Extending Aryne Chemistry: Coupling Benzynes with Tropones, Alcohols, Azirines, Allylthioethers and More

Thesis Submitted to AcSIR

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In

CHEMICAL SCIENCES

By

Manikandan T
(Registration Number: 10CC12A26059)

Under the guidance of
Dr. A. T. Biju

Organic Chemistry Division
CSIR-National Chemical Laboratory
Pune-411 008, India.

Nov 2017

Dedicated to.....

my loving parents and Sister

सीएसआयआर-राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा मार्ग, पुणे - 411 008. भारत
CSIR-NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411 008. India.

Dr. A. T. Biju
Senior Scientist
at.biju@ncl.res.in
Organic Chemistry Division

Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Extending Aryne Chemistry: Coupling Benzynes with Tropones, Alcohols, Azirines, Allylthioethers and More"** submitted by **Mr. Manikandan T.** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

Manikandan T.
(Research Student)

Dr. A. T. Biju
(Research Supervisor)

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"Extending Aryne Chemistry: Coupling Benzynes with Tropones, Alcohols, Azirines, Allylthioethers and More"** 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.

Manikandan T
(Research Student)

Nov 2017
CSIR-National Chemical Laboratory
Pune-411 008

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Above all I thank God, the Almighty for guiding me in my life. Because of his grace this work is made possible.

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Manikandan T

List of Abbreviations

Ac	:	Acetyl
t-Am	:	tertiary Amyl
Ar	:	Aryl
bs	:	Broad singlet
Bn	:	Benzyl
Boc	:	Butyloxycarbonyl
BOX	:	Bisoxazoline
t-Bu	:	tertiary Butyl
n-BuLi	:	*n*-Butyl lithium
Cat.	:	Catalytic
CHD	:	Cyclohexadiene
CNS	:	Central nervous system
DBU	:	1 8-Diazabicyclo 5.4.0 undec-7-ene
Dba	:	Dibenzylideneacetone
DCE	:	1,2-Dichloroethane
DCM	:	Dichloromethane
DDQ	:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMA	:	Dimethylacetamide
DME	:	1,2-Dimethoxyethane
DMF	:	*N*,*N*-Dimethylformamide
DMAP	:	4-Dimethylaminopyridine
DMSO	:	Dimethyl sulfoxide
DMS	:	Dimethylsulfide
dr	:	Diastereomer
ee	:	Enantiomeric excess
Et_3N	:	Triethyl amine
Et	:	Ethyl
g	:	gram(s)
h	:	hour(s)
HMDS	:	Bis(trimethylsilyl)amine
HOBt	:	Hydroxybenzotriazole

HRMS	:	High-resolution mass spectrometry
Hz	:	Hertz
IR	:	Infra-red
J	:	Coupling constant in NMR
m	:	Multiplet
*m*CPBA	:	*m*-Chloroperbenzoic acid
Me	:	Methyl
min	:	Minute(s)
mL	:	Milliliter(s)
mmol	:	Millimole(s)
NMR	:	Nuclear magnetic resonance
ORTEP	:	Oak Ridge Thermal Ellipsoid Plot
Piv	:	Pivaloyl
PIFA	:	Bis(trifluoroacetoxy)iodobenzene
Ph	:	Phenyl
PNP	:	*p*-Nitrophenyl
i-Pr	:	Isopropyl
q	:	Quartet
rt	:	Room temperature
s	:	Singlet
t	:	Triplet
TBAF	:	Tetrabutylammonium fluoride
TBAT	:	Tetrabutylammonium difluorotriphenylsilicate
TBS	:	Tertiary butyl silyl
TFA	:	Trifluoroacetic acid
THP	:	Tetrahydropyran
TMEDA	:	Tetramethyl ethylenediamine
Tf	:	Trifluromethanesulfonyl
Tf_2O	:	Trifluoromethanesulfonic anhydride
THF	:	Tetrahydofuran
TLC	:	Thin layer chromatography
Tol	:	Tolyl
Ts	:	Tosyl
TMS	:	Trimethylsilyl

Synopsis

Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	Mr. Manikandan T.
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Research Supervisor	Dr. A. T. Biju (CSIR-NCL, Pune)

The proposed thesis is divided into five chapters. The first chapter deals with a brief introduction to aryne chemistry. The Diels-Alder reaction of tropones with arynes leading to the synthesis of functionalized benzocycloheptenones is described in the second chapter. The third chapter deals with temperature dependent reactions of arynes with aliphatic alcohols for the synthesis of alkyl aryl ethers proceeding via either the insertion reaction or the multicomponent strategy. The focal theme of the fourth chapter is the reaction of arynes with azirines for the selective synthesis of *N*-unsubstituted and *N*-aryl Indoles. In the last chapter, an interesting aryne induced [2,3]-Stevens rearrangement of allylthioethers resulting in the synthesis of functionalized β-keto arylthioethers has been described. The details are given below.

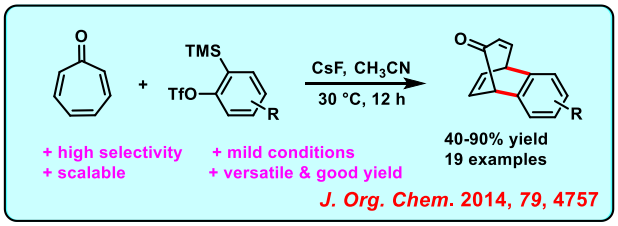
Chapter 1: **A Brief Introduction to Aryne Chemistry**

Arynes are highly reactive intermediates having several applications in organic synthesis for the construction of various *ortho*-disubstituted arenes.[1] Due to the installation of the carbon-carbon triple bond in a six-membered ring, compared to normal alkynes, the unhybridized *p*-orbitals in arynes are no longer parallel to each other. The high reactivity of arynes is due to this ring strain. Consequently, arynes are useful as valuable intermediates for the functionalization of arenes. Traditionally, arynes are generated in solution from haloarenes under strong basic conditions. However, the scope of many of the aryne reactions is limited due to the harsh conditions used for their generation. The renaissance of interest in aryne chemistry is mainly due to the mild condition for their generation by the fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates.[2] A brief account of the transition-metal-free applications of arynes in carbon-carbon and carbon-heteroatom bond-forming reactions is presented in the introduction chapter.

Chapter 2: **Diels-Alder Reaction of Tropones with Arynes: Synthesis of Functionalized Benzocycloheptenones**

Tropones are a valuable class of compounds that have attracted much attention of organic chemists from synthetic and theoretical perspectives. Depending on the reaction conditions and the coupling partner, tropones can react as a 4π, 6π, or 8π component in cycloaddition reactions. The synthetic utility of tropones as a 4π component in Diels−Alder reaction can result in the straightforward access to bicyclo[3.2.2] compounds. In the context of our interest in aryne chemistry, we have developed a new protocol for the mild, practical and scalable Diels-Alder reaction of tropones with arynes leading to the synthesis of benzobicyclo[3.2.2]nonatrienone derivatives in good yields.[3] Differently substituted tropones

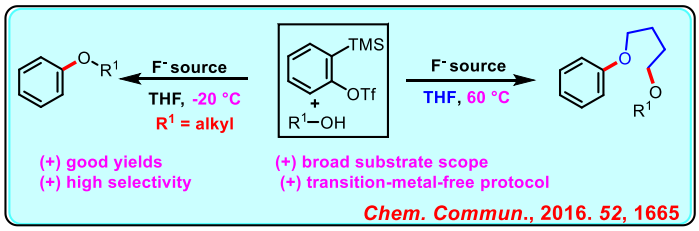
undergo selective [4 + 2] cycloaddition with arynes generated in situ by the fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates, allowing the synthesis of cycloadducts in moderate to good yields.



Scheme 1: Diels-Alder Reaction of Tropones with Arynes

Chapter 3: **From Insertion to Multicomponent Coupling: Temperature Dependent Reactions of Arynes with Aliphatic Alcohols**

Transition-metal-free aryne multicomponent couplings (MCCs) and insertion reactions provide straightforward access to various 1,2- disubstituted arenes. Moreover, transition-metal-catalyzed *O*-arylation using aliphatic alcohols is a powerful strategy for the construction of alkyl aryl ethers. In this context, syntheses of alkyl aryl ethers under transition-metal-free conditions have the economic and ecological advantage. Despite successful aryne insertion to O-H bond of phenols and carboxylic acids, the related insertion of arynes into O-H bond of aliphatic alcohols are underexplored. In this chapter, the transition-metal-free, and temperature dependent selectivity switch observed in the reaction of arynes with aliphatic alcohols has been presented. At -20 °C, arynes smoothly insert into the O-H bond of alcohols to form alkyl aryl ethers. Interestingly, at 60 °C, highly selective multicomponent coupling occurs with solvent THF acting as the nucleophilic trigger affording (4-(alkoxy)butoxy)arenes.[4] Both reactions tolerate a broad range of functional groups, and the desired products are formed in moderate to good yields and high selectivities.

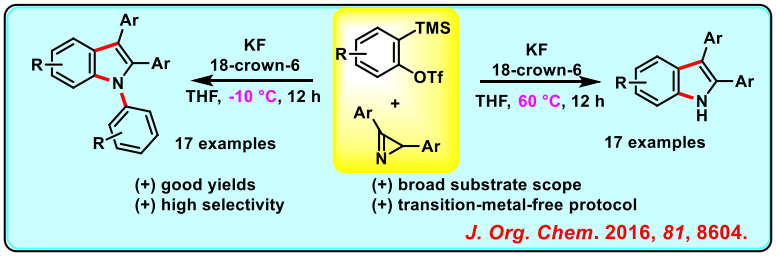


Scheme 2: Temperature Dependent Reaction of Arynes with Aliphatic Alcohols

Chapter 4: **The Reaction of Arynes with Azirines: Selective Synthesis of *N*-Unsubstituted and *N*-Aryl Indoles**

The indole nucleus is a common structural motif present in numerous biologically active natural products, pharmaceutical compounds and agrochemicals. Consequently, development of straightforward, cheap and flexible synthetic routes for the construction of functionalized indoles is of great importance. The transition-metal-free and temperature dependent highly selective reaction of arynes with 2*H*-azirines allowing the synthesis of either *N*-unsubstituted or *N*-aryl indoles forms the subject matter of this chapter. At 60 °C, arynes generated from 2-(trimethylsilyl)aryl triflates smoothly insert into 2*H*-azirines to form 2,3-diaryl indoles with high

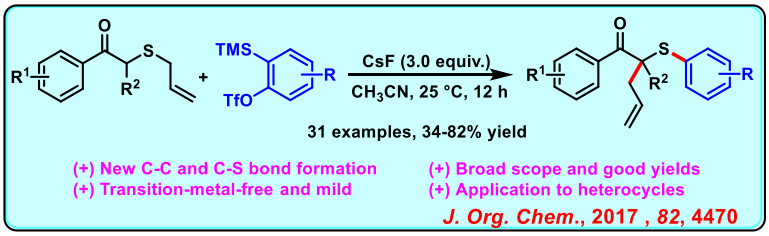
selectivity. Interestingly, when the reaction was performed at -10 °C, the selectivity was switched to the formation of 1,2,3-triaryl indoles in good yields.[5]



Scheme 3: Temperature Dependent Switchable Reaction of Arynes with 2*H*-Azirines

Chapter 5: **Aryne Induced [2,3] Stevens Rearrangement of Allylthioethers: Synthesis of Functionalized β-Keto Arylthioethers**

Organosulfur compounds are endowed with diverse applications in pharmaceutical chemistry and crop protection, and have attracted considerable attention from both industry and academia. Among the organosulfur compounds, the β-keto thioethers are important as they are valuable core structure in various biologically active molecules. In view of this, a mild and transition-metal-free synthesis of β-keto arylthioethers has been developed by the aryne triggered [2,3] Stevens rearrangement of allylthioethers. The key sulfur ylide intermediate for the rearrangement was formed by the *S*-arylation of allylthioethers with arynes generated from 2-(trimethylsilyl)aryl triflates using CsF. A series of allylthioethers and differently substituted arynes are tolerated under the present reaction conditions. Later, the reaction products are converted into valuable heterocycles such as furan, thiophene and pyridazine derivatives in two-step procedure.[6]



Scheme 4: Aryne Triggered [2,3] Stevens Rearrangement of Allylthioethers

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Chapter 1

A Brief Introduction to Aryne Chemistry

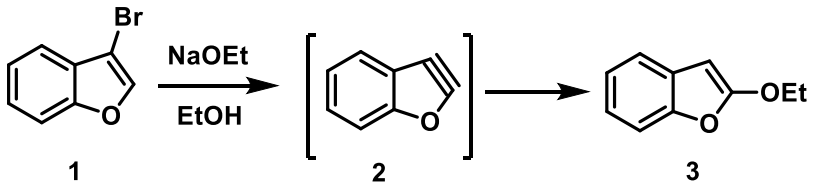
Arynes represent a class of unique and highly versatile synthetic intermediates. In the recent years, arynes, particularly those that can be generated from the corresponding *o*-(trimethylsilyl)aryl triflates, have emerged as powerful synthons in organic synthesis. The very convenient, mild method for generating arynes from *o*-(trimethylsilyl)aryl triflates developed by Kobayashi and co-workers in 1983 allows one to conveniently generate a highly reactive benzyne intermediate at mild condition, using readily accessible solvents and only moderately basic fluoride ion. This chapter deals with a brief account of recent developments on aryne cycloaddition, insertion, multicomponent and rearrangement reactions.

1.1. Introduction

Arynes are highly reactive intermediates having numerous applications in organic synthesis for the construction of various *ortho*-disubstituted arenes.[1] In the past decades, chemistry of arynes has encountered an unprecedented resurgence and facilitated access to an array of 1,2-disustituted benzene derivatives for the construction of benzo-fused carbocycles and heterocycles, which are otherwise difficult to achieve by conventional methods. Our research aims at developing transition-metal-free carbon–carbon and carbon–heteroatom bond-forming reactions using arynes. The focal theme of this chapter is to summarize the recent developments on aryne cycloaddition, insertion, multicomponent and rearrangement reactions. In order to put things on perspective, a brief introduction to arynes, methods for generation and their application in Diels-Alder reaction, insertion, multi component and rearrangement reaction of arynes is given in the following sections.

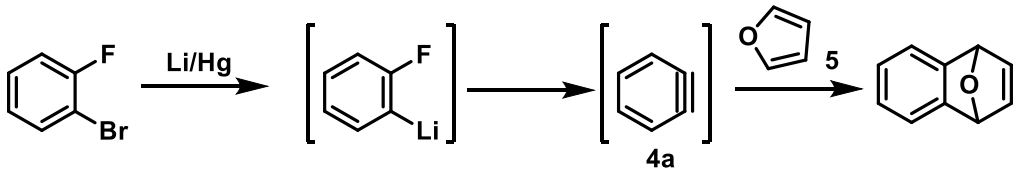
1.2. History and structure

The very first hint for the existence of an aryne was reported in 1902 by Stoermer and Kahlert when they observed the formation of 2-ethoxybenzofuran **3** on treatment of 3-bromobenzofuran **1** with NaOEt in ethanol and postulated the formation of *o*-didehydrobenzofuran (2, 3-didehydrobenzofuran) **2** as a reactive intermediate (Scheme 1.1).[2] But this intermediate was having no direct experimental evidence at that time.



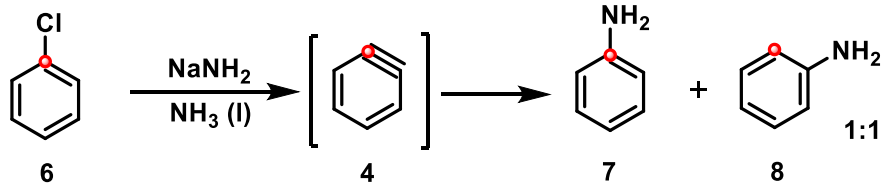
Scheme 1.1: Generation of Arynes from 3-Bromobenzofuran

Later, in 1942, Wittig and co-workers proposed the existence of benzyne intermediate **4a** and trapped it with furan **5** in a [4+2] cycloaddition in 1956 (Scheme 1.2).[3] This initial report sparked tremendous activity in the field of aryne chemistry.



Scheme 1.2: Aryne Generation via Dehalogenation of Dihalobenzene

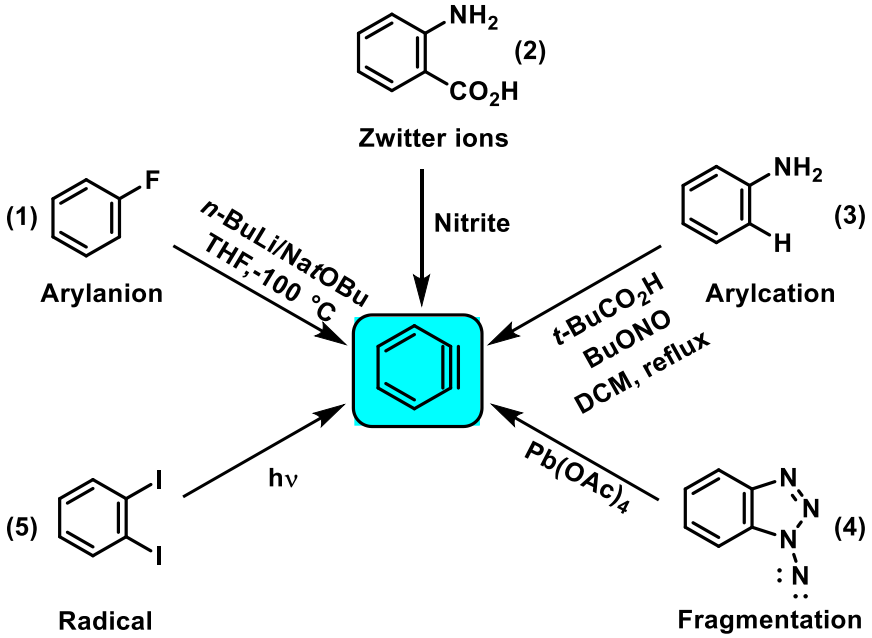
Moreover, In 1953, Roberts and co-workers confirmed the structure of benzyne **4** by ^{14}C labelling experiment. The reaction of ^{14}C labelled chlorobenzene **6** with sodium or potassium amide was conducted and analysed the ^{14}C-label incorporation into the resulting aniline: equal amounts of aniline with ^{14}C incorporation at C-1 (**7**) and C-2 (**8**) were observed (Scheme 1.3).[4] This result necessitated a symmetrical intermediate – now known as benzyne.



Scheme 1.3: Experiment to Confirm Symmetrical Nature of Intermediate

1.3. Methods of Aryne Generation

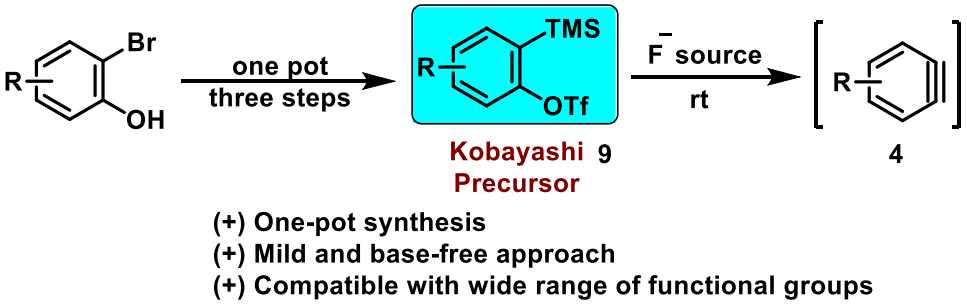
Arynes can be generated from aryl anions, aryl cations, zwitterions, aryl radicals, and by fragmentation reactions. Even at low temperatures, arynes are highly reactive and they must be generated in situ (Scheme 1.4). The traditional method for the generation of arynes is by treating aromatic halides with strong bases such as sodium amide or organometallic reagents derived from Li, and Mg (eq 1). However, the harsh and basic reaction condition is not favorable for substrates containing base sensitive functional groups.



Scheme 1.4: Methods of Aryne Generation

Additionally, arynes can also be generated by the decomposition of benzenediazonium 2-carboxylates obtained by the aprotic diazotization of anthranilic acids and diazotisation of aniline with *tert*-Butyl nitrite (eq 2, 3). Notably, the explosive character of diazonium compounds intends a serious limitation of this method. Fragmentation of aminotriazole produces aryne with evolution of nitrogen gas but required stoichiometric amount of oxidant such as lead tetraacetate, resulting in less functional group tolerance (eq 4).[5] Furthermore, generation of aryne from diiodo compound via photochemical reaction leads to low yield of expected products with unwanted side reactions (eq 5).

In 1983 Kobayashi and co-workers developed the very convenient and practical method for the generation of arynes **4** by the fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates **9** (Scheme 1.5).[6] This mild method is tolerable with a wide range of functional groups, reagents and presently, this is the most efficient method for the generation of arynes.



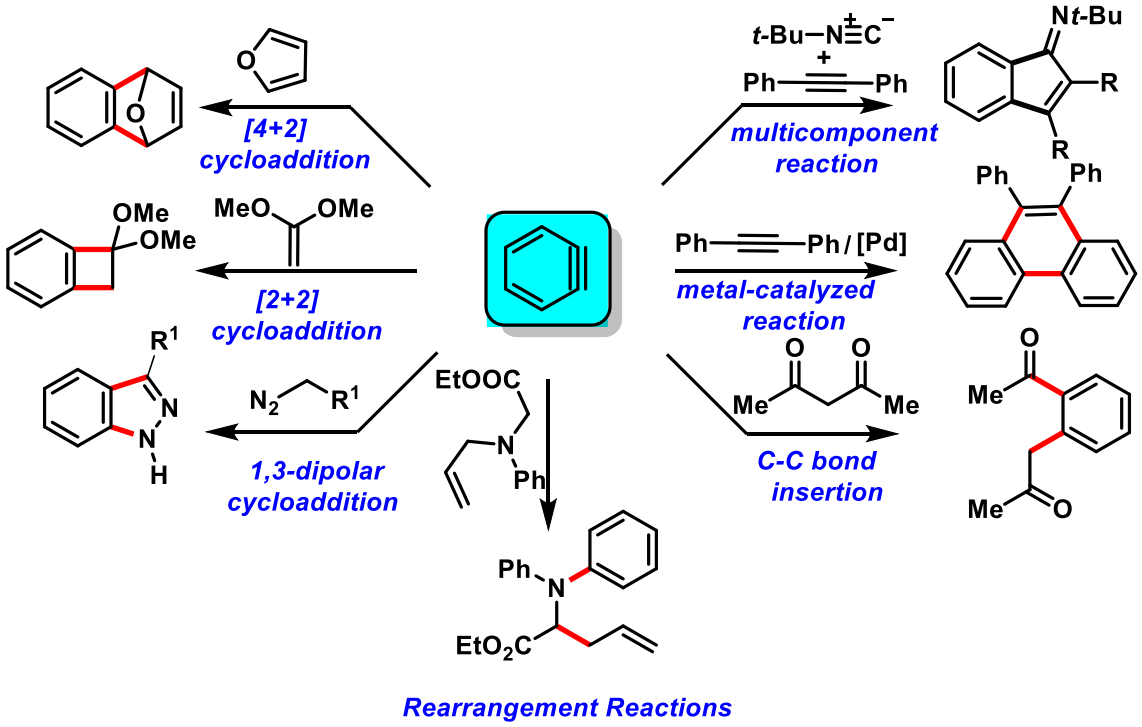
Scheme 1.5: Generation of Benzyne Using the Kobayashi Method

There are mainly three commonly used fluoride sources for aryne generation from Kobayashi precursor. They are CsF in CH_3CN, KF (along with 18-crown-6 as additive) in THF, and tetrabutyl ammonium fluoride (TBAF) in THF. The great advantage of generating a benzyne by the Kobayashi route is the ability to control the rate of benzyne generation by varying the concentration of the fluoride ion in solution. Thus, one can instantly generate a benzyne in THF using tetrabutylammonium fluoride (TBAF), which is quite soluble in THF. It is possible to slow down the rate of benzyne generation by employing CsF in MeCN (at low and elevated temperatures) or CsF in THF (at elevated temperatures). To further slowdown the formation of the benzyne, CsF in toluene (Tol)–MeCN mixtures can be used. The nature and amount of the added fluoride source, the solvent, and the temperature of the reaction can have a profound effect on the overall rate and success of such aryne reactions.

Before the discovery of Kobayashi aryne precursor, the scope of synthetic applications using aryne was somewhat limited by the harsh reaction conditions required to produce the aryne species. Many of the traditional methods required strong bases, such as *n*-BuLi, high temperatures and stiochiometric oxidants such as $Pb(OAc)_4$ (Scheme 1.4). However, with the development of milder methods for the generation of arynes increased interest in employing them in the synthesis of more complex polycyclic systems.

1.4. Various Modes of Reactivity of Arynes

Due to the electron deficient nature, arynes undergo different modes of action in various bond-forming reactions (Scheme 1.6). The pronounced electrophilicity of arynes renders them excellent dienophiles in cycloaddition reactions. Recent developments in aryne chemistry have been devoted to transition-metal free reactions, which include the initial



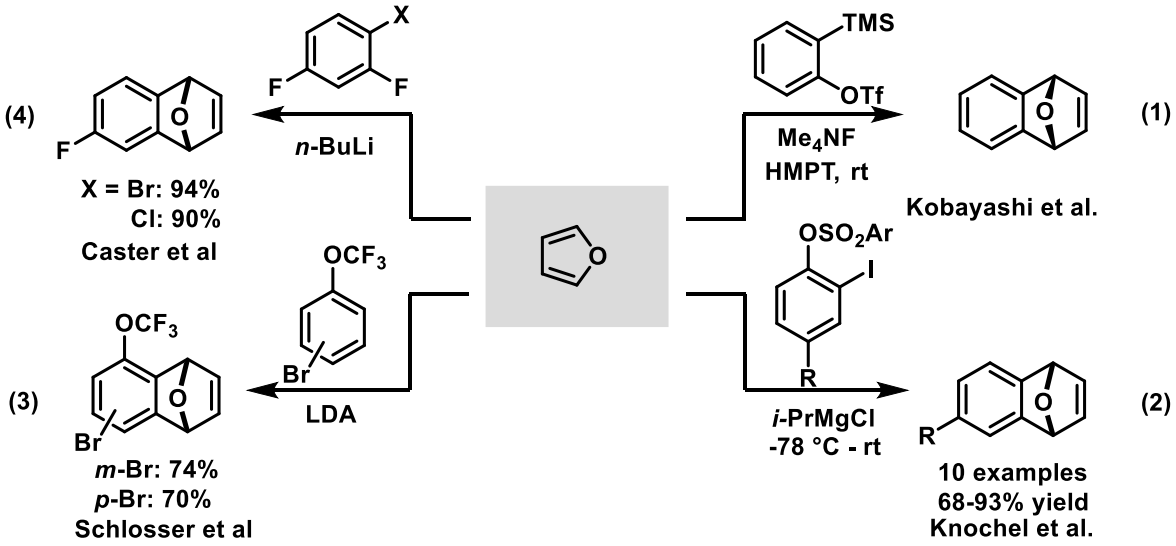
Scheme 1.6: Various Modes of Action of Arynes

addition of nucleophiles to arynes and subsequent trapping of the aryl anion intermediate with electrophiles. If the nucleophile and electrophile do not belong to the same molecule, the overall process is a unique three component coupling, where the aryne is inserted between the other two coupling partners. Furthermore, arynes can insert into element–element (X–Y) σ-bonds and π-bonds. In addition to the above reactivity, it can also undergo rearrangement

reaction leading to the formation of polysubstituted arenes. Moreover, arynes have been extensively utilized in transition-metal-catalyzed reactions. The objective of this chapter is to provide a concise account of the cycloaddition, insertion, multicomponent and rearrangement reactions using arynes.[1]

1.5. 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.

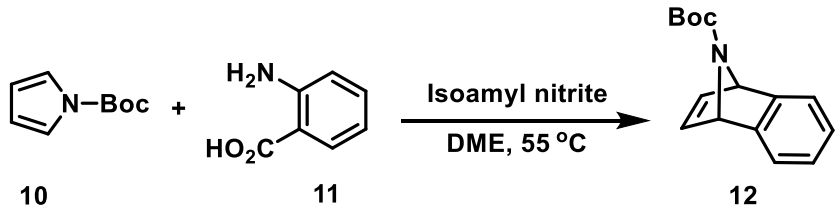


Scheme 1.7: Trapping of Arynes in Diels-Alder Reaction with Furan

Kobayashi and co-workers reported the efficiency of aryne generation from 2-(trimethylsilyl)aryl triflates in the Diels-Alder reaction with furan. They have observed almost quantitative formation of the 1,4-dihydro-1,4-epoxynaphthalene product in the presence of tetramethylammonium fluoride as fluoride source in HMPT (Scheme 1.7, eq 1). Knochel and co-workers developed a new and general method for the preparation of

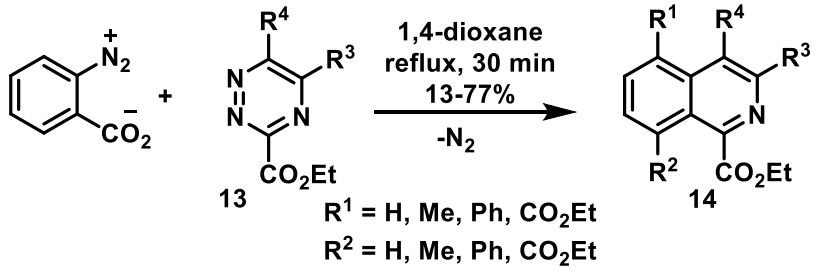
functionalized arynes by the readily tuneable elimination of 2-magnesiated aryl sulfonates and illustrated efficiency by trapping with furan.[7] The leaving-group ability of the sulfonate group ($ArSO_2O$-) was found to be crucial for the aryne generation (Scheme 1.7, eq 2). Schlosser reported that 1-bromo-3- or -4-(trifluoromethoxy)benzene can be added to a solution of LDA in THF and furan leading to the formation of corresponding 1,4-dihydro-1,4-epoxy-5- or 6-(trifluoromethoxy) naphthalenes in good yields (Scheme 1.7, eq 3).[8] A series of fluorinated benzonorbornadienes were prepared by Caster and co-workers in high yields and selectivities by trapping the in situ generated benzynes with furan (Scheme 1.7, eq 4).[9]

Interestingly, *N*-substituted pyrroles have also been employed in Diels-Alder reaction with arynes (Scheme 1.8). [10] Lautens and co-workers reported the cycloaddition reaction of benzyne, generated in situ from anthranilic acid **11** and isoamyl nitrite, and commercially available *N*-Boc pyrrole **10**. Notably, this reaction afforded *N*-Boc cycloadduct **12** in up to 20 g scale and 60-70% yield.



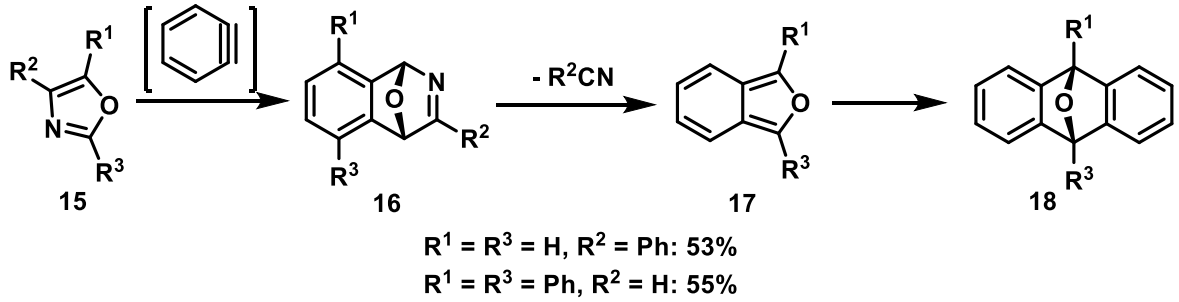
Scheme 1.8: Diels-Alder Reaction of Arynes with Pyrroles

In 1992, Gonsalves and co-workers developed a Diels-Alder reaction of several 1,2,4-triazines **13** with arynes generated from benzenediazonium 2-carboxylate (Scheme 1.9).[11] The reaction afforded the functionalized isoquinoline derivatives **14** in moderate to good yields with high regioselectivity.



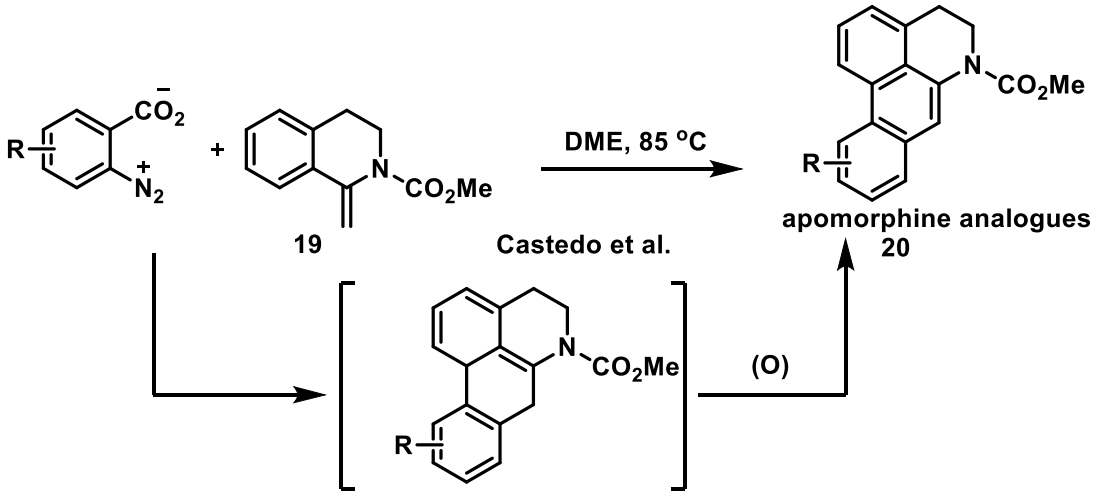
Scheme 1.9: Diels-Alder Reaction of Arynes with 1,2,4-Triazines

Rickborn and co-workers reported that variously-substituted oxazoles **15** can react with arynes to give the bis(benzyne) adducts **18.** This outcome occurs sequentially, aryne on Diels–Alder reaction with the oxazole generate intermediate **16,** which on retro-Diels–Alder with extrusion of the nitrile produces isobenzofuran **17**. In situ formed isobenzofuran again undergoes Diels–Alder reaction with another molecule of aryne to furnish the desired product **18** (Scheme 1.10).[12]



Scheme 1.10: Synthesis of Bis(benzyne) Adducts

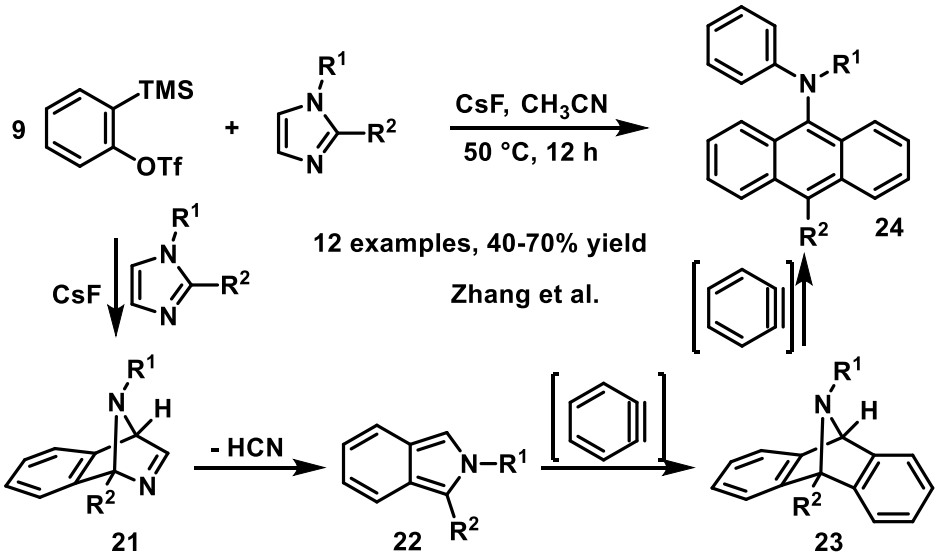
Castedo and co-workers reported a highly convergent, regioselective synthesis of apomorphine analogues **19** via the intermolecular cycloaddition between 1-methylene-1,2,3,4-tetrahydroisoquinoline **20** and an asymmetrically substituted arynes. (Scheme 1.11).[13]



Scheme 1.11: Synthesis of Analogues

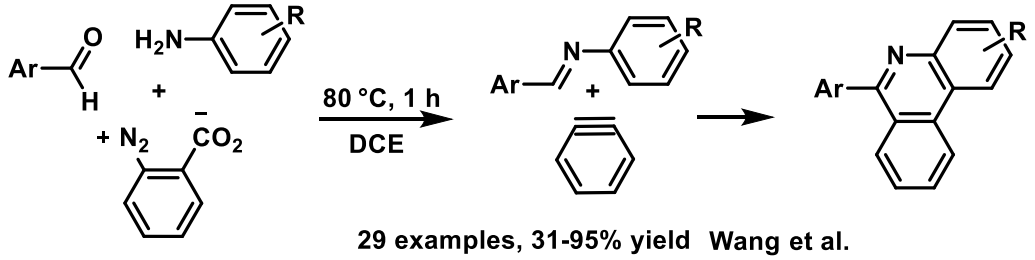
The Diels-Alder reaction can be combined with various intermolecular processes in tandem manner to synthesize molecules, which are otherwise difficult to obtain. In 2007, Xie and Zhang reported the reaction of aryne with *N*-substituted imidazoles, which proceeds via a tandem process involving a Diels-Alder reaction and an intermolecular coupling reaction

leading to the formation of aryl amines incorporating anthracene **24** in moderate to good yields (Scheme 1.12).[14] The initially formed Diels-Alder adduct **21** between aryne and imidazole undergoes a retro Diels-Alder reaction to generate the intermediate **22**, the latter undergoes a second Diels-Alder reaction with the aryne to generate **23**. Then ring-opening of the latter and intermolecular nucleophilic addition to excess aryne afforded the final product.



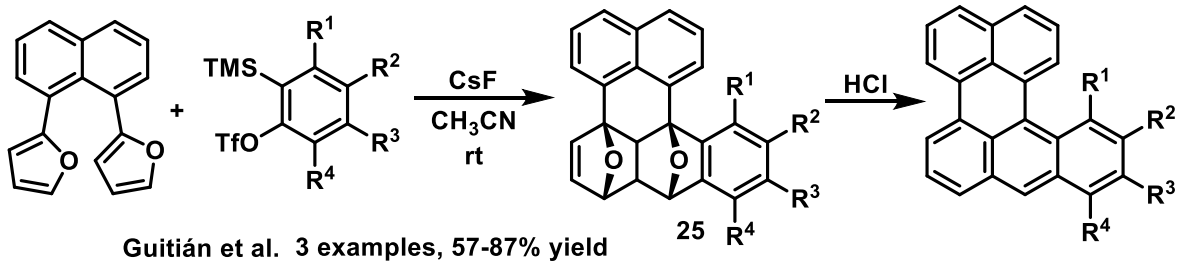
Scheme 1.12: Tandem Reaction of Arynes with Imidazoles

Interestingly, Wang and co-workers reported the three-component cascade synthesis of phenanthridine derivatives by the aza-Diels-Alder reaction of arynes generated from benzenediazonium-2-carboxylates and the imines generated from aromatic aldehydes and aniline derivatives (Scheme 1.13).[15] The noteworthy features of this reaction include the efficient process involving easily available starting materials and the one-pot procedure under metal-free and mild conditions.



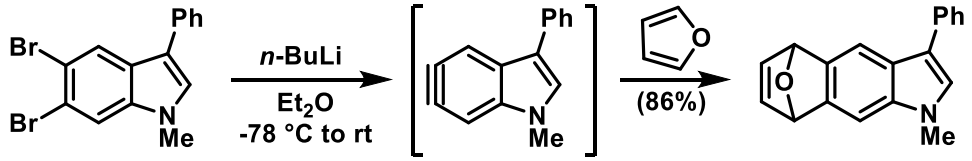
Scheme 1.13: Aza-Diels-Alder Reaction of Arynes

The synthesis of polycyclic aromatic hydrocarbons by a domino Diels-Alder cycloaddition involving arynes is reported by Guitián and co-workers (Scheme 1.14).[16] Two successive Diels-Alder reactions proceed simultaneously in a stereoselective manner leading to the cycloadduct **25**, which on treatment with acid afforded perylene derivatives, thus opening a new pathway to access elusive polyarenes.

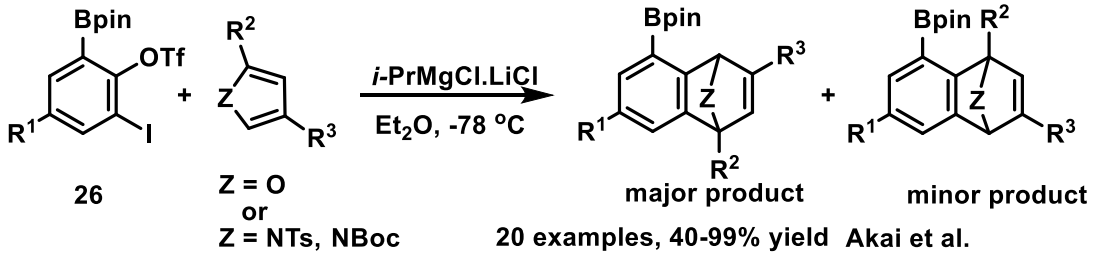


Scheme 1.14: Domino Diels-Alder Reaction of Arynes

Generation of aryne from 1,2-dihalogenated indoles by treatment with butyl lithium and its Diels-Alder reaction with furan was developed by Buszek and co-workers (Scheme 15).[17a] In addition, they applied the intermolecular indole-aryne cycloaddition in the synthesis of indole natural products including *cis*-trikentrin A and Herbindole A.[17b] Subsequently, they provided experimental and theoretical support for the regioselectivity in indole-derived aryne cycloadditions.[17c] These studies revealed that 6,7-indolynes showed remarkable regioselectivity in its cycloaddition reactions with 2-substituted furans, whereas 4,5-and 5,6-indolynes showed no regioselectivity.The generation of 3-boryl benzyne and its subsequent Diels-Alder reaction with substituted furans or pyrroles providing highly functionalized boronic acid derivatives has been uncovered by Akai and co-workers.[18] The 2-boryl-6-iodophenyl triflate **26** upon treatment with *i*-PrMgCl.LiCl generates the 3-boryl benzyne, which immediately undergoes Diels-Alder reaction affording the products in good yields (Scheme 1.16).

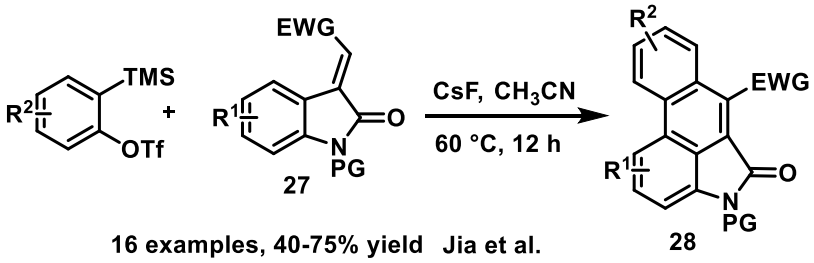


Scheme 1.15: Generation and Subsequent Diels-Alder Reaction of Indolyne



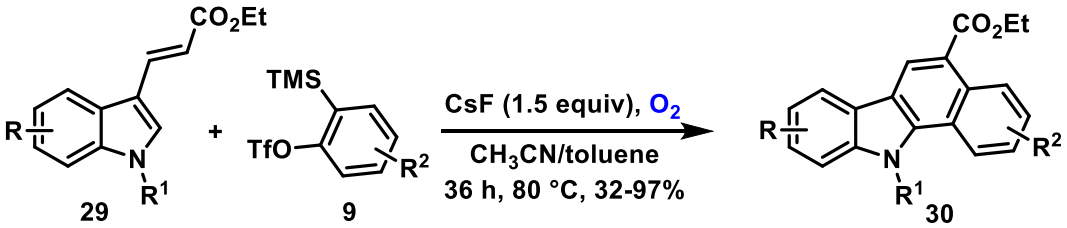
Scheme 1.16: Generation and Diels-Alder Reaction of 3-Boryl Benzynes

Jia and co-workers revealed the cycloaddition reactions of methyleneindolinones **27** and arynes to generate structurally unusual naphtho-fused oxindoles **28** in good yields, which proceeds through an unusual [4+2] cycloaddition followed by isomerization and dehydrogenation processes (Scheme 1.17).[19]

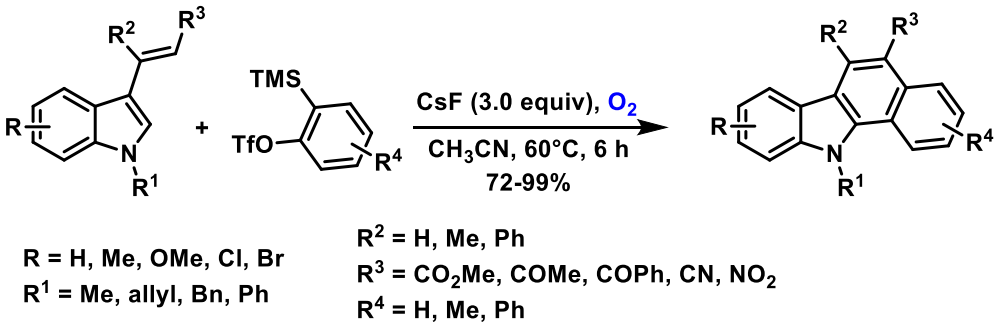


Scheme 1.17: Diels-Alder Reaction of Methyleneindolinones with Arynes

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 co-workers employed *N*-alkyl protected as well as *N*-unprotected indoles **29** as a dienes in [4 + 2] cycloaddition with arynes generated from **9** in the presence of CsF in CH_3CN/toluene mixture at 80 °C leading to the synthesis of benzo[*a*]carbazole-5-carboxylates **30** in good to excellent yields (Scheme 1.18).[20a] Liang, Pi group utilized similar



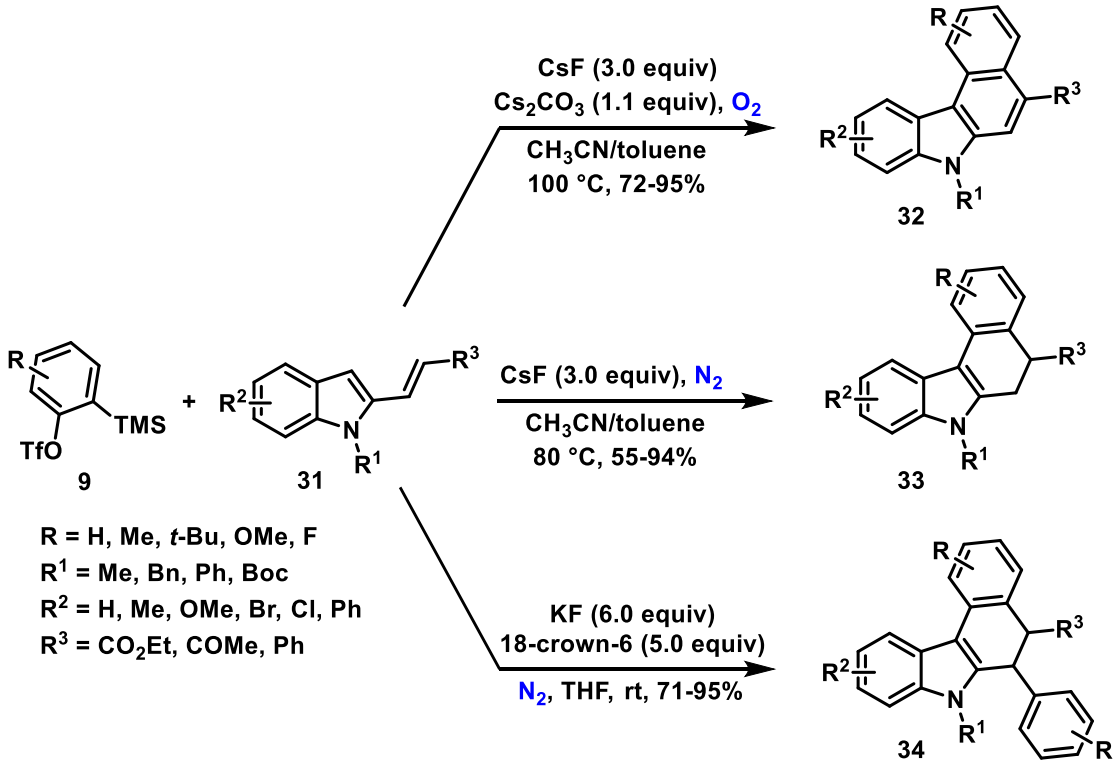
R = H, Me, OMe, Cl, Br, F, CN, CO_2Me, NO_2
R^1 = H, Me
R^2 = H, Me, $(CH_2)_3$, F



Scheme 1.18: Diels-Alder Reaction of Arynes with 3-Alkenyl Indoles

reaction conditions to accomplish the cycloaddition of 3-vinyl-indoles with arynes.[20b] 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.

Subsequently, Wu, Sha and co-workers applied this strategy for the synthesis of benzo[*c*]carbazole derivatives via Diels-Alder reaction of arynes and of 2-alkenyl indoles

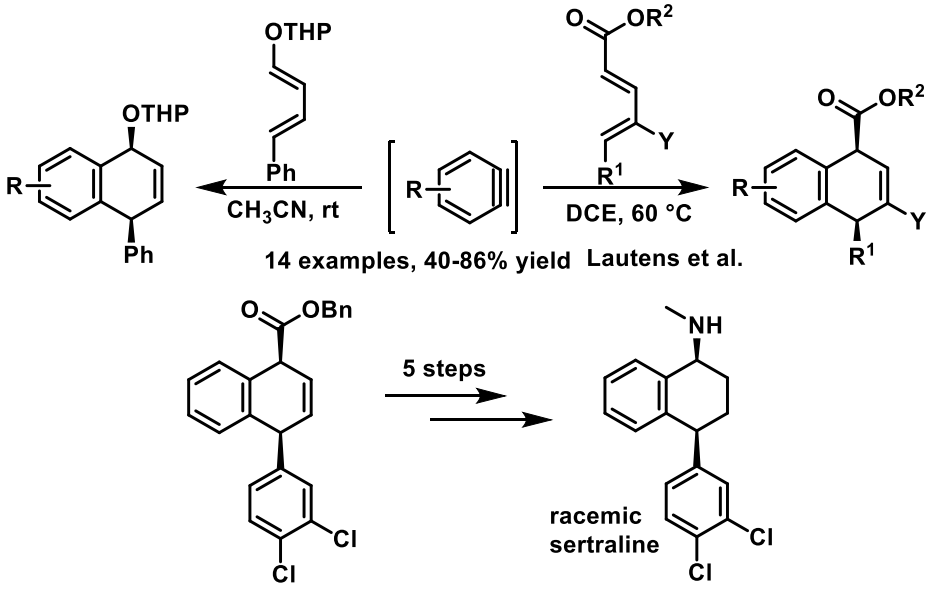


Scheme 1.19: Diels-Alder Reaction of Arynes with 2-Alkenyl Indoles

31.[20c] 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 **33** (1.5 equiv

of **9**) and aryl substituted 7,11b-dihydrobenzo [*c*]carbazoles **34** (3.0 equiv of **9**). Alternatively, when the reactions were carried out under oxygen atmosphere afforded oxidized/aromatized product benzo[*c*]carbazoles **32**. Interestingly, the benzo[*c*]carbazole amide derivatives have good antitumor activity (Scheme 1.19).

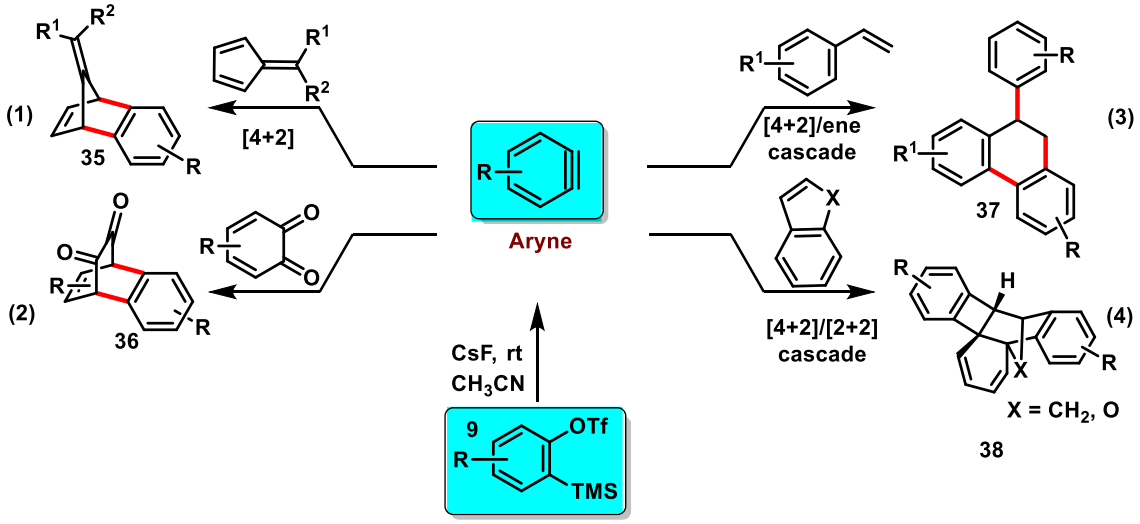
In an attempt to expand the scope and utility of Diels-Alder reaction of arynes with acyclic dienes, Lautens and co-workers used 1,4-disubstituted acyclic dienes as the coupling partner for arynes leading to a straightforward synthesis of 1,4-dihydronaphthalene derivatives with excellent levels of selectivity (Scheme 1.20).[21] The reaction worked well with electron- releasing and electron-withdrawing substituents on the diene system. They also applied this methodology to a short synthesis of racemic sertraline.



Scheme 1.20: Highly Diastereoselective Aryne Diels-Alder Reaction with Acyclic Dienes

Our group is also working on the Diels-Alder reaction involving arynes. We have demonstrated the exceptional utility of aryne Diels-Alder reaction with challenging dienes like pentafulvenes, 1,2 benzoquinone, styrenes, indenes, benzofurans to access complex benzo-fused compounds. Diels-Alder reaction of pentafulvenes with arynes leading to the formation of benzonorbornadiene derivatives **35** was reported by our group.[22] This reaction was found to be scalable, and worked well under mild conditions. The reaction was well tolerated with electron-releasing and -withdrawing groups at the 6-aryl moiety, and heteroaromatic and alkyl functionalities to afford desired product in good to excellent yields (Scheme 1.21, eq 1). Subsequently, the reaction of 1,2-benzoquinone with the aryne

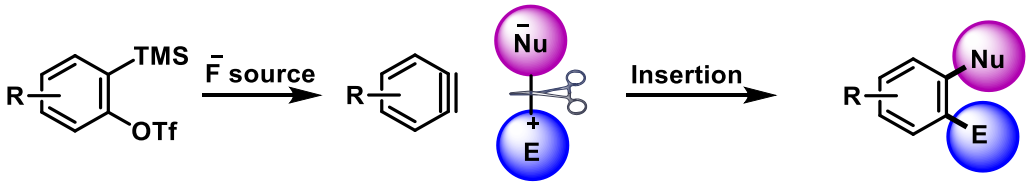
generated from 2(trimethylsilyl)aryltriflate **9** using KF and 18-crown-6 in THF under mild reaction conditions resulting in the synthesis of dioxobenzobicyclooctadienes **36** in moderate to excellent yields (Scheme 1.21, eq 2) was developed.[23] The synthetic potential of this cycloaddition reaction has been demonstrated in the one-pot synthesis of benzoquinoxalinobarrelene and naphthalene derivatives in good yields. In addition, we have developed the reaction of arynes with styrenes leading to the formation of 9-aryldihydrophenanthrene derivatives **37** (Scheme 1.21, eq 3).[24a] The reaction proceeds via a cascade process initiated by a Diels-Alder reaction of styrenes with arynes followed by a selective ene reaction. Moreover, we have revealed a facile and general tandem [4+2]/[2+2] cycloaddition reaction involving arynes with indene/benzofurans to afford the corresponding dihydrobenzocyclobutaphenanthrene derivatives **38** in moderate to good yields with excellent diastereoselectivity (Scheme 1.21, eq 4).[24b]



Scheme 1.21: Diels-Alder Reaction of Aryne with Pentafulvenes, Tropones, Styrenes, Indenes, Benzofurans

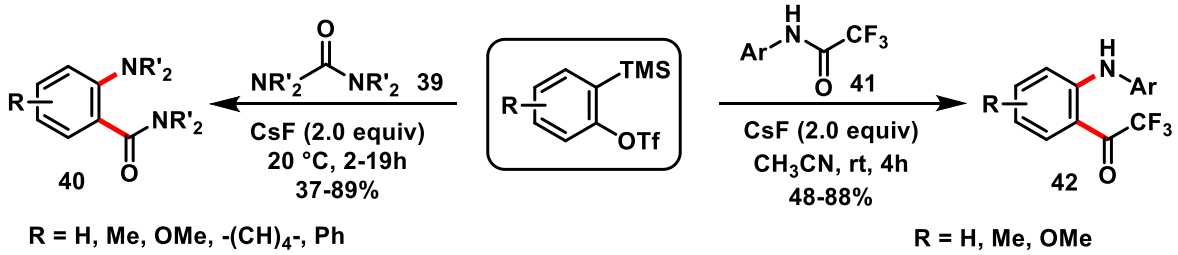
1.6. Insertion Reactions

Insertion into a σ-bond between a nucleophilic site and an electrophilic site (Nu-E σ bond) via intramolecular nucleophilic substitution have attracted considerable attention as a powerful method for the straightforward synthesis of highly functionalized compounds. 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 (Scheme 1.22).[1]



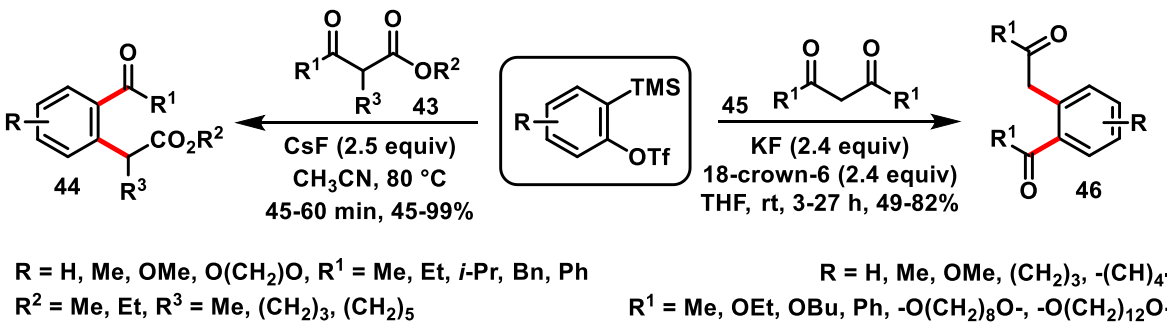
Scheme 1.22: Insertion Reactions of Arynes

Shirakawa, Hiyama and co-workers synthesized benzodiazepines and 2-aminobenzamides **40** by the insertion of arynes into the N-CO bond of cyclic and acyclic ureas **39** under mild reaction conditions, which are difficult to access by conventional methods (Scheme 1.23).[25] Benzodiazepines are valuable substrates due to their fluorescence properties and pharmaceutical application. Moreover, Liu and Larock demonstrated an efficient insertion of arynes to the C-N bond of amides **41** and S-N bond of sulfinamides leading to a transition-metal-free synthesis of 1,2-disubstituted arenes **42** under mild reaction conditions with broad substrate scope.[26] 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.



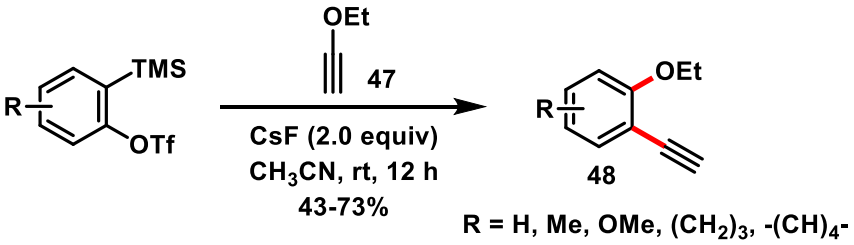
Scheme 1.23: Insertion of Arynes to Various Carbon-Nitrogen σ-Bonds

The first report on the direct and efficient insertion of arynes into a carbon-carbon σ-bond of acyclic and cyclic β-ketoesters **43** leading to interesting 1,2-disubstituted arenes **44** has been appeared from Stoltz's group in 2005.[27] 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.[28] Subsequently, Yoshida, Kunai and co-workers reported a mild and straightforward protocol for the synthesis of diverse polysubstituted arenes **46** by a facile insertion of arynes to C-C σ-bond of various β-dicarbonyl compounds **45** in good yields.[29]



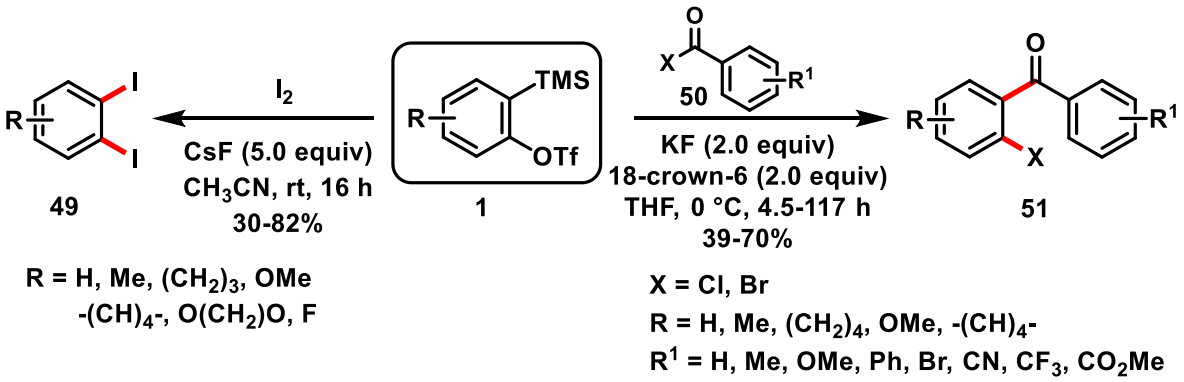
Scheme 1.24: Insertion of Arynes to Various Carbon-Carbon *σ*-Bonds

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 co-workers.[30] In 2011, the same group developed a chemo- and regioselective formal insertion of arynes into the ethoxy acetylene **47** leading to the formation of 2-ethoxyethynylaryl derivatives **48** in good yields (Scheme 1.25).[31] 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.



Scheme 1.25: Insertion of Arynes to Carbon-Oxygen and Nitrogen-Sulphur *σ*-Bonds

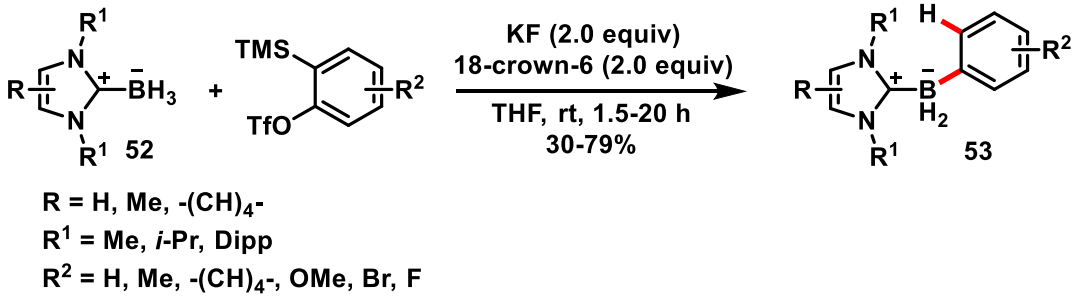
Additionally, the Guitián's group revealed an efficient procedure for the synthesis of *ortho*-diiodoarenes **49** by the insertion of arynes into the I-I *σ*-bond (Scheme 1.26).[32] Aryne insertion into the I-I *σ*-bond using traditional methods of aryne generation in moderate yields was reported by Friedman and Logullo as early as 1965.[33] Mild reaction conditions involved in generation of aryne form precursors **9** afforded the *ortho*-diiodoarenes in good yields. In



Scheme 1.26: Insertion of Arynes into I-I and Carbon-Halogen *σ*-Bonds

2007, Yoshida, Kunai and co-workers disclosed the regioselective synthesis of diverse halogenated benzophenone derivatives **51** via the insertion of arynes into the C-halogen *σ*-bond of acid halides **50** in moderate to good yields (Scheme 1.26).[34] 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.

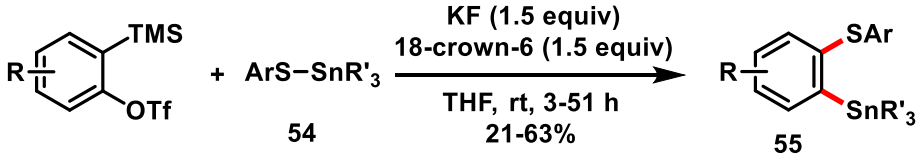
Synthesis of aryl-substituted boranes by the hydroboration of arynes is complicated process, because the resulting aryl boranes are again reactive and both products and starting materials are not compatible with the fluoride source used for the aryne generation. Recently, Taniguchi and Curran employed stable *N*-heterocyclic carbene boranes (NHC-boranes) **52** for the hydroboration of arynes and prepared B-aryl NHC-boranes **53** with broad substrate scope (Scheme 1.27).[35] 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



Scheme 1.27: Hydroboration of Arynes with *N*-Heterocyclic Carbene Boranes

unusual *ortho*-regioisomers, which indicates a hydroboration process with hydride-transfer character.

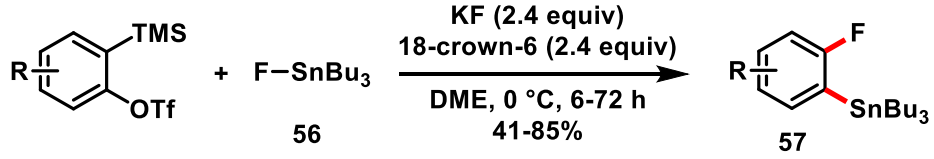
Apart from this, insertion of arynes to various element-element σ-bonds is given in Scheme 1.28. In 2004, Yoshida, Kunai and co-workers reported the insertion of arynes to the Sn-S σ-bond of stannyl sulfides **54**. This thiostannylation reaction furnished the versatile 2-(arylthio) arylstannanes **55**, which are amenable for further transformations by means of traditional metal-catalyzed cross-coupling reactions.[36]



R = H, Me, Ph, OMe, $(CH_2)_3$, -$(CH)_4$-, F
R' = Me, Bu

Scheme 1.28: Insertion of Arynes into the S-Sn σ-Bonds

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 Yoshida group developed the fluorostannylation reaction by the insertion of arynes into the F-Sn σ-bond of tin fluoride **56** leading to the synthesis of diverse 2-fluoroarylstannanes **57** under mild reaction conditions.[37] 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.

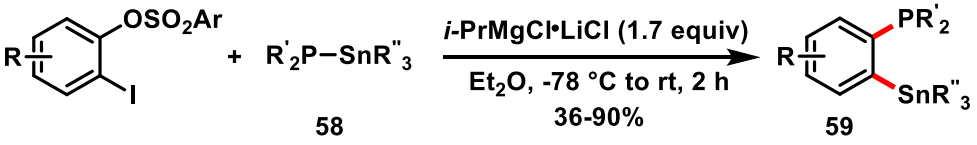


R = H, Me, Ph, OMe, $(CH_2)_3$, -$(CH)_4$-, Cl, Br

Scheme 1.29: Insertion of Arynes into the F-Sn σ-Bonds

In their efforts to develop a transition-metal-free reaction for the preparation of *ortho*-functionalized arylphosphanes, Studer and co-workers disclosed a practical and efficient approach for the synthesis of functionalized *ortho*-trialkylstannyl arylphosphanes **59** by the

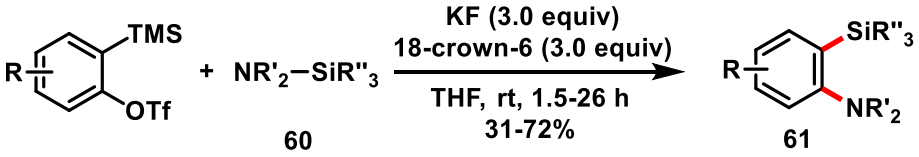
insertion of arynes into the Sn-P σ-bond of stannylated phosphanes **58**. However, attempted reaction of **58** with aryne generated form 2-(trimethylsilyl)-aryl triflate **9** using KF as a fluoride source with 18-crown-6 additive was not successful, due to the instability of stannylated phosphanes towards the fluoride anion. Consequently, the Knochel procedure for aryne generation from sulfonate in the presence of *i*-PrMgCl.LiCl at -78 °C in Et_2O solvent with stannylated phosphanes **58** furnished the expected insertion products in good to excellent yields.[38] Additionally, stannylated products were employed in the synthesis of valuable *ortho*-substituted arylphosphanes.



R = H, Me, *i*-Pr, *t*-Bu, OMe, $(CH_2)_4$, -$(CH)_4$-, Cl, CF_3, CO_2Me
R' = Ph, *p*-Tol
R'' = Me, Bu

Scheme 1.30: Insertion of Arynes into the S-Sn, F-Sn, and P-Sn σ-Bonds

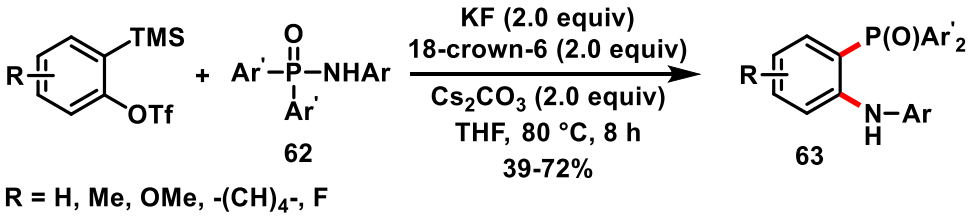
Insertion of arynes into the nitrogen-silicon σ-bond of aminosilanes **60** resulting in variety of functionalized 2-silylaniline derivatives **61** in moderate to good yields was uncovered by Yoshida, Kunai and co-workers (Scheme 1.31).[39] Notably, this aminosilylation reaction worked under mild reaction conditions.



R = H, Me, $(CH_2)_3$, $(CH_2)_4$, OMe, -$(CH)_4$-
R' = Me, Et, Bu
R'' = Me, Et, $(CH_2)_5$, Bn, Ph

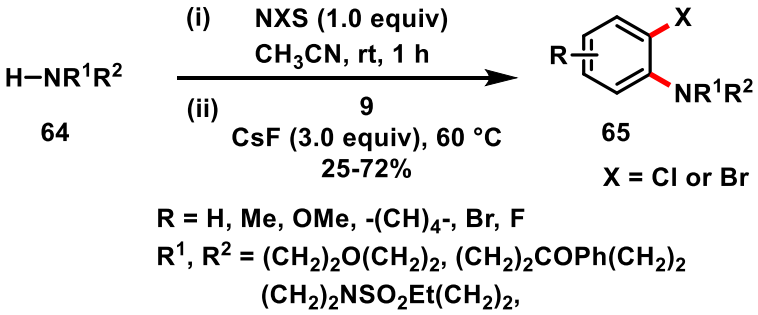
Scheme 1.31: Insertion of Arynes into the Nitrogen-Heteroatom σ-Bonds

In 2013, Zhang and co-workers reported the insertion reaction of arynes to P-N bond of arylphosphoryl amides **62** leading to the formation of *ortho*-amine substituted arylphosphine oxides **63**.[40] 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.



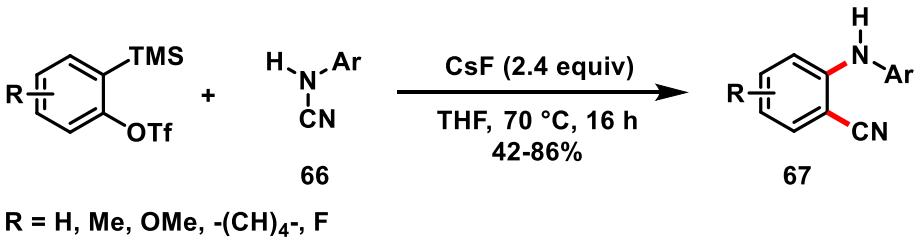
Scheme 1.32: Insertion of Arynes into the Nitrogen-Heteroatom σ-Bonds

Subsequently, Wang and co-workers disclosed a transition-metal-free one-pot procedure for the synthesis of *ortho*-haloaminoarenes **65** by the insertion of arynes into a nitrogen-halide bond (N-X) with broad substrate scope.[41] In this case, the nitrogen-halogen bond (N-X) was formed in situ by the treatment of secondary amines **64** 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.



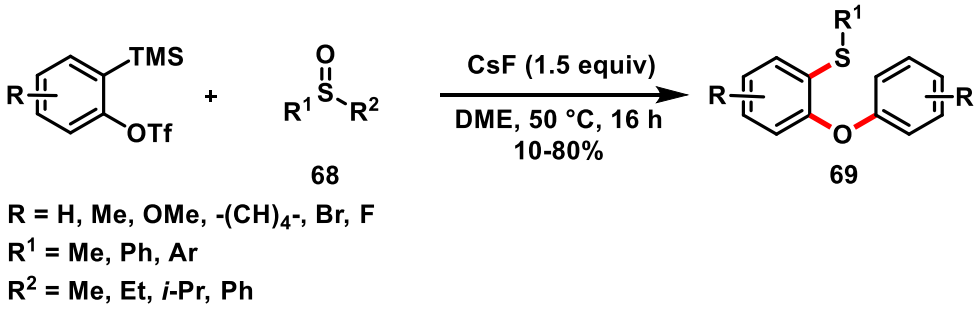
Scheme 1.33: Insertion of Arynes into the Nitrogen-Heteroatom σ-Bonds

Recently, Zeng and co-workers developed an efficient protocol for the synthesis of 1,2-bifunctional aminobenzonitriles **67** by the insertion of arynes to N-CN bond of aryl cyanamides **66**.[42] 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 1.34: Insertion of Arynes into the Nitrogen-Heteroatom σ-Bonds

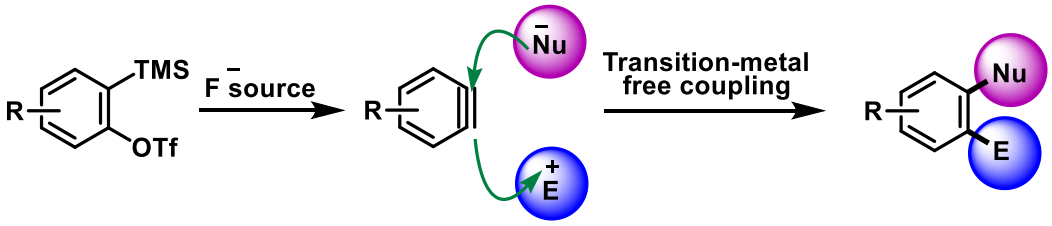
Subsequently, Wang and co-workers developed an insertion reaction of arynes to the S-O bond of sulfoxides **68** leading to the formation of thioethers **69**.[43] Mechanistic experiments carried out in the presence of carbonyl compounds resulted in the formation of epoxide and thioether products. This experiment sheds light on the reaction mechanism and indicates that the reaction proceeds through the 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 1.35: Construction of C_{aryl}-S Bond using Arynes

1.7. Multicomponent Couplings (MCCs) Involving Arynes

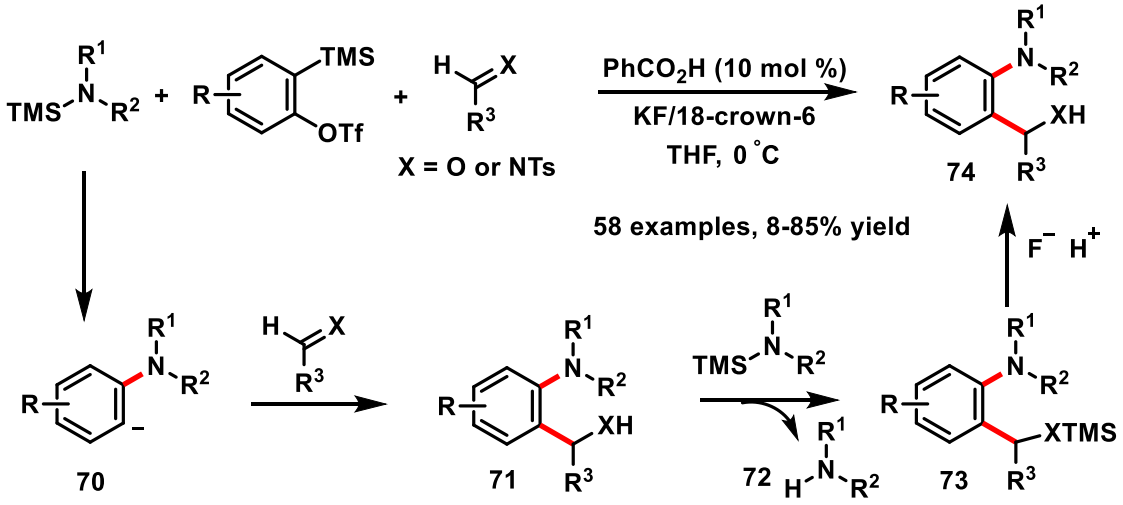
Another mode of reactivity of aryne chemistry is multicomponent coupling (MCCs), found application for the synthesis of benzoannulated structures and 1,2-disubstituted arene scaffolds. MCCs generally initiates by the addition of nucleophiles to arynes and subsequent trapping of the corresponding aryl anion intermediate with other electrophiles. (Scheme 1.36). The commonly used nucleophilic triggers in aryne MCCs are amines, imines, isocyanides, solvents such as DMF, THF, DMSO, and electrophilic partners usually used are carbonyls including CO_2. A brief account of aryne MCCs and primarily their applications in the synthesis of valuable heterocycles is provided in the present section.[1]



Scheme 1.36: Transition-Metal-Free MCCs Involving Arynes

1.7.1. Aryne MCCs Initiated by Amines

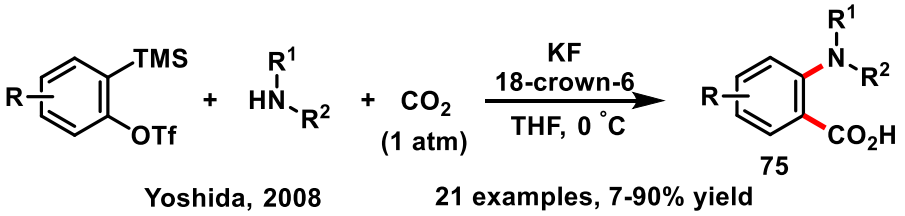
Yoshida and co-workers disclosed, MCCs employing arynes, aminosilanes and aldehydes in the presence of catalytic amount of benzoic acid, which is responsible for the generation of free amine leading to the formation of 2-amino benzhydrol derivatives **74** (Scheme 1.37).[44] Plausible reaction pathway involves the subsequent nucleophilic coupling



Scheme 1.37: MCCs of Arynes, Amines and Carbonyls/Imines/Ketones

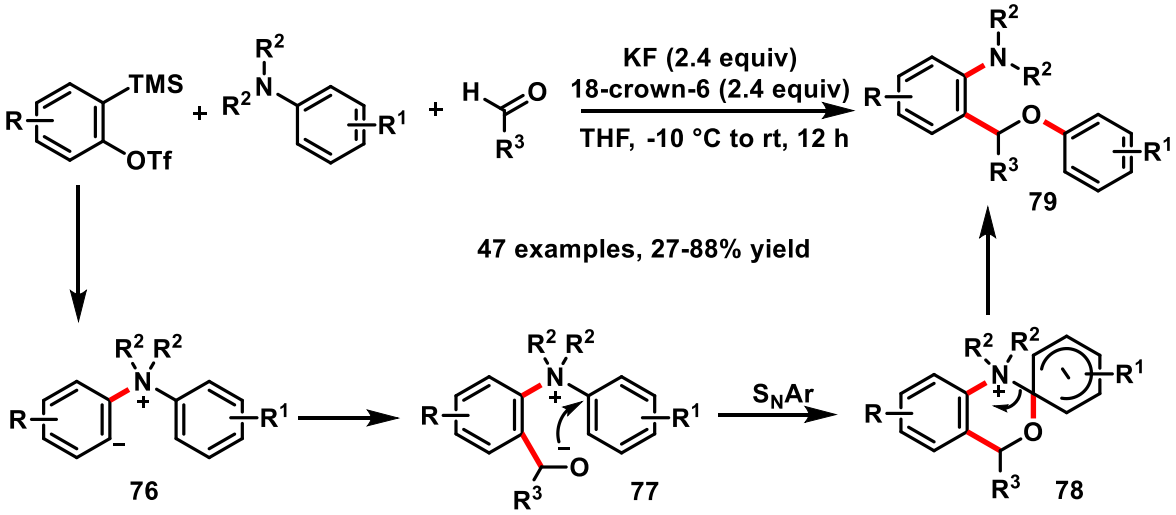
of **70** with an aldehyde to furnish **71**, which then reacts with aminosilane to give silyl ether **73** with regeneration of amine **72**. The obtained silyl ether would be transformed in to desired product **74** during work-up process. Moreover, imines as well as activated ketones also have shown excellent reactivity.

Subsequently, the same group has reported the use of secondary amine as the nucleophilic trigger in a three-component coupling reaction generating anthranilic acid derivatives **75** in good yields (Scheme 1.38).[45] Zwitterions arising from nucleophilic attack of amines to arynes serve as key intermediates in the coupling.



Scheme 1.38: MCR of Arynes, Amines and CO_2

Recently our group has revealed a transition-metal-free multicomponent coupling of arynes, aromatic tertiary amines, and aldehydes to the rapid synthesis of 2-functionalized tertiary amines proceeding via aryl to aryl amino group transfer.[46] The scope of this aryne MCC with various aldehydes and differently substituted arynes and tertiary amines have been well studied. In all the cases, the *ortho*-functionalized tertiary amines were obtained in good



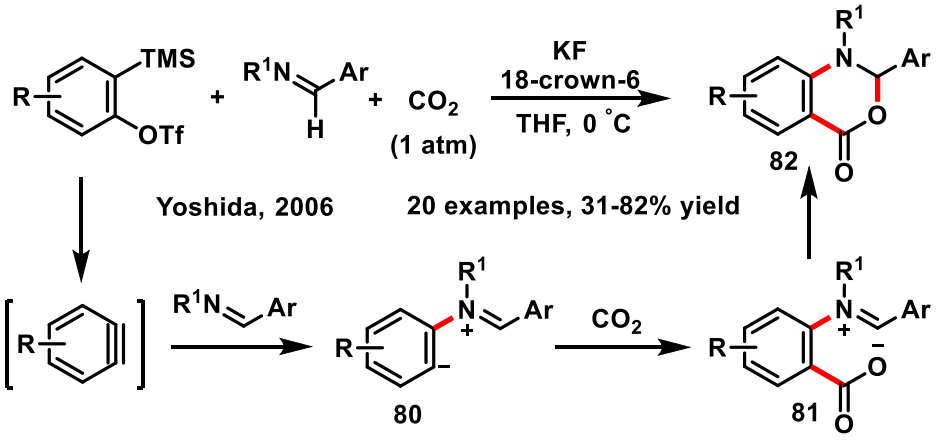
Scheme 1.39: MCC Involving Aryne, Carbonyls and Tertiary Amines

yields. Also activated carbonyls like various isatins, phenyl ethyl glyoxylate etc. also works well under the optimized condition (Scheme 1.39). Mechanistically, initial nucleophilic attack of tertiary amine on aryne generates the dipolar intermediate **76**, followed by addition to carbonyl forming the key tetrahedral intermediate **77**. The intermediate **77** undergoes an intramolecular nucleophilic aromatic substitution reaction (S_NAr) resulting in the formation of the desired product **79** via the σ-complex **78**.

