Employing Arynes in Transition-Metal-Free Carbon-Carbon and Carbon-Heteroatom Bond-Forming Reactions

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In

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By

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February 2016

Dedicated to

My Parents and Teachers

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Thesis Certificate

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

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Declaration by the Candidate

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

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I wish to thank great scientific community whose achievements are constant source of inspiration for me.

Sachin Suresh Bhojgude

List of Abbreviations

Ac	Acetyl
Ar	Aryl
1-Ad	1-Adamantyl
bs	Broad singlet
BSA	Bis(trimethylsilyl)acetamide
Bn	Benzyl
t-Bu	tertiary Butyl
n-BuLi	*n*-Butyllithium
Cy	Cyclohexyl
Cat.	Catalytic
DCE	1,2-Dichloroethane
DCM	Dichloromethane
Dipp	2,6-Diisopropylphenyl
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
E^+	Electrophile
Et	Ethyl
g	gram(s)
h	hour(s)
HMDS	Bis(trimethylsilyl)amine
HMPT	Hexamethylphosphoramide
HRMS	High-resolution mass spectrometry
Hz	Hertz
IR	Infra red
j	Coupling constant in NMR
LDA	Lithium diisopropyl amide
m	Multiplet
Me	Methyl

min	Minute(s)
mL	Milliliter(s)
mmol	Millimole(s)
MW	Microwave
NMR	Nuclear magnetic resonance
Nu^-	Nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
Ph	Phenyl
i-Pr	Isopropyl
q	Quartet
rt	Room temperature
s	Singlet
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Trifluromethanesulfonyl
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
p-Tol	*para*-Tolyl

Synopsis

Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	Mr. Sachin Suresh Bhojgude
Degree Enrolment No. & Date	Ph. D in Chemical Sciences (10CC11A26016); August 2011
Title of the Thesis	**Employing Arynes in Transition-Metal-Free Carbon-Carbon and Carbon-Heteroatom Bond-Forming Reactions**
Research Supervisor	Dr. A. T. Biju (AcSIR, CSIR-NCL, Pune)

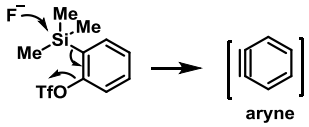
Introduction

Arynes are highly reactive intermediates discovered more than a century ago. Presence of the carbon-carbon triple bond in a six-membered ring creates a ring strain, which make them highly electrophilic in nature and kinetically unstable.[1] Owing to their intrinsic electrophilic nature, arynes have been extensively studied by both organic as well as theoretical chemists. Organic chemists recognized the synthetic utility of arynes in the 1,2-functionalisation of aromatic ring along with the construction of benzo-fused carbocycles and heterocycles in a single operation, which are otherwise difficult to achieve by other methods.[2]

Statement of the Problem

Due to the high reactivity, arynes are generated *in situ* in solution. In last decades, various research groups realized diverse approaches for aryne generation but all these methods required strongly basic or harsh reaction conditions.[2] Strongly basic conditions and high temperature were not compatible with large number of functional groups, which limits the scope of aryne reactions in organic synthesis. The pioneering work of Kobayashi and co-workers for the generation of arynes under base-free and mild reaction conditions by the fluoride-induced 1,2-elimanation of 2-(trimethylsilyl)aryl triflates as aryne precursor led to a rapid development in the field of aryne chemistry (Scheme 1).[3] Kobayashi's method is compatible with a range of functional groups, substrates, reagents and even with transition metal catalysts also. Now a days, this method is the most widely used and efficient one for aryne generation. Recently, many of the traditional aryne reactions have been revisited using Kobayashi's procedure of aryne generation to enhance the scope and yield and to improve the regioselectivity.[4] Many of the aryne reactions are important alternatives to classical organic transformations due to their economic and environmentally friendly nature.

Scheme 1: Mild method for the generation of arynes



Methodology used

Our focus was on transition-metal-free applications of arynes in pericyclic reactions, insertion reactions, and multicomponent reactions. If successful, these studies will result in the rapid synthesis of complex organic scaffolds by forming multiple carbon-

carbon and carbon-heteroatom bonds in a single process. Moreover, this can highlight the synthetic utility of this highly reactive intermediate in organic synthesis.

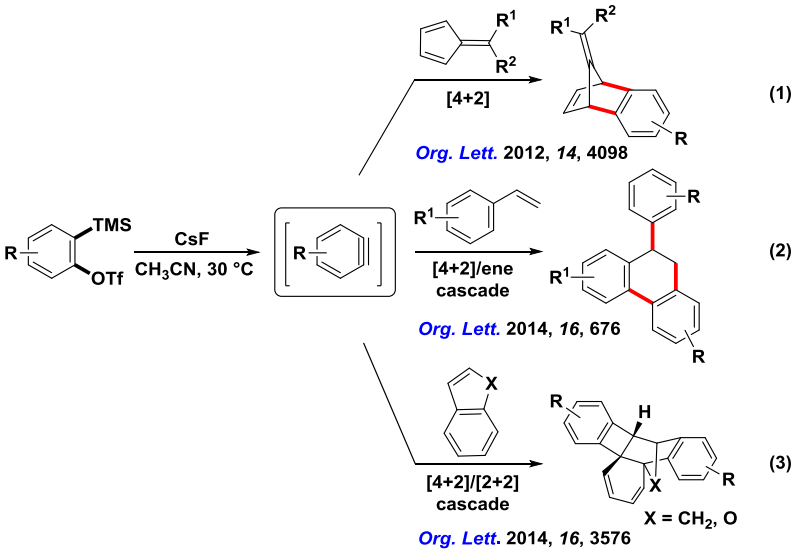
Noteworthy Findings

Diels-Alder Reactions Involving Arynes

The Diels-Alder reaction of aryne is a unique and straightforward method for the construction of wide range of benzo-fused carbocycles and heterocycles, which are common structural units in various biologically important natural products. Due to their pronounced electrophilic nature, arynes act as excellent dienophile with various dienes and diopoles. The detailed study on Diels-Alder reaction of arynes with challenging dienes has been carried out.

1. We have developed a high yielding, practical and scalable Diels-Alder reaction of pentafulvenes with arynes under mild reaction conditions leading to the formation of benzonorbornadiene derivatives, having potential application in organic synthesis (Scheme 2, eq 1).[5]
2. In addition, Diels-Alder reaction of aryne can be coupled with other intermolecular process thereby leading to efficient tandem reactions. We have demonstrated the reaction of arynes with styrenes leading to the synthesis of 9-aryldihydrophenanthrene derivatives (Scheme 2, eq 2).[6] The reaction proceeds via a cascade process initiated by a Diels-Alder reaction of styrenes with arynes followed by a selective ene reaction. Notably, the utility of styrenes as the 4π-component in Diels−Alder reactions utilizing a carbon-carbon double bond, which is involved in aromaticity appears interesting.
3. Moreover, We have revealed a facile and general procedure for the synthesis of dihydrobenzocyclobutaphenanthrene derivatives by a tandem [4 + 2]/[2 + 2] cycloaddition reaction involving arynes with indene/benzofurans (Scheme 2, eq 3).[7] Present method is unique for the synthesis of these strained and complex carbocycles in moderate to good yields with excellent diastereoselectivity.

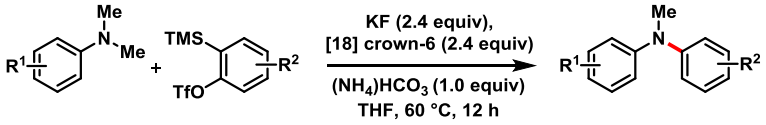
Scheme 2: Diels-Alder Reaction of Arynes with Unconventional Dienes



Transition-Metal-Free N-arylation of Aromatic Tertiary Amines

Arynes have been utilized in various arylation reactions. The *N*-arylation of primary and secondary amines are known using arynes as aryl source. However, the transition-metal-free *N*-arylation of aromatic tertiary amines using arynes as aryl source, to the best of our knowledge is unknown. We have developed a highly monoselective and transition-metal-free *N*-arylation of aromatic tertiary amines using arynes leading to the formation of functionalized diaryl amine derivatives in good to excellent yield (Scheme 3).[8] High yields, broad substrate scope, wide range of functional group tolerance especially with donor-acceptor systems, dyes, halogen containing substrate are the noteworthy features of this reaction.

Scheme 3: Transition-Metal-Free Monoarylation of Aromatic Tertiary Amines Using Arynes

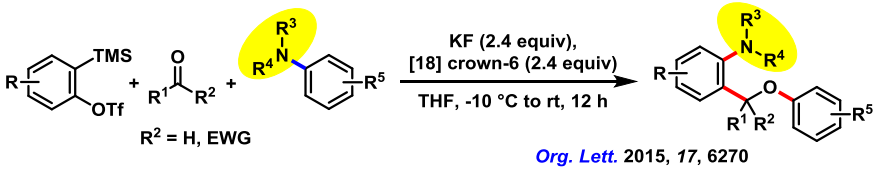


Org. Lett. 2013, *15*, 5452

Three-Component Coupling Involving Arynes, Aromatic Tertiary Amines, and Aldehydes via Aryl−Aryl Amino Group Migration

Transition-metal-free aryne MCCs provides straightforward access to various 1,2-disustituted arenes. We have recently uncovered a novel multicomponent reaction involving arynes, aldehydes and aromatic tertiary amines leading to the rapid synthesis of 2-functionalized tertiary amines proceeding via aryl to aryl amino group transfer (Scheme 4).[9] The reaction is not only limited to aldehydes, various cyclic and acyclic ketones also efficiently engaged as a third component in the present method. Mild reaction conditions, broad substrate scope, and ease of variation of the three components are the important features of the present reaction.

Scheme 4: Three-Component Coupling Involving Arynes, Aromatic Tertiary Amines and Aldehydes via Aryl-Aryl Amino Group Migration



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CHAPTER 1

Application of Arynes in Organic Synthesis: An Overview

1.1. Introduction

Arynes are highly reactive intermediates discovered more than a century ago. In the past decades, chemistry of arynes has encountered an unprecedented resurgence and facilitated access to an array of 1,2-disustituted benzene derivatives along with the construction of benzo-fused carbocycles and heterocycles, which are otherwise difficult to achieve by conventional methods.[1] Our focus has been on the utilization of arynes in transition-metal-free carbon-carbon and carbon-heteroatom bond-forming reactions. To put things in perspective, a brief overview of the aryne chemistry from its discovery, methods of generation, and particularly recent advances in transition-metal-free applications of arynes in pericyclic reactions, insertion reactions and multicomponent reactions is provided in the following sections.

Simplest form of aryne is benzyne (1,2-didehydrobenzene) and the term aryne is used to refer their heterocyclic analogues (heteroarynes) also. Initial speculation for the existence of aryne intermediate appeared in 1902. Stoermer and Kahlert observed the formation 2-ethoxybenzofuran from 3-bromobenzofuran under basic reaction conditions, and suggested that the reaction proceeds via the formation of 2,3-didehydrobenzofuran intermediate.[2] In 1942, Wittig proposed a benzyne as intermediate in the reaction of fluorobenzene with phenyllithium and isolated the biphenyl product.[3] Later, he successfully trapped the benzyne intermediate in [4 + 2] cycloaddition with furan. However, structure of benzyne proposed by Wittig was confirmed by Roberts and coworkers in 1953 by treating ^{14}C labeled chlorobenzene with potassium amide.[4] Arynes are uncharged reactive intermediate derived from aromatic systems by the elimination of two adjacent hydrogen atoms. In arynes, carbon-carbon triple bond is present in the six-

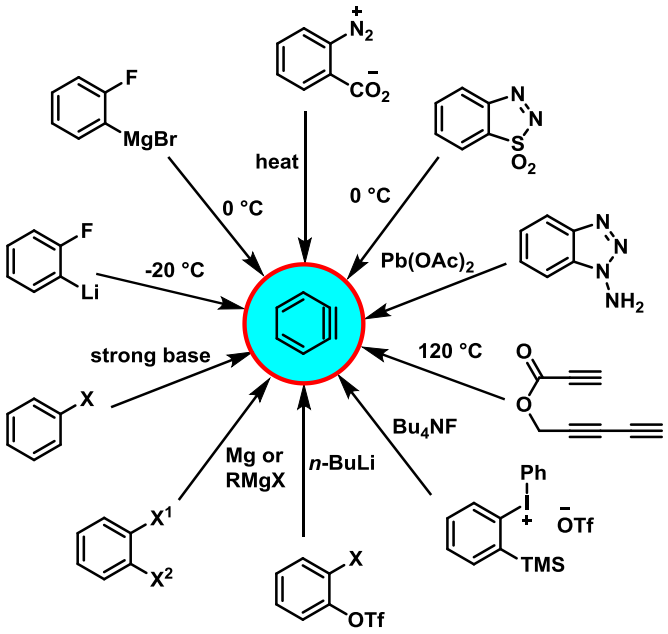
membered ring, the unhybridized *p*-orbitals are outside the aromatic ring and perpendicular to the π-system holding two electrons between them, which are not involved in aromaticity. Due to the reduced bond angle, these *p*-orbitals are distorted and not parallel to each other like in normal alkynes, so arynes are better described as strained alkynes. Presence of the carbon-carbon triple bond in a six-membered ring creates a ring strain, which is responsible for the low-lying LUMO in arynes and makes them highly electrophilic and kinetically unstable intermediate. Owing to their intrinsic electrophilic nature, arynes have been extensively studied by both organic as well as theoretical chemists.

1.2. Methods of Aryne Generation

Due to the high reactivity, arynes are generated *in situ* in solution. In last decades, various research groups realized diverse approaches for aryne generation (Scheme 1.1).[5] Traditional methods of arynes generation involve deprotonation of aryl halides with strong bases such as sodium amide or *n*-BuLi, which proceeds via the dehalogenation of the anionic intermediate.[6] Moreover, another approach involves the metal-halogen exchange/elimination of 1,2-disubtituted haloarenes or haloaryl triflates with the action of metals (Mg or Li) or organometallic reagents derived from Li, and Mg.[7] However, strong basic reaction conditions are not compatible for the base-sensitive functional groups, and organometallic reagents can act as nucleophile towards arynes. Additionally, arynes can also be generated from anthranilic acids, converting them into the zwitterionic benzenediazonium 2-carboxylates in the reaction course, which undergo decomposition on heating to form arynes with the liberation of nitrogen and carbon dioxide.[8] The main problem associated with this method is the explosive nature of diazonium compounds. Fragmentation of aminotriazole produces aryne with evolution of nitrogen gas but required lead tetraacetate oxidant, resulting in less functional group tolerance.[9] Fluoride-induced elimination of the aryne precursor phenyl(2-(trimethylsilyl)phenyl)iodonium triflate is an additional process for the generation of aryne, but preparation of starting material is a complex process.[10] With this method, synthesis of functionalized aryne precursor is unfeasible. All these methods required strongly basic or harsh reaction conditions. Strongly basic conditions and high temperature are not compatible with large number of functional groups, which drastically limited the scope of aryne reactions in

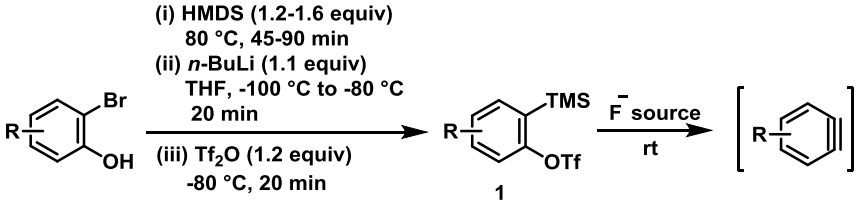
organic synthesis. Very recently, Hoye and coworkers developed a new method of aryne generation by the intramolecular hexadehydro Diels-Alder reaction of triynes. This method allows reagent-free and metal-free generation of arynes, but required elevated temperature to ensure the formation of arynes.[11]

Scheme 1.1: Methods for the Generation of Arynes



The pioneering work of Kobayashi and coworkers for the generation of arynes under base-free and mild reaction conditions by the fluoride-induced 1,2-elimanation of 2-(trimethylsilyl)aryl triflates **1** as aryne precursor led to a rapid development in the field of aryne chemistry (Scheme 1.2).[12]

Scheme 1.2: Kobayashi's Method of Aryne Generation



(+) One-pot synthesis
(+) Broad substrate scope
(+) Mild and base-free conditions for aryne generation
(+) Compatible with various functional groups

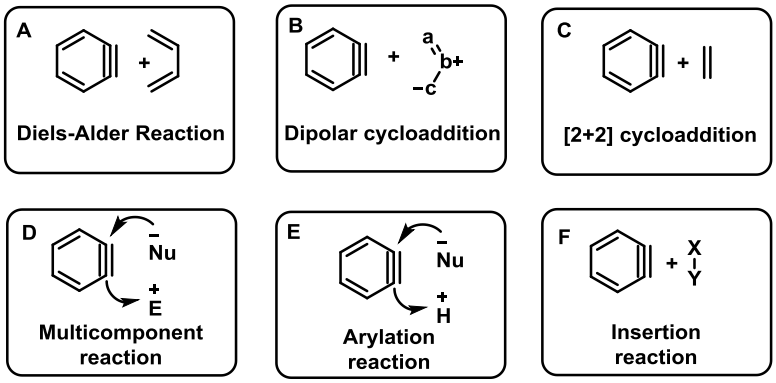
Kobayashi's method is compatible with a range of functional groups, substrates, reagents and even with transition metal catalysts also. KF (with 18-crown-6 as additive) in THF, CsF in CH_3CN, and tetrabutyl ammonium fluoride (TBAF) in THF are the

commonly used fluoride sources and solvents for the generation aryne from **1**. Careful selection of fluoride source and solvent combination was found to be beneficial to control the rate of aryne generation as well as the regioselectivity in the product formation. Since now a days, this method is the most widely used and efficient one for aryne generation. Recently, many of the traditional aryne reactions have been revisited using Kobayashi's procedure of aryne generation to enhance the scope and yield and to improve the regioselectivity. Many of the transition-metal-free aryne reactions are important alternatives to classical organic transformations due to their economic and environmental friendly nature.

1.3. Possible Reactivity Modes of Arynes

Arynes are one of the most important class of reactive intermediates primarily due to their electron-deficient nature and have been widely used as substrate in various reactions. In recent years, these fascinating intermediates garnered much attention of organic chemists by virtue of their different modes of action in various bond forming processes. Transition-metal-free reactions of arynes can be rationalized into three main groups such as pericyclic reactions,[13] multicomponent couplings (MCCs)[14] and insertion reactions[15] (Scheme 1.3).

Scheme 1.3: Possible Modes of Action of Arynes in Various Bond-Forming Reactions



Owing to their pronounced electrophilic nature, arynes constitute as excellent dienophile and dipolarophile in Diels-Alder reactions (A) and dipolar cycloaddition reactions (B) respectively. It gives [2 + 2] cycloaddition reaction with electron-rich olefins (C). Arynes holds the ability to react with wide range of nucleophiles, even neutral nucleophiles can add to arynes. Recently, arynes have been efficiently involved in various transition-metal-free multicomponent couplings (MCCs). The fundamental

concept involves the addition of nucleophiles to arynes to form the aryl anion intermediate, which is successfully trapped by various electrophiles leading to MCCs (D). Transition-metal-free MCC involving arynes allows rapid construction of multiple bonds leading to the straightforward synthesis of complex 1,2-disustituted benzene derivatives in a single operation. In presence of acidic proton source the aryl anion intermediate is quenched to offer arylated products in arylation reactions (E). Moreover, arynes can insert into various element-element σ-bonds and π-bonds resulting in the formation of functionalized 1,2-disubstituted arenes (F).

1.4. Diels-Alder Reaction of Arynes

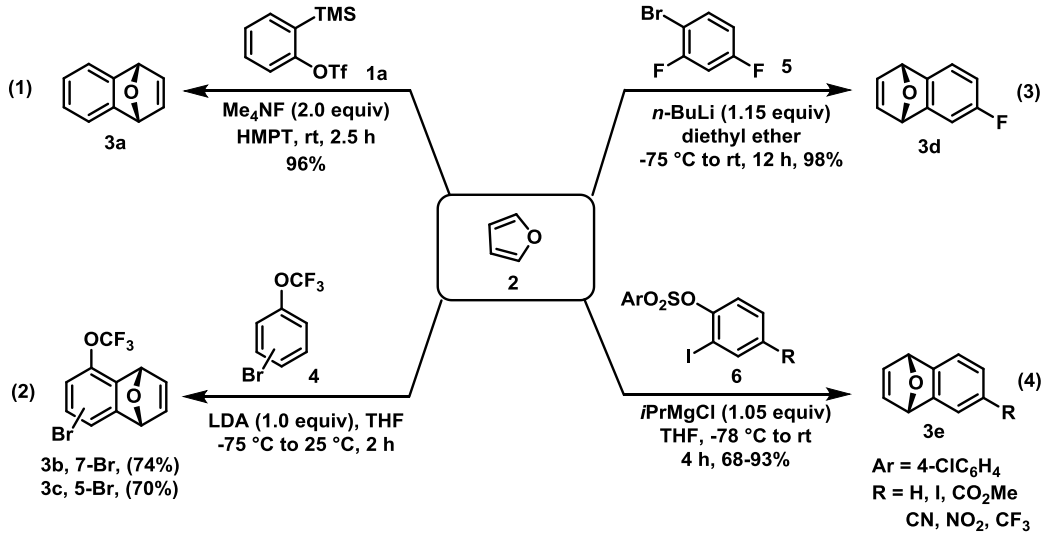
Diels-Alder reaction involving arynes constitutes one of the important reactions of arynes for the rapid construction of various carbocycles and heterocycles of synthetic importance. After Wittig's first demonstration on Diels-Alder reaction of furan with arynes, this protocol is mostly studied for the detection of arynes generated from different aryne precursors. Consequently, organic chemists recognized the potential of Diels-Alder reaction involving arynes and it appeared as a promising tool for the synthesis of complex benzenoid products with various substitution patterns. Furan reacts efficiently with arynes to offer [4 + 2] cycloadducts, endoxide bridge in furan-aryne cycloadducts can be easily cleaved by acids, and this method is useful in the synthesis of functionalized naphthalene derivatives.

Kobayashi and coworkers demonstrated the efficiency of aryne generation from 2-(trimethylsilyl)aryl triflates **1a** in the Diels-Alder reaction with furan **2**.[12a] They screened different fluoride source and solvent combinations, and observed almost quantitative formation of the 1,4-dihydro-1,4-epoxynaphthalene product **3a** using tetramethylammonium fluoride as fluoride source in HMPT solvent under mild reaction conditions (Scheme 1.4, eq 1). Moreover, Schlosser and Castagnetti generated the 3-trifluoromethoxy benzyne by the reaction of 1-bromo-3- or -4-(trifluoromethoxy) benzene **4** with LDA in THF solvent at -75 °C and intercepted with furan leading to the formation of 7-bromo-5-(trifluoromethoxy)- and 5-bromo-8-(trifluoromethoxy)-1,4-dihydro-1,4-epoxynaphthalene (**3b**, **3c**) in 74% and 70% yields, respectively (eq 2).[16]

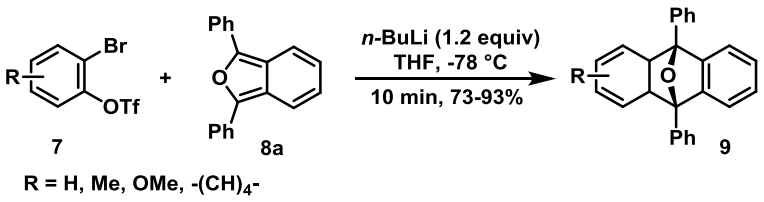
In addition, the synthetic utility of [4 + 2] cycloadduct **3b** and **3c** has been demonstrated in the synthesis of 1- and 2-(trifluoromethoxy)naphthalenes via reduction

using zinc powder. A scalable and high yielding method for the synthesis of fluorinated epoxynaphthalenes by the Diels-Alder reaction involving arynes and furan was reported by Caster and coworkers.[17] For instance, the reaction of 1-bromo-2,4-difluorobenzene **5** with *n*-BuLi in diethyl ether at low temperature resulted in the formation of aryne intermediate through a metal-halogen exchange, which was trapped with furan to afford the [4 + 2] cycloadduct **3d** in 94% yield (eq 3). In 2004, Knochel and coworkers introduced a general method for the synthesis of functionalized arynes by the elimination of 2-magnesiated aryl sulfonates, prepared from the corresponding 2-iodo derivates **6** via an iodine-magnesium exchange. The reaction of sulfonate **6** with *i*PrMgCl at -78 °C in THF furnished the Grignard reagent in solution, which upon elimination generates arynes. Subsequent addition of furan in the reaction mixture led to the formation of functionalized epoxynaphthalene products **3e** in good yields (eq 4).[18] The leaving-group ability of the sulfonate group ($ArSO_2O$-) was found to be crucial for the aryne generation.

Scheme 1.4: Trapping of Arynes in Diels-Alder Reaction with furan



Scheme 1.5: Diels-Alder Reaction of Arynes with Isobenzofuran

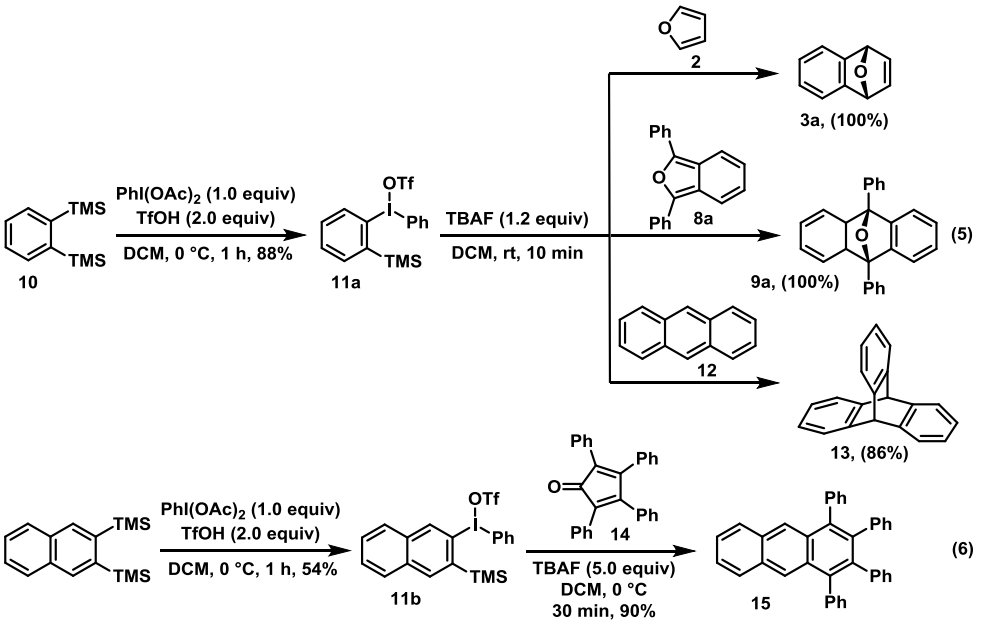


In 1991, Suzuki and coworkers developed a clean and rapid protocol for the aryne generation by lithium-halogen exchange of *ortho*-haloaryl triflates **7** using *n*-BuLi

base in THF as a solvent at -78 °C and trapped with 1,3-diphenylisobenzofuran **8a** leading to the formation of [4 + 2] cycloaddition products **9** in excellent yields (Scheme 1.5).[7]

Kitamura's group introduced a hypervalent iodine compound phenyl(2-(trimethylsilyl)phenyl)iodonium triflate **11a** as the aryne precursor, prepared form the *ortho*-bis(trimethylsilyl)benzene **10** using $PhI(OAc)_2$ followed by the treatment with trifluoromethanesulfonic acid in DCM (Scheme 1.6, eq 5).[10] In order to illustrate the efficiency of this method, the generated aryne was intercepted with various cyclic dienes. The aryne was generated under mild reaction conditions using TBAF in DCM and trapped with furan **2**, 1,3-diphenylisobenzofuran **8a**, and anthracene **12** leading to the formation of cycloadducts 1,4-dihydro-1,4-epoxynaphthalene **3a**, 9,10-epoxy-9,l0-diphenyl-9,l0-dihydroanthracene **9a**, and tripticene **13** respectively in excellent yields (eq 5). Additionally, the hypervalent iodine precursor has been also applied in the generation of symmetrical naphthalyne from phenyl(3-(trimethylsilyl)-2-naphthyl)iodonium triflate **11b** and intercepted in [4 + 2] cycloaddition reaction with tetraphenylcyclopentadienone **14**. The reaction afforded the polycyclic aromatic hydrocarbon 1,2,3,4-tetraphenyl-anthracene **15** in 90% yield (eq 6).[19]

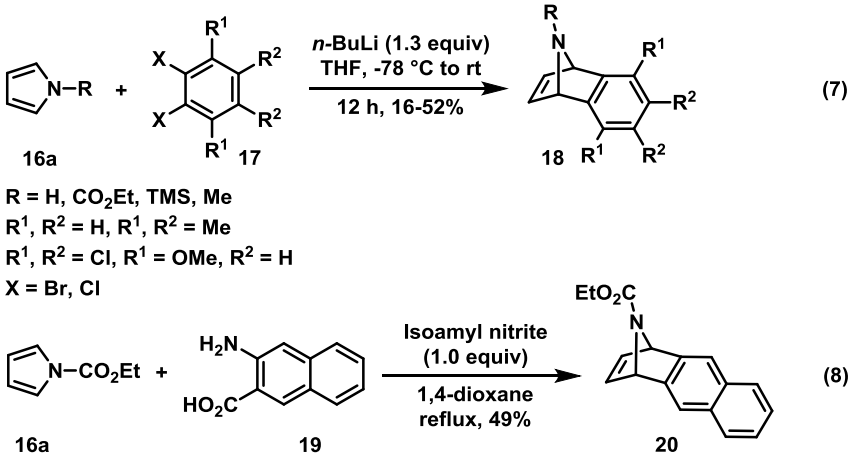
Scheme 1.6: Generation of Aryne from Phenyl(2-(trimethylsilyl)phenyl)iodonium triflate



Interestingly, *N*-substituted pyrroles have also been employed in Diels-Alder reaction with arynes. Treatment of *ortho*-dihaloarenes **16** with pyrroles **17** using *n*-BuLi

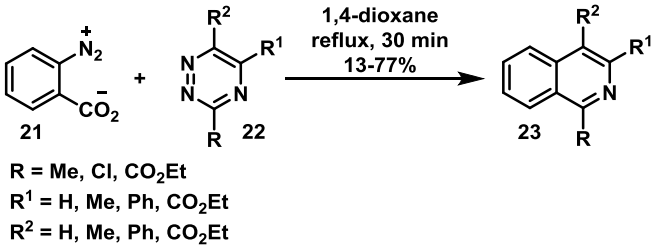
in THF at -78 °C furnished the 1,4-dihydro-1,4-iminonaphthalenes **18** in moderate yields (Scheme 1.7, eq 7).[20] Moreover, the reaction of ethyl 1*H*-pyrrole-1-carboxylate **16a** with naphthalyne generated from 2-aminonaphthoic acid **19** using isoamyl nitrite in 1,4-dioxane under reflux reaction conditions afforded 1,4-dihydro-1,4-aminoanthracene **20** in 49% yield (eq 8).

Scheme 1.7: Diels-Alder Reaction of Arynes with Pyrroles



The Diels-Alder Reaction of 1,2,4-triazines **22** with arynes generated from benzenediazonium 2-carboxylate **21** has been established by Gonsalves and coworkers (Scheme 1.8).[21] The reaction furnished the functionalized isoquinoline derivatives **23** with the elimination of a molecule of nitrogen from the initially formed [4 + 2] adduct.

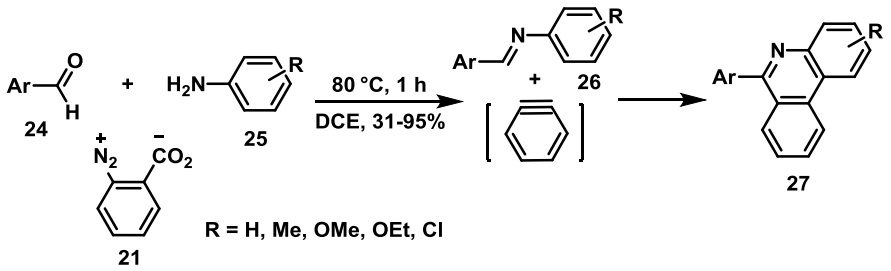
Scheme 1.8: Diels-Alder Reaction of Arynes with 1,2,4-Triazines



In 2006, Wang and coworkers developed a one-pot method for the rapid and direct construction of phenanthridine derivatives **27** from readily available starting materials such as aromatic aldehydes **24**, anilines **25**, and benzenediazonium-2-carboxylate **21** in DCE at 80 °C via a three-component cascade process (Scheme 1.9).[22] This outcome occurs sequentially, starting with the condensation of aromatic aldehyde with aniline generating imine **26** in the reaction mixture, which on aza-Diels-Alder

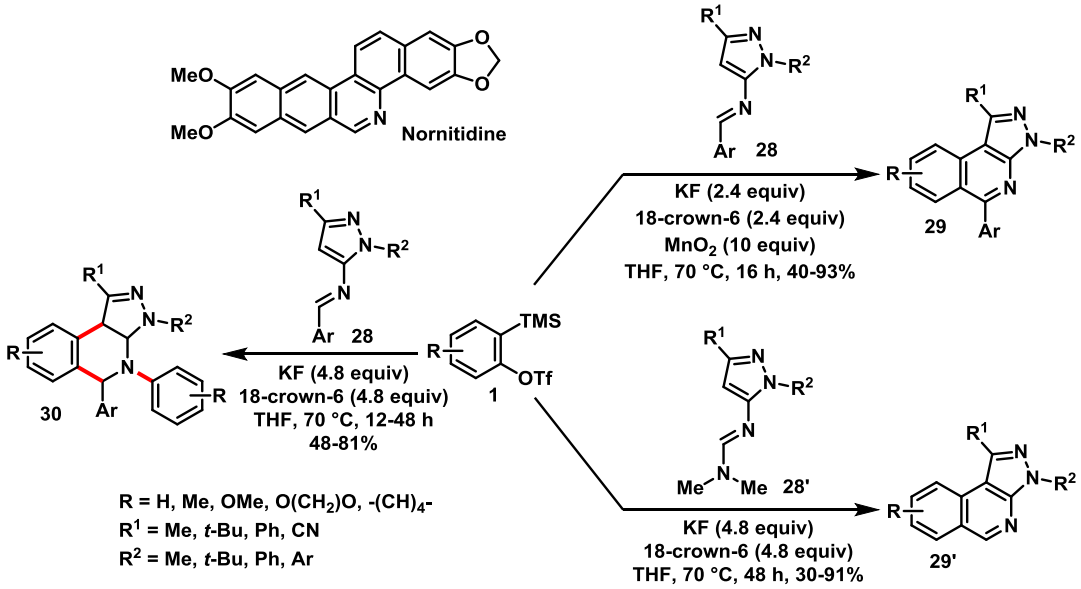
reaction with aryne generated from benzenediazonium-2-carboxylate offers the [4 + 2] cycloadduct. Dehydrogenation of [4 + 2] cycloadduct with another molecule of aryne resulted in the formation 6-aryl-phenanthridine derivatives **27**.

Scheme 1.9: Aza-Diels-Alder Reaction of Arynes



Very recently, Rodriguez, Coquerel and coworkers revealed flexible cascade reactions of electron-rich *N*-aryl imines and arynes leading to the synthesis of functionalized heteropolycyclic products with an isoquinoline core.[23]

Scheme 1.10: Aryne Aza-Diels-Alder Reaction with Electron-rich *N*-Aryl Imines

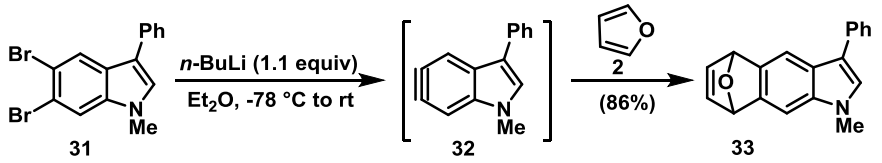


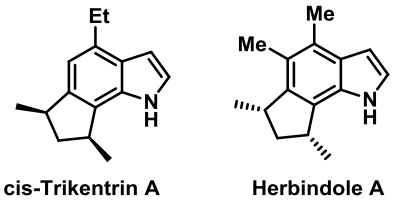
Reaction of *N*-pyrazolyl aldimine derivatives **28** with arynes generated from precursor **1** using KF and 18-crown-6 in THF at 70 °C resulted in the formation of aza-Diels-Alder cycloadducts, which on rapid in situ oxidation in the presence of excess MnO_2 furnished the isoquinoline derivatives **29** in good yields (Scheme 1.10).[23a] Another approach involves the introduction of a labile dimethylamino group on *N*-aryl imines **28'**, this method provided straightforward access to the isoquinolines **29'** by the elimination of amine molecule from the initially formed aza-Diels-Alder adduct devoid of oxidant. In

addition, the potential of this aryne aza-Diels-Alder reaction has been examined in a concise total synthesis of the natural benzo[*c*]-phenanthridine alkaloid nornitidine. Moreover, during optimization of the aryne aza-Diels-Alder reaction, they noticed the formation of *N*-arylated product of aza-Diels-Alder adduct 1,2-dihydroisoquinoline. By using excess of aryne, they observed a pseudo-three-component process of *N*-aryl imines and arynes for the selective synthesis of *N*-aryl-1,2-dehydroisoquinoline derivatives **30** in good yields.[23b]

Generation of three isomeric indole-arynes in the benzenoid core by metal-halogen exchange of *ortho*-dihalo indoles has been developed by Buszek and coworkers. For instance, treatment of 5,6-dibromoindole **31** with *n*-BuLi resulted in the formation of 5,6-indolyne **32**, which was trapped with furan **2** to give Diels-Alder cycloadduct **33** in 86% yield (Scheme 1.11).[24] In addition, they accomplished the total synthesis of indole natural products *cis*-trikentrin A and Herbindole A via an intermolecular indole-aryne Diels-Alder cycloaddition with cyclopentadiene.[24b] Subsequently, they carried out experimental and theoretical studies to gain insight into the regioselectivity of three isomeric indole-derived aryne cycloadditions.[24c] They found that cycloaddition reactions of 6,7-indolynes with 2-substituted furans were remarkably regioselective, whereas the cycloaddition reactions of 4,5- and 5,6-indolynes furnished a mixture of regioisomers.

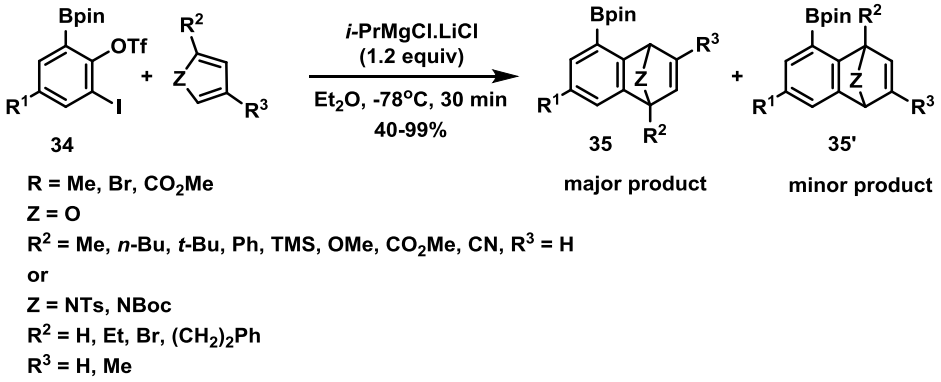
Scheme 1.11: Generation of Indolynes and Diels-Alder Reaction with Furan





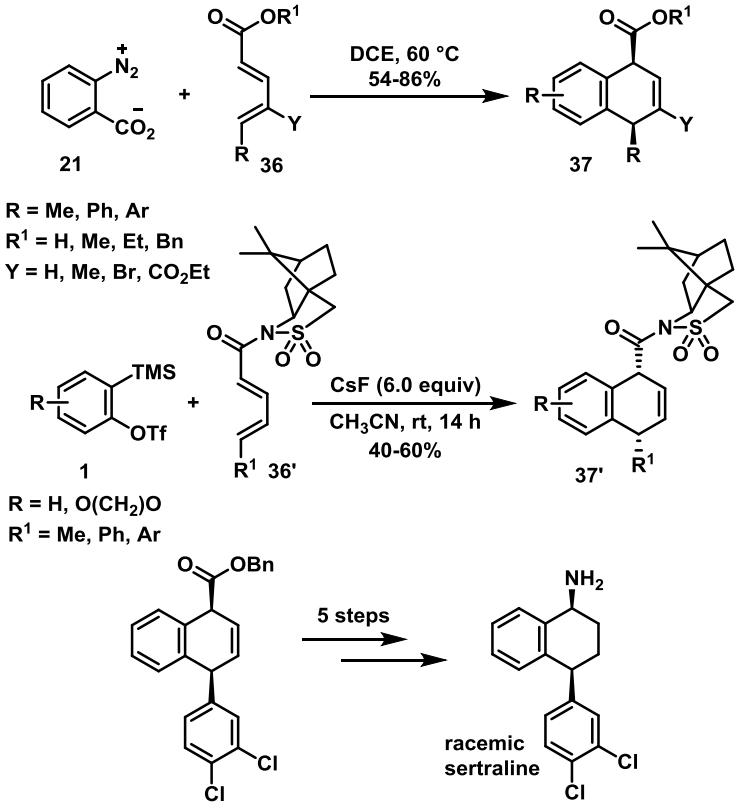
Akai and coworkers uncovered a route for the synthesis of highly functionalized arylboronic acid derivatives **35** by the Diels-Alder reaction of substituted furans or pyrroles with 3-borylbenzyne generated form 2-boryl-6-iodophenyl triflate **34** using *i*PrMgCl.LiCl (Scheme 1.12).[25] The reaction was found to be regioselective and other isomers were isolated in only trace amount.

Scheme 1.12: Generation of 3-Boryl Benzynes and Diels-Alder with Furans/Pyrroles



A very attractive strategy for the synthesis 1,4-dihydronaphthalene by the Diels-Alder reaction of aryne with acyclic diene was reported by Wittig as early as 1960. However, the scope and utility of this approach was very limited.[26] Lautens and coworkers expanded the scope and utility of Diels-Alder reaction of arynes with 1,4-disubstituted acyclic dienes and prepared *cis*-substituted 1,4-dihydronaphthalene derivatives in good yields. Treatment of acyclic dienes **36** with aryne generated from

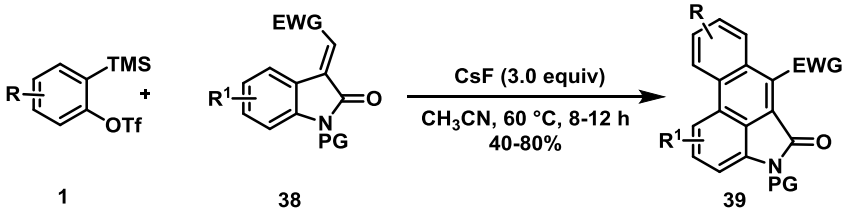
Scheme 1.13: Highly Diastereoselective Diels-Alder Reaction of Aryne with Acyclic Dienes



benzenediazonium-2-carboxylate **21** in 1,2-dichloroethane at 60 °C furnished the desired cycloadducts **37** with excellent levels of selectivity (Scheme 1.13).[27] Moreover, they also developed the highly diastereoselective Diels-Alder reaction of diene **36'** possessing oppolzer's sultam as chiral auxiliary attached to its carbonyl group with aryne generated from 2-(trimethylsilyl)phenyl triflates **1** using CsF in CH_3CN leading to the formation of enantiomerically enriched cycloadducts **37'** under mild reaction conditions. Synthetic utility of this method has been demonstrated in a short racemic synthesis of medicinally important product sertraline.

Li, Jia and coworkers synthesized structurally unusual naphtho-fused oxindoles by the Diels-Alder reaction of arynes with methyleneindolinones as diene components. The aryne generated from **1** using CsF in CH_3CN at 60 °C reacted with isatilidenes **38** to afford the naphtho-fused oxindoles **39** in moderate to good yields (Scheme 1.14).[28] This reaction proceeds via the [4 + 2] cycloaddition followed by isomerization and dehydrogenation sequence to offer the polycyclic skeletons.

Scheme 1.14: Construction of Naphtho-Fused Oxindoles

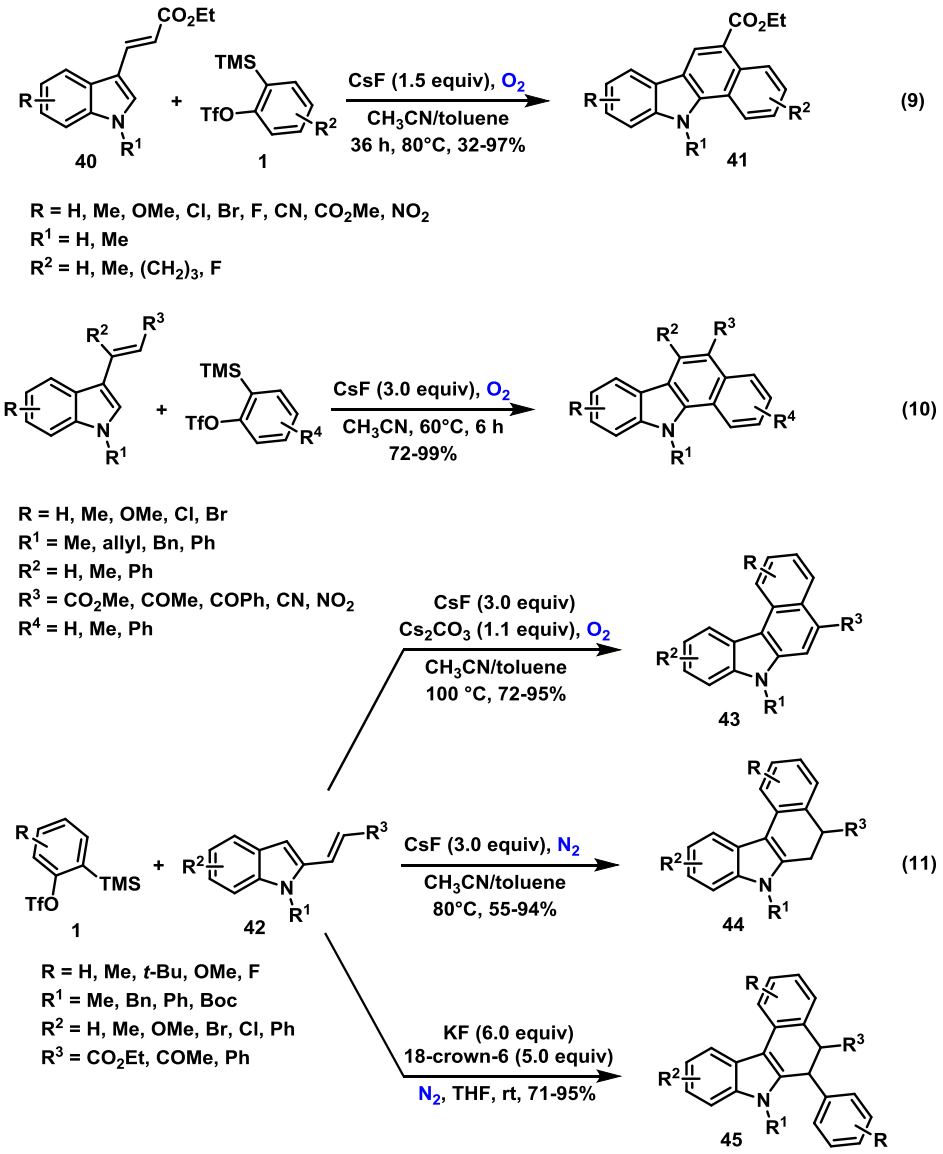


EWG = CO_2Et, COAr
R = H, Me, OMe
R^1 = H, Me, OMe, Cl, Br, F

The group of Wu, Sha and Liang, Pi independently disclosed an expeditious and efficient strategy for the construction of diverse functionalized biologically active benzo[*a*]carbazole-5-carboxylates via the Diels-Alder reaction of arynes and 3-alkenyl indoles. Wu, Sha and coworkers employed *N*-alkyl protected as well as *N*-unprotected indoles **40** as a dienes in [4 + 2] cycloaddition with arynes generated from **1** in the presence of CsF in CH_3CN/toluene mixture at 80 °C leading to the synthesis of benzo[*a]*carbazole-5-carboxylates **41** in good to excellent yields (Scheme 1.15, eq 9).[29a] Liang, Pi group utilized similar reaction conditions to accomplish the cycloaddition of 3-vinyl-indoles with arynes (eq 10).[29b] In both the cases, reactions were performed under

the oxygen atmosphere for the aromatization of initially formed Diels-Alder adducts to ensure the product formation.

Scheme 1.15: Diels-Alder Reaction of Arynes with 3- and 2-Alkenyl Indoles

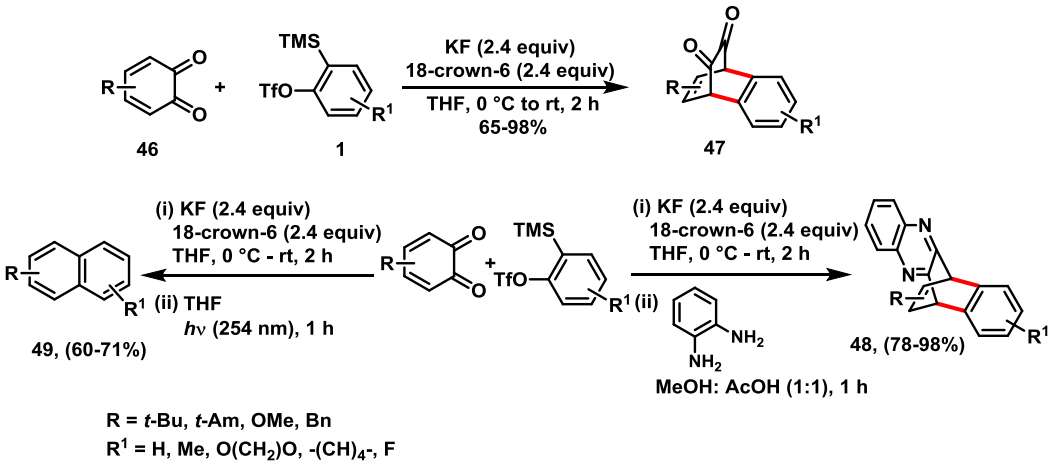


Subsequently, Wu, Sha and coworkers applied this strategy for the synthesis of benzo[*c*]carbazole derivatives through the Diels-Alder reaction of arynes and of 2-alkenyl indoles **42** (eq 11).[29c] By careful optimization of reaction conditions and aryne precursor loading, they synthesized diverse functionalized benzo[*c*]carbazole derivatives in excellent yields. Under the nitrogen atmosphere reaction furnished the 6,7-dihydrobenzo[*c*]carbazoles **44** (1.5 equiv of **1**) and aryl substituted 7,11b-dihydrobenzo [*c*]carbazoles **45** (3.0 equiv of **1**). Alternatively, when the reactions were carried out

under oxygen atmosphere afforded oxidized/aromatized product benzo[*c*]carbazoles **43**. Interestingly, the benzo[*c*]carbazole amide derivatives have good antitumor activity.

In addition, a new protocol for the synthesis of dioxobenzobicyclooctadienes by the Diels-Alder reaction of 1,2-benzoquinones with arynes has been developed from our group. 1,2-benzoquinones can exhibit different reactivity profile in Diels-Alder reactions, which primarily depends on the reacting partner and the substituents. Despite this, 1,2-benzoquinones selectively displayed carbodiene reactivity in the Diels-Alder reactions with arynes. The reaction of 1,2-benzoquinone **46** with the aryne generated from 2-(trimethylsilyl)aryl triflate **1** using KF and 18-crown-6 in THF under mild reaction conditions furnished the dioxobenzobicyclooctadienes **47** in moderate to excellent yields (Scheme 1.16).[30] The synthetic potential of this cycloaddition reaction has been demonstrated in the one-pot synthesis of benzoquinoxalinobarrelene **48** and naphthalene **49** derivatives in good yields.

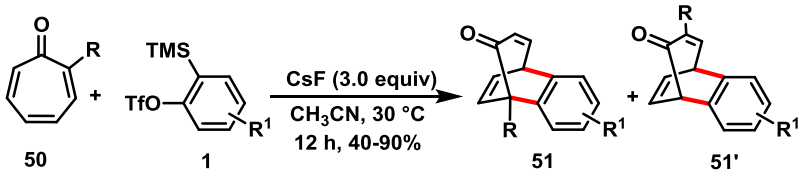
Scheme 1.16: Diels-Alder Reaction of Arynes with 1,2-Benzoquinones



Akin to 1,2-benzoquinones, tropones also demonstrate unusual reactivity profile in pericyclic reactions. Depending on the reaction conditions and coupling partner, they can acts as a 4π, 6π, or 8π component in cycloaddition reactions. The Diels-Alder reaction of tropone, engaging them as 4π components with arynes generated from benzenediazonium 2-carboxylates leading to the formation of bicyclo [3.2.2] system in low yield has been reported by Kende and coworkers in 1967.[31a] However, Tamano and coworkers observed [6 + 2] cycloaddition product in addition to the Diels-Alder adduct under Kende's reaction conditions.[31b] Detailed investigation carried out in our laboratory

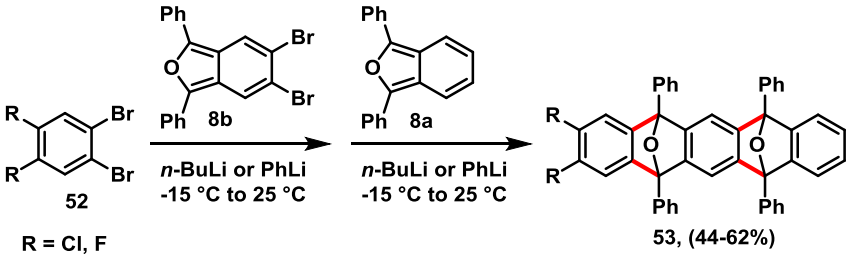
on the Diels-Alder reactions of tropones with arynes, uncovered an efficient method for the synthesis of functionalized bicyclo [3.2.2] systems with high yields and broad substrate scope. Treatment of tropones **50** with arynes generated from 2-(trimethylsilyl)aryl triflates **1** in the presence of CsF selectively afforded the benzobicyclo[3.2.2]nonatrienones **51** under mild reaction conditions (Scheme 1.17).[32] Additionally, the application of this tropone-aryne [4 + 2] cycloaddition reaction has been demonstrated in the synthesis of functionalized naphthalene derivative by a photochemical rearrangement of benzobicyclo[3.2.2]nonatrienone.

Scheme 1.17: Diels-Alder Reaction of Arynes with Tropones



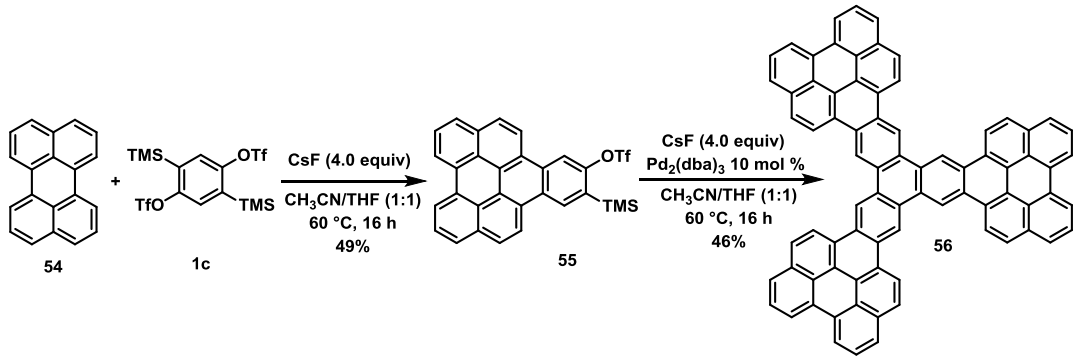
Tandem cycloadditions reactions are playing a key role in organic synthesis due to atom and step economy. Recently, Hamura and coworkers achieved the one-pot dual [4 + 2] cycloadditions with two different arynophiles leading to the synthesis of polycyclic compounds.[33] They employed dibromoisobenzofuran **8b** as suitable equivalent to didehydroisobenzofuran which is performing a dual role of donor-acceptor and 1,2-dibromobenzene **52** as aryne precursor using *n*-BuLi base (Scheme 1.18). Notably, selective bromine-lithium exchange allows the tandem generation of arynes and dual cycloadditions with two different arynophiles dibromoisobenzofuran **8b** and isobenzofuran **8a** respectively to offer the bis-cycloadduct **53**. The bis-cycloadducts are valuable scaffolds, and are found to be amenable to further transformation to provide substituted pentacene derivatives.

Scheme 1.18: Tandem Generation of Arynes and Dual Cycloadditions



Diels-Alder reactions of arynes have significant applications in the synthesis of large polycyclic aromatic hydrocarbons (PAHs), which are valuable molecules in material science and nano-graphenes.[1e] Recently Peña and coworkers accomplished synthesis of a three-fold symmetric molecule, nanographene with 22 fused benzene rings.[34] The mono-selective [4 + 2] cycloaddition reaction of aryne generated from the bis-aryne precursor **1c** with perylene **54** using CsF in CH_3CN/THF mixture furnished the aryne precursor **55** (Scheme 1.19). Subsequent aryne generation from precursor **55** followed by palladium-catalyzed [2 + 2 + 2] cycloaddition afforded the aromatic hydrocarbon **56** in 46% yield. Notably, careful selection of solvent mixture and temperature were found to be crucial in the generation of arynes.

Scheme 1.19: Synthesis of Large Polycyclic Aromatic Hydrocarbons

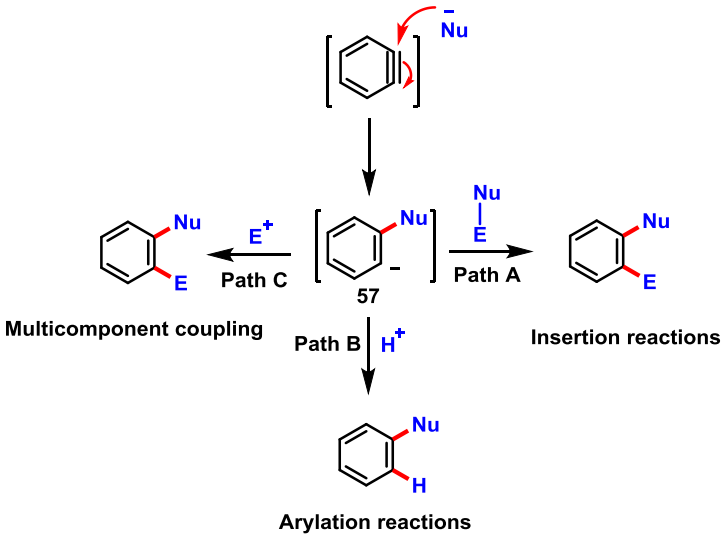


1.5. Nucleophilic Addition to Arynes

It is well understood that, due to the low-lying LUMO in arynes, even neutral nucleophiles can add to the electrophilic carbon-carbon triple bond of arynes. Initial nucleophilic addition to aryne generates a transient aryl anion intermediate **57**, which can be utilized in three different processes as shown in Scheme 1.20, leading to the direct installation of diverse functional groups into the *ortho*-positions of aromatic ring. If the 1,3-zwitterionic intermediate **57** attacks on the electrophilic site of nucleophilic molecule (Nu-E), then the aryne adds across the Nu-E resulting in the formation of insertion product (Scheme 1.20, path A). Insertion of arynes to a carbon-hydrogen, heteroatom-hydrogen σ-bonds or quenching of aryl anion **57** in presence of acidic proton source offers arylated product (Scheme 1.20, path B). Interestingly, consequent trapping of aryl anion intermediate with electrophiles leading to the insertion of arynes into two coupling partners, referred as multicomponent couplings (MCCs) involving arynes (Scheme 1.20,

path C). All these transition-metal-free protocol constitutes concise route for the rapid *ortho*-functionalization of arenes having complexity and diversity.

Scheme 1.20: Aryne Insertion/Arylation Reactions and MCCs

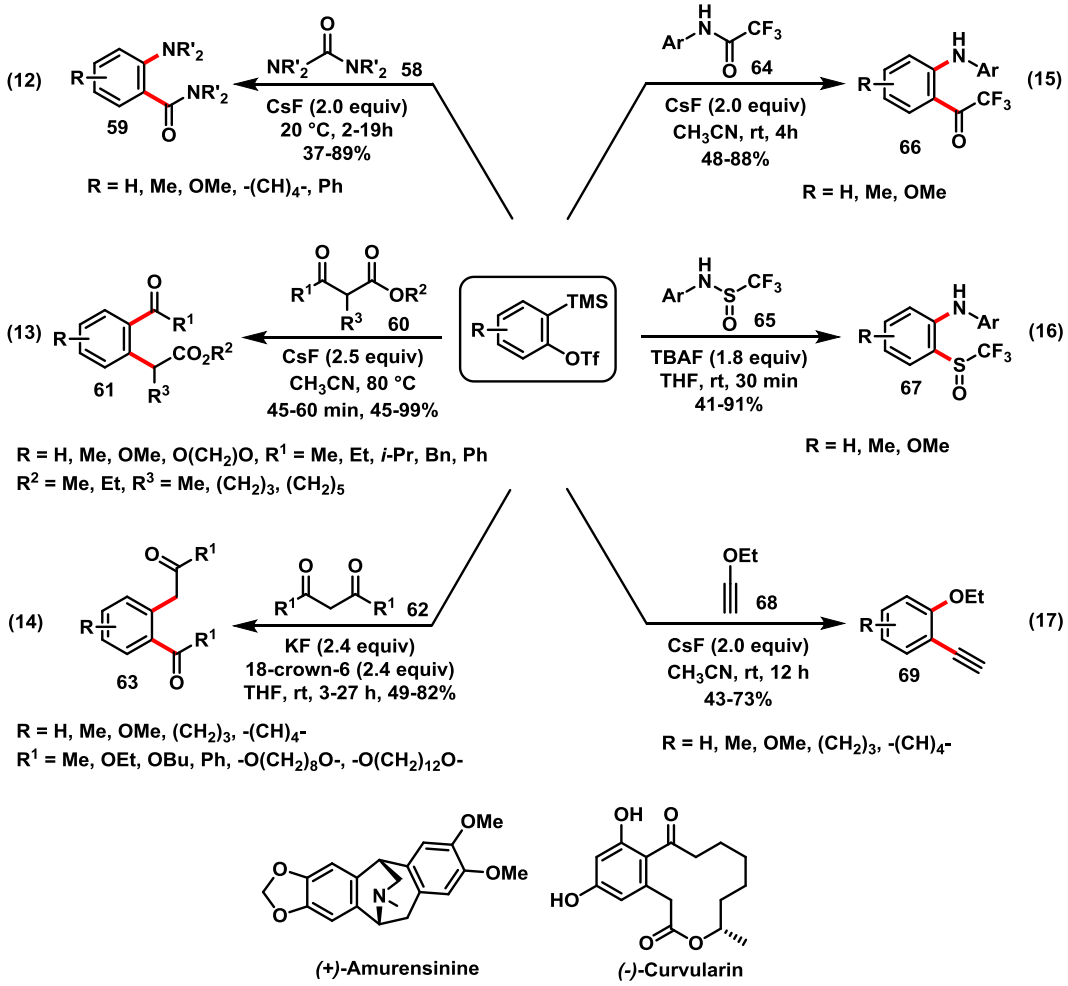


1.5.1. Insertion Reactions

With the introduction of mild methods for aryne generation and their ability to insert into various element-element σ-bonds and π-bonds, arynes have been extensively employed in the synthesis of functionalized 1,2-disubstituted arenes.[1c,15] In all the reports described in this section, arynes were generated by the fluoride-induced 1,2-elimanation of 2-(trimethylsilyl)aryl triflates **1**.

Shirakawa, Hiyama and coworkers synthesized benzodiazepines and 2-aminobenzamides **59** by the insertion of arynes into the N-CO bond of cyclic and acyclic ureas **58** under mild reaction conditions, which are difficult to access by conventional methods (Scheme 1.21, eq 12).[35] Benzodiazepines are valuable substrates due to their fluorescence properties and pharmaceutical application. The first report on the direct and efficient insertion of arynes into a carbon-carbon σ-bond of acyclic and cyclic β-ketoesters **60** leading to interesting 1,2-disubstituted arenes **61** has been appeared from Stoltz's group in 2005 (eq 13).[36] This acyl-alkylation reaction resulted in the formation of two new C-C bonds and cyclic β-ketoesters furnished the medium-size carbocyclic products. Aryne insertion occurred into the α,β C-C bond of β-ketoester. In this case, the reaction presumably proceeds through a formal [2 + 2] cycloaddition/fragmentation cascade. In addition, they applied this methodology to the enantioselective synthesis of

Scheme 1.21: Insertion of Arynes to Various Carbon-Carbon and Carbon-Heteroatom *σ*-Bonds

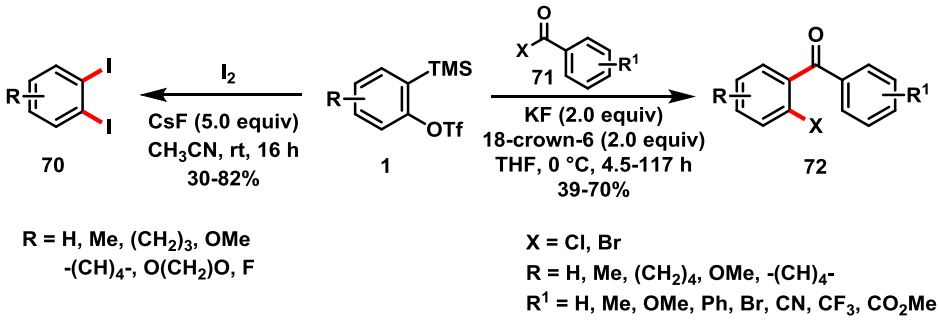


alkaloid amurensinine via selective aryne insertion to C-H and C-C bonds and the macrolactone natural product curvularin.[37] Subsequently, Yoshida, Kunai and coworkers reported a mild and straightforward protocol for the synthesis of diverse polysubstituted arenes **63** by a facile insertion of arynes to C-C *σ*-bond of various *β*-dicarbonyl compounds **62** in good yields (eq 14).[38] Moreover, Liu and Larock demonstrated an efficient insertion of arynes to the C-N bond of amides **64** and S-N bond of sulfinamides **65** leading to a transition-metal-free synthesis of 1,2-disubstituted arenes **66** and **67** under mild reaction conditions with broad substrate scope (eqs 15, 16).[39] Interestingly, the selection of CF_3 containing substrates are essential for this insertion reaction, because CF_3 group attached to the carbonyl carbon of amide and the sulfinyl sulfur of sulfinamide increases its electrophilicity which results in the increase in acidity of the amide.

In this context, it is important to note that insertion of aryne into carbon-oxygen σ-bonds is trickier than nitrogen-carbon/nitrogen-heteroatom σ-bonds due to the less nucleophilic nature of the oxygen compared to nitrogen. Interestingly, aryne insertion to C-O σ-bond of styrene oxides has been disclosed by Guitián and coworkers.[40] In 2011, same group developed a chemo- and regioselective formal insertion of arynes into the ethoxy acetylene **68** leading to the formation of 2-ethoxyethynylaryl derivatives **69** in good yields (Scheme 1.21, eq 17).[41] This procedure afforded 2-ethoxyethynylaryl derivatives in one step, which have previously been synthesized by the multistep transition-metal catalyzed reactions. The computational study suggests that, the reaction is initiated by the nucleophilic addition of the triple bond of ethoxy acetylene to aryne. Subsequent ring closure/1,2-hydrogen migration and ring-opening furnished the final product.

Additionally, the Guitián's group revealed an efficient procedure for the synthesis of *ortho*-diiodoarenes **70** by the insertion of arynes into the I-I σ-bond (Scheme 1.22).[42] Aryne insertion into the I-I σ-bond using traditional methods of aryne generation in moderate yields was reported by Friedman and Logullo as early as 1965.[43] Mild reaction conditions involved in generation of aryne form precursors **1** afforded the *ortho*-diiodoarenes in good yields.

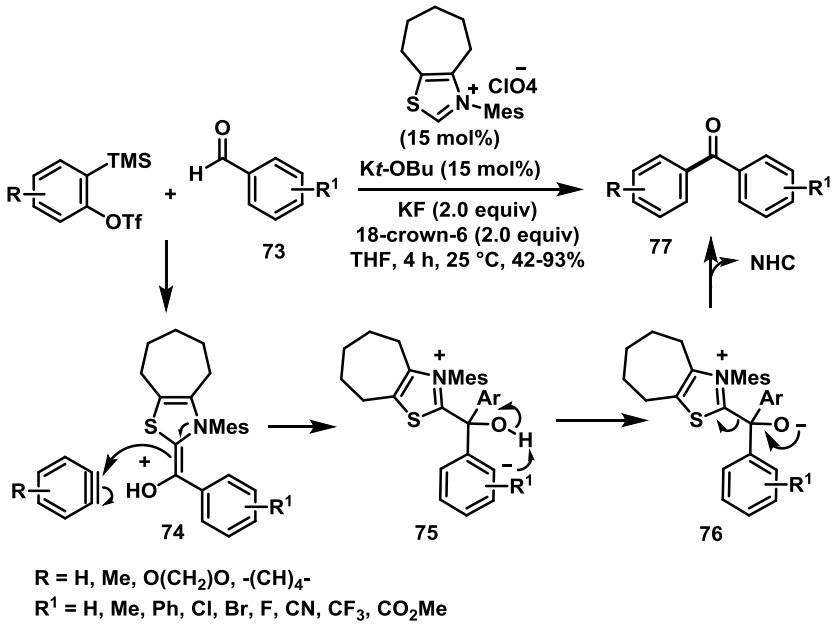
Scheme 1.22: Insertion of Arynes into I-I and Carbon-Halogen σ-Bonds



In 2007, Yoshida, Kunai and coworkers disclosed the regioselective synthesis of diverse halogenated benzophenone derivatives **72** via the insertion of arynes into the C-halogen σ-bond of acid halides **71** in moderate to good yields (Scheme 1.22).[44] Under mild reaction conditions, acyl and halogen moieties were incorporated at 1,2-positions of aromatic rings furnishing halogenated aryl ketones, which are difficult to synthesis by conventional Friedel-Crafts acylation in regioselective manner.

The transition-metal-free hydroacylation of arynes through the N-heterocyclic carbene (NHC)-catalyzed formal insertion of arynes into the C_{formyl}-H bond of aldehydes **73** leading to the formation of aryl ketones **77** has been uncovered by Biju and Glorius (Scheme 1.23).[45] This is a unique transformation, where nucleophilic carbenes were found to be compatible with electrophilic arynes. In this case, the reaction was initiated by the formation of nucleophilic Breslow intermediate **74** from aldehyde and NHC, which adds to aryne to give the alkoxide **76** via the intermediate **75**. Alternatively, a concerted transition state can also lead to the alkoxide **76** in analogy to the reaction of 1,3-dipoles with arynes. Finally, release of the NHC catalyst from **76** results in the formation of ketone product.

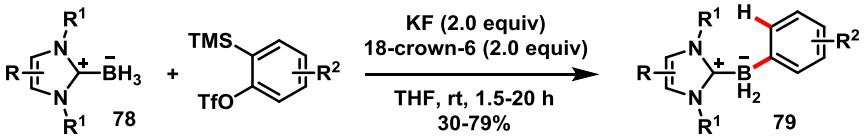
Scheme 1.23: Insertion of Arynes into the C_{formyl}-H σ-Bond of Aldehydes



Synthesis of aryl-substituted boranes by the hydroboration of arynes is complicated process, because the resulting aryl boranes are again reactive and both products and starting materials are not compatible with the fluoride source used for the aryne generation. Recently, Taniguchi and Curran employed stable N-heterocyclic carbene boranes (NHC-boranes) **78** for the hydroboration of aryns and prepared B-aryl NHC-boranes **79** with broad substrate scope (Scheme 1.24).[46] Arynes insertion selectively occurred in B-H bond and corresponding products were isolated in good yields. Previously, these products were synthesized from boronic acids in three steps but

present protocol is one step and operating under mild reaction conditions. Arynes with an electron-withdrawing group upon hydroboration furnished unusual *ortho*-regioisomers, which indicates a hydroboration process with hydride-transfer character.

Scheme 1.24: Hydroboration of Arynes with N-Heterocyclic Carbene Boranes

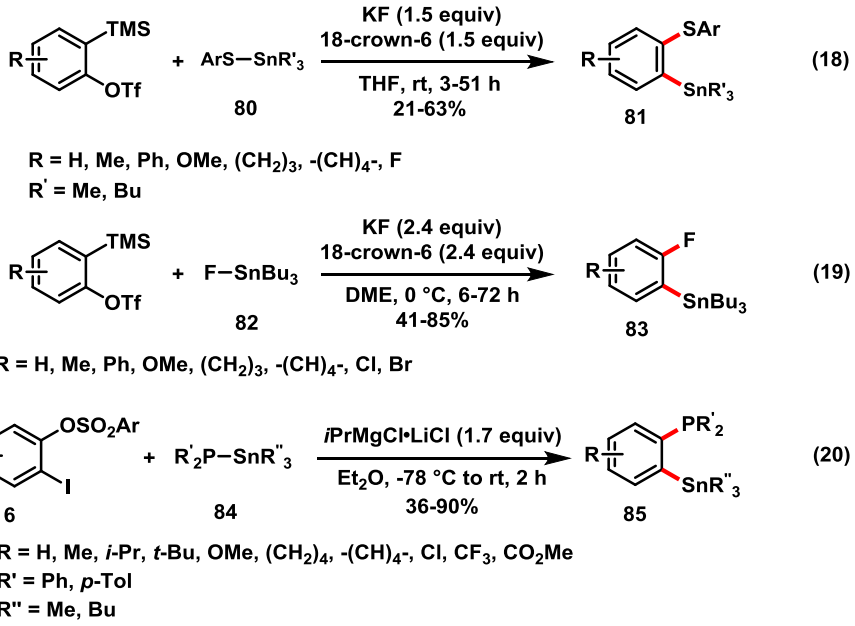


R = H, Me, -(CH)$_4$-
R^1 = Me, *i*-Pr, Dipp
R^2 = H, Me, -(CH)$_4$-, OMe, Br, F

Apart from this, insertion of arynes to various element-element σ-bonds is given in Scheme 1.25. In 2004, Yoshida, Kunai and coworkers reported the insertion of arynes to the Sn-S σ-bond of stannyl sulfides **80**. This thiostannylation reaction furnished the versatile 2-(arylthio) arylstannanes **81**, which are amenable for further transformations by means of traditional metal-catalyzed cross-coupling reactions (Scheme 1.25, eq 18).[47] Installation of the fluorine atoms into aromatic frameworks is the topic of immense interest, because fluorinated aromatic compounds are extensively utilized in pharmaceuticals and agrochemicals. The same group developed the fluorostannylation reaction by the insertion of arynes into the F-Sn σ-bond of tin fluoride **82** leading to the synthesis of diverse 2-fluoroarylstannanes **83** under mild reaction conditions (eq 19).[48] Moreover, 2-Fluoroarylstannanes were further utilized in the synthesis of fluorinated biaryls via Migita-Kosugi-Stille reaction. Mechanistic experiments indicate that fluoride ion plays a vital role in fluorostannylation reaction because it increases the solubility of Bu_3SnF which initiates the insertion process. In addition, synthetic utility of present method has been demonstrated in the formal total synthesis of anti-inflammatory drug flurbiprofen. In their efforts to develop a transition-metal-free reaction for the preparation of *ortho*-functionalized arylphosphanes, Studer and coworkers disclosed a practical and efficient approach for the synthesis of functionalized *ortho*-trialkylstannyl arylphosphanes **85** by the insertion of arynes into the Sn-P σ-bond of stannylated phosphanes **84**. However, attempted reaction of **84** with aryne generated form 2-(trimethylsilyl)-aryl triflate **1a** using KF as a fluoride source with 18-crown-6 additive was not successful, due to the instability of stannylated phosphanes towards the fluoride

anion. Consequently, the Knochel procedure for aryne generation from sulfonate **6** in the presence of *i*PrMgCl.LiCl at -78 °C in Et_2O solvent with stannylated phosphanes **84** furnished the expected insertion products in good to excellent yields (eq 20).[49] Additionally, stannylated products were employed in the synthesis of valuable *ortho*-substituted arylphosphanes.

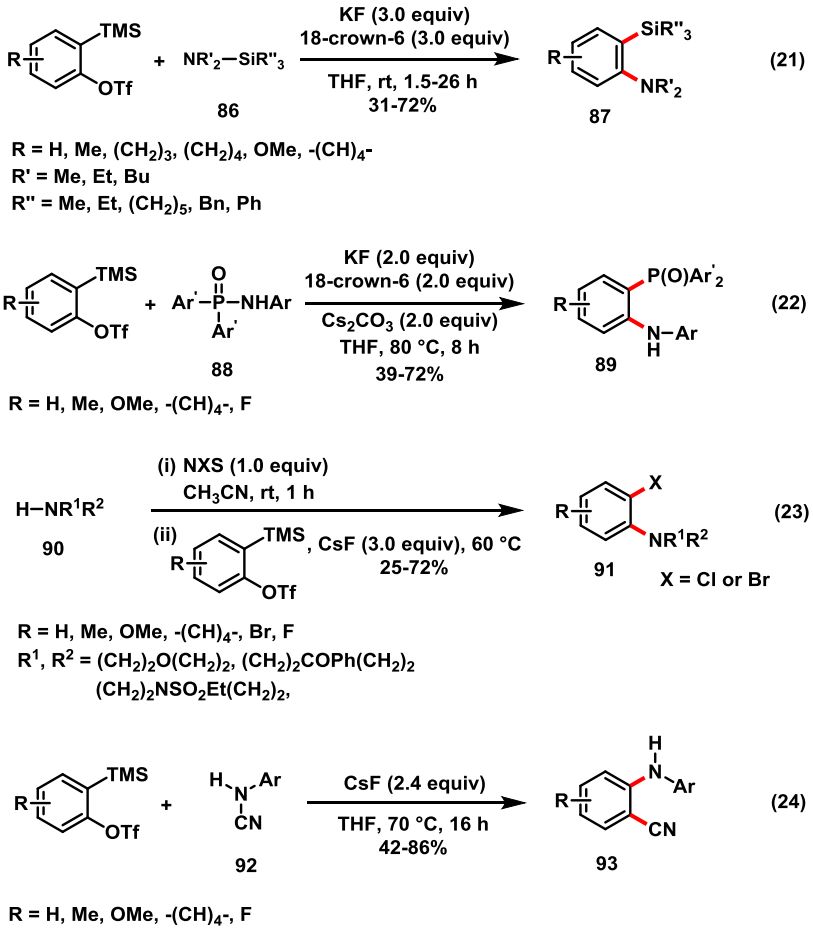
Scheme 1.25: Insertion of Arynes into the S-Sn, F-Sn, and P-Sn σ-Bonds



Insertion of arynes into the nitrogen-silicon σ-bond of aminosilanes **86** resulting in variety of functionalized 2-silylaniline derivatives **87** in moderate to good yields was uncovered by Yoshida, Kunai and coworkers (Scheme 1.26, eq 21).[50] Notably, this aminosilylation reaction worked under mild reaction conditions. In 2013, Zhang and coworkers reported the insertion reaction of arynes to P-N bond of arylphosphoryl amides **88** leading to the formation of *ortho*-amine substituted arylphosphine oxides **89** (eq 22).[51] Synthesis of arylphosphines with bulky *ortho*-substituted functional groups is difficult to accomplish because of its inherent properties. However, present method provided straightforward access to the number of useful bidentate aminophosphine ligands. Subsequently, Wang and coworkers disclosed a transition-metal-free one-pot procedure for the synthesis of *orhto*-haloaminoarenes **91** by the insertion of arynes into a nitrogen-halide bond (N-X) with broad substrate scope (eq 23).[52] In this case, the nitrogen-halogen bond (N-X) was formed in situ by the treatment of secondary amines **90** with *N*-

halosuccinimide. Labile N-X bond easily underwent an insertion into arynes to furnish *ortho*-haloaminoarenes in good yields. However, insertion product was not observed with N-I bond. Additionally, *ortho*-haloaminoarenes were easily transformed to *ortho*-substituted aniline derivatives using Pd-catalyzed coupling reactions demonstrating the synthetic utility of present method. Recently, Zeng and coworkers developed an efficient protocol for the synthesis of 1,2-bifunctional aminobenzonitriles **93** by the insertion of arynes to N-CN bond of aryl cyanamides **92** (eq 24).[53] Broad substrate scope, transition-metal-free conditions and good yields of products are the noteworthy features of this method. In addition, post-synthetic functionalization of aminocyanation products furnished the diverse and important 1,2-disubstituted benzene derivatives.

Scheme 1.26: Insertion of Arynes into the Nitrogen-Heteroatom σ-Bonds

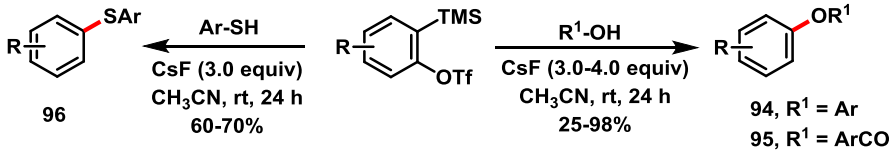


1.5.2. Arylation Reactions

An efficient, mild and transition-metal-free method for the *O*-arylation of phenols and arylcarboxylic acids, and *S*-arylation of arene thiols by the insertion of arynes into

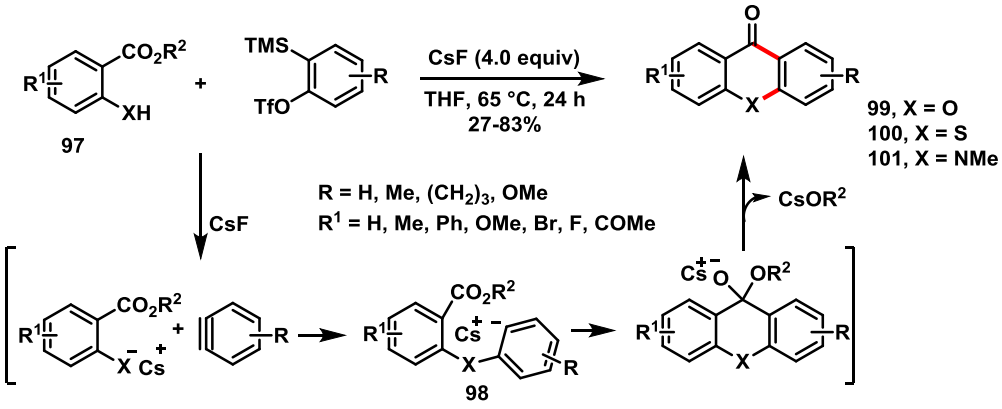
the O-H, and S-H bonds leading to the formation of diaryl ethers **94**, aryl esters **95**, and diaryl thiols **96** respectively has been uncovered by Liu and Larock (Scheme 1.27).[54] Notably, these reactions worked under mil reaction conditions with excellent functional group compatibility and high regioselectivity.

Scheme 1.27: *O*-Arylation of Phenols, Arylcarboxylic Acids and *S*-Arylation Arene Thiols



Additionally, this methodology was applied in the synthesis of biologically interesting xanthones **99**, thiaxanthones **100** and acrydones **101** derivatives via a tandem insertion-cyclization sequence of arynes with 2-substituted benzoates **97** in excellent yields (Scheme 1.28).[55] The reaction proceeds via the intermolecular nucleophilic addition of the substituted benzoates to the arynes to form the aryl anion intermediate **98**, subsequent intramolecular electrophilic cyclization of **98** furnished the final product.

