Diaryliodonium Salts

Development of Synthetic Methodologies and α-Arylation of Enolates

Marcin Bielawski
The most exciting phrase to hear in science, the one that heralds the most discoveries, is not "Eureka!" (I found it!) but "That's funny..."

Isaac Asimov
(1920–1992)
Abstract

This thesis describes novel reaction protocols for the synthesis of diaryliodonium salts and also provides an insight to the mechanism of α-arylation of carbonyl compounds with diaryliodonium salts.

The first chapter gives a general introduction to the field of hypervalent iodine chemistry, mainly focusing on recent developments and applications of diaryliodonium salts.

Chapter two describes the synthesis of electron-rich to electron-poor diaryliodonium triflates, in moderate to excellent yields from a range of arenes and iodoarenes.

In chapter three, it is described that molecular iodine can be used together with arenes in a direct one-pot, three-step synthesis of symmetric diaryliodonium triflates. A large scale synthesis of bis(4-tert-butylphenyl)-iodonium triflate is also described, controlled and verified by an external research group, further demonstrating the reliability of this methodology.

The fourth chapter describes the development of a sequential one-pot synthesis of diaryliodonium salts from aryl iodides and boronic acids, furnishing symmetric and unsymmetric, electron-rich to electron-poor diaryliodonium tetrafluoroborates in moderate to excellent yields. This method was developed to overcome the regiochemical limitations imposed by the reaction mechanism in the protocols described in the preceding chapters.

Chapter five describes a one-pot synthesis of heteroaromatic iodonium salts under similar conditions described in chapter two.

The final chapter describes the reaction of enolates with chiral diaryliodonium salts or together with a phase transfer catalyst yielding racemic products. DFT calculations were performed, which revealed a low lying energy transition state (TS) between intermediates, which is believed to be responsible for the lack of selectivity observed in the experimental work. It is also proposed that a [2,3] rearrangement is preferred over a [1,2] rearrangement in the α-arylation of carbonyl compounds.

The synthetic methodology described in this thesis is the most generally applicable, efficient and high-yielding to date for the synthesis of diaryliodonium salts, making these reagents readily available for various applications in synthesis.
This thesis is based on the following publications, in the text referred to by their Roman numerals I-V and Appendix B. My contribution to these papers is summarized in Appendix A.

I. **High-Yielding One-Pot Synthesis of Diaryliodonium Triflates from Arenes and Iodine or Aryl Iodides**
   Marcin Bielawski and Berit Olofsson
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II. **Efficient and General One-Pot Synthesis of Diaryliodonium Triflates: Optimization, Scope and Limitations**
    Marcin Bielawski, Mingzhao Zhu and Berit Olofsson
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III. **Efficient One-pot Synthesis of Bis(4-tert-Butylphenyl)Iodonium Trflate**
     Marcin Bielawski and Berit Olofsson

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     **Regiospecific One-Pot Synthesis of Diaryliodonium Tetrafluoroborates from Arylboronic Acids and Aryl Iodides**
     Marcin Bielawski, David Aili and Berit Olofsson
     Copyright 2011 American Chemical Society.
V. α-Arylation by Rearrangement: On the Reaction of Enolates with Diarylidoonium Salts
Per-Ola Norrby, Tue B. Petersen, Marcin Bielawski and Berit Olofsson
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One-Pot Synthesis of Heteroaromatic Iodonium Salts
Marcin Bielawski, Leticia M. Pardo, Ylva Wikmark and Berit Olofsson
Appendix B.

Paper not included in the thesis:

Metal-Free Synthesis of Indanes by Iodine(III)-Mediated Ring Contraction of 1,2-Dihydronaphthalenes
Submitted to Tetrahedron.
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Abbreviations

The abbreviations and acronyms are used in agreement with the standards of the subject[1]. Only nonstandard abbreviations that appear in the thesis are listed here.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CSA</td>
<td>(1S)-10-Camphorsulfonic acid</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EDG</td>
<td>Electron donating group</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalent(s)</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess–Martin periodinane</td>
</tr>
<tr>
<td>IBX</td>
<td>2-Iodoxybenzoic acid</td>
</tr>
<tr>
<td>mCBA</td>
<td>meta-Chlorobenzoic acid</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-Chloroperbenzoic acid</td>
</tr>
<tr>
<td>PTC</td>
<td>Phase Transfer Catalyst</td>
</tr>
<tr>
<td>TFE</td>
<td>2,2,2-Trifluoroethanol</td>
</tr>
<tr>
<td>TfOH</td>
<td>Trifluoromethanesulfonic acid</td>
</tr>
<tr>
<td>Tol</td>
<td>Toluene</td>
</tr>
<tr>
<td>TS</td>
<td>Transition state</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction to Hypervalent Iodine Compounds

Unglaublich! meaning incredible, may have been the first word uttered by the German chemist Conrad Willgerodt while watching chlorine gas passing through a vessel containing an ice-cold iodobenzene solution. The year was 1886 when he realized that he had discovered a way to synthesize (dichloroiodo)benzene (Figure 1), the first organic hypervalent iodine compound, which precipitated as yellow needles from the solution.[2]

Figure 1. (Dichloroiodo)benzene.

What Willgerodt probably did not anticipate was that he had laid the foundation of a completely new branch of organic chemistry. In the following decade, Willgerodt and Victor Meyer discovered new and important hypervalent iodine compounds such as iodosyl-,[3] iodyl-,[4] iodoxy-benzene[5] and diphenyliodonium salts[6] (Figure 2).

Figure 2. Important hypervalent iodine compounds.
In 1914, Willgerodt completed the book *Die Organischen Verbindungen mit Mehrwertigen Jod*, a comprehensive summary of all known hypervalent iodine chemistry at that time.\(^7\) Over the course of the First World War and the Great Depression, the field of hypervalent iodine chemistry was "forgotten" and only sporadic contributions were made to the area. However, in the midst of World War II, Reuben Sandin collated all of the new additions to the field since Willgerodt’s book, together with older works, and published the first review on hypervalent iodine written in English.\(^8\)

The next major contributor to the field was Frederick Marshall Beringer, who during the 1950s and 1960s improved synthetic routes towards various hypervalent iodine compounds and also used the reagents systematically in various applications. For example, he was the first to study α-arylations of enolizable carbonyl compounds with diaryliodonium salts.\(^9\)

Although the field of hypervalent iodine chemistry had constantly been intriguing for some, it was isolated and considered obscure by the wider chemical community. It was not until the discovery of the reagent now known as Dess-Martin periodinane (DMP) by Dess and Martin in the 1980s, that the field of hypervalent iodine reached out into mainstream organic synthesis, as DMP exhibited unique properties in the oxidation of alcohols under mild conditions (Figure 3).\(^10\)

Nowadays, hypervalent iodine compounds frequently demonstrate their power as mild, non-toxic and selective reagents in a wide range of applications.\(^{11-13}\) Novel reactions and reagents are frequently discovered and the utility of old reagents is brought to light. For example, the usefulness of IBX, which was first discovered in 1893, was unveiled as late as 1994,\(^{14}\) proving to be an even more versatile reagent than DMP in many oxidation reactions.\(^{15}\)

\[\text{Figure 3. Examples of compounds with different oxidation states on I. The X-I-L notation is used describing number of electrons (X), and number of ligands (L) around the central atom (I).}\]
1.1 Nomenclature, Oxidation State and Bonding

Hypervalent iodine compounds are generally classified according to the oxidation state of iodine, e.g. the iodine in an aryl iodide is defined to have an oxidation state of +I and is not hypervalent. An easy way to determine whether or not an iodine compound is hypervalent is by electron counting i.e. compounds that have more than eight electrons in their valence shell are described as hypervalent. Examples of hypervalent iodine compounds with the oxidation state of +III and +V are shown in Figure 3 and according to IUPAC rules, compounds with those oxidation states can be termed as \(^{3}\) and \(^{5}\)-iodanes, respectively. Scheme 1 depicts how iodine compounds are oxidized.

![Scheme 1. General oxidation of iodine compounds.](image)

To describe the hypervalent bond, a \(^{3}\)-iodane will be used as an example. The geometry is best depicted as a pseudotrigonal bipyramid (T-shape), with an aryl group and two free electron pairs in the equatorial positions whereas the two ligands (L) are in the apical positions (Figure 4, left). The L–I–L bond is derived from a doubly occupied 5p orbital with two electrons from iodine, and two electrons from the ligands. This is referred to as a three-center four-electron bond (3c-4e) or a hypervalent bond. Hypervalent iodine compounds react as electrophiles, which can be understood by looking at the molecular orbitals (MOs) (Figure 4, right).

![Figure 4. Left: Geometry of a \(^{3}\)-iodane. Right: MOs of the hypervalent bond.](image)

The HOMO is the non-bonding orbital, which has a node at the iodine atom. Hence more electrons are distributed at the ligands, rendering the iodine a soft electrophilic center that can be attacked by many nucleophiles.
1.2 Some \( \lambda^3 \)- and \( \lambda^5 \)-Iodanes and their Applications

The application area of hypervalent compounds is vast, encompassing areas such as C-C, C-heteroatom and heteroatom-heteroatom bond formation, oxidations, radical reactions and rearrangements.\textsuperscript{[11-13]}

Iodine(V) reagents such as DMP, IBX and their analogues\textsuperscript{[11, 15]} are frequently used as mild reagents for the oxidation of alcohols, e.g. in total synthesis of natural products.\textsuperscript{[17-19]} They are also employed as oxygen transfer reagents and IBX can effect oxidative transformations of a variety of other functional groups via a Single Electron Transfer (SET) mechanism. An example of this is the synthesis of \( \alpha,\beta \)-unsaturated ketones from ketones or alcohols in a toluene/DMSO solvent mixture (Scheme 2).\textsuperscript{[20]}

\begin{center}
\textbf{Scheme 2}. Selective IBX-mediated oxidation.
\end{center}

Iodine(III) compounds with two heteroatom ligands, such as (diacetoxyiodo)benzene, are also frequently employed in oxidations of alcohols and alkenes, synthesis of quinones, in rearrangements and also in \( \alpha \)-functionalization of carbonyl compounds.\textsuperscript{[21]} It was recently shown that \( \alpha \)-acetoxylation of carbonyl compounds could be performed with a catalytic amount of iodobenzene. The iodobenzene is oxidized in situ to the catalytically active species (diacetoxyiodo)benzene by the stoichiometric oxidant \( m \text{CPBA} \) (Scheme 3).\textsuperscript{[22]} Other catalytic reactions have also recently been developed, especially within the area of alcohol oxidation.\textsuperscript{[23-24]}

\begin{center}
\textbf{Scheme 3}. Catalytic \( \alpha \)-acetoxylation of ketones.
\end{center}
In 2006 the Togni group developed novel cyclic iodine(III) compounds that are used as trifluoromethylation reagents. The group has explored several application areas including the trifluoromethylation of α-nitro esters,[25] thiols,[25] β-ketoesters,[25–26] aryls,[27–28] phosphines,[29] alcohols[30] and nitrogen atoms in a Ritter type reaction,[31] all in moderate to high yields under mild conditions. The MacMillan group recently utilized Togni’s reagent in combination with organocatalysis, obtaining α-trifluoro-methylated aldehydes in high yields and excellent enantiomeric excess (ee) (Scheme 4).[32]

![Scheme 4. Trifluoromethylation of aldehydes with Togni's reagent combined with organocatalysis leading to a diversity of products.](image)

Iodine(III) compounds in which the iodine bears two carbon ligands can undergo reactions whereby they transfer one of the ligands to a range of nucleophiles. They can also be used to oxidize metals to unusual oxidation states (e.g. Pd(II→IV)). One type of these reagents, namely diaryliodonium salts, is the main focus of this thesis and will be discussed in detail below.

1.3 Diaryliodonium Salts

A general structure of a diaryliodonium salt, also referred to as a diaryl-\(\lambda^3\)-iodane, is shown in Figure 5. The salt is referred to as a symmetric salt if \(R^1 = R^2\), and as an unsymmetric salt if \(R^1 \neq R^2\).

![Figure 5. General structure of diaryliodonium salts.](image)
The anion (X) of the diaryliodonium salt not only influences the solubility but also the reactivity. Generally, non-nucleophilic anions such as BF$_4^-$ and TfO$^-$, are preferred over anions such as Cl$^-$, Br$^-$ and I$^-$ in applications.$^{[33]}$

The configuration of diaryliodonium salts in solution is still debated and has not been proven, but a certain amount of dissociation is expected depending on the anion of the salt and the type of solvent used. However, in the solid state a majority of all X-ray structural data reported for diaryliodonium salts shows significant secondary bonding between the anion and the iodine atom.$^{[13, 34]}$ The geometry is also in agreement with that shown in Figure 6, i.e. T-shaped.

![Figure 6. Structure in solution versus solid state.](image)

### 1.3.1 Synthesis

The first synthesis of a diaryliodonium salt was accomplished over 100 years ago by Victor Meyer$^{[6]}$ and refined by Beringer in the 1950s to a working one-pot reaction, albeit with a small substrate scope (Scheme 5).$^{[35]}

\[
\begin{align*}
\text{PhNO}_2\text{I} + \text{Ph} & \xrightarrow{\text{K}_2\text{SO}_3, \text{H}_{2}\text{SO}_4} \text{PhNO}_2\text{HSO}_4^+ \\
& \xrightarrow{\text{KI, Anion Exchange}} \text{PhNO}_2\text{I} \\
\end{align*}
\]

**Scheme 5.** Beringer’s one-pot synthesis of a diaryliodonium salt.

### Acidic Syntheses of Diaryliodonium Salts

Acidic routes are most common in synthesis of diaryliodonium salts. There are three different approaches (A–C) as summarized in Scheme 6. The most frequently used strategy is A, where the salt is isolated after a 2-3 step procedure. It is however quite common to start from a commercially available iodine(III) reagent, in order to shorten the synthetic route and examples of these are given below.
Scheme 6. General acidic routes to diaryliodonium salts.

