New Reactivity in Diaryliodonium Salt Chemistry

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Abstract

Diarylodium salts (Ar₂IX) have emerged as versatile multi-purpose reagents with desirable properties such as easy accessibility, low toxicity and applicability under mild and metal-free reaction conditions. Despite displaying broad utility in arylation of both carbon and heteroatom nucleophiles, the overall sustainability of these protocols is compromised by featuring poor atom economy due to the formation of stoichiometric iodoarene byproducts. In this thesis, this imperative drawback was addressed by development of a novel class of diarylodium salts with unprecedented reactivity that prevents the formation of iodoarene waste by incorporating both aryl groups as well as the iodine-component into the final products.

The first project concerns the development and design of ortho-fluorinated iodonium salts, where updated synthetic protocols were established to attain extensive salt scopes with diverse functionalities. The unique design of these reagents unveiled a cascade reaction whereby heteroatom-diarylated products were formed through concomitant nucleophilic aromatic substitution and intramolecular aryl transfer. The second project focuses on the applications of the ortho-fluorinated salts in diarylations of aliphatic amines, anilines, ammonia and water to attain industrially important diaryl- and triaryl amines as well as diaryl ethers (>100 examples). This atom-efficient methodology allows for transfer of two different aryl groups in a single step under mild and metal-free conditions, giving structurally diverse multi-aryl products that would otherwise require expensive and time-consuming multi-step synthesis.

The third project explores the potent combination of the diarylation strategy with the structural diversification of secondary aliphatic amines in the preparation of densely functionalized diarylamines. Cyclic amines constitute essential cornerstones in drug discovery and incorporation of such valuable moieties in Ar₂IX reagents is of considerable interest. By further exploiting the S₆/Ar reactivity of the ortho-fluorinated diarylodium salts, a previously inaccessible class of amino-functionalized Ar₂IX were prepared by reactions with cyclic amines. These N-functionalized reagents were utilized in a one-pot sequential arylation/ring opening pathway, where intramolecular arylation afforded diarylammonium salts in situ, which upon reaction with external nucleophiles underwent deconstructive C-N functionalizations. The methodology enables atom- and step-economical access to value-added diarylamines with versatile functionalities at both the C- and N-terminal.

The final project emphasizes the applicability of the diarylated products as versatile building blocks in various downstream functionalizations. The retention of the iodine-component enables diversification by a range of transition metal-catalysed cross-couplings, delivering products with increased structural complexity. The significance of the diarylation methodology was further demonstrated in the three-step synthesis of the drug molecule NMP-7. Two protocols were developed for transformation of the ortho-iododiaryl ethers into oxygen-bridged cyclic diarylodium salts and acyclic arylxoy salts. The synthetic utility of these unexplored Ar₂IX reagents was demonstrated in metal-free, chemoselective functionalizations of common nucleophiles.

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Populärvetenskaplig sammanfattning

Organisk kemi behandlar livets viktigaste element: kol. Faktum är att alla kända levande varelser på jorden är beroende av kol. Proteiner, DNA, fetter och kolhydrater är alla kolbaserade föreningar som i kombination med andra atomer som väte, kväve, syre, svavel och fosfor m.m. bildar dessa livsviktiga molekyler. Att förstå hur molekylerna är uppbyggda och huruvida dessa strukturer påverkar deras egenskaper är ett stort fokus för en organisk kemist. Samhällets avsevärda beroende av organiska molekyler ställer höga krav på den industriell produktionen av dessa, då de även utgör byggestenarna i våra läkemedel, jordbruks kemikalier och alla de material som vi använder och är beroende av dagligen. Detta medför ett stort ansvar för att framställningsmetoderna är hållbara, miljövänliga och så kostnadseffektiva som möjligt. Ett av de huvudsakliga forskningsområdena inom organisk kemi är därför utveckling av nya och förbättrade metoder för att tillverka (syntetisera) kolbaserade molekyler.

Vår forskargrupp fokuserar på syntes och användning av hypervalenta jodföreningar. Detta forskningsområde har fått stor uppmärksamhet de senaste åren då sådana föreningar kan användas för miljövänlig tillverkning av industriellt relevanta molekyler. Hypervalenta jodföreningar har många olika användningsområden och besitter ett flertal önskvärda egenskaper såsom låg toxicitet samt tillämpbarhet under milda och metallfria betingelser. Forskningen som behandlas i denna avhandling fokuserar på en specifik typ av hypervalenta föreningar som kallas ”diaryljodoniumsalter”. Dessa används för att överföra arylgrupper (t. ex bensen eller pyridin) till olika funktionella grupper (t. ex aminer, alkoholer, halogener, svavelföreningar m.m.), vilket medför nya egenskaper hos produkterna.

Trots det stora erkännandet diaryljodoniumsalterna har fått som effektiva aryleringsreagens, är deras reaktioner förknipprade med en viktig nackdel: bildandet av en biprodukt som kallas ”aryljodider”. Detta förnämmar metodernas övergripande hållbarhet då kostnads- och reaktionseffektiviteten minskar. Detta avhandlingsarbete har fokuserat på utvecklingen av en ny typ av diaryl-jodoniumsalter med nya egenskaper som inte medför sådant avfall.

Nästföljande kapitel fokuserar på användning av de nya jodoniumsalterna i funktionaliseringar av cykliska aminer. Dessa kväveföreningar är vanligt förekommande i läkemedel, vilket medför ett stort intresse för metoder som bidrar till expansion och förbättring av deras mångsidiga biologiska egenskaper. En metod utvecklades för diarylering samt ringöppning av de cykliska kväveföreningarna, vilket gav mycket komplexa diyralaminer som slutprodukt. Slutligen demonstrerades användandet av dessa diarylerade produkter som byggnadsmaterial i framställandet av ytterligare komplexa föreningar, inklusive tillverkningen av en läkemedelsmolekyl.
List of publications

This report is based on the following publications:

I. **Advancements in the synthesis of diaryliodonium salts: updated protocols**
   E. Linde, S. Mondal and B. Olofsson
   Selected as a VIP article

II. **Diarylation of N- and O-nucleophiles through a metal-free cascade reaction**
    E. Linde, D. Bulfield, G. Kervefors, N. Purkait and B. Olofsson
    *Chem* **2022**, 8, 850-865

III. **A one-pot cascade protocol for diarylation of amines and water**
     E. Linde and B. Olofsson
     *STAR protocols* **2022**, *3*, 101700

IV. **Synthesis of complex diarylamines through a ring-opening difunctionalization via ammonium salts**
    E. Linde and B. Olofsson
    *Submitted manuscript*. Preliminary version:

V. **Synthesis of cyclic and acyclic ortho-aryloxy diaryliodonium salts for chemoselective functionalizations**
   E. Linde, N. Knippenberg and B. Olofsson

Publications by the author not included in this thesis:

I. **Conceptually novel diarylation for sustainable synthesis**
   E. Linde
   *Chem* **2022**, 8, 601-603

II. **Regiospecific N-arylation of Aliphatic Amines Under Mild and Metal-free Reaction Conditions**
    N. Purkait, G. Kervefors, E. Linde and B. Olofsson
Previous documents based on this work

This thesis is in part based on the author’s half-time report entitled “Diarylation of Heteroatom Nucleophiles. Atom-efficient Applications of Diaryliodonium Salts under Metal-Free Conditions” (presented on June 29th 2021).

Chapter 1 (the introduction) has been updated to include a more detailed background on the synthesis and applications of cyclic diaryliodonium salts as well as more recent literature concerning the field of hypervalent iodine chemistry.

Chapter 2 (Papers I-II) has in part been presented in the half-time report, this chapter was completely rewritten and updated with new results.

Chapter 3 (Papers II-III) was presented in the half-time report and has been revised in the introduction, results and discussion sections. This chapter has also been updated to include new results.

Chapter 4 (Paper IV) was not presented in the half-time report and has been written for this thesis.

Chapter 5 (Paper II, V) was not presented in the half-time report and has been written for this thesis, with the exception of the derivatizations described in Scheme 46.
# Table of Contents

**Abstract**

1

**Populärvetenskaplig sammanfattning**

iii

**List of publications**

v

**Previous documents based on this work**

vi

**Abbreviations**

ix

1. **Introduction**

   1.1 Diaryliodonium salts
      
      1.1.1 Properties and reactivity
      1.1.2 Chemoselectivity
      1.1.3 Synthesis of diaryliodonium salts
      1.2 Atom-economical applications of diaryliodonium salts
         1.2.1 Cyclic diaryliodonium salts
         1.2.2 Acyclic diaryliodonium salts
      1.3 Nucleophilic aromatic substitution
      1.4 Aim of the thesis

2. **Preparation of Fluorinated Diaryliodonium Salts with Novel Reactivity (Papers I, II)**

   2.1 Introduction
   2.2 Method A
   2.3 Updated Method A
   2.4 Updated Method B
   2.5 Comparison of the Updated Methods A and B
   2.6 Updated Methods C and D
   2.7 Comparison of the Updated Methods C and D
   2.8 Conclusion

3. **Diarylation of N- and O-Nucleophiles through a Metal-Free Cascade Reaction (Papers II, III)**

   3.1 Introduction
   3.2 Diarylation of aliphatic amines
      3.2.1 Optimization
      3.2.2 Scope studies
   3.3 Diarylation of ammonia
      3.3.1 Optimization
      3.3.2 Scope studies
   3.4 Diarylation of anilines
   3.5 Diarylation of water
      3.5.1 Optimization

vii
3.5.2 Scope studies
3.6 Limitations of the diaryliodonium salt scope
3.7 Mechanistic studies
  3.7.1 Investigation of Pathway I
  3.7.2 Investigation of Pathway II
  3.7.3 S_NAr versus LC reaction routes
  3.7.4 Reactions with aryne and radical traps
3.8 Conclusion

4. Synthesis of Complex Diarylamines through a Ring-Opening Difunctionalization via Ammonium Salts (Paper IV)
  4.1 Introduction
  4.2 Proof of concept experiments
  4.3 Synthesis of N-functionalized iodonium salts
  4.4 Optimization of arylation/ring-opening sequence
  4.5 Substrate scope studies
    4.5.1 Diaryliodonium salt scope
    4.5.2 Nucleophile scope – Method A
    4.5.2 Nucleophile scope – Method B
    4.5.3 Unexpected products
  4.6 Synthesis of ammonium salts
  4.7 Conclusion

5. Applications of ortho-Iodinated Diarylamines and Diaryl Ethers in Late-Stage Functionalizations (Papers II, V)
  5.1 Introduction
  5.2 Derivatization of diarylamines and diaryl ethers
  5.3 Synthesis of cyclic diaryliodonium salts
  5.4 Applications of cyclic diaryliodonium salts
  5.5 Synthesis of aryloxy-diaryliodonium salts
  5.6 Applications of aryloxy-diaryliodonium salts
  5.7 Conclusion

6. Concluding remarks

Appendix A – Contribution list
Appendix B – Reprint permissions
Acknowledgements
References
Abbreviations

Abbreviations are used in agreement with standards of the subject.* Additional abbreviations used in this thesis are listed below.

3c-4e  3-Center-4-electron
DACH  1,2-Diaminocyclohexane
DCE   1,2-Dichloroethane
DIB   (Diacetoxyiodo)benzene
DPE   1,1-Diphenyl ethylene
Dba   Dibenzylideneacetone
DIPEA N,N-Diisopropylethylamine
DMA   Dimethylacetamide
DMAP  4-Dimethylaminopyridine
DMEDA 1,2-Dimethylethylenediamine
Dtbpy 4,4′-Di-tert-butyl-2,2′-dipyridyl
EAS   Electrophilic aromatic substitution
EDG   Electron donating group
EWG   Electron withdrawing group
HFIP  1,1,1,3,3,3-Hexafluoroisopropanol
HTIB  [Hydroxy(tosyloxy)iodo]benzene
LC    Ligand coupling
LG    Leaving group
m-CPBA meta-Chloroperbenzoic acid
Mes   Mesityl
NIS   N-iodosuccinimide
n.d.  Not detected
OTf   Triflate
OTs   Tosylate
Oxone Potassium peroxymonosulfate
1,10-Phen 1,10-Phenanthroline
S_EAr Electrophilic aromatic substitution
Selectfluor® (1-chloromethyl-4-fluoro-1,4-diaziobicyclo[2.2.2]octane bis(tetrafluoroborate)
SET   Single electron transfer
S_NAr Nucleophilic aromatic substitution
TfOH  Trifluoromethanesulfonic acid
TsOH  p-Toluenesulfonic acid
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFA</td>
<td>Trifluoroacetate</td>
</tr>
<tr>
<td>TFE</td>
<td>Trifluoroethanol</td>
</tr>
<tr>
<td>TS</td>
<td>Transition state</td>
</tr>
<tr>
<td>TMB</td>
<td>1,3,5-Trimethoxybenzene</td>
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1. Introduction

1.1 Diaryliodonium salts

Diaryliodonium salts (Ar₂IX) are versatile electrophilic arylating agents that have found widespread applications in modern organic synthesis. The rapidly expanding interest for these hypervalent iodine reagents stem from their easy accessibility, high reactivity and stability as well as their applicability under mild reaction conditions. The multi-purpose properties of diaryliodonium salts has enabled their utilization in a range of fields, including both material and supramolecular chemistry. Perhaps most interestingly, these iodine(III) reagents display reactivities similar to those of some organometallic reagents and can thus provide mild and low-toxic complements to conventional transition metal-catalyzed transformations. As a result, diaryliodonium salts have received increased recognition as the demand for sustainable arylation strategies continuously grows, giving preference to metal-free transformations.

1.1.1 Properties and reactivity

The term hypervalency refers to elements in group 15-18 that violate the octet rule by accommodating more than 8 electrons in their valence shell. Organoiodine compounds are relatively easily oxidized into their hypervalent state due to their moderately low electronegativity. Hypervalent bonding is commonly described by the 3-center 4-electron (3c-4e) bonding model, where three molecular orbitals are formed by combination of two filled orbitals from the ligands with one empty orbital from the iodine (Figure 1a). The electron density is distributed towards the ligands in the hypervalent bond due to the node on the iodine atom in the occupied non-bonding orbital, resulting in an electrophilic iodine center. Diaryliodonium salts adopt a T-shaped structure, caused by the linear hypervalent bond with a 180 ° bond angle. This T-shaped structure has been confirmed by X-ray analysis, which shows one aryl group and the counterion residing in the hypervalent bond. Studies suggest that diaryliodonium salts exist in two conformers in solution, where the aryl groups are interchanged between the equatorial and the apical positions. Due to the
uncertainty of which aryl group resides in the hypervalent bond, unsymmetrical salts (Ar¹ ≠ Ar²) are often drawn in their ionic form (Figure 1b) whereas symmetrical salts are depicted with covalent bonds (Figure 1c).

Figure 1. a) Bonding and b-c) structure of diaryliodonium salts.

The reactivity of diaryliodonium salts is governed by the charge separation in the hypervalent bond as well as the excellent inherent leaving group ability of the iodoarene. Under metal-free conditions, the arylations mainly occur through a ligand coupling pathway where one of the aryl groups is transferred to a suitable nucleophile (Scheme 1). The mechanism is initiated by a ligand exchange between the nucleophile and the counterion of the salt by either an associative or dissociative mechanism to deliver the T-shaped intermediate A. Subsequent ligand coupling (LC) from A by transfer of the aryl group in the equatorial position yields the arylated nucleophile. In this step, the hypervalent iodine is reduced to its energetically favored monovalent state, which constitutes the thermodynamic driving force of the reaction.