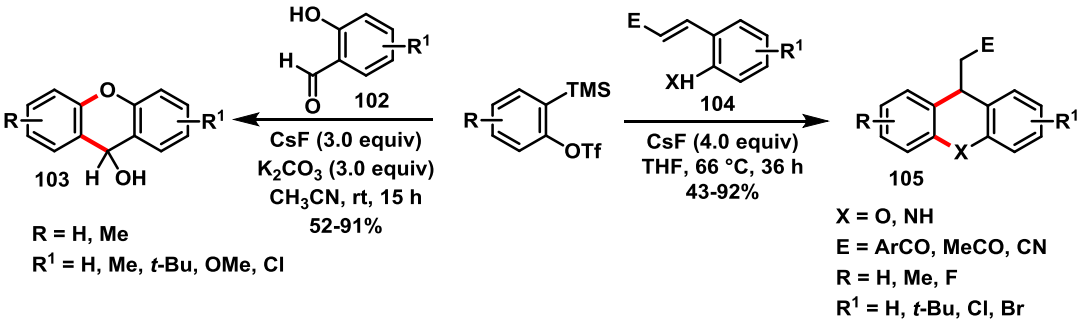
Scheme 1.28: Tandem Insertion-Cyclization of Arynes with 2-Substituted Benzoates



Moreover, Okuma and coworkers used similar strategy for the synthesis of 9-hydroxy xanthenes **103** by the reaction of the salicylaldehydes **102** with arynes in presence of base under mild reaction conditions (Scheme 1.29).[56] The reaction proceeds via the nucleophilic addition of -OH group to arynes followed by subsequent cyclization affording 9-hydroxy xanthenes **103** in good yields. In addition, Huang and Zhang uncovered a cascade process for the synthesis of 9-functionalized xanthenes/acridines **105**.[57] The reaction involves the nucleophilic addition of -OH/NH_2 groups of

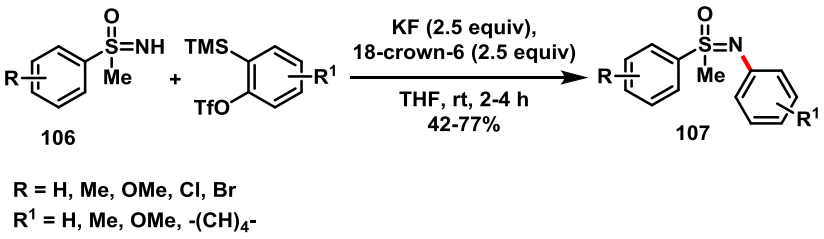
phenols/anilines **104** having a Michael acceptor at the 2-position to arynes followed by intramolecular cyclic Michael addition of in situ generated aryl anion intermediate to give final products **105**.

Scheme 1.29: Cascade Insertion-Cyclization Involving Arynes



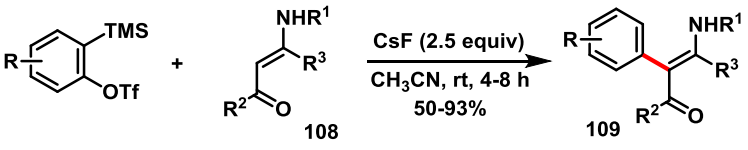
Very recently, a transition-metal-free process for the *N*-arylation of sulfoximines **106** via the insertion of arynes to the N-H bond leading to the synthesis of *N*-aryl sulfoximine derivatives **107** has been reported by Singh and coworkers (Scheme 1.30).[58] Mild reaction conditions, shorter reaction time, and broad substrate scope are the noteworthy features of this method.

Scheme 1.30: *N*-Arylation of Sulfoximines



Aryne insertion to the element-element σ-bond is well established but the insertion of aryne to C-H σ-bond to provide C-arylated product is still under exploration. In their seminal report, Ramtohul and Chartrand developed a mild, efficient, and transition-metal-free method for the C-arylation of β-enamino esters and ketones **108** via

Scheme 1.31: C-Arylation of β-Enamino Esters and Ketones with Arynes

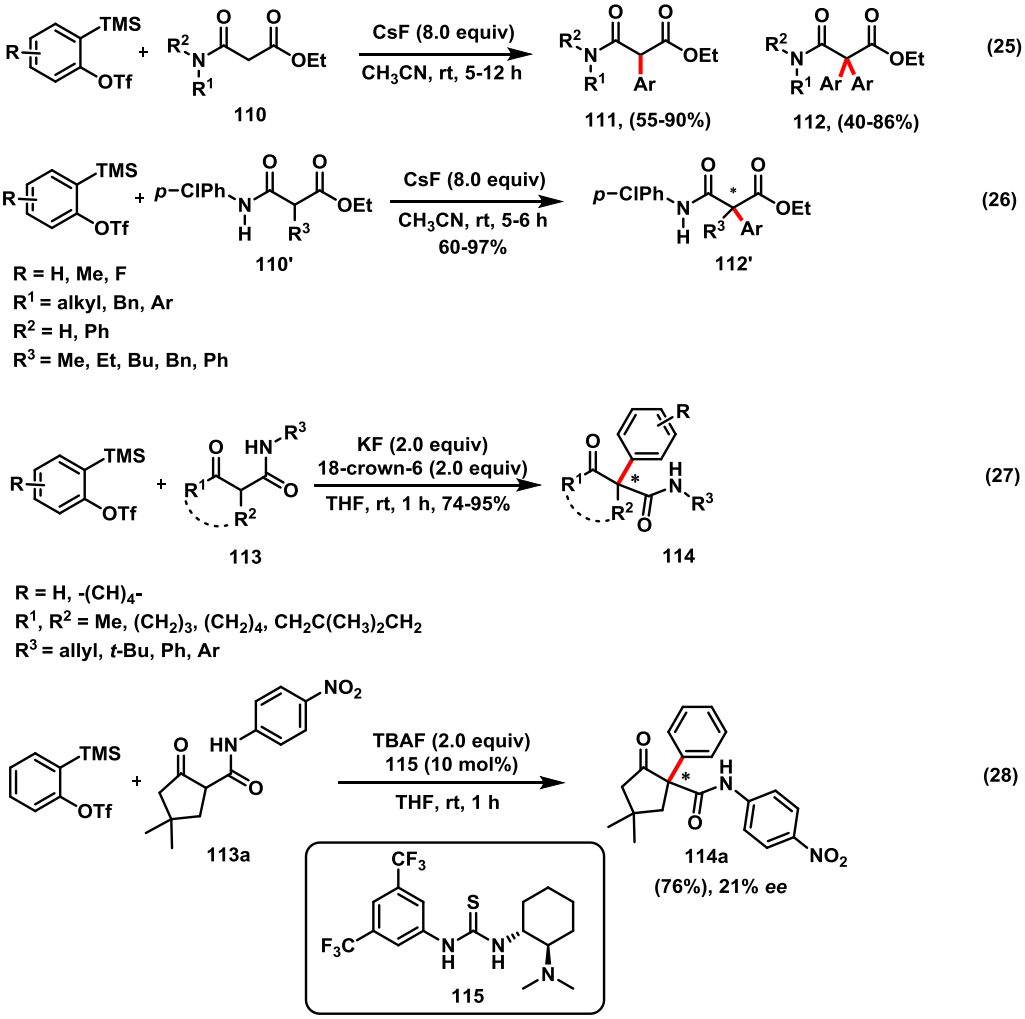


R = H, Me, $(CH_2)_3$, $O(CH_2)O$, F
R^1 = *i*-Pr, Ph, Ar
R^2 = OMe, OEt, Me, Ph
R^3 = Me, CO_2Me, Ar

formal insertion of arynes to the *β* C-H bond. Present method furnished the variety of substituted aromatic *β*-enamino esters **109** with high functional group tolerance in moderate to excellent yields (Scheme 1.31).[59]

Notably, *α*-arylation of *β*-dicarbonyl compounds is typically based on the transition-metal catalyzed cross-coupling reactions and few organocatalytic methods are also known.[60] The group of Mhaske and Rodrigues independently reported a transition-metal-free C-arylation of *β*-dicarbonyl compounds by the insertion of arynes into the *α* C-H *σ*-bond under mild reaction conditions. *β*-Dicarbonyl compounds so far known to offer C-C insertion product with arynes.[36,38] Mhaske's group achieved chemoselective *α*-arylation of *α*-substituted/unsubstituted malonamide esters **110**/**110**' (Scheme 1.32, eq 25).[61] Interestingly, under optimized reaction conditions, present reaction enabled the

Scheme 1.32: *α* C-Arylation of *β*-Dicarbonyl Compounds with Arynes

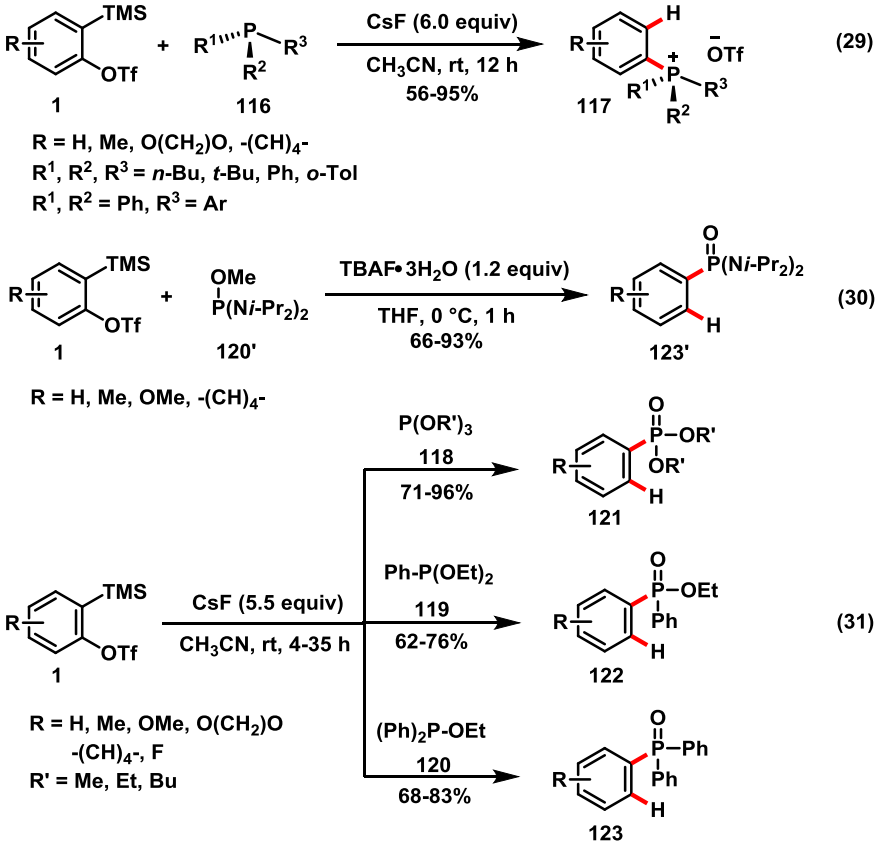


selective mono- or diarylation **111**, **112** of malonamide esters. Additionally, synthetic utility of this transformation has been further extended in the synthesis of compounds containing racemic benzylic quaternary stereocentres **112'** (eq 26). Moreover, Rodrigues, Coquerel and coworkers synthesized densely functionalized aromatic compounds **114** containing all carbon quaternary stereocentre by the *α*-arylation of secondary *β*-keto amides **113** using arynes as the aryl source (eq 27).[62] Interestingly, for the first time they employed arynes in asymmetric transformations, for instance the attempted *α*-arylation of **113a** with aryne by using thiourea based chiral catalyst **115** afforded the product **114a** in 76% yield with 21% *ee* (eq 28).

Carbon-phosphorus bond-forming reactions are very important in organic chemistry because organo-phosphurus compounds have huge applications in pharmaceutical, agrochemical, materials science, and organometallic chemistry. In 1961, Griffin and Castellucci reported the *P*-arylation of alkoxyphosphines using aryne as aryl source generated from *ortho*-bromofluorobenzene in the presence of magnesium at reflux conditions leading to the formation of aryloxophosphorus compounds.[63] However, this reaction afforded products in low yields. Later, Juge and coworkers developed a mild and efficient method for the synthesis of various achiral and chiral phosphonium salts **117** by the reaction of organophosphines **116** with arynes (Scheme 1.33, eq 29).[64] The reaction is initiated by the nucleophilic addition of phosphines to the aryne generated from the precursor **1** using CsF in CH_3CN to form the phosphonium anion, which is protonated by the CH_3CN to furnish the *P*-arylated salt. Additionally, the group of Hosoya[65] and Mhaske[66] independently reported the *P*-arylation of alkoxyphosphines **118**, **119**, and **120** using arynes generated from **1** (Scheme 1.33, eqs 30, 31). Hosoya and Yoshida performed a deuterium labeling experiment using TBAF.*n*D_2O. They observed the incorporation of deuterium at the *ortho*-position of the product, which clearly indicates the role of hydrated water of TBAF in the protonation of aryl anion intermediate formed by the initial nucleophilic addition of phosphine to aryne. This reaction afforded *P*-arylated products **123'** in excellent yields (eq 30). Moreover, synthetic utility of present reaction has been demonstrated in aryne MCCs using CO_2 as the third-component leading to the synthesis of *ortho*-substituted aromatic organophosphorus compounds. Mhaske and

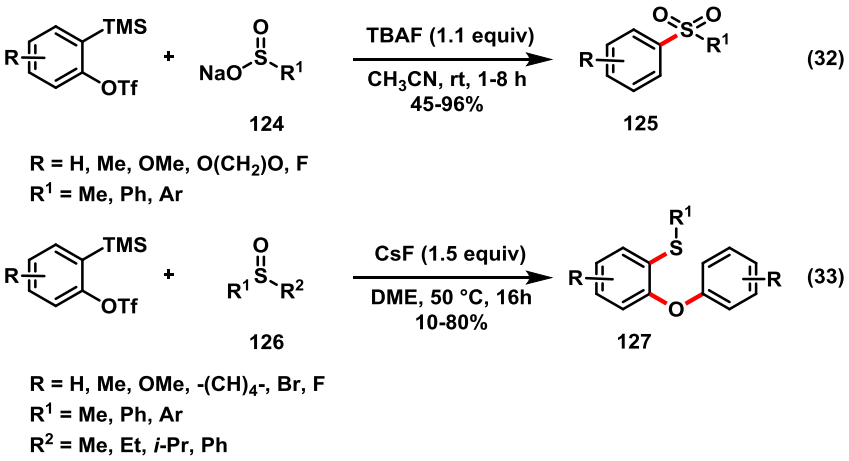
coworkers prepared functionalized aryl-phosphonates **121**, aryl-phosphinates **122**, and aryl-phosphine oxides **123** by the *P*-arylation reaction using aryne (eq 31).

Scheme 1.33: *P*-Arylation of Organophosphines and Alkoxyphosphines using Arynes



Recently, Mhaske and coworkers described the transition-metal-free method for the construction of C-S bond by the *S*-arylation of alkyl/aryl sodium sulfinates **124** using arynes as aryl source and synthesized variety of aryl sulfones **125** under mild reaction condition with good yields (Scheme 1.34, eq 32).[67] Subsequently, Wang and coworkers developed an insertion reaction of arynes to the S-O bond of sulfoxides **126** leading to the formation of thioethers **127** (eq 33).[68] Mechanistic experiments carried out in the presence of carbonyl compounds resulted in the formation of epoxide and thioether products. This experiment sheds light on the reaction mechanism and indicates that the reaction proceeds through an insertion of arynes into the S-O bond followed by the generation of sulfur ylide as the key intermediate. Sulfur ylide transfers the methylene group to carbonyl compound to form epoxide and corresponding thioether product.

Scheme 1.34: Construction of C_{aryl}-S Bond using Arynes

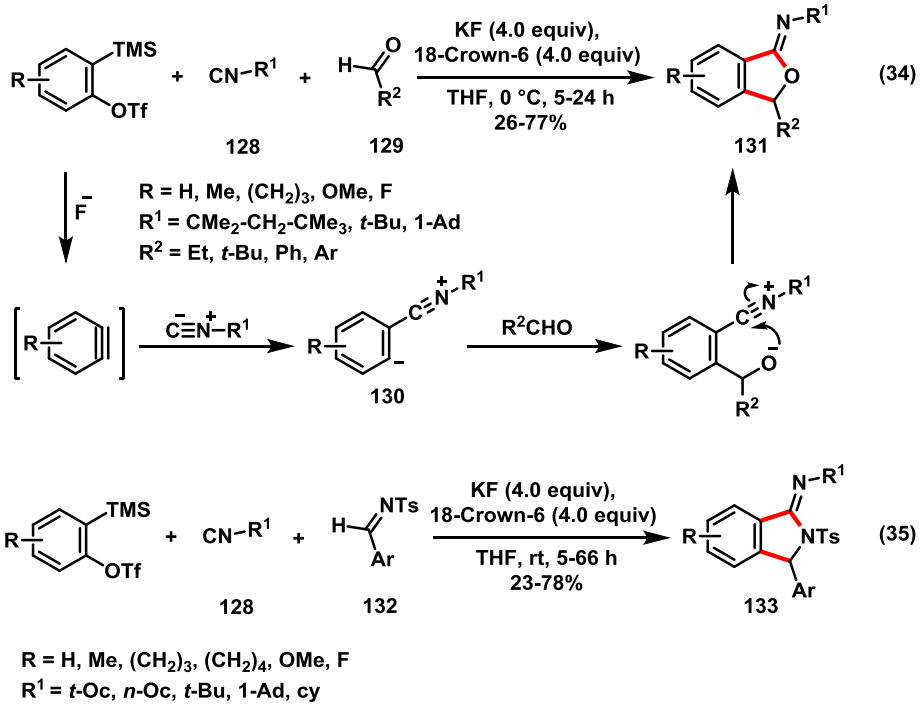


1.5.3. Multicomponent Couplings (MCCs)

In recent years, aryne-based reactions have achieved remarkable success, particularly in transition-metal-free multicomponent couplings (MCCs). MCCs involving arynes introduced a novel and versatile tool in synthetic organic chemistry for the facile construction of benzoannulated structures and 1,2-disubstituted arene scaffolds in one step.[14] The key to success of these reactions is the mild reaction conditions involved in Kobayashi's method for aryne generation, which allows arynes to serve as connector between the nucleophilic and electrophilic components. A brief account of aryne MCCs and primarily their applications in the synthesis of valuable heterocycles is provided in the present section.

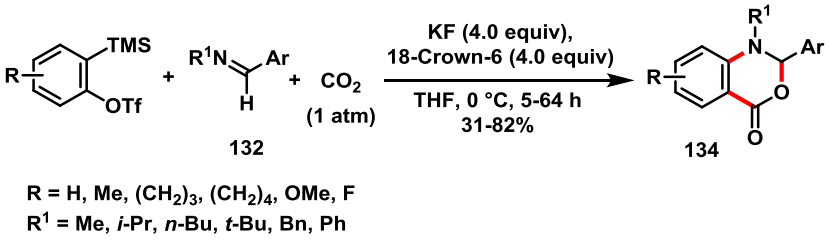
In their first report on the use of isocyanide as a neutral nucleophilic trigger in aryne MCCs, Yoshida, Kunai, and coworkers reported a unique three-component reaction of arynes with isocyanides **128** and aldehydes **129** under mild reaction conditions and synthesized iminoisobenzofurans **131** in good yields (Scheme 1.35, eq 34).[69] Moreover, activated imines **132**, ketones, and 1,4-benzoquinones have also been utilized as the electrophilic component instead of aldehydes and the corresponding products **133** were isolated in good yields (eq 35).[70] The reaction is initiated by the nucleophilic attack of isocyanide to aryne to form the 1,3-zwitterionic intermediate **130**, which is subsequently trapped by the aldehyde followed by intramolecular cyclization to furnish the final product.

Scheme 1.35: MCCs Involving Arynes, Isocyanides and Aldehydes or Activated Imines



Additionally, the same group extended their efforts for successful utilization of CO_2 as a C_1 source and revealed the aryne MCCs initiated by imines **132**. The resultant zwitterion was intercepted using CO_2 as a third-component leading to the synthesis of pharmacologically important benzoxazinone derivatives **134** under mild reaction conditions (Scheme 1.36).[71]

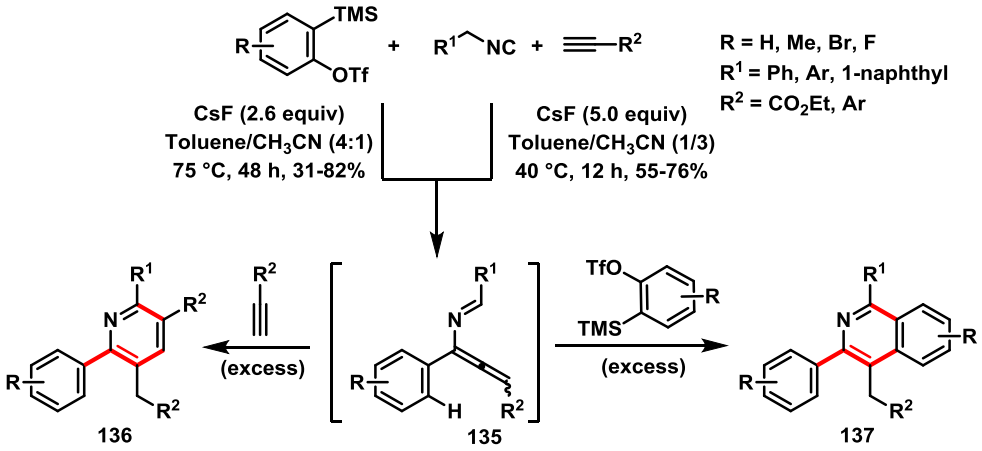
Scheme 1.36: MCCs Involving Arynes, Imines and CO_2



Sha and Huang developed the arynes MCCs involving isocyanides and terminal alkynes.[72a] Appropriate selection of the reaction conditions facilitated the direct access to polysubstituted pyridines and isoquinolines with excellent selectivity. In this case, initially formed isocyanide-aryne 1,3-zwitterionic intermediate was intercepted by the terminal alkyne to generate the allenyl imine intermediate **135**. Subsequent cycloaddition of **135** with excess terminal alkynes furnished pyridines **136** or with excess arynes

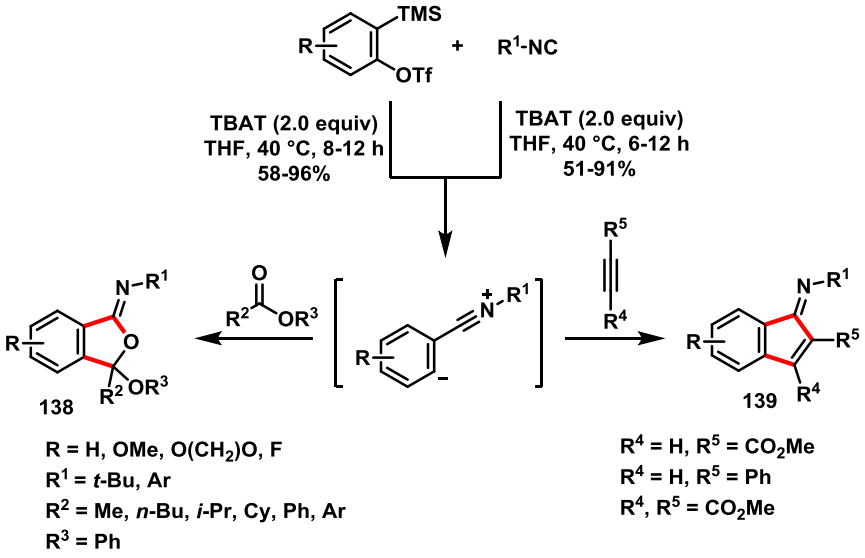
resulted in the formation of isoquinolines **137** (Scheme 1.37). Moreover, interception of the aryne-isocyanide 1,3-zwitterionic intermediate with 3-bromopropyne afforded the disubstituted pyridines in good yields.[72b]

Scheme 1.37: MCCs Involving Arynes, Isocyanides and Terminal Alkynes



In MCCs aryne acts as both an electrophile and a latent nucleophile during the course of the reaction like aldehydes in Passerini reaction. In 2011, Stoltz and coworkers developed an aryne-intercepted version of the Passerini reaction for the synthesis of *ortho*-ketobenzamides by the three-component reaction of arynes, isocyanides and phenyl esters. Surprisingly, these aryne MCCs furnished the phenoxy iminoisobenzofuran motifs **138** in good yields (Scheme 1.38).[73] Notably, they developed one-pot procedure to

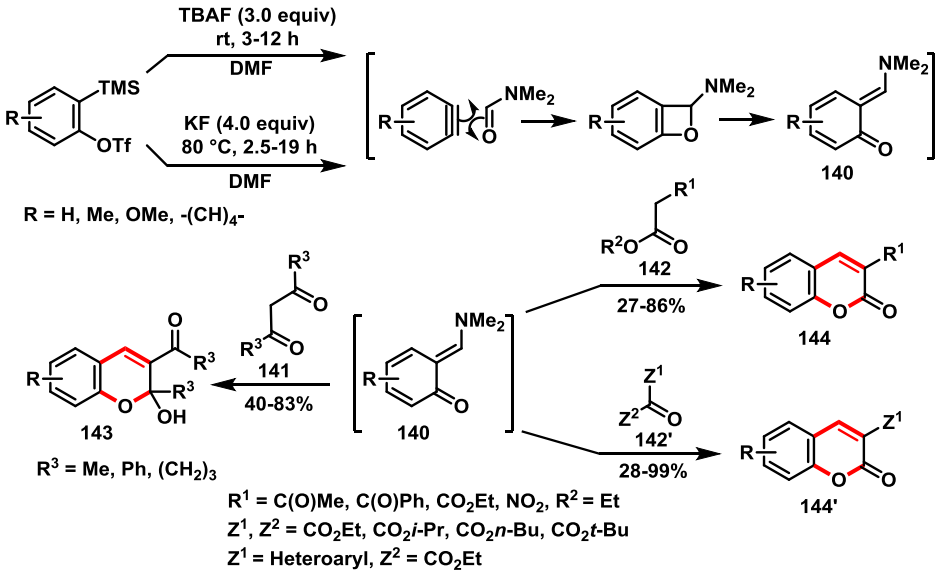
Scheme 1.38: MCCs Involving Arynes, Isocyanides and Phenyl Ester or Electrophilic Alkynes



prepare an originally targeted *ortho*-ketobenzamides. The MCC was carried out under optimized reaction conditions followed by the treatment of reaction mixture with saturated aqueous solution of oxalic acid resulted in the hydrolytic cleavage of **138** to furnish *ortho*-ketobenzamides. Furthermore, when electron-deficient internal and terminal alkynes were used in place of the ester component, the reaction furnished carbocyclic imino indenones **139**.

Interestingly, the multicomponent coupling reaction based on the insertion of arynes became an attractive process for the preparation of complex molecules. The underlying principle in these transformations involves the insertion of arynes into the π-bonds of various olefins and carbon-heteroatom bonds through a formal [2 + 2] cycloaddition to form a benzannulated four-membered ring, which on subsequent retro-4π electrocyclic ring opening generates an *ortho*-quinomethide intermediate or the analogues in reaction mixture. *ortho*-Quinomethide intermediate can be intercepted with third component to give MCC product.

Scheme 1.39: MCCs of Arynes with DMF and Active Methylene Compounds

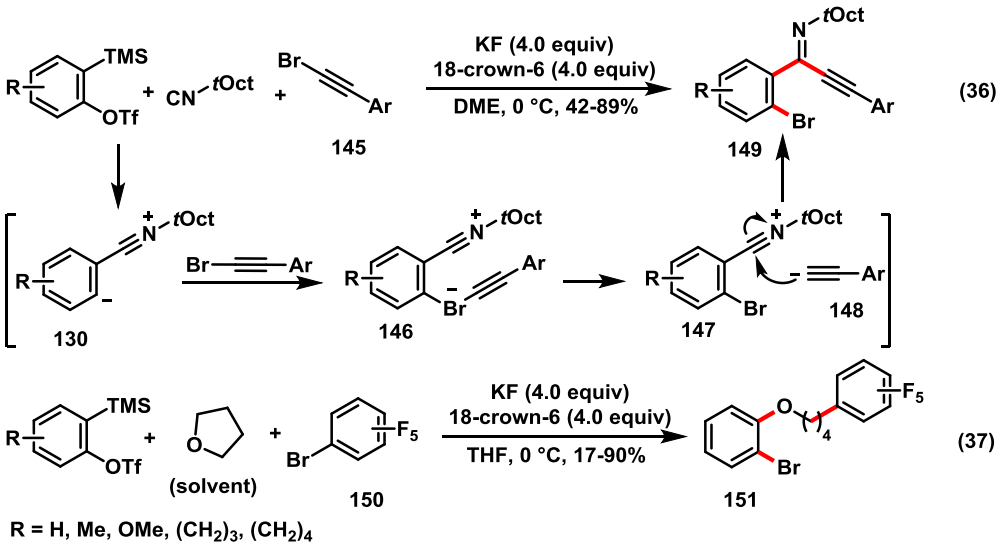


The research group of Miyabe and Yoshida independently reported the trapping of the *ortho*-quinone methide intermediate **140** generated by the insertion of arynes into the C=O bond of dimethyl formamide (DMF) with active methylene compounds. The reaction of aryne, DMF and cyclic/acyclic 1,3-diketones **141** or β-ketoester/α-(hetero)aryl esters **142** as the third component afforded 2*H*-chromenes **143** or coumarine derivatives

144 respectively (Scheme 1.39).[74] Moreover, Miyabe and coworkers extended their efforts in one-pot synthesis of *ortho*-disubstituted arene using arynes, formamides and dialkylzincs.[75] Additionally, Similar strategy utilized in the synthesis of dihydrobenzofurans and benzofurans involving insertion of arynes into the C=O bond of formamides followed by trapping with zinc enolates of α-chlorinated methines in [4 + 1] annulation reaction.[76]

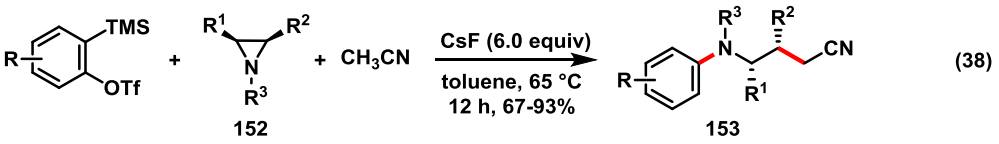
In an attempt to expand the scope and utility of aryne MCCs with isocyanide, Yoshida group used alkynyl bromides **145** or polyfluorinated aryl bromides **150** as the third component to intercept the isocyanide-aryne 1,3-zwitterionic intermediate **130**.[77] The 1,3-zwitterionic intermediate reacts with the alkynyl bromides **145** to form the aryl-bromide bond in **147** and produces the aryl acetylide **148** through the bromine ate complex **146**. Subsequent attack of aryl acetylide **148** on the nitrilium cation **147** furnished the *ortho*-functionalized bromoarenes **149** with the formation of two C-C bonds and a C-Br bond (Scheme 1.40, eq 36). Interestingly, THF and cyclic ethers have also been employed as the nucleophilic trigger to generate the 1,4-dipole, which was effectively captured with polyfluoro aryl or alkynyl bromides under mild reaction conditions with good functional group compatibility (eq 37). Moreover, the synthetic utility of bromoarenes has been demonstrated in the synthesis of multisubstituted isoquinolines and a benzo[*b*]oxepine-based nonsteroidal estrogen.

Scheme 1.40: MCCs of Arynes and Isocyanides (or Cyclic Ethers) with Alkynyl (or Polyfluoro Aryl) Bromides

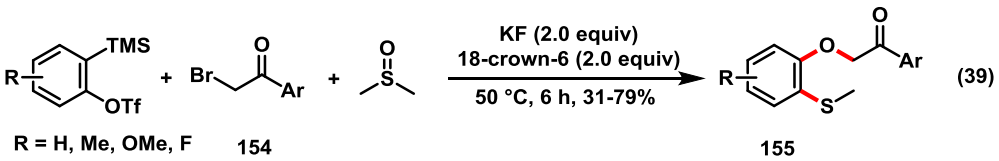


Recently, a stereospecific aryne MCCs triggered by aziridines **152** with CH_3CN as the third-component was uncovered by Larionov and coworkers. This protocol furnished the *N*-aryl γ-aminobutyronitriles **153** in good yields (Scheme 1.41, eq 38).[78] Moreover, Chen, Xiao and coworkers reported the aryne MCCs initiated by insertion of arynes into the S=O bond of dimethyl sulfoxide (DMSO) using α-bromo carbonyl compound **154** as the third-component leading to the formation of aryl methyl thioethers **155** (eq 39).[79] This reaction provided access to the biologically important aryl methyl thioethers in good yields, and DMSO served as both methyl thiolation agent and oxygen source.

Scheme 1.41: Arynes MCCs Involving Solvents CH_3CN and DMSO



R = H, Me, OMe, -(CH)$_4$-, F
R^1 = H, Bn
R^2 = allyl, Ph, Ar
R^3 = *i*-Pr, Cy, Bn, Ph



R = H, Me, OMe, F 154 155

1.6. Focal Theme of the Thesis

From the above discussion, it is clear that the success of arynes in organic synthesis can be attributed to their intrinsic electrophilic nature and the mild reaction conditions involved in Kobayashi's method for aryne generation by fluoride-induced 1,2-elimanation of 2-(trimethylsilyl)aryl triflates. The central theme of this thesis is the transition-metal-free applications of arynes in pericyclic reactions, insertion reactions and multicomponent reactions by using Kobayashi's method of aryne generation. If successful, these studies will result in the rapid synthesis of complex organic scaffolds by forming multiple carbon-carbon and carbon-heteroatom bonds in a single process. Moreover, this can highlight the synthetic utility of this highly reactive intermediate in organic synthesis.

The detailed study on Diels-Alder reaction of arynes with challenging dienes like pentafulvenes, styrenes, indene and benzofurans has been carried out. Depending upon the coupling partner, pentafulvene can act as 2π, 4π, or 6π component in cycloaddition reactions. In addition, employing styrenes, and indene/benzofurans as the 4π-component in Diels-Alder reactions utilizing a carbon-carbon double bond, which is involved in aromaticity appears interesting. The details are presented in Chapter 2-4.

Moreover, Arynes have been utilized in various arylation reactions. The *N*-arylation of primary and secondary amines are known using arynes as aryl source. Various transition-metal-catalyzed cross-coupling reactions are well-established for the *N*-arylation of primary and secondary amines. However, the transition-metal-free as well as transition-metal-catalyzed *N*-arylation of aromatic tertiary amines, to the best of our knowledge is unknown. The systematic investigation of the transition-metal-free N-arylation of aromatic tertiary amines using arynes as aryl source has been carried out and this forms the subject of chapter 5 of the thesis.

Transition-metal-free aryne MCCs provides straightforward access to various 1,2-disustituted arenes. Amines as nucleophilic trigger in the realm of aryne MCCs have received only scant attention because it gives *N*-arylated products on reaction with arynes. In this context, the multicomponent reaction involving arynes, aldehydes and aromatic tertiary amines has been investigated. An interesting reactivity of arynes observed is presented in chapter 6.

1.7. References

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CHAPTER 2

A Practical and General Diels-Alder Reaction of Pentafulvenes with Arynes

2.1. Introduction

Pentafulvenes are non-aromatic cyclic cross-conjugated trienes.[1] Owing to their intrinsic electronic nature, pentafulvenes can exhibit diverse cycloaddition profiles. Depending upon the coupling partner, pentafulvene can function as 2π, 4π, or 6π component in cycloaddition reactions. Therefore, pentafulvenes are valuable building blocks that have been extensively studied by both organic and theoretical chemists.

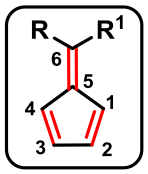


Fig 2.1: Pentafulvenes

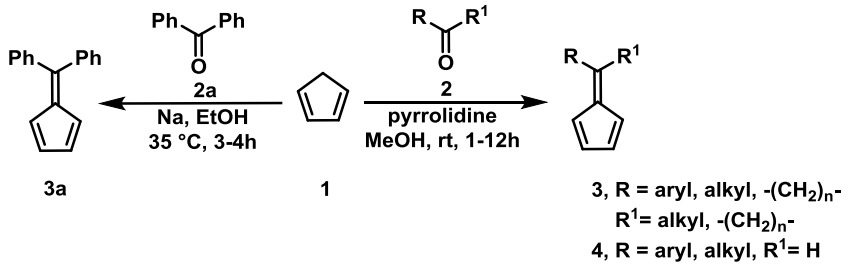
Interestingly, pioneering work of Houk and coworkers on the cycloaddition reactions of pentafulvenes, clearly rationalizes the difference in periselectivity of cycloadditions to fulvenes by an application of frontier molecular orbital theory.[2] Fulvenes act as dienophile by utilizing their HOMO with the LUMO of electron deficient diene system in inverse electron demand Diels-Alder reactions. Electron deficient nature of dienophiles results in its low-lying LUMO, causing decrease in energy barrier between LUMO of dienophile and HOMO of fulvenes to offer [4 + 2] cycloaddition reactions. Only strong electron-donating substituent at 6-position of fulvenes raises its HOMO sufficiently and fulvenes function as trienes with electron deficient 4π and 2π systems to give [6 + 4] and [6 + 2] cycloaddition reactions respectively. HOMO of the sufficiently electron rich dienes interact with the LUMO of fulvenes across C-1 and C-6 position to afford [6 + 4] cycloaddition products. The theoretical predictions for the different modes of action of fulvenes in various cycloaddition reactions were confirmed later by

experimental results. The present chapter describes the Diels-Alder reaction of arynes with pentafulvenes derived from aldehydes and ketones. Before going into the details, a brief account of cycloaddition reactions of pentafulvenes is given in the following sections.

2.2. Synthesis of Pentafulvenes

Pentafulvenes are coloured oils. The condensation of aldehydes/ketones **2** with cyclopentadiene **1** can result in the convenient synthesis of 6,6-disubstituted fulvenes **3** or 6-monosubstituted fulvenes **4** (Scheme 2.1).[3] Specifically, 6,6-diphenyl pentafulvene **3a** was synthesized by the condensation reaction of cyclopentadiene **1** with benzophenone **2a** using sodium in ethanol solvent. These are very reactive hydrocarbons sensitive to heat, which can undergo dimerization via [4 + 2] cycloaddition reaction even at 20 °C.[4]

Scheme 2.1: Synthesis of Fulvenes from Aldehydes and Ketones



2.3. Cycloaddition Reactions of Pentafulvenes

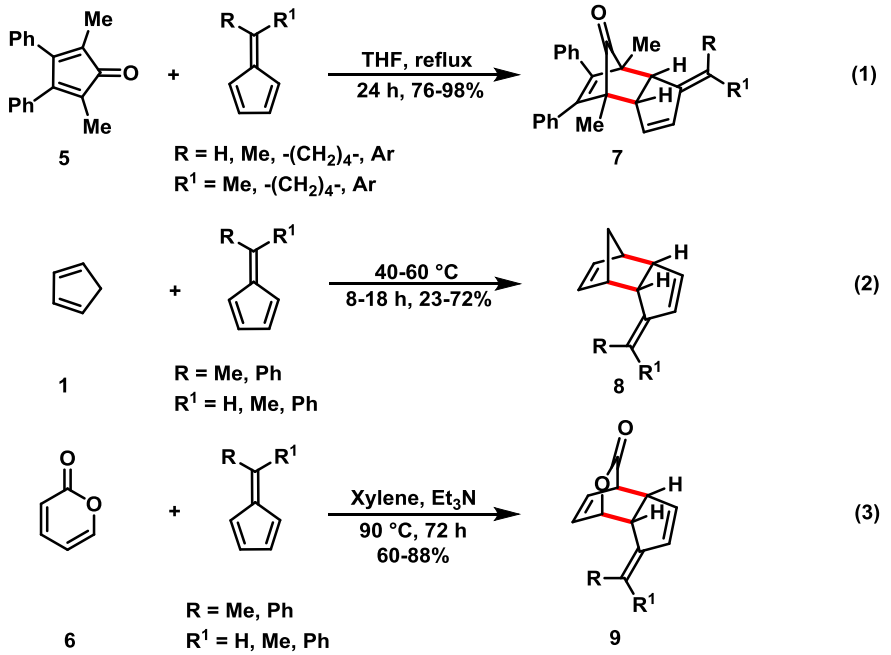
Pentafulvene cycloaddition reactions have been employed in the synthesis of diverse bridged bicyclic compounds. These are the versatile substrates in cycloaddition reaction displaying multiple reactivity modes towards dienes and dienophiles leading to a straightforward access to a variety of natural and unnatural organic molecules. The various modes of action of fulvenes in cycloaddition reactions are documented in the following pages.

2.3.1. Pentafulvenes as 2π Component

Houk and coworkers efficiently engaged 6-substituted and 6,6-disubstituted pentafulvenes as dienophile in Diels-Alder reaction with cyclic dienes such as 2,5-dimethyl-3,4-diphenylcyclopenta-2,4-dien-1-one **5** (eq 1), cyclopentadiene **1** (eq 2), and 2-pyrone **6** (eq 3) to afford the cycloaddition products **7**, **8**, and **9** respectively (Scheme 2.2).[5] They observed the formation of only *endo* [4 + 2] cycloadducts. Experimental

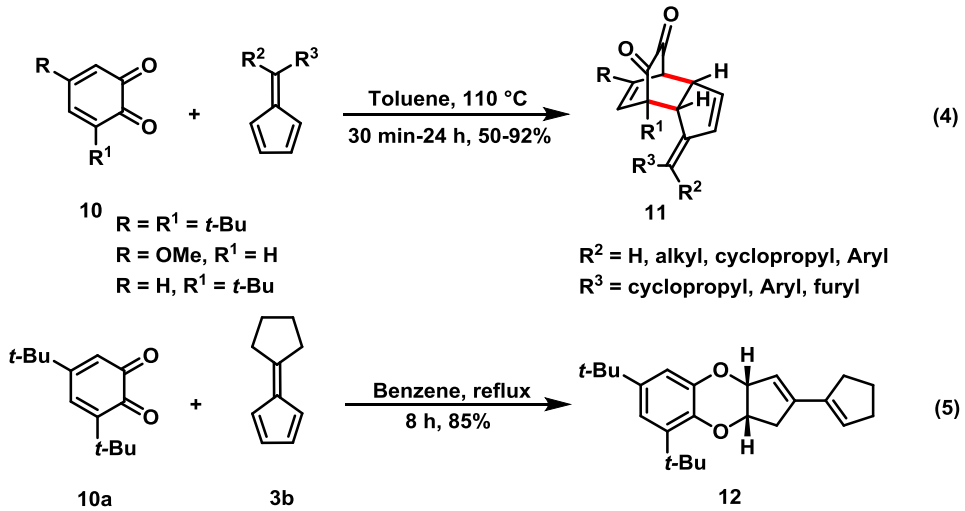
results regarding regioselectivity of these cycloadditions were found to be in agreement with the results of frontier orbital analysis.

Scheme 2.2: Diels-Alder Reaction of Cyclic Dienes with Fulvenes



Akin to fulvenes, 1,2-benzoquinones also demonstrate diverse reactivity profile in cycloaddition reactions.[6] They can show carbodiene, heterodiene, or dienophile reactivity in Diels-Alder reactions.[7] It is interesting to see the reactivity of 1,2-benzoquinones towards fulvenes, either the 1,2-benzoquinones or the fulvene can function as the diene or the dienophile. Detailed investigation led by Nair's group on the Diels-Alder reactions of 1,2-benzoquinones **10** with various symmetrical and unsymmetrical fulvenes, uncovered a very efficient protocol for the synthesis of functionalized bicyclo[2.2.2]octen-7,8-diones **11** in good yields (Scheme 2.3, eq 4).[8] Herein, 1,2-benzoquinones function as the carbodiene and the fulvene as the dienophile leading to the formation of predominantly *endo* cycloaddition products. Surprisingly, the reaction of cycloalkylfulvene **3b** with 3,5-di-*tert*-butylcyclohexa-3,5-diene-1,2-dione **10a** furnished the Diels-Alder adduct **12**. The product formed presumably from the rearranged fulvene due to isomerisation of **3b,** with the benzoquinone acting as 1,4-dioxabutadiene (eq 5).[9]

Scheme 2.3: Diels-Alder Reaction of 1,2-Benzoquinones with Pentafulvenes

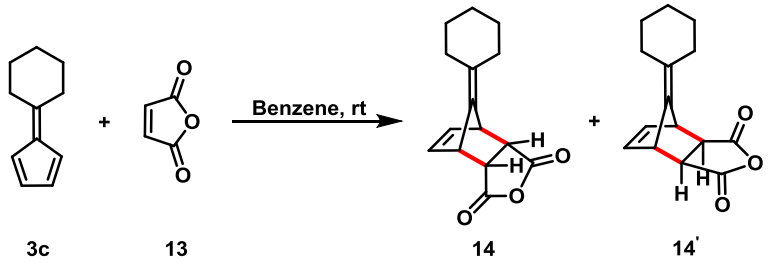


2.3.2. Pentafulvenes as 4π Component

Fulvenes are reactive dienes towards range of electron deficient dienophiles. In past decades thorough experimental and theoretical investigation of fulvene in Diels-Alder reactions has been carried out leading to a clear understanding of the transition state for these reactions.[10] 6,6-diphenylfulvene, 6,6-dimethylfulvene and 6-phenylfulvene functioning as a diene in [4 + 2] cycloaddition reaction with maleic anhydride was first observed by Diels and Alder.[11] Later, in 1935 Kohler and Kable synthesized cyclohexanone and cyclopentanone derived pentafulvenes. These fulvenes were colored oils in nature and are highly reactive. When the fulvene was left to itself, it undergoes dimerization and becomes colorless. For the characterization purpose, they transformed these fulvenes to a suitable solid through a [4 + 2] cycloaddition reaction with maleic anhydride.[12] However, their observation was striking, fulvene-maleic anhydride cycloadducts as well as those synthesized earlier by Diels and Alder were stable only in solid state. In solution it rapidly dissociated into their components, even in solution in the cold conditions in different solvents. Woodward and Baer shown that [4 + 2] cycloaddition reaction of cyclohexanone derived pentafulvene **3c** with maleic anhydride **13** at room temperature with benzene as solvent furnishes the mixture of *endo* **14** and *exo* **14'** cycloadducts, *endo* product **14** dissociates rapidly under reaction conditions with increase in the reaction temperature and time, while *exo* isomer **14'** was stable (Scheme

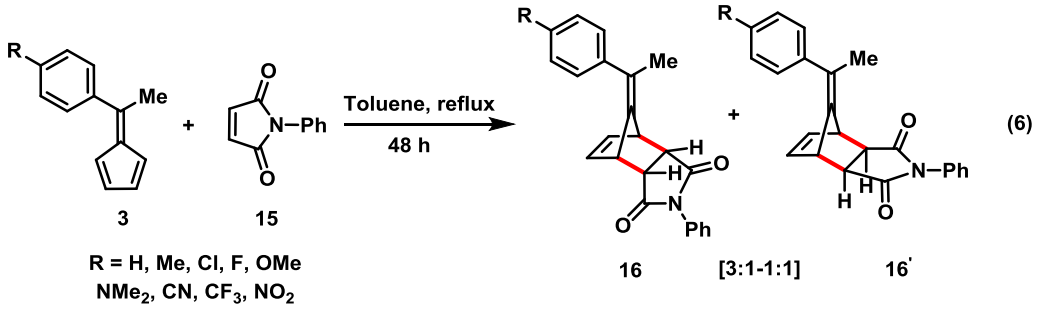
2.4).[13] First time they provided the direct experimental proof for the formation of these stereoisomers **14** and **14'**.

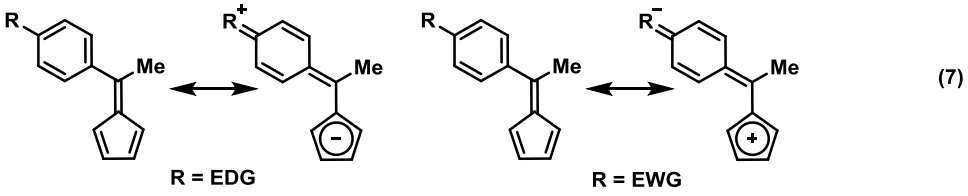
Scheme 2.4: Diels-Alder Reaction of Pentafulvenes with Maleic Anhydride



Remote substituent effects in *p*-substituted 6-phenyl-6-methylfulvenes **3** on the reactivity and stereoselectivity in Diels-Alder reactions with *N*-phenylmaleimide **15** leading to the formation of *endo* **16** and *exo* **16'** [4 + 2] cycloaddition products has been well studied by Gugelchuk and coworkers (Scheme 2.5, eq 6).[14]

Scheme 2.5: Diels-Alder Reaction of 6-Arylfulvenes with *N*-Phenylmaleimide

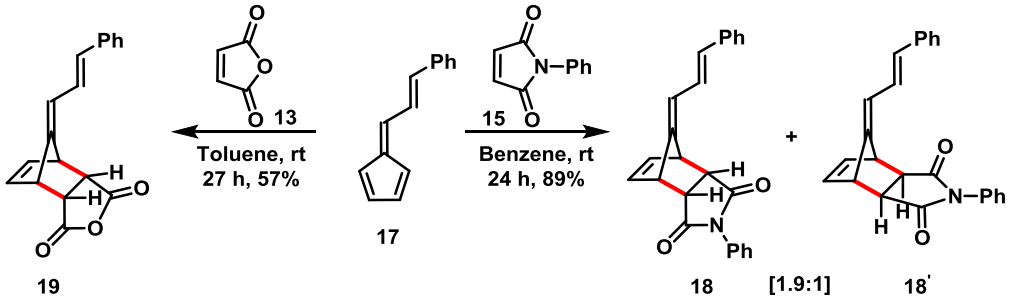




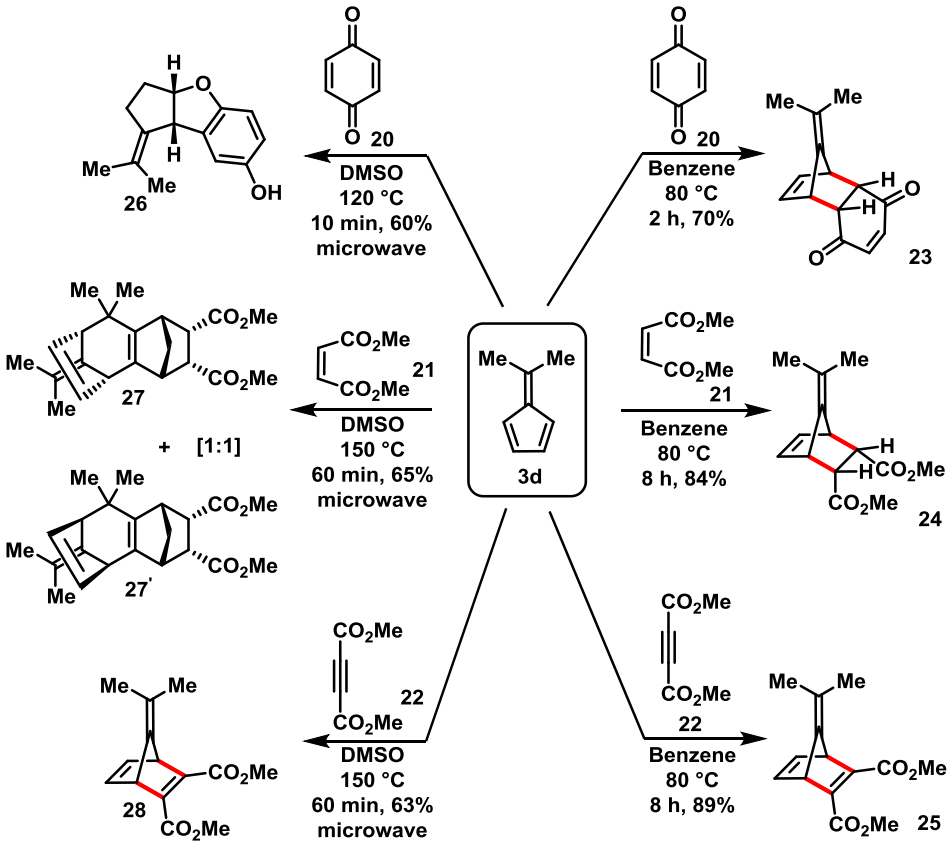
6-Arylfulvenes are known to have potential application as organic nonlinear optical materials via extended π-systems.[15] It has been suggested that the *p*-substitution on 6-arylfulvenes plays a key role in charge transfer interactions. Electron donor substituent at 4-position of the aromatic ring of **3** makes the cyclopentadiene ring more electron rich and these fulvenes could function as nonbenzenoid aromatics. In contrast, strong electron withdrawing substituent in **3** creates charge transfer in the opposite sense and fulvenes could exhibit antiaromatic properties (eq 7).[16] The experimental and theoretical results of this study clearly indicates that the reactivity of 6-arylfulvenes

towards the *N*-phenylmaleimide is an outcome of subtle interplay among electronic and steric influences that depends on the nature of each substituent on fulvenes.

Scheme 2.6: Diels-Alder Reaction of 6-Arenyl Fulvene with *N*-Phenylmaleimide and Maleic Anhydride



Scheme 2.7: Reactions of Dimethylfulvene with Alkenes and Alkyne



The cycloaddition reaction of pentafulvenes with extended conjugation having 8π-system, for instance 6-arenyl fulvenes offer the possibility of higher order cycloaddition. Nair and coworkers reported that 6-(2-phenylethenyl)fulvene **17** on reaction with *N*-phenylmaleimide **15** and maleic anhydride **13** selectively furnished the [4

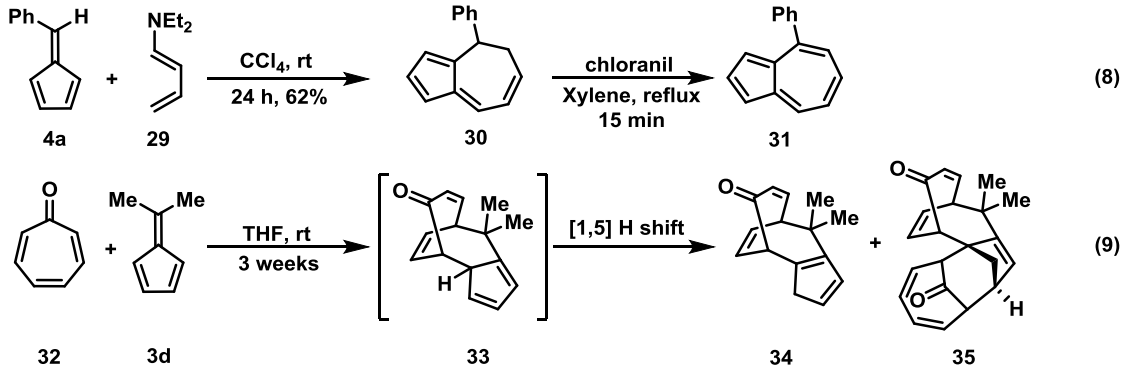
+ 2] cycloaddition products **18** and **19** respectively (Scheme 2.6).[17] In case of maleic anhydride, the *exo* isomer was observed only in trace amount.

In an attempt to expand the scope and utility of Diels-Alder reaction of pentafulvenes with a various dienophiles, the Hong group used dimethylfulvene **3d** as a diene component with 1,4-benzoquinone **20**, dimethyl maleate **21**, and dimethyl acetylenedicarboxylate **22** leading to the formation of [4 + 2] cycloadducts **23**, **24,** and **25** respectively in good yields. Additionally, they demonstrated the effect of microwave irradiation on the cycloaddition of fulvenes resulting in the formation of interesting polycyclic ring systems **26** and **27** (Scheme 2.7).[18]

2.3.3. Pentafulvenes as 6π Component

Houk and coworkers developed a selective [6 + 4] cycloaddition reaction of 6-phenylfulvene **4a** with 1-diethylaminobutadiene **29**. The reaction afforded dihydroazulene **30** in 62% yield with the loss of diethylamine from initially generated 1:1 adduct (Scheme 2.8, eq 8).[19a] Subsequently, the potential of this method has been demonstrated in a synthesis of novel azulene derivative **31** via dehydrogenation of dihydroazulene skeleton **30** with chloranil in xylene or 5%-Pd/C.[19b]

Scheme 2.8: [6 + 4] Cycloaddition Reactions of Pentafulvenes with 1-Diethylaminobutadiene and Tropone

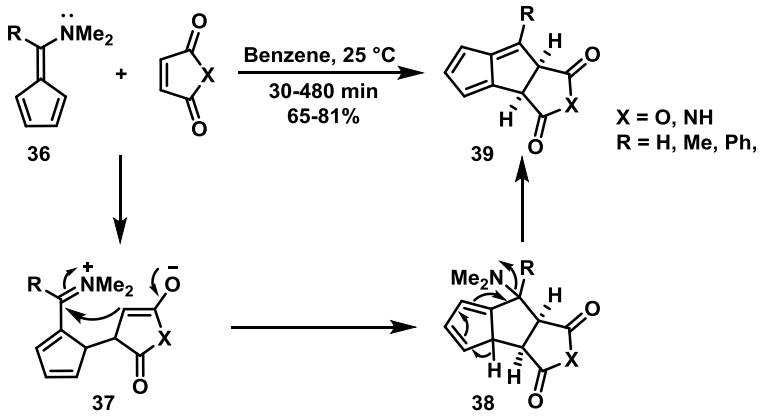


The same group developed the [6 + 4] cycloaddition reaction of dimethylfulvene with tropone. Tropone adds across the fulvene 6π system because of ideal secondary orbital interactions. Reaction of dimethylfulvene **3d** with tropone **32** in THF as a solvent at room temperature for longer reaction time of 3 weeks resulted in the formation of [6 + 4] cycloaddition product **34** in 22% yield and 1:2 adduct of fulvene-tropone **35** (66% yield based on tropone) along with [4 + 2] cycloaddition product in 4% yield. The

adducts **34** and **35** are formed via the initial [6 + 4] cycloaddition reaction of fulvene with tropone to generate cycloadduct **33,** followed by a [1,5] sigmatropic hydrogen shift to afford thermodynamically more stable cyclopentadiene **34**. Cycloadduct **34** subsequently underwent a second [6 + 4] cycloaddition reaction with another molecule of tropone to furnish the steriospecifically *exo* cycloaddition product **35** (eq 9).[20]

In 2002, Hong and coworkers reported the [6 + 2] cycloaddition reaction of electron-rich 6-aminofulvenes **36** with maleic anhydride and maleimide leading to the straightforward synthesis of pentaleno[1,2-*c*]furan and pentaleno[1,2-*c*]pyrrole (Scheme 2.9).[21] The difference in the chemoselectivity between 6-dimethyl aminofulvene and 6-alkylfulvenes or 6-arylfulvenes may be due to the electron-donating effect of amino group in **36**.

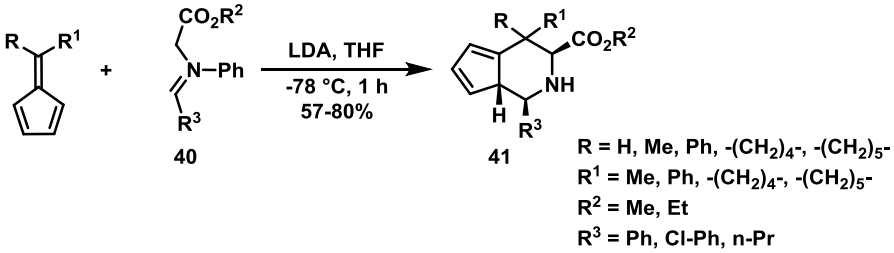
Scheme 2.9: [6 + 2] Cycloaddition Reaction of 6-Aminofulvenes with Maleic Anhydride and Maleimide



Mechanistically, this reaction proceeds via a stepwise pathway, initial addition of **36** to maleic anhydride or maleimide generates the zwitterionic intermediate **37** followed by nucleophilic attack at the C-6 position of fulvene to form the cycloadduct **38**. Elimination of dimethylamine molecule from adduct **38** resulted in the formation of product **39**. Compounds **39** are important structural motifs in various biologically active natural products such as anislactone, merrilactones and different other important synthetic intermediates.[22] Additionally, the same group developed a method for the synthesis of [2]-pyrindine **41** derivatives via a stereoselective [6 + 3] cycloaddition reaction of *N*-alkylidene glycine ester **40** with pentafulvenes in good yields (Scheme

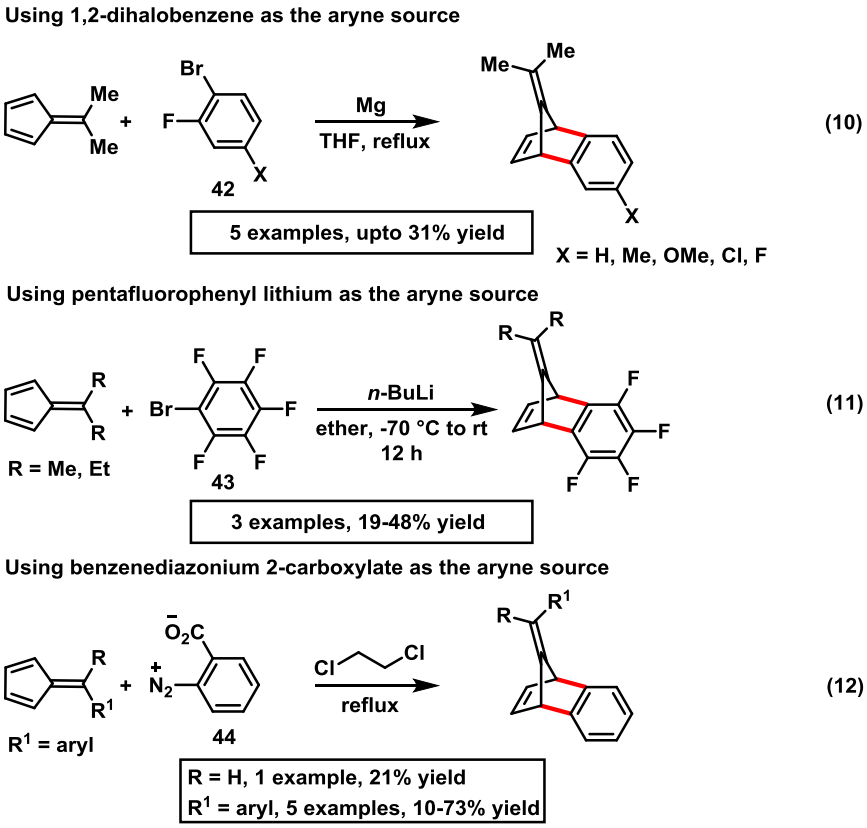
2.10).[23] [2]-Pyrindine skeleton has been found in a variety of natural products like delavayine A, incarvillateine.[24]

Scheme 2.10: [6 + 3] Cycloaddition Reaction of Pentafulvenes with *N*-Alkylidene Glycine Esters



2.4. Diels-Alder Reaction of Arynes with Pentafulvenes

Scheme 2.11: Diels-Alder Reaction of Arynes with Pentafulvenes



Arynes are versatile intermediate in a wide range of useful organic transformations.[25,26] Due to their pronounced electrophilic nature they act as excellent dienophile, with various dienes[27] and dipoles.[28] Diels-Alder reaction of aryne is an elegant method for the construction of synthetically important benzofused carbocycles

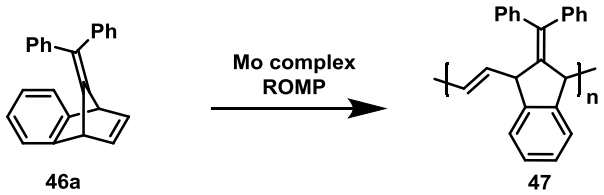
and heterocycles, which are common structural units in various biologically important natural products.

Detailed literature survey revealed that fulvenes function as dienes with arynes to give [4 + 2] cycloaddition reaction products. In 1966, Muneyuki and Tanida reported the Diels-Alder reactions of 6,6-dimethylfulvene with aryne generated from 2-bromofluorobenzene **42** using magnesium in THF as a solvent at reflux conditions leading to the formation of the benzonorbornadiene derivative (Scheme 2.11, eq 10).[29] However, this reaction is limited to only one fulvene. Later, the cycloaddition reaction of 6,6-dialkylfulvenes with tetrahalogenoarynes generated from pentafluorophenyl lithium by the reaction bromopentafluorobenzene **43** using *n*-BuLi as base in ether solvent was developed by Heaney and coworkers (eq 11).[30] Moreover, Adam and coworkers reported the reaction of aryne generated from benzenediazonium 2-carboxylate **44** with fulvenes. Interestingly in this report, a single example of the 6-substituted benzaldehyde-derived pentafulvene cycloaddition with aryne was documented in 21% yield (eq 12).[31]

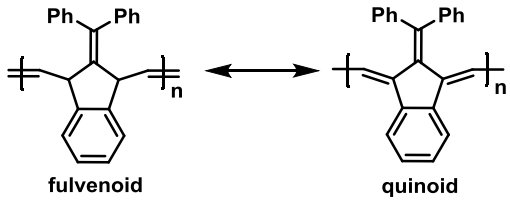
2.5. Synthetic Utility of the Benzonorbornadienes

The benzonorbornadiene derivatives are known to have very useful applications in organic chemistry. Stelzer and Schirnetta developed the ring-opening metathesis polymerization (ROMP) of fulvene-aryne cycloadduct **46a** using Mo carbene initiators leading to the formation of highly stereoregular polymers **47** (Scheme 2.12, eq 13).[32]

Scheme 2.12: Ring-Opening Metathesis Polymerization of Benzonorbornadiene



(13)



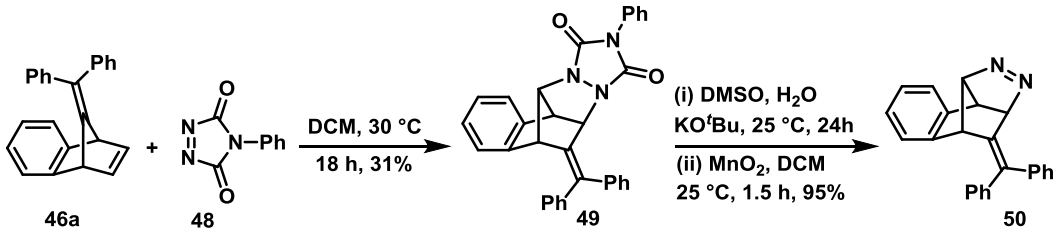
(14)

Interestingly, conjugated aromatic polymers have gained more attention, because of their mechanical, electronic, and optical properties. These polymers are valuable in the production of optoelectronic devices such as LEDS or optical switches. Regarding these

applications, a highly stereoregularity of polymers is a vital criterion for optimal properties. Variation of the substituents at 6-position on pentafulvenes allows to control the stereoregularity of these polymers. These polymers contain two very reactive bridgehead hydrogens that are both allylic and benzylic which on elimination offers a fully conjugated polymer that could be endowed with fulvenoid or quinoid geometry (eq. 14).

Cycloaddition of 4-phenyl-4*H*-1,2,4-triazole-3,5-dione (PTAD) **48** to strained benzonorbornadiene derivative **46a** offered an urazoles adduct **49** via skeletal rearrangement of dipolar intermediates. Oxidative hydrolysis of the urazoles adduct **49** resulted in a convenient entry to polycyclic azoalkane **50**, which are valuable target molecules (Scheme 2.13).[31,33,34]

Scheme 2.13: Synthesis of Polycyclic Azoalkanes

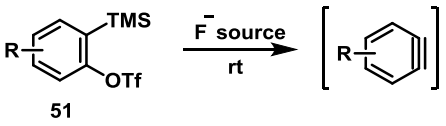


2.6. Statement of the Problem

As mentioned in the previous section, the Diels-Alder adduct of pentafulvenes and arynes *viz.* benzonorbornadiene derivatives have potential application in organic synthesis. However, in known methods for the synthesis of these cycloadducts, the substrate scope is very limited, yields are not yet optimal and a general system remains to be unexplored. The reason for less yields and narrow substrate scope lies in lower stability of pentafulvenes, utilization of strongly basic and harsh reaction conditions for the generation of arynes were not compatible for the pentafulvenes. In view of the potential synthetic utility of benzonorbornadienes, a high yielding and broad scope synthesis of these compounds is highly desirable. We envisioned to use mild condition for the generation of arynes by the fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates **51** which could be compatible with pentafulvene substrates (Scheme 2.14).[35] A detailed study of the Diels-Alder reaction of arynes with 6-substituted and 6,6-disubstituted pentafulvenes was carried out in the present chapter. This

investigation revealed a high yielding method for the synthesis of benzonorbornadiene derivatives with broad substrate scope.

Scheme 2.14: Mild Method for the Generation of Arynes

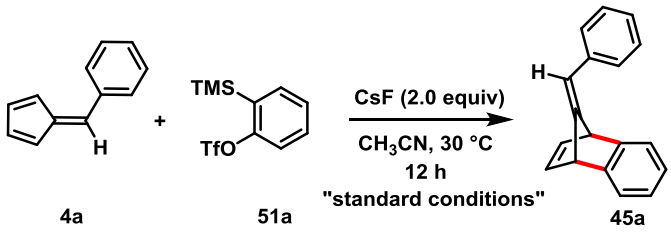


2.7. Results and Discussion

2.7.1. Optimization Studies

We started the optimization study by the treatment of (cyclopenta-2,4-dien-1-ylidenemethyl) benzene **4a** with the aryne generated in situ from 2-(trimethylsilyl)aryl triflate **51a** using 2.0 equiv of CsF in CH_3CN as a solvent at 30 °C. Interestingly, under these mild reaction conditions benzonorbornadiene derivative **45a** was formed in 94% yield (based on ^{1}H NMR spectroscopy, Table 2.1, entry 1).

Table 2.1: Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions[a]	yield of **45a** (%)[b]
1	None	94
2	KF and 18-crown-6 instead of CsF, THF as the solvent	93
3	TBAF instead of CsF, THF as the solvent	<1
4	1.2 equiv of **4a** instead of 1.5 equiv	87
5	Reaction time 6 h instead of 12 h	80
6	*2.5 equiv of CsF instead of 2.0 equiv*	*>99 (98)*

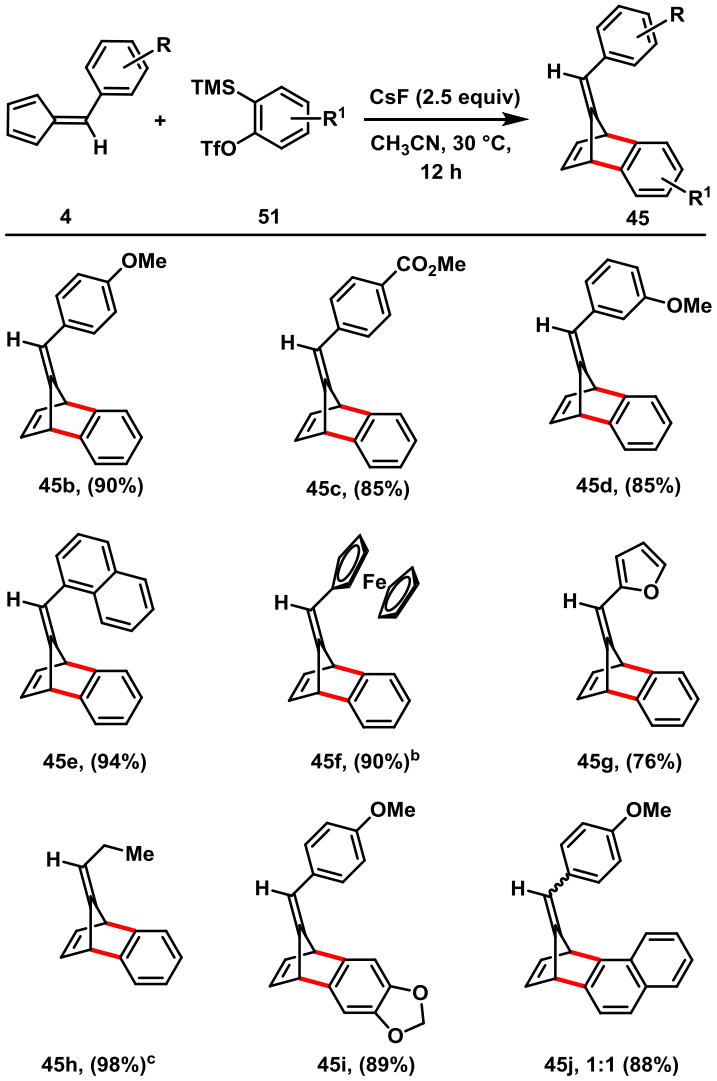
[a]Standard conditions: **51a** (0.25 mmol), **4a** (0.38 mmol), CsF (2.0 equiv), CH_3CN (1.0 mL), 30 °C and 12 h. [b]The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard. Isolated yield in 0.50 mmol scale in parentheses.

The reaction carried out using KF as the fluoride source with 18-crown-6 as additive in THF solvent furnished the cycloadduct in 93% yield (entry 2). CsF and KF gave almost similar results, but the use of tetrabutylammonium fluoride (TBAF) as fluoride source resulted in the decomposition of both starting materials (entry 3). Lowering the amount of **4a** to 1.2 equiv or reducing the reaction time to 6 h lowered the yield of cycloadduct **45a** (entries 4, 5). Finally, increasing the amount of CsF to 2.5 equiv we observed almost quantitative conversion, with **45a** isolated in 98% yield (entry 6). The reaction was found be scalable, same yield was obtained from a 2.0 mmol scale reaction demonstrating synthetic utility of present method.

2.7.2. Diels-Alder Reaction of Arynes with 6-Substituted Pentafulvenes

After optimizing reaction conditions, first we evaluated the substrate scope of this fulvene-aryne Diels-Alder reaction with 6-substituted pentafulvenes **4** (Scheme 2.15). In view of the lower stability of the fulvenes, we used freshly prepared fulvenes for all the reactions. 6-Arylfulvenes derived from aromatic aldehydes with electron-donating and -withdrawing group at the 4-position of the aromatic ring of **4** were well tolerated, furnishing the cycloadducts in excellent yields (**45b, 45c**). Moreover, the fulvenes derived from 3-methoxy benzaldehyde and 1-naphthaldehyde resulted in a smooth conversion to the benzonorbornene derivatives in excellent yields (**45d, 45e**). Interestingly, fulvenes derived from challenging aldehydes like ferrocene carboxaldehyde and furan-2-carbaldehyde also furnished the desired cycloaddition product further expanding the scope of present aryne Diels-Alder reaction (**45f, 45g**). Additionally, the reaction is not limited to pentafulvenes synthesized from aromatic aldehydes. Gratifyingly, fulvenes derived from aliphatic aldehyde also delivered the desired product in 98% yield (**45h**). Notably, the reaction needs 2.0 equiv of fulvene **4h** for better result. Finally, we further investigated the scope of present reaction using substituted aryne precursors with fulvene **4b** derived from 4-methoxy benzaldehyde. A symmetric aryne having electron-donating substituent generated from **51b** afforded the expected product **45i** in 89% yield. Moreover, unsymmetrical naphthalyne resulted in the formation of a diastereomeric mixture of a cycloadduct in a 1:1 ratio with 88% yield (**45j**).

Scheme 2.15: Diels-Alder Reaction of Arynes with 6-Substituted Pentafulvenes[a]



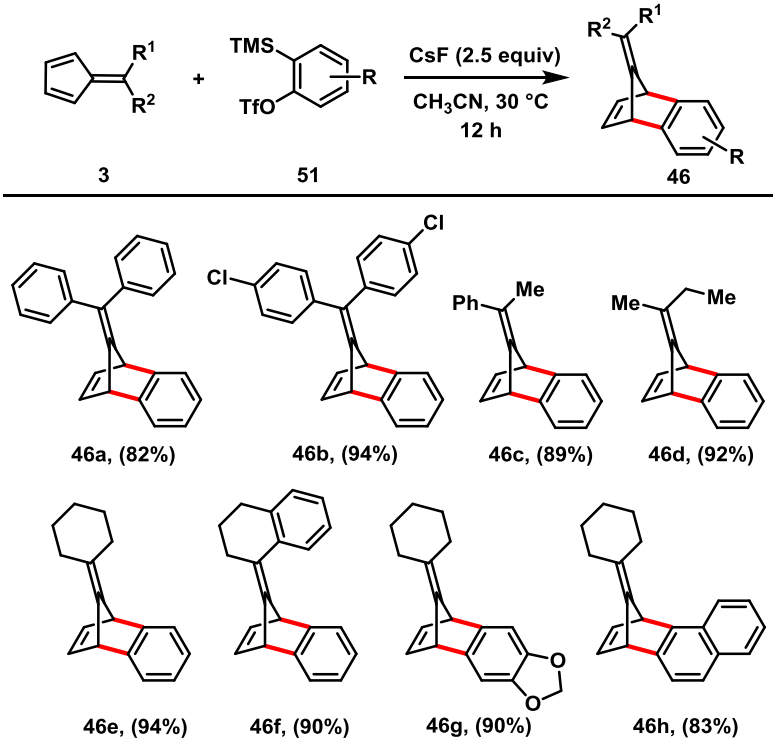
[a]General Conditions: **51** (0.50 mmol), **4** (0.75 mmol), CsF (2.5 equiv), CH_3CN (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given. [b]Reaction run on 0.2 mmol scale. [c]The reaction run using 2.0 equiv of fulvene **4h**.

2.7.3. Diels-Alder Reaction of Arynes with 6,6-Disubstituted Pentafulvenes

Inspired by interesting results on the Diels-Alder reactionof arynes with aldehyde-derived fulvenes, we then extended our efforts on the sterically more congested 6,6-disubstituted fulvenes **3** (Scheme 2.16), which are prepared by the condensation of cyclopentadiene and the corresponding ketones. Fulvenes derived from electronically different benzophenones worked well to afford the desired cycloaddition products in excellent yields (**46a, 46b)**. Fulvene synthesized from acetophenone readily furnished the product **46c** in 89% yield. Delightfully, fulvenes derived from acyclic and cyclic ketone

resulted in the smooth conversion to the bicyclic product in excellent yield (**46d-f**) significantly expanding the scope this reaction. In addition, symmetric and unsymmetric arynes generated from the corresponding precursors react with pentafulvenes **3c** derived from cyclohexanone to furnish the benzonorbornadiene derivatives in high yields (**46g, 46h**).

Scheme 2.16: Diels-Alder Reaction of Arynes with 6,6-Disubstituted Pentafulvenes[a]



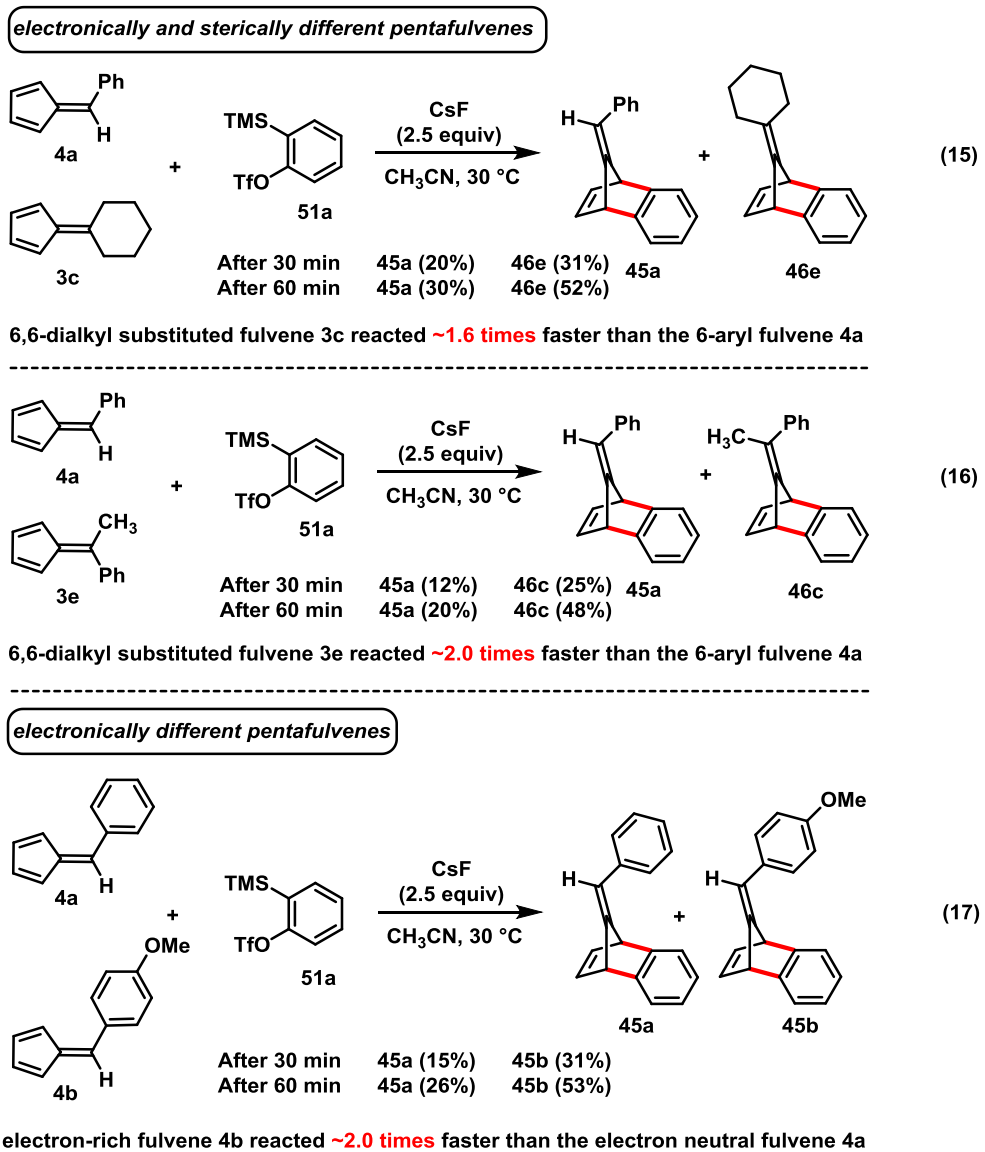
[a]General Conditions: **51** (0.50 mmol), **3** (0.75 mmol), CsF (2.5 equiv), CH_3CN (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given.

2.7.4. Mechanistic Studies

We carried out intermolecular competition experiment, to confirm the effect of substitution at 6-position in pentafulvenes on the reactivity toward arynes. For this purpose, we performed ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as the internal standard to determine the yield of products. First intermolecular competition experiment was accomplished using electronically and sterically different pentafulvenes **4a** and **3c**. Surprisingly, sterically more congested 6,6-dialkyl substituted fulvene **3c** reacted ~1.6 times faster than the 6-aryl fulvene **4a** (Scheme 2.17, eq 15). Simillar results were observed, when intermolecular competition experiment was carried out using

pentafulvenes **4a** and **3e**. The 6,6-alkylaryl substituted fulvene **3e** reacted ~2.0 times faster than the 6-aryl fulvene **4a** (eq 16). This indicates that the dialkyl substitution at the 6-position in 6,6-disubstituted pentafulvenes **3c** and **3e** makes the diene system more electron-rich, thus increasing its reactivity toward arynes. Results of these experiment suggest that the electronic nature of the fulvenes is more prominent than its steric factor

Scheme 2.17: Intermolecular Competition Experiments[a]



[a]The yields were determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as the internal standard.

in the Diels-Alder reaction with arynes. Interestingly, competition experiments carried out using electronically different 6-substituted pentafulvenes **4a** and **4b** revealed that the

fulvene **4b** having electron-donating methoxy group substituent at 4-posiiton on aromatic ring reacted ~2.0 times faster than the electron neutral one (eq 17).

2.8. Conclusion

In conclusion, we have developed a high yielding, practical and scalable Diels-Alder reaction of pentafulvenes with arynes under mild reaction conditions.[36] Present protocol offers straightforward access to various benzonorbornadiene derivatives, which are expected to have potential application in organic synthesis. High levels of functional group tolerance, mild reaction conditions, and high yields of products are the significant features of the present reaction. It is reasonable to assume that the protocol presented in this chapter is likely to find application in organic synthesis.

2.9. Experimental Details

2.9.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. All reactions were carried out at room temperature (30 °C). Dry CH_3CN was purchased from commercial sources and stored under argon over 4 Å molecular sieves. CsF was dried by heating at 110 °C for 12 h and left to cool under argon. The aldehydes were purchased from Aldrich or Acros and were purified either by distillation or washing with $NaHCO_3$ after dissolving in ether or dichloromethane, prior to use. The ketones were purchased from commercial sources and were used without further purification. The fulvenes were synthesized by the condensation of cyclopentadiene (freshly cracked from dicyclopentadiene) with either aldehydes or ketones.[3] The aryne precursors **51a**, **51b**, and **51c** were synthesized following literature procedure.[35]

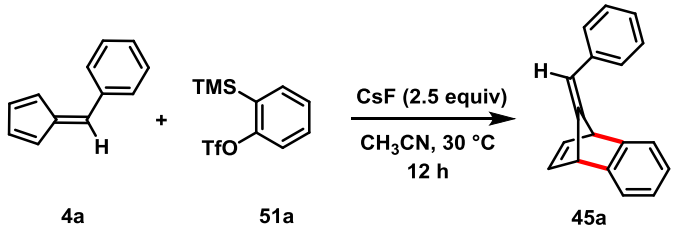
Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with mixtures of petroleum ether-ethyl acetate as solvents.

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

a Perkin-Elmer 1615 FT Infrared Spectrophotometer Model 60B. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS data were recorded on either Synapt MALDI-MS (Waters, UK) or AB SCIEX Tof Tof^{TM} 5800 using 2,5-dihydroxybenzoic acid as the solid matrix.

2.9.2. General Procedure for the Optimization of Reaction Conditions

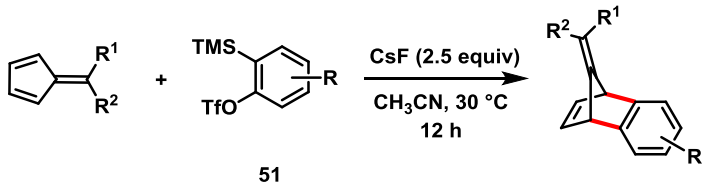
Scheme 2.18: Optimization of Reaction Conditions



To a flame-dried screw-capped Schlenk tube equipped with a magnetic stir bar was added dry CsF (0.095 g, 0.625 mmol) and (cyclopenta-2,4-dien-1-ylidenemethyl)benzene **4a** (0.057 g, 0.375 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in CH_3CN under argon atmosphere (1.0 mL). To the stirring solution 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **51a** (0.074 g, 61 μL, 0.25 mmol) was added. Then the reaction mixture kept for stirring at room temperature (30 °C). After 12 h, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^1H NMR analysis using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard.

