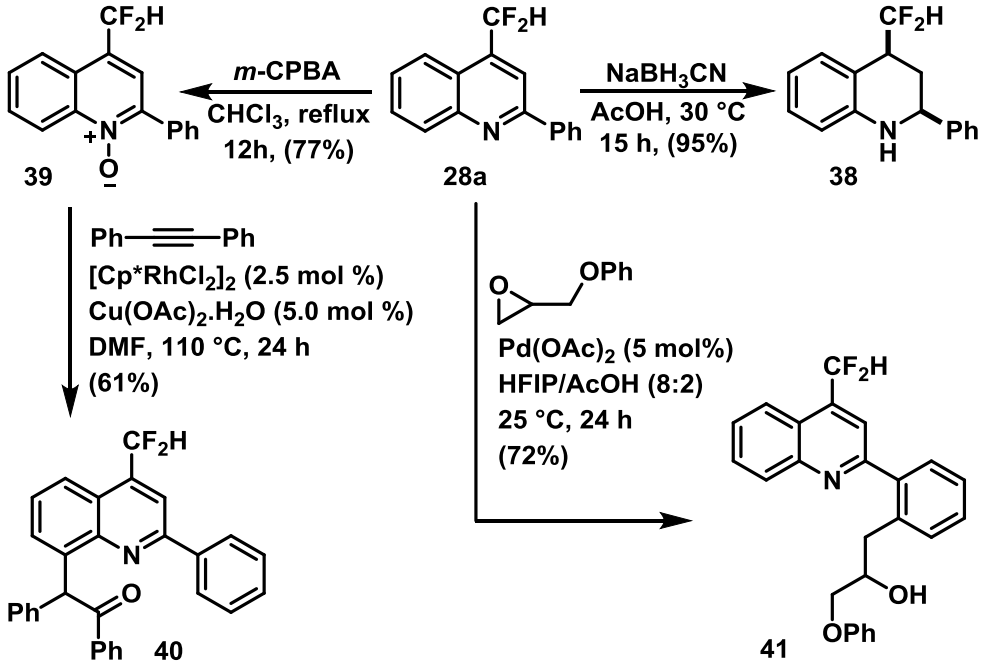


5.4.6. Product Functionalization

We also performed the functionalization of difluoromethylated quinoline derivative **28a**. Stereoselective reduction of the heterocyclic ring of **28a** using $NaBH_3CN$ afforded the tetrahydroquinoline derivative **38** in 95% yield (Scheme 5.14).[18] Moreover, the oxidation of **28a**

using *m*-CPBA resulted in the formation of the quinoline *N*-oxide **39** in 77% yield. The Rh(III)-catalyzed directed C-H bond activation of the quinoline *N*-oxide derivative **39** followed by coupling with diphenyl acetylene resulted in the formation of the 8-functionalized quinoline derivative **40** in 61% yield, proceeding via a cascade process involving remote C−H bond activation, alkyne insertion, and intramolecular oxygen atom transfer.[19] In addition, Pd-catalyzed cross-coupling reaction of **28a** with oxiranes utilizing the quinolinyl moiety as a directing group resulted in the formation of the functionalized quinoline **41** with a secondary alcohol moiety 72% yield.[20]

Scheme 5.14: Functionalization of 2-Aryl 4-Difluoromethyl Quinolines



5.5. Conclusion

In conclusion, we have developed a transition-metal-free synthesis of 2-aryl 4-difluoromethyl quinolines by the NHC-catalyzed umpolung of aldimines. This imino-Stetter reaction proceeds via the generation of the *aza*-Breslow intermediates, which undergoes interception with the moderately electron-poor carbon-carbon double bond to afford the quinolines in moderate to good yields. The NHC generated from the bicyclic triazolium salt using DBU as base was effective for this transformation.

5.6. Experimental Details

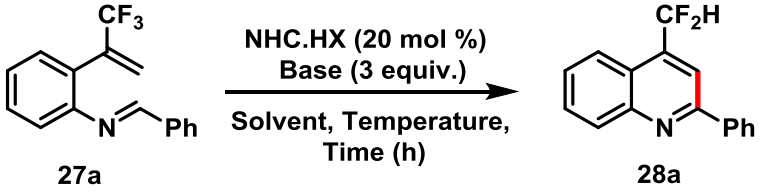
5.6.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw cap. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. Dry DMF was purchased from commercial sources and stored under argon over 4 Å molecular sieves. The 2-nitro benzaldehyde and other aldehydes were purchased from commercial sources and were used without any further purification. AgOTf and $PdBr_2$ were purchased from Sigma Aldrich, and both were stored in glove-box, and 2-bromo-3,3,3-trifluoropropene (BTP) from Fluorochem, and were used as received. The aldimines (**27a-27q**)[21] were synthesized from corresponding aldehydes following the literature procedure and aldimines (**27r-27y**)[22] were synthesized from corresponding aniline derivatives following the literature procedure. DBU was purchased from commercial source and distilled before used. The triazolium salt **29** was synthesized following the literature procedure.[23]

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, ^{13}C and ^{19}F NMR spectra were recorded on Bruker AV 400 and DXP 300 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 ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm or relative to external $CFCl_3$: δ_F = 0 ppm and DMSO-d^6: δ_H = 2.50 ppm, δ_C = 39.50 ppm). Infrared spectra were recorded on a Perkin-Elmer 1615 FT Infrared Spectrophotometer Model 60B or Perkin-Elmer Paragon 100 (ATR) FTIR spectrometer. 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 or Waters LCT Premier Instrument.

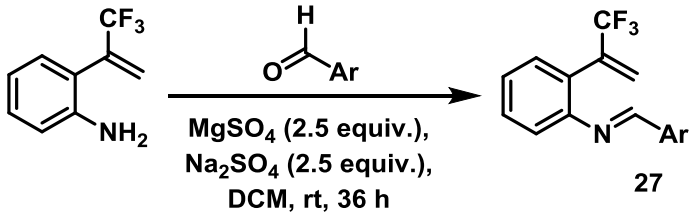
5.6.2. General Procedure for the Optimization of Reaction Conditions



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the azolium salt (0.05 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture, solvent was added (2.0 mL) under argon atmosphere. To this mixture was added the aldimine **27a** (0.25 mmol) and base (0.75 mmol). Then the reaction mixture was stirred at 100 °C for 36 h. After 36 h stirring, the reaction mixture cooled to rt and H_2O (10 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (Pet. ether/EtOAc = 95/5) on silica gel to afford the corresponding quinoline derivative **28a**.

5.6.3. General Procedure for the Synthesis of Aldimines

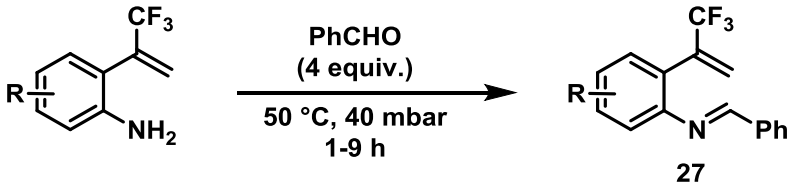
Procedure A for the Synthesis of Aldimines (27a-27q)[21]



To a solution of 2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (0.50 g, 2.643 mmol.), in DCM (30 mL) was added an aromatic aldehyde (0.280 g, 2.643 mmol.), followed by the addition of $MgSO_4$ (0.795 g, 6.607 mmol.) and Na_2SO_4 (0.938 g, 6.607 mmol.) under Ar atmosphere. The reaction mixture was stirred at rt for 36 h. The reaction mixture was filtered through filter paper, rinsed with DCM and the filtrate was concentrated in vacuo. The crude imine, was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine **27**.

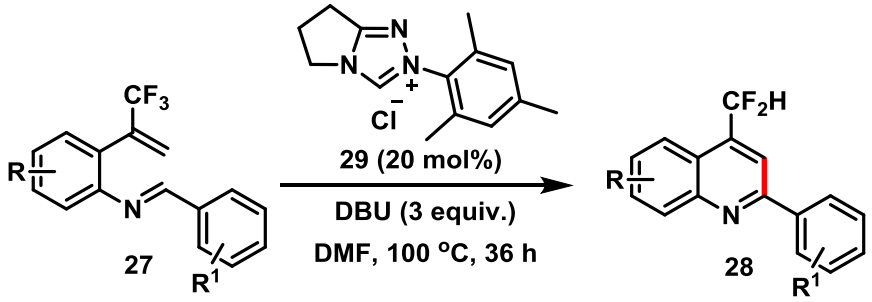
Procedure B for the Synthesis of Aldimines (27r-27y)[22]

To the desired amine (1 equiv) was added benzaldehyde (4 equiv). The reaction mixture was heated at 50 °C under 40 mbar for 1 to 9 h until the reaction was completed (monitored by TLC). Excess of benzaldehyde was removed under high vaccum (10^{-1} mbar) at 45 °C for 1 h.



The crude imine, was purified via flash column chromatography with deactivated silica gel (eluting with Pet. ether/Et_3N) to afford the corresponding aldimine **27**.

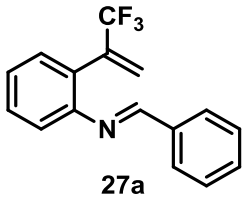
5.6.4. General Procedure for the Synthesis of Difluoromethylated Quinoline Derivatives



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the triazolium salt **29** (27 mg, 0.10 mmol) was added. Then the screw-capped tube was evacuated and backfilled with argon. To this dry DMF (4.0 mL) was added under argon atmosphere. To this mixture aldimine **27** (0.50 mmol) and DBU as a base (0.75 mmol.) were added under argon flow. Then the reaction mixture was stirred at 100° C for 36 h. After 36 hour stirring, work-up of the reaction mixture was done using EtOAc (10 mL) twice, organic fractions were dried with Na_2SO_4 and solvent was evaporated. The crude residue was purified by flash column chromatography (Pet ether: Ethyl acetate = 95:5) on silica gel to afford the corresponding quinoline derivative **28.**

5.6.5. Synthesis and Characterization of Aldimines

(*E*)-N-Benzylidene-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (27a)



Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.50 g, 2.643 mmol.), benzaldehyde (0.280 g, 2.643 mmol.), $MgSO_4$ (0.795 g, 6.607 mmol.) and Na_2SO_4 (0.938 g, 6.607 mmol.) in DCM (30 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-N-benzylidene-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27a** (0.473 g, 65 % yield) as a yellow liquid.

R_f (Pet. ether /EtOAc = 95/05): 0.50.

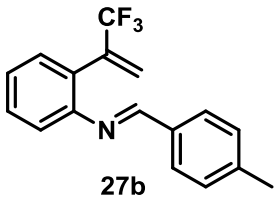
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (s, 1H), 7.91-7.86 (m, 2H), 7.50-7.45 (m, 3H), 7.42-7.35 (m, 2H), 7.28-7.20 (m, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.12 (d, *J* = 1.3 Hz, 1H), 5.59 (d, *J* = 1.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.21, 150.71, 137.70, 134.76, 130.26, 130.20, 130.13, 129.23, 128.49, 125.90, 124.04 (q, J_{C-F} = 5.1 Hz), 118.52.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{13}NF_3$: 276.0995, found: 276.0995.

FTIR (cm^{-1}): 3392, 3021, 2402, 1697, 1627, 1594, 1522, 1419, 1347, 1216, 1178, 1126, 1042, 929, 765, 669.

(*E*)-1-*p*-Tolyl-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27b)



Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), 4-methylbenzaldehyde (0.280 g, 1.586 mmol.), $MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 3.965 mmol.) in DCM (15 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-*p*-tolyl-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27b** (0.240 g, 52 % yield) as a yellow liquid.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.49.

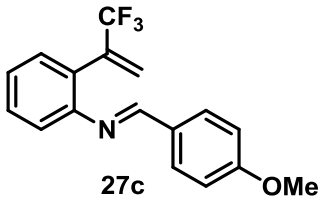
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.34-7.28 (m, 2H), 7.22-7.16 (m, 3H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.04 (s, 1H), 5.52 (s, 1H), 2.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.65, 151.34, 142.18, 136.87 (q, J_{C-F} = 31.0 Hz), 133.78, 130.05, 129.64, 129.06, 128.19, 125.41, 124.06 (q, J_{C-F} = 5.1 Hz), 118.81, 21.77.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{15}NF_3$: 290.1151, found: 290.1156.

FTIR (cm^{-1}): 3415, 3020, 1624, 1410, 1347, 1216, 1176, 1125, 1071, 946, 856, 817, 764.

