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The Preparation of Diaryliodonium Salts for Application in Arylation Chemistry

by

Thomas Ludwig Seidl

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

Doctor of Philosophy
in
Chemistry

Dissertation Committee:
David R. Stuart, Chair
David Peyton
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Portland State University
2018

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Abstract

Diaryliodonium salts offer potential as novel reagents for arylation chemistry. An overall goal and successful outcome of this work has been to further understanding of diaryliodonium salt chemistry by developing practical methods that enable chemists more convenient access to these reagents, for the purpose of reaction development. To this end a robust and convenient preparation method has been developed and resulted in novel commercially available diaryliodonium salts. The remainder of the work described, has focused on understanding the parameters important to diaryliodonium mediated arylation and has resulted in a solid framework that multiple future development efforts can build upon.

A strategy adopted throughout this work was to use multivariate methodologies such as Design of Experiments (DoE). Applicable chapters show the results of optimization studies that were carried out using DoE, during the course of this work. Additionally, the desire to further realize the potential that DoE has to offer inspired of a search for parameters to study fundamental reactivity. Chapter 2 details the development of a practical diaryliodonium salt synthesis that is convenient, facile, and economical. A detailed procedure is also included and was drafted to the requirements for publication in the journal Organic Synthesis. Finally, limitations and future directions of the method are discussed. Chapter 3 describes studies aimed at understanding the role of the counter anion; a very practical counter anion screening method is presented. Future directions are discussed and include detailed characterization of diaryliodonium salts by NMR. Chapter 3 also describes a practical, scalable, and rapid salt exchange method

developed during this work. Chapter 4 describes the results obtained in studying an azidation reaction via solubility parameters. All Supporting Information, including characterization data and experimental details, are provided in Chapter 5.

Dedication

To my wife and parents who have supported me on this exciting and informative path towards a doctorate.

I'm a lucky man... and the more I practice and work at things the luckier I get!

- adapted from Efren Reyes

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My sincere thanks go to Dr. David Stuart for welcoming me into his new group. I am honored to be among his first doctoral students. I will always value Dr. Stuart for being invested in and advocating for his students, for patiently allowing his students to develop as chemists and for maintaining high standards, without apparent judgement of students' mistakes. Thanks also to Dr. McCormick, Dr. Peyton and Dr. Sanchez, who benefited my studies by sharing their knowledge and experience. Special thanks to Dr. Strongin for his openness and kind support throughout my doctoral program.

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1. Introduction

1.1. Significance

Molecules containing aryl motifs are important to our daily lives and are implicated in pharmaceuticals, agrochemicals, engineering plastics, dyes for textiles and diagnostic sensing, and many other technologies that help to shape the way we live. Figure 1 shows several molecules that have impacted the lives of people globally and demonstrates that substituted aryl groups are a common feature of molecules in diverse and impactful applications. Notably the active pharmaceutical ingredients (APIs) of non-steroidal anti-inflammatory drugs (NSAID; **1,2,3**); fluorescent dyes, such as rhodamine (**4**); polyethersulfone (PES, **7**); and sulfonated PES (**8**).

Arguably, the types of substitutions and the substitution pattern of a given arene define its behavior and structure-function relationship (SFR). For example, substituting a single hydrogen for a sulfonate group converts the commodity polymer, PES (**7**) into sulfonated-PES (**8**), (Figure 1). Comparison of **7** and **8** nicely shows how a single substitution sufficiently alters the SFR so that the new material now finds application as a cation exchange resin. Sulfonated-PES is no longer a suitable engineering thermoplastic as is **7**. Figure 2 shows a generalized arylation reaction, wherein a single aryl hydrogen is substituted for another functional group. Broadly defined, arylation is the set of chemical transformations that result in the functionalization of arenes. To this end, the work described here focuses on the discovery and improvement of reagents useful for arylation reactions. Generally applicable reactions lead to simplified synthetic preparations of aromatic compounds, thereby reducing the resource demands of chemical synthesis and also facilitating the creation of novel compounds. Therefore, developing more general arylation chemistry would, in effect, render it more useful to synthetic chemists. Simplified syntheses and preparations of novel chemicals are two key outcomes that justify continued reaction development within this niche. One long term benefit of continued development could be an increased variety of chemicals available to chemists. Greater variety of available chemicals will increase the number of potential applications as well as further understanding of structure-to-function.

1.2. The status of contemporary arylation

Arylation has been the subject of intense research for over two centuries. The current state-of-the-art for arylation is dominated by transition metal catalysis (TMC), which has brought tremendous advances to synthetic chemistry.¹ Despite its popularity, there are situations which clearly demonstrate the need for alternatives. Specifically, the combination of late-stage synthesis and TMC can be problematic due to the difficulty of removing trace metals from reaction products.² Removal or reclamation/reworking of the metals used in catalysts may serve to reduce manufacturing costs associated with waste. Additionally, products manufactured in regulated industries are required to comply with requirements of the applicable regulatory agency. For example, the FDA has set strict criteria for acceptable trace metal content in APIs.³ Trace metal removal is challenging, in part, because the allowable concentration limits for trace metals are very low in comparison to commonly employed catalyst loading used in chemical synthesis. For example, the Losartan synthesis, shown in Figure 3, used a one mole percent loading of palladium acetate, which corresponds to roughly 1600 ppm palladium.⁴ The limit in

APIs for residual palladium is less than 10 ppm for oral administration and less than 1 ppm for parenteral administration.⁵ As reported by Garrett, even after treatment with

tributyl phosphine, about 50 ppm palladium remained.⁶ Notably, tributyl phosphine is itself moderately toxic, has a strongly unpleasant smell, and generally must be used in an air free environment.

A metal-free arylation reaction could simplify syntheses in regulated industries by eliminating the need for catalyst removal and associated verification testing. The cost of TMC can also be very high, in particular, when precious metals and custom ligands are required. There are many examples that suggest the cost of designer ligands far outweighs the cost even of the precious metal component. For example, 100 mg of the generation 3, Buchwald Palladacycle, CAS 1536473-72-9, from Strem Chemicals, sold for seventy dollars (December, 2015). Based on the December 28th, 2015 closing price of one troy ounce of palladium (\$554), one hundred milligrams would have cost just shy of two dollars.⁷ Based on the cost of one gram of palladium chloride, roughly sixty dollars, the cost for one hundred milligrams is about six dollars. The significantly higher price of the palladacycle when compared to a precious metal is plausibly indicative of the development cost associated with catalysts bearing designer ligands. An inherent characteristic of TMC with designer ligands is that they catalyze a specific transformation very well, but are not generally applicable to many different transformations. This keeps the likelihood of ligand development high, whenever novel reactivity is considered. Also, TMCs are frequently moisture- and/or air-sensitive and greater availability of bench-stable reagents would lessen the environmental controls and maintenance needed for storage and processing. Finally, an important distinction to remember is that TMC's are catalysts and not reactants. Developing reagents that

accommodate a broad substrate scope without added catalysts is a useful effort because, it is complementary to current technology. Although the point has been made that reagents capable of metal-free reactivity will avoid the cost of transition metal catalysts and associated ligand development, it is noteworthy that this does not preclude the addition of a TMC if needed. The reagents that will be discussed in this work are not catalysts and are not offered as a competing technology to TMC. A more realistic view would be that efforts to develop reagents capable of metal-free reactivity are complementary and so will hopefully lower dependence on TMC by offering the chemist greater flexibility in chemical synthesis. A particularly attractive scenario would include the discovery of reagents that undergo specific transformations that may be tuned with reaction conditions.

1.3. Diaryliodonium salts as arylation reagents

Diaryliodonium salts represent a potential alternative for arylation reagents and have been shown to mitigate several of the gaps in the toolkit currently available to chemists. In his 2016 review, Zhadankin asserts that iodine reagents, in general, are viable as sustainable alternatives to metals, because iodine is itself relatively more environmentally benign, cheap, and sufficiently abundant.⁸ Global crude iodine reserves are primarily found in Chile and Japan and its price is listed as \$23/kg by the United States Geological Survey (USGS).⁹ In contrast the 2016 prices of platinum and palladium listed by the USGS were \$1000 per oz. (\$32,151 per kg) and \$615 per oz. (\$19,773 per kg), respectively. Currently, 30,000 metric tons of iodine are harvested

annually and the estimated worldwide reserves are about 15 million metric tons.¹⁰

While this is not by any means a rigorous cost analysis, it seems that given the chance to become mainstream reagents, iodine based compounds could be economically competitive to their more expensive transition metal based counterparts.

Diaryliodonium salts enable transfer of aryl groups to heteroatoms as well as carbon atoms and are generally used under mild conditions, do not require inert environments or forcing conditions and may be used alone or with a transition metal. The vast majority are bench stable compounds and require minimal environmental controls to use. Together, the characteristically mild conditions, broad substrate scope, and regiospecificity possible with diaryliodonium salts make them a potentially useful reagent for late stage functionalization of complex arenes. The ability to perform specific and selective late stage transformations with a metal-free reagent is of particular value in the pharmaceutical industry, where strict limits on residual metal content must be met.

1.4. Historical overview of diaryliodonium salts

First discovered in the 1890's by Wilgerodt,¹¹ the potential breadth of arylation reactions with diaryliodonium salts was first demonstrated by Beringer in the 1950's.¹² Later, in the 1970's, efforts were made to characterize their structures and to begin understanding basic reactivity of hypervalent iodine compounds including, diaryliodonium salts. Several reviews are available for further reading on the overall class of hypervalent iodine reagents and their application for small molecule synthesis.¹³

In the 1970's, Crivello and coworkers reported that diaryliodonium salts may be used as photo-acid-generators (PAGs).¹⁴ As polymerization initiators in photoresists, diaryliodonium salts have had an enormous impact on the development of modern electronics.¹⁵ Today, research into hypervalent iodine reagents is gaining popularity as they offer an attractive combination of qualities including generally good stability and versatile chemical reactivity. They offer the potential for tuning reactivity according to reaction conditions, and as nonmetals, may eliminate the need for metal removal. To date, hypervalent iodine reagents, including diaryliodonium salts have become accepted reagents for natural products and pharmaceutical synthesis.¹⁶ While this work is focused on the development of specific diaryliodonium reagents and some aspects of their behavior in closed-shell arylation reactions, it is warranted to provide a brief discussion of hypervalent iodine as well as some of its history.

1.5. Overview of diaryliodonium salt structure and reactivity

Every organic chemistry student is first introduced to organoiodine with iodine existing as an organoiodide. Undergraduate courses rarely, if ever, mention the higher oxidation states, (+III) and (+V), which have found considerable use in small molecule synthesis, functional group transformation and polymer chemistry. Figure 4 shows the general structures of aromatic organoiodine compounds in various commonly encountered configurations. Diaryliodonium salts, less commonly called λ^3 -diaryliodanes, are a subclass of hypervalent iodine(III) reagents. The T-shaped structure in Figure 4 and Figure 5, has been experimentally determined by X-ray crystallography for numerous

diaryliodonium compounds.¹⁷ It follows that for crystalline diaryliodonium salts, the T-shape structure has been used to rationalize the thermodynamic stability of diaryliodonium salts. There has been controversy in the literature over whether these compounds are really salts. For clarity, referring to a diaryliodonium compound as a “diaryliodane” suggests that it is not a salt and that the X-group is bound to the iodine via a dative bond. Whether these compounds exist in the diaryliodane form, or in the ionic diaryliodonium form is debated in the literature. This author contends that the structure at any given moment likely depends foremost on the state of solvation as well as the identity of **X**. Regardless, the T-shape is also important for understanding the outcome of the putative reductive-elimination pathway that has been described for diaryliodonium mediated arylation.^{12k}

Many derivatives of the general structures shown in Figure 3, are bench stable and commercially available from mainstream chemical suppliers. In fact, polycordinate compounds have been reported for the entire halide family, except fluorine and are collectively referred to as halonium compounds.

Reagents such as hydroxy(tosyloxy)iodoarenes (HTIA, Figure 4a) and Dess-Martin periodinane (DMP, Figure 4c) act as oxidants and have been widely used. HTIA additionally has been used for ligand transfer of the sulfonate group. Iodoaryl dihalides have been used to access high oxidation states in metal reagents and also may be used as ligand transfer reagents, for example halogenation of an alkene. Both the dihalide and diacetoxy species may be used as chain transfer reagents in radical polymerizations. The diacetoxy species may also be used in oxidative coupling reactions, for example in the homocoupling of *n*-heterocyclic carbenes (NHCs). Uniquely, diaryl-, alkenyl- and alkynyliodonium salts are carbon transfer reagents. Chapter 2 presents the detailed

development of a diaryliodonium reagent, which transfers aryl groups to nucleophiles and lies at the heart of the work presented here.

The full scope of described structures is more complicated than might be expected, based on Figure 3. In fact, depending on the R-group and the environment, many of these structures can form dimers and oligomeric networks with potentially significantly different physical and chemical properties relative to the monomeric species. Further discussion of these somewhat esoteric structures is beyond the scope of the material presented here.

The stability of diaryliodonium salts that have the general, T-shaped, crystal structure shown in Figure 4 is thought to depend on the configuration of ligands around the iodine center. In the 1970's, Shustorovich studied the, axially oriented, three-center-four-electron (3c-4e) bond and its constituents.

He suggests that both of the apical ligands of the 3c-4e bond of hypervalent iodine (III) compounds exert an inductive *trans*-influence on the opposite ligand, the strength of which depends on the σ -donating ability of both ligands. The stronger σ -donor will have stronger bonding to the iodine center and will simultaneously weaken the opposite iodine-ligand bond. Shustorovich posited that, because of the *trans*-influence, the combination of one strong and one moderate sigma donating ligand would likely allow the 3c-4e bond the greatest thermodynamic stability.¹⁸ Accepting this rationale, it becomes clear that in a diaryliodonium salt, the 3c-4e bond will virtually always include one arene and the X-group, but a configuration with two apical arenes is very unlikely to

occur. Examples of all-carbon ligated iodine species have been reported, however, they were prepared at -80 °C and were extremely unstable.¹⁹

The reactivity of diaryliodonium salts as electrophilic carbon transfer agents is justified by the charge polarization of the 3c-4e bond. The iodine center effectively carries a +1 charge, making it inherently electrophilic and allowing for attack by nucleophiles. A second feature that is often cited is the excellent leaving ability of the aryl iodide moiety which has been called a *hypernucleofuge*. An example of the leaving ability of Ar-I is presented in Figure 6 below.²⁰

There are three main modes of reactivity by which arylation reactions of diaryliodonium salts are thought to proceed. Of the three pathways (Figure 7), the ionic (closed-shell) pathway is most developed, in particular, for arylation with heteroatoms^{21a-l}. The work here is primarily concerned with reagent development and the work presented here on coupling reactions is exclusively using nucleophiles that proceed through the ionic pathway. The radical and benzyne pathways will not be discussed further.

The ionic mechanism is thought to occur according to Figure 8. The nucleophile undergoes metathesis with the **X**-group, followed by formation of a three membered transition state, wherein the nucleophile is transferred to the *equatorial*-aryl group by reductive elimination. The reaction results in arylation of the nucleophile and a stoichiometric amount of an aryl iodide co-product.

An inherent advantage of diaryliodonium salts, undergoing coupling via reductive elimination, is that they affect an *ipso*-substitution and so offer excellent and predictable regioselectivity. It is immediately apparent that chemoselectivity is not an issue for the reaction shown in Figure 8. This is because the diaryliodonium salt shown

has two identical aryl groups. Such a diaryliodonium salt is termed symmetrical. In contrast, chemoselectivity does become important when considering arylation with unsymmetrical diaryliodonium salts. Figure 10 shows two aspects of unsymmetrical diaryliodonium salts that are needed to understand how chemoselectivity occurs and ultimately how it may be controlled.

Firstly, the T-shape helps to visualize that once the nucleophile replaces the X-group it can only reductively eliminate with a ligand in the equatorial position. Secondly, isomerization via pseudorotation means that both arenes may occupy the equatorial position. This means that both aryl groups have opportunity to enter the transition state preceding reductive coupling and that the product distribution will be determined by the relative energies of the two possible isomers of the transition state.

1.6. Selectivity with unsymmetrical salts

In practice, selectivity of the reaction and the resultant product distribution may be modulated by tuning the physicochemical properties of both arenes. Considering the

case, where one arene always leaves as its iodide, then it becomes reasonable to

label it as an auxiliary group (Aux). Unsymmetrical diaryliodonium salts are contrasted with their symmetrical counterparts in Figure 10 and may be described as consisting of four components: the iodine center, the X-group, the Ar group and AuX-group. In a coupling reaction, the Ar-group is the intended coupling partner and the Aux-group is intended to leave as its iodide.

The practical result of the distinction between **Ar** and **Aux** is that when a symmetrical salt undergoes a coupling reaction an equivalent of **Ar** is lost. The potential significance of losing an equivalent of **Ar** is explained by the hypothetical late stage functionalization of Flubendiamide (Figure 11).

While the aryl iodide co-product from reaction of the symmetrical salt in Figure 11 can potentially be reworked, such an undertaking would at best be mitigating and cannot be viewed as a solution. This limitation makes symmetrical diaryliodonium mediated arylation of elaborate products untenable. On the other hand, if the leaving moiety can reliably be the iodide of a simple arene, then waste is minimized and a workable situation may be realized.

The source of selectivity was studied in detail by Togni.²² He suggests that in the absence of sterics, the 3c-4e bond polarity, and in particular the charge of the *ipso*-carbon in the 3c-4e bond, determine the selectivity. More specifically, Togni calculates the partial charge on the *ipso*-carbon of both arenes when they are in the axial position. The difference of partial charges at the *ipso*-carbon for variously substituted rings is

shown to correlate well with the activation barrier to reach the transition state (Figure 12).

There are numerous examples in the literature that corroborate Togni's findings and it generally holds true that the more electron poor ring will couple to a nucleophile. Togni was also able to show that the correlation between *ipso*-carbon charge and activation barrier does not hold when one of the ligands is sterically congested. These results support experimental observations that the more electron rich ring, if bulky, can be the favored coupling partner (Figure 13).

Wiegend, who first suggested the *ortho*-effect, performed pyrolysis experiments with diaryliodonium halides and showed that steric bulk in the *ortho*-position influences the

reaction outcome, however, no unambiguous trend was presented.²³ Consequently, it is assumed that the bulkier group occupies the “roomier” equatorial position in the transition state. The cumulative data from the literature regarding this so-called *ortho*-effect is not straightforward. For example, Olofsson provides data showing that, in certain cases, steric bulk of the nucleophile may also play a role in determining selectivity of coupling (Figure 5).²⁴ Olofsson reported that the bulky nucleophile exerted an “*anti-ortho*-effect”, much to the chagrin of the encumbered ring. Pike and Widdowson additionally have shown evidence of the *ortho*-effect in fluorination reactions.²⁵ As such it is difficult to outline a general trend across all nucleophiles with a single sterically and electronically defined diaryliodonium salt. The observed *anti-ortho*-effect strongly alludes to the importance of including all components comprising the

transition state as well as those that are part of intermediate structures leading to the transition state. These components necessarily include the auxiliary, the aryl group, the **X**-group and the nucleophile. The **X**-group and the nucleophile have received very little attention to date. Even empirical studies of the **X**-group are rare and not comprehensive to the point that no parameter with which to evaluate the counteranion has been proposed. Most often, authors have simply stated that “non-coordinating” anions are preferable, such as triflate or tetrafluoroborate.²⁶ An interesting consideration to include would be solvent identity, simply because salts or salt-like species are directly involved in the reaction until reductive elimination occurs. In particular with salts, the coordinating effect of certain solvents could play a role. It is conceivable that a certain coordinating solvent would increase solvation and drive apart the **X**-group and leave the iodonium center available for attack. It is also conceivable that a solvent could coordinate too effectively, replace the **X**-group, but also hamper approach of the nucleophile.

1.7. Trimethoxyphenyl as an auxiliary

The value of the computational work by Togni is that it helps to rationalize a conceptual framework that corroborates empirical observations that sterically unhindered, electron rich, arenes preferentially leave the coupling reaction as their iodide. Diaryliodonium salts bearing a 2,4,6-trimethoxyphenyl (TMP) group have been demonstrated by several authors, notably Olofsson and Pike, to provide excellent selectivity across several nucleophiles (Figure 14).²⁷

The realization of a diaryliodonium salt with generally excellent selectivity completes a paradigm shift away from the symmetrical diaryliodonium salt. Despite the advantages

of the trimethoxyphenyl auxiliary being reported already a decade ago, no convenient preparation of

these reagents was described. As a result, reaction development efforts have rarely focused on TMP containing diaryliodonium salts and selectivity remained an issue. Previously reported syntheses of TMP containing diaryliodonium salts required an I(III) starting material and took multiple steps with overall moderate yield. The work described in Chapter 2 shows that aryl(TMP)iodonium salts are now readily prepared in under an hour, greatly facilitating reaction development with these promising reagents.