2.9.3. General Procedure for the Diels-Alder Reaction of Pentafulvenes with Arynes

Scheme 2.19: Synthesis of Benzonorbornadiene Derivatives

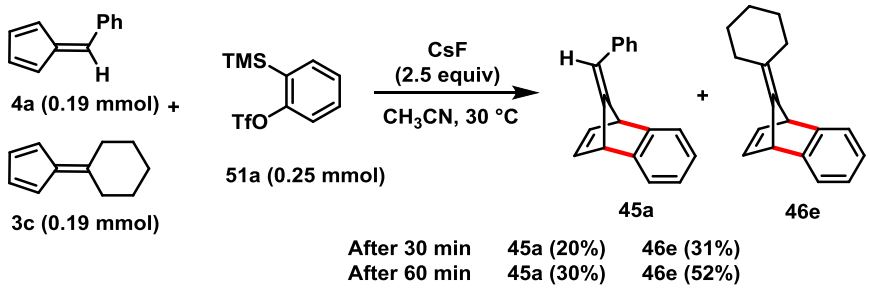


To a flame-dried screw-capped schlenk tube equipped with a magnetic stir bar was taken dry CsF (0.190 g, 1.25 mmol) and the corresponding pentafulvene (0.75 mmol)

was added (in view of the less stability of the fulvenes, we used freshly prepared fulvenes for all the reactions in Scheme 2.15). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture, CH_3CN was added (2.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C (rt). To this stirring solution was added 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **51** (0.50 mmol). Then the reaction mixture kept for stirring at 30 °C (rt). When TLC control showed the completion of the reaction (typically after 12 h), the mixture was diluted with CH_2Cl_2 (5.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (15 mL). The solvent was evaporated and the crude residue was purified by column chromatography on silica gel to afford the corresponding benzonorbornadiene derivatives in good to excellent yields.

2.9.4. Competition Experiments

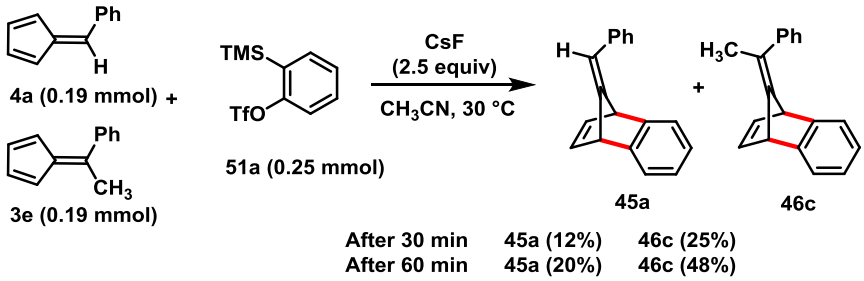
Scheme 2.20: Competition Experiment between Electronically and Sterically Different Pentafulvenes **4a** and **3c**



To a flame-dried screw-capped schlenk tube equipped with a magnetic stir bar was taken CsF (0.095 g, 0.625 mmol), the 6-aryl substituted fulvene **4a** (0.028 g, 0.19 mmol), and 6,6-dialkyl substituted fulvene **3c** (0.027 g, 0.19 mmol). Then the screw-capped tube was evacuated and backfilled with argon. After that the mixture was dissolved in CH_3CN under argon atmosphere (1.0 mL). The resultant mixture was kept stirring at 30 °C (rt). To this stirring solution was added 2-(trimethylsilyl)aryl triflate **51a** (0.074 g, 61µL, 0.25 mmol) and the reaction mixture stirred at 30 °C for 30 minutes (for reaction 1) and 60 minutes (for reaction 2). The reaction mixture was then diluted with CH_2Cl_2 (1.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^1H NMR using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. The ^1H NMR

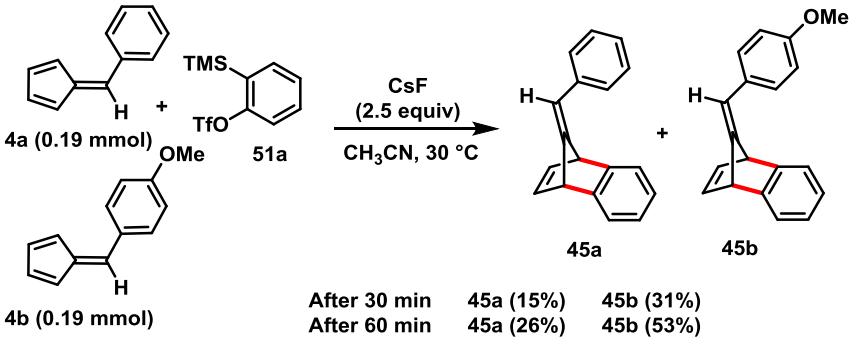
revealed that the 6,6-dialkyl substituted fulvene **3c** reacted ~1.6 times faster than the 6-aryl fulvene **4a**.

Scheme 2.21: Competition Experiment between Electronically and Sterically Different Pentafulvenes **4a** and **3e**



To a flame-dried screw-capped schlenk tube equipped with a magnetic stir bar was taken CsF (0.095 g, 0.625 mmol), the 6-aryl substituted fulvene **4a** (0.028 g, 0.19 mmol), and 6,6-alkylaryl substituted fulvene **3e** (0.031 g, 0.19 mmol). Then the screw-capped tube was evacuated and backfilled with argon. After that the mixture was dissolved in CH_3CN under argon atmosphere (1.0 mL). The resultant mixture was kept stirring at 30 °C (rt). To this stirring solution was added 2-(trimethylsilyl)aryl triflate **51a** (0.074 g, 61µL, 0.25 mmol) and the reaction mixture stirred at 30 °C for 30 minutes (for reaction 1) and 60 minutes (for reaction 2). The reaction mixture was then diluted with CH_2Cl_2 (1.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^1H NMR using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. The ^1H NMR revealed that the 6,6-disubstituted fulvene **3e** reacted ~2.0 times faster than the 6-aryl fulvene **4a**.

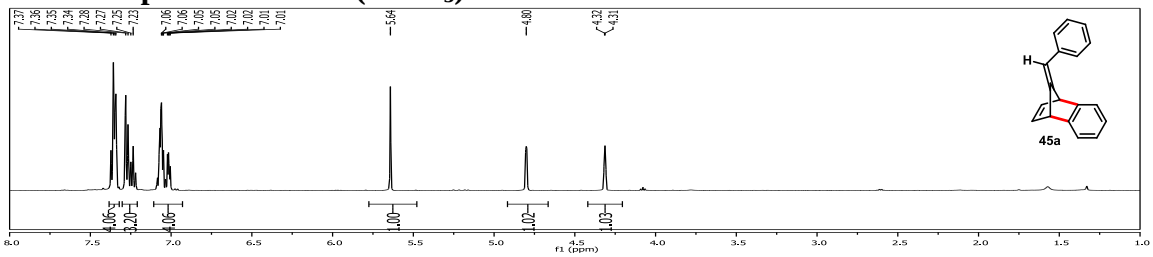
Scheme 2.22: Competition Experiment between Electronically Different 6-substituted Pentafulvenes **4a** and **4b**



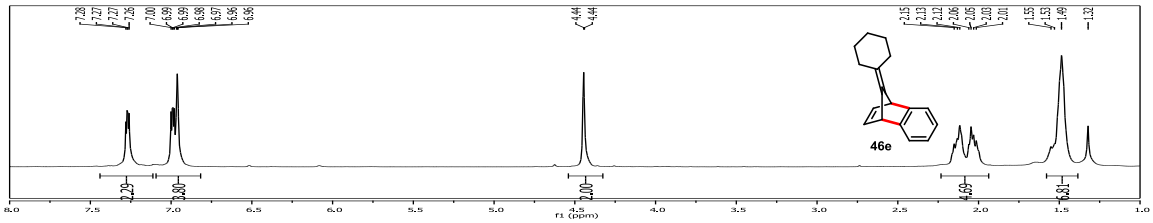
To a flame-dried screw-capped Schlenk tube equipped with a magnetic stir bar was taken CsF (0.095 g, 0.625 mmol), the 6-aryl substituted fulvene **4a** (0.028 g, 0.19 mmol), and 4-substituted 6-aryl fulvene **4b** (0.035 g, 0.19 mmol). Then the screw-capped tube was evacuated and backfilled with argon. After that the mixture was dissolved in CH_3CN under argon atmosphere (1.0 mL). The resultant mixture was kept stirring at 30 °C (rt). To this stirring solution was added 2-(trimethylsilyl)aryl triflate **51a** (0.074 g, 61μL, 0.25 mmol) and the reaction mixture stirred at 30 °C for 30 minutes (for reaction 1) and 60 minutes (for reaction 2). The reaction mixture was then diluted with CH_2Cl_2 (1.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10 mL). The solvent was evaporated to obtain the crude product, which was analyzed using ^1H NMR using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard. The ^1H NMR revealed that the 4-substituted 6-aryl fulvene **4b** reacted ~2.0 times faster than the 6-aryl fulvene **4a**.

Partial ^{1}H NMR of Crude Reaction Mixture of Scheme 2.20

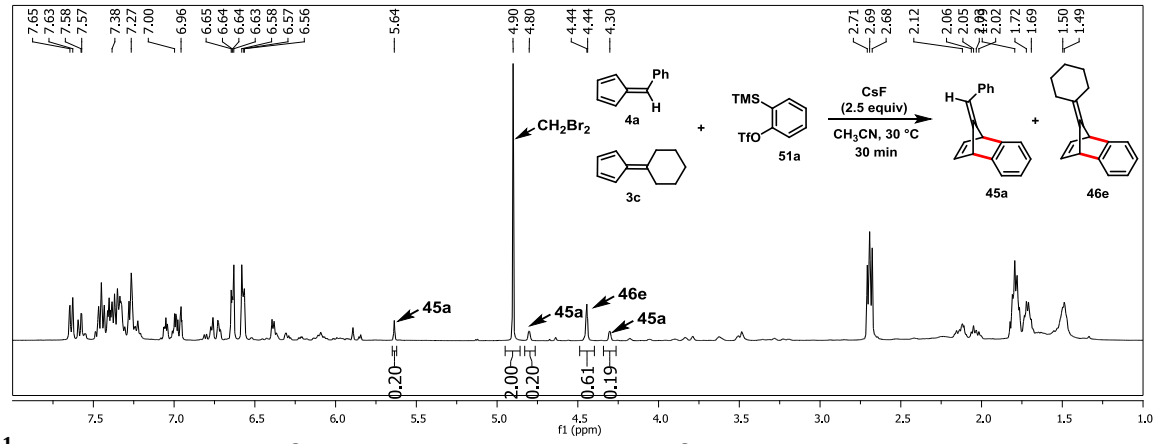
^{1}H NMR Spectrum of 45a ($CDCl_3$)



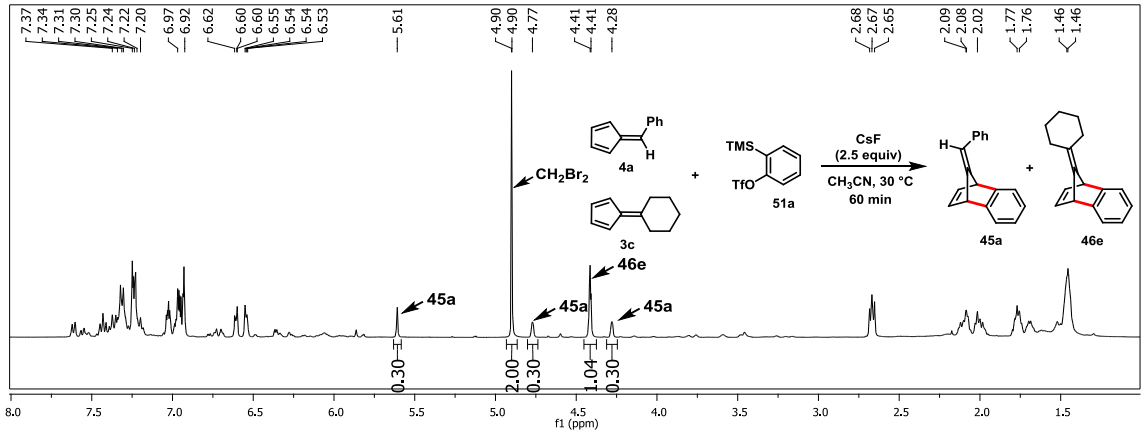
^{1}H NMR Spectrum of 46e ($CDCl_3$)



^{1}H NMR Spectrum of Crude Reaction Mixture (after 30 minutes)

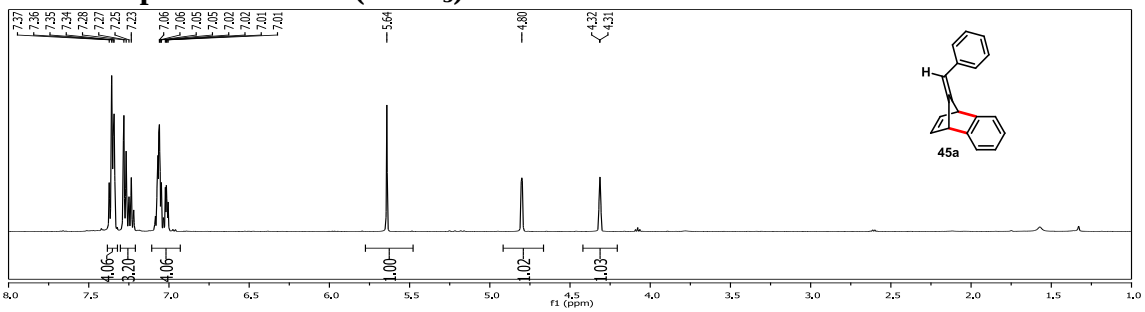


^{1}H NMR Spectrum of Crude Reaction Mixture (after 60 minutes)

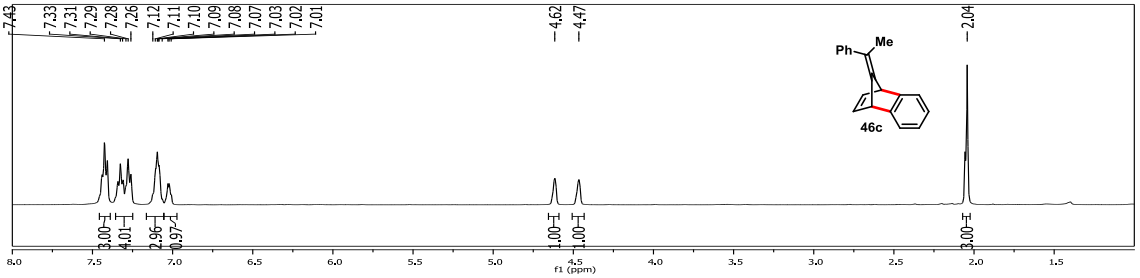


Partial ^{1}H NMR of Crude Reaction Mixture of Scheme 2.21

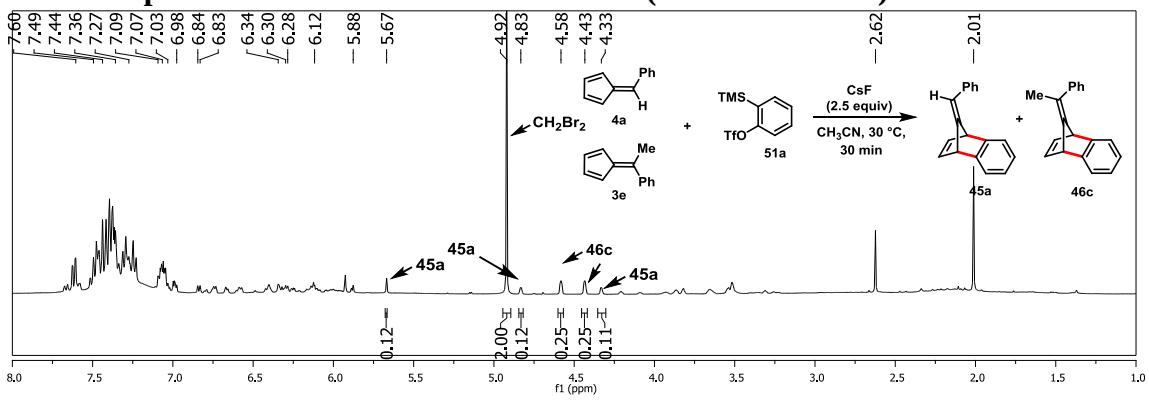
^{1}H NMR Spectrum of 45a ($CDCl_3$)



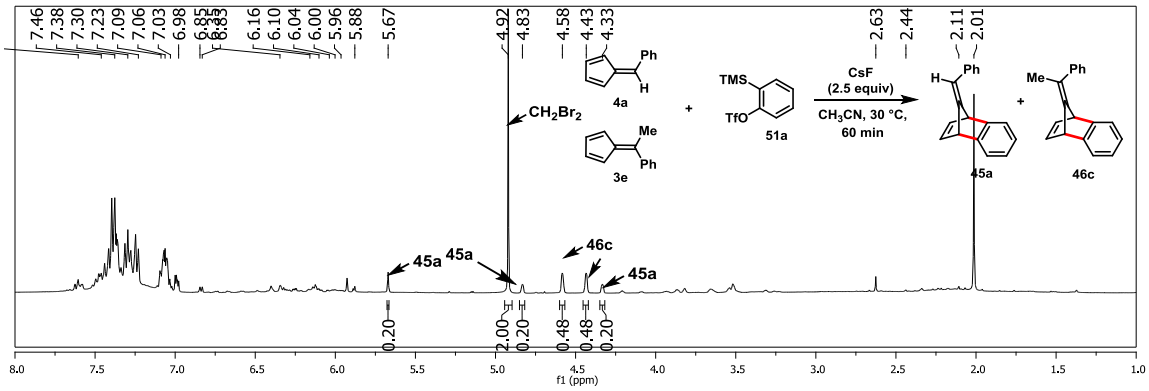
^{1}H NMR Spectrum of 46c ($CDCl_3$)



^{1}H NMR Spectrum of Crude Reaction Mixture (after 30 minutes)

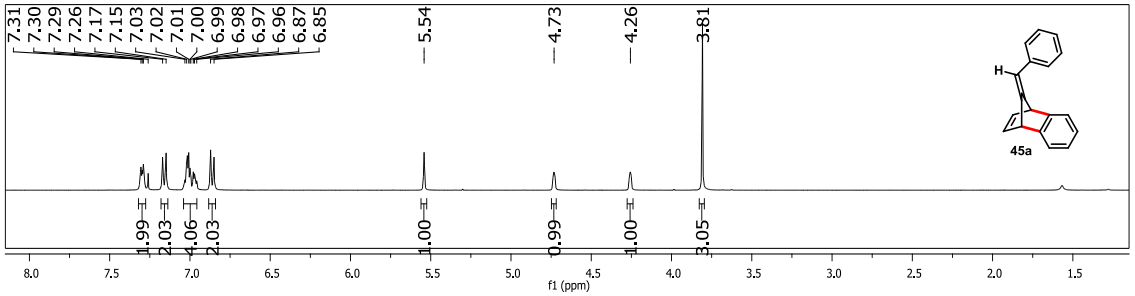


^{1}H NMR Spectrum of Crude Reaction Mixture (after 60 minutes)

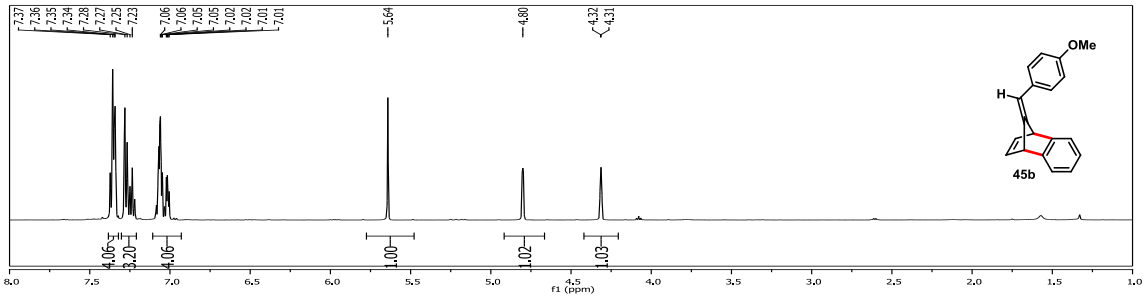


Partial ^{1}H NMR of Crude Reaction Mixture of Scheme 2.22

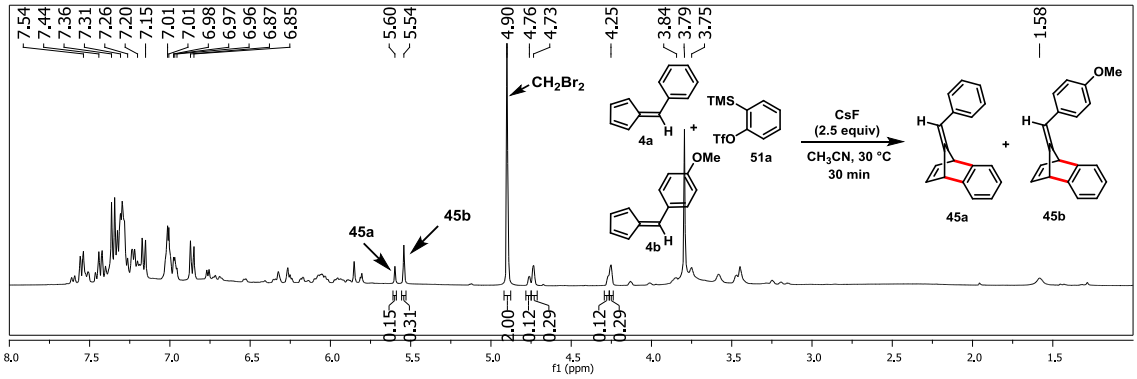
^{1}H NMR Spectrum of 45a ($CDCl_3$)



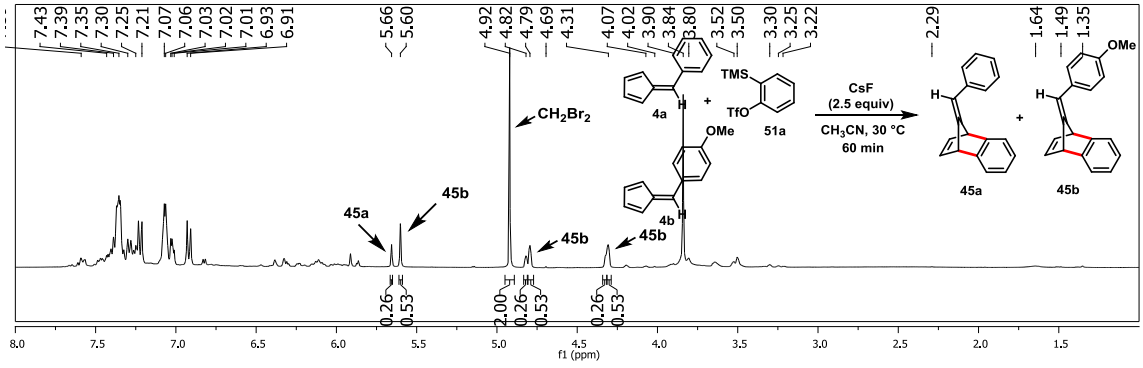
^{1}H NMR Spectrum of 45b ($CDCl_3$)



^{1}H NMR Spectrum of Crude Reaction Mixture (after 30 minutes)

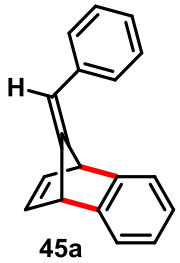


^{1}H NMR Spectrum of Crude Reaction Mixture (after 60 minutes)



2.9.5. Synthesis and Characterization of Benzonorbornadiene Derivatives

9-Benzylidene-1,4-dihydro-1,4-methanonaphthalene (45a)



45a

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and (cyclopenta-2,4-dien-1-ylidenemethyl) benzene **4a** (0.115 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 9-benzylidene-1,4-dihydro-1,4-methano naphthalene **45a** as a light yellow oil (0.112 g, 98%).

R_f (pet. ether): 0.50.

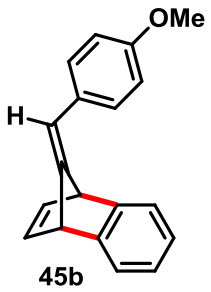
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.38 (m, 4H), 7.32-7.27 (m, 3H), 7.13-7.09 (m, 3H), 7.06-7.05 (m, 1H), 5.68 (s, 1H, CHPh), 4.84 (bs, 1H, CH), 4.35-4.36 (m, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.46, 149.61, 149.17, 142.91, 142.51, 136.96, 128.42, 128.19, 126.27, 125.24, 125.06, 121.52, 121.53, 102.45, 54.96, 50.37.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{15}$: 231.1168, found: 231.1184.

FTIR (cm^{-1}): 3064, 3020, 2927, 1689, 1598, 1495, 1451, 1278, 1340, 1311, 1216, 1170, 1074, 1028, 1010, 915, 849, 806, 751.

9-(4-Methoxybenzylidene)-1,4-dihydro-1,4-methanonaphthalene (45b)



45b

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and 1-(cyclopenta-2,4-dien-1-ylidenemethyl)-4-methoxybenzene **4b** (0.138 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 9-(4-methoxybenzylidene)-1,4-dihydro-1,4-methanonaphthalene **45b** as a white solid (0.117 g, 90%).

R_f (pet. ether /CH_2Cl_2=80/20): 0.26.

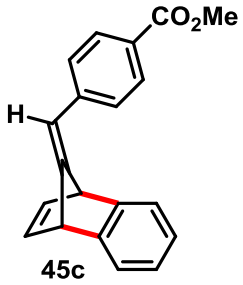
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.29 (m, 2H), 7.17-7.15 (d, *J* = 8.6 Hz 2H), 7.03-6.99 (m, 3H), 6.98-6.96 (m, 1H), 6.85-6.87 (d, *J* = 8.6 Hz, 2H), 5.54 (s, 1H, CHPh), 4.73 (bs, 1H, CH), 4.26 (bs, 1H, CH),3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.49, 158.16, 149.79, 149.32, 143.0, 142.56, 129.42, 129.24, 125.16, 124.96, 121.43, 121.26, 113.89, 101.90, 55.39, 54.91, 50.28.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{17}O$: 261.1274, found: 261.1285.

FTIR (cm^{-1}): 3066, 3004, 2956, 2933, 2835, 1688, 1608, 1510, 1463, 1456, 1297, 1248, 1176, 1034, 855, 754, 699, 676.

Methyl 4-(1,4-dihydro-1,4-methanonaphthalen-9-ylidene)methyl benzoate (45c)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and methyl 4-(cyclopenta-2,4-dien-1-ylidenemethyl)benzoate **4c** (0.159 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded methyl 4-(1,4-dihydro-1,4-methanonaphthalen-9-ylidene)methylben zoate **45c** as a light yellow oil (0.123 g, 85%).

R_f (pet. ether /CH_2Cl_2 = 50/50): 0.40.

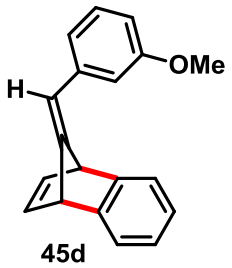
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.99 (d, *J* = 8 Hz, 2H), 7.34-7.32 (m, 2H), 7.30-7.28 (m, *J* = 8 Hz, 2H), 7.08-7.03 (m, 3H), 6.98-6.93 (m, 1H), 5.63 (s, 1H, CHPh), 4.77 (bs, 1H, CH), 4.29 (bs, 1H, CH), 3.92 (s,3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.66, 167.11, 149.02, 148.57, 142.75, 142.24, 141.86, 129.74, 127.98, 127.75, 125.45, 125.25, 121.60, 121.45, 101.88, 54.92, 52.13, 50.26.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{17}O_2$: 289.1223, found: 289.1276.

FTIR (cm^{-1}): 3124, 3069, 3017, 2952, 2929, 2873, 2855, 1935, 1722, 1715, 1695, 1683, 1606, 1567, 1455, 1435, 1412, 1309, 1278, 1217, 1191, 1178, 1108, 1018, 967, 901, 874, 845, 813, 804, 783, 768, 754, 711.

9-(3-Methoxybenzylidene)-1,4-dihydro-1,4-methanonaphthalene (45d)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and 1-(cyclopenta-2,4-dien-1-ylidenemethyl)-3-methoxybenzene **4d** (0.138 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 9-(3-methoxybenzylidene)-1,4-dihydro-1,4-methanonaphthalene **45d** as a light yellow oil (0.110 g, 85%).

R_f (pet. ether /DCM): 0.43.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (bs, 2H), 7.33-7.29 (t, *J*=7.6 Hz, 1H), 7.12-7.08 (m, 3H), 7.04-7.02 (m, 1H), 6.93-6.91 (d, *J* =7.6 Hz, 1H), 6.85-6.82 (m, 2H), 5.65 (s, 1H,

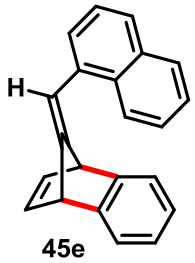
CHPh), 4.85 (bs, 1H, CH), 4.33 (bs, 1H, CH), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.53, 159.60, 149.43, 149.01, 142.79, 142.40, 138.28, 129.33, 125.21, 125.03, 121.47, 120.68, 113.80, 111.64, 102.28, 55.19, 54.81, 50.36.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{17}O$: 261.1274, found: 261.1276.

FTIR (cm^{-1}): 3123, 3068, 3046, 3009, 2957, 2939, 2835, 1687, 1598, 1488, 1464, 1452, 1432, 1331, 1318, 1290, 1270, 1255, 1238, 1217, 1199, 1158, 1147, 1045, 929, 902, 881 ,866 ,807, 788, 756.

9-(Naphthalen-1-ylmethylene)-1,4-dihydro-1,4-methanonaphthalene (45e)



45e

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and 1-(cyclopenta-2,4-dien-1-ylidenemethyl)naphthalene **4e** (0.153 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 9-(naphthalen-1-ylmethylene)-1,4-dihydro-1,4-methanonaphthalene **45e** as a white solid (0.131 g, 94%).

R_f (pet. ether): 0.56.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.4 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.57-7.51 (m, 3H), 7.46 (d, *J* = 6.8 Hz, 1H), 7.41 (d, *J* = 7.0 Hz, 1H), 7.35 (d, *J* = 6.8 Hz, 1H), 7.17-7.09 (m, 3H), 7.05-7.03 (m, 1H), 6.19 (s, 1H, C-$H_{olefinic}$), 4.57 (bs, 1H, CH), 4.51 (bs, 1H, CH).

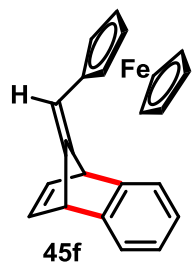
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.74, 149.65, 149.25, 142.84, 142.71, 133.72, 133.67, 132.07, 128.43, 127.03, 126.15, 125.83, 125.80, 125.51, 125.18, 125.12, 125.06, 121.59, 121.36, 99.56, 54.47, 50.83.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{17}$: 281.1325, found: 281.1366.

FTIR (cm^{-1}): 3123, 3063, 3045, 3008, 2928, 1687, 1618, 1590, 1507, 1452, 1395, 1319, 1216, 1189, 1167, 1155, 1013, 860, 799, 777, 753, 697, 676.

9-Ferrocenylidene-1,4-dihydro-1,4-methanonaphthalene (45f)

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **51a** (0.059 g, 49 μL, 0.20 mmol) and (cyclopenta-2,4-dien-1-ylidenemethyl) ferrocene **4f** (0.078 g, 0.30 mmol) with CsF (0.075 g, 0.5 mmol) in CH_3CN (1.0 mL) at



45f

30 °C for 12 h followed by column chromatography afforded 9-ferrocenylidene-1,4-dihydro-1,4-methano naphthalene **45f** as a red oil (0.059 g, 90%).

***R*$_f$ (**pet. ether/CH_2Cl_2 = 80/20): 0.50.

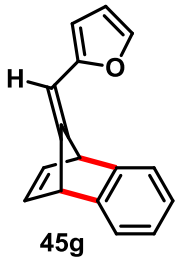
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.28 (m, 2H), 7.03-6.98 (m, 4H), 5.23 (s, 1H, CHPh), 4.73 (bs, 1H, CH), 4.30 (bs, 2H), 4.19 (bs, 3H), 4.07 (bs, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.05, 149.73, 149.46, 143.00, 142.29, 125.05, 124.87, 121.24, 121.06, 99.86, 82.45, 69.08, 68.28, 68.14, 68.09, 54.74, 50.95.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{19}Fe$: 339.0831, found: 339.0831.

FTIR (cm^{-1}): 3093, 3068, 3015, 2929, 1693, 1651, 1603, 1453, 1411, 1313, 1282, 1240, 1218, 1105, 1043, 1027, 1001, 928, 900, 807, 785, 754.

1,4-Dihydro-1,4-methanonaphthalen-9-ylidene)methyl)furan (45g)



45g

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and 2-(cyclopenta-2,4-dien-1-ylidenemethyl)furan **4g** (0.108 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 1,4-dihydro-1,4-methano naphthalen-9-ylidene)methyl)furan **45g** as a red oil (0.084 g, 76%).

***R*$_f$** (pet. ether): 0.33.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (bs, 1H), 7.35-7.33(m, 1H), 7.30-7.28 (m, 1H), 7.02-7.00 (m, 4H), 6.35-6.33(m, 1H), 6.10 (bs, 1H), 5.41 (s, 1H, CHPh), 5.05 (bs, 1H, CH), 4.22(bs, 1H, CH).

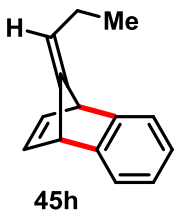
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.92, 152.14, 149.43, 149.21, 142.78, 142.74, 141.40, 125.19, 125.15, 121.67, 121.21, 111.08, 107.56, 92.47, 54.40, 51.14.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{13}O$: 221.0961, found: 221.1003.

FTIR (cm^{-1}): 3119, 3068, 3044, 3011, 2927, 2855, 1781, 1698, 1637, 1492, 1452, 1321, 1283, 1254, 1191, 1168, 1151, 1077, 1013, 927, 848, 793, 808, 758.

9-Propylidene-1,4-dihydro-1,4-methanonaphthalene (45h)

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and 5-propylidenecyclopenta-1,3-diene **4h**



45h

(0.108 g, 1.0 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 9-propylidene-1,4-dihydro-1,4-methanona phthalene **45h** as a colorless oil (90 mg, 98%).

***R**f* (Pet. ether): 0.80.

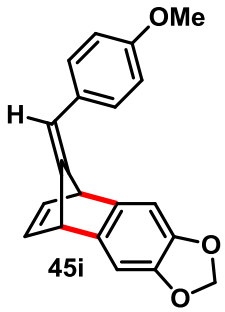
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.29 (m, 2H), 7.05-6.97 (m, 4H), 4.55-4.51 (m, 1H, C-$H_{Olefinic}$), 4.45 (bs, 1H, CH), 4.17 (m, 1H, CH), 2.06-1.95(m, 2H, CH_2), 0.98-0.94(m, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.19, 150.37, 149.93, 143.16, 142.61, 124.74, 124.61, 121.14, 121.01, 120.75, 53.98, 49.61, 20.90, 14.68.

HRMS: calculated $[M]^+$ for $C_{14}H_{14}$: 182.1096, found: 182.1099.

FTIR (cm^{-1}): 3067, 3047, 3007, 2964, 2931, 2872, 1705, 1455, 1448, 1301, 1285, 1216, 1190, 1164, 1070, 842, 808, 752, 700, 689, 667.

10-(4-Methoxybenzylidene)-5,8-dihydro-5,8-methanonaphtho[2,3-*d*][1,3]dioxole (45i)



45i

Following the general procedure, treatment of 6-(trimethylsilyl) benzo[*d*][1,3]dioxol-5-yltrifluoromethanesulfonate **51b** (0.171 g, 0.50 mmol) and 1-(cyclopenta-2,4-dien-1-ylidenemethyl)-4-methoxy benzene **4b** (0.138 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 10-(4-methoxybenzylidene)-5,8-dihydro-5,8-methanonaphtho[2,3-*d*][1,3]dioxole **45i** as a light yellow oil (0.135 g, 89%).

***R**f* (pet. ether/CH_2Cl_2=50/50): 0.50.

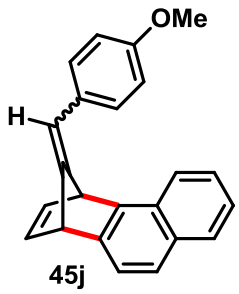
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.18 (m, 2H), 7.06-7.04 (m, 1H), 7.01-6.99 (m, 1H), 6.91-6.89 (m, 4H), 5.92-5.89 (m,2H), 5.49 (s, 1H, CHPh), 4.69 (bs, 1H, CH), 4.20 (bs, 1H, CH), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.64, 158.02, 144.59, 144.39, 143.41, 143.04, 142.82, 142.57, 129.34, 129.11, 113.82, 104.35, 104.24, 100.85, 100.24, 55.25, 54.72, 50.11.

HRMS: calculated $[M]^+$ for $C_{20}H_{16}O_3$: 304.1099, found: 304.1079; calculated $[M+H]^+$ for $C_{20}H_{17}O_3$: 305.1172, found: 305.1101.

FTIR (cm^{-1}): 3122, 3065, 3007, 2959, 2935, 2892, 2837, 2766, 2064, 1685, 1608, 1576, 1505, 1463, 1418, 1326, 1284, 1248, 1218, 1175, 1129, 1072, 1035, 1003, 938, 909, 856, 822, 790, 759, 701.

11-(4-Methoxybenzylidene)-1,4-dihydro-1,4-methanophenanthrene (45j)



45j

Following the general procedure, treatment of 1-(trimethylsilyl) naphthalen-2-yl trifluoromethanesulfonate **51c** (0.174 g, 0.50 mmol) and 1-(cyclopenta-2,4-dien-1-ylidenemethyl)-4-methoxybenzene **4b** (0.138 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 11-(4-methoxybenzylidene)-1,4-dihydro-1,4-methanophenanthrene **45j** as a light yellow oil as a mixture of diastereomers in the ratio 1:1 (0.136 g, 88%).

R_f (pet. ether/CH_2Cl_2 = 80/20): 0.36.

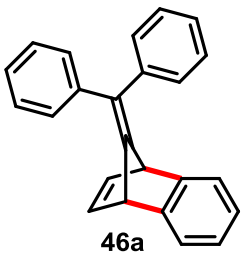
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11-8.09 (d, *J* =8.3 Hz, 1H), 7.96-7.94 (d, *J* =8.3 Hz, 1H), 7.70-7.67 (m, 2H), 7.60 (bs, 1H), 7.51-7.47 (m,1H), 7.31-7.22 (m, 4H), 6.99-6.98 (m, 2H), 5.62 (s, 1H, CHPh), 5.46 (s, 0.5H, CH),5.05 (s, 0.5H, CH), 4.94 (s, 0.5H, CH), 4.56 (s, 0.5H, CH), 3.88(s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.67, 167.59, 158.10, 148.18, 147.49, 147.39, 146.77, 144.26, 143.79, 142.94, 142.49, 131.95, 131.84, 129.34, 129.25, 129.17, 128.95, 128.91, 126.04, 125.96, 125.21, 122.05, 124.76, 124.70, 123.13, 122.98, 120.73, 120.66, 113.91, 160.03, 99.63, 55.75, 55.28, 52.62, 51.19, 47.87.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{19}O$: 311.1430, found: 311.1417.

FTIR (cm^{-1}): 3119, 3052, 3008, 2956, 2934, 2909, 2836, 1684, 1608, 1576, 1557, 1509, 1464, 1441, 1417, 1365, 1345, 1296, 1278, 1248, 1216, 1175, 1152, 1135, 1110, 1084, 1034, 955, 929, 909, 862, 847, 823, 807, 784, 756, 702.

9-(diphenylmethylene)-1,4-dihydro-1,4-methanonaphthalene (46a)


46a

Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and (cyclopenta-2,4-dien-1-ylidenemethylene)dibenzene **3a** (0.173 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 9-(diphenylmethylene)-1,4-dihydro-1,4-methanonaphth

alene **46a** as a white solid (0.126 g, 82%).

R_f (pet. ether): 0.36.

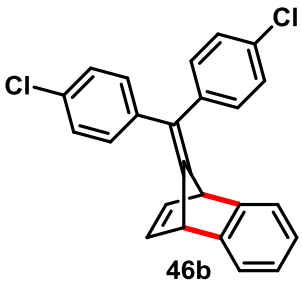
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 8H), 7.14-7.12 (m, 4H), 7.06-7.03 (m, 4H), 4.50-4.49 (m, 2H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.41, 149.68, 142.98, 140.48, 128.08, 126.71, 125.11, 121.43, 115.18, 52.35.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{19}$: 307.1481, found: 307.1495.

FTIR (cm^{-1}): 3062, 3017, 2403, 1950, 1899, 1812, 1765, 1667, 1599, 1452, 1317, 1218, 1075, 1030, 844, 787.

9-[(Bis(4-chlorophenyl)methylene]-1,4-dihydro-1,4-methanonaphthalene (46b)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 µL, 0.50 mmol) and 4,4'-(cyclopenta-2,4-dien-1-ylidenemethylene) bis (chlorobenzene) **3f** (0.224 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 9-[bis(4-chlorophenyl)meth ylene]-1,4-dihydro-1,4-methanonaphthalene **46b** as a white solide (0.177 g, 94%).

R_f (pet. ether): 0.30.

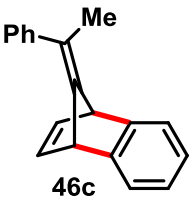
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.29 (m, 6H), 7.06-7.00 (m, 8H), 4.42 (bs, 2H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.84, 149.11, 142.80, 138.45, 132.81, 131.17, 128.43, 125.37, 121.53, 113.09, 52.22.

HRMS: calculated [M+H]+ for $C_{24}H_{17}Cl_2$: 375.0702, found: 375.0664.

FTIR (cm^{-1}): 3068, 3014, 2926, 2855, 1905, 1787, 1664, 1592, 1567, 1488, 1456, 1397, 1310, 1294, 1283, 1217, 1157, 1135, 1091, 1014, 964, 897, 882, 854, 820, 755, 709.

9-(1-Phenylethylidene)-1,4-dihydro-1,4-methanonaphthalene (46c)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 µL, 0.50 mmol) and (1-(cyclopenta-2,4-dien-1-ylidene)ethyl)benzene **3e** (0.126 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 9-(1-phenylethylidene)-

1,4-dihydro-1,4-methanonaphthalene **46c** as a light yellow oil (0.110 g, 89%).

R_f (pet. ether): 0.50.

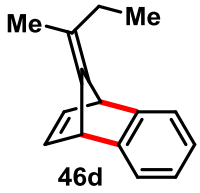
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.41 (m, 3H), 7.34-7.28 (m, 4H), 7.12-7.07 (m, 3H), 7.03-7.01 (m, 1H), 4.62 (bs, 1H, CH), 4.47 (bs, 1H, CH), 2.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.41, 150.11, 150.00, 143.11, 142.71, 141.52, 128.10, 128.02, 126.35, 124.84, 124.78, 121.19, 121.12, 107.91, 51.69, 51.29, 18.54.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{17}$: 245.1325, found: 245.1359.

FTIR (cm^{-1}): 3065, 3010, 2918, 2857, 1694, 1599, 1492, 1451, 1443, 1375, 1299, 1217, 1168, 1155, 1135, 1076, 1026, 1010, 928, 913, 898, 815, 788, 753, 705.

9-(Butan-2-ylidene)-1,4-dihydro-1,4-methanonaphthalene (46d)



46d

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and 5-(butan-2-ylidene)cyclopenta-1,3-diene **3g** (0.090 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 9-(butan-2-ylidene)-1,4-dihydro-1,4-methanonaphthalene **46d** as a light yellow oil (0.090 g, 92%).

R_f (pentane): 0.80.

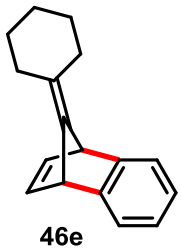
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.26 (m, 2H), 6.99-6.95 (m, 4H), 4.41-4.40 (m, 2H, CH), 2.05-1.93 (m, 2H, CH_2), 1.58 (s, 3H), 0.95-0.92 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.67, 150.70, 150.61, 143.06, 143.01, 124.48, 120.88, 120.79, 107.85, 50.77, 50.47, 26.19, 16.21, 12.69.

HRMS: calculated $[M+H]^+$ for $C_{15}H_{17}$: 197.1325, found: 197.1326.

FTIR (cm^{-1}): 3123, 3046, 3067, 3002, 2965, 2932, 2873, 2858, 1714, 1456, 1449, 1376, 1296, 1289, 1216, 1166, 1153, 1099, 1071, 1011, 788, 751, 704.

9-Cyclohexylidene-1,4-dihydro-1,4-methanonaphthalene (46e)


46e

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and cyclo penta-2,4-dien-1-ylidenecyclohexane **3c** (0.109 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 9-cyclohexylidene-1,4-dihydro-1,4-methanonaphthalene **46e** as a light yellow oil (0.104 g, 94%).

R_f (pentane): 0.56;

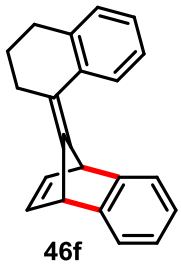
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.27 (m, 2H), 7.01-6.97 (m, 4H), 4.46-4.45 (m, 2H, CH), 2.16-2.13 (m, 2H, CH_2), 2.07-2.03 (m, 2H, CH_2), 1.50 (bs, 6H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.20, 150.83, 143.22, 124.41, 120.84, 110.32, 50.21, 29.73, 27.42, 26.78.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{19}$: 223.1481, found: 223.1496.

FTIR (cm^{-1}): 3123, 3067, 3045, 3003, 2926, 2853, 2792, 2668, 1715, 1680, 1447, 1348, 1332, 1317, 1296, 1289, 1260, 1240, 1217, 1178, 1165, 1156, 1104, 1011, 996,928,896 ,880 .851, 820, 782, 755.

9-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-1,4-dihydro-1,4-methanonaphthalene (46f)


46f

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **51a** (0.149 g, 121 μL, 0.50 mmol) and 1-(cyclopenta-2,4-dien-1-ylidene)-1,2,3,4-tetrahydronaphthalene **3h** (0.145 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography 9-(3,4-dihydro naphthalen-1(2*H*)-ylidene)-1,4-dihydro-1,4-methanonaphthalene **46f** as a colorless oil (0.122 g, 90%).

R_f (pentane): 0.30;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.39 (m, 3H), 7.29 (t, *J* = 7.0 Hz, 1H), 7.24-7.21 (m, 1H), 7.18-7.16 (m, 1H), 7.10-7.07 (m, 4H), 4.89 (bs, 1H, CH), 4.61 (bs, 1H, CH), 2.83-2.71 (m, 2H, CH_2), 2.59-2.41 (m, 2H, CH_2), 1.94-1.79 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.20, 150.05, 149.87, 143.33, 142.47, 138.90, 135.76, 128.35, 127.76, 126.20, 125.38, 124.84, 121.13, 121.11, 108.30, 51.50, 51.28, 29.89, 27.33, 23.57.

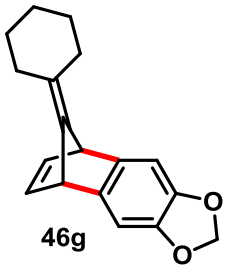
HRMS: calculated $[M+H]^+$ for $C_{21}H_{19}$: 271.1481, found: 271.1496.

FTIR (cm^{-1}): 3065, 3014, 2854, 1738, 1715, 1681, 1600, 1481, 1454, 1376, 1367, 1340, 1327, 1216, 1178, 1156, 1011, 821, 791, 760, 729, 688.

10-Cyclohexylidene-5,8-dihydro-5,8-methanonaphtho[2,3-*d*][1,3]dioxole (46g)

Following the general procedure, treatment of 6-(trimethylsilyl) benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate **51b** (0.171 g, 0.50 mmol) and cyclopenta-2,4-dien-1-ylidene cyclohexane **3c** (0.109 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL)

at 30 °C for 12 h followed by column chromatography afforded 10-cyclohexylidene-5,8-dihydro-5,8-methanonaphtho[2,3-*d*][1,3]dioxole **46g** as a light yellow oil (0.119 g, 90%).



46g

R_f (pentane/DCM=80/20): 0.46.

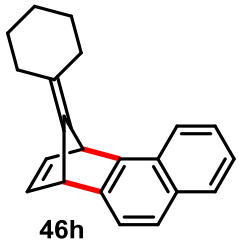
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (s, 2H), 6.82 (s, 2H), 5.90-5.85 (m, 2H), 4.33 (s, 2H, CH), 2.08-2.04 (m, 2H), 1.99-1.96 (m, 2H), 1.45 (bs, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.71, 144.48, 143.98, 143.36, 108.72, 104.06, 100.77, 50.14, 2 9.62, 27.39, 26.75.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{19}O_2$: 267.1380, found: 267.1346.

FTIR (cm^{-1}): 3122, 3066, 3002, 2926, 2854, 2765, 2790, 1734, 1715, 1618, 1558, 1498,1459, 1323, 1288, 1261, 1240, 1217, 1172, 1130, 1105, 1072, 1037, 1002, 939, 910, 864, 853, 825, 756, 719.

11-Cyclohexylidene-1,4-dihydro-1,4-methanophenanthrene (46h)


46h

Following the general procedure, treatment of 1-(trimethylsilyl) naphthalen -2-yl trifluoromethanesulfonate **51c** (0.174 g, 0.50 mmol) and cyclopenta-2,4-dien-1-ylidenecyclohexane **3c** (0.109 g, 0.75 mmol) with CsF (0.190 g, 1.25 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography afforded 11-cyclo hexylidene-1,4-dihydro-1,4-methanophenanthrene **46h** as a light yellow oil (0.113 g, 83%).

R_f (pentane): 0.56.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08-8.06 (d, *J=8.3* Hz, 1H), 7.93-7.91 (d, *J=8.3* Hz, 1H), 7.63 (bs, 2H), 7.58-7.54 (t, *J=7.4* Hz, 1H), 7.47-7.43 (t, *J=7.*4 Hz,1H), 7.17 (bs, 2H), 5.12 (s, 1H, CH), 4.71 (s, 1H, CH), 2.23 (bs, 2H), 2.14-2.12 (m,2H),1.54 (bs,6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.87, 149.04, 148.39, 143.14, 131.61, 128.86, 128.28, 125.68, 124.41, 123.13, 120.62, 108.22, 51.23, 47.83, 29.61, 29.51, 27.39, 27.37, 26.77.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{21}$: 273.1638, found: 273.1638.

FTIR (cm^{-1}): 3119, 3053, 3003, 2922, 2851, 2800, 1714, 1626, 1584, 1557, 1516, 1447, 1382, 1364, 1344, 1289, 1260, 1240, 1200, 1178, 1152, 1135, 1105, 1093, 1080, 1017, 996, 954s, 908, 893, 860, 851, 805, 744, 765, 707.

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CHAPTER 3

Efficient Synthesis of 9-Aryl dihydrophenanthrenes by a Cascade Reaction Involving Arynes and Styrenes

3.1. Introduction

9,10-Dihydrophenanthrene derivatives are important structural motifs found in various biologically active natural products.[1] For example, the natural product juncusol has been reported to possess anticancer and antimicrobial activity, was isolated by Miles and coworkers in 1977 from the plant *Juncus roemerianus*.[2] In 1990, Lusianthridin was isolated by Majumder and Lahiri from the orchid *Lusia indiuis*, has been found to show *α*,*α*-diphenyl-2-piorylhydrasyl (DPPH) free-radical scavenging activity and valuable as an antioxidant.[3] Additionally, 9,10-dihydrophenanthrene derivative orchinol[4] isolated from *Orchis militaris* shows antifungal activity (Figure 3.1). Owing to the diverse biological activity of this class of natural products and their various substitution patterns, 9,10-dihydrophenanthrene structural motifs are interesting synthetic target. Consequently, the search for efficient, straightforward and economical method for the synthesis of multisubstituted 9,10-dihydrophenanthrenes has attracted much attention in synthetic organic chemistry. The present chapter includes a detailed investigation of the Diels-Alder/ene cascade reaction of arynes with styrenes leading to the transition-metal-free synthesis of 9,10-dihydrophenanthrene derivatives. Before going into the details, a brief account of methods for the synthesis of 9,10-dihydrophenanthrene derivatives is provided in the following sections.

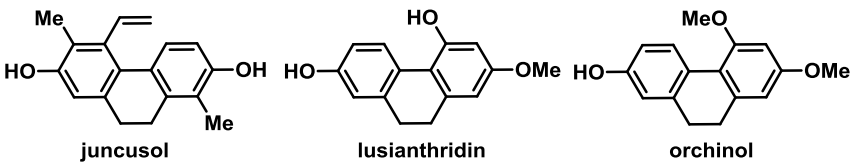


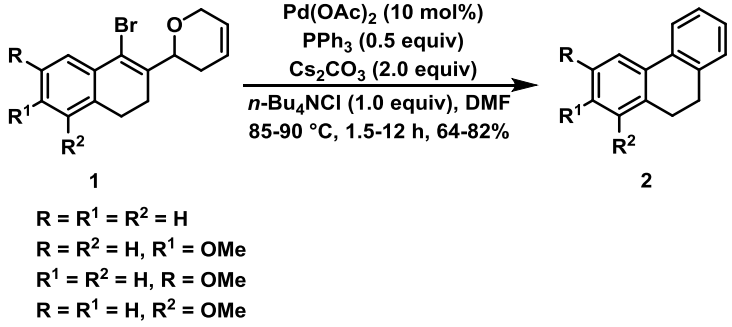
Figure 3.1: Selected naturally occurring 9,10-dihydrophenanthrenes

3.2. Synthesis of 9,10-Dihydrophenanthrenes

3.2.1. Transition-Metal-Catalyzed and Transition-Metal-free Synthesis of 9,10-Dihydrophenanthrenes

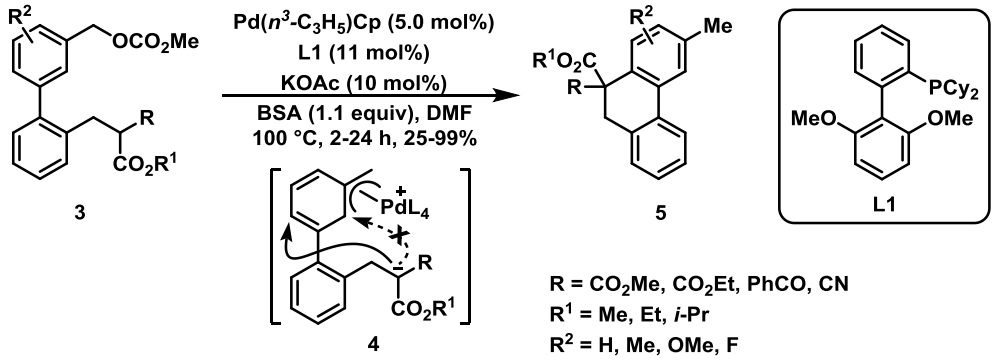
In 2008, Ray and coworkers developed a method for the synthesis of 9,10-dihydrophenanthrene derivatives by the palladium-catalyzed electrocyclization strategy. Treatment of **1** with 10 mol% of $Pd(OAc)_2$ in DMF as solvent at 85-90 °C afforded the 9,10-dihydrophenanthrenes **2** in good yields (Scheme 3.1).[5] A fused aromatic ring in product was formed via the cleavage of the pyran ring present in the substrate. Mechanistically, the reaction presumably proceeds through a palladium-catalyzed 6π electrocyclic reaction followed by the elimination of formaldehyde molecule.

Scheme 3.1: Synthesis of 9,10-Dihydrophenanthrenes via the Palladium-Catalyzed Electrocyclic Reaction



Kuwano and coworkers demonstrated that the benzylic carbonates with an active methine group, which is installed at the *meta*-position through an *ortho*-phenylene tether were cyclized by using palladium catalyst. Heating of *meta*-substituted benzyl esters **3** in

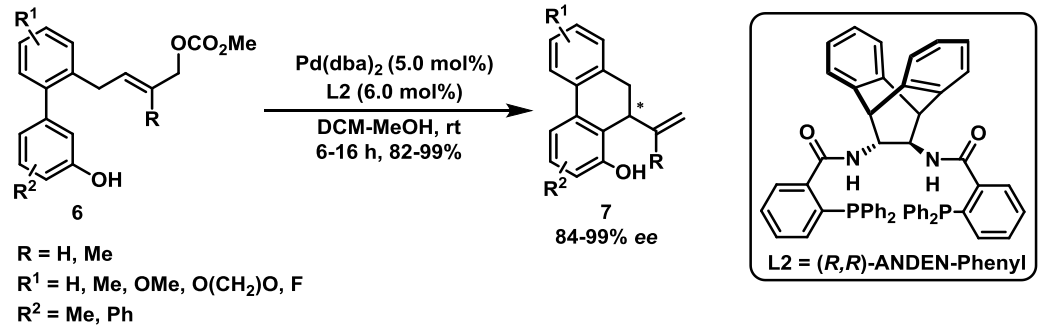
Scheme 3.2: Synthesis of 3-Methyl-9,10-dihydrophenanthrenes via the Palladium-Catalyzed Intramolecular S_N'-Type Aromatic Substitution



the presence of Pd(η^3-C_3H_5)Cp-S-Phos catalyst in DMF as solvent readily afforded the 3-methyl-9,10-dihydrophenanthrene derivatives **5** (Scheme 3.2).[6] The catalytic cyclization proceeds through a palladium-catalyzed intramolecular S_N'-type aromatic substitution exclusively at *para*-position of the benzyl ester not at *ortho*-position through an zwitterionic (η^3-benzyl)palladium **4** intermediate.

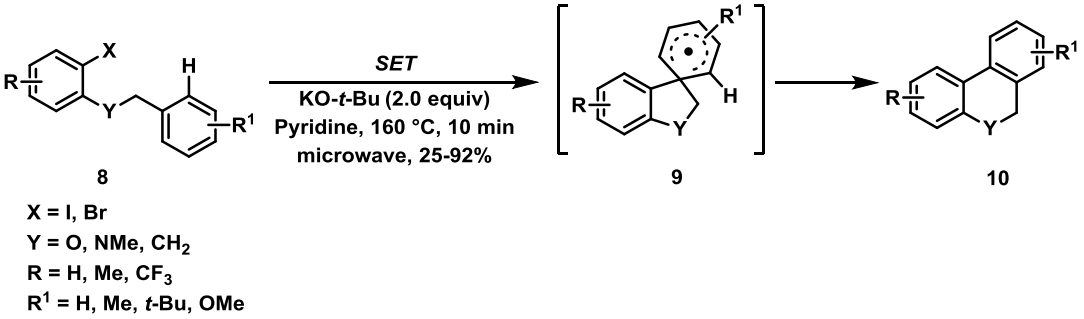
Subsequently, Hamada group developed a novel palladium-catalyzed asymmetric intramolecular Friedel-Crafts allylic alkylation of phenols for the synthesis of a range of 10-vinyl and 10-isopropenyl 9,10-dihydrophenanthrene derivatives in high yield with high enantiomeric excess. The reaction of substrates **6** using 5 mol% of $Pd(dba)_2$ and 6 mol% of (R,R)-ANDEN-phenyl ligand **L2** in DCM-MeOH mixed solvent system at room temperature resulted in the formation of corresponding products **7** (Scheme 3.3).[7]

Scheme 3.3: Palladium-Catalyzed Asymmetric Synthesis of 10-Vinyl and 10-Isopropenyl 9,10-Dihydrophenanthrenes



Charette and coworkers reported a highly regioselective potassium *tert*-butoxide mediated intramolecular cyclization of aryl ether and amine derivatives without using any transition metal catalyst. This method is operationally very simple, just heating of the starting material **8** with potassium *tert*-butoxide in pyridine solvent under microwave irradiation afforded the corresponding cyclized products **10** in good yields (Scheme 3.4).[8]

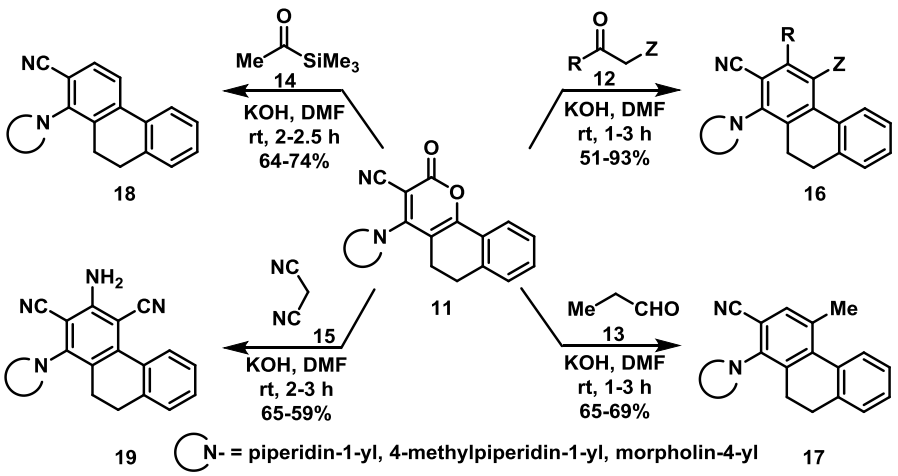
Scheme 3.4: KO-*t*-Bu Mediated Intramolecular Cyclization of Aryl Halides



The notable feature of this reaction is the combination of an inorganic base and a pyridine solvent, which initiate single electron transfer (SET) to a carbon-halide bond at high temperature to form an aryl radical. Aryl radical can undergo kinetically favored 5-*exo*-trig ipso cyclization to give spirocyclohexadienyl radical **9** which upon ring expansion resulted in the formation of product. Moreover, substituted aryl halides exclusively furnished single regioisomers, hence it ruled out the possibility of formation of aryne intermediate under these basic reaction conditions.

Additionally, another transition-metal-free approach involving base-catalyzed ring transformation of 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbo nitriles **11** leading to the straightforward synthesis of substituted 9,10-dihydro-1-*sec*-aminophenanthrene-2-carbonitriles **16**, **17**, **18**, and **19** by carbanion generated from various ketones **12**, aldehyde **13**, acetyltrimethylsilane **14**, and malononitrile **15** respectively has been uncovered by Ram and Pratap (Scheme 3.5).[9a] 9,10-Dihydro-phenanthren derivatives possessing a carboxyl group at 2 position has been found useful in the treatment of pharmacological disorders related with high levels of dihydrotestosterone and known as an inhibitor of 5α-reductase.[2a,9b]

Scheme 3.5: Base-Catalyzed Synthesis of Substituted 9,10-Dihydro-1-*sec*-aminophenanthrene-2-carbonitriles

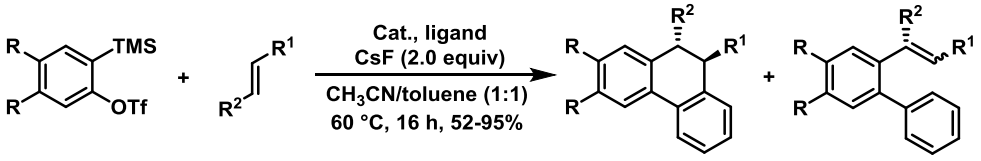


3.2.2. Transition-Metal-Catalyzed Synthesis of 9,10-Dihydrophenanthrenes Involving Arynes

Transition-metal-catalyzed cyclization reactions of arynes with alkenes for the synthesis of 9,10-dihydrophenanthrenes are documented in the present section. In 1998,

Guitián and coworkers, for the first time reported generation of arynes in the presence of catalytic amounts of palladium complexes leading to the cyclotrimerization of arynes and alkynes to give triphenylene.[10a] They utilized this strategy in the synthesis of various polycyclic aromatic hydrocarbons via [2 + 2 + 2] cycloaddition of polycyclic arynes.[10b] Subsequently, the same group developed the palladium- and nickel-catalyzed cotrimerization of arynes generated from 2-(trimethylsilyl)aryl triflates **20** with electron-deficient acyclic alkenes **21** to offer the 9,10-dihydrophenanthrenes **22** or *ortho*-olefinated biphenyls (*E*/*Z*) **23** depending on the catalytic system employed (Scheme 3.6).[11] Ni-catalyst was found to be more efficient than palladium complexes in present cotrimerization process, but with $Pd_2(dba)_3$ as the catalyst, cotrimerization was highly dependent on the ligand used. Mixtures of $Pd_2(dba)_3$ and PPh_3 afforded 9,10-dihydrophenanthrenes as major product and the use of P(*o*-tolyl)$_3$ as a ligand favored the formation *ortho*-olefinated biaryls.

Scheme 3.6: Transition-Metal-Catalyzed Reactions of Arynes with Alkenes



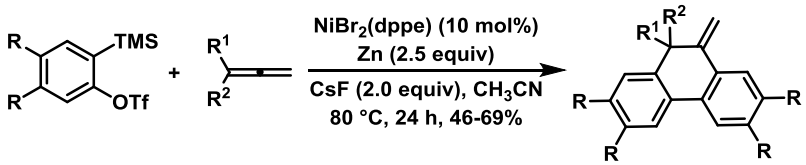
20 **21** **22** **23 (*E*/*Z*)**

R = H, O(CH$_2$)O, (CH$_2$)$_3$
R^1 = CO$_2$Me, COMe, CN, SO$_2$Me, R^2 = H
R^1 = R^2 = CO$_2$Me
R^1 = CO$_2$Me, R^2 = Me

Cat., ligand = i. $Pd_2(dba)_3$ (5.0 mol%), PPh_3 (20 mol%)
ii. $Pd_2(dba)_3$ (5.0 mol%), P(*o*-tol)$_3$ (20 mol%)
iii. Ni(Cod)$_2$ (10 mol%), PPh_3 (20 mol%)

Ni-catalyzed [2 + 2 + 2] cocyclotrimerization of two aryne molecules with an allene leading to the synthesis of dihydrophenanthrene derivatives has been achieved by Cheng and coworkers. Treatment of aryne precursors 20 with allenes 24 in the presence of $NiBr_2$(dppe), zinc powder and CsF in CH_3CN solvent at 80 °C afforded the

Scheme 3.7: Nickel-Catalyzed Cocyclotrimerization of Arynes with Allenes



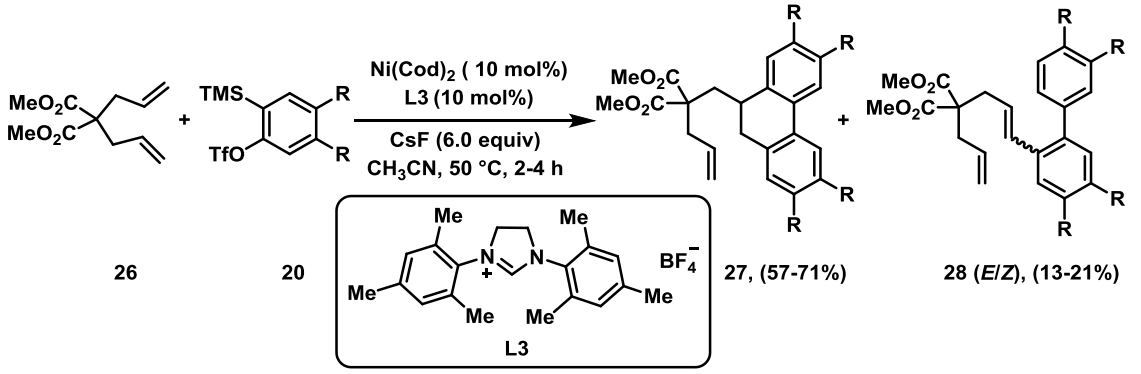
20 **24** **25**

R = H, Me
R^1 = H, Me
R^2 = Me, cyclohexyl, *t*-butyl, *n*-butyl, *n*-hexyl, *n*-octyl

corresponding 9-cyclohexyl-10-methylene-9,10-dihydrophenanthrene derivatives **25** in moderate to good yields (Scheme 3.7).[12]

Later, in 2009 Sato group revealed a nickel-catalyzed [2 + 2 + 2] cycloaddition of unactivated alkene moiety in a α,ω-dienes with two molecules of arynes furnishing the 9,10-dihydrophenanthrene derivatives. Treatment of diene **26** with aryne generated from the **20** using CsF in the presence of 10 mol% of $Ni(cod)_2$ catalyst and SIMes.HBF_4 ligand in CH_3CN as solvent at 50 °C resulted in the formation of 9,10-dihydrophenathrene derivative **27** along with *ortho*-olefinated biaryls (*E*/*Z*) **28** (Scheme 3.8).[13] It has been suggested that the unreacted tethered alkene played a key role in the progress of the co-trimerization process.

Scheme 3.8: Nickel-Catalyzed Co-trimerization of Arynes with Unactivated Alkenes

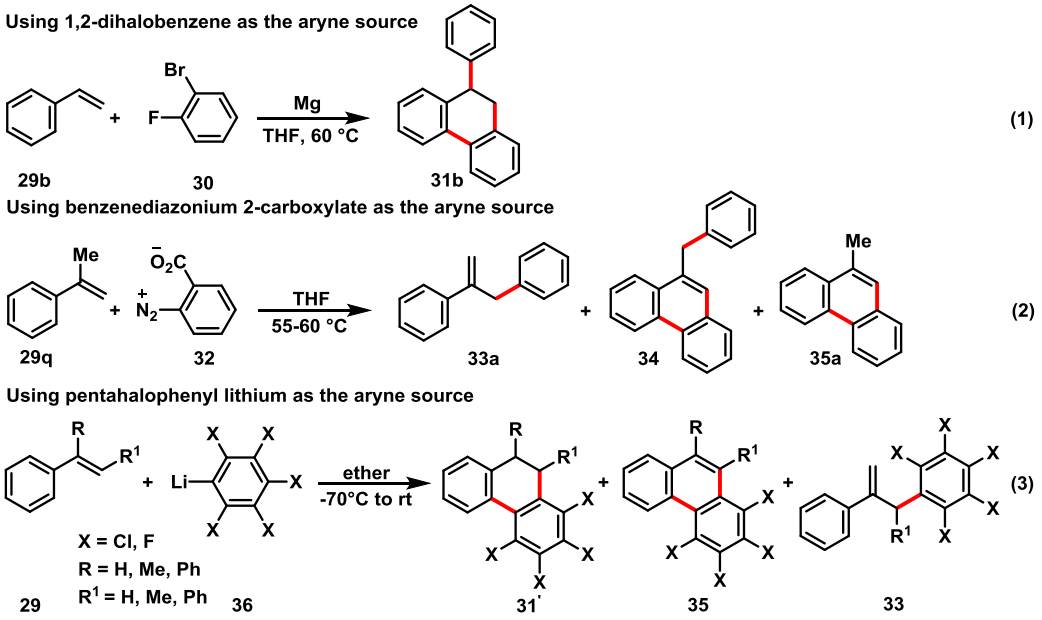


3.3. Statement of the Problem

As already discussed in the previous section, various methods have been reported for the synthesis of dihydrophenanthrenes by the use of transition-metal-catalyzed ring annulations, intermolecular and intramolecular cyclization reactions. Most of these procedures have certain limitations such as use of toxic and costly transition-metal catalysts, accessibility of the specific substrates and ligands which require multiple steps for synthesis. Particularly, these reactions require harsh reaction conditions and having less functional group tolerance, and lack of regioselectivity. 9,10-dihydrophenanthrenes are endowed with diverse biological activities, and convenient and efficient methods for the synthesis of these compounds without use of any transition-metal-catalyst and readily available stating materials remains a significant challenge.

Based on our interest in the Diels-Alder reaction of arynes with challenging dienes,[14,15] we envisioned that the [4 + 2] cycloaddition reaction of arynes generated under mild reaction conditions, by the fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates[16] with styrenes could result in a straightforward access to 9,10-dihydrophenanthrenes. This is a very interesting concept, utilizing styrenes as 4π-component in Diels-Alder reactions where one of the double bond of diene system is involved in aromaticity.[17] Notably, the reaction of styrene **29b** with aryne generated from 2-bromofluorobenzene **30** using magnesium in THF as a solvent at 60 °C leading to the formation of 9-phenyl 9,10-dihydrophenanthrene **31b** was reported by Dilling as early as 1966 (Scheme 3.9, eq 1).[18] However, this reaction is limited to only one example. Subsequently, the reaction of aryne generated from benzenediazonium 2-carboxylate **32** with α-methyl styrene **29q** furnishing the three products 2,3-diphenylpropene **33a**, 9-benzylphenanthrene **34**, and 9-methylphenanthrene **35a** in low yields was developed by Wolthuis and Cady (eq 2).[19] Moreover, Heaney and coworkers reported the reaction of tetrahalogenated arynes generated from pentahalophenyl lithium **36** with styrenes leading to the formation of either 9,l0-dihydrophenanthrene **31'**, or phenanthrene derivatives **35** or mixture of both the products.[20] In α-methyl styrene case, they isolated the mixture of these products along with 2,3-diphenylpropene derivatives **33** (eq 3), similar to the Cady's observation (eq 2). In contrast to Dilling's report (eq 2), Heaney did not observe

Scheme 3.9: Reactions of Arynes with styrenes



the formation of 9-phenyl 9,10-dihydrophenanthrenes in the reaction of styrenes with arynes.

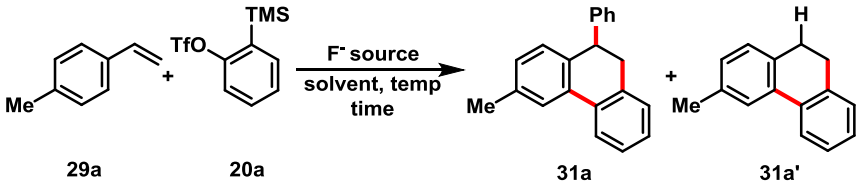
Although these cycloaddition reactions have been known for decades, exclusive synthesis of single product among the different possibilities remains a great challenge for the organic chemists. In all these reports, the substrate scope appears to be very limited, and the yields are relatively low and therefore a general method remains to be uncovered. Strongly basic and harsh reaction conditions used for the generation of arynes were not compatible for styrenes, and this can undergo polymerization as side reaction.[21] To overcome these difficulties, a systematic study of the Diels-Alder reaction of arynes with styrenes was carried out in the present chapter. The results of these studies leading to the transition-metal-free synthesis of 9,10-dihydrophenanthrene derivatives via Diels-Alder/ene cascade reaction are described in the next sections.

3.4. Results and Discussion

3.4.1. Optimization Studies

We initiated our present study with the treatment of 1-methyl-4-vinylbenzene **29a** with the aryne generated in situ from 2-(trimethylsilyl)aryl triflate **20a** using 4.8 equiv of

Table 3.1: Optimization of the Reaction Conditions[a]



entry	F^- source	solvent	temp (°C)	time (h)	yield of **31a** (%)[b]	yield of **31a'** (%)[b]
1	*CsF*	*CH_3CN*	*30*	*12*	*77 (73)*	*<5*
2[c]	KF	THF	30	12	59	21
3	TBAF	THF	30	12	<1	<1
4	CsF	CH_3CN	60	12	71	<5
5	CsF	CH_3CN	30	6	69	<5
6[d]	CsF	CH_3CN	30	12	74	<5

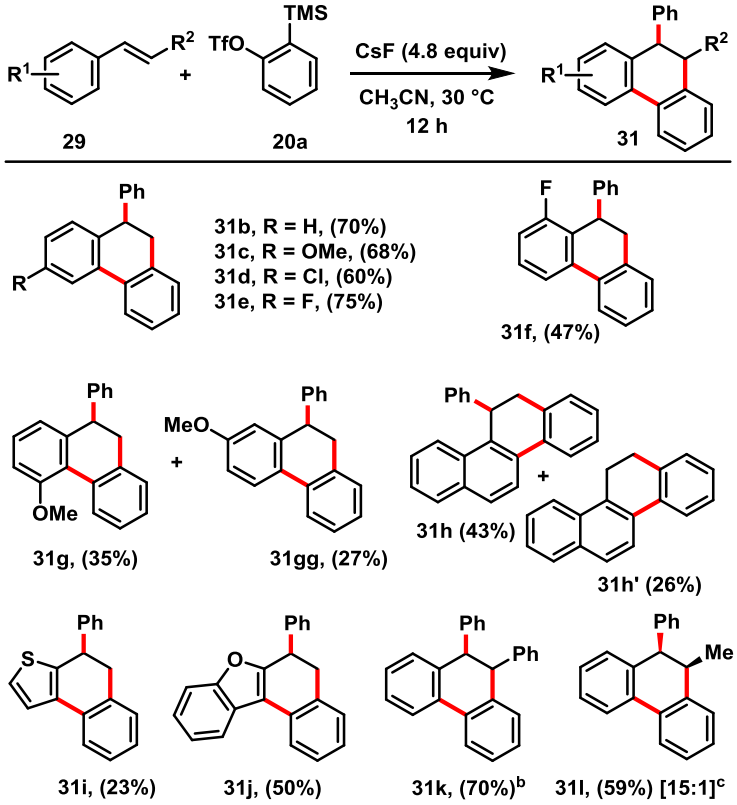
[a]Standard conditions: **29a** (0.25 mmol), **20a** (0.60 mmol), fluoride source (4.8 equiv), solvent (1.0 mL), 30 °C and 12 h. [b]The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard. Isolated yield in 0.50 mmol scale in parentheses. [c]4.8 equiv of 18-crown-6 was used as an additive. [d]2.0 equiv of **20a** and 4.0 equiv of CsF was used.

CsF. Interestingly, the reaction afforded the 9-phenyl-9,10-dihydrophenanthrene derivative **31a** in 77% yield and the product **31a**' (1:1 adduct) was observed only in trace amounts (based on ^{1}H NMR spectroscopy, Table 3.1, entry 1). 1:1 Adduct **31a'** formed via the proton transfer of initially generated Diels-Alder adduct. Notably, the reaction worked under mild reaction conditions in CH_3CN as the solvent. The reaction carried out using KF (in the presence of 18-crown-6) as the fluoride source resulted in a reduced yield of **31a**, whereas **31a'** was formed in 21% yield (entry 2). The use of tetrabutylammonium fluoride (TBAF) as fluoride source did not afford the expected product (entry 3). Increasing the reaction temperature to 60 °C and reducing reaction time to 6 h lowered the yield of **31a** (entries 4, 5). Lowering the amount of **20a** decreased the yield of **31a** (entry 6).

3.4.2. Cascade Reaction of Arynes and Styrenes: Scope of Styrenes

With the optimized reaction conditions, we then evaluated the substrate scope of styrenes in this unique Diels-Alder/ene cascade reaction with arynes (Scheme 3.10). The unsubstituted styrene worked well and various styrenes with electronically diverse functional groups at the 4-position of the aromatic ring of **29** were well tolerated, expected 9-phenyl-9,10-dihydrophenanthrene derivatives were isolated in good yields with excellent selectivity for the cascade product (**31b-e**). Moreover, fluoro-substitution at 2-position of the aromatic ring of **29** was also tolerated resulting in the formation of cascade product in 47% yield (**31f**). As expected, styrenes substituted at 3-position of the aromatic ring with -OMe group delivered regioisomers **31g** and **31gg**, which were easily separated by column chromatography in 35% and 27% yield, respectively. Additionally, 1-vinylnaphthalene furnished desired cascade product **31h** in 43% yield along with 1:1 adduct **31h'** in 26% yield. Gratifyingly, challenging styrene analogues like 2-vinylthiophene and 2-vinylbenzofuran also afforded the desired product in low to moderate yields, further expanding the scope of this Diels-Alder/ene cascade reaction (**31i, 31j**). Additionally, *trans*-stilbene resulted in a smooth conversion to the cascade product 9,10-diaryl 9,10-dihydrophenanthrene **31k** in 70% along with the 1:1 adduct **31b** in 17% yield. Moreover, the reaction of *β*-methyl styrene delivered the cascade reaction product 9-methyl-10-phenyl-9,10-dihydrophenanthrene **31l** in 59% yield with a good diastereomeric ratio of 15:1 in favor of the *cis* isomer.

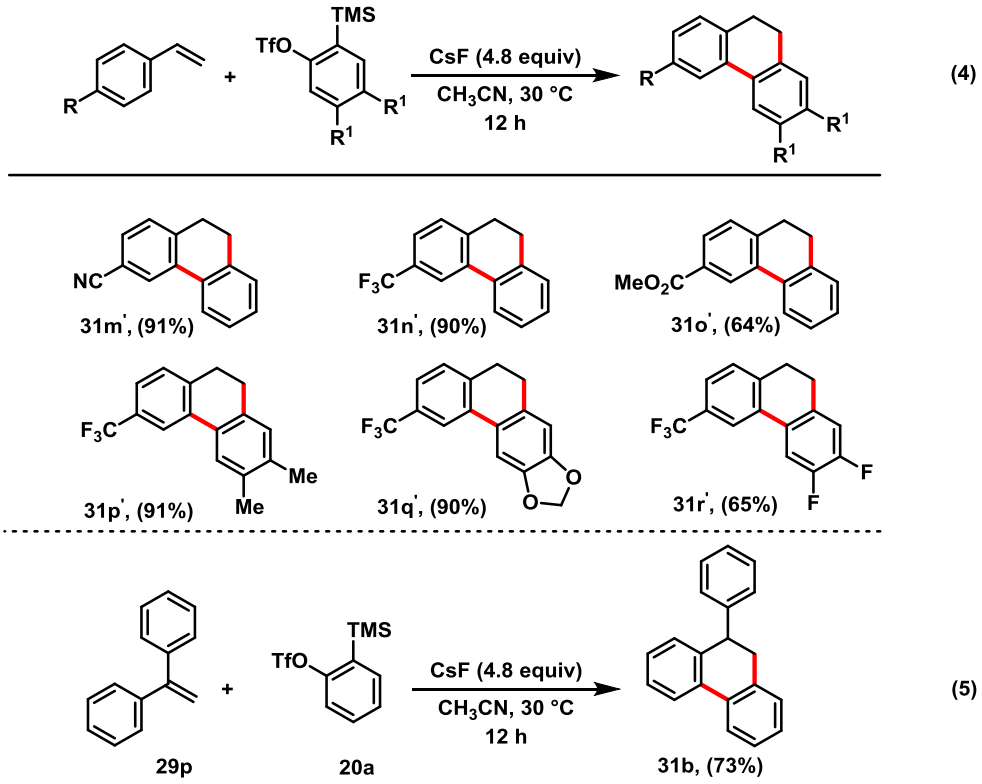
Scheme 3.10: Diels-Alder/Ene Cascade Reaction of Styrenes with Arynes: Variation of Styrenes[a]



[a]General Conditions: **29** (0.50 mmol), **20a** (1.20 mmol), CsF (4.8 equiv), CH_3CN (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given. [b]17% of 1:1 adduct was also isolated. [c]Determined by ^1H NMR.

Surprisingly, the reaction of aryne with styrenes having an electron-withdrawing group at the 4-position of the aromatic ring of **29** underwent efficient reaction leading to the formation of 1:1 adduct 9,10-dihydrophenanthrenes in good yields (Scheme 3.11, eq 4, **31m′-o′**). Moreover, this reaction was found to be efficient with electronically different aryne precursors leading to the synthesis of dihydrophenanthrenes in good yields (**31p′−r′**). In these cases, presumably owing to electronic nature of styrenes initially generated Diels-Alder adduct favors proton transfer instead of ene reaction to offer 1:1 adduct, and the cascade product was observed in only <10% yield. Additionally, the reaction of 1,1-diphenylethylene **29p** with aryne furnished exclusively 1:1 adduct **31b** in 73% yield (Scheme 3.11, eq 5). Possibly, due to the steric effect of phenyl group substituent in initially generated Diels-Alder adduct, it prefers proton shift.