Addition of iodosobenzene (1a) to a solution of peracetic acid in Ac₂O, furnishes PhI(OAc)₂ (3) in good yield and short reaction time (Scheme 7).²⁶ Compound 3 can smoothly be converted to iodosylbenzene (4) by treatment with aqueous NaOH.²⁷ Kitamura developed a procedure whereby 4 was treated with TfOH, followed by addition of benzene (2a) to obtain diphenyliodonium triflate (5a) in 65% yield.²⁸ This route was shortened by the same group when they found that 3 could be treated directly with TfOH for one hour before the addition of 2a to obtain salt 5a in 85% yield.²⁹

Scheme 7. Examples of how diphenyliodonium triflate can be synthesized via method A and B. Also showed is the direct synthesis from arenes and elemental iodine.

Other methods included in strategy A are routes employing silanes,²⁰ stannanes²¹⁻²³ or boron reagents²⁴⁻²⁶ together with pre-formed iodine(III) reagents. Kita and co-workers recently showed that by mixing Koser's reagent with an arene in 2,2,2-trifluoroethanol (TFE), diaryliodonium tosylates are obtained.²⁷
An example of strategy B is the one-pot reaction developed by Kitamura and co-workers, where 1a is oxidized with K$_2$SzO$_8$ (Scheme 7). In the presence of benzene, diphenyliodonium triflate is obtained in 78% yield after an anion exchange. Another method that was recently developed by the same group, is the reaction of benzene and molecular iodine with the same oxidant and acid as in their previous method (Scheme 7). After 72 h at 40 °C, an anion exchange was performed delivering 5a in 71% yield. Another interesting synthesis exemplifying strategy B was developed by Skulski and co-workers in 1995. CrO$_3$ is used to oxidize iodoarenes to an iodine(III) intermediate, which then reacts with an arene to give diaryliodonium salts in moderate yields. A drawback with this protocol is the toxicity of the oxidant, and the products are obtained with a halo anion.

Few diaryliodonium salts have been synthesized via strategy C. Zhdankin and co-workers developed a method in the early 1990s in which the iodine(III) source is iodosyl fluorosulfate (Scheme 8). In the presence of an arene, symmetric diaryliodonium salts are obtained in moderate to good yields. The iodine(III) compound is, however, not commercially available and needs to be prepared in advance.

\[
\begin{align*}
\text{H}_2\text{SzO}_8 + \text{I}_2 + 8 \text{HSO}_3\text{F} & \rightarrow \text{rt, 24 h} \\
\text{5O-SO}_3\text{F}^{-} + 3 \text{H}_3\text{O}^{+} + 3 \text{SO}_4^{2-} & \\
2\text{eq.} \quad \begin{array}{c}
\text{ benzene } \\
0=\text{OSO}_2\text{F}^{-}
\end{array} & \rightarrow \quad \begin{array}{c}
\text{71%} \\
\text{ product with \text{HSO}_4}^{-}
\end{array}
\end{align*}
\]

**Scheme 8.** Zhdankin’s synthesis of symmetric diaryliodonium salts utilizing iodosyl fluorosulfate.

### Basic Syntheses of Diaryliodonium Salts

Routes using basic conditions are not widely reported, although for certain types of diaryliodonium salts it remain the only viable synthetic route, *e.g.* for symmetric heteroaryliodonium salts. A frequently used method is ligand exchange on β-(dichloroiodo)chloroethylene with a lithiated arene, in which symmetric salts are obtained in a regiospecific manner (Scheme 9). The iodine(III) reagent needs to be prepared immediately prior to use as it is extremely unstable.

\[
\begin{align*}
\text{H} & \quad \rightarrow \quad \begin{array}{c}
\text{ICl}_3 \\
\text{HCl, H}_2\text{O}
\end{array} \\
\text{Cl} & \quad \rightarrow \quad \begin{array}{c}
2\text{Ar-Li} \\
-2\text{LiCl} \\
-\text{C}_2\text{H}_2
\end{array}
\end{align*}
\]

**Scheme 9.** Synthesis of symmetric diaryliodonium salts via β-(dichloroiodo)chloroethylene.
Other related methods also utilize organometallic reagents, which are reacted with a pre-formed vinyliodonium salt as shown in Scheme 10. This type of protocol has the advantage that unsymmetric salts can be obtained, in contrast to the method shown above.

![Scheme 10. Diaryliodonium salts can be obtained by adding lithiated arenes to vinyl iodonium salts.](image)

1.3.2 Mechanistic Limitations

To realize some of the limitations of the synthetic routes discussed above, it is important to understand the reaction mechanism. Starting from an iodoarene, the first step is an oxidation, usually in the presence of a strong acid. This gives the general structure Ar-I-X₂, which can be isolated or used in situ for further reactions (Scheme 11).

![Scheme 11. Oxidation of iodine(I) to iodine(III).](image)

Upon addition of an arene, an electrophilic aromatic substitution (EAS) takes place (Scheme 12). As normal EAS rules apply, activated arenes (R = EDG) would give a mixture of ortho- and para-products. In reactions with iodine(III) species the selectivity is usually extremely high for the para-position. Deactivated arenes (R = EWG) are usually too unreactive, leading to by-product formation as the intermediate decomposes or reacts with the starting iodoarene or the oxidant.

![Scheme 12. The mechanistic limitation in the EAS step.](image)
This issue is to be regarded as a major limitation, as numerous symmetric ortho- and meta-substituted diaryliodonium salts are inaccessible. The problem can however be circumvented by the use of organometallic reagents or boronic acids in place of the arene. In Scheme 13, an example from Wid-dowson’s group is highlighted where a boronic acid reacts regiospecifically at the ipso-position with (diacetoxyiodo)benzene.\[44\]

![Scheme 13](image)

**Scheme 13.** Widdowson’s regiospecific synthesis of diaryliodonium triflates.

### 1.3.3 Application Areas

When utilizing diaryliodonium salts in reactions with nucleophiles, one of the two aryl groups will be transferred. Symmetric diaryliodonium salts are thus generally preferred over unsymmetric salts as no chemoselectivity problems arise. In some situations, the use of unsymmetric salts is desirable, such as when the starting materials are prohibitively expensive.

Fortunately there are some rules of thumb one can follow; in metal mediated reactions with unsymmetric salts, the least sterically hindered arene is selectively transferred; if steric bulk is not a factor, then the most electron-rich arene is preferentially transferred.\[33, 59\] Conversely, when diaryliodonium salts are employed in non-metal-mediated reactions the most electron-deficient arene is normally transferred, although there are reports of different reactivity when an ortho-substituent is present in one of the arenes (i.e. the ortho-effect).\[33, 60\]

The most widely reported use of diaryliodonium salts as a reagent is in combinations with either a copper or palladium catalyst. Sanford and co-workers have been very active in the palladium field and have spurred interesting mechanistic investigations on the oxidation state of Pd.\[61-62\] An example of methodology developed by the Sanford group is given in Scheme 14, where indoles are selectively arylated in the C2-position under mild conditions.\[63\]

![Scheme 14](image)

**Scheme 14.** Use of diaryliodonium salts in the selective 2-arylation of indoles.

Gaunt and co-workers explored indole chemistry further and developed a copper-catalyzed protocol in which the C2 or the C3 position could be aryl-
ated selectively.\cite{64} Their work with Cu and diaryliodonium salts has resulted in several publications in the intriguing area of C-H activation (Figure 7).\cite{65-67} Recent findings by the group indicate that some of the reactions also work without the copper catalyst, although higher temperature is needed.\cite{66-67}

![Figure 7. New C-H activation developed by Gaunt and co-workers.](image)

The Szabó group has found that Pd pincer complexes react readily with diaryliodonium salts, arylating allylic acetates and electron-rich trans-alkenes through a proposed Pd(II)/Pd(IV) cycle (Scheme 15). The same group also performed calculations on the reaction mechanism, supporting the observed reactivity pattern when metals are employed with diaryliodonium salts.\cite{68}

![Scheme 15. Powerful Heck-type coupling with Pd pincer complexes.](image)
Diaryliodonium salts are also efficient arylating agents when used under metal-free conditions due to their highly electron-deficient nature and the hyperleaving group ability of iodoarenes.\textsuperscript{69-72} An example is shown in Scheme 16, where a symmetric pyridyl salt is employed in the key step in the total synthesis of \((-\)-epibatidine).\textsuperscript{69} The arylation of the 4-substituted cyclohexanone after enolization with a chiral base gives the product with excellent \textit{ee} and diastereomeric ratio (\textit{dr}), albeit in moderate yield.

\begin{center}
\textbf{Scheme 16.} Key step in the shortest synthesis of \((-\)-epibatidine).
\end{center}

Rawal and co-workers have shown that trimethylsilyl enol ethers are readily arylated with (2-nitrophceny1)(phenyl)iodonium fluoride, and that the reaction shows complete chemoselectivity \textit{i.e.} only transferring the electron deficient arene.\textsuperscript{73} This methodology was applied as a key step in their stereocontrolled synthesis of (±)-tabersonine.\textsuperscript{74}

\begin{center}
\textbf{Scheme 17.} Total synthesis of (±)-tabersonine was achieved in only 12 steps and a 30\% overall yield. The key step with the iodonium salt is highlighted.
\end{center}

Other application areas of diaryliodonium salts include the arylation of heteroatoms, as benzyn precursors, as photoinitiators in polymerizations and also as precursors to \textsuperscript{19}F-labelled radio-ligands. The synthesis and current applications of diaryliodonium salts have recently been summarized in an comprehensive review.\textsuperscript{33}
1.4 Objectives of This Thesis

The previously described strategies for the synthesis of diaryliodonium salts have many drawbacks. To summarize:

Usually the protocols are confined to the synthesis of either electron-rich or electron-poor diaryliodonium salts and often with a narrow substrate scope. This makes the synthesis of these reagents less attractive, especially for non-specialists who will find a swarm of synthetic protocols but none that is general and can deliver diaryliodonium salts ranging from electron-rich to electron-poor.

The protocols often employ pre-formed iodine(III) compounds that are either expensive or not commercially available. This adds a synthetic step as the iodine(III) reagent has to be synthesized prior to the synthesis of the desired diaryliodonium salt. This is, of course, time consuming and lowers the overall yield.

In those few one-pot protocols that exist, reagents such as CrO$_3$ are employed, which is highly toxic and not attractive to work with. The protocols often also suffer from limited substrate scope and long reaction times.

With the drawbacks presented in mind, we envisioned a general one-pot procedure that would neither be constrained by the electronic properties of the substrates nor require special conditions. The protocol should be quick, high yielding and easy applicable for non-specialists, in order to make the synthesis of these reagents more attractive and thus widen their use in various applications.

We also envisioned the development of a novel and general pathway to $\alpha$-arylation of carbonyl compounds that was not based on the use of chiral bases or of diaryliodonium salts bearing a chiral backbone.
Chapter 2

One-Pot Synthesis of Diaryliodonium Triflates from Aryl Iodides and Arenes (Paper I & II)

A simple and atom efficient one-pot synthesis of diaryliodonium salts would involve treatment of an aryl iodide 1 with a commercially available oxidant in the presence of an arene 2 and a suitable acid, the conjugated base of which would end up as the anion in the diaryliodonium salt 5 (Scheme 18).

Scheme 18. Envisioned one-pot synthesis of diaryliodonium salts.

The greatest challenge in finding such a procedure would be to find reagents that are compatible with each other. Thus, a screening of possible oxidants, acids and solvents that could be employed in the selected model reaction between iodobenzene (1a) and benzene (2a) to yield diphenyliodonium salts (5) was undertaken.

2.1 Initial Experiments

The initial attempts with BF$_3$·Et$_2$O in dichloromethane with K$_2$S$_2$O$_8$ as oxidant did indeed give a diaryliodonium species (Scheme 19), but numerous anionic peaks could be detected in the mass spectrum. Problems with isolation of the salts were a major drawback as well formation of (4-iodophenyl)(phenyl)iodonium salt as by-product.
Scheme 19. In our first protocol we had difficulties in assigning the anion (X') of the different products.

Consequently a screening of other acids began; changing BF₃·Et₂O to TsOH only resulted in recovered starting materials whereas TfOH produced the desired triflate salt 5a, however only in 8%, isolated from a tarry black residue.

Despite our limited success with K₂S₂O₈ as oxidant, the problems associated with it were too many and other oxidation reagents were screened. At that same time Kitamura and co-workers published a paper, describing how they utilized this oxidant in combination with excess trifluoroacetic acid (see Chapter 1.3, Scheme 7).[46]

Oxone® is a powerful oxidant, but it is not readily soluble in organic solvents. If the cation in Oxone® (i.e. K⁺) is changed to e.g. n-Bu₄N⁺, the oxidant also shows higher solubility in organic solvents, and especially in dichloromethane.[55] Regrettably, when applying this oxidant in our reaction only starting materials were recovered.

Recently, Stavber and co-workers[76-77] showed that aqueous H₂O₂ could oxidize 1⁻ to I⁺ in their environmentally benign protocol for iodination of arenes, and we were keen to apply it in our system. Trace amounts of 5a could be detected by ¹H-NMR, however, only when the reaction was performed in MeCN with TFOH (Scheme 20).

Scheme 20. Reaction with hydrogen peroxide.