1.7.2. Aryne MCRs Triggered by Imine

Yoshida, Kunai and co-workers developed a unique three-component coupling of aryne, imine and CO_2. The 1,3-zwitterionic intermediate **80** generated by the addition of

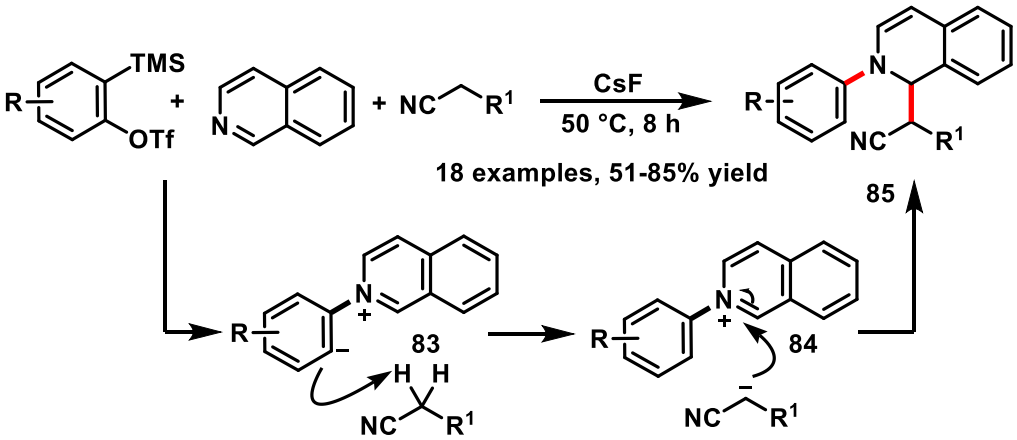
imines to arynes were trapped using CO_2 to form the carboxylate **81**, which undergoes cyclization leading to the formation of benzoxazinone derivatives **82** (Scheme 1.40).[47]



Scheme 1.40: MCR of Arynes, Imines and CO_2

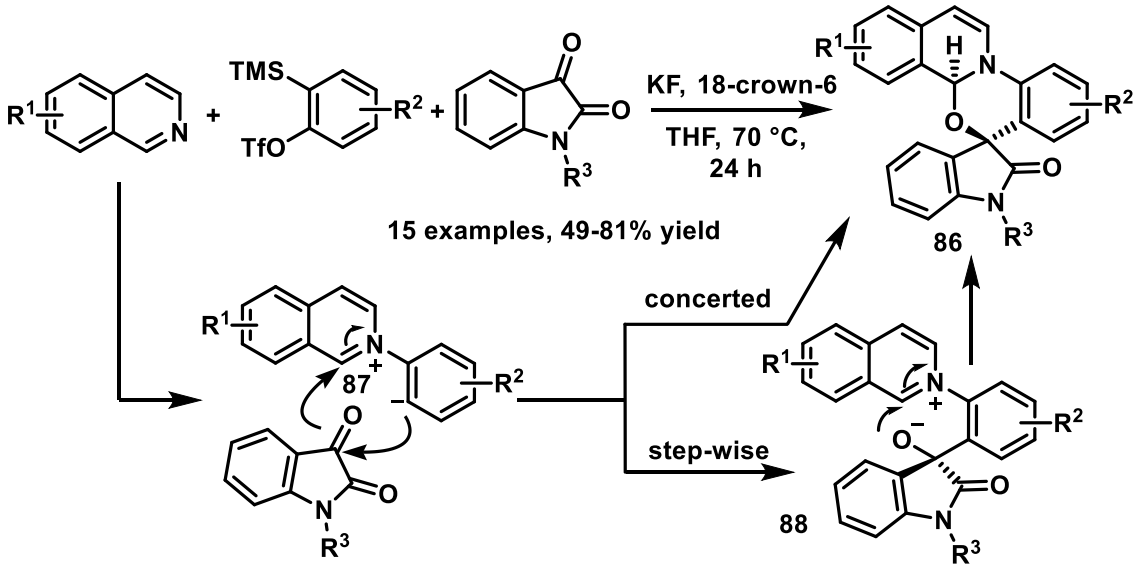
1.7.3. Aryne MCCs Triggered by *N*-Heterocycles

In 2006, the Cheng group disclosed the aryne MCCs employing *N*-heterocycles such as pyridine, and (iso)quinoline.[48a] The reaction of *N*-heterocycles with aryne and nitriles bearing an α-hydrogen afforded the 2-aryl isoquinoline derivative **85** in good yields. Interestingly, nitriles act as solvent as well as the third-component. Plausible mechanism involves the initially formed 1,4-zwitterionic intermediate **83** from isoquinoline and aryne, generated aryl anion was protonated by the nitrile, thus forming the isoquinolinium salt **84**. The nucleophilic attack of the nitrile anion on **84** afforded the product **85** (Scheme 1.41). Moreover, they used terminal alkynes and methyl ketones as third-component in aryne MCCs triggered by *N*-heterocycles.[48b]



Scheme 1.41: MCC Involving *N*-Heterocycles with Aryne and Nitriles

Recently, our group developed an efficient route to the synthesis of spirooxazino (iso)quinoline derivatives, employing *N*-hetercycles (such as isoquinoline and quinoline), arynes and *N*-substituted isatins as the electrophilic component. Interestingly, the reaction of isoquinoline and *N*-substituted isatin with aryne generated from **9** using KF and 18-crown-6 afforded the spirooxazinoisoquinoline derivative **86** as inseparable mixture of diastereomers in good yield and moderate to good diastereoselectivity (Scheme 1.42).[49] This reaction was

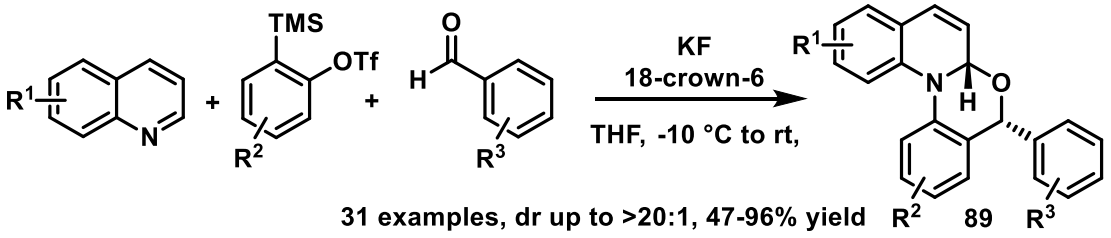


Scheme 1.42: MCCs Involving (Iso)Quinoline, Arynes and *N*-substituted Isatins

well tolerated with various *N*-substituted isatins having electron-rich and electron-poor functional groups, as well as various electronically different arynes were well tolerated. The reaction proceeds via the generation of 1,4-zwitterionic intermediate **87** from aryne and isoquinoline. The intermediate **87** can add to the electrophilic C=O bond of isatins in a concerted pathway to obtain oxazinoisoquinoline derivative **88**. Alternatively, it is also likely that the zwitterion **87** adds to the C=O group in a stepwise manner to generate the intermediate **88** and the latter on further cyclization to afford **86**.

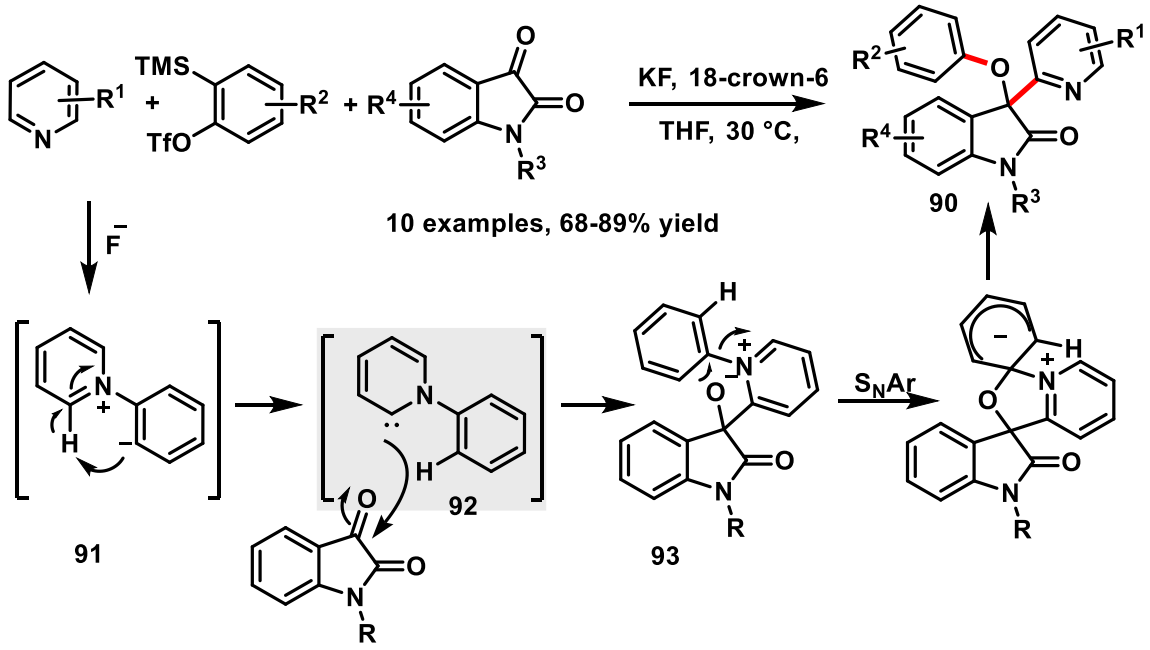
Moreover, to expand the scope of this reaction beyond the use of isatins as the coupling partner, we employed various carbonyl compounds as the electrophilic trapping agents. Treatment of quinoline and arynes with aldehydes in the presence of KF and 18-crown-6 resulted in the formation of benzoxazino quinoline derivatives **89** as an inseparable mixture of diastereomers in good yield and excellent diastereoselectivity (Scheme 1.43).[50] A wide variety of (hetero)aromatic and aliphatic aldehydes are well tolerated under the

optimized reaction conditions. In addition, various carbonyl compounds such as benzophenone, 1,4-benzoquinone, as well as α-ketoester were used as the carbonyl component in this reaction.



Scheme 1.43: MCCs Involving Isoquinoline, Arynes and Aldehydes

Surprisingly, when the aryne MCCs with isatins were carried out using pyridine as the nucleophilic trigger, the reaction furnished indolin-2-one derivatives **90** instead of the expected spirooxazino pyridine derivatives. This reaction likely proceeds *via* a conceptually a new bis-(hetero)arylation reaction of isatin involving the C–H bond functionalization of pyridine. First, the nucleophilic attack of pyridine on aryne generates the 1,4-dipolar



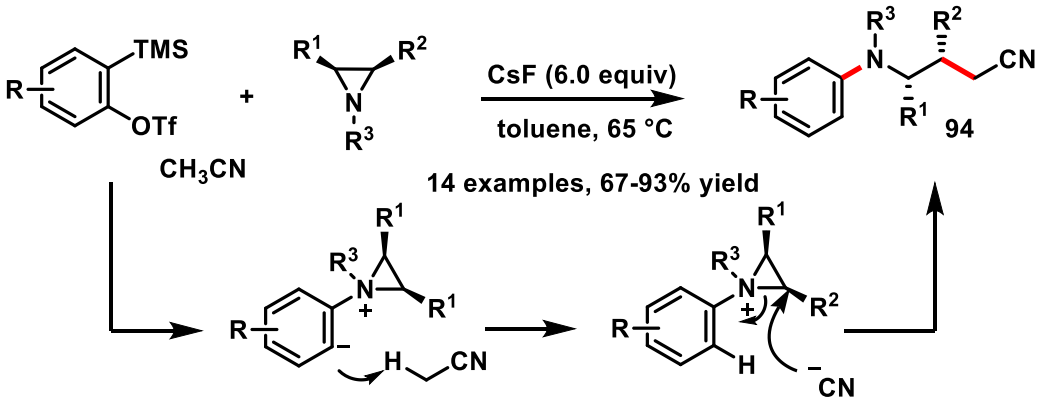
Scheme 1.44: MCC involving Arynes, Pyridine and Isatins

intermediate **91**, which undergo an intramolecular proton transfer in the absence of external proton source to generate the pyridylidene intermediate **92**. This nucleophilic intermediate intercept with isatin to form the tetrahedral intermediate **93**, followed by intramolecular nucleophilic aromatic substitution reaction to provide the indolin-2-one (Scheme 1.44).[51]

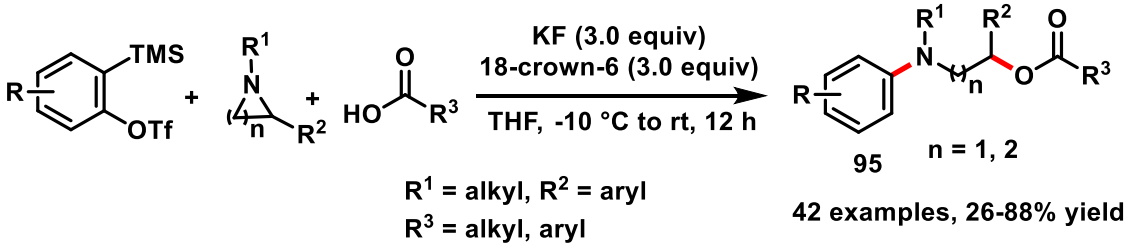
Notably, a similar type of transformation proceeding via the pyridylidene intermediate was reported by Rodriguez, Coquerel and co-workers.

1.7.4. Aryne MCCs Triggered by Aziridines

Recently, Larionov and co-workers reported aryne MCCs triggered by aziridines and the solvent CH_3CN as a third-component resulting in the synthesis of *N*-aryl *γ*-aminobutyronitriles **94** in good yields (Scheme 1.45).[52] Subsequently, our group disclosed the three-component coupling involving *N*-substituted aziridines or azetidines, arynes, and carboxylic acids to access the *N*-aryl *β*-amino alcohol derivatives and *N*-aryl *γ*-amino alcohol derivatives **95** (Scheme 1.46).[53]

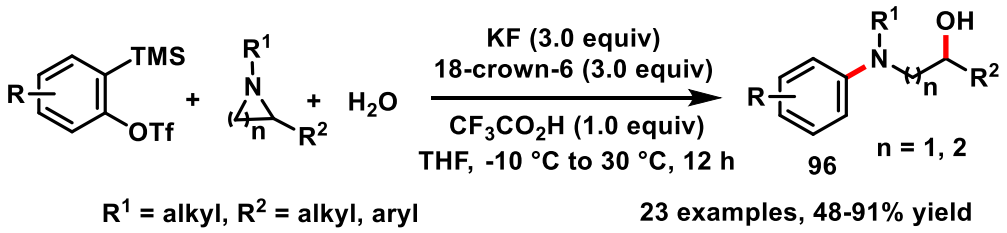


Scheme 1.45: Reaction Aziridines with Arynes and Acetonitrile



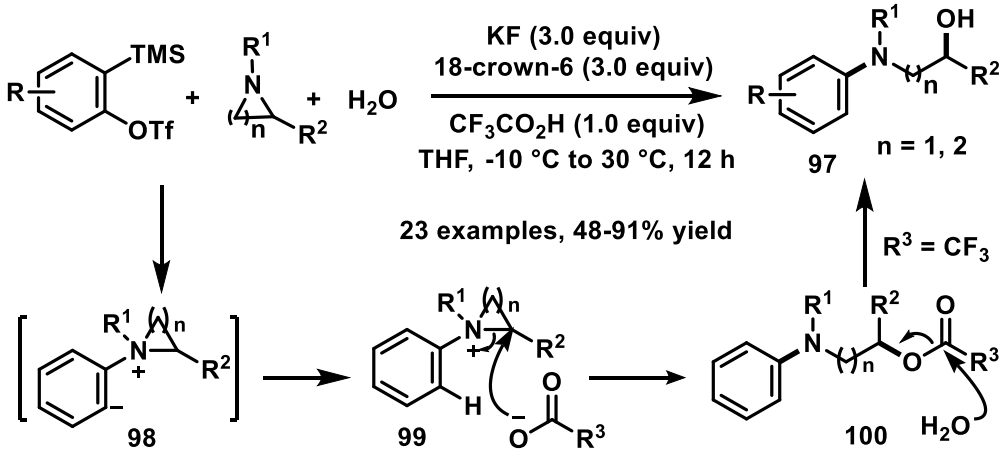
Scheme 1.46: MCCs Involving Aziridines/Azetidines, Arynes and Carboxylic Acids

These reactions proceeds under mild conditions to afforded the desired products in good yields with broad substrate scope. Moreover phenols are used as acid surrogates in the present aryne MCCs. Gratifyingly, the use of water as the third-component in aryne three-component coupling initiated by aziridines/azetidines promoted by trifluoroacetic acid (TFA) leads to the *N*-aryl *β*-amino alcohols and *N*-aryl *γ*-amino alcohols **96** in moderate to good yields (Scheme 1.47).[54]



Scheme 1.47: MCCs Involving Aziridines, Arynes and Water

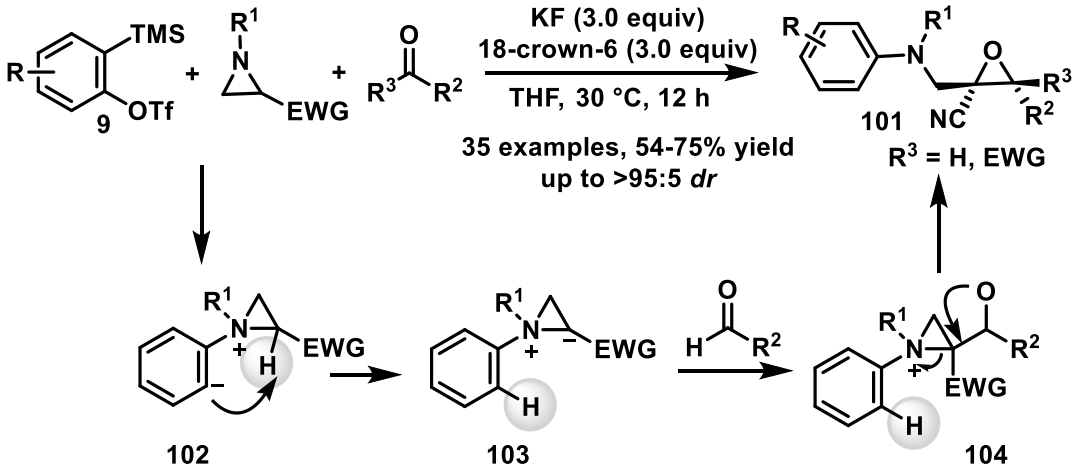
In this case the reaction proceeds via initial attack of aziridine on aryne to form the zwitterionic intermediate **98**, which undergo protonation by carboxylic acid or TFA/H_2O to generate the quaternary ammonium salt **99** and the carboxylate or trifluoroacetate anion (Scheme 1.48). Subsequently the attack of the corresponding acetate ion on intermediate **99** via S_N2 pathway results in the ring-opening to afford the acyl derivative of *N*-aryl *β*-amino alcohols **100**. In the case of trifluoroacetyl derivative of *N*-aryl *β*-amino alcohols undergo hydrolysis to form *N*-aryl *β*-amino alcohols **97**.



Scheme 1.48: Mechanism of Aziridines/Azetidines-Triggered Aryne MCCs

Recently, our group uncovered the aryne three-component coupling triggered by electron-deficient aziridines with aldehydes as the third-component leading to formation of trisubstituted *N*-aryl *α*-amino epoxides **101** in moderate to good yields and diastereoselectivity (Scheme 1.49).[55] The present methodology allows straightforward access to *α*-amino epoxides in a single step under mild reaction conditions. Additionally, we examined the scope of this aziridine triggered aryne three-component coupling with *N*-substituted isatins as the third-component and results the spiroepoxy oxindoles in good yields and excellent diastereoselectivity. Mechanistically, this reaction proceeds through the

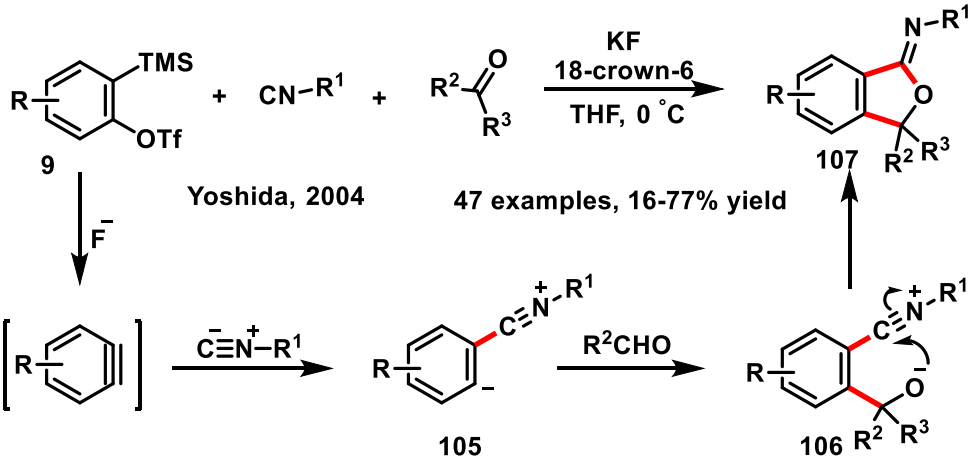
generation of cyclic nitrogen ylide intermediate **103** via intramolecular proton transfer from aziridine-aryne zwitterion **102,** which intercepts with aldehyde to obtain alkoxide intermediate **104**. Consequent ring-opening of aziridinium **104** by alkoxide afforded the *N*-aryl α-amino epoxides.



Scheme 1.49: MCCs Involving Arynes, Aziridines and Carbonyls

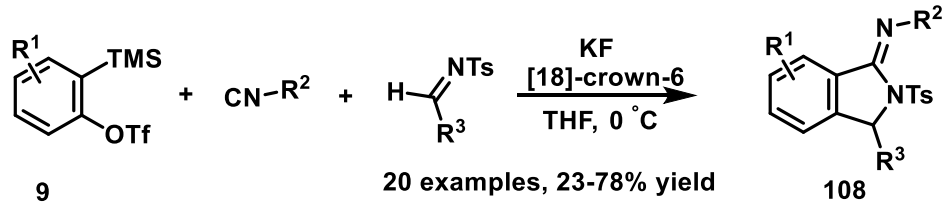
1.7.5. Aryne MCRs Triggered by Isocyanides

In 2004, Yoshida, Kunai and co-workers developed an unprecedented three-component reaction involving arynes, isocyanides and aldehydes resulting in the formation of benzannulated iminobenzofurans in good yields. The isocyanide acts as a nucleophile and the aldehyde acts as the electrophile (Scheme 1.50).[56] Mechanistically, the reaction proceeds via the nucleophilic addition of isocyanide to aryne to form the 1,3-zwitterionic intermediate **105**, which is intercepted by the carbonyl component to generate the intermediate **106** followed by intramolecular cyclization to deliver the desired iminoisobenzofurans **107**. This protocol shows that suitable combination of nucleophiles and electrophiles allows arynes to undergo highly selective three-component coupling. The reaction worked well with a variety of aldehydes and differently substituted arynes are also well tolerated. Aliphatic aldehydes also participate in this unique MCR to form alkyl substituted iminoisobenzofurans. Moreover, this MCR worked well with ketones and benzoquinones as the third components.



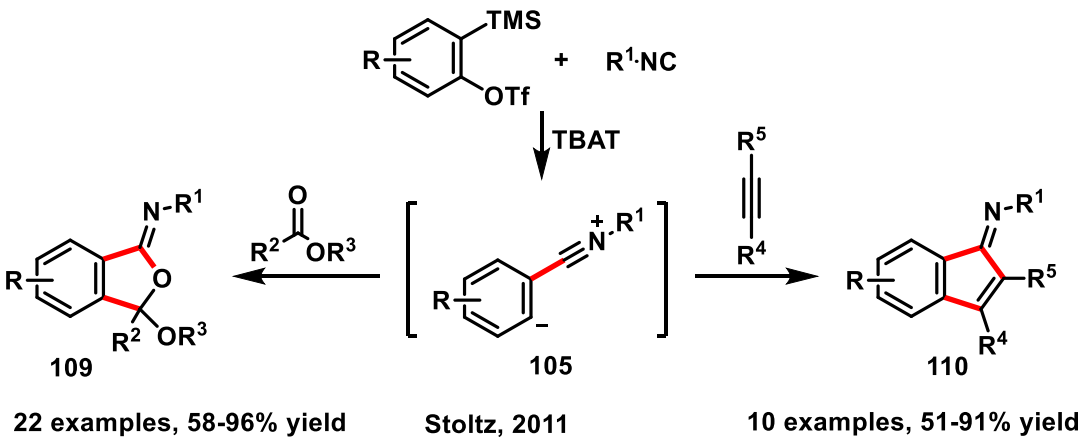
Scheme 1.50: MCR of Arynes, Isocyanides with either Aldehydes or Activated Ketones

Further studies from the same group revealed that the reaction is not only limited to aldehydes as the electrophilic component, but instead activated imines, can also be used as the electrophilic third-component furnishing iminoisoindolines **108** in moderate to good yields (Scheme 1.51) .[57]



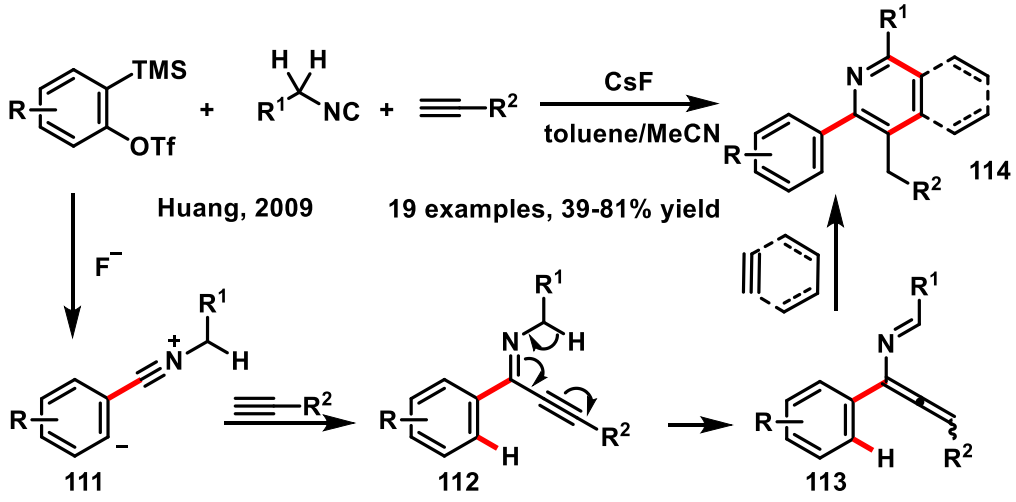
Scheme 1.51: Synthesis of Iminoisoindolines using Aryne MCRs

Stoltz and co-workers disclosed a similar three-component reaction of arynes, isocyanides and phenyl esters that afforded the phenoxy iminoisobenzofuran derivatives **109** in good yields (Scheme 1.52).[58] This MCR proceeds in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT) as a fluoride source in THF at 40 °C resulted the desired products in good yield. This reaction was well tolerated with different substitution on three reaction partners to generate a wide range of heterocycles. Intriguingly, when the ester component of this MCR was replaced by an electron deficient alkyne, the reaction afforded carbocyclic iminoindenones **110** in good yields. The reaction proceeds with the initially formed isocyanide-aryne zwitterions **105**.



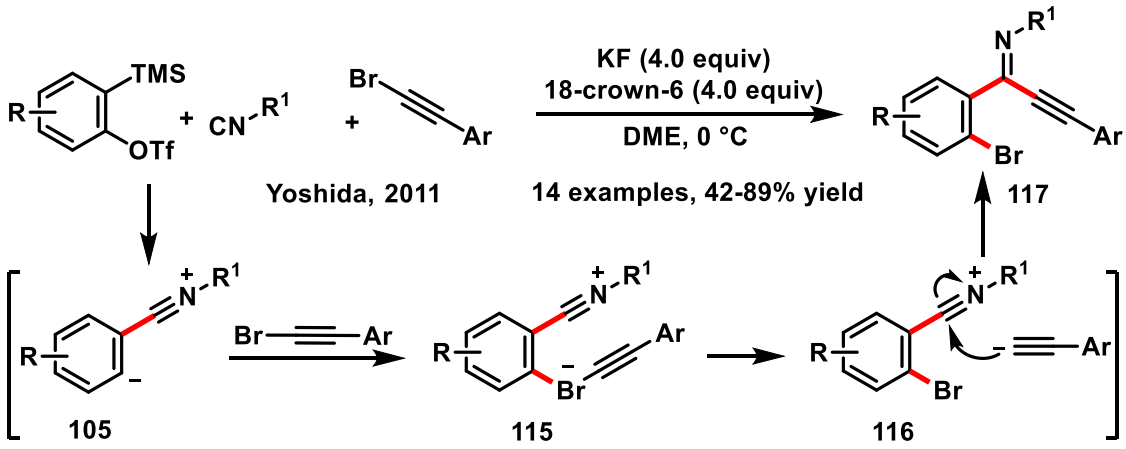
Scheme 1.52: Arynes MCRs Isocyanides and either Phenyl Ester or Electrophilic Alkynes

In 2009, Sha and Huang demonstrated the three-component reaction involving arynes, isocyanides and terminal alkynes to access polysubstituted pyridines and isoquinolines (Scheme 1.53).[59] The key to success for the observed selectivity arose from the appropriate reaction conditions: with excess of terminal alkynes, pyridines were formed and with excess of arynes, isoquinoline were formed. The reaction proceeds via the formation of 1,3-zwitterionic intermediate **111** from aryne and isocyanide, which is intercepted by the terminal alkyne to generate the intermediate **112**, which undergoes [1,5] H shift to form allenyl imine intermediate **113**. The successive cycloaddition of **113** with another molecule of terminal alkyne or aryne afforded either pyridine or isoquinoline derivatives **114** respectively.



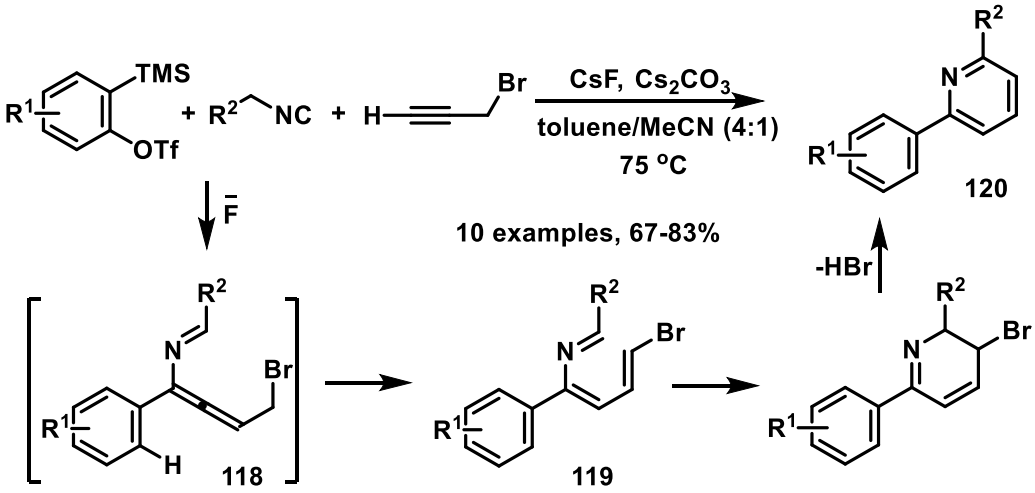
Scheme 1.53: MCR of Arynes, Isocyanides and Terminal Alkynes

The Yoshida group has recently disclosed a unique coupling of isocyanides, alkynyl bromides and arynes to form bromoarenes **117** (Scheme 1.54).[60] The 1,3-zwitterionic intermediate **105** generated from isocyanide and aryne reacts with alkynyl bromides involves *ortho*-bromination to form intermediate **115** followed by addition of acetylide to nitriniumcation 116 to generate bromoarenes **117**.

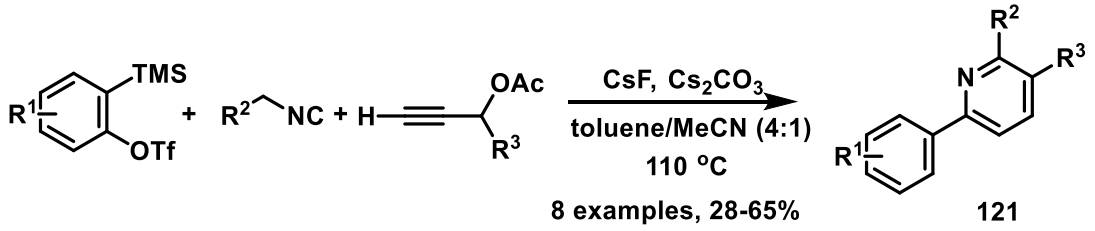


Scheme 1.54: Aryne MCRs with Isocyanides and Organic Bromides

Sha, Wu and co-workers subsequently developed the MCR involving arynes, isocyanides and 3-bromo or 3-acetoxypropynes leading to the synthesis of di and tri substituted pyridines with high regioselectivity.[61] The MCR of arynes with isocyanides and 3-bromopropyne furnished disubstituted pyridines in good yields.



Scheme 1.55: Synthesis of Disubstituted Pyridine Derivatives using Aryne MCRs

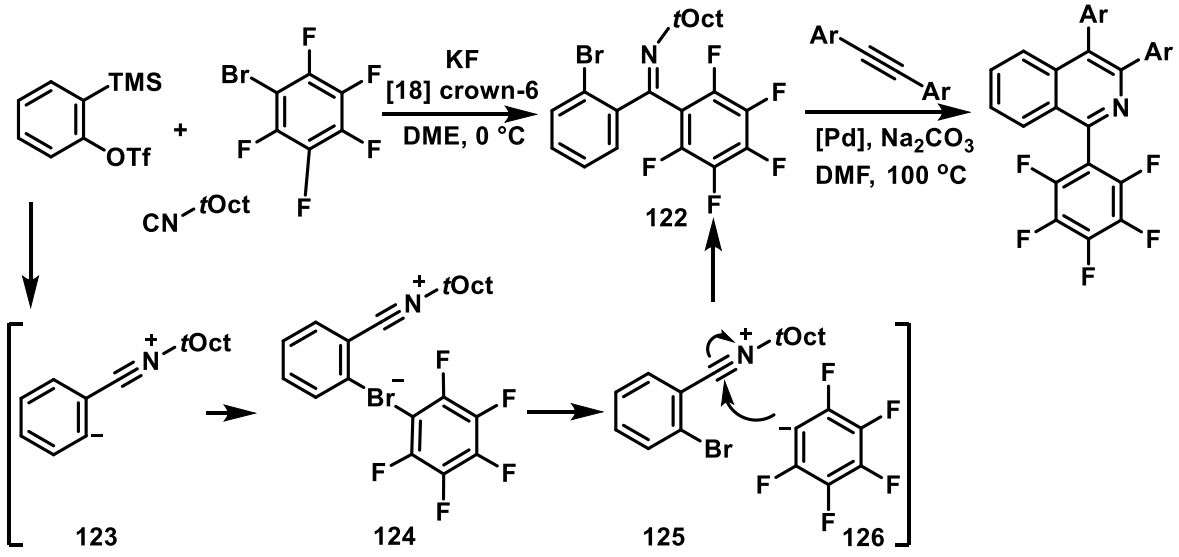


Scheme 1.56: Synthesis of Trisubstituted Pyridine Derivatives using Aryne MCRs

The reaction proceeds via generation of the allenyl imine intermediate **118.** The intermediate **118** undergoes a 1,3-hydrogen shift to give azatriene intermediate **119**, followed pericyclization, and extrusion of a molecule of HBr to furnishes the pyridine derivatives **120** (Scheme 1.55). Interestingly, when 3-acetoxypropyne was used instead of 3-bromopropyne, under similar conditions the reaction resulted in the formation of trisubstituted pyridine derivatives **121** in moderate yields (Scheme 1.56).

1.7.6. Aryne MCRs Involving Isocyanide and Perfluorinated Bromoarene

Interestingly, Yoshida and co-workers utilized alkynyl (polyfluorinated aryl) bromides as the third component in aryne MCRs with isocyanides. The reaction resulted in the formation of ketimines **122** in good yields. The 1,3-zwitterionic intermediate **123** generated from isocyanide and aryne reacts with perfluorinated bromoarene resulting in the generation of iminium intermediate **125** and aryl anion **126** through the bromine ate complex **124**. Further C-C bond formation afforded ketimines **122** (Scheme 1.57).[62] Subsequent

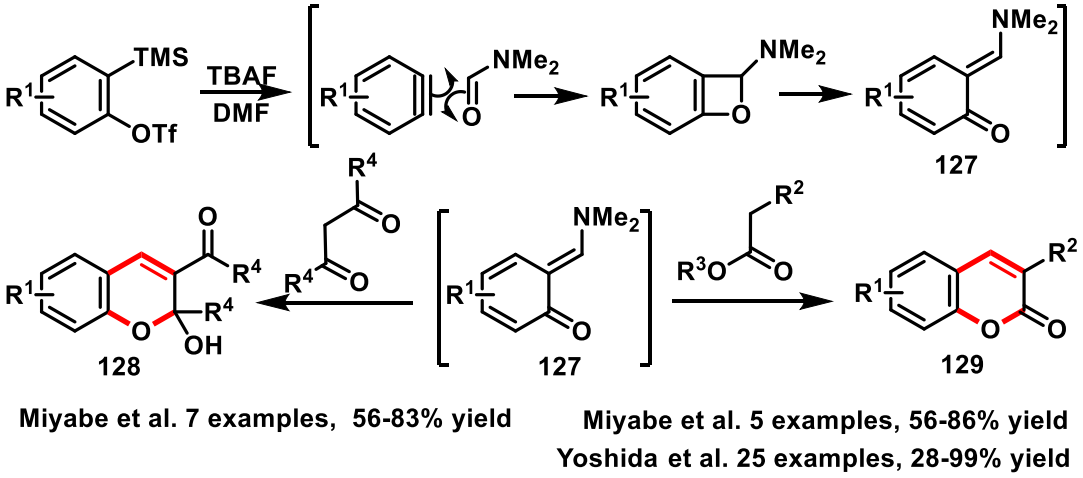


Scheme 1.57: Synthesis of Isoquinolines Initiated by Aryne MCR

treatment of ketimines with diarylalkynes in the presence of catalytic amount of Pd-catalyst afforded the multisubstituted isoquinolines via the annulation reaction.

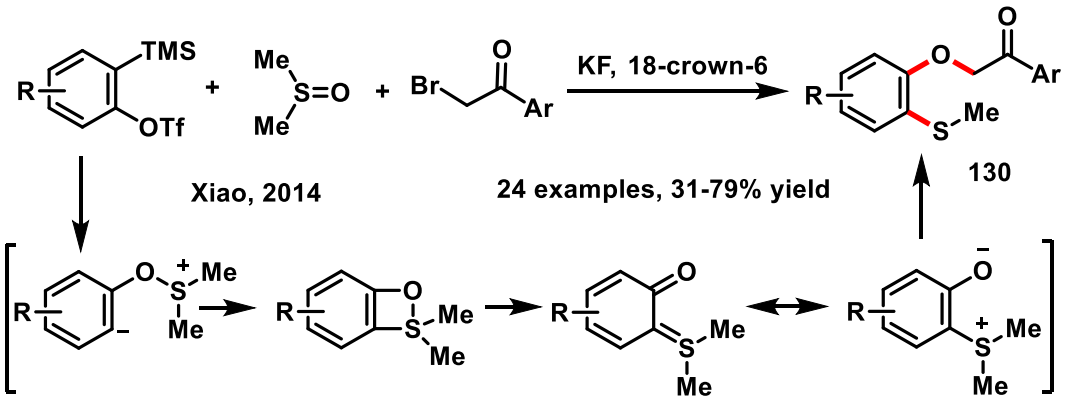
1.7.6. Miscellaneous Aryne MCCs Triggered by Solvents

The aryne MCCs involving dimethyl formamide (DMF) and an active methylene compound was recently demonstrated independently by the research groups of Miyabe[63a] and Yoshida.[63b] The key intermediate is the *o*-quinonemethides **127** generated from DMF and aryne. Interception of **127** with 1,3-diketones as the third-component delivered the 2*H*-chromenes **128** and with the use of β-ketoesters as the third-component afforded coumarines **129** in moderate to excellent yields (Scheme 1.58).



Scheme 1.58: MCCs of Arynes with DMF and Active Methylene Compounds

Chen, Xiao and co-workers developed the aryne MCCs triggered by dimethyl sulfoxide (DMSO).[64] With the use of α-bromo carbonyl compound as a third-component

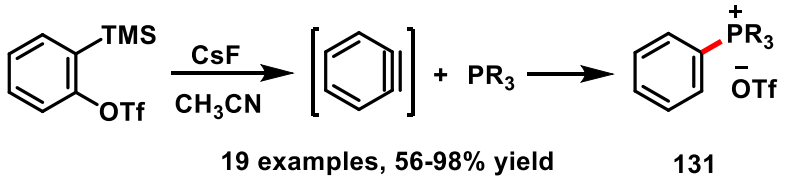


Scheme 1.59: MCCs Triggered by Dimethyl Sulfoxide (DMSO)

results the arylmethyl thioethers **130** in good yields, where DMSO acts as a methyl thiolation agent and oxygen source (Scheme 1.59).

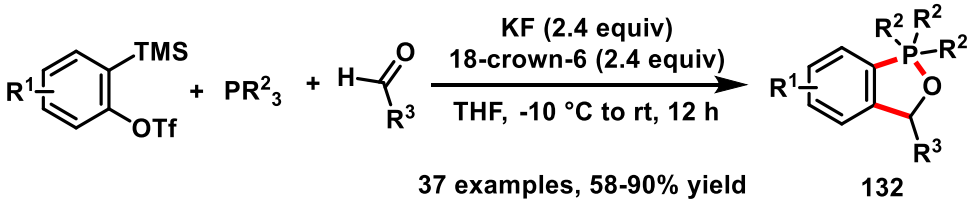
1.7.7. Phosphine-Triggered Aryne MCCs

Recently, Juge and Leroux synthesized various achiral and chiral phosphonium salts **131** by the reaction of organophosphines with arynes.[65] Organophosphines adds to the aryne molecule generated in situ by the fluoride mediated *β*-elimination of silyl aryltriflates to form phosphonium anion that is protonated by acetonitrile solvent to form *P*-arylated salt.



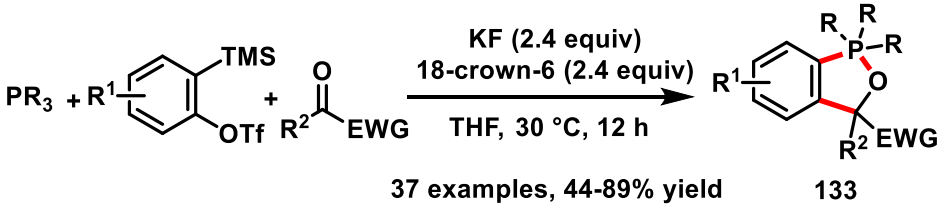
Scheme 1.60: Organophosphines with Arynes

Our group recently uncovered the highly efficient phosphine-triggered aryne MCCs involving aldehydes as the third-component. The method access the diverse range of stable benzooxaphosphole derivatives **132** in good to excellent yields (Scheme 1.61).[66] The reaction proceeds via a formal [3+2] cycloaddition of the initially generated phosphine- aryne zwitterion with the carbonyl moiety of aldehydes. A wide variety of aldehydes, symmetrical and unsymmetrical arynes, and several alkyl and aryl phosphines are well tolerable.

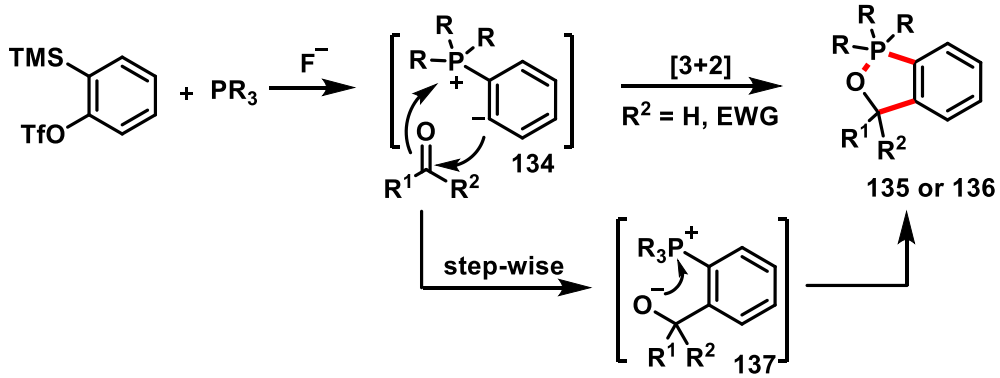


Scheme 1.61: MCCs Involving Phosphines, Arynes and Aldehydes

Subsequently, we have disclosed the operationally simple MCC involving phosphines, arynes and various acyclic and cyclic activated carbonyl compounds. Diverse range activated ketones such as trifluoroacetophenone, diaryl 1,2-diones, α-ketoesters and β,γ-unsaturated α–ketoesters can be used as the third-component in this reaction to afford the benzooxaphospholes **133** in moderate to good yield (Scheme 1.62).[67] Moreover, *N*-substituted isatins can also be used as the electrophilic component in this MCCs delivering rapid access to spirobenzooxaphospholes.



Scheme 1.62: MCCs Involving Phosphines, Arynes and Acyclic and Cyclic Ketones



Scheme 1.63: Mechanism of Phosphine-triggered Aryne MCCs

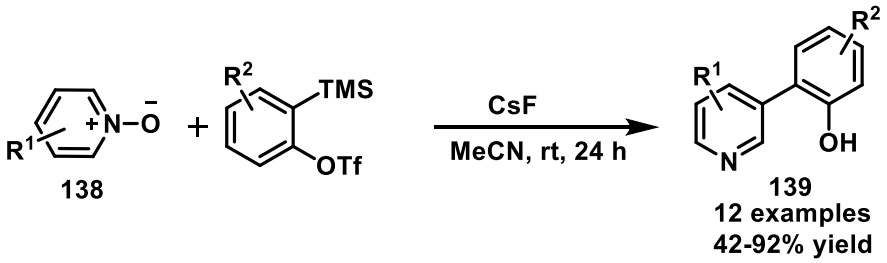
Mechanistically, 1,3-zwitterionic intermediate **134** generated from phosphine and aryne, can undergo a formal [3+2] cycloaddition reaction with carbonyl group of aldehyde/ketone resulting in the formation of the benzooxaphosphole **135** or **136**. The expected product can also be formed by a stepwise pathway proceeding through the alkoxide intermediate **137** (Scheme 1.63).

1.8. Rearrangement Reactions involving Arynes

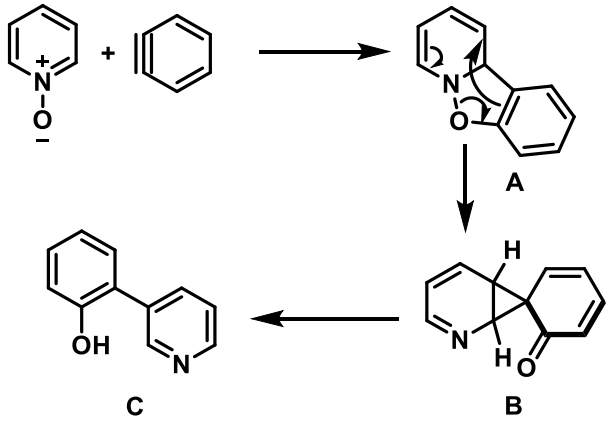
Rearrangement reaction is a broad class of organic reactions where the carbon skeleton of a molecule is rearranged to give a structural isomer of the original molecule. Often a substituent move from one atom to another atom in the same molecule. In the present section, rearrangement reaction, which involves arynes has been discussed in detail.

3-Arylpyridines are a particularly interesting class of alkaloids, which can be prepared via intermolecular radical addition using pyridine derivatives. However, Larock and co-workers showed that a variety of substituted 3-(2-hydroxyphenyl)pyridines **139** have been prepared regioselectively by a transition-metal-free, mild, one-step route, which involves the reaction of pyridine *N*-oxides **138** with silylaryl triflates in the presence of CsF in acetonitrile at room temperature (Scheme 1.64).[68] Mechanism involves the initial [3+2] cycloaddition leading to the formation of oxazolopyridine intermediate (**A**), which

underwent rearrangement to the cyclopropane intermediate (**B**). This intermediate open up forming the final biaryls (**C**) in good yields (Scheme 1.65).

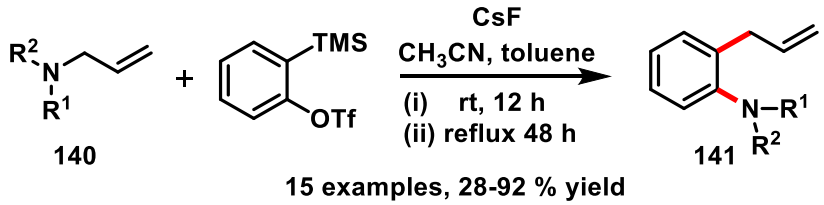


Scheme 1.64: Reaction of Benzyne with Pyridine *N*-oxides



Scheme 1.65: Mechanism for the Reaction of Benzyne with Pyridine *N*-oxides

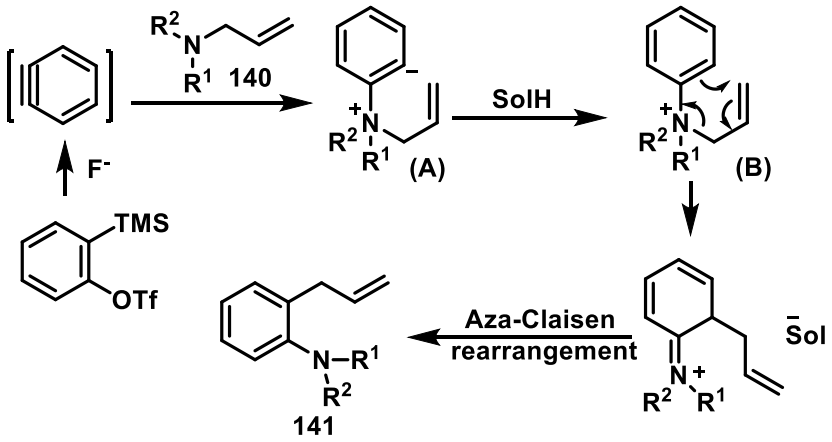
Conventioaal Aza-Claisen reactions require stoichiometric amounts of Lewis acids such as $BF_3.(OEt)_2$ and high reaction temperatures. To overcome the harsh conditions, Greaney and co-workers came up with a simpler protocol by using benzyne. They anticipated that the addition of benzyne to a tertiary allylamine **140** could set up an aza-Claisen rearrangement pathway, to synthesize functionalized anilines **141** (Scheme 1.66).[69]



Scheme 1.66: Benzyne Aza-Claisen Rearrangement

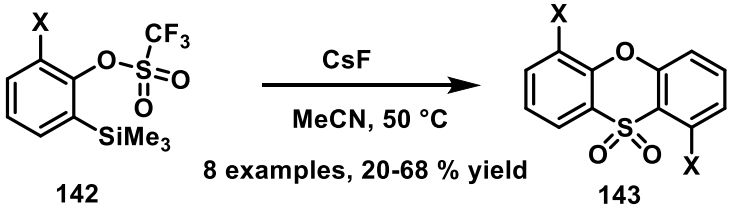
Proposed mechanism involves initial attack of tertiary allylic amine **140** to the aryne generating the zwitterionic intermediate (**A**). This intermediate gets protonated by the solvent

to give the quaternary salt (**B**). This salt undergoes an Aza-Claisen rearrangement to deliver the functionalised anilines **141** (Scheme 1.67).



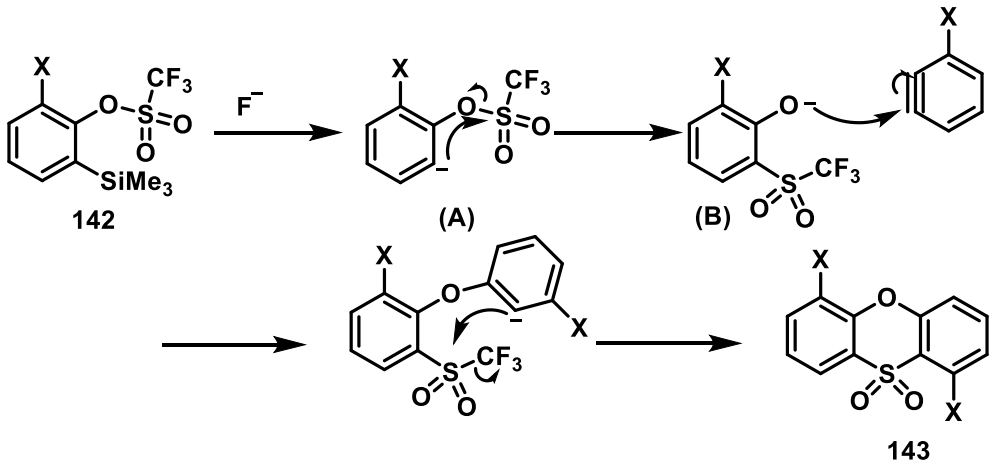
Scheme 1.67: Mechanism for the Benzyne Aza-Claisen Rearrangement

2-(Trimethylsilyl) aryl trifluoromethanesulfonate benzyne precursors, underwent thia-Fries rearrangement on simple fluoride treatment affording phenoxathiin-dioxides **143** is reported by Greaney and co-workers. Halogen or nitro-containing aryne precursors **142** are used to explore substrate scope forming phenoxathiin-dioxides and this new route that does not require the preparation of a phenoxathiin and subsequent oxidation (Scheme 1.68).[70]



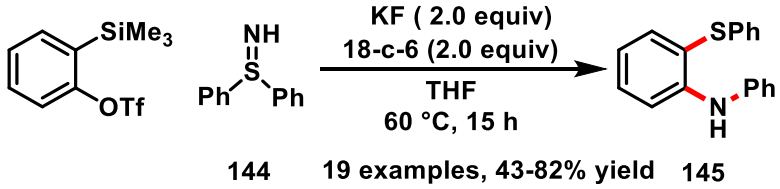
Scheme 1.68: Benzyne Thia-Fries rearrangement

Mechanistically, fluoride ion attacks the TMS group on **142** which results in the formation of aryl anion intermediate **A**. Which undergo sulfonyl group migration afforded the corresponding phenoxide ion **B.** The key phenoxide ion intermediate **B** reacts with another molecule of insitu generated benzyne leading to the formation of phenoxathiin-dioxides **143**.



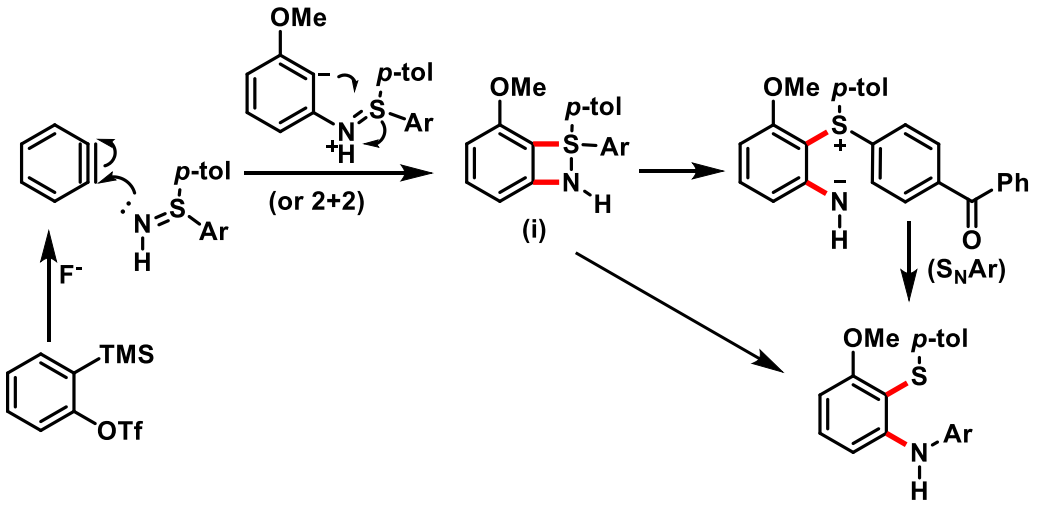
Scheme 1.69: Mechanism for the Benzyne Thia-Fries rearrangement

In 2015, a novel method for preparing a diverse range of *o*-sulfanylanilines has been described by Hosoya and co-workers. Direct thioamination of arynes with sulfilimines **144** gives *o*-sulfanylanilines **145**, involving C−N and C−S bond formations and migratory *N*-arylation. Thus a double heteroatom functionalization has been achieved (Scheme 1.70).[71]



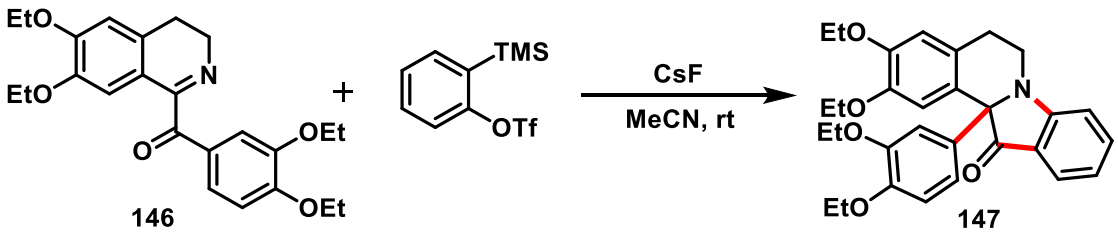
Scheme 1.70: Thioamination of Arynes

The reaction is proposed to proceed through a four-membered ring intermediate (i), which is produced either via nucleophilic addition of sulfilimine to the aryne followed by cyclization or via a direct [2+2] cycloaddition. Cleavage of the S−N bond of C and subsequent intramolecular ipso-substitution at the more electron-deficient aryl group provided the *N*-arylated product. However, the authors are not excluding the possibility of a pathway involving direct ligand coupling on the sulfur of intermediate (i) (Scheme 1.71).



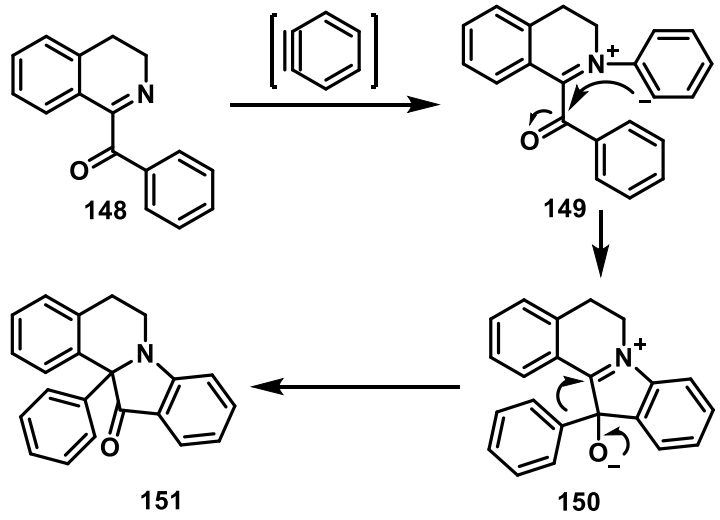
Scheme 1.71: Mechanistic Proposal for the Thioamination of Arynes

Recently Voskressensky and co-workers describe an elegant and effective synthesis of indoxylisoquinolines **147** through Michael addition/aryl-anion migration domino protocol induced by arynes in 1-aryloxy substituted 3,4- dihydroisoquinolines **146**. The reaction condition was optimized with CsF as the fluoride source and acetonitrile as the solvent at room temperature. The scope of the reaction was general with variation on both the components (Scheme 1.72).[72]



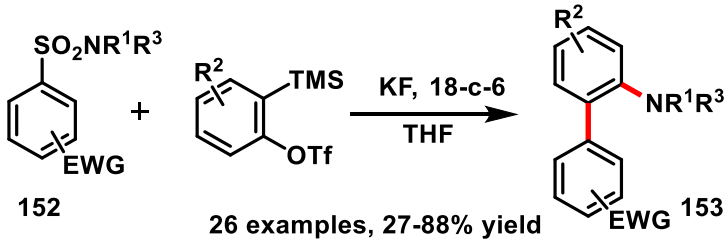
Scheme 1.72: Synthesis of Indoxylisoquinolines from Arynes

Proposed mechanism involves initial nucleophilic attack of the isoquinoline **148** nitrogen on generated in situ aryne leading to formation of zwitterion **149**, the anionic center of which attacks further carbonyl group, giving oxyanion **150**. Re-formation of the carbonyl group with subsequent migration of aryl substituent afforded the corresponding indoloisoquinolinones **151** (scheme 1.73).



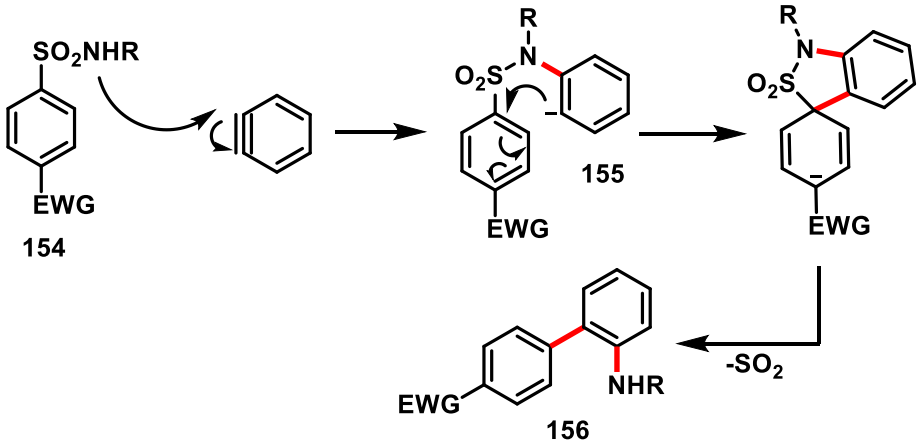
Scheme 1.73: Proposed Mechanism for the Synthesis of Indoxylisoquinolines

The biaryl motif is a widely represented functionality in natural products, materials, pharmaceuticals, and agrochemicals. In 2016, Greaney and co-workers disclosed a facile protocol for the synthesis of biaryls **153** with aryl sulfonamides **152** adding to benzyne followed by an aryl Truce–Smiles rearrangement. It afforded biaryls with sulfur dioxide extrusion (Scheme 1.74).[73]



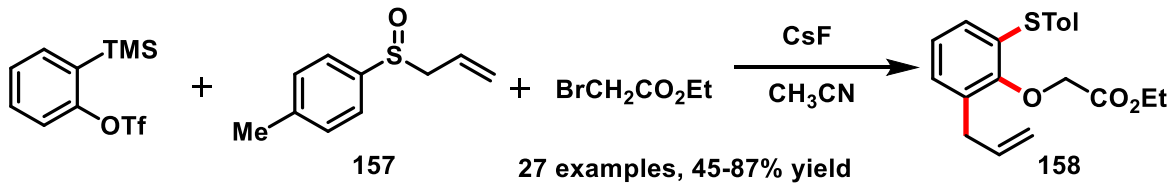
Scheme 1.74: Benzyne Truce–Smiles rearrangement

Aryl sulphonamides **154** upon addition of a benzyne generated from a 2-trimethylsilyl-(phenyl) triflate precursor upon treatment with fluoride leading to the formation of adduct **155**. This intermediate undergo a Smiles-type ipso substitution with SO_2 extrusion, afforded 2-amino-biaryls **156** (Scheme 1.75).



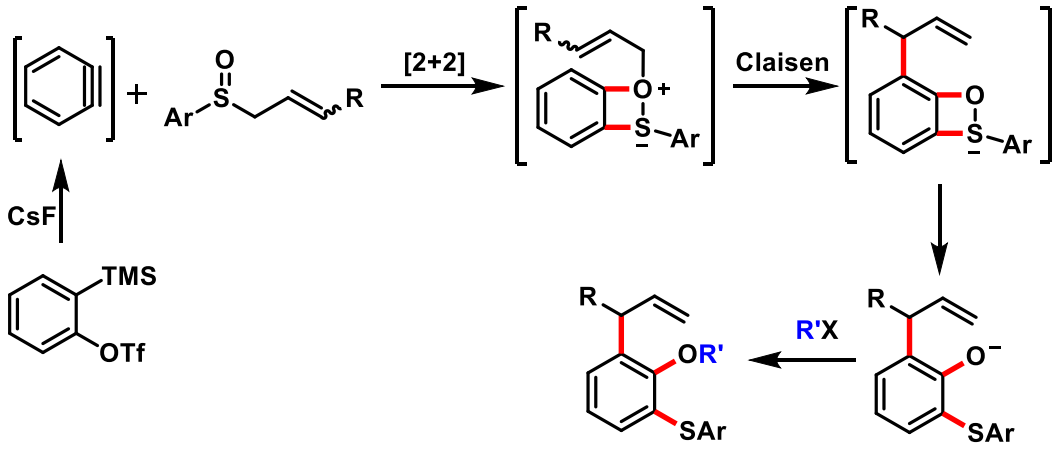
Scheme 1.75: Mechanistic Proposal for the Benzyne Truce-Smiles Rearrangement

Recently Li and co-workers demonstrated an aryne 1,2,3-trisubstitution with aryl allyl sulfoxides **157** and three new bonds including C-S, C-O, and C-C bonds were formed in a single transformation on the consecutive positions of a benzene ring **158**. The reaction



Scheme 1.76: Aryne 1,2,3-Trifunctionalization

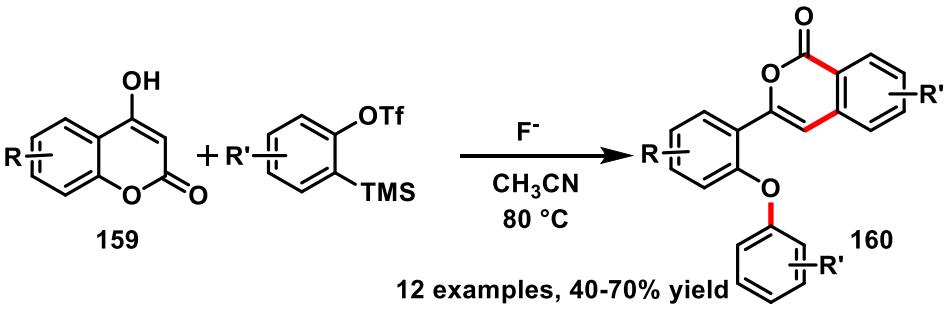
condition is mild with broad substrate scope. They anticipated functionalising the 3-position of a benzyne intermediate and convert this C−H bond to other types of bonds in an aryne process. For the first time, aryne 1,2,3-trifunctionalization with smartly designed aryl allyl sulfoxides. (Scheme 1.76).[74]



Scheme 1.77: Mechanistic Proposal for Aryne 1,2,3-Trifunctionalization

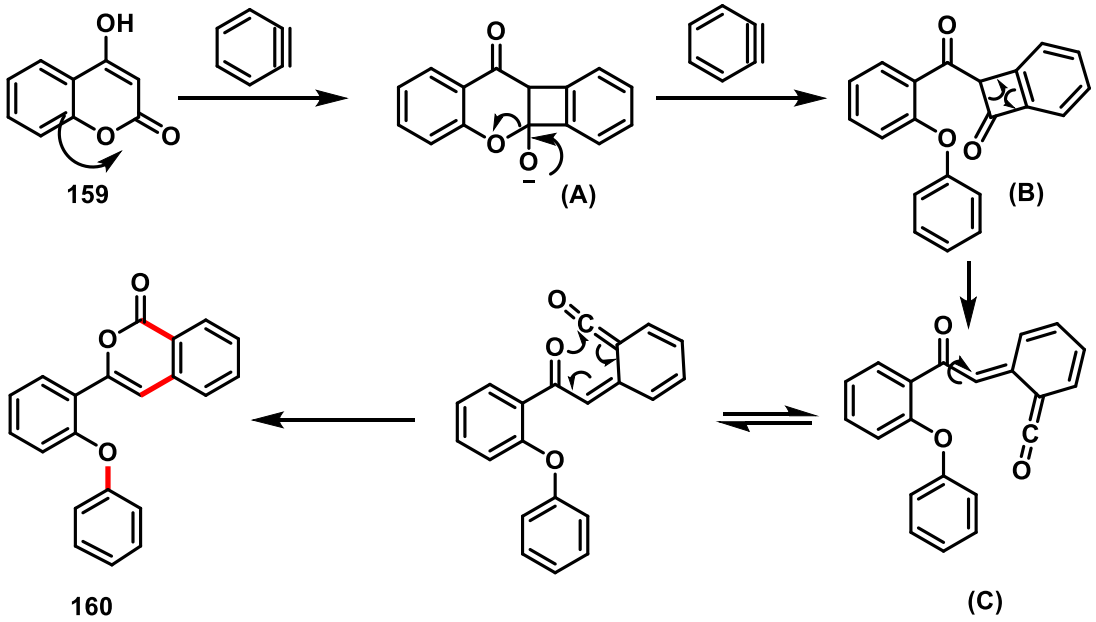
Preliminary mechanistic study suggests a cascade formal [2+2] reaction of aryne with S-O bond, an allyl S→O migration, and a Claisen rearrangement (Scheme 1.77).

Very recently a novel transition-metal-free direct synthesis of 3-substituted isocoumarin **160** from 4-hydroxycoumarin **159** and a benzyne precursor is developed by Gogoi and co-workers. This synthetic strategy proceeds via C−O and C−C bond cleavage as well as C−O and C−C bond formations in a single reaction (Scheme 1.78).[75]



Scheme 1.78: Synthesis of 3-Substituted Isocoumarins from Coumarins

Mechanistically, 4-hydroxycoumarin **159** reacts with two molecules of benzyne, which leads to the four-membered ring intermediate (**B**) via anion intermediate (**A**). Intermediate (**B**) undergoes rapid rearrangement to the corresponding ketene intermediate (**C**), which undergoes ring closure to the desired six-membered isocoumarin **160** (Scheme 1.79).



Scheme 1.79: Mechanistic Proposal for the Coumarin to Isocoumarin Transformation

1.9. Conclusion and Focal Theme of the Present Work

This Chapter has described the various types of cycloaddition, insertion, multicomponent and rearrangement reactions of arynes and their synthetic potential for constructing highly functionalized aromatic compounds. As discussed in the previous sections, the successes of these aryne reactions are mainly attributed to the use of Kobayashi's 2-(trimethylsilyl)aryl triflates as aryne precursors, which allows the generation of arynes under extremely mild conditions. The main focus of this thesis is to extend the aryne chemistry to couple benzynes with tropones, alcohols, azirines, allylthioethers and more 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 step process. Moreover, this can highlight the synthetic utility of this highly reactive intermediate in organic synthesis.

In this context, Diels-Alder reaction of arynes with challenging diene like tropone has been presented in the second Chapter. The aryne generated by the fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates undergoes a facile Diels-Alder reaction with tropone under mild conditions affording the various bridged benzobicyclo[3.2.2]nonatrienone derivatives in moderate to good yields. In addition, the application of the tropone-aryne [4+2] cycloaddition reaction has been examined by the photochemical rearrangement of the benzobicyclo[3.2.2]nonatrienone to form the functionalized naphthalene derivative. Detailed discussion of these reactions are presented in the 2nd Chapter of the thesis.

Transition-metal-free aryne multicomponent couplings (MCCs) and insertion reactions provide straightforward access to various 1,2- disubstituted arenes. Moreover, transition-metal-catalyzed *O*-arylation using aliphatic alcohols is a powerful strategy for the construction of alkyl aryl ethers. In this context, syntheses of alkyl aryl ethers under transition-metal-free conditions have the economic and ecological advantage. Despite successful aryne insertion to O-H bond of phenols and carboxylic acids, the related insertion of arynes into O-H bond of aliphatic alcohols are underexplored. In Chapter 3, the transition-metal-free, and temperature dependent selectivity switch reaction of arynes with aliphatic alcohols has been presented.

The indole nucleus is a common structural motif present in numerous biologically active natural products, pharmaceutical compounds and agrochemicals. Consequently, development of straightforward, cheap and flexible synthetic routes for the construction of functionalized indoles is of great importance. In these context, the transition-metal-free and temperature dependent highly selective reaction of arynes with 2*H*-azirines allowing the synthesis of either *N*-unsubstituted or *N*-aryl indoles forms the subject matter of the Chapter 4 of this thesis.

Organosulfur compounds are endowed with diverse applications in pharmaceutical chemistry and crop protection, and have attracted considerable attention from both industry and academia. Among the organosulfur compounds, the β-keto thioethers are important as they are valuable core structure in various biologically active molecules. In view of this, a mild and transition-metal-free synthesis of β-keto arylthioethers has been developed by the aryne triggered [2,3] Stevens rearrangement of allylthioethers. Later, the reaction products are converted into valuable heterocycles such as furan, thiophene and pyridazine derivatives in two-step procedure. These details form the subject matter of the 5th Chapter of the thesis.

1.10. References

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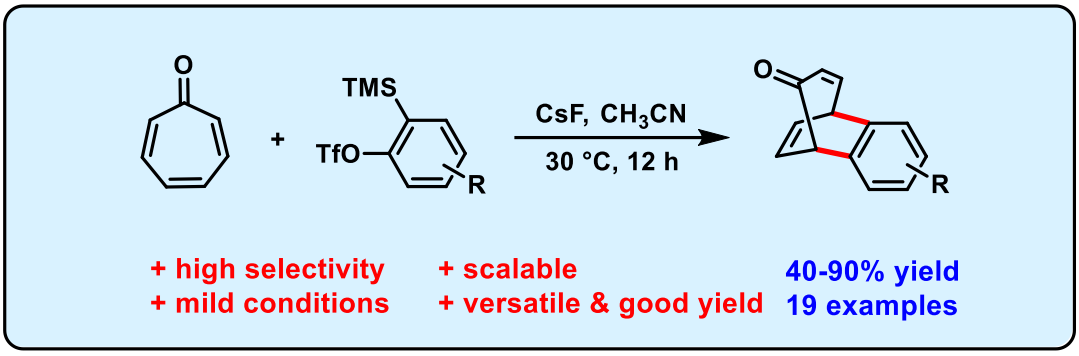
Chapter 2

Diels-Alder Reaction of Tropones with Arynes: Synthesis of Functionalized Benzocycloheptenones

A new procedure for the mild, practical and scalable Diels-Alder reaction of tropones with arynes is presented in this chapter. Differently substituted tropones undergo selective [4+2] cycloaddition with arynes generated in situ by the fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates, allowing the synthesis of benzobicyclo[3.2.2]nonotrienone derivatives in moderate to good yields. In addition, the photophysical properties of the cycloadducts has been discussed.



J. Org. Chem. **2014**, *79*, 4757−4762

2.1. Introduction

Tropones are a valuable class of compounds that have attracted much attention of organic chemists from synthetic and theoretical perspectives.[1] The members of the troponoid family are known as important precursors for natural product synthesis,[2] and are appropriate substrates for higher order cycloaddition reactions.[3] Depending on the reaction conditions and the coupling partner, tropones can react as a 2π, 4π, 6π, or 8π component in cycloaddition reactions (Fig 2.1). The present chapter describes the Diels-Alder reaction of arynes with tropones. Before going into the details, a brief account of cycloaddition reactions of tropones is given in the following sections.

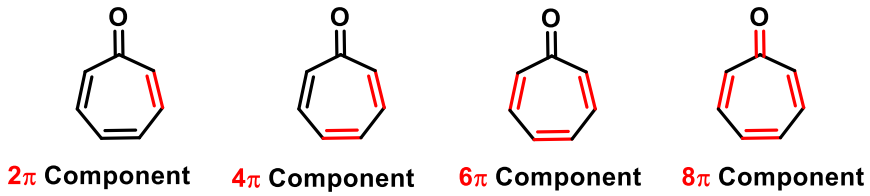
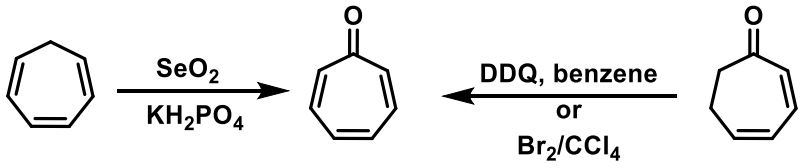


Fig 2.1: Reactive Sites in Tropone

2.2. Synthesis of Tropone

Tropone is prepared by the oxidation of cycloheptatriene with selenium dioxide.[4a] It can also be accessed from the corresponding tropionone oxidation either with DDQ or bromine in CCl_4 leading to the formation in moderate to good yield (Scheme 2.1).[4b]



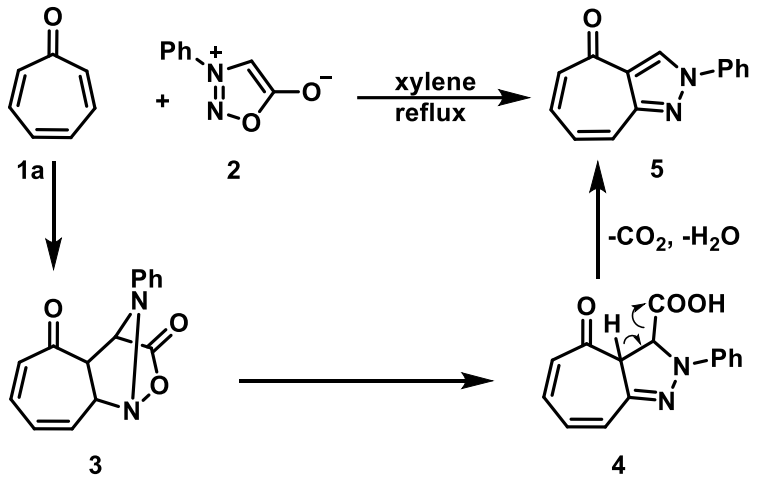
Scheme 2.1: Synthesis of Tropone from Cycloheptatriene and Tropionone

2.3. Cycloaddition Reactions of Tropones

The cycloaddition chemistry of tropones have been explored in great detail. It can function as two, four, six, or eight-member synthons to furnish [4 + 2], [6 + 3], [6 + 4], [8 + 2] or [8 + 3] annulation products, that are valuable in the synthesis of bioactive molecules and natural products. The various modes of action of tropones based on the reaction partner has been discussed in the following sections.

2.3.1. Tropones as 2π Component

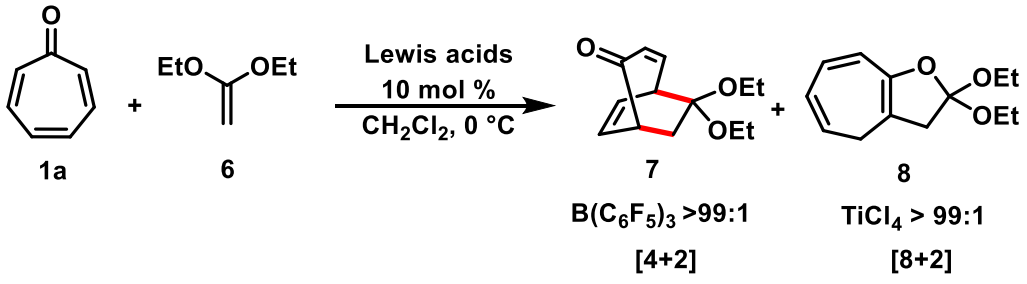
Kato and co-workers reported the reaction of mesoionic compounds with tropones.[5a] These reactions proceed via [4π + 2π] cycloaddition selectively, depending on the structure of the starting mesoionic compounds (Scheme 2.2). The cycloaddition reaction of tropone **1a** with 3-phenylsydnone **2** proceeded *peri*- and regio-selectively in a [4π + 2π] mode to give the cycloadduct **3,** followed by extrusion of carbon dioxide and dehydrogenation of **4** afforded the corresponding heterocycle **5**. A careful literature search revealed that electron-deficient dipoles (nitrile oxide, nitrile imine and sydnone) prefer [4π + 2π] cycloadditions to tropones.[5b]



Scheme 2.2: Diels-Alder Reaction of Tropone with 3-Phenylsydnone

2.3.2. Tropones as 4π Component

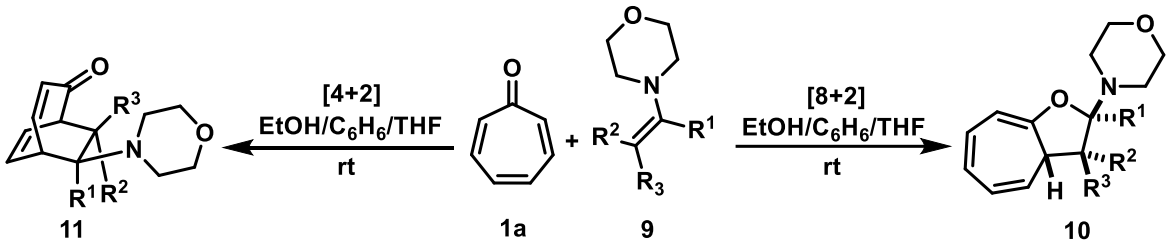
Yamamoto and co-workers developed the Lewis acid-catalyzed switchable cycloaddition reactions between tropone **1a** and ketene diethyl acetal **6**. The reaction selectivity is varied based on Lewis acid, in case of $B(C_6F_5)_3$, the reaction afforded the



Scheme 2.3: Lewis Acid-catalysed Cycloaddition Reaction of Tropone

corresponding [4+2] cycloadduct **7**, whereas with $TiCl_4$ the reaction switched to [8+2] adduct **8** with high selectivity and good yield (Scheme 2.3).[6]

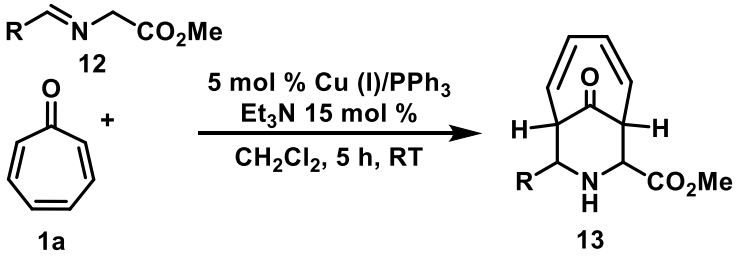
Takayasu and co-workers demonstrated the reaction of tropone **1a** with enamines **9** to deliver different products depending on the substituents on the enamine. Thus, 1-morpholinocyclohexene reacted with tropone to afford the corresponding [8+2]-type adduct **10** in 77% yield (Scheme 2.4).[7] 1-Morpholinocyclopentene also gave a similar cycloadduct in good yield. The product may be considered to arise via an [8+2] cycloaddition or via a nucleophilic addition of the enamine **9** to tropone and subsequent ring closure. On the other hand, 1-morpholinopropene afforded a [4+2]-type adduct **11** in 66% yield as shown in Scheme 2.4.



Scheme 2.4: Diels-Alder Reaction of Tropone with Enenamines

2.3.3. Tropones as 6π Component

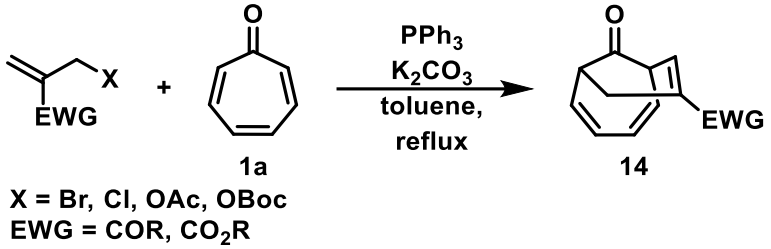
Wang,[8a] Guo[8b] and co-workers independently reported an unprecedented Cu(I)-catalyzed asymmetric [6 + 3] cycloaddition reaction of tropone **1a** with azomethine ylides **12**, which performs well with the broad reaction scope and offers a unique and facile access to the synthetically useful bridged azabicyclo[4.3.1]decadiene derivatives **13** in good yields with high diastereoselectivities and enantioselectivities under mild conditions (Scheme 2.5).



Scheme 2.5: Metal-Catalyzed [6 + 3] Cycloaddition of Tropone with Azomethine Ylides

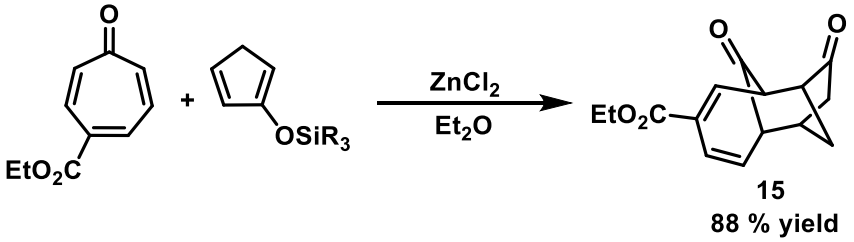
Lu and co-workers demonstrated a novel phosphine-catalyzed reaction of modified allylic compounds, including acetates, bromides, chlorides, or *tert*-butyl carbonates derived

from the Morita-Baylis-Hillman reaction with tropone **1a** to yield [3+6] annulation products **14** in good to excellent yields (Scheme 2.6).[9] This reaction offers a simple and convenient method for construction of bridged nine-membered carbocycles.



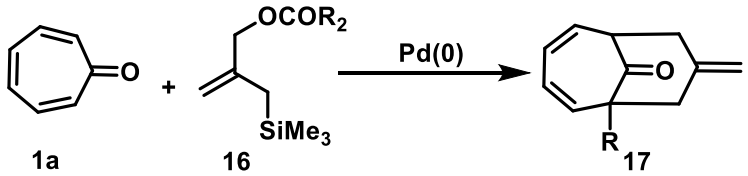
Scheme 2.6: Phosphine-Catalyzed [3+6] Annulation Reaction of Tropone

Later, Gleason and co-workers synthesised the carbocyclic core of CP-225,917 and CP-263,114 via [6+4] cycloaddition of tropone with 2-substituted cyclopentadiene followed by Baeyer-Villiger oxidation and subsequent *syn*-elimination of a tricyclic diketone **15** (Scheme 2.7).[10] Detailed study of this reaction revealed that this cycloaddition reaction is catalyzed by Lewis acids. Cycloaddition reactions of several substituted tropones with 2-silyloxycyclopentadienes using $ZnCl_2$ catalysis are found to proceed in good yield and in many cases excellent diastereoselectivity.



Scheme 2.7: [6+4] Cycloaddition Reaction of Tropone with Substituted Cyclopentadiene

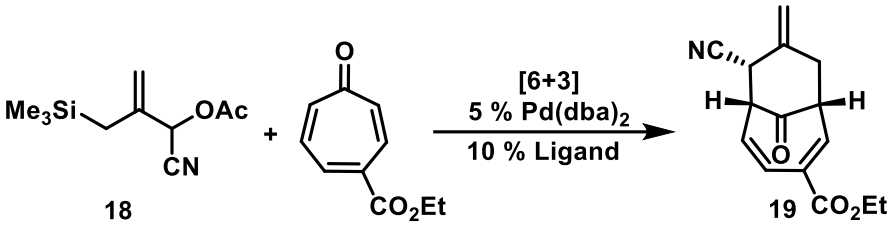
Trost and co-workers demonstrated the palladium-catalyzed reaction of 2-[(trimethylsilyl)methyl]allyl carboxylates and their substituted analogues with tropone,



Scheme 2.8: [6+3] Cycloaddition to Nine Membered Ring Carbocycles

which undergoes exclusive [6 + 3] cycloaddition resulting in the formation of nine-membered carbocycles (Scheme 2.8).[11]

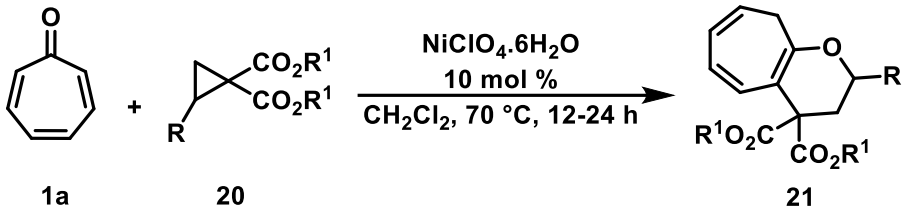
Almost thirty years later, the same group developed the first asymmetric synthesis of bicyclo[4.3.1] decadienes and bicyclo[3.3.2]decadienes **19** via a [6+3] trimethylenemethane cycloaddition with tropones (Scheme 2.9).[12] Moreover, they have performed a facile thermal rearrangement to yield the corresponding asymmetric bicyclo[3.3.2]decadienes.



Scheme 2.9: Asymmetric [6 + 3] Cycloaddition Reaction of Trimethylenemethane

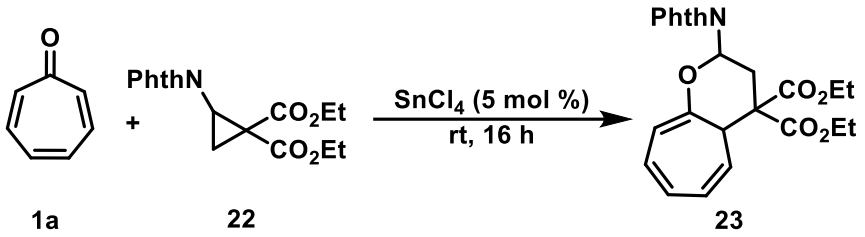
2.3.4. Tropones as 8π Component

Carretero and co-workers have synthesised a variety of cycloheptapyrane derivatives via Ni-catalysed formal [8+3] cycloaddition reaction of tropone **1a** with donor-acceptor cyclopropane **20**. The asymmetric version of this reaction was achieved by using either an enantiomerically enriched cyclopropane as the starting material or the combination of a racemic cyclopropane and an appropriate chiral ligand (Scheme 2.10).[13]



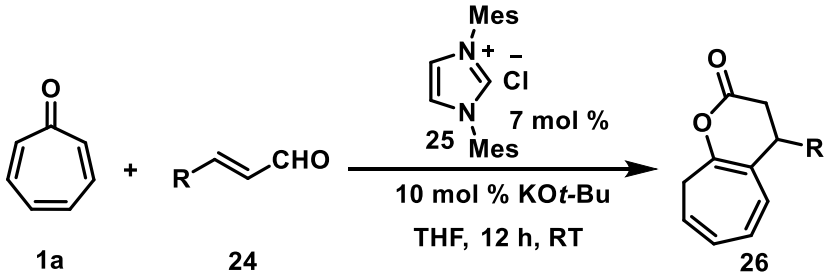
Scheme 2.10: Ni-catalyzed [8+3] Cycloaddition of Tropones with Cyclopropanediesters

Later, Sierra and co-workers developed a novel $SnCl_4$-catalyzed [8+3]-cycloaddition reaction of tropone **1a** with donor-acceptor aminocyclopropanes **22** (Scheme 2.11).[14] This process leads to the formation of the amino-substituted tetrahydrocyclohepta[*b*]pyrans derivatives **23** with complete regio- and diastereoselectivity. Density functional theory calculations suggest that the cycloaddition proceeds via a stepwise process through an aromatic zwitterionic intermediate.