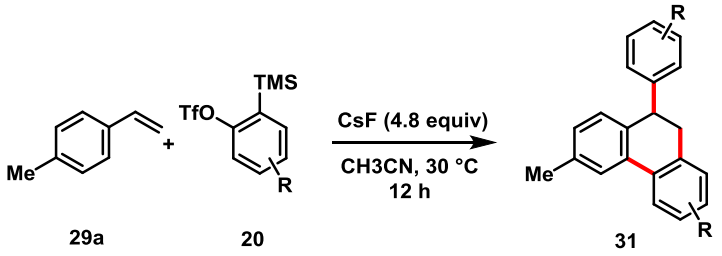
Scheme 3.11: Reaction of Arynes with Substituted Styrenes

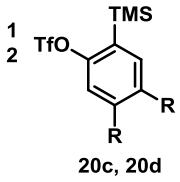
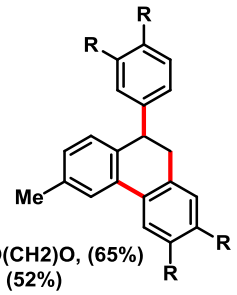
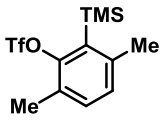
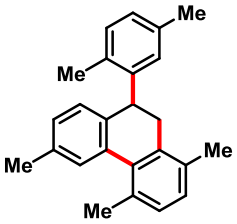
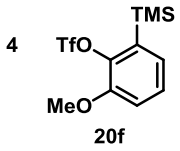
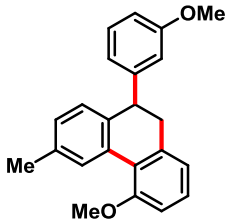
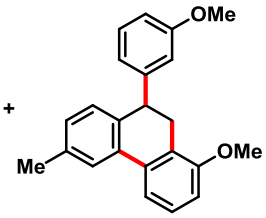


3.4.3. Cascade Reaction of Arynes and Styrenes: Scope of Arynes

Next, we examined the scope of this unique cascade reaction with various substituted arynes (Table 3.2). 4,5-Disubstituted symmetrical aryne precursors **20c**, **20d** with electron-donating and -withdrawing group resulted in the smooth conversion to the cascade product 9-aryl-9,10-dihydrophenanthrene **31s**, and **31t** in good yields (entries 1, 2). In the case of **31s**, the structure was unequivocally confirmed by single-crystal X-ray analysis (Figure 3.2).[22] Notably, some of the fluorinated 9,10-dihydrophenanthrenes are known to have potential applications as liquid crystalline materials.[23] Moreover, the symmetrical 3,6-dimethylaryne also furnished the desired product **31u** in 82% yield (entry 3). In addition, this Diels-Alder/ene cascade reaction worked well with unsymmetric 3-methoxyaryne generated from **20f**, delivered a separable mixture of regioisomers **3v** and **3vv** in 3:1 ratio and overall yield of 67% (entry 4). Two products formed in this case is due to the possibility of two Diels-Alder adducts produced between styrene **29a** and aryne **20f**.

Table 3.2: Diels-Alder/Ene Cascade Reaction of Styrenes with Arynes: Variation of Aryne Moiety[a]



entry	aryne precursor	product, yield (%)	entry	aryne precursor	product, yield (%)
1 2			3		
4			+		

[a]General Conditions: **20** (1.20 mmol), **29a** (0.50 mmol), CsF (4.8 equiv), CH_3CN (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given. [b]Reaction was run on 0.25 mmol scale.

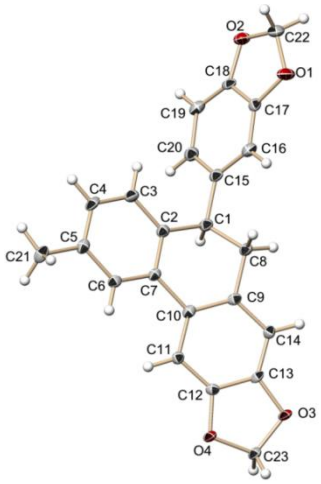
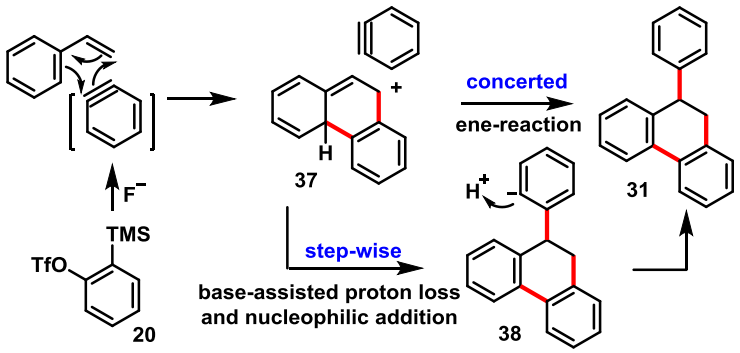


Figure 3.2: X-ray crystal structure of **31s**

3.4.4. Mechanistic Studies

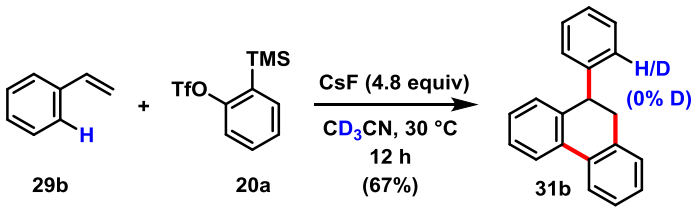
The mechanistic rationale for this cascade reaction is revealed in Scheme 3.12. Aryne generated from **20** gives [4 + 2] cycloaddition reaction with styrene **29** to form the adduct **37**. This adduct **37** can add to another molecule of electrophilic aryne in a concerted ene reaction leading to the formation of the desired product **31**.[24] Alternatively, in a stepwise pathway, deprotonation of **37** under basic reaction medium followed by nucleophilic addition to another molecule of aryne generating intermediate **38**, which can be protonated leading to the formation of **31**. Styrene-aryne Diels-Alder adduct **37** upon proton transfer can leads to the formation of 1:1 adduct **31'**.

Scheme 3.12: Plausible Reaction Mechanism



A strong support for the propossed mechanism of the reaction, proceeding via Diels-Alder/ene cascade pathway comes from the fact that when we carried out reaction of styrene **29b** with **20a** in CD_3CN as a solvent resulted in the formation of the corresponding protonated product **31b** in 67% yield (Scheme 3.13). No deuterium incorporation in the product supports our hypothesis that the second step is a concerted process.

Scheme 3.13: Reaction in CD_3CN



3.5. Conclusion

In conclusion, we have developed an efficient and transition-metal-free procedure for the synthesis of functionalized 9,10-dihydrophenanthrenes by a unique cascade

reaction involving arynes and styrenes.[25] The present method utilized styrenes as an unconventional diene component in the Diels-Alder reaction. Broad substrate scope, mild reaction conditions, and selective synthesis of one product are the noteworthy features of the present method. The protocol outlined in the present chapter is likely to find application for the transition-metal-free synthesis of 9,10-dihydrophenanthrene derivatives.

3.6. Experimental Details

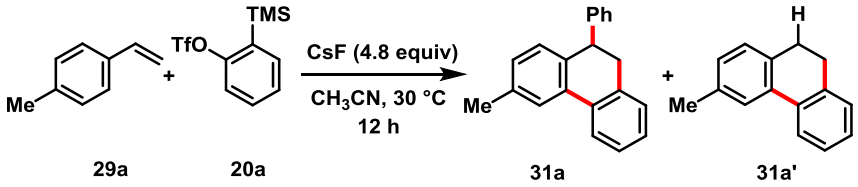
3.6.1. General Information

General information about experimental details is given in Section 2.9.1, Chapter 2. The styrenes **31b, 31e** and **31k** were purchased from Sigma Aldrich and were used without further purification. Other styrenes were synthesized from commercially available carbonyl compounds by Wittig reaction following literature procedure.[26] The 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20a** and the other symmetric and unsymmetric aryne precursors (**20b-f**) were synthesized following literature procedure.[16b, 27]

Infra-red spectra were recorded on a Bruker Alpha-E Infra-red Spectrophoto meter. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS data were recorded on either Waters SYNAPT G2 High Definition Mass Spectrometer or AB SCIEX Tof Tof TM 5800 using 2,5-dihydroxybenzoic acid as the solid matrix.

3.6.2. General Procedure for the Optimization of Reaction Conditions

Scheme 3.14: Optimization of Reaction Conditions

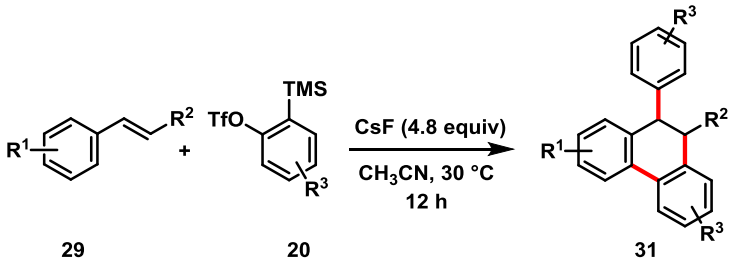


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry CsF (0.182 g, 1.20 mmol). Then the screw-capped tube was evacuated and backfilled with argon and dissolved in CH_3CN under argon atmosphere (1.0 mL). To the stirring solution were added 1-methyl-4-vinylbenzene **29a** (0.030 g, 0.25 mmol) and 2(trimethylsilyl)phenyl trifluoromethanesulfonate **20a** (0.179 g, 146 µL, 0.60 mmol). Then the reaction mixture kept for stirring at 30 °C. After 12 h, the reaction mixture was

diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^1H NMR analysis using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard.

3.6.3. General Procedure for the Cascade Reaction Involving Arynes with Styrenes

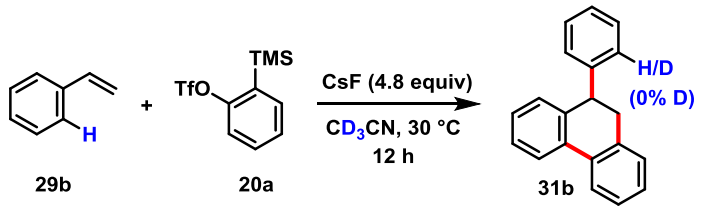
Scheme 3.15: Synthesis of 9,10-Dihydrophenanthrene Derivatives



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken dry CsF (0.365 g, 2.40 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this CH_3CN was added (2.0 mL) under argon atmosphere. The resultant solution was kept stirring at 30 °C. To this stirring solution were added corresponding styrene **29** (0.50 mmol) and aryne precursor **20** (1.2 mmol). Then the reaction mixture kept for stirring at 30 °C. When TLC control showed the completion of the reaction (typically after 12 h), the mixture was diluted with CH_2Cl_2 (5.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (15 mL). The solvent was evaporated and the crude residue was purified by column chromatography on silica gel to afford the corresponding 9,10-dihydrophenanthrene derivatives **31** in moderate to good yields.

3.6.4. Reactions Carried out in CD_3CN

Scheme 3.16: Reactions of **29b** and **20a** in CD_3CN as Solvent

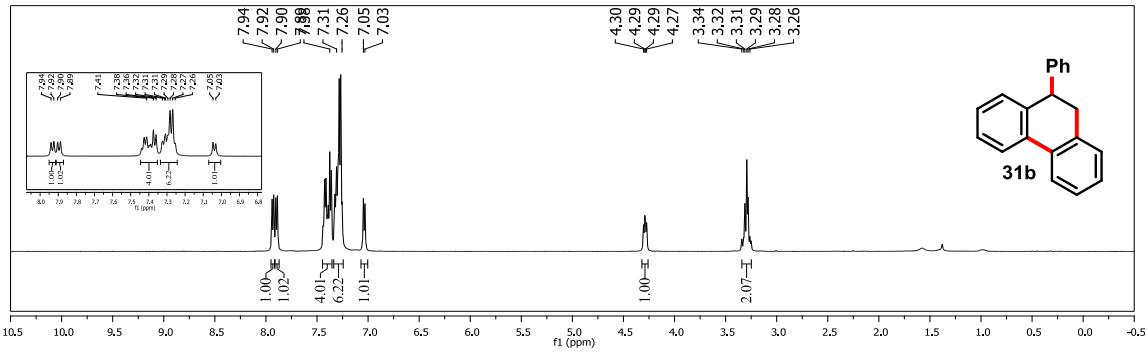


To a flame-dried screw-capped Schlenk tube equipped with a magnetic stir bar was added dry CsF (0.182 g, 1.20 mmol). Then the screw-capped tube was evacuated and

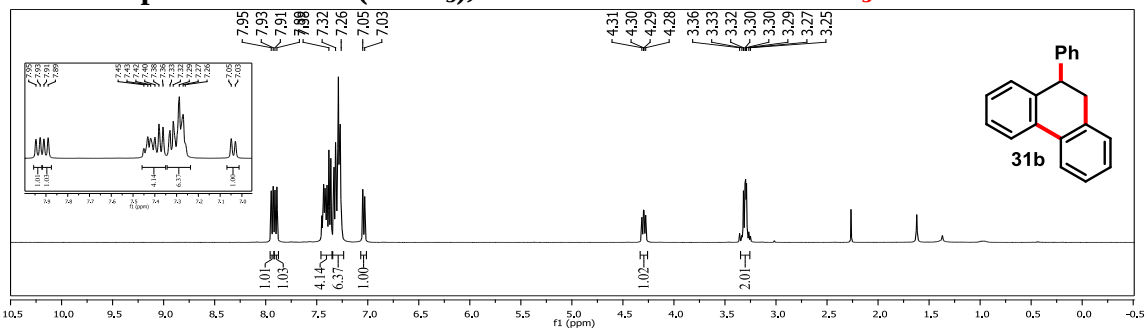
backfilled with argon and dissolved in **CD_3CN** under argon atmosphere (1.0 mL). To the stirring solution were added styrene **29b** (0.026 g, 0.25 mmol) and 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **20a** (0.179 g, 146 μL, 0.60 mmol). Then the reaction mixture kept for stirring at room temperature (30 °C). After 12 h, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated and the crude residue was purified by column chromatography on silica gel to afford the 9-phenyl-9,10-dihydrophenanthr ene **31b** as a white solid (0.043 g, 67%).

Comparison of Partial NMR of isolated product 31b in Scheme 3.10 and Scheme 3.16

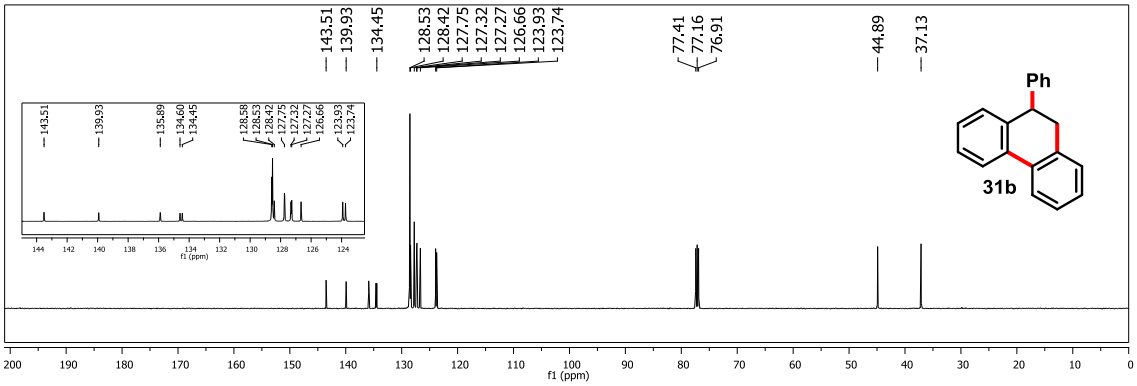
^{1}H NMR Spectrum of 31b ($CDCl_3$), Reaction Carried out in CH_3CN



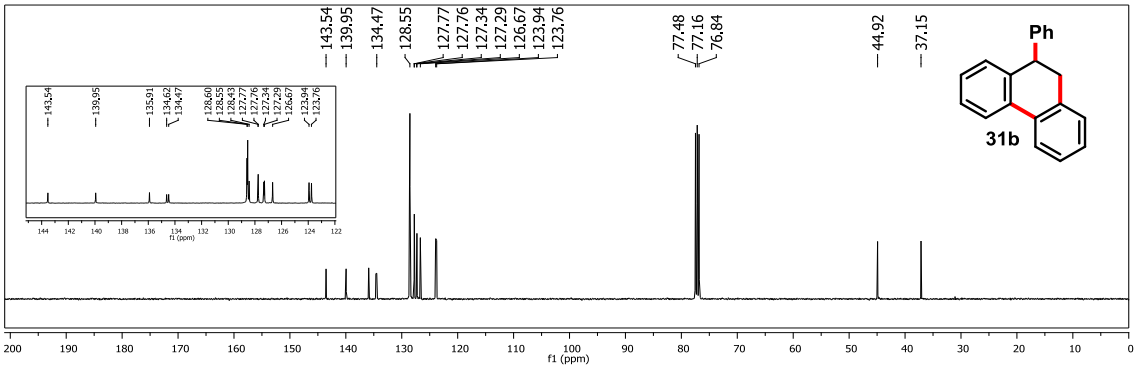
^{1}H NMR Spectrum of 31b ($CDCl_3$), Reaction Carried out in CD_3CN



^{13}C NMR Spectrum of 31b ($CDCl_3$), Reaction Carried out in CH_3CN

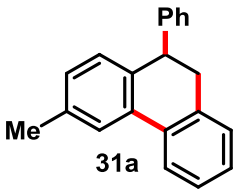


^{13}C NMR Spectrum of 31b ($CDCl_3$), Reaction Carried out in CD_3CN



3.6.5. Synthesis and Characterization of 9-Aryl-9,10-dihydrophenanthrene Derivatives

3-Methyl-10-phenyl-9,10-dihydrophenanthrene (31a)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 1-methyl-4-vinylbenzene **29a** (0.059 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 3-methyl-10-phenyl-9,10-dihydrophenanthrene **31a** as a colorless viscous oil (0.099 g, 73%).

R_f (Pet. ether): 0.60.

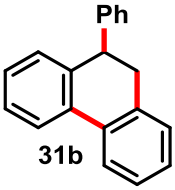
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.73 (s, 1H), 7.39-7.32 (m, 3H), 7.29-7.21 (m, 5H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.22 (t, *J* = 7.9 Hz, 1H), 3.26-3.23 (m, 2H), 2.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.77, 137.06, 136.74, 136.00, 134.53, 134.43, 128.55, 128.51, 128.33, 127.62, 127.19, 126.58, 124.61, 123.67, 44.56, 37.34, 21.47.

HRMS: calculated $[M]^+$ for $C_{21}H_{18}$: 270.1409, found: 270.1410 and $[M+H]^+$ for $C_{21}H_{19}$: 271.1487, found: 271.1441.

FTIR (cm^{-1}): 3026, 2924, 2854, 1606, 1493, 1449, 1304, 1218, 1076, 1036, 971, 883, 819, 769, 696, 669.

9-Phenyl-9,10-dihydrophenanthrene (31b)[18a]



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and styrene **29b** (0.052 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 9-phenyl-9,10-dihydrophenanthrene **31b** as a white solid (0.090 g, 70%).

R_f (Pet. ether): 0.53.

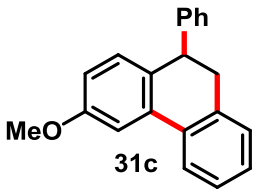
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.44-7.36 (m, 4H), 7.32-7.26 (m, 6H), 7.04 (d, *J* = 7.4 Hz, 1H), 4.30-4.27 (m, 1H), 3.34-3.26 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.51, 139.93, 135.89, 134.60, 134.45, 128.58, 128.53, 128.42, 127.75, 127.32, 127.27, 126.66, 123.93, 123.74, 44.89, 37.13.

HRMS: calculated $[M]^+$ for $C_{20}H_{16}$: 256.1252, found: 256.1254 and $[M+H]^+$ for $C_{20}H_{17}$: 257.1330, found: 257.1280.

FTIR (cm^{-1}): 3062, 3026, 2932, 2890, 1598, 1489, 1446, 1303, 1220, 1161, 1082, 1036, 1004, 971, 942, 847, 772, 700.

3-Methoxy-10-phenyl-9,10-dihydrophenanthrene (31c)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 1-methoxy-4-vinylbenzene **29c** (0.067 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 90/10) afforded 3-methoxy-10-phenyl-9,10-dihydrophenanthrene **31c** as a colorless viscous oil (0.097 g, 68%).

R_f (Pet. ether/DCM = 90/10): 0.47.

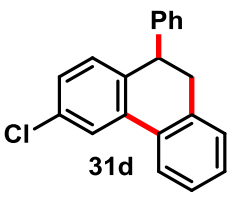
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.32-7.24 (m, 3H), 7.22-7.15 (m, 5H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.74 (dd, J_1 = 8.4 Hz, J_2 = 2.6 Hz, 1H), 4.15-4.11 (m, 1H), 3.84 (s, 3H), 3.22-3.13 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.00, 143.88, 136.13, 135.71, 134.38, 132.38, 129.43, 128.58, 128.54, 128.47, 127.87, 127.22, 126.58, 123.74, 112.93, 109.62, 55.46, 44.18, 37.47.

HRMS: calculated $[M]^+$ for $C_{21}H_{18}O$: 286.1358, found: 286.1364 and $[M+H]^+$ for $C_{21}H_{19}O$: 287.1436, found: 287.1436.

FTIR (cm^{-1}): 3024, 2935, 2835, 1608, 1565, 1493, 1448, 1416, 1364, 1298, 1215, 1175, 1136, 1041, 971, 940, 875, 815, 768, 695.

3-Chloro-10-phenyl-9,10-dihydrophenanthrene (31d)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 1-chloro-4-vinylbenzene **29d** (0.069 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 3-chloro-10-phenyl-9,10-dihydrophenanthrene **31d** as a colorless viscous oil (0.087 g, 60%).

***R*$_f$** (Pet. ether): 0.40.

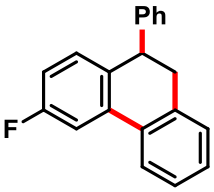
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.81 (d, *J* = 1.9 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.35-7.22 (m, 5H), 7.19-7.14 (m, 4H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.17-4.14 (m, 1H), 3.23-3.14 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 143.00, 138.34, 136.39, 135.97, 133.35, 133.19, 129.83, 128.72, 128.65, 128.45, 127.50, 127.46, 126.89, 124.00, 123.87, 44.43, 37.20.

HRMS: calculated $[M]^+$ for $C_{20}H_{15}Cl$: 290.0862, found: 290.0855.

FTIR (cm^{-1}): 3743, 3060, 3028, 2932, 2892, 1949, 1886, 1747, 1594, 1557, 1487, 1447, 1397, 1302, 1220, 1164, 1100, 1025, 971, 878, 847, 819, 768, 734, 701.

3-Fluoro-10-phenyl-9,10-dihydrophenanthrene (31e)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 1-fluoro-4-vinylbenzene **29e** (0.061 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 3-fluoro-10-phenyl-9,10-dihydroph enanthrene **31e** as a colorless viscous oil (0.103 g, 75%).

***R*$_f$** (Pet. ether): 0.53.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 10.2 Hz, 1H), 7.40-7.28 (m, 5H), 7.24-7.21 (m, 3H), 6.95-6.90 (m, 2H), 4.22-4.19 (m, 1H), 3.30-3.19 (m, 2H).

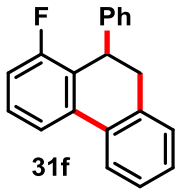
^{13}C NMR (100 MHz, CDCl$_3$): δ 162.42 (d, *J* = 243.1 Hz), 143.29, 136.56 (d, *J* = 7.4 Hz), 135.96, 135.54, 135.52, 133.58, 129.94 (d, *J* = 7.8 Hz), 128.64 (d, *J* = 4.5 Hz), 128.41 (d, *J* = 4.7 Hz), 127.39, 126.80, 123.88, 114.22 (d, *J* = 21.3 Hz), 110.63 (d, *J* = 22.0 Hz), 44.27, 37.16.

HRMS: calculated $[M]^+$ for $C_{20}H_{15}F$: 274.1158, found: 274.1155.

FTIR (cm^{-1}): 3063, 3029, 2935, 2891, 1603, 1571, 1491, 1448, 1416, 1303, 1276, 1217, 1181, 1126, 1082, 1033, 971, 943, 903, 869, 817, 765, 695.

1-Fluoro-10-phenyl-9,10-dihydrophenanthrene (31f)

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 1-fluoro-2-vinylbenzene **29f** (0.061 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h



31f

followed by column chromatography (Pet. ether/DCM = 98/02) afforded 1-fluoro-10-phenyl-9,10-dihydrophenanthrene **31f** as a colorless viscous oil (0.065 g, 47%).

***R**f* (Pet. ether): 0.47.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.37-7.30 (m, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.15-7.08 (m, 4H), 7.05-7.01 (m, 3H), 4.68 (d, *J* = 6.5 Hz, 1H), 3.47 (dd, J_1 = 15.4 Hz, J_2 = 6.7 Hz, 1H), 3.16 (d, *J* = 15.4 Hz, 1H).

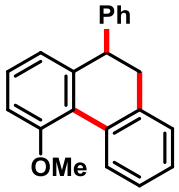
^{13}C NMR (100 MHz, $CDCl_3$): δ 160.57 (d, *J* = 244.9 Hz), 142.56, 136.76 (d, *J* = 4.6 Hz), 134.51, 133.65 (d, *J* = 3.4 Hz), 129.40, 128.50, 128.42, 128.32, 127.55, 127.27, 126.42, 125.97 (d, *J* = 17.0 Hz), 123.85, 119.67 (d, *J* = 2.9 Hz), 114.56 (d, *J* = 22.2 Hz), 36.07, 35.74 (d, *J* = 3.2 Hz).

HRMS: calculated $[M]^+$ for $C_{20}H_{15}F$: 274.1158, found: 274.1162 and $[M+H]^+$ for $C_{20}H_{16}F$: 275.1236, found: 275.1224.

FTIR (cm^{-1}): 3026, 2933, 1947, 1593, 1564, 1492, 1457, 1290, 1219, 1160, 1126, 1069, 1035, 970, 890, 768, 750, 693, 661.

4-Methoxy-10-phenyl-9,10-dihydrophenanthrene (31g) and 2-Methoxy-10-phenyl-9,10-dihydrophenanthrene (31gg)

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 1-methoxy-3-vinylbenzene **29g** (0.067 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 4-methoxy-10-phenyl-9,10-dihydrophenanthrene **31g** (colorless viscous oil, 0.050 g, 35%) and 2-methoxy-10-phenyl-9,10-dihydrophenanthrene **31gg** (colorless viscous oil, 0.039 g, 27%) as two regioisomers.



31g

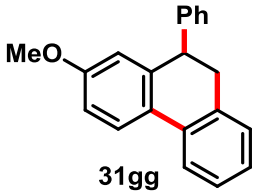
***R**f* (Pet. ether/DCM = 90/10): 0.57.

^{1}H NMR (400 MHz, $CDCl_3$) of 31g: δ 8.42 (d, *J* = 7.9 Hz, 1H), 7.35-7.29 (m, 3H), 7.26-7.18 (m, 6H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 1H), 4.16-4.13 (m, 1H), 3.97 (s, 3H), 3.24-3.15 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) of 31g: δ 157.11, 143.18, 143.04, 136.77, 132.57, 128.56, 128.50, 128.46, 128.05, 127.94, 127.09, 126.53, 126.40, 123.71, 120.93, 110.51, 55.73, 45.60, 37.46.

HRMS: calculated $[M]^+$ for $C_{22}H_{20}O_2$: 316.1463, found: 316.1466 and $[M+H]^+$ for $C_{22}H_{21}O_2$: 317.1541, found: 317.1538.

FTIR (cm^{-1}): 3061, 3018, 2937, 2836, 1588, 1498, 1445, 1287, 1252, 1219, 1160, 1100, 1065, 1003, 976, 941, 872, 769, 731, 694.



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

^{1}H NMR (400 MHz, $CDCl_3$) of 31gg: δ 7.81 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.35-730 (m, 3H), 7.27-7.18 (m, 5H), 6.92 (dd, J_1 = 8.6 Hz, J_2 = 2.6 Hz, 1H), 6.54 (d, *J* = 2.5 Hz, 1H), 4.21-4.17 (m, 1H), 3.76 (s, 3H), 3.23-3.19 (m, 2H).

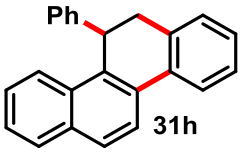
^{13}C NMR (100 MHz, $CDCl_3$) of 31gg: δ 159.34, 143.39, 141.66, 135.07, 134.43, 128.61, 128.51, 128.47, 127.65, 127.24, 126.87, 126.72, 125.21, 123.05, 114.17, 112.50, 55.29, 45.27, 37.23.

HRMS: calculated $[M]^+$ for $C_{22}H_{20}O_2$: 316.1463, found: 316.1462 and $[M+H]^+$ for $C_{22}H_{21}O_2$: 317.1541, found: 317.1532.

FTIR (cm^{-1}): 3026, 2936, 2835, 1604, 1481, 1452, 1366, 1270, 1218, 1154, 1093, 1043, 971, 872, 817, 765, 732, 697.

5-Phenyl-5,6-dihydrochrysene (31h) and 5,6-Dihydrochrysene (31h')[28]

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 1-vinylnaphthalene **29h** (0.077 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 5-Phenyl-5,6-dihydrochry sene **31h** (colorless viscous oil, 0.066 g, 43%) and 5,6-dihydrochrysene **31h'** (white solid, 0.030 g, 26%).



***R**f* (Pet. ether): 0.37.

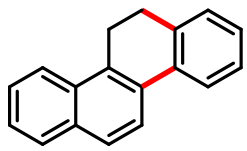
^{1}H NMR (400 MHz, $CDCl_3$) of 31h: δ 8.13 (d, *J* = 8.6 Hz, 1H), 8.06-8.04 (m, 1H), 7.98-7.91 (m, 3H), 7.49-7.47 (m, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.16-7.11 (m, 4H), 7.08-7.06 (m, 2H), 5.08 (d, *J* = 6.6 Hz, 1H), 3.63 (dd, J_1 = 15.2 Hz, J_2 = 6.6 Hz, 1H), 3.26 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) of 31h: δ 142.68, 135.08, 134.08, 133.94, 133.48, 132.18, 131.96, 129.00, 128.65, 128.36, 128.14, 127.83, 127.80, 127.25, 126.69, 126.30, 125.69,

124.17, 123.98, 122.57, 39.62, 37.36.

HRMS: calculated $[M]^+$ for $C_{24}H_{18}$: 306.1409, found: 306.1409 and $[M+H]^+$ for $C_{24}H_{19}$: 307.1487, found: 307.1465.

FTIR (cm^{-1}): 3060, 3020, 2932, 1599, 1519, 1489, 1451, 1427, 1376, 1277, 1217, 1079, 1033, 969, 863, 820, 746, 694, 667.



31h'

***R**f* (Pet. ether): 0.53.

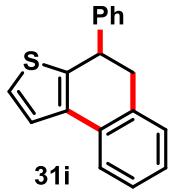
^{1}H NMR (400 MHz, $CDCl_3$) of 31h': δ 8.17 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.92-7.84 (m, 3H), 7.58-7.54 (m, 1H), 7.52-7.48 (m, 1H), 7.41-7.27 (m, 3H), 3.33 (t, *J* = 7.9 Hz, 2H), 3.03 (t, *J* = 7.9 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) of 31h': δ 137.10, 135.17, 133.24, 133.03, 131.79, 131.58, 128.71, 127.97, 127.45, 127.15, 126.31, 125.60, 124.33, 123.85, 122.53, 28.78, 23.90.

HRMS: calculated $[M]^+$ for $C_{18}H_{14}$: 230.1096, found: 230.1094 and $[M+H]^+$ for $C_{18}H_{15}$: 231.1174, found: 231.1133.

FTIR (cm^{-1}): 3022, 2932, 2888, 2834, 1595, 1514, 1482, 1432, 1376, 1218, 1164, 1026, 943, 863, 818, 769, 672.

4-Phenyl-4,5-dihydronaphtho[2,1-*b*]thiophene (31i)



31i

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 2-vinylthiophene **29i** (0.055 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 4-phenyl-4,5-dihydronaphtho[2,1-*b*]thiophene **31i** as a yellow viscous oil (0.030 g, 23%).

***R**f* (Pet. ether): 0.47.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 5.2 Hz, 1H), 7.36-7.29 (m, 6H), 7.22-7.16 (m, 3H), 4.35 (t, *J* = 8.5 Hz, 1H), 3.28 (d, *J* = 8.3 Hz, 2H).

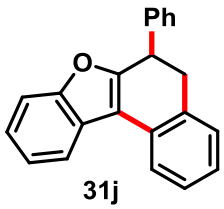
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.76, 141.68, 136.19, 134.01, 132.15, 128.73, 128.45, 127.99, 127.29, 127.23, 126.78, 124.19, 123.30, 123.07, 42.02, 38.90.

HRMS: calculated $[M]^+$ for $C_{21}H_{18}O$: 286.1358, found: 286.1364 and $[M+H]^+$ for $C_{21}H_{19}O$: 287.1436, found: 287.1436.

FTIR (cm^{-1}): 3060, 3028, 2929, 1602, 1532, 1492, 1453, 1428, 1383, 1349, 1296, 1220,

1145, 1079, 1030, 944, 884, 829, 768, 722, 697, 660.

6-Phenyl-5,6-dihydronaphtho[2,1-*b*]benzofuran (31j)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 2-vinylbenzofuran **29j** (0.072 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. Ether/DCM = 90/10) afforded 6-phe nyl-5,6-dihydronaphtho[2,1-*b*]benzofuran **31j** as a yellow liquid (0.074 g, 50%).

***R*$_f$** (Pet. ether): 0.20.

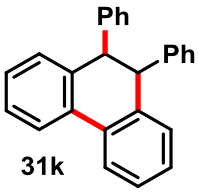
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08-8.07 (m, 1H), 7.93-7.91 (m, 1H), 7.53-7.51 (m, 1H), 7.40-7.38 (m, 2H), 7.36-7.20 (m, 8H), 4.49 (t, *J* = 6.3 Hz, 1H), 3.63 (dd, d, J_1 = 7.8 Hz, J_2 = 15.6 Hz, 1H), 3.33 (dd, d, J_1 = 5.3 Hz, J_2 = 15.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.52, 155.57, 141.17, 132.71, 131.36, 128.83, 128.52, 127.71, 127.27, 127.19, 126.40, 125.61, 123.94, 123.32, 122.89, 120.43, 114.42, 111.89, 40.06, 39.00.

HRMS: calculated $[M]^+$ for $C_{22}H_{16}O$: 296.1201, found: 296.1176 and $[M+H]^+$ for $C_{22}H_{17}O$: 297.1274, found: 297.1271. HRMS data was recorded on Synapt MALDI-MS (Waters, UK) using α-cyano 4-hydroxy cinnamic acid as the solid matrix.

FTIR (cm^{-1}): 1619, 1500, 1451, 1323, 1251, 1214, 1187, 1153, 1103, 993, 929, 740, 669.

9,10-Diphenyl-9,10-dihydrophenanthrene (31k) and 9-phenyl-9,10-dihydrophenan threne (31b)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and (*E*)-1,2-diphenylethene **29k** (0.090 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 9,10-diphenyl-9,10-dihydrophenan threne **31k** (white solid, 0.116 g, 70%) and 9-phenyl-9,10-dihydrophenanthrene **31b** (white solid, 0.022 g, 17%).

***R*$_f$** (Pet. ether): 0.31.

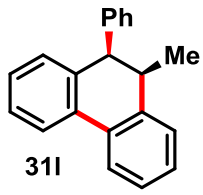
^{1}H NMR (400 MHz, $CDCl_3$) of 31k: δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.21-7.16 (m, 6H), 7.13-7.08 (m, 6H), 7.00 (d, *J* = 7.5 Hz, 2H), 4.47 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) of 31k: δ 143.92, 137.19, 134.40, 130.11, 128.45, 128.28, 128.20, 127.71, 126.42, 123.69, 52.73.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{21}$: 333.1643, found: 333.1664.

FTIR (cm^{-1}): 3061, 3025, 2905, 1598, 1490, 1447, 1218, 1182, 1077, 1032, 945, 916, 816, 770, 699, 671.

9-Methyl-10-phenyl-9,10-dihydrophenanthrene (31l)[29]



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and prop-1-en-1-ylbenzene (E:Z = 80:20) **29l** (0.059 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 9-methyl-10-phenyl-9,10-dihydrophenanthrene **31l** as inseparable mixture of diastereomers as a colorless viscous oil (0.080 g, 59%, *dr* determined by ^{1}H NMR analysis is 15:1).

R$_f$ (Pet. ether/DCM = 90/10): 0.64.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.35-7.28 (m, 2H), 7.25-7.21 (m, 1H), 7.19-7.13 (m, 5H), 7.03-7.01 (m, 2H), 4.06 (d, *J* = 3.4 Hz, 1H), 3.32-3.26 (m, 1H), 1.29 (d, *J* = 7.1 Hz, 3H).

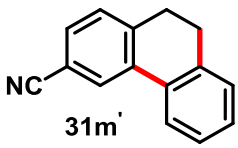
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.23, 140.13, 137.43, 133.90, 133.23, 130.38, 128.43, 128.36, 128.11, 128.00, 127.54, 127.14, 126.25, 123.77, 123.75, 51.79, 41.52, 22.08.

Representative Peaks of Minor Isomer: **^{1}H NMR:** δ 4.17 (d, *J* = 5.6 Hz), 3.46-3.40(m).

HRMS: calculated $[M]^+$ for $C_{21}H_{18}$: 270.1409, found: 270.1436 and $[M+H]^+$ for $C_{21}H_{19}$: 271.1487, found: 271.1437. HRMS data was recorded on Synapt MALDI-MS (Waters, UK) using 2,5-dihydroxybenzoic acid as the solid matrix.

FTIR (cm^{-1}): 3062, 3024, 2962, 2920, 1598, 1488, 1446, 1372, 1217, 1160, 1074, 1037, 1001, 942, 906, 839, 734, 694.

9,10-Dihydrophenanthrene-3-carbonitrile (31m')



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 4-vinylbenzonitrile **29m** (0.065 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by

column chromatography (Pet.ether/DCM = 90/10) afforded 9,10-dihydrophenanthrene-3-carbonitrile **31m'** as a colorless viscous oil (0.094 g, 91%).

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

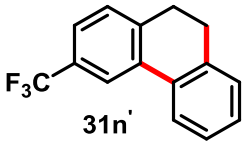
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 1.3 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.51 (dd, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 7.38-7.31 (m, 3H), 7.30-7.29 (m, 1H), 2.96-2.88 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.79, 137.28, 135.87, 132.52, 130.71, 129.10, 128.78, 128.50, 127.51, 127.40, 123.97, 119.35, 110.97, 29.30, 28.35.

HRMS: calculated $[M+Na]^+$ for $C_{15}H_{11}NNa$: 228.0784, found: 228.0766. HRMS data was recorded on Synapt MALDI-MS (Waters, UK) using 2,5-dihydroxybenzoic acid as the solid matrix.

FTIR (cm^{-1}): 2946, 2223, 1599, 1493, 1441, 832.

3-(Trifluoromethyl)-9,10-dihydrophenanthrene (31n')[30]



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and 1-(trifluoromethyl)-4-vinylbenzene **29n** (0.086 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (in Pet. ether) afforded 3-(trifluoromethyl)-9,10-dihydrophenanthrene **31n'** as a colorless oil (0.112 g, 90%).

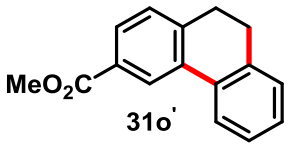
R_f (Pet. ether): 0.83.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.38-7.35 (m, 2H), 7.32-7.26 (m, 2H), 2.96-2.89 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.32, 137.44, 135.35, 133.39, 129.55 (q, *J* = 32.4 Hz), 128.67, 128.42, 127.40, 124.03, 123.99, 123.95, 120.64 (q, *J* = 4.2 Hz), 29.11, 28.70.

FTIR (cm^{-1}): 3037, 2942, 2896, 2838, 1910, 1619, 1497, 1419, 1330, 1264, 1163, 1114, 1072, 1023, 945, 897, 829, 768, 727, 655, 625.

Methyl 9,10-dihydrophenanthrene-3-carboxylate (31o')



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and methyl 4-vinylbenzoate **29o** (0.081 g, 0.50 mmol)

with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 95/05) afforded methyl 9,10-dihydrophenanthrene-3-carboxylate **31o'** as a yellow liquid (0.076 g, 64%).

R_f (Pet. ether): 0.24.

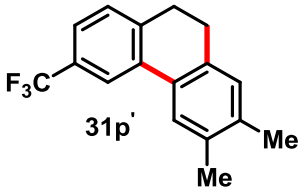
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.91 (dd, J_1 = 1.6 Hz, J_2 = 7.7 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.37-7.33 (m, 1H), 7.31-7.26 (m, 3H), 3.96 (s, 3H, CH_3), 2.94-2.87 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.24, 142.67, 134.79, 133.68, 129.63, 128.49, 128.32, 128.22, 127.99, 127.23, 124.97, 124.03, 52.09, 29.24, 28.64.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{15}O_2$: 239.1067, found: 239.1073.

FTIR (cm^{-1}): 3024, 2947, 2839, 1716, 1608, 1580, 1460, 1437, 1367, 1303, 1278, 1242, 1200, 1143, 1107, 1027, 972, 911, 847, 749, 700, 667, 631.

2,3-Dimethyl-6-(trifluoromethyl)-9,10-dihydrophenanthrene (31p')



Following the general procedure, treatment of 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20b** (0.392 g, 1.20 mmol) and and 1-(trifluoromethyl)-4-vinylbenzene **29n** (0.086 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 2,3-dimethyl-6-(trifluoromethyl)-9,10-dihydrophenanthrene **31p'** as a white solid (0.126 g, 91%).

R_f (Pet. ether): 0.70.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.55 (s, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.04 (s, 1H), 2.92-2.88 (m, 2H), 2.84-2.81 (m, 2H), 2.34 (s, 3H), 2.30 (s, 3H).

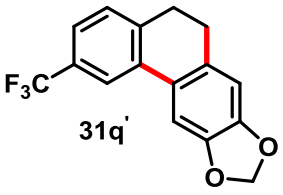
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.09, 137.03, 135.49, 135.45, 134.82, 130.89, 129.69, 129.05 (q, J = 32.0 Hz), 128.59, 125.16, 123.47 (q, J = 3.7 Hz), 123.28, 120.20 (q, J = 3.6 Hz), 23.98, 28.16, 19.80, 19.68.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{16}F_3$: 277.1199, found: 277.1254. HRMS data was recorded on Synapt MALDI-MS (Waters, UK) using α-cyano-4-hydroxycinnamic acid as the solid matrix.

FTIR (cm^{-1}): 2936, 1503, 1433, 1338, 1268, 1154, 1111, 1077, 1022, 878, 824, 726, 685,

656, 630, 595.

2-(Trifluoromethyl)-5,6-dihydrophenanthro[2,3-*d*][1,3]dioxole (31q')



Following the general procedure, treatment of 6-(trimethylsilyl) benzo[*d*][1,3]dioxol-5-yltrifluoromethanesulfonate **20c** (0.205 g, 0.60 mmol) and 1-(trifluoromethyl)-4-vinylbenzene **29n** (0.043 g, 0.25 mmol) with CsF (0.182 g, 1.2 mmol) in CH_3CN (1.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 90/10) afforded 2-(trifluoromethyl)-5,6-dihydrophenanthro[2,3-*d*][1,3]dioxole **31q'** as a white solid (0.066 g, 90%).

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

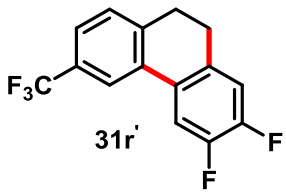
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.24 (s, 1H), 6.72 (s, 1H), 5.97 (s, 2H), 2.88-2.85 (m, 2H), 2.78-2.75 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.63, 147.31, 140.49, 135.41, 131.81, 129.48 (q, *J* = 32.0 Hz), 128.46, 127.14, 123.25 (q, *J* = 3.7 Hz), 119.99 (q, *J* = 3.7 Hz), 108.69, 104.51, 101.27, 29.28, 28.83.

HRMS: calculated $[M]^+$ for $C_{16}H_{11}F_3O_2$: 292.0711, found: 292.0670. HRMS data was recorded on Synapt MALDI-MS (Waters, UK) using α-cyano-4-hydroxycinnamic acid as the solid matrix.

FTIR (cm^{-1}): 2961, 2891, 2842, 2364, 2344, 1619, 1561, 1489, 1426, 1331, 1276, 1228, 1164, 1076, 901, 829, 811, 669.

2,3-Difluoro-6-(trifluoromethyl)-9,10-dihydrophenanthrene (31r')



Following the general procedure, treatment of 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20d** (0.401 g, 1.20 mmol) and 1-(trifluoromethyl)-4-vinylbenzene **29n** (0.086 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (in Pet. ether) afforded 2,3-difluoro-6-(trifluoromethyl)-9,10-dihydrophenanthrene **31r'** as a white solid (0.092 g, 65%).

***R*$_f$** (Pet. ether): 0.78.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.57-7.49 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.06 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 1H), 2.93-2.90 (m, 2H, CH_2), 2.85-2.81 (m, 2H,

CH_2).

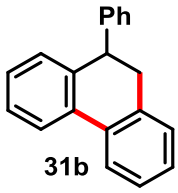
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.10 (dd, J_1 = 12.7 Hz,J_2 = 250.5 Hz), 148.64 (dd, J_1 = 12.9 Hz,J_2 = 245.9 Hz), 140.69, 134.18-134.09 (m), 133.75, 130.16-129.98 (m), 128.88, 125.71, 124.51 (d, *J* = 3.6 Hz), 123.00, 120.54 (d, *J* = 3.6 Hz), 117.09 (d, *J* = 17.3 Hz), 113.04 (d, *J* = 18.4 Hz), 28.81, 27.98.

^{19}F (376 MHz, $CDCl_3$): δ -62.47 (CF_3), -138.47 (d, *J* = 21.9 Hz), -140.17 (d, *J* = 21.9 Hz).

HRMS: calculated $[M]^+$ for $C_{15}H_9F_5$: 284.0624, found: 284.0752. HRMS data was recorded on Synapt MALDI-MS (Waters, UK) using α-cyano-4-hydroxycinnamic acid as the solid matrix.

FTIR (cm^{-1}): 2950, 2848, 1913, 1786, 1736, 1609, 1580, 1511, 1438, 1345, 1324, 1303, 1238, 1177, 1166, 1149, 1115, 1077, 1030, 1002, 964, 906, 879, 844, 830, 789, 721.

Synthesis of 9-Phenyl-9,10-dihydrophenanthrene (31b) by using Ethene-1,1-diyldi benzene (29p)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20a** (0.358 g, 292 µL, 1.20 mmol) and ethene-1,1-diyldibenzene **29p** (0.090 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 9-phenyl-9,10-dihydrophenanthrene **31b** as a white solid (0.094 g, 73%).

R$_f$ (Pet. ether): 0.53.

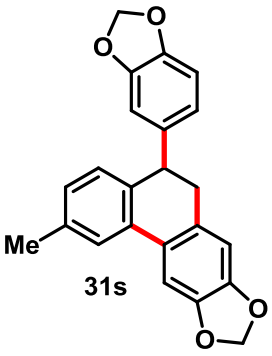
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.44-7.36 (m, 4H), 7.32-7.26 (m, 6H), 7.04 (d, *J* = 7.4 Hz, 1H), 4.30-4.27 (m, 1H), 3.34-3.26 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.51, 139.93, 135.89, 134.60, 134.45, 128.58, 128.53, 128.42, 127.75, 127.32, 127.27, 126.66, 123.93, 123.74, 44.89, 37.13.

HRMS: calculated $[M]^+$ for $C_{20}H_{16}$: 256.1252, found: 256.1254 and $[M+H]^+$ for $C_{20}H_{17}$: 257.1330, found: 257.1280.

FTIR (cm^{-1}): 3062, 3026, 2932, 2890, 1598, 1489, 1446, 1303, 1220, 1161, 1082, 1036, 1004, 971, 942, 847, 772, 700.

5-(Benzo[*d*][1,3]dioxol-5-yl)-2-methyl-5,6-dihydrophenanthro[2,3-*d*][1,3]dioxole (31s)



31s

Following the general procedure, treatment of 6-(trimethylsilyl) benzo[*d*][1,3]dioxol-5-yltrifluoromethanesulfonate **20c** (0.411 g, 1.20 mmol) and 1-methyl-4-vinylbenzene **29a** (0.059 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether /DCM = 98/02) afforded 5-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-5,6-dihydrophenanthro[2,3-*d*][1,3]dioxole **31s** as a white solid (0.116 g, 65%).

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

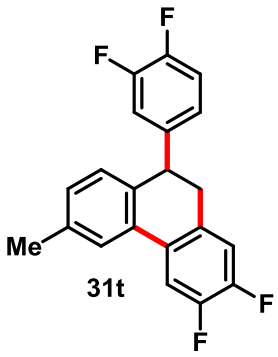
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.28 (s, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 7.4 Hz, 1H), 6.44-6.61 (m, 3H), 5.96-5.95 (m, 2H), 5.91 (s, 2H), 4.06-4.03 (m, 1H), 3.10-2.99 (m, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.70, 147.15, 147.02, 146.16, 137.63, 136.88, 136.20, 134.43, 129.85, 128.30, 127.86, 124.17, 121.51, 108.95, 108.72, 108.25, 104.36, 101.05, 100.96, 44.25, 37.53, 21.48.

HRMS: calculated $[M]^+$ for $C_{23}H_{18}O_4$: 358.1205, found: 358.1205 and $[M+H]^+$ for $C_{23}H_{19}O_4$: 359.1283, found: 359.1243.

FTIR (cm^{-1}): 3013, 2889, 2774, 1856, 1736, 1612, 1481, 1438, 1357, 1222, 1168, 1122, 1093, 1036, 934, 862, 813, 769, 671.

9-(3,4-Difluorophenyl)-2,3-difluoro-6-methyl-9,10-dihydrophenanthrene (31t)



31t

Following the general procedure, treatment of 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20d** (0.401 g, 1.20 mmol) and 1-methyl-4-vinylbenzene **29a** (0.059 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether /DCM = 98/02) afforded 9-(3,4-Difluorophenyl)-2,3-difluoro-6-methyl-9,10-dihydrophenanthrene **31t** as a colorless viscous oil (0.089 g, 52%).

***R*$_f$** (Pet. ether): 0.40.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.54 (m, 1H), 7.51 (s, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.04-6.99 (m, 1H), 6.96-6.91 (m, 1H), 6.90-6.79 (m, 3H), 4.13 (t, *J* = 6.6 Hz, 1H), 3.16 (dd, J_1 = 15.1 Hz, J_2 = 5.6 Hz, 1H), 3.03 (dd, J_1 = 15.1 Hz, J_2 = 7.5 Hz, 1H), 2.42 (s, 3H).

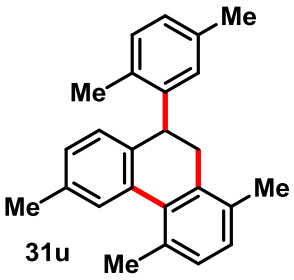
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.63 (dd, J_1 = 12.8 Hz, J_2 = 248.3 Hz), 150.97 (m), 150.50 (dd, J_1 = 12.9 Hz, J_2 = 247.4 Hz), 148.56 (m), 140.17 (t, *J* = 4.3 Hz), 137.74, 135.18, 132.78, 131.59 (dd, J_1 = 3.4 Hz, J_2 = 5.1 Hz), 131.16 (t, *J* = 5.4 Hz), 129.24, 128.62, 124.79, 124.14 (dd, J_1 = 3.6 Hz, J_2 = 5.9 Hz), 117.42 (dd, J_1 = 8.0 Hz, J_2 = 17.1 Hz), 117.05 (d, *J* = 17.3 Hz), 112.75 (d, *J* = 18.3 Hz), 43.24, 36.48, 21.45.

^{19}F NMR (376 MHz, $CDCl_3$): δ -137.57 (d, *J* = 21.30 Hz), -139.45 (d, *J* = 21.4 Hz), -140.22 (d, *J* = 21.4 Hz), -140.82 (d, *J* = 21.3 Hz).

HRMS: calculated $[M]^+$ for $C_{21}H_{14}F_4$: 342.1032, found: 342.1040 and $[M+H]^+$ for $C_{21}H_{15}F_4$: 343.1110, found: 343.1088. HRMS data was recorded on Synapt MALDI-MS (Waters, UK) using 2,5-dihydroxybenzoic acid as the solid matrix.

FTIR (cm^{-1}): 3015, 2925, 2856, 1907, 1733, 1608, 1572, 1507, 1432, 1418, 1380, 1344, 1324, 1277, 1240, 1210, 1192, 1181, 1134, 1113, 1039, 1020, 989, 962, 945, 919, 873, 814, 794, 772, 756, 723, 710, 691, 668.

9-(2,5-Dimethylphenyl)-1,4,6-trimethyl-9,10-dihydrophenanthrene (31u)



31u

Following the general procedure, treatment of 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20e** (0.392 g, 1.20 mmol) and 1-methyl-4-vinylbenzene **29a** (0.059 g, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether /DCM = 98/02) afforded 9-(2,5-dimethylphenyl)-1,4,6-trimethy l-9,10-dihydrophenanthrene **31u** as a colorless viscous liquid (0.133 g, 82%).

***R*$_f$** (Pet. ether): 0.57.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.25-7.22 (m, 2H), 7.18 (s, 1H), 7.13 (d, *J* = 7.7 Hz, 2H), 7.02 (d, *J* = 7.1 Hz, 1H), 6.22 (d, *J* = 7.7 Hz, 1H), 4.17 (dd, J_1 = 13.4 Hz, J_2 = 3.9 Hz, 1H), 3.14 (dd, J_1 = 14.7 Hz, J_2 = 4.1 Hz, 1H), 3.07-3.00 (m, 1H), 2.75 (s, 3H), 2.46 (s, 3H), 2.41-2.39 (m, 6H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.75, 139.35, 138.09, 135.78, 135.21, 134.92, 134.62,

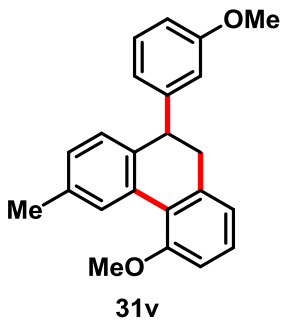
134.21, 132.29, 132.01, 130.39, 129.94, 129.26, 128.92, 128.12, 127.45, 127.33, 125.76, 40.52, 32.94, 22.86, 21.50, 21.32, 20.05, 19.31.

HRMS: calculated $[M]^+$ for $C_{25}H_{26}$: 326.2035 found: 326.2026.

FTIR (cm^{-1}): 3013, 2923, 1611, 1500, 1460, 1380, 1217, 1034, 891, 813, 745, 668.

5-Methoxy-10-(3-methoxyphenyl)-3-methyl-9,10-dihydrophenanthrene (31v) and 1-Methoxy-9-(3-methoxyphenyl)-6-methyl-9,10-dihydrophenanthrene (31vv)

Following the general procedure, treatment of 2-methoxy-6-(trimethylsilyl)phenyltriflu oromethanesulfonate **20f** (0.197 g, 0.60 mmol) and 1-methyl-4-vinylbenzene **29a** (0.030 g, 0.25 mmol) with CsF (0.182 g, 1.20 mmol) in CH_3CN (1.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 5-methoxy-10-(3-methoxyphenyl)-3-methyl-9,10-dihydrophenanthrene **31v** (colorless viscous oil, 0.041 g, 49%) and 1-methoxy-9-(3-methoxyphenyl)-6-methyl-9,10-dihydro phenanthrene **31vv** (colorless viscous oil, 0.015 g, 18%) as two regioisomers.



31v

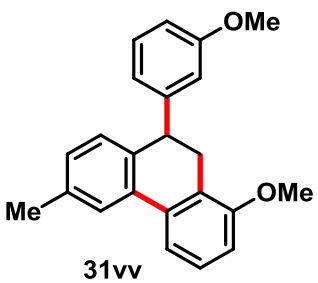
R_f (Pet. ether): 0.43.

^{1}H NMR (400 MHz, $CDCl_3$) of 31v: δ 8.26 (s, 1H), 7.25-7.17 (m, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.85 (t, *J* = 7.7 Hz, 2H), 6.82-6.79 (m, 3H), 4.07 (dd, J_1 = 9.7 Hz, J_2 = 4.6 Hz, 1H), 3.94 (s, 3H), 3.77 (s, 3H), 3.19 (dd, J_1 = 14.3 Hz, J_2 = 9.9 Hz, 1H), 3.10 (dd, J_1 = 14.3 Hz, J_2 = 4.6 Hz, 1H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) of 31v: δ 159.72, 156.95, 144.91, 139.21, 138.03, 135.63, 132.51, 129.41, 129.38, 128.06, 127.76, 127.29, 123.42, 121.11, 121.04, 114.31, 111.85, 110.56, 55.74, 55.19, 44.82, 37.86, 21.69.

HRMS: calculated $[M]^+$ for $C_{23}H_{22}O_2$: 330.1620, found: 330.1621 and $[M+H]^+$ for $C_{23}H_{23}O_2$: 331.1698, found: 331.1648.

FTIR (cm^{-1}): 3002, 2935, 2836, 1586, 1487, 1457, 1257, 1141, 1076, 1044, 977, 872, 820, 771, 740, 695. The structure of **31v** was further confirmed by HMBC analysis.



31vv

R_f (Pet. ether): 0.47.

^{1}H NMR (400 MHz, $CDCl_3$) of 31vv: δ 8.22 (s, 1H), 7.18 (t, *J* = 8.3 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.6 Hz,

1H), 6.90-6.88 (m, 3H), 6.80-6.76 (m, 3H), 4.54 (dd, J_1 = 8.9 Hz, J_2 = 5.0 Hz, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 3.19 (dd, J_1 = 14.6 Hz, J_2 = 9.0 Hz, 1H), 3.00 (dd, J_1 = 14.6 Hz, J_2 = 5.0 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) of 31vv: δ 157.47, 156.90, 139.75, 137.98, 135.44, 133.09, 131.07, 129.29, 129.12, 127.94, 127.83, 127.44, 127.19, 123.55, 121.28, 120.57, 110.44, 55.78, 55.54, 37.63, 36.40, 21.72.

HRMS: calculated $[M]^+$ for $C_{23}H_{22}O_2$: 330.1620, found: 330.1623 and $[M+H]^+$ for $C_{23}H_{23}O_2$: 331.1698, found: 331.1662.

FTIR (cm^{-1}): 3004, 2928, 2839, 1735, 1587, 1491, 1459, 1241, 1152, 1103, 1076, 1030, 978, 933, 821, 770, 673.

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CHAPTER 4

Tandem [4 + 2]/[2 + 2] Cycloaddition Reactions Involving Indene or Benzofurans and Arynes

4.1. Introduction

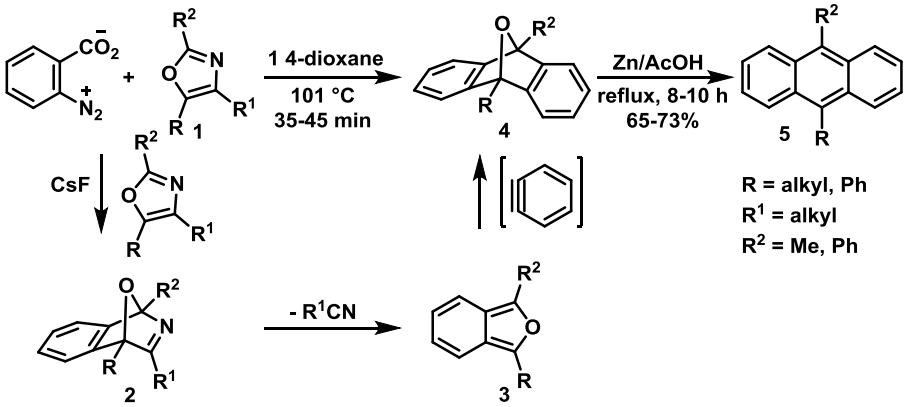
The Diels-Alder reaction of arynes is a unique and straightforward method for the construction of wide range of benzo-fused carbocycles and heterocycles.[1] Since, Wittig's first report on the Diels-Alder reaction of benzyne with furan,[2] the organic chemist recognized the synthetic utility of highly electrophilic arynes as a dienophile in Diels-Alder reaction with various cyclic and acyclic dienes. Initially, the Diels-Alder reaction employing arynes suffer from the limitations including low yields of products and narrow substrate scope as the conventional methods of aryne generation required strongly basic or harsh reaction conditions.[3] However, with the introduction of mild method for the generation of arynes by the fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates,[4] the applications of these reactive intermediates have increased substantially in organic synthesis.[5] In addition, Diels-Alder reaction of aryne can be coupled with other intermolecular processes resulting in efficient tandem reactions. In a single operation, these cascade reactions facilitated access to the various complex benzannulated carbocycles and heterocycles, which are difficult to synthesize by other methods. The present chapter mainly focuses on a stereoselective tandem [4 + 2]/[2 + 2] cycloaddition reaction of arynes with indene or benzofurans. The protocol presented herein furnished a straightforward access to the highly strained dihydrobenzocyclobutaphenanthrene derivatives in moderate to good yields with excellent diastereoselectivity. Before going into the details, a brief account of the tandem reactions involving arynes are documented in the following sections.

4.2. Tandem Reactions Involving Arynes

4.2.1. Tandem Cycloaddition Reactions Involving Arynes

A tandem cycloaddition reaction of trisubstituted oxazoles **1** with the aryne generated from *ortho*-benzenediazonium carboxylate in 1,4-dioxane as a solvent under reflux conditions (101 °C) resulted in the formation of bis(aryne) adducts **4** was reported by Reddy and Bhatt as early as 1980 (Scheme 4.1).[6a] This outcome occurs sequentially, aryne undergoes the Diels-Alder reaction with substituted oxazole to produce oxygen-bridged bicyclic strained intermediate **2**, which on retro Diels-Alder reaction leads to the expulsion of the nitrile molecule and generates the intermediate isobenzofuran **3**. In situ formed isobenzofuran **3** underwent the second Diels-Alder reaction with another molecule of aryne to furnish the bis(aryne) adduct. Additionally, synthetic utility of the present tandem process has been demonstrated in the synthesis of 9,l0-disubstituted anthracene derivatives **5** in good yields, via the deoxygenation of bis(aryne) adducts using Zn/AcOH. After ten years, Rickborn and coworkers investigated the substituent effects in oxazoles on oxazoles-aryne tandem cycloaddition reaction and the role of reaction temperature on retro Diels-Alder reaction step.[6b] Interestingly, they isolated 1:1 Diels-Alder adduct **2** of oxazoles and aryne in quantitative yield, using modified reaction procedure at lower temperature. It has been suggested that the reaction temperature is the key parameter for retro Diels-Alder reaction of 1:1 Diels-Alder adduct **2**.

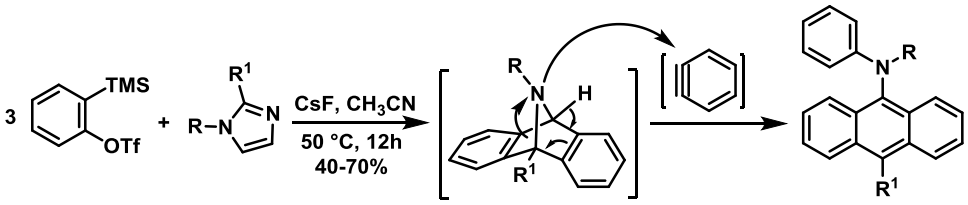
Scheme 4.1: Tandem Cycloaddition Reaction of Arynes with Oxazoles



In 2007, Xie and Zhang applied the similar tandem cycloaddition approach for the transition-metal-free synthesis of aryl amines containing anthracene moiety in a single step. Treatment of *N*-substituted imidazoles **7** with aryne generated from aryne precursor

6a using CsF in CH_3CN at 50 °C resulted in the formation of corresponding aryl amine product **9** in moderate to good yields (Scheme 4.2).[7] The reaction mechanism is similar to the oxazoles-aryne reaction (Scheme 4.1), proceeding via a tandem Diels-Alder reaction, retro Diels-Alder reaction, the expulsion of the nitrile molecule, and a second Diels-Alder reaction sequence to form the bis(aryne) adduct **8** of imidazole and aryne. The intermolecular nucleophilic addition of intermediate **8** to the excess aryne resulted in the ring opening to offer the final product **9**. In principal three molecules of arynes were incorporated in the final product in a single operation.

Scheme 4.2: Tandem Cycloaddition Reaction of Arynes with Imidazoles

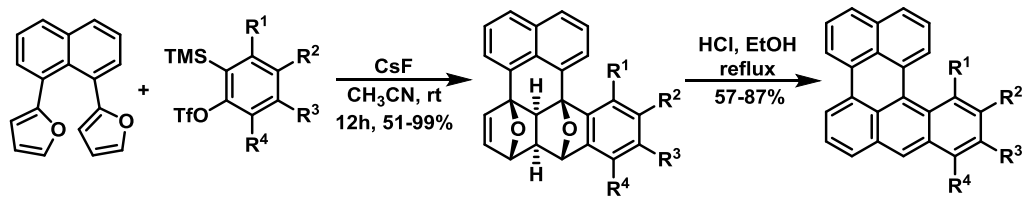


6a **7** **8** **9**

R = Me, Et, *n*-Bu, Bn, Ar
R^1 = Me, Ph

A novel method for the synthesis of elusive polyarenes through a highly stereoselective domino Diels-Alder cycloaddition reactions of 1,8-difurylnaphthalene **10** with arynes generated from 2-(trimethylsilyl)aryl triflates **6** using CsF in CH_3CN as solvent under mild reaction conditions was uncovered by Guitián and coworkers (Scheme 4.3).[8] The reaction involves two successive Diels-Alder reactions with the formation of four carbon-carbon bonds and six new stereocentres leading to the exclusive formation of single diastereoisomer **11**. Treatment of cycloadduct **11** with acid furnished perylene derivatives **12** having potential applications in molecular electronics, particularly in the development of organic semiconductors.

Scheme 4.3: Domino Diels-Alder Cycloaddition Reaction of Arynes



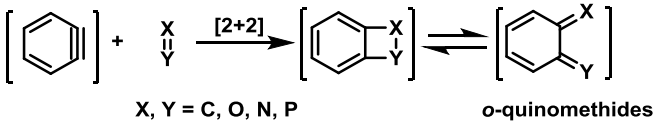
10 **6** ***exo,exo*-11** **12**

$R^1 = R^2 = R^3 = R^4 = H$
$R^1 = R^4 = H$, R^2, $R^3 = (CH)_4$
R^1, $R^4 = R^2$, $R^3 = (CH)_4$

4.2.2. Tandem Cycloaddition Reactions Involving Arynes via Generation of *ortho*-Quinomethide Intermediate

Interestingly, insertion of aryne into π-bonds of various olefins and carbon-heteroatom bonds through a formal [2 + 2] cycloaddition reaction offers a benzannulated four-membered ring, which can undergo subsequent retro-4π electrocyclic ring opening under the same or different reaction conditions to give *ortho*-quinomethide intermediate or the analogues *in situ* (Scheme 4.4).[9] These intermediates were efficiently engaged in further intramolecular tandem cycloaddition reactions such as 6π-electrocyclization or [4 + 2] cycloaddition reactions that are attractive strategies for the synthesis of complex carbocycles and heterocycles.

Scheme 4.4: Generation of *ortho*-Quinomethides Intermediate

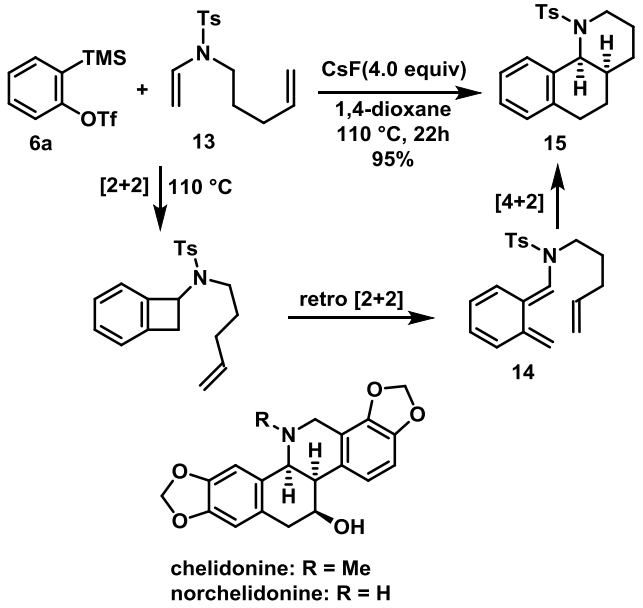


Hsung and coworkers developed an efficient [2 + 2] cycloaddition of arynes with enamides leading to the formation of amidobenzocyclobutane derivatives, which are useful precursors for the generation of amido-*o*-quinonedimethides[10] via thermal electrocyclic ring-opening. They applied this process for the construction of nitrogen heterocycles **15** through a tandem reaction of *N*-tethered enamides **13** with an unactivated double bond with aryne generated from precursor **6a** using CsF in 1,4-dioxane at 110 °C in 95% yield (Scheme 4.5).[11a] This reaction proceeds sequentially through a tandem process involving [2 + 2] cycloaddition followed by the electrocyclic ring-opening to generate an amido-*o*-quinonedimethides **14**, subsequent intramolecular [4 + 2] cycloaddition of **14** with *N*-tethered double bond leads to the stereoselective formation of *aza*-tricycle **15** as a single diastereomer. In addition, they applied this tandem aryne-enamide reaction process in the total synthesis of alkaloids chelidonine and norchelidonine.[11b]

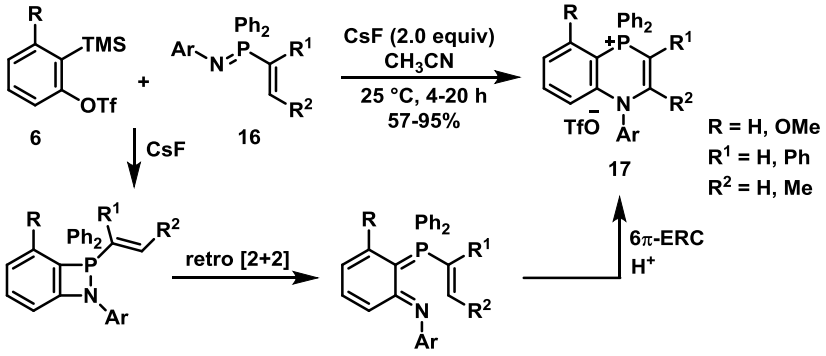
Alajarin and coworkers isolated the 4-benzazaphosphorinium triflate derivatives **17** by the reaction of 2-(trimethylsilyl)aryl triflates **6** with *P*-alkenyl phosphazenes **16** in the presence of CsF in CH_3CN as a solvent under mild reaction conditions in good yields (Scheme 4.6).[12] Although, these organophosphorus compounds are well recognized as

heterobutadienyl systems to furnish 1,4-addition products due to their P^{+}-N^{-} ylidic nature,[13] with aryne it selectively underwent [2 + 2] cycloaddition reaction. In this case, the reaction proceeds via a cascade process involving insertion of arynes into the P=N bond of *P*-alkenyl phosphazenes through a formal [2 + 2] cycloaddition followed by retro [2 + 2] cycloaddition/6π-electrocyclization and a subsequent protonation to furnish the final 1,4-benzazaphosphorinium salt.

Scheme 4.5: Construction of Nitrogen Heterocycles via Tandem Aryne-Enamide [2 + 2]-retro [2 + 2]-[4 + 2] Sequence



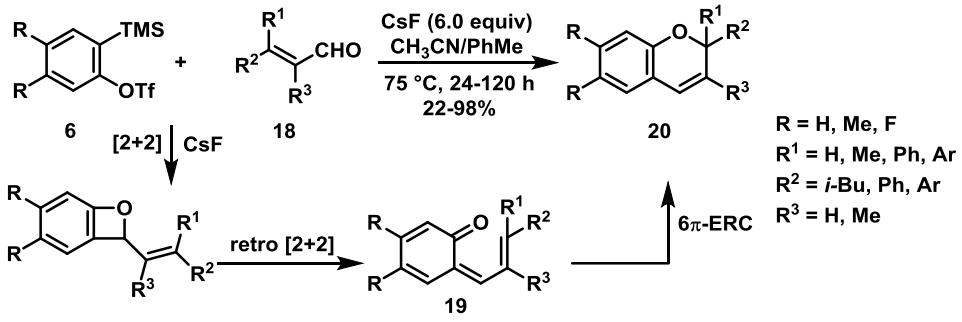
Scheme 4.6: Synthesis of 4-Benzazaphosphorinium Triflate Derivatives



Additionally, synthesis of 2*H*-chromenes **20** involving similar type of cascade annulations of arynes generated from **6** with enals **18** using CsF in CH_3CN/PhMe mixed solvent system at 75 °C has been achieved by Wu and coworkers.[14] The reaction is likely initiated by the formal [2 + 2] cycloaddition reaction of aryne with C=O bond of enal

followed by thermal electrocyclic ring-opening to form *ortho*-quinonemethide intermediate **19** and subsequent 6π-electrocyclization of **19** furnished the 2*H*-chromene derivative (Scheme 4.7).

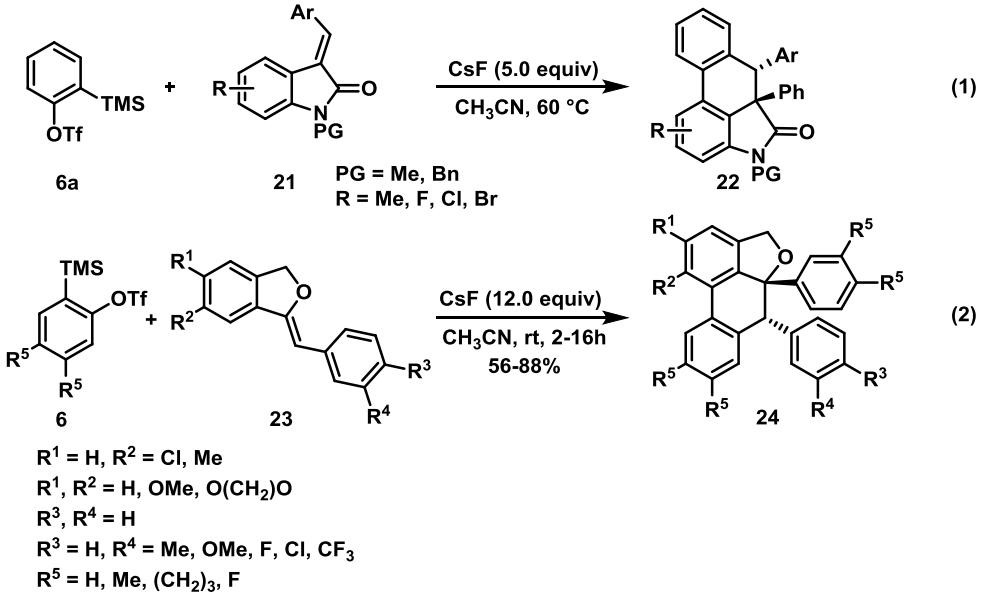
Scheme 4.7: Synthesis of 2*H*-Chromenes via Tandem Reaction Involving Arynes and Enals



4.2.3. Cascade Reaction involving Arynes and Styrene Analogues

As described in the previous chapter, we have developed an efficient Diels-Alder/ene cascade reaction of styrenes and arynes leading to the formation of functionalized 9-aryl 9,10-dihydrophenanthrenes.[15] In an attempt to expand the synthetic utility and scope of Diels-Alder/ene cascade reaction of arynes, Li and coworkers used arylidenoxindole **21** as the diene component with arynes leading to the synthesis of structurally unusual dihydronaphtho-fused oxindoles scaffolds **22** (Scheme 4.8, eq 1).[16] Subsequently, Liu and coworkers uncovered an efficient transition-metal-free method for the synthesis of various phenanthro[10,1-*bc*]furans **24** by the tandem reaction of functionalized benzylidenephthalans **23** and arynes generated from **6** under mild reaction conditions (Scheme 4.8, eq 2).[17] This outcome occurs via a stereoselective tandem reaction with incorporation of two aryne molecules in the final product. In both cases, reaction proceeds via the [4 + 2] cycloaddition reaction of **21** and **23** with aryne followed by the nucleophilic addition of the cycloadduct to another molecule of aryne. Exclusive formation of *trans*-diastereoselective products in the both reactions strongly support the concerted Diels-Alder/ene reaction pathway, which was revealed in our styrene-aryne work.[15]

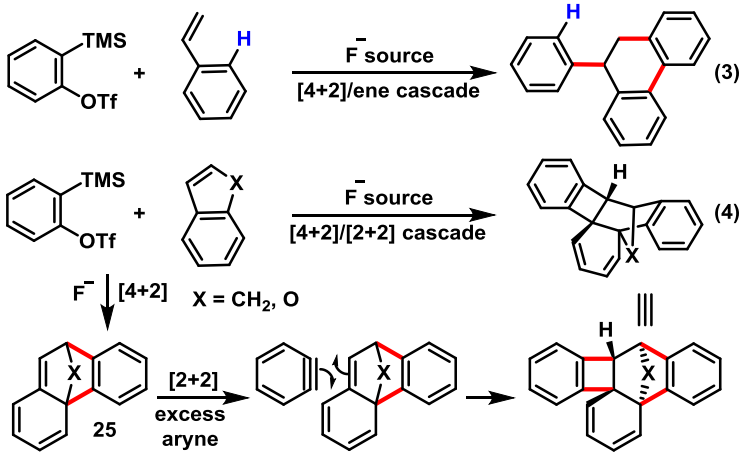
Scheme 4.8: Cascade Reaction involving Arynes and Styrene Analogues



4.3. Statement of the Problem

The reaction of styrenes with arynes proceeds via an efficient cascade process initiated by the Diels-Alder reaction followed by a selective ene reaction leading to the formation of 9-aryl-9,10-dihydrophenanthrene derivatives. This appears to be an interesting strategy, where styrenes acting as an unconventional 4π-component in Diels-Alder reactions by utilizing a carbon-carbon double bond involved in aromaticity (Scheme 4.9, eq 3).

Scheme 4.9: Reaction of Arynes with Styrene and Indene/Benzofuran



In this perspective, we envisioned that the reaction between aryne with cyclic styrene analogues such as indene or benzofurans could result in isolation of initially

generated Diels-Alder adducts **25** as the ene reaction can be avoided in this case (eq 4). Surprisingly, the reaction of arynes with indene or benzofurans resulted in the formation of dihydrobenzocyclobutaphenanthrenes derivatives through a stereoselective tandem [4 + 2]/[2 + 2] process, the expected Diels-Alder adducts **25** were not isolated.[18] Intriguingly, to the best of our knowledge, a single example documented in the literature on the reaction of benzofuran with aryne generated by the thermolysis of *o*-benzene diazonium carboxylate leading to the formation of tandem cycloaddition product in 32% yield by Anthony and Wege.[19]

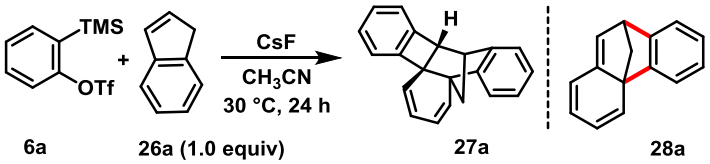
A detailed investigation of a tandem [4 + 2]/[2 + 2] cycloaddition reaction involving indene or benzofurans, and arynes was carried out in the present chapter. Present protocol furnished straightforward access to the highly strained dihydrobenzocyclobutaphenanthrene derivatives in moderate to good yields with excellent diastereoselectivity are explained in the following sections.

4.4. Results and Discussion

4.4.1. Reaction of Arynes with Indene

In an attempt to isolate Diels-Alder adduct of aryne and indene, our present study commenced with the treatment of indene **26a** with aryne generated in situ from 2-(trimethylsilyl)aryltriflate **6a** (1.2 equiv) using 2.4 equiv of CsF and CH_3CN as the solvent. Under these conditions, a facile reaction took place, leading to the formation of dihydrobenzocyclobutaphenanthrene **27a** in 48% yield with excellent diastereoselectivity of >20:1 (Scheme 4.10).

Scheme 4.10: Reaction of Benzyne with Indene



With 1.2 equiv of 6a and 2.4 equiv of CsF, 27a = 48% (*dr* > 20:1), 28a = <1%
With 2.4 equiv of 6a and 4.8 equiv of CsF, 27a = 86% (*dr* > 20:1), 28a = <1%

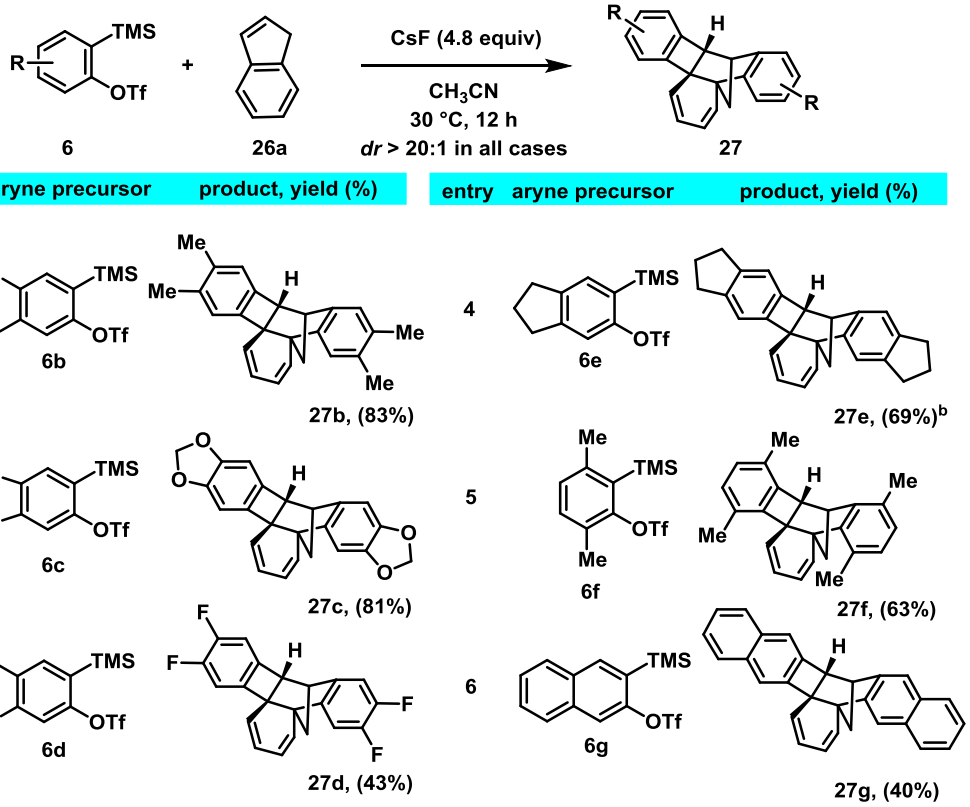
The present reaction proceeds via a tandem Diels-Alder reaction involving indene **26a** and aryne to generate Diels-Alder adduct **28a**, which subsequently underwent a stereoselective [2 + 2] cycloaddition reaction with another molecule of aryne to furnish the final product **27a**. Since the two molecules of aryne are incorporated in the final

product, the reaction was carried out using 2.4 equiv of **6a** and 4.8 equiv of CsF, the yield of **27a** was improved to 86% maintaining the diastereoselectivity of >20:1. Notably, CsF as the fluoride source in CH_3CN solvent, was found to be the best for this tandem reaction.

4.4.2. Substrate Scope of the Tandem [4 + 2]/[2 + 2] Reaction of Indene with Arynes

Next, we examined the scope of this tandem [4 + 2]/[2 + 2] cycloaddition reaction of indene **26a** with various symmetrically substituted arynes (Table 4.1). Symmetrical 4,5-disustituted aryne precursors **6b-e** having electron-donating and -withdrawing substituent were well tolerated, furnishing the tandem cycloaddition product dihydrobenzocyclobutaphenanthrene derivatives **27b-e** in good to excellent yields (entries 1-4).

Table 4.1: Tandem [4 + 2]/[2 + 2] Reaction of Indene with Arynes: Variation of the Aryne Moiety[a]



[a]General conditions: **6** (1.20 mmol), **26a** (0.50 mmol), CsF (4.8 equiv), CH_3CN (2.0 mL), 30 °C and 12 h. Yields of isolated products are given. [b]Reaction was run on 0.25 mmol scale.

In the case of product **27c**, the structure and stereochemistry was unambiguously confirmed by single-crystal X-ray analysis (Figure 4.1). Additionally, the symmetrical 3,6-dimethyl aryne and the naphthalyne also worked well and the expected strained carbocyclic products were isolated in 63% and 40% yields respectively (entries 5, 6). Gratifyingly, present tandem cycloaddition reaction is highly diastereoselective, in all cases the desired products were obtained in excellent *dr* of >20:1.

