Discovering new organocatalytic organic transformations using N-heterocyclic carbene as a catalyst

A thesis submitted for the partial fulfilment of

the degree of Doctor of Philosophy

by

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Dedicated To My Parents

AKKA AND JIJA

(Sanjavani & Bhagwatrao)

DECLARATION

The work presented in this thesis titled ***"Discovering new organocatalytic organic transformations using N-heterocyclic carbene as a catalyst"*** has been carried out by me under the supervision of **Dr. R. Vijaya Anand** in the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Punjab.

This work has not been submitted in part or full for a degree, diploma or a fellowship to any other university or institute.

Whenever contributions of others are involved, every effort is made to indicate this clearly with due acknowledgements of collaborative work and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

PANJAB BHAGWATRAO ARDE

Date:

Place:

In my capacity as the supervisor of the candidate's thesis work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. R. Vijaya Anand

Associate Professor

Department of Chemical Sciences Indian

Institute of Science Education and Research Mohali

Date:

Place:

Acknowledgements

Without acquiring any help from others, nobody succeeds in any field. I hope with this completed Ph.D thesis, am entering into organic field to unravel the present challenges. It's obvious, similar to other researchers I received support to reach this level. Here, I would like to acknowledge all people, who directly or indirectly contributed to my research. In particular, scientific field, Ph.D supervisor's participation is a primeval one to learn and perceive intellectual ability.

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Abstract

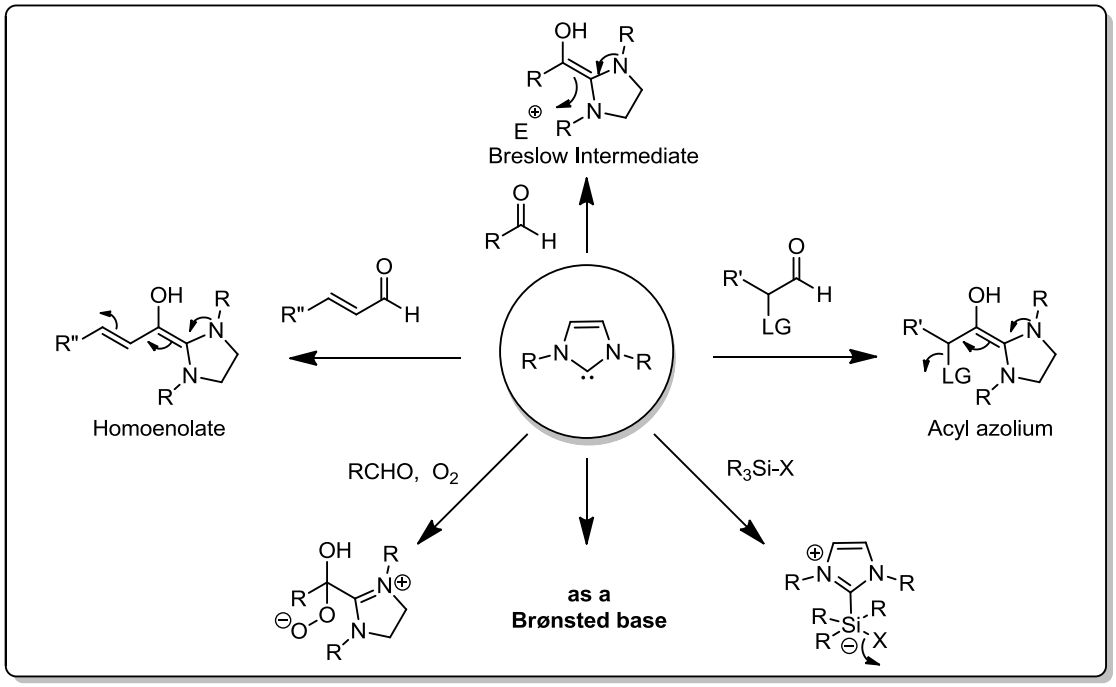
The research work carried out in this thesis involves the development of new synthetic methodologies using N-heterocyclic carbene (NHC) as an organocatalyst.

This thesis is divided into **four chapters**.

Chapter 1:

General introduction to N-heterocyclic carbene (NHC) catalysis.

In recent years, persistent carbene chemistry has become one of the fascinating areas in organic chemistry. Among these, N-heterocyclic carbenes (NHCs) have found an important role in organocatalytic transformations, mainly in carbon–carbon, carbon–heteroatom bond formation and annulation reactions. The utility of NHCs has also been explored in other organic transformations such as; oxidation reactions, transesterification and silyl activation. The versatility of N-heterocyclic carbenes is due to their different modes of activation towards different functional groups (Scheme 1). In this chapter, the applications of NHC as an organocatalyst for various types of organic reactions are highlighted.



Scheme 1: Different modes of activation of NHC toward various functional groups

Chapter 2: *N*-Heterocyclic carbene as a Brønsted base catalyst

This chapter is sub-divided into two parts namely **Part A** and **Part B**.

PART A: <u>N-heterocyclic carbene catalyzed access to diaryl- and triarylmethyl phosphonates through the 1,6-conjugate addition of dialkylphosphites to *p*-quinone methides and fuchsones.</u>

Organophosphorous derivatives are found to be an imperative class of organic compounds due to their widespread applications in many areas including organometallic chemistry, medicinal chemistry and pharmaceutical industries. These are also used as metal extractants and flame retardants. Their utility has been further extended in organic synthesis as starting materials in the synthesis of olefin derivatives. Among the organophosphorous compounds, the diaryl- and triarylmethyl phosphonate derivatives have been realized as vital derivatives due to their remarkable applications in medicinal chemistry (Figure 1).

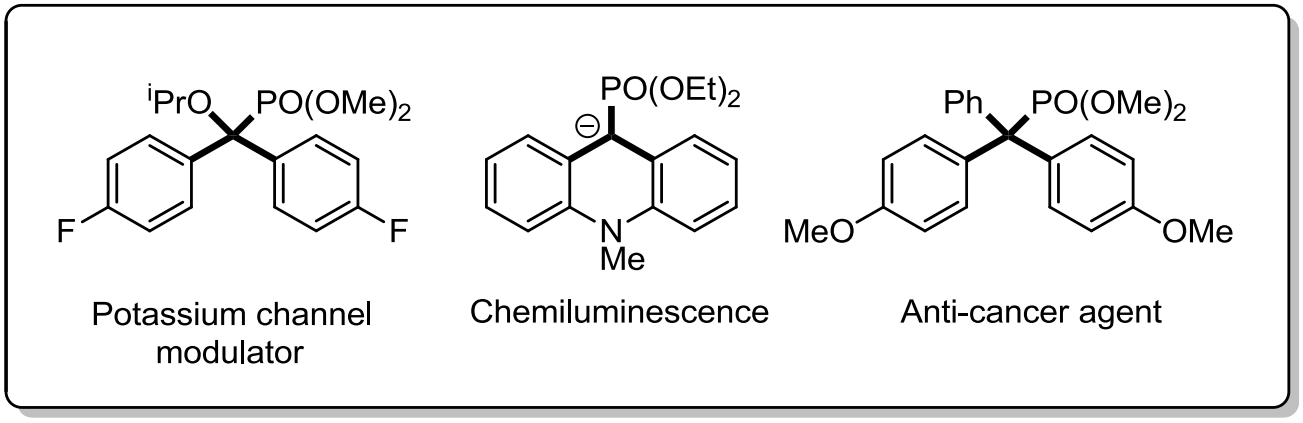
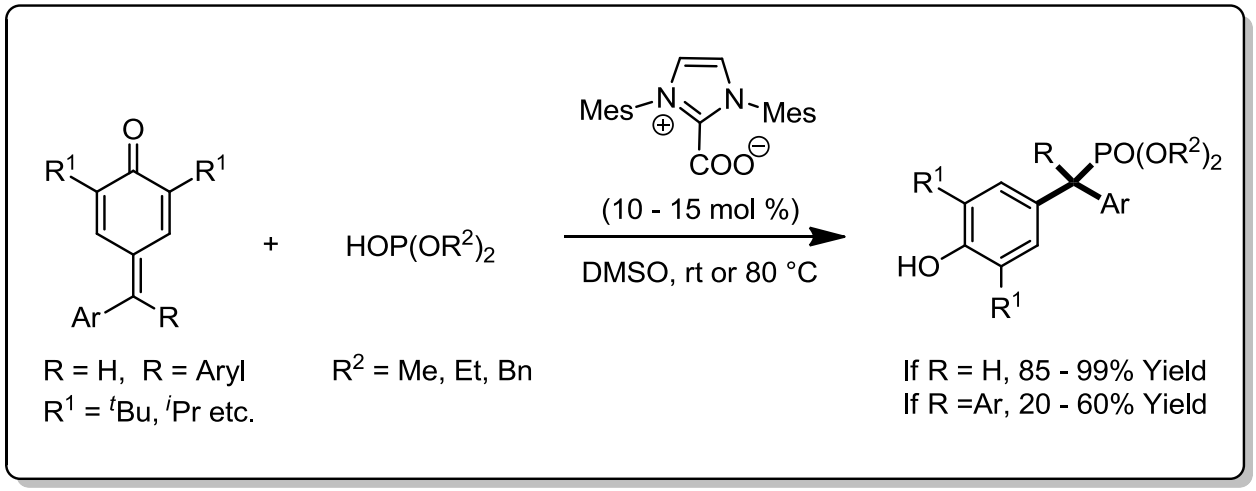


Figure 1: Some important diaryl- and triarylmethyl phosphonates

The classical methods for the synthesis of arylated methyl phosphonates involve the Arbuzov reaction and Friedel−Crafts type of reactions. However, harsh reaction conditions and narrow substrate scope limit the applications of this protocol. In order to overcome these shortcomings, recently, many strategies have emerged for the synthesis of diaryl- and triarylmethyl phosphonates which involve $FeCl_3$-mediated Friedel-Crafts reaction and transition metal catalyzed coupling reactions. Although these methods involve relatively mild conditions

and good regioselectivity, utilization of stoichiometric amount of $FeCl_3$ and metal catalysts remains challenging. Despite their extensive applications, very limited number of reports are available for the synthesis of arylated methyl phosphonates, particularly diaryl- and triarylmethyl phosphonates. Therefore, developing an alternative and more efficient method for the synthesis of these compounds remains a demanding task, especially under organocatalytic conditions. In this part of Chapter 2, we disclose NHC catalyzed atom economical 1,6-conjugate addition of dialkylphosphites to *p*-quinone methides and fuchsones to access diaryl- and triarylmethyl phosphonates (Scheme 2).



Scheme 2: NHC catalyzed synthesis of diaryl- and triarylmethyl phosphonates

Optimization studies have been carried out by using NHC-CO_2 adducts as pre-catalyst for the NHC catalyzed 1,6-conjugate addition of dialkylphosphites to *p*-quinone methides and fuchsones. After screening different reaction conditions, IMes.CO_2 was found to be the best pre-catalyst for this transformation. Having optimal reaction conditions in hand, the scope and limitations of this methodology were explored by using a wide range of *p*-quinone methides and dialkylphosphites. Irrespective of the nature of substituents on *p*-quinone methides and dialkylphosphites, the corresponding diaryl phosphonates were obtained in good to excellent yields. Triarylmethyl phosphonates were obtained in low to moderate yields at 80 °C.

PART B: <u>N-heterocyclic carbene catalyzed 1,6-conjugate addition of 2-naphthol to *p*-quinone methides: Expedient access to unsymmetrical triarylmethanes.</u>

While working on NHC catalyzed 1,6-conjugate addition of dialkylphosphites to *p*-quinone methides we envisioned that it is possible to access unsymmetrical triarylmethane derivatives through 1,6-conjugate addition of 2-naphthol to *p*-quinone methides using NHC as a Brønsted base catalyst. Unsymmetrical triarylmethanes and their derivatives are remarkable synthetic targets, due to their widespread utility as building blocks in many natural products, biologically active compounds and dyes. Few of the biologically active triarylmethanes are shown in Figure 2.

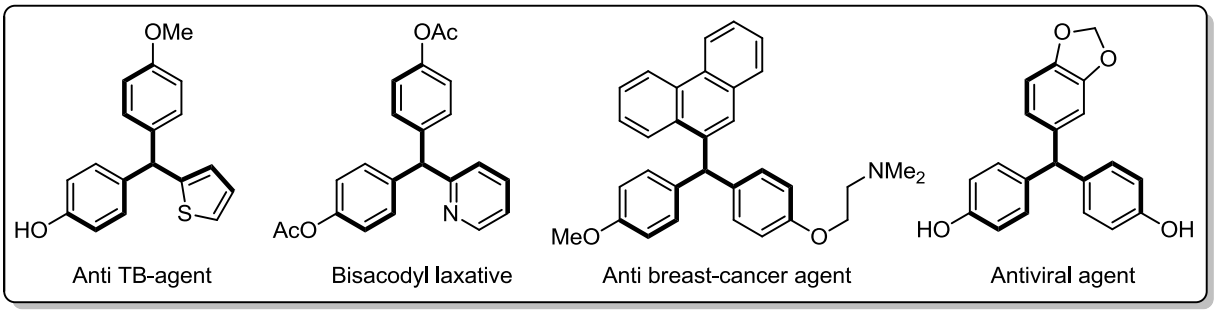
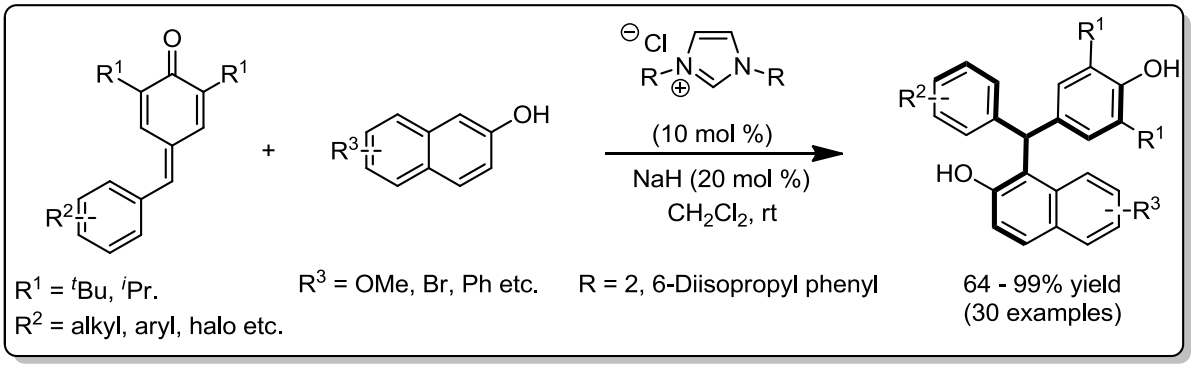


Figure 2: Important biologically active triarylmethane derivatives

Although numerous methods have been developed for the synthesis of unsymmetrical triarylmethanes, traditionally triarylmethanes are accessed through Friedel-Crafts type reactions of diarylmethanols or reductive dehydroxylation of triarylmethanols. Though these methods are simple and widely used the utilization of electron-rich arenes and harsh reaction conditions limit the efficacy of these protocols. To address these issues, recently, the transition metal catalyzed reactions have been developed. Ever since the extensive utility of unsymmetrical triarylmethanes, developing a simple and atom economical approach for the synthesis of unsymmetrical triarylmethanes, especially under organocatalytic conditions is always in high demand. In this part of Chapter 2, we unveiled NHC as a Brønsted base for the 1,6-conjugate addition of 2-naphthol to *p*-quinone methides for obtaining unsymmetrical triarylmethane derivatives (Scheme 3).



Scheme 3: NHC catalyzed synthesis of triarylmethane derivatives

After screening different reaction conditions, IPr.HCl was found to be the best pre-catalyst and dichloromethane was found to be the most appropriate solvent. Having optimized reaction conditions in hand, the scope and limitations of this methodology were further elaborated using variety of *p*-quinone methides as well as 2-naphthols. Regardless of the nature of substrates, the corresponding triarylmethanes were isolated in good to excellent yields. 100% atom economy and simple reaction condition are the significant features of this protocol.

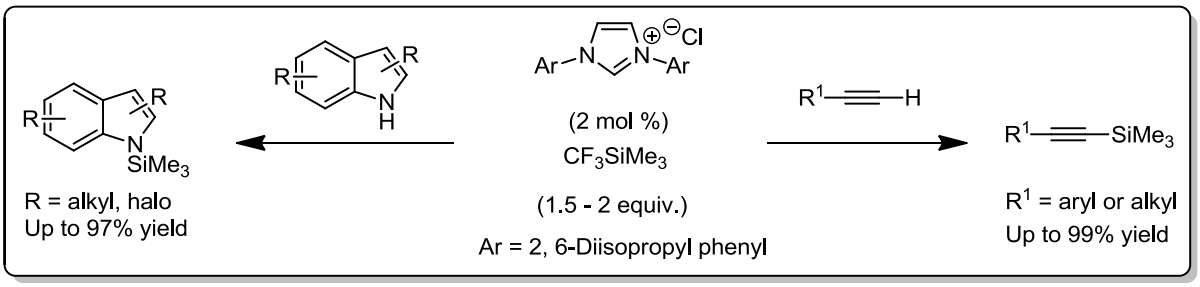
***Chapter 3*:**

<u>*N*-heterocyclic carbene catalyzed trimethylsilylation of terminal acetylenes and indoles using Ruppert's reagent as a silyl source under solvent free conditions.</u>

Alkynylsilicon reagents are considered important synthetic targets due to their wide-ranging utility in many organic transformations, such as, metal catalyzed cross-coupling reactions, alkynylation reactions and metathesis reactions. Conventionally, alkynylsilicon compounds are synthesized by deprotonation of terminal acetylenes by using strong bases such as organolithium and Grignard reagents followed by quenching with silyl electrophiles. Some other metal catalyzed or mediated protocols have also been developed to avoid some of the limitations of the traditional methods, such as utilization of strong bases and quantitative production of inorganic salts as by-products. Thence, developing an efficient and fluoride free synthetic route for the synthesis of alkynylsilicon compounds is a desirable task.

It is well known in the literature that NHCs could form hypervalent complexes with silicon compounds. This concept has been applied to activate Ruppert's reagent for the

trifluoromethylation of different electrophiles. Herein we report NHC-catalyzed trimethylsilylation of terminal acetylenes using CF_3 anion as a traceless base under solvent free conditions. The reaction conditions were optimized by treating phenyl acetylene and Ruppert's reagent under different conditions; to our surprise, the reaction worked pretty well under solvent free condition to produce trimethylsilylated acetylenes in excellent yields (Scheme 4).



Scheme 4: NHC catalyzed trimethylsilylation of terminal acetylenes and indoles.

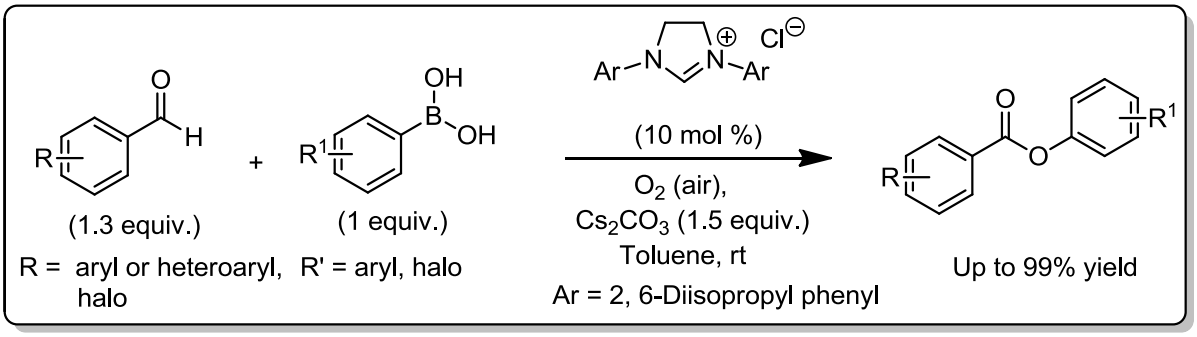
Encouraged by the above results, we applied this strategy for indoles as well to access *N*-silylated indoles. *N*-silylatedindoles are found to be fascinating intermediates in synthetic organic chemistry, as indoles are vital synthons in many natural product syntheses. Traditionally, *N*-silylated indoles are synthesized by deprotonation of indoles by using strong bases followed by quenching with a silyl electrophile. Recently, metal catalyzed dehydrogenative Si–N coupling methods[21] have also been developed. Under optimized conditions, most of the substituted indoles were converted to their *N*-silylatedindoles (Scheme 4). Solvent free conditions, high yield of products, less reaction time, simple work-up procedure are the key features of this methodology.

Chapter 4:

N-heterocyclic carbene catalyzed oxidative esterification of aldehydes with aryl boronic acids.

Aryl benzoate derivatives have served as significant building blocks in many natural products and active pharmaceutical ingredients (APIs). Numerous approaches have been reported for the construction of ester functionality. Traditionally, aryl benzoate derivatives are synthesized either by acid catalyzed esterification or by transesterification reactions. Apart from these strategies, Baeyer-Villiger oxidation, organocatalytic esterification and transition metal catalyzed coupling reactions are the additional alternatives. While working on *N*-heterocyclic

carbene catalyzed organic transformations, we envisioned that aryl benzoates could be directly accessed through NHC catalyzed aerobic oxidation of aryl aldehydes using boronic acids, especially in the absence of metal catalyst. In this chapter, the NHC-catalyzed oxidative esterification of aldehydes with aryl boronic acids are discussed (Scheme 5).



Scheme 5: NHC catalyzed aerobic oxidation of aryl aldehydes to aryl benzoates.

The extensive optimization studies revealed that the NHC derived from SIPr.HCl worked exceptionally well for NHC-catalyzed oxidative esterification of aldehydes with aryl boronic acids. Having the optimal reaction conditions in hand, scope and limitations of this transformation were screened by using diverse range of aldehydes and aryl boronic acids and in most of the cases the esters were obtained in excellent yields. Unfortunately, this methodology was not suitable for aliphatic aldehydes and boronic acids. Mechanistic details have been thoroughly investigated through the isotopic labelling experiment.

ABBREVIATIONS

AcOH	Acetic acid
Ac_2O	Acetic anhydride
ACN	Acetonitrile
CD_3CN	Acetonitrile-D_3
Ac	Acetyl
acac	Acetylacetonate
aq	Aqueous
BQ	1,4-Benzoquinone
Bn	Benzyl
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppo	1,8-Bis(diphenylphosphino)octane
DPPPent	1,5-Bis(diphenylphosphino)pentane)
brs	Broad singlet
NBS	*N*-Bromosuccinimide
CsOAc	Caesium acetate
calcd	Calculated
CSA	Camphorsulfonic acid
CO	Carbon monoxide
Cbz	Carboxybenzyl
cm	Centimeter
δ	Chemical shift
$CDCl_3$	Chloroform-D
J	Coupling constant
Cy	Cyclohexyl
cod	1,5-Cyclooctadiene
CPME	Cyclopentyl methyl ether
°C	Degree celsius
dr	Diastereomeric ratio

DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DCE	Dichloroethane
DCM	Dichloromethane
Et_2O	Diethyl ether
DME	Dimethoxyethane
DMF	*N*,*N*'-Dimethyl formamide
DMSO	Dimethyl sulfoxide
d	Doublet
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
dt	Doublet of triplets
EWG	Electron withdrawing
ESI	Electrospray ionization
ee	Enantiomeric excess
er	Enantiomeric ratio
EtOH	Ethanol
EtOAc	Ethylacetate
equiv	Equivalents
FT-IR	Fourier transform infrared spectroscopy
Hz	Hertz
HRMS	High-resolution Mass Spectrum
HFIP	Hexafluoroisopropanol
h	Hour(s)
i-Pr	*iso*-Propyl
LHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
^{t}BuOLi	Lithium-*tert*-butoxide
m/z	Mass/Charge
MHz	Megahertz
m.p.	Melting point

Mes	Mesityl
MeOH	Methanol
mg	Milligram(s)
mL	Milliliter(s)
mmol	Millimole(s)
min	Minute(s)
M.S.	Molecular sieves
m	Multiplet
NHC	N-heterocyclic carbene
NMR	Nuclear Magnetic Resonance
$POCl_3$	Phosphoryl chloride
^{t}BuOK	Potassium-*tert*-butoxide
n-Pr	Propyl
Q	Quartet
R_f	Retention factor
rt	Room temperature
s	Singlet
sept	Septet
tert	Tertiary
^{t}Bu	*tert*-Butyl
Boc	*tert*-Butyloxycarbonyl
TBAF	Tetrabutylammonium fluoride
HBF_4	Tetrafluoroboric acid
THF	Tetrahydrofuran
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Tetramethylsilane
t	Triplet
td	Triplet of doublets
tt	Triplet of triplet

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Chapter 4: N-heterocyclic carbene catalyzed oxidative esterification of aldehydes with aryl boronic acids

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4.2.4) NHC-catalyzed oxidative esterification

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Chapter 1

General introduction to *N*-heterocyclic carbene (NHC) catalysis

1.1) General introduction to Carbenes

The term 'carbene'[1] was introduced by Geuther and Hermann in their report on generation of dichlorocarbene intermediate through alkaline hydrolysis of chloroform.[2] Later, Nef realized that the Reimer–Tiemann reaction also proceeds through similar reaction intermediate[3] but the hypothesis of carbene as reactive species has begun after Staudinger's remarkable work on the decomposition of diazo compounds and ketenes in 1910.[4] Later, in the early 1960's, the existence of stable carbenes was further elaborated by Wanzlick and co-workers during their attempt to generate a carbene center flanked between two nitrogens of an imidazole ring due to which it's enhanced stability was expected.[5] Although Wanzlick and co-workers failed to isolate the free carbene, they demonstrated the *in situ* generation of free carbene by trapping imidazol-2-ylidenes with phenyl isothiocyanate and mercury salts.[6] Following these results, Bertrand and co-workers reported the discovery and isolation of phosphinocarbene (**1a,** Figure 1) as a distillable red oil in 1988.[7]

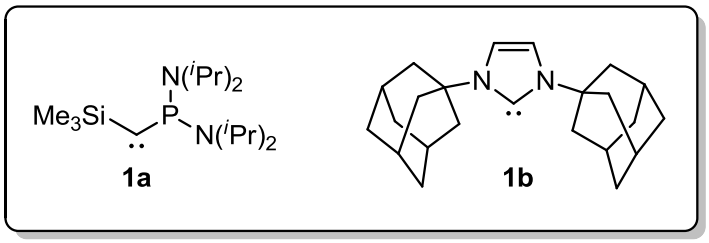


Figure 1: Stable singlet carbenes

Later, for the first time in 1991, Arduengo and co-workers isolated the imidazol-2-ylidene (**1b,** Figure 1) as a stable crystalline carbene by the deprotonation of 1,3-di(1-adamantyl)imidazolium chloride.[8] These types of scaffolds are commonly known as N-heterocyclic carbenes (**1b**) (NHCs).

This revolutionary finding by Arduengo and co-workers opened a new era in organometallic chemistry[9] and the emerging field of organocatalysis. NHCs are implemented as ligands in metal catalyzed reactions and as nucleophilic catalysts in organocatalytic reactions.[10]

1.1.1) Structure and Reactivity of NHCs

The stability of the N-hetrocyclic carbene is believed to be mainly dependent on two factors – the electronic as well as the steric factor of the bulky substituents present on the adjacent heteroatom. The two bulky substituents present on the adjacent heteroatom in NHCs control the reactivity of the carbene center towards the external reagents as well as self-dimerization to the corresponding olefin. Furthermore, in 1992, Arduengo and co-workers showed that the electronic factor might dominate over the steric factor after the successful isolation of a less hindered carbene.[11] The computational and X-ray analysis studies reveal that the N-heterocyclic carbenes exhibit singlet ground-state electronic configuration. The paired electrons occupy an in-plane *σ*-orbital leaving a *p*-orbital vacant (**2a,** Figure 2). The "push-pull" synergistic effect stabilizes the anti Hund's rule electronic configuration of singlet carbene by allowing π donation into the vacant *p*-orbital of carbene from the out-of-the-plane π orbital of the adjacent heteroatom (mesomeric effects: ±M, **2a**, Figure 2). On the other hand, the more electronegative character of the adjacent heteroatom as compared to the carbene center plays an important role in stabilizing the singlet state by *σ*-electron-withdrawal (negative inductive effect: −I, **2b**, Figure 2) from filled non-bonding orbital of carbine. This results in to moderation of the nucleophilic reactivity of the carbene by increasing its *s*-character.[12] The cyclic nature of NHCs also plays a significant role in favoring the singlet state of carbene center C-2 by allowing the carbene carbon into a bent, more sp^2 -like arrangement (**2c,** Figure 2).

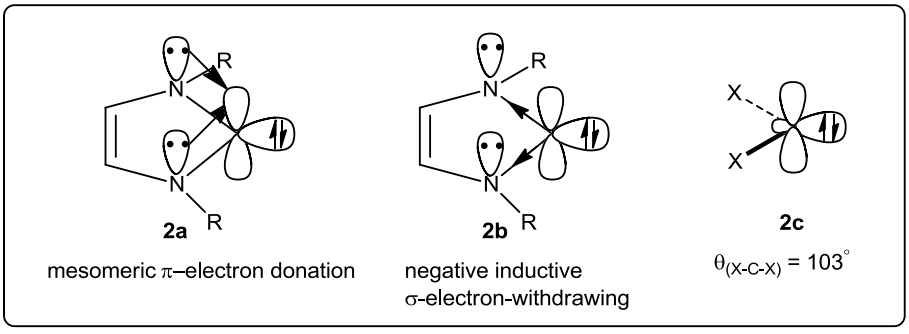


Figure 2: Stabilization of singlet carbene

In general, most transient carbenes typically show electrophilic nature but the noteworthy electronic properties of NHCs discussed above make them more nucleophilic and strong σ-donors. The NHCs are known to serve as Lewis bases (single electron-pair donors) having distinct characteristics like σ-basicity and moderate π acidity.

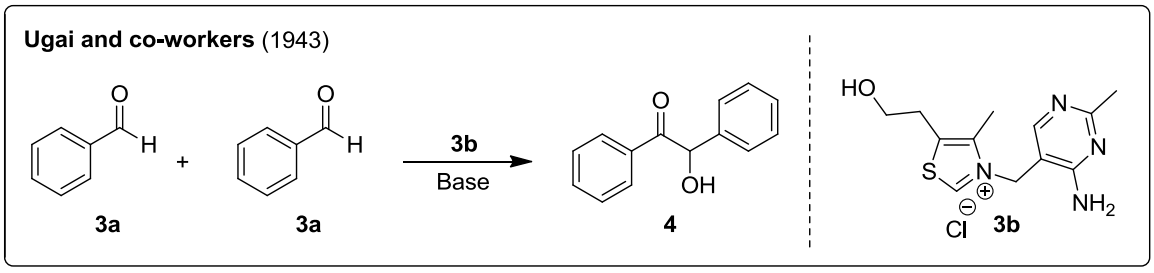
The aforementioned significant properties of NHCs allow the formation of an acyl anion equivalent when added to electrophilic aldehydes. This conversion of electrophilic carbonyl center of aldehyde to the nucleophilic center is defined as polarity inversion. Seebach and co-workers introduced the concept of polarity inversion commonly called as "Umpolung reactivity".[13] The combination of all these characteristics makes NHCs as a powerful tool in many organic transformations. Some of the NHC-catalyzed transformations are overviewed below.

1.2) N-heterocyclic carbene catalysis

In the last two decades, N-heterocyclic carbene catalysis has made astonishing contributions in the field of organocatalysis through its umpolung or non-umpolung reactivity towards different functional moieties. Some of the selected reports are discussed in this section.

1.2.1) Benzoin condensation

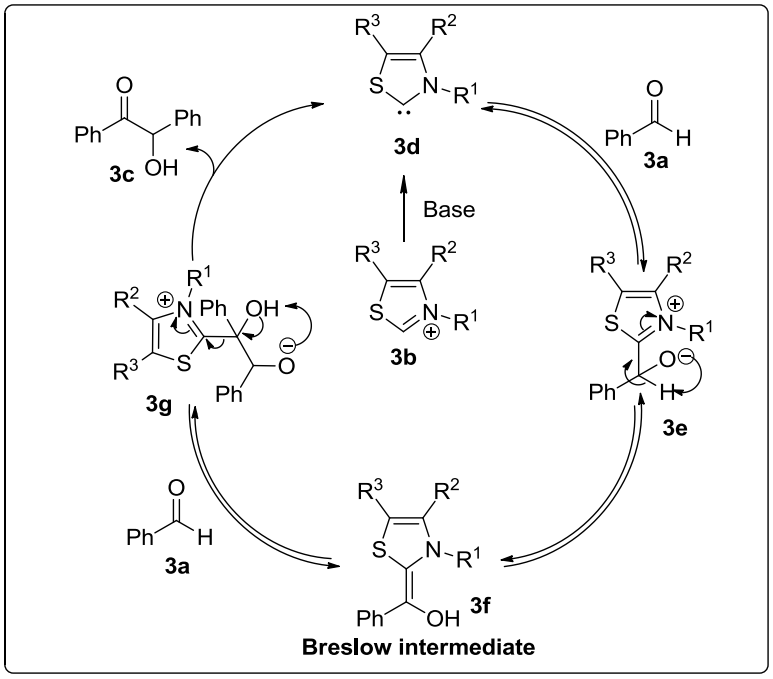
Among the numerous N-heterocyclic carbene catalyzed transformations reported to date, the benzoin condensation is one of the most explored. Wöhler and Liebig published the benzoin condensation reaction for the first time in 1832.[14] They synthesized benzoin product by homo-dimerization of aldehydes in the presence of cyanide as a catalyst. Further in 1903, Lapworth proposed the possible mechanism for benzoin condensation, where he postulated that cyanide reacts with an aldehyde followed by the proton migration to generate acyl anion (carbanion) intermediate. This intermediate further reacts with another molecule of aldehyde to furnish the corresponding benzoin product.[15]



Scheme 1: Thiazolium salt catalyzed benzoin condensation

In 1943, Ugai and co-workers reported their earliest revolutionary finding that the thiazolium salts (**3b**) can also furnish the homodimerized benzoin product (**4**) of aldehydes (**3a**) in the presence of a base (Scheme 1).[16]

Later on, based on Ugai's and Lapworth's work, Breslow proposed the mechanism for thiazolium salt (**3b**) catalyzed benzoin condensation in 1958.[17] He anticipated that the active catalytic species for this transformation is thiazolin-2-ylidene (**3d**), the carbene generated from deprotonation of thiazolium salt (**3b**). This thiazolin-2-ylidene (**3d**) reacts with the aldehyde (**3a**) to produce an intermediate commonly known as "Breslow intermediate" (**3f**). The postulated catalytic cycle for this transformation is shown in Scheme 2.



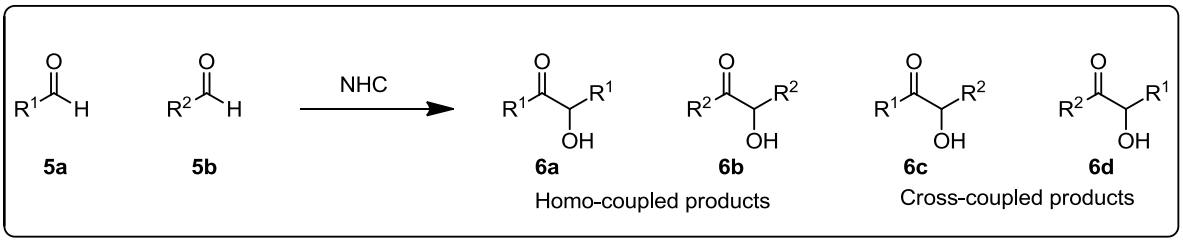
Scheme 2: Mechanism of the benzoin condensation as proposed by Breslow

Breslow presumed that the nucleophilic thiazolin-2-ylidene (**3d**) generated *in situ* by deprotonation of thiazolium salt (**3b**), reacts with aldehyde (**3a**) and leads to a tetrahedral intermediate (**3e**). Subsequent intramolecular proton migration of **3e** gives the nucleophilic enaminol derivative (**3f**). The electrophilic carbonyl carbon of the aldehyde has now been converted to the nucleophilic acylation reagent (**3f**). The acyl anion equivalent (**3f**) then reacts with another molecule of aldehyde (**3a**) to furnish alkoxide intermediate (**3g**). Proton transfer and successive elimination of thiazolin-2-ylidene (**3d**) leads to benzoin (**4**). Lemal *et al.*[18] and

Calahorra and co-workers[19] came up with an alternative proposition for the catalytic cycle of benzoin condensation but the mechanism proposed by Breslow has been widely accepted. Recently the Breslow intermediate has been isolated and characterized by X-ray and NMR analysis.[20]

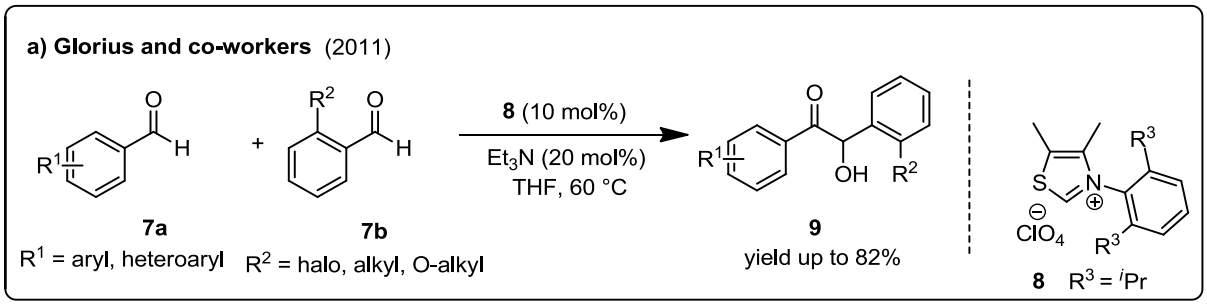
1.2.1.1) Cross-benzoin Condensation

The benzoin reaction typically deals with the homocoupling of two aldehydes, which leads to the limited scope of synthetic utility of this reaction. The cross-coupling between two different aldehydes for aldehydes and ketones, opens the access to a wide variety of benzoin products. Cookson and Lane demonstrated the intra-molecular cross-coupling of two aldehydes for the first time in 1976.[21] The main drawback of this reaction is the lack of chemoselectivity, which leads to two possible products in intra-molecular cross-coupling. In intermolecular reactions, four products are possible (Scheme 3).



Scheme 3: General cross-benzoin condensation

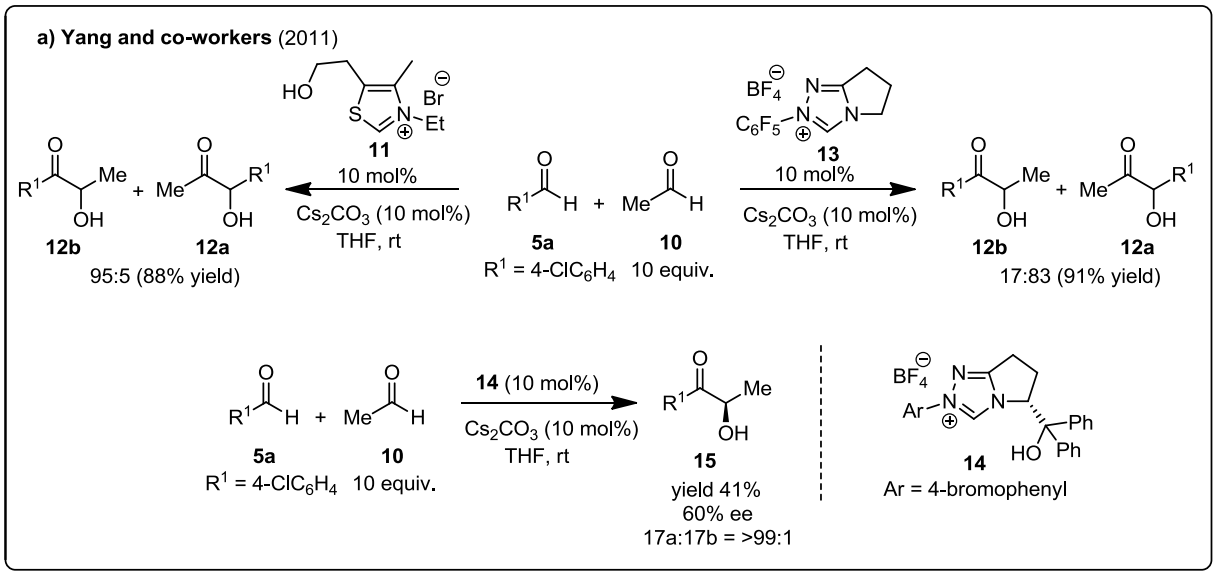
Many attempts have been made to improve the chemoselectivity of cross-benzoin reactions. Stetter and Dämbkes demonstrated that the product ratio can be controlled by increasing the equivalents of one of the aldehydes.[22] Recently, Glorius and co-workers proposed the selective cross-coupling of an aromatic aldehyde (**7a**) with sterically hindered 2-substituted benzaldehyde (**7b**) to improve the product selectivity (Scheme 4).[23]



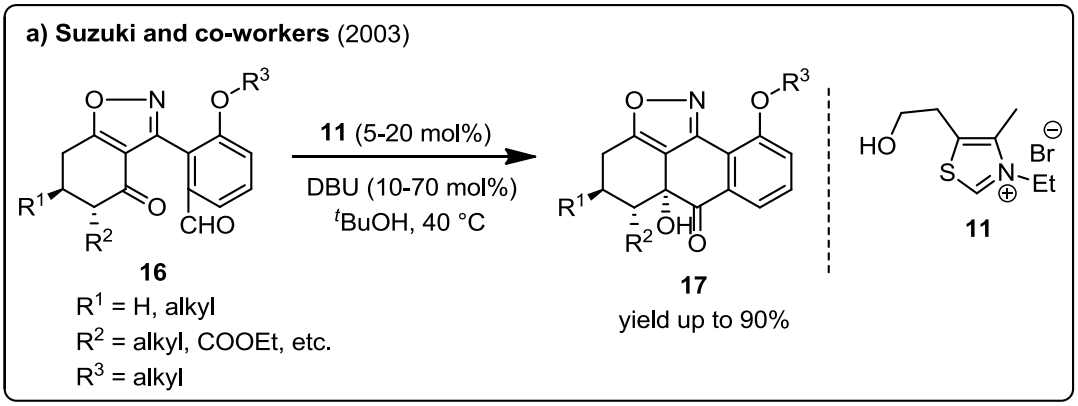
Scheme 4: Chemoselective cross-benzoin condensation

The pentafluorophenyl-substituted triazolium based NHC-catalyzed highly chemoselective processes between a range of aliphatic and aromatic aldehydes were reported by Zeitler and co-workers.[24] Further, Yang and co-workers reported interesting findings on different reactivity of NHC-catalysts derived from thiazolium (**11**) and triazolium (**13**) pre-catalysts towards aromatic (**5a**) and aliphatic aldehydes (**10**).[25] The NHC-catalyst derived from thiazolium precursor (**11**) favoured Breslow intermediate formation with aromatic aldehydes (**5a**), whereas triazolium based NHC-catalyst (**13**) favored Breslow intermediate formation with aliphatic aldehydes (**10**). In both the cases, the desired products have obtained in excellent selectivity. The authors further provided one example of asymmetric cross-benzoin condensation using pyroglutamic acid-derived (**14**) chiral NHC-catalyst to access the benzoin product with extremely high selectivity and moderate ee (60%). Unfortunately the yield of the product remained low (Scheme 5).

In 2003, Suzuki and co-workers reported an important breakthrough in the NHC-catalyzed cross-benzoin condensation reaction.[26] In their attempt to synthesize a natural product through intramolecular cross-benzoin condensation using thiazolium derived catalyst (**11**), they found that ketones can be served as electrophiles for benzoin-condensation to furnish corresponding cross-benzoin products (**17**) in good to excellent yields (Scheme 6).

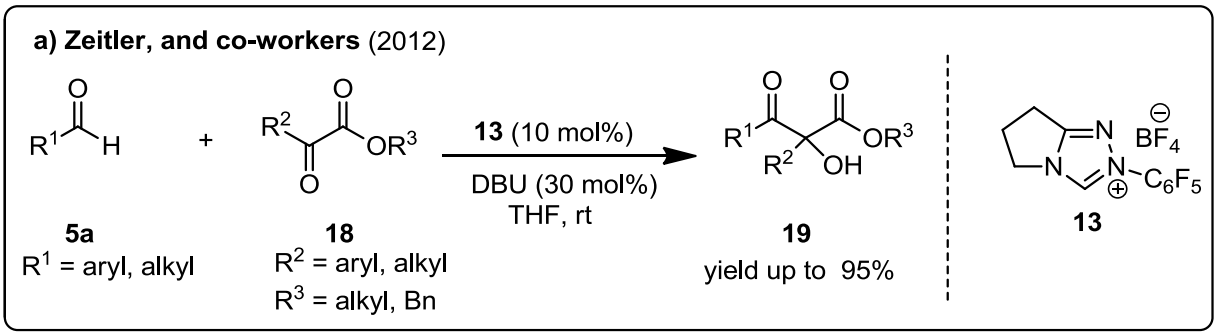


Scheme 5: Yang's cross-benzoin condensation



Scheme 6: Intramolecular cross-benzoin condensation between aldehydes and ketones

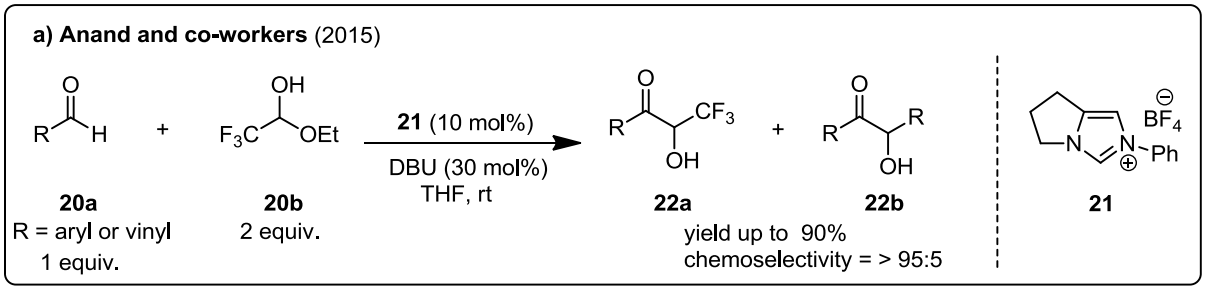
After Suzuki's remarkable work, many attempts have been made by various groups to evolve intramolecular cross-benzoin condensation using ketones.[27] Along with intramolecular cross-benzoin condensation, a number of reports have also appeared in the light of intermolecular cross-benzoin condensation using a variety of coupling partners.[28] In 2012, Zeitler and co-workers introduced *α*-keto ester as an acceptor in the direct intermolecular cross-benzoin condensation using a triazolium based NHC (**13**).[29] The reaction has proved to be efficient as a range of aliphatic and aromatic aldehydes (**5a**) as well as a number of derivatives of α-keto esters (**18**) worked well to afford highly functionalized corresponding products containing a quaternary stereocentre in up to 95% yield (Scheme 7).



Scheme 7: Asymmetric cross-benzoin condensation of *α*-keto esters

Very recently, Anand and co-workers developed a highly chemoselective intermolecular cross-acyloin condensation where trifluoroacetaldehyde ethyl hemiacetal (**20b**) has been used as an acceptor.[30] A wide variety of aryl aldehydes (**20a**) underwent smooth reaction to afford the

corresponding trifluoromethyl containing acyloin derivatives (**22a, 22b**) with excellent chemoselectivity and moderate to good yields (Scheme 8).

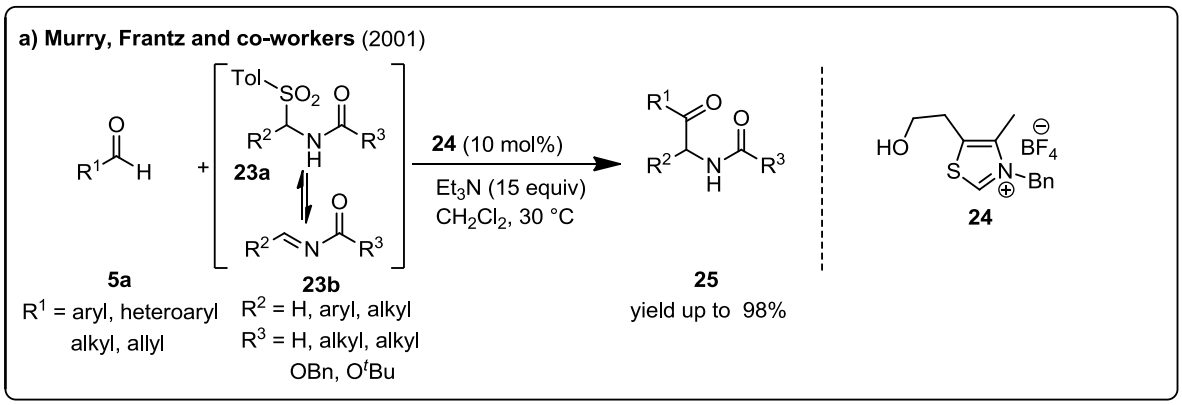


Scheme 8: Highly chemoselective intermolecular cross-benzoin condensation of aromatic aldehydes with trifluoroacetaldehyde ethyl hemiacetal

1.2.1.2) Aldehyde−Imine Cross-Benzoin Condensation

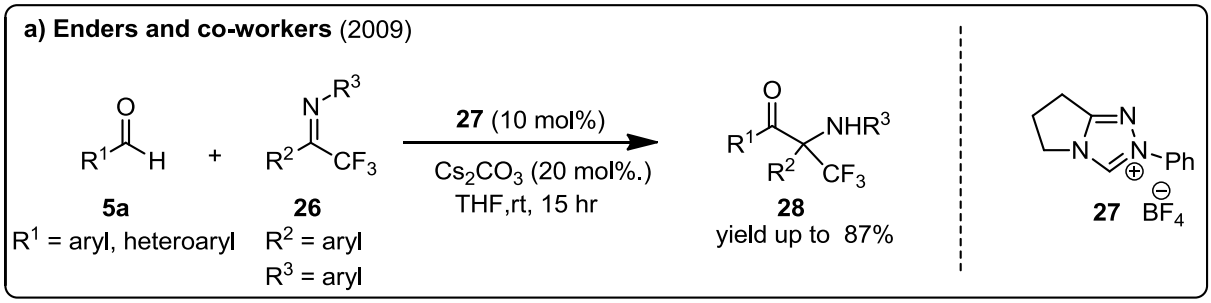
Imines are found to be fascinating coupling partners in cross-benzoin condensation as these offer simple routes for the synthesis of α-amino ketone derivatives. Some of the selected reports have been discussed in this section.

In 2001, Murry, Frantz and co-workers reported the first thiazolium (**24**) based NHC-catalyzed addition of acyl anion generated from aldehyde (**5a**) to *in situ* derived acylimines (**23b**).[31] The resultant α-amino ketones (**25**) were acquired in moderate to excellent yields (Scheme 9).



Scheme 9: NHC-catalyzed cross-aza-benzoin condensation

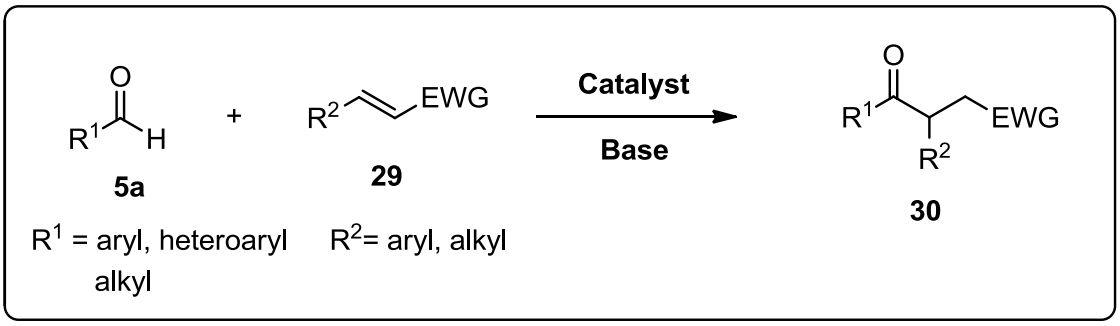
In 2009, Enders and co-workers reported the first cross-aza-benzoin condensation catalyzed by triazolium salts (**27**) as pre-catalyst where trifluoromethyl ketimines (**26**) was used as an aza electrophile to produce moderate to good yields (32−87%) (Scheme 10).[32]



Scheme 10: NHC-catalyzed cross-aza-benzoin condensation

1.2.2) The Stetter Reaction

In 1973, Stetter and co-workers extended the cyanide or thiazolylidene carbenes catalyzed Umpolung reactivity of aldehydes (**5a**) towards *α,β*-unsaturated acceptors (**29**), which is commonly known as Stetter Reaction.[33] The addition of generated acyl anion equivalents to Michael acceptors (**29**), such as *α,β*-unsaturated ketones, esters, and nitriles provides a new catalytic pathway for the synthesis of wide range of 1,4-bifunctional molecules (**30**) (Scheme 11).



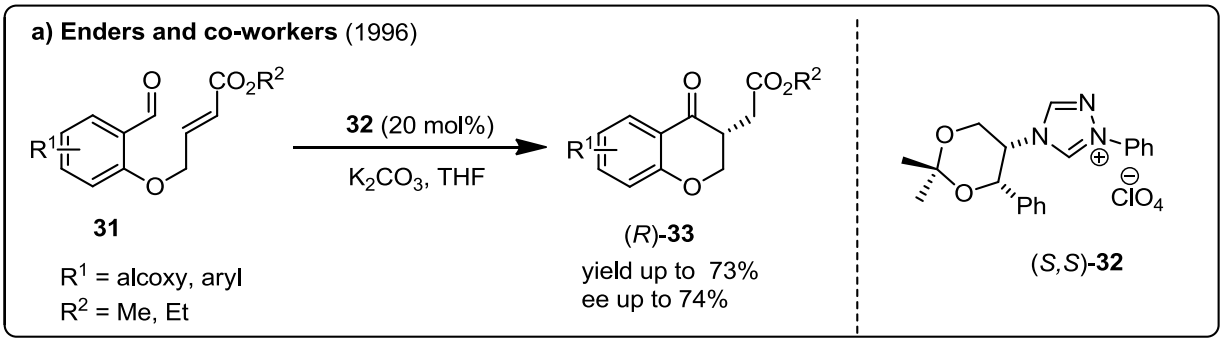
Scheme 11: General Stetter reaction

In the development of intermolecular Stetter reaction, a variety of aromatic and aliphatic aldehydes as well as different Michael acceptors were successfully employed by Stetter and co-workers. Widespread work by Stetter and others in this field revealed that the Michael acceptors with a *β*-substitution resulted in reduced reactivity.

1.2.2.1) Intramolecular Stetter Reactions:

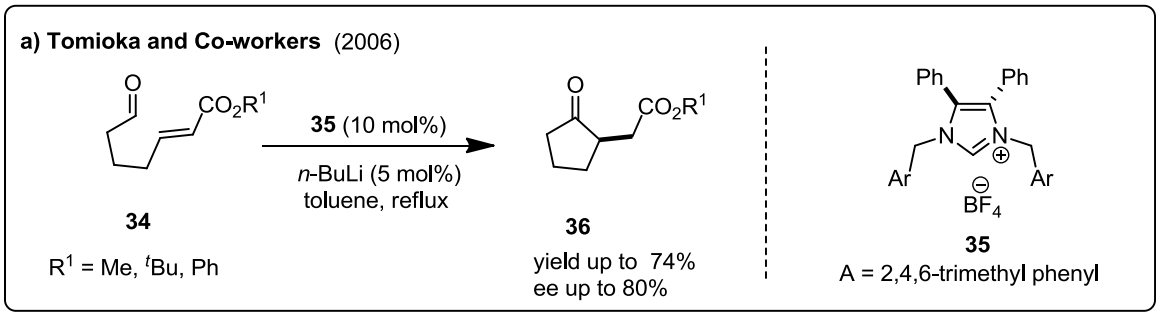
After the initial report, Ciganek reported an intramolecular version of the Stetter reaction using thiazolium pre-catalyst.[34] In 1996, Enders and co-workers demonstrated the first

asymmetric intramolecular Stetter reaction by utilizing chiral triazolium salt (**32**) as a pre-catalyst.[35] The enantioselective synthesis of different chromanone derivatives (**33**) had been achieved by the cyclization of salicylaldehyde derived substrates (**31**) with up to 73% yields and 74% ee (Scheme 12).



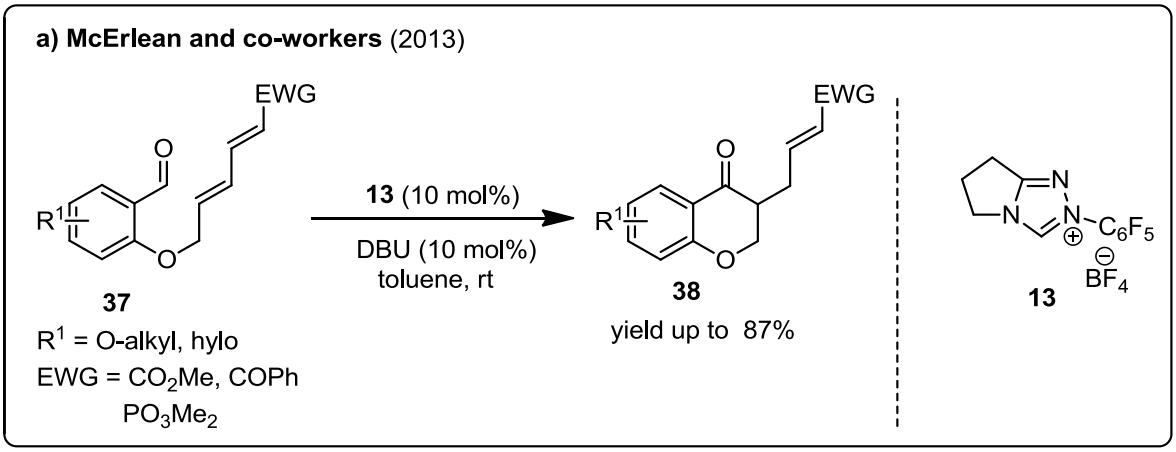
Scheme 12: First asymmetric intramolecular Stetter reaction

In 2006, Matsumoto and Tomioka reported the intramolecular Stetter reaction of aliphatic aldehydes (**34**), where they applied C_2-symmetric imidazolium salt (**35**) as a pre-catalyst and succeeded in achieving up to 80% ee (Scheme 13).[36]



Scheme 13: Development in Asymmetric intramolecular Stetter reaction

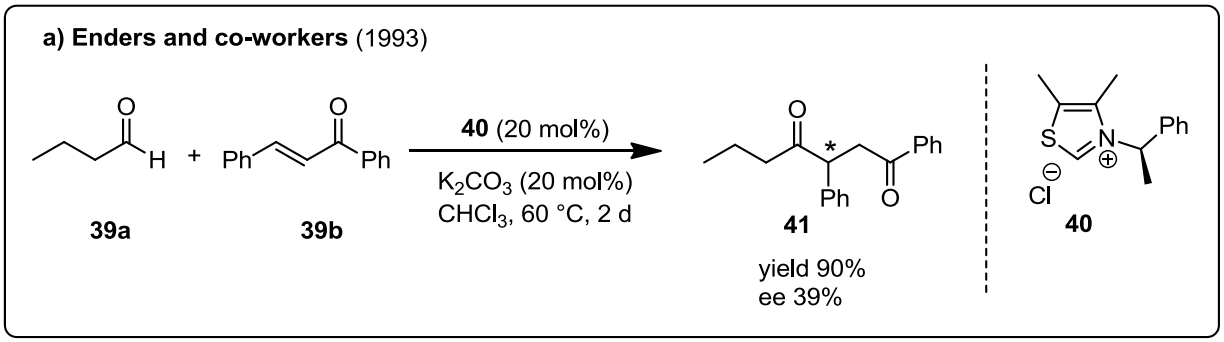
Furthermore, the applications of intramolecular Stetter reaction have been broadened to access different biologically important compounds by varying the heteroatoms of the chromanone scaffold.[37] In 2013, McErlean and co-workers extended the intramolecular Stetter reaction by using 1,6- Michael acceptors as a substrate (**37**) (Scheme 14).[38]



Scheme 14: Intramolecular vinylogous Stetter reaction

1.2.2.2) Intermolecular Stetter Reactions:

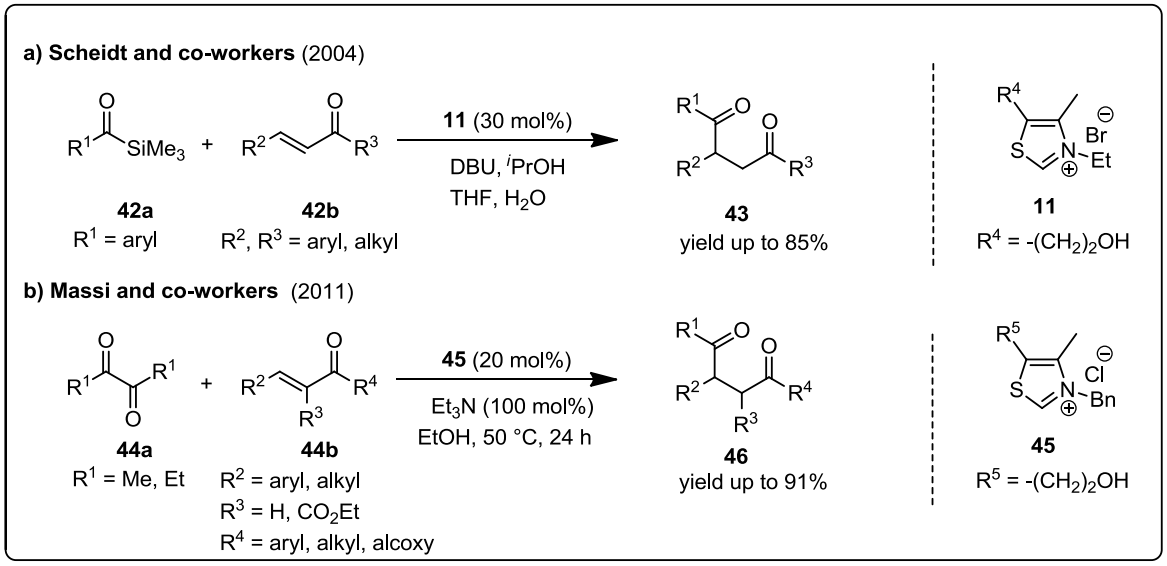
After the first report by Enders in 1973, the Stetter reaction has been extensively studied using different substrates and numerous achiral catalysts. However, intermolecular Stetter reaction has been found to be more challenging as compared to their intramolecular version. The first enantioselective intermolecular Stetter reaction was reported by Enders and co-workers in 1993 and in this case the corresponding 1,4-diketone (**41**) obtained in 39% of enantiomeric excess (Scheme 15).[39]



Scheme 15: NHC-catalyzed asymmetric intermolecular Stetter reaction

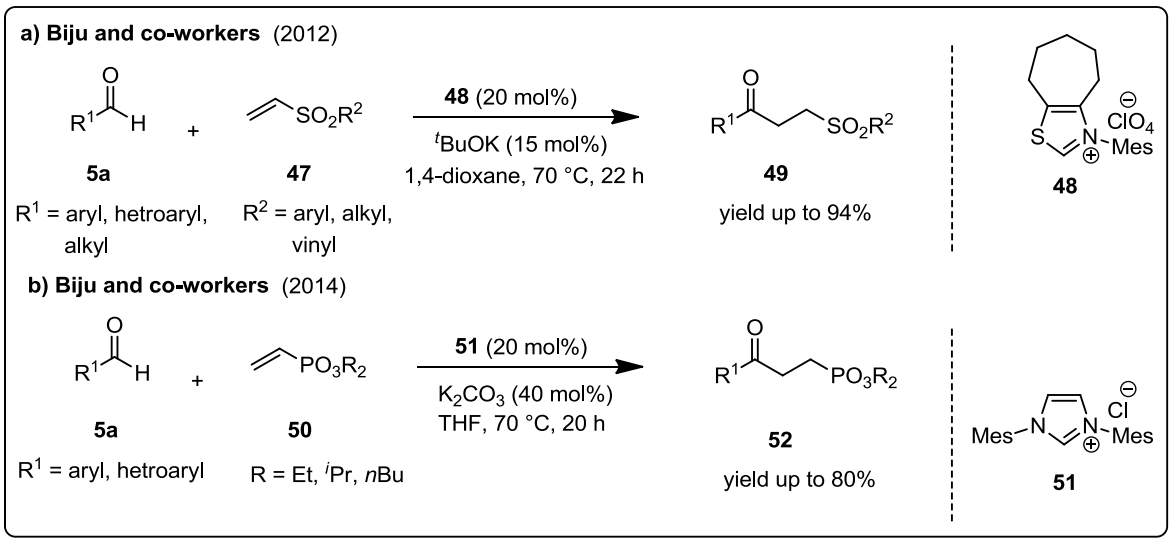
Scheidt and co-workers developed an intermolecular Stetter reaction, where they performed reaction between acyl silanes (**42a**), as an aldehyde equivalent, and *α,β*-unsaturated conjugate acceptors (**42b**) to synthesize the corresponding 1,4-dicarbonyl products (**43**) in good yields (a, Scheme 16).[40] Massi and co-workers used alkyl *α*-diketones (**44a**) as aldehyde donors

in intermolecular Stetter reaction with chalcones (**44b**) to obtain corresponding products in moderate to good yields (b, Scheme 16).[41]



Scheme 16: Intermolecular Stetter Reaction using different donor partners

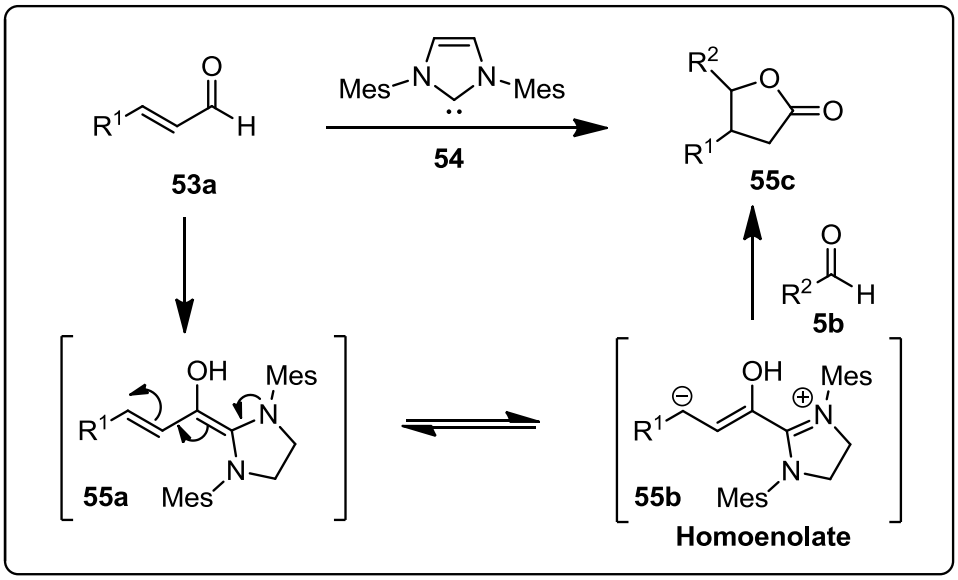
In addition to different donor partners, different acceptors have also been explored to expand the scope of intermolecular Stetter reaction. Biju and co-workers demonstrated the NHC-catalyzed intermolecular Stetter reaction of aldehydes (**5a**) with *α,β*-unsaturated sulfones (**47**) and *α,β*-unsaturated phosphonates (**50**) as Michael acceptors to access *γ*-keto sulfones (**49**) and *γ*-ketophosphonates (**52**) respectively in moderate to good yields (a,b, Scheme 17).[42]



Scheme 17: Intermolecular Stetter reaction using different Michael acceptors

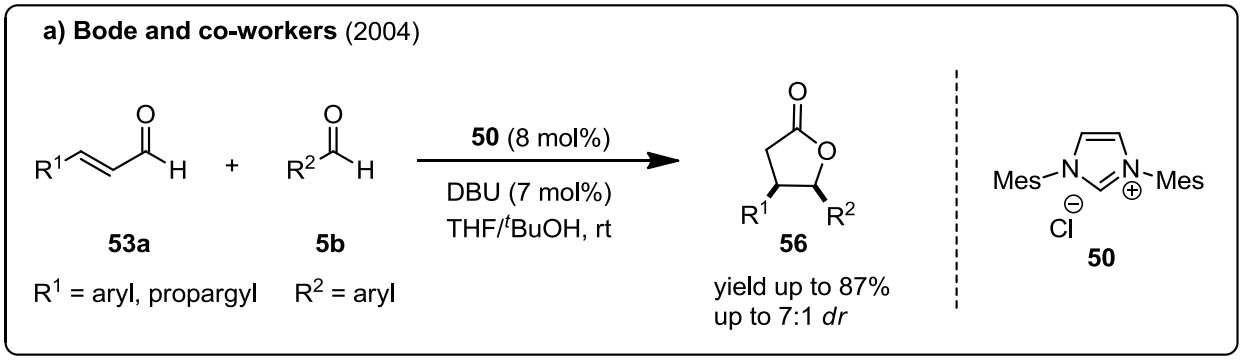
1.2.3) Catalysis Involving Extended Breslow Intermediates (Homoenolates):

The concept of extension of the nucleophilic character of Breslow intermediate at C-1 of the α,*β*-unsaturated aldehyde to the C-3 through conjugation is termed as "homoenolate". Although the concept of homoenolate anion was first time described by Nickon and Lambert while working on base-catalyzed racemisation of (+)-camphenilone in 1962,[43] the synthetic utility of homoenolates was not well explored until 2004. In 2004, Bode[44] and Glorius[45] independently reported a groundbreaking NHC-catalyzed new approach to the generation of a homoenolate (**55b**) from α,*β*-unsaturated aldehyde (**53a**). In their seminal works, they showed that the *in situ* generated carbene catalyst, from NHC precursors reacts with *α,β*-unsaturated aldehydes to produce a conjugated acyl anion (**55b**) (homoenolate equivalent). This further reacts with electrophilic aldehydes (**5b**) leading to corresponding *γ*-butyrolactones (**55c**) in good yields (Scheme 18).

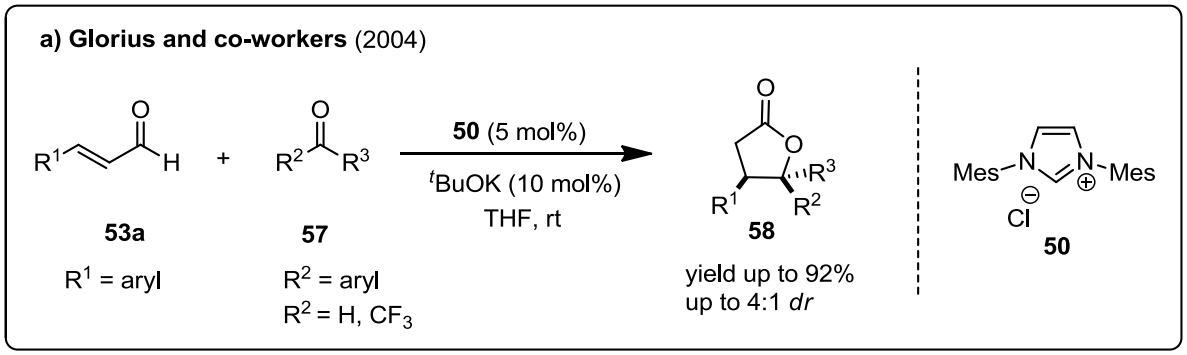


Scheme 18: NHC mediated formation of homoenolate

Bode and co-workers used a range of aryl and propargyl *α,β*-unsaturated aldehydes (**52a**) as coupling partners with aryl aldehydes (**5b**), to synthesize corresponding annulated *γ*-lactones (**56**) in up to 87% yields and up to 7:1 diastereoselectivity (Scheme 19). Whereas Glorius and co-workers reacted aryl enals (**52a**) with aryl aldehydes and trifluoromethyl ketones (**57**) as coupling partners to get corresponding *γ*-lactones in up to 92% yields and up to 4:1 diastereoselectivity (Scheme 20)



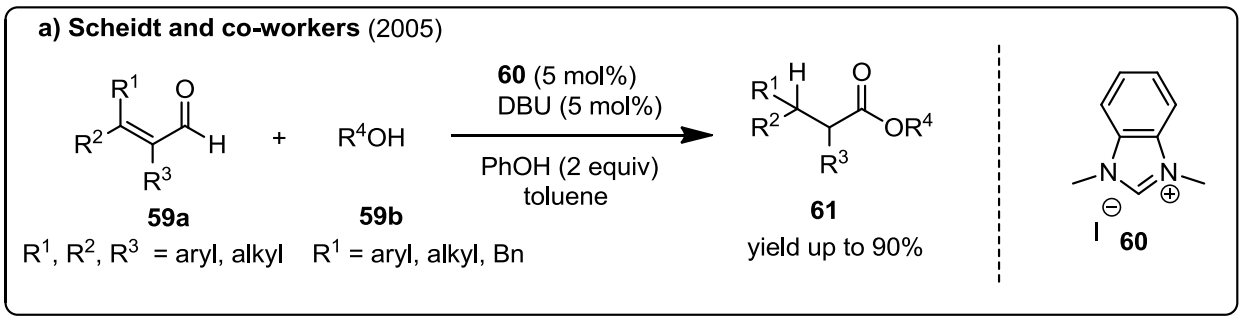
Scheme 19: NHC-catalyzed homoenolate addition reaction



Scheme 20: Annulation of enals and aryl aldehydes *via* a homoenolate

1.2.3.1) Reactions of homoenolates with various Michael acceptors

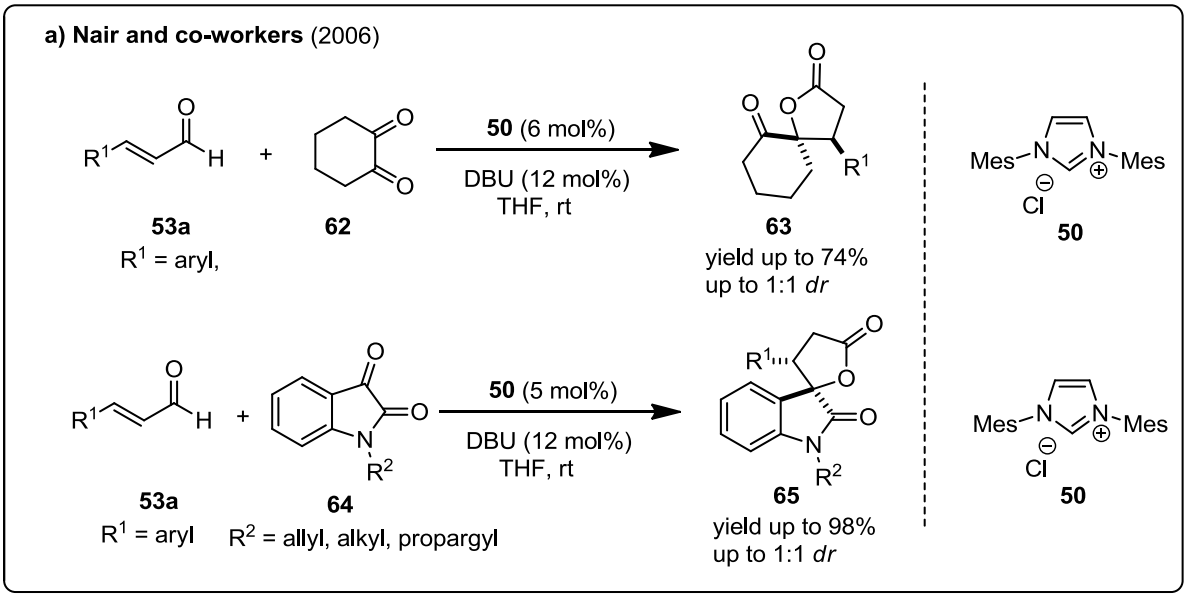
Based on the revolutionary findings by Bode and Glorius, several research groups have revealed numerous synthetic protocols by reacting different Michael acceptors with homoenolates, generated from enals. In 2005, Scheidt and co-workers trapped homoenolate derived from N-heterocyclic carbenes and α,β-unsaturated aldehydes (**59a**) with proton.[46]



Scheme 21: NHC-catalyzed trapping of homoenolate with proton

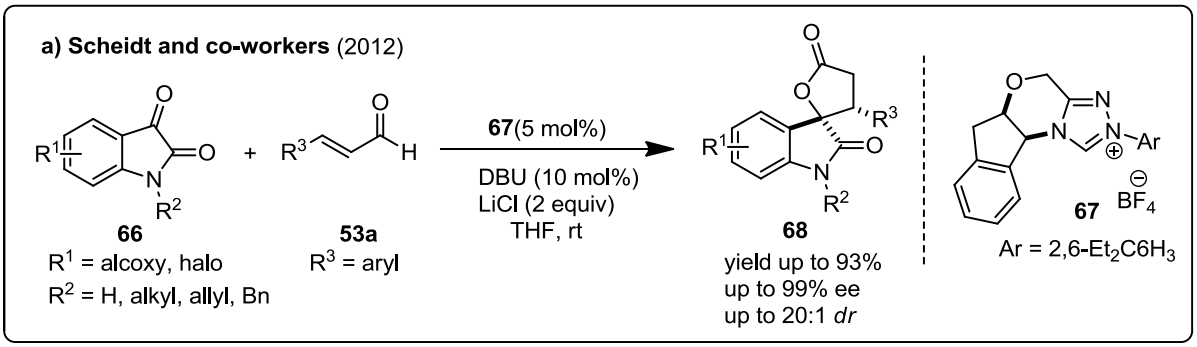
The activated carbonyl unit generated after the protonation of nucleophilic intermediate, further trapped with nucleophilc alcohol (**59b**) to provide the corresponding saturated ester (**61**) in up to 90% isolated yields (Scheme 21).

Nair and co-workers used α-diketones as Michael acceptors for the nucleophilic addition of homoenolate of enals to furnish the respective spiro γ-lactones (**63, 65**).[47] 1,2-Cyclohexanediones (**62**) and isatins (**64**) were used for this purpose (Scheme 22).



Scheme 22: Reaction of homoenolates with various Michael acceptors

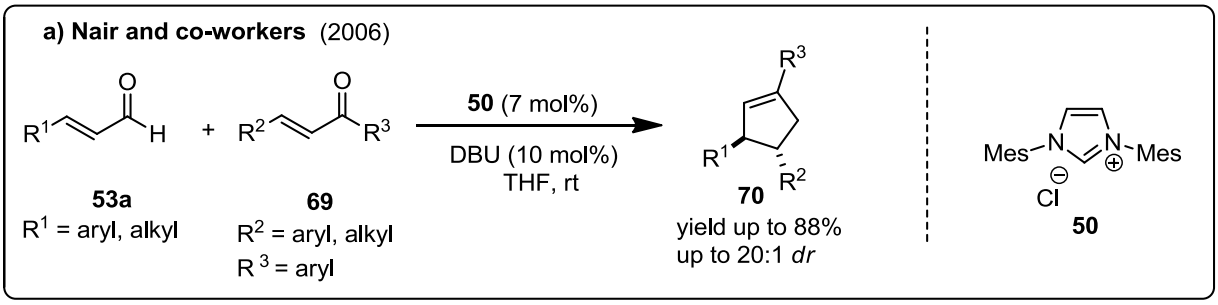
Meanwhile, numerous research groups successfully reported the asymmetric variant of this methodology.[48]



Scheme 23: NHC-catalyzed diastereo- and enantioselective formal [3+2] cycloaddition

Notably, in 2012, Scheidt and co-workers demonstrated the chiral NHC/Lewis acid co-operative catalyzed diastereo- and enantioselective formal [3+2] cycloaddition of α,*β*-unsaturated aldehydes (**53a**) with isatins (**66**) to furnish the corresponding spirooxindole lactones (**68**) in up to 93% yield with 20:1 diastereoselectivity and 99% ee (Scheme 23).[49]

Later, Nair and co-workers elaborated the use of NHC-catalyzed homoenolate addition reaction for the synthesis of five-membered carbocycles for the first time.[50] They performed the addition of homoenolate of enals to the chalcones (**69**) for the synthesis of 1,3,4-trisubstituted cyclopentenes (**70**) with up to 88% yield and excellent 20:1 diastereoselectivity (Scheme 24).

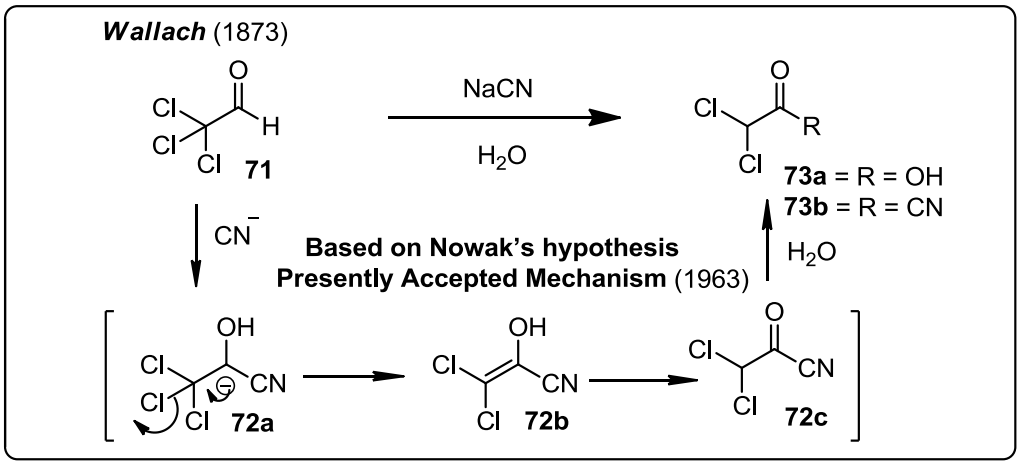


Scheme 24: NHC-catalyzed synthesis of cyclopentenes through homoenolate addition

In addition to the synthesis of the *γ*-lactone derivatives through addition of NHC-generated homoenolates to variety of carbonyl compounds, numbers of reports have been published for the synthesis of nitrogen-containing heterocycles such as *γ*-lactams, using imines as electrophiles.[51]

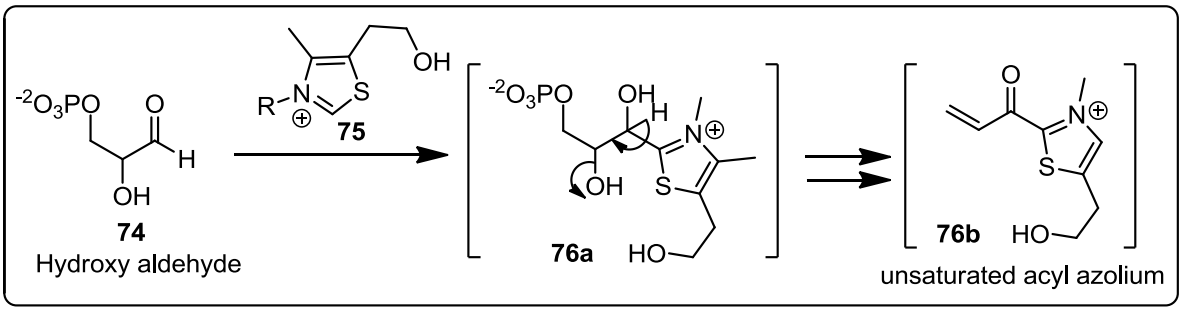
1.2.4) Reactions of *α*-Reducible Aldehydes *via* Acyl Azoliums:

In addition to the umpolung reactivity, NHCs have also been proved to be efficient catalysts in an array of reactions *via* non-umpolung intermediates, especially, NHC-catalyzed redox reactions through acyl azolium intermediates. Wallach in 1873 first demonstrated the aqueous potassium cyanide catalyzed redox conversion of chloral (**71**) to dichloroacetic acid (**73a**) (Scheme 25).[52] In 1963, Nowak proposed the widely accepted mechanistic pathway for the aqueous cyanide catalyzed conversion of chloroacetaldehyde (**72c**) to 2-chloro-1-cyanoethyl acetate (**73b**) (Scheme 25).[53]



Scheme 25: Cyanide-catalyzed redox and Nowak's presently accepted mechanism

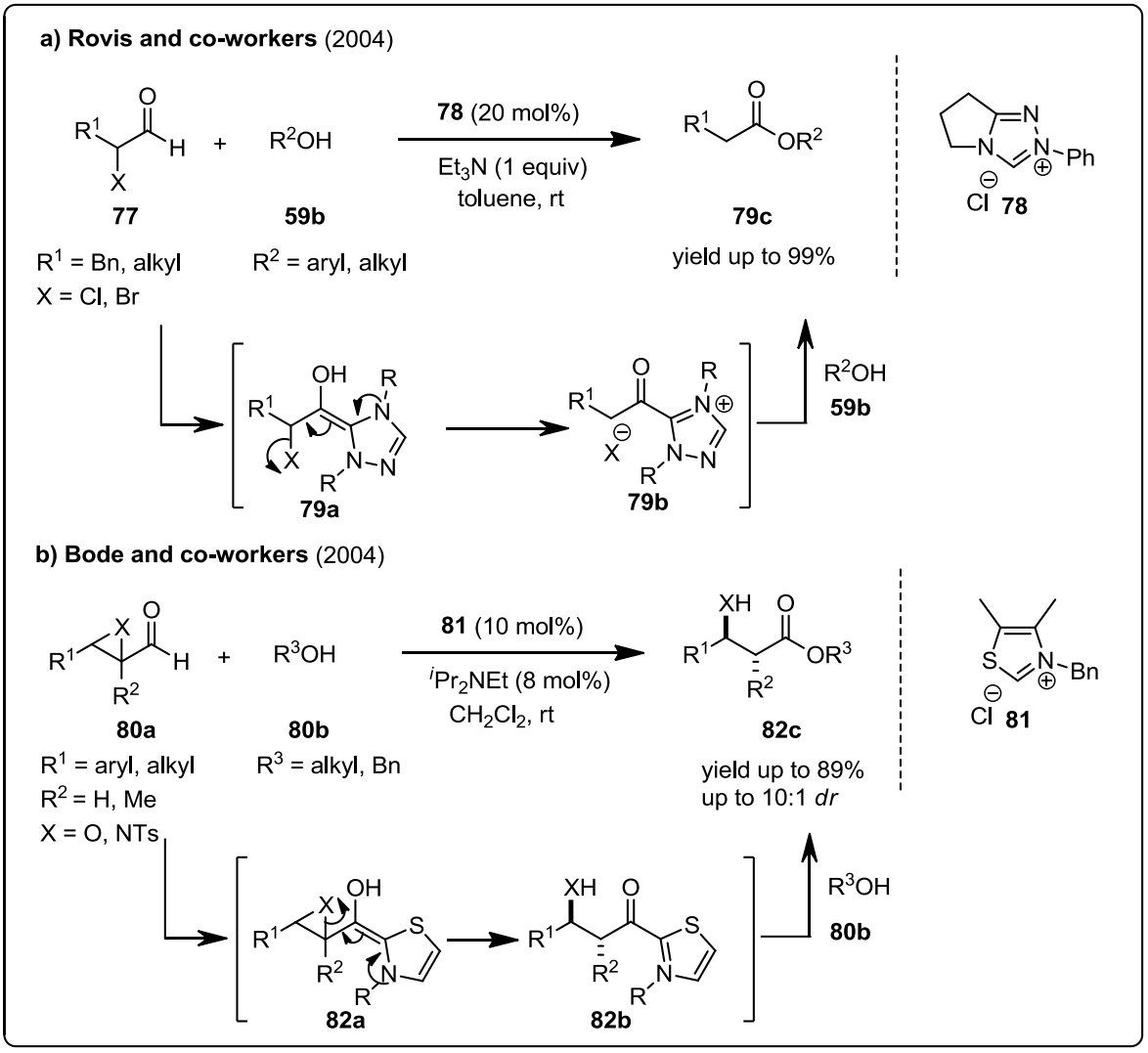
Townsend and co-workers first time reported the thiamine-catalyzed generation of α,*β*-unsaturated acyl azolium intermediate (**76b**) in their study of thiamine-mediated biosynthesis of clavulanic acid (Scheme 26).[54]



Scheme 26: Townsend's proposed unsaturated acyl azolium intermediate

In 2004, Rovis[55] and Bode[56] in their independent findings on N-heterocyclic carbene catalyzed esterification of α-reducible aldehydes in the presence of alcohols demonstrated the generation of acyl azolium intermediate. Rovis and co-workers used *α*-Halo aldehydes (**77**) as substrate with alcohols (**59b**) to afford saturated esters (**79c**). They proposed the generation of NHC-catalyzed acyl azolium intermediate (**79b**) through the conjugated elimination of α-Halo substituent present in Breslow intermediate (**79a**). The nucleophilic alcohols (**59b**) react with acyl azolium intermediate (**79b**) to afford saturated esters (**79c**) in up to 99% yields (a, Scheme 27).

Whereas Bode and co-workers utilized the *α*,*β*-epoxy- and *α*,*β*-aziridinyl aldehydes (**80a**) as substrates for the NHC-catalyzed redox esterification with a range of alcohols (**80b**) to access *β*-hydroxy esters and *β*-amino esters (**82c**) in up to 89% yields and up to 10:1 diastereoselectivity, respectively (b, Scheme 27).



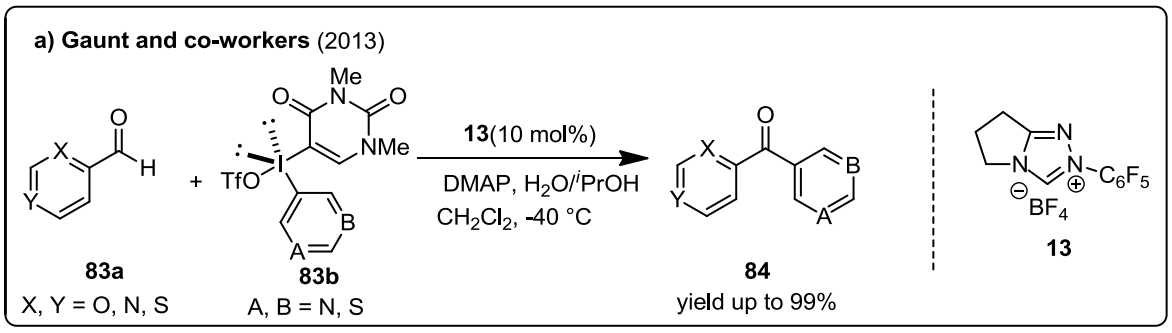
Scheme 27: Redox esterification of α-reducible aldehydes

Further detail description on NHC-catalyzed redox reactions has been explained in chapter 4.

1.3) N-Heterocyclic Carbene Catalysis: Some Selected Literature Reports

Gaunt and co-workers developed an N-heterocyclic carbene catalyzed C-H arylation of heteroaryl aldehydes with diaryliodonium salts as coupling partners.[57] The transient carbogenic nucleophile generated from the reaction between aldehydes (**83a**) and NHC was successfully

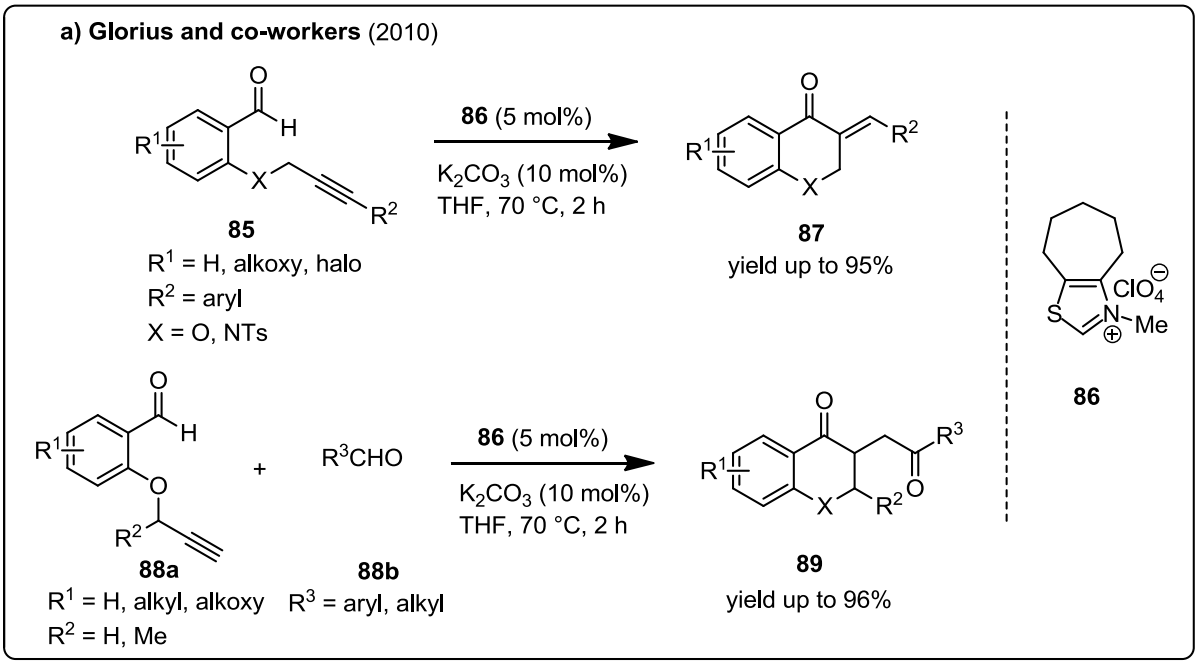
added to the electrophilic diaryliodonium salts (**83b**) to produce complex heteroaryl ketones (**84**) up to 98% yields. The addition of protic additive had been found to be beneficial for the homogeneity of the reaction mixture. The bis-heteroaryl ketone derivatives (**84**) had also been synthesized by using nonsymmetrical heteroaryliodonium salts (**83b**) as substrates (Scheme 28).



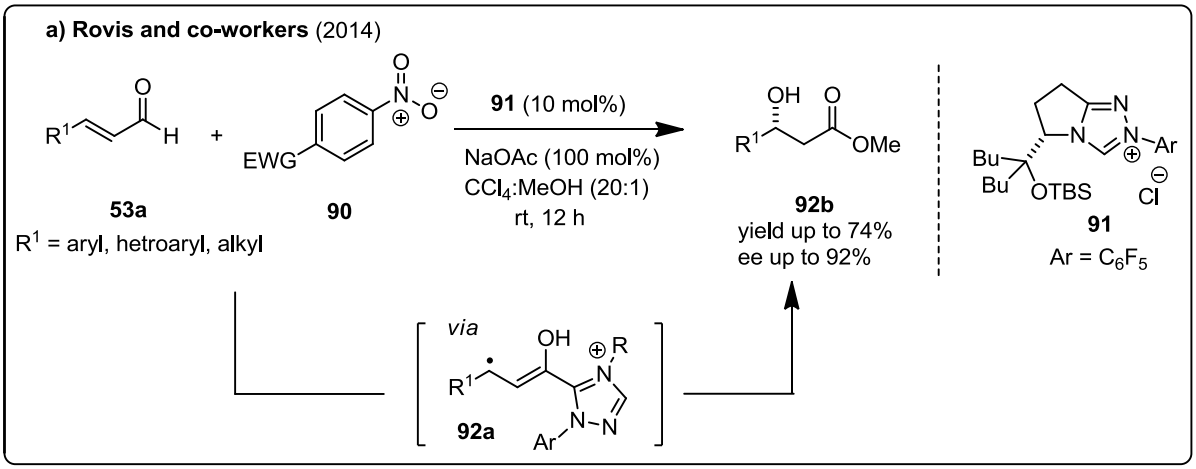
Scheme 28: Organocatalytic C-H bond arylation of aldehydes

In 2010, Glorius and co-workers published a fascinating results on N-heterocyclic carbene catalyzed cascade hydroacylation of unactivated alkynes (**85**), which leads to the subsequent *α,β*-unsaturated chromanone derivatives (**87**) in the presence of second aldehyde (**88a**) as the coupling partner.[58] The *in situ* generated *α,β*-unsaturated chromanone acts as Michael acceptor in the cascade intermolecular Stetter reaction for the synthesis of chromanones containing 1,4-diketone (**89**). This reaction efficiently delivers *α,β*-unsaturated chromanone derivatives (**87**) in up to 95% yields and the chromanones containing a 1,4-diketone moiety (**89**) in up to 96% yields (Scheme 29).

In 2014, Rovis and co-workers reported a novel oxidative N-heterocyclic carbene catalyzed *β*-hydroxylation of alkyl and aryl *α,β*-unsaturated aldehydes (**53a**).[59] The reaction led to the acyl azolium intermediate through oxygen atom transfer from electron-deficient nitrobenzenes (**90**) to homoenolate equivalent, and was further trapped by solvent to provide the corresponding *β*-hydroxy esters (**92b**), in good yields and enatioselactivity. The scope of the reaction had been broad as it included aryl, heteroaryl, and alkyl substitution at the *β*-position of the enals. The author believed that the reaction proceeded through single electron transfer pathway. They observed that the oxygen transfer takes place from the nitro group and not from *N*-oxy substituent of 4-nitropyridine *N*-oxide (**90**), as the reaction also worked with nitrobenzene (Scheme 30).



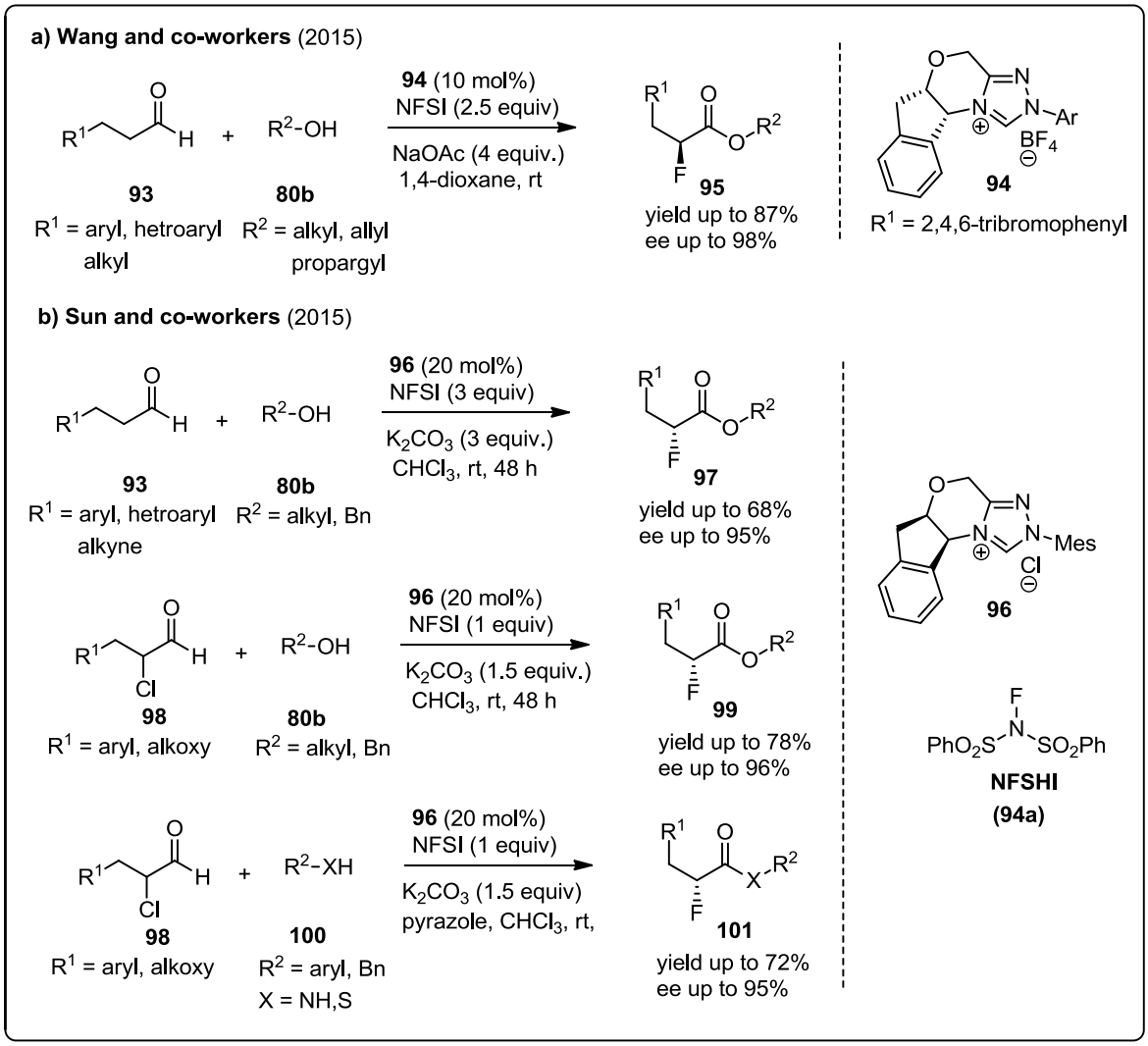
Scheme 29: NHC-catalyzed hydroacylation of unactivated alkynes



Scheme 30: NHC-catalyzed *β*-hydroxylation of enals using nitroarenes

Recently, Wang[60] and Sun[61] in their independent findings, reported the first N-heterocyclic carbene catalyzed enantioselective *α*-fluorination of aliphatic aldehydes (**93, 98**) through electrophilic fluorination. The *N*-fluorobis(phenyl)-sulfonimide had been used as an electrophilic fluorinating source as well as an oxidant. Wang and co-workers believed that the reaction proceeds through azolium enolate intermediate. The α-fluorinated acyl azolium

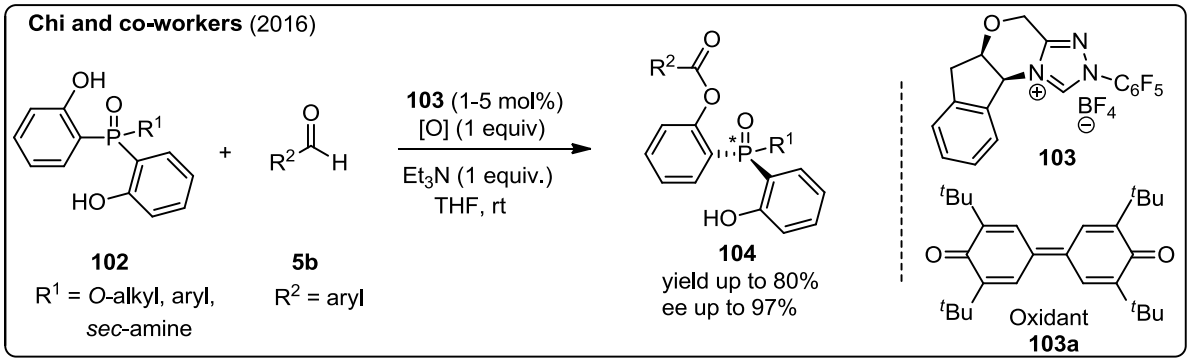
intermediate, generated after the nucleophilic addition of azolium enolate to NFSI (**94a**), reacts with alcohols (**80b**) to give corresponding enolizable *α*-fluoro esters (**95**) in 87% yield and 98% ee. Apart from simple aliphatic aldehydes, Sun and co-workers also examined the viability of the reaction using α-reducible aldehydes (**98**) as starting materials. The scope of reaction had been further extended to the synthesis of *α*-fluoro- thioester and amide derivatives (**97**) by using thiols and amines as coupling partners (Scheme 31).