(*E*)-N-(4-Methoxybenzylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (27c)



Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.254 g, 1.343 mmol.), 4-methoxybenzaldehyde (0.183 g, 1.343 mmol.), $MgSO_4$ (0.404 g, 3.357 mmol.) and Na_2SO_4 (0.477 g, 3.357 mmol.) in DCM (15 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-N-(4-methoxybenzylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27c** (0.207 g, 50 % yield) as a yellow liquid.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.39.

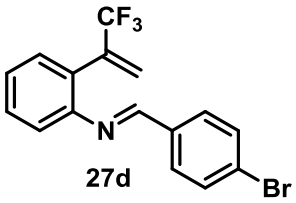
^{1}H NMR (DMSO-d^6, 400 MHz) δ 8.47 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.33-7.25 (m, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.17 (s, 1H), 5.69 (s, 1H).

^{13}C NMR (DMSO-d^6, 100 MHz) δ 162.06, 160.23, 150.68, 136.06 (q, *J* = 30.6 Hz), 130.49, 130.21, 129.66, 128.92, 127.84, 125.24, 124.91 (q, J_{C-F} = 5.1 Hz), 118.68, 114.25, 55.34.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{15}ONF_3$: 306.1100, found: 306.1098.

FTIR (cm^{-1}): 3415, 2992, 2254, 2128, 1657, 1508, 1454, 1312, 1256, 1223, 1170, 1122, 1016, 827, 768.

(*E*)-1-(4-Bromophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27d)



27d

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.414 g, 2.189 mmol.), 4-bromobenzaldehyde (0.405 g, 2.189 mmol.), $MgSO_4$ (0.659 g, 5.472 mmol.) and Na_2SO_4 (0.777 g, 5.472 mmol.) in DCM (20 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(4-bromophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27d** (0.327 g, 42 % yield) as a yellow liquid.

***R**$_f$* (Pet. ether /EtOAc = 95/05): 0.48.

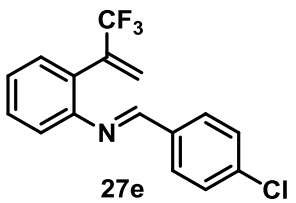
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (s, 1H), 8.02 (s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.43-7.40 (m, 1H), 7.37-7.33 (m, 2H), 7.27-7.25 (m, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.12 (bs, 1H), 5.58 (bs, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.04, 150.59, 138.25, 136.87 (q, J_{C-F} = 31.1 Hz), 134.48, 131.71, 130.44, 130.29, 130.13, 128.46, 127.70, 126.03, 124.14 (q, J_{C-F} = 5.2 Hz), 123.17, 118.55.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}NBrF_3$: 354.0100, found: 354.0109.

FTIR (cm^{-1}): 3423, 3027, 2098, 1634, 1481, 1435, 1349, 1272, 1216, 1180, 1122, 1074, 766.

(*E*)-1-(4-Chlorophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27e)



27e

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), 4-chlorobenzaldehyde (0.223 g, 1.586 mmol.), $MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 3.965 mmol.) in DCM (15 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with

deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(4-chlorophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27e** (0.235 g, 48 % yield) as a yellow liquid.

R_f (Pet. ether /EtOAc = 95/05): 0.48.

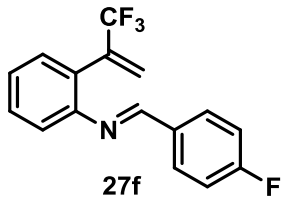
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.46-7.40 (m, 3H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.28-7.24 (m, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.12 (s, 1H), 5.57 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.21, 150.71, 137.70, 136.99 (q, $J_{C\text{-}F}$ = 31.0 Hz), 134.76, 130.26, 130.20, 130.13, 129.23, 128.49, 125.90, 124.04 (d, $J_{C\text{-}F}$ = 5.1 Hz), 118.52.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}NClF_3$: 310.0605, found: 310.0612.

FTIR (cm^{-1}): 3425, 2111, 1640, 1412, 1216, 1176, 1126, 764.

(*E*)-N-(4-Fluorobenzylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (27f)



27f

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), 4-fluorobenzaldehyde (0.197 g, 1.586 mmol.), $MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 3.965 mmol.) in DCM (15 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-N-(4-fluorobenzylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27f** (0.216 g, 46 % yield) as a yellow liquid.

R_f (Pet. ether /EtOAc = 95/05): 0.43.

^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.57 (s, 1H), 7.98-7.95 (m, 2H), 7.50-7.47 (m, 1H), 7.38-7.28 (m, 4H), 7.24 (d, *J* = 7.8 Hz, 1H), 6.19 (s, 1H), 5.70 (s, 1H).

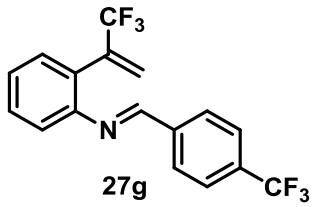
^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 164.12 (d, $J_{C\text{-}F}$ = 249.5 Hz), 159.89, 150.18, 135.85 (q, $J_{C\text{-}F}$ = 30.9 Hz), 132.65, 131.07, 130.98, 130.28, 129.75, 127.97, 125.75, 125.16 (q, $J_{C\text{-}F}$ = 5.0 Hz), 118.70, 116.05, 115.83.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}NF_4$: 294.0900, found: 294.0900.

FTIR (cm^{-1}): 3414, 2995, 2467, 2254, 2128, 1639, 1503, 1448, 1404, 1345, 1306, 1223, 1177, 1124, 1015, 827, 768.

(*E*)-1-(4-(Trifluoromethyl)phenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27g)

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), 4-(trifluoromethyl)benzaldehyde (0.276 g, 1.586 mmol.),



27g

$MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 3.965 mmol.) in DCM (15 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(4-(trifluoromethyl)phenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27g** (0.261 g, 48 % yield) as a yellow liquid.

R_f (Pet. ether /EtOAc = 95/05): 0.38.

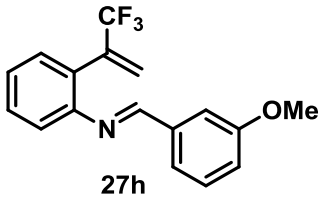
^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.69 (s, 1H), 8.10 (d, *J* = 7.8 Hz, 2H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.53-7.49 (m, 1H), 7.35-7.28 (m, 3H), 6.20 (s, 1H), 5.70 (s, 1H).

^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 160.08, 149.78, 139.46, 135.71 (q, $J_{C\text{-}F}$ = 31.1 Hz), 131.21 (q, $J_{C\text{-}F}$ = 32.0 Hz), 130.35, 129.84, 129.27, 128.17, 126.31, 125.79, 125.76, 125.39, 125.34, 118.71.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{12}NF_6$: 344.0868, found: 344.0868.

FTIR (cm^{-1}): 3413, 3021, 2887, 2403, 1916, 1809, 1634, 1582, 1485, 1410, 1324, 1214, 1174, 1128, 1068, 1024, 949, 880, 844, 767, 671.

(*E*)-1-(3-Methoxyphenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27h)



27h

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.40 g, 2.115 mmol.), 3-methoxybenzaldehyde (0.288 g, 2.115 mmol.), $MgSO_4$ (0.636 g, 5.287 mmol.) and Na_2SO_4 (0.751 g, 5.287 mmol.) in DCM (20 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(3-methoxyphenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27h** (0.271 g, 42 % yield) as a yellow liquid.

R_f (Pet. ether /EtOAc = 95/05): 0.39.

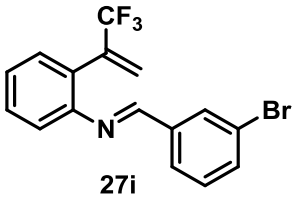
^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.54 (s, 1H), 7.48 (s, 3H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.35-7.28 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.19 (s, 1H), 5.70 (s, 1H).

^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 160.94, 159.54, 150.17, 137.43, 136.02 (q, $J_{C\text{-}F}$ = 31.0 Hz), 130.30, 129.94, 129.79, 128.04, 125.81, 125.17, 121.47, 118.64, 117.52, 113.15, 55.12.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{15}ONF_3$: 306.1100, found: 306.1100.

FTIR (cm^{-1}): 3416, 2989, 2253, 2127, 1657, 1489, 1454, 1395, 1341, 1259, 1224, 1175, 1123, 1016, 825, 769.

(*E*)-1-(3-Bromophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27i)



27i

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), 3-bromobenzaldehyde (0.293 g, 1.586 mmol.), $MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 3.965 mmol.) in DCM (30 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(3-bromophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27i** (0.309 g, 55 % yield) as a yellow liquid.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.44.

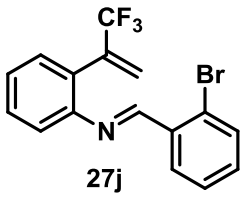
^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.57 (s, 1H), 8.07 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.52-7.47 (m, 2H), 7.35-7.30 (m, 2H), 7.25 (d, *J* = 7.8 Hz, 1H), 6.20 (s, 1H), 5.71 (s, 1H).

^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 159.81, 149.77, 138.22, 135.78 (q, $J_{C\text{-}F}$ = 31.0 Hz), 134.13, 131.06, 130.96, 130.32, 129.83, 128.11, 127.63, 126.14, 125.37 (q, $J_{C\text{-}F}$ = 5.1 Hz), 122.13, 118.67.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}NBrF_3$: 354.0100, found: 354.0102.

FTIR (cm^{-1}): 3423, 3024, 2094, 1637, 1482, 1432, 1349, 1271, 1216, 1178, 1126, 1071, 765.

(*E*)-1-(2-Bromophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27j)



27j

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), 2-bromobenzaldehyde (0.293 g, 1.586 mmol.), $MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 3.965 mmol.) in DCM (15 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(2-bromophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27j** (0.217 g, 39 % yield) as a yellow liquid.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.47.

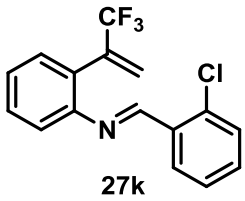
^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.57 (s, 1H), 8.06 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.52-7.47 (m, 2H), 7.35-7.32 (m, 2H), 7.25 (d, *J* = 7.8 Hz, 1H), 6.20 (s, 1H), 5.71 (s, 1H).

^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 159.81, 149.77, 138.22, 135.78 (q, J_{C-F} = 30.9 Hz), 134.13, 131.06, 130.96, 130.32, 129.83, 128.11, 127.63, 126.14, 125.35, 122.13, 118.67.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}NBrF_3$: 354.0100, found: 354.0103.

FTIR (cm^{-1}): 3421, 3065, 3021, 2873, 2752, 2403, 1933, 1696, 1626, 1581, 1479, 1435, 1402, 1349, 1270, 1212, 1178, 1127, 1072, 1033, 952, 873, 768.

(*E*)-1-(2-Chlorophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27k)



27k

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), 2-chlorobenzaldehyde (0.223 g, 1.586 mmol.), $MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 6.607 mmol.) in DCM (15 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(2-chlorophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27k** (0.491 g, 52 % yield) as a yellow liquid.

***R**$_f$* (Pet. ether /EtOAc = 95/05): 0.48.

^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.81 (s, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.59-7.47 (m, 4H), 7.37-7.32 (m, 2H), 7.25 (d, *J* = 7.7 Hz, 1H), 6.21 (s, 1H), 5.72 (s, 1H).

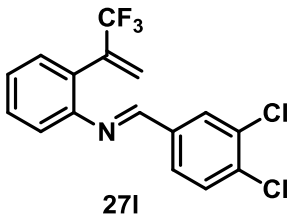
^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 157.03, 150.11, 135.45 (q, J_{C-F} = 31.0 Hz), 135.05, 133.07, 132.50, 130.42, 130.06, 129.80, 128.37, 127.85, 127.67, 126.21, 125.50 (q, J_{C-F} = 5.2 Hz), 118.78.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}NClF_3$: 310.0605, found: 310.0612.

FTIR (cm^{-1}): 3414, 2255, 2129, 1656, 1221, 996, 827, 770.

(*E*)-1-(3,4-Dichlorophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27l)

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), 3,4-dichlorobenzaldehyde (0.277 g, 1.586 mmol.), $MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 3.965 mmol.) in DCM (15 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography



27l

with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(3,4-dichlorophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27l** (0.275 g, 50 % yield) as a yellow liquid.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.42.

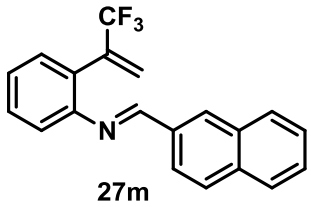
^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.60 (s, 1H), 8.09 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.52-7.49 (m, 1H), 7.35 (bs, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 6.21 (s, 1H), 5.71 (s, 1H).