1.8. Overview of the preparation of diaryliodonium salts

Most often, the route to build diaryliodonium salts involves first oxidation of an iodoarene to the +3 oxidation state, followed by installation of the second arene via electrophilic aromatic substitution. Figure 15 shows four distinct methods to build diaryliodonium salts. Of these methods, the simplest in practice are those using an oxidant in conjunction with a Bronsted acid as cooling below zero centigrade is rarely required. The reaction using molecular iodine is useful for symmetrical salts and when more than one arene is present a statistical product mixture will result. Reactions employing boron trifluoride etherate tend to require lower temperatures often and moisture can be an issue. The reaction using boronic acids has the benefit of good

tolerance for electron rich iodoarenes, which have been problematic in reactions employing Bronsted acids.

Figure 15. Common routes to prepare diaryliodonium salts.

1.9. Design of Experiments (DoE)

Design of Experiments (DoE) is a methodology that employs multivariate analysis to test a given hypothesis. It originated from the work of William Gosset, who was working to improve batch consistency at the Guinness Brewing Company and so was concerned over statistics with small sample sizes. Gosset's work was published under the pseudonym, Student, and his ideas on "designed experiments" were later developed by scientists like Fisher and Taguchi. Today, industry commonly employs DoE during the development phases of R&D projects and heavily relies upon DoE for the creation of

robust manufacturing processes. DoE is rare in academic organic chemistry laboratories in North America and formal training is hard to find. It was successfully implemented for the optimization of a diaryliodonium salt preparation (Chapter 2) as well as for an azidation reaction (Chapter 3). The workflow in Figure 16 describes one, albeit simple, implementation of DoE. Importantly, optimization may be considered complete when the results of confirmation runs are in sufficient agreement with results predicted by the model.

An initial, 2-level fractional factorial design allows the relative contributions of many factors to be efficiently assessed and unimportant factors need not be studied further (Figure 16, Phase 0). Because the designs in Phases 0 and 1 vary factors over 2-levels, data is necessarily fit to a linear model. Despite the linear model, the use of center points in the initial 2-level design allows deviations from the linear fit to be detected. That is, if center point runs are statistically significant and do not fit to the linear model, curvature is indicated. After culling unimportant factors the remaining ones can then be studied in enough detail to quantify interaction effects between them (Figure 16, Phase 1). An interaction occurs when the contribution of one factor on a chosen output depends on the level of at least one other factor. Without simultaneously varying the levels of factors, the interaction effects may be overlooked and the importance of a factor may be overlooked. The ability to assess interaction effects makes DoE inherently more accurate than the traditional *One Variable At A Time* (OVAT) method. Using OVAT relies on luck to stumble upon the optimal conditions.

Not immediately obvious from the workflow is that data from successive experiment designs may be combined. The ability to grow the relevant pool of data by accretion is one way that using DoE can make optimization more efficient. Curvature detected in Phase 0 or 1 may be characterized by augmenting the data set obtained from the 2-level factorial with the additional data points (levels) needed to apply a higher order model (Figure 16, Phase 2). At this point the designs are often termed response surface analyses (RSA). Finally, regression analysis like ANOVA, various statistical tests and confirmation runs, are tools for objective evaluation of design models as well as, troubleshooting, and evaluation of design matrixes as well as results.

A final comments regarding the usefulness of DoE for research in chemistry, is that the work presented here is only the tip of the iceberg. This work only has dealt with the optimization of reaction environment and other variables that are easily controlled and continuous. In other words, only conditions were studied. Consider, however, the case where physicochemical parameters are used as inputs to experiment designs. Then, conceptually, it becomes possible to use DoE and its advantages to study fundamental aspects of reactivity. Here, useful physicochemical parameters include any quantifiable value that is directly or indirectly related to the fundamental properties of a molecule. For example, Hammet constants, peak locations of various substrates on a given type of spectrum, redox potentials, solubility parameters and even results from DFT calculations are all of potential use. In chapter 3, the beginning of such work is presented by the study of yield as a function Hansen Solubility Parameters (HSP). A difficulty that is not

immediately obvious is that it can be difficult to design symmetrical matrixes when using physicochemical parameters. For example, the DoEs shown above use symmetrical ranges of input variables and this is possible, because the variables are continuous. Here, physicochemical parameters are discussed as discrete variables with values that describe an inherent characteristic of a molecule. The nature of DoE is that results are most reliable when the levels of input variables can be set over regular intervals. As a result, when dealing with physicochemical parameters of molecules, DoE matrices will not be perfect arrays of orthogonal factors and the methods to adjust both the designs and their analysis are beyond the scope of this work.

Figure 16. Example DoE work-flow.

2. Developing the synthesis of aryl(TMP)iodonium tosylate

2.1. Previously reported syntheses

With the belief that diaryliodonium salts will only gain traction as mainstream arylation reagents after the described issues relating to selectivity have been overcome, the development of a practical synthesis of a selective diaryliodonium salt reagent became a priority. In particular for functionalization of elaborate molecules, it is necessary to move away from symmetrical salts in order to overcome an inherent limitation.

Arylation with diaryliodonium salts has excellent precedent. Still, current knowledge falls short when it comes to understanding exactly what reaction conditions, which combinations of reagents, and how the specific configuration of the diaryliodonium salt results in preference of one mechanism (ionic vs. radical vs. benzyne) over another and transfer of one aryl group over another. Critics have alleged that these reagents are

difficult to prepare and that they are not practical for use in modification of elaborate molecules, as encountered in late-stage synthesis of pharmaceuticals or in the post-modification of polymers. Our work, to date, has resulted in the development of a significantly improved method for the preparation of a variety of diaryliodonium salts and demonstrates successful coupling to elaborate arenes. Our data shows successful use of Design of Experiment (DoE) approach in order to develop a practical synthesis of diaryliodonium salts. The preparation is shown to be very repeatable and accommodates a broad scope of iodoaryl substrates. The preparation described below has been published and has been adapted into an Org Syn method, which is presented in Chapter 2b. As a final proof of success, several of the reagents have been made commercially available by TCI and are available in North America, Japan and Europe.

2.2. Feasibility

We have developed a robust synthesis of unsymmetrical (Figure 17b), aryl(TMP)iodonium tosylates and used DoE to arrive at optimized conditions with a model substrate. Precedent for diaryliodonium salts and the justification for choosing trimethoxyphenyl based arylidonium salts are discussed in previous sections.

The research groups of Olofsson and Pike previously demonstrated the importance of the trimethoxyphenyl auxiliary in diaryliodonium salts.^{28,29} The three methoxy groups on TMP are stable and sufficiently electron-donating to help to ensure that the auxiliary will be relatively more electron rich than the other arene. The tosylate counteranion was selected according to precedent methods from the chemical literature. Tonic acid is consumed during oxidation of the aryl iodide (stage 1) and its conjugate base takes on the role of counter anion in the iodonium product. Fortunately, the tosylate anion has proven to be very amenable to exchange by various alkali salts. Counter anion identity has been shown to significantly affect reaction outcomes and is discussed in detail in Chapter 3.

Preparation of **10** was previously accomplished by first preparing the hydroxy (tosyloxy)iodoarene (HTIA) by Olofsson's method³⁰ (Figure 19, Pot 1) and then reacting it further with TMB similarly to a method from Pike¹³ (Figure 19, Pot 2). During feasibility experiments, it was observed that the rate of HTIA formation dramatically increased upon raising the concentration from 0.1 M to 1 M. It was evident that Olofsson's procedure had unrealized potential. Feasibility tests also showed that it was possible to form the aryl(TMB)iodonium tosylate by adding TMB directly to the crude HTIA intermediate. In order to further simplify and also to make the reaction more environmentally friendly, a single solvent, acetonitrile, was used for both steps of the reaction. Using acetonitrile avoids the use of perfluorinated alcohols, which are costly and hazardous.

Upon successful demonstration of feasibility, our one-pot reaction was optimized using DoE. The optimization substrate chosen was 4-methyl-iodobenzoate. The moderate yields of this substrate under feasibility conditions were thought to be directly related to the electron withdrawing nature of the ester group. Feasibility work, performed with 4-trifluoromethyl-iodobenzene and 4-tolyl-iodobenzene followed literature trends for formation of the HTIA intermediate. Consistent with expectations, more electron rich iodoarenes required shorter reaction times to form the HTIA analogue. The literature shows that similar, two-pot, preparations of diaryliodonium tosylates, bearing auxiliaries other than TMP, were most challenging for iodoarenes bearing electron withdrawing substituents. Initial one-pot experiments resulted in encouraging yields between 60% and 70%, indicating that the iodobenzoate substrate was a useful choice for optimization.

Optimization of the reaction shown in Figure 20 followed the work flow presented in Chapter 1, Figure 16, and resulted in model-predicted yields that agreed with experimentally obtained yields. The predictive value of the model is supported by the confirmation run data listed in Table 9 and also plotted on the response surface in Figure 26. The optimization was considered successfully concluded upon observing that the mean and standard deviation of the confirmation runs fell within those predicted by the model. A very interesting result of early DoE runs was the unexpectedly fast reaction to install the TMP auxiliary. As a result, the reaction time of stage 2 was shortened to a practical limit of 5 minutes. A detailed description of the optimization process is provided in the following section.

2.3. Optimization Details

General comments and a brief overview of DoE were given in Section 1.9.

2.3.1. Assessment of main effects of 5 factors under study

thereby reducing the subsequent work-load. As mentioned, factors are studied over two levels and linear models necessarily apply. Nonetheless, the addition of replicate center points serves to: 1) provide an early assessment as to the presence or absence of curvature, and 2) provide an estimate of the experimental error, which here is taken as the standard deviation of the replicate runs. An estimate of the experimental error is important as it determines the signal-to-noise ratio (S/N) of the results. The S/N value is critical to determining the size of an observed change in an output that one may distinguish from noise, at a chosen level of confidence.³² Estimating experimental error in this way makes the assumption that error is constant across the design space. This is generally true, provided that whatever mechanism is driving the process under study also remains constant over the design space.

Factor	Description^b	low level^a	center level^a	high level^a
A	Conc. (M)	0.1 (-1)	0.55 (0)	1 (1)
B	Time 1 (min)	2 (-1)	16 (0)	30 (1)
C	Time 2 (min)	2 (-1)	16 (0)	30 (1)
D	Temp. (°C)	25 (-1)	53 (0)	80 (1)
E	TMB (equiv)	1 (-1)	2.0 (0)	3 (1)

Table 1. Summary of Plackett-Burman design ^a Low and high levels are coded to -1 and +1 in order to assess the relative effect of each factor on %yield. ^b “Time 1” and “Time 2” refer to reaction times for “Stage 1” and “Stage 2”, respectively.

In this case, twelve experiments were required to study five factors and five center points were added (Table 1). For perspective, up to 28 experiments could be run in one regular work day. Additionally, the use of coded and actual values to describe the levels factors are set at (Table 1) is discussed in Section 2.3.2.

The Results of the Plackett-Burman design are shown in Table 2 and Figure 22. Factors considered significant effects (**A, B, D**) are bolded in Table 2 and account for ~90% of the contribution to the measured response. The “equivalents of TMB” factor was rejected from subsequent work because its effect was inversely proportional to yield. Despite the low effect on yield, the reaction time of Stage 2 was included in subsequent experiment designs simply to satisfy the author’s curiosity. However, it would have been justifiable to exclude Time 2 from further study.

Factor	Description	%contribution
A	Conc. (M)	7.71
B	Time 1 (min)	19.35
C	Time 2 (min)	0.12
D	Temp. (°C)	30.35
curvature	-	31.94
E	TMB (equiv)	2.77
AB		1.85
AC		1.09
AD	Interaction	3.81
AE	Terms	0.12
BC		0.03
BE		0.82
Pure error	-	0.033
		Sum = ~100%

Table 2. Contribution of factors, interactions and curvature to yield are shown (calculated with Design Expert software).

2.3.2. Full Factorial to assess interaction effects of A, B, C, D

The full factorial design allows identification of interactions between factors (Figure 16, Phase 1). This design, with the four factors selected in the previous design, required sixteen experiments. It would be possible to have first run the full-factorial and skipped the fractional factorial design altogether. However, the total number of runs is equal to the number of levels raised to number of factors under study. This optimization was started with five factors, studied at two levels. Starting with a full factorial in lieu of the fractional factorial design would have required 25, or 32, experiments. Some replicate points would still be needed to estimate experimental error. If Time 2 had been

omitted from further study then the total number of experiments at this point would have been twenty-five: seventeen from the Plackett Burman plus another eight for the full factorial with factors A, B, D. Hence, the stepwise approach to the methodology in Figure 16 is aimed at increasing efficiency of the overall process and this benefit should increase with the number of factors initially selected for study.

Factor	Description ^b	low level ^a	high level ^a
A	Conc. (M)	0.1 (-1)	1 (1)
B	Time 2 (min)	2 (-1)	30 (1)
C	Time 1 (min)	2 (-1)	30 (1)
D	Temp. (°C)	25 (-1)	80 (1)

Table 3. Summary of full factorial design.

Factor	Description	Standardized Effect	Sum of Squares	% Contribution
A-Conc	Temp. (°C)	20.27	1642.37	10.93
B-Time 1	Time 1 (min)	21.32	1817.60	12.09
C-Time 2	Time 2 (min)	-1.41	8.42	0.056
D-temperature	Conc. (M)	52.25	10918.68	72.65
AB		3.37	45.39	0.30
AC		-0.55	1.18	7.87E-003
AD		6.04	145.87	0.97
BC		1.4	7.97	0.053
BD		0.059	0.014	9.19E-005
CD	Interaction Terms	-2.01	16.64	0.11
ABC		1.38	7.71	0.051
ABD		-10.19	415.24	2.76
ACD		0.50	0.98	6.49E-003
BCD		0.52	1.21	8.03E-003
ABCD		0.34	0.54	3.57E-003

Table 4. Regression analysis of factorial study. Bolded rows were selected as model terms.

Results				Conclusion
F-value	388.83	p-value (Prob > F)	< 0.0001	The model is significant and there a 0.01% chance this F-value could be due to noise
Std. Dev.	2.35	R-Squared	0.9971	Predicted and Adjusted R-Squared values are <0.2 apart, indicating the model is appropriate for the data collected
Mean	45.69	Adj. R-Squared	0.9945	
CV%	5.14	Pred R-Squared	0.9883	
PRESS	176.35	Adeq Precision	50.456	This model can be used to navigate the design space due to sufficient signal-to-noise ratio.

Table 5. Evaluation of overall Factorial Model (Design Expert)

The model at this point linear and already has good value for prediction. The linear equations including main effects and interaction effects are shown below. Readers are encouraged to pay particular attention to Figures 23, 24 and 25 as they graphically show the importance of interaction effects. Note that because each factor is varied over two levels, it is possible to code the lower level as (-1) and the higher level as (1). The coded factors are each varied over the same range and so their contribution to the output may be directly compared and their relative importance assessed. The relative contribution of factors A, B, D and their interaction effects, AB, AD, BD and ABD can be seen Table 5. The equation using the actual levels is predictive within the tested design space. That is, the equation in terms of actual factors may be used to navigate the design space, but should not be used to extrapolate beyond the tested design.

Factor	Description	Sum of Squares	% Contribution	F-value	p-value Prob > F
A	Conc. (M)	1642.37	10.93	298.02	<0.0001
B	Time 1 (min)	1817.60	12.09	329.82	<0.0001
D	Temp. (°C)	10918.68	72.65	1981.30	<0.0001
AB		45.39	0.30	8.24	0.0208
AD	Interaction	145.87	0.97	26.47	0.0009
BD	terms	0.014	9.19E-005	2.505E-003	0.9613
ABD		415.24	2.76	75.35	<0.0001

Equation in terms of coded factors:

$$\%yield = 45.2 + 10.1A + 10.7B + 26.7D + 1.7AB + 3.0AD + 0.03BD - 5.0ABD$$

Equation in terms of actual factors:

$$\%yield = -5.37 - 23.1A - 0.25B + 0.52D + 1.93AB + 0.78AD + 0.02BD - 0.032ABD$$

Table 6. Factors selected as model terms based on ANOVA and corresponding model equations. Factors that are not statistically significant are not included in the model unless required to support hierarchy, as with interaction term BD. Prob > F values of less than 0.0500 are statistically significant and those greater than 0.1 are not significant.

Figure 23 A) 3D-plot of factorial response at $T=77^{\circ}\text{C}$, Stage 2 = 5min, B) illustration of temperature/concentration interaction. The effect of changing concentration from 0.1M to 1M on yield is more pronounced at higher temperature. For both graphs y-axis shows % yield from 10% to 80%; Stage 2 = 5 min.

Figure 25. A) 3D-plot of factorial response at conc. = 1M, Stage 2 = 5min, B) illustration of temperature/Time 1 interaction. The effect of changing temperature from 25°C to 77°C on yield is less pronounced at longer Stage 1 times when concentration is at 1M. At 0.1M concentration this interaction is negligible, indicating the ABD interaction. For both graphs, the y-axis (%yield) ranges from 0% to 100%; Stage 2 = 5 min.

2.3.3. Optimization via a Response Surface Model (RSM)

Results from the factorial design above are augmented with additional points necessary to apply a quadratic model. Ten additional points were needed to achieve the response surface in Figure 26. The additional points were applied in a face-centered design with respect to the factorial model discussed above. Additional points were then taken to confirm the model. Confirmation runs were performed in triplicate (Table 9). The results and model equation based on actual factors are given in Table 7. The evaluation of the results, as calculated by Design Expert, is given in Table 7.

Factor	Description	Sum of Squares	F-value	p-value Prob > F
A-Concentration	Temp. (°C)	2067.46	37.36	< 0.0001
B-Time 1	Time 1 (min)	1559.98	19.64	0.0002
D-temperature	Conc. (M)	13732.11	14.82	0.0009
A ²		291.92	130.47	< 0.0001
D ²	Quadratic terms	1152.60	2.77	0.1107

Equation based on actual factors:
 $\%yield = 73.8 + 10.7A + 9.3B + 27.6D - 10.2A^2 - 20.2D^2$

Table 7. Factors selected as RSM model terms based on ANOVA and associated model equation.

Results				Conclusion
F-value	37.36	p-value (Prob > F)	< 0.0001	The model is significant and there a 0.01% chance this F-value could be due to noise
Std. Dev.	10.26	R-Squared	0.8989	Predicted and Adjusted R-Squared values are <0.2 apart, indicating the model is appropriate for the data collected
Mean	54.85	Adj. R-Squared	0.8749	
CV%	18.7	Pred R-Squared	0.8247	
PRESS	3833.68	Adeq Precision	18.578	This model can be used to navigate the design space due to sufficient signal-to-noise ratio.

Table 8. Evaluation of RSM

Conc. (M)	Time1 (min)	Time2 (min)	Temp (C)	Yield (%)	Predicted (%)	Scale (mmol)
1.0	30	5	77	94 +/- 1.7	92 +/- 10	5
0.8	30	5	70	93 +/- 3.3	95 +/- 10	5
0.5	30	5	60	89 +/- 0.3	88 +/- 10	5

Table 9. Data for confirmation runs of RSM (n=3)

2.3.4. Conclusion

Figure 28 shows the published scope of materials prepared to our procedure. Some examples of diaryliodonium salts that were challenging to make are presented at the end of this chapter and feasibility is demonstrated for a modified procedure that may enable access to challenging diaryliodonium salts.

The aryl(TMP)iodonium tosylates we have encountered have good bench stability and may be stored indefinitely at 4 °C or colder. Compared to existing procedures, our method has a broader substrate scope, as good or better functional group tolerance and works well with elaborate iodoarenes (Figure 24: **27**, **29**, **30**). An unforeseen benefit of the tosylate group is that it readily lends itself to anion exchange (Figure 27).

The procedure is scalable and has been run between 0.2 mmol and 50 mmol scale without noticeable effect on yield. Starting materials that feed the development of diaryliodonium mediated chemistry are now more readily available and preparation time has been reduced from two days to less than 2 hours. This contribution was recognized as a key factor in the expedient development of novel benzyne reactivity that was recently published by the Stuart Research Group. Additionally, the broadened substrate scope of accessible diaryliodonium starting materials has enabled access to etherification of electron rich and elaborate arenes. Both of these advancements are examples of limitations in arylation chemistry with diaryliodonium salts that areprecedented in the literature and have now been significantly improved.

2.3.5. Stability Studies

As previously mentioned, diaryliodonium salts are used as photo-acid generators and will degrade rapidly upon exposure to UV light. Direct exposure to UV, including direct sunlight through a window will degrade many diaryliodonium salts in less than one day.

In order to gauge their bench stability in the laboratory, a qualitative stability study was performed. Samples in clear/transparent scintillation vials were placed on a window sill. Control samples, wrapped in aluminum foil, were placed near the window as well. The control samples did not appear to be degraded upon visual inspection at any point during the study. Figure 29 shows results for two aryl(TMP)liodonium salts, one with an electron poor arene and one electron rich. The tosylate salts appear to be generally more stable than the hexafluorophosphate salts. Thermal stability was tested using DSC and results are also shown in Figure 29.

The internal reaction temperature was also monitored in order to be aware of potential exothermic events, since even the possibility of a run-away reaction must be taken seriously. This data was collected with an in-situ temperature probe and readings were manually recorded from a digital readout. Two trials were performed, one at ambient temperature with no heat bath and the other in a 77 °C silicone oil bath.

Figure 31. Shot glass diaryliodonium synthesis.