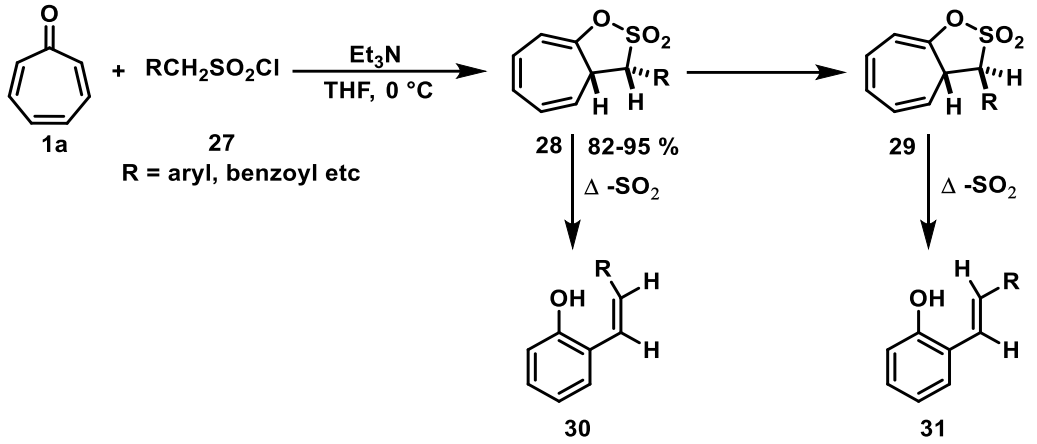
Scheme 2.11: [8+3] Cycloaddition Reaction of Tropone and Donor-Acceptor Amino Cyclopropane

Nair and co-workers reported an unprecedented N-heterocyclic carbene catalyzed [8 + 3] annulation reaction of tropone **1a** and enals via homoenolate. The carbene generated from the imidazolium salt **25** using KO*t*-Bu as base was found to be the best catalyst for this transformation. The reaction scope was investigated using a number of substituted cinnamaldehydes affording the corresponding γ-lactones **26** with moderate to good yield (Scheme 2.12).[15]



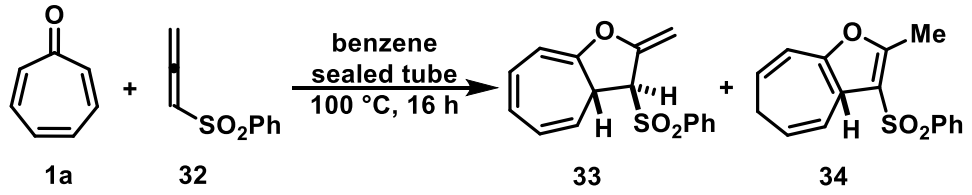
Scheme 2.12: Reaction of Cinnamaldehyde with Tropone

Truce and co-workers demonstrated the reaction of tropone **1a** with sulfene resulting in the formation of [8+2] adducts **28, 29** in the ratio 1:1. Detailed study revealed that the cycloadduct isolated was the *cis* isomer. On treatment with base, the primary *cis* cycloadduct was transformed to the corresponding *trans* isomer (Scheme 2.13).[16] The initial exclusive formation of the *cis* cycloadduct indicates that the reaction either proceeds via a concerted pathway or the zwitterionic intermediate collapses to the *cis* cycloadduct before the bond rotation. The adducts on heating liberates SO_2 to form the corresponding *cis* or *trans* hydroxystilbenes or styrenes (**30, 31**).



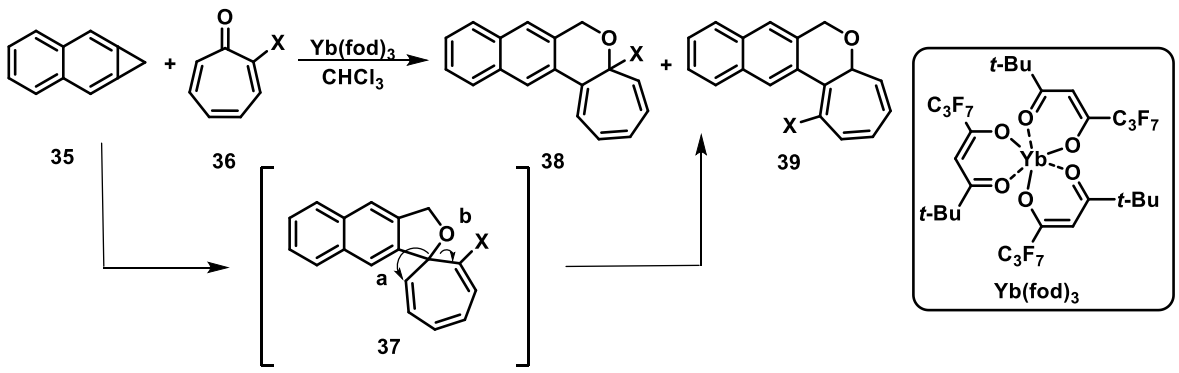
Scheme 2.13: Stereoselective Sulfene-Tropone Cycloadditions

Hayakawa and co-workers has showed that tropones undergo exclusive [8+2] cycloaddition reaction with phenyl sulfonyl allene **32** upon heating at 100 °C either without solvent or in benzene, the [8+2] adduct (**33, 34**) was isolated in 41% and 31% yields, respectively. In CH_3CN, the product **34** was observed, which is proposed to proceed via sigmatropic hydrogen shift from **33**. Presumably, the trace amount of acid present in CH_3CN facilitates the reaction (Scheme 2.14).[17]

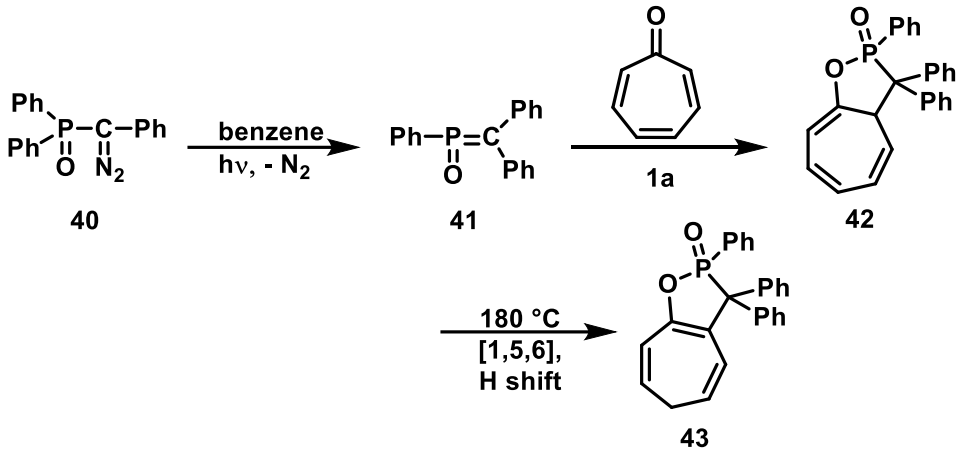


Scheme 2.14: Reaction of Tropone with Sulfonylallene

Saito and co-workers demonstrated the reaction of tropone **36** with naphthocyclopropenes **35** via an [8+2]-type pathway to yield cyclic ethers (**38, 39)** as shown in Scheme 2.15. The reaction was proposed to proceed through the intermediate **37**, which rearranges either via pathway **a** or **b** as shown (Scheme 2.15).[18] Maas and co-workers reported the reaction of phosphine oxide **41** generated photolytically from α-diazo phosphine oxide **40** underwent [8+2] cycloaddition reaction with tropone **1a** leading to the synthesis of the cycloadduct **42**. The cycloadduct **42** on heating afforded **43** through a [1,5] sigmatropic hydrogen shift (Scheme 2.16).[19]

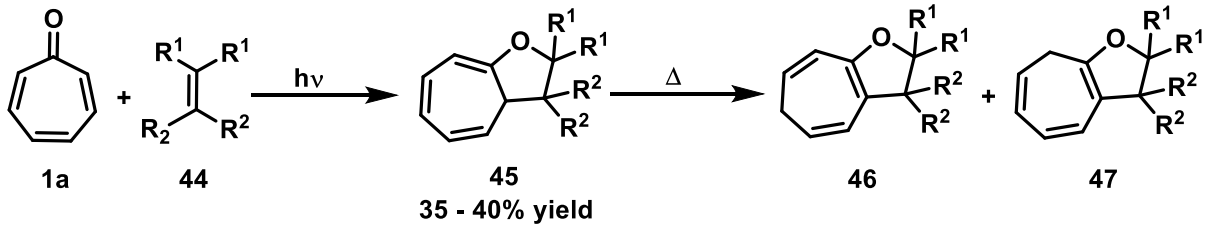


Scheme 2.15: Reaction of Tropone with Naphthocyclopropenes



Scheme 2.16: [8+2] Cycloaddition Reaction of Phosphine oxide with Tropone

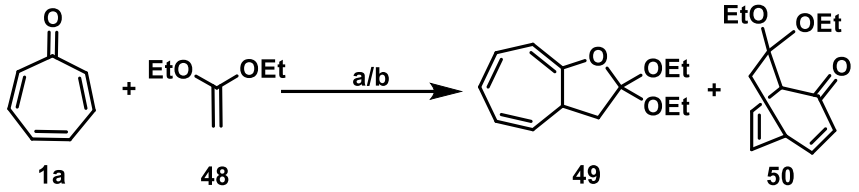
Cantrell and co-workers demonstrated the photochemical [8+2] cycloaddition reaction of tropone **1a** with simple alkenes **44** to yield the 8-oxabicyclo[5.3.0] ring system (Scheme 2.17).[20] The reaction is proposed to proceed via the tropone triplet species involving an $n \rightarrow \pi^*$ transition from the carbonyl oxygen to the alkene moiety. Product **45**, on heating underwent sigmatropic hydrogen shifts to afford the corresponding isomers **46** and **47**.



Scheme 2.17: Photochemical Reaction of Tropone with Alkene

Subsequently, the same group reported the photochemical reaction of tropone **1a** with 1,1-dialkoxyethenes derivative **48** to afford the corresponding [8+2] adducts in 40%

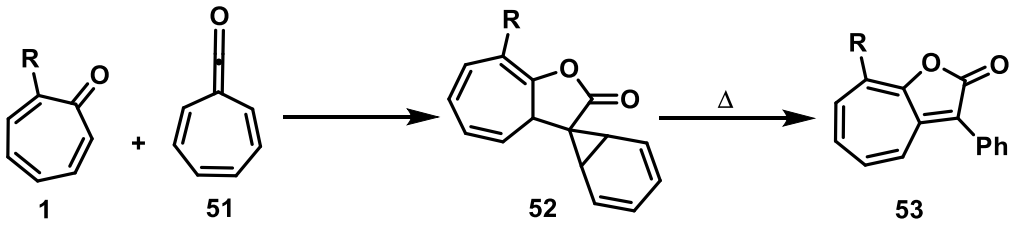
yield (Scheme 2.18).[21] Interestingly, the thermal reaction of tropone **1a** with 1,1-diethoxyethene **48** afforded the corresponding [8+2] cycloadduct **49** (60%) along with the [4+2] cycloadduct **50** (22%).



Reagents and conditions: (a) hν, 49 (40%); (b) Δ, 49 (60%) + 50 (22%)

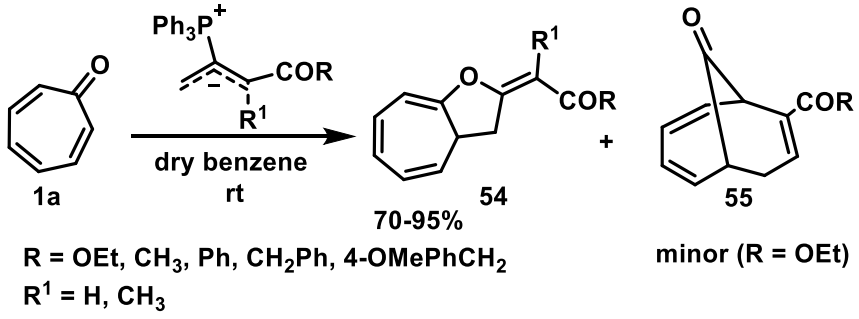
Scheme 2.18: Cycloaddition Reaction of Tropone with Dialkoxyethenes

8-Oxoheptafulvene **51** reacted with tropones **1** to give the cycloadducts **52** incorporating a norcaradiene ring system has been reported by Morita and co-workers (Scheme 2.19).[22] The reaction is proposed to proceed via [8+2] cycloaddition reaction of tropones **1** to 8-oxoheptafulvene **51**. Product **52** was found to undergo rearrangement to **53** on heating in presence of oxygen.



Scheme 2.19: [8+2] Cycloaddition Reaction of 8-Oxoheptafulvene with Tropone

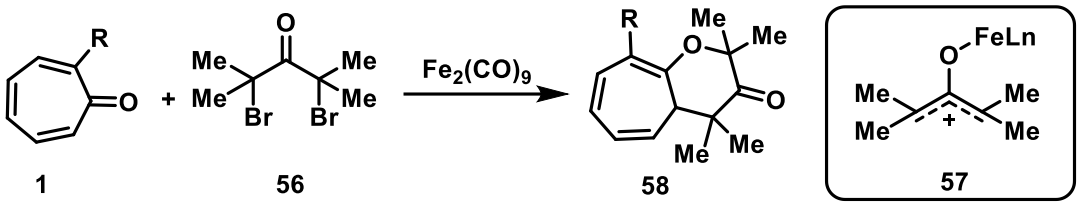
Ishar and co-workers developed all-carbon 1,3-dipoles derived from allenic ester/ketones, by catalytic interaction with triphenylphosphine in dry benzene at RT, which undergo an unusual [8+2] annulation reaction with tropone **1a**, leading to the formation of



Scheme 2.20: Reactions of Allenic Ester/Ketone-Derived 1,3-Dipoles with Tropone

8-oxa-9-(ethoxycarbonyl/acylalkylidene) bicyclo[5.3.0]deca-1,3,5-trienes derivatives **55**. 1,3-Dipoles derived from allenic ketones as well as an α-methyl-substituted allenic ester display high reactivity and selectivity (Scheme 2.20).[23]

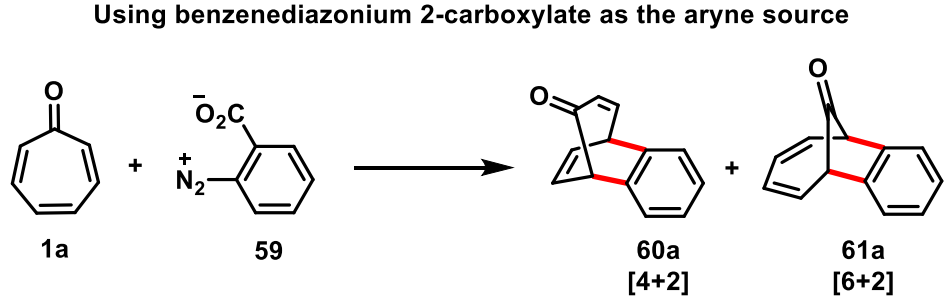
Kanematu and co-workers reported [8+2] cycloaddition reaction of tropone **1** with Oxaallyl cation **57** generated from corresponding bromo compound **56** with $Fe_2(CO)_9$ to afford the cyclic ether **58** (Scheme 2.21).[24]



Scheme 2.21: Cycloaddition Reaction of Tropone with Oxallylcation

2.4. Diels-Alder Reaction of Arynes with Tropones

As we have seen in the previous sections, depending on the reaction conditions and the coupling partner, tropones can react as a 2π, 4π, 6π, or 8π component in cycloaddition reactions. Detailed literature survey revealed that the synthetic utility of tropones as a 4π component in Diels-Alder reaction can result in the straightforward access to bicyclo[3.2.2] compounds. Tropones react with various electron-poor dienophiles[25] and electron-rich ones.[26] The use of highly electrophilic arynes[27] (generated from o-benzenediazonium carboxylate **59**) as coupling partner for tropone Diels-Alder reaction was developed by Kende and co-workers in 1967.[28] However, the reaction was limited to only one example in low yield and suffers from selectivity issues (Scheme 2.22).



Scheme 2.22: Diels-Alder Reaction of Arynes with Tropone

2.5. Statement of the Problem

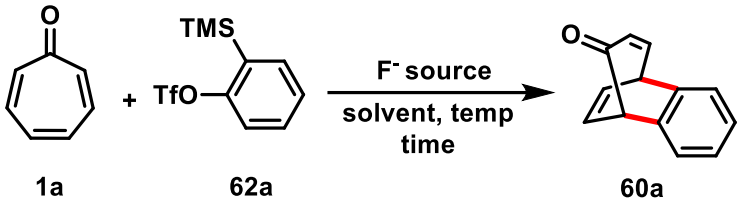
In view of the potential biological properties of benzobicyclo[3.2.2]nonatrienones,[29] a high yielding and broad scope synthesis of these compounds is highly desirable. We have been working on Diels-Alder reaction of arynes with interesting dienes such as pentafulvenes,[30a] 1,2-benzoquinones,[30b] and styrenes.[30c] We envisioned a selective, scalable, and broad scope Diels-Alder reaction of tropones with arynes generated from 2-(trimethylsilyl)aryl triflates leading to the practical synthesis of benzobicyclo[3.2.2] nonatrienone derivatives **60a** and the results are presented in the following sections. A detailed study of the Diels-Alder reaction of arynes with tropone was carried out in the present chapter. This investigation revealed a high yielding method for the synthesis of benzobicyclo[3.2.2]nonatrienones derivatives with broad substrate scope.

2.6. Results and Discussion

2.6.1. Optimization Studies

The present study was initiated with the optimization of reaction conditions for the selective [4+2] cycloaddition of tropones with arynes. In an initial experiment, treatment of tropone **1a** with aryne generated in situ from the triflate **62a**[31] using CsF in CH_3CN as solvent resulted in the formation of the Diels-Alder adduct **60a** in 62% yield (determined by ^{1}H NMR spectroscopy, Table 2.1, entry 1). It is noteworthy that the [6+2] adduct **61a** was observed in <3% yield (based on ^{1}H NMR) under the present reaction conditions. Compared to CsF, other common fluoride sources for aryne generation from **62a** such as KF/18-crown-6 and tetrabutylammonium fluoride (TBAF) afforded **60a** in low yields (entries 2, 3). The reaction carried out at 0 °C to rt furnished comparable results (entry 4). Interestingly, when the reaction was performed using 1.5 equiv of aryne precursor **62a** and 3.0 equiv of CsF, the desired product **60a** was formed in 77% yield (76% isolated yield, entry 5). Further experiments to improve the yield of **60a** by increasing the reaction time, performing the reaction at 60 °C, and carrying out the reaction under dilute conditions were not successful (entries 6-8). Moreover, when the reaction was carried out in a 10 mmol scale under the optimized conditions (entry 5), the product **60a** was obtained in 76% yield indicating that the present reaction is easily scalable.

Table 2.1. Optimization of the Reaction Conditions[a]



1a 62a 60a

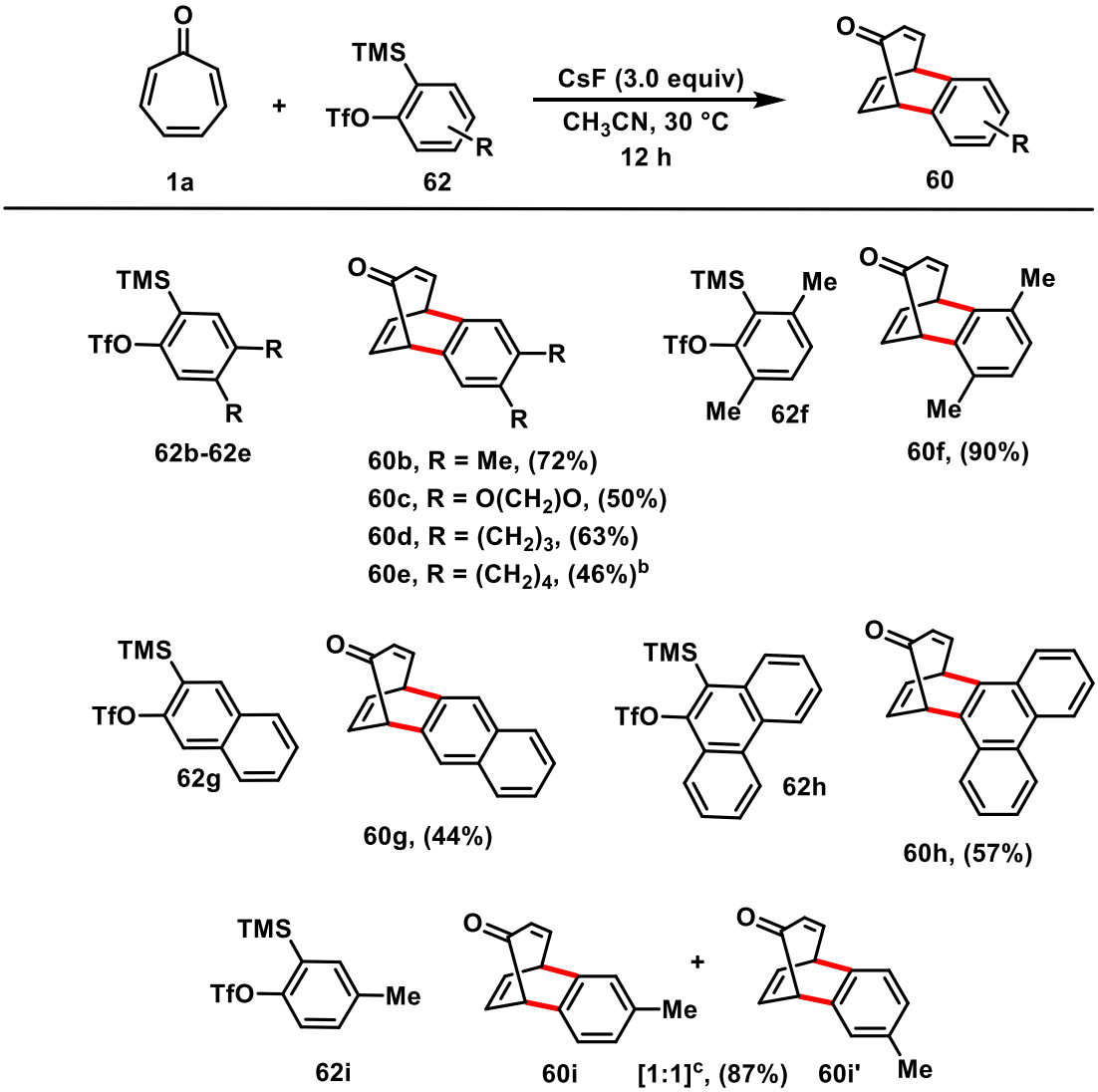
entry	F⁻ source	solvent	Temp (°C)	Time (h)	yield of **60a** (%)[b]
1	CsF	CH_3CN	30	12	62
2[c]	KF	THF	30	12	39
3	TBAF	THF	30	12	<5
4	CsF	CH_3CN	0-rt	12	61
5[d]	*CsF*	*CH_3CN*	*30*	*12*	*77(76)*
6[d]	CsF	CH_3CN	30	24	75
7[d]	CsF	CH_3CN	60	12	71
8[d,e]	CsF	CH_3CN	30	12	74

[a] Standard conditions: **1a** (0.25 mmol), **62a** (0.30 mmol), fluoride source (0.6 mmol), 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 on 0.50 mmol scale in parentheses. [c] 0.6 mmol of 18-crown-6 was used as an additive. [d] The reaction performed using 1.5 equiv of **62a** and 3.0 equiv of CsF. [e] 10 mL CH_3CN was used.

2.6.2. Substrate Scope of the Diels-Alder Reaction of Tropone with Aryne

After establishing the optimized condition for the selective Diels-Alder reaction of tropones with arynes, we then examined the generality of this reaction (Table 2.2).[32] The parent benzyne derived from **62a** worked well and the symmetrical aryne precursors **62b** and **62c** which are electronically dissimilar resulted in the formation of the benzobicyclo[3.2.2]nonatrienones **60b-60c** in moderate to good yields. Moreover, the indane and tetrahydronaphthalene-derived arynes generated from **62d** and **62e** furnished the desired product **60d-60e** in moderate yields. In addition, the 3,6-dimethyl benzyne derived from **62f** underwent smooth Diels-Alder reaction with tropone, and the symmetrical naphthalene and phenanthrene-derived arynes generated from **62g** and **62h** afforded the target bicyclic product **60g-60h** in moderate yields. Furthermore, the Diels-Alder reaction of the unsymmetrical aryne generated from **62i** with tropone resulted in the formation of an inseparable mixture of regioisomers **60i/60i'** in a 1:1 ratio and 87% yield.

Table 2.2. Substrate Scope: Variation of the Aryne Moiety[a]



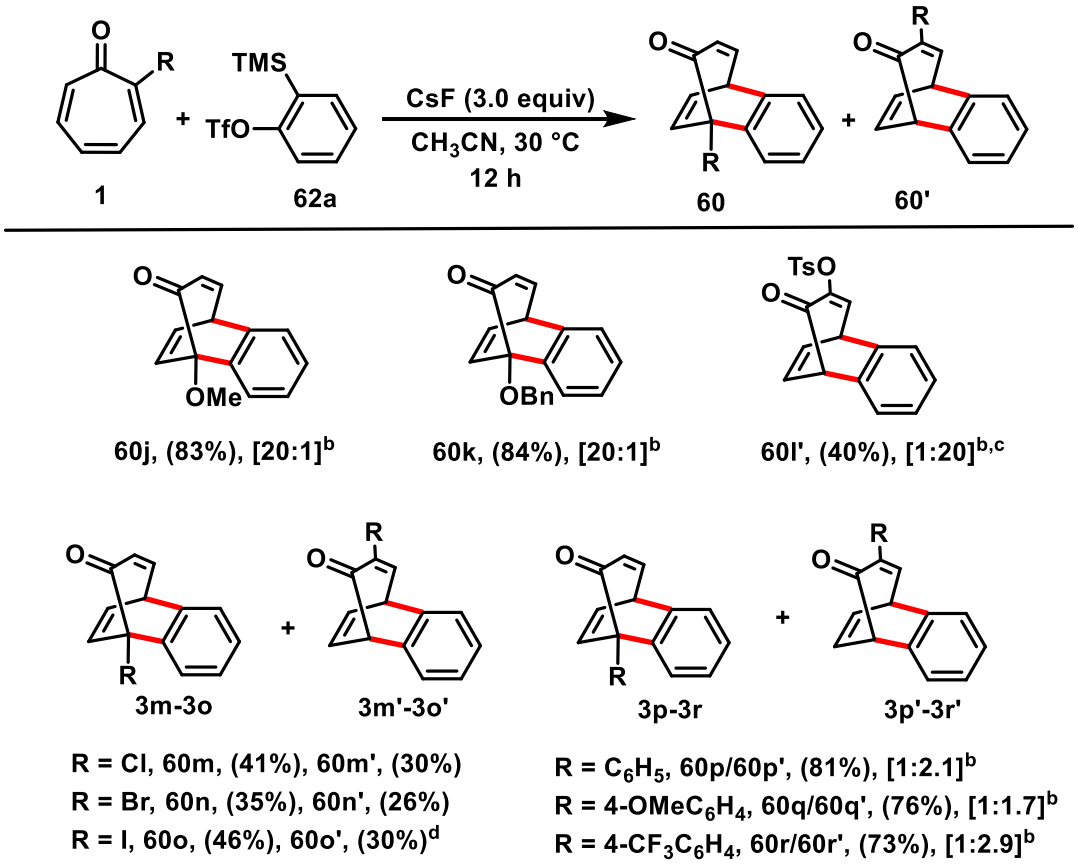
[a] General conditions: **1a** (0.50 mmol), **62** (0.75 mmol), CsF (1.5 mmol), CH_3CN (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given. [b] Reaction was run on 0.25 mmol scale. [c] The regioisomer ratio determined by ^1H NMR of the crude reaction mixture.

2.6.3. Diels-Alder Reaction of 2-Substituted Tropones with Aryne

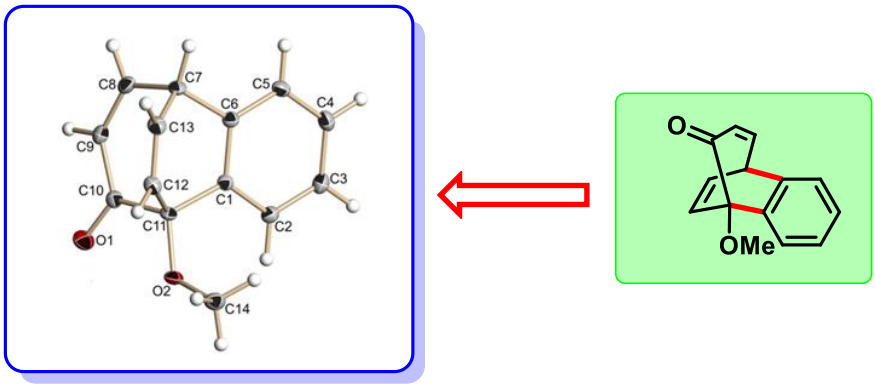
We then focused our attention on the feasibility of this reaction with various tropone derivatives (Table 2.3). The 2-methoxy tropone reacted with aryne generated from **62a** to afford the product **60j** in 83% yield and with a high regioselectivity of 20:1. The high regioselectivity in this case is attributed to the relative electron-richness of the diene system near to the -OMe group. The structure of the regioisomer **60j** was confirmed by single crystal X-ray analysis. The 2-benzyloxy tropone also showed the similar reactivity profile and furnished the product **60k** in 84% yield and 20:1 ratio. Interestingly, the reaction of

aryne with 2-tosyloxy tropone resulted in the formation of the opposite regioisomer **60l'** in 40% yield and 1:20 ratio. The regioselectivity in this case may be due to the stereoelectronic effect. Moreover, 2-halogenated tropones are well tolerated under the present reaction conditions leading to the formation of separable regioisomers in good yields (**60m-60o**, **60m'-60o'**). tropones having electron-donating and -withdrawing group at the 4-position of aryl tropones having electron-donating and -withdrawing group at the 4-position of aryl ring underwent smooth Diels-Alder reaction with arynes, and the desired products are formed as inseparable mixture of regioisomers in good yields.

Table 2.3. Substrate Scope: Variation of Tropones[a]



[a] General Conditions: **1** (0.5 mmol), **62a** (0.75 mmol), CsF (1.5 mmol), CH_3CN (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given. [b] The regioisomer ratio determined by ^1H NMR analysis of the crude reaction mixture. [c] The reaction was carried out using 2.0 equiv of **62a**. [d] Reaction was run on 0.25 mmol scale.

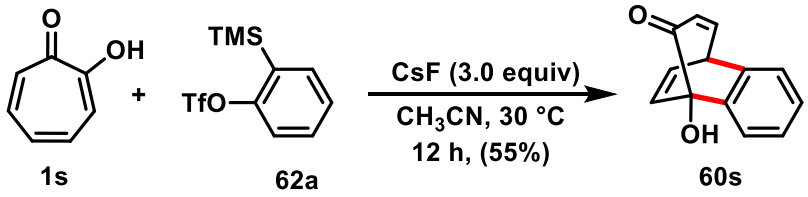


CCDC-992511

Fig 2.2: Single-Crystal X-ray Analysis of **60j**

2.6.4. Diels-Alder Reaction of Tropolone with Aryne

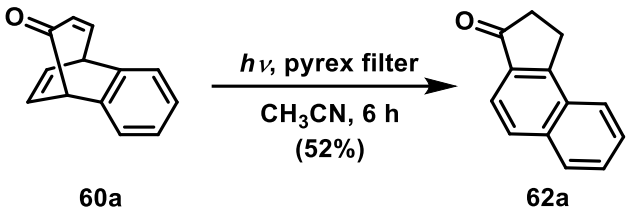
The reaction of tropolone **1s** with aryne resulted in the formation of the cycloadduct **60s** in 55% yield as a single regioisomer (Scheme 2.23).[33] The regioselectivity may be due to the involvement of the diene near to the electron-donating -OH group in cycloaddition reaction. Moreover, the *O*-arylation product was not observed under this reaction conditions. This also indicates that the Diels-Alder reaction proceeds faster than the aryne O-H insertion in the reaction of tropolone with arynes.



Scheme 2.23: Reaction of Tropolone with Aryne

2.6.5. One-Pot Synthesis of Naphthalene Derivatives

The application of the tropone-aryne [4+2] cycloaddition reaction has been examined by the photochemical rearrangement of the cycloadduct **60a** to form the functionalized naphthalene derivative **63**. Thus irradiation of the CH_3CN solution of **60a** using medium pressure mercury lamp (450 W) for 6 h resulted in the formation of **62a** in 52% yield (Scheme 2.24).[28] It may be mentioned that the reaction proceeds via the photochemical 1,3-acyl migration followed by isomerization.



Scheme 2.24: Photochemical 1,3-acyl migration

2.6.6. Photophysical Properties of Some of the Cycloadducts

Finally, we carried out preliminary studies on the photophysical properties of some of the cycloadducts. Absorption and emission spectra of compounds **60a**, **60c** and **60l'** are presented in Fig 2.3. Notably, **60a** possesses an isolated C-C double bond, enone and benzene chromophores in a non-conjugated arrangement. Absorption spectrum of **60a** (22 μM, CH_3CN at 30 °C) showed peaks at 275 nm, 225 nm and 195 nm, and the peak at 275 nm corresponds to n-π* transition of the enone moiety. All the three derivatives **60a**, **60c** and **60l'** showed weak fluorescence while exciting at 270 nm, and 290 nm. Emission spectrum of **60a** (λ_{ex} = 270 nm, CH_3CN at 30 °C) showed a weak emission centered at 323 nm and 400 nm.

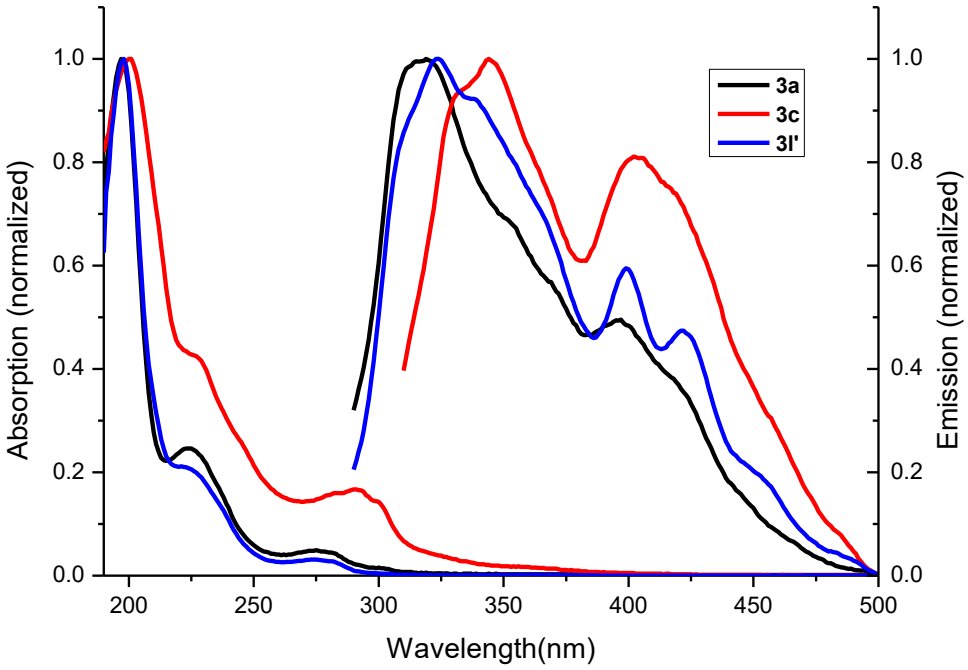


Fig 2.3: Normalized Absorption and Fluorescence Spectra of **60a, 60c,** and **60l'** in CH_3CN

2.7. Conclusion

In conclusion, we have developed a new protocol for the scalable and mild Diels-Alder reaction of tropones with arynes. The reaction allows the synthesis of various bridged benzobicyclo[3.2.2]nonatrienone derivatives in moderate to good yields. Given the importance of functionalized benzobicyclo[3.2.2]nonatrienones, the method presented in this chapter is a practical method to synthesize these molecules.

2.8. Experimental Details

2.8.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. All reactions were carried out at room temperature (30 °C) unless otherwise specified. Dry CH_3CN was purchased from commercial sources and was stored under argon over 4 Å molecular sieves. The tropone **1a** and tropolone **1s** were purchased from Alfa Aesar and were used without further purification. Other substituted tropones were synthesized from commercially available tropolone following literature procedure.[31] The 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** and the other symmetrical and unsymmetrical aryne precursors (**62b-62i**) were synthesized following literature procedure. CsF was dried by heating at 110 °C for 12 h and left to cool under argon.

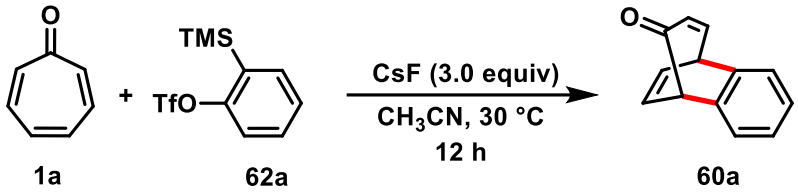
Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with solvents as indicated.

All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400, in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Infra-red spectra were recorded on a Bruker Alpha-E Infra-red 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. Absorption spectra were recorded in UV-Vis Spectrophotometer-Specord 210 plus of Analytic Jena. Emission spectra were recorded in Cary Fluorescence

Spectrophotometer. For photochemical reaction, Ace-Hanovia-Medium Pressure Mercury vapour arc lamp (450 W) was used.

2.8.2. General Procedure for the Optimization of Reaction Conditions

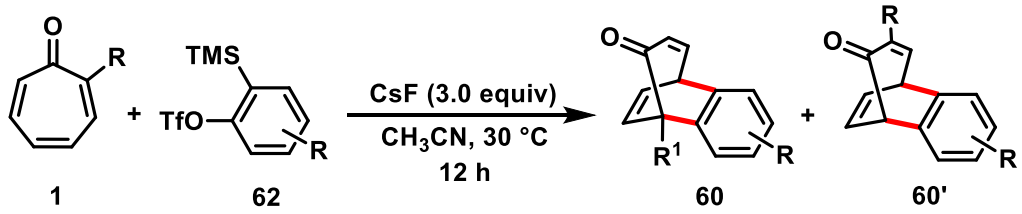
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry CsF (0.114 g, 0.75 mmol). Then the screw-capped tube was evacuated and backfilled with argon and dissolved in CH_3CN under argon atmosphere (1.0 mL). To the stirring solution were added tropone **1a** (0.027 g, 24 µL, 0.25 mmol) and 2(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.112 g, 91 µL, 0.38 mmol). Then



the reaction mixture was 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.

2.8.3. General Procedure for the Diels-Alder Reaction of Tropones with Arynes

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken dry CsF (0.228 g, 1.50 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 correspon-

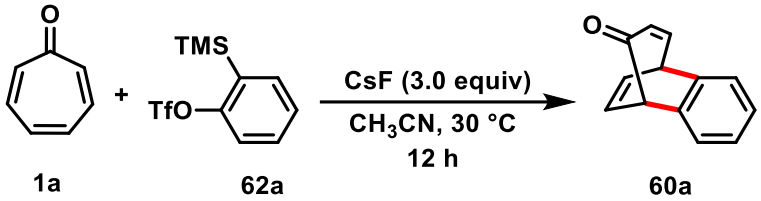


ding tropone derivative **1** (0.50 mmol) and aryne precursor **62** (0.75 mmol). Then the reaction mixture was kept stirring at 30 °C. When TLC control showed the completion of the reaction (typically after 12 h), the mixture was diluted with CH_2Cl_2 (5.0 mL) and filtered through a short pad of silica 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 benzocycloheptenone derivatives **60** in moderate to good yields.

2.8.4. Scalable Procedure for the Diels-Alder Reaction of Tropone with Aryne

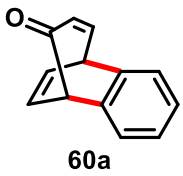
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added dry CsF (4.56 g, 30.0 mmol). Then the screw-capped tube was evacuated and backfilled with argon and dissolved in CH_3CN under argon atmosphere (40.0 mL). To the stirring solution were added tropone **1a** (1.10 g, 0.960 mL, 10.0 mmol) and 2(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (4.47 g, 3.64 mL, 15 mmol).



Then the reaction mixture kept for stirring at 30 °C. After 12 h, the reaction mixture quenched with 20 ml water and extracted with CH_2Cl_2 (3x 20.0 mL). The combined organic layer was washed with water, and dried over Na_2SO_4. The solvent was evaporated and the crude residue was purified by column chromatography on silica gel to afford the corresponding benzocycloheptenone derivative **60a** as a yellow solid (1.385 g, 76%)

2.8.5. Synthesis and Characterization of Benzocycloheptenone derivatives

5,9-Dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60a)

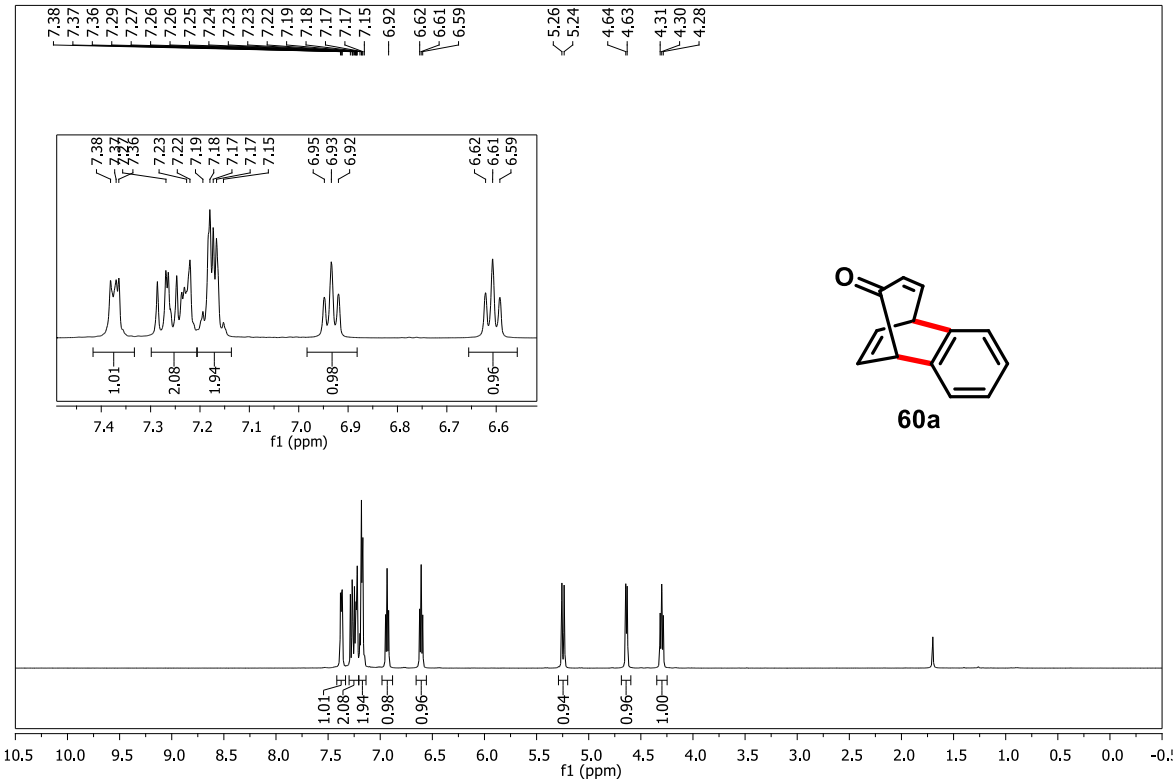


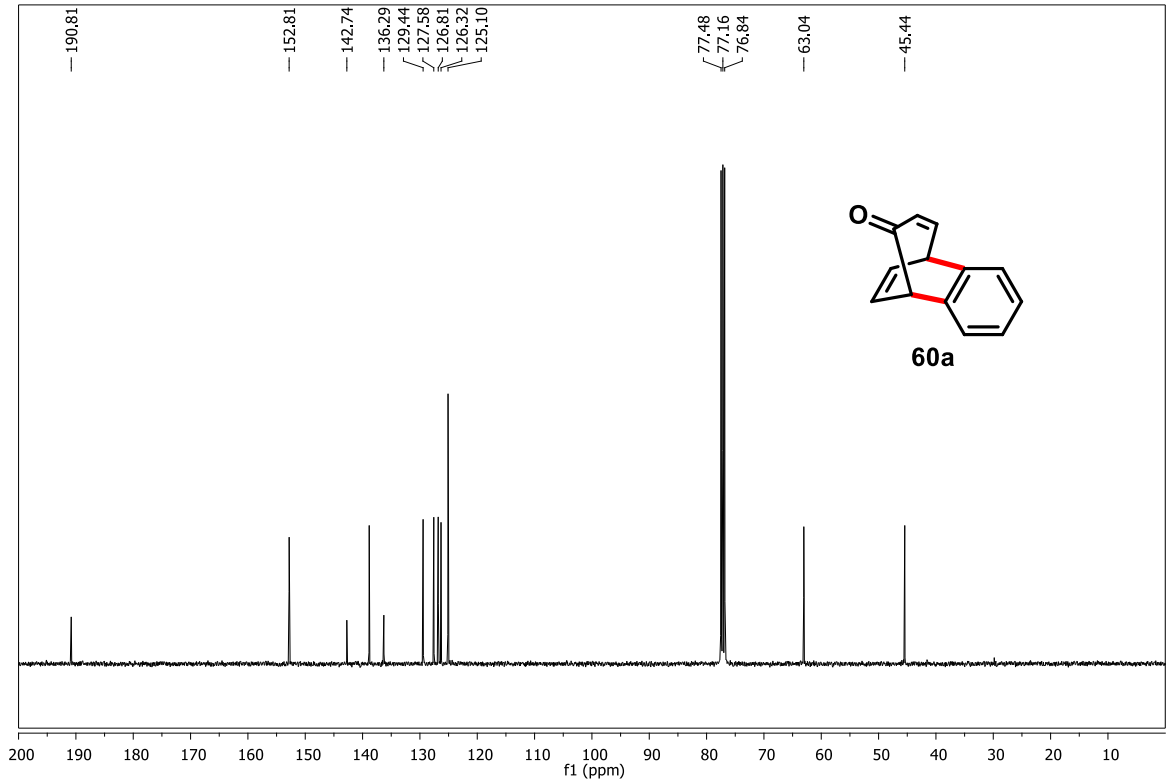
Following the general procedure, treatment of tropone **1a** (0.053 g, 48 μL, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60a** as a yellow solid (0.069 g, 76%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.36; mp 81 − 83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.36 (m, 1H), 7.29-7.22 (m, 2H), 7.19-7.15 (m, 2H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.61 (t, *J* = 7.3 Hz, 1H), 5.25 (d, *J* = 10.9 Hz 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.30 (t, *J* = 7.4 Hz, 1H).

^{1}H and ^{13}C Spectrum of 5,9-Dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60a)



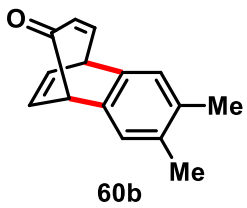


^{13}C NMR (100 MHz, $CDCl_3$): δ 190.81, 152.81, 142.74, 138.84, 136.29, 129.44, 127.58, 126.81, 126.32, 125.10, 63.04, 45.44.

HRMS calculated $[M+H]^+$ for $C_{13}H_{11}O$: 183.0804, found: 183.0806.

FTIR (cm^{-1}): 3618, 1740, 1664, 1626, 1546, 1515, 1461, 1338, 1230, 1155, 912.

2,3-Dimethyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60b)



60b

Following the general procedure, treatment of tropone **1a** (0.053 g, 48 μL, 0.50 mmol) and 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62b** (0.245 g, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 2,3dimethyl -5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60b** as a brown solid (0.076 g, 72%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.38; mp 91 - 93 °C.

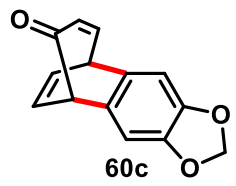
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.24 (dd, J_1 = 8.5 Hz, J_2 = 10.9 Hz, 1H), 7.18 (s, 1H), 7.03 (s, 1H), 6.93 (t, J = 7.2 Hz, 1H), 6.60 (t, J = 7.3 Hz, 1H), 5.25 (d, J = 10.9 Hz, 1H), 4.58 (d, J = 6.7 Hz, 1H), 4.24 (t, J = 7.2 Hz, 1H), 2.25 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.18, 153.15, 140.37, 139.04, 134.83, 134.29, 133.55, 129.50, 128.88, 126.48, 125.01, 62.48, 44.93, 19.52, 19.43.

HRMS calculated $[M+H]^+$ for $C_{15}H_{15}O$: 211.1117, found: 211.1120.

FTIR (cm^{-1}): 3743, 3565, 1741, 1674, 1515, 1462, 1425, 1395, 1228, 772.

5,9-Dihydro-6*H*-5,9-ethenocyclohepta[4,5]benzo[1,2-d][1,3]dioxol-6-one (60c)



60c

Following the general procedure, treatment of tropone **1a** (0.053 g, 48 μL, 0.50 mmol) and 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate **62c** (0.257 g, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 5,9-dihydro-6H-5,9-ethenocyclo hepta[4,5]benzo[1,2-d][1,3]dioxol-6-one **60c** as a brown solid (0.057 g, 50%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.22

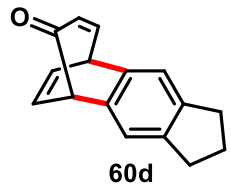
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.22 (m, 1H), 6.93 (t, J = 7.4 Hz, 1H), 6.86 (s, 1H), 6.73 (s, 1H), 6.60 (t, J = 7.1 Hz, 1H), 5.94 (d, J = 5.5 Hz, 2H), 5.22 (d, J = 11.0 Hz 1H), 4.50 (d, J = 6.7 Hz, 1H), 4.16 (t, J = 7.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.79, 152.94, 146.28, 145.88, 139.05, 137.01, 129.79, 129.60, 124.96, 108.74, 106.57, 101.47, 62.66, 45.16.

HRMS calculated $[M+H]^+$ for $C_{14}H_{11}O_3$: 227.0703, found: 227.0703.

FTIR (cm^{-1}): 3648, 1741, 1706, 1692, 1676, 1647, 1626, 1546, 1531, 1514, 1478, 1151, 939.

2,3,5,9-Tetrahydro-5,9-ethenocyclohepta[*f*]inden-6(1*H*)-one (60d)



60d

Following the general procedure, treatment of tropone **1a** (0.053 g, 48 μL, 0.50 mmol) and 6-(trimethylsilyl)-2,3-dihydro-1H-inden-5-yl trifluoromethanesulfonate **62d** (0.254 g, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 2,3,5,9-tetrahydro-5,9-ethenocyclo hepta[*f*]inden-6(1*H*)-one **60d** as a yellow solid (0.070 g, 63%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.52

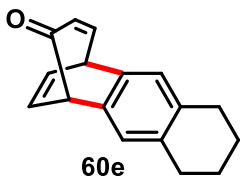
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.27 (m, 2H), 7.13 (s, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.63 (t, *J* = 7.3 Hz, 1H), 5.29 (d, *J* = 10.9 Hz 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.28 (t, *J* = 7.5 Hz, 1H), 2.95-2.86 (m, 4H), 2.12 (p, *J* = 7.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.27, 153.16, 142.94, 142.37, 141.07, 139.05, 134.33, 129.59, 125.01, 123.73, 121.29, 62.98, 45.43, 32.56, 32.46, 25.73.

HRMS calculated $[M+H]^+$ for $C_{16}H_{15}O$: 223.1117, found: 223.1119.

FTIR (cm^{-1}): 3678, 1770, 1741, 1705, 1692, 1674, 1659, 1626. 1546, 1531, 1515, 1483, 1372, 1230, 888.

1,2,3,4,6,10-Hexahydro-7*H*-6,10-ethenocyclohepta[*b*]naphthalen-7-one (60e)



60e

Following the general procedure, treatment of tropone **1a** (0.027 g, 24 μL, 0.25 mmol) and 3-(trimethylsilyl)-5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate **62e** (0.134 g, 0.38 mmol) with CsF (0.114 g, 0.75 mmol) in CH_3CN (1.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 1,2,3,4,6,10-hexahydro-7*H*-6,10-ethenocyclohepta[*b*]naphthalen-7-one **60e** as a yellow solid (0.028 g, 46%).

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

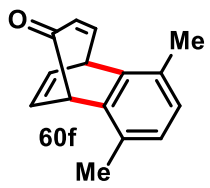
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.26 (m, 1H), 7.11 (s, 1H), 6.96-6.92 (m, 2H), 6.60 (t, *J* = 7.4 Hz, 1H), 5.29 (dd, J_1 = 11.0 Hz, J_2 = 1.7 Hz, 1H), 4.58 (d, *J* = 6.6 Hz, 1H), 4.24 (t, *J* = 7.4 Hz, 1H), 2.75 (bs, 4H, CH_2), 1.82-1.79 (m, 4H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.33, 153.11, 139.87, 139.02, 135.52, 135.00, 133.21, 129.54, 128.35, 125.79, 125.24, 62.58, 45.04, 29.33, 29.21, 23.26.

HRMS calculated $[M+H]^+$ for $C_{17}H_{17}O$: 237.1274, found: 237.1276.

FTIR (cm^{-1}): 3678, 1770, 1740, 1661, 1626, 1547, 1426, 1315, 1150, 771.

1,4-Dimethyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60f)



Following the general procedure, treatment of tropone **1a** (0.053 g, 48 μL, 0.50 mmol) and 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethane sulfonate **62f** (0.245 g, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 1,4-dimethyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7] annulen-6-one **60f** as a white solid (0.095 g, 90%).

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

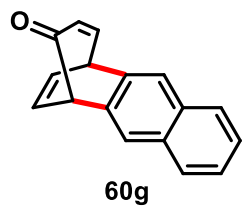
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, *J* = 9.1 Hz, 1H), 6.94-6.89 (m, 3H), 6.59 (t, *J* = 7.4 Hz, 1H), 5.26 (d, *J* = 10.9 Hz, 1H), 4.93 (d, *J* = 6.9 Hz, 1H), 4.57 (t, *J* = 7.6 Hz, 1H), 2.39 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.92, 152.19, 141.24, 138.78, 134.26, 133.82, 130.37, 129.72, 128.35, 127.87, 125.61, 59.24, 41.31, 19.39, 19.00.

HRMS calculated $[M+H]^+$ for $C_{15}H_{15}O$: 211.117, found: 211.1119.

FTIR (cm^{-1}): 3743, 1834, 1741, 1665, 1547, 1514, 1497, 1460, 1375, 1229, 1034, 771.

6,10-Dihydro-7*H*-6,10-ethenocyclohepta[*b*]naphthalen-7-one (60g)



Following the general procedure, treatment of tropone **1a** (0.053 g, 48 μL, 0.50 mmol) and 3-(trimethylsilyl)naphthalen-2-yl trifluoromethane sulfonate **62g** (0.261 g, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 6,10-dihydro-7H-6,10-ethenocyclo hepta[*b*]naphthalen-7-one **60g** as a yellow solid (0.051 g, 44%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.38; mp 158 − 160 °C.

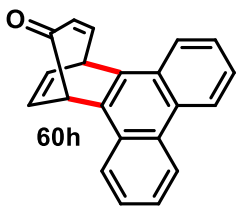
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.80-7.76 (m, 2H), 7.64 (s, 1H), 7.48-7.45 (m, 2H), 7.30 (dd, J_1 = 8.6 Hz, J_2 = 10.9 Hz, 1H), 6.96 (t, J = 7.2 Hz, 1H), 6.64 (t, J = 7.4 Hz, 1H), 5.37 (d, J = 10.9 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.44 (t, J = 7.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.27, 152.61, 139.40, 138.63, 133.66, 132.35, 132.07, 129.43, 127.85, 127.51, 126.54, 126.51, 126.28, 125.82, 123.38, 62.74, 45.24.

HRMS calculated $[M+H]^+$ for $C_{17}H_{13}O$: 233.0961, found: 233.0962.

FTIR (cm^{-1}): 3565, 1740, 1673, 1513, 1462, 1395, 1230, 811.

9,13-Dihydro-10*H*-9,13-ethenocyclohepta[*l*]phenanthren-10-one (60h)



Following the general procedure, treatment of tropone **1a** (0.053 g, 48 μL, 0.50 mmol) and 10-(trimethylsilyl)phenanthren-9-yl trifluoromethanesulfonate **62h** (0.299 g, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 95/05) afforded 9,13-dihydro-10*H*-9,13-ethenocyclohepta[*l*]phenanthren-10-one **60h** as a brown solid (0.081 g, 57%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.24; mp 178 − 180 °C.

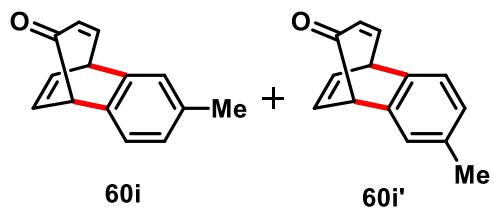
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78-8.74 (m, 2H), 8.34 (d, J = 8.2 Hz, 1H), 8.22-8.19 (m, 1H), 7.71-7.64 (m, 4H), 7.46-7.41 (m, 1H), 7.09 (t, J = 7.1 Hz, 1H), 6.80 (t, J = 7.1 Hz, 1H), 5.68 (d, J = 6.8 Hz, 1H), 5.31-5.25 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.88, 152.87, 139.55, 139.18, 130.98, 130.26, 129.96, 129.84, 129.47, 128.71, 127.40, 127.17, 126.68, 126.45, 125.87, 123.73, 123.57, 123.42, 122.62, 58.19, 39.97.

HRMS calculated $[M+Na]^+$ for $C_{21}H_{14}ONa$: 305.0937, found: 305.0935.

FTIR (cm^{-1}): 3619, 1740, 1673, 1512, 1453, 1425, 1373, 1338, 1278, 1230, 839.

2-Methyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60i) and 2-methyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60i')



Following the general procedure, treatment of tropone **1a** (0.053 g, 48 μL, 0.50 mmol) and 4-methyl-2-(trimethylsilyl) phenyl trifluoro methanesulfonate **62i** (0.234 g, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 2-

methyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **(60i)** and 2-methyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **(60i')** as an inseparable mixture of regioisomers yellow solid (0.085 g, 87%, the regioisomer ratio determined by ^{1}H NMR analysis of crude reaction mixture is 1:1).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.36

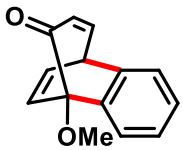
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.28-7.22 (m, 2H), 7.20 (s, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.94-6.89 (m, 1H), 6.61-6.56 (m, 1H), 5.25-5.22 (m, 1H), 4.60-4.57 (m, 1H), 4.27-4.22 (m, 1H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 191.01, 153.13, 142.82, 139.05, 136.01, 129.58, 128.43, 127.33, 126.02, 125.12, 124.82, 63.0, 45.37, 21.14.

HRMS calculated $[M+H]^+$ for $C_{14}H_{13}O$: 197.0961, found: 197.0963.

FTIR (cm^{-1}): 3618, 1740, 1665, 1626, 1515, 1497, 1462, 1425, 1374, 1289, 1014, 771.

5-Methoxy-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60j)



60j

Following the general procedure, treatment of 2-methoxytropone **1j** (0.068 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 5-methoxy-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60j** as a brown solid (0.088 g, 83%, the regioisomer ratio 20:1 determined using ^{1}H NMR of the crude reaction mixture). **60j** was subsequently recrystallized from Pet. ether/CH_2Cl_2.

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.2; mp 126 − 128 °C.

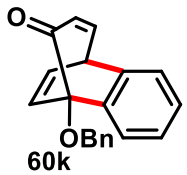
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.56 (d, *J* = 7.2 Hz, 1H), 7.29-7.20 (m, 4H), 6.99 (dd, J_1 = 6.7 Hz, J_2 = 8.6 Hz, 1H), 6.60 (d, *J* = 8.7 Hz, 1H), 5.33 (d, *J* = 11.1 Hz, 1H), 4.34 (t, *J* = 7.4 Hz, 1H), 3.57 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 187.97, 152.14, 140.80, 137.06, 136.77, 132.0, 127.55, 126.43, 125.26, 125.24, 124.54, 90.90, 52.78, 45.17.

HRMS calculated $[M+Na]^+$ for $C_{14}H_{12}O_2Na$: 235.0730, found: 235.0729.

FTIR (cm^{-1}): 3565, 1834, 1741, 1681, 1547, 1515, 1463, 1425, 1396, 1369, 1340, 1288, 1229, 928.

5-(Benzyloxy)-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60k)



60k

Following the general procedure, treatment of 2-(benzyloxy)cyclohepta-2,4,6-trien-1-one **1k** (0.106 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 92/08) afforded 5-(benzyloxy)-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60k** as inseparable mixture of regioisomers as a yellow viscous liquid (0.121 g, 84%, regioisomer ratio determined by ^{1}H NMR analysis of crude reaction mixture is 20:1).

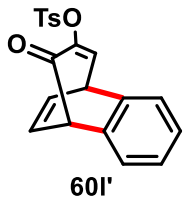
***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.26

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.77-7.76 (m, 1H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.33-7.25 (m, 4H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 5.43 (d, *J* = 11 Hz, 1H), 5.04 (d, *J* = 12.7 Hz, 1H), 4.89 (d, *J* = 12.7 Hz, 1H), 4.38 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) (3h): δ 188.24, 152.16, 140.51, 138.99, 137.65, 136.88, 132.11, 128.48, 127.42, 126.96, 126.40, 125.06, 124.97, 124.63, 91.21, 67.18, 45.06. **HRMS** calculated $[M+Na]^+$ for $C_{20}H_{16}O_2Na$: 311.1043, found: 311.1040.

FTIR (cm^{-1}): 3567, 1741, 1681, 1515, 1459, 1372, 1340, 1117, 1026, 917.

6-Oxo-6,9-dihydro-5*H*-5,9-ethenobenzo[7]annulen-7-yl-4-methylbenzenesulfonate (60l')



60l'

Following the general procedure, treatment of 2-tosyltropone **1l** (0.138 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.299 g, 243 μL, 1.0 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 6-oxo-6,9-dihydro-5*H*-5,9-ethenobenzo [7]annulen-7-yl 4-methylbenzenesulfonate **60l'** as a yellow solid (0.070 g, 40%, the regioisomer ratio determined by ^{1}H NMR analysis of crude reaction mixture is 1:20).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.14; mp 100 − 102 °C.

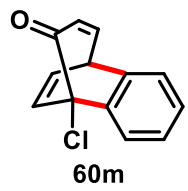
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 9.5 Hz, 1H), 7.28-7.13 (m, 6H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.53 (t, *J* = 7.3 Hz, 1H), 4.61 (d, *J* = 6.8Hz, 1H), 4.42-4.38 (m, 1H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.84, 145.20, 144.13, 141.97, 138.50, 137.68, 135.25, 132.21, 129.51, 129.28, 128.70, 127.61, 127.16, 126.53, 125.32, 61.82, 42.94, 21.81.

HRMS calculated $[M+Na]^+$ for $C_{20}H_{16}O_4NaS$: 375.0662, found: 375.0661.

FTIR (cm^{-1}): 3643, 1834, 1692, 1514, 1462, 1374, 1229, 1061, 1031, 970.

5-Chloro-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60m)



60m

Following the general procedure, treatment of 2-chlorotropone **1m** (0.070 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 5-chloro-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60m** as a yellow solid (0.044 g, 41%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.29; mp 80 − 82 °C.

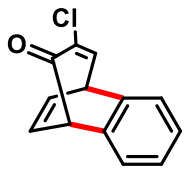
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.25 Hz, 1H), 7.37-7.27 (m, 4H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 8.4Hz, 1H), 5.48 (d, *J* = 10.9 Hz, 1H), 4.37 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 182.68, 153.27, 140.20, 136.66, 136.38, 136.32, 128.06, 126.80, 126.53, 124.87, 123.87, 80.99, 45.07.

HRMS calculated $[M+Na]^+$ for $C_{13}H_9OClNa$: 239.0234, found: 239.0237.

FTIR (cm^{-1}): 3678, 1687, 1514, 1464, 1367, 1229, 1138, 955, 898.

7-Chloro-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60m')



60m'

Following the general procedure, treatment of 2-chlorotropone **1m** (0.070 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 7-chloro-5,9-dihydro-6H-5,9-ethenobenzo[7] annulen-6-one **60m'** as a yellow solid (0.033 g, 30%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.47; mp 74 − 76 °C.

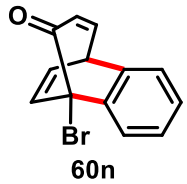
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 9.3 Hz, 1H), 7.38-7.36 (m, 1H), 7.24-7.20 (m, 1H), 7.18-7.14 (m, 2H), 6.95 (t, *J* = 7.0 Hz, 1H), 6.62 (t, *J* = 7.1 Hz, 1H), 4.86 (d, *J* = 6.88 Hz, 1H), 4.36 (t, *J* = 8.3Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.77, 149.32, 141.97, 139.0, 135.51, 129.60, 127.83, 127.74, 127.23, 126.64, 125.28, 61.90, 45.16.

HRMS calculated $[M+Na]^+$ for $C_{13}H_9OClNa$: 239.0234, found: 239.0236.

FTIR (cm^{-1}): 3744, 1832, 1743, 1686, 1649, 1540, 1514, 1459, 1423, 1396, 1331, 957.

5-Bromo-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60n)



60n

Following the general procedure, treatment of 2-bromotropone **1n** (0.093 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 5-bromo-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60n** as a yellow solid (0.045 g, 35%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.26; mp 110 − 112 °C.

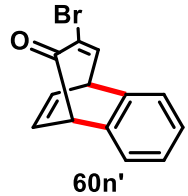
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.3 Hz, 1H), 7.34-7.21 (m, 4H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 5.49 (d, *J* = 10.9 Hz, 1H), 4.34 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 181.90, 153.33, 140.05, 137.39, 136.95, 136.29, 129.14, 128.15, 126.93, 124.87, 123.40, 45.20.

HRMS calculated $[M+H]^+$ for $C_{13}H_9OBrNa$: 282.9729, found: 282.9734.

FTIR (cm^{-1}): 3648, 1835, 1740, 1681, 547, 1515, 1478, 1228, 1139, 925.

7-Bromo-5,9-dihydro-6H-5,9-ethenobenzo[7]annulen-6-one (60n')



60n'

Following the general procedure, treatment of 2-bromotropone **1n** (0.093 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 7-bromo-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60n'** as a yellow solid (0.034 g, 26%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.52; mp 119 − 121 °C.

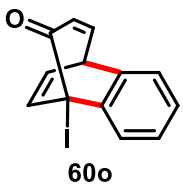
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 9.3 Hz, 1H), 7.37-7.35 (m, 1H), 7.23-7.21 (m, 1H), 7.18-7.15 (m, 2H), 6.95 (t, *J* = 7.1 Hz, 1H), 6.61 (t, *J* = 7.2 Hz, 1H), 4.91 (d, *J* = 6.8 Hz, 1H), 4.31 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.16, 153.55, 141.81, 138.86, 135.51, 129.66, 127.82, 127.22, 126.66, 125.30, 120.25, 61.64, 46.57.

HRMS calculated $[M+Na]^+$ for $C_{13}H_9OBrNa$: 282.9729, found: 282.9729.

FTIR (cm^{-1}): 1681, 1476, 1319, 1231, 1196, 1143, 900.

5-Iodo-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60o)



60o

Following the general procedure, treatment of 2-iodotropone **1o** (0.058 g, 0.250 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.112 g, 91 μL, 0.375 mmol) with CsF (0.114 g, 0.750 mmol) in CH_3CN (1.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 5-iodo-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60o** as a yellow solid (0.035 g, 46%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.26; mp 155 − 157 °C.

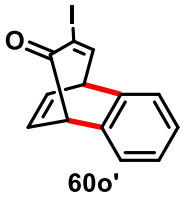
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.89 (m, 1H), 7.34-7.29 (m, 1H), 7.26-7.18 (m, 2H), 7.14-7.12 (m, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.74-6.70 (m, 1H), 5.50 (d, *J* = 10.8 Hz, 1H), 4.32 (t, *J* = 7.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 182.28, 153.40, 140.19, 139.36, 137.60, 136.88, 133.69, 128.20, 127.11, 124.91, 121.62, 65.77, 45.45.

HRMS calculated $[M+Na]^+$ for $C_{13}H_9OINa$: 330.9590, found: 330.9589.

FTIR (cm^{-1}): 1670, 1625, 1468, 1451, 1366, 1222, 919, 820.

7-Iodo-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60o')



60o'

Following the general procedure, treatment of 2-iodotropone **1o** (0.058 g, 0.250 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.112 g, 91 μL, 0.375 mmol) with CsF (0.114 g, 0.750 mmol) CH_3CN (1.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 7-iodo-5,9-dihydro-6*H*-5,9-ethenobenzo[7] annulen-6-one **60o'** as a yellow viscous liquid (0.023 g, 30%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.52

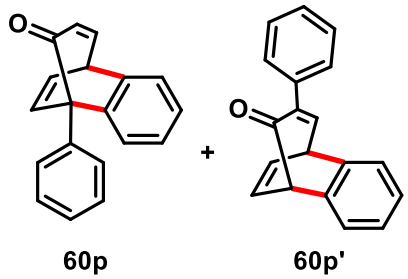
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 9.1 Hz, 1H), 7.39-7.37 (m, 1H), 7.26-7.17 (m, 3H), 6.98 (t, *J* = 6.8 Hz, 1H), 6.63 (t, *J* = 7.1 Hz, 1H), 4.96 (d, *J* = 6.7 Hz, 1H), 4.24 (t, *J* = 7.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.28, 161.32, 141.96, 138.96, 135.64, 129.78, 127.81, 127.21, 126.71, 125.71, 125.34, 60.42, 48.54.

HRMS calculated $[M+Na]^+$ for $C_{13}H_9OINa$: 330.9590, found: 330.9589.

FTIR (cm^{-1}): 1754, 1678, 1625, 1574, 1461, 1437, 1366, 1245, 1142, 1010, 922, 745.

5-Phenyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60p) and 7-Phenyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60p')



Following the general procedure, treatment of 2-phenyltropone **1p** (0.091 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded inseparable mixture of 5-phenyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **(60p)** and 7-phenyl-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **(60p')** as a yellow viscous liquid (0.105 g, 81%, the regioisomer ratio 1:2.1 was determined using ^{1}H NMR of the crude reaction mixture).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.5

Major isomer **(60p')**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 1H), 7.53-7.49 (t, *J* = 7.4 Hz, 1H), 7.46-7.41 (m, 2H), 7.33-7.20 (m, 5H), 7.17-7.13 (m, 1H), 7.04-7.0 (m, 1H), 6.75-6.68 (m, 1H), 4.84 (d, *J* = 6.7 Hz, 1H), 4.45 (t, *J* = 7.6 Hz, 1H).

Representative Peaks of Minor isomer **(60p)**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m), 7.04-7.0 (m), 6.82 (d, *J* = 8.1 Hz), 6.75-6.68 (m), 5.42 (d, *J* = 10.9 Hz), 4.35 (t, *J* = 7.3 Hz).

Major isomer **(60p')**

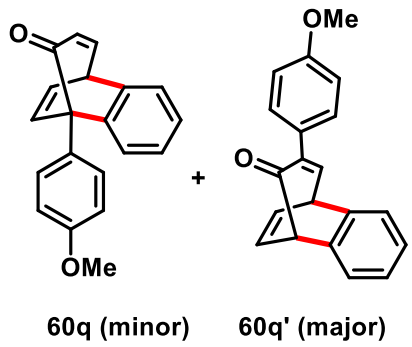
^{13}C NMR (100 MHz, $CDCl_3$): δ 190.03, 149.65, 142.51, 139.03, 138.58, 137.88, 129.80, 129.03, 127.81, 127.47, 127.37, 126.86, 125.37, 125.01, 124.72, 63.61, 45.54.

Representative Peaks of Minor isomer **(60p)**: δ 189.11, 150.91, 143.10, 140.11, 139.29, 136.48, 135.01, 133.92. 130.15, 128.70, 128.11, 127.53, 126.71, 126.24, 125.94, 67.83, 45.34.

HRMS calculated $[M+H]^+$ for $C_{19}H_{15}O$: 259.1117, found: 259.1116.

FTIR (cm^{-1}): 3618, 1673, 1465, 1229, 1154, 1035, 911, 869.

5-(4-Methoxyphenyl)-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60q) and 7-(4-Methoxyphenyl)-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60q')



Following the general procedure, treatment of 2-(4-methoxyphenyl)cyclohepta-2,4,6-trien-1-one **1q** (0.106 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 95/05) afforded 5-(4-methoxyphenyl)-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60q** (minor) and 7-(4-methoxyphenyl)-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60q'** (major) as inseparable mixture of regioisomers as a yellow viscous liquid (0.110 g, 76%, regioisomer ratio determined by ^{1}H NMR analysis of crude reaction mixture is 1:1.7).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.34

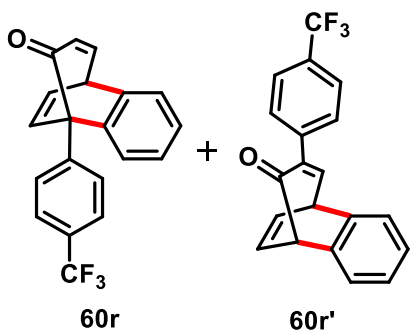
^{1}H NMR (400 MHz, $CDCl_3$) Major isomer **(60q'):** δ 7.46-7.44 (m, 1H), 7.30-7.01 (m, 8H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.43 (t, *J* = 7.7 Hz, 1H), 3.78 (s, 3H). Representative Peaks of Minor Isomer **(60q)**: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.53 (d, *J* = 8.6 Hz), 7.30-7.01 (m), 6.78 (d, *J* = 8.1 Hz), 6.73-6.70 (m), 5.39 (d, *J* = 10.9 Hz), 4.34 (t, *J* = 7.4 Hz), 3.89 (s).

^{13}C NMR (100 MHz, $CDCl_3$) of Major isomer (60q'): δ 190.33, 159.06, 150.97, 148.69, 139.11, 138.63, 131.20, 130.19, 129.75, 128.62, 127.40, 126.80, 126.15, 124.95, 113.24, 63.60, 55.25, 45.51. Representative Peaks of Minor Isomer **(60q)**: δ 189.37, 158.61, 143.03, 142.62, 140.52, 136.54, 134.39, 134.11, 131.10, 130.33, 126.64, 125.90, 125.35, 124.67, 113.45, 67.31, 55.31, 45.34.

HRMS calculated $[M+Na]^+$ for $C_{20}H_{16}O_2Na$: 311.1043, found: 311.1040.

FTIR (cm^{-1}): 3648, 1669, 1609, 1558, 1540, 1510, 1456, 1339, 1149, 1036, 770.

5-(4-(Trifluoromethyl)phenyl)-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60r) and 7-(4-(trifluoromethyl)phenyl)-5,9-dihydro-6*H*-5,9-etheno benzo[7]annulen-6-one (60r')



Following the general procedure, treatment of 2-(4-(trifluoromethyl)phenyl)cyclohepta-2,4,6-trien-1-one[1d] **1r** (0.125 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75

mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 5-(4-(trifluoromethyl)phenyl)-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **(60r)** and 7-(4-(trifluoromethyl)phenyl)-5,9-dihydro-6*H*-5,9-etheno benzo[7]annulen-6-one **(60r')** as a yellow viscous liquid (0.119 g, 73%). (0.025 g, pure **60r'**, 0.094 g mixture of isomers)

Data of Major Isomer 60r':

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.4

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.46-7.44 (m, 1H), 7.37-7.35 (m, 1H), 7.31-7.26 (m, 1H), 7.24-7.22 (m, 4H), 7.03 (t, *J* = 7.1 Hz, 1H), 6.73 (t, *J* = 7.2 Hz, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.48 (t, *J* = 7.7 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.63, 150.88, 142.25, 141.45, 138.58, 136.25, 134.20, 129.91, 129.80, 129.50, 127.69, 127.10, 126.53, 125.21, 124.82 (q, *J* = 3.7 Hz), 63.55, 45.64.

HRMS calculated $[M+Na]^+$ for $C_{20}H_{13}OF_3Na$: 349.0811, found: 349.0810.

FTIR (cm^{-1}): 3618, 1741, 1675, 1515, 1463, 1396, 1326, 1230, 1068, 753.

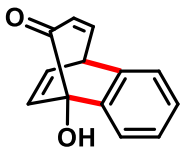
Data of Minor Isomer 60r:

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

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.73 (m), 7.32-7.18 (m), 6.75-6.74 (m), 5.42 (d, *J* = 10.8 Hz), 4.4 (t, *J* = 7.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$**):** δ 188.60, 151.28, 143.22, 143.02, 142.23, 141.45, 139.23, 136.23, 134.17, 133.32, 130.65, 129.88, 128.47, 127.66, 126.51, 128.47, 127.09, 124.81, (q, *J* = 3.6 Hz), 67.56, 45.35.

5-Hydroxy-5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one (60s)



60s

Following the general procedure, treatment of 2-hydroxytropone **1s** (0.061 g, 0.50 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **62a** (0.224 g, 182 μL, 0.75 mmol) with CsF (0.228 g, 1.50 mmol) in CH_3CN (2.0 mL) at 30 °C for 12 h followed by column chromatography (Pet. ether/EtOAc = 96/04) afforded 5-hydroxy-5,9-dihydro-6*H*-5,9-ethenobenzo[7] annulen-6-one **60s** as a white solid (0.055 g, 55%).

***R*$_f$** (Pet. ether/EtOAc = 90/10): 0.25; mp 102 − 104 °C.

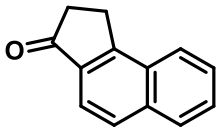
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (m, 1H), 7.42-7.36 (m, 1H), 7.25-7.16 (m, 3H), 6.85-6.80 (m, 1H), 6.39 (d, *J* = 8.2 Hz, 1H), 5.51 (d, *J* = 10.7 Hz, 1H), 5.16 (bs, 1H), 4.41 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.74, 154.95, 139.71, 139.65, 139.97, 134.92, 127.30, 126.51, 124.85, 124.22, 122.33, 85.19, 45.83.

HRMS calculated $[M+Na]^+$ for $C_{13}H_{10}O_2Na$: 221.0573, found: 221.0573.

FTIR (cm^{-1}): 3768, 1667, 1628, 1462, 1372, 1328, 1231,918, 829, 744.

1,2-Dihydro-3*H*-cyclopenta[*a*]naphthalen-3-one (63)



63

To a flame-dried screw-capped Schlenk tube equipped with a magnetic stir bar was taken 5,9-dihydro-6*H*-5,9-ethenobenzo[7]annulen-6-one **60a** (0.046mg, 0.25mmol). The cycloadduct was dissolved in CH_3CN (50.0 mL) under argon atmosphere and then the mixture was degassed with argon for 15 minutes followed by irradiation using low pressure Mercury lamp, 400W for 6 h. Then the reaction stopped and the crude reaction mixture was added Et_3N (0.5mmol, 0.051mg, 70 μL) and stirred for 2 hours in 30 °C, then the solvent was evaporated and purified by column chromatography on silica gel to afford 1,2-Dihydro-3*H*-cyclopenta[*a*]naphthalen-3-one **63** as a white solid (0.024 g, 52% yield).

***R*$_f$** (Pet. Ether/EtOAc=80/20): 0.32; mp 131 −132 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.81-7.73 (m, 2H), 7.70-7.61 (m, 2H), 3.43 (t, *J* = 5.2 Hz, 2H), 2.84 (t, *J* = 5.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.93, 156.54, 136.66, 134.80, 130.67, 129.31, 129.03, 128.62, 127.19, 124.52, 119.62, 36.27, 24.45.

HRMS calculated $[M+H]^+$ for $C_{13}H_{11}O$: 183.0804, found: 183.0804.

FTIR (cm^{-1}): 3672, 1699, 1625, 1587, 1460, 1381, 1302, 1242, 867, 744.

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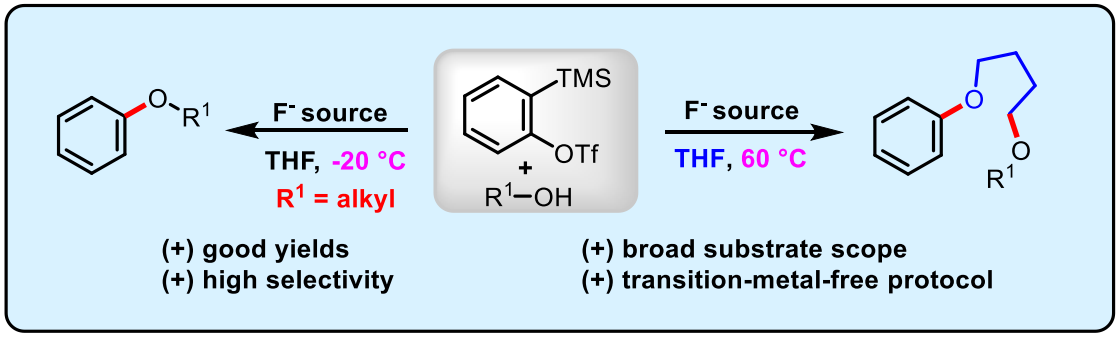
Chapter 3

From Insertion to Multicomponent Coupling: Temperature Dependent Reactions of Arynes with Aliphatic Alcohols

The temperature dependent selectivity switch observed in the reaction of arynes with aliphatic alcohols in THF has been presented in this chapter. At -20 °C, arynes smoothly insert into the O-H bond of alcohols to form alkyl aryl ethers. Interestingly, at 60 °C, highly selective multicomponent coupling occurs with solvent THF acting as the nucleophilic trigger to afford (4-(alkoxy)butoxy)arenes. The substrate scope of the insertion as well as the multicomponent coupling has been examined.



Chem. Commun., **2016**, *52*, 1665-1668.

3.1. Introduction:

In the past decades, arynes have emerged as one of the powerful synthons, which is widely used in several heterocycles and complex natural products synthesis.[1] This is mainly because of the development of 2-(trimethylsilyl)aryl triflates as aryne precursors, which allow us to generate arynes under mild and easily controlled conditions in the presence of a fluoride source.[2] Two of the important modes of aryne reactions include the insertion reactions[3] and the multicomponent couplings (MCCs).[4] In insertion reactions, arynes are added to various element-element bonds to form various 1,2-disubstituted benzene derivatives (Fig 3.1, eq 1).[5] The MCC results by the addition of nucleophiles (devoid of acidic protons) to arynes followed by the interception of the resulting aryl anion intermediate with electrophiles (eq 2).

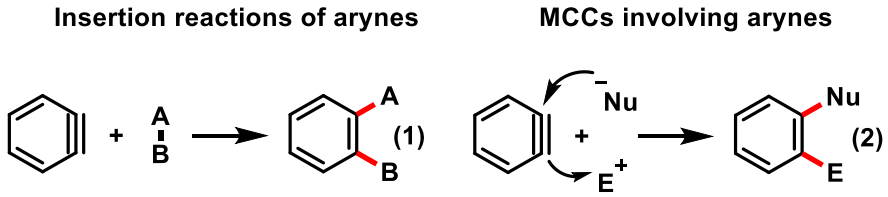
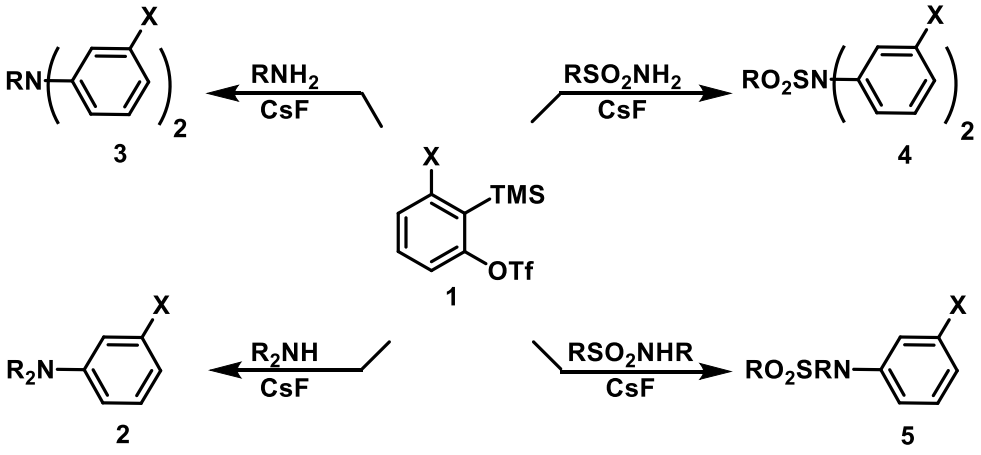


Fig 3.1: Insertion and Multicomponent Reactions of Arynes

3.2. Insertion Reactions Leading to Arylation using Arynes

3.2.1. Insertion of Aryne into N-H Bond

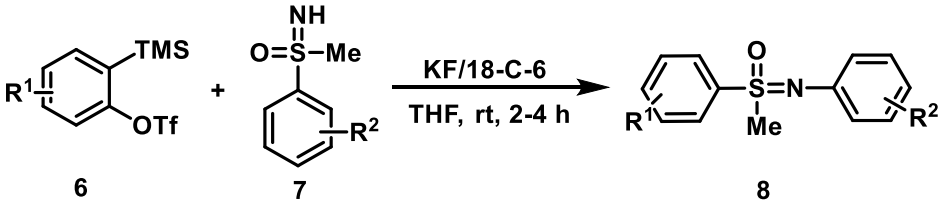
In 2003, Larock and co-workers reported a facile, transition-metal-free *N*-arylation of amines and sulfonamides, which afforded good to excellent yields of arylated products



Scheme 3.1: Facile *N*-Arylation of Amines and Sulfonamides

under very mild reaction conditions. A variety of functional groups are compatible with the reaction conditions. A methoxy-substituted aryl triflate **1** affords *N*-arylated products (**2,3** and **4, 5**) in high yields with excellent regioselectivity (Scheme 3.1).[6]

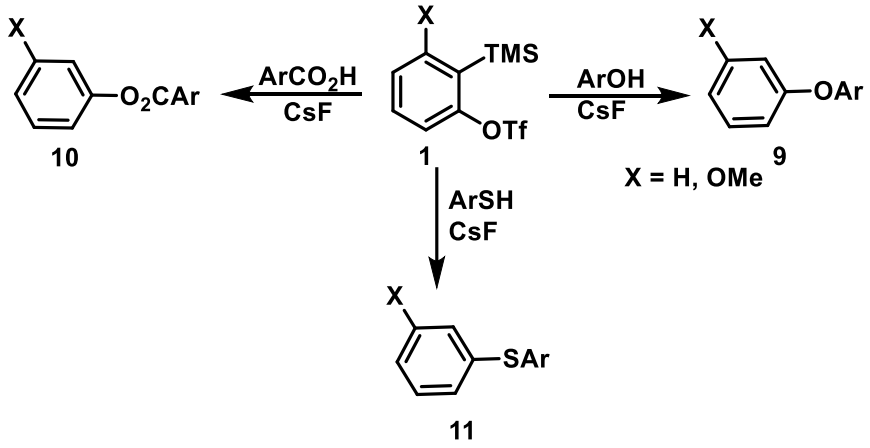
A metal-free and operationally simple *N*-arylation of NH-sulfoximines **7** with aryne precursors **6** leading to the formation of *N*-arylated product **8** is reported by Singh and co-workers (Scheme 3.2).[7] Transition metal-free reaction conditions and shorter reaction times are the highlights of this methodology. The optimized mild condition was also found to be suitable with enantiopure substrates.