Peracetic acid[36] can easily oxidize iodine compounds and more recently mCPBA has also been utilized.[22-23, 78] Surprisingly, mCPBA had never been used in the direct synthesis of diaryliodonium salts.

Gratifyingly, when mCPBA and BF₃·Et₂O were used in our model reaction, pure diphenyliodonium meta-chlorobenzoate (6a) was obtained in 33% yield (Scheme 21). A drawback of this method was that an excess of benzene was needed, together with long reaction times.

We thus continued exploring this reaction and found that it was improved when TFOH was used in place of BF₃·Et₂O. The amount of 2a and acid could be reduced and the diaryliodonium salt could be obtained in higher yield than with BF₃·Et₂O (Scheme 21). A problem however, was that the
crude mixture contained an inseparable mixture of 6a and 5a, in a ratio of 10:1.

Scheme 21. Initial experiments with mCPBA as oxidant.

When quenching the reactions in Scheme 21 with a saturated solution of NaHCO₃, we could always observe a significant change of color. Hence, we decided to see what happened if we concentrated the solution without quenching the reaction. Fortunately, addition of diethyl ether to the crude concentrated reaction mixture precipitated out a solid that was identified as pure diphenyliodonium triflate (5a) in high yield, while the 3-chlorobenzoic acid stayed in solution. The basic workup used initially, apparently gives a rapid anion exchange, expelling the weaker triflate anion to m-chlorobenzoate. These promising initial results lead us to further investigations.

2.2 Optimization Studies

When using stoichiometric amounts of all reagents, the reaction was sluggish and only delivered the product in low yield (Table 1, entry 1). We could not recover any iodobenzene, which is an indication of a working oxidation process but an inefficient EAS. Hence, the amount of TfOH was increased to 2 eq. which resulted in that 5a could be isolated in a high yield compared to the first entry (entry 2). An increase of mCPBA to 2 eq. instead resulted in decreased yield (entry 3), which could be due to over-oxidation to iodine (V). The amount of benzene also had a slight impact on the reaction outcome, as shown in entries 4 and 5. Increasing the temperature considerably reduced the reaction time, delivering 5a in good yields after 3 h at 40 °C (entry 6) or 10 min at 80 °C (entry 7). The best results could be obtained
when 3 eq. of TfOH was used, in which case 5a was obtained in 89% yield after only 10 minutes at room temperature (entry 8).

A subsequent temperature study using 3 eq. TfOH revealed that the reaction is much faster than we had anticipated. Amazingly, the reaction was complete within 10 min even at temperatures as low as -50 ºC. However 0 ºC or room temperature (Table 1, entry 9) was deemed to be the most convenient temperature for further reactions. The use of anhydrous reaction conditions (inert atmosphere, anhydrous solvent) was tested and shown to have no beneficial effect on the outcome of the reaction.

Table 1. Optimization of reaction conditions for synthesis of salt 5a.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>2a (eq.)</th>
<th>mCPBA (eq.)</th>
<th>TfOH (eq.)</th>
<th>T (ºC)</th>
<th>Time</th>
<th>Yield (%)[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>rt</td>
<td>18 h</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>1.1</td>
<td>2.0</td>
<td>rt</td>
<td>18 h</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>2.0</td>
<td>2.0</td>
<td>rt</td>
<td>18 h</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>1.1</td>
<td>2.0</td>
<td>rt</td>
<td>18 h</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>5.0</td>
<td>1.1</td>
<td>2.0</td>
<td>rt</td>
<td>21 h</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>1.1</td>
<td>2.0</td>
<td>40</td>
<td>3 h</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>1.1</td>
<td>1.1</td>
<td>2.0</td>
<td>80</td>
<td>10 min</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>1.1</td>
<td>3.0</td>
<td>80</td>
<td>10 min</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>1.1</td>
<td>1.1</td>
<td>3.0</td>
<td>rt</td>
<td>10 min</td>
<td>92</td>
</tr>
</tbody>
</table>

[^a] Reaction conditions: 1a (1.0 eq. 0.23 mmol), 2a and mCPBA were dissolved in CH₂Cl₂ (1 mL), TfOH was added dropwise at 0 ºC and the reaction was stirred at the indicated temperature and time. [^b] Isolated yield.

Performing control experiments with 2 eq. of TfOH showed that the rate is reduced considerably with less acid (Table 2, entries 1 and 2). Changing the solvent to Et₂O, CHCl₃ or CH₂CN resulted in decreased yields (entries 3-5), whereas changes in concentration were less important (entries 6 and 7). The reaction also proceeded under solvent free conditions, however it gave a lower yield (entry 8). We continued our investigation by checking whether TfOH was needed in the oxidation or only mediated the EAS step. Reacting
iodobenzene, benzene and mCPBA in the absence of TfOH, indeed gave a slow oxidation (seen by $^1$H-NMR) but no diaryliodonium salt was formed (entry 9). Purification by flash chromatography in CH$_2$Cl$_2$/MeOH instead of precipitation gave 5a in slightly lower yield (entry 10).

<table>
<thead>
<tr>
<th>Entry</th>
<th>TfOH (eq.)</th>
<th>Solvent</th>
<th>T ($^\circ$C)</th>
<th>Yield (%)$^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>CH$_2$Cl$_2$</td>
<td>rt</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>Et$_2$O</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>CHCl$_3$</td>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>CH$_3$CN</td>
<td>0</td>
<td>.$^{[e]}$</td>
</tr>
<tr>
<td>6</td>
<td>3.0</td>
<td>CH$_2$Cl$_2^{[c]}$</td>
<td>0</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>3.0</td>
<td>CH$_2$Cl$_2^{[d]}$</td>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>3.0</td>
<td>Neat</td>
<td>0</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
<td>.$^{[e]}$</td>
</tr>
<tr>
<td>10</td>
<td>3.0</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
<td>79$^{[f]}$</td>
</tr>
</tbody>
</table>

$^{[a]}$ Reaction conditions: As described under Table 1. All reactions employed benzene (1.1 eq.) and mCPBA (1.1 eq.) and were run for 10 minutes at the temperature indicated above. $^{[b]}$ Isolated yield. $^{[c]}$ 2 mL. $^{[d]}$ 0.5 mL. $^{[e]}$ No product formed. $^{[f]}$ Isolated by flash chromatography.

2.3 Arene Scope

Most previous protocols have been restricted to the synthesis of either electron-rich or electron-deficient diaryliodonium salts, as the reactivity of the iodoarenes and arenes varies with the electronic properties.$^{[39-44, 57, 79]}$ To determine the generality of this novel one-pot reaction, it was applied to the synthesis of various diaryliodonium salts 5 by reaction of iodobenzene (1a) with a range of arenes 2 (Table 3).

The use of iodobenzene as iodoarene and arene yielded (4-iodophenyl)-(phenyl)iodonium triflate (5b), as a single regioisomer (entry 2). Other aryl halides also participated in the reaction, giving salts 5c-e with small amounts of ortho-substituted product detectable by NMR (entries 3-5). We continued by reacting 1a with various alkyl-substituted arenes, which delivered salts 5f-j in good yields, surprisingly also for sterically hindered arene 2i (entries
Regioselectivity became an issue with 1-bromo-3,5-dimethylbenzene (2k), which gave an inseparable mixture of salts 5k’ and 5k” (entry 11). The electron-rich arenes acetanilide (2l), anisole (2m) and thiophene (2n) were, as expected, very reactive under the standard conditions. By decreasing the temperature, salts 5l-n could be obtained in good yields (entries 12-14).

**Table 3.** Synthesis of substituted diaryliodonium salts 5 from PhI (1a) and arenes 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar-H</th>
<th>Salt 5[a]</th>
<th>Yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhH</td>
<td>5a</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>PhI</td>
<td>5b</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>PhBr</td>
<td>5c</td>
<td>71[c]</td>
</tr>
<tr>
<td>4</td>
<td>PhCl</td>
<td>5d</td>
<td>57[c]</td>
</tr>
<tr>
<td>5</td>
<td>PhF</td>
<td>5e</td>
<td>92[c]</td>
</tr>
<tr>
<td>6</td>
<td>PhMe</td>
<td>5f</td>
<td>85</td>
</tr>
</tbody>
</table>
[a] Formed with complete regioselectivity unless stated otherwise. The anion is omitted for clarity. [b] Isolated yield. [c] Less than 5% ortho-isomer detectable by ¹H-NMR.
2.4 Aryl Iodide Scope

We subsequently investigated the aryl iodide scope, and the results are shown in Table 4. When 4-bromoiodobenzene (1b) reacted with benzene, salt 5c was obtained in good yield (entry 1). Further reactions with 1b delivered symmetric salt 5o, and anisole was also successfully employed to give the novel salt 5p (entries 2 and 3). The chloro-substituted substrate 1c showed similar reactivity to 1b, as shown in entries 4-6. 2-Iodotoluene (1d) was deemed an interesting substrate as it showed similar reactivity to 1b, as shown in entries 4-6. 2-Iodotoluene (1d) was therefore reacted with various arenes, giving salts 5s-z in high yields (entries 7-14). The sterically hindered arene 2i yet again afforded the desired product, albeit in moderate yield (entry 12). As expected, 1d was more reactive than 1a, but still delivered salts with high purity, including in the reaction with anisole (entry 14). Similar to 1d, 4-iodotoluene (1e) was reacted with benzene and toluene, respectively, to deliver salts 5f and 5aa (entries 15 and 16). The reason for the moderate yield of 5aa is unclear, as the reactivity of 1e should be similar to 1d.

Table 4. Synthesis of substituted diaryliodonium salts 5 from aryl iodides 1 and arenes 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar^1-I</th>
<th>Ar^2-H</th>
<th>Salt 5[^a]</th>
<th>Yield (%)[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>PhH</td>
<td>5c</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>PhBr</td>
<td>5o</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>PhOMe</td>
<td>5p</td>
<td>58</td>
</tr>
</tbody>
</table>

[^a]: Synthesis of substituted diaryliodonium salts 5 from aryl iodides 1 and arenes 2
[^b]: Yield (%)
<table>
<thead>
<tr>
<th>No.</th>
<th>Compound 1</th>
<th>Compound 2</th>
<th>Compound 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>1d</td>
<td>2j</td>
<td>5y</td>
</tr>
<tr>
<td>14</td>
<td>1d</td>
<td>2m</td>
<td>5z</td>
</tr>
<tr>
<td>15</td>
<td>1e</td>
<td>2a</td>
<td>5f</td>
</tr>
<tr>
<td>16</td>
<td>1e</td>
<td>2f</td>
<td>5aa</td>
</tr>
<tr>
<td>17</td>
<td>1f</td>
<td>2a</td>
<td>5g</td>
</tr>
<tr>
<td>18</td>
<td>1g</td>
<td>2a</td>
<td>5ab</td>
</tr>
<tr>
<td>19</td>
<td>1h</td>
<td>2a</td>
<td>5ac</td>
</tr>
<tr>
<td>20</td>
<td>1i</td>
<td>2a</td>
<td>5ad</td>
</tr>
<tr>
<td>21</td>
<td>1j</td>
<td>2a</td>
<td>5ae</td>
</tr>
</tbody>
</table>
2.5 Limitations to the Developed Protocol

2.5.1 Electron-Rich Aryl Iodides

All reactions with electron-rich iodoarenes resulted in a black tarry solution when TfOH was added (Appendix C). A brief investigation was thus performed with 4-idoanisole (1I). In the absence of TfOH we found that mCPBA smoothly oxidized 1I and compound 7 could be isolated in 80% yield (Scheme 22).
Scheme 22. Oxidation of the highly electron-rich 4-iodoanisole works fine without TIOH. Sequential synthesis of 6b or 5m from 7 was however unsuccessful.

Addition of benzene to 7 resulted in recovered starting materials, whereas addition of benzene together with TIOH resulted in a black tarry solution. This indicates that the acid is needed in the EAS step, however, it causes side reactions when added to very electron-rich systems. As this limits the possibility to synthesize symmetric electron-rich salts, another method was developed in our group to obtain such salts.81

2.5.2 Electron-Poor Arenes

In reactions starting from iodobenzene and an electron-deficient arene, the formation of 5b was the major product (Figure 8).

Figure 8. Salt 9 was obtained instead of the expected product 8.

Heating 1-iodo-4-nitrobenzene (1g) with nitrobenzene at 80 °C for 14 h was expected to deliver the unsymmetrical (4-nitrophenyl)(3-nitrophenyl)-iodonium triflate 8. Surprisingly, compound 9, where mCBA had reacted as an arene, was isolated as the only product in 35% yield (Figure 8). This demonstrates a limitation to our developed protocol as arenes that are more deactivated than mCBA are not suitable, hence symmetric deactivated salts cannot be obtained.

Another limitation is the regioselectivity restriction. As the last step is an EAS, the regioselectivity is dependent on the arene (see Chapter 1.3.2,
Scheme 12), and we have seen that the reaction is highly regioselective in delivering only para-products, thus, symmetric ortho- and meta-substituted products are inaccessible.

2.6 Conclusions

In conclusion, we have developed a powerful and efficient one-pot procedure for the preparation of diaryliodonium triflates. The protocol is high yielding, has a broad substrate scope, easy applicability and very short reaction times.

The general strategy for the synthesis of unsymmetric salts is to start from the less electron-rich aryl iodide and the more electron-rich arene rather than from the reverse reaction pathway.
Chapter 3

One-Pot Synthesis of Diaryliodonium Triflates from Iodine and Arenes
(Paper I, II & III)

Aryl iodides are readily available but more costly than the parent arene. Formation of diaryliodonium salts directly from iodine and arenes, via *in situ* generation of the aryl iodide, would conveniently circumvent the need for aryl iodides as a starting material. Finding such a reaction pathway would greatly simplify the synthesis of these reagents.

