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Aryne-Guided C-H Functionalization of Benzenoid Rings Using Diaryliodonium Salts

by

Aleksandra Nilova

A dissertation submitted in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
in
Chemistry

Dissertation Committee:
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Portland State University
2020

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Abstract

The benzenoid core is a frequent and irreplaceable component of biologically active molecules. Structure function relationship of these compounds has been broadly analyzed and presented in numerous literature reports. Herein, we augmented existing knowledge by a broad analysis of the benzenoid substitution patterns in small molecule active pharmaceutical ingredients approved by the FDA. Our findings reveal a strong correlation that the most represented substitution patterns are those achieved via S_EAr . Despite the rapid development of methods to functionalize benzenoid rings, the lack of synthetic methodologies to access sterically and electronically unfavorable positions is highlighted. We sought to establish a protocol to fulfill the synthetic gap to inaccessible benzenoids. The realization of this goal was achieved through aryne enabled C-H functionalization.

Disubstituted aryl(mesityl)iodonium tosylates were demonstrated to undergo aryne formation upon *ortho*-deprotonation under basic conditions. Functionalization of these intermediates with a broad scope of arynophiles resulted in a variety of sterically congested tetra-substituted benzenoids. The practicality of the established protocol was supported by a successful performance of a gram scale reaction. The compatibility with halogen substituents on the aryne precursor provided an opportunity for sequential functionalization of the coupling products in transition metal catalyzed reactions.

With our focus on the application of diaryliodonium salts, the diverse mechanistic possibilities of aryl(2,4,6-trimethoxyphenyl)iodonium tosylates in arylation reactions

were expanded and incorporated access to aryne intermediates. The choice of the reaction conditions depends on the electronic nature of the substituents. The exceptionally mild conditions for aryne formation via deprotonation of the corresponding aryl iodides are viable in a telescoped reaction through iodonium intermediate.

Dedication

To my beautiful and strong mother.

Thank you for always believing in me.

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1 Introduction

1.1 Importance of benzenoid rings

The importance of benzenoid rings is hard to overstate due to their abundance in various societally important industries. Applications of benzenoid containing compounds range from plastics and dyes to vital medicines and agrochemicals. Figure 1 shows several examples that include the biologically active natural product morphine, synthetic drugs cobimetinib and meclofenamic acid, as well as the herbicide tembotrione, petroleum-derived dye Sunset Yellow, and thermoplastic polymer polycarbonate. The ability of synthetic chemists to form new bonds to aromatic rings, and in a desired position is of the utmost importance to the discovery of new compounds that may have important societal applications.

Figure 1. Examples of benzenoid-containing molecules with benzenoid rings highlighted in blue.

1.2 Substitution patterns: existing analyses, identifying a gap

Aromatic rings are a prevalent motif in drug molecules.¹ Benzenoid rings in particular are the most common ring type in drug candidates² and small molecule new molecular entities (NME) approved by the U.S. FDA.³ The structure-function relationship of active pharmaceutical ingredients (API) is a strong tool for predicting druglikeness and guides synthesis of drug candidates. Previous analyses of APIs by both academic and industrial medicinal chemistry groups have focused on physiological properties^{1,4,5}, common frameworks^{3,6}, and the reagents⁷ and reactions^{2,8,9} to synthesize them. For instance, Ritchie and Macdonald looked at the connection between aromatic ring count in oral drug candidates and lipophilicity and solubility as properties reflecting the binding ability of a potential drug and its availability for interaction with a biological target.¹ They concluded that molecules with three or fewer aromatic rings correlate with higher success in developability and reaching the market. Taylor et al. analyzed marketed drugs approved by the FDA and found that 1175 ring containing molecules are represented by only 351 ring systems.³ Considering the timeline associated with the introduction of drugs to the market the authors noticed that from year to year most of new drugs repeat previously introduced ring systems. Meanwhile, the overall number of drug candidates has been continuously increasing for several decades.¹⁰ As medicinal chemists rely on previously present ring systems in new drug development, the synthesis of new drug candidates is based on functional group modification reactions that stand up among other types of reactions.^{2,9} Comparison of the most favorable reactions for medicinal chemists between 1984 and 2014 revealed that nucleophilic aromatic substitution (S_NAr), reaction

of aryl lithium, and Sonogashira coupling were preferred for aromatic ring functionalization in both analyzed periods. With the further development of Pd catalysis, Suzuki-Miyaura coupling and Buchwald-Hartwig amination became irreplaceable in derivatization of haloarenes.

Among substituted benzenoid ring-containing starting materials used for synthesis of drug candidates the preference for *para*-substituted rings over other substitution patterns is discerned.⁹ Specifically, Brown et al. noted that *para*-chloro substituted benzenoid is prevalent in various screening collections and known drugs over its *meta*- and *ortho*- analogs.⁷ Moreover, further analysis of chemical databases revealed similar trend for other groups and their similarly substituted analogs (e.g., di-Cl, di-F, di-OMe). In an attempt to determine the origin of this event, the ease of accessing the *para* position through electrophilic aromatic substitution (S_EAr) reactions was seen as the most plausible explanation (historical synthetic route). However, a broader analysis of benzenoid substitution patterns in APIs has not been previously reported in literature.

1.3 Functionalization of benzenoid rings

Substituted benzenoids can be produced through various general ways, including electrophilic and nucleophilic aromatic substitution, transition metal catalyzed reactions, and aryne reactions. In contrast to S_EAr and more recent transition metal catalyzed reactions, the other methods require a leaving group to proceed. Thus, reaction in which the leaving group is replaced by a new group are synthetically useful, but do not create a new substitution pattern.

1.3.1 Electrophilic aromatic substitution

Discovered in the late 19th century, electrophilic aromatic substitution (S_EAr) reactions represent one of the most important and well-studied transformations for arene functionalization. It is widely utilized to access valuable intermediates and products in various industries.¹¹ An important aspect of this approach is an ability to install a new functionality in place of a hydrogen substituent and, therefore, increase the number of substituents on a benzenoid ring. The general pathway of S_EAr involves two important intermediates: 1) the formation of a π -complex between the π -system of an arene and an electrophile represented by either cationic or dipolar species, 2) the formation of a σ -complex (arenium ion or Wheland complex) between a ring carbon and the electrophile (Figure 2, A). Rearomatization occurs as a result of a removal of the *ipso* proton with base. The nature of substituents on the aromatic ring dictates the direction of the electrophilic attack and the resulting substitution pattern of the benzenoid ring. Electron donating groups (such as R, OR, NR₂) that are capable of resonance donation, including halogen substituents, direct the attack in positions 2 or 4 relative to the substituent, thus, resulting in 1,2-, 1,4-, and/or 1,2,4-substituted benzenoids. Further functionalization of trisubstituted benzenoids relies not only on the electronic effect of substituents but also on a steric accessibility of the functionalized position. In this case an installation of the fourth substituent generally produces 1,2,4,5-substituted arene (Figure 2, B). Presence of strong electronegative substituents (NO₂, CF₃, COOR, CN) causes destabilization of a σ -complex, and electrophilic aromatic substitution is feasible only at the position 3. As a

result, 1,3-substituted benzenoids are produced in some cases, though these reactions are more rare.

Figure 2. Electrophilic aromatic substitution reaction: A. Mechanism; B. Example of synthetic application.¹²

1.3.2 Nucleophilic aromatic substitution

The presence of a strong electron-withdrawing group (EWG) on a benzenoid ring opens an opportunity for nucleophilic aromatic substitution (S_NAr) when an appropriate leaving group is present (typically a halide).¹³ Additionally, the leaving group must be positioned *ortho* or *para* to the EWG. The mechanism of this transformation has been intensely studied since the 19th century, and the most favored addition-elimination mechanism was proposed by J. Meisenheimer.^{14,15} In this process the σ -complex (Meisenheimer complex) is formed upon addition of a nucleophile and stabilized by the EWG. Leaving group expulsion results in a new functionality installed in its place (Figure 3). C-H functionalization is rather uncommon for S_NAr and the transformation conserves the substitution pattern of a starting material.

Figure 3. Mechanism of nucleophilic aromatic substitution reaction.

1.3.3 Transition metal catalyzed reactions

A century after the discovery of S_EAr and S_NAr reactions, aryl halides became a prominent element of novel transformations facilitated by the transition metals. Since then, transition metal catalyzed reactions, and Pd catalyzed reactions in particular, have proven to be a reliable method for synthesis of various biologically active molecules.^{2,16} This approach allows previously challenging carbon-carbon and carbon-heteroatom bonds formation to occur. Transition metal catalysis obviates the formation of charge intermediates and, therefore, does not rely on the electron deficiency of an aromatic ring in comparison to the S_NAr . The general steps of a metal catalyzed cross-coupling reaction include oxidative addition of aryl halide to a metal complex, transmetalation of a nucleophile on a transition metal, and reductive elimination (Figure 4). The overall outcome is a replacement of a leaving group with a nucleophile. Similar to S_NAr reactions, the retention of substitution pattern in the final product is observed.

Figure 4. General mechanism of metal catalyzed cross-coupling reaction.

1.3.4 Aryne enabled functionalization

Arynes are recognized as useful intermediates to functionalize aromatic rings. The traditional approach to aryne formation includes deprotonation of the benzenoid ring under basic conditions followed by the loss of a leaving group in an adjacent position (Figure 5). This process results in the formation of a highly strained cycloalkyne.¹⁷ Although the observation of aryne reactivity had originated in early 20th century,¹⁸ the first structural assignment of an aryne intermediate was revealed in 1953 by Roberts *et al.*¹⁹ Strain caused by the direction of orbitals of the triple bond makes it highly reactive electrophile. Aryne intermediates can be used for building multiple new carbon-carbon and carbon-heteroatom bonds in a single step.²⁰ Attack by charged and uncharged nucleophiles leads to a direct approach to 1,2-difunctionalization of aromatic rings.²¹

Figure 5. Aryne formation reaction.

1.4 Application of aryne intermediate

Aryne formation reactions (Scheme 1. A.) have found a broad application in the pericyclic reactions such as [4+2] cycloaddition reaction with dienes²², [2+2] cycloaddition with alkenes²³, and [3+2] cycloaddition with dipolar substrates²⁴ (i.e. azides). In addition, arynes can insert in the element-element bond of a polar σ -bond where one of the components serves as a nucleophile and the other as an electrophile.^{25–28} Similar to the insertion reaction, 1,2-disubstituted products are formed in the process of the multicomponent reactions.²⁹ However, in this case a nucleophile and an electrophile are represented by distinct molecules. Multicomponent and bond insertion reactions may lead not only to vicinal difunctionalization of aromatic ring, but also to *ipso* or *cine* substitution in the case where a proton plays a role of an electrophile.^{30,31} The substituents on an aryne intermediate have a significant influence on the direction of nucleophilic attack. Thus, σ -withdrawing groups (including halides and alkoxides) direct nucleophilic attack to the distal carbon of the triple bond in highly selective manner (Scheme 1. B.). The released pair of electrons attacks an electrophile producing 1,2,3-substituted pattern.

Scheme 1. A. Representative reactions of benzyne. B. Influence of substituent on attack direction.

1.4.1 Recent advances in aryne formation reactions

A number of aromatic ring containing compounds can serve as starting materials for generating highly reactive benzyne intermediate (Figure 6). Aryl monohalides were the first precursors for generating aryne intermediates.^{19,32} Treating the substrate with alkali metal amide in boiling ammonia leads to C–H deprotonation followed by halogen elimination to form benzyne. However, the presence of multiple halogens results in unselective elimination of the leaving group in some cases.³³ The reaction conditions also preclude this method with base-sensitive substituents. In addition, the strong base required for deprotonation may act as a competitive nucleophile for attack on the aryne. Nevertheless, the availability of aryl halides makes this type of precursors highly attractive for application as aryne precursor. Significant improvements to the classical approach were presented by the groups of Olafs Daugulis and Qiu Wang over the last few years.^{25,30,34–36} Aryl chlorides, bromides, and triflates are shown to undergo aryne

formation reaction with a broad range of arynophiles resulting in carbon-carbon and carbon-heteroatom bonds formation. Additionally, selective elimination of a triflate group over chloride is achieved under the reaction conditions.

An approach to synthesize benzyne intermediate from *ortho*-dihalobenzenes and pseudohalocontaining analogs has been proposed by multiple groups. This type of the transformation is enabled by metalation reaction with lithium containing compounds followed by the elimination of a leaving group (halide) and generally requires cryogenic temperatures.^{37–40} Benzenediazonium-2-carboxylates can alternatively generate an aryne intermediate upon thermolysis.⁴¹ Although this approach does not require chemical facilitation, it is limited due to the explosive nature of diazotized anthranilic acid.⁴² Among other precursors *ortho*-(trimethylsilyl)aryl triflates remain one of the most widely used starting materials. This method was developed by Kobayashi in 1983 and has received considerable attention from the scientific community due to moderately basic conditions used for the formation of aryne.⁴³ Under similar reaction conditions phenyl[2-(trimethylsilyl)aryl]iodonium triflates generate aryne intermediates. Proposed by Kitamura in 1995, this transformation is advanced by the higher nucleofugality of iodonium group relative to triflate.⁴⁴

Figure 6. Methods to generate benzyne and required conditions. Hal = halogen.

1.4.2 Current synthetic challenges in aryne formation

The ability of aryne intermediates to form multiple new bonds in one step has amplified an interest in these species. Its profound capability for rapid construction of diverse molecular frameworks has been demonstrated for synthesis of pharmaceutically and biologically relevant small molecules and natural products.^{20,45} The method developed by Kobayashi is greatly appealing for this purpose. Along with the use of a mild base to generate aryne, the rate of reaction can be controlled by the choice of solvent, fluoride source, and combination of thereof.⁴⁶ However, this method is not free of disadvantages. The relatively high price and lack of commercially available substituted benzyne precursors bring the need for an on-site synthesis. Installation of the required substituents in adjacent positions takes 3-5 steps along with multiple distillations or column chromatography purifications.^{43,47-49} For example, 3-chlorobenzyne precursor can be obtained from 2-chlorophenol in 68 % yield (Scheme 2). Total synthesis of this precursor takes 20 hours of reaction time and includes three chromatography purifications.⁴⁸

Scheme 2. Synthesis of 3-chlorobenzyne precursor.

On the other hand, a large variety of substituted aryl(pseudo)halides is commercially available. The requirement to have a single substituent (halide or

pseudohalide) and available C-H bond in adjacent position for aryne formation gives an opportunity for introducing additional functionality. The conversion of aryl(pseudo)halides to aryne intermediates has been successfully used as a key transformation in natural product syntheses.^{45,50–52} Despite the recent advances, the use of lithium containing bases and need of cryogenic temperatures are a practical limitation. The discovery of a new base lithium diadamantylamide (LDAM) allows for a reaction to proceed at 0 °C.²⁵ The hindrance of this amide base suppresses its nucleophilic property and consequently results in an enhanced selectivity of aryne coupling (Scheme 3, top). Nevertheless, LDAM promoted aryne formation has only been reported in air-free atmosphere. A milder base NaOt-Bu has been shown to successfully convert aryl chlorides to aryne intermediates for *o*-arylation of phenols (Scheme 3, bottom). This transformation is facilitated by high temperature (135-155 °C) and usually requires AgOAc as an additive.³⁰

Scheme 3. Aryl halides in aryne formation reactions.

1.5 Diaryliodonium salts as aryne precursor: from the first evidence

The application of diaryliodonium salts for aryne synthesis was initially demonstrated in 1974.⁵³ The symmetrical diaryliodonium halide **1** was utilized as an

arylation agent in the reaction with phenyltetrazolide **2** (Figure 7). Refluxing of the reaction mixture for 24 hours in *tert*-butanol resulted in the formation of three pairs of products consisted of meta and para-substituted structural isomers **3–5** consistent with aryne reactivity. The authors confirmed their hypothesis of aryne formation by treating the same iodonium salt with NaOt-Bu in *t*-BuOH where a mixture of *p*-tolyl and *m*-tolyl *t*-butyl ethers was obtained in 1:1 ratio and overall yield of 27%. A year later Cadogan et.al. synthesized arynes through thermolysis of diaryliodonium acetate and its substituted derivatives prepared by admixing of corresponding iodonium halides with KOAc.⁵⁴ Trapping of an intermediate with tetraphenylcyclopentadienone gave corresponding 1,2,3,4-tetraphenylnaphthalenes in 3–12% yield. Since these initial reports the formation of arynes from diaryliodonium salts via deprotonation is sparse in the recent literature and have typically been noted as a minor by-product when reductive elimination is desired.⁵⁵ Despite the observation of aryne formation in the reactions of diaryliodonium salts this approach continued to remain undeveloped until our discovery in 2016.⁵⁶ This approach will be introduced in Chapter 3.

Figure 7. First evidence for aryne formation from diaryliodonium salt.

1.6 Synthesis of unsymmetrical diaryliodonium salts

In addition to their ability to act as aryne precursors, hypervalent iodine compounds are of high interest in contemporary organic synthesis as aryl transfer reagents and an alternative to transition metal catalysis; they are known to be nontoxic and relatively bench-stable materials.^{57–59} Diaryliodanes, commonly known as diaryliodonium salts, are represented by structure shown in Figure 8 where λ^3 -iodane center is covalently bound to two (hetero)aromatic rings and associated with an anionic ligand. It was experimentally determined that in the solid state substituents of diaryliodonium salts favor a T-shape orientation with an Ar-I-Ar angle close to 90°.

Figure 8. Structure of diaryliodonium salt.

Unsymmetrical diaryliodonium salts are especially advantageous when one aryl group can be transferred selectively. Aryl(mesityl)iodonium tosylates represent a valuable group of hypervalent iodine compounds. The arylation properties of these substrates are conveniently complemented by an access via multiple synthetic routes and in one-pot (Scheme 4). Boronic acid of the functionalized arene of interest can be introduced into the reaction with an auxiliary containing aryl- λ^3 -iodane to produce corresponding aryl(mesityl)iodonium salt in the presence of Lewis acid. The application of simple arenes was demonstrated by several research groups. Electron-rich arenes are used in the reaction with aryl- λ^3 -iodane electrophiles such as hydroxy(tosyloxy)iodomesitylene. The scope of shown substrates is limited to 1,3,5-

trimethoxybenzene (TMB), anisole, and thiophen and its derivatives.⁶⁰ A broader scope of possible electron-rich substrates was demonstrated when fluorinated solvents were utilized.⁶¹ The oxidation of aryl iodides with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of *p*-toluenesulfonic acid (HOTs) followed by addition of mesitylene affords aryl(mesityl)iodonium tosylate in under 4 hours.⁵⁹ The ubiquity of Suzuki cross-coupling has made aryl iodides and aryl boronic acids widely commercially available.

Scheme 4. Synthetic routes to aryl(Mes)iodonium tosylates (left) and aryl(TMP)iodonium tosylates (right).

The examples of synthetic application of 2,4,6-trimethoxyphenyl (TMP) containing iodonium salts had been sparse from literature due to a lack of a convenient method of preparation. A robust one-pot protocol was reported only in 2016 and provided a routine access to these substrates in under an hour (Scheme 4, right).⁵⁹ This discovery accelerated the reaction development methods focused on aryl(TMP)iodonium salts (Scheme 5). Thus, the ability of these compounds to undergo metal-free *ipso*-substitution reactions has been demonstrated with various nucleophiles. They have been shown to selectively react with N- and O-nucleophiles as well as undergo radiofluorination in this type of transformation.^{59,62–66} Likewise, the reports of transition metal catalyzed arylation of

amides and imines with TMP salts have been recently presented in the literature.^{67,68} Additionally, aryl(TMP)iodonium salts can undergo transformations via radical mechanism, and the methods for arylation of N-heteroaromatics and a rapid access to 3-arylsulfonylquinolines have been established.^{69,70} The work described in Chapter 4 reveals new synthetic possibilities of aryl(TMP)iodonium tosylates as an aryne precursor. Thus, this specific ability of TMP containing iodonium reagents to undergo various types of transformations selectively on an aryl group rather than the auxiliary makes these substrates highly attractive and prospective universal iodonium substrates as an arylating agent.

Scheme 5. Synthetic possibilities of aryl(TMP)iodonium salts via various mechanistic routes.

2 Analysis of benzenoid substitution patterns

2.1 Parameters of analysis

An overview of synthetic methods to functionalize aromatic rings was presented in Chapter 1 and was proposed to influence the substitution patterns of aromatic rings in a variety of industries. The pharmaceutical industry has been particularly proactive in assessing structure-function relationships of API, though a broad analysis of aromatic ring substitution patterns has not previously appeared in the literature. Our analysis of benzenoid substitution patterns in APIs is focused on small molecule drugs approved by the FDA up to the end of 2019. We used the database publicly available on DrugBank (drugbank.ca)⁷¹ with the following filters applied: “small molecule drugs”, “approved”, and “US”. The original search was performed on January 31, 2019 and revealed 1793 approved small molecule drugs, and the NMEs approved during 2019 were obtained from a list of novel drug approvals for 2019 published by the FDA.⁷² Benzenoid containing small molecule drugs were manually extracted, excluding benzenoid rings fused to other (hetero)aromatic systems (i.e., naphthalene, (iso)quinoline, indole, etc.) previously identified as distinct ring systems.³ The dataset was narrowed to 904 APIs. Our analysis included the number of benzenoid rings in each API and the substitution pattern for each ring; we also included time as an additional dimension of our analysis. Substitution patterns were assigned based on the position of substituents on the benzenoid ring, but neglecting the substituents identity, and, therefore the chemical space of benzenoid rings consists of twelve different substitution patterns shown in Figure 9 (1-; 1,2-; 1,3-; 1,4-; 1,2,3-; 1,2,4-; 1,3,5-; 1,2,4,5-; 1,2,3,5-; 1,2,3,4-; 1,2,3,4,5-; 1,2,3,4,5,6-). Our analysis

across time employed the FDA drug approval reports by month; the search was performed based on submission classification only including drugs classified as “Type 1 - New Molecular Entity”. The chemical structures of the NMEs identified from the FDA were retrieved from DrugBank⁷¹ and PubChem⁷³. The druglikeness, complexity, and similarity of the APIs within each substitution pattern were calculated for a slightly reduced dataset where multi-component and metal containing entries were excluded from the database along with several compounds that failed the data processing protocols of our collaborators at Merck. This modification reduced the dataset to 864 molecules. The complexity of small molecule drugs was estimated by the use of software developed in-house at Merck and reflects a correlation with synthetic tractability and process mass intensity.⁷⁴ According to this approach the complexity ranges from 1 to 5, where 1 is the least complex and 5 is the most complex molecule. The druglikeness of the elements in the dataset was quantified using Lipinski’s rule-of-five⁷⁵ and a rule-of-six model⁷⁶ developed at Merck. Similarity was calculated using Dice similarity based on 2-dimensional atom pair descriptor. According to this method a cluster centroid is determined and its pairwise combination of atom pairs is compared to those of other molecules.⁷⁷ Based on a magnitude of the match the molecules are clustered, and the similarity ranges from 0 (nothing in common) to 1 (identical). Similarity of the molecules was measured separately for the individual groups of substitution patterns with Dice similarity cutoff of 0.5 and 0.6.

Figure 9. Possible benzenoid substitution patterns.

2.2 Analysis

We began our analysis by looking at the distribution of benzenoid rings in a given API for a dataset of 904 small molecule drugs. It was found that about 60% (539 molecules) of the APIs contain only one benzenoid ring, 34% (307 molecules) contain two benzenoid rings, and only 5% contain 3 benzenoid rings (Figure 10). This result aligns with the previously reported correlation of the number of aromatic rings with the developability of molecules where it was noticed that molecules with less than three aromatic rings were more developable.¹

Figure 10. Distribution of the number of benzenoid rings in a given API.

The total number of benzenoid rings in the dataset of 904 molecules was 1364, and the substitution pattern of every ring was visually identified (Figure 11). The most abundant substitution patterns are 1,4-, 1-, 1,2,4-, and 1,2-substituted arenes. These four substitution patterns represent 76% of benzenoid rings and are the most synthetically accessible via S_EAr and correlate with those purchased by medicinal chemists as starting materials.⁹ The remaining eight substitution patterns represent only 24% of benzenoid rings and their individual appearance is attributed to not more than 5%. This sparse representation may be explained by a lack of synthetic pathways and low commercial availability of starting materials. As mentioned in Chapter 1.2, among the most prevalent synthetic methodologies, those used for benzenoid ring functionalization are nucleophilic aromatic substitution (S_NAr), reaction with aryl lithium, Sonogashira coupling, Suzuki-Miyaura coupling, and Buchwald-Hartwig amination.^{2,8} However, these reactions replace an existing substituent with a new one, but do not create a new substitution pattern. The relative position of individual substituents in the underrepresented benzenoid rings are categorized as contra-electronic by means of S_EAr (1,3- and 1,3,5-) and sterically congested (1,2,3-, 1,2,3,5-, 1,2,4,5-, 1,2,3,4-, 1,2,3,4,5,6-, and 1,2,3,4,5-).