The results are shown in Figure 30. Note that the ambient temperature trial exhibits exothermic and endothermic events that are attributed to the reaction progressing as well as dissolution of freshly added reagent. The apparatus for the ambient temperature reaction is shown in Figure

31. The 77 °C reaction has an uneventful temperature profile and was removed from the heat bath at about 35 min (~2100 sec.). This indicates that a standard silicone oil bath without agitation provides sufficient heat exchange to control the reaction temperature.

2.4. Applications

Figure 32 shows several application examples of the aryl(TMP)iodonium salts. The examples underscore the wide substrate scope that diaryliodonium salts can accommodate. Good to excellent yields were achieved with *C*-, *N*-, *O*-, *S*-nucleophiles. None of the reactions shown in Figure 32 were optimized.

2.5. Preparation of (4-methylbenzoate)(2',4',6'-trimethoxyphenyl)iodonium tosylate

With the intention of increasing awareness of diaryliodonium salts worldwide, the synthesis developed in Chapter 2 has been submitted to the journal Organic Synthesis. The purpose of this journal is to provide organic chemists with a source of experimentally checked procedures. At the time of this writing, the checking process at Org Syn is in progress. Dr. Katherine Liebman, an experienced researcher and synthetic organic chemist at Portland State University, kindly volunteered to perform the procedure stated below. Both the author and Dr. Liebman carried out the procedure on different days, using the same equipment, and obtained pure product in 91% yield on 50 mmol scale. Dr. Liebman carried out this synthesis for the first time without input beyond the written procedure.

An oil bath (Note 1) is heated to 77 °C with a digitally controlled hot-plate/stirrer, which is on a lab jack. A 500-mL two-neck (24/40) round-bottom flask equipped with a Teflon-coated magnetic stir bar (25 mm × 15 mm, elliptical) is clamped above the oil bath (Note 2). A jacketed, water-cooled, reflux condenser (24/40) and a powder funnel (24/40, glass or polypropylene) are placed on each neck of the round bottom flask as shown in

Figure 34A. Methyl-4-iodobenzoate (Note 3) (13.1 g, 50.0 mmol, 1 equiv.) and *p*-toluenesulfonic acid monohydrate (Note 4) (9.5 g, 50.0 mmol, 1 equiv.) are weighed out and transferred sequentially into the round bottom flask via the powder funnel. Acetonitrile (Note 5) (40 mL) is added to the round bottom flask through the powder funnel. The reagents are vigorously stirred (Note 6) while still outside the oil bath (Figure 34B). *m*-Chloroperoxybenzoic acid (Note 7) (10.7 g, 50.0 mmol, 1 equiv.) is weighed out and added to the round bottom flask through the powder funnel. An additional 10 mL of acetonitrile is used to wash residual powder on the funnel into the flask. The powder funnel is replaced with a stopper (24/40; ground glass or Teflon), which is secured with a Keck clip. The lab jack is raised until the solvent line of the reaction is below the surface of the pre-heated oil bath (Figure 34C). The reaction mixture is stirred at 77 °C (bath temperature) for 30 minutes. A fleeting yellow color may develop, followed by formation of thick slurry (Figure 34C) (Note 8).

The stopper is removed and 1,3,5-trimethoxybenzene (Note 9) (8.4 g, 50.0 mmol, 1 equiv.) is added to the reaction via the powder funnel (Note 10). The stopper is replaced on the round bottom flask, secured with a Keck clip, and the reaction is stirred at 77 °C for 5 minutes. Upon addition of trimethoxybenzene, the slurry (Figure 34C) dissolves immediately and the homogeneous solution becomes a deep amber color (Figure 35A). The lab jack is lowered and the reaction mixture is allowed to air-cool for 5 minutes with continued stirring. The reaction color lightens to an opaque orange upon cooling (Figure 35B). The reaction color lightens to an opaque orange upon cooling (Figure 35B).

The reaction product, **20**, is trituated from the reaction mixture by addition of diethyl ether (Note 11) (300 mL) and the mixture is stirred at room temperature for 15 minutes, during which time, an off-white precipitate forms in a light yellow mother liquor (Figure 35C). Product, **20**, is isolated by suction filtration of the reaction mixture using a 150-mL, medium porosity, fritted-glass funnel. The precipitate is rinsed with diethyl ether (3 × 40 mL) (Figure 36A). During each rinse cycle, suction is interrupted suction, the filter

cake re-suspended in diethyl ether, and any clumps are broken up with a spatula before suction is resumed in order to remove the rinse solution (Note 12) (Figure 36B). The filtrate discarded. The product is left under suction for 5 minutes, the filter cake is broken up into a powder using a spatula that is left under suction for an additional 15 minutes. The product, **20**, is obtained as a free-flowing, off-white to pale pink powder (27.3 g, 45.5 mmol, 91%) (Figure 36C). The product was determined to be 97.9 wt% pure by qNMR (Note 13, 14, and 15).

Notes & Safety:

1. The oil bath is prepared in a crystallization dish (8 cm × 15 cm) half-filled with silicon oil.
2. The round bottom flask should not be immersed in the oil bath, until indicated in the instructions.
3. Methyl-4-iodobenzoate was purchased from (Oakwood, 079685, 99% used as received).

4. *p*-Toluenesulfonic acid monohydrate was purchased from (Sigma Aldrich, T35920, Reagent Plus $\geq 98\%$, used as received).
5. Acetonitrile was purchased from VWR
6. *m*-Chloroperoxybenzoic acid was purchased from (Aldrich, 273031, $\leq 77\%$) and dried under vacuum until the flask was no longer cool to touch.
7. The stir bar will continue to agitate the reaction, no additional solvent is necessary.
8. 1,3,5-Trimethoxybenzene was purchased from (Aldrich, 138827, $\geq 99\%$), used as received.
9. The round bottom flask is not removed from the oil bath during addition of 1,3,5-trimethoxybenzene. Additional acetonitrile (up to 10 mL) may be used to wash any precipitate stuck to the side walls of the round bottom flask.
10. Diethyl ether was purchased from (Fisher, ACS grade and as used as received)
11. The diethyl ether rinse solvent can also be used to wash out the 500 mL round bottom flask into the filter funnel.
12. The purity of **20** (MW 600.4; 57.8 mg) was determined by qNMR in DMSO- d_6 as solvent and 4,4'-dihydroxybiphenyl (> 99 wt% purity; MW 186.2; 15.2 mg) as internal standard; the relaxation time (D1) set to 30 seconds.
13. The remaining ~ 2 wt% was residual solvent (acetonitrile and diethyl ether) which we were unable to remove even when the sample was placed under reduced pressure.
14. Characterization of **20**: ^1H NMR (400 MHz, DMSO- d_6) δ 8.06 (d, $J = 8.4$ Hz, 2H), 7.96 (d, $J = 8.5$ Hz, 2H), 7.49 (d, $J = 7.9$ Hz, 2H), 7.11 (d, $J = 7.8$ Hz, 2H), 6.49 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 3.86 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 166.3, 165.1, 159.4, 145.5, 137.6, 134.5, 132.0, 131.7, 128.0, 125.4, 121.0, 92.1, 86.7, 57.3, 56.1, 52.6, 20.7. FT-IR: 3041, 2949, 2842, 1721, 1646, 1582, 1457, 1343, 1282, 1186, 1034,

816 cm^{-1} . HRMS (ESI⁺): Calculated for $\text{C}_{17}\text{H}_{18}\text{IO}_5^+$ [M - OTs]⁺: 429.0193; Observed 429.0167. Melting point: 169-175 °C.

2.6. Future directions: Aryl(TMB)iodonium tosylates

2.6.1. Limitations

During the development efforts described in section 2.1 it became clear that some limitations exist. Figure 37 shows various diaryliodonium salts that proved to be challenging to make, as they failed to produce diaryliodonium salts in synthetically useful yield and purity. Depending on the substrate, the failure appeared to occur during the initial oxidation step or during installation of the auxiliary.

An interesting and fortunate feature of the response surface generated during optimization (Figure 26) is its gentle curvature, which is taken as an indication that acceptable yields may be obtained even when running the reaction of lower temperature. For example, Figure 28 shows several examples where reaction

temperature had to be lowered in order to be successful. As such, when a challenging substrate is encountered it is recommended that the first measure taken is to lower the temperature at Stage I, optionally increasing the reaction time. It was noted that challenging aryl substrates included functional groups prone to oxidation, like aldehydes and ketones. Nitrogen containing substrates are generally challenging, regardless whether aliphatic or aromatic, and relatively few examples exist in the literature. Diaryliodonium salts have been built from a few pyridyl, protected primary and secondary aliphatic amines as well as anilines. Another grouping of challenging substrates includes those that furnish a clean material in good yield with unexpected structure. An interesting example was observed with the *ortho*-nitrile, which was

converted into a primary amide upon analysis of the diaryliodonium salt product. Proton NMR and high-resolution mass spectrometry supported this finding. Similarly, iodoindole was not converted into the expected product. Interestingly, a good yield was achieved of a clean material with a ^1H NMR spectrum that is consistent with a diaryliodonium salt, but not the expected product. This author expects the difficulties with nitrogen containing substrates are in part due to the nucleophilicity of the nitrogen and its state of protonation. Examples of hypervalent iodine compounds in which

ligands are bonded to the iodine via nitrogen are well known in the literature, for example, Barluenga's Reagent. However, it seems mostly relevant that the initial oxidation occurs in the presence of a Bronsted acid. It is very likely that protonation of a nitrogen, thus changing the ionization state to +1, will have a significant effect on chemical and physical properties. For example, in the case of a pyridyl or aniline substrate, conversion of the nitrogen into the ammonium form will inductively cause the substrate to become more electron deficient and potentially slow the rate of the oxidation step. The oxidized substrate would essentially be a dication and require two equivalents of the X-group. From a practical standpoint it seems very plausible that understanding the ionization state of nitrogen functionalities throughout the procedure will increase likelihood of successful workup and isolation of the target product. Of course, the first step would include simply adding a second equivalent of the Bronsted acid. Removal of the Bronsted acid from the procedure and the feasibility of acid-free preparation of diaryliodonium salt will be discussed in the next section.

Finally, certain substrates undergo reactions that seem to fail upon addition of the auxiliary. A control experiment showed that mCPBA and TMB react quickly and with release of heat. Based on this result, it is assumed that when a diaryliodonium salt synthesis fails upon addition of the auxiliary, it is likely due to unexpectedly slow progress of the oxidation step. If the oxidation step is slow, then significant mCPBA will remain available to react and consume the auxiliary when it is added to the drink. From experience, the resulting product mixture will very likely not triturate.

2.6.2. Bronsted acid-free preparation of aryl(TMB)iodonium tosylate

At some point upon entering a laboratory focused on diaryliodonium salts it is likely that any person will question the need for the additional protic acid during the oxidation step. In the academic research lab a viable work-around could be to perform slow addition of the oxidant and/or the auxiliary. At the expense of increased time to install the auxiliary, it may also help to introduce the auxiliary in an ethyl ether solution, as the ethyl ether will adjust the solubility properties of the reaction and encourage any diaryliodonium salt to precipitate as it forms.

In an attempt to overcome the limitations discussed in the previous section, the reaction was attempted using sodium tosylate in place of tosic acid. In this formulation, mCPBA is initially the strongest acid with a pKa of 7.48, which is about 1 million times weaker than tosic acid. The rationale for this formulation was that the oxidant properties of mCPBA would be attenuated. Importantly, the reaction is not free of protic acid as the mCPBA is converted to its benzoic acid derivative with a pKa of about 3.5. The first substrate tested was 4-methyl iodobenzoate and analysis of its oxidation product has not been possible due to its insolubility in any solvent tested. On visual inspection, the oxidation reaction appeared to progress as expected and a thixotropic paste was formed. The intermediate nonetheless reacted with TMB in acetonitrile. Because the diaryliodonium salt of this substrate is known to be soluble at 77 °C, it was expected that reacting the intermediate with TMB would result in at least part of the reaction going into solution. The reaction proceeded at a sluggish pace and was left to

reflux for one week. Upon removal of insoluble material, evaporation of the solvent, and trituration with ethyl ether, the diaryliodonium salt was realized at 39% yield. Based on this initial result, the 3- and 4-iodoanisole substrates were reacted as shown in Figure 39.

The results in Figure 39 are encouraging because the reaction at 77°C did not work with the iodoanisole starting substrates. The reaction conditions have been made milder using the conjugate base of the Bronsted acid.

Initial attempts to prepare diaryliodonium salts from iodoaniline were not successful, however, formation of the product was not rigorously ruled out. That is, the product was not worked up with the ionization state of the aniline moiety in mind. In such cases, failure of the product to triturate in ethyl ether should not be used as a conclusive assessment whether an iodonium salt has formed. While feasibility of the

method has been shown in terms of the chemistry, it is not overwhelmingly obvious whether the acid-free synthesis may be developed into a practicable method.

Recommendations for future work are listed below.

- Can product be formed without even the addition of an X-group salt?
- How does varying the X-group salt affect the reaction and solubility of the intermediate?
- What is the intermediate?
- What is the effect of adding a Lewis acid to the oxidation product?

The significance of the acid-free diaryliodonium synthesis could potentially go beyond simply expanding the substrate scope of current diaryliodonium salt preparations.

Without Bronsted acid it is possible to envision a reaction cycle whereby a chemical transformation is accomplished and catalyzed by a polyvalent organoiodine reagent that cycles between diaryl and monoaryl species. From the hypothetical catalytic cycle shown in Figure 40, it is clear that nucleophiles are required for two steps. One of these serves to generate the diaryliodonium salt from the oxidized iodoarene. The second nucleophile is the intended coupling partner in arylation. Because two nucleophiles are present in one pot, it will be necessary for them to be orthogonal reagents. The absence of acid would potentially allow the use of reagents such as the readily prepared aryl-boronates and aryl-silicates that have been demonstrated to impart nucleophilic character on the carbon atom *ipso* to boron or silicon. Both of these reagents are acid sensitive. Although not for arylation, Wirth has also used *in-situ* generation of the

hypervalent iodine species, using sodium perborate or a 1:1 admixture of boron trifluoride etherate and trimethylsilyl triflate.³³

One interesting alternative would be to devise a method that electrochemically generates the hypervalent iodine species. The schematic in Figure 41 depicts the concept-design of such a process.³⁴ The electrolyte would be comprised of the X-group salt as the anode of a platinum wire. As diaryliodonium salts are known to react non-reversibly at electrodes, the voltage would need to be carefully poised. Additionally, considerations such as pulsed current and/or switching between multiple working electrodes may benefit the reaction by limiting the amount of reactive intermediate and avoiding poisoning of the electrode surface.

Anodic oxidation of iodobenzene to phenyliodine(III)bis(trifluoroethoxide)], (PIFE) has been reported and the oxidant solution is stable in a refrigerator for one week.³⁵ The difficulty with electrochemical methods is the reoxidation, given that the reduction potential of iodobenzene is 1.9V, versus Ag/AgCl electrode. Still, this does not conclusively demonstrate lack of potential to use electrochemistry for the *in-situ* generation of reactive intermediates in hypervalent iodine chemistry. Very few reports exist on the electrochemical preparation of hypervalent organoiodine compounds and this area seems to be largely undiscovered. Furthermore, it is known that reduction potentials may be significantly modulated depending on conditions in the electrochemical cell as well as by functional groups on the ring. Electrochemical reactions are attractive because of the possibility to generate reactive intermediates that may otherwise not be possible.

3. An admix approach to determine the effect of the counter anion on arylation

3.1. Introduction to the counter anion and its significance

Diaryliodonium salts are increasingly studied for arylation of nucleophiles and the counter anion (X) is an important lever for reactivity. Of the three ligands, Ar and Aux have been discussed in both experimental and computational reports. Chapter 1 and Chapter 2 also discussed aspects of how Ar and Aux affect diaryliodonium mediated arylation. However, within the context of arylation, there is little information regarding the influence X has on the reactivity of diaryliodonium salts. Most importantly, no convenient method to select a counteranion has been proposed. It follows that this component of diaryliodonium salts is understudied and little information exists on how X potentially could interact with other reaction parameters. It is clear from Figure 42 that the three most commonly used X-groups including OTf, BF₄ and OTs are the conjugate bases of the Bronsted acids called out by the three most popular diaryliodonium salt syntheses (see Figure 42).

Within the context of arylation of nucleophiles proceeding through the ionic pathway, many reports on diaryliodonium salts include a counteranion screening study. However about 25% of recent reports (2011 to 2016) we reviewed did not test more than one counter anion (see Figure 42, green).³⁶ This is surprising given the potentially large influence counteranion identity can have on reactivity. The data in Figure 42 give insight into the recent use of counteranions in diaryliodonium research. Perhaps most striking is that there is no clear “best” counter anion. This supports the notion that contribution

of the counter anion to the progression of arylation reactions is not well enough

understood to allow rational selection of a counter anion for a given set of reaction conditions. An obvious and undesirable result of the current level of understanding of the X-group is that efforts to study it have been heuristic. A further complication is that varying the X-group for a single salt may necessitate additional development. More often than not, varying the X-group is more easily accomplished by anion exchange rather than by varying the type of Bronsted acid used in the diaryliodonium synthesis. While anion exchange tends to be a simple procedure, it is sensitive to the composition and structure of the aryl ligands. A particularly challenging anion exchange, for example, is the conversion of tosylate to acetate. In fact, the reaction does not proceed without resorting to forcing conditions. Interestingly, the exchange of tosylate into

trifluoroacetate could be readily accomplished, while trichloroacetate required further method development, which is described in Section 3.10. Importantly, development of a counter anion screening method will potentially improve the odds of successful reaction development and help diaryliodonium salts gain traction as mainstream arylation reagents. If the method is also facile and practicable with small amounts of reagents, it would also enable study of novel, hard to access counteranions, such as the conjugate base of the allylic Bronsted acid, 1,1,3,3-tetratriflylpropene (TTP). TTP was very recently developed by List *et al* and shown in Figure 43a.³⁷ Another recent report studied the effect of the counter anion on reactivity and solubility on diaryliodonium salts as photoinitiators of polymerization reactions. They found one example of a diaryliodonium salt that exists as an oil at room temperature and therefore would qualify as an ionic liquid. This diaryliodonium salt was soluble even in nonpolar solvents,

such as diethyl ether, but only when paired with the bistriflimide counter anion shown (Figure 43b). Importantly, almost every reported synthesis of diaryliodonium salts prescribes diethyl ether for trituration and washing of the product. This result is also intriguing simply because hypervalent iodine compounds often exhibit poor solubility in

many solvents. Diaryliodonium electrophiles often perform well in inhomogenous reactions, however, characterization methods that require dissolved analytes would certainly benefit from better solubility. In summary, the most important requirements for this screening method is to overcome the need for laborious anion exchanges and to provide reliable results when performed on very small scale reactions.

3.2. Feasibility of counter anion screening by the admix method

We set out to develop a screening method and started with the literature survey shown in Figure 42. According to the forty-two articles surveyed, the contribution to yield due to counter anion identity spans a large range. Reactions have been reported that seem insensitive to X-group identity.³⁸ On the other hand, one reaction exclusively worked in the presence of the acetate anion, which is one of the least often used X-groups.³⁹ Reported counteranion screening studies tested between 2 and 5 counteranions and on average the best counteranion gave a 29% higher yield than the worst, when other conditions were held constant. While iodonium triflates could be seen as a frontrunner, there are frequent examples of other counteranions that give equivalent or better results. This underscores both the potential importance of counteranion identity as well as the necessity for a practicable screening method.

3.3. Development of the salt screen

The envisioned method was conceptualized according to the scheme shown in Figure 44b. It was envisioned that an admixed salt would insert itself into the putative mechanism in Figure 44b. In theory, if *in-situ* anion exchange occurs and the product of this exchange more readily undergoes metathesis with the nucleophile, then the measured yield would increase relative to the reaction with no additive. On the other hand, if metathesis with the nucleophile is fastest with the initial diaryliodonium ion pair, then the yield will either be slowed or remain unaffected. Testing feasibility of implementation required a selection of a model reaction (Figure 45), for which we chose the well precededented diaryliodonium mediated azide arylation reaction.^{40,41} Sodium azide was selected as the azide source in order to avoid further complication of the system with additional cations. We chose to use unsymmetrical diaryliodonium salts bearing a trimethoxyphenyl (TMP) auxiliary for reasons discussed in Chapter 2. A

convenient and economical method of screening for diaryliodonium counteranions as a tool for reaction and process development is presented below.

Feasibility reactions were carried out similarly to the reaction in Figure 46, albeit using a stoichiometric amount of a sodium salt rather than an excess. The results of these reactions clearly demonstrated that ad-mixing the electrophile with various sodium salts had a significant effect on yield. Next, a solvent study was performed based on the expectation that solvent identity would affect the behavior of any salts in the reaction mixture. It is well known that, depending on the solvent, the ions in solution may be differently stabilized, potentially impacting the reaction at hand. A rational approach was used for the solvent selection process and is detailed in Chapter 4. The remaining azidation studies included an electron-rich and an electron-poor aromatic substrate reacting in nine different solvents. It was found that that acetonitrile and diglyme were good solvents, in that synthetically useful yields were obtained without having performed any optimization. The electronically distinct substrates were also not sterically hindered and were included in order to observe potential interaction of ring electronics and the identity of the dope salt.