Halogenation of arenes is usually performed with $X_2$ and a Lewis acid, which withdraws electrons from the diatomic molecule, thereby polarizing the bond. This is regarded as a standard procedure for chlorination and bromination of arenes. Iodination of arenes is, however, usually carried out in the presence of an oxidant (e.g. peroxo acid) to generate the iodine electrophile $I^+$.\[^{[82]}\]

Kitamura and co-workers showed that (diacetoxyiodo)arenes could be formed directly from arenes and iodine in the presence of $K_2S_2O_8$, presumably with the corresponding aryl iodide as intermediate.\[^{[83]}\] Hence, we envisioned a direct one-pot synthesis of diaryliodonium triflates (5), from arenes (2) and molecular iodine with $m$CPBA and TfOH.

3.1 Optimization

A complete transformation of molecular iodine into two molecules of diaryliodonium salt would require 3 equivalents of $m$CPBA and four equivalents of arene. We thus started our investigation with that reagent stoichiometry (Scheme 23).
Scheme 23. Schematic overview of the formation of two equivalents of 5a from I₂ and benzene.

To keep the triflic acid:product ratio at 2:1,[84] 4 eq. of TfOH was added which indeed delivered salt 5a in 45% yield in this one-pot, three-step reaction (Table 5, entry 1).[85] Longer reaction time resulted in 61% yield (entry 2), and an increase of the triflic acid:product ratio to 3:1 gave 5a in 92% yield within 10 min at rt (entry 3). Increasing the amount of mCPBA to 4 eq. or the use of excess benzene increased the yield slightly (entries 4-6) at longer reaction times.

Table 5. Synthesis of salt 5a directly from benzene and iodine.^[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>2a (eq.)</th>
<th>mCPBA (eq.)</th>
<th>TfOH (eq.)</th>
<th>T(°C)</th>
<th>Time</th>
<th>Yield 5a (%)^[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.1</td>
<td>3</td>
<td>4</td>
<td>rt</td>
<td>10 min</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>4.1</td>
<td>3</td>
<td>4</td>
<td>rt</td>
<td>20 h</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>4.1</td>
<td>3</td>
<td>6</td>
<td>rt</td>
<td>10 min</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>4.1</td>
<td>4</td>
<td>4</td>
<td>rt</td>
<td>21 h</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>4.1</td>
<td>4</td>
<td>4</td>
<td>rt</td>
<td>10 min</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
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<td>rt</td>
<td>22 h</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>4.1</td>
<td>3</td>
<td>4</td>
<td>60</td>
<td>10 min</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>4.1</td>
<td>3</td>
<td>4</td>
<td>80</td>
<td>10 min</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>4.1</td>
<td>3</td>
<td>3</td>
<td>80</td>
<td>10 min</td>
<td>46</td>
</tr>
<tr>
<td>10^[c]</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>80</td>
<td>10 min</td>
<td>(51)</td>
</tr>
<tr>
<td>11^[c]</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>80</td>
<td>10 min</td>
<td>(66)</td>
</tr>
<tr>
<td>12^[c]</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>80</td>
<td>10 min</td>
<td>(72)</td>
</tr>
</tbody>
</table>

^[a] Reaction conditions: I₂ (1.0 eq.), 2a, mCPBA and TfOH were stirred in CH₂Cl₂ at the indicated temperature and time.^[b] Isolated yield. Numbers in parentheses are results obtained after flash chromatography.^[c] LiI (1 eq.) was used instead of I₂.
As seen in the aryl iodide reactions, the reaction time could be shortened drastically by increasing the temperature, and 5a was obtained in excellent yields with 4 eq. of TfOH (entries 7 and 8). It is thus possible to choose reaction conditions depending on which parameter is deemed most important; time, reagent quantity or temperature, which should be of interest when scaling up the reaction (see Section 3.3). Further investigations showed that decreasing the amount of triflic acid lowered the yield (entry 9). Lithium iodide could successfully be employed as iodine source, although an excess of reagents was needed to give useful yields of 5a (entries 10-12). The formation of lithium triflate complicated the isolation of salt 5a in these last reactions and purification was thus performed with flash chromatography instead of precipitation from diethyl ether.

3.2 Substrate Scope

To determine the substrate scope of this efficient reaction, a number of arenes were tested (Table 6). The aryl halides 2c-e gave symmetric salts 5o, 5q and 5ah with complete para-selectivity (entries 2-4). Toluene (2f) yielded a mixture of salts 5u and 5aa with 3:1 regioselectivity favoring ortho-iodination (entry 5). Pure 5u was obtained, albeit in low yield, when the reaction was run for one hour at 0 °C (entry 6). Tert-butylbenzene (2g) proved to be an excellent substrate and delivered salt 5ai in 78% yield (entry 7). Other alkyl-substituted arenes, such as p-xylene (2h) and mesitylene (2j), gave salts in moderate yields (entries 8 and 9). Even highly substituted arene 2o participated in the reaction to give salt 5al (entry 10) in modest yield.

Table 6. Direct synthesis of salts 5 from arenes and iodine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar–H</th>
<th>Salt 5[a]</th>
<th>Yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhH 2a</td>
<td><img src="image" alt="5a" /></td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>PhBr 2c</td>
<td><img src="image" alt="5o" /></td>
<td>64</td>
</tr>
</tbody>
</table>
3  PhCl  2d  

4  PhF  2e  

5  PhMe  2f  

6[c]  PhMe  2f  

7  Ph'Bu  2g  

8  2h  

9  2j  

3:1  5u:5aa  52  31  78  47  52  57  71
As this one-pot reaction involves several sequential steps and many possible sources of byproducts, it is surprising that salts in Table 6 are easily and cleanly obtained in moderate to excellent yields.

All attempts with electron-rich arenes under our reaction conditions only resulted in black tar (See Appendix D). To obtain electron-rich symmetric salts another method developed by our group can be used. Attempts were also made to obtain unsymmetric diaryliodonium salts by using two different arenes in the reaction, however, this always resulted in product mixtures.

After the completion of this work, Kitamura and co-workers also published a direct synthesis of diaryliodonium triflates from iodine. Their protocol however required heating for 72 h and a subsequent anion exchange step to obtain the products (see Chapter 1, Scheme 7).

3.3 Large Scale Synthesis

The open access journal *Organic Syntheses* has, since 1921, provided the chemistry community with detailed, reliable, and carefully checked procedures for the synthesis of organic compounds. Anyone can submit a proposal for the journal. If the proposed procedure is accepted by the board, the submitters needs to carry out the proposed reaction on a large scale (generally 5-50 g, depending on the reaction) and must be written in considerably more detail than typical experimental procedures in other journals. After resubmission of the large scale procedure, one of the board members undertakes the mission to check the procedure for reproducibility and that all characterization data is correctly assigned. This is unique to this journal and gives procedures reported therein a quality stamp.

As the procedure shown earlier in this chapter has so many advantages in the preparation of symmetric diaryliodonium salts, we predicted that it would be worthy publication in *Organic Syntheses*.

3.3.1 Selection of a Suitable Substrate

Our first suggestion and submission was a synthetic protocol for diphenyliodonium triflate (5a) but the board thought that it was too similar to a pro-
procedure published in the 1950s (Scheme 24). Thus, they suggested us to prove the efficiency on a different substrate.

\[
\text{C}_{6}H_{5}C\equiv C + \text{C}_{6}H_{5}NO_{2} \xrightarrow{\text{NaOH/H}_{2}O} \text{Ph}-\text{I} \xrightarrow{\text{KI/H}_{2}O} 30 \text{ g Scale}
\]

**Scheme 24.** Published synthesis of diphenyliodonium iodide by Kennedy and co-workers.

A SciFinder® search for diaryliodonium triflates revealed a large number of hits for salt 5ai, which piqued our interest in this compound. Furthermore, 5ai is one of few commercial available salts. The scale-up of the synthesis of 5ai would also demonstrate the efficiency of the procedure as the use of costly iodoarenes such as 4-iodo-tert-butylbenzene could be avoided (Figure 9).

![Figure 9. Approximate costs for tert-butylbenzene (2g) and 4-iodo-tert-butylbenzene (1f).](image)

Bis(4-tert-butylphenyl)iodonium triflate (5ai, Scheme 25) was therefore chosen as target based on both the popularity of this compound and to demonstrate the power of the protocol.

\[
\text{I}_{2} + \text{2g} \xrightarrow{\text{mCPBA, TiOCl}_{2}} \text{5ai}
\]

**Scheme 25.** The diaryliodonium salt (5ai) chosen for scale-up reactions.

### 3.3.2 Scale-up, Isolation and Results

Several factors change when scaling up a reaction such as: stirring problems, reagent addition issues, handling difficulties associated with hazardous reagents, unpredictable exotherms, cumbersome purification, and costly optimization. All these factors need to be taken into consideration when scal-
ing up. A stepwise scale up is often necessary, as predicting a 100 fold scale up effect is harder and less accurate than for example a 10 fold increase.

In Section 3.1 it was shown that several parameters, such as time, reagent amount and temperature can be altered to suit the current need. Increasing the temperature of a solvent above its boiling point is not only hazardous, but also impractical at larger scales, as large pressure vessels are expensive and rarely used in academia. Thus, we decided that other parameters would be investigated first, and that a temperature increase would be considered only as a last resort.

By scrutinizing Table 5 (Section 3.1) it becomes evident that the reaction time is dependent on the amount of TfOH used, and that increasing the amount of arene from 4.1 to 10 eq. has small impact on the yield or rate of the reaction. The use of anhydrous reaction conditions (inert atmosphere, anhydrous solvent) was once again shown to have no beneficial effect on the outcome of the reaction.

When salt 5ai was previously synthesized from I$_2$ and tert-butylbenzene, it had proved to be difficult to precipitate from diethyl ether. It was believed that the aliphatic groups made the salt more lipophilic and slightly soluble in diethyl ether and in combination with remaining mCBA and TfOH in the mixture, caused the observed difficulties with precipitation. Thus, several work-up methods were tried, firstly the use of other ethers such as diisopropyl ether and tert-butyl-methyl ether, neither of which promoted precipitation. Secondly, pentane and diethyl ether/pentane mixtures were tried, but also turned out to be ineffective. Adding the crude reaction mixture directly on a silica plug to separate the mCBA also failed to improve precipitation. Hence, we turned our focus to TfOH. Indeed, washing the crude reaction mixture with distilled water before concentrating it to dryness removed most of the acid from the solution, and it was found that salt 5ai then precipitated directly from diethyl ether without any difficulties.
Table 7 summarizes the scale-up reactions ranging from 0.21 mmol to 21 mmol. Entry 1 shows a scale-up reaction between iodine and benzene not reported by us before. It is noteworthy as it can directly be compared to Kitamura’s reported large scale procedure (Scheme 26, see also Section 3.2).[47]

Scheme 26. Kitamura’s one-pot synthesis from I₂ and benzene.

The optimized reaction between tert-butylbenzene (2g) and iodine on a 0.2 mmol scale is shown in entry 2 (Table 7), which delivers the product in 79% yield. This reaction was scaled up by a factor of 8 and isolated with a similar yield (entry 3). Entries 4-6 demonstrates further scale-up, up to a 100-fold increase over entry 2, which to our delight gave yields in the same range as in the small scale reactions, even after lowering the amount of TfOH from 6 eq. to 5 eq. Entry 7 and 8 are the results obtained by the checkers, verifying that the procedure works and that the yield is within the range submitted by us.

Table 7. Summary of the scale-up reactions.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arene</th>
<th>TfOH (eq.)</th>
<th>Scale (mmol)[b]</th>
<th>Isolated (g)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>6</td>
<td>11.6</td>
<td>4.5</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>2g</td>
<td>6</td>
<td>0.212</td>
<td>0.090</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>2g</td>
<td>6</td>
<td>1.75</td>
<td>0.77</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>2g</td>
<td>6</td>
<td>13.6</td>
<td>6.2</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>2g</td>
<td>5</td>
<td>20.8</td>
<td>8.8</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td>5</td>
<td>18.1</td>
<td>8.2</td>
<td>83</td>
</tr>
<tr>
<td>7[c]</td>
<td>2g</td>
<td>5</td>
<td>18.1</td>
<td>7.7</td>
<td>78</td>
</tr>
<tr>
<td>8[c]</td>
<td>2g</td>
<td>5</td>
<td>9.10</td>
<td>3.9</td>
<td>79</td>
</tr>
</tbody>
</table>

[a] mCPBA (3.1 eq.), Arene (4.1 eq.), CH₂Cl₂ (~ 1 mL/0.1 mmol I₂). The product is isolated within 45 min. Isolated yields are reported after drying under vacuum for 14 h. [b] Theoretical amount of product. [c] Reactions done by the checkers.
3.4 Conclusions

A novel, direct synthesis of diaryliodonium triflates from iodine and arenes has been devised. The reaction times are often short and yields range from moderate to excellent. The utilization of molecular iodine and the use of both iodine atoms is seldom seen in the literature, which makes this protocol highly attractive, as it is atom efficient and also circumvents the need for expensive aryl iodides. We have shown that the reaction is easily scaled up without reduction in yield (Scheme 27).

\[
\text{I}_2 + \text{2g} \xrightarrow{\text{mCPBA (3.1 eq.), TFOH (5.0 eq.)}} \text{CH}_2\text{Cl}_2 \text{45 min, rt.} \quad \text{5ai} \quad 78\% \text{ at 21 mmol scale}
\]

**Scheme 27.** Optimized conditions for the large scale reaction. The product is isolated within 45 minutes at a 21 mmol scale.