Figure 11. Distribution of benzenoid substitution patterns in APIs.

I further analyzed both the number of benzenoid rings in a given API and the substitution patterns over time. The discovery of palladium-catalyzed reactions has had a dramatic impact on synthetic chemistry, especially coupling reaction of aromatic rings. Developed at the end of the 20th century Sonogashira, Suzuki-Miyaura, and Buchwald-Hartwig Pd-catalyzed cross-coupling reactions became a prominent and reliable tool to incorporate benzenoid rings in drug candidates. In this analysis we compared two time periods roughly separated by the “named reactions” described above. The first period includes NMEs for the period of 1959-1979, at the end of which aryl-alkyne and aryl-aryl coupling reactions were reported. For the second period we chose two decades of post-cross-coupling 1999-2019. We first looked at the distribution of the number of benzenoid rings in a given API in each time-period in comparison to the distribution of approved drug molecules. It can be seen in Figure 12 that the overall trend remains the same, and the

drug molecules containing only one benzenoid ring are still prevalent and attributed to more than 50% of all molecules. However, a slight change in distribution between two time periods is evident. The number of compounds incorporating one benzenoid ring decreases from 58% in the pre-palladium catalysis era (1959-1979) to 53% in the post-palladium catalysis era (1999-2019). This moderate change results in an increase in the number of those APIs with two or more benzenoid rings in comparison to the previous time period. Although this difference may seem insignificant, it reflects analogous changes observed in screening libraries over the last two decades.⁸

Figure 12. Historical insight in distribution of benzenoid rings in a given API.

We considered the influence of transition-metal catalysis on distribution of benzenoid substitution patterns. Over the two time periods described above the distribution of substitution patterns did not significantly change in comparison to the complete dataset. The most prevalent substitution patterns in both time periods were 1,4-, 1-, 1,2,4-, and 1,2-substituted benzenoids comprising 78% in 1959-1979 and 74% in

1999-2019 (Figure 13). Meanwhile, a number of NMEs approved in a later time period, and a number of benzenoid rings accordingly, increased drastically from 100 molecules (150 benzenoid rings) to 333 molecules (536 rings). Despite an impressive synthetic reliability and applicability of Sonogashira, Suzuki-Miyaura, and Buchwald-Hartwig cross-coupling reactions, these strategies mostly rely on previously installed substitution pattern of starting materials and, thus, do not have a significant influence on synthesis of sterically congested and contra-electronic benzenoids.

Figure 13. Distribution of benzenoid substitution patterns in historical perspective.

Although the dataset is comprised of small molecule NMEs approved by the FDA, we wanted to estimate the druglikeness of molecules across the substitution patterns to evaluate if there is a difference in druglikeness based on substitution pattern. It was done by applying the parameters of Lipinski's rule-of-five (RO5) and Merck's rule-of-six (RO6). Analysis demonstrated there was not substantial difference among substitution patterns and between the models applied. The distribution of druglikeness among substitution

patterns can be seen in Figure 14. The vast majority of the molecules meet the requirements of druglikeness and are quantified on average as 85% for Lipinski's rule and 72% of NMEs when RO6 is applied. Both approaches allow for only a single rule violation to "pass". Overall, 96% of the molecules that did not pass RO5 or RO6 exceeded the molecular weight limit of 500 Da for RO5. Noticeably, over 60% of 1,2,3,4,5,6-substituted benzenoid containing molecules violate both RO5 and RO6. This group represents the most substituted benzenoids and has the highest average molecular weight in comparison to others, that causes the first violation. Additionally, most of these molecules have a prohibited excess of hydrogen bond acceptors (≥ 10) and donors (≥ 5). Despite failure to meet theoretical requirements, these APIs include important classes of drugs, such as anthracyclins (e.g. epirubicin and daunorubicin) and iodinated contrast agents (e.g. iopromide and iohexol).

Figure 14. Percent of "druglike" molecules based on rule-of-five and rule-of-six.

The complexity of small molecule NMEs was assessed for every group of benzenoid substitution pattern and the standard deviation was calculated. A moderate

increase in complexity from more abundant substitution patterns towards underrepresented benzenoids can be seen on Figure 15. As complexity in this analysis correlates with synthetic difficulty, these data support our hypothesis that underrepresented patterns are harder to obtain via synthetic methodologies favored by medicinal chemists.

Figure 15. Average complexity and standard deviation of substitution patterns.

To connect the complexity of approved drugs to structural appearance, we decided to gain an insight on the similarity of the molecules within every substitution pattern. Additionally, this analysis would provide an estimate of structural diversity. For this analysis we chose the largest cluster of each benzenoid substitution pattern and calculated an input in a total number of molecules in every group. It appeared that most of the substitution patterns are represented by very diverse structures and the size of the largest cluster is accounted to not more than 15% of the total substitution pattern with a similarity cutoff of 0.5 and 10% when similarity is set to 0.6 (Figure 16). However, NMEs

of 4 out of 12 substitution patterns are represented by less diverse chemical structures, and the contribution of the largest cluster varies from 21% to 45%. Interestingly, these benzenoid substitution patterns are synthetically challenging: 1,3,5- (21%, 3-molecule cluster), 1,2,3,4,5,6- (21%, 5-molecule cluster), 1,2,3,4,5- (27-32%), and 1,2,3,4-substituted benzenoids (39-45%). Noticeably, the least structurally diverse is 1,2,3,4-substituted pattern; that is also the most complex with average complexity of 3.8 and highly druglike (88% of druglike molecules based on RO5) pattern. An explanation for this relationship arises from the nature (structural appearance) of the largest cluster. Almost half of the small molecules NMEs of this substitution pattern are represented by natural product morphine and its derivatives. These molecules are synthetically challenging with calculated complexity above 4 and pass both RO5 and RO6. The subsequent chapters describe the development of synthetic methods that address the limited access to contra-electronic and sterically congested benzenoid rings.

Figure 16. Largest cluster input.

3 Aryl(mesityl)iodonium salts as aryne precursors.

3.1 Modern synthetic approach to aryne formation from diaryliodonium salts

The approach to aryne formation from diaryliodonium salts via C-H deprotonation remained underdeveloped since the first observation in 1974 in which an aryne was trapped in low-yield.⁵³ In 2016, two high-yielding methods to access arynes from diaryliodonium salts with strong base were described. First, the Stuart research group⁵⁶ demonstrated the formation of aryne intermediates from aryl(mesityl)iodonium tosylates using LiHMDS as a base, and the highly reactive intermediate was trapped with furan. The method was applied to more than 20 distinct aryl(mesityl)iodonium tosylates as substituted aryne precursors (Table 1). Soon after, the Wang research group demonstrated N-phenylation of various amides using symmetrical diphenyliodonium triflates as the benzyne precursor and KO^t-Bu as base, followed by insertion into N-H bond.³¹ Later, the aryne reactivity of aryl(Mes)iodonium tosylates was expanded with N-aryl pyrroles and tertiary amines.^{78,79}

Table 1. Representative examples of aryl(Mes)iodonium tosylates as aryne precursors.

3.2 Synthesis of sterically congested benzenoid rings

We became particularly interested in the development of a synthetic methodology that would provide an easy access to the underrepresented benzenoids described in Chapter 2. The precedent for the functionalization of a sterically congested C-H position (position 2, Table 1) using iodonium salts inspired us to apply this approach in building densely functionalized benzenoid rings. Therefore, we aimed to establish a protocol to synthesize 1,2,3,4-substituted benzenoids from disubstituted aryl(Mes)iodonium tosylates which are readily available from the corresponding 1,2,4-substituted arenes, which are common starting materials.

3.2.1 Optimization

As a starting point, 3-chloro-4-methylphenyl(Mes)iodonium tosylate **6a** was chosen as a disubstituted aryne precursor. Dimethylimidazolidinone (DMI) has been shown to act as an arynophile that provides an access to aryl diazepinone analogs via σ -bond insertion into a C-N bond of urea.⁸⁰ The coupling of these two substrates under the previously developed reaction conditions provided the expected compound in 64% yield. Switching the base to NaOt-Bu, that was previously shown to enable aryne formation, increased the reaction outcome to 72 %. Reducing the amount of DMI from 5.5 to 3 equivalents drastically reduced the yield of this reaction with LiHMDS (29%) but had less significant effect when NaOt-Bu was used (56%). Based on these preliminary results, the interaction effects of equivalents of NaOt-Bu and arynophile and temperature was explored by applying the design of experiments. A 2³ full factorial design consisted of eight experiments revealed that the optimal reaction conditions consist of 1.5 equivalents of

NaOt-Bu, 3 equivalents of DMI, and 25 °C reaction temperature, resulting in 69% yield of product (Scheme 6). The consumption of the iodonium salt as the limiting reagent was assessed based on the formation of mesityl iodide as the main by-product in this transformation and was found to be 95%. An immediate color change was observed in the reaction and therefore the reaction time was also tested. Indeed, an identical yield was observed after 15 minutes, and the yield was slightly reduced to 55% within 5 minutes of reaction time. Toluene was found to be a suitable solvent for this transformation not only with LiHMDS as a base but also with NaOt-Bu (66% yield). The use of acetonitrile led to a reduced reaction yield of 45%. The iodonium moiety is crucial for aryne formation under the developed conditions, and the product formation was not observed when the corresponding iodide was used instead. Even a significant increase in temperature to 135 °C and time to 24 hours³⁰ did not provide useful reactivity of the aryl iodide (Scheme 6, Entry 7).

Scheme 6. Optimization of reaction conditions.

3.2.2 Scope

3.2.2.1 Scope of iodonium salts as aryne precursor

The scope of disubstituted aryl(Mes)iodonium tosylates compatible in the transformation with DMI is shown in Table 2. The reaction was conducted under the conditions indicated in Scheme 6, entry 1. To ensure the complete conversion of the iodonium salts, the reaction time was increased to 40 min for most substrates. The yield ranged between 41-71% with the average yield 55%. A wide range of substituents is well tolerated including halogen substituents (F, Cl, Br) known to form aryne intermediates as described in Chapter 1.4. Fluorinated groups prevalent in biologically active compounds are not impacted in this transformation. The attempt of aryne insertion in an amide bond of 6-membered urea, N,N'-dimethylpropylene urea, did not lead to the formation of the desired product under the optimized condition despite the structural similarity.

Surprisingly, the formation of coupling product was observed only when LiHMDS was used as a base and the reaction was performed in toluene yielding 37% of 8-membered insertion product **8da**.

Table 2. Scope of 1,2,3,4-substituted arenes via aryne and cyclic ureas.

3.2.2.2 Scope of arynophiles

The difunctionalization of arynes to access sterically congested benzenoid rings was further assessed by the scope of arynophiles. TMS protected 2-hydroxyfuran **7c**, similar to its unsubstituted analog, participates in [4+2] cycloaddition reaction, followed by deprotection under acidic conditions and oxidation under exposure to air yield the naphthoquinone in 47% yield (Table 3, entry 1). Phenyl N-*tert*-butylnitron **7d** underwent

[3+2] cycloaddition with 3-chloro-4-methylbenzyne intermediate resulting in an excellent 92% yield (Table 3, entry 2). However, in this case an 11:1 mixture of sterically congested regioisomers was isolated. Coupling with benzyl azide **7e** gave the cycloaddition product in 47% yield (Table 3, entry 3). The formation of pyridyl substituted phenol in 29% yield was enabled in the reaction with pyridine N-oxide **7f** accompanied with rearrangement (Table 3, entry 4). The insertion in an amide bond of cyclic ureas was extended to N-heteroatom bond insertion reactions. This type of reaction of 3-chloro-4-fluorobenzyne with N-trimethylsilyl morpholine **7g** resulted in the formation of new C-N and C-Si bonds. Similarly, the use of *N*-chloromorpholine **7h** provided a tri-chlorinated benzenoid from the corresponding aryne in 56% yield. Although the previous examples demonstrated the selective formation of 1,2,3,4-substituted aryne coupling products from 3-chloro-4-fluoro(Mes)iodonium tosylate, 1,2,4,5-substituted benzenoid was produced as a minor isomer in the reaction with chloroazepane **7i**. Nevertheless, the expected sterically congested benzenoid was obtained in 47% yield (Table 3, entry 6).

Table 3. Scope of arynephiles.

3.2.3 Practical considerations

Reaction development typically focuses on mg-scale quantities of starting materials and scaling up a process can often be problematic.⁸¹ While our standard protocol is designed for 0.5 mmol of the limiting reagent, we applied it in a tenfold scale reaction (5 mmol), which would correspond to gram-scale quantities of product. The reaction was conducted in a flask open to air and the final aryl diazepinone **8na** was isolated in slightly reduced 62% yield (compared to 71%). No visible changes, including a dramatic temperature change, were observed upon increasing the scale of the reaction.

Scheme 7. Gram-scale synthesis.

3.2.4 Derivatization via transition metal catalysis

The development of transition metal catalyzed reactions has enabled previously challenging synthetic transformations, and these methods have become irreplaceable in medicinal chemists' toolbox. The compatibility of halides in the formation of arynes demonstrated here allows for further derivatization of the aryne coupling products via transition metal catalyzed reactions. Bromo-substituted aryl diazepinone was chosen for further derivatization based on known high reactivity of this substituent. The conditions of Suzuki-Miyaura coupling, Buchwald-Hartwig amination and Heck coupling reactions were successfully applied and the products of these transformations were isolated in excellent yield. Although Heck reaction with methyl acrylate yielded 99%, the coupling product was isolated as a mixture of *E* and *Z* isomers with the useful ratio of 9.6:1. Overall, despite the steric hindrance of the aryne coupling compound, it demonstrated high reactivity in the transition metal catalyzed reactions.

Scheme 8. Derivatization of aryl diazepinone.

3.2.5 Sequential dual C-H functionalization of disubstituted arenes

The ability of arenes to participate in diaryliodonium salt formation from Koser's type reagents was envisioned as an opportunity to functionalize two adjacent C-H bonds. In this way an electron-rich 1,2-substituted arene may be converted into a 1,2,3,4-substituted arene. Ultimately, first C-H bond is cleaved in the iodonium salt formation step, where electron donating group dictates the regioselectivity of a $S_E\text{Ar}$ -type reaction. The second C-H bond is cleaved by deprotonation of the most sterically congested position and results in aryne formation followed by trapping with an arynophile. This approach was successfully applied for the functionalization of *o*-fluoroanisole in two step synthetic sequence (Scheme 9). First, the corresponding iodonium salt was produced under acidic conditions in 74% isolated yield. Then, coupling of 3-fluoro-4-methoxybenzyne with nitrone yielded substituted benzoisoxazoline in 85%; the yield over two steps is 63% and corresponds to cleavage of two C-H bonds and formation of C-O and C-C bonds. The same substrate underwent dual C-H functionalization, however, in one-

pot protocol. To minimize the conflict of reaction media used in the two sequential steps, a catalytic amount of tosic acid was used to facilitate aryl(Mes)iodonium tosylate formation. The aryne intermediate formed under basic conditions was trapped with furan and isolated in 38% yield. It is important to note that the reactivity of every step was not assessed individually, and the overall yield has potential for improvement.

Scheme 9. Functionalization of two adjacent C-H bonds via iodonium salts formation.

3.2.6 Unexpected aryne reactivity in the reaction with cyclic ureas

As it has been noted, the consumption of aryl(Mes)iodonium tosylates was assessed based on the formation of Mes-I. In the optimization process we observed the complete consumption of the aryne precursor based on the 95% yield of this by-product (Mes-I), while the formation of the desired product was 69%. Analysis of the crude reaction mixture by GC-MS revealed an unexpected discovery: a peak with a mass corresponding to the addition of two aryne intermediates with DMI ($m/z = 363$) accounted for 5-10%, which corresponds to 10-20% of the aryne precursor. Our initial hypothesis was that an aryne inserted into each of the urea C-N bonds to yield a symmetrical 9-membered ring product (Scheme 10). However, further analysis of this side

product using NMR spectroscopy demonstrated that the aryl groups were in fact inequivalent and that the ethylene unit had been modified. Indeed, the presence of a single CH₂ group with H resonances at ~ 4.5 ppm and a CH group with a downfield resonance of ~6.5 ppm was determined from ¹H, DEPT, and HSQC NMR experiments. The literature precedent for arylation of tertiary amines with aryne intermediate via dealkylation⁷⁸ along with obtained data resulted in a new hypothesis. A mixture of plausible structural isomers was proposed as an outcome of the nucleophilic attack by either nitrogen atom of the aryl diazepinone **8aa** followed by the ring opening.

Scheme 10. Discovery of unexpected side products.

The formation of aryl diazepinone as an intermediate was confirmed when it was successfully reacted with iodonium salt upon treatment with NaOt-Bu. The aryne coupling product **8aa** underwent ring opening in the presence of 3-fluoro-trifluoromethylphenyl(TMP)iodonium tosylate **6d** under basic conditions and yielded a mixture of structural isomers **10c** and **10d** in 80% (Scheme 11). Additionally, the substituted starting materials were switched; the ring opening of aryl diazepinone **8ma**

produced corresponding compounds **10e** and **10f** in 50% isolated yield. In both cases, the ratio of products is approximately 2-3: 1, though the identity of the major and minor isomers was hampered by overlapping signals in the NMR spectra.

Scheme 11. Ring opening of aryl diazepinones.

To validate the C-N bond cleavage in the ring opening process, phenyl morpholine was reacted under the demonstrated conditions (Scheme 12). As expected, N-arylation took place in the reaction with iodonium salt **6a** producing the corresponding diarylamine **8ah** in 63% yield. Similarly, a strong downfield resonance at ~6.4 ppm of the vinyl proton of the CH group was found in the ^1H NMR experiment characteristic for this functional group.

Scheme 12. N-arylation of phenyl morpholine.

3.2.7 Dimerization of aryl(mesityl)iodonium salts

The X-ray analysis of aryl(mesityl)iodonium tosylates used in the reactions presented in this chapter revealed the formation of centrosymmetric dimer with bridging tosylate groups (Figure 17, A). It was questioned whether similar behavior is observed in solution. To probe this, an experiment using ^1H NMR spectroscopy in which spectra of solutions of different concentrations are recorded and the change in chemical shift of signals demonstrates an interaction between molecules present in solution was performed. As the solubility of diaryliodonium salts is known to be extremely low in many common solvents, their characterization by ^1H NMR is typically performed in deuterated dimethyl sulfoxide ($\text{DMSO}-d_6$). In the initial experiment three samples of 3-chloro-4-methylphenyl(mesityl)iodonium tosylate **6a** of three different concentrations were prepared by dilution. We observed no shift for any of the signals. This may be explained by the coordinating nature of DMSO and competitive association of DMSO to break up the dimer.⁸² When the experiment was repeated using deuterated chloroform (CDCl_3) as a solvent, considerable shifts can be seen for all signals of aromatic protons indicating dynamic intermolecular interaction dependent on concentration. Similar tendency was observed when phenyl(mesityl)iodonium tosylate was analyzed as an unsubstituted analogue under the same conditions (Figure 17, B). With the increase of concentration of iodonium salt in solution, the upfield shift of aromatic protons can be observed with an exception for signals for hydrogen atoms located in ortho-position to iodonium. However, X-ray analysis also demonstrated that some iodonium salts do not dimerize in solid state. 2-chloro-4-methoxyphenyl(mesityl)iodonium tosylate is one of the examples of this

group. Nonetheless, when the experiment described above was performed using this compound the same trend in shifts of signals was revealed. Thus, the formation of dimer can be hypothesized and does not necessarily correlates with data obtained from X-ray analysis.

Figure 17. A. X-ray structure of **6a** and **6i**. B. Stack of ^1H NMR spectra of concentrations (bottom to top) 0.1 M, 0.01 M, 0.001 M in CDCl_3 .

4 Aryl(TMP)iodonium salts as aryne precursor

The diverse synthetic possibilities of aryl(TMP)iodonium salts have been discussed in Chapter 1. Herein, we describe the development of a complimentary mechanistic pathway for these substrates as an arylating agent. In particular, the ability of these substrates to form arynes is demonstrated.

4.1 Tuning the reactivity for aryne formation

We envisioned the formation of aryne intermediates from aryl(TMP)iodonium salts to be feasible under the reaction conditions similar to those described in Chapter 3. However, the use of NaOt-Bu has been previously reported to facilitate the formation of alkyl aryl ethers from diaryliodonium salts and alcohols. Moreover, tert-butoxide anion was shown to form tert-butyl aryl ether with highly electron-poor diaryliodonium salts; particularly, *para*-nitrophenyl tert-butyl ether was obtained upon treatment with aforementioned base (Figure 18, A).^{83,84} Thus, overriding *ipso*-substitution became a priority in order to achieve the formation of aryne from aryl(TMP)iodonium salts.

In order to assess the effect of aryl substituent electronic effects on the competing mechanisms of *ipso*-substitution and aryne formation several *para*-substituted aryne precursors were selected (Figure 18, B). The substrates ranged from highly electron-withdrawing nitro substituent ($\sigma^- = 1.27$) to electron-donating methoxy substituent ($\sigma^+ = -0.78$). It was found that the formation of a significant amount of the *ipso*-substitution product was observed for electron-poor aryne precursors with π -EWG (i.e., NO₂, CN, CO₂Me, and CF₃). A very small amount of *ipso*-substitution product was observed for

mildly electron-withdrawing Cl substituent, and only aryne formation was observed for those substrates with electron-donating substituents.

Figure 18. A. Literature precedent for alkyl aryl ether formation. B. Effect of substituents on mechanistic outcome.

The undesirable reactivity of the electron-poor aryne precursors was envisioned to be restrained by the use of less nucleophilic base LiHMDS, that has demonstrated to be effective in this type of transformation.⁵⁶ The combination of the effect of base, nature of the substituent, and its relative position on aryne formation and trapping with furan was more broadly assessed (Figure 19). To our delight, the electron-poor aryl group of iodonium salt was successfully converted into aryne intermediate when LiHMDS was used as base. This observation is valid for both *meta* and *para*-substituted aryl(TMP)iodonium salts. On the other hand, the reactivity of methoxy-substituted aryne precursor was not dramatically affected by the identity of base. These feasibility experiments demonstrated milder NaOt-Bu to be a suitable base for the majority of the substrates and LiHMDS needed for select examples.

Figure 19. Effect of base and substituent on aryne formation; circles represent yields.

4.2 Scope

The scope of the aryne trapping products from compatible aryl(TMP)iodonium salts is shown in Table 4. In the cycloaddition reaction with furan or benzyl azide the yield ranged from 54% to 97%. The presence of a *meta*-substituent on the aryl group of iodonium salts allowed the use of NaOt-Bu as a base to facilitate aryne formation. Various functional groups are tolerated in this strategy, including such strong EWG as NO₂ and CN. However, in case of 2-methyl-5-nitrophenyl(TMP)iodonium tosylate the use of LiHMDS was necessary for aryne formation. Moreover, CO₂Me functional group is reactive under the reaction conditions and likely undergoes transesterification with *tert*-butoxide; this results in the formation of a mixture of aryne products. As it has been highlighted previously, a significant increase in yield of the aryne adduct was observed for

this substrate in the presence of LiHMDS. The use of this base also promoted the formation of aryne intermediate with *para*-nitro and *para*-cyanophenyl(TMP)iodonium tosylates. Furthermore, various benzenoid substitution patterns were accessed via this route and included 1,2,3-, 1,2,4-, 1,2,3,4-, 1,2,3,5-, and 1,2,3,4,5-substituted benzenoids.

Table 4. Scope of aryne trapping products.

4.3 Multistep one-pot functionalization of aryl iodides

The developed aryne formation approach was successfully adjoined to the iodonium salt synthesis mentioned in Chapter 1. However, these two processes occur in fundamentally different surroundings: synthesis of aryl(TMP)iodonium salts is conducted

in acidic media, while the presence of base is required for aryne formation. The insolubility of iodonium salts in TBME was exploited to merge the two steps in a solvent switch, which resulted in the removal of *meta*-chlorobenzoic acid, the reduction product of *m*-CPBA, and potential impurities with a minimal loss of the aryne precursor (Scheme 13). The main advantage of this one-pot protocol is the depletion of the quantity of solvent required for the trituration of iodonium salts as a purification method. The synthesis of aryne coupling adduct from corresponding aryl iodide is conveniently accomplished in a timeframe of 2 hours. These examples demonstrate an improvement of our previously developed approach to the same substrates from aryl(Mes)iodonium tosylates.⁵⁶ For comparison, the formation of **12jg** was reported in analogous 69% isolated yield, however, this result did not account for the yield of iodonium salt. Similarly, the yield of **12vg** is slightly reduced in the developed protocol to 78% from previously reported 84%.