3.4. The screening study

A screening study was performed with four equivalents of dope salt and two equivalents of sodium azide as shown in Figure 46. The layout of the study is conceptually simple and is shown along with screening results. Four groupings of sodium salts were tested, including those based on halides, acetates, and mesylates as counteranions. The fourth group can loosely be described as containing conjugate bases of fluorinated super acids. The data clearly showed that salt doping has an effect on azidation yield and Table 10 highlights important results from the screening experiment. The data used to build Figure 46 is available in the Supporting Information for Chapter 3.

Electrophile	Solvent	Over all range of yield	Range for reactions doped with the three most popular anions (OTf, BF ₄ , OTs)
diglyme	0% to 64%	10 % to 64%
diglyme	16% to 64%	53% to 63%
MeCN	0% to 42%	0% to 38%
MeCN	18% to 65%	35% to 63%

Table 10. Results calculated from data in Figure 46. ^a The average coefficient of variation over about one year for reactions in diglyme was 14% (t-Bu) and 17%(COOMe). ^b the average coefficient of variation over about one year for control reactions (no dope salt) was 10% (t-Bu) and 9% (COOMe).

3.5. Comparison of pre-exchanged and admixed azidation

For this to be a viable counter anion screening method, it was also necessary to compare the results of doped reactions with those of pre-exchanged salts bearing the analogous X-group. The results of side-by-side experiments, comparing salt-doped azidation reactions of diaryliodonium tosylates to those of pre-exchanged diaryliodonium salts, are shown in Figure 47. The results indicate sufficient correlation between doped and pre-exchanged reactions and further support the use of salt additives as a screening method. The reactions to which BF₄ and OTf were added did not track well in comparison to the remaining trials. In order to better understand these results, the azidation reactions were repeated with diaryliodonium tetrafluoroborate and diaryliodonium triflate starting materials. In both cases, four equivalents of

common anion were added as sodium salts and the yields converged with those of the screening results.

One of the more intriguing results had been increased yield obtained when sodium acetate was the additive in the azidation of **14**. The data for triplicate runs of the control reaction (yield = $66.5\% \pm 0.8$) and the sodium acetate doped reaction (yield = $76\% \pm 1.2$) suggests that the means are significantly different. This result was unexpected as, in our hands, exchanging tosylate for acetate has not been possible without first converting to a halide and then forcing the exchange with silver acetate. Unfortunately, the beneficial effect of adding acetate was not repeated during optimization. During optimization it was observed that addition of acetate had no statistically significant effect on yield. The conflicting results observed with acetate doping were taken as a welcome reminder that when assessing replicate results, day-to-day variation must be considered. As previously mentioned, the S/N value is key in objectively assigning a change in output to any effect. Interestingly, Table 10 points out that the coefficient of variation calculated from about one year's worth of the control reaction with **14** was 10%. Because of this variation in the longer term data, a more rigorous assessment would be needed in order to more confidently make any conclusions regarding the effect of acetate anion on azidation of **14**. Nonetheless, the often close correlation of doped to pre-exchanged yield results, points to the possibility that anion-exchange may not always be necessary in a process.

3.6. Scope of the screening method

We then moved on to test the general applicability of salt doping as a primary screen by adapting reported reactions to be compatible with salt doping. Care was taken to follow the literature procedures as closely as possible.⁴² Figure 48 shows that upon normalizing results to 100%, we observed significant correlation between our results. These results not only demonstrated the applicability of salt-doping as primary screen, but also demonstrate its practicality by using only one diaryliodonium starting material (see Figure 46).

3.7. Optimization and some azidation examples

Optimization was performed with the more electron rich substrate as shown in Figure 48. The tosylate was selected as the best X-group for the azidation reaction and the reaction was optimized. The DoE workflow, presented in Figure 16, was again followed. A full factorial design was performed to study the effect on azidation yield of temperature, equivalents of sodium azide, and the presence or absence of sodium acetate in the reaction. There was no statistically significant difference in reaction yield whether or not sodium acetate was included. The optimization was continued with two factors, temperature and azide-stoichiometry, in order to generate the quadratic model described by the contour plot below (Figure 50). The graph below nicely shows the importance of interaction effects, which are clearly present between the factors, temperature and azide concentration. A chemist using the OVAT method may reasonably decide to study the effect of azide concentration. The importance of azide concentration may be overlooked if the reaction were to be run below around 40 °C, because the contour lines are nearly parallel to the ordinate. If azide concentration is deemed to have little effect, then temperature would likely be studied next. However, the two hour reaction using 2 equivalents of sodium azide will reach its maximum yield of about 70% at 64 °C. The take home message is that DoE can provide high quality data in relatively few experiments as compared to the OVAT method.

With optimization complete, several azidations were performed in order to demonstrate the substrate scope of the reaction with aryl(TMP)iodonium tosylates. A variety of functional groups were tolerated, including a pyridyl, a phenethyl alcohol and one elaborate arene (Figure 51). The experimental details may be found in the Supporting Information for Chapter 3.

3.8. Discussion of unexpected BF₄ and OTf doping results

According to the putative mechanism shown in Figure 8, it is generally assumed that formation of the transition state immediately preceding reductive elimination comprises the rate limiting step. More specifically, displacement of the counteranion by a nucleophile is not commonly considered as influential over the reaction yield and the product distribution. However, this is not entirely consistent with our observations, that upon adding excess common anion, as in the case of BF₄ and OTf salts, the yield of aryl azide was reduced. The reduced yield was clearly related to addition of excess common anion and GC/MS data did not indicate any appreciable change in chemoselectivity and no unexpected products were observed. A series of experiments was performed in order to collect more complete data regarding the effect of the added

common anion on reaction yield. A common characteristic of diaryliodonium salts is their poor solubility, which often results in inhomogeneous reaction mixtures. Addition of an excess of the common anion should force precipitation of the diaryliodonium salt according to its solubility product. It was assumed that metathesis between the nucleophile and the counter anion could not occur while the diaryliodonium salt is precipitated. However, while working on a related project, to develop a rapid and scalable counter anion exchange method (Section 3.10), it seemed that anion exchange is possible so long as one of reactants is soluble. It was observed that if a diaryliodonium tosylate is eluted through a plug of granulated salt (NaX), then ion exchange occurs during the course of elution and solid sodium tosylate is presumably left behind. It seems reasonable that this would likely also apply to ionic nucleophiles participating in inhomogeneous reactions. Furthermore, the data shown in Figures 53, 54 and 55 show an unexpected increase in yield when roughly one equivalent or less of the dope salt is added. Based on these observations, two additional considerations potentially become relevant. Firstly, a change in ionic strength of the reaction medium due to addition of some amount of salt is a reasonable possibility. Secondly, aside from simply precipitating, the common ion effect could also influence unknown equilibria that exist due to secondary interactions between dissolved diaryliodonium salts. This concept was also suggested by a group studying polymerization reactions using diaryliodonium salt initiators (Figure 52). They found that conductivity correlated with polymerization rate, which should be proportional to the rate at which the diaryliodonium salt transforms into an active initiator. Of particular note, the

polymerization rate and the conductivity did not correlate with the solubility of the iodonium salts under study.

Reaction stoichiometries were studied in more detail and some noteworthy results were obtained. The importance of these experiments is that they directly study the possible effect of salt equilibria on the azidation reaction. While further study beyond the figures below has not been possible, the data does seem to be consistent with the notion that more than one mechanism is influencing the azidation reaction. Without replicating these results and further study, it is difficult to say more. The data is quite compelling in that it could indicate that the metathesis step is a stronger lever for reaction yield that is traditionally believed.

Figure 53. Azidation yield is plotted as a function of the amount of dope salt added.

Figure 54. Azidation yield is plotted as a function of the amount of dope salt added.

3.9. Spectator salt or *in-situ* anion exchange?

NMR studies were conducted in an attempt to better understand the chemical processes that are affected by changes in counter anion identity. Because of the limited solubility of diaryliodonium salts, solvents could not be varied and DMSO-*d*₆ was used for the majority of NMR experiments.

After rigorous assignment of chemical shifts for proton and carbon NMR spectra, peak shifts were analyzed for changes that could be correlated to counter anion identity (see Supporting Information). As expected, the *ipso*-carbon signals corresponding to both iodine-arene bonds are affected by counter anion identity. The greatest differences were noted among the halide anions (Figure 59). Also, exchanging trifluoroacetate for acetate resulted in a significant deshielding of the *ipso*-carbons in a diaryliodonium salt with a TMP auxiliary (Figure 59).

An interesting, observation occurred when tetrabutylammonium chloride was added to the NMR solution of diaryliodonium salts with either the TMP or the Mes auxiliary. The

Mes salt is significantly more sterically encumbered than TMP. Further, being alkyl substituted, Mes is electron rich, however, not to the same extent as TMP (Figure 57). Considering the *trans*-influence, TMP would be the more σ -donating of the two auxiliaries and

Figure 58. A) ^{13}C NMR Peak assignments for TMP salt B) added tetrabutyl ammonium chloride shifts the ipso-carbon peak towards the location of the neat iodonium chloride salt. (aux = TMP)

so more destabilizing to the X-group, which is the assumed *trans*-ligand. The hypothesis was that adding chloride anion to an NMR solution of diaryliodonium tosylate would effect a counter anion exchange and that depending on the chloride concentration the ipso-carbon peaks in the ^{13}C NMR spectrum should converge on the shift of the neat diaryliodonium chloride. In fact, this was observed when an NMR solution of aryl(mesityl)iodonium tosylate was exposed to chloride anion (Figure 59). However, when the same experiment was performed with an aryl(TMP)iodonium tosylate, the expected shift did not occur and instead the *ipso*-carbon peaks in the ^{13}C NMR spectrum became increasingly broadened with increasing chloride concentration (Figure 58a). Upon adding up to a four-fold excess of chloride anion, the peaks do clearly indicate conversion to the chloride salt. However, a puzzling feature of the ^{13}C NMR scans of the aryl(TMP)iodonium tosylate is that even at half an equivalent added chloride, the *ipso*-carbon peaks are no longer appreciable. The peaks that are visibly affected with increasing chloride concentration were assigned to the Ar-group and not the Aux-group (see Figure 58b).

These recent findings could potentially be explained by a difference in the ground-state stability when using either a TMP or Mes auxiliary. More specifically, the TMP auxiliary is by far the most electron-rich of any of the arenes that were part of this experiment and so should exert the largest *trans*-influence on the *trans*-ligand bound to iodine. It is conceivable that the larger *trans*-influence of TMP and its lack of steric bulk allow it to spend more time in the *axial* position. If this is the case, then association of any X-group in solution with the iodine may be destabilized and the result could be a rapid

equilibrium between associated and dissociated states. Additionally, the shifting peaks, “c” and “d” are assigned to the Ar-group and the peaks, “h” and “g” are unchanged and assigned to the tosylate group. This indicates that whatever change is occurring is due to the manner in which the chloride anion is interacting with the iodine center.

3.10. Rapid anion exchange method

Several anion exchange methods exist for diaryliodonium salts. Figure 61a shows the anion exchange method preferred in this document as it usually avoids extractions, is facile and often removes trace impurities. Several authors report anion exchanges by

first dissolving the diaryliodonium salt into dichloromethane or chloroform and then vigorously mixing the solution with a saturated solution aqueous solution bearing the target anion. This, DCM-extraction method, often results in emulsions and messy extractions and is poorly suited for scale-up. The method in Figure 61a is superior because extractions are usually not needed. Nonetheless a more rapid method is desirable if preparing many different types of

salts. Based on observations of the anion exchange process, it was noticed that both components may not necessarily need to be substantially in solution in order to undergo anion exchange. In fact, precedent for this exists with ion exchange resins that undergo metathesis with an eluent.

The work in this section simply describes the feasibility demonstration of an anion exchange method that functions by elution of a dissolved diaryliodonium salt through a column packed with a sodium salt comprised of the target anion. Immediately, it became clear that each different substrate will require some amount of development as

the method is somewhat finicky. For example, while exchanging tosylate for TFA, the rate of elution of a diaryliodonium-methanol solution was found to quickly diminish to the point that the liquid could not be eluted with pressure nor with suction. This clogging was assumed to occur as sodium tosylate fines precipitated within the column. The solution was to include a filter-aid in the column packing. Celite and coral sand both worked as filter aids, with coral sand being superior. In this way, some mindfulness and attention to engineering solutions may be necessary for certain salts to be anion exchanged by this method. When the method works, however, several millimol of diaryliodonium salt may be exchanged within minutes, plus the time to remove the solvent. Figure 63 shows that excellent conversion was achieved for several different starting diaryliodonium tosylate salts. These salts could be anion exchanged in moderate

Starting material	run order	Aryl (Ar)	scale (mmol)	NaTFA (equiv)	yield (%)	conversion (%)	purity (%)	impurity	elution time (min:sec)
OTs^- $\text{Ar}-\text{I}^+-\text{TMP}$	1		2	100	85	99%	100%	ne detect	1:22
	2		1	198	70	100%	98%	biphen	1:57
	3		2	98.5	88	95%	100%	pyridyl	1:26
	4		1	195	61	98%	95%	ester	4:14
	5		2	97	88	99%	100%	pyridyl	7:20
	6		2	96	78	99%	100%	pyridyl	9:32
	7		1	190	85	99%	100%	ne detect	1:27

Figure 64. Feasibility study for re-use of anion exchange cartridge

to excellent yield, using a scalable process, in less than 10 minutes, which would previously take at least 2 hours. Finally, the columns were fabricated from plastic syringes and based on feasibility experiments in Figure 64 they are reusable. Based on the reusability and scalability of this method it is likely that one such cartridge, or column would last a research laboratory months. A particularly time saving experiment was realized when diaryliodonium tosylate was eluted through a layer of bromide salt followed by a layer of a silver acetate or silver tetrafluoroborate salt. By using layers of solid salts it was possible to exchange tosylate into acetate, which normally takes several steps and is laborious. As such this was a successful side project.

4. Details on solvent selection: use of Hansen Solubility Parameters

Solvents for the azidation reactions presented in Chapter 3 were selected based on their Hansen Solubility Parameters (HSP). Briefly, HSP are an improvement on the Hildebrandt solubility parameter, which was based on the idea that the enthalpy of vaporization of a solvent is a function of the affinity between solvent molecules. Dr. Charles Hansen further developed the Hildebrand parameter by suggesting that the affinity between solvent molecules is the combination of dispersion, polar, and hydrogen bonding forces. Using these three parameters Hansen empirically determined and published the HSP values for thousands of small molecules and polymers. The concept and practical utility of HSP is easily visualized if the three parameters are used as the axes on a 3D graph. By empirically determining the limit of solubility of an analyte on each axes one can estimate its HSP values. A molecule will be readily soluble when mixed in a solvent with similar HSP.

In this case, HSP were used to select solvents with the intention of adequately representing the possible solvent space. Ideally, nine readily available solvents would be selected so that their HSP would form a cube with a center point in HSP space. It was quickly obvious that at best the solvents selected would resemble some very distorted polyhedron comprised of 8 vertices and a point somewhere within its volume. The solvents were additionally cross-referenced against principal component analysis values (PCA) reported by Rolph Carlson.⁴³ The PCA analysis is not trivial and includes

numerous parameters. The solvents selected for our study were found to adequately represent the solvent space according to both HSP and Carlson's PCA analysis.

The azidation reactions in Figure 45 were performed using one electron rich and one electron poor aryl(TMP)iodonium tosylate. Table 12 shows the azidation yield for each solvent as well as the HSP values and fractional HSP values.

solvent	Disp	Polar	H-bond	D%	P%	H%	tBu %yield	COOMe %yield
pentane	14.5	0.0	0.0	100%	0%	0%	0	0
water	15.6	16.0	42	21%	22%	57%	2	1
toluene	18.0	1.4	2.0	84%	7%	9%	12	7
Ethylene Glycol	16.0	12.0	20.0	33%	25%	42%	20	29
1,4 dioxane	19.0	1.8	7.4	67%	6%	26%	39	24
Dichloroethane	19.0	7.4	4.1	62%	24%	13%	37	28
Ethanol	15.8	8.8	19.4	36%	20%	44%	42	25
Acetonitrile	15.3	18.0	6.1	39%	46%	15%	30	41
propylene carbonate	21.0	18.0	6.1	47%	40%	14%	32	41
diglyme	16.2	7.8	12.6	44%	21%	34%	45	41

Table 11. Solvent screening for aryl azidation using HSP and fractional HSP. Unoptimized conditions were used.

Fractional HSP values simply are the geometric average of the standard HSP values. For example, the fractional dispersion parameter of pentane is found by taking the ratio of the regular dispersion HSP value and sum of all three regular HSP values. The fractional polar and hydrogen bonding parameters may be calculated the same way. The fractional values allow the reaction yields from Table 12 to be shown as contour lines on the ternary diagrams in Figure 65 and Figure 66.

Figure 65: Ternary contour plot showing the relationship between Hansen Solubility Parameters (H, D, P) for the azidation of 4-methoxybenzoate. Ternary contour plot showing the relationship between Hansen Solubility Parameters, using unoptimized reaction conditions.

index	D%	P%	H%
a	46	20	34
b	43	22	35
c	47.5	26.5	26
d	44	28	28
average	45	24	31

Table 12. The coordinates for the vertices of the area of maximum yield on both Figure 65 and Figure 66.

The area of maximum yield shared by the ternary plots in Figure 65 and Figure 66 is bounded by the coordinates that correspond to the fractional HSP listed in Table 13. A particularly useful aspect of HSP is that they are additive according to mole fraction. That is, if two or more hypothetical, miscible, solvents are mixed then the HSP of the mixture may be calculated according to the new solvent systems composition. Similarly, Table 12 shows the average fractional HSP that correspond to maximum yield can be used to look up a solvent with the closest matching HSP. Based on the results shown in the two ternary diagrams, it is clear that parameters such as HSP have potential for use as inputs to experiment designs. This sets the framework for future studies that use physicochemical properties as inputs to experiment designs, thus studying the chemistry directly and not just the effect of reaction conditions.

5. Supporting Information

5.1. General information for all Supporting Information herein.

Materials. Commercially available reagents and solvents were used without further purification unless otherwise stated. *m*-CPBA was purchased from Sigma-Aldrich, dried, and assayed by iodometric titration before use according to literature procedures.⁴⁴ Starting materials for Figure 51⁴⁵, **14-TFA**⁴⁶, **52**⁴⁷ were prepared to previously reported procedures. 4'-iodo-[1,1'-biphenyl]-4-carbonitrile⁴⁸ and 2-(4-iodobenzyl)isoindoline-1,3-dione⁴⁹ was prepared according to literature procedure. All other materials were prepared as described in detail below.

Methods. Reactions were performed in borosilicate, Teflon-lined, screw-cap vials or round bottom flasks without exclusion of ambient air or moisture, unless otherwise stated. Reactions heated above room temperature were done in an aluminum block or oil bath, heated externally by a digitally controlled hotplate/stirrer. Solvents were removed by rotary evaporation.

Proton (¹H), carbon (¹³C) and fluorine (¹⁹F) nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AVANCE III spectrometer with a 9.4 T magnet, 5 mm BBO probe and operating at 400.13 MHz. If indicated, a Bruker Avance III with 5mm PATXI probe, operating at 599.88 MHz, was used. Each spectrum shown below was recorded at 298 K in DMSO-*d*₆ or CDCl₃. Chemical shifts in proton and carbon spectra are referenced to the tetramethylsilane (TMS) signal. Multiplicity is given as follows: s = singlet, d = doublet, t = triplet, q = quartet, dq = doublet of quartets, m = multiplet. NMR yields were

determined from ^1H NMR spectra of crude reaction products using anhydrous dimethylformamide (ACROS, 99.8%) as an internal standard.

Thin layer chromatography (TLC) was performed using plastic-backed silica gel plates (Silicagel 60 Å, F-254) and visualization was accomplished using ultraviolet light (254 nm). Flash column chromatography was performed on SiliCycle silica gel, (*SiliaFlash*, P60, 40-63 μm , 60Å).

FT-IR spectroscopy was performed on a ThermoScientific, Nicolet iS5 spectrometer in transmission mode, using OMNIC software, version 9.2.98. Samples were dissolved in dichloromethane, applied to a salt plate and the solvent allowed to evaporate.

Molecular weight determinations were made on a ThermoElectron, LTQ-Orbitrap, high resolution mass spectrometer with dedicated Accela HPLC system and electrospray ionization (ESI). High resolution MS of compound **S1** was obtained from the Oregon State University, Mass Spectrometry Facility and used a Water Synapt G2 coupled to Agilent APGC. Low resolution molecular weight determinations were made using an Agilent 5973 GC-MS system, using EI.

Melting point (mp) measurements were recorded using Mel-Temp instruments and reported as uncorrected values. Melting point samples were taken from the product produced to the following procedures without further purification.