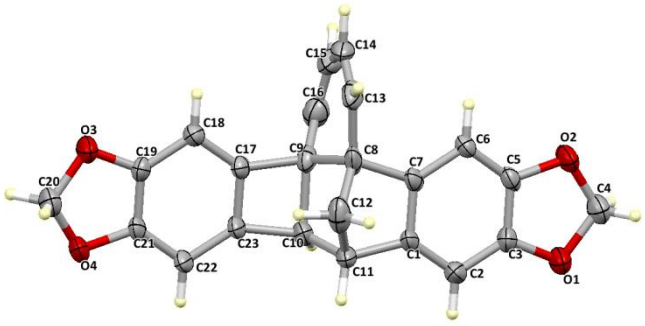
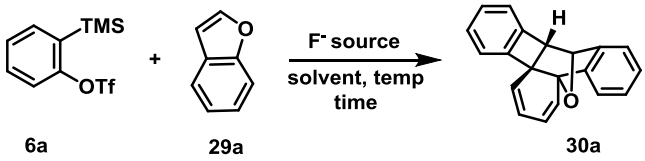


Figure 4.1: ORTEP diagram of **27c** (35% probability factor for the thermal ellipsoids)

4.4.3. Reaction of Arynes with Benzofurans: Optimization Studies

Inspired by the tandem cycloaddition reaction of arynes with indene, we then focused our attention on the reaction of arynes with benzofurans. We initiated our present

Table 4.2: Optimization of the Reaction Conditions[a]



entry	F^- source	solvent	temp (°C)	time (h)	yield of **30a** (%)[b]
1	CsF	CH_3CN	30	12	54
2	CsF	CH_3CN	40	12	55
3[c]	CsF	CH_3CN	30	12	52
4[d]	KF	THF	30	12	22
5	CsF	CH_3CN	30	24	60
6	CsF	CH_3CN	40	24	64
7[c]	*CsF*	*CH_3CN*	*30*	*24*	*66(65)*

[a]Standard conditions: **29a** (0.25 mmol), **6a** (0.60 mmol), fluoride source (4.8 equiv), solvent (1.0 mL), 30 °C and 12 h. [b]The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard. Isolated yield in 0.50 mmol scale in parentheses. [c]The reaction performed using 3.0 equiv of **6a** and 6.0 equiv of CsF. [d]4.8 equiv of 18-crown-6 was used as an additive.

study with the treatment of benzofuran **29a** with the aryne generated from 2-(trimethylsilyl)aryl triflate **6a** (2.4 equiv) using 4.8 equiv of CsF in CH_3CN as solvent at 30 °C. Under these conditions, the reaction afforded the [4 + 2]/[2 + 2] cascade product **30a** in 54% yield (based on ^1H NMR spectroscopy, Table 4.2, entry 1). Increasing the reaction temperature and using excess of aryne precursor **6a** (3.0 equiv), product yield was not improved (entries 2, 3). The use of KF as the fluoride source in the presence of 18-crown-6 additive was not found to be useful (entry 4). Notably, increase in the reaction time enhanced the yield of product **30a** (entry 5). When the reaction was carried at 40 °C for 24 h gave better results, and **30a** was formed in 64% yield (entry 6). Finally, increasing the amount of aryne precursor **6a** to 3.0 equiv with 6.0 equiv of CsF and a longer reaction time of 24 h at 30 °C improved the reactivity, and **30a** was obtained in 66% yield (65% isolated yield, entry 7).

4.4.4. Tandem [4 + 2]/[2 + 2] Reaction of Benzofuran with Arynes: Scope of Arynes

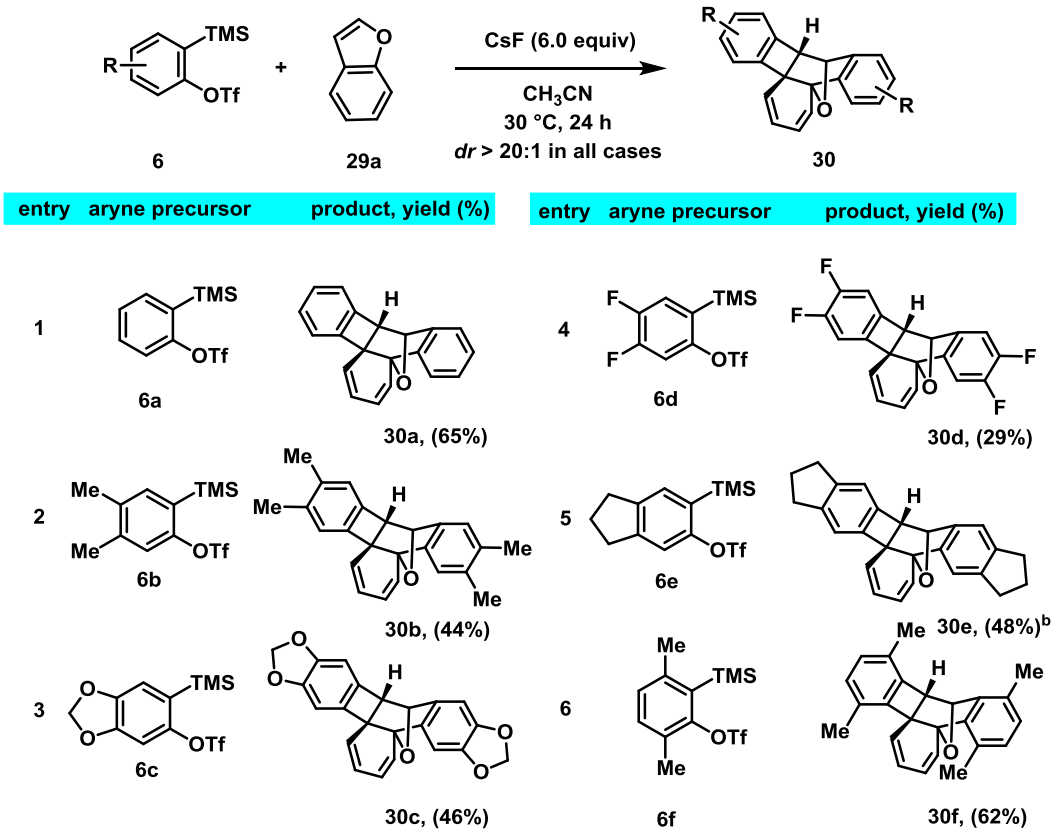
With the optimized reaction conditions in hand, we evaluated the scope of this tandem [4 + 2]/[2 + 2] cycloaddition reaction of benzofuran with electronically different 4,5-disubstituted symmetrical aryne precursors **6a-e** (Table 4.3). These reactions worked well, expected cascade products **30a-e** were isolated in moderate yields and in high diastereoselectivity (entries 1-5). In the case of **30b**, the structure and stereochemistry was unambiguously confirmed by single-crystal X-ray analysis (Figure 4.2). Moreover, the symmetrical 3,6-dimethyl aryne precursor **6f** readily afforded the tandem cycloaddition product **30f** in 62% yield.

4.4.5. Tandem [4 + 2]/[2 + 2] Reaction of Benzofuran with Arynes: Scope of Benzofurans

Then we evaluated the scope of this tandem process with substituted benzofurans (Scheme 4.11). Benzofurans having halogen substituent at different position in the carbocyclic ring resulted in the formation of cascade products in moderate yields (**30g-i**). Notably, the halogenated cycloadducts could be further derivatized by the use of conventional metal-catalyzed cross-coupling reactions. Additionally, 9-bromonaphtho-furan afforded the desired product **30j** in 38% yield. In this case, [2 + 2] cycloadduct with aryne was isolated in 17% yield, however in other cases, the [2 + 2] cycloadduct was

observed in only <5% yield. Interestingly, the naphtho[1,2-*b*]furan underwent efficient tandem cycloaddition reaction with arynes leading to the formation of the expected cycloadduct in excellent to moderate yields expanding the scope of the present reaction (**30k-m**).

Table 4.3: Tandem [4 + 2]/[2 + 2] Reaction of Benzofuran with Arynes: Scope of Arynes[a]



[a]General conditions: **6** (1.50 mmol), **29a** (0.50 mmol), CsF (6.0 equiv), CH_3CN (2.0 mL), 30 °C and 24 h. Yields of isolated products are given. [b]Reaction was run on 0.25 mmol scale.

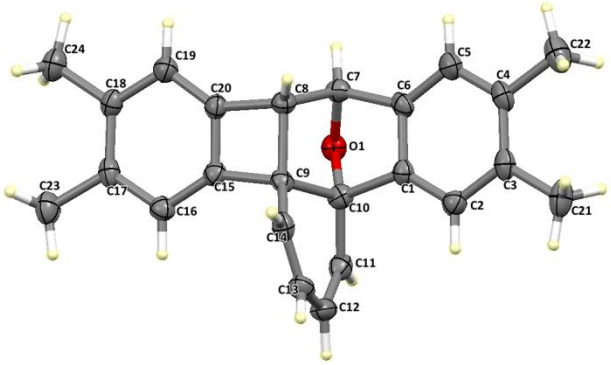
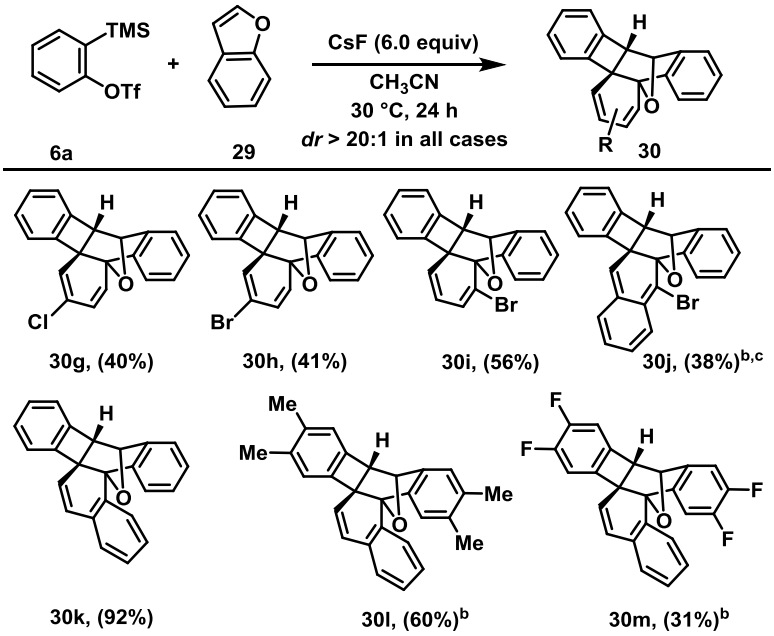


Figure 4.2: ORTEP diagram of **30b** (40% probability factor for the thermal ellipsoids)

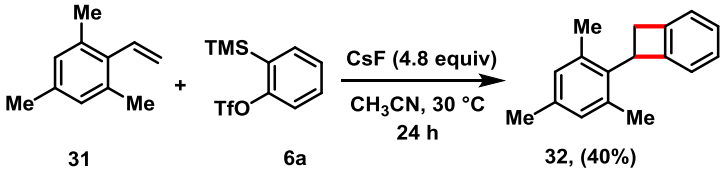
Scheme 4.11: Scope of Benzofurans in the Tandem [4 + 2]/[2 + 2] Reaction[a]



[a]General conditions: **6a** (1.50 mmol), **29** (0.50 mmol), CsF (6.0 equiv), CH_3CN (2.0 mL), 30 °C and 24 h. Yields of isolated products are given. [b]Reaction was run on 0.25 mmol scale. [c]17% of [2 + 2] adduct was isolated.

Moreover, the attempt to engage the *N*-methylindole and benzothiophene in tandem [4 + 2]/[2 + 2] cycloaddition reaction with arynes under the present reaction conditions was not successful. Notably, the reaction of 1,3,5-trimethyl-2-vinylbenzene **31** with **6a** (1.2 equiv) using 4.8 equiv of CsF in CH_3CN solvent for 24 h resulted in the formation of the [2 + 2] cycloaddition product **32** in 40% yield (Scheme 4.12). In this case, the tandem [4 + 2]/[2 + 2] cycloaddition product was not observed.

Scheme 4.12: [2 + 2] cycloaddition of 1,3,5-trimethyl-2-vinylbenzene with Aryne

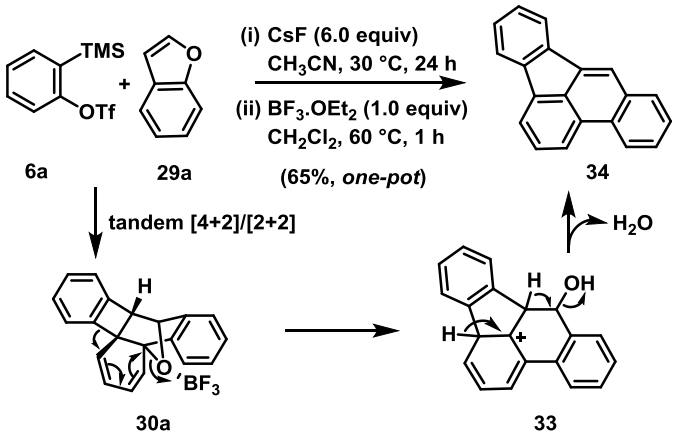


4.4.6. One-Pot Synthesis of Benzo[*b*]fluoranthene

In addition, the tandem [4 + 2]/[2 + 2] cycloaddition reaction of aryne-benzofuran has been utilized in the one-pot synthesis of polynuclear aromatic hydrocarbon benzo[*b*]fluoranthene, which is a potent carcinogenic hydrocarbon.[20] This demonstrates the synthetic potential of present protocol. The reaction of benzofuran with **6a** under

optimized reaction conditions followed by the addition of $BF_3.OEt_2$ to the reaction mixture resulted in a one-pot synthesis of benzo[*b*]fluoranthene **34** in 65% yield (Scheme 4.13). The reaction proceeds via the initial formation of the cascade cycloaddition product **30a** followed by Lewis acid coordination to the bicyclic system, which results in the opening of benzocyclobutane ring to generate intermediate **33**. The cationic intermediate **33** upon aromatisation with the elimination of a water molecule furnished the final product **34**.

Scheme 4.13: Synthesis of Benzo[*b*]fluoranthene



4.5. Conclusion

In conclusion, we have revealed a facile and general procedure for the synthesis of dihydrobenzocyclobutaphenanthrene derivatives by a tandem [4 + 2]/[2 + 2] cycloaddition reaction involving arynes with indene/benzofurans.[21] Present method is unique for the synthesis of strained and complex carbocycles in moderate to good yields with excellent diastereoselectivity, which are difficult to synthesize by other methods. Additionally, the synthetic utility of this tandem process has been demonstrated by the one-pot synthesis of benzo[*b*]fluoranthene.

4.6. Experimental Details

4.6.1. General Information

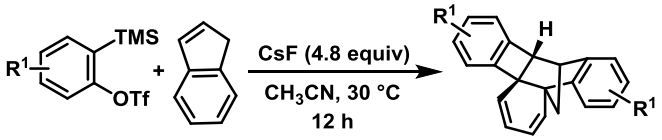
General information about experimental details is given in Section 2.9.1, Chapter 2. Indene **26a** and benzofuran **29a** were purchased from Alfa Aesar and were used without further purification. Substituted benzofurans were synthesized from commercially available compounds following literature procedure.[22] The 2-

(trimethylsilyl) phenyl trifluoromethanesulfonate **6a** and the other symmetrically substituted aryne precursors (**6b-g**) were synthesized following literature procedure.[4]

HRMS data were recorded on either Waters SYNAPT G2 High Definition Mass Spectrometer or Agilent Technologies 7200 Accurate-Mass Q-ToF GC/MS.

4.6.2. General Procedure for the Tandem [4 + 2]/[2 + 2] Cycloaddition Reaction Involving Indene and Arynes

Scheme 4.14: Synthesis of Dihydromethanobenzocyclobutaphenanthrene Derivatives

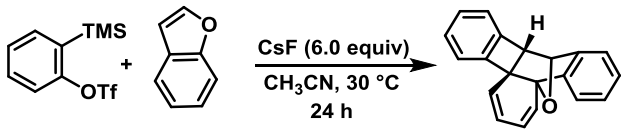


6 **26a** **27**

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken dry CsF (0.365 g, 2.40 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this CH_3CN was added (2.0 mL) under argon atmosphere. The resultant solution was kept stirring at 30 °C. To this stirring solution were added indene **26a** (0.50 mmol) and aryne precursor **6** (1.20 mmol). Then the reaction mixture kept for stirring at 30 °C. When TLC control showed the completion of the reaction (typically after 12 h), the mixture was diluted with CH_2Cl_2 (5.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (15 mL). The solvent was evaporated and the crude residue was purified by column chromatography on silica gel to afford the corresponding dihydromethanobenzocyclobutaphenanthrene derivatives **27** in moderate to good yields.

4.6.3. General Procedure for the Optimization of Reaction Conditions for Benzofuran and Aryne

Scheme 4.15: Optimization of Reaction Conditions



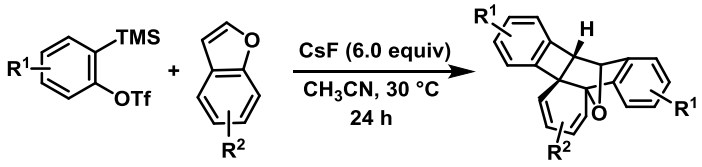
6a **29a** **30a**

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry CsF (0.228 g, 1.50 mmol). Then the screw-capped tube was evacuated and backfilled with argon and dissolved in CH_3CN under argon atmosphere (1.0 mL). To the

stirring solution were added benzofuran **29a** (0.029 g, 28 μL, 0.25 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6a** (0.224 g, 182 μL, 0.75 mmol). Then the reaction mixture kept for stirring at room temperature (30 °C). After 24 h, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^1H NMR analysis using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard.

4.6.4. General Procedure for the Tandem [4 + 2]/[2 + 2] Cycloaddition Reaction Involving Benzofurans and Arynes

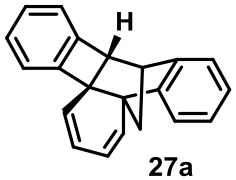
Scheme 4.16: Synthesis of Dihydroepoxybenzocyclobutaphenanthrene Derivatives



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken dry CsF (0.456 g, 3.0 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this CH_3CN was added (2.0 mL) under argon atmosphere. The resultant solution was kept stirring at 30 °C. To this stirring solution were added corresponding benzofuran **29** (0.50 mmol) and aryne precursor **6** (1.50 mmol). Then the reaction mixture kept for stirring at 30 °C. When TLC control showed the completion of the reaction (typically after 24 h), the mixture was diluted with CH_2Cl_2 (5.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (15 mL). The solvent was evaporated and the crude residue was purified by column chromatography on silica gel to afford the corresponding dihydroepoxybenzocyclobutaphenanthrene derivatives **30** in moderate to good yields.

4.6.5. Synthesis and Characterization of Products

8b,9-Dihydro-9,13b-methanobenzo[3,4]cyclobuta[1,2-*k*]phenanthrene (27a)



27a

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6a** (0.358 g, 292 μL, 1.20 mmol) and 1*H*-indene **26a** (0.058 g, 0.059 μL, 0.50 mmol)

with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 8b,9-dihydro-9,13b-methanobenzo [3,4]cyclobuta[1,2-*k*]phenanthrene **27a** as a white solid (0.115 g, 86%).

R_f (Pet. ether): 0.40.

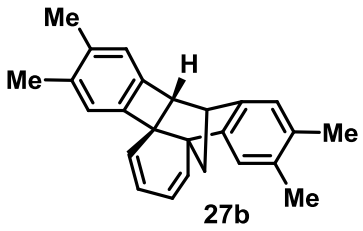
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.20 (m, 3H), 7.16-7.08 (m, 5H), 6.41 (dd, J_1 = 9.4 Hz, J_2 = 4.9 Hz, 1H), 6.13 (d, J = 9.4 Hz, 1H), 5.99 (dd, J_1 = 9.3 Hz, J_2 = 4.9 Hz, 1H), 5.90 (d, J = 9.4 Hz, 1H), 3.38 (s, 1H), 3.33 (s, 1H), 1.85 (d, J = 9.4 Hz, 1H), 1.65 (d, J = 9.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.80, 146.17, 144.14, 142.99, 131.56, 128.43, 128.01, 127.88, 127.78, 126.07, 125.19, 124.53, 122.21, 121.79, 121.62, 121.15, 60.41, 53.01, 52.72, 45.89, 45.64.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{17}$: 269.1325, found: 269.1325.

FTIR (cm^{-1}): 3062, 3035, 2966, 2877, 1456, 1413, 1218, 1155, 1129, 1004, 942, 747, 694.

6,7,11,12-Tetramethyl-8b,9-dihydro-9,13b-methanobenzo[3,4]cyclobuta[1,2-*k*] phenanthrene (27b)



27b

Following the general procedure, treatment of 4,5dimethyl -2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6b** (0.392 g, 1.20 mmol) and 1*H*-indene **26a** (0.058 g, 0.059 µL, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 6,7,11,12-tetramethyl-8b,9-dihydro-9,13b-methanobenzo[3,4]cyclobuta[1,2-*k*]phenanthrene **27b** as yellow solid (0.135 g, 83%).

R_f (Pet. ether): 0.37.

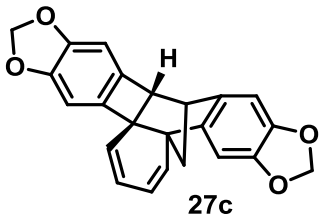
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (s, 1H), 6.92-6.91 (m, 3H), 6.41-6.38 (m, 1H), 6.13 (d, J = 9.7 Hz, 1H), 6.0-5.92 (m, 2H), 3.28 (s, 1H), 3.26 (s, 1H), 2.28-2.25 (m, 12H), 1.80 (d, J = 9.3 Hz, 1H), 1.68 (d, J = 9.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.64, 143.85, 141.87, 140.45, 136.79, 136.20, 133.83, 132.83, 131.92, 128.30, 127.52, 124.28, 123.59, 122.68, 60.27, 52.76, 52.69, 45.78, 45.65, 20.63, 20.50, 20.12, 19.98.

GC-HRMS: calculated $[M-15]^+$ for $C_{24}H_{21}$: 309.1643, found: 309.1650; calculated $[M-104]^+$ for $C_{17}H_{16}$: 220.1252, found: 220.1233.

FTIR (cm^{-1}): 3007, 2965, 2942, 1689, 1459, 1415, 1247, 1216, 1143, 986, 876, 845, 759, 715.

Compound (27c)



27c

Following the general procedure, treatment of 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yltrifluoromethanesulfonate **6c** (0.410 g, 1.20 mmol) and 1*H*-indene **26a** (0.058 g, 0.059 µL, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded compound **27c** as a white solid (0.145 g, 81%).

Rf (Pet. ether/EtOAc = 95/05): 0.62.

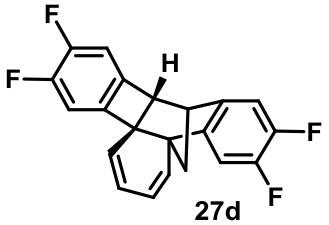
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (s, 1H), 6.66-6.64 (m, 2H), 6.60 (s, 1H), 6.35 (dd, J_1 = 9.2 Hz, J_2 = 4.7 Hz, 1H), 6.06 (d, J = 9.2 Hz, 1H), 5.96-5.88 (m, 6H), 3.19 (s, 1H), 3.11 (s, 1H), 1.81 (d, J = 9.1 Hz, 1H), 1.63 (d, J = 9.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.81, 147.21, 145.42, 145.10, 142.04, 138.60, 136.64, 136.47, 131.73, 127.87, 127.74, 124.45, 104.72, 103.78, 103.42, 100.69, 100.19, 55.81, 52.71, 51.49, 45.77, 45.66.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{17}O_4$: 357.1121, found: 357.1106.

FTIR (cm^{-1}): 3028, 2957, 2887, 2772, 1459, 1301, 1235, 1118, 1038, 941, 856, 804, 751, 692.

6,7,11,12-Tetrafluoro-8b,9-dihydro-9,13b-methanobenzo[3,4]cyclobuta[1,2-*k*] phenanthrene (27d)



27d

Following the general procedure, treatment of 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6d** (0.401 g, 1.20 mmol) and 1*H*-indene **26a** (0.058 g, 0.059 µL, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 6,7,11,12-tetrafluoro-8b,9-dihydro-9,13b-methanobenzo [3,4]cyclobuta[1,2-*k*]phenanthrene **27d** as a white solid (0.073 g, 43%).

R_f (Pet. ether): 0.40.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07-7.03 (m, 1H), 6.96-6.87 (m, 3H), 6.39 (dd, J_1 = 9.4 Hz, J_2 = 5.0 Hz, 1H), 6.08 (d, J = 9.4 Hz, 1H), 5.99 (dd, J_1 = 9.4 Hz, J_2 = 5.0 Hz, 1H), 5.84 (d, J = 9.4 Hz, 1H), 3.31 (s, 1H), 3.23 (s, 1H), 1.87 (d, J = 9.7 Hz, 1H), 1.61 (d, J = 9.8 Hz, 1H).

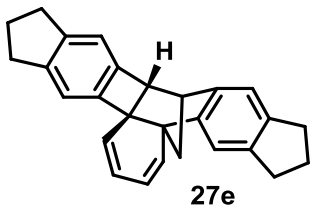
^{13}C NMR (100 MHz, $CDCl_3$): δ 153.30 (dd, J_1 = 247.4 Hz, J_2 = 13.0 Hz), 152.90 (dd, J_1 = 248.9 Hz, J_2 = 13.6 Hz), 150.26 (m), 147.68 (t, J = 13.3 Hz), 143.80 (dd, J_1 = 6.3 Hz, J_2 = 3.5 Hz), 140.97 (t, J = 4.5 Hz), 138.88 (m), 130.67, 128.19, 127.12, 125.12, 112.33 (dd, J_1 = 131.2 Hz, J_2 = 19.0 Hz), 118.84 (d, J = 18.5 Hz), 59.51, 52.77, 51.88, 45.60, 45.23.

^{19}F NMR (376 MHz, $CDCl_3$): δ -136.99 (d, J = 17.5 Hz), -137.55 (d, J = 17.3 Hz), -141.54 (d, J = 18.8 Hz), -142.18 (d, J = 18.9 Hz).

HRMS: calculated $[M+H]^+$ for $C_{21}H_{13}F_4$: 341.0948, found: 341.0948.

FTIR (cm^{-1}): 3038, 2972, 1616, 1471, 1428, 1344, 1261, 1192, 1155, 1120, 1054, 873, 845, 792, 755, 710.

6,7,8,9b,10,12,13,14-Octahydro-10,15b-methanocyclopenta[*b*]indeno[5',6':3,4] cyclobuta[1,2-*k*]phenanthrene (27e)



27e

Following the general procedure, treatment of 6-(trimethylsilyl)-2,3-dihydro-1*H*-inden-5-yltrifluoromethanesulfonate **6e** (0.203 g, 0.60 mmol) and 1*H*-indene **26a** (0.029 g, 0.029 µL, 0.25 mmol) with CsF (0.183 g, 1.20 mmol) in CH_3CN (1.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 6,7,8,9b,10,12,13,14-Octahydro-10,15b-methano cyclopenta[*b*]indeno[5',6':3,4]cyclobuta[1,2-*k*]phenanthrene **27e** as a yellow viscous liquid (0.060 g, 69%).

***R*$_f$** (Pet. ether): 0.45.

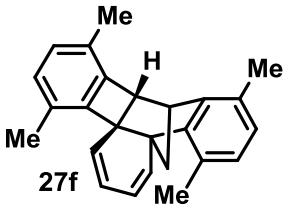
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (s, 1H), 7.02 (s, 3H), 6.42-6.39 (m, 1H), 6.13 (d, J = 9.3 Hz, 1H), 5.98-5.96 (m, 2H), 3.31 (s, 1H), 3.27 (s, 1H), 2.92-2.86 (m, 8H), 2.12-2.05 (m, 4H), 1.84 (d, J = 9.2 Hz, 1H), 1.72 (d, J = 9.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.29, 144.09, 143.97, 143.42, 142.0, 141.58, 141.26, 140.70, 132.14, 128.33, 127.57, 124.24, 118.53, 117.96, 117.90, 117.44, 59.38, 52.80, 51.97, 45.89, 45.80, 33.38, 33.25, 32.91, 32.88, 25.61, 25.52.

GC-HRMS: calculated $[M-116]^+$ for $C_{18}H_{16}$: 232.1252, found: 232.1315.

FTIR (cm^{-1}): 3007, 2951, 2848, 1455, 1322, 1258, 1215, 1138, 873, 760, 670.

5,8,10,13-Tetramethyl-8b,9-dihydro-9,13b-methanobenzo[3,4]cyclobuta[1,2-*k*]phenanthrene (27f)



Following the general procedure, treatment of 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6f** (0.392 g, 1.20 mmol) and 1*H*-indene **26a** (0.058 g, 0.059 µL, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 5,8,10,13-tetramethyl-8b,9-dihydro-9,13b-methanobenzo[3,4]cyclobuta[1,2-*k*] phenanthrene **27f** as a white solid (0.102 g, 63%).

***R*$_f$** (Pet. ether): 0.39.

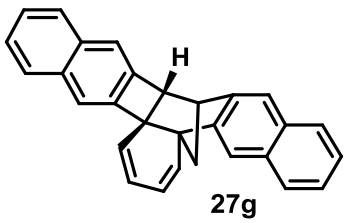
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 9.5 Hz, 1H), 6.38-6.34 (m, 1H), 6.13 (s, 2H), 3.38 (s, 1H), 3.22 (s, 1H), 2.41 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H), 2.17 (s, 3H), 1.82 (d, *J* = 9.3 Hz, 1H), 1.60 (d, *J* = 9.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ148.54, 144.44, 142.62, 139.56, 132.19, 130.97, 130.92, 130.83, 130.72, 129.91, 129.13, 128.89, 128.18, 127.53, 127.27, 125.29, 61.41, 54.48, 49.41, 45.71, 42.90, 20.63, 18.14, 17.83, 16.20.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{25}$: 325.1951, found: 325.1946.

FTIR (cm^{-1}): 3032, 2964, 2927, 1492, 1449, 1376, 1217, 1035, 1004, 802, 759, 671.

10b,11-Dihydro-11,17b-methanonaphtho[2',3':3,4]cyclobuta[1,2-*e*]tetraphene (27g)



Following the general procedure, treatment of 3-(trimethylsilyl)naphthalen-2-yltrifluoromethanesulfonate **6g** (0.418 g, 1.20 mmol) and 1*H*-indene **26a** (0.058 g, 0.059 µL, 0.50 mmol) with CsF (0.365 g, 2.40 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 10b,11-dihydro-11,17b-methanonaphtho[2',3':3,4]cyclobuta[1,2-*e*]tetraphene **27g** as a yellow solid (0.073 g, 40%).

***R*$_f$** (Pet. ether): 0.24.

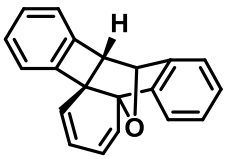
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.80 (m, 4H), 7.71 (s, 1H), 7.59-7.57 (m, 3H), 7.46-7.41 (m, 4H), 6.58 (dd, J_1 = 9.5 Hz, J_2 = 4.9 Hz, 1H), 6.25 (d, J = 9.5 Hz, 1H), 6.08 (dd, J_1 = 9.4 Hz, J_2 = 4.9 Hz, 1H), 5.94 (d, J = 9.4 Hz, 1H), 3.68 (s, 1H), 3.56 (s, 1H), 1.90 (d, J = 9.6 Hz, 1H), 1.85 (d, J = 9.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.54, 144.51, 142.39, 141.21, 135.05, 134.57, 133.14, 132.51, 131.70, 128.41, 128.38, 128.13, 128.09, 128.06, 127.69, 125.36, 125.17, 125.13, 125.10, 124.46, 120.64, 119.98, 119.72, 119.02, 60.47, 53.79, 52.68, 46.82, 44.83.

HRMS: calculated $[M+H]^+$ for $C_{29}H_{21}$: 369.1638, found: 369.1632.

FTIR (cm^{-1}): 3038, 3007, 2968, 1505, 1435, 1216, 951, 879, 757, 695.

8b,9-Dihydro-9,13b-epoxybenzo[3,4]cyclobuta[1,2-*k*]phenanthrene (30a)[19]



30a

Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **6a** (0.448 g, 364 µL, 1.50 mmol) and benzofuran **29a** (0.059 g, 0.056 µL, 0.50 mmol) with CsF (0.456 g, 3.0 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded 8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta[1,2-*k*]phenanthrene **30a** as a white solid (0.088 g, 65%).

Rf (Pet. ether/EtOAc = 95/05): 0.40.

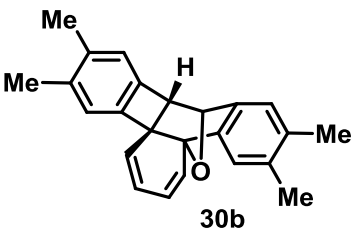
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 6.5 Hz, 1H), 7.35-7.20 (m, 7H), 6.47-6.39 (m, 2H), 6.24 (d, J = 9.4 Hz, 1H), 6.10-6.07 (m, 1H), 5.40 (s, 1H), 3.60 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.28, 144.80, 142.45, 140.86, 132.06, 128.76, 128.09, 127.46, 127.11, 126.36, 126.30, 125.16, 126.63, 121.57, 121.49, 119.41, 88.05, 82.11, 61.64, 53.25.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{15}O$: 271.1117, found: 271.1129.

FTIR (cm^{-1}): 3041, 3006, 2965, 1459, 1367, 1251, 1197, 1151, 1032, 907, 752, 694.

6,7,11,12-Tetramethyl-8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta[1,2-*k*]phenanthrene (30b)



30b

Following the general procedure, treatment of 4,5-dimethyl -2-(trimethylsilyl)phenyltrifluoromethanesulfonate **6b** (0.489 g, 1.50 mmol) and benzofuran **29a** (0.059 g, 0.056 µL, 0.50 mmol) with CsF (0.456 g, 3.0 mmol) in CH_3CN

(2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded 6,7,11,12-tetramethyl-8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta [1,2-*k*]phenanthrene **30b** as a white solid (0.072 g, 44%).

Rf (Pet. ether/EtOAc = 95/05): 0.42.

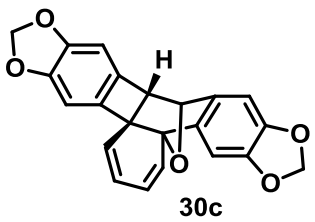
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (s, 1H), 6.96-6.93 (m, 3H), 6.43-6.29 (m, 2H), 6.23-6.18 (m, 1H), 6.07-5.99 (m, 1H), 5.25 (s, 1H), 3.49 (s, 1H), 2.27-2.24 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.30, 142.41, 140.21, 138.52, 137.37, 136.60, 135.20, 134.33, 132.36, 127.23, 126.61, 125.00, 122.85, 122.63, 120.89, 87.92, 82.11, 61.58, 53.28, 20.69, 20.59, 20.17, 20.09.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{23}O$: 327.1743, found: 327.1746.

FTIR (cm^{-1}): 3008, 2963, 2927, 2863, 1460, 1410, 1379, 1325, 1220, 1079, 1029, 995, 947, 915, 880, 860, 816, 753, 666.

Compound (30c)



30c

Following the general procedure, treatment of 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yltrifluoromethanesulfonate **6c** (0.513 g, 1.50 mmol) and benzofuran **29a** (0.059 g, 0.056 µL, 0.50 mmol) with CsF (0.456 g, 3.0 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 90/10) afforded compound **30c** as a white solid (0.081 g, 46%).

Rf (Pet. ether/EtOAc = 90/10): 0.29.

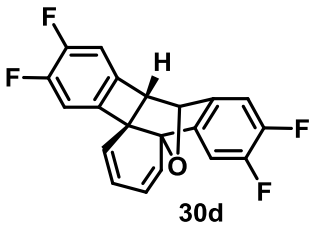
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 1H), 6.69 (s, 1H), 6.65 (d, J = 2.4 Hz, 2H), 6.35 (dd, J_1 = 9.7 Hz, J_2 = 4.7 Hz, 1H), 6.29 (d, J = 9.7 Hz, 1H), 6.17 (d, J = 9.5 Hz, 1H), 6.01 (dd, J_1 = 9.4 Hz, J_2 = 4.8 Hz, 1H), 5.95 (dd, J_1 = 4.5 Hz, J_2 = 1.3 Hz, 2H), 5.89 (d, J = 1.4 Hz, 1H), 5.86 (d, J = 1.4 Hz, 1H), 5.16 (s, 1H), 3.34 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.19, 147.51, 146.73, 146.35, 139.99, 137.25, 134.89, 134.69, 132.25, 127.50, 126.02, 125.17, 103.97, 103.77, 103.74, 101.67, 101.34, 100.38, 87.74, 81.88, 59.95, 51.99.

HRMS: calculated $[M+Na]^+$ for $C_{22}H_{14}O_5Na$: 381.0733, found: 381.0738.

FTIR (cm^{-1}): 2958, 2899, 2769, 1461, 1371, 1306, 1120, 1070, 1034, 940, 847, 814, 688.

6,7,11,12-Tetrafluoro-8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta[1,2-*k*] phenanthrene (30d)



30d

Following the general procedure, treatment of 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6d** (0.501 g, 1.50 mmol) and 2,3-benzofuran **29a** (0.059 g, 0.055 µL, 0.50 mmol) with CsF (0.456 g, 3.0 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded 6,7,11,12-tetrafluoro-8b,9-dihydro-9,13b-epoxybenzo [3,4]cyclobuta[1,2-*k*]phenanthrene **30d** as a white solid (0.049 g, 29%).

***R*$_f$** (Pet. Ether/EtOAc = 95/05): 0.35.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.14 (m, 1H), 7.01-6.92 (m, 3H), 6.43-6.39 (m, 1H), 6.32 (d, *J* = 9.8 Hz, 1H), 6.18 (d, *J* = 9.5 Hz, 1H), 6.09-6.05 (m, 1H), 5.26 (s, 1H), 3.48 (s, 1H).

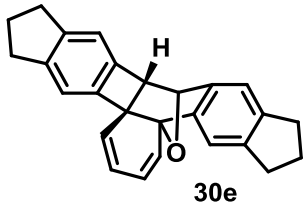
^{13}C NMR (100 MHz, $CDCl_3$): δ 153.51 (dd, J_1 = 266.8 Hz, J_2 = 13.4 Hz), 153.07 (dd, J_1 = 249.6 Hz, J_2 = 13.9 Hz), 151.07 (dd, J_1 = 13.4 Hz, J_2 = 2.13 Hz), 148.61 (dd, J_1 = 20.8 Hz, J_2 = 13.4 Hz), 141.54 (m), 139.77 (t, *J* = 4.9 Hz), 137.27 (m), 136.96 (m), 131.33, 127.99, 125.84, 125.57, 111.90 (m), 111.71 (m), 109.67, 109.47, 87.86, 81.38, 60.79, 52.51.

^{19}F NMR (376 MHz, $CDCl_3$): δ -136.42 (d, *J* = 18.2 Hz), -137.03 (d, *J* = 18.3 Hz), -138.81 (d, *J* = 18.8 Hz), -139.50 (d, *J* = 18.8 Hz).

HRMS: calculated $[M+H]^+$ for $C_{20}H_{11}F_4O$: 343.0741, found: 343.0745.

FTIR (cm^{-1}): 3050, 2966, 2920, 2853, 1618, 1474, 1431, 1345, 1274, 1189, 1125, 1079, 863, 824.

6,7,8,9b,10,12,13,14-Octahydro-10,15b-epoxycyclopenta[*b*]indeno[5',6':3,4]cyclobuta [1,2-*k*] phenanthrene (30e)



30e

Following the general procedure, treatment of 6-(trimethyl silyl)-2,3-dihydro-1*H*-inden-5-yl trifluoromethanesulfonate **6e** (0.254 g, 0.75 mmol) and benzofuran **29a** (0.029 g, 0.028 µL, 0.25 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (1.0

mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded 6,7,8,9b,10,12,13,14-octahydro-10,15b–epoxycyclopenta[*b*]indeno[5',6':3,4]cyclobuta[1,2-*k*]phenanthrene **30e** a white solid (0.042 g, 48%).

R_f (Pet. Ether/EtOAc = 95/05): 0.38.

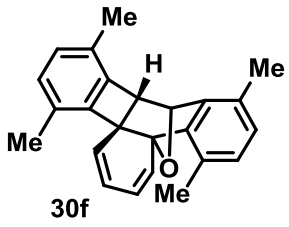
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.06 (s, 2H), 7.04 (s, 1H), 6.41-6.38 (m, 1H), 6.34 (d, *J* = 9.7 Hz, 1H), 6.25 (d, *J* = 9.4 Hz, 1H), 6.06-6.03 (m, 1H), 5.27 (s, 1H), 3.49 (s, 1H), 2.94-2.85 (m, 8H), 2.13-2.02 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.06, 144.60, 143.75, 143.08, 142.51, 142.28, 140.31, 139.45, 132.62, 127.27, 126.59, 124.96, 117.93, 117.86, 115.70, 87.93, 82.26, 60.70, 52.57, 33.38, 33.26, 32.77, 25.80, 25.39.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{23}O$: 351.1743, found: 351.1754.

FTIR (cm^{-1}): 3005, 2951, 2844, 1448, 1326, 1238, 1076, 1034, 946, 915, 876, 851.

5,8,10,13-Tetramethyl-8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta[1,2-*k*] phenanthrene (30f)



30f

Following the general procedure, treatment of 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6f** (0.489 g, 1.50 mmol) and benzofuran **29a** (0.059 g, 0.056 µL, 0.50 mmol) with CsF (0.456 g, 3.0 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded 5,8,10,13-tetramethyl-8b,9-dihydro-9,13b-epoxybenzo [3,4]cyclobuta[1,2-*k*] phenanthrene **30f** as a white solid (0.101 g, 62%).

Rf (Pet. ether/EtOAc = 95/05): 0.44.

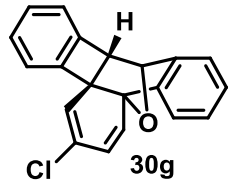
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (d, *J* = 7.9 Hz, 1H), 6.95-6.90 (m, 2H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.63 (d, *J* = 9.7 Hz, 1H), 6.41 (dd, J_1 = 9.7 Hz, J_2 = 4.7 Hz, 1H), 6.34 (d, *J* = 9.4 Hz, 1H), 6.21 (dd, J_1 = 9.4 Hz, J_2 = 4.7 Hz, 1H), 5.30 (s, 1H), 3.45 (s, 1H), 2.40-2.38 (m, 6H), 2.31 (s, 3H), 2.23 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.11, 142.97, 140.94, 137.82, 131.12, 130.88, 130.76, 130.66, 130.35, 129.39, 128.52, 128.41, 128.13, 126.36, 125.97, 89.08, 80.06, 62.57, 49.82, 19.05, 17.86, 17.40, 16.13.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{23}O$: 327.1743, found: 327.1740.

FTIR (cm^{-1}): 3038, 2922, 2860, 1617, 1545, 1494, 1449, 1408, 1327, 1255, 1218, 1160, 1083, 1039, 989, 922, 871, 812, 742.

3-Chloro-8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta[1,2-*k*]phenanthrene (30g)



30g

Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **6a** (0.448 g, 364 µL, 1.50 mmol) and 5-chlorobenzofuran **29b** (0.076 g, 0.50 mmol) with CsF (0.456 g, 3.0 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded 3-chloro-8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta [1,2-*k*]phenanthrene **30g** as a pale yellow solid (0.061 g, 40%).

Rf (Pet. ether/EtOAc = 95/05): 0.40.

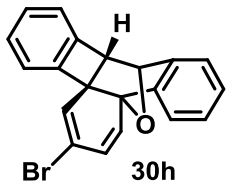
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.42 (m, 1H), 7.38-7.28 (m, 5H), 7.26-7.23 (m, 2H), 6.50 (d, J = 9.8 Hz, 1H), 6.41 (dd, J_1 = 9.9 Hz, J_2 = 1.4 Hz, 1H), 6.28 (s, 1H), 5.41 (s, 1H), 3.64 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.81, 143.74, 142.15, 140.40, 129.94, 129.22, 129.14, 128.33, 127.88, 127.53, 126.80, 121.81, 121.64, 121.15, 119.60, 87.14, 82.23, 62.58, 54.13.

HRMS: calculated $[M+Na]^+$ for $C_{20}H_{13}ClONa$: 327.0547, found: 327.0551.

FTIR (cm^{-1}): 3067, 3013, 2969, 1602, 1456, 1392, 1257, 1190, 1151, 1093, 1042, 976, 907, 841, 756, 658.

3-Bromo-8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta[1,2-*k*]phenanthrene (30h)



30h

Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **6a** (0.448 g, 364 µL, 1.50 mmol) and 5-bromobenzofuran **29c** (0.099 g, 0.50 mmol) with CsF (0.456 g, 3.0 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded 3-bromo-8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta[1,2-*k*]phenanthrene **30h** as a yellow solid (0.071 g, 41%).

R_f (Pet. Ether/EtOAc = 95/05): 0.45.

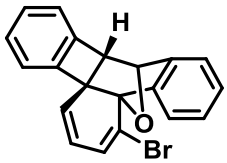
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.39 (m, 1H), 7.35-7.20 (m, 7H), 6.49 (d, J = 9.2 Hz, 2H), 6.40 (d, J = 9.9 Hz, 1H), 5.37 (s, 1H), 3.62 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.81, 143.51, 142.15, 140.34, 132.06, 131.68, 129.24, 128.35, 127.91, 127.54, 126.84, 121.84, 121.64, 121.17, 119.62, 117.40, 86.77, 82.24, 63.53, 54.21.

HRMS: calculated $[M+H]^+$ for $C_{20}H_{14}BrO$: 349.0223, found: 349.0220.

FTIR (cm^{-1}): 3066, 3011, 1597, 1456, 1220, 1191, 1151, 1088, 1033, 973, 905, 841, 753, 646.

1-Bromo-8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta[1,2-*k*]phenanthrene (30i)



30i

Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **6a** (0.448 g, 364 µL, 1.50 mmol) and 7-bromobenzofuran **29d** (0.099 g, 0.50 mmol) with CsF (0.456 g, 3.0 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded 1-bromo-8b,9-dihydro-9,13b-epoxybenzo[3,4]cyclobuta[1,2-*k*]phenanthrene **30i** as a white solid (0.098 g, 56%).

Rf (Pet. ether/EtOAc = 95/05): 0.36.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 6.9 Hz, 1H), 7.32-7.15 (m, 7H), 6.76 (d, J = 5.7 Hz, 1H), 6.21 (d, J = 9.3 Hz, 1H), 5.92 (dd, J_1 = 9.2 Hz, J_2 = 5.6 Hz, 1H), 5.39 (s, 1H), 3.66 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.12, 143.98, 141.97, 138.95, 131.20, 129.23, 129.06, 128.54, 127.80, 126.75, 125.14, 121.70, 121.52, 121.10, 120.68, 119.80, 89.29, 81.95, 63.17, 54.76.

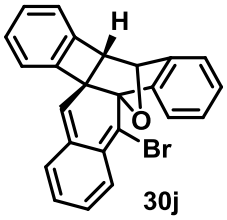
HRMS: calculated $[M+Na]^+$ for $C_{20}H_{13}BrONa$: 371.0042, found: 371.0053.

FTIR (cm^{-1}): 3043, 1608, 1536, 1452, 1383, 1354, 1139, 1077, 1037, 982, 904, 863, 816, 744, 707.

15-Bromo-9b,10-dihydro-10,14b-epoxybenzo[3,4]cyclobuta[1,2-*g*]tetraphene (30j) and 6-Bromo-4b,11b-dihydrobenzo[3,4]cyclobuta[1,2-*b*]naphtho[2,3-*d*]furan (30j')

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.223 g, 182 µL, 0.75 mmol) and 9-bromonaphtho[2,3-*b*]furan **29e** (0.062 g, 0.25 mmol) with CsF (0.227 g, 1.5 mmol) in CH_3CN (1 .0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 95/05) afforded 15-bromo-9b,10-dihydro-10,14b-epoxybenzo[3,4]cyclobuta[1,2-*g*]tetraphene **30j** (yellow solid,

0.038 g, 38%) and 6-bromo-4b,11b-dihydrobenzo[3,4]cyclobuta[1,2-*b*]naphtho [2,3-*d*]furan **30j'** (yellow solid, 0.014 g, 17%).



30j

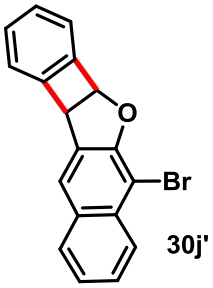
Rf (Pet. ether/EtOAc = 95/05): 0.18.

^{1}H NMR (400 MHz, $CDCl_3$) 30j: δ 8.21 (d, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 7.1 Hz, 1H), 7.41-7.38 (m, 1H), 7.33-7.24 (m, 5H), 7.18 (d, *J* = 7.1 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 6.85-6.78 (m, 2H), 6.56 (d, *J* = 1.9 Hz, 1H), 5.68 (s, 1H), 5.12 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.56, 150.44, 145.53, 141.57, 140.05, 139.81, 137.24, 129.72, 128.50, 128.04, 126.86, 126.78, 126.47, 126.08, 125.14, 125.07, 124.79, 122.22, 121.57, 119.00, 97.23, 83.90, 67.26, 47.43.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{16}BrO$: 399.0379, found: 399.0385.

FTIR (cm^{-1}): 3065, 3011, 2926, 1455, 1298, 1237, 1158, 999, 933, 884, 755.



30j'

Rf (Pet. ether/EtOAc = 95/05): 0.50.

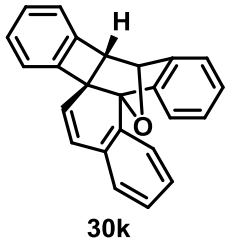
^{1}H NMR (400 MHz, $CDCl_3$) 30j': δ 8.09 (d, *J* = 8.5 Hz, 1H), 7.77-7.75 (m, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.43-7.25 (m, 5H), 6.27 (d, *J* = 4.1 Hz, 1H), 5.39 (d, *J* = 4.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.09, 147.88, 143.56, 132.79, 130.82, 130.72, 130.58, 128.81, 128.18, 127.21, 125.45, 124.28, 124.22, 123.18, 122.03, 99.87, 83.97, 53.34.

HRMS: calculated $[M+Na]^+$ for $C_{18}H_{11}BrONa$: 344.9885, found: 344.9889.

FTIR (cm^{-1}): 3057, 3022, 2983, 2956, 2928, 1637, 1455, 1427, 1227, 1142, 1072, 994, 921, 890, 757.

9,9a-Dihydro-4b,9-epoxybenzo[*c*]benzo[3,4]cyclobuta[1,2-*m*]phenanthrene (30k)



30k

Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **6a** (0.448 g, 364 µL, 1.50 mmol) and naphtho[1,2-*b*]furan **29f** (0.084 g, 0.50 mmol) with CsF (0.456 g, 3.0 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded 9,9a-dihydro-4b,9-epoxybenzo[*c*]benzo[3,4]cyclobuta[1,2-*m*]phenanthrene **30k** as a white solid (0.147 g, 92%).

Rf (Pet. ether/EtOAc = 95/05): 0.38.

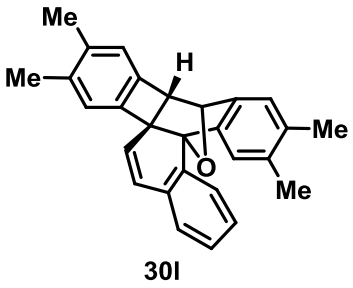
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.37 (m, 4H), 7.33-7.19 (m, 4H), 7.13-7.08 (m, 2H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 9.5 Hz, 1H), 6.26 (d, *J* = 9.5 Hz, 1H), 5.49 (s, 1H), 3.70 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.86, 145.83, 143.96, 142.33, 134.31, 133.39, 130.60, 129.05, 128.85, 128.45, 128.21, 127.02, 126.87, 126.55, 124.26, 122.10, 121.58, 121.33, 119.25, 88.24, 81.90, 61.82, 54.50.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{17}O$: 321.1274, found: 321.1275.

FTIR (cm^{-1}): 3065, 3010, 2971, 1455, 1339, 1207, 1151, 1078, 1003, 955, 909, 846, 750, 670.

6,7,11,12-Tetramethyl-9,9a-dihydro-4b,9-epoxybenzo[*c*]benzo[3,4]cyclobuta[1,2-*m*]phenanthrene (30l)



30l

Following the general procedure, treatment of 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6b** (0.245 g, 0.75 mmol) and naphtho[1,2-b]furan **29f** (0.042 g, 0.25 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (1.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded 6,7,11,12-tetramethyl-9,9a-dihydro-4b,9-epoxybenzo[*c*]benzo[3,4]cyclobuta[1,2-*m*]phenanthrene **30l** a white solid (0.056 g, 60%).

R_f (Pet. Ether/EtOAc = 95/05): 0.43.

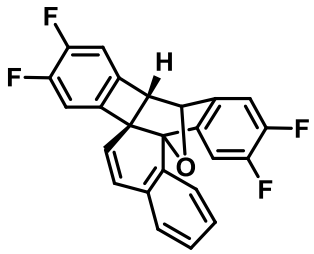
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.38 (m, 3H), 7.34-7.31 (m, 1H), 7.18 (s, 1H), 7.01 (s, 1H), 6.62 (d, *J* = 9.4 Hz, 1H), 6.53 (s, 1H), 6.44 (s, 1H), 6.30 (d, *J* = 9.5 Hz, 1H), 5.40 (s, 1H), 3.64 (s, 1H), 2.28 (s, 3H), 2.25 (s, 3H), 2.16 (s, 3H), 2.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.82, 143.48, 141.75, 139.97, 137.38, 136.66, 135.12, 134.54, 134.34, 133.79, 130.99, 128.80, 128.31, 127.99, 126.78, 124.30, 123.23, 122.75, 122.23, 120.63, 88.05, 81.87, 61.69, 54.41, 20.67, 20.42, 20.08, 20.04.

HRMS: calculated $[M+H]^+$ for $C_{28}H_{25}O$: 377.1900, found: 377.1904.

FTIR (cm^{-1}): 3066, 3011, 1597, 1456, 1220, 1151, 1088, 1033, 973, 905, 841, 753, 646.

6,7,11,12-Tetrafluoro-9,9a-dihydro-4b,9-epoxybenzo[*c*]benzo[3,4]cyclobuta[1,2-*m*] phenanthrene (30m)



30m

Following the general procedure, treatment of 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6d** (0.250 g, 0.75 mmol) and naphtho[1,2-*b*]furan **29f** (0.042 g, 0.25 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (1.0 mL) at 30 °C for 24 h followed by column chromatography (Pet. ether/ EtOAc = 99/01) afforded 6,7,11,12-tetrafluoro-9,9a-dihydro-4b,9-epoxybenzo[*c*]benzo[3,4]cyclobuta[1,2-*m*]phenanthrene **30m** as a pale yellow solid (0.030 g, 31%).

Rf (Pet. ether/EtOAc = 95/05): 0.38.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.32 (m, 4H), 7.20-7.16 (m, 1H), 7.03-7.00 (m, 1H), 6.61 (d, *J* = 9.5 Hz, 1H), 6.57-6.53 (m, 1H), 6.44-6.40 (m, 1H), 6.20 (d, *J* = 9.4 Hz, 1H), 5.39 (s, 1H), 3.61 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.48 (dd, J_1 = 247.4 Hz, J_2 = 12.7 Hz), 153.05 (dd, J_1 = 248.9 Hz, J_2 = 13.5 Hz), 150.86 (d, *J* = 33.5 Hz), 148.47 (m), 141.14 (dd, J_1 = 6.4 Hz, J_2 = 3.3 Hz), 140.84 (t, *J* = 4.6 Hz), 139.88 (dd, J_1 = 5.8 Hz, J_2 = 3.1 Hz), 137.14 (t, *J* = 5.3 Hz), 133.55, 131.83, 129.74, 129.40, 129.05, 128.95, 127.37, 124.22, 112.26 (d, *J* = 19.9 Hz), 111.97 (dd, J_1 = 43.1 Hz, J_2 = 18.4 Hz), 109.37 (d, *J* = 20.1 Hz), 88.01, 81.11, 60.95, 53.67.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{13}F_4O$: 393.0897, found: 393.0905.

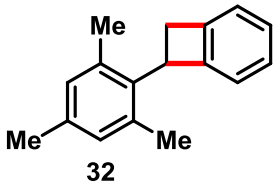
FTIR (cm^{-1}): 3041, 3012, 2968, 1620, 1476, 1433, 1356, 1261, 1193, 1126, 1082, 955, 874, 794, 749.

[2 + 2] cycloaddition of 1,3,5-trimethyl-2-vinylbenzene 31 with Aryne (Scheme 4.12):

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry CsF (0.365 g, 2.40 mmol). Then the screw-capped tube was evacuated and backfilled with argon and dissolved in CH_3CN under argon atmosphere (2.0 mL). To the stirring solution were added 1,3,5-trimethyl-2-vinylbenzene **31** (0.073 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6a** (0.358 g, 292 µL, 1.20 mmol). Then the reaction mixture kept for stirring at room temperature (30 °C). After 24 h, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of

silica gel and eluted with CH_2Cl_2 (15.0 mL). The solvent was evaporated followed by column chromatography (Pet. ether) afforded 7-mesitylbicyclo[4.2.0]octa-1(6),2,4-triene **32** as a colorless viscous liquid (0.045 g, 40%).

7-Mesitylbicyclo[4.2.0]octa-1(6),2,4-triene (32)



32

***R**f* (Pet. ether): 0.54.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.26 (m, 2H), 7.19 (d, *J* = 6.8 Hz, 1H), 7.13 (d, *J* = 7.0 Hz, 1H), 6.90 (s, 2H), 5.17-5.16 (m, 1H), 3.73 (dd, J_1 = 14.2 Hz, J_2 = 5.9 Hz, 1H), 3.38 (dd, J_1 = 14.0 Hz, J_2 = 3.1 Hz, 1H), 2.34 (s, 3H), 2.23 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.93, 143.63, 137.36, 135.97, 134.07, 129.98, 127.03, 126.95, 122.91, 122.82, 43.75, 37.48, 21.07, 20.84.

GC-HRMS: calculated $[M]^+$ for $C_{17}H_{18}$: 222.1409, found: 222.1452.

FTIR (cm^{-1}): 3065, 3004, 2960, 2922, 2861, 1608, 1453, 1378, 1240, 1191, 1025, 975, 852, 752.

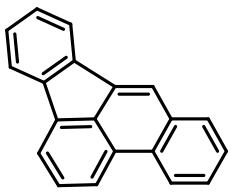
Procedure for the One-Pot Synthesis of Benzo[*e*]acephenanthrylene 34 (Scheme 4.13):

To a flame-dried screw-capped Schlenk tube equipped with a magnetic stir bar was added dry CsF (0.228 g, 1.50 mmol). Then the screw-capped tube was evacuated and backfilled with argon and dissolved in CH_3CN under argon atmosphere (1.0 mL). To the stirring solution were added benzofuran **29a** (0.029 g, 28 µL, 0.25 mmol) and 2(trimethylsilyl)phenyl trifluoromethanesulfonate **6a** (0.224 g, 182 µL, 0.75 mmol). Then the reaction mixture kept for stirring at room temperature (30 °C) for 24 h followed by the addition of $BF_3.OEt_2$ (0.035 g, 31µL, 0.25 mmol, 1.0 equiv) in DCM (3.0 mL). The reaction mixture stirred for 1 h at 60 °C. Then the reaction stopped and the crude reaction mixture was purified by column chromatography on silica gel (Pet. ether/EtOAc = 98/01) to afford the corresponding benzo[*e*]acephenanthrylene **34** as a white solid (0.040 g, 65%).

Benzo[*e*]acephenanthrylene (34)[19]

***R**f* (Pet. ether): 0.32.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 8.1 Hz, 1H), 8.17 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 8.00-7.91 (m, 3H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.71-7.61



34

(m, 2H), 7.47-7.40 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.80, 138.64, 137.08, 135.16, 134.11, 132.20, 130.82, 130.31, 128.27, 128.18, 127.66, 127.54, 127.10, 126.86, 123.24, 122.03, 121.74, 121.60, 121.47, 119.63.

GC-HRMS: calculated $[M]^+$ for $C_{20}H_{12}$: 252.0939, found: 252.0906.

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CHAPTER 5

Employing Arynes in Transition-Metal-Free Monoarylation of Aromatic Tertiary Amines

5.1. Introduction

Aromatic amines are important building blocks in various natural products, pharmaceuticals, agrochemicals, dyes, fine chemicals, polymer chemistry and materials.[1] Owing to their numerous applications, development of efficient and straightforward methods for the synthesis of aromatic amine have attracted considerable attention of synthetic chemists, and various cross-coupling reactions for C-N bond-formation have been developed in the last century. The present chapter describes an efficient and facile transition-metal-free, selective monoarylation of aromatic tertiary amines using arynes as the aryl source. Before going into the details, a brief summary of the methods for the synthesis of aromatic amines with special emphasis on the transition-metal-free approach for the construction of C_{aryl}-N bonds is outlined in the following sections.

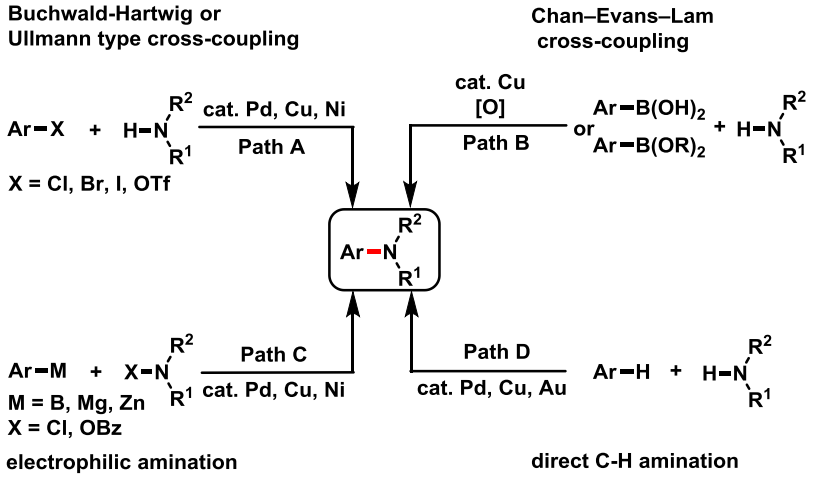
5.2. Methods for the Synthesis of Aromatic Amines

5.2.1. Transition-Metal-Catalyzed Construction of C_{aryl}-N Bonds

Initially, aromatic amines were synthesized by the classical methods such as nucleophilic aromatic substitution of electron poor aryl halides using highly basic reaction conditions and electrophilic substitution of nitro group on an aromatic ring followed by reduction. Pioneering work of Ullmann and Goldberg at the beginning of the 20th century on copper-mediated and copper-catalyzed construction of C_{aryl}-C, C_{aryl}-O, and C_{aryl}-N bonds by the reaction of aryl halides with various nucleophiles gave access to the wide range of new products.[2] However, Ullmann-Goldberg method for the synthesis of aryl amines often suffers from the harsh reaction conditions, stoichiometric amounts of copper salts as reagent, extended reaction time, limited substrate scope, and moderate yields of products, leading to major limitations in the general use of this reaction.[3]

The past decades witnessed notable advances in the field of transition-metal-catalyzed cross-coupling reactions and the N-arylation of primary or secondary amines with aryl halides or aryl triflates were more dominated by the use of Pd, Cu, Ni-based catalysts in well established Buchwald-Hartwig or Ullmann-type coupling (Scheme 5.1, path A).[4] These methods have overcome the synthetic problems associated with classical Ullmann-Goldberg method leading to the development of user friendly and sustainable laboratory procedures. Buchwald-Hartwig cross-coupling reactions furnished a variety of N-aryl amines in excellent yields with the aid of suitable diamine or phosphine ligands. Nevertheless, high cost, air and moisture sensitivity of Pd-catalysts have encouraged researchers to reconsider other transition metals in cross coupling reactions.

Scheme 5.1: Transition-Metal-Catalyzed Methods for the Construction of C_{aryl}-N Bonds



In 1998, a major breakthrough in Cu-catalyzed N-arylation of amines was achieved by Chan, Evans, and Lam. These groups independently reported a mild oxidative coupling reaction of primary and secondary aryl amines with easily accessible arylboronic acids or esters as the aryl source.[5] Generally, these reactions have been carried out in air at room temperature using inexpensive Cu-metal, which make them more beneficial and operationally simple (Scheme 5.1, path B). Transition-metal-catalyzed electrophilic amination of organometallic reagents derived from B, Mg, Zn, etc. with an electrophilic nitrogen source such as N-halo-amines and O-protected hydroxylamines has been emerged as an alternative strategy for the construction of C_{aryl}-N bonds (Scheme 5.1, path C).[6] Moreover, direct installation of amine moiety on the non-preactivated (hetero)aromatic rings via transition-metal-catalyzed C-H bond activation

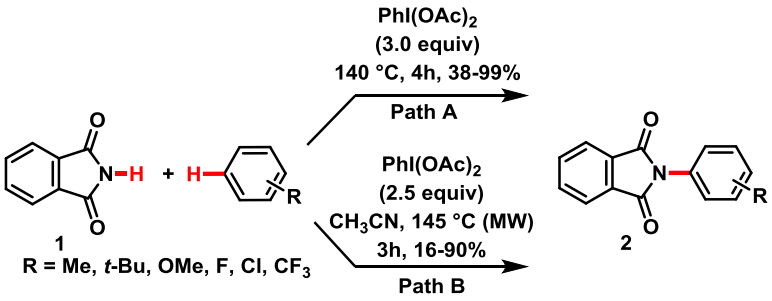
has also been useful and straightforward method for the construction of C_{aryl}-N bonds because of its economical advantages over previous procedures employing prefunctionalized substrates (Scheme 5.1, path D).[7]

5.2.2. Transition-Metal-Free Construction of C_{aryl}-N Bonds

Despite these significant advances in transition-metal-catalyzed C_{aryl}-N bond forming reactions, the major problem associated with use of transition-metals are cost of metal catalysts, accessibility of the specific ligands which require multiple steps for synthesis, air and moisture sensitivity of metal catalysts, and metal wastes. Therefore development of an economical, environmental benign and straightforward method devoid of metal-catalysts and using readily available feedstock are in great demand.

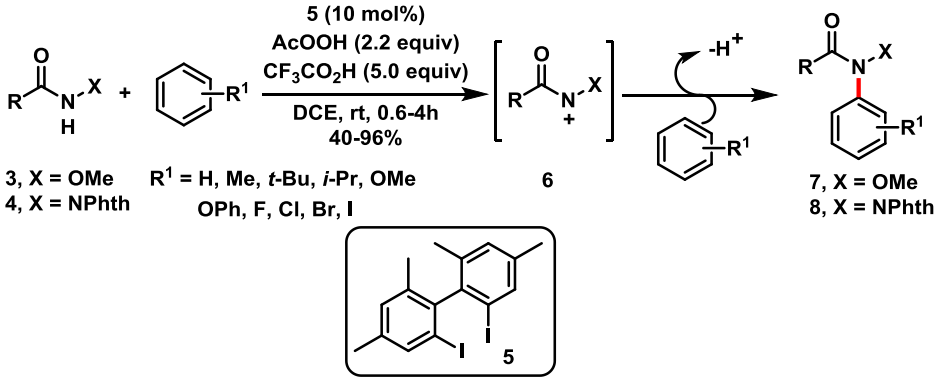
The group of Chang and DeBoef independently reported a direct hypervalent-iodide-mediated oxidative C-N bond formation reaction of non-prefunctionalized arenes under transition-metal-free conditions. Chang employed cheap and easily detachable phthalimide **1** as a nitrogen source with corresponding arenes using hypervalent iodine (III) oxidant $PhI(OAc)_2$ at 140 °C, which readily furnished aryl imidation products **2** in good yields (Scheme 5.2, path A).[8a] Notably, complete control of chemoselectivity between aryl sp^2 and benzylic sp^3 C-H bonds has been achieved with the aid of different nitrogen sources. Dibenzenesulfonimide exclusively afforded benzylic imidation products under these reaction conditions. DeBoef applied microwave heating conditions instead of conventional heating to carry out the same oxidative amination and based on the observed regioselectivity in product formation, proposed a single electron-transfer mechanism (Scheme 5.2, path B).[8b] A strong support to this mechanism came from the fact that reaction was completely inhibited in presence of radical inhibitor TEMPO.

Scheme 5.2: Transition-Metal-Free Oxidative Imidation of Arenes with Phthalimide



Subsequently, Antonchick and coworkers developed organocatalytic iodine (III)-mediated oxidative intermolecular process for the direct installation of amine or hydrazine groups into the unactivated arenes under mild reaction conditions. Reaction of *N*-methoxybenzamide **3** or *N*-(1,3-dioxoisoindolin-2-yl)acetamide **4** as an amination reagent with non-prefunctionalized arenes using aryl iodide catalyst **5** in presence of oxidant peracetic and trifluoroacetic acid combination in DCE as a solvent furnished the monoamination and hydrazination products of corresponding arenes **7** and **8** respectively in good yields (Scheme 5.3).[9] In this case, reaction proceeds via the in situ generation of iodine (III) species by oxidation of aryl iodide catalyst **5** with peracetic acid, which facilitate the formation of nitrenium ion **6**. Subsequent electrophilic substitution of electron-deficient nitrenium ion **6** on an aromatic system afforded the final product.

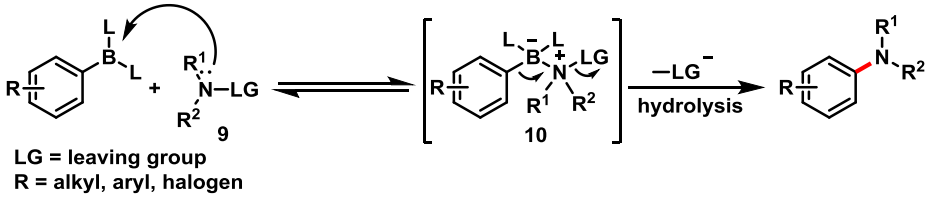
Scheme 5.3: Organocatalytic Iodine (III)-Mediated Intermolecular Oxidative Amination and Hydrazination of Arenes



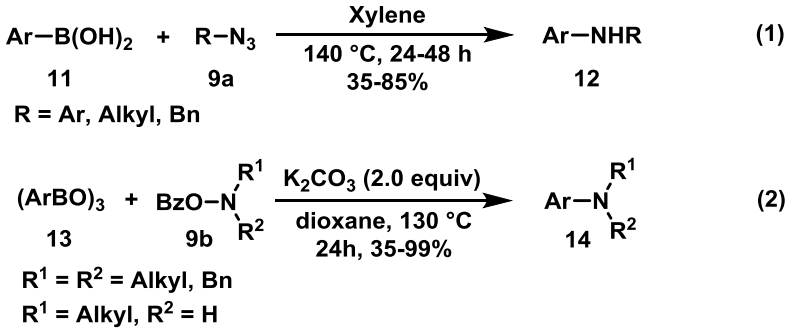
Recently, transition-metal-free amination of aryl boronic acids or derivatives with electrophilic aminating reagent has been emerged as an attractive strategy for the synthesis of aryl amines because of the high stability, low toxicity, and commercial availability of organoboron compounds.[10] Amination of organoboron compounds generally proceeds via the nucleophilic addition of aminating reagent **9** to a trivalent boron reagent to generate the reversible tetravalent boron "ate" complex **10**, subsequent 1,2 aryl B-N migration with the loss of leaving group results in the formation of C_{aryl}-N bond and delivers the aryl amine product after hydrolysis (Scheme 5.4). First report on this concept appeared in 2011, the Yu group reported a novel metal-free C_{aryl}-N bond forming reaction between aryl boronic acids and alkyl or aryl azides. Heating of aryl boronic acids **11** with organic azides **9a** at 140 °C in xylene as a solvent resulted in the

formation of N-substituted anilines **12** in moderate to good yields (Scheme 5.5, eq 1).[11] However, under these reaction conditions, heteroaryl boronic acids did not afford the desired secondary amines. Subsequently, Wang and coworkers reported the electrophilic amination reaction of readily available arylboroxines **13** with aminating reagent *O*-benzoylhydroxylamines **9b** in the presence of only base K_2CO_3 in 1,4-dioxane solvent at 130 °C (eq 2).[12] When reaction was carried out in presence of TEMPO, the amination was almost unaffected, which ruled out the possibility of radical mechanism. Therefore, it has been suggested that the reaction proceeds via a direct substitution mechanism shown in Scheme 5.4. Moreover, this method was found to be useful in the synthesis of wide range of functionalized secondary and tertiary aromatic amines **14**.

Scheme 5.4: Amination of Aryl Boronic Acids or Derivatives with Electrophilic Aminating Reagent



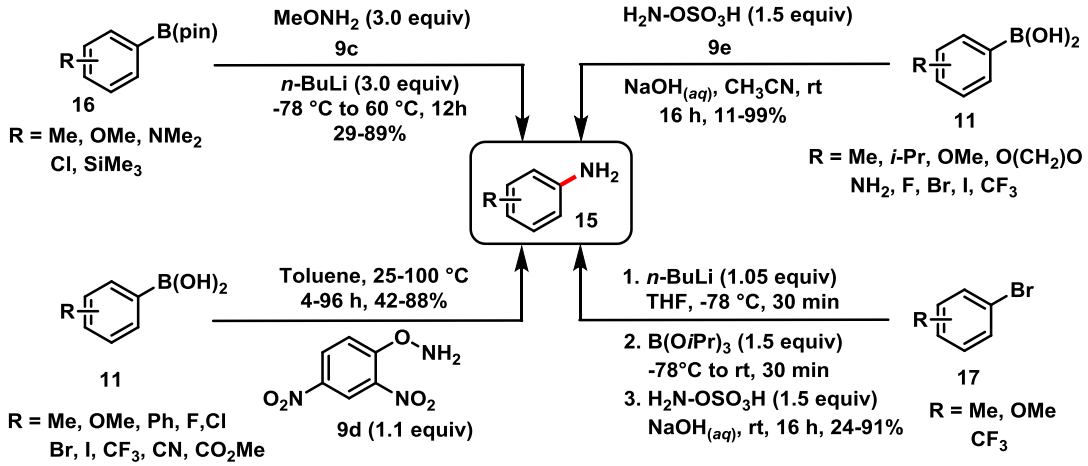
Scheme 5.5: Transition-Metal-Free Electrophilic Amination of Aryl Boron Compounds Using Organic Azides and *O*-Benzoylhydroxylamines



Additionally, the groups of Morken[13] and Kürti[14] independently uncovered a transition-metal-free amination reaction for the direct synthesis of primary aromatic amines **15** (Scheme 5.6). These compounds are generally prepared via a reduction of aromatic nitro compounds using catalytic hydrogenation or metals, another method involves direct substitution of aryl halides with ammonia but high pressure, temperature, and transition-metal-catalysts are usually required to ensure the formation of products.[15] Morken's group has disclosed the direct amination of aryl pinacol boronates **16** with

methoxyamine **9c** as an aminating reagent in presence of *n*-BuLi and THF at -78 °C. Usually common aminating agents such as alkyl azides, chloroamines, and hydroxylamine are found to be unreactive with common boronic esters. The fundamental principle of this transformation involves the nucleophilic addition of aminating reagent to boron compound to form boronate complex, which depends on the Lewis acidity of borane reagent. Enhancement in Lewis acidity of boronate esters can be achieved by the preactivation, converting them into dichloroboranes, difluoroboranes, trialkylboranes, which enables association with the weak Lewis base and facilitates formation of boronate complex. In this case, more nucleophilic lithiated methoxyamine has been utilized as an alternative to the preactivation of pinacol boronates, which facilitated the formation of boronate complex leading to the formation of amination products in good yields. Moreover, chiral alkyl pinacol boronates furnished the corresponding amination products with retention of configuration at the carbon atom, which suggests that 1,2 B-N bond migration is stereospecific.

Scheme 5.6: Transition-Metal-Free Synthesis of Primary Aromatic Amines via Electrophilic Amination of Aryl Boronic Acids and Esters



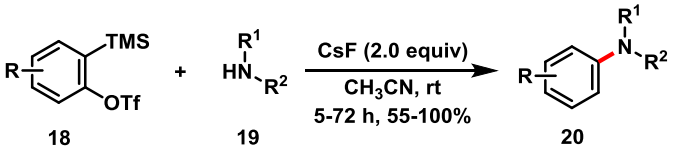
Furthermore, Kürti and coworkers revealed the first metal-free synthesis of primary aryl amines using readily available aryl boronic acids **11** and *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) **9d** as an aminating reagent. Notably, in few examples, the use of Cs_2CO_3 was found to be beneficial for better yields. Density functional theory (DFT) calculations showed that reaction mechanism involves concerted

1,2-aryl migration and *ortho* nitro group in the aminating agent **9d** plays an important role in the 1,2-aryl migration step by lowering the free energy barrier.

In an attempt to expand the scope and utility of electrophilic amination of boronic acids and derivatives, McCubbin and coworkers used inexpensive hydroxylamine-*O*-sulfonic acid (HSA) **9e** as aminating reagent with arylboronic acids leading to a operationally simple method for the synthesis of primary anilines with broad substrate scope.[16] Treatment of arylboronic acids **11** and HAS **9e** in a 1:1 mixture of CH_3CN/1.0 M NaOH(aq) at room temperature resulted in the formation of anilines in good yields. Additionally, synthetic potential of this method has been demonstrated in the one-pot synthesis of primary aromatic amines using aryl halides **17**, proceeding via metal-halogen exchange/amination sequence.

In 2003, Larock and coworkers developed an efficient transition-metal-free method for the N-arylation of primary and secondary amines and sulfonamides by the insertion of arynes into the N-H bonds.[17] Arynes are highly electrophilic reactive intermediates in organic chemistry, having potential applications in the synthesis of complex multisubstituted arenes of synthetic importance.[18] Due to presence of extremely strained carbon-carbon triple bond, arynes undergo facile insertion into various element-element σ-bonds and π-bonds leading to the formation of functionalized 1,2-disubstituted arenes.[19] Even neutral nucleophiles which are unreactive with activated alkynes can add to arynes.

Scheme 5.7: N-Arylation of Amines and Sulfonamides by the Insertion of Arynes into the N-H Bond



Treatment of amines **19** with arynes generated from 2-(trimethylsilyl)aryl triflates **18**[20] using CsF in CH_3CN as solvent under mild reaction conditions furnished the N-arylated products **20** in excellent yields with broad substrate scope (Scheme 5.7).

Interestingly, monoarylation and diarylation of primary amines has easily been achieved by the simple control of the ratio of the reactants.

5.3. Statement of the Problem

As described in previous section, due to the importance of aromatic amines, various transition-metal-catalyzed cross coupling reactions are well-established for the N-arylation of primary and secondary amines; however, the transition-metal-free methods are relatively rare. Interestingly, use of aromatic tertiary amines for the constructions of analogues C_{aryl}-N bond, to the best of our knowledge, has not been reported (in the absence of N-H bond). All previous methods are not applicable for the N-arylation of tertiary amines. In this context, based on our interest in transition-metal-free bond-forming reactions using arynes,[21] we envisioned that the N-arylation of aromatic tertiary amines using aryne as aryl source could result in the constructions of C_{aryl}-N bond. This protocol is highly desirable, because -NMe_2 groups are present in the several donor-acceptor systems and dyes which can be easily N-arylated and useful in the final step modification of tertiary amines. A detailed investigation of the transition-metal-free N-arylation of aromatic tertiary amines using arynes forms the subject of this chapter. The results of our studies revealed an efficient, environmentally benign and facile method for the monoselective N-arylation of aromatic tertiary amine derivatives devoid of metal-catalysts, and detailed mechanistic studies of this arylation process are presented in the following sections.

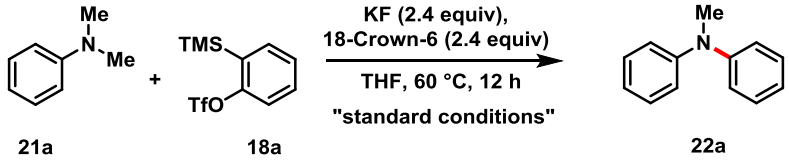
5.4. Results and Discussion

5.4.1. Optimization Studies

The present study was initiated with the treatment of *N*,*N*-dimethylaniline **21a** with the benzyne generated in situ from 2-(trimethylsilyl)aryl triflate **18a** using 2.4 equiv each of KF and 18-crown-6 in THF as solvent at 60 °C. Interestingly, the reaction afforded the N-arylation product *N*-methyl-*N*-phenylaniline **22a** in 33% yield (based on ^{1}H NMR spectroscopy, Table 5.1, entry 1). Use of CsF as fluoride sources was not found to be beneficial, furnishing very less yield of expected product **22a** (entry 2), but the use of tetrabutylammonium fluoride (TBAF) furnished good results (entry 3). Employing 1.0 equiv of $(NH_4)HCO_3$ as additive with TBAF increased yield of desired product to 80% (entry 4). The use of $(NH_4)HCO_3$ as additive with KF and 18-crown-6 improved the

reactivity, leading to the formation of N-arylated product **22a** in 98% yield (95% isolated yield, entry 5). Use of other additives like $NaHCO_3$, H_2O decreased the yield (entries 6, 7). Reducing the reaction temperature and time with $(NH_4)HCO_3$ as additive, lowered the yield of **22a** (entries 8, 9). The present reaction is highly selective for N-arylation, and C-arylated product was not observed. [22]

Table 5.1: Optimization of the Reaction Conditions[a]



21a 18a 22a

entry	variation from the standard conditions[a]	yield of **22a** (%)[b]
1	none	33
2	CsF instead of KF and 18-crown-6, CH_3CN as the solvent	6
3	TBAF instead of KF and 18-crown-6	73[c]
4	$(NH_4)HCO_3$ 1.0 equiv as a additive with TBAF	80[c]
5	*$(NH_4)HCO_3$ 1.0 equiv as a additive with KF and 18-crown-6*	*98 (95)[d]*
6	$NaHCO_3$ 1.0 equiv as a additive with KF and 18-crown-6	67
7	H_2O 1.0 equiv as a additive with KF and 18-crown-6	70
8	Reaction temperature 40 ºC instead of 60 ºC with $(NH_4)HCO_3$ 1.0 equiv as a additive	88
9	Reaction time 6 h instead of 12 h with $(NH_4)HCO_3$ 1.0 equiv as a additive	78

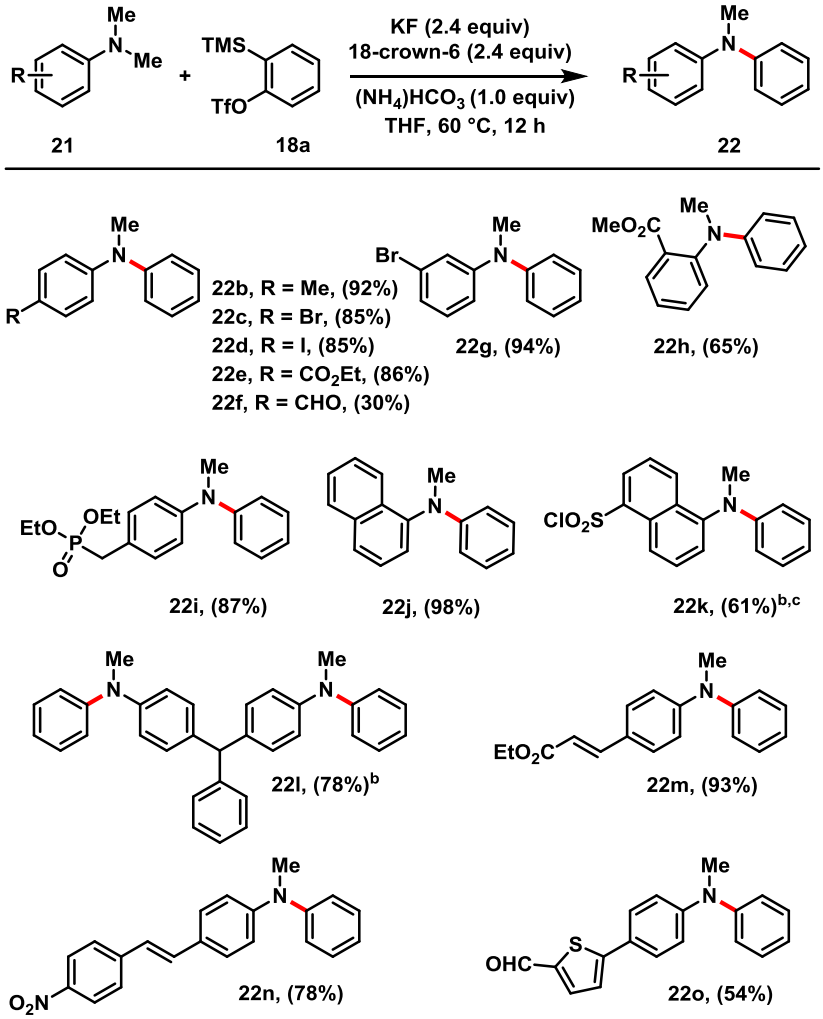
[a]Standard conditions: **21a** (0.25 mmol), **18a** (0.30 mmol), KF (2.4 equiv), 18-crown-6 (2.4 equiv), THF (1.0 mL), 60 °C and 12 h. [b]The yields were determined by ^1H NMR analysis of crude products using CH_2Br_2 as the internal standard. [c]Isolated yield at 0.25 mmol scale. [d]Isolated yield at 0.50 mmol scale in parentheses.

5.4.2. Transition-Metal-Free N-arylation of Aromatic Tertiary Amines Using Arynes: Scope of Tertiary Amines

With the optimized reaction conditions, we then evaluated the substrate scope of this unique transition-metal free N-arylation reaction with variety of *N,N*-dimethyl aniline derivatives (Scheme 5.8). Various *N,N*-dimethyl anilines with electronically different substituents on the aromatic ring of **21** were well tolerated, and the expected diaryl amine derivatives were isolated in good to excellent yields (**22b-h**). Electron-rich aldehydes usually react with two molecules of arynes through the formation of *o*-quinonemethide

intermediate, via the [2 + 2] cycloaddition of aryne with C=O bond of aldehyde followed by thermal electrocyclic ring-opening, leading to the formation of 1:2 addition product, that is 9-arylxanthenes.[23] However, 4-dimethylamino benzaldehyde **21f** still furnished the desired N-arylated product **22f** in 30% yield, lower yield in this case attributed to the electron-withdrawing nature of formyl goup, resulted in the decreased nucleophilicity of aniline.