Scheme 1. Mechanism for ligand coupling pathway.

The LC pathway is the most common arylation pathway of diaryliodonium salts, and has been supported by both experimental and computational studies. Nevertheless, under certain conditions, alternative pathways may operate e.g. via aryne or radical intermediates. In the presence of a strong base, arynes can be derived from Ar₂IX reagents by ortho-
deprotonation followed by a subsequent elimination of the iodoarene (Scheme 2a).\textsuperscript{[9, 8c]} These reactions often lead to regioisomeric product mixtures as the aryne intermediate possesses two competing electrophilic sites susceptible to the nucleophilic addition.\textsuperscript{[10]} Arynes are known to be excellent dienophiles and react rapidly with dienes to form Diels-Alder adducts (Scheme 2b). Furan is therefore a commonly employed additive in mechanistic studies to detect aryne intermediates.\textsuperscript{[8a, 8c]}

\textbf{Scheme 2a)} General aryne arylation pathway. b) Trapping of aryne with furan.

While single electron transfer (SET) mechanisms are possible as well, they are far less common than LC routes and are highly dependent on the reaction conditions.\textsuperscript{[11]} SET pathways may, however, enable otherwise unfeasible transformations from closed shell intermediates, as demonstrated by Kita and co-workers in the synthesis of biaryls by oxidative cross-couplings with Ar\textsubscript{2}IX and electron-rich arenes.\textsuperscript{[8b, 12]} The authors suggested the mechanism to proceed via the formation of a radical pair by SET from electron-rich arenes to an iodonium center, followed by subsequent transfer of one aryl group to the external arene to afford the biaryl product (Scheme 3).

\textbf{Scheme 3.} General SET arylation mechanism.
1.1.2 Chemoselectivity

Unsymmetrical diaryliodonium salts \((\text{Ar}^1 \neq \text{Ar}^2)\) are associated with a range of benefits both in their synthesis and applications.\[^{[13]}\] While the synthesis of diaryliodonium salts with two ligands of opposite electronic properties is generally straightforward, preparation of symmetrical salts with two significantly electron-rich or electron-deficient ligands may pose a substantial challenge.\[^{[1d]}\] Moreover, when the aryl group to be transferred is valuable or difficult to obtain from commercial sources, it is beneficial to use an inexpensive "dummy ligand" that forms the aryl iodide byproduct. However, controlling which of the two aryl groups that is transferred to the nucleophile is the main obstacle in reactions with unsymmetrical iodonium salts. This chemoselectivity is governed by a delicate balance of electronic and steric factors, where the choice of a suitable "dummy ligand" is essential for development of selective reactions.\[^{[14, 13]}\]

Following a standard LC route, unsymmetrical iodonium salts with different electronic properties exist as the two intermediates \(A_{EWG}\) and \(A_{EDG}\) upon ligand exchange with a nucleophile (Scheme 4).\[^{[15]}\] As these intermediates are rapidly interchanged by an equilibrium, the product ratio is under strict Curtin-Hammett control where the major pathway is preceded by the lowest energy transition state.\[^{[6]}\] Thus, aryl groups bearing EWG-substituents are preferentially transferred as these stabilize the partial negative charge that is being built up in TS \(A\).

![Scheme 4. Electronic model for chemoselectivity.](image)

While the electronic factors are generally dominant in determining the chemoselectivity of a reaction, they can sometimes be overruled by steric effects, where aryl groups with ortho-substituents are selectively transferred.
This trend is defined as an ortho-effect and is more difficult to predict as it is largely nucleophile dependent. Whilst no definite explanation has been concluded, it is commonly accepted in literature that this effect stems from the preference of the ortho-substituted aryl to reside in the equatorial position to avoid steric strain from the lone pairs of the iodine. Thus, this unfavorable steric interaction causes destabilization of $\text{TS A}_{\text{phenyl}}$, which reduces the rate of this route compared to the alternative path via $\text{TS A}_{\text{aryl}}$. In 2013, the groups of Olofsson and Himo presented an extensive chemoselectivity study where the selectivity trends of $\text{O}$-, $\text{N}$- and $\text{C}$-nucleophiles were investigated in reactions with unsymmetrical diaryliodonium salts.\[14\] The study demonstrated a clear ortho-effect in arylations of phenols, whereas electronic factors mainly dictated the outcome of anilines. On the contrary, the malonate $\text{C}$-nucleophiles reacted with anti ortho-selectivity where transfer of the ortho-substituted aryl was always disfavored, despite any electronic differences. This trend has also been observed with other relatively soft nucleophiles such as boron.\[17\] It is likely that the anti ortho-effect is caused by the large steric requirement of $\text{TS A}_{\text{aryl}}$ when a sterically demanding aryl group is transferred to a bulky nucleophile. This results in a more dominant destabilization of $\text{TS A}_{\text{aryl}}$, and thereby a higher rate of the unsubstituted aryl group transfer via $\text{TS A}_{\text{phenyl}}$.\[14\]

1.1.3 Synthesis of diaryliodonium salts

The high accessibility of diaryliodonium salts from available starting materials and inexpensive synthetic routes constitutes one of the key factors in their growing popularity.\[18\] The Olofsson group pioneered this field and presented the first synthetically useful one-pot protocol for Ar$_2$IX synthesis with a broad scope using $m$-CPBA as the oxidant.\[18b\] Before this, routes to diaryliodonium salts generally consisted of two or more steps, often in...
combination with toxic organometallic reagents such as arylstannanes.\textsuperscript{[1d]} To date, a variety of one-pot protocols are available and the recent advancements in the field have enabled preparation of highly complex \textit{Ar}_2\textit{IX} reagents with versatile applications.\textsuperscript{[18d, 19]}

Diaryliodonium salts are commonly prepared by oxidation of iodoarenes or elemental iodine by inexpensive and robust oxidants such as \(m\)-CPBA or oxone in the presence of a Brønsted or Lewis acid (Scheme 6a-b). The acid functions as an activator of the oxidant and must be chosen carefully to assure successful Ar\(_2\)IX preparation. Olofsson and co-workers have developed efficient one-pot routes to both diaryliodonium triflates\textsuperscript{[20]} and tosylates\textsuperscript{[21]}, where the use of the stronger triflic acid (TfOH) allowed for a significantly broader substrate scope. As tosic acid (TsOH) is a weaker acid, it is given preference in the synthesis of electron-rich iodonium salts to avoid competing arene oxidation. The choice of synthetic route is hence dictated by the electronic properties and the substitution pattern of the target diaryliodonium salt. For unsymmetrical salts, the most electron-deficient aryl (Ar\(_1\)) is commonly the one bearing the iodine to be oxidized. Upon \textit{in situ} formation of the iodine(III) intermediate \(\textbf{I}\), the second ligand (Ar\(_2\)) is incorporated via an electrophilic aromatic substitution (EAS) pathway and must therefore possess sufficient EAS-reactivity. Consequently, the reaction generally proceeds with strong \textit{para}-selectivity with respect to any substituents on Ar\(_2\). If Ar\(_2\)IX with two electron-deficient and/or \textit{ortho-meta}-substituted aryl groups is desired, arylboronic acids are preferred coupling partners to deliver the Ar\(_2\)-ligand.\textsuperscript{[18c]}

![Scheme 6. Strategies for synthesis of diaryliodonium salts. Routes from a) iodoarenes b) elemental iodine c) isolated iodine(III) reagents.](image)

To attain diaryliodonium salts with oxidation- or acid sensitive Ar\(_2\)-ligands, two step routes are commonly employed utilizing pre-formed iodine(III) reagents of ArI(L)\(_2\) character (Scheme 6c).\textsuperscript{[22, 19b]} The target diaryliodonium
salt is delivered after a ligand exchange with a suitable arene, arylboronic acid, arylsilane or arylstannane.\textsuperscript{[14]} In recent years, electrochemical and flow synthesis methods have emerged as compelling complementary routes to yield Ar₂IX.\textsuperscript{[23]} While these methods avoid the use of chemical oxidants and reduce the waste production, they are associated with limited substrate scopes.

1.2 Atom-economical applications of diaryliodonium salts

Atom economy (AE) is a useful concept for estimating the conversion efficiency of a method and is defined as the quotient between the molar mass of the products divided by the molar mass of the reactants.\textsuperscript{[24]} Ideally, a reaction should display 100\% atom efficiency where all of the atoms in the reactants are incorporated in the final product. Most organic reactions fall short of attaining complete atom efficiency as it is generally difficult to avoid the use of excess reagents and/or formation of waste products.\textsuperscript{[24-25]}

 Arylations with diaryliodonium salts generally feature poor atom economy as their standard arylation pathways proceed with transfer of only one of the aryl groups. The stoichiometric iodoarene formation is considered to be the main drawback of these transformations, where the monoarylation routes are restricted to 10-20\% AE (Scheme 7a).\textsuperscript{[26]} While the aryl iodide byproduct can often be recovered and reused, it is still an important obstacle to overcome in the pursuit of more sustainable synthetic methods.\textsuperscript{[26]} Diarylation methods with transfer of both aryl groups to the nucleophile improve the AE to 30-40\%, however, they remain limited by the loss of the heavy iodine atom and the counterion (Scheme 7b). Diarylation protocols with retention of the iodine constitute a more desirable strategy that increases the AE drastically to 60-80\%, whereas complete AE can only be attained if the counterion is intramolecularly bound to one of the aryl groups (Scheme 7c). While the latter sounds compelling in theory, this would imply a highly limited number of counterions that could be incorporated, starting from less reactive pseudocyclic diaryliodonium salts.\textsuperscript{[26a]}
Since stoichiometric reagents are the origin of the undesired iodoarene waste products, the solution would be rather simple if these could be replaced by catalytic systems. While such arylations with Ar₂IX have thus far been elusive, organocatalytic oxidation reactions employing aryl iodides as precatalysts in combination with stoichiometric oxidants have indeed been presented. In these reactions, the aryl iodide is transformed in situ to the active iodine(III) species, which undergoes the desired substrate oxidation. This process simultaneously regenerates the aryl iodide that reenters in the catalytic cycle. After the pioneering work of Ochiai and Kita in 2005 which demonstrated the iodine(III) catalyzed α-acetoxylation of ketones and dearomatization of phenols, this strategy has been utilized in various oxidative functionalizations, many of which even include enantioselective examples. The challenge of translating arylations with diaryliodonium salts into catalytic systems arises from the incompatibility of the acidic conditions of the Ar₂IX synthesis with the basic conditions required for the arylations. Fortunately, other innovative strategies have been developed for atom efficient applications of these reagents as described below.

1.2.1 Cyclic diaryliodonium salts

Cyclic diaryliodonium salts have in recent years gained increased recognition as versatile multi-purpose reagents with utility as dual arylating agents, halogen-bond donors and organocatalysts. Arylations with cyclic Ar₂IX are not restricted by the poor atom economy of acyclic salts as the reduced iodoarene ends up intramolecularly bound to the transferred aryl group (Scheme 8a). Atom economical applications of these reagents are well established for construction of heterocyclic compounds, chiral ligands and for various large conjugated systems. Cyclic Ar₂IX display relatively low reactivity compared to their acyclic analogues due to their rigid geometry and enhanced stability. The vast majority of their transformations are
hence dependent on metal catalysis, where dual functionalizations are achieved by two sequential Pd- or Cu-catalyzed cross-couplings. While metal-free applications of these reagents are scarce, some important examples include halogenations by thermolysis,\textsuperscript{[36]} sulfur/selenium-iodine exchange reactions\textsuperscript{[37]} and phenol arylations via aryne intermediates.\textsuperscript{[38]}

Cyclic iodonium salts with carbon backbones are commonly prepared under similar conditions to the acyclic Ar\textsubscript{2}IX (see section 1.1.3). However, stepwise synthesis of the iodo-biaryl precursors is generally required as these are not commercially available.\textsuperscript{[39]} Advancements in the field have enabled preparation of under-explored heterocyclic diaryliodonium salts,\textsuperscript{[40]} as well as heteroatom-bridged cyclic salts, which until recently only were reported without scope or reactivity studies.\textsuperscript{[41, 31b]} In 2022, Nachtshheim and co-workers reported an aryne-mediated route to O- and N-bridged diaryliodonium salts starting from ortho-iodinated phenols and sulfonamides (Scheme 8b).\textsuperscript{[42]} Treatment of the phenols and sulfonamides with \textit{in situ}-generated aryne intermediates followed by subsequent oxidation by excess Selectfluor\textsuperscript{®}, allowed one-pot formation of the target salts in moderate to good yields. While a variety of ortho-iodinated substrates proved productive, decomposition or regioselectivity issues limited the reaction to only two aryne precursors. Sequential reactivity studies of these novel salts demonstrated their utility in various atom-economical arylations, primarily under metal-catalyzed conditions.\textsuperscript{[42]}

\textbf{Scheme 8.} \textbf{a)} General use of cyclic Ar\textsubscript{2}IX. \textbf{b)} Heteroatom-bridged Ar\textsubscript{2}IX.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=\textwidth]{scheme8.png}};
\end{tikzpicture}
\end{center}

\subsection{1.2.2 Acyclic diaryliodonium salts}

Atom-economical applications of acyclic diaryliodonium salts remain limited in literature and are restricted to consecutive transition metal-catalyzed cross-couplings or intramolecular arylations.\textsuperscript{[26a]} Sequential diarylations generally proceed by one metal-catalyzed or metal-free arylation followed by a consecutive metal-catalyzed cross-coupling with the resulting iodoarene. This strategy was first utilized in 1995 by Bumagin and co-workers in their biaryl
synthesis via Pd-catalyzed couplings of symmetrical diaryliodonium salts with sodium tetraphenylborate. While this work primarily served as a proof of concept, it required unstable organoboron reagents with a substrate scope of only 3 entries. In 2015, Greaney presented the first synthetically useful protocol for sequential diarylation from acyclic Ar₂IX by tandem C/N-arylations of indoles (Scheme 9a). In this pioneering work, a wide scope of indoles were selectively arylated with both symmetrical and unsymmetrical diaryliodonium salts by a combination of literature methods for Cu-catalyzed C- and N-arylations. Later this tandem approach was expanded to dual arylations of other electron-rich heterocycles under Ru catalysis, and into the synthesis of triarylamines by sequential Cu-catalyzed diarylations of anilines (Scheme 9b). While these important discoveries enable arylations with increased AE of 40-50%, the dependence on metal catalysis limits the overall sustainability of these protocols.

Scheme 9. Intermolecular examples of diarylations from Ar₂IX.