5.2. Supporting Information for Chapter 2

5.2.1. General procedure for the synthesis of aryl(TMB)iodonium tosylates

Aryl iodide (5 mmol, 1 equiv.) and acetonitrile (5 mL) were added to a 50 mL round-bottom flask, equipped with a magnetic stir bar. Toluenesulfonic acid (5.05 mmol, 1.01 equiv.) was added in one portion, followed by one portion of *m*-CPBA (5.05 mmol, 1.01 equiv.). After attaching a reflux condenser, the reaction was lowered into an oil bath set to 77 °C and stirred vigorously. After 30 minutes, the reflux condenser is removed in order to add (5.05 mmol, 1.01 equiv) 1,3,5-trimethoxybenzene (TMB) 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 crude residue was triturated with diethyl ether. The precipitate was isolated by vacuum filtration and washed by slurry filtration with diethyl ether (3 × 20 mL). After drying under high vacuum the diaryliodonium salt was obtained in analytically pure form.

5.2.2. Characterization data for aryl(TMB)iodonium tosylates

Compound **11** – Prepared according to the general procedure above on 10 mmol scale and obtained in 96% yield (5.353 g) as an off-white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.83 – 7.75 (m, 2H), 7.52 – 7.45 (m, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.45 (s, 2H), 3.94 (s, 6H), 3.86 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.0, 159.3, 145.5, 141.8, 137.6, 134.3, 132.0, 128.0, 125.4, 112.4, 91.9, 87.2, 57.2, 56.1, 20.7 (one carbon signal unaccounted for due to overlapping methyl signals). FT-IR: 3023, 1642, 1585, 1458, 1414, 1207, 1185, 1035, 816 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₈H₁₈IO₃⁺ [M - OTs]⁺: 385.0295; Observed 385.0265. Mp decomposed 168 °C.

Compound **12** – Prepared according to the general procedure above with the exception of running both stages at room temperature. The 5 mmol scale reaction yielded 85% (2.621 g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.92 – 7.87 (m, 2H), 7.54 – 7.44 (m, 4H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.45 (s, 2H), 4.70 (s, 2H), 3.94 (s, 6H), 3.86 (s, 3H), 2.28 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.0, 159.2, 145.4, 141.5, 137.6, 134.6, 132.0, 128.0, 125.4, 115.8, 91.9, 87.7, 57.2, 56.1, 32.7, 20.7. FT-IR: 3090, 3033, 2978, 2945, 2844, 1643, 1583, 1413, 1186, 815, 682, 565 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₆H₁₇BrIO₃⁺ [M - OTs]⁺: 462.9400 Observed 462.9383. Mp decomposed 157 °C

Compound **13** – Prepared according to the general procedure above on 5 mmol scale with the following deviations: i) Stage 1 was run at ambient temperature, ii) stage 2 was run at ambient temperature, iii) Stage 2 reaction progress was assessed by TLC and Stage 2 reaction time was one hour. The product was isolated in 87% yield (2.49 g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.45 (s, 2H), 5.50 – 5.25 (br. s, 1H), 4.52 (s, 2H), 3.94 (s, 6H), 3.85 (s, 3H), 2.27 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.0, 159.2, 146.5, 145.4, 137.6, 134.1, 129.1, 128.0, 125.4, 113.6, 91.9, 87.2, 61.9, 57.2, 56.0, 20.7. FT-IR: 3410, 3080, 3033, 2995, 2918, 2852, 1644, 1572, 1443, 1412, 1340, 1040, 821 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₆H₁₈IO₄⁺ [M - OTs]⁺: 401.0244; Observed 401.0219. Mp 184-186 °C

Compound **14** – Prepared according to the general procedure above on 10 mmol scale and obtained in 93% yield (5.570g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.87 – 7.80 (m, 2H), 7.53 – 7.44 (m, 4H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.47 (s, 2H), 3.96 (s, 6H), 3.87 (s, 3H), 2.28 (s, 3H), 1.23 (s, 9H). ¹³C NMR (101 MHz, DMSO) δ 166.0, 159.3, 154.5, 145.6, 137.5, 134.1, 128.5, 128.0, 125.4, 112.6, 91.9, 87.0, 57.3, 56.1, 34.7, 30.6, 20.7. FT-IR: 3071, 2953, 2867, 2840, 1036, 1634, 1583, 1467, 1412, 1208, 1125, 815 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₉H₂₄IO₃⁺ [M - OTs]⁺: 427.0765; Observed 427.0746. Mp 190-192 °C

Compound **15** – Prepared according to the general procedure above on 5 mmol scale with the following deviations: i) in Stage 2, mesitylene was added in place of TMB, ii) Stage 2 reaction time was six hours and reaction progress was monitored by TLC. The product was obtained in 84% yield (2.303g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.19 (s, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 2.60 (s, 6H), 2.28 (s, 6H), 1.23 (s, 9H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 154.6, 145.4, 142.8, 141.4, 137.5, 134.1, 129.6, 128.8, 127.9, 125.4, 122.6, 111.0, 34.7, 30.6, 26.2, 20.7, 20.4. FT-IR: 3090, 3062, 3039, 2965, 2871, 2843, 1640, 1393, 1214, 1187, 816 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₉H₂₄I⁺ [M - OTs]⁺: 379.0917; Observed 379.0895. Mp decomposed 175 °C

Compound **16** – Prepared according to the general procedure above on 5 mmol scale with

the following deviation: i) in Stage 2, thiophene was used in place of TMB. The product was obtained in 71% yield (1.186g) as a white powder. ^1H NMR (400 MHz, DMSO- d_6) δ 8.20 – 8.13 (m, 2H), 8.11 – 8.05 (m, 1H), 7.99 – 7.92 (m, 1H), 7.57 – 7.44 (m, 4H), 7.17 – 7.07 (m, 3H), 2.28 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 154.9, 145.1, 140.2, 137.8, 137.0, 134.3, 129.4, 128.6, 128.0, 125.4, 115.8, 100.7, 34.7, 30.6, 20.7. FT-IR: 3094, 3059, 2962, 2927, 2867, 1652, 1392, 1214, 1188, 1032, 816 cm^{-1} . HRMS (ESI $^+$): Calculated for $\text{C}_{14}\text{H}_{16}\text{IS}^+ [\text{M} - \text{OTs}]^+$: 343.0012; Observed 342.9998. Mp 125-136 $^\circ\text{C}$

Compound **17** – Prepared according to the general procedure above on 5 mmol scale with

the following three deviations: i) in Stage 2, anisole was used in place of TMB, ii) Stage 2 reaction time was one hour and reaction progress was assessed by TLC; iii) the solvent was not removed from the crude reaction and instead immediately triturated with ethyl ether. The product was filtered and washed according to the general procedure and

obtained in 84% yield (2.250g) as a white powder ^1H NMR (400 MHz, DMSO- d_6) δ 8.24 – 8.17 (m, 2H), 8.16 – 8.10 (m, 2H), 7.56 – 7.51 (m, 2H), 7.50 – 7.45 (m, 2H), 7.12 (d, J = 7.9 Hz, 2H), 7.06 – 7.01 (m, 2H), 3.77 (s, 3H), 2.28 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 161.7, 154.7, 145.5, 137.6, 137.2, 134.6, 128.5, 128.0, 125.5, 117.2, 113.5, 105.4, 55.6, 34.7, 30.6, 20.7. FT-IR: 3091, 3061, 3050, 2963, 2902, 2869, 2840, 1395, 1254, 1184, 817 cm^{-1} . HRMS (ESI $^+$): Calculated for $\text{C}_{17}\text{H}_{20}\text{IO}^+ [\text{M} - \text{OTs}]^+$: 367.0553; Observed 367.0528 Mp 177-180 $^\circ\text{C}$

Compound **18** – Prepared according to the general procedure above on 5 mmol scale and

obtained in 93% yield (2.520 g) as a white powder. ^1H NMR (400 MHz, DMSO- d_6) δ 7.92 (d, J = 7.5 Hz, 2H), 7.64 – 7.38 (m, 5H), 7.10 (d, J = 7.5 Hz, 2H), 6.47 (s, 2H), 3.94 (s, 6H), 3.86 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 166.1, 159.3, 145.5, 137.6, 134.2, 131.4(2), 131.3(6), 128.0, 125.4, 116.0, 92.0, 87.0, 57.2, 56.1, 20.7. FT-IR: 3041, 2949, 2842, 2842, 1721, 1646, 1582, 1457, 1343, 1282, 1186, 1034, 816 cm^{-1} . HRMS (ESI $^+$): Calculated for $\text{C}_{15}\text{H}_{16}\text{IO}_3^+ [\text{M} - \text{OTs}]^+$: 371.0139; Observed 371.0121. Mp decomposed 167 $^\circ\text{C}$.

Compound **19** – Prepared according to the general procedure above on 10 mmol scale

and obtained in 90% yield (5.533g) as an off-white powder. ^1H NMR (400 MHz, DMSO- d_6) δ 7.99 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.6 Hz, 2H), 7.70 – 7.62 (m, 2H), 7.56 – 7.32 (m, 5H), 7.10 (d, J = 7.9 Hz, 2H), 6.49 (s, 2H), 3.97 (s, 6H), 3.88 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 166.1, 159.3, 145.6, 143.1, 138.1, 137.5, 134.8, 129.5, 129.0, 128.5, 128.0, 126.9, 125.4, 114.5, 92.0, 87.0, 57.3, 56.1, 20.7. FT-IR: 3089, 3068, 2967, 2943, 2878, 2839, 1646, 1586, 1468, 1339, 1209, 1033, 816, 765, 684

cm⁻¹. HRMS (ESI⁺): Calculated for C₂₁H₂₀IO₃⁺ [M - OTs]⁺: 447.0452; Observed 447.0431. Mp 162-164 °C

Compound **20** – Prepared according to the general procedure above on 5 mmol scale and

obtained in 93% yield (2.52 g) as a pale yellow powder. ¹H NMR (400 MHz, DMSO) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.49 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 3.86 (s, 3H), 2.28 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 166.3, 165.1, 159.4, 145.5, 137.6, 134.5, 132.0, 131.7, 128.0, 125.4, 121.0, 92.1, 86.7, 57.3, 56.1, 52.6, 20.7. FT-

IR: 3041, 2949, 2842, 1721, 1646, 1582, 1457, 1343, 1282, 1186, 1034, 816 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₇H₁₈IO₅⁺ [M - OTs]⁺: 429.0193; Observed 429.0167. Mp 169-175 °C.

Compound **21** – Prepared according to the general procedure above on 30 mmol scale

and obtained in 90% yield (16.527 g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.13 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.52 – 7.43 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.50 (s, 2H), 3.96 (s, 6H), 3.89 (s, 3H), 2.29 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.4, 159.4, 145.5, 137.6, 135.0, 131.3 (q, *J*_{C-F} = 32.4 Hz), 128.1 (q,

*J*_{C-F} = 3.5 Hz), 128.0, 125.4, 123.4 (q, *J*_{C-F} = 272.8 Hz), 120.3 (br. s), 92.1, 87.0, 57.3, 56.2, 20.7. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -61.6. FT-IR: 3090, 2979, 2847, 1467, 1644, 1584, 2949, 1414, 1210, 1182, 1034, 816 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₆H₁₅F₃IO₃⁺ [M - OTs]⁺: 439.0013; Observed 438.9989. Mp 167-170 °C.

Compound **22** – Prepared according to the general procedure above on 1 mmol scale and

obtained in 75% yield (0.428 g) as a pink powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 (dd (appears as triplet), *J* = 1.5 Hz, 1H), 8.22 – 8.17 (m, 1H), 8.10 – 8.03 (m, 1H), 7.65 (dd (appears as triplet), *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.48 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 2.29 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.3, 159.3, 145.4, 138.8, 137.6, 137.3, 135.2, 132.2, 128.0, 125.4, 116.9, 116.1, 113.6, 92.0,

87.1, 57.3, 56.1, 20.7. FT-IR: 3088, 2946, 2846, 2232, 1647, 1583, 1468, 1413, 1229, 1187, 1035, 785 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₅H₁₅INO₃⁺ [M - OTs]⁺: 396.0091; Observed 396.0076. Mp 175-178 °C.

Compound **23** – Prepared according to the general procedure above on 5 mmol scale with

the following exceptions: i) the reaction was removed from the heat bath for 10 minutes before starting Stage 2, ii) Stage 2 was run for 10 minutes at room temperature. The product was obtained in 81% yield (2.478 g) as a light pink powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 (d, *J* = 1.8 Hz, 2H), 7.83 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.50 (s, 2H), 3.97 (s, 6H), 3.89 (s, 3H), 2.29 (s, 3H). ¹³C

NMR (101 MHz, DMSO-*d*₆) δ 166.5, 159.4, 145.3, 137.7, 135.5, 132.1, 131.4, 128.0, 125.4, 116.6, 92.1, 87.3, 57.3, 56.2, 20.7. FT-IR: 3067, 3037, 2980, 2959, 2939, 2839, 1646, 1587,

1409, 1211, 1188, 816, 795, 657, 563 cm^{-1} . HRMS (ESI⁺) Calculated for $\text{C}_{15}\text{H}_{14}\text{Cl}_2\text{IO}_3^+$ [M - OTs]⁺: 438.9359; Observed 438.9342. Mp 193-196 °C.

Compound **24** – Prepared according to the general procedure above on 5 mmol scale and

obtained in 85% yield (2.750 g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 (s, 1H), 7.95 (s, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.47 (s, 2H), 3.95 (s, 6H), 3.86 (s, 3H), 2.27 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 166.4, 159.5, 145.2, 140.4, 138.0, 135.9 – 135.5 (m), 131.1, 130.6 – 130.3 (m), 129.1 (q, *J*_{C-F} = 33.1 Hz), 128.2, 125.5, 122.7 (q, *J*_{C-F} = 273.1 Hz), 120.1, 92.2, 87.6, 57.1, 56.2, 20.8. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -61.4. FT-IR: 3032, 2942, 2847, 1643, 1590, 1457, 1407, 1212, 1072, 1037 cm^{-1} . HRMS (ESI⁺) Calculated for $\text{C}_{16}\text{H}_{14}\text{ClF}_3\text{IO}_3^+$ [M - OTs]⁺: 472.9623; Observed 472.9594. Mp 168-170 °C.

Compound **25** – Prepared according to the general procedure above on 5 mmol scale and

obtained in 89% yield (2.532 g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.55 (s, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.21 (s, 1H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.46 (s, 2H), 3.95 (s, 6H), 3.86 (s, 3H), 2.32 – 2.22 (m, 9H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.0, 159.3, 145.6, 141.0, 137.5, 132.9, 131.6, 128.0, 125.4, 115.6, 92.0, 86.7, 57.2, 56.1, 20.7, 20.5. FT-IR: 3086, 3054, 3010, 2976, 2945, 2916, 2840, 1582, 1413, 1207, 1189, 1034, 815 cm^{-1} . HRMS (ESI⁺) Calculated for $\text{C}_{17}\text{H}_{20}\text{IO}_3^+$ [M - OTs]⁺: 399.0452; Observed 399.0434. Mp 166-168 °C.

Compound **27** – Prepared according to the general procedure above on 5 mmol scale and

obtained in 90% yield (3.164 g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 – 7.79 (m, 6H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.44 (s, 2H), 4.81 (s, 2H), 3.94 (s, 6H), 3.85 (s, 3H), 2.27 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 167.6, 166.1, 159.3, 145.5, 140.3, 137.6, 134.5, 131.4, 130.2, 129.1, 128.0, 125.4, 123.2, 114.6, 91.9, 87.1, 57.2, 56.0, 40.2, 20.7. FT-IR: 3021, 2968, 2842, 1700, 1643, 1392, 1229, 1184, 788, 729 cm^{-1} . HRMS (ESI⁺): Calculated for $\text{C}_{24}\text{H}_{21}\text{INO}_5^+$ [M - OTs]⁺: 530.0459; Observed 530.0438. Mp decomposed 172 °C.

Compound precursor for **27** – Prepared according to the literature procedure⁵⁰ on 10 mmol scale and obtained in 51% yield (2.349 g) as a white powder. ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, *J* = 2.2 Hz, 1H), 7.52 (dd, *J* = 17.0, 2.3 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.02 (d (appears as a triplet), *J* = 1.8 Hz, 1H), 6.90 (d, *J* = 1.8 Hz, 2H), 5.01 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 159.1, 138.5, 137.5, 137.3, 135.5, 134.2, 121.9, 121.9, 113.9, 92.7, 69.0. FTIR: 3053, 1573, 1265 cm⁻¹. HRMS (AP⁺) Calculated for [C₁₃H₈BrCl₂IO]⁺: 455.8180; Observed: 455.8203; R_f: 0.20 in 100% hexane.

Compound **28** – Prepared according to the general procedure above on 20 mmol scale and obtained in 90% yield (11.258 g) as a white powder. ¹H NMR (400 MHz, DMSO) δ 8.36 (dd, *J* = 6.6, 1.8 Hz, 1H), 8.27 – 8.18 (m, 1H), 7.66 – 7.56 (m, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.50 (s, 2H), 3.96 (s, 6H), 3.89 (s, 3H), 2.29 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.4, 160.3 (d, *J*_{C-F} = 259.6 Hz), 159.3, 145.4, 141.5 (d, *J*_{C-F} = 9.9 Hz), 137.7, 133.3 (d, *J*_{C-F} = 4.6 Hz), 128.0, 125.4, 121.3(5) (q, *J*_{C-F} = 540.4, 267.6 Hz), 120.7 (d, *J*_{C-F} = 21.8 Hz), 118.8 (dq, *J*_{C-F} = 33.3, 13.3 Hz), 110.5 (d, *J*_{C-F} = 3.7 Hz), 92.1, 87.5, 57.3, 56.2, 20.7. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -60.4 (d, *J* = 12.5 Hz), -110.5 (q, *J* = 12.5 Hz). FT-IR: 3091, 3063, 3034, 2947, 2886, 2886, 2846, 1469, 1345, 1229, 1210, 1033, 816, 682, 665, 566 cm⁻¹. HRMS (ESI⁺) Calculated for C₁₆H₁₄F₄IO₃⁺ [M - OTs]⁺: 456.9918; Observed 456.9895. Mp 133-136 °C.

Compound **29** – Prepared according to the general procedure above on 5 mmol scale and obtained in 93% yield (2.586 g) as a white powder. ¹H NMR (400 MHz, DMSO) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.28 (t, *J* = 9.1 Hz, 1H), 7.15 – 7.06 (m, 3H), 6.93 – 6.85 (m, 1H), 6.46 (s, 2H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.95 (s, 6H), 3.86 (s, 3H), 3.04 (t, *J* = 6.4 Hz, 2H), 2.28 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.0, 159.3, 154.8 (d, *J* = 2.1 Hz), 151.7 (d, *J* = 238.8 Hz), 145.6, 142.4, 137.5, 134.3, 132.1, 128.0, 125.4, 119.6 (d, *J* = 19.0 Hz), 117.1 (d, *J* = 22.3 Hz), 115.8, 114.9 (d, *J* = 6.9 Hz), 113.5, 92.0, 87.0, 68.3, 57.2, 56.1, 34.19, 20.7. ¹⁹F NMR (376 MHz, DMSO) δ -127.1. FT-IR: 3092, 3059, 2960, 2927, 2867, 1657, 1394, 1214, 1187, 816 cm⁻¹. HRMS (ESI⁺) Calculated for C₂₃H₂₂ClFIO₄⁺ [M - OTs]⁺: 543.0230; Observed 543.0206. Mp 128 - 130 °C.

Compound precursor for **29** – Prepared according to the literature procedure⁵⁰ on 10 mmol scale and obtained in 77% yield (2.915 g) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 7.64 – 7.56 (m, 2H), 7.04 – 7.02 (m, 3H), 6.91-6.89 (m, 1H), 6.74-6.70 (m, 1H), 4.09 (t, *J* = 6.7 Hz, 2H), 3.02 (t, *J* = 6.7 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 154.9 (d, *J*_{C-F} = 2.4 Hz), 152.7 (d, *J*_{C-F} = 241.3 Hz), 137.6, 137.5, 131.0, 121.0 (d, *J*_{C-F} = 19.1 Hz), 116.7 (d, *J*_{C-F} = 22.5 Hz), 116.2, 114.0 (d, *J*_{C-F} = 6.7 Hz), 91.9, 69.0, 35.1. ¹⁹F NMR (376 MHz, CDCl₃) δ -126.1. FTIR: 3024, 2253, 1499, 1202, 909

cm⁻¹. HRMS (EI) Calculated for C₁₄H₁₁ClFIO: 375.9527; Observed: 375.9516. R_f: 0.26 in 100% hexane.

Compound **30** – Prepared according to the general procedure above on 5 mmol scale and

obtained in 92% yield (2.871 g) as a white powder. ¹H NMR (400 MHz, DMSO) δ 7.98 (d, *J* = 2.1 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 1.7 Hz, 1H), 7.14 – 7.06 (m, 4H), 6.45 (s, 2H), 5.19 (s, 2H), 3.92 (s, 6H), 3.88 (s, 3H), 2.28 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.2, 159.2, 159.1, 145.5, 138.4, 137.6,

135.5, 135.4, 134.6, 134.4, 128.0, 126.1, 125.4, 121.0, 114.7, 114.0, 91.9, 87.1, 69.0, 57.2, 56.1, 20.7. FT-IR: 3033, 2945, 2845, 1640, 1580, 1413, 1212, 1186, 815, 680 cm⁻¹. HRMS (ESI⁺) Calculated for C₂₂H₁₉BrCl₂IO₄⁺ [M - OTs]⁺: 622.8883; Observed 622.8856. Mp decomposed 180 °C.