The procedure was also controlled and verified by an external research group, further demonstrating the reliability and reproducibility of this methodology.
Limitations in synthetic protocols are common and usually arise from incompatibility between reagents and substrates. In some special cases, however, the reactivity pattern of the substrates can be a limitation. This was evident in our one-pot procedure from aryl iodides and arenes, as the synthesis of symmetric salts with ortho- and meta-substituents is not possible.

Searching the literature for procedures that circumvent the electrophilic aromatic substitution (EAS) rules, only a handful can be found. Surprisingly, all of them employed pre-formed iodine(III) reagents in reaction with silanes,[40] stannanes,[41-42] boron reagents[43-44] or lithiated arenes[57-58] (Scheme 28).

Scheme 28. Regiospecific routes to diaryliodonium salts.

To increase the range of readily accessible diaryliodonium salts and circumvent the need for preformed iodine(III) reagents, we thus envisioned a regiospecific one-pot reaction starting from iodoarenes and a suitably activated arene source.
4.1 Initial Experiments

Due to their high reactivity and low toxicity compared to silanes and stannanes respectively, arylboronic acids were deemed as the most interesting arene source to start our investigation with. We also decided to continue employing mCPBA and TfOH, as they were well established reagents in our previous work.

When mixing mCPBA and phenylboronic acid (10a) an unwanted reaction took place, resulting in a black tarry mixture. Fortunately, this could be avoided by adding the boronic acid as the last reagent, delivering 5a in 24% yield, with 5b as a minor by-product (Scheme 29).

\[
\begin{align*}
\text{Scheme 29. Initial experiments with TfOH.}
\end{align*}
\]

After initial optimization attempts, the use of triflic acid was abandoned in this model reaction, as the yield remained stubbornly low. BF\(_3\)-Et\(_2\)O was deemed as an interesting alternative, as it could give rise to diaryliodonium salts with a tetrafluoroborate anion \textit{in situ}.\textsuperscript{91-92, 93} Such salts are highly attractive and have been employed in several recent papers on Pd-catalyzed arylation reactions.\textsuperscript{59, 63, 94} There is, however, no general and easy method to synthesize various diaryliodonium tetrafluoroborates.\textsuperscript{43, 95-98} When iodobenzene and phenylboronic acid were reacted in the presence of mCPBA and BF\(_3\)-Et\(_2\)O at room temperature, diphenyliodonium tetrafluoroborate (11a) was indeed formed, albeit in 29% yield (Table 8, entry 1).

4.2 Optimization

As in the reactions with TfOH, an unwanted reaction between mCPBA and 10a was observed. Upon delaying the addition of the boronic acid \textit{i.e.} when the pre-oxidation time was between 15-60 minutes, we observed a dramatic increase in the yield of 11a (Table 8, entries 2-4). Temperature variation did not improve the results, neither during the pre-oxidation step I (entries 5 and 6) nor in step II. Shortening the time in step II did not lower the yield significantly (entry 7).
Table 8. Optimization of the synthesis of 11a.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>BF$_3$Et$_2$O (eq.)</th>
<th>Step I (min)</th>
<th>Step II (°C)</th>
<th>Step II (min)</th>
<th>Yield (%)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>0</td>
<td>30 rt</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>15</td>
<td>rt</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>30</td>
<td>rt</td>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>60</td>
<td>rt</td>
<td>60</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>30</td>
<td>0</td>
<td>60</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>30</td>
<td>40</td>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>30</td>
<td>rt</td>
<td>30</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>2.5</td>
<td>30</td>
<td>rt</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>2.5</td>
<td>30</td>
<td>rt</td>
<td>15</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>3.0</td>
<td>30</td>
<td>rt</td>
<td>15</td>
<td>78</td>
</tr>
<tr>
<td>11(^{[c]})</td>
<td>2.5</td>
<td>30</td>
<td>rt</td>
<td>15</td>
<td>83</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Reaction conditions: 1a (0.27 mmol) and mCPBA (0.30 mmol) were dissolved in CH$_2$Cl$_2$ (1 mL), BF$_3$Et$_2$O was added and the reaction was stirred at the indicated temperature for the time given in Step I. 10a (0.30 mmol) was subsequently added at 0 °C, the mixture was then stirred at rt for the time given in Step II.\(^{[b]}\) Isolated yield.\(^{[c]}\) 1 g scale.

The use of 2.5 eq. of BF$_3$Et$_2$O resulted in a slightly higher yield (entry 8), and lowering the time in step II furnished 11a in only 45 min reaction time (entry 9). Increasing the amount of BF$_3$Et$_2$O to 3.0 eq. resulted in similar yield (entry 10). The isolation of salt 11a was easily done by a fast elution of the crude reaction mixture through a silica plug, followed by precipitation from diethyl ether, which gave the salt in high yield and purity. Furthermore, the protocol was easily scaled up to 1 g without loss in yield or purification efficiency (entry 11).
4.3 Arylboronic Acid Scope

To investigate the scope of this reaction, the optimized conditions were subsequently applied to other substrates. Iodobenzene was reacted with electron-deficient and electron-rich arylboronic acids 10 to give unsymmetrical salts 11b–p in high yields (Table 9). The halo-substituted arylboronic acids 10b–f participated exceptionally in the reaction, yielding ortho-, meta- and para-substituted salts 11b–f (entries 2–6). Likewise, ortho- and meta-methyl-substituted boronic acids 10g, h delivered salts 11g, h (entries 7 and 8). Sterically hindered substrates such as 2,6-dimethylphenylboronic acid (10i) could also be employed (entry 9).

The synthesis of electron-deficient diaryliodonium salts generally requires heating and prolonged reaction time. It was therefore satisfying that salts 11j–m, obtained from electron-deficient boronic acids with various substitution patterns, could be isolated in good yields in only 45 minutes (entries 10-13). Electron-rich substrates, such as para-methoxy- and 1-naphthylboronic acids (10o, p), delivered salts 11o, p in high yields when the reactions were performed at low temperature (entries 15 and 16). Unfortunately, meta-methoxy-phenylboronic acid did not give the expected meta-substituted iodonium salt. A para-substituted salt was obtained instead, presumably via the electrophilic aromatic substitution pathway.

Table 9. Synthesis of salts 11 from 1a and arylboronic acids 10

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar-B(OH)₂</th>
<th>Salt 11</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>11a</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>11b</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>10c</td>
<td>11c</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>10d</td>
<td>11d</td>
<td>75</td>
</tr>
</tbody>
</table>
O was added and the reaction was stirred for 30 min at rt. 10 (0.30 mmol) was subsequently added at 0 °C and stirred for 15 min. [b] Anion omitted for clarity. [c] Isolated yield. [d] 10 was added at -78 °C.
4.4 Aryl Iodide Scope

Substituted symmetric salts are generally difficult to obtain, as the system either becomes too unreactive (electron-poor substrates) or too reactive (electron-rich substrates). Reported procedures are generally limited in scope and give moderate yields. Gratifyingly, our protocol delivered both electron-poor and electron-rich salts, as depicted in Table 10.

Halogenated iodoarenes 1m and 1b were smoothly oxidized and coupled with 10b and 10e, respectively, yielding symmetric salts 11q and r (entries 2 and 3). Likewise, 2-iodotoluene (1d) and ortho-tolylboronic acid (10g) gave salt 11s (entry 4). Again, the deactivated substrates showed high reactivity, giving salts 11t-v within 1.5 hours at rt (entries 5-7). The low yield reported for compound 11v, is due to competitive Baeyer-Villiger oxidation.

Table 10. Synthesis of symmetric salts 11 from aryl iodides 1 and arylboronic acids 10.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar-I</th>
<th>Ar-B(OH)_2</th>
<th>Salt</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>10a</td>
<td>11a</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>1m</td>
<td>10b</td>
<td>11q</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>10e</td>
<td>11r</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>10g</td>
<td>11s</td>
<td>74</td>
</tr>
<tr>
<td>5^{[c]}</td>
<td>1i</td>
<td>10j</td>
<td>11t</td>
<td>51</td>
</tr>
</tbody>
</table>
Highly activated iodoarenes 11 and 1o also participated in the reactions with the corresponding arylboronic acids 10o and p, but even at –78 °C side reactions took place and moderate yields were obtained (entries 8 and 9). Although the yields in entries 5–9 are moderate, the synthesis retains its appeal due to its simplicity, short reaction time, easy purification and large substrate scope.

As previously stressed, our developed one-pot synthesis of triflate salts (Chapter 2 and 3) was unable to deliver symmetric ortho- and meta-salts due to mechanistic reasons. It was therefore of interest to investigate whether the boronic acid route could, in a short reaction time, deliver diaryliodonium triflates via an in situ anion exchange. This was attempted on tetrafluoroborate salt 11q, which was synthesized as described above. TfOH was added to the reaction mixture and after 15 minutes of stirring at rt, the corresponding triflate salt 12 was obtained in high yield (Scheme 30).

Scheme 30. In situ anion exchange from tetrafluoroborate to triflate.
4.5 Conclusions

We have demonstrated an efficient and fast novel one-pot synthesis of symmetric and unsymmetric diaryliodonium tetrafluoroborates from iodo-arenes and arylboronic acids. Both electron-deficient and electron-rich salts can be synthesized in a regiospecific manner, and the substitution pattern can easily be varied. An \textit{in situ} anion exchange with triflic acid also gives access to the corresponding diaryliodonium triflates, some of which were inaccessible with previous protocols.
Chapter 5

Synthesis of Heteroaromatic Iodonium Salts
(Appendix B)

Numerous synthetic routes to diaryliodonium salts have been published since the discovery of the compounds more than a century ago. Few of these routes are however applicable when at least one aryl group is a heterocycle. It is easy to envisage the importance of these compounds, as with the newly developed metal-mediated couplings, the use of heteroaromatic iodonium salts would indeed be interesting, as would their application in medicinal chemistry.

Section 1.3.1 summarized two synthetic routes towards heteroaromatic iodonium salts, none of which is performed under acidic conditions. The Carroll group has recently published a route to (phenyl)(3-pyridyl)iodonium salt in their pursuit for efficient Positron Emission Tomography (PET) imaging reagents. This route however is a time consuming four step procedure which includes the use of chlorine gas (Scheme 31). They also point out in their paper that there is no one-step procedure to different (aryl)-(3-pyridyl)iodonium salts directly from 3-iodopyridine.

Scheme 31. Caroll and co-workers approach to (aryl)(3-pyridyl)iodonium salts.

In Chapter 2 we showed that the synthesis of heteroaryl containing iodonium salts indeed is possible under acidic and oxidative conditions, but no general route to these products was investigated. We thus decided to
study this reaction further by using different heteroaromatic substrates under the conditions developed previously (Scheme 32).

![Scheme 32. The first one-pot synthesis of pyridyl containing substrates under oxidative and acidic conditions reported.](image)

5.1 Initial Experiments and Optimization

Based on our previous results with the heteroaromatic substrates from Chapter 2, we decided that 3-iodopyridine would be a suitable model substrate, as the substitution in the 3-position remains and the chlorine is removed which we did not expect to differ in the outcome of the reaction too much from the original protocol.

Reacting 3-iodopyridine under the conditions described in Scheme 32 with benzene unfortunately resulted in a mixture of by-products. Protonated and oxidized starting material could be indentified together with some product. Different addition orders were tried but all gave mixtures containing either protonated or oxidized starting material.

After initial optimization (see Appendix B) we eventually found that if the nitrogen is protonated before the addition of mCPBA, the reaction proceeds smoothly with selective oxidation of the iodine. The product then forms in the typical EAS manner. Scheme 33 summarizes the optimum conditions found for 3-iodopyridine. Next we decided to investigate the substrate scope of this methodology.

![Scheme 33. The optimum conditions found for 3-iodopyridine.](image)

5.2 Substrate Scope and the Identity of the Products

Initially we decided to synthesize products in which one of the arenes bore bulky substituents. In Section 1.3.3, it was stated that the least sterically hindered aryl group is selectively transferred in metal catalyzed reactions. However, in metal-free arylation reactions it is necessary to differentiate the
arenes by varying the electronic properties of the substituents, as the most electron-deficient aryl group is transferred preferentially. Thus, we undertook the synthesis of heteroaromatic iodonium salts that had a bulky- or an electron-rich aryl group in parallel to each other.

Subjecting 1p and anisole to slightly modified conditions appeared to deliver the expected product. However, the yield was significantly higher than the theoretical maximum for 5an (Scheme 34).

![Scheme 34. Reaction that indicated something fishy.](image)

After repeating the reaction several times with similar results, it was concluded that the product 5an may have been isolated as the pyridinium triflate (5an'). If this proved to be the case, then the yields reported for the products synthesized in parallel and presented in Table 11 (vide infra) might be wrong, including those previously prepared.

The products from Chapter 2 were thus re-confirmed of their structure. 5af could be compared to a sample of the same compound prepared via a basic route i.e. no protonation was possible, and it was found once again to have identical analytical data. From the spectroscopic data, it was concluded that neither salt 5af nor 5ag were protonated (Figure 10).

![Figure 10. Products previously synthesized were not protonated.](image)

It had been observed that the 1H-NMR spectrum of 5an changes depending on the concentration of the solution. This concentration effect was not observed for compound 5af, which matched our theory that 5an was protonated and the concentration therefore affected the pH of the solution in the NMR tube. In order to investigate this effect, two more 1H-NMR spectra of 5an were recorded. The first of these was run with the addition of triethyla-
mine to the sample in order to provide a non-protonated reference, and the second was run with the addition of TfOH giving a fully protonated reference spectrum. With spectra for the two extremes of protonation in hand, it could be seen that the 'H-NMR data obtained from solutions containing different concentrations of 5an fitted between the two reference spectra, indicating different degrees of protonation (Figure 11).