^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 158.95, 149.52, 136.48, 135.74 (q, J_{C-F} = 31.1 Hz), 134.05, 131.78, 131.26, 130.34, 130.20, 129.88, 128.24, 126.33, 125.43 (q, J_{C-F} = 5.0 Hz), 118.62.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{11}NCl_2F_3$: 344.0215, found: 344.0218.

FTIR (cm^{-1}): 3413, 2255, 2130, 1653, 1227, 1014, 826, 769.

(*E*)-1-(Naphthalen-2-yl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27m)



27m

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.150 g, 0.793 mmol.), 2-naphthaldehyde (0.124 g, 0.793 mmol.), $MgSO_4$ (0.238 g, 1.982 mmol.) and Na_2SO_4 (0.282 g, 1.982 mmol.) in DCM (10 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(naphthalen-2-yl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27m** (0.180 g, 70 % yield) as a yellow liquid.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.46.

^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.72 (s, 1H), 8.37 (s, 1H), 8.09-7.97 (m, 4H), 7.65-7.59 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.37-7.28 (m, 3H), 6.22 (s, 1H), 5.75 (s, 1H).

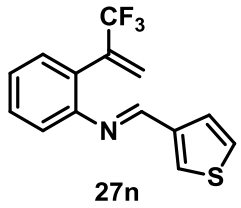
^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 161.62, 150.88, 135.01, 134.18, 133.08, 132.17, 130.83, 130.27, 129.22, 129.02, 128.43, 128.33, 127.38, 126.26, 125.77 (q, J_{C-F} = 5.2 Hz), 123.75, 119.22.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{15}NF_3$: 326.1151, found: 326.1157.

FTIR (cm^{-1}): 3413, 3020, 2923, 2308, 1619, 1448, 1347, 1217, 1177, 1126, 765.

(*E*)-1-(Thiophen-3-yl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27n)

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.409 g, 2.162 mmol.), thiophene-3-carbaldehyde (0.242 g, 189 µL, 2.162 mmol.), $MgSO_4$ (0.651 g, 5.405 mmol.) and Na_2SO_4 (0.768 g, 5.405 mmol.) in DCM (20 mL) at



27n

rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(thiophen-3-yl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27n** (0.382 g, 63 % yield) as a yellow liquid.

R_f (Pet. ether /EtOAc = 95/05): 0.39.

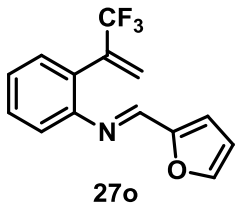
^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.53 (s, 1H), 8.16 (s, 1H), 7.64 (bs, 1H), 7.54 (d, *J* = 5.0 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.33-7.26 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 6.17 (s, 1H), 5.70 (s, 1H).

^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 155.58, 150.55, 140.59, 135.94 (q, J_{C-F} = 30.8 Hz), 132.23, 130.31, 129.73, 127.82, 127.74, 125.54, 125.37, 125.14 (q, J_{C-F} = 5.0 Hz), 118.66.

HRMS: calculated $[M+H]^+$ for $C_{14}H_{11}NF_3S$: 282.0559, found: 282.0561.

FTIR (cm^{-1}): 3417, 3020, 2402, 2094, 1629, 1487, 1411, 1345, 1216, 1175, 1125, 1073, 954, 872, 766.

(*E*)-1-(Furan-2-yl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27o)



27o

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), furan-2-carbaldehyde (0.152 g, 131 µL, 1.586 mmol.), $MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 3.965 mmol.) in DCM (15 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(furan-2-yl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27o** (0.328 g, 78 % yield) as a red liquid.

R_f (Pet. ether /EtOAc = 95/05): 0.39.

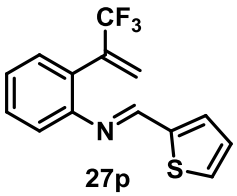
^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.34 (s, 1H), 7.96 (s, 1H), 7.48-7.45 (m, 1H), 7.32-7.26 (m, 2H), 7.19-7.14 (m, 2H), 6.71 (s, 1H), 6.18 (s, 1H), 5.69 (s, 1H).

^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 151.80, 150.54, 149.24, 146.68, 135.40 (q, J_{C-F} = 30.6 Hz), 130.32, 129.67, 127.77, 125.63, 125.33 (q, J_{C-F} = 5.1 Hz), 118.78, 117.47, 112.52.

HRMS: calculated $[M+H]^+$ for $C_{14}H_{11}ONF_3$: 266.0787, found: 266.0786.

FTIR (cm^{-1}): 3414, 2256, 2130, 1666, 1394, 1229, 1044, 826, 772.

(*E*)-1-(Thiophen-2-yl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine (27p)



27p

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), thiophene-2-carbaldehyde (0.178 g, 150 µL, 1.586 mmol.), $MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 3.965 mmol.) in DCM (30 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (*E*)-1-(thiophen-2-yl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27p** (0.261 g, 58% yield) as a yellow liquid.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.42.

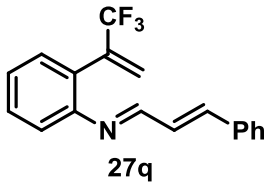
^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.69 (s, 1H), 7.80-7.79 (m, 1H), 7.68 (bs, 1H), 7.47 (bs, 1H), 7.31-7.21 (m, 4H), 6.17 (s, 1H), 5.68 (s, 1H).

^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 154.38, 149.82, 142.44, 135.87 (q, $J_{C\text{-}F}$ = 30.7 Hz), 133.61, 131.60, 130.26, 129.75, 128.17, 127.99, 125.70, 125.04, 118.74.

HRMS: calculated $[M+H]^+$ for $C_{14}H_{11}NF_3S$: 282.0559, found: 282.0559.

FTIR (cm^{-1}): 3416, 2124, 1649, 1536, 1442, 1336, 1292, 1220, 1171, 1127, 994, 765.

(1*E*,2*E*)-3-Phenyl-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)prop-2-en-1-imine (27q)



27q

Following the general known procedure, treatment of 2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine (0.30 g, 1.586 mmol.), cinnamaldehyde (0.210 g, 1.586 mmol.), $MgSO_4$ (0.477 g, 3.965 mmol.) and Na_2SO_4 (0.563 g, 3.965 mmol.) in DCM (15 mL) at rt for 36 h. After 36 h the crude reaction mixture was purified via flash column chromatography with deactivated silica gel (eluting with hexanes/Et_3N (20:1 v/v)) to afford the corresponding aldimine (1*E*,2*E*)-3-phenyl-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)prop-2-en-1-imine **27q** (0.189 g, 39 % yield) as a yellow liquid.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.41.

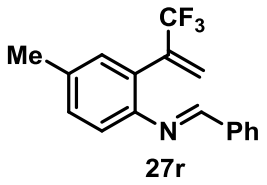
^{1}H NMR (DMSO-*d*^{6}, 400 MHz) δ 8.29 (d, *J* = 8.9 Hz, 1H), 7.68 (d, *J* = 7.1 Hz, 2H), 7.47-7.35 (m, 5H), 7.31-7.25 (m, 2H), 7.17-7.10 (m, 2H), 6.18 (s, 1H), 5.66 (s, 1H).

^{13}C NMR (DMSO-*d*^{6}, 100 MHz) δ 163.18, 151.00, 144.85, 135.37 (q, $J_{C\text{-}F}$ = 30.7 Hz), 135.29, 130.24, 129.70, 129.61, 128.93, 128.21, 127.71, 127.49, 125.42, 125.15 (d, $J_{C\text{-}F}$ = 5.0 Hz), 118.77.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{15}NF_3$: 302.1151, found: 302.1152.

FTIR (cm^{-1}): 3412, 2256, 2131, 1658, 1221, 997, 827, 768, 674.

(*E*)-*N*-(Phenylmethylene)- 4-methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine (27r)



27r

Following the general procedure, treatment of 4-methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (322 mg, 1.60 mmol, 1 equiv.) with benzaldehyde (678 mg, 650 µL, 6.40 mmol, 4 equiv.) at 50 °C under 40 mbar for 2 h followed by high vacuum then a column chromatography with deactivated silica gel using petroleum ether/Et_3N as eluent (from 100/0 to 98/2) afforded **27r** (413 mg, 1.43 mmol, 89%) as a yellowish oil.

***R**$_f$* (Pet. ether/Et_3N = 98/2): 0.56.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.39 (s, 1H), 7.90-7.83 (m, 2H), 7.51-7.42 (m, 3H), 7.25-7.14 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.10 (d, *J* = 1.1 Hz, 1H), 5.57 (d, *J* = 1.1 Hz, 1H), 2.38 (s, 3H).

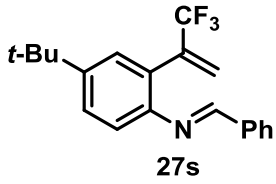
^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8, 148.4, 137.1 (q, *J* = 31.1 Hz), 136.5, 135.5, 131.3, 130.6, 130.6, 128.9, 128.7, 128.6, 123.8 (q, *J* = 5.3 Hz), 123.5 (q, *J* = 274.1 Hz), 118.3, 20.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ -65.5 (s).

HRMS: calculated $[M+H]^+$ for $C_{17}H_{15}F_3N$: 290.1157, found: 290.1158.

FTIR (cm^{-1}): 3027, 1629, 1503, 1341, 1157, 1117, 1067, 947, 877, 816, 750, 691, 558, 452.

(*E*)-*N*-(Phenylmethylene)-4-*tert*-butyl-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine (27s)



27s

Following the general procedure, treatment of 4-(*tert*-butyl)-2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (185 mg, 0.76 mmol, 1 equiv.) with benzaldehyde (322 mg, 309 µL, 3.04 mmol, 4 equiv.) at 50 °C under 40 mbar for 1 h followed by high vacuum then a column chromatography with deactivated silica gel using petroleum ether/Et_3N as eluent (from 100/0 to 97/3) afforded **27s** (177 mg, 0.54 mmol, 70%) as a white solid.

***R**$_f$* (Pet. ether/Et_3N = 98/2): 0.60; **m.p.** 41-42 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (s, 1H), 7.91-7.83 (m, 2H), 7.51-7.40 (m, 4H), 7.38-7.34 (m, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.11 (d, *J* = 1.1 Hz, 1H), 5.58 (d, *J* = 1.1 Hz, 1H), 1.35 (s, 9H).

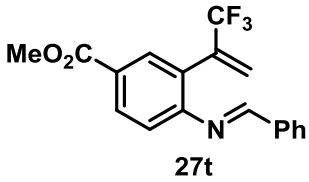
^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.1, 148.8, 148.4, 137.3 (q, *J* = 31.1 Hz), 136.5, 131.4, 129.0, 128.9, 128.1, 127.1, 127.0, 123.9 (q, *J* = 5.3 Hz), 123.4 (q, *J* = 274.1 Hz), 118.1, 34.6, 31.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -65.5 (s).

HRMS: calculated $[M+H]^+$ for $C_{20}H_{21}F_3N$: 332.1626, found: 332.1620.

FTIR (cm^{-1}): 2957, 2866, 1627, 1494, 1395, 1338, 1184, 1149, 1134, 1118, 1072, 957, 834, 751, 690, 583, 516, 448.

(*E*)-Methyl 4-(benzylideneamino)-3-(3,3,3-trifluoroprop-1-en-2-yl)benzoate (27t)



27t

To a solution of amine methyl 4-amino-3-(3,3,3-trifluoroprop-1-en-2-yl)benzoate (130 mg, 0.53 mmol, 1 equiv.) and benzaldehyde (225 mg, 2.12 mmol, 4 equiv.) in Toluene (10 mL) under argon was added Na_2SO_4 (750 mg, 5.3 mmol, 10 equiv.). The reaction mixture was heated at reflux for 48 h. The reaction mixture was filtered, rinsed with DCM and the filtrate was concentrated in vacuo. The crude imine, was purified via flash column chromatography with deactivated silica gel using petroleum ether/Et_3N as eluent (from 100/0 to 96/4) afforded **27t** (95 mg, 0.29 mmol, 72%) as a yellowish oil.

***R**_f* (Pet. ether/Et_2O = 95/55): 0.35.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, 1H), 8.09 (dd, *J* = 8.3 and 1.8 Hz, 1H), 7.92-7.85 (m, 2H), 7.56-7.40 (m, 3H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.15 (s, 1H), 5.62 (s, 1H), 3.93 (s, 3H).