Atom-economic utilization of acyclic Ar₂IX is more frequently achieved by intramolecular arylations. Shafir and co-workers recently presented an elegant route to N-arylated imidazoles by use of heterocyclic imidazolium salts that underwent intramolecular aryl migrations under Cu catalysis (Scheme 10a). This novel transformation proceeds via a Cu^{III}-nitrogen intermediate upon the deprotonation of the imidazolium salts. Transfer of the Ar¹-ligand to the Cu-center followed by subsequent reductive elimination affords 1,5-difunctionalised products with retention of the iodine-component, achieving a remarkable 80% AE.
Iodonium ylides are 1,4-zwitterionic compounds with a positively charged iodine(III) center stabilized by a negatively charged heteroatom within the molecule. These reagents readily undergo intramolecular aryl migrations by direct nucleophilic substitution on the ipso-carbon of Ar^2, proceeding via a 5-membered transition state, to yield diarylated products with the iodine retained in the final structure. The chemistry of iodonium ylides is well documented and the first syntheses and applications of diphenyliodonium ylides were reported in 1977. More recent work by Han and Wang demonstrates the use of ortho-substituted diaryliodonium salts as iodonium ylide precursors in the synthesis of ortho-iodinated diaryl ethers and sulfonamides (Scheme 10b). The method relies on diaryliodonium salts with protected O- and N-nucleophiles embedded in the salt structure, which upon in situ deprotection afford iodonium ylides. These reagents undertake the desired intramolecular arylation at elevated temperatures, to deliver the diarylated products. While these indeed are important examples of metal-free and atom-efficient applications of acyclic Ar_2IX, these methods are limited to use of complex diaryliodonium salts with preinstalled nucleophiles. This is a considerable drawback as these salts can be challenging to prepare, resulting in highly limited nucleophile scopes. Moreover, due to the prefuctionalization requirement, this type of diarylation cannot be performed in one pot.

1.3 Nucleophilic aromatic substitution

Nucleophilic aromatic substitution (S_NAr) constitutes one of the most important metal-free pathways for construction of C–C, C–N, C–O and C–S bonds. The high efficiency and selectivity of these transformations has enabled their extensive use in the pharmaceutical industry for modification of...
aromatic building blocks.\textsuperscript{[51]} The classical $S_N$Ar mechanism proceeds by a two-step addition/elimination pathway where a suitable nucleophile displaces a leaving group (LG) on an electron-deficient arene (Scheme 11a). The nucleophile adds to the ipso-carbon of the LG to yield an anionic Meisenheimer complex, which constitutes the rate-determining step for most nucleophiles.\textsuperscript{[52]} The aromaticity of the ring is regained by expulsion of the leaving group, affording the arylated nucleophile. Halogens are typical leaving groups with LG abilities following the opposite trends of $S_N$1/$S_N$2 reactions, \textit{e.g.} F>Cl>Br>I. Since the addition of the nucleophile is the rate-determining step, the ability to activate the aromatic system is the defining factor for the efficiency of the leaving group. Thus, despite the high $C-F$ bond dissociation energy, fluoride is generally the superior LG as fluoroarenes contain an electron-deficient aromatic core prone to nucleophilic addition with minimal steric interaction with the incoming nucleophile due to its small radius.\textsuperscript{[39a][51a]} Moreover, the favorable electronegativity of fluorine facilitates the stabilization of the Meisenheimer intermediate. Thus, typical $S_N$Ar substrates commonly bear fluorine substituents in conjugation with EWGs in \textit{ortho}- or \textit{para}-position to further aid the stabilization of this dearomatized intermediate.\textsuperscript{[52]}

\begin{center}
\textbf{Scheme 11.} $S_N$Ar pathway via a) two-step mechanism b) concerted mechanism.
\end{center}

The major drawback associated with $S_N$Ar reactions is the limited substrate scopes as only electron-deficient arenes are suitable substrates.\textsuperscript{[53]} Furthermore, these reactions often require high reaction temperatures to be efficient. Interestingly, recent studies suggest the feasibility of a concerted mechanism in systems where the Meisenheimer intermediate is energetically inaccessible (Scheme 11b).\textsuperscript{[54]} The concerted mechanism would be favored for less activated substrates bearing leaving groups with lower bond dissociation energies under specific conditions.
1.4 Aim of the thesis

The aim of this thesis is to address the current atom-economy limitations in the field of Ar$_2$IX mediated arylations relating to the principal drawback of stochiometric iodoarene byproduct formation. We aimed to develop a novel class of Ar$_2$IX reagents with unprecedented reactivity, which would allow transfer of both aryl groups as well as the iodine-substituent into the final products. Such diarylations would hence circumvent the formation of iodoarene waste and represent av conceptual expansion of iodine(III) chemistry.

A compelling alternative to the existing Ar$_2$IX diarylation methods would be a high yielding, metal-free one-pot protocol where the atom efficiency of S$_N$Ar is combined with the mild conditions and wide scope of Ar$_2$IX LC arylations. To this end, we anticipated that diaryliodonium salts bearing a typical S$_N$Ar leaving group in conjugation with an EWG could enable previously unexplored S$_N$Ar reactivity of diaryliodonium salts (Scheme 12). Rather than undertaking a standard LC route, the first nucleophile arylation would deliver a unique iodine(III) intermediate B, which could undergo a second arylation by intramolecular aryl migration. This strategy would allow transfer of two structurally different aryl groups in one single reaction to afford diarylated products in a highly atom economical manner. Furthermore, this transformation would occur with retention of the iodine-component into the final products, which would constitute a versatile handle for downstream functionalizations. We envisioned the applicability of this sustainable methodology in the diarylation of various heteroatom nucleophiles to attain industrially relevant multi-arene products.

2. Preparation of Fluorinated Diaryliodonium Salts with Novel Reactivity (Papers I, II)

2.1 Introduction

To date, an array of efficient one-pot protocols for the synthesis of diaryliodonium salts has been developed. Nevertheless, syntheses of certain \( \text{Ar}_2\text{IX} \) with mixed electron-deficient and electron-rich ligands as well as salts with two highly electron-poor ligands remain challenging as the starting materials are either too reactive or too unreactive.

Diaryliodonium triflate salts offer advantages in both scope and applications. A protocol for facile \( \text{Ar}_2\text{IOTf} \) synthesis with a broad substrate scope was previously developed within our group, utilizing a \( m\)-CPBA/TfOH reagent combination (Method A, Scheme 13). However, introduction of highly electron-rich \( \text{Ar}^2 \) groups such as anisyl, diaryl ethers, biphenyls and some heteroaryls can be challenging in the presence of triflic acid, as these arenes are prone to competing oxidation. While this issue can sometimes be overcome by employing a milder acid such as tosic acid, sufficient oxidation of electron-poor iodoarenes \( \mathbf{1} \) cannot be achieved under such conditions. Moreover, since electron-poor iodoarenes \( \mathbf{1} \) react slowly with the oxidant, the risk of competing arene oxidation is further enhanced. For incorporation of particularly oxidation- and acid-sensitive \( \text{Ar}^2 \) groups, the two-step Method B is given preference, where the iodine(III) intermediate \( \mathbf{4} \) is isolated prior to the reaction with the \( \text{Ar}^2 \)- source.

Method C constitutes the superior route to \( \text{Ar}_2\text{IX} \) with electron-deficient and/or ortho/meta-substituted \( \text{Ar}^2 \)-groups via couplings with organoboron reagents. Our group has previously reported a one-pot protocol for \( \text{Ar}_2\text{IBF}_4 \) synthesis from iodoarenes and arylboronic acids with a complementary scope to Method A. The challenges associated with preparation of highly electron-deficient \( \text{Ar}_2\text{IX} \) by this method concern the slow oxidation of the corresponding iodoarenes \( \mathbf{1} \) in the presence of a weak Lewis acid, as well as the insufficient nucleophilicity of electron-poor arylboronic acids.
2.2 Method A

In the synthesis of the novel diaryliodonium salts 3, fluorine was chosen as the leaving group due to its superior leaving group ability in S_N_Ar pathways compared to other halogens.\[^{[53]}\] While most of the fluoro-iodoarene 1 precursors are commercially available, we chose to prepare them either by an S_E_Ar iodination of the corresponding fluoroarene with NIS (Method I, Scheme 14)\[^{[56]}\] or from anilines by a Sandmeyer procedure (Method II).\[^{[57]}\] The Ar_2IX scope was prepared in part by the literature Method A, where the electron-poor iodoarene 1 (Ar^1I) was oxidized by m-CPBA in the presence of triflic acid and reacted with an EAS reactive arene 2.\[^{[20b]}\] This method was used to prepare diaryliodonium salts bearing numerous EWGs on the S_N_Ar aryl (Ar^1) with varied substitution patterns, as well as a diverse selection of functionalized Ar^2 ligands, providing diaryliodonium triflates 3-OTf in good to excellent yields (50-93%). The robustness of this method enabled the salt synthesis to be performed at >10 mmol scale.
2.3 Updated Method A

To synthesize salts 3-OTf with electron-rich Ar² groups, Method A²⁰[b] was applied with some careful modifications to address the limitations of the literature protocol concerning competing arene 2 oxidation (Scheme 15). For installation of moderately electron-rich arenes 2 such as tert-butyl benzene and mesitylene, it proved beneficial to pre-oxidize the iodoarenes 1 for 10-60 min prior to the addition 2, which afforded salts 3u-z in 55-94% yields. For highly electron-rich arenes 2 such as anisyl and thiophenyl, addition of 2.0 equivalents of water prior to the EAS reaction of 2 was required to efficiently obtain the corresponding products 3aa-ab. The efficacy of water as an additive relates to the quenching of triflic acid upon completed iodine oxidation, forming a weaker acid (H₃O⁺) that circumvents the unwanted arene oxidation.[⁵⁸] In the presence of this additive, the previously challenging incorporation of anisole occurred smoothly and increased the yield of 3aa from 40% to 72%.
2.4 Updated Method B

For introduction of particularly oxidation- or acid-sensitive arenes 2, utilization of a two-step route according to Method B proved advantageous (Scheme 16). The Kosher’s reagents 4 ([hydroxy(tosyloxy)jodo]arenes, HTIB) were chosen as the intermediate iodine(III) reagents, due to their ease of preparation and favorable reactivity. A protocol for synthesis of HTIB reagents was previously developed within the group using equimolar amounts of \( m \)-CPBA and tosic acid in TFE at 40 °C for 1 h.\(^{[59]} \) However, since tosic acid cannot activate \( m \)-CPBA sufficiently towards oxidation of the electron-poor iodoarenes 1, modification of the conditions was necessary to synthesize 4. Gratifyingly, by performing the reaction at 60 °C for 2 h while using a slight excess of the oxidant and acid, the Kosher’s reagents 4a-c were obtained in high yields. The isolated compounds 4 smoothly underwent ligand exchange with arenes 2, affording the corresponding products 3ac-ah in 58-97% yields following a slightly modified procedure by Kita.\(^{[22a]} \) To facilitate the isolation of salt 3af, an in situ counterion exchange was performed by addition of 2.0 equivalents of TfOH.

In the original protocol, the authors describe improved product yields by use of 2.0 equivalents of the Kosher’s reagent.\(^{[22a]} \) We observed better results by
increasing the loading of arene 2 instead, as excess of 4 is difficult to isolate from product 3. This alteration enabled a significant increase in the yield of pyridinyl salt 3ae from 57% to 95%. Moreover, Method B was preferentially chosen over Method A in the preparation of this salt to avoid undesired nitrogen protonation by TfOH or oxidation of the electron-rich heteroarene. Fluorinated solvents are known to enhance the reactivity of Koser’s reagent in ligand exchange pathways and were hence chosen to match the nucleophilicity of 2. For most substrates 2, the use of TFE or TFE:CH$_2$CH$_2$ solvent mixtures was sufficient (3ac-ae and 3af-OTf), whereas less reactive arenes such as benzene required further activation of 4 by use of HFIP or TFA to obtain 3ag and 3ah in high yields. Although the triflate analogues of the latter can be readily made by Method A, the updated Method B is a valuable alternative when aiming for diaryliodonium tosylates from highly electron-deficient iodoarenes 1, as the counterion exchange from OTf to OTs is avoided.

**Scheme 16.** Kosers’s reagents and Ar$_2$IX scope by the updated Method B. [a]: Obtained after in situ counterion exchange by addition of TfOH (2.0 equiv).
2.5 Comparison of the Updated Methods A and B

Previous attempts to synthesize the diaryl ether salt 3ac-OTf by the updated conditions of Method A were unsuccessful. Pre-oxidation of 1a for 1 h prior to the addition of the diphenyl ether 2a afforded the product in low yield as the reaction turned black directly upon addition of the arene (Scheme 17). Repeating the reaction with water as an additive improved the outcome by circumventing the direct oxidation of 2a, however the yield remained unsatisfactory. Fortunately, under the updated conditions of Method B, the target product 3ac was obtained in a significantly improved yield of 77%.

![Scheme 17. Comparison of methods for synthesis of salt 3ac. Conditions a) 1 h pre-oxidation prior to addition of 2a. Conditions b) 1 h pre-oxidation prior to addition of H2O, followed by 2a. [a]: NMR yields determined by use of TMB as internal standard.](image)

2.6 Updated Methods C and D

Updated Method C and Method D were used to prepare Ar2IX with electron-deficient and/or ortho/meta-substituted Ar2-groups via couplings with organoboron reagents (Schemes 18,19). The original literature procedure for Method C[18c] suggests a pre-oxidation time of the iodoarene for 15-60 minutes prior to the addition of the boronic acids, to avoid decomposition of the latter. However, these conditions were not compatible with iodoarenes 1 bearing multiple EWG’s, and it proved beneficial to extend the pre-oxidation time to 60-90 minutes and the coupling duration with the boronic acid to 16 hours (Scheme 18). Notably, further extended pre-oxidation times led to significantly decreased yields due to decomposition. With this modified
procedure, the corresponding products 3ai-ak were obtained in yields of 44-57%. Since triflate salts generally offer application and purification benefits over their BF$_4$ analogues,\textsuperscript{[55]} an \textit{in situ} counterion exchange was performed in the preparation of 3aj-ak by addition of 2.0 equivalents of TfOH upon completion of the reaction.\textsuperscript{[22a]}

**Updated Method C: One-pot route**

![Scheme 18. Ar:IX scope by the updated Method C.](image)

An alternative Method D was sought to attain a wider scope of electron-poor diaryliodonium salts as the yields from route C were only moderate. To overcome the challenging oxidation of 1 under the weakly acidic conditions, a similar strategy to Method B was employed, by use of a pre-activated iodine(III) intermediate (Scheme 19). Despite literature reports demonstrating the applicability of both HTIB and DIB in couplings with organoboron reagents,\textsuperscript{[62a-d, 19b, 62e]} successful outcomes were only achieved with (diacetoxyiodo)arenes 6, whereas reagents 4 proved unreactive in these transformations. The (diacetoxyiodo)arenes 6a-c were prepared by oxidation of iodoarenes 1 by sodium hypochlorite at room temperature for 30 minutes,\textsuperscript{[62c]} giving the corresponding products in 67-71% yield. Thorough regulation of the reaction time and temperature proved instrumental into achieving good yields of 6 as prolonged reaction times and/or elevated temperatures often led to product decomposition.
Activation of the isolated reagents 6 was achieved by pre-stirring in the presence of boron trifluoride at -78 °C for 30 min.\cite{63} Subsequent coupling with boronic acids 5 was achieved within 1-2 hours even with low-reactive 5, delivering the desired salts 3al-ap and 3a-BF$_4$ in 67-79% yields. Method D allowed preparation of a range of iodonium salts bearing electron-deficient aryls as well as heteroaryl groups in improved yields and in significantly reduced reaction times compared to Method C.