Scheme 31: NHC-catalyzed oxidative enantioselective *α*-fluorination of aliphatic aldehydes

Very recently, Chi and co-workers reported the fascinating desymmetrization of pro-chiral bisphenol compounds bearing remote P-stereogenic centers through NHC-catalyzed oxidative esterification of aldehydes.[62] The bis(2-hydroxyphenyl) phosphinate (**102**) was used as

prochiral bisphenol substrate where as aryl aldehyde (**5b**) as acylting reagent. The reaction between **102** and **5b** in presence of chiral NHC-catalyst and quinone led to the enantiomerically enriched P-stereogenic phosphinates (**104**) in moderate to good yields with excellent enantiomeric excess (Scheme 32).



Scheme 32: NHC-catalyzed desymmetrization of bisphenols

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Chapter 2

N-Heterocyclic carbene as a Brønsted base catalyst

This chapter describes the synthesis of diaryl- and triarylmethane derivatives through I,6-conjugate addition reactions of dinones using NHC as a Brønsted base catalyst This chapter also covers a general introduction on reactions, where NHC was utilized as a Brønsted.

This chapter is mainly divided into two parts namely part A and part B

Part A: *N*-heterocyclic carbene catalyzed 1,6-conjugate addition of dialkylphosphites to *p*-quinone methides and fuchsones: Synthesis of diaryl- and triarylmethyl phosphonates.

Part B: *N*-heterocyclic carbene catalyzed 1,6-conjugate addition of 2-naphthol to *p*-quinone methides: Expedient access to unsymmetrical triarylmethanes.

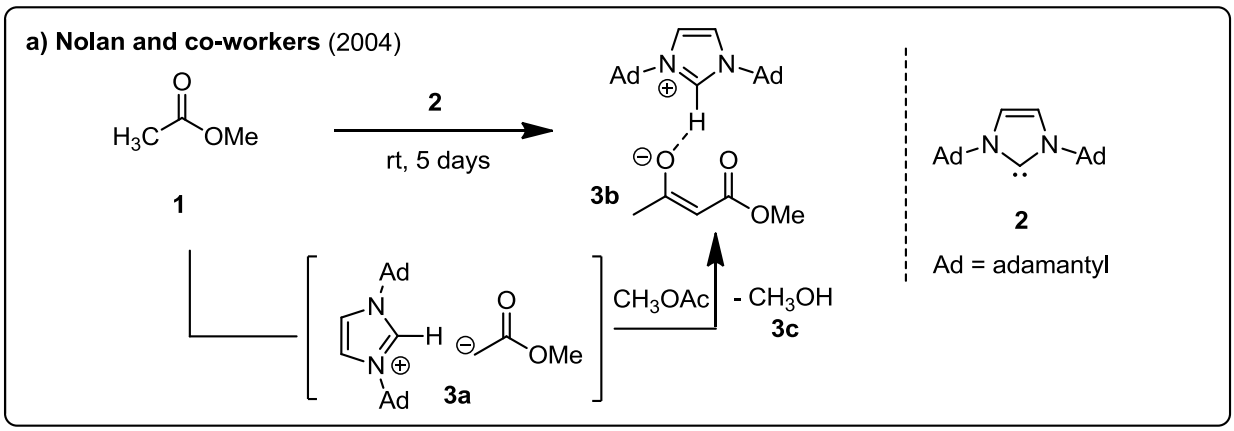
2.1) General introduction on NHC as a Brønsted base catalyst

Apart from their unique reactivity towards carbonyl functionality in umpolung/non-umpolung reactions, they have also found applications in other organic transformations.[1] Generally, the unique properties of NHCs such as, *σ*-donation and basicity play a significant role in these conversions. The *σ*-donation allows NHCs to perform reactions such as transesterifications,[2] Morita−Baylis−Hillman reactions,[3] silyl activation reactions[4] and Claisen-type rearrangements[5]. They can also acts as Brønsted base to accomplish transformations like silyl enolether formation[6] and Michael addition reactions[7] as the pK_a value of NHC has been documented to be in the range of 21–25.[8] Some literature reports, where NHC have been used as Brønsted base are reviewed in this section.

2.1.1) Transformations using NHC as a Brønsted base

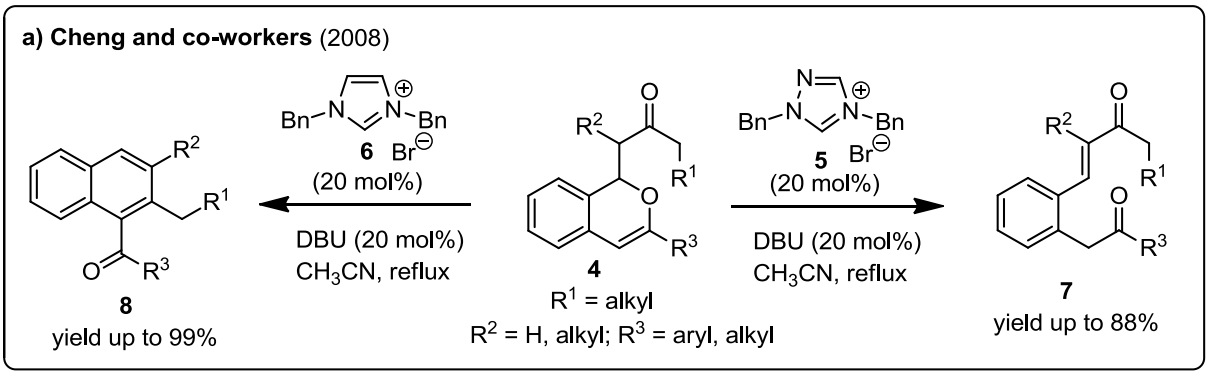
2.1.1.1) Reactions through Enolate intermediate

In 2002, Davidson and co-workers documented the successful isolation of NHC-amine and NHC-phenol adducts to study the interactions between organic acids and carbenes.[9] Nolan and co-workers reported an unprecedented NHC catalyzed C-H activation of pseudo-acids.[10] In their study, they observed that the deprotonation of *α*-acidic proton of methyl acetate (**1**) by IAd NHC (**2**) at room temperature to form unstable enolate anion (**3a**), which further reacts with excess methyl acetate (**1**) to from the Claisen condensation adduct (**3b**) (Scheme 1).



Scheme 1: Formation of NHC-Claisen adduct

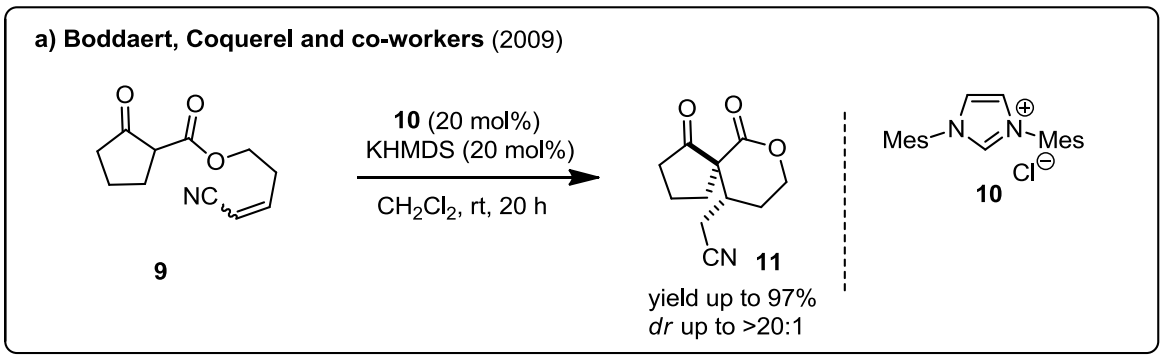
In 2012, Cheng and co-workers demonstrated an interesting finding on catalyst controlled transformations of isochromene derivatives (**4**) using NHC as Brønsted base.[11] The carbene generated from triazolium salt (**5**) led to the isomerization of isochromene (**4**) to *α*,*β*-unsaturated diketone derivatives (**7**) in up to 88% yield. On the other hand, the more basic imidazolium based carbene facilitates an intramolecular aldol condensation followed by aromatization of bisketone intermediate (**7**) to furnish the multi-substituted naphthalene derivatives (**8**) in up to 99% yield (Scheme 2).



Scheme 2: NHC-catalyzed transformations of isochromene derivatives

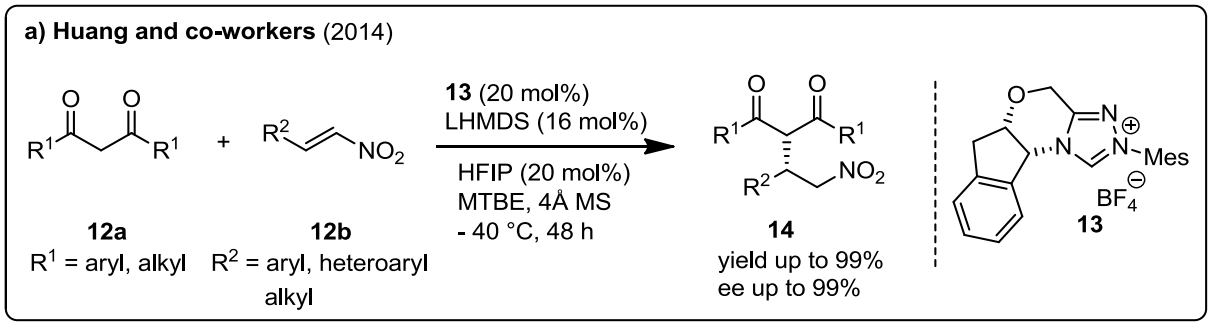
2.1.1.2) Conjugate additions

Coquerel and co-workers, while working on one-pot cross metathesis spirocyclisation cascade, reported the serendipitous finding on NHC-catalyzed intramolecular Michael addition of 1,3-dicarbonyl compounds (**9**) to furnish spiro compounds (**11**) in good to excellent yields with high distereoselectivity.[12] (Scheme 3).



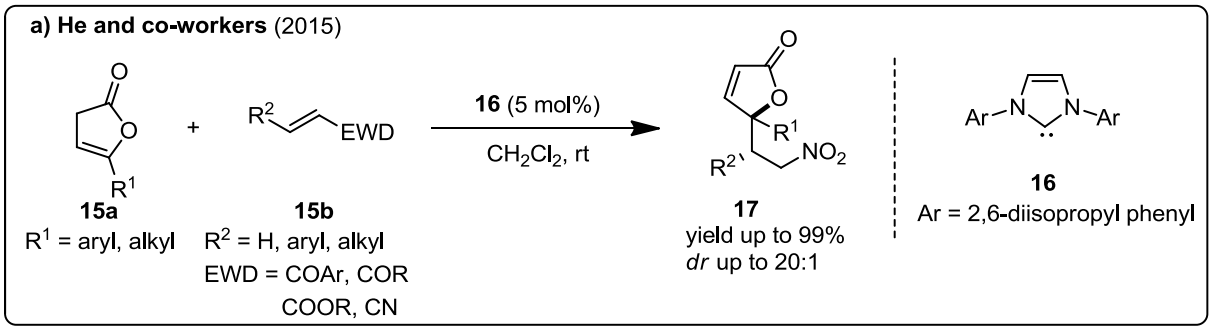
Scheme 3: NHC-catalyzed Michael additions of 1,3-dicarbonyl compounds

In 2014, Huang and co-workers demonstrated an asymmetric variant for carbo-Michael addition reaction.[13] They used moderately basic triazolium-derived NHC as catalyst and hexafluoroisopropanol (HFIP) as an acidic additive, which acts as a proton shuttle for smooth hydrogen transfer, to afford high-reaction rates and high enantioselectivity. The reaction between 1,3-diketones (**12a**) and nitroolefins (**12b**) led to the resultant products (**14**) in excellent yields and up to 99% ee (Scheme 4).



Scheme 4: NHC-catalyzed enantioselective Michael addition

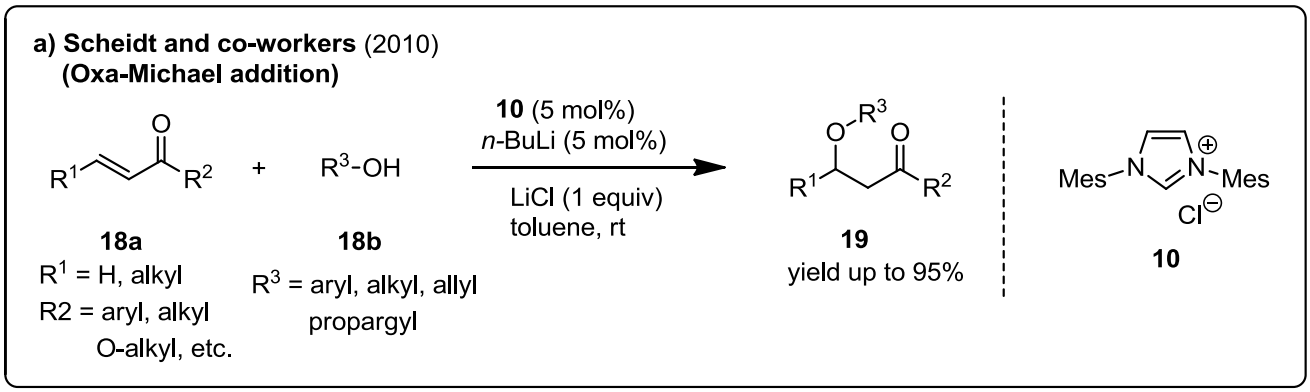
Very recently, He and co-workers published a fascinating NHC-catalyzed vinylogous Michael addition of γ-substituted deconjugated butenolides (**15a**) over a range of Michael acceptors (**15b**).[14] Irrespective of the electronic nature and positions of the substituents on the substrates, the reaction worked well and the derivatives of γ,γ-disubstituted butenolides (**17**) were obtained in good yields. The resultant butenolides (**17**) bearing adjacent quaternary and tertiary carbon centers were obtained in 20:1 diastereoselectivity (Scheme 5).



Scheme 5: NHC-catalyzed Michael addition of γ-substituted deconjugated butenolides

2.1.1.3) Hetero-Michael additions

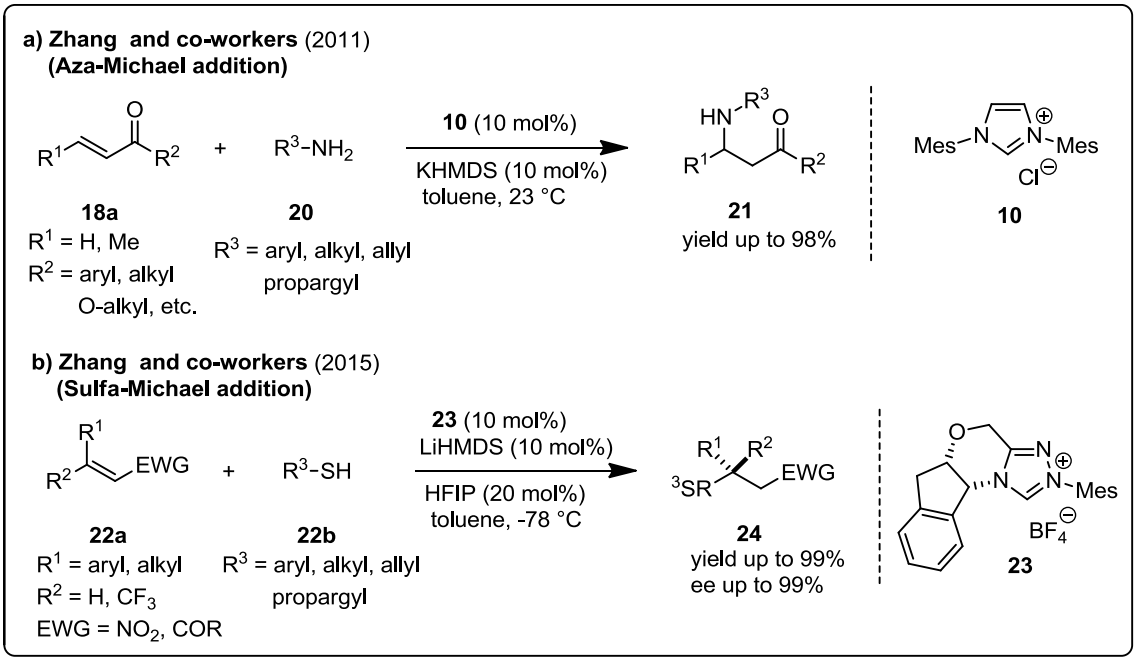
Recently, Scheidt and co-workers accomplished an NHC-catalyzed conjugate addition of various alcohols (**18b**) to the activated alkenes (**18a**).[15] The *in situ* generated imidazolium carbene acts as a Brønsted base to furnish *β*-alkoxy ketone derivatives (**19**) in good to excellent yields through 1,4-conjugate addition of primary and secondary alcohols (**18b**). Unfortunately only 11% of enantiomeric excess was observed when the chiral NHC-catalyst was used (Scheme 6).



Scheme 6: NHC-catalyzed conjugate addition of alcohols to activated alkenes

Zhang and co-workers reported an NHC-catalyzed 1,4-conjugate addition of aromatic and aliphatic amines (**20**) to the Michael acceptors (**18a**).[16] The corresponding *β*-amino ketone derivatives (**21**) were synthesized in up to 98% yield (a, Scheme 7).

Later, Huang and co-workers disclosed the first NHC-catalyzed asymmetric sulfa-Michael addition reaction between thiols (**22b**) and *α,β*-unsaturated olefins (**22a**) to access the corresponding products (**24**) in good to excellent yields and high enantioselectivity.[17] A wide range of thiols (**22b**) and olefins (**22a**), including electron-deficient and *β,β*- disubstituted olefins, were efficiently converted to the resulting products (**24**). A variety of CF_3 and sulfur containing compounds with quaternary chiral centers have been synthesized with excellent enantioselectivity (b, Scheme 7).

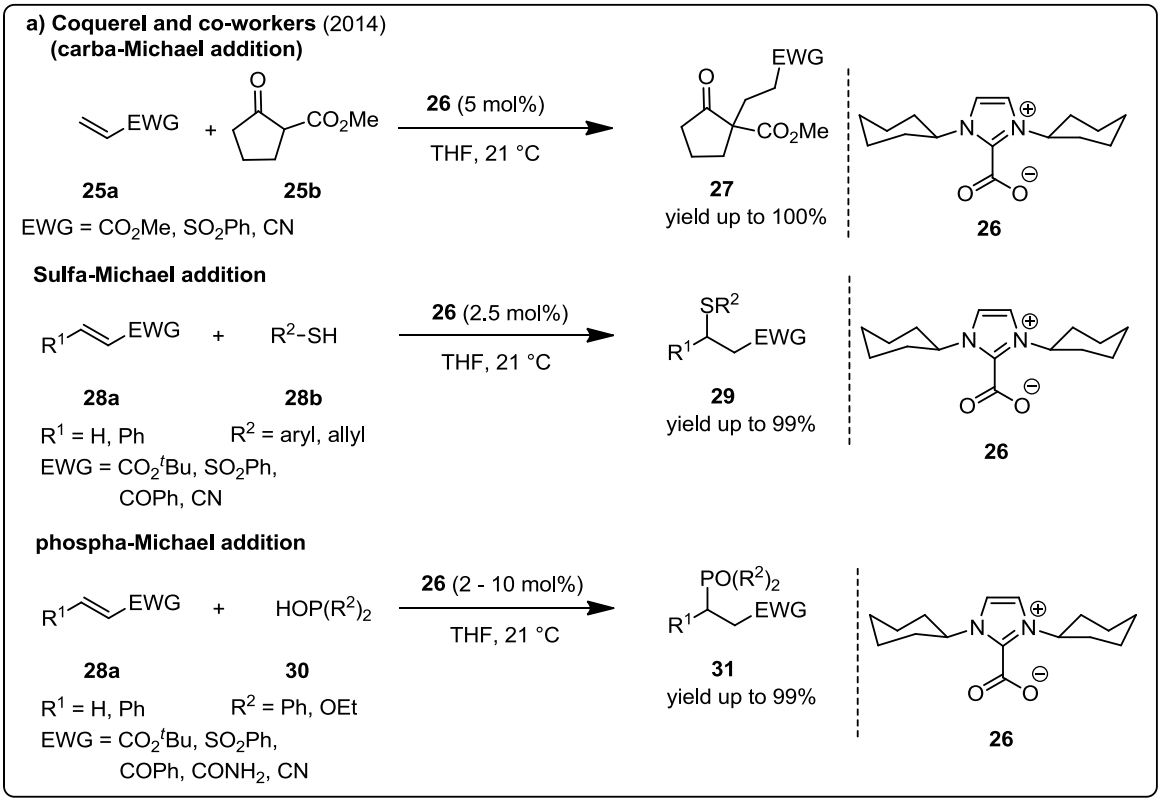


Scheme 7: NHC-catalyzed Hetero-Michael addition reactions

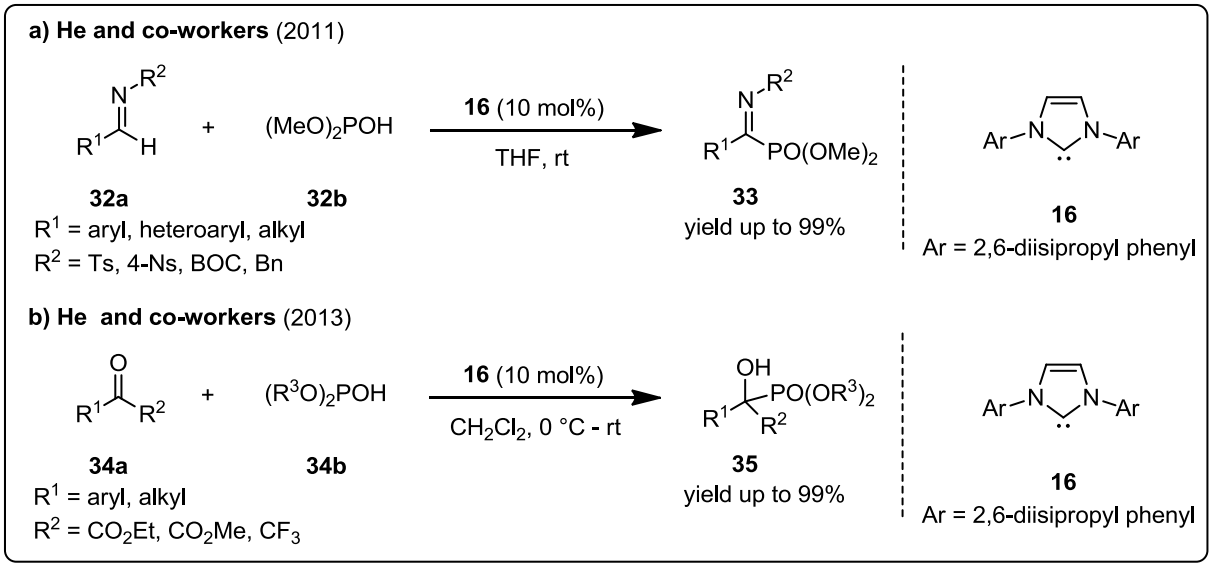
Coquerel and co-workers recently developed an efficient 1,4-conjugate addition of carba- (**25a**), sulfa- (**28b**), and phospha-nucleophiles (**30**) to α,β-unsaturated compounds (**25a**, **28a**) using NHC-CO_2 adduct (**26**) as pre-catalyst.[18] Recently, NHC-CO_2 adducts have been broadly used as NHC precursor in various transformations.[19] This protocol provides an extended scope of resultant carba-(2**7)**, sulfa-(**29)**, and phospha-Michael adducts (**31**) in up to quantitative yields. When 2-aminobenzenethiol was treated with methyl vinyl ketone, the chemoselective sulfa-Michael adduct was formed chemoselectively over aza-Michael adduct (Scheme 8).

Besides 1,4-conjugate addition reactions, NHCs have also been used as a Brønsted base in 1,2-hydrophosphonylation of aldehydes and imines. He's group demonstrated an NHC-catalyzed hydrophosphonylation of the aldimines (**32a**).[20] Treatment of Dialkyl phosphite (**32b**) with aldimines (**32a**) in the presence of NHC (**16**) furnished the corresponding (α-aminoalkyl)phosphonates (**33**) in moderate to excellent yields (a, Scheme 9). Later, the same group reported an NHC-catalyzed 1,2-hydrophosphonylation of α-ketoesters and α-trifluoromethyl ketones (**34a**).[21] The dialkyl phosphites (**34b**) were reacted with activated ketones (**34a**) in the presence of pre-generated NHC (**16**) as a catalyst to afford quaternary α-

hydroxyphosphonates (**35**) in good to excellent yields. Unfortunately, the reaction did not proceed with less reactive ketones such as acetophenone (b, Scheme 9).



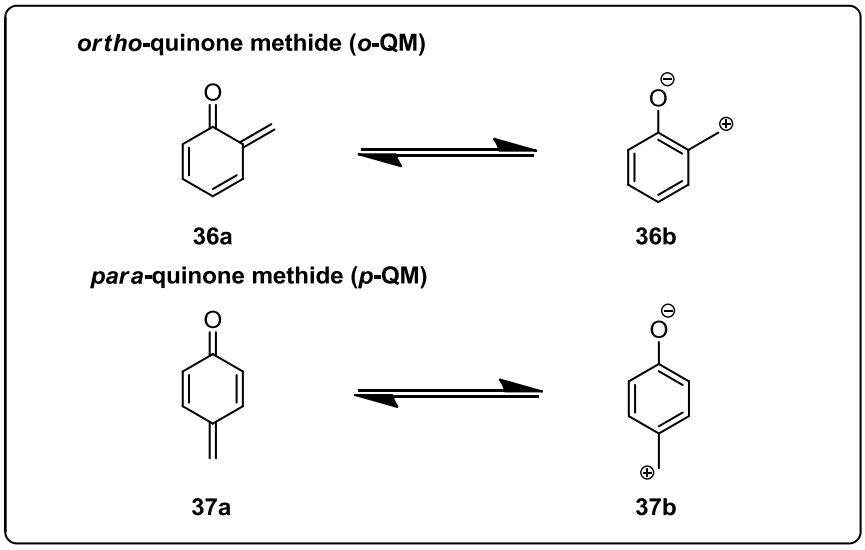
Scheme 8: NHC-catalyzed Hetero-Michael addition reactions



Scheme 9: NHC catalyzed hydrophosphonylation of imines and aldehydes

2.2) General introduction on the reactions of *para*-quinone methides

The *ortho*-quinone methides (*o*-QMs) and *para*-quinone methides (*p*-QMs) are formally neutral and zwitterionic resonance structural isomers (**36b, 37b**) (Scheme 10). These are integral parts of a wide range of natural products and bioactive molecules.[22] Generally, these quinone methides act as Michael acceptors in organic synthesis to generate new C−C and C−hetero bonds through 1,4- and 1,6-conjugate addition reactions.[23]

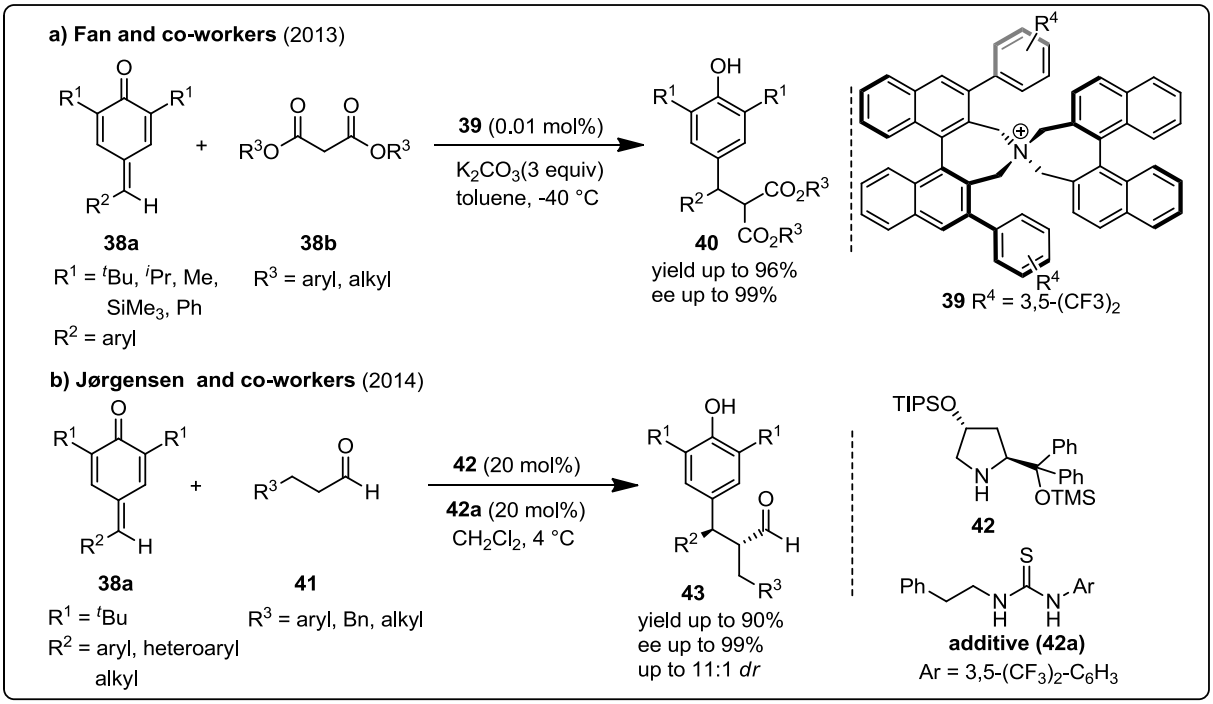


Scheme 10: Neutral and zwitterionic resonance structural isomers of quinone methides

In case of *p*-QMs, the aromatization of the cyclohexadiene ring is the driving force for the 1,6- conjugate addition of nucleophiles at benzylic position. Although the *o*-QMs have been broadly studied in organic transformations for decades,[24] the synthetic utility of *p*-QMs have gained considerable attention only in recent times. Some selected literature reports are discussed in this section.

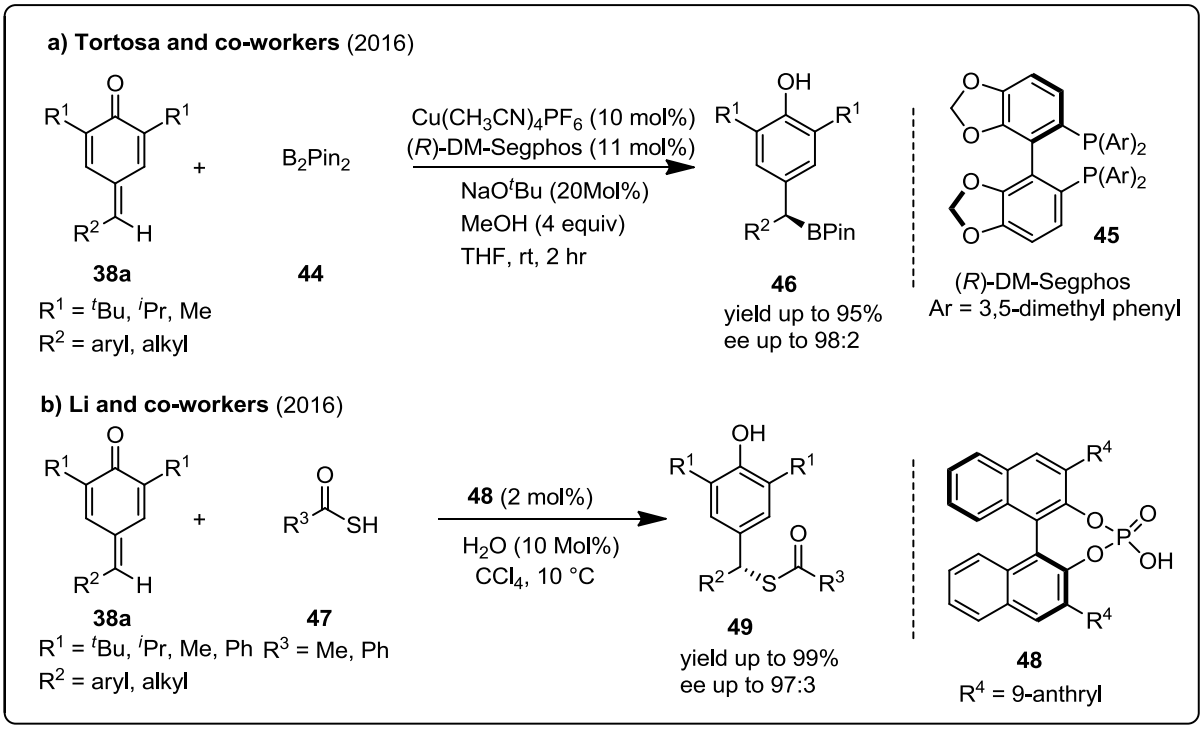
In 2013, Fan and co-workers disclosed a chiral quaternary ammonium salt-catalyzed enantioselective addition of malonates to *p*-QMs.[25] A wide range of *p*-QMs (**38a**) and malonates (**38b**) were reacted under phase-transfer catalysis (**39**) to form the corresponding functionalized diarylmethine derivatives centers (**40**) in excellent yields and up to 99% ee (a, Scheme 11). Recently, Jørgensen and co-workers reported the 1,6-conjugated addition of *in situ* generated enamines to *p*-QMs (**38a**) by using chiral secondary amine catalyst (**42**).[26] The asymmetric *α*-

alkylation of diverse aldehydes (**41**) led to the formation of two contiguous stereocenters in resultant diarylmethine derivatives (**43**) in up to 90% yield with excellent enantioselectivity and up to 11:1 diastereoselectivity (b, Scheme 11).



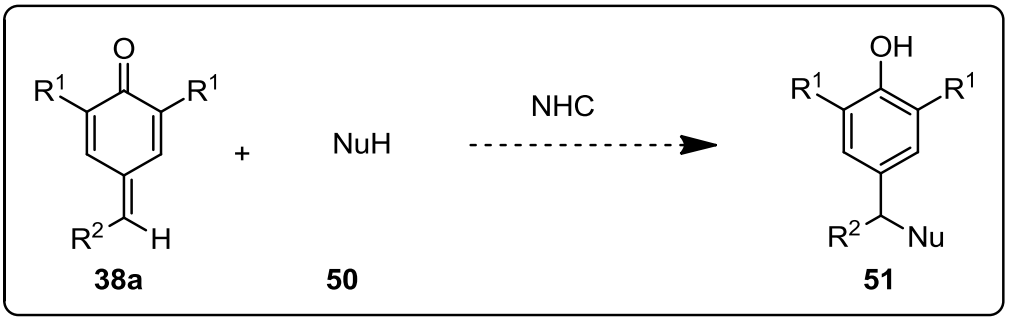
Scheme 11: 1,6-Conjugated addition of different nucleophiles to *p*-QMs

Very recently, Tortosa's group further extended the scope of *p*-QMs as Michael acceptor by introducing an exciting enantioselective addition of boron as nucleophile to *p*-QMs.[27] The enantioselective Cu-catalyzed borylation of *p*-QMs (**38a**) with bis(pinacolato)diboron (**44**) led to the access of chiral monobenzylic and dibenzylic boronic ester derivatives (**46**) in moderate to excellent yields with excellent enantiomeric ratios. The monobenzylic and dibenzylic boronic esters (**46**) are important substrates for many transition-metal-catalyzed reactions (a, Scheme 12). Recently, Li and co-workers demonstrated the chiral phosphoric acid (**48**) catalyzed enantioselective 1,6-conjugate addition of thioacetic acid (**47**) to *p*-QMs (**38a**).[28] This protocol offered a simple route for the synthesis of wide range of enantioselective diaryl sulfur-containing compounds (**49**) in up to 99% yield and up to 97:3 enantiomeric ratio (b, Scheme 12).



Scheme 12: 1,6-Conjugated addition of different nucleophiles to *p*-QMs

Recently, Anand's group also contributed in the area of *para*-quinone methides chemistry through Palladium catalyzed domino electrophilic cyclization–extended conjugate addition and bis-(dialkyl amino)cyclopropenylidene-catalyzed 1,6-conjugate addition of aldehydes to *p*-QMs.[29] While continuing our ongoing research in this field and NHC-catalysis, we envisioned that NHC could also act as a Brønsted base catalyst to perform nucleophilic 1,6-conjugate addition to to *p*-QMs.



Scheme 13: Proposed scheme for NHC-catalyzed nucleophilic addition to *p*-QMs

Part A: N-heterocyclic carbene catalyzed 1,6-conjugate addition of dialkylphosphites to *p*-quinone methides and fuchsones: Synthesis of diaryl- and triarylmethyl phosphonates

In this section, the NHC-catalyzed 1,6-conjugate addition of dialkyl phosphites to synthesize of diaryl- and triarylmethyl phosphonate and unsymmetrical triarylmethane derivatives have been discussed.

Over many decades, organophosphorous derivatives have been considered as a vital class of organic compounds due to their extensive applications in materials chemistry,[30] medicinal chemistry[31] and pharmaceutical industry.[32] These are also used as metal extractants, flame retardants and in shrinkage reduction.[33] In organic chemistry, these compounds play an important role in several areas including organocatalysis and organometallic chemistry as ligands.[34] In synthetic chemistry, organophosphorous compounds are used as reagents in numerous olefination reactions such as Wittig reaction and Horner–Wadsworth–Emmons (HWE) reaction.[35] Among the organophosphorous compounds, the diaryl- and triarylmethyl phosphonate derivatives appeared to be synthetically important derivatives due to their significant applications in drug discovery[36] and as chemiluminescence materials.[37] Some of the important biologically active compounds are shown in figure 1.

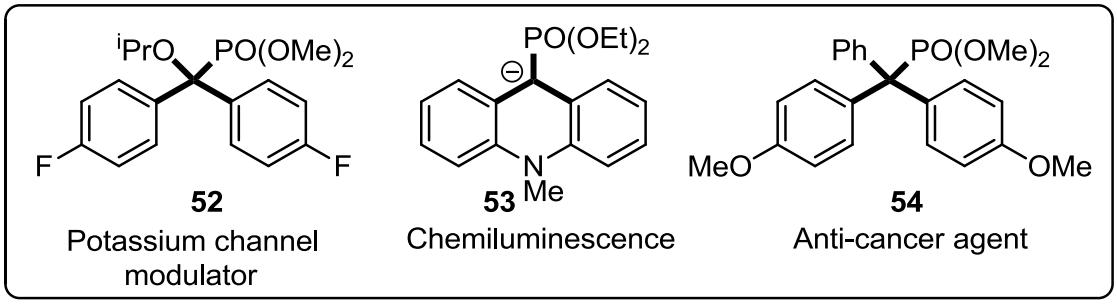
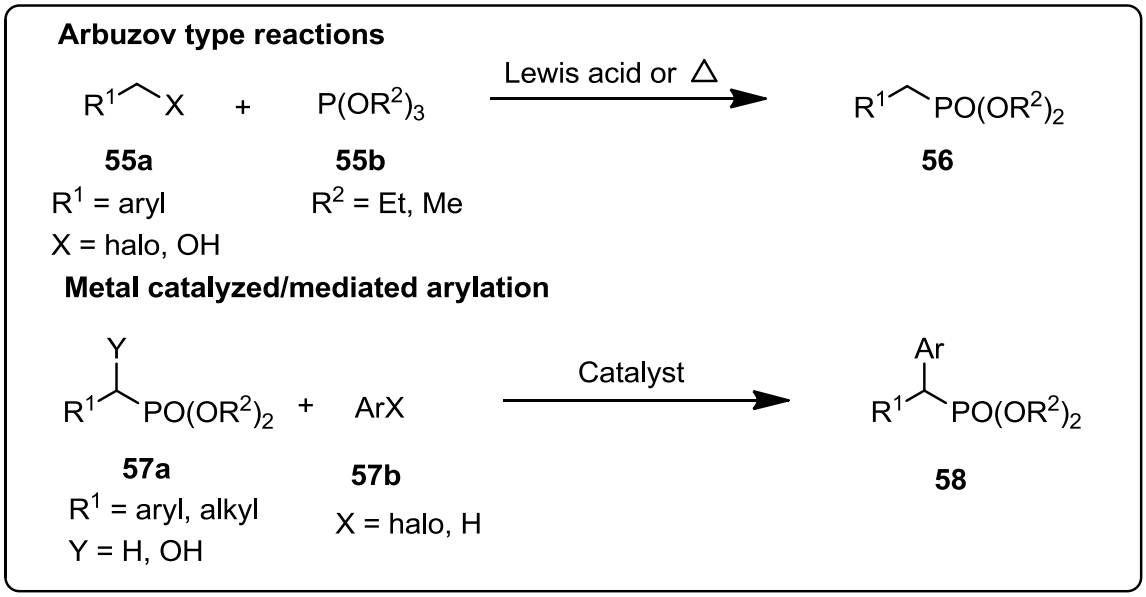


Figure 1: Some important diaryl- and triarylmethyl phosphonates

2.3) Literature overview on the synthesis of arylated methyl phosphonates

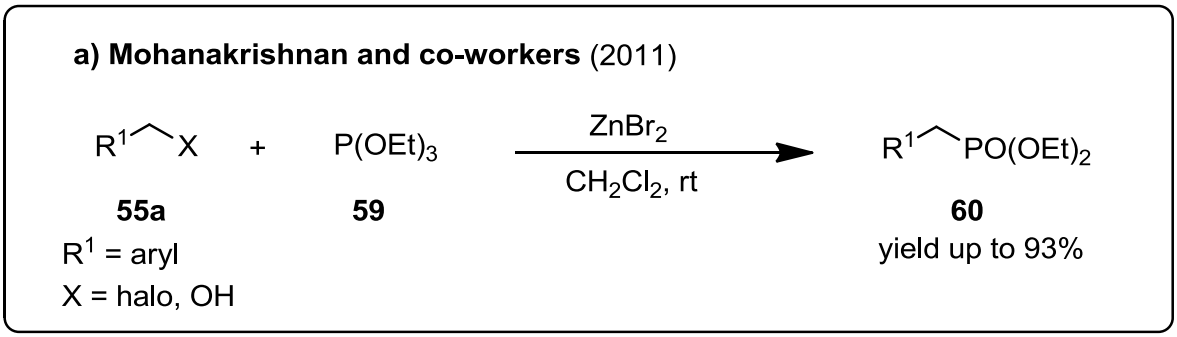
Due to their widespread utility organophosphorous compounds have been received escalating attention from synthetic chemists. Despite several methods developed for the introduction of phosphate or phosphonate groups in organic compounds,[38] only a handful of

methods available for the synthesis of arylated-methyl phosphonates, particularly diaryl- and triarylmethyl phosphonates. The most commonly used approaches include Michaelis–Arbuzov type reactions[39] and the transition-metal catalyzed/mediated arylation of alkyl phosphonates (Scheme 14).



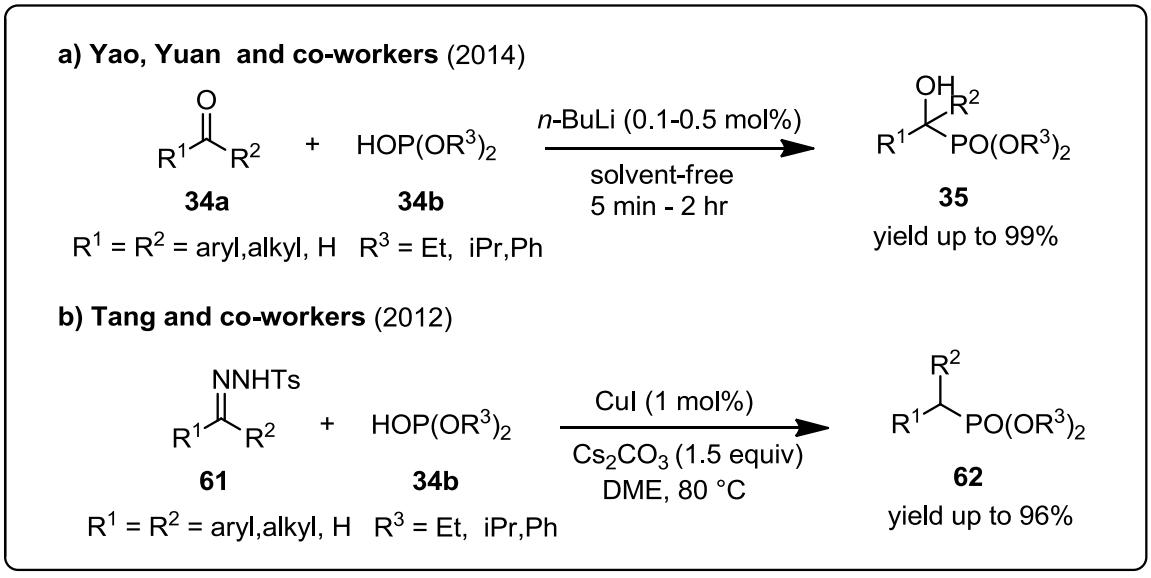
Scheme 14: General routes for the synthesis of arylated-methyl phosphonates

In 2011, Mohanakrishnan and co-workers reported the synthesis of arylmethyl and heteroarylmethyl phosphonate ester derivatives (**60**) through Lewis acid mediated Michaelis–Arbuzov reaction between arylmethyl halides/alcohols (**55a**) and triethyl phosphite (**59**).[40] This protocol worked well for all the arylmethyl halides (**55a**) including electron-withdrawing arylmethyl halides, except 3-chloromethylindole, in up to 93% yield (Scheme 15).



Scheme 15: Lewis acid mediated Michaelis–Arbuzov type reactions

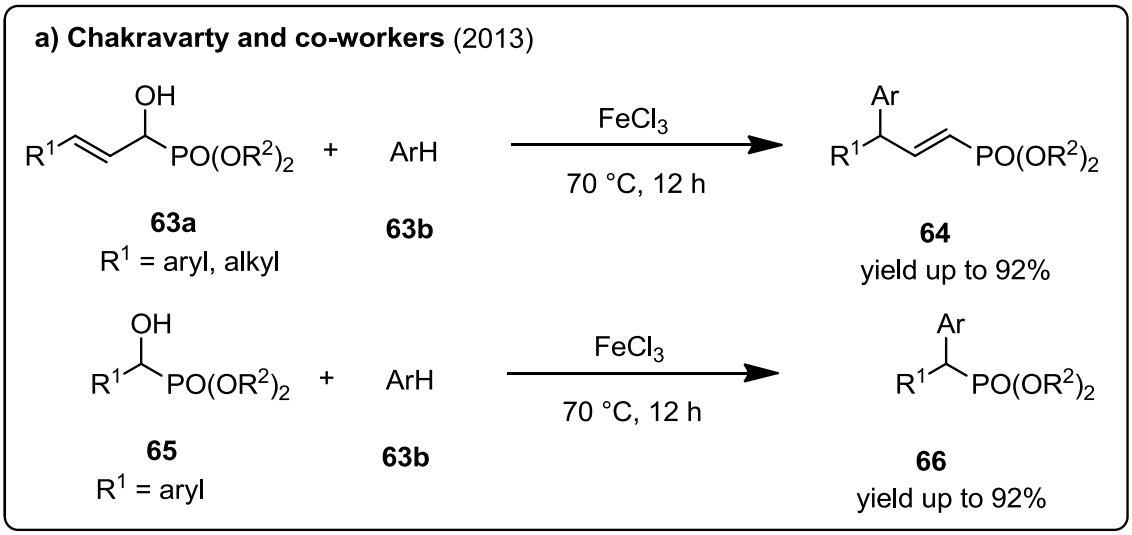
Despite the widespread scope of traditional Michaelis–Arbuzov method, the harsh reaction conditions and low stability of trivalent phosphorus compounds limit the synthetic utility of these reactions. In order to overcome these limitations, recently, many transition-metal-catalyzed strategies have been emerged. Yuan and co-workers introduced the organic alkali metal compounds as pre-catalyst for solvent-free hydrophosphonylation of aldehydes and ketones (**34a**).[41] The wide range of *α*-hydroxy phosphonates (**35**) were accessed in good yields by treating aldehydes and ketones (**34a**) with dialkyl phosphites (**34b**) (a, Scheme 16). In 2012, Tang's group published a fascinating ligand free copper-catalyzed addition of dialkyl phosphite (**34b**) to the *N*-tosylhydrazones (**61**) for the synthesis of aryl- and alkyl-methyl phosphonates (**62**) in up to 96% yield.[42] The author proposed that the reaction proceeds through Cu-carbene complex intermediate, a result of the combination of copper and *in situ* generated diazo compound from base mediated thermolysis of *N*-tosylhydrazone (**61**) (b, Scheme 16).



Scheme 16: Hydrophosphonylation of aldehydes, ketones and imines

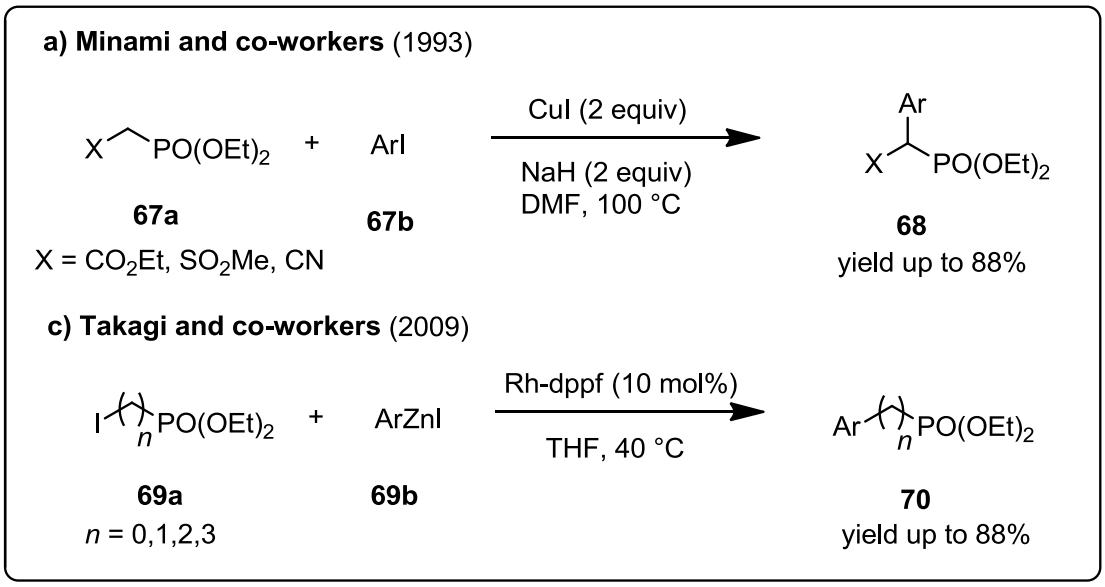
Chakravarty's group demonstrated a simple and efficient tool for the synthesis of *γ*-aryl-substituted vinylphosphonates (**64**) through $FeCl_3$-mediated Friedel−Crafts type reaction between vinylphosphonates (**64**) and arylated-methyl phosphonates (**66**).[43] This method afforded the corresponding *γ*-aryl-substituted vinylphosphonates (**64)** in up to 92% yield by extended conjugated arylation of *α*-hydroxy allylphosphonates (**63a**). The reaction was further extended

for the arylation of α-hydroxyphosphonates (**65**) to access diarylmethyl phosphonates (**66**) in up to 92% yield (Scheme 17).



Scheme 17: Friedel−Crafts type arylation of α-Hydroxyphosphonates

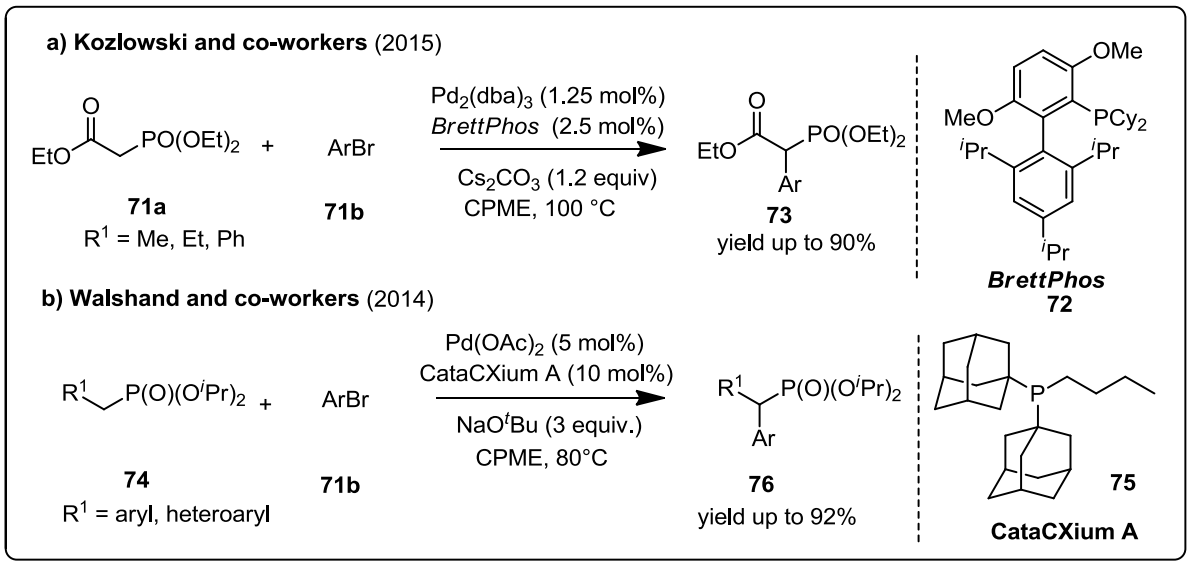
Minami and co-workers in 1993 published a copper-mediated arylation of alkyl phosphonates (**67a**) containing electron-withdrawing functionality at α-position with aryl halides (**67b**).[44] In the presence of excess amount of strong base, α-substituted alkyl phosphonates (**67a**) were converted to phosphinyl-stabilized carbanions, which further reacted with aryl halides (**67b**) to produce arylated-methyl phosphonates (**68**) in good yields (a, Scheme 18). In 2009, Takagi and co-workers developed Rh-catalyzed alkyl-aryl Negishi cross-coupling reaction between **69a** and phenylzinc iodide (**69b**).[45] The corresponding cross-coupled products (**70**) were accessed in moderate to excellent yields. In case of alkylphosphonates (**69a**), the reaction worked well when n = 1. Although β-hydride elimination was expected to be dominant when n = 2 or 3, the effective attachment of phosphoryl group of alkyl electrophiles to the metallic center of alkyl-Rh intermediates reduce the possibility of β-hydride elimination. The arylzinc iodide (**69b**) with ortho substitution suppressed the preferred cross-coupling reaction (b, Scheme 18).



Scheme 18: Metal-catlyzed/mediated α-arylation of different alkyl phosphonates

Furthermore, a few Pd-catalyzed approaches have also appeared in the literature. Recently, Kozlowski and co-workers demonstrated an efficient Pd-catalyzed α-arylation of phosphonoacetates (**71a**) with aryl halides (**71b**).[46] This protocol provided a diverse array of substrate scope; both electron-rich as well as electron-poor aryl halides (**71b**) including heteroaryl substrates worked smoothly. Both aryl bromides and aryl chlorides found to be the good substrates for this transformation. The corresponding arylmethyl phosphonates (**73**) were synthesized in up to 90% yield (a, Scheme 19).

Walsh's group disclosed a fascinating deprotonative cross-coupling approach for the synthesis of diarylmethyl phosphonates (**74**).[47] This approach involves Pd-catalyzed α-arylation of benzyl diisopropyl phosphonate (**74**) with aryl bromides (**71b**) to furnish subsequent diarylmethyl phosphonates (**76**) in up to 92% yield. Surprisingly, when diisopropyl phosphonate was replaced with more commonly used diethyl phosphonate, the yield reduced to 33%. Further yield was improved up to 64% by the slow addition of a base (b, Scheme 19).



Scheme 19: Pd-catlyzed α-arylation of different alkyl phosphonates

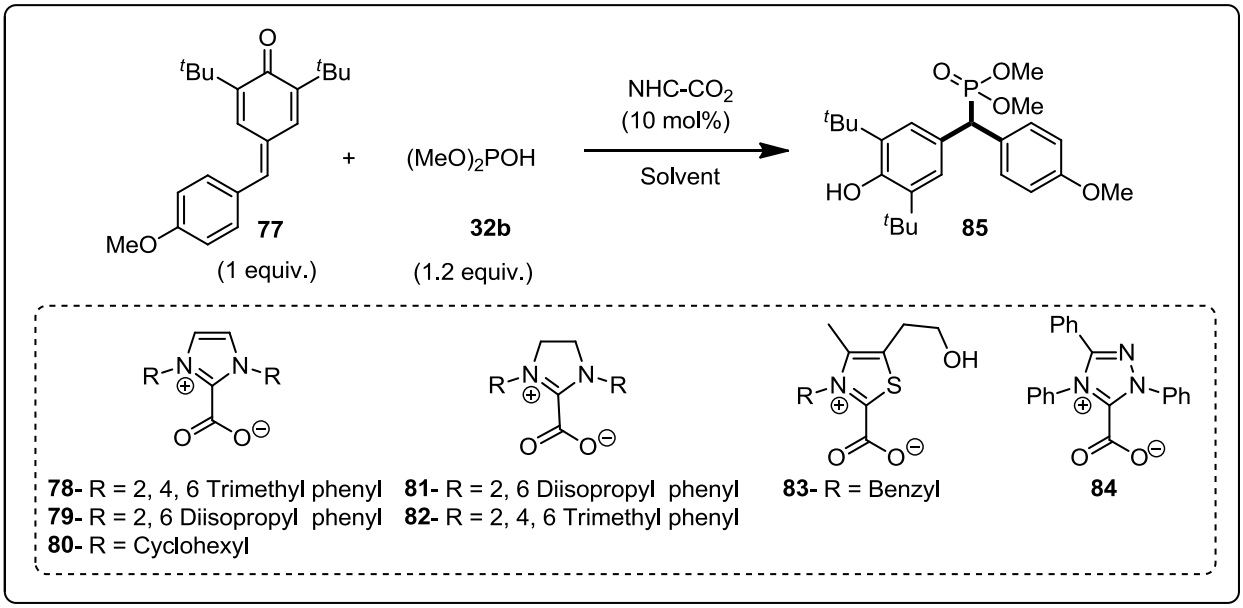
Although the transition-metal-catalyzed approach provides a wide substrate scope, the harsh reaction conditions and expensive metal catalysts made these transformations unattractive. Apart from these methods no other general approaches are available for the synthesis of both diaryl- and triaryl phosphonates in an atom-economical manner. Therefore, developing an alternative and more efficient method for the synthesis of these compounds, especially under organocatalytic conditions, would be more attractive and highly desired.

2.4) Results and Discussions

While developing new synthetic methodologies using N-heterocyclic carbene as a catalyst, we envisioned that it is possible to access diaryl- and triarylmethyl phosphonates through a 1,6-conjugate addition of dialkylphosphites to *p*-quinone methides using NHC as a Brønsted base catalyst. The vinylogous Michael reaction of dialkylphosphites to *p*-quinone methides (*p*-QMs) leading to diarylmethyl phosphonates using NHC as a Brønsted base is not divulged yet, which triggered us to investigate this reaction scrupulously.

The optimization studies for the reaction between *p*-QM (**77**) and dimethylphosphite (**32b**) were carried out using a wide range of NHC–CO_2 adducts (**78**–**84**) as pre-catalysts and the results are summarized in Table 1. It is well known in the literature that NHC–CO_2 could be

Table 1: **Optimization studies**[a]



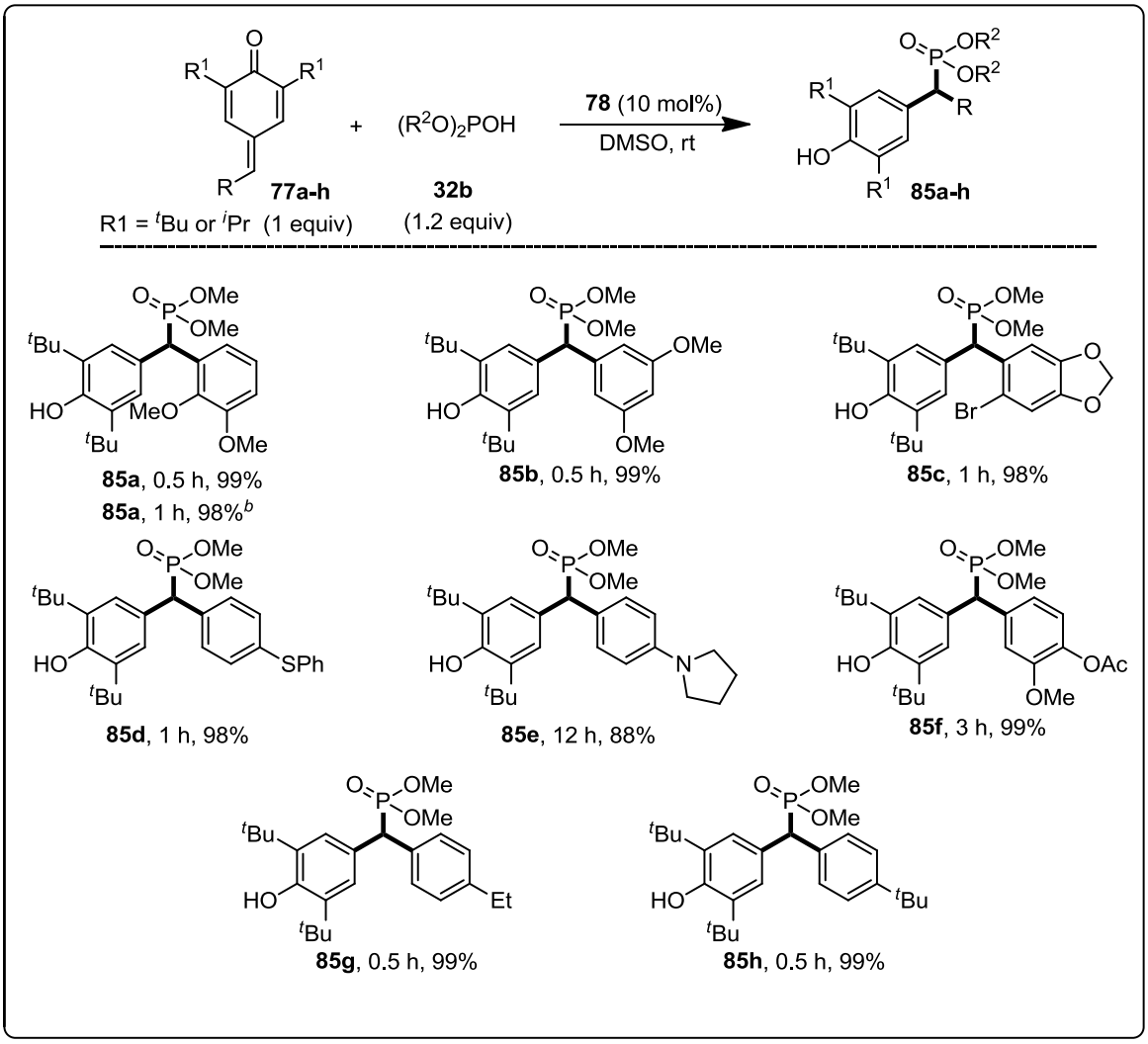
Entry	Pre-catalyst	Solvent	Time [h]	Yield [%]
1	**78**	THF	6	95
2	**78**	Et_2O	10	48
3	**78**	DCM	5	97
4	**78**	DCE	8	94
5	**78**	PhMe	10	70
6	**78**	**DMSO**	**1**	**99**
7	**79**	DMSO	2	80
8	**80**	DMSO	4	97
9	**81**	DMSO	6	90
10	**82**	DMSO	1	96
11	**83**	DMSO	6	95
12	**84**	DMSO	12	Trace
13	–	DMSO	24	0

[a]Reaction conditions: all reactions were carried out with 0.062 mmol of **77** in 0.3 mL of solvent at room temperature.

effectively used as a NHC precursor since the formation of NHC–CO_2 is a reversible reaction in solution under ambient conditions.[48] Another advantage of using NHC–CO_2 is that one can perform the reaction under neutral conditions without using any external base. Moreover, the solid form of these adducts are highly stable towards moisture and air, so the handling of these compounds becomes very convenient. Due to these inherent advantages, we have decided to use NHC–CO_2 adducts as pre-catalysts for our optimization studies. To our surprise, when the adduct **78** was used as a pre-catalyst, in the initial reaction itself, the expected diarylmethyl phosphonate **85** was obtained in 95% isolated yield after 6 h (entry 1). Encouraged by this observation, we extended the optimization studies using other solvents (entries 2–6). Out of many solvents tried, DMSO was found to be the best, because in this particular case, the reaction was completed within an hour and the product **85** was obtained in 99% isolated yield (entry 6).

Further standardization studies were performed in DMSO using other NHC precursors (**79**–**84**), but in all those cases, it was found that either the yield of **85** was inferior or the reaction took a long time for completion (entries 7–12). The use of 1.2 equivalents of **32b** with respect to **77** was found to be optimal. Importantly, no product was obtained without using the pre-catalyst, which clearly reveals that NHC is required for this transformation (entry 13).

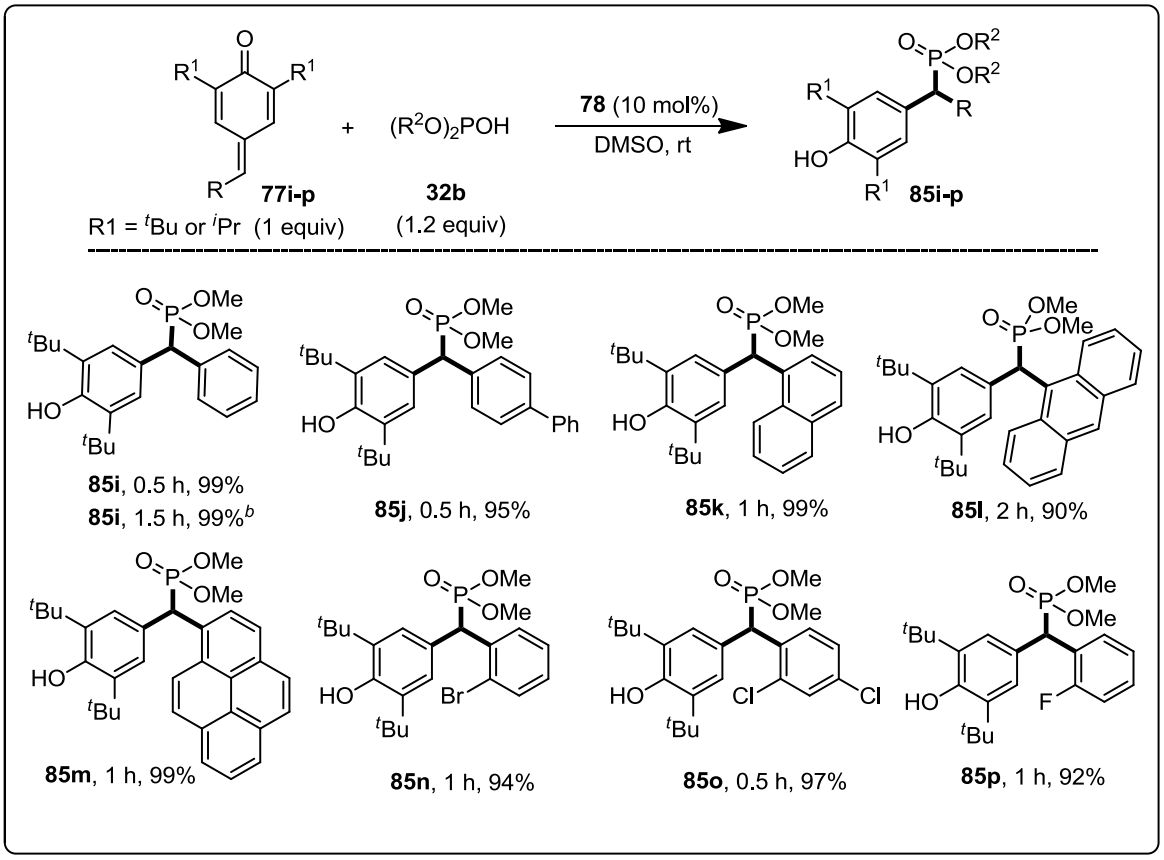
After establishing the optimal reaction conditions, the scope and limitations of this methodology were examined using a wide range of *p*-quinone methides and dialkylphosphites and the results are shown in Scheme 19-21. It is evident from Scheme 20-22 that irrespective of the electronic nature of the aryl group present in *p*-QMs, in most of the cases, the required products were obtained in excellent yield within a short reaction time. This protocol worked very well in the cases of *p*-QMs (**77a**–**h**) derived from electron rich aldehydes and in all those cases the desired unsymmetrical diarylmethyl phosphonates (**85a**–**h**) were obtained in excellent yields (88–99%).



[a]Reaction conditions: all reactions were carried out with 0.062 mmol of **77** in 0.3 mL of solvent at room temperature. [b] 5 mol% of **78** was used. Yields reported are isolated yields.

Scheme 20: Synthesis of diarylmethyl phosphonates [a]

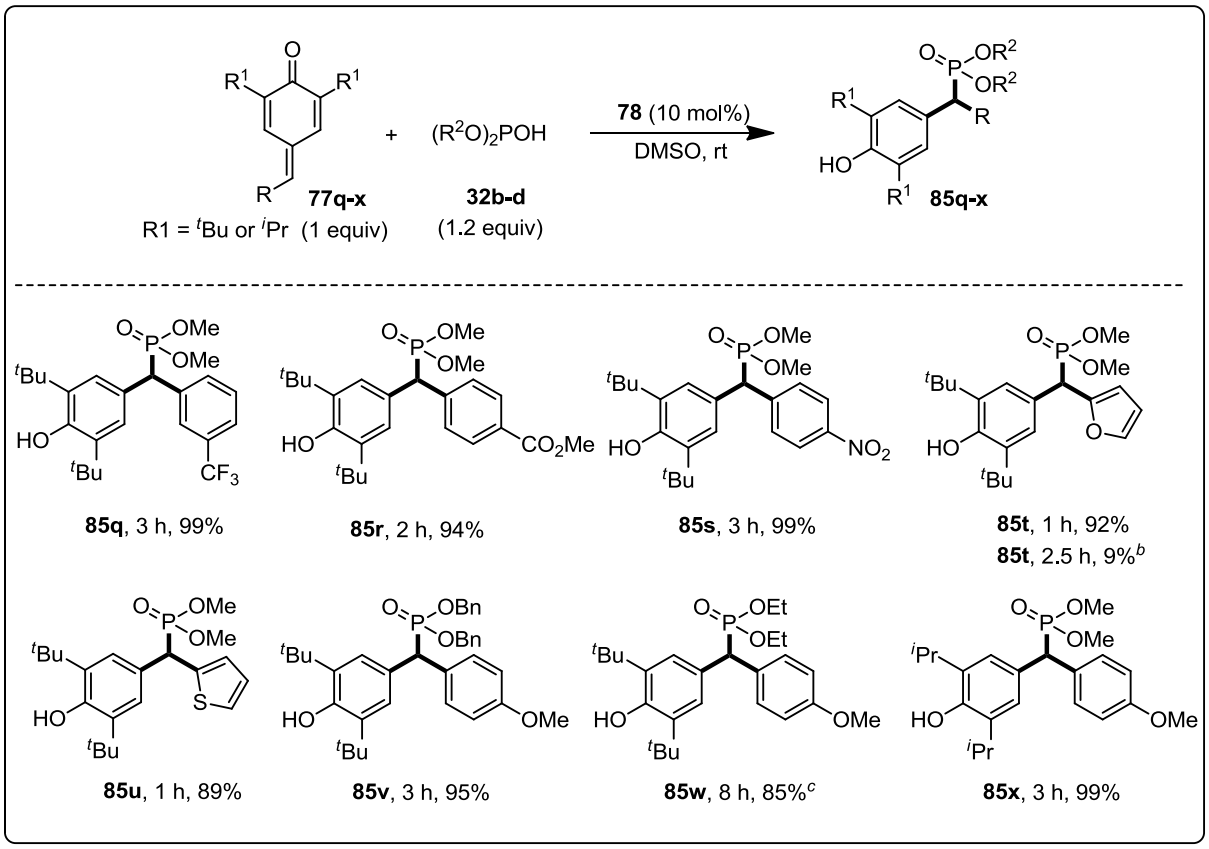
In the cases of *p*-QMs derived from a simple benzaldehyde (**77i**) and arylsubstituted (**77j**) or aryl-fused benzaldehydes (**77k**–**m**), the corresponding phosphonates (**85i**–**m**) were obtained in >90% isolated yield under the standard conditions. The *p*-QMs (**77n**–**p**) derived from halo-substituted benzaldehydes also underwent smooth conversion to their respective phosphonates (**85n**–**p**) in very high yields (Scheme 21).



[a]Reaction conditions: all reactions were carried out with 0.062 mmol of **77** in 0.3 mL of solvent at room temperature. [b] 5 mol% of **78** was used. Yields reported are isolated yields.

Scheme 21: Synthesis of diarylmethyl phosphonates [a]

The generality of this method was also examined with *p*-QMs derived from electron-poor aromatic aldehydes such as, 3-trifluoromethyl benzaldehyde (**77q**), methyl-4- formylbenzoate (**77r**) and 4-nitro-benzaldehyde (**77s**). In all the cases, the corresponding diarylmethyl phosphonates (**85q**–**s**) were isolated in >94% yields, albeit the reaction took a bit longer time for completion. This method was found to be very effective even for the synthesis of heteroaryl containing diarylmethyl phosphonates (**85t** & **85u**) (Scheme 22).



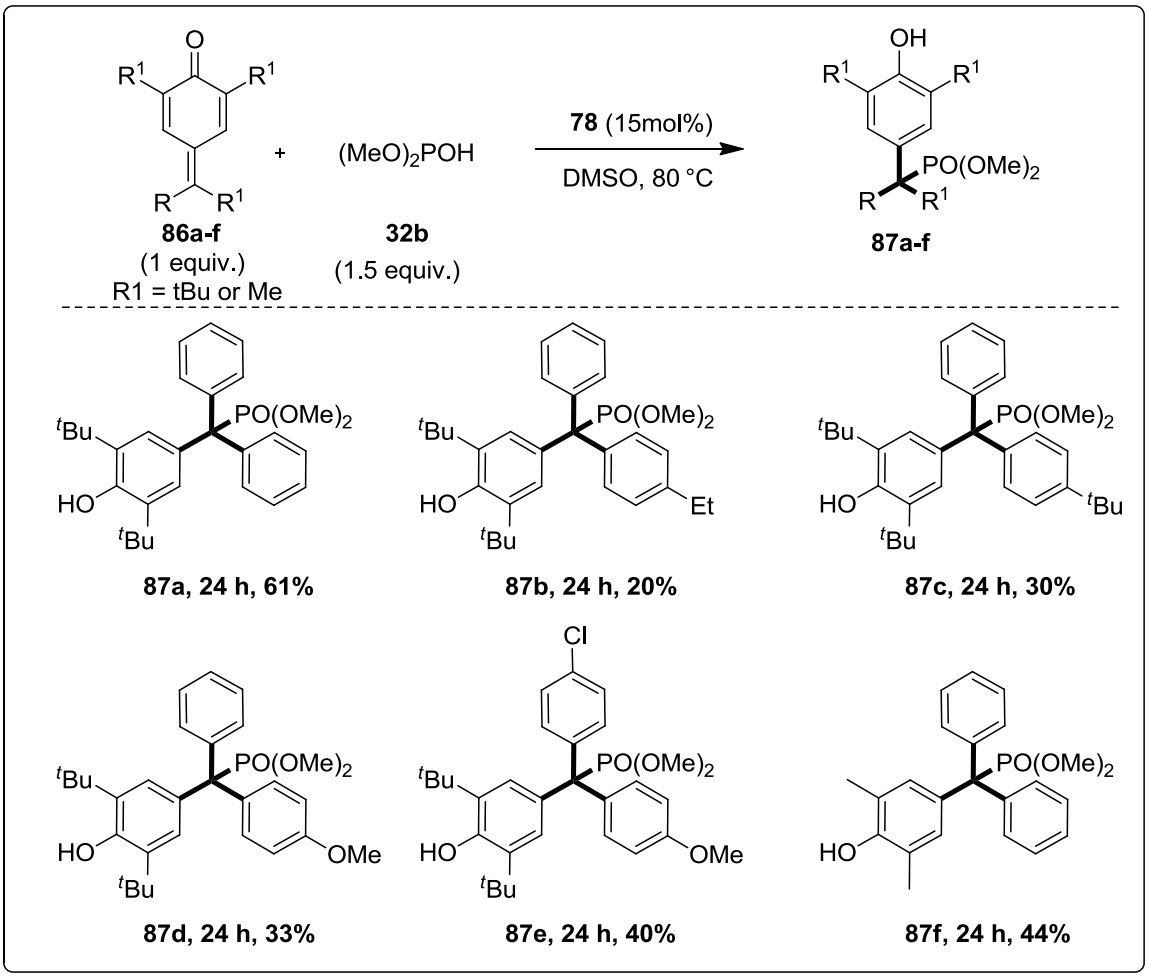
[a]Reaction conditions: all reactions were carried out with 0.062 mmol of **77** in 0.3 mL of solvent at room temperature. [b] 5 mol% of **78** was used. [c] CH_2Cl_2 was used as a solvent. Yields reported are isolated yields.

Scheme 22: Synthesis of diarylmethyl phosphonates [a]

Finally, the substrate scope was elaborated with other dialkylphosphites such as dibenzylphosphite (**32c**) and diethylphosphite (**32d**) using **77a** as an acceptor under optimised conditions. Though the reactions were a bit slow, both the phosphites were found to be efficient in generating the desired diarylmethyl phosphonates (**85v** & **85w**) in excellent yield. Further extension of the substrate scope was carried out using a *p*-QMs derived from 2,6-diisopropylphenol and 2,6-dimethylphenol. In the case of *p*-QM derived from 2,6-diisopropylphenol (**77x**), the required diarylmethylphosphonate **85x** was obtained in quantitative yield after 3 h, although the product **85x** was found to degrade slowly on isolation. However, only decomposition of the reaction mixture was observed when *p*-QM, derived from 2,6-

dimethylphenol, was subjected to 1,6- hydrophosphonylation reaction under the optimal conditions.

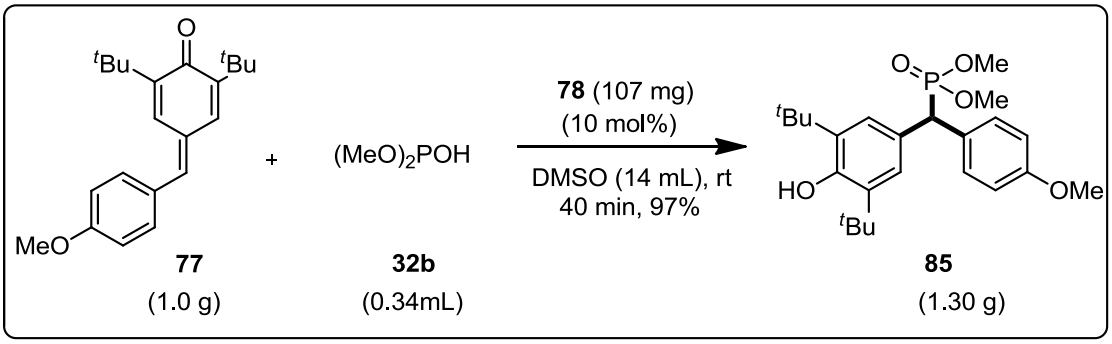
Next, we shifted our attention to develop a straightforward method to access unsymmetrical triarylmethyl phosphonates through 1,6-hydrophosphonylation of fuchsones.[49] Initially, we applied the optimised reaction conditions (entry 6, Table 1) to convert the fuchsone **86a** (R = R^1 = Ph and R^2 = ^{t}Bu) to its respective triarylmethyl phosphonate **87a**.



[a]Reaction conditions: all reactions were carried out with 0.054 mmol of **86** in 1 mL of solvent at 80 °C. Yields reported are isolated yields.

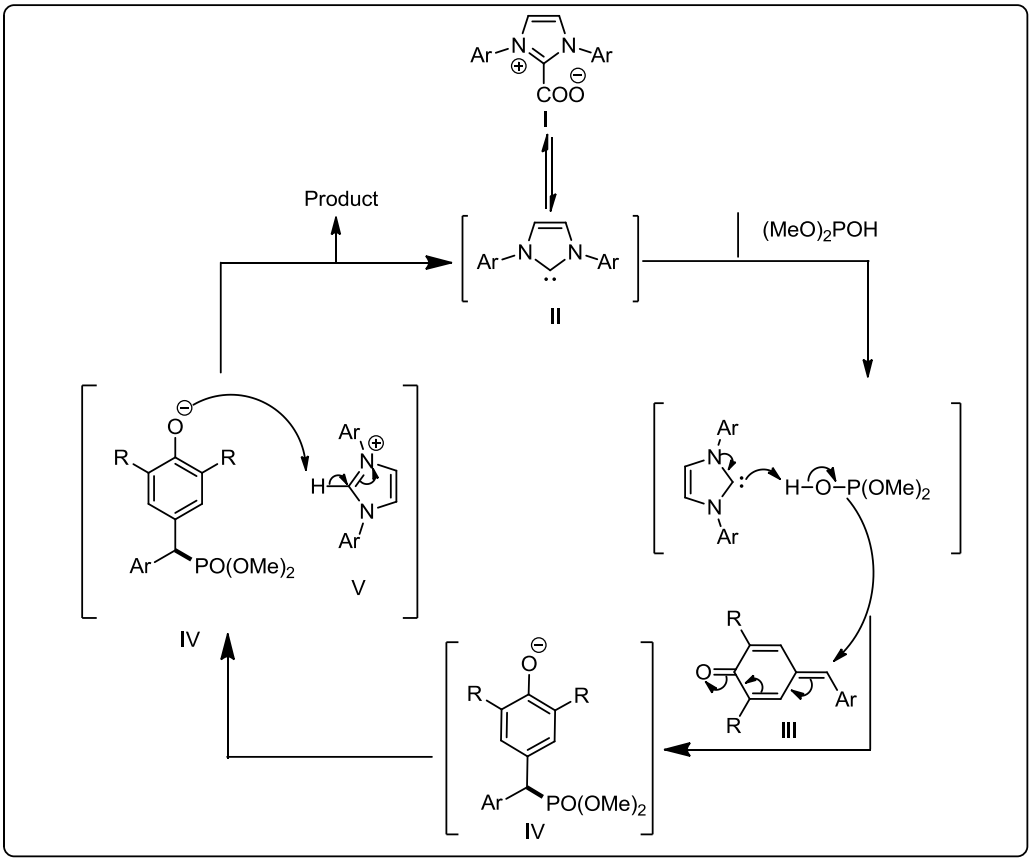
Scheme 23: Synthesis of triarylmethyl phosphonates [a]

Unfortunately, this reaction did not give the expected product at room temperature. Nevertheless, when the same reaction was carried out using 15 mol% of 4 at 80 °C for a longer period (24 h), the product **87a** was obtained in 61% isolated yield. A couple of optimisation studies were performed in other solvents, such as dioxane and DMF at higher temperature, but no improvement was observed in the chemical yield of the product. Therefore, further substrate scope studies were carried out in DMSO at 80 °C. Scheme 23 illustrates the scope and limitation of this transformation. Unlike *p*-QMs, fuchsones reacted with dialkylphosphites at slower rates, and the corresponding triarylmethyl phosphonates were obtained in relatively low yields. The sluggishness of the reaction is probably due to the involvement of steric factors, which shield the electrophilic centre of the fuchsone from the attack by dialkylphosphite. It is clear from Scheme 22 that a range of fuchsones, derived from a variety of diaryl ketones and 2,6-di(tert-butyl)phenol,[49a] underwent 1,6- hydrophosphonylation to generate the unsymmetrical triaryl phosphonates (**87b**–**e**) in less to moderate yields (20–40%). In the case of fuchsone **86f**, derived from 2,6-dimethylphenol, the product **87f** was obtained in 44% yield after 24 h. Since, the yield of the products was moderate or below reasonable in most of the cases, we did not elaborate the substrate scope further. To show the synthetic applicability of this protocol, the 1,6-hydrophosphonylation reaction was carried out on a gram scale using 77 under optimal conditions. As expected, the product **85** was obtained in 97% yield in 40 min (Scheme 24).



Scheme 24: Gram scale reaction

Based on the outcome of the reaction and similar kinds of literature reports, we proposed a plausible mechanism for this transformation (Scheme 25).



Scheme 25: Plausible mechanism

Initially, the NHC–CO_2 adduct (**I**) decomposes to free NHC (**II**), which abstracts the acidic proton of the dimethylphosphite and generates a dialkylphosphate anion and imidazolium salt (**V**). The dialkylphosphate anion then immediately reacts with *p*-QM (**III**) to generate intermediate **IV**, which then abstracts the acidic proton of the imidazolium salt **V** to produce the product with the expulsion of NHC (**II**).

2.5) Conclusion

We described in this article an atom economical and straight forward organocatalytic method for the construction of unsymmetrical diarylmethyl phosphonates through 1,6-hydrophosphonylation of *p*-quinone methides using N-heterocyclic carbene as a Brønsted base catalyst. This general protocol was also elaborated for the synthesis of unsymmetrical triarylmethyl phosphonates in moderate yields.

2.6) Experimental section

Experimental Section

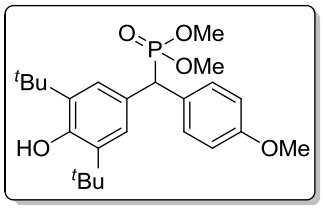
General methods

All reactions were carried out under an argon atmosphere in an oven dried vials. Solvents were dried over calcium hydride, distilled and stored with molecular sieves. Most of the reagents and starting materials were purchased from commercial sources and used as such. NHC precursors were prepared according to the literature procedure.[50] All *p*-quinone methides were prepared by following a literature procedure.[51] Melting points were recorded on SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C, ^{19}F and ^{31}P spectra were recorded in $CDCl_3$ (400, 100, 376 and 162 MHz respectively) on Bruker FT-NMR spectrometer. Chemical shift (δ) values are reported in parts per million relative to TMS (for ^{1}H and ^{13}C), $BF_3.Et_2O$ (for ^{19}F) and H_3PO_4:D_2O [85:15] (for ^{31}P). High resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Perkin–Elmer FTIR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent.

General procedure for the 1,6-hydrophosphonylation of *p*-quinone methides:

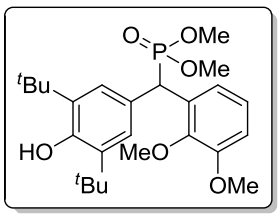
Anhydrous DMSO (0.3 mL) was added to the mixture of *p*-quinone methide (20 mg, 0.062 mmol), dimethyl phosphite (8 µL, 0.074 mmol) and NHC-CO_2 adduct **78** (2 mg, 0.0062 mmol) under argon atmosphere, and the resulting suspension was stirred at room temperature until *p*-quinone methide was completely consumed. The reaction was quenched by 5 ml of water and extracted with (5 x 3 mL) dichloromethane. Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and the residue was purified through silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]phosphonate (85)



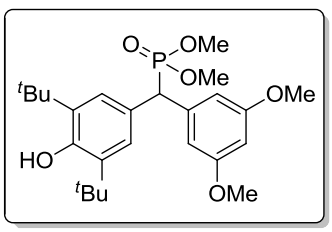
White solid; yield 99% (26.7 mg); R_f = 0.5; (50% EtOAc in hexane); m.p. 114–116 °C; FT-IR (KBr) 3631, 2954, 2918, 1511, 1435, 1252, 1034, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.6, 1.6 Hz, 2H), 7.29 (d, J_{H-P} = 1.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.14 (s, 1H), 4.31 (d, J_{H-P} = 25.4 Hz, 1H), 3.78 (s, 3H), 3.54 (d, J_{H-P} = 7.4 Hz, 3H), 3.52 (d, J_{H-P} = 7.3 Hz, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (d, J_{C-P} = 2.1 Hz), 153.0 (d, J_{C-P} = 2.5 Hz), 136.0 (d, J_{C-P} = 1.4 Hz), 130.6 (d, J_{C-P} = 8.0 Hz), 129.3 (d, J = 5.2 Hz), 127.2 (d, J_{C-P} = 5.0 Hz), 126.1 (d, J_{C-P} = 8.0 Hz), 114.1 (d, J_{C-P} = 1.1 Hz), 55.3, 53.5 (d, J_{C-P} = 7.0 Hz), 53.3 (d, J_{C-P} = 7.1 Hz), 49.8 (d, J_{C-P} = 137.1 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.47; HRMS (ESI): *m/z* calcd for $C_{24}H_{36}O_5P$ $[M+H]^+$: 435.2300; found: 435. 2283.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(2,3-dimethoxyphenyl)methyl]-phosphonate (85a)



Pale yellow gummy solid; yield 99% (28.8 mg); R_f = 0.5; (50% EtOAc in hexane); FT-IR (KBr) 3625, 2954, 1511, 1460, 1435, 1250, 1160, 1060, 1035, 828, 510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 1H), 7.36 (d, J_{H-P} = 1.7 Hz, 2H), 7.06 (t, J = 8.1 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 5.11 (s, 1H), 5.06 (d, J_{H-P} = 24.8 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.56 (d, J_{H-P} = 9.2 Hz, 3H), 3.53 (d, J_{H-P} = 9.1 Hz, 3H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0 (d, J_{C-P} = 2.4 Hz), 152.7, 146.5 (d, J_{C-P} = 10.8 Hz), 135.9 (d, J_{C-P} = 1.4 Hz), 131.6 (d, J_{C-P} = 2.9 Hz), 127.1 (d, J_{C-P} = 5.2 Hz), 126.3 (d, J_{C-P} = 7.9 Hz), 124.1 (d, J_{C-P} = 2.1 Hz), 121.9 (d, J_{C-P} = 4.9 Hz), 111.1, 60.9, 55.8, 53.5 (d, J_{C-P} = 6.9 Hz), 53.2 (d, J_{C-P} = 7.1 Hz), 41.5 (d, J_{C-P} = 139.9 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.87; HRMS (ESI): *m/z* calcd for $C_{25}H_{38}O_6P$ $[M+H]^+$: 465.2406; found: 465.2400.

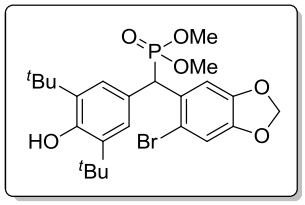
Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(3,5-dimethoxyphenyl)methyl]-phosphonate (85b)



Pale yellow gummy solid; yield 99% (29.0 mg); R_f = 0.4; (50% EtOAc in hexane); FT-IR (KBr) 3627, 2955, 1596, 1462, 1435, 1249, 1159, 1035, 828, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

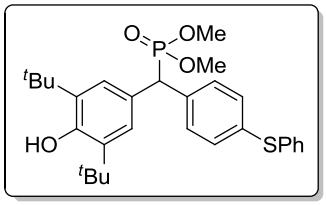
7.32 (d, J_{H-P} = 1.9 Hz, 2H), 6.72 (t, J_{H-P} = 2.0 Hz, 2H), 6.35 (q, J = 2.2 Hz, 1H), 5.16 (s, 1H), 4.27 (d, J_{H-P} = 25.1 Hz, 1H), 3.78 (s, 6H), 3.58 (d, J_{H-P} = 10.7 Hz, 3H), 3.51 (d, J_{H-P} = 10.6 Hz, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8 (d, J_{C-P} = 1.1 Hz), 153.2 (d, J_{C-P} = 2.5 Hz), 139.3 (d, J_{C-P} = 4.6 Hz), 135.9 (d, J_{C-P} = 1.5 Hz), 126.6 (d, J_{C-P} = 5.7 Hz), 126.1 (d, J_{C-P} = 7.9 Hz), 107.6 (d, J_{C-P} = 8.1 Hz), 99.3 (d, J_{C-P} = 2.0 Hz), 55.4, 53.6 (d, J_{C-P} = 7.0 Hz), 53.4 (d, J_{C-P} = 7.2 Hz), 50.8 (d, J_{C-P} = 136.8 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.93; HRMS (ESI): *m/z* calcd for $C_{25}H_{38}O_6P$ $[M+H]^+$: 465.2406; found: 465.2413.

Dimethyl{[6-bromobenzo(d)(1,3)dioxol-5-yl](3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl} phosphonate (85c)



Pale yellow solid; yield 98% (32.4 mg); R_f = 0.6; (50% EtOAc in hexane); m.p. 188–190 °C; FT-IR (KBr) 3634, 2956, 1481, 1260, 1037, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 1.9 Hz, 1H), 7.37 (d, J_{H-P} = 1.6 Hz, 2H), 6.99 (d, J = 1.2 Hz, 1H), 5.97 (d, J = 1.4 Hz, 1H), 5.94 (d, J = 1.4 Hz, 1H), 5.16 (s, 1H), 4.98 (d, J_{H-P} = 25.7 Hz, 1H), 3.62 (d, J_{H-P} = 10.7 Hz, 3H), 3.54 (d, J_{H-P} = 10.6 Hz, 3H), 1.42 (s, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2 (d, J_{C-P} = 2.1 Hz), 147.7 (d, J_{C-P} = 2.1 Hz), 147.5 (d, J_{C-P} = 2.0 Hz), 136.1 (d, J_{C-P} = 1.0 Hz), 130.2 (d, J_{C-P} = 2.8 Hz), 126.5 (d, J_{C-P} = 4.5 Hz), 126.2 (d, J_{C-P} = 8.3 Hz), 115.5 (d, J_{C-P} = 13.5 Hz), 112.8, 110.5 (d, J_{C-P} = 4.7 Hz), 101.9, 53.7 (d, J_{C-P} = 6.8 Hz), 53.2 (d, J_{C-P} = 7.1 Hz), 47.9 (d, J_{C-P} = 139.7 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.89; HRMS (ESI): *m/z* calcd for $C_{24}H_{33}BrO_6P$ $[M+H]^+$: 527.1198; found: 527.1213.

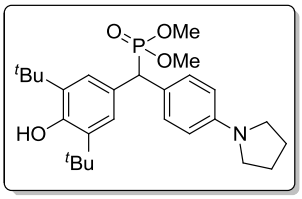
Dimethyl{(3,5-di-*tert*-butyl-4-hydroxyphenyl)[4-(phenylthio)phenyl]methyl}-phosphonate (85d)



Yellow gummy solid; yield 98% (31.5 mg); R_f = 0.6; (50% EtOAc in hexane); FT-IR (KBr) 3634, 2955, 1435, 1249, 1059, 1035, 821, 557 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 8.3, 1.7 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.30 – 7.21 (m, 7H), 5.16 (s, 1H), 4.33 (d, J_{H-P} = 25.4 Hz, 1H), 3.57 (d, J_{H-P} = 10.7 Hz, 3H), 3.52 (d, J_{H-P} = 10.6 Hz, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2 (d, J_{C-P} = 2.4 Hz), 136.2 (d, J_{C-P} = 5.0 Hz), 136.1 (d, J_{C-P} = 1.4 Hz), 135.6, 134.7 (d, J_{C-P} = 2.5 Hz), 131.4, 131.0 (d, J_{C-P} = 1.3 Hz), 130.3 (d, J_{C-P} = 7.9 Hz), 129.3, 127.3, 126.5 (d, J_{C-P} = 5.5 Hz), 126.2 (d, J_{C-P} = 7.9 Hz), 53.7 (d, J_{C-P} = 7.1 Hz), 53.4 (d, J_{C-P} =

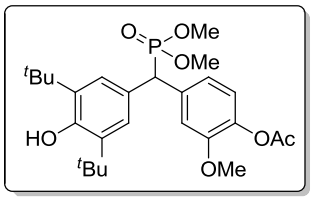
7.1 Hz), 50.3 (d, $J_{C\text{-}P}$ = 138.2 Hz), 34.6, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.80; HRMS (ESI): *m/z* calcd for $C_{29}H_{36}O_2PS$ $[M\text{-}H]^+$: 511.2071; found: 511.2050.

Dimethyl{(3,5-di-*tert*-butyl-4-hydroxyphenyl)[4-(pyrrolidin-1-yl)phenyl]methyl}-phosphonate (85e)



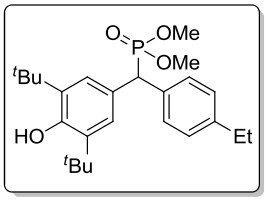
Red gummy solid; yield 88% (25.5 mg); R_f = 0.4; (50% EtOAc in hexane); FT-IR (KBr) 3637, 2954, 1614, 1520, 1435, 1374, 1249, 1060, 1035, 837, 764, 552 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 8.5, 1.6 Hz, 2H), 7.31 (d, $J_{H\text{-}P}$ = 1.6 Hz, 2H), 6.52 (d, J = 8.5 Hz, 2H), 5.09 (s, 1H), 4.25 (d, $J_{H\text{-}P}$ = 25.5 Hz, 1H), 3.54 (d, $J_{H\text{-}P}$ = 2.4 Hz, 3H), 3.51 (d, $J_{H\text{-}P}$ = 2.4 Hz, 3H), 3.25 (t, J = 6.4 Hz, 4H), 1.99 – 1.96 (m, 4H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9 (d, $J_{C\text{-}P}$ = 2.4 Hz), 147.1 (d, $J_{C\text{-}P}$ = 1.5 Hz), 135.8 (d, $J_{C\text{-}P}$ = 1.3 Hz), 130.2 (d, $J_{C\text{-}P}$ = 7.9 Hz), 127.8 (d, $J_{C\text{-}P}$ = 4.5 Hz), 126.0 (d, $J_{C\text{-}P}$ = 8.1 Hz), 123.5 (d, $J_{C\text{-}P}$ = 5.5 Hz), 111.8 (d, $J_{C\text{-}P}$ = 1.0 Hz), 53.4 (d, $J_{C\text{-}P}$ = 1.6 Hz), 53.3 (d, $J_{C\text{-}P}$ = 1.5 Hz), 49.8 (d, $J_{C\text{-}P}$ = 136.6 Hz), 47.7, 34.5, 30.4, 25.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.09; HRMS (ESI): *m/z* calcd for $C_{27}H_{41}NO_4P$ $[M+H]^+$: 474.2773; found: 474.2786.