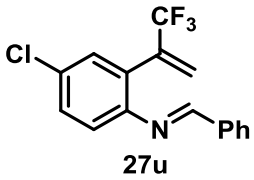
^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 161.8, 155.2, 136.3 (q, *J* = 31.8 Hz), 135.8, 132.1, 131.7, 130.7, 129.3, 129.0, 128.4, 127.2, 124.7 (q, *J* = 5.2 Hz), 123.0 (q, *J* = 274.0 Hz), 118.9, 52.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -65.7 (s).

HRMS: calculated $[M+H]^+$ for $C_{18}H_{15}F_3NO_2$: 334.1055, found: 334.1054.

FTIR (cm^{-1}): 2950, 1714, 1596, 1435, 1283, 1250, 1166, 1121, 1069, 969, 881, 776, 758, 691, 637, 618, 513, 470, 434.

(*E*)-*N*-(Phenylmethylene)-4-chloro-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine (27u)



27u

Following the general procedure, treatment of 4-chloro-2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (187 mg, 0.85 mmol, 1 equiv.) with benzaldehyde (360 mg, 345 µL, 3.40 mmol, 4 equiv.) at 50 °C under 40 mbar for 6 h followed by high vacuum then a column chromatography with deactivated silica gel using petroleum ether/Et_3N as eluent (from 100/0 to 97/3) afforded **27u** (212 mg, 0.69 mmol, 81%) as a yellowish oil.

***R**_f* (Pet. ether/Et_3N = 96/4): 0.63.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.37 (s, 1H), 7.90-7.83 (m, 2H), 7.54-7.43 (m, 3H), 7.41-7.33 (m, 2H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.14 (d, *J* = 1.2 Hz, 1H), 5.61 (d, *J* = 1.2 Hz, 1H).

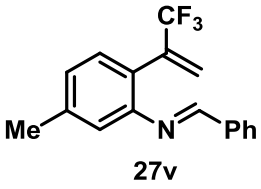
^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.0, 149.6, 136.0, 135.0 (q, *J* = 31.1 Hz), 131.9, 131.0, 130.0, 130.0, 129.9, 129.1, 128.9, 124.8 (q, *J* = 5.3 Hz), 123.0 (q, *J* = 274.1 Hz), 119.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ -65.6 (s).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}{}^{35}ClF_3N$: 310.0610, found: 310.0604.

FTIR (cm^{-1}): 3065, 2880, 1628, 1579, 1476, 1335, 1167, 1121, 1065, 951, 877, 817, 749, 690, 637, 538, 424.

(*E*)-*N*-(Phenylmethylene)-5-methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine (27v)



27v

Following the general procedure, treatment of 5-methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (126 mg, 0.63 mmol, 1 equiv.) with benzaldehyde (266 mg, 255 µL, 2.51 mmol, 4 equiv.) at 50 °C under 40 mbar for 2 h followed by high vacuum then a column chromatography with deactivated silica gel using petroleum ether/Et_3N as eluent (from 100/0 to 95/5) afforded **27v** (166 mg, 0.57 mmol, 92%) as a yellowish oil.

***R*$_f$** (Pet. ether/Et_3N = 95/5): 0.60.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, 1H), 7.91-7.84 (m, 2H), 7.51-7.42 (m, 3H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.86 (s, 1H), 6.09 (d, *J* = 1.1 Hz, 1H), 5.56 (d, *J* = 1.1 Hz, 1H), 2.40 (s, 3H).

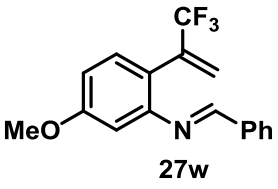
^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.4, 151.0, 140.1, 136.7 (q, *J* = 31.1 Hz), 136.4, 131.5, 129.8, 129.0, 128.8, 126.3, 125.4, 123.9 (q, *J* = 5.3 Hz), 123.4 (q, *J* = 274.1 Hz), 119.3, 21.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -65.6 (s).

HRMS: calculated $[M+H]^+$ for $C_{17}H_{15}F_3N$: 290.1157, found: 290.1148.

FTIR (cm^{-1}): 3031, 2866, 1631, 1504, 1452, 1343, 1167, 1117, 1066, 944, 818, 757, 690, 614, 493.

(*E*)-*N*-(Phenylmethylene)-5-methoxy-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine (27w)



27w

Following the general procedure, treatment of 5-methoxy-2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (157 mg, 0.72 mmol, 1 equiv.) with benzaldehyde (305 mg, 292 µL, 2.88 mmol, 4 equiv.) at 50 °C under 40 mbar for 1 h followed by high vacuum then a column chromatography with deactivated silica gel using petroleum ether/Et_3N as eluent (from 100/0 to 95/5) afforded **27w** (198 mg, 0.65 mmol, 90%) as a yellowish oil.

***R*$_f$** (Pet. ether/Et_3N = 95/5): 0.36.

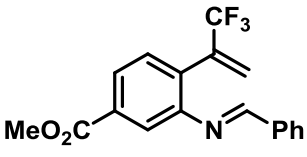
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, 1H), 7.91-7.84 (m, 2H), 7.52-7.43 (m, 3H), 7.29 (d, *J* = 8.5 Hz, 1H), 6.78 (dd, *J* = 8.5 and 2.6 Hz, 1H), 6.58 (d, *J* = 2.6 Hz, 1H), 6.07 (d, *J* = 1.1 Hz, 1H), 5.54 (d, *J* = 1.1 Hz, 1H), 3.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8, 160.8, 152.4, 136.3 (q, *J* = 31.1 Hz), 136.1, 131.7, 130.9, 129.0, 128.8, 123.8 (q, *J* = 5.3 Hz), 123.4 (q, *J* = 274.1 Hz), 120.5, 110.7, 104.5, 55.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -65.7 (s).

HRMS: calculated $[M+H]^+$ for $C_{17}H_{15}F_3NO$: 306.1106, found: 306.1114. **FTIR (cm^{-1}):** 2840, 1632, 1599, 1503, 1345, 1291, 1246, 1160, 1114, 1073, 1035, 948, 835, 759, 690, 507.

(*E*)-Methyl 3-(benzylideneamino)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzoate (27x)



27x

Following the general procedure, treatment of methyl 3-amino-4-(3,3,3-trifluoroprop-1-en-2-yl)benzoate (165 mg, 0.67 mmol, 1 equiv.) with benzaldehyde (284 mg, 272 µL, 2.68 mmol, 4 equiv.) at 50 °C under 40 mbar for 9 h followed by high vacuum then a column chromatography with deactivated silica gel using petroleum ether/Et_3N as eluent (from 100/0 to 95/5) afforded **27x** (207 mg, 0.62 mmol, 92%) as a yellowish oil.

***R**$_f$* (Pet. ether/Et_3N = 97/3): 0.26.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 7.93-7.86 (m, 3H), 7.74 (d, *J* = 1.5 Hz, 1H), 7.56-7.41 (m, 4H), 6.18 (d, *J* = 1.2 Hz, 1H), 5.65 (d, *J* = 1.2 Hz, 1H), 3.95 (s, 3H).

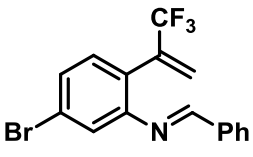
^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3, 161.5, 151.1, 136.1 (q, *J* = 31.6 Hz), 135.9, 132.7, 131.8, 131.7, 130.1, 129.1, 128.8, 126.4, 124.8 (q, *J* = 5.3 Hz), 123.0 (q, *J* = 274.1 Hz), 119.6, 52.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -65.4 (s).

HRMS: calculated $[M+H]^+$ for $C_{18}H_{15}F_3NO_2$: 334.1055, found: 334.1056.

FTIR (cm^{-1}): 2959, 1722, 1631, 1563, 1437, 1345, 1290, 1228, 1166, 1120, 1101, 1063, 975, 907, 760, 690, 612, 482.

(*E*)-*N*-(Phenylmethylene)-5-bromo-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine (27y)



27y

Following the general procedure, treatment of 5-bromo-2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (292 mg, 1.10 mmol, 1 equiv.) with benzaldehyde (465 mg, 446 µL, 4.39 mmol, 4 equiv.) at 50 °C under 40 mbar for 2 h followed by high vacuum then a column chromatography with deactivated silica gel using petroleum ether/Et_3N as eluent (from 100/0 to 95/5) afforded **27y** (344 mg, 0.97 mmol, 89%) as a yellowish oil.

***R*$_f$** (Pet. ether/Et_3N = 95/5): 0.64.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.37 (s, 1H), 7.91-7.83 (m, 2H), 7.56-7.43 (m, 3H), 7.37 (dd, *J* = 8.2 and 2.0 Hz, 1H), 7.25-7.19 (m, 2H), 6.13 (d, *J* = 1.2 Hz, 1H), 5.59 (d, *J* = 1.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.5, 152.2, 135.9 (q, *J* = 31.5 Hz), 135.8, 132.0, 131.3, 129.2, 128.9, 128.4, 127.2, 124.6 (q, *J* = 5.3 Hz), 123.6, 123.3 (q, *J* = 274.0 Hz), 123.2.

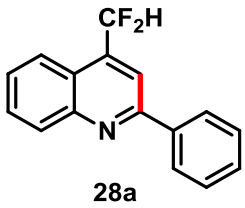
^{19}F NMR (282 MHz, $CDCl_3$) δ -65.7 (s).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}{}^{79}BrF_3N$: 354.0105, found: 354.0104.

FTIR (cm^{-1}): 3065, 2878, 1629, 1578, 1481, 1343, 1166, 1120, 1085, 1063, 949, 896, 877, 818, 763, 742, 689, 610, 481.

5.6.6. Synthesis and Characterization of Difluoromethylated Quinoline Derivatives

4-(difluoromethyl)-2-phenylquinoline (28a)[22c]



28a

Following the general procedure, treatment of (*E*)-*N*-benzylidene-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27a** (137.6 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-phenylquinoline **28a** as a yellowish liquid (0.096 g, 75%).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.40.

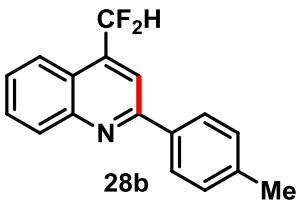
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 7.4 Hz, 2H), 8.09-8.06 (m, 2H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.57-7.48 (m, 3H), 7.20 (t, *J* = 54.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.08, 148.86, 138.77 (t, $J_{C\text{-}F}$ = 24.7 Hz), 130.74, 130.25, 129.99, 129.11, 127.66, 127.55, 123.20, 116.07 (t, $J_{C\text{-}F}$ = 8.0 Hz), 113.65 (t, $J_{C\text{-}F}$ = 240.5 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}NF_2$: 256.0932, found: 256.0934.

FTIR (cm^{-1}): 3407, 3021, 2976, 2403, 1609, 1372, 1216, 1117, 1047, 928, 887, 767, 669.

4-(Difluoromethyl)-2-(*p*-tolyl)quinoline (28b)[22c]



28b

Following the general procedure, treatment of (*E*)-1-*p*-tolyl-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27b** (144.6 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h

followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-(*p*-tolyl)quinoline **28b** as a yellowish solid (0.115 g, 79%).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.41.

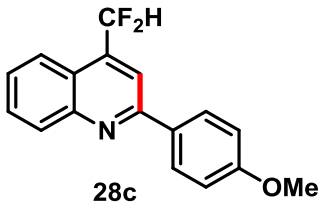
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.25 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 7.9 Hz, 2H), 8.07-8.04 (m, 2H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 54.6 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 157.01, 148.88, 140.18, 138.46 (t, $J_{C\text{-}F}$ = 21.6 Hz), 136.11, 130.65, 130.14, 129.83, 127.50, 127.30, 123.18, 123.07 (t, $J_{C\text{-}F}$ = 3.1 Hz), 115.89 (t, $J_{C\text{-}F}$ = 7.9 Hz), 113.72 (t, $J_{C\text{-}F}$ = 240.7 Hz), 21.49.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{14}NF_2$: 270.1089, found: 270.1094.

FTIR (cm^{-1}): 3420, 3023, 1640, 1412, 1218, 1113, 766.

4-(Difluoromethyl)-2-(4-methoxyphenyl)quinoline (28c)



28c

Following the general procedure, treatment of (*E*)-N-(4-methoxybenzylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27c** (123.0 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-(4-methoxyphenyl)quinoline **28c** as a yellowish solid (0.118 g, 83%).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.32.