2.7 Comparison of the Updated Methods C and D

The efficiency of Method D made it possible to reverse the coupling partners to deliver the highly electron-deficient S$_N$Ar ligand from the commercially available boronic acid 5a (Scheme 20). Previous attempts to synthesize 3a-BF$_4$ from iodobenzene 1b and 5a through the updated Method C were unsuccessful. On the contrary, utilization of Method D afforded clean product formation in 67% yield, starting from the commercially available DIB. Thus, the use of the pre-activated (diacetoxyiodo)arenes efficiently eliminates the
barrier to access highly electron-poor diaryliodonium salts by couplings with unreactive boronic acids.

Updated Method C:

\[
\begin{array}{c}
\text{AcO} \quad \text{OAc} \\
\text{DIB (1.0 equiv)}
\end{array}
\begin{array}{c}
\frac{\text{I}}{\text{OAc}} \\
1b (1.0 \text{ equiv})
\end{array}
\begin{array}{c}
\xrightarrow{\text{BF}_3\cdot\text{OEt}_2 (2.5 \text{ equiv})} \\
\text{CH}_2\text{Cl}_2, \text{rt, 60 min}
\end{array}
\begin{array}{c}
\frac{\text{m-CPBA (1.1 equiv)}}{\text{O}_2\text{N}} \\
\text{CH}_2\text{Cl}_2, \text{rt, 60 min}
\end{array}
\begin{array}{c}
5a (1.1 \text{ equiv}) \\
0 \text{ °C to rt, 16 h}
\end{array}
\begin{array}{c}
\frac{\text{O}_2\text{N}}{\text{I}^+} \\
3a-\text{BF}_4 \text{ not formed.}
\end{array}
\]

Method D:

\[
\begin{array}{c}
\text{AcO} \quad \text{OAc} \\
\text{DIB (1.0 equiv)}
\end{array}
\begin{array}{c}
\frac{\text{I}}{\text{OAc}} \\
5a (1.2 \text{ equiv})
\end{array}
\begin{array}{c}
\xrightarrow{\text{BF}_3\cdot\text{OEt}_2 (2.5 \text{ equiv})} \\
\text{CH}_2\text{Cl}_2, \text{-78 °C, 15 min}
\end{array}
\begin{array}{c}
\frac{\text{I}}{\text{OAc}} \\
\text{-78 °C to rt, 2 h}
\end{array}
\begin{array}{c}
\frac{\text{F}}{\text{O}_2\text{N}} \\
3a-\text{BF}_4, 67\%
\end{array}
\]

Scheme 20. Comparison of Methods C and D for salt 3a-BF\textsubscript{4} synthesis.

2.8 Conclusion

A broad scope of novel fluorinated diaryliodonium salts were designed with the aspiration of obtaining unprecedented S\textsubscript{N}Ar reactivity of Ar\textsubscript{2}IX with dual arylation applications. The salts were prepared in part by literature procedures previously developed within the group. To synthesize more challenging salts, where the S\textsubscript{N}Ar-ligand was combined with either a highly electron-rich or electron-poor aryl group, updated protocols were developed. The new conditions efficiently overcame the previous synthetic limitations such as insufficient oxidation of electron-deficient iodoarenes, competing oxidation of the electron-rich arenes and couplings with unreactive arylboronic acids. The application of these novel iodonium salts in diarylations of N- and O-nucleophiles is discussed in detail in Chapter 3 and 4.
3. Diarylation of $N$- and $O$-Nucleophiles through a Metal-Free Cascade Reaction (Papers II, III)

3.1 Introduction

$N$- and $O$-arylated compounds play a pivotal role in the pharmaceutical, agrochemical and material industries,\cite{64} thereby prompting substantial investment in the development of innovative and practical strategies for their preparation.\cite{65} While diarylamines and diaryl ethers are commonly obtained by high yielding and well established transition metal-catalyzed cross-couplings,\cite{66} the overall sustainability of these methods is compromised by the requirement of scarce metals and sometimes complex designer ligands.\cite{67,65b} Moreover, methods for simultaneous introduction of two different aryl groups are lacking, often resulting in expensive and time-consuming multi-step synthesis.

To this end, we aimed to develop a conceptually novel method for dual functionalization of $N$- and $O$-nucleophiles, by use of the new EWG-bound diaryliodonium salts that were described in Chapter 2 (Scheme 21).

![Scheme 21](image_url)
The method would enable metal-free incorporation of two structurally different aryl groups onto various external nucleophiles in one single reaction, as well as retention of the iodine component in the final products. We envisioned this diarylation strategy to grant access to industrially relevant diaryl- and triarylamines as well as diaryl ethers from common nucleophiles such as aliphatic amines, ammonia, anilines and water.

3.2 Diarylation of aliphatic amines

3.2.1 Optimization

A proof of concept experiment was conducted between amine 7a and the model Ar₂IX 3a under the literature conditions for monoarylation of aliphatic amines developed within our group. Gratifyingly, the desired product 8a was formed as the only product in 68% yield, with no detection of competing ligand-coupling products despite full conversion of the starting material (Table 1, entry 1). A thorough screening of the reaction conditions was initiated, demonstrating acetonitrile as the superior solvent (entries 1-4), which allowed lowering of the temperature to 50 °C in combination with prolonged reaction time (entries 5, 7-10). While the diarylation occurred even at room temperature, large amounts of unreacted starting material 7a remained in the reaction mixture after 24 h (entry 7). Carbonate bases were superior to the organic base triethylamine, and potassium carbonate was chosen as the most suitable base (entries 6, 11-12). Using 1.1 equivalents of the amine resulted in an excellent yield of 7a, and the reaction time could be lowered to 7 h (entry 13-15). The reaction was not moisture sensitive, but the presence of air in the solvent notably reduced the yield of 8a (entries 16-17). With these results, the substrate scope evaluation was performed under the conditions of entry 14, as we were delighted by the efficiency of the reaction under these mild conditions without the requirement of excess reagents.
Table 1. Selected results from the diarylation optimization with 7a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>7a (equiv)</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>8a (%)[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>Na₂CO₃</td>
<td>Toluene</td>
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<td>78</td>
</tr>
</tbody>
</table>

[^a]: Reaction conditions: Salt 3a (0.1 mmol) and the base were dissolved in anhydrous and degassed solvent followed by addition of the amine 8a. [^b]: Isolated yields. [^c]: Wet degassed MeCN. [^d]: Wet non-degassed MeCN.

3.2.2 Scope studies

The substrate scope was explored with the novel, fluorinated diaryliodonium salts 3 described in Chapter 2. Facile scale up with the model substrate 3a (1 g) was achieved, affording product 3a (0.89 g) in 97% yield (Scheme 22A). Transfer of a diverse selection of electron-rich (8b-d), and electron-poor (8e,f) Ar²-groups was feasible, delivering the corresponding diarylamines in good to excellent yields (66-96%). Carbonyl functionalities such as esters and amides, as well as thienyl moieties were tolerated on Ar², providing products 8g-i. Arylations with highly sterically congested groups such as mesityl (Mes) and triisopropylphenyl (TRIP) are generally challenging,[69] and these are indeed described as non-transferable groups in metal-catalyzed monoaarylations with Ar₂JX.[70] Furthermore, transfer of aryl halides is sometimes an additional limitation of such protocols due to the risk of metal insertion into...
the C–X bond.\(^{[65b]}\) Thus, we were pleased to demonstrate the efficient transfer of Mes, TRIP and a variety of halogen-substituted aryls, delivering the corresponding products 8j–m in high to excellent yields.

![Scheme 22. Diaryliodonium salt scope (0.1-0.3 mmol scale unless otherwise stated). [a]: 1.0 g scale of 3a. [b]: In toluene, 110 °C, 4 h. [c]: 2.0 equiv of 3. [d]: At 90 °C.](image)

High tolerance for variation of the S\(_{N}\)Ar-ligand (Ar\(^1\)) was also demonstrated, allowing diversification of the EWG and the substitution pattern of this ligand (8n-o, Scheme 22B). However, certain sensitivity to steric strain on Ar\(^1\) was detected, as the diarylation with the salt 3j bearing the NO\(_2\)-group in ortho-
position was associated with a moderate product yield (8o). The reaction was extended beyond the use of nitro as the activating group, and a range of substituents with diverse electron-withdrawing capacities were employed while simultaneously varying Ar² (8p-y). To compensate for the reduced SNAr reactivity of salts 3 with weaker EWGs on Ar¹, it proved beneficial to increase the temperature to 90 °C and extend the reaction time to 16 h. With these alterations, EWG substituents such as ester (8p,q), cyano (8r-t), methyl- and trifluoromethyl-sulfonyl groups (8u,v) provided the corresponding products in good to excellent yields. Interestingly, exchanging the Ar²-ligand of the CO₂Me salt from phenyl (3c) to mesityl (3z) increased the product yield significantly from 70% (8p) to 94% (8q). Even weak electron-withdrawing groups such as CF₃ and SF₅ proved productive, affording products 8w-y in good yields.

Lastly, the aliphatic amine scope was evaluated in reactions with salt 3a (Scheme 23). Amines containing heteroaryl functionalities such as thienyl, furanyl, pyridyl and indolyl were smoothly diarylated to yield products 8z-ac in 50-81% yield. Benzylamine and the allylic geranyl amine were productive as well, delivering 8ad-ae in high yields. To further demonstrate the versatility of the scope, biologically active and naturally occurring compounds were employed such as the OMe-protected neurotransmitter dopamine, the pharmaceutical baclofen and the glycine methyl ester, which successfully afforded the corresponding products 8af-8ah. The methodology was applicable on highly volatile nucleophiles such as ethylamine (bp 16.6 °C), giving the product 8ai in quantitative yield when using excess amine. In agreement with the observation of sensitivity to steric strain on Ar¹, the reaction with the bulky cyclohexyl amine resulted in substantial decomposition of 3a and a modest yield of the corresponding product 8aj.
3.3 Diarylation of ammonia

3.3.1 Optimization

Ammonia was evaluated as a potential nucleophile to access the secondary diarylamines 9 (Table 2). To maintain our user friendly/practical reaction set up with this highly volatile nucleophile, various ammonia sources were evaluated with salt 3a under the literature conditions for mono-arylation of amines. Using 0.4 M ammonia in dioxane was deemed most suitable as the methanol and aqueous solutions led to decomposition (entries 1-3). While the reaction was feasible under the milder conditions for diarylation of aliphatic amines as well, the product was obtained in a modest yield together with the side-product 12a (entry 4). This side-product stemmed from the competing O-diarylation of trace water from the solvent and suppressing its formation was the main obstacle of the reaction. Fortunately, complete selectivity of the N-diarylation was achieved by increasing the ammonia loading (entries 5-7). Excluding MeCN as a co-solvent proved advantageous (entries 8-9) and product 9a was obtained in a satisfying yield when using 5.0 equivalents of ammonia. The requirement of excess nucleophile and longer reaction time...
compared to the diarylation of aliphatic amines most likely relates to the high volatility and low nucleophilicity of ammonia.

**Table 2.** Selected results from the diarylation optimization with ammonia.\[^{[a]}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>NH(_3) source (equiv)</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield 9a (%)</th>
<th>Yield 12a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25% aqueous (1.0)</td>
<td>Na(_2)CO(_3)</td>
<td>PhMe</td>
<td>110</td>
<td>4</td>
<td>Complex mixture</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>7 M in MeOH (1.0)</td>
<td>Na(_2)CO(_3)</td>
<td>PhMe</td>
<td>110</td>
<td>4</td>
<td>Complex mixture</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>0.4 M in dioxane (1.0)</td>
<td>Na(_2)CO(_3)</td>
<td>PhMe</td>
<td>110</td>
<td>4</td>
<td>50 n.i.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.4 M in dioxane (1.0)</td>
<td>K(_2)CO(_3)</td>
<td>MeCN</td>
<td>50</td>
<td>16</td>
<td>42 50</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.4 M in dioxane (2.0)</td>
<td>K(_2)CO(_3)</td>
<td>MeCN</td>
<td>50</td>
<td>16</td>
<td>42 n.d.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.4 M in dioxane (3.0)</td>
<td>K(_2)CO(_3)</td>
<td>MeCN</td>
<td>50</td>
<td>16</td>
<td>50 n.d.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.4 M in dioxane (5.0)</td>
<td>K(_2)CO(_3)</td>
<td>MeCN</td>
<td>50</td>
<td>16</td>
<td>61 n.d.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.4 M in dioxane (3.0)</td>
<td>K(_2)CO(_3)</td>
<td>-</td>
<td>50</td>
<td>16</td>
<td>50 n.d.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.4 M in dioxane (5.0)</td>
<td>K(_2)CO(_3)</td>
<td>-</td>
<td>50</td>
<td>16</td>
<td>70 n.d.</td>
<td></td>
</tr>
</tbody>
</table>

[a]: Reaction conditions: Salt 3a (0.1 mmol) and the base were dissolved in anhydrous and degassed solvent followed by addition of the ammonia. N.d. = Not detected. N.i. = Observed, not isolated.

### 3.3.2 Scope studies

A small substrate scope evaluation was performed, providing a range of structurally diverse secondary diarylamines in good to high yields (Scheme 24). Similar trends in the salt 3 scope were observed with ammonia as with the aliphatic amines, where both Ar\(^2\) and Ar\(^1\) could be diversified. The S\(_{N}\)Ar-aryl group (Ar\(^1\)) could be altered by additional substituents (9b,c), variation of the substitution pattern (9c) and by replacing the nitro group with a trifluoromethyl sulfonyl group (9d). Weaker EWG on Ar\(^1\) proved unproductive due to the low nucleophilicity of ammonia. In terms of the Ar\(^2\) ligand, arylations with electron-neutral, electron-rich, and electron-poor aryls were generally well tolerated delivering the products 9a, 9e-g in 70-81% yield.
3.4 Diarylation of anilines

An expansion of the method was sought for diarylation of anilines to attain industrially important triarylamines, with high prevalence in various functional materials such as solar cells and LEDs.\cite{64ib, 71} Synthesis of triarylamines with three structurally different aryl groups can be challenging and this in combination with the relatively low nucleophilicity of anilines\cite{72} rendered them incompatible with the developed conditions for the aliphatic amines. The initial screenings led to trace amount of product 11a, which was obtained in a mixture with competing LC products (See section 3.7.3). Gratifyingly, after careful re-optimization of the conditions, the product could be obtained in a high yield by performing the reaction in pyridine at 40 °C for 20 h. Excluding the base and using 2.0 equivalents of the aniline together with MgSO$_4$ afforded the target product with complete selectivity in 80% yield at 2 g scale. The role of the additive is not fully realized, however the magnesium could potentially assist in the fluoride removal after the S$_{N}$Ar step.

A substrate scope study was conducted, which demonstrated efficient transfer of various electron-poor (11b-d) and electron-rich (11e-i) Ar$_2$-groups in accordance with the previous scope studies with amines and ammonia (Scheme 25A). We were delighted that arylations with Mes and triethylphenyl indeed were possible, since triarylamines with this level of steric congestion around the nitrogen center (11j-k) are rare in literature. Diversification on the S$_{N}$Ar-aryl (Ar$^1$) was feasible by altering the activating EWG, adding substituents to the ring and varying the substitution patterns, affording
products 11l-o in 50–87% yield (Scheme 25B). It is worth noting that product 11o was obtained with complete regioselectivity, despite the two competing fluorides on Ar1.