4-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(dimethoxyphosphoryl)methyl]-2-methoxyphenylacetate (85f)



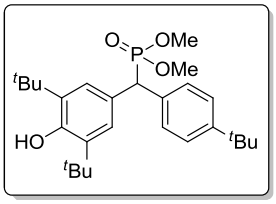
Pale yellow solid; yield 99% (30.5 mg); R_f = 0.3; (50% EtOAc in hexane); m.p. 43–45 °C; FT-IR (KBr) 3637, 2956, 1767, 1511, 1435, 1275, 1200, 1126, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.31 (d, $J_{H\text{-}P}$ = 1.8 Hz, 2H), 7.22 (t, J = 1.8 Hz, 1H), 7.07 (dt, J = 8.2, 1.9 Hz, 1H), 6.97 (dd, J = 8.2, 1.0 Hz, 1H), 5.17 (s, 1H), 4.32 (d, $J_{H\text{-}P}$ = 25.2 Hz, 1H), 3.83 (s, 3H), 3.56 (d, $J_{H\text{-}P}$ = 10.7 Hz, 3H), 3.50 (d, $J_{H\text{-}P}$ = 10.6 Hz, 3H), 2.29 (s, 3H), 1.26 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1 (d, $J_{C\text{-}P}$ = 1.0 Hz), 153.2 (d, $J_{C\text{-}P}$ = 2.5 Hz), 150.9 (d, $J_{C\text{-}P}$ = 1.3 Hz), 138.8 (d, $J_{C\text{-}P}$ = 2.6 Hz), 136.1 (d, $J_{C\text{-}P}$ = 1.4 Hz), 136.0 (d, $J_{C\text{-}P}$ = 4.8 Hz), 126.5 (d, $J_{C\text{-}P}$ = 5.4 Hz), 126.1 (d, $J_{C\text{-}P}$ = 7.9 Hz), 122.7 (d, $J_{C\text{-}P}$ = 1.3 Hz), 121.8 (d, $J_{C\text{-}P}$ = 8.5 Hz), 113.7 (d, $J_{C\text{-}P}$ = 7.6 Hz), 55.9, 53.7 (d, $J_{C\text{-}P}$ = 7.0 Hz), 53.3 (d, $J_{C\text{-}P}$ = 7.1 Hz), 50.4 (d, $J_{C\text{-}P}$ = 137.3 Hz), 34.5, 30.4, 20.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.80; HRMS (ESI): *m/z* calcd for $C_{26}H_{38}O_7P$ $[M+H]^+$: 493.2355; found: 493.2344.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-ethylphenyl)methyl]phosphonate (85g)



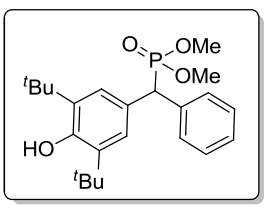
Pale yellow gummy solid; yield 99% (26.6 mg); R_f = 0.6; (50% EtOAc in hexane); FT-IR (KBr) 3639, 2956, 1512, 1435, 1252, 1061, 1035, 751cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 8.2, 1.8 Hz, 2H), 7.32 (d, $J_{H\text{-}P}$ = 1.8 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 5.14 (s, 1H), 4.33 (d, $J_{H\text{-}P}$ = 25.3 Hz, 1H), 3.52 (apparent t, $J_{H\text{-}P}$ = 10.8 Hz, 6H), 2.61 (q, J = 7.6 Hz, 2H), 1.41 (s, 18H), 1.21 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1 (d, $J_{C\text{-}P}$ = 2.5 Hz), 143.1 (d, $J_{C\text{-}P}$ = 2.4 Hz), 135.9 (d, $J_{C\text{-}P}$ = 1.4 Hz), 134.4 (d, $J_{C\text{-}P}$ = 5.1 Hz), 129.3 (d, $J_{C\text{-}P}$ = 7.9 Hz), 128.2 (d, $J_{C\text{-}P}$ = 1.3 Hz), 127.1 (d, $J_{C\text{-}P}$ = 5.2 Hz), 126.2 (d, $J_{C\text{-}P}$ = 8.0 Hz), 53.5 (d, $J_{C\text{-}P}$ = 7.0 Hz), 53.3 (d, $J_{C\text{-}P}$ = 7.2 Hz), 50.4 (d, $J_{C\text{-}P}$ = 136.7 Hz), 34.5, 30.4, 28.6, 15.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.44; HRMS (ESI): *m/z* calcd for $C_{25}H_{38}O_4P$ $[M+H]^+$: 433.2507; found: 433.2506.

Dimethyl{[4-(*tert*-butyl)phenyl](3,5-di-tert-butyl-4-hydroxyphenyl)methyl}phosphonate (85h)



Pale yellow solid; yield 99% (28.5 mg); R_f = 0.7; (50% EtOAc in hexane); m.p. 46–48°C; FT-IR (KBr) 3640, 2956, 1435, 1251, 1061, 1035, 766, 571cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.4, 1.8 Hz, 2H), 7.38 – 7.30 (m, 4H), 5.14 (s, 1H), 4.33 (d, $J_{H\text{-}P}$ = 25.3 Hz, 1H), 3.54 (d, $J_{H\text{-}P}$ = 10.6 Hz, 3H), 3.50 (d, $J_{H\text{-}P}$ = 10.5 Hz, 3H), 1.42 (s, 18H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1 (d, $J_{C\text{-}P}$ = 2.4 Hz), 149.9 (d, $J_{C\text{-}P}$ = 2.5 Hz), 136.0 (d, $J_{C\text{-}P}$ = 1.4 Hz), 134.1 (d, $J_{C\text{-}P}$ = 5.2 Hz), 129.0 (d, $J_{C\text{-}P}$ = 7.8 Hz), 127.0 (d, $J_{C\text{-}P}$ = 5.3 Hz), 126.2 (d, $J_{C\text{-}P}$ = 8.1 Hz), 125.6 (d, $J_{C\text{-}P}$ = 1.4 Hz), 53.6 (d, $J_{C\text{-}P}$ = 7.0 Hz), 53.2 (d, $J_{C\text{-}P}$ = 7.2 Hz), 50.3 (d, $J_{C\text{-}P}$ = 137.4 Hz), 34.54, 34.51, 31.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.46; HRMS (ESI): *m/z* calcd for $C_{27}H_{42}O_4P$ $[M+H]^+$: 461.2821; found: 461.2832.

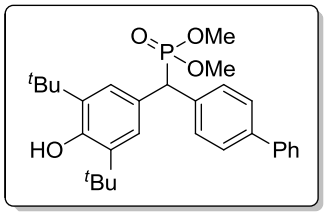
Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl]phosphonate (85i)



Pale yellow gummy solid; yield 99% (25.1 mg); R_f = 0.5; (50% EtOAc in hexane); FT-IR (KBr) 3637, 2955, 1435,1254, 1058, 1032, 751, 540cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.54–7.51 (m, 2H), 7.35–7.31 (m, 4H),

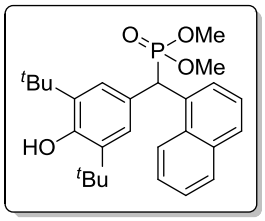
7.27–7.22 (m, 1H), 5.16 (s, 1H), 4.36 (d, $J_{H\text{-}P}$ = 25.3 Hz, 1H), 3.54 (d, $J_{H\text{-}P}$ = 3.7 Hz, 3H), 3.52 (d, $J_{H\text{-}P}$ = 3.6 Hz, 3H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1 (d, $J_{C\text{-}P}$ = 2.5 Hz), 137.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 136.0 (d, $J_{C\text{-}P}$ = 1.4 Hz), 129.5 (d, $J_{C\text{-}P}$ = 8.0 Hz), 128.7 (d, $J_{C\text{-}P}$ = 1.2 Hz), 127.2 (d, $J_{C\text{-}P}$ = 2.2 Hz), 126.8 (d, $J_{C\text{-}P}$ = 5.4 Hz), 126.2 (d, $J_{C\text{-}P}$ = 8.0 Hz), 53.5 (d, $J_{C\text{-}P}$ = 7.0 Hz), 53.3 (d, $J_{C\text{-}P}$ = 7.1 Hz), 50.7 (d, $J_{C\text{-}P}$ = 136.8 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.19; HRMS (ESI): *m/z* calcd for $C_{23}H_{34}O_4P$ $[M+H]^+$: 405.2194; found: 405.2188.

Dimethyl[(1,1'-biphenyl)-4-yl(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)phosphonate (85j)



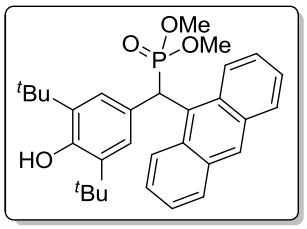
Pale yellow solid; yield 95% (28.3 mg); R_f = 0.6; (50% EtOAc in hexane); m.p. 62–63 °C; FT-IR (KBr) 3634, 2955, 1488, 1435, 1249, 1060, 1035, 736, 529 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.63–7.56 (m, 6H), 7.45–7.41 (m, 2H), 7.36 (d, $J_{H\text{-}P}$ = 1.8 Hz, 2H), 7.05–7.01 (m, 1H), 5.18 (s, 1H), 4.42 (d, $J_{H\text{-}P}$ = 25.3 Hz, 1H), 3.59 (d, $J_{H\text{-}P}$ = 10.7 Hz, 3H), 3.55 (d, $J_{H\text{-}P}$ = 10.6 Hz, 3H), 1.44 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2 (d, $J_{C\text{-}P}$ = 2.4 Hz), 140.8 (d, $J_{C\text{-}P}$ = 1.0 Hz), 139.9 (d, J = 2.3 Hz), 136.3 (d, J = 5.0 Hz), 136.1 (d, J = 1.4 Hz), 129.8 (d, $J_{C\text{-}P}$ = 7.9 Hz), 128.9, 127.4 (d, $J_{C\text{-}P}$ = 1.3 Hz), 127.3, 127.1, 126.8 (d, $J_{C\text{-}P}$ = 5.4 Hz), 126.2 (d, $J_{C\text{-}P}$ = 7.9 Hz), 53.6 (d, $J_{C\text{-}P}$ = 7.0 Hz), 53.3 (d, $J_{C\text{-}P}$ = 7.1 Hz), 50.4 (d, $J_{C\text{-}P}$ = 137.0 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.12; HRMS (ESI): *m/z* calcd for $C_{29}H_{38}O_4P$ $[M+H]^+$: 481.2507; found: 481.2506.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(naphthalen-1-yl)methyl]phosphonate (85k)



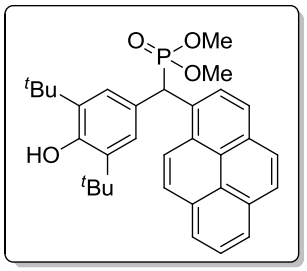
Pale yellow solid; yield 99% (28.1 mg); R_f = 0.6; (50% EtOAc in hexane); m.p. 148–150 °C; FT-IR (KBr) 3627, 2955, 1435, 1246, 1060, 1037, 777, 510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.23–8.20 (m, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.85 (dd, J = 8.0, 1.2 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.55–7.50 (m, 2H), 7.48–7.44 (m,1H), 7.38 (d, $J_{H\text{-}P}$ = 2.1 Hz, 2H), 5.24 (d, $J_{H\text{-}P}$ = 26.5 Hz, 1H), 5.13 (s, 1H), 3.54 (d, $J_{H\text{-}P}$ = 10.6 Hz, 3H), 3.48 (d, $J_{H\text{-}P}$ = 10.7 Hz, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1 (d, $J_{C\text{-}P}$ = 2.8 Hz), 135.9 (d, $J_{C\text{-}P}$ = 2.0 Hz), 134.3, 133.1(d, $J_{C\text{-}P}$ = 2.8 Hz),131.8, 131.7, 129.2, 127.9 (d, $J_{C\text{-}P}$ = 1.6 Hz), 127.5 (d, $J_{C\text{-}P}$ = 6.4 Hz), 126.5, 126.4, 126.3, 125.6 (d, $J_{C\text{-}P}$ = 2.4 Hz), 123.2, 53.6 (d, $J_{C\text{-}P}$ = 7.0 Hz), 53.3 (d, $J_{C\text{-}P}$ = 7.2 Hz), 45.0 (d, $J_{C\text{-}P}$ = 139.3 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.87; HRMS (ESI): *m/z* calcd for $C_{27}H_{36}O_4P$ $[M+H]^+$: 455.2351; found: 455.2370.

Dimethyl[anthracen-9-yl(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]phosphonate (85l)



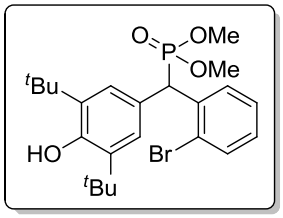
Pale yellow solid; yield 90% (28.2 mg); R_f = 0.6; (50% EtOAc in hexane); m.p. 146–148 °C; FT-IR (KBr) 3633, 2955, 1437, 1261, 1275, 1063, 1037, 750, 513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.54 (d, J = 8.8 Hz, 1H), 8.47 (d, J = 2.5 Hz, 1H), 8.36 (d, J = 8.9 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.58–7.48 (m, 2H), 7.43–7.34 (m, 2H), 7.22 (s, 2H), 6.24 (d, J_{H-P} = 32.8 Hz, 1H), 5.08 (s, 1H), 3.81 (d, J_{H-P} = 11.0 Hz, 3H), 2.95 (d, J_{H-P} = 10.6 Hz, 3H), 1.26 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4 (d, J_{C-P} = 1.5 Hz), 135.6, 131.9 (d, J_{C-P} = 1.7 Hz), 131.4 (d, J_{C-P} = 2.8 Hz), 131.3 (d, J_{C-P} = 1.2 Hz), 131.2 (d, J_{C-P} = 1.0 Hz), 129.8, 128.9, 128.6 (d, J_{C-P} = 6.7 Hz), 128.6, 128.4 (d, J_{C-P} = 4.1 Hz), 127.8 (d, J_{C-P} = 3.1 Hz), 126.7, 125.6 (d, J_{C-P} = 8.4 Hz), 125.2, 125.0, 124.8, 123.6, 53.6 (d, J_{C-P} = 6.9 Hz), 52.5 (d, J_{C-P} = 7.3 Hz), 44.0 (d, J_{C-P} = 139.0 Hz), 34.4, 30.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 2922; HRMS (ESI): *m/z* calcd for $C_{31}H_{38}O_4P$ $[M+H]^+$: 505.2507; found: 505.2503.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(pyren-1-yl)methyl]phosphonate (85m)



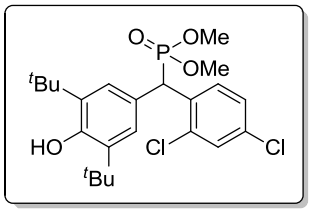
Pale yellow solid; yield 99% (32.7 mg); R_f = 0.5; (50% EtOAc in hexane); m.p. 171–172 °C; FT-IR (KBr) 3634, 2955, 1640, 1435, 1260, 1275, 1034, 764, 750, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J = 8.1, 1.9 Hz, 1H), 8.43 (d, J = 9.4 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H), 8.18–8.13 (m, 3H), 8.06 (s, 2H), 8.00 (t, J = 7.6 Hz, 1H), 7.47 (d, J_{H-P} = 1.7 Hz, 2H), 5.58 (d, J_{H-P} = 26.6 Hz, 1H), 5.13 (s, 1H), 3.62 (d, J_{H-P} = 10.6 Hz, 3H), 3.40 (d, J_{H-P} = 10.6 Hz, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1 (d, J_{C-P} = 2.4 Hz), 136.0, 131.5, 131.1 (d, J_{C-P} = 3.6 Hz), 130.8, 130.5 (d, J_{C-P} = 1.7 Hz), 129.0 (d, J_{C-P} = 11.1 Hz), 128.1, 127.7, 127.6, 127.4, 127.2 (d, J_{C-P} = 5.4 Hz), 126.4 (d, J_{C-P} = 7.8 Hz), 126.1, 125.44, 125.4, 125.1 (d, J_{C-P} = 1.9 Hz), 125.1, 125.0, 122.7, 53.6 (d, J_{C-P} = 7.1 Hz), 53.4 (d, J_{C-P} = 7.1 Hz), 45.5 (d, J_{C-P} = 139.0 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.71; HRMS (ESI): *m/z* calcd for $C_{33}H_{38}O_4P$ $[M+H]^+$: 529.2507; found: 529.2525.

Dimethyl[(2-bromophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]phosphonate (85n)



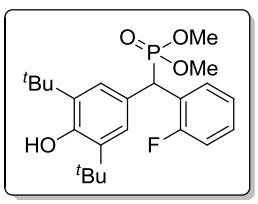
Pale yellow gummy solid; yield 94% (28.2 mg); R_f = 0.6; (50% EtOAc in hexane); FT-IR (KBr) 3641, 2955, 1472, 1435, 1252, 1036, 752, 546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dt, J = 7.9, 1.7 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.37 (d, J_{H-P} = 1.7 Hz, 2H), 7.36 – 7.29 (m, 1H), 7.13 – 7.05 (m, 1H), 5.15 (s, 1H), 5.06 (d, J_{H-P} = 25.4 Hz, 1H), 3.57 (d, J_{H-P} = 10.7 Hz, 3H), 3.53 (d, J_{H-P} = 10.6 Hz, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2 (d, J_{C-P} = 2.4 Hz), 137.0 (d, J_{C-P} = 2.0 Hz), 136.0 (d, J_{C-P} = 1.4 Hz), 133.2, 130.9 (d, J_{C-P} = 5.0 Hz), 128.7 (d, J_{C-P} = 1.7 Hz), 127.9 (d, J_{C-P} = 1.8 Hz), 126.4 (d, J_{C-P} = 7.9 Hz), 126.0 (d, J_{C-P} = 5.3 Hz), 125.3 (d, J_{C-P} = 13.3 Hz), 53.7 (d, J_{C-P} = 6.9 Hz), 53.3 (d, J_{C-P} = 7.1 Hz), 48.3 (d, J_{C-P} = 139.6 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.81; HRMS (ESI): *m/z* calcd for $C_{23}H_{33}BrO_4P$ $[M+H]^+$: 483.1300; found: 483.1294.

Dimethyl[(3,5-di-tert-butyl-4-hydroxyphenyl)(2,4-dichlorophenyl)methyl]phosphonate (85o)



Pale yellow gummy solid; yield 97% (28.5 mg); R_f = 0.7; (50% EtOAc in hexane); FT-IR (KBr) 3637, 2956, 1587, 1471, 1435, 1249, 1061, 1037, 827, 773, 567cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.5, 1.9 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.31 (d, J_{H-P} = 1.7 Hz, 2H), 7.27 (dd, J = 8.3, 2.4 Hz, 1H), 5.18 (s, 1H), 4.96 (d, J_{H-P} = 25.4 Hz, 1H), 3.60 (d, J_{H-P} = 10.8 Hz, 3H), 3.52 (d, J_{H-P} = 10.6 Hz, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (d, J_{C-P} = 2.4 Hz), 136.2 (d, J_{C-P} = 1.4 Hz), 134.9 (d, J_{C-P} = 12.8 Hz), 134.2 (d, J_{C-P} = 2.0 Hz), 133.5 (d, J_{C-P} = 2.2 Hz), 131.6 (d, J_{C-P} = 4.9 Hz), 129.6, 127.5 (d, J_{C-P} = 1.8 Hz), 126.3 (d, J_{C-P} = 7.9 Hz), 125.5 (d, J_{C-P} = 5.3 Hz), 53.9 (d, J_{C-P} = 6.9 Hz), 53.2 (d, J_{C-P} = 7.2 Hz), 45.0 (d, J_{C-P} = 140.7 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.36; HRMS (ESI): *m/z* calcd for $C_{23}H_{32}ClO_4P$ $[M+H]^+$: 473.1415; found: 473.1397.

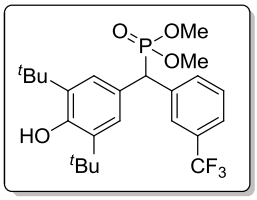
Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(2-fluorophenyl)methyl]phosphonate (85p)



Pale yellow solid; yield 92% (24.1 mg); R_f = 0.6; (50% EtOAc in hexane); m.p. 37–39 °C; FT-IR (KBr) 3640, 2955, 1491, 1472, 1435, 1231, 1060, 1035, 834, 758, 634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (tt, J = 7.7,

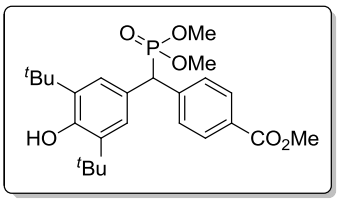
1.9 Hz, 1H), 7.34 (d, J_{H-P} = 1.8 Hz, 2H), 7.26 – 7.18 (m, 1H), 7.17 – 7.13 (m, 1H), 7.06 – 7.01 (m, 1H), 5.17 (s, 1H), 4.81 (d, J_{H-P} = 25.3 Hz, 1H), 3.58 (d, J_{H-P} = 10.7 Hz, 3H), 3.54 (d, J_{H-P} = 10.6, 4.1 Hz, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (dd, $J_{C-F,C-P}$ = 244.2, 10.4 Hz), 153.2 (d, J_{C-P} = 2.5 Hz), 136.1 (d, J_{C-P} = 1.5 Hz), 130.8 (dd, $J_{C-F,C-P}$ = 5.1, 2.6 Hz), 128.7 (dd, $J_{C-F,C-P}$ = 8.3, 1.9 Hz), 126.3 (d, J_{C-P} = 7.8 Hz), 126.0 (d, J_{C-P} = 5.3 Hz), 124.7 (dd, $J_{C-F,C-P}$ = 14.5, 3.7 Hz), 124.3 (dd, J = 3.5, 2.1 Hz), 115.5 (d, J_{C-F} = 22.5 Hz), 53.7 (d, J_{C-P} = 6.9 Hz), 53.2 (d, J_{C-P} = 7.2 Hz), 41.1 (dd, $J_{C-F,C-P}$ = 3.5, 140.7 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.65 (d, J_{P-F} = 4.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.11 (d, J_{F-P} = 4.5 Hz); HRMS (ESI): *m/z* calcd for $C_{23}H_{33}FO_4P$ $[M+H]^+$: 423.2100; found: 423.2090.

Dimethyl[(3,5-di-*tert-butyl*-4-hydroxyphenyl)(3-(trifluoromethyl)phenyl]methyl] phosphonate (85q)



Pale yellow gummy solid; yield 99% (29.1 mg); R_f = 0.7; (50% EtOAc in hexane); FT-IR (thin film, neat) 3639, 2957, 1435, 1330, 1253, 1164, 1126, 1060, 1036, 830, 628 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.75 (m, 2H), 7.51 (d, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.29 (d, J_{H-P} = 1.9 Hz, 2H), 5.21 (s, 1H), 4.41 (d, J_{H-P} = 25.4 Hz, 1H), 3.57 (d, J_{H-P} = 10.7 Hz, 3H), 3.52 (d, J_{H-P} = 10.6 Hz, 3H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (d, J_{C-P} = 2.5 Hz), 138.3 (d, J_{C-P} = 4.8 Hz), 136.3 (d, J_{C-P} = 1.6 Hz), 132.8 (dd, $J_{C-F,C-P}$ = 7.2, 1.0 Hz), 130.9 (q, J_{C-F} = 32.2 Hz), 129.2 (d, J_{C-P} = 1.4 Hz), 126.3 (q, J_{C-F} = 4.0 Hz), 126.2 (d, J_{C-P} = 7.8 Hz), 125.9 (d, J_{C-P} = 5.8 Hz), 124.1 (q, J_{C-F} = 172.1 Hz), 124.1 – 123.9 (m), 53.8 (d, J_{C-P} = 7.0 Hz), 53.3 (d, J_{C-P} = 7.3 Hz), 50.5 (d, J_{C-P} = 137.5 Hz), 34.6, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.13; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.56; HRMS (ESI): *m/z* calcd for $C_{24}H_{33}F_3O_4P$ $[M+H]^+$: 473.2068; found: 473.2069.

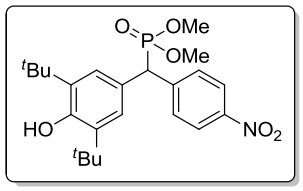
Methyl4-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(dimethoxyphosphoryl)methyl)benzoate (85r)



Pale Yellow gummy solid; yield 94% (27.0 mg); R_f = 0.5; (50% EtOAc in hexane); FT-IR (KBr) 3635, 1723, 1611, 1435, 1282, 1253, 1115, 1061, 1035, 829, 759, 555 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.29 (d, J_{H-P} = 1.4 Hz, 2H), 5.18 (s, 1H), 4.42 (d, J_{H-P} = 25.2 Hz, 1H), 3.90 (s, 3H), 3.54 (apparent t,

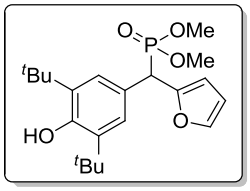
$J_{H\text{-}P}$ = 10.6 Hz, 6H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (d, $J_{C\text{-}F}$ = 0.5 Hz), 153.3 (d, $J_{C\text{-}F}$ = 2.5 Hz), 142.6 (d, $J_{C\text{-}F}$ = 4.7 Hz), 136.2 (d, $J_{C\text{-}F}$ = 1.5 Hz), 130.0 (d, $J_{C\text{-}F}$ = 1.2 Hz), 129.6 (d, $J_{C\text{-}F}$ = 7.9 Hz), 128.0 (d, $J_{C\text{-}F}$ = 2.2 Hz), 126.2 (d, $J_{C\text{-}F}$ = 7.9 Hz), 126.1 (d, $J_{C\text{-}F}$ = 5.8 Hz), 53.7 (d, $J_{C\text{-}F}$ = 7.0 Hz), 53.4 (d, $J_{C\text{-}F}$ = 7.2 Hz), 52.2, 50.8 (d, $J_{C\text{-}F}$ = 137.3 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.26; HRMS (ESI): *m/z* calcd for $C_{25}H_{35}O_6PNa$ $[M+Na]^+$: 485.2069; found: 485.2046.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-nitrophenyl)methyl]phosphonate (85s)



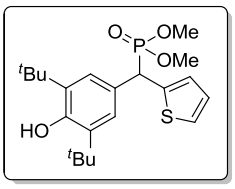
Pale yellow solid; yield 99% (27.6 mg); R_f = 0.4; (50% EtOAc in hexane); m.p. 146–148°C; FT-IR (KBr) 3627, 2956, 1596, 1521, 1435, 1348, 1254, 1060, 1035, 767, 556 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.6 Hz, 2H), 7.69 (dd, J = 8.7, 1.5 Hz, 2H), 7.28 (d, $J_{H\text{-}P}$ = 1.5 Hz, 2H), 5.23 (s, 1H), 4.46 (d, $J_{H\text{-}P}$ = 25.3 Hz, 1H), 3.60 (d, $J_{H\text{-}P}$ = 10.8 Hz, 3H), 3.53 (d, $J_{H\text{-}P}$ = 10.6 Hz, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6 (d, $J_{C\text{-}P}$ = 2.3 Hz), 147.1 (d, $J_{C\text{-}P}$ = 2.5 Hz), 145.1 (d, $J_{C\text{-}P}$ = 4.6 Hz), 136.5 (d, $J_{C\text{-}P}$ = 1.3 Hz), 130.4 (d, $J_{C\text{-}P}$ = 7.7 Hz), 126.2 (d, $J_{C\text{-}P}$ = 7.9 Hz), 125.4 (d, $J_{C\text{-}P}$ = 5.7 Hz), 123.9 (d, $J_{C\text{-}P}$ = 1.1 Hz), 54.0 (d, $J_{C\text{-}P}$ = 7.0 Hz), 53.2 (d, $J_{C\text{-}P}$ = 7.3 Hz), 50.5 (d, $J_{C\text{-}P}$ = 137.9 Hz), 34.6, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.46; HRMS (ESI): *m/z* calcd for $C_{23}H_{33}NO_6P$ $[M+H]^+$: 450.2045; found: 450.2057.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(furan-2-yl)methyl]phosphonate (85t)



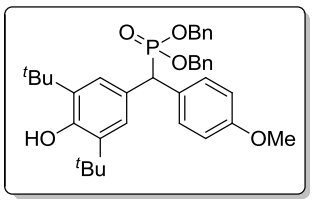
Pale yellow gummy solid; yield 92% (22.5 mg); R_f = 0.4; (50% EtOAc in hexane); FT-IR (KBr) 3636, 2956, 1435, 1253, 1060, 1037, 833, 739, 527 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 1.0 Hz, 1H), 7.24 (d, $J_{H\text{-}P}$ = 2.1 Hz, 2H), 6.45 (t, J = 3.0 Hz, 1H), 6.38 – 6.33 (m, 1H), 5.18 (s, 1H), 4.48 (d, $J_{H\text{-}P}$ = 26.0 Hz, 1H), 3.65 (d, $J_{H\text{-}P}$ = 10.7 Hz, 3H), 3.50 (d, $J_{H\text{-}P}$ = 10.6 Hz, 3H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (d, $J_{C\text{-}P}$ = 3.1 Hz), 150.2 (d, $J_{C\text{-}P}$ = 3.1 Hz), 142.1 (d, $J_{C\text{-}P}$ = 2.3 Hz), 136.0 (d, $J_{C\text{-}P}$ = 2.3 Hz), 126.2 (d, $J_{C\text{-}P}$ = 6.3 Hz), 124.4 (d, $J_{C\text{-}P}$ = 6.4 Hz), 110.8 (d, $J_{C\text{-}P}$ = 2.0 Hz), 108.7 (d, $J_{C\text{-}P}$ = 5.5 Hz), 53.7 (d, $J_{C\text{-}P}$ = 6.9 Hz), 53.5 (d, $J_{C\text{-}P}$ = 7.1 Hz), 44.6 (d, $J_{C\text{-}P}$ = 139.6 Hz), 34.5, 30.40; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.16; HRMS (ESI): *m/z* calcd for $C_{21}H_{30}O_5P$ $[M-H]^+$: 393.1831; found: 393.1816.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(thiophen-2-yl)methyl]phosphonate (85u)



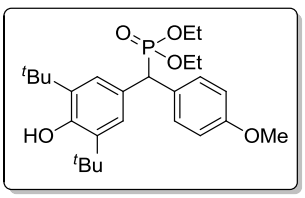
Pale yellow gummy solid; yield 89% (22.7 mg); R_f = 0.5; (50% EtOAc in hexane); FT-IR (KBr) 3636, 2956, 1435, 1251, 1184, 1059, 1035, 831, 754, 533 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.32 (d, J_{H-P} = 2.0 Hz, 2H), 7.20–7.18 (m, 2H), 6.96 (dd, J = 5.1, 3.6 Hz, 1H), 5.20 (s, 1H), 4.61 (d, J_{H-P} = 25.7 Hz, 1H), 3.63 (d, J_{H-P} = 10.7 Hz, 3H), 3.48 (d, J_{H-P} = 10.5 Hz, 3H), 1.43 (s, 18H)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (d, J_{C-P} = 2.8 Hz), 139.4 (d, J_{C-P} = 5.4 Hz), 136.1 (d, J_{C-P} = 1.9 Hz), 127.0 (d, J_{C-P} = 2.9 Hz), 126.9 (d, J_{C-P} = 2.2 Hz), 126.3 (d, J_{C-P} = 5.8 Hz), 126.1 (d, J_{C-P} = 7.0 Hz), 124.9 (d, J_{C-P} = 2.8 Hz), 53.8 (d, J_{C-P} = 7.0 Hz), 53.4 (d, J_{C-P} = 7.2 Hz), 45.9 (d, J_{C-P} = 139.6 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.16; HRMS (ESI): *m/z* calcd for $C_{21}H_{32}O_4PS$ $[M+H]^+$: 411.1759; found: 411.1747.

Dibenzyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]phosphonate (85v)



Colourless gummy solid; yield 95% (34.5 mg); R_f = 0.8; (50% EtOAc in hexane); FT-IR (KBr) 3634, 2956, 1512, 1435, 1252, 1035, 997, 770, 535 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.7, 1.9 Hz, 2H), 7.34 (d, J_{H-P} = 1.7 Hz, 2H), 7.29 – 7.21 (m, 6H), 7.16 – 7.09 (m, 2H), 7.03 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.15 (s, 1H), 4.96 – 4.65 (m, 4H), 4.40 (d, J_{H-P} = 25.7 Hz, 1H), 3.79 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (d, J_{C-P} = 2.3 Hz), 153.1 (d, J_{C-P} = 2.4 Hz), 136.7 (d, J_{C-P} = 6.1 Hz), 136.6 (d, J_{C-P} = 6.9 Hz), 136.0 (d, J_{C-P} = 1.4 Hz), 130.6 (d, J_{C-P} = 7.8 Hz), 129.2 (d, J_{C-P} = 5.2 Hz), 128.5 (d, J_{C-P} = 2.3 Hz), 128.2 (d, J_{C-P} = 2.9 Hz), 127.8 (d, J_{C-P} = 15.0 Hz), 127.3 (d, J_{C-P} = 5.0 Hz), 126.2 (d, J_{C-P} = 8.1 Hz), 114.1 (d, J_{C-P} = 1.3 Hz), 67.9 (d, J_{C-P} = 5.4 Hz), 67.9 (d, J_{C-P} = 5.5 Hz), 55.4, 50.4 (d, J_{C-P} = 136.6 Hz), 34.5, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.00; HRMS (ESI): *m/z* calcd for $C_{36}H_{44}O_5P$ $[M+H]^+$: 587.2926; found: 587.2903.

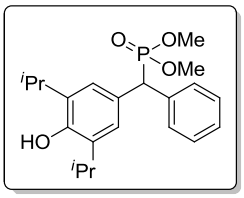
Diethyl [(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]phosphonate (85w)



Pale yellow gummy solid; yield 85% (24.4 mg); R_f = 0.6; (50% EtOAc in hexane); FT-IR (KBr) 3636, 2956, 1435, 1251, 1184, 1059, 1035, 831, 754, 533 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.7,

1.8 Hz, 2H), 7.29 (d, J_{H-P} = 1.8 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 5.12 (s, 1H), 4.28 (d, J_{H-P} = 25.5 Hz, 1H), 4.20 – 4.07 (m, 1H), 4.01 – 3.88 (m, 2H), 3.87 – 3.73 (m, 1H), 3.78 (s, 3H), 1.41 (s, 18H), 1.11 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (d, J_{C-P} = 2.1 Hz), 152.9 (d, J_{C-P} = 2.5 Hz), 135.8 (d, J_{C-P} = 1.6 Hz), 130.6 (d, J_{C-P} = 7.9 Hz), 129.5 (d, J_{C-P} = 5.0 Hz), 127.4 (d, J_{C-P} = 5.0 Hz), 126.2 (d, J_{C-P} = 7.8 Hz), 114.0 (d, J_{C-P} = 1.2 Hz), 62.7 (d, J_{C-P} = 6.9 Hz), 62.5 (d, J_{C-P} = 7.1 Hz), 55.3, 50.3 (d, J_{C-P} = 136.9 Hz), 34.5 , 30.4, 16.5 (d, J_{C-P} = 5.7 Hz), 16.4 (d, J_{C-P} = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.20; HRMS (ESI): *m/z* calcd for $C_{26}H_{39}O_5PNa$ $[M+Na]^+$: 485.2433; found: 485.2437.

Dimethyl[(4-hydroxy-3,5-diisopropylphenyl)(phenyl)methyl]phosphonate (85x)

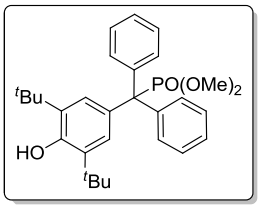


Pale yellow gummy solid; yield 99% (25.0 mg); R_f = 0.5; (50% EtOAc in hexane); FT-IR (KBr) 3630, 2959, 1470, 1435, 1250, 1199, 1152, 1059, 1035, 834, 701, 542 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.7 Hz, 2H), 7.34 – 7.30 (m, 2H), 7.24 (d, J = 7.2 Hz, 1H), 7.21 (d, J_{H-P} = 1.0 Hz, 2H), 4.84 (brs, 1H), 4.38 (d, J_{H-P} = 25.4 Hz, 1H), 3.55 (d, J_{H-P} = 9.3 Hz, 3H), 3.52 (d, J_{H-P} = 9.6 Hz, 3H), 3.25 – 3.04 (m, 2H), 1.25 (d, J_{H-P} = 6.9 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4 (d, J_{C-P} = 2.2 Hz), 137.2 (d, J_{C-P} = 5.1 Hz), 133.9 (d, J_{C-P} = 1.3 Hz), 129.4 (d, J_{C-P} = 7.8 Hz), 128.7 (d, J_{C-P} = 1.4 Hz), 128.2 (d, J_{C-P} = 5.3 Hz), 127.2 (d, J_{C-P} = 2.3 Hz), 124.8 (d, J_{C-P} = 8.2 Hz), 53.6 (d, J_{C-P} = 7.0 Hz), 53.3 (d, J_{C-P} = 7.2 Hz), 50.7 (d, J_{C-P} = 137.0 Hz), 27.4, 22.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.00; HRMS (ESI): *m/z* calcd for $C_{21}H_{30}O_4P$ $[M+H]^+$: 377.1881; found: 377.1868.

General procedure for the hydrophosphonylation of fuchsones:

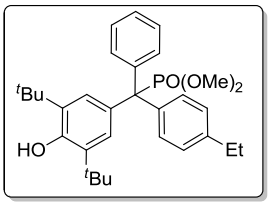
Anhydrous DMSO (1 mL) was added to the mixture of *p*-quinone methide (20 mg, 0.054 mmol), dimethyl phosphite (9 µL, 0.081 mmol) and NHC-CO_2 adduct **78** (2.8 mg, 0.0081 mmol) under argon atmosphere, and the resulting suspension was stirred at 80°C for 24 h. The reaction was quenched by 5 ml of water and extracted with (5 x 3 mL) dichloromethane. Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and the residue was purified through silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)diphenylmethyl]phosphonate (87a)



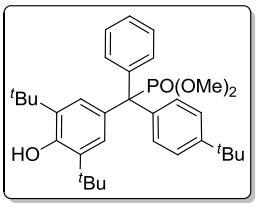
Pale yellow solid; yield 61% (15.8 mg); R_f = 0.5; (50% EtOAc in hexane); m.p. 138–140°C FT-IR (KBr) 3639, 2955, 2931, 1594, 1438, 1228, 1113, 1057, 819, 702, 566cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 10H), 7.07 (d, $J_{H\text{-}P}$ = 1.5 Hz, 2H), 5.16 (s, 1H), 3.52 (d, $J_{H\text{-}P}$ = 10.5 Hz, 6H), 1.31 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7 (d, $J_{C\text{-}P}$ = 2.2 Hz), 142.1 (d, $J_{C\text{-}P}$ = 5.2 Hz), 134.9 (d, $J_{C\text{-}P}$ = 1.7 Hz), 131.0 (d, $J_{C\text{-}P}$ = 6.0 Hz), 130.8 (d, $J_{C\text{-}P}$ = 6.4 Hz), 128.0, 127.9 (d, $J_{C\text{-}P}$ = 1.3 Hz), 127.0 (d, $J_{C\text{-}P}$ = 1.7 Hz), 62.8 (d, $J_{C\text{-}P}$ = 135.1 Hz), 53.9 (d, $J_{C\text{-}P}$ = 8.0 Hz), 34.6, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.08; HRMS (ESI): *m/z* calcd for $C_{29}H_{37}O_4PNa$ $[M+Na]^+$: 503.2327; found: 503.2334.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-ethylphenyl)(phenyl)methyl] phosphonate (87b)



Pale yellow solid; yield 20% (6.0 mg); R_f = 0.6; (50% EtOAc in hexane); m.p. 157–159°C; FT-IR (KBr) 3642, 2956, 2927, 1438, 1228, 1123, 1058, 1029, 817, 749, 583 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.28 – 7.23 (m, 3H), 7.20 (dd, J = 8.4, 1.7 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 7.06 (d, $J_{H\text{-}P}$ = 1.9 Hz, 2H), 5.16 (s, 1H), 3.53 (d, $J_{H\text{-}P}$ = 4.6 Hz, 3H), 3.51 (d, $J_{H\text{-}P}$ = 4.6 Hz, 3H), 2.63 (q, J = 7.6 Hz, 2H), 1.31 (s, 7H), 1.23 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6 (d, $J_{C\text{-}P}$ = 2.2 Hz), 142.8 (d, $J_{C\text{-}P}$ = 1.8 Hz), 142.3 (d, $J_{C\text{-}P}$ = 5.2 Hz), 139.1 (d, $J_{C\text{-}P}$ = 5.6 Hz), 134.8 (d, $J_{C\text{-}P}$ = 1.6 Hz), 131.2 (d, $J_{C\text{-}P}$ = 5.6 Hz), 130.7 (d, $J_{C\text{-}P}$ = 6.4 Hz), 130.6 (d, $J_{C\text{-}P}$ = 6.4 Hz), 128.0 (d, $J_{C\text{-}P}$ = 6.2 Hz), 127.8 (d, $J_{C\text{-}P}$ = 1.1 Hz), 127.4 (d, $J_{C\text{-}P}$ = 1.3 Hz), 126.9 (d, $J_{C\text{-}P}$ = 1.6 Hz), 62.5 (d, $J_{C\text{-}P}$ = 135.2 Hz), 53.8 (apparent t, J = 8.0 Hz), 34.6, 30.4, 28.5, 15.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.29; HRMS (ESI): *m/z* calcd for $C_{31}H_{41}O_4PNa$ $[M+Na]^+$: 531.2640; found: 531.2618.

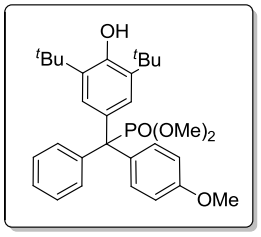
Dimethyl{[4-(*tert*-butyl)phenyl](3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl} phosphonate (87c)



Pale yellow solid; yield 30% (8.7 mg); R_f = 0.7; (50% EtOAc in hexane); m.p. 86–88°C; FT-IR (KBr) 3642, 2955, 1438, 1228, 1122, 1058, 1028, 817, 764, 702, 580 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m,

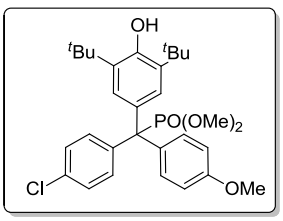
2H), 7.31 – 7.23 (m, 5H), 7.19 (dd, J = 8.6, 1.7 Hz, 2H), 7.03 (d, $J_{H\text{-}P}$ = 1.9 Hz, 2H), 5.15 (s, 1H), 3.53 (d, $J_{H\text{-}P}$ = 7.9 Hz, 3H), 3.50 (d, $J_{H\text{-}P}$ = 7.9 Hz, 3H), 1.31 (s, 18H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6 (d, $J_{C\text{-}P}$ = 2.2 Hz), 149.7 (d, $J_{C\text{-}P}$ = 2.0 Hz), 142.3 (d, $J_{C\text{-}P}$ = 5.4 Hz), 138.8 (d, $J_{C\text{-}P}$ = 5.4 Hz), 134.6 (d, $J_{C\text{-}P}$ = 1.7 Hz), 131.2 (d, $J_{C\text{-}P}$ = 5.5 Hz), 130.7 (d, $J_{C\text{-}P}$ = 6.3 Hz), 130.3 (d, $J_{C\text{-}P}$ = 6.4 Hz), 127.9 (d, $J_{C\text{-}P}$ = 6.2 Hz), 127.8 (d, $J_{C\text{-}P}$ = 1.2 Hz), 126.9 (d, $J_{C\text{-}P}$ = 1.9 Hz), 124.8 (d, $J_{C\text{-}P}$ = 1.1 Hz), 62.4 (d, $J_{C\text{-}P}$ = 135.3 Hz), 53.9 (d, $J_{C\text{-}P}$ = 7.9 Hz), 53.8 (d, $J_{C\text{-}P}$ = 8.2 Hz), 34.6, 34.5, 31.4, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.29; HRMS (ESI): *m/z* calcd for $C_{33}H_{45}O_4PNa$ $[M+Na]^+$: 559.2953; found: 559.2929.

Dimethyl[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)(phenyl)methyl] phosphonate (87d)



Pale yellow solid; yield 33% (9.1 mg); R_f = 0.5; (50% EtOAc in hexane); m.p. 178–180°C; FT-IR (KBr) 3631, 2956, 2927, 1511, 1439, 1256, 1186, 1032, 817, 748, 580 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 5H), 7.22 (dd, J = 8.9, 1.8 Hz, 2H), 7.08 (d, $J_{H\text{-}P}$ = 1.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.16 (s, 1H), 3.80 (s, 3H), 3.53 (d, $J_{H\text{-}P}$ = 5.8 Hz, 3H), 3.51 (d, $J_{H\text{-}P}$ = 5.7 Hz, 3H), 1.32 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (d, $J_{C\text{-}P}$ = 1.9 Hz), 152.7 (d, $J_{C\text{-}P}$ = 2.3 Hz), 142.4 (d, $J_{C\text{-}P}$ = 5.1 Hz), 134.9 (d, $J_{C\text{-}P}$ = 1.7 Hz), 134.0 (d, $J_{C\text{-}P}$ = 5.5 Hz), 131.9 (d, $J_{C\text{-}P}$ = 6.4 Hz), 131.3 (d, $J_{C\text{-}P}$ = 5.7 Hz), 130.7 (d, $J_{C\text{-}P}$ = 6.5 Hz), 127.9 (d, $J_{C\text{-}P}$ = 1.4 Hz), 127.8, 126.9 (d, $J_{C\text{-}P}$ = 1.8 Hz), 113.2 (d, $J_{C\text{-}P}$ = 1.3 Hz), 62.1 (d, $J_{C\text{-}P}$ = 135.4 Hz), 55.3, 53.9 (d, $J_{C\text{-}P}$ = 8.1 Hz), 53.8 (d, $J_{C\text{-}P}$ = 8.1 Hz), 34.6, 30.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.31; HRMS (ESI): *m/z* calcd for $C_{30}H_{38}O_5P$ $[M-H]^+$: 509.2456; found: 509.2434.

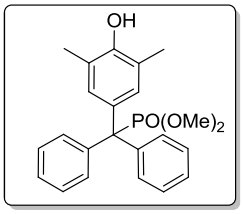
Dimethyl[(4-chlorophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl) methyl]phosphonate (87e)



Pale yellow solid; yield 40% (11.8 mg); R_f = 0.6; (50% EtOAc in hexane); m.p. 223–225°C; FT-IR (KBr) 3635, 2955, 1511, 1438, 1253, 1186, 1057, 1032, 816, 760, 564 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 4H), 7.19 (dd, J = 8.9, 1.8 Hz, 2H), 7.07 (d, $J_{H\text{-}P}$ = 1.9 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.19 (s, 1H), 3.80 (s, 3H), 3.54 (d, $J_{H\text{-}P}$ = 3.6 Hz, 3H), 3.51 (d, $J_{H\text{-}P}$ = 3.6 Hz, 3H), 1.32 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5 (d, $J_{C\text{-}P}$ = 1.8 Hz), 152.8 (d, $J_{C\text{-}P}$ = 2.1 Hz), 141.1 (d, $J_{C\text{-}P}$ = 5.2 Hz), 135.1 (d, $J_{C\text{-}P}$ = 1.6 Hz),

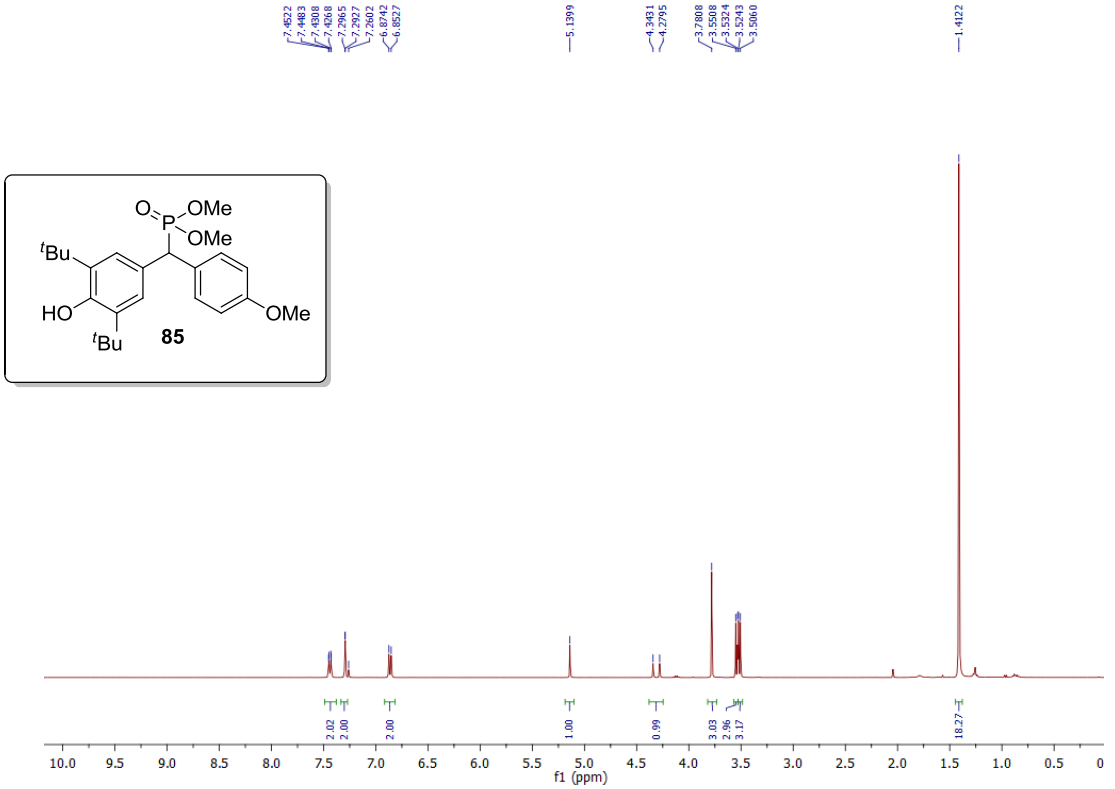
133.5 (d, J_{C-P} = 5.5 Hz), 132.8 (d, J_{C-P} = 2.2 Hz), 132.1 (d, J_{C-P} = 6.4 Hz), 131.8 (d, J_{C-P} = 6.4 Hz), 130.9 (d, J_{C-P} = 5.7 Hz), 128.0 (d, J_{C-P} = 1.3 Hz), 127.7 (d, J_{C-P} = 6.2 Hz), 113.3 (d, J_{C-P} = 1.2 Hz), 61.6 (d, J_{C-P} = 136.0 Hz), 55.3, 54.0 (d, J_{C-P} = 3.9 Hz), 53.9 (d, J_{C-P} = 3.8 Hz), 34.6, 30.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.84; HRMS (ESI): *m/z* calcd for $C_{30}H_{37}ClO_5P$ $[M-H]^+$: 543.2066; found: 543.2042.

Dimethyl[(4-hydroxy-3,5-dimethylphenyl)diphenylmethyl]phosphonate (87f)

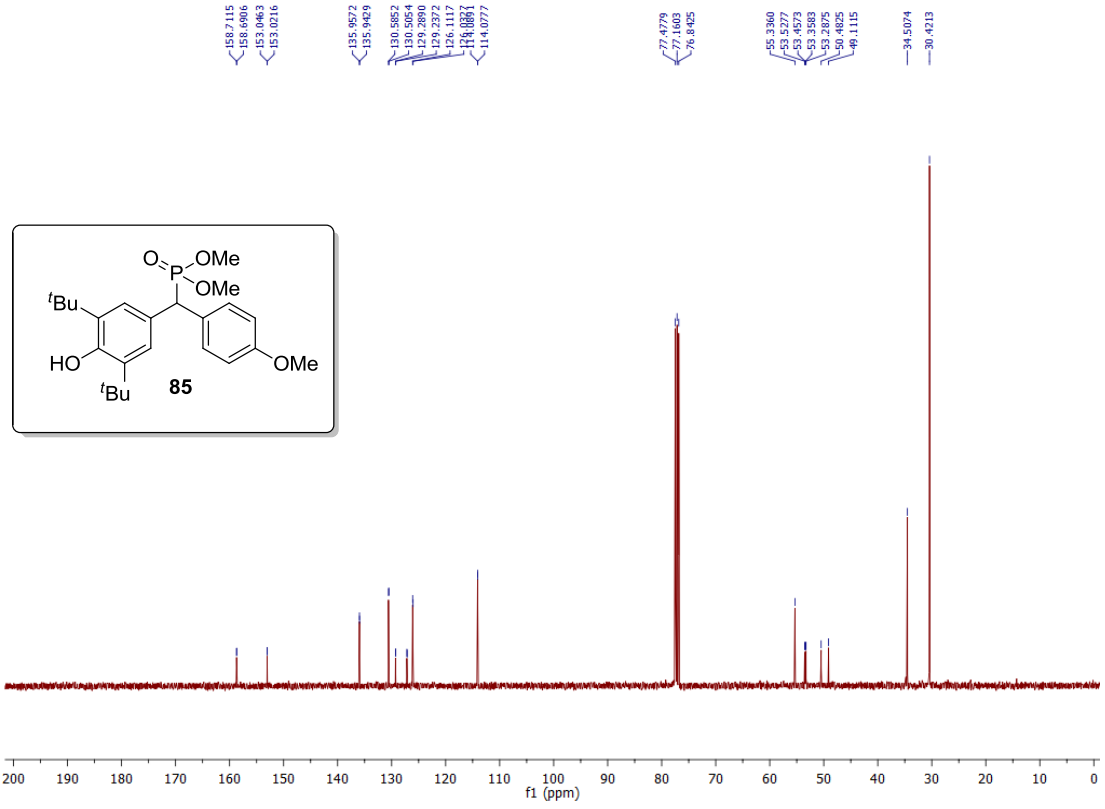


Pale yellow solid; yield 44% (9.4 mg); R_f = 0.3; (50% EtOAc in hexane); m.p. 248–250°C; FT-IR (KBr) 3634, 2922, 1489, 1277, 1206, 1131, 1054, 1020, 749, 699, 573 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 10H), 6.85 (s, 2H), 5.01 (s, 1H), 3.58 (d, *J* = 10.5 Hz, 6H), 2.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5 (d, *J* = 1.5 Hz), 141.7 (d, *J* = 5.5 Hz), 132.5 (d, *J* = 5.6 Hz), 130.9 (d, *J* = 6.6 Hz), 130.8 (d, *J* = 6.3 Hz), 128.0 (d, *J* = 1.4 Hz), 127.1 (d, *J* = 1.8 Hz), 122.6 (d, *J* = 1.3 Hz), 62.4 (d, *J* = 135.7 Hz), 54.0 (d, *J* = 8.1 Hz), 16.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.20; HRMS (ESI): *m/z* calcd for $C_{23}H_{25}O_4PNa$ $[M+Na]^+$: 419.1388; found: 419.1372.