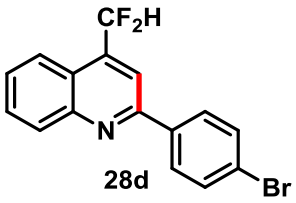
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.23 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.7 Hz, 2H), 8.04-8.00 (m, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.31-7.04 (m, 3H), 3.88 (s, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 161.36, 156.54, 148.77, 138.47 (t, $J_{C\text{-}F}$ = 21.6 Hz), 131.35, 130.42, 130.17, 129.03, 127.12, 123.16, 122.85 (t, $J_{C\text{-}F}$ = 3.1 Hz), 115.58 (t, $J_{C\text{-}F}$ = 7.8 Hz), 114.46, 113.68 (t, $J_{C\text{-}F}$ = 240.5 Hz), 55.52.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{14}ONF_2$: 286.1038, found: 286.1036.

FTIR (cm^{-1}): 3415, 3020, 1607, 1514, 1370, 1218, 1175, 1115, 1041, 839, 767.

2-(4-Bromophenyl)-4-(difluoromethyl)quinoline (28d)[22c]



Following the general procedure, treatment of (*E*)-1-(4 bromophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27d** (177.1 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2-(4-bromophenyl)-4-(difluoromethyl)quinoline **28d** as a yellowish solid (0.130 g, 76%).

***R**f* (Pet. ether /EtOAc = 90/10): 0.39.

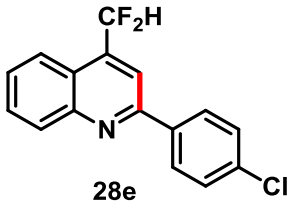
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, *J* = 8.5 Hz, 1H), 8.08-8.05 (m, 3H), 8.01 (s, 1H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.67-7.61 (m, 3H), 7.20 (t, *J* = 54.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.76, 148.83, 138.82 (t, J_{C-F} = 21.8 Hz), 137.72, 132.25, 130.74, 130.42, 129.12, 127.78, 124.66, 123.26 (t, J_{C-F} = 3.1 Hz), 123.20, 115.47 (t, J_{C-F} = 7.9 Hz), 113.46 (t, J_{C-F} = 240.9 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{11}NBrF_2$: 334.0037, found: 334.0041.

FTIR (cm^{-1}): 3417, 3021, 2403, 1606, 1409, 1217, 1114, 1060, 927, 766.

2-(4-Chlorophenyl)-4-(difluoromethyl)quinoline (28e)



Following the general procedure, treatment of (*E*)-1-(4-chlorophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl) methanimine **27e** (154.8 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2-(4-chlorophenyl)-4-(difluoromethyl)quinoline **28e** as a yellowish liquid (0.130 g, 84%).

***R**f* (Pet. ether /EtOAc = 90/10): 0.39.

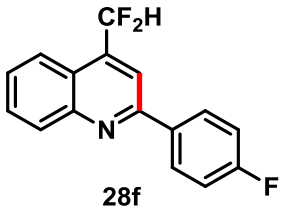
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, *J* = 8.6 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 2H), 8.06 (d, *J* = 8.5 Hz, 1H), 8.01 (s, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.20 (t, *J* = 54.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.71, 148.82, 139.03, 138.81 (t, J_{C-F} = 21.8 Hz), 137.28, 136.25, 130.73, 130.40, 129.29, 128.87, 127.75, 123.19, 115.53 (t, J_{C-F} = 7.9 Hz), 113.47 (t, J_{C-F} = 240.7 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{11}NClF_2$: 290.0543, found: 290.0551.

FTIR (cm^{-1}): 3415, 3022, 1627, 1372, 1218, 1050, 767.

4-(Difluoromethyl)-2-(4-fluorophenyl)quinoline (28f)



28f

Following the general procedure, treatment of (*E*)-1-(4-fluorophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27f** (136.0 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-(4-fluorophenyl)quinoline **28f** as a yellowish solid (0.097 g, 71%).

***R**$_f$* (Pet. ether /EtOAc = 90/10): 0.38.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25-8.17 (m, 3H), 8.06 (d, *J* = 8.3 Hz, 1H), 8.01 (s, 1H), 7.79 (t, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.34-7.06 (m, 3H).

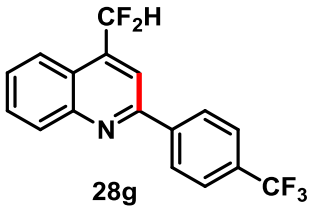
^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.22 (d, J_{C-F} = 250.2 Hz) 155.92, 148.76, 138.81 (t, J_{C-F} = 21.6 Hz), 135.02, 130.62, 130.39, 129.61, 129.53, 127.62, 123.19, 123.10 (t, J_{C-F} = 3.1 Hz), 116.20, 115.99, 115.63 (t, J_{C-F} = 7.9 Hz), 113.50 (t, J_{C-F} = 240.8 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{11}NF_3$: 274.0838, found: 274.0836.

FTIR (cm^{-1}): 3389, 3021, 2402, 1604, 1513, 1415, 1370, 1218, 1157, 1115, 1052, 926, 883, 846, 762.

4-(Difluoromethyl)-2-(4-(trifluoromethyl)phenyl)quinoline (28g)[22c]

Following the general procedure, treatment of (*E*)-N-(4-(trifluoromethyl)benzylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27g** (171.6 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-(4-(trifluoromethyl)phenyl)quinoline **28g** as a yellowish solid (0.125 g, 78%).



28g

***R**f* (Pet. ether /EtOAc = 90/10): 0.33.

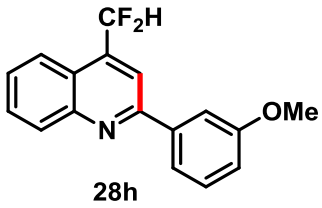
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29-8.24 (m, 3H), 8.07-8.04 (m, 2H), 7.82-7.77 (m, 3H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 54.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.31, 148.79, 142.04, 139.02 (t, J_{C-F} = 21.6 Hz), 131.68 (q, J_{C-F} = 32.4 Hz), 130.86, 130.53, 128.12, 127.88, 125.98, 125.95, 123.45 (t, J_{C-F} = 3.0 Hz), 123.19, 115.67 (t, J_{C-F} = 7.8 Hz), 113.37 (t, J_{C-F} = 240.9 Hz).

HRMS: calculated $[M+H]^+$ for $C_{17}H_{11}NF_5$: 324.0806, found: 324.0804.

FTIR (cm^{-1}): 3418, 3023, 1642, 1368, 1219, 1113, 1056, 766.

4-(Difluoromethyl)-2-(3-methoxyphenyl)quinoline (28h)



28h

Following the general procedure, treatment of (*E*)-N-(3-methoxybenzylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27h** (152.6 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-(3-methoxyphenyl)quinoline **28h** as a yellowish solid (0.113 g, 79%).

***R**f* (Pet. ether /EtOAc = 90/10): 032.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* = 8.5 Hz, 1H), 8.08-8.04 (m, 2H), 7.80-7.77 (m, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.33-7.04 (m, 2H), 3.94 (s, 3H).

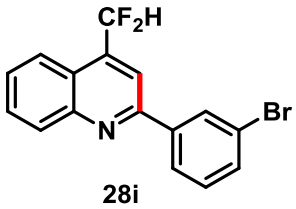
^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.35, 156.80, 148.73, 140.27, 138.62 (t, J_{C-F} = 21.5 Hz), 130.69, 130.24, 130.07, 127.57, 123.24 (t, J_{C-F} = 3.1 Hz), 123.19, 120.06, 116.15 (t, J_{C-F} = 7.9 Hz), 115.99, 113.64 (t, J_{C-F} = 240.4 Hz), 112.81, 55.56.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{14}ONF_2$: 286.1038, found: 286.1039.

FTIR (cm^{-1}): 3416, 3018, 2971, 2840, 2403, 1602, 1553, 1501, 1462, 1367, 1326, 1217, 1173, 1124, 1048, 879, 766.

2-(3-Bromophenyl)-4-(difluoromethyl)quinoline (28i)

Following the general procedure, treatment of (*E*)-N-(3-bromobenzylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27i** (177.0 mg, 0.50 mmol) with the triazolium salt **3** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h



28i

followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2-(3-bromophenyl)-4-(difluoromethyl)quinoline **28i** as a yellowish solid (0.139 g, 83%).

***R**f* (Pet. ether /EtOAc = 90/10): 0.37.

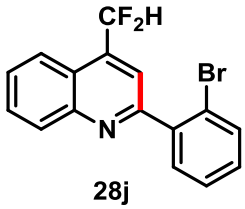
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 2H), 8.02 (s, 1H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.66-7.61 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.21 (t, *J* = 54.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.36, 148.76, 140.82, 138.98 (t, $J_{C\text{-}F}$ = 21.4 Hz), 132.91, 130.79, 130.72, 130.58, 130.51, 127.97, 126.15, 123.44, 123.40 (t, $J_{C\text{-}F}$ = 3.1 Hz), 123.23, 115.71 (t, $J_{C\text{-}F}$ = 7.9 Hz), 113.46 (t, $J_{C\text{-}F}$ = 240.6 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{11}NBrF_2$: 334.0037, found: 334.0045.

FTIR (cm^{-1}): 3418, 3022, 1640, 1367, 1218, 1115, 1055, 766.

2-(2-Bromophenyl)-4-(difluoromethyl)quinoline (28j)



28j

Following the general procedure, treatment of (*E*)-1-(2-bromophenyl)-N-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanimine **27j** (176.0 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2-(2-bromophenyl)-4-(difluoromethyl)quinoline **28j** as a white solid (0.140 g, 84%).

***R**f* (Pet. ether /EtOAc = 90/10): 0.41.

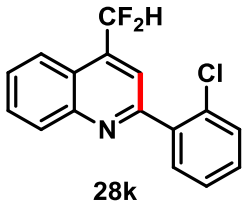
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.93 (s, 1H), 7.84-7.81 (m, 1H), 7.74-7.65 (m, 3H), 7.49-7.46 (m, 1H), 7.35-7.06 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.51, 151.73, 148.53, 137.58 (t, $J_{C\text{-}F}$ = 21.9 Hz), 133.53, 131.75, 130.72, 130.57, 130.32, 128.12, 127.98, 123.40, 123.19 (t, $J_{C\text{-}F}$ = 3.1 Hz), 121.89, 120.04 (t, $J_{C\text{-}F}$ = 7.7 Hz), 113.67 (t, $J_{C\text{-}F}$ = 240.7 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{11}NBrF_2$: 334.0037, found: 334.0039.

FTIR (cm^{-1}): 3426, 2107, 1641, 1433, 1218, 1115, 767.

2-(2-Chlorophenyl)-4-(difluoromethyl)quinoline (28k)



28k

Following the general procedure, treatment of (*E*)-N-(2-chlorobenzylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27k** (188.0 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2-(2-chlorophenyl)-4-(difluoromethyl)quinoline **28k** as a yellowish solid (0.127 g, 88%).

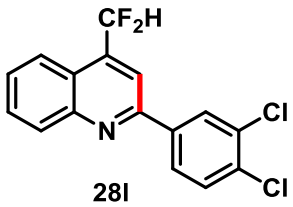
***R**f* (Pet. ether /EtOAc = 90/10): 0.38.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 7.4 Hz, 2H), 8.09-8.06 (m, 2H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.57-7.48 (m, 3H), 7.20 (t, *J* = 54.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.24, 148.70, 138.94, 137.58 (t, $J_{C\text{-}F}$ = 21.9 Hz), 132.48, 131.81, 130.71, 130.47, 130.35, 130.27, 128.08, 127.44, 123.40, 123.17 (t, $J_{C\text{-}F}$ = 3.0 Hz), 120.06 (t, $J_{C\text{-}F}$ = 7.9 Hz), 113.68 (t, $J_{C\text{-}F}$ = 241.1 Hz). **HRMS**: calculated $[M+H]^+$ for $C_{16}H_{11}NClF_2$: 290.0543, found: 290.0548.

FTIR (cm^{-1}): 3419, 3022, 2403, 1640, 1371, 1217, 1117, 1051, 766.

2-(3,4-Dichlorophenyl)-4-(difluoromethyl)quinoline (28l)



28l

Following the general procedure, treatment of (*E*)-N-(3,4-dichlorobenzylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27l** (172.0 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2-(3,4-dichlorophenyl)-4-(difluoromethyl)quinoline **28l** as a yellowish solid (0.146 g, 90%).