Scheme 3.2: Insertion of Arynes into the N-H Bond of Imines

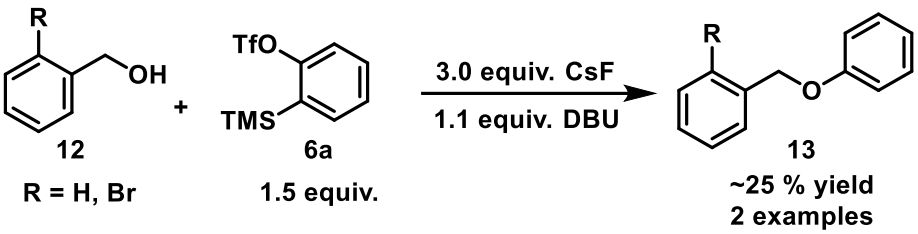
3.2.2. Insertion of Aryne into O-H Bond

Later the same group reported an efficient, mild and transition-metal-free method for the *O*-arylation of phenols and aromatic carboxylic acids afforded the *O*-arylated product (**9, 10**). A variety of functional groups have been tested, which is compatible with the reaction conditions (Scheme 3.3).[8] The regioselectivity of the methoxy-substituted aryl triflate **1** was excellent. In addition, in the same report, they have also demonstrated that aromatic thiols also reacted well with silylaryl triflate to afford the corresponding *S*-arylated product **11** in a fairly good yield.



Scheme 3.3: Facile *O*-Arylation of Phenols and Carboxylic Acids

In general, the above methodology is limited to phenols and carboxylic acids, alcohols **12** do not react with the benzyne precursor **6a** to give good yields of aryl ethers. For example, benzyl alcohol afforded only 25% yield of the corresponding aryl ether **13**, even when after adding a stronger base, such as DBU (Scheme 3.4).[8]

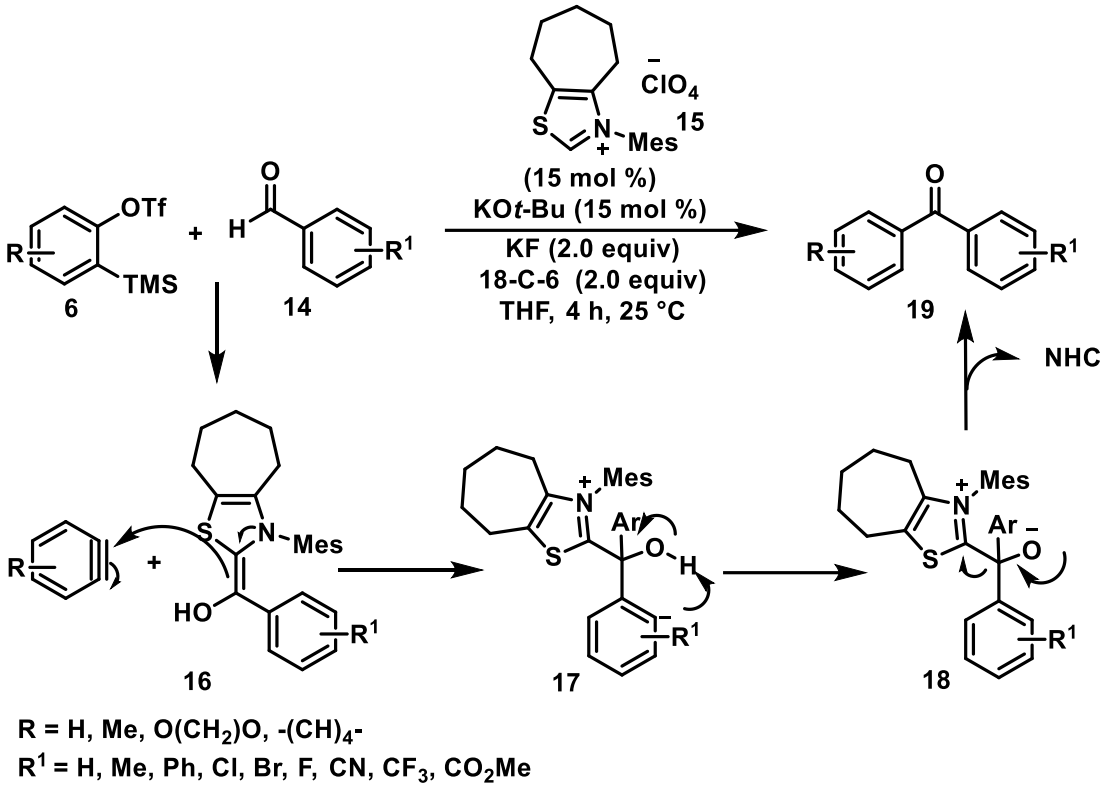


Scheme 3.4: Reaction of Aryne with Benzyl Alcohol

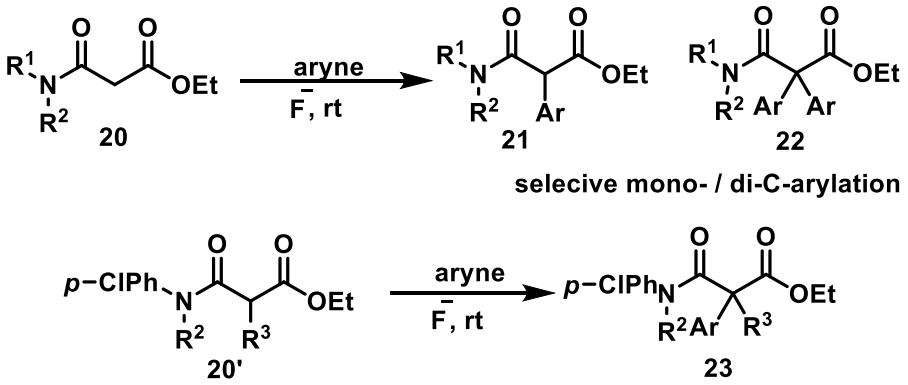
3.2.3. Insertion of Arynes into the C-H σ-Bond of Aldehydes

Glorius and co-workers uncovered the transition-metal-free NHC-organocatalyzed intermolecular hydroacylation of benzyne to furnish benzophenones **19** as well as α,β-unsaturated and other aryl ketones. This is the first time that NHCs have been found to be compatible with benzyne, and these study reveals an unprecedented formal insertion of arynes into C_{formyl} -H bonds under mild conditions. The proposed mechanism involves the formation of nucleophilic Breslow intermediate **16** from aldehyde **14** and NHC generated from the salt **15**, which attacks on benzyne to give the alkoxide via the intermediate **17**. Alternatively, a concerted transition state leads to the alkoxide **18** in analogy to the reaction of 1,3-dipoles with benzyne. Finally, release of the NHC catalyst from **18** results in the formation of ketone product (Scheme 3.5).[9]

Mhaske and co-workers developed an efficient facile and fluoride-induced transition-metal-free chemoselective α-arylation of β-dicarbonyl compounds **(20, 20')** at room temperature using benzyne intermediates. Selective mono- or diarylated product **(21, 22)** and generation of a quaternary benzylic stereocenter **23** have also been achieved (Scheme 3.6).[10] The methodology will be highly useful for the synthesis of a library of Central Nervous System (CNS) depressant barbiturate drugs like Phenobarbital.

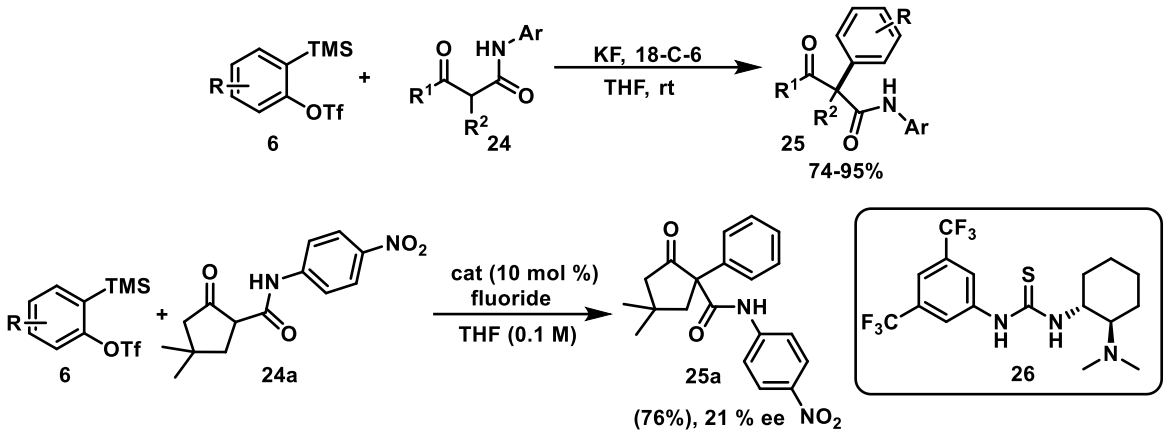


Scheme 3.5: Insertion of Arynes into the C_{formyl}-H σ-Bond of Aldehydes



Scheme 3.6: Insertion of Arynes into the C -H Bond of Malonamide Esters

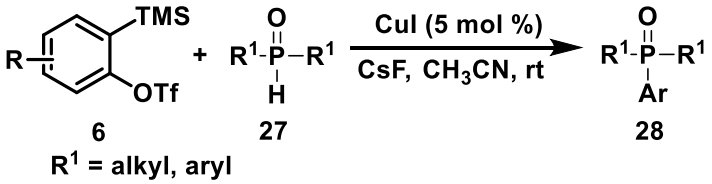
Independently, Rodriguez and co-workers reported the transition-metal-free direct α-arylation of secondary β-keto amides (**24, 24a)** with arynes, generated by fluoride-induced elimination of ortho-silyl aryltriflates **6** (Scheme 3.7).[11] The reaction proceeds via an interrupted insertion reaction of arynes and leads to densely functionalized aromatic compounds containing a chiral 'all carbon' quaternary center **(25, 25a)**. The feasibility of an organocatalytic asymmetric version could be evidenced with a bifunctional thiourea/ tertiary amine catalyst **26**.



Scheme 3.7: Insertion of Arynes into the C -H Bond of Amides

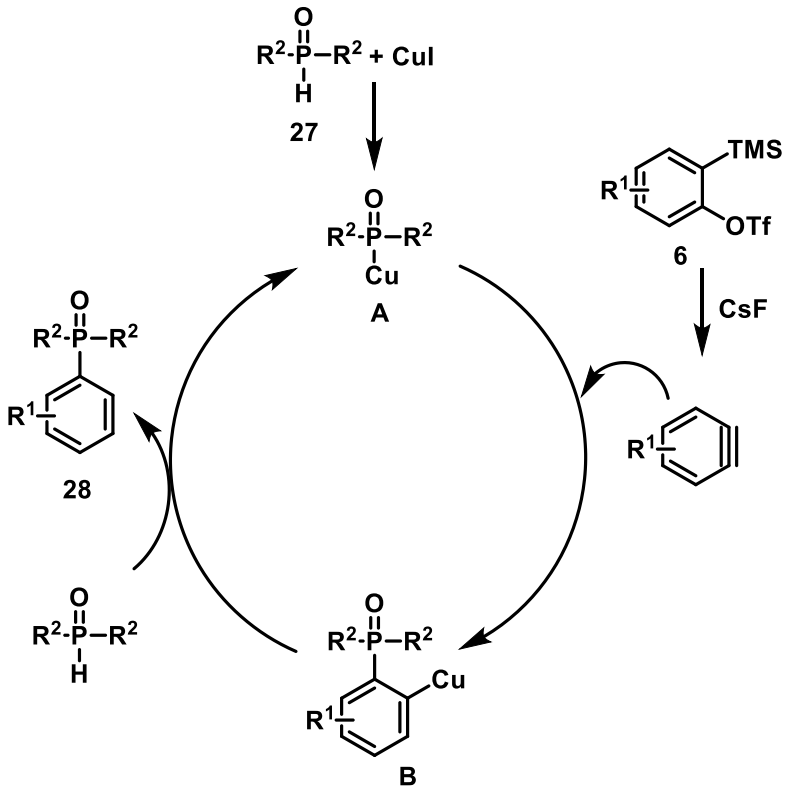
3.2.4. Insertion of Arynes into the P-H Bond of Aldehydes

Chen and co-workers demonstrated an efficient P-arylation of secondary phosphine oxides **27** through the ligand-free copper-catalyzed addition of H-P(O) bonds to in situ generated benzyne at room temperature. This transformation provides a straightforward route to the formation of the aryl-P bond with wide functional group compatibility, which produces arylphosphine oxides **28** up to 99% yield (Scheme 3.8).[12]



Scheme 3.8: Copper-catalyzed Addition of H-P(O) Bonds to Arynes

The reaction proceeds via addition of CuI to secondary phosphine oxides **27** to forms the corresponding active [R^2_2P(O)Cu] **A** intermediates. Insertion of in situ generated benzyne into Cu-P bonds of **A** gives arylcopper intermediates **B**. Protonolysis of **B** by secondary phosphine oxides **27** results in the formation of arylphosphine oxides **28** and regenerates the active catalysts **A** (Scheme 3.9).[12]

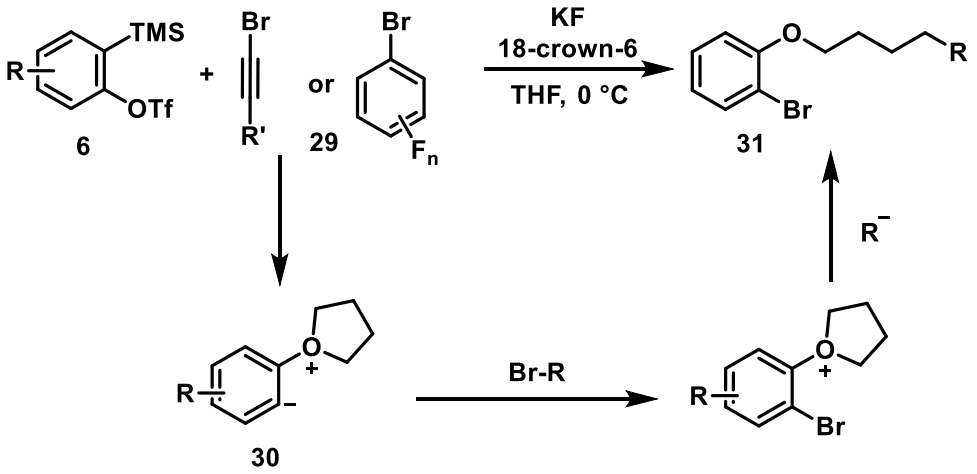


Scheme 3.9: Mechanism of Copper-Catalyzed Addition of H-P(O) Bonds to Arynes

3.3. MCRs Involving Aryne, Cyclic Ether or Amines and Nucleophiles

3.3.1. MCRs Involving Aryne, Cyclic Ether and Organic Bromides

In 2011, Yoshida and co-workers demonstrated the three-component reaction of aryne precursor **6**, THF and organic halide **29** and showed that organic halides are an excellent third component for capturing 1,3-dipoles **30.** They further investigated the

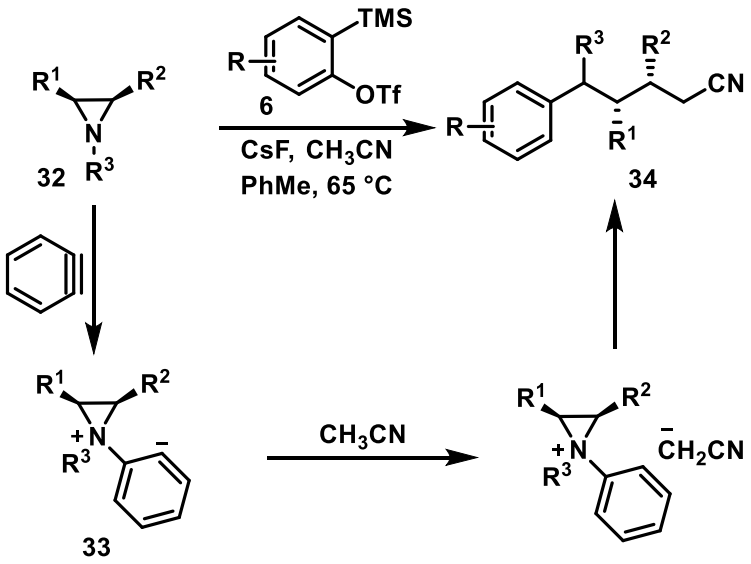


Scheme 3.10: Aryne MCRs with Cyclic Ether and Organic Bromides

reaction of 1, *n*-dipoles derived from arynes and other nucleophiles, and found that cyclic ethers performed well in the three-component coupling. The three-component coupling was found to selectively proceed when benzyne was treated with on THF at 0 °C, thus providing a 78% yield of 1-bromo-2-(6-phenylhex-5-ynyloxy)benzene **31**. (Scheme 3.10).[13]

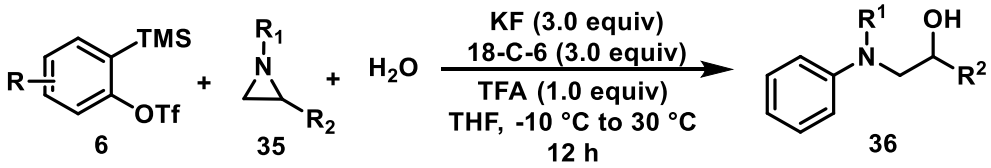
3.3.2. MCC involving Cyclic Amine (aziridine), aryne and H-Nucleophiles

Later, in 2013 Larionov and co-workers reported a three-component reaction of aziridines **32** or azetidines, benzyne **6** and acetonitrile that leads to the formation of *N*-aryl-γ-amino nitriles **34**. The reaction proceeds with a high degree of stereoselectivity and allows the transfer of chirality from aziridine to the product. The benzyne plays a crucial role by effecting dual activation of the small-ring tertiary amine and the nitrile in a stepwise fashion via zwitterionic intermediate **33** (Scheme 3.11).[14]



Scheme 3.11: MCC involving Aziridine, Aryne and Acetonitrile

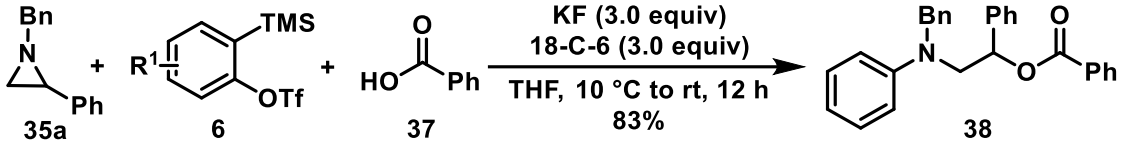
Recently our group has demonstrated a transition-metal-free, three-component coupling involving *N*-substituted aziridines **35**, arynes **6**, and water promoted by trifluoro-



Scheme 3.12: MCC Involving Aziridine, Aryne and Water

acetic acid (TFA). The reaction afforded medicinally important *N*-aryl β-amino alcohol derivatives **36** in moderate to good yields (Scheme 3.12).[15] In addition, the use of azetidines in this reaction afforded *N*-aryl γ-aminoalcohol derivatives.

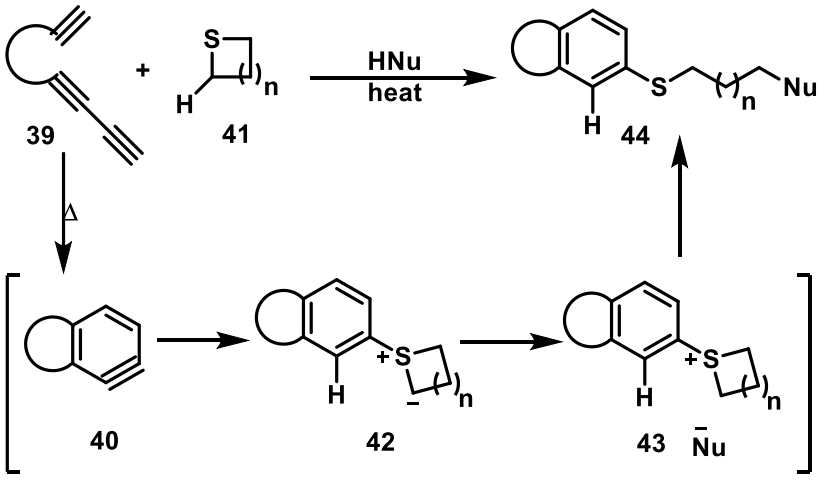
Our group further extended this methodology to carboxylic acid as a third-component and developed a practical and efficient MCC involving arynes **6**, aziridines/azetidines **35a** and carboxylic acids **37**. The reaction resulted in a transition-metal-free route to *N*-aryl β- amino alcohol derivatives **38** and *N*-aryl γ-amino alcohol derivatives in good yields (Scheme 3.13).[16] The utility of carboxylic acids in aryne MCCs has been demonstrated and phenols can also be used as acid surrogates in this reaction.



Scheme 3.13: MCC Involving *N*-benzyl Aziridine, Aryne and Benzoic acid

3.3.3. MCR involving HDDA Benzynes, Cyclic Sulfides, and H-Nucleophiles

Recently, Hoye and co-workers reported the reaction of alkyl sulfides **41** with benzynes **40** thermally generated by the hexadehydro-Diels–Alder (HDDA) cycloisomerization of triyne **39**. The initially produced 1,3-betaine (*o*-sulfonium/aryl



Scheme 3.14: Three-Component Reactions of HDDA Benzynes, Cyclic Sulfides, and H-Nucleophiles

carbanion) **42** undergoes intramolecular proton transfer to generate a more stable *S*-aryl sulfur ylide, which can react in various manners, including weak acids (HA) in the reaction

medium. This can produce transient ion pairs $ArSR_2^+A^-$ **43** that proceed to the products ArSR + RA. When cyclic sulfides are used, A^- opens the ring and is incorporated into the product **44**, an outcome that constitutes a versatile, three-component reaction (Scheme 3.14).[17]

3.4. Statement of Problem

As mentioned in the previous section, Larock and co-workers reported the insertion of arynes into the O-H bond of phenols and carboxylic acids to form diaryl ethers and aryl esters.[8] Intriguingly, the aryne insertion to aliphatic alcohols has been underexplored.[18] This will be interesting as the resultant alkyl aryl ethers are having potential application in medicine, crop protection, and fine organic chemicals.[19] Moreover, transition-metal-catalyzed *O*-arylation using aliphatic alcohols is a powerful strategy for the construction of alkyl aryl ethers.[20] In this context, synthesis of alkyl aryl ethers under transition-metal-free conditions have the economic and ecological advantage.[21] In this chapter, a detailed study of transition-metal-free, and temperature dependent switchable reactions of arynes with aliphatic alcohols in THF for the synthesis of alkyl aryl ethers has been presented. At -20 °C, arynes undergo smooth insertion to O-H bond of alcohols to afford the alkyl aryl ethers in high selectivity.[8,22] However, when the reaction was performed at 60 °C, highly selective MCC occurs with THF acting as the nucleophilic trigger furnishing (4-(alkoxy)butoxy)arenes.[13,23,24]

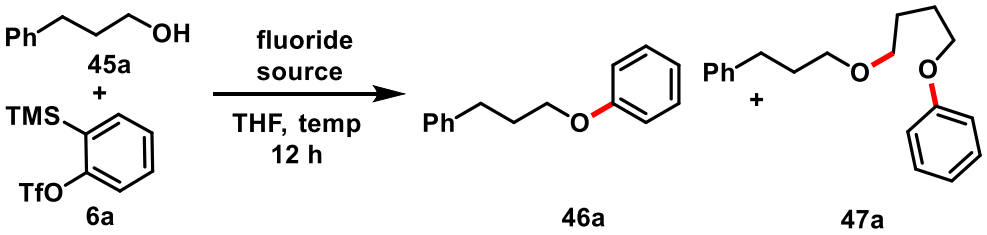
3.5. Results and Discussion

3.5.1. Optimization Studies

The present study commenced with treating 3-phenyl propanol **45a** with aryne generated from 2-(trimethylsilyl)aryl triflate **6a**.[2] When the reaction was performed using KF as the fluoride source (using [18] crown-6 as additive) at 30 °C, the *O*-arylated product **46a** was isolated in 12% yield and the MCC product **47a** was isolated in 44% yield with a selectivity of 20:80 (Table 3.1, entry 1). When the reaction was carried out using tetrabutyl ammonium fluoride (TBAF), better selectivity for **46a** was observed while CsF returned almost similar results (entries 2, 3). Interestingly, using KF at 0 °C, **46a** was formed in 59% yield with 82:18 selectivity (entry 4). Moreover, when the temperature was further reduced to -20 °C, **46a** was isolated in 75% yield and excellent selectivity of 95:5 (entry 5). Under similar conditions, TBAF and CsF furnished inferior results (entries 6, 7). Gratifyingly,

performing the reaction at 60 °C using KF, the selectivity was switched to MCC product **47a** (**46a: 47a** 13:87; 56% yield; entry 8). Using slight excess of **6a** and under dilution conditions, the selectivity for **47a** was improved to 9:91 and **47a** was isolated in 61% yield (entry 9). The optimization studies revealed that low temperature prefers the insertion of arynes to O-H bond of **45a** where as high temperature shifts the selectivity towards the MCC product **47a** where THF is the nucleophilic trigger.

Table 3.1. Optimization of Reaction Conditions[a]

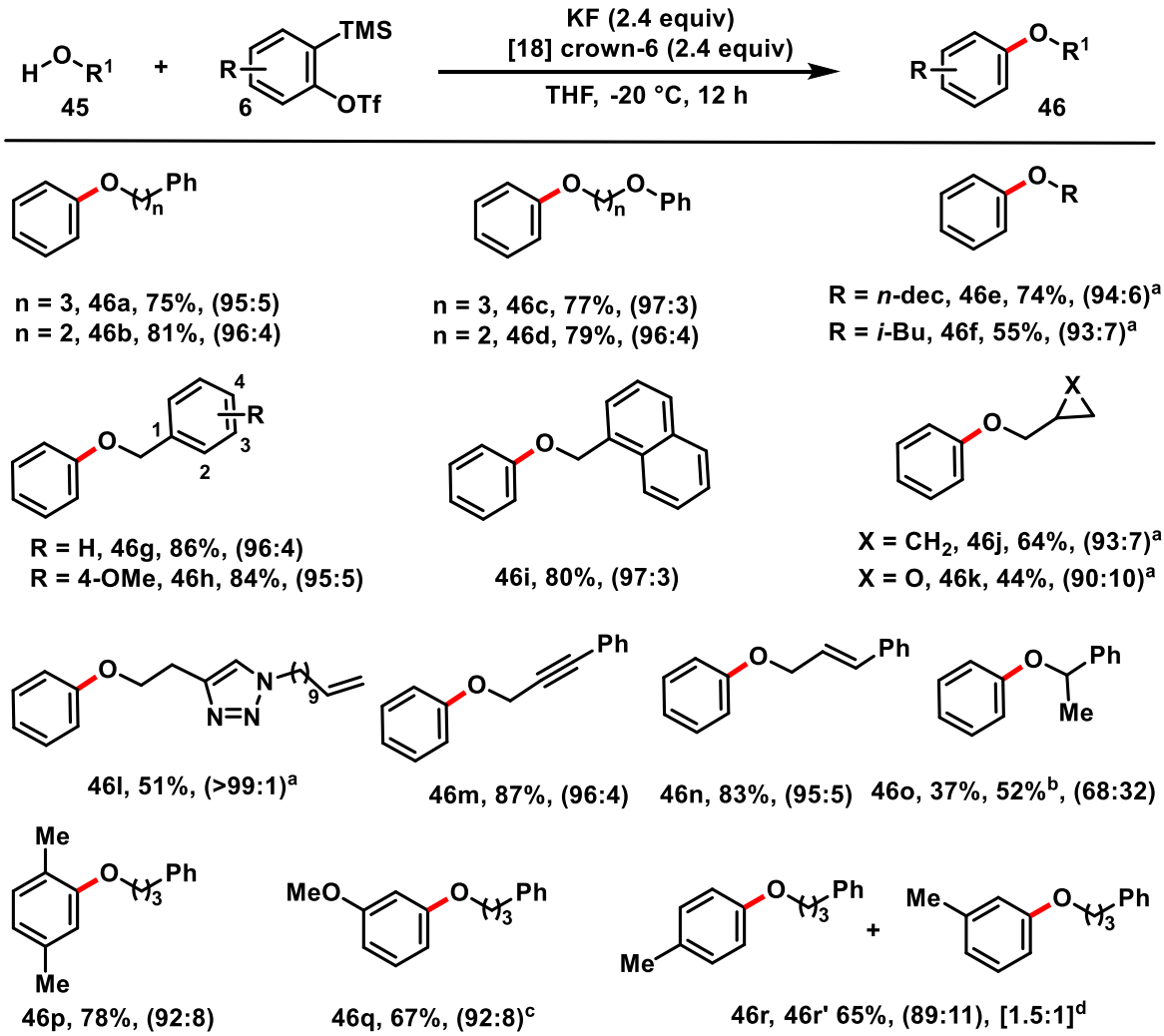


entry	fluoride source	temp (°C)	yield of **46a**[b]	yield of **47a**[b]	**46a:47a**[c]
1	KF/[18] crown-6	30	12	44	20:80
2	TBAF	30	25	<5	95:5
3[d]	CsF	30	11	43	19:81
4	KF/[18] crown-6	0	59	12	82:18
5	*KF/[18] crown-6*	*-20*	*75*	*<5*	*95:5*
6	TBAF	-20	41	<5	95:5
7[d]	CsF	-20	<5	11	27:73
8	KF/[18] crown-6	60	9	56	13:87
9[e]	*KF/[18] crown-6*	*60*	*<5*	*61*	*9:91*

[a] General conditions: **45a** (0.25 mmol), **6a** (0.30 mmol), KF (2.4 equiv), [18] crown-6 (2.4 equiv), THF (1.5 mL), for the indicated temperature and 12 h. [b] The yields of the isolated products are given. [c] Selectivity was determined using GC analysis of the crude reaction mixture. [d] Reaction performed using 1:1 CH_3CN:THF. [e] Using 1.5 equiv of **6a**, 3.0 equiv of KF and [18]-crown-6 and 2.0 mL of THF.

3.5.2. Substrate Scope of the Aryne Insertion to O-H Bond of Alcohols.

Having established a temperature dependent procedure for the selective aryne insertion to O-H bond of alcohols and THF triggered aryne MCCs, we then examined the scope of this reaction. First, we evaluated the scope of aryne insertion to O-H bond of alcohols (Scheme 3.15). A series of linear, *O*-tethered, and branched aliphatic alcohols underwent smooth aryne insertion at -20 °C affording the alkyl phenyl ethers in good yields and high selectivity (**46a-46f**). Moreover, benzyl



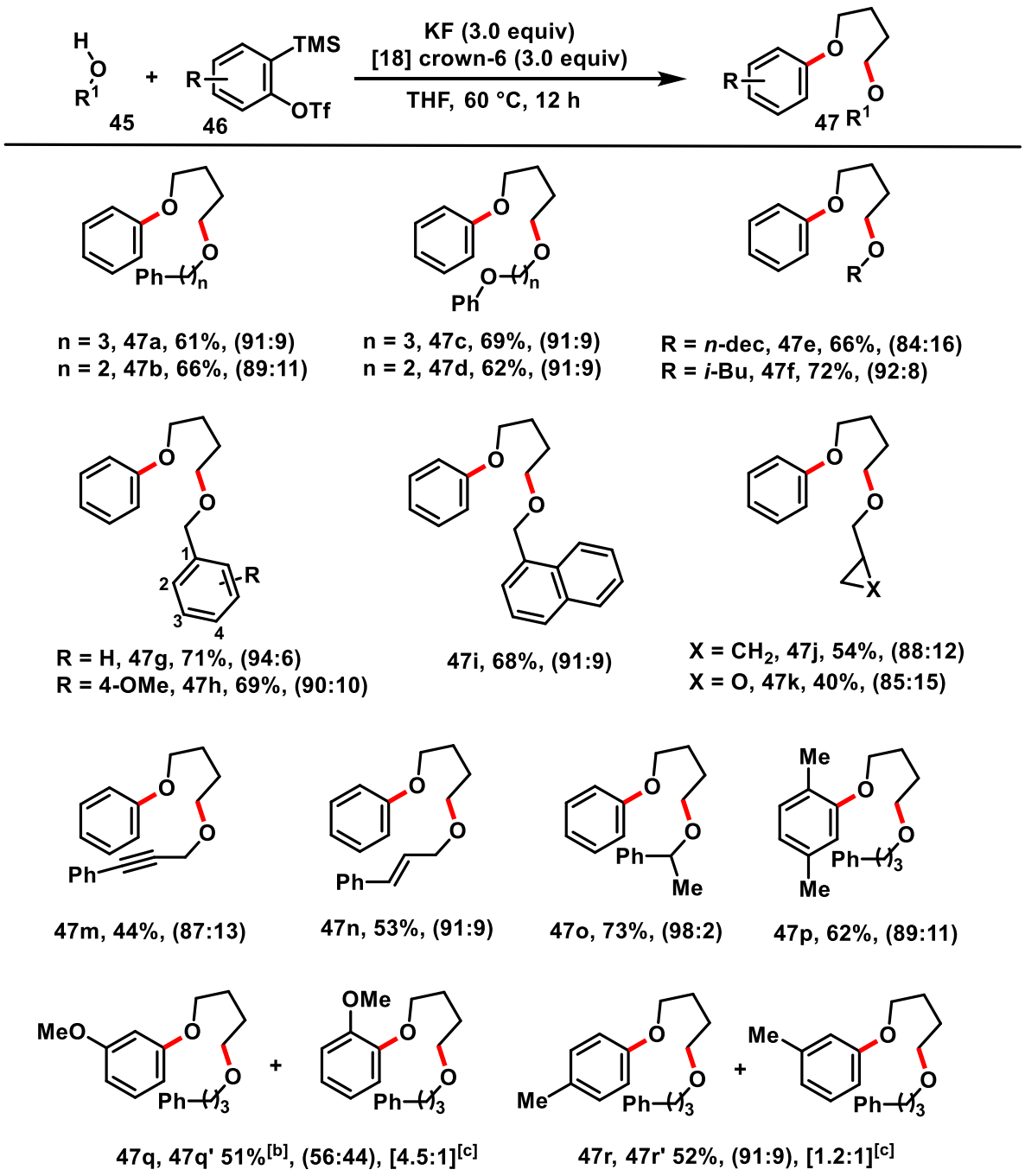
General conditions: **45** (0.5 mmol), **6** (0.6 mmol), KF (1.2 mmol), [18] crown-6 (1.2 mmol), THF (3.0 mL), -20 °C, 12 h. Yields of the isolated products are given. Selectivity ratio determined by GC analysis of crude reaction mixture is given in parentheses. [a] Reaction was run using 2.0 equiv of **6**, 4.0 equiv of KF and 4.0 equiv of [18]-crown-6. [b] Yield based on recovered **45**. [c]Reaction run on 0.25 mmol scale. [d] The regioisomer ratio determined by GC analysis

Scheme 3.15: Scope of Aryne Insertion to O-H bond of Alcohols

alcohols were well-tolerated to furnish the benzyl phenyl ethers in good yield and high selectivity (**46g, 46h**). Additionally, cyclopropyl and epoxy substituted alcohols (**46j, 46k**), alcohol having a triazole functionality (**46l**) and alcohols with C-C triple bond and double bond (**46m, 46n**) worked well under the optimized conditions. Notably, secondary alcohol resulted in aryne inserted products in moderate yield and selectivity (**46o**). We also studied the variation of the aryne moiety. Symmetrical aryne generated from the corresponding precursors returned the desired products in good yield and selectivity (**46p**). Interestingly, the unsymmetrical 3-methoxy benzyne afforded a single regioisomer **46q** in 67% yield and 89:11 selectivity. Furthermore, the unsymmetrical 4-methyl benzyne afforded the regioisomeric mixture (in ratio 1.5:1) of *O*-arylated products **46r** and **46r'** in 65% yield, thereby further expanding the scope of this reaction.

3.5.3. Substrate Scope of the aryne MCCs triggered by THF.

Next, we examined the substrate scope of this THF triggered aryne MCCs (Scheme 3.16). Almost all aliphatic alcohols (except the alcohol with the triazole group **45l**), where smooth aryne insertion was taking place at -20 °C underwent aryne MCCs initiated by THF at 60 °C affording the (4-(alkoxy)butoxy)arenes **47** in moderate to good yields and good selectivities. Interestingly, various linear and benzyl alcohols were well-tolerated under the present MCC conditions to furnish the desired alkyl aryl ethers (**47a-47i**). Notably, the epoxy methyl alcohol **45k** afforded the MCC product **47k** in 44% yield and in 85:15 selectivity. In this case, the product derived from the nucleophilic attack of epoxide oxygen was not observed. THF appears to be a competant nucleophilic trigger at 60 °C in the presence of phenyl propargyl alcohol or cinnamyl alcohol, and the corresponding propargyl and allyl ethers were isolated in moderate yields (**47m, 47n**). Delightfully, 1-phenylethanol underwent efficient aryne MCC affording the desired product **47o** in 73% yield and an excellent selectivity of 98:2. Finally, symmetrical arynes generated from their precursors afforded the target products in moderate to good yields (**47p**) and unsymmetrical arynes furnished regioisomeric mixture of products in moderate yields (**47q, 47q'** and **47r, 47r'**).

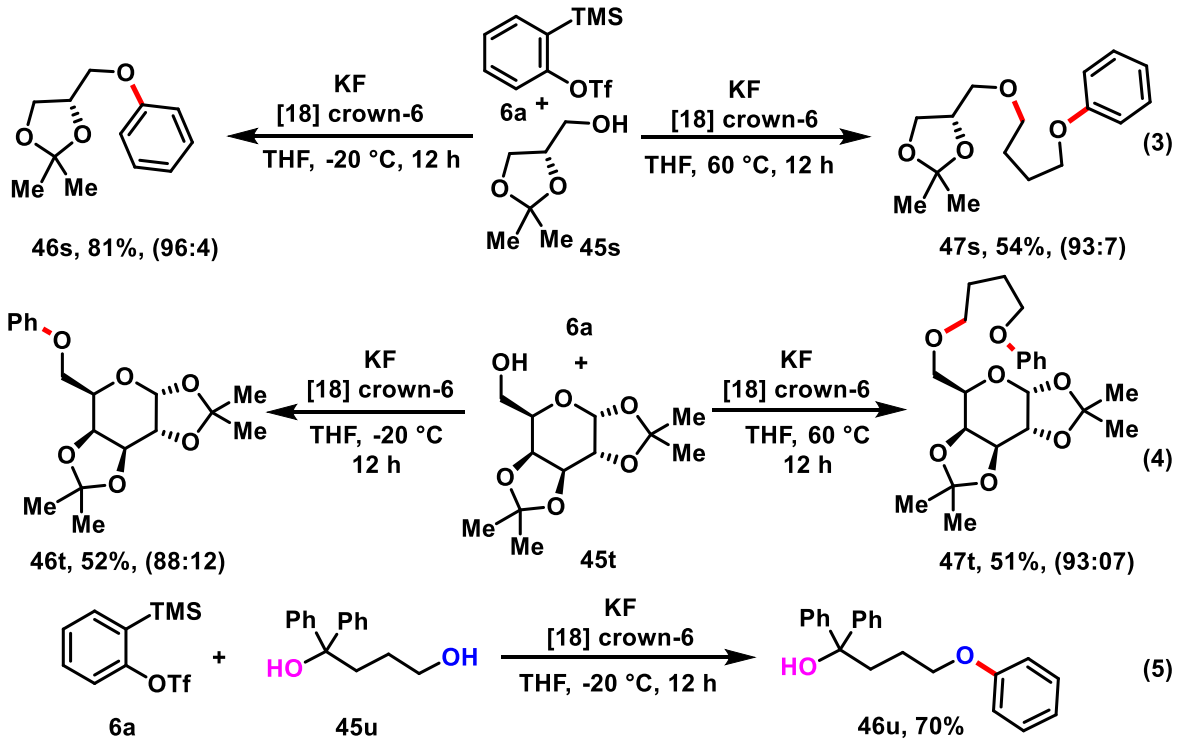


General conditions: **45** (0.5 mmol), **6** (0.75 mmol), KF (1.5 mmol), [18] crown-6 (1.5 mmol), THF (4.0 mL), 60 °C, 12 h. Yields of the isolated products are given. Selectivity ratio determined by GC analysis of crude reaction mixture is given in parentheses. [a] Yield based on recovered **45**. [b] Reaction run on 0.25 mmol scale. [c] The regioisomer ratio determined by GC analysis.

Scheme 3.16: Scope of the Aryne MCCs Triggered by THF

3.5.4. Substrate Scope of the Enantiomerically Pure Acetal Protected Primary Alcohol with Benzyne

Interestingly, when the reaction of aryne was performed at -20 °C in THF using the enantiomerically pure acetal protected primary alcohol **45s**, the *O*-arylated product **46s** was isolated in 81% yield and 96:4 selectivity (eq 3). Moreover, when the reaction was carried out at 60 °C in THF, the corresponding MCC product **47s** was obtained in 54% yield and 93:7 selectivity. It is noteworthy that the acetal

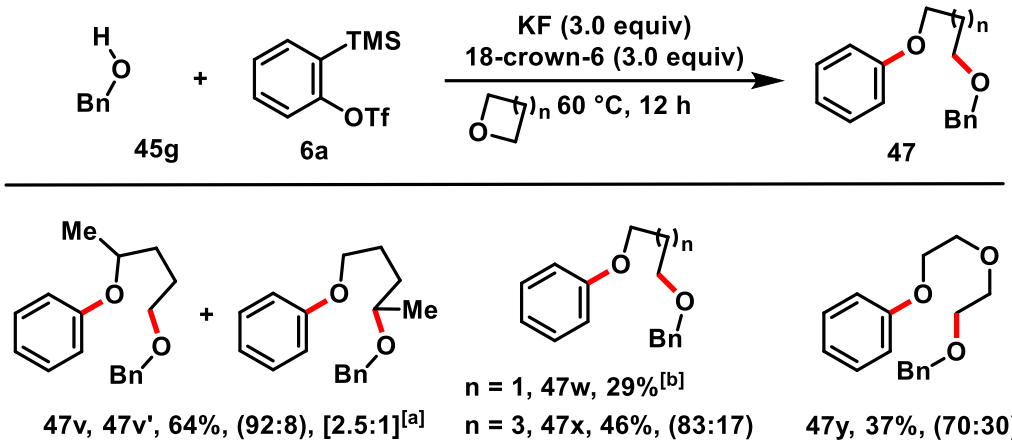


Scheme 3.17: Scope of the Enantiomerically Pure Acetal Protected Primary Alcohol with Benzyne

protection was not affected under the reaction conditions. Similar results were obtained with acetal protected primary alcohol **45t** (eq 4). In addition, the utility of diol **45u** containing primary and tertiary alcohol moieties in the aryne reaction at -20 °C afforded the product **46u** (70% yield) derived from the selective insertion to primary O-H group into aryne whereas the tertiary alcohol moiety remained intact (eq 5).

3.5.5. Scope of the MCR Involving Arynes, Cyclic Ethers and Aliphatic Alcohol

Gratifyingly, this aryne MCC is not limited to THF as the nucleophilic trigger, but instead other cyclic ethers afforded the products in moderate yields (Scheme 3.18). The reaction of **45g** with aryne generated from **6a** in 2-methyl tetrahydrofuran afforded the regiosomeric mixture of MCC products **47v** and **47v'** in 64% yield and 2.5:1 regioselectivity. A high selectivity of 92:8 for MCC product was observed over the arylation product. Moreover, the reaction performed in oxetane, tetrahydropyran and 1,4-dioxane afforded the respective MCC products in moderate yields (**47w-47y**).



Yields of the isolated products are given and selectivity ratio determined by GC analysis of crude reaction mixture is given in parentheses. [a] The regioisomer ratio determined by GC analysis. [b] NMR yield of the product given

Scheme 3.18: Scope of the MCR Involving Other Cyclicethers

3.5.6. Variation of Temperature on Aryne Reaction with Benzyl Alcohol

To get insight into the temperature dependence of the aryne reactions with aliphatic alcohols, we have carried out a series of experiments under varying temperature using benzyl alcohol **45g** and aryne generated from **6a**. It was found that as the temperature increases from -20 °C, the yield of O-H inserted product **46g** decreases whereas the yield of MCC product **47g** increases.[25] The results are plotted in figure 3.2, it is clear that at ~25 °C, both **46g** and **47g** are formed in 1:1 ratio.

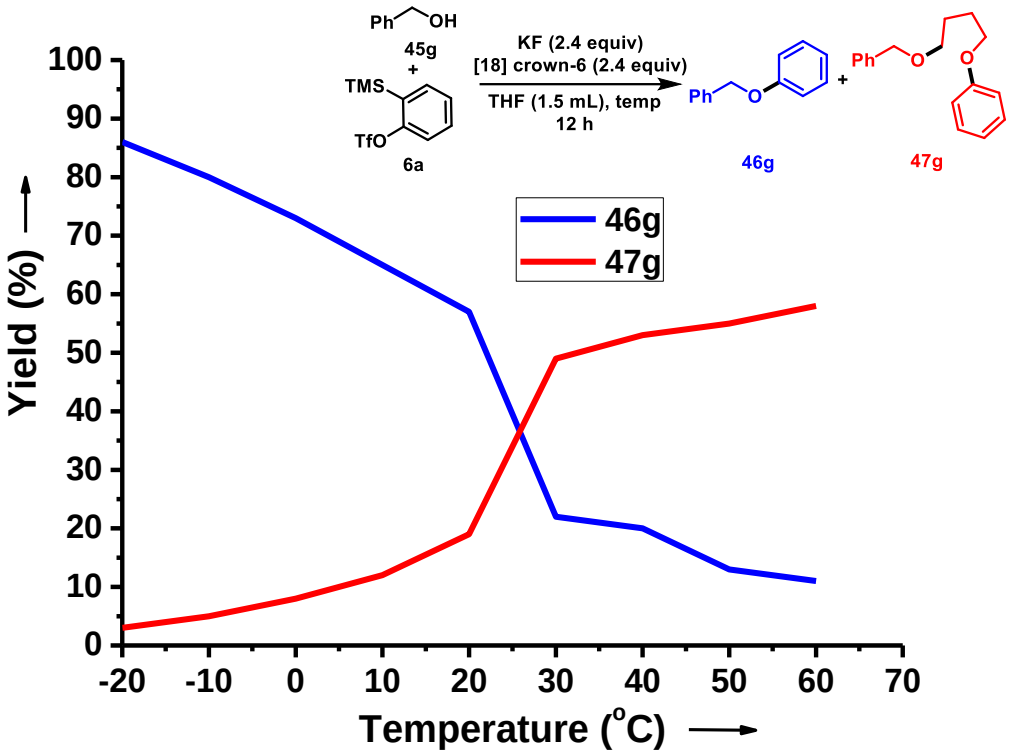
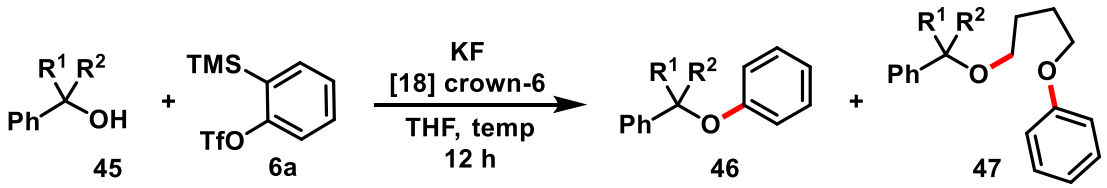


Figure 3.2: Variation of Temperature on Aryne Reaction with Benzyl Alcohol

3.5.7. Comparative study of various alcohols

We also studied the reactivity of primary, secondary and tertiary alcohols with arynes (Table 3.2). Benzyl alcohol **45h** afforded 86% yield of insertion product **46h** at -20 °C (96:4 selectivity) where as 71% the MCC product **47h** (6:94 selectivity) was isolated at 60 °C (entries 1, 2). Interestingly, benzhydrol **45z** afforded a 1:1 ratio of insertion product **46z** and MCC product **47z** at -20 °C. However, the selectivity was completely switched to **47z** at 60 °C (entries 3, 4). Moreover, trityl alcohol **45aa** furnished only traces of insertion product **46aa** and 32% of MCC product **47aa** at -20 °C. At 60 °C, exclusive MCC product formation took place isolating **47aa** in 64% yield and 1:99 selectivity.[23] These studies clearly indicate that the ability of arynes to insert into O-H bond of alcohols are in the order primary>secondary>tertiary with arynes do not undergoing insertion to tertiary alcohols even at -20 °C.

Table 3.2: Comparative Study of Various Alcohols



$R^1 = R^2 = H$, 45g
$R^1 = H$, $R^2 = Ph$, 45z
$R^1 = R^2 = Ph$, 45aa

entry	R^1	R^2	temp (°C)	yield of **46** (%)[c]	yield of **47** (%)[c]	**46:47**[d]
1[a]	H	H	-20	86	<5	96:4
2[b]	H	H	60	<5	71	6:94
3[a]	Ph	H	-20	18	17	50:5
4[b]	Ph	H	60	<5	65	1:99
5[a]	Ph	Ph	-20	<5	32	1:99
6[b]	Ph	Ph	60	<5	64	1:99

[a] Conditions: **1** (0.5 mmol), **2a** (0.6 mmol), KF (2.4 equiv), [18] crown-6 (2.4 equiv), THF (3.0 mL), 12 h. [b] Conditions: **1** (0.5 mmol), **2a** (0.75 mmol), KF (3.0 equiv), [18] crown-6 (3.0 equiv), THF (4.0 mL), 12 h. [c] Isolated yields. [d] Selectivity was determined using GC analysis of the crude reaction mixture.

3.6. Computational Studies

The geometry optimizations were conducted employing density functional theory (DFT) with the Turbomole 6.4 suite of programs.[27] The Perdew, Burke, and Ernzerhof (PBE)[28] functional was used for the geometry optimization calculations. The triple-ζ basis set augmented by a polarization function (Turbomole basis set TZVP) was used for all the atoms. The resolution of identity (RI)[29] along with the multipole accelerated resolution of identity (marij)[30] approximations were employed for an accurate and efficient treatment of the electronic Coulomb term. Solvent effects were accounted for as follows: we have done full geometry optimizations of all intermediates and transition states calculations using the COSMO model. The solvent used in this study is THF (ε =7.52). To improve the calculation of the energy values, a further correction was made through single-point B3-LYP calculations[31, 32] for the DFT (PBE)-optimized structures. The contributions of internal energy and entropy were obtained from frequency calculations done on the DFT structures:

thus, the energies reported in the figures are the ΔG values. With regard to the transition states obtained during the investigation process, care was taken to ensure that the obtained transition state structures possessed only one imaginary frequency corresponding to the correct normal mode.

To gain insight into the mechanism, we performed quantum chemical calculations by using density functional theory (DFT), employing the TZVP/PBE/B3LYP approach with Turbomole 6.4.[26] Herein we proposed two different reaction pathways based on the temperature effect. In the first pathway, at -20 °C direct attack of alcohol (**45b**) on aryne followed by intramolecular proton transfer resulted in the formation of phenethoxybenzene and in the second pathway, at 60 °C, the THF attacked the aryne resulting in the formation of 1,4 dipolar intermediate, the dipolar intermediate abstracted the hydrogen of alcohol (**45b**) to afford the oxonium ion and alkoxyanion. When oxonium cation was finally attacked by alkoxyanion, the corresponding (4-phenethoxybutoxy)benzene were formed. In both the pathways, first step is the formation common aryne through **int.1**. The results are summarized in terms of a free energy diagram as depicted in Figure 3.3.

In the lower temperature (-20 °C) mechanism, the generation of aryne through the intermediate (**int.1**=0.4 kcal/mol) from aryne precursor and potassium fluoride. The addition of alcohol in presence of THF to the aryne to form the unstable intermediate

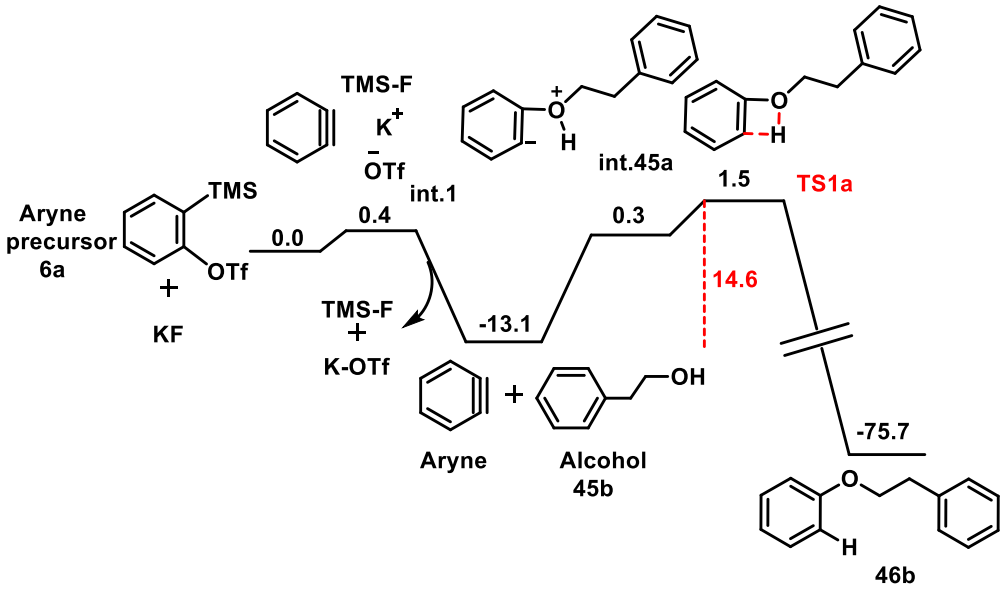


Figure 3.3

int.45a, followed by transfer of hydrogen via transition state (**TS1a**) to form the exergonic aryl ether product **46b** (ΔG= -75.7) having transition state barrier 14.6 kcal/mol.

The proposed mechanism at higher temperature (60 °C), after formation of the aryne, the THF attacks on the aryne to form the 1,4 dipolar species (**int.2b**, ΔG= -1.8). Then the attack of **45b** on the **int.2b** to form the **int.3b** through the **TS2b**, the transition state barrier was found to be 19.6 kcal/mol. This is followed to formation of less exergonic product **47b** (ΔG= -68.3) comparison to lower temperature product **46b**. The experimental yields found to be 81% and 66% at low and high temperature respectively. Our proposed mechanism gives the thermodynamic products -75.7 kcal/mol and -68.3 kcal/mol, which are agreement with experimental work.

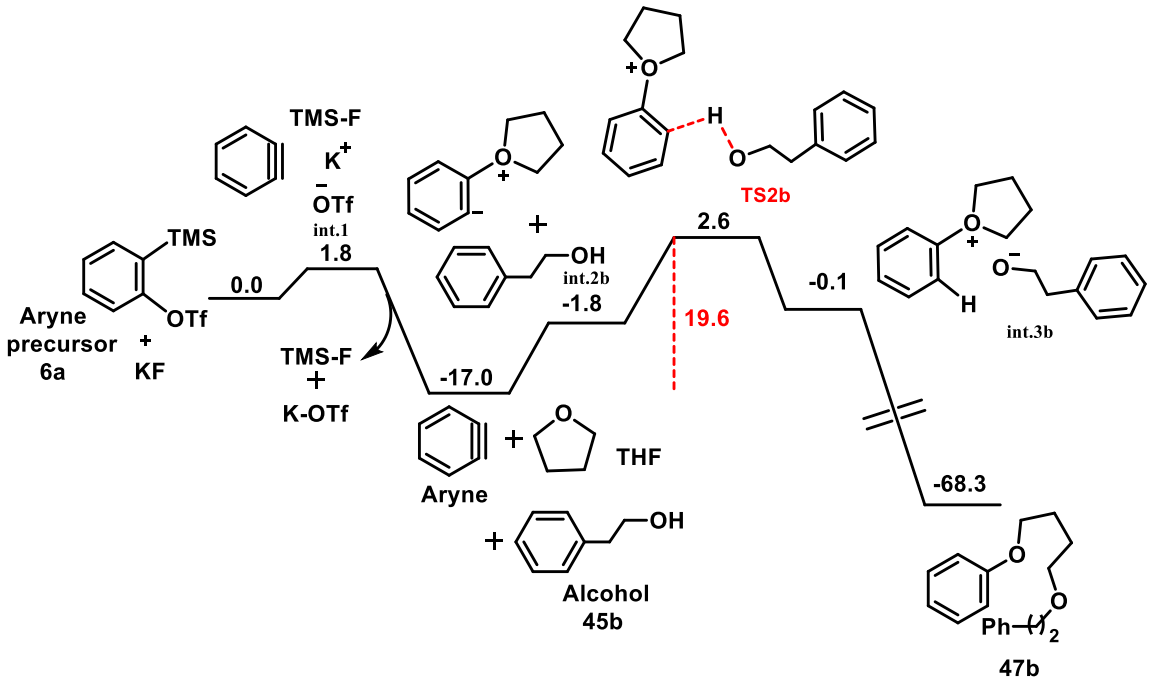


Figure 3.4

The formation of **int.1a** and **int.2b** was found to 13.4 kcal/mol and 15.2 kcal/mol higher in energy at low and high temperature mechanisms respectively. This is an indication that at low temperature arylation will be prefered and at high temperature, the formation of MCR products will be preferred.

3. 7. Conclusion

In conclusion, we have developed a transition-metal-free temperature dependent switchable reactivity in the reaction of arynes with aliphatic alcohols. At -20 °C, arynes insert into O- H bond of alcohols to afford alkyl aryl ethers. However, at 60 °C, efficient aryne MCCs resulted where THF acts as the nucleophilic trigger. Both the reactions are highly selective, and the products are formed in good yields.

3.8. Experimental Details

3.8.1. General Information

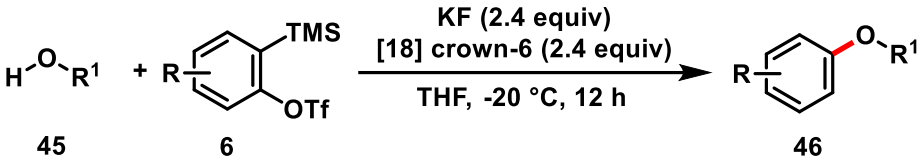
Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with teflon screw caps. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel 30 °C corresponds to the room temperature of the lab, when the experiments were carried out. THF was freshly purified by distillation over Na-benzophenone and was transferred under argon. 18-Crown-6 was recrystallized from dry CH_3CN and KF was dried by heating at 110 °C for 12 h and left to cool under argon and stored in glove box. The 2(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** and the other symmetric and unsymmetric aryne precursors were synthesized following literature procedure.[2] The alcohols are used in this work are either commercially available or prepared from the corresponding aldehydes by standard $NaBH_4$ reduction. The alcohol **45c**, **45d** and **45l** are prepared following the known procedure.[26]

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

All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400 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). Gas Chromatography was recorded on Agilent 7890 B GC. GCMS data were recorded on Agilent 7890 B GC and 5977 A MSD mass analyser. Infrared spectra were recorded on a Bruker Alpha-E Infrared Spectrophotometer.

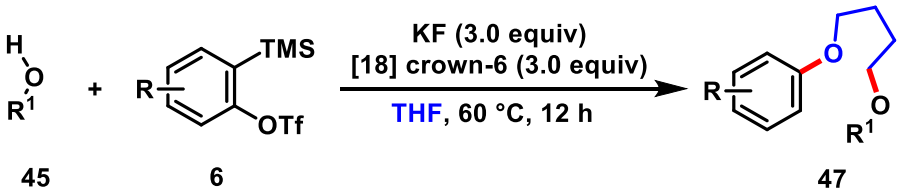
The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

3.8.2. General Procedure for the Insertion (Arylation) of Aliphatic Alcohols with Arynes



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.317 g, 1.2 mmol), KF (0.070 g, 1.2 mmol) inside the glove box. The mixture was dissolved in 3.0 mL of THF outside the glove box under argon. To the stirring solution was added corresponding alcohol **45** (0.5 mmol). The resultant reaction mixture was cooled to -20 °C and kept stirring for 5 min. To the stirring solution was added aryne precursor **6** (0.60 mmol) and kept stirring at -20 °C for 12 h. When TLC control showed the completion of the reaction (typically after 12 h), 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 alkyl aryl ether derivatives **46** in moderate to good yields. Selectivity ratio was determined by GC analysis of crude reaction mixture.

3.8.3. General Procedure for the MCR Involving Aliphatic Alcohols, THF and Aryne

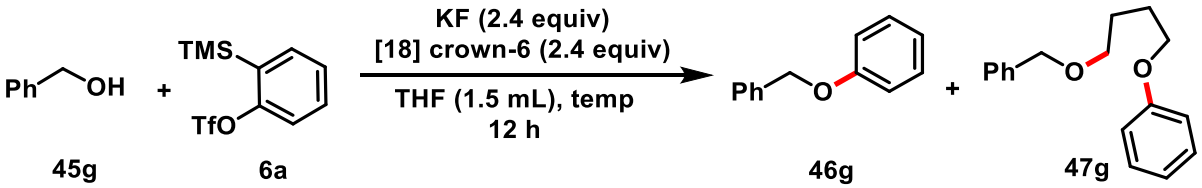


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.396 g, 1.5 mmol), KF (0.087 g, 1.5 mmol) inside the glove box. The mixture was dissolved in 4.0 mL of THF outside the glove box under argon. To the stirring solution was added corresponding alcohol **45** (0.5 mmol) and the resultant reaction mixture kept stirring at 30 °C for 5 min. To the stirring solution was added aryne precursor **6** (0.75 mmol). Then the reaction mixture was placed in a preheated oil bath at 60 °C. When TLC

control showed the completion of the reaction (typically after 12 h), the reaction mixture cooled to room temperature and the solvent was evaporated. Subsequently, the crude residue was purified by flash column chromatography on silica gel to afford the corresponding (4-(alkoxy)butoxy)arenes **47** in moderate to good yields. Selectivity ratio was determined by GC analysis of crude reaction mixture.

3.8.4. Variation of Temperature on Aryne Reactions with Benzyl Alcohol

We have carried out a series of experiments with benzyl alcohol **45g** and aryne generated from **6a** under varying temperature from -20 °C to 60 °C. To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.158 g, 0.6 mmol), KF (0.035 g, 0.6 mmol) inside the glove box. The mixture was dissolved in 1.5 mL of THF outside the glove box under argon. To the stirring solution was added benzyl alcohol **45g** (0.027 g, 0.25 mmol). Then the resultant reaction mixture was cooled to -20 °C and kept stirring for 5 min. To the stirring solution was added aryne precursor **6a** (0.089 g, 73µL, 0.30 mmol) and kept stirring at -20°C for 12 h. After 12 h, the reaction was quenched and subsequently purified by flash column chromatography on silica gel to afford the corresponding ether derivatives **46g** and **47g.** Selectivity ratio was determined by GC analysis of crude reaction mixture.

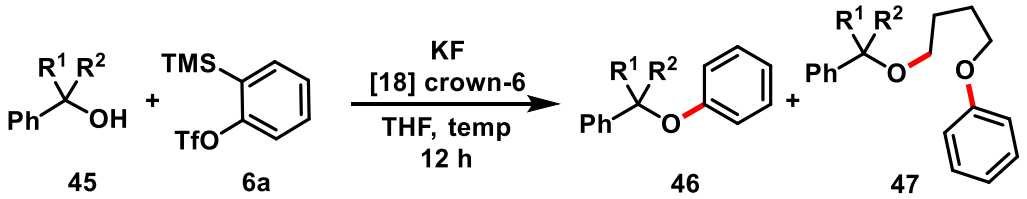


The same procedure was followed for other reactions carried out at different temperature (-20 °C to 60 °C), and the results are summarized in the following table 3.3.

entry	temp (°C)	Yield of **46g** (%)[b]	Yield of **47g** (%)[b]	selectivity **46g:47g**[c]
1	-20 °C	86	<5	96:04
2	-10 °C	80	<5	94:06
3	0 °C	73	8	91:09
4	10 °C	63	14	83:17
5	20 °C	57	19	70:30
6	30 °C	22	49	32:68
7	40 °C	20	53	31:69
8	50 °C	13	55	14:86
9	60 °C	11	58	14:86

[a] General conditions: **45g** (0.25 mmol), **6a** (0.30 mmol), KF (2.4 equiv), [18] crown-6 (2.4 equiv), THF (1.5 mL), for the indicated temperature and 12 h. [b] The yields of the isolated products are given. [c] Selectivity was determined using GC analysis of the crude reaction mixture.

3.8.5. Comparative Study of Primary, Secondary and Tertiary Alcohols



45 6a 46 47

$R^1 = R^2 = H$, 45g
$R^1 = H$, $R^2 = Ph$, 45z
$R^1 = R^2 = Ph$, 45aa

Procedure for the Comparative Experiments of Primary, Secondary and Tertiary Alcohols at -20 °C

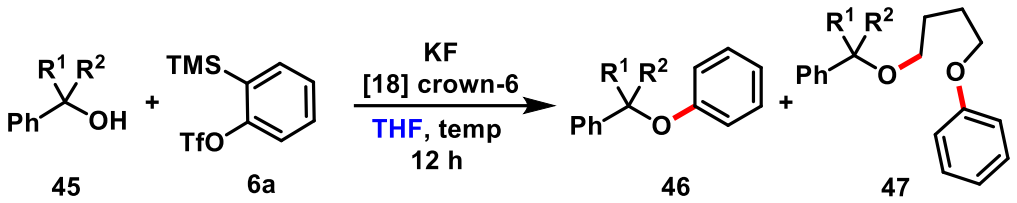
Three reactions were carried out in parallel. To each of the flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.317 g, 1.2 mmol), KF (0.070 g, 1.2 mmol) inside the glove box. The mixture was dissolved in 3.0 mL of THF outside the glove box under argon. To the stirring solution was added corresponding alcohol **45** (0.5 mmol). The resultant reaction mixture was cooled to -20 ℃ and kept stirring for 5 min. To the stirring solution was added aryne precursor **6** (0.60 mmol) and kept stirring at -20 ℃ for another 12 h. 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 ether derivatives **46** and **47**. Selectivity ratio was determined by GC analysis of crude reaction mixture.

Procedure for the Comparative Experiment of Primary, Secondary and Tertiary Alcohols at 60 °C

Three reactions were carried out in parallel. To each of the flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.396 g, 1.5 mmol), KF (0.087 g, 1.5 mmol) inside the glove box. The mixture was dissolved in 4.0 mL of THF outside the glove box under argon. To the stirring solution was added corresponding alcohol **45** (0.5 mmol). The resultant reaction mixture was kept stirring at 30 ℃ for 5 min. To the stirring solution was added aryne precursor **6** (0.750 mmol). Then the reaction mixture was placed in preheated oil bath at 60 ℃. After 12 h, 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 ether derivatives **46** and **47**. Selectivity ratio was determined by GC analysis of crude reaction mixture. the results are summarized in Table 3.2.

These studies indicate that the ability of arynes to insert into O-H bond of alcohols are in the order primary>secondary>tertiary with arynes do not undergoing insertion to tertiary alcohols even at -20 ℃.

Table 3.2: Comparative Study of Various Alcohols



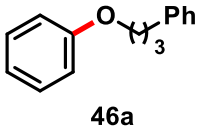
$R^1 = R^2 = H$, 45g
$R^1 = H$, $R^2 = Ph$, 45z
$R^1 = R^2 = Ph$, 45aa

entry	R^1	R^2	temp (°C)	yield of **46** (%)[c]	yield of **47** (%)[c]	**46:47**[d]
1[a]	H	H	-20	86	<5	96:4
2[b]	H	H	60	<5	71	6:94
3[a]	Ph	H	-20	18	17	50:50
4[b]	Ph	H	60	<5	65	1:99
5[a]	Ph	Ph	-20	<5	32	1:99
6[b]	Ph	Ph	60	<5	64	1:99

[a] Conditions: **45** (0.50 mmol), **6a** (0.60 mmol), KF (2.4 equiv), [18] crown-6 (2.4 equiv), THF (3.0 mL), 12 h. [b] Conditions: **45** (0.50 mmol), **6a** (0.75 mmol), KF (3.0 equiv), [18] crown-6 (3.0 equiv), THF (4 mL), 12 h. [c] Isolated yields. [d] Selectivity was determined using GC analysis of the crude reaction mixture.

3.8.6 Synthesis and Characterization of Alkyl Aryl Ethers

(3-Phenoxypropyl)benzene (46a)



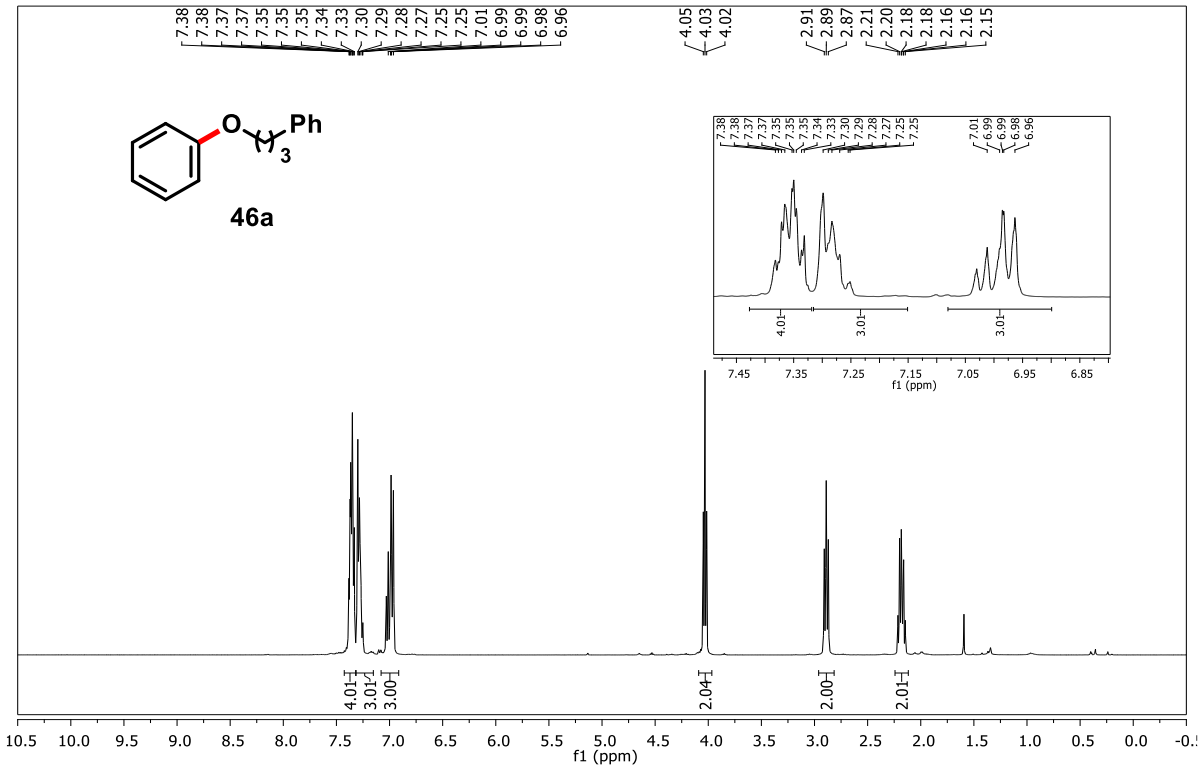
46a

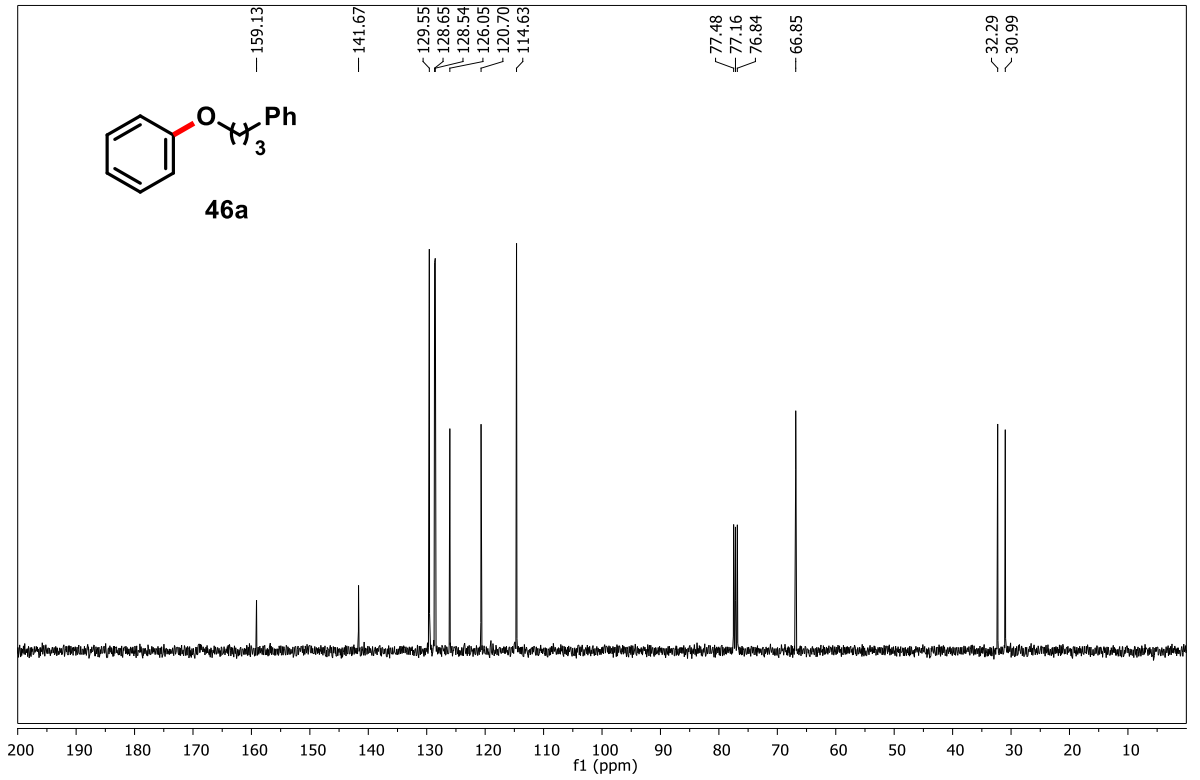
Following the general procedure, treatment of 3-phenylpropan-1-ol **45a** (0.068 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 µL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded (3-phenoxypropyl)benzene as a **22b** (1.3 equiv) 1,2-DCE, 60 °C, 10 hcolourless oil **46a** (0.079 g, 75% yield, selectivity determined by GC analysis of crude reaction mixture is 95:05).

***R*f** (Pet. ether /EtOAc = 95/05): 0.53

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.33 (m, 4H), 7.30-7.25 (m, 3H), 7.01-6.96 (m, 3H), 4.03 (t, *J* = 6.3 Hz, 2H), 2.89 (t, *J* = 7.8 Hz, 2H), 2.21-2.15 (m, 2H).

^{1}H and ^{13}C NMR Spetrum of (3-Phenoxypropyl)benzene (46a)



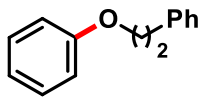


^{13}C NMR (100 MHz, $CDCl_3$) δ 159.13, 141.67, 129.55, 128.65, 128.54, 126.05, 120.70, 114.63, 66.85, 32.29, 30.99.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{15}H_{16}ONa$: 235.1093, found: 235.1082.

FTIR (cm^{-1}) 3021, 2943, 2871, 1596, 1489, 1391, 1295, 1222, 1170, 1037, 761, 698.

Phenethoxybenzene (46b)



46b

Following the general procedure, treatment of 2-phenylethan-1-ol **45b** (0.061 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 μL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded phenethoxybenzene as a colourless oil **46b** (0.080 g, 81% yield, selectivity determined by GC analysis of crude reaction mixture is 96:04).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.50

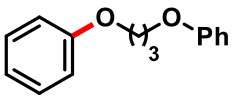
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 7H), 6.98-6.96 (m, 3H), 4.23 (t, *J* = 7.2 Hz, 2H), 3.17 (t, *J* = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.90, 138.39, 129.58, 129.14, 128.62, 126.62, 120.84, 114.67, 77.48, 77.16, 76.84, 68.67, 35.93.

GCMS (EI) calculated $[M]^+$ for $C_{14}H_{14}O$: 198.1, found: 198.1.

FTIR (cm^{-1}) 3022, 2938, 2875, 1595, 1489, 1387, 1297, 1232, 1170, 762.

1,3-Diphenoxypropane (46c)



46c

Following the general procedure, treatment of 3-phenylpropan-1-ol **45c** (0.076 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 μL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded 1,3-diphenoxypropane as a colourless oil **46c** (0.088 g, 77% yield, selectivity determined by GC analysis of crude reaction mixture is 97:03).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.38

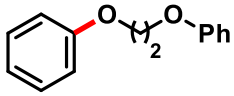
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 4H), 7.0-6.94 (m, 6H), 4.20 (t, *J* = 6.1 Hz, 4H), 2.30 (p, *J* = 6.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.99, 129.60, 120.86, 114.64, 64.47, 29.49.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{15}H_{16}O_2Na$: 251.1043, found: 251.1046.

FTIR (cm^{-1}) 3369, 3023, 2941, 1944, 1848, 1648, 1594, 1390, 1097, 1029, 991.

1,2-Diphenoxyethane (46d)



46d

Following the general procedure, treatment of 2-phenoxyethan-1-ol **45d** (0.069 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 µL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded 1,2-diphenoxyethane as a colourless oil **46d** (0.085 g, 79% yield, selectivity determined by GC analysis of crude reaction mixture is 96:04).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.50

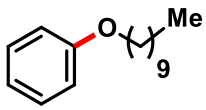
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.33 (m, 4H), 7.04-7.0 (m, 6H), 4.37 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.78, 129.63, 121.23, 114.84, 66.58.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{14}H_{14}O_2Na$: 237.0886, found: 237.0884.

FTIR (cm^{-1}) 3018, 2932, 2880, 1599, 1497, 1218, 772.

(Decyloxy)benzene (46e) Following the general procedure, treatment of decan-1-ol **45e**



46e

(0.079 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.298 g, 242 µL, 1.0 mmol) in the presence of KF (0.116 g, 2.0 mmol) and 18-crown-6 (0.528 g, 2.0 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded (decyloxy)benzene as a colourless oil **46e** (0.086 g, 74% yield, selectivity determined by GC analysis of crude reaction mixture is 94:06).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.61

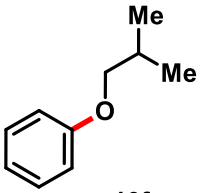
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 6.95-6.90 (m, 3H), 3.96 (t, *J* = 6.6 Hz, 2H), 1.79 (quin, *J* = 6.6 Hz, 2H), 1.50-1.43 (m, 2H), 1.36-1.30 (m, 12H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.29, 129.52, 120.57, 114.63, 68.01, 32.06, 29.74, 29.72, 29.57, 29.47, 29.46, 26.22, 22.83, 14.26.

HRMS (ESI) calculated $[M+H]^+$ for $C_{16}H_{27}O$: 235.2056, found: 235.2061.

FTIR (cm^{-1}) 3020, 1595, 1487, 1387, 1296, 1171, 1038, 931, 882, 767.

Isobutoxybenzene (46f)



46f

Following the general procedure, treatment of 3-phenylpropan-1-ol **45f** (0.037 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.298 g, 242 μL, 1.0 mmol) in the presence of KF (0.116 g, 2.0 mmol) and 18-crown-6 (0.529 g, 2.0 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded isobutoxybenzene as a colourless oil **46f** (0.041 g, 55% yield, selectivity determined by GC analysis of crude reaction mixture is 93:07).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.65

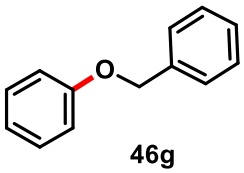
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.0-6.95 (m, 3H), 3.78 (d, *J* = 6.6 Hz, 2H), 2.14 (m, 1H), 1.09 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.40, 129.52, 120.55, 114.66, 74.45, 28.43, 19.42.

HRMS (ESI) calculated $[M+H]^+$ for $C_{10}H_{15}O$: 151.1117, found: 151.1120.

FTIR (cm^{-1}) 3021, 2963, 2874, 1594, 1487, 1398, 1293, 1219, 1171, 1075, 926, 847.

(Benzyloxy)benzene (46g)



46g

Following the general procedure, treatment of phenylmethanol **45g** (0.054 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 μL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded (benzyloxy)benzene as a colourless oil **46g** (0.079 g, 86% yield, selectivity determined by GC analysis of crude reaction mixture is 96:04).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.50

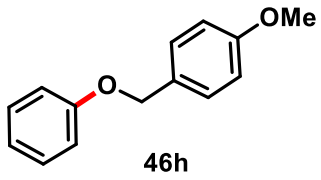
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H), 7.36-7.32 (m, 2H), 7.27-7.23 (m, 3H), 6.95-6.92 (m, 3H), 5.02 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.90, 137.18, 129.61, 128.71, 128.06, 127.61, 121.06, 114.95, 70.0.

HRMS (ESI) calculated $[M+H]^+$ for $C_{13}H_{13}O$: 185.0961, found: 185.0961.

FTIR (cm^{-1}) 3035, 2922, 2870, 1593, 1493, 1459, 1379, 1168, 1113, 1079, 761.

1-Methoxy-4-(phenoxymethyl)benzene (46h)



46h

Following the general procedure, treatment of (4-methoxy phenyl)methanol **45h** (0.069 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 μL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1-methoxy-4-(phenoxymethyl)benzene as a white solid **46h** (0.090 g, 84% yield, selectivity determined by GC analysis of crude reaction mixture is 95:05).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.56; mp 86 – 88 °C.

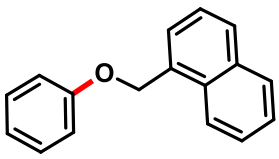
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.35-7.31 (m, 2H), 7.03-6.95 (m, 5H), 5.02 (s, 2H), 3.84 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.54, 158.94, 129.57, 129.35, 129.18, 120.95, 114.94, 114.09, 69.77, 55.38.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{14}H_{14}O_2Na$: 237.0886, found: 237.0886.

FTIR (cm^{-1}) 3019, 1600, 1506, 1378, 1224, 1033, 930, 818.

1-(Phenoxymethyl)naphthalene (46i)



46i

Following the general procedure, treatment of naphthalen-1-ylmethanol **45i** (0.079 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 μL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1-(phenoxymethyl)naphthalene as a colourless oil **46i** (0.094 g, 80% yield, selectivity determined by GC analysis of crude reaction mixture is 97:03).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.39

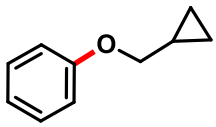
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.16 (m, 1H), 8.01-7.99 (m, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.67-7.60 (m, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.47-7.43 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 5.57 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.95, 133.86, 132.42, 131.62, 129.64, 129.08, 128.78, 126.68, 126.53, 125.99, 125.42, 123.82, 121.16, 114.98, 68.59.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{14}ONa$: 257.0937, found: 257.0936.

FTIR (cm^{-1}) 3020, 1594, 1494, 1295, 1070, 1021, 923, 766, 675.

(Cyclopropylmethoxy)benzene (46j)



46j

Following the general procedure, treatment of 3-phenylpropan-1-ol **45j** (0.036 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.298 g, 242 μL, 1.0 mmol) in the presence of KF (0.116 g, 2.0 mmol) and 18-crown-6 (0.529 g, 2.0 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded (cyclopropylmethoxy)benzene as a colourless oil **46j** (0.047 g, 64% yield, selectivity determined by GC analysis of crude reaction mixture is 93:07).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.25

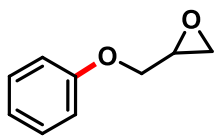
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 6.99-6.93 (m, 3H), 3.84 (d, *J* = 7.0 Hz, 2H), 1.34-1.28 (m, 1H), 0.70-0.66 (m, 2H), 0.40-0.37 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.10, 129.55, 120.71, 114.67, 72.76, 10.42, 3.31.

HRMS (ESI) calculated $[M+H]^+$ for $C_{10}H_{13}O$: 149.0961, found: 149.0959.

FTIR (cm^{-1}) 3075, 3020, 2924, 2871, 1591, 1485, 1404, 1367, 1024, 924.

2-(Phenoxymethyl)oxirane (46k)



46k

Following the general procedure, treatment of oxiran-2-ylmethanol **45k** (0.037 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.298 g, 242 μL, 1.0 mmol) in the presence of KF (0.116 g, 2.0 mmol) and 18-crown-6 (0.529 g, 2.0 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded 2-(phenoxymethyl)oxirane as a colourless oil **46k** (0.033 g, 44% yield, selectivity determined by GC analysis of crude reaction mixture is 90:10).

***R*f** (Pet. ether /EtOAc = 95/05): 0.27

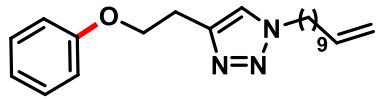
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 2H), 7.02-6.95 (m, 3H), 4.25 (dd, J_1 = 3.2 Hz, J_2 = 11.0 Hz, 1H), 4.0 (dd, J_1 = 5.6 Hz, J_2 = 11.1 Hz, 1H), 3.41-3.37 (m, 1H), 2.93 (t, *J* = 4.6 Hz, 1H), 2.80-2.78 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.57, 129.62, 121.33, 114.72, 68.76, 50.26, 44.84.

GCMS (EI) calculated $[M]^+$ for $C_9H_{10}O_2$: 150.0, found: 150.1.

FTIR (cm^{-1}) 3058, 3011, 2926, 2876, 1595, 1493, 1347, 1295, 1169, 1142, 915.