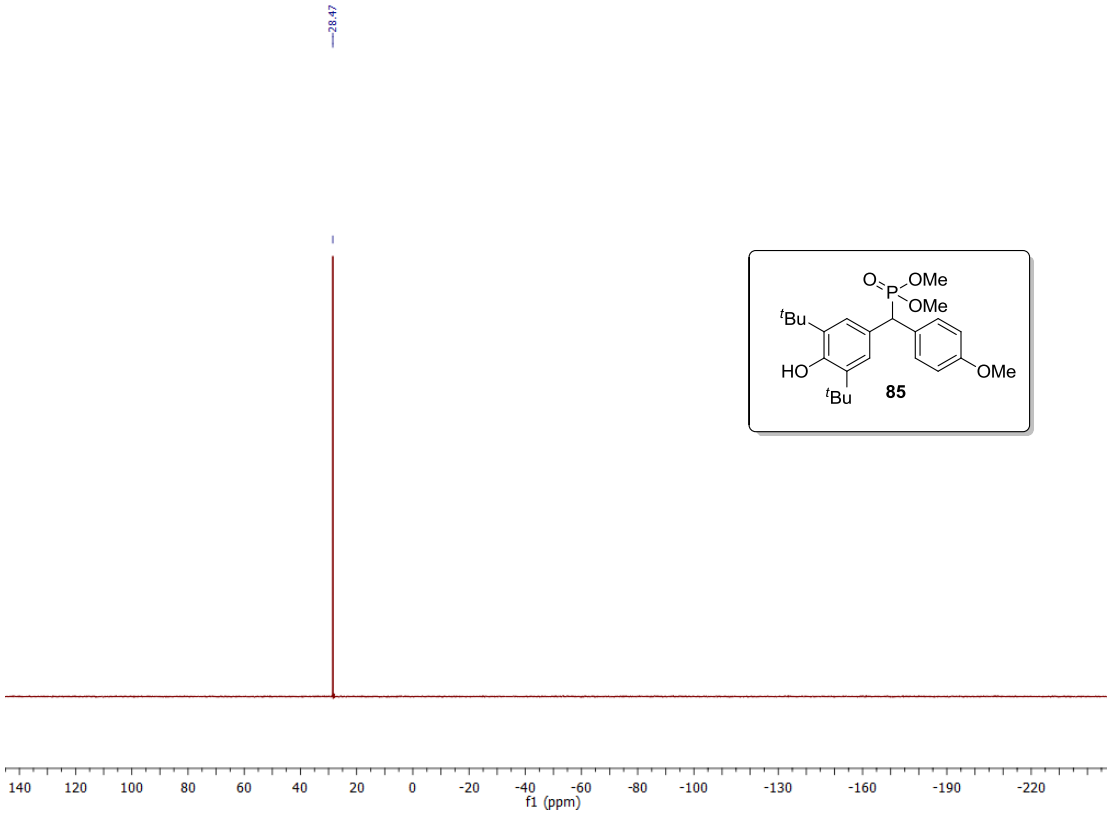
^{1}H NMR Spectrum of 85



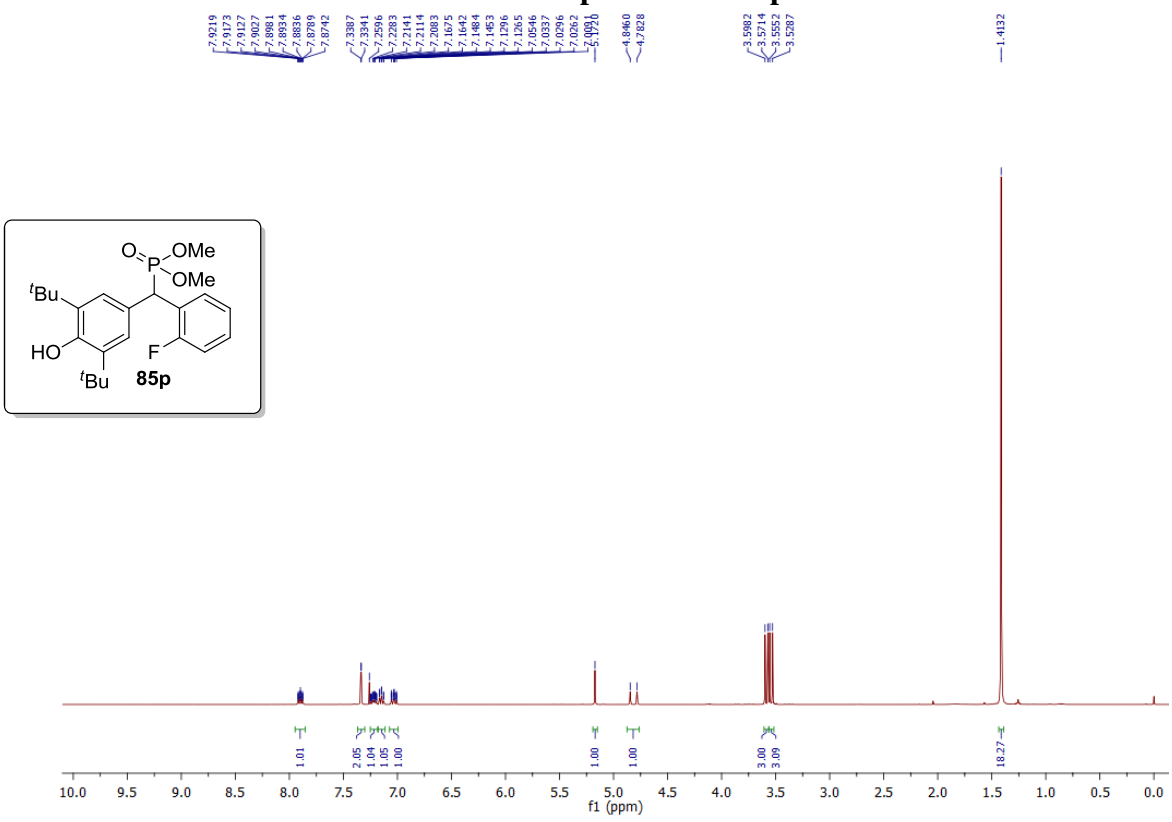
^{13}C NMR Spectrum of 85



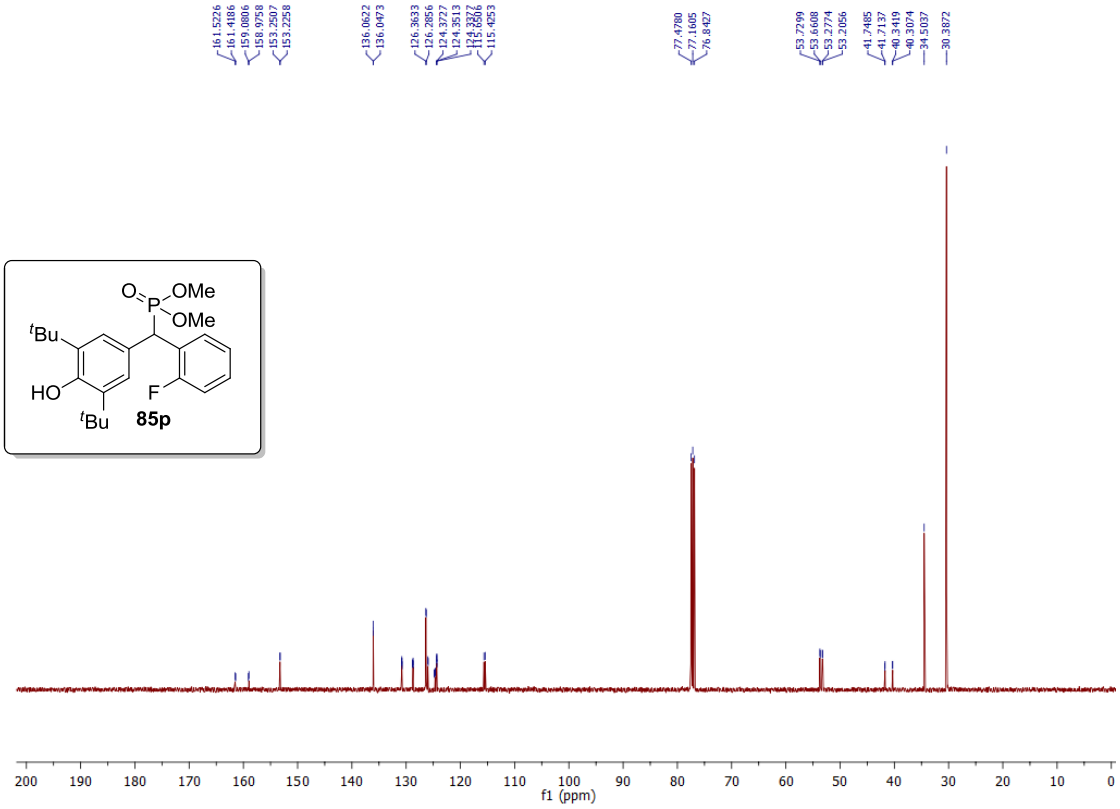
^{31}P NMR Spectrum of 85



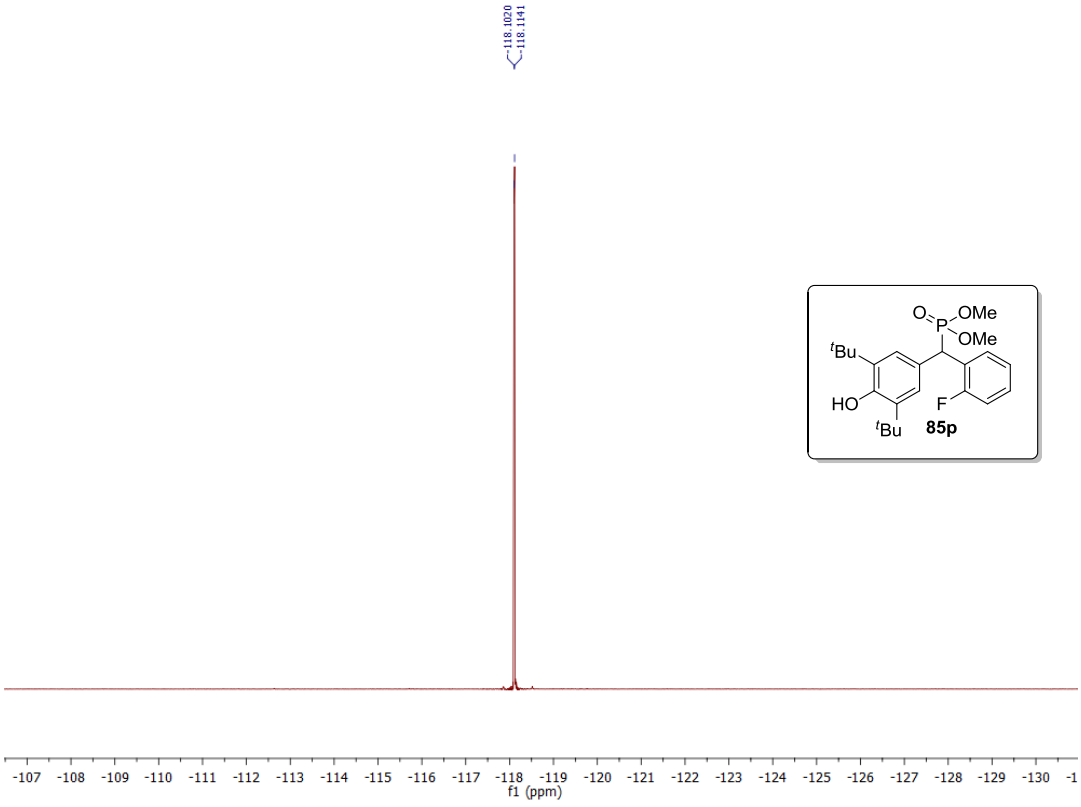
^{1}H NMR Spectrum of 85p



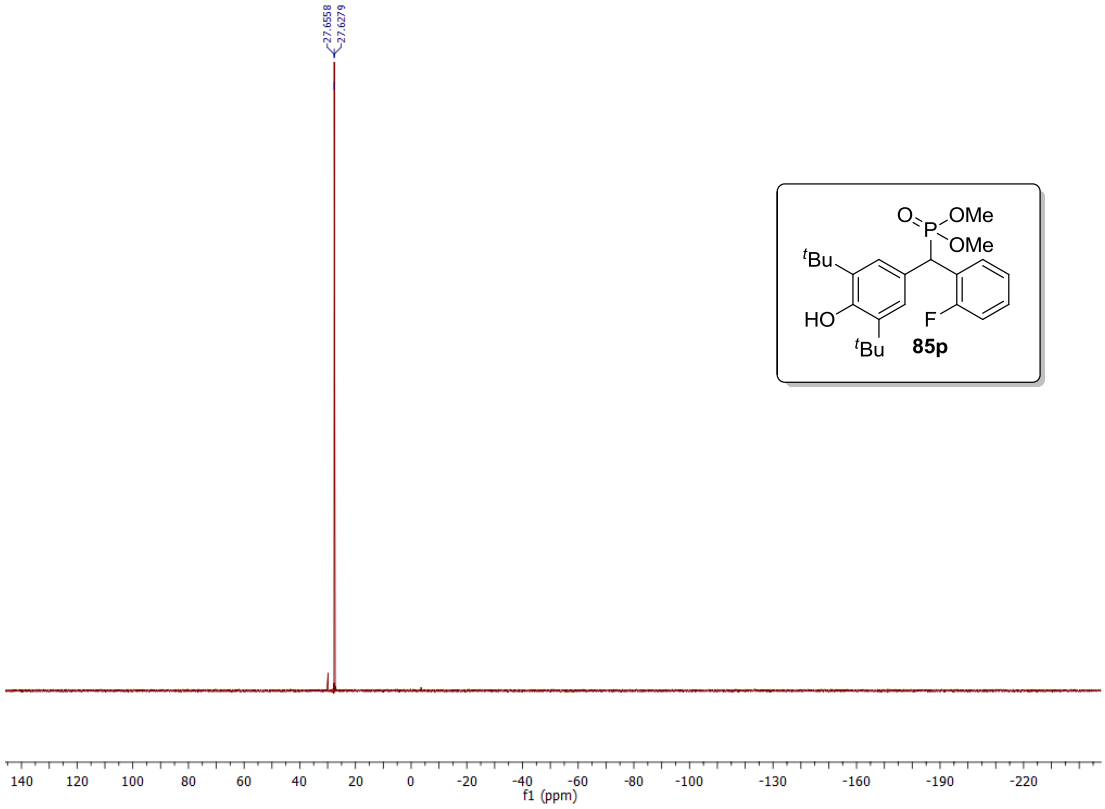
^{13}C NMR Spectrum of 85p



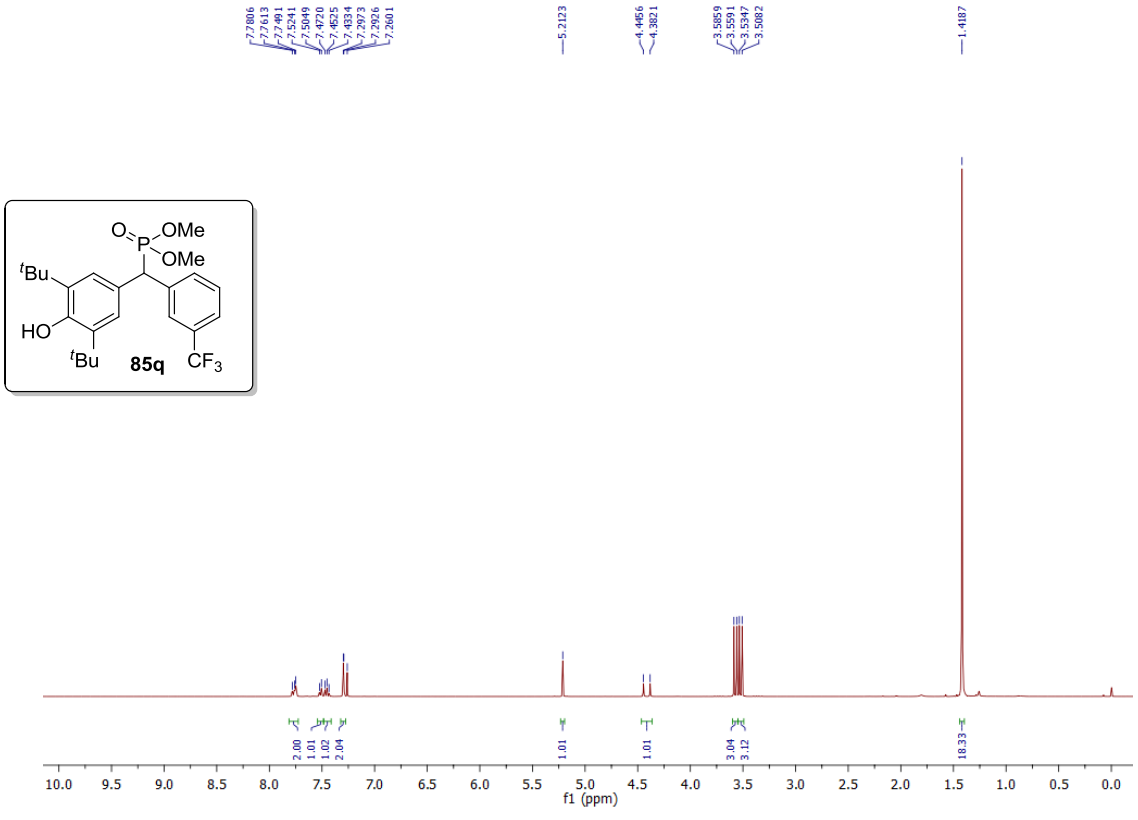
^{19}F NMR Spectrum of 85p



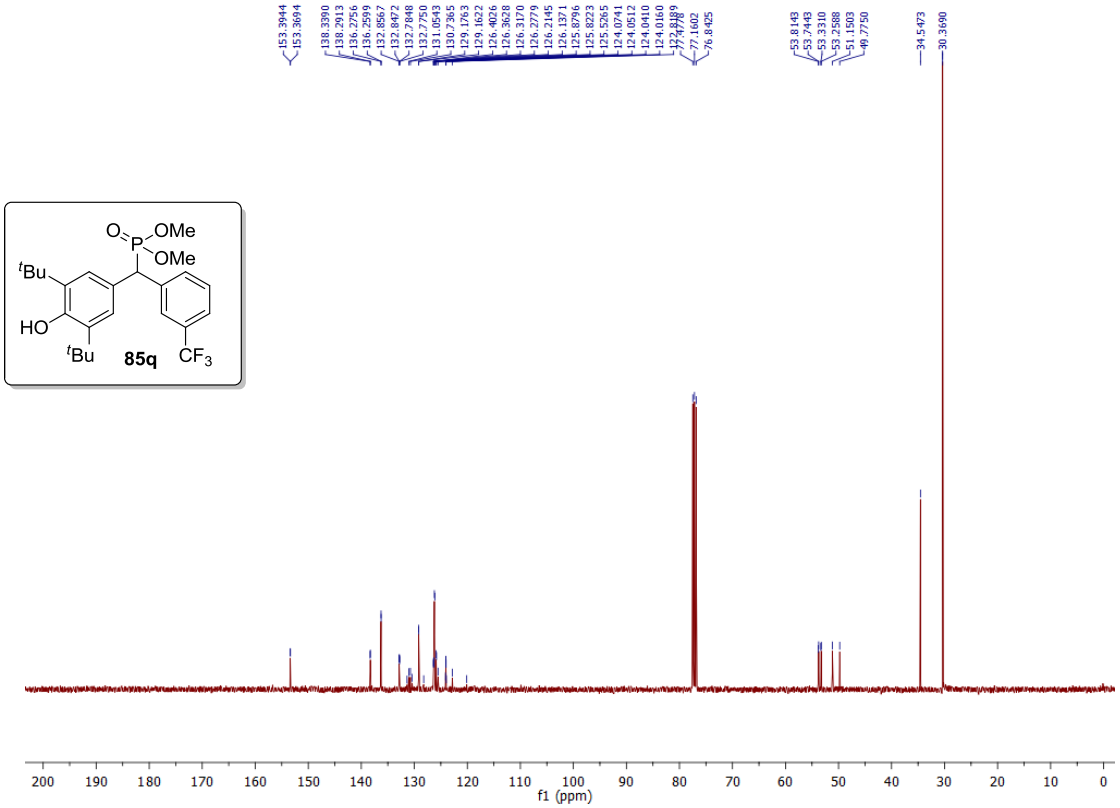
^{31}P NMR Spectrum of 85p



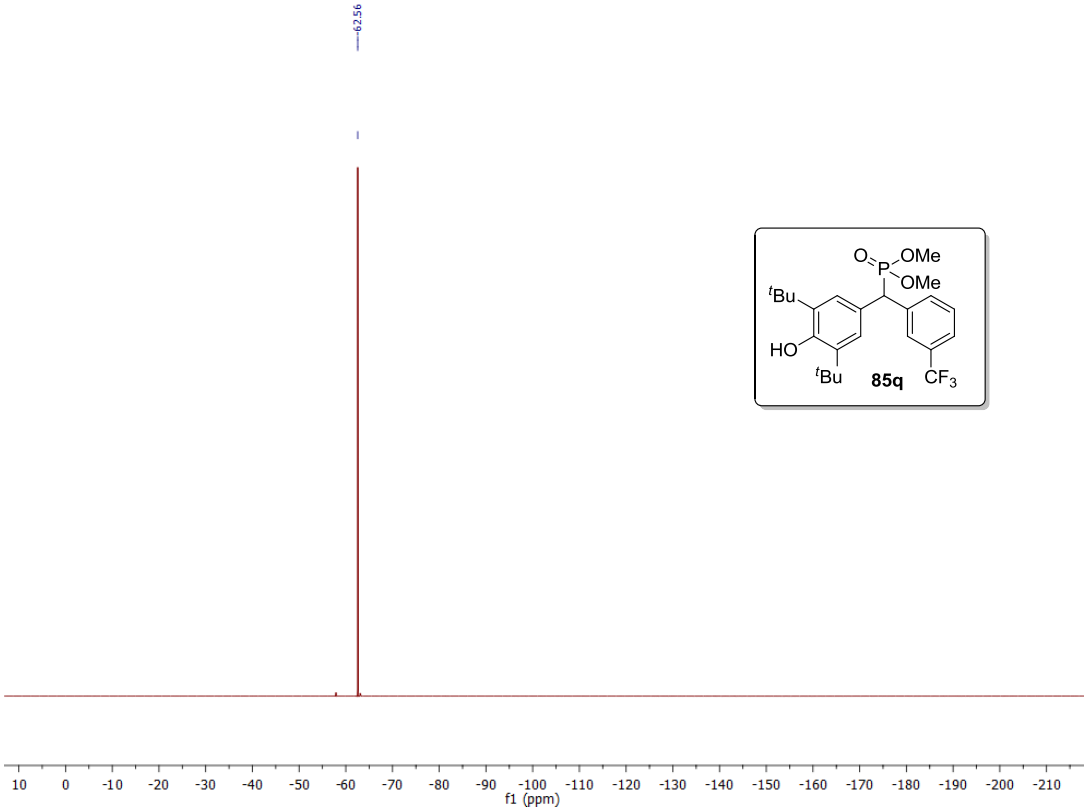
^{1}H NMR Spectrum of 85q



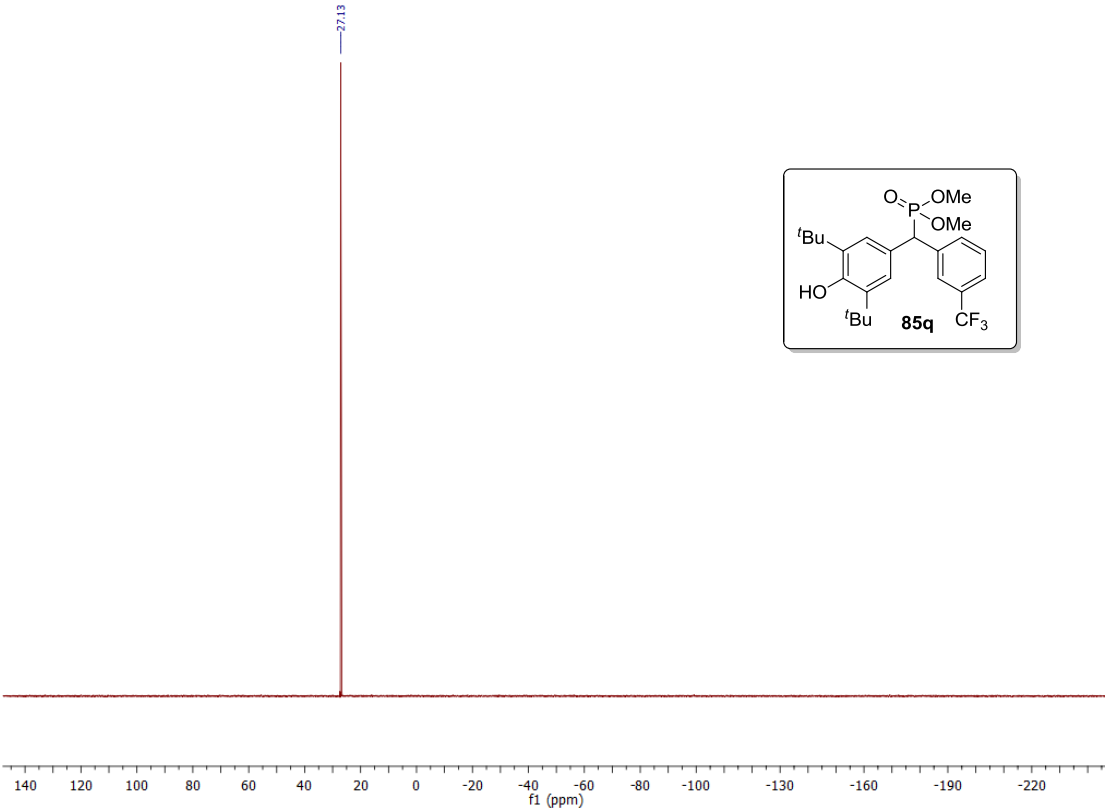
^{13}C NMR Spectrum of 85q



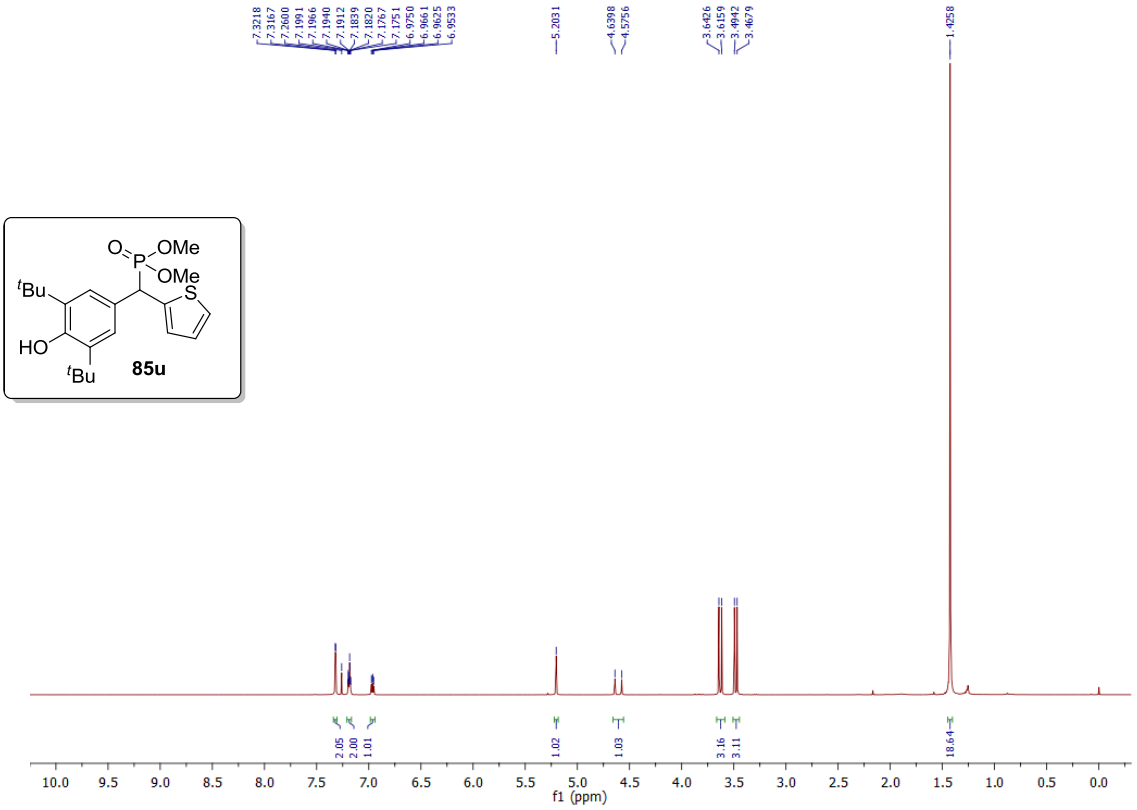
^{19}F NMR Spectrum of 85q



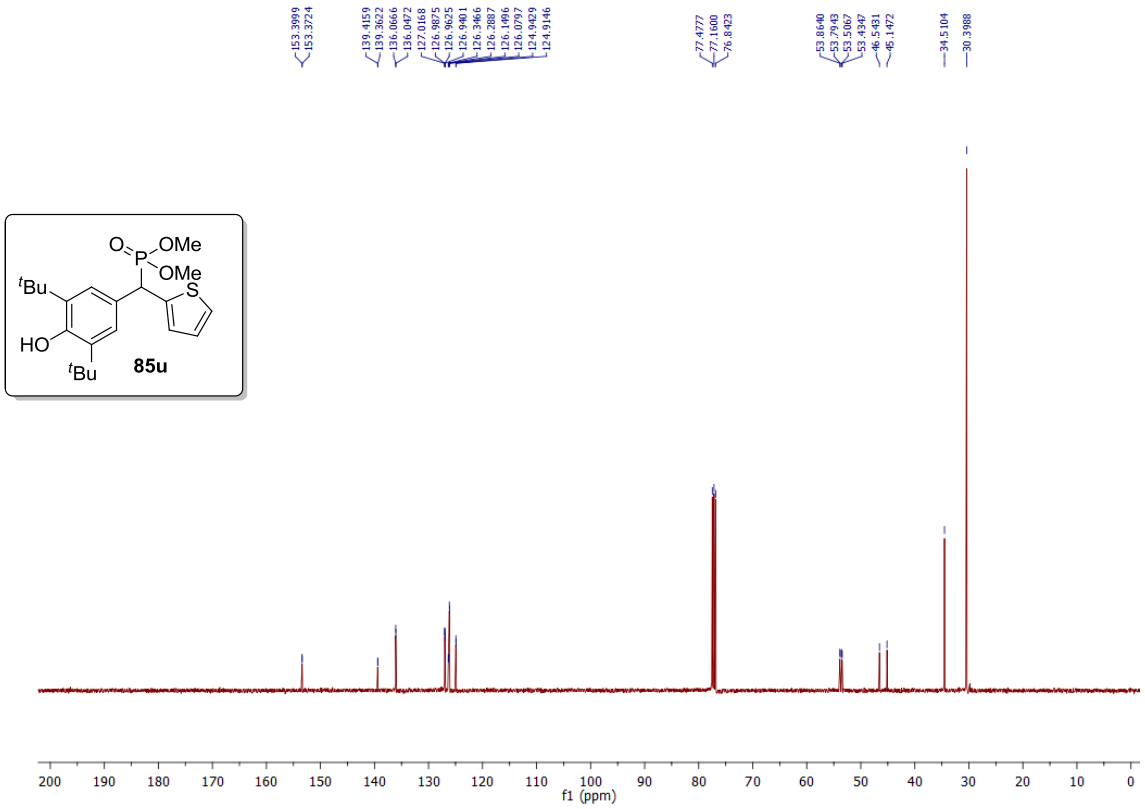
^{31}P NMR Spectrum of 85q



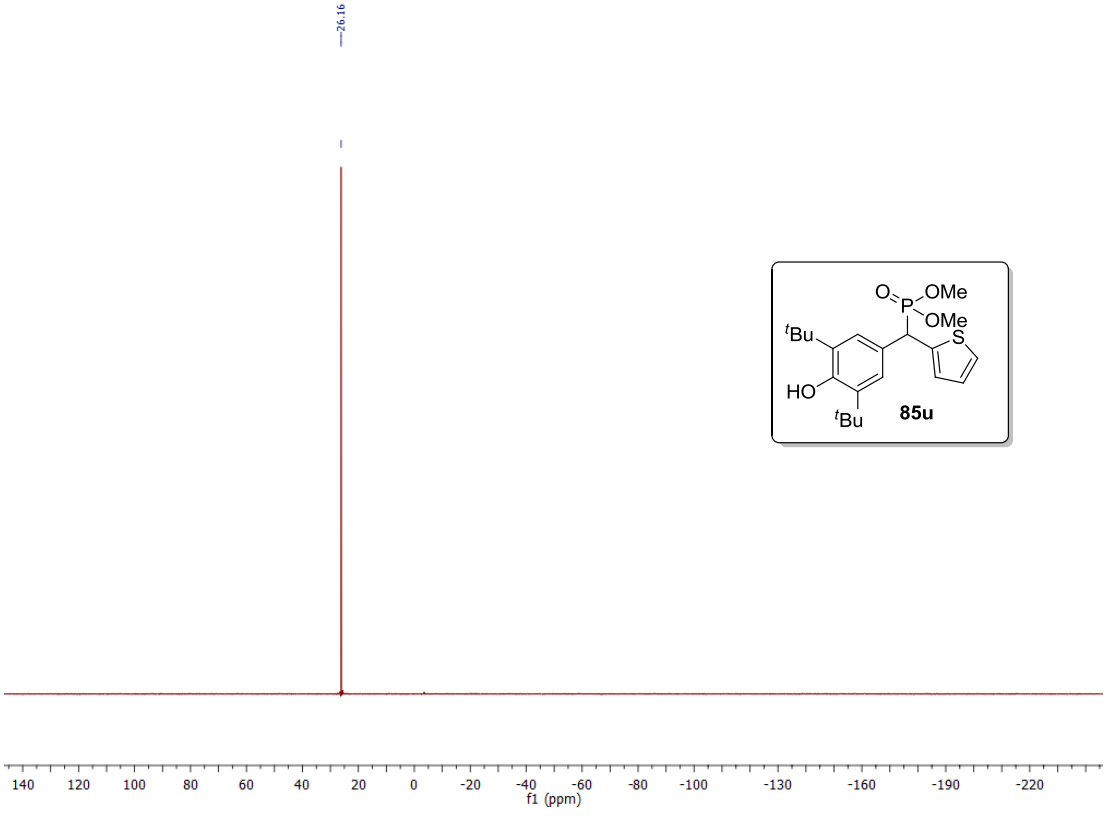
^{1}H NMR Spectrum of 85u



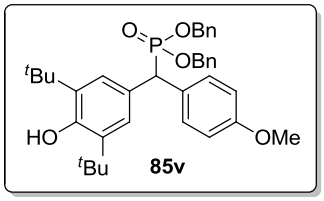
^{13}C NMR Spectrum of 85u



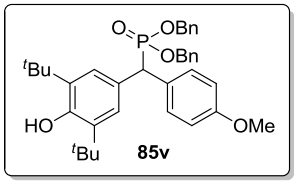
^{31}P NMR Spectrum of 85u



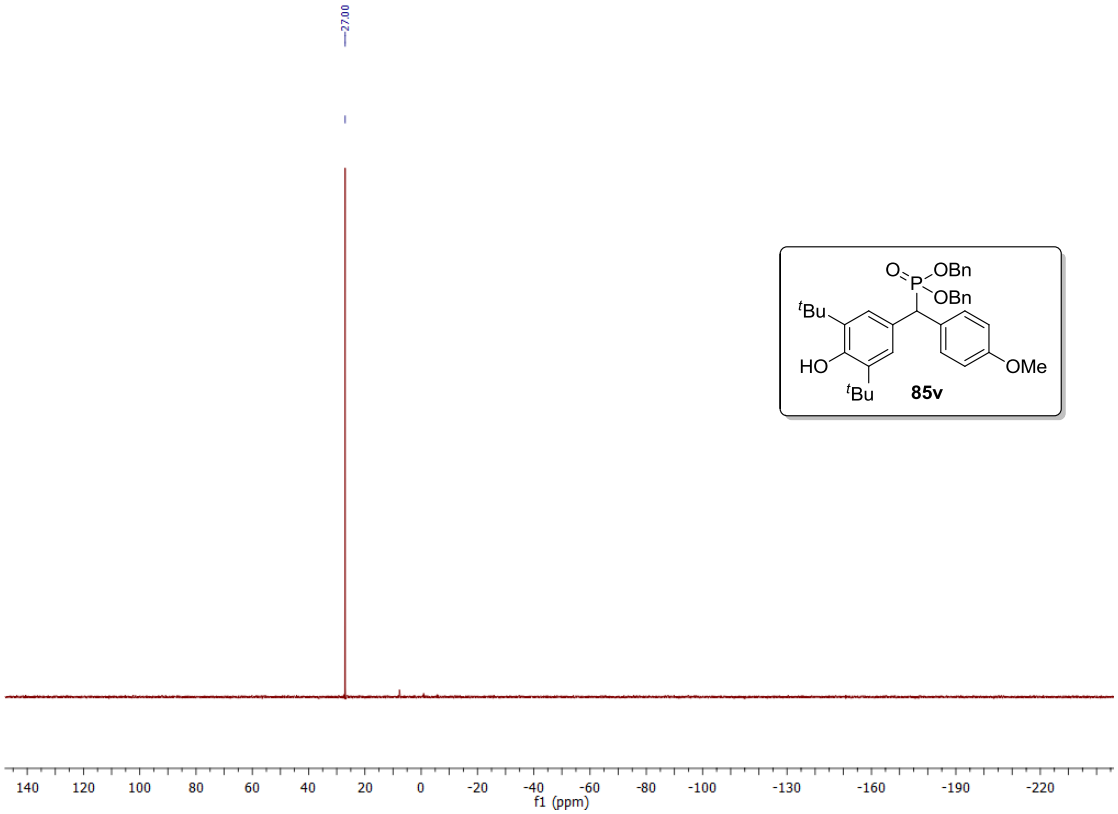
^{1}H NMR Spectrum of 85v



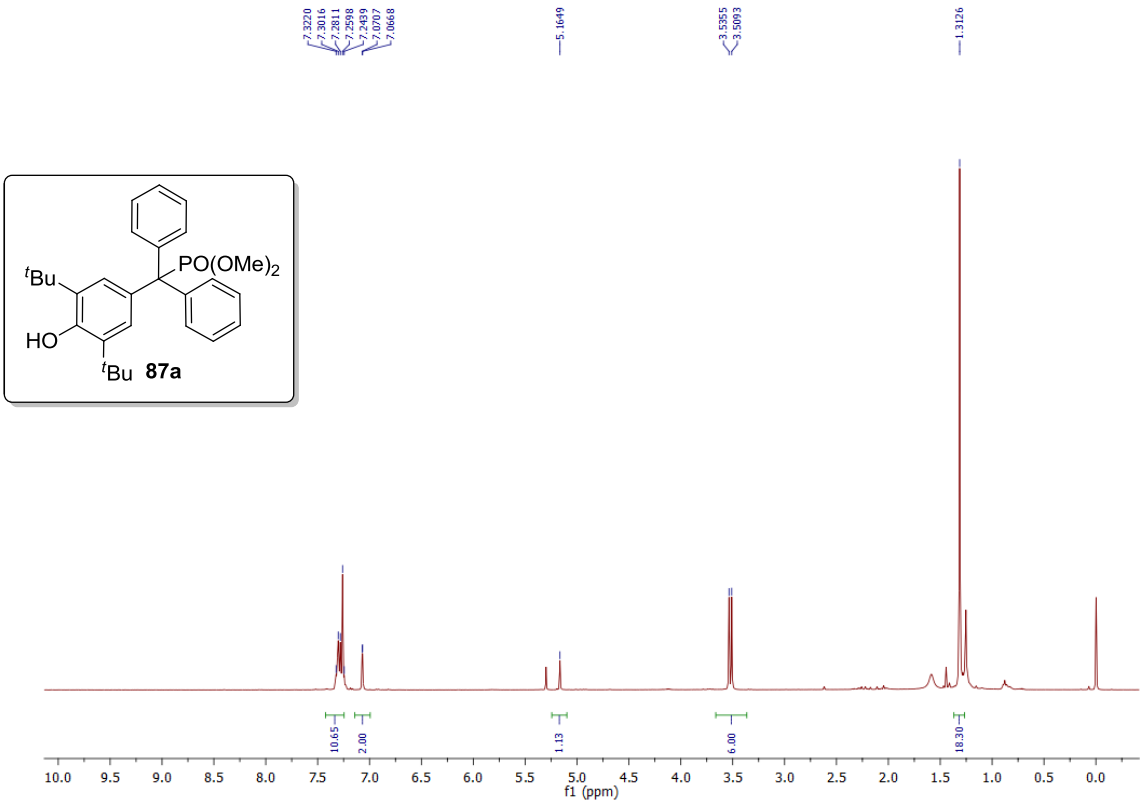
^{13}C NMR Spectrum of 85v



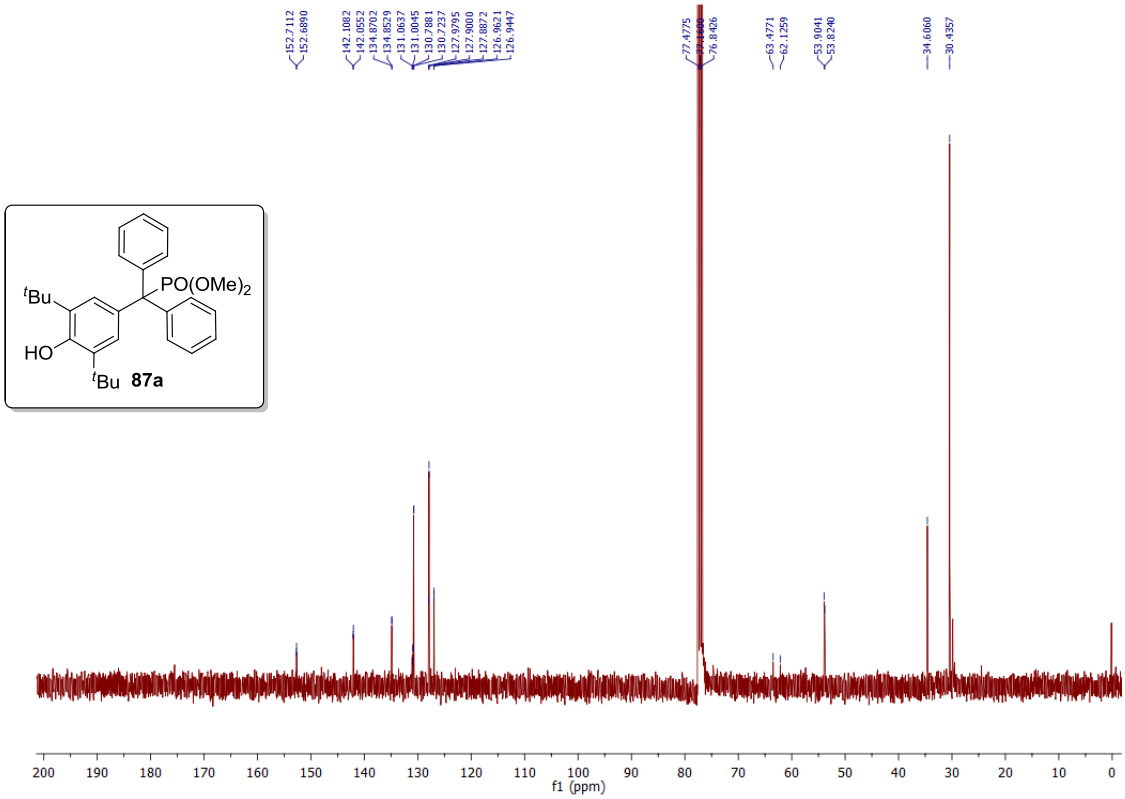
^{31}P NMR Spectrum of 85v



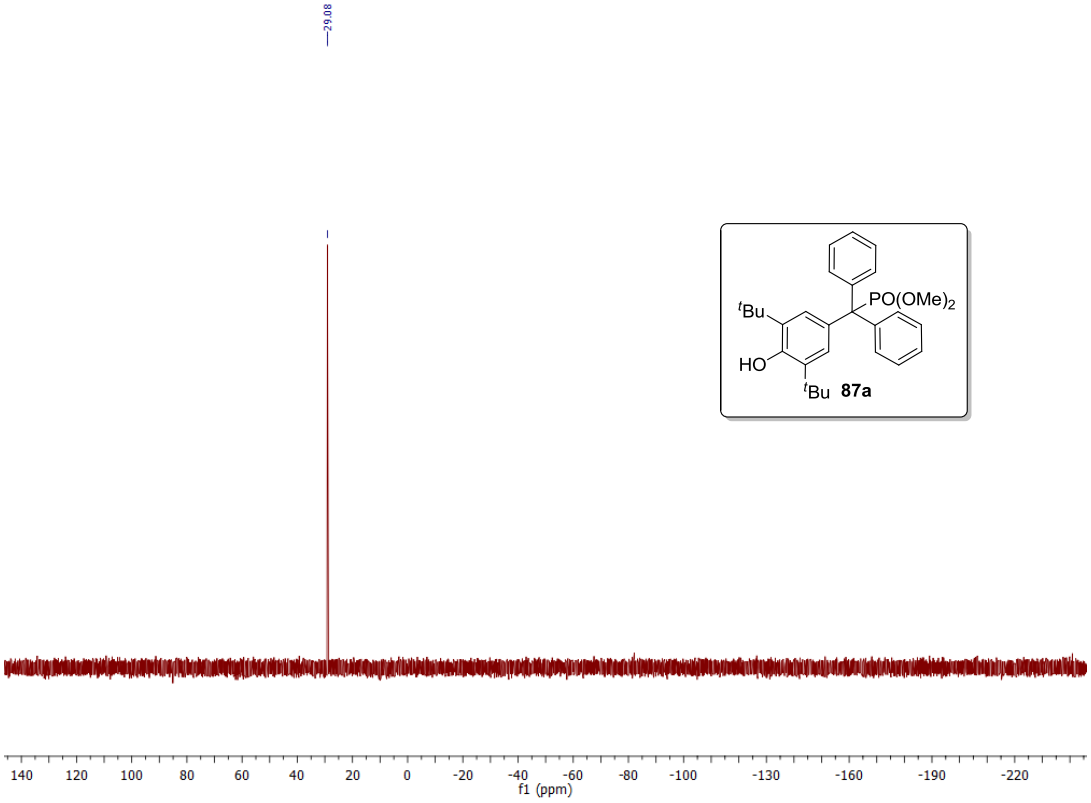
^{1}H NMR Spectrum of 87a



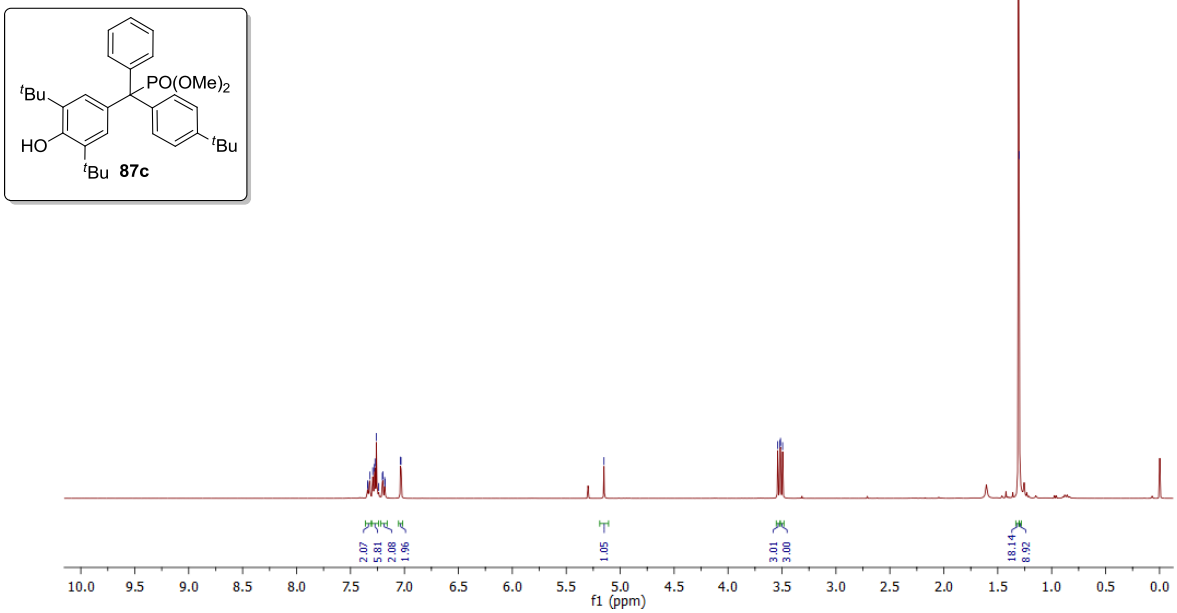
^{13}C NMR Spectrum of 87a



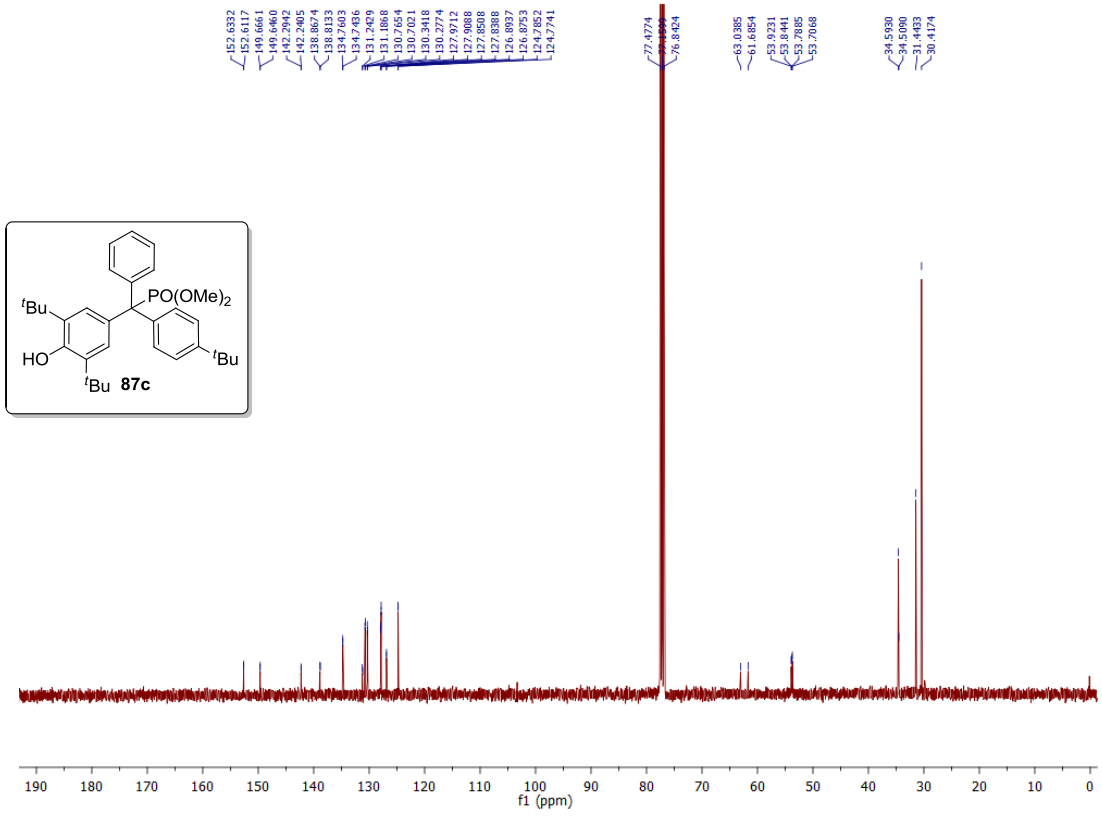
^{31}P NMR Spectrum of 87a



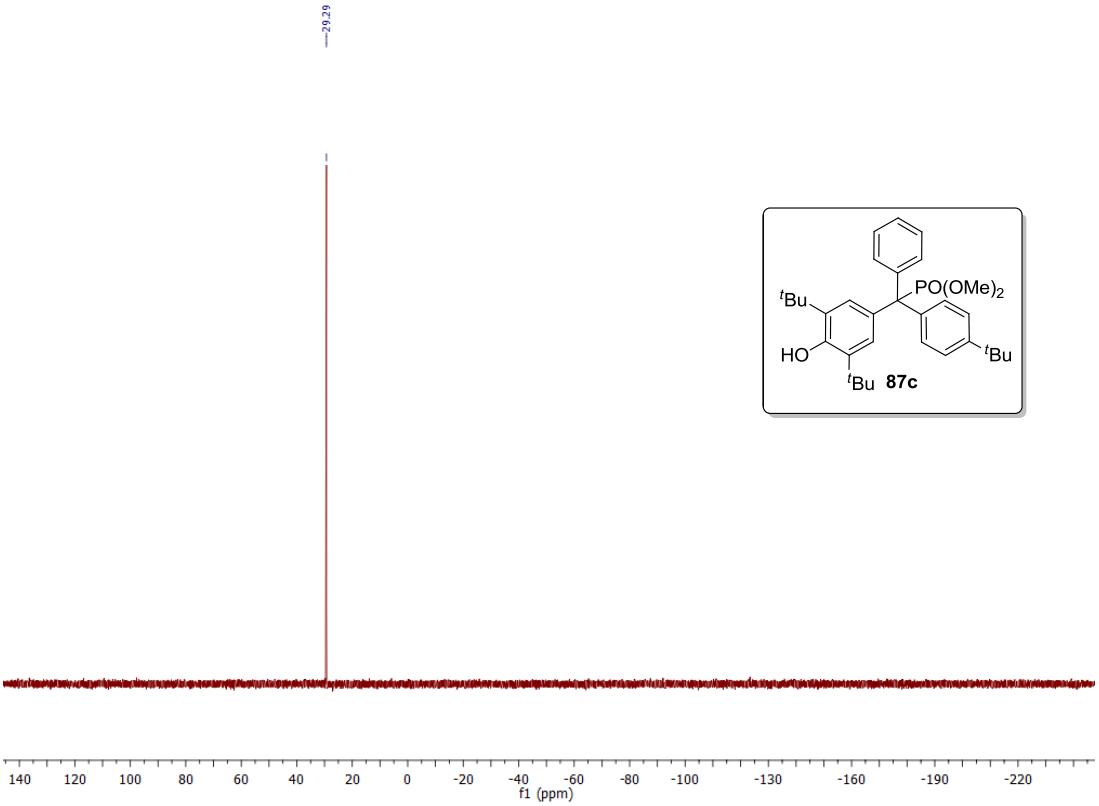
^{1}H NMR Spectrum of 87c



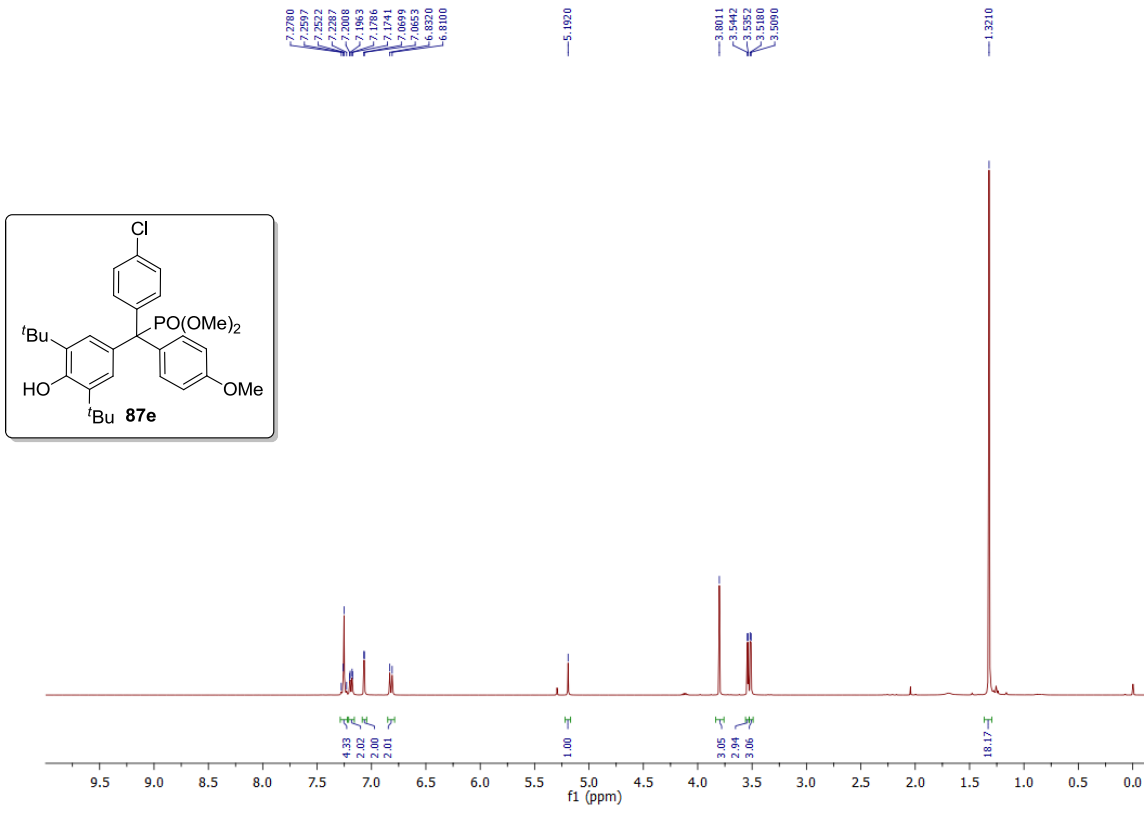
^{13}C NMR Spectrum of 87c



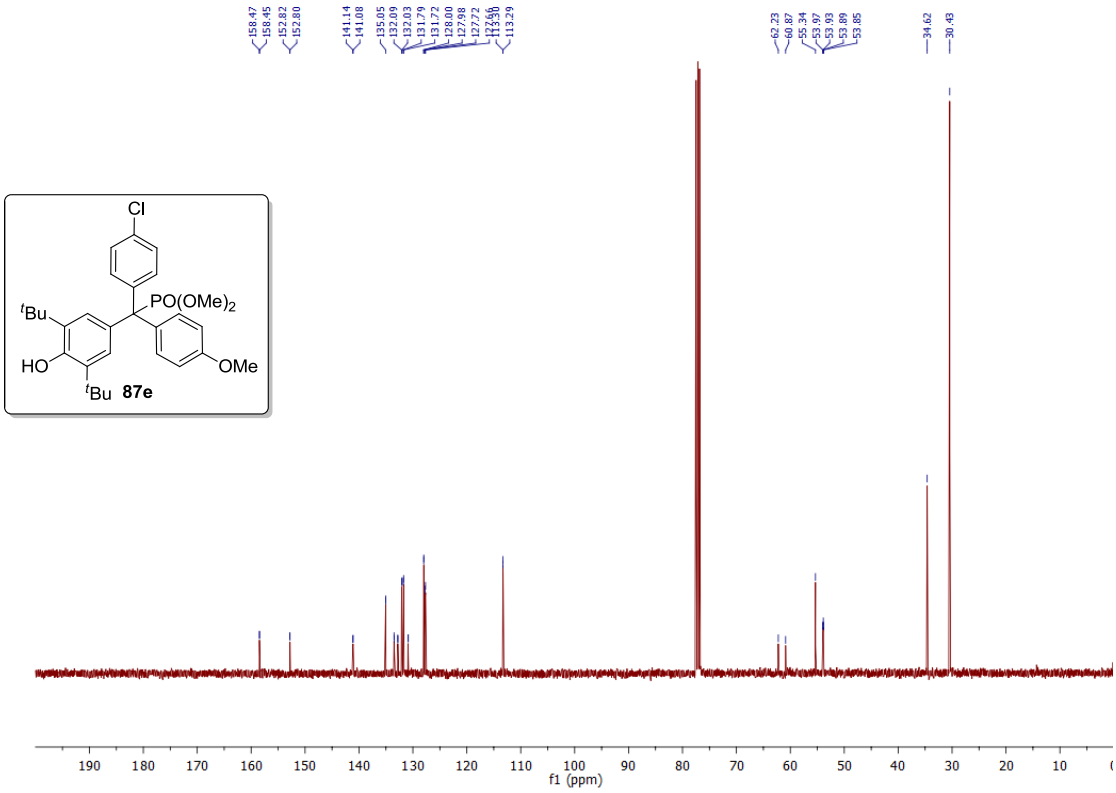
^{31}P NMR Spectrum of 87c



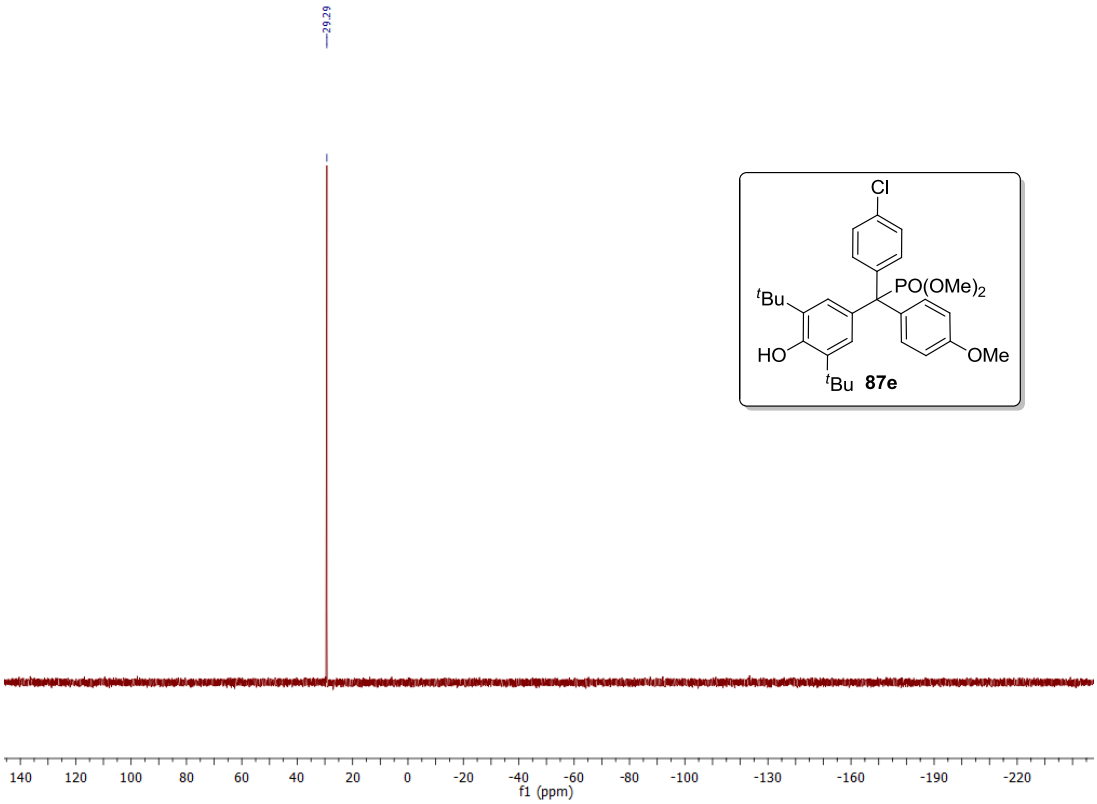
^{1}H NMR Spectrum of 87e



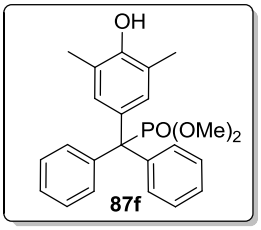
^{13}C NMR Spectrum of 87e



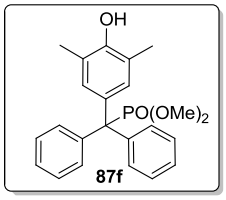
^{31}P NMR Spectrum of 87e



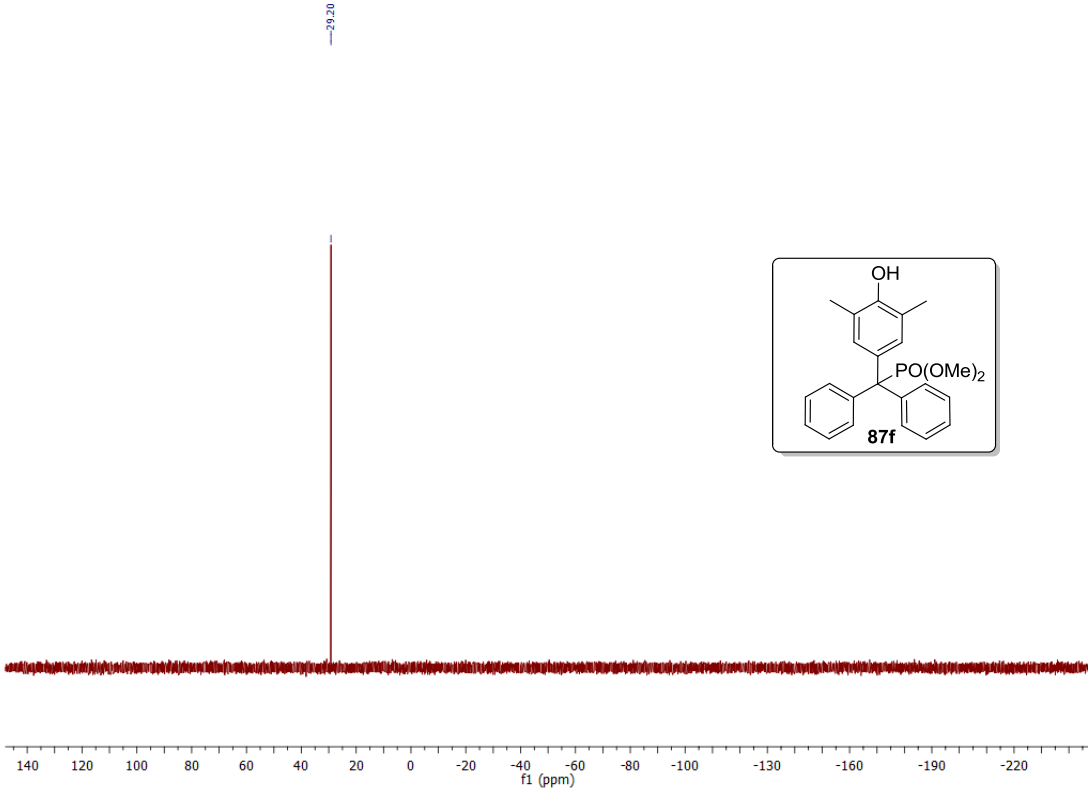
^{1}H NMR Spectrum of 87f



^{13}C NMR Spectrum of 87f



^{31}P NMR Spectrum of 87f



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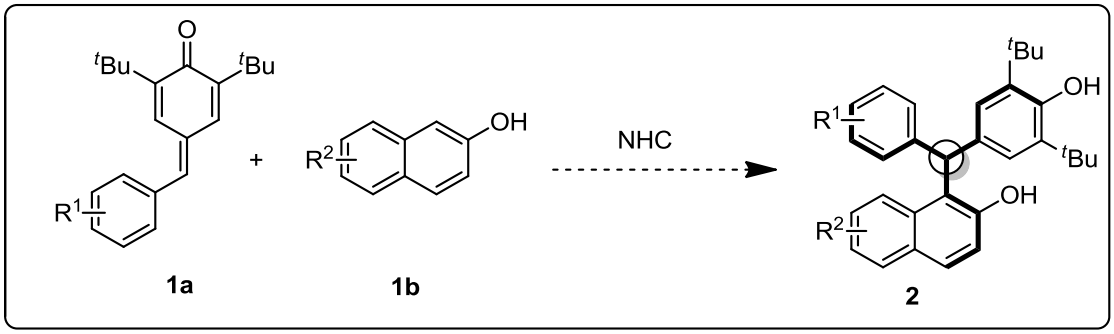
Part B: *N*-heterocyclic carbene catalyzed 1,6-conjugate addition of 2-naphthol to *p*-quinone methides: Expedient access to unsymmetrical triarylmethanes

In this part, the NHC-catalyzed synthesis of unsymmetrical triarylmethane derivatives has been discussed.

1.1) Introduction

After successfully implementing the NHC as a Brønsted base catalyst in vinylogous Michael addition of dialkylphosphites to *p*-quinone methides, we became interested in further extend the scope of these reactions by considering 2-naphthols (**1b**) as a nucleophile. At this point we envisioned that the unsymmetrical triarylmethane derivatives (**2**) could be easily accessed through NHC-catalyzed 1,6-conjugate addition of 2-naphthol (**1b**) to *p*-quinone methides (**1a**) (Scheme 1).



Scheme 1: Proposed scheme for NHC-catalyzed synthesis of unsymmetrical triarylmethanes

Triarylmethane derivatives have gained a great deal of attention from the scientific community due to their unique structural and physical properties. They are often found as building blocks in many biologically active compounds,[1] natural products,[2] fluorescent probes[3] and especially in dyes.[4] These compounds also hold several important applications in medicinal chemistry, such as anticancer agents,[5] antiproliferative agents[4c] and potassium ion channel blockers.[6] Their importance in materials science has also been exploared.[7] Some of the selected biologically active triarylmethanes are shown in figure 1.

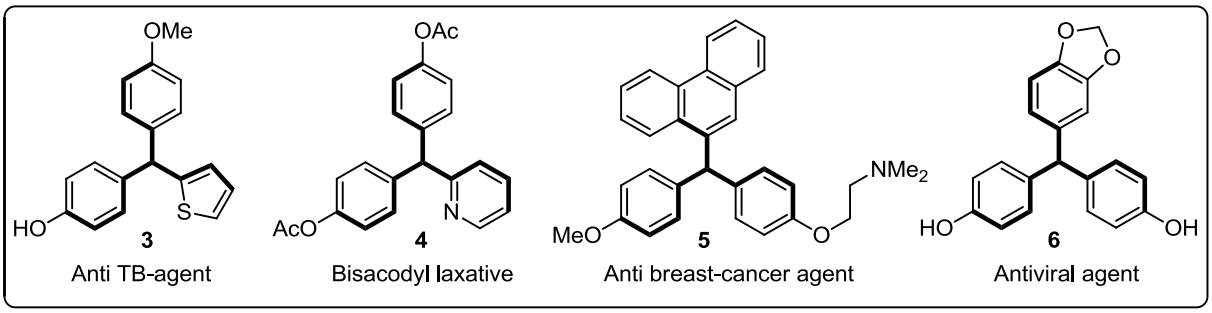
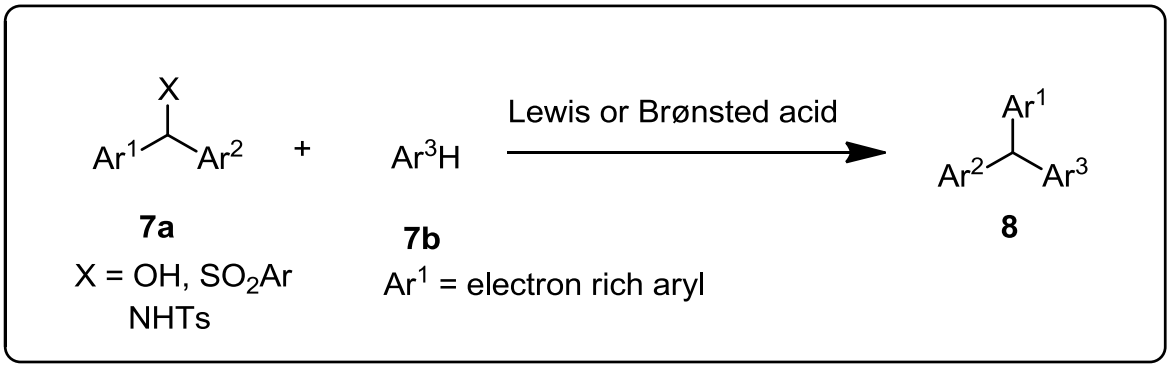


Figure 1: Important biologically active triarylmethane derivatives

2.2) Literature overview on the synthesis of triarylmethane derivatives

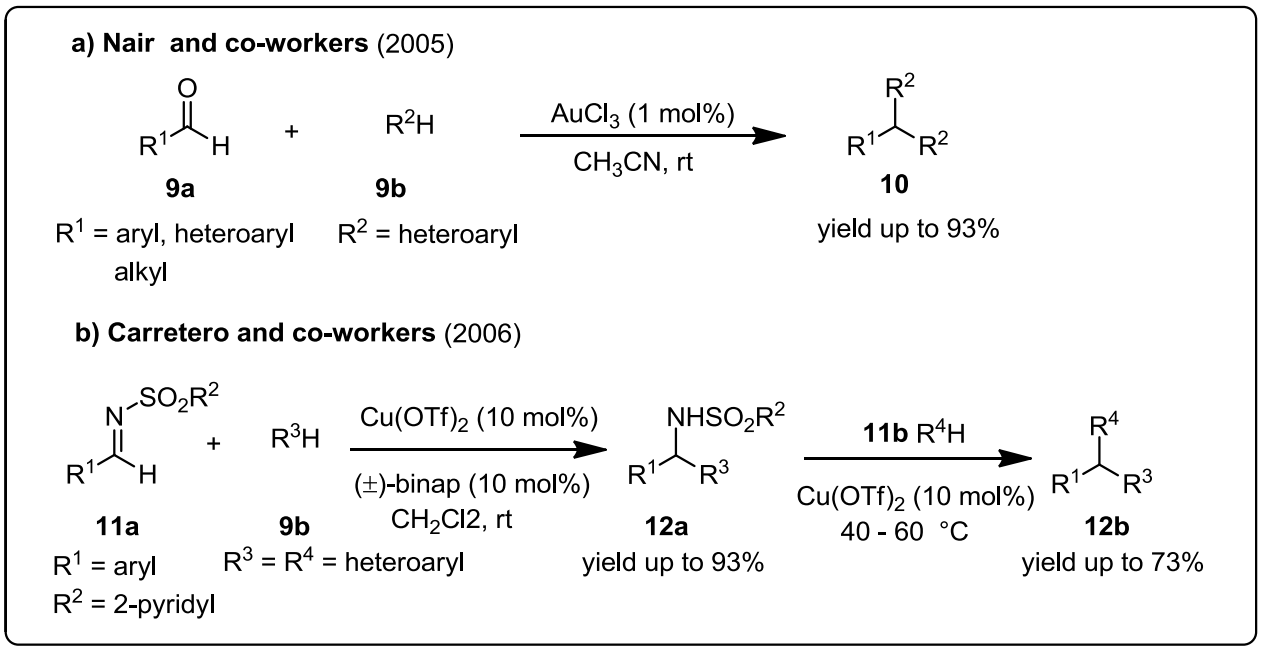
Due to their growing applications in various fields, enormous efforts have been made to the development of efficient methods for the synthesis of symmetrical and unsymmetrical triarylmethanes. The traditional methods mainly include Lewis[8] or Brønsted acid[9] catalyzed/mediated Friedel-Crafts type reactions[10] of diarylmethanols and their derivatives (**7a**) and reductive dehydroxylation of triarylmethanols.[11]



Scheme 2: General routes for the synthesis of triarylmethane derivatives

Although these methods provide simple and widely accepted path for the synthesis of symmetrical and unsymmetrical triarylmethanes, the requirement of nucleophilic electron-rich arenes and low regioselectivity of the products endures utility of these methods. To overcome these issues, recently transition metal-catalyzed approaches have been developed by many groups. Some of the selected methods for the synthesis of triarylmethanes are discussed below. Nair's group in 2005 developed an efficient method for the synthesis of triaryl- and triheteroarylmethanes (**10**).[12] The condensation between a range of aldehydes (**9a**) and variety of

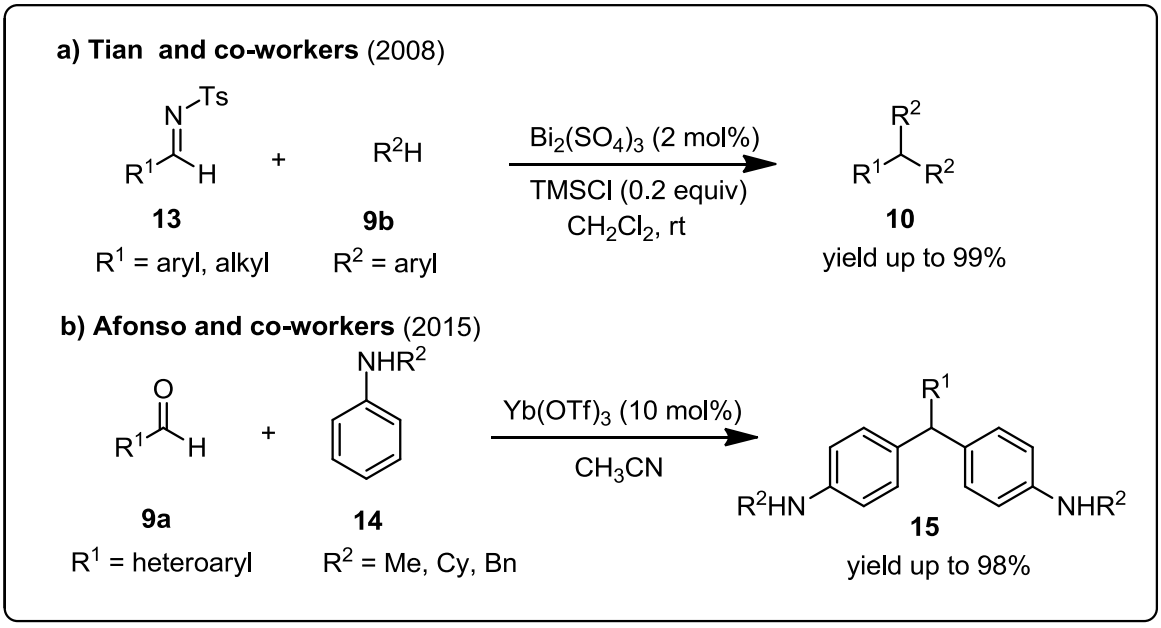
electron-rich arenes (**9b**) were promoted by Au(III) to access the corresponding triarylmethanes (**10**) in moderate to excellent yields (a, Scheme 3). Carretero and co-workers reported an interesting metal-controlled synthesis of unsymmetrical diaryl amines (**12a**) and triarylmethanes (**12b**) through Lewis acid-catalyzed aza-Friedel–Crafts reaction.[13] The addition of electron-rich aromatic derivatives (**9b**) to aldehydes, ketones and imines (**9b**) were performed in the presence of Cu(II) as a catalyst to synthesize the products (**12a, 12b**) in good yields. It was observed that, when sulfonyl substitution of sulfonyl imines was replaced with 2-pyridylsulfonyl group, only mono Friedel–Crafts product (**12a**) was obtained in up to 90% yield at room temperature. Whereas at elevated temperature the diaryl amines were successfully converted to corresponding triarylmethanes (**12b**) in excellent yields (b, Scheme 3).



Scheme 3: Lewis acid catalyzed synthesis of triarylmethanes

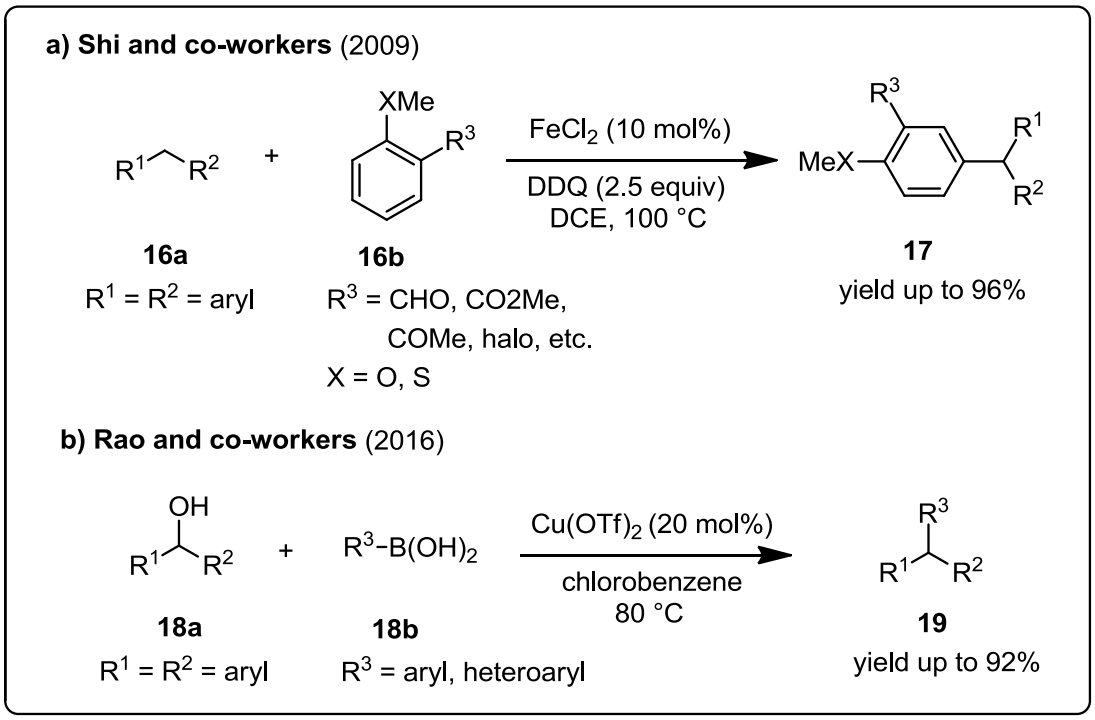
Tian and co-workers published an efficient double Friedel–Crafts reaction of imines (**13**) with moderately less active aromatic compounds (**9b**) such as anisole, phenol and thioanisole.[14] The corresponding triarylmethanes (**10**) were prepared in good to excellent yields with high regioselectivity using $Bi_2(SO_4)_3$–TMSCl as catalyst. The combination of Lewis acids with chlorotrimethylsilane promotes the addition of less activated nucleophilic species, which allows broad substrate scope for this reaction (a, Scheme 4). Recently, Afonso and co-workers

accomplished a ytterbium-catalyzed general approach for the synthesis of symmetrical triarylmethanes (**15**) through Friedel–Crafts reaction.[15] The aryl/heteroaryl aldehydes (**9a**) were treated with secondary anilines (**10**) to afford respective symmetrical triarylmethanes (**15**) in up to 98% yield. The rate and the yield of the reaction found to be inversely related with steric bulk around aniline nitrogen atom at 1 bar (b, Scheme 4).



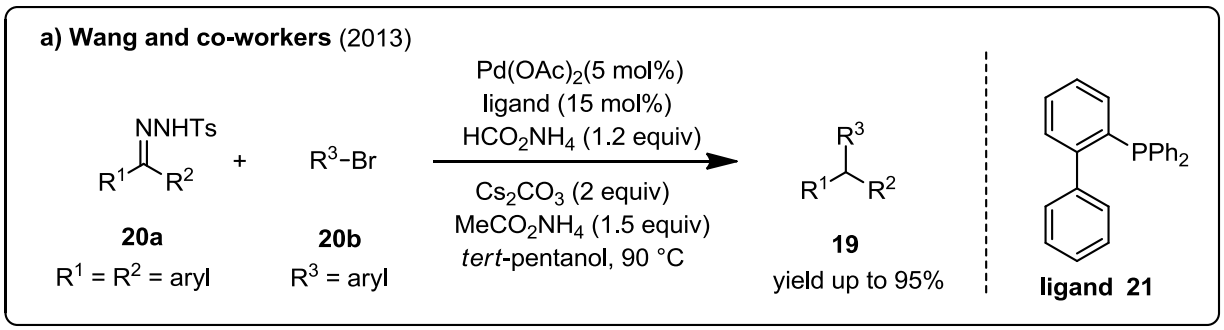
Scheme 4: Lewis acid catalyzed synthesis of triarylmethanes

Shi and coworkers demonstrated the synthesis of unsymmetrical triarylmethanes (**17**) by iron-catalyzed cross dehydrogenative arylation.[16] Highly regio- and chemoselective cross-coupling reaction between diarylmethanes (**16a**) bearing benzylic C–H bond and electron-rich anisole derivatives (**16b**) gave the desired triarylmethanes (**17**) in up to 96% yield. The reaction proceeds through single-electron-transfer oxidation followed by Friedel–Crafts alkylation. Electronic effect played a significant role as the electron-withdrawing diarylmethanes (**17**) were obtained in comparatively low yields. Prominently, iron appeared as an efficient catalyst when compared with other metals such as Pd, Ni, Cu, Co (a, Scheme 5). Very recently, Rao and co-workers developed a Cu-catalyzed synthesis of symmetric and unsymmetric triarylmethanes (**19**).[17] The reaction between diarylmethanols (**18a**) and arylboronic acids (**18b**) in presence of Cu(II)-catalyst gave the desired triarylmethanes (**19**) in up to 92% yield. This protocol was further used for the synthesis of high yielding anti-breast-cancer drug candidate (b, Scheme 5).



Scheme 5: Transition-metal-catalyzed synthesis of triarylmethane derivatives

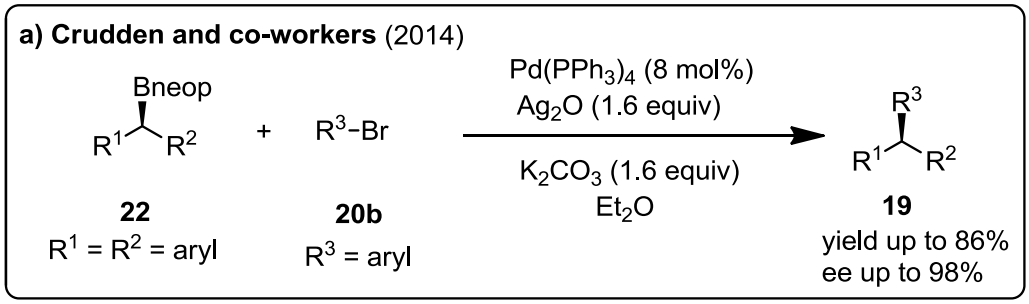
In 2013, Wang's group described the synthesis of triarylmethanes (**19**) through reductive cross-coupling between *N*-tosylhydrazones (**20a**) and aryl halides (**20b**).[18] This Pd-catalyzed approach for the construction of $C(sp^3)$–$C(sp^2)$ bond between diarylmethyl (**20a**) and aryl halide (**20b**) offered an easy route for the synthesis of triarylmethane (**19**) derivatives in up to 95% yield (Scheme 6).



Scheme 6: Pd-catalyzed synthesis of triarylmethane derivatives

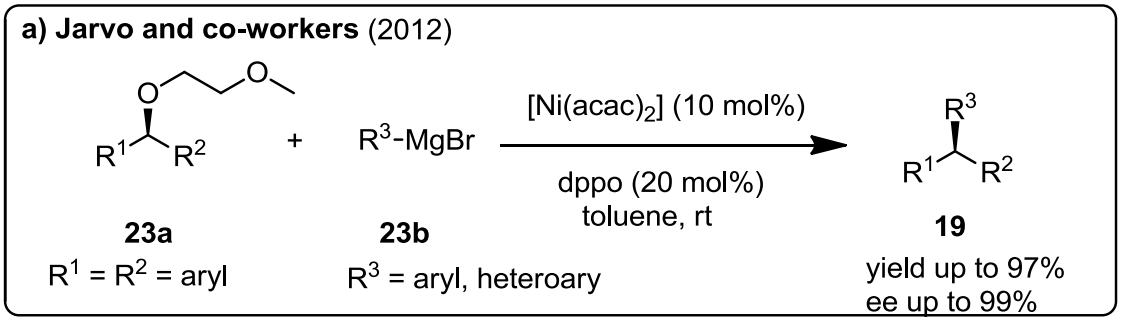
Crudden and co-workers demonstrated a novel Pd-catalyzed approach to an enantiomerically enriched triarylmethanes (**19**) by Suzuki–Miyaura cross-coupling reaction

between enantiomerically pure dibenzylic boronic (**22**) esters and iodobenzene derivatives (**20b**).[19] The enantiomerically enriched triarylmethanes (**19**) were isolated in up to 86% yield and up to 98% ee. The functional groups present on aryl ring (acetyl, formyl, and chloro), which could lead to further derivatization of chiral product, were successfully tolerated. The 100% stereoretention of products was observed mainly due to the absence of directing heteroatom (Scheme 7).



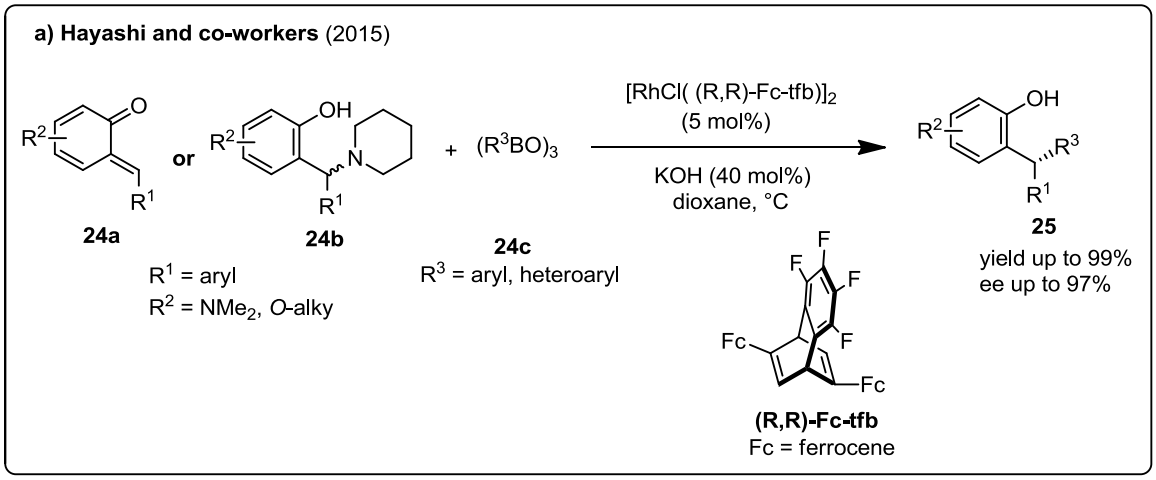
Scheme 7: Pd-catalyzed synthesis of enantiomerically enriched triarylmethanes

In addition, other transition metal-catalyzed coupling reactions such as Ni-, Rh- were also developed for the synthesis of triarylmethanes. Jarvo's group published a novel Ni-catalyzed cross-coupling of enantioenriched diarylmethanol derivatives (**23a**) with aryl Grignard reagents (**23b**) to afford chiral triarylmethanes (**19**) in excellent enantiomeric excess.[20] The coupling proceeds *via* a cleavage of relatively inert benzylic C−O bond followed by transmetallation of Ni with Mg of Grignard reagents (**23b**). The methoxyethyl group accelerates the transmetallation through coordination of the ether with Mg. The scope of this method was further extended for the synthesis of enantioenriched anti-breast-cancer agent in 72% yield (Scheme 8).



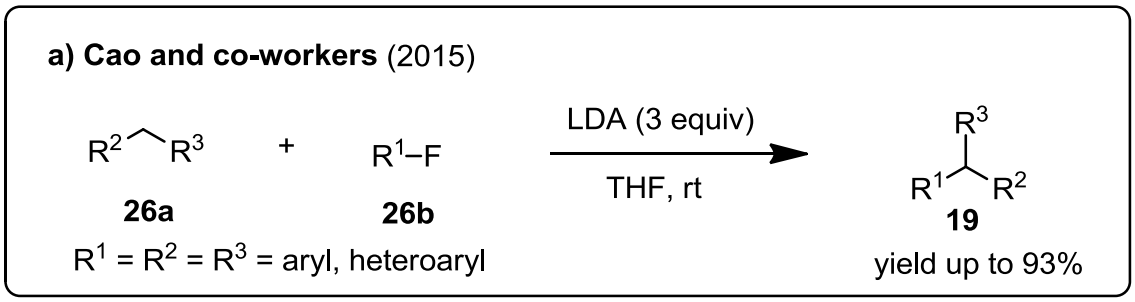
Scheme 8: Ni-catalyzed synthesis of enantiomerically enriched triarylmethanes

Recently, Hayashi and co-workers developed Rh-catalyzed asymmetric approach to synthesize chiral triarylmethane derivatives (**25**) through enantioselective arylation of recemic *o*-quinone methides (**24a**) with arylboroxines (**24c**).[21]Diarylmethyl amines (**24b**) with 2-hydroxy group were also implemented to synthesize corresponding products (**25**) through C−N bond cleavage. In both the cases, resultant chiral triarylmethanes (**25**) were afforded in up to 99% yield and up to 97% ee (Scheme 9).



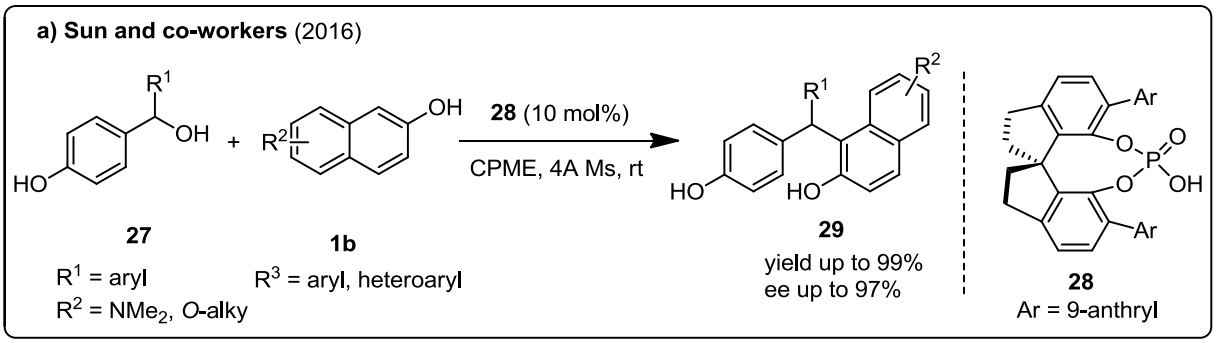
Scheme 9: Rh-catalyzed synthesis of enantiomerically enriched triarylmethanes

Even though transition-metal-catalyzed strategies provide a wide substrate scope and excellent functional group tolerance, they suffer from the use of toxic and expensive catalysts, and complicated ligands. On the other hand, the metal free organocatalytic approaches for the synthesis of triarylmethanes, show high advantages. In 2015, Cao's group developed a metal-free base mediated approach for the synthesis of triarylmethanes (**19**) *via* direct C−H arylation of diarylmethanes (**26a**) with variety of fluoroarenes (**26b**).[22] This protocol displayed wide range of substrate scope, as LDA-mediated arylation of different diarylmethanes such as 9*H*-fluorenes, and 9*H*-xanthenes were succesively achieved with moderate to high yields. Though the C−F bond cleavage followed by functionalization requires low temperature (-70 °C), the present protocol worked smoothly at room temperature (Scheme 10).



Scheme 10: Base mediated synthesis of triarylmethane derivatives

Very recently, Sun and co-workers reported an efficient organocatalytic enantioselective synthesis of triarylmethanes (**29**) by intermolecular 1,6-conjugative addition of naphthols (**1b**) to *para*-quinone methides.[23] The *p*-hydroxybenzyl alcohols (**27**) were used as a precursor for *in situ* generation of *p*-QMs. Corresponding enantioselective triarylmethanes (**29**) were accessed in up to 99% yield with 93% ee using chiral phosphoric acid as catalyst. Although the substrate scope was limited, this methodology imparted a mild and efficient route for the synthesis of triarylmethanes (**29**) bearing tertiary chiral stereocenters (Scheme 11).



Scheme 11: Chiral phosphoric acid catalyzed 1,6-conjugate addition of naphthol to *p*-QMs

2.3) Results and Discussions

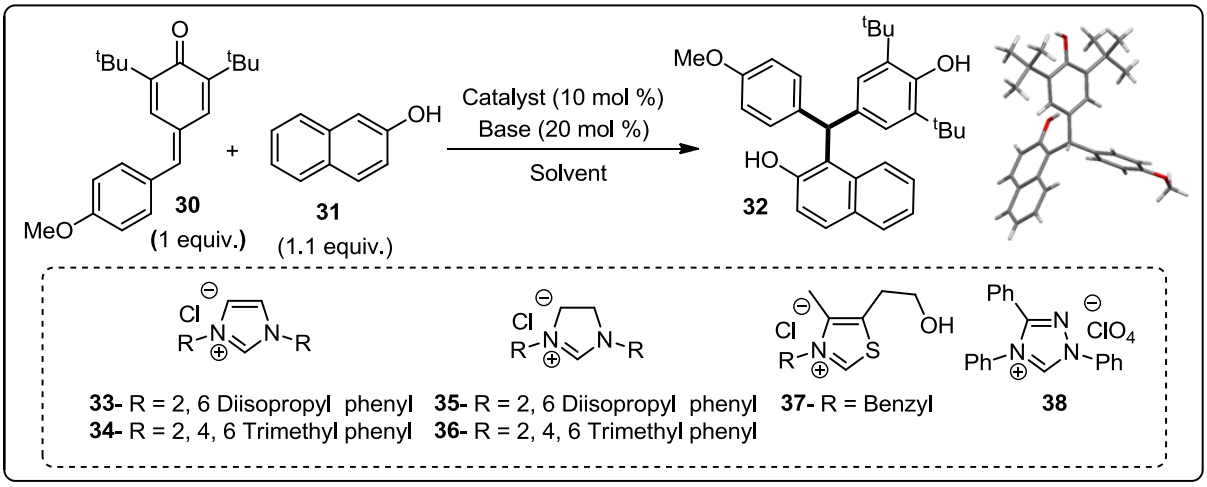
Although all the above mentioned coupling and metal-free strategies show a wide substrate scope and excellent functional group tolerance, none of these methods meet 100% atom economy. Therefore, developing a simple and atom economical approach for the synthesis of triarylmethanes, especially under organocatalytic conditions, would be more striking and highly desirable.

Herein, we disclose the synthesis of highly functionalised triarylmethane derivatives through 1,6-conjugate addition of 2-naphthols to *p*-QMs using NHC as a Brønsted base catalyst.

The optimisation studies were carried out with *p*-QM **30** and 2- naphthol under various reaction conditions using different NHC precursors (**33**–**38**), and the results are shown in Table 1. When the reaction was performed using **33** as a NHC precursor and NaH as a base in THF, the expected product **32** was obtained in 60% yield in 24 h (entry 1). The structure of **32** was indisputably confirmed by spectroscopic methods as well as X-ray analysis (Table 1). Prompted by this result, we elaborated the optimisation studies in different solvents (entries 2–7). Out of several solvents screened, dichloromethane was found to be the most suitable solvent for this methodology, as **32** was obtained almost in quantitative yield in 18 h under this condition (entry 3). Further experiments were carried out using other NHC precursors (**34**–**38**) in CH_2Cl_2. However, in all those cases (entries 8–12), the product **32** was obtained in relatively less yield when compared to entry 3. The effectiveness of other bases such as K_3PO_4 and Cs_2CO_3 for this transformation were found to be inferior when compared to NaH (entries 13 & 14). To confirm the role of NHC in this transformation, a couple of experiments were performed only in the presence of base without NHC precursors (entries 15 & 16), but in both the cases, the product was obtained in <10% yield. Surprisingly, when the reaction was carried out with DBU as a base without NHC precursor, **32** was isolated in 67% yield though the reaction was not completed even after 48 h (entry 17). In another experiment, the reaction between **30** and **31** was carried out with IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) in the absence of base and, in this case, **32** was obtained in 87% yield after 24 h. This observation clearly indicates that the NHC is actually acting as a catalyst.

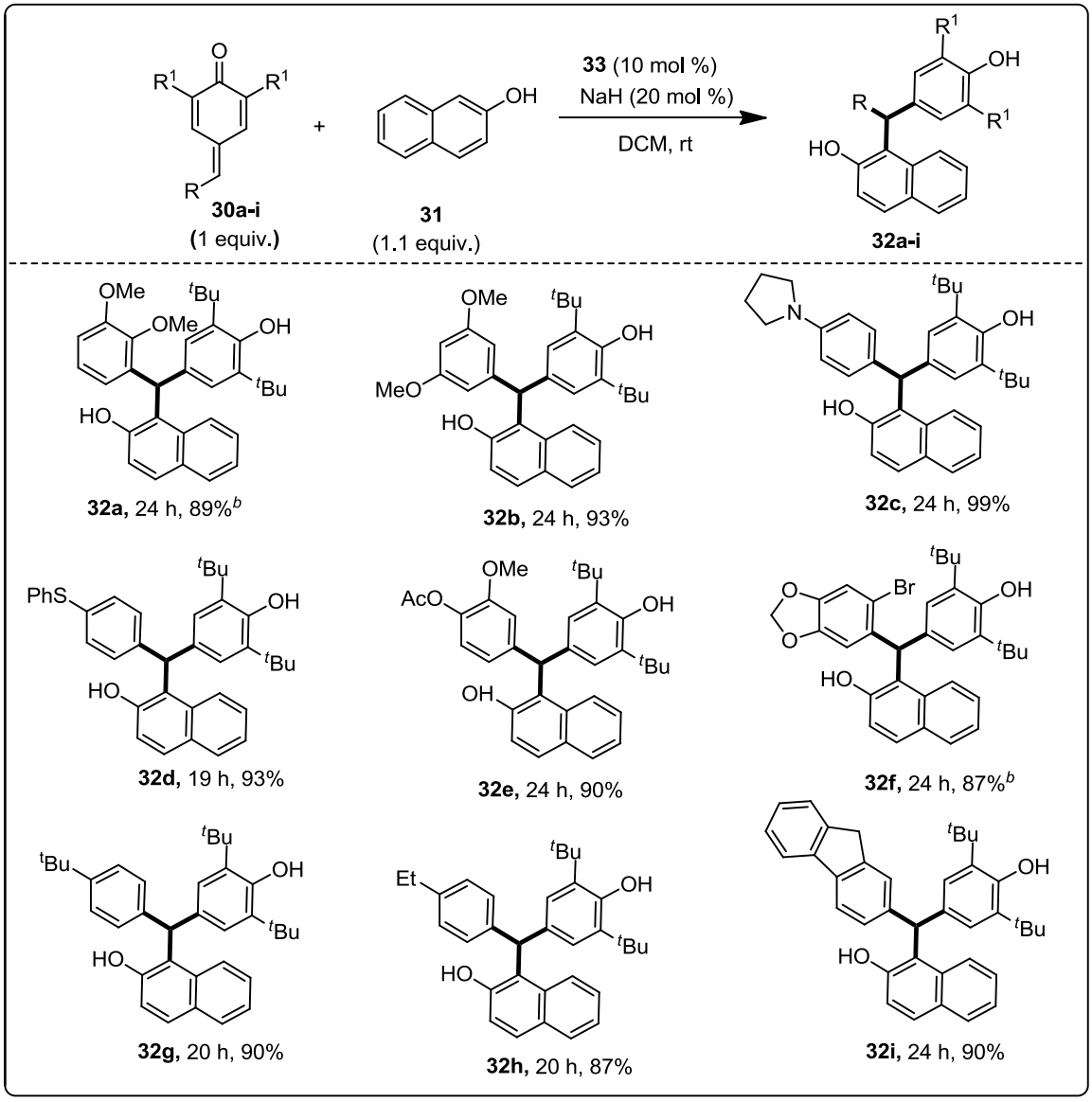
Having found the optimal reaction conditions (entry 3, Table 1), we went on to study the scope and limitations of this transformation using 2-naphthol and a diverse set of *p*-quinone methides, and the results are shown in Scheme 12-14. Electronic effects of the aryl substituents in *p*-QMs were found to have minimal influence in the reaction as the *p*-QMs derived from both electron-poor and electron-rich aromatic aldehydes underwent smooth conversion to their corresponding triarylmethanes in very high yields.

Table 1: **Optimization studies**[a]



Entry	Pre-catalyst	Base	Solvent	Time [h]	Yield [%]
1	**33**	NaH	THF	24	60
2	**33**	NaH	Et_2O	24	80
3	**33**	**NaH**	**CH_2Cl_2**	**18**	**99**
4	**33**	NaH	DCE	24	91
5	**33**	NaH	PhMe	21	93
6	**33**	NaH	DMSO	24	90
7	**33**	NaH	MeCN	24	20
8	**34**	NaH	DCE	22	93
9	**35**	NaH	DCE	24	78
10	**36**	NaH	CH_2Cl_2	24	80
11	**37**	NaH	CH_2Cl_2	24	60
12	**38**	NaH	CH_2Cl_2	24	84
13	**33**	K_3PO_4	CH_2Cl_2	24	90
14	**33**	Cs_2CO_3	CH_2Cl_2	24	94
15	–	NaH	CH_2Cl_2	24	7
16	–	Cs_2CO_3	CH_2Cl_2	24	5
17	–	DBU	CH_2Cl_2	48	67
18[b]	IPr	–	CH_2Cl_2	24	87

[a]Reaction conditions: all reactions were carried out with 0.062 mmol of **30** in 0.3 mL of solvent at room temperature. [b] The reaction was carried out with free IPr NHC.

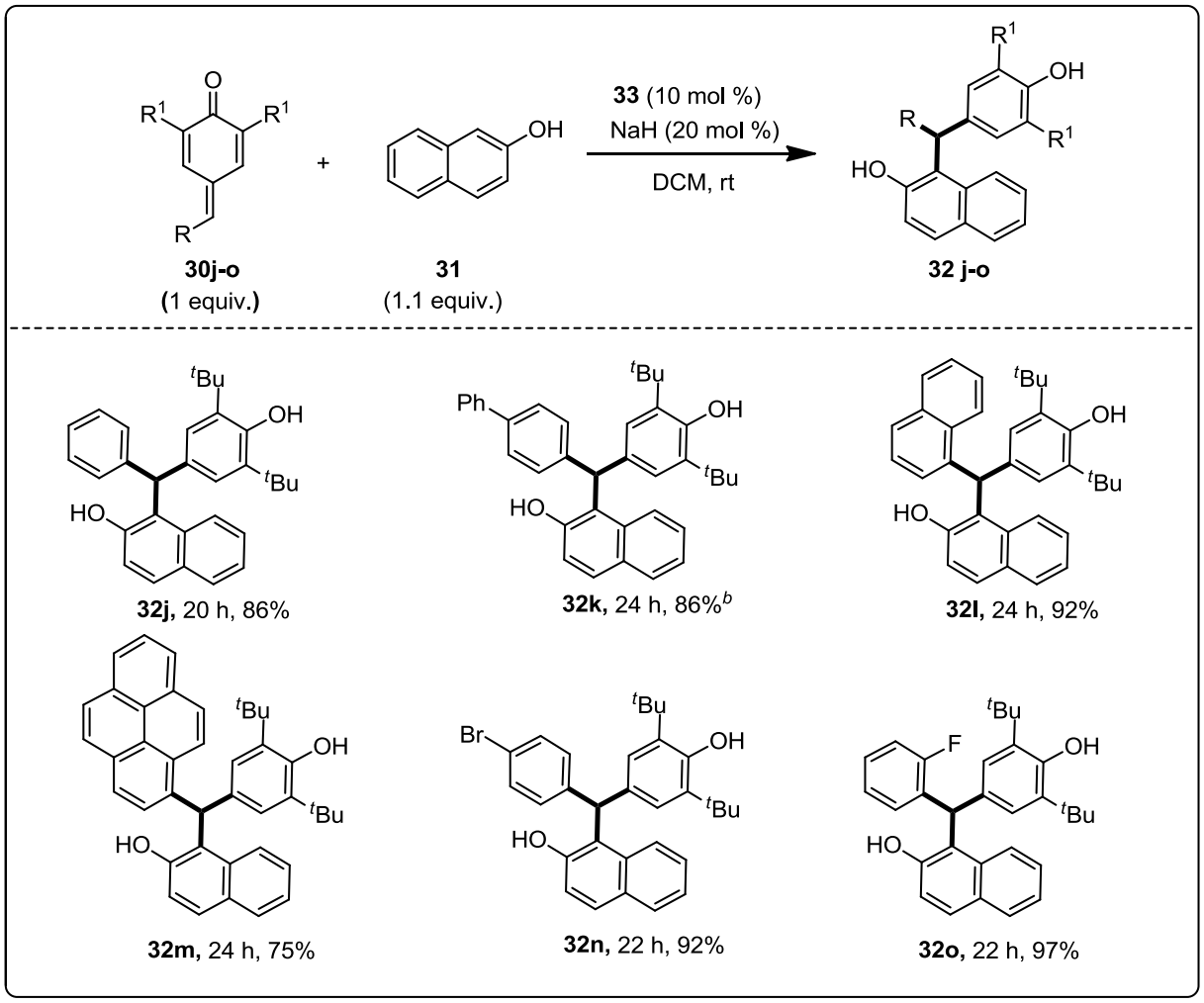


[a]Reaction conditions: all reactions were carried out with 20 mg scale of **30** in 0.3 mL of solvent at room temperature. [b] Reactions were carried out with 100 mg scale of **30** in 1.5 mL of solvent at room temperature.

Scheme 12: Synthesis of unsymmetrical triarylmethans[a]

In general, this methodology worked extremely well in the cases of *p*-QMs (**30a**–**h**) derived from electron-rich aromatic aldehydes as the expected triarylmethanes (**32a**–**h**) were obtained in excellent isolated yields (89–99%). Other *p*-QMs (**30i**–**m**) derived from benzaldehyde or arylated benzaldehydes also underwent 1,6-conjugate addition and provided the respective triarylmethanes (**32i**–**m**) in good to excellent yields (75–92%).This method was found to be

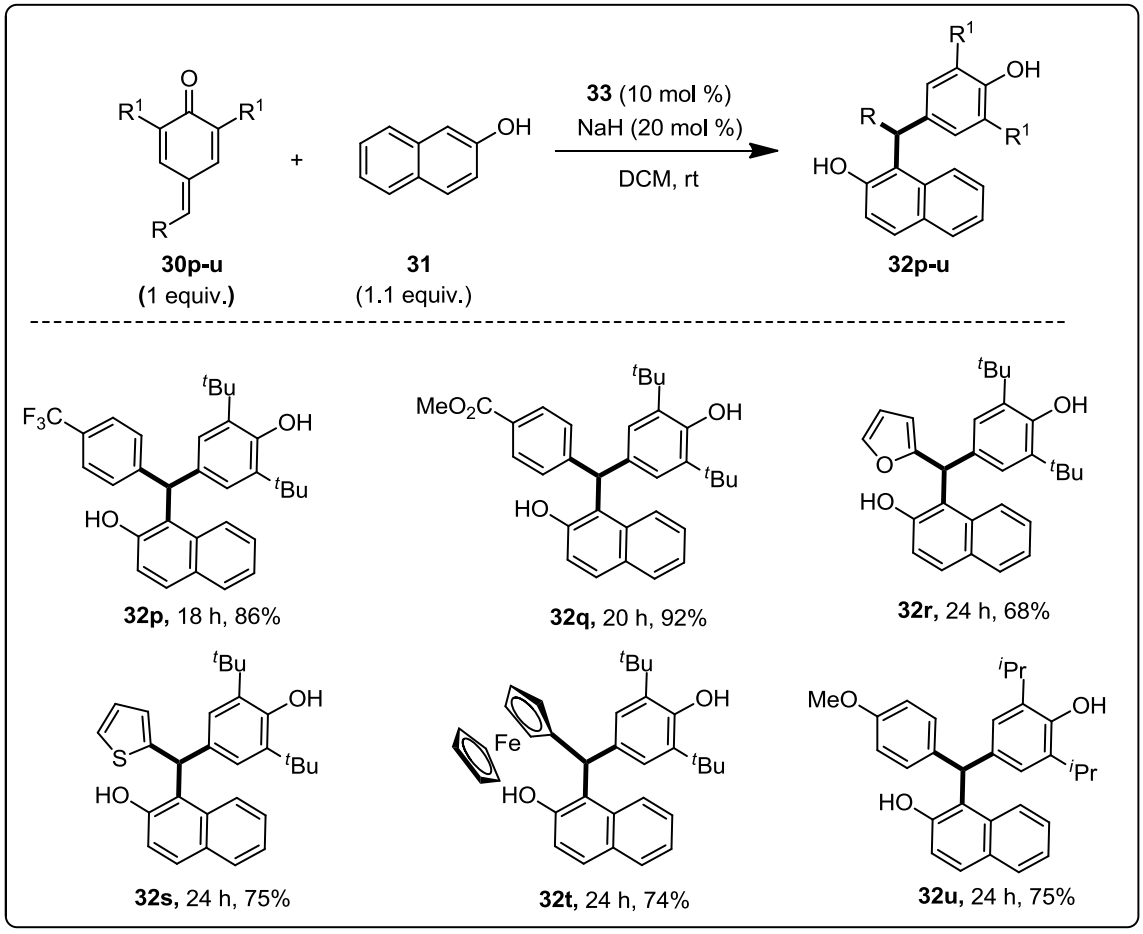
robust for the *p*-QMs derived from halogen substituted aromatic aldehydes. For example, *p*-QMs **30n** and **30o** reacted with 2-naphthol under the optimal conditions and gave the corresponding products **32n** and **32o** respectively in very high yields (Scheme 12-13).



[a]Reaction conditions: all reactions were carried out with 20 mg scale of **30** in 0.3 mL of solvent at room temperature. [b] Reactions were carried out with 100 mg scale of **30** in 1.5 mL of solvent at room temperature.

Scheme 13: Synthesis of unsymmetrical triarylmethanes[a]

In the cases of electron-poor aryl substituted *p*-QMs (**30p**–**q**), the products **32p** and **32q** were isolated in 86 and 92% yields correspondingly. The heteroaryl-containing triarylmethanes **32r** and **32s** were obtained in moderate yields from the *p*-QMs (**30r** and **30s**), prepared from furan-2-carboxaldehyde and thiophene-2- carboxaldehyde respectively. The ferrocene containing



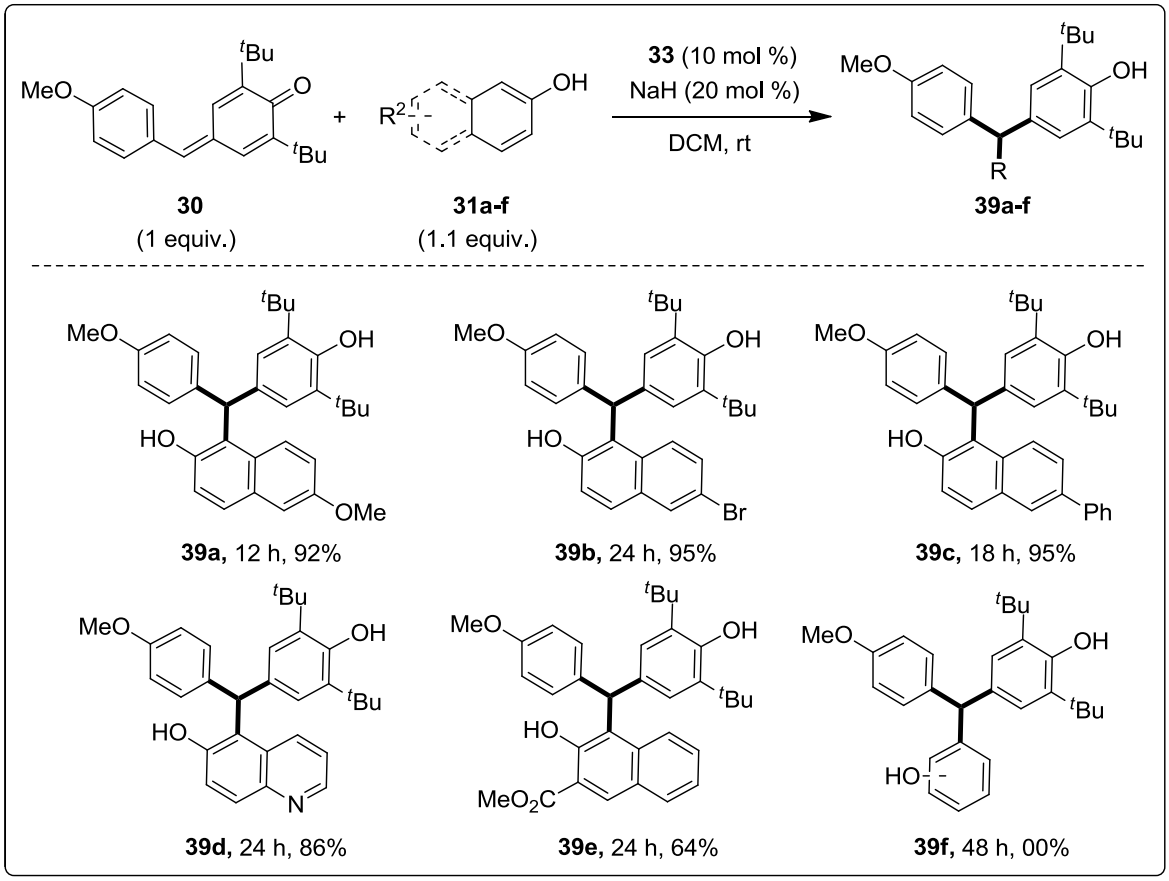
[a]Reaction conditions: all reactions were carried out with 20 mg scale of **30** in 0.3 mL of solvent at room temperature.

Scheme 14: Synthesis of unsymmetrical triarylmethanes[a]

triarylmethane **32t** was obtained from **30t** in 74% yield under the standard conditions. The efficacy of this protocol was also examined with *p*-QM **30u**, derived from 2,6-diisopropyl phenol, and in this case, the product **32u** was obtained in 75% isolated yield (Scheme 15).

To elaborate the substrate scope further, **30** was subjected to 1,6-conjugate addition reaction with various 2-naphthol derivatives under optimised reaction conditions and the results are summarised in Scheme 14. It is evident from Table 3 that this protocol worked efficiently for all the 2-naphthol derivatives tried. For instance, the reaction of **30** with 6-methoxy-2-naphthol provided the desired triarylmethane 10a in 92% yield in 12 h. Other naphthol derivatives such as 6-bromo-2-naphthol and 6-phenyl-2-naphthol reacted smoothly with **30** to give the products **39b**

and **39c** respectively in 95% yield. Under the reaction conditions, 6-hydroxyquinoline gave the corresponding product **39d** in 86% isolated yield.



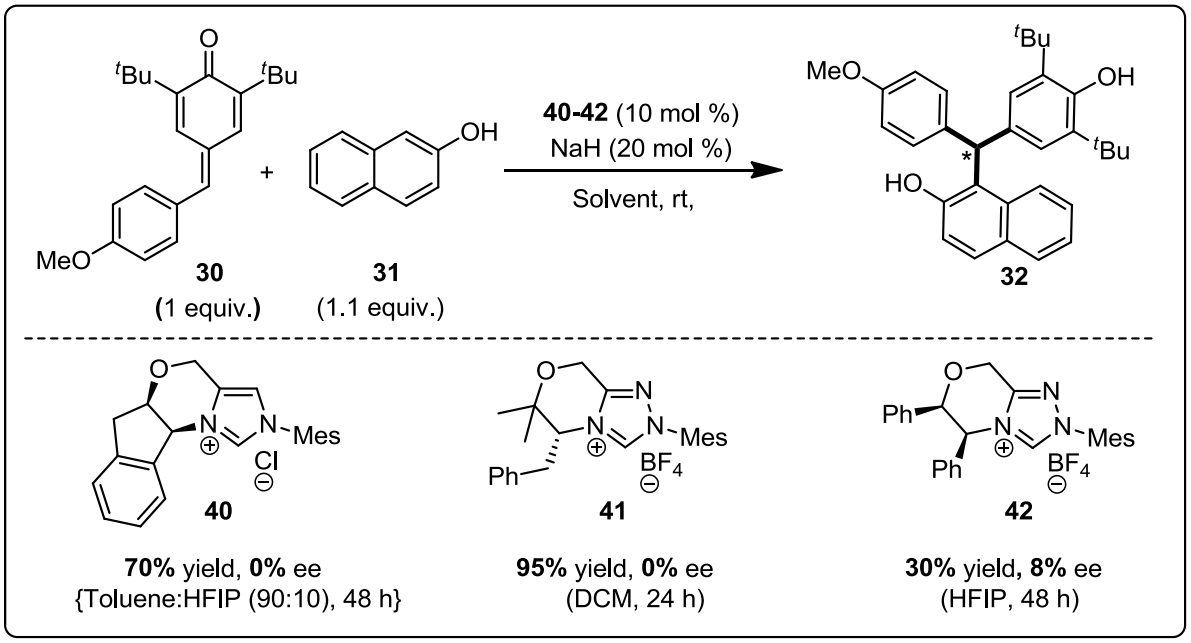
[a]Reaction conditions: all reactions were carried out with 0.062 mmol of **30** in 0.3 mL of solvent at room temperature.

Scheme 15: Synthesis of unsymmetrical triarylmethanes

However, in the case of relatively electron-poor 2-naphthol derivative **31e**, the triarylmethane **39e** was obtained only in 64% yield. Unfortunately, simple phenol failed to react with 1 under the optimal reaction conditions.

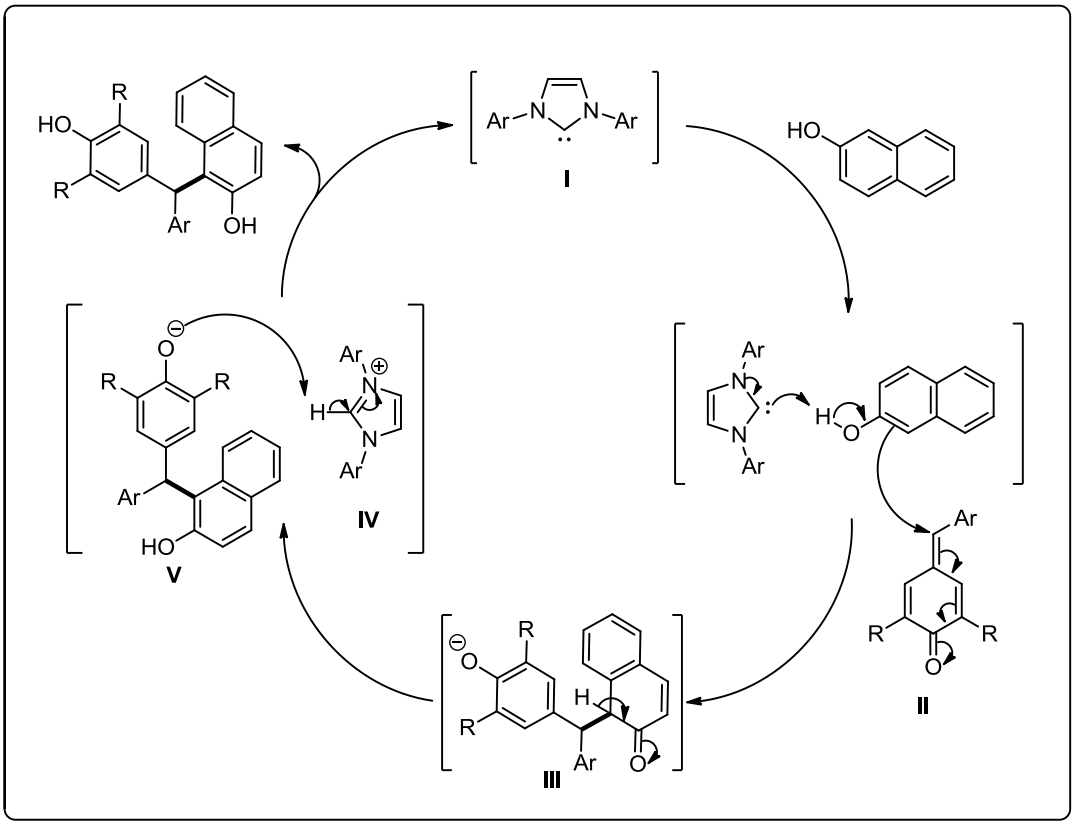
An enantioselective version of this reaction was also attempted. It is known in the literature that the enantioselective version of similar type of reactions is very challenging due to the potential reversibility of the reaction.[24] Many different reaction conditions were employed for this transformation using a variety of chiral NHC pre-catalysts (**40**–**42**). When **40** and **41** were used as a catalyst for the reaction between **30** and **31**, the product **32** was isolated in 70% and

95% yields respectively (Scheme 16). However, in both the cases, the product **32** was obtained as a racemic mixture at room temperature. Lowering the reaction temperature to sub-zero resulted in substantial lowering of the yield of **32** without any improvement in the enantioselectivity. When the reaction was carried out using **42** as a precatalyst in hexafluoroisopropanol (HFIP) as a solvent,[25] **32** was obtained in 30% yield with a marginal improvement in the enantioselectivity (8% ee).



Scheme 16: Enantioselective addition of 2-naphthol to p-QM **30**

A plausible mechanism for this reaction has been proposed based on the outcome of the reaction as well as the literature reports for similar kind of transformations (Scheme 17). In the initial step, NHC (**I**) abstracts the phenolic proton of 2-naphthol to generate the 2-naphthoxide anion, which immediately adds to the *p*-QM **II** in an 1,6-fashion to generate the intermediate **III**. Aromatization of the intermediate **III** followed by proton abstraction from **IV** leads to the formation of the product with the release of NHC **I**.



Scheme 17: Plausible mechanism

2.4) Conclusions

In conclusion, we have disclosed here an atom-economical method for the synthesis of highly functionalised unsymmetrical triarylmethane derivatives through 1,6-conjugate addition of 2-naphthols to *p*-QMs using NHC as a Brønsted base catalyst. Further studies toward enhancing the asymmetric induction in this transformation are currently ongoing.

2.5) Experimental Section

General methods

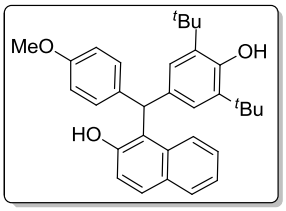
All reactions were carried out under an argon atmosphere in an oven dried vial. Solvents were dried over calcium hydride, distilled and stored with molecular sieves. Melting points were recorded on SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C and^{19}F spectra were

recorded in $CDCl_3$ (400, 100 and 376 MHz respectively) on Bruker FT-NMR spectrometer. Chemical shift (δ) values are reported in parts per million relative to TMS (for ^1H and ^{13}C) and $BF_3.Et_2O$ (for ^{19}F). High resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Perkin–Elmer FTIR spectrometer. Single crystal X-ray data was collected using XtaLabmini X-ray difractometer. Enantiomeric excess was determined by using Waters Chiral HPLC. Most of the reagents and starting materials were purchased from commercial sources and used as such. NHC precursors were prepared according to the literature procedure.[1] All *p*-quinone methides were prepared by following a literature procedure.[2]Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent.

General procedure for the 1,6-conjugate addition of2-naphthol to *p*-quinone methides:

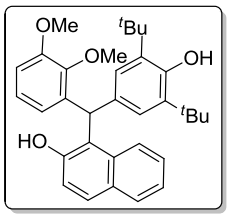
Anhydrous CH_2Cl_2 (0.3 mL) was added to the mixture of *p*-quinone methide (20 mg, 0.0620 mmol), 2-naphthol (9.8 mg, 0.0680 mmol), catalyst **33** (2.6 mg, 0.0062 mmol) and sodium hydride [0.6 mg (55-60% suspension in mineral oil), 0.0124 mmol] under argon atmosphere, and the resulting suspension was stirred at room temperature until *p*-quinone methide was completely consumed. The reaction mixture was purified through silica gel column without furtherworkup, using EtOAc/Hexane mixture as an eluent to get the pure product.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]naphthalen-2-ol (32)



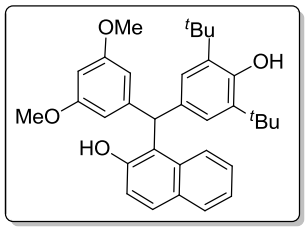
The reaction was performed at 0.062 mmol scale of *p*-quinone methide (**30**); pale yellow solid; yield 99% (28.6 mg); R_f = 0.5 (20% EtOAc in hexane); m.p. 170–172 °C; FT-IR (KBr) 3627, 3462, 2959, 1510, 1435, 1250, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), *δ* 8.02 (d, *J* = 8.6 Hz, 1H), 7.78 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.43 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.34–7.30 (m, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.02 (s, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.23 (s, 1H), 5.44 (s, 1H), 5.20 (s, 1H), 3.78 (s, 3H), 1.33 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.5, 153.14, 153.13, 136.8, 134.1, 133.5, 132.2, 130.1, 129.6, 129.5, 128.8, 126.8, 125.7, 123.1, 123.0, 120.6, 120.1, 114.4, 55.4, 47.9, 34.5, 30.3; HRMS (ESI): *m/z* calcd for $C_{32}H_{37}O_3$ $[M+H]^+$: 469.2742; found: 469.2736.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(2,3-dimethoxyphenyl)methyl]naphthalen-2-ol (32a)



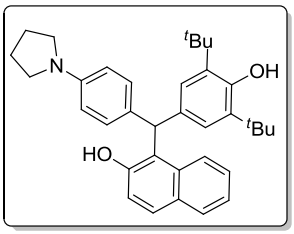
The reaction was performed at 0.056 mmol scale of *p*-quinone methide (**30a**); yellow solid; yield 89% (125 mg); R_f = 0.6 (20% EtOAc in hexane); m.p. 169–171 °C; FT-IR (KBr) 3627, 3462, 2959, 1477, 1435, 1273, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.08 (d, J = 8.6 Hz, 1H), 7.75 (dd, J = 8.1, 1.0 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.42 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.32–7.28 (m, 1H), 7.06 (d, J, = 8.9 Hz, 1H), 7.03 (s, 2H), 6.99–6.95 (m, 1H), 6.84 (dd, J = 8.2, 1.4 Hz, 1H), 6.76 (dd, J = 7.8, 1.4 Hz, 1H), 6.67 (s, 1H), 5.78 (s, 1H), 5.20 (s, 1H), 3.88 (s, 3H), 3.49 (s, 3H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 153.1, 152.9, 146.8, 136.8, 136.6, 133.7, 131.8, 129.6, 129.3, 128.6, 126.8, 125.6, 124.5, 123.3, 123.1, 121.7, 120.4, 120.0, 111.4, 60.6, 55.9, 42.7, 34.6, 30.4; HRMS (ESI): *m/z* calcd for $C_{33}H_{39}O_4$ $[M+H]^+$: 499.2848; found: 499.2837.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(3,5-dimethoxyphenyl)methyl]naphthalen-2-ol(32b)



The reaction was performed at 0.056 mmol scale of *p*-quinone methide (**30b**); pale yellow solid; yield 93% (26.2 mg); R_f = 0.5 (20% EtOAc in hexane); m.p. 72–74 °C; FT-IR (KBr) 3627, 3462, 2959, 1435, 1205, 1157, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.04 (d, J = 8.6 Hz, 1H), 7.79 (dd, J = 8.0, 1.0 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.45 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.35–7.31 (m, 1H), 7.08 (d, J = 8.8 Hz, 1H), 7.07 (s, 2H), 6.41 (d, J = 2.2 Hz, 2H), 6.36 (t, J = 2.2 Hz, 1H), 6.21 (s, 1H), 5.50 (s, 1H), 5.20 (s, 1H), 3.70 (s, 6H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 153.3, 153.1, 145.2, 136.7, 133.6, 131.2, 129.63, 129.56, 128.8, 126.8, 125.7, 123.1, 123.0, 120.3, 120.1, 107.3, 98.9, 55.4, 48.9, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{33}H_{37}O_4$ $[M-H]^+$: 497.2692; found: 497.2681.

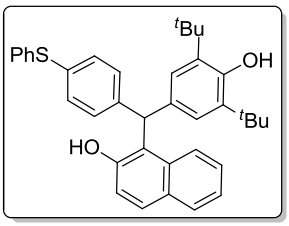
1[(3,5-di-*tert*-butyl-4-hydroxyphenyl){4-(pyrrolidin-1-yl)phenyl}methyl]naphthalen-2-ol (32c)



The reaction was performed at 0.055 mmol scale of *p*-quinone methide (**30c)**; red solid; yield 99% (27.7 mg); R_f = 0.5 (20% EtOAc in hexane); m.p. 109–111 °C; FT-IR (KBr) 3644, 3457, 2958, 1615,

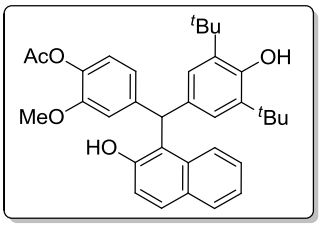
1519, 1435, 1361, 817, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.08 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.10 (s, 2H), 7.08–7.04 (m, 3H), 6.52 (d, J = 8.6 Hz, 2H), 6.20 (s, 1H), 5.63 (s, 1H), 5.15 (s, 1H), 3.30–3.22 (m, 4H), 2.01–1.96 (m, 4H), 1.36 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 152.8, 147.0, 136.4, 133.7, 132.3, 129.7, 129.6, 129.2, 128.7, 128.4, 126.6, 125.8, 123.1, 123.0, 121.2, 120.1, 112.3, 47.8, 47.7, 34.5, 30.4, 25.6; HRMS (ESI): *m/z* calcd for $C_{35}H_{40}NO_2$ $[M+H]^+$: 508.3215; found: 508.3200.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl){4-(phenylthio)phenyl}methyl]naphthalen-2-ol (32d)



The reaction was performed at 0.050 mmol scale of *p*-quinone methide (**30d**); pale yellow solid; yield 93% (25.4 mg); R_f = 0.4 (20% EtOAc in hexane); m.p. 171–173 °C; FT-IR (KBr) 3627, 3461, 2959, 1478, 1435, 1210, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.00 (d, J = 8.6 Hz, 1H), 7.81 (dd, J =8.0, 1.0, Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 7.46 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.37–7.34 (m, 3H), 7.30–7.21 (m, 7H), 7.08 (d, J = 8.8 Hz, 1H), 7.01 (s, 2H), 6.29 (s, 1H), 5.41 (s, 1H), 5.26 (s, 1H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 153.2, 141.5, 137.0, 136.5, 133.7, 133.5, 132.3, 131.7, 130.4, 130.1, 129.78, 129.74, 129.2, 128.9, 126.87, 126.86, 125.7, 123.3, 122.9, 120.1, 119.9, 48.3, 34.6, 30.3; HRMS (ESI): *m/z* calcd for $C_{37}H_{37}O_2S$ $[M-H]^+$: 545.2515; found: 545.2508.

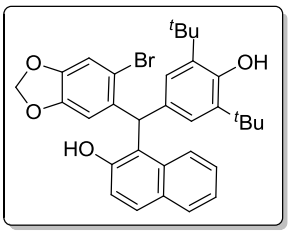
4-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(2-hydroxynaphthalen-1-yl)methyl]-2-methoxyphenyl acetate (32e)



The reaction was performed at 0.052 mmol scale of *p*-quinone methide (**30e**); pale yellow solid; yield 91% (25.1 mg); R_f = 0.2 (20% EtOAc in hexane); m.p. 171–173 °C; FT-IR (KBr) 3626, 3459, 2959, 1510, 1435, 1200, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.02 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.47–7.42 (m, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.08 (d, J = 8.9 Hz, 1H), 7.03 (s, 2H), 6.98 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 1.7 Hz, 1H), 6.80 (dd, J = 8.2, 1.8 Hz, 1H), 6.27 (s, 1H), 5.40 (s, 1H), 5.22 (s, 1H), 3.69 (s, 3H), 2.30 (s, 3H), 1.34 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 153.23, 153.16, 151.5, 141.2, 138.7, 136.9, 133.6, 131.6, 129.72, 129.69, 128.8, 126.9, 125.7,

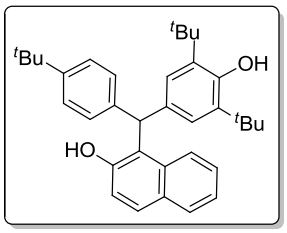
123.3, 123.1, 123.0, 121.2, 120.2, 120.1, 113.2, 56.0, 48.5, 34.6, 30.3, 20.8; HRMS (ESI): *m/z* calcd for $C_{34}H_{37}O_5$ $[M-H]^+$: 525.2641; found: 525.2620.

1-[{6-bromobenzo(d)(1,3)dioxol-5-yl}(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl} naphthalen-2-ol (32f)



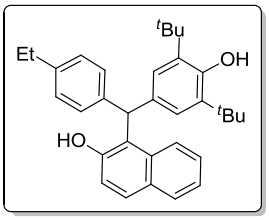
The reaction was performed at 0.048 mmol scale of *p*-quinone methide (**30f**); white solid; yield 87% (116.5 mg); R_f = 0.4 (20% EtOAc in hexane); m.p. 186–188 °C; FT-IR (KBr) 3633, 3461, 2959, 1477, 1234, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.87 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 7.3 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.47 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.36–7.33 (m, 1H), 7.12 (s, 1H), 7.06 (d, J = 8.9 Hz, 1H), 6.92 (s, 2H), 6.64 (s, 1H), 6.43 (s, 1H), 5.96 (d, J = 1.3 Hz, 1H), 5.85 (d, J = 1.2 Hz, 1H), 5.46 (s, 1H), 5.25 (s, 1H), 1.34 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 153.5, 147.9, 147.3, 137.2, 134.2, 133.6, 130.0, 129.9, 129.7, 128.8, 127.1, 125.2, 123.4, 123.0, 120.2, 119.8, 115.7, 113.0, 110.5, 101.8, 48.7, 34.6, 30.4; HRMS (ESI): *m/z* calcd for $C_{32}H_{34}BrO_4$ $[M+H]^+$: 561.1640; found: 561.1632.

1-{[4-(*tert*-butyl)phenyl](3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl}naphthalen-2-ol (32g)



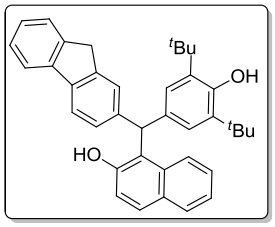
The reaction was performed at 0.057 mmol scale of *p*-quinone methide (**30g**); pale yellow solid; yield 90% (25.3 mg); R_f = 0.7 (20% EtOAc in hexane); m.p. 182–184 °C; FT-IR (KBr) 3633, 3465, 2961, 1435, 1210, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.08 (d, J = 8.6 Hz, 1H), 7.80 (dd, J = 8.0, 1.0 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.46 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H), 7.36–7.32 (m, 3H), 7.18 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.8 Hz, 1H), 7.03 (s, 2H), 6.28 (s, 1H), 5.42 (s, 1H), 5.20 (s, 1H), 1.35 (s, 18H), 1.31 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 153.0, 150.0, 139.1, 136.6, 133.6, 131.9, 129.7, 129.4, 128.8, 128.6, 126.8, 126.0, 125.8, 123.1, 123.0, 120.7, 120.1, 48.1, 34.6, 34.5, 31.5, 30.3; HRMS (ESI): *m/z* calcd for $C_{35}H_{41}O_2$ $[M-H]^+$: 493.3107; found: 493.3100.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-ethylphenyl)methyl]naphthalen-2-ol (32h)



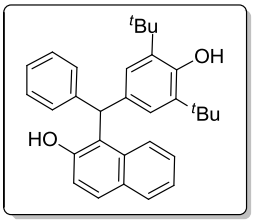
The reaction was performed at 0.062 mmol scale of *p*-quinone methide (**30h**); pale yellow solid; yield 87% (25.2 mg); R_f = 0.6 (20% EtOAc in hexane); m.p. 129–131 °C; FT-IR (KBr) 3633, 3465, 2959, 1435, 1206, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.06 (d, J = 8.6 Hz, 1H), 7.79 (dd, J = 8.0, 1.0 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.44 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.35–7.31 (m, 1H), 7.16 (s, 4H), 7.08 (d, J = 8.8 Hz, 1H), 7.03 (s, 2H), 6.27 (s, 1H), 5.43 (s, 1H), 5.20 (s, 1H), 2.62 (q, J = 7.6 Hz, 2H), 1.34 (s, 18H), 1.21 (t, J = 7.6 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.14, 153.06, 143.0, 139.4, 136.7, 133.6, 131.9, 129.6, 129.5, 129.0, 128.8, 128.6, 126.8, 125.8, 123.1, 123.0, 120.7, 120.1, 48.3, 34.5, 30.3, 28.6, 15.7; HRMS (ESI): *m/z* calcd for $C_{33}H_{39}O_2$ $[M+H]^+$: 467.2950; found: 467.2938.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(9H-fluoren-2-yl)methyl]naphthalen-2-ol (32i)



The reaction was performed at 0.052 mmol scale of *p*-quinone methide (**30i**); pale yellow solid; yield 90% (24.8 mg); R_f = 0.5 (20% EtOAc in hexane); m.p. 212–214 °C; FT-IR 3629, 3465, 2958, 1435, 1210, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.08 (d, J = 8.6 Hz, 1H), 7.81 (dd, J = 8.0, 1.0 Hz, 1H), 7.78–7.74 (m, 3H), 7.52 (d, J = 7.4 Hz, 1H), 7.47–7.43 (m, 2H), 7.39–7.27 (m, 4H), 7.11 (d, J, = 8.9 Hz, 1H), 7.08 (s, 2H), 6.39 (s, 1H), 5.53 (s, 1H), 5.24 (s, 1H), 3.88 (d, J = 22.0 Hz, 1H), 3.79 (d, J = 22.0 Hz, 1H),3.49 (s, 3H), 1.34 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 153.2, 144.2, 143.5, 141.6, 140.9, 140.7, 136.9,136.9, 133.6, 132.1, 129.7, 129.6, 128.8, 127.9, 126.8, 126.7, 125.8, 125.7, 125.2, 123.2, 123.0, 120.5, 120.3, 120.1, 120.0, 48.9, 37.1, 34.6, 30.4; HRMS (ESI): *m/z* calcd for $C_{38}H_{39}O_2$ $[M+H]^+$: 527.2950; found: 527.2941.

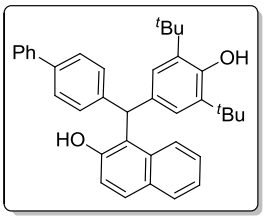
1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl]naphthalen-2-ol (32j)



The reaction was performed at 0.068 mmol scale of *p*-quinone methide (**30j**); pale yellow solid; yield 86% (25.6 mg); R_f = 0.7 (20% EtOAc in hexane); m.p. 129–131 °C; FT-IR (KBr) 3644, 3465, 2924, 1749, 1615, 1435, 747cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.04 (d, J = 8.6 Hz, 1H),

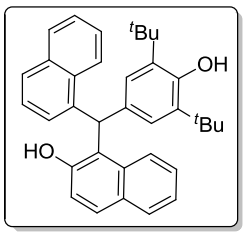
7.80 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.45 (ddd, *J* = 8.5, 6.8, 1.3 Hz, 1H), 7.36–7.24 (m, 6H), 7.09 (d, *J* = 8.9 Hz, 1H), 7.03 (s, 2H), 6.31 (s, 1H), 5.43 (s, 1H), 5.23 (s, 1H), 1.35 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.22, 153.17, 142.2, 136.8, 133.6, 131.9, 129.7, 129.6, 129.1, 129.0, 128.8, 127.0, 126.8, 125.8, 123.2, 123.0, 120.3, 120.1, 48.7, 34.6, 30.3; HRMS (ESI): *m/z* calcd for $C_{31}H_{33}O_2$ $[M-H]^+$: 437.2481; found: 437.2469.

1-[(1,1'-biphenyl)-4-yl(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]naphthalen-2-ol (32k)



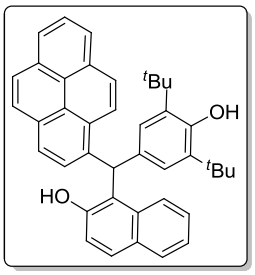
The reaction was performed at 0.054 mmol scale of *p*-quinone methide (**30k**); pale yellow solid; yield 86% (119 mg); R_f = 0.5 (20% EtOAc in hexane); m.p. 135–137 °C; FT-IR (KBr) 3629, 3465, 2922, 1435, 1266, 746cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.08 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 1H), 7.61–7.56 (m, 4H), 7.48–7.42 (m, 3H), 7.37–7.32 (m, 4H), 7.10 (d, *J* = 8.9 Hz, 1H), 7.07 (s, 2H), 6.36 (s, 1H), 5.47 (s, 1H), 5.24 (s, 1H), 1.35 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ153.2, 153.2, 141.3, 140.8, 139.7, 136,9, 133.6, 131.8, 129.7, 129.6, 129.5, 128.9, 128.8, 127.7, 127.4, 127.1, 126.8, 125.8, 123.2, 123.0, 120.3, 120.1, 48.4, 34.6, 30.3; HRMS (ESI): *m/z* calcd for $C_{37}H_{37}O_2$ $[M-H]^+$: 513.2794; found: 513.2789.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(naphthalen-1-yl)methyl]naphthalen-2-ol (32l)



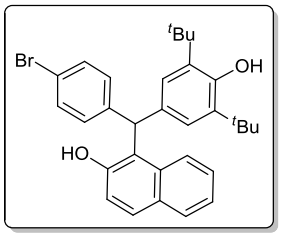
The reaction was performed at 0.058 mmol scale of *p*-quinone methide (**30l**); pale yellow solid; yield 92% (26.1 mg); R_f = 0.6 (20% EtOAc in hexane); m.p. 170–172 °C; FT-IR (KBr) 3629, 3465, 2959, 1435, 1210, 742 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 1H), 7.90 (dd, *J* = 8.2, 2.7 Hz, 2H), 7.81 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.52–7.46 (m, 1H), 7.43–7.30 (m, 4H), 7.16 (d, *J* = 7.1 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 7.01 (brs, 2H), 6.89 (s, 1H), 5.62 (s, 1H), 5.20 (s, 1H), 1.29 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 153.2, 138.5, 136.9, 136.8, 134.2, 133.4, 132.0, 131.5, 129.7, 129.6, 129.0, 128.8, 128.3, 127.0, 126.9, 126.6, 126.0, 125.9, 125.8, 124.2, 123.2, 122.8, 120.0, 46.0, 34.5, 30.3;HRMS (ESI): *m/z* calcd for $C_{35}H_{37}O_2$ $[M+H]^+$: 489.2793; found: 489.2787.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(pyren-1-yl)methyl]naphthalen-2-ol (32m)



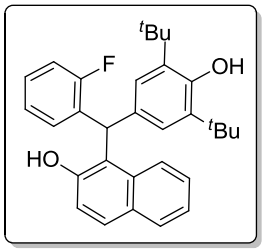
The reaction was performed at 0.048 mmol scale of *p*-quinone methide (**30m**); yellow solid; yield 75% (20.2 mg);R_f = 0.5 (20% EtOAc in hexane); m.p. 226–228 °C; FT-IR (KBr) 3629, 3465, 2959, 1435, 1210, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25–8.15 (m, 3H), 8.10–7.99 (m, 5H), 7.98–7.92 (m, 1H), 7.84–7.79 (m, 1H), 7.77 (d, *J* = 8.9 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.36–7.27 (m, 3H), 7.23 (s, 1H), 7.09 (d, *J* = 8.9 Hz, 2H), 7.06 (brs, 1H), 5.57 (s, 1H), 5.23 (s, 1H), 1.27 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 153.3, 137.08, 137.06, 135.9, 133.5, 131.9, 131.6, 130.9, 130.7, 129.7, 129.2, 128.8, 128.2, 127.7, 127.4, 127.0, 126.9, 126.1, 126.0, 125.5, 125.48, 125.44, 125.3, 125.0, 123.4, 123.2, 122.9, 120.4, 120.1, 46.4, 34.5, 30.3; HRMS (ESI): *m/z* calcd for $C_{41}H_{39}O_2$ $[M+H]^+$: 563.2950; found: 563.2945.

1-[(4-bromophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]naphthalen-2-ol (32n)



The reaction was performed at 0.054 mmol scale of *p*-quinone methide (**30n**); pale yellow solid; yield 92% (25.5 mg); R_f = 0.5 (20% EtOAc in hexane); m.p. 158–160 °C; FT-IR (KBr) 3627, 3460, 2960, 1486, 1435, 1210, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.95 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.45–7.42 (m, 3H), 7.34 (t, *J*= 7.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 1H), 7.00 (s, 2H), 6.26 (s, 1H), 5.37 (s, 1H), 5.26 (s, 1H), 1.34 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 153.1, 141.3, 137.1, 133.4, 132.0, 131.4, 131.0, 129.8, 129.7, 128.9, 126.9, 125.7, 123.3, 122.9, 120.8, 120.0, 119.8, 48.2, 34.6, 30.3; HRMS (ESI): *m/z* calcd for $C_{31}H_{32}BrO_2$ $[M-H]^+$: 515.1586; found: 515.1579.

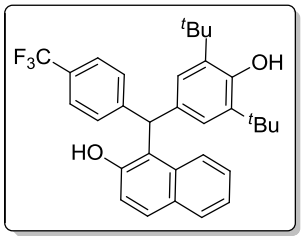
1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(2-fluorophenyl)methyl]naphthalen-2-ol (32o)



The reaction was performed at 0.064 mmol scale of *p*-quinone methide (**30o**); pale yellow solid; yield 97% (28.4 mg); R_f = 0.6 (20% EtOAc in hexane); m.p. 134–136 °C; FT-IR (KBr) 3629, 3459, 2959, 1487, 1435, 1228, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.28–7.22 (m, 1H), 7.18–7.09 (m, 2H),

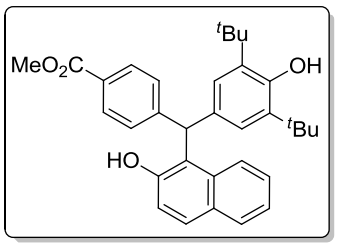
7.08–7.02 (m, 2H), 6.97 (s, 2H), 6.58 (s, 1H), 5.50 (s, 1H), 5.25 (s, 1H), 1.32 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$)δ 160.7 (d, J = 245.0 Hz), 153.7, 153.5, 137.2, 133.5, 130.7 (d, J = 3.7 Hz), 130.6, 129.8, 129.6, 128.9, 128.8 (d, J = 4.2 Hz), 128.7, 127.0, 125.1, 124.7 (d, J = 3.5 Hz), 123.3, 122.7, 120.1, 119.2, 115.5 (d, J = 22.3 Hz), 41.4 (d, J = 3.3 Hz), 34.6, 30.3;^{19}F NMR (376 MHz, $CDCl_3$) δ -117.2; HRMS (ESI): *m/z* calcd for $C_{31}H_{34}FO_2$ $[M+H]^+$: 457.2543; found: 457.2533.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl){4-(trifluoromethyl)phenyl}methyl]naphthalen-2-ol (32p)



The reaction was performed at 0.055 mmol scale of *p*-quinone methide (**30p**); pale yellow solid; yield 86% (24.1 mg); R_f = 0.7 (20% EtOAc in hexane); m.p. 160–162 °C; FT-IR 3637, 3462, 2961, 1435, 1326, 1123, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.95 (d, J = 8.6 Hz, 1H), 7.81 (dd, J = 8.0, 1.0 Hz, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.46–7.44 (m, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.37–7.33 (m, 1H), 7.09 (d, J = 8.9 Hz, 1H), 6.99 (s, 2H), 6.37 (s, 1H), 5.37 (s, 1H), 5.28 (s, 1H), 1.34 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 153.2, 146.6 (apparent d, J = 1.0 Hz), 137.1, 133.4, 131.2, 130.0, 129.8, 129.6, 129.3, 129.0, 128.6, 127.0, 125.8 (q, J = 3.7 Hz), 125.7, 124.3 (q, J = 270.3 Hz), 123.4, 122.8, 120.0, 119.6, 48.5, 34.6, 30.3;^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4; HRMS (ESI): *m/z* calcd for $C_{32}H_{34}F_3O_2$ $[M+H]^+$: 507.2511; found: 507.2502.