***R**f* (Pet. ether /EtOAc = 90/10): 0.35.

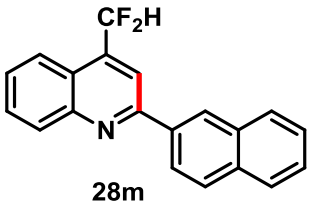
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 8.03-8.00 (m, 2H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.21 (t, *J* = 54.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.36, 148.76, 139.12 (t, J_{C-F} = 21.5 Hz), 138.67, 134.33, 133.53, 131.02, 130.79, 130.62, 129.49, 128.11, 126.60, 123.43 (t, J_{C-F} = 3.1 Hz), 123.23, 115.27 (t, J_{C-F} = 7.9 Hz), 113.34 (t, J_{C-F} = 240.6 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{10}NCl_2F_2$: 324.0153, found: 324.0153.

FTIR (cm^{-1}): 3414, 3022, 1637, 1392, 1217, 1083, 765.

4-(Difluoromethyl)-2-(naphthalen-2-yl)quinoline (28m)



28m

Following the general procedure, treatment of (*E*)-N-(naphthalen-2-ylmethylene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27m** (162.6 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-(naphthalen-2-yl)quinoline **28m** as a yellowish solid (0.108 g, 71%).

***R**$_f$* (Pet. ether /EtOAc = 90/10): 0.34.

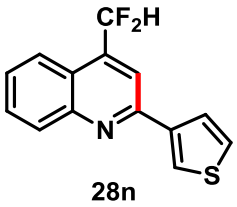
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63 (s, 1H), 8.39 (d, *J* = 8.5 Hz, 1H),8.32 (d, *J* = 8.5 Hz, 1H), 8.19 (s, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 2H), 7.90-7.89 (m, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.56-7.54 (m, 2H), 7.21 (t, *J* = 54.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.77, 148.81, 138.68 (t, J_{C-F} = 21.6 Hz), 136.02, 134.19, 133.52, 130.65, 130.31, 129.02, 128.87, 127.86, 127.58, 127.47, 127.17, 126.63, 124.82, 123.22, 116.14 (t, J_{C-F} = 7.8 Hz), 113.66 (t, J_{C-F} = 240.7 Hz).

HRMS: calculated $[M+H]^+$ for $C_{20}H_{14}NF_2$: 306.1089, found: 306.1088.

FTIR (cm^{-1}): 3415, 3022, 1639, 1384, 1218, 1118, 1048, 767.

4-(Difluoromethyl)-2-(thiophen-3-yl)quinoline (28n)



28n

Following the general procedure, treatment of (*E*)-N-(thiophen-3-ylmethylene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27n** (137.6 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-(thiophen-3-yl)quinoline **28n** as a brownish solid (0.095 g, 73%).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.31.

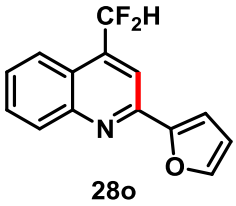
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.20 (d, *J* = 8.5 Hz, 1H), 8.10-8.09 (m, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.92-7.89 (m, 2H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.46-7.44 (m, 1H), 7.17 (t, *J* = 54.7 Hz, 1H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 152.93, 148.72, 141.94, 138.51 (t, $J_{C\text{-}F}$ = 21.5 Hz), 130.39, 130.25, 127.30, 126.81, 126.79, 125.52, 123.16, 123.02 (t, $J_{C\text{-}F}$ = 3.1 Hz), 116.08 (t, $J_{C\text{-}F}$ = 7.9 Hz), 113.47 (t, $J_{C\text{-}F}$ = 240.4 Hz).

HRMS: calculated $[M+H]^+$ for $C_{14}H_{10}NF_2S$: 262.0497, found: 262.0495.

FTIR (cm^{-1}): 3425, 2111, 1641, 1415, 1216, 1178, 1125, 765.

4-(Difluoromethyl)-2-(furan-2-yl)quinoline (28o)



28o

Following the general procedure, treatment of (*E*)-N-(furan-2-ylmethylene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27o** (132.6 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-(furan-2-yl)quinoline **28o** as a brownish solid (0.099 g, 81%).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.36.

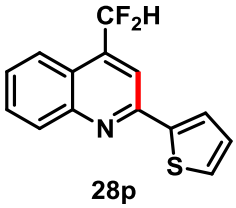
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.91-7.87 (m, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.53 (s, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.17-6.90 (m, 2H), 6.49 (bs, 1H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 153.16, 148.70, 148.62, 138.51 (t, $J_{C\text{-}F}$ = 21.7 Hz), 130.37, 130.25, 127.34, 123.27, 123.02 (t, $J_{C\text{-}F}$ = 3.0 Hz), 114.71 (t, $J_{C\text{-}F}$ = 8.0 Hz), 113.45 (t, $J_{C\text{-}F}$ = 241.0 Hz), 112.55, 111.03.

HRMS: calculated $[M+H]^+$ for $C_{14}H_{10}ONF_2$: 246.0725, found: 246.0724.

FTIR (cm^{-1}): 3416, 3016, 1615, 1557, 1500, 1364, 1218, 1161, 1118, 1050, 942, 889, 765.

4-(Difluoromethyl)-2-(thiophen-2-yl)quinoline (28p)



28p

Following the general procedure, treatment of (*E*)-N-(thiophen-2-ylmethylene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27p** (140.6 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet.

ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-2-(thiophen-2-yl)quinoline **28p** as a yellowish solid (0.104 g, 80%).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.34.

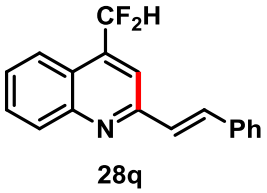
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.17 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 7.78-7.73 (m, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 4.7 Hz, 1H), 7.30-7.02 (m, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 152.09, 148.59, 144.60, 138.52 (t, J_{C-F} = 21.5 Hz), 130.40, 130.17, 129.46, 128.39, 127.29, 126.74, 123.21, 123.12 (t, J_{C-F} = 3.0 Hz), 114.81 (t, J_{C-F} = 7.9 Hz), 113.38 (t, J_{C-F} = 240.7 Hz).

HRMS: calculated $[M+H]^+$ for $C_{14}H_{10}NF_2S$: 262.0497, found: 262.0496.

FTIR (cm^{-1}): 3425, 3020, 2403, 2357, 1965, 1806, 1611, 1544, 1523, 1465, 1428, 1372, 1217, 1173, 1123, 1056, 922, 877, 840, 769.

(*E*)-4-(Difluoromethyl)-2-styrylquinoline (28q)



28q

Following the general procedure, treatment of (*E*)-N-((*E*)-3-phenylallylidene)-2-(1,1,1-trifluoroprop-2-en-2-yl)benzenamine **27q** (150.6 mg, 0.50 mmol) with the triazolium salt **29** (27.0 mg, 0.10 mmol), DBU (228.4 mg, 224 μL, 1.50 mmol) in DMF (4.0 mL) at 100 °C for 36 h followed by work-up of the reaction mixture using EtOAc and subsequent flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded (*E*)-4-(difluoromethyl)-2-styrylquinoline **28q** as a brownish solid (0.077 g, 55%).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.32.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.17 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.79-7.72 (m, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.45-7.40 (m, 3H), 7.37-7.33 (m, 1H), 7.17 (t, *J* = 54.6 Hz, 1H).

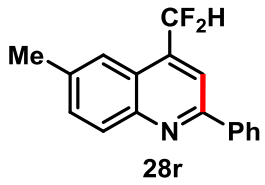
^{13}C NMR (CDCl$_3$, 100 MHz) δ 155.79, 148.68, 138.29 (t, J_{C-F} = 21.6 Hz), 136.25, 135.75, 130.39, 130.10, 129.16, 129.01, 128.21, 127.56, 127.43, 123.28, 116.41 (t, J_{C-F} = 7.8 Hz), 113.52 (t, J_{C-F} = 240.4 Hz).

HRMS: calculated $[M+H]^+$ for $C_{18}H_{14}NF_2$: 282.1089, found: 282.1090.

FTIR (cm^{-1}): 3418, 3021, 2969, 2403, 2353, 1958, 1814, 1674, 1611, 1549, 1508, 1436, 1384, 1217, 1174, 1123, 1052, 971, 893, 743.

4-(Difluoromethyl)-6-methyl-2-phenylquinoline (28r)

Following the general procedure (on 0.25 mmol scale), treatment of (*E*)-*N*-(phenylmethylene)- 4-methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine **27r** (72.3 mg, 0.25 mmol.) with the triazolium salt **29** (13.2 mg, 0.05 mmol.), DBU (114 mg, 0.75 mmol.) in DMF (2 mL) at 100 °C for 36 h followed by a work-up of the reaction mixture using EtOAc and a subsequent flash column chromatography (Pet. ether/EtOAc = 95/5) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-6-methyl-2-phenylquinoline **28r** as a white solid (49.8 mg, 74%).



28r

***R**f* (Pet. ether/EtOAc = 95/5): 0.33; **m.p.** 63-64 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22-8.11 (m, 3H), 8.02 (s, 1H), 7.82 (s, 1H), 7.62 (dd, *J* = 8.6 and 1.6 Hz, 1H), 7.59-7.44 (m, 3H), 7.18 (t, *J* = 54.7 Hz, 1H), 2.58 (s, 3H).

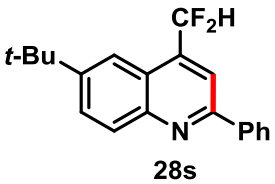
^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 147.5, 139.0, 137.8 (t, *J* = 21.4 Hz), 137.7, 132.4, 130.4, 129.7, 129.0, 127.5, 123.2 (t, *J* = 3.1 Hz), 122.1, 115.9 (t, *J* = 7.9 Hz), 113.7 (t, *J* = 240.4 Hz), 22.1.

^{19}F NMR (282 MHz, $CDCl_3$) δ -115.7 (d, *J* = 54.7 Hz).

HRMS: calculated $[M+H]^+$ for $C_{17}H_{14}F_2N$: 270.1094, found: 270.1088.

FTIR (cm^{-1}): 3058, 2922, 1609, 1557, 1450, 1375, 1355, 1196, 1113, 1039, 880, 819, 773, 753, 689, 651, 555, 518.

6-*tert*-Butyl-4-(difluoromethyl)-2-phenylquinoline (28s)



28s

Following the general procedure, treatment of (*E*)-*N*-(phenylmethylene)-4-*tert*-butyl-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine **27s** (165.5 mg, 0.50 mmol.) with the triazolium salt **29** (26.4 mg, 0.10 mmol.), DBU (228 mg, 1.5 mmol.) in DMF (4 mL) at 100 °C for 36 h followed by a work-up of the reaction mixture using EtOAc and a subsequent flash column chromatography (Pet. ether/EtOAc = 95/5) of the crude reaction mixture using silica gel afforded 6-*tert*-butyl-4-(difluoromethyl)-2-phenylquinoline **28s** as a white solid (127 mg, 81%).

***R**f* (Pet. ether/EtOAc = 95/5): 0.38; **m.p.** 86-87 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23-8.14 (m, 3H), 8.04 (s, 1H), 7.98 (s, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.60-7.45 (m, 3H), 7.24 (t, *J* = 54.7 Hz, 1H), 1.46 (s, 9H).

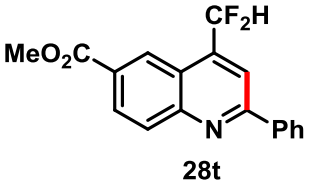
^{13}C NMR (CDCl$_3$, 75 MHz) δ 156.3, 150.4, 147.4, 139.0, 138.2 (t, *J* = 21.4 Hz), 130.2, 129.7, 129.1, 129.0, 127.5, 122.8 (t, *J* = 2.8 Hz), 118.0, 115.8 (t, *J* = 7.9 Hz), 113.8 (t, *J* = 240.3 Hz), 35.3, 31.2.

^{19}F NMR (282 MHz, CDCl$_3$) δ -115.7 (d, *J* = 54.7 Hz).

HRMS: calculated $[M+H]^+$ for $C_{20}H_{20}F_2N$: 312.1564, found: 312.1556.

FTIR (cm^{-1}): 2959, 1866, 1706, 1600, 1560, 1450, 1378, 1363, 1264, 1175, 1127, 1101, 1065, 1038, 1013, 885, 832, 768, 733, 687, 622, 587, 556, 514, 424.