4-(2-Phenoxyethyl)-1-(undec-10-en-1-yl)-1*H*-1,2,3-triazole (46l)



46l

Following the general procedure, treatment of 2-(1-(undec-10-en-1-yl)-1*H*-1,2,3-triazol-4-yl)ethan-1-ol **45l** (0.066 g, 0.25 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.298 g, 121 μL, 0.5 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (1.5 mL) at -20 °C for 12 h. After 12 h the reaction was quenched with H_2O (5ml) and the reaction mixture was extracted with EtOAc (3 x 5mL). The combined organic layers were dried over anhydrous Na2SO4, concentrated under reduced pressure to get the crude product which was purified by silica gel column chromatography (silica gel 100-200 mesh, DCM) to afford the compound 4-(2-phenoxyethyl)-1-(undec-10-en-1-yl)-1*H*-1,2,3-triazole as a brown colour oil **46l** (0.043 g, 51% yield).

***R*f** (Pet. ether /EtOAc = 50/50): 0.4

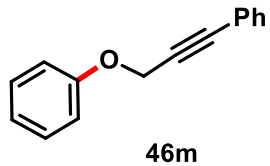
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.29-7.25 (m, 2H), 6.96-6.89 (m, 3H), 5.85-5.75 (m, 1H), 5.00-4.91 (m, 2H), 4.30 (t, *J* = 7.2 Hz, 2H), 4.24 (t, *J* = 6.4 Hz, 2H), 3.21 (t, *J* = 6.4 Hz, 2H), 2.05-2.00 (m, 2H), 1.89-1.85 (m, 2H), 1.37-1.34 (m, 2H), 1.30-1.26 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.72, 139.23, 129.59, 120.98, 114.60, 114.26, 66.81, 50.35, 33.86, 30.41, 29.41, 29.12, 29.06, 28.95, 26.58, 26.29.

HRMS (ESI) calculated $[M+H]^+$ for $C_{21}H_{32}ON_3$: 342.2540, found: 342.2531.

FTIR (cm^{-1}) 3016, 1638, 1595, 1381, 1297, 1043, 915, 768, 674.

(3-Phenoxyprop-1-yn-1-yl)benzene (46m)



46m

Following the general procedure, treatment of 3-phenylprop-2-yn-1-ol **45m** (0.066 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 µL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded (3-phenoxyprop-1-yn-1-yl)benzene as a pale yellow oil **46m** (0.090 g, 87% yield, selectivity determined by GC analysis of crude reaction mixture is 96:04).

***R*f** (Pet. ether /EtOAc = 95/05): 0.53

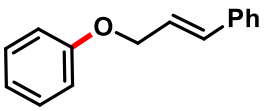
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.46 (m, 2H), 7.37-7.32 (m, 5H), 7.09-7.02 (m, 3H), 4.94 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.92, 131.93, 129.59, 128.77, 128.40, 122.41, 121.54, 115.09, 87.24, 84.09, 56.71.

HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{13}O$: 209.0961, found: 209.0958.

FTIR (cm^{-1}) 3021, 2920, 2867, 1594, 1491, 1451, 1297, 1220, 922, 882.

(Cinnamyloxy)benzene (46n)



46n

Following the general procedure, treatment of (E)-3-phenylprop-2-en-1-ol **45n** (0.067 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 µL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded (cinnamyloxy)benzene as a pale yellow oil **46n** (0.087 g, 83% yield, selectivity determined by GC analysis of crude reaction mixture is 95:05).

***R*f** (Pet. ether /EtOAc = 95/05): 0.45

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.39-7.28 (m, 5H), 7.03-7.01 (m, 3H), 6.81-6.77 (d, *J* = 16.1 Hz, 1H), 6.51-6.44 (m, 1H), 4.76 (d, *J* = 5.9 Hz, 2H).

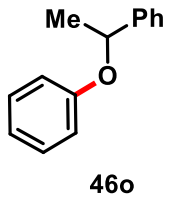
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.75, 136.58, 133.09, 129.63, 128.72, 128.02, 126.71, 124.64, 121.03, 114.90, 68.67.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{15}H_{14}ONa$: 233.0937, found: 233.0938.

FTIR (cm^{-1}) 3021, 2926, 1593, 1492, 1379, 1297, 1220, 1076, 1023, 972.

(1-Phenoxyethyl)benzene (46o)

Following the general procedure, treatment of 1-phenylethan-1-ol **45o** (0.061 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 µL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 9.5/0.5) of the crude reaction mixture using silica gel afforded (1-phenoxyethyl)benzene as a colourless oil **46o** (0.037 g, 37% yield, 52% yield based on starting material recovery, selectivity determined by GC analysis of crude reaction mixture is 68:32).



46o

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.55

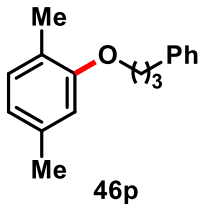
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44-7.23 (m, 7H), 6.94-6.91 (m, 3H), 5.37 (q, *J* = 6.4 Hz, 1H), 1.70 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 158.11, 143.40, 129.44, 128.73, 127.53, 125.67, 120.76, 116.05, 75.99, 24.62.

HRMS (ESI) calculated [M+H]$^+$ for $C_{14}H_{14}ONa$: 221.0937, found: 221.0941.

FTIR (cm^{-1}) 3391, 3021, 1594, 1491, 1370, 1220, 1075, 926, 767, 683.

1,4-Dimethyl-2-(3-phenylpropoxy)benzene (46p)



46p

Following the general procedure, treatment of 3-phenylpropan-1-ol **45a** (0.068 g, 0.5 mmol) with 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6b** (0.196 g, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded 1,4-dimethyl-2-(3-phenylpropoxy)benzene as a colourless oil **46p** (0.094 g, 78% yield, selectivity determined by GC analysis of crude reaction mixture is 92:08).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.42

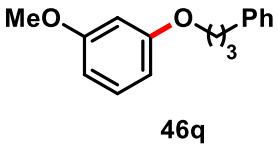
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36-7.33 (m, 2H), 7.28-7.23 (m, 3H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 6.66 (s, 1H), 4.00 (t, *J* = 6.2 Hz, 2H), 2.89 (t, *J* = 7.9 Hz, 2H), 2.36 (s, 3H), 2.28 (s, 3H), 2.21 – 2.14 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.08, 141.83, 136.59, 130.43, 128.66, 128.53, 126.01, 123.73, 120.81, 112.09, 66.76, 32.40, 31.18, 21.53, 15.95.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{21}O$: 241.1587, found: 241.1583.

FTIR (cm^{-1}) 3019, 1598, 1507, 1422, 1262, 1162, 1039, 925, 849, 767.

1-Methoxy-3-(3-phenylpropoxy)benzene (46q)



46q

Following the general procedure, treatment of 3-phenylpropan-1-ol **45a** (0.034 g, 0.25 mmol) with 2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **6c** (0.099 g, 0.3 mmol) in the presence of KF (0.035 g, 0.6 mmol) and 18-crown-6 (0.159 g, 0.6 mmol) in THF (1.5 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1-methoxy-4-(3-phenylpropoxy)benzene and 1-methoxy-3-(3-phenylpropoxy)benzene as a colourless oil **46q** (0.041 g, 67% yield, selectivity determined by GC analysis of crude reaction mixture is 92:08).

R_f (Pet. ether /EtOAc = 95/05): 0.37

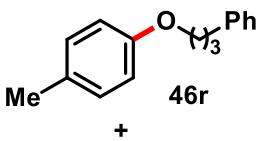
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.26-7.19 (m, 4H), 6.55-6.50 (m, 3H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.17-2.10 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.95, 160.42, 141.65, 129.98, 128.66, 128.55, 126.06, 106.86, 106.32, 101.10, 67.01, 55.38, 32.29, 30.95.

HRMS (ESI) calculated $[M+H]^+$ for $C_{16}H_{19}O_2$: 243.1380, found: 243.1373.

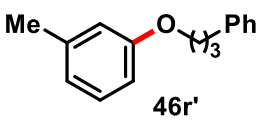
FTIR (cm^{-1}) 3018, 1598, 1484, 1458, 1277, 1209, 1043, 966, 841.

1-Methyl-4-(3-phenylpropoxy)benzene (46r) and 1-Methyl-3-(3-phenylpropoxy) benzene (46r')



46r

+



46r'

Following the general procedure, treatment of 3-phenylpropan-1-ol **45a** (0.068 g, 0.5 mmol) with 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6d** (0.187 g, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded 1-Methyl-4-(3-phenylpropoxy)benzene **46r** and 1-Methyl-3-(3-phenylpropoxy)benzene **46r'** as a colourless oil (0.074 g, 65% yield,

selectivity and regioisomeric ratio determined by GC analysis of crude reaction mixture is 89:11 and 1.5:1).

***R*f** (Pet. ether /EtOAc = 95/05): 0.64

^{1}H NMR (400 MHz, $CDCl_3$) of major isomer δ 7.38-7.14 (m, 6H), 6.89-6.77 (m, 3H), 4.04-3.99 (m, 2H), 2.88 (t, *J* = 7.4 Hz, 2H), 2.40 (s, 3H), 2.19-2.15 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) of major isomer δ 159.15, 147.71, 129.99, 128.66, 126.02, 114.51, 111.49, 66.79, 32.29, 21.65.

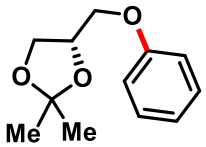
^{1}H NMR (400 MHz, $CDCl_3$) of minor isomer δ 4.04-3.99 (m, 2H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) of minor isomer δ 157.01, 139.55, 129.28, 128.52, 121.54, 115.51, 67.03, 31.02, 20.59.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{16}H_{18}ONa$: 249.1250, found: 249.1239.

FTIR (cm^{-1}) 3020, 1598, 1502, 1390, 1252, 1164, 1041, 948, 815, 762.

(*S*)-2,2-Dimethyl-4-(phenoxymethyl)-1,3-dioxolane (46s)



46s

Following the general procedure, treatment of (S)-2,2-dimethyl-4-(phenoxymethyl)-1,3-dioxolane **45s** (0.066 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 μL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 96/04) of the crude reaction mixture using silica gel afforded (*S*)-2,2-dimethyl-4-(phenoxymethyl)-1,3-dioxolane as a colourless oil **46s** (0.084 g, 81% yield, selectivity determined by GC analysis of crude reaction mixture is 96:04).

***R*f** (Pet. ether /EtOAc = 90/10): 0.5

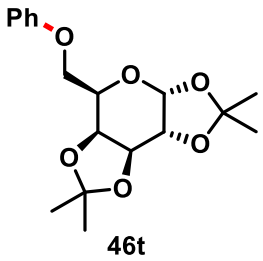
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 7.01-6.94 (m, 3H), 4.54-4.46 (m, 1H), 4.22-4.18 (m, 1H), 4.11-4.07 (m, 1H), 3.98-3.92 (m, 2H), 1.50 (s, 3H), 1.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.63, 129.57, 121.20, 114.60, 109.82, 74.12, 68.78, 66.97, 26.89, 25.47.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{12}H_{16}O_3Na$: 231.0992, found: 231.0993.

FTIR (cm^{-1}) 3061, 1596, 1493, 1463, 1375, 1243, 1158, 1052, 985, 846, 750.

(3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-Tetramethyl-5-(phenoxymethyl)tetrahydro-5*H*-bis([1,3]dioxolo) [4,5-b:4',5'-d]pyran (46t)



46t

Following the general procedure, treatment of galactose **45t** (0.130 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 µL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded (3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyl-5-(phenoxymethyl)tetrahydro-5*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran as a white solid **46t** (0.088 g, 52% yield, selectivity determined by GC analysis of crude reaction mixture is 88:12).

***R*f** (Pet. ether /EtOAc = 90/10): 0.46; mp 67 – 69 °C.

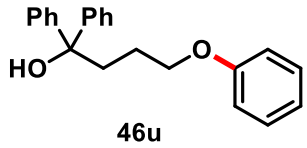
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 6.98-6.95 (m, 3H), 5.61 (d, J = 5.0 Hz, 1H), 4.68 (dd, J_1 = 2.3 Hz, J_2 = 8.0 Hz, 1H), 4.41-4.36 (m, 2H), 4.23-4.12 (m, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.68, 129.51, 121.05, 114.94, 109.56, 108.87, 96.51, 71.08, 70.76, 66.56, 66.26, 26.15, 26.12, 25.08, 24.58.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{24}O_6Na$: 359.1465, found: 359.1460.

FTIR (cm^{-1}) 3015, 1596, 1493, 1465, 1380, 1249, 1216, 1169, 1006, 762.

4-Phenoxy-1,1-diphenylbutan-1-ol (46u)



46u

Following the general procedure, treatment of 1,1-diphenylbutane-1,4-diol **45u** (0.121 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 µL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 94/06) of the crude reaction mixture using silica gel afforded 4-phenoxy-1,1-diphenylbutan-1-ol as a colourless oil **46u** (0.112 g, 70% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.3

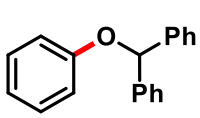
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 4H), 7.37-7.24 (m, 8H), 6.98-6.89 (m, 3H), 4.0 (t, J = 6.1 Hz, 2H), 2.55-2.50 (m, 3H, the tertiary O-H signal exchangeable with D_2O), 1.88-1.81 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.95, 147.07, 129.56, 128.34, 127.01, 126.20, 120.83, 114.62, 78.14, 68.10, 38.75, 24.16.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{22}H_{22}O_2Na$: 341.1512, found: 341.1515.

FTIR (cm^{-1}) 3066, 1597, 1487, 1385, 1297, 1241, 1167, 1093, 1040, 909, 736.

(Phenoxymethylene)dibenzene (46z)



46z

Following the general procedure, treatment of diphenylmethanol **45z** (0.092 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.179 g, 146 μL, 0.6 mmol) in the presence of KF (0.070 g, 1.2 mmol) and 18-crown-6 (0.317 g, 1.2 mmol) in THF (3.0 mL) at -20 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded (phenoxymethylene)dibenzene as a white solid **46z** (0.024 g, 18% yield, selectivity determined by GC analysis of crude reaction mixture is 50:50).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.45; mp 94 – 96 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.45 (m, 4H), 7.39-7.36 (m, 4H), 7.32-7.23 (m, 4H), 7.0-6.94 (m, 3H), 6.25 (s, 1H).

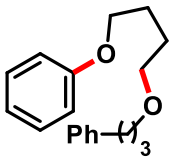
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.23, 141.41, 129.49, 128.73, 127.86, 127.03, 121.10, 116.22, 81.79.

GCMS (EI) calculated $[M]^+$ for $C_{19}H_{16}O$: 260.1, found: 260.1.

FTIR (cm^{-1}) 3021, 1721, 1592, 1487, 1462, 1365, 1222, 1114, 1072, 1024, 924.

3.8.7. Synthesis and Characterization of (4-(Alkoxy)butoxy)arenes

(3-(4-Phenoxybutoxy)propyl)benzene (47a)

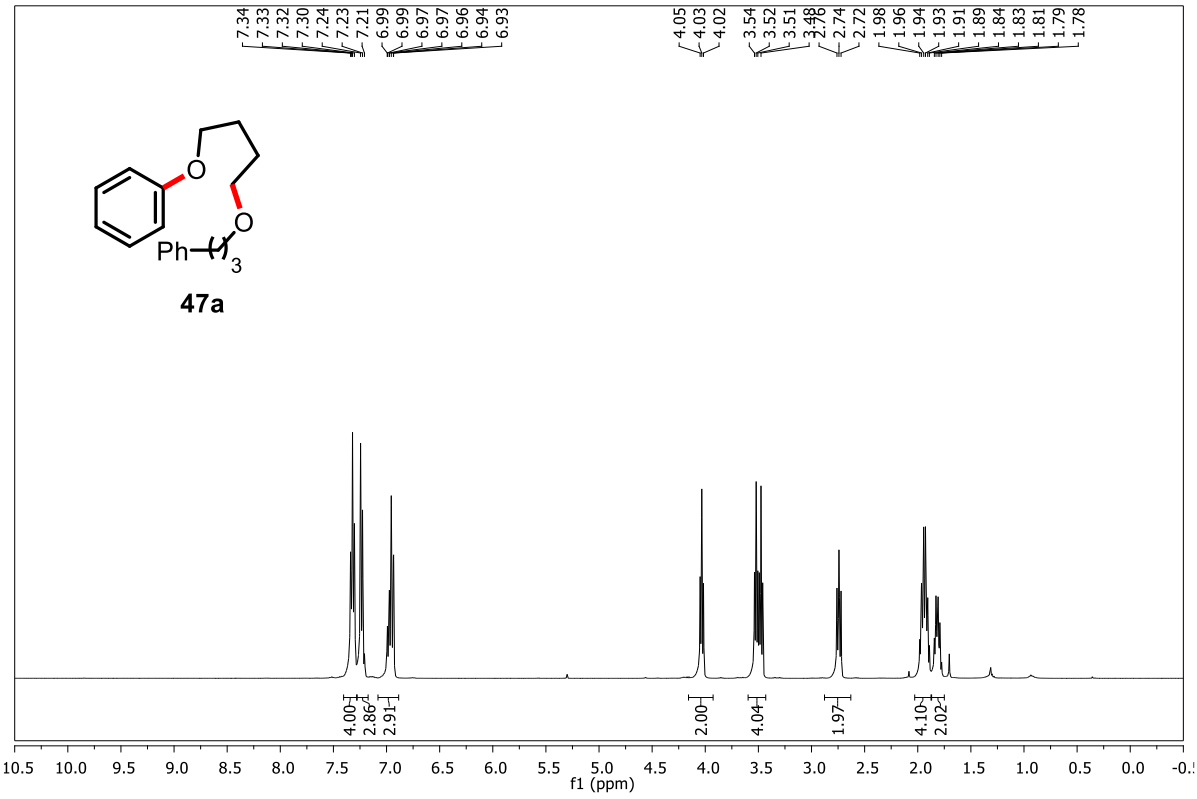


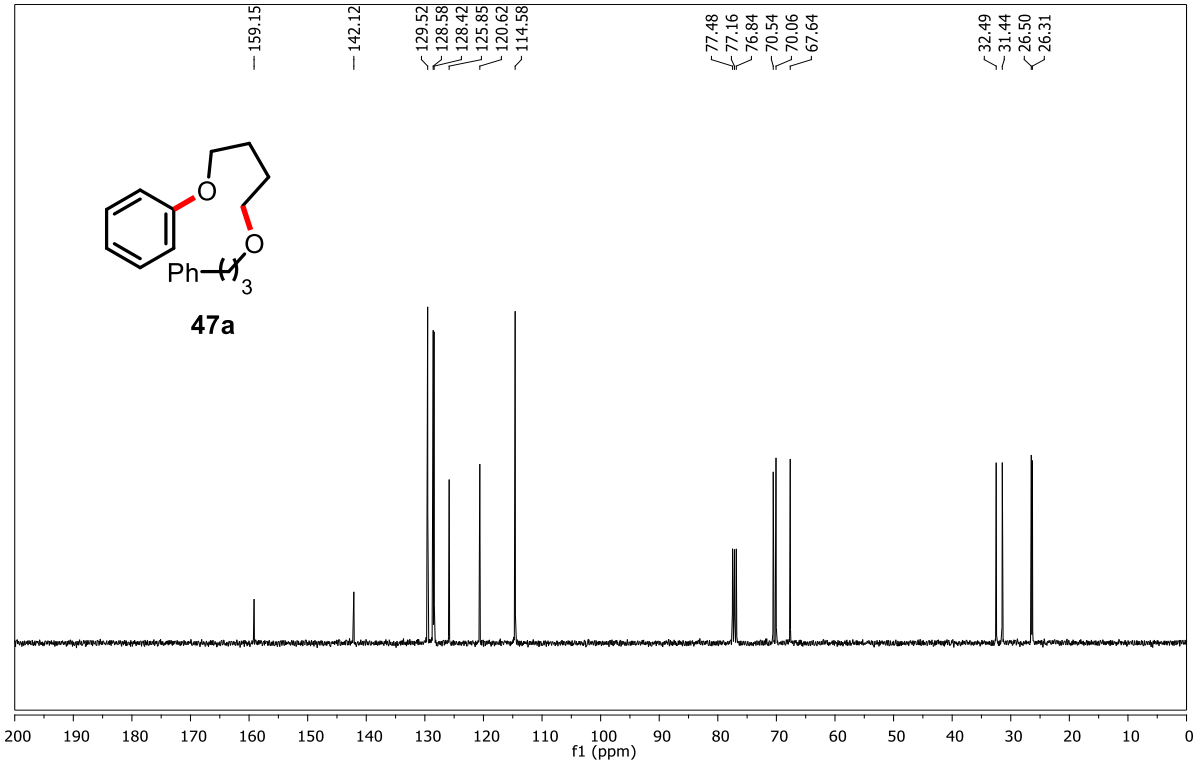
47a

Following the general procedure, treatment of 3-phenylpropan-1-ol **45a** (0.068 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **2a** (0.224 g, 182 μL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded (3-(4-phenoxybutoxy)propyl)benzene as a colourless oil **47a** (0.087 g, 61% yield, selectivity determined by GC analysis of crude reaction mixture is 91:09).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.45

^{1}H and ^{13}C NMR Spectra of (3-(4-Phenoxybutoxy)propyl)benzene (47a)





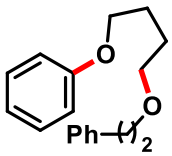
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (m, 4H), 7.24-7.21 (m, 3H), 6.99-6.93 (m, 3H), 4.03 (t, *J* = 6.0 Hz, 2H), 3.54 -3.46 (m, 4H), 2.74 (t, *J* = 7.4 Hz, 2H), 1.98-1.89 (m, 4H), 1.84-1.78 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.15, 142.12, 129.52, 128.58, 128.42, 125.85, 120.62, 114.58, 70.54, 70.06, 67.64, 32.49, 31.44, 26.50, 26.31.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{24}O_2Na$: 307.1669, found: 307.1669.

FTIR (cm^{-1}) 3018, 2942, 2866, 1596, 1489, 1379, 1295, 1219, 1171, 1112, 1043, 763, 701, 682.

(4-Phenethoxybutoxy)benzene (47b)



47b

Following the general procedure, treatment of 2-phenylethan-1-ol **45b** (0.061 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded (4-phenethoxybutoxy)benzene as a colourless oil **47b** (0.089 g, 66% yield, selectivity determined by GC analysis of crude reaction mixture is 89:11).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.48

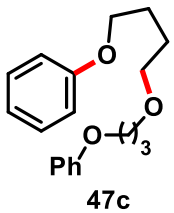
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 7H), 6.98-6.92 (m, 3H), 4.0 (t, *J* = 6.1 Hz, 2H), 3.69 (t, *J* = 7.2 Hz, 2H), 3.55 (t, *J* = 6.2 Hz, 2H), 2.94 (t, *J* = 7.1 Hz, 2H), 1.91-1.87 (m, 2H), 1.82-1.78 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.15, 139.18, 129.53, 129.03, 128.45, 126.28, 120.63, 114.60, 71.95, 70.65, 67.60, 36.51, 26.43, 26.25.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{22}O_2Na$: 293.1512, found: 293.1510.

FTIR (cm^{-1}) 3018, 2942, 2865, 2797, 1595, 1488, 1373, 1296, 1111, 762.

(3-(4-Phenoxybutoxy)propoxy)benzene (47c)



47c

Following the general procedure, treatment of 3-phenoxypropan-1-ol **45c** (0.076 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc =

99/01) of the crude reaction mixture using silica gel afforded (3-(4-phenoxybutoxy)propoxy)benzene as a colourless oil **47c** (0.104 g, 69% yield, selectivity determined by GC analysis of crude reaction mixture is 91:09).

***R*f** (Pet. ether /EtOAc = 95/05): 0.42

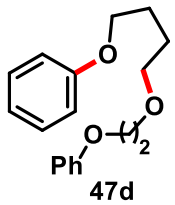
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.29 (m, 4H), 6.97-6.91 (m, 6H), 4.10 (t, *J* = 6.1 Hz, 2H), 4.0 (t, *J* = 6.0 Hz, 2H), 3.65 (t, *J* = 6.1 Hz, 2H), 3.54 (t, *J* = 6.1 Hz, 2H), 2.11-2.07 (m, 2H), 1.91-1.87 (m, 2H), 1.81-1.78 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.14, 129.54, 120.70, 120.64, 114.63, 114.60, 70.72, 67.60, 67.42, 64.87, 29.90, 26.46, 26.26.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{24}O_3Na$: 323.1618, found: 323.1618.

FTIR (cm^{-1}) 3013, 2950, 2871, 1587, 1497, 1472, 1301, 1218, 1118, 770.

(2-(4-Phenoxybutoxy)ethoxy)benzene (47d)



Following the general procedure, treatment of 2-phenoxyethan-1-ol **45d** (0.069 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded (2-(4-phenoxybutoxy)ethoxy)benzene as a colourless oil **47d** (0.088 g, 62% yield, selectivity determined by GC analysis of crude reaction mixture is 91:09).

***R*f** (Pet. ether /EtOAc = 95/05): 0.33

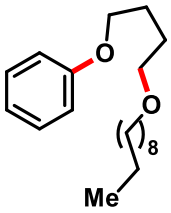
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 4H), 6.98-6.92 (m, 6H), 4.15 (t, *J* = 4.7 Hz, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.83 (t, *J* = 4.8 Hz, 2H), 3.64 (t, *J* = 6.3 Hz, 2H) 1.95-1.88 (m, 2H), 1.87-1.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.11, 158.91, 129.51, 120.93, 120.61, 114.74, 114.57, 71.20, 69.34, 67.55, 67.41, 26.37, 26.17.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{22}O_3Na$: 309.1461, found: 309.1459.

FTIR (cm^{-1}) 3041, 2937, 2869, 1595, 1489, 1382, 1295, 1242, 1166, 1125, 921.

(4-(Decyloxy)butoxy)benzene (47e)



47e

Following the general procedure, treatment of decan-1-ol **45e** (0.079 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99.5/0.5) of the crude reaction mixture using silica gel afforded (4-(decyloxy)butoxy)benzene as a colourless oil **47e** (0.101 g, 66% yield, selectivity determined by GC analysis of crude reaction mixture is 84:16).

***R*f** (Pet. ether /EtOAc = 95/05): 0.50

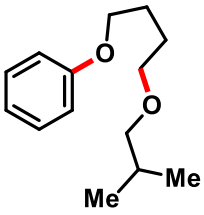
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 6.96-6.89 (m, 3H), 3.99 (t, *J* = 6.4 Hz, 2H), 3.48 (t, *J* = 6.3 Hz, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 1.91-1.84 (m, 2H), 1.80-1.73 (m, 2H), 1.63-1.55 (m, 2H), 1.32-1.28 (m, 14H), 0.90 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.17, 129.49, 120.59, 114.57, 71.14, 70.50, 67.64, 32.03, 29.91, 29.75, 29.71, 29.64, 29.46, 26.49, 26.35, 26.32, 22.81, 14.24.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{20}H_{34}O_2Na$: 329.2451, found: 329.2455.

FTIR (cm^{-1}) 3019, 1721, 1595, 1487, 1381, 1295, 1109, 929, 882, 768.

(4-Isobutoxybutoxy)benzene (47f)



47f

Following the general procedure, treatment of 2-methylpropan-1-ol **45f** (0.037 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded (4-isobutoxybutoxy)benzene as a colourless oil **47f** (0.080 g, 72% yield, selectivity determined by GC analysis of crude reaction mixture is 92:08).

***R*f** (Pet. ether /EtOAc = 95/05): 0.51

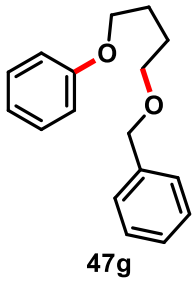
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 6.98-6.92 (m, 3H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 3.32 (d, *J* = 6.8 Hz, 2H), 1.94-1.86 (m, 3H), 1.82-1.76 (m, 2H), 0.95 (d, *J* =6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.20, 129.54, 120.62, 114.62, 78.02, 70.66, 67.72, 28.61, 26.50, 26.34, 19.56.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{14}H_{22}O_2Na$: 245.1512, found: 245.1516.

FTIR (cm^{-1}) 3017, 2957, 2868, 1595, 1487, 1382, 1296, 1219, 1169, 1106.

(4-(Benzyloxy)butoxy)benzene (47g)



Following the general procedure, treatment of phenylmethanol **45g** (0.054 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded (4-(benzyloxy)butoxy)benzene as a colourless oil **47g** (0.091 g, 71% yield, selectivity determined by GC analysis of crude reaction mixture is 94:06).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.45

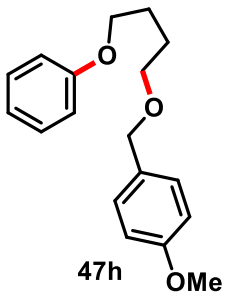
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.38 (m, 4H), 7.33-7.29 (m, 3H), 6.97-6.91 (m, 3H), 4.55 (s, 2H), 4.01 (t, *J* = 5.9 Hz, 2H), 3.58 (t, *J* = 6.3 Hz, 2H), 1.95-1.91 (m, 2H), 1.86-1.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.13, 138.66, 129.52, 128.49, 127.75, 127.65, 120.62, 114.59, 73.02, 70.05, 67.59, 26.49, 26.27.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{20}O_2Na$: 279.1356, found: 279.1354.

FTIR (cm^{-1}) 3018, 2943, 2864, 1595, 1488, 1368, 1296, 1231, 1104, 764.

1-Methoxy-4-((4-phenoxybutoxy)methyl)benzene (47h)



Following the general procedure, treatment of (4-methoxyphenyl) methanol **45h** (0.069 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1-methoxy-4-((4-phenoxybutoxy)methyl)benzene as a colourless oil **47h** (0.099 g, 69% yield, selectivity determined by GC analysis of crude reaction mixture is 90:10).

***R*f** (Pet. ether /EtOAc = 95/05): 0.37

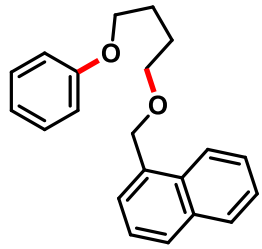
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 4H), 6.98-6.90 (m, 5H), 4.48 (s, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.82 (s, 3H), 3.55 (t, *J* = 6.3 Hz, 2H), 1.95-1.88 (m, 2H), 1.85-1.79 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.22, 159.11, 130.71, 129.48, 129.34, 120.58, 114.56, 113.84, 72.63, 69.69, 67.56, 55.32, 26.44, 26.24.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{22}O_3Na$: 309.1461, found: 309.1473.

FTIR (cm^{-1}) 3017, 1600, 1506, 1298, 1220, 1099, 1039, 767.

1-((4-Phenoxybutoxy)methyl)naphthalene (47i)



47i

Following the general procedure, treatment of naphthalen-1-ylmethanol **45i** (0.079 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1-((4-Phenoxybutoxy) methyl)naphthalene as a colourless oil **47i** (0.105 g, 68% yield, selectivity determined by GC analysis of crude reaction mixture is 91:09).

***R*f** (Pet. ether /EtOAc = 95/05): 0.54

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.63-7.55 (m, 3H), 7.52-7.48 (m, 1H), 7.36-7.32 (m, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.95-6.93 (m, 2H), 5.03 (s, 2H), 4.00 (t, *J* = 6.1 Hz, 2H), 3.69 (t, *J* = 6.1 Hz, 2H), 1.95-1.90 (m, 4H).

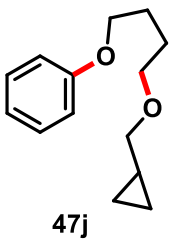
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.10, 134.05, 133.84, 131.82, 129.47, 128.60, 126.40, 126.22, 125.83, 125.29, 124.13, 120.57, 114.55, 71.52, 70.06, 67.50, 26.49, 26.25.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{22}O_2Na$: 329.1512, found: 329.1514.

FTIR (cm^{-1}) 3018, 1595, 1494, 1293, 1169, 1095, 1045, 765.

(4-(Cyclopropylmethoxy)butoxy)benzene (47j)

Following the general procedure, treatment of cyclopropylmethanol **45j** (0.036 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in


47j

THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded (4-(cyclopropylmethoxy)butoxy)benzene as a colourless oil **47j** (0.059 g, 54% yield, selectivity determined by GC analysis of crude reaction mixture is 88:12).

***R*f** (Pet. ether /EtOAc = 95/05): 0.33

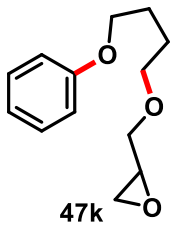
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 6.97-6.91 (m, 3H), 4.02 (t, *J* = 6.1 Hz, 2H), 3.53 (t, *J* = 6.5 Hz, 2H), 3.31 (d, *J* = 7.0 Hz, 2H), 1.92-1.88 (m, 2H), 1.82-1.78 (m, 2H), 1.11-1.07 (m, 1H), 0.58-0.54 (m, 2H), 0.25-0.21 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.15, 129.52, 120.62, 114.60, 75.70, 70.33, 67.65, 26.49, 26.28, 10.78, 3.09.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{14}H_{20}O_2Na$: 243.1356, found: 243.1351.

FTIR (cm^{-1}) 3020, 1596, 1488, 1430, 1217, 1108, 1044, 925, 769, 673.

2-((4-Phenoxybutoxy)methyl)oxirane (47k)


47k

Following the general procedure, treatment of oxiran-2-ylmethanol **45k** (0.033 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2-((4-phenoxybutoxy)methyl)oxirane as a colourless oil **47k** (0.044 g, 40% yield, selectivity determined by GC analysis of crude reaction mixture is 85:15).

***R*f** (Pet. ether /EtOAc = 95/05): 0.15

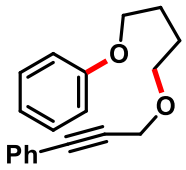
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 6.97-6.91 (m, 3H), 4.01 (t, *J* = 6.2 Hz, 2H), 3.77 (dd, J_1 = 2.8 Hz, J_2 = 11.1 Hz, 1H), 3.63 -3.56 (m, 2H), 3.42 (dd, J_1 = 5.8 Hz, J_2 = 11.5 Hz, 1H) 3.19-3.16 (m, 1H) 2.82 (t, *J* = 4.7 Hz, 1H), 2.65-2.63 (m, 1H), 1.93-1.86 (m, 2H), 1.84-1.77 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.12, 129.54, 120.66, 114.59, 71.59, 71.26, 67.57, 51.0, 44.41, 26.45, 26.16.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{13}H_{18}O_3Na$: 245.1148, found: 245.1145.

FTIR (cm^{-1}) 3019, 2945, 2868, 1656, 1595, 1488, 1462, 1295, 1221, 1088, 923.

(3-(4-Phenoxybutoxy)prop-1-yn-1-yl)benzene (47m)



47m

Following the general procedure, treatment of 3-phenylprop-2-yn-1-ol **45m** (0.066 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded (3-(4-phenoxybutoxy)prop-1-yn-1-yl)benzene as a yellow oil **47m** (0.061 g, 44% yield, selectivity determined by GC analysis of crude reaction mixture is 87:13).

***R*f** (Pet. ether /EtOAc = 95/05): 0.36

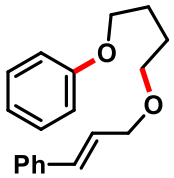
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.48 (m, 2H), 7.36-7.31 (m, 5H), 6.99-6.93 (m, 3H), 4.42 (s, 2H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.71 (t, *J* = 6.5 Hz, 2H), 1.97-1.92 (m, 2H), 1.90-1.86 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.12, 131.87, 129.52, 128.51, 128.39, 122.79, 120.63, 114.60, 86.17, 85.45, 69.78, 67.49, 58.93, 26.33, 26.18.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{20}O_2Na$: 303.1356, found: 303.1348.

FTIR (cm^{-1}) 3020, 2946, 2872, 1596, 1489, 1437, 1358, 1091, 928, 767.

(4-(Cinnamyloxy)butoxy)benzene (47n)



47n

Following the general procedure, treatment of (E)-3-phenylprop-2-en-1-ol **45n** (0.067 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded (4-(cinnamyloxy)butoxy)benzene as a yellow oil **47n** (0.075 g, 53% yield, selectivity determined by GC analysis of crude reaction mixture is 91:09).

***R*f** (Pet. ether /EtOAc = 95/05): 0.36

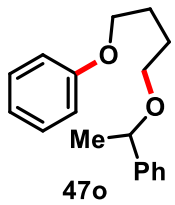
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.38-7.26 (m, 6H), 6.99-6.93 (m, 2H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.38-6.31 (m, 1H), 4.20 (d, *J* = 5.9 Hz, 2H), 4.04 (t, *J* = 6.2 Hz, 2H), 3.60 (t, *J* = 6.6 Hz, 2H), 1.98-1.91 (m, 2H), 1.89-1.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.15, 136.86, 132.33, 129.54, 128.66, 127.75, 126.60, 126.41, 120.64, 114.61, 71.56, 70.09, 67.62, 26.53, 26.30.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{22}O_2Na$: 305.1512, found: 305.1516.

FTIR (cm^{-1}) 3018, 2943, 2864, 1723, 1595, 1488, 1365, 1295, 1229, 971.

(1-(4-Phenoxybutoxy)ethyl)benzene (47o)



47o

Following the general procedure, treatment of 1-phenylethan-1-ol **45o** (0.061 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded (1-(4-phenoxybutoxy)ethyl)benzene as a colourless oil **47o** (0.099 g, 73% yield, selectivity determined by GC analysis of crude reaction mixture is 98:02).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.45

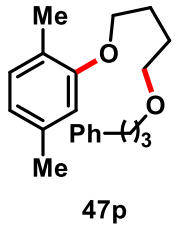
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.32 (m, 7H), 7.01-6.93 (m, 3H), 4.48 (q, *J* = 6.4 Hz, 1H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.44 (t, *J* = 6.3 Hz, 2H), 1.97-1.90 (m, 2H), 1.88-1.76 (m, 2H), 1.53 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.13, 144.23, 129.49, 128.50, 127.45, 126.23, 120.58, 114.57, 78.09, 68.27, 67.61, 26.61, 26.28, 24.27.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{22}O_2Na$: 293.1512, found: 293.1516.

FTIR (cm^{-1}) 3018, 2941, 2871, 1595, 1487, 1218, 1105, 764.

1,4-Dimethyl-2-(4-(3-phenylpropoxy)butoxy)benzene (47p)



47p

Following the general procedure, treatment of 3-phenylpropan-1-ol **45a** (0.068 g, 0.5 mmol) with 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6b** (0.245 g, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1,4-dimethyl-2-(4-(3-phenylpropoxy)butoxy)benzene as a colourless oil **47p** (0.096 g, 62% yield, selectivity determined by GC analysis of crude reaction mixture is 89:11).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.63

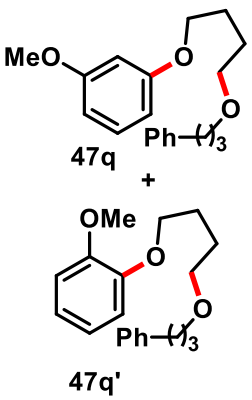
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.23-7.19 (m, 3H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.70-6.66 (m, 2H), 4.00 (t, *J* = 6.2 Hz, 2H), 3.52 (t, *J* = 6.4 Hz, 2H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.34 (s, 3H), 2.21 (s, 3H), 1.97-1.88 (m, 4H), 1.85-1.78 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.15, 142.16, 136.58, 130.41, 128.60, 128.43, 125.87, 123.73, 120.75, 112.07, 70.64, 70.09, 67.65, 32.52, 31.47, 26.63, 26.44, 21.54, 15.95.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{28}O_2Na$: 335.1982, found: 335.1964.

FTIR (cm^{-1}) 3017, 1877, 1722, 1599, 1455, 1380, 1259, 1117, 1040, 928, 848, 766.

1-Methoxy-3-(4-(3-phenylpropoxy)butoxy)benzene (47q) and 1-Methoxy-2-(4-(3-phenyl propoxy)butoxy)benzene (47q')



Following the general procedure, treatment of 3-phenylpropan-1-ol **45a** (0.034 g, 0.25 mmol) with 2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **6c** (0.123 g, 0.375 mmol) in the presence of KF (0.044 g, 0.75 mmol) and 18-crown-6 (0.198 g, 0.75 mmol) in THF (2.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/02) of the crude reaction mixture using silica gel afforded region isomeric mixture of 1-methoxy-3-(4-(3-phenylpropoxy)butoxy)benzene **47q** and 1-methoxy-2-(4-(3-phenylpropoxy) butoxy)benzene **47q'** oil (0.040 g, 51% yield, selectivity and regioisomeric ratio determined by GC analysis of crude reaction mixture is 56:44 and 4.5:1).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.47

^{1}H NMR (400 MHz, $CDCl_3$) of major isomer δ 7.33-7.28 (m, 2H), 7.23-7.18 (m, 4H), 6.54-6.49 (m, 3H), 4.02-3.99 (m, 2H), 3.81 (s, 3H), 3.52-3.45 (m, 4H), 2.72 (t, *J* = 7.5 Hz, 2H), 1.96-1.87 (m, 4H), 1.82-1.77 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) of major isomer δ 160.95, 142.16, 129.97, 128.44, 106.82, 106.28, 70.56, 70.12, 67.80, 55.39, 31.47, 26.51, 26.14.

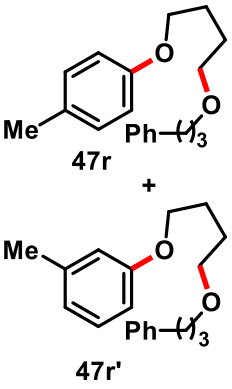
^{1}H NMR (400 MHz, $CDCl_3$) of minor isomer δ 4.05-4.03 (m), 2.01-1.98 (m).

^{13}C NMR (100 MHz, $CDCl_3$) of minor isomer δ 160.46, 128.61, 125.88, 106.38, 101.08, 67.57, 32.52, 26.30.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{20}H_{26}O_3Na$: 337.1774, found: 337.1760.

FTIR (cm^{-1}) 3021, 1599, 1525, 1485, 1214, 1156, 1044, 926, 775.

1-Methyl-4-(4-(3-phenylpropoxy)butoxy)benzene (47r) and 1-Methyl-3-(4-(3-phenyl propoxy)butoxy)benzene (47r')



Following the general procedure, treatment of 3-phenylpropan-1-ol **45a** (0.068 g, 0.5 mmol) with 4-methyl-2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6d** (0.234 g, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1-methyl-4-(4-(3-phenylpropoxy)butoxy) benzene **47r** and 1-methyl-3-(4-(3-phenyl propoxy)butoxy) benzene **47r'** as a colourless oil (0.078 g, 52% yield, selectivity and regioisomeric ratio determined by GC analysis of crude reaction mixture is 91:9 and 1.2:1).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.36

^{1}H NMR (400 MHz, CDCl$_3$) OF major isomer δ 7.37-7.33 (m, 2H), 7.28-7.21 (m, 4H), 7.15-7.13 (m, 1H), 6.88-6.77 (m, 2H), 4.06-4.01 (m, 2H), 3.56-3.49 (m, 4H), 2.77 (t, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 1.99-1.92 (m, 4H), 1.86-1.80 (m, 2H).

^{1}H NMR (400 MHz, CDCl$_3$) OF minor isomer δ 4.06-4.01 (m, 2H), 2.35 (s, 3H).

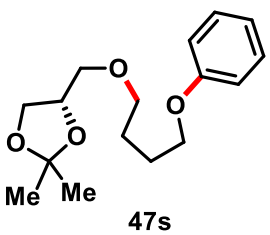
^{13}C NMR (100 MHz, CDCl$_3$) of major isomer δ 159.17, 142.12, 129.95, 128.58, 125.85, 115.45, 111.45, 70.55, 67.80, 67.58, 32.48, 31.44, 26.33, 21.63).

^{13}C NMR (100 MHz, CDCl$_3$) of minor isomer δ 157.03, 139.50, 129.78, 129.26, 128.41, 121.46, 114.45, 70.05, 26.49, 20.56.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{20}H_{26}O_2Na$: 321.1825, found: 321.1808.

FTIR (cm^{-1}) 3016, 1597, 1379, 1221, 1164, 1047, 923, 816, 767.

(S)-2,2-Dimethyl-4-((4-phenoxybutoxy)methyl)-1,3-dioxolane (47s)



Following the general procedure, treatment of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol **45s** (0.066 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 94/06) of the crude

reaction mixture using silica gel afforded (S)-2,2-dimethyl-4-((4-phenoxybutoxy)methyl)-1,3-dioxolane as a colourless oil **47s** (0.075 g, 54% yield, selectivity determined by GC analysis of crude reaction mixture is 93:07).

***R*f** (Pet. ether /EtOAc = 90/10): 0.33

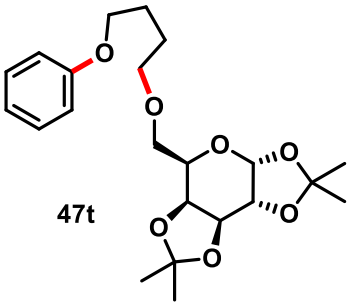
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 6.97-6.90 (m, 3H), 4.32-4.26 (m, 1H), 4.09-4.06 (m, 1H), 4.0 (t, *J* = 6.1 Hz, 2H), 3.77-3.73 (m, 1H), 3.62-3.52 (m, 3H), 3.49-3.45 (m, 1H), 1.92-1.85 (m, 2H), 1.83-1.76 (m, 2H), 1.45 (s, 3H), 1.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.05, 129.47, 120.59, 114.51, 109.44, 74.80, 71.91, 71.36, 67.49, 66.89, 26.84, 26.27, 26.10, 25.49.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{16}H_{24}O_4Na$: 303.1567, found: 303.1568.

FTIR (cm^{-1}) 3055, 1597, 1487, 1380, 1261, 1085, 911, 843, 741.

(3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyl-5-((4-phenoxybutoxy)methyl)tetrahydro-5H- bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (47t)



Following the general procedure, treatment of galactose **45t** (0.130 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded (3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyl-5-((4-phenoxybutoxy)methyl)tetrahydro-5*H*- bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran as a colourless oil **47t** (0.105 g, 51% yield, selectivity determined by GC analysis of crude reaction mixture is 93:07).

***R*f** (Pet. ether /EtOAc = 90/10): 0.37

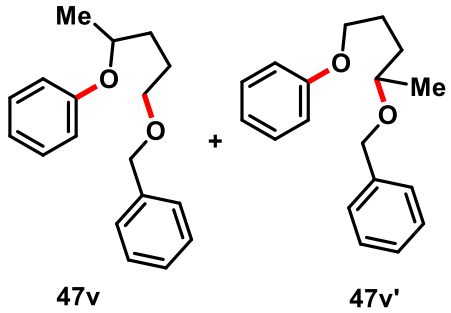
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 6.95-6.89 (m, 3H), 5.56 (d, *J* = 5.1 Hz, 1H), 4.62 (dd, J_1 = 2.2 Hz, J_2 = 7.8 Hz, 1H), 4.33-4.24 (m, 2H), 4.01-3.96 (m, 3H), 3.65-3.54 (m, 4H), 1.89-1.76 (m, 4H), 1.54 (s, 3H), 1.46 (s, 3H), 1.34 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.17, 129.51, 120.59, 114.61, 109.35, 108.66, 96.50, 71.35, 71.15, 70.77, 70.71, 69.57, 67.64, 66.89, 26.33, 26.20, 26.11, 25.06, 24.56.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{22}H_{32}O_7Na$: 431.2040, found: 431.2038.

FTIR (cm^{-1}) 2997, 1595, 1488, 1380, 1298, 1247, 1217, 1169, 891, 680.

((5-(Benzyloxy)pentan-2-yl)oxy)benzene (47v) and ((4-(Benzyloxy)pentyl)oxy)benzene (47v')



47v 47v'

Following the general procedure, treatment of phenylmethanol **45g** (0.054 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in 2-methyltetrahydrofuran (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded ((5-(benzyloxy)pentan-2-yl)oxy)benzene **47v** and ((4-(benzyloxy)pentyl)oxy)benzene **47v'** as a colourless oil (0.086 g, 64% yield, selectivity and regio isomeric ratio determined by GC analysis of crude reaction mixture is 92:08 and 2.5:1).

***R*f** (Pet. ether /EtOAc = 95/05): 0.45

^{1}H NMR of major isomer (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 5H), 7.35-7.29 (m, 2H), 7.0-6.92 (m, 3H), 4.55 (s, 2H), 4.66-4.40 (m, 1H), 3.56 (t, *J* = 5.8 Hz, 2H), 1.85-1.75 (m, 4H), 1.36 (d, *J* = 6.0Hz, 3H).

^{1}H NMR of minor isomer (400 MHz, $CDCl_3$) δ 4.04-3.96 (m), 3.67-3.63 (m), 1.99-1.95 (m), 1.30 (d, *J* = 6.0Hz).

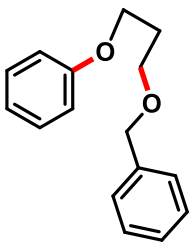
^{13}C NMR of major isomer (100 MHz, $CDCl_3$) δ 158.29, 138.71, 129.57, 127.79, 127.64, 120.62, 116.0, 74.60, 73.01, 70.30, 33.30, 25.94, 19.89.

^{13}C NMR of minor isomer (100 MHz, $CDCl_3$) δ 159.20, 139.12, 128.48, 127.76, 127.55, 116.05, 114.65, 73.60, 70.49, 67.93, 33.25, 25.53, 19.76.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{22}O_2Na$: 293.1512, found: 293.1511.

FTIR (cm^{-1}) 3022, 1643, 1524, 1427, 1216, 1039, 928, 774, 673.

(3-(Benzyloxy)propoxy)benzene (47w)



47w

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.149 g, 121 µL, 0.5 mmol) with Oxetane and benzyl alcohol **45g** (1.0 mL, 0.5 mL each) in presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of

the crude reaction mixture using silica gel afforded (3-(benzyloxy)propoxy)benzene as a colourless oil **47w** (0.029 g, 24% yield, NMR yield 29% determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard.

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.45

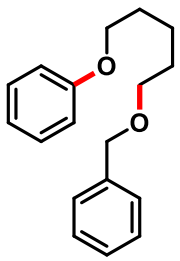
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 7H), 6.99-6.92 (m, 3H), 4.56 (s, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 3.70 (t, *J* = 6.2 Hz, 2H), 2.13 (p, *J* = 6.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.10, 138.53, 129.55, 128.52, 127.77, 127.72, 120.72, 114.65, 73.19, 67.01, 64.84, 29.90.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{16}H_{18}O_2Na$: 265.1199, found: 265.1199.

FTIR (cm^{-1}) 3022, 1817, 1717, 1595, 1491, 1460, 1376, 1171, 922.

((5-(Benzyloxy)pentyl)oxy)benzene (47x)


47x

Following the general procedure, treatment of phenylmethanol **45g** (0.054 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in tetrahydro-2*H*-pyran (4.0 mL) at 80 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded ((5-(benzyloxy)pentyl)oxy) benzene as a colourless oil **47x** (0.062 g, 46% yield, NMR yield 48% determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as the internal standard, selectivity determined by GC analysis of crude reaction mixture is 83:17).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.45

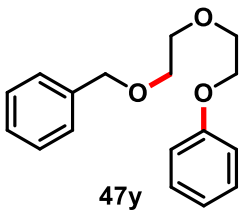
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 7H), 6.98-6.92 (m, 3H), 4.55 (s, 2H), 3.99 (t, *J* = 6.3 Hz, 2H), 3.54 (t, *J* = 6.3 Hz, 2H), 1.86-1.81 (m, 2H), 1.75-1.72 (m, 2H), 1.62-1.60 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.14, 138.68, 129.51, 128.47, 127.74, 127.62, 120.58, 114.55, 73.03, 70.33, 67.74, 29.63, 29.21, 22.91.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{22}O_2Na$: 293.1512, found: 293.1508.

FTIR (cm^{-1}) 3018, 2940, 2864, 1595, 1487, 1222, 1095, 1037, 769.

(2-(2-(Benzyloxy)ethoxy)ethoxy)benzene (47y)



Following the general procedure, treatment of phenylmethanol **45g** (0.054 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in 1,4-dioxane (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded (2-(2-(benzyloxy)ethoxy)ethoxy)benzene as a colourless oil **47y** (0.050 g, 37% yield, selectivity determined by GC analysis of crude reaction mixture is 70:30).

***R*f** (Pet. ether /EtOAc = 95/05): 0.13

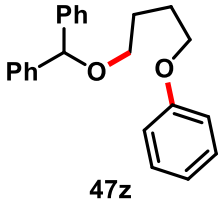
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 7H), 6.99-6.95 (m, 3H), 4.62 (s, 2H), 4.18 (t, *J* = 4.5 Hz, 2H), 3.91 (t, *J* = 5.1 Hz, 2H), 3.81-3.78 (m, 2H), 3.72-3.69 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.86, 138.31, 129.51, 128.47, 127.87, 127.71, 120.94, 114.73, 73.39, 70.98, 69.89, 69.56, 67.41.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{20}O_3Na$: 295.1305, found: 295.1313.

FTIR (cm^{-1}) 3017, 2925, 2873, 1595, 1491, 1458, 1359, 1294, 1220, 928.

((4-Phenoxybutoxy)methylene)dibenzene (47z)



Following the general procedure, treatment of diphenylmethanol **45z** (0.092 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 µL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded ((4-phenoxybutoxy)methylene)dibenzene as a white crystalline solid **47z** (0.108 g, 65% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

***R*f** (Pet. ether /EtOAc = 95/05): 0.39; mp 61 – 63 °C.

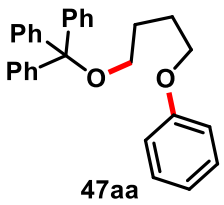
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 12H), 6.98-6.90 (m, 3H), 5.39 (s, 1H), 4.01 (t, *J* = 6.3 Hz, 2H), 3.56 (t, *J* = 6.3 Hz, 2H), 2.0-1.93 (m, 2H), 1.90-1.83 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.15, 142.62, 129.53, 128.50, 127.50, 127.06, 120.63, 114.61, 83.78, 68.78, 67.67, 26.60, 26.41.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{23}H_{24}O_2Na$: 355.1669, found: 355.1651.

FTIR (cm^{-1}) 3019, 2945, 2868, 1656, 1595, 1488, 1462, 1295, 1221, 1088, 923.

((4-Phenoxybutoxy)methanetriyl)tribenzene (47aa)



47aa

Following the general procedure, treatment of triphenylmethanol **45aa** (0.130 g, 0.5 mmol) with 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **6a** (0.224 g, 182 μL, 0.75 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (4.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded ((4-phenoxybutoxy)methanetriyl)tribenzene as a white crystalline solid **47aa** (0.131 g, 64% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.46; mp 110 – 112 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51-7.49 (m, 6H), 7.35-7.25 (m, 11H), 6.99-6.90 (m, 3H), 3.98 (t, *J* = 6.6 Hz, 2H), 3.19 (t, *J* = 6.3 Hz, 2H), 1.98-1.91 (m, 2H), 1.87-1.80 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 159.16, 144.52, 129.52, 128.82, 127.87, 127.0, 120.62, 114.64, 86.54, 67.75, 63.27, 26.74, 26.45.

HRMS (ESI) calculated $[M+H]^+$ for $C_{29}H_{29}O_2$: 409.2162, found: 409.2162.

FTIR (cm^{-1}) 3020, 2935, 1596, 1487, 1217, 1041, 761, 667.

3.9. References

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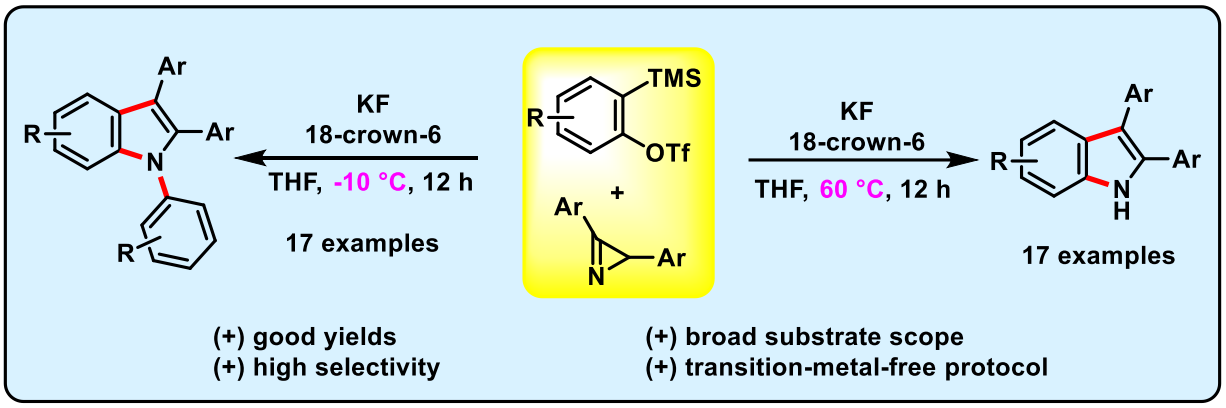
Chapter 4

Selective Synthesis of *N*-Unsubstituted and *N*-Aryl Indoles by the Reaction of Arynes with Azirines

The transition-metal-free and temperature dependent highly selective reaction of arynes with 2*H*-azirines allowing the synthesis of either *N*-unsubstituted or *N*-aryl indoles has been discussed in this chapter. At 60 °C, arynes generated from 2-(trimethylsilyl)aryl triflates smoothly insert into 2*H*-azirines to form 2,3-diaryl indoles with high selectivity. Interestingly, when the reaction was performed at -10 °C, the selectivity was switched to the formation of 1,2,3-triaryl indoles in good yields.



J. Org. Chem. **2016**, *81*, 8604−8611.

4.1. Introduction

The indole ring system is the most widely distributed heterocycle found in nature. Since indole was first isolated by treatment of indigo dye with oleum, the name indole is a combination of the words indigo and oleum. First reported in 1883, the Fischer reaction remains the pre-eminent method for the synthesis of indoles.[1] Among the numerous structurally diverse derivatives, many indoles show significant biological activity such as serotin, mytomycin C, sumitraptan etc. Hence, it is not surprising that this structural motif is also an important component in many of today's pharmaceuticals (Fig. 4.1).

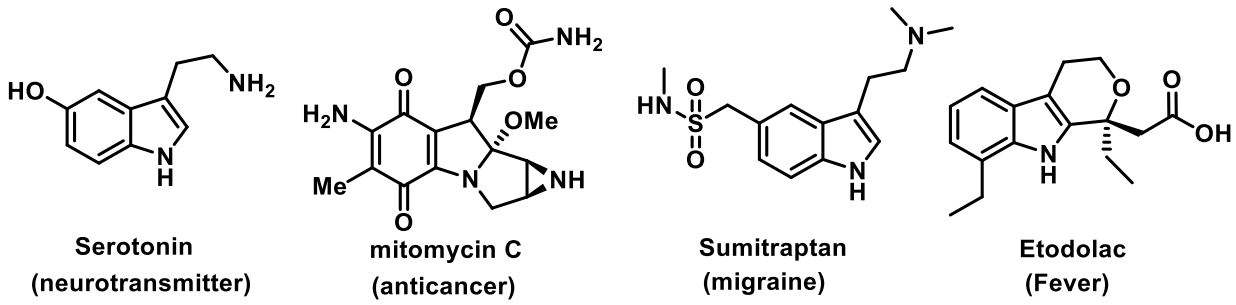


Fig 4.1: Selected Examples of Biologically Active Indoles

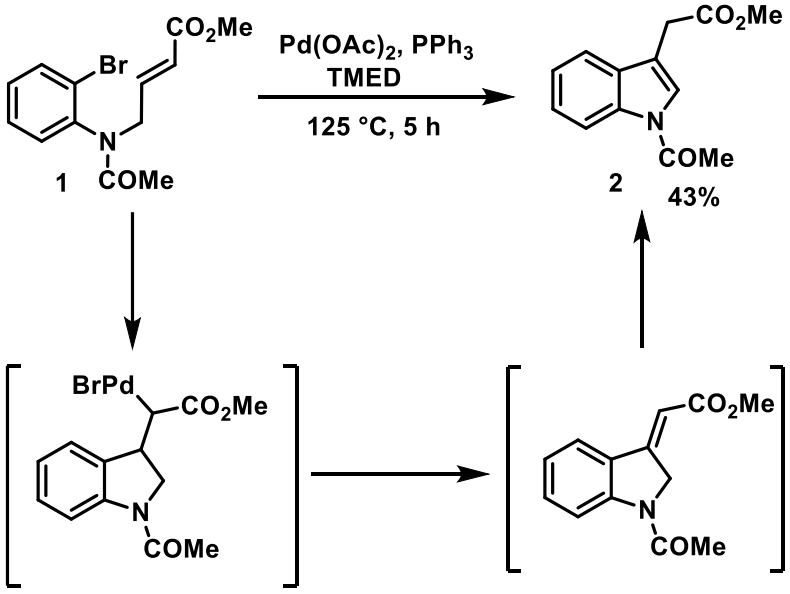
The development of practical methods towards indole synthesis has been a central theme in organic synthesis over the last century. Because of their importance.[2] However, there are still limitations on the chemical space which is easily accessible; this can be readily observed by comparison of the naturally occurring indole drugs with their synthetic counterparts. Unusual and complex molecular architectures occur among their natural derivatives. This important ring system continues to attract attention from the international chemical community.

The present chapter describes an efficient and facile transition-metal-free synthesis of indole using arynes as the aryl source. Before going into the details, a brief summary of the methods for the synthesis of indoles with special emphasis on the transition-metal-catalyzed and transition-metal-free approach for the construction of indole is outlined in the following sections.

4.2. Methods for the Synthesis of Indoles

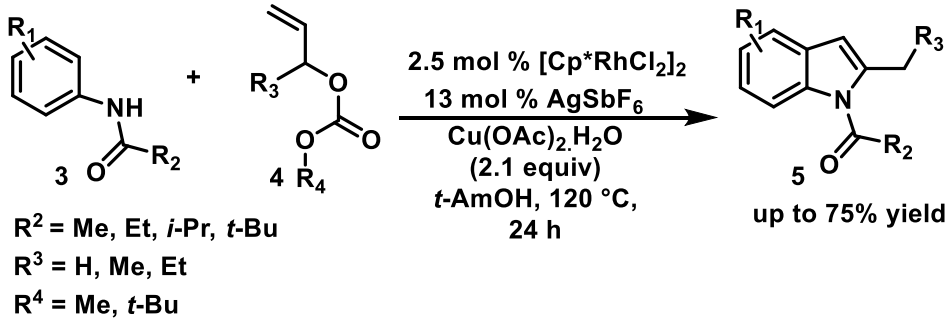
4.2.1. Transition Metal-Catalysed Indole Synthesis

Of the many methods developed in recent years for the synthesis of indoles, many have involved the use of transition-metal catalysis. The first synthesis of indoles based on the intramolecular Heck reaction was described by Mori and co-workers in 1977 (Scheme 4.1).[3] In this method, indole derivatives **2** were synthesised from *o*-halo-*N*-allylanilides **1** containing the side-chain olefin conjugated to a carbonyl group.



Scheme 4.1: Cyclization of Alkenes via Intramolecular Heck Reaction

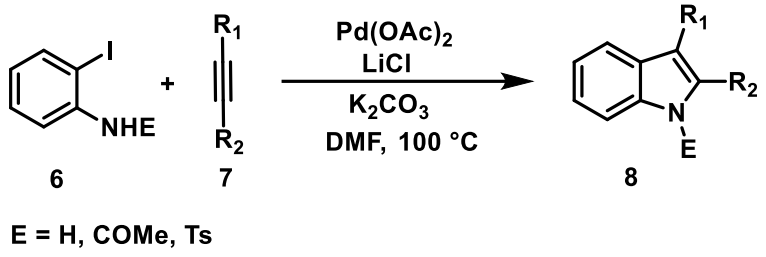
Later, Saa and co-workers developed the Rh(III)-catalyzed tandem C-H allylation and oxidative cyclization of anilides **3** with allyl carbonates **4** in the presence of a slight excess of $AgSbF_6$ salt and $Cu(OAc)_2$ as oxidant resulting in the formation of the bioactive



Scheme 4.2: Rhodium-Catalyzed Cyclization of Anilide with Allyl Carbonate

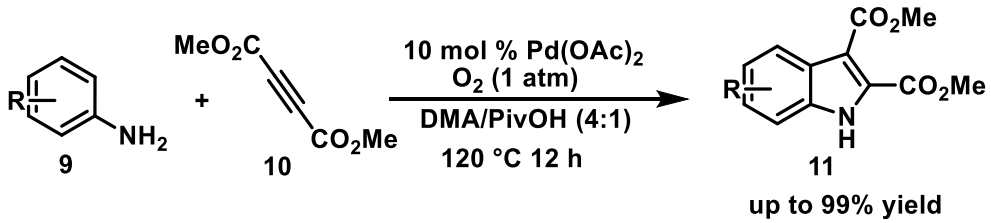
2-methyl indole **5** (Scheme 4.2).[4] This reaction works well for the wide range of functional groups on the anilide substrate.

In 1991, Larock and co-workers reported the palladium-catalyzed coupling of 2-iodoaniline containing *N*-methyl, -acetyl, and -tosyl moieties **6** with a variety of internal alkynes **7** leading to the formation of 2,3-disubstituted indoles **8** in good to excellent yields (Scheme 4.3).[5] The best results were obtained by employing an excess of alkyne and a sodium or potassium acetate or carbonate base along with 1 equiv of either lithium chloride or tetrabutylammonium chloride, occasionally adding 5 mol % triphenylphosphine. The yields with lithium chloride appear to be good and more reproducible than those obtained with tetrabutylammonium chloride. The process is quite general and works well for variety of substituents on the nitrogen of aniline and two ends of the alkyne triple bond.



Scheme 4.3: Cyclization of Alkynes with 2-Iodoanilines

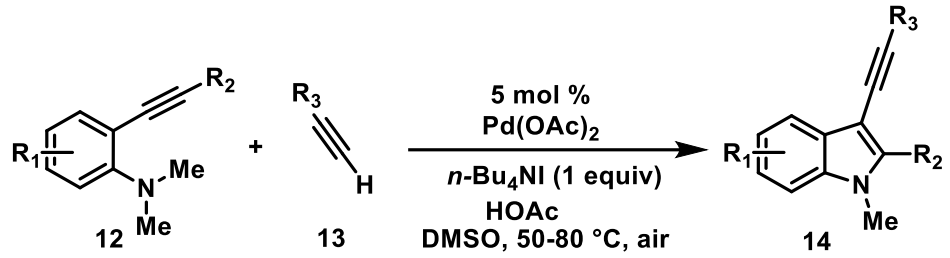
Jiao and co-workers discovered a unique and direct approach for the synthesis of indoles **11** from simple and readily available anilines **9** and alkynes **10** by C-H bond activation. Oxygen (1 atm) is used as the oxidant for this transforation. In this method, both *N*-unsubstituted and *N*-alkyl mono substituted anilines are tolerated under the present reaction condition and can be efficiently transformed into the corresponding indoles (Scheme 4.4).[6] These reaction conditions are mild and do not require any ligand or base.



Scheme 4.4: Palladium Catalyzed Annulations of Anilines with Alkynes

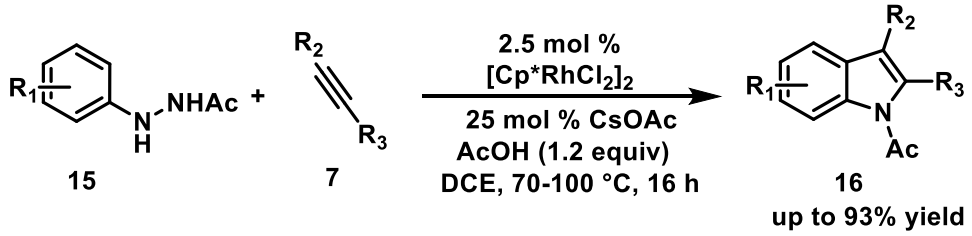
Zhu and co-workers demonstrated the efficient palladium-catalyzed coupling of *O*-alkynylanilines **12** with terminal alkynes **13** or alkenes gave 3-alkynyl- or 3-alkenylindoles

14 (Scheme 4.5).[7] This domino reaction displayed broad substrate scope, good functional group tolerance, and high synthetic efficiency.



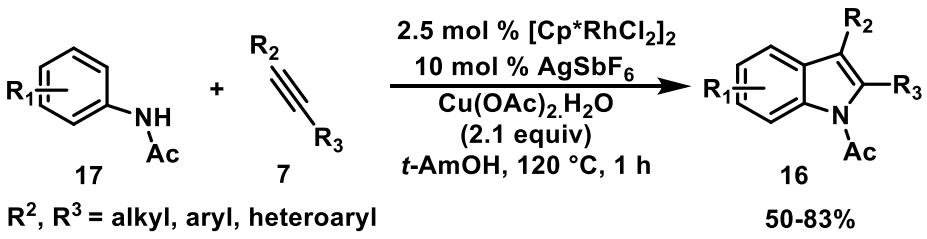
Scheme 4.5: Cyclization of *o*-Alkynylanilines with Terminal Alkyne

Mild and efficient rhodium(III)-catalyzed synthesis of *N*-acylindole **16** by the reaction of 2-acetyl-1-arylhydrazines **15** with alkynes **7** is developed by Glorius and co-workers. The reaction did not require any external oxidant, and because of the cleavage of the N-N bond, the directing group was traceless in the product (Scheme 4.6).[8] In addition, this reaction protocol was highly regioselective in case of unsymmetrical internal alkynes. Starting from similar hydrazine substrates, this method provides an alternative to the Fischer indole synthesis.



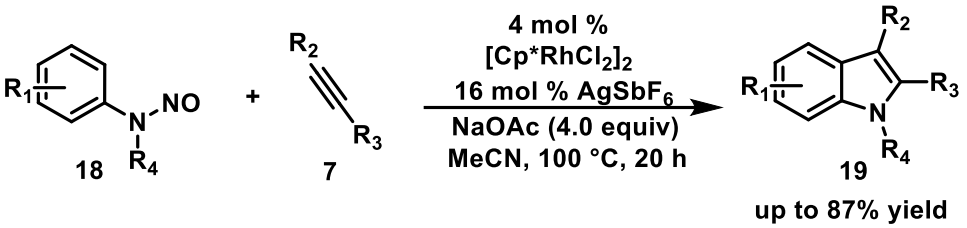
Scheme 4.6: Rhodium Catalysed Annulations of Arylhydrazines with Alkynes

Fagnou and co-workers reported indole synthesis via rhodium-catalyzed oxidative coupling of acetanilides **17** and internal alkynes **7** (Scheme 4.7).[9] With $[Cp^*Rh(MeCN)_3][SbF_6]$ as the precatalyst under atmospheric oxygen the same reactions could be conducted at 60 °C to achieve up to 90% yield for the target indole products **16**.



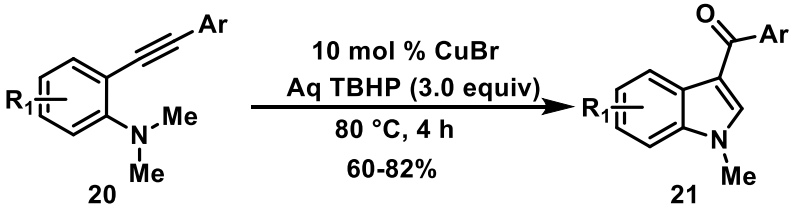
Scheme 4.7: Indole Synthesis via Cyclization of Alkyne and Aniline

Recently, the Zhu group revealed a Rh(III)-catalyzed cyclization of *N*-nitrosoanilines **18** with alkynes **7** to give indoles **19** in the absence of an external oxidant (Scheme 4.8).[10] The N−N bond based internal oxidant approach offers a valuable complement to the thus far exclusively used N−O variant for the synthesis of azaheterocycles.



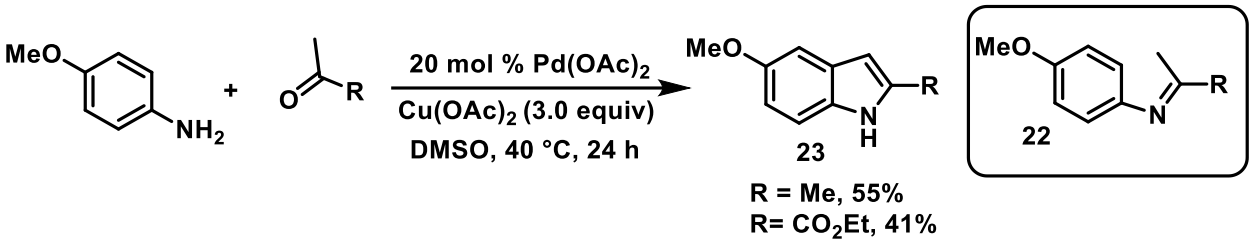
Scheme 4.8: Rhodium Catalysed Annulations of *N*-Nitrosoanilines with Alkynes

Subsequently, Patel and co-workers developed an efficient Cu(I)-catalyzed synthesis of 3-aroylindoles **21** from *O*-alkynylated *N,N*-dimethylamines **20** via a sp^3 C-H bond activation R_1 to the nitrogen atom followed by an intramolecular nucleophilic attack with the alkyne using an aqueous solution of *tert*-butyl hydroperoxide (TBHP) as the oxidant. In this tandem catalytic synthesis of 3-aroylindoles, both C-C and C-O bonds are installed at the expense of two sp^3 C-H bond cleavages (Scheme 4.9).[11]



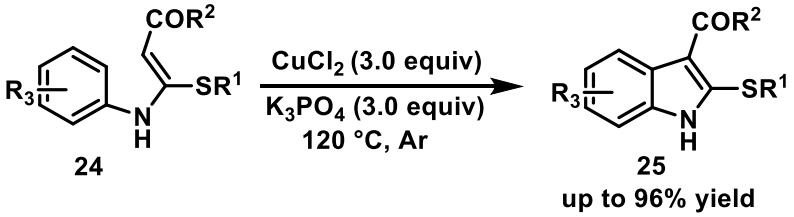
Scheme 4.9: Copper-Catalyzed Oxidative Cyclization of *o*-Alkynylated *N,N*-Dimethylamines

An operationally simple, palladium-catalyzed cyclization reaction of in situ generated *N*-aryl imines **22**, resulting in the formation of indoles **23** via the oxidative linkage of two C−H bonds under mild conditions using molecular oxygen as the sole oxidant has been revealed by Yoshikai and co-workers (Scheme 4.10).[12] The process allows quick and atom-economical assembly of indole rings from inexpensive and readily available anilines and ketones and tolerates a broad range of functional groups.



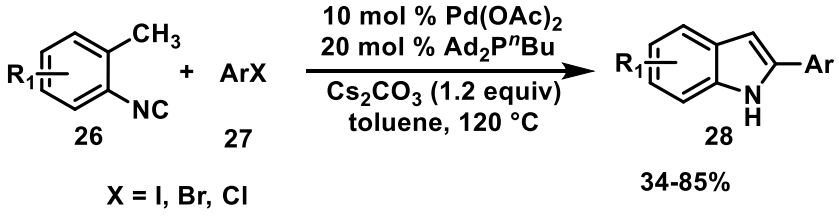
Scheme 4.10: Cyclization of In situ Generated Enamine

Copper-mediated intramolecular oxidative C−H/C−H cross-coupling of α-oxo ketene *N*,*S*-acetals **24** has been documented by Yu and co-workers for the synthesis of indoles **25**. Readily tunable C-S bond transformation of the resultant products renders the present method a promising alternative route to access highly functionalized indole derivatives (Scheme 4.11).[13]



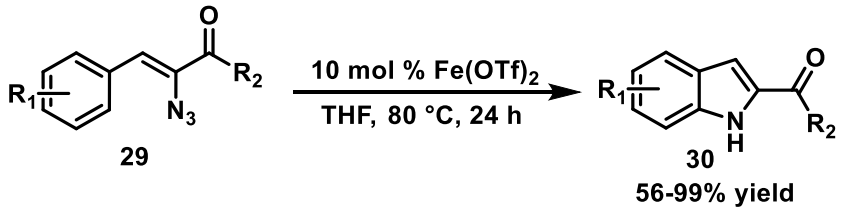
Scheme 4.11: Copper Mediated Cyclization of Alkene

Takemoto and co-workers achieved the synthesis of indole skeleton **28** using a Pd-catalyzed cascade process consisting of isocyanide insertion and benzylic C(sp^3)-H activation of substrates **26** and **27** (Scheme 4.17).[14] In this reaction, slow addition of isocyanide is effective for reducing the amount of catalyst needed, and bulky phosphine ligand is necessary for the reaction to smoothly proceed. The construction of the tetracyclic carbazole skeleton was also achieved by a Pd-catalyzed domino reaction incorporating alkyne insertion.



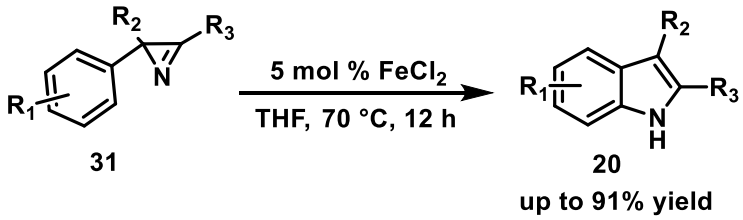
Scheme 4.12: Palladium-Catalysed Cyclization of Isocyanides

Bolm and co-workers reported a practical iron-catalyzed intramolecular C-H amination reaction of azidoacrylates **29** and their application in the synthesis of indole derivatives **30** (Scheme 4.13).[15] The reaction scope is quite broad and afforded the corresponding product in good to excellent yields. Commercially available iron(II) triflate was used as a catalyst.



Scheme 4.13: Iron-Catalyzed Cyclization of Alkenyl Azides

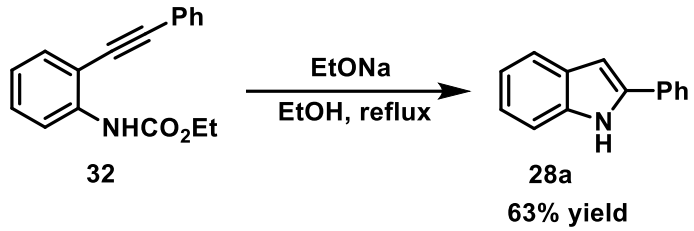
Zheng and co-workers developed a general method for the synthesis of 2,3-disubstituted indoles **20**.[16] Amination of aromatic C-H bonds via $FeCl_2$-catalyzed ring opening of 2*H*-azirines **31** is the key feature of this method. The method tolerates a wide variety of functional groups. The method can also be extended to the synthesis of azaindoles.



Scheme 4.14: Iron Catalyzed Cyclization of Azirines

4.2.2. Transition-Metal Free Method for the Synthesis of Indole

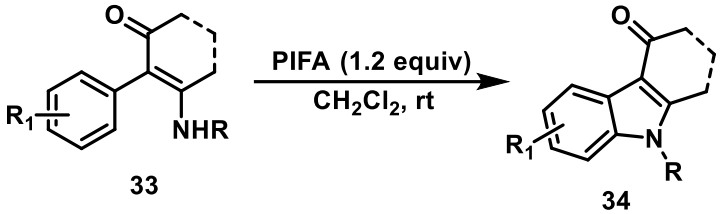
Yamaka and co-workers revealed a base-mediated method for the synthesis of indoles. Treatment of crude *o*-(phenylethynyl)-N-ethoxycarbonylanilide **32** with a strong base such as sodium ethoxide was found to give 2-phenylindole **28a** in good overall yield, demonstrating that the cyclization of *o*-alkynylanilides can be performed through base-mediated reactions as well (Scheme 4.15).[17]



32 28a 63% yield

Scheme 4.15: Base Mediated Cyclization of *o*-Alkynylanilides

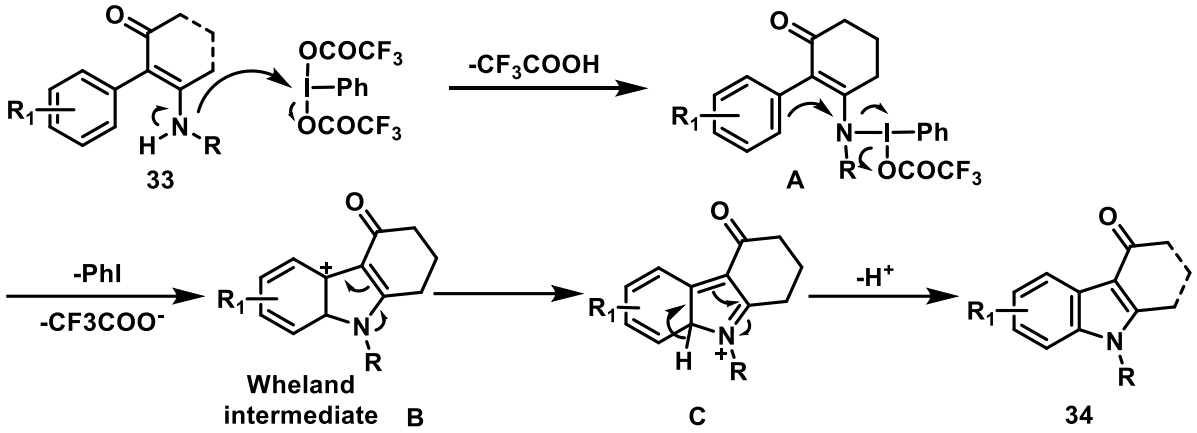
Zhao and co-workers developed a methodology to synthesis 3-acetylindoles **34** via metal-free oxidative aromatic C–N bond formation through bis(trifluoroacetoxy)iodobenzene mediated annulation of 2-aryl enaminones **33** (Scheme 4.16).[18] This method allows the nitrogen moiety on the side-chain to be annulated with the benzene ring.



33 34 17 examples 64-90% yield

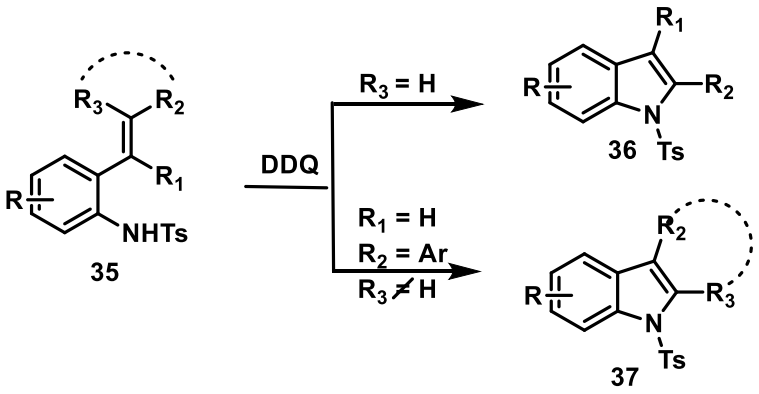
Scheme 4.16: Hypervalent Iodine Mediated C-N Bond Formation

A plausible reaction mechanism is proposed in Scheme 4.17. Intermolecular reaction of enaminone **33** and PIFA results in the formation of *N*-iodo intermediate **A** by losing one molecule of trifluoroacetic acid. Next, electrophilic attack of the *N*-center on the phenyl ring in a concerted fashion leading to the formation of Wheland intermediate **B**. Ca rbocation **B** can be stabilized by the lone pair on nitrogen through conjugation to give the iminium salt **C**. Finally, the rapid elimination of a proton from **C** regenerates the aromatic system of the phenyl ring to afford the title indole **34**.



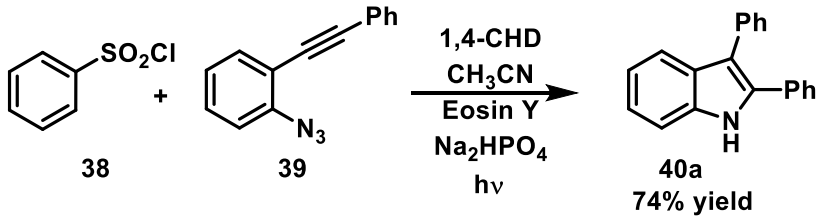
Scheme 4.17: Possible Mechanism for PIFA-Mediated Cyclization

An effective metal-free C-H amination of *N*-Ts-2-alkenylanilines **35** by using DDQ as an oxidant resulting in the formation of the corresponding substituted indoles (**36, 37)** has been reported by Youn and co-workers (Scheme 4.18).[19] This procedure is operationally simple and robust, obviates the need of expensive transition-metal catalysts, and offers a broad substrate scope. A mechanism involving a radical cation generated by SET and a migratorial process via a phenonium ion intermediate was proposed by the author.



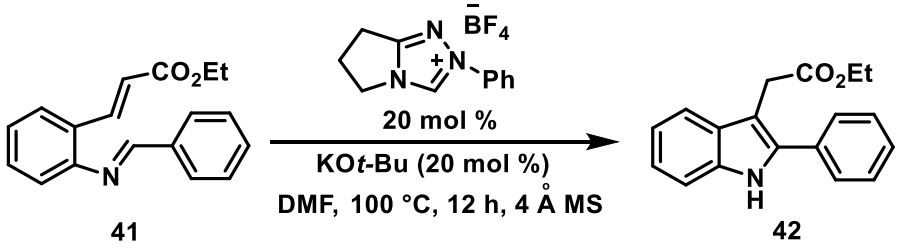
Scheme 4.18: Indole Synthesis from 2-Alkenylanilines

Gu and co-workers demonstrated the room temperature, visible-light-catalyzed synthesis of unsymmetrical 2,3-disubstituted indoles **40a** from arylsulfonyl chlorides **38** and *o*-azidoarylalkynes **39**. This reaction exhibits excellent substrate scope and functional group tolerance. The use of inexpensive catalyst eosin Y and easy operation makes this protocol very practical (Scheme 4.19).[20]



Scheme 4.19: Synthesis of 2,3-Diaryl Substituted Indoles

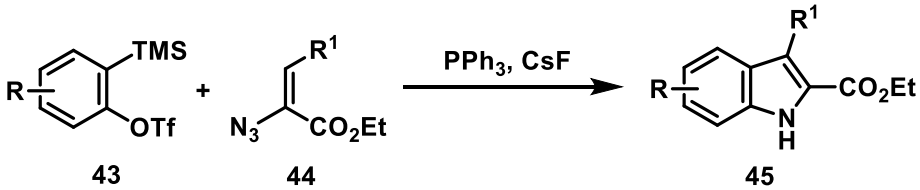
Recently, our group revealed the N-heterocyclic carbene (NHC) catalyzed umpolung of aldimines **41** and the reaction proceeds via aza-Breslow intermediates (Scheme 4.20).[21] The NHC catalyzed intramolecular cyclization of aldimines bearing a Michael acceptor leading to the formation of indole 3-acetic-acid derivatives **42** in moderate to good yields. The carbene generated from the triazolium salt using KOH as a base was found to be efficient.



Scheme 4.20: NHC-Catalyzed Umpolung of Imines for the Synthesis of Indoles

4.2.3. Transition-Metal-Free Synthesis of Indoles Involving Arynes

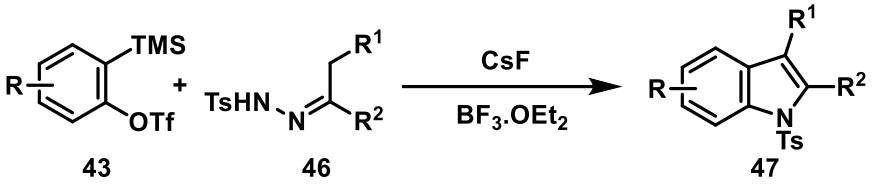
Wang and co-workers reported the reaction of 2-azidoacrylates **44** with benzynes **43** in presence of PPh_3 and CsF leading to the formation of substituted indoles **45** in good yields (Scheme 4.21).[22] The reaction involves the formation of iminophosphorane and benzyne and a subsequent double cyclization/hydrolysis/air-oxidation cascade. This methodology was utilized to synthesize 10*H*-indolo[1,2-a]indol-10-ones.