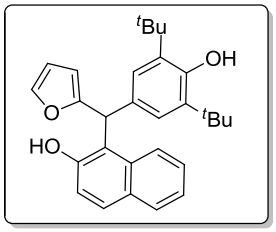
Methyl-4-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(2-hydroxynaphthalen-1-yl)methyl]benzoate (32q)



The reaction was performed at 0.057 mmol scale of *p*-quinone methide (**30q**); pale yellow solid; yield 92% (25.93 mg); R_f = 0.4 (20% EtOAc in hexane); m.p. 184–186 °C;FT-IR (KBr) 3620, 3455, 2955, 1712, 1510, 1433, 1200, 745cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.44–7.38 (m, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 7.3 Hz, 1H), 7.08 (d, J = 8.9 Hz, 1H), 6.98 (s, 2H), 6.34 (s, 1H), 5.38 (s, 1H), 5.25 (s, 1H), 3.89 (s, 3H), 1.32 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 153.4, 153.2, 147.8, 137.1, 133.4,

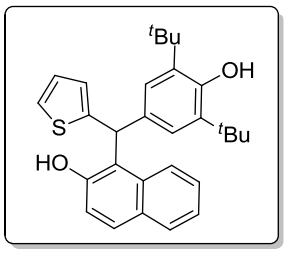
131.3, 130.2, 129.9, 129.7, 129.3, 128.9, 128.8, 126.9, 125.7, 123.3, 122.9, 120.0, 119.6, 52.2, 48.8, 34.6, 30.3;HRMS (ESI): *m/z* calcd for $C_{32}H_{35}O_4$ $[M-H]^+$: 495.2536; found: 495.2517.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(furan-2-yl)methyl]naphthalen-2-ol (32r)



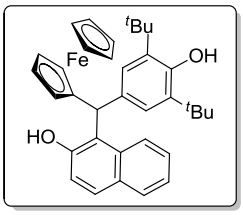
The reaction was performed at 0.070 mmol scale of *p*-quinone methide (**30r**); brown solid; yield 68% (20.5 mg); R_f = 0.5 (20% EtOAc in hexane);m.p. 71–73 °C; FT-IR (KBr) 3628, 3468, 2959, 1436, 1234, 741 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.47 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.43 (d, *J* = 1.1 Hz, 1H), 7.38–7.31 (m, 1H), 7.10 (d, *J* = 8.9 Hz, 1H), 7.04 (s, 2H), 6.34 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.31 (s, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 5.77 (s, 1H), 5.21 (s, 1H), 1.35 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) *δ*155.9, 153.3, 142.6, 136.7, 133.3, 129.80, 129.78, 129.6, 128.9, 126.9, 124.9, 123.2, 122.5, 119.8, 117.8, 110.5, 108.8, 42.2, 34.5, 30.3; HRMS (ESI): *m/z* calcd for $C_{29}H_{33}O_3$ $[M+H]^+$: 429.2429; found: 429.2425.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(thiophen-2-yl)methyl]naphthalen-2-ol (32s)



The reaction was performed at 0.067 mmol scale of *p*-quinone methide (**30s**); yellow solid; yield 75% (22.2 mg); R_f = 0.6 (20% EtOAc in hexane);m.p. 119–121 °C;FT-IR (KBr) 3627, 3464, 2959, 1435, 1210, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.47 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.37–7.33 (m, 1H), 7.27–7.25 (m, 1H), 7.16 (s, 2H), 7.10 (d, *J* = 8.9 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.83 (d, *J* = 3.5 Hz, 1H), 6.48 (s, 1H), 5.59 (s, 1H), 5.22 (s, 1H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 153.3, 153.1, 146.8, 136.7, 133.1, 131.5, 129.8, 129.6, 128.9, 127.0, 126.9, 126.8, 125.7, 125.2, 123.3, 122.7, 120.5, 120.0, 43.7, 34.6, 30.3; HRMS (ESI): *m/z* calcd for $C_{29}H_{33}O_2S$ $[M+H]^+$: 445.2201; found: 445.2208.

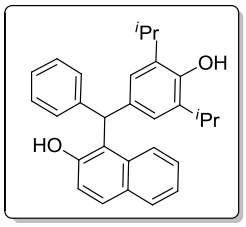
Cyclopenta-2,4-dien-1-yl[2-{(3,5-di-tert-butyl-4-hydroxyphenyl)(3-hydroxynaphthalen-2-yl)methyl}cyclopenta-2,4-dien-1-yl]iron (32t)



The reaction was performed at 0.050 mmol scale of *p*-quinone methide (**30t**); dark green solid; yield 74% (20.1 mg); R_f = 0.7 (20% EtOAc in hexane); m.p. 139–141 °C; FT-IR (KBr) 3637, 3467, 2958, 1435, 1232,

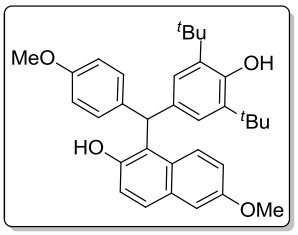
820, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.17 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.20 (s, 2H), 7.06 (d, J = 8.8 Hz, 1H), 6.06 (s, 1H), 5.59 (s, 1H), 5.11 (s, 1H), 4.27–4.25 (m, 2H), 4.20 (s, 1H), 4.05 (s, 5H), 3.97 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.67, 152.65, 136.0, 133.2, 132.5, 129.5, 129.1, 128.9, 126.5, 125.2, 123.1, 123.0, 121.9, 120.1, 91.9, 69.4,69.4, 69.3, 68.6, 67.6, 43.2, 34.5, 30.5; HRMS (ESI): *m/z* calcd for $C_{35}H_{39}FeO_2$ $[M+H]^+$: 547.2299; found: 547.2288.

1-[(4-hydroxy-3,5-diisopropylphenyl)(phenyl)methyl]naphthalen-2-ol (32u)



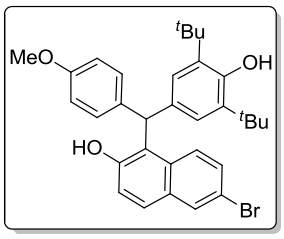
The reaction was performed at 0.074 mmol scale of *p*-quinone methide (**30s**); pale yellow solid; yield 75% (22.93 mg); R_f = 0.5 (20% EtOAc in hexane); m.p. 119–121 °C; FT-IR (KBr) 3626, 3459, 2959, 1510, 1435, 1200, 746 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.6 Hz, 1H), 7.83–7.72 (m, 3H), 7.44 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.36–7.26 (m, 4H), 7.15–7.09 (m, 1H), 7.09 (d, J = 8.9 Hz, 1H), 6.91 (s, 2H), 6.33 (s, 1H), 5.43 (s, 1H), 4.82 (s, 1H), 3.11 (sept, J = 6.9 Hz, 1H), 1.16 (d, J = 1.0 Hz, 6H), 1.14 (d, J = 1.0 Hz, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 149.4, 142.0, 134.8, 133.4, 129.6, 129.13, 129.06, 128.8, 127.9, 127.1, 126.8, 126.5, 124.3, 122.9, 120.1, 117.9, 109.6, 48.6, 27.5, 22.8, 22.7;HRMS (ESI): *m/z* calcd for $C_{29}H_{29}O_2$ $[M-H]^+$: 409.2167; found: 409.2152.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]-6-methoxynaphthalen-2-ol (39a)



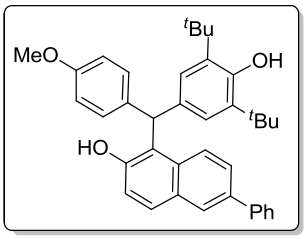
The reaction was performed at 0.062 mmol scale of *p*-quinone methide (**30**); orange solid; yield 92% (28.3 mg); R_f = 0.3 (20% EtOAc in hexane);m.p. 81–83 °C; FT-IR (KBr) 3627, 3468, 2958, 1606, 1510, 1435, 1233, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.94 (d, J = 9.6 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 7.13–7.10 (m, 2H), 7.05 (d, J = 8.8 Hz, 1H), 7.03 (s, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.20 (s, 1H), 5.28 (s, 1H), 5.21 (s, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 1.34 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 155.7, 153.1, 151.5, 136.7, 134.2, 132.2, 130.6, 130.1, 128.7, 128.2, 125.7, 124.6, 121.0, 120.6, 118.9, 114.4, 107.2, 55.5, 55.4, 48.0, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{33}H_{39}O_4$ $[M+H]^+$: 499.2848; found: 499.2838.

6-bromo-1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]naphthalen-2-ol (39b)



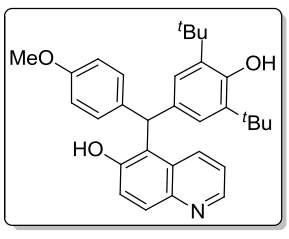
The reaction was performed at 0.062 mmol scale of *p*-quinone methide (**30**); pale yellow solid; yield 95% (32.1 mg); R_f = 0.4 (20% EtOAc in hexane); m.p. 151–153 °C; FT-IR (KBr) 3629, 3461, 2958, 1509, 1435, 1251 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$), δ 7.92 (d, J = 2.1 Hz, 1H), 7.87 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 8.9 Hz, 1H), 7.47 (dd, J = 9.2,2.1Hz, 1H), 7.13 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.9 Hz, 1H), 6.99 (s, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.16 (s, 1H), 5.47 (s, 1H), 5.22 (s, 1H), 3.78 (s, 3H), 1.33 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 153.4, 153.2, 136.9, 133.7, 132.1, 131.7, 130.9, 130.6, 130.1, 129.9, 128.6, 125.6, 124.9, 121.2, 120.9, 116.9, 114.5, 55.4, 47.9, 34.6, 30.3; HRMS (ESI): *m/z* calcd for $C_{32}H_{34}BrO_3$ $[M-H]^+$: 545.1692; found: 545.1680.

1-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]-6-phenylnaphthalen-2-ol(39c)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide (**30**); yellow solid; yield 64% (99%); R_f = 0.4 (20% EtOAc in hexane); m.p. 89–91 °C; FT-IR (KBr) 3626, 3460, 2922, 1436, 1265, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 1.8 Hz, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.83–7.72 (m, 3H),7.68 (s, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.20 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.8 Hz, 1H), 7.06 (s, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.27 (s, 1H), 5.49 (s, 1H), 5.23 (s, 1H), 3.79 (s, 3H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 153.3, 153.2, 141.0, 136.8, 135.9, 134.0, 132.7, 132.1, 130.1, 129.9, 129.8, 128.9, 127.3, 127.2, 126.7, 126.4, 125.7, 123.6, 120.6, 120.5, 114.4, 55.4, 48.0, 34.6, 30.4; HRMS (ESI): *m/z* calcd for $C_{38}H_{39}O_3$ $[M-H]^+$: 543.2899; found: 543.2880.

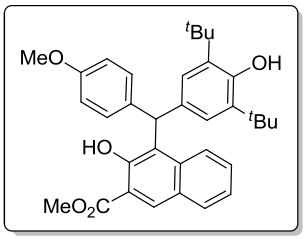
5-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]quinolin-6-ol (39d)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide (**30**); yellow solid; yield 86% (24.9 mg); R_f = 0.3 (50% EtOAc in hexane); m.p. 239–241 °C; FT-IR (KBr) 3636, 3450, 2958, 1509, 1248,

739 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$), δ 8.71 (d, J = 4.2 Hz, 1H), 8.32 (d, J = 8.6 Hz, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.30–7.28 (m, 1H), 7.14 (d, J = 8.6 Hz, 2H), 7.02 (s, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.53 (s, 1H), 6.24 (s, 1H), 5.23 (s, 1H), 3.78 (s, 3H), 1.33 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 153.5, 153.1, 146.9, 144.6, 136.8, 134.0, 132.1, 131.7, 130.2, 130.1, 128.7, 125.7, 123.7, 121.2, 120.7, 114.4, 55.4, 47.4, 34.5, 30.3; HRMS (ESI): *m/z* calcd for $C_{31}H_{36}NO_3$ $[M+H]^+$: 470.2695; found: 470.2685.

Methyl-4-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]-3-hydroxy-2-naphthoate (39e)



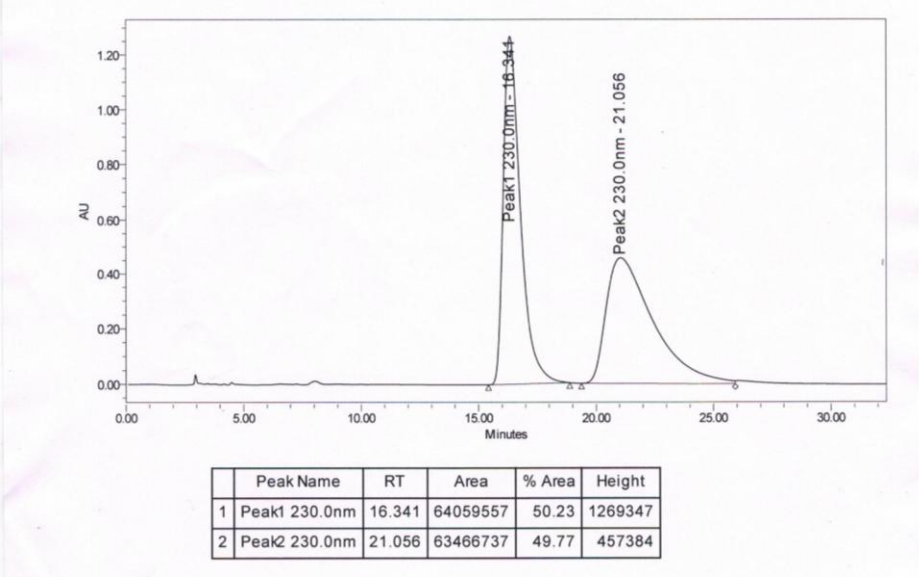
The reaction was performed at 0.062 mmol scale of *p*-quinone methide (**30**); yellow solid; yield 64% (20.8 mg); R_f = 0.4 (20% EtOAc in hexane);m.p. 148–150°C;FT-IR (KBr) 3635, 2957, 1710, 1510, 1439, 750 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$), δ 10.98 (s, 1H), 8.48 (s, 1H), 7.78 (d, J = 7.9 Hz, 2H), 7.28–7.21 (m, 2H), 7.13 (d, J = 8.3 Hz, 2H), 7.12 (s, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.57 (s, 1H), 5.05 (s, 1H), 4.02 (s, 3H), 3.76 (s, 3H), 1.31 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 157.5, 154.4, 152.0, 136.8, 136.7, 135.4, 132.5, 132.2, 132.1, 130.3, 129.8, 128.2, 127.7, 126.4, 124.6, 123.2, 113.9, 113.5, 55.3, 52.8, 45.5, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{34}H_{37}O_5Na$ $[M+Na]^+$: 549.2617; found: 549.2605.

Enantioselective 1,6-conjugate addition of 2-naphthol to1:

Anhydrous HFIP (0.5 mL) was added to the mixture of *p*-quinone methide (**30**) (20 mg, 0.0620 mmol), 2-naphthol (8 mg, 0.0680 mmol), catalyst (3 mg, 0.0062 mmol) and sodium hydride [0.6 mg (55-60% suspension in mineral oil), 0.0124 mmol] under argon atmosphere, and the resulting suspension was stirred at room temperature. After 48 h the reaction was quenched by 2 mL of water and extracted with CH_2Cl_2 (2X3 mL). The organic layer dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The residue was purified through silica gel column, using EtOAc/Hexane mixture as an eluent, to gate pale yellow solid (8 mg, 30%, 8% ee). The enantiomeric excess was determined by HPLC: CHIRALCEL AD-H, n-hexane/i-PrOH (99/1).

HPLC data for 32 (racemic)

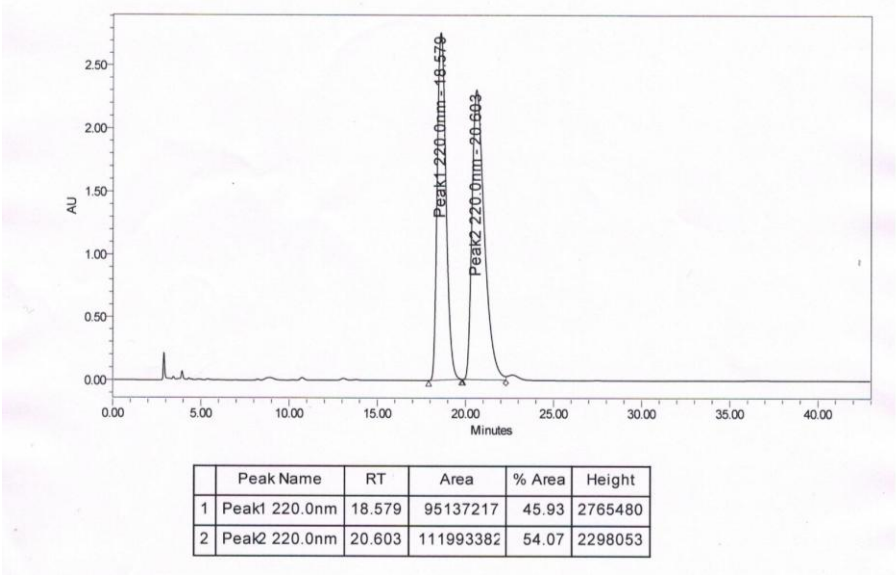
Retention time1.0 mL min^{-1}, 220 nm.



	Peak Name	RT	Area	% Area	Height
1	Peak1 230.0nm	16.341	64059557	50.23	1269347
2	Peak2 230.0nm	21.056	63466737	49.77	457384

HPLC data for 32 (enentioenriched)

Retention time 1.0 mL min^{-1}, 220 nm,18.58 min (minor enantiomer), 20.60 min (major enantiomer).

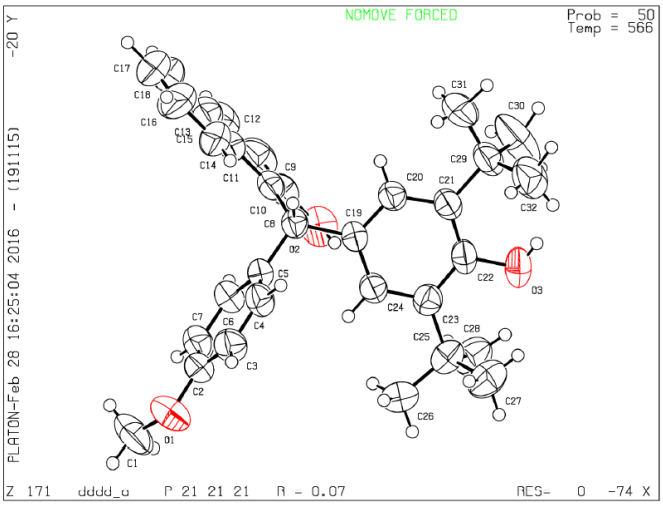


	Peak Name	RT	Area	% Area	Height
1	Peak1 220.0nm	18.579	95137217	45.93	2765480
2	Peak2 220.0nm	20.603	111993382	54.07	2298053

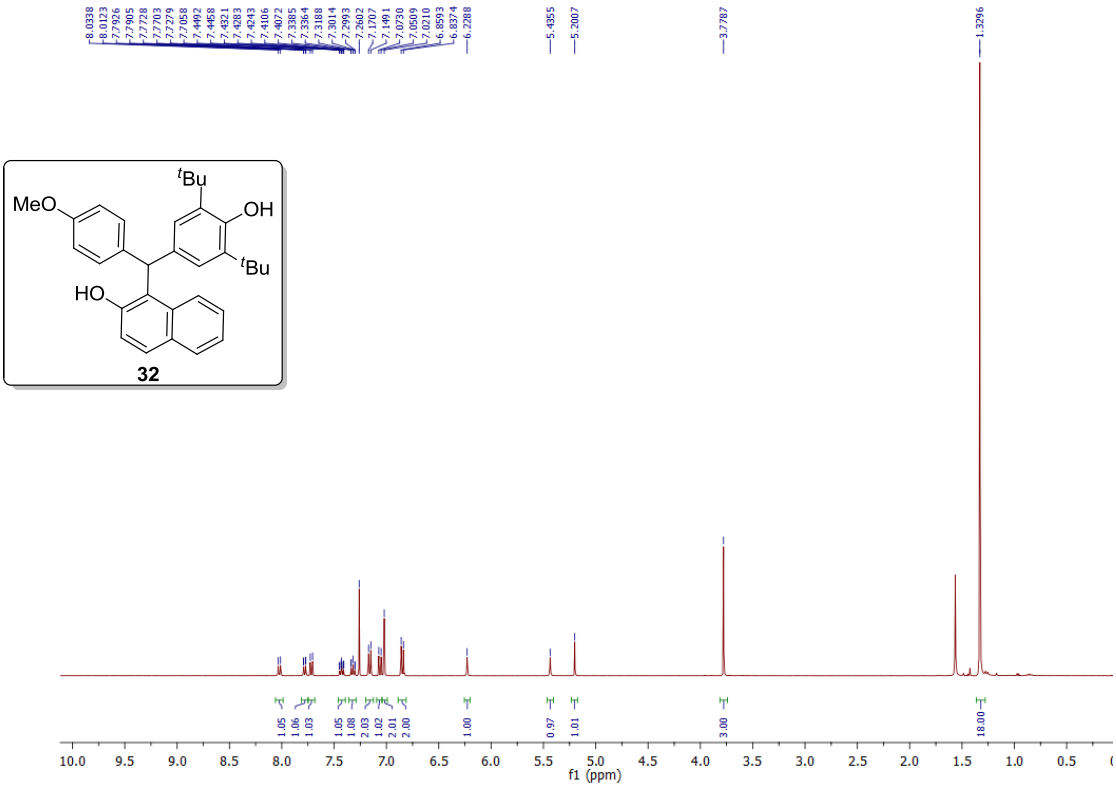
X-Ray crystallographic analysis for compound 32:[28]

Crystal data and structure refinement for compound 32.

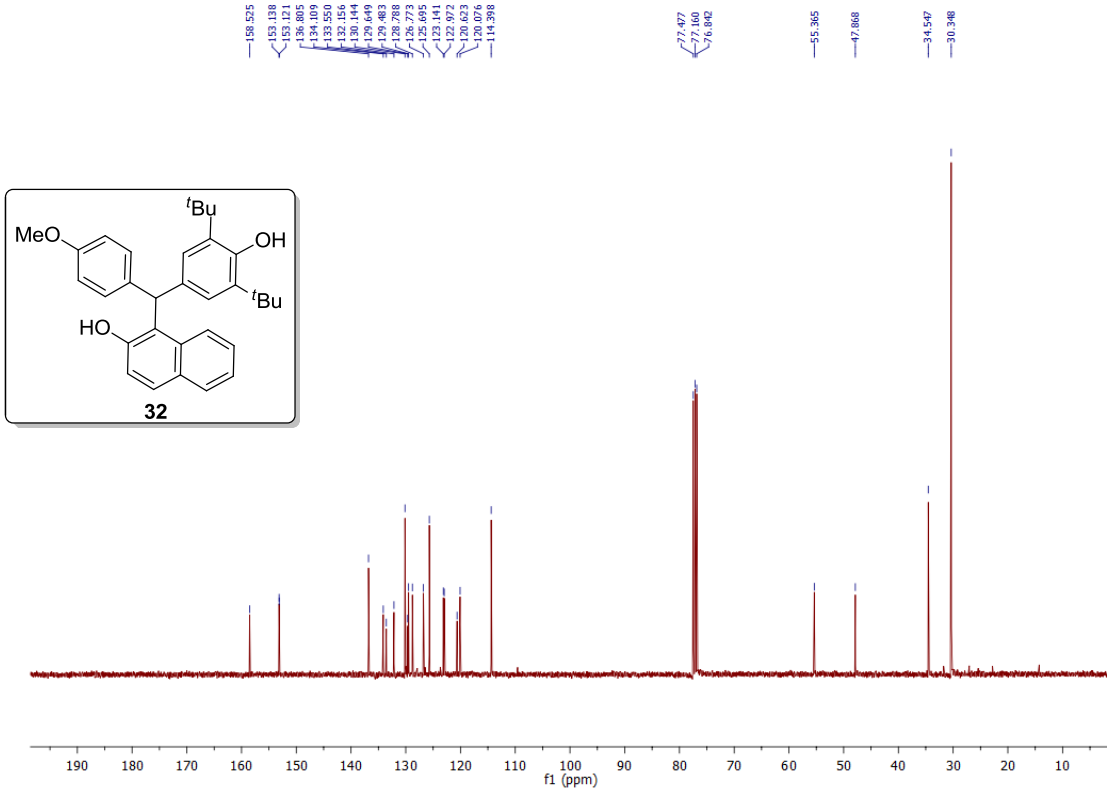
Identification code	**32**
Empirical formula	$C_{32}H_{36}O_3$
Formula weight	468.61
Temperature/K	566(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.9865(10)
b/Å	11.6624(10)
c/Å	20.9000(17)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2677.9(4)
Z	4
ρ_{calc}g/cm^3	1.162
μ/mm^{-1}	0.073
F(000)	1008.0
Crystal size/mm^3	0.200 × 0.200 × 0.200
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.416 to 54.954
Index ranges	$-14 \leq h \leq 14$, $-15 \leq k \leq 15$, $-27 \leq l \leq 27$
Reflections collected	29152
Independent reflections	6127 [R_{int} = 0.2643, R_{sigma} = 0.1361]
Data/restraints/parameters	6127/0/325
Goodness-of-fit on F^2	0.957
Final R indexes [I>=2σ (I)]	R_1 = 0.0738, wR_2 = 0.2027
Final R indexes [all data]	R_1 = 0.1081, wR_2 = 0.2382
Largest diff. peak/hole / e Å^{-3}	0.22/-0.15
Flack parameter	-2.8(10)



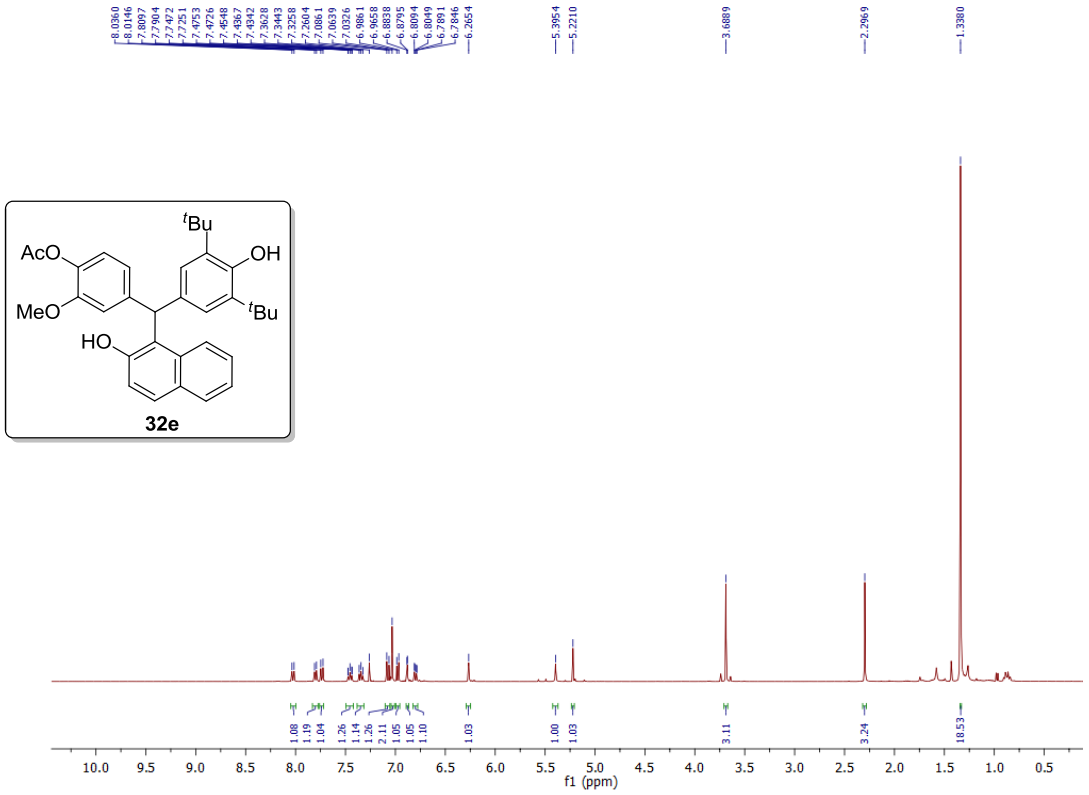
^{1}H NMR Spectrum of 32



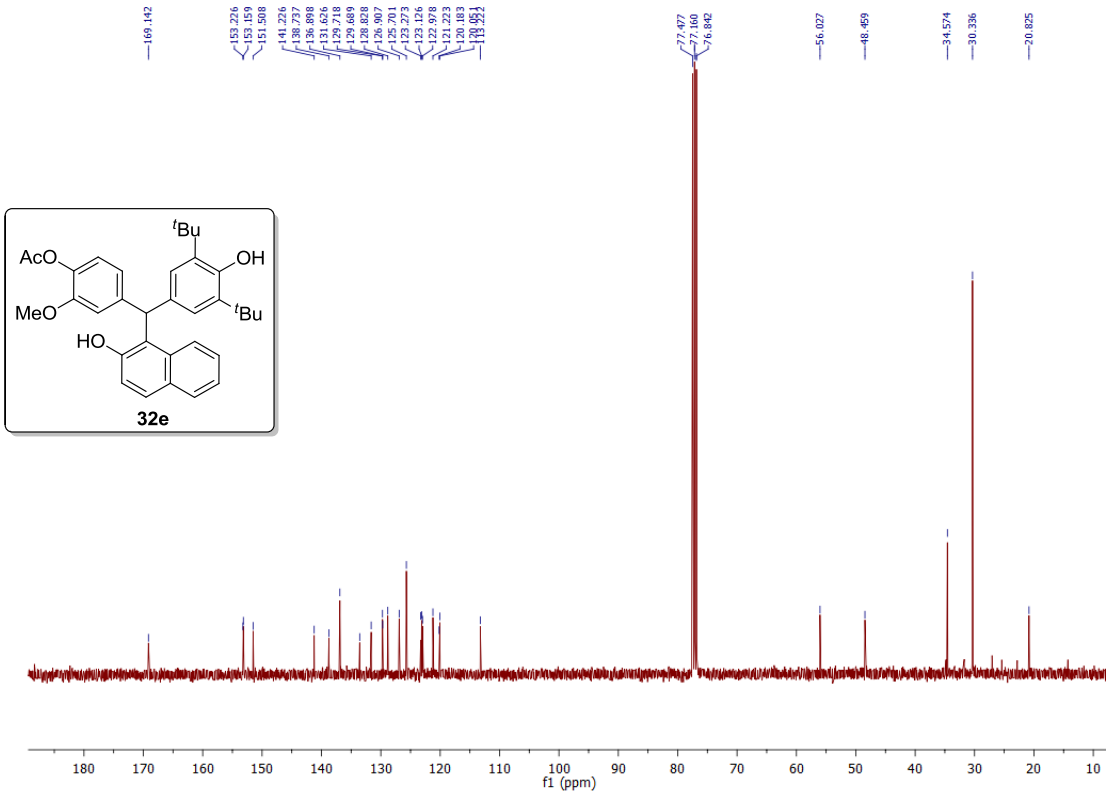
^{13}C NMR Spectrum of 32



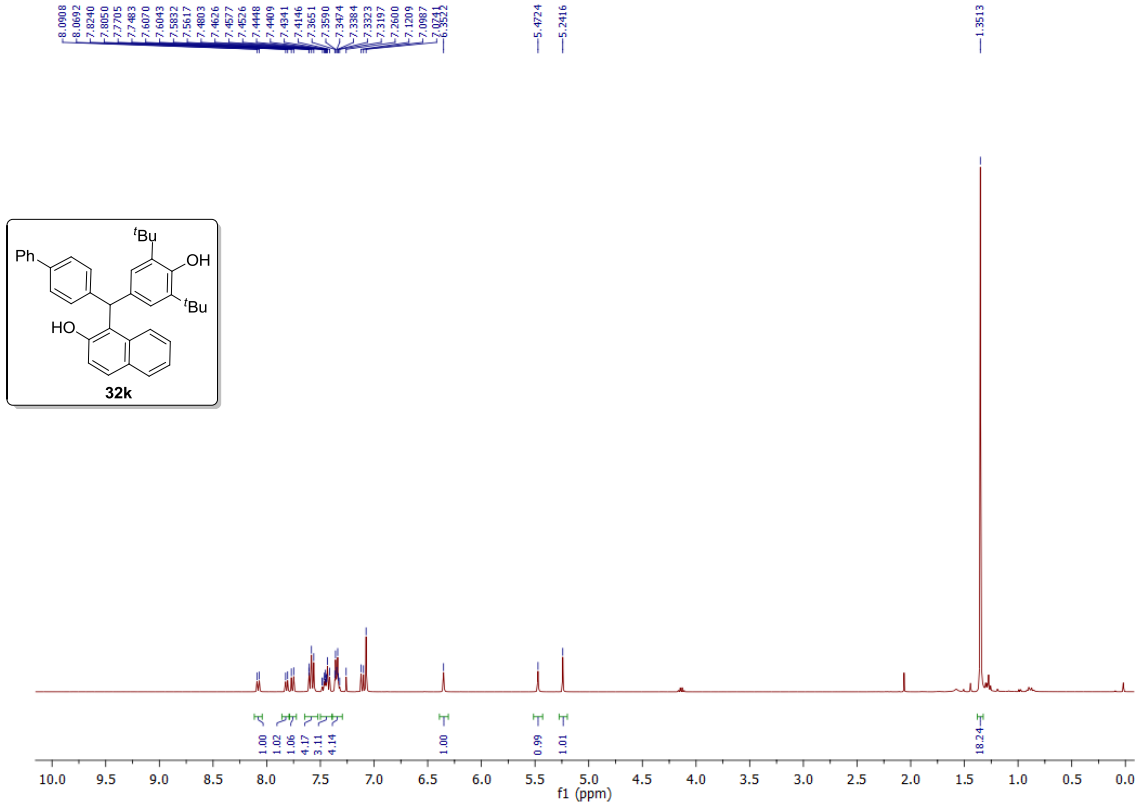
^{1}H NMR Spectrum of 32e



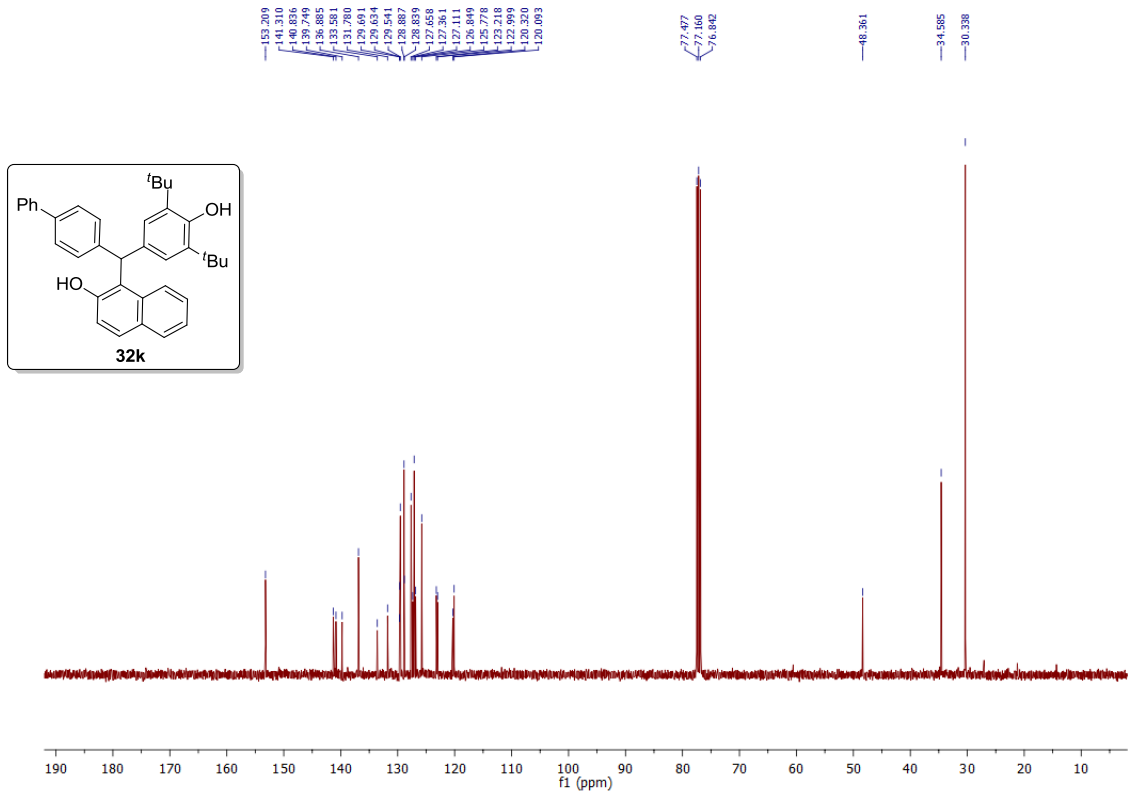
^{13}C NMR Spectrum of 32e



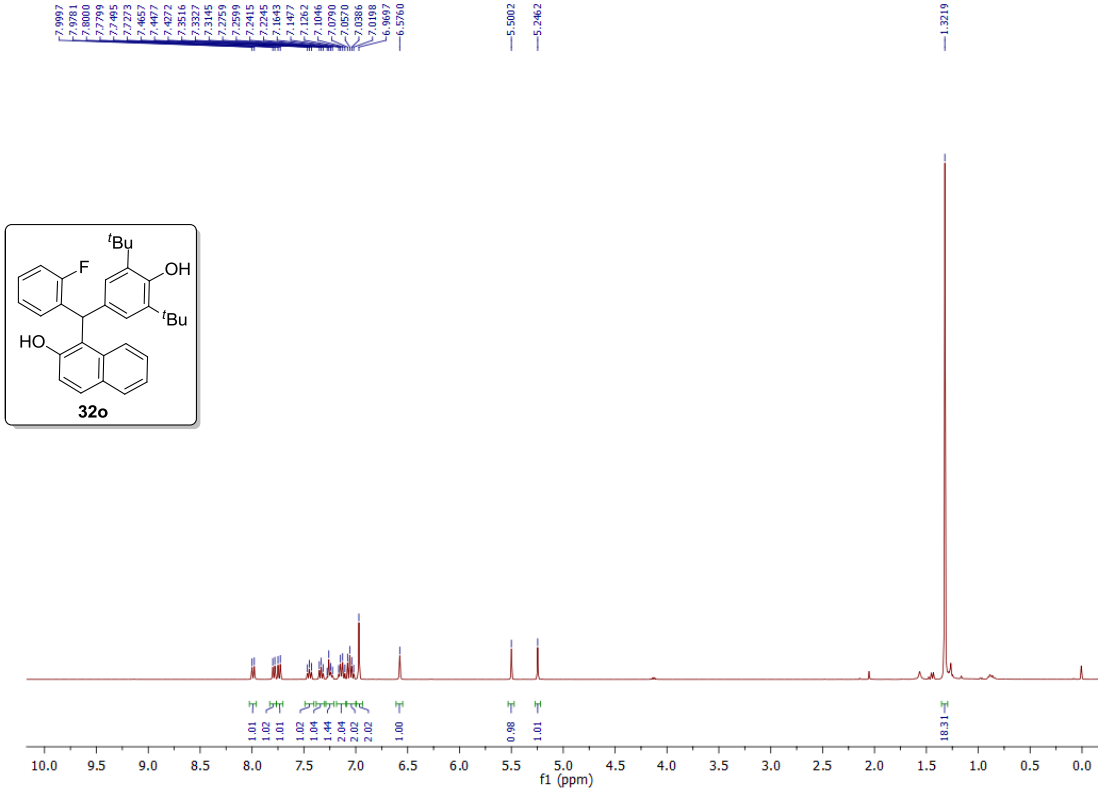
^{1}H NMR Spectrum of 32k



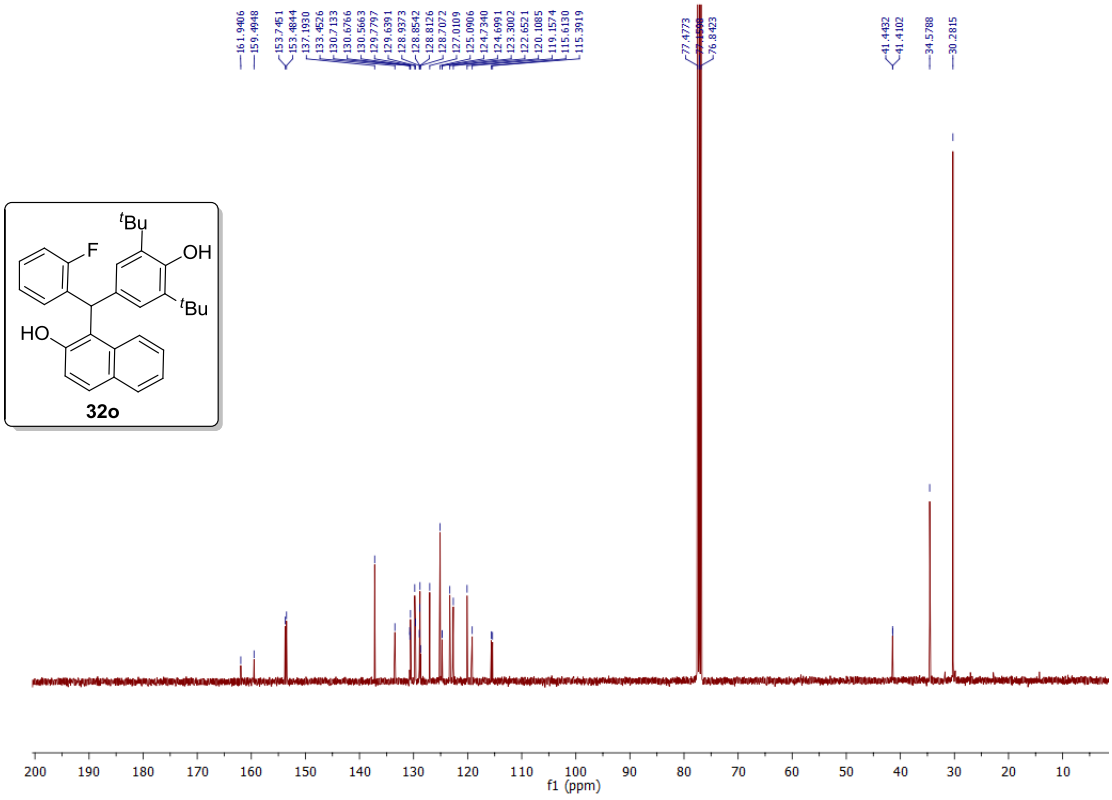
^{13}C NMR Spectrum of 32k



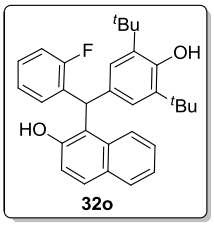
^{1}H NMR Spectrum of 32o



^{13}C NMR Spectrum of 32o

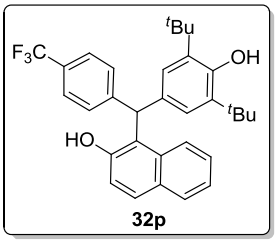


^{19}F NMR Spectrum of 32o



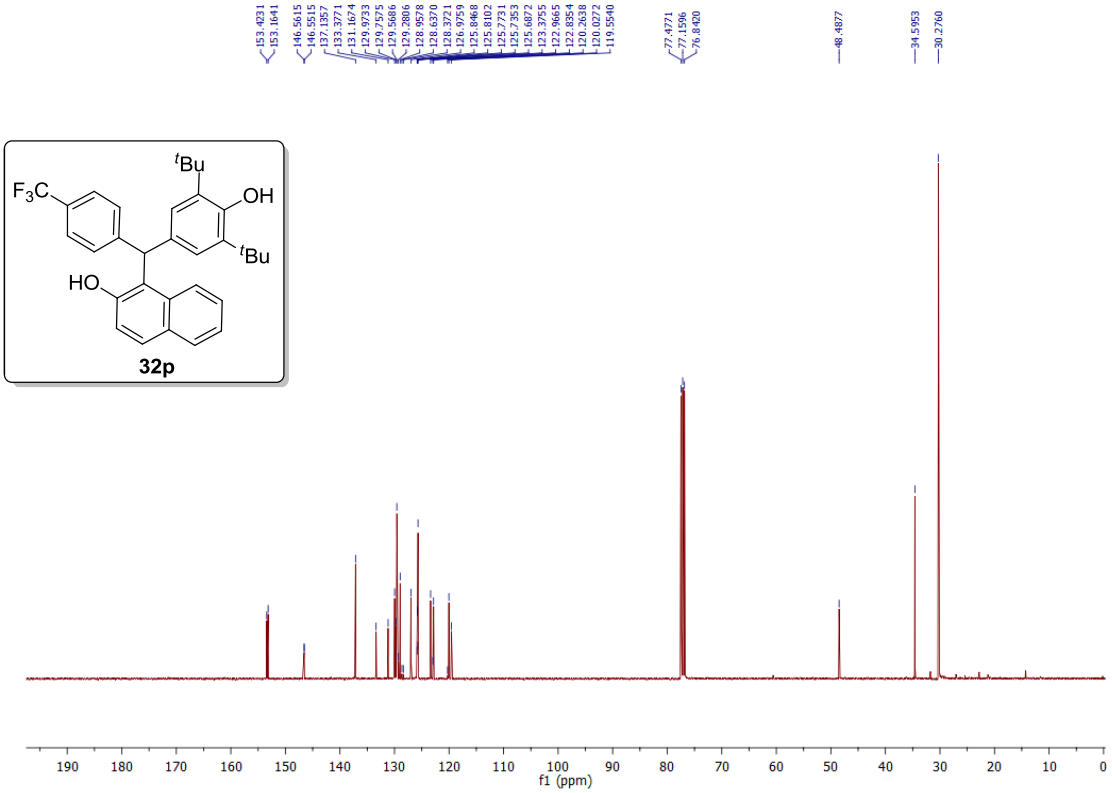
32o

^{1}H NMR Spectrum of 32p

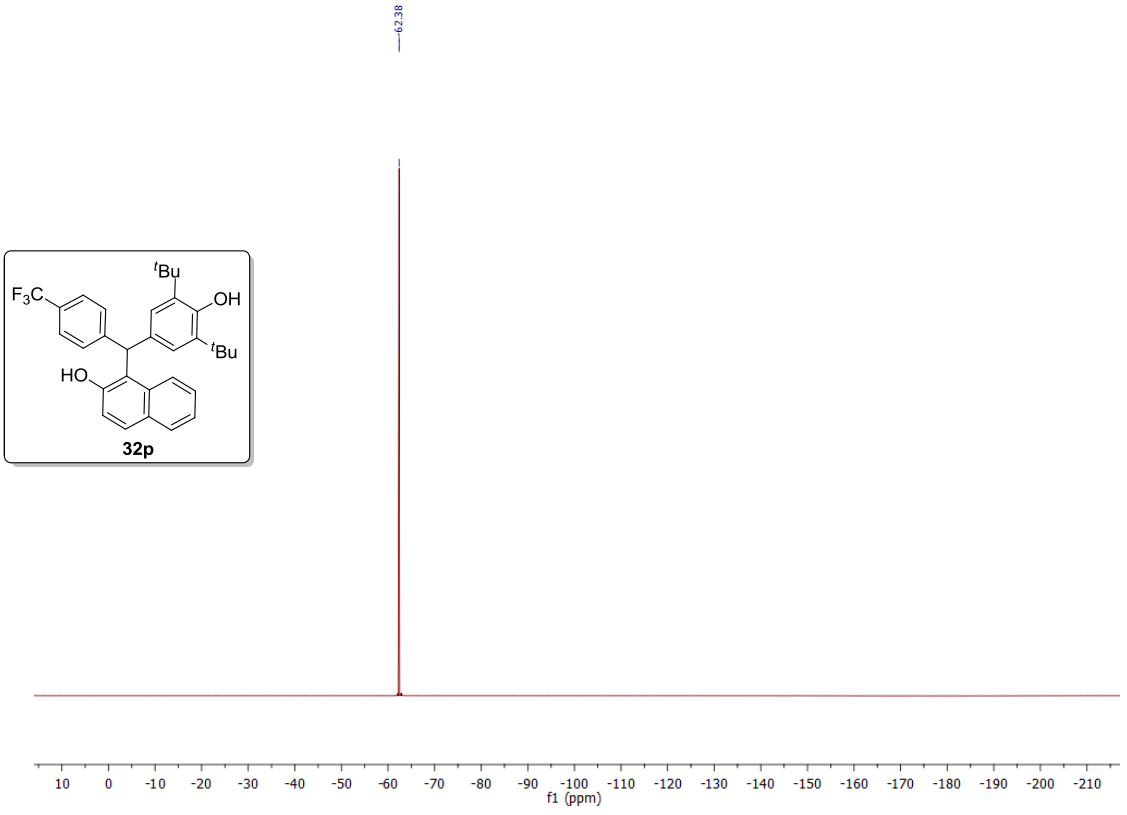


32p

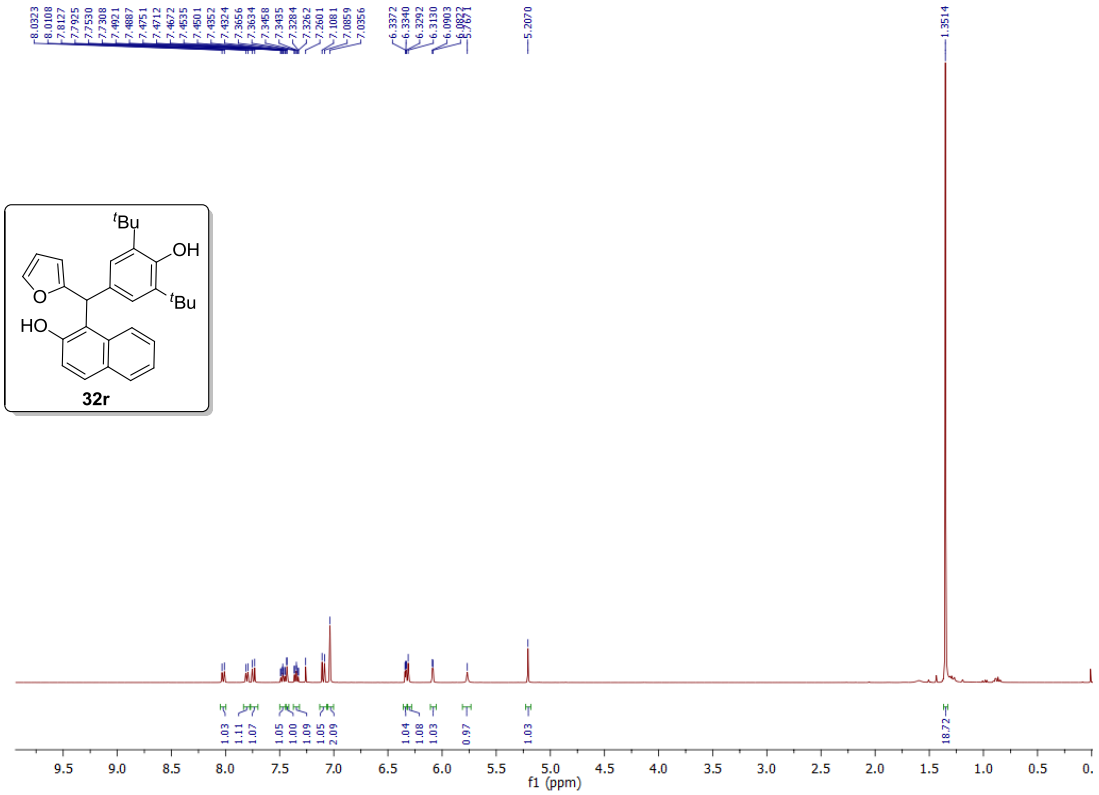
^{13}C NMR Spectrum of 32p



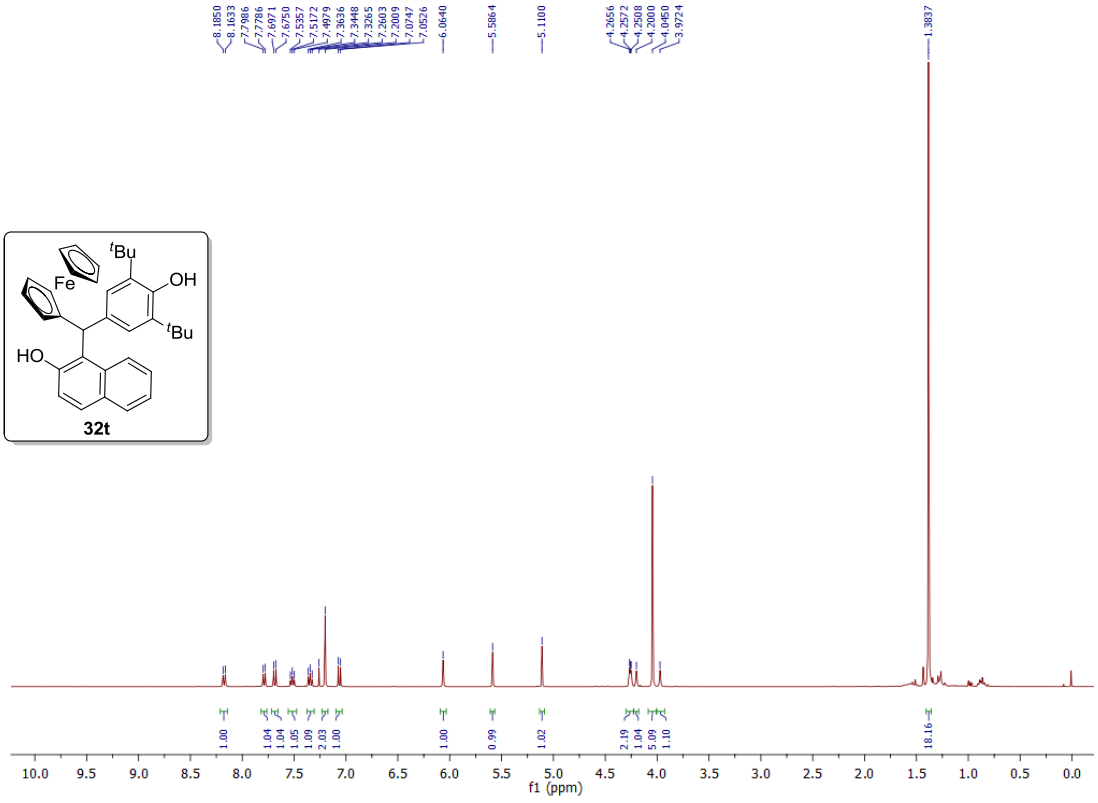
^{19}F NMR Spectrum of 32p



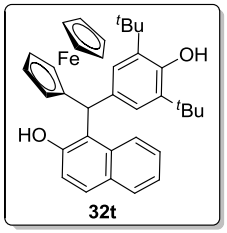
^{1}H NMR Spectrum of 32r



^{1}H NMR Spectrum of 32t

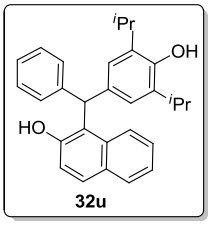


^{13}C NMR Spectrum of 32t



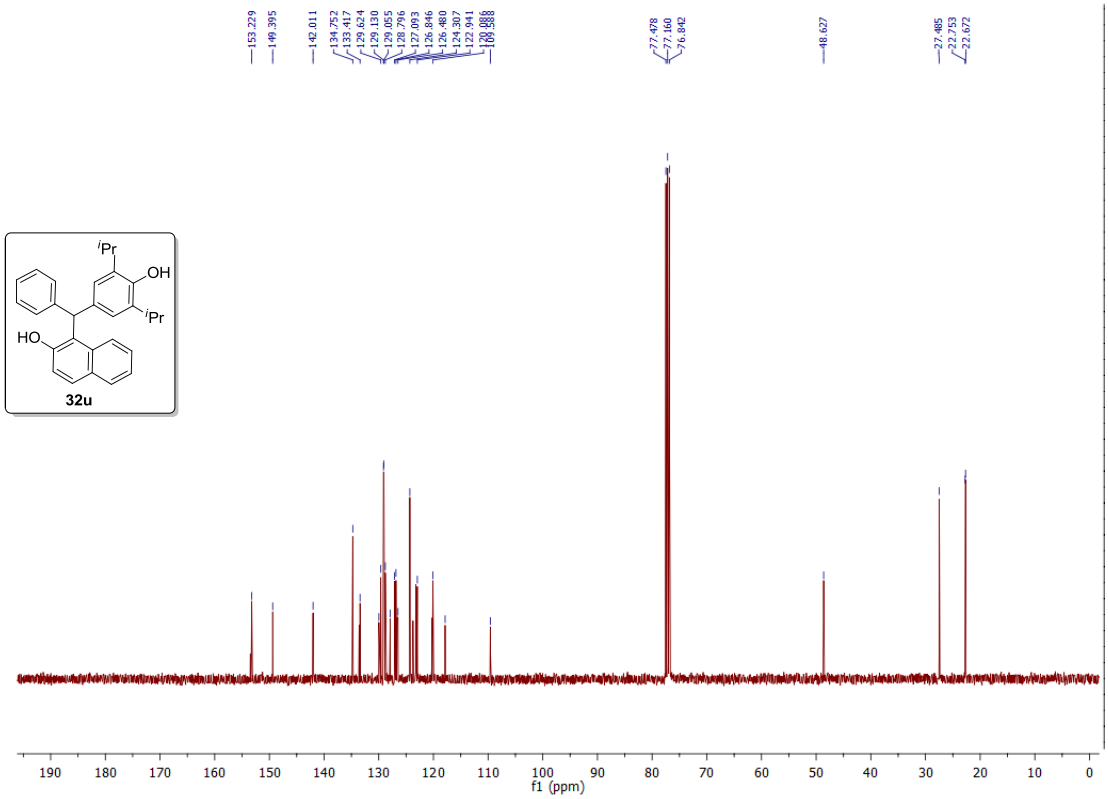
32t

^{1}H NMR Spectrum of 32u

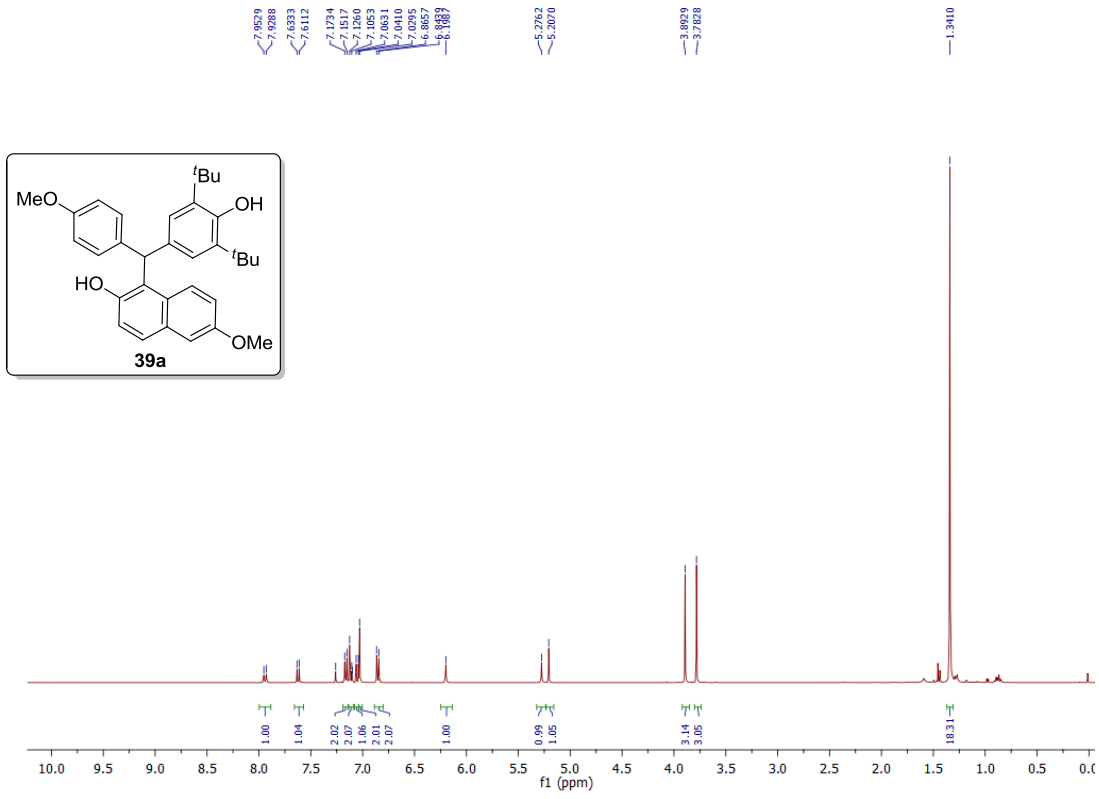


32u

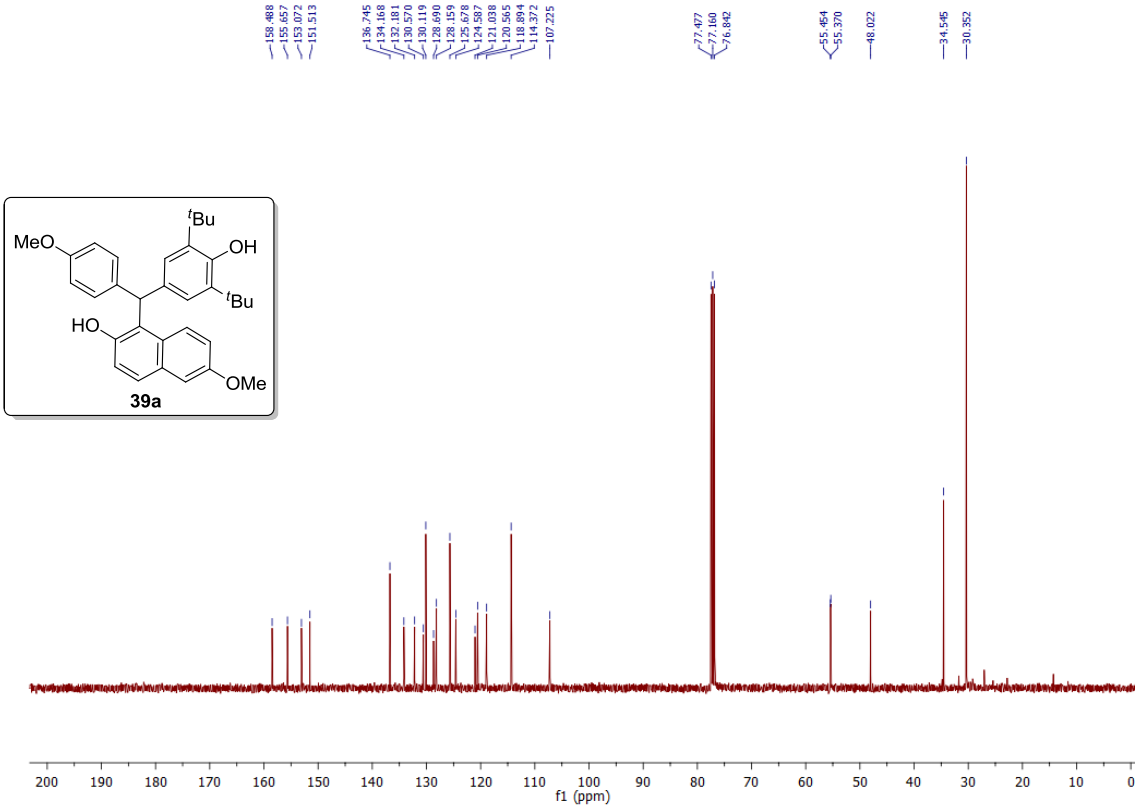
^{13}C NMR Spectrum of 32u



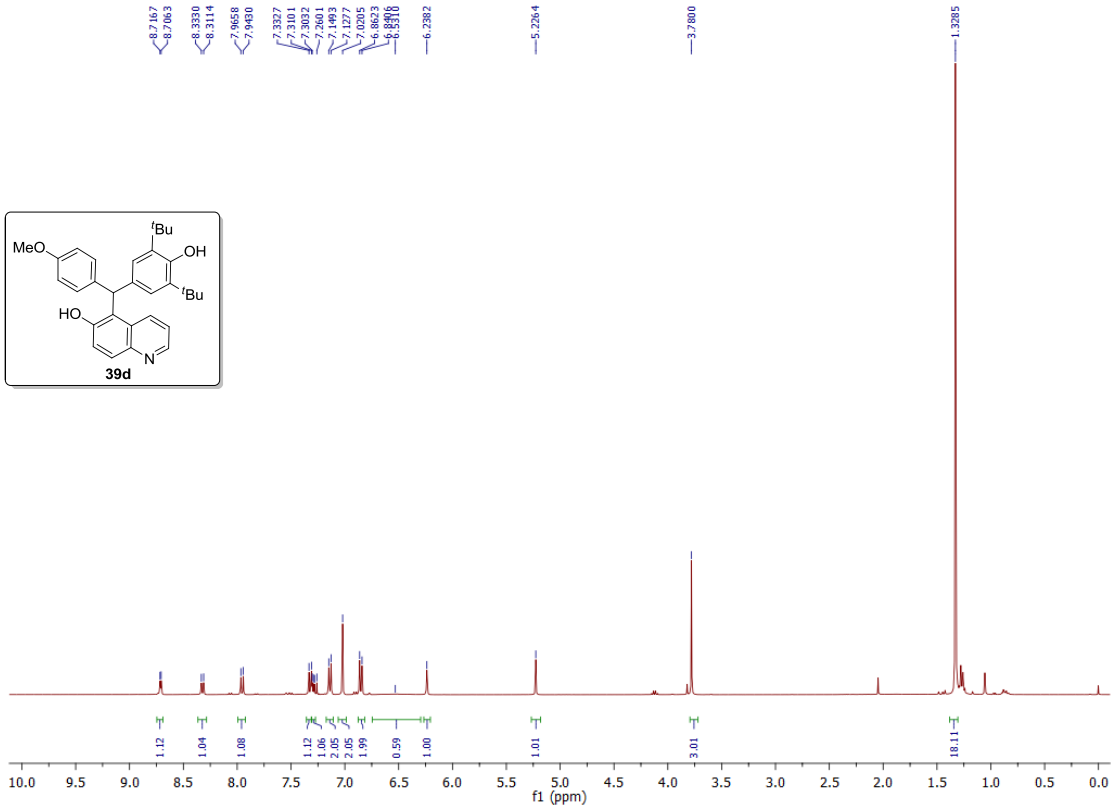
^{1}H NMR Spectrum of 39a



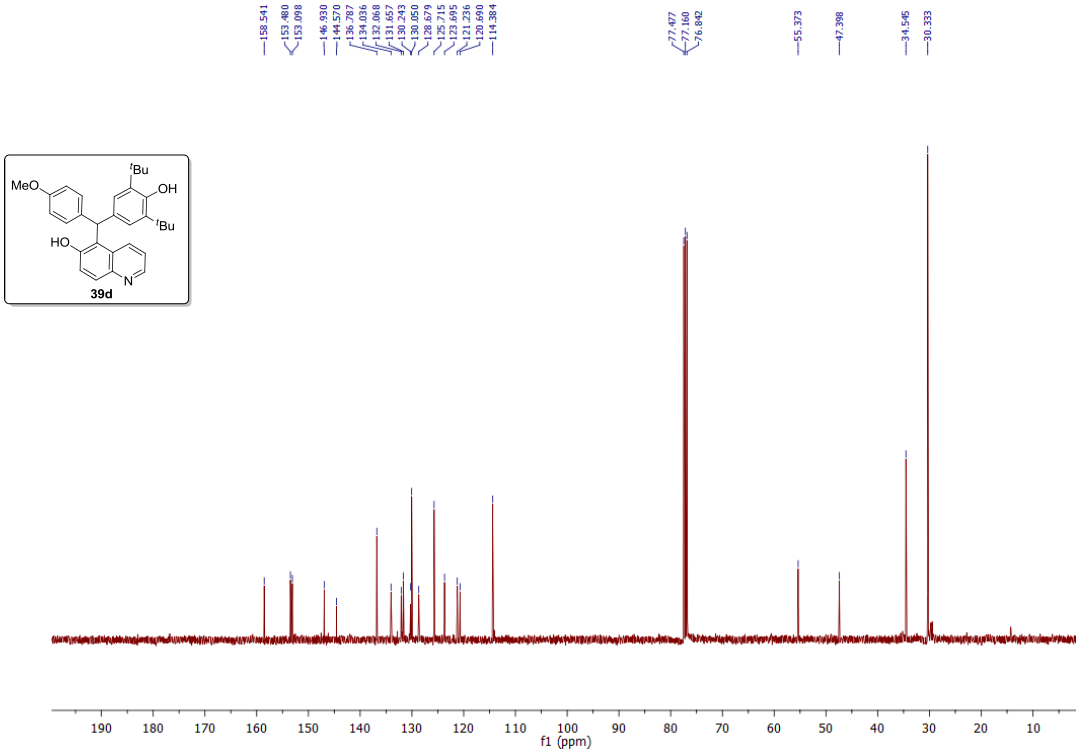
^{13}C NMR Spectrum of 39a



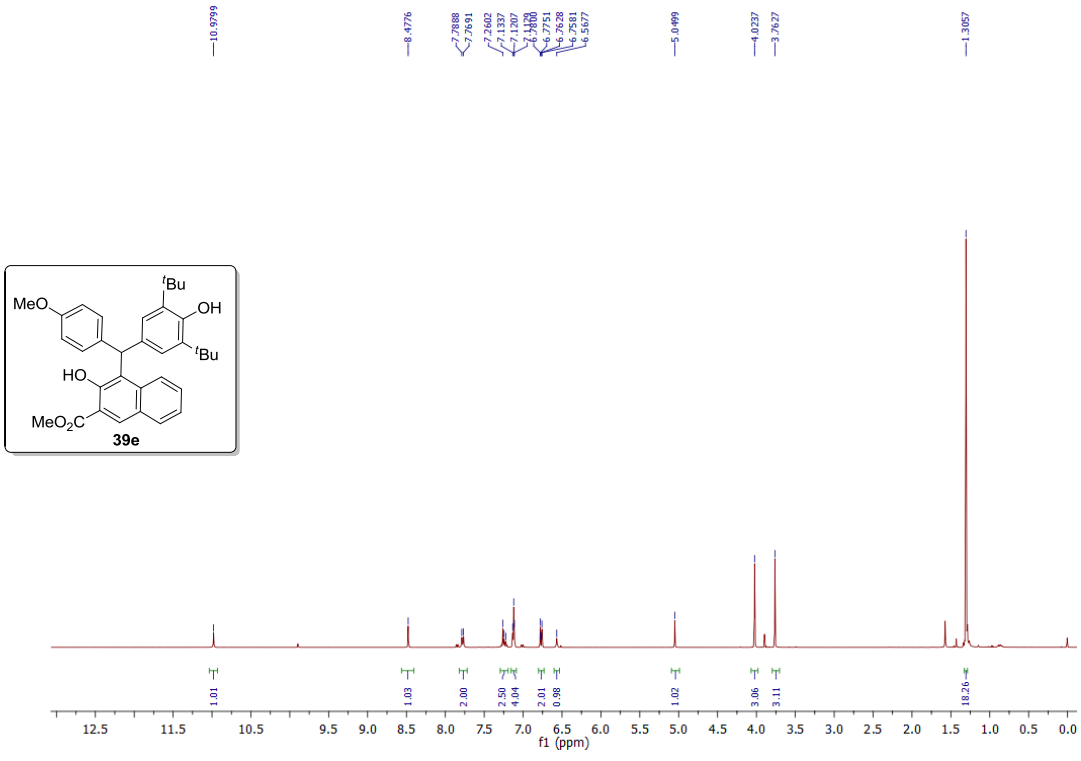
^{1}H NMR Spectrum of 39d



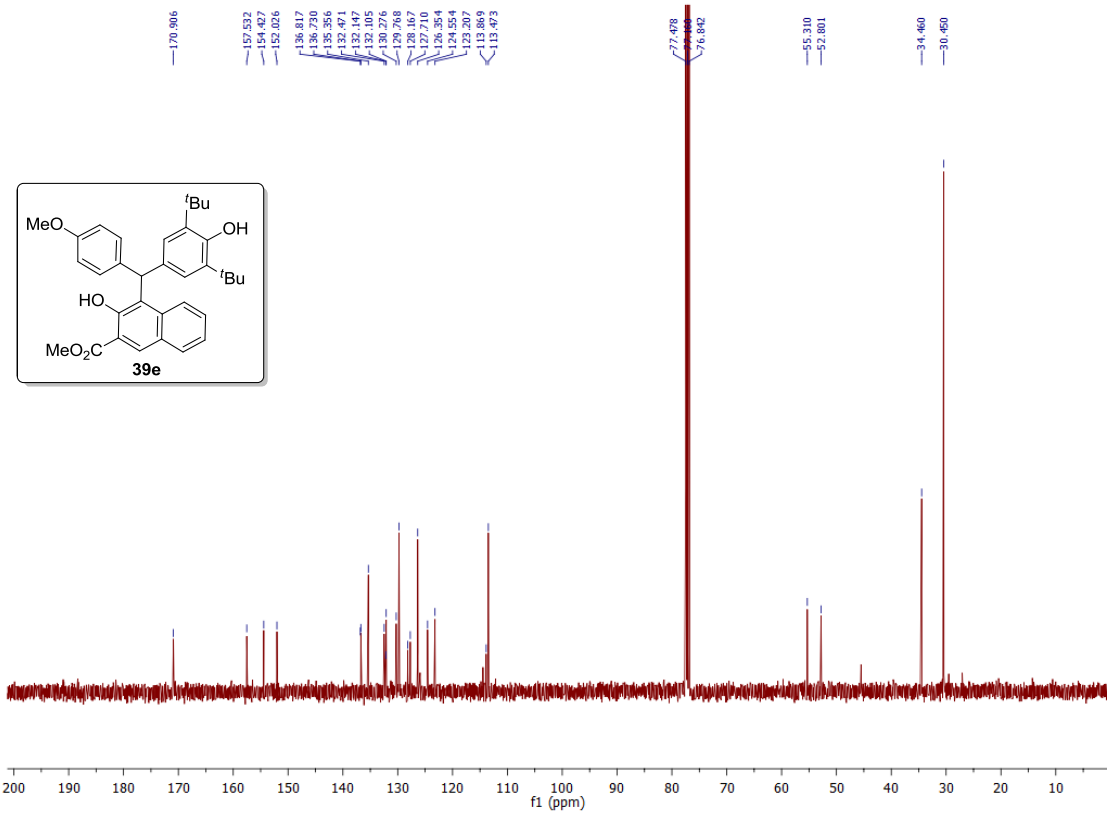
^{13}C NMR Spectrum of 39d



^{1}H NMR Spectrum of 39e



^{13}C NMR Spectrum of 39e



2.5) References

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28. CCDC NO: 1452070.

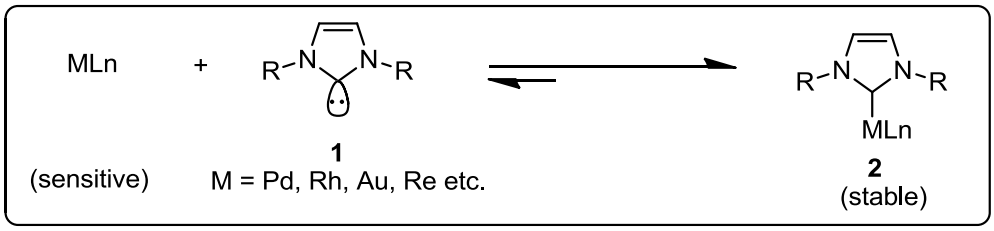
Chapter 3

***N*-heterocyclic carbene catalyzed trimethylsilylation of terminal acetylenes and indoles using Ruppert's reagent as a silyl source under solvent free conditions**.

In this chapter, the NHC-catalyzed solvent free protocol for the synthesis of alkynylsilanes and *N*-silyl indole derivatives is discussed. This chapter also covers a general introduction and literature review on NHC-catalyzed Si–C bond activation and related reactions.

3.1) Introduction

In past several decades, there is growing interest in N-heterocyclic carbene chemistry due to their incredible applications in the fields of organometallics[1] and organocatalysis.[2] The distinguishing structural and electronic properties of N-heterocyclic carbene plays a significant role in their reactivity. Presence of high directional sp^2-type lone pair allows them to show stronger σ-donation toward metals and electrophiles. The strong σ-donation and weak π-backbonding interaction of NHC towards metal increases the electron density at metal centre and, as a result the thermal stability of metal complexes found to be improved (Scheme **1**).[3]



Scheme 1: NHC–Metal complexes

Beside transition-metals, NHC can also form complexes with boranes and silicon compounds.[4] The literature report reveals that NHCs can form hypervalent complexes with tetravalent silicon compounds.[5] Due to the strong σ-donation, the NHC–Si bond is comparatively stronger than the simple Si–C bond of organosilicon reagents. This extra stability of NHC–Si at

hypervalent stage provides driving force for the cleavage of Si–C bond of organosilicon reagents (Figure 1).

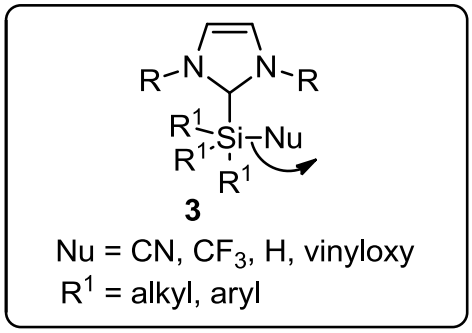


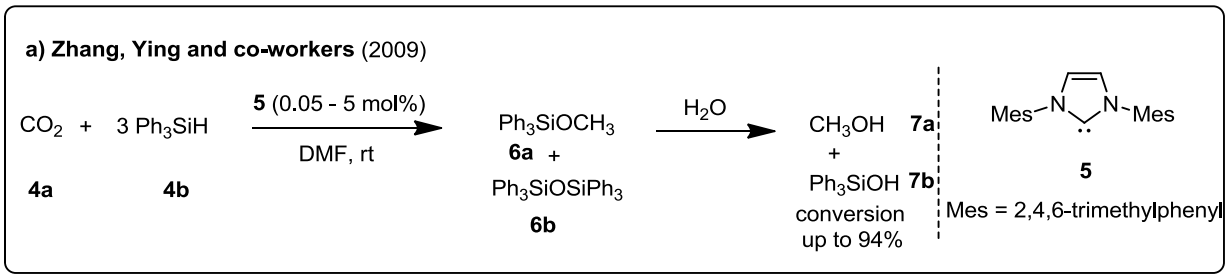
Figure 1

By using this phenomenon numerous organic transformations have been reported. Some of the selected NHC-catalyzed transformations using silicon reagents are discussed below.

3.2) Literature reports for the NHC-catalyzed transformations using silicon reagents

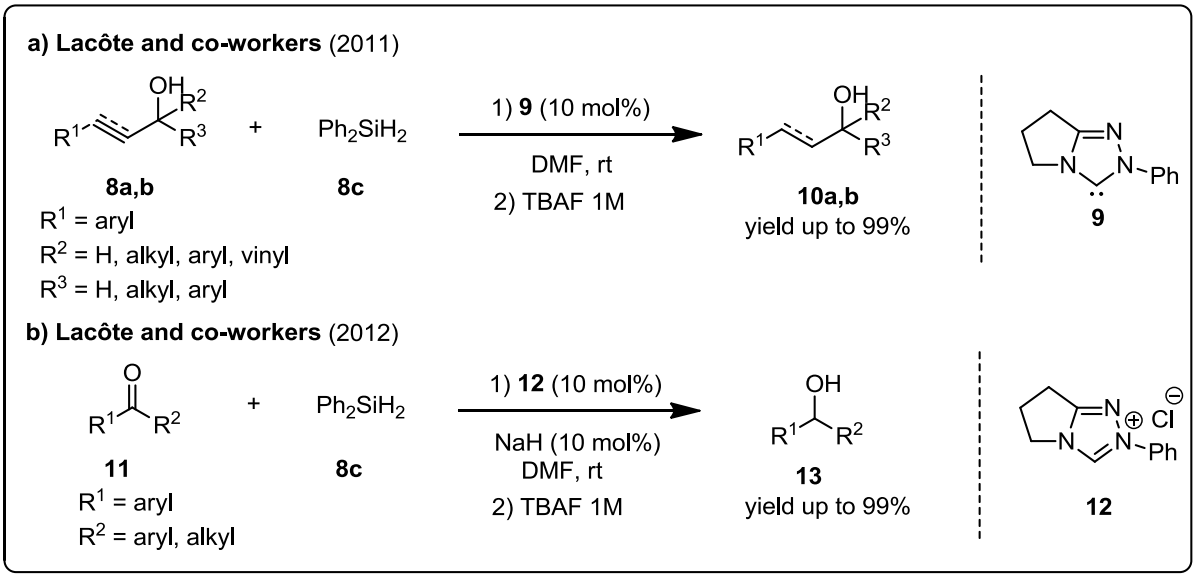
3.2.1) NHC-catalyzed hydrosilylation reactions

Zhang, Ying and co-workers reported the first NHC-catalyzed hydrosilylation of carbon dioxide (**4a**) in 2009.[6] NHC was found to be more efficient catalyst compared to most of the transition-metals used for this reaction. The treatment of diphenylsilane (**4b**) with CO_2 (**4a**) at room temperature gave the corresponding reduced methanol (**7a**) in 90% conversion after 24 h, whereas transition-metal-catalysts required more than a week to complete the reaction. The detailed NMR analysis of the reaction mixture revealed that, the reaction proceeds through a number of intermediates such as formoxysilanes and silylacetal adduct which has further reduced to the methoxide products (**6a**, **6b**) (Scheme 2).



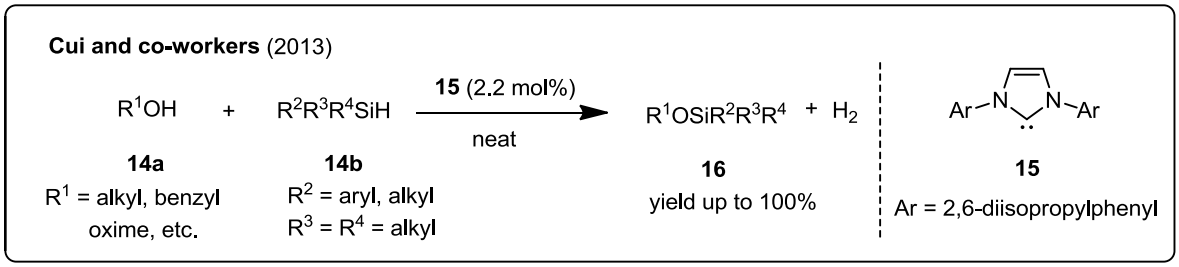
Scheme 2: NHC-catalyzed hydrosilylation of carbon dioxide

Lacôte and co-workers developed an interesting protocol for the NHC-catalyzed hydrosilylation of nonactivated olefins and alkynes (**8a,b**).[7] The reaction between allyl and propargylic alcohols (**8a,b**) with dihydrosilanes (**8c**) leads to the corresponding reduced alcohols (**10a,b**) in up to 99% yield under mild condition. The *in situ* generated hypervalent silicon intermediate acts as Lewis acid to activate olefins and as hydride donor (a, Scheme 3). Furthermore, in 2012, the same group reported a NHC-catalyzed reduction of carbonyl compounds (**11**) with dihydrosilanes (**8c**).[8] The products (**13**) were isolated in up to 99% yield with high chemo- and regioselectivity. Sensitive functional groups such as epoxide and cyclopropene were tolerated under the reaction conditions (b, Scheme 3).



Scheme 3: NHC-catalyzed hydrosilylation of olefins and carbonyl compounds

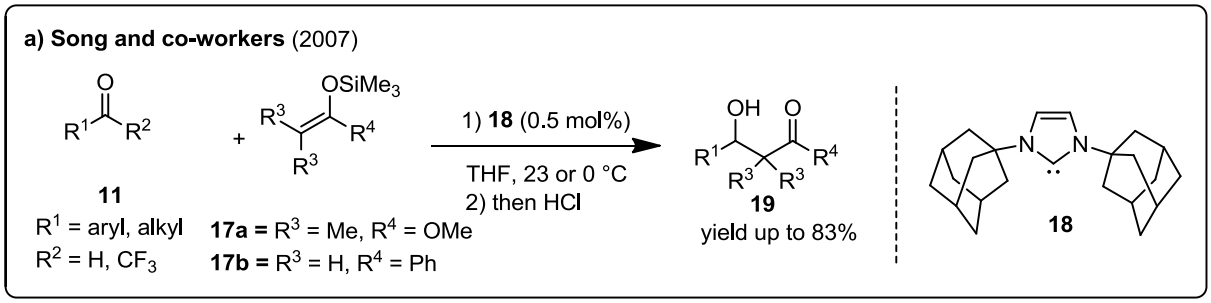
Cui's group accomplished a highly chemoselective and atom-economic route for the synthesis of silyl ethers (**16**) in 2013.[9] This solvent free NHC-catalyzed dehydrogenative coupling of different silanes (**14b**) with hydroxyl compounds (**14a**) afforded the corresponding silyl ethers (**16**) in excellent yields. Chemoselective silylation of hydroxyl group was preferred over secondary amine functionality when diphenylprolinol was treated with silane. Other reactive functional groups such as alkyne, ester, keto and imino were also tolerated (Scheme **4**).



Scheme 4: NHC-catalyzed dehydrogenative coupling of silanes with hydroxyl compounds

3.2.2) NHC-catalyzed Mukaiyama aldol type reactions

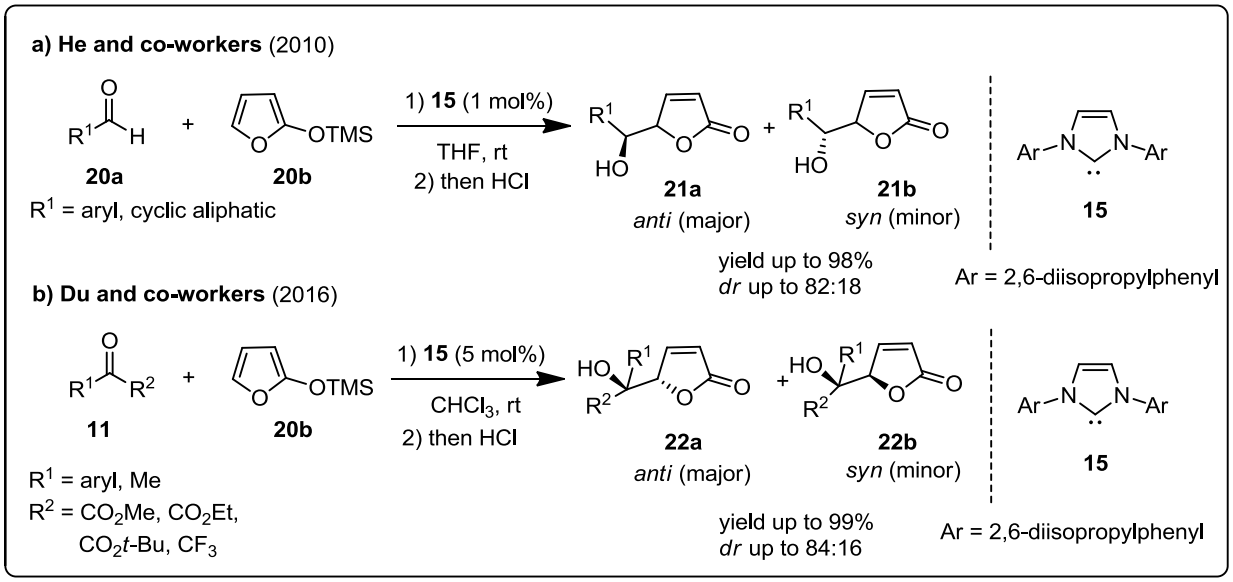
Apart from the above mentioned reports, some other NHC-catalyzed reports on aldol type reactions have also been appeared in the literature. In 2007, Song and coworkers published the highly efficient NHC-catalyzed Mukaiyama aldol reaction.[10] The corresponding aldol adducts (**19**) were isolated in moderate to good yields when the aldehydes and activated ketones (**11**) were treated with enoxysilanes (**17a**) in the presence of NHC as a catalyst. The reaction worked well at room temperature when trimethylsilyl ketene acetals (**17a**) were used as nucleophiles, whereas in case of trimethylsilyl enol ethers (**17b**), it required low temperature (0 °C) to avoid byproducts (Scheme 5).



Scheme 5: NHC-catalyzed Mukaiyama aldol reaction

He and co-workers developed a novel NHC-catalyzed vinylogous Mukaiyama aldol reaction between aldehydes (**20a**) and 2-(trimethylsililoxy)furan (**20b**) for the synthesis of γ-substituted butenolides (**21a, 21b**).[11] The corresponding products were isolated in excellent yields with anti-selectivity (**20a**). The efficiency of the reaction was maintained even when catalyst loading was decreased to 1 mol%. Although, the cyclic aliphatic carboxaldehyde (**20a**) worked smoothly, the linear aliphatic aldehydes failed to give required products (a, Scheme 6).

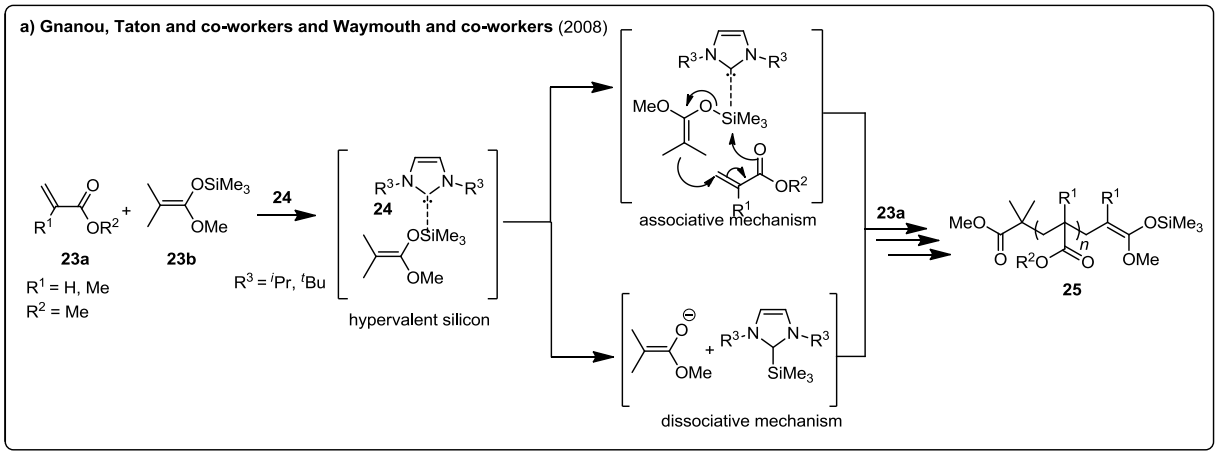
Very recently, Du and co-workers further extended the scope of NHC-catalyzed vinylogous Mukaiyama aldol reaction by successfully replacing the aldehydes to activated ketones (**11**).[12] This protocol affords the high-yielding γ-substituted butenolides (**22a, 22b**) bearing adjacent tertiary and quaternary carbon center with high diasterioselectivity (b, Scheme 6).



Scheme 6: NHC-catalyzed vinylogous Mukaiyama aldol reaction

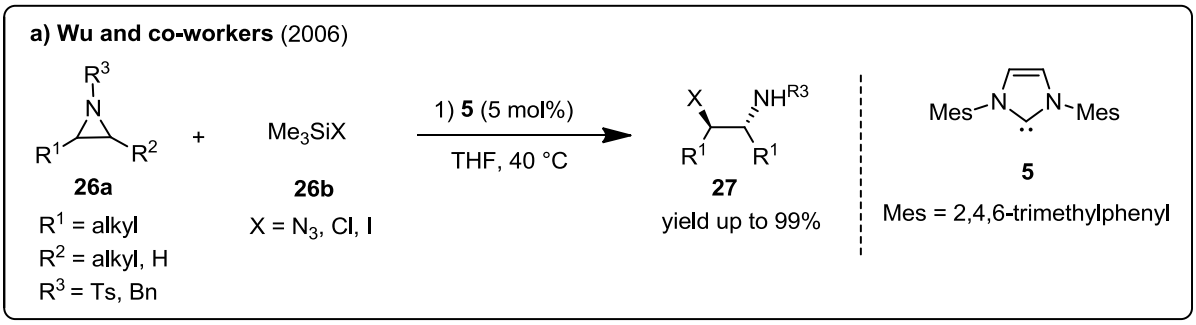
3.2.3) NHC-catalyzed polymerization and ring opening reactions

Taton and [13] and Waymouth [14] in their independent findings demonstrated a nice piece of work on NHC-catalyzed group-transfer polymerisation (GTP) of silylketene acetals (**23b**) and methyl methacrylates (**23a**). Both groups proposed a plausible mechanism for GTP. Taton and co-workers, on the basis of their NMR studies, proposed an associative mechanism where as Waymouth and co-workers believed that the reaction proceeds a through dissociative mechanism. So the exact mechanism of nucleophilic GTP is still under substantial debate (Scheme 7).



Scheme 7: NHC-catalyzed group-transfer polymerisation

Wu's group developed a fascinating NHC-catalyzed aziridine ring opening reaction in 2006.[15] The variety of silylated nucleophiles (**26b**) were activated by NHC toward aziridines (**26a**) to access the corresponding products (**27**) in up to 99% yield with anti-stereochemistry. The highly regioselective addition of the nucleophiles from the less hindered side was observed when unsymmetrically substituted aziridines were used (Scheme 8).

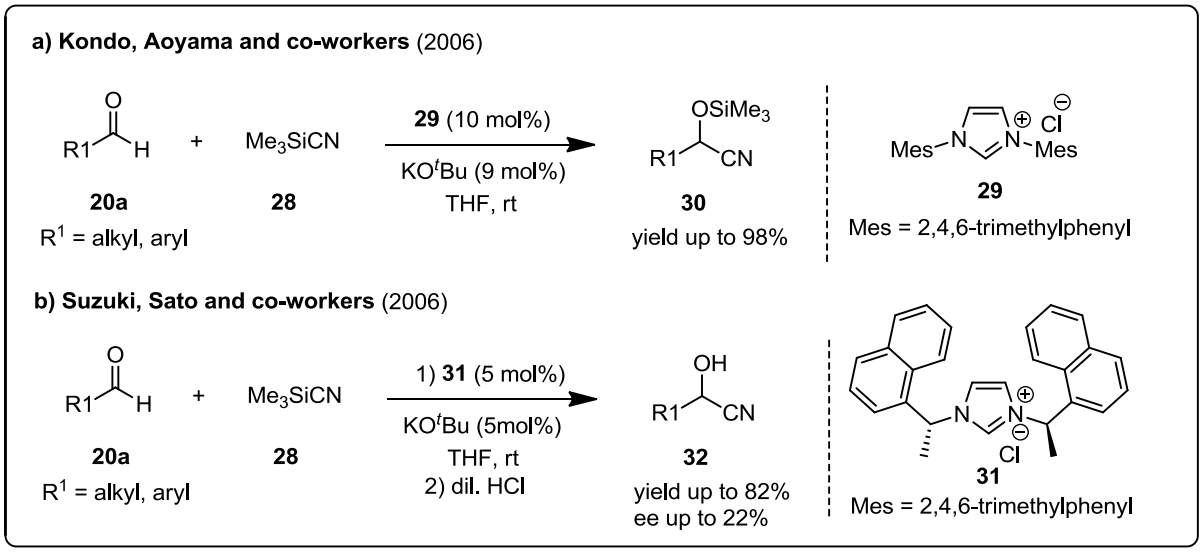


Scheme 8: NHC-catalyzed aziridine ring opening

3.2.4) NHC-catalyzed 1,2-addition reactions

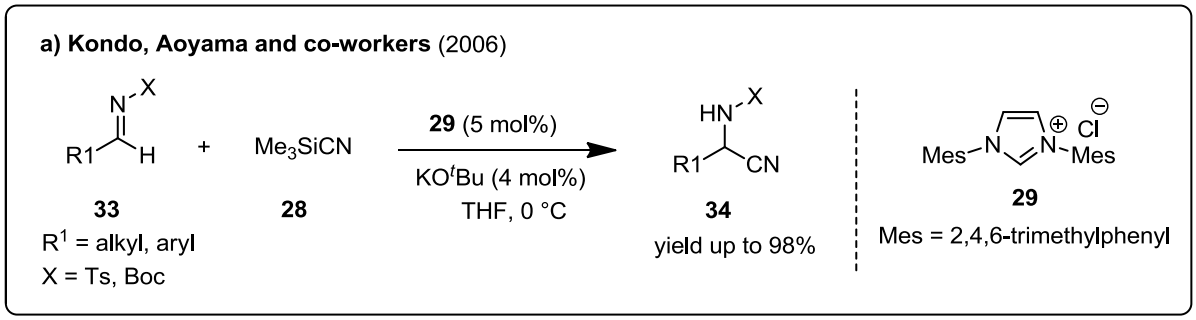
NHC-catalyzed 1,2-addition of silylated nucleophiles to the electrophilic functional groups such as carbonyl, imines and esters have been broadly studied. Some of the selected reports are reviewed below. In 2006, Aoyama and co-workers reported the first NHC-catalyzed synthesis of cyanohydrin derivatives (**30**) *via* cyanosilylation of aldehydes (**20a**).[16] The NHC derived from the imidazolium salt (**29**) promoted the 1,2-addition of trimethylsilyl cyanide (**28**)

towards a range of aldehydes (**20a**) to afford the corresponding cyanohydrins and silyl ethers (**30**) in up to 98% yield (a, Scheme 9). Furthermore, in the same year, Suzuki and co-workers, in their similar work, reported the asymmetric version of this reaction using C_2-symmetric imidazolidenyl carbene as catalyst (b, Scheme 9).[17]



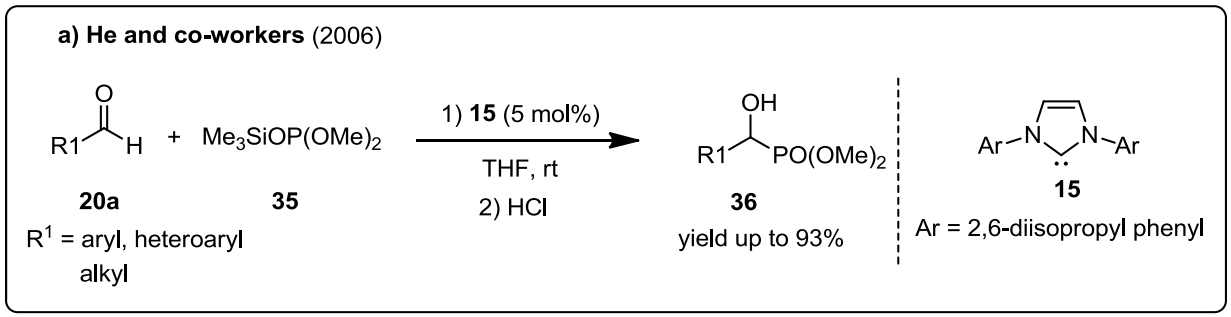
Scheme 9: NHC-catalyzed 1,2-cyanosilylation of aldehydes

Thereafter, Kondo's group elaborated the scope of cyanosilylation reaction by performing the Strecker reaction of aldemines (**33**) using NHC as a catalyst.[18] The reaction between trimethylsilyl cyanide (**28**) and aldimines (**33**) led to the synthesis of α-aminonitriles (**34**) in excellent yields (Scheme 10). α-Aminonitriles are important intermediate in natural product synthesis.