Methyl 4-(difluoromethyl)-2-phenylquinoline-6-carboxylate (28t)



28t

Following the general procedure (on 0.25 mmol scale), treatment of (*E*)-methyl 4-(benzylideneamino)-3-(3,3,3-trifluoroprop-1-en-2-yl)benzoate **27t** (83.3 mg, 0.25 mmol.) with the triazolium salt **29** (13.2 mg, 0.05 mmol.), DBU (114 mg, 1.5 mmol.) in DMF (2 mL) at 100 °C for 36 h followed by a work-up of the reaction mixture using EtOAc and a subsequent flash column chromatography (Pet. ether/EtOAc = 93/7) of the crude reaction mixture using silica gel afforded methyl 4-(difluoromethyl)-2-phenylquinoline-6-carboxylate **28t** as a white solid (43 mg, 55%).

R$_f$ (Pet. ether/EtOAc = 90/10): 0.19; **m.p.** 153-154 °C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.81 (s, 1H), 8.42-8.35 (m, 1H), 8.31-8.26 (m, 1H), 8.25-8.20 (m, 2H), 8.14 (s, 1H), 7.61-7.51 (m, 3H), 7.28 (t, *J* = 54.2 Hz, 1H), 4.02 (s, 3H).

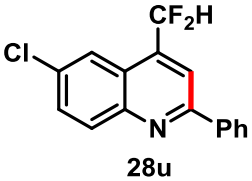
^{13}C NMR (CDCl$_3$, 75 MHz) δ 166.4, 159.0, 150.6, 139.8 (t, *J* = 21.4 Hz), 138.3, 130.9, 130.5, 129.8, 129.2, 128.6, 127.7, 126.1, 122.3 (t, *J* = 2.8 Hz), 116.5 (t, *J* = 7.9 Hz), 113.1 (t, *J* = 240.3 Hz), 52.7.

^{19}F NMR (282 MHz, CDCl$_3$) δ -115.7 (d, *J* = 54.2 Hz).

HRMS: calculated $[M+H]^+$ for $C_{18}H_{14}F_2NO_2$: 314.0993, found: 314.0990.

FTIR (cm^{-1}): 3052, 2962, 2930, 2853, 1703, 1610, 1469, 1452, 1434, 1406, 1280, 1229, 1098, 1032, 898, 775, 725, 688, 552, 465.

6-Chloro-4-(difluoromethyl)-2-phenylquinoline (28u)



28u

Following the general procedure, treatment of (*E*)-*N*-(phenylmethylene)-4-chloro-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine **27u** (154.5 mg, 0.50 mmol.) with the triazolium salt **29** (26.4 mg, 0.10 mmol.), DBU (228 mg, 1.5 mmol.) in DMF (4 mL) at 100 °C for 36 h followed by a work-up of

the reaction mixture using EtOAc and a subsequent flash column chromatography (Pet. ether/EtOAc = 95/5) of the crude reaction mixture using silica gel afforded 6-chloro-4-(difluoromethyl)-2-phenylquinoline **28u** as a white solid (90.9 mg, 63%).

***R*$_f$** (Pet. ether/EtOAc = 95/5): 0.42; **m.p.** 78-79 °C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.21-8.14 (m, 3H), 8.06 (app. s, 2H), 7.72 (dd, *J* = 9.0 and 2.0 Hz, 1H), 7.59-7.47 (m, 3H), 7.12 (t, *J* = 54.5 Hz, 1H).

^{13}C NMR (CDCl$_3$, 75 MHz) δ 157.0, 147.2, 138.3, 137.7 (t, *J* = 21.8 Hz), 133.4, 132.1, 131.1, 130.2, 129.1, 127.5, 123.6 (t, *J* = 2.8 Hz), 122.4, 116.7 (t, *J* = 7.9 Hz), 113.4 (t, *J* = 240.9 Hz).

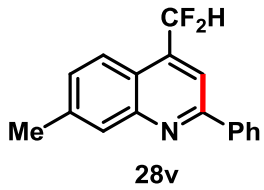
^{19}F NMR (282 MHz, CDCl$_3$) δ -114.9 (d, *J* = 54.5 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{11}{}^{35}ClF_2N$: 290.0548, found: 290.0535.

FTIR (cm^{-1}): 3065, 1608, 1548, 1493, 1456, 1373, 1356, 1337, 1218, 1127, 1087, 1063, 1037, 1008, 885, 827, 811, 767, 728, 683, 550, 510, 416.

4-(Difluoromethyl)-7-methyl-2-phenylquinoline (28v)

Following the general procedure (on 0.25 mmol scale), treatment of (*E*)-*N*-(phenylmethylene)-5-methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine **27v** (72.3 mg, 0.25 mmol.) with the triazolium salt **29** (13.2 mg, 0.05 mmol.), DBU (114 mg, 0.75 mmol.) in DMF (2 mL) at 100 °C for 36 h followed by a work-up of the reaction mixture using EtOAc and a subsequent flash column chromatography (Pet. ether/EtOAc = 95/5) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-7-methyl-2-phenylquinoline **28v** as a white solid (60.0 mg, 89%).



28v

***R*$_f$** (Pet. ether/EtOAc = 95/5): 0.48; **m.p.** 72-73 °C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.10-8.03 (m, 2H), 7.92 (s, 1H), 7.86 (s, 1H), 7.83 (d, *J* = 8.6, 1H), 7.48-7.34 (m, 3H), 7.31 (dd, *J* = 8.6 and 1.5 Hz, 1H), 7.04 (t, *J* = 54.7 Hz, 1H), 2.46 (s, 3H).

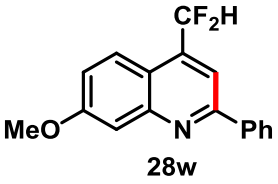
^{13}C NMR (CDCl$_3$, 75 MHz) δ 156.9, 149.1, 140.5, 139.0, 138.3 (t, *J* = 21.5 Hz), 129.8, 129.7, 129.0, 127.5, 122.8, 121.1 (t, *J* = 3.0 Hz), 115.1 (t, *J* = 7.9 Hz), 113.7 (t, *J* = 240.4 Hz), 21.8.

^{19}F NMR (282 MHz, CDCl$_3$) δ -115.5 (d, *J* = 54.7 Hz).

HRMS: calculated $[M+H]^+$ for $C_{17}H_{14}F_2N$: 270.1094, found: 270.1087.

FTIR (cm^{-1}): 2919, 1605, 1515, 1453, 1372, 1358, 1165, 1119, 1034, 1003, 876, 819, 792, 763, 684, 672, 599, 541, 470. Note that one ^{13}C NMR signal is overlapped with another signal.

4-(Difluoromethyl)-7-methoxyl-2-phenylquinoline (28w)[22c]



28w

Following the general procedure, treatment of (*E*)-*N*-(phenylmethylene)-5-methoxy-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine **27w** (152.5 mg, 0.50 mmol.) with the triazolium salt **29** (26.4 mg, 0.10 mmol.), DBU (228 mg, 1.5 mmol.) in DMF (4 mL) at 100 °C for 36 h followed by a work-up of the reaction mixture using EtOAc and a subsequent flash column chromatography (Pet. ether/EtOAc = 95/5) of the crude reaction mixture using silica gel afforded 4-(difluoromethyl)-7-methoxyl-2-phenylquinoline **28w** as a white solid (115 mg, 81%).

***R*$_f$** (Pet. ether/EtOAc = 95/5): 0.21; **m.p.** 115-116 °C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.20-8.13 (m, 2H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.91 (s, 1H), 7.61-7.44 (m, 4H), 7.28 (dd, *J* = 9.2 and 2.6 Hz, 1H), 7.15 (t, *J* = 54.7 Hz, 1H), 4.00 (s, 3H).

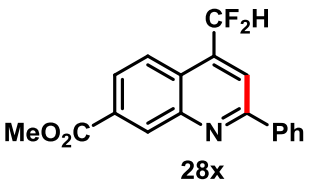
^{13}C NMR (CDCl$_3$, 75 MHz) δ 161.0, 157.3, 150.7, 139.0, 138.3 (t, *J* = 21.6 Hz), 129.7, 129.0, 127.5, 124.1, 120.5, 118.1 (t, *J* = 3.0 Hz), 113.7 (t, *J* = 240.5 Hz), 113.7 (t, *J* = 7.8 Hz), 108.5, 55.5.

^{19}F NMR (282 MHz, CDCl$_3$) δ -115.1 (d, *J* = 54.7 Hz).

HRMS: calculated $[M+H]^+$ for $C_{17}H_{14}F_2NO$: 286.1043, found: 286.1039.

FTIR (cm^{-1}): 3019, 2966, 2833, 1621, 1602, 1520, 1457, 1375, 1360, 1340, 1269, 1209, 1174, 1109, 1030, 1003, 875, 826, 793, 778, 667, 611, 541, 478.

Methyl 4-(difluoromethyl)-2-phenylquinoline-6-carboxylate (28x)



28x

Following the general procedure, treatment of (*E*)-methyl 3-(benzylideneamino)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzoate **27x** (166.5 mg, 0.50 mmol.) with the triazolium salt **29** (26.4 mg, 0.10 mmol.), DBU (228 mg, 1.5 mmol.) in DMF (4 mL) at 100 °C for 36 h followed by a work-up of the reaction mixture using EtOAc and a subsequent flash column chromatography (Pet. ether/EtOAc = 95/5) of the crude reaction mixture using silica gel afforded methyl 4-(difluoromethyl)-2-phenylquinoline-6-carboxylate **28x** as a white solid (48.1 mg, 31%).

***R*$_f$** (Pet. ether/EtOAc = 95/5): 0.14; **m.p.** 152-153 °C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.95 (s, 1H), 8.25-8.17 (m, 3H), 8.16-8.09 (m, 2H), 7.62-7.48 (m, 3H), 7.21 (t, *J* = 54.5 Hz, 1H), 4.02 (s, 3H).

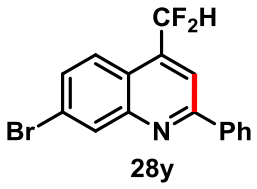
^{13}C NMR (CDCl$_3$, 75 MHz) δ 166.6, 157.9, 148.3, 138.6 (t, *J* = 21.8 Hz), 138.3, 133.0, 131.6, 130.3, 129.2, 127.6, 126.9, 125.6 (t, *J* = 2.9 Hz), 123.6, 117.6 (t, *J* = 7.8 Hz), 113.4 (t, *J* = 240.9 Hz), 52.7.

^{19}F NMR (282 MHz, CDCl$_3$) δ -115.7 (d, *J* = 54.5 Hz).

HRMS: calculated $[M+H]^+$ for $C_{18}H_{14}F_2NO_2$: 314.0993, found: 314.1004.

FTIR (cm^{-1}): 3039, 2966, 1722, 1607, 1436, 1359, 1328, 1304, 1253, 1227, 1162, 1097, 1028, 911, 887, 798, 755, 684, 528, 477, 444.

7-Bromo-4-(difluoromethyl)-2-phenylquinoline (28y)



28y

Following the general procedure, treatment of (*E*)-*N*-(phenylmethylene)-5-bromo-2-(3,3,3-trifluoroprop-1-en-2-yl)benzenamine **27y** (176.5 mg, 0.50 mmol.) with the triazolium salt **29** (26.4 mg, 0.10 mmol.), DBU (228 mg, 1.5 mmol.) in DMF (4 mL) at 100 °C for 36 h followed by a work-up of the reaction mixture using EtOAc and a subsequent flash column chromatography (Pet. ether/EtOAc = 95/5) of the crude reaction mixture using silica gel afforded 7-bromo-4-(difluoromethyl)-2-phenylquinoline **28y** as a white solid (136 mg, 81%).

R$_f$ (Pet. ether/EtOAc = 95/5): 0.35; **m.p.** 71-72 °C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.47 (d, *J* = 1.9 Hz, 1H), 8.27-8.20 (m, 2H), 8.07 (s, 1H), 7.96 (d, *J* = 8.9 Hz, 1H), 7.72 (dd, *J* = 8.9 and 1.9 Hz, 1H), 7.67-7.54 (m, 3H), 7.17 (t, *J* = 54.5 Hz, 1H).

^{13}C NMR (CDCl$_3$, 75 MHz) δ 157.5, 149.2, 138.5 (t, *J* = 21.8 Hz), 138.0, 132.7, 130.6, 130.2, 129.0, 127.4, 124.4, 124.3, 121.5 (t, *J* = 2.8 Hz), 115.9 (t, *J* = 7.9 Hz), 113.4 (t, *J* = 241.0 Hz).

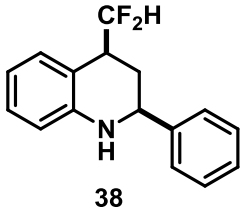
^{19}F NMR (282 MHz, CDCl$_3$) δ -115.2 (d, *J* = 54.5 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{11}{}^{79}BrF_2N$: 334.0043, found: 334.0034.