Scheme 4.21: Synthesis of Indoles from 2-Azidoacrylates and *o*-Silyl Aryltriflates

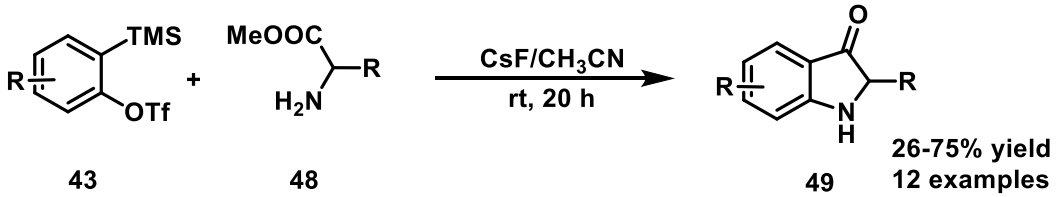
Greaney and co-workers developed a new approach to the Fischer-indole synthesis that uses the reactive intermediate benzyne. The addition of *N*-tosyl hydrazones **46** to

benzyne, generated through fluoride activation of 2-(trimethylsilyl)phenyl triflate precursors **43**, leading to the formation of *N*-arylated product initially. Addition of a Lewis acid to the same reaction vessel then afforded *N*-tosylindole products **47** via Fischer indole cyclization (Scheme 4.22).[23]



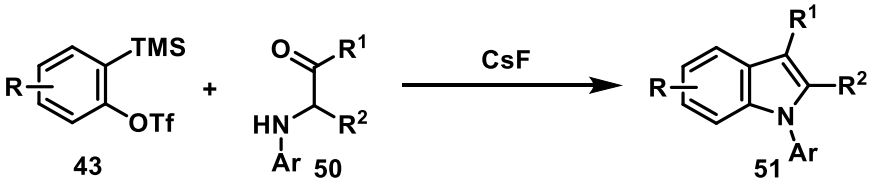
Scheme 4.22: *N*-Arylation and Fischer Cyclization of *N*-Tosylhydrazones with Benzyne

Okuma and co-workers reported an efficient route to a variety of 2-phenylindolin-3-ones **49** from amino acid methyl esters **48** (Scheme 4.23).[24] The reaction of amino acid methyl esters with benzyne prepared from 2-(trimethylsilyl)phenyl triflate **43** and cesium fluoride leading to the formation of 2-phenylindolin-3-ones in moderate to good yields.



Scheme 4.23: Reaction of Arynes with Amino Acid Esters

Zhu and co-workers demonstrated heteroannulation reaction of 2-(trimethylsilyl)aryl triflates **43** with *N*-aryl-α-amino ketones **50** resulting in the formation of *N*-aryl-2,3-disubstituted indoles **51** in good to excellent yields. This methodology allowed for the first time a one-step synthesis of unsymmetrical 2,3-dialkyl substituted indoles in a regiospecific manner (Scheme 4.74).[25]



Scheme 4.24: Reaction of Arynes with *N*-Aryl-α-aminoketones to form *N*-Arylindoles

4.3. Statement of the Problem

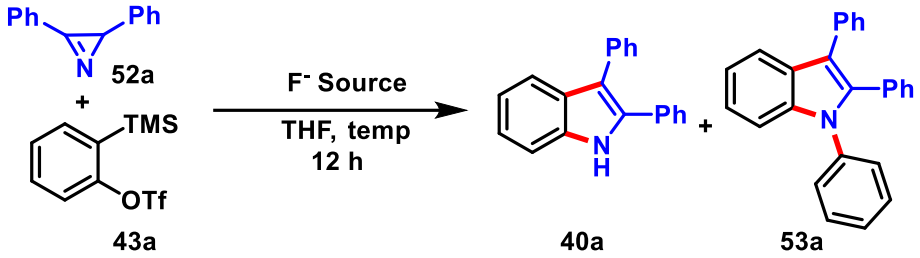
As mentioned in the previous sections, the Fischer indole synthesis stands as one of the most widely used procedure for the synthesis of indole.[1] Additionally, methods employing transition-metal-catalyzed C-H bond functionalization reactions have emerged as one of the convenient and efficient protocols for the synthesis of indoles. Furthermore, transition-metal-free transformations are also uncovered recently for the synthesis of indole derivatives. The transition-metal-free synthesis of indoles e loying arynes[26] as the aryl source has been a convenient method. The use of 2-(trimethylsilyl)aryl triflate precursor in the presence of fluoride source allows the mild method for aryne generation.[27] In this context, herein, a detailed study on the transition-metal-free and highly selective synthesis of both *N*-unsubstituted and *N*-aryl indoles by the reaction of arynes with 2*H*-azirines has been presented. Importantly, the product selectivity depends on the temperature used. When the reaction was carried out at -10 °C, *N*-aryl indoles are formed in high yields. Gratifyingly, when the reaction was performed at 60 °C, 2,3-diaryl *N*-unprotected indoles are formed in moderate to good yields and excellent selectivity.

4.4. Results and Discussion

4.4.1. Optimization Studies

The present study was initiated by treating 2,3-diphenyl-1-azirine **52a** with the benzyne generated from the 2-(trimethylsilyl)aryl triflate precursor **43a** using KF in presence of 18-crown-6 as additive in THF at 30 °C. Under these conditions, the 2,3-diaryl indole **40a** was formed in 40% yield and 1,2,3-triaryl indole **53a** was formed in 21% yield in 54:46 ratio (Table 4.1, entry 1). Interestingly, when the reaction was performed at 60 °C, **40a** was isolated in 65% yield and 97:3 selectivity (entry 2). Under this condition, only traces of **53a** was formed. The use of other fluoride sources such as CsF and tetrabutyl ammonium fluoride (TBAF) did not improve the yield of **40a** and **53a** (entries 3,4). When the reaction was carried out at -10 °C and warmed to 30 °C, a complete switching in selectivity from **40a** to **53a** was observed (98:2) and **53a** was isolated in 76% yield. Finally, the yield of **53a** was improved to 83% when the reaction was carried out at -10 °C (entry 6).

Table 4.1. Optimization of the Reaction Conditions[a]



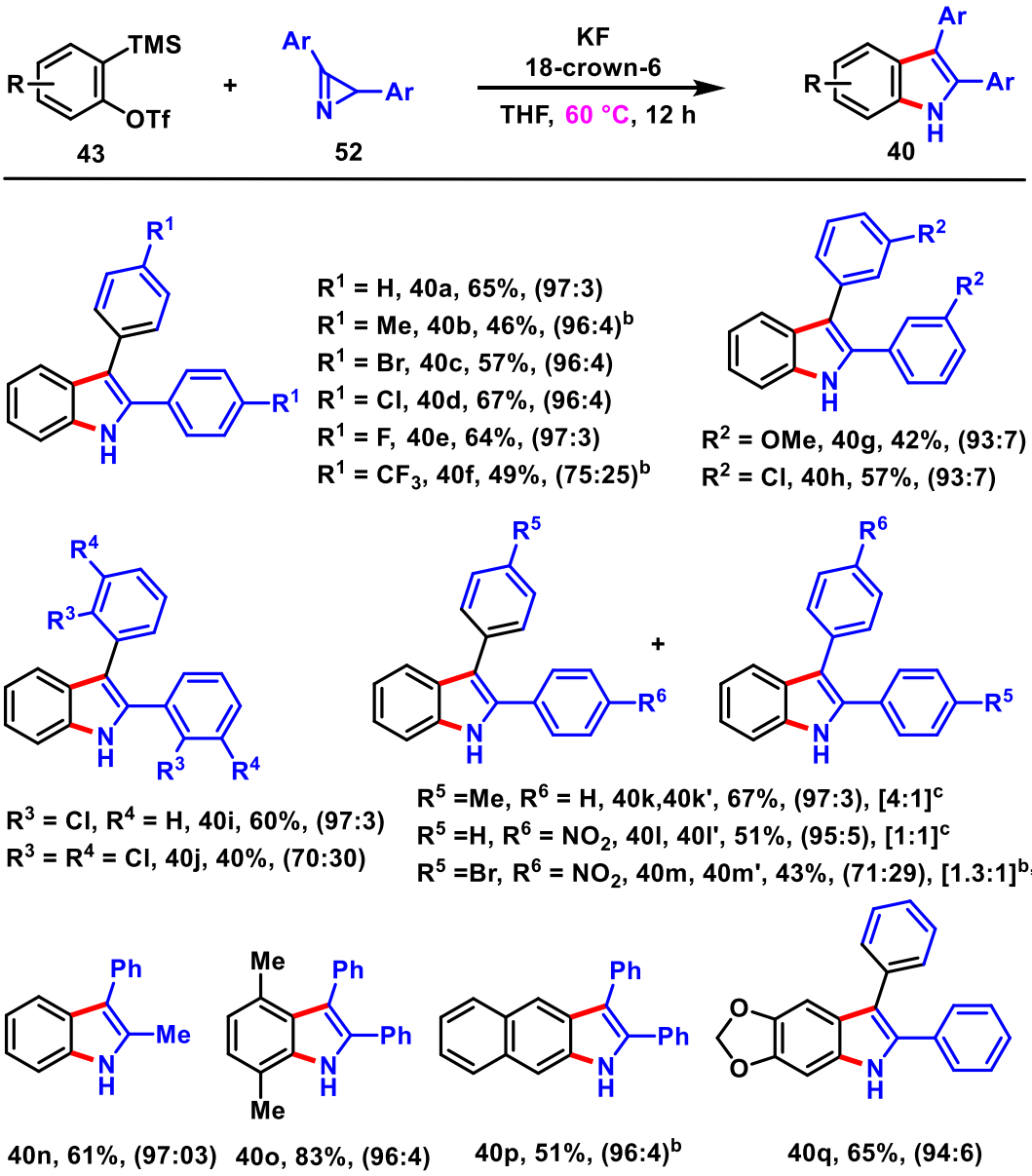
entry	fluoride source	temp (°C)	yield of **40a** (%)[b]	yield of **53a** (%)[b]	**40a:53a**[c]
1	KF/18-crown-6	30	40	21	54:46
2[d]	*KF/18-crown-6*	*60*	*65*	*<5*	*97:3*
3[e]	CsF	60	57	<5	83:17
4	TBAF.3H$_2$O	60	<5	<5	ND
5[f]	KF/18-crown-6	-10 to 30	<5	76	2:98
6[f]	*KF/18-crown-6*	*-10*	*<5*	*83*	*1:99*

[a] General conditions: **52a** (0.25 mmol), **43a** (0.30 mmol), KF (2.4 equiv), 18-crown-6 (2.4 equiv), THF (1.0 mL), for the indicated temperature and 12 h. [b] Yield of the isolated products are given. [c] Selectivity was determined using GC analysis of the crude reaction mixture. [d] Reaction performed using 1.8 equiv of **43a** and 3.6 equiv of KF/18-crown-6 and 6.0 mL THF. [e] Reaction performed using 1.0 mL CH_3CN. [f] Reaction carried out using 3.0 equiv of **43a** and 6.0 equiv of KF/18-crown-6 and 1.0 mL THF.

4.4.2. Substrate Scope for the Synthesis of *N*-Unsubstituted Indoles

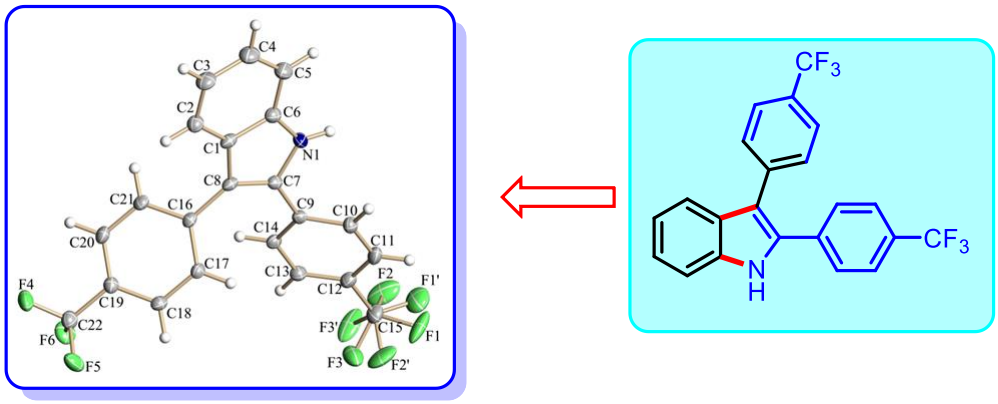
After optimizing the reaction conditions for the selective synthesis of *N*-unsubstituted and *N*-aryl indoles, we then examined the substrate scope of both transformations. First, we evaluated the scope of the synthesis of N-H indoles (Scheme 4.25). A series of symmetrical 2*H*-azirines bearing electron-releasing and -withdrawing groups at the 4-position of the aryl moiety of **52** are well tolerated at 60 °C leading to the selective synthesis of 2,3-diaryl indoles in moderate to good yield and good selectivity (**40a-40f**). Notably, in the case of 4-CF_3 substituted 2*H*-azirine, the selectivity was only moderate. The structure of **40f** was further confirmed by single-crystal X-ray analysis (Fig 4.2). Moreover, the substitution at the 2-position, 1-position as well as disubstitution on the 2,3-diaryl moiety of **52** did not affect the aryne reactivity and furnished the desired products in moderate yield and high selectivity (**40g-40j**). As expected, the unsymmetrical 2*H*-azirines afforded the inseparable

mixture of regioisomers in moderate to good yield (**40k-40m**). Interestingly, unsymmetrical 2-methyl-3-phenyl-2*H*-azirine afforded the single regioisomer **40n** in 61% yield and 97:3 selectivity. Additionally, symmetrical arynes generated from the corresponding precursors readily underwent smooth reaction with 2*H*-azirine **52a** to furnish the N-H indoles in moderate to good yields and high selectivity (**40o-40q**).



[a] General conditions: **52** (0.50 mmol), **43** (0.90 mmol), KF (1.80 mmol), 18-crown-6 (1.80 mmol), THF (12.0 mL), 60 °C, 12 h. Yields of the isolated products are given. Selectivity determined by GC analysis of crude reaction mixture is given in parentheses. [b] Reaction run on 0.25 mmol scale. [c] Regioisomer ratio determined by GC analysis.

Scheme 4.25: Substrate Scope for the Synthesis of *N*-Unsubstituted Indoles

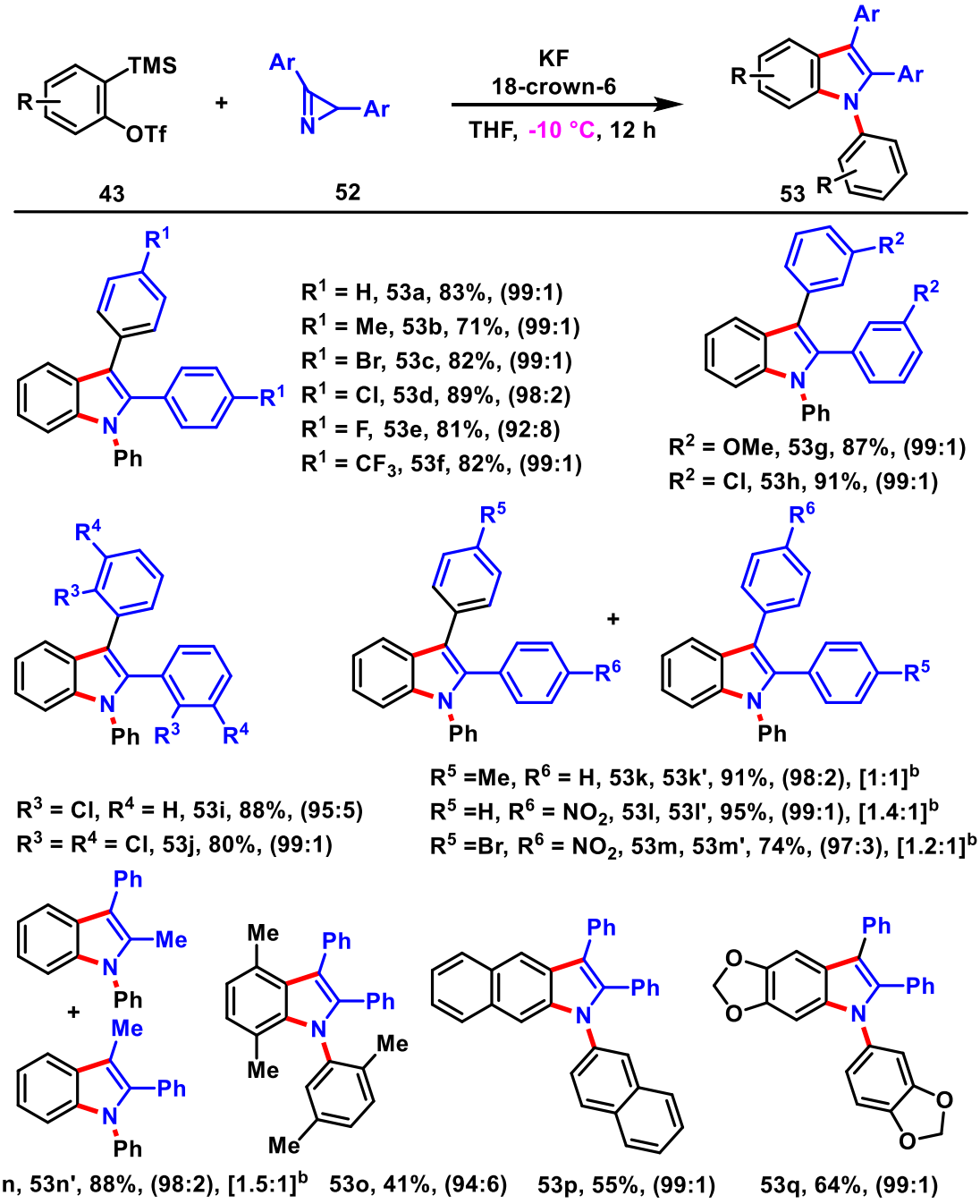


CCDC 1476910

Fig 4.2: Single-Crystal X-ray Analysis of **40f**

4.4.3. Substrate Scope for Synthesis of *N*-Aryl Indoles

Next, we then focused our attention on the synthesis of 1,2,3-trisubstituted indoles (Scheme 4.26). As in the case of reactions performed at 60 °C for the selective synthesis of N-H indoles, the experiments carried out at -10 °C also showed good functional group compatibility and high selectivity towards the synthesis of trisubstituted indoles. A wide variety of symmetrical 2*H*-azirines with different substitution pattern readily underwent efficient aryne reactions leading to the synthesis of 1,2,3-triaryl indoles in good yields (>71% in all cases) and excellent selectivity (>92:8 in all cases) (**53a-53j**). In the case of **53h**, the structure was confirmed by single-crystal X-ray analysis (Fig 4.3). Moreover, the reaction of arynes with unsymmetrical 2*H*-azirines at -10 °C furnished the regioisomeric mixture of 1,2,3-triaryl indoles, where the selectivity over the N-H indoles are excellent in all cases (**53k-53m**). In contrast to the reaction of 2-methyl-3-phenyl-2*H*-azirine with aryne at 60 °C, the reaction at -10 °C afforded regioisomeric mixture of products (1.5:1) **53n** and **53n'** in 88% yield. Furthermore, the variation of aryne moiety was also feasible, leading to the formation of the corresponding trisubstituted indoles in moderate to good yield and high selectivity thus further expanding the scope of this aryne reaction (**53o-53q**).



[a] General conditions: **52** (0.25 mmol), **43** (0.75 mmol), KF (1.5 mmol), 18-crown-6 (1.5 mmol), THF (1.0 mL), -10 °C, 12 h. Yields of the isolated products are given. Selectivity was determined by GC analysis of crude reaction mixture is given in parentheses. [b] Regioisomer ratio determined by GC analysis.

Scheme 4.26: Substrate Scope for Synthesis of *N*-Aryl Indoles

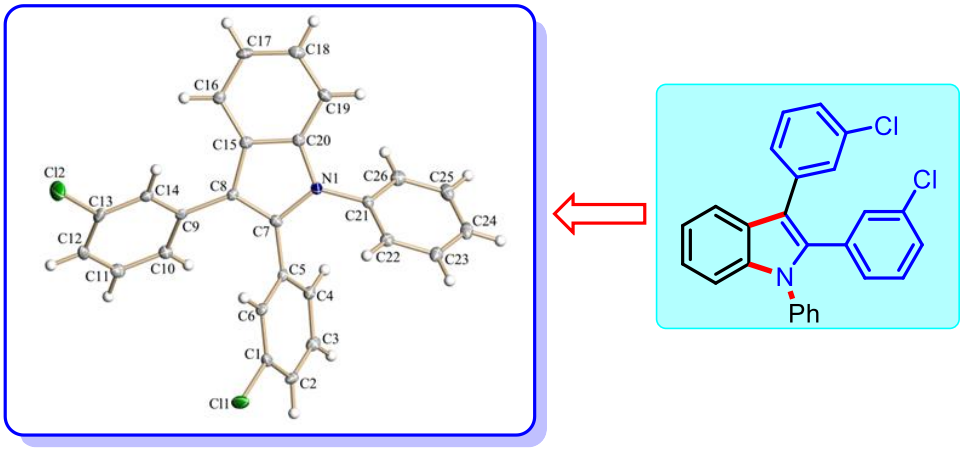


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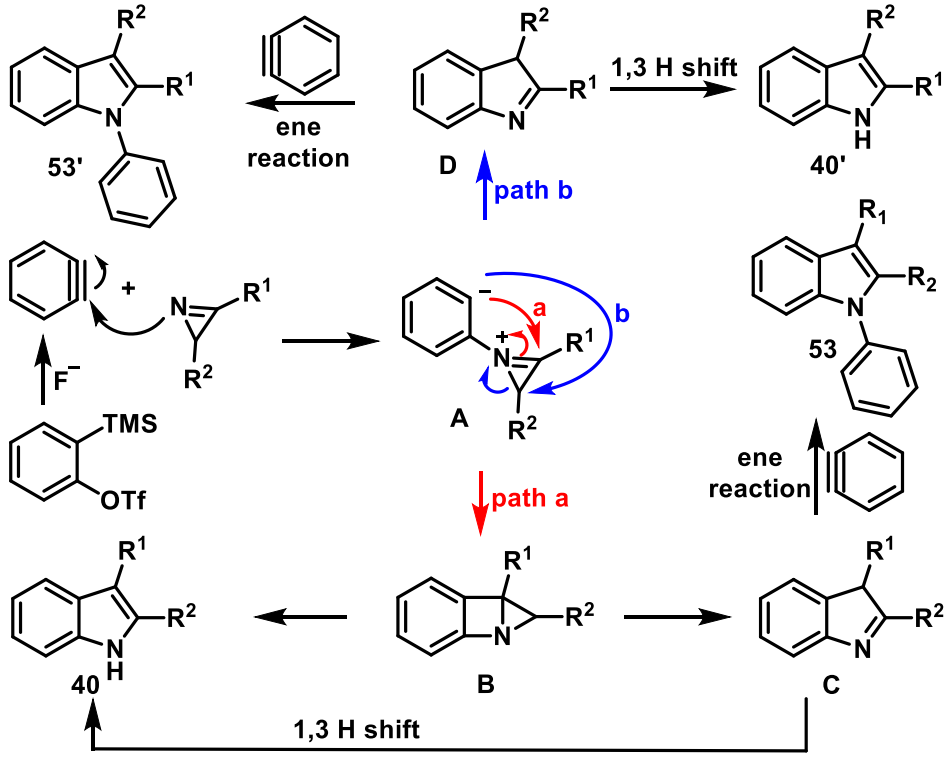
Fig 4.3: Single-Crystal X-ray Analysis of **53h**

4.4.4. Proposed Mechanism

Considering the mixture of regioisomers obtained in the reaction of arynes with unsymmetrical 2*H*-azirines, a tentative mechanism of this reaction is proposed in Scheme 4.27. The nucleophilic addition of 2*H*-azirines onto arynes generate the 1,4 zwitterionic intermediate **A**.[28,29] The zwitterion **A** could cyclize in two pathways. In path a, the aryl

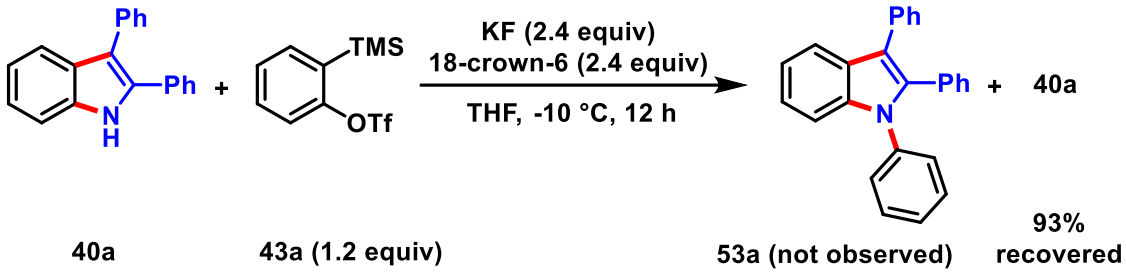


Scheme 4.27: Proposed Mechanism of the Reaction

anion adds to the C=N bond (1,2-addition) to generate the intermediate **B**. A 1,2-hydrogen shift to nitrogen can result in the formation of **40**. Alternatively, a 1,2-hydrogen shift to carbon can generate the intermediate **C**, which can undergo another 1,3 hydrogen shift to afford **40**.[30] An ene reaction of **C** with another molecule of aryne can furnish **53**. In path b, the aryl anion adds to carbon attached to R^2 (breaking of C-N bond) to generate the intermediate **D**. A 1,3-hydrogen shift on **D** can afford the regioisomer **40'**. Moreover, the ene reaction of **D** with another molecule of aryne can result in the formation of *N*-aryl indole **53'**.

4.4.5. Mechanistic Experiment

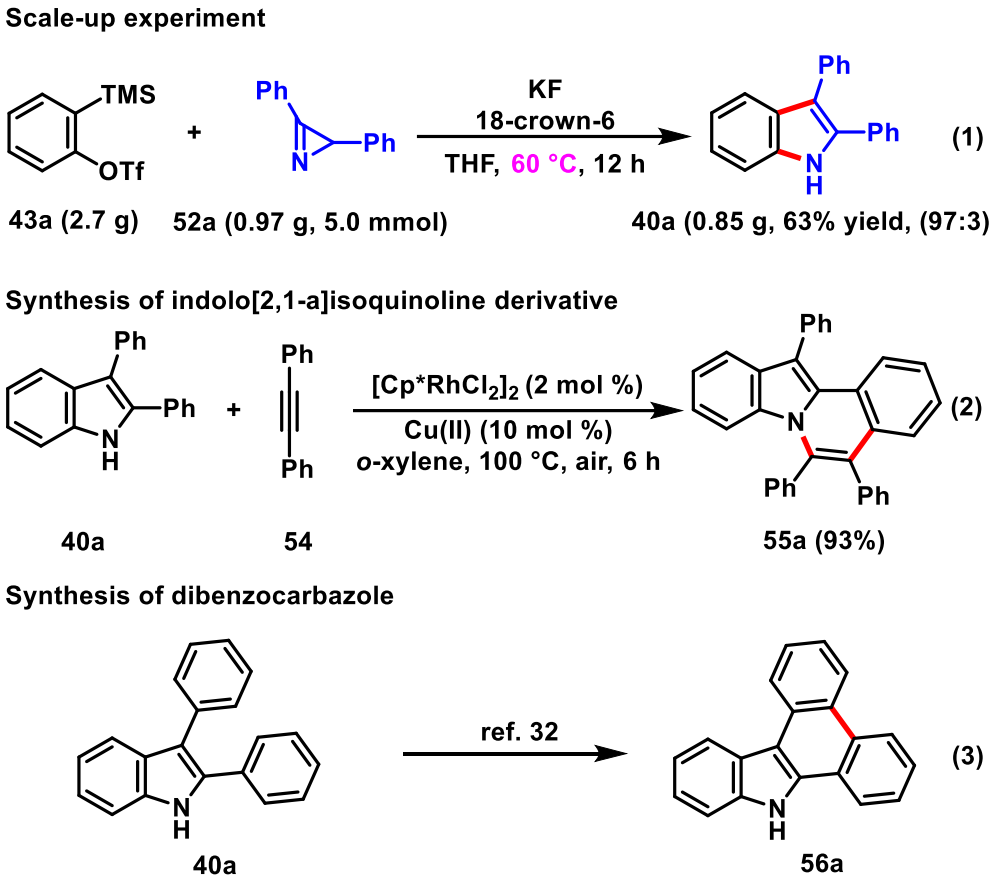
Treatment of the N-H indole **40a** with excess aryne at -10 °C did not afford the *N*-aryl indole **53a** (Scheme 4.28). This experiment rules out the possibility of initial formation of **40a** in the reaction of **52a** and **43a** for the synthesis of **53a**. This also sheds light on the mechanism proposed in Scheme 4.27.



Scheme 4.28: Attempted Reaction of **40a** with Arynes

4.4.6. Synthetic utility

To demonstrate the synthetic utility of the reaction, a scale-up experiment was performed. Carrying out the reaction in a 5.0 mmol scale of **52a** afforded **40a** in 63% yield and 97:3 selectivity indicating the practical nature of the reaction (Scheme 4.29, eq 1). Reaction of **40a** with alkyne **54** under Rh(III)-catalysis following the procedure of Miura, Satoh and co-workers with a minor modification afforded the indolo[2,1-a]isoquinoline derivative **55a** in 93% yield (eq 2).[31] Moreover, **40a** could easily be transformed to the dibenzocarbazole derivative **56a** via dehydrogenative coupling reaction (eq 3).[32] Compounds **55a** and **56a** are nitrogen-doped conjugated systems (π-expanded) having potential organic semiconductor applications.

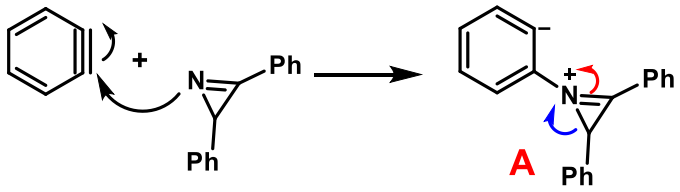


Scheme 4.29: Synthetic Utility of the Method

4.5. Computational Studies

The geometry optimizations were conducted employing density functional theory (DFT).[35, 36] The triple-ζ basis set augmented by a polarization function was used for all the atoms. The resolution of identity (RI)[37] along with the multipole accelerated resolution of identity (marij)[38] approximations were employed for an accurate and efficient treatment of the electronic Coulomb term. Solvent effects were accounted for as follows: we have done full geometry optimizations of all intermediates and transition states calculations using the COSMO model. The solvent used in this study is THF (ε =7.58). The contributions of internal energy and entropy were obtained from frequency calculations done on the DFT structures: thus, the energies reported in the figures are the ΔG values. To gain insight into the mechanism, we performed quantum chemical calculations by using density functional theory (DFT), employing the TZVP/PBE approach.

Herein we proposed two mechanisms based on the temperature effect. In the first pathway, at 60 °C formation of **40** is preferred, and in second pathway, at -10 °C, the formation of **53** is preferred. In both the pathways, common intermediate **A** is forming. The results are summarized in terms of a free energy values.



ΔG = -7.3 at -10 °C, ΔG = -5.8 at 25 °C, ΔG = -4.2 at 60 °C.

Fig 4.2: Formation of Intermediate **A**

Formation of intermediate **A** was found to -5.8 kcal/mol at room temperature, this is an indication that it is common intermediate for both the pathways (a and b). These results are confirming the formation of intermediate **A** in the reaction course.

ΔG at 60°C in Kcal/mol

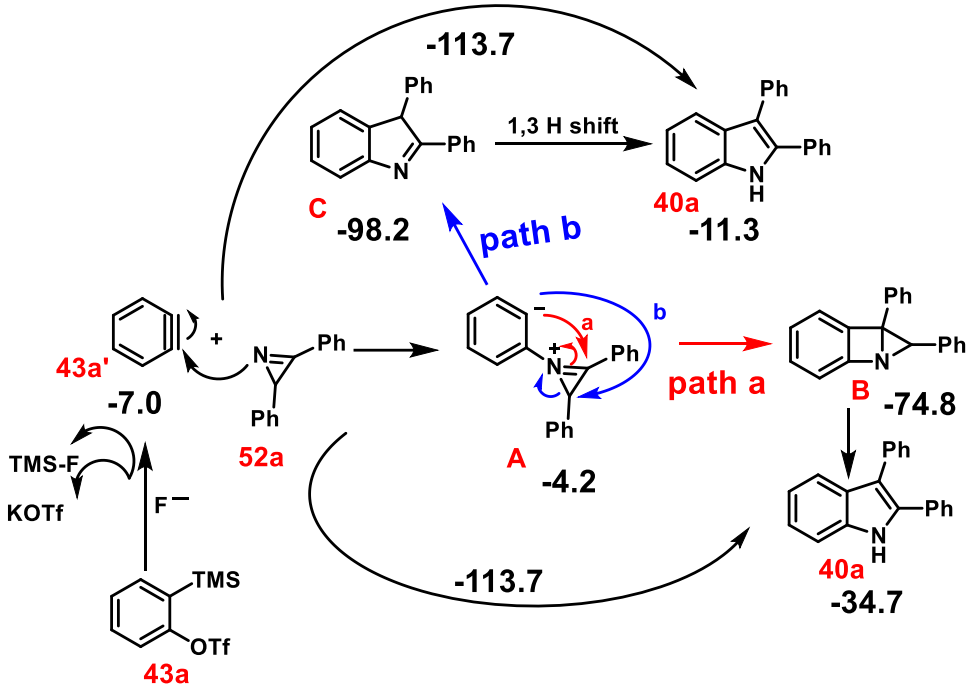


Fig 4.4: Formation of Product **40**

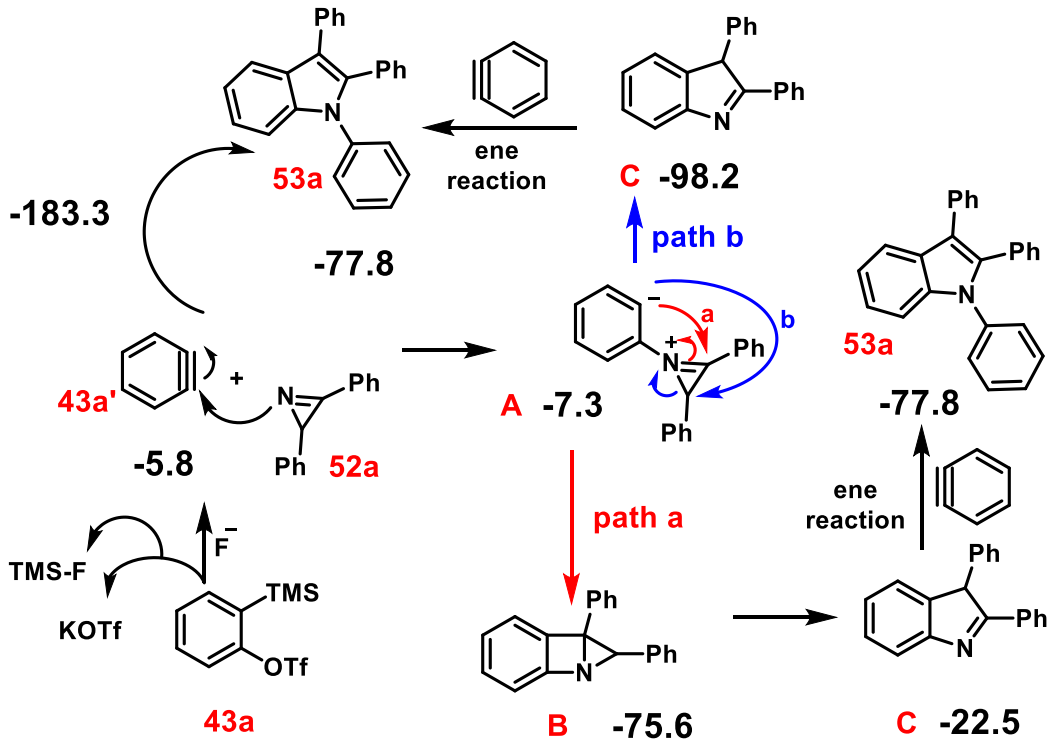


Fig 4.5: Formation of Product **53**

The formation of Product **40** proceeds via both the pathways (a and b), which is -113.7 kcal/mol stabilized, with respect to azirine **52a** and benzyne **43a'** at 60°C. The formation of Product **53** proceeds via both the pathways (a and b) which is -183 kcal/mol stabilized with respect to azirine **52a** and benzyne **43a'**at -10°C.

4.6. Conclusion

In conclusion, we have developed a highly selective and transition-metal-free reaction of arynes with 2*H*-azirines leading to the synthesis of either *N*-unsubstituted or *N*-aryl indoles. The reaction of arynes with 2*H*-azirines at 60 °C afforded 2,3-diaryl indoles. Interestingly, the selectivity was switched to the formation of 1,2,3-triaryl indoles when the reaction was performed at -10 °C. Both reactions took place with high selectivity and broad substrate scope.

4.7. Experimental Details

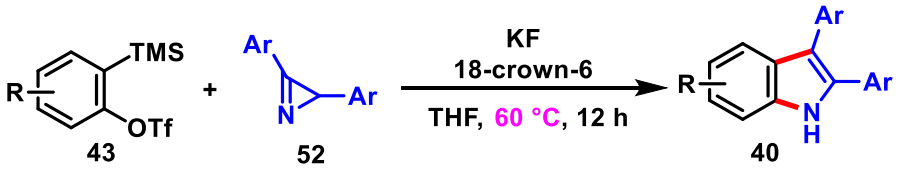
4.7.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with teflon screw caps. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. 30 °C corresponds to the room temperature of the lab, when the experiments were carried out. THF was freshly purified by distillation over Na-benzophenone and was transferred under argon. 18-Crown-6 was recrystallized from dry CH_3CN and KF was dried by heating at 110 °C for 12 h and left to cool under argon and stored in glove box. The 2(trimethylsilyl)phenyl trifluoromethane sulfonate **43a** and the other symmetric and unsymmetric aryne precursors were synthesized following literature procedure.[33] The azirines used in this work were prepared the following the literature procedure.[34]

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

All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400 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). Gas Chromatography were recorded on Agilent 7890 B GC. 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.

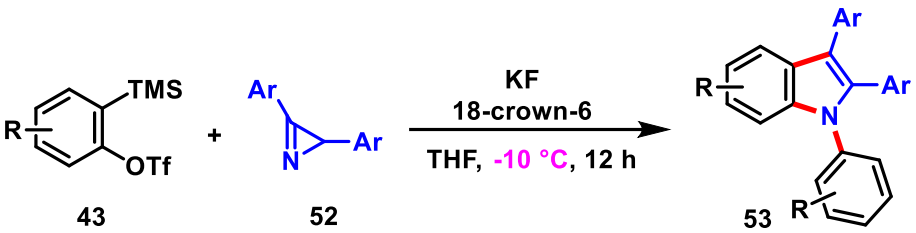
4.7.2. General Procedure for the synthesis of *N*-Unsubstituted indoles



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.475 g, 1.8 mmol), KF (0.105 g, 1.8 mmol) inside the glove box. Then

the corresponding 2*H*-azirine **52** (0.5 mmol) was added outside the glovebox. Then the mixture was dissolved in 12.0 mL of THF and the resultant reaction mixture kept stirring at 30 °C for 5 min. To the stirring solution was added aryne precursor **43** (0.90 mmol). Then the reaction mixture was immediately placed in a preheated oil bath at 60° C. When TLC control showed the completion of the reaction (typically after 12 h), the solvent was evaporated and subsequently the crude residue was purified by flash column chromatography on silica gel to afford the corresponding *N*-unsubstituted indoles **40** in moderate to good yields. Selectivity ratio was determined by GC analysis of crude reaction mixture.

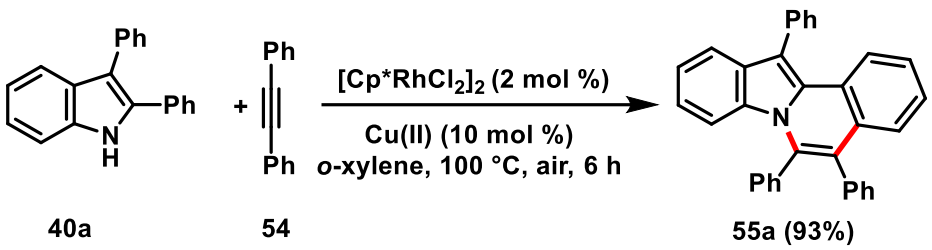
4.7.3. General Procedure for the synthesis of N-Aryl Indoles



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18-crown-6 (0.396 g, 1.5 mmol), KF (0.087 g, 1.5 mmol) inside the glove box. Then the corresponding 2*H*-azirine **52** (0.5 mmol) was added outside the glovebox. Then the mixture was dissolved in 1.0 mL of solvent. The resultant reaction mixture was cooled to -10 °C and kept stirring for 5 min. To the stirring solution was added aryne precursor **43** (0.75 mmol) and kept stirring at -10 °C for 12h. When TLC control showed the completion of the reaction (typically after 12 h), the reaction was quenched and the solvent was evaporated and subsequently the crude residue was purified by flash column chromatography on silica gel to afford the corresponding *N*-aryl indole derivatives **53** in moderate to good yields. Selectivity ratio was determined by GC analysis of crude reaction mixture.

4.7.4. Procedure for the reaction involving NH indole and diphenyl acetylene

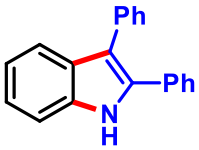
To a 5 mL tube equipped with a magnetic stir bar, 2,3-diphenyl-1*H*-indole (**40a**, 30 mg, 0.1 mmol), 1,2-diphenylacetylene (**54**, 24 mg, 0.13 mmol, 1.2 equiv), $[(Cp^*RhCl_2)_2]$



(1.0 mg, 0.02 mmol, 2 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 mg, 0.1 mmol, 10 mol %), and 1 mL *o*-xylene were added sequentially. The tube (not sealed) was immersed in an oil bath (100 °C) and stirred vigorously under air. When TLC control showed the completion of the reaction (after 6 h), the solvent was evaporated and subsequently the crude residue was purified by flash column chromatography on silica gel to afford the corresponding indolo[2,1-a]isoquinoline derivative **55a** in good yields.

4.7.5. Synthesis and Characterization of *N*-Unsubstituted indoles

2,3-Diphenyl-1*H*-indole (40a)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.269 g, 218 µL, 0.9 mmol) with 2,3-diphenyl-2*H*-azirine **52a** (0.097 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-diphenyl-1*H*-indole as a pale yellow solid **40a** (0.087 g, 65% yield, selectivity determined by GC analysis of crude reaction mixture is 97:03).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.35; mp 109 −111 °C.

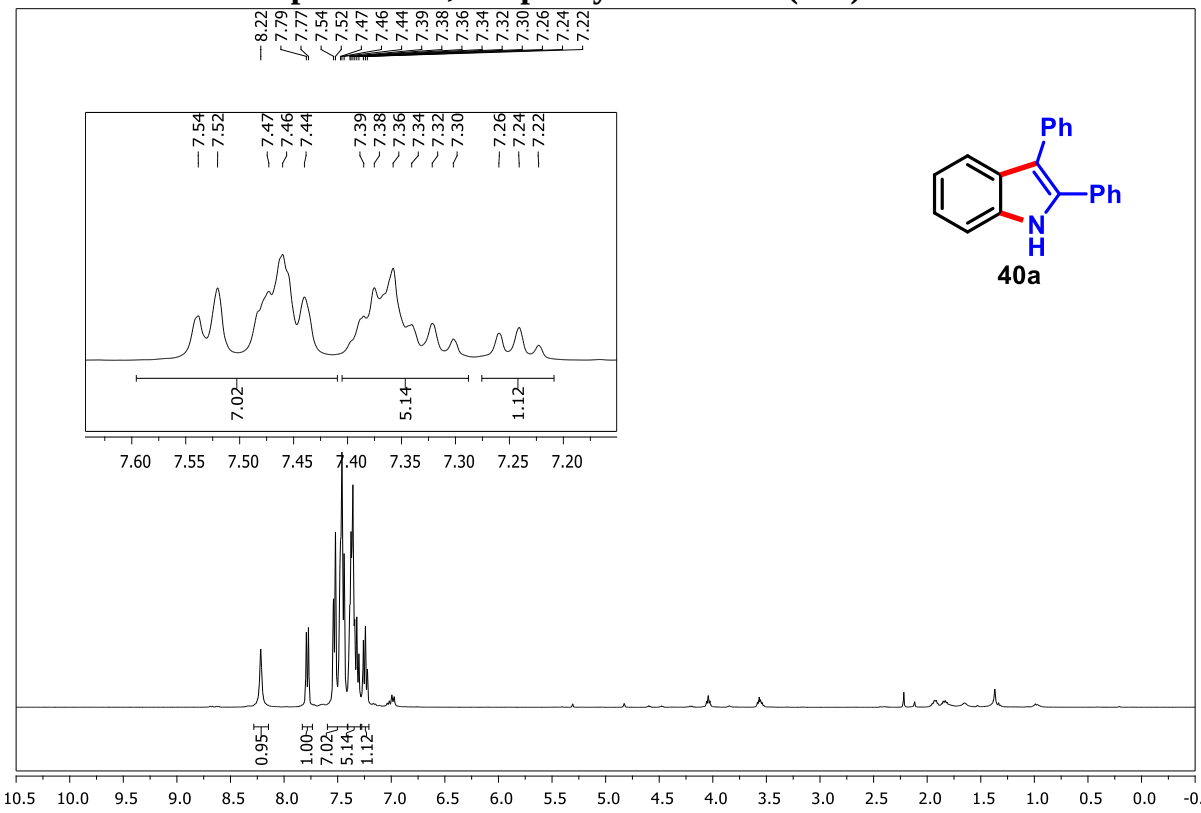
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (bs, 1H), 7.78 (d, *J* = 7.90 Hz, 1H), 7.54 -7.44 (m, 7H), 7.39 -7.30 (m, 5H), 7.24 (t, *J* = 7.4 Hz, 1H).

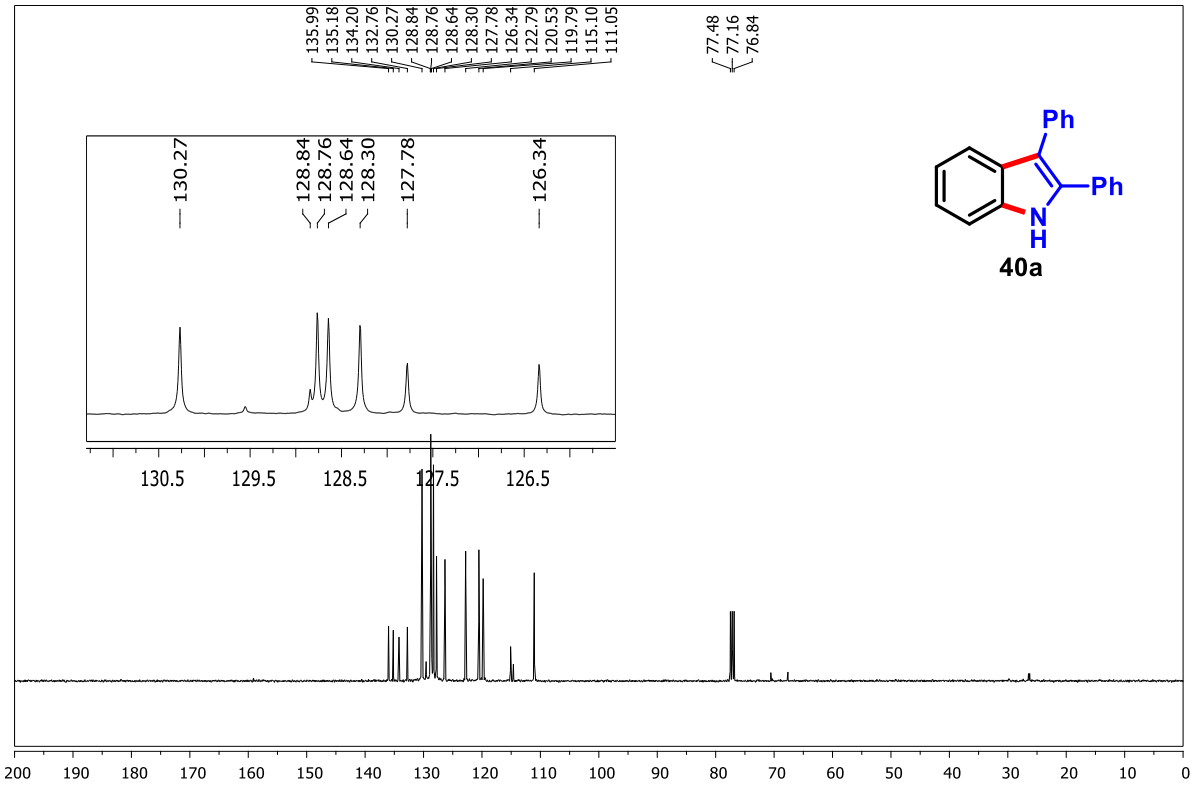
^{13}C NMR (100 MHz, $CDCl_3$) δ 135.99, 135.18, 134.20, 132.76, 130.27, 128.84, 128.76, 128.64, 128.30, 127.78, 126.34, 122.79, 120.53, 119.79, 115.10, 111.05.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{16}N$: 270.1277, found: 270.1278.

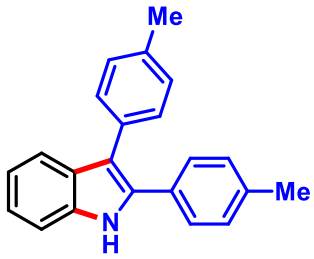
FTIR (cm^{-1}): 3679, 3458, 3415, 3060, 3018, 1722, 1670, 1598, 1496, 1449, 1319, 1217, 1031, 764, 702.

^{1}H and ^{13}C NMR Spectra of 2,3-Diphenyl-1*H*-indole (40a)





2,3-Di-*p*-tolyl-1*H*-indole (40b)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.134 g, 109 μL, 0.9 mmol) with 2,3-di-p-tolyl-2*H*-azirine **52b** (0.055 g, 0.25 mmol) in the presence of KF (0.053 g, 0.9 mmol) and 18-crown-6 (0.238 g, 0.9 mmol) in THF (6.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-di-*p*-tolyl-1*H*-indole as a pale sticky yellow liquid **40b** (0.034 g, 46% yield, selectivity determined by GC analysis of crude reaction mixture is 96:04).

***R*f** (Pet. ether /EtOAc = 95/05): 0.35

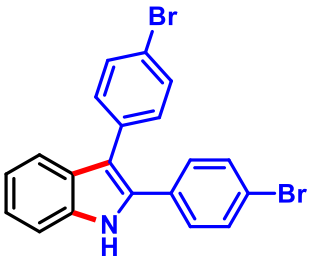
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (bs, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.45-7.37 (m, 5H), 7.30 -7.17 (m, 6H), 2.46 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.60, 135.93, 135.80, 134.15, 132.28, 130.11, 130.04, 129.51, 129.38, 129.05, 128.11, 122.57, 120.38, 119.77, 114.65, 110.92, 21.38.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{20}N$: 298.1590, found: 298.1585.

FTIR (cm^{-1}): 3463, 3018, 1605, 1582, 1453, 1326, 1248, 1115, 1043, 930, 821, 772.

2,3-Bis(4-bromophenyl)-1*H*-indole (40c)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.269 g, 218 μL, 0.9 mmol) with 2,3-bis(4-bromophenyl)-2*H*-azirine **52c** (0.176 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-bis(4-bromophenyl)-1*H*-indole as a yellow solid **40c** (0.122 g, 57% yield, selectivity determined by GC analysis of crude reaction mixture is 96:04).

***R*f** (Pet. ether /EtOAc = 95/05): 0.24; mp 151 −153 °C.

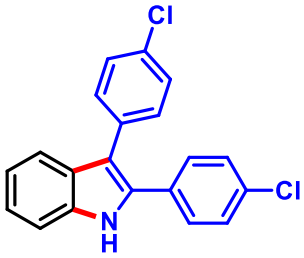
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (bs, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.55-7.44 (m, 5H), 7.32-7.28 (m, 5H), 7.20 (t, *J* = 7.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.10, 133.84, 133.19, 132.18, 132.00, 131.79, 131.39, 129.78, 128.47, 123.36, 122.23, 120.99, 120.56, 119.61, 114.44, 111.20.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{14}NBr_2$: 425.9488, found: 425.9484.

FTIR (cm^{-1}): 3458, 3018, 1587, 1544, 1499, 1453, 1392, 1312, 1215, 1070, 996, 772.

2,3-Bis(4-chlorophenyl)-1*H*-indole (40d)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.269 g, 218 μL, 0.9 mmol) with 2,3-bis(4-chlorophenyl)-2*H*-azirine **52d** (0.131 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-bis(4-chlorophenyl)-1*H*-indole as a pale yellow solid **40d** (0.114 g, 67% yield, selectivity determined by GC analysis of crude reaction mixture is 96:04).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.25; mp 129 −131 °C.

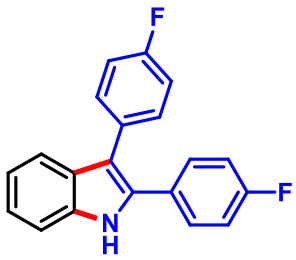
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (bs, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.41 -7.29 (m, 9H), 7.23 -7.20 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.06, 133.98, 133.37, 133.20, 132.38, 131.43, 130.94, 129.50, 129.19, 129.03, 128.51, 123.28, 120.93, 119.59, 114.35, 111.19.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{14}NCl_2$: 338.0498, found: 338.0500.

FTIR (cm^{-1}): 3450, 3058, 1546, 1482, 1432, 1328, 1296, 1215, 1014, 966, 831, 769.

2,3-Bis(4-fluorophenyl)-1*H*-indole (40e)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.269 g, 218 μL, 0.9 mmol) with 2,3-bis(4-fluorophenyl)-2*H*-azirine **52e** (0.115 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-bis(4-fluorophenyl)-1*H*-indole as a pale yellow solid **40e** (0.098 g, 64% yield, selectivity determined by GC analysis of crude reaction mixture is 97:03).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.28; mp 130 −132 °C.

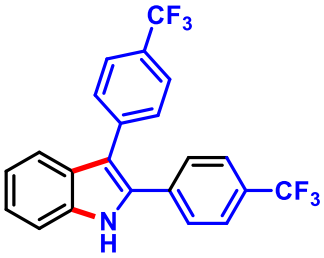
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (bs, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.47-7.38 (m, 5H), 7.31 -7.27 (m, 1H), 7.21 -7.18 (m, 1H), 7.13-7.04 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.51 (d, *J* = 248.2 Hz), 161.78 (d, *J* = 245.97), 135.93, 133.35, 131.71 (d, *J* = 7.8 Hz), 130.88 (d, *J* = 3.4 Hz), 130.05 (d, *J* = 8.5 Hz), 128.77, 123.05, 120.79, 119.58, 116.02 (d, *J* = 21.9 Hz), 115.73 (d, *J* = 21.5 Hz), 114.19, 111.09.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{14}NF_2$: 306.1089, found: 306.1083.

FTIR (cm^{-1}): 3460, 3018, 1651, 1560, 1494, 1436, 1328, 1218, 1096, 838, 772.

2,3-Bis(4-(trifluoromethyl)phenyl)-1*H*-indole (40f)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.269 g, 218 µL, 0.9 mmol) with 2,3-bis(4-(trifluoromethyl)phenyl)-2*H*-azirine **52f** (0.165 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-bis(4-(trifluoromethyl)phenyl)-1*H*-indole as a yellow solid **40f** (0.099 g, 49% yield, selectivity determined by GC analysis of crude reaction mixture is 75:25).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.27; mp 130 −132 °C.

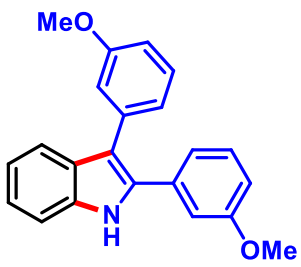
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.68-7.66 (m, 3H), 7.63 (d, *J* = 7.7 Hz, 2H), 7.55-7.49 (m, 5H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.60, 136.33, 135.88, 133.19, 130.39, 128.53, 128.37, 126.05 (q, *J* = 3.7Hz), 125.86 (q, *J* = 3.5 Hz), 123.88, 121.34, 121.13, 119.75, 118.68, 115.22, 111.41.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{14}NF_6$: 406.1025, found: 406.1024.

FTIR (cm^{-1}): 3457, 1674, 1494, 1323, 1216, 1125, 1066, 966, 845, 768.

2,3-Bis(3-methoxyphenyl)-1*H*-indole (40g)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **43a** (0.269 g, 218 µL, 0.9 mmol) with 2,3-bis(3-methoxyphenyl)-2*H*-azirine **52g** (0.127 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h

followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-bis(3-methoxyphenyl)-1*H*-indole as a yellow viscous liquid **40g** (0.069 g, 42% yield, selectivity determined by GC analysis of crude reaction mixture is 93:07).

***R*f** (Pet. ether /EtOAc = 95/05): 0.14

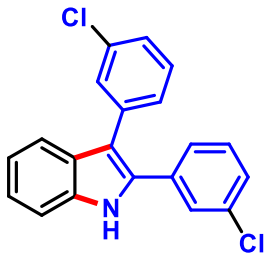
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (bs, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.29-7.24 (m, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.08-7.05 (m, 3H), 7.00 (s, 1H), 6.90-6.85 (m, 2H), 3.78 (s, 3H), 3.69 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.78, 159.68, 136.57, 135.90, 134.08, 133.97, 129.81, 129.60, 128.80, 122.90, 122.88, 120.56, 120.51, 119.84, 115.57, 115.18, 113.83, 113.58, 112.29, 111.05, 55.30, 55.22.

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

FTIR (cm^{-1}): 3459, 3017, 1603, 1583, 1482, 1430, 1284, 1216, 1046, 771, 668.

2,3-Bis(3-chlorophenyl)-1*H*-indole (40h)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.269 g, 218 µL, 1.8 mmol) with 2,3-bis(3-chlorophenyl)-2*H*-azirine **52h** (0.131 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-bis(3-chlorophenyl)-1*H*-indole as a pale sticky yellow liquid **40h** (0.097 g, 57% yield, selectivity determined by GC analysis of crude reaction mixture is 93:07).

***R*f** (Pet. ether /EtOAc = 95/05): 0.28

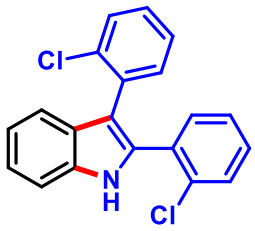
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (bs, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.49-7.44 (m, 3H), 7.33 -7.21 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.66, 136.06, 134.82, 134.51, 134.16, 133.01, 130.16, 130.03, 129.99, 128.45, 128.41, 128.12, 127.93, 126.78, 126.70, 123.48, 121.04, 119.70, 114.59, 111.24.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{14}NCl_2$: 338.0498, found: 338.0503.

FTIR (cm^{-1}): 3457, 3019, 1597, 1487, 1328, 1217, 1077, 928, 771, 699.

2,3-Bis(2-chlorophenyl)-1*H*-indole (40i)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **43a** (0.269 g, 218 µL, 0.9 mmol) with 2,3-bis(2-chlorophenyl)-2*H*-azirine **52i** (0.131 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-bis(2-chlorophenyl)-1*H*-indole as a yellow solid **40i** (0.101 g, 60% yield, selectivity determined by GC analysis of crude reaction mixture is 97:03).

***R*f** (Pet. ether /EtOAc = 95/05): 0.34; mp 129 −131 °C

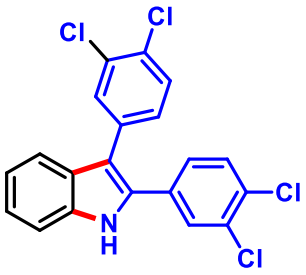
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (bs, 1H), 7.52-7.45 (m, 4H), 7.34-7.11 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.54, 134.82, 133.86, 133.28, 133.13, 132.82, 132.79, 131.51, 130.31, 129.94, 129.58, 128.38, 127.75, 126.87, 126.69, 123.01, 120.42, 120.33, 114.70, 111.19.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{14}NCl_2$: 338.0498, found: 338.0496.

FTIR (cm^{-1}): 3457, 3060, 3010, 1596, 1489, 1330, 1244, 1122, 1063, 1033, 969, 754.

2,3-Bis(3,4-dichlorophenyl)-1*H*-indole (40j)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.269 g, 218 µL, 1.8 mmol) with 2,3-bis(3,4-dichlorophenyl)-2*H*-azirine **52j** (0.165 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-bis(3,4-dichlorophenyl)-1*H*-indole as a sticky yellow liquid **40j** (0.081 g, 40% yield, selectivity determined by GC analysis of crude reaction mixture is 70:30).

***R*f** (Pet. ether /EtOAc = 95/05): 0.28

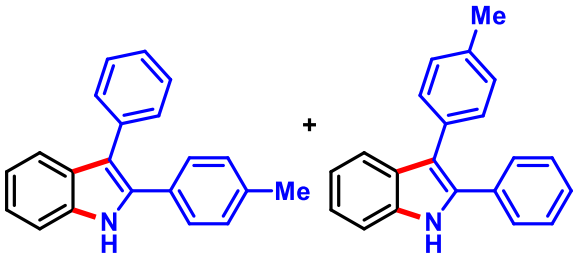
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (bs, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.44-7.42 (m, 2H), 7.33 -7.28 (m, 2H), 7.19-7.13 (m, 2H), 7.10-7.03 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.13, 134.73, 133.33, 132.93, 132.40, 132.17, 131.65, 131.04, 130.89, 130.81, 129.54, 128.17, 127.76, 123.86, 121.35, 119.53, 114.62, 113.90, 111.38.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{12}NCl_4$: 405.9718, found: 405.9723.

FTIR (cm^{-1}): 3453, 3019, 1648, 1595, 1469, 1377, 1215, 1134, 1030, 928, 883, 757.

3-Phenyl-2-(*p*-tolyl)-1*H*-indole (40k) and 2-Phenyl-3-(*p*-tolyl)-1*H*-indole (40k')



Following the general procedure, treatment of 2-(trimethylsilyl)phenyltrifluoro methane sulfonate **43a** (0.269 g, 218 µL, 0.9 mmol) with 2-phenyl-3-(*p*-tolyl)-2*H*-azirine **52k** (0.104 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 3-phenyl-2-(*p*-tolyl)-1*H*-indole **40k** and 2-phenyl-3-(*p*-tolyl)-1*H*-indole **40k'** as a mixture of regioisomers in 4:1 ratio (0.095 g, 67% yield, yellow viscous oil, regioisomer-ratio and selectivity determined by GC analysis of crude reaction mixture is 97:03).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.29

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (bs, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.47-7.14 (m, 12H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.02, 135.92, 133.99, 132.95, 132.10, 130.12, 129.42, 128.79, 128.26, 127.73, 126.27, 122.76, 120.46, 119.90, 110.99, 21.40.

Representative peaks of Minor Isomer:

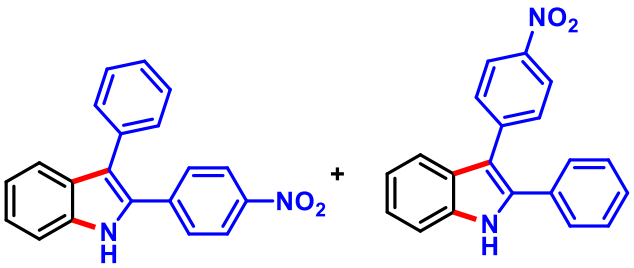
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s).

^{13}C NMR (100 MHz, $CDCl_3$) δ 130.28, 129.54, 128.99, 128.63, 128.16, 122.65, 119.70, 115.11.

HRMS (ESI) calculated $[M+H]^+$ for $C_{21}H_{18}N$: 284.1434, found: 284.1436.

FTIR (cm^{-1}): 3460, 3018, 1602, 1514, 1452, 1327, 1043, 929, 771, 697.

2-(4-Nitrophenyl)-3-phenyl-1*H*-indole (40l) and 3-(4-Nitrophenyl)-2-phenyl-1*H*-indole (40l')



Following the general procedure, treatment of 2-(trimethylsilyl)phenyltrifluoro methane sulfonate **43a** (0.269 g, 218 μL, 0.9 mmol) with 2-(4-nitrophenyl)-3-phenyl-2*H*-azirine **52l** (0.119 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 3-(4-nitrophenyl)-2-phenyl-1*H*-indole **40l** and 2-(4-nitrophenyl)-3-phenyl-1*H*-indole **40l'** as a mixture of regioisomers in 1.2:1 ratio (0.080 g, 51% yield, orange solid, regioisomer-ratio and selectivity determined by GC analysis of crude reaction mixture is 1:1 and 95:05).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.14

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42-8.38 (m, 1H), 8.22 (d, *J* = 8.6 Hz, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 7.73-7.65 (m, 1H), 7.60-7.55 (m, 2H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.43-7.29 (m, 6H), 7.25-7.17 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.69, 145.98, 142.86, 139.26, 136.68, 136.11, 134.27, 132.00, 131.40, 130.44, 130.27, 129.21, 129.07, 128.91, 128.72, 128.67, 128.36, 127.89, 127.24, 124.24, 124.20, 124.08, 123.44, 121.39, 121.16, 120.42, 119.23, 118.41, 112.97, 111.45, 111.35.

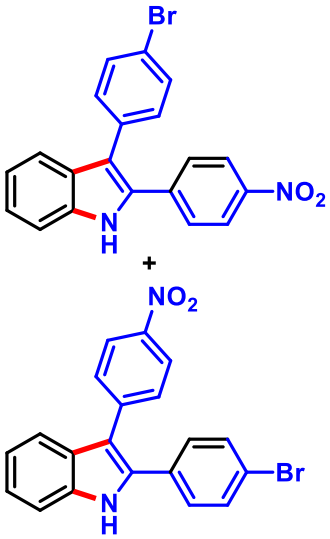
HRMS (ESI) calculated $[M+Na]^+$ for $C_{20}H_{14}O_2N_2Na$: 337.0974, found: 337.0945.

FTIR (cm^{-1}): 3455, 3020, 1596, 1552, 1451, 1343, 1250, 1150, 1072, 855, 756.

3-(4-Bromophenyl)-2-(4-nitrophenyl)-1*H*-indole (40m) and 2-(4-Bromophenyl)-3-(4-nitrophenyl)-1*H*-indole (40m')

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.134 g, 109 μL 0.45 mmol) with 3-(4-bromophenyl)-2-(4-nitrophenyl)-2*H*-azirine **52m** (0.079 g, 0.25 mmol) in the presence of KF (0.052 g, 0.9 mmol) and 18-crown-6 (0.238 g, 0.9 mmol) in THF (6.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 3-(4-bromophenyl)-2-(4-nitrophenyl)-1*H*-indole **40m** and 2-(4-bromophenyl)-3-(4-nitrophenyl)-1*H*-indole **40m'** as a red solid (0.042 g, 43% yield,

regioisomeric ratio and selectivity determined by GC analysis of crude reaction mixture is 1.3:1 and 71:29).



***R*f** (Pet. ether /EtOAc = 95/05): 0.14

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53-8.51 (m, 1H), 8.26-8.18 (m, 2H), 7.64-7.48 (m, 6H), 7.39-7.24 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.83, 146.12, 138.91, 136.66, 134.70, 133.30, 132.41, 132.27, 130.45, 130.10, 128.48, 124.35, 124.29, 124.18, 123.72, 122.91, 121.35, 120.04, 119.28, 116.88, 111.48.

Representative peaks of Minor Isomer:

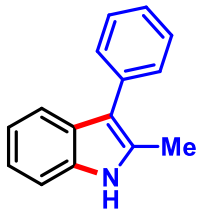
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (bs).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.46, 136.21, 131.83, 121.54, 111.52.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{14}O_2N_2Br$: 393.0233, found: 393.0233.

FTIR (cm^{-1}): 3393, 3061, 1658, 1513, 1451, 1343, 1247, 1109, 855, 754.

2-Methyl-3-phenyl-1*H*-indole (40n)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.269 g, 218 μL, 1.8 mmol) with 2-methyl-3-phenyl-2*H*-azirine **52n** (0.066 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2-methyl-3-phenyl-1*H*-indole as a pale sticky yellow liquid **40n** (0.104 g, 61% yield, selectivity determined by GC analysis of crude reaction mixture is 97:03).

***R*f** (Pet. ether /EtOAc = 95/05): 0.25

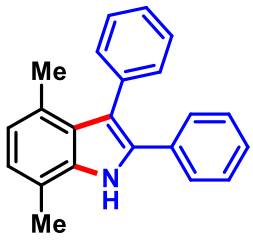
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (bs, 1H), 7.79 (d, *J* = 7.3 Hz, 1H), 7.62-7.54 (m, 4H), 7.42 -7.34 (m, 2H), 7.27-7.20 (m, 2H), 2.52 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.54, 135.30, 131.60, 129.51, 128.62, 127.90, 125.90, 121.61, 120.06, 118.87, 114.50, 110.48, 12.55.

HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{14}N$: 208.1121, found: 208.1118.

FTIR (cm^{-1}): 3464, 3058, 1618, 1562, 1495, 1330, 1255, 1188, 1019, 771.

4,7-Dimethyl-2,3-diphenyl-1*H*-indole (40o)



Following the general procedure, treatment of 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43o** (0.294 g, 1.8 mmol) with 2,3-diphenyl-2*H*-azirine **52a** (0.165 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 4,7-dimethyl-2,3-diphenyl-1*H*-indole as a pale sticky yellow liquid **40o** (0.124 g, 83% yield, selectivity determined by GC analysis of crude reaction mixture is 96:04).

***R*f** (Pet. ether /EtOAc = 95/05): 0.38

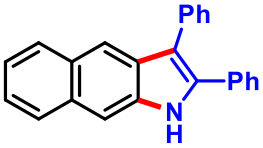
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (bs, 1H), 7.50-7.41 (m, 7H), 7.36-7.27 (m, 3H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 7.1 Hz, 1H), 2.62 (s, 3H), 2.19 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.15, 135.17, 133.86, 133.02, 131.93, 129.58, 129.25, 128.75, 128.61, 127.92, 127.82, 127.32, 127.06, 126.82, 123.09, 122.05, 117.76, 117.06, 20.24, 16.52.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{20}N$: 298.1590, found: 298.1587.

FTIR (cm^{-1}): 3316, 3058, 1659, 1599, 1477, 1317, 1217, 1072, 801, 766.

2,3-Diphenyl-1*H*-benzo[*f*]indole (40p)



Following the general procedure, treatment of 3-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate **43p** (0.157 g, 0.45 mmol) with 2,3-diphenyl-2*H*-azirine **52a** (0.049 g, 0.25 mmol) in the presence of KF (0.52 g, 0.9 mmol) and 18-crown-6 (0.238 g, 0.9 mmol) in THF (6.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 2,3-diphenyl-1*H*-benzo[*f*]indole as a pale yellow viscous liquid **40p** (0.041 g, 51% yield, selectivity determined by GC analysis of crude reaction mixture is 96:04).

***R*f** (Pet. ether /EtOAc = 95/05): 0.23

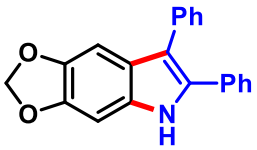
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (bs, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.67-7.59 (m, 2H), 7.55-7.47 (m, 5H), 7.38-7.21 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.29, 132.85, 132.75, 132.41, 131.58, 130.15, 128.93, 128.73, 127.57, 127.33, 127.19, 125.58, 124.16, 123.35, 122.10, 118.10, 112.57.

HRMS (ESI) calculated $[M+H]^+$ for $C_{24}H_{18}N$: 320.1434, found: 320.1432.

FTIR (cm^{-1}): 3459, 3018, 1602, 1494, 1370, 1320, 1216, 1067, 926, 765, 669.

6,7-Diphenyl-5*H*-[1,3]dioxolo[4,5-*f*]indole (40q)



Following the general procedure, treatment of 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate **43q** (0.308 g, 0.9 mmol) with 2,3-diphenyl-2*H*-azirine **52a** (0.097 g, 0.5 mmol) in the presence of KF (0.105 g, 1.8 mmol) and 18-crown-6 (0.475 g, 1.8 mmol) in THF (12.0 mL) at 60 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded 6,7-diphenyl-5*H*-[1,3]dioxolo[4,5-*f*]indole as brown solid **40q** (0.102 g, 65% yield, selectivity determined by GC analysis of crude reaction mixture is 94:06).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.1; mp 135 − 137 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (bs, 1H), 7.50-7.39 (m, 5H), 7.37 -7.28 (m, 5H), 7.08 (s, 1H), 6.91 (s, 1H), 5.97 (s, 2H).

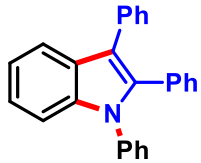
^{13}C NMR (100 MHz, $CDCl_3$) δ 145.48, 143.66, 135.26, 132.93, 131.01, 130.73, 130.15, 128.77, 128.70, 128.07, 127.80, 127.34, 126.39, 123.06, 115.54, 105.20, 102.82, 100.83, 98.42, 91.92.

HRMS (ESI) calculated $[M+H]^+$ for $C_{21}H_{16}O_2N$: 314.1176, found: 314.1170.

FTIR (cm^{-1}): 3460, 3018, 1602, 1502, 1485, 1437, 1284, 1216, 1064, 949, 770.

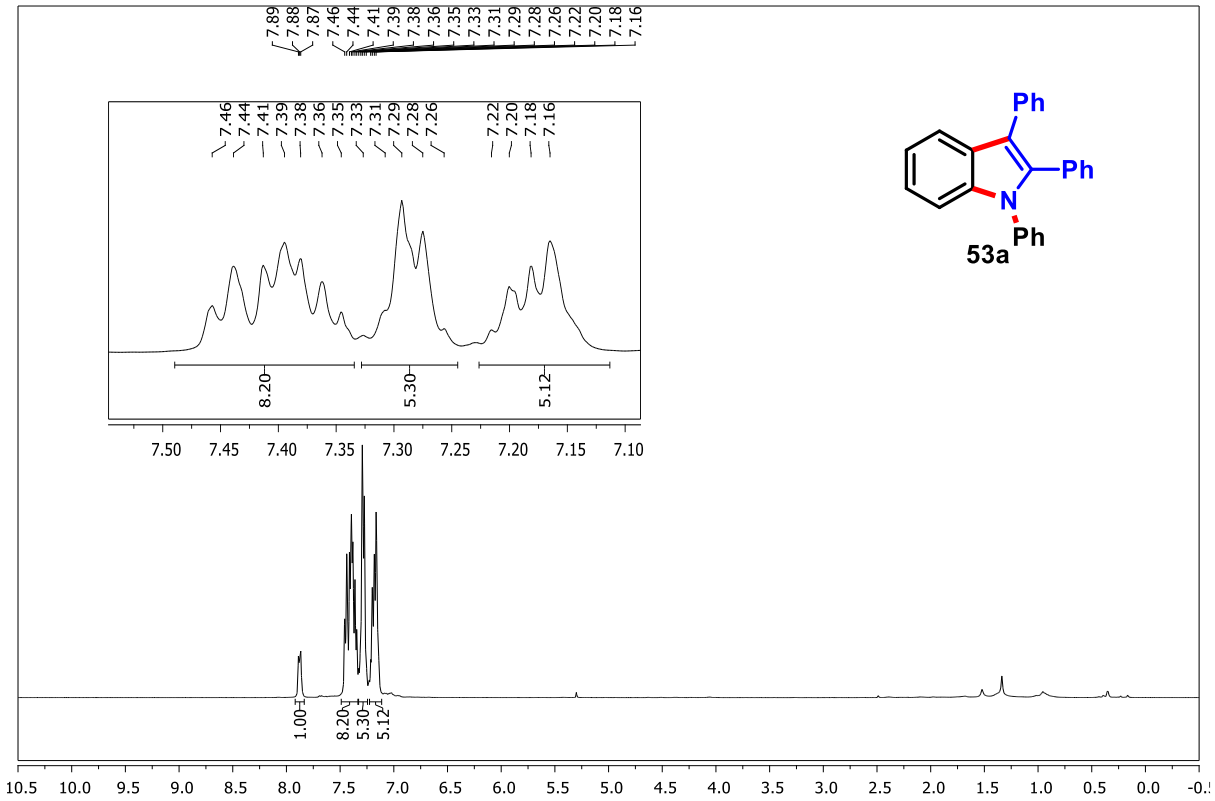
4.7.6. Synthesis and Characterization of *N*-Aryl Indoles

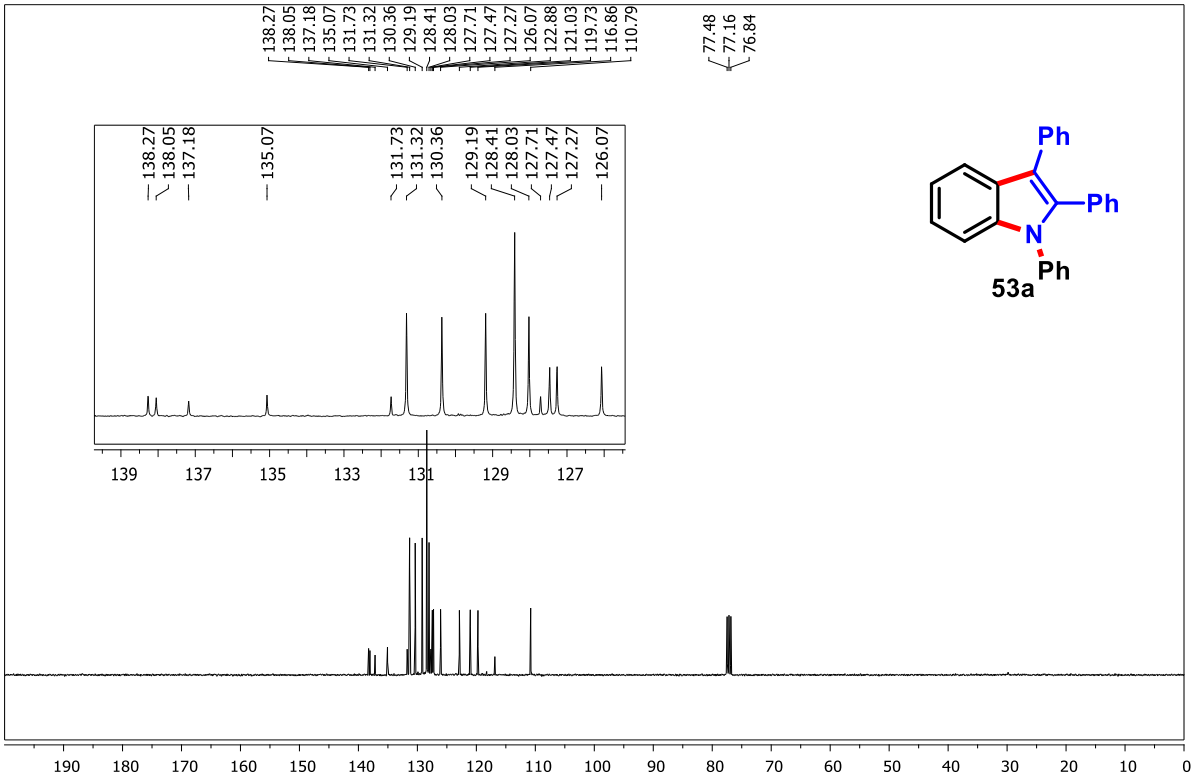
1,2,3-Triphenyl-1*H*-indole (53a)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 μL, 0.75 mmol) with 2,3-diphenyl-2*H*-azirine **52a** (0.048 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1,2,3-triphenyl-1*H*-indole **53a** as a white solid (0.072 g, 83% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

^{1}H and ^{13}C NMR Spectra of 1,2,3-Triphenyl-1*H*-indole (53a)





***R*f** (Pet. ether /EtOAc = 95/05): 0.75; mp 184 −186 °C.

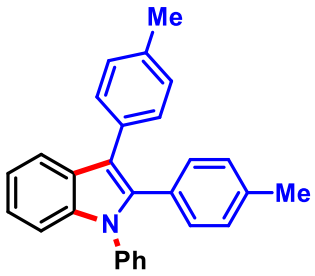
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 -7.87 (m, 1H), 7.46 -7.35 (m, 8H), 7.33 -7.26 (m, 5H), 7.22 -7.16 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.27, 138.05, 137.18, 135.07, 131.73, 131.32, 130.36, 129.19, 128.41, 128.03, 127.71, 127.47, 127.27, 126.07, 122.88, 121.03, 119.73, 116.86, 110.79.

HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{20}N$: 346.1590, found: 346.1589.

FTIR (cm^{-1}): 3018, 2925, 1598, 1547, 1495, 1450, 1371, 1219, 1073, 1025, 763.

1-Phenyl-2,3-di-*p*-tolyl-1*H*-indole (53b)

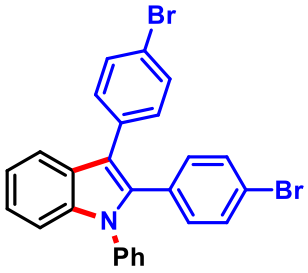


Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2,3-di-p-tolyl-2*H*-azirine **52b** (0.055 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1-phenyl-2,3-di-*p*-tolyl-1*H*-indole **(53b)** as a yellow solid (0.066 g, 71% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

***R*f** (Pet. ether /EtOAc = 95/05): 0.58; mp 175 −177 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.85 (m, 1H), 7.45 -7.35 (m, 6H), 7.31-7.25 (m, 4H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.07-6.96 (m, 4H), 2.44 (s, 3H), 2.33(s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.46, 138.01, 137.09, 135.47, 132.18, 131.13, 130.19, 129.59, 129.15, 128.82, 128.78, 128.45, 127.88, 127.14, 122.64, 120.86, 119.69, 116.49, 114.60, 110.69, 21.39, 21.37. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{28}H_{24}N$: 374.1903, found: 374.1901. **FTIR (cm^{-1})**: 3017, 1596, 1499, 1369, 1217, 1103, 832, 771, 668.

2,3-Bis(4-bromophenyl)-1-phenyl-1*H*-indole (53c)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2,3-bis(4-bromophenyl)-2*H*-azirine **52c** (0.088 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h

followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2,3-bis(4-bromophenyl)-1-phenyl-1*H*-indole **53c** as a yellow solid (0.103 g, 82% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

***R*f** (Pet. ether /EtOAc = 95/05): 0.69; mp 223 −225 °C.

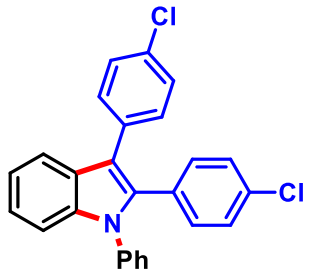
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.44-7.40 (m, 2H), 7.38-7.29 (m, 4H), 7.27-7.22 (m, 6H), 6.95 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.18, 137.81, 135.90, 133.75, 132.68, 131.87, 131.77, 131.50, 130.36, 129.45, 128.35, 127.67, 127.27, 123.36, 122.11, 121.40, 120.30, 119.48, 116.03, 110.95.

HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{18}NBr_2$: 501.9801, found: 501.9791.

FTIR (cm^{-1}): 3045, 1592, 1545, 1452, 1370, 1243, 1167, 1068, 822, 771, 746.

2,3-Bis(4-chlorophenyl)-1-phenyl-1*H*-indole (53d)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2,3-bis(4-chlorophenyl)-2*H*-azirine **52d** (0.066 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2,3-bis(4-chlorophenyl)-1-phenyl-1*H*-indole **53d** as a white solid (0.092 g, 89% yield, selectivity determined by GC analysis of crude reaction mixture is 98:02).

***R*f** (Pet. ether /EtOAc = 95/05): 0.73; mp 200 −202 °C.

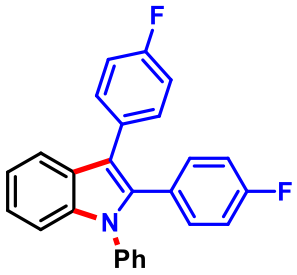
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 -7.77 (m, 1H), 7.46 -7.24 (m, 12H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.15, 137.85, 135.94, 133.79, 133.29, 132.41, 132.14, 131.52, 129.93, 129.44, 128.82, 128.55, 128.36, 127.65, 127.35, 123.33, 121.37, 119.49, 116.03, 110.94.

HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{18}NCl_2$: 414.0811, found: 414.0810.

FTIR (cm^{-1}): 3019, 1650, 1571, 1498, 1406, 1369, 1216, 1106, 1016, 837, 772.

2,3-Bis(4-fluorophenyl)-1-phenyl-1*H*-indole (53e)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2,3-bis(4-fluorophenyl)-2*H*-azirine **52e** (0.057 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2,3-bis(4-fluorophenyl)-1-phenyl-1*H*-indole **53e** as a pale yellow solid (0.077 g, 81% yield, selectivity determined by GC analysis of crude reaction mixture is 92:08).

***R*f** (Pet. ether /EtOAc = 95/05): 0.55; mp 148 −150 °C.

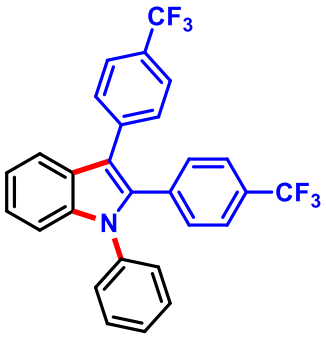
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 -7.79 (m, 1H), 7.46 -7.36 (m, 6H), 7.32-7.26 (m, 4H), 7.12-7.07 (m, 4H), 6.93-6.88 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.21, (d, *J* = 248.3 Hz), 161.58 (d, *J* = 245.5 Hz), 137.98 (d, *J* = 5.4 Hz), 136.16, 132.93 (d, *J* = 8.9 Hz), 131.75 (d, *J* = 7.7 Hz), 130.79 (d, *J* = 3.2 Hz), 129.35, 128.39, 127.51, 123.11, 121.21, 119.48, 115.98, 115.48 (d, *J* = 21.3 Hz), 115.34 (d, *J* = 21.53 Hz), 110.86.

HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{18}NF_2$: 382.1402, found: 382.1400.

FTIR (cm^{-1}): 3048, 1597, 1497, 1369, 1216, 1157, 1093, 841, 801, 772.