Scheme 13. Telescoped approach to aryne from aryl iodides.

4.4 Formal synthesis of bioactive compound

The practicality of the one-pot protocol was evaluated by the efficient synthesis of a bioactive compound. Anaplastic Lymphoma Kinase (ALK) and tyrosine-protein kinase Met (c-Met) inhibitor is a potential cancer treatment. The synthesis of this bioactive

compound has been patented and includes the formation of an aryl diazepinone intermediate.⁸⁵ The previously reported route to this intermediate required six steps and resulted in an overall yield of 3% from 2,6-dinitrotoluene. The telescoped approach from 3-nitrophenyl iodide with a solvent switch shown in the previous section was successfully applied to synthesize the required aryl diazepinone. *m*-Nitrophenyl(TMP)iodonium tosylate formation followed by the aryne insertion in the amide bond of DMI **7a** resulted in 55% yield of the desired substrate **12ia** (Scheme 14). Although the purification by column chromatography provided a solution of this compound in excess of DMI, it was effectively crystallized out of this solution.

Scheme 14. Application of telescoped reaction in formal synthesis of bioactive compound.

4.5 Selectivity

The nature of substituents on an aryne intermediate is known to dictate the site of the nucleophilic attack on it. The regioselectivity of the attack by a nucleophile is described by the aryne distortion model, according to which the attack occurs at the more linear site of aryne triple bond. The distortion model for arynes bearing two substituents adjacent to triple bond has been proposed by Garg *et al.* based on density functional

theory (DFT) study in 2014 (Figure 20, A).⁸⁶ The degree of distortion is assessed as a difference in internal angles, where a 4° angle or greater results in useful regioselectivity. Among the tested substrates the periodic trend of decreasing electronegativity of halides is interrupted by the methoxy substituent that is the second strongest σ -EWG after fluoride in this sequence. The authors noted that these computational predictions relied exclusively on the optimized geometry of the arynes and did not consider the steric effect of the substituents. To date experimental verification of these predictions has been limited by the synthesis of suitable aryne precursors.

However, in this case the aforementioned type of aryne intermediate is successfully generated from the corresponding aryl(TMP)iodonium tosylates and trapped with furan (Table 4). To test the selectivity of nucleophilic attack the representative examples of aryne precursors were chosen based on the commercial availability. With calculated distortion of 5°, 3-chloro-6-methoxybenzyne demonstrated extreme selectivity (18:1) in the reaction with morpholine (Figure 20). One can suggest this result to be caused by *ipso*-substitution process. However, both regioisomers of aryl(TMP)iodonium tosylate showed the preference for nucleophilic attack is distal to the methoxy group. The distortion of 3-bromo-6-fluorobenzyne is reported to be 10°. The same set of experiments was performed on the corresponding iodonium salts. Despite the high predicted selectivity, the mixture of regioisomers was obtained in less than 2:1 ratio, yet with the major isomer as predicted.

High selectivity was observed in the reaction of 5-halotolyl(TMP)iodonium tosylates with morpholine. Although no computational data were provided for these substrates, the σ -donating nature of methyl group can be expected to lead the nucleophilic attack to the adjacent position. However, the control experiment to evaluate the competing pathway of *ipso*-substitution failed, resulting in less than 10% yield for each substrate. Consequently, the nature of the intermediate cannot be confirmed for this group of aryne precursors.

Figure 20. A. Predicted distortion angles and selectivity. B. Observed selectivity of nucleophilic attack.

Uneven distribution of the benzenoid substitution patterns within small molecule active pharmaceutical ingredients motivated us to provide an access to challenging examples via new synthetic routes. We see the potential of diaryliodonium salts in achieving this goal. Comparably mild conditions for aryne formation via C-H deprotonation (a combination of relatively moderate base and room temperature) open an opportunity for diverse functionalization in a timely manner. Our preliminary data demonstrate several examples of underrepresented substitution patterns. Although 1,3-substituted benzenoids are underrepresented, the available feedstock of these iodides can provide formal *ipso*-substitution product via aryne intermediate. Thus, arylation of piperidine was observed in the presence of NaOt-Bu in 77% (Scheme 15, top left). Difunctionalization of the same aryne intermediate in the reaction with furan resulted in 1,2,3-substituted benzenoid under the same conditions (Scheme 15, top right). New possibilities of readily available 1,2,4-substituted benzenoids are recognized when the leaving group (iodonium) is located in position 1. Substitutive *ortho*-transposition (or cine-substitution) with a nucleophile is directed towards the formation of a contra-electronic substitution pattern. As an example, deprotonation of the single available position *ortho* to the iodonium of 4-bromo-2-fluorophenyl(TMP)iodonium tosylate followed by a nucleophilic attack resulted in 1,3,5-substitution pattern (Scheme 15, bottom left). On the other hand, difunctionalization of the same aryne intermediate provides results in a new

steric cluster. Trapping the aforementioned aryne intermediate with phenyl *N*-*tert*-butyl nitronone yielded a 1,2,3,5-substituted benzenoid (Scheme 15, top right).

Scheme 15. Access to underrepresented substitution patterns via aryne intermediate.

The development of a telescoped approach from readily commercially available aryl iodides is highly appealing and anticipated to dramatically reduce solvent consumption required for iodonium salt isolation as well as overall time to achieve the final arylation product. A solvent switch method has been briefly introduced in this manuscript. Alternatively, the neutralization of acid can be performed with base. However, a careful choice is necessary due to the exothermicity of this interaction and a successful result was not achieved with NaOt-Bu. A recent additional screen of bases revealed an unexpected result. Use of K_3PO_4 facilitates the formation of aryne intermediate from diaryliodonium tosylates (Scheme 16), and good yield of aryne trapping products was observed independently of the auxiliary. Thus, 3-trifluoromethoxyphenyl(Mes)iodonium tosylate in the reaction with furan yielded the product in 56%. Trapping of 3-fluoro-4-methylbenzyne from the corresponding

aryl(TMP)iodonium salt resulted in 65% yield. These results are the subject of intense future investigation in the Stuart group.

Scheme 16. Phosphate promoted aryne formation.

6 Experimental section

6.1 General considerations

Commercially available reagents and solvents were used without further purification. *m*-CPBA was assayed by iodometric titration and determined to contain 71-74% active oxidant. Compounds **6d**, **6i**, **11a**, **11d-f**, **11i-k**, **11m**, **11n**, **11q**, and **11u** were prepared according to a literature procedure.^{56,65,87} *N*-chloroamines **7h** and **7i** were prepared according to a literature procedure⁸⁸ using sodium hypochlorite solution (10-15% available chlorine) and the spectral data were consistent with those previously reported.^{88,89} All other materials were prepared as described in detail below.

Crude reaction mixtures were analyzed by ¹H NMR spectroscopy, GC-MS, and/or thin-layer chromatography (TLC) on silica gel plates (60 Å F-254) or basic alumina plates (F-254) and visualized by UV irradiation and/or iodine stain. Crude material was purified by flash column chromatography on silica gel unless otherwise stated. Proton (¹H), carbon (¹³C {¹H}), and fluorine (¹⁹F {¹H}) nuclear magnetic resonance (NMR) spectra were obtained at 298 K in CDCl₃, DMSO-*d*₆, or (CD₃)₂CO on a Bruker Avance II+ 400 MHz spectrometer or Bruker Avance III 600 MHz spectrometers and referenced to residual solvent peaks⁹⁰ or tetramethylsilane when applicable. The following notation is used: s – singlet, d – doublet, dd – doublet of doublets, ddd – doublet of doublet of doublets, t – triplet, q – quartet, n – nonet, br – broad signal. Molecular weight was determined on Thermo Scientific Q-exactive high resolution mass spectrometer with electrospray ionization (ESI). Infrared spectra were recorded on Thermo Scientific Nicolet iS5 FTIR

spectrometer in transmission mode. Melting points (°C) were recorded on Melt-Temp (Thermo Scientific™) and are uncorrected.

6.2 Supporting information for Chapter 2

Database of benzenoid rings in FDA approved small molecule drugs is available online as a searchable [Excel](#)™ spreadsheet with ChemDraw® extension enabled. The database includes the following sheets: FDA approved, Sub1 through Sub123456, and Approval by year. FDA approved and Sub1 through Sub123456 sheets consist of small molecule APIs organized by alphabetical order and contain the specific information for each molecule that was included in our analysis. Sub1 is monosubstituted, Sub12 is 1,2-substituted, Sub13 is 1,3-substituted and so on. A user-guide to the database is available as [PDF](#).

6.3 Supporting information for Chapter 3

6.3.1 Preparation of hydroxy(tosyloxy)iodomesitylene

Scheme 17. Synthesis of hydroxy(tosyloxy)iodomesitylene.

Mesityl iodide (0.738 g, 3 mmol), acetonitrile (3 mL), and toluenesulfonic acid monohydrate (0.651 g, 3.03 mmol, 1.01 equiv.) were added to a round bottom flask equipped with a magnetic stir bar. *m*-CPBA (0.706 g, 3.03 mmol, 1.01equiv.) was added in one portion at room temperature and the flask was placed into an oil bath set to 77 °C. After 40 min reaction was removed from heat, the contents were allowed to reach

ambient room temperature, and the crude residue was triturated with diethyl ether. The precipitate was isolated by vacuum filtration and washed by slurry filtration with diethyl ether to provide analytically pure product in 85% yield (1.11 g, 2.6 mmol) as white powder. Spectral data are consistent with those previously reported.^{91,92}

¹H NMR (CD₃OD, 400 MHz) δ = 7.61 (d, J = 7.9 Hz, 2H), 7.28 (s, 2H), 7.20 (d, J = 8.0 Hz, 2H), 2.72 (s, 6H), 2.41 (s, 3H), 2.36 (s, 3H).

¹³C NMR (CD₃OD, 101 MHz) δ = 147.4, 144.2, 142.9, 141.9, 130.6, 129.8, 126.9, 26.7, 21.3(4), 21.3(0).

6.3.2 Preparation of aryl(Mes)iodonium tosylates

6.3.2.1 General procedure A

Scheme 18. Synthesis of aryl(Mes)iodonium salts from iodides.

Prepared according to the literature procedure.⁵⁹ Aryl iodide (1.0 equiv.) and acetonitrile (1 mL/mmol) were added to a round bottom flask, equipped with a magnetic stir bar. Toluenesulfonic acid monohydrate (1.01 equiv.) was added in one portion, followed by one portion of *m*-CPBA (1.01 equiv.). The flask was lowered into an oil bath set to 77 °C and stirred vigorously. After 30 min 1,3,5-trimethylbenzene (1.01 equiv.) was added in one portion and stirring was continued at 77 °C for 3 hours. The reaction was removed from heat and concentrated under reduced pressure. The resulting crude residue was triturated with diethyl ether. The precipitate was isolated by vacuum

filtration and washed by slurry filtration with diethyl ether to give analytically pure aryl(mesityl)iodonium tosylate.

6.3.2.2 General procedure B

Scheme 19. Synthesis of aryl(Mes)iodonium tosylates from aryl boronic acids.

Prepared according to the literature procedure.⁹³ Arylboronic acid (5.0 mmol, 1.0 equiv.) was weighed and transferred to a round bottom flask equipped with a magnetic stir bar. The flask was sealed with a rubber septum, flushed with nitrogen, and left under a static nitrogen atmosphere. DCM (30 mL) was added via syringe to the aryl boronic acid and the solution was cooled to 0 °C in an ice-water bath with stirring. BF₃·OEt₂ (1.1 mL, 9.0 mmol, 3.0 equiv.) was added via syringe to the aryl boronic acid solution and the reaction mixture was stirred for 10 min at 0 °C. Mesitylene iododiacetate (1.20 g, 3.3 mmol, 1.1 equiv.) was weighed and transferred to a separate pear-shaped flask. The flask was sealed with a rubber septum, flushed with nitrogen, and left under a static nitrogen atmosphere. DCM (9 mL) was added to the mesitylene iododiacetate via syringe. The mesitylene iododiacetate solution was added to the aryl boronic acid/BF₃·OEt₂ solution dropwise via syringe at 0 °C. The reaction mixture was allowed to warm to ambient room temperature and stirred overnight. The septum was removed, and an aqueous solution of NaOTs (60 mmol, 20 equiv. in 30 mL of water) was added with vigorous stirring for ~30 min. The biphasic mixture was added to a separatory funnel, and the DCM/water layers

were separated. The water layer was extracted with DCM (3 × 30 mL). The combined DCM layers were dried over MgSO₄, filtered, and solvent was removed under reduced pressure. The resulting crude residue was triturated with diethyl ether. The precipitate was isolated by vacuum filtration and washed by slurry filtration with diethyl ether to give analytically pure aryl(mesityl)iodonium tosylate. See below for the specific scale of reactions and characterization data of individual compounds.

6.3.2.3 General procedure C

Scheme 20. Synthesis of aryl(Mes)iodonium tosylates from simple arenes.

Hydroxy(tosyloxy)iodomesitylene (0.434 g, 1mmol), acetonitrile (1 mL), 2-haloanisole (1.01 equiv.), and toluenesulfonic acid monohydrate (0.190 g., 1 equiv.) were added to a round bottom flask equipped with a magnetic stir bar. The flask was placed into an oil bath set to 50 °C and the mixture was stirred at this temperature for 3 hours. The flask was removed from heat and brought to room temperature. The crude mixture was triturated with diethyl ether. The precipitate was isolated by vacuum filtration and washed by slurry filtration with diethyl ether to give analytically pure aryl(mesityl)iodonium tosylate.

6.3.3 Characterization of aryl(Mes)iodonium tosylates

Compound **6a**

Prepared according to the general procedure A on 15.0 mmol scale of 2-chloro-4-iodotoluene and obtained in 63% yield (5.12 g, 9.1 mmol) as white powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 8.13 (s, 1H), δ 7.78 (d, J = 8.2 Hz, 1H), δ 7.48-7.46 (m, 3H), δ 7.22 (s, 2H), δ 7.11 (d, J = 7.6, 2H), δ 2.60 (s, 6H), δ 2.36 (s, 3H), 2.30-2.29 (m, 6H).

^{13}C NMR (DMSO- d_6 , 101 MHz) δ = 145.7, 143.2, 141.6, 140.1, 137.6, 135.3, 134.0, 133.9, 133.0, 129.8, 128.0, 125.5, 122.8, 111.2, 26.3, 20.8, 20.5, 19.5.

FT-IR: 2976, 1574, 1466, 1218, 1150, 1005, 810 cm^{-1} .

HRMS: Calculated for $\text{C}_{16}\text{H}_{17}\text{ClI}^+ [\text{M} - \text{OTs}]^+$: 371.0058; Found 371.0057.

Melting point: 187 – 189 $^{\circ}\text{C}$.

Compound 6b

Prepared according to the general procedure B on 5.0 mmol scale of 3,4-dichlorophenyl boronic acid and obtained in 84% yield (2.36 g, 4.2 mmol) as white powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 8.35 (s, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 7.3 Hz, 2H), 7.23 (s, 2H), 7.10 (d, J = 7.5 Hz, 2H), 2.59 (s, 6H), 2.30 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (DMSO- d_6 , 101 MHz) δ = 145.5, 143.4, 141.8, 137.7, 135.6, 135.3, 134.3, 133.4, 133.3, 129.9, 128.1, 125.5, 122.9, 112.5, 26.3, 20.8, 20.5.

FT-IR: 2982, 1449, 1215, 1170, 1008, 865 cm^{-1} .

HRMS: Calculated for $\text{C}_{15}\text{H}_{14}\text{Cl}_2\text{I}^+ [\text{M} - \text{OTs}]^+$: 390.9512; found 390.9531.

Melting point: 192 – 193 $^{\circ}\text{C}$.

Compound 6c

Prepared according to the general procedure A with the following modification: the reaction was conducted on 5.0 mmol scale of mesityl iodide. After 30 min 2-chloroanisole was added in one portion. After standard workup the resulting solid was recrystallized from MeOH/MeCN mixture to provide the product in 45% yield (1.162 g, 2.3 mmol) as off-white to light brown powder. Spectral data are consistent with those previously reported.⁵⁶

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.16 (d, *J* = 2.2 Hz, 1H), 7.89 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.23-7.20 (m, 3H), 7.10 (d, *J* = 7.9 Hz, 2H), 3.88 (s, 3H), 2.60 (s, 6H), 2.29-2.28 (m, 6H).

¹³C NMR (DMSO-*d*₆, 101 MHz) δ = 157.2, 145.7, 143.0, 141.5, 137.6, 135.3, 129.7, 128.0, 125.5, 123.3, 123.1, 115.7, 102.9, 56.7, 26.3, 20.8, 20.5.

Compound **6e**

Prepared according to the general procedure A on 5.0 mmol scale of methyl 2-fluoro-4-iodotoluene and obtained in 60% yield (1.59 g, 3.0 mmol) as white powder.

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 7.93 (m, 1H), 7.68 (m, 1H), 7.48-7.41 (m, 3H), 7.22 (s, 2H), 7.11 (d, *J* = 7.9, 2H), 2.60 (s, 6H), 2.29 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H).

¹³C NMR (DMSO-*d*₆, 101 MHz) δ = 160.6 (d, *J*_{C-F} = 251.2), 145.7, 143.1, 141.6, 137.6, 134.5 (d, *J*_{C-F} = 4.9), 130.5 (d, *J*_{C-F} = 3.7), 129.8, 129.2 (d, *J*_{C-F} = 16.9), 128.0, 125.5, 122.9, 121.2 (d, *J*_{C-F} = 25.7), 110.5 (d, *J*_{C-F} = 8.1), 26.3, 20.8, 20.5, 14.1 (d, *J*_{C-F} = 3.0).

¹⁹F{¹H} NMR (DMSO-*d*₆, 376 MHz) δ = -111.6.

FT-IR: 3092, 2921, 1573, 1481, 1212, 1165, 1118, 852 cm⁻¹.

HRMS: Calculated for C₁₆H₁₇FI⁺ [M – OTs]⁺: 355.0356; found 355.0371.

Melting point: 172 – 173 °C.

Compound **6f**

Prepared according to the general procedure B on 5.0 mmol scale of 3,4-difluorophenyl boronic acid and obtained in 86% yield (2.28 g, 4.3 mmol) as white powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 8.26 (m, 1H), 7.82 (m, 1H), 7.61 (m, 1H), 7.46 (d, J = 7.2 Hz, 2H), 7.23 (s, 2H), 7.11 (d, J = 7.5, 2H), 2.61 (s, 6H), 2.31 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (DMSO- d_6 , 101 MHz) δ = 151.7 (dd, $J_{\text{C-F}}$ = 251.2, 10.5), 150.0 (dd, $J_{\text{C-F}}$ = 253.6, 12.6), 145.5, 143.3, 141.7, 137.7, 132.3 (dd, $J_{\text{C-F}}$ = 7.2, 4.0), 129.8, 128.1, 125.5, 124.3 (d, $J_{\text{C-F}}$ = 20.1), 123.2, 120.8 (d, $J_{\text{C-F}}$ = 18.3), 107.7 (dd, $J_{\text{C-F}}$ = 5.7, 4.0), 26.3, 20.8, 20.5.

$^{19}\text{F}\{^1\text{H}\}$ NMR (DMSO- d_6 , 376 MHz) δ = -132.19 (d, J = 21.8), -132.75 (d, J = 21.7).

FT-IR: 2979, 1496, 1272, 1162, 1116, 1030, 812 cm^{-1} .

HRMS: Calculated for $\text{C}_{15}\text{H}_{14}\text{F}_2\text{I}^+$ [$\text{M} - \text{OTs}$] $^+$: 359.0103; found 359.0121.

Melting point: 192 – 193 $^{\circ}\text{C}$.

Compound 6g

Prepared according to the general procedure C on 1.0 mmol scale using 2-fluoroanisole (0.113 mL, 1.01 equiv.) and obtained in 74 %yield (0.404 g, 0.7 mmol) as white powder.

^1H NMR (DMSO- d_6 with 1% v/v TMS, 400 MHz) δ = 8.01 (dd, J = 10.2, 2.1, 1H), 7.77-7.76 (m, 1H), 7.46 (d, J = 8.0, 2H), 7.27 (dd, appears as triplet, J = 8.8 Hz, 1H), 7.20 (s, 2H), 7.10 (d, J = 7.9, 2H), 3.87 (s, 3H), 2.60 (s, 6H), 2.29-2.28 (m, 6H).

^{13}C NMR (DMSO- d_6 , 101 MHz) δ = 151.56 (d, $J_{\text{C-F}}$ = 261.8 Hz), 150.4, 145.4, 143.1, 141.5, 137.9, 132.3 (d, $J_{\text{C-F}}$ = 3.7 Hz), 129.8, 128.2, 125.6, 123.3, 122.4 (d, $J_{\text{C-F}}$ = 21.3 Hz), 116.6, 101.8 (d, $J_{\text{C-F}}$ = 6.9 Hz), 56.5, 26.3, 20.8, 20.6.

$^{19}\text{F}\{^1\text{H}\}$ NMR (DMSO- d_6 , 376 MHz) δ = -130.2.

FT-IR: 2980, 2842, 1592, 1496, 1208, 1171, 1031, 1009, 815, 680 cm^{-1} .

HRMS: Calculated for $C_{16}H_{17}FIO^+$ $[M - OTs]^+$: 371.0303; found 371.0295.

Melting point: 179.7 – 180.8 °C.

Compound **6h**

Prepared according to the general procedure B on 2.0 mmol scale of 3-fluoro-4-trifluoromethoxyphenyl boronic acid and obtained in 74% yield (0.879 g, 1.5 mmol) as white powder.

1H NMR (DMSO- d_6 , 400 MHz) δ = 8.29 (dd, J = 9.2, 2.0 Hz, 1H, 7.86-7.84 (m, 1H), 7.75-7.71 (m, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.25 (s, 2H), 7.10 (d, J = 7.9 Hz, 2H), 2.60 (s, 3H), 2.31 (s, 3H), 2.28 (s, 2H).

^{13}C NMR (DMSO- d_6 , 101 MHz) δ = 153.7 (d, J_{C-F} = 258.3 Hz), 145.4, 143.4, 141.8, 137.8-137.7 (m, two overlapping signals), 131.9 (d, J_{C-F} = 4.1 Hz), 129.8, 128.0, 126.6, 125.4, 124.0 (d, J_{C-F} = 21.9 Hz), 123.0, 119.8 (q, J_{C-F} = 259.4 Hz), 112.3 (d, J_{C-F} = 6.5 Hz), 26.3, 20.7, 20.5.

$^{19}F\{^1H\}$ NMR (DMSO- d_6 , 376 MHz) δ = -57.8 (d, J = 5.2 Hz), -124.3 (q, J = 5.2 Hz).

FT-IR: 2981, 1491, 1255, 1164, 1118, 1008, 813 cm^{-1} .

HRMS: Calculated for $C_{16}H_{14}F_4IO^+$ $[M - OTs]^+$: 425.0020; found 425.0011.

Melting point: 186.3 – 186.7 °C.

Compound **6j**

Prepared according to the literature procedure⁶¹ overnight on 1.0 mmol scale of hydroxy(mesityl)iodonium tosylate and 2-bromoanisole and obtained in 52% yield (0.313 g, 0.52 mmol) as off-white powder.

1H NMR (DMSO- d_6 , 400 MHz) δ = 8.29 (d, J = 2.1, 1H), 7.93 (d, J = 8.9, 2.1, 1H), 7.47 (d, J = 8.0, 2H), 7.21-7.18 (m, 3H), 7.11 (d, J = 7.8, 2H), 3.89 (s, 3H), 2.61 (s, 6H), 2.30 (m, 6H).

^{13}C NMR (DMSO- d_6 , 101 MHz) δ = 158.3, 145.3, 143.3, 141.7, 138.2(2), 138.1(8), 136.0, 130.0, 128.3, 125.7, 123.3, 115.7, 112.9, 103.5, 57.0, 26.4, 21.0, 20.7.

FT-IR: 2978, 2842, 1473, 1439, 1219, 1046, 1030, 814, 679 cm^{-1} .

HRMS: Calculated for $\text{C}_{16}\text{H}_{17}\text{BrIO}^+ [\text{M} - \text{OTs}]^+$: 430.9502; found 430.9495.

Melting point: 183.8 – 186.4 $^{\circ}\text{C}$.