Scheme 25. Diaryliodonium salt scope. [a]: 2 g scale of 10. The complete optimization and scope study with anilines was conducted by David Bulfield.

Next, the aniline scope was evaluated in reactions with salt 3a (Scheme 26). Alkylated anilines readily underwent the diarylation with salt 3a, giving products 11p-s in high to excellent yield. To address the reduced reaction rates with bulky anilines, an excess of substrate 10 was used, leading to a satisfactory yield of 11t. Conjugating substituents on Ar3, such as phenyls and olefins, were tolerated and delivered product 11u,v in modest to high yields. The reaction efficacy strongly correlated with the electronic properties of the anilines 10, and substrates bearing OMe, SMe and NHAc functionalities were efficiently diarylated, even in the presence of electron-withdrawing halides in the meta-position (11w-ad). Less electron-rich anilines with halides or carboxylic acids substituents were productive as well (11ae-aj), although
excess reagent was often required to obtain good yields. Diarylation of indolyl- and pyridyl-anilines was feasible and proved most efficient with electron-rich heteroaryls (compare 11al and 11am).

Scheme 26. Aniline scope. [a]: 5.0 equiv of 10. The complete optimization and scope study with anilines was conducted by David Bulfield.

To our delight, the method was applicable on complex substrates such as the drug molecule cytadren (11an), anilines with large \( \pi \)-systems (11ao), amino-acid derivatives (11ap), peptides (11aq) and the natural product cholic acid (11ar).
3.5 Diarylation of water

3.5.1 Optimization

Diaryl ethers are privileged scaffolds in agrochemicals, natural products and commercial drugs due to their favorable biological features such as anticancer, anti-inflammatory, antiviral, antibacterial properties etc.⁶⁴c Considering the tremendous value of these compounds, water was evaluated as an accessible and environmentally benign O-nucleophile to afford densely functionalized ortho-iodo diaryl ethers using the diarylation strategy. The compatibility of water with this method had been indicated during the screening of conditions for the diarylation of ammonia (section 3.3.1, Table 2), where the diaryl ether 12a was observed as a side-product in up to 50% yield. We anticipated the formation of this ether to stem from the O-diarylation of trace water from the reaction solvent. We were hence pleased to obtain the desired compound 12a in 65% yield by stirring salt 3a in MeCN under the optimized conditions for the diarylation of aliphatic amines (Table 3, entry 1). By using 2.0 equivalents of added water, various polar solvents were screened and ethyl acetate was associated with the cleanest product formation (entries 2-5). The reaction was most efficient when performed at 50 °C, whereas further elevated temperatures lowered the yield (entries 6-8). Carbonate bases performed well, and cesium carbonate proved superior (entries 9-12). Lowering the water loading to 1.0 equivalent (compare entries 3 and 9) and increasing the reaction molarity to 0.4 M delivered 12a in an excellent yield (entry 14). Performing the reaction under inert conditions and for 16 h proved beneficial, whereas shorter times caused decreased yields (entries 15-16).
Table 3. Optimization of reaction conditions for synthesis of 12a.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>H₂O (equiv)</th>
<th>Solvent</th>
<th>Conc (M)</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield 12a (%)</th>
<th>YIELD 12a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>MeCN</td>
<td>0.2</td>
<td>K₂CO₃</td>
<td>50</td>
<td>16</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>MeCN</td>
<td>0.2</td>
<td>K₂CO₃</td>
<td>50</td>
<td>16</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>EtOAc</td>
<td>0.2</td>
<td>K₂CO₃</td>
<td>50</td>
<td>16</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>Dioxane</td>
<td>0.2</td>
<td>K₂CO₃</td>
<td>50</td>
<td>16</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>Water</td>
<td>0.2</td>
<td>K₂CO₃</td>
<td>50</td>
<td>16</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>EtOAc</td>
<td>0.2</td>
<td>K₂CO₃</td>
<td>60</td>
<td>16</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>EtOAc</td>
<td>0.2</td>
<td>K₂CO₃</td>
<td>70</td>
<td>16</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>EtOAc</td>
<td>0.2</td>
<td>K₂CO₃</td>
<td>40</td>
<td>16</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1.0</td>
<td>EtOAc</td>
<td>0.2</td>
<td>K₂CO₃</td>
<td>50</td>
<td>16</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.0</td>
<td>EtOAc</td>
<td>0.2</td>
<td>NEt₃</td>
<td>50</td>
<td>16</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1.0</td>
<td>EtOAc</td>
<td>0.2</td>
<td>Na₂CO₃</td>
<td>50</td>
<td>16</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1.0</td>
<td>EtOAc</td>
<td>0.2</td>
<td>Cs₂CO₃</td>
<td>50</td>
<td>16</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1.0</td>
<td>EtOAc</td>
<td>0.1</td>
<td>Cs₂CO₃</td>
<td>50</td>
<td>16</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1.0</td>
<td>EtOAc</td>
<td>0.4</td>
<td>Cs₂CO₃</td>
<td>50</td>
<td>16</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>15[c]</td>
<td>1.0</td>
<td>EtOAc</td>
<td>0.4</td>
<td>Cs₂CO₃</td>
<td>50</td>
<td>16</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1.0</td>
<td>EtOAc</td>
<td>0.4</td>
<td>Cs₂CO₃</td>
<td>50</td>
<td>6</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

[a]: Reaction conditions: Salt 3a and the base were dissolved in anhydrous and degassed solvent followed by addition of water. [b]: Isolated yields. [c]: Reaction under air atmosphere.

3.5.2 Scope studies

The substrate scope was evaluated under the conditions of entry 14, i.e. without an excess of substrate or reagents (Scheme 27). Analogous to the N-nucleophiles, a broad scope of salts 3 were compatible with the diarylation of water. A diverse set of sterically congested (12b,c), halogen-containing (12d-g), electron-rich (12h-j) and electron-poor (12k,l) Ar²-groups were transferred in 58-91% yields. Functionalities prone to hydrolysis, such as esters (12m), remained unaltered under the applied conditions, and transfer of a bicyclic aryl was achieved as well (12n). In some instances, salts 3 with electron-rich Ar²-ligands reacted slowly under the optimized conditions. Fortunately, this issue was overcome by performing the reaction at 70 °C, affording the products 12g-i and 12m in good to excellent yields. In contrast, some salts with electron-deficient Ar²-ligands such as 3t (p-CF₃) exhibited sufficient
reactivity to undergo competing LC pathways with water, resulting in a low yield of the desired product 12k, which was obtained in a mixture with various LC products. Surprisingly, performing the reaction at 70 °C resulted in complete selectivity towards product 12k, which was obtained in a significantly increased yield of 71%.

The tunability of the fluorinated Ar1-group was demonstrated in the preparation of products 12o-s. Despite the relatively low nucleophilicity of water, a range of different EWGs could be employed, such as CN, SO2Me, and SO2CF3 groups, affording the diaryl ethers 12q-s in 70-93% yield. To attain satisfying yields of products 12p and 12r-s, it proved advantageous to conduct the reaction at 70 °C to compensate for the lower reactivity of the corresponding salts resulting from increased steric hindrance (o-NO2 substituent of 3j) or weaker EWGs (p-CN of 1d and p-SO2Me of 1g).

Scheme 27. Substrate scope with water (0.2 mmol scale). [a]: At 70 °C.
3.6 Limitations of the diaryliodonium salt scope

Utilization of a fluoride leaving group on salts 3 proved essential to attain the novel N- and O-diarylation reactivity, as the corresponding chlorinated salt 3b proved unreactive under the optimized conditions (Figure 2). Furthermore, the activating EWG should be placed in para-position to the fluorine, as the reactions with salts bearing EWGs in meta-position (3k and 3l) were unproductive with the evaluated nucleophiles. This trend is in agreement with the stability of the intermediate Meisenheimer complex, which is most efficiently stabilized by EWGs in ortho- and para-position.[50d] Salts bearing two CF₃-groups in both meta-positions could not compensate for this loss of Meisenheimer stability and salt 3m also proved unreactive.

Figure 2. Unreactive salts for diarylation.

![Unreactive salts](image-url)
3.7 Mechanistic studies

Metal-free arylations with Ar₂IX most commonly occur via ligand coupling pathways (LC), to afford the arylated nucleophile and aryl iodide as a byproduct (see section 1.1.1).[27b, 4b] While the feasibility of a direct S\textsubscript{N}Ar on the \textit{ipso}-position of the iodine has been investigated by DFT calculations, such reactivity was only observed under highly specific conditions.[7c] Moreover, S\textsubscript{N}Ar functionalizations of Ar₂IX on positions other than the iodine \textit{ipso}-position is unprecedented in the literature.

To explore the mechanistic rationale of the diarylation methodology, a thorough mechanistic investigation was conducted by experimental and computational studies. Considering the two electrophilic sites of salts 3, two potential pathways for generation of diarylated products \textbf{P} were envisioned (Scheme 28). Hypothetically, Pathway I is possible where a conventional ligand exchange, followed by ligand coupling from intermediate \textbf{A} would generate the phenylated nucleophile \textbf{C} and the aryl iodide \textbf{1a}. Formation of the product \textbf{P} is then achieved by an S\textsubscript{N}Ar reaction between \textbf{C} and \textbf{1a}.

Conversely, the envisioned Pathway II is initiated by a direct S\textsubscript{N}Ar reaction of the nucleophile on the diaryliodonium salt \textbf{3a}, proceeding \textit{via} a Meisenheimer complex, stabilized by the two electron-withdrawing substituents of the ring. Upon elimination of fluoride, intermediate \textbf{B} is formed, from which the second arylation could occur intramolecularly to yield product \textbf{P}. This type of nucleophilic displacement, where the iodine(III) core of the diaryliodonium salt is retained, is unprecedented in the literature as reactions between nucleophiles and Ar₂IX (except counterion ligand exchanges) consistently result in reduction of the iodine(III) to iodine(I).[4b] The second arylation is then anticipated to proceed in accordance with the known aryl migrations of iodonium ylides.[48a]
3.7.1 Investigation of Pathway I

Since Pathway I proceeds by the established iodonium reaction pathways ligand exchange and LC, this proposal was evaluated first. The feasibility of Pathway I relies on the conditions of selective phenylation over transfer of the fluorinated aryl group from intermediate A in the first step. This type of chemoselectivity is considered unlikely since arylations from unsymmetrical diaryliodonium salts generally proceed with transfer of the more electron-deficient aryl group.\cite{6, 14, 13} The selective phenylation with salt 3a would therefore only be possible if the arylation of aliphatic amines displayed a strong anti ortho-effect, where transfer of ortho-substituted aryls e.g. Ar\(^1\) was disfavored.\cite{14, 13}

To explore the possibility of a prevailing anti ortho-effect, a chemoselectivity study was conducted where the diaryliodonium salts 13a-e were reacted with amine 7a under our previously reported conditions for monoarylation of amines (Table 4).\cite{68} Should an anti-ortho effect be dominant, reactions with the salts 13a-c would result in preferential phenylations, whereas low reactivity would be expected from the symmetrical salt 13d. On the contrary, the study demonstrated a clear ortho-effect, where the ortho-substituted aryl groups were preferentially transferred in all instances, yielding 14b-d as the major products (entries 1-4). Furthermore, the arylations with salt 13c-d delivered the corresponding products in high to excellent yields (entries 3-4), and these substrates were therefore included in the protocol for monoarylation instead.\cite{68} The ortho-effect became increasingly evident by comparing the reactions of salt 13b to salt 13e (entries 2 and 5). In the reaction with 13e, phenylation was favored over arylation due to the electron-donating properties of the para-methyl group, whereas the reaction with the ortho-methylated salt

---

**Scheme 28.** Mechanistic proposals.
13b resulted in selective aryl transfer with 2:1 selectivity. Based on the results of this chemoselectivity study, Pathway I was deemed improbable.

**Table 4. Chemoselectivity study of aliphatic amines.**[^a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Salt 13</th>
<th>Phenylated Product[^b]</th>
<th>Arylated Product[^b]</th>
<th>Ratio Ph:Ar</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="13a" /></td>
<td>14a, 27%</td>
<td>14b, 62%</td>
<td>1:2.3</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="13b" /></td>
<td>14a, 21%</td>
<td>14c, 35%</td>
<td>1:1.7</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="13c" /></td>
<td>14a, &lt;5%</td>
<td><img src="image4.png" alt="14d" /></td>
<td>1:15</td>
</tr>
<tr>
<td>4</td>
<td><img src="image5.png" alt="13d" /></td>
<td>14a, 0%</td>
<td><img src="image6.png" alt="14b" /></td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td><img src="image7.png" alt="13e" /></td>
<td>14a, 44%</td>
<td>14c, 24%</td>
<td>1.8:1</td>
</tr>
</tbody>
</table>

[^a]: Reaction conditions: Salt 13 and Na₂CO₃ were mixed and the atmosphere was exchanged to argon. Degassed toluene was added to the solids followed by amine 7a.

[^b]: Yields were determined by analysis of the crude ¹H NMR spectra with TMB as internal standard, unless otherwise stated.

Further control experiments were conducted to investigate the viability of Pathway I. The second step of the mechanism suggests an S_NAr reaction between the phenylated nucleophile C and iodoarene 1a (Scheme 28). Therefore, the reaction between these two presumed intermediates was set up under the optimized conditions for the diarylation of amines (Scheme 29). The reaction was performed both in the absence and presence of diphenyliodonium triflate, to evaluate whether the Lewis acidic properties of the Ar₂IX would be crucial for the reaction to proceed. Nevertheless, no S_NAr reactivity was
detected. Moreover, considering the lack of reactivity in the latter experiment between the nucleophile and Ph₂IOTf, the unfeasibility of a conventional LC mechanism under the mild diarylation conditions is demonstrated. With these results considered, Pathway I was discarded.

![Scheme 29. Attempted S_N Ar on external iodoarene 1a.](image)

### 3.7.2 Investigation of Pathway II

Next, the evaluation of mechanistic pathway II was initiated. To support this mechanism, the possibility of trapping the key intermediate B was envisioned, which would demonstrate a completely novel reaction pathway for these fluorinated diaryliodonium salts. To test this hypothesis, salt 3a was reacted with N- and O-nucleophiles at low temperatures and short reaction times to inhibit the second arylation from occurring. The initial screening with primary amines was unsuccessful, since the diarylation occurred already at room temperature, without the possibility to detect intermediate B. Delightfully, strong support for the unprecedented pathway II was obtained when the reaction of 3a with water was conducted at 40 °C for 2 h instead of 50 °C for 7 h, affording the key S_N Ar intermediate 15 in a remarkable isolated yield of 94% (Scheme 30). To verify that this hydroxy-substituted salt 15 indeed was a reaction intermediate, successful conversation to the diaryl ether product 12a was achieved by heating 15 in EtOAc in the presence of base.

![Scheme 30. Trapping of reaction intermediates.](image)

To investigate whether the second arylation occurs intramolecularly, a crossover experiment was conducted (Scheme 31). The salts 3n and 3d, consisting of four different aryl groups, were reacted with 2.0 equivalents of 7a under the optimized reaction conditions. Since salts with weak EWGs at the fluorinated aryl, *e.g.* CN groups, require 90 °C to be productive, the experiment was performed at this temperature. The intramolecular nature of the second arylation would be supported if no scrambling of the aryl groups
would occur, providing 8m and 8r as the only products of the experiments. Should the second arylation instead occur in an intermolecular fashion, products containing mixed aryls from 3n and 3d would be expected, which in theory could lead to 10 unique products by different combinations of Ar\textsuperscript{1}, Ar\textsuperscript{2}, Ar\textsuperscript{3} and Ar\textsuperscript{4}. Fortunately, the experiment provided further support to the mechanistic pathway II as no scrambling of the aryl groups was observed, providing only products 8m and 8r in 80% and 63% yield, respectively.