Compound **31** – Prepared according to the general procedure above on 10 mmol scale

and obtained in 95% yield (5.715 g) as a pale yellow powder. ¹H NMR (400 MHz, DMSO) δ 8.58 (dd, *J* = 9.1, 4.7 Hz, 1H), 7.83 – 7.71 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.15 – 7.06 (m, 3H), 6.62 (s, 2H), 3.97 (s, 3H), 3.93 (s, 6H), 2.29 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 167.8, 165.7 (d, *J*_{C-F} = 262.8 Hz), 160.3, 145.4, 143.0 (d, *J*_{C-F} = 2.9 Hz), 137.7, 130.2 (d, *J*_{C-F} = 10.2 Hz), 128.0, 125.4, 119.5 (d, *J*_{C-F} = 23.6 Hz), 118.9 (d, *J*_{C-F}

= 27.7 Hz), 110.8 (d, *J*_{C-F} = 7.8 Hz), 92.5, 84.6, 57.5, 56.4, 20.7. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -98.1. FT-IR: 3090, 2949, 2847, 2847, 1643, 1582, 1525, 1460, 1347, 1347, 1212, 1187, 1034, 869 cm⁻¹. HRMS (ESI⁺) Calculated for C₁₅H₁₄FINO₅⁺ [M - OTs]⁺: 433.9895; Observed 433.9876. Mp 173-174 °C.

Compound **32** – Prepared according to the general procedure above on 10 mmol scale

and obtained in 95% yield (5.715 g) as a white powder. ¹H NMR (400 MHz, DMSO) δ 8.50 (d, *J* = 1.8 Hz, 1H), 8.06 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.49 – 7.41 (m, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.48 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H), 2.51 (s, 3), 2.28 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.3, 159.3, 149.3, 145.5, 138.1, 137.6, 136.5, 135.4, 129.7, 128.0, 125.4, 112.5, 92.1, 87.3, 57.3, 56.1, 20.7, 19.3. FT-

IR: 3079, 2975, 2942, 2841, 1581, 1455, 1411, 1272, 1161, 1024 cm⁻¹. HRMS (ESI⁺) Calculated for C₁₆H₁₇INO₅⁺ [M - OTs]⁺: 430.0146; Observed 430.0116. Mp decomposed 113 °C.

Compound **33** – Prepared according to the general procedure above on 5 mmol scale and

obtained in 90% yield (2.656 g) as a pale yellow powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.27 – 8.11 (m, 4H), 7.50 – 7.43 (m, 2H), 7.14 – 7.05 (m, 2H), 6.50 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 2.28 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.4, 159.4, 149.0, 145.5, 137.6, 135.4, 128.0, 125.9, 125.4, 122.3, 92.1, 87.1, 57.3, 56.2, 20.7. FT-

IR: 3094, 3058, 3017, 2981, 2946, 2846, 1643, 1583, 1527, 1468, 1346, 1346, 1210, 1034, 848, 816 cm^{-1} . HRMS (ESI⁺): Calculated for $\text{C}_{15}\text{H}_{15}\text{INO}_3^+$ [M - OTs]⁺: 415.9989; Observed 415.9963. Mp 158-165 °C.

Compound **34** – Prepared according to the general procedure above on 1 mmol scale and

obtained in 85% yield (0.4933 g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.86 (d, *J* = 2.2 Hz, 1H), 8.38 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.47 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H), 2.29 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.3, 159.2, 153.5, 152.6, 145.3, 145.1, 137.7, 128.0, 127.4, 125.4, 113.8, 92.0, 87.2, 57.3, 56.1, 20.7. FT-IR: 3035, 2943, 2847, 1581, 1455, 1413, 1301, 1210, 1186, 1031, 815 cm^{-1} . HRMS (ESI⁺) Calculated for $\text{C}_{14}\text{H}_{14}\text{ClINO}_3^+$ [M - OTs]⁺: 405.9701; Observed 405.9684. Mp decomposed 165 °C

Compound **35** – Prepared according to the general procedure above on 5 mmol scale and

obtained in 92% yield (2.931g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.06 – 7.78 (m, 8H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.49 (s, 2H), 3.97 (s, 6H), 3.88 (s, 3H), 2.28 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 167.6, 166.1, 159.2, 145.6, 140.3, 137.5, 134.5(3), 134.5(0), 134.2, 131.4, 130.1, 127.9, 125.4, 123.2, 114.4, 91.9, 87.0, 57.2, 56.0, 20.7. FT-IR: 3089, 3056, 2980, 2946, 2839, 2227, 1645, 1582, 1413, 1164, 815. HRMS (ESI⁺): Calculated for $\text{C}_{22}\text{H}_{19}\text{INO}_3^+$ [M - OTs]⁺: 472.0404; Observed 472.0375. Mp 174-179 °C.

Compound **36** – Prepared according to the general procedure above on 1 mmol scale and

obtained in 67% yield (0.397g) as a white powder. ¹H NMR (400 MHz, DMSO) δ 7.98 – 7.96 (m, 1H), 7.76 – 7.72 (m, 1H), 7.50 – 7.39 (m, 3H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.47 (s, 2H), 3.95 (s, 6H), 3.87 (s, 3H), 2.33 (s, 3H), 2.28 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.2, 159.3, 145.5, 139.7, 137.6, 134.8, 133.7, 133.6, 132.8, 128.0, 125.4, 112.8, 92.0, 87.2, 57.3, 56.1, 20.7, 19.4. FT-IR: 3093, 2945, 2845, 1649, 1582, 1467, 1414, 1186, 1211, 1033 cm^{-1} . HRMS (ESI⁺) Calculated for $\text{C}_{16}\text{H}_{17}\text{ClIO}_3^+$ [M - OTs]⁺: 418.9905; Observed 418.9877. Mp 176-178 °C.

Compound **37** – Prepared according to the general procedure above on 5 mmol scale and

obtained in 86% yield (2.395 g) a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 – 7.82 (m, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.40 (m, 4H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.48 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 2.28 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.3, 161.7 (d, *J*_{C-F} = 251.9 Hz), 159.4, 145.5, 137.7, 133.2 (d, *J*_{C-F} = 7.8 Hz), 130.3 (d, *J*_{C-F} = 3.2 Hz), 128.0, 125.4 121.2 (d, *J*_{C-F} = 24.6 Hz), 118.7 (d, *J*_{C-F} = 20.8 Hz), 115.6 (d, *J*_{C-F} = 7.4 Hz), 92.0, 87.2, 57.3, 56.1, 20.7. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -108.1. FT-IR: 3086,

2945, 2845, 1650, 1581, 1468, 1414, 1344, 1209, 1035 cm^{-1} . HRMS (ESI⁺) Calculated for $\text{C}_{15}\text{H}_{15}\text{FIO}_3^+$ [M - OTs]⁺: 389.0044; Observed 389.0021. Mp 181-182 °C.

Compound **38** – Prepared according to the general procedure above on 5 mmol scale with

the following deviations: i) Stage 1 was run at ambient temperature, ii) stage 2 was run at ambient temperature, iii) Stage 2 reaction progress was assessed by TLC and Stage 2 reaction time was thirtyfive minutes. The product was obtained in 86% yield

(2.504 g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.45 (s, 2H), 4.68 (s, 1H), 3.94 (s, 6H), 3.85 (s, 3H), 3.58 (t, *J* = 6.6 Hz, 2H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.27 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.0, 159.3, 145.4, 143.9, 137.7, 134.1, 132.0, 128.0, 125.4, 112.9, 91.9, 87.1, 61.4, 57.2, 56.1, 38.8, 20.7. FT-IR: 3424, 3083, 3030, 2948, 2906, 1640, 1577, 1339, 1218, 1177, 1033, 562 cm^{-1} . HRMS (ESI⁺): Calculated for $\text{C}_{17}\text{H}_{20}\text{IO}_4^+$ [M - OTs]⁺: 415.0401; Observed 415.0382. Mp 181-184 °C

Compound **39** – Prepared according to the general procedure above on 5 mmol scale and

obtained in 77% yield (2.251g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.46 (s, 2H), 3.95 (s, 6H), 3.86 (s, 3H), 2.90 (septet, *J* = 6.8 Hz, 1H), 2.28 (s, 3H), 1.16 (d, *J* = 6.9 Hz, 6H). ¹³C NMR (101 MHz, DMSO-*d*₆): δ 166.0, 159.3, 152.3,

145.7, 137.5, 134.4, 129.6, 127.9, 125.4, 112.6, 91.9, 87.0, 57.2, 56.1, 33.1, 23.4, 20.7. FT-IR: 3090, 3059, 3032, 2961, 2867, 2840, 1651, 1583, 1412, 1213, 1186, 815 cm^{-1} . HRMS (ESI⁺): Calculated for $\text{C}_{18}\text{H}_{22}\text{IO}_3^+$ [M - OTs]⁺: 413.0608; Observed 413.0587. Mp 149-152 °C

5.2.3. General procedure for anion exchange of aryl(TMB)iodonium tosylates

Aryl(TMB)iodonium tosylate (~ 1 g, 1 equiv) is added to 50 mL boiling water. If the iodonium salt does not dissolve after boiling for 1-2 minutes, then methanol is added portion wise until the material is dissolved or the solution has homogenous appearance. While still hot, a salt containing the target anion is added in excess. The exact amount required depends on the exchange salt and the iodonium salt and an excess of 10 or more equivalents is recommended. The resulting solution is allowed to naturally cool to ambient temperature, before chilling further in an ice-bath. The mixture is suction filtered and the filter cake washed by slurry filtration with water (3 x 30 mL). The cake is dried under suction for 10 – 20 min and then washed by slurry filtration with ethyl ether (3x30mL). The sample is finally dried under high vacuum to remove residual solvent. If iodonium salt is suspected to remain in the aqueous filtrate then it may be extracted with a suitable solvent such as dichloromethane or ethyl acetate.

5.2.4. Characterization data for anion exchanged aryl(TMB)iodonium salts

Compound **19-Br** – Prepared according to the general anion exchange procedure above on 2.5 mmol scale, using potassium bromide (20 equiv., 50 mmol, 6.00 g) and obtained in 96% yield (1.28 g) as an off-off-white to light brown powder. ^1H NMR (400 MHz, DMSO- d_6) δ 8.00 – 7.95 (m, 2H), 7.71 (d, J = 8.6 Hz, 2H), 7.68 – 7.63 (m, 2H), 7.53 – 7.37 (m, 3H), 6.45 (s, 2H), 3.95 (s, 6H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 165.6, 159.2, 142.6, 138.3, 134.6, 129.3, 129.0, 128.3, 126.8, 116.5, 91.9, 89.9, 57.2, 56.0. FT-IR: 3072, 2944, 2836, 1636, 1587, 1467, 1338, 1232, 1158, 1033, 824 cm^{-1} . HRMS (ESI $^+$): Calculated for $\text{C}_{21}\text{H}_{20}\text{IO}_3^+$ [M - Br] $^+$: 447.0452; Observed 447.0423. Mp 193-195 $^{\circ}\text{C}$.

Compound **19-I** – Prepared according to the general anion exchange procedure above on 1 mmol scale, using potassium iodide (11 equiv., 10.6 mmol, 1.765 g) and obtained in 95% yield (0.544 g) as a off-white to light brown powder. ^1H NMR (400 MHz, DMSO- d_6) δ 8.03 – 7.95 (m, 2H), 7.77 – 7.70 (m, 2H), 7.70 – 7.62 (m, 2H), 7.54 – 7.39 (m, 3H), 6.47 (s, 2H), 3.97 (s, 6H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 165.8, 159.2, 142.8, 138.2, 134.8, 129.4, 129.0, 128.4, 126.8, 115.6, 92.0, 88.6, 57.3, 56.1. FT-IR: 3055, 3036, 2970, 2833, 1645, 1585, 1468, 1229, 1162, 1030, 808 cm^{-1} . HRMS (ESI $^+$): Calculated for $\text{C}_{21}\text{H}_{20}\text{IO}_3^+$ [M - I] $^+$: 447.0452; Observed 447.0422. Mp 164-165 $^{\circ}\text{C}$.

Compound **19-CF₃COO** – Prepared according to the general anion exchange procedure above on 1 mmol scale, using sodium trifluoroacetate (20 equiv., 20.2 mmol, 2.758 g) and obtained in 86% yield (0.481 g) as a off-white to light brown powder. ^1H NMR (400 MHz, DMSO- d_6) δ 7.99 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 7.4 Hz, 2H), 7.53 – 7.35 (m, 3H), 6.47 (s, 2H), 3.97 (s, 6H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 166.1, 159.5, 158.1 (q, $J_{\text{C-F}}$ = 30.9 Hz), 143.1, 138.2, 134.8, 129.5, 129.1, 128.5, 126.9, 117.2 (q, $J_{\text{C-F}}$ = 300.4 Hz), 114.9, 92.0, 87.4, 57.2, 56.0. ^{19}F NMR (376 MHz, DMSO- d_6) δ -73.4. FT-IR: 3061, 2946, 2843, 1681, 1583, 1414, 1230, 1160, 1026, 803 cm^{-1} . HRMS (ESI $^+$): Calculated for $\text{C}_{21}\text{H}_{20}\text{IO}_3^+$ [M - CF₃COO] $^+$: 447.0452; Observed 447.0431. Mp 175-177 $^{\circ}\text{C}$.

Compound **19-OTf** – Prepared according to the general anion exchange procedure above on 2 mmol scale with sodium triflate (20 equiv., 40.6 mmol, 6.99g) and obtained in 90% yield (1.094g) as a off-white to light brown powder. ^1H NMR (400 MHz, DMSO- d_6) δ 8.01 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.59 – 7.38 (m, 3H), 6.50 (s, 2H), 3.99 (s, 6H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 166.2, 159.4, 143.2, 138.1, 134.9, 129.6, 129.1, 128.5, 126.9, 120.7 (q, J = 322.3 Hz), 114.5, 92.0, 87.0, 57.3, 56.1. ^{19}F NMR (376 MHz, DMSO) δ -77.7. FT-IR: 3090, 3063, 2944, 2883, 2846, 1578, 1457, 1415, 1259, 1162, 1027, 815 cm^{-1} . HRMS (ESI $^+$): Calculated for $\text{C}_{21}\text{H}_{20}\text{IO}_3^+$ [M - OTf] $^+$: 447.0452; Observed 447.0471. Mp decomposed 93 $^{\circ}\text{C}$.

Compound **19-PF₆** – Prepared according to the general anion exchange procedure above on 1 mmol scale with potassium hexafluorophosphate (20.8 equiv., 20.8 mmol, 3.821 g) and obtained in 90% yield (0.556 g) as a off-white to light brown powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04 (d, *J* = 7.9 Hz, 2H), 7.76 (d, *J* = 7.9 Hz, 2H), 7.67 (d, *J* = 7.1 Hz, 2H), 7.59 – 7.36 (m, 3H), 6.51 (s, 2H), 4.00 (s, 6H), 3.90 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.2, 159.4, 143.2, 138.2, 134.9, 129.6, 129.1, 128.5, 126.9, 114.5, 92.0, 87.0, 57.3, 56.1. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -70.1 (d, *J*_{F-P} = 711.5 Hz). FT-IR: 3109, 1636, 2949, 1583, 2848, 3065, 1473, 1415, 1231, 1163, 1065, 843 cm⁻¹. HRMS (ESI⁺): Calculated for C₂₁H₂₀IO₃⁺ [M – PF₆]⁺: 447.0452; Observed 447.0425. Mp decomposed 127 °C.

Compound **19-BF₄** – Prepared according to the general anion exchange procedure above on 1 mmol scale, using sodium tetrafluoroborate (104 equiv, 104 mmol, 11.438 g) and obtained in 96% yield (0.532 g) as a off-white to light brown powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 2H), 7.53 – 7.38 (m, 3H), 6.49 (s, 2H), 3.97 (s, 6H), 3.88 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.2, 159.4, 143.2, 138.1, 134.9, 129.6, 129.1, 128.6, 126.9, 114.5, 92.0, 87.0, 57.3, 56.1. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -148.3. FT-IR: 3088, 3061, 2945, 2845, 1625, 1582, 1472, 1413, 1230, 1034, 817 cm⁻¹. HRMS (ESI⁺): Calculated for C₂₁H₂₀IO₃⁺ [M – BF₄]⁺: 447.0452; Observed 447.0427. Mp 160-162 °C.

Compound **28-PF₆** – Prepared according to the general procedure above on 1 mmol scale and obtained in 61% yield (0.365 g) as a white powder. ¹H NMR (600 MHz, DMSO) δ 8.39 – 8.35 (m, 1H), 8.26 – 8.18 (m, 1H), 7.68 – 7.54 (m, 1H), 6.49 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 166.7, 160.6 (dd, *J* = 260.1, 1.8 Hz), 159.6, 141.7 (d, *J*_{C-F} = 9.6 Hz), 133.6, (d, *J*_{C-F} = 3.9 Hz), 121.54 (q, *J* = 273.1 Hz), 120.9 (d, *J* = 21.8 Hz), 119.2 (dq, *J* = 33.2, 13.2 Hz), 110.5 (d, *J* = 3.7 Hz), 92.2, 87.5, 57.4, 56.2. ¹⁹F NMR (376 MHz, DMSO) δ -60.6 (d, *J* = 12.5 Hz), -70.2 (d, *J*_{P-F} = 711.3 Hz), -110.3 (q, *J* = 12.5 Hz). FT-IR: 3116, 3064, 2952, 2952, 2848, 1414, 1311, 1163, 845 cm⁻¹. HRMS (ESI⁺) Calculated for C₁₆H₁₄F₄IO₃⁺ [M – PF₆]⁺: 456.9889; Observed 456.9895. Mp decomposed 126 °C.

Compound **35-Br** – Prepared according to the general anion exchange procedure above on 1.9 mmol scale, using (19 equiv., 36 mmol, 4.5 g) and obtained in 91% yield (1.733g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.11 – 7.69 (m, 8H), 6.45 (s, 2H), 3.96 (s, 6H), 3.87 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.6, 159.2, 142.8, 140.4, 134.6, 132.9, 129.6, 127.8, 118.7, 118.6, 110.9, 91.9, 90.9, 57.2, 56.0. FT-IR: 3089, 3056, 2980, 2946, 2839, 2227, 1645, 1582, 1413, 1164, 815 cm⁻¹. HRMS (ESI⁺) Calculated for C₂₂H₁₉INO₃⁺ [M - Br]⁺: 472.0404; Observed 472.0375. Mp 175-176 °C.

**5.2.5. Representative procedure for one-pot preparation of
aryl(TMB)iodonium bromides**

4-methyl-3-nitro iodobenzene (1.33 g, 5.1 mmol) and acetonitrile (5 mL) are added to a 250 mL round-bottom flask, equipped with a stir bar. Toluenesulfonic acid monohydrate (0.965 g, 5.1 mmol, 1.0 equiv.) is added in one portion, followed by one portion of pre-dried *m*-CPBA (1.09 g, 5.1 mmol, 1.0 equiv.). After attaching a reflux condenser, the reaction is lowered into a heat bath set to 77 °C and stirred vigorously. After 30 minutes, the reflux condenser is removed in order to add 1,3,5-trimethoxybenzene (0.858 g, 5.1 mmol, 1.0 equiv.) in one portion and stirring is continued at 77 °C for 5 minutes. The reaction is removed from heat and 100 mL of water are added. The mixture is brought to near boiling until dissolved and 6.0 g of KBr are added. After stirring for 2 minutes the solution is removed from heat and allowed to cool naturally, before chilling further by briefly swirling in an ice-water bath. The mixture is suction filtered and the filter cake washed by slurry filtration with water (3 x 30 mL). The cake is dried under suction for 10 – 20 min and then washed by slurry filtration with ethyl ether (3x30mL). The sample is finally dried under high vacuum to remove trace solvent. If iodonium salt is suspected to remain in the aqueous filtrate then it may be extracted with a suitable solvent such as dichloromethane or ethyl acetate. After drying under high vacuum, the diaryliodonium salt **23-Br** was obtained in 83% yield (2.15 g, 4.2 mmol) as a white powder.

5.2.6. Characterization data of aryl(TMB)iodonium bromides

Compound **32-Br** – Prepared according to the representative one-pot preparation of iodonium bromides above on 5 mmol scale in 82% yield (2.112g), as a pale yellow powder. ^1H NMR (400 MHz, DMSO- d_6) δ 8.51 (d, J = 1.7 Hz, 1H), 8.06 (dd, J = 8.2, 1.8 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 6.44 (s, 2H), 3.95 (s, 6H), 3.87 (s, 3H), 2.51 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 165.7, 159.1, 149.1, 138.0, 135.8, 135.0, 129.4, 116.2, 91.9, 91.8, 57.2, 56.0, 19.3. FT-IR: 3079, 2975, 2942, 2841, 1581, 1524, 1455, 1411, 1342, 1272, 1161, 1024, 815 cm^{-1} . HRMS (ESI $^+$) Calculated for $\text{C}_{16}\text{H}_{17}\text{INO}_5^+$ [M - Br] $^+$: 430.0146; Observed 430.0125. Mp 166-167 $^\circ\text{C}$.