Compound 6k

Prepared according to the general procedure B on 3.0 mmol scale of 3,4-dimethoxybenzene boronic acid with the following modification: the reaction was performed with 0.4 mL (1.1 equiv.) of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and resulted in 65% yield (1.09 g, 2.0 mmol) as light brown powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 7.58 (d, J = 2.0 Hz, 1H), 7.47-7.45 (m, 3H), 7.19 (s, 3H), 7.10 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 8.7 Hz, 1H), 3.77(5)-3.77(0) (m, 6H), 2.62 (s, 6H), 2.28 (s, 6H).

^{13}C NMR (DMSO- d_6 , 101 MHz) δ = 151.6, 150.1, 145.6, 142.8, 141.4, 137.6, 129.6, 128.0(3), 128.0(0), 125.5, 123.1, 117.7, 114.2, 102.8, 56.2, 55.8, 26.3, 20.8, 20.5.

FT-IR: 2982, 2920, 1502, 1143, 100, 794, 677 cm^{-1} .

HRMS: Calculated for $\text{C}_{17}\text{H}_{20}\text{IO}_2^+ [\text{M} - \text{OTs}]^+$: 383.0502; found 383.0493.

Melting point: 186.1 – 187.3 $^{\circ}\text{C}$.

Compound 6l

Prepared according to the general procedure A on 3.0 mmol scale of 4-iodo-2-nitrotoluene and obtained in 78% yield (1.29 g, 2.3 mmol) as off-white powder. Spectral data are consistent with those previously reported.⁵⁶

^1H NMR (DMSO- d_6 , 400 MHz) δ = 8.60 (d, J = 1.7 Hz, 1H), 8.05 (dd, J = 8.3, 1.8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.22 (s, 2H), 7.10 (d, J = 7.9, 2H), 2.59 (s, 6H), 2.51 (c, 3H, overlapped with DMSO), 2.30 (s, 3H), 2.28 (s, 3H).

¹³C NMR (DMSO-*d*₆, 101 MHz) δ = 149.7, 145.5, 143.4, 141.7, 138.2, 137.7, 136.7, 135.7, 130.0, 129.9, 128.1, 125.5, 123.0, 111.0, 26.4, 20.8, 20.6, 19.3.

Compound **6m**

Prepared according to the general procedure B on 2.0 mmol scale of 4-methoxy-3-trifluoromethylphenyl boronic acid and obtained in 98% yield (1.16 g, 1.96 mmol) as white powder.

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.28 (d, *J* = 1.9 Hz, 1H), 8.11 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 9.0 Hz, 1H), 7.21 (s, 1H), 7.10 (d, *J* = 7.9, 2H), 3.92 (s, 3H), 2.60 (s, 6H), 2.30 (s, 3H), 2.28 (s, 3H).

¹³C NMR (DMSO-*d*₆, 101 MHz) δ = 159.4, 145.5, 143.2, 141.6, 140.7, 137.8, 133.1 (q, *J*_{C-F} = 5.2 Hz), 129.8, 128.1, 125.5, 123.2, 122.6 (q, *J*_{C-F} = 261.5 Hz), 119.2 (q, *J*_{C-F} = 31.5 Hz), 116.5, 102.8, 56.9, 26.3, 20.8, 20.5.

¹⁹F{¹H} NMR (DMSO-*d*₆, 376 MHz) δ = -61.44.

FT-IR: 2979, 1599, 1485, 1119, 1008, 829 cm⁻¹.

HRMS: Calculated for C₁₇H₁₇F₃IO⁺ [M – OTs]⁺: 421.0276; Found 421.0286.

Melting point: 215 – 216 °C.

Compound **6n**

Prepared according to the general procedure A on 5.0 mmol scale of 1-fluoro-4-iodo-2-trifluoromethylbenzene and obtained in 67% yield (1.96 g, 3.4 mmol) as white powder.

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.50-8.48 (m, 1H), 8.19-8.15 (m, 1H), 7.64 (dd, appears as triplet, *J* = 9.8 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.24 (s, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 2.59 (s, 6H), 2.31 (s, 3H), 2.28 (s, 3H).

¹³C NMR (DMSO-*d*₆, 101 MHz) δ = 160.5 (d, *J*_{C-F} = 260.1 Hz), 145.4, 143.4, 141.8, 141.3 (d, *J*_{C-F} = 9.7 Hz), 137.8, 133.6 (d, *J*_{C-F} = 4.0 Hz), 129.9, 128.1, 125.5, 123.0, 121.3 (q, *J*_{C-F} = 261.0 Hz), 121.0 (d, *J*_{C-F} = 21.8 Hz), 119.1 (dq, *J*_{C-F} = 33.3, 13.2 Hz), 108.8 (d, *J*_{C-F} = 3.6 Hz), 26.3, 20.8, 20.5.

¹⁹F{¹H} NMR (DMSO-*d*₆, 376 MHz) δ = -55.53 (d, *J* = 12.3 Hz), -105.51 (q, *J* = 12.5 Hz).

FT-IR: 3059, 1575, 1282, 1127, 1030, 1004, 812, 679 cm⁻¹.

HRMS: Calculated for C₁₆H₁₄F₄I⁺ [M – OTs]⁺: 409.0071; found 409.0072.

Melting point: 178 – 180 °C.

6.3.4 Synthesis and characterization of 1,2,3,4-substituted arenes with arynophile **7a**

6.3.4.1 General procedure D

The iodonium salt (0.5 mmol, 1 equiv.) was weighed out and placed in a 12 mL vial containing a magnetic stir bar. TBME (2.5 mL) and **7a** (0.16 mL, 1.5 mmol, 3 equiv.) were added sequentially forming slurry. Ground to fine powder NaOt-Bu (0.0721g, 0.75 mmol, 1.5 equiv. or as indicated) was weighed out in air and added to the vial with stirring in one portion. The vial was sealed with a cap, and the reaction mixture was vigorously stirred at the room temperature for 40 minutes or as indicated. The reaction was quenched with saline solution (7 mL) and extracted with EtOAc (3x3 mL). The combined organic phases were dried with MgSO₄, drying agent was removed by vacuum filtration, and solvent was removed on rotary evaporator. The crude residue was purified by column chromatography on silica gel with acetone/hexanes mixture as eluent.

6.3.4.2 Gram scale reaction

The iodonium salt **6n** (2.9019 g, 5 mmol) was weight out and placed in 100 mL round bottom flask containing a magnetic stir bar. MTBE (25 mL) and 1,2-dimethyl-2-imidazolidinone (DMI, 1.62 mL, 15 mmol, 3 equiv.) were added sequentially forming white slurry (Figure 21, A). Ground to fine powder NaOt-Bu (0.7208 g, 7.5 mmol, 1.5 equiv.) was weighed out in air and added to the round bottom flask with stirring in one portion with a powder funnel (Figure 1, B), and the reaction mixture turned yellow within 1 min (Figure

1, C). The contents were vigorously stirred for 40 min. at room temperature without further change in color. The reaction was quenched with saline solution and extracted with EtOAc (3x10 mL). The combined organic phases were dried with MgSO₄, drying agent was removed by vacuum filtration, and solvent was removed on rotary evaporator. The crude residue was purified by column chromatography on silica gel with acetone/hexanes mixture as eluent to provide the product in 62% yield (0.8570 g, 3.1 mmol) as a white solid.

Figure 21. Aryne coupling reaction on 5 mmol scale: A. Slurry of iodonium salt in MTBE and DMI; B. Appearance of the reaction mixture after addition of NaOt-Bu; C. Appearance of the reaction mixture after 1 min at stirring.

Compound **8aa**

Prepared from **6a** according to the general procedure D for 15 min. and obtained in 55% yield (0.0666 g, 0.28 mmol) as a white solid.

R_f = 0.34 in 35% acetone/hexane.

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.18 (d, J =8.1 Hz, 1H), 6.74 (d, J =8.1 Hz, 1H), 3.87-3.33 (br, 2H), 3.21 (s, 3H), 2.76 (s, 3H), 2.33 (s, 3H).

Note: two H's of ethelene group are not reported as they appear as broad signals between ~ 4-2 ppm, consistent with previous reports on related compounds.⁸⁰

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 167.7, 145.8, 132.4, 132.2, 131.0, 129.3, 116.0, 57.0, 47.9, 40.1, 33.3, 19.8.

FT-IR: 2944, 1647, 1596, 1482, 1446, 1425, 826 cm^{-1} .

HRMS (ESI⁺): calculated for $\text{C}_{12}\text{H}_{16}\text{ClN}_2\text{O}^+$ [$\text{M} + \text{H}$]⁺ 239.0948; found 239.0942.

Melting point: 110 – 111°C.

Compound **8ba**

Prepared from **6b** according to the general procedure D and obtained in 75% yield (0.0980 g, 0.38 mmol) as an off-white solid.

R_f = 0.22 in 30% acetone/hexane

^1H NMR ($(\text{CD}_3)_2\text{CO}$, 400 MHz) δ = 7.51 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 3.50 (br, 2H), 3.14 (s, 3H), 2.80 (s, 3H).

Note: two H's of ethelene group are not reported as they appear as a broad signal between ~ 4-2 ppm, consistent with previous reports on related compounds.⁸⁰

^{13}C NMR ($(\text{CD}_3)_2\text{CO}$, 101 MHz) δ = 166.3, 147.8, 132.2, 132.1, 131.0, 126.5, 118.7, 57.6, 48.0, 40.3, 33.1.

FT-IR: 2942, 2812, 1642, 1579, 1450, 1405, 1255, 1172, 1060, 822, 731 cm^{-1} .

HRMS (ESI⁺): calculated for $\text{C}_{11}\text{H}_{13}\text{Cl}_2\text{N}_2\text{O}^+$ [$\text{M} + \text{H}$]⁺ 259.0399; found 259.0412.

Melting point: 90.6 – 91.6 °C.

Compound **8ca**

Prepared from **6c** according to the general procedure D. The product was isolated by column chromatography with diethyl ether as eluent and obtained in 52% yield (0.0664 g, 0.26 mmol) as a yellow oil.

R_f = 0.08 in 100% ethyl ether.

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 6.93 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 3.86 (s, 3H), 3.76-3.30 (br, 2H) 3.21 (s, 3H), 2.75 (s, 3H).

Note: two H's of ethelene group are not reported as they appear as broad signals between ~ 4-2 ppm, consistent with previous reports on related compounds.⁸⁰

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 167.0, 151.4, 141.0, 130.9, 121.3, 116.5, 113.8, 57.1, 56.7, 48.0, 40.2, 33.3.

FT-IR: 2937, 2843, 1645, 1456, 1433, 1269, 1048, 812, 686 cm^{-1} .

HRMS (ESI⁺): calculated for $\text{C}_{12}\text{H}_{15}\text{ClN}_2\text{NaO}_2^+$ $[\text{M} + \text{Na}]^+$ 277.0714; found 277.0708.

Compound **8da**

Prepared from **6d** according to the general procedure D for 25 min. and obtained in 63% yield (0.0761 g, 0.31 mmol) as an off-white solid.

R_f = 0.31 30% acetone/hexanes

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.11 (dd, appears as triplet, J = 8.7 Hz, 1H), 6.79 (dd, J = 8.9, 4.2 Hz, 1H), 3.53-3.31 (br, 2H), 3.21 (s, 3H), 2.77 (s, 3H).

Note: : two H's of ethelene group are not reported as they appear as broad signals between ~ 4-2 ppm, consistent with previous reports on related compounds.⁸⁰

^{13}C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 166.1 (d, $J_{\text{C-F}}$ = 2.6 Hz), 154.3 (d, $J_{\text{C-F}}$ = 243.5 Hz), 143.7 (d, $J_{\text{C-F}}$ = 2.7 Hz), 130.5, 119.9 (d, $J_{\text{C-F}}$ = 19.6 Hz), 117.6 (d, $J_{\text{C-F}}$ = 22.1 Hz), 117.0 (d, $J_{\text{C-F}}$ = 6.8 Hz), 57.1, 47.8, 40.2, 33.4.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl₃ with 1% v/v TMS, 376 MHz) δ = -121.9.

FT-IR: 2949, 2863, 1650, 1482, 1459, 1428, 1258, 826, 759 cm⁻¹.

HRMS (ESI⁺): calculated for C₁₁H₁₃ClFN₂O⁺ [M + H]⁺ 243.0695; found 243.0706.

Melting point: 113.4 – 113.7 °C.

Compound **8ea**

Prepared from **6e** according to the general procedure D and obtained in 53% yield (0.0587 g, 0.26 mmol) as a white solid.

R_f = 0.13 in 30% acetone/hexane

^1H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.13 (dd, appears as triplet, J = 8.3 Hz, 1H), 6.57 (d, J = 8.2 Hz, 1H), 3.43 (t, J = 5.7 Hz, 2H), 3.19-3.18 (m, 5H), 2.77 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 166.1, 158.8 (d, $J_{\text{C-F}}$ = 251.1 Hz), 146.1 (d, $J_{\text{C-F}}$ = 5.2 Hz), 133.1 (d, $J_{\text{C-F}}$ = 7.5 Hz), 118.8 (d, $J_{\text{C-F}}$ = 18.1 Hz), 117.6 (d, $J_{\text{C-F}}$ = 14.8 Hz), 112.8 (d, $J_{\text{C-F}}$ = 3.4 Hz), 57.4, 47.8, 40.2, 33.5, 14.1 (d, $J_{\text{C-F}}$ = 3.8 Hz).

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl₃ with 1% v/v TMS, 376 MHz) δ = -116.9.

FT-IR: 2945, 2811, 1639, 1491, 1261, 1170, 826 cm⁻¹.

HRMS (ESI⁺): calculated for C₁₂H₁₅FN₂NaO⁺ [M + Na]⁺ 245.1061; found 245.1055.

Melting point: 107.9 – 109.1 °C.

Compound **8fa**

Prepared from **6f** according to the general procedure D and obtained in 53% yield (0.0602 g, 0.27 mmol) as a colorless oil.

R_f = 0.18 in 30% acetone/hexane.

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.13 (m, 1H), 6.61-6.57 (m, 1H), 3.44 (t, J = 5.8 Hz, 2H), 3.22-3.20 (m, 5H), 2.78 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 164.7 (d, $J_{\text{C-F}}$ = 2.7 Hz), 148.5 (dd, $J_{\text{C-F}}$ = 254.6, 14.2 Hz), 146.2 (dd, $J_{\text{C-F}}$ = 243.0, 13.2 Hz), 143.5 (m), 119.8 (d, $J_{\text{C-F}}$ = 10.7 Hz), 118.6 (dd, $J_{\text{C-F}}$ = 17.7, 2.0 Hz), 112.9 (dd, $J_{\text{C-F}}$ = 5.9, 3.7 Hz), 57.4, 47.8, 40.3, 33.6.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) δ = -137.26 (d, J = 21.8 Hz), -145.5 (d, J = 21.8 Hz).

FT-IR: 2944, 1645, 1492, 1396, 1262, 1173, 685 cm^{-1} .

HRMS (ESI $^+$): calculated for $\text{C}_{11}\text{H}_{13}\text{F}_2\text{N}_2\text{O}^+$ $[\text{M} + \text{H}]^+$ 227.0991; found 227.1002.

Compound **8ga**

Prepared from **6g** according to the general procedure D and obtained in 50% yield (0.0599 g, 0.25 mmol) as a white solid.

R_f = 0.14 in 30% acetone/hexane

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 6.96 (dd, appears as triplet, J = 9.0 Hz, 1H), 6.59 (dd, J = 8.8, 1.5 Hz, 1H), 3.85 (s, 3H), 3.41 (t, J = 5.8 Hz, 2H), 3.20 (s, 3H), 3.14 (t, J = 5.7 Hz, 3H), 2.76 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 165.5, 150.5 (d, $J_{\text{C-F}}$ = 253.7 Hz), 143.5 (d, $J_{\text{C-F}}$ = 11.2 Hz), 140.9 (d, $J_{\text{C-F}}$ = 4.3 Hz), 119.6 (d, $J_{\text{C-F}}$ = 11.4 Hz), 115.9 (d, $J_{\text{C-F}}$ = 3.6 Hz), 112.6 (d, $J_{\text{C-F}}$ = 3.6 Hz), 57.4, 57.0, 47.9, 40.3, 33.5.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) $\delta = -134.1$.

FT-IR: 2953, 2817, 1636, 1494, 1457, 1267, 1059, 814, 695 cm^{-1} .

HRMS (ESI^+): calculated for $\text{C}_{12}\text{H}_{15}\text{FN}_2\text{NaO}_2^+$ $[\text{M} + \text{Na}]^+$ 261.1010; found 261.1005.

Melting point: 106.5 – 108.9 $^\circ\text{C}$.

Compound **8ha**

Prepared from **6h** according to the general procedure D and obtained in 53% yield (0.0778 g, 0.27 mmol) as a pale-yellow solid.

$R_f = 0.27$ in 30% acetone/hexane

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) $\delta = 7.28\text{--}7.23$ (m, 1H), 6.64 (dd, $J = 9.0, 1.6$ Hz, 1H), 3.47 (t, $J = 5.7$ Hz, 2H), 3.27 (t, $J = 5.7$ Hz, 2H), 3.20 (s, 3H), 2.81 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) $\delta = 164.5, 152.9$ (d, $J_{\text{C-F}} = 258.4$ Hz), 146.8 (d, $J_{\text{C-F}} = 4.7$ Hz), 131.1–131.0 (m), 125.6, 120.6 (q, $J_{\text{C-F}} = 258.3$ Hz), 118.9 (d, $J_{\text{C-F}} = 12.0$), 113.1 (d, $J_{\text{C-F}} = 3.5$ Hz), 57.2, 47.6, 40.2, 33.6.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) $\delta = -59.1$ (d, $J = 4.2$ Hz), -128.2 (q, $J = 4.8$ Hz).

FT-IR: 3060, 2964, 2821, 1643, 1617, 1495, 1256, 1209, 1158, 827 cm^{-1} .

HRMS (ESI^+): calculated for $\text{C}_{12}\text{H}_{12}\text{F}_4\text{N}_2\text{NaO}_2^+$ $[\text{M} + \text{Na}]^+$ 315.0727; found 315.0720.

Melting point: 120.5 – 121.0 $^\circ\text{C}$.

Compound **8ia**

Prepared from **6i** according to the general procedure D using NaOt-Bu (0.1441, 1.5 mmol, 3.0 equiv.) for 20 min. and obtained in 51% yield (0.0720 g, 0.25 mmol) yield; on 2 mmol scale for 40 min and obtained in 55% yield (average of 3 trials) as a white solid.

R_f = 0.22 in 30% acetone/hexane.

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.19 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 3.88-3.40 (br, 2H), 3.27-3.02 (br, 1H, overlaps with singlet at 3.21 ppm), 3.21 (s, 3H, overlaps with broad signal), 2.88-2.56 (br, 1H, overlaps with singlet at 2.75 ppm), 2.75 (s, 3H, overlaps with broad signal), 2.37 (s, 3H).

Note: the protons of the ethelene group appear as broad signals at δ = 3.88-3.40, 3.27-3.02, and 2.88-2.56 ppm.

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 168.5, 145.7, 133.0, 132.0, 131.5, 123.2, 116.7, 56.9, 48.0, 40.1, 33.3, 22.9.

FT-IR: 2942, 1648, 1591, 1415, 1424, 827, 729 cm^{-1} .

HRMS (ESI⁺): calculated for $\text{C}_{12}\text{H}_{16}\text{BrN}_2\text{O}^+$ [$\text{M} + \text{H}$]⁺ 283.0441; found 283.0452.

Melting point: 119.0 – 120.0 °C.

Compound **8ja**

Prepared from **6j** according to the general procedure D. The product was isolated by column chromatography with diethyl ether as eluent and obtained in 46% yield (0.0684 g, 0.23 mmol) as an off-white solid.

R_f = 0.16 in 30% acetone/hexane

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 6.90 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 3.87 (s, 3H), 3.68-3.40 (br, 2H), 3.25-3.06 (br, 1H, overlaps with singlet at 3.22 ppm), 3.22 (s, 3H, overlaps with broad signal), 2.76 (s, 3H), 2.72-2.50 (br, 1H).

Note: the H's of the ethelene group appear as broad signals between ~ 4-2 ppm.

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 167.8, 152.4, 141.2, 133.2, 117.3, 113.6, 111.1, 57.0, 56.9, 48.1, 40.2, 33.4.

FT-IR: 2937, 2800, 1648, 1436, 1266, 1049, 808, 683 cm^{-1} .

HRMS (ESI⁺): calculated for $\text{C}_{12}\text{H}_{15}\text{BrN}_2\text{NaO}_2^+$ $[\text{M} + \text{Na}]^+$ 321.0209; found 321.0203.

Melting point: 143.1 – 143.8 $^{\circ}\text{C}$.

Compound **8ka**

Prepared from **6k** according to the general procedure D using NaOt-Bu (0.144 g, 1.5 mmol, 3 equiv.). The crude mixture was filtered through a pad of celite eluting with EtOAc. The product was obtained in 43% yield (0.0540 g, 0.22 mmol) as an orange solid.

R_f = 0.014 in 30% acetone/hexane

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 6.90 (d, J = 8.8 Hz, 1H), 6.59 (1H, J = 8.8 Hz, 1H), 3.96 (s, 3H), 3.84 (s, 3H), 3.53-3.27 (br, 2H), 3.19 (s, 3H), 2.74 (s, 3H).

Note: two H's of ethelene group are not reported as they appear as broad signals between ~ 4-2 ppm, consistent with previous reports on related compounds.⁸⁰

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 167.6, 148.8, 147.6, 140.6, 125.7, 114.4, 112.5, 61.8, 57.2, 56.2, 48.1, 40.3, 33.4.

FT-IR: 2937, 2810, 1641, 1411, 1432, 1261, 1044, 1011, 827 cm^{-1} .

HRMS (ESI⁺): calculated for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{NaO}_3^+$ $[\text{M} + \text{Na}]^+$ 273.1210; found 273.1205.

Melting point: 117.5 – 118.5 $^{\circ}\text{C}$.

Compound **8la**

Prepared from **6l** according to the general procedure D using NaOt-Bu (0.144 g, 1.5 mmol, 3.0 equiv.) for 25 min. and obtained in 41% yield (0.0517 g, 0.21 mmol) as a yellow solid.

R_f = 0.17 in 30% acetone/hexane.

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.23 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 3.54 (t, *J* = 5.7 Hz, 2H), 3.29 (t, *J* = 5.7 Hz, 2H), 3.17 (s, 3H), 2.82 (s, 3H), 2.29 (s, 3H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 166.3, 150.5, 145.2, 133.8, 123.5, 123.2, 120.2, 57.1, 47.8, 40.1, 33.8, 17.2.

FT-IR: 2942, 1639, 1524, 1493, 1434, 1367, 836 cm⁻¹.

HRMS (ESI⁺): calculated for C₁₂H₁₆N₃O₃⁺ [M + H]⁺ 250.1186; found 250.1195.

Melting point: 199 °C.

Compound **8ma**

Prepared from **6m** according to the general procedure D and obtained in 60% yield (0.0867 g, 0.30 mmol) as a white solid.

R_f = 0.11 in 30% acetone/hexane

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.05-7.00 (m, 2H), 3.86 (s, 3H), 3.67-3.58 (m, 1H), 3.53-3.46 (m, 1H), 3.23-3.18 (m, 4H), 2.77 (s, 3H), 2.67-2.64 (m, 1H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 168.1, 154.0 (m), 139.2, 131.7 (q, *J*_{C-F} = 2.6 Hz), 123.3 (q, *J*_{C-F} = 274.7 Hz), 121.8, 117.0 (q, *J*_{C-F} = 30.7 Hz), 114.9, 56.8, 56.4, 48.3, 40.3, 33.1.

¹⁹F{¹H} NMR (CDCl₃ with 1% v/v TMS, 376 MHz) δ = -57.4.

FT-IR: 2937, 2817, 1643, 1485, 1301, 1274, 1120, 1050, 712 cm⁻¹.

HRMS (ESI⁺): calculated for C₁₃H₁₆F₃N₂O₂⁺ [M + H]⁺ 289.1158; found 289.1167.

Melting point: 197 – 199 °C.

Compound **8na**

Prepared from **6n** according to the general procedure D and obtained in 71% yield (0.0983 g, 0.36 mmol) as a white solid.

R_f = 0.22 in 30% acetone/hexane.