Another approach taken in order to verify the protonation was to synthesize compound 5ao, as integration of the peaks in the 19F-NMR spectrum of the product should provide a measure of the number of equivalents of triflate anion present. The 19F-NMR would be expected to show peaks with a 1:3 ratio in the non-protonated case, versus a 1:6 ratio for the protonated product (Figure 12).

![Figure 11. Various amounts of compound 5an in 0.5 ml of MeOD-d4.](image)

Another approach taken in order to verify the protonation was to synthesize compound 5ao, as integration of the peaks in the 19F-NMR spectrum of the product should provide a measure of the number of equivalents of triflate anion present. The 19F-NMR would be expected to show peaks with a 1:3 ratio in the non-protonated case, versus a 1:6 ratio for the protonated product (Figure 12).
Indeed, it was found that the $^{19}$F-NMR integration gave a value of 1:5.5, indicating that 5ao' is the true structure.

This work was made as a last entry to this project and the compounds tabulated in Table 11 summarize the experiments done before, thus their structure is not verified yet. This is the reason for the doubly tabulated yields, where column A gives the yield if non-protonated and B if the compound is protonated.

**Table 11.** Synthesis of (aryl)(heteroaryl)iodonium triflates 5am-5ax from iodoarenes 1 and arenes 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodoarene 1</th>
<th>Ar-H 2</th>
<th>Product 5</th>
<th>Yield$^{[a]}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1p</td>
<td>PhH 2a</td>
<td>5am</td>
<td>93 69</td>
</tr>
<tr>
<td>1</td>
<td>1p</td>
<td>Me 2j</td>
<td>5ap</td>
<td>97 74</td>
</tr>
</tbody>
</table>

**Figure 12.** Experiment that showed us amount of fluorine present in the product.
In the reaction between 3-iodopyridine with mesitylene (2j) or 1,3,5-triisopropylbenzene (2p), salts 5ap and 5aq were obtained (Table 11, entries 2 and 3). 2-iodopyridine unfortunately did not react under these conditions, and protonated starting material was recovered. 4-Iodopyridine was not tried, as the same results were expected, based on the strongly electron-deficient

\[
\text{Mes} = \text{Mesityl, TRIP} = 2,4,6-\text{Triisopropylphenyl}^{[2]} \quad \text{A: Yield if product is not protonated on N. B: Yield if product is protonated on N.}
\]
nature of these protonated species (see Appendix B). Pyridine 1k also reacted with 2j, delivering 5ar (entry 4). 3-iodoquinoline reacted with 2j and 2p delivering 5as and 5at, respectively (entries 5 and 6). Pyrazoles 1r and 1s also furnished the corresponding MES- and TRIP-substituted products in good yields (entries 7-10).

5.3 Future Work and Conclusions

The degree of protonation of the products in Table 11 has not been identified completely and this remains to be done. It is interesting to note that products 5af and 5ag, which have a chlorine substituent ortho to the pyridyl nitrogen, are isolated as non-protonated products. A simple explanation might be that the chloride substituent withdraws electrons from the nitrogen making it less basic.

A thorough investigation of the effect of both substituent type (EWG, EDG, sterics) and substitution pattern (o-, m-, p- to N) on different hetero iodoarenes would be interesting. Also, a workup where the products can be isolated in the non-protonated form needs to be developed.
α-Arylation of Enolates by Rearrangement (Paper V)

α-Functionalized carbonyl compounds are of great interest as they are frequently used as intermediates for further transformations. A plethora of methods exists to prepare these compounds, depending on what kind of substituent is to be introduced. Alongside both classical enolate chemistry and cutting-edge organocatalysis, stands the field of hypervalent iodine chemistry, contributing many reagents capable of effecting e.g. oxygenation, halogenations, trifluoromethylation, alkenylation, alkylation and arylation.\textsuperscript{[21]}

6.1 α-Arylation of Carbonyl Compounds

α-Arylation of carbonyl compounds is a great challenge in organic chemistry and it is only in the late 1990s that reliable methods employing metal catalysis have been developed.\textsuperscript{[102-105]} As mentioned previously, hypervalent iodine reagents can be used for the arylation of carbonyl compounds, which was showed by Beringer and co-workers in 1960 (Scheme 35).\textsuperscript{[9]}

\textbf{Scheme 35.} The first reported α-arylation with diphenyliodonium chloride.

The reported yields were low and diarylation was a problem, but the group continued to pursue this new application area of diaryliodonium salts.\textsuperscript{[106-109]} They also observed that when unsymmetric diaryliodonium salts were used, the most electron deficient aryl group was transferred preferentially.
A more recent metal-free example includes the excellent umpolung strategy on Weinreb amides with Grignard reagents developed by the Somfai group (Scheme 36).\(^{[110-112]}\)

\[
\begin{align*}
\text{Ph-N} & \text{N-O} \quad 1) \text{LDA, THF, -78 }^\circ\text{C} \\
\text{N-OBu} & \quad 2) \text{ArMgX} \\
\text{Me} & \quad -78 \rightarrow 25^\circ\text{C} \\
\text{Ph-N} & \text{N-H} \\
\text{Ar} & \text{Me} \\
\end{align*}
\]

7 examples 76-92% yield

**Scheme 36.** \(^{\alpha}\)-Arylation of Weinreb amides developed by the Somfai group.

Metal catalyzed \(^{\alpha}\)-arylation reactions were developed independently by the groups of Hartwig, Buchwald and Miura in 1997.\(^{[102-104]}\) The methods are very similar and initially faced the same difficulties, but the challenges were overcome in different ways (i.e. the pK\(_a\) span of carbonyl compounds and condensation by-product formation).\(^{[113]}\) An example of the power within this methodology is the one-step synthesis of the tert-butyl ester of Naproxen shown in Scheme 37.\(^{[114-115]}\)

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{O} & \quad \text{O} \\
\text{Buchwald} & \quad 79\% \\
\text{Buchwald: 2.3 eq. EtCO_2Bu, 2.5 eq. NaHMDS, 3 mol\% Pd(OAc)_2, 6 mol\% ligand A, Tol, rt, 15 h.} \\
\text{Hartwig: 1.1 eq. EtCO_2Bu, 2.3 eq. NaHMDS, 1 mol\% Pd(dba)_2, 1 mol\% ligand B, Tol, rt, 12 h.} \\
\end{align*}
\]

**Scheme 37.** One-step reaction to a Naproxen derivative developed independently by Buchwald and Hartwig.

Enantioselective \(^{\alpha}\)-arylation of enolates is still an ongoing challenge. It is only recently that enantioselective metal-mediated arylations have been successful, and even then, only for special substrates.\(^{[106]}\) Likewise, only a limited number of metal-free enantioselective arylations have been reported. The Jørgensen group utilized chiral phase transfer catalysts (PTCs) to suc-
cessfully α-arylate β-ketoesters.\textsuperscript{[116-117]} The quaternary ammonium salt efficiently blocks one face of the enolate which upon S$_2$Ar attack on the electron deficient fluoroarene, yields enantiomerically enriched products (Scheme 38).

![Scheme 38](image)

Scheme 38. The stereoselective α-arylation of a β-ketoester with a chiral PTC developed by the Jørgensen group.

There is only one example in the literature where a chiral diaryliodonium salt has been utilized in α-arylations of carbonyl compounds. Ochiai and co-workers beautifully demonstrated the α-phenylation of β-ketoesters with an diaryliodonium salt bearing a binaphthyl core (Scheme 39).

![Scheme 39](image)

Scheme 39. The only asymmetric α-phenylation with a chiral diaryliodonium salt reported.

Another approach, mentioned already in Chapter 1.3.3, Scheme 16, is the use of a chiral base to desymmetrize the substrate before addition of the diaryliodonium salt. In this case the ee and dr were very high but the substrate scope is small.\textsuperscript{[118]}

Recently, new chiral diaryliodonium salts have been reported by the Olofsson group, however they have not yet been used in organic synthesis.\textsuperscript{[119]} The Ishihara group reported a $C_2$-symmetric iodoarene that was used catalytically in enantioselective α-spirolactonizations.\textsuperscript{[120]} Fujita and co-workers have adopted a similar strategy for the oxylactonization of 2-vinylbenzoic acids type compounds, giving the products in up to 97% ee.\textsuperscript{[121]} It will be interesting to see if any of these novel compounds will be tested in α-arylations of carbonyl compounds after an conversion to the corresponding diaryliodonium salt.
6.1.1 Aim of the Project

Evidently, α-arylation of carbonyl compounds is possible but chemists are still looking for a general method where any given carbonyl compound can be α-arylated. With easily accessible electrophilic diaryliodonium salts, we were eager to explore whether these reagents could be employed in new metal-free methods and extend it to enable asymmetric induction and thus enantioselective α-arylation.

As the approach of having diaryliodonium salts with a chiral backbone, or the use of a chiral base had previously been investigated, two easier and alternative approaches were deemed interesting to investigate: one in which diaryliodonium salts having a chiral anion (e.g. (1S)-10-camphorsulfonate, (CSA)), and a second where chiral Phase Transfer Catalysts (PTCs) are employed. In the former approach, it is hypothesized that the chiral counterion directs the electrophile to a preferred face of the enolate; in the latter approach, the PTC blocks one face of the enolate so that arylation can only occur from the other face. These strategies would yield enantiomerically enriched products, as the final step of the reaction is generally believed to be a reductive elimination (red. elim.) and is expected to proceed with retention between the carbon attached to the iodine and one of its ligands (i.e. aryl group) (Scheme 40).[122][123]

Scheme 40. Hypothesized reaction pathway in which enantiomerically enriched compounds can be obtained.

6.2 Approaching α-Arylation– the Asymmetric Way

As model substrates in our reactions the cyclic five- and six-membered β-ketoesters (Figure 13) were chosen for ready comparison with other related approaches.[60, 108, 116-117, 124]

Figure 13. β-keto esters to be used in our α-arylation study.
6.2.1 α-Arylation with Diaryliodonium Salts having a Chiral Counterion

**Preparation of Diaryliodonium Salts with a Chiral Counterion**

The literature contains many examples of chiral Koser type reagents that have been synthesized from either (diacetoxy)iodobenzene or Koser's reagent via an ligand exchange (Figure 14).\[125-126\] Also other hypervalent reagents having internal chiral anions / auxiliaries are known and are mainly of the benziodoxole or benziodazole types (Figure 14).\[127-129\]

![Figure 14. Chiral Koser type of reagents previously reported in the literature.](image)

On the other hand, reports of diaryliodonium salts bearing chiral anions are sparse, indeed, only one paper dating back to 1907 was found, in which the synthesis of diphenyliodonium tartrate was reported.\[130\] The basis of this claim was that the optical rotation value was greater in solution with the diphenyliodonium tartrate, than an equivalent amount of free tartaric acid in solution.\[8\]

We decided to synthesize novel diaryliodonium salts bearing the anion from (1S)-10-camphorsulfonic acid (CSA). By replacing TfOH with CSA in the synthesis described in Chapter 2, we expected that diphenyliodonium (1S)-10-camphorsulfonate would be formed. However, no product was isolated from this reaction, likely due to CSA being a much weaker acid.\[131\] Thus, these products were prepared by performing an anion exchange on the relevant diaryliodonium triflate using an aqueous solution of sodium (1S)-10-camphorsulfonate. It was necessary to repeat the extraction procedure four times to obtain pure diaryliodonium (1S)-camphor-10-sulfonates 13a and 13b (Scheme 41) as determined by $^1$H-NMR and $^{19}$F-NMR.
Scheme 41. Anion exchange from TfO− to CSA− on diarylodonium salts 5a and 5ai.

**Arylation Results**

Initial arylation reactions with compound 13a were carried out in toluene using CsOH as the base, it was hoped that tight electrostatic interactions in this solvent would increase the chance of chiral induction by the anion (Table 12, entries 1 and 2). These reactions were isolated in moderate yield however, no ee was observed. This could be attributed in part to solubility problems with the diarylodonium salts.

**Table 12.** Conditions tested for β-ketoesters 14 and 15 with salt 13a and 13b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>β-ketoester</th>
<th>Base</th>
<th>Solvent</th>
<th>Salt 13</th>
<th>ee</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>CsOH</td>
<td>Toluene</td>
<td>13a</td>
<td>0</td>
<td>14a</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>CsOH</td>
<td>Toluene</td>
<td>13a</td>
<td>0</td>
<td>15a</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>NaO Bü</td>
<td>THF</td>
<td>13b</td>
<td>0</td>
<td>14b</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>NaO Bü</td>
<td>THF</td>
<td>13b</td>
<td>0</td>
<td>15b</td>
</tr>
</tbody>
</table>

It was therefore decided that the reactions would be run in THF, which gave rise to a homogeneous solution (entries 3 and 4). To our disappointment, the reactions proceeded with the complete absence of any chiral induction, providing only racemic product.
6.2.2 α-Arylation Using a Phase Transfer Catalyst

Choice of PTC

In the introduction to this Chapter, Jørgensen’s successful asymmetric enolate arylation using PTCs was discussed.\[116-117\] The PTC (16) depicted in Figure 15 was shown to give the highest selectivity with respect to C vs. O-arylation, as well as the highest yield and ee in their reactions, and thus it became the PTC of choice in our arylation reactions. Catalyst 16 was synthesized according to the procedure reported in their first paper,\[116\] as the subsequent paper\[117\] does not report the same analytical data.