Compound **32-Br** – Prepared according to the representative one-pot procedure for preparation of iodonium bromides above on 5 mmol scale in 74% yield (2.298 g), as an off-white powder. Ten equivalents, 7.497 g KBr were used for the exchange. ^1H NMR (400 MHz, DMSO- d_6) δ 8.83 (d, J = 2.2 Hz, 1H), 8.36 (dd, J = 8.5, 2.4 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 6.44 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 165.6, 159.0, 153.2, 151.8, 144.7, 127.0, 117.7, 92.1, 91.9, 57.2, 56.1. FT-IR: 3075, 3039, 2971, 2942, 2842, 1582, 1454, 1412, 1342, 1161, 817, 731 cm^{-1} . HRMS (ESI $^+$) Calculated for $\text{C}_{14}\text{H}_{14}\text{ClINO}_3^+$ [M - Br] $^+$: 405.9701; Observed 405.9684. Mp 161-163 $^\circ\text{C}$.

5.2.7. Preparation of compounds in Applications section

Compound **6** – Prepared according to literature procedure⁵⁰ on 1 mmol scale and obtained in 70% yield after purification (0.215g) as a white powder. The crude product was purified by column chromatography with silica gel and gradient elution (hexane, 1% ethyl ether, 2% ethyl ether). Mixed fractions were again chromatographed by the same procedure for a combined 70% of **33**. ^1H NMR (400 MHz, CDCl_3) δ 7.68 – 7.55 (m, 4H), 7.53 – 7.43 (m, 2H), 7.02 – 6.91 (m, 2H), 3.98 (t, J = 6.6 Hz, 2H), 1.88 – 1.70 (m, 2H), 1.52 – 1.21 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.9, 145.2, 132.6, 131.2, 128.3, 127.0, 119.1, 115.1, 110.0, 68.2, 31.9, 29.4, 29.2(9), 29.2(8), 26.1, 22.7, 14.2. The spectral data were consistent with that previously reported.⁵¹

Compound **40** – Prepared according to the literature procedure⁵² on 0.4 mmol scale and obtained in 55% yield (0.070 g) as white powder. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dt, *J* = 8.9, 2.0 Hz, 4H), 7.46 – 7.39 (m, 2H), 7.37 – 7.28 (m, 3H), 4.31 – 4.19 (m, 2H), 2.88 – 2.76 (m, 1H), 2.66 – 2.54 (m, 2H), 2.37 (ddd, *J* = 10.5, 6.9, 3.1 Hz, 1H), 2.09 – 1.94 (m, 1H), 1.93 – 1.72 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 206.6, 171.2, 140.6, 140.4, 135.8, 128.8, 128.2, 127.4, 127.1, 127.1, 66.2, 61.8, 40.9, 35.4, 27.7, 22.3, 14.0. FT-IR: 3054, 2985, 1713, 1265, 1133 cm⁻¹. HRMS (ESI⁺) Calculated for C₂₁H₂₃O₃⁺ [M+H]⁺: 323.1647; Observed: 323.1619. Mp 130.8-132.3 °C. R_f: 0.22 in 15% diethyl ether/hexane.

Compound **43** – Prepared according to the literature procedure⁵³ on 1.0 mmol scale and obtained in 78% (0.235 g) as white powder. ¹H NMR (400 MHz, CDCl₃) δ 8.03 – 7.95 (m, 4H), 7.73 – 7.67 (m, 2H), 7.60 – 7.36 (m, 8H). ¹³C NMR (101 MHz, CDCl₃) δ 146.2, 141.8, 140.1, 139.2, 133.2, 129.3, 129.1, 128.6, 128.2, 127.9, 127.6, 127.3. FT-IR: 1637, 1265, 1158 cm⁻¹. HRMS (ESI⁺) Calculated for C₁₈H₁₅O₂S⁺ [M+H]⁺: 295.0793; Observed: 295.0763; Mp 142.8-147 °C. R_f: 0.20 in 20% diethyl ether/hexane.

Compound **45** – Prepared according to the literature procedure⁵⁴ on 1.0 mmol scale and obtained in 80% (0.213 g) as white powder. ¹H NMR (400 MHz, CDCl₃) δ 7.58 – 7.52 (m, 4H), 7.45 – 7.39 (m, 2H), 7.35 – 7.30 (m, *J* = 5.9, 4.7, 2.3 Hz, 1H), 7.09 – 6.99 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 160.1, 157.7, 157.3, 152.8, 140.5, 136.2, 128.6 (d, *J*_{C-F} = 33.3 Hz), 127.0, 126.8, 120.6 (d, *J*_{C-F} = 8.2 Hz), 118.4, 116.3 (d, *J*_{C-F} = 23.2 Hz). ¹⁹F NMR (376 MHz, CDCl₃) δ -119.9. FT-IR: 1500, 1265, 1214 cm⁻¹. HRMS (EI⁺) Calculated for C₁₈H₁₃FO: 264.0950; Observed: 264.0942; Mp 76.2-78.2 °C. R_f: 0.6 in 100% hexane.

5.2.8. Qualitative Stability Study

Small samples of powdered iodonium salts were placed into scintillation vials and left adjacent to a window, exposed to ambient sunlight. A second sample of each salt was placed into a scintillation vial and wrapped with aluminum foil. The samples were periodically photographed. Any discoloration or change in consistency, appreciable upon visual inspection, was taken as evidence for decomposition. The photographs below are selected in order to illustrate the range of decomposition observed. See Figure below for a summary of results. Decomposition has not been observed when these compounds are stored in a freezer.

Figure 67. Qualitative stability study, light samples were exposed to ambient sunlight, dark samples were covered with aluminium foil.

5.2.9. NMR spectra for aryl(TMB)iodonium tosylates

Figure 68. ¹H NMR spectrum of 6 at 400 MHz in CDCl₃ at 298K

Figure 69. ¹³C NMR spectrum of 6 at 101 MHz in CDCl₃ at 298K.

Figure 70. ¹H NMR spectrum of 11 at 400 MHz in DMSO-*d*₆ at 298K

Figure 71. ¹³C NMR spectrum of 11 at 101 MHz in DMSO-*d*₆ at 298K

Figure 72. ¹H NMR spectrum of 12 at 400 MHz in DMSO-*d*₆ at 298K

Figure 73. ¹³C NMR spectrum of 12 at 101 MHz in DMSO-*d*₆ at 298K

Figure 74. ¹H NMR spectrum of 13 at 400 MHz in DMSO-*d*₆ at 298K

Figure 75. ¹³C NMR spectrum of 13 at 101 MHz in DMSO-*d*₆ at 298K

Figure 76. ¹H NMR spectrum of 14 at 400 MHz in DMSO-*d*₆ at 298K

Figure 77. ¹³C NMR spectrum of 14 at 101 MHz in DMSO-*d*₆ at 298K

Figure 80. ¹H NMR spectrum of 16 at 400 MHz in DMSO-*d*₆ at 298K

Figure 81. ¹³C NMR spectrum of 16 at 101 MHz in DMSO-*d*₆ at 298K

Figure 82. ¹H NMR spectrum of 17 at 400 MHz in DMSO-*d*₆ at 298K

Figure 83. ¹³C NMR spectrum of 17 at 101 MHz in DMSO-*d*₆ at 298K

Figure 84. ¹H NMR spectrum of 18 at 400 MHz in DMSO-*d*₆ at 298K

Figure 85. ¹³C NMR spectrum of 18 at 101 MHz in DMSO-*d*₆ at 298K

Figure 86. ¹H NMR spectrum of 19 at 400 MHz in DMSO-*d*₆ at 298K

Figure 87. ¹³C NMR spectrum of 19 at 101 MHz in DMSO-*d*₆ at 298K

Figure 88. ¹H NMR spectrum of 19-Br at 400 MHz in DMSO-*d*₆ at 298K

Figure 89. ¹³C NMR spectrum of 19-Br at 101 MHz in DMSO-*d*₆ at 298K

Figure 90. ¹H NMR spectrum of 19-I at 400 MHz in DMSO-*d*₆ at 298K

Figure 91. ¹³C NMR spectrum of 19-I at 101 MHz in DMSO-*d*₆ at 298K

Figure 92. ¹H NMR spectrum of 19-CF₃COO at 400 MHz in DMSO-*d*₆ at 298K

Figure 93. ¹³C NMR spectrum of 19-CF₃COO at 101 MHz in DMSO-*d*₆ at 298K

Figure 94. ^{19}F NMR spectrum of 19-CF₃COO at 376 MHz in DMSO-*d*₆ at 298K

Figure 95. ^1H NMR spectrum of 19-OTf at 400 MHz in DMSO-*d*₆ at 298K

Figure 96. ^{13}C NMR spectrum of 19-OTf at 101 MHz in $\text{DMSO}-d_6$ at 298K

Figure 97. ^{19}F NMR spectrum of 19-OTf at 376 MHz in $\text{DMSO}-d_6$ at 298K

Figure 98. ¹H NMR spectrum of 19-PF₆ at 400 MHz in DMSO-*d*₆ at 298K

Figure 99. ¹³C NMR spectrum of 19-PF₆ at 101 MHz in DMSO-*d*₆ at 298K

Figure 100. ¹⁹F NMR spectrum of 19-PF₆ at 376 MHz in DMSO-*d*₆ at 298K

Figure 101. ¹H NMR spectrum of 19-BF₄ at 400 MHz in DMSO-*d*₆ at 298K

Figure 102. ¹³C NMR spectrum of 19-BF₄ at 101 MHz in DMSO-*d*₆ at 298K

Figure 103. ¹⁹F NMR spectrum of 19-BF₄ at 376 MHz in DMSO-*d*₆ at 298K

Figure 104. ¹H NMR spectrum of 20 at 400 MHz in DMSO-*d*₆ at 298K

Figure 105. ¹³C NMR spectrum of 20 at 101 MHz in DMSO-*d*₆ at 298K

Figure 106. ¹H NMR spectrum of 21 at 400 MHz in DMSO-*d*₆ at 298K

Figure 107. ¹³C NMR spectrum of 21 at 101 MHz in DMSO-*d*₆ at 298K

Figure 108. ^{19}F NMR spectrum of 21 at 376 MHz in $\text{DMSO}-d_6$ at 298K

Figure 109. ^1H NMR spectrum of 22 at 400 MHz in $\text{DMSO}-d_6$ at 298K

Figure 110. ¹³C NMR spectrum of 22 at 101 MHz in DMSO-*d*₆ at 298K

Figure 111. ¹H NMR spectrum of 24 at 400 MHz in DMSO-*d*₆ at 298K

Figure 112. ¹³C NMR spectrum of 24 at 101 MHz in DMSO-*d*₆ at 298K

Figure 113. ¹⁹F NMR spectrum of 24 at 376 MHz in DMSO-*d*₆ at 298K

Figure 114. ¹H NMR spectrum of 25 at 400 MHz in DMSO-*d*₆ at 298K

Figure 115. ¹³C NMR spectrum of 25 at 101 MHz in DMSO-*d*₆ at 298K

Figure 116. ¹H NMR spectrum of 26 at 400 MHz in DMSO-*d*₆ at 298K

Figure 117. ¹³C NMR spectrum of 26 at 101 MHz in DMSO-*d*₆ at 298K

Figure 118. ¹H NMR spectrum of 27 at 400 MHz in DMSO-*d*₆ at 298K

Figure 119. ¹³C NMR spectrum of 27 at 101 MHz in DMSO-*d*₆ at 298K

Figure 120. ^1H NMR spectrum of 28 at 400 MHz in $\text{DMSO}-d_6$ at 298K

Figure 121. ^{13}C NMR spectrum of 28 at 101 MHz in $\text{DMSO}-d_6$ at 298K

Figure 122. ^{19}F NMR spectrum of 28 at 376 MHz in $\text{DMSO}-d_6$ at 298K

Figure 123. ^1H NMR spectrum of 28-PF₆ at 600 MHz in $\text{DMSO}-d_6$ at 298K

Figure 124. ¹³C NMR spectrum of 28-PF₆ at 101 MHz in DMSO-*d*₆ at 298K

Figure 125. ¹⁹F NMR spectrum of 28-PF₆ at 376 MHz in DMSO-*d*₆ at 298K

Figure 126. ¹H NMR spectrum of 29 at 400 MHz in DMSO-*d*₆ at 298K

Figure 127. ¹³C NMR spectrum of 29 at 101 MHz in DMSO-*d*₆ at 298K

Figure 128. ^{19}F NMR spectrum of 29 at 376 MHz in $\text{DMSO}-d_6$ at 298K

Figure 129. ^1H NMR spectrum of precursor for 29 at 400 MHz in CDCl_3 at 298K

Figure 130. ^{13}C NMR spectrum of precursor for 29 at 101 MHz in CDCl_3 at 298K

Figure 131. ^{19}F NMR spectrum of precursor for 29 at 376 MHz in CDCl_3 at 298K

Figure 132. ¹H NMR spectrum of 30 at 400 MHz in DMSO-*d*₆ at 298K

Figure 133. ¹³C NMR spectrum of 30 at 101 MHz in DMSO-*d*₆ at 298K

Figure 134. ¹H NMR spectrum of precursor for 30 at 400 MHz in CDCl₃ at 298K

Figure 135. ¹³C NMR spectrum of precursor for 30 at 101 MHz in CDCl₃ at 298K

Figure 136. ¹H NMR spectrum of 31 at 400 MHz in DMSO-*d*₆ at 298K

Figure 137. ¹³C NMR spectrum of 31 at 101 MHz in DMSO-*d*₆ at 298K

Figure 138. ¹⁹F NMR spectrum of 31 at 376 MHz in DMSO-*d*₆ at 298K

Figure 139. ¹H NMR spectrum of 32 at 400 MHz in DMSO-*d*₆ at 298K

Figure 140. ¹³C NMR spectrum of 32 at 101 MHz in DMSO-*d*₆ at 298K

Figure 141. ¹H NMR spectrum of 32-Br at 400 MHz in DMSO-*d*₆ at 298K

Figure 142. ¹³C NMR spectrum of 32-Br at 101 MHz in DMSO-*d*₆ at 298K

Figure 143. ¹H NMR spectrum of 33 at 400 MHz in DMSO-*d*₆ at 298K

Figure 144. ¹³C NMR spectrum of 33 at 101 MHz in DMSO-*d*₆ at 298K

Figure 145. ¹H NMR spectrum of 34 at 400 MHz in DMSO-*d*₆ at 298K

Figure 146. ¹³C NMR spectrum of 34 at 101 MHz in DMSO-*d*₆ at 298K

Figure 147. ¹H NMR spectrum of 34-Br at 400 MHz in DMSO-*d*₆ at 298K

Figure 152. ¹³C NMR spectrum of 35-Br at 101 MHz in DMSO-*d*₆ at 298K

Figure 153. ¹H NMR spectrum of 36 at 400 MHz in DMSO-*d*₆ at 298K

Figure 154. ¹³C NMR spectrum of 36 at 101 MHz in DMSO-*d*₆ at 298K

Figure 155. ¹H NMR spectrum of 37 at 400 MHz in DMSO-*d*₆ at 298K

Figure 156. ¹³C NMR spectrum of 37 at 101 MHz in DMSO-*d*₆ at 298K

Figure 157. ¹⁹F NMR spectrum of 37 at 376 MHz in DMSO-*d*₆ at 298K

Figure 158. ¹H NMR spectrum of 38 at 400 MHz in DMSO-*d*₆ at 298K

Figure 159. ¹³C NMR spectrum of 38 at 101 MHz in DMSO-*d*₆ at 298K

Figure 160. ¹H NMR spectrum of 39 at 400 MHz in DMSO-*d*₆ at 298K

Figure 161. ¹³C NMR spectrum of 39 at 101 MHz in DMSO-*d*₆ at 298K

Figure 162. ¹H NMR spectrum of 40 at 400 MHz in CDCl₃ at 298K

Figure 163. ¹³C NMR spectrum of 40 at 101 MHz in CDCl₃ at 298K

Figure 164. ¹H NMR spectrum of 43 at 400 MHz in CDCl₃ at 298K

Figure 165. ¹³C NMR spectrum of 43 at 101 MHz in CDCl₃ at 298K

Figure 166. ¹H NMR spectrum of 45 at 400 MHz in CDCl₃ at 298K

Figure 167. ¹³C NMR spectrum of 45 at 101 MHz in CDCl₃ at 298K

Figure 168. ^{19}F NMR spectrum of 45 at 376 MHz in CDCl_3 at 298K

5.3. Supporting Information for Chapter 3

5.3.1. Procedure A: Synthesis of aryl(TMP)iodonium tosylates²

Figure 169. Synthesis of aryl(TMP)iodonium tosylates

Aryl iodide (5 mmol, 1 equiv.) and acetonitrile (5 mL) were added to a 50 mL round-bottom flask, equipped with a magnetic stir bar. Toluenesulfonic acid (5.05 mmol, 1.01 equiv.) was added in one portion, followed by one portion of *m*-CPBA (5.05 mmol, 1.01 equiv.) at room temperature. After attaching a reflux condenser, the reaction was lowered into an oil bath set to 77 °C and stirred vigorously. After 30 minutes, the reflux condenser was removed in order to add (5.05 mmol, 1.01 equiv.) 1,3,5-trimethoxybenzene (TMB) 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 crude residue was triturated with diethyl ether. The precipitate was isolated by vacuum filtration and washed by slurry filtration with diethyl ether (3 × 20 mL). After drying under high vacuum the diaryliodonium salt was obtained in analytically pure form.

5.3.2. Procedure B: Anion exchange of aryl(TMP)iodonium tosylates²

Figure 170. Anion exchange of aryl(TMP)iodonium tosylates

Aryl(TMP)iodonium tosylate (~ 1 g, 1 equiv) is added to 50 mL boiling water. If the iodonium salt does not dissolve after boiling for 1-2 minutes, then methanol is added in small portions until the material is dissolved or the solution has homogenous appearance. While still hot, a salt containing the target anion is added in excess. The exact amount required depends on the exchange salt and the iodonium salt and an excess of 10 or more equivalents is recommended. The resulting solution is allowed to naturally cool to ambient temperature, before chilling further in an ice-bath. The precipitate is isolated by suction filtration and the filter cake washed by slurry filtration with water (3 x 30 mL). The cake is dried under suction for 10 – 20 min and then washed by slurry filtration with ethyl ether (3 x 30 mL). The sample is finally dried under high vacuum to remove residual solvent. If product is suspected in the aqueous wash then it may be recovered by extraction with dichloromethane or ethyl acetate.

5.3.3. Procedure C: Aryl(TMP)iodonium bromides to acetate exchange

Figure 171. Aryl(TMP)iodonium bromides to acetate exchange

Aryl(TMP)iodonium bromide, (2 mmol) is added to an Erlenmeyer flask with a Teflon coated magnetic stirbar and dissolved in 50 mL of hot acetonitrile. Silver acetate (2 g, 12 mmol) is added to the stirred solution and a yellow precipitate immediately forms. The flask is removed from heat, allowed to cool naturally and the precipitate gradually turns grey. When cool, the solution is repeatedly filtered through a fine fritted funnel containing packed Celite® until grey color is not observed. The solvent is evaporated under reduced pressure and the product triturated with ethyl ether to yield a white or off-white powder.

5.3.4. Determination of GC response factors for 2a and 2b

Response factor 1a = 1.51 Response factor 20 = 1.77				Area MesBr/azide	mol MesBr/azide
mes-Br	0.0099	0.0000	0.0100	0.002	0.000
tBuPhN ₃	0.0101	0.0020	0.0080	0.441	0.246
		0.0040	0.0060	1.108	0.656
		0.0060	0.0040	2.171	1.476
	conc (M)	vol MesBr	vol azide	Area MesBr/azide	mol MesBr/azide
mes-Br	0.0080	0.001	0.009	0.22	0.11
COOMePh	0.0072	0.002	0.008	0.42	0.25
		0.003	0.007	0.76	0.43
		0.004	0.006	1.15	0.67
		0.005	0.005	1.74	1.00

Table 13. Determination of GC response factors for 2a and 2b.

Figure 172. Determination of GC response factors for 2a

Figure 173. Determination of GC response factors for 2b

5.3.5. Procedure D: Aryl azidation with pre-exchanged diaryliodonium salts

Figure 174. Aryl azidation with pre-exchanged diaryliodonium salts

Aryl(TMP)iodonium salt (0.1 mmol, 1eq) is added to a vial with a magnetic stirbar.

Sodium azide (0.2 mmol, 2 equiv.) is added, followed by 1 mL anhydrous diglyme. The solution is stirred at 50°C for two hours, removed from heat and diluted with 1 mL of aqueous bicarbonate solution. Upon addition of 10 μL of internal standard (bromomesitylene), the reaction is extracted with ethyl acetate, filtered through a Celite® plug and analyzed by GC/MS.