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.15 (dd, appears as triplet, J = 9.6 Hz, 1H), 7.07-7.04 (m, 1H), 3.67-3.50 (m, 2H), 3.24 (dd, J = 14.5, 3.7 Hz, 1H), 3.18 (m, 3H), 2.79-2.73 (m, 4H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 166.9 (d, $J_{\text{C-F}}$ = 2.4 Hz), 155.8 (d, $J_{\text{C-F}}$ = 252.3 Hz), 142.4 (d, $J_{\text{C-F}}$ = 2.7 Hz), 130.8 (d, $J_{\text{C-F}}$ = 2.1 Hz), 122.6 (d, $J_{\text{C-F}}$ = 8.5 Hz), 122.4 (dq, $J_{\text{C-F}}$ = 274.5, 1.8 Hz), 118.7 (d, $J_{\text{C-F}}$ = 23.0 Hz), 116.6 (dq, $J_{\text{C-F}}$ = 32.7, 13.4 Hz), 56.4, 40.1, 40.2, 33.2.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) δ = -56.8 (d, J = 20.5 Hz), -120.6 (q, J = 20.5 Hz).

FT-IR: 2876, 16.48, 1489, 13.94, 1288, 1124, 694 cm^{-1} .

HRMS (ESI $^+$): calculated for $\text{C}_{12}\text{H}_{13}\text{F}_4\text{N}_2\text{O}^+$ $[\text{M} + \text{H}]^+$ 277.0959; found 277.0973.

Melting point: 105.0 – 106.0 $^{\circ}\text{C}$.

6.3.5 Synthesis and characterization of 1,2,3,4-substituted arenes with other arynophiles

6.3.5.1 General procedure E

The iodonium salt (0.5 mmol, 1 equiv.) was weighed out and placed in a 12 mL vial containing a magnetic stir bar. TBME (2.5 mL) and arynophile (1.1 – 3 equiv.) were added sequentially forming a slurry. Ground to fine powder NaOt-Bu (0.1442g, 1.5 mmol, 3 equiv. or as indicated) was weighed out in air and added to the vial with stirring in one portion. The vial was sealed with a cap, and the reaction mixture was vigorously stirred at the indicated temperature for 40 minutes to 3 hours. The reaction was quenched with saline solution (7 mL) and extracted with EtOAc (3x3 mL). The combined organic phases were dried with MgSO_4 , drying agent was removed by vacuum filtration, and solvent was

removed on rotary evaporator. The crude residue was purified by column chromatography on silica gel with acetone/hexanes mixture as eluent.

6.3.5.2 Dual C-H functionalization of 2-fluoroanisole

Scheme 21. Dual C-H functionalization of 2-fluoroanisole.

Hydroxy(tosyloxy)iodomesitylene (0.217 g, 0.5 mmol, 1 equiv.) and 2-fluoroanisole (0.57 mL, 0.5 mmol, 1 equiv.) were added to a 12 mL vial containing a stir bar. Acetonitrile (0.5 mL) was added to the vial followed by *p*-toluenesulfonic acid monohydrate (0.0095 g, 10 mol%). The vial was placed in an aluminum block set to 50 °C, and the mixture was stirred at this temperature for 3 hours. The vial was removed from heat and allowed to cool to room temperature. TBME (2.5 mL) was added at stirring, followed by arynophile **7g** (0.11 mL, 0.75 mmol, 3 equiv.) and NaOt-Bu (0.144 g, 0.75 mmol, 3 equiv.), and the mixture was allowed to react for 40 min. The reaction was quenched with saline solution (7 mL) and extracted with EtOAc (3x3 mL). The combined organic phases were dried with MgSO₄, drying agent was removed by vacuum filtration, and solvent was removed on rotary evaporator. The crude residue was purified by column chromatography on silica gel. Compound **8gg** was obtained in 38 % yield as a white solid.

Compound **8gg**

R_f = 0.31 in 20% Et₂O/hexane

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.03-6.98 (2H, m), 6.91 (1H, d, *J* = 7.6 Hz), 6.47 (1H, dd, appears as triplet, *J* = 7.5 Hz), 5.94 (1H, s), 5.68 (1H, s), 3.82 (3H, s).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 146.6 (d, $J_{\text{C-F}}$ = 248.5 Hz), 146.5 (d, $J_{\text{C-F}}$ = 11.4 Hz), 143.4, 142.4 (d, $J_{\text{C-F}}$ = 2.9 Hz), 141.7, 134.6 (d, $J_{\text{C-F}}$ = 17.7 Hz), 115.5 (d, $J_{\text{C-F}}$ = 3.5 Hz), 108.6, 82.2, 79.6, 56.5.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) δ = -141.4.

FT-IR: 3091, 3036, 2949, 1488, 1460, 1279, 1265, 1056, 821, 723 cm^{-1} .

HRMS (ESI⁺): calculated for $\text{C}_{11}\text{H}_9\text{FO}_2^+$ [$\text{M} + \text{H}$]⁺ 193.0659; found 193.0656.

Melting point: 62.9 – 63.9 °C.

Compound **8db**

Prepared from **6d** and obtained in 37% yield (0.0473 g, 0.18 mmol) as an off-white solid according to the general procedure E with the following modification: the reaction was conducted at room temperature in toluene (2.5 mL) using *N,N*'-dimethylpropylene urea (0.181 mL, 3 equiv.) and LiHMDS (1 M in toluene, 0.5 mL, 1 equiv.) for 40 min.

R_f = 0.18 in 25% Acetone/hexane

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.02 (1H, dd, J = 9.2, 8.2 Hz), 6.70 (1H, dd, J = 9.3, 4.2 Hz), 3.60-3.52 (1H, m), 3.48-3.41 (1H, m), 3.22-3.16 (1H, m), 3.07 (3H, s), 2.99-2.92 (4H, m), 1.98-1.87 (1H, m), 1.77-1.69 (1H, m).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 168.8 (d, $J_{\text{C-F}}$ = 2.0 Hz), 152.1 (d, $J_{\text{C-F}}$ = 240.8 Hz), 146.1 (d, $J_{\text{C-F}}$ = 2.4 Hz), 125.9, 119.5 (d, $J_{\text{C-F}}$ = 19.1 Hz), 116.9 (d, $J_{\text{C-F}}$ = 22.1 Hz), 115.8 (d, $J_{\text{C-F}}$ = 6.7 Hz), 50.8, 48.2, 43.1, 33.5, 26.7.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) δ = -125.6.

FT-IR: 2961, 2921, 1634, 1496, 1463, 1431, 1404, 1267, 1202, 941, 788 cm^{-1} .

HRMS (ESI⁺): calculated for $\text{C}_{12}\text{H}_{14}\text{ClFN}_2\text{NaO}^+$ [$\text{M} + \text{Na}$]⁺ 279.0671; found 279.0667.

Melting point: 103.6 – 105.4 °C.

Compound **8ac**

Prepared from **6a** according to the general procedure E with the following modification: the reaction was conducted at room temperature using 2-(trimethylsiloxy)furan (0.126 mL, 1.5 equiv.) for 40 min. The reaction mixture was quenched with 0.1 M HCl, extracted with EtOAc (3x3 mL), and combined organic layers were washed with brine. The product was obtained in 47% yield (0.0489 g, 0.24 mmol) as a yellow to brown solid.

R_f = 0.52 (20% acetone:hexanes)

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.96 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 6.95-6.89 (m, 2H), 2.53 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 184.0, 183.8, 145.5, 140.4, 136.5, 135.2, 134.3, 132.5, 128.0, 125.3, 21.5.

FT-IR: 3053, 2923, 1661, 1610, 1579, 1310, 1272, 1089, 1067, 845, 818, 802 cm^{-1} .

HRMS (ESI⁺): calculated for $\text{C}_{11}\text{H}_8\text{ClO}_2^+$ [$\text{M} + \text{H}$]⁺ 207.0207; found 207.0208.

Melting point: 134.5 – 135.7 °C.

Compound **8ad**

Prepared from **6a** according to the general procedure E under the following conditions: the reaction was conducted at room temperature using *N*-tert-Butyl- α -phenylnitrone (0.266 g, 3 equiv.) for 1 hour. The crude product was purified by column chromatography with ethyl acetate/hexanes mixture as eluent and obtained in 92% yield (0.139 g, 0.46 mmol, mixture of regioisomers, 11.1:1 ratio) as a yellow oil. Characterization for major isomer is provided below.

R_f = 0.71 10% ethyl acetate/hexane

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.32-7.22 (m, 5H, Ph₆, overlaps with minor isomer), 7.05 (d, 1H, *J* = 8.2 Hz, H₃), 6.66 (d, 1H, *J* = 8.1 Hz, H₄, overlaps with minor isomer), 5.57 (s, 1H, H₁), 2.22 (s, 3H, CH₃₂), 1.17 (s, 9H, *t*-Bu₅).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 156.7, 141.9, 131.1, 129.2, 128.4, 128.2, 128.0, 127.7, 127.5, 104.8, 67.0, 61.5, 25.3, 18.8.

FT-IR: 2971, 2866, 1601, 1465, 1364, 1298, 804, 695 cm⁻¹.

HRMS (ESI⁺): calculated for C₁₈H₂₀ClNNaO⁺ [M + Na]⁺ 324.1126; found 324.1118.

Compound **8gd**

Prepared from **6g** according to the general procedure E under the following conditions: the reaction was conducted at room temperature using *N*-tert-Butyl- α -phenylnitrone (0.266 g, 3 equiv.) for 1 hour. The crude product was purified by column chromatography with ethyl acetate/hexanes mixture as eluent and obtained in 85% yield (0.128 g, 0.43 mmol) as a red solid.

R_f = 0.47 10% ethyl acetate:hexane

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.41 (d, *J* = 7.5 Hz, 2H), 7.31 (dd, appears as triplet, *J* = 7.5 Hz, 2H), 7.26-7.22 (m, 1H), 6.79 (dd, appears as triplet, *J* = 8.4, 8.4 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 5.71 (s, 1H), 3.77 (s, 3H), 1.17 (s, 9H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 152.9 (d, *J*_{C-F} = 6.2 Hz), 147.8 (d, *J*_{C-F} = 249.3 Hz), 142.1 (d, *J*_{C-F} = 10.3 Hz), 142.0, 128.6, 127.6, 127.2, 118.0 (d, *J*_{C-F} = 17.4 Hz), 115.1 (d, *J*_{C-F} = 1.5 Hz), 101.0 (d, *J*_{C-F} = 4.3 Hz), 64.7 (d, *J*_{C-F} = 2.1 Hz), 61.4, 57.5, 25.4.

¹⁹F{¹H} NMR (CDCl₃ with 1% v/v TMS, 376 MHz) δ = -138.0.

FT-IR: 2972, 2937, 1423, 1364, 1262, 1021, 804, 718, 696 cm⁻¹.

HRMS (ESI⁺): calculated for C₁₈H₂₀FNNaO₂⁺ [M + Na]⁺ 324.1370; found 324.1366.

Melting point: 77.9 – 79.7 °C.

Compound **8ge**

Prepared from **6g** according to the general procedure E under the following conditions: the reaction was conducted using benzyl azide (0.069 mL, 1.1 equiv.); NaOt-Bu (0.0721 g, 1.5 equiv.) was added at 0 °C and the mixture was allowed to react at this temperature for 40 min. The crude product was purified by column chromatography with ethyl acetate/hexanes mixture as eluent and obtained in 44% yield (0.0560 g, 0.22 mmol) as a white solid.

R_f = 0.29 in 25% ethyl acetate/hexane

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.36-7.25 (m, 5H), 7.19 (dd, J = 8.9, 6.9 Hz, 1H), 7.02 (dd, J = 8.9, 1.1 Hz, 1H), 5.81 (s, 3H), 3.96 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 142.8 (d, $J_{\text{C-F}}$ = 7.4 Hz), 142.5 (d, $J_{\text{C-F}}$ = 257.6 Hz), 137.9 (d, $J_{\text{C-F}}$ = 16.1 Hz), 134.3, 130.5 (d, $J_{\text{C-F}}$ = 5.1 Hz), 129.1, 128.6, 127.6, 119.2, 104.9 (d, $J_{\text{C-F}}$ = 5.6 Hz), 59.1 (d, $J_{\text{C-F}}$ = 2.0 Hz), 52.5.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) δ = -145.8.

FT-IR: 3021, 2939, 1524, 1455, 1288, 1234, 1089, 1071, 1032, 800, 708, 692, 681 cm^{-1} .

HRMS (ESI $^+$): calculated for $\text{C}_{14}\text{H}_{12}\text{FN}_3\text{NaO}^+$ [$\text{M} + \text{Na}$] $^+$ 280.0857; found 280.0850.

Melting point: decomposed at 118.9 °C.

Compound **8af**

Prepared from **6a** according to the general procedure E under the following conditions: the reaction was conducted at room temperature using pyridine *N*-oxide (0.143 g, 3 equiv.) and NaOt-Bu (0.0721 g, 1.5 equiv.) for 40 min. The product was obtained in 29% yield (0.0324 g, 0.15 mmol) as an orange solid.

R_f = 0.07 20% acetone:hexane

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 9.73 (br, 1H), 8.53 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.41 (d, *J* = 1.6 Hz, 1H), 7.66 (ddd, appears as doublet of triplet, *J* = 7.8, 1.9, 1.9 Hz, 1H), 7.45 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 2.27 (s, 3H).

¹³C NMR (DMSO-*d*₆, 101 MHz) δ = 154.2, 150.6, 148.1, 138.0, 133.0, 132.2, 130.9, 126.0, 124.4, 123.2, 114.2, 19.7.

FT-IR: 3051, 2922, 2818, 1591, 1394, 1374, 1290, 1183, 1045, 914, 913, 799, 706, cm⁻¹.

HRMS (ESI⁺): calculated for C₁₂H₁₁ClNO⁺ [*M* + *H*]⁺ 220.0524; found 220.0520.

Melting point: decomposed at 233 °C.

Compound **8dg**

Prepared from **6d** according to the general procedure E under the following conditions: the reaction was conducted using 4-(trimethylsilyl)morpholine (0.133 mL, 1.5 equiv.) at 0 °C for 40 min. The crude product was purified by column chromatography with ethyl acetate/hexanes mixture as eluent and obtained in 41% yield (0.0584 g, 0.2 mmol) as a white solid.

R_f = 0.43 in 16% ethyl acetate/hexane

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.20 (dd, *J* = 8.8, 4.4 Hz, 1H), 7.13 (dd, appears as triplet, *J* = 8.4 Hz, 1H), 3.89-3.86 (m, 2H), 3.81-3.75 (m, 2H), 2.96-2.90 (m, 2H), 2.72-2.69 (m, 2H), 0.45 (s, 9H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 156.1 (d, *J*_{C-F} = 3.6 Hz), 156.0 (d, *J*_{C-F} = 247.7 Hz), 139.4 (d, *J*_{C-F} = 3.4 Hz), 127.2 (d, *J*_{C-F} = 16.1 Hz), 122.3 (d, *J*_{C-F} = 6.9 Hz), 117.5 (d, *J*_{C-F} = 23.3 Hz), 66.7, 54.8, 3.2.

¹⁹F{¹H} NMR (CDCl₃ with 1% v/v TMS, 376 MHz) δ = -115.0.

FT-IR: 2952, 2860, 2815, 1436, 1260, 1245, 1111, 839, 820, 729 cm⁻¹.

HRMS (ESI⁺): calculated for C₁₃H₂₀ClFNO⁺ [*M* + *H*]⁺ 288.0981; found 288.0978.

Melting point: 91.3 – 92.5 °C.

Compound **8bh**

Prepared from **6b** according to the general procedure E under the following conditions: the reaction was conducted using 4-chloromorpholine (0.182 g, 3 equiv.); NaOt-Bu (0.240 g, 5 equiv.) was added at 0 °C and the mixture was allowed to react at this temperature for 80 min. The crude product was purified by column chromatography with ethyl acetate/hexanes mixture as eluent and obtained in 56% yield (0.0750 g, 0.28 mmol) as a white solid.

R_f = 0.39 20% ethyl acetate:hexane

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.34 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 3.88-3.86 (m, 4H), 3.04-3.01 (m, 4H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 149.4, 132.7, 129.2, 128.3, 128.1, 118.8, 67.0, 51.7.

FT-IR: 2969, 2865, 2824, 1440, 1372, 1236, 1114, 958, 810, 695 cm^{-1} .

HRMS (ESI⁺): calculated for $\text{C}_{10}\text{H}_{11}\text{Cl}_3\text{NO}^+$ $[\text{M} + \text{H}]^+$ 265.9901; found 265.9901.

Melting point: 90.1 – 91.9 °C.

Compound **8ai**

Prepared from **6a** according to the general procedure E under the following conditions: the reaction was conducted using 1-chloroazepane (0.200 g, 3 equiv.); NaOt-Bu (0.240 g, 5 equiv.) was added at 0 °C and the mixture was allowed to react at this temperature for 3 h. The crude product was purified by column chromatography with petroleum ether as eluent and obtained in 47% yield (0.0610 g, 0.24 mmol, mixture of regioisomers, 22:1 ratio) as a red oil. Characterization for major isomer is provided below.

R_f = 0.50 in petroleum ether

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.02 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.17-3.14 (m, 4H), 2.34 (s, 3H), 1.85-1.76 (m, 4H), 1.72-1.69 (m, 4H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 151.7, 133.6, 131.1, 128.2, 127.9, 119.8, 55.2, 29.2, 27.1, 20.6.

FT-IR: 2922, 2853, 1592, 1464, 1444, 1032, 808 cm^{-1} .

HRMS (ESI $^+$): calculated for $\text{C}_{13}\text{H}_{18}\text{Cl}_2\text{N}^+$ $[\text{M} + \text{H}]^+$ 258.0811; found 258.0809.

6.3.6 Derivatization of aryne coupling product by transition metal catalysis

6.3.6.1 Suzuki-Miyaura Coupling

Scheme 22. Functionalization via Suzuki-Miyaura coupling.

Prepared according to the literature procedure⁹⁴. An oven-dried vial was charged with $\text{Pd}_2(\text{dba})_3$ (0.0090 g, 4 mol% Pd), SPhos (0.0164 g, 8 mol%), (4-isobutylphenyl)boronic acid (0.1335 g, 1.5 equiv.), **6i** (0.1416 g, 0.5 mmol, 1 equiv.), and K_3PO_4 (0.3180 g, 3 equiv.) and equipped with a magnetic stir bar. The vial was capped with a rubber septum, flushed with nitrogen and left under static nitrogen atmosphere. Toluene (1 mL) was added via syringe through the septum and the septum was replaced with a screwcap. The resulting mixture was heated at 100 °C under stirring overnight then allowed to cool to room temperature, diluted with diethyl ether, filtered through a thin pad of celite eluting with diethyl ether, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel with acetone/hexane mixture and the product was obtained in 95% yield (0.1605 g, 0.48 mmol) as a white solid.

Compound **9a**

$R_f = 0.39$ (30% acetone/hexane)

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) $\delta = 7.22\text{--}7.20$ (m, 1H), 7.17–6.89 (br, 4H), 6.81 (d, $J = 8.2$ Hz, 1H), 3.00 (s, 3H), 2.79 (s, 3H), 2.47 (d, $J = 7.2$ Hz, 2H), 2.06 (s, 3H), 1.89 (n, $J = 6.7$ Hz, 1H), 0.92 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) $\delta = 169.7, 144.3, 141.1, 139.9, 137.3, 131.8, 131.0, 130.8, 128.5$ (two overlapping signals), 116.2, 57.1, 48.1, 45.4, 40.2, 33.2, 30.1, 22.5, 19.9.

FT-IR: 2953, 2865, 2802, 1651, 1449, 1443, 1384, 1177, 1093, 817.

HRMS (ESI^+): calculated for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{NaO}^+$ $[\text{M} + \text{Na}]^+ 359.2088$; found 359.2094.

Melting point: 157.1 – 158.3 °C.

6.3.6.2 Buckwald-Hartwig coupling

Scheme 23. Functionalization via Buchwald-Hartwig amination.

Prepared according to the modified literature procedure.⁹⁵ An oven-dried vial was charged with $\text{Pd}_2(\text{dba})_3$ (6.9 mg, 5 mol% Pd), BrettPhos (0.0161 g, 5 mol%), **6i** (0.0850 g, 0.3 mmol), and K_2CO_3 (0.0995 g, 0.72 mmol, 2.4 equiv.) and equipped with a magnetic stir bar. The vial was capped with a rubber septum, purged with nitrogen and left under static nitrogen atmosphere. Toluene (0.6 mL) followed by 3,5-bis(trifluoromethyl)aniline (0.056 mL, 0.36 mmol, 1.2 equiv.) were added via syringe. The resulting mixture was heated at 110 °C under stirring for 4.5 hours, then a mixture of $\text{Pd}_2(\text{dba})_3$ (6.9 mg, 5 mol% Pd) and BrettPhos (0.0161 g, 5 mol%) was added to the reaction mixture, and the reaction was left at 110 °C under stirring for 17.5 hours. The reaction mixture was cooled to room

temperature, diluted with ethyl acetate, filtered through a thin pad celite eluting with ethyl acetate, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel with acetone/hexane mixture as eluent and obtained in 78% yield (0.1014 g, 0.24 mmol) as a white solid.

Compound **9b**

R_f = 0.30 20% acetone:hexane

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 8.06 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.20 (s, 1H), 6.91 (s, 2H), 6.77 (d, J = 8.3 Hz, 1H), 3.37-3.36 (m, 2H), 2.27-3.16 (br, 2H), 3.11 (s, 3H), 2.82 (s, 3H), 2.05 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 169.2, 146.6, 146.2, 138.0, 133.8, 132.2 (q, $J_{\text{C-F}}$ = 32.8 Hz), 128.1, 124.5, 123.5 (q, $J_{\text{C-F}}$ = 272.7 Hz), 115.3, 114.4 (m), 111.5-111.4 (m), 57.7, 48.2, 40.5, 33.8, 18.1.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) δ = -63.1.

FT-IR: 3231, 3073, 2946, 2805, 1630, 1620, 1480, 1392, 1272, 1161, 1119, 856, 679.

HRMS (ESI⁺): calculated for $\text{C}_{20}\text{H}_{19}\text{F}_6\text{N}_3\text{NaO}^+$ [$\text{M} + \text{Na}$]⁺ 454.1324; found 454.1317.

Melting point: 232.1 – 233.9 °C.

6.3.6.3 Heck coupling

Scheme 24. Functionalization via Heck coupling.

Palladium diacetate (0.0034 g, 5 mol%), triphenylphosphine (0.0079 g, 10 mol%), and **6i** (0.0850 g, 0.3 mmol) were placed into an oven-dried vial equipped with a magnetic stir bar. The vial was capped with a rubber septum, purged with nitrogen, and left under

static nitrogen atmosphere. DMF (0.6 mL) followed by triethylamine (0.084 mL, 1 mmol, 2 equiv.) and methyl acrylate (0.052 mL, 1 mmol, 2 equiv.) were added via syringe. The resulting mixture was heated at 100 °C under stirring overnight, then cooled to room temperature and subjected to column chromatography on basic alumina with acetone/hexane mixture as eluent. Mixture of *E/Z* isomers was isolated in 99% yield (0.0856 g, 0.3 mmol, *E:Z* = 9.6:1) as a bright yellow solid. Characterization for *E* isomer is provided below.

Compound **9c**

R_f = 0.39 30% acetone:hexane

^1H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.93 (d, *J* = 16.2 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.95 (d, *J* = 16.2 Hz, 1H), 3.77 (s, 3H), 3.48-3.45 (m, 2H), 3.18 (s, 3H), 3.16-3.12 (m, 2H), 2.77 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 169.7, 166.7, 144.6, 143.9, 134.1, 132.6, 130.9, 130.3, 122.9, 118.0, 56.8, 51.6, 48.2, 40.1, 33.4, 20.0.

FT-IR: 2947, 2813, 1710, 1634, 1434, 1396, 1300, 1190, 1166, 987, 839.

HRMS (ESI⁺): calculated for C₁₆H₂₀N₂NaO₃⁺ [*M* + Na]⁺ 311.1366; found 311.1361.

Melting point: 137.4 – 138.9 °C.

6.3.7 Unexpected aryne reactivity in reactions with tertiary amines

6.3.7.1 Sequential ring expansion and ring opening of DMI

The iodonium salt **6a** (0.285 g, 0.525 mmol, 2.1 equiv.) was weighed out and placed in a 12 mL vial containing a magnetic stir bar. TBME (2.5 mL) and **7a** (0.027 mL, 0.25 mmol, 1 equiv.) were added sequentially forming slurry. Ground to fine powder NaOt-Bu (0.151 g, 1.575 mmol, 6.3 equiv.) was weighed out in air and added to the vial

with stirring in one portion. The vial was sealed with a cap, and the reaction mixture was vigorously stirred at the room temperature for 40 minutes. The reaction was quenched with saline solution (7 mL) and extracted with EtOAc (3x3 mL). The combined organic phases were dried with MgSO_4 , drying agent was removed by vacuum filtration, and solvent was removed on rotary evaporator. The crude residue was purified by column chromatography on silica gel with Et_2O /hexanes mixture as eluent. The mixture of **10a** and **10b** was isolated in 73% yield as a yellow oil.