![Scheme 31. Crossover experiment with 7a.](image)

### 3.7.3 SNAr versus LC reaction routes

As mentioned in section 3.6, the substitution pattern on Ar\textsuperscript{1} was instrumental in achieving the intended SNAr reactivity with salts 3. The reaction with the regioisomeric meta-substituted salt 3k delivered the LC product 14f in 62% yield, with complete selectivity under the literature conditions a for monoarylation of amines (Scheme 32).\textsuperscript{[68]} Performing the reaction under the milder diarylation conditions b led to no product formation, which further emphasizes the incompatibility of LC pathways with amines under these conditions. Conversely, reacting the model salt 3a under both conditions a and b, afforded the diarylated product 8a in 68-92% yield, with no trace of a competing LC product.
In contrast to the amines, anilines underwent competing LC routes under conditions a, giving a mixture of the diarylated product 10a and monoarylated products 16 (Scheme 33). Moreover, other weak nucleophiles such as p-toluic acid, predominantly underwent the LC pathway to yield 17 under literature conditions for O-monoarylation. This O-nucleophile proved unreactive under the milder diarylation conditions.

To further explore the balance between the SNAr and ligand coupling pathway, preliminary computational studies were conducted for the first arylation step with aliphatic amines and salt 3a. The study showed an initial coordination of the amine to the iodine(III) center, giving an intermediate from which both LC and SNAr could occur, with a 10 kcal/mol lower energy barrier for the SNAr route. An extensive computational study was performed during a later
diarylation project within the group, providing further support for the suggested novel SNAr route.\cite{61b}

3.7.4 Reactions with aryne and radical traps

To exclude the possibility of the diarylation occurring via an aryne intermediate or a radical pathway, the reactions with amine 7a and water were performed in the presence of furan as an aryne trap and 1,1-diphenylethylene (DPE) as a radical scavenger (Table 5). When amine 7a was reacted with salt 3a under the standard conditions a, in the absence of additives, product 8a was obtained in 93% yield (entry 1). Performing the reaction in the presence of furan or DPE did not affect the yield of the N-arylination (entries 2-3).

To evaluate whether radical or aryne pathways were causing the moderate yield in the O-diarylation with salt 3y (entry 4), this reaction was also repeated in the presence of DPE and furan (entries 5-6). These additives had an insignificant effect on the yield and no new products were detected. The possibility of arynes or radical pathways was therefore discarded for both the N- and O-diarylation.

Table 5. Reactions with aryne and radical traps.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Salt</th>
<th>Nucleophile</th>
<th>Additive</th>
<th>Product (%)[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[a]</td>
<td>3a</td>
<td>Amine 7a</td>
<td>-</td>
<td>8a: 93</td>
</tr>
<tr>
<td>2[a]</td>
<td>3a</td>
<td>Amine 7a</td>
<td>Furan</td>
<td>8a: 93</td>
</tr>
<tr>
<td>3[a]</td>
<td>3a</td>
<td>Amine 7a</td>
<td>DPE</td>
<td>8a: 91</td>
</tr>
<tr>
<td>4[b]</td>
<td>3y</td>
<td>H2O</td>
<td>-</td>
<td>12c: 58</td>
</tr>
<tr>
<td>5[b]</td>
<td>3y</td>
<td>H2O</td>
<td>Furan</td>
<td>12c: 60</td>
</tr>
<tr>
<td>6[c]</td>
<td>3y</td>
<td>H2O</td>
<td>DPE</td>
<td>12c: 50</td>
</tr>
</tbody>
</table>

[a]: K2CO3 (1.0 equiv), MeCN, 50 °C, 7 h. [b]: Cs2CO3 (1.0 equiv), EtOAc, 50 °C, 16 h. [c]: Isolated yields.
3.8 Conclusion

We herein present the first metal-free sequential diarylation from acyclic diaryliodonium salts. In this transformation, construction of two new carbon-heteroatom bonds is achieved in one pot, to deliver structurally diverse di- and triarylamines as well as diaryl ethers by use of novel fluorinated diaryliodonium salts. Comprehensive mechanistic studies support the unprecedented reactivity of these salts, which enables potent cascade reactions whereby diarylated products are formed by concomitant $S_N$Ar and intramolecular aryl transfer. The method demonstrated a broad substrate scope in terms of both diaryliodonium salts and nucleophiles (>100 examples). The mild conditions permit high functional group tolerance and extensive synthetic flexibility, allowing for preparation of variable multi-arene products, as well as late-stage functionalization of various pharmaceuticals and natural products. This methodology addresses two crucial elements of sustainable arylations; Firstly, the atom-economy drawbacks associated with $\text{Ar}_2\text{IX}$ arylations are effectively resolved by incorporation of the iodoarene component into the final product with metal salts as the only formal waste of the reaction. Indeed, a remarkable 59-83% AE of the transformations was achieved. Secondly, accomplishing two consecutive arylations in one-pot greatly enhances the overall process- and time-efficiency of the reaction, while minimizing the waste production by avoiding consecutive purification steps. We anticipate this methodology to be a competitive alternative to established arylation methods due to its efficacy as well as the simple reaction setup, allowing its utility outside of advanced organic chemistry laboratories.
4. Synthesis of Complex Diarylamines through a Ring-Opening Difunctionalization via Ammonium Salts (Paper IV)

4.1 Introduction

Cyclic amines are pivotal cornerstones in drug discovery, where methods to expand and harness their versatile medicinal properties by means of derivatization are highly valued.\textsuperscript{[74]} Although N-functionalizations\textsuperscript{[75, 66c]} as well as peripheral C-H derivatizations\textsuperscript{[76]} are well established, strategies for skeletal diversification by ring-opening, expansion, fusion or contraction remain highly limited, especially for unstrained cyclic amines.\textsuperscript{[77]} Achieving efficient and selective cleavage of the strong C–N σ-bonds\textsuperscript{[78]} would constitute a valuable approach to diversify this important compound class and enable improved versatility in their applications. Ideally, this type of deconstructive functionalization should occur with simultaneous introduction of versatile functionalities at both the N- and C-terminal to attain value-added products with enhanced structural complexity.\textsuperscript{[79, 74a, 77]} Such transformations remain scarce in the literature as the most common means for C–N cleavage occurs via oxidative\textsuperscript{[80]} or reductive\textsuperscript{[81]} pathways, often with low selectivity and poor functional group tolerance (Scheme 34A, routes a,b). The von Braun reaction allows for dual N,C-functionalization via ring-opening of ammonium salt intermediates, however these routes are associated with limited substrate scopes (route c).\textsuperscript{[82]} A more recent variant of this strategy highlights on difluorocarbene transfer,\textsuperscript{[83]} demonstrating structural diversification of a broader scope of common cyclic amines (route d).\textsuperscript{[83b]} Moreover, Sarpong and co-workers recently presented an elegant silver-mediated deconstructive fluorination with cyclic amines as alkyl radical precursors (route e).\textsuperscript{[84]}
Considering the lacking methods for skeletal diversification of cyclic amines by dual N,C-functionalization, we envisioned the ability of attaining the complex diarylamines 21, 22 by expanding our diarylation methodology to secondary amines (Scheme 34B). As demonstrated during the mechanistic studies of Chapter 3, trapping of the S_N_Ar intermediate with water was indeed feasible, giving access to the hydroxy-substituted Ar_2IX reagent 15 (see section 3.7.2). While the reaction with primary amines could not be stopped after the S_N_Ar step, we anticipated that the reaction with a secondary amine would allow isolation of iodonium salt 19, as the intramolecular arylation rate would expectedly be reduced. Diaryliodonium salts bearing unprotected amino functionalities are unprecedented in the literature, which likely stems from the incompatibility of such functionalities with the acidic/oxidative conditions required for Ar_2IX synthesis. Thus, 19 would constitute a novel class of diaryl-iodonium salts and provide access to unexplored chemical space. The diaryl-iodonim salts 19 could potentially find applications beyond the scope of standard ligand coupling routes, by undertaking a sequential arylation/ring-opening pathway. Intramolecular arylation from 19 would afford ammonium salt 20 in situ, which upon reaction with an external nucleophile could undergo ring-opening to yield products 21, 22. The full
benefit of this strategy would be the efficient synthesis of structurally complex amines in a highly atom- and step economical manner with versatile functionalities at both the N- and C-terminal, available for downstream derivatization.

4.2 Proof of concept experiments

Piperidine derivates are ubiquitous in medicinal products due to their versatile properties as anti-Alzheimer’s, anti-psychotic and anti-cancer agents.\textsuperscript{[74b]} Since the derivatization of this moiety would be of special interest, piperidine 18a was used as the model substrate. A proof-of-concept experiment was conducted to explore whether the complete sequence of the envisioned N-diarylation/ring-opening reaction was possible to achieve in one pot, starting from salt 3a and 2.0 equivalents of piperidine (Scheme 35). The diarylation of 18 would afford the key ammonium intermediate 20 in Scheme 34 prior to the ring-opening with a second equivalent of piperidine. It is worth nothing that trialkyl/aryl ammonium salts are generally challenging to obtain, with only a few examples known in literature.\textsuperscript{[85]} Moreover, the highly sterically strained ammonium salt 20 with two aryl groups and a bulky ortho-iodo substituent could pose a substantial challenge as no such examples exist in the literature. The ammonium salt formation would probably be significantly slower compared to the diarylation of primary amines and would therefore require more rigorous conditions. To our delight, conducting the reaction under the high-temperature conditions for LC with aliphatic amines,\textsuperscript{[68]} the target product 21a was indeed formed, although in a modest yield together with the side-products 23 and 24 (Scheme 35a). Two competing pathways were evidently operating, where the major product 23 was formed by a dominant LC pathway upon \textit{in situ} formation of iodonium salt 19a. We anticipated the side-product 24 to stem from a competing reduction of salt 19a caused by the use of excess amine (see section 4.3). Repeating the reaction under conditions analogous to the diarylation of aliphatic amines (Chapter 3) led to a complex reaction mixture with no formation of the diarylated product 21a. To circumvent the competing pathways, the reaction was set up in a sequential manner by \textit{in situ} formation of salt 19a, intramolecular arylation to form 20a at 100 °C followed by ring-opening by a second equivalent of piperidine at rt (Scheme 35b). Nevertheless, also this attempt was unsuccessful giving 24 and 1b as the major species of the reaction.
4.3 Synthesis of N-functionalized iodonium salts

An optimization study for the synthesis of iodonium salt 19a was initiated under the conditions used for the isolation of the S_N-Ar intermediate 15 with water (EtOAc, 40 °C, 2 h, see section 3.7.2). Gratifyingly, the target product 19a was obtained in almost quantitative yield (Table 6, entry 1). The reaction was equally productive in MeCN, where a 2 h reaction time was deemed most suitable since prolonged time was associated with lower yields (entries 2-3). Moreover, it proved instrumental to use equimolar amounts of 18a since excess substrate led to a competing reductive pathway, generating the two side-products 24 and 1b in 75% yield in a 1:1 ratio (entry 4).
Table 6. Optimization for synthesis of 19a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>18a (equiv)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield 19a (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>Yield 24+1b (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOAc</td>
<td>1.0</td>
<td>40</td>
<td>2</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>1.0</td>
<td>40</td>
<td>2</td>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>1.0</td>
<td>40</td>
<td>4</td>
<td>78</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>2.0</td>
<td>40</td>
<td>2</td>
<td>not detected</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>EtOAc</td>
<td>2.0</td>
<td>40</td>
<td>2</td>
<td>76</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>PhMe</td>
<td>1.0</td>
<td>40</td>
<td>2</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>PhMe</td>
<td>1.0</td>
<td>rt</td>
<td>4</td>
<td>69</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>PhMe</td>
<td>1.0</td>
<td>rt</td>
<td>6</td>
<td>88</td>
<td>0</td>
</tr>
</tbody>
</table>

[a]: Isolated yields after filtration of the crude reaction mixture through a short silica plug eluted with PhMe:MeOH (4:1).

The reductive pathway was less pronounced in EtOAc, where formation of 19a was achieved in 76% yield in the presence of excess 18b (entry 5). To avoid competing pathways, the apolar solvent toluene was screened as well, which proved equally efficient as EtOAc and MeCN (entry 6). While the reaction could also be performed at room temperature, a prolonged reaction time was required to achieve full conversion of 3a (entries 7-8).

The substrate scope was mainly conducted under the conditions of entry 6 (toluene at 40 °C for 2 h) to avoid the competing reductive pathway as well as product 19 decomposition, which was observed in MeCN and EtOAc when varying the Ar<sup>2</sup>-group on salts 3. In toluene, piperidine 18a underwent efficient S<sub>N</sub>Ar with salts 3 bearing Ar<sup>2</sup>-groups of diverse electronic properties with substituents in ortho-, meta- and para-position, giving the corresponding products 19b-h in 78-96% yield (Scheme 36A). Functionalities prone to nucleophilic addition, such as amides (19i) and esters (19j), remained unaltered in reactions with 18a and sterically congested as well as pyridinyl salts could be functionalized to give 19k and 19l-OTs in good to excellent yields. Diversification of Ar<sup>1</sup> was feasible, although with less flexibility compared to Ar<sup>2</sup>, to retain the S<sub>N</sub>Ar reactivity of this aryl ligand. The NO<sub>2</sub> group was exchangeable to SO<sub>2</sub>CF<sub>3</sub> and CN, and additional substituents such as CF<sub>3</sub> were successfully introduced on Ar<sup>1</sup>, giving products 19m-o in good
yields. Other explored iodonium salts 3 with CO$_2$Me or SO$_2$Me activating groups were unproductive and resulted in decomposition.

\[ \begin{array}{c}
\text{Ar}^1 & + & \overset{\text{Ar}^2}{\underset{\text{EWG}}{\text{I}}}^+ \quad \overset{\text{R}}{\underset{\text{N}}{\text{N}}} \quad \overset{\text{X}}{\overset{\text{O}}{\text{Me}}} \\
\text{K}_2\text{CO}_3 (1.0 \text{ equiv}) & \rightarrow \\
\text{Toluene, } 40 \, ^\circ\text{C, } 2 \text{ h} & \rightarrow \\
\end{array} \]

**A) Scope of salts 3**

- $X = \text{OTf}$: 19a, 92%
- $OTs$: 19a-OTs, 88%

**B) Scope of amines 18**

- 19p, 76%
- 19q, 74%

**Scheme 36.** Scope of salts 19. [a]: EtOAc as solvent [b]: Reaction performed at -78 °C to rt, 6 h.

The scope of amines 18 was explored next, demonstrating the applicability of cyclic amines containing additional heteroatoms such as morpholine and
thiomorpholine (19p,q, Scheme 36B). Further amine functionality was achieved by decorating the carbon framework with substituents in the 4- and 3-position to afford products 19r-v in good to high yields. Moreover, variation of the amine ring-size was achieved by using 5- and 7-membered amines (19w,x). Limitations of the scope were encountered in reaction with acyclic amines, as these caused decomposition of salts 3.