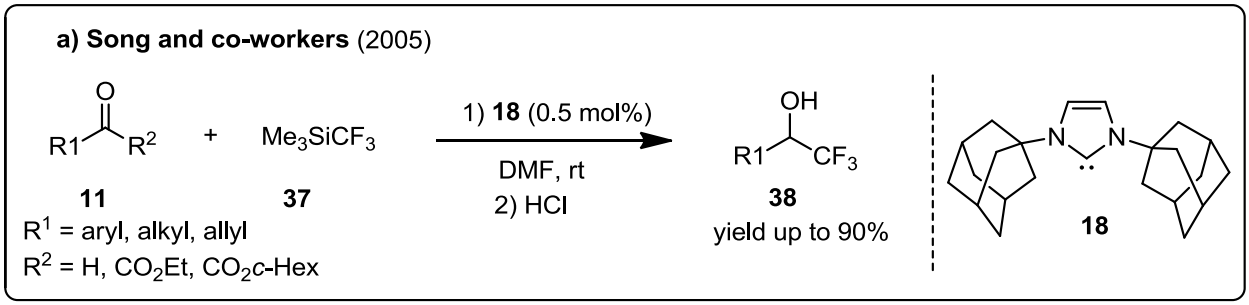
Scheme 10: NHC-catalyzed 1,2-cyanosilylation of imines

He and co-workers disclosed a novel approach for the synthesis of *α*-hydroxyphosphonate derivatives (**36**) *via* NHC-catalysis.[19] The Pudovik-type reaction between aldehydes (**20a**) and dimethyl trimethylsilyl phosphite (**35**) afforded the phosphonates (**36**) in good yields. Aromatic aldehydes with electron-donating group were found to be more suitable substrates compared to the aldehydes bearing electron-withdrawing groups. Heteroaromatic and aliphatic aldehydes were also converted to the corresponding products with moderate yields (Scheme 11).



Scheme 11: NHC-catalyzed Pudovik-type reaction

Song and co-workers accomplished an efficient NHC-catalyzed trifluoromethylation of aldehydes and activated ketones (**11**) to access desired CF_3-containing alcohols (**38**) in moderate to excellent yields.[20] The Ruppert's reagent (**37**) has been used as trifluoromethyl source. The chemoselective trifluoromethylation of both enolizable and nonenolizable aldehydes and *α*-keto esters (**11**) were performed at mild and simple conditions. Regardless of the electronic nature, all aromatic and aliphatic aldehydes and *α*-keto esters worked smoothly at standard condition (Scheme 12).

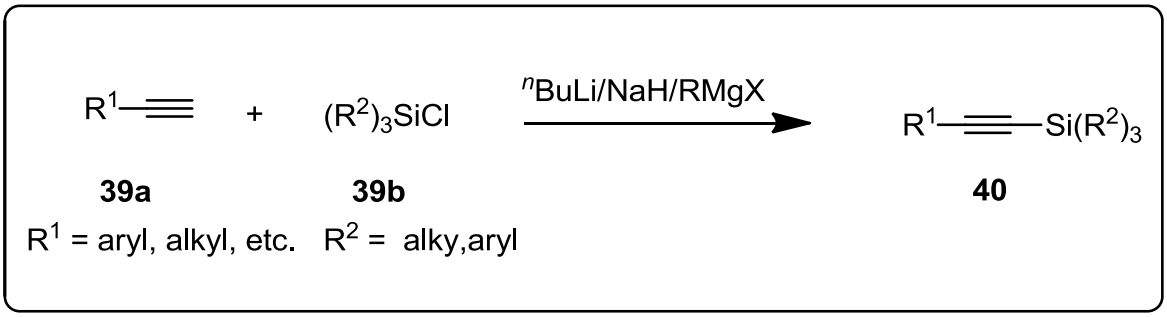


Scheme 12: NHC-catalyzed trifluoromethylation of aldehyds and ketones

3.3) Introduction and literature reports for the synthesis of Alkynylsilicon compounds

Alkynylsilicon compounds are considered as valuable scaffolds in synthetic organic chemistry due to their widespread applications. Alkynylsilicon reagents serve as stable and appropriate source of alkynyl carboanions in the synthesis of many natural products.[21] These are also used as coupling partners in many transition-metal-catalyzed cross-coupling reaction[22] and in C–C bond formation reactions such as alkynylation reactions[23] and metathesis reactions.[24] Recently their utility has been remarkably increased as alkynyl carboanions source in the construction of optoelectronic materials, liquid crystals and other engineering materials.[25]

Due to their extensive utility, several approaches have been developed for the synthesis of alkynylsilicon compounds. Conventional method for the synthesis of alkynylsilicon compounds (**40**) includes deprotonation of terminal acetylene (**39a**) with strong bases such as organolithium or Grignard reagent followed by quenching with a silyl electrophiles (**39b**) (Scheme 13).[26]



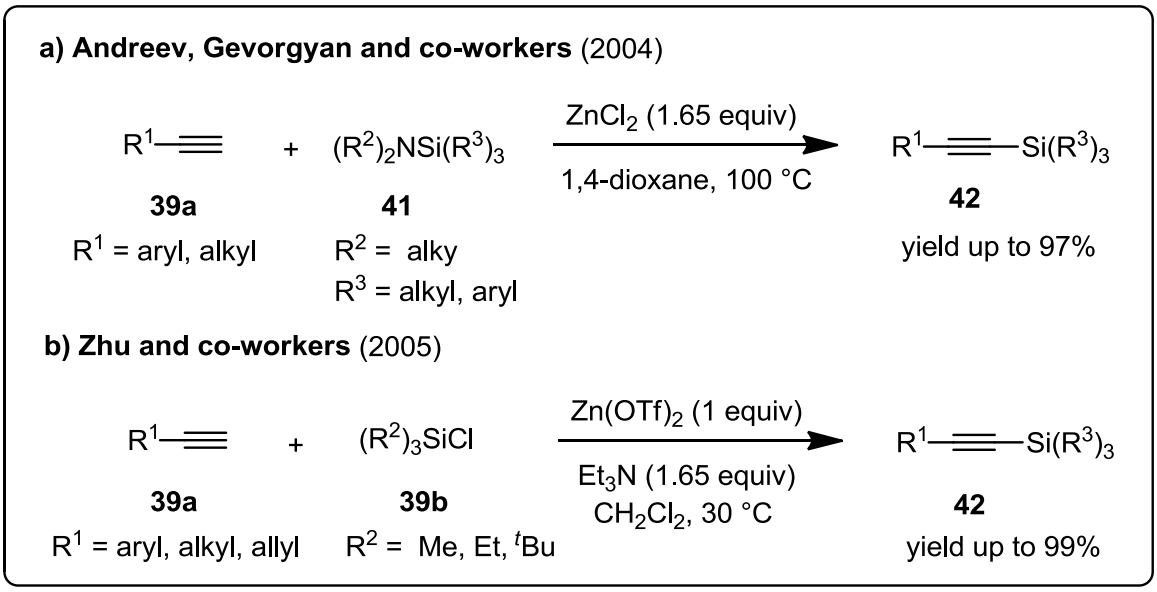
Scheme 13: General routes for the synthesis of alkynylsilicon compounds

Use of strong bases and generation of equimolar quantities of salt as byproduct limits the scope of these methods. To address these issues several metal-catalyzed/mediated approaches have been developed. Some of the selected reports are overviewed below.

3.3.1) Literature reports for the synthesis of Alkynylsilicon compounds

3.3.1.1) Metal-catalyzed/mediated approach

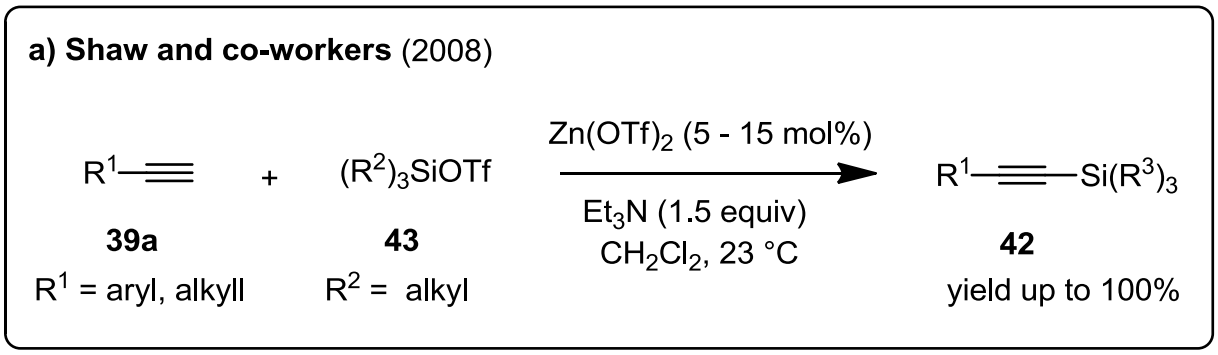
Apart from conventional methods, another commonly used approach for the synthesis of alkynyl silanes includes Zn-catalyzed/mediated reactions. Some of the reports are discussed here. In 2004, Andreev, Gevorgyan and co-workers developed a Lewis acid-mediated method for the synthesis of alkynylsilanes (**42**).[27] Aminosilanes (**41**) were used as silyl source to afford corresponding products (**42**) in up to 97% yield using $ZnCl_2$ as a Lewis acid. Nucleophile- and base-sensitive functional group containing substrates were smoothly tolerated (a, Scheme 14). Zhu's group reported the zinc triflate-mediated trimethylsilylation of terminal acetylenes (**39a**) with chlorosilanes (**39b**) to access alkynylsilanes (**42**) in good to excellent yields.[28] Except chlorotriphenylsilane, all other chlorosilanes, bearing sterically hindered group worked nicely (b, Scheme 14).



Scheme 14: Zn-mediated synthesis of alkynylsilanes

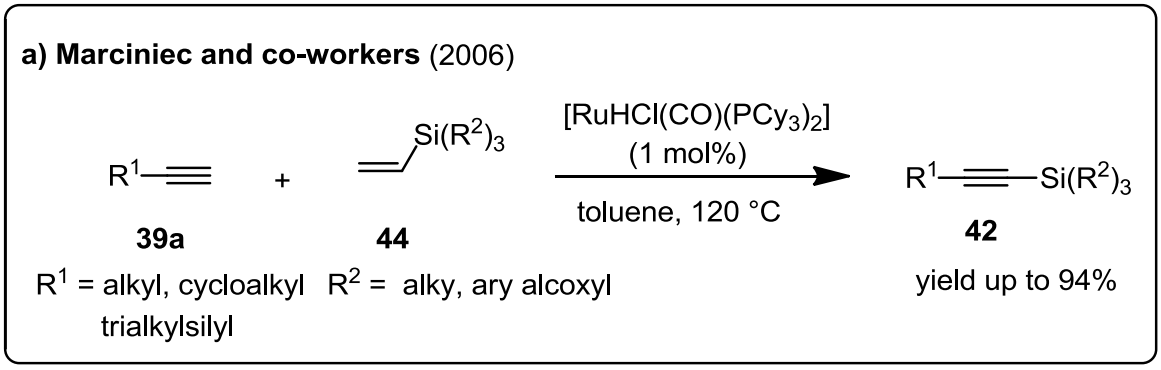
Shaw and co-workers accomplished a highly efficient zinc triflate-catalyzed protocol for the synthesis of alkynylsilanes (**42**) by the reaction of terminal alkynes with trimethylsilyl trifluoromethanesulfonate (**43**) as a silyl source.[29] The corresponding alkynylsilanes (**42**) were isolated in quantitative yields at room temperature. This method allows broad substrate scope as

alkynes (**39a**) containing aryl and alkyl substitutes including reactive ester functionality were well tolerated (Scheme 15).



Scheme 15: Zn-catalyzed/mediated synthesis of alkynylsilanes

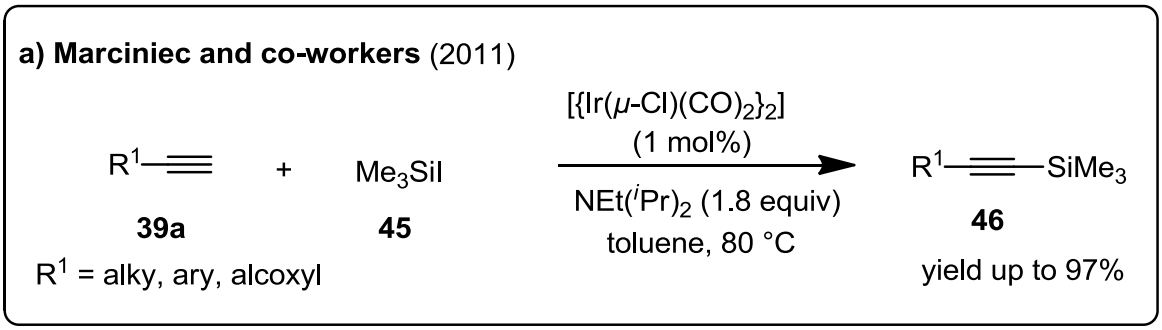
It has found that Ir and Ru can also catalyze silylation of terminal acetylenes. In 2006, Marciniec and co-workers developed an interesting approach towards the synthesis of alkynylsilanes (**42**) through Ru-catalyzed sp-hybridized C–H bond activation.[30] Vinylsilanes (**44**) had been used as a silylating agent as well as a hydrogen acceptor. The coupling between terminal acetylenes (**39a**) and vinylsilanes (**44**) afforded the corresponding alkynylsilanes (**42**) in up to 94% isolated yield with the evolution of ethylene as byproduct (Scheme 16).



Scheme 16: Ru-catalyzed cross-coupling between vinylsilanes and alkynes

Later, the same group extended their work to sp-hybridized C–H bond activation to develop highly efficient protocol for the synthesis of alkynylsilane derivatives. Iridium-catalyzed coupling of terminal alkynes (**39a**) with iodosilane (**45**) produced the resultant alkynylsilanes

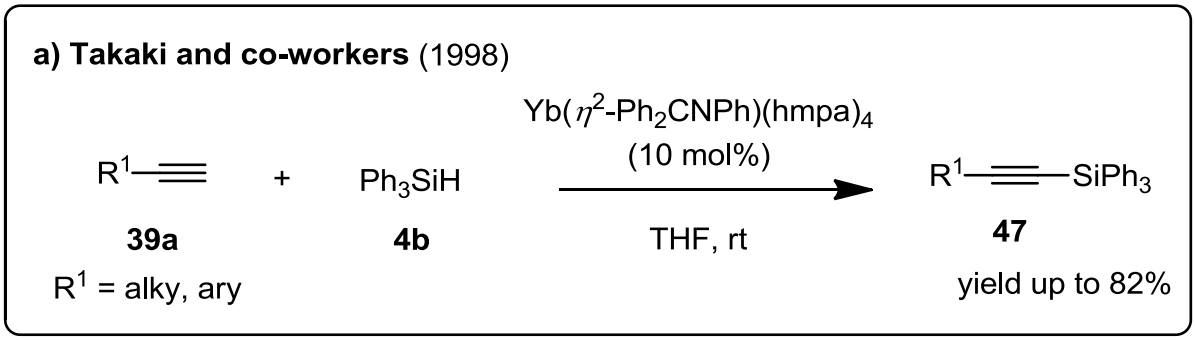
(**46**) in up to 97% isolated yield.[31] Sensitive functional groups toward silylation such as hyroxy and amino groups were effectively tolerated (Scheme 17).



Scheme 17: Ir-catalyzed cross-coupling between iodosilanes and alkynes

3.3.1.2) Dehydrogenative coupling approach

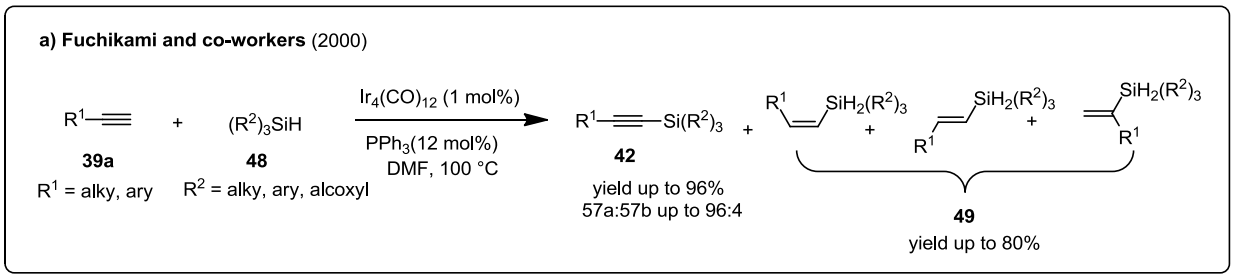
Another fascinating approach towards alkynylsilanes involves metal catalyzed dehydrogenative coupling between terminal alkynes and silyl hydrides. Takaki and co-workers in 1998 demonstrated the synthesis of alkynylsilanes (**47**) through dehydrogenative coupling between terminal alkynes (**39a**) and triphenylsilane (**4b**) using Yb-imine complexes as catalyst.[32] The corresponding products (**47**) were accessed in up to 82% yield. The yields were decreased considerably when trialkylsilane and alkoxysilane were used as coupling partners. Yb-imine complexes with electron-withdrawing substituent on nitrogen of imine found to be more active as compared to the complexes with electron-donating and bulky substituents (Scheme 18).



Scheme 18: Yb-catalyzed dehydrogenative coupling between alkynes and hydrosilanes

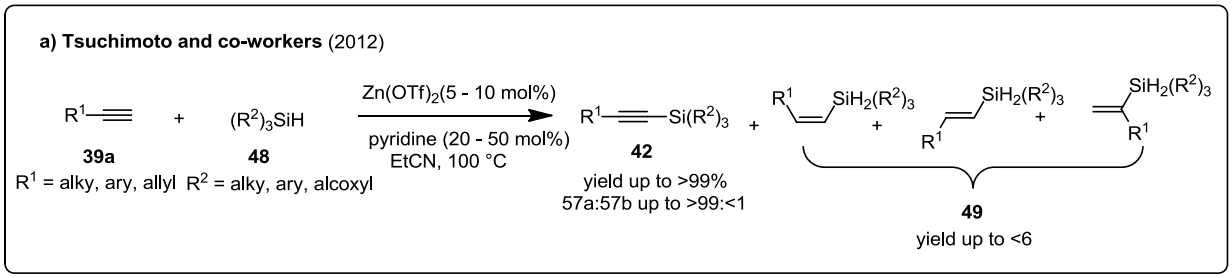
Fuchikami and co-workers reported the Ir-catalyzed dehydrogenative coupling of terminal alkynes (**39a**) and hydrosilanes (**48**) to make alkynylsilane derivatives (**42**) in good

yields.[33] The addition of an additive, in this case phospine, played an important role in selectivity. In absence of additive, further hydrosilylation of alkynylsilane (**42**) to corresponding styrene (80%) (**49**) was observed (Scheme 19).



Scheme 19: Ir-catalyzed dehydrogenative coupling between alkynes and hydrosilanes

Tsuchimoto and coworkers developed the first Lewis acid catalyzed dehydrogenative coupling of terminal alkynes (**39a**) with hydrosilanes (**48**) to access alkynylsilanes (**42**).[34] It was observed that, the addition of catalytic amount of pyridine with zinc triflate helped to complete the reaction and also averted the side reaction such as hydrosilylation. The reaction allowed broad substrate scope with good to excellent yields. Substrates containing olefin functionality were successfully converted to the corresponding products without any side products (Scheme 20).

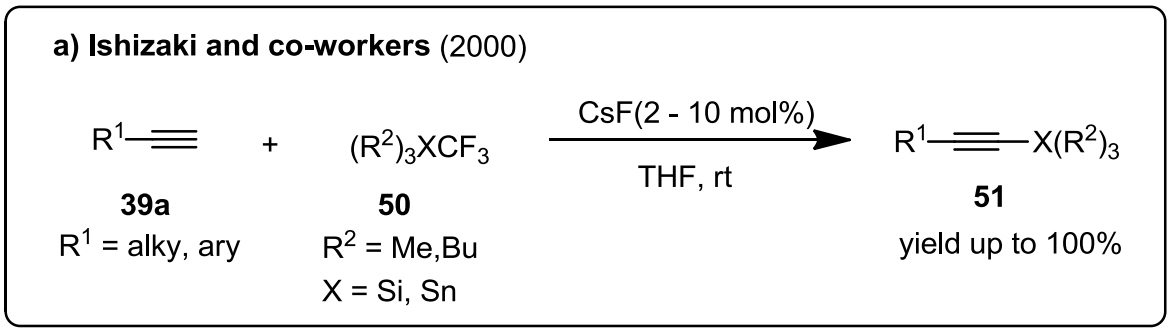


Scheme 20: Lewis acid-catalyzed dehydrogenative coupling between alkynes and hydrosilanes

3.3.3) Literature reports for the silylation using Ruppert's reagent (Me_3SiCF_3) as a silyl source

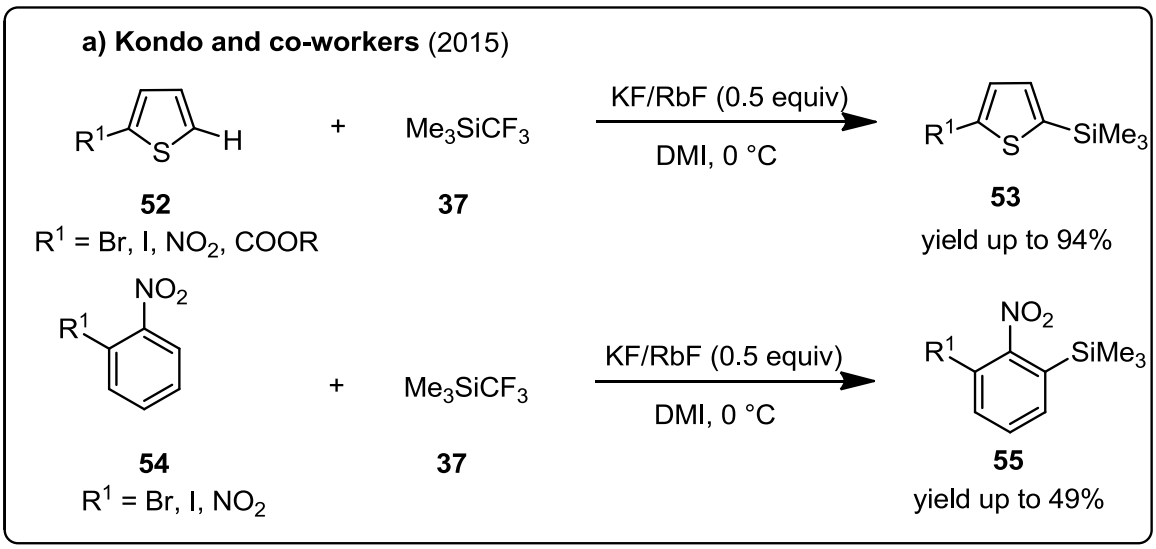
Ishizaki's group reported the trialkylsilylation and tributylstannylation of terminal alkynes (**39a**) using Ruppert's reagent as silyl source and Bu_3SnCF_3 as stannyl source

respectively.[35] Catalytic amount of CsF/KF triggered the reaction to afford the respective products (**51**) in quantitative yield (Scheme 21).



Scheme 21: CsF-catalyzed trialkylsilylation and tributylstannylation of terminal alkynes

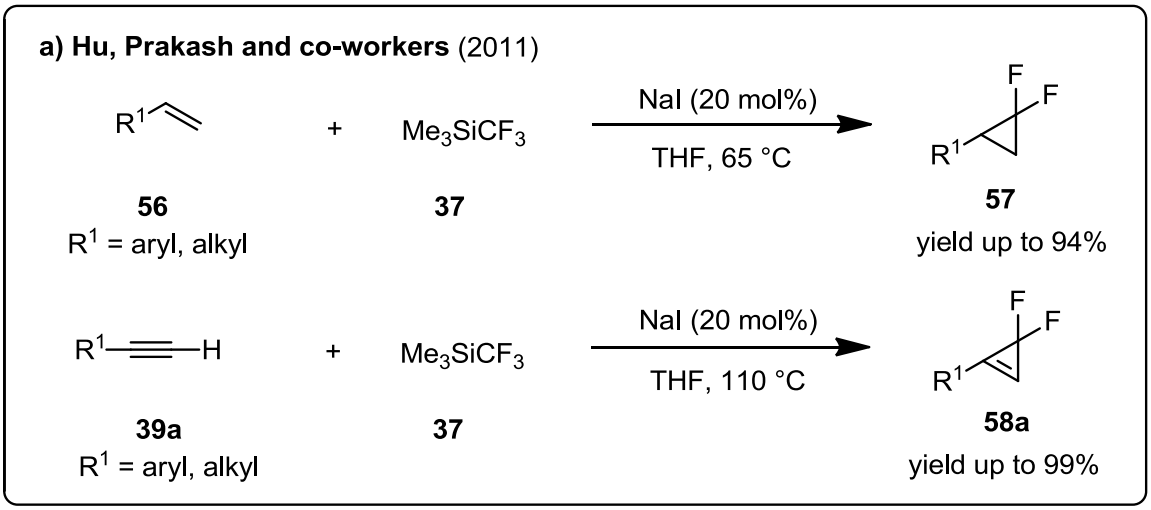
Recently, Kondo's group developed a deprotonative silylation of functionalized arenes (**52**) and heteroarenes (**54**) with Ruppert's reagent (**37**) using alkali metal fluoride as an activating reagent.[36] In this transformation the Ruppert's reagent (**37**) performs dual role such as base precursor as well as silylating agent. The CF_3 anion, generated after activation of Me_3SiCF_3 (**37**) was found to be sufficiently basic to deprotonate activated aromatic ring protons to give corresponding products (**53, 55**) in up to 94% isolated yields. With functionalized nitrobenzenes silylation took place at sixth position with low to moderate yields (Scheme 22).



Scheme 22: Alkali metal fluoride catalyzed deprotonative silylation

3.4) Results and Discussions

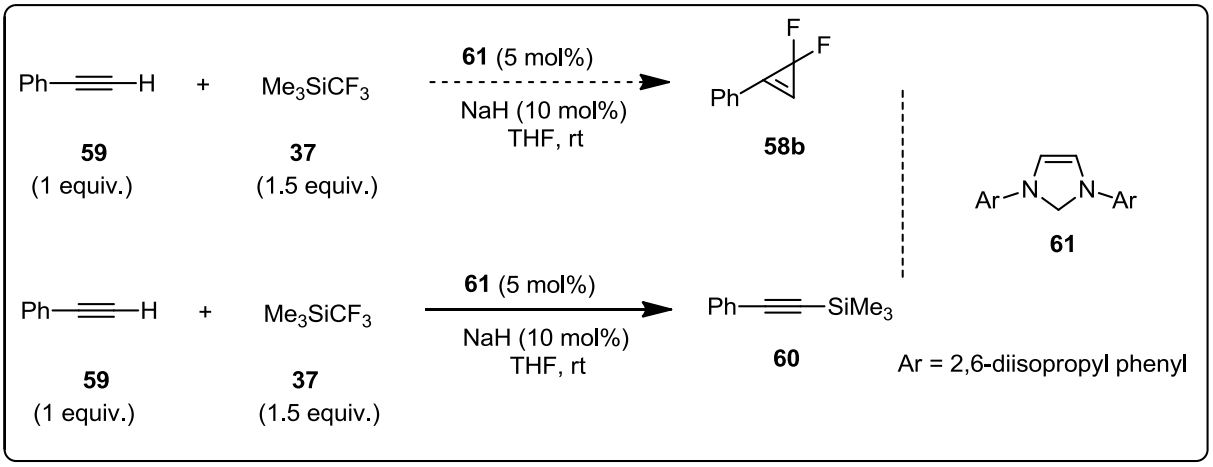
In 2011, Hu, Prakash and co-workers developed fascinating NaI-promoted approach towards the synthesis of *gem*-difluorinated Cyclopropanes (**57**) and cyclopropenes (**58a**) using Ruppert's reagent (**37**) as a difluorocarbene precursor.[37] The *in situ* decomposition of CF_3 anion results into moderately stabilized difluorocarbene. Further addition of difluorocarbene to styrene or phenylacetylene generated the different cyclopropenes in up to 99% yield. NaI was found to be the best catalyst for this transformation (Scheme 23).



Scheme 23: NaI-promoted synthesis of *gem*-difluorinated Cyclopropanes and cyclopropenes

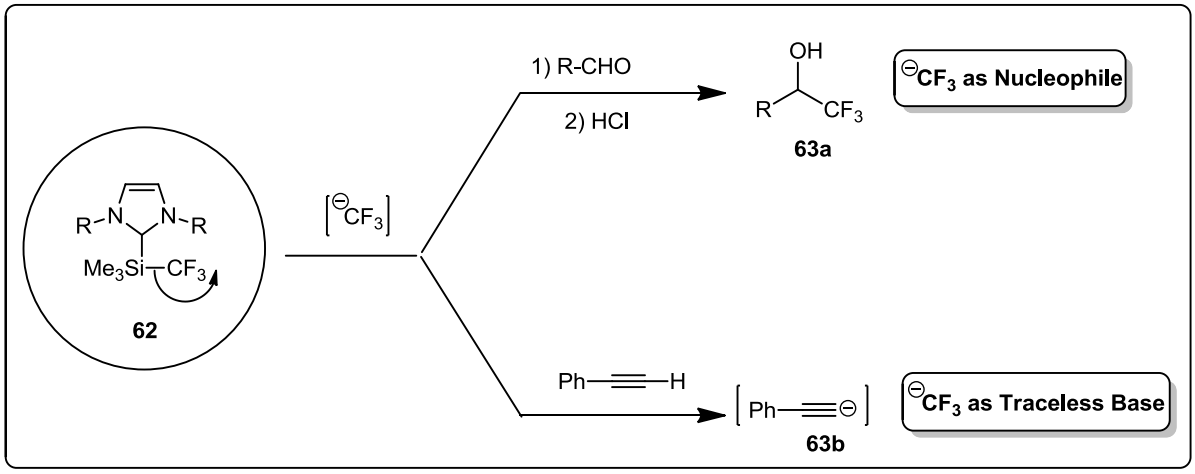
It is well known that NHCs can activate Ruppert's reagent through hypervalent intermediate.[20] While working on NHC catalysis, we envisioned that it is possible to effect this transformation using NHC as a catalyst.

We started our studies with phenyl acetylene (**59**) and Me_3SiCF_3 (**37**) in the presence of imidazolium salt (**61**) as NHC precursor and NaH as base in THF. A vigorous reaction has been observed at room temperature with complete consumption of starting materials (Scheme 24).



Scheme 24: Proposed scheme for NHC-catalyzed synthesis of *gem*-difluorinated cyclopropene

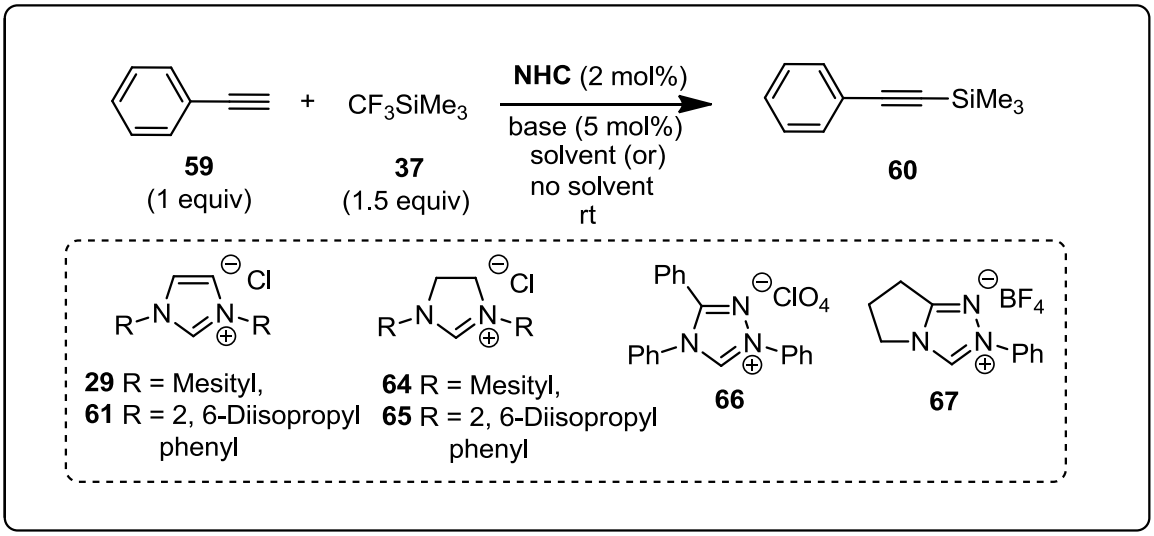
The detailed characterization of isolated product revealed that, the expected **58b** was not observed at all. Instead the silylation of the acetylene took place to furnish corresponding trimethylphenylsilane (**60**). By considering the possibility of reaction conditions, it has been cleared that, in the given conditions CF_3 anion prefer to act as a base instead of acting as nucleophile (Scheme 25). These interesting findings triggered the idea of using trifluoromethyl anion as traceless base to perform NHC-catalyzed trifluoromethylation of terminal acetylenes.



Scheme 25: NHC-catalyzed trifluoromethylation and trimethylsilylation reactions with CF_3SiMe_3

Further detailed optimization studies were performed using phenyl acetylene (**59**) and CF_3SiMe_3 (**37**). A wide range of NHCs derived from NHC precursors (**61, 64-67**) were utilized

Table 1: **Optimization studies**[a]

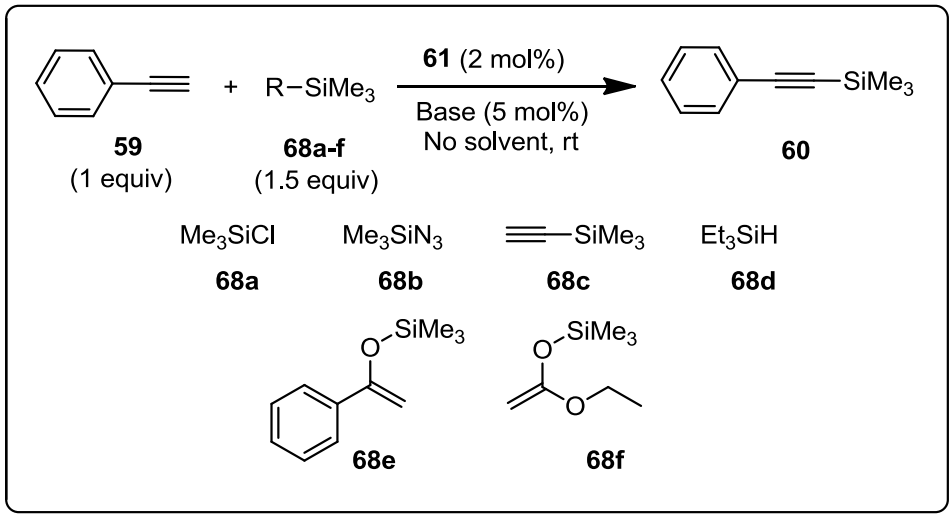


S. No	Catalyst	Base	Solvent	Time [Min]	Yield [a] [%]
1	**61**	NaH	THF	20	50
2	**61**	NaH	DCM	20	76
3	**61**	NaH	Et_2O	20	30
4	**61**	**NaH**	–	**7**	**98**
5	**61**	DBU	–	360	72
6	**61**	–	–	360	–
7	**29**	NaH	–	60	50
8	**64**	NaH	–	20	81
9	**65**	NaH	–	30	50
10	**66**	NaH	–	120	23
11	**67**	NaH	–	120	7
12	–	NaH	–	360	trace
13	**61**	$NaNH_2$	–	20	85
14	**61**	KO^tBu	–	15	92

[a]Isolated yields; rt = 31 – 33 °C.

for this purpose. When an experiment was conducted using 2 mol% of NHC, derived from **61** and NaH in THF, and **37** as a silyl source, the expected product **60** was obtained in 50% yield. Encouraged by this observation, further optimization experiments were carried out under different conditions with or without solvent (Table 1).

Table 2: Optimization with different silyl pronucleophiles

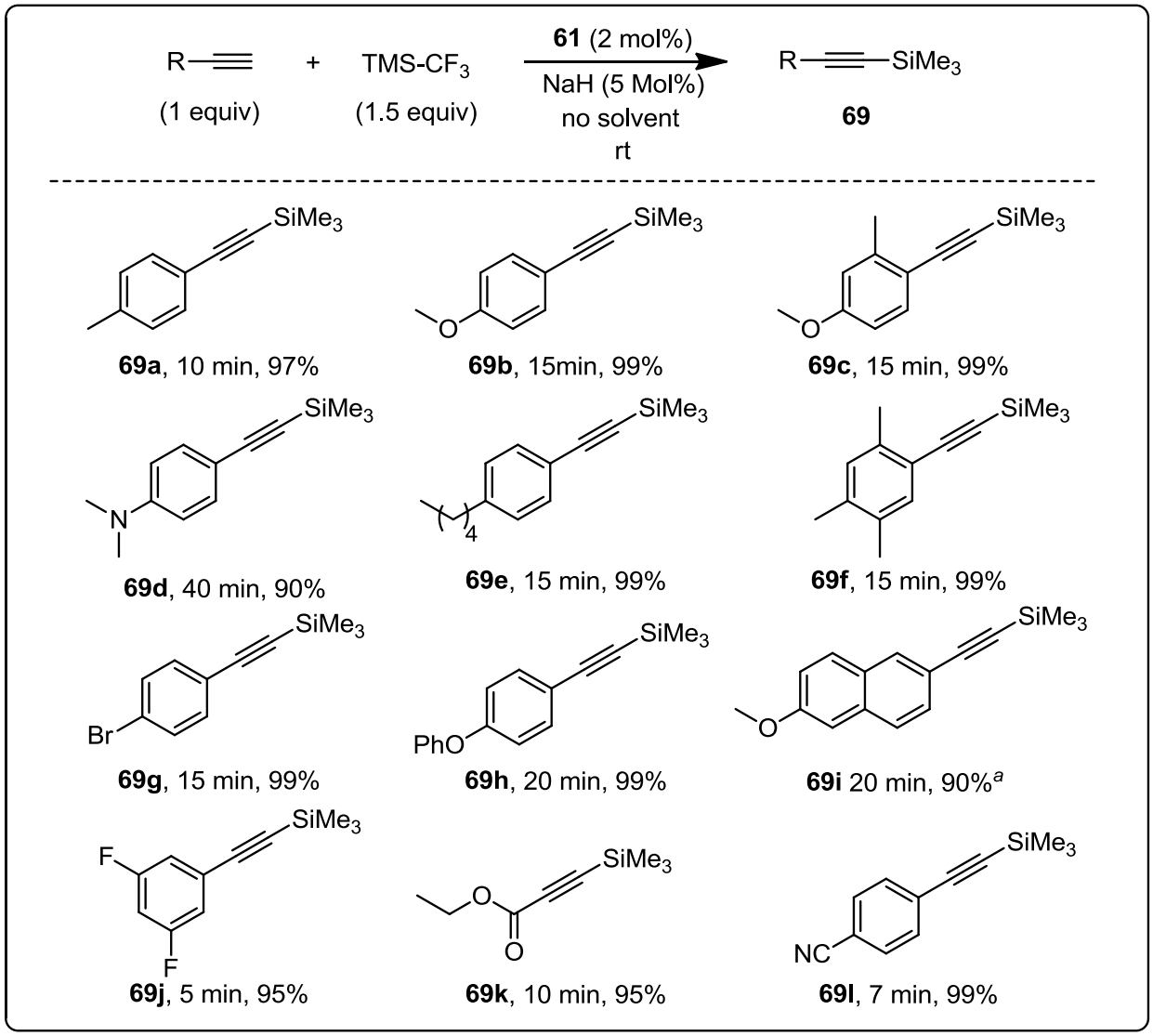


S. No	Catalyst	$RSiMe_3$	Base	Solvent	Time [Min]	Yield[a] [%]
1	**61**	68a	NaH	–	12	–
2	**61**	68b	NaH	–	12	–
3	**61**	68c	NaH	–	12	–
4	**61**	68d	NaH	–	12	–
5	**61**	68d	NaH	THF	12	–
6	**61**	68e	NaH	–	12	–
7	**61**	68e	NaH	THF	12	–
8	**61**	68f	NaH	–	12	–
9	**61**	68f	NaH	THF	12	–

[a]Isolated yields; rt = 31 – 33 °C.

Surprisingly, the reaction rate and the yield of the product **60** were found to be higher when the reaction was performed under solvent free conditions. Out of several conditions

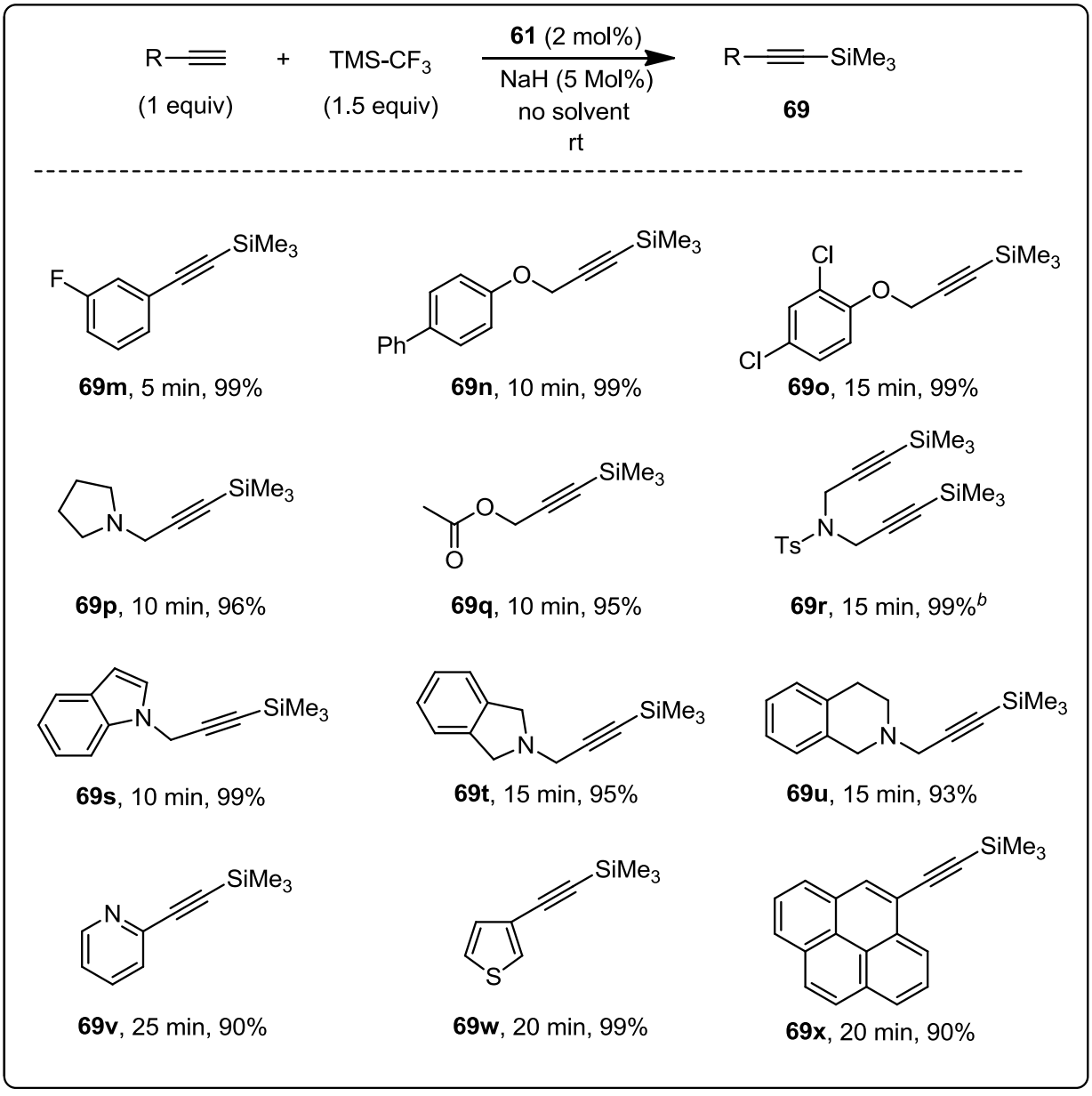
screened, the best result was obtained (98% yield in 7 min) using NHC derived from **61** under neat conditions, thus chosen as standard condition (Entry 4). No product or only traces of product was observed if the reaction was conducted without base (Entry 6) or without NHC (Entry 12, Table 1). We also tried the silylation of phenyl acetylene (**59**) with other silyl pronucleophiles including Et_3SiH[38] using 5 mol% of NHC derived from **61** as a catalyst under various conditions. Unfortunately, the desired silylated product was not observed in any of the cases (Table 2).



[a] 2 equiv. of CF_3SiMe_3 was used; [b] 3 equiv. of CF_3SiMe_3 was used; rt = 31– 33 °C.

Scheme 26: NHC-catalyzed trimethysilylation of terminal alkynes

To generalize this protocol, a variety of terminal alkynes bearing aromatic and aliphatic substituents were subjected to silylation reaction under optimized reaction conditions and the results are summarized in Scheme 26-27. It is apparent from Scheme 26 that, irrespective of the nature of the substituents, most alkynes gave the corresponding trimethylsilylated products in



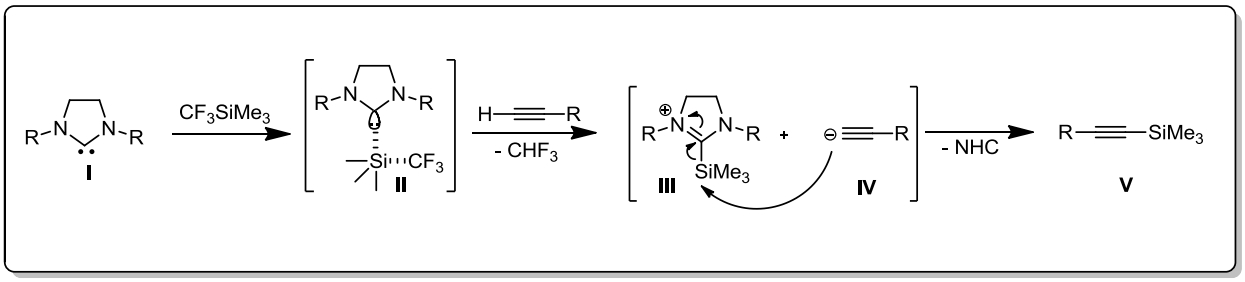
[a] 2 equiv. of CF_3SiMe_3 was used; [b] 3 equiv. of CF_3SiMe_3 was used; rt = 31– 33 °C.

Scheme 27: NHC-catalyzed trimethysilylation of terminal alkynes

quantitative yields. Almost in all the cases, the reaction was completed within a few minutes. Phenyl acetylenes with electron-withdrawing substituents on the aromatic ring (**69j**–**69m**) reacted at relatively faster rates than the alkynes attached with electron rich aromatic groups (**69a**–**69i**). Alkynes substituted with aliphatic groups also underwent smooth conversion to the corresponding silylated alkynes (**69n**–**69u**) under the standard conditions. This method was found to be efficient for the trimethysilylation of alkynes bearing hetero-aromatic substituents as well (**69v** and **69w**).

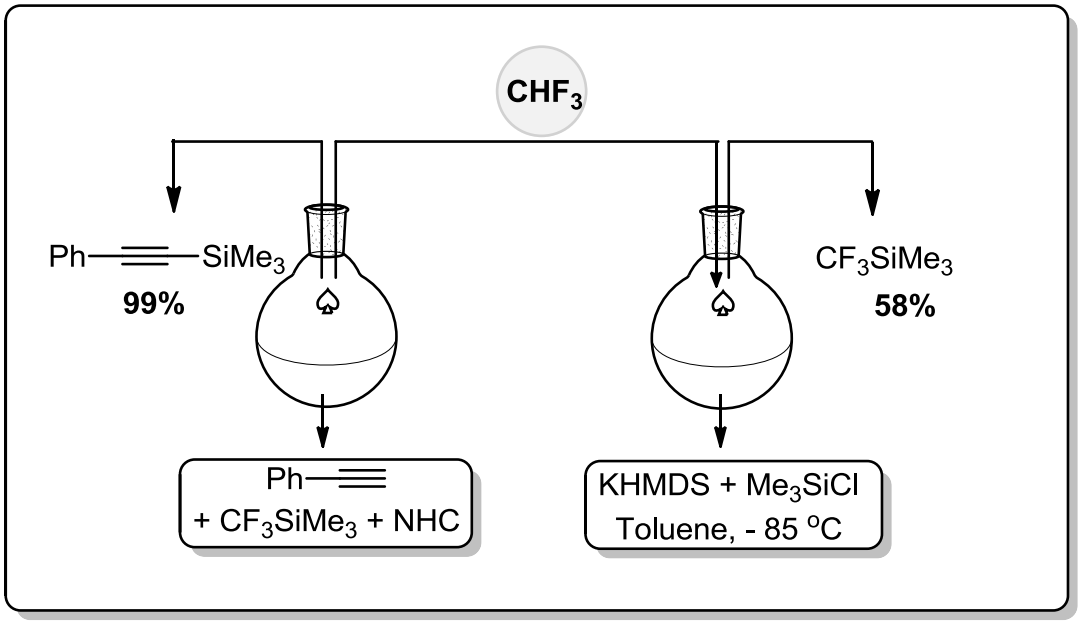
At this stage, our attention was shifted towards elucidating a suitable mechanism for this transformation. Careful monitoring of the reaction revealed that the reaction was exothermic and some gas evolution was taking place in the reaction vessel when CF_3SiMe_3 was added to NHC and phenyl acetylene. Since fluoroform is the only by-product possible in this methodology and also it is a gas, we presumed that the evolved gas was CHF_3. To confirm this, the reaction mixture was analyzed by ^{19}F NMR spectroscopy. The spectrum showed a peak at 78.6 ppm (please see SI for ^{19}F spectrum), which clearly confirms the presence of CHF_3 in the reaction mixture.[39]

Based on the above experimental investigations, a plausible mechanism has been proposed (Scheme 28). We presume that NHC (**I**) reacts with CF_3SiMe_3 and generates a penta co-ordinated silicon complex **II**, which immediately deprotonates the terminal alkyne to give the intermediate **III** along with acetylide anion **IV** and CHF_3. Nucleophillic attack of **IV** on the electrophillic silicon center of **III** gives the silylated product **V** with the expulsion of NHC (Scheme 26).



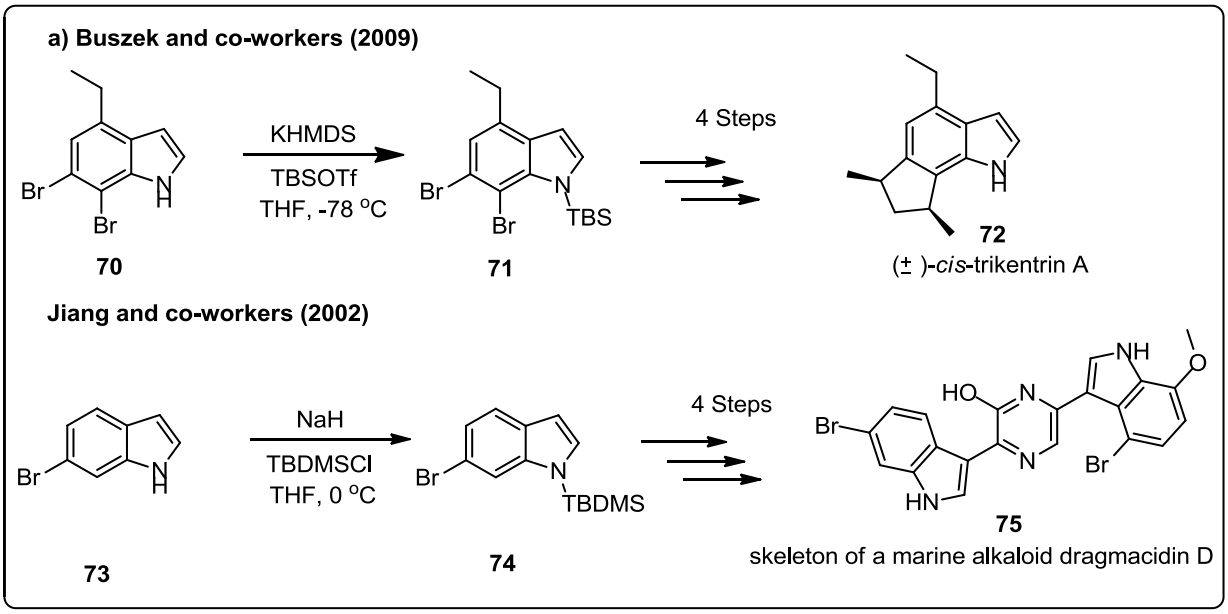
Scheme 28: Plausible mechanism for silylation of acetylenes

Although fluoroform is considered to be a potential green house gas,[40] it has been widely employed as a trifluoromethyl source to introduce CF_3 group in organic molecules.[41] Since CHF_3 is the by-product in our methodology, in order to make our process sustainable, we thought of utilizing it for the regeneration of CF_3SiMe_3 using a protocol reported by Surya Prakash and co-workers.[42] Scheme 29 portrays the experimental set up adapted for the synthesis of CF_3SiMe_3. The fluoroform (2.1 equiv.) generated during the reaction was purged in to another reaction flask containing KHMDS (1 equiv.) and Me_3SiCl (1 equiv.) in toluene at -85 °C. The reaction proceeded smoothly and the product CF_3SiMe_3 was obtained in 58% yield. It was confirmed by ^{19}F and ^{29}Si NMR spectroscopy. The yield of the product was assigned based on ^{19}F NMR using an internal standard (please refer ESI for more details).



Scheme 29: Regeneration of Me_3SiCF_3 from CHF_3

After successfully implementing *in situ* generated CF_3 anion as traceless base to deprotonate terminal alkynes, we become interested in expanding the scope of this method by incorporating indoles as a substrate, to access *N*-silylated indoles. Heteroarenes are considered as one of the most useful intermediates in natural product synthesis, particularly indoles and pyrroles.[43] To access high chemoselectivity N–H protection is highly recommended.[44] *N*-silylation of heteroarenes was found to be relatively labile protected intermediate.

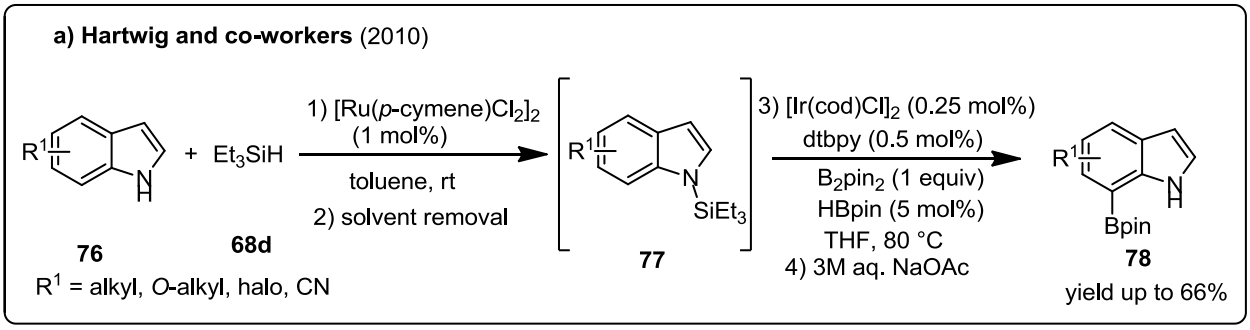


Scheme 30: Application of *N*-silylated indoles in natural product synthesis

The conventional synthetic route for the preparation of *N*-silyl indoles involves deprotonation of indole using an excess of a strong base such as ^{n}BuLi or NaH followed by quenching with silylating agents.[45] Although these methods are commonly used, the generation of equimolar quantities of salts and base sensitive side reactions are notable demerits. Due to their wide spread utility in synthetic chemistry handful metal-catalyzed approaches have been developed by different groups. Selected literature reports are overviewed below.

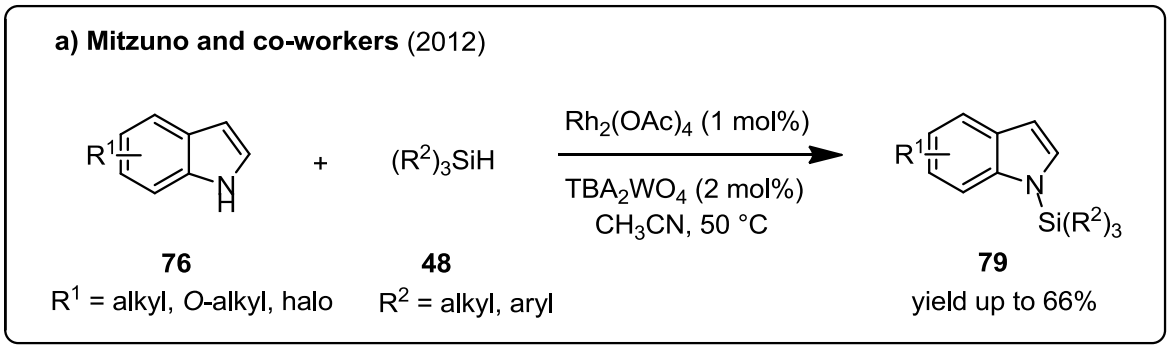
3.4.1) Literature reports for the *N*-silylation of indoles

In 2010, Hartwig and co-workers in their report on silyl directed borylation of nitrogen containing heterocycles, disclosed the Ru-catalyzed *in situ* silylation of indoles (**76**).[46] Although the *N*-silylated indoles (**77**) were not isolated, the synthesis of *N*-silylated intermediate has been confirmed as the *N*-silyl functionality directed the Ir-catalyzed borylation of heterocycles at 7-position. In absence of *N*-silylated group, the borylation were observed at more reactive 2-position (Scheme 31).



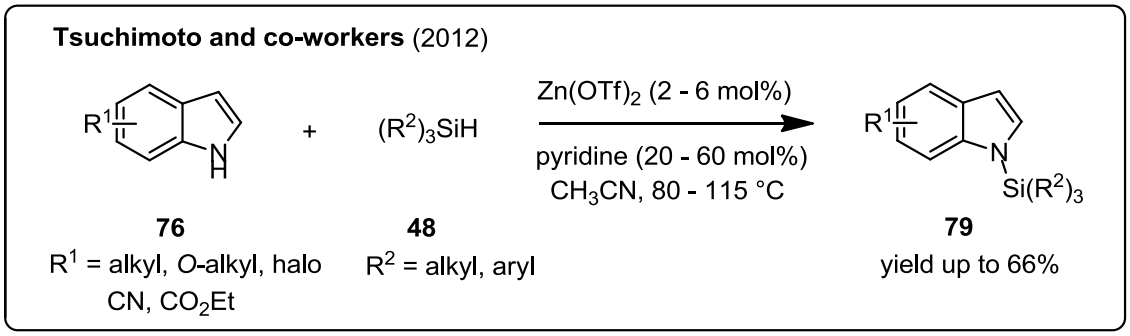
Scheme 31: Ru-catalyzed *in situ* silylation of indoles

Further, Mitzuno and co-workers in 2012 reported the Rh-catalyzed cross-coupling of indoles (**76**) with hydrosilanes (**48**) to access *N*-silylated indoles (**79**) in up to 99% yield.[47] Indoles (**48**) bearing halo substitution were tolerated without any side products. O-directing base and solvent played an important role in this transformation. The detailed NMR analysis confirmed that the hydrogen-bonding interaction between base and indole weaken the N–H bond where as solvent played an important role in regenerating the catalyst and base by hydrogenation (Scheme 32).



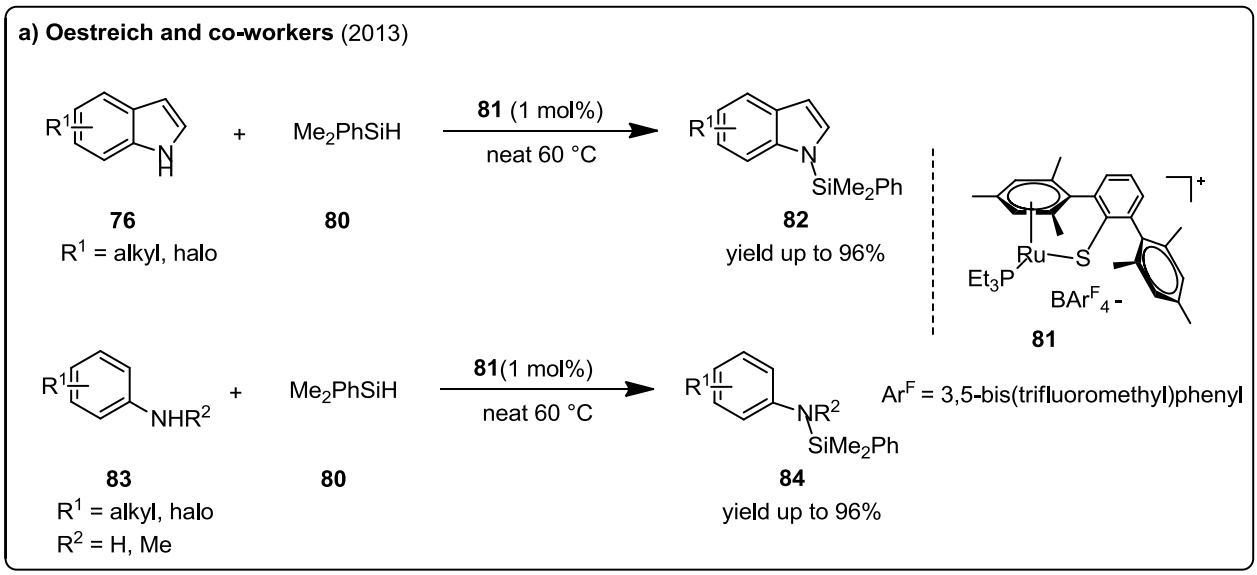
Scheme 32: Rh-catalyzed *N*-silylation of indoles

In the same year Tsuchimoto and co-workers developed an efficient Lewis acid catalyzed dehydrogenative *N*-silylation of indoles (**76**) with hydrosilanes (**48**).[48] A variety of indoles (**76**) were converted to corresponding *N*-silylated products (**79**) in good yields using $Zn(OTf)_2$ as catalyst. Although the role of pyridine remained debatable, acetonitrile as H_2 acceptor has been confirmed by NMR analysis of the reaction mixture (Scheme 33).



Scheme 33: Zn-catalyzed *N*-silylation of indoles

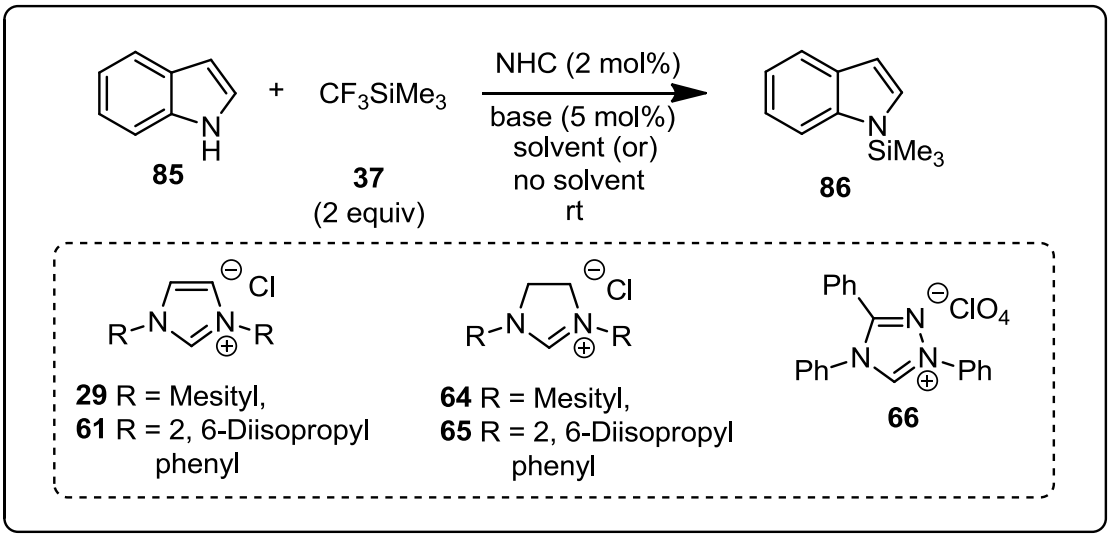
Oestreich and co-workers accomplished a fascinating straightforward base and hydrogen acceptor free route for the synthesis of *N*-silylated heteroarenes (**82**) and anilines (**84**) through dehydrogenative cross-coupling.[49] The corresponding *N*-silylated products (**82, 84**) were isolated in good to excellent yields through Ru-catalyzed coupling between nitrogen containing heterocycles (**76**) and hydrosilanes (**80**). The cooperative activation of Si–H bond by the treatment of Ru–S bond of the catalyst (**81**) leads to the formation of electrophilic Si–N bond before the deprotonation of N–H bond, which affords the formation of silylated products (**82, 84**) in absence of base with evolution of H_2 from Ru–H (Scheme 34).



Scheme 34: Ru-catalyzed *N*-silylation of indoles

So far, organo-catalytic version for the synthesis of *N*-silylated indoles is not reported in the literature. It is highly desired to develop an organocatalytic *N*-silylation of indoles to avoid the use of expensive or toxic metal catalysts.

Table 3: Optimization for Silylation of Indoles



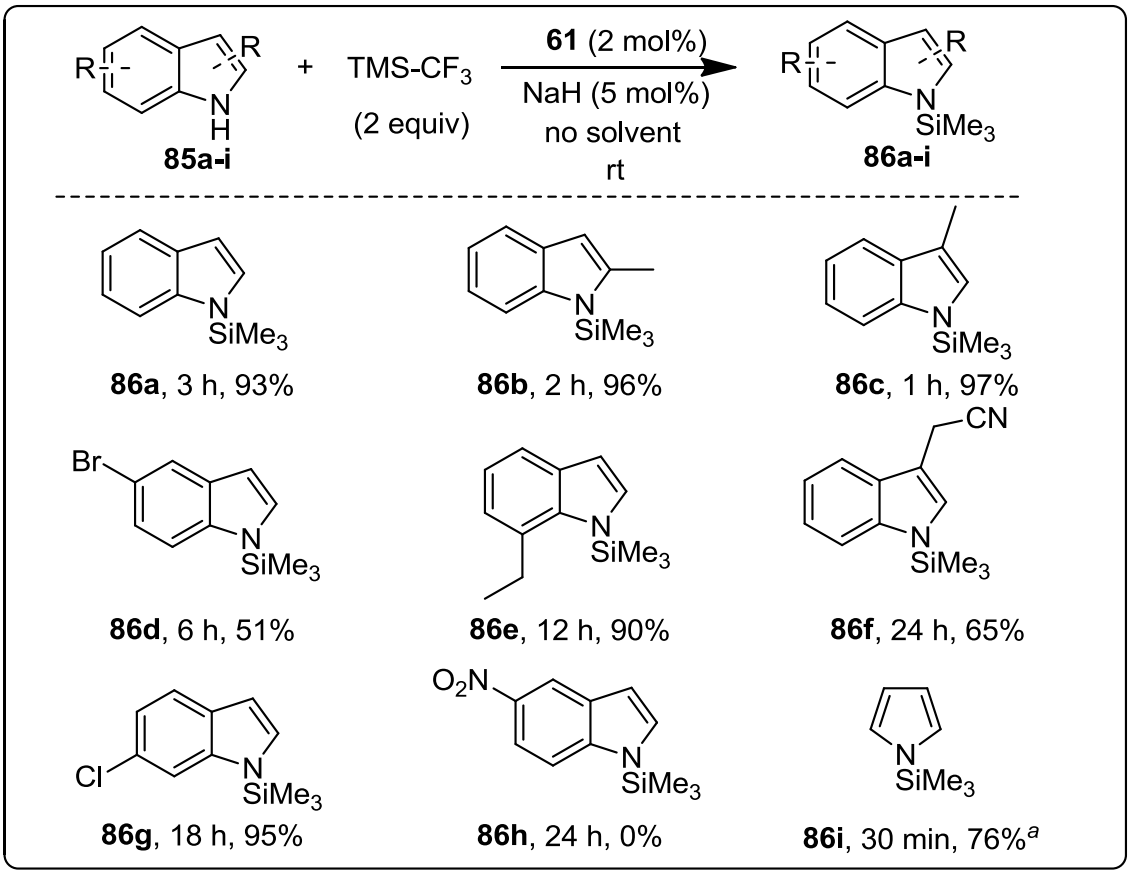
S. No	Catalyst	Base	Solvent	Time [Min]	Yield[a] [%]
1	**61**	NaH	THF	12	–
2	**61**	NaH	DMF	12	–
3	**61**	NaH	Dioxane	12	–
4	**61**	**NaH**	**–**	**3**	**93**
5	**61**	DBU	–	6	9
6	**29**	NaH	–	6	63
7	**64**	NaH	–	6	75
8	**65**	NaH	–	6	78
9	**66**	NaH	–	6	17

[a]Isolated yields; rt = 31 – 33 °C.

Since we have demonstrated that the NHC–CF_3SiMe_3 combination was very effective for the silylation of terminal alkynes. We thought of exploring the reagent for the *N*-silylation of

indoles. Optimization for the *N*-silylation of indoles under solvent free conditions has been performed by using **85** as model substrate. To our surprise, when indole was treated with 2 equiv. of CF_3SiMe_3 and a NHC (2 mol%) derived from **61**, the silylated product **86** was obtained in 93% isolated yield after 3 h under solvent free condition at room temperature (Entry 4, Table 3). A couple of optimization experiments were carried out using other NHCs, but the yield of the *N*-silylated indole was inferior when compared to the above mentioned condition (Table 3).

To demostrate the scopes of this methodology, a wide range of substituted indoles were subjected to Nsilylation reaction under the above mentioned reaction conditions and the results are presented in Scheme 35.



[a] CF_3SiMe_3 was added at 0 °C

Scheme 35: NHC-catalyzed trimethysilylation of terminal alkynes

It is clear from Scheme 35 that, most of the indoles tried underwent smooth conversion to their corresponding *N*-silylated products in moderate to good yields at room temperature. Surprisingly, 2- and 3-methyl substituted indoles (**86b** and **86c**) reacted at a faster rate when compared to indole. In the case of 5- bromo indole (**87d**), the product was obtained in moderate yield. The reaction also worked well in the case of pyrrole and the silylated product **86i** was obtained in 76% yield. Unfortunately, 5-nitroindole failed to give the corresponding silylated product **86h** even after 24 h. The silylation reaction of 5-nitroindole was even tried in the presence of solvents such as THF, DMF and 1,4-dioxane, but in all those cases the product **86** was not observed.

We believe that the mechanism of N-silylation reaction is similar to silylation of acetylenes. A general observation in N-silylation reactions was that the reaction time was longer when compared to silylation of acetylenes. This could be due to the less nucleophilicity of indole anion (when compared with acetylide anion) towards reaction with NHC–silicon complex **III** (Scheme 28). This reaction was found to be chemospecific as no C-3 or C-2 silylated products were observed in any of the cases.

3.5) Conclusion

An efficient and metal free process for the synthesis of trimethylsilyl acetylenes has been developed using NHC as a catalyst under solvent free conditions. We have shown that the by-product, fluoroform, can be effectively utilised for the regeneration of CF_3SiMe_3. We have also demonstrated the first organocatalytic N-silylation of indoles using NHC as a catalyst. High yield of the products, low catalyst loading (2 mol%), less reaction time and simple work-up procedure are the prominent features of this methodology.

3.6) Exprimental section

General Methods:

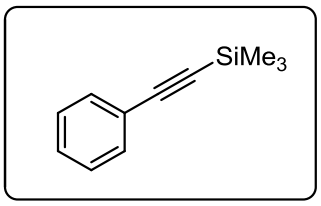
All reactions were carried out under Argon atmosphere. All the reagents including *N*-heterocyclic carbene precursors used were purchased from commercial sources and used as such.

^{1}H, ^{13}C, ^{19}F and ^{29}Si NMR spectra were recorded in $CDCl_3$ using 400 MHz Bruker FT-NMR spectrometer. Chemical shifts values are reported in parts per million relative to TMS and BF_3Et_2O. High-resolution mass spectroscopy was performed on a Waters Q-TOF Premier-HAB213 spectrometer. FTIR spectra were recorded on a Bruker FTIR spectrometer equipped with a PIKE MIRacle ATR and Perkin Elmer FTIR spectrometer. Thin layer chromatography was performed on Merck Silica gel 60 F_{254} TLC plates using Hexane/EtOAc mixture as an eluent. Column chromatography was carried out through silica gel (100-200 mesh) and neutral alumina.

General procedure for the silylation of terminal acetylenes:

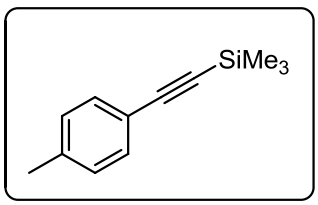
Trifluoromethyl trimethylsilane (67µL, 0.45 mmol) was added to a mixture of **61** (2.5 mg, 0.006 mmol), Sodium hydride [0.8 mg (55-60% suspension in mineral oil), 0.015 mmol] and terminal acetylene (33 µL, 0.3 mmol) and the resulting suspension was stirred for few minutes at room temperature until the terminal acetylene was completely consumed. The reaction mixture was diluted with hexane (2 mL) and passed through a silica gel column at ambient temperature. Removal of volatiles under vacuum furnished the pure trimethylsilyl acetylene derivative.

Trimethyl(2-phenylethynyl)silane (60):[50]



98% Yield. Colourless liquid; FT IR (ATR) = 2160, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.49 (m, 2H), 7.35 – 7.31 (m, 3H), -0.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 128.5, 128.2, 123.2, 105.2, 94.1, 0.01.

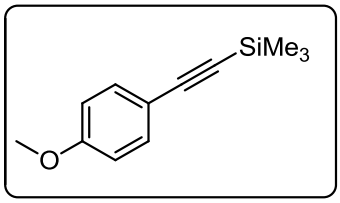
Trimethyl(2-p-tolylethynyl)silane (69a):[50]



97% Yield. Colourless liquid; FT IR (ATR) = 2151 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 2.31 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

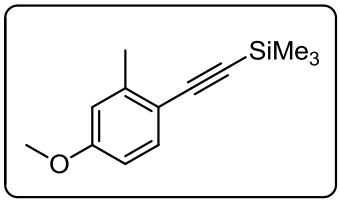
138.6, 131.9, 128.9, 120.1, 105.4, 93.2, 21.5, 0.05.

(2-(4-methoxyphenyl)ethynyl)trimethylsilane (69b):[50]



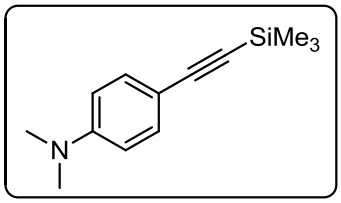
99% Yield. Colourless liquid; FT IR (ATR) = 2155 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 133.5, 115.2, 113.8, 105.2, 92.4, 55.3, 0.08.

(2-(4-methoxy-2-methylphenyl)ethynyl)trimethylsilane (69c):



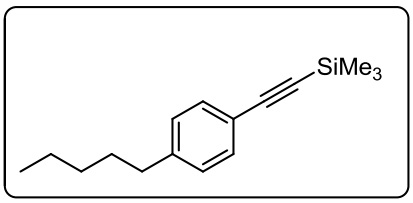
99% Yield. Light yellow liquid; FT IR (ATR) = 2148 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.5 Hz, 1H), 6.75 (d, J = 2.3 Hz, 1H), 6.68 (dd, J = 8.5, 2.3 Hz, 1H), 3.81 (s, 3H) 2.44 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 142.5, 133.5, 115.2, 114.9, 111.1, 104.2, 96.4, 55.2, 20.9, 0.17; HRMS (ESI): *m/z* calcd for $C_{13}H_{18}OSi$ 218.1127; found 218.1125.

N, N-dimethyl-4-(2-(trimethylsilyl)ethynyl)benzenamine (69d):[51]



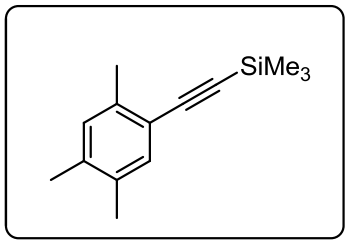
90% Yield. Brown solid; mp 87 – 90 ºC; FT IR (ATR) = 2140 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.9 Hz, 2H), 2.96 (s, 6H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 133.1, 111.7, 109.8, 106.5, 91.2, 40.2, 0.24.

Trimethyl(2-(4-pentylphenyl)ethynyl)silane (69e):



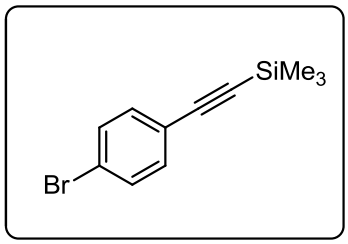
99% Yield. Colourless liquid; FT IR (ATR) = 2158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 1.65 – 1.58 (m, 2H), 1.38 – 1.28 (m, 4H), 0.91 (t, J = 6.7, 3H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 131.9, 128.3, 120.2, 105.4, 93.3, 35.9, 31.4, 30.9, 22.5, 14.1, 0.06; HRMS (ESI): *m/z* calcd for $C_{16}H_{24}Si$ 244.1647; found 244.1647.

Trimethyl(2-(2,4,5-trimethylphenyl)ethynyl)silane (69f):



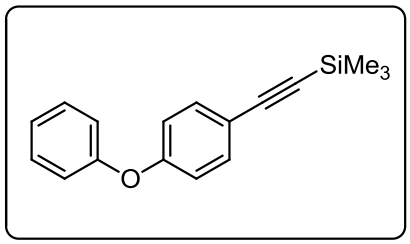
99% Yield. White solid; mp 57 – 59ºC; FT IR (ATR) = 2147 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.97 (s, 1H), 2.38 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H), 0.27 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 137.3, 133.6, 133.1, 130.8, 120.0, 104.5, 96.9, 20.0, 19.7, 19.0, 0.15; HRMS (ESI): *m/z* calcd for $C_{14}H_{20}Si$ 216.1334; found 216.1338.

(2-(4-bromophenyl)ethynyl)trimethylsilane (69g):[52]



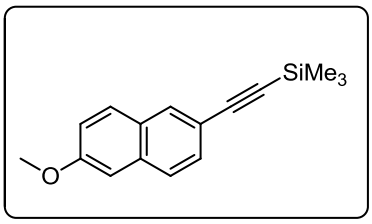
99% Yield. White solid; mp 64 – 66 ºC; FT IR (ATR) = 2158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 131.5, 122.8, 122.1, 103.9, 95.6, -0.10.

Trimethyl(2-(4-phenoxyphenyl)ethynyl)silane (69h):



99% Yield. Light yellow liquid; FT IR (ATR) = 2157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.6 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 0.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 156.4, 133.6, 129.9, 123.9, 119.4, 118.2, 117.7, 104.7, 93.4, 0.05; HRMS (ESI): *m/z* calcd for $C_{17}H_{18}OSi$ 266.1127; found 266.1128.

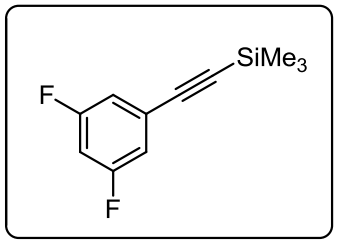
(2-(2-methoxynaphthalen-6-yl)ethynyl)trimethylsilane (69i):[53]



90% Yield. White solid; mp 105 – 107 ºC; FT IR (ATR) = 2154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.71 – 7.66 (m, 2H), 7.51 – 7.48 (m, 1H), 7.18 – 7.15 (m, 1H), 7.11 (d, J = 2.5 Hz, 1H), 3.94 (s, 3H), 0.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 134.2, 131.9, 129.4, 129.2, 128.3, 126.7,

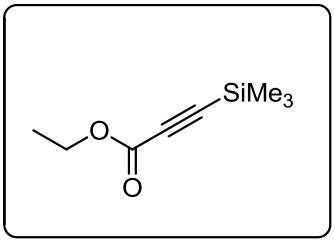
119.4, 118.0, 105.8, 105.7, 93.7, 55.4, 0.08.

(2-(3,5-difluorophenyl)ethynyl)trimethylsilane (69j):



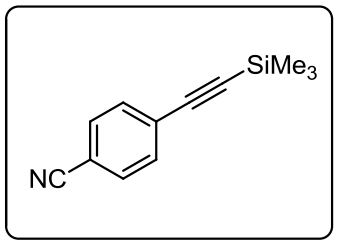
95% Yield. Yellow liquid; FT IR (ATR) = 2360 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02–6.96 (m, 2H), 6.83 – 6.78 (m, 1H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (dd, $^{1}J_{C\text{-}F}$ = 247.2, 13.2 Hz, 2C), 125.8, 114.9 (d, $J_{C\text{-}F}$ = 26.2 Hz, 1C), 104.7 (t, $J_{C\text{-}F}$ = 25.5 Hz, 1C), 102.4, 96.8, -0.25; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}F_2Si$ 210.0676; found 210.0677.

Ethyl 3-(trimethylsilyl)propiolate (69k):[54]



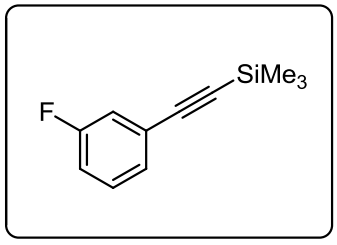
95% Yield. Colourless liquid; FT IR (ATR) = 2183, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (q, J = 7.1, Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H) 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 94.7, 93.6, 62.0, 14.0, -0.88.

4-(2-(trimethylsilyl)ethynyl)benzonitrile (69l):[50]



99% Yield. White solid; mp 102–104 ºC; FT IR (ATR) = 2234, 2157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H) 0.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 131.9, 118.5, 111.8, 103.0, 99.6, 92.3, -0.26.

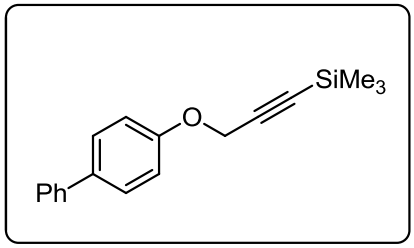
(2-(3-fluorophenyl)ethynyl)trimethylsilane (69m):



99% Yield. Yellow liquid; FT IR (ATR) = 2190 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.20 – 7.16 (m, 1H), 7.07 – 7.02 (m, 1H), 0.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, $^{1}J_{C\text{-}F}$ = 245.0 Hz, 1C), 129.8 (d, $J_{C\text{-}F}$ = 8.8 Hz, 1C), 127.8 (d, $J_{C\text{-}F}$ = 3.0 Hz, 1C), 124.9 (d, $J_{C\text{-}F}$ = 9.5 Hz, 1C), 118.8 (d, $J_{C\text{-}F}$ = 22.6 Hz,

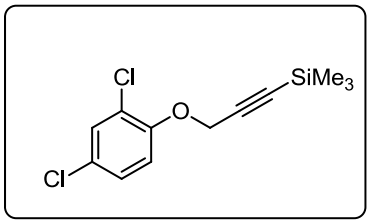
1C), 115.8 (d, $J_{C\text{-}F}$ = 21.0 Hz, 1C), 103.6 (d, $J_{C\text{-}F}$ = 3.7 Hz, 1C), 95.4,-0.12; HRMS (ESI): *m/z* calcd for $C_{11}H_{13}FSi$ 192.0771; found 192.0770.

(3-(4-phenylphenoxy)prop-1-ynyl)trimethylsilane (69n):



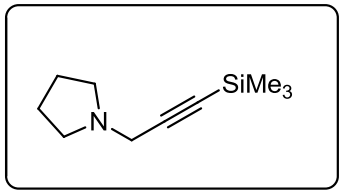
99% Yield. White solid; mp 65 – 67 ºC; FT IR (ATR) = 2174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 4H), 7.47 – 7.43 (m, 2H), 7.36 – 7.32 (m, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 4.74 (s, 2H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 148.1, 140.7, 134.5, 128.8, 128.1, 126.8, 115.3, 100.0, 92.9, 56.9, -0.26; HRMS (ESI): *m/z* calcd for $C_{11}H_{13}FSi$ 280.1283; found 280.1287.

(3-(2,4-dichlorophenoxy)prop-1-ynyl)trimethylsilane (69o):



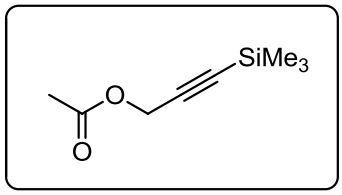
99% Yield. White solid; mp 68 – 70 ºC; FT IR (ATR) = 2170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.5 Hz, 1H), 7.21 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.05 (d, *J* = 8.8Hz, 1H), 4.76 (s, 2H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 130.1, 127.4, 126.7, 124.2, 115.6, 99.0, 94.1, 58.1, -0.37.

1-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidine (69p):[55]



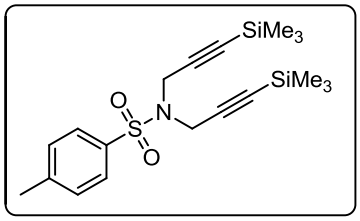
96% Yield. Yellow liquid; FT IR (ATR) = 2167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.42 (s, 2H), 2.63 – 2.60 (m, 4H), 1.83 – 1.80 (m, 4H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.9, 88.8, 52.6, 44.1, 23.7, 0.04.

3-(trimethylsilyl)prop-2-ynyl acetate (69q):[50]



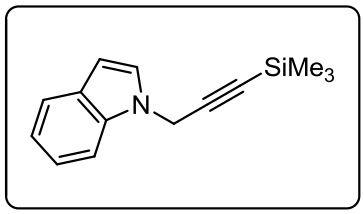
99% Yield. Colourless liquid; FT IR (ATR) = 2186, 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 2H), 2.13 (s, 3H) 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 98.9, 92.1, 52.8, 20.8, -0.30.

3-(trimethylsilyl)-N-tosylprop-2-yn-1-amine (69r):



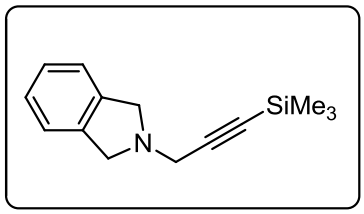
99% Yield. Light yellow solid; mp 59 – 61 ºC; FT IR (ATR) = 2174 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 4.17 (s, 4H), 2.44 (s, 3H), 0.08 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7,135.4, 129.6, 127.9, 97.7, 91.0, 37.2, 21.6, -0.34; HRMS (ESI): *m/z* calcd for $C_{19}H_{29}NO_2SSi_2H$ 392.1536; found 392.1540.

1-(3-(trimethylsilyl)prop-2-ynyl)-1H-indole (69s):



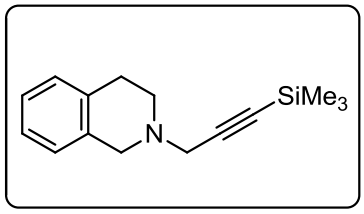
99% Yield. Yellow liquid; FT IR (ATR) = 2181 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.67 (m, 1H), 7.45 – 7.43 (m, 1H), 7.30 – 7.26 (m, 2H), 7.19 – 7.15 (m, 1H), 6.57 – 6.56 (m, 1H), 4.92 (s, 2H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 128.8, 127.2, 121.7, 121.0, 119.7, 109.4, 101.8, 99.1, 90.7, 36.8, -0.22.

2-(3-(trimethylsilyl)prop-2-ynyl)isoindoline (69t):



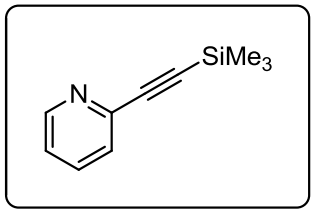
95% Yield. Light brown liquid; FT IR (ATR) = 2158, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 4H), 4.08 (s, 4H), 3.67 (s, 2H) 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 126.8, 122.4, 101.2, 90.8, 57.3, 43.8, 0.03.

1,2,3,4-tetrahydro-2-(3-(trimethylsilyl)prop-2-ynyl)isoquinoline (69u):



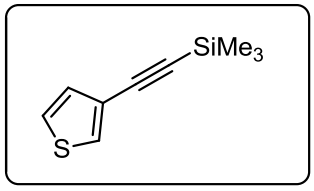
93% Yield. Yellow liquid; FT IR (ATR) = 2163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.07 (m, 4H), 3.80 (s, 2H), 3.56 (s, 2H), 2.98 (t, J = 6.0 Hz, 2H), 2.86 (t, J = 6.0 Hz, 2H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 133.7, 128.7, 126.6, 126.2, 125.7, 100.4, 90.4, 54.2, 49.6, 47.7, 29.1, 0.04.

2-(2-(trimethylsilyl)ethynyl)pyridine (69v):[56]



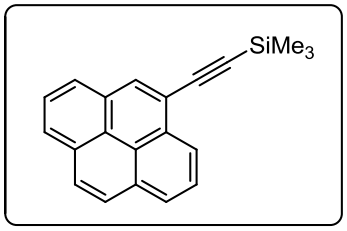
90% Yield. Yellow liquid; FT IR (ATR) = 2166 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.57 (m, 1H), 7.67 – 7.63 (m, 1H), 7.48 – 7.45 (m, 1H), 7.29 – 7.22 (m, 1H), 0.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 143.0, 136.1, 127.3, 123.1, 103.6, 94.8, -0.27.

T**rimethyl(2-(thiophen-3-yl)ethynyl)silane (69w)**:[56]



99% Yield. Yellow liquid; FT IR (ATR) = 2154, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J = 3.0, 1.2 Hz, 1H), 7.26 (dd, J = 5.0, 3.0 Hz, 1H), 7.15 (dd, J = 5.0, 1.1 Hz, 1H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.1, 129.6, 125.2, 122.3, 99.9, 93.9, -0.28.

Trimethyl(2-(pyren-4-yl)ethynyl)silane (69x):[57]

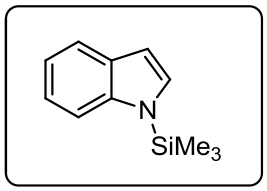


90% Yield. Yellow solid, mp 104 – 106 ºC; FT IR (ATR) = 2150 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 9.1 Hz, 1H), 8.25 – 8.18 (m, 4H), 8.11 – 8.02 (m, 4H), 0.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3, 131.4, 131.2, 131.0, 129.9, 128.4, 128.2, 127.2, 126.2, 125.7, 125.6, 125.5, 124.4, 124.3,124.2, 117.6, 104.2, 100.2, 0.28.

General procedure for the silylation of indoles:

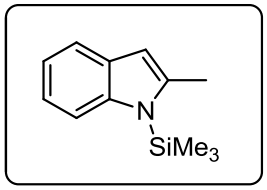
Trifluoromethyl trimethylsilane (103µL, 0.7 mmol) was added to a mixture of **61** (2.8 mg, 0.007 mmol), Sodium hydride [0.8 mg (55-60% suspension in mineral oil), 0.017 mmol] and indole (41 mg, 0.35 mmol) and the resulting suspension was stirred for few minutes at room temperature until the indole was completely consumed. The reaction mixture was diluted with hexane (2 mL) and passed through a neutral alumina column at ambient temperature. Removal of volatiles under vacuum furnished the pure trimethylsilyl indole derivative.

1-(trimethylsilyl)-1H-indole (86a):[58]



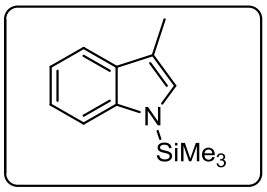
93% Yield. Colourless liquid; FT IR = 2959, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.70 (m, 1H), 7.58–7.54 (m, 1H), 7.27 – 7.17 (m, 3H), 6.66 (d, J = 3.2 Hz, 1H), 0.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 131.6, 129.9, 121.4, 120.9, 119.9, 112.9, 104.6, -0.06.

2-methyl-1-(trimethylsilyl)-1H-indole (86b):



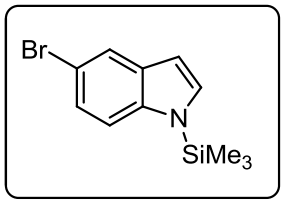
96% Yield. Colourless liquid; FT IR = 2958, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.57 (m, 2H), 7.1 9– 7.16 (m, 2H), 6.40 (s, 1H), 2.56 (d, J = 1.0 Hz, 3H) 0.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 141.4,131.5, 120.5, 119.8, 119.5, 113.1, 105.6, 17.1, 2.33.

3-methyl-1-(trimethylsilyl)-1H-indole (86c):



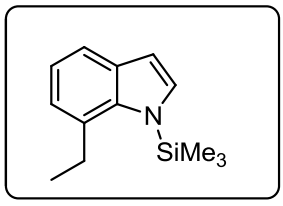
97% Yield. Colourless liquid; FT IR = 2958, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.27 – 7.23 (m, 2H), 7.02 (s, 1H), 2.40 (s, 3H), 0.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 132.0, 127.2, 121.4, 119.3, 119.1, 113.5, 112.9, 9.7, 0.04.

5-bromo-1-(trimethylsilyl)-1H-indole (86d):



51% Yield. Yellow liquid; FT IR = 2958, 1444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 2.0 Hz, 1H), 7.398 – 7.36 (m, 1H), 7.29 – 7.26 (m, 1H), 7.19 (d, J = 3.2 Hz, 1H), 6.55 (d, J = 3.2 Hz, 1H), 0.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 133.6, 131.1, 124.2, 123.3, 114.2, 113.3, 104.1, -0.15.

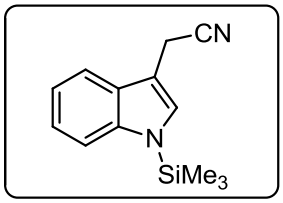
7-ethyl-1-(trimethylsilyl)-1H-indole (86e) :



90% Yield. Colourless liquid; FT IR = 2965, 1413 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.55 (m, 1H), 7.33 (d, J = 3.3 Hz, 1H),7.23 – 7.09 (m, 2H), 6.66 (d, J = 3.3 Hz, 1H), 3.14 (q, J = 7.4 Hz, 2H), 1.41 (t,

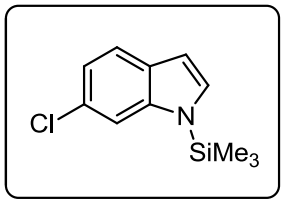
J = 7.4 Hz, 3H), 0.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 132.9, 131.8, 128.8, 122.0, 120.7, 118.4, 105.0, 26.0, 15.9, 2.68.

2-(1-(trimethylsilyl)-1H-indol-3-yl)acetonitrile (86f):



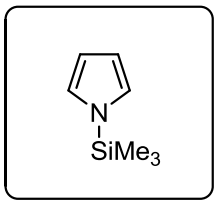
65% Yield. Colourless liquid; FT IR = 2959, 2254, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.23 (m, 2H), 7.02 (s, 1H), 3.85 (s, 3H), 0.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 129.5, 128.4, 122.3, 120.3, 118.3, 118.2, 113.3, 106.4, 14.4, -0.08.

6-chloro-1-(trimethylsilyl)-1H-indole (86g):



95% Yield. Colourless liquid; FT IR = 2961, 1460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 1H), 7.50 (s, 1H),7.20 (d, *J* = 3.2 Hz, 1H), 7.16 – 7.13 (m, 1H), 6.61 (d, *J* = 8.4 Hz, 1H), 0.59(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ140.6, 130.6, 130.1, 127.3, 121.5, 120.6, 112.8, 104.6, -0.10.

1-(trimethylsilyl)-1H-pyrrole (86i):[58]



76% Yield. Colourless liquid; FT IR = 2960, 1472 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ, 6.87 (t, *J* = 2.0 Hz, 2H), 6.39 (t, *J* = 2.0 Hz, 2H), 0.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.0, 110.8, -0.26.

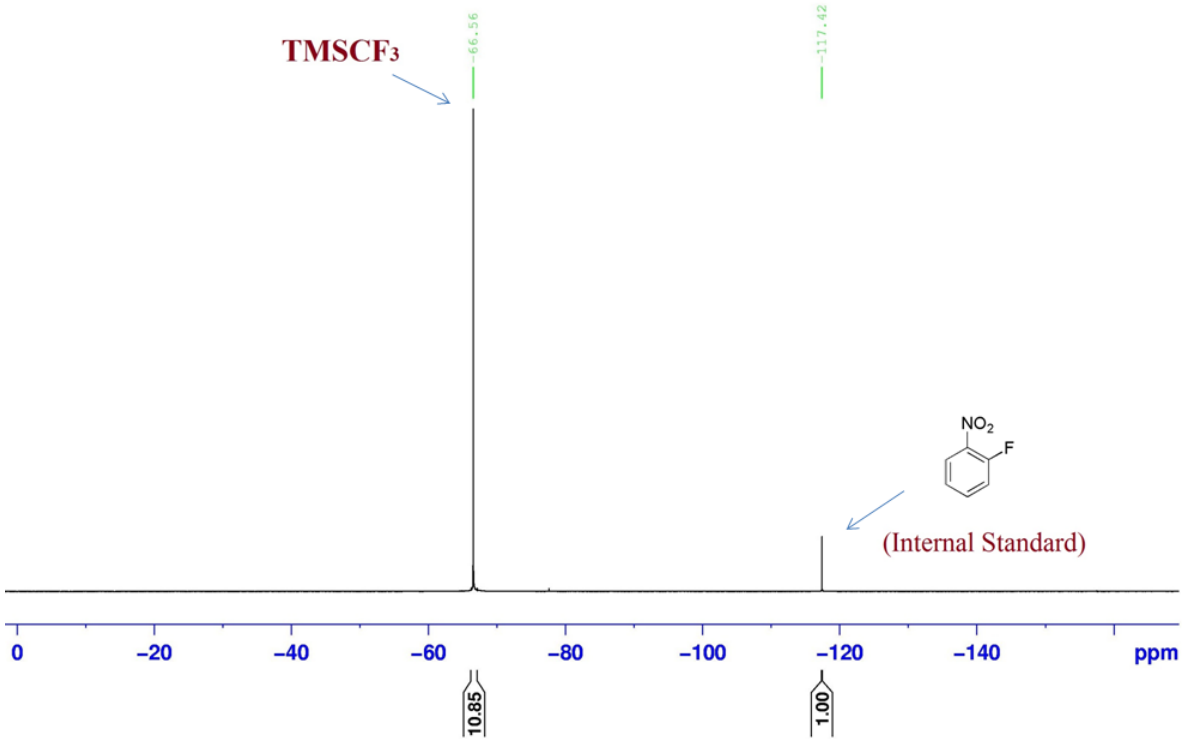
Procedure for the regeneration of Me_3SiCF_3 from CHF_3:[59]

Trifluoromethyl trimethylsilane (490 µL, 3.3 mmol) was added to a mixture of **61** (20.0 mg, 0.044 mmol), Sodium hydride [8.0 mg (55% suspension in mineral oil), 0.11 mmol] and phenylacetylene (490 µL, 2.2 mmol) and the resulting suspension was stirred for few minutes at room temperature. During the reaction CHF_3 (approx. 2.2 mmol) was generated. It was passed through cannula to another reaction flask containing potassium hexamethyldisilazide [0.5 M in

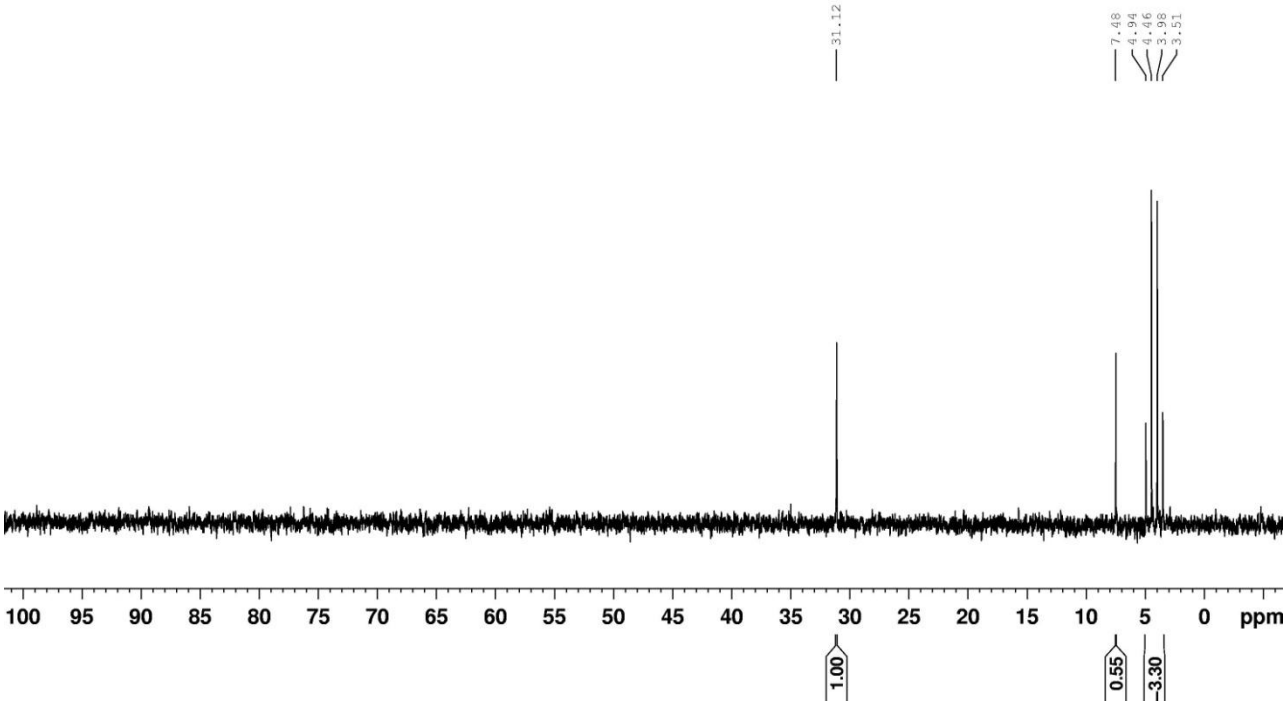
toluene] (0.2 mL, 1 mmol) and chlorotrimethylsilane (108 µL, 1 mmol) at -85 °C for 30 minutes. Resulting mixture was stirred vigorously at -85°C for 5 hours. The reaction mixture was then slowly warmed to room temperature and stirred for 3 hours. *o*-Fluoro nitrobenzene (45 mg, 0.32 mmol) was added as an internal standard to the crude mixture and it was analysed by ^{29}Si and ^{19}F NMR (Figure 1). Yield 58% (by ^{19}F NMR); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ – 66.6 (s); ^{29}Si NMR (79.5 MHz, $CDCl_3$) δ 4.22 (q, $J_{Si\text{-}F}$ = 38.0 Hz, 1Si).