Compounds **10a** and **10b**

$R_f = 0.28$ 14% Et_2O :hexane

Major isomer:

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) $\delta = 7.29$ (d, overlaps with minor isomer, $J = 8.2$ Hz, 1H), 7.03 (d, $J = 8.2$ Hz, 1H), 6.97 (d, overlaps with minor isomer, $J = 8.2$ Hz, 1H), 6.65 (d, overlaps with minor isomer, $J = 2.4$ Hz, 1H), 6.49 (dd, overlaps with minor isomer, $J = 15.4, 9.1$ Hz, 1H), 6.44 (dd, overlaps with minor isomer, $J = 8.4, 2.6$ Hz, 1H), 4.40 (dd, $J = 15.3, 1.1$ Hz, 1H), 4.22 (dd, $J = 9.1, 1.1$ Hz, 1H), 3.10 (s, 3H), 3.09 (s, 3H), $2.40(9)$ (s, overlaps with minor isomer, 3H), 2.23 (s, overlaps with minor isomer, 3H).

Minor isomer:

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) $\delta = 7.55$ (dd, $J = 16.0, 9.3$ Hz, 1H), 7.29 (overlaps with major isomer, 1H), 7.05 (d, $J = 8.2$ Hz, 1H), 6.99 (overlaps with major isomer, 1H), 6.65 (overlaps with major isomer, 1H), 6.53 - 6.43 (overlaps with major isomer, 1H), 4.49 (d, $J = 2.6$ Hz, 1H), 4.46 (d, $J = 9.5$ Hz, 1H), 3.12 (s, 3H), 2.88 (s, 3H), $2.41(5)$ (s, overlaps with major isomer, 3H), 2.24 (s, overlaps with major isomer, 3H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 166.1, 165.7, 148.4, 148.3, 145.4, 145.0, 135.4, 135.0(3), 135.0(1), 134.9(9), 134.4(3), 134.3(7), 132.5, 132.3, 131.7, 131.6, 131.5, 130.9, 130.8, 126.9, 126.8, 125.8, 125.7, 115.7, 115.4, 114.1, 113.6, 95.3, 93.8, 40.7(4), 40.6(9), 32.7, 28.4, 28.1, 19.9, 18.9, 18.8.

Table 5. Main ¹H-¹H and ¹H-¹³C correlations for major isomer (N.D. – not determined).

	Chemical shift, ppm											
¹ H	7.29	7.03	6.97	6.65	6.49	6.44	4.40	4.22	3.10	3.09	2.41(9)	2.23
COSY	7.03	7.03	6.44	NO	4.40, 4.22	6.97	6.49	6.49	NO	NO	NO	NO
NOESY	2.41	3.09	2.23	N.D.	3.09	3.10	3.10	NO	4.4	7.03	7.29	6.97
HSQC	132.5	126.8	130.8	115.7	134.37	114.1	93.8	93.8	28.1	40.69	19.9	18.8
HMBC	145.4, 19.9	135.03	148.4, 18.9	114.1, 125.8	166.1, 28.4	115.7, 125.8	N.D.	N.D.	134.37	145.4, 148.4	N.D.	N.D.

FT-IR: 2921, 1662, 1624, 1499, 1477, 1086, 1037, 730.

HRMS (ESI⁺): calculated for C₁₉H₂₀Cl₂N₂O⁺ [M + H]⁺ 363.1025; found 363.1018.

6.3.7.2 General procedure F

Amine (0.5 mmol, 1.0 equiv.) was placed in a 12 mL vial containing a magnetic stir bar. TBME (2.5 mL) and iodonium salt (0.55 mmol, 1.1 equiv.) were added sequentially forming slurry. Ground to fine powder NaOt-Bu (0.0721 g, 0.75 mmol, 1.5 equiv.) was weighed out in air and added to the vial with stirring in one portion. The vial was sealed with a cap, and the reaction mixture was vigorously stirred at the room temperature for 1 hour. The reaction was quenched with saline solution (7 mL) and extracted with EtOAc (3x3 mL). The combined organic phases were dried with MgSO₄, drying agent was removed by vacuum filtration, and solvent was removed on rotary evaporator. The crude residue was purified by column chromatography on silica gel with Et₂O/hexanes mixture as eluent.

Compounds **10c** and **10d**

Prepared from **8aa** and **6n** according to the general procedure F and obtained in 80% yield (0.159 g, 0.40 mmol) as a yellow oil.

R_f = 0.28 14% Et₂O:hexane

Major isomer:

¹H NMR (CDCl₃ with 1% v/v TMS, 600 MHz) δ = 7.33 (d, overlaps with minor isomer, J = 8.1 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.96 (dd, appears as triplet, overlaps with minor isomer, J = 9.6 Hz, 1H), 6.81-6.73 (m, overlaps with minor isomer, 2H), 6.44 (dd, J = 15.3, 9.1 Hz, 1H), 4.42 (dd, J = 15.3, 0.8 Hz, 1H), 4.22 (dd, J = 9.0, 0.9 Hz, 1H), 3.13 (s, 3H), 3.08 (s, 3H), 2.43 (s, overlaps with minor isomer, 3H).

¹⁹F{¹H} NMR (Acetone-*d*₆ with 1% v/v TMS, 376 MHz) δ = -61.4(3) (d, J = 13.5 Hz), -128.7(1) (q, J = 12.7 Hz).

Minor isomer:

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.53 (dd, J = 16.0, 9.3 Hz, 1H), 7.33 (overlaps with major isomer, 1H), 7.05 (d, overlaps with major isomer, J = 8.3 Hz, 1H), 7.00-6.95 (overlaps with major isomer, 1H), 6.81-6.73 (overlaps with major isomer, 2H), 4.51-4.47 (m, 2H), 3.16 (s, 3H), 2.43 (overlaps with major isomer, 3H).

¹⁹F{¹H} NMR (Acetone-*d*₆ with 1% v/v TMS, 376 MHz) δ = -61.4(1) (d, J = 12.3 Hz), -128.7(0) (q, J = 13.1 Hz).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 165.9, 165.4, 154.2 (m), 151.7 (m), 145.6 (d, J_{C-F} = 2.1 Hz), 145.5 (d, J_{C-F} = 2.2 Hz), 144.9, 144.6, 135.7, 135.5, 135.1, 134.1, 132.8, 132.6, 131.8, 131.7, 131.6, 126.9, 122.7 (dq, J_{C-F} = 272.9, 1.6 Hz), 120.0 (d, J_{C-F} = 7.5 Hz), 119.7 (d, J_{C-F} = 7.3 Hz), 118.6-117.4 (m), 117.2 (d, J_{C-F} = 22.0 Hz), 117.1 (d, J_{C-F} = 21.7 Hz), 112.6 (q, J_{C-F} = 4.8 Hz), 112.3 (q, J_{C-F} = 5.1 Hz), 95.6, 94.3, 41.1, 41.0, 32.6, 28.1, 20.0.

FT-IR: 2925, 1664, 1625, 1505, 1314, 1235, 1123, 1077, 1046, 815.

HRMS (ESI⁺): calculated for C₁₉H₁₇ClF₄N₂O⁺ [M + H]⁺ 401.1038; found 401.1027.

Compounds **10e** and **10f**

Prepared from **8na** and **6a** according to the general procedure F and obtained in 50% yield (0.0995 g, 0.45 mmol) as a yellow oil.

R_f = 0.57 30% acetone:hexane

Major isomer:

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.39 (dd, *J* = 8.8, 4.5 Hz, 1H), 7.29 (dd, appears as triplet, overlaps with minor isomer, *J* = 9.4 Hz, 1H), 6.98 (d, overlaps with minor isomer, *J* = 7.9 Hz, 1H), 6.63 (d, overlaps with minor isomer, 1H), 6.44 (dd, overlaps with minor isomer, *J* = 15.3, 9.1 Hz, 1H), 6.40 (dd, overlaps with minor isomer, *J* = 8.4, 2.5 Hz, 1H), 4.42 (dd, *J* = 15.2, 1.4 Hz, 1H), 4.24 (dd, *J* = 9.1, 1.5 Hz, 1H), 3.11 (s, 3H), 3.06 (s, 3H), 2.24 (s, 3H).

¹⁹F{¹H} NMR (Acetone-*d*₆ with 1% v/v TMS, 376 MHz) δ = -58.9 (d, *J* = 17.7 Hz), -114.7(5) (q, *J* = 17.7 Hz).

Minor isomer:

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.51 (dd, *J* = 16.0, 9.3 Hz, 1H), 7.43 (dd, *J* = 8.9, 4.5 Hz, 1H), 7.30-7.26 (overlaps with major isomer, 1H), 7.00 (d, overlaps with major isomer, *J* = 8.6 Hz, 1H), 6.63 (overlaps with major isomer, 1H), 6.46-6.39 (overlaps with major isomer, 1H), 4.50 (dd, *J* = 9.3, 1.1 Hz, 1H), 4.47 (dd, *J* = 16.0, 1.1 Hz, 1H), 3.09 (s, 3H), 2.85 (s, 3H), 2.25 (3H).

¹⁹F{¹H} NMR (Acetone-*d*₆ with 1% v/v TMS, 376 MHz) δ = -58.8 (d, *J* = 17.7), -114.7(4) (q, *J* = 17.7).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 164.8 (d, *J*_{C-F} = 2.6 Hz), 164.3 (d, *J*_{C-F} = 3.2 Hz), 159.7 (m), 157.1 (m), 148.3, 148.2, 143.0 (d, *J*_{C-F} = 3.7 Hz), 142.5 (d, *J*_{C-F} = 3.8 Hz),

136.1, 135.8, 135.2, 135.1, 135.0, 134.7, 134.6, 134.0, 131.5, 131.1, 130.9, 126.4, 126.2, 121.9 (dq, $J_{C-F} = 273.7, 1.7$ Hz), 121.8 (dq, $J_{C-F} = 275.5, 1.5$ Hz), 119.4(d, $J_{C-F} = 22.7$ Hz), 117.4-116.3 (m), 115.5, 115.1, 113.9, 113.4, 95.7, 94.3, 40.8, 33.4, 28.5, 18.9.

FT-IR: 3035, 2923, 1664, 1624, 1502, 1484, 1269, 1140, 1119, 832.

HRMS (ESI⁺): calculated for C₁₉H₁₇ClF₄N₂ONa⁺ [M + Na]⁺ 423.0858; found 423.0850.

Compound **8ah**

Prepared from **6a** and **7h** according to the general procedure F and obtained in 63% yield (0.0995 g, 0.45 mmol) as a colorless oil.

$R_f = 0.27$ in hexane

¹H NMR (CDCl₃ with 1% v/v TMS, 600 MHz) δ = 7.26 (H5, dd, $J = 8.5, 7.4$ Hz, 2H), 7.07 (H3, d, $J = 8.3$ Hz, 1H), 7.02-7.01 (H1, H4, m, 3H), 6.97 (H6, dd, appears as triplet, $J = 7.3$ Hz, 1H), 6.80 (H2, dd, $J = 8.3, 2.4$ Hz, 1H), 6.43 (H9, dd, $J = 14.3, 6.8$ Hz, 1H), 4.15 (H11, dd, $J = 14.3, 2.1$ Hz, 1H), 3.98 (H10, dd, $J = 6.8, 2.1$ Hz, 1H), 3.96 (H7, t, $J = 6.1$ Hz, 2H), 3.86 (H8, t, $J = 6.1$ Hz, 2H), 2.29 (s, 3H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 151.5, 147.3, 146.8, 134.8, 131.3, 129.4, 128.6, 122.0, 121.4, 121.0, 119.1, 86.9, 64.8, 51.0, 19.2.

FT-IR: 3025, 2921, 2875, 1598, 1492, 1195, 1040, 814.

HRMS (ESI⁺): calculated for C₁₇H₁₈ClNO⁺ [M + H]⁺ 288.1150; found 288.1142.

6.3.8 X-ray structure details

X-ray crystallographic analysis was performed by Dr. Edward Valente at the University of Portland.

Crystals of **6g** were obtained by the use of vapor diffusion of diethyl ether into methanol solution at room temperature. Crystals of **8ma** and **9c** were obtained by slow evaporation of acetone solution at room temperature. Single crystals of **6g**, **8ma**, and **9c** were chosen for crystallographic study with Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$) or Cu K α ($\lambda = 1.5418 \text{ \AA}$) radiation. Data were collected on an Oxford Gemini system. Relevant details of the crystallographic experiments are given in Table 6. The structures were solved with SHELXS-86 and refined with SHELXL-97.⁹⁶ All non-H atoms were found in initial E-maps, and their positions were refined with attendant anisotropic librational parameters. H-atoms on carbons were assigned locations riding on the heavier atoms and given isotropic librational parameters equal to 150% of the equivalent isotropic librational parameter of the attached atom.

Table 6. Selected crystallographic information for structures **6g**, **8ma**, **9c**. Esteemed standard deviations in parentheses.

	Compound 6g	Compound 8ma	Compound 9c
Formula	C ₂₃ H ₂₄ F I O ₄ S	C ₁₃ H ₁₅ F ₃ N ₂ O ₂	C ₁₆ H ₂₀ N ₂ O ₃
System	monoclinic	monoclinic	triclinic
Space Group	P 2(1)/n (#14)	P 2(1)/n (#14)	P -1 (#2)
Cell constants			
a (Å)	8.5731(2)	8.6744(3)	9.1953(8)
b (Å)	11.0903(3)	14.6490(4)	10.6663(7)
c (Å)	23.6152(6)	10.4584(3)	15.3224(9)
α (°)	90	90	91.639(5)
β (°)	92.859(2)	103.035(3)	101.895(7)
γ (°)	90	90	90.755(6)
Data, parameters	7372, 271	4263, 181	7253, 380
R₁ (I>4σI)	0.053	0.037	0.052
CCDC	1916592	1916589	1916591

6.3.9 Spectral data

Figure 22. ¹H NMR of hydroxy(tosyloxy)iodomesitylene in CD₃OD at 400 MHz.

Figure 23. ¹³C {¹H} NMR of hydroxy(tosyloxy)iodomesitylene in CD₃OD at 101 MHz.

Figure 24. ¹H NMR of **6a** in DMSO-*d*₆ at 400 MHz.

Figure 25. ¹³C {¹H} NMR of **6a** in DMSO-*d*₆ at 101 MHz.

Figure 26. ¹H NMR of **6b** in DMSO-d₆ at 400 MHz.

Figure 27. ¹³C {¹H} NMR of **6b** in DMSO-d₆ at 101 MHz.

Figure 28. ¹H NMR of **6c** in DMSO-d₆ at 400 MHz.

Figure 29. ¹³C {¹H} NMR of **6c** in DMSO-d₆ at 101 MHz.

Figure 30. ¹H NMR of **6e** in DMSO-d₆ at 400 MHz.

Figure 31. ¹³C {¹H} NMR of **6e** in DMSO-d₆ at 101 MHz.

Figure 32. ^{19}F $\{^1\text{H}\}$ NMR of **6e** in DMSO-d_6 at 376 MHz.

Figure 33. ^1H NMR of **6f** in DMSO-d_6 at 400 MHz.

Figure 34. ¹³C {¹H} NMR of **6f** in DMSO-d₆ at 101 MHz.

Figure 35. ¹⁹F {¹H} NMR of **6f** in DMSO-d₆ at 376 MHz.

Figure 36. ¹H NMR of **6g** in DMSO-d₆ with 0.05% v/v TMS at 400 MHz.

Figure 37. ¹³C {¹H} NMR of **6g** in DMSO-d₆ with 0.05% v/v TMS at 101 MHz.

Figure 38. ^{19}F $\{^1\text{H}\}$ NMR of **6g** in DMSO-d_6 with 0.05% v/v TMS at 376 MHz.

Figure 39. ^1H NMR of **6h** in DMSO-d_6 at 400 MHz.

Figure 40. ^{13}C $\{^1\text{H}\}$ NMR of **6h** in DMSO- d_6 at 101 MHz.

Figure 41. ^{19}F $\{^1\text{H}\}$ NMR of **6h** in DMSO- d_6 at 376 MHz.

Figure 42. ¹H NMR of **6j** in DMSO-d₆ at 400 MHz.

Figure 43. ¹³C {¹H} NMR of **6j** in DMSO-d₆ at 101 MHz.

Figure 44. ¹H NMR of **6k** in DMSO-d₆ at 400 MHz.

Figure 45. ¹³C {¹H} NMR of **6k** in DMSO-d₆ at 101 MHz.

Figure 46. ¹H NMR of **6I** in DMSO-d₆ at 400 MHz.

Figure 47. ¹³C {¹H} NMR of **6I** in DMSO-d₆ at 101 MHz.

Figure 48. ¹H NMR of 6n in DMSO-d₆ at 400 MHz.

Figure 49. ¹³C {¹H} NMR of 6n in DMSO-d₆ at 101 MHz.

Figure 50. ^{19}F $\{^1\text{H}\}$ NMR of **6n** in DMSO- d_6 at 376 MHz.

Figure 51. ^1H NMR of **6m** in DMSO- d_6 at 400 MHz.

Figure 52. ¹³C {¹H} NMR of **6m** in DMSO-d₆ at 101 MHz.

Figure 53. ¹⁹F {¹H} NMR of **6m** in DMSO-d₆ at 376 MHz.

Figure 54. ¹H NMR of **8aa** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 55. ¹³C {¹H} NMR of **8aa** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 56. ¹H NMR of **8ba** in (CD₃)₂CO at 400 MHz.

Figure 57. ¹³C {¹H} NMR of **8ba** (CD₃)₂CO at 101 MHz.

Figure 58. ¹H NMR of **8ca** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 59. ¹³C {¹H} NMR of **8ca** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 60. ¹H NMR of **8da** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 61. ¹³C {¹H} NMR of **8da** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 62. ^{19}F $\{^1\text{H}\}$ NMR of **8da** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 63. ^1H NMR of **8ea** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 64. ^{13}C $\{^1\text{H}\}$ NMR of **8ea** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 65. ^{19}F $\{^1\text{H}\}$ NMR of **8ea** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 66. ¹H NMR of **8fa** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 67. ¹³C {¹H} NMR of **8fa** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 68. ^{19}F $\{^1\text{H}\}$ NMR of **8fa** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 69. ^1H NMR of **8ga** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 70. ^{13}C $\{^1\text{H}\}$ NMR of **8ga** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 71. ^{19}F $\{^1\text{H}\}$ NMR of **8ga** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 72. ¹H NMR of **8ha** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 73. ¹³C {¹H} NMR of **8ha** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 74. ^{19}F $\{^1\text{H}\}$ NMR of **8ha** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 75. ^1H NMR of **8ia** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 76. ^{13}C $\{^1\text{H}\}$ NMR of **8ia** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 77. ^1H NMR of **8ja** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 78. ^{13}C $\{^1\text{H}\}$ NMR of **8ja** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 79. ^1H NMR of **8ka** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 80. ^{13}C $\{^1\text{H}\}$ NMR of **8ka** in CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 81. ^1H NMR of **8la** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 82. ^{13}C $\{^1\text{H}\}$ NMR of **8la** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 83. ^1H NMR of **8na** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 84. ^{13}C $\{^1\text{H}\}$ NMR of **8na** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 85. ^{19}F $\{^1\text{H}\}$ NMR of **8na** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 86. ¹H NMR of **8ma** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 87. ¹³C {¹H} NMR of **8ma** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 88. ^{19}F $\{^1\text{H}\}$ NMR of **8ma** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 89. ^1H NMR of **8gg** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 90. ^{13}C $\{^1\text{H}\}$ NMR of **8gg** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 91. ^{19}F $\{^1\text{H}\}$ NMR of **8gg** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 92. ¹H NMR of **8vg** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 93. ¹³C {¹H} NMR of **8vg** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 94. ¹H NMR of **8db** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 95. ¹³C {¹H} NMR of **8db** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 96. ^{19}F $\{^1\text{H}\}$ NMR of **8db** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 97. ^1H NMR of **8ac** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 98. ^{13}C $\{^1\text{H}\}$ NMR of **8ac** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 99. ^1H NMR of **8ad** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 100. ^{13}C $\{^1\text{H}\}$ NMR of **8ad** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 101. ^1H NMR of **8gd** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 102. ^{13}C $\{^1\text{H}\}$ NMR of **8gd** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 103. ^{19}F $\{^1\text{H}\}$ NMR of **8gd** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 104. ¹H NMR of **8ge** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 105. ¹³C {¹H} NMR of **8ge** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 106. ^{19}F $\{^1\text{H}\}$ NMR of **8ge** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 107. ^1H NMR of **8af** in DMSO-d_6 at 400 MHz.

Figure 108. ^{13}C $\{^1\text{H}\}$ NMR of **8af** DMSO- d_6 at 101 MHz.

Figure 109. ^1H NMR of **8dg** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 110. ^{13}C $\{^1\text{H}\}$ NMR of **8dg** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 111. ^{19}F $\{^1\text{H}\}$ NMR of **8dg** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 112. ¹H NMR of **8bh** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 113. ¹³C {¹H} NMR of **8bh** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 114. ^1H NMR of **8ai** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 115. ^{13}C $\{^1\text{H}\}$ NMR of **8ai** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 116. ¹H NMR of **9a** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 117. ¹³C {¹H} NMR of **9a** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 118. ¹H NMR of **9b** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 119. ¹³C {¹H} NMR of **9b** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 120. ^{19}F $\{^1\text{H}\}$ NMR of **9b** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 121. ^1H NMR of **9c** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 122. ¹³C {¹H} NMR of **9c** CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 123. ¹H NMR of **10a** and **10b** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 124. ^{13}C $\{^1\text{H}\}$ NMR of **10a** and **10b** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 125. COSY of **10a** and **10b** in CDCl_3 with 1% v/v TMS at 600 MHz.

Figure 126. NOESY of **10a** and **10b** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 127. Stacked ^{13}C NMR spectra of **10a** and **10b**.

Figure 128. HSQC of **10a** and **10b** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 129. HMBC of **10a** and **10b** in CDCl_3 with 1% v/v TMS at 400 MHz (unambiguous correlations shown).

Figure 130. ^1H NMR of **10c** and **10d** in CDCl_3 with 1% v/v TMS at 600 MHz.

Figure 131. ^{13}C $\{^1\text{H}\}$ NMR of **10c** and **10d** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 132. ¹⁹F {¹H} NMR of **10c** and **10d** in CDCl₃ with 1% v/v TMS at 376 MHz.

Figure 133. ¹H NMR of **10e** and **10f** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 134. $^{13}\text{C} \{^1\text{H}\}$ NMR of **10e** and **10f** CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 135. $^{19}\text{F} \{^1\text{H}\}$ NMR of **10e** and **10f** in acetone- d_6 with 1% v/v TMS at 376 MHz.

Figure 136. ¹H NMR of **8ah** in CDCl₃ with 1% v/v TMS at 600 MHz.

Figure 137. ¹³C {¹H} NMR of **8ah** CDCl₃ with 1% v/v TMS at 151 MHz.

Figure 138. Stacked ^{13}C NMR spectra of **8ah**.

Figure 139. COSY of **8ah** in CDCl_3 with 1% v/v TMS at 600 MHz.

Figure 140. NOESY of **8ah** in CDCl₃ with 1% v/v TMS at 400 MHz.

6.4 Supporting information for Chapter 4

6.4.1 Preparation of aryl(TMP)iodonium tosylates

6.4.1.1 General procedure G

Scheme 25. Synthesis of aryl(TMP)iodonium salts from aryl iodides.

Prepared according to the literature procedure.⁵⁹ Aryl iodide (1.0 equiv.) and acetonitrile (1 mL/mmol) were added to a round bottom flask, equipped with a magnetic stir bar. Toluenesulfonic acid monohydrate (1.01 equiv.) was added in one portion, followed by one portion of *m*-CPBA (1.01 equiv.). The flask was lowered into an oil bath set to 77°C and stirred vigorously. After 30 min 1,3,5-trimethoxybenzene (1.01 equiv.) was added in one portion and stirring was continued at 77°C for 5 minutes. The reaction was removed from heat and concentrated under reduced pressure. The resulting crude residue was triturated with diethyl ether. The precipitate was isolated by vacuum filtration and washed by slurry filtration with diethyl ether to give analytically pure aryl(2,4,6-trimethoxyphenyl)iodonium tosylate.