1-Phenyl-2,3-bis(4-(trifluoromethyl)phenyl)-1*H*-indole (53f)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2,3-bis(4-(trifluoromethyl)phenyl)-2*H*-azirine **52f** (0.079 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1-phenyl-2,3-bis(4-(trifluoromethyl)phenyl)-1*H*-indole **(53f)** as a pale yellow solid (0.098 g, 82% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

***R*f** (Pet. ether /EtOAc = 95/05): 0.69; mp 168 −170 °C.

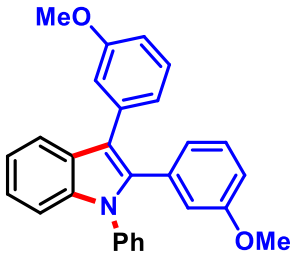
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 6.8 Hz, 1H), 7.65 (d, *J* = 7.4 Hz, 2H), 7.50-7.37 (m, 8H), 7.34-7.29 (m, 2H), 7.26-7.22 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) 138.53, 138.43, 137.61, 135.95, 135.01, 131.44, 130.47, 129.89, 129.59, 128.61, 128.36, 127.96, 127.20, 125.64 (q, *J* = 3.6), 125.26 (q, *J* = 3.4), 123.82, 123.17, 122.75, 121.73, 119.58, 116.57, 111.16.

HRMS (ESI) calculated $[M+H]^+$ for $C_{28}H_{18}NF_6$: 482.1338, found: 482.1337.

FTIR (cm^{-1}): 3020, 1610, 1495, 1365, 1219, 1119, 1019, 929, 850, 745, 668.

2,3-Bis(3-methoxyphenyl)-1-phenyl-1*H*-indole (53g)



Following the general procedure, treatment of 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2,3-bis(3-methoxyphenyl)-2*H*-azirine **52g** (0.088 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2,3-bis(3-methoxyphenyl)-1-phenyl-1*H*-indole **53g** as a yellow solid (0.088 g, 87% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.37; mp 123 −125 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.83 (m, 1H), 7.42-7.39 (m, 2H), 7.35-7.32 (m, 2H), 7.28-7.22 (m, 5H), 7.07 (t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.97 (s, 1H), 6.82 (dd, J_1 = 8.2 Hz, J_2 = 1.9 Hz, 1H), 6.75-6.71 (m, 2H), 6.64 (s, 1H), 3.71 (s, 3H), 3.53 (s, 3H).

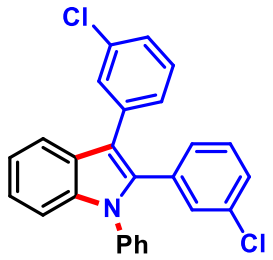
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.59, 159.07, 138.31, 138.01, 137.04, 136.41, 132.88, 129.35, 129.25, 129.03, 128.37, 127.58, 127.34, 123.87, 122.94, 122.87, 121.07, 119.81, 116.80, 116.23, 115.51, 113.93, 112.17, 110.80, 55.23, 55.16.

HRMS (ESI) calculated $[M+H]^+$ for $C_{28}H_{24}O_2N$: 406.1802, found: 406.1800.

FTIR (cm^{-1}): 3011, 2835, 1598, 1498, 1429, 1368, 1284, 1217, 1154, 1046, 756, 667.

2,3-Bis(3-chlorophenyl)-1-phenyl-1*H*-indole (53h)

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2,3-bis(3-chlorophenyl)-2*H*-azirine **52h** (0.066 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column



chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2,3-bis(3-chlorophenyl)-1-phenyl-1*H*-indole **53h** as a white solid (0.094 g, 91% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

***R*f** (Pet. ether /EtOAc = 95/05): 0.63; mp 159 − 161 °C.

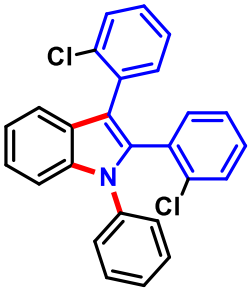
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.81 (m, 1H), 7.48 -7.36 (m, 5H), 7.33-7.26 (m, 6H), 7.22-7.20 (m, 2H), 7.15-7.11 (m, 2H), 7.03 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.13, 137.68, 136.57, 135.82, 134.31, 133.98, 133.17, 131.01, 130.06, 129.79, 129.44, 128.52, 128.34, 127.95, 127.77, 127.19, 126.50, 123.47, 121.46, 119.58, 116.11, 110.99.

HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{18}NCl_2$: 414.0811, found: 414.0812.

FTIR (cm^{-1}): 3064, 1596, 1487, 1425, 1319, 1239, 1078, 997, 888, 758.

2,3-Bis(2-chlorophenyl)-1-phenyl-1*H*-indole (53i)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 μL, 0.75 mmol) with 2,3-bis(2-chlorophenyl)-2*H*-azirine **52i** (0.066 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2,3-bis(2-chlorophenyl)-1-phenyl-1*H*-indole **(53i)** as a yellow solid (0.091 g, 88% yield, selectivity determined by GC analysis of crude reaction mixture is 95:05).

***R*f** (Pet. ether /EtOAc = 95/05): 0.57; mp 147 − 149 °C.

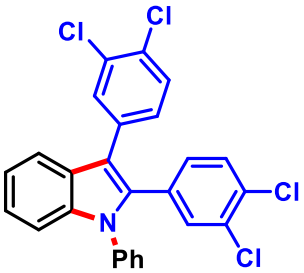
^{1}H NMR (400 MHz, $CDCl_3$) 7.61-7.53 (m, 1H), 7.48-7.43 (m, 2H), 7.40-7.28 (m, 7H), 7.27-7.22 (m, 4H), 7.20-7.14 (m, 2H), 7.13-7.09 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.83, 137.29, 135.58, 135.37, 134.86, 133.74, 133.33, 131.39, 131.07, 129.93, 129.80, 129.43, 128.96, 128.52, 127.82, 127.26, 126.57, 126.05, 122.94, 120.83, 120.53, 116.12, 114.58, 110.82.

HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{18}NCl_2$: 414.0811, found: 414.0809.

FTIR (cm^{-1}): 3059, 1596, 1499, 1435, 1320, 1216, 1121, 1062, 1032, 749.

2,3-Bis(3,4-dichlorophenyl)-1-phenyl-1*H*-indole (53j)



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2,3-bis(3,4-dichlorophenyl)-2*H*-azirine **52j** (0.083 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2,3-bis(3,4-dichlorophenyl)-1-phenyl-1*H*-indole **53j** as a yellow solid (0.097 g, 80% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.65; mp 164−166 °C.

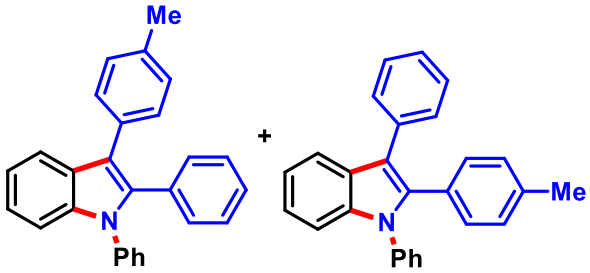
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 (d, *J* = 7.4 Hz, 1H), 7.59 (s, 1H), 7.49-7.42 (m, 4H), 7.35-7.24 (m, 6H), 7.18 (s, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 138.23, 137.37, 134.78, 134.66, 132.72, 132.62, 132.52, 132.27, 131.71, 131.17, 130.69, 130.54, 130.38, 130.33, 129.65, 129.60, 128.31, 128.07, 126.93, 123.83, 121.73, 119.40, 117.49, 115.37, 111.11.

HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{16}NCl_4$: 482.0031, found: 482.0035.

FTIR (cm^{-1}): 3061, 1594, 1498, 1451, 1375, 1258, 1215, 1110, 888, 757.

1,2-Diphenyl-3-(*p*-tolyl)-1*H*-indole (53k) and 1,3-Diphenyl-2-(*p*-tolyl)-1*H*-indole (53k')



Following the general procedure, treatment of 2-(trimethylsilyl) phenyltrifluoro methane sulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2-phenyl-3-(*p*-tolyl)-2*H*-azirine **52k** (0.052 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1,2-diphenyl-3-(*p*-tolyl)-1*H*-indole **53k** and 1,3-diphenyl-2-(*p*-tolyl)-1*H*-indole **53k'** as a mixture of regioisomers in 1:1 ratio (0.082 g, 91% yield, white solid, regioisomer-ratio and selectivity determined by GC analysis of crude reaction mixture is 1:1 and 98:02).

***R*f** (Pet. ether /EtOAc = 95/05): 0.64

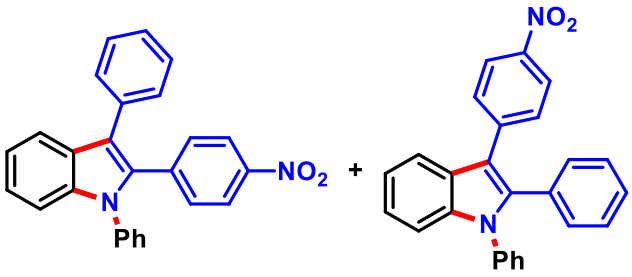
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.81 (m, 2H), 7.41-7.11 (m, 30H), 6.99 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.38, 138.33, 138.01, 137.32, 137.20, 136.98, 135.59, 135.24, 131.99, 131.86, 131.32, 131.13, 130.37, 130.19, 129.18, 128.80, 128.66, 128.46, 128.42, 128.38, 128.01, 127.79, 127.76, 127.40, 127.21, 125.98, 122.80, 122.70, 120.94, 119.80, 119.61, 110.74, 21.40, 21.37.

HRMS (ESI) calculated $[M+H]^+$ for $C_{27}H_{22}N$: 360.1747, found: 360.1747.

FTIR (cm^{-1}): 3011, 1597, 1500, 1454, 1369, 1320, 1216, 1168, 1074, 1025, 827, 766, 699.

2-(4-Nitrophenyl)-1,3-diphenyl-1*H*-indole (53l) and 3-(4-Nitrophenyl)-1,2-diphenyl-1*H*-indole (53l')



Following the general procedure, treatment of 2-(trimethylsilyl) phenyltrifluoromethane sulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2-(4-nitrophenyl)-3-phenyl-2*H*-azirine **52l** (0.060 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 3-(4-Nitrophenyl)-1,2-diphenyl-1*H*-indole **53l** and 2-(4-Nitrophenyl)-1,3-diphenyl-1*H*-indole **53l'** as a mixture of regioisomers in 1.4:1 ratio (0.093 g, 95% yield, yellow viscous liquid, regioisomer-ratio and selectivity determined by GC analysis of crude reaction mixture is 1.4:1 and 99:01).

***R*f** (Pet. ether /EtOAc = 95/05): 0.46

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.86-7.80 (m, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.47-7.20 (m, 13H), 7.12-7.10 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.61, 142.75, 138.77, 137.77, 137.58, 134.30, 134.12, 131.73, 130.92, 130.43, 129.66, 128.81, 128.40, 128.28, 127.82, 127.64, 126.76, 124.04, 123.30, 121.80, 120.59, 119.27, 114.64, 111.25, 110.97.

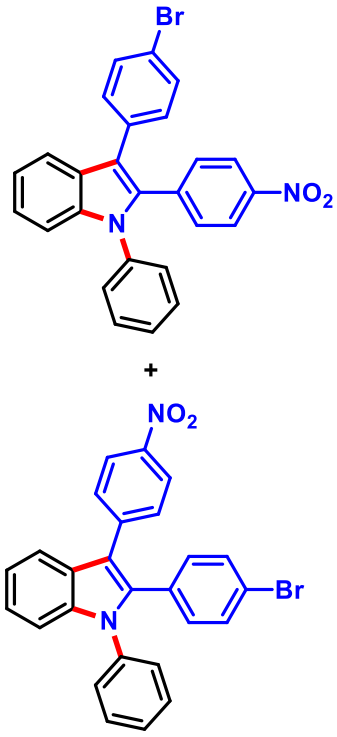
Representative peaks of Minor Isomer:

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.75, 138.24, 131.23, 138.61, 129.36, 128.47, 127.90, 126.88, 123.84, 123.45, 121.55, 120.21, 119.10.

HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{19}O_2N_2$: 391.1441, found: 391.1438.

FTIR (cm^{-1}): 3064, 1596, 1548, 1454, 1369, 1288, 1215, 1105, 910, 859, 777.

3-(4-Bromophenyl)-2-(4-nitrophenyl)-1-phenyl-1*H*-indole (53m) and 2-(4-Bromophenyl)-3-(4-nitrophenyl)-1-phenyl-1*H*-indole (53m')



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43a** (0.224 g, 182 µL, 0.75 mmol) with 2-(4-bromophenyl)-3-(4-nitrophenyl)-2*H*-azirine **52m** (0.079 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 2-(4-bromophenyl)-3-(4-nitrophenyl)-1-phenyl-1*H*-indole **(53m)** and 3-(4-bromophenyl)-2-(4-nitrophenyl)-1-phenyl-1*H*-indole **(53m')** as a yellow solid (0.087 g, 74% yield, regio isomeric ratio and selectivity determined by GC analysis of crude reaction mixture is 1.2:1 and 97:03).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.46

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.84-7.76 (m, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.48-7.39 (m, 3H), 7.37-7.31 (m, 4H), 7.28-7.25 (m, 4H), 7.0 (d, *J* = 7.1 Hz, 1H).

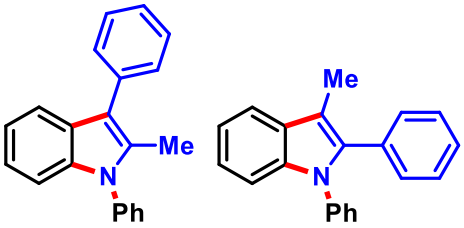
^{13}C NMR (100 MHz, $CDCl_3$) δ 146.74, 145.91, 138.33, 138.20, 137.52, 134.43, 133.14, 132.65, 131.77, 131.71, 130.48, 130.39, 129.85, 129.68, 127.24, 123.96, 123.72, 123.42, 122.72, 121.92, 121.73, 120.88, 119.15, 117.81, 111.25, 111.07.

Representative peaks of Minor Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.30, 138.62, 137.32, 137.17, 132.00, 131.90, 129.55, 128.34, 128.23, 128.03, 126.70, 124.16, 120.56, 119.83, 115.02, 114.56.

HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{18}O_2N_2Br$: 469.0546, found: 469.0544.

FTIR (cm^{-1}): 1595, 1514, 1497, 1411, 1395, 1344, 1289, 1174, 1071, 860, 753.

2-Methyl-1,3-diphenyl-1*H*-indole (53n) and 3-Methyl-1,2-diphenyl-1*H*-indole (53n')



Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43b** (0.224 g, 182 µL, 0.75 mmol) with 2-methyl-3-phenyl-2*H*-azirine **52n** (0.033 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded regioisomeric mixture of 2-methyl-1,3-diphenyl-1*H*-indole **(53n)** and 3-methyl-1,2-diphenyl-1*H*-indole **(53n')** as a yellow viscous liquid (0.062 g, 88% yield, selectivity and regioisomeric ratio determined by GC analysis of crude reaction mixture is 98:02 and 1.5:1).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.50

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 -7.68 (m, 1H), 7.53 -7.49 (m, 2H), 7.37-7.33 (m, 4H), 7.24-7.20 (m, 6H), 7.18 (m, 1H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.77, 137.71, 135.63, 132.23, 129.84, 129.13, 128.32, 128.0, 127.44, 126.72, 122.60, 120.51, 119.02, 110.82, 110.23, 12.19.

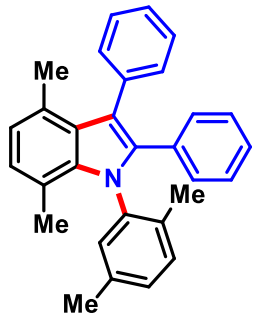
^{1}H NMR (400 MHz, $CDCl_3$) for minor isomer: 7.75-7.73 (m), 7.61-7.56 (m), 7.47-7.43 (m), 7.32-7.27 (m), 7.18-7.16 (m), 2.37 (s).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.04, 137.02, 133.66, 130.71, 129.65, 128.65, 128.08, 127.24, 126.07, 120.83, 120.21, 118.84, 110.47, 9.72.

HRMS (ESI) calculated $[M+H]^+$ for $C_{21}H_{18}N$: 284.1434, found: 284.1433.

FTIR (cm^{-1}): 3057, 1597, 1499, 1397, 1247, 1177, 1074, 915, 794, 700.

1-(2,5-Dimethylphenyl)-4,7-dimethyl-2,3-diphenyl-1*H*-indole (53o)



Following the general procedure, treatment of 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **43o** (0.245 g, 0.75 mmol) with 2,3-diphenyl-2*H*-azirine **52a** (0.083 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1-(2,5-dimethylphenyl)-4,7-dimethyl-2,3-diphenyl-1*H*-

indole **53o** as a yellow viscous liquid (0.041 g, 41% yield, selectivity determined by GC analysis of crude reaction mixture is 94:06).

***R*f** (Pet. ether /EtOAc = 95/05): 0.38

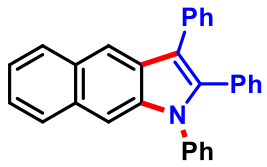
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.43 (m, 1H), 7.33-7.24 (m, 5H), 7.08-7.0 (m, 7H), 6.90-6.84 (m, 2H), 2.34 (s, 3H), 2.20 (s, 3H), 1.90 (s, 3H), 1.89 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.09, 138.73, 137.28, 135.33, 135.30, 134.99, 132.52, 132.02, 131.78, 131.24, 129.67, 129.33, 129.03, 127.29, 127.06, 126.60, 126.27, 124.99, 121.98, 119.58, 117.79, 20.94, 20.77, 18.83, 17.28.

HRMS (ESI) calculated $[M+H]^+$ for $C_{30}H_{28}N$: 402.2216, found: 402.2213.

FTIR (cm^{-1}): 3006, 1647, 1507, 1414, 1352, 1285, 1113, 1033, 989, 842, 753.

1,2,3-Triphenyl-1*H*-benzo[*f*]indole (53p)



Following the general procedure, treatment of 3-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate **43p** (0.261 g, 0.75 mmol) with 2,3-diphenyl-2*H*-azirine **52a** (0.048 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 1,2,3-triphenyl-1*H*-benzo[*f*]indole **53p** as a yellow viscous liquid (0.054 g, 55% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

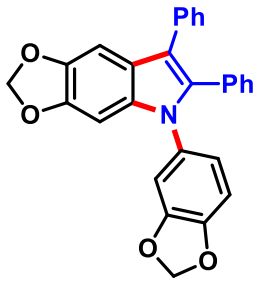
***R*f** (Pet. ether /EtOAc = 95/05): 0.49

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.0-7.83 (m, 7H), 7.59 -7.52 (m, 4H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.39 -7.33 (m, 3H), 7.25-7.16 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.06, 140.71, 139.02, 136.18, 134.93, 133.68, 132.21, 131.48, 131.24, 130.96, 130.48, 129.72, 129.57, 129.23, 128.60, 128.36, 128.19, 128.08, 127.99, 127.87, 127.63, 126.80, 126.70, 126.67, 126.53, 126.34, 124.18, 123.13, 117.31, 116.30, 106.11.

FTIR (cm^{-1}): 3020, 1660, 1596, 1502, 1443, 1383, 1216, 1110, 1061, 925, 862, 763.

5-(Benzo[*d*][1,3]dioxol-4-yl)-6,7-diphenyl-5*H*-[1,3]dioxolo[4,5-*f*]indole (53q)



Following the general procedure, treatment of 6-(trimethylsilyl)benzo[*d*][1,3] dioxol-5-yl trifluoromethanesulfonate **43q** (0.257 g, 0.75 mmol) with 2,3-diphenyl-2*H*-azirine **52a** (0.048 g, 0.25 mmol) in the presence of KF (0.087 g, 1.5 mmol) and 18-crown-6 (0.396 g, 1.5 mmol) in THF (1.0 mL) at -10 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 5-(benzo[*d*][1,3]dioxol-4-yl)-6,7-diphenyl-5*H*-[1,3]dioxolo[4,5-*f*]indole **53q** as a brown solid (0.069 g, 64% yield, selectivity determined by GC analysis of crude reaction mixture is 99:01).

***R*f** (Pet. ether /EtOAc = 95/05): 0.27; mp 184−186 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 4H), 7.25-7.21 (m, 1H), 7.16-7.13 (m, 4H), 7.09-7.06 (m, 2H), 6.78-6.67 (m, 4H), 5.99 (s, 2H), 5.93 (s, 2H).

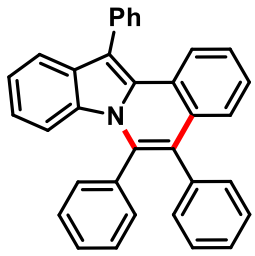
^{13}C NMR (100 MHz, $CDCl_3$) δ 148.09, 146.85, 145.49, 143.91, 136.05, 135.15, 133.74, 132.21, 131.84, 131.09, 130.16, 128.43, 128.01, 127.18, 126.03, 121.97, 121.44, 116.78, 109.41, 108.30, 101.81, 100.88, 98.21, 91.84.

HRMS (ESI) calculated $[M+H]^+$ for $C_{28}H_{20}O_4N$: 434.1387, found: 434.1380.

FTIR (cm^{-1}): 3019, 1602, 1489, 1464, 1334, 1291, 1180, 946, 879, 770, 700.

4.7.7. Synthesis and Characterization of indolo[2,1-a]isoquinoline derivative

5,6,12-Triphenylindolo[2,1-*a*]isoquinoline (55a)

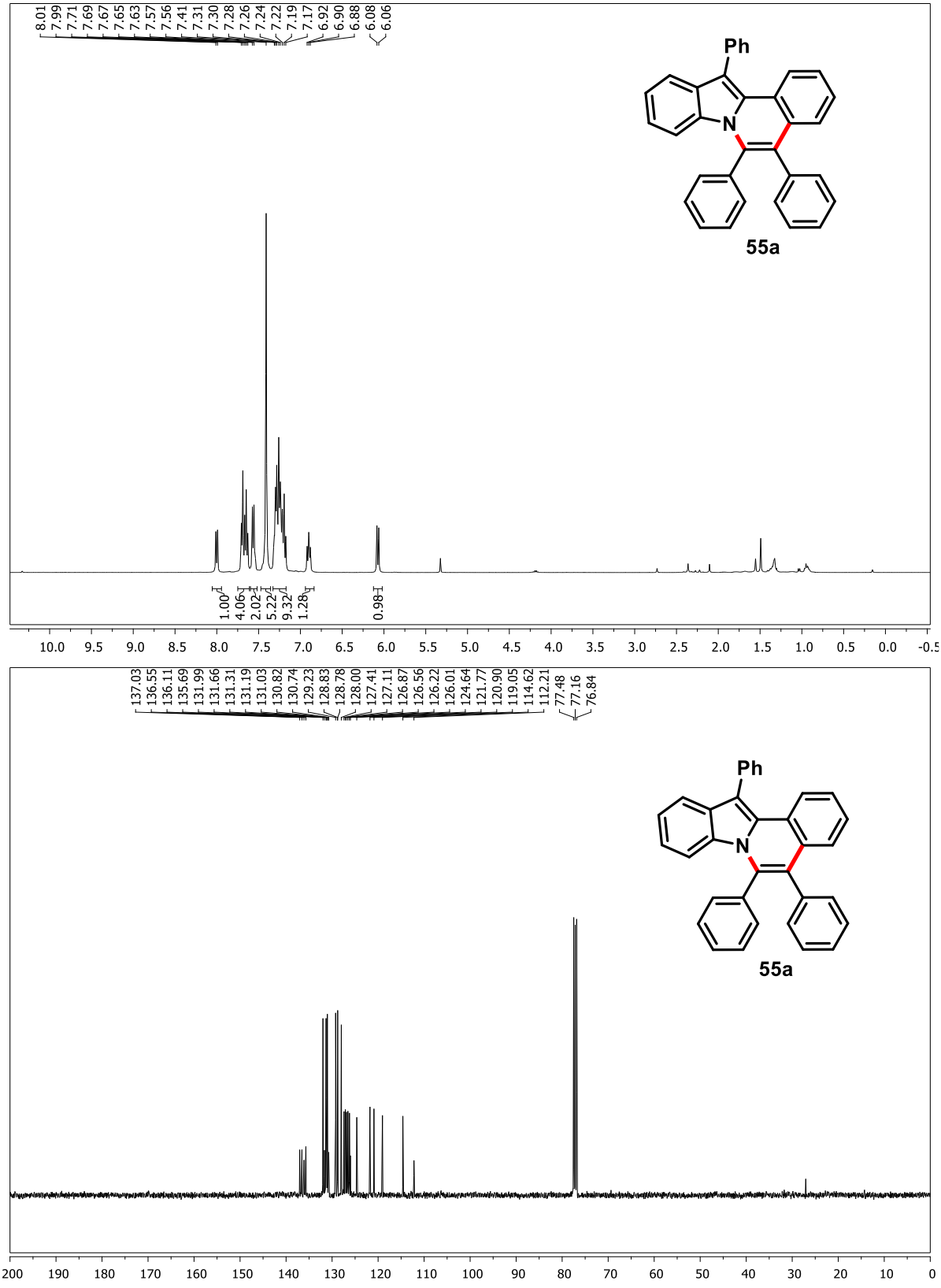


Treatment of 2,3-diphenyl-1*H*-indole **40a** (0.030 g, , 0.1114 mmol) with 1,2-diphenylacetylene **54** (0.024 g, 0.1337 mmol) in the presence of $[(Cp^*RhCl_2)_2]$ (0.002 g, 0.00223 mmol, 2 mol %) and $Cu(OAc)_2 \cdot H_2O$ (0.002 g, 0.01114 mmol, 10 mol %) in *o*-xylene (1.0 mL) at 100 °C for 6 h followed by flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture using silica gel afforded 5,6,12-triphenylindolo[2,1-*a*]isoquinoline **55a** as a yellow solid (0.046 g, 93% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.54; mp 193 −195 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.9 Hz, 1H), 7.71 -7.63 (m, 4H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.41 (s, 5H), 7.31-7.17 (m, 9H), 6.90 (t, *J* = 7.8 Hz, 1H), 6.08 (d, *J* = 8.9 Hz, 1H).

^{1}H and ^{13}C NMR Spectra of 5,6,12-Triphenylindolo[2,1-*a*]isoquinoline (55a)



^{13}C NMR (100 MHz, $CDCl_3$) δ 137.03, 136.55, 136.11, 135.69, 131.99, 131.66, 131.31, 131.19, 131.03, 130.82, 130.74, 129.23, 128.83, 128.78, 128.00, 127.41, 127.11, 126.87, 126.56, 126.22, 126.01, 124.64, 121.77, 120.90, 119.05, 114.62, 112.21.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{24}N$: 446.1903, found: 446.1900.

FTIR (cm^{-1}): 3063, 1603, 1549, 1483, 1379, 1332, 1216, 1109, 1030, 924, 766, 670.

4.8. References

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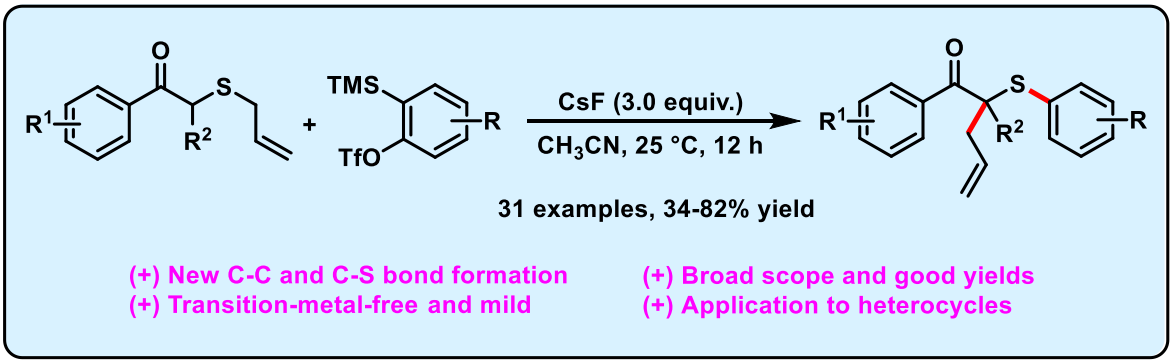
Chapter 5

Synthesis of Functionalized β-Keto Arylthioethers by the Aryne Induced [2,3] Stevens Rearrangement of Allylthioethers

A mild and transition-metal-free synthesis of β-keto arylthioethers has been developed by the aryne triggered [2,3] Stevens rearrangement of allylthioethers. The key sulfur ylide intermediate for the rearrangement was formed by the *S*-arylation of allylthioethers with arynes generated from 2-(trimethylsilyl)aryl triflates using CsF. Later, the reaction products are converted into valuable heterocycles in two steps.



J. Org. Chem. **2017**, *82*, 4470−4476.

5.1. Introduction

Organosulfur compounds are endowed with diverse applications in pharmaceutical chemistry, crop protection, and have attracted considerable attention from both industry and academia.[1] Among the organosulfur compounds, the β-keto thioethers are important as they are valuable core structure in various biologically active molecules. For instance, the indane 1,3-dione derived aryl thioethers (A) has been known as serine protease inhibitor (Figure 5.1).[2] Moreover, the cyclohexanone containing thioether (B) is a precursor for the synthesis of Gabosines, epoforminand epiepoformin,[3] and the benzothiazine derivative (C) shows anti-inflammatory activity.[4] In addition, the 2-amino aryl thioethers (D) shows antitumor activity.[5] In view of the relevance of these molecules, studies towards the development of a facile and straightforward synthetic routes to β-keto aryl allylthioethers by the aryne induced [2,3] Stevens rearrangement of allylthioethers forms the focal theme of this chapter. Before going into the details, a brief summary of [2,3] sigmatropic rearrangements is outlined in the following sections.

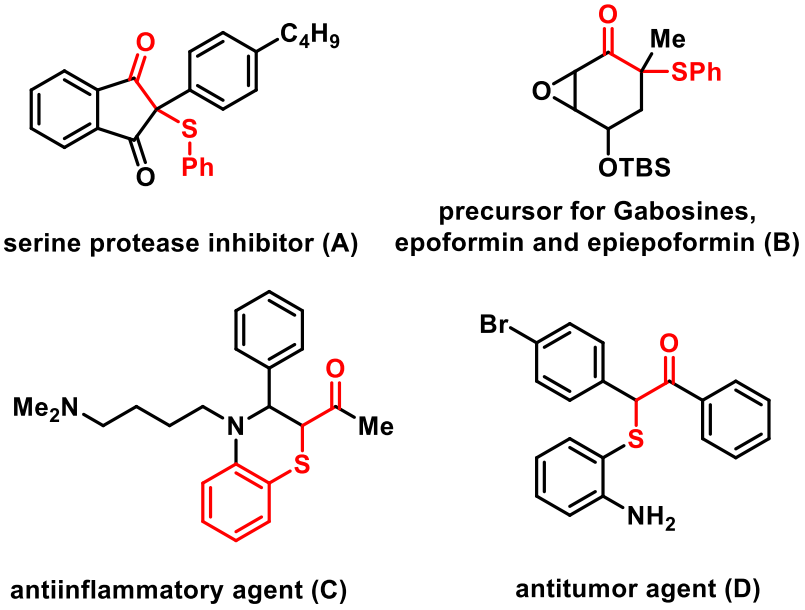


Figure 5.1: Biologically Active Molecules Having β-Keto Thioethers Moiety

5.2. General Classifications of [2,3]-Sigmatropic Rearrangements

[2,3]-sigmatropic rearrangements have great utility in organic synthesis.[6,7] In particular, the ability to form carbon-carbon bonds with high diastereo- and enantioselectivity through well-defined and predictable transition states under often mild

reaction conditions makes [2,3]-sigmatropic rearrangements attractive for the synthesis of complex targets. [2,3]-sigmatropic processes can be broadly classified into two main types: (a) neutral rearrangements involving ylides and (b) anionic rearrangements (Figure 5.2). These reactions always involve at least one heteroatom and allow a number of different products containing various functional groups to be accessed.

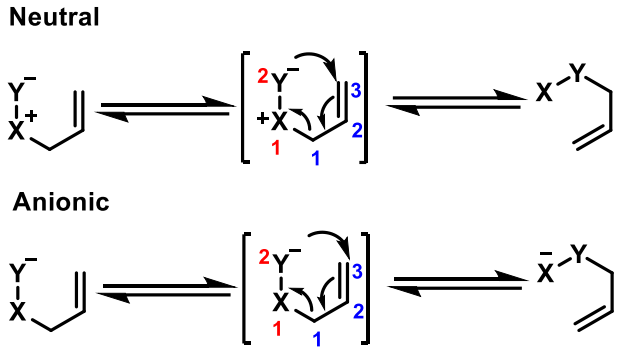
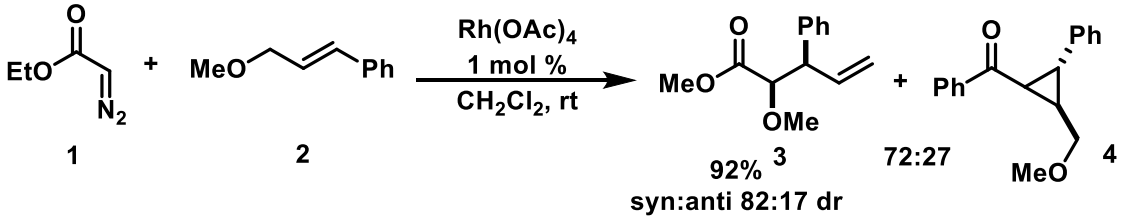


Fig 5.2: General Classification of [2,3]-Sigmatropic Rearrangements

5.3 Neutral [2,3]-Sigmatropic Rearrangements

5.3.1. Metal-Catalyzed Onium Ylide Formation and [2,3]-Rearrangements via Metal Carbenoids

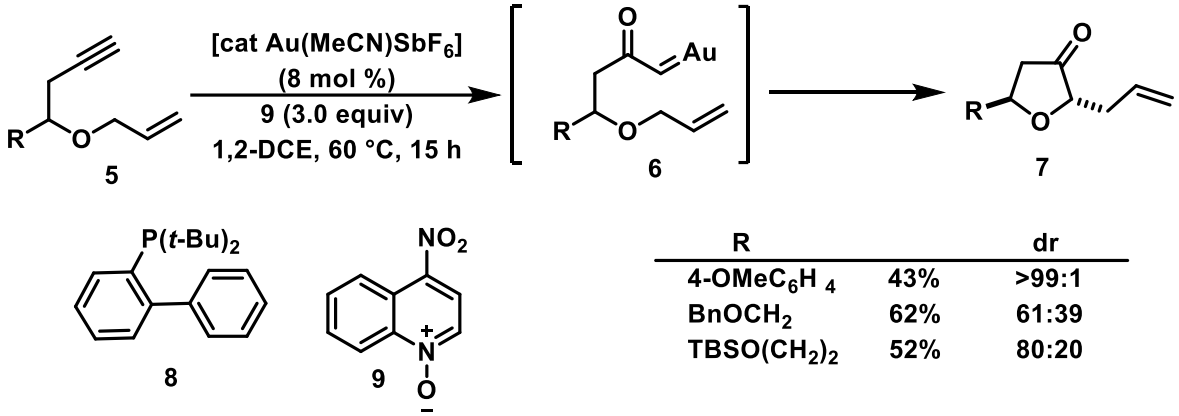
Doyle and co-workers reported the diastereoselective [2,3]-rearrangement of oxonium ylides from the reaction of catalytically generated rhodium carbenoids and allylic ethers. For example, the dropwise addition of ethyl diazoacetate **1** to a solution of Rh (1 mol %) and allylic ether **2** leads to the selective formation of [2,3]-rearrangement product **3** in 92% yield and 83:17 dr (*syn:anti*), along with competitive cyclopropanation product **4** as side product (Scheme 5.1).[8] The reaction was applicable to both diazoacetates and diazoacetophenones,



Scheme 5.1: Diastereoselective Intermolecular Oxonium Ylide Formation and [2,3]-Rearrangement

alongside a small range of substituted allylic ethers, with [2,3]-rearrangement favoured over cyclopropanation in all cases.

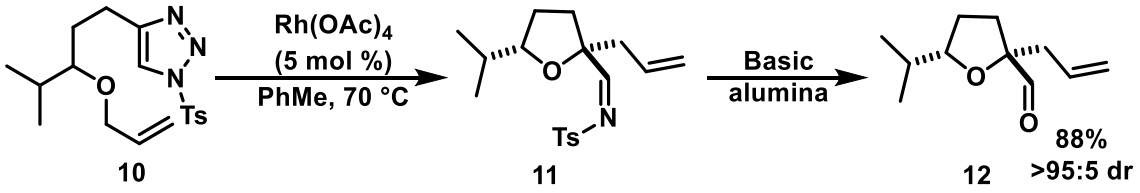
Tae and co-workers developed a flexible and general method for the synthesis of various 2,5-disubstituted dihydrofuran-3(2*H*)-ones via [2,3]-sigmatropic rearrangements. Treatment of oxonium ylides generated from α-oxo gold carbenes **6**, which are formed by the gold-catalyzed intermolecular oxidation of the allyl homopropargyl ethers **5** with *N*-oxide **9** afforded the corresponding 2,5-disubstituted dihydrofuran-3(2*H*)-ones **7** (Scheme 5.2).[9] The synthetic utility of the current method has been proved by concise formal synthesis of (±)-kumausallene.



R		dr
4-OMeC$_6$H$_4$	43%	>99:1
BnOCH$_2$	62%	61:39
TBSO(CH$_2$)$_2$	52%	80:20

Scheme 5.2: Alkynes as Gold Carbenoid Precursors

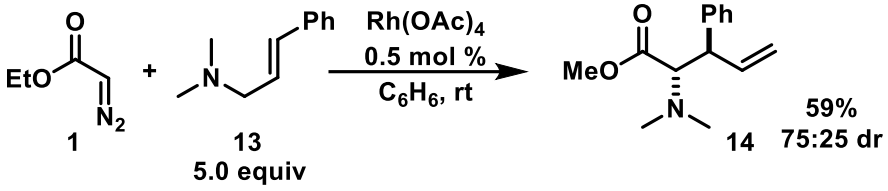
Boyer and co-workers reported the rhodium(II) acetate catalyzed denitrogenative reaction of 5-substituted and 4,5-disubstituted 1-sulfonyl-1,2,3-triazoles with pendent allyl and propargyl ether motifs **10** to oxonium ylides that undergo [2,3]-sigmatropic rearrangement to form the substituted dihydrofuran-3-imines **11** (Scheme 5.3).[10] The intermediate *N*-tosyl imine **11** was unstable to purification but was readily hydrolyzed into aldehyde **12** in an overall 88% yield as a single diastereoisomer.



Scheme 5.3: Diastereoselective Synthesis of C(2)-Tetrasubstituted Saturated Heterocycles

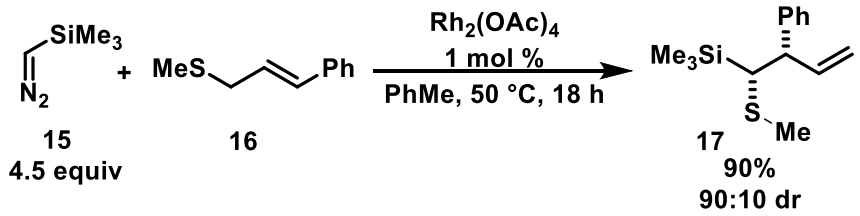
In 1981, Doyle and co-workers revealed the diastereoselective intermolecular ammonium ylide formation and [2,3]-rearrangement from the catalytic decomposition of a

diazo compound. Reaction of ethyl diazoacetate **1** with $Rh_2(OAc)_4$ (0.5 mol %) and an excess of tertiary allylic amine **13** resulted in the formation of the rearranged α-amino acid derivative **14** in 59% yield with 75:25 mixture of *anti:syn* diastereoisomers (Scheme 5.4).[11]



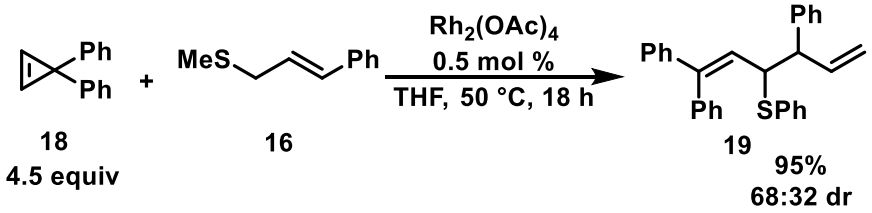
Scheme 5.4: Diastereoselective Allylic Ammonium Ylide Generation and [2,3]-Rearrangement

Aggarwal and co-workers developed the reaction of trimethylsilyldiazomethane **15** with allylic sulfides **16** in the presence of catalytic amount of $Rh_2(OAc)_4$ (1 mo l%) to afford the corresponding homoallylic sulphides **17** in good yields and with high diastereoselectivity.[12]



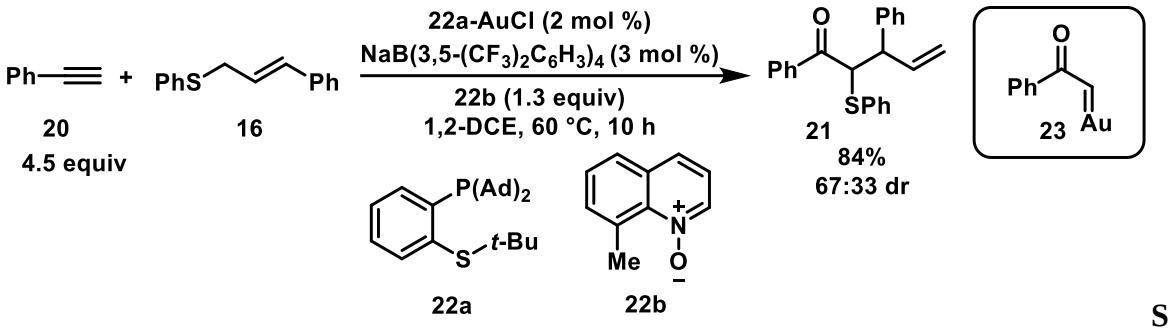
Scheme 5.5: Use of Trimethylsilyl Diazomethane as a Sulfonium Ylide Precursor

Wang and co-workers reported a new type of $Rh_2(OAc)_4$-catalyzed [2,3]-sigmatropic rearrangement of sulfur ylides. A variety of cyclopropenes **18** were successfully employed for [2,3]-sigmatropic rearrangement by the reaction with either allylic or propargylic sulfides **16**.[13] The reaction afforded the products **19** in moderate to excellent yields. The vinyl metal carbenes generated in situ from the cyclopropenes were effectively trapped by sulfides in these transformations, resulting in the formation of corresponding products upon [2,3]- sigmatropic rearrangements.



Scheme 5.6: Use of Cyclopropenes as Rhodium Carbenoid Precursors

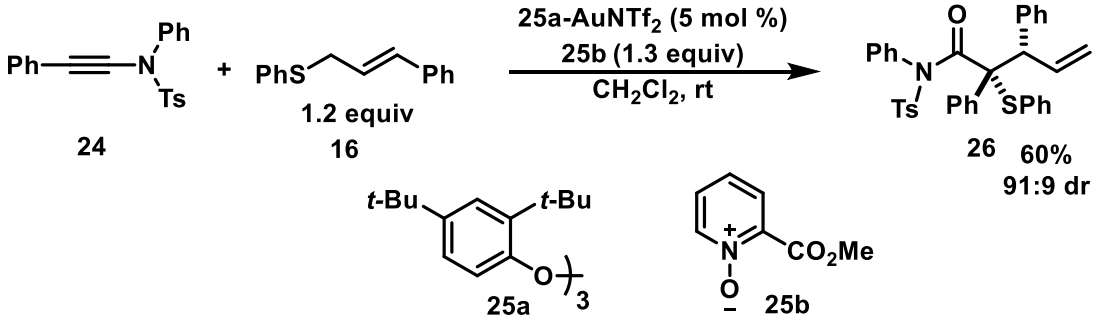
Zhang and co-workers developed a new P, S-bidentate phosphine **22a** as the ligand to gold(I), the α-oxo gold carbenes **23** generated in situ via gold-catalyzed intermolecular oxidation of terminal alkynes **20.** Effective trapping of **23** by various allylic sulphides **16** resulted in the formation of α-aryl(alkyl)thio-γ,δ-unsaturated ketones **21** upon facile [2,3]-sigmatropic rearrangements (Scheme 5.7).[14]



S

cheme 5.7: Alkynes as Metal Carbenoid Precursors

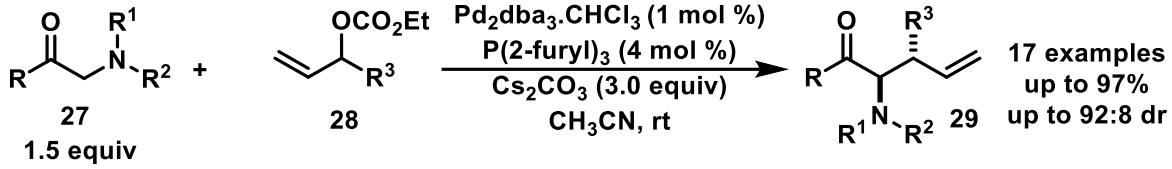
An efficient gold-catalyzed C–O, C–S and C–C bond-forming sequence resulting in functionalized compounds bearing sulfur-substituted quaternary carbons **26** was revealed by Davies and co-workers. Ynamides **24** are employed as diazo-equivalents to access the [2,3]-sigmatropic rearrangements of allyl sulfonium ylides generated from allylthioether **16** by a three-component chemoselective oxidation and intermolecular ylide formation. In this case, pyridine *N*-oxide **25b** was utilized as the stoichiometric oxidant alongside gold complexed with ligand **25a** as the catalyst. This report also demonstrates that ynamides can be used as synthetically attractive replacements to 1,1-disubstituted diazocompounds in intermolecular processes.[15]



Scheme 5.8: Diastereoselective [2,3]-Rearrangement Using Ynamide as a Gold Carbene Precursor

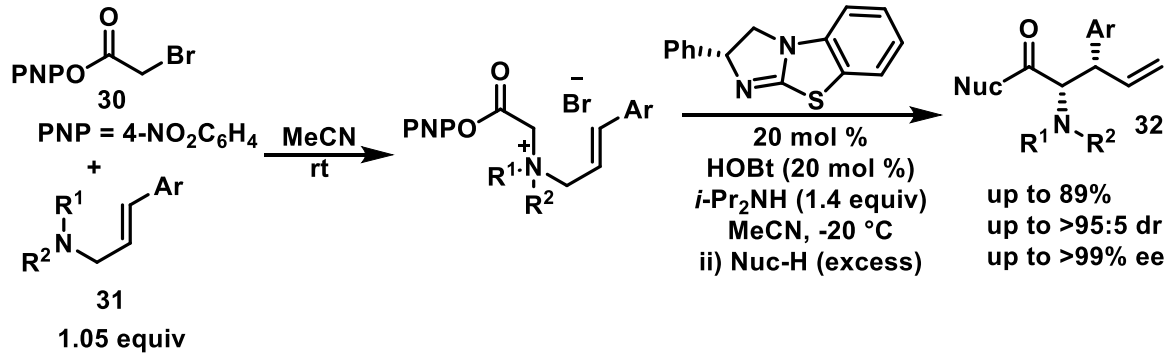
5.3.2. [2,3]-Rearrangements of Ammonium Ylides from Allylic Quaternary Ammonium Salts

Tambar and co-workers developed a palladium-catalyzed allylic amination involving tertiary amines **27** and allylcarbonates **28** that generates ammonium ylides, which rearrange under the reaction conditions to give unnatural amino acid derivatives and complex *R*-amino ketones **29** with unprecedented levels of stereocontrol (Scheme 5.9).[16] This process is employed in a tandem ammonium ylide generation/[2,3]-rearrangement reaction, which formally represents a palladium-catalyzed Stevens rearrangement. The mild reaction conditions allow the use of a wide variety of tertiary amine nucleophiles and allylcarbonates.



Scheme 5.9: Palladium-Catalyzed Allylic Amination to form [2,3]-Rearrangement Precursors

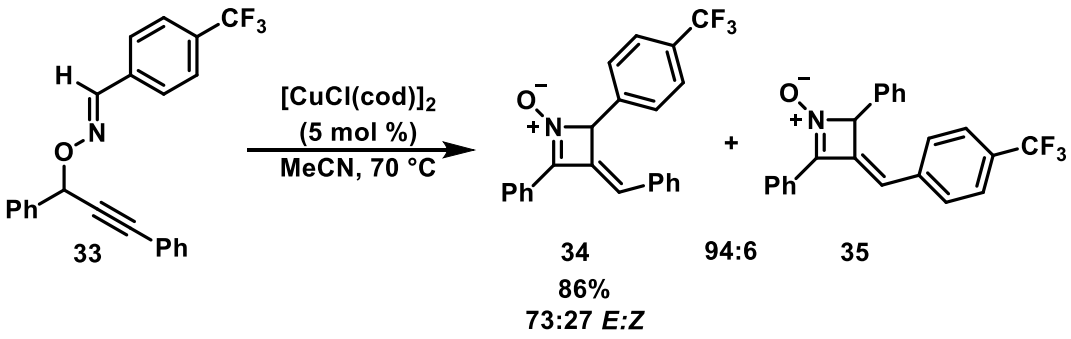
Smith and co-workers developed the catalytic asymmetric [2,3]-rearrangement of allylic ammonium ylides.[17] Benzotetramisole promoted the catalytic asymmetric [2,3]-rearrangement of allylic quaternary ammonium salts, which can be either isolated or prepared in situ from the corresponding *p*-nitrophenyl bromoacetate **30** and allylic amine **31**, resulting in the synthesis of syn-α-amino acid derivatives **32** with excellent diastereo- and enantioselectivity (up to >95:5 dr; up to >99% ee).



Scheme 5.10: Stereoselective [2,3]-Rearrangement of Allylic Ammonium Salts

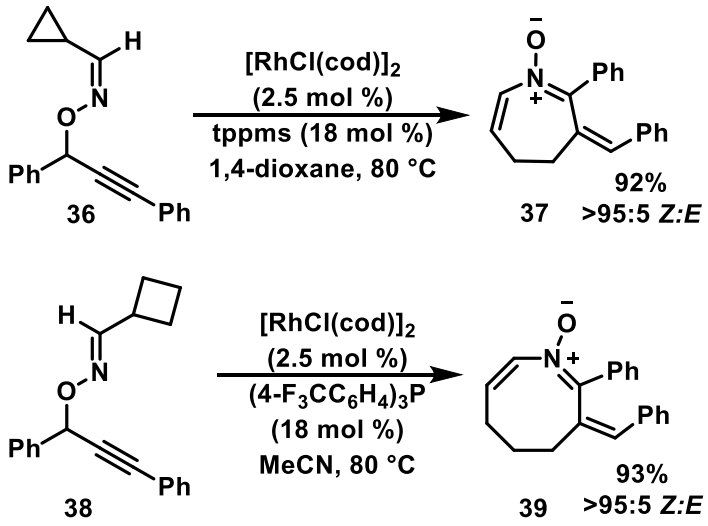
5.3.3. [2,3]-Rearrangement of *o*-Propargylic Oximes

Terada and co-workers developed a novel and efficient synthetic method for the construction of highly strained four-membered cyclic nitrones (**34, 35**) from readily available *o*-propargylic arylaldoximes **33** (Scheme 5.11).[18] The reactions proceeded via a tandem [2,3]-rearrangement and 4π-electrocyclization of the *N*-allenylnitrone intermediate and involved cleavage of the carbon-oxygen bond.



Scheme 5.11: Copper-Catalyzed Rearrangement of *o*-Propargylic Aryl Aldoximes

Subsequently the same group developed a new approach for the synthesis of seven and eight membered aza-heterocycles (**37, 39**) from the corresponding *o*-propargylic arylaldoximes (**36, 38**) under mild reaction conditions (Scheme 5.12).[19] This method can be employed to synthesize azepine derivatives, which are an important class of biologically

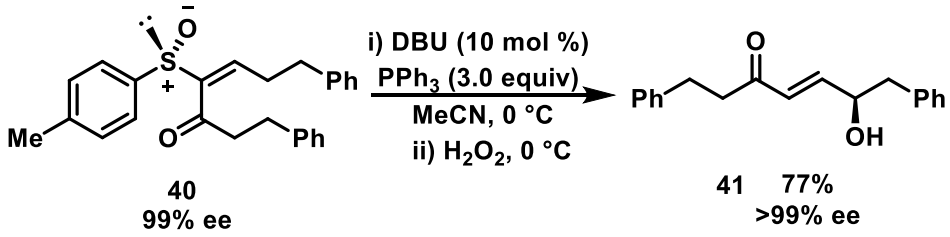


Scheme 5.12: [2.3]-Rearrangement of (a) *o*-Propargylic Cyclopropyl- and (b) Cyclobutylcarbaldoximes

active molecules, in an efficient manner. Moreover, the chirality of the substrate was maintained throughout the cascade process afforded the corresponding optically active aza-heterocycles.

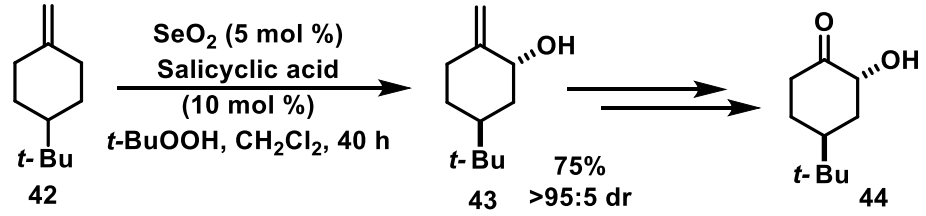
5.3.4. [2,3]-Rearrangement of Allylic Sulfoxides, Selenoxides, Sulfimides and *N*-Oxides

Miura and co-workers developed a stereoselective organocatalytic [2,3]-rearrangement of α-sulfinyl enones. Treatment of enantiomerically pure enone **40** with catalytic amount of DBU (10 mol %) in the presence of an excess of triphenyl phosphine promotes isomerization into allylic sulfoxide, which spontaneously undergoes a stereoselective [2,3]-rearrangement. Quenching the reaction with aqueous hydrogen peroxide to hydrolyze the initially formed sulfinyl ester afforded the corresponding allylic alcohol **41** in 77% yield and 99% ee (Scheme 5.13).[20]



Scheme 5.13: Organocatalytic [2,3]-Rearrangement of α-Sulfinyl Enones

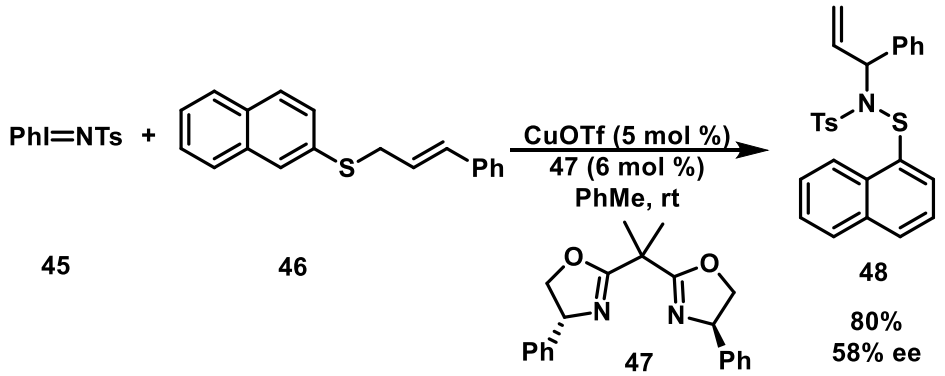
Catalytic diastereoselective Riley oxidation in the synthesis of cyclohexanone **44** is reported by Paquette and Lobben, which was used as a substrate for investigating the facial selectivity of indium promoted allylations of various 2-hydroxycyclohexanone (Scheme 5.14).[21] Treatment of exo-methylenecyclohexane **42** with catalytic SeO_2 (5 mol %) and an equivalent of *t*-butyl hydroperoxide afforded the corresponding allylic alcohol **43** in 75% yield as a single diastereoisomer.



Scheme 5.14: Catalytic Diastereoselective Riley Oxidation

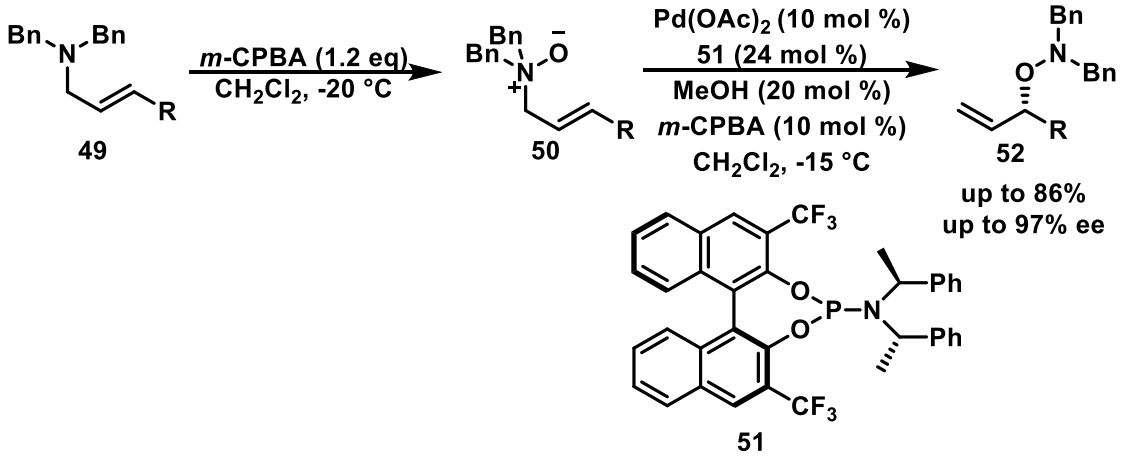
In 1996, Uemura and co-workers developed the enantioselective copper-catalyzed sulfimidation using *N*-tosyliminobenzyliodinane **45** as a nitrene source. Applying these

conditions to allylic sulfides resulted in sulfimidation followed by [2,3]-rearrangement leading to the formation of sulphonamides. For example, treatment of allylic sulfide **46** with **45** in the presence of CuOTf (5 mol %) and BOX ligand **47** (6 mol %) afforded the corresponding sulfonamide **48** in 80% yield and 58% ee (Scheme 5.15). [22]



Scheme 5.15: Enantioselective Sulfimidation Followed by [2,3]-Rearrangement

Tambar and co-workers revealed a Pd-catalyzed enantioselective [2,3]-rearrangement of allylic amine *N*-oxides **50** prepared from the corresponding allylamine **49** via *m*-CPBA oxidation.[23] Treating allylic *N*-oxides **50** with $Pd(OAc)_2$ (10 mol %) and phosphoramidite ligand **51** (24 mol %) promoted the highly enantioselective [2,3]-rearrangement into allylic hydroxylamines **52**. The mild reaction conditions allow the

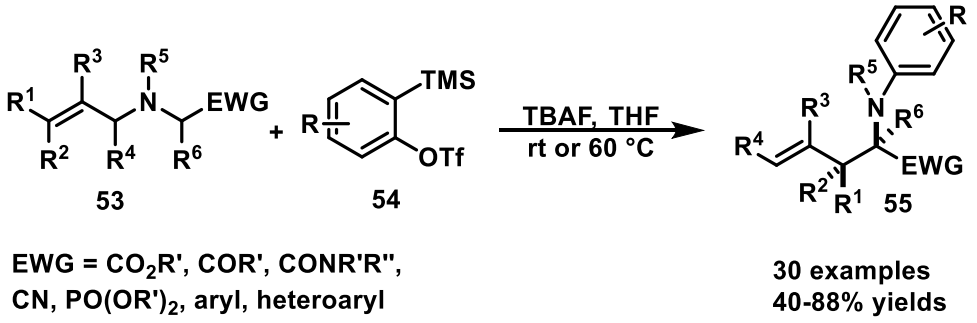


Scheme 5.16: Palladium Catalyzed [2,3]-Rearrangement of Allyic *N*-Oxides to Form Hydroxylamines

generation of chiral hydroxylamines **52** with traditionally reactive functional groups, which may be difficult to access via known protocols for the synthesis of chiral alcohol derivatives. The N-O bond in the products can be easily cleaved to chiral secondary alcohols.

5.3.5. Aryne-Mediated [2,3]-Sigmatropic Rearrangement

Recently, the Tian, Biju, Sweeney groups independently revealed a new strategy for the [2,3]-sigmatropic rearrangement of in situ generated quaternary allylic ammonium ylides via tertiary allylic amines **53** with benzyne precursor **54** under mild conditions. A variety of tertiary allylic amines bearing electron-withdrawing groups underwent [2,3]-sigmatropic rearrangement to afford structurally diverse homoallylic amines **55** in moderate to good yields (Scheme 5.17).[24] Construction of quaternary stereocenters with excellent enantiopurity and functionalized cyclopropanes with extremely high diastereoselectivity are the key features of this reaction.

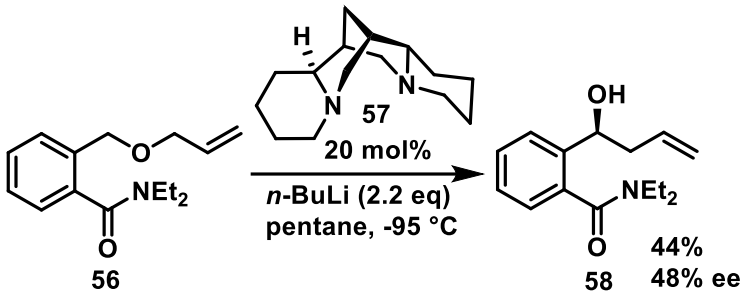


Scheme 5.17: Aryne-Mediated [2,3]-Sigmatropic Rearrangement of Tertiary Allylic Amines

5.4. Anionic [2,3]-Sigmatropic Rearrangements

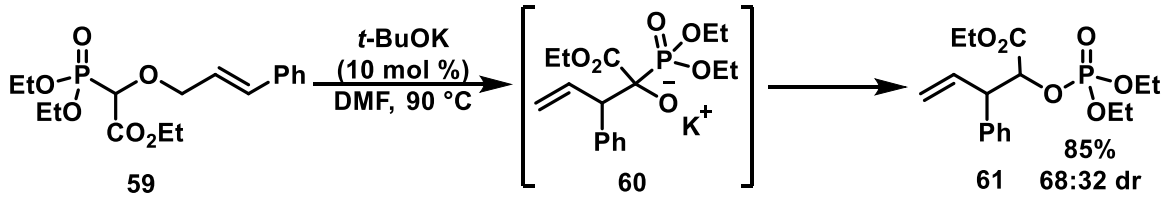
5.4.1. [2,3]-Wittig Rearrangements

Kimachi and co-workers reported [2,3]-rearrangement of allylic ether with a catalytic amount of chiral ligand. Treatment of **56** with excess of *n*-BuLi and catalytic amount of (-)-sparteine **57** (20 mol %) at low temperature afforded the corresponding homoallylic alcohol **58** in 44% yield and 48% ee, when an excess of (-)-sparteine (2.2 equiv) was used the yield and enantioselectivity increased to 83% and 60% ee respectively (Scheme 5.18).[25].



Scheme 5.18: Base-Mediated [2,3]-Wittig Rearrangements Using Catalytic Chiral Ligands

Terada and co-workers developed a novel rearrangement reaction of 2-allyloxy-2-phosphonoacetate derivatives **59** with Brønsted base catalysis. Treating allyloxyphosphonate **59** with catalytic KO*t*-Bu (10 mol %) resulted in deprotonation followed by [2,3]-rearrangement into alkoxide **60.** Subsequent phospha-Brook rearrangement of **60** followed by protonation to regenerate the catalyst afforded the corresponding product **61** in 85% yield and 68:32 dr. This is the first example of a catalytic [2,3]-Wittig rearrangement initiated by a Brønsted base catalyst (Scheme 5.19).[26]



Scheme 5.19: Catalytic Tandem [2,3]-Wittig Rearrangement and Phospha-Brook Rearrangement

5.5. Statement of the Problem

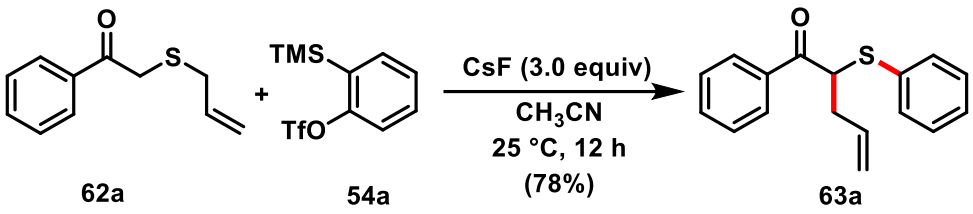
Recently, the Tian, Biju, Sweeny groups independently reported Aryne-Mediated [2,3]-sigmatropic rearrangement of *tert*-allylamine (Scheme 5.17).[27] Moreover, in view of the relevance of the allylthioethers (Figure 5.1), the synthesis of facile and straightforward synthetic routes to β-keto aryl allylthioethers are highly desirable. Based on these facts, we envisage synthesis of functionalized β-keto arylthioethers by the [2,3] Stevens rearrangement of allylthioethers triggered by arynes. A detailed study of the [2,3] Stevens rearrangement of allylthioethers with arynes has been presented in this chapter. This investigation revealed a high yielding method for the synthesis of β-keto aryl allylthioethers derivatives with broad substrate scope. In addition to that, the synthetic utility of the β-keto

arylthioethers has been demonstrated by the conversion of these compounds to valuable heterocycles in two steps.

5.6. Results and Discussion

5.6.1. Optimization Studies

The present study was initiated by treating the allylthioether **62a** with aryne generated from 2-(trimethylsilyl)aryl triflate **54a**[28] using CsF as the fluoride source in CH_3CN solvent. Interestingly, under these conditions, the β-keto arylthioethers[29] **63a** was formed in 78% yield in 12 h (Scheme 5.20). During the search for the suitable allylthioether substrate, it was found that the reaction of allyl benzylthioether with arynes resulted in the formation of low yield of the rearranged product. This indicates that the carbonyl moiety in **62a** was essential for the reactivity as it increases the acidity of α C-H protons, which enables the smooth generation of the sulfur ylide. The reactions performed using KF in the presence of 18-crown-6 as additive and tetrabutyl ammonium fluoride (TBAF) resulted in inferior results. It may be noted that closely related [1,2] Stevens rearrangement[30] of thioethers for the synthesis of functionalized β-keto thioethers has been demonstrated very recently by Guo, He and co-workers.[31,32]

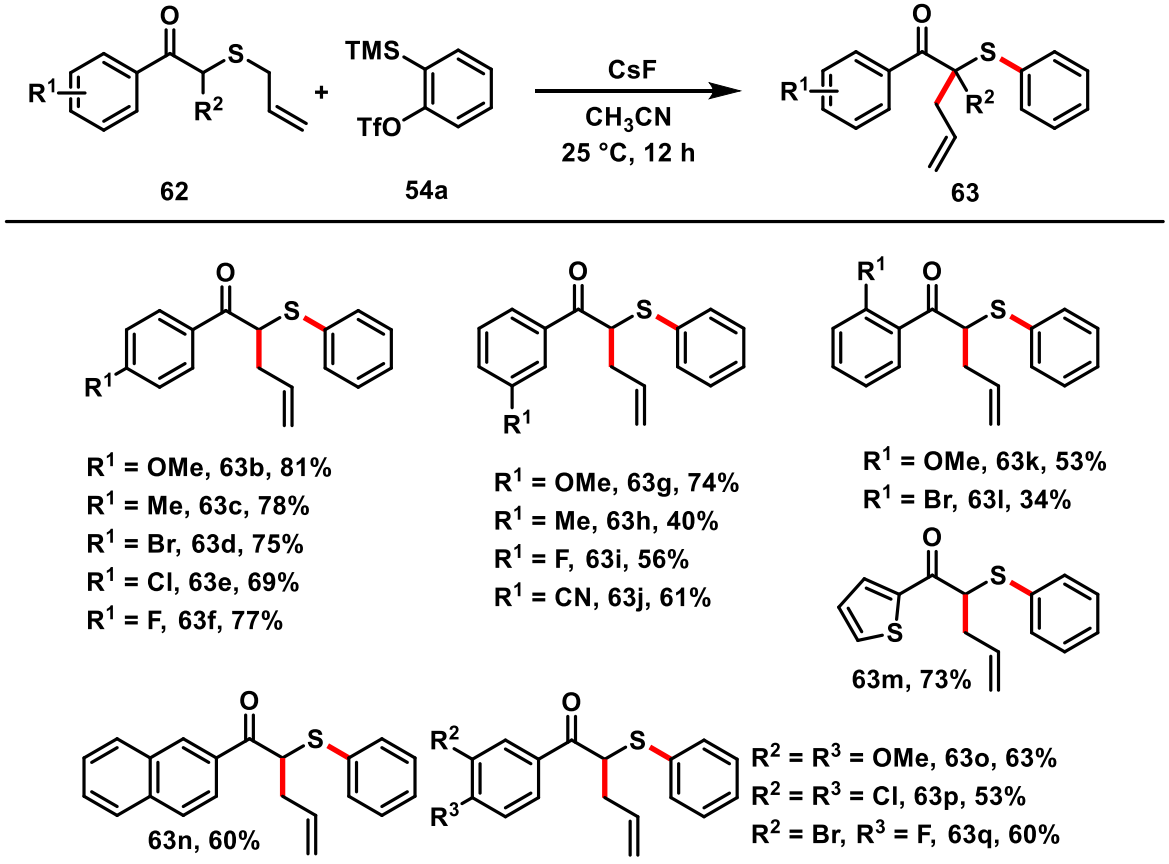


Scheme 5.20. Aryne Triggered [2,3] Stevens Rearrangement of Allylthioether

5.6.2. Scope of Allylthioethers in the Aryne Induced [2,3] Stevens Rearrange ment.

With the reaction conditions for the [2,3] Stevens rearrangement in hand, we then explored the substrate scope of this reaction. First, we evaluated the scope of the reaction using various allylthioethers having a benzoyl moiety at the β-position of allylthioether (Scheme 5.21). A series of electron-releasing and -withdrawing groups at the 4-position of benzene ring of the benzoyl moiety are well tolerated and in all cases, the β-keto arylthioethers are formed in good yields (**63b-63f**). Moreover, substrates having substitution at the 3-position as well as 2-position of the aryl ring of benzoyl moiety

underwent smooth rearrangement reaction to form the expected aryl homoallyl thioethers in moderate to good yields (**63g-63l**). Interestingly, the thioether having the β-heteroaryl keto group also furnished the desired product **63m** in 73% yield. In addition, disubstitution at the aryl moiety also did not affect the outcome of this aryne triggered rearrangement reaction (**63n-63q**).[33]



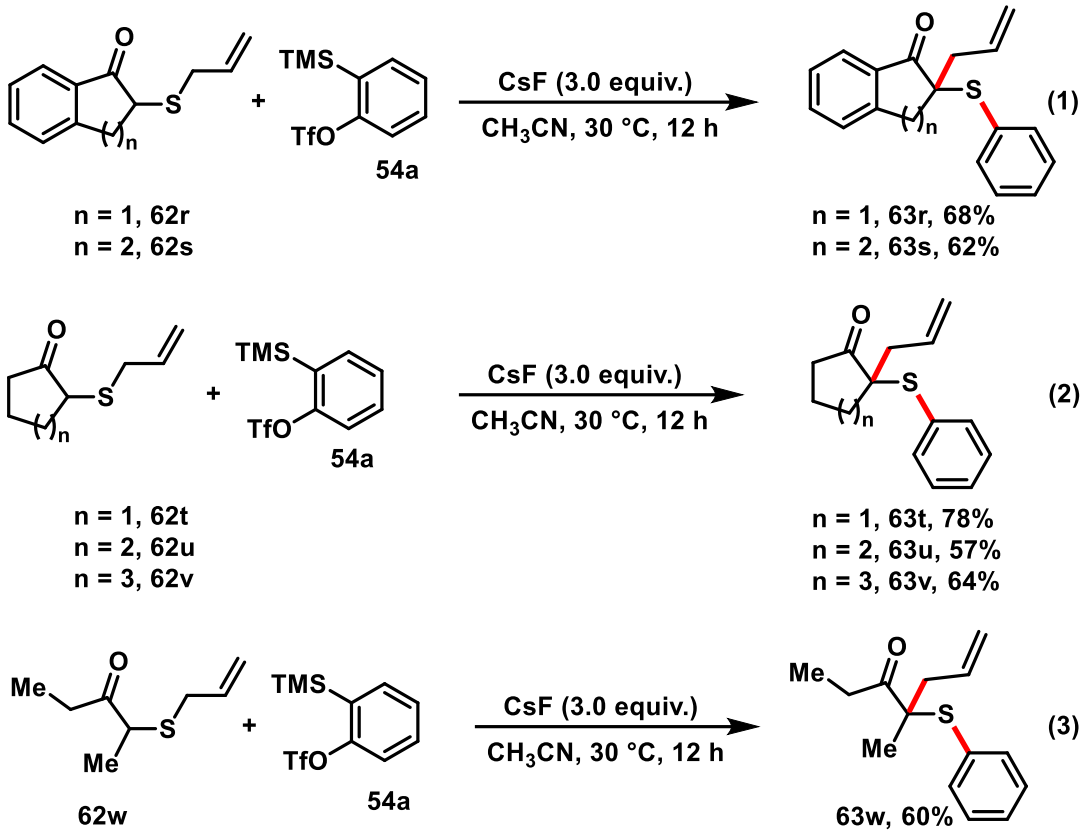
General conditions: **62** (0.50 mmol), **54a** (0.75 mmol), CsF (3.0 equiv), CH_3CN (3.0 mL), 25 °C and 12 h. Yields of the isolated products are given.

Scheme 5.21. Scope of Allylthioethers in the Aryne Induced [2,3] Stevens Rearrangement

5.6.3. Synthesis of Quaternary β-Keto Aryl Allylthioethers.

Next, we examined the scope of the reaction using cyclic ketone-derived allylthioethers with a view to synthesize quaternary β-keto allylthioethers (Scheme 5.22). Gratifyingly, the allyl thioethers synthesized from indanone (**62r**) and tetralone (**62s**) underwent smooth aryne-induced Stevens rearrangement leading to the formation of highly functionalized aryl allylthioethers **63r** and **63s** in good yields (eq 1). Interestingly, this rearrangement is not limited to allylthioethers having aryl ketones at the β-position, but

instead other cyclic ketones-derived allylthioethers (**62t-62v**) and an acyclic ketone-derived thioethers (**62w**) were also useful for the sulfur ylide generation followed by [2,3] Stevens rearrangement sequence and in all cases, the thioethers with a quaternary centre (**63t-63w**) were formed in moderate to good yields (eq 2,3).



General conditions: **62** (0.50 mmol), **54a** (0.75 mmol), CsF (3.0 equiv), CH_3CN (3.0 mL), 25 °C and 12 h. Yields of the isolated products are given.

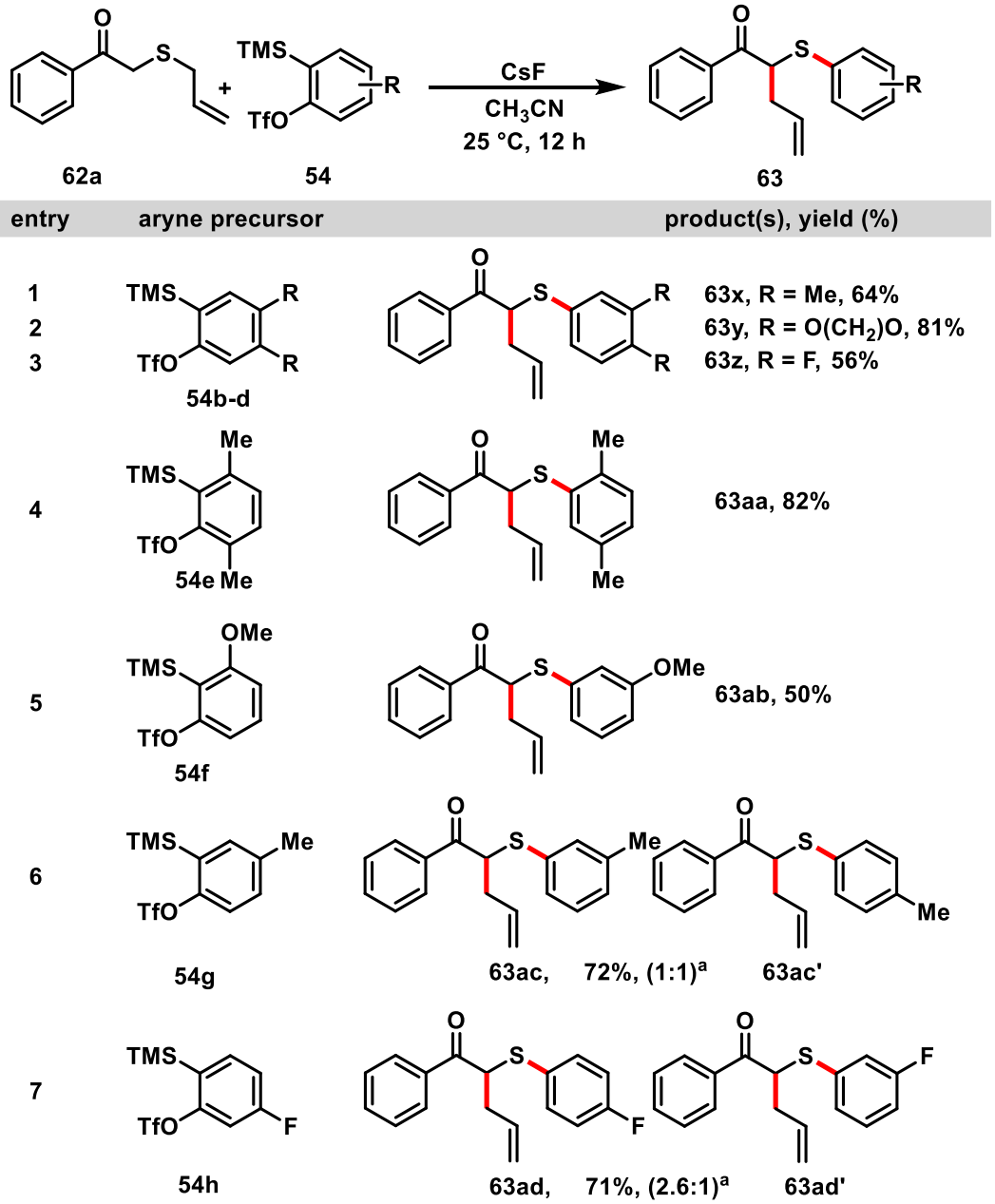
Scheme 5.22. Synthesis of Quaternary β-Keto Aryl Allylthioethers

5.6.4. Variation of the Aryne Moiety

The scope of this [2,3] rearrangement was also examined with various arynes (Table 5.1). Differently substituted and electronically dissimilar symmetrical arynes generated from the corresponding triflate precursors (**54b-54e**) reacted with the β-benzoyl allyl thioether **62a** under the present reaction conditions to afford the expected aryl thioethers (**63x-63aa**) in good yields. It is noteworthy that the unsymmetrical 3-methoxy benzyne generated from the precursor **54f** afforded a single regioisomer **63ab** in 50% yield. Additionally, the reaction of **62a** with unsymmetrical 4-methyl benzyne generated from the

triflate **54g** resulted in the formation of two regioisomers **63ac** and **63ac'** in 72% yield and 1:1 ratio. Furthermore, the reaction using 4-fluoro benzyne resulted in the formation of two regioisomeric aryl allylthioethers **63ad** and **63ad'** in 71% yield and 2.6:1 ratio thus demonstrating the versatility of this rearrangement reaction.

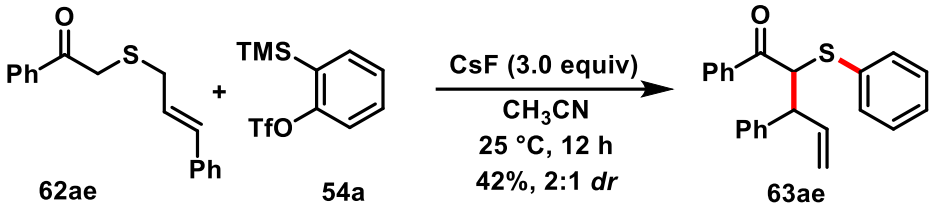
Table 5.1. Variation of the Aryne Moiety



General conditions: **62a** (0.50 mmol), **54** (0.75 mmol), CsF (3.0 equiv), CH_3CN (3.0 mL), 25 °C and 12 h. Yields of the isolated products are given. [a]The regioisomer ratio was determined either by GC or ^1H NMR analysis of crude reaction mixture.

5.6.5. Aryne Induced [2,3] Stevens Rearrangement of Cinnamyl Thioether

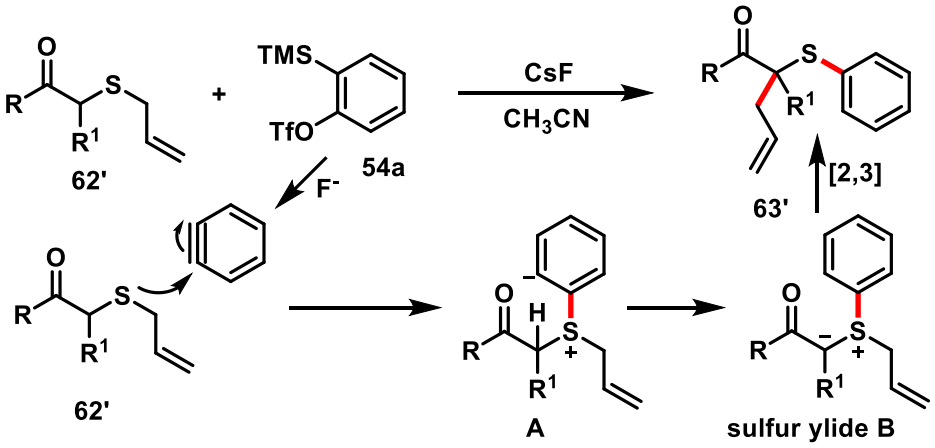
We also tested the feasibility of this reaction using allylthioether having a substituent at the allylic position. Treatment of β-keto cinnamyl thioether **62ae** with aryne generated from **54a** under the present reaction conditions furnished the arylthioethers **63ae** in 42% yield and 2:1 *dr* (Scheme 5.23). Additional experiments to improve the yield and *dr* of this transformation returned inferior results.



Scheme 5.23. Aryne Induced [2,3] Stevens Rearrangement of Cinnamyl Thioether

5.6.6. Proposed Mechanism

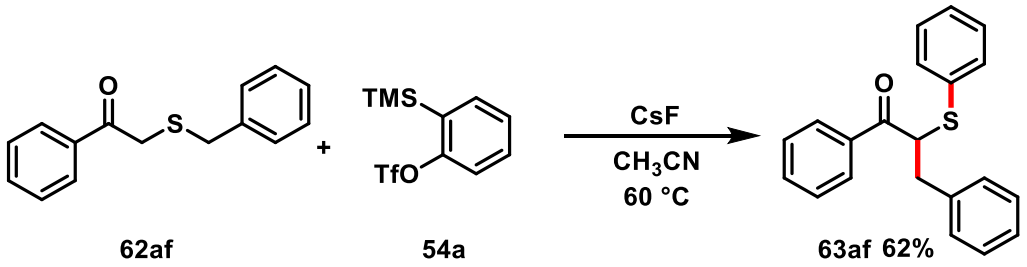
The proposed mechanism involves the reaction of arynes with allylthioethers such as **62'** having an α-C-H proton could generate the acyclic sulfur ylide intermediate **B** via the aryl anion intermediate **A**. The [2,3] Stevens rearrangement of ylide **B** could lead to the formation of functionalized β-keto arylthioethers **63'**. The acidity of α-C-H proton in **62'** will be crucial for the sulfur ylide generation and the subsequent rearrangement.



Scheme 5.24. Proposed Mechanism of the Reaction

5.6.7. Aryne Induced [1,2] Stevens Rearrangement

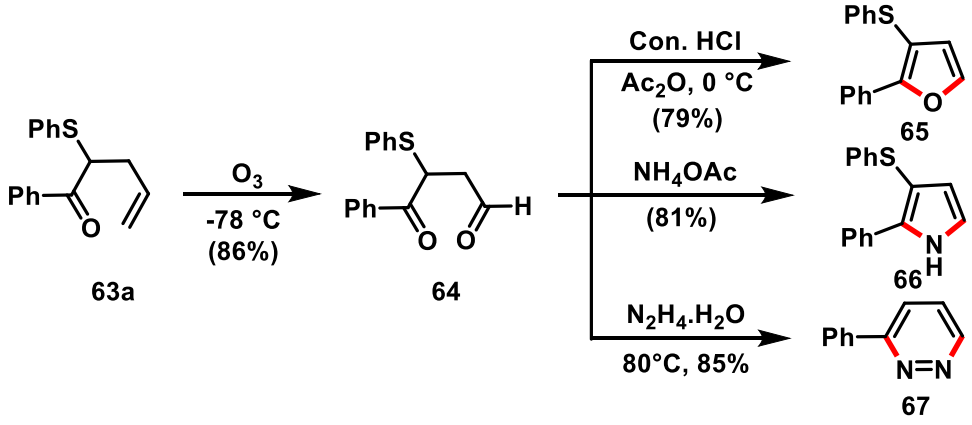
We have also performed a preliminary study on the [1,2] Stevens rearrangement. Treatment of benzyl thioether derivative **62af** with the aryne generated from **54a** using CsF in MeCN at 60 °C resulted in the formation of the functionalized β-keto arylthioether **63af** in 62% yield (Scheme 5.24). Increasing the concentration of aryne did not improve the yield of **63af** under the present conditions. It is likely that the reaction proceeds via the initial generation of sulphur ylide with aryne, which undergoes a [1,2] rearrangement leading to the formation of desired product **63af**.



Scheme 5.24. Aryne Induced [2,3] Stevens Rearrangement

5.6.8. Synthetic utility

The synthetic utility of the β-keto arylthioethers has been demonstrated by the conversion of these compounds to valuable heterocycles in two steps. The ozonolysis of **63a** resulted in the formation of the 1,4-dicarbonyl compound **64** containing the thioethers moiety in 86% yield (Scheme 5.25). Treatment of the dicarbonyl compound **64** in the presence of Conc. HCl at 0 °C afforded the disubstituted furan **65** in 79% yield. Moreover, the reaction of **64** with NH_4OAc resulted in the formation of the disubstituted pyrrole **66** in



Scheme 5.25. Synthesis of Heterocycles from Allylthioethers

81% yield. In addition, treatment of **64** with hydrazine hydrate at 80 °C furnished the 3-phenyl pyridazine **67** in 85% yield.

5.7. Conclusion

In conclusion, we have developed a transition-metal-free procedure for the synthesis of β-keto arylthioethers by the aryne triggered [2,3] Stevens rearrangement of allylthioethers. The reaction proceeds via the generation of the sulfur ylide intermediate from arynes and allylthioethers and results in the formation of a new carbon-carbon and carbon-sulfur bonds. A series of allylthioethers and differently substituted arynes are tolerated under the present reaction conditions. Moreover, the reaction products are converted into arylheteroaryl thioethers in a two-step procedure.