Figure 2:

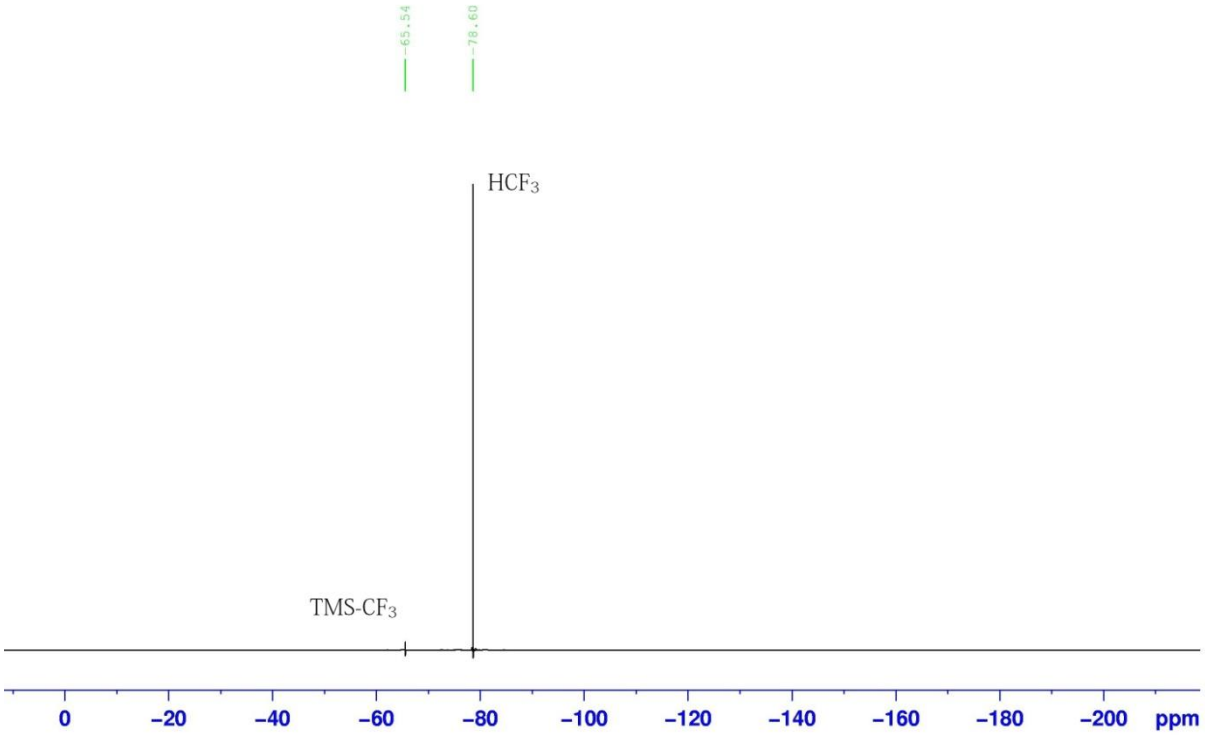
^{19}F Spectrum of the crude mixture



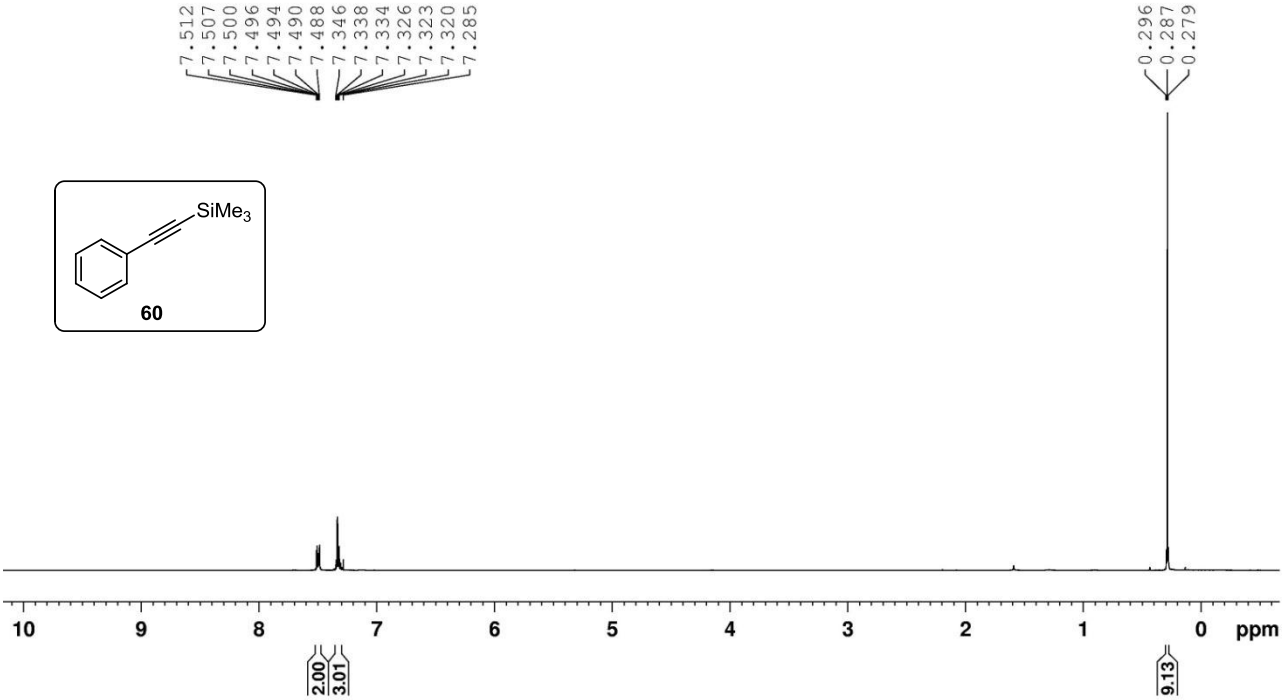
^{29}Si Spectrum of the crude mixture



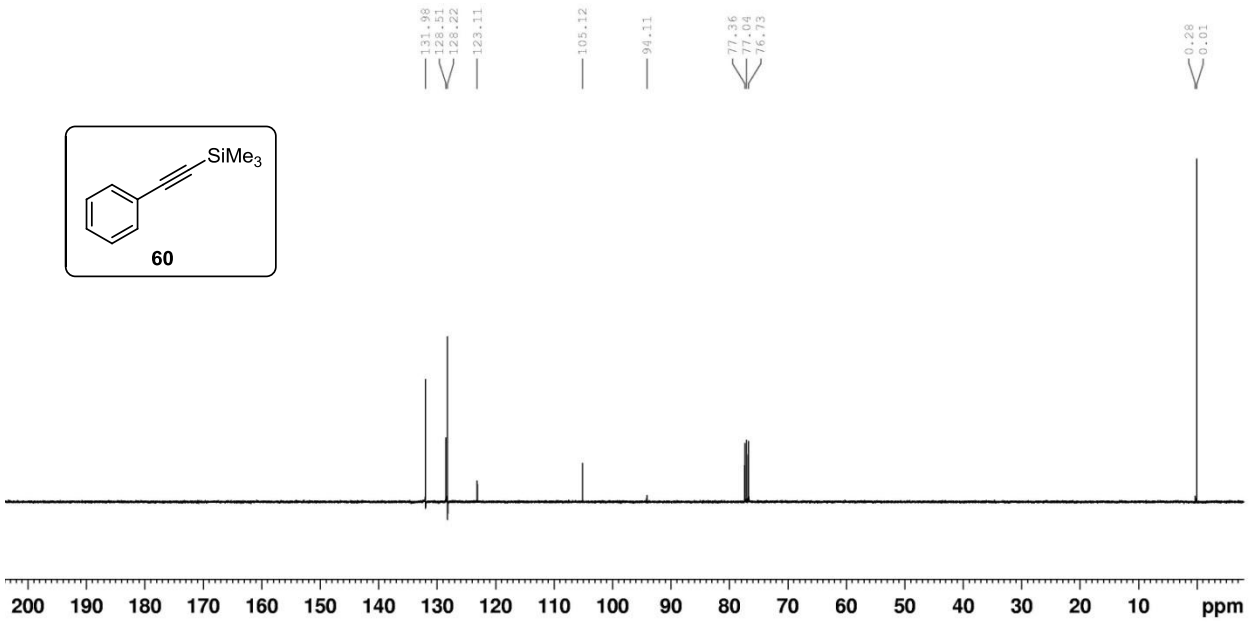
^{19}F Spectrum the reaction mixture (entry 4 in Table 1)



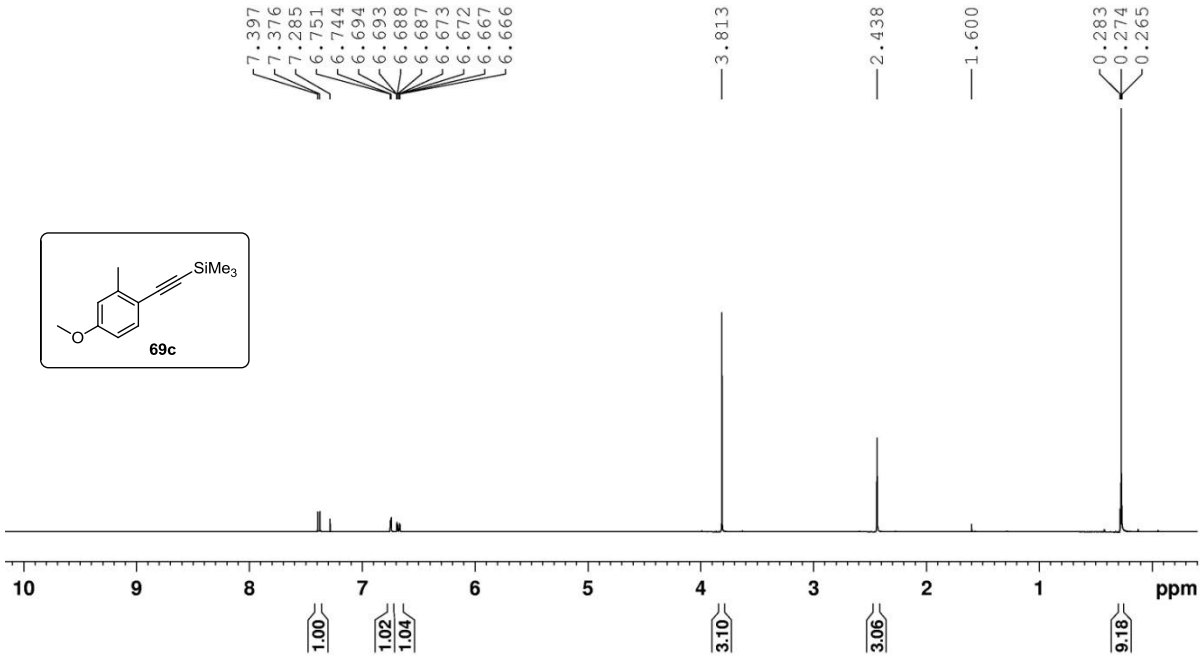
^{1}H NMR Spectrum of **60**



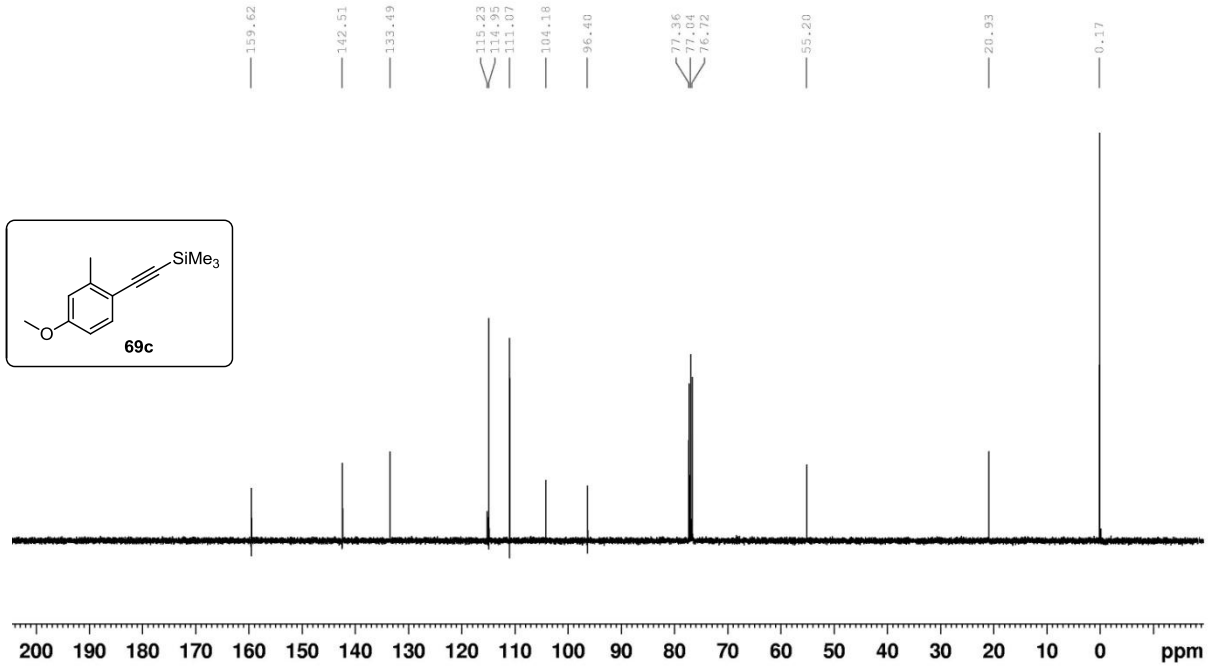
^{13}C NMR Spectrum of 60



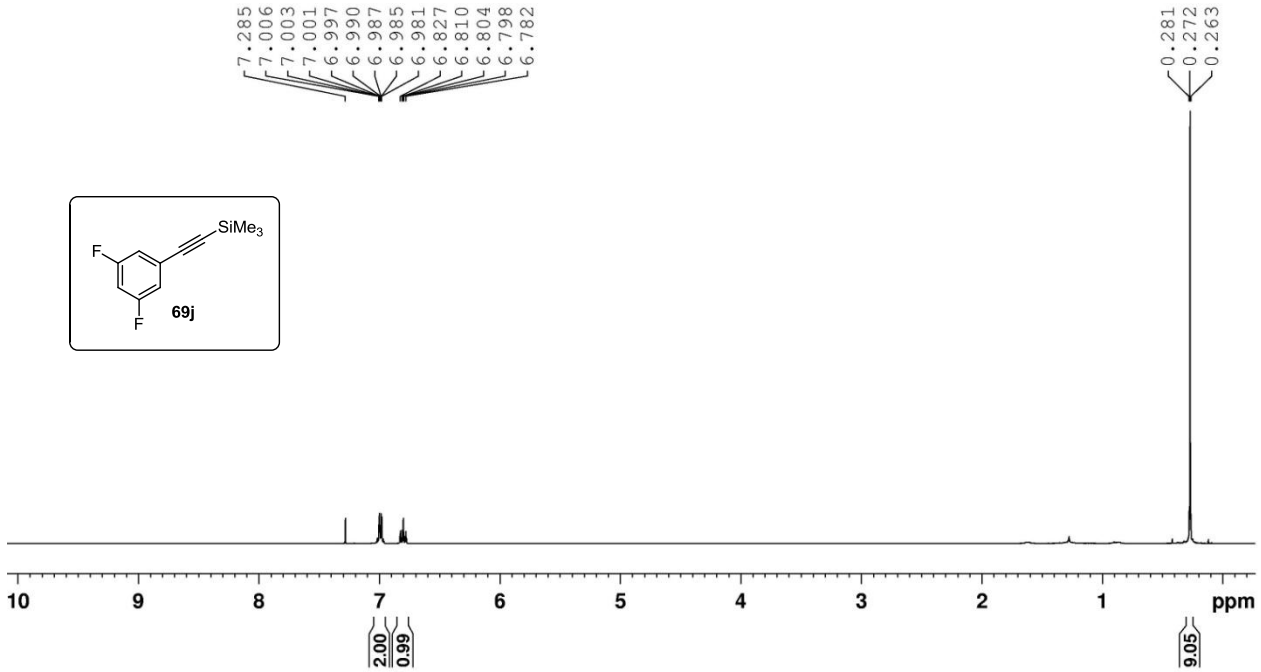
^{1}H NMR Spectrum of **69c**



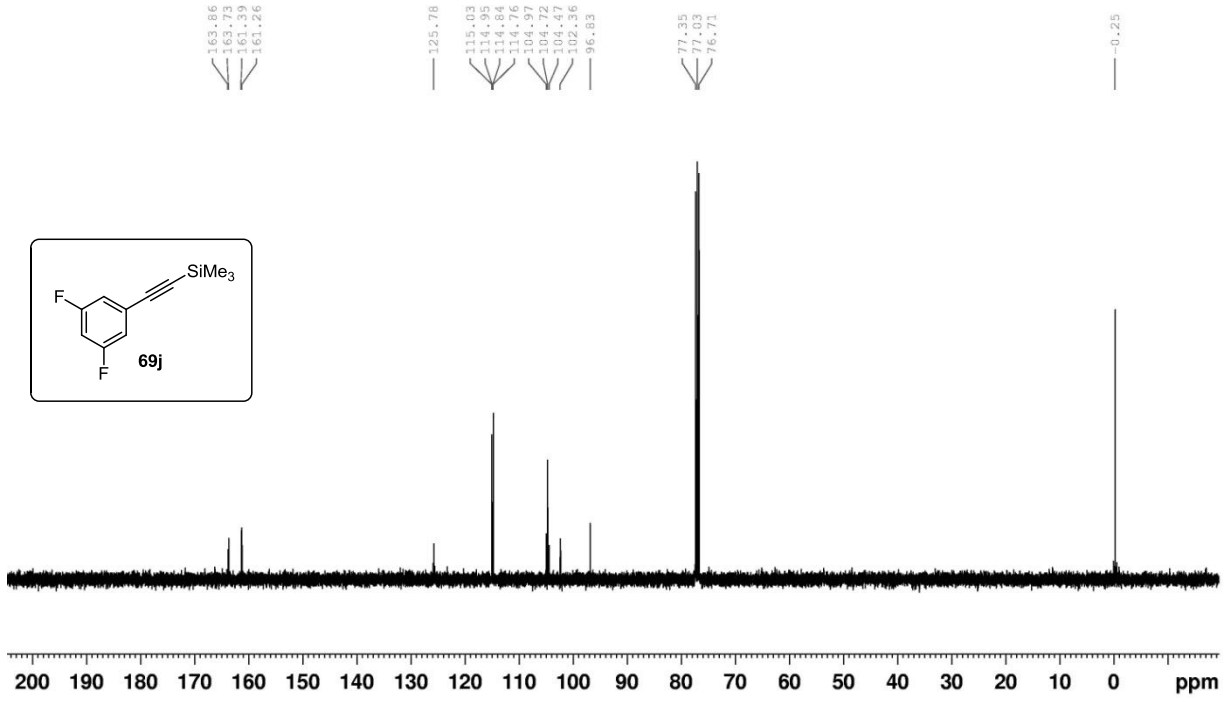
^{13}C NMR Spectrum of **69c**



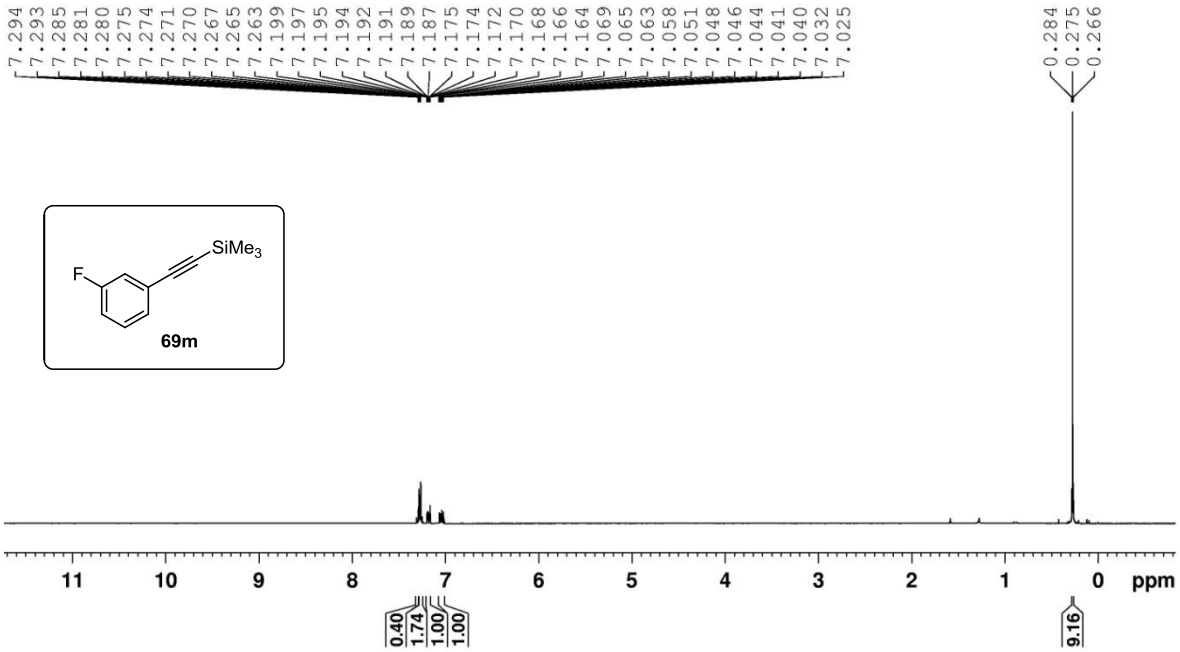
^{1}H NMR Spectrum of **69j**



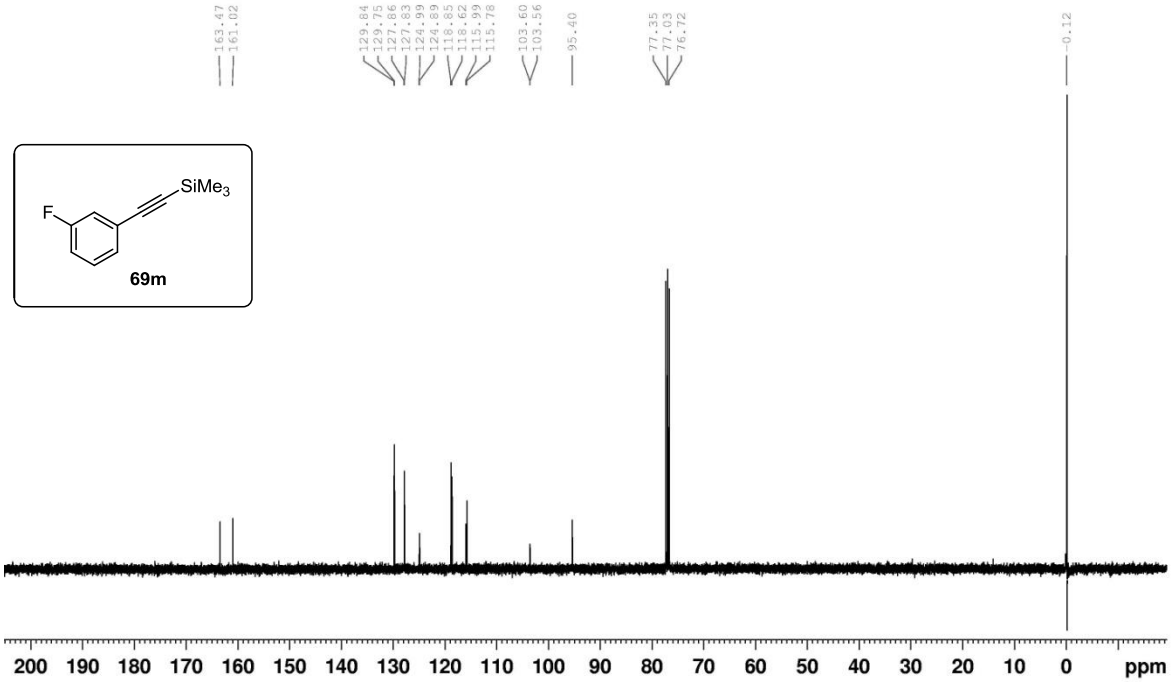
^{13}C NMR Spectrum of **69j**



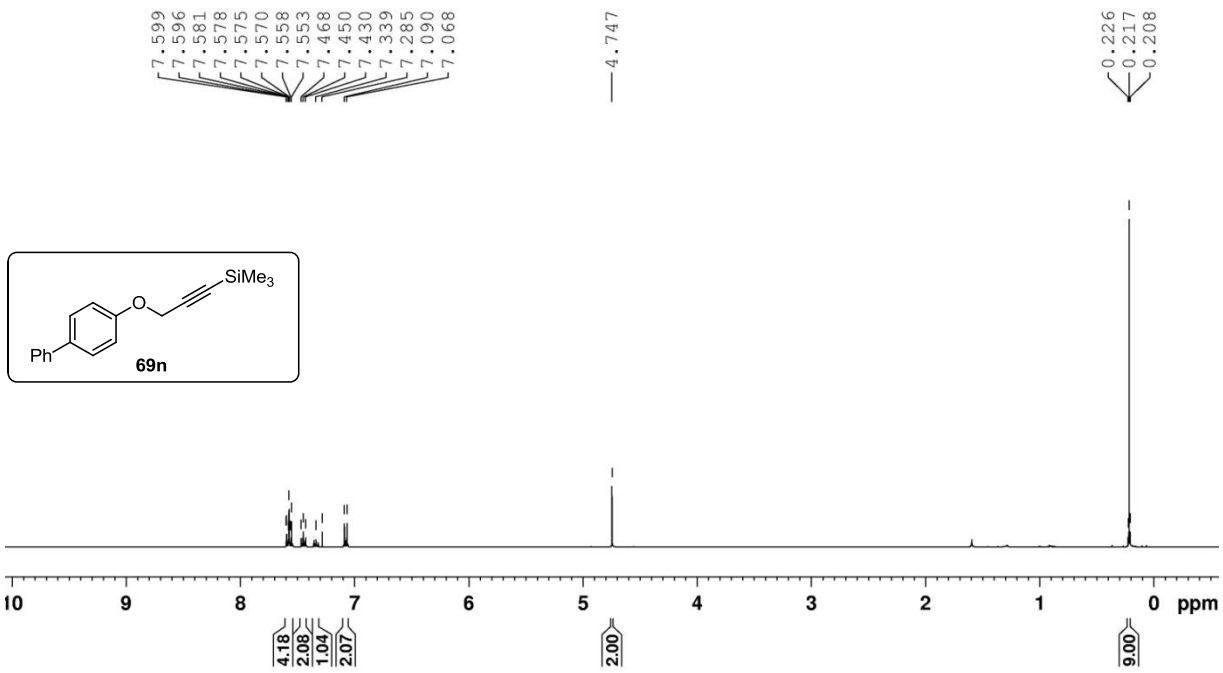
^{1}H NMR Spectrum of **69m**



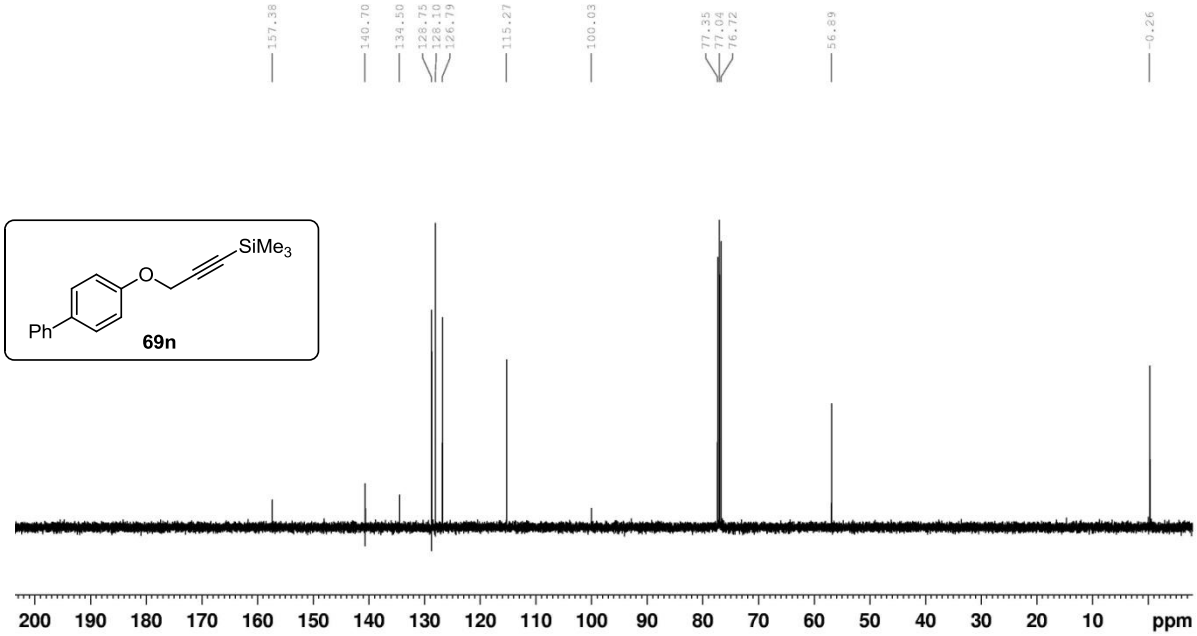
^{13}C NMR Spectrum of **69m**



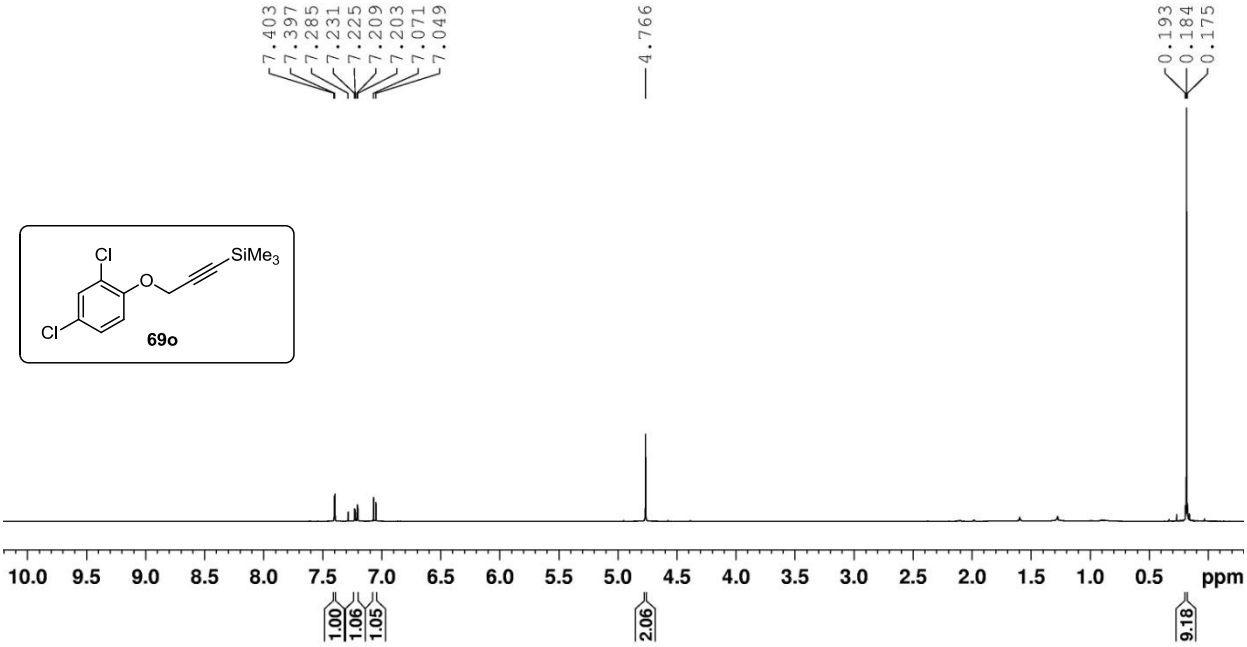
^{1}H NMR Spectrum of **69n**



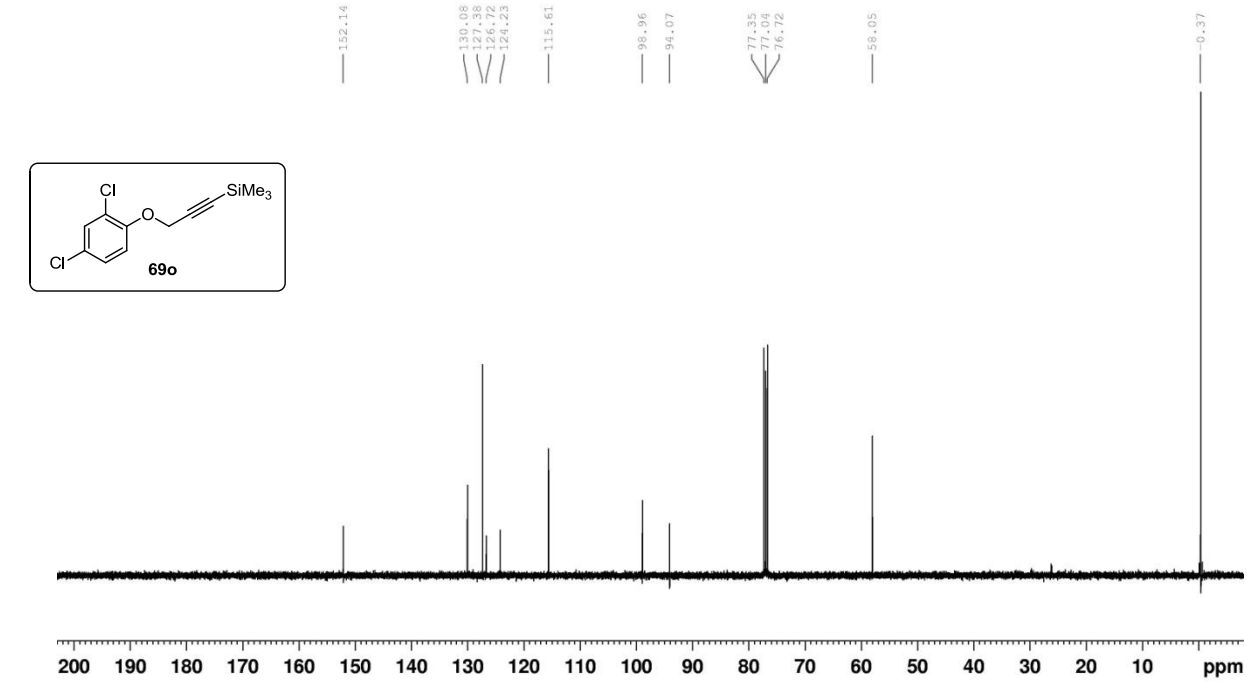
^{13}C NMR Spectrum of **69n**



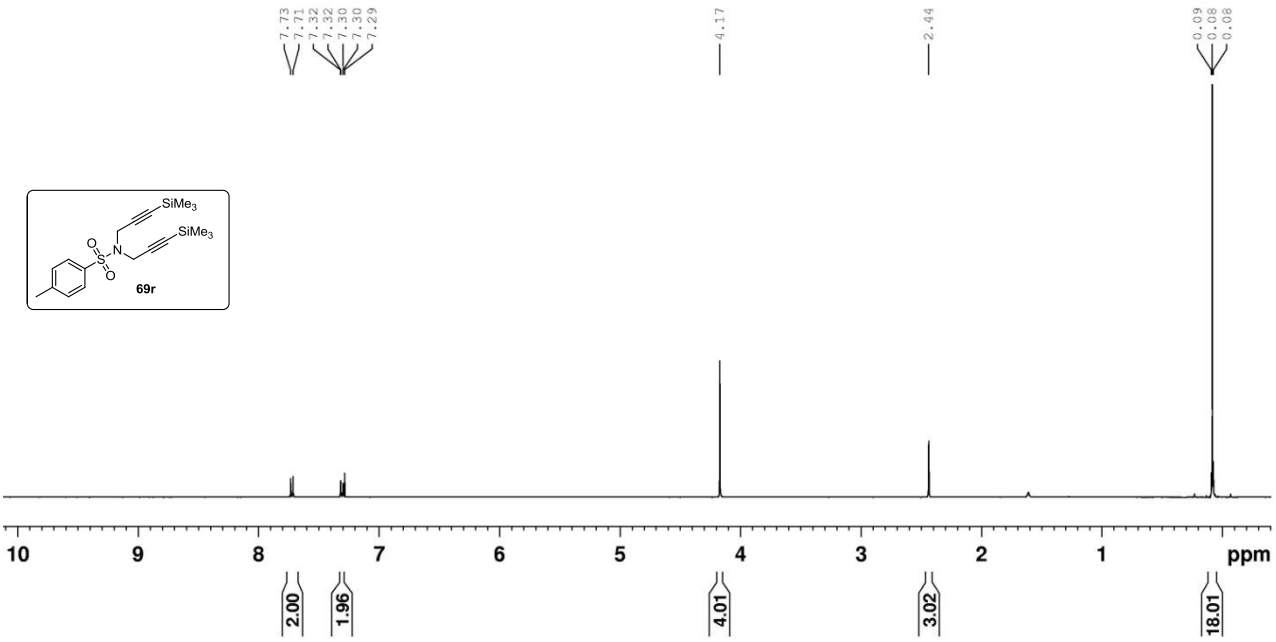
^{1}H NMR Spectrum of **69o**



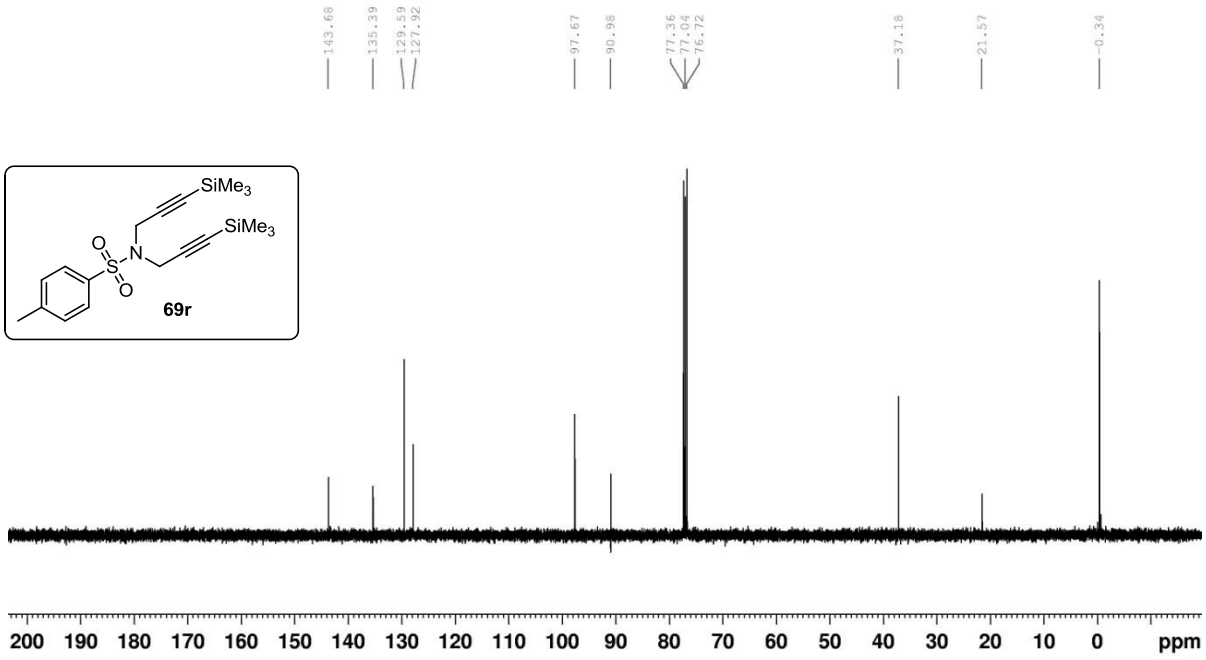
^{13}C NMR Spectrum of **69o**



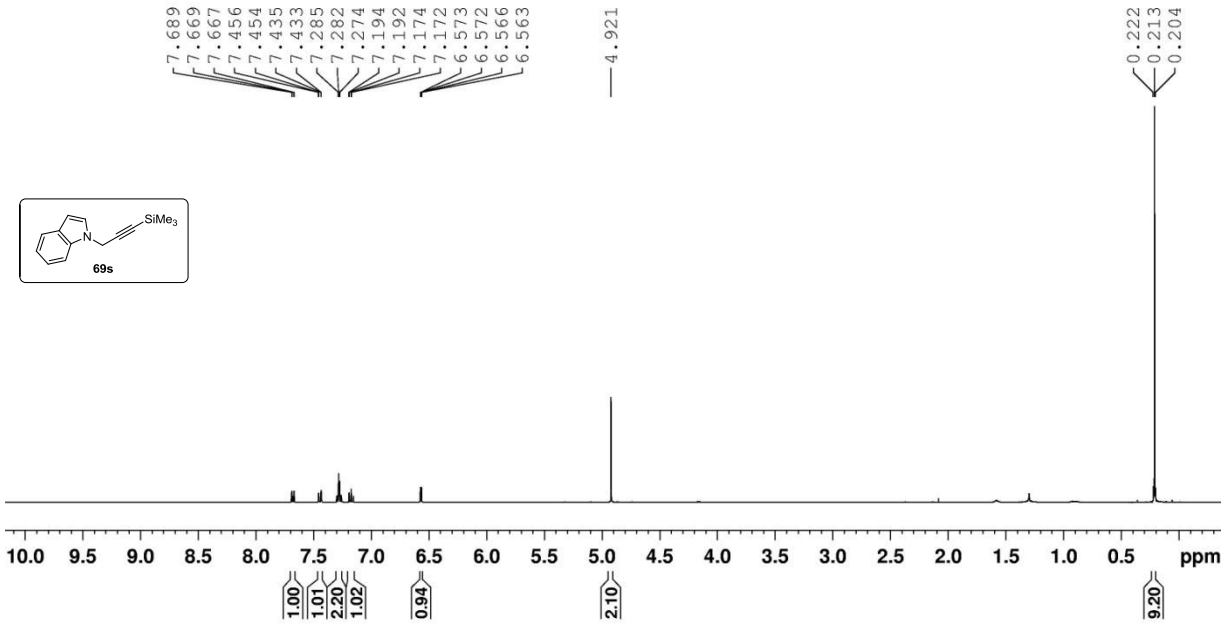
^{1}H NMR Spectrum of **69r**



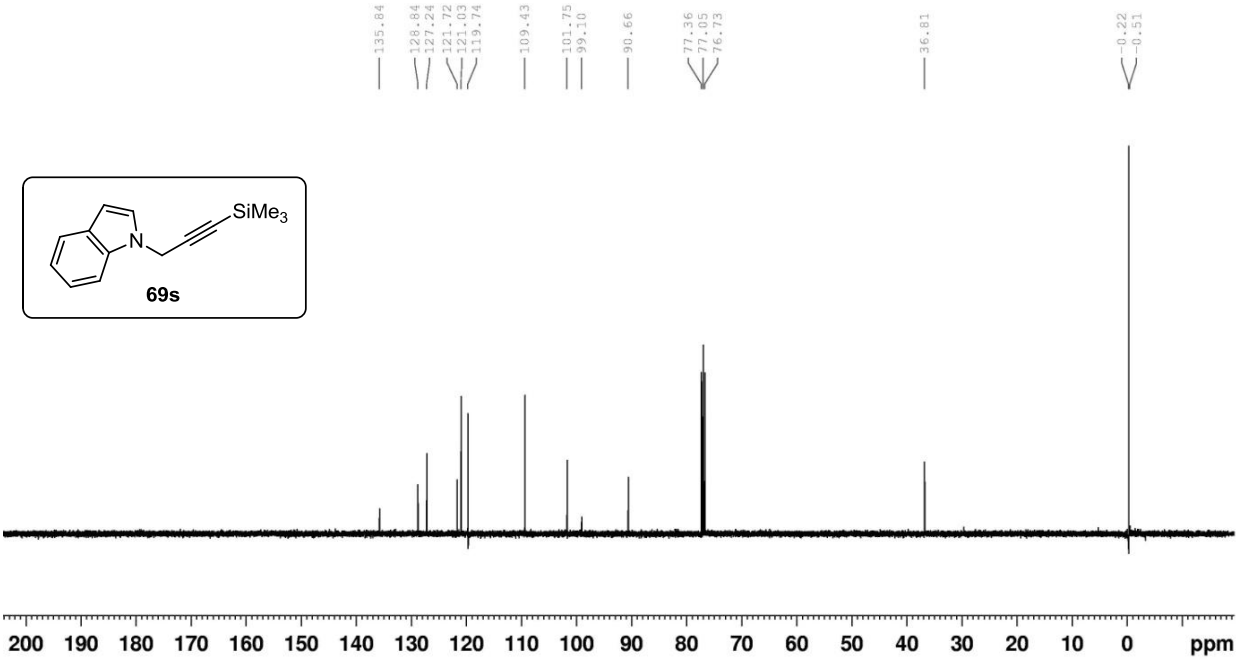
^{13}C NMR Spectrum of **69r**



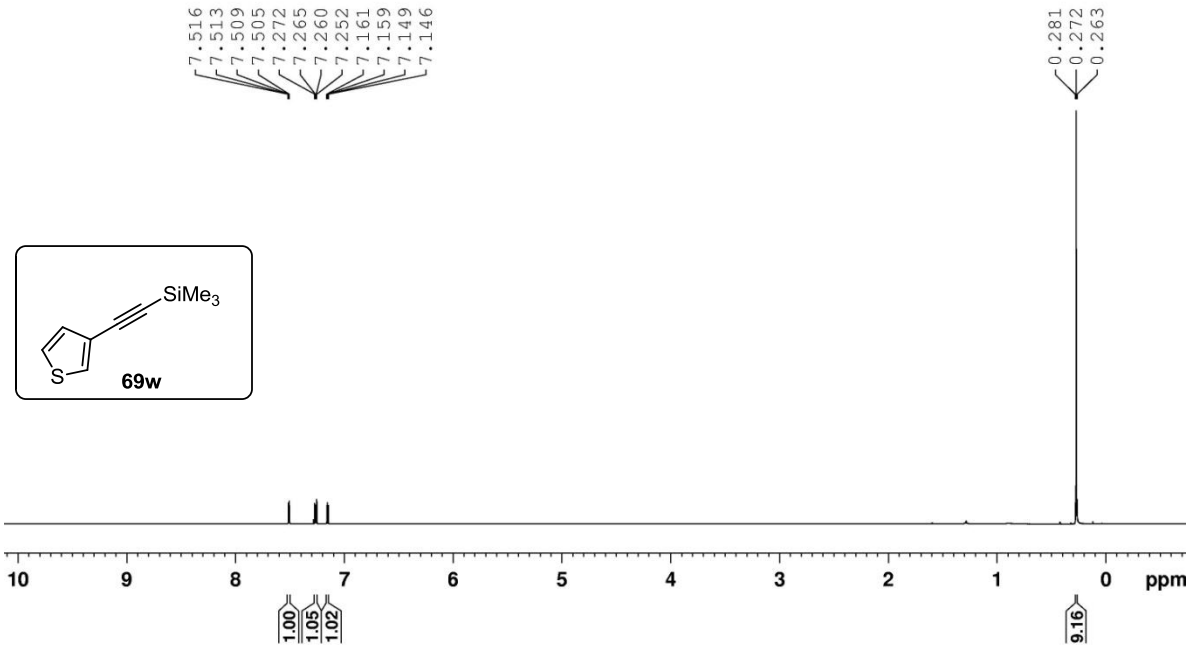
^{1}H NMR Spectrum of **69s**



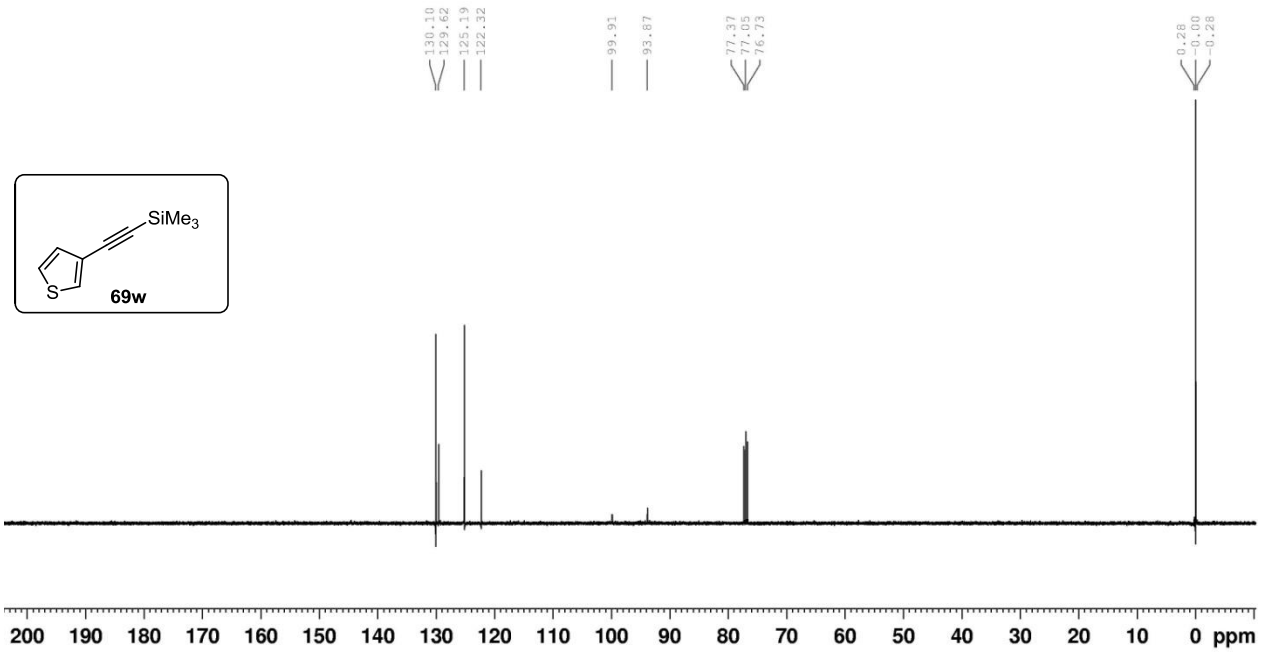
^{13}C NMR Spectrum of **69s**



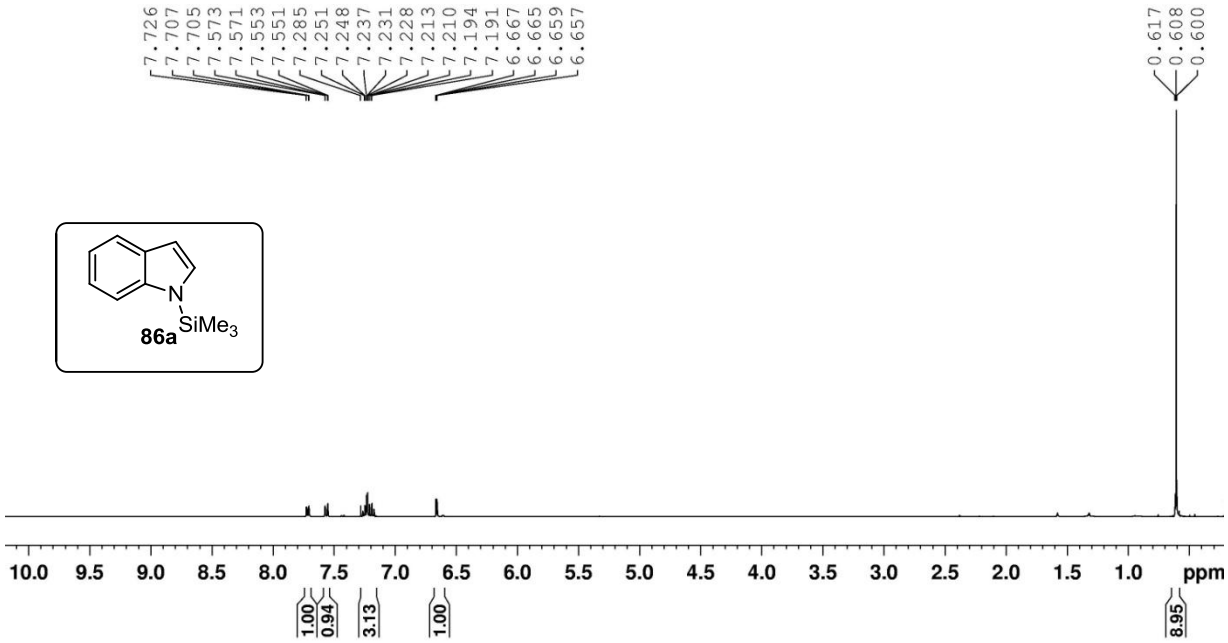
^{1}H NMR Spectrum of **69w**



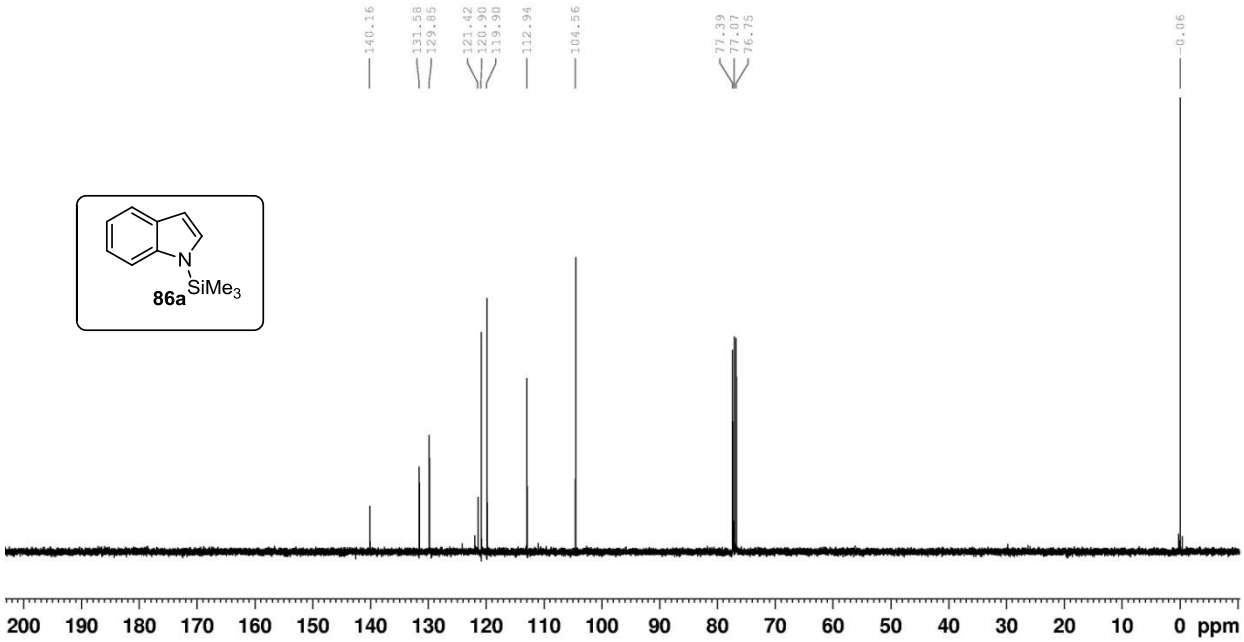
^{13}C NMR Spectrum of **69w**



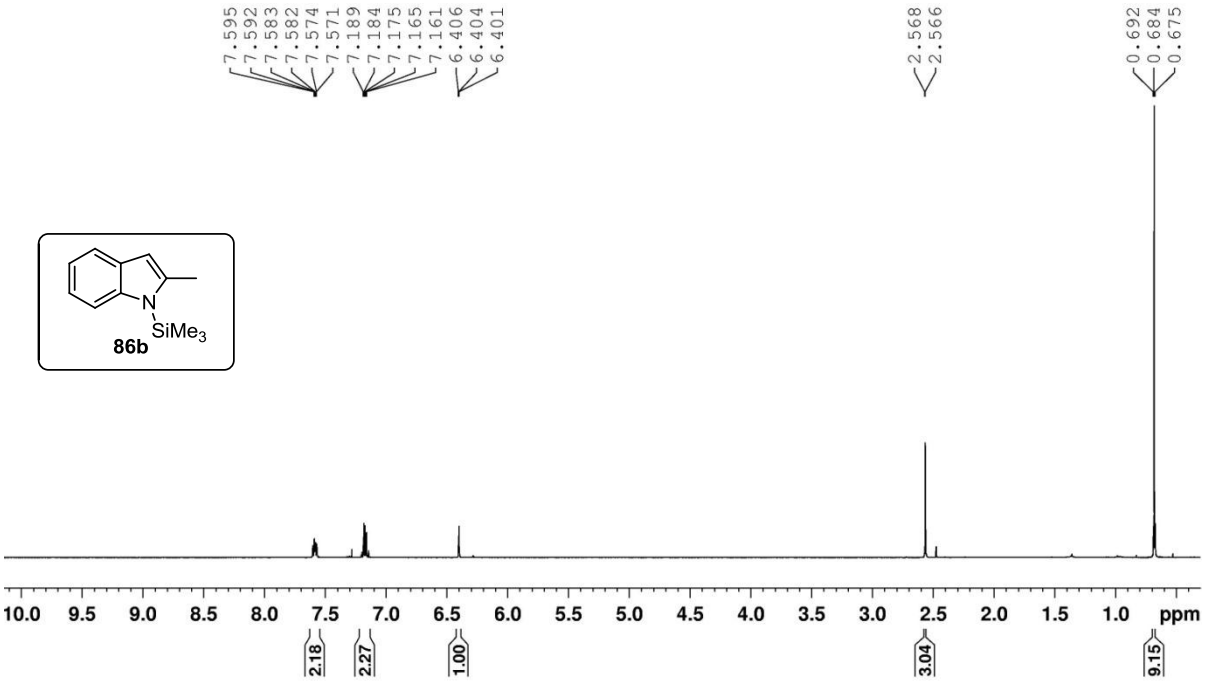
^{1}H NMR Spectrum of **86a**



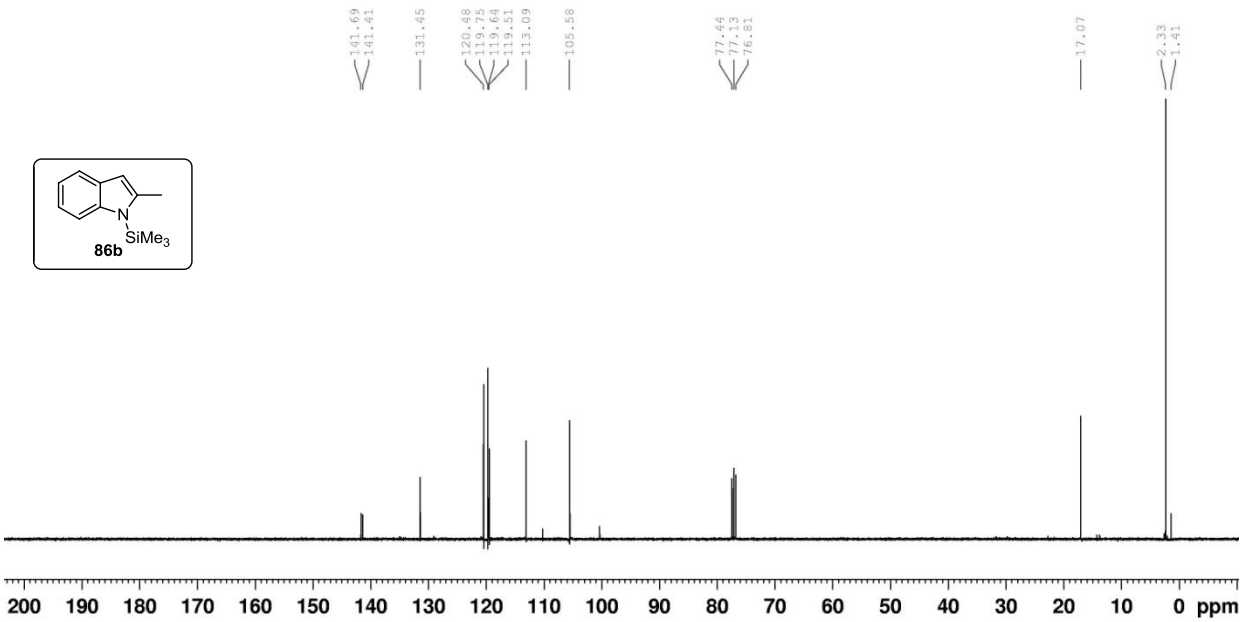
^{13}C NMR Spectrum of **86a**



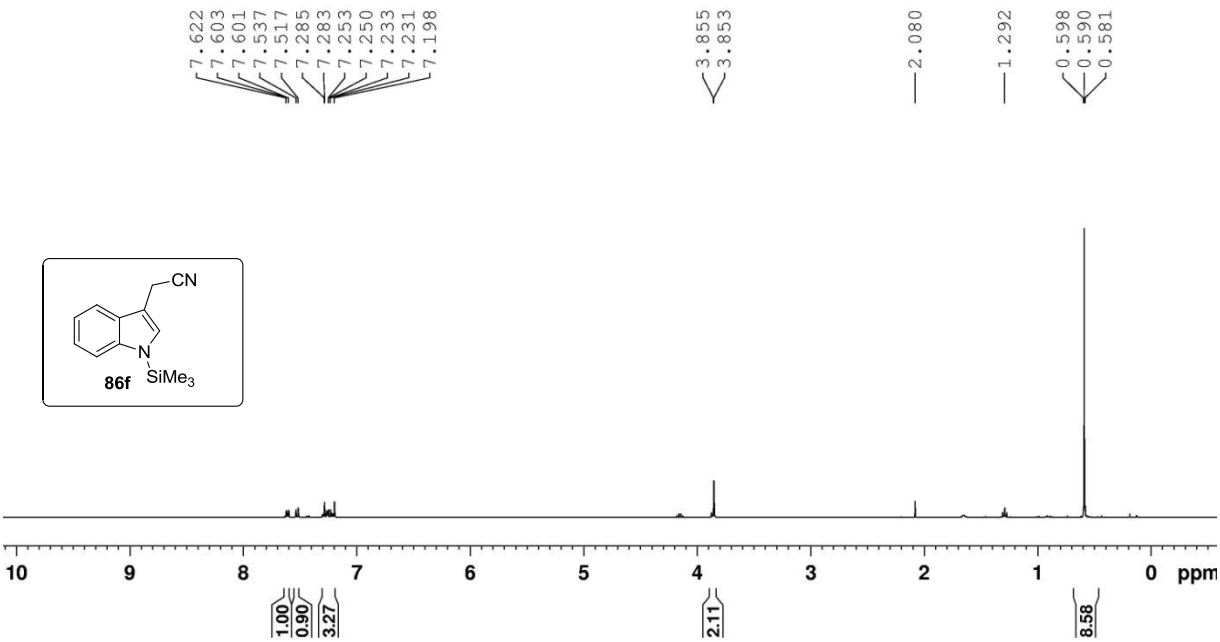
^{1}H NMR Spectrum of **86b**



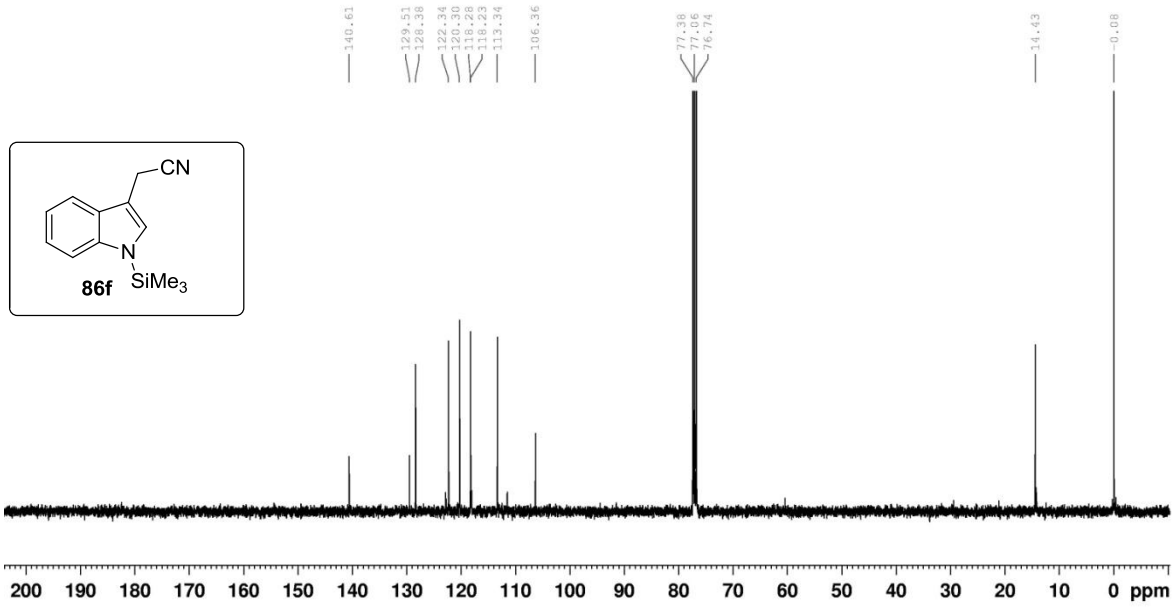
^{13}C NMR Spectrum of **86b**



^{1}H NMR Spectrum of **86f**



^{13}C NMR Spectrum of **86f**



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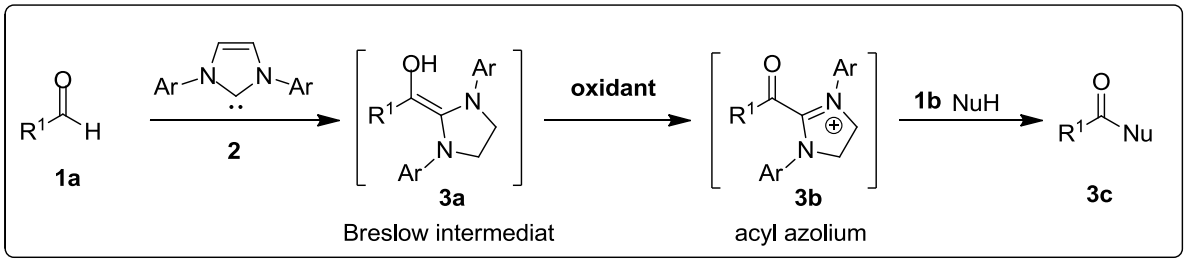
Chapter 4

N-heterocyclic carbene catalyzed oxidative esterification of aldehydes with aryl boronic acids

This chapter describes a direct and organocatalytic protocol for the oxidative esterification of aromatic aldehydes under "oxidative NHC catalysis". This chapter also covers a general introduction and application of NHC-catalyzed oxidative transformations.

4.1) General introduction on NHC-catalyzed oxidative reactions

Over the past few years, NHC-catalyzed oxidative approach has been emerged as a fascinating tool for the construction of carbon-carbon and carbon-heteroatom bond formation reaction.[1] The primary step for this type of transformation is the oxidation of nucleophilic Breslow intermediate (**3a**) to the highly electrophilic acyl azolium intermediate (**3b**). Oxidation of Breslow intermediate has been carried out by using external oxidants. There are mainly three types of oxidants used for these transformation – inorganic oxidants, organic oxidants and atmospheric oxygen as an oxidant.[1b]



Scheme 1: Generation of acyl azolium intermediate using external oxidant

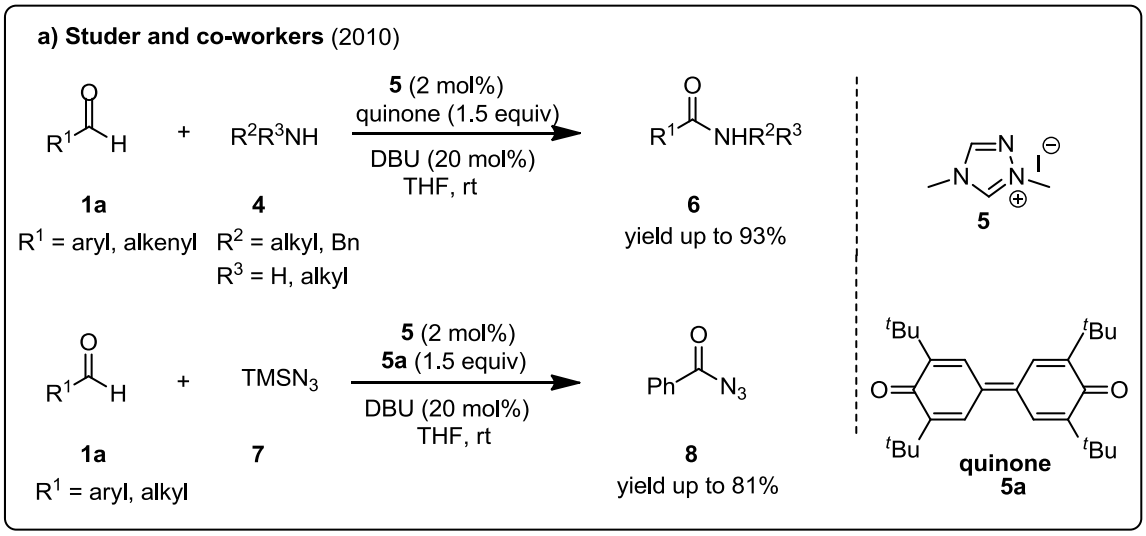
Some of the selected approaches have been discussed below.

4.2) Literature reports on NHC-catalyzed oxidative transformations

4.2.1) NHC-catalyzed oxidative amidation and azidation

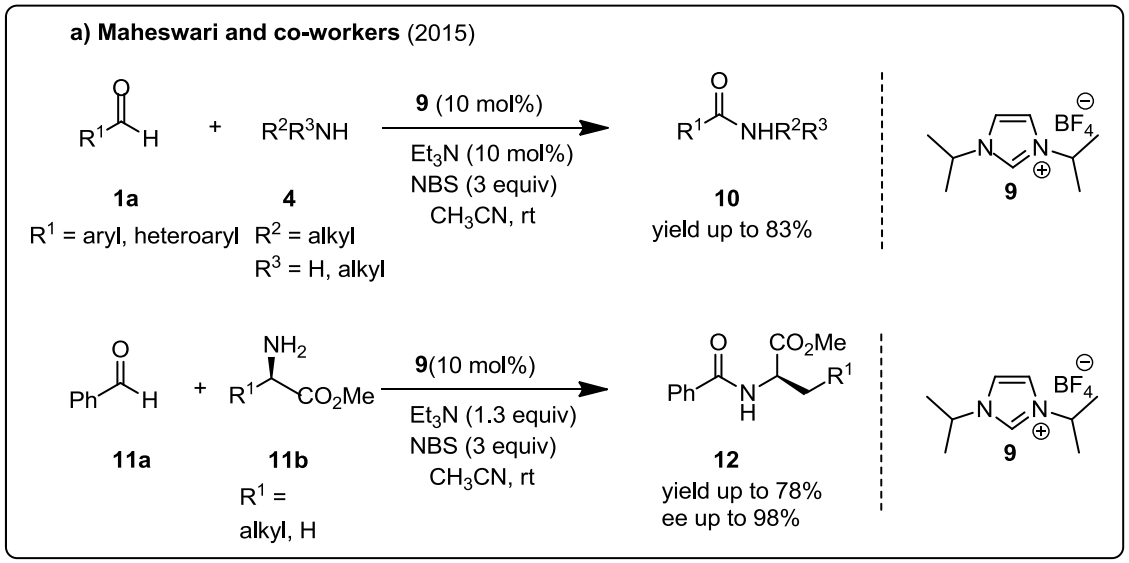
Amides are important structural units found in many biologically active natural products. Construction of amide functionality has gained tremendous attention from synthetic chemists. Some of the selected NHC-catalyzed approaches have been discussed in this section.

Studer and co-workers developed a novel NHC-catalyzed amidation and azidation of aldehydes (**1a**) with amines (**4**) and $TMSN_3$ (**7**) respectively.[2] They used quinone (3,3',5,5'-tetra-tert-butyldiphenoquinone) as an external oxidant for the oxidation of Breslow intermediate to generate the acyl azonium intermediate. The single electron transfer (SET) pathway for this transformation has been confirmed by trapping acyl azonium intermediate with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) radical. A wide range of aldehydes (**1a**) were converted to corresponding products (**6**) in up to 93% isolated yield, in case of cinnamaldehyde the external additive was required to get good conversion (Scheme 2).



Scheme 2: NHC-catalyzed direct amidation and azidation of aldehydes

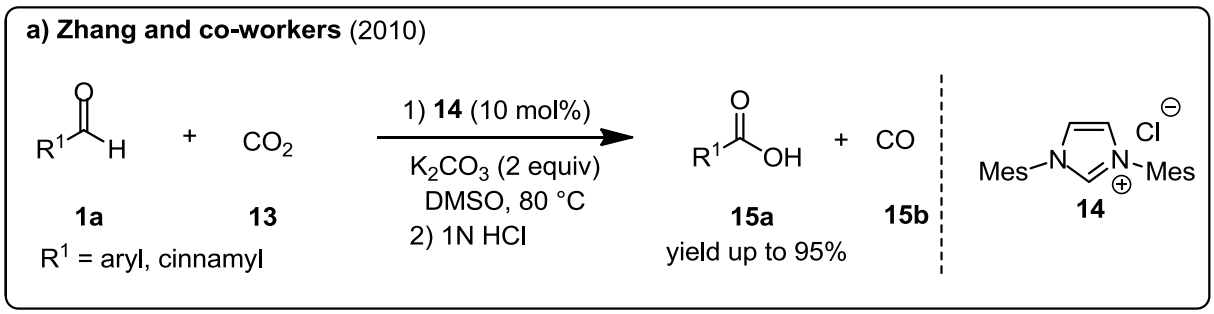
Recently, Maheswari and co-workers accomplished an oxidative amidation of aldehydes (**1a**) with amines (**4**) using NHC-catalysis.[3] Regardless of their electronic nature a variety of aromatic and heteroaromatic aldehydes (**1a**) undervent smooth conversion to the corresponding products (**10**) in moderate to excellent yields using *N*-bromosuccinimide (NBS) as an oxidant. The primary amines and secondary cyclic amines (**4**) were used as coupling partners in this transformation. In presence of chiral amines (**11b**) as coupling partner the expected products (**12**) were obtained in good yields without any loss in the enantioselectivity (Scheme 3).



Scheme 3: NHC-catalyzed direct amidation of aldehydes

4.2.2) NHC-catalyzed oxidation of aldehydes to acids

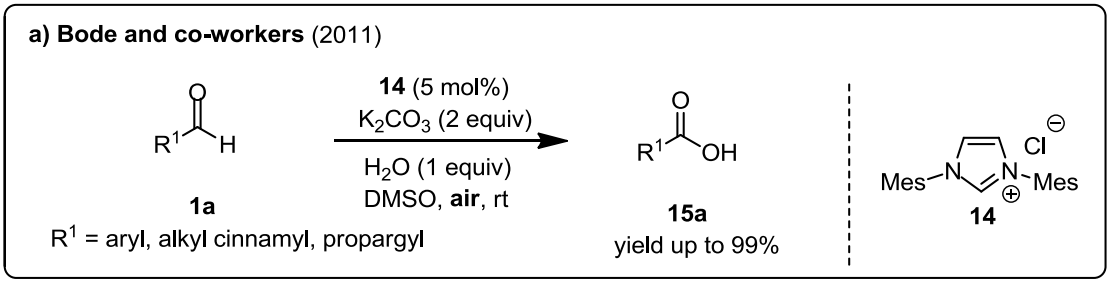
In 2010, Zhang and co-workers reported an unexpected and groundbreaking NHC-catalyzed oxidation of aldehydes (**1a**) to their corresponding acids (**15a**) using carbon dioxide (**13**) as an oxidant.[4] The author propose that, the reaction proceeds through NHC-catalyzed splitting of carbon dioxide (**13**) to generate carbon monoxide (**15b**) and oxygen atom followed by the trapping of oxygen by aldehyde (**1a**), which results into the expected product (**15a**) (Scheme 4).



Scheme 4: NHC-catalyzed oxidation of aldehydes

However, in 2011, Bode and coworkers further investigated the role of CO_2 in this reaction by performing detailed isotopic labeling and NMR studies.[5] In their findings, they

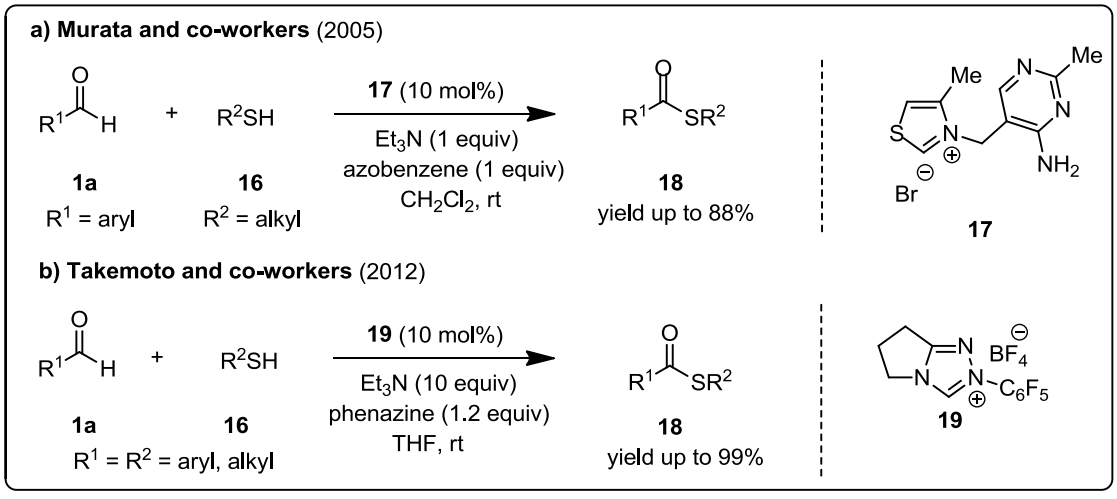
explained that instead of CO_2 exogenous oxygen acts as an oxidant; whereas CO_2 helps in suppressing the side products (Scheme 5).



Scheme 5: NHC-catalyzed oxidation of aldehydes to acids

4.2.3) NHC-catalyzed oxidative thioesterification

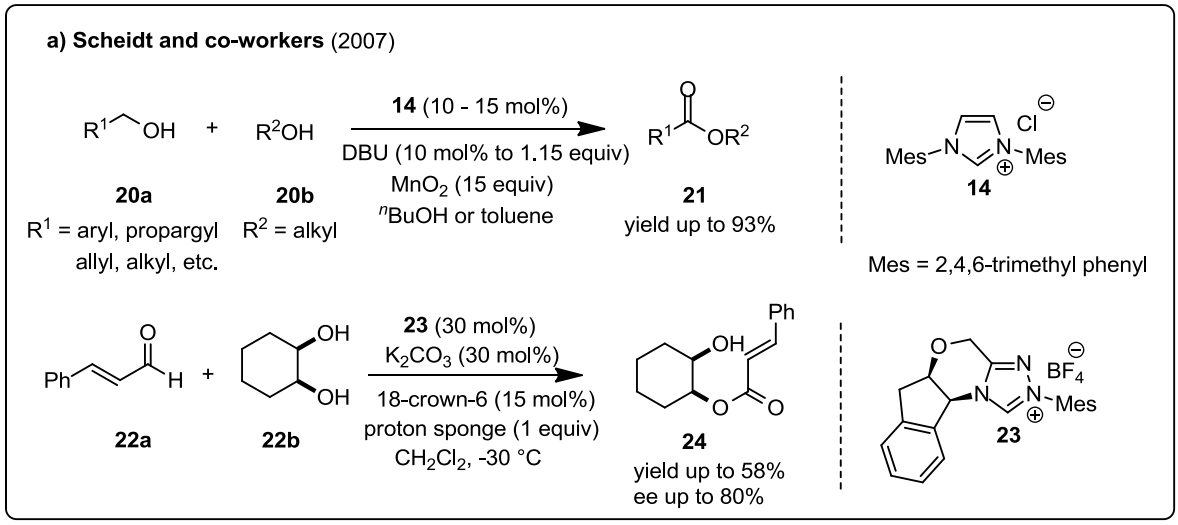
Murata and co-workers developed an NHC-catalyzed thioesterification of aldehydes (**1a**) with thiols (**16**).[6] Azobenzene was used as an external oxidant to afford expected thioesters (**18**) in up to 88% yield. Electron-deficient aldehydes worked smoothly when compared to electron-rich aldehydes (a, Scheme 6). Later, Takemoto's group disclosed an efficient approach for the synthesis of thioesters (**18**) through NHC-catalyzed oxidative thioesterification of aldehydes (**1a**) with thiols (**16**) using phenazine as an external oxidant.[7] Regardless of their electronic nature a variety of aryl and heteroaryl aldehydes (**1a**) have been coupled with a range of aryl as well as alkyl thiols (**16**) to access the corresponding products (**18**) in up to 99% yield (b, Scheme 6).



Scheme 6: NHC-catalyzed oxidative thioesterification

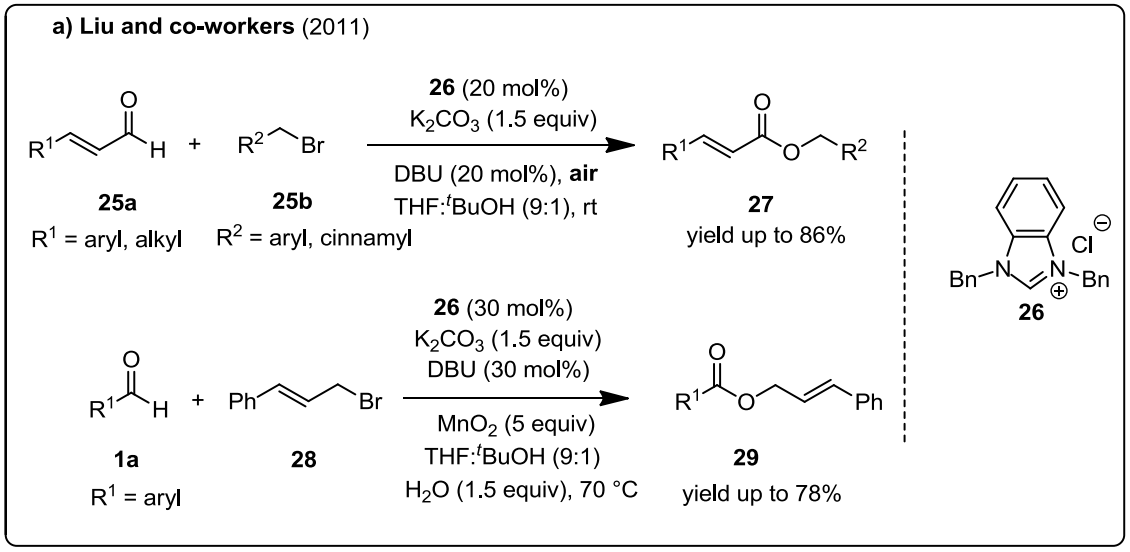
4.2.4) NHC-catalyzed oxidative esterification

In 2007, Scheidt and co-workers reported an NHC-catalyzed tandem direct oxidative esterification of allylic and benzylic alcohols (**20a**) to ester (**21**) in presence of excess amount of inorganic oxidant (MnO_2).[8] The scope of reaction has been further extended to the desymmetrization of *meso*-1,2-diols (**22b**) with cinnamaldehyde (**22a**) by applying chiral NHC to afford good enantioselectivity. Saturated aldehydes were also converted to the corresponding esters in up to 95% yield (Scheme 7).



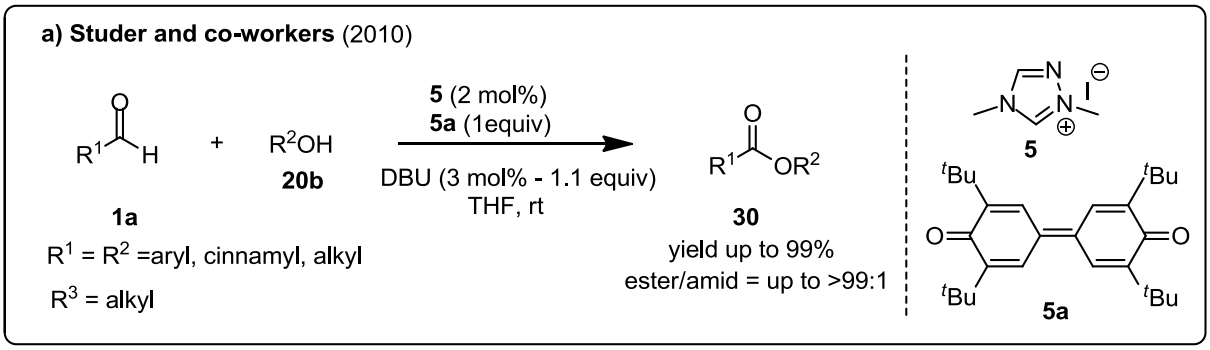
Scheme 7: NHC-catalyzed oxidative esterification of allylic and benzylic alcohols

Liu's group published an unprecedented finding on NHC-catalyzed aerobic oxidative esterification of *α,β*-unsaturated and aromatic aldehydes (**25a**, **1a**) with reactive cinnamyl bromides (**25b**, **28**).[9] Although *α,β*-unsaturated aldehydes (**25a**) worked nicely to synthesize expected products in moderate to good yields, aromatic aldehydes required inorganic oxidant (MnO_2) in excess to provide the required products. In case of benzyl bromide and propargyl bromide very poor yields of products were observed. The insertions of atmospheric oxygen into the products were confirmed by isotopic labeling experiment. Further, the treatment of benzoic acid with cinnamyl bromide at standard condition delivered desired ester in 92% yield, which clearly indicates that the reaction proceeds through acid intermediate (Scheme 8).



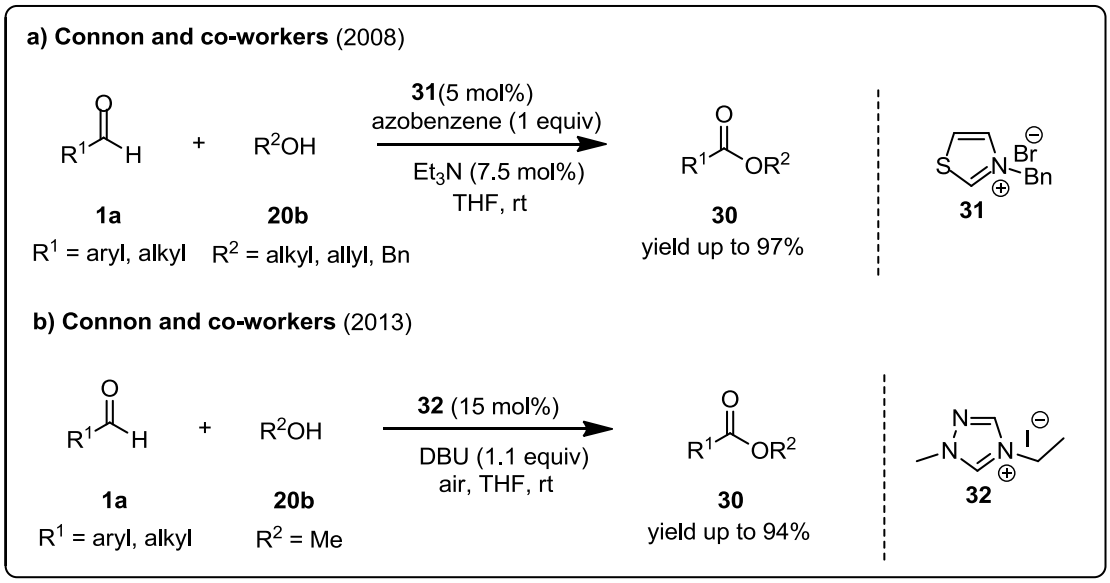
Scheme 8: NHC-catalyzed oxidative esterification of aldehydes with cinnamyl bromides

In 2010, Studer and co-workers developed an NHC-catalyzed highly chemoselective oxidative esterification of aldehydes (**1a**) with alcohols (**20b**) implementing **5a** as an oxidant.[10] An efficient *O*-selective acylation of variety of aldehydes (**1a**) bearing amino and thio functionality have been successfully performed to produce corresponding esters (**30**) in up to 99% yield. The quantum chemical calculations prove the strong H-bonding interaction between NHC-alcohol as compared to the NHC-amine, which is believed to be the driving force for the high chemoselectivity (Scheme 9).



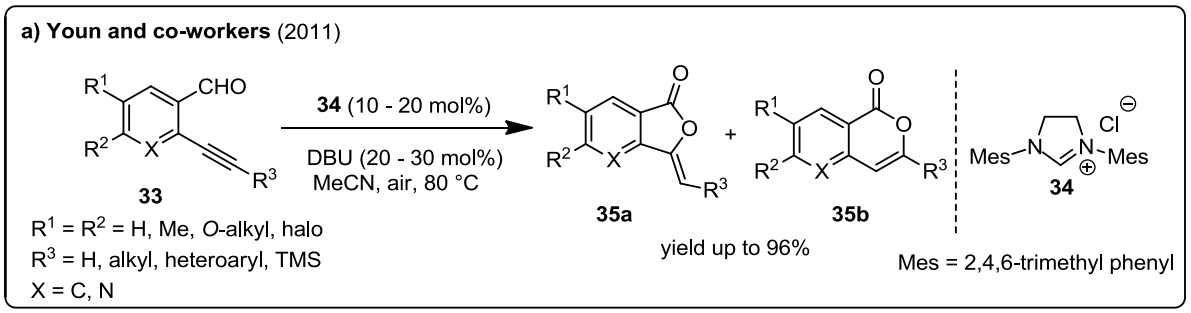
Scheme 9: NHC-catalyzed *O*-selective acylation of aldehydes

Connon and co-workers accomplished an efficient protocol for the synthesis of ester derivatives (**30**) through NHC-catalyzed oxidative esterification of aldehydes (**1a**) with primary and secondary alcohols (**20b**) using azobenzene as an external oxidant.[11] This protocol was found to be applicable to a range of aldehydes (**1a**) including aromatic, cinnamyl and alkyl aldehydes to furnish subsequent ester derivatives (**30**) in excellent yields (a, Scheme 10). Later, the same group reported an additive free NHC-catalyzed oxidative esterification of aldehydes (**1a**) and alcohols (**20b**) in presence of atmospheric oxygen as an oxidant.[12] In this method, the esters (**30**) were synthesized in good yields (b, Scheme 10).



Scheme 10: NHC-catalyzed oxidative esterification of aldehydes

In 2011, Youn and co-workers developed a novel approach for the synthesis of phthalides (**27a**) and isocoumarins (**35b**) derivatives through NHC-catalyzed intramolecular oxidative cyclization of 2-alkyneylbenzaldehyde (**33**) under aerobic conditions.[13] The reaction proceeds through the activation of aldehydes with NHC followed by addition to unactivated alkyne functionality, which leads to the formation of cyclized products (**35a**, **35b**) with region- and sterioselectivity. The auther proposed that the reaction proceeds through an acid intermediate (Scheme 11).

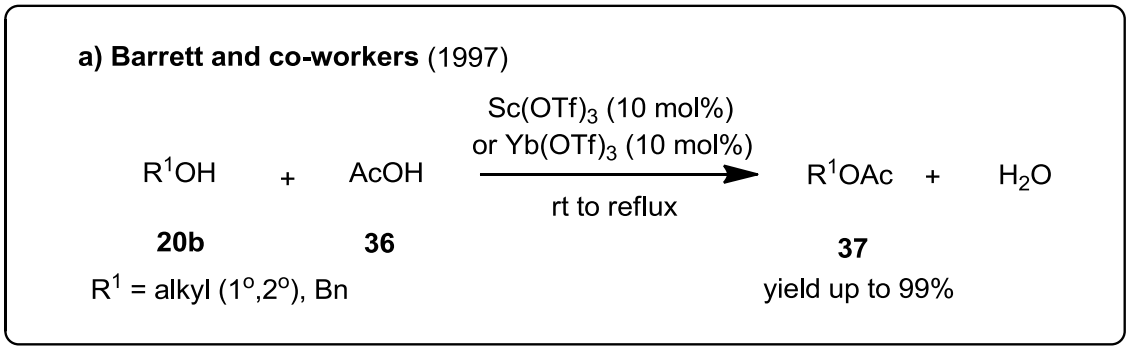


Scheme 11: NHC-catalyzed oxidative synthesis of phthalides and isocoumarins derivatives

4.3) Literature reports on synthesis of ester derivatives

4.3.1) Lewis acid catalyzed esterification

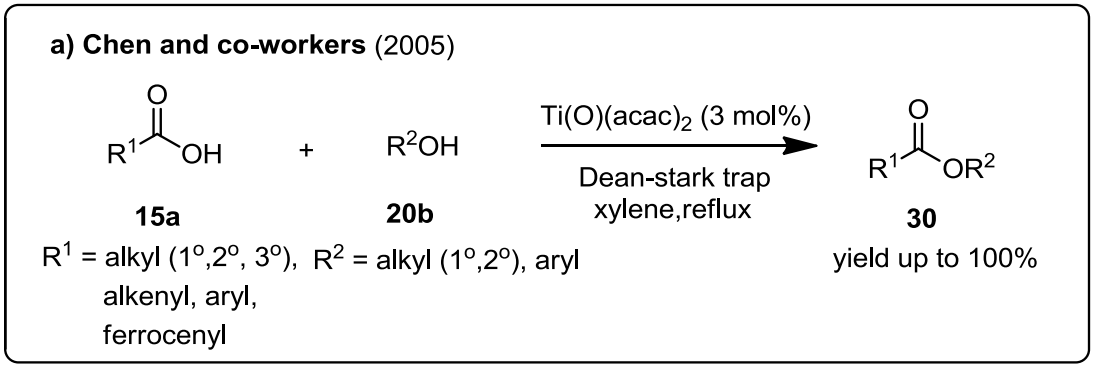
In 1997, Barrett and co-workers developed an efficient approach for the synthesis of ester derivatives (**37**) through scandium (III) or lanthanide (III) triflate catalyzed direct acylation of alcohols (**20b**) with acetic acid (**36**).[14] Although primary alcohols (**20b**) were acylated smoothly at room temperature to afford corresponding esters (**37**) in up to 99% yield, the secondary alcohols required elevated temperature to get good conversion. Unfortunately tertiary alcohols failed to produce the expected products even at reflux condition. The catalyst could be recycled by simple water workup and reused without affecting the activity (Scheme 12).



Scheme 12: Scandium (III) or lanthanide (III) triflate catalyzed direct acylation of alcohols

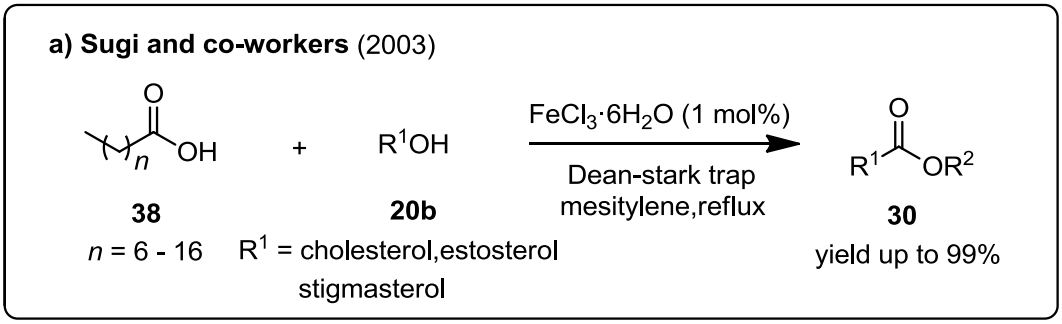
Chen and co-workers reported a novel water-tolerant oxometallic catalyst system for the esterification of carboxylic acids (**15a**) with variety of alcohols (**20b**).[15] This protocol allows an

atom-efficient condensation between different acids (**15a**) and alcohols (**20b**) to synthesize ester derivatives (**30**) in quantitative yields using $Ti(O)(acac)_2$ as a catalyst (Scheme 13).



Scheme 13: $Ti(O)(acac)_2$ catalyzed esterification of carboxylic acid

Sugi's group accomplished an interesting iron(III)-catalyzed esterification of steroid alcohols (**20b**) with fatty acids (**38**) to access corresponding ester derivatives (**30**) in excellent yields.[16] The condensation of steroid alcohols (**20b**) with fatty acids (**38**) has been carried out using $FeCl_3 \cdot 6H_2O$ as an efficient catalyst (Scheme 14).[17]

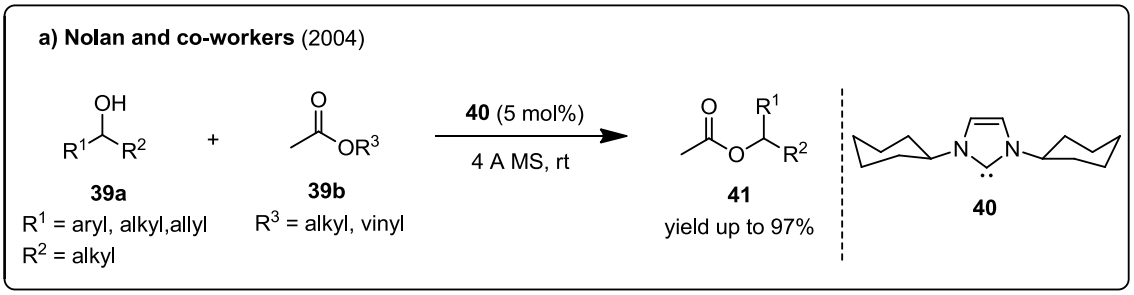


Scheme 14: $FeCl_3 \cdot 6H_2O$ catalyzed esterification of steroid alcohols with fatty acids

4.3.2) Organocatalytic esterification

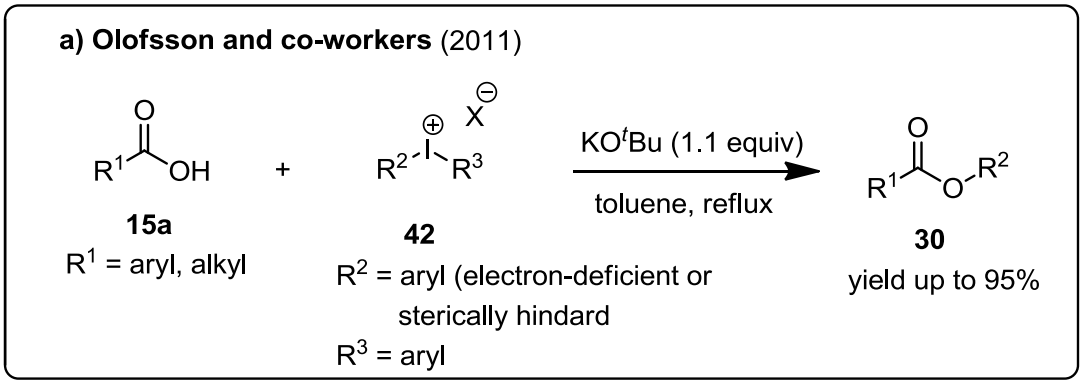
In 2004, Nolan and co-workers developed a straightforward NHC-catalyzed synthesis of ester derivatives (**41**) through transesterification of carboxylic acid esters (**39b**) with secondary alcohols (**39a**).[18] This catalyst was found to be proficient catalyst for the acylation of variety of a cyclic and acyclic secondary alcohols (**39a**) to provide esters (**41**) in excellent yields.

Unfortunately tertiary alcohols did not react under standard condition, though the increased catalyst loading afforded the corresponding esters in low to moderate yields (Scheme 15).



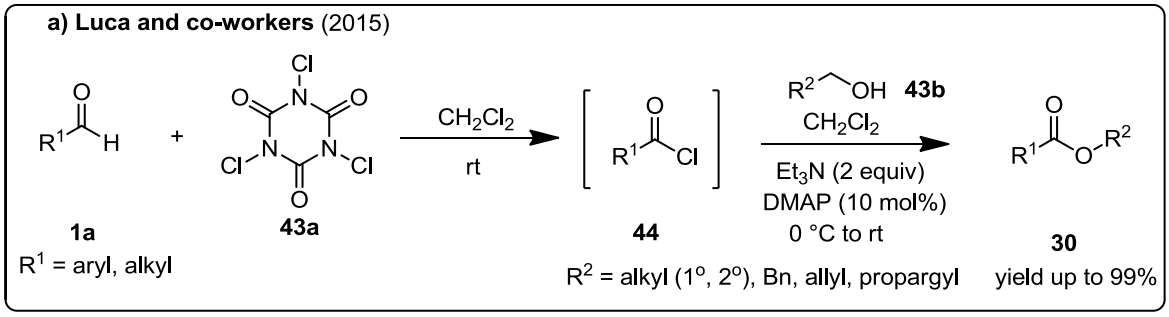
Scheme 15: NHC-catalyzed acylation of secondary alcohols through transesterification

Recently, Olofsson's group demonstrated a metal-free synthesis of aryl benzoate derivatives through arylation of carboxylic acids (**15a**) with symmetrical and unsymmetrical diaryliodonium salts (**42**).[19] In case of unsymmetric diaryliodonium salts, the electron-deficient and sterically hindered aryl groups were migrated over the electron-rich or less sterically hindered aryl groups (Scheme 16).