6.4.1.2 General procedure H

Prepared according to the literature procedure.⁶⁶ Aryl iodide (1.0 equiv.) and dichloromethane (7 mL/mmol) were added to a round bottom flask, equipped with a magnetic stir bar followed by the addition of *m*-CPBA (1.1 equiv.) at stirring. After the mixture was stirred at room temperature for 4 hours, toluenesulfonic acid monohydrate

(1.1 equiv.) was added followed by 1,3,5-trimethoxybenzene (1.1 equiv.). The reaction mixture was stirred at room temperature for 30 min, and solvent was evaporated under reduced pressure. The resulting crude residue was triturated with diethyl ether. The precipitate was isolated by vacuum filtration and washed by slurry filtration with diethyl ether to give analytically pure aryl(2,4,6-trimethoxyphenyl)iodonium tosylate.

6.4.2 Characterization of aryl(TMP)iodonium tosylates

Compound **11c**

Prepared according to the general procedure G on 3.0 mmol and obtained in 87% yield (1.56 g, 2.6 mmol) as a white powder.

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.43 (dd, appears as triplet, J = 1.6 Hz 1H), 8.13 (dd, J = 7.9, 1.7 Hz, 2H), 7.62 (dd, appears as triplet, J = 7.9 Hz, 1H), 7.47 (d, J = 8.0, 2H), 7.10 (d, J = 7.8, 2H), 6.48 (s, 2H), 3.95 (s, 6H), 3.88 (s, overlaps with singlet at 3.87, 3H), 3.87 (s, overlaps with singlet at 3.88, 3H), 2.28 (s, 3H).

¹³C{¹H} NMR (DMSO-*d*₆, 101 MHz) δ = 166.3, 164.4, 159.3, 145.8, 138.4, 137.5, 134.4, 132.1, 131.9, 131.8, 128.0, 125.5, 116.1, 92.2, 87.0, 57.4, 56.2, 52.8, 20.8.

FT-IR: 2943, 1725, 1578, 1344, 1158, 1100, 1031, 814, 677 cm⁻¹.

HRMS: Calculated for C₁₇H₁₈O₅I⁺ [M – OTs]⁺: 429.0193; Found: 429.0179.

Melting point: 195.4 - 199.5 °C.

Compound **11g**

Prepared according to the general procedure G on a 3 mmol scale and obtained in 81% yield (1.38 g, 2.4 mmol) as a white powder. Spectral data are consistent with those previously reported.⁸⁷

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.06 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.49 (s, 2H), 3.93 (s, 6H), 3.87 (s, 3H), 2.28 (s, 3H).

¹³C NMR (DMSO-*d*₆, 101 MHz) δ = 166.5, 159.4, 145.7, 137.6, 134.8, 134.8, 128.0, 125.5, 121.0, 117.5, 114.1, 92.2, 87.0, 57.4, 56.2, 20.8.

Compound 11l

Prepared according to the general procedure G on a 1 mmol scale and obtained in 79% yield (0.496 g, 0.79 mmol) as a white powder.

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.00 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.63-7.61 (m, 2H), 7.47 (d, *J* = 7.7 Hz, 2H), 7.10 (d, *J* = 7.7 Hz, 2H), 6.48 (s, 3H), 3.94 (s, 6H), 3.88 (s, 3H), 2.28 (s, 3H).

.01 (s, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.66-7.59 (m, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.48 (s, 2H), 3.94 (s, 6H), 3.87 (s, 3H), 2.29 (s, 3H).

¹³C NMR (DMSO-*d*₆, 101 MHz) δ = 166.3, 159.3, 148.4 (m), 145.6, 137.5, 137.5, 133.2, 133.1, 127.9, 126.7, 125.4, 124.3, 115.9, 119.7 (q, *J*_{C-F} = 257.9), 92.0, 87.1, 57.2, 56.1, 20.7.

¹⁹F{¹H} NMR (DMSO-*d*₆, 376 MHz) δ = -57.1.

FTIR: 3056, 2963, 2925, 2902, 2846, 1572, 1161, 1114, 1029, 744, 704 cm⁻¹.

HRMS: Calculated for C₁₆H₁₅O₄F₃I⁺ [M – OTs]⁺: 454.9962; Found: 454.9951.

Melting Point: 173.7-175.0 °C.

Compound 11o

Prepared according to the general procedure G on a 2.0 mmol scale and obtained in 68% yield (0.830g, 1.38 mmol) as an off-white powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 8.81 (d, J = 1.3 Hz, 1H), 8.33 (dd, J = 8.4, 1.3 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 6.46 (s, 2H), 3.97 (s, 6H), 3.85 (s, 3H), 2.71 (s, 3H), 2.28 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 , 101 MHz) δ = 165.6, 158.6, 147.6, 145.4, 144.9, 137.0, 131.1, 130.7, 127.4, 126.0, 124.8, 120.2, 91.6, 86.7, 56.6, 55.5, 24.2, 20.1.

FTIR: 3100, 2923, 2856, 1601, 1511, 1342, 1012, 727, 680 cm^{-1} .

HRMS: Calculated for $\text{C}_{16}\text{H}_{17}\text{NO}_5\text{I}^+$ [$\text{M} - \text{OTs}$] $^+$: 430.0146; Found: 430.0133.

Melting point: 216.9 - 217.9 $^{\circ}\text{C}$

Compound **11p**

Prepared according to the general procedure G on 2.0 mmol and obtained in 85% yield (1.11 g, 1.7 mmol) as a white powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 8.39 (d, J = 6.7 Hz, 1H), 7.61 (d, J = 9.5 Hz, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.11 (d, J = 7.7 Hz, 2H), 6.45 (s, 2H), 3.96 (s, 6H), 3.86 (s, 3H), 2.55 (s, 3H), 2.29 (s, 3H)

$^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 , 101 MHz) δ = 166.0, 160.0 (d, $J_{\text{C-F}}$ = 248.4 Hz), 159.15, 145.6, 143.3 (d, $J_{\text{C-F}}$ = 8.6 Hz), 140.8, 137.4, 127.8, 125.3, 118.8 (d, $J_{\text{C-F}}$ = 23.4 Hz), 115.9, 106.6 (d, $J_{\text{C-F}}$ = 22.1 Hz), 92.0, 86.9, 57.0, 56.0, 24.2, 20.5

$^{19}\text{F}\{^1\text{H}\}$ NMR (DMSO- d_6 , 376 MHz) δ = -102.86.

FTIR: 3021, 2980, 2844, 1584, 1177, 1117, 1030, 1007, 875, 678 cm^{-1} .

HRMS: Calculated for $\text{C}_{16}\text{H}_{16}\text{BrFO}_3\text{I}^+$ [$\text{M} - \text{OTs}$] $^+$: 480.9306; Found: 480.9298

Melting Point: 195.0-197.0 $^{\circ}\text{C}$.

Compound **11r**

Prepared according to the general procedure G on a 3 mmol scale and obtained in 83% yield (1.58 g, 2.5 mmol) as a white powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 8.12 (d, J = 1.5 Hz, 1H), 7.77 (dd, J = 8.1, 1.5 Hz, 1H), 7.47-7.42 (m, 3H), 7.10 (d, J = 7.9 Hz, 2H), 6.47 (s, 2H), 3.94 (s, 6H), 3.87 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 , 101 MHz) δ = 166.2, 159.3, 145.7, 141.6, 137.6, 136.6, 133.7, 133.3, 128.0, 125.5, 125.5 (overlapping peak), 113.1, 92.1, 87.2, 57.3, 56.2, 22.3, 20.8.

FTIR: 3091, 2936, 1578, 1160, 1116, 1031, 1008 cm^{-1} .

HRMS: Calculated for $\text{C}_{16}\text{H}_{17}\text{BrO}_3\text{I}^+$ 462.9400; Found: 462.9392.

Melting point: 223.5 – 226 $^{\circ}\text{C}$.

Compound 11s

Prepared according to the general procedure G on a 3 mmol scale and obtained in 90% yield (1.55 g, 2.7 mmol) as a white powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 7.89 (dd, J = 6.8, 1.6 Hz, 1H), 7.80-7.76 (m, 1H), 7.46 (d, J = 7.99 Hz, 2H), 7.25 (t, J = 9.2 Hz, 1H), 7.10 (d, J = 7.9 Hz, 2H), 6.45 (s, 2H), 3.94 (s, 6H), 3.88 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 , 101 MHz) δ = 166.2, 160.3 (d, $J_{\text{C-F}}$ = 250.9 Hz), 159.3, 145.7, 137.6, 134.2 (d $J_{\text{C-F}}$ = 4.7 Hz), 130.2 (d, $J_{\text{C-F}}$ = 3.3 Hz), 128.9 (d, $J_{\text{C-F}}$ = 16.7 Hz), 128.0, 125.5, 120.9 (d, $J_{\text{C-F}}$ = 25.4 Hz), 112.1 (d, $J_{\text{C-F}}$ = 7.2 Hz), 92.0, 87.3, 57.3, 56.2, 20.7, 14.1 (d, $J_{\text{C-F}}$ = 2.9 Hz).

$^{19}\text{F}\{^1\text{H}\}$ NMR (DMSO- d_6 , 376 MHz) δ = -111.4.

FTIR: 3090, 2941, 1580, 1175, 1117, 1031, 1008 cm^{-1} .

HRMS: Calculated for $\text{C}_{16}\text{H}_{17}\text{FO}_3\text{I}^+$ [M – OTs] $^+$: 403.0201; Found: 403.0191.

Melting point: 207.0 - 209.2 °C.

Compound 11w

Prepared according to the general procedure H on 2.0 mmol and obtained in 84% yield (1.02 g, 1.7 mmol) as a white powder. Spectral data are consistent with those previously reported.⁹⁷

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.03 (d, *J* = 2.3 Hz, 1H), 7.65 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.42 (s, 2H), 3.93 (s, 6H), 3.87 (s, 3H), 3.84 (s, 3H), 2.28 (s, 3H).

¹³C{¹H} NMR (DMSO-*d*₆, 101 MHz) δ = 165.4, 158.9, 155.1, 145.2, 136.9, 135.1, 133.0, 127.4, 124.9, 124.6, 113.4, 106.2, 91.4, 86.0, 56.7, 56.6, 55.5, 20.2.

Compound 11w'

Prepared according to the general procedure H on 2.0 mmol with the following modifications: the reaction was conducted at 30 °C in the presence of toluenesulfonic acid. The product was obtained in 60% yield (0.727 g, 1.2 mmol) as a white powder.

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 7.71 (d, *J* = 2.9 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.20 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.44 (s, 2H), 3.94 (s, 6H), 3.86 (s, 3H), 3.80 (s, 3H), 2.28 (s, 3H).

¹³C{¹H} NMR (DMSO-*d*₆, 101 MHz) δ = 165.59, 158.87, 157.96, 145.18, 136.93, 129.66, 127.41, 126.24, 124.87, 122.85, 119.01, 118.35, 91.42, 86.81, 56.52, 55.59, 55.54, 20.16.

FTIR: 3082, 2943, 2834, 1576, 157, 1117, 1030, 1005, 677 cm⁻¹.

HRMS: Calculated for C₁₆H₁₇ClO₄I⁺ [M – OTs]⁺: 434.9855; Found: 434.9845.

Melting Point: 214.1-216.0 °C

Compound 11x

Prepared according to the general procedure G on 3.0 mmol and obtained an isolated yield of 82% (1.57 g, 2.5 mmol) as a white powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 8.31-8.29 (m, 1H), 7.90-7.84 (m, 1H), 7.56-7.45 (m, 3H), 7.10 (d, J = 7.8 Hz, 2H), 6.45 (s, 2H), 3.94 (s, 6H), 3.85 (s, 3H), 2.28 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 , 101 MHz) δ = 166.3, 159.3, 158.8 (d, $J_{\text{C-F}}$ = 250.0 Hz), 145.7, 138.6, 137.6, 137.5, 128.0, 125.5, 118.6 (d, $J_{\text{C-F}}$ = 24.3 Hz), 117.5 (d, $J_{\text{C-F}}$ = 3.4 Hz), 105.0 (d, $J_{\text{C-F}}$ = 26.4 Hz), 92.1, 87.4, 57.2, 56.2, 20.8.

$^{19}\text{F}\{^1\text{H}\}$ NMR (DMSO- d_6 , 376 MHz) δ = -100.0.

FTIR: 3094, 2992, 2873, 1577, 1157, 1118, 1030, 835, 681 cm^{-1} .

HRMS: Calculated for $\text{C}_{15}\text{H}_{14}\text{BrFO}_3\text{I}^+$ [$\text{M} - \text{OTs}$] $^+$: 466.9150; Found: 466.9142.

Melting Point: 222.0 - 223.0 °C.

Compound 11x'

Prepared according to the general procedure G on 1.0 mmol and obtained in 87% yield (0.556 g, 0.87 mmol) as a white powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 8.12 (dd, J = 7.5, 3.0 Hz, 1H), 7.95 (dd, J = 8.9, 5.1 Hz, 1H), 7.47-7.44 (m, 3H), 7.10 (d, J = 7.8 Hz, 2H), 6.44 (s, 2H), 3.94 (s, 6H), 3.86 (3H), 2.28 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 , 101 MHz) δ = 166.2, 160.3 (d, $J_{\text{C-F}}$ = 252.2), 159.3, 145.6, 137.4, 134.4 (d, $J_{\text{C-F}}$ = 7.7), 127.9, 125.8 (d, $J_{\text{C-F}}$ = 25.2), 125.3, 121.9 (d, $J_{\text{C-F}}$ = 7.2), 121.6 (d, $J_{\text{C-F}}$ = 3.2), 121.1 (d, $J_{\text{C-F}}$ = 22.3), 91.9, 87.4, 57.0, 56.0, 20.6.

$^{19}\text{F}\{^1\text{H}\}$ NMR (DMSO- d_6 , 376 MHz) δ = -111.09

FTIR: 3089, 2972, 2864, 1577, 1155, 1117, 1030, 805, 677 cm^{-1} .

HRMS: Calculated for $\text{C}_{15}\text{H}_{14}\text{BrFO}_3\text{I}^+$ [M – OTs] $^+$: 466.9150; Found: 466.9140.

Melting Point: 200.3 – 203.0 $^{\circ}\text{C}$.

Compound 11y

Prepared according to the general procedure G on 1.0 mmol and obtained in 89% yield (0.568 g, 0.89 mmol) as a white powder.

^1H NMR (DMSO- d_6 , 400 MHz) δ = 8.22 (d, J = 2.0 Hz, 1H), 7.73 (dd, J = 8.2, 2.0 Hz, 1H), 7.49-7.45 (m, 3H), 7.10 (d, J = 7.8 Hz, 2H), 6.45 (s, 2H), 3.95 (s, 6H), 3.85 (s, 3H), 2.28 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 , 101 MHz) δ = 166.1, 159.3, 145.8, 139.8, 138.5, 137.5, 135.0, 132.7, 128.0, 125.5, 121.8, 119.5, 92.2, 86.8, 57.2, 56.1, 24.2, 21.8.

FTIR: 3078, 2981, 2923, 1591, 1154, 1114, 1031, 1006, 818, 676 cm^{-1} .

HRMS: Calculated for $\text{C}_{16}\text{H}_{17}\text{BrO}_3\text{I}^+$ [M – OTs] $^+$: 462.9400; Found: 462.9391.

Melting Point: 211.0 – 213.1 $^{\circ}\text{C}$.

Compound 11z

Prepared according to the general procedure G on 3.0 mmol and obtained in 90% yield (1.60 g, 2.7 mmol) as a white powder.

^1H NMR (DMSO- d_6 , 600 MHz) δ = 8.1 (d, J = 2.2 Hz, 1H), 7.61 (dd, J = 8.2, 2.2 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 7.9 Hz, 2H), 6.45 (s, 2H), 3.95 (s, 6H), 3.86 (s, 3H), 2.57 (s, 3H), 2.28 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 , 101 MHz) δ = 161.1, 156.3, 142.7, 136.5, 134.6, 132.8, 129.2, 129.1, 128.5, 125.0, 122.5, 118.4, 89.2, 83.8, 54.2, 53.2, 21.1, 17.8.

FTIR: 2981, 1577, 1219, 1203, 1155, 1115, 1007, 820, 679 cm^{-1} .

HRMS: Calculated for $\text{C}_{15}\text{H}_{14}\text{BrFO}_3\text{I}^+$ [$\text{M} - \text{OTs}$] $^+$: 418.9914; Found: 418.9905.

Melting Point: 155.7 – 166.6 $^{\circ}\text{C}$.

Compound 11aa

Prepared according to the general procedure G on 3.0 mmol and obtained in 89% yield (1.53 g, 2.7 mmol) as a white powder.

^1H NMR (DMSO- d_6 , 600 MHz) δ = 7.94 (dd, J = 7.6, 2.7 Hz, 1H), 7.57 (dd, J = 8.5, 5.8 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.41 (ddd, J = 8.4, 8.4, 2.7 Hz, 1H), 7.10 (d, J = 7.8 Hz, 2H), 3.95 (s, 6H), 3.86 (s, 3H), 2.57 (s, 3H), 2.28 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 , 101 MHz) δ = 166.1, 159.7 (d, $J_{\text{C-F}}$ = 249.5 Hz), 159.3, 145.7, 137.6, 136.8 (d, $J_{\text{C-F}}$ = 3.3 Hz), 132.0 (d, $J_{\text{C-F}}$ = 7.6 Hz), 128.0, 125.5, 123.5 (d, $J_{\text{C-F}}$ = 24.1 Hz), 120.2 (d, $J_{\text{C-F}}$ = 7.5 Hz), 119.3 (d, $J_{\text{C-F}}$ = 20.7 Hz), 92.1, 86.8, 57.2, 56.2, 23.8, 20.8.

$^{19}\text{F}\{^1\text{H}\}$ NMR (DMSO- d_6 , 376 MHz) δ = -113.5 (dd, $J_{\text{F-H}}$ = 7.2 Hz).

FTIR: 2940, 1580, 1228, 1153, 1152, 1007, 812, 687 cm^{-1} .

HRMS: Calculated for $\text{C}_{15}\text{H}_{14}\text{BrFO}_3\text{I}^+$ [$\text{M} - \text{OTs}$] $^+$: 403.0212; Found: 403.0201.

Melting Point: 186.6 – 187.5 $^{\circ}\text{C}$.

6.4.3 Synthesis and characterization of aryne trapping products

6.4.3.1 General procedure I

The iodonium salt (0.5 mmol, 1 equiv.) was weighed out and placed in a 12 mL vial containing a magnetic stir bar. TBME (2.5 mL) and arynophile **7g** (0.16 mL, 1.5 mmol, 3 equiv.) or **7e** (0.07 mL, 0.55 mmol, 1.1 equiv.) were added sequentially forming slurry. Ground to fine powder NaOt-Bu (0.0721g, 0.75 mmol, 1.5 equiv. or as indicated) was weighed out in air and added to the vial with stirring in one portion. The vial was sealed with a cap, and the reaction mixture was vigorously stirred at the room temperature (with **7g**) or at 0 °C (with **7e**) for 1 hour. The reaction was quenched with an aqueous solution of ammonium chloride (7 mL) and extracted with EtOAc (3x3 mL). The combined organic phases were dried with MgSO₄, drying agent was removed by vacuum filtration, and solvent was removed on rotary evaporator. The crude residue was purified by column chromatography on silica gel with diethyl ether/hexanes mixture or ethyl acetate/hexanes mixture as eluent.

6.4.3.2 General procedure J: telescoped reaction

Aryl iodide (0.5 mmol, 1 equiv.) was weighed out and added to a 12 mL vial containing a stir bar. Acetonitrile (0.5 mL) was added to the vial followed by *p*-toluenesulfonic acid monohydrate (0.095 g, 0.5 mmol, 1 equiv.) and m-CPBA (0.122 g, 0.5 mmol, 1 equiv.). The vial was placed in an aluminum block set to 77 °C, and the mixture was stirred at this temperature for 30 mins. 1,3,5-Trimethoxybenzene (0.084 g, 0.5 mmol, 1 equiv.) was added in one portion and the reaction was stirred for 5 mins. The vial was

removed from heat and allowed to cool down. TBME was added at stirring, and iodonium salt was allowed to precipitate out of the solution until free-flowing powder was observed. The vial was removed from a stir plate and, after the solid settled, the liquid phase was removed with a pipette. Washing with TBME was repeated two more times to remove the majority of contaminants. TBME (2 mL) was added to the resulted slurry followed by arynophile (3 equiv.). NaOt-Bu (1.5 equiv. with **7g** or 3 equiv. with **7a**) was added at stirring, and the mixture was allowed to react for 1 hour at room temperature. The reaction was quenched with saline solution (7 mL) and extracted with EtOAc (3x3 mL). The combined organic phases were dried with MgSO₄, drying agent was removed by vacuum filtration, and solvent was removed on rotary evaporator. The crude residue was purified by column chromatography on silica gel.

Compound **12ag**

Prepared from **11a** with furan (0.2 mL, 2.75 mmol, 5.5 equiv.) according to the general procedure I on 0.5 mmol scale with the following modification: reaction was conducted at 0 °C, LiHMDS (1 M in toluene, 0.5 mL, 1 equiv.) was used instead of NaOt-Bu. The product was obtained in 69% yield (0.0700 g, 0.35 mmol) as a white solid. Spectral data are consistent with those previously reported.⁹⁸

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.87 (s, 1H), 7.75 (d J = 7.4 Hz, 1H), 7.29 (d, J = 7.4 Hz, 1H), 7.05-7.00 (m, 2H), 5.75-5.74 (m, 2H), 3.89 (s, 3H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 166.9, 154.4, 149.5, 143.3, 142.4, 128.1, 127.3, 120.7, 119.9, 82.1(5), 82.1(2), 52.1.

Compound **12cg**

Prepared from **11c** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I with the following modification: LiHMDS (1 M in toluene, 0.5 mL, 1 equiv.) was used instead of NaOt-Bu, and the reaction was performed at 0 °C. The product was isolated in 70% yield (0.0704 g, 0.35 mmol) as a colorless oil. Structural isomer **12ag** resulted from deprotonation of the more sterically accessible position and was isolated in 8% yield (0.008 g, 0.04 mmol). Characterization for the major isomer is shown below.

$R_f = 0.18$ in 20% Et₂O/hexanes

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.55 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 7.0 Hz, 1H), 7.09-7.01 (m, 3H), 6.37 (s, 1H), 5.74 (s, 1H), 3.92 (s, 3H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 166.4, 152.4, 150.2, 143.7, 142.6, 125.4, 125.2, 123.7(3), 123.6(9), 82.7, 82.8, 52.0.

FTIR: 3008, 2950, 2843, 1713, 1274, 1118 cm⁻¹.

HRMS: Calculated for C₁₂H₁₁O₃⁺ [M + H]⁺: 203.0708; Found: 203.0698.

Compound **12eg**

Prepared from **11e** with furan (0.2 mL, 5.5 equiv.) according to the general procedure I on 0.5 mmol scale with the following modification: LiHMDS (1 M in toluene, 0.5 mL, 1 equiv.) was used instead of NaOt-Bu. The product was obtained in 57% yield (0.0539 g, 0.29 mmol) as a golden solid. Spectral data are consistent with those previously reported.⁹⁸

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 8.04 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.10 (dd, J = 5.5, 1.8 Hz, 1H), 7.05 (dd, J = 5.5, 1.8 Hz, 1H), 5.81-5.79 (m, 2H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 156.4, 151.3, 145.7, 143.4, 142.3, 122.3, 120.0, 115.2, 82.0(2), 82.0(1).

Compound **12gg**

Prepared from **11g** with furan (0.2 mL, 5.5 equiv.) according to the general procedure I on 0.5 mmol scale with the following modification: LiHMDS (1 M in toluene, 0.5 mL, 1 equiv.) was used instead of NaOt-Bu. The product was obtained in 78% yield (0.0663 g, 0.39 mmol) as a yellow crystalline solid. Spectral data are consistent with those previously reported.⁵⁶

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.46 (br, 1H), 7.36-7.31 (m, 2H), 7.06-7.02 (m, 2H), 5.76 (t, J = 1.92, 2H)

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 154.6, 150.5, 143.1, 142.5, 130.9, 122.8, 120.7, 119.1, 108.8, 82.1, 81.9.

Compound **12ig**

Prepared from **11i** and furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I on a 0.5 mmol scale and obtained in 82% yield (0.0834 g, 0.41 mmol) as a yellow solid.

R_f = 0.2 in 10% ether/hexanes

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.72 (dd, J = 8.4, 0.7 Hz 1H), 7.48 (d, J = 7.0 Hz, 1H), 7.17-7.12 (m, 3H), 6.49 (m, 1H), 5.83 (m, 1H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 152.6, 146.7, 144.3, 142.4, 142.0, 126.7, 124.9, 119.3, 82.6, 81.9.

FTIR: 3100, 2922, 2856, 1511, 1342, 1276, 727 cm⁻¹.