Overall, the practical and generally high yielding synthesis of the salts 19 was achieved without the need for excess substrates, which allowed for quick and easy isolation of the products by simple filtration.

4.4 Optimization of arylation /ring-opening sequence

After establishing efficient access to the iodonium salts 19, an extensive screening of conditions for the arylation/ring-opening transformation was conducted (Table 7). The reaction was performed in a sequential manner to allow formation of 20 prior to the addition of nucleophile and base. The optimization was continued with piperidine 18a as the external nucleophile for the ring-opening step to incorporate this valuable moiety into the products. Preheating salt 19a in MeCN at 100 °C for 4 h, followed by addition of piperidine and K$_2$CO$_3$ at room temperature, did indeed yield 21a with complete selectivity in 47% yield and with no trace of the previously competing products 23, 24 (entry 1). Extending the reaction time of the first step to allow complete formation of 20a prior to the addition of piperidine proved beneficial, affording the product in an excellent yield (entry 2). The reaction was most efficient at 100 °C, as lower temperatures caused significantly slower formation of intermediate 20a (entry 3). The solvent MeCN was deemed most suitable as insufficient S$_2$2 ring-opening was observed in the other screened solvents, despite the reactions being performed at elevated temperatures (entries 4-6). The optimal outcome was achieved by performing the reaction with the mild base potassium carbonate, as stronger bases such as NaH and 'BuOK caused decomposition of 20a (entries 7,8). Increasing the temperature (entry 9) or the time (entry 10) of the ring-opening step had an insignificant effect on the product yield. Notably, using excess base resulted in a considerable loss in yield, which further highlights the challenges of performing the full reaction sequence from 3a to 21a in one pot (entry 11). The reaction displayed certain sensitivity to non-inert and non-anhydrous conditions, particularly to the use of wet MeCN (entries 12-13). The requirement for anhydrous MeCN relates to the anticipated Ritter reactivity between 20a and water (see section 4.5.3).
Under the optimal conditions of entry 2, the full synthesis sequence from the ortho-fluorinated salt $3a$ to the final product $21a$ was achieved without the need for column purification as the final product was isolated by a basic wash.

Table 7. Selected results for optimization towards product $21a$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>$T_1$ (°C)</th>
<th>$T_2$ (°C)</th>
<th>Yield of $21a$ (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$K_2$CO$_3$</td>
<td>MeCN</td>
<td>4</td>
<td>100</td>
<td>rt</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>$K_2$CO$_3$</td>
<td>MeCN</td>
<td>16</td>
<td>100</td>
<td>rt</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>$K_2$CO$_3$</td>
<td>MeCN</td>
<td>24</td>
<td>90</td>
<td>rt</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>$K_2$CO$_3$</td>
<td>MeCN</td>
<td>16</td>
<td>100</td>
<td>100</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>$K_2$CO$_3$</td>
<td>MeCN</td>
<td>16</td>
<td>100</td>
<td>100</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>$K_2$CO$_3$</td>
<td>MeCN</td>
<td>16</td>
<td>100</td>
<td>100</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>NaH</td>
<td>MeCN</td>
<td>24</td>
<td>100</td>
<td>rt</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>tBuOK</td>
<td>MeCN</td>
<td>24</td>
<td>100</td>
<td>rt</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>$K_2$CO$_3$</td>
<td>MeCN</td>
<td>16</td>
<td>100</td>
<td>100</td>
<td>84</td>
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<tr>
<td>10</td>
<td>$K_2$CO$_3$</td>
<td>MeCN</td>
<td>16</td>
<td>100</td>
<td>rt</td>
<td>89$^b$</td>
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<td>11</td>
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<td>16</td>
<td>100</td>
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<td>60$^c$</td>
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<tr>
<td>12</td>
<td>$K_2$CO$_3$</td>
<td>MeCN</td>
<td>16</td>
<td>100</td>
<td>rt</td>
<td>63$^d$</td>
</tr>
<tr>
<td>13</td>
<td>$K_2$CO$_3$</td>
<td>MeCN</td>
<td>16</td>
<td>100</td>
<td>rt</td>
<td>36$^e$</td>
</tr>
</tbody>
</table>

$^a$: Crude yields determined from $^1$H NMR with TMB as internal standard. $^b$: Step 2: 3 h $^c$: 2.0 equiv of $K_2$CO$_3$. $^d$: Oxygen atmosphere. $^e$: Non-anhydrous MeCN used.
4.5 Substrate scope studies

4.5.1 Diaryliodonium salt scope
With the established optimized conditions, the scope of $N$-functionalized salts 19 was evaluated in the arylation/ring-opening pathway (Scheme 37). High synthetic flexibility was demonstrated in the transfer of various aryl groups ($\text{Ar}^2$) with versatile electronic properties and functionalities such as halogens, CF$_3$, alkyls, OPh ($21\text{b-h}$) in 61-92% yield. Synthesis of the sterically hindered $\text{o-Me}$ product 21h was achieved in good yield, whereas the Mes-salt 19k proved unreactive and was recovered in 83% yield after the reaction. Transfer of aryl groups bearing more sensitive functionalities such as amides ($21\text{i}$) and esters ($21\text{j}$) were achieved in high yields. Salts 19 with variations on $\text{Ar}^1$ proved productive as well, affording $21\text{k-m}$ in 78-86% yield. An additional limitation in the intramolecular arylation step was encountered with the pyridinyl salt 19-OTs that underwent decomposition under the applied conditions.

Structural diversification of a range of cyclic amines was achieved by utilization of salts 19r-w. Piperidine derivatives with substituents in the 3- and 4-position efficiently underwent the arylation/ring-opening route to give products 21n-r in high to excellent yields. Even substrate 19u with a competing nucleophilic hydroxy-substituent undertook the intended pathway, affording the amino alcohol product 21q with complete chemoselectivity in a good yield. Application of salt 19v, with a 3-Me substituent on the amine core, resulted in nucleophilic ring-opening at the least hindered position, giving product 21r as the only regioisomer in 73% yield. Arylation/ring-opening of the 7-membered substrate 19w was feasible and afforded product 21s in 51% yield, whereas the 5-membered salt 19x decomposed under the applied conditions.
4.5.2 Nucleophile scope – Method A

The scope of potential nucleophiles for the ring-opening step was explored next (Scheme 38). To include less potent nucleophiles than piperidine, two methods were developed where the reaction time and temperature for the S_N2-step was varied according to the nucleophilicity. By use of Method A, a range of cyclic and acyclic secondary amines, as well as primary amines containing heteroaryls and alkenyl groups smoothly underwent the reaction to give products 22a-g in 67-98% yield. Late-stage functionalization of densely functionalized nucleophiles such as the proline-methyl ester and the monoterprenoid geranyl amine, which is a common starting material in the total synthesis of various natural products, was achieved to give 22c and 22h in 95% and 76% yield, respectively. Interestingly, utilization of the ambident nucleophile ethanolamine resulted in completely chemoselective N-alkylation, giving 22i as the only product in 81% yield. Furthermore, we were pleased to achieve selective monoalkylation of the applied primary amine...
nucleophiles, as overalkylation is a common problem in $N$-alkylation strategies.\cite{86} Weaker nucleophiles such as anilines efficiently underwent the arylation/ring-opening sequence to give 22j-1 in high yields. This allowed incorporation of indolyl-moieties into the final products as well as difunctionalization of the pharmaceutical cytadren.

The methodology was expanded beyond the use of nitrogen nucleophiles, and the high yielding chlorination (22m) and bromination (22n) were achieved as well. The nucleophile 2,5-dimethylphenol smoothly underwent the intended pathway to give 22o in 81% yield, whereas non-hindered phenols undertook an unproductive competing $S_N{Ar}$ pathway.

![Scheme 3. Substrate scope of nucleophiles with Method A.](image)

The competing $S_N{Ar}$ pathway proceeds via the ammonium intermediate 20, which possesses two sufficiently electrophilic sites for nucleophilic attack. Apart from the desired $S_N{2}$ pathway, the ammonium moiety can be utilized as leaving group in an $S_N{Ar}$ (Scheme 39a). Small and unhindered nucleophiles preferentially undertook the competing pathway and the reaction with phenol yielded the corresponding $S_N{Ar}$ products in 86% yield (1:1 ratio, Scheme 39b). Although the other halogenations had been productive, fluorine reacted
with low selectivity, giving an inseparable mixture of the corresponding \( S_N2 \), \( S_NAr \) and \( E_2 \) product in 2:2:1 ratio (Scheme 39c). Other screened nucleophile classes such as thiols, cyanides, alcohols and carboxylic acids were also unproductive under the conditions of Method A, either by lacking reactivity or by causing decomposition of the ammonium intermediate. Fortunately, most of these nucleophiles could be incorporated into the final products by use of the alternative Method B.

**Scheme 39.** Competing pathways observed with Method A.

### 4.5.2 Nucleophile scope – Method B

A complementary method was designed to allow incorporation of more challenging nucleophiles, which relies on the use of 19-\( OTs \) salts (Scheme 40). These salts undertake a different pathway compared to their triflate analogues as the tosylate counterion possesses sufficient nucleophilicity to spontaneously ring-open the corresponding ammonium salt 20-\( OTs \) in solution, giving the intermediate product 25 in quantitative yield with 100% atom efficiency. This compound is an excellent \( S_N2 \)-substrate and can undergo an *in situ* nucleophilic displacement, as demonstrated in the synthesis of...
product \textit{22p} from the previously unproductive \textit{S}-nucleophile benzyl mercaptan (Scheme 40). It proved instrumental to perform this \textit{S}-alkylation in the absence of light, to avoid a competing radical route that caused deiodination of the product.

Through a small optimization of the conditions for Method B, it proved beneficial to exchange the solvent to DMF during the \textit{S}_2\textit{N}^2-step as the yield of \textit{22p} could be considerably increased to 94\% in this solvent (Scheme 41). Utilizing Method B, aliphatic/aromatic thiols and thioamides were efficiently alkylated to yield \textit{22p}-r in high to excellent yields. Fluorine-incorporation into organic molecules has attracted considerable research interest due to the versatile applications of such compounds in medicinal chemistry and for radiolabeling.\cite{87, 84} Thus, we were pleased to achieve quantitative formation of fluorinated product \textit{22s}, which was isolated without need for column purification. The \textit{S}_2\textit{N}^2-step was performed under literature conditions for \textit{F}-alkylation in 'BuOK at 80 °C for 16 h.\cite{88} Previously unproductive \textit{C}- and \textit{O}-nucleophiles such as KCN (\textit{22t}) and phenols were smoothly alkylated, including the late-stage derivatization of estrone (\textit{22u}). The highly functionalized esters \textit{22v,w} were prepared in high yields by alkylation of the corresponding carboxylic acids. Moreover, complete selectivity for carboxylate alkylation was observed with the unprotected natural product cholic acid, with three competing nucleophilic hydroxy-substituents.
Scheme 4. Nucleophile scope with Method B. [a] Reaction performed under dark conditions. [b] tBuOH, 80 °C, 16 h.

4.5.3 Unexpected products

Some of the screened nucleophiles did not react in direct accordance with either Method A or B due to unexpected solvent interference. The formation of an amino alcohol product was anticipated by using water as the nucleophile through a ring-opening of 20a by hydroxide under the conditions of Method A. Nevertheless, such product was not observed, instead the amide product 26 was obtained in 19% yield together with 57% unreacted ammonium salt 20a (Scheme 42).

Scheme 42. Synthesis of amide product 26.

By tweaking the conditions and performing the reaction at 100 °C with excess water, the isolated yield of 26 could be increased to 55%. The reaction is
anticipated to proceed via a Ritter-type route by combination of water with MeCN.\[^{89}\]

Conducting the reaction in DMF enabled an unexpected pathway to afford the products 27 and 28 in excellent yields (Scheme 43). The formate 27 was obtained by heating 19a at 100 °C in DMF overnight followed by aqueous work-up. If instead piperidine was added prior to the aqueous work-up, the alternative amino alcohol 28 was formed with complete selectivity in quantitative yield. The formation of these products can be rationalized through a Vilsmeier-Haack type reaction,\[^{90}\] where an iminium intermediate II is formed upon ring-opening of 20a by DMF. Direct hydrolysis of II yields 27, whereas addition of piperidine results in a nucleophilic addition to II, giving the tetrahedral intermediate III which collapses to afford 28 and side-product 29. Performing the reaction with other nucleophiles, such as anilines and ammonia, yielded the same product 28. Moreover, the anticipated formamide byproduct 29 was observed by crude \(^1\)H NMR.

\[ \text{Scheme 43. Suggested routes to formation of products 27 and 28.} \]
4.6 Synthesis of ammonium salts

To demonstrate that the diarylammonium salts 20 indeed are reaction intermediates in the synthesis of 21 and 22, a small scope of these compounds was prepared (Scheme 44). Furthermore, the salts 20 are potentially interesting compounds considering the versatile applications of organic ammonium salts as antimicrobial,[91] antistatic[92] and surfactant[93, 91b] agents. Intramolecular aryl migration from 19 by heating in MeCN afforded salts 20a-c in 65-99% yield with 100% atom efficiency. Facile isolation of the products was achieved by evaporation of the solvent.

Scheme 44. Scope of ammonium salts.
4.7 Conclusion

A highly atom- and step-economical method for synthesis of densely functionalized diarylamines was demonstrated by combined diarylation and skeletal diversification of cyclic amines. The core of the strategy highlights the use of a previously inaccessible class of amino-functionalized diaryliodonium salts, which were attained by an S_NAr pathway between cyclic aliphatic amines and fluorinated Ar_2IX reagents. These novel iodonium salts were utilized in a sequential arylation and ring-opening reaction, where intramolecular aryl transfer to the nitrogen center affords cyclic ammonium salts in situ, which upon reaction with an external nucleophile result in chemoselective breakage of the strong C–N bond. High synthetic flexibility was demonstrated as transfer of aryl groups of diverse electronic properties was achieved with high functional group tolerance. Deconstructive functionalizations of a range of cyclic amines were attained with alkylation of >20 common nucleophiles in the assembly of new C–N, C–O, C–S, C–C and C–halogen bonds. Late-stage functionalization of pharmaceuticals and natural products was demonstrated, contributing to the wide scope of novel diarylamines that represents an expansion of the unexplored chemical space. The vast majority of the products contain a range of unprotected reactive sites and polar functionalities, which increase their probability of finding medicinal pertinence.
5. Applications of *ortho*-Iodinated Diaryl-amines and Diaryl Ethers in Late-Stage Functionalizations (Papers II, V)

5.1 Introduction

The diarylation methodology described in Chapters 3 and 4 was utilized in the preparation of a wide scope of diarylamines and ethers with the iodine-component from the iodonium salt retained in the final product structures. This iodine retention is not only largely beneficial for the overall atom economy of these transformations, but the intrinsic reactivity of the C–I bond enables these compounds as valuable aromatic building blocks in the synthesis of complex structures and natural products.

In this Chapter, we aimed to explore the diversification possibilities of these *ortho*-iodo diaryl compounds, mainly through transformations of the iodine substituent (Scheme 45). We envisioned the diarylated amines and ethers to be versatile coupling partners in transition metal-catalyzed cross couplings to provide products with enhanced structural complexity. Moreover, we anticipated them to find applications beyond the scope of established C-I derivatizations by oxidation of the iodine handle to afford various heterocyclic iodine(III) reagents with further broadened applicability.