Scheme 16: Metal-free arylation of carboxylic acids with unsymmetric diaryliodonium salts

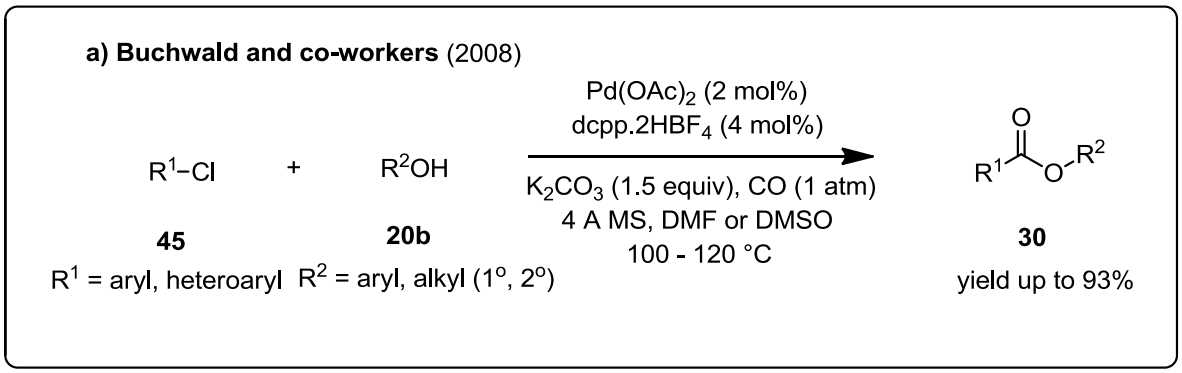
Recently, Luca and co-workers developed a metal-free oxidative esterification of aldehydes (**1a**) using of trichloroisocyanuric acid (TCCA) [**43a**] as an oxidant.[30] Wide range of aryl and aliphatic aldehydes (**1a**) were treated with aliphatic, benzylic, allylic, and propargylic alcohols (**43b**) to furnish the expected esters (**30**) excellent yields. It was proposed that the reaction proceeds through *in situ* synthesis of acyl chloride (**44**) from aldehydes (**1a**) followed by nucleophilic addition of alcohols (**43b**) (Scheme 17).



Scheme 17: Metal-free oxidative esterification of aldehydes

4.3.3) Metal-catalyzed esterification reactions

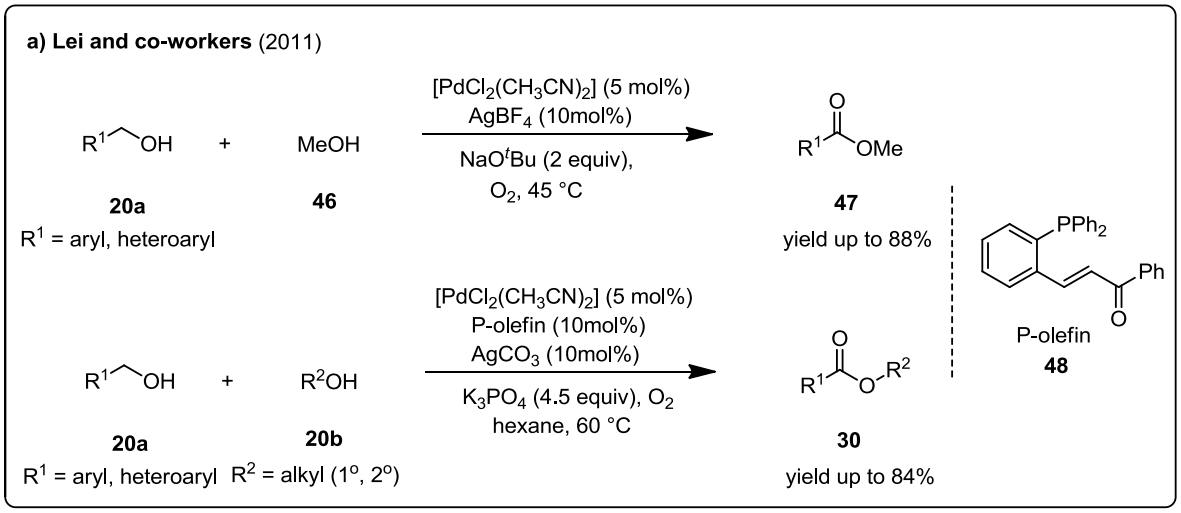
In 2008, Buchwald's group disclosed a mild and efficient Pd-catalyzed synthesis of aryl and alkyl esters (**30**) from aryl chlorides (**45**) through carbonylation using carbon monoxide at atmospheric pressure.[21] The resultant ester derivatives (**30**) were obtained in good yields (Scheme 18).



Scheme 18: Pd-catalyzed synthesis of aryl and alkyl esters from aryl chlorides

In 2011, Lei and co-workers developed fascinating method for the synthesis of ester derivatives (**47**, **30**) through Pd-catalyzed oxidative esterification of alcohols (**20a**).[22] The treatment of benzylic alcohols (**20a**) with aliphatic alcohols (**46**, **20b**) as coupling partner in presence of Pd-catalyst afforded corresponding esters (**47**, **30**) in up to 88% yield. The yields of the products depend on the electronic nature of the substituent attached to the benzylic alcohols. It was proposed that the reaction proceeds through an aldehyde intermediate, which results from *β*-hydride elimination of benzylic alcohol. Further nucleophilic addition of another alcohol

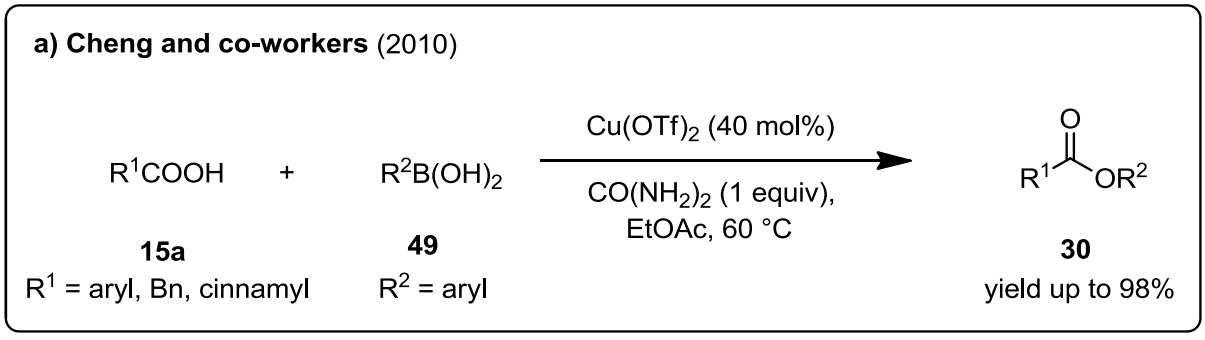
substituent generates hemiacetal, which gives the desired ester through second *β*-hydride elimination (Scheme 19).



Scheme 19: Pd-catalyzed oxidative direct esterification of alcohols

4.3.4) Metal-catalyzed esterification using arylboronic acids

Cheng and co-workers accomplished the synthesis of phenolic ester derivatives (**30**) through Cu(II)-mediated Chan-Lam coupling of carboxylic acids (**15a**).[23] The desired esters (**30**) were accessed in moderate to excellent yields by $Cu(OTf)_2$-mediated reaction between variety of

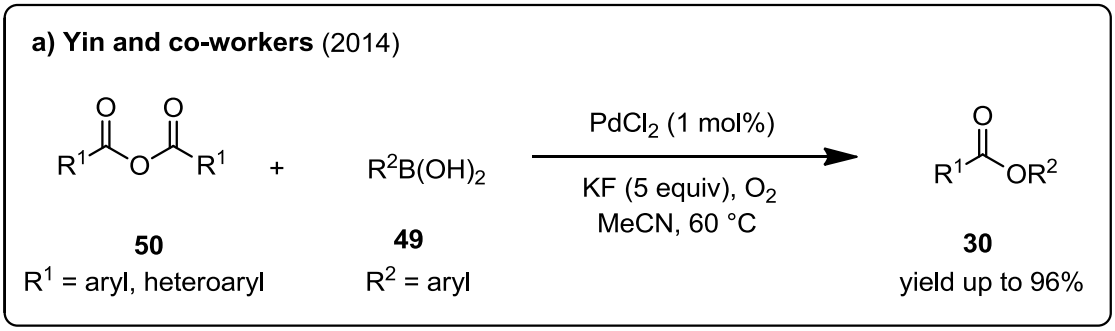


Scheme 20: $Cu(OTf)_2$-mediated Chan-Lam coupling of carboxylic acids

arylboronic acids (**49**) and carboxylic acids (**15a**). The number of functional groups such as acetoxy, hydroxy, vinyl, nitro, methoxy and halo were effectively tolerated under this reaction

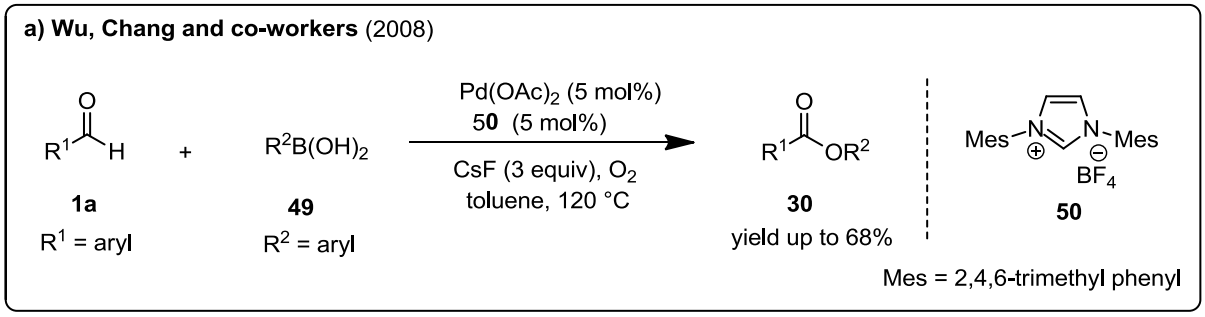
conditions. Carboxylic acids (**15a**) bearing electron-donating substitution produced higher yields compared to electron-withdrawing substitution. Unfortunately, *ortho*-substituted and high electron-donating substituted arylboronic acids (**49**) failed to deliver resultant products (Scheme 20).

In 2014, Yin and co-workers developed a novel approach for the synthesis of aryl benzoate derivatives (**30**) by ligand-free Pd-catalyzed oxidative coupling between carboxylic anhydrides (**50**) and arylboronic acids (**49**) under aerobic condition.[24] Irrespective of the electronic nature of substitution, all aromatic carboxylic anhydrides (**50**) except *ortho*-substituted aromatic carboxylic anhydrides gave the desired esters (**30**) in up to 96% yield. The insertion of atmospheric oxygen into the product has been confirmed by isotopic labeling experiment (Scheme 21).



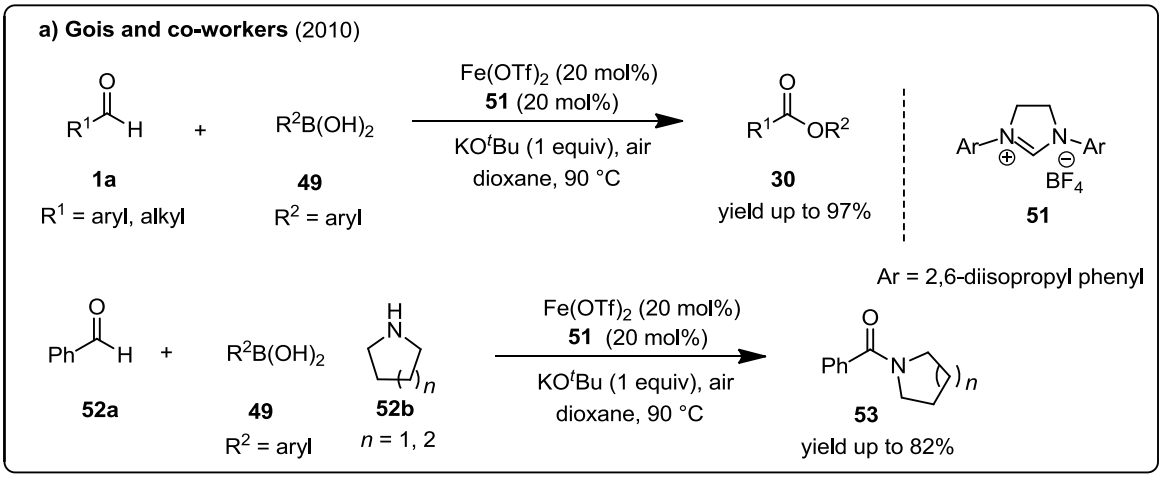
Scheme 21: Ligand-free Pd-catalyzed oxidative esterification of carboxylic anhydrides

Wu, Cheng reported the straightforward Pd-catalyzed oxidative esterification of aldehydes (**1a**) with arylboronic acids (**49**) in presence of atmospheric oxygen.[25] Range of functional groups such as cyano, nitro, acetoxy and halo were well tolareted under the reaction conditions. Electron-rich aldehyds worked very well as compared to electron-poor aldehydes. Unfortunately, aliphatic aldehydes were not found to be suitable substrates for this transformation. The role of atmospheric oxygen has been confirmed by isotope labeling (Scheme 22).



Scheme 22: Pd-catalyzed oxidative esterification of aldehydes

In 2010, Gois's group modified the Wu and Cheng's methodology by developing highly efficient iron-catalyzed alternative protocol.[26] They performed Fe(II)-catalyzed aerobic oxidative esterification of aromatic aldehydes (**1a**) with arylboronic acids (**49**) to prepare the corresponding esters (**30**). Irrespective of electronic nature all aromatic aldehydes (**1a**) and arylboronic acids (**49**) underwent smooth conversion. Interestingly aliphatic aldehydes also worked well to furnish the corresponding esters in moderate yields. The reaction between benzaldehyde (**52a**) and phenol at standard condition provided the product in 88% of phenyl benzoate. This experiment suggests that phenol could be possible intermediate for this transformation. The scope of this protocol was further extended for the one-pot synthesis of amides. Treatment of benzaldehyde (**52a**) with arylboronic acids (**49**) and secondary amines (**52b**) gave the corresponding amides (**53**) in moderate to good yields (Scheme 23).



Scheme 23: Fe(II)-catalyzed oxidative esterification of aldehydes

4.4) Results and Discussions

Since NHC-catalyzed oxidative esterification of aryl aldehydes with alkyl halides or alcohols has been well documented in the literature,[5–14] we believed that NHC itself, without any assistance from a metal catalyst, would promote the aerobic oxidation of aryl aldehydes in the presence of boronic acids to furnish the corresponding esters. We became interested in exploring the organocatalytic activity of NHCs in this particular aerobic oxidation reaction using a few commercially available N-heterocyclic carbene precursors **14, 34, 54,** & **55** (Fig. 1).

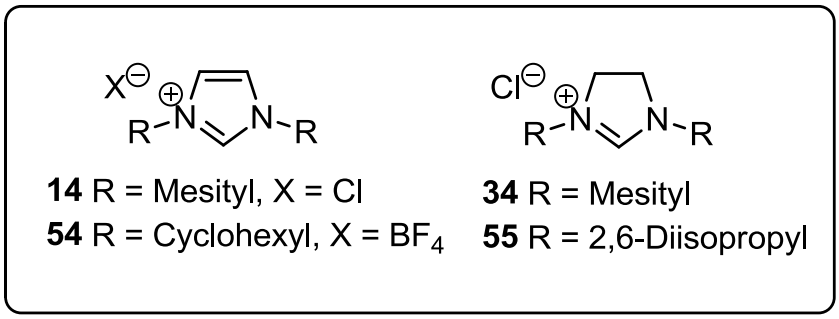
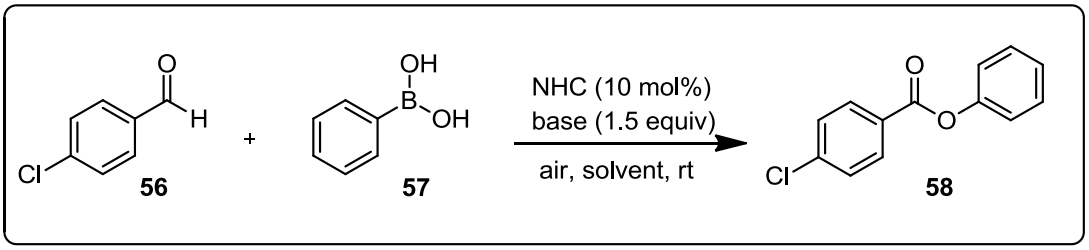


Figure 1: NHC precursors

We began the optimization studies using *p*-chlorobenzaldehyde (**56**) and phenylboronic acid (**57**) as model substrates (Table 1). The initial experiments on the reaction between **56** and **57** under aerobic conditions were discouraging as no desired product (**58**) was obtained using either **14** or **54** (10 mol%) at RT (Entries 1 and 2, Table 1). Surprisingly, when the same reaction was performed at RT in toluene using **34** as a catalyst and Cs_2CO_3 as a base, **58** was isolated in 64% yield (Entry 3). Encouraged by this result, further optimization experiments were carried out by employing 10 mol% of **34** or **55** as a catalyst (Entries 3–19). In all the cases, ester **58** was formed in moderate to excellent yields and, in most of the cases, **55** was found to be more active than **87**. Use of a slight excess of aldehyde helped in improving the yield of **58** considerably (Entries 17–19). No product was obtained when the reaction was carried out in the absence of NHC. It was also observed that 1.5 equivalent of base is essential to carry out this transformation. Based on the above observations, the optimal reaction was found to be the reaction where the ester **58** was obtained almost in quantitative yield using 1.3 equivalent of **56** with respect to **57** in the presence of 10 mol% of **55** (Entry 17).

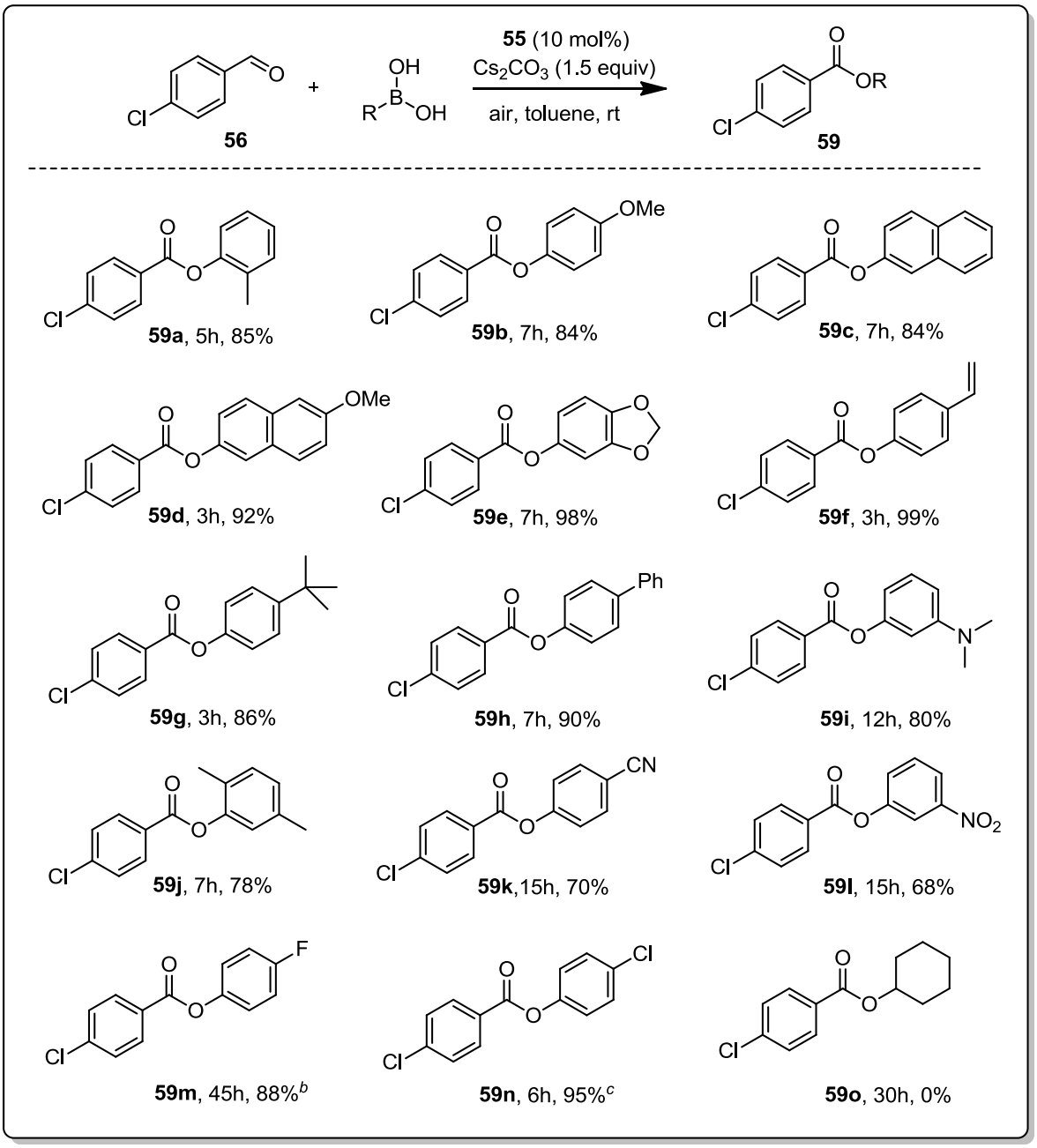
Table 1: **Optimisation of reaction conditions**[a]



Entry	NHC	Base	Solvent	Time [h]	Yield [%][b]
1	**14**	DBU	Toluene	24	0
2	**54**	Cs_2CO_3	Toluene	24	0
3	**34**	Cs_2CO_3	Toluene	6	64
4	**34**	Cs_2CO_3	Dioxane	8	58
5	**34**	Cs_2CO_3	THF	8	60
6	**34**	Cs_2CO_3	DCE	8	28
7	**34**	Cs_2CO_3	MeCN	8	38
8	**34**	Cs_2CO_3	DME	8	56
9	**34**	KO^tBu	Toluene	12	48
10	**34**	DBU	Toluene	8	53
11	**34**	NaH	Toluene	8	24
12	**34**	DBU	THF	8	45
13	**55**	Cs_2CO_3	THF	5	50
14	**55**	Cs_2CO_3	Dioxane	5	64
15	**55**	Cs_2CO_3	Toluene	6	75
16	**55**	Cs_2CO_3	DMF	5	19
17[c]	**55**	**Cs_2CO_3**	**Toluene**	**5**	**99**
18[d]	**55**	Cs_2CO_3	Toluene	5	95
19[e]	**55**	**Cs_2CO_3**	**Toluene**	**5**	86

[a] Reaction conditions: **56**/**57** = 1/1.1, 0.06 M of **56** in solvent, RT = 31 °C. [b] Isolated yield. [c] **56**/**57** = 1.3/1. [d] **56**/**57** = 1.2/1. [e] **56**/**57** = 1.1/1

To generalize this synthetic methodology, the aerobic oxidative esterification of **56** with a variety of boronic acids was evaluated under the optimized reaction conditions and the results are summarized in Scheme 24.

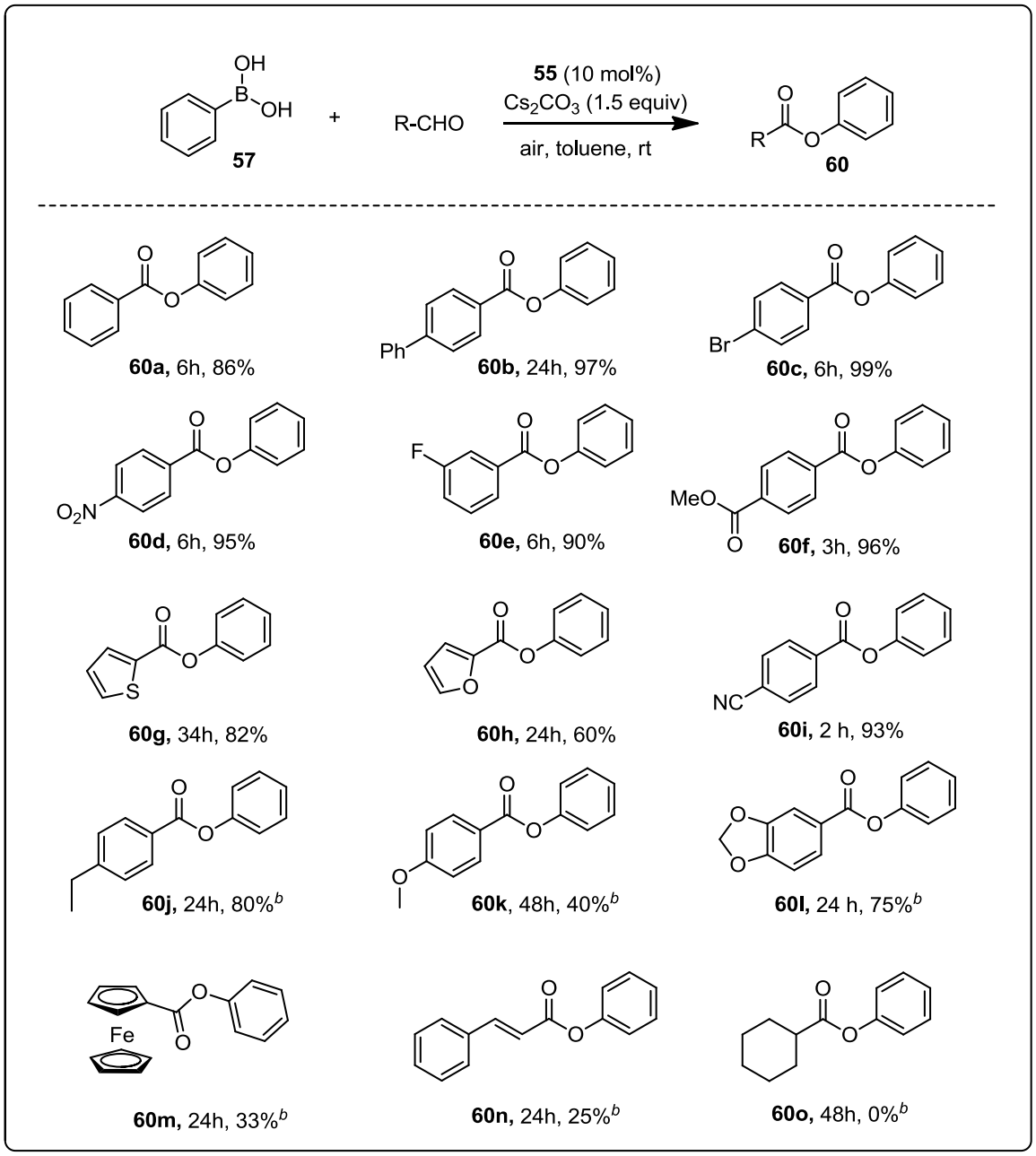


[a] Reaction conditions: **56**/R-B(OH)$_2$ = 1.3/1, 0.06 M of **56** in toluene, rt = 31-33 ^{o}C. [b] Conversion started after 24 h. [c] Performed at 60 ^{o}C

Scheme 24: Oxidative esterification of **56** with boronic acids[a]

It is apparent from Scheme 24 that boronic acids with various substituents having different electronic and steric properties reacted smoothly with **56** under the given reaction conditions and produced the corresponding aryl esters in good to excellent yields. Electron rich boronic acids (Examples **59b**, **59d**, **59e**, **59g** and **59i**) reacted faster than electron deficient boronic acids (Examples **59k**, **59l**, **59m** and **59n**) as expected. Interestingly, esters were obtained in excellent yields in the cases of other activated boronic acids (Examples **59c**, **59f** and **59h**). Sterically hindered boronic acids (Examples **59a** and **59j**) also underwent smooth conversion under standard conditions. It was observed that this transformation is applicable only for aromatic boronic acids as cyclohexylboronic acid (Example **59o**) failed to react with **56** even at 80 ◦C.

In order to explore the significance of this transformation further, phenylboronic acid (**57**) was treated with different aromatic and heteroaromatic aldehydes under standard conditions and the results are tabulated in Scheme 25. Except in a few cases, aromatic esters were obtained in modest to excellent yields. The reactivity of the aldehyde was greatly influenced by the electronic and steric properties of the substituents attached to it. Electron poor aldehydes reacted at a faster rate when compared to electron rich aldehydes. For example, *p*-cyanobenzaldehyde was converted to its corresponding ester **60i** in 93% yield in just 2 h. Other electron poor aldehydes such as *p*-nitrobenzaldehyde and methyl-4-formyl benzoate reacted with **57** efficiently and provided esters **60d** and **60f** in 95% and 96% yields respectively. But, electron rich aldehydes (Examples **60j**–**60l**) did not react with **57** at RT, but were converted to the esters in reasonably good yields at 60 °C. Activated aldehydes such as *p*-phenylbenzaldehyde and *p*-bromobenzaldehyde were oxidized to their corresponding esters in excellent yields at RT (Examples **60b** and **60c**). It is also evident from Scheme 25 that the substrate scope was not limited to aromatic aldehydes as heteroaromatic aldehydes (Examples **60g** and **60h**) could also be converted to esters in moderate to good yields. Ferrocene carboxaldehyde reacted at a much slower rate and the ester **60m** was obtained in only 33% yield even at 60 °C. In the case of cinnamaldehyde, a considerable amount of cinnamic acid was formed during the reaction. As a result, ester **60n** was isolated only in 25% yield. Since the reaction is carried out under basic conditions, aliphatic aldehydes could not be used as substrates. For example, cyclohexane carboxaldehyde did not give **60o** but decomposed under the given reaction conditions.

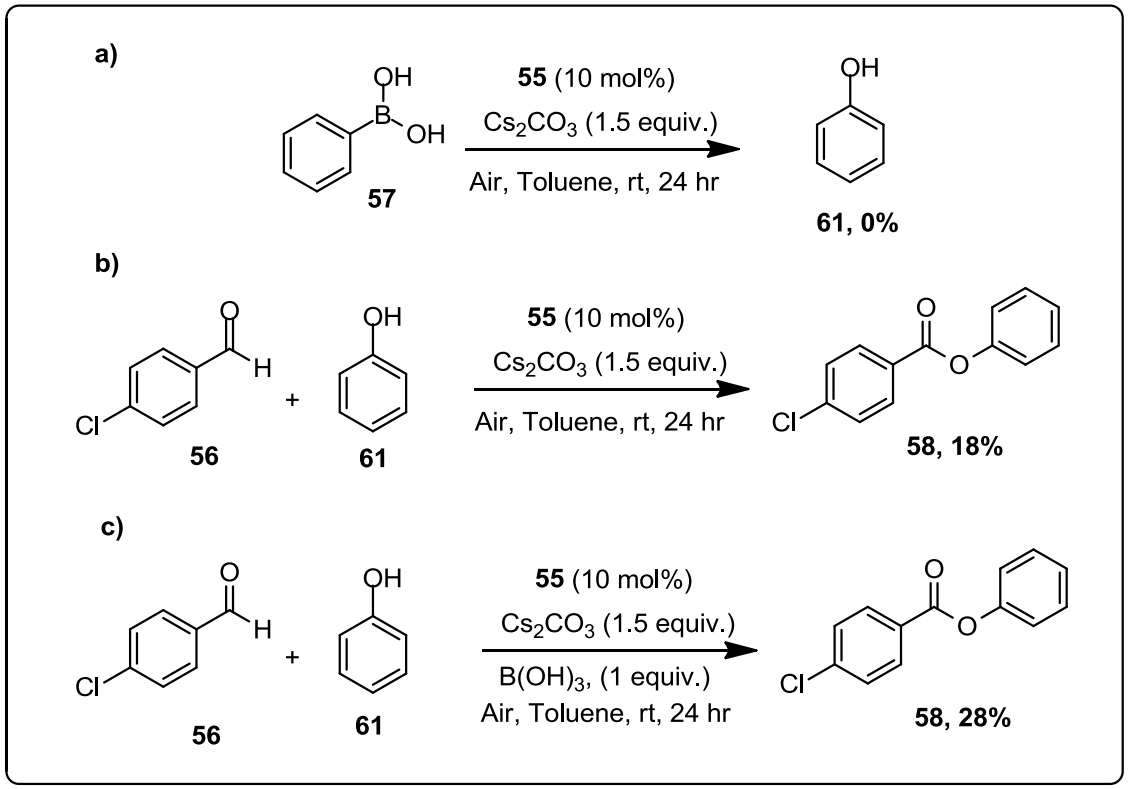


[a] Reaction conditions: R-CHO/R-B(OH)$_2$ = 1.3/1, 0.06 M of R-CHO in toluene, rt = 31-33 ^{o}C. [b] Performed at 60 ^{o}C.

Scheme 25: Oxidative esterification reaction of aldehydes with phenyl boronic acid[a]

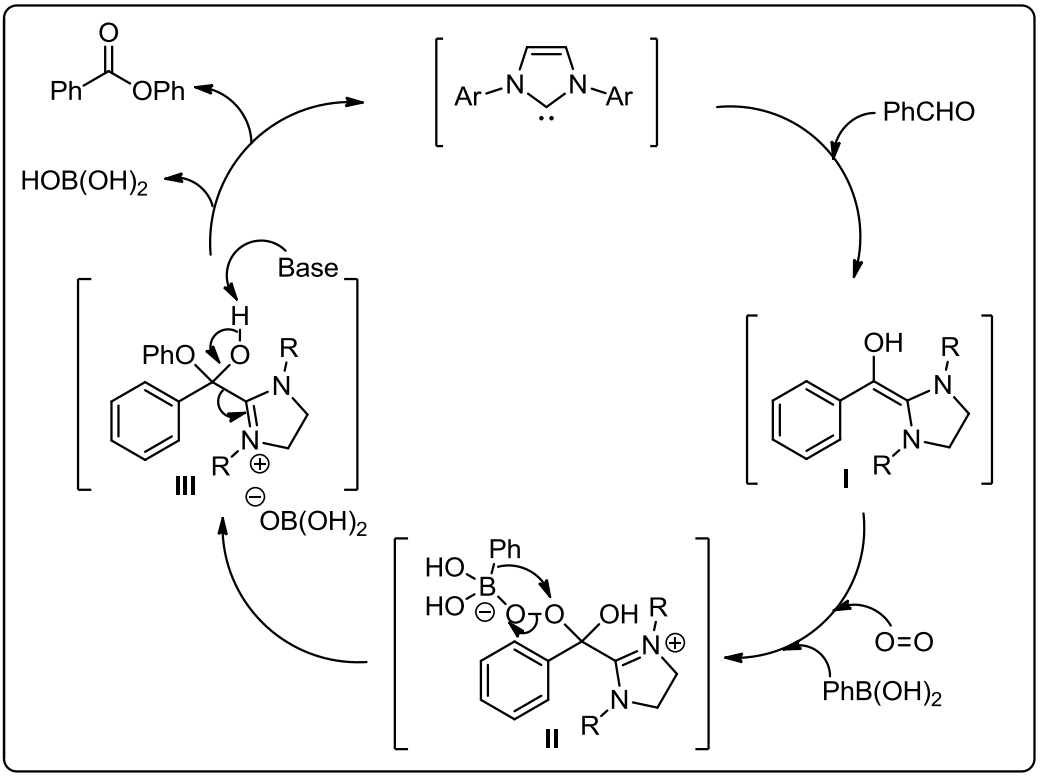
In order to comprehend the mechanism in detail, the reaction between **56** and **57** under standard reaction conditions was carefully monitored by TLC at equal time intervals. Interestingly, phenol was not detected during the course of the reaction, which is in parallel with

the findings reported by Gois' group.[35] Moreover, phenol was not formed at all when the reaction was conducted in the absence of aldehyde, without changing other parameters. Although, NHC-metal catalysed oxidative esterification of aldehydes with phenol at elevated temperature has been reported,[36] we strongly believe that phenol is not involved as an intermediate in our methodology based on the above experimental observations. To obtain a better understanding of this transformation, an experiment was run using **56** and phenol under optimal aerobic conditions, but the ester **58** was obtained only in 18% yield even after stirring the reaction for a long period (over 24 h). Addition of 1 equivalent of boric acid to the reaction mixture helped in improving the yield of **58** but not significantly (28% yield after 24 h) (Scheme 26).[37] But, as discussed earlier, the reaction of phenylboronic acid with **56** under the same conditions provided **58** in quantitative yield in less than 5 h (Entry 17, Table 1). This clearly indicates a different kind of mechanism is operating in the boronic acid case, without the involvement of phenol as an intermediate.



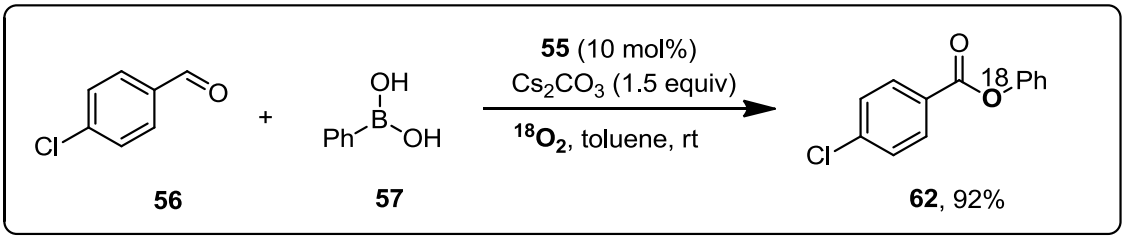
Scheme 26: Control experiments

Based on the above experimental observations, a plausible mechanism has been proposed (Scheme 27). We presume that the intermediate **II** is formed by the reaction of **I** with oxygen and boronic acid, and decomposes rapidly to **III** i.e., transfer of the phenyl group to the peroxy linkage and formation of the borate anion, both are probably occurring in a concerted manner. Finally, intermediate **III** expels the NHC along with the ester and boric acid.



Scheme 27: Plausible mechanism for the oxidative esterification

To confirm the participation of atmospheric oxygen in this transformation, an isotopic labeling experiment was conducted using $^{18}O_2$ (Scheme **28**).



Scheme 28: Isotopic labeling experiment using $^{18}O_2$

The HRMS spectrum clearly showed the presence of the ester **62** (calcd for $C_{13}H_9ClO^{18}O$ 235.0412 [M + H], found 235.0419). The EI MS spectrum also showed a strong peak at m/z 234.91, which is attributed to the $[M + H]^+$ ion of ester **62**. The fragmentation pattern showed the base peak at m/z 139.03 (100%), which could be attributed to the $[ClC_6H_4CO]^+$ fragment. An additional peak appeared at m/z 141.00 (34% with respect to the base peak), which could be due to the presence of the chlorine isotope or oxygen isotope of $[ClC_6H_4CO]^+$. But, we strongly believe that the peak at m/z 141.00 does not correspond to the $[ClC_6H_4CO^{18}]^+$ fragment because the peak (at m/z 143.00) for the chlorine isotope of $[ClC_6H_4CO^{18}]^+$ was not at all observed in the spectrum. So, it is conclusive from the mass spectral data that the oxygen labeling did not take place at the carbonyl oxygen, which sturdily supports the concerted mechanism operating in the reaction (Scheme **27**). The above experiment also indicates the involvement of atmospheric oxygen in the esterification reaction.

4.5) Conclusion

The studies described in this article have led to the development of a mild and efficient method for the oxidative esterification of aromatic aldehydes using NHC as an organocatalyst under aerobic conditions. The practicability of this methodology has been demonstrated using various boronic acids and aldehydes.

4.6) Experimental details

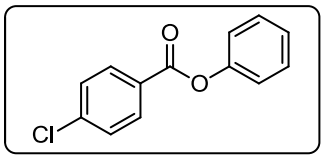
General Methods:

All reactions were carried out in open flask. All the reagents including *N*-heterocyclic carbene precursors used were purchased from commercial sources and used as such. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using 400 MHz Bruker FT-NMR spectrometer. Chemical shifts values are reported in parts per million relative to TMS. High Resolution Mass spectra (HRMS) were recorded on a Bruker maXis spectrometer. The IR spectra were recorded on a Perkin – Elmer FT IR spectrometer. Thin layer chromatography was performed on Merck Silica gel 60 F_{254} TLC plates using Hexane/EtOAc mixture as an eluent. Column chromatography was carried out through silica gel (100-200 mesh).

General procedure for NHC catalysed aerobic oxidation of aryl aldehydes with aryl boronic acids:

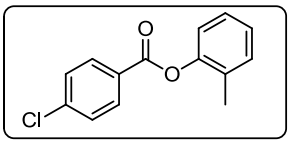
Aromatic aldehyde (91 mg, 0.65 mmol) was added to a suspension of boronic acid (60 mg, 0.5 mmol), NHC **55** (20 mg, 0.05 mmol) and cesium carbonate (244.4 mg, 0.75 mmol) in Toluene (5 mL) at room temperature. Stirring was continued at room temperature or at 60 ºC (in some cases) under open atmosphere (in the presence of air) until the reaction was complete. The reaction mass was then filtered through a pad of celite®, washed with EtOAc (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified through silical gel column using EtOAc/Hexane mixture as an eluent.

Phenyl-4-chloro benzoate (58):[29]



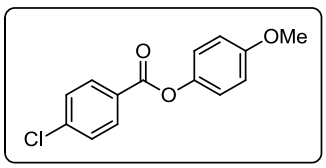
99% Yield. White solid; mp 104 - 106 ºC; FT IR 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.47 – 7.43 (m, 2H), 7.32 – 7.28 (m, 1H), 7.24 – 7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 150.8, 140.1, 131.6, 129.6, 128.9, 128.1, 126.1, 121.6.

2-Methyl phenyl-4-chloro benzoate (59a):



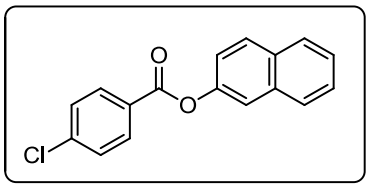
85% Yield. Semi-solid; FT IR 1745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.21 – 7.17 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 149.4, 140.2, 131.6, 131.3, 130.2, 129.0, 128.0, 127.1, 126.3, 121.9, 16.3; HRMS (ESI) calcd for $C_{14}H_{11}ClO_2Na$ 269.0448, found 269.0345.

4-Methoxy phenyl-4-chloro benzoate (59b):[30]



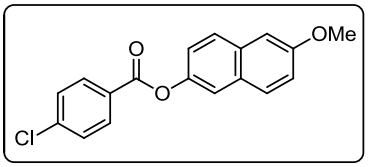
84% Yield. White solid; mp 103 - 105 ºC; FT IR 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 157.4, 144.2, 140.1, 131.5, 128.9, 128.1, 122.4, 114.6, 55.6.

2-Naphthyl-4-chloro benzoate (59c):[31]



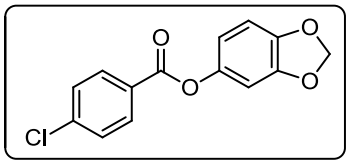
84% Yield. White solid; mp 122 - 124 ºC; FT IR 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.7 Hz, 2H), 7.92 (d, J = 8.9 Hz, 1H), 7.90 – 7.84 (m, 2H), 7.70 (d, J = 2.2 Hz, 1H), 7.55 – 7.48 (m, 4H), 7.36 (dd, J = 8.8, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 148.4, 140.2, 133.8, 131.6, 131.5, 129.6, 129.0, 128.0, 127.8, 127.7, 126.7, 125.9, 121.1, 118.7.

6-Methoxy naphthyl-4-chloro benzoate (59d):



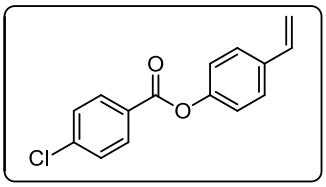
92% Yield. White solid; mp 153 - 155 ºC; FT IR 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.9 Hz, 2H), 7.80 (d, J = 8.9 Hz, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.31 (dd, J = 8.8, 2.4 Hz, 1H), 7.21 (d, J = 2.5 Hz, 1H), 7.18 (s, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 157.7, 146.8, 140.2, 132.8, 131.6, 129.1, 129.0, 128.9, 128.2, 128.1, 121.4, 119.6, 118.6, 105.8, 55.4; HRMS (ESI) calcd for $C_{18}H_{13}ClO_3Na$ 335.0553, found 335.0445.

Benzo[d][1,3]dioxol-6-yl 4-chlorobenzoate (59e):



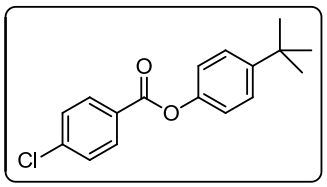
98% Yield. White solid; mp 92 – 94 ºC; FT IR 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 2.3 Hz, 1H), 6.66 (dd, J = 8.4, 2.3 Hz, 1H), 6.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 148.1, 145.6, 145.0, 140.2, 131.5, 128.9, 127.9, 114.0, 108.1, 103.8, 101.8; HRMS (ESI) calcd for $C_{14}H_9ClO_4Na$ 299.0189, found 299.0082.

4-Vinylphenyl-4-chlorobenzoate (59f):[32]



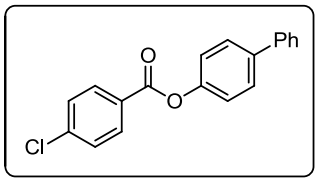
99% Yield. White solid; mp 104 - 106 ºC; FT IR 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.7 Hz, 2H), 7.52 – 7.46 (m, 4H), 7.18 (d, J = 8.6 Hz, 2H), 6.74 (dd, J = 17.6, 10.9 Hz, 1H), 5.74 (dd, J = 7.6, 0.7 Hz, 1H), 5.28 (dd, J = 10.9, 0.7 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 150.3, 140.2, 135.9, 135.6, 131.6, 129.0, 127.9, 127.3, 121.7, 114.2.

4-tert-Butylphenyl-4-chlorobenzoate (59g):



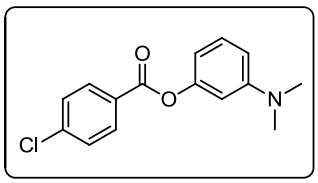
86% Yield. White solid; mp 117 – 118 ºC; FT IR 1747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 148.9, 148.4, 140.0, 131.5, 128.9, 128.2, 126.5, 120.9, 34.5, 31.4; HRMS (ESI) calcd for $C_{17}H_{17}ClO_2Na$ 311.0917, found 311.0809.

(4-Phenyl) phenyl-4-chlorobenzoate (59h):[33]



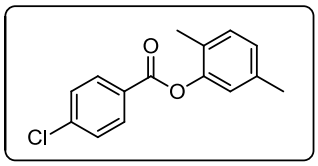
90% Yield. White solid; mp 169 - 171 ºC; FT IR 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.62 – 7.60 (m, 2H), 7.52 (d, J = 8.7 Hz, 2H), 7.49 – 7.45 (m, 2H), 7.40 – 7.36 (m, 1H), 7.30 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 150.2, 140.3, 140.2, 139.2, 131.6, 129.0, 128.9, 128.3, 128.0, 127.4, 127.2, 121.9.

3-(Dimethylamino) phenyl-4-chlorobenzoate (59i):



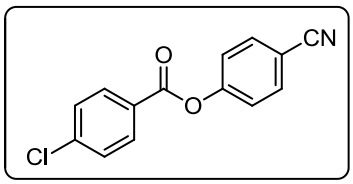
80% Yield. White solid; mp 142 – 144 ºC; FT IR 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 7.28 (t, J = 8.2 Hz, 1H), 6.64 (dd, J = 8.4, 1.9 Hz, 1H), 6.57 – 6.53 (m, 2H), 2.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 151.9, 151.7, 139.9, 131.5, 129.8, 128.9, 128.3, 110.2, 109.3, 105.5, 40.5; HRMS (ESI) calcd for $C_{15}H_{14}ClNO_2Na$ 298.0713, found 298.0605.

2,5-dimethylphenyl-4-chlorobenzoate (59j):



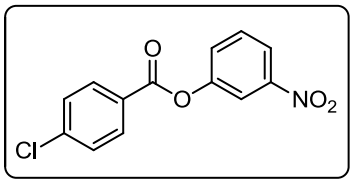
78% Yield. Semi-solid; FT IR 1746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 7.7 Hz, 1H), 7.02 (d, J = 7.7 Hz, 1H), 6.98 (s, 1H), 2.37 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 149.2, 140.1, 137.0, 131.5, 130.9, 129.0, 128.0, 127.0, 126.9, 122.4, 20.9, 15.8; HRMS (ESI) calcd for $C_{15}H_{13}ClO_2Na$ 283.0604, found 283.0496.

4-Cyano phenyl-4-chlorobenzoate (59k):[30]



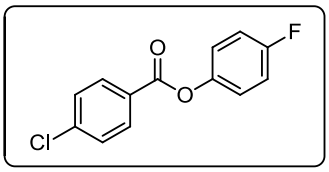
70% Yield. White solid; mp 110 - 112 ºC; FT IR 2360, 1738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 154.0, 140.8, 133.8, 131.7, 129.2, 127.1, 122.9, 118.2, 110.1.

3-Nitro phenyl-4-chlorobenzoate (59l):[34]



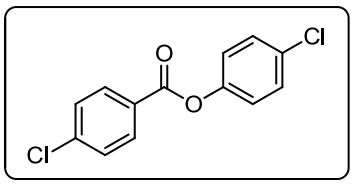
68% Yield. White solid; mp 134 - 136 ºC; FT IR 1745, 1523, 1358 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.14 (m, 2H), 8.15 (d, J = 8.6 Hz, 2H), 7.66 – 7.58 (m, 2H), 7.53 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 151.0, 148.9, 140.9, 131.7, 130.2, 129.2, 128.2, 127.0, 121.0, 117.5.

4-Fluoro phenyl-4-chlorobenzoate (59m):[35]



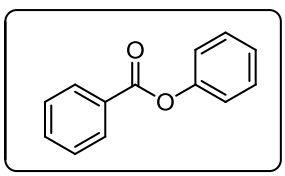
88% Yield. White solid; mp 96 - 98 ºC; FT IR 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.21 – 7.09 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 161.6, 146.6, 140.3, 131.6, 129.0, 127.7, 123.1, 123.0, 116.3, 116.1.

4-Chloro phenyl-4-chlorobenzoate (59n):[36]



95% Yield. White solid; mp 96 - 98 ºC; FT IR 1744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 149.2, 140.4, 131.6, 131.5, 129.6, 129.0, 127.6, 123.0.

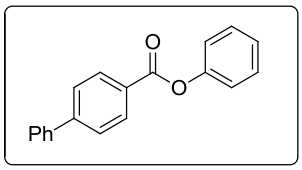
Phenyl benzoate (60a):[29]



86% Yield. White solid; mp 68 - 70 ºC; FT IR 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.22 (m, 2H), 7.68 – 7.64 (m, 1H), 7.56 –

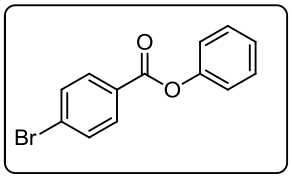
7.52 (m, 2H), 7.48 – 7.43 (m, 2H), 7.32 – 7.28 (m, 1H), 7.25 – 7.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 151.0, 133.6, 130.2, 129.6, 129.5, 128.6, 125.9, 121.7.

Phenyl-(4-phenyl) benzoate (60b):[37]



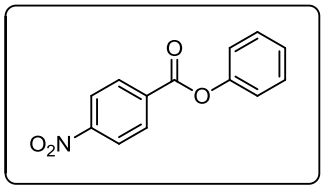
97% Yield. White solid; mp 160 - 162 ºC; FT IR 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.66 – 7.63 (m, 2H), 7.50 – 7.38 (m, 5H), 7.29 – 7.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 151.0, 146.4, 139.9, 130.7, 129.5, 129.0, 128.4, 128.3, 127.4, 127.3, 125.9, 121.8.

Phenyl-(4-bromo) benzoate (60c):[29]



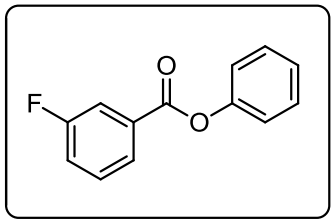
99% Yield. White solid; mp 120 - 122 ºC; FT IR 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 8.6 Hz, 2H), 7.48 – 7.42 (m, 2H), 7.32 – 7.28 (m, 1H), 7.23 – 7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 150.8, 131.9, 131.7, 129.6, 128.9, 128.5, 126.1, 121.6.

Phenyl-(4-nitro) benzoate (60d):[38]



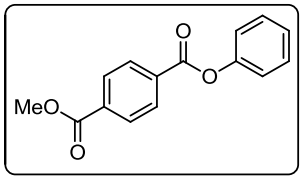
95% Yield. White solid; mp 129 - 131 ºC; FT IR 1741, 1520, 1347 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.36 (m, 4H), 7.50 – 7.45 (m, 2H), 7.35 – 7.31 (m, 1H), 7.26 – 7.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 150.9, 150.5, 135.0, 131.3, 129.7, 126.4, 123.7, 121.4.

Phenyl-(3-fluoro) benzoate (60e):[39]



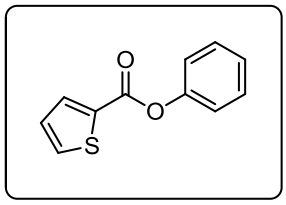
90% Yield. White solid; mp 53 - 55 ºC; FT IR 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 8.01 (m, 1H), 7.91 – 7.88 (m, 1H), 7.54 – 7.43 (m, 3H), 7.38 – 7.28 (m, 2H), 7.24 – 7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 150.8, 130.3, 130.2, 129.6, 126.1, 125.9, 121.6, 120.8, 120.6, 117.2, 116.9.

Phenyl-(4-methylester) terephalate (60f):[29]



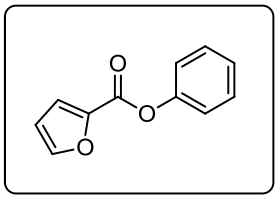
96% Yield. White solid; mp 110 - 112 ºC; FT IR 1734, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.6 Hz, 2H), 8.18 (d, J = 8.6 Hz, 2H), 7.48 – 7.43 (m, 2H), 7.33 – 7.22 (m, 3H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 164.4, 150.8, 134.5, 133.4, 130.2, 129.7, 129.6, 126.2, 121.6, 52.55.

Phenyl thiophene-2-carboxylate (60g):[40]



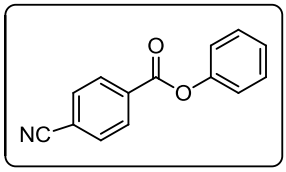
82% Yield. Semi-solid; FT IR 1741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 3.8, 1.2 Hz, 1H), 7.68 (d, J = 5.0 Hz, 1.3 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.31 – 7.22 (m, 2H), 7.19 (dd, J = 5.0, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 150.6, 134.7, 133.5, 132.9, 129.5, 128.1, 126.0, 121.7.

Phenyl furan-2-carboxylate (60h):[38]



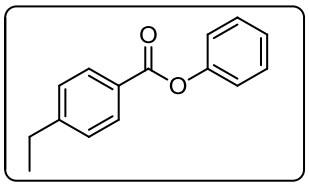
60% Yield. White solid; mp 54 - 56 ºC; FT IR 1738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 1.7, 0.9 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.40 (dd, J = 3.5, 0.9 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.24 – 7.21 (m, 2H), 6.61 (dd, J = 3.5, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 150.2, 147.1, 144.0, 129.5, 126.1, 121.6, 119.4, 120.2.

Phenyl-(4-cyano) benzoate (60i):[29]



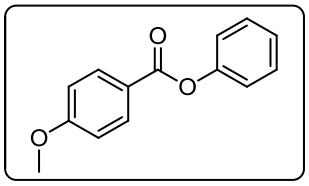
93% Yield. White solid; mp 89 - 91 ºC; FT IR 2233, 1741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.2 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H), 7.48 – 7.45 (m, 2H), 7.34 – 7.30 (m, 1H), 7.23 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 150.5, 133.4, 132.4, 130.7, 129.7, 126.4, 121.5, 117.9, 117.0.

Phenyl-(4-ethyl) benzoate (60j):[41]



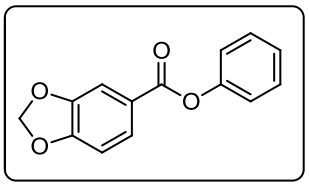
80% Yield. Semi-solid; FT IR 1723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.3 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.32 – 7.20 (m, 3H), 2.76 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 151.0, 150.6, 130.4, 129.5, 128.1, 127.0, 125.8, 121.8, 29.1, 15.3.

Phenyl-(4-methoxy) benzoate (60k):[38]



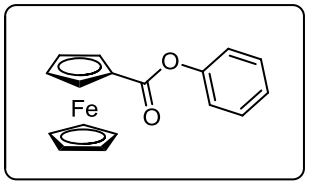
40% Yield. White solid; mp 74 - 76 ºC; FT IR 1727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.6 Hz, 2H), 7.47 – 7.43 (m, 2H), 7.31 – 7.27 (m, 1H), 7.23 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 163.9, 151.1, 132.3, 129.5, 125.7, 121.9, 121.8, 113.9, 55.5.

Phenyl benzo[d][1,3]dioxole-5-carboxylate (60l):[29]



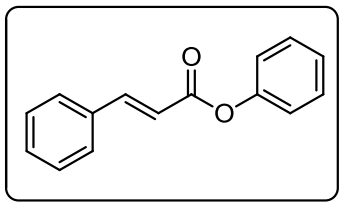
75% Yield. White solid; mp 73 - 75 ºC; FT IR 1724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.2, 1.7 Hz, 1H), 7.63 (d, J = 1.7 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.30 – 7.26 (m, 1H), 7.22 – 7.20 (m, 2H), 6.91 (d, J = 8.2 Hz, 1H), 6.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 152.2, 151.0, 147.9, 129.5, 126.2, 125.8, 123.5, 121.8, 109.9, 108.2, 101.9.

Phenyl-(ferrocene)-1-carboxylate (60m):[42]



33% Yield. White solid; mp 117 - 119 ºC; FT IR 1723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.31 – 7.27 (m, 1H), 7.22 (d, J = 8.0 Hz, 2H), 5.00 (s, 2H), 4.53 (s, 2H), 4.34 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 150.9, 129.5, 125.6, 121.8, 71.9, 70.7, 70.1, 69.9.

(E)-Phenyl cinnamate (60n):[38]

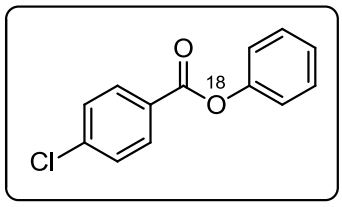


25% Yield. White solid; mp 76 - 77 ºC; FT IR 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 16.0 Hz, 1H), 7.63 – 7.59 (m, 2H), 7.46 – 7.39 (m, 5H), 7.29 – 7.22 (m, 1H), 7.20 – 7.17 (m, 2H), 6.65 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 150.6, 146.6, 134.2, 130.7, 129.5, 129.0, 128.3, 125.8, 121.6, 117.3.

Isotopic labelling experiment:

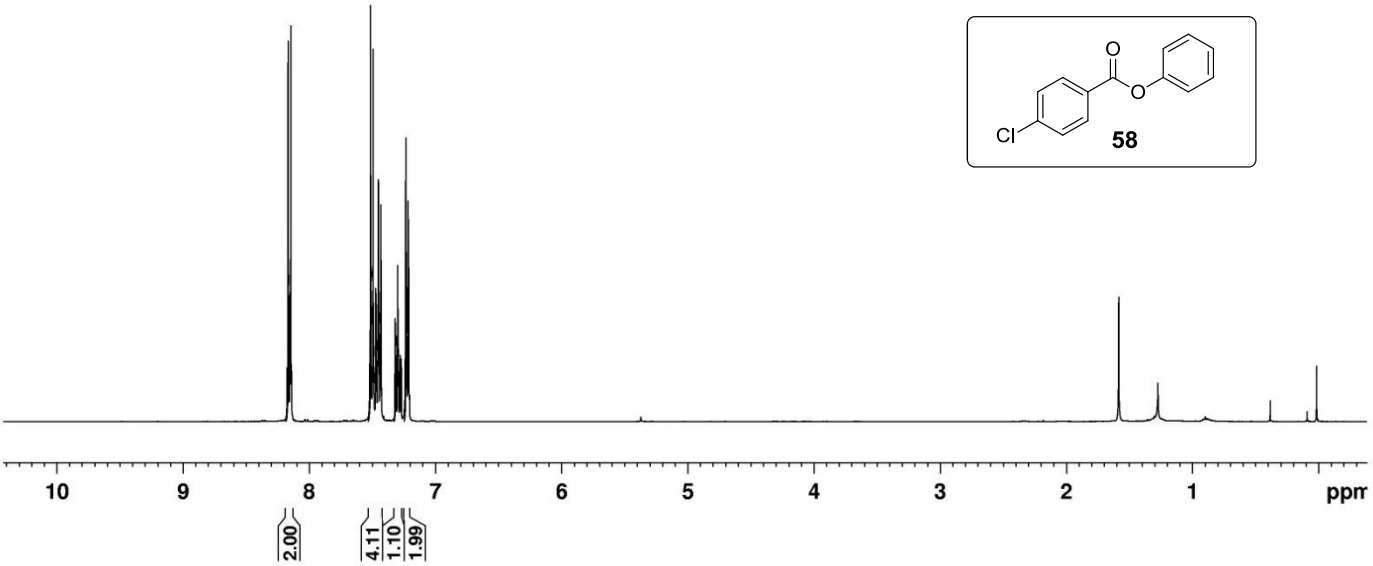
A solution of *p*-chlorobenzaldehyde (60.0 mg, 0.43 mmol) and phenyl boronic acid (40.0 mg, 0.33 mmol) in toluene (2 mL) was added to a suspension of NHC **55** (14.0 mg, 0.033 mmol) and cesium carbonate (160.0 mg, 0.49 mmol) in Toluene (2 mL) at room temperature. The reaction mixture was stirred under $^{18}O_2$ atmosphere at room temperature for 5 h. The reaction mass was then filtered through a pad of celite®, washed with EtOAc (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified through silical gel column using EtOAc/Hexane mixture to give **61** as a white solid.

Phenyl-4-chloro benzoate (62):

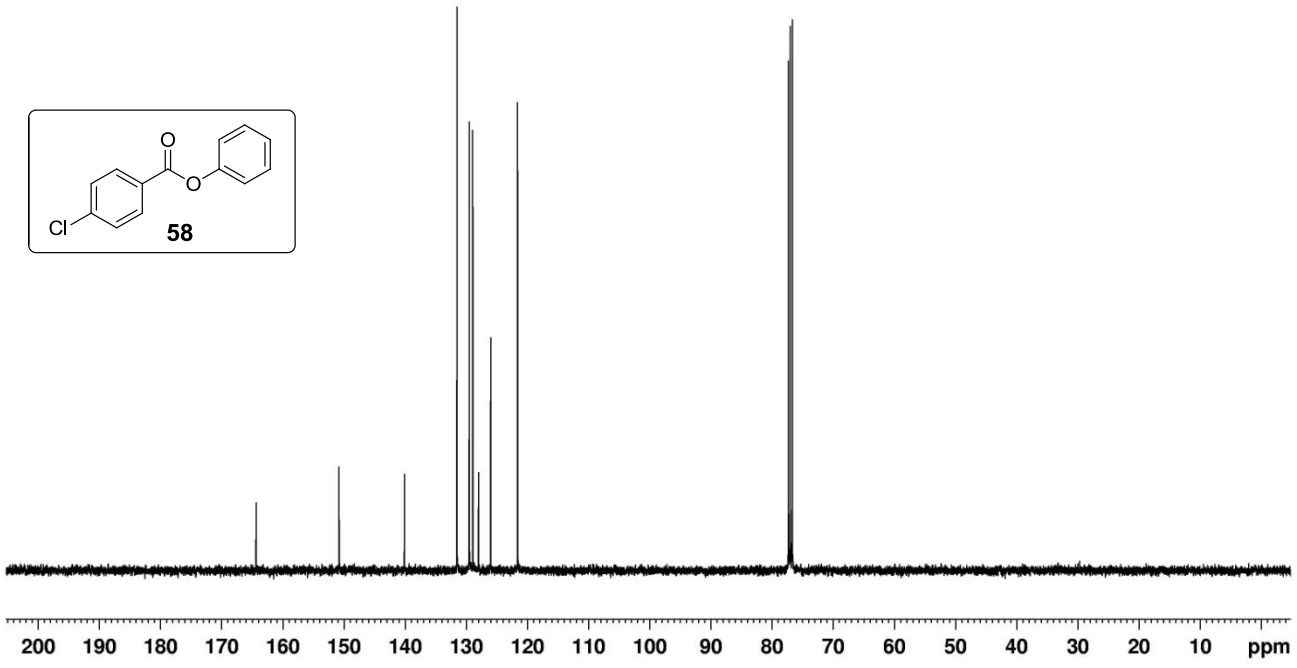


Yield 92%; White solid; mp 104 - 106 ºC; FT IR 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.32 – 7.27 (m, 1H), 7.24 – 7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 150.8, 140.1, 131.6, 129.6, 128.9, 128.0, 126.1, 121.6; HRMS (ES) calcd for $C_{13}H_9ClO_2$ 235.0412 [M+H], found 235.0419; EI MS: *m/z* 234.91 $(M + H)^+$, 141.00, 139.03 (base peak).

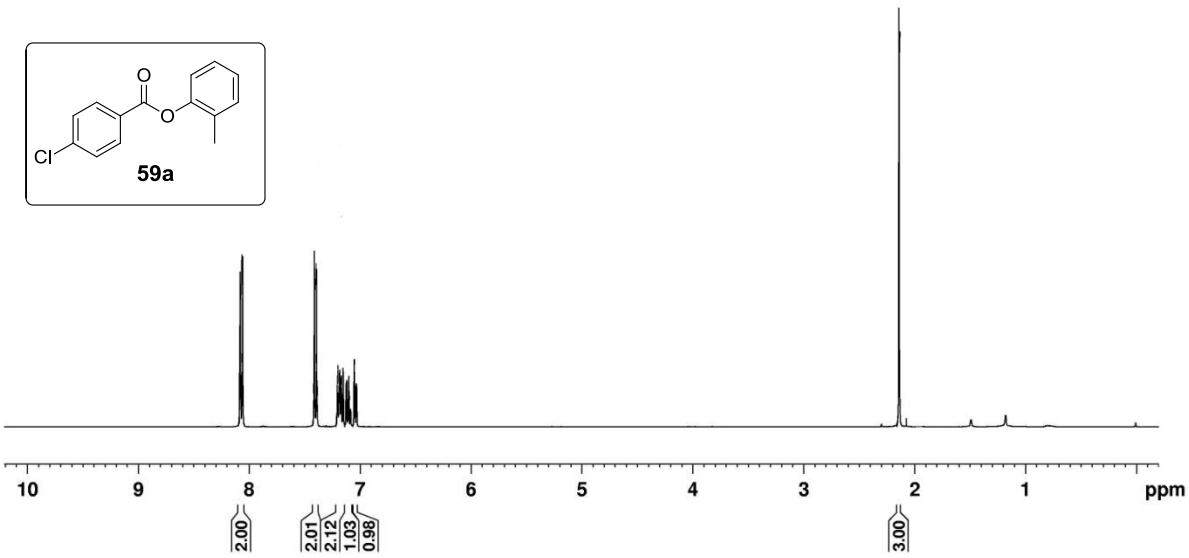
^{1}H NMR Spectrum of **58**



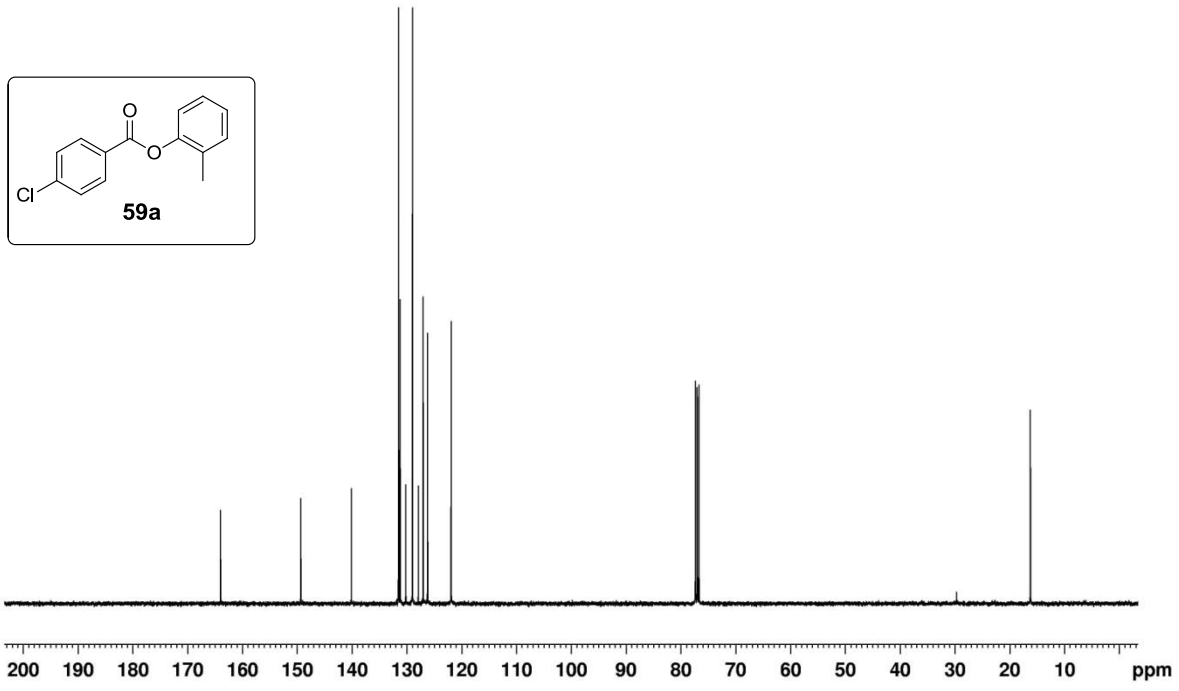
^{13}C NMR Spectrum of **58**



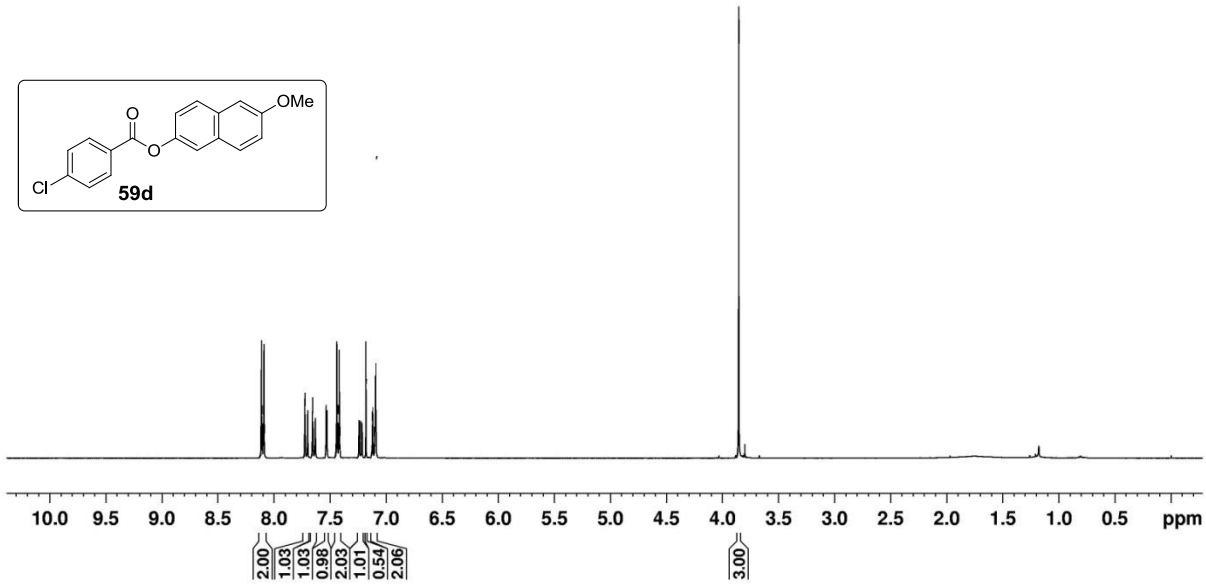
^{1}H NMR Spectrum of **59a**



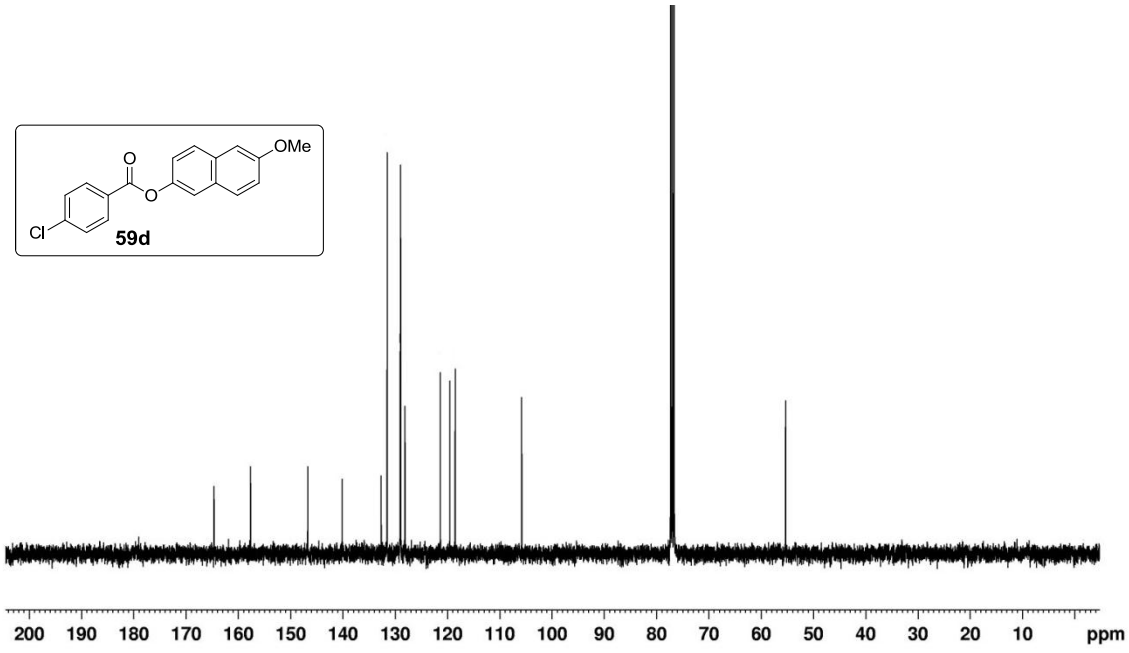
^{13}C NMR Spectrum of **59a**



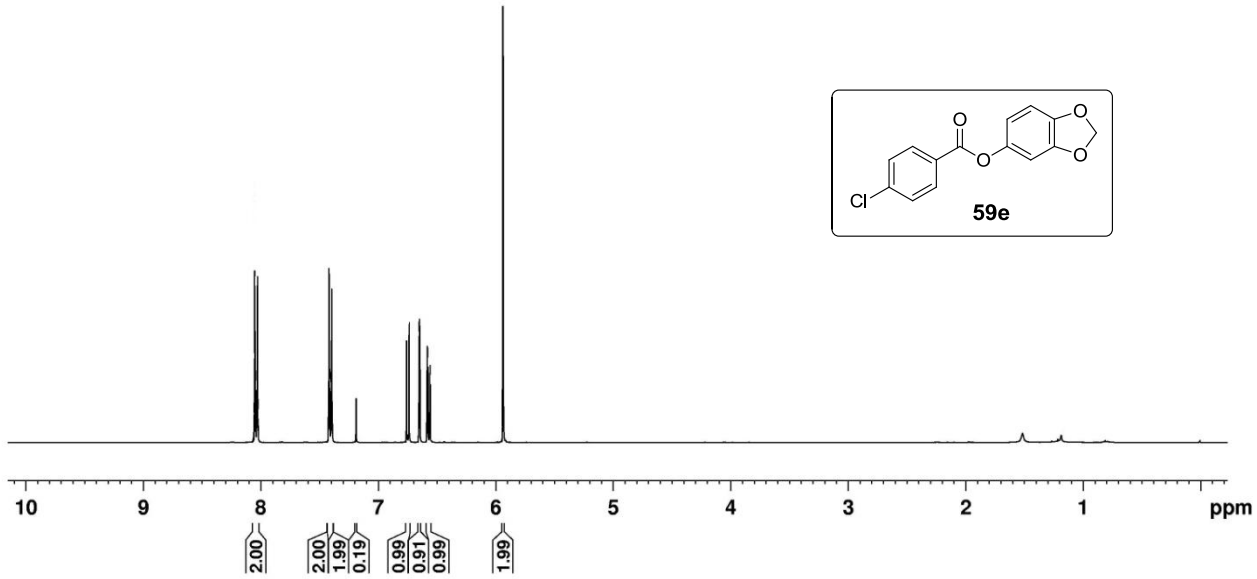
^{1}H NMR Spectrum of **59d**



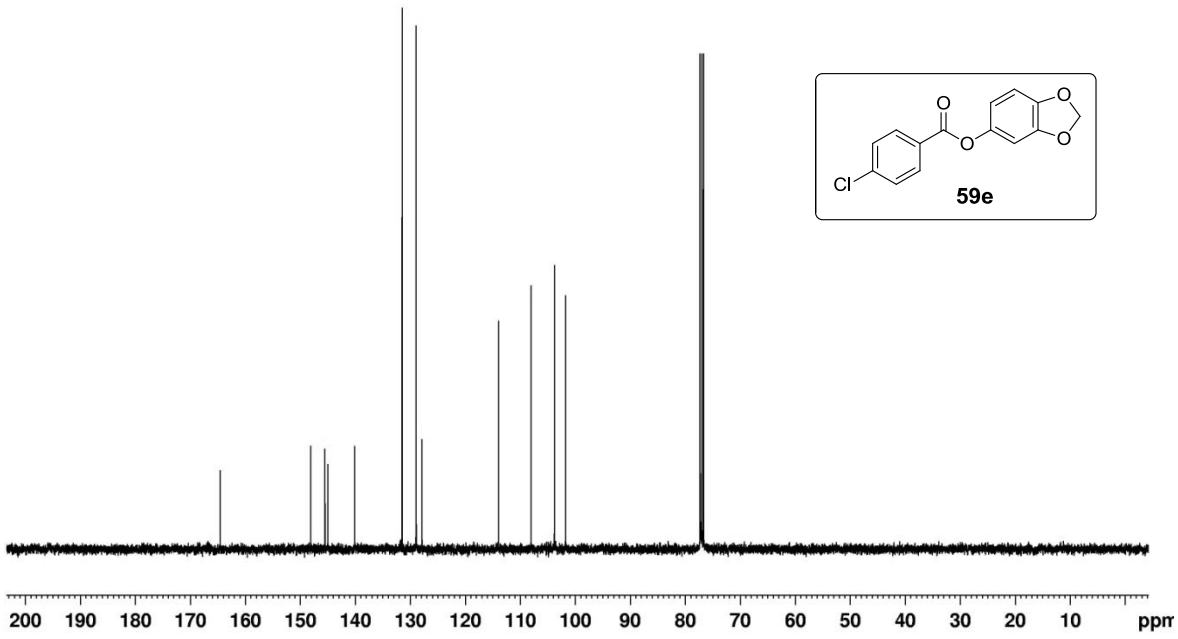
^{13}C NMR Spectrum of **59d**



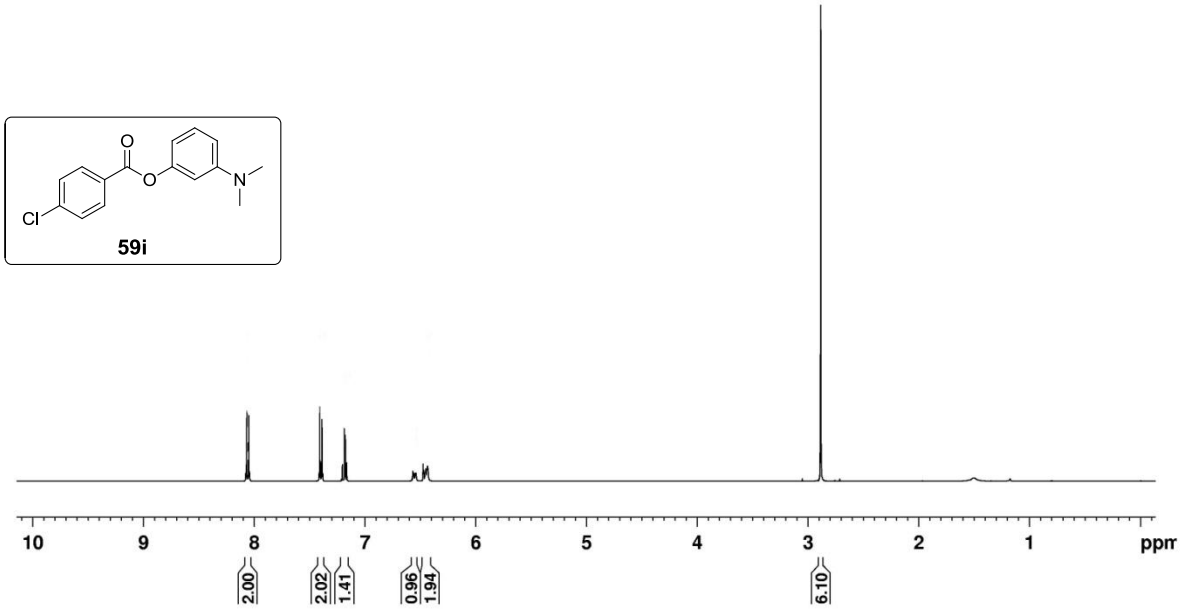
^{1}H NMR Spectrum of **59e**



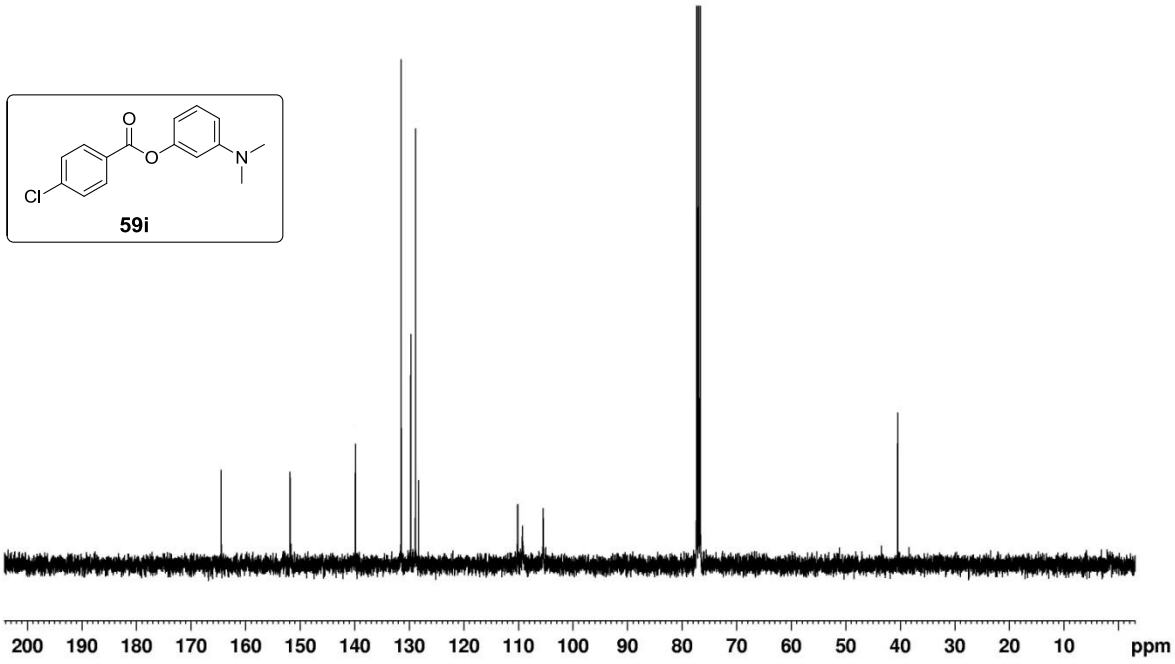
^{13}C NMR Spectrum of **59e**



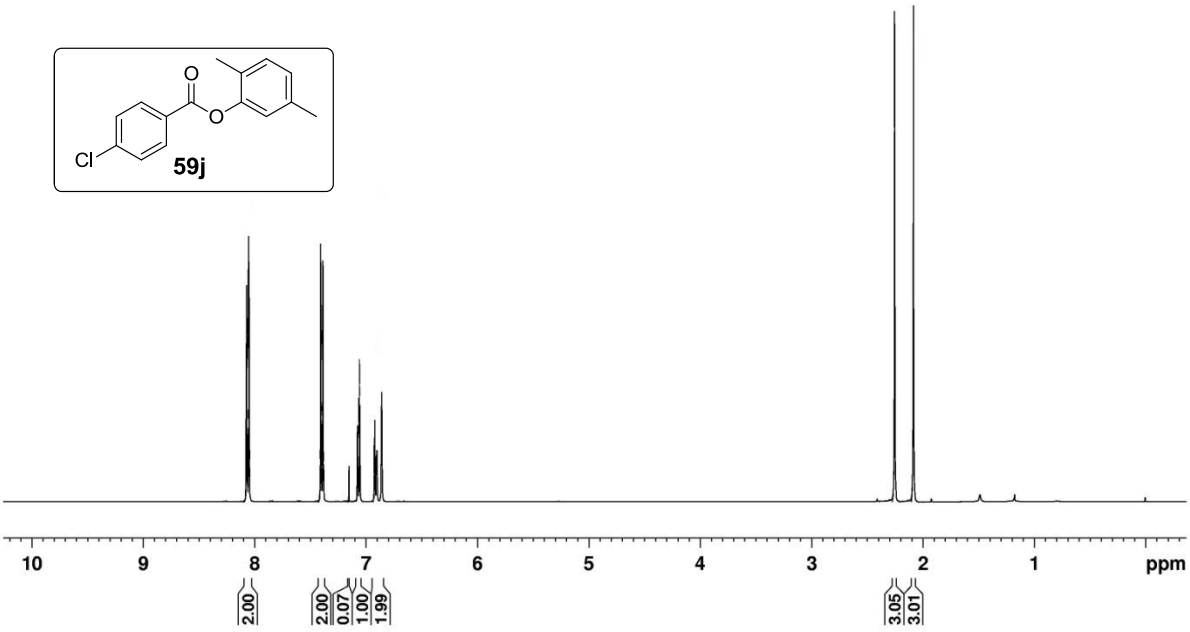
^{1}H NMR Spectrum of **59i**



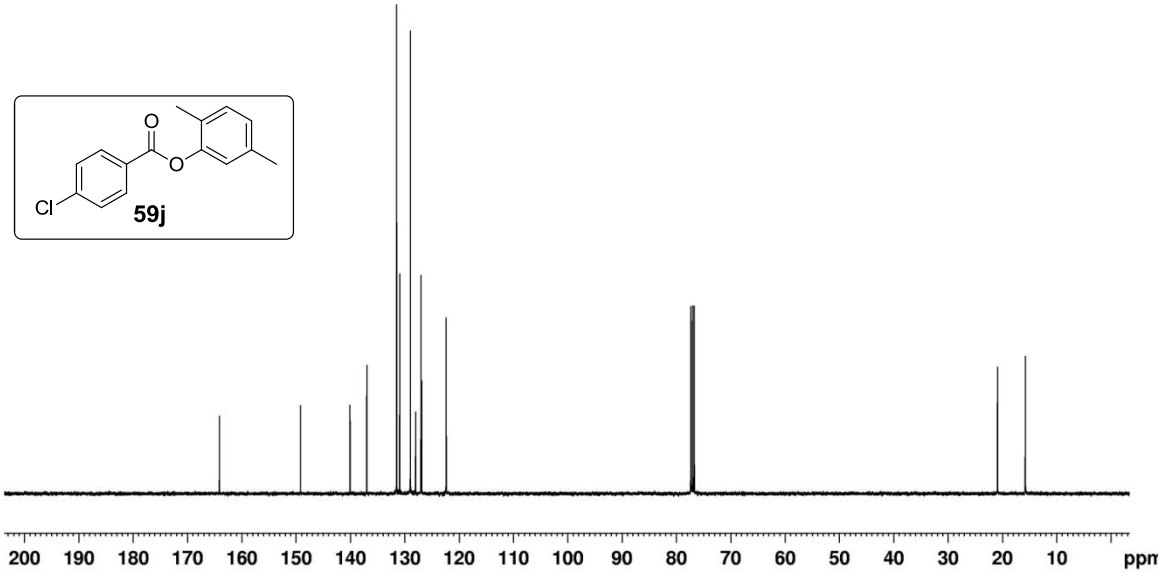
^{13}C NMR Spectrum of **59i**



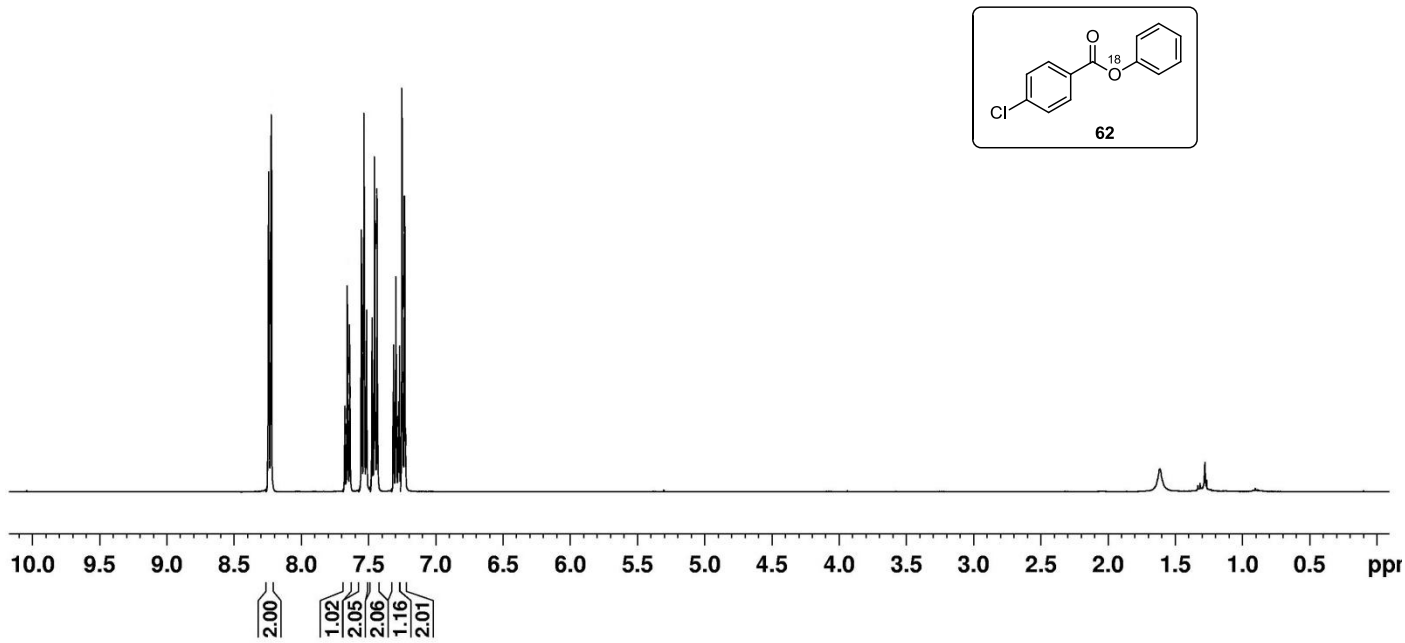
^{1}H NMR Spectrum of **59j**



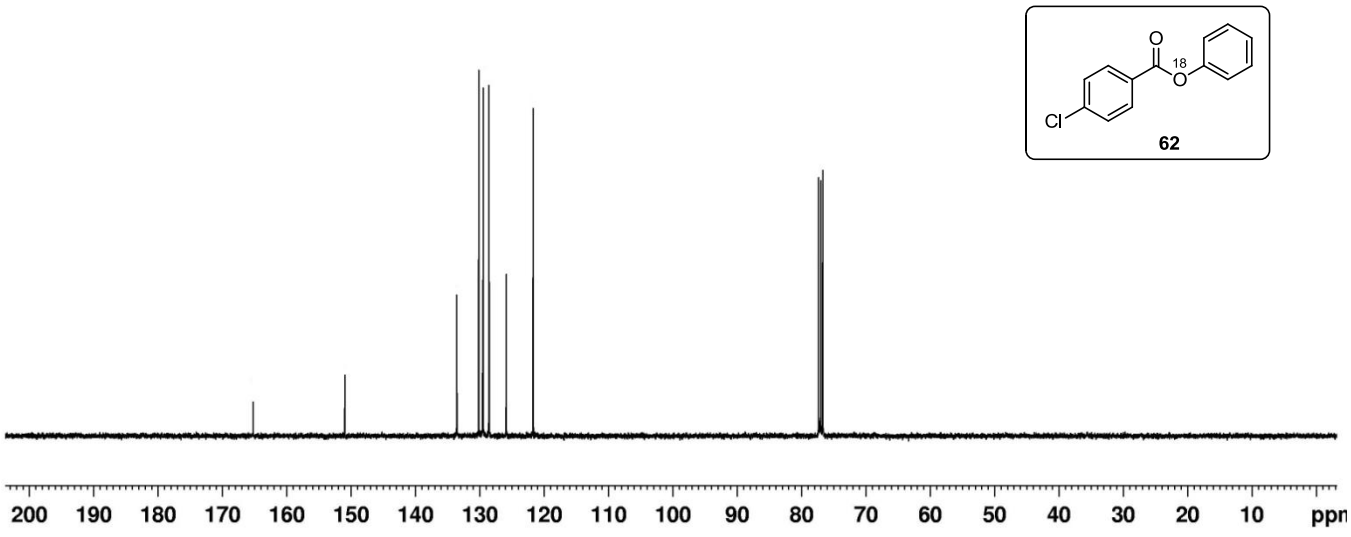
^{13}C NMR Spectrum of **59j**



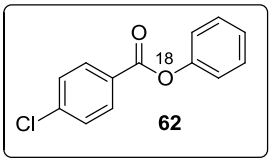
^{1}H NMR Spectrum of **62**



^{13}C NMR Spectrum of **62**



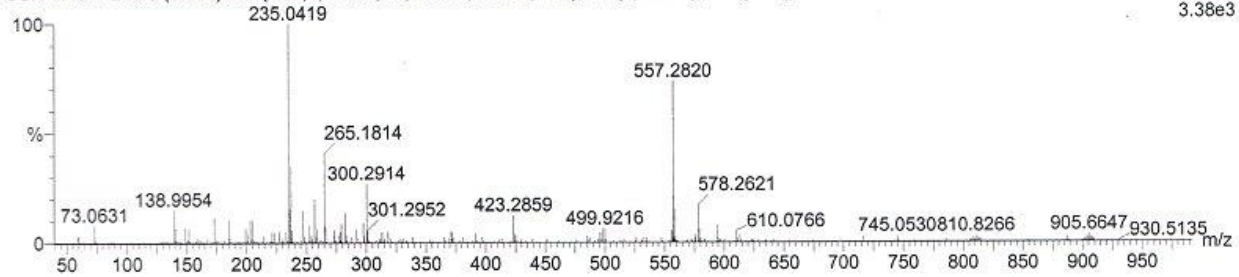
HRMS Spectrum of **62**



Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

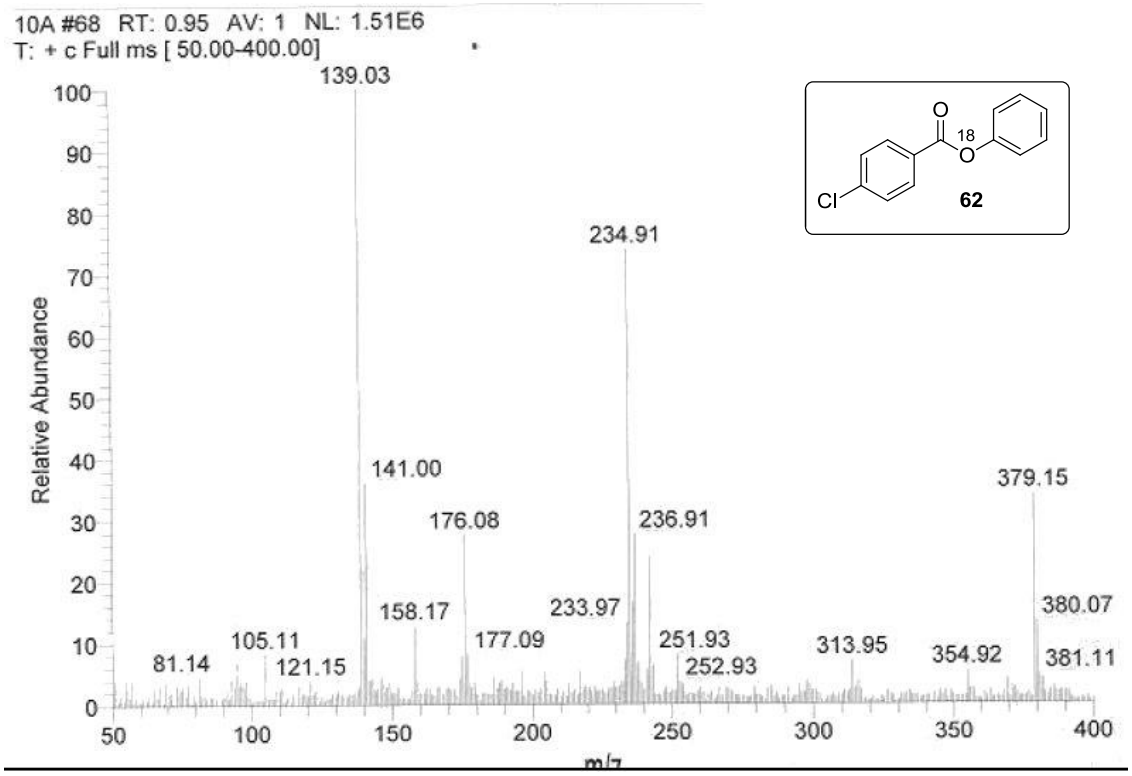
Monoisotopic Mass, Odd and Even Electron Ions
40 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Micromass : Q-Tof micro (YA-105) Dept. Of Chemistry I.I.T.(B) 17-Oct-201111:22:45
C13H9ClO2(O-16; O-18)
SSK-VAS-4-210 3 (0.030) AM (Cen,5, 80.00, Ht,5000.0,556.28,1.00); Sb (5,40.00); Cm (1:41) TOF MS ES+
3.38e3



Minimum:				-1.5		
Maximum:		200.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
235.0419	235.0412	0.7	3.0	8.5	1	C13 H10 16O 18O Cl

ES-MS Spectrum of **62**



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28. Boric acid was added in this experiment to make the reaction condition identical with our optimised reaction condition; because boric acid was the by-product in the case of reactions involving boronic acids under oxidative conditions.
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List of publications:

1) **Arde, P**; Anand, R. V. *RSC Adv*. **2016**, *6*, 77111.
2) **Arde, P**; Anand, R. V. *Org. Biomol. Chem*. **2016**, *14*, 5550. (*Invited Article for a Themed issue"New Talent"*)
3) **Arde, P**.; Reddy, V.; Anand, R. V. *RSC Adv*. **2014**, *4*, 49775.
4) **Arde, P**.; Ramanjaneyulu, B. T.; Reddy, R.; Saxena, A.; Anand, R. V. *Org. Biomol. Chem*. **2012**, *10*, 848.

   -This article was one of the top ten most accessed articles in December 2011

   -This article has been featured in SYNFACTS (Synfacts 2012, 8, 0216)
5) Ramanjaneyulu, B. T.; Reddy, V.; **Arde, P.**; Mahesh, S.; Anand, R. V. *Chem. Asian J.* **2013**, *8*, 1489.

Conferences:

- Attended the *National Seminar on Biocatalysis and Biomimetic Catalysis in Organic Synthesis* organized by Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University (Dr. B.A.M.U), Aurangabad, Maharashtra, India (20-21st March 2009).
- Delivered a short talk in the *7th Junior National Organic Symposium (J-NOST)* held at the Department of Chemistry, Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (15-18th December, 2011).
- Delivered a short talk in the *9th Junior National Organic Symposium (J-NOST)* held at the Department of Chemistry, Indian Institute of Science Education and Research (IISER) Bhopal, India (4-6th December, 2013).
- Attended the *National Seminar on Crystallography 43A* held at Department of Chemistry, Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (28-30th March 2014).

Curriculum Vitae

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Education

2011-Present Ph. D. in Organic Chemistry (Indian Institute of Science Education and Research Mohali, Punjab, India

2007-2009 M.Sc. in Chemistry (Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India

2005-2007 B.Sc. in Analytical Chemistry from Shree S. B. E. S. College Aurangabad (B.A.M.U. Aurangabad), India

Doctoral Detail

Thesis Title: "*Discovering new organocatalytic organic transformations using N-heterocyclic carbene as a catalyst*"
Supervisor: Dr. R. Vijaya Anand, Associate Professor, IISER Mohali, India

Academic Achievements

- 69th all India rank in Joint CSIR-UGC junior research fellowship (June-2010), India
- CSIR- Junior Research Fellowship (June-2010), India

Research Interest

- Development of organocatalytic reactions
- Development of new synthetic methodologies
- Development of new synthetic methodologies under continuous flow condition
- Asymmetric synthesis
- Design of new N-heterocyclic carbene catalysts