HRMS: Calculated for C₁₀H₇NO₃⁺ [M + H]⁺: 190.0504; Found: 190.0499.

Melting point: 120.9 - 122.6 °C.

Compound **12jg**

Prepared from **11j** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I on 0.5 mmol scale and obtained in 78% yield (0.0701g, 0.39 mmol) as a white solid; prepared according to the general procedure J and obtained in 67% yield. Spectral data are consistent with those previously reported.⁵⁶

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.14-7.09 (m, 1H), 7.08-7.04 (m, 2H), 6.91 (m, 2H), 5.87 (s, 1H), 5.74 (s, 1H)

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 151.5, 147.2, 143.3, 142.4, 126.9, 126.5, 125.7, 118.5, 82.9, 81.2.

Compound **12kg**

Prepared from **11k** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I on 0.5 mmol scale and obtained in 81% yield (0.0688 g, 0.41 mmol) as a white solid. Spectral data are consistent with those previously reported.⁵⁶

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 77.42 (d, J = 7.1 Hz, 1H), 7.19 (dd, J = 7.9, 1.0 Hz, 1H), 7.10-7.05 (m, 3H), 5.9 (s, 1H), 5.7 (s, 1H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 154.6, 150.7, 143.7, 142.2, 127.1, 126.1, 123.8, 116.7, 105.1, 82.4, 81.4.

Compound **12mg**

Prepared from **11m** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I on 0.5 mmol scale and obtained in 87% yield (0.0926 g, 0.44 mmol) as a white solid.

R_f = 0.47 in 10% ether/hexanes

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.11 (s, 1H), 7.07 (d, J = 5.5 Hz, 1H), 7.02 (d, J = 5.5, 1H), 6.94 (s, 1H), 5.84 (s, 1H), 5.71 (s, 1H)

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 153.0, 145.9, 142.9, 142.6, 131.8, 126.5, 125.1, 119.7, 82.6, 81.0.

FTIR: 3069, 3030, 2958, 1580, 1276, 817 cm^{-1} .

HRMS: Calculated for $\text{C}_{10}\text{H}_6\text{OCl}_2^+$ $[\text{M} + \text{H}]^+$: 212.9874; Found: 203.0698.

Melting point: 36.0 - 39.1 $^{\circ}\text{C}$.

Compound **12ng**

Prepared from **11n** with furan (0.109 mL, 2.75 mmol, 5.5 equiv) according to the general procedure I on 0.5 mmol scale and obtained in 54% yield (0.27 mmol, 0.066 g) as a yellow oil.

R_f = 0.65 6% EtOAc/hexanes

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.15-7.04 (m, 4H), 6.03 (s, 1H), 5.92 (s, 1H)

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 150.5 (q, $J_{\text{C-F}}$ = 2.7 Hz), 148.8, 143.1, 142.9, 129.8, 126.6, 123.7 (q, $J_{\text{C-F}}$ = 272.5 Hz), 123.2 (q, $J_{\text{C-F}}$ = 3.9 Hz), 122.3 (q, $J_{\text{C-F}}$ = 34.0 Hz), 82.3 (q, $J_{\text{C-F}}$ = 1.62 Hz), 81.1.

FTIR: 1603, 1314, 1280, 1162, 1093, 875 cm^{-1} .

HRMS: Calculated for $\text{C}_{11}\text{H}_6\text{OClF}_3^+$ $[\text{M} + \text{H}]^+$: 247.0132; Found: 247.0128.

Compound **12og**

Prepared from **11o** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I on 0.5 mmol scale with the following modification: LiHMDS (1 M in toluene, 0.5 mL, 1 equiv.) was used instead of NaOt-Bu. The product was obtained in 72% yield (0.36 mmol, 0.073 g) as an orange crystalline solid.

R_f = 0.20 in 10% Et₂O/hexanes

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.63 (d, J = 8.5 Hz, 1H), 7.14 (m, 1H), 6.9 (d, J = 8.5 Hz, 1H), 6.4 (s, 1H), 5.4 (s, 1H), 2.3 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 150.6, 146.4, 143.8, 142.2, 140.8, 135.9, 128.3, 119.5, 82.9, 80.5, 18.2.

FTIR: 3100, 2922, 2856, 1511, 1342, 794 cm^{-1} .

HRMS: Calculated for $\text{C}_{11}\text{H}_9\text{ON}_3^+$ $[\text{M} + \text{H}]^+$: 204.0665; Found: 204.0654.

Melting point: 148.0 - 150.5 $^{\circ}\text{C}$.

Compound **12pg**

Prepared from **11p** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I on 0.5 mmol and obtained in 76% yield (0.0969 g, 0.38 mmol) as a white solid.

R_f = 0.39 in 10% ether/hexanes

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.08 (s, 2H), 6.53 (d, J = 9.7 Hz, 1H), 5.84 (s, 1H), 5.78 (s, 1H), 2.25 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 156.3 (d, $J_{\text{C-F}}$ = 246.5 Hz), 152.1 (d, $J_{\text{C-F}}$ = 1.3 Hz), 144.7 (d, $J_{\text{C-F}}$ = 2.2 Hz), 143.8, 142.2, 130.0 (d, $J_{\text{C-F}}$ = 7.4 Hz), 113.5 (d, $J_{\text{C-F}}$ = 23.4 Hz), 100.1 (d, $J_{\text{C-F}}$ = 25.0 Hz), 83.0 (d, $J_{\text{C-F}}$ = 2.9 Hz), 81.7, 17.5 (d, $J_{\text{C-F}}$ = 1.0 Hz).

FTIR: 3019, 2925, 2849, 1455, 1275, 1126, 879 cm^{-1} .

HRMS: Calculated for $\text{C}_{11}\text{H}_9\text{OBrF}^+$ $[\text{M} + \text{H}]^+$: 254.9815; Found: 254.9811.

Melting point: 59.6 - 61.5 $^{\circ}\text{C}$.

Compound **12qg**

Prepared from **11q** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I on 0.5 mmol scale and obtained in 70% yield (0.0747 g, 0.37mmol) contaminated with 3% of 2,4,6-trimethoxyphenyl iodide, as a dark yellow solid. Spectral data are consistent with those previously reported.⁵⁶

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.26 (d, J = 7.1 Hz, 1H), 7.16 (dd, J = 5.5, 1.6 Hz, 1H), 7.10 (dd, J = 5.5, 1.6 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 6.11 (s, 1H), 5.77 (s, 1H), 2.5 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 150.0, 147.2, 144.1, 143.7, 142.1, 129.3, 129.1, 123.4, 82.7, 82.0, 19.7.

Compound **12rg**

Prepared from **11r** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I on 0.5 mmol scale and obtained in 87% yield (0.103 g, 0.44 mmol) as an off-white solid. Spectral data are consistent with those previously reported.⁵⁶

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.08-7.02 (m, 3H), 6.82 (dd, J = 7.0, 0.5 Hz, 1H), 5.78 (s, 1H), 5.75 (s, 1H), 2.3 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 150.5, 148.7, 143.7, 142.2, 134.6, 127.1, 118.7, 117.4, 83.3, 83.2, 23.0

Compound **12sg**

Prepared from **11s** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I on 0.5 mmol scale and obtained in 77% yield (0.0680 g, 0.385 mmol) as a white solid.

R_f = 0.24 in 20% Et_2O /hexanes

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.03-7.00 (m, 2H), 6.91 (d, J = 7.0 Hz, 1H), 6.77 (dd, appears as triplet, J = 6.8 Hz, 1H), 5.9 (s, 1H), 5.69-5.68 (m, 1H), 2.20 (d, J = 1.6 Hz, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 154.8 (d, $J_{\text{C-F}}$ = 245.8 Hz), 150.0 (d, $J_{\text{C-F}}$ = 4.4 Hz), 143.3, 142.3, 133.4 (d, $J_{\text{C-F}}$ = 21.4 Hz), 128.2 (d, $J_{\text{C-F}}$ = 3.5 Hz), 123.3 (d, $J_{\text{C-F}}$ = 17.8 Hz), 115.9 (d, $J_{\text{C-F}}$ = 3.1 Hz), 82.4, 79.5, 14.4 (d, $J_{\text{C-F}}$ = 3.4 Hz).

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) δ = -125.4.

FTIR: 3032, 2952, 2860, 1472, 1235, 823 cm^{-1} .

HRMS: Calculated for $C_{11}H_{10}OF^+$ $[M + H]^+$: 177.0710; Found: 177.0706.

Melting point: 28.3 - 30.9 °C.

Compound **12tg**

Prepared from **11t** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure I on 0.5 mmol scale and obtained in 81% yield (0.078g, 0.405mmol) contaminated with a 2% of 2,4,6-trimethoxyphenyl iodide, as a white solid.

R_f = 0.66 in 16% EtOAc/hexanes

1H NMR ($CDCl_3$ with 1% v/v TMS, 400 MHz) δ = 7.09-7.05 (m, 2H), 7.02 (d, J = 7.1 Hz, 1H), 6.84 (dd, J = 7.1, 0.7 Hz, 1H), 5.87 (s, 1H), 5.72 (s, 1H), 2.30 (s, 3H).

^{13}C NMR ($CDCl_3$ with 1% v/v TMS, 101 MHz) δ = 148.8, 147.7, 143.6, 142.2, 133.1, 127.3, 127.2, 118.1, 82.9, 81.5, 19.4.

FTIR: 3032, 2943, 2850, 1488, 1279, 835 cm^{-1} .

HRMS: Calculated for $C_{11}H_{10}OCl^+$ $[M + H]^+$: 193.0415; Found: 193.0413.

Melting point: 66.3 - 68.5 °C.

Compound **12vg**

Prepared from **11v** with furan (0.109 mL, 1.5 mmol, 3 equiv.) according to the general procedure J on 0.5 mmol scale and obtained in 78% yield (0.0876 g, 0.39 mmol) as a white solid. Spectral data are consistent with those previously reported.⁹⁹

1H NMR ($CDCl_3$ with 1% v/v TMS, 400 MHz) δ = 7.15 (d, J = 6.9 Hz, 1H), 7.09-7.14 (m, 3H), 6.84 (dd, appears as triplet, J = 7.6 Hz, 1H), 5.79 (s, 1H), 5.77 (s, 1H),

^{13}C NMR ($CDCl_3$ with 1% v/v TMS, 101 MHz) δ = 151.6, 149.8, 143.4, 142.4, 128.4, 127.1, 119.0, 114.5, 83.2, 82.8.

Compound **12de**

Prepared from **11d** and benzyl azide according to the general procedure I on 0.5 mmol and obtained in 97% yield (0.116 g, 0.49 mmol) as an off-white solid. Spectral data are consistent with those previously reported.¹⁰⁰

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.32-7.24 (m, overlaps with solvent peak, 6H), 6.89 (d, J = 8.3 Hz, 1H), 6.66 (d, J = 7.7 Hz, 1H), 5.81 (s, 2H), 4.10 (s, 3H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 151.7, 138.3, 134.7(9), 134.7(5), 128.9, 128.6, 128.4, 127.5, 103.3, 101.8, 56.2, 52.2.

Compound **12he**

Prepared from **11h** and benzyl azide according to the general procedure I on 0.5 mmol and obtained in 59% yield (0.0636 g, 0.28 mmol) as an off-white solid. Spectral data are consistent with those previously reported.¹⁰¹

R_f = 0.29 in 16% EtOAc/Hexanes

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.3-7.37 (m, overlaps with solvent peak, 4H), 7.26-7.28 (m, 2H), 7.13 (d, J = 8.4 Hz, 1H), 6.99 (dd, J = 10.0, 7.8 Hz, 1H), 5.85 (s, 2H).

¹³C NMR (CDCl₃ with 1% v/v TMS, 101 MHz) δ = 153.4 (d, J_{C-F} = 259.4), 136.5 (d, J_{C-F} = 18.9), 135.6 (d, J_{C-F} = 6.5), 134.2, 129.0, 128.9, 128.2 (d, J_{C-F} = 6.8), 127.5, 108.5 (d, J_{C-F} = 16.9), 105.8 (d, J_{C-F} = 5.0), 52.5.

Compound **12le**

Prepared from **11l** and benzyl azide according to the general procedure I on 0.5 mmol and obtained in 66% yield (0.0967 g, 0.33 mmol) as an orange solid.

R_f = 0.31 in 16% EtOAc/Hexanes

¹H NMR (CDCl₃ with 1% v/v TMS, 400 MHz) δ = 7.39-7.31 (m, 4H), 7.29-7.25 (m, overlaps with solvent signal, 3 H), 7.18 (dd, J = 7.7, 1.1 Hz, 1H), 5.86 (s, 2H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 140.1 (q, $J_{\text{C-F}}$ = 1.94 Hz), 139.4, 135.1, 134.2, 129.1, 128.7, 127.8, 127.7, 120.7 (q, $J_{\text{C-F}}$ = 259.81 Hz), 114.3 (d, $J_{\text{C-F}}$ = 0.94 Hz), 108.5, 52.6.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) δ = -57.7.

FTIR: 3090, 2918, 2850, 1626, 1508, 1216, 1143, 721, 693 cm^{-1} .

HRMS: Calculated for $\text{C}_{14}\text{H}_{11}\text{F}_3\text{N}_3\text{O}^+$ $[\text{M} + \text{H}]^+$: 294.0849; Found: 294.0839.

Melting point: 73.7 - 75.1 $^{\circ}\text{C}$.

Compound **12ue**

Prepared from **11s** and benzyl azide according to the general procedure I on 0.5 mmol and obtained in 60% yield (0.0884 g, 0.30 mmol) as an orange crystalline solid.

R_f = 0.32 in 29% EtOAc/hexanes

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) δ = 7.48 (m, 1H), 7.38-7.31 (m, 3H), 7.28-7.24 (m, overlaps with solvent peak, 3H), 5.88 (s, 2H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) δ = 158.4 (m), 155.8 (q, J = 2.9 Hz), 142.8 (m), 133.8, 130.1, 129.3, 129.0, 127.6, 124.12 (dq, J = 274.9, 1.5 Hz), 118.0 (d, $J_{\text{C-F}}$ = 27.9 Hz), 114.9 (d, $J_{\text{C-F}}$ = 11.0 Hz), 52.9.

$^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 with 1% v/v TMS, 376 MHz) δ = -56.4 (d, J = 19.1 Hz), -117.1 (q, J = 19.1 Hz).

FTIR: 3093, 2923, 1602, 1428, 1319, 1263, 780, 710 cm^{-1} .

HRMS: Calculated for $\text{C}_{14}\text{H}_{10}\text{F}_4\text{N}_3^+$ $[\text{M} + \text{H}]^+$: 296.0805; Found: 296.0796.

Melting point: 149.0 - 152.0 $^{\circ}\text{C}$.

Compound **12ia**

Prepared from 3-nitrophenyl iodide according to the general procedure J and obtained in 55% yield (0.0646 g, 0.27 mmol) as a yellow solid.

$R_f = 0.20$ in 30% acetone/hexanes

^1H NMR (CDCl_3 with 1% v/v TMS, 400 MHz) $\delta = 7.44\text{--}7.38$ (m, 2H), 7.07 (dd, $J = 7.1, 2.2$ Hz, 1H), 3.60 (t, $J = 5.7$, 2H), 3.33 (t, $J = 5.7$, 2H), 3.21 (s, 3H), 2.86 (s, 3H).

^{13}C NMR (CDCl_3 with 1% v/v TMS, 101 MHz) $\delta = 166.3, 150.1, 147.1, 130.9, 124.7, 121.9, 116.7, 56.8, 47.9, 40.2, 33.6$.

FTIR: 3089, 2906, 2827, 1663, 1522, 1487, 1430, 1353, 849 cm^{-1} .

HRMS: Calculated for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_3^+$ $[\text{M} + \text{H}]^+$: 236.1030; Found: 236.1021.

Melting Point: 155.0–156.4 $^\circ\text{C}$.

6.4.4 Selectivity study

Scheme 26. Regioselectivity of trapping aryne formed from **11w**.

Figure 141. A. ^1H NMR spectrum of crude reaction mixture of **11w** with morpholine recorded at 400 MHz in CDCl_3 ; B. ^1H NMR spectrum of the major product recorded at 400 MHz in CDCl_3 ; C. ^1H NMR spectrum of the minor product recorded at 400 MHz in CDCl_3 .

Scheme 27. Regioselectivity of trapping aryne formed from **11x**.

Figure 142. A. ^1H NMR spectrum of crude reaction mixture of **11x** with piperidine recorded at 400 MHz in CDCl_3 ; B. ^1H NMR spectrum of the major product recorded at 400 MHz in CDCl_3 ; C. ^1H NMR spectrum of the minor product recorded at 400 MHz in CDCl_3 .

Scheme 28. Regioselectivity of trapping aryne formed from **11y**.

Figure 143. ^1H NMR spectrum of crude reaction mixture of **11y** with morpholine recorded at 400 MHz in CDCl_3 .

Scheme 29. Regioselectivity of trapping aryne formed from **11z**.

Figure 144. ^1H NMR spectrum of crude reaction mixture of **11z** with morpholine recorded at 400 MHz in CDCl_3 .

Scheme 30. Regioselectivity of trapping aryne formed from **11aa**.

Figure 145. ^1H NMR spectrum of crude reaction mixture of **11aa** with morpholine recorded at 400 MHz in CDCl_3 .

6.4.5 Spectral data

Figure 146. ¹H NMR of **11c** in DMSO at 400 MHz.

Figure 147. ¹³C{¹H} NMR of **11c** in DMSO-d₆ at 101 MHz.

Figure 148. ¹H NMR of **11g** in DMSO-d₆ with 1% v/v TMS at 400 MHz.

Figure 149. ¹³C{¹H} NMR of **11g** in DMSO-d₆ at 101 MHz.

Chemical Structure: 2-methyl-4-nitrophenyltrimethylammonium tosylate. The cation consists of a benzene ring with a methyl group at position 2 and a nitro group at position 4. A trimethylammonium group is attached to the ring at position 1. The anion is a tosylate group (OTs).

¹H NMR Spectrum (DMSO-d₆):

- Aromatic protons (7.09–8.81 ppm):** Multiplet, integration 1.00, 1.02, 1.04, 2.00, 2.04.
- Trimethylammonium methyl groups (2.28–2.71 ppm):** Singlet, integration 3.09, 3.11.
- Tosylate methyl group (3.85 ppm):** Singlet, integration 6.09.
- Reference peak (0.00 ppm):** TMS.

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Figure 154. ¹³C{¹H} NMR of **11o** in DMSO-d₆ with 1% v/v TMS at 101 MHz.

Figure 155. ¹H NMR of **11p** in DMSO-d₆ with 1% v/v TMS at 400 MHz.

Figure 156. $^{13}\text{C}\{^1\text{H}\}$ NMR of **11p** in DMSO- d_6 with 1% v/v TMS at 101 MHz.

Figure 157. $^{19}\text{F}\{^1\text{H}\}$ NMR of **11p** in DMSO- d_6 with 1% v/v TMS at 376 MHz.

Figure 158. ¹H NMR of **11r** in DMSO-d₆ with 1% v/v TMS at 400 MHz.

Figure 159. ¹³C{¹H} NMR of **11r** in DMSO-d₆ at 101 MHz.

Figure 160. ¹H NMR of **11s** in DMSO-d₆ with 1% v/v TMS at 400 MHz.

Figure 161. ¹³C{¹H} NMR of **11s** in DMSO-d₆ with 1% v/v TMS at 101 MHz.

Figure 162. $^{19}\text{F}\{^1\text{H}\}$ NMR of **11s** in DMSO- d_6 with 1% v/v TMS at 376 MHz.

Figure 163. ^1H NMR of **11w** in DMSO- d_6 with 1% v/v TMS at 400 MHz.

Figure 164. $^{13}\text{C}\{^1\text{H}\}$ NMR of **11w** in DMSO- d_6 with 1% v/v TMS at 101 MHz.

Figure 165. ^1H NMR of **11w'** in DMSO- d_6 with 1% v/v TMS at 400 MHz.

Figure 166. $^{13}\text{C}\{^1\text{H}\}$ NMR of **11w'** in DMSO- d_6 with 1% v/v TMS at 101 MHz.

Figure 167. ^1H NMR of **11x** in DMSO- d_6 with 1% v/v TMS at 400 MHz.

Figure 168. ¹³C{¹H} NMR of **11x** in DMSO-d₆ at 101 MHz.

Figure 169. ¹⁹F{¹H} NMR of **11x** in DMSO-d₆ with 1% v/v TMS at 376 MHz.

Figure 170. ¹H NMR of **11x'** in DMSO-d₆ with 1% v/v TMS at 400 MHz.

Figure 171. ¹³C{¹H} NMR of **11x'** in DMSO-d₆ with 1% v/v TMS at 101 MHz.

Figure 172. $^{19}\text{F}\{^1\text{H}\}$ NMR of **11x'** in DMSO-d_6 with 1% v/v TMS at 376 MHz.

Figure 173. ^1H NMR of **11y** in DMSO-d_6 with 1% v/v TMS at 400 MHz.

Figure 174. $^{13}\text{C}\{^1\text{H}\}$ NMR of **11y** in DMSO- d_6 at 101 MHz.

Figure 175. ^1H NMR of **11z** in DMSO- d_6 with 1% v/v TMS at 600 MHz.

Figure 176. $^{13}\text{C}\{^1\text{H}\}$ NMR of **11z** in DMSO-d_6 at 101 MHz.

Figure 177. ^1H NMR of **11aa** in DMSO-d_6 with 1% v/v TMS at 600 MHz.

Figure 178. $^{13}\text{C}\{^1\text{H}\}$ NMR of **11aa** in DMSO- d_6 at 101 MHz.

Figure 179. $^{19}\text{F}\{^1\text{H}\}$ NMR of **11aa** in DMSO- d_6 at 376 MHz.

Figure 180. ¹H NMR of **12ag** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 181. ¹³C{¹H} NMR of **12ag** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 182. ¹H NMR of **12cg** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 183. ¹³C{¹H} NMR of **12cg** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 184. ¹H NMR of **12eg** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 185. ¹³C{¹H} NMR of **12eg** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 186. ¹H NMR of **12gg** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 187. ¹³C{¹H} NMR of **12gg** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 188. ¹H NMR of **12ig** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 189. ¹³C{¹H} NMR of **12ig** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 190. ¹H NMR of **12jg** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 191. ¹³C{¹H} NMR of **12jg** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 192. ¹H NMR of **12kg** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 193. ¹³C{¹H} NMR of **12kg** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 194. ¹H NMR of **12mg** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 195. ¹³C{¹H} NMR of **12mg** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 196. ¹H NMR of **12ng** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 197. ¹³C{¹H} NMR of **12ng** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 198. $^{19}\text{F}\{^1\text{H}\}$ NMR of **12ng** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 199. ^1H NMR of **12og** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 200. $^{13}\text{C}\{^1\text{H}\}$ NMR of **12og** in CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 201. ^1H NMR of **12pg** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 202. $^{13}\text{C}\{^1\text{H}\}$ NMR of **12pg** in CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 203. $^{19}\text{F}\{^1\text{H}\}$ NMR of **12pg** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 204. ¹H NMR of **12qg** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 205. ¹³C{¹H} NMR of **12qg** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 206. ¹H NMR of **12rg** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 207. ¹³C{¹H} NMR of **12rg** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 208. ¹H NMR of **12sg** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 209. ¹³C{¹H} NMR of **12sg** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 210. $^{19}\text{F}\{^1\text{H}\}$ NMR of **12sg** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 211. ^1H NMR of **12tg** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 212. $^{13}\text{C}\{^1\text{H}\}$ NMR of **12tg** in CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 213. ^1H NMR of **12de** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 214. $^{13}\text{C}\{^1\text{H}\}$ NMR of **12de** in CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 215. ^1H NMR of **12he** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 216. $^{13}\text{C}\{^1\text{H}\}$ NMR of **12he** in CDCl_3 with 1% v/v TMS at 101 MHz.

Figure 217. $^{19}\text{F}\{^1\text{H}\}$ NMR of **12he** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 218. ¹H NMR of **12le** in CDCl₃ with 1% v/v TMS at 400 MHz.

Figure 219. ¹³C{¹H} NMR of **12le** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 220. $^{19}\text{F}\{^1\text{H}\}$ NMR of **12le** in CDCl_3 with 1% v/v TMS at 376 MHz.

Figure 221. ^1H NMR of **12ue** in CDCl_3 with 1% v/v TMS at 400 MHz.

Figure 222. ¹³C{¹H} NMR of **12ue** in CDCl₃ with 1% v/v TMS at 101 MHz.

Figure 223. ¹⁹F{¹H} NMR of **12ue** in CDCl₃ with 1% v/v TMS at 376 MHz.

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