![Scheme 45. Downstream diversifications of *ortho*-iodo diaryl compounds.](image)
5.2 Derivatization of diarylamines and diaryl ethers

The diarylamine 8a was chosen as the model substrate for attempted C-I functionalizations under various literature conditions. Although aryl iodides are common coupling partners in classical metal-catalyzed cross coupling reactions, the substantial sterical hindrance from the ortho-heteroatom in 8a could potentially impede these transformations. To our delight, phenylation, alkynylation and vinylation of 8a by Suzuki-Miyaura,[94] Sonogashira[95] and Heck couplings[96] were achieved to afford compounds 30a-c in 81-99% yield (Scheme 46). Carbazoles are industrially relevant compounds due to their versatile photophysical and medicinal properties,[97] and we were hence pleased to achieve high yielding carbazole formation to 30d through Pd-catalyzed C-H activation.[98] The applications were expanded beyond C-C couplings by demonstration of an efficient Buchwald-Hartwig amidation[99] of 8a, to give 30e in 78% yield. Similar derivatizations were also feasible for the more hindered triarylamines.[61a]

![Scheme 46. Metal-catalyzed C-I functionalizations of 8a.](image-url)
The diarylated products share the common structural feature of bearing an ortho-iodo substituent and a para-EWG on Ar\(^1\). Facile transformations of these functionalities were demonstrated with diaryl ether 12a (Scheme 47). The iodo substituent could readily be cleaved off by treatment of 12a with \(n\)-BuLi, providing the dehalogenated product 31a in 93% yield. Selective reduction of the NO\(_2\) group afforded the aniline derivate 31b in the presence of Fe under acidic conditions,\(^{[100]}\) whereas full reduction of both the iodine and NO\(_2\) moiety was feasible by Cu-mediated borohydride reduction (31c).\(^{[101]}\)

![Scheme 47. Derivatization of diaryl ether 12a.](image)

To further demonstrate the significance of the diarylation method, it was utilized in the total synthesis of the T-type channel inhibitor NMP-7 (Scheme 48a). Preparation of this drug molecule was achieved by a short three-step route, where diarylation of pentyamine with salt 3c yielded diarylamine 8ak with sufficient purity to allow direct use of the crude in the next reaction step. Pd-catalyzed intramolecular C-H activation\(^{[102]}\) afforded the carbazole intermediate 30f in 52% yield over two steps without column purification. Subsequent amidation from the carbazole delivered the target product NMP-7 in 85% yield, with an overall yield of 44%. This strategy offers a compelling complement to the literature route to NMP-7, which in 4 steps affords the final product starting from the commercially available carbazole (Scheme 48b).\(^{[103]}\) The benefit of our strategy is the circumvention of purification between the key steps, as only one column purification is required at the final step to obtain NMP-7 with complete purity. This enhances the overall sustainability of the method by ensuring waste-minimization in terms of both solvents and purification materials while also significantly improving the time-efficiency. Moreover, considering the broad substrate scope of amines and aryl groups compatible with the one-pot diarylation method, this route would facilitate structure-activity studies by straightforward access to various NMP-7 derivatives without increasing the number of synthetic steps.
Scheme 48. Synthetic routes to NMP-7.

a) Our route - 3 steps, overall yield 44%

\[
\text{NH}_2 + \text{MeO}_2\text{C} + \text{I}^+ \text{OTf} \xrightarrow{\text{K}_2\text{CO}_3 (1.0 \text{ equiv})} \text{MeCN, 90 °C, 15 h} \xrightarrow{\text{Pd(OAc)}_2 (20 \text{ mol%})} \frac{\text{K}_2\text{CO}_3 (1.0 \text{ equiv})}{\text{DMSO, 130 °C, 16 h}} \xrightarrow{\text{3c (1.0 equiv) Pd(OAc)}_2} \text{8ak not isolated}
\]

b) Literature route - 4 steps, overall yield 36%

Literature synthesis of NMP-7 B)[103] a) n-pentylbromide (1.2 equiv), Cs\(_2\)CO\(_3\) (1.5 equiv), in DMF µW at 140 °C for 1 h. b) 1) POCl\(_3\) (2.0 equiv) in DMF at 0 to 20 °C for 1 h. 2) µW at 100 °C for 1 h. c) KMnO\(_4\) (1.0 equiv) at reflux in H\(_2\)O:acetone for 1 h. d) Piperidine (1.5 equiv), DIPEA (2.0 equiv), DMAP (1.1 equiv), EDC (1.7 equiv) in DCM at 0 °C to rt for 16 h.

5.3 Synthesis of cyclic diaryliodonium salts

Considering the versatile utility of cyclic diaryliodonium salts as multi-purpose reagents, the applicability of the ortho-iodo diarylated compounds as building blocks towards the under-explored class of heteroatom bridged diaryliodonium salts was assessed. The major challenge of this transformation is achieving selective iodine oxidation in the presence of other heteroatoms and/or electron-rich aromatic systems that are prone to oxidation. Efficient iodine(III) formation was anticipated by use of cheap and common oxidants to give intermediate IV, which upon spontaneous intramolecular cyclization with an EAS reactive Ar\(^2\)-ligand would afford the target cyclic salt D (Scheme 49).
The preliminary studies with the di- and triarylamines 8a and 11a were unsuccessful due to overoxidation of the substrate, which emphasizes the need for strong EWGs on the nitrogen center in the literature reports on N-heteroatom-bridged iodonium salts. Gratifyingly, the diaryl ether 12a proved compatible with the oxidizing conditions, and an optimization study was initiated towards synthesis of oxygen-bridged salts 32 (Table 8). Performing the reaction under our literature conditions for acyclic salts with m-CPBA and TfOH did indeed afford the target product 32a-OTf, although in an inseparable mixture with an unidentified side-product (entry 1). To evaluate whether this side-product could be the unreacted intermediate 33, the reaction was repeated with prolonged reaction time and with excess sulfuric acid to facilitate the cyclization step (entries 2-3). Nevertheless, the reaction outcome was unaltered by these changes. While the Lewis acid boron trifluoride proved unproductive (entry 4), efficient oxidation of 12a was achieved by use of tosic acid however no cyclization occurred and the Koser’s intermediate 33-OTs was isolated in 93% yield (entry 5). To expediate the ring-closing step, the reaction was performed as a one-pot/two-step sequence, where the Koser’s reagent was formed in situ followed by addition of the stronger acid TfOH to activate the iodine(III) intermediate. Fluorinated solvents have a documented efficacy of improving the reactivity of these reagents and by employing the TfOH additive and performing the reaction in a CH₂Cl₂:TFE solvent mixture, the desired product 32a-OTf was isolated in quantitative yield (entry 6).
Table 8. Optimization towards 32a-X.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (equiv)</th>
<th>Solvent</th>
<th>Additive (equiv)</th>
<th>X</th>
<th>32a (%)[^a]</th>
<th>33 (%)[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[^b]</td>
<td>TfOH (2.0)</td>
<td>CH₂Cl₂</td>
<td>OTf</td>
<td>Impure</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>TfOH (2.0)</td>
<td>CH₂Cl₂</td>
<td>OTf</td>
<td>Impure</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3[^c]</td>
<td>TfOH (2.0)</td>
<td>CH₂Cl₂</td>
<td>H₂SO₄ (5.0)</td>
<td>OTf</td>
<td>Impure</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>BF₃·OEt₂ (2.5)</td>
<td>CH₂Cl₂</td>
<td>BF₃</td>
<td>&lt;10</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>TsOH·H₂O (3.5)</td>
<td>CH₂Cl₂</td>
<td>OTs</td>
<td>0</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>6[^c,d]</td>
<td>TsOH·H₂O (1.5)</td>
<td>CH₂Cl₂·TFE</td>
<td>TfOH (2.0)</td>
<td>OTs</td>
<td>98</td>
<td>0</td>
</tr>
</tbody>
</table>

[^a]: Isolated yields. [^b]: Reaction time: 3 h. [^c]: The additive was added after 16 h at 0 °C and the reaction was stirred for additional 6 h. [^d]: Solvent ratio 1:1.

With these conditions at hand, the generality of the method was evaluated with diaryl ethers 12 (Scheme 50). Substrates with alkylated Ar² groups efficiently underwent the cyclization (32b,c), rendering the TfOH activation unnecessary in the high yielding synthesis of 32c-OTs. The corresponding triflate salt could be obtained by an in situ counterion exchange with 3.0 equiv TfOH, however, this was associated with a notably lowered product yield. The cyclization rate of the ethers 12 strongly correlated with the electronic properties of Ar². To overcome the reduced rates of the electron-deficient substrates, the reaction time and/or temperature were increased during the cyclization step to afford the halogenated cyclic salts 32d-f in 70-88% yield. Diaryl ethers with variations on Ar¹ proved equally efficient as demonstrated in the preparation of salts 32g-i. Notably, introduction of an additional CF₃ substituent on Ar¹ bypassed the requirement of TfOH activation, providing 32h-OTs and 32i-OTs in high yields in the absence of this additive. The enhanced cyclization rates observed with these substrates likely relates to the increased electrophilicity of the iodine center in conjugation with the additional EWG substituent. Limitations of the scope were observed with highly electron-rich and electron-poor Ar² ligands, as these substrates were either too reactive (p-OPh, p-OMe) and led to decomposition, or too unreactive (p-CF₃) to undergo cyclization.

This method provides a useful complement to the previous literature protocol for hetero-atom bridged Ar₂IX reagents by Nachtsheim[^42] (see section 1.2.1), as our synthetic route offers advantages in higher yields, no requirement for excess reagents or expensive oxidants while also being unfazed by the structural limitations related to the aryne chemistry.
5.4 Applications of cyclic diaryliodonium salts

The reactivity of salt 32a was explored in various atom efficient transformations inspired by the previous work by Nachtsheim on unsubstituted cyclic salts (Scheme 51). Given the limited literature on these reagents, our study constitutes the first reactivity and chemoselectivity evaluation of unsymmetrical oxygen-bridged iodonium salts. Ring-closing reactions, either by direct annulation or via sulfur-iodine exchange were achieved to afford the heterocyclic products 34a,b in high to excellent yields. Ring-opened products were proficiently obtained by Cu-catalyzed iodination and acetylation, giving products 34c,d in 71-86% yield. Notably, complete selectivity for Ar2-functionalization was attained in the acetylation of 32a, highlighting the reverse chemoselectivity associated with metal-catalyzed procedures compared to metal-free Ar2IX arylations. The relatively low reactivity of cyclic iodonium salts and the general requirement for transition metals in their transformations are well-documented. We were hence pleased to achieve metal-free azidation of 32a, to obtain product 34e in a modest yield yet with complete chemoselectivity in favor of Ar1-functionalization. Other explored transformations, such as aminations, did indeed proceed in a high yield, however, the reaction occurred with low selectivity and afforded the products 34f,g in an inseparable 2:1 regioisomeric
mixture. On the contrary, attempted bromination by thermolysis\textsuperscript{[36]} led to decomposition of 32a, which demonstrates the reactivity difference between the more electron-deficient 32a and the literature known unsubstituted oxygen-bridged Ar$_2$IX.\textsuperscript{[42]}

5.5 Synthesis of arylxy-diaryliodonium salts

While cyclic Ar$_2$IX reagents generally provide advantages in atom economy, acyclic salts offer the benefit of wide utility under metal-free conditions. By careful regulation of the reaction conditions, selective formation of either the cyclic salt 32 or an acyclic salt analogue 35 was anticipated, as ligand exchange by a suitable “dummy” ligand with Koser’s intermediate 33 would yield the latter (Table 9). Gratifyingly, by performing the reaction with the isolated 33 and 2.0 equivalents of anisole under Kita’s conditions,\textsuperscript{[22a]} the target product 35a was obtained in 69\% yield over two steps (entry 1). The reaction could be performed in one pot by \textit{in situ} formation of 33 followed by subsequent addition of TFE and anisole, providing 35a in excellent yield (entry 2). The fluorinated solvent had low impact on the ligand exchange efficacy (entry 3), while it was essential to exclude TFE during the oxidation step as this led to competing cyclization, affording 32a-OTs as the only
product of the reaction (entry 4). Applying shorter reaction time for the ligand exchange and lowering the loading of tosic acid resulted in reduced yields (entries 5-6). In the absence of TFE, the reaction could be performed with the anisole present from the start, i.e. without the sequential addition, though it led to a slightly lowered yield (entry 7).

Table 9. Optimization of conditions for synthesis of acyclic salt 35a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent1</th>
<th>TsOH·H2O (equiv)</th>
<th>t2 (h)</th>
<th>Solvent2</th>
<th>Yield 35a (%)^[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1^[b]</td>
<td>CH2Cl2</td>
<td>3.5</td>
<td>24</td>
<td>TFE</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>CH2Cl2</td>
<td>3.5</td>
<td>24</td>
<td>TFE</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>CH2Cl2</td>
<td>3.5</td>
<td>24</td>
<td>--</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>CH2Cl2:TFE (1:1)</td>
<td>3.5</td>
<td>24</td>
<td>--</td>
<td>0^[c]</td>
</tr>
<tr>
<td>5</td>
<td>CH2Cl2</td>
<td>3.5</td>
<td>6</td>
<td>TFE</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>CH2Cl2</td>
<td>1.5</td>
<td>24</td>
<td>TFE</td>
<td>87</td>
</tr>
<tr>
<td>7^[d]</td>
<td>CH2Cl2</td>
<td>3.5</td>
<td>--</td>
<td>--</td>
<td>86</td>
</tr>
</tbody>
</table>

^[a]: Isolated yields. ^[b]: Koser’s reagent 33 was isolated in 93% yield before being reacted with anisole for 16 h; yield calculated over two-steps.^[c]: Salt 32a-OTs was obtained in 85% yield [d]: Anisole (1.1 equiv) present from the start of the reaction. [d]: Isolated yields.

A substrate scope study was conducted under the conditions of entry 2 (Scheme 52). Since diaryliodonium triflates offer application advantages over salts with other counterions,^[55] the feasibility of facile conversion of 35a to the triflate analogue 35a-OTf was demonstrated in 94% yield by an in situ counterion exchange. Furthermore, as the sterically demanding mesityl is a superior dummy ligand for metal-catalyzed arylation with Ar2IX,^[108] the mesityl salt 32b was prepared in a high yield under slightly modified conditions. Conversely to the cyclic salt scope, a range of electron-deficient substrates with halogens, CF3, and OCF3 functionalities on Ar^2 were smoothly converted into products 35c-g in 72-91% yield under mild conditions. Alkylated and highly sterically congested substrates (35i,h) as well as ethers with variations on Ar^1 (35j,k) also underwent the desired transformation in high yields. Notably, to attain selective formation of products 35i-k and avoid competing cyclization of 33, it proved essential to perform the reaction with excess anisole present from the start while excluding TFE. To showcase the
applicability of this method beyond diaryl ethers \(12\) with electron-deficient \(Ar^1\)-groups, efficient synthesis of salt \(36\) was demonstrated in 74\% yield from the electron neutral (2-iodophenyl)phenyl ether. Limitations of the scope were encountered in reactions with ethers bearing highly electron