Scheme 5.8: Substrate Scope of the N-arylation Reaction: Variation of the Tertiary Amines[a]



[a]General conditions: **21** (0.50 mmol), **18a** (0.60 mmol), KF (2.4 equiv), 18-crown-6 (2.4 equiv), THF (2.0 mL), 60 °C and 12 h. Yields of the isolated products are given. [b]Reaction was run on 0.25 mmol scale. [c]The reaction was carried out using 2.0 equiv of **18a** and 4.0 equiv each of KF and 18-crown-6.

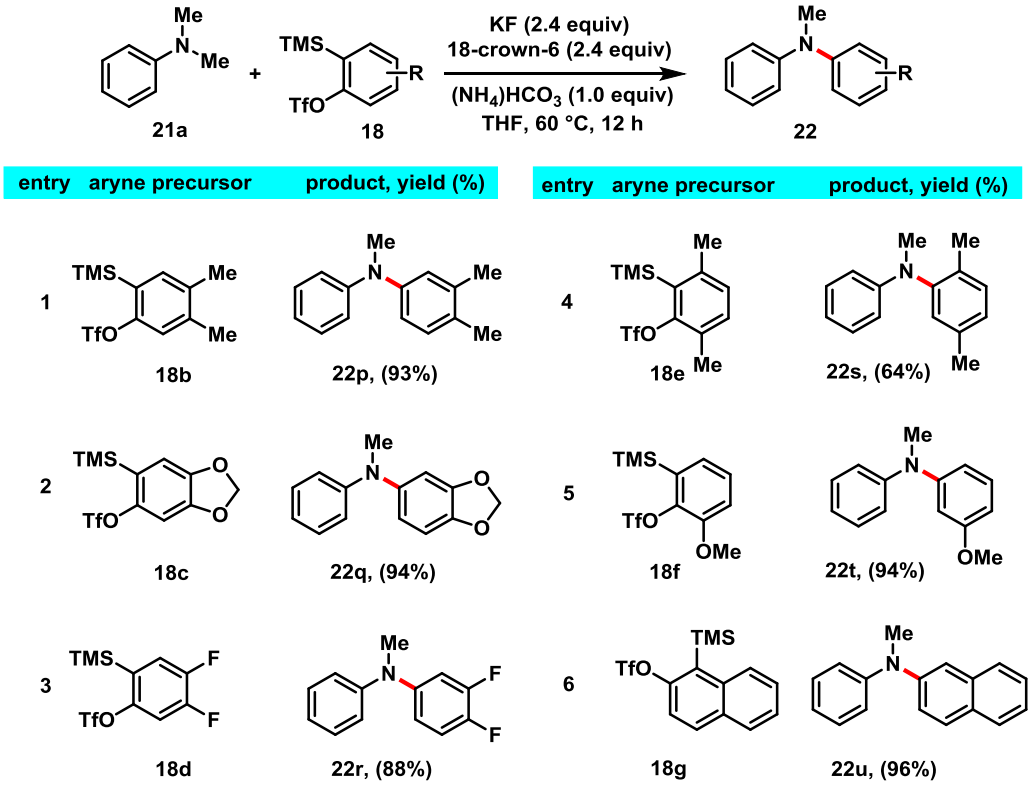
Remarkably, the anilines bearing a halide substitution on aromatic ring are very difficult to survive under transition-metal-catalyzed reaction conditions,[4,5] are well

tolerated under the present N-arylation method (**22c, 22d, 22g**). Moreover, *N*,*N*-dimethyl aniline having a phosphonate group substituent worked well leading to the formation of desired product **22i** in 87% yield, demonstrating the functional group compatibility of this N-arylation protocol. Additionally, the naphthyl substituted amine readily afforded the N-arylated product **22j** in 98% yield. Interestingly, challenging substrates such as dansyl chloride and leucomalachite green dye resulted in the smooth conversion to the desired products in good yields highlighting the versatility of the present method (**22k, 22l**). Gratifyingly, *N*,*N*-dimethyl anilines derived from donor-acceptor systems also delivered the N-arylated product in excellent yields further expanding the scope of the reaction (**22m-o**).

5.4.3. Transition-Metal-Free N-arylation of Aromatic Tertiary Amines Using Arynes: Scope of Arynes

After examining the scope of various tertiary amines in the N-arylation reaction, then we studied the influence of substituent on the arynes (Table 5.2). This arylation reac-

Table 5.2: Substrate Scope of the N-arylation Reaction: Variation of the Aryne Moiety[a]



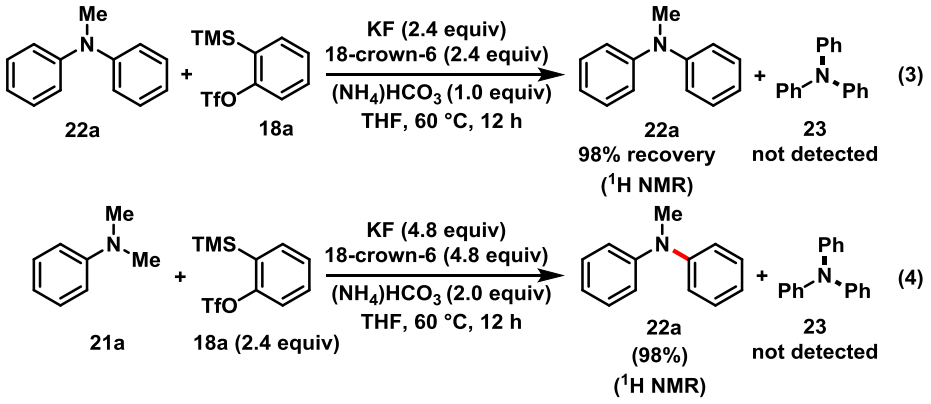
[a]General conditions: **21a** (0.50 mmol), **18** (0.60 mmol), KF (2.4 equiv), 18-crown-6 (2.4 equiv), THF (2.0 mL), 60 °C and 12 h. Yields of the isolated products are given.

tion was found to be efficent with various sustituted arynes. Electron-rich and electron-poor 4,5-disubstituted symmetrical arynes gave easy access to the desired product diphenylamines **22p-r** in excellent yields (entries 1-3). Moreover, the symmetrical 3,6-dimethyl aryne also afforded the N-arylated product **22s** in 64% yield (entry 4). Interestingly, the unsymmetrical arynes, 3-methoxy benzyne and naphthalyne underwent efficient N-arylation to produce the single regioisomers **22t** and **22u** in excellent yields (entries 5, 6).

5.5. Mechanistic Studies

The present N-arylation reaction is highly efficient and monoarylated products were isolated in high yields. Then, we carried out detailed mechanistic studies to probe the mechanism of this N-arylation reaction. To examine the possibility of diarylation of aromatic tertiary amines and the stability of product **22a** under the present reaction conditions, reaction product diphenylamine **22a** was further subjected to N-arylation with aryne precursor **18a** under the optimized reaction conditions (Scheme 5.9, eq 3). In this reaction starting material **22a** was recovered quantitatively.

Scheme 5.9: Experiments to Illustrate Selective Monoarylation[a]



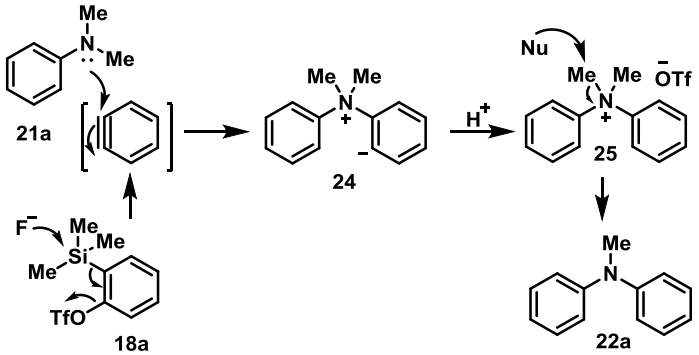
[a]The yields were determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as the internal standard.

Another experiment was carried out using an excess of aryne precursor **2a** (2.4 equiv) and 4.8 equiv of KF and 18-crown-6 with **21a**, the reaction delivered only monoarylated product **3a** in 98% yield (Scheme 5.9, eq 4). In both cases, diarylated product **23** was not detected. These experiments confirm that under the optimized reaction conditions present arylation reaction is highly monoselective. Possibly, the lone pair of electrons on nitrogen in **21a** is easily available for nucleophilic attack on aryne.

However, in the case of diphenylamine **22a**, since the lone pair of electrons on nitrogen is delocalized between two benzene rings, it may not be available for nucleophilic attack on aryne.

The mechanistic rationale for this N-arylation reaction is explained in Scheme 5.10 using **21a** and **18a** as the representative substrates. Initial nuclephilic addition of *N,N*-dimethylaniline **21a** to the aryne generated from **18a** leads to the formation of zwitterionic intermediate **24**, which is protonated to form the dimethyl diphenyl ammonium salt **25**. Subsequent demethylation of the intermediate **25** induced by the basic reaction medium or the fluoride ion delivers the desired product **22a**.

Scheme 5.10: Plausible Reaction Mechanism



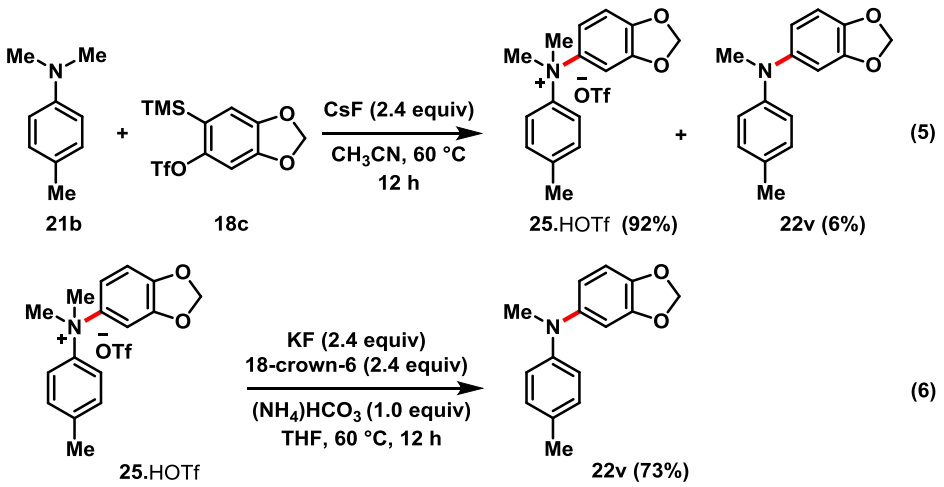
5.5.1. Isolation of the Key Intermediate

During optimization of reaction conditions, we observed that use of CsF as fluoride source in CH_3CN solvent furnished the product **22a** in only 6% yield (Table 5.1, entry 2). Careful analysis of ^{1}H NMR of the crude reaction mixture revealed that both the starting materials **21a** and **18a** were fully consumed under the reaction conditions. Due to the absence of characteristics peaks in ^{1}H NMR, information was insufficient to find the reason for this reactivity. To resolve this issue, substituted tertiary amines **21b** and aryne precursor **18c** were subjected under the CsF reaction conditions (Scheme 5.11, eq 5). Surprisingly, the reaction resulted in a smooth conversion to the quaternary ammonium salt **25.**HOTf[24] in 92% yield along with 6% of the N-arylated product **22v**.

We proposed the formation of dimethyl diphenyl ammonium salt intermediate **25** in the reaction course. A strong indication for the presence of **25** comes from the fact that the reaction of salt **25.**HOTf under the optimized reaction conditions readily afforded the desired arylated product **22v** in 73% yield (eq 6). This experiment confirms that **25** is the

intermediate in the reaction, which on demethylation leads to the formation of N-arylated product. In presence of CsF in CH_3CN solvent, salt **25.**HOTf was formed in quantitative amount. However, demethylation process was not efficient to complete the reaction.

Scheme 5.11: Experiments to Confirm **25**.HOTf as the Intermediate

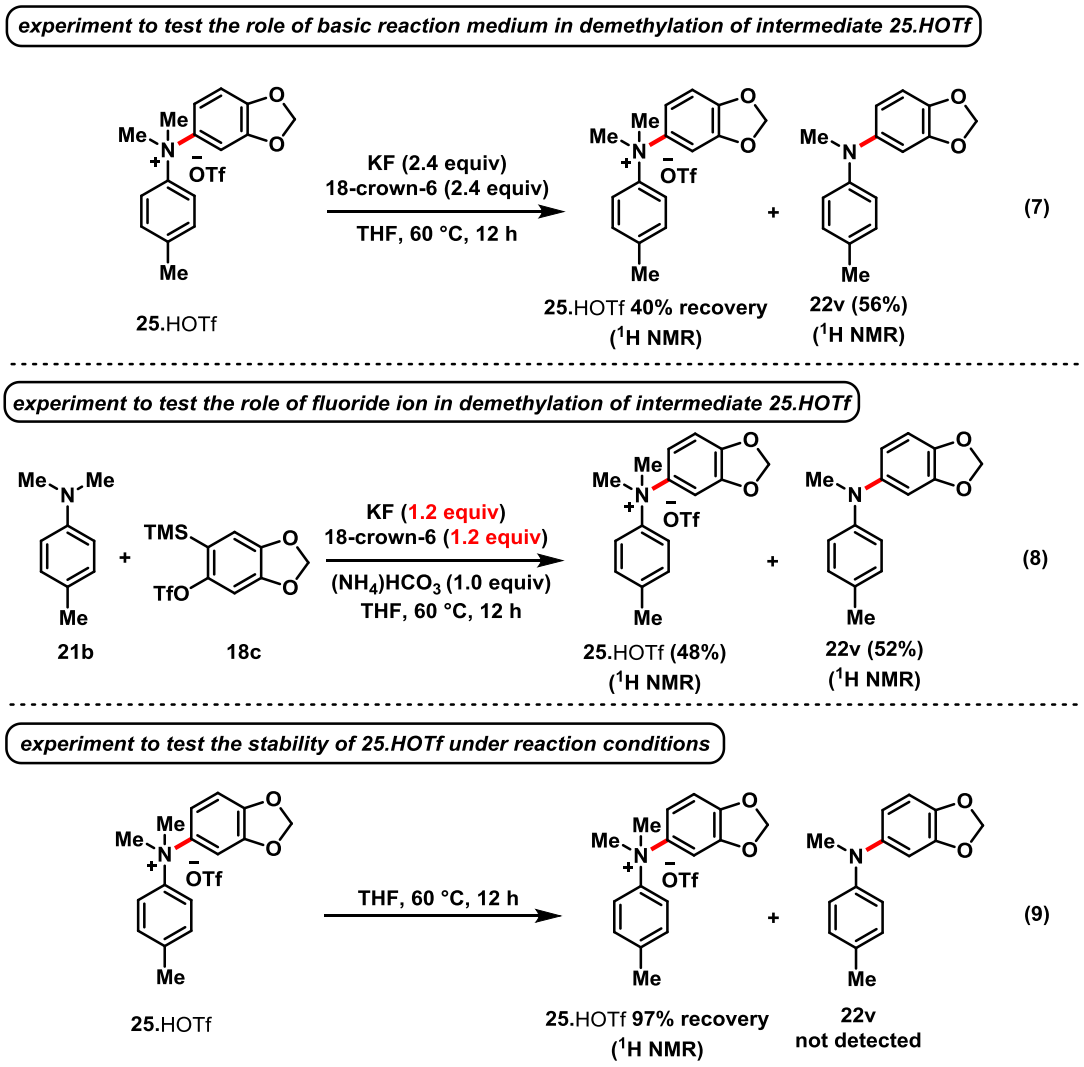


5.5.2. Experiments to Realize the Role of Fluoride Ion and Basic Reaction Medium in Demethylation of Intermediate 25.HOTf

Next, we carried out series of experiments to realize the role of fluoride ion and basic reaction medium in demethylation process of intermediate **25.**HOTf. For these experiments, the reaction was carried out in the absence of additive $(NH_4)HCO_3$. Treatment of the salt **25.**HOTf in presence of 2.4 equiv each of KF and 18-crown-6 at 60 °C for 12h resulted in the conversion to the N-arylated product **22v** in 56% yield and 40% of **25.**HOTf was unreacted (Scheme 5.12, eq 7). This experiment signifies the role of base in demethylation process. In the absence of $(NH_4)HCO_3$ additive, conversion to arylated product **22v** was relatively low. To uncover the role of fluoride ion in demethylation of salt **25.**HOTf, the reaction was performed by treating **21b** with aryne precursor **18c** in the presence of 1.2 equiv each of KF and 18-crown-6 at 60 °C for 12h (eq 8). The reaction afforded N-arylated product **22v** in 52% yield along with 48% of **25.**HOTf. This experiment clearly indicates the role of fluoride source in the demethylation process, reduced amount of fluoride source decreased the conversion of **25.**HOTf to **22v**. Finally, in order to know the stability of salt **25.**HOTf under the reaction conditions and to exclude the possibility of counteranion triflate has any role in demethylation process, the salt **25.**HOTf was dissolved in THF solvent and kept for

heating at 60 °C for 12 h (eq 9). This reaction returned **25.**HOTf quantitatively without formation of N-arylated product **22v**. This experiment shows that **25.**HOTf is stable under reaction conditions and the counteranion triflate has no role in the demethylation of intermediate **25.**HOTf. From these experiments, it is reasonable to assume that combined effect of both fluoride ion and basic reaction medium playing a vital role in demethylation of salt **25.**HOTf.

Scheme 5.12: Experiments to Realize the Demethylation Process of Intermediate **25**.HOTf[a]

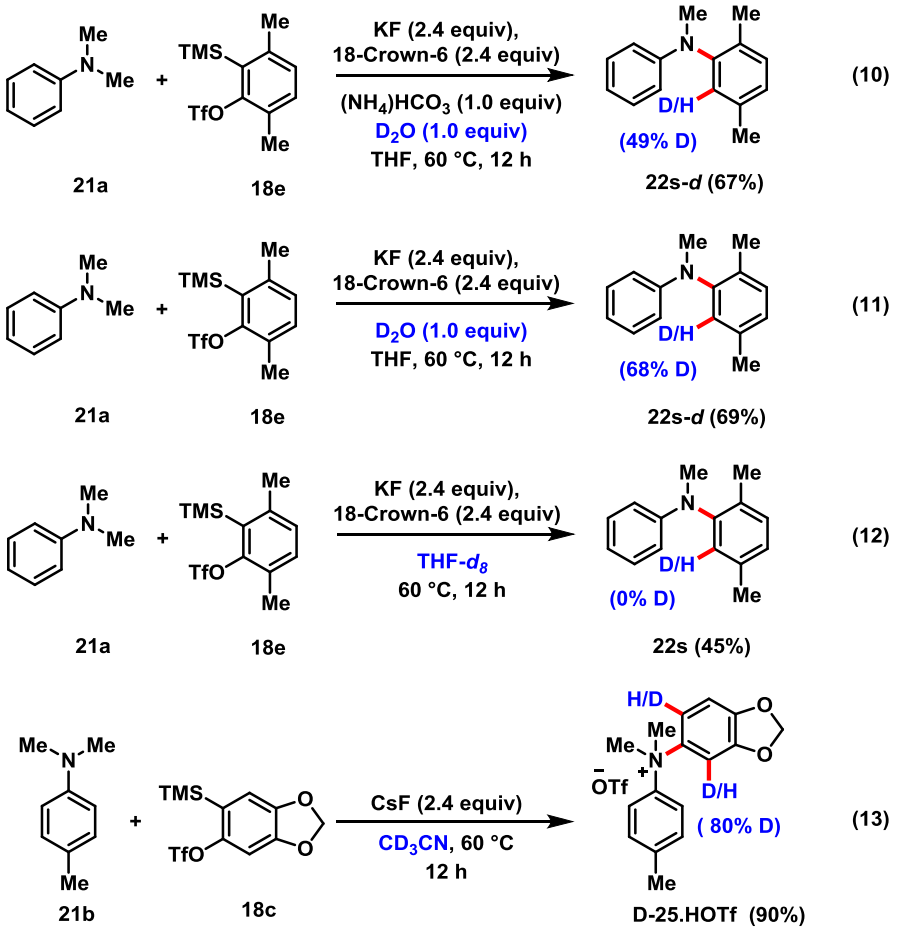


[a]The yields were determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as the internal standard.

5.5.3. Experiments to Determine the Role of Additives in the Protonation of Zwitterionic Intermediate 24: Deuterium Labelling Experiments

In mechanism we proposed protonation of zwitterionic intermediate **24** to form the dimethyl diphenyl ammonium salt **25**. During the optimization of reaction conditions, we realized that use of additives improved the yield of N-arylated product **22a** (Table 5.1, entries 4, 5). We carried out series of experiment using deuterated additives and solvents to probe the role of additives in the protonation of zwitterionic intermediate **24**.

Scheme 5.13: Deuterium Labelling Experiments



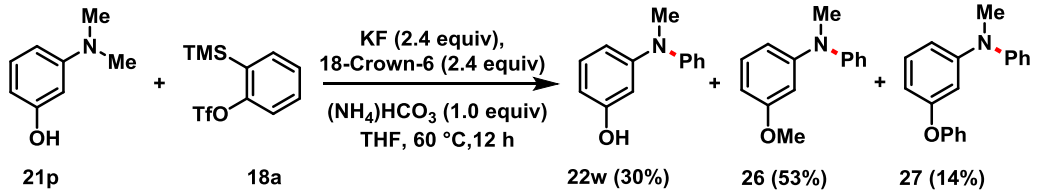
In an initial experiment, we subjected tertiary amine **21a** and aryne precursor **18e** under optimized reaction conditions with D_2O as an additive, desired N-arylated product **22s-*d*** was formed in 67% yield with 49% deuterium incorporation at the 2-position (Scheme 5.13, eq 10). Moreover, treatment of **21a** and **18e** in presence of fluoride source using only D_2O as the additive furnished the expected product **22s-*d*** in 69% yield with 68% deuterium incorporation (eq 11). Result of these experiments tends to indicate that,

additive is useful in the protonation of zwitterionic intermediate **24**, and use of additive furnished the N-arylated products **22** in good yields (Scheme 5.8). Additionally, the reaction of **21a** and **18e** was performed in the absence of additive with fluoride source and THF-d_8 as a solvent, N-arylated product **22s** was isolated in 45% yield without deuterium incorporation (eq 12). Another reaction was carried out using **21b** and **18c** in presence of CsF and CD_3CN as a solvent, which furnished the quaternary ammonium salt **D-25.**HOTf in 90% yield with 80% deuterium incorporation (eq 13). These two experiments suggest that only CH_3CN solvent has role in the protonation of zwitterionic intermediate **24**, therefore dimethyl diphenyl ammonium salt **25** formation was almost quantitative under this reaction condition.

5.5.4. Intramolecular Competition Experiment

Furthermore, we carried out an intramolecular competition experiment, to test the possibility of the competing O-arylation under the present reaction conditions. The amine **21p** having both functionalities (-NMe_2 and phenolic -OH) was treated with **18a** under optimized reaction conditions (Scheme 5.14). The reaction resulted in the formation of three products, N-arylated product **22w** was isolated in 30% yield along with O-methylated product **26** in 53% yield, which is possibly formed by the demethylation of intermediate **25** by the phenol **22w**. Another product **27** was formed in 14% yield via the O-arylation of initially formed N-arylated product **22w**. In overall process, N-arylation of aromatic tertiary amines was rapid than O-arylation.

Scheme 5.14: N-arylation *vs* O-arylation



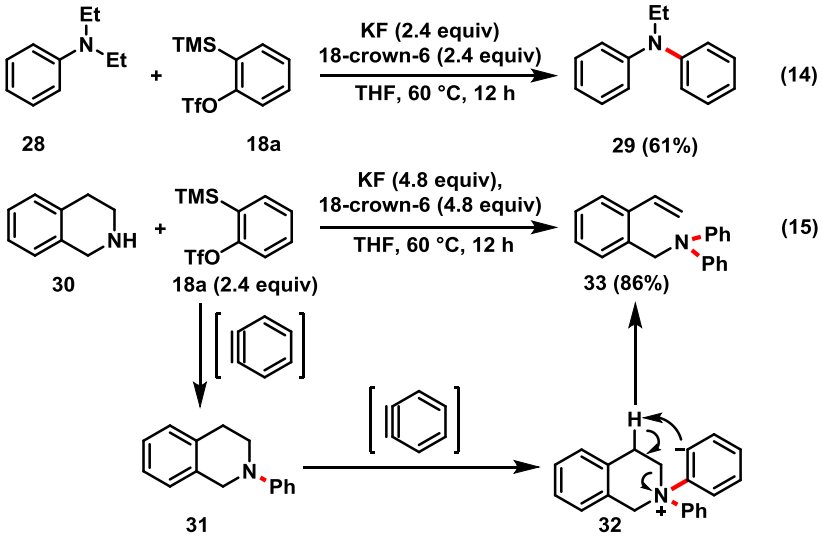
21p 18a 22w (30%) 26 (53%) 27 (14%)

5.5.5. Arylation of Tertiary Amines in the Absence of Additive via an Intramolecular Proton Transfer

This N-arylation reaction is not limited to *N*,*N*-dimethyl aniline derivatives, in the absence of additive other tertiary amines underwent efficient N-arylation via an intramolecular proton transfer. Treatment of *N*,*N*-diethyl aniline **28** with **18a** in presence of fluoride source in THF solvent at 60 °C resulted in the formation of N-arylated product

29 in 61% yield presumably by the expulsion of a molecule of ethylene (Scheme 5.15, eq 14). Even more interestingly, treatment of tetrahydroisoquinoline **30** with 2.4 equiv of aryne precursor **18a** in the presence fluoride source readily underwent efficient cascade arylation leading to the synthesis of styrene derivative **33** in 86% yield (eq 15). This reaction proceeds via the initial N-H insertion of aryne to generate the N-arylamine **31**, nucleophilic addition of **31** to the excess aryne offers the zwitterionic intermediate **32**. In absence of additive for the protonation, zwitterion **32** underwent intramolecular proton transfer followed by the ring opening to furnish the final product **30**.

Scheme 5.15: Arylation of *N*,*N*-Diethyl Aniline and Tetrahydroisoquinoline



5.6. Conclusion

In conclusion, we have developed a highly monoselective and transition-metal-free N-arylation of aromatic tertiary amines using arynes leading to the formation of functionalized diaryl amine derivatives in good to excellent yield.[25] High yields, broad substrate scope, wide range of functional group tolerance especially with donor-acceptor systems, dyes, halogen containing substrate and clear evidences for the mechanism are the noteworthy features of the present reaction.

5.7. Experimental Details

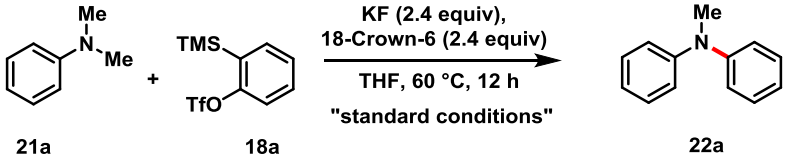
5.7.1. General Information

General information about experimental details is given in Section 2.9.1, Chapter 2. 18-Crown-6 was recrystallized from dry CH_3CN and KF was dried by heating at 110 °C for 12 h and left to cool under argon. The 2(trimethylsilyl)phenyl trifluoromethane sulfonate **18a** and the other symmetric and unsymmetric aryne precursors (**18b-g**) were synthesized following literature procedure.[20] The *N*,*N*-dimethylaniline derivatives **21a-h**, **21j-l**, as well as the tertiary amines **22p**, **28** and **30** were purchased from either from Sigma Aldrich or Alfa Aesar and used as received, without any further purification. $(NH_4)HCO_3$ was purchased from local sources and used as received, without any further purification.

Infrared spectra were recorded on a Perkin-Elmer 1615 FT Infrared Spectrophotometer Model 60B. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS data were recorded either on a Thermo Scientific Q-Exactive, Accela 1250 pump or using Waters SYNAPT G2 High Definition Mass Spectrometry System.

5.7.2. General Procedure for the Optimization of Reaction Conditions

Scheme 5.16: Optimization of Reaction Conditions

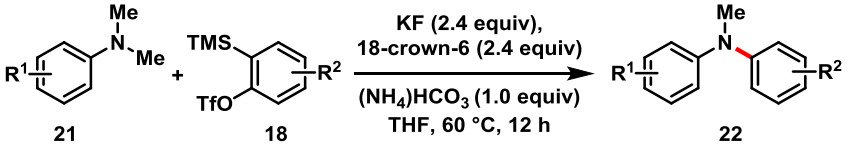


To a flame-dried screw-capped tube equipped with a magnetic stir bar were added 18-crown-6 (0.159 g, 0.60 mmol), KF (0.035 g, 0.60 mmol) and $(NH_4)HCO_3$ (0.020 g, 0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (1.0 mL) under argon atmosphere and then to the stirring solution were added the *N*,*N*-dimethylaniline **21a** (0.032g, 33 μL, 0.25 mmol) and 2-(trimethylsilyl) phenyl trifluoromethane sulfonate **18a** (0.090 g, 73 μL, 0.30 mmol) at room temperature. Then screw-capped tube was kept in a pre-heated oil bath at 60 °C for 12 h. The reaction mixture was cooled and then diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was

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

5.7.3. General Procedure for the Selective Monoarylation of Aromatic Tertiary Amines

Scheme 5.17: Synthesis of *N*-Methyl-*N*-phenylaniline Derivatives



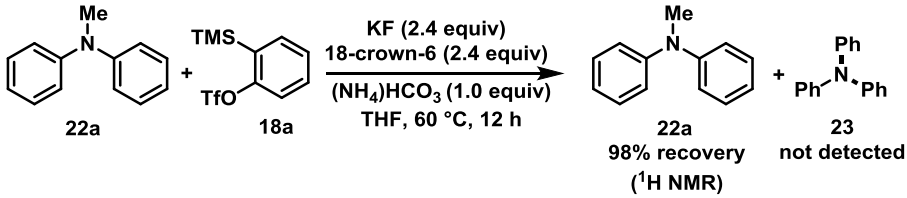
To a flame-dried screw-capped test tube equipped with a magnetic stir bar were added 18-crown-6 (0.317 g, 1.2 mmol), KF (0.070 g, 1.2 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol).Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere and then to the stirring solution were added the tertiary amine **21** (0.50mmol) and the aryne precursor **18** (0.60 mmol) at room temperature. Then the screw-capped tube was kept in a pre-heated oil bath at 60 °C for 12 h. The reaction mixture was subsequently cooled. The solvent was evaporated and the residue on column chromatography afforded *N*-methyl-*N*-phenylaniline derivative **22**.

5.8. Mechanistic Experiments

5.8.1. Experiments to Show Selective Monoarylation

Reaction of Product 22a with Aryne

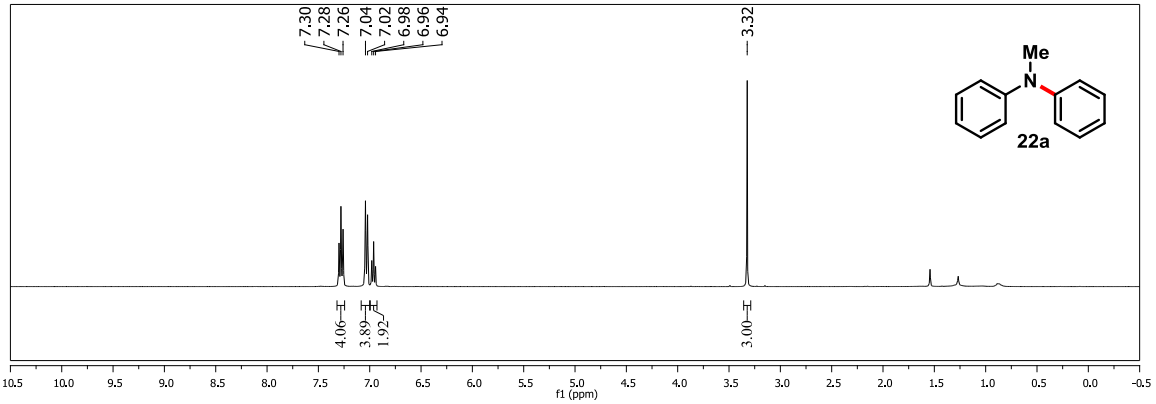
Scheme 5.18: Reaction of Product **22a** with Aryne Generated from **18a**



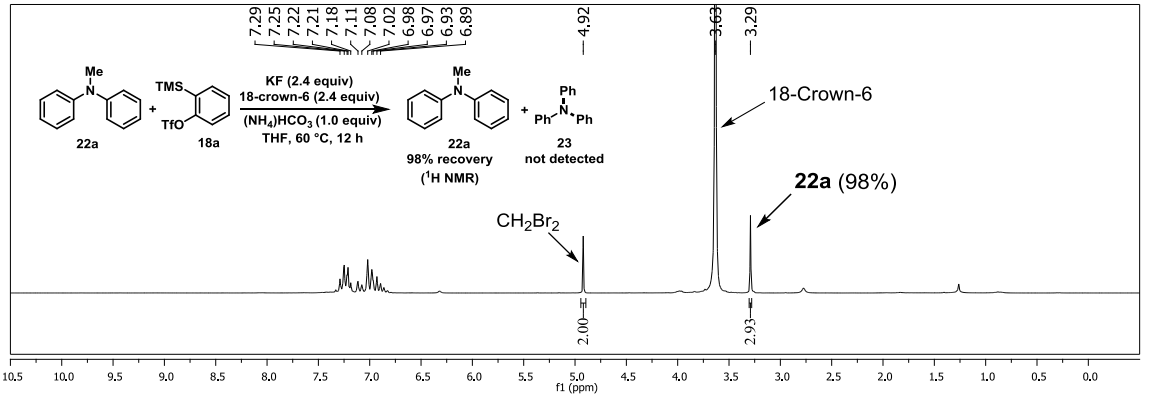
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.158 g, 0.60 mmol), KF (0.035 g, 0.60 mmol) and $(NH_4)HCO_3$ (0.020 g, 0.25 mmol).Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (1.0 mL) under argon atmosphere. To the resulting stirring solution at room temperature were added *N*-methyl-*N*-phenylaniline **22a** (0.046 g, 0.25 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18a** (0.089

g, 73 µL, 0.30 mmol) . Then the reaction mixture kept in pre-heated oil bath at 60 °C for 12 h. The reaction mixture cooled and diluted with CH_2Cl_2 (2.0 mL) and filtered through silica pad and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. ^{1}H NMR spectrum of crude reaction mixture showed 98% recovery of the starting material *N*-methyl-*N*-phenylaniline **22a**.

^{1}H NMR Spectrum of *N*-Methyl-*N*-phenylaniline 22a ($CDCl_3$)

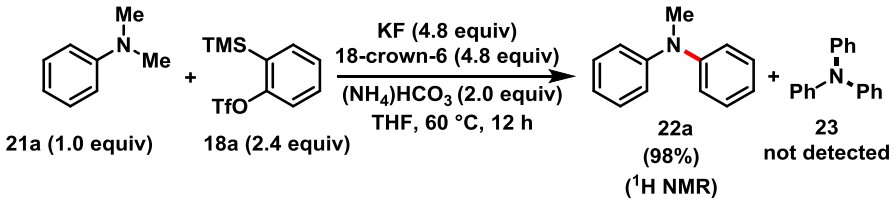


^{1}H NMR Spectrum of Crude Reaction Mixture after 12 h ($CDCl_3$)



Reaction of N, N-Dimethyl Aniline 21a with Excess of Aryne

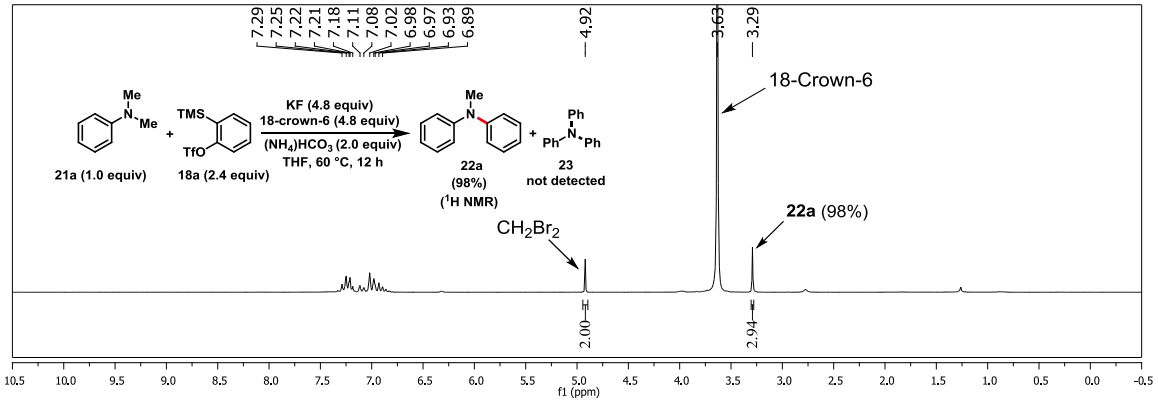
Scheme 5.19: Reaction of Product *N*, *N*-dimethyl aniline **21a** with Excess Aryne Generated from **18a**



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.317g, 1.20 mmol), KF (0.070 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040

g, 0.50 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere. To the resulting stirring solution at room temperature were added *N*,*N*-dimethylaniline **21a** (0.030 g, 32 µL, 0.25 mmol), and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18a** (0.179 g, 146µL, 0.60 mmol) . Then the reaction mixture kept in preheated oil bath at 60 °C for 12 h. The reaction mixture cooled and diluted with CH_2Cl_2 (2.0 mL) and filtered through silica pad and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. ^{1}H NMR spectrum of crude reaction mixture recorded showed 98% formation of *N*-methyl-*N*-phenylaniline **22a** and no formation of the diarylated product **23**.

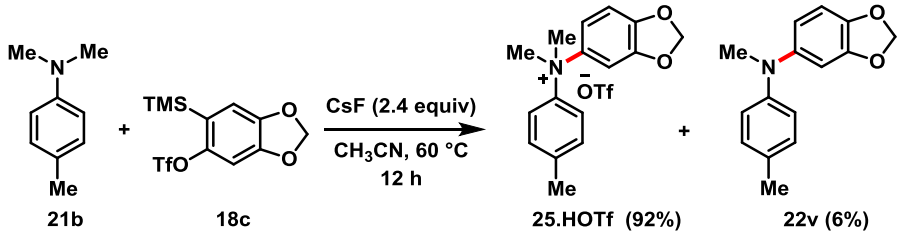
^{1}H NMR Spectrum of Crude Reaction Mixture after 12 h ($CDCl_3$)



5.8.2. Experiments to Show 25.HOTf as Intermediate in the Reaction

Isolation of Key Intermediate

Scheme 5.20: Isolation of Intermediate **25.**HOTf

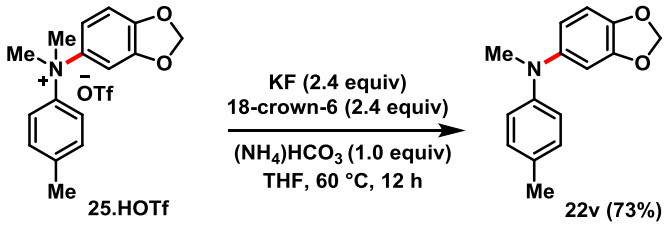


To a flame-dried screw-capped tube equipped with a magnetic stir bar was added dry CsF (0.092 g, 0.60 mmol) and then CH_3CN (1.0 mL) under argon atmosphere. To the stirring solution *N*,*N*,4-trimethylaniline **21b** (0.034 g, 37 µL, 0.25 mmol) and 6-(trimethyl

silyl)benzo[*d*][1,3]dioxol-5-yltrifluoromethanesulfonate **18c** (0.102 g, 0.3 mmol) were added at room temperature. Then tube was kept in a preheated oil bath at 60 °C for 12 h. The reaction mixture cooled and diluted with MeOH (2.0 mL) and filtered through silica pad and eluted with MeOH (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. ^{1}H NMR spectrum of crude reaction mixture showed 92% yield of *N*,*N*-dimethyl-*N*-(*p*-tolyl)benzo[*d*][1,3]dioxol-4-aminium salt **25**.HOTf along with 6% formation of the arylated product **22v**. Moreover, column chromatography (MeOH) afforded *N*,*N*-dimethyl-*N*-(*p*-tolyl)benzo[*d*][1,3]dioxol-4-ammonium salt **25**.HOTf as a brown solid (0.094 g, 92%).

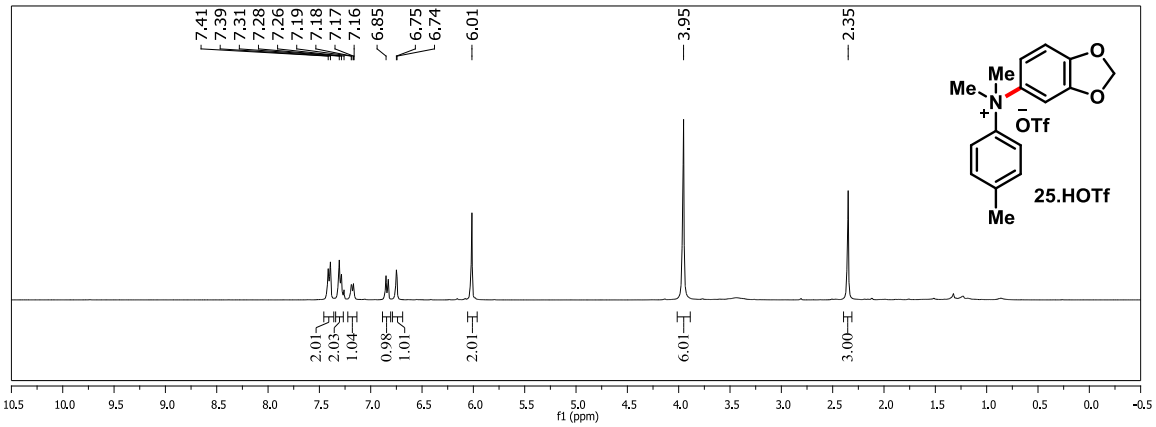
Conversion of Key Intermediate to N-Arylated Product

Scheme 5.21: Conversion of Intermediate **25.**HOTf to **22v** under Optimized Reaction Conditions

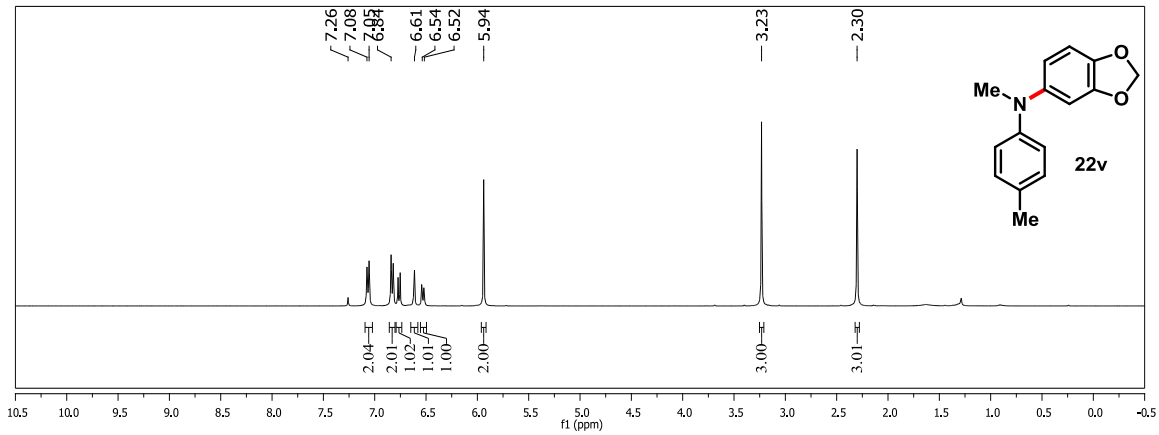


To a flame-dried round bottom flask equipped with a magnetic stir bar were added *N*,*N*-dimethyl-*N*-(*p*-tolyl)benzo[*d*][1,3]dioxol-4-aminium salt **25.**HOTf (0.102 g, 0.25 mmol), 18-crown-6 (0.158 g, 0.60 mmol), KF (0.035 g, 0.60 mmol) and $(NH_4)HCO_3$ (0.020 g, 0.25 mmol) at room temperature. Then the mixture was dissolved in THF (1.0 mL) under argon atmosphere and round bottom flask kept in a pre-heated oil bath at 60 °C for 12 h. The reaction mixture cooled and diluted with MeOH (2.0 mL) and filtered through silica pad and eluted with MeOH (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. ^{1}H NMR analysis of crude reaction mixture showed that **22v** was formed in 73% yield and **25.**HOTf was recovered in 24% yield. The crude residue on column chromatography (Pet. ether/DCM = 90/10) afforded *N*-methyl-*N*-(*p*-tolyl)benzo[*d*][1,3]dioxol-5-amine afforded **22v** as colorless oil (0.043 g, 70%).

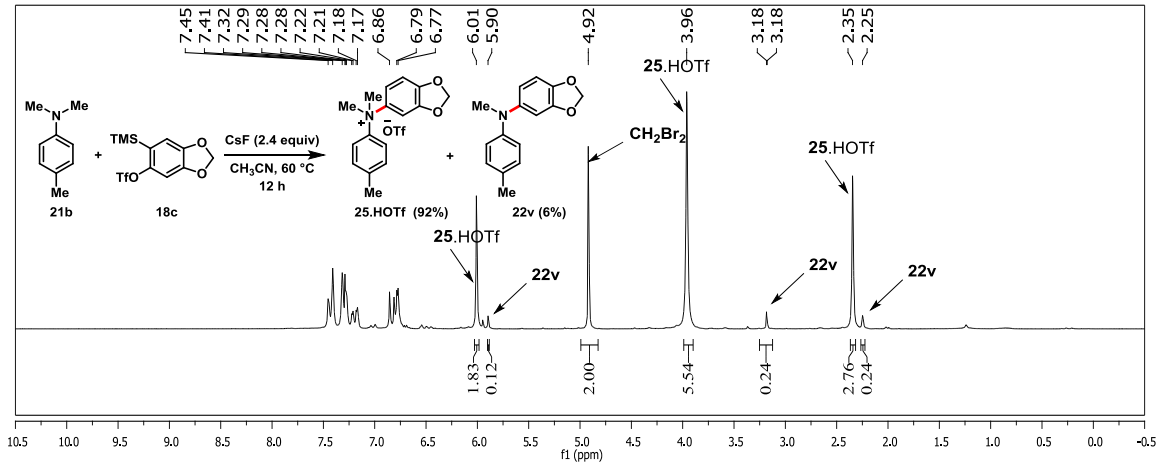
^{1}H NMR Spectrum of 25.HOTf ($CDCl_3$)



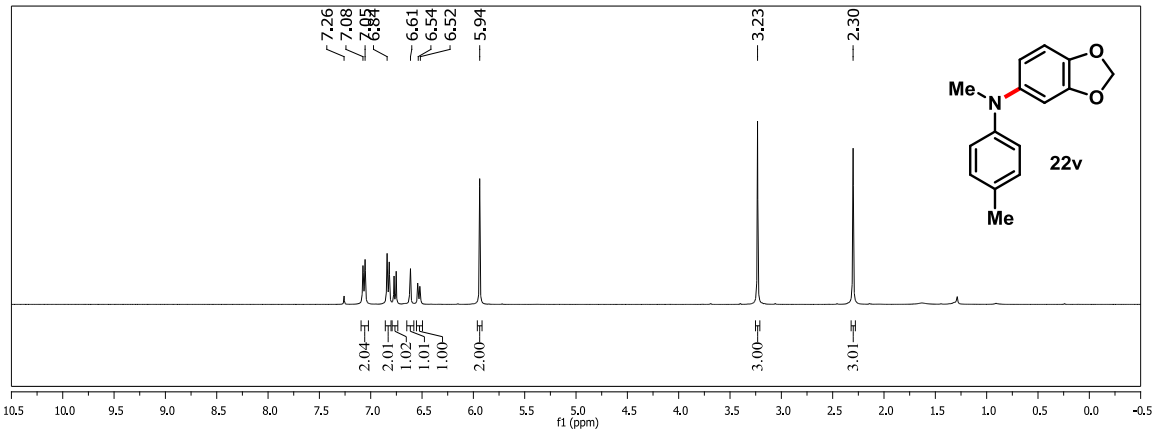
^{1}H NMR Spectrum of 22v ($CDCl_3$)



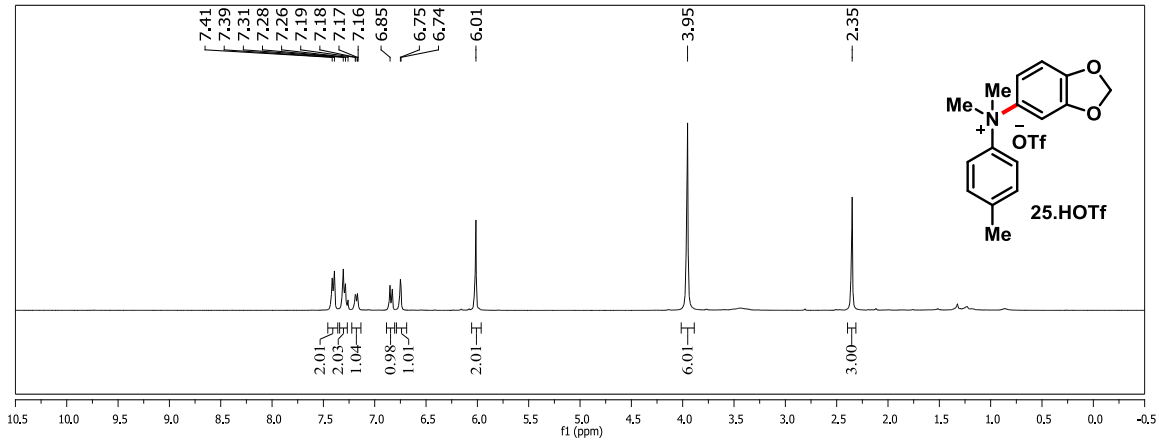
^{1}H NMR of Crude Reaction Mixture of Scheme 5.20 after 12 h ($CDCl_3$)



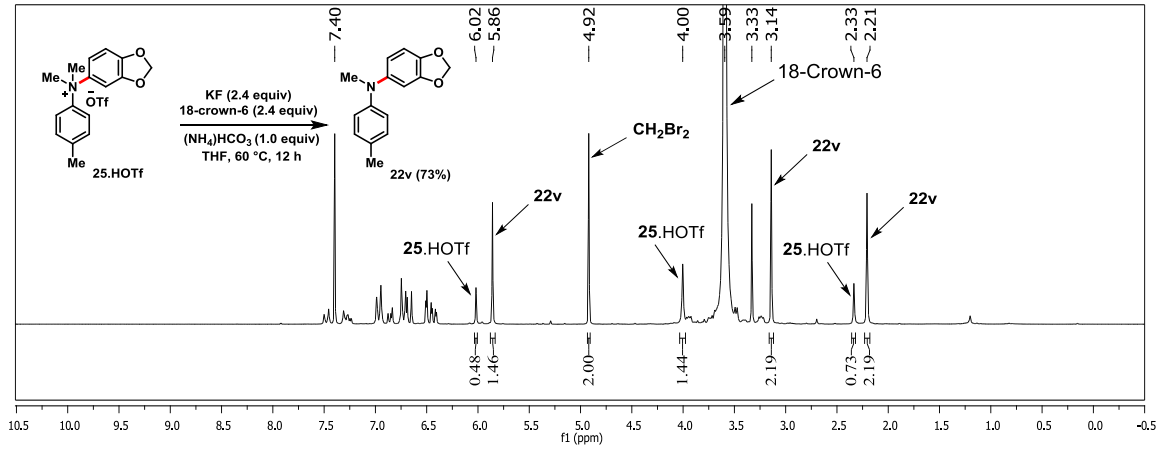
^{1}H NMR Spectrum of 22v ($CDCl_3$)



^{1}H NMR Spectrum of 25.HOTf ($CDCl_3$)



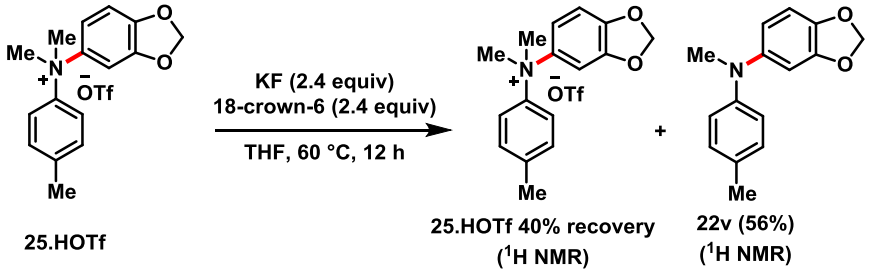
^{1}H NMR Spectrum of crude Reaction Mixture of Scheme 5.21 after 12 h ($CDCl_3$)



5.8.3. Experiments to Show the Role of Fluoride Ion and Basic Reaction Medium in Demethylation of Intermediate 25.HOTf

Role of $(NH_4)HCO_3$

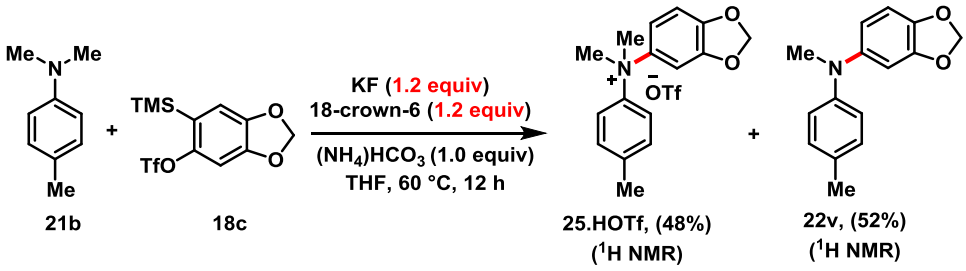
Scheme 5.22: Reaction Carried out in the Absence of **$(NH_4)HCO_3$**



To a flame-dried round bottom flask equipped with a magnetic stir bar were added *N*,*N*-dimethyl-*N*-(*p*-tolyl)benzo[*d*][1,3]dioxol-4-aminium salt **25**.HOTf (0.102 g, 0.25 mmol), 18-crown-6 (0.158 g, 0.60 mmol), KF (0.035 g, 0.60 mmol) at room temperature. Then the mixture was dissolved in THF (1.0 mL) under argon atmosphere and round bottom flask kept in a pre-heated oil bath at 60 °C for 12 h. The reaction mixture cooled and diluted with MeOH (2.0 mL) and filtered through silica pad and eluted with MeOH (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. ^{1}H NMR spectrum of crude reaction mixture showed that **22v** was formed in 56% yield and 40% of **25**.HOTf was recovered.

Role of Fluoride source

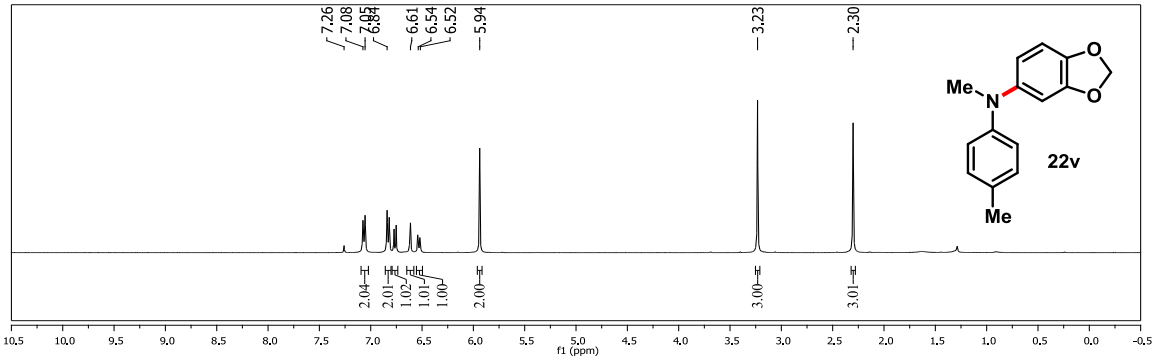
Scheme 5.23: Experiment to Test the Role of Fluoride Source in Demethylation of **25.**HOTf



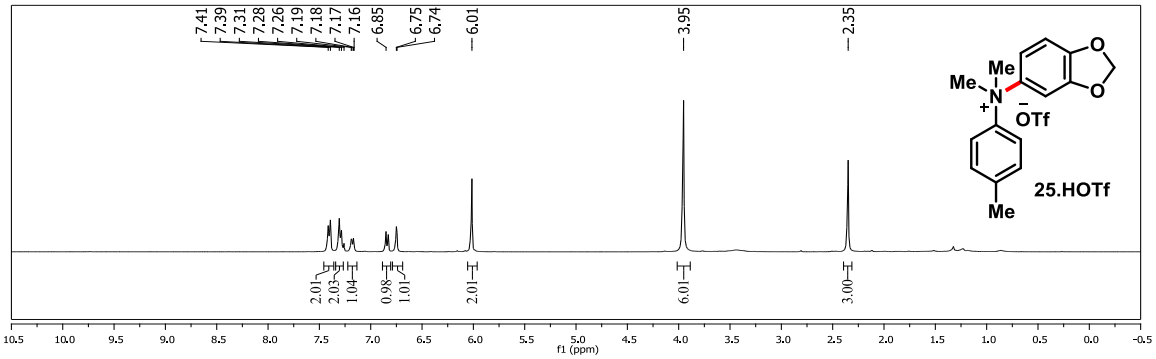
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.079 g, 0.30 mmol), KF (0.017 g, 0.30 mmol) and $(NH_4)HCO_3$ (0.020 g, 0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (1.0 mL) under argon atmosphere. To the

resulting stirring solution at room temperature was added *N*,*N*,4-trimethylaniline **21b** (0.034 g, 37 µL, 0.25 mmol) and 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yltrifluoromethanesulfonate **18c** (0.102 g, 0.3 mmol). Then the reaction mixture kept in pre-heated oil bath at 60 °C for 12 h. The reaction mixture cooled and diluted with MeOH (2.0 mL) and filtered through silica pad and eluted with MeOH (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. ^{1}H NMR spectrum of crude reaction mixture showed that **22v** was formed in 52% yield along with 48% of **25**.HOTf.

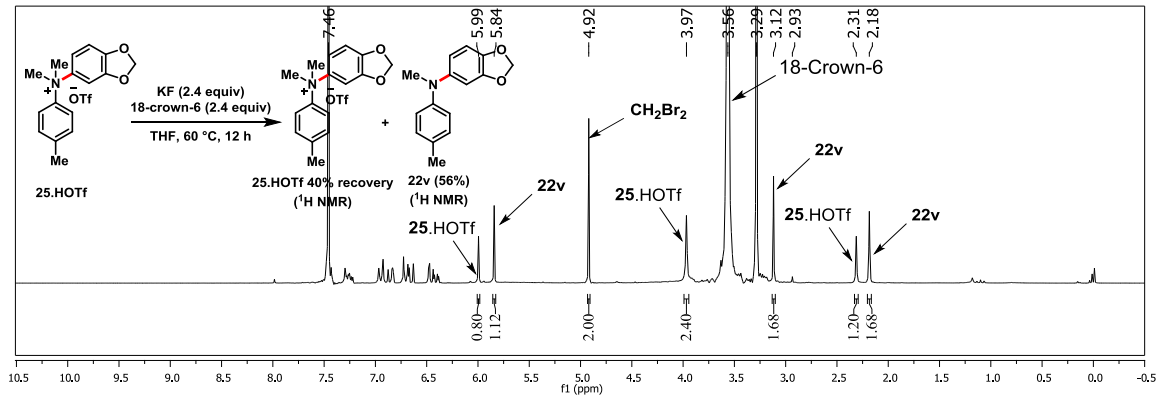
^{1}H NMR Spectrum of 22v ($CDCl_3$)



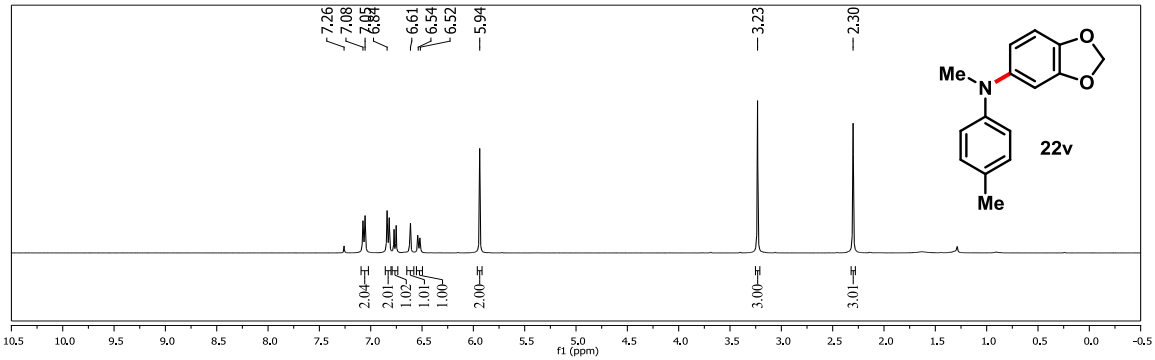
^{1}H NMR Spectrum of 25.HOTf ($CDCl_3$)



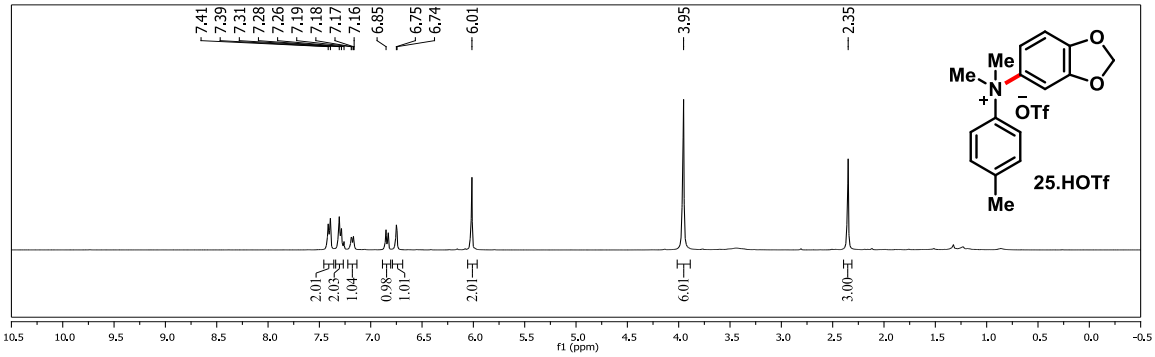
^{1}H NMR Spectrum of crude Reaction Mixture of Scheme 5.22 after 12 h ($CDCl_3$)



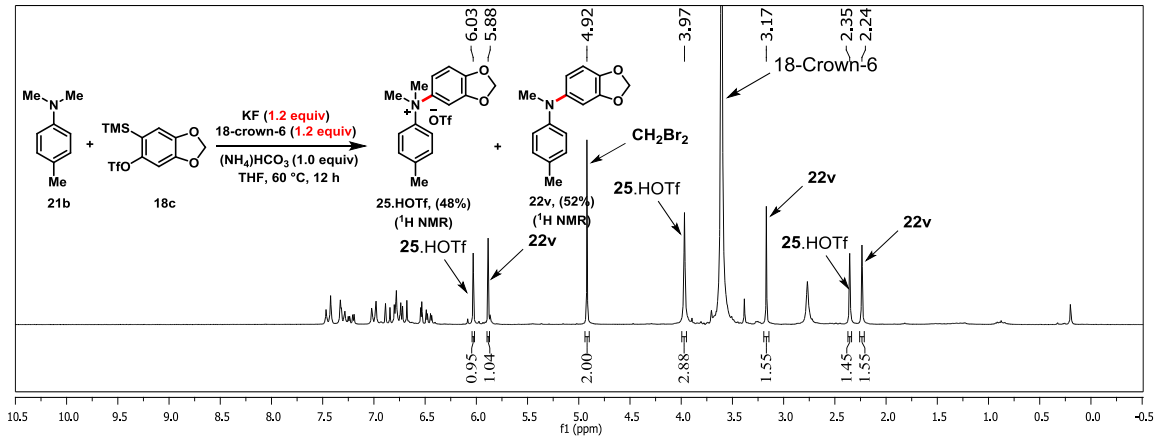
^{1}H NMR Spectrum of 22v ($CDCl_3$)



^{1}H NMR Spectrum of 25.HOTf ($CDCl_3$)

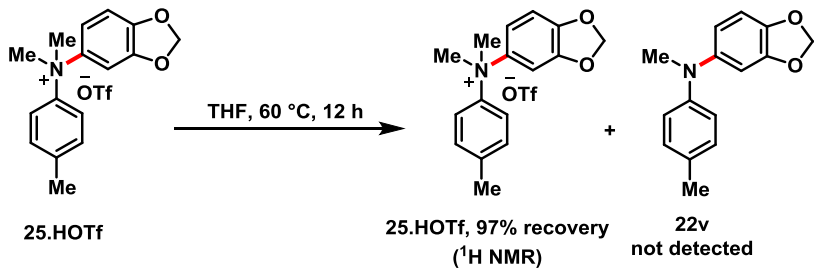


^{1}H NMR Spectrum of Crude Reaction Mixture of Scheme 5.23 after 12 h ($CDCl_3$)



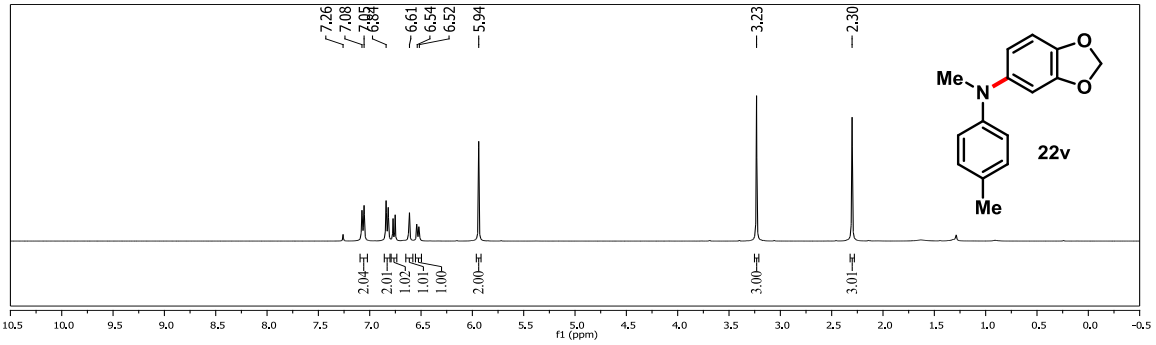
Stability of Key Intermediate under Reaction Conditions

Scheme 5.24: Experiment to Test the Stability of **25.**HOTf under Reaction Conditions

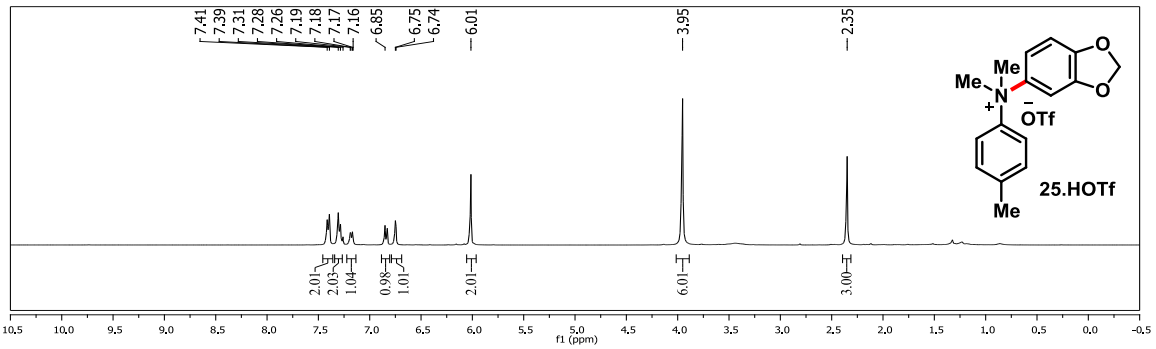


To a flame-dried round bottom flask equipped with a magnetic stir bar, *N*,*N*-dimethyl-*N*-(*p*-tolyl)benzo[*d*][1,3]dioxol-4-aminium salt **25**.HOTf (0.102 g, 0.25 mmol) was dissolved in THF (1.0 mL) under argon atmosphere at room temperature. Then the reaction mixture kept in pre-heated oil bath at 60 °C for 12 h. The reaction mixture cooled and diluted with MeOH (2.0 mL) and filtered through silica pad and eluted with MeOH (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard. ^{1}H NMR spectrum of crude reaction mixture showed that 97% **25**.HOTf unreacted.

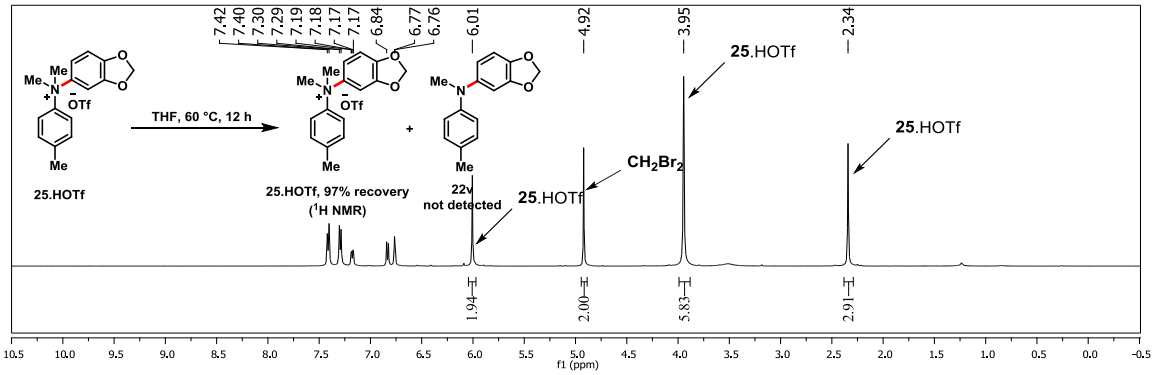
^{1}H NMR Spectrum of 22v ($CDCl_3$)



^{1}H NMR Spectrum of 25.HOTf ($CDCl_3$)



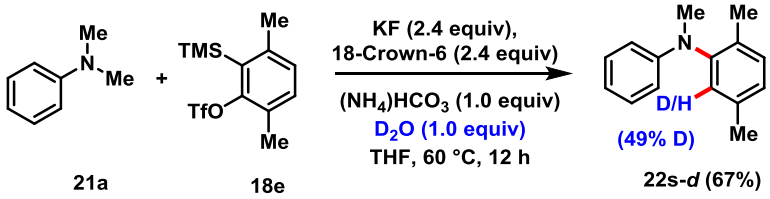
^{1}H NMR Spectrum of Crude Reaction Mixture of Scheme 5.24 after 12 h ($CDCl_3$)



5.8.4. Experiments to Determine the Role of Additives in the Protonation of Zwitterionic Intermediate 24: Deuterium Labelling Experiments

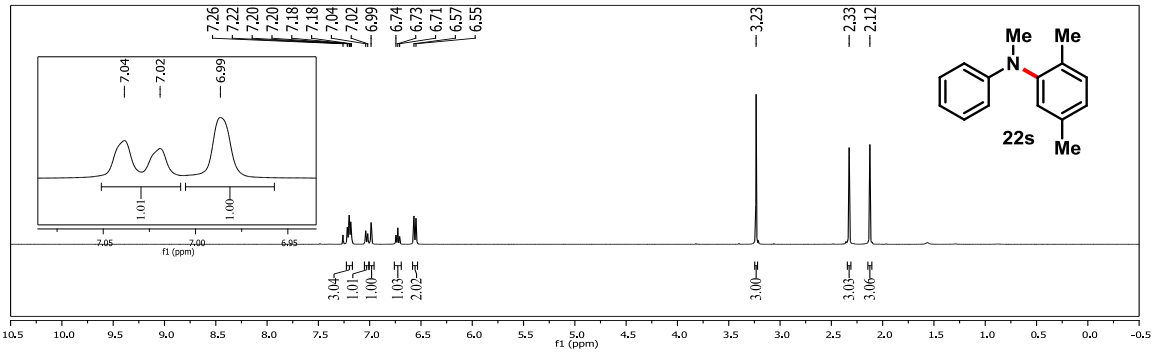
Experiment with D_2O and $(NH_4)HCO_3$ as Additives

Scheme 5.25: Experiment under Optimized Reaction Condition with **D_2O** as Additive

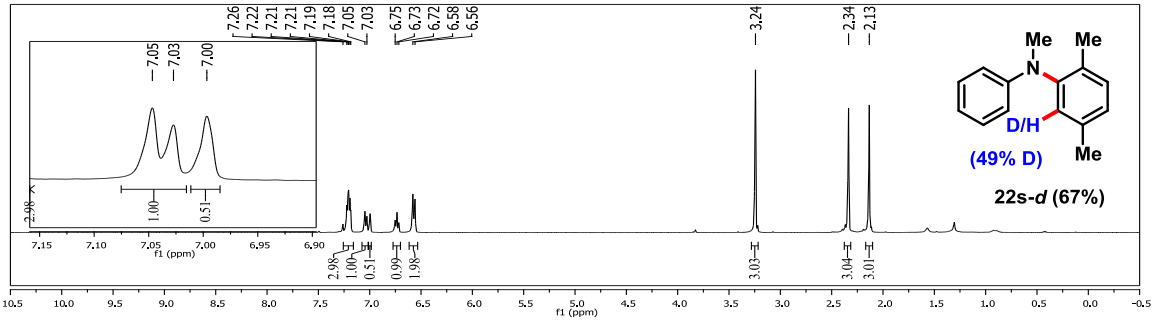


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.158 g, 0.60 mmol), KF (0.035 g, 0.60 mmol) and $(NH_4)HCO_3$ (0.020 g, 0.25mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (1.0 mL) under argon atmosphere. To the resulting stirring solution at room temperature was added *N*,*N*-dimethylaniline **21a** (0.030 g, 32 µL, 0.25 mmol), 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18e** (0.098 g, 0.30 mmol) and D_2O (0.005 g, 4.6 µL, 0.25 mmol). Then the reaction mixture kept in pre-heated oil bath at 60 °C for 12 h. The reaction mixture was subsequently cooled and the solvent was evaporated. The crude residue on column chromatography (Pet. ether/EtOAc = 99/01) afforded *N*,2,5-trimethyl-*N*-phenylaniline **22s-*d*** as colorless oil (0.035 g, 67%) with 49% incorporation of Deuterium at 2-position.

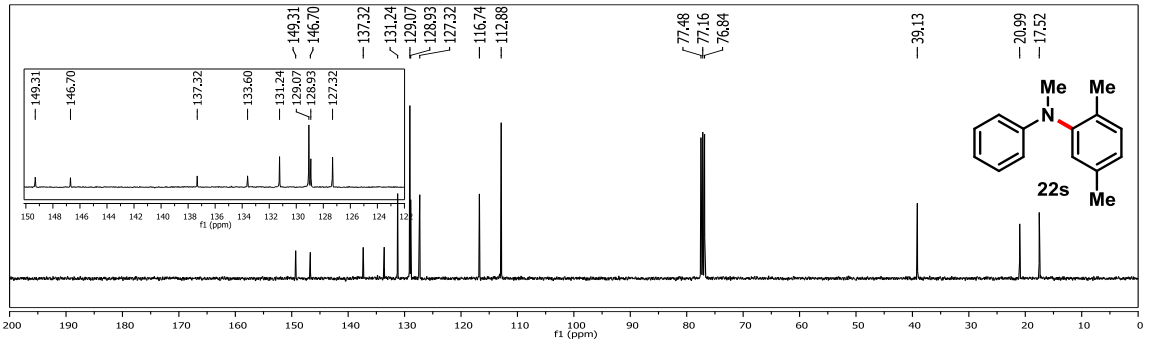
^{1}H NMR Spectrum of 22s ($CDCl_3$)



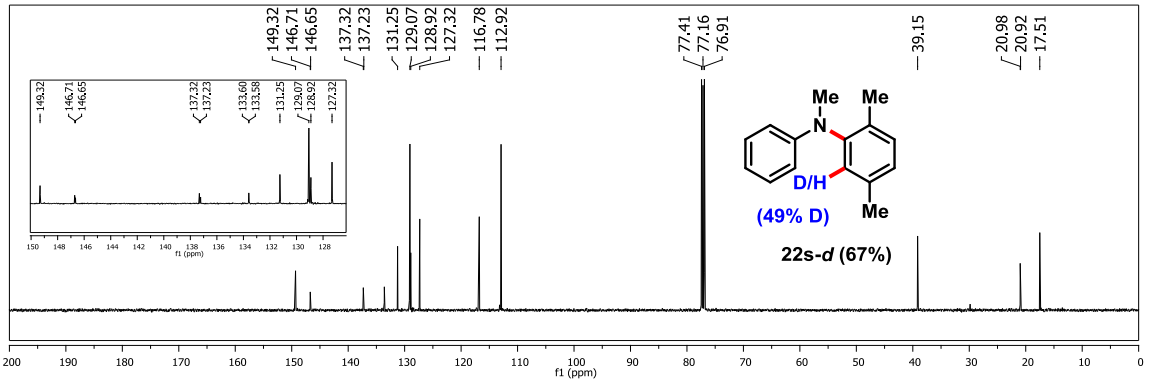
^{1}H NMR Spectrum of product 22s-*d* ($CDCl_3$)



^{13}C NMR Spectrum of 22s ($CDCl_3$)

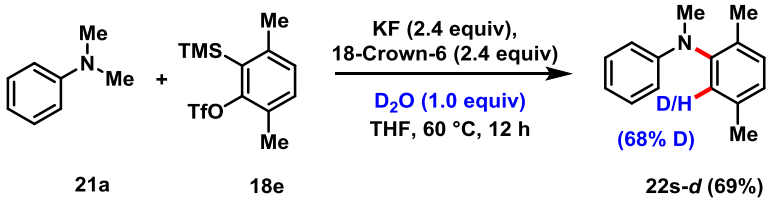


^{13}C NMR Spectrum of product 22s-*d* ($CDCl_3$)



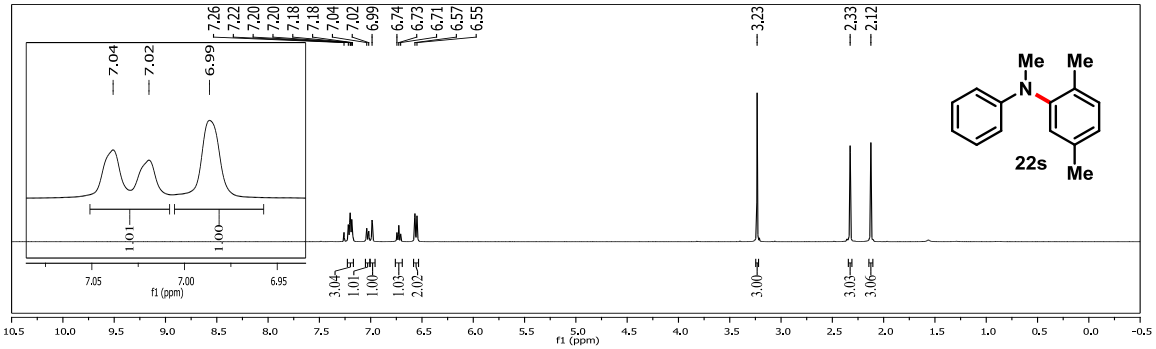
Experiment with only D_2O as the Additive

Scheme 5.26: Experiment Using only **D_2O** as the Additive

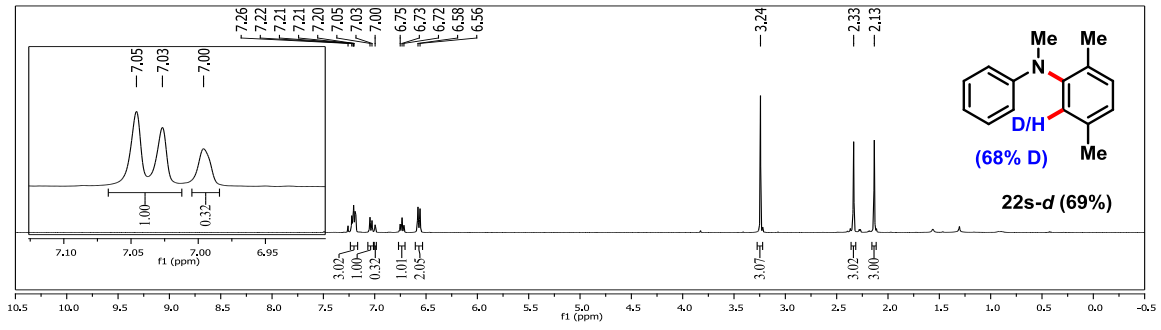


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.158 g, 0.60 mmol) and KF (0.035 g, 0.60 mmol) .Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (1.0 mL) under argon atmosphere. To the resulting stirring solution at room teperature was added *N*,*N*-dimethylaniline **21a** (0.030 g, 32 µL, 0.25 mmol), 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18e** (0.098 g, 0.30 mmol) and D_2O (0.005 g, 4.6 µL,0.25 mmol). Then the reaction mixture kept in pre-heated oil bath at 60 °C for 12 h. The reaction mixture was subsequently cooled and the solvent was evaporated. The crude residue on column chromatography (Pet. ether/EtOAc = 99/01) afforded *N*,2,5-trimethyl-*N*-phenylaniline **22s-*d*** as a colorless oil (0.036 g, 69%). ^{1}H NMR analysis of product showed 68% incorporation of Deuterium at 2-position.

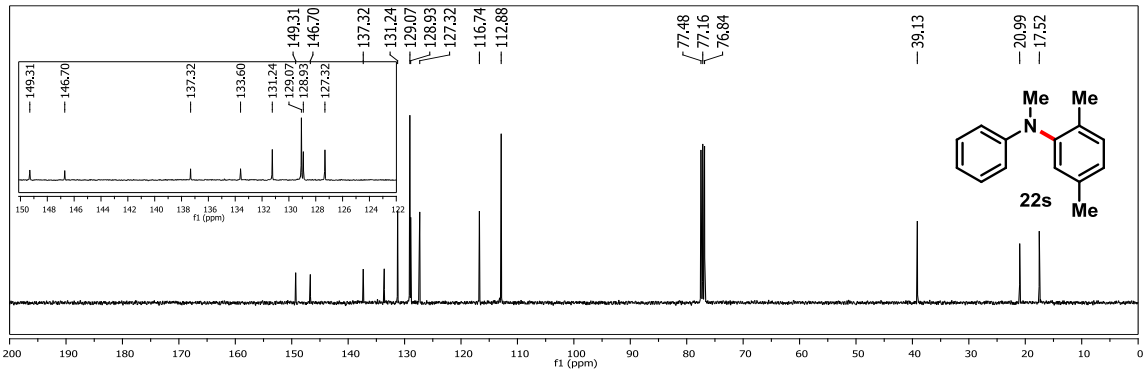
^{1}H NMR Spectrum of 22s ($CDCl_3$)



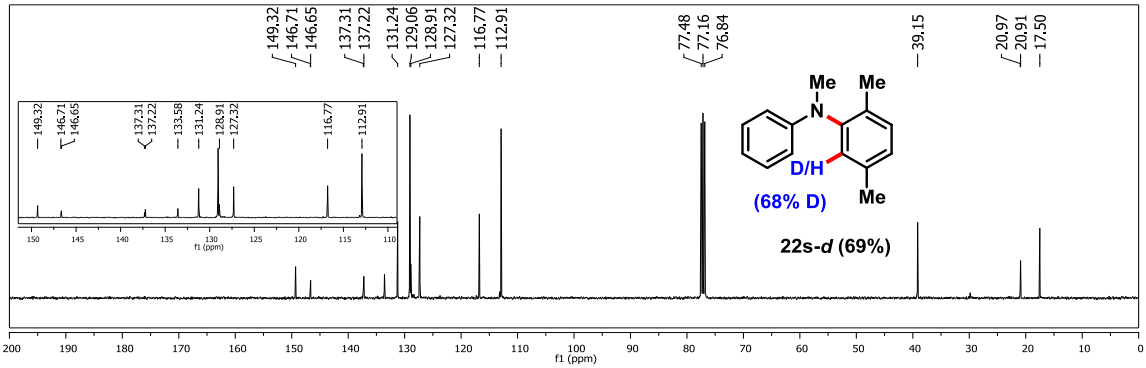
^{1}H NMR Spectrum of product 22s-*d* with only D_2O as additive ($CDCl_3$)



^{13}C NMR Spectrum of 22s ($CDCl_3$)

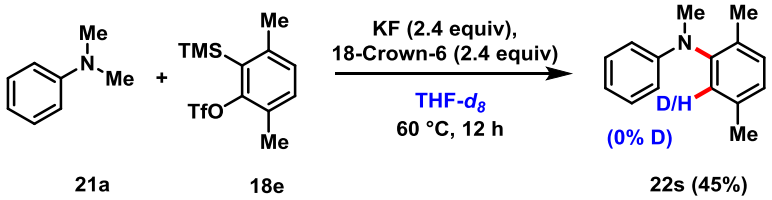


^{13}C NMR Spectrum of 22s-*d* with only D_2O as additive



Experiments to Determine the Role of Solvent THF-d_8 in the Protonation of Zwitterionic Intermediate

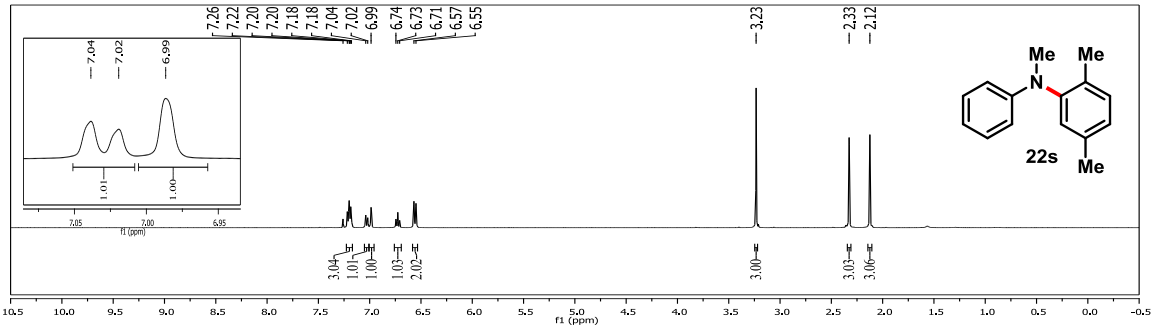
Scheme 5.27: Reaction in **THF-*d_8*** as a Solvent



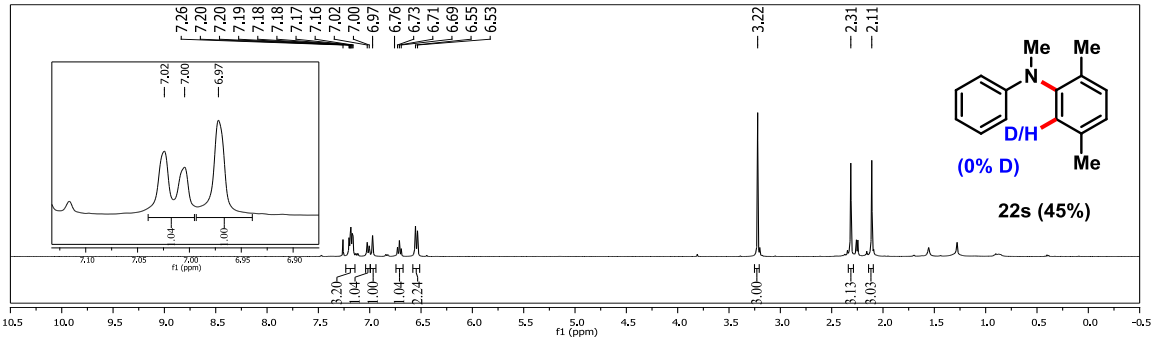
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.095 g, 0.36 mmol) and KF (0.021 g, 0.36 mmol). Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF-d_8 (0.50 mL) under argon atmosphere. To the resulting stirring solution at room temperature were added *N*, *N*-dimethylaniline **21a** (0.018 g, 20 µL, 0.15 mmol), and 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18e** (0.059 g, 0.18 mmol). Then the reaction mixture kept in pre-heated oil bath at 60°C for 12 h. The reaction mixture was subsequently cooled and the solvent was evaporated. The crude residue on column chromatography (Pet. ether/EtOAc = 99/01) afforded *N*,2,5-trimethyl-*N*-

phenylaniline **22s** as a colorless oil (0.014 g, 45%). ^{1}H NMR analysis of product showed no incorporation of Deuterium from the solvent THF-d_8.