![Figure 15. PTC 16 that was used in our arylation reactions.](image)

Arylation Results

We adopted similar conditions to those used by Jørgensen and co-workers.\[116-117\] Thus, we were surprised when subjecting 14 to either CsOH or KOH with a catalytic amount of PTC (16) gave only racemic product (Table 13, entries 1-3). To suppress any possible background reaction, we added the PTC in stoichiometric amounts which unfortunately also returned racemic product (entries 4-6) in moderate yield.
Table 13. Conditions tested for β-ketoesters 14 and 15 with PTC 16.

<table>
<thead>
<tr>
<th>Entry</th>
<th>β-ketoester</th>
<th>Salt 5</th>
<th>Base</th>
<th>PTC 16 (eq.)</th>
<th>ee</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>5a</td>
<td>CsOH</td>
<td>0.2</td>
<td>0</td>
<td>14a</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>5ai</td>
<td>CsOH</td>
<td>0.2</td>
<td>0</td>
<td>14b</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>5a</td>
<td>KOH</td>
<td>0.2</td>
<td>0</td>
<td>14a</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>5a</td>
<td>KOH</td>
<td>1.0</td>
<td>0</td>
<td>14a</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>5a</td>
<td>KOH</td>
<td>1.0</td>
<td>0</td>
<td>15a</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>5a</td>
<td>CsOH</td>
<td>1.0</td>
<td>0</td>
<td>15a</td>
</tr>
</tbody>
</table>

It was both unexpected and disappointing to find that even in the presence of stoichiometric amounts of PTC no ee was observed.

These results, combined with the results from the arylation with chiral salts made us question the previous hypothesized reaction pathway. Thus, we decided to investigate the reaction mechanism further by means of a theoretical study, as the expected reductive elimination (i.e. [1,2] rearrangement) did not seem to be concerted (Scheme 42).

![Scheme 42](image)

Scheme 42. The expected reductive elimination did not seem to be concerted as the product was racemic.
6.3 Mechanistic Considerations

To apprehend the results one has to understand the underlying mechanistic background. The reactions of diaryliodonium salts with nucleophiles takes place via an initial ligand exchange on iodine, either by an associative or a dissociative pathway (Scheme 43).\textsuperscript{[16]}

![Associative Pathway](image)

![Dissociative Pathway](image)

**Scheme 43.** Schematic presentation of two suggested ligand exchange pathways.

The associative pathway involves association of a ligand \( \text{Nu}^- \), to the diaryl-\( \lambda^3 \)-iodane in the first step, followed by pseudorotations (e.g. Berry or turnside rotations)\textsuperscript{[1331]} and release of another ligand, \( \text{L}^- \), to reform the neutral diaryl-\( \lambda^3 \)-iodane. In contrast, the dissociative mechanism involves the formation of an ionic intermediate from the diaryl-\( \lambda^3 \)-iodane structure and the exchange of ligands (\( \text{L}^- \) to \( \text{Nu}^- \)). This is, as in the first step, in equilibrium with the T-shaped diaryl-\( \lambda^3 \)-iodane.

From here the reaction takes on one or both of the following paths: A) Reductive elimination leading to the coupling products directly or B) Homolytic cleavage leading to a pair of radicals before the recombination, forming the products (Scheme 44).

![Scheme 44](image)

**Scheme 44.** Two different pathways leading to product formation.

It was discovered by Sandin and co-workers in the 1930s, that decomposition of diaryliodonium salts occurs by formation of radicals.\textsuperscript{[134]} However,
it was not until the work of Barton et al. in the 1980s that the reductive elimination pathway was proven with the addition of radical traps, revealing that the radical mechanism is a competitive side reaction to the reductive elimination.\textsuperscript{[135]} More recent studies have shown that the radical mechanism is unlikely to be operating in enolate arylation at all.\textsuperscript{[60, 136]}

Let us then consider our results again. We argued in Section 6.2 that the final step of the reaction is expected to be a [1,2] rearrangement and the chiral information thus \textit{must} be transferred,\textsuperscript{[137]} regardless of whether any pseudorotations take place, as the reductive elimination is a concerted reaction and proceeds with retention of configuration of the ligands. In \(\alpha\)-arylation of ketones with diaryliodonium salts, it is generally believed that the product forms via a “C-I” intermediate and as such, we never considered the optional “O-I” intermediate with the enolate oxygen acting as a ligand. Although it has previously been suggested that an “O-I” intermediate may be formed\textsuperscript{[124, 138-140]} such a compound had never been isolated until recently as shown by Quideau and co-workers in their mechanistic investigation on de-aromatization of phenols (Figure 16).\textsuperscript{[141]}

\begin{center}
\textbf{Figure 16.} Isolated intermediate by Quideau and co-workers.
\end{center}

Thus we widened our mechanistic view to include the “O-I” intermediate as a possibility in our \(\alpha\)-arylation reaction (Scheme 45).

\begin{center}
\textbf{Scheme 45.} The “C-I” [1,2] and the “O-I” [2,3] rearrangement routes.
\end{center}

Suddenly the reaction profile becomes much more interesting. Intermediates C and D may initially form via the associative or the dissociative pathway from A and B. Thus, it becomes evident that it is only via the “C-I”
pathway and intermediate D that enantiomerically enriched compounds can be obtained in our project, as the “O-I” pathway and formation of intermediate C, would not retain any chiral information due to the rotation around the “C-O” bond.

6.4 Calculations

As the experimental results were disappointing yet intriguing, we decided to initiate collaboration with Prof. Per-Ola Norrby to perform calculations on the two different mechanisms. Thus, Prof. Norrby executed B3LYP calculations\(^\text{[142]}\) on a model reaction of the smallest enolizable compound (i.e. acetaldehyde) with diphenyliodonium chloride (Ph\(_2\)ICl), both in the gas phase and in THF. The chloride anion was chosen to ensure that any results indicating a dissociative pathway would be general also for more weakly coordinated anions, such as triflate or tetrafluoroborate.\(^\text{[16, 143]}\) The obtained results from the calculations in THF are depicted in Figure 17.

![Energy levels (in kJ/mol) of possible intermediates and TS structures in the reaction of ethenolate with diphenyliodonium chloride in THF. Dotted lines indicate rapid association and/or dissociation equilibria.](image)

Figure 17. Energy levels (in kJ/mol) of possible intermediates and TS structures in the reaction of ethenolate with diphenyliodonium chloride in THF. Dotted lines indicate rapid association and/or dissociation equilibria.
Structures A and B are too close in energy to determine whether the initial ligand exchange follow a dissociative or an associative pathway, as we are comparing a neutral species with an ionic species. With less coordinating anions, e.g. TfO or BF₄⁻, structure B is more likely to be an intermediate with the direct formation of C and D. If the reaction is operating via the associative mechanism, intermediates E and F would initially form but rapidly lose a ligand to the more stable complexes C and D. The energy barrier going from anionic intermediates E and F directly to the product G is very high and unlikely. Surprisingly, the TS to form product G from C or D is slightly lower for the [2,3] rearrangement (C → G) than for the [1,2] rearrangement (D → G). The most interesting finding is the low energy η³-TS between the isoenergetic intermediates C and D as any chiral induction obtained in the first part of the mechanism will be lost in this fast equilibrium.

Calculations were also performed on the competing [1,2] and [2,3] rearrangements for compound 14 (Figure 18), and once again the [2,3] rearrangement was favored, implying that the results shown in Figure 17 are valid for various types of enolizable compounds.

![Figure 18. Favored [2,3] rearrangement TS in the arylation of compound 14 with diphenyliodonium chloride.](image)

Consequently, the calculations thus provide us with a degree of insight into the lack of enantioselectivity observed in the experimental work.

6.5 Conclusions

It is not possible to determine whether the reaction initially follows the dissociative or the associative pathway. Regardless of this, we found a low lying η³-TS between two intermediates which will destroy any asymmetric induction obtained in the first step of the reaction. We have also found that there is a slight preference for the [2,3] rearrangement over the [1,2] rearrangement in the transition state to product formation (Scheme 46). The calculations thus support the lack of selectivity observed in the experimental data.
Scheme 46. Summary of the possible reaction pathways, with a fast equilibrium between the intermediates leading to product formation via the [2,3] rearrangement.

It may be possible to improve the asymmetric induction of enolates with diaryliodonium salts by influencing the neutral, prochiral intermediate C, if one of the arenes has a chiral backbone similar to the binaphthyl core shown in Scheme 39, or by increasing the energy barrier between intermediates C and D. It is possible to differentiate the enantiotopic faces irreversibly by using a chiral base for the enolate formation as shown in Scheme 16 (Chapter 1.3.3), however, this approach have a rather small substrate scope. Ionic species such as the CSA– anion are not expected to influence neutral complex C, likewise with chiral Lewis bases (e.g. to form ionic compounds like E and F in Figure 17), as the following reductive elimination is expected to be too high in energy.
Concluding Remarks

New efficient methodology for the synthesis of diaryliodonium salts has been developed. The methodologies have broad substrate scopes, delivering a range of electron-poor to electron-rich diaryliodonium salts in high yields and short reaction times. The need for preformed iodine(III) reagents is circumvented as aryl iodides or molecular iodine can be used directly. The reactions are successful on a multigram scale, are tolerant of air and moisture and can be conducted from readily available starting materials. It is hoped that such features will broaden the appeal of these reagents in synthesis by making them readily accessible.

A new mechanism of α-arylation of enolizable carbonyl compounds by diaryliodonium salts has been presented and is supported by DFT calculations. The finding of a low energy η3-TS between two intermediates explained the lack of chiral induction in our experiments.
Appendix A

Contribution to Papers I – V

The following is a description of my contribution to publications I - V:

I. Shared the synthetic work with Dr. Berit Olofsson. Contributed to the writing of the supporting information.

II. I performed the major part of the synthetic work from aryl iodides and arenes. Dr. Mingzhao Zhu did most of the direct synthesis from arenes and iodine. I wrote parts of the supporting information.

III. I supervised the diploma worker David Aili, who made initial optimizations and experiments with different aryl boronic acids. I continued his work with further optimization and finished the project. I took part in writing the article and wrote the supporting information.

IV. I performed the synthetic work and took part in writing the article.

V. I designed parts of the project and performed initial experiments. Prof. Per-Ola Norrby performed the calculations and Dr. Tue B. Petersen finished the synthetic work.
Appendix B

Experimental Part to Chapter 5

Figure B 1 summarize heteroaromatic iodoarenes tried in the synthesis of (aryl)(heteroaryl)iodonium triflates but failed.

![Figure B 1](image)

**Figure B 1.** Heteroaromatics that gave no or poor yield of the desired products with mesitylene or triisopropylbenzene.

Table B 1 summarizes the optimization reactions between 3-iodopyridine and benzene. The yields are tabulated in columns A and B, where the yields in A are values before the findings that this compound was isolated in the protonated form.

Initial experiments were based on the conditions from Scheme 32. We began the investigation by determining whether an excess of the oxidant improved the yield of the reaction (Table B 1, entries 1-3). As 1.5 eq. of mCPBA gave the best yield, we then increased the amount of TfOH to 4eq., which in turn increased the yield further (entry 4). It was found that the reaction proceeds extremely rapidly, and that the product can be isolated in good yield after only 10 minutes (entry 5). Increasing the time to 30 minutes gave a significantly higher yield (entry 6). Unfortunately, lowering the reaction temperature to rt or 40 °C (entries 7 and 8) resulted in loss of reactivity as no product could be isolated, at temperature of 60 °C furnished the product in 93% yield A (entry 9).
Table B 1. Summary of the optimization between 3-iodopyridine (1p) and benzene (2a).

<table>
<thead>
<tr>
<th>Entry</th>
<th>mCPBA (eq.)</th>
<th>TFOH (eq.)</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)\textsuperscript{[a]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>3.0</td>
<td>80</td>
<td>3</td>
<td>78\textsuperscript{[b]} 54</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>3.0</td>
<td>80</td>
<td>3</td>
<td>76\textsuperscript{[b]} 52</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>3.0</td>
<td>80</td>
<td>3</td>
<td>84\textsuperscript{[b]} 60</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>4.0</td>
<td>80</td>
<td>3</td>
<td>92               68</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>4.0</td>
<td>80</td>
<td>10 min</td>
<td>72               48</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>4.0</td>
<td>80</td>
<td>0.5</td>
<td>84               60</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>4.0</td>
<td>rt</td>
<td>0.5</td>
<td>\textsuperscript{[c]} -</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>4.0</td>
<td>40</td>
<td>0.5</td>
<td>\textsuperscript{[c]} -</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>4.0</td>
<td>60</td>
<td>0.5</td>
<td>93               69</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} A: Yield if product is not protonated on N. B: Yield if product is protonated on N. \textsuperscript{[b]} NMR yields. \textsuperscript{[c]} No product could be isolated.

General Experimental Conditions for Products 5am – 5ax

NMR spectra were recorded using MeOD-\textsubscript{d\textregistered} as solvent. Chemical shifts are given in ppm relative to the residual peak for MeOD-\textsubscript{d\textregistered} (\textsuperscript{1}H-NMR δ 3.31, \textsuperscript{13}C-NMR 49.0) with multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad, app: apparent), integration and coupling constants (Hz). All reaction were carried out in sealed tubes to allow for reactions above the boiling point of CH\textsubscript{2}Cl\textsubscript{2}, and run without any precautions to avoid moisture or air, \textit{i.e.} without inert gas or dried solvent. TFOH (≥ 99%) was stored under an argon atmosphere. Newly purchased mCPBA contains a variable quantity of H\textsubscript{2}O. Prior to use, mCPBA was dried in batches under vacuum for 1 h and the percentage of active oxygen determined by iodometric titration. The dried, titrated mCPBA was then stored at 4 °C for future use.\textsuperscript{[144]} All other reagents were used as received (or synthesized according to the literature where stated) without further purification.
General Procedure for the Synthesis of Products 5am, 5ap–5ax

A typical example is shown between 1p and 2j yielding product 5ap:

3-iodopyridine (50 mg, 0.24 mmol) was dissolved in CH₂Cl₂ (1 mL) and TfOH (4 eq.) was added. The mixture was stirred for 5 minutes before the addition of mCPBA (1.5 eq.) followed by the addition of mesitylene (2j, 1.1 eq.). The reaction was stirred at 60 °C for 30 minutes before cooled down to room temperature and concentrated. Et₂O was added (1 mL) to the vial, cooled to 0 °C and stirred for 30 minutes to give a precipitate. The precipitate was washed with Et₂O (3 x 1 mL) to give compound 5ap as a beige solid (A: 97%; B: 74%).