5.8. Experimental Details

5.8.1. General Information

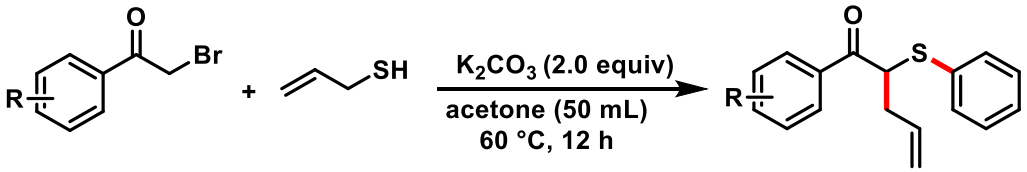
Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with teflon screw caps. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. 25 °C corresponds to the room temperature of the lab, when the experiments were carried out. THF was freshly purified by distillation over Na-benzophenone and was transferred under argon. 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 and stored in glove box. The 2(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** and the other symmetric and unsymmetric aryne precursors were synthesized following literature procedure.[28]

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

All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400 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). Gas chromatography analysis was carried out on Agilent 7890 B GC. 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. LCMS data were recorded on a Agilent technologies 6120 quadrupole LC/MS (Coloumn: Poroshell 120 EC-C18 4.6*50mm, 2.7 micron).

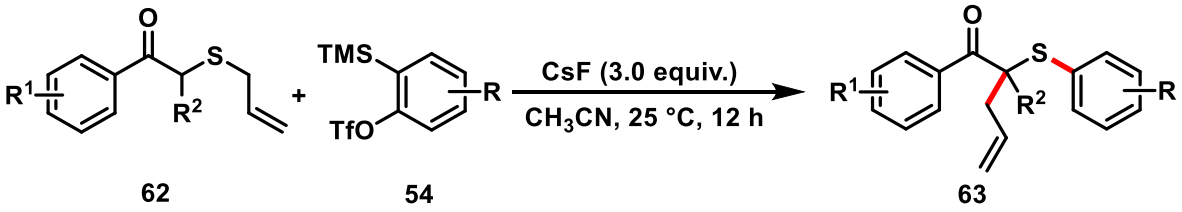
5.8.2. General Procedure for the preparation of Allylthioethers



Following the modified literature procedure[34], the phenacyl bromide (1g, 1.0 equiv) is treated with the corresponding allyl mercaptan (1.5 equiv) in presence of potassium carbonate (2 equiv) and acetone as a solvent at 60 °C for 12 h afforded the corresponding 2-(allylthio)-1-phenylethan-1-one substrate. The data are matching with the corresponding literature procedure.[35]

5.8.3. General Procedure for the Aryne [2,3]-Stevens Rearrangement

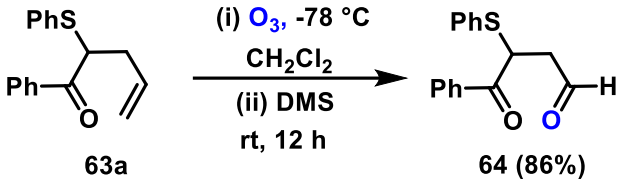
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the CsF (228 mg, 1.5 mmol) in a glove box. The mixture was dissolved in CH_3CN (3.0 mL) under argon atmosphere. 2-(Allylthio)-1-phenylethan-1-one **62** (0.50 mmol) was added



outside the glove box under argon atmosphere. To the stirring solution, aryne precursor **54** (0.75 mmol) was added. Then the reaction mixture was allowed to react at 25 °C for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography by using Pet. ether /EtOAc system on silica gel to afford the corresponding 1-phenyl-2-(phenylthio)pent-4-en-1-ones **63** in moderate to good yields.

5.8.4. Procedure for the Product Functionalization

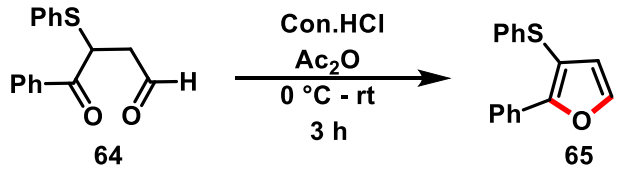
Procedure for Ozonolysis Reaction



A solution of 1-phenyl-2-(phenylthio)pent-4-en-1-ones **63a** (1.5 mmol) in 30 mL of CH_2Cl_2 was stirred at −78 °C as ozone was passed through the solution. After 5-10 min, the colourless reaction mixture changed to blue in colour. Once blue colour observed oxygen was passed to remove excess of ozone until reaction mixture was become colourless. Then to the reaction mixture dimethyl sulfide (15 ml) was added and continued the stirring at -78 °C for another 20 min. Then the reaction mixture was allowed to warm up to room temperature, and then continued stirring for another 12 h. The solvent was removed under reduced pressure. Purification of the crude material on a silica gel column chromatography ethyl acetate and pet ether afforded desired product **64** as yellow oil (350 mg, 86%).

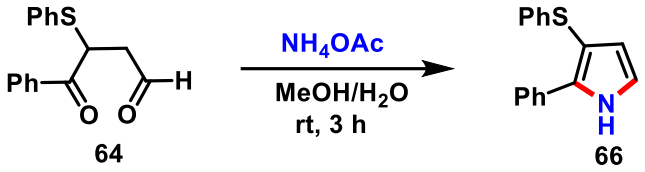
Procedure for the Synthesis of Disubstituted Furan

To a stirred suspension of 1,4-dicarbonyl compound **64** (0.25 mmol, 68.0 mg) in 4.0 mL of Ac_2O at 0 °C, 1.0 mL con. HCl was added in dropwise under Argon protection. After the vigorous reaction, the reaction mixture was allowed to warm up to room temperature, and kept stirring for 3 h. The solvent was removed under reduced pressure. Purification of the crude material on a silica gel column chromatography ethyl acetate and pet ether afforded desired furan derivative **65** as yellow oil (50 mg, 79%).



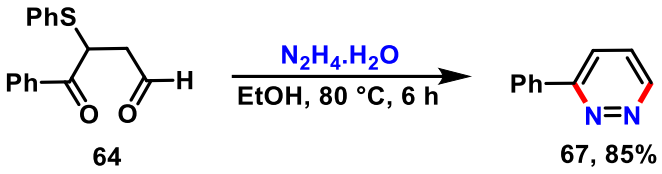
Procedure for the Synthesis of Disubstituted Pyrrole

The mixture of 4-oxo-4-phenyl-3-(phenylthio)butanal **64** (0.25 mmol, 68.0 mg), ammonium acetate (1.25 mmol, 96.0 mg) and MeOH/H_2O (12:3 mL) was stirred for 3h at room temperature. Then the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the crude material on a silica gel column chromatography ethyl acetate and pet ether afforded desired pyrrole derivative **66** as yellow oil (51mg, 81%).



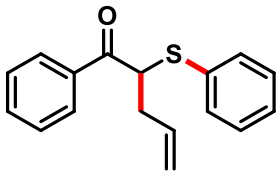
Procedure for the Synthesis of Disubstituted Pyridazine

The dicarbonyl compound **64** (0.25 mmol, 68.0 mg) was dissolved in ethanol (15 mL) and hydrazine hydrate (1.25mmol, 63.0 mg) was added. The reaction mixture was refluxed at 80°C for 6h. The solvent was removed under reduced pressure. Purification of the crude material on a silica gel column chromatography ethyl acetate and pet ether afforded desired pyridazine derivative **67** as white solid (33mg, 85%).



5.8.5. Synthesis and Characterization of Benzocycloheptenone derivatives

1-Phenyl-2-(phenylthio)pent-4-en-1-one (63a):



Following the general procedure, treatment of ethyl 2-(allylthio)-1-phenylethan-1-one **62a** (0.096 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 1-phenyl-2-(phenylthio)pent-4-en-1-one **63a** as viscous yellow oil (0.104 g, 78% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.38

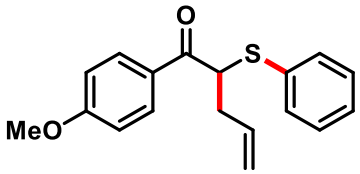
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.4 Hz, 2H), 7.59 (t,*J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.40-7.28 (m, 5H), 5.97-5.89 (m, 1H), 5.19-5.12 (m, 2H), 4.55 (t, *J* = 7.3 Hz, 1H), 2.85-2.79 (m, 1H), 2.67-2.62 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 136.1, 134.8, 133.1, 131.6, 131.1, 129.2, 129.0, 128.8, 128.6, 128.6, 127.1, 117.8, 50.8, 35.1.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{17}OS$: 269.09946, found: 269.09955.

FTIR (cm^{-1}) 3018, 1678, 1597, 1580, 1474, 1439, 1344, 1276, 1025, 924.

1-(4-Methoxyphenyl)-2-(phenylthio)pent-4-en-1-one (63b):



Following the general procedure, treatment of 2-(allylthio)-1-(4-methoxyphenyl)ethan-1-one **62b** (0.111 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **54a** (0.224 g, 182 μL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 1-(4-methoxyphenyl)-2-(phenylthio)pent-4-en-1-one **63b** as colouress oil (0.121 g, 81% yield).

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

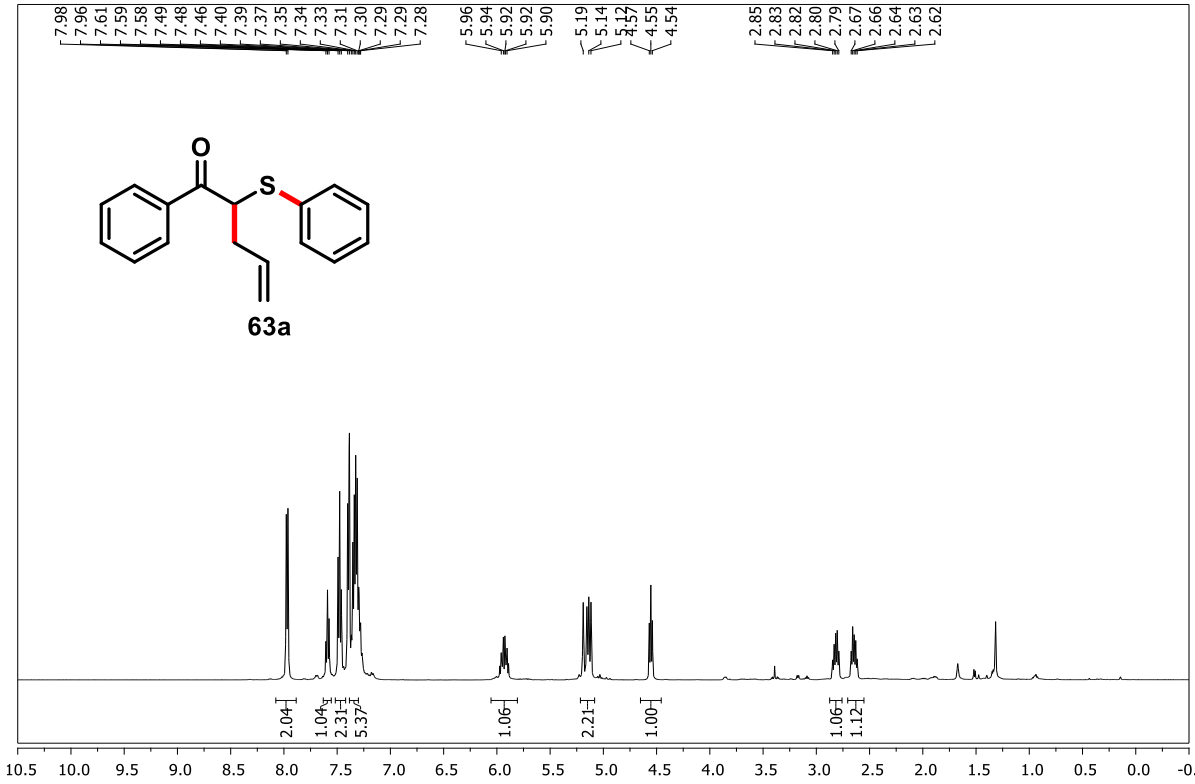
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.30 (t, *J* = 6.8 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 3H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.93 – 5.84 (m, 1H), 5.11 (dd, J_1 = 18.7 Hz, J_2 = 13.9 Hz, 2H), 4.50 (t, *J* = 7.2 Hz, 1H), 3.88 (s, 3H), 2.82 – 2.75 (m, 1H), 2.64 – 2.57 (m, 1H).

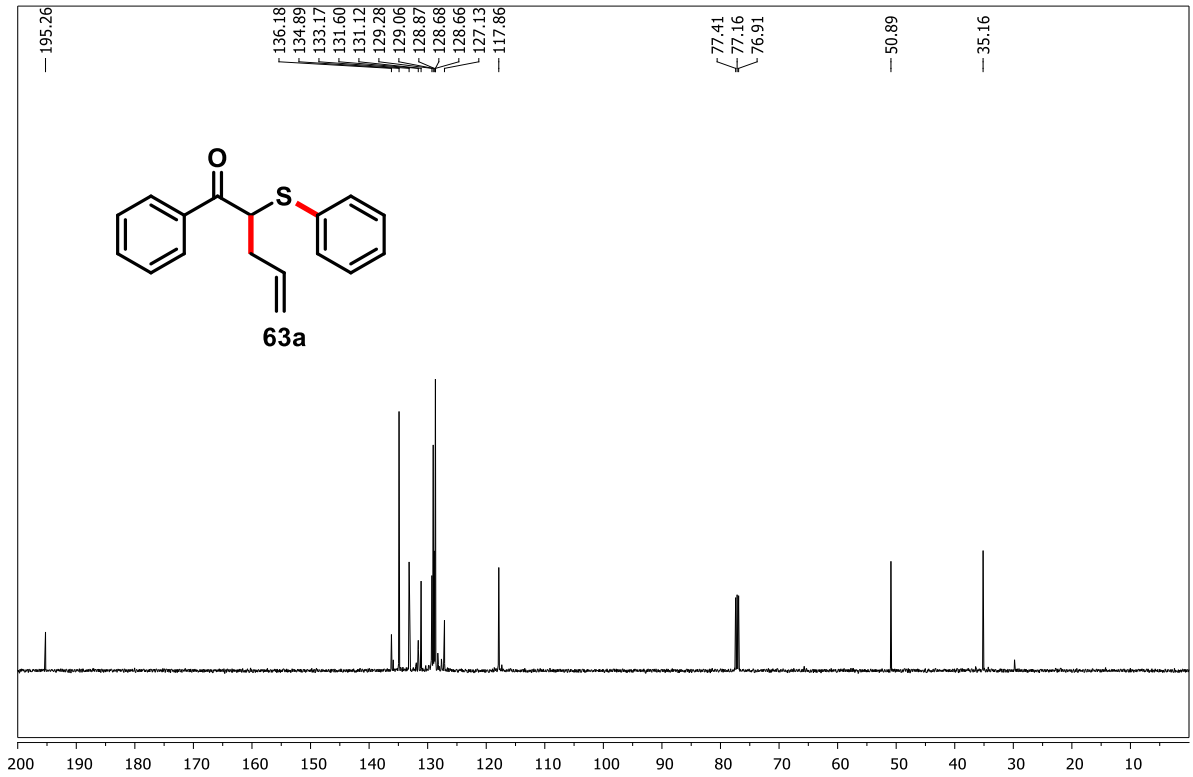
^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 163.6, 135.0, 134.6, 132.0, 131.0, 129.0, 128.6, 117.7, 113.8, 55.5, 50.7, 35.3.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{19}O_2S$: 299.1100, found: 299.1095.

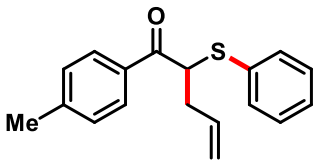
FTIR (cm^{-1}) 3019, 2937, 2835, 2401, 1742, 1642, 1514, 1464, 1373, 1216, 1030, 959, 772.

^{1}H and ^{13}C NMR Spectra of 1-Phenyl-2-(phenylthio)pent-4-en-1-one (63a)





2-(Phenylthio)-1-(*p*-tolyl)pent-4-en-1-one (63c):



Following the general procedure, treatment of 2-(allylthio)-1-(p-tolyl)ethan-1-one **62c** (0.103 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 2-(phenylthio)-1-(p-tolyl)pent-4-en-1-one **63c** as viscous yellow oil (0.110 g, 78% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.23

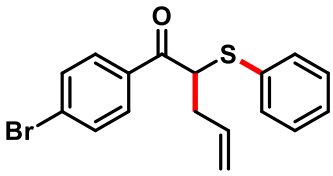
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz,2H), 7.40 - 7.38 (m, 2H), 7.34 - 7.26 (m, 5H), 5.97 - 5.86 (m, 1H), 5.17 - 5.09 (m, 2H), 4.53 (t, *J* = 7.2 Hz, 1H), 2.84 - 2.76 (m, 1H), 2.66 - 2.59 (m, 1H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 144.0, 134.9, 134.7, 133.5, 131.7, 129.3, 129.0, 128.7, 128.7, 117.7, 77.1, 50.8, 35.2, 21.7.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{19}OS$: 283.1151, found: 283.1155.

FTIR (cm^{-1}) 3018, 1673, 1607, 1573, 1438, 1340, 1216, 1025, 924.

1-(4-Bromophenyl)-2-(phenylthio)pent-4-en-1-one (63d):



Following the general procedure, treatment of 2-(allylthio)-1-(4-bromophenyl)ethan-1-one **62d** (0.136 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /DCM = 80/20) of the crude reaction mixture using silica gel afforded 1-(4-bromophenyl)-2-(phenylthio)pent-4-en-1-one (**63d**) as pale yellow oil (0.130 g, 75 % yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.39

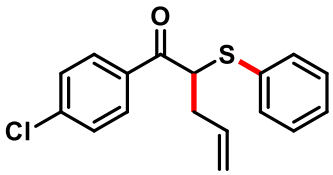
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.34-7.27 (m, 5H), 5.94-5.84 (m, 1H), 5.16-5.09 (m, 2H), 4.43 (t, *J* = 7.5 Hz, 1H), 2.80-2.73 (m, 1H), 2.63-2.56 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 135.0, 134.9, 134.7, 131.9, 131,2, 130.2, 129.1, 129.1, 128.3, 118.0, 50.9, 34.9.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{16}OBrS$: 347.0100, found: 347.0092.

FTIR (cm^{-1}) 3019, 1679, 1585, 1475, 1438, 1396, 1273, 1217, 1071, 1010,926, 772, 691, 669.

1-(4-Chlorophenyl)-2-(phenylthio)pent-4-en-1-one (63e)



Following the general procedure, treatment of 2-(allylthio)-1-(4-chlorophenyl)ethan-1-one **62e** (0.113 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /DCM = 80/20) of the crude reaction mixture using silica gel afforded 1-(4-chlorophenyl)-2-(phenylthio)pent-4-en-1-one (**63e**) as pale yellow oil (0.104 g, 69% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.41

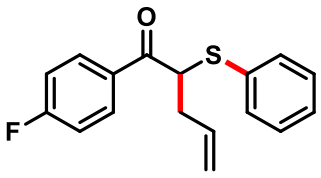
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.37-7.29 (m, 5H), 5.96-5.86 (m, 1H), 5.18-5.11 (m, 2H), 4.46 (t, *J* = 7.3 Hz, 1H), 2.82-2.75 (m, 1H), 2.66-2.59 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 139.6, 135.0, 134.7, 134.4, 131.2, 130.1, 129.1, 129.1, 129.0, 118.0, 50.9, 35.0.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{16}OClS$: 303.0605, found: 303.0600.

FTIR (cm^{-1}) 3019, 1678, 1589, 1477, 1438, 1400, 1274, 1218, 1093, 1045, 927, 848, 772, 669.

1-(4-Fluorophenyl)-2-(phenylthio)pent-4-en-1-one (63f)



Following the general procedure, treatment of ethyl 2-(allylthio)-1-(4-fluorophenyl)ethan-1-one **62f** (0.105 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 1-(4-fluorophenyl)-2-(phenylthio)pent-4-en-1-one **63f** as viscous yellow oil (0.110 g, 77% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.30

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 - 7.95 (m, 2H), 7.37 - 7.28 (m, 5H), 7.12 (t, *J* = 8.2 Hz, 2H), 5.95-5.85 (m, 1H), 5.17 - 5.10 (m, 2H), 4.47 (t, *J* = 7.1 Hz, 1H), 2.82 - 2.75 (m, 1H),

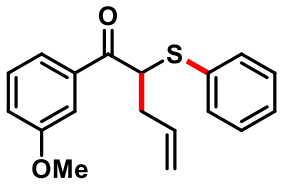
2.65 - 2.58 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 165.8 (d, *J* = 254.1 Hz), 134.9, 134.8, 131.3 (d, *J* = 9.6 Hz), 129.1, 129.0, 117.9, 115.7 (d, *J* = 21.7 Hz), 50.9, 35.1.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{16}OFS$: 287.09004, found: 287.08997.

FTIR (cm^{-1}) 3077, 3018, 1678, 1598, 1474, 1300, 1157, 924, 851.

1-(3-Methoxyphenyl)-2-(phenylthio)pent-4-en-1-one (63g)



Following the general procedure, treatment of 2-(allylthio)-1-(3-methoxyphenyl)ethan-1-one **62g** (0.111 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **54a** (0.224 g, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 1-(3-methoxyphenyl)-2-(phenylthio)pent-4-en-1-one **63g** as colouress oil (0.110 g, 74% yield).

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

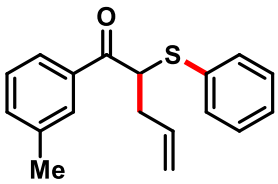
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 2H), 7.30 – 7.16 (m, 6H), 7.02 (d, *J* = 7.8 Hz, 1H), 5.83 – 5.77 (m, 1H), 5.07 – 4.99 (m, 2H), 4.40 (t, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 2.72 – 2.64 (m, 1H), 2.55 – 2.48 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 159.9, 137.5, 134.8, 131.7, 129.6, 129.1, 128.8, 121.1, 119.7, 117.9, 113.0, 55.5, 51.0, 35.2.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{19}O_2S$: 299.1100, found: 299.1096.

FTIR (cm^{-1}) 3019, 2937, 2401, 1742, 1514, 1443, 1373, 1241, 1216, 1030, 926, 815, 772.

2-(Phenylthio)-1-(m-tolyl)pent-4-en-1-one (63h)



Following the general procedure, treatment of 2-(allylthio)-1-(m-tolyl)ethan-1-one **62h** (0.103 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 μL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol)

MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /DCM = 80/20) of the crude reaction mixture using silica gel afforded 2-(phenylthio)-1-(m-tolyl)pent-4-en-1-one (**63h**) as yellow oil (0.055 g, 40 % yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.36

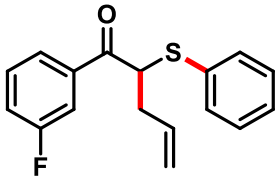
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.71 (m, 2H), 7.39-7.28 (m, 7H), 5.96-5.86 (m, 1H), 5.17-5.12 (m, 2H), 4.52 (t, *J* = 7.3 Hz, 1H), 2.82-2.75 (m, 1H), 2.65-2.58 (m, 1H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 138.4, 136.2, 134.9, 133.9, 131.8, 129.2, 129.0, 128.8, 128.5, 125.8, 117.8, 50.9, 35.1, 21.4.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{19}OS$: 283.1151, found: 283.1146.

FTIR (cm^{-1}) 3018, 1676, 1640, 1602, 1584, 1475, 1438, 1339, 1279, 1256, 1216, 924, 769, 691, 668.

1-(3-Fluorophenyl)-2-(phenylthio)pent-4-en-1-one (63i)



Following the general procedure, treatment of 2-(allylthio)-1-(3-fluorophenyl)ethan-1-one **62i** (0.105 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 μL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 1-(3-fluorophenyl)-2-(phenylthio)pent-4-en-1-one **63i** as pale yellow oil (0.080 g, 56% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.33

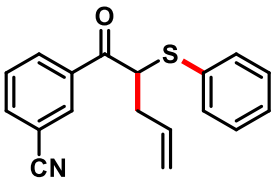
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.1 Hz, 1H), 7.64 - 7.61 (m, 1H), 7.46-7.40 (m, 1H), 7.37 - 7.25 (m, 6H), 5.46 - 5.40 (m, 1H), 5.17 - 5.10 (m, 2H), 4.44 (t, *J* = 7.6 Hz, 1H), 2.81 - 2.74 (m, 1H), 2.65 - 2.58 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 162.9 (d, *J* = 248.6 Hz), 138.3, 135.1, 134.6, 131.1, 130.3 (d, *J* = 8.1 Hz), 129.1, 124.3, 124.3, 120.1 (d, *J* = 21.8 Hz), 118.0, 115.5 (d, *J* = 22.7 Hz), 51.1, 34.9.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{16}OFS$: 287.0900, found: 287.0893.

FTIR (cm^{-1}) 3077, 3018, 1681, 1588, 1483, 1339, 1273, 1216, 1148, 994.

3-(2-(Phenylthio)pent-4-enoyl)benzonitrile (63j)



Following the general procedure, treatment of 3-(2-(allylthio)acetyl)benzonitrile **62j** (0.109 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /DCM = 70/30) of the crude reaction mixture using silica gel afforded 3-(2-(phenylthio)pent-4-enoyl)benzonitrile (**63j**) as pale yellow oil (0.090 g, 61 % yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.12

· **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14-8.12 (m, 2H), 7.82 (d, *J*= 7.75 Hz, 1H), 7.57 (t, *J*=8.2 Hz, 1H), 7.38-7.27 (m, 5H), 5.94-5.78 (m, 1H), 5.17-5.11 (m, 2H), 4.40 (t, *J* = 7.2 Hz, 1H), 2.80-2.72 (m, 1H), 2.65-2.58 (m, 1H).

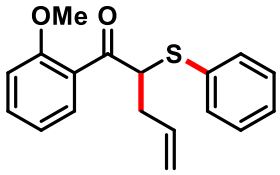
^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 137.0, 135.9, 135.2, 134.4, 132.6, 132.3, 130.7, 129.6, 129.4, 129.2, 118.3, 117.9, 113.1, 51.1, 34.6.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{16}ONS$: 294.0947, found: 294.0940.

FTIR (cm^{-1}) 3019, 2977, 2349, 1686, 1600, 1525, 1477, 1425, 1215, 1045, 928, 877, 849, 755, 669.

1-(2-Methoxyphenyl)-2-(phenylthio)pent-4-en-1-one (63k)

Following the general procedure, treatment of 2-(allylthio)-1-(2-methoxyphenyl)ethan-1-one **62k** (0.111 g, 0.5 mmol) and2-(trimethylsilyl)phenyl trifluoromethanesulfonate **54a**



(0.224 g, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 1-(2-methoxyphenyl)-2-(phenylthio)pent-4-en-1-one **63k** as colouress oil (0.079 g, 53% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.39

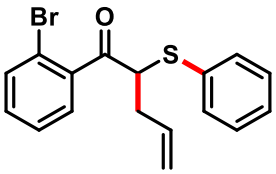
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.25 – 7.08 (m, 5H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 5.92 - 5.81 (m, 1H), 5.03 (dd, J_1 = 17.7 Hz, J_2 = 14.1 Hz, 2H), 4.72 (t, *J* = 7.2 Hz, 1H), 3.68 (s, 3H), 2.72 – 2.65 (m, 1H), 2.47 – 2.39 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 158.0, 135.4, 134.1, 133.5, 132.5, 131.4, 128.7, 128.2, 127.4, 120.9, 117.2, 111.5, 55.5, 55.2, 34.7.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{19}O_2S$: 299.1100, found: 299.1096.

FTIR (cm^{-1}) 3015, 2981, 1642, 1600, 1503, 1455, 1423, 1347, 1229, 1131, 992, 872, 752.

1-(2-Bromophenyl)-2-(phenylthio)pent-4-en-1-one (63l)



Following the general procedure, treatment of 2-(allylthio)-1-(2-bromophenyl)ethan-1-one **62l** (0.136 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 μL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /DCM = 80/20) of the crude reaction mixture using silica gel afforded 1-(2-bromophenyl)-2-(phenylthio)pent-4-en-1-one (**63l**) as yellow oil (0.050 g, 34% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.3

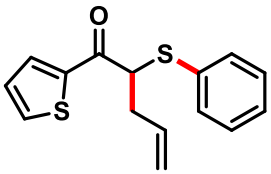
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.23-7.19 (m, 3H), 7.17-7.10 (m, 4H), 5.94-5.82 (m, 1H), 5.11-5.03 (m, 2H), 4.37 (t, *J* = 7 Hz, 1H), 2.74-2.67 (m, 1H), 2.51-2.44 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 140.6, 134.5, 134.0, 133.5, 132.1, 131.7, 130.2, 129.0, 128.5, 127.3, 119.4, 118.2, 55.1, 34.4.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{16}OBrS$: 347.0100, found: 347.0096.

FTIR (cm^{-1}) 3019, 2977, 1693, 1640, 1587, 1525, 1476, 1430, 1216, 1045, 1027, 927, 773, 690, 669.

2-(Phenylthio)-1-(thiophen-2-yl)pent-4-en-1-one (63m)



Following the general procedure, treatment of 2-(allylthio)-1-(thiophen-2-yl)ethan-1-one **62m** (0.099 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 μL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /DCM = 80/20) of the crude reaction mixture using silica gel afforded 2-(phenylthio)-1-(thiophen-2-yl)pent-4-en-1-one **(63m)** as yellow oil (0.100 g, 73% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.31

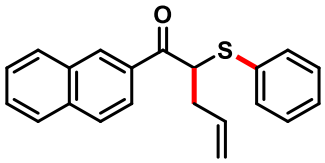
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.62 (m, 2H), 7.43-7.41 (m, 2H), 7.31-7.29 (m, 3H), 7.10-7.07 (m, 1H), 5.94-5.84 (m, 1H), 5.18-5.09 (m, 2H), 4.35-4.31 (m, 1H), 2.80-2.75 (m, 1H), 2.64-2.57 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 143.2, 134.6, 134.1, 132.3, 129.1, 128.8, 128.1, 118.0, 53.0, 35.3.

HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{15}OS_2$: 275.0559, found: 275.0564.

FTIR (cm^{-1}) 3018, 1657, 1583, 1516, 1475, 1438, 1345, 1218, 1066, 926.

1-(Naphthalen-2-yl)-2-(phenylthio)pent-4-en-1-one (63n)



Following the general procedure, treatment of 2-(allylthio)-1-(naphthalen-2-yl)ethan-1-one **62n** (0.121 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 μL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 1-(naphthalen-2-yl)-2-(phenylthio)pent-4-en-1-one **63n** as yellow oil (0.095 g, 60% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.28

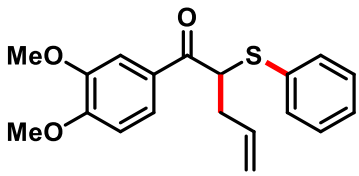
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.40 - 7.38 (m, 2H), 7.34 - 7.26 (m, 5H), 5.97 - 5.86 (m, 1H), 5.17 - 5.09 (m, 2H), 4.53 (t, *J* = 7.2 Hz, 1H), 2.84 - 2.76 (m, 1H), 2.66 - 2.59 (m, 1H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 135.8, 134.7, 134.4, 134.0, 132.7, 132.4, 130.8, 128.9, 128.5, 128.4, 127.9, 127.0, 126.6, 125.9, 124.2, 118.2, 55.0, 35.6.

HRMS (ESI) calculated $[M+H]^+$ for $C_{21}H_{19}OS$: 319.1151, found: 319.1145.

FTIR (cm^{-1}) 3019, 1677, 1583, 1509, 1476, 1328, 1215, 1087, 1025.

1-(3,4-Dimethoxyphenyl)-2-(phenylthio)pent-4-en-1-one (63o)



Following the general procedure, treatment of 2-(allylthio)-1-(3,4-dimethoxyphenyl)ethan-1-one **62o** (0.126 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 μL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixture using silica gel

afforded 1-(3,4-dimethoxyphenyl)-2-(phenylthio)pent-4-en-1-one **63o** as pale yellow oil (0.103 g, 63% yield).

***R*f** (Pet. ether /EtOAc = 70/30): 0.48

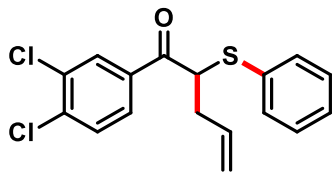
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.7 Hz, 1H), 7.49 (s, 1H), 7.39 - 7.37 (m, 2H), 7.30 - 7.28 (m, 3H), 6.86 (d, *J* = 8.2 Hz, 1H), 5.94 - 5.84 (m, 1H), 5.15 - 5.07 (m, 2H), 4.50 (t, *J* = 7.6 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 2.82 - 2.75 (m, 1H), 2.64 - 2.58 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 153.4, 149.0, 134.9, 134.4, 132.3, 129.1, 129.0, 128.6, 123.1, 117.7, 110.9, 110.0, 56.1, 55.9, 50.6, 35.5.

HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{21}O_3S$: 329.1206, found: 329.1209.

FTIR (cm^{-1}) 3020, 1668, 1595, 1464, 1418, 1216, 1134, 1023.

1-(3,4-Dichlorophenyl)-2-(phenylthio)pent-4-en-1-one (63p)



Following the general procedure, treatment of 2-(allylthio)-1-(3,4-dichlorophenyl)ethan-1-one **62p** (0.131 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 μL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 1-(3,4-dichlorophenyl)-2-(phenylthio)pent-4-en-1-one **63p** as pale yellow oil (0.090 g, 53% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.30

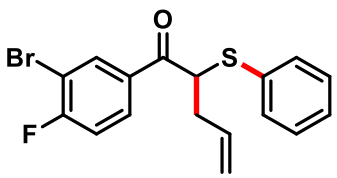
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.36 - 7.28 (m, 5H), 5.93-5.84 (m, 1H), 5.18 - 5.04 (m, 2H), 4.37 (t, *J* = 7.1 Hz, 1H), 2.79 - 2.72 (m, 1H), 2.64 - 2.57 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 137.6, 135.8, 135.2, 134.5, 133.3, 130.7, 130.7, 129.3, 129.2, 127.7, 118.2, 51.1, 34.8.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{15}OCl_2S$: 337.0215, found: 337.0209.

FTIR (cm^{-1}) 3016, 1681, 1583, 1469, 1385, 1276, 1212, 1136, 1064, 1029.

1-(3-Bromo-4-fluorophenyl)-2-(phenylthio)pent-4-en-1-one (63q)



Following the general procedure, treatment of 2-(allylthio)-1-(3-bromo-4-fluorophenyl)ethan-1-one **62q** (0.145 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 μL, 0.75 mmol) in the presence of CsF

(0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 1-(3-bromo-4-fluorophenyl)-2-(phenylthio)pent-4-en-1-one **63q** as pale yellow oil (0.110 g, 60% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.40

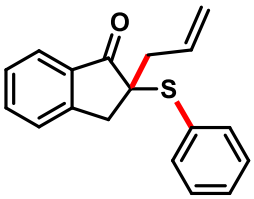
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 - 8.09 (m, 1H), 7.89 - 7.85 (m, 1H), 7.38 - 7.28 (m, 5H), 7.20 - 7.15 (m, 1H), 5.94 - 5.84 (m, 1H), 5.17 - 5.11 (m, 2H), 4.38 (t, *J* = 7.3 Hz, 1H), 2.80 - 2.72 (m, 1H), 2.64 - 2.57 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 162.0 (d, *J* = 256.2), 135.1, 134.6 (d, *J* = 4.2 Hz), 131.1, 129.9 (d, *J* = 8.5 Hz), 129.3, 129.2, 118.2, 116.7 (d, *J* = 22.9 Hz), 109.9, 109.7, 51.0, 34.9.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{15}OBrFS$: 365.0006, found: 365.0000.

FTIR (cm^{-1}) 3019, 1681, 1590, 1492, 1438, 1396, 1251, 1046.

2-Allyl-2-(phenylthio)-2,3-dihydro-1*H*-inden-1-one (63r)



Following the general procedure, treatment of 2-(allylthio)-2,3-dihydro-1*H*-inden-1-one **62r** (0.102 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **54a** (0.224 g, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 2-allyl-2-(phenylthio)-2,3-dihydro-1*H*-inden-1-one **63r** as colouress oil (0.96 g, 68% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.36

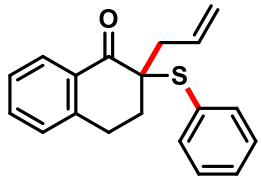
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.28 (t, *J* = 7.4 Hz, 2H), 5.84 – 5.74 (m, 1H), 5.16 (dd, J_1 = 19.9 Hz, J_2 = 13.7 Hz, 2H), 3.42 (d, *J* = 17.9 Hz, 1H), 3.14 (d, *J* = 17.9 Hz, 1H), 2.67 (d, *J* = 7.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 150.5, 137.2, 135.5, 135.0, 133.1, 130.2, 129.6, 128.6, 127.8, 126.2, 124.7, 119.4, 58.6, 39.4, 38.5.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{17}OS$: 281.0995, found: 281.1002.

FTIR (cm^{-1}) 3020, 2984, 1744, 1631, 1522, 1421, 1392, 1373, 1187, 1117, 927.

2-Allyl-2-(phenylthio)-3,4-dihydronaphthalen-1(2*H*)-one (63s)



Following the general procedure, treatment of 2-(allylthio)-3,4-dihydronaphthalen-1(2*H*)-one **62s** (0.109 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /DCM = 80/20) of the crude reaction mixture using silica gel afforded 2-Allyl-2-(phenylthio)-3,4-dihydronaphthalen-1(2*H*)-one (**63s**) as yellow oil (0.098 g, 62% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.36

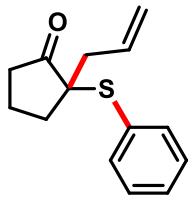
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.42-7.26 (m, 7H), 5.96-5.85 (m, 1H), 5.17-5.13 (m, 2H), 3.52-3.43 (m, 1H), 2.94-2.89 (m, 1H), 2.70-2.65 (m, 1H), 2.58-2.53 (m, 1H), 2.48-2.40 (m, 1H), 2.30-2.25 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 142.5, 137.5, 133.8, 133.1, 131.6, 129.6, 129.2, 128.8, 128.6, 128.4, 126.8, 118.8, 57.5, 40.2, 32.3, 25.6.

HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{19}OS$: 295.1151, found: 295.1154.

FTIR (cm^{-1}) 3019, 1674, 1638, 1601, 1474, 1430, 1355, 1308, 1218, 1126, 1044, 922, 772, 691, 669.

2-Allyl-2-(phenylthio)cyclopentan-1-one (63t)



Following the general procedure, treatment of 2-(allylthio)cyclopentan-1-one **62t** (0.078 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 2-allyl-2-(phenylthio)cyclopentan-1-one **63t** as pale yellow oil (0.090 g, 78% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.18

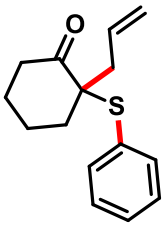
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.28 (m, 5H), 5.86 -5.76 (m, 1H), 5.16 - 5.10 (m, 2H), 2.73 - 2.63 (m, 1H), 2.48 - 2.43 (m, 1H), 2.32 - 2.27 (m, 1H), 2.22 - 2.07 (m, 3H), 2.03 - 1.90 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 137.3, 133.4, 129.9, 129.7, 128.8, 118.9, 59.6, 37.9, 36.0, 33.9, 18.0.

HRMS (ESI) calculated $[M+H]^+$ for $C_{14}H_{17}OS$: 233.0995, found: 233.0996.

FTIR (cm^{-1}) 3018, 1727, 1639, 1523, 1473, 1319, 1215, 1165, 1068, 1002.

2-Allyl-2-(phenylthio)cyclohexan-1-one (63u)



Following the general procedure, treatment of 2-(allylthio)cyclohexan-1-one **62u** (0.085 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 2-allyl-2-(phenylthio)cyclohexan-1-one **63u** as yellow solid (0.070 g, 57% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.75

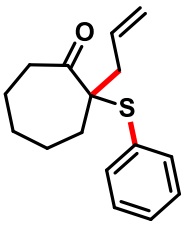
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.28 (m, 5H), 5.92 -5.82 (m, 1H), 5.14 - 5.04 (m, 2H), 3.44 - 3.35 (m, 1H), 2.37 - 2.32 (m, 3H), 2.16 - 2.07 (m, 3H), 1.98 - 1.91 (m, 1H), 1.27 - 1.64 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 136.3, 134.0, 130.4, 129.5, 129.0, 118.5, 60.3, 39.8, 37.8, 36.8, 27.0, 21.3.

HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{19}OS$: 247.1151, found: 247.1153.

FTIR (cm^{-1}) 3018, 1698, 1474, 1316, 1291, 1149, 1122, 1025, 998.

2-Allyl-2-(phenylthio)cycloheptan-1-one (63v)



Following the general procedure, treatment of 2-(allylthio)cycloheptan-1-one **62v** (0.092 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 2-allyl-2-(phenylthio)cycloheptan-1-one **63v** as pale yellow oil (0.083 g, 64% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.25

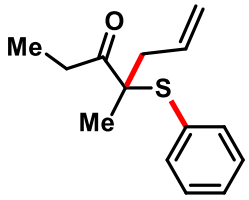
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.29 (m, 5H), 6.08 -5.98 (m, 1H), 5.17 - 5.06 (m, 2H), 3.26 - 3.21 (m, 1H), 2.49 - 2.39 (m, 2H), 2.27 - 2.18 (m, 2H), 1.97 - 1.83 (m, 3H), 1.61 - 1.55 (m, 1H), 1.44 - 1.40 (m, 2H), 1.23 - 1.18 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 136.7, 134.4, 130.6, 129.5, 128.9, 118.3, 62.4, 39.6, 36.3, 32.3, 30.4, 26.5, 24.5.

HRMS (ESI) calculated $[M+H]^+$ for $C_{16}H_{21}OS$: 261.1308, found: 261.1310.

FTIR (cm^{-1}) 3017, 1692, 1439, 1217, 1156, 1065, 1022, 921.

4-Methyl-4-(phenylthio)hept-6-en-3-one (63w):



Following the general procedure, treatment of 2-(allylthio)pentan-3-one **62w** (0.079 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 4-methyl-4-(phenylthio)hept-6-en-3-one **63w** as colorless oil (0.070 g, 60% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.42

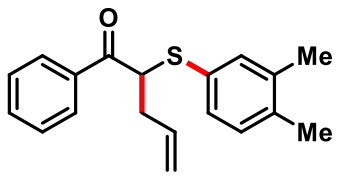
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.29 (m, *5*H), 5.82-5.73 (m, 1H), 5.15-5.11 (m, 2H), 2.83 (q, *J* = 7.2 Hz, 2H), 2.63-2.59 (m, 1H), 2.47-2.43 (m, 1H), 1.39 (s, 3H), 1.14 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.09, 136.30, 133.32, 130.84, 129.40, 128.97, 119.01, 59.23, 41.30, 29.85, 21.30, 8.60.

HRMS (ESI) calculated $[M+H]^+$ for $C_{14}H_{19}OS$: 235.1151, found: 235.1150.

FTIR (cm^{-1}) 3018, 1700, 1473, 1457, 1414, 1376, 1216, 1083, 976, 754, 667.

2-((3,4-Dimethylphenyl)thio)-1-phenylpent-4-en-1-one (63x):



Following the general procedure, treatment of 2-(allylthio)-1-phenylethan-1-one **62a** (0.096 g, 0.5 mmol) and 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **54b** (0.245 g, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /DCM = 80/20) of the crude reaction mixture using silica gel afforded 2-((3,4-dimethylphenyl)thio)-1-phenylpent-4-en-1-one (**63x**) as yellow oil (0.094 g, 64% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.39

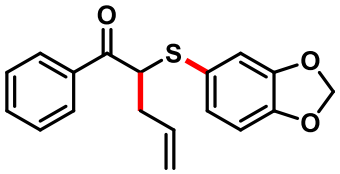
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.9 Hz, 1H), 7.58-7.54 (m, 2H), 7.47-7.43 (m, 2H), 7.10-7.03 (m, 3H), 5.94-5.84 (m, 1H), 5.15-5.06 (m, 2H), 4.44 (t, *J* = 7.3 Hz, 1H), 2.78-2.71 (m, 1H), 2.61-2.54 (m, 1H), 2.23 (s, 3H), 2.19 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 138.0, 137.4, 136.5, 136.3, 135.1, 133.0, 132.8, 130.3, 128.7, 128.6, 127.7, 117.7, 50.9, 35.0, 19.7, 19.6.

HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{21}OS$: 297.1308, found: 297.1318.

FTIR (cm^{-1}) 3081, 2924, 1678, 1640, 1597, 1580, 1485, 1448, 1383, 1344, 1217, 924, 814, 771, 687, 668.

2-(Benzo[*d*][1,3]dioxol-5-ylthio)-1-phenylpent-4-en-1-one (63y)



Following the general procedure, treatment of ethyl 2-(allylthio)-1-phenylethan-1-one **62a** (0.096 g, 0.5 mmol) and 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yltrifluoromethanesulfonate **54c** (0.257 g, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixture using silica gel afforded 2-(benzo[*d*][1,3]dioxol-5-ylthio)-1-phenylpent-4-en-1-one **63y** as colouress oil (0.127 g, 81% yield).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.48

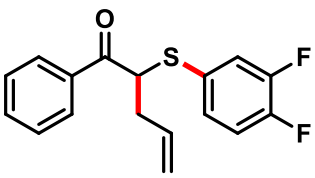
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 6.84 - 6.79 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.96 (s, 2H), 5.93-5.82 (m, 1H), 5.11 (dd, J_1 = 19.3 Hz, J_1 = 13.8 Hz, 2H), 4.39 (t, *J* = 7.3 Hz, 1H), 2.76 - 2.69 (m, 1H), 2.59 - 2.52(m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 149.0, 147.8, 136.2, 134.9, 133.1, 130.6, 128.7, 128.6, 122.5, 117.8, 115.9, 108.7, 101.6, 51.0, 34.7.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{17}O_3S$: 313.0893, found: 313.0888.

FTIR (cm^{-1}) 3011, 2935, 1745, 1600, 1505, 1422, 1350, 1185, 1026, 991, 770.

2-((3,4-Difluorophenyl)thio)-1-phenylpent-4-en-1-one (63z):



Following the general procedure, treatment of 2-(allylthio)-1-phenylethan-1-one **62a** (0.096 g, 0.5 mmol) and 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **54d** (0.251 g, 179 μL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5

mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /DCM = 80/20) of the crude reaction mixture using silica gel afforded 2-((3,4-difluorophenyl)thio)-1-phenylpent-4-en-1-one **(63z)** as pale yellow oil (0.084 g, 56% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.39

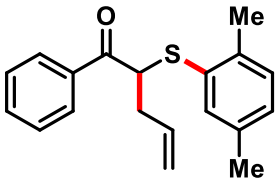
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.6 Hz, 2H), 7.60-7.56 (m, 1H), 7.48-7.45 (m, 2H), 7.16 (t, *J* = 8.7 Hz, 1H), 7.10-7.02 (m, 2H), 5.91-5.81 (m, 1H), 5.16-5.09 (m, 2H), 4.48 (t, *J* = 7.5 Hz 1H), 2.77-2.70 (m, 1H), 2.59-2.52 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 152.0 (J_1= 14.2 Hz, J_2 = 136.0 Hz), 150.1 (J_1 = 14.0 Hz, J_2 = 136.6 Hz), 135.9, 134.4, 133.5, 132.1 (t, *J* = 4.81 Hz), 128.8, 128.6, 127.2 (t, *J* = 4.6 Hz), 124.4 (dd, J_1 = 3.7 Hz, J_2 = 14.5 Hz), 118.2, 117.8 (dd, J_1 = 7.9 Hz, J_2 = 11.0 Hz), 50.7, 34.8.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{15}OF_2S$: 305.0806, found: 305.0805.

FTIR (cm^{-1}) 3019, 1678, 1597, 1525, 1483, 1423, 1217, 1045, 928, 669.

2-((2,5-Dimethylphenyl)thio)-1-phenylpent-4-en-1-one (63aa):



Following the general procedure, treatment of ethyl 2-(allylthio)-1-phenylethan-1-one **62a** (0.096 g, 0.5 mmol) and 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **54e** (0.245 g, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 2-((2,5-dimethylphenyl)thio)-1-phenylpent-4-en-1-one **63aa** as viscous yellow oil (0.121 g, 82% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.23

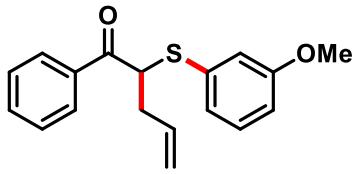
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.0 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.18 (s, 1H), 7.08 - 7.0 (m, 2H), 5.97-5.87 (m, 1H), 5.18-5.09 (m, 2H), 4.56 – 4.53 (m, 1H), 2.93 – 2.86 (m, 1H), 2.72 - 2.65 (m, 1H), 2.28 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 138.5, 136.4, 136.0, 135.5, 134.9, 133.1, 131.5, 130.4, 129.5, 128.5, 128.5, 117.8, 50.9, 35.6, 20.7, 20.5.

HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{21}OS$: 297.1308, found: 297.1302.

FTIR (cm^{-1}) 3060, 2855, 1679, 1649, 1379, 1276, 997, 812.

2-((3-Methoxyphenyl)thio)-1-phenylpent-4-en-1-one (63ab):



Following the general procedure, treatment of ethyl 2-(allylthio)-1-phenylethan-1-one **62a** (0.096 g, 0.5 mmol) and 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **54f** (0.246 g, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 2-((3-methoxyphenyl)thio)-1-phenylpent-4-en-1-one **63ab** as yellow oil (0.075 g, 50% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.23

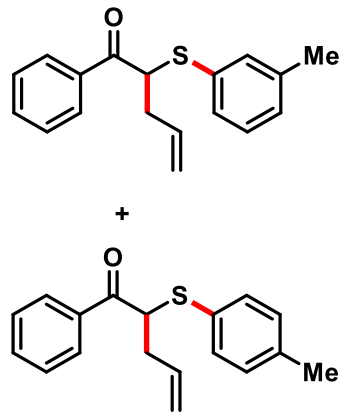
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.1 Hz, 2H), 7.58 (t,*J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.98 (d,*J* = 7.7 Hz,1H), 6.89 - 6.86 (m, 2H), 5.96 - 5.86 (m, 1H), 5.18 - 5.09 (m, 2H), 4.55 (t,*J* = 7.1 Hz,1H), 3.75 (s, 3H), 2.86 - 2.79 (m, 1H), 2.67 - 2.66 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 159.6, 136.1, 134.8, 133.2, 133.0, 129.8, 128.6, 126.5, 119.4, 117.9, 114.8, 55.3, 51.0, 35.2.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{19}O_2S$: 299.1100, found: 299.1109.

FTIR (cm^{-1}) 3018, 1678, 1590, 1479, 1446, 1343, 1309, 1281, 1215, 1183, 996, 924, 777.

1-Phenyl-2-(*m*-tolylthio)pent-4-en-1-one (63ac) and 1-Phenyl-2-(*p*-tolylthio)pent-4-en-1-one (63ac'):



Following the general procedure, treatment of ethyl 2-(allylthio)-1-phenylethan-1-one **62a** (0.096 g, 0.5 mmol) and 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **54g** (0.234 g, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded the regioisomeric mixture of 1-phenyl-2-(m-tolylthio)pent-4-en-1-one **(63ac)** and 1-phenyl-2-(p-tolylthio)pent-4-en-1-one **(63ac')** as viscous yellow oil (0.101 g, 72% yield). The regioisomeric ratio was determined by GC analysis of the cude reaction mixture is (1:1).

***R*f** (Pet. ether /EtOAc = 95/05): 0.23

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (t, *J* = 8.8 Hz, 2H), 7.58 - 7.44 (m, 3H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.19 - 7.10 (m, 3H), 5.96 - 5.85 (m, 1H), 5.17 -5.09 (m, 2H), 4.52 (t, *J* = 7.2 Hz, 1H), 2.84 - 2.71 (m, 1H), 2.65 - 2.55 (m, 1H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 138.8, 136.3, 135.5, 135.0, 133.1, 131.7, 129.0, 128.9, 117.8, 51.0, 35.2, 21.3.

Representative peak for other isomer:

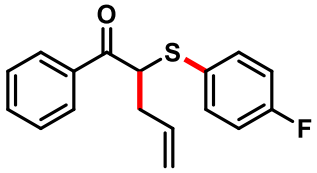
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (t, *J* = 7.1 Hz), 2.35 (s).

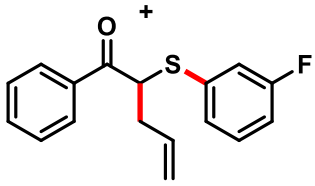
^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 139.3, 136.2, 135.4, 135.0, 133.1, 131.4, 129.7, 128.7, 117.7, 50.8, 34.9, 21.3.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{19}OS$: 283.1151, found: 283.1154.

FTIR (cm^{-1}) 3018, 1678, 1580, 1475, 1344, 1275, 1181, 1000, 923.

2-((4-Fluorophenyl)thio)-1-phenylpent-4-en-1-one (63ad) and 2-((3-Fluorophenyl)thio)-1-phenylpent-4-en-1-one (63ad'): Following the general procedure, treatment of ethyl 2-(allylthio)-1-phenylethan-1-one **62a** (0.096 g, 0.5 mmol) and 5-fluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **54h** (0.237 g, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded regioisomeric mixture of 2-((4-fluorophenyl)thio)-1-phenylpent-4-en-1-one **(63ad)** and 2-((3-fluorophenyl)thio)-1-phenylpent-4-en-1-one **(63ad')** as pale yellow oil (0.102 g, 71% yield). The regioisomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture (2.6:1)





***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.25

^{1}H NMR (400 MHz, $CDCl_3$) of major isomer δ 7.95 (d, *J* = 7.1 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.35 - 7.25 (m, 1H), 7.15 – 7.10 (m, 1H), 7.02 6.97 (m, 2H), 5.93 - 5.84 (m, 1H), 5.17 - 5.10 (m, 2H), 4.46 (t, *J* = 7.2 Hz, 1H), 2.85 - 2.53 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) of major isomer δ 194.9, 163.6 (d, *J* = 246.9 Hz), 137.8 (d, *J* = 8.8 Hz), 134.7, 134.5, 133.4, 133.2, 128.6, 117.9, 116.2 (d, *J* = 21.8 Hz), 50.7, 34.8.

Representative peak for minor isomer:

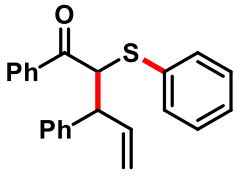
^{1}H NMR (400 MHz, $CDCl_3$) of minor isomer δ 4.57 (t, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) of minor isomer δ 195.2, 136.1, 136.0, 130.3 (d, *J* = 8.4 Hz), 130.0 (d, *J* = 3.1 Hz,), 128.7, 121.0 (d, *J* = 23.1 Hz), 118.1, 115.8 (d, *J* = 20.7 Hz), 50.9, 35.2.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{16}OFS$: 287.0900, found: 287.0901.

FTIR (cm^{-1}) 3023, 1678, 1590, 1489, 1447, 1432, 1343, 1222, 921.

1,4-Diphenyl-2-(phenylthio)pent-4-en-1-one (63ae):



Following the general procedure, treatment of 2-(cinnamylthio)-1-phenylethan-1-one **62ae** (0.134 g, 0.5 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded 1,4-diphenyl-2-(phenylthio)pent-4-en-1-one **63ae** as yellow solid (0.073 g, 42% yield). The regioisomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture (2:1).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.30

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.7 Hz, 2H), 7.37-7.25 (m, 10H), 7.12-7.04 (m, 3H), 6.47-6.38 (m, 1H), 5.02-4.84 (m, 3H), 4.08-4.03 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 141.7, 139.1, 136.7, 135.0, 132.8, 132.0, 129.0, 128.8, 128.6, 128.5, 128.2, 126.8, 117.7, 56.2, 50.1.

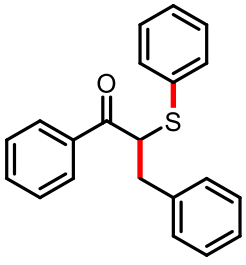
Representative peak for minor isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.6 Hz), 7.57 (t, *J* = 7.5 Hz), 7.51-7.40 (m), 7.21-7.16 (m), 6.04-5.96 (m), 5.34-5.18 (m), 4.14-4.11 (m).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 140.5, 138.6, 136.9, 133.1, 132.3, 129.1, 128.9, 128.7, 128.5, 128.0, 127.1, 117.0, 56.4, 50.7.

HRMS (ESI) calculated $[M+H]^+$ for $C_{23}H_{21}OS$: 345.1308, found: 345.1320.

FTIR (cm^{-1}) 3027, 1678, 1597, 1580, 1474, 1449, 1268, 1215, 1183, 1025, 921, 753.



1,3-Diphenyl-2-(phenylthio)propan-1-one (63af):

Following the general procedure, treatment of 2-(benzylthio)-1-phenylethan-1-one **62af** (0.121 g, 0.5 mmol) and 2-(trimethylsilyl) phenyl trifluoromethane sulfonate **54a** (0.224 g, 182 µL, 0.75 mmol) in the presence of CsF (0.228 g, 1.5 mmol) MeCN (3.0 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 1,3-diphenyl-2-(phenylthio)propan-1-one **63af** as yellow solid (0.099 g, 62% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.35

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 6.7 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.35-7.27 (m, 10H), 4.76-4.72 (m, 1H), 3.45 (dd, *J* = 14.2 Hz, 1H), 3.19 (dd, *J* = 14.4 Hz, 1H).

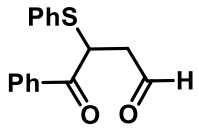
^{13}C NMR (100 MHz, $CDCl_3$) δ 195.34, 138.78, 136.28, 134.69, 133.16, 132.08, 129.45, 129.13, 128.88, 128.64, 128.61, 126.72, 53.0, 37.40.

HRMS (ESI) calculated $[M+H]^+$ for $C_{21}H_{19}OS$: 319.1151, found: 319.1162.

FTIR (cm^{-1}) 3019, 1676, 1585, 1477, 1456, 1343, 1319, 1260, 1210, 1154, 924, 779.

5.8.6. Synthesis and Characterization of 1,4-Dicarbonyl Compound

4-Oxo-4-phenyl-3-(phenylthio)butanal (64):



Following the procedure, treatment of ethyl 2-(allylthio)-1-phenylethan-1-one **63a** (0.400 g, 1.5 mmol) and ozone in CH_2Cl_2 (30.0 mL) at -78 °C for 5-10 min. Then to the reaction mixture dimethyl sulfide (15 ml) was added and continued stirring at -78 °C for another 20 min. Then the reaction mixture was allowed to warm up to RT, and continued stirring for another 12 h. The solvent was removed under reduced pressure. Purification of the crude material on a silica gel column chromatography ethyl acetate and pet ether afforded 4-oxo-4-phenyl-3-(phenylthio)butanal **(64)** as viscous yellow oil (350mg, 86%).

***R*f** (Pet. ether /EtOAc = 90/10): 0.25

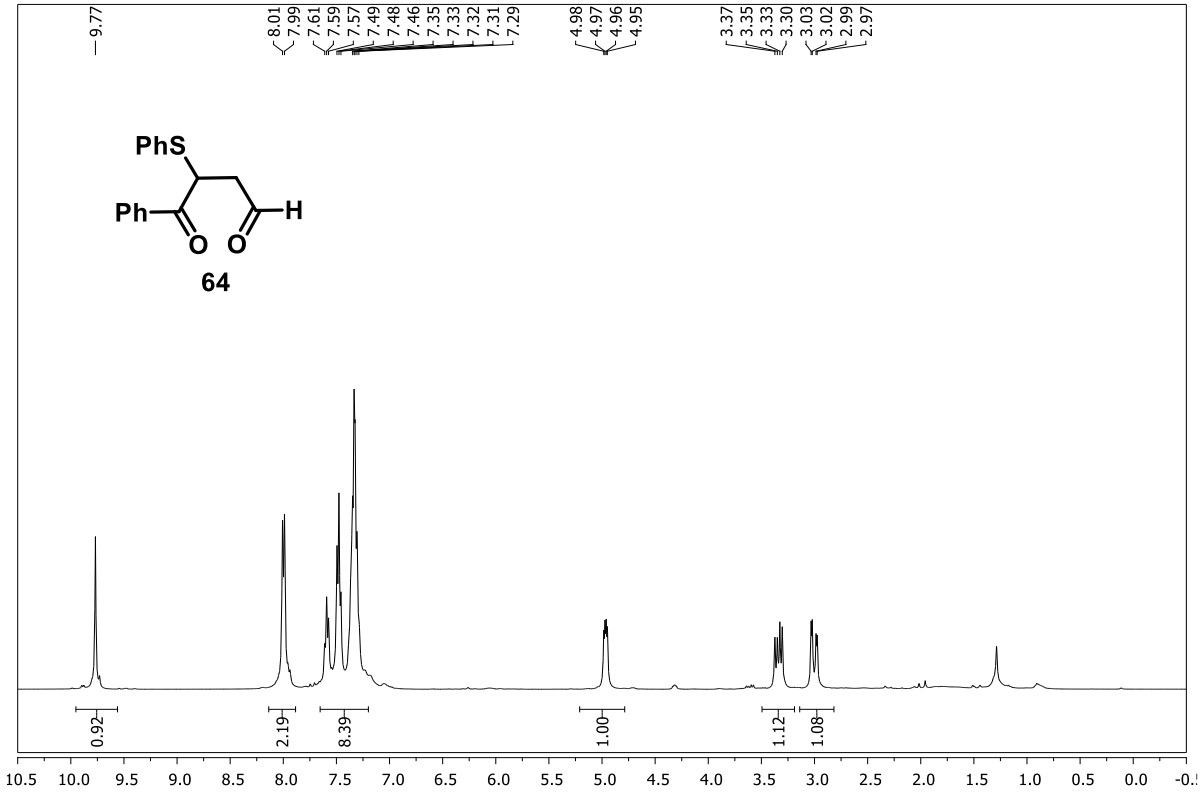
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.61-7.29 (m, 8H), 4.98-4.95 (m, 1H), 3.57-3.30 (m, 1H), 3.03-2.97 (m, 1H).

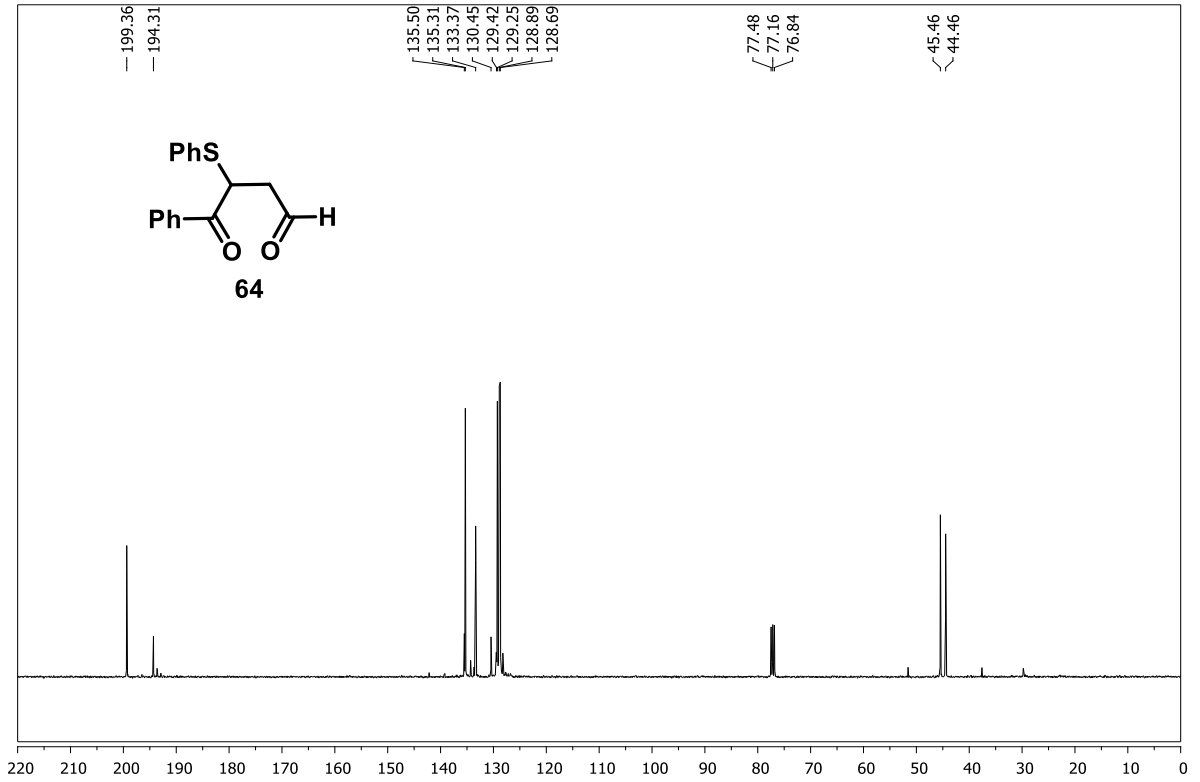
^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 194.3, 135.5, 135.3, 133.3, 130.4, 129.4, 129.2, 128.8, 128.6, 45.4, 44.4.

HRMS (ESI) calculated $[M+H]^+$ for $C_{16}H_{15}O_2S$: 271.0787, found: 271.0785.

FTIR (cm^{-1}) 3019, 2852, 1720, 1680, 1597, 1474, 1439, 1399, 1352, 1216, 1069, 972, 771.

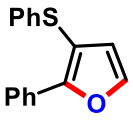
^{1}H and ^{13}C NMR Spectra of 4-Oxo-4-phenyl-3-(phenylthio)butanal (64)





5.8.7. Synthesis and Characterization of Heterocycles

2-Phenyl-3-(phenylthio)furan (65):



Following the procedure, To a stirred suspension of 1,4-dicarbonyl compound **64** (0.25 mmol, 68.0 mg) in 4.0 mL of Ac_2O at 0 °C, 1.0 mL con. HCl was added in dropwise under Argon protection. After the vigorous reaction, the reaction mixture was allowed to warm up to room temperature, and kept stirring for 3 h. The solvent was removed under reduced pressure. Purification of the crude material on a silica gel column chromatography ethyl acetate and pet ether afforded 2-phenyl-3-(phenylthio)furan **(65)** as viscous yellow oil (50mg, 79%).

***R*f** (Pet. ether /EtOAc = 95/05): 0.63

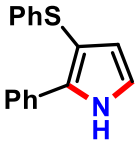
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 2H), 7.56 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.37-7.35 (m, 1H), 7.30-7.28 (m, 4H), 7.21-7.19 (m, 1H), 6.51 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 141.9, 137.0, 130.1, 129.1, 128.6, 128.3, 127.2, 126.1, 125.8, 117.7, 109.4.

HRMS (ESI) calculated $[M+H]^+$ for $C_{16}H_{13}OS$: 253.0682, found: 253.0692.

FTIR (cm^{-1}) 3064, 3015, 2926, 2854, 1670, 1513, 1478, 1216, 1146, 1082, 1025, 885, 770.

2-Phenyl-3-(phenylthio)-1*H*-pyrrole (66):



Following the procedure, A mixture of 4-oxo-4-phenyl-3-(phenylthio)butanal **64** (0.25 mmol, 68.0 mg), ammonium acetate (1.25 mmol, 96.0 mg) and MeOH/H_2O (12:3 mL) was stirred for 3h at room temperature. Then the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the crude material on a silica gel column chromatography ethyl acetate and pet ether afforded desired 2-phenyl-3-(phenylthio)-1*H*-pyrrole **(66)** as dark brown oil (51mg, 81%).

***R*f** (Pet. ether /EtOAc = 90/10): 0.28

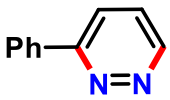
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (bs, 1H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.33-7.10 (m, 6H), 6.94-6.93 (m, 1H), 6.45 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 135.6, 131.8, 128.8, 128.7, 127.5, 127.0, 125.7, 124.6, 118.7, 117.2, 105.9.

HRMS (ESI) calculated $[M+H]^+$ for $C_{16}H_{14}NS$: 252.0841, found: 252.0840.

FTIR (cm^{-1}) 3461, 3019, 2927, 2854, 1659, 1603, 1582, 1496, 1441, 1216, 1081, 1025, 770.

3-Phenylpyridazine (67):



Following the procedure, the dicarbonyl compound **64** (0.25 mmol, 68.0 mg) was dissolved in ethanol (15 mL) and hydrazine hydrate (1.25mmol, 63.0 mg) was added. The reaction mixture was refluxed at 80°C for 6h. The solvent was removed under reduced pressure. Purification of the crude material on a silica gel column chromatography ethyl acetate and pet ether afforded 3-phenylpyridazine **(67)** as white solid (33mg, 85%).

***R*$_f$** (Pet. ether /EtOAc = 50/50): 0.38; mp 94 – 96 °C.

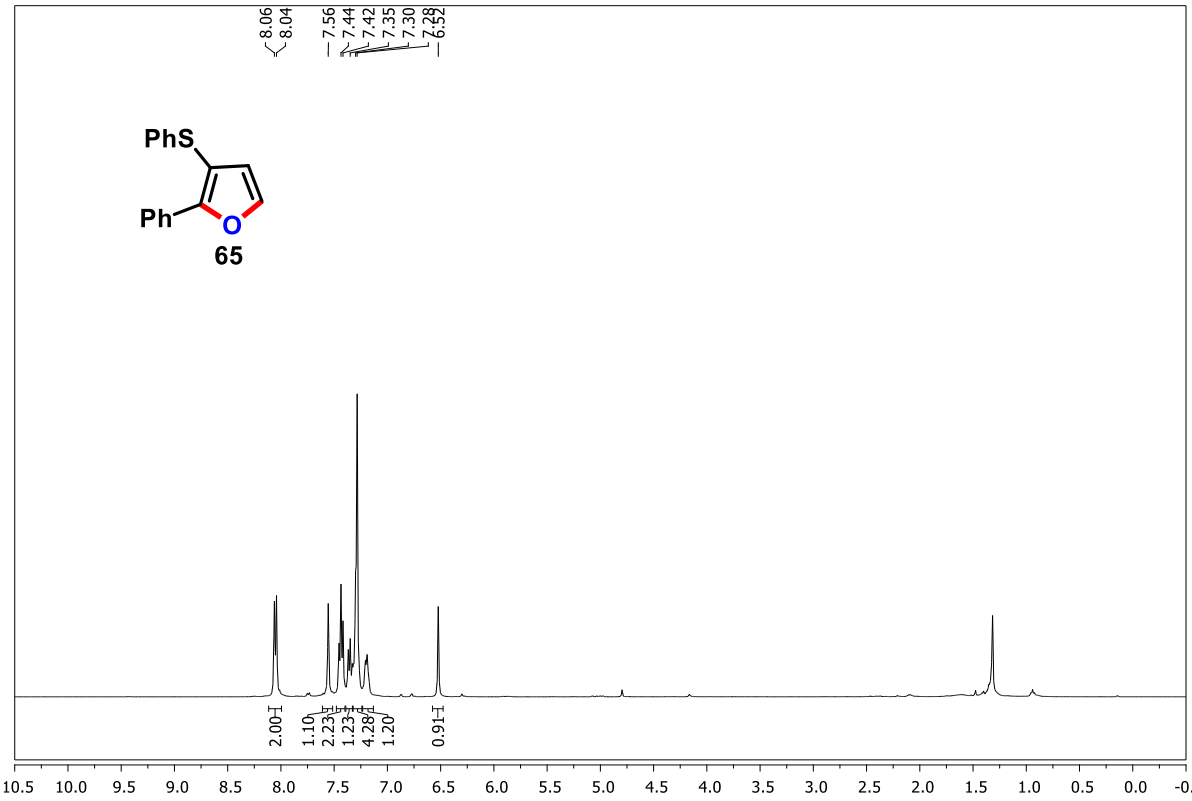
^{1}H NMR (400 MHz, CDCl$_3$) δ 9.18-9.17 (m, 1H), 8.11 (d, *J* = 6.4 Hz, 2H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.57-7.53 (m, 4H).

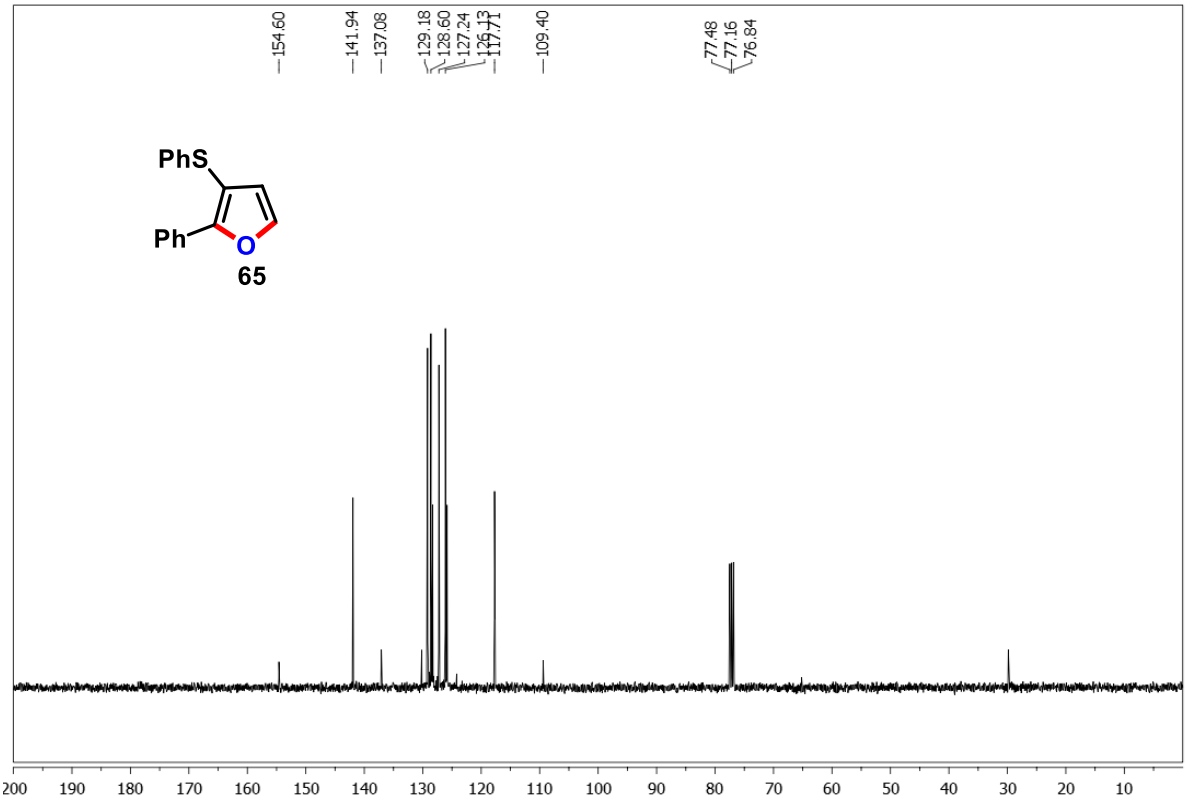
^{13}C NMR (100 MHz, CDCl$_3$) δ 159.6, 150.1, 136.4, 130.2, 129.1, 127.2, 126.9, 124.0.

HRMS (ESI) calculated $[M+H]^+$ for $C_{10}H_9N_2$: 157.0760, found: 157.0762.

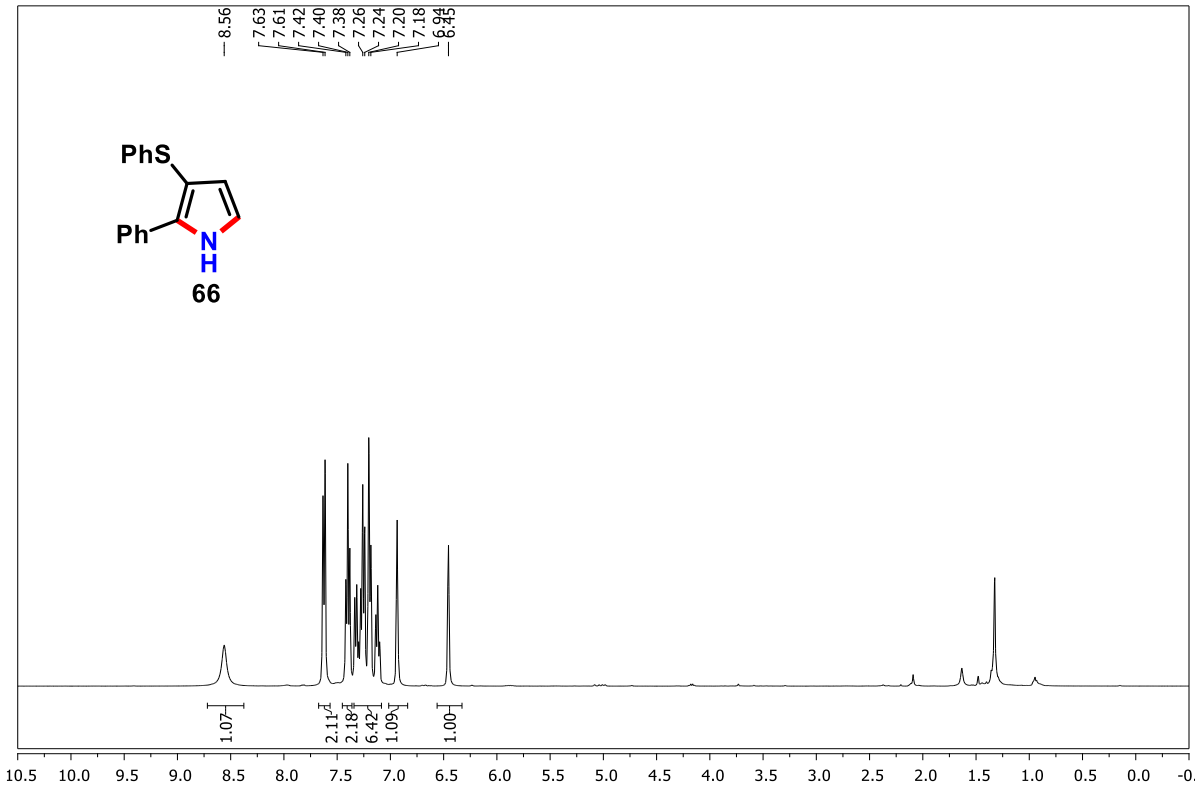
FTIR (cm^{-1}) 3011, 1727, 1658, 1580, 1547, 1452, 1432, 1374, 1297, 1217, 1099, 1028, 821.

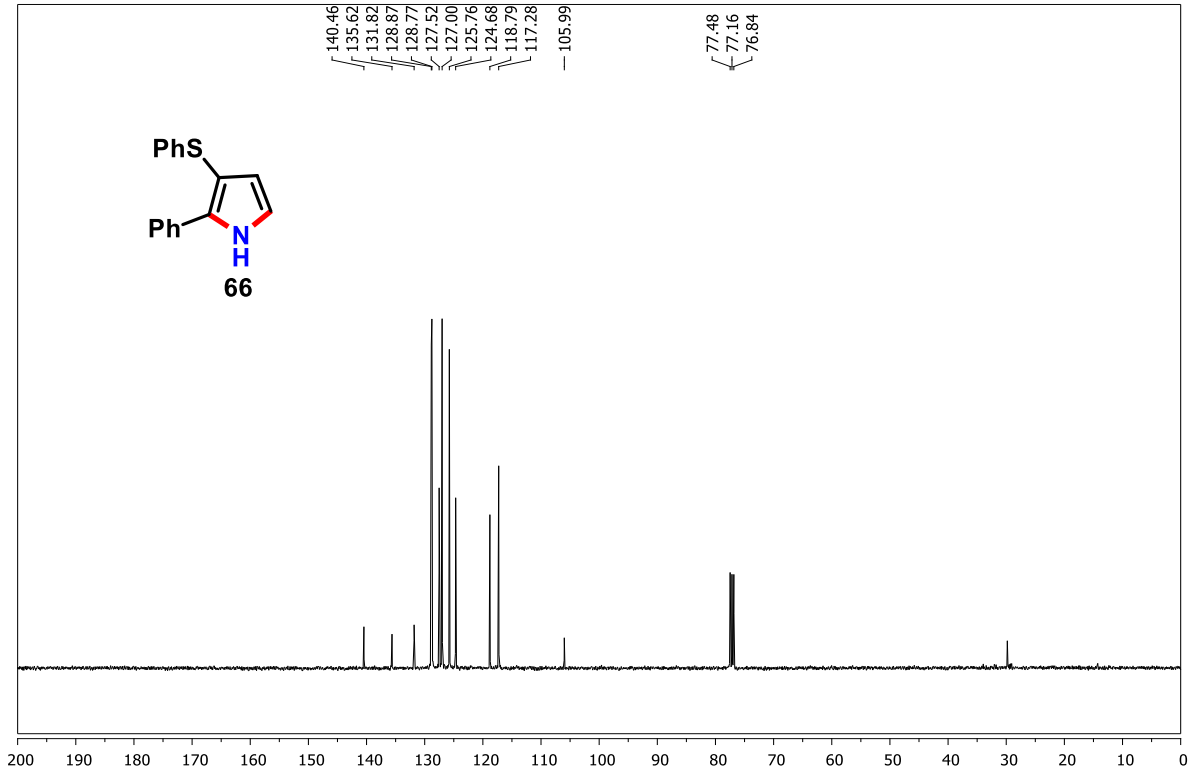
^{1}H and ^{13}C NMR Spectra of 2-Phenyl-3-(phenylthio)furan (65)



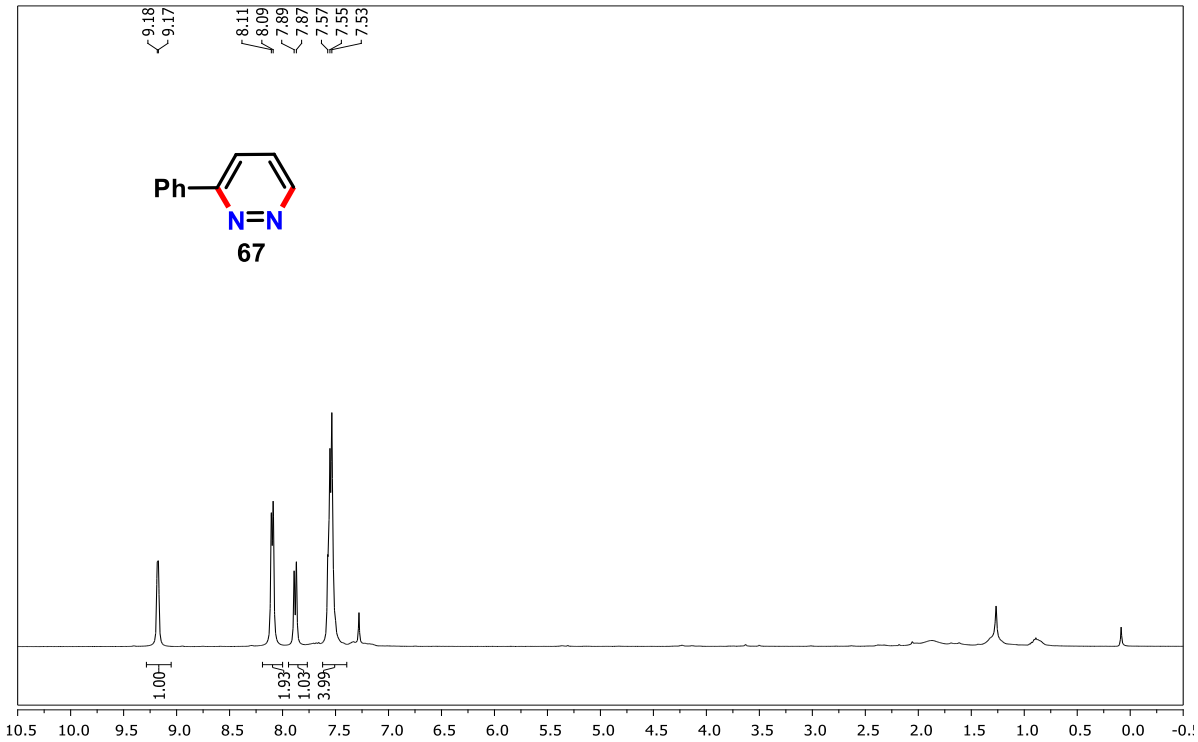


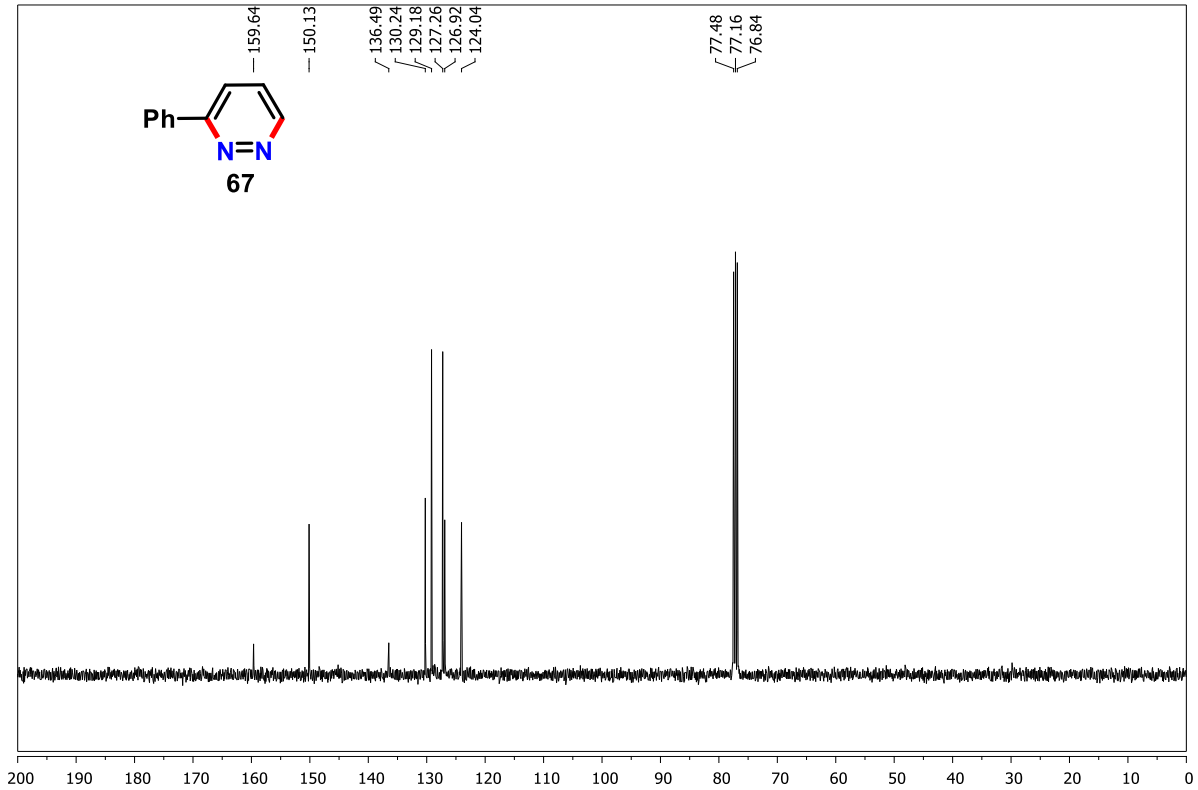
^{1}H and ^{13}C NMR Spectra of 2-Phenyl-3-(phenylthio)-1*H*-pyrrole (66)





^{1}H and ^{13}C NMR Spectra of 3-Phenylpyridazine (67)





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