^{1}H NMR Spectrum of 22s ($CDCl_3$)

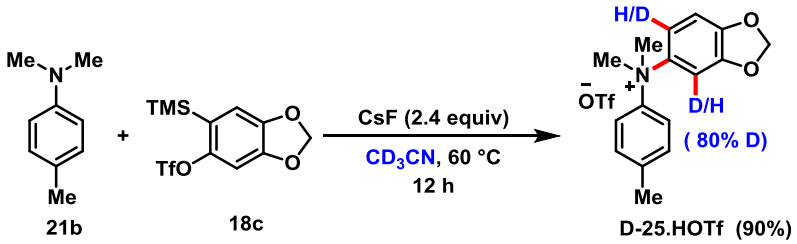


^{1}H NMR Spectrum of product 22s isolated from the reaction in THF-d_8 ($CDCl_3$)



Experiments to Determine the Role of solvent CD_3CN in the Protonation of Zwitterionic Intermediate

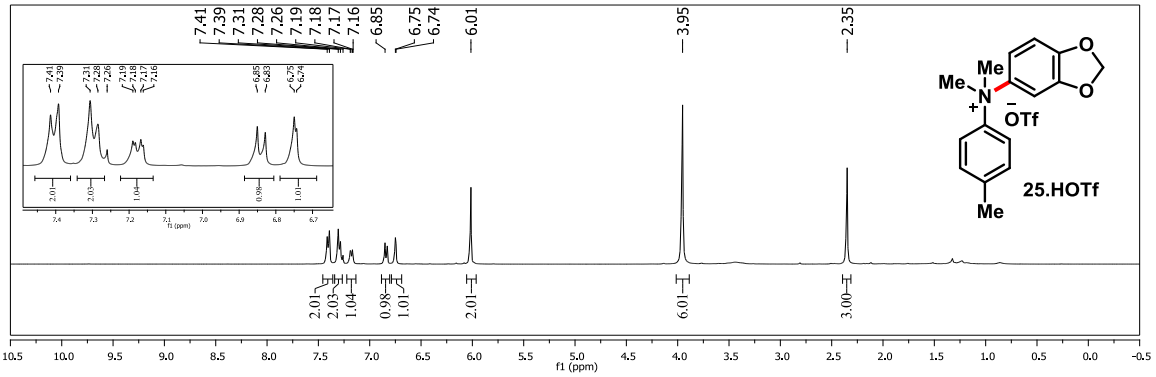
Scheme 5.28: Isolation of **D-25**.HOTf by Reaction in **CD_3CN** as a Solvent



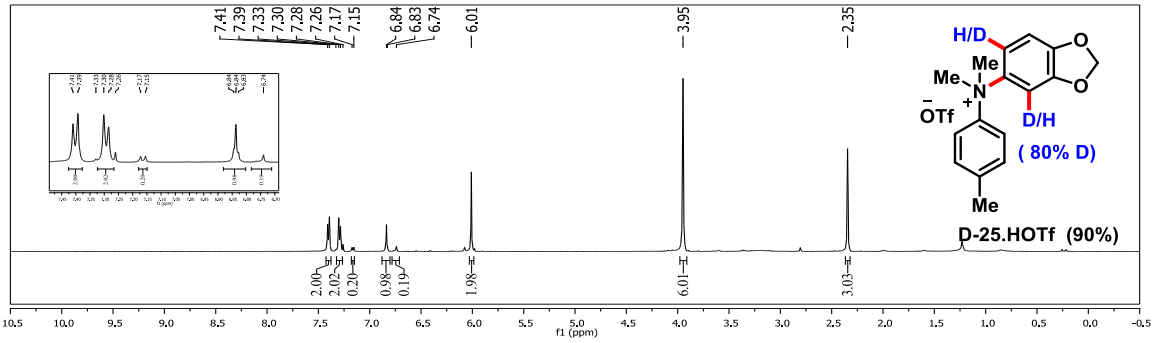
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry CsF (0.092 g, 0.60 mmol) and then CD_3CN (1.0 mL) under argon atmosphere. To the stirring solution *N*,*N*,4-trimethylaniline **21b** (0.034 g, 37 µL, 0.25 mmol) and 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yltrifluoromethanesulfonate **18c** (0.102 g, 0.30 mmol) were added at rt. Then the reaction mixture kept in pre-heated oil bath at 60 °C for 12 h. The reaction mixture was subsequently cooled and the solvent was evaporated. The crude residue purified on column chromatography (MeOH) to afford *N*,*N*-dimethyl-*N*-(*p*-

tolyl)benzo[*d*][1,3]dioxol-4-ammonium salt **D-25.**HOTf as a brown solid (0.092 g, 90%) with 80% incorporation of Deuterium at 2-positions.

^{1}H NMR Spectrum of 25.HOTf ($CDCl_3$)

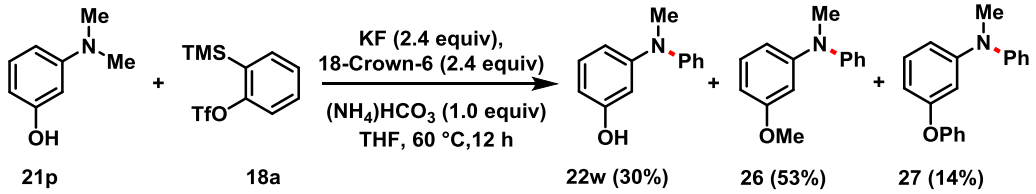


^{1}H NMR Spectrum of D-25.HOTf ($CDCl_3$)



5.8.5. Intramolecular Competition Experiment

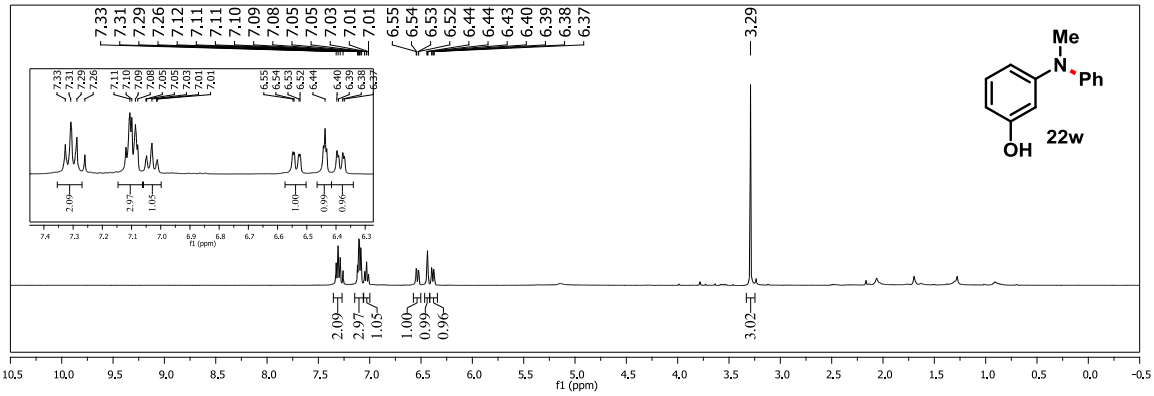
Scheme 5.29: N-arylation *vs* O-arylation



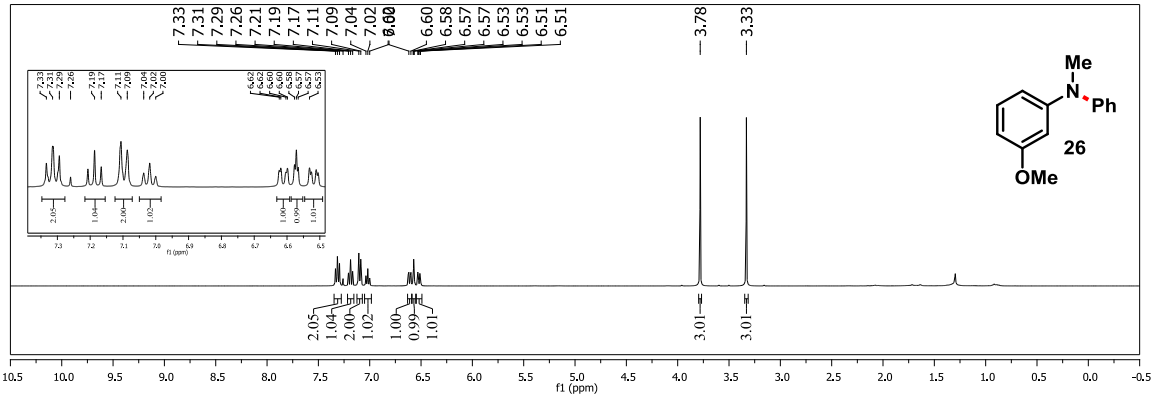
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.317g, 1.20 mmol), KF (0.070 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol).Then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere. To the resulting stirring solution at room temperature were added 3-(dimethylamino)phenol **21p** (0.069 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 µL, 0.60 mmol). Then the reaction mixture was kept in a pre-heated oil bath at 60 °C for 12 h.

The reaction mixture was subsequently cooled and the solvent was evaporated. The crude residue on column chromatography (Pet. ether/DCM = 98/02) afforded three product as follows, 3-(methyl(phen yl)amino)phenol **22w** as a brown oil (0.030 g, 30%), 3-methoxy-*N*-methyl-*N*-phenyl aniline **26** as a colorless oil (0.057 g, 53%) and *N*-methyl-3-phenoxy-*N*-phenylaniline **27** as a colorless oil (0.020 g, 14%).

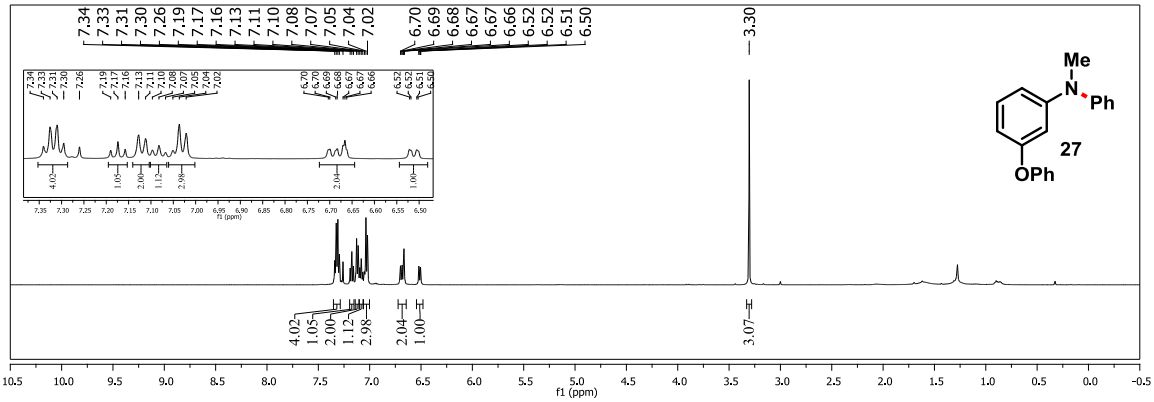
^{1}H NMR Spectrum of 3-(Methyl(phenyl)amino)phenol (22w) ($CDCl_3$)



^{1}H NMR Spectrum of 3-Methoxy-*N*-methyl-*N*-phenylaniline (26) ($CDCl_3$)

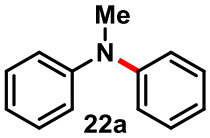


^{1}H NMR Spectrum of *N*-Methyl-3-phenoxy-*N*-phenylaniline (27) ($CDCl_3$)



5.8.6. Synthesis and Characterization of Products

***N*-Methyl-*N*-phenylaniline (22a)**[26]



Following the general procedure, treatment of *N*,*N*-dimethylaniline **21a** (0.061 g, 65 µL, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoro methanesulfonate **18a** (0.179 g, 146µL , 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/ DCM = 98/02) afforded *N*-methyl-*N*-phenylaniline **22a** as a colorless oil (0.087 g, 95%).

***R*$_f$** (Pet. ether/DCM = 90/10): 0.66.

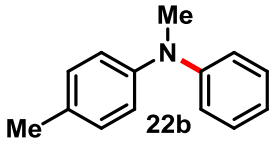
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, *J* = 7.6 Hz, 4H), 7.03 (d, *J* = 8.2 Hz, 4H), 6.96 (t, *J* = 7.3 Hz, 2H), 3.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.18, 129.33, 121.39, 120.58, 40.38.

HRMS: calculated $[M+H]^+$ for $C_{13}H_{14}N$: 184.1121, found: 184.1118.

FTIR (cm^{-1}): 3036, 2929, 2879, 1591, 1496, 1342, 1271, 1253, 1186, 1156, 1131, 1092, 1074, 1029, 864, 750, 693.

***N*,4-Dimethyl-*N*-phenylaniline (22b)**[27]



Following the general procedure, treatment of *N*,*N*,4-trimethyl aniline **21b** (0.068g, 73 µL, 0.50 mmol) with 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded *N*,4-dimethyl-*N*-phenylaniline **22b** as a colorless oil (0.091 g, 92%).

***R*$_f$** (Pet. ether/DCM = 90/10): 0.64.

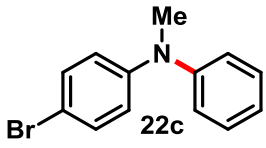
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.98-6.95 (m, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 3.33 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.50, 146.73, 132.19, 130.05, 129.15, 122.69, 119.93, 118.33, 40.46, 20.88.

HRMS: calculated $[M+H]^+$ for $C_{14}H_{16}N$: 198.1277, found: 198.1275.

FTIR (cm^{-1}): 3059, 3027, 2923, 2870, 1597, 1572, 1512, 1497, 1342, 1296, 1268, 1254, 1187, 1131, 1089, 1067, 868, 822, 751, 696.

4-Bromo-*N*-methyl-*N*-phenylaniline (22c)



Following the general procedure, treatment of 4-bromo-*N*,*N*-dime thylaniline **21c** (0.100 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 4-bromo-*N*-methyl-*N*-phenylaniline **22c** as a white solid (0.112 g, 85%).

***R*$_f$ (**Pet. ether/DCM = 90/10): 0.62.

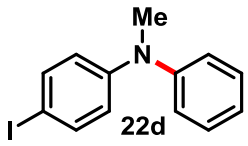
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.29 (m, 4H), 7.07-7.01 (m, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.67, 148.26, 132.07, 129.55, 122.71, 122.09, 120.71, 112.80, 40.42.

HRMS: calculated $[M+H]^+$ for $C_{13}H_{13}NBr$: 262.0226, found: 262.0256.

FTIR (cm^{-1}): 3062, 3037, 2926, 2882, 2815, 1583, 1489, 1454, 1343, 1254, 1185, 1133, 1119, 1075, 866, 815, 754, 734, 696 (C-Br).

4-Iodo-*N*-methyl-*N*-phenylaniline (22d)



Following the general procedure, treatment of 4-iodo-*N*,*N*-dimethyl aniline **21d** (0.124 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 µL , 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/ DCM = 98/02) afforded 4-iodo-*N*-methyl-*N*-phenylaniline **22d** as a white solid (0.131 g, 85%).

***R*$_f$** (Pet. ether/DCM = 90/10): 0.64.

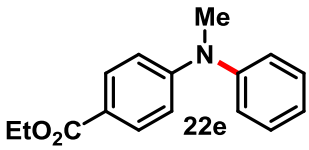
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.32 (t, *J* = 8.2 Hz, 2H), 7.10-7.04 (m, 3H), 6.72 (d, *J* = 8.8 Hz, 2H), 3.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.85, 148.46, 137.95, 129.60, 123.13, 122.68, 120.66, 82.20, 40.34.

HRMS: calculated $[M+H]^+$ for $C_{13}H_{13}IN$: 310.0092, found: 310.0100.

FTIR (cm^{-1}): 3025, 2923, 2815, 1577, 1481, 1333, 1237, 1118, 1056, 805, 746, 687.

Ethyl 4-(methyl(phenyl)amino)benzoate (22e)[28]



Following the general procedure, treatment of ethyl 4-(dimeth ylamino)benzoate **21e** (0.097g, 0.50 mmol) with 2-(trimethyl silyl)phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded ethyl 4-(methyl(phenyl)amino) benzoate **22e** as a colorless oil (0.110 g, 86%).

R_f (Pet. ether/EtOAc = 95/05): 0.63.

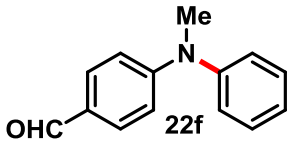
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.9 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.22-7.18 (m, 3H), 6.77 (d, *J* = 8.9 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.90, 152.57, 147.66, 131.06, 129.89, 125.89, 125.36, 119.67, 113.98, 60.41, 40.33, 14.57.

HRMS: calculated $[M+H]^+$ for $C_{16}H_{18}O_2N$: 256.1332, found: 256.1353.

FTIR (cm^{-1}): 3061, 3038, 2980, 2820, 1705 (ester), 1609, 1591, 1567, 1515, 1495, 1351, 1314, 1276, 1181, 1107, 870, 840, 768, 730, 698.

4-(Methyl(phenyl)amino)benzaldehyde (22f)



Following the general procedure, treatment of 4-(dimethyl amino)benzaldehyde **21f** (0.075 g, 0.50 mmol) with 2-(trimethyl silyl)phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 µL , 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 95/05) afforded 4-(methyl(phenyl) amino)benzaldehyde **22f** as a yellow solid (0.032 g, 30%).

R_f (Pet. ether/EtOAc = 90/10): 0.37.

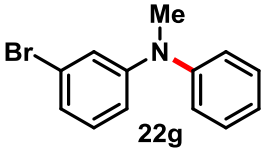
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.69 (d, *J* = 8.9 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.28-7.27 (m, 1H), 7.23 (d, *J* = 7.8 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 3.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.52, 153.88, 147.00, 131.78, 130.13, 126.79, 126.67, 126.33, 113.51, 40.43.

HRMS: calculated $[M+H]^+$ for $C_{14}H_{14}ON$: 212.1070, found: 212.1074.

FTIR (cm^{-1}): 3061, 3037, 2918, 2818, 2732, 1683, 1604, 1587, 1560, 1516, 1494, 1355, 1310, 1257, 1232, 1167, 1135, 1119, 1135, 1119, 1069, 1025, 872, 822, 769, 715, 699.

3-Bromo-*N*-methyl-*N*-phenylaniline (22g)



Following the general procedure, treatment of 3-bromo-*N*,*N*-dimethylaniline **21g** (0.100 g, 0.50 mmol) with 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 µL , 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded 3-bromo-*N*-methyl-*N*-phenylaniline **22g** as a colorless oil (0.123 g, 94%).

R_f (Pet. ether/DCM = 90/10): 0.63.

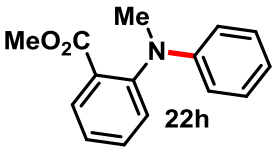
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.33 (m, 2H), 7.13-7.06 (m, 5H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 3.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.54, 148.34, 130.35, 129.68, 123.60, 123.39, 123.15, 122.62, 120.54, 116.47, 40.39.

HRMS: calculated $[M+H]^+$ for $C_{13}H_{13}NBr$: 262.0226, found: 262.0229.

FTIR (cm^{-1}): 3402, 3062, 3037, 2927, 2814, 1586, 1560, 1495, 1481, 1343, 1247, 1133, 1101, 1081, 1070, 984, 887, 835, 760, 699 (C-Br).

Methyl 2-(methyl(phenyl)amino)benzoate (22h)[29]



Following the general procedure, treatment of methyl 2-(dimethy lamino)benzoate **21h** (0.090 g, 0.50 mmol) with 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 µL , 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 99/01) afforded methyl 2-(methyl(phenyl)amino) benzoate **22h** as a yellow oil (0.079 g, 65%).

R_f (Pet. ether/EtOAc = 95/05): 0.63.

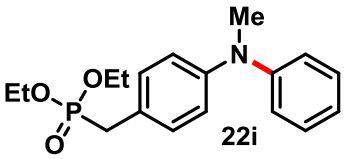
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.30-7.27 (m, 2H), 7.18-7.15 (m, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 2H), 3.60 (s, 3H), 3.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.62, 149.38, 148.25, 133.36, 131.54, 129.44, 129.15, 129.01, 125.35, 118.11, 114.40, 52.15, 40.47.

HRMS: calculated $[M+H]^+$ for $C_{15}H_{16}O_2N$: 242.1176, found: 242.1176.

FTIR (cm^{-1}): 3384, 3062, 3036, 2997, 2949, 2884, 2814, 1732 (ester), 1594, 1500, 1454, 1433, 1349, 1293, 1247, 1189, 1127, 1097, 1080, 1068, 991, 965, 871, 772, 749, 716, 693.

Diethyl (4-(methyl(phenyl)amino)benzyl)phosphonate (22i)



Following the general procedure, treatment of diethyl (4-(di methylamino)benzyl)phosphonate **21i** (0.135 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18a** (0.179 g, 146µL , 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 50/50) afforded diethyl (4-(methyl(phenyl)amino)benzyl)phosphonate **22i** as a yellow oil (0.144 g, 87%).

R_f (Pet. ether/EtOAc = 40/60): 0.41.

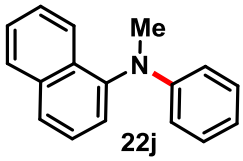
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, *J* = 8.1 Hz, 2H), 7.22 (dd, J_1 = 8.5 Hz, J_2 = 2.4 Hz, 2H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.99-6.96 (m, 3H), 4.09-4.02 (m, 4H), 3.32 (s, 3H), 3.12 (d, *J* = 21.3 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.06, 147.98 (d, *J* = 3.26 Hz), 130.63 (d, *J* = 6.65 Hz), 129.29, 123.97 (d, *J* = 9.34 Hz), 121.47, 120.65, 120.48 (d, *J* = 2.64 Hz), 62.21 (d, *J* = 6.71 Hz), 40.34, 33.01 (d, *J* = 139.1 Hz), 16.51 (d, *J* = 5.91 Hz).

HRMS: calculated $[M+H]^+$ for $C_{18}H_{25}O_3NP$: 334.1567, found: 334.1562.

FTIR (cm^{-1}): 3463, 3299, 3059, 3033, 2982, 2930, 2907, 2814, 1596, 1571, 1513, 1497, 1452, 1391, 1366, 1343, 1252 (P=O), 1190, 1163, 1131, 1097, 1054, 1028, 962, 870, 850, 770, 754, 700.

***N*-Methyl-*N*-phenylnaphthalen-1-amine (22j)**[22b]



Following the general procedure, treatment of *N*,*N*-dimethylnaphth alen-1-amine **21j** (0.086g, 83 µL, 0.50 mmol) with 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded *N*-methyl-*N*-phenylnaphthalen-1-amine **22j** as a colorless oil (0.115 g, 98%).

***R*$_f$** (Pet. ether/DCM = 90/10): 0.56.

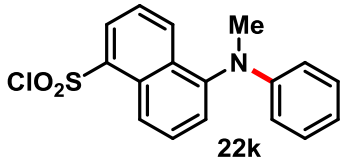
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (t, *J* = 8.7 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.55-7.51 (m, 2H), 7.46 (t, *J* = 7.1 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 2H), 3.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.22, 145.48, 135.25, 131.44, 129.05, 128.58, 126.76, 126.58, 126.47, 126.35, 125.37, 123.95, 117.32, 113.64, 40.32.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{16}N$: 234.1277, found: 234.1293.

FTIR (cm^{-1}): 3058, 2931, 2881, 2811, 1600, 1575, 1498, 1453, 1394, 1338, 1297, 1266, 1243, 1187, 1140, 1106, 1032, 1010, 885, 867, 806, 776, 750, 693.

5-(Methyl(phenyl)amino)naphthalene-1-sulfonyl chloride (22k)



Following the general procedure, treatment of 5-(dimethyla mino)naphthalene-1-sulfonyl chloride **21k** (0.067 g, 0.25 mmol) with 2-(trimethylsilyl)phenyl trifluoromethanesulfo nate **18a** (0.149 g, 121µL, 0.50 mmol) in the presence of KF (0.058 g, 1.0 mmol), 18-crown-6 (0.264 g, 1.0 mmol) and $(NH_4)HCO_3$ (0.020 g, 0.25 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 90/10) afforded 5-(methyl(phenyl)amino)naphthalene-1-sulfonyl chloride **22k** as a yellow oil (0.050 g, 61%).

***R*$_f$** (Pet. ether/DCM = 80/20): 0.30.

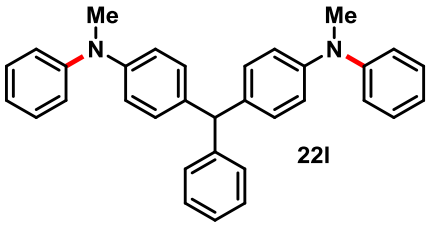
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (dd, J_1 = 8.7 Hz, J_2 = 2.6 Hz, 1H), 8.39-8.36 (m, 2H), 7.80 (t, *J* = 8.1 Hz, 1H), 7.57-7.54 (m, 2H), 7.19 (t, *J* = 8.0 Hz, 2H), 6.81 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.9 Hz, 2H), 3.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.01, 147.01, 132.99, 132.47, 131.63, 131.62, 130.43, 130.10, 129.30, 126.89, 124.58, 122.59, 118.63, 114.54, 40.82.

HRMS: calculated $[M]^+$ for $C_{17}H_{14}ClNO_2S$: 331.0434, found: 331.0812. HRMS data was recorded on Synapt MALDI-MS (Waters, UK) using Synapt MALDI-MS (Waters, UK) or AB SCIEX Tof TofTM 5800 using α-cyano-4-hydroxycinnamic acid as the solid matrix.

FTIR (cm^{-1}): 3329, 3061, 2928, 1600, 1572, 1498, 1415, 1400 (S=O), 1341, 1261, 1223, 1211 (S=O), 1148, 1110, 1044, 832, 792, 773, 748, 694, 640, 591.

4,4'-(Phenylmethylene)bis(*N*-methyl-*N*-phenylaniline (22l)



Following the general procedure, treatment of 4,4'-(ph enylmethylene)bis(*N*,*N*-dimethylaniline) **21l** (0.082 g, 0.25 mmol) with 2-(trimethylsilyl)phenyl trifluoro methanesulfonate **18a** (0.179 g, 146 µL , 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 80/20) afforded 4,4'-(phenylmet hylene)bis(*N*-methyl-*N*-phenylaniline) **22l** as a green oil (0.088 g, 78%).

R_f (Pet. ether/DCM = 80/20): 0.30.

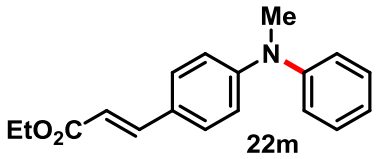
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.17 (m, 9H), 7.05-7.00 (m, 8H), 6.96-6.91 (m, 6H), 5.44 (s, 1H), 3.29 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.13, 147.25, 144.70, 137.27, 130.20, 129.49, 129.25, 128.38, 126.27, 121.12, 120.48, 120.25, 55.72, 40.35.

HRMS: calculated $[M+H]^+$ for $C_{33}H_{30}N_2$: 455.2482, found: 455.1764. HRMS data was recorded on Synapt MALDI-MS (Waters, UK) using Synapt MALDI-MS (Waters, UK) or AB SCIEX Tof TofTM 5800 using α-Cyano-4-hydroxycinnamic acid as the solid matrix.

FTIR (cm^{-1}): 3083, 3058, 3026, 2935, 2876, 2841, 1594, 1568, 1496, 1451, 1342, 1298, 1273, 1253, 1186, 1156, 1131, 1117, 1086, 1067, 1029, 1016, 868, 820, 797, 752, 711, 697.

Ethyl (*E*)-3-(4-(methyl(phenyl)amino)phenyl)acrylate (22m)



Following the general procedure, treatment of ethyl (*E*)-3-(4-(dimethylamino)phenyl)acrylate **21m** (0.110g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethanesul fonate **18a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 98/02) afforded ethyl (*E*)-3-(4-(methyl(phenyl)amino)phenyl)acrylate **22m** as a yellow oil (0.130 g, 93%).

R_f (Pet. ether/EtOAc = 95/05): 0.50.

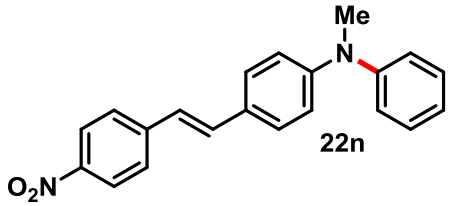
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 16.0 Hz, 1H), 7.40-7.35 (m, 4H), 7.19-7.14 (m, 3H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.25 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.35 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.83, 150.77, 147.88, 144.80, 129.77, 129.48, 125.03, 125.84, 124.68, 115.79, 113.98, 60.30, 40.28, 14.50.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{20}O_2N$: 282.1489, found: 282.1484.

FTIR (cm^{-1}): 3061, 3035, 2980, 2936, 2902, 1705 (ester), 1628, 1606, 1591, 1559, 1515, 1495, 1350, 1330, 1258, 1215, 1166, 1137, 1122, 1040, 983, 868, 821, 768, 700.

(*E*)-*N*-Methyl-4-(4-nitrostyryl)-*N*-phenylaniline (22n)[30]



Following the general procedure, treatment of (*E*)-*N*,*N*-dimethyl-4-(4-nitrostyryl)aniline **21n** (0.067 g, 0.25 mmol) with 2-(trimethylsilyl)phenyl trifluoro methanesulfonate **18a** (0.090 g, 73 µL, 0.3 mmol) in the presence of KF (0.035 g, 0.6 mmol), 18-crown-6 (0.159 g, 0.6mmol) and $(NH_4)HCO_3$ (0.020 g, 0.25 mmol) in THF (1.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 92/8) afforded (*E*)-*N*-methyl-4-(4-nitrostyryl)-*N*-ph enylaniline **22n** as a colorless oil (0.064 g, 78%).

R_f (Pet. ether/EtOAc = 90/10): 0.56.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.28, (t, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 10.7 Hz, 1H), 7.11-7.08 (m,

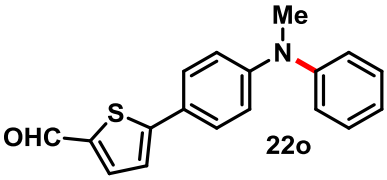
2H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 16.2 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 3.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.70, 148.28, 146.29, 144.78, 133.38, 129.68, 128.23, 127.42, 126.43, 124.29, 123.97, 123.89, 123.09, 117.21, 40.35.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{19}O_2N_2$: 331.1441, found: 331.1438.

FTIR (cm^{-1}): 2927, 1606, 1585, 1509 (NO_2), 1339 (NO_2), 1254, 1188, 1114, 971, 837, 806, 776, 749.

5-(4-(Methyl(phenyl)amino)phenyl)thiophene-2-carbaldehyde (22o)



22o

Following the general procedure, treatment of 5-(4-(dimethylamino)phenyl)thiophene-2-carbaldehyde **21o** (0.116 g, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 μL , 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 90/10) afforded 5-(4-(methyl(phenyl)amino)phenyl) thiophene-2-carbaldehyde **22o** as a green color solid (0.079 g, 54%).

R_f (Pet. ether/EtOAc = 90/10): 0.39.

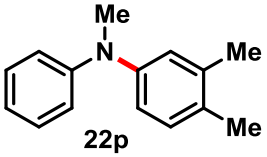
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.71 (d, *J* = 3.9 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.40, (t, *J* = 7.7 Hz, 2H)7.29 (d, *J* = 3.5 Hz, 1H), 7.22-7.16 (m, 3H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 182.66, 155.46, 150.21, 148.01, 140.86, 138.03, 129.79, 127.44, 124.64, 124.46, 123.65, 122.31, 116.58, 40.32.

HRMS: calculated $[M+H]^+$ for $C_{18}H_{16}ONS$: 294.0947, found: 294.0941.

FTIR (cm^{-1}): 3373, 2925, 2855, 2726, 1655 (CHO), 1590, 1458, 1377, 1231, 1081, 801, 773.

***N*,3,4-Trimethyl-*N*-phenylaniline (22p)**[17b]



22p

Following the general procedure, treatment of *N*,*N*-dimethyl aniline **21a** (0.061 g, 65 μL, 0.50 mmol) with 4,5-dimethyl-2-(tri methylsilyl)phenyl trifluoromethanesulfonate **18b** (0.196 g, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50,mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column

chromatography (Pet. ether/DCM = 96/4) afforded *N*,3,4-trimethyl-*N*-phenyl aniline **22p** as a colorless oil (0.098 g, 93%).

R_f (Pet. ether/DCM = 90/10): 0.50.

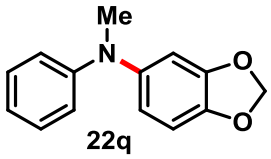
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.98-6.89 (m, 5H), 3.34 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.51, 147.0, 137.68, 131.15, 130.55, 129.11, 124.31, 120.43, 119.64, 118.0, 40.49, 20.10, 19.21.

HRMS: calculated $[M+H]^+$ for $C_{15}H_{18}N$: 212.1434, found: 212.1433.

FTIR (cm^{-1}): 3022, 2920, 2809, 1595, 1496, 1450, 1343, 1300, 1117, 998, 751.

***N*-Methyl-*N*-phenylbenzo[*d*][1,3]dioxol-5-amine (22q)**



Following the general procedure, treatment of *N*,*N*-dimethyl aniline **21a** (0.061g, 65 μL, 0.50mmol) with 6-(trimethylsilyl) benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate **18c** (0.205 g, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50,mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 96/4) afforded *N*-methyl-*N*-phenylbenzo [*d*][1,3]dioxol-5-amine **22q** (0.106 g, 94%).

R_f (Pet. ether/DCM = 90/10): 0.33.

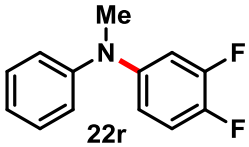
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.23 (m, 2H), 6.88-6.81 (m, 4H), 6.70-6.63 (m, 2H), 5.99 (s, 2H), 3.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.70, 148.39, 144.12, 143.80, 129.10, 119.11, 117.41, 116.69, 108.71, 106.31, 101.33, 40.78.

HRMS: calculated $[M+H]^+$ for $C_{14}H_{14}O_2N$: 228.1019, found: 228.1013.

FTIR (cm^{-1}): 2886, 2810, 1598, 1577, 1485, 1326, 1241, 1214, 1115, 1038, 939, 927, 751.

3,4-Difluoro-*N*-methyl-*N*-Phenylaniline (22r)



Following the general procedure, treatment of *N*,*N*-dimethylaniline **21a** (0.061g, 65 μL, 0.50 mmol) with 4,5-difluoro-2-(trimethylsilyl) phenyl trifluoromethanesulfonate **18d** (0.201 g, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50,mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column

chromatography (Pet. ether/DCM = 96/4) afforded 3,4-difluoro-*N*-methyl-*N*-phenyl aniline **22r** as a colorless oil (0.097 g, 88%).

R_f (Pet. ether/DCM = 90/10): 0.65.

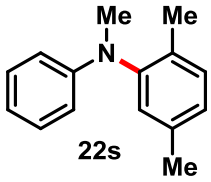
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (t, *J* = 9.7 Hz, 2H), 7.57-7.52 (m, 4H), 7.25-7.18 (m, 1H), 7.09-7.04 (m, 1H), 2.85 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.75 (dd, J_1 = 16.8 Hz, J_2 = 307.5 Hz), 166.46, 163.69 (dd, J_1 = 16.5 Hz, J_2 = 302.0 Hz), 163.36 (dd, J_1 = 2.8 Hz, J_2 = 9.7 Hz), 142.67, 134.01, 132.17, 127.42 (d, *J* = 21.4 Hz), 124.4 (q, *J* = 3.07), 116.3 (d, *J* = 24.2 Hz), 31.54.

HRMS: calculated $[M+H]^+$ for $C_{13}H_{12}NF_2$: 220.0932, found: 220.0930.

FTIR (cm^{-1}): 3038, 2887, 2815, 1597, 1516, 1495, 1277 (C-F), 1119, 1083, 828, 774.

***N*,2,5-Trimethyl-*N*-Phenylaniline (22s)**[31]



Following the general procedure, treatment of *N*,*N*-dimethylaniline **21a** (0.061g, 65 μL, 0.50 mmol) with 3,6-dimethyl-2-(trimethylsilyl) phenyl trifluoromethanesulfonate **18e** (0.196 g, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50,mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 96/4) afforded *N*,2,5-trimethyl-*N*-phenyl aniline **22s** as a colorless oil (0.067 g, 64%).

R_f (Pet. ether/DCM = 90/10): 0.65.

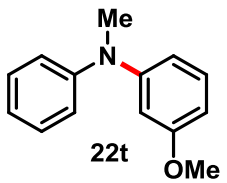
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.18 (m, 3H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.99 (s, 1H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 2H), 3.23 (s, 3H) 2.33 (s, 3H), 2.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.31, 146.7, 137.32, 133.60, 131.24, 129.07, 128.93, 127.32, 127.32, 116.74, 112.88, 39.13, 20.99, 17.52.

HRMS: calculated $[M+H]^+$ for $C_{15}H_{18}N$: 212.1434, found: 212.1432.

FTIR (cm^{-1}): 3088, 3024, 2921, 2809, 1575, 1499, 1450, 1340, 1115, 1066, 815, 748.

3-Methoxy-*N*-methyl-*N*-Phenylaniline (22t)[27]



Following the general procedure, treatment of *N*,*N*-dimethylaniline **21a** (0.061 g, 65 μL, 0.50 mmol) with 2-methoxy-6-(trimethylsilyl) phenyl trifluoromethanesulfonate **18f** (0.197 g, 0.60 mmol) in the

presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 96/4) afforded 3-methoxy-*N*-methyl-*N*-phenylaniline **22t** as a colorless oil (0.087 g, 94%).

R_f (Pet. ether/DCM = 90/10): 0.33.

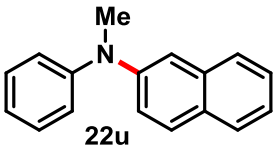
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.10 (d, J = 7.9 Hz, 2H), 7.02, (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.58 (s, 1H) 6.52(d, *J* = 7.9 Hz, 1H), 3.79 (s, 3H), 3.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.67, 150.50, 148.98, 129.88, 129.36, 122.11, 121.72, 112.33, 106.04, 105.72, 55.30, 40.42.

HRMS: calculated $[M+H]^+$ for $C_{14}H_{16}ON$: 214.1226, found: 214.1229.

FTIR (cm^{-1}): 2999, 2936, 2834, 1595, 1494, 1437, 1436, 1347, 1169, 1127, 1049, 991, 754.

***N*-Methyl-*N*-Phenylnaphthalen-2-amine (22u)**[32]



22u

Following the general procedure, treatment of *N*,*N*-dimethyl aniline **21a** (0.061g, 65 μL, 0.50 mmol) with 2-(trimethylsilyl) naphthalen-1-yl trifluoromethanesulfonate **18g** (0.209 g, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol), 18-crown-6 (0.317 g, 1.20 mmol) and $(NH_4)HCO_3$ (0.040 g, 0.50,mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 96/4) afforded *N*-methyl-*N*-phenylnaphthalen-2-amine **22u** as a colorless oil (0.112 g, 96%).

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

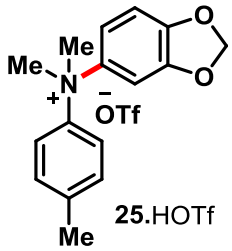
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.2 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 2H), 7.48-7.45 (m, 1H),7.39-7.34 (m, 4H), 7.29-7.25 (m, 1H), 7.16 (d, *J* = 7.7, 2H), 7.07 (t, *J* = 7.3, 1H), 3.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.16, 146.68, 134.80, 129.42, 129.26, 128.71, 127.67, 126.87, 126.40, 123.87, 122.13, 121.92, 121.53, 114.74, 40.78.

HRMS: calculated $[M+H]^+$ for $C_{17}H_{16}N$: 234.1277, found: 234.1274.

FTIR (cm^{-1}): 3056, 2940, 2811, 1628, 1593, 1494, 1364, 1297, 1281, 1321, 1119, 813, 747, 699.

***N*,*N*-Dimethyl-*N*-(*p*-tolyl)benzo[*d*][1,3]dioxol-4-aminium salt (25.**HOTf**)**



25.HOTf

Compound **25.**HOTf synthesized by following the procedure given in Scheme 5.20.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.18 (dd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 6.75 (d, *J* = 2.6 Hz, 1H), 6.01 (s, 2H), 3.95 (s, 6H), 2.35 (s, 3H).

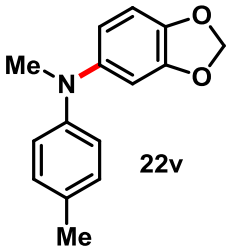
^{13}C NMR (100 MHz, $CDCl_3$): δ 149.30, 149.14, 146.39, 142.56, 141.16, 131.18, 120.84, 114.84, 108.41, 103.02, 102.89, 58.99, 20.90.

^{19}F NMR (376 MHz, $CDCl_3$): δ -78.41.

HRMS: calculated $[M]^+$ for $C_{16}H_{18}O_2N$: 256.1332, found: 256.1334.

FTIR (cm^{-1}): 3504, 3114, 3059, 3016, 2919, 1615, 1508, 1488, 1383, 1263, 1226, 1159, 1125, 1112, 1031, 971, 927, 898, 819, 756, 639.

***N*-Methyl-*N*-(*p*-tolyl)benzo[d][1,3]dioxol-5-amine (22v)**



22v

Compound **22v** synthesized by following the procedure given in Scheme 5.21.

***R*$_f$ (**Pet. ether/DCM = 80/20): 0.32.

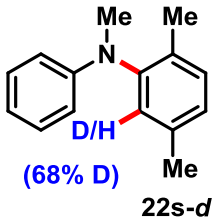
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 2.1 Hz, 1H), 6.53 (dd, J_1 = 8.3 Hz, J_2 = 2.1 Hz, 1H), 5.94 (s, 2H), 3.23 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.30, 147.52, 144.58, 143.17, 129.76, 129.58, 118.67, 115.21, 108.56, 104.65, 101.17, 40.99, 20.63.

HRMS: calculated $[M+H]^+$ for $C_{15}H_{16}O_2N$: 242.1176, found: 242.1162.

FTIR (cm^{-1}): 2920, 2883, 2808, 1611, 1514, 1504, 1485, 1324, 1284, 1241, 1214, 1155, 1113, 1039, 940, 927, 841, 811, 781, 726.

***N*,2,5-Trimethyl-*N*-phenylaniline-6-*d* (22s-*d*)**



22s-*d*

Compound **22s-*d*** synthesized by following the procedure given in Scheme 5.26.

***R*$_f$** (Pet. ether/DCM = 90/10): 0.65.

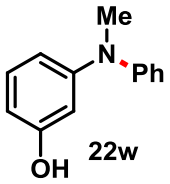
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.18 (m, 3H), 7.04 (d, *J* = 7.7 Hz, 1H), 7.00 (s, 32% H), 6.73 (t, *J* = 7.9 Hz, 1H), 6.57 (d, *J* = 7.9 Hz,

2H), 3.24 (s, 3H) 2.33 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.34, 146.73, 146.67, 137.32, 137.23, 133.60, 133.58, 131.24, 129.07, 128.92, 127.32, 116.77, 112.92, 39.15, 20.91, 17.51.

HRMS: calculated $[M+H]^+$ for $C_{15}H_{17}{}^2HN$: 213.1497, found: 213.1490.

3-(Methyl(phenyl)amino)phenol (22w)[33]



Compound **22w** synthesized by following the procedure given in Scheme 5.29.

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

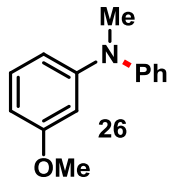
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.9 Hz, 2H), 7.12-7.08 (m, 3H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.53 (dd, J_1 = 8.1 Hz,J_2=*1.5* Hz,1H), 6.44 (t, *J* = 2.2 Hz, 1H), 6.39 (dd, J_1 = 8.1 Hz, J_2 = 2.3 Hz, 1H), 3.29 (s, 3H) .

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.57, 150.71, 148.88, 130.11, 129.42, 122.59, 122.49, 111.43, 107.49, 105.90, 40.38.

HRMS: calculated $[M+H]^+$ for $C_{13}H_{14}ON$: 200.1070, found: 200.1072.

FTIR (cm^{-1}): 3381, 3060, 3037, 2929, 2814, 1591, 1496, 1459, 1349, 1275, 1195, 1165, 1126, 1092, 1027, 992, 955, 943, 829, 758, 693.

3-Methoxy-*N*-methyl-*N*-phenylaniline (26)[27]



Compound **26** synthesized by following the procedure given in Scheme 5.29.

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

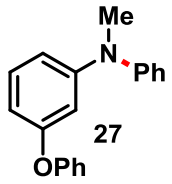
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.61 (dd, J_1 = 8.1 Hz, J_2 = 1.8 Hz, 1H), 6.57 (t, *J* = 2.2 Hz, 1H), 6.52 (dd, J_1 = 8.1, J_2=2.3 Hz, 1H), 3.78 (s, 3H), 3.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.66, 150.50, 148.98, 129.89, 129.36, 122.11, 121.73, 112.33, 106.04, 105.71, 55.30, 40.42.

HRMS: calculated $[M+H]^+$ for $C_{14}H_{16}ON$: 214.1226, found: 214.1226.

FTIR (cm^{-1}): 2999, 2932, 2834, 1592, 1493, 1467, 1347, 1274, 1215, 1169, 1127, 1094, 1048, 929, 754.

***N*-Methyl-3-phenoxy-*N*-phenylaniline (27)**



Compound **27** synthesized by following the procedure given in Scheme 5.29.

***R*$_f$** (Pet. ether/DCM = 90/10): 0.50.

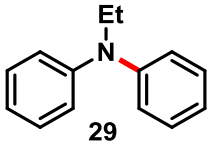
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.30 (m, 4H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.05-7.02 (m, 3H), 6.69 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 1H), 6.67 (t, *J* = 2.0 Hz, 1H), 6.51 (dd, J_1 = 8.2, J_2=1.5 Hz, 1H), 3.30 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 158.12, 157.44, 150.75, 148.70, 130.03, 129.77, 129.49, 123.15, 122.87, 122.68, 118.84, 113.63, 110.50, 109.33, 40.41.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{18}ON$: 276.1383, found: 276.1385.

FTIR (cm^{-1}): 3063, 3038, 2925, 2814, 1588, 1488, 1347, 1260, 1222, 1163, 1125, 1092, 1072, 1024, 993, 959, 847, 769, 754, 691.

***N*-Ethyl-*N*-phenylaniline (29)**



Following the general procedure, treatment of *N*,*N*-diethylaniline **28** (0.075g, 81 µL, 0.50 mmol) with 2-(trimethylsilyl)phenyl trifluoro methanesulfonate **18a** (0.179 g, 146 µL, 0.60 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded *N*-ethyl-*N*-phenylaniline **29** as a colorless oil (0.060 g, 61%).

***R*$_f$** (Pet. ether/DCM = 90/10): 0.66.

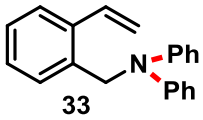
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.28-7.25 (m, 4H), 7.00 (d, *J* = 7.5 Hz, 4H), 6.94 (t, *J* = 7.4 Hz, 2H), 3.80-3.76 (m, 2H), 1.24-1.21 (m, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 147.89, 129.38, 121.22, 121.06, 46.54, 12.82.

HRMS: calculated $[M+H]^+$ for $C_{14}H_{16}N$: 198.1277, found: 198.1277.

FTIR (cm^{-1}): 3060, 3036, 2972, 2929, 2870, 1588, 1495, 1371, 1348, 1261, 1241, 1131, 1100, 783, 748, 693.

***N*-Phenyl-*N*-(2-vinylbenzyl)aniline (33)**



Treatment of 1,2,3,4-tetrahydroisoquinoline **30** (0.033 g, 32 µL, 0.25 mmol) with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **18a** (0.179 g, 146 µL , 0.60 mmol) in the presence of KF (0.070 g, 1.20

mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by column chromatography (Pet. ether/DCM = 98/02) afforded *N*-phenyl-*N*-(2-vinyl benzyl)aniline **33** as a white solid (0.060 g, 86%).

R_f (Pet. ether/DCM = 90/10): 0.65.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.0 Hz, 1H), 7.42 (d, *J* = 7.0 Hz, 1H), 7.27-7.18 (m, 6H), 7.07 (d, *J* = 7.9 Hz, 4H), 7.02-6.94 (m, 3H), 5.68 (d, *J* = 17.3 Hz, 1H), 5.37 (d, *J* = 11.0 Hz, 1H), 5.04 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.06, 136.10, 135.49, 133.76, 129.40, 128.07, 127.08, 126.85, 126.23, 121.59, 120.77, 116.66, 54.37.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{20}N$: 286.1595, found: 286.1592.

FTIR (cm^{-1}): 3061, 3028, 2921, 2853, 1579, 1485, 1338, 1227, 1062, 986, 914, 848.

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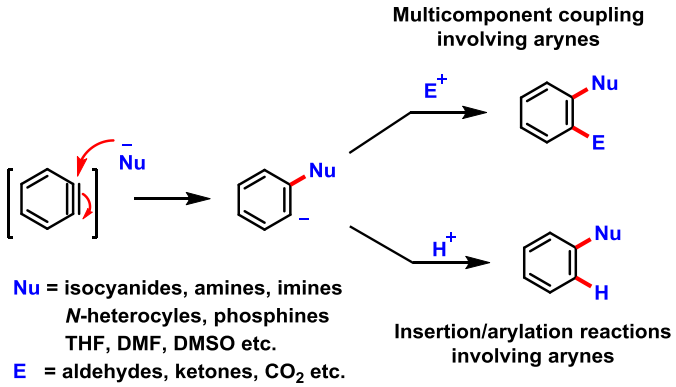
CHAPTER 6

Three-Component Coupling Involving Arynes, Aromatic Tertiary Amines, and Aldehydes via Aryl-Aryl Amino Group Migration

6.1. Introduction

Transition-metal-free multicomponent coupling (MCC) involving arynes offers straightforward access to the complex and diverse 1,2-disustituted benzene derivatives in a single operation.[1] Arynes are one of the well studied intermediates from decades, and the fascinating chemistry of arynes is an area of immense interest in synthetic organic chemistry by virtue its various modes of action in several bond forming reactions.[2] Owing to their highly electrophilic nature, arynes hold the ability to react with wide range of nucleophiles, even neutral nucleophiles can add to arynes. The fundamental principle of these transformations involve the initial addition of nucleophile to aryne generating a transient aryl anion intermediate, which is subsequently trapped by an electrophile leading to MCCs. In presence of acidic proton source, the aryl anion intermediate is quenched to furnish simple arylated products in arylation/insertion reactions (Scheme 6.1).

Scheme 6.1: Aryne MCCs *vs* Arylation

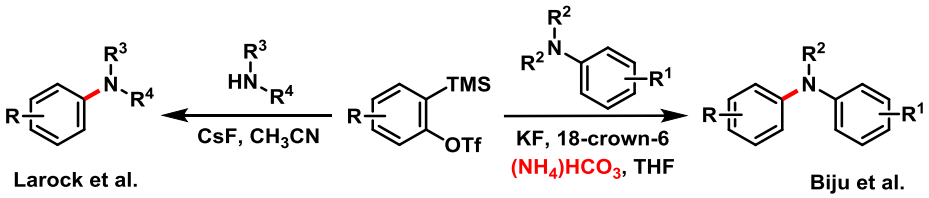


Commonly used nucleophiles in aryne MCCs are isocyanides,[3] imines,[4] phosphines,[5] cyclic ethers,[6] DMF,[3c,7] DMSO,[8] and *N*-heterocycles[9] (such as pyridine and isoquinoline). Electrophiles are usually aldehydes, ketones including CO_2.[10] The focal theme of the present chapter is to employ aromatic tertiary amines as nucleophilic trigger in aryne MCCs and interception of the amine-aryne zwitterionic intermediate with various carbonyl compounds. Before going into details, the reports on aryne MCCs triggered by amines are discussed in the following sections.

6.2. Amines as Nucleophilic Trigger in Aryne MCCs

Aryne MCCs constitute a powerful tool for the transition-metal free synthesis of complex 1,2-disustituted arenes and heterocyclic scaffolds, which are difficult to obtain by conventional methods. Despite this, amines as nucleophilic trigger in the realm of aryne MCCs have received only scant attention. This is mainly due to the spontaneous protonation of aryl anion generated from amine and aryne resulting in the formation of *N*-arylated products,[11,12] which was already discussed in previous chapter (Scheme 6.2).

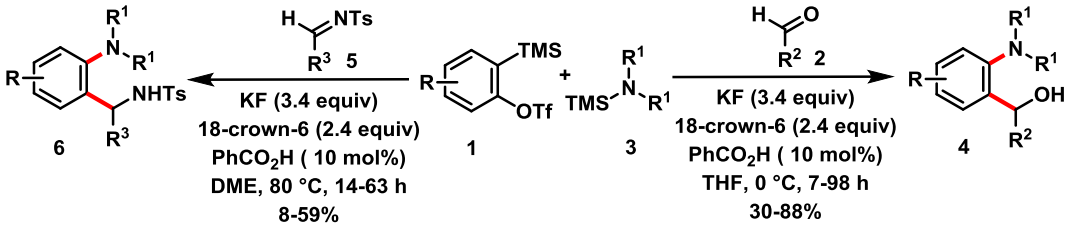
Scheme 6.2: *N*-Arylation of Amines using Arynes



In 2007, Yoshida and coworkers developed the aryne MCCs initiated by silyl-protected amines using aldehydes as the third component leading to the incorporation of amino and hydroxymethyl group at 1,2-position of arenes. Reaction of aminosilanes **3** with arynes generated in situ from precursors **1**[13] and aldehydes **2** using KF/18-crown-6 in presence of 10 mol% benzoic acid resulted in the formation of diverse 2-aminobenzhydrol derivatives **4** in good yields (Scheme 6.3).[14a] The reaction proceeds via the formation of 1,3-zwitterionic intermediate produced by the nucleophilic addition of in situ generated free amines to aryne, which was subsequently trapped by aldehydes to afford the product. Use of protected amines excluded the possibility of *N*-arylation. Additionally, activated imines **5** were also employed as the electrophilic coupling partner leading to the introduction of both amino and aminomethyl moieties into 1,2-position of benzene ring **6** in low to moderate yields.[14b] In the absence of catalytic benzoic acid

MCCs products were not detected, which confirms that benzoic acid plays a crucial role in the reaction process by in situ generating the free amines.

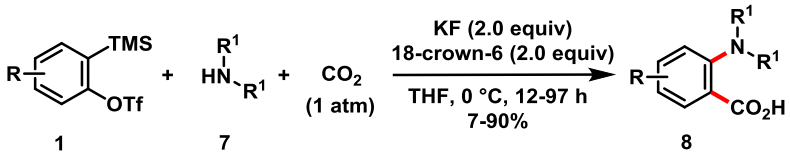
Scheme 6.3: Aryne MCCs involving Aminosilanes and Aldehydes (or Activated Imines)



R = H, Me, $(CH_2)_3$, $(CH_2)_4$, OMe, F
R^1 = Me, Et, *n*-Bu, $(CH_2)_5$, $(CH_2)_2OMe$
R^2 = alkyl, aryl, heteroaryl
R^3 = aryl, heteroaryl

Extending an effort to engage amines in MCC with arynes, the same group reported three-component coupling of secondary amine and arynes with CO_2 as a third-component leading to the synthesis of diverse anthranilic acid derivatives. Treatment of amines **7** with arynes generated from **1** in THF at 0 °C under a CO_2 atmosphere (1 atm) afforded corresponding MCCs products **8** (Scheme 6.4).[15] Except the Yoshida's work, the synthetic utility of tertiary amines as nucleophilic trigger in aryne MCCs remains underexplored.[16] Notably, Greaney and coworkers utilized tertiary allylamines in an aryne aza-Claisen rearrangement and demonstrated a novel route for the synthesis of functionalized anilines.[17]

Scheme 6.4: Aryne MCCs involving Amines and CO_2



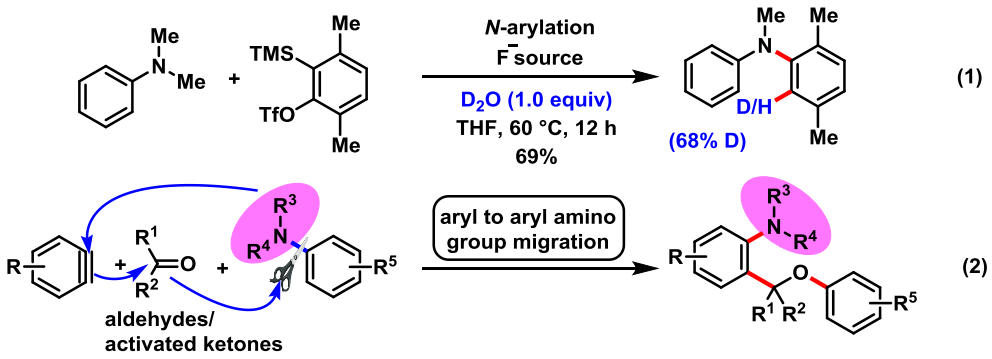
R = H, Me, $(CH_2)_3$, $(CH_2)_4$, OMe, F
R^1 = Et, *i*-Pr, *n*-Pr, *n*-Bu, Cy, $(CH_2)_4$, $(CH_2)_5$

6.3. Statement of the Problem

In previous chapter, we disclosed an efficient transition-metal-free method for the selective monoarylation of aromatic tertiary amines using arynes as aryl source, where we used ammonium bicarbonate as an additive for the protonation of aniline-aryne 1,3-zwitterionic intermediate.[12] The role of additive in the protonation of amine-aryne zwitterionic intermediate was confirmed by using D_2O as an additive (Scheme 6.5, eq 1).

Prompted by this results, we envisioned that the instead of using the proton source for quenching of aniline-aryne 1,3-zwitterionic intermediate, addition of electrophile could result in the formation of MCC product. The three-component coupling of arynes, aromatic tertiary amines, and aldehydes resulting in the formation of *ortho*-functionalized tertiary amines forms the subject of this chapter (eq 2). The results of our investigations revealed an unprecedented three bond forming process, leading to the rapid construction of series of elaborate *ortho*-functionalized tertiary amines and detailed mechanistic studies to understand the intramolecular aryl to aryl amino group migration are illustrated in the following sections.

Scheme 6.5: Reaction of Arynes with Aromatic Tertiary Amines and Carbonyl Compounds

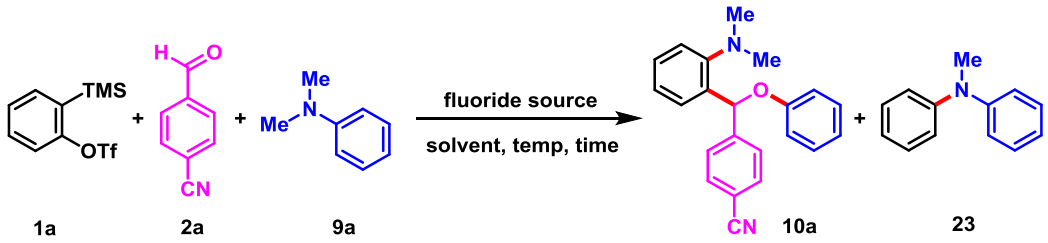


6.4. Results and Discussion

6.4.1. Optimization Studies

The present study was initiated by treating *N*,*N*-dimethyl aniline **9a** and aldehyde **2a** with the aryne generated in situ from 2-(trimethylsilyl)-aryl triflate **1a** using 2.4 equiv each KF and 18-crown-6 at 60 °C. Gratifyingly, under these conditions, a facile reaction took place resulting in the formation of *O*-arylated 2-(dimethylamino)benzhydrol **10a** in 73% yield along with *N*-arylated product *N*-methyl-*N*-phenylaniline **23** in 20% yield (based on ^{1}H NMR spectroscopy, Table 6.1, entry 1). Notably, from a synthetic perspective, product of the multicomponent reaction *ortho*-substituted tertiary amine **10a** has higher synthetic value. Lewis acid catalyzed electrophilic substitution at *para*-position of aromatic tertiary amines is well established. However, *ortho*-functionalization is difficult to accomplish.[18]

Table 6.1: Optimization of the Reaction Conditions[a]



1a 2a 9a 10a 23

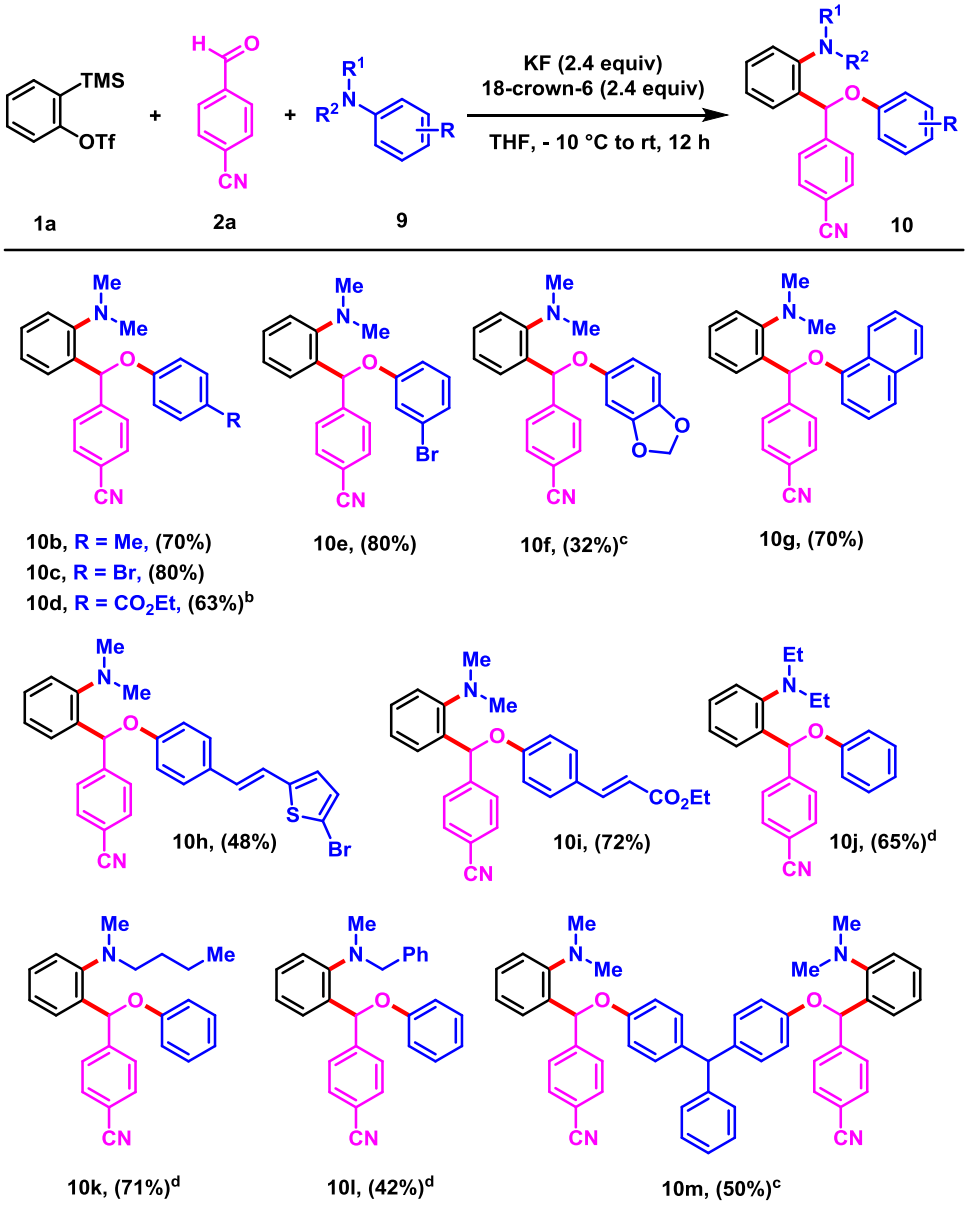
entry	**1a** (equiv)	**2a** (equiv)	**9a** (equiv)	F^- source	solvent	temp (°C)	yield of **10a** (%)[b]	yield of **23** (%)[b]
1	1.2	2	1	KF/18-crown-6	THF	60	73	20
2	1.2	2	1	KF/18-crown-6	THF	40	83	10
3	1.2	2	1	KF/18-crown-6	THF	30	81	<5
4	*1.2*	*2*	*1*	*KF/18-crown-6*	*THF*	*-10 to rt*	*81(76)*	*<5*
5	1.2	2	1	CsF	CH_3CN	30	76	<5
6	1.2	1.5	1	KF/18-crown-6	THF	30	67	<5
7	1.5	1	1	KF/18-crown-6	THF	30	35	21
8	1.5	1.2	1	KF/18-crown-6	THF	30	42	20
9	1.5	1	1.2	KF/18-crown-6	THF	30	49	12

[a]Standard conditions: **1a** (0.30 mmol), **2a** (0.50 mmol), **9a** (0.25 mmol), fluoride source (2.4 equiv), solvent (2.0 mL), temperature and 12 h. [b]The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard. Isolated yield at 0.50 mmol scale in parentheses.

Encouraged by this result, we started the optimization of reaction conditions to avoid the formation of *N*-arylated product **23** by lowering the reaction temperature. Reducing the reaction temperature to 40 °C improved the yield of **10a** and reduced the formation of **23** (entry 2), further decrease in the reaction temperature to 30 °C did not increase the yield of **10a** but *N*-arylated product **23** was formed in <5% yield (entry 3). This indicates that as temperature decreases, yield of the MCC product **10a** increases and the decrease in the formation of *N*-arylated product **23**. When the reaction was performed at -10 °C and slowly warmed to rt, **10a** was formed in 81% yield (76% isolated yield) with traces amount of **23** (entry 4). When the reaction was carried out using CsF as the fluoride source in CH_3CN solvent, **10a** was formed in less yield of 76% (entry 5). Variation in amount of either **1a**, **2a** and **9a** were not proved to be beneficial leading to decrease in the yield of MCC product **10a** and increase in the formation of undesired *N*-arylated product **23** (entries 6-9).

6.4.2. MCCs Involving Arynes, Aldehydes and Tertiary amines: Scope of Tertiary Amines

Scheme 6.6: Substrate Scope of the Aryne MCCs: Variation of the Tertiary Amines[a]



[a]General conditions: **1a** (0.6 mmol), **2a** (1.0 mmol), **9** (0.5 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), -10 °C to rt, 12 h. Yields of the isolated products are given. [b]23% of *N*-arylated product was also isolated. [c]Run on 0.25 mmol scale. [d]Reaction run at 60 °C for 12 h.

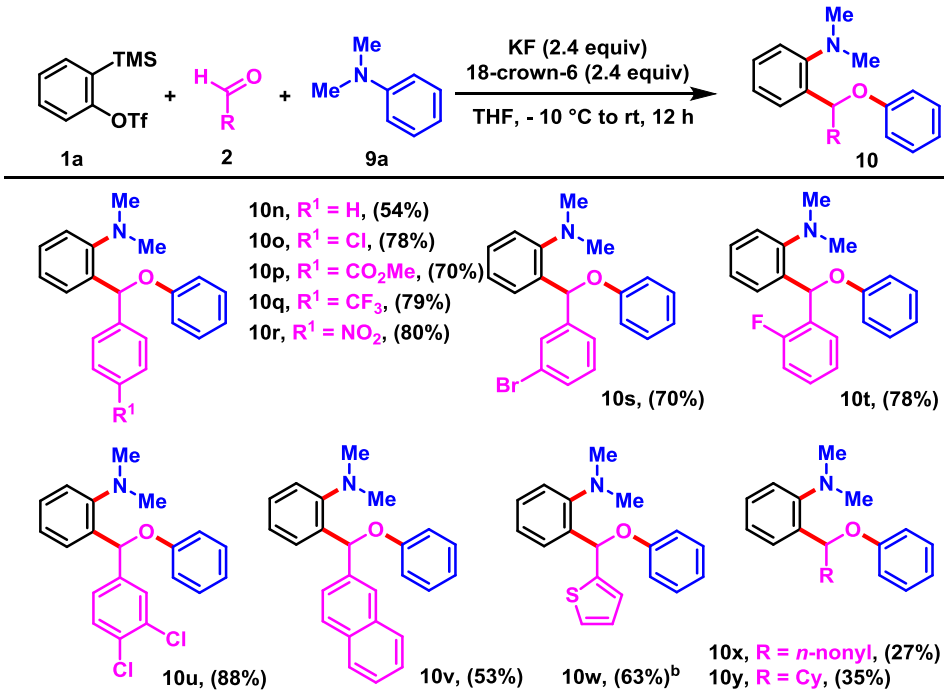
With the optimized reaction conditions for the synthesis of *ortho*-functionalized tertiary amines, we then evaluated the substrate scope of this multicomponent reaction with variety of tertiary amines (Scheme 6.6). *N*,*N*-dimethyl anilines having different

substituents on the aromatic ring were well tolerated, and the expected 2-aminobenzhydrol derivatives were isolated in good yields (**10b-e**). Notably, electron-releasing group on the aryl ring of **9** afforded MCC product in moderate yield (**10f**). Moreover, naphthyl substituted amine furnished the corresponding product **10g** in 70% yield. Gratifyingly, the donor-acceptor tertiary amines readily underwent aryne MCCs with aryl-aryl NMe_2 migration, thereby further expanding the scope of the present reaction (**10h**, **10i**). Furthermore, this MCC is not only limited to only *N*,*N*-dimethyl aniline derivatives. Variations at the NMe_2 moiety in **9** were possible, and these tertiary amines afforded the desired products in moderate to good yields when the reaction was performed at 60 °C, demonstrating the versatility of the present reaction (**10j-l**). Intriguingly, the commonly used dye leuco-malachite green underwent 2-fold MCC upon treatment with **1a** and **2a** leading to the formation of product **10m** in 50% yield.

6.4.3. MCCs Involving Arynes, Aldehydes and Tertiary amines: Scope of Aldehydes

Next, we examined the scope of the aryne MCC with electronically different aldehydes (Scheme 6.7). A series of aromatic aldehydes with electron-releasing and -withdrawing substituents at the 4-position of the ring were well-tolerated, and the expected 1,2-disubstituted arenes were isolated in good yields (**10n-r**). Moreover, 3-substituted and 2-substituted aromatic aldehydes smoothly furnished the MCC products in good yields (**10s, 10t**). Additionally, 3,4-dichloro benzaldehyde and 1-naphthaldehyde worked well to afford the desired products in excellent to good yields (**10u, 10v**). Notably, thiophene-2-carbaldehyde and aliphatic aldehydes also underwent aryne MCCs thereby significantly expanding the scope of this reaction (**10w-y)**.

Scheme 6.7: Substrate Scope of the Aryne MCCs: Variation of the Aldehydes[a]

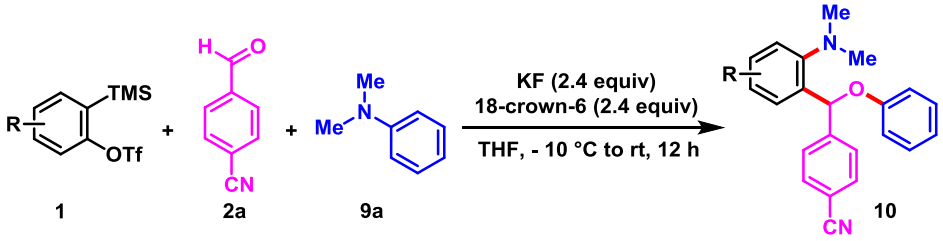


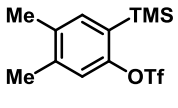
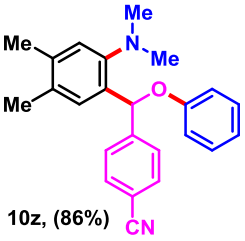
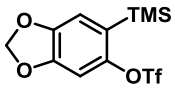
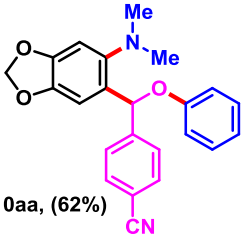
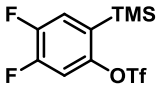
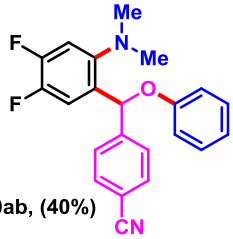
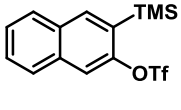
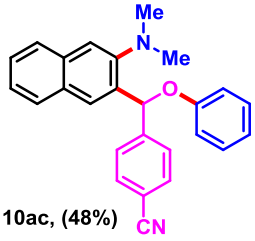
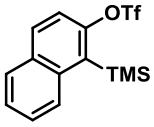
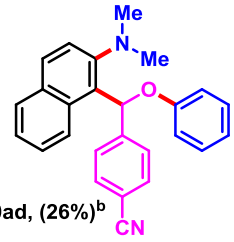
[a]General conditions: **1a** (0.6 mmol), **2** (1.0 mmol), **9a** (0.5 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), -10 °C to rt, 12 h. Yields of the isolated products are given. [b]Given is ^{1}H NMR yield.

6.4.4. MCCs Involving Arynes, Aldehydes and Tertiary amines: Scope of Arynes

Expanding the versatility of present aryne MCC, we studied the scope of the reaction by varying the substituents on the aryne precursor **1** (Table 6.2). Electronically different 4,5-disubstituted symmetrical arynes generated from corresponding precursors readily afforded the functionalized tertiary amines **10z-ab** in moderate to good yields (entries 1-3). In the case of dimethyl derivative **10z**, the structure was unambiguously confirmed by single-crystal X-ray analysis (Figure 6.1). Moreover, symmetrical naphthalyne worked well to afford the product **10ac** in 48%yield (entry 2). Interestingly, the reaction of *N*,*N*-dimethyl aniline **9a** and aldehydes **2a** with the unsymmetrical naphthalyne resulted in the formation of the single regioisomer **10ad** in 26% yield. In this case, the corresponding *N*-arylated product was also isolated in 41% yield.

Table 6.2: Substrate Scope of the Aryne MCCs: Variation of the Arynes[a]



entry	aryne precursor	product, yield (%)
1	 1b	 10z, (86%)
2	 1c	 10aa, (62%)
3	 1d	 10ab, (40%)
4	 1e	 10ac, (48%)
5	 1f	 10ad, (26%)[b]

[a]General conditions: **1** (0.6 mmol), **2a** (1.0 mmol), **9a** (0.5 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), -10 °C to rt, 12 h. Yields of the isolated products are given. [b]41% of *N*-arylated product was also isolated.

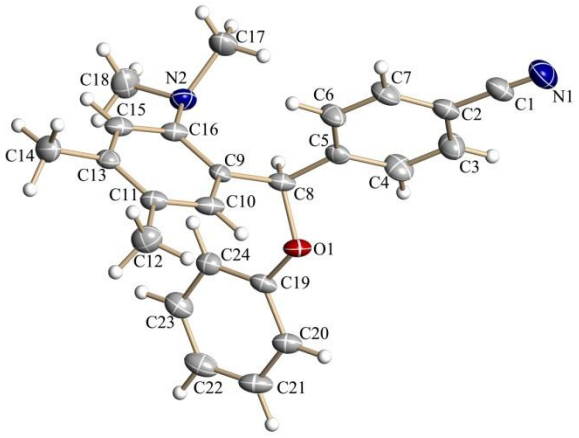
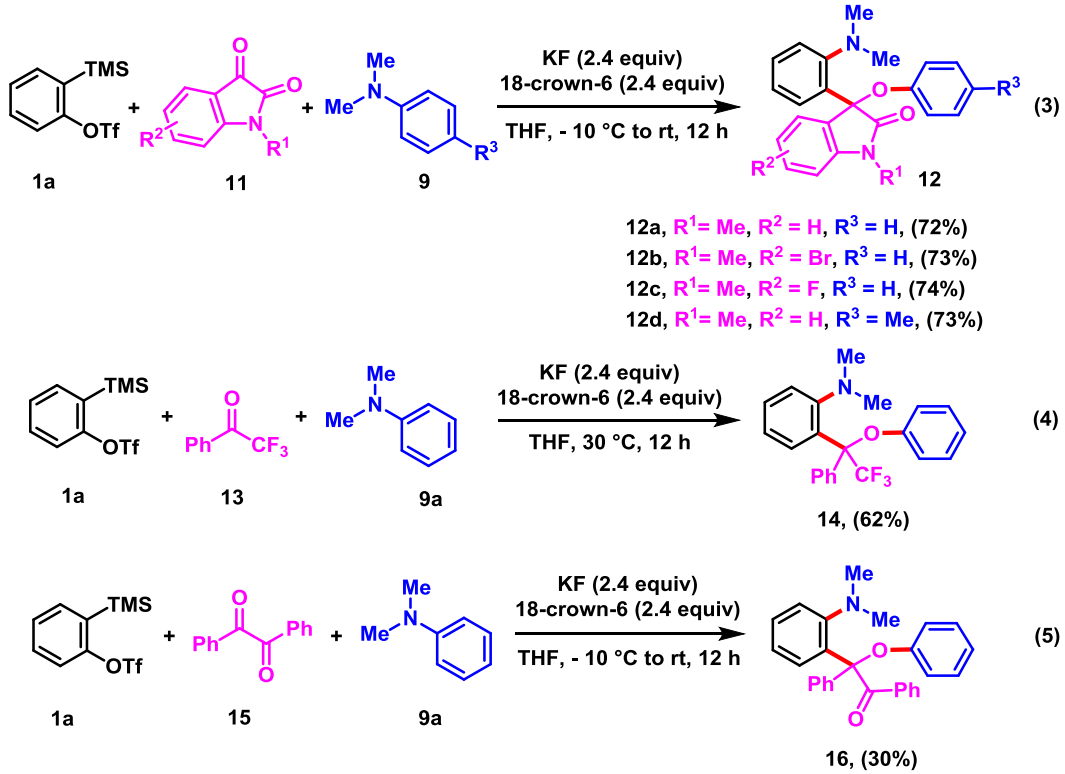


Figure 6.1: X-ray crystal structure of **10z**

6.4.5. MCCs Involving Arynes, Activated Ketones and Tertiary amines

Encouraged by these results, we explored the feasibility of present multicomponent reaction with different carbonyl compounds. To our delight, we found that present method is not only limited to aldehydes as the third component but instead applicable to various cyclic and acyclic activated ketones. For instance, reaction of **1a**, with *N*-methyl isatin **11a** and *N*,*N*-dimethyl aniline **9a** under optimized reaction conditions afforded the oxindole derivative **12a** in 72% yield (Scheme 6.8, eq. 3). Moreover, halogen substituents on carbocyclic ring of *N*-methyl isatin were well tolerated to furnish the expected products in good yields (**12b-d**). The structure of the oxindole derivative **12d** was unequivocally confirmed by single-crystal X-ray analysis (Figure 6.2). Additionally, the reaction of **9a** and aryne generated from **1a** using trifluoroacetophenone **13** and benzil **15** as the carbonyl surrogate afforded the MCC products **14** and **16** in 62% and 30% yield respectively (eqs 4, 5).

Scheme 6.8: Aryne MCCs Employing Activated Ketones



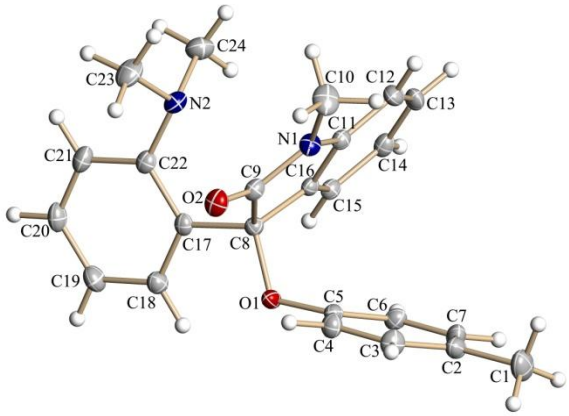
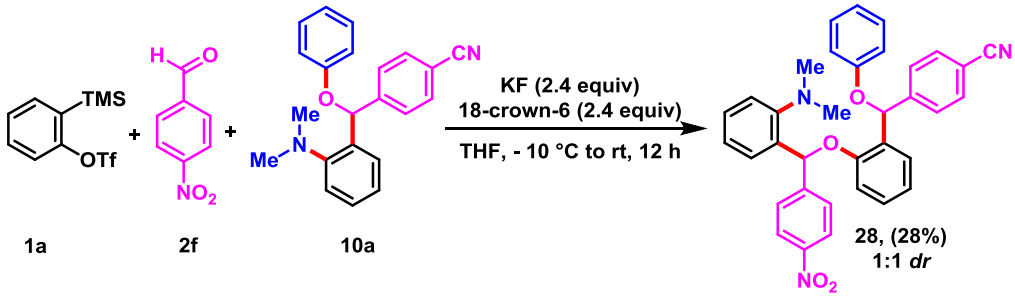


Figure 6.1: X-ray crystal structure of **12d**

Interestingly, the NMe_2 moiety in **10a** has been further engaged in another MCC with aryne generated from **1a** and aldehyde **2f** leading to the formation of the functionalized tertiary amine **28** in 28% yield and 1:1 *dr* (Scheme 6.9).