FTIR (cm^{-1}): 3052, 1607, 1506, 1494, 1451, 1374, 1355, 1451, 1216, 1165, 1118, 1066, 1026, 1000, 885, 789, 763, 670, 661, 581, 538, 515, 466.

5.6.7. Functionalization of Difluoromethylated Quinoline Derivatives

4-(Difluoromethyl)-2-phenyl-1,2,3,4-tetrahydroquinoline (38)



38

4-(difluoromethyl)-2-phenylquinoline **28a** (0.059 g, 0.231 mmol.) was taken in a flame dried round bottom flask with N_2 inlet. Glacial acetic acid (9 mL) was added to it. To this stirring solution sodium cyanoborohydride (0.073 g, 1.155 mmol.) was added in one portion. The reaction suspension

was stirred for 15 h at rt. To the flask was then slowly added a saturated aqueous solution of Na_2CO_3, along with EtOAc and the mixture was stirred for further 30 minutes. Two layers were separated, and the aqueous layer was further extracted twice more with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on rotary evaporator. The crude residue was purified by flash column chromatography (Pet. ether /EtOAc = 90/10) on silica gel to afford the corresponding 4-(difluoromethyl)-2-phenyl-1,2,3,4-tetrahydroquinoline **38** (0.057 g, 95% yield) as yellowish liquid**.**

R_f (Pet. ether /EtOAc = 80/20): 0.32.

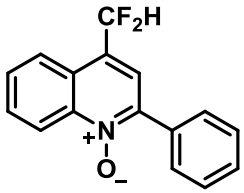
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47-7.39 (m, 4H), 7.37-7.30 (m, 2H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.77 (t, *J* = 7.7 Hz, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 5.91 (dt, J_1 = 5.0 Hz, J_2 = 56.2 Hz, 1H), 4.44-4.40 (m, 1H), 4.07 (bs, 1H), 3.63-3.51 (m, 1H), 2.36-2.30 (m, 1H), 2.14-2.05 (m,1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.05, 143.47, 128.93, 128.35, 128.10, 126.75, 118.28, 118.08 (t, $J_{C\text{-}F}$ = 243.5 Hz), 115.34, 55.67, 40.76 (t, $J_{C\text{-}F}$ = 20.3 Hz), 31.77 (t, $J_{C\text{-}F}$ = 5.0 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{16}NF_2$: 260.1245, found: 260.1247.

FTIR (cm^{-1}): 3420, 3021, 2402, 2347, 2099, 1642, 1487, 1439, 1389, 1313, 1217, 1107, 1042, 926, 768.

4-(Difluoromethyl)-2-phenylquinoline 1-oxide (39)



39

4-(difluoromethyl)-2-phenylquinoline **28a** (0.100 g, 0.390 mmol.) and *m*-Chloroperoxybenzoic acid (0.169 g, 0.98 mmol.) were taken in a flame dried round bottom flask with N_2 inlet. Dry $CHCl_3$ (2 mL) was added to it the mixture was refluxed for 12 h. To this stirring solution ethylchloroformate was added dropwise. The suspension was allowed to cool to room temperature, saturated aqueous $NaHCO_3$ solution were added. The aqueous layer was extracted with dichloromethane and the combined organic extracts were dried over Na_2SO_4, filtered. The crude *N*-oxide **39** was obtained by removing the solvent under reduced pressure. The crude residue was purified by flash column chromatography (DCM /MeOH = 93/02) on silica gel to afford the corresponding 4-(difluoromethyl)-2-phenylquinoline 1-oxide **39** (0.081 g, 77% yield) as a white solid**.**

R_f (DCM /MeOH = 95/05): 0.51.

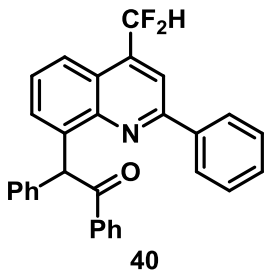
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.92 (d, *J* = 8.8 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 2H), 7.86 (t, *J* = 8.0 Hz, 1H), 7.77-7.73 (m, 2H), 7.57-7.49 (m, 3H), 7.12 (t, *J* = 54.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.33, 142.89, 132.80, 131.10, 129.61, 129.53, 128.62, 125.87, 124.16, 121.76 (t, $J_{C\text{-}F}$ = 9.3 Hz), 121.12, 113.35 (t, $J_{C\text{-}F}$ = 240.5 Hz).

HRMS: calculated $[M+H]^+$ for $C_{16}H_{12}ONF_2$: 272.0881, found: 272.0880.

FTIR (cm^{-1}): 3417, 3021, 2403, 2352, 2124, 1640, 1514, 1413, 1336, 1217, 1163, 1114, 1043, 924, 766.

2-(4-(Difluoromethyl)-2-phenylquinolin-8-yl)-1,2-diphenylethan-1-one (40)



40

To an oven-dried Schlenk tube (5 mL) $[Cp^*RhCl_2]_2$ (3.0 mg, 2.5 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.0 mg, 5 mol %), 4-(difluoromethyl)-2-phenylquinoline 1-oxide **39** (0.053 g, 0.195 mmol), and 1,2-diphenylethyne (0.029 g, 0.156 mmol) were added under an argon atmosphere. Subsequently, solvent (0.5 mL) was added using a laboratory syringe. The reaction mixture was put in a preheated oil bath at 110 °C for 24 h with vigorous stirring. After cooling to room temperature, the reaction mixture was filtered through Celite and washed with EtOAc. The organic layer was further washed with water (5 mL × 3) to remove traces of DMF and copper salt and dried over Na_2SO_4. Finally, the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using Pet. ether/EtOAc as the eluent on silica gel to afford the corresponding 2-(4-(difluoromethyl)-2-phenylquinolin-8-yl)-1,2-diphenylethan-1-one **40** (0.053 g, 61% yield) as brownish solid**.**

R_f (Pet. ether /EtOAc = 90/10): 0.35.

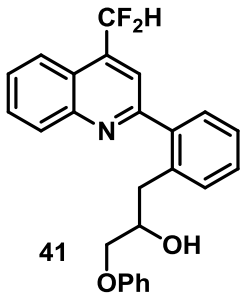
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (d, *J* = 7.8 Hz, 2H), 8.09 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 2H), 7.61-7.58 (m, 1H), 7.54-7.43 (m, 7H), 7.41-7.33 (m, 4H), 7.28-7.06 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.81, 155.62, 146.10, 141.03, 139.04 (t, $J_{C\text{-}F}$ = 21.7 Hz), 138.46, 137.36, 137.26, 132.92, 130.74, 130.18, 129.74, 129.29, 128.75, 127.68, 127.44, 127.30, 123.34, 122.28, 115.57 (t, $J_{C\text{-}F}$ = 7.7 Hz), 113.56 (t, $J_{C\text{-}F}$ = 240.7 Hz), 55.13.

HRMS: calculated $[M+Na]^+$ for $C_{30}H_{21}ONF_2Na$: 472.1483, found: 472.1483.

FTIR (cm^{-1}): 3444, 3022, 2403, 2351, 2096, 1677, 1643, 1509, 1446, 1374, 1290, 1217, 1149, 1045, 931, 887, 773.

1-(2-(4-(Difluoromethyl)quinolin-2-yl)phenyl)-3-phenoxypropan-2-ol (41)



4-(difluoromethyl)-2-phenylquinoline **28a** (31.0 mg, 0.200 mmol), 2-(phenoxymethyl)oxirane (60.1 mg, 0.400 mmol) and $Pd(OAc)_2$ (4.49 mg, 0.0200 mmol) were taken in a flame dried round bottom flask with argon inlet. HFIP (0.80 mL) and acetic acid (0.20 mL) were added to it. The reaction suspension was stirred for 24 h at 25 °C under argon atmosphere. The reaction mixture was quenched with saturated aq. Na_2CO_3 (5.0 mL), and the mixture was extracted with ethyl acetate (3 x 25 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (Pet. ether /EtOAc = 75/25) on silica gel to afford the corresponding 1-(2-(4-(difluoromethyl)quinolin-2-yl)phenyl)-3-phenoxypropan-2-ol **41** (0.063 g, 72% yield) as a yellow solid**.**

R_f (Pet. ether /EtOAc = 70/30): 0.19.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.91 (s, 1H), 7.85-7.82 (m, 1H), 7.73-7.70 (s, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.53-7.48 (m, 2H), 7.44-7.41 (m, 1H), 7.33-7.11 (m, 4H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 4.40-4.37 (m, 1H), 4.18-4.16 (m, 1H), 4.05-4.02 (m, 1H), 3.21-3.16 (m, 1H), 3.10-3.06 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.11, 158.37, 146.69, 139.17, 137.97, 131.79, 131.06, 130.53, 129.93, 129.54, 129.45, 128.32, 127.01, 123.35, 122.88, 120.85, 119.87 (t, $J_{C\text{-}F}$ = 7.8 Hz), 114.73, 113.29 (t, $J_{C\text{-}F}$ = 240.9 Hz), 71.99, 71.79, 36.80, 29.82.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{22}O_2NF_2$: 406.1613, found: 406.1612.

FTIR (cm^{-1}): 3431, 2921, 2864, 2404, 2094, 1637, 1620, 1601, 1558, 1496, 1467, 1425, 1378, 1340, 1317, 1290, 1246, 1173, 1117, 1079, 1045, 950, 920, 882, 836, 754, 739.

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List of Publications:

1. Combining Oxidative NHC-Catalysis with Imine Umpolung, Rapid Synthesis of Benzoxazoles.

   Patra, A.; James, A.; Biju, A. T. (*Manuscript in Preparation*)

2. Synthesis of 4-Difluoromethyl Quinolines by N-Heterocyclic Carbene (NHC)-Catalyzed Umpolung of Imines.

   Patra, A.; Gelat, F.; Pannecoucke, X.; Poisson, T.; Besset, T.; Biju A. T. *Org. Lett.* **2018**, *20*, 1086.

3. N-Heterocyclic Carbene-Catalyzed Umpolung of Imines.

   Patra, A.; Mukherjee, S.; Das, T. K.; Jain, S.; Gonnade, R. G.; Biju, A. T. *Angew. Chem. Int. Ed.* **2017**, *56*, 2730.

   This work has been Highlighted in *Synfacts* **2017**, *13*, 466.

   This work has been Highlighted in Organic Chemistry Portal.

4. Diastereoselective synthesis of cyclopentanone-fused spirooxindoles by N-heterocyclic carbene-catalyzed homoenolate annulation with isatilidenes.

   Patra, A.; Bhunia, A.; Yetra, S. R.; Gonnade, R. G.; Biju, A. T. *Org. Chem. Front.* **2015**, *2*, 1584.

5. N-Heterocyclic Carbene-Catalyzed Diastereoselective Synthesis of *β*-lactone-fused Cyclopentanes Using Homoenolate Annulation Reaction.

   Mukherjee, S.; Mondal, S.; **Patra, A.**; Gonnade, R. G.; Biju, A. T. *Chem. Commun.* **2015**, *51*, 9559.

6. Recent Advances in the N-Heterocyclic Carbene (NHC)-Organocatalyzed Stetter Reaction and Related Chemistry.

   Yetra, S. R.; **Patra, A.**; Biju, A. T. *Synthesis* **2015**, *47*, 1357.

7. N-Heterocyclic carbene-catalyzed enantioselective synthesis of functionalized cyclopentenes via *α,β*-unsaturated acyl azoliums.

   Mondal, S.; Yetra, S. R.; **Patra, A.**; Kunte, S. S.; Gonnade, R. G.; Biju, A. T. *Chem. Commun.* **2014**, *50*, 14539.

8. Facile Synthesis of *γ*-Ketophosphonates by an Intermolecular Stetter Reaction Onto Vinylphosphonates.

   Patra, A.; Bhunia, A.; Biju, A. T. *Org. Lett.* **2014**, *16*, 4798.

This work has been selected for abstracts in Organic Chemistry Portal.

9. Enantioselective N-Heterocyclic Carbene-Catalyzed Annulations of 2-Bromoenals with 1,3-Dicarbonyl Compounds and Enamines via Chiral α,β-Unsaturated Acyl Azoliums.
   Yetra, S. R.; Bhunia, A.; **Patra, A.**; Mane, M. V.; Vanka, K.; Biju, A. T. *Adv. Synth. Catal.* **2013**, *355*, 1089.
10. NHC-Catalyzed Reaction of Enals with Hydroxy Chalcones:Diastereoselective Synthesis of Functionalized Coumarins.
    Bhunia, A.; **Patra, A.**; Puranik, V.; Biju, A. T. *Org. Lett.* **2013**, *15*, 1756.