Analytic Data for Compounds 5am, 5ap–5ax

**Phenyl(3-pyridyl)iodonium triflate (5am)**

\[
\text{\begin{array}{c}
\text{\textbf{N}}
\end{array}}
\]

Synthesized from 1p and 2a in (A: 93%; B: 69%) yield as light grey solid; mp: 127-130 °C; \(^1\text{H-NMR}\) (5 mg in 0.5 mL MeOD-\(d_4\), 400 MHz): δ 9.29 (d, J = 1.6, 1H), 8.86 (dd, J = 1.2, 4.8, 1H), 8.70 (ddd, J = 1.2, 2.0, 8.4, 1H), 8.25 (app. d, J = 8.5, 2H), 7.73 (app. t, J = 7.6, 1H), 7.65 (ddd, J = 0.8, 5.2, 8.4, 1H), 7.57 (app. t, J = 8.0, 2H); \(^{13}\text{C-NMR}\) (20 mg in 0.5 mL MeOD-\(d_4\), 100 MHz): δ 152.3, 151.1, 147.2, 136.9, 134.2, 133.5, 129.2, 121.8 (q, J = 316), 116.3, 115.4; HRMS (ESI): \(m/z\) calcd for C\(_{11}\)H\(_9\)NI [M]\(^+\): 281.9774; found: 281.9759. Note: Concentration effect found.

**Mesityl(3-pyridyl)iodonium triflate (5ap)**

\[
\text{\begin{array}{c}
\text{\textbf{N}}
\end{array}}
\]

Synthesized from 1p and 2j in (A: 97%; B: 74%) yield as a beige solid; mp: 153-155 °C; \(^1\text{H-NMR}\) (5 mg in 0.5 mL MeOD-\(d_4\), 400 MHz): δ 9.07 (dd, J = 0.8, 2.4, 1H), 8.84 (dd, J = 1.2, 4.8, 1H), 8.44 (ddd, J = 1.4, 2.4, 8.4, 1H), 7.66 (ddd, J = 0.8, 4.8, 7.0, 1H), 7.28 (s, 2H), 2.68 (s, 6H), 2.38 (s, 3H); \(^{13}\text{C-NMR}\) (20 mg in 0.5 mL MeOD-\(d_4\), 100 MHz): δ 150.6, 150.0, 147.1, 146.6, 143.8, 131.7, 129.7, 122.4, 121.7 (q, J = 317), 113.4, 27.1, 21.0; HRMS (ESI): \(m/z\) calcd for C\(_{14}\)H\(_{12}\)NI [M]\(^+\): 324.0244; found: 324.0252. Note: Concentration effect found.
2,4,6-Triisopropylphenyl(3-pyridyl)iodonium triflate (5al)

Synthesized from 1p and 2p in (A: 74%; B: 59%) yield as a white solid; mp: 149-150 °C; $^1$H-NMR (5 mg in 0.5 mL MeOD-$d_4$, 400 MHz): δ 9.00 (dd, $J = 0.6$, 2.3, 1H), 8.82 (dd, $J = 1.3$, 4.8, 1H), 8.34 (ddd, $J = 1.3$, 2.3, 8.3, 1H), 7.64 (ddd, $J = 0.8$, 4.8, 8.4, 1H), 7.37 (s, 2H), 3.45-3.40 (m, 2H), 3.06-3.01 (m, 2H), 2.79-2.75 (s, 9H), 1.31 (d, $J = 6.8$, 12H), 1.27 (d, $J = 7.0$, 6H); $^{13}$C-NMR (20 mg in 0.5 mL MeOD-$d_4$, 100 MHz): δ 157.6, 153.6, 151.0, 150.6, 145.9, 129.5, 126.8, 123.3, 121.8 (q, $J = 316$), 114.1, 40.8, 35.4, 24.5, 24.0; HRMS (ESI): m/z calcd for C$_{20}$H$_{17}$NI [M]$: 408.1183; found: 408.1192. Note: Concentration effect found.

Mesityl(6-Chloro-3-pyridyl)iodonium triflate (5ar)

Synthesized from 1k and 2j in (A: 61%; B: 47%) yield as a brown solid; mp: 163-164 °C; $^1$H-NMR (MeOD-$d_4$, 400 MHz): δ 8.82 (dd, $J = 0.7$, 2.4, 1H), 8.28 (dd, $J = 2.4$, 8.6, 1H), 7.58 (dd, $J = 0.5$, 8.5, 1H), 7.26 (s, 2H), 2.67 (s, 6H), 2.36 (s, 3H); $^{13}$C-NMR (MeOD-$d_4$, 100 MHz): δ 155.9, 154.3, 146.3, 145.4, 143.5, 131.5, 129.2, 122.4, 121.8 (q, $J = 314$), 111.4, 27.0, 21.0; HRMS (ESI): m/z calcd for C$_{14}$H$_{13}$ClNI [M]$: 357.9854; found: 357.9843.

Mesityl(3-quinolyl)iodonium triflate (5as)

Synthesized from 1q$^{[145]}$ and 2j in (A: 99%; B: 77%) yield as a light brown solid; mp: 155-156 °C; $^1$H-NMR (MeOD-$d_4$, 400 MHz): δ 9.45 (d, $J = 1.9$, 1H), 9.41 (d, $J = 2.1$, 1H), 8.27-8.15 (m, 3H), 7.95-7.94 (m, 1H), 7.30 (s, 2H), 2.77 (s, 6H), 2.38 (s, 3H); $^{13}$C-NMR (MeOD-$d_4$, 100 MHz): δ 150.2, 149.5, 146.5, 144.2, 143.8, 136.7, 131.6, 131.5, 131.2, 130.5, 125.8, 122.8, 121.7 (q, $J = 316$), 107.3, 27.2, 21.0; HRMS (ESI): m/z calcd for C$_{18}$H$_{17}$NI [M]$: 374.0400; found: 374.0399.
2,4,6-Triisopropylphenyl(3-quinolyl)iodonium triflate (5at)

Synthesized from 1q\textsuperscript{[145]} and 2p in (A: >100% (102%); B: 82%) yield as an off-white solid; mp: 135-138 °C; \textsuperscript{1}H NMR (MeOD-\textit{d}_4, 400 MHz): δ 9.34-9.32 (m, 2H), 8.21-8.19 (m, 2H), 8.14-8.10 (m, 1H), 7.95-7.91 (m, 1H), 7.40 (s, 2H), 3.61-3.54 (m, 2H), 3.07-3.00 (m, 1H), 1.36 (d, J = 6.7, 12H), 1.28 (d, J = 7.0, 6H); \textsuperscript{13}C NMR (MeOD-\textit{d}_4, 100 MHz): δ 157.6, 153.7, 150.4, 148.1, 145.5, 136.2, 131.4, 131.0, 130.3, 127.1, 126.9, 123.9, 121.9 (q, J = 316), 108.4, 40.9, 35.5, 24.7, 24.1; HRMS (ESI): m/z calcd for C\textsubscript{24}H\textsubscript{30}NI [M]\textsuperscript{+}: 458.1339; found: 458.1314.

3,5-Dimethyl-1H-pyrazol-4-yl(mesityl)iodonium triflate (5au)

Synthesized from 1r and 2j in (A: 93%; B: 71%) yield as a slightly brown solid; mp: 156-158 °C; \textsuperscript{1}H NMR (MeOD-\textit{d}_4, 400 MHz): δ 7.20 (s, 2H), 2.64 (s, 6H), 2.36 (s, 9H); \textsuperscript{13}C NMR (MeOD-\textit{d}_4, 100 MHz): δ 150.0, 145.4, 142.9, 131.4, 121.3, 121.8 (q, J = 317), 81.8, 26.1, 20.8, 12.2; HRMS (ESI): m/z calcd for C\textsubscript{14}H\textsubscript{18}N\textsubscript{2}I [M]\textsuperscript{+}: 341.0509; found: 341.0515.

3,5-Dimethyl-1H-pyrazol-4-yl(2,4,6-triisopropylphenyl)iodonium triflate (5av)

Synthesized from 1r and 2p in (A: 79%; B: 62%) yield as an off-white solid; mp: 139-140 °C; \textsuperscript{1}H NMR (MeOD-\textit{d}_4, 400 MHz): δ 7.30 (s, 2H), 3.43-3.36 (m, 2H), 3.05-2.98 (m, 1H), 2.37 (s, 6H), 1.29 (d, J = 6.8, 12H), 1.25 (d, J = 7.0, 6H); \textsuperscript{13}C NMR (MeOD-\textit{d}_4, 100 MHz): δ 156.5, 153.0, 149.7, 126.3, 122.8, 121.8 (q, J = 317), 81.9, 40.5, 35.3, 24.4, 24.0, 12.3; HRMS (ESI): m/z calcd for C\textsubscript{20}H\textsubscript{30}N\textsubscript{2}I [M]\textsuperscript{+}: 425.1448; found: 425.1451.
1H-Pyrazol-4-yl(mesityl)iodonium triflate (5aw)

Synthesized from 1s and 2j in (A: 84%; B: 63%) yield as a brown solid; mp: 172-173 °C; 1H-NMR (MeOD-d4, 400 MHz): δ 8.23 (s, 2H), 7.18 (s, 2H), 2.71 (d, 6H), 2.32 (s, 3H); 13C-NMR (MeOD-d4, 100 MHz): δ 145.4, 142.6, 140.3, 131.0, 124.2, 121.8 (q, J = 316), 79.0, 27.0, 20.9; HRMS (ESI): m/z calcd for C15H13N3I [M]+: 316.0196; found: 313.0192.

1H-Pyrazol-4-yl(2,4,6-triisopropylphenyl)iodonium triflate (5ax)

Synthesized from 1s and 2p in (A: >100% (101%); B: 79%) yield as an off-white solid; mp: 170-174 °C; 1H-NMR (MeOD-d4, 400 MHz): δ 8.17 (s, 2H), 7.27 (s, 2H), 3.57-3.48 (m, 2H), 3.03-2.96 (m, 1H), 1.36 (d, J = 6.7, 12H), 1.26 (d, J = 6.9, 6H); 13C-NMR (MeOD-d4, 100 MHz): δ 156.5, 152.5, 140.1, 125.9, 125.6, 121.8 (q, J = 317), 79.7, 40.4, 35.3, 24.4, 24.0; HRMS (ESI): m/z calcd for C18H26N3I [M]+: 397.1135; found: 397.1142.
Appendix C

Limitations from Chapter 2

Figure C 1 and Figure C 2 summarize different combinations tried in the synthesis of diaryliodonium triflates but failed.

Figure C 1. Arenes that gave no or poor yield of the desired iodonium salts with iodosobenzene.

Figure C 2. Aryl iodide and arene combinations that gave no or poor yield of the desired diaryliodonium salts.
Appendix D

Limitations from Chapter 3

Figure D 1 summarizes all arenes that were too activated/deactivated or for some other reason gave very low or no yield in the direct synthesis with iodine.

\[
\begin{align*}
\text{Ar} + I_2 & \xrightarrow{mCPBA, TFOH, CH_2Cl_2} \text{Ar}^+ \text{Ar}^- \text{OTf} \\
\end{align*}
\]

**Figure D 1.** Substrates that gave no or poor yield in reactions with iodine.
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References

[1] Following ACS Standard Abbreviations/Acronyms. The list can be found at the homepage for Organic Letters: Information for Authors: Guidelines for Authors.


For the synthesis and use of 5af, see B. Olofsson and V. K. Aggarwal, *Proc. 2nd Int. Conf. on Hypervalent Iodine, 2006*, 47-50.

The attempts to synthesize salt 5ag are unpublished.


See section 2.2; at least 2 eq. of TfOH is needed to obtain 1 eq. of diphenyliodonium triflate.

Iodobenzene was detected in reactions with short reaction time, supporting the assumption that iodobenzene is an intermediate in the reaction.

These mixtures were tried: benzene + chlorobenzene; benzene + toluene or benzene + anisole.


Unfortunately we found that the melting point differed by about 40 °C. The salt synthesized via the basic route is believed to be contaminated by LiCl impurities from its synthesis.


Compounds not containing N(Boc)₂ substituent gave much higher yields.

No stereochemical investigation has been performed on iodane compounds but its occurrence have clearly been demonstrated for hypervalent sulphur and phosphorus compounds. See the following reference.

No stereochemical investigation has been performed on iodane compounds but its occurrence have clearly been demonstrated for hypervalent sulphur and phosphorus compounds. See the following reference.


[132] The quasienantiomer was synthesized and it was confirmed that the data reported for compound 16 in the full paper is the data for the quasienantiomer.


[137] This would be valid for the associate pathway when the chiral salts and when the PTC is employed. In the dissociate pathway the use of PTC would transfer the chiral information whereas the chiral salt might not.


[142] Free energies at the B3LYP/6-31G* level in Jaguar 7.5.