Scheme 6.9: Iterative Aryne MCC Employing **10a** and **2f**

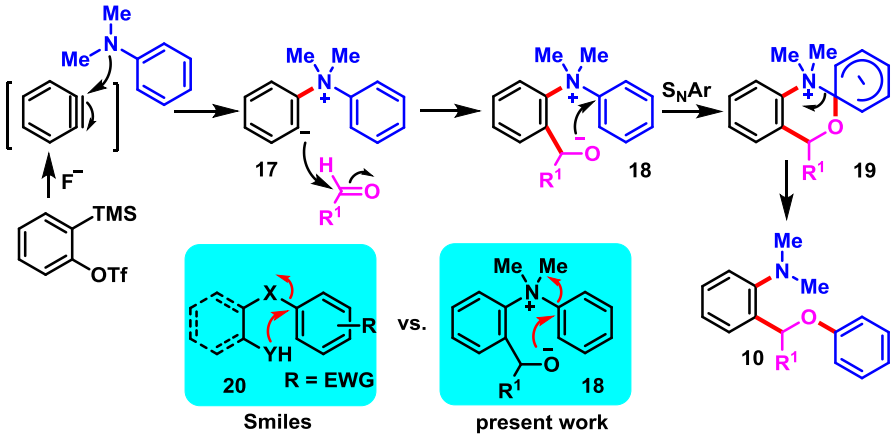


6.5. Mechanistic Studies

The mechanism of this aryne MCC involving aryl-aryl amino group migration can be elucidated as follows (Scheme 6.10). The reaction is likely initiated by the nucleophilic addition of tertiary amine to the aryne forming the 1,3-zwitterionic intermediate **17**, which adds to the electrophilic carbonyl group of aldehyde generating the key tetrahedral intermediate **18**. The intermediate **18** in the absence of proton source could undergo an intramolecular nucleophilic aromatic substitution reaction (S_NAr) followed by aryl-aryl NMe_2 group migration to furnish the desired product **10** via the σ-complex **19**. Remarkably, the mechanism of the present amino group migration is similar with the Smiles rearrangement.[19] The key intermediate in Smiles rearrangement is **20**, and the rearrangement primarily depends on the electron deficiency of the ring (required strong electron-withdrawing group substituent at *ortho*/*para*-position on aromatic ring) to

facilitate S_NAr, leaving group ability of X and nucleophilicity of Y. Usually, Smiles rearrangement proceeds via a five-membered intermediate, but in rare cases, proceed via six-membered intermediates.[20] In our tertiary amine triggered aryne MCC, the key intermediate is the 1,5-zwitterion **18** and the reaction proceeds via the six-membered intermediate **19**.[21] The driving force for the aryl to aryl amino group migration is the presence of the quaternary ammonium salt in **18**, and crucial in facilitating S_NAr. In addition, the electronic nature of the tertiary amine is also important for nucleophilic aromatic substitution (S_NAr), as the substrate with electron-releasing group afforded moderate yield of the product (Scheme 6.6, **10f**).

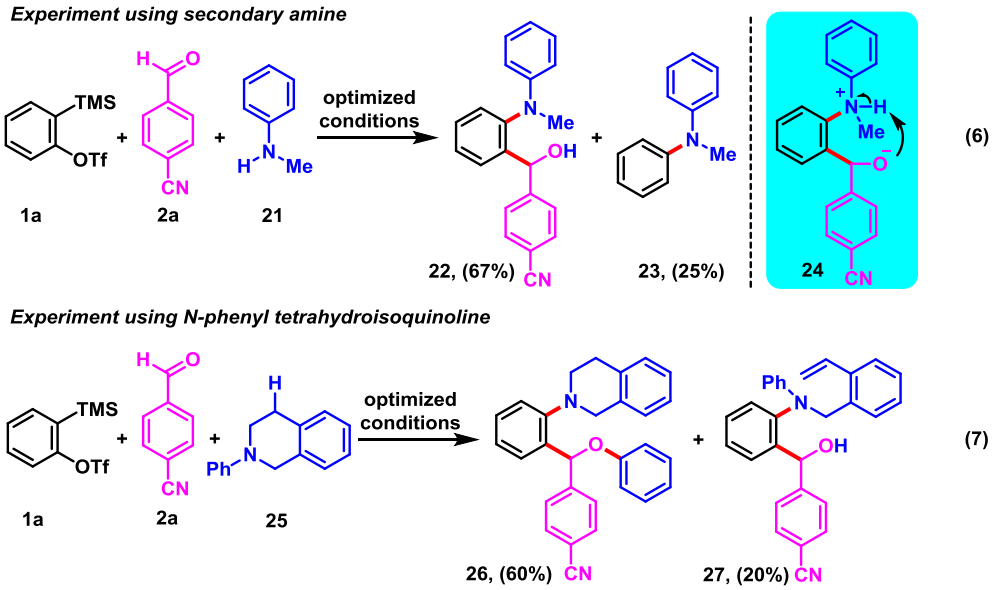
Scheme 6.10: Tentative Mechanism for the MCC



To gain insight into the reaction mechanism, we have carried out mechanistic experiments. A strong indication for the formation of 1,5-zwitterionic intermediate comes from the fact that the reaction of secondary amines **21** with **1a** and **2a** under optimized conditions resulted in the formation of benzhydrol derivative **22** in 67% yield along with *N*-arylated product **23** in 25% yield (Scheme 6.11, eq. 6). In this case, the aryl-aryl amino group migration was not observed. The reaction proceeds via the formation of 1,5-zwitterionic intermediate **24**, which undergoes an intramolecular proton transfer (in preference to aryl-aryl amino migration) to afford **22**. Moreover, to test the possibility of intramolecular proton transfer in 1,5-zwitterionic intermediate, the reaction using 2-phenyl-1,2,3,4-tetrahydroisoquinoline **25** as the amine source with **1a** and **2a** under optimized reaction conditions furnished MCC product **26** in 60% yield along with styrene derivative **27** in 20% yield (eq 7). The styrene **27** was formed by an intramolecular proton

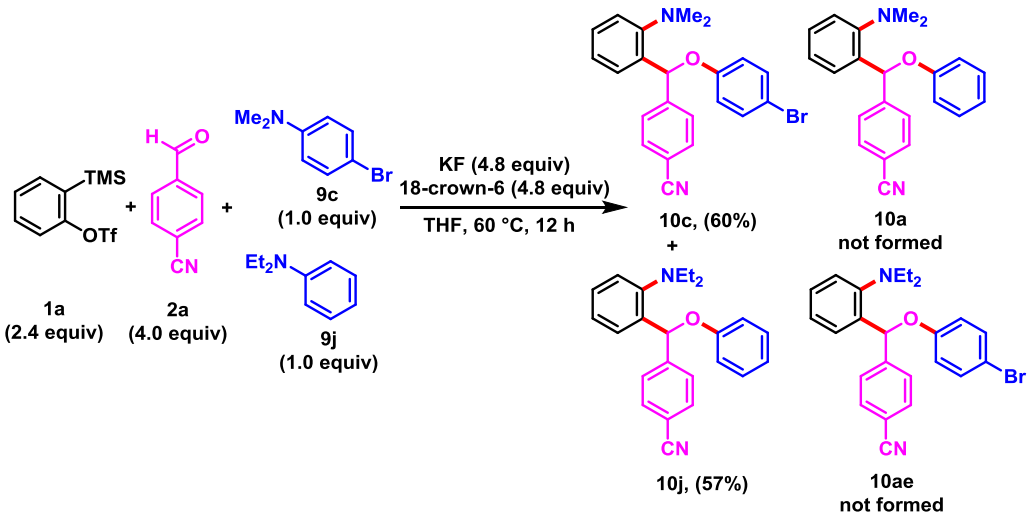
transfer of the initial amine-aryne-aldehyde 1,5-zwitterionic intermediate without the amino group migration.

Scheme 6.11: Mechanistic Experiments



In addition, a crossover experiment was carried out using a mixture that contained an equimolar amount of amines **9c** and **9j** with aryne generated from **1a** and aldehyde **2a**. The reaction afforded the products **10c** (60%) and **10j** (57%), and the cross-over products **10a** or **10ae** were not formed under the reaction conditions (Scheme 6.12). This result clearly suggests that the present aryl-aryl amino group migration is intramolecular in nature.

Scheme 6.12: Cross-over Experiment



6.6. Conclusion

In conclusion, we have developed a novel three-component coupling involving arynes, aldehydes and aromatic tertiary amines leading to the rapid construction of a series of elaborate 2-functionalized tertiary amines.[22] This transition-metal-free tandem three bond forming process proceeds via the aryl to aryl amino group migration, which is mechanistically similar to the Smiles rearrangement. The reaction is not only limited to aldehydes, various cyclic and acyclic ketones also efficiently engaged as a third component in the present method. Mild reaction conditions, broad substrate scope and ease of variation of the three components are the important features of the present reaction.

6.7. Experimental Details

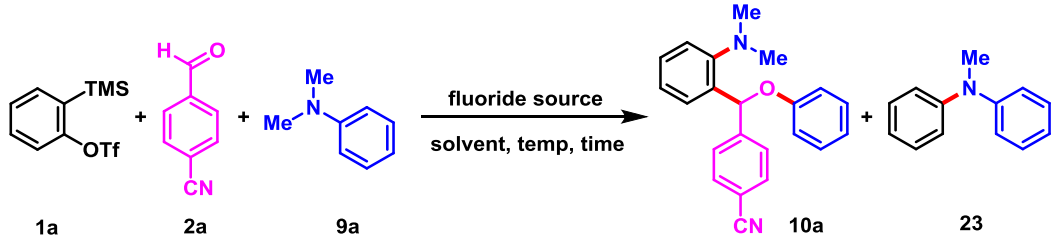
6.7.1. General Information

General information about experimental details is given in Section 2.9.1 of Chapter 2. The 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **1a** and the other symmetric aryne precursors **1b-f** were synthesized following literature procedure.[13] The tertiary amines derivatives **9a-e**, **9g**, **9j** and **9m** were purchased from either from Sigma Aldrich or Alfa Aesar and used as received, without further purification. Tertiary amine derivatives **9f**, **9k,** and **9l** were synthesized following literature procedure.[23]

Infrared spectra were recorded on a Bruker Alpha-E Infrared Spectrophotometer. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

6.7.2. General Procedure for the Optimization of Reaction Conditions

Scheme 6.13: Optimization of Reaction Conditions

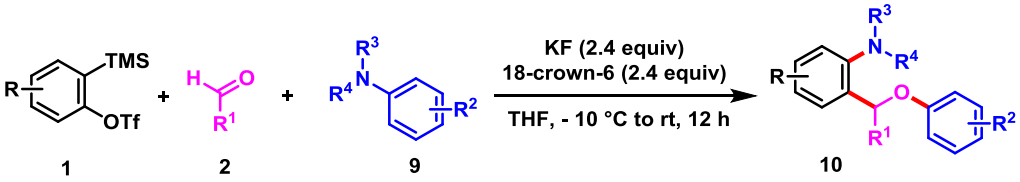


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the fluoride source (0.60 mmol), and aldehyde **2a** (0.066 g, 0.50 mmol) inside the glove box. The mixture was dissolved in 2.0 mL of THF outside the glove box under

argon and to this stirring solution was added *N*,*N*-dimethyl aniline **9a** (0.032 g, 33 µL, 0.25 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.090, 73 µL, 0.30 mmol) at room temperature. Then the screw-capped tube was stirred for the indicated time and temperature. The reaction mixture was then diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated to obtain the crude product whose yield was determined by ^1H NMR analysis using CH_2Br_2 (18.0 µL, 0.25 mmol) as the internal standard.

6.7.3. General Procedure for the MCC Involving Arynes, Aldehydes and Tertiary Amines

Scheme 6.14: Synthesis of 2-Amino Benzhydrol Derivatives



Procedure A:

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the 18-crown-6 (0.317 g, 1.20 mmol), KF (0.070 g, 1.20 mmol) inside the glove box. The mixture was dissolved in 2.0 mL of THF outside the glove box under argon. To this mixture was added 1.0 mmol of the aldehyde **2** (*solid* aldehydes were weighed in air and transferred to the screw-capped test tube by closing the argon flow and *liquid* aldehydes were transferred via syringe with argon flow), and tertiary amine **9** (0.50 mmol). The resultant reaction mixture was cooled to -10 °C and kept stirring for five minutes. To the stirring solution was added the aryne precursor **1** (0.60 mmol). Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. Then the reaction was quenched and the solvent was evaporated. Subsequently the crude residue was purified by flash column chromatography on silica gel to afford the corresponding 2-amino benzhydrol derivatives **10** in moderate to good yields.

Procedure B:

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the 18-crown-6 (0.317 g, 1.20 mmol), KF (0.070 g, 1.20 mmol) inside the glove box. The mixture was dissolved in 2.0 mL of THF outside the glove box under argon. To

this mixture was added 1.0 mmol of the aldehyde **2** (*solid* aldehydes were weighed in air and transferred to the screw-capped test tube by closing the argon flow and *liquid* aldehydes were transferred via syringe with argon flow), and tertiary amine **9** (0.50 mmol). The resultant reaction mixture was cooled to -10 °C and kept stirring for five minutes. To the stirring solution was added the aryne precursor **1** (0.60 mmol). Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. Then the reaction mixture was diluted with CH_2Cl_2 (4.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (20.0 mL). The solvent was evaporated to obtain the crude reaction mixture, which was dissolved in 4.0 mL of MeOH and cooled to 0 °C followed by addition of $NaBH_4$ (0.047 g, 1.25 mmol) in portions with stirring. The reaction mixture was slowly warmed to rt, and stirred for 2 h at rt. The reaction was quenched with 10 mL of water and the resulting aqueous solution extracted with CH_2Cl_2 (10 mL x 3). The organic phase was combined, dried over anhydrous Na_2SO_4, filtered and concentrated to provide the crude product. The crude product was purified by flash column chromatography on silica gel to afford the corresponding 2-amino benzhydrol derivatives **10** in good yields.

In few cases, product of the MCC, 2-amino benzhydrol derivatives **10** have very close R_f with excess aldehyde **2** used in the reaction, so attempted purification of the product by flash column chromatography on silica gel with different solvent systems was not successful. Excess aldehyde **2** reduced to corresponding benzyl alcohol which shows better R_f difference with the product **10**. This procedure allows easy purification of the product **10** by flash column chromatography.

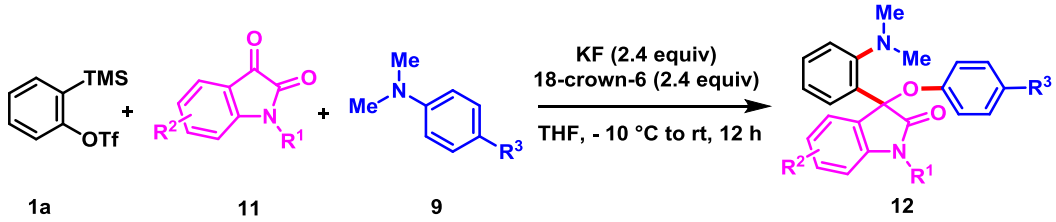
Procedure C:

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the 18-crown-6 (0.317 g, 1.2 mmol), KF (0.070 g, 1.2 mmol) and aldehyde **2** (1.0 mmol) inside the glove box. The mixture was dissolved in 2.0 mL of THF outside the glove box under argon atmosphere and then to the stirring solution was added the tertiary amine **9** (0.50 mmol) and the aryne precursor **1** (0.60 mmol) at room temperature. Then the screw-capped tube was kept in a pre-heated oil bath at 60 °C for 12 h. The reaction mixture was subsequently cooled. The solvent was evaporated and the crude residue was

purified by flash column chromatography on silica gel to afford the corresponding 2-amino benzhydrol derivatives **10** in good yields.

6.7.4. General Procedure for the MCC involving Arynes, Isatins and Tertiary Amines

Scheme 6.15: Synthesis of Oxindole Derivatives

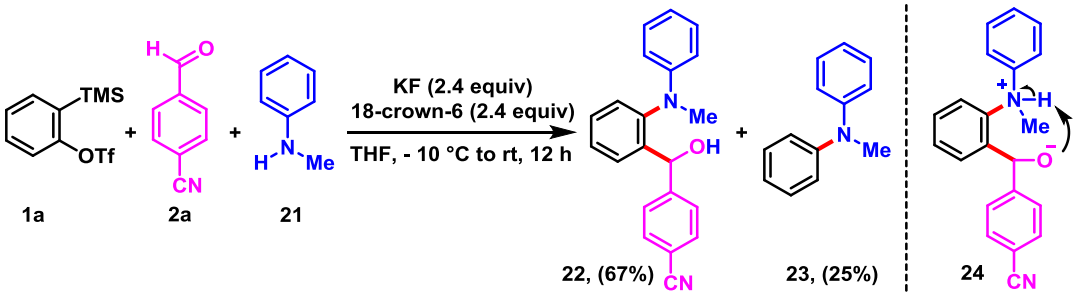


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the 18-crown-6 (0.317 g, 1.2 mmol) and KF (0.070 g, 1.2 mmol) inside the glove box. Outside the glove box isatin **11** (1.0 mmol) was added then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was cooled to -10 °C and kept stirring for five minutes. To the stirring solution was added the tertiary amine **9** (0.50 mmol) and the aryne precursor **1** (0.60 mmol). Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. Then the reaction quenched and the solvent was evaporated. Subsequently, the crude residue was purified by flash column chromatography on silica gel to afford the corresponding oxindole derivative **12** in good yields.

6.8. Mechanistic Experiments

6.8.1. Experiment to Confirm Formation of Tetrahedral Intermediate (18)

Scheme 6.16: Attempted MCC of Aryne, Aldehyde and *N*-Methyl aniline

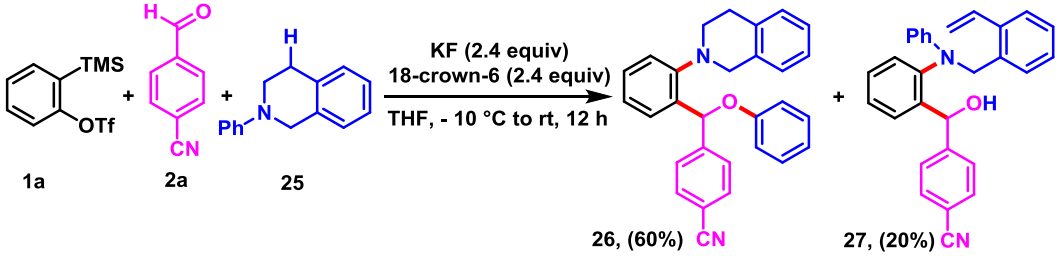


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the 18-crown-6 (0.317 g, 1.2 mmol), KF (0.070 g, 1.2 mmol) and 4-formyl

benzonitrile **2a** (0.131 g, 1.0 mmol) inside the glove box. The mixture was dissolved in 2.0 mL of THF outside the glove box under argon. The resultant reaction mixture was cooled to -10 °C and kept stirring for five minutes. To the stirring solution was added *N*-methylaniline **21** (0.053 g, 54 µL, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol). Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. Then the reaction quenched and the solvent was evaporated. The crude residue was purified by flash column chromatography on silica gel to afford the 4-(hydroxy(2-(methyl(phenyl)amino)phenyl)methyl)benzo nitrile **22** colourless viscous oil (0.105 g, 67% yield) along with *N*-arylated product *N*-methyl-*N*-phenylaniline **23**[12] colourless oil (0.023g, 25% yield). In this case, the aryl-aryl amino group migration was not observed.

6.8.2. Experiments to Test the Possibility of Intramolecular Protonation of Tetrahedral Intermediate (18)

Scheme 6.17: MCC of Aryne, Aldehyde and 2-Phenyl-1,2,3,4-tetrahydroisoquinoline

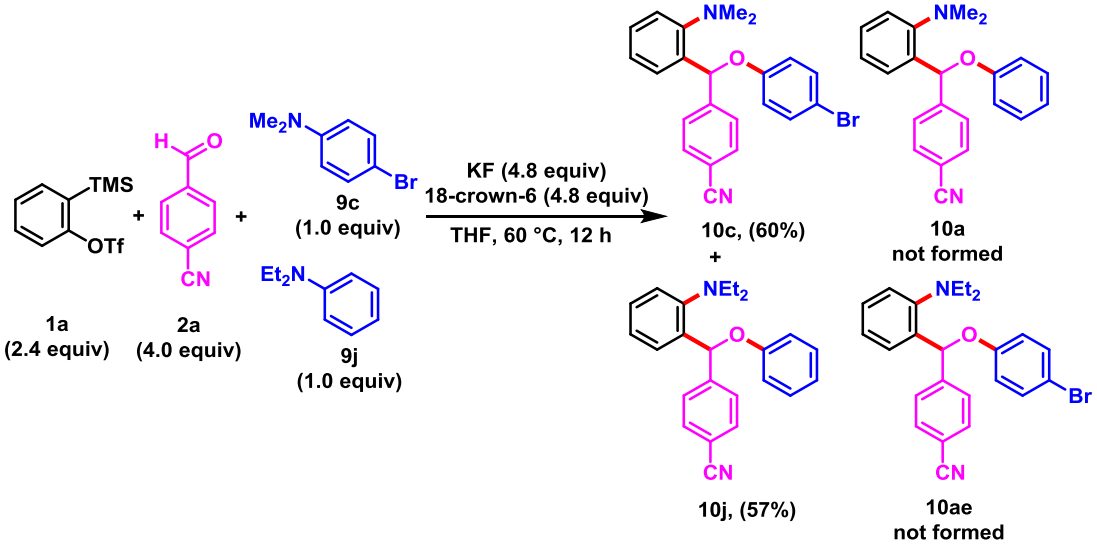


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the 18-crown-6 (0.317 g, 1.2 mmol), KF (0.070 g, 1.2 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) inside the glove box. Outside the glove box 2-phenyl-1,2,3,4-tetrahydroisoquinoline **25** (0.105 g, 0.50 mmol) was added then the screw-capped tube was evacuated and backfilled with argon. The mixture was dissolved in THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was cooled to -10 °C and kept stirring for five minutes. To the stirring solution 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) was added. Then the reaction mixture was slowly warmed to rt and kept stirring for 12 h. Then the reaction quenched and the solvent was evaporated. The crude residue was purified by flash column chromatography on silica gel to afford the MCC product 4-((2-(3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)(phenoxy)methyl)benzonitrile **26** as a yellow solid (0.125 g, 60% yield)

and the styrene derivative 4-(hydroxy(2-(phenyl(2-vinylbenzyl)amino)phenyl)methyl) benzonitrile **27** as a yellow viscous solid (0.041 g, 20% yield).

6.8.3. Cross-over Experiment to Confirm Intramolecular Aryl-Aryl Amino Group Migration

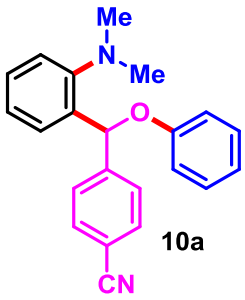
Scheme 6.18: Reaction of Aryne, Aldehyde with a Mixture of Tertiary Amines **9c** and **9j**



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the 18-crown-6 (0.317 g, 1.2 mmol), KF (0.070 g, 1.2 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) inside the glove box. The mixture was dissolved in 2.0 mL of THF outside the glove box under argon atmosphere and then to the stirring solution was added 4-bromo-*N*,*N*-dimethylaniline **9c** (0.050 g, 0.25 mmol), *N*,*N*-diethylaniline **9j** (0.037 g, 40 µL, 0.25 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) at room temperature. Then the screw-capped tube was kept in a pre-heated oil bath at 60 °C for 12 h. The reaction mixture was subsequently cooled. The solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel afforded only two products 4-((4-bromophenoxy)(2-(dimethylamino)phenyl)methyl)benzonitrile **10c** (0.061 g, 60% yield) and 4-((2-(diethylamino)phenyl)(phenoxy)methyl)benzonitrile **10j** (0.050 g, 57% yield). Cross-over products **10a** and **10ae** were not formed.

6.9. Synthesis and Characterization of 2-Amino Benzhydrol Derivatives

4-((2-(Dimethylamino)phenyl)(phenoxy)methyl)benzonitrile (10a)



Following the general procedure **A**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((2-(dimethylamino)phenyl)(phenoxy)methyl)benzonitrile **10a** as a colourless viscous oil (0.125 g, 76% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.52.

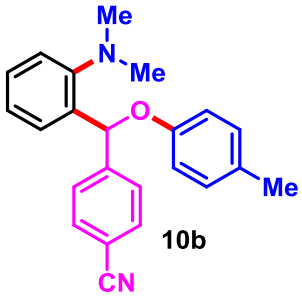
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.27-7.24 (m, 1H), 7.21-7.15 (m, 3H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.92-6.85 (m, 4H), 2.61 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 157.89, 152.59, 147.28, 135.37, 132.25, 129.54, 129.32, 128.72, 128.07, 124.90, 121.26, 120.93, 118.90, 115.83, 111.23, 75.32, 45.86.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{21}ON_2$: 329.1648, found: 329.1644.

FTIR (cm^{-1}): 3021, 2941, 2833, 2787, 2231, 1595, 1492, 1224, 1022, 760.

4-((2-(Dimethylamino)phenyl)(*p*-tolyloxy)methyl)benzonitrile (10b)



Following the general procedure **A**, treatment of 2-(trimethylsil yl)phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*,*N*,4-trimethylaniline **9b** (0.068 g, 73 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((2-(dimethylamino)phenyl)(*p*-tolyloxy)methyl)benz onitrile **10b** as a colourless viscous oil (0.121 g, 70% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.52.

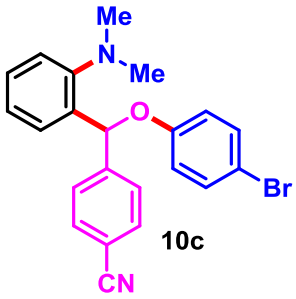
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.40 (dd, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 1H), 7.34-7.30 (m, 1H), 7.27-7.25 (m, 1H), 7.14-7.10 (m, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.92 (s, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 2.67 (s, 6H), 2.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.80, 152.60, 147.51, 135.60, 132.24, 130.51, 130.01, 129.26, 128.75, 128.04, 124.89, 120.91, 118.95, 115.69, 111.16, 75.45, 45.86, 20.55.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{23}ON_2$: 343.1805, found: 343.1805.

FTIR (cm^{-1}): 3020, 2938, 2867, 2833, 2787, 2230, 1603, 1503, 1293, 1224, 1015, 762.

4-((4-Bromophenoxy)(2-(dimethylamino)phenyl)methyl)benzonitrile (10c)



10c

Following the general procedure **A**, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with 4-bromo-*N*,*N*-dimethylaniline **9c** (0.100 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((4-bromophenoxy)(2-(dimethylamino)phenyl)methyl)benzonitrile **10c** as a colourless viscous oil (0.163 g, 80% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.46.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.37-7.31 (m, 4H), 7.28-7.26 (m, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.90 (s, 1H), 6.86 (d, *J* = 8.9 Hz, 2H), 2.67 (s, 6H).

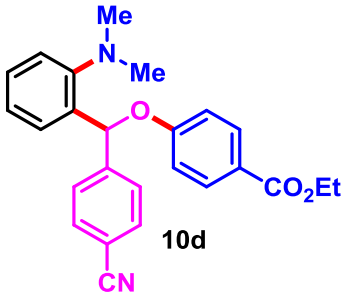
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.98, 152.70, 146.67, 134.75, 132.37, 132.31, 129.54, 128.67, 128.14, 124.97, 120.98, 118.79, 117.65, 113.50, 111.50, 75.57, 45.91.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{20}ON_2Br$: 407.0754, found: 407.0750.

FTIR (cm^{-1}): 3020, 2941, 2787, 2230, 1591, 1489, 1227, 1006, 819, 760.

Ethyl-4-((4-cyanophenyl)(2-(dimethylamino)phenyl)methoxy)benzoate (10d)

Following the general procedure **A**, treatment of 2-(trimethylsilyl)phenyl trifluoro methanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with ethyl 4-(dimethylamino)benzoate **9d** (0.097 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0



10d

mL) at -10 °C to rt for 12 h followed by flash column chromatography of the crude reaction mixture using silica gel afforded ethyl 4-(methyl(phenyl)amino)benzoate[12] as a colourless oil (Pet. ether/EtOAc = 98/02; 0.030 g, 23%) and ethyl-4-((4-cyanophenyl)(2-(dimethylamino)phenyl) methoxy)benzoate **10d** as a colourless viscous oil (Pet. ether/EtOAc = 96/04; 0.126 g, 63% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.61.

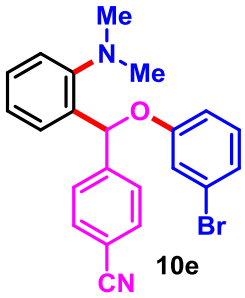
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.95 (d, *J* = 8.9 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.39-7.31 (m, 2H), 7.28-7.26 (m, 1H), 7.14-7.10 (m, 1H), 7.02-6.99 (m, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.69 (s, 6H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 166.30, 161.50, 152.73, 146.41, 134.48, 132.33, 131.59, 129.61, 128.65, 128.21, 124.98, 123.45, 120.98, 118.74, 115.35, 111.58, 75.42, 60.72, 45.91, 14.43.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{25}O_3N_2$: 401.1860, found: 401.1852.

FTIR (cm^{-1}): 3019, 2932, 2861, 2787, 2230, 1709, 1601, 1500, 1455, 1364, 1279, 1237, 1171, 1109, 1011, 853, 760.

4-((3-Bromophenoxy)(2-(dimethylamino)phenyl)methyl) (10e)



10e

Following the general procedure **A**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with 3-bromo-*N*,*N*-dimethylaniline **9e** (0.100 g, 71 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((3-bromophenoxy)(2-(dimethylamino)phenyl)methyl) **10e** as a yellow viscous oil (0.162 g, 80% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.50.

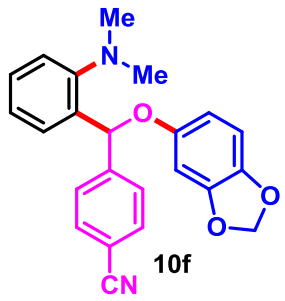
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.35-7.31 (m, 2H), 7.27-7.25 (m, 1H), 7.20 (t, *J* = 1.9 Hz, 1H), 7.14-7.03 (m, 3H), 6.90-6.87 (m, 2H) 2.69 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.63, 152.83, 146.54, 134.43, 132.35, 130.65, 129.64, 129.36, 128.80, 128.32, 125.01, 124.34, 122.88, 120.90, 119.00, 118.83, 114.82, 111.60, 75.26, 46.02.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{20}O_2BrN2O$: 407.0754, found: 407.0750.

FTIR (cm^{-1}): 3020, 2940, 2788, 2231, 1585, 1482, 1222, 1008, 765, 673.

4-((Benzo[*d*][1,3]dioxol-5-yloxy)(2-(dimethylamino)phenyl)methyl)benzonitrile (10f)



10f

Following the general procedure **A**, treatment of 2-(trimethyl silyl)phenyl trifluoromethanesulfonate **1a** (0.090 g, 73 µL, 0.30 mmol) and 4-formylbenzonitrile **2a** (0.066 g, 0.50 mmol) with *N*,*N*-dimethylbenzo[*d*][1,3]dioxol-5-amine **9f** (0.041 g, 0.25 mmol) in the presence of KF (0.035 g, 0.60 mmol) and 18-crown-6 (0.159 g, 0.60 mmol) in THF (1.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography of the crude reaction mixture using silica gel afforded two product as follows 4-((benzo[*d*][1,3]dioxol-5-yloxy)(2-(dimethyl amino)phenyl)methyl)benzonitrile **10f** as a colourless viscous oil (0.030 g, 32% yield).

R_f (Pet. ether /EtOAc = 80/20): 0.66.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 7.36 (dd, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H), 7.32-7.28 (m, 1H), 7.25-7.23 (m, 1H), 7.13-7.09 (m, 1H), 6.81 (s, 1H), 6.62 (d, J = 8.5 Hz, 1H), 6.55 (d, J = 2.5 Hz, 1H), 6.36 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 5.87 (s, 2H), 2.64 (s, 6H).

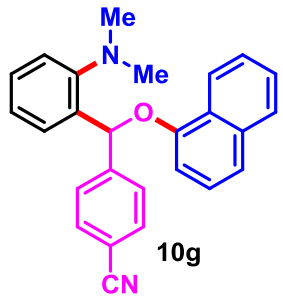
^{13}C NMR (100 MHz, $CDCl_3$): δ 153.32, 152.68, 148.28, 147.33, 142.03, 135.44, 132.28, 129.37, 128.73, 128.08, 124.95, 120.99, 118.93, 111.29, 108.08, 107.66, 101.27, 99.15, 76.33, 45.90.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{21}O_3N_2$: 373.1547, found: 373.1548.

FTIR (cm^{-1}): 3020, 2938, 2883, 2785, 2230, 1611, 1490, 1355, 1212, 1185, 1134, 1097, 1037, 939, 767, 667.

4-((2-(Dimethylamino)phenyl)(naphthalen-1-yloxy)methyl)benzonitrile (10g)

Following the general procedure **A**, treatment of 2-(trimethylsilyl)phenyl trifluoro methanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*,*N*-dimethylnaphthalen-1-amine **9g** (0.086 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0



mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((2-(dimethylamino) phenyl)(naphthalen-1-yloxy)methyl)benzonitrile **10g** as a white solid (0.133 g, 70% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.44.

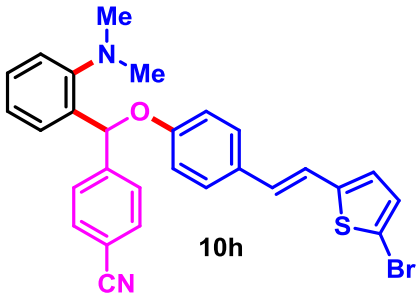
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.40-8.38 (m, 1H), 7.84-7.82 (m, 1H), 7.66-7.62 (m, 4H), 7.55-7.50 (m, 3H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.37-7.28 (m, 3H), 7.17-7.13 (m, 2H), 6.84 (d, *J* = 7.7 Hz, 1H), 2.71 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 153.39, 152.70, 147.34, 135.46, 134.71, 132.37, 129.42, 128.66, 128.05, 127.68, 126.58, 125.88, 125.49, 125.01, 122.24, 120.97, 120.82, 118.96, 111.36, 106.91, 75.53, 45.93.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{23}ON_2$: 379.1805, found: 379.1802.

FTIR (cm^{-1}): 3059, 3020, 2937, 2862, 2786, 2230, 1586, 1496, 1454, 1399, 1271, 1227, 1097, 1057, 759.

(*E*)-4-((4-(2-(5-Bromothiophen-2-yl)vinyl)phenoxy)(2-(dimethylamino)phenyl) methyl)benzonitrile (10h)



Following the general procedure **A**, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzo nitrile **2a** (0.131 g, 1.0 mmol) with (*E*)-4-(2-(5-bromo thiophen-2-yl)vinyl)-*N*,*N*-dimethylaniline **9h** (0.154 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-4-((4-(2-(5-bromothiophen-2-yl)vinyl) phenoxy)(2-(dimethylamino)phenyl)methyl)benzonitrile **10h** as a yellow viscous oil (0.124 g, 48%).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.33.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.38

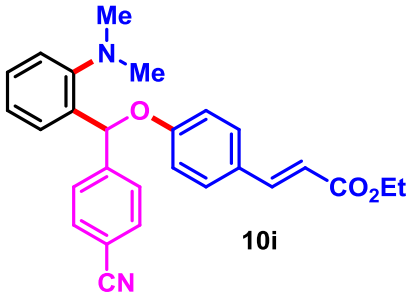
(dd, J_1 = 7.8, J_2 = 1.3 Hz, 1H), 7.35-7.26 (m, 4H), 7.15-7.11 (m, 1H), 6.96-6.93 (m, 5H), 6.75-6.71 (m, 2H), 2.68 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.77, 152.66, 146.97, 144.86, 135.06, 132.30, 130.50, 129.90, 129.45, 128.73, 128.29, 128.12, 127.68, 125.71, 124.94, 120.95, 119.53, 118.87, 116.13, 111.38, 45.91.

HRMS: calculated $[M+H]^+$ for $C_{28}H_{24}BrOSN_2$: 515.0787, found: 515.0789.

FTIR (cm^{-1}): 3021, 2942, 2788, 2231, 1604, 1504, 1223, 1011, 766, 670.

Ethyl (*E*)-3-(4-((4-cyanophenyl)(2-(dimethylamino)phenyl)methoxy)phenyl)acrylate (10i)



10i

Following the general procedure **B** (reduction carried out in EtOH as a solvent), treatment of 2-(trimethyl silyl)phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with ethyl (*E*)-3-(4-(dimethylamino)phenyl) acrylate **9i** (0.110 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 94/06) of the crude reaction mixture using silica gel afforded ethyl (*E*)-3-(4-((4-cyanophenyl)(2-(dimethylamino)phenyl)methoxy)phenyl)acrylate **10i** as a colourless viscous oil (0.154 g, 72% yield).

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

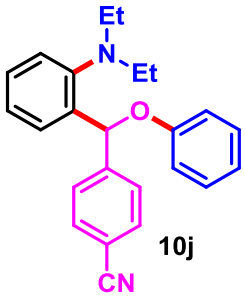
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.60 (m, 3H), 7.55 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.40-7.32 (m, 2H), 7.28 (d, J = 7.1 Hz, 1H), 7.13 (t, J = 7.1 Hz, 1H), 6.99-6.96 (m, 3H), 6.30 (d, J = 16.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.69 (s, 6H), 1.34 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.31, 159.57, 152.66, 146.60, 144.10, 134.68, 132.31, 129.73, 129.54, 128.66, 128.13, 127.69, 124.95, 120.97, 118.76, 116.08, 111.50, 75.43, 60.41, 45.89, 14.39.

HRMS: calculated $[M+H]^+$ for $C_{27}H_{27}O_3N_2$: 427.2016, found: 427.2015.

FTIR (cm^{-1}): 3020, 2941, 2230, 1705, 1633, 1602, 1502, 1455, 1312, 1236, 1170, 1035, 998, 824, 759.

4-((2-(Diethylamino)phenyl)(phenoxy)methyl)benzonitrile (10j)



Following the general procedure **C**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*,*N*-diethylaniline **9j** (0.075 g, 80 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet.ether/EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((2-(diethylamino)phenyl)(phenoxy)methyl)benzonitrile **10j** as a colourless viscous oil (0.116 g, 65% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.48.

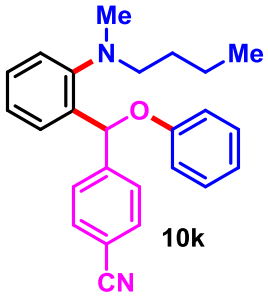
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.24-7.21 (m, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.98 (s, 1H), 6.94-6.91 (m, 3H), 2.93 (q, *J* = 7.1 Hz, 4H), 0.95 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.07, 149.75, 147.33, 137.14, 132.28, 129.50, 128.95, 128.89, 128.28, 124.97, 123.49, 121.24, 118.94, 115.92, 111.29, 75.68, 48.57, 12.65.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{25}ON_2$: 357.1961, found: 357.1955.

FTIR (cm^{-1}): 3021, 2972, 2929, 2230, 1595, 1491, 1226, 1021, 760.

4-((2-(Butyl(methyl)amino)phenyl)(phenoxy)methyl)benzonitrile (10k)



Following the general procedure **C**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*-butyl-*N*-methylaniline **9k** (0.082 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((2-(butyl(methyl)amino)phenyl)(phenoxy)methyl)benzonitrile **10k** as a colourless viscous oil (0.132 g, 71% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.65.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.46 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 7.39-7.34 (m, 1H), 7.31-7.26 (m, 3H), 7.18 (t, *J* = 7.4

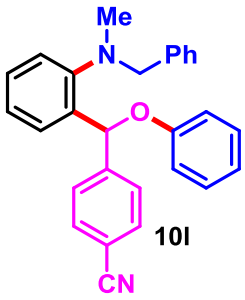
Hz, 1H), 7.03-6.96 (m, 4H), 2.96-2.81 (m, 2H), 2.64 (s, 3H), 1.58-1.46 (m, 2H), 1.33-1.23 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.93, 152.32, 147.19, 135.89, 132.21, 129.45, 129.18, 128.67, 128.16, 124.88, 122.02, 121.19, 118.85, 115.80, 111.20, 75.45, 57.75, 43.33, 30.18, 20.43, 14.03.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{27}ON_2$: 371.2118, found: 371.2117.

FTIR (cm^{-1}): 3020, 2953, 2863, 2802, 2230, 1595, 1491, 1224, 1020, 759.

4-((2-(Benzyl(methyl)amino)phenyl)(phenoxy)methyl)benzonitrile (10l)



10l

Following the general procedure **C**, treatment of 2-(trimethylsilyl) phenyltrifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*-benzyl-*N*-methylaniline **9l** (0.099 g, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((2-(benzyl(methyl)amino)phenyl)(phenoxy)methyl)benzonitrile **10l** as a colourless viscous oil (0.084 g, 42% yield).

R$_f$ (Pet. ether /EtOAc = 95/05): 0.60.

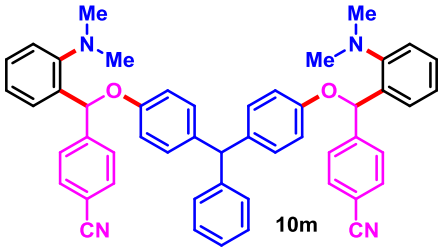
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.40-7.37 (m, 3H), 7.32-7.29 (m, 5H), 7.24-7.17 (m, 3H), 7.03 (s, 1H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 4.06 (q, *J* = 13.5 Hz, 2H), 2.55 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.96, 151.89, 147.04, 138.25, 135.88, 132.34, 129.57, 129.34, 128.91, 128.81, 128.51, 128.26, 127.38, 125.43, 122.66, 121.30, 118.91, 115.87, 111.34, 75.69, 62.30, 43.36.

HRMS: calculated $[M+H]^+$ for $C_{28}H_{25}ON_2$: 405.1961, found: 405.1961.

FTIR (cm^{-1}): 3021, 2941, 2800, 2231, 1595, 1491, 1220, 1022, 763.

Compound (10m)



10m

Following the general procedure **A**, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-formylbenzo nitrile **2a** (0.131 g, 1.0 mmol) with 4,4'-(phenyl

methylene)bis(*N*,*N*-dimethylaniline) **9n** (0.083 g, 0.25 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture using silica gel afforded compund **10m** as a yellow solid (0.094 g, 50%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.42.

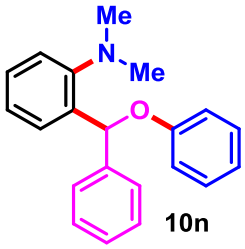
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.63 (d, *J* = 8.3 Hz, 4H), 7.56 (d, *J* = 8.2 Hz, 4H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.37-7.26 (m, 6H), 7.21 (d, *J* = 7.1 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 2H), 7.08 (d, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 4H), 6.90-6.86 (m, 6H), 5.39 (s, 1H), 2.66 (s, 12H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 156.39, 152.48, 147.31, 144.42, 136.81, 135.38, 132.24, 130.31, 129.33, 129.28, 128.60, 128.31, 128.13, 126.26, 124.92, 120.97, 118.91, 115.51, 111.22, 55.27, 45.87.

HRMS: calculated $[M+H]^+$ for $C_{51}H_{45}O_2N_4$: 745.3537, found: 745.3528.

FTIR (cm^{-1}): 2976, 2892, 1639, 1391, 1321, 1220, 1083, 1047, 880, 768, 669.

***N*,*N*-Dimethyl-2-(phenoxy(phenyl)methyl)aniline (10n)**



10n

Following the general procedure **B**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and benzaldehyde **2b** (0.106 g, 101 µL, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 99/01) of the crude reaction mixture using silica gel afforded *N*,*N*-dimethyl-2-(phenoxy(phenyl)methyl)aniline **10n** as a colourless viscous oil (0.082 g, 54% yield).

***R*$_f$** (Pet. ether /EtOAc = 97/03): 0.46.

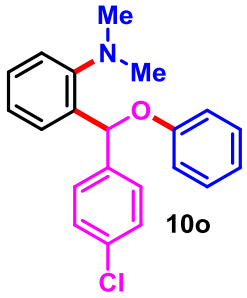
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.58 (dd, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H), 7.53 (d, *J* = 7.4 Hz, 2H), 7.43-7.27 (m, 7H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.08-7.06 (m, 2H), 7.01 (s, 1H), 6.98-6.95 (m, 1H), 2.75 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 158.47, 152.66, 141.60, 136.08, 129.38, 129.11, 128.76, 128.44, 127.75, 127.55, 124.50, 120.67, 120.41, 115.86, 75.71, 45.89.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{22}ON$: 304.1696, found: 304.1689.

FTIR (cm^{-1}): 3020, 2940, 2786, 1594, 1492, 1221, 764.

2-((4-Chlorophenyl)(phenoxy)methyl)-*N*,*N*-dimethylaniline (10o)



Following the general procedure **B**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-chlorobenzaldehyde **2c** (0.140 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2-((4-chlorophenyl)(phenoxy)methyl)-*N*,*N*-dimethylaniline **10o** as a colourless viscous oil (0.132 g, 78% yield).

***R*$_f$** (Pet. ether /EtOAc = 97/03): 0.50.

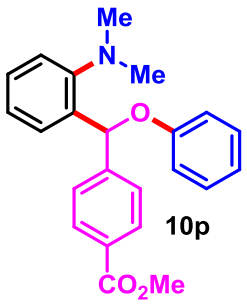
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.31-7.28 (m, 3H), 7.24-7.20 (m, 3H), 7.13-7.09 (m, 1H), 6.96 (d, J = 7.9 Hz, 2H), 6.92-6.88 (m, 2H), 2.66 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.23, 152.64, 140.30, 135.81, 133.35, 129.46, 129.10, 129.00, 128.85, 128.63, 124.68, 120.92, 120.64, 115.87, 75.22, 45.90.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{21}ONCl$: 338.1306, found: 338.1300.

FTIR (cm^{-1}): 3018, 2939, 2832, 2785, 1592, 1490, 1224, 1091, 1015, 761.

Methyl-4-((2-(dimethylamino)phenyl)(phenoxy)methyl)benzoate (10p)



Following the general procedure **A**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and methyl 4-formylbenzoate **2d** (0.164 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded methyl-4-((2-(dimethylamino)phenyl)(phenoxy)methyl)benzoate **10p** as a colourless viscous oil (0.126 g, 70%).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.44.

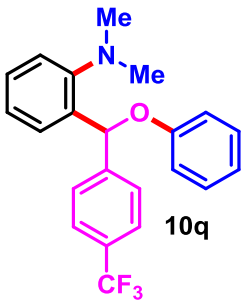
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.47 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.28 – 7.23 (m, 3H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.02 – 7.00 (m, 3H), 6.94 (t, *J* = 7.3 Hz, 1H), 3.93 (s, 3H), 2.70 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.99, 158.20, 152.68, 146.99, 135.81, 129.77, 129.46, 129.30, 129.07, 128.97, 127.49, 124.74, 121.00, 120.74, 115.90, 75.58, 52.14, 45.88.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{24}O_3N$: 362.1751, found: 362.1744.

FTIR (cm^{-1}): 3023, 2937, 1716, 1597, 1285, 1219, 1171, 1022, 768, 673.

***N*,*N*-Dimethyl-2-(phenoxy(4-(trifluoromethyl)phenyl)methyl)aniline (10q)**



10q

Following the general procedure **B**, treatment of 2-(trimethylsilyl) phenyltrifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-(trifluoromethyl)benzaldehyde **2e** (0.174 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded *N*,*N*-dimethyl-2-(phenoxy(4-(trifluoromethyl)phenyl)methyl)aniline **10q** as a yellow solid (0.146 g, 79%).

***R*$_f$** (Pet. ether /EtOAc = 97/03): 0.48.

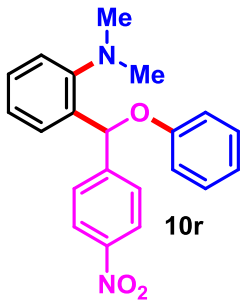
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.61 (m, 4H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.38-7.34 (m, 1H), 7.32-7.27 (m, 3H), 7.17 (t, *J* = 7.4Hz, 1H), 7.05-7.03 (m, 3H), 6.98 (t, *J* = 7.3 Hz, 1H), 2.73 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.17, 152.71, 145.94, 135.74, 129.54, 129.05 (d, *J* = 28.5 Hz), 127.85, 125.44 (d, *J* = 3.5 Hz), 124.85, 121.12, 120.82, 115.91, 75.38, 45.92.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{21}F_3ON$: 372.1570, found: 372.1566.

FTIR (cm^{-1}): 3020, 2940, 2788, 1593, 1491, 1325, 1220, 1021, 768, 675.

***N*,*N*-Dimethyl-2-((4-nitrophenyl)(phenoxy)methyl)aniline (10r)**



10r

Following the general procedure **A**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 4-nitrobenzaldehyde **2f** (0.151 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in

THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 98/02) of the crude reaction mixture using silica gel afforded *N*,*N*-dimethyl-2-((4-nitrophenyl)(phenoxy)methyl)aniline **10r** as a yellow viscous oil (0.140 g, 80% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.63.

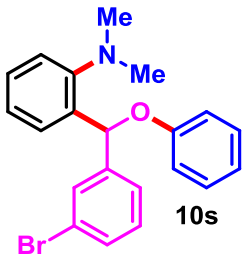
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.44 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 7.37-7.32 (m, 1H), 7.30-7.25 (m, 3H), 7.17-7.13 (m, 1H), 7.03-6.94 (m, 4H), 2.71 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 157.85, 152.60, 149.37, 147.22, 135.39, 129.58, 129.40, 128.70, 128.15, 124.98, 123.69, 121.36, 121.04, 115.87, 75.26, 45.88.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{21}O_3N_2$: 349.1547, found: 349.1546.

FTIR (cm^{-1}): 3022, 2940, 2864, 2833, 2786, 1595, 1522, 1492, 1346, 1225, 1022, 759.

2-((3-Bromophenyl)(phenoxy)methyl)-*N*,*N*-dimethylaniline (10s)



10s

Following the general procedure **B**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 3-bromobenzaldehyde **2g** (0.185 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 2-((3-bromophenyl)(phenoxy)methyl)-*N*,*N*-dimethylaniline **10s** as a colourless viscous oil (0.135 g, 70%).

***R*$_f$** (Pet. ether /EtOAc = 97/03): 0.43.

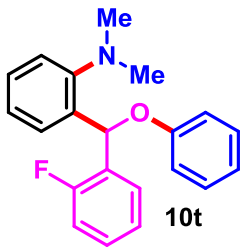
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.70 (s, 1H), 7.52 (dd, J_1 = 7.8, J_2 = 1.4 Hz, 1H), 7.44 (t, *J* = 8.3 Hz, 2H), 7.37-7.33 (m, 1H), 7.30-7.22 (m, 4H), 7.19-7.15 (m, 1H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.98-6.95 (m, 2H), 2.72 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 158.15, 152.60, 144.16, 135.68, 130.66, 130.64, 130.01, 129.46, 129.04, 128.81, 126.16, 124.77, 122.62, 120.98, 120.72, 115.87, 75.22, 45.90.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{21}BrON$: 382.0801, found: 382.0798.

FTIR (cm^{-1}): 3064, 3018, 2941, 2866, 2831, 2785, 1724, 1590, 1487, 1297, 1225, 1017, 765, 684.

2-((2-Fluorophenyl)(phenoxy)methyl)-*N*,*N*-dimethylaniline (10t)



Following the general procedure **B**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 2-fluorobenzaldehyde **2h** (0.124 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 2-((2-fluoro phenyl)(phenoxy)methyl)-*N*,*N*-dimethylaniline **10t** as a colourless viscous oil (0.126 g, 78%).

***R*$_f$** (Pet. ether /EtOAc = 97/03): 0.44.

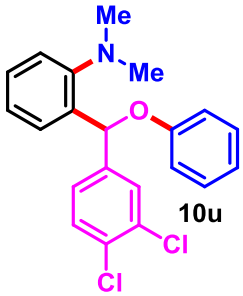
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.51 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.35-7.20 (m, 6H), 7.15-7.05 (m, 3H), 6.99-6.97 (m, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 2.64 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 160.81 (d, *J* = 248.1 Hz), 158.24, 152.97, 134.98, 129.45, 129.14 (d, *J* = 3.4 Hz), 129.0 (d, *J* = 7.8 Hz), 124.34, 124.07 (d, *J* = 3.2 Hz), 120.90, 120.87, 115.80, 115.6 (d, *J* = 21.7 Hz), 70.30, 45.65.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{21}FON$: 322.1602, found: 322.1599.

FTIR (cm^{-1}): 3019, 2942, 2866, 2831, 2784, 1591, 1490, 1458, 1296, 1225, 1018, 765, 680.

2-((3,4-Dichlorophenyl)(phenoxy)methyl)-*N*,*N*-dimethylaniline (10u)



Following the general procedure **B**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 3,4-dichlorobenzaldehyde **2i** (0.175 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2-((3,4-dichlorophenyl)(phenoxy)methyl)-*N*,*N*-dimethylaniline **10u** as a colourless viscous oil (0.165 g, 88% yield).

***R*$_f$** (Pet. ether /EtOAc = 97/03): 0.50.

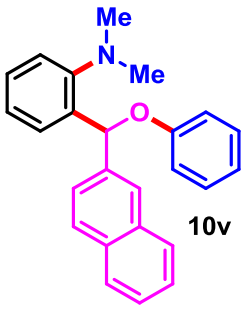
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 1.8 Hz, 1H), 7.45-7.39 (m, 2H), 7.33-7.21 (m, 5H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.96-6.90 (m, 3H), 6.85 (s, 1H), 2.67 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.00, 152.60, 142.24, 135.47, 132.59, 131.54, 130.44, 129.60, 129.54, 129.23, 128.64, 126.92, 124.91, 121.18, 120.88, 115.88, 74.87, 45.92.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{20}ONCl_2$: 372.0916, found: 372.0915.

FTIR (cm^{-1}): 3020, 2937, 1593, 1486, 1221, 1031, 765, 676.

***N,N*-Dimethyl-2-(naphthalen-2-yl(phenoxy)methyl)aniline (10v)**



Following the general procedure **A**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 2-naphthaldehyde **2j** (0.156 g, 1.0 mmol) with *N,N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded *N,N*-dimethyl-2-(naphthalen-2-yl(phenoxy)methyl)aniline **10v** as a yellow viscous oil (0.93 g, 53%).

***R*$_f$** (Pet. ether /EtOAc = 97/03): 0.38.

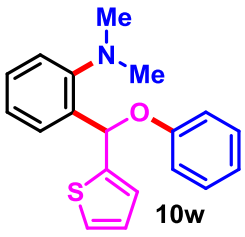
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.80 (m, 4H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.48-7.46 (m, 2H), 7.34-7.21 (m, 4H), 7.14-7.10 (m, 2H), 7.07-7.03 (m, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 2.71 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.55, 152.79, 139.13, 135.93, 133.34, 132.95, 129.43, 129.36, 128.88, 128.28, 127.74, 126.33, 126.15, 126.06, 125.97, 124.51, 120.77, 120.42, 115.94, 75.94, 45.92.

HRMS: calculated $[M+H]^+$ for $C_{25}H_{24}ON$: 354.1852, found: 354.1844.

FTIR (cm^{-1}): 3019, 2977, 2831, 2789, 1598, 1493, 1452, 1216, 1047, 1030, 772, 669.

***N,N*-Dimethyl-2-(phenoxy(thiophen-2-yl)methyl)aniline (10w)**



Following the general procedure **A**, treatment of 2-(trimethylsilyl) phenyltrifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and thiophene-2-carbaldehyde **2k** (0.112 g, 94 µL, 1.0 mmol) with *N,N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in

THF (2.0 mL) at -10 °C to rt for 12 h. The reaction mixture was diluted with CH_2Cl_2 (4.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (20.0 mL). The solvent was evaporated to obtain the crude product which was purified by preparative thin-layer chromatography (Pet. ether) to get *N*,*N*-dimethyl-2-(phenoxy(thio phen-2-yl)methyl)aniline **10w** since the product was unstable in column chromatography. [63% yield was determined by ^{1}H NMR analysis of crude reaction using CH_2Br_2 (36.0 µL, 0.50 mmol) as the internal standard].

***R*$_f$** (Pet. ether /EtOAc = 97/03): 0.43.

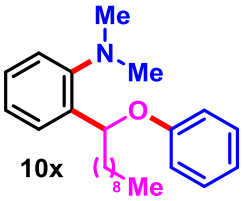
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.43-7.37 (m, 2H), 7.30-7.26 (m, 3H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.12 (s, 1H), 7.08-7.02 (m, 4H), 6.96 (t, *J* = 7.3 Hz, 1H), 2.79 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.93, 152.28, 145.47, 135.48, 129.36, 129.12, 128.53, 126.72, 126.57, 126.14, 124.48, 120.90, 120.04, 115.85, 71.55, 45.88.

HRMS: calculated $[M+H]^+$ for $C_{19}H_{20}ONS$: 310.1260, found: 310.1255.

FTIR (cm^{-1}): 3066, 3015, 2934, 2862, 2786, 1930, 1592, 1490, 1450, 1299, 1224, 1088, 1038, 991, 944, 832, 764, 702.

***N*,*N*-Dimethyl-2-(1-phenoxydecyl)aniline (10x)**



10x

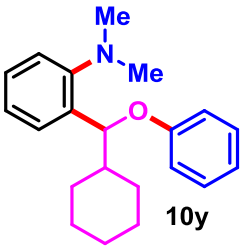
Following the general procedure **A**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and decanal **2l** (0.156 g, 188 µL, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether) of the crude reaction mixture using silica gel afforded *N*,*N*-dimethyl-2-(1-phenoxydecyl)aniline **10x** as a colourless viscous oil (0.048 g, 27% yield).

***R*$_f$** (Pet. ether /EtOAc = 97/03): 0.67.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.6 Hz, 1H), 7.18-7.08 (m, 4H), 7.01 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.76 (t, *J* = 7.3 Hz, 1H), 5.61 (dd, J_1 = 9.3 Hz, J_2 = 2.8 Hz, 1H), 2.70 (s, 6H), 2.05-1.96 (m, 1H), 1.76-1.57 (m, 2H), 1.49-1.40 (m, 1H), 1.31-1.22 (m, 12H), 0.84 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.75, 151.79, 137.87, 129.26, 128.22, 127.20, 124.62, 120.23, 115.77, 74.02, 45.95, 37.77, 32.04, 29.72, 29.58, 29.48, 26.78, 22.82, 14.26.
HRMS: calculated $[M+H]^+$ for $C_{24}H_{36}ON$: 354.2791, found: 354.2788.
FTIR (cm^{-1}): 3018, 2929, 2859, 2785, 1593, 1490, 1457, 1297, 1223, 1042, 941, 767, 677.

2-(Cyclohexyl(phenoxy)methyl)-*N*,*N*-dimethylaniline (10y)



10y

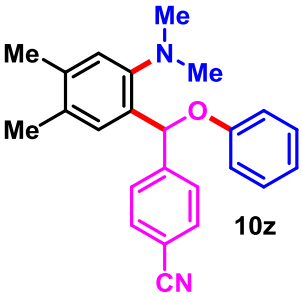
Following the general procedure **A**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and cyclohexanecarbaldehyde **2m** (0.112 g, 121 µL, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether) of the crude reaction mixture using silica gel afforded 2-(cyclohexyl(phenoxy) methyl)-*N*,*N*-dimethylaniline **10y** as a colourless viscous oil (0.055 g, 35% yield).

R_f (Pet. ether /EtOAc = 97/03): 0.61.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 3.6 Hz, 2H), 7.21 (t, *J* = 7.9 Hz, 2H), 7.17-7.13 (m, 1H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.88 (t, *J* = 7.3 Hz, 1H), 5.59 (d, *J* = 6.2 Hz, 1H), 2.74 (s, 6H), 2.09-2.06 (m, 1H), 1.97-1.90 (m, 1H), 1.78-1.73 (m, 2H), 1.54-1.52 (m, 1H), 1.38-1.25 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.17, 152.83, 137.12, 129.23, 128.16, 128.00, 124.85, 121.38, 120.44, 116.49, 79.33, 46.40, 44.37, 30.34, 28.58, 26.76, 26.70, 26.52.
HRMS: calculated $[M+H]^+$ for $C_{21}H_{28}ON$: 310.2165, found: 310.2164.
FTIR (cm^{-1}): 3017, 2931, 2857, 2783, 1592, 1490, 1450, 1295, 1229, 1177, 988, 760.

4-((2-(Dimethylamino)-4,5-dimethylphenyl)(phenoxy)methyl)benzonitrile (10z)



10z

Following the general procedure **A**, treatment of 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1b** (0.196 g, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 98/02) of the crude reaction

mixture using silica gel afforded 4-((2-(dimethylamino)-4,5-dimethylphenyl)(phenoxy) methyl)benzonitrile **10z** as a white solid (0.154 g, 86% yield).

R_f (Pet. ether /EtOAc = 95/05): 0.54.

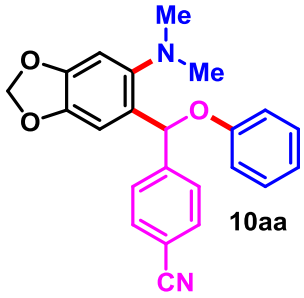
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.26-7.22 (m, 2H), 7.10 (s, 1H), 7.04 (s, 1H), 6.99-6.92 (m, 4H), 2.65 (s, 6H), 2.25 (s, 3H), 2.18 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.07, 150.33, 147.69, 137.85, 133.29, 132.74, 132.28, 129.56, 129.53, 127.94, 122.12, 121.15, 119.04, 115.86, 111.05, 75.13, 46.10, 19.93, 19.50.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{25}ON_2$: 357.1961, found: 357.1961.

FTIR (cm^{-1}): 3021, 2976, 2231, 1598, 1496, 1218, 1036, 768, 671.

4-((6-(Dimethylamino)benzo[*d*][1,3]dioxol-5-yl)(phenoxy)methyl)benzonitrile (10aa)



10aa

Following the general procedure **A**, treatment of 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yltrifluoromethanesulfonate **1c** (0.205 g, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((6-(dimethylamino)benzo[*d*][1,3] dioxol-5-yl)(phenoxy)methyl)benzonitrile **10aa** as a colourless viscous oil (0.116 g, 62% yield).

R_f (Pet. ether /EtOAc = 80/20): 0.66.

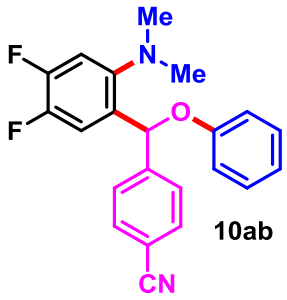
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.28-7.23 (m, 2H), 6.98-6.93 (m, 4H), 6.84-6.82 (m, 2H), 5.93-5.92 (m, 2H), 2.60 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.82, 148.24, 147.45, 147.13, 145.15, 132.33, 129.56, 129.12, 127.95, 121.33, 118.95, 115.96, 111.25, 107.56, 102.31, 101.48, 75.30, 46.33.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{21}O_3N_2$: 373.1547, found: 373.1542.

FTIR (cm^{-1}): 3021, 2896, 2784, 2231, 1597, 1490, 1223, 1040, 764.

4-((2-(Dimethylamino)-4,5-difluorophenyl)(phenoxy)methyl)benzonitrile (10ab)



10ab

Following the general procedure **A**, treatment of 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1d** (0.201 g, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 μL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((2-(dimethylamino)-4,5-difluorophenyl)(phenoxy)methyl) benzonitrile **10ab** as a colourless viscous oil (0.073 g, 40% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.44.

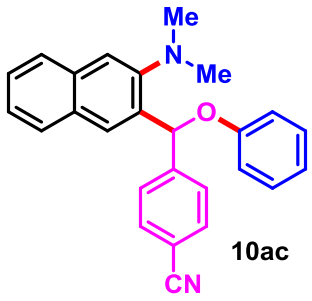
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.27-7.18 (m, 3H), 7.08-7.04 (m, 1H), 6.97-6.92 (m, 3H), 6.87 (s, 1H), 2.62 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.45, 151.40 (dd, J_1 = 251.6 Hz, J_2 = 13.6 Hz), 147.71 (dd, J_1 = 246.5 Hz, J_2 = 13.0 Hz), 146.37, 132.50, 129.70, 127.94, 121.73, 118.74, 117.09 (d, *J* = 18.4 Hz), 115.85, 111.74, 110.44 (d, *J* = 16.7 Hz), 74.67, 46.01.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{19}ON_2F_2$: 365.1460, found: 365.1454.

FTIR (cm^{-1}): 3022, 2789, 2404, 2232, 1599, 1506, 1219, 766, 673.

4-((3-(dimethylamino)naphthalen-2-yl)(phenoxy)methyl)benzonitrile (10ac)



10ac

Following the general procedure **A**, treatment of 3-(trimethyl silyl)naphthalen-2-yl trifluoromethanesulfonate **1e** (0.210 g, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 μL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((3-(dimethylamino)naphthalen-2-yl)(phen oxy)methyl)benzonitrile **10ac** as a colourless viscous oil (0.096 g, 48%).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.46.

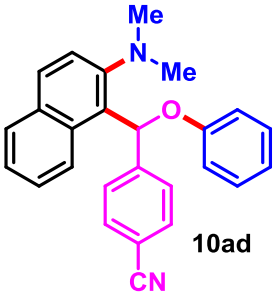
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92, (s, 1H), 7.78 (t, *J* = 8.2 Hz, 2H), 7.66-7.61 (m, 5H), 7.47-7.45 (m, 1H), 7.42-7.38 (m, 1H), 7.30-7.26 (m, 2H), 7.05-7.02 (m, 3H), 6.97 (t, *J* = 7.3 Hz, 1H), 2.79 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.00, 150.71, 147.29, 135.31, 133.93, 132.26, 131.18, 130.76, 129.61, 128.66, 128.19, 128.03, 126.89, 126.63, 125.23, 121.40, 118.90, 118.26, 115.92, 111.31, 77.48, 77.16, 76.84, 76.03, 45.93.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{23}ON_2$: 379.1805, found: 379.1802.

FTIR (cm^{-1}): 3020, 2941, 2788, 2230, 1595, 1492, 1221, 1022, 760, 673.

4-((2-(Dimethylamino)naphthalen-1-yl)(phenoxy)methyl)benzonitrile (10ad)



10ad

Following the general procedure **A**, treatment of 1-(trimethylsilyl) naphthalen-2-yl trifluoromethanesulfonate **1f** (0.209 g, 0.60 mmol) and 4-formylbenzonitrile **2a** (0.131 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-((2-(dimethylamino)naphthalen-1-yl)(phenoxy)methyl)benzo nitrile **10ad** as a yellow viscous oil (0.050 g, 26%) and *N*-methyl-*N*-phenylnaphthalen-2-amine[3] as a colourless oil (0.047 g, 41%).[12] ^{1}H NMR analysis of crude reaction mixture shows formation of single regioisomer, no decteable amount of **10ad'**.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.46.

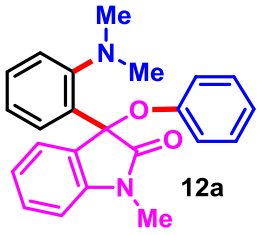
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.71 (s, 1H), 7.61-7.59 (m, 2H), 7.53-7.47 (m, 3H), 7.37-7.27 (m, 2H), 7.23-7.19 (m, 2H), 7.12-7.10 (m, 2H), 6.90 (t, *J* = 7.3 Hz, 1H), 2.78 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.42, 151.54, 147.77, 132.22, 131.92, 131.05, 129.43, 128.48, 127.84, 127.63, 127.10, 126.17, 124.90, 121.36, 119.37, 119.04, 116.08, 110.97, 75.03, 46.13.

HRMS: calculated $[M+H]^+$ for $C_{26}H_{23}ON_2$: 379.1805, found: 379.1805.

FTIR (cm^{-1}): 3019, 2937, 2866, 2837, 2789, 2230, 1596, 1495, 1301, 1224, 1016, 992, 820, 760, 680.

3-(2-(Dimethylamino)phenyl)-1-methyl-3-phenoxyindolin-2-one (12a)



12a

Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 1-methylindoline-2,3-dione **11a** (0.161 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded 3-(2-(dimethylamino)phenyl)-1-methyl-3-phenoxyindolin-2-one **12a** as a white solid (0.128 g, 72% yield).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.63.

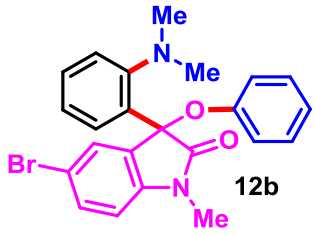
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.20-8.18 (m, 1H), 7.36-7.29 (m, 2H), 7.24-7.20 (m, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 7.07-7.01 (m, 3H), 6.93-6.84 (m, 4H), 6.57 (d, *J* = 7.8 Hz, 1H), 3.03 (s, 3H), 2.39 (bs, 3H), 1.62 (bs, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 174.35, 154.56, 150.93, 144.98, 138.46, 129.72, 129.08, 128.98, 128.48, 127.40, 126.47, 125.34, 124.16, 123.53, 123.39, 121.93, 107.69, 84.22, 45.32, 44.51, 25.93.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{23}O_2N_2$: 359.1754, found: 359.1755.

FTIR (cm^{-1}): 3020, 1720, 1608, 1484, 1217, 926, 768, 670.

5-Bromo-3-(2-(dimethylamino)phenyl)-1-methyl-3-phenoxyindolin-2-one (12b)



12b

Following the general procedure, treatment of 2-(trimethyl silyl)phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 5-bromo-1-methylindoline-2,3-dione **11b** (0.240 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded 5-bromo-3-(2-(dimethylamino)phenyl)-1-methyl-3-phenoxyindolin-2-one **12b** as a white solid (0.160 g, 73% yield).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.60.

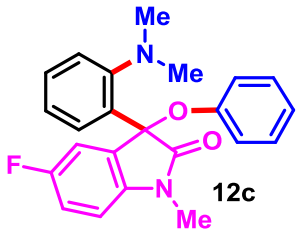
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.18 (m, 1H), 7.42-7.38 (m, 2H), 7.33 (dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, 1H), 7.29-7.27 (m, 1H), 7.24 (d, J = 1.9 Hz, 1H), 7.13-7.10 (m, 2H), 7.00 (t, J = 7.3 Hz, 1H), 6.89 (d, J = 7.7 Hz, 2H), 6.51 (d, J = 8.3 Hz, 1H), 3.05 (s, 3H), 2.42 (bs, 3H), 1.73 (bs, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.71, 154.32, 150.90, 144.04, 137.77, 132.48, 131.37, 129.37, 128.69, 128.25, 127.43, 126.74, 124.48, 123.69, 123.32, 114.36, 109.23, 83.93, 45.61, 44.58, 26.04.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{22}O_2N_2Br$: 437.0859, found: 437.0852.

FTIR (cm^{-1}): 3018, 2938, 2868, 2830, 2786, 1725, 1602, 1484, 1346, 1216, 1100, 769, 701.

3-(2-(Dimethylamino)phenyl)-5-fluoro-1-methyl-3-phenoxyindolin-2-one (12c)



12c

Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 5-fluoro-1-methylindoline-2,3-dione **11c** (0.179 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded 3-(2-(dimethylamino)phenyl)-5-fluoro-1-methyl-3-phenoxyindolin-2-one **12c** as a white solid (0.139 g, 74% yield).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.58.

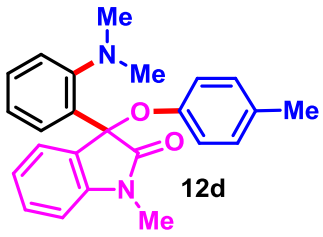
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.20 (m, 1H), 7.43-7.37 (m, 2H), 7.29-7.27 (m, 1H), 7.14-7.10 (m, 2H), 7.01 (t, J = 7.3 Hz, 1H), 6.94-6.87 (m, 4H), 6.56 (dd, J_1 = 8.4 Hz, J_2 = 4.0 Hz, 1H), 3.08 (s, 3H), 2.44 (bs, 3H), 1.72 (bs, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.25, 158.87 (d, J = 240.9 Hz), 154.38, 150.98, 141.10, 137.89, 130.76 (d, J = 7.2 Hz), 129.38, 128.72, 127.44, 126.78, 124.52, 123.72, 123.45, 115.95 (d, J = 23.5 Hz), 113.25 (d, J = 24.5 Hz), 108.24 (d, J = 7.7 Hz), 84.24, 45.58, 44.63, 26.18.

HRMS: calculated $[M+H]^+$ for $C_{23}H_{22}O_2N_2F$: 377.1660, found: 377.1659.

FTIR (cm^{-1}): 3017, 2938, 2868, 2829, 2785, 1722, 1599, 1489, 1460, 1266, 1214, 1132, 879, 767, 673.

3-(2-(Dimethylamino)phenyl)-1-methyl-3-(*p*-tolyloxy)indolin-2-one (12d)



12d

Following the general procedure, treatment of 2-(trimethyl silyl)phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 1-methylindoline-2,3-dione **11a** (0.161 g, 1.0 mmol) with *N*,*N*,4-trimethylaniline **9b** (0.068 g, 73 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet.ether/EtOAc = 90/10) of the crude reaction mixture using silica gel afforded 3-(2-(dimethylamino)phenyl)-1-methyl-3-(*p*-tolyloxy)indolin-2-one **12d** as a white solid (0.136 g, 73% yield).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.65.

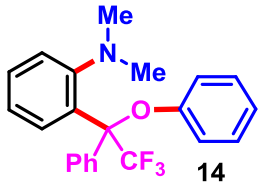
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23-8.19 (m, 1H), 7.39-7.32 (m, 2H), 7.25-7.22 (m, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.60 (d, *J* = 7.8 Hz, 1H), 3.07 (s, 3H), 2.41 (bs, 3H), 2.18 (s, 3H), 1.62 (bs, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.65, 152.29, 150.98, 145.12, 138.64, 133.60, 129.68, 129.28, 129.09, 129.01, 127.52, 126.57, 125.46, 123.56, 123.23, 121.96, 107.74, 84.19, 45.50, 44.63, 26.05, 20.84.

HRMS: calculated $[M+H]^+$ for $C_{24}H_{25}O_2N_2$: 373.1911, found: 373.1906.

FTIR (cm^{-1}): 3021, 2785, 2354, 1720, 1612, 1499, 1217, 929, 769, 671.

***N*,*N*-Dimethyl-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)aniline (14)**



14

Following the general procedure **A**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 µL, 0.60 mmol) and 2,2,2-trifluoro-1-phenylethan-1-one **13** (0.174 g, 140 µL, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 µL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at 30 °C for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 99.50/0.50) of the crude reaction mixture using silica gel afforded *N*,*N*-dimethyl-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)aniline **14** as a colourless viscous oil (0.116 g, 62% yield).

***R*$_f$** (Pet. ether /EtOAc = 97/03): 0.67.

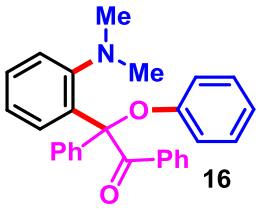
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 6.4 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.39-7.28 (m, 5H), 7.15-7.11 (m, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 2H), 1.86 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.31, 155.04, 140.33, 135.46, 130.87, 128.95-128.93 (m), 128.83, 127.56, 127.45, 127.35, 126.62, 125.31, 123.73, 122.36, 120.08, 85.87-85.55 (m), 45.19.

HRMS: calculated $[M+H]^+$ for $C_{22}H_{21}ONF_3$: 372.1570, found: 372.1568.

FTIR (cm^{-1}): 3065, 3025, 2937, 2860, 2826, 2780, 1590, 1489, 1453, 1217, 1165, 1034, 945, 763, 704, 660.

2-(2-(Dimethylamino)phenyl)-2-phenoxy-1,2-diphenylethan-1-one (16)



16

Following the general procedure **A**, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (0.179 g, 146 μL, 0.60 mmol) and benzil **15** (0.210 g, 1.0 mmol) with *N*,*N*-dimethylaniline **9a** (0.061 g, 64 μL, 0.50 mmol) in the presence of KF (0.070 g, 1.20 mmol) and 18-crown-6 (0.317 g, 1.20 mmol) in THF (2.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2-(2-(dimethylamino) phenyl)-2-phenoxy-1,2-diphenylethan-1-one **16** as a yellow solid (0.061 g, 30%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.70.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 3H), 7.47-7.31 (m, 8H), 7.24-7.20 (m, 1H), 7.07 (t, *J* = 8 Hz, 2H), 6.85-6.80 (m, 3H), 2.40 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.37, 155.10, 152.96, 139.83, 138.10, 137.01, 131.80, 130.72, 130.01, 129.90, 129.56, 128.74, 127.85, 127.75, 127.47, 124.78, 124.66, 121.06, 119.20, 91.85, 76.84, 45.10.

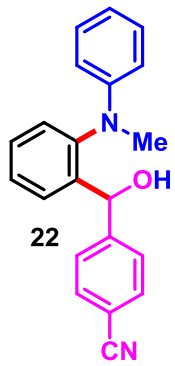
HRMS: calculated $[M+H]^+$ for $C_{28}H_{26}O_2N$: 408.1958, found: 408.1956.

FTIR (cm^{-1}): 3021, 2941, 2833, 2787, 2231, 1595, 1492, 1224, 1022, 760.

4-(Hydroxy(2-(methyl(phenyl)amino)phenyl)methyl)benzonitrile (22)

Compound **22** synthesized by following the procedure given in Scheme 6.16.

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.35.



22

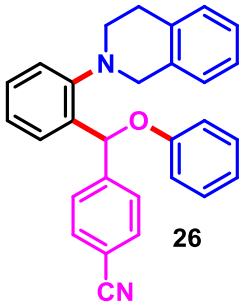
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.51 (m, 3H), 7.41-7.33 (m, 4H), 7.19-7.12 (m, 3H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 8.1 Hz, 2H), 5.93 (s, 1H), 3.23 (bs, 1H), 2.97 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.36, 149.01, 146.20, 141.34, 132.09, 130.10, 129.17, 128.69, 128.08, 127.39, 127.34, 118.89, 118.16, 113.73, 110.79, 71.68, 40.03.

HRMS: calculated $[M+H]^+$ for $C_{21}H_{19}ON_2$: 315.1492, found: 315.1488.

FTIR (cm^{-1}): 3455, 3021, 2244, 1598, 1494, 1218, 1033, 759, 669.

4-((2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)phenyl)(phenoxy)methyl)benzonitrile (26)



26

Compound **26** synthesized by following the procedure given in Scheme 6.17.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.48.

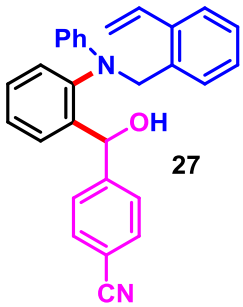
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.58-7.53 (m, 3H), 7.44-7.36 (m, 2H), 7.28-7.20 (m, 6H), 7.01-6.97 (m, 5H), 4.19 (d, *J* = 15.0 Hz, 1H), 3.97 (d, *J* = 15.0 Hz, 1H), 3.37-3.31 (m, 1H), 3.20-3.14 (m, 1H), 3.07-2.93 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.82, 151.22, 147.10, 136.14, 134.95, 134.06, 132.23, 129.54, 129.46, 129.00, 128.69, 128.06, 126.48, 126.36, 125.87, 125.56, 121.89, 121.38, 118.87, 115.91, 111.25, 75.74, 56.08, 51.54, 29.80.

HRMS: calculated $[M+H]^+$ for $C_{29}H_{25}ON_2$: 417.1961, found: 417.1959.

FTIR (cm^{-1}): 3020, 2924, 2811, 2743, 2230, 1729, 1595, 1492, 1457, 1378, 1222, 1024, 934, 768, 675.

4-(Hydroxy(2-(phenyl(2-vinylbenzyl)amino)phenyl)methyl)benzonitrile (27)



27

Compound **27** synthesized by following the procedure given in Scheme 6.17.

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.45.

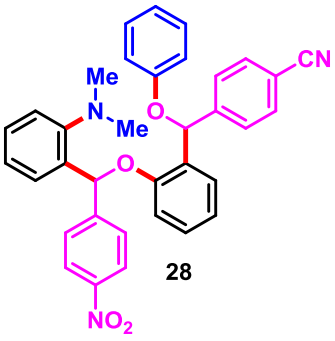
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.45 (m, 3H), 7.37-7.33 (m, 1H), 7.31-7.27 (m, 3H), 7.25-7.13 (m, 7H), 6.84-6.77 (m, 2H), 6.58-6.56 (m, 2H), 5.91 (s, 1H), 5.60 (dd, J_1 = 17.3 Hz, J_2 = 1.1 Hz, 1H), 5.30 (dd, J_1 = 11.0 Hz, J_2 = 1.1 Hz, 1H), 4.81 (d, *J* = 16.0 Hz, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 2.09 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.33, 148.50, 145.32, 141.91, 136.78, 134.51, 133.51, 132.04, 130.15, 129.53, 129.39, 129.07, 128.54, 127.90, 127.78, 127.62, 127.42, 126.36, 118.94, 118.80, 117.16, 114.85, 110.95, 70.50, 54.44.

HRMS: calculated $[M+H]^+$ for $C_{29}H_{25}ON_2$: 417.1961, found: 417.1956.

FTIR (cm^{-1}): 3456, 3019, 2926, 2231, 1595, 1492, 1450, 1359, 1220, 1027, 918, 852, 765, 680.

4-((2-((2(Dimethylamino)phenyl)(4-nitrophenyl)methoxy)phenyl)(phenoxy)methyl) benzonitrile (28)



28

Following the general procedure **B**, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.090 g, 73 μL, 0.30 mmol) and 4-nitrobenzaldehyde **2f** (0.076 g, 0.50 mmol) with 4-((2-(dimethylamino)phenyl)(phenoxy)methyl) benzonitrile **10a** (0.082 g, 0.25 mmol) in the presence of KF (0.035 g, 0.60 mmol) and 18-crown-6 (0.159 g, 0.60 mmol) in THF (1.0 mL) at -10 °C to rt for 12 h followed by flash column chromatography (Pet. ether/EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4-((2-((2(dimethylamino)phenyl)(4-nitrophenyl)methoxy)phenyl) (phenoxy)methyl)benzonitrile **28** as a yellow viscous oil (0.039 g, 28% yield) in 1:1 diastereomeric ratio.

R_f (Pet. ether /EtOAc = 95/05): 0.52.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18-8.13 (m, 4H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.56-7.54 (m, 4H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.44-7.42 (m, 3H), 7.40-7.25 (m, 10H), 7.23-7.14 (m, 6H), 7.09-7.04 (m, 3H), 7.01-6.93 (m, 6H), 6.90 (t, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.71 (s, 1H), 6.61 (s, 1H), 2.67 (s, 6H), 2.57 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.80, 157.74, 154.62, 154.46, 152.71, 152.42, 148.73, 148.50, 147.37, 146.23, 146.06, 134.85, 134.74, 132.25, 132.19, 129.76, 129.67, 129.59, 129.55, 128.72, 128.53, 128.42, 128.14, 127.87, 127.81, 127.74, 125.10, 124.97, 123.86, 123.72, 121.68, 121.66, 121.48, 121.22, 121.09, 118.83, 115.98, 115.86, 113.31, 113.10, 111.54, 111.35, 75.99, 75.62, 75.40, 75.38, 45.95, 45.80.

HRMS: calculated $[M+H]^+$ for $C_{35}H_{30}O_4N_3$: 556.2231, found: 556.2233.

FTIR (cm^{-1}): 3068, 3023, 2933, 2861, 2787, 2229, 1596, 1522, 1490, 1454, 1345, 1230, 1108, 1015, 846, 754.

6.10. References

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List of Publications:

1. Thangaraj, M.; **Bhojgude, S. S.**; Gonnade, R. G.; Biju, A. T. Selective Synthesis of *N*-Unsubstituted and *N*-Aryl Indoles by the Reaction of Arynes with Azirines. *(Manuscript* under revision in *J. Org. Chem.)*.

2. Employing Arynes in Transition-Metal-Free Carbon-Carbon and Carbon-Heteroatom Bond-Forming Reactions.
   Bhojgude, S. S.; Bhunia, A.; Biju, A. T. (*Acc. Chem. Res*. Manuscript communicated).

3. From Insertion to Multicomponent Coupling: Temperature Dependent Reactions of Arynes with Aliphatic Alcohols.
   Thangaraj, M.; **Bhojgude, S. S**.; Mane, M. V.; Biju, A. T. *Chem. Commun*. **2016**, *52*, 1665.

4. Employing Carboxylic Acids in Aryne Multicomponent Coupling Triggered by Aziridines/Azetidines.
   Roy, T; **Bhojgude, S. S.**; Kaicharla, T.; Thangaraj, M.; Garai, B.; Biju, A. T. *Org. Chem. Front.* **2016**, *3*, 71.

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7. Diels-Alder Reaction of Tropones with Arynes: Synthesis of Functionalized Benzobicyclo[3.2.2]nonatrienones.
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10. Efficient Diels-Alder Reaction of 1,2-Benzoquinones with Arynes and Its Utility in One-Pot Reactions.
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    Bhojgude, S. S.; Biju. A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520.

Patents:

1. An Efficient Process For the Synthesis of 2*H*-Chromens.
   Biju, A. T.; **Bhojgude, S. S**.; Kaicharla, T.
   Application No. 1114/DEL/2013. Publication Date. 12.12.2014.

2. Transition-Metal-Free *N*-Arylation of Tertiary Amines Using Arynes.
   Biju, A. T.; **Bhojgude, S. S.**; Kaicharla,
   Pub. No. WO/2014/207761, PCT/IN2014/000418, Publication Date. 31.12.2014.