5.3.6. Procedure E: Aryl azidation of aryl(TMP)iodonium tosylates with a dope salt.

Figure 175. Aryl azidation of aryl(TMP)iodonium tosylates with a dope salt

Aryl(TMP)iodonium tosylate (0.1 mmol, 1eq) and is added to a vial with a magnetic stirbar. A sodium salt with the desired anion is added (0.4 mmol, 4 equ), followed by 1 mL of anhydrous diglyme. The mixture is vigorously stirred at room temperature for 15 min. Sodium azide (2 mmol, 2 equiv) is added and the mixture is stirred at 50°C for two hours and then removed from heat and diluted with 1 mL of aqueous sodium

bicarbonate solution. Upon addition of (10 μ L, ~1 eq) of internal standard (bromomesytilene), the reaction is extracted with ethyl acetate, filtered through a celite plug and analyzed by GC/MS.

5.3.7. Screening Table: Corrected GC-MS yields (2 equiv. NaN_3 , 50 $^\circ\text{C}$, 2 hours)

salt additive solvent → ↓	NaF	NaCl	NaBr	NaTFA	NaTCA	NaOAc	NaOTf	NaMsCl ₃	NaMs	NaBF ₄	NaPF ₆	NaSbF ₆	none
1a-diglyme	60	34	0	11	0	54	10	17	59	18	6	6	64
1b-diglyme	64	58	16	61	25	60	59	51	44	63	60	44	53
1a-MeCN	39	35	0	5	3	42	0	0	38	0	0	0	38
1b-MeCN	44	65	30	64	50	60	35	34	46	55	48	18	63

Table 14. Screening Table: Corrected GC-MS yields (2 equiv. NaN_3 , 50 $^\circ\text{C}$, 2 hours).

5.3.8. Raw (uncorrected) GC-MS data for recapitulation of literature screening

Each of the three examples below were adapted from the indicated literature preparation. The literature preparations were modified only as follows: i) diphenyliodonium tosylate was used in each case, ii) diphenyliodonium tosylate, solvent and the sodium salt of the indicated x-group were stirred for fifteen minutes at ambient temperature before adding other reactants. Product formation was confirmed by spiking a GC/MS sample with the authentic compound.

	X-group	Literature % yield	uncorr GC/MS
PF ₆	58	311
	TFA	54	303
	OTs	47	229
	BF ₄	40	245
	OTf	38	218
	Br	0	0
OAc	77	55
	PF ₆	0	0
	Cl	0	0
	OTf	0	2
Otf	87	38
	BF ₄	97	98
	Br	90	15
	Ots	19	62

Figure 176. Raw GC/MS data (uncorrected) that is shown in Figure 49 as normalized data.

5.3.9. Characterization data

Compound **14-Br** – Prepared from **14** according to Procedure B on 2 mmol scale, using potassium bromide (12 g, 10 equiv.) and obtained in 95% yield (1.138 g) as a white powder. ¹H NMR (600 MHz, DMSO-*d*₆ & CD₃OD) δ 7.81 (d, *J* = 7.0 Hz, 2H), 7.43 (d, *J* = 7.0 Hz, 2H), 6.39 (s, 2H), 3.92 (s, 6H), 3.83 (s, 3H), 1.24 (s, 9H). ¹³C NMR (151 MHz, DMSO-*d*₆ & CD₃OD) δ 165.58, 159.27, 153.86, 133.89, 128.31, 114.65, 91.92, 90.28, 57.20, 56.06, 34.70, 30.73. FTIR: 3051, 2953, 2868, 2841, 1576, 1458, 1409, 1207, 1121, 814 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₉H₂₄IO₃⁺ [M - Br]⁺: 427.0765; Observed: 427.0768. Mp 194 °C.

Compound **14-Cl** – Prepared from **14** according to Procedure B on 2 mmol scale, using sodium chloride (12.6 g, 100 equiv.) and obtained in 94% (0.873 g) yield as a white powder. ¹H NMR (600 MHz, DMSO-*d*₆ & CD₃OD) δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 6.40 (s, 2H), 3.92 (s, 6H), 3.84 (s, 3H), 1.23 (s, 9H). ¹³C NMR (151 MHz, DMSO-*d*₆ & CD₃OD) δ 166.6, 159.9, 155.0, 134.4, 128.7, 113.4, 92.0, 88.0, 57.1, 56.0, 34.9, 30.7. FT-IR: 3068, 3004, 2955, 2901, 2868, 1586, 1410, 1231, 1119, 1059,

810, 670 cm^{-1} . HRMS (ESI⁺): Calculated for $\text{C}_{19}\text{H}_{24}\text{IO}_3^+$ [M - Cl]⁺: 427.0765, Observed: 427.0759. Mp 207 °C.

Compound **14-OAc** – Prepared to Procedure C by stirring **14-Br** (3.8 g, 7.5 mmol) into hot acetonitrile until completely dissolved. Silver acetate (1.704 g, 10.3 mmol) was added and a yellow powder immediately precipitated and gradually turned grey. The product was obtained as a white powder in 70% yield. ¹H NMR (400 MHz, CD₃OD) δ 7.90 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 6.43 (s, 2H), 4.01 (s, 6H), 3.91 (s, 3H), 1.88 (s, 3H), 1.32 (s, 9H). ¹³C NMR (101 MHz, MeOD) δ 178.7, 167.2, 160.1, 155.7, 134.3, 128.6, 111.3, 91.5, 85.3, 56.3, 55.3, 34.6, 30.0, 22.9. FT-IR: 3101, 3068, 3023, 2960, 2911, 2869, 2845, 1581, 1552, 1382, 1338, 1235, 1117, 1069, 824, 637 cm^{-1} . HRMS (ESI⁺): Calculated for $\text{C}_{19}\text{H}_{24}\text{IO}_3^+$ [M - OAc]⁺: 427.0765, Observed: 427.0747. Mp 149 - 151 °C.

Compound **14-OTf** – Prepared from **14** according to Procedure B on 2 mmol scale, using sodium triflate (5.0 g, 29 equiv.) and obtained in 92% (1.06 g, 1.8 mmol) yield as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.84 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 6.48 (s, 2H), 3.96 (d, J = 5.8 Hz, 6H), 3.87 (d, J = 4.7 Hz, 3H), 1.25 (s, 9H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.1, 159.3, 154.7, 134.2, 128.7, 120.7 (q, $J_{\text{C-F}}$ = 322.5 Hz), 112.5, 92.0, 86.9, 57.3, 56.1, 34.8, 30.7. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ (ppm): -77.7. FT-IR: 3070, 2955, 2870, 2847, 1580, 1471, 1415, 1243, 1210, 1125, 1026, 814, 635 cm^{-1} . HRMS (ESI⁺): Calculated for $\text{C}_{19}\text{H}_{24}\text{IO}_3^+$ [M - OTf]⁺: 427.0765, Observed: 427.0765. Mp 78 – 79 °C.

Compound **14-BF₄** – Prepared from **14** according to Procedure B on 2 mmol scale, using sodium tetrafluoroborate (22 g, 95 equiv.) and obtained in 91% yield (0.930 g, 1.81 mmol) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 6.48 (s, 2H), 3.97 (s, 6H), 3.88 (s, 3H), 1.25 (s, 9H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.6, 159.9, 155.2, 134.7, 129.2, 113.0, 92.5, 87.4, 57.8, 56.6, 35.3, 31.2. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ (ppm): -148.3. FT-IR: 3022, 2903, 2870, 1579, 1462, 1347, 1232, 1126, 1050, 995, 808, 665 cm^{-1} . HRMS (ESI⁺): Calculated for $\text{C}_{19}\text{H}_{24}\text{IO}_3^+$ [M - BF₄]⁺: 427.0765, Observed: 427.0747. Mp 162 °C.

Compound **20-Br** – Prepared from **20** according to Procedure B on 2 mmol scale, using potassium bromide (12 g, 100 equiv.) and obtained in 85% yield (0.930 g, 1.81 mmol) as a white powder. ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.27 – 7.79 (m, 4H), 6.49 (s, 2H), 3.97 (s, 6H), 3.89 – 3.52 (m, 6H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 166.9, 165.6, 159.9, 135.1, 132.7, 132.3, 121.4, 92.6, 87.3, 57.8, 56.6, 53.1. FT-IR: 3086, 2988, 2972, 2901, 1721, 1579, 1279, 1121 cm^{-1} .

HRMS (ESI⁺): Calculated for C₁₇H₁₈IO₅⁺ [M - Br]⁺: 429.0193; Observed 429.0167. Mp 152 °C.

Compound **20-Cl** – Prepared from **20** according to Procedure B on 3.25 mmol scale,

using sodium chloride (14 g, 74 equiv.) and obtained in 94 % yield (1.42 g) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆ and CD₃OD) δ 8.03 – 7.83 (m, 4H), 6.37 (s, 2H), 3.90 (s, 6H), 3.82 (s, 3H), 3.82 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆ & CD₃OD) δ 166.4, 165.0, 159.4, 134.0, 132.1, 131.2, 121.1, 91.4, 87.3, 56.4, 55.3, 51.7. FT-IR: 3071, 2988, 2971, 2944, 2901, 1733, 1577,

1280, 1116, 748 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₇H₁₈IO₅⁺ [M - Cl]⁺: 429.0193; Observed 429.0170. Mp 167 °C.

Compound **20-TFA** – Prepared from **20** according to Procedure B on 2 mmol scale,

using sodium trifluoroacetate (14 g, 50 equiv.) and obtained in 33 % yield (1.42 g) as a white powder. The filtrate in the final wash step was not extracted. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.06 (d, *J* = 7.8 Hz, 2H), 7.96 (d, *J* = 7.9 Hz, 2H), 6.48 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 3.84 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 166.7, 165.7, 160.0, 151.8 (q, *J*_{C-F} = 31.1 Hz), 134.9, 132.4, 132.1, 117.7 (q, *J*_{C-F} = 300.1 Hz), 92.5, 88.1, 57.7, 56.6, 53.0. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -73.4 (ppm): FT-IR: 3092, 3070,

2988, 2972, 2956, 2901, 1723, 1662, 1581, 1273, 1108, 763 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₇H₁₈IO₅⁺ [M - CF₃COO]⁺: 429.0193; Observed 429.0200. Mp 168 °C.

Compound **20-OAc** – Prepared to Procedure C by stirring **20-Br** (2.314 g, 4.55 mmol)

into hot acetonitrile until completely dissolved. Silver acetate (2.3 g, 3 equiv) was added and a yellow powder immediately precipitated and gradually turned grey. The product was obtained as a white powder in 47% yield (1.033 g, 2.12 mmol). ¹H NMR (400 MHz, CD₃OD) δ 8.12 – 8.00 (m, 4H), 6.45 (s, 2H), 4.00 (s, 6H), 3.95 – 3.91 (m, 6H), 1.89 (s, 3H). ¹³C NMR (101

MHz, CD₃OD) δ 178.4, 167.5, 165.4, 160.1, 134.3, 133.1, 131.8, 119.5, 91.6, 85.1, 56.4, 55.3, 51.8, 22.6. FTIR: 3079, 3053, 3028, 2947, 2907, 2834, 1716, 1579, 1549, 1388, 1339, 1277, 1225, 1158, 1116, 1066, 807, 761, 643 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₇H₁₈IO₅⁺ [M - OAc]⁺: 429.0193; Observed 429.0191. Mp 111 °C.

Compound **20-OTf** – Prepared from **20** according to Procedure B on 1 mmol scale,

using sodium triflate (3 g, 17.5 equiv) and obtained in 84 % yield as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.05 (d, *J* = 8.6 Hz, 2H), 7.98 (d, *J* = 8.6 Hz, 2H), 6.49 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 3.86 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.4, 165.1, 159.4, 134.6, 132.2, 131.8, 120.8, 120.7 (q, *J*_{C-F} = 322.4 Hz), 92.1, 86.8, 57.3, 56.2, 52.6. ¹⁹F NMR (376 MHz,

DMSO-*d*₆) δ -77.7 (s). FTIR: 3107, 2950, 2849, 1732, 1576, 1464, 1352, 1275, 1229, 1159, 1029, 816, 665 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₇H₁₈IO₅⁺ [M – OTf]⁺: 429.0193; Observed 429.0191. Mp 104 °C.

Compound **20-BF₄** – Prepared from **20** according to Procedure B on 2 mmol scale, using sodium tetrafluoroborate (11 g, 50 equiv) and obtained in 77 % yield (0.8079 g) as a white powder. The filtrate was not extracted to recover more product. ¹H NMR (400 MHz, DMSO-*d*₆ and CD₃OD) δ 8.61 – 7.78 (m, 4H), 6.49 (s, 2H), 4.01 (s, 6H), 3.92 – 3.78 (m, 6H). ¹³C NMR (101 MHz, DMSO-*d*₆ and CD₃OD) δ 166.9, 165.6, 159.9, 135.1, 132.7, 132.3, 121.4, 92.6, 87.3, 57.8, 56.6, 53.1. ¹⁹F NMR (376 MHz, DMSO-*d*₆ and CD₃OD) δ -148.30 (s). FT-IR: 3089, 2988, 2971, 2901, 1716, 1578, 1549, 1277, 1159, 1115, 1066, 642 cm⁻¹. HRMS (ESI⁺): Calculated for C₁₇H₁₈IO₅⁺ [M – BF₄]⁺: 429.0193; Observed 429.0186. Mp 168 °C (decomposed).

Compound **50** – Prepared according to Procedure D on 0.5 mmol scale and obtained in 94% (0.0818 g, 0.47 mmol) yield as a pale yellow oil. The crude product was adsorbed onto silica and purified by column chromatography using hexanes as the eluent. The characterization data agree with previously reported values.⁵⁵ ¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 1.27 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 147.9, 137.2, 126.6, 119.0, 34.5, 31.3.

Compound **51** – Prepared according to Procedure D on 0.1 mmol scale with the following deviations: i) the crude reaction was extracted with pentane and purified by column chromatography on silica using 5% ethyl ether followed by 10% ethyl ether in pentane. The product was obtained in 95% (0.0167 g, 0.095 mmol) yield as a pale yellow solid. The characterization data agree with previously reported values.⁵⁶ ¹H NMR (600 MHz, CDCl₃) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 3.91 (s, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 166.3, 144.8, 131.4, 126.7, 118.8, 52.2.

Compound **56** – Prepared according to Procedure D on 0.1 mmol scale with the following deviations: i) acetonitrile was used as the solvent, ii) the crude reaction was extracted with ethyl ether and purified by column chromatography on silica using ethyl ether in hexanes (1:1) followed by neat ethyl ether. The product was obtained in 86% (0.014 g, 0.086 mmol) yield as a colorless oil. The characterization data agree with previously reported values.⁵⁷ ¹H NMR (600 MHz, CDCl₃) δ 7.21 (d, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 7.4 Hz, 2H), 3.84 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.4 Hz, 2H), 1.70 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 138.3, 135.5, 130.5, 119.2, 65.9, 38.6.

Compound **57** – Prepared according to Procedure D on 0.5 mmol scale and obtained in 93% (0.0828 g, 0.465 mmol) yield as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.17 (dd, *J* = 8.3, 2.4 Hz, 1H), 2.57 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 149.7, 139.3, 134.1, 130.0, 123.4, 115.2, 20.0. FT-IR: 3081, 2988, 2938, 2901, 2110, 1527, 1303, 1338, 1066, 907, 872, 729 cm⁻¹. HRMS (ESI⁺) Calculated for C₇H₆N₄O₂⁺ [*M* - H]⁺: 178.0491; Observed 178.0507. Mp 67 - 68 °C

Compound **58** – Prepared according to Procedure D on 0.5 mmol scale and obtained in 92% (0.172 g, 0.462 mmol) yield. ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 2.7 Hz, 1H), 7.01 (t, *J* = 1.8 Hz, 1H), 6.91 – 6.85 (m, 3H), 5.04 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 159.1, 140.0, 137.0, 135.6, 133.9, 121.9, 120.0, 119.2, 117.2, 114.0, 69.4. FT-IR: 3095, 3055, 2920, 2842, 2115, 2075, 1590, 1572, 1299, 1057, 804, 662 cm⁻¹. HRMS (ESI⁺) Calculated for C₁₃H₈BrCl₂N₃O [*M* - H]⁺: 370.9228; Observed 370.9250. Mp 98 - 99 °C

Compound **59** – Prepared according Procedure D on 0.1 mmol scale with the following deviations: i) acetonitrile was used as the solvent. The crude product was purified by column chromatography on silica using 10% ethyl ether in hexanes. The product was obtained in 74% (0.0114 g, 0.074 mmol) yield as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.14 (dd, *J* = 2.1, 1.5 Hz, 1H), 7.45 – 7.25 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 147.1, 140.7, 136.4, 128.9, 125.0. FT-IR: 3086, 3055, 2131, 2099, 1455, 1299, 824, 565 cm⁻¹. HRMS (ESI⁺) Calculated for C₅H₃ClN₄ [*M* - H]⁺: 154.0046 Observed 154.0066. Mp 39 °C.

5.3.10. NMR spectra for aryl(TMP)iodonium tosylates

Figure 177. ¹H NMR spectrum of 14-Br at 600 MHz in DMSO-*d*₆ and CD₃OD at 298K

Figure 178. ¹³C NMR spectrum of 14-Br at 101 MHz in DMSO-*d*₆ and CD₃OD at 298K

Figure 179. ¹H NMR spectrum of 14-Cl at 400 MHz in DMSO-*d*₆ and CD₃OD at 298K

Figure 180. ¹³C NMR spectrum of 14-Cl at 101 MHz in DMSO-*d*₆ and CD₃OD at 298K

Figure 181. ^1H NMR spectrum of 14-OAc at 400 MHz in CD_3OD at 298K

Figure 182. ^{13}C NMR spectrum of 14-OAc at 101 MHz in CD_3OD at 298K

Figure 183. ¹H NMR spectrum of 14-OTf at 400 MHz in DMSO-*d*₆ at 298K

Figure 184. ¹³C NMR spectrum of 14-OTf at 101 MHz in DMSO-*d*₆ at 298K

Figure 185. ^{19}F NMR spectrum of 14-OTf at 376 MHz in $\text{DMSO}-d_6$ at 298K

Figure 186. ^1H NMR spectrum of 14-BF₄ at 400 MHz in $\text{DMSO}-d_6$ at 298K

Figure 187. ^1H NMR spectrum of 20-Br at 600 MHz in $\text{DMSO}-d_6$ at 298K

Figure 188. ^{13}C NMR spectrum of 20-Br at 151 MHz in $\text{DMSO}-d_6$ and CD_3OD at 298K

Figure 189. ¹H NMR spectrum of 20-Cl at 400 MHz in DMSO-*d*₆ and CD₃OD at 298K

Figure 190. ¹³C NMR spectrum of 20-Cl at 101 MHz in DMSO-*d*₆ and CD₃OD at 298K

Figure 191. ¹H NMR spectrum of 20-TFA at 600 MHz in DMSO-*d*₆ at 298K

Figure 192. ¹³C NMR spectrum of 20-TFA at 151 MHz in DMSO-*d*₆ at 298K

Figure 193. ¹⁹F NMR spectrum of 20-TFA at 376 MHz in DMSO-*d*₆ 298K

Figure 194. ¹H NMR spectrum of 20-OAc at 600 MHz in CD₃OD at 298K

Figure 195. ¹³C NMR spectrum of 20-OAc at 151 MHz in CD₃OD at 298K

Figure 196. ¹H NMR spectrum of 20-OTf at 400 MHz in DMSO-*d*₆ at 298K

Figure 197. ^{13}C NMR spectrum of 20-OTf at 101 MHz in $\text{DMSO-}d_6$ at 298K

Figure 198. ^{19}F NMR spectrum of 20-OTf at 376 MHz in $\text{DMSO-}d_6$ at 298K

Figure 199. ¹H NMR spectrum of 20-BF₄ at 400 MHz in DMSO-*d*₆ at 298K

Figure 200. ¹³C NMR spectrum of 20-BF₄ at 101 MHz in DMSO-*d*₆ at 298K

Figure 201. ¹⁹F NMR spectrum of 20 - BF₄ at 376 MHz in DMSO-*d*₆ at 298K

Figure 202. ¹H NMR spectrum of 50 at 400 MHz in CDCl₃ at 298K

Figure 203. ¹³C NMR spectrum of 50 at 101 MHz in CDCl₃ at 298K

Figure 204. ¹H NMR spectrum of 51 at 600 MHz in CDCl₃ at 298K

Figure 205. ¹³C NMR spectrum of 51 at 151 MHz in CDCl₃ at 298K

Figure 206. ¹H NMR spectrum of 56 at 101 MHz in CDCl₃ at 298K

Figure 207. ¹³C NMR spectrum of 56 at 101 MHz in CDCl₃ at 298K

Figure 208. ¹H NMR spectrum of 57 at 400MHz in CDCl₃ at 298K

Figure 209. ¹³C NMR spectrum of 57 at 101 MHz in CDCl₃ at 298K

Figure 210. ¹H NMR spectrum of 58 at 400MHz in CDCl₃ at 298K

Figure 211. ¹³C NMR spectrum of 58 at 101 MHz in CDCl₃ at 298K

Figure 212. ¹H NMR spectrum of 59 at 400MHz in CDCl₃ at 298K

Figure 213. ^{13}C NMR spectrum of 59 at 101 MHz in CDCl_3 at 298K

5.3.11. References for Chapter 3

5.3.11.1. References for counteranion review (Figure 44, Chapter 3, also listed in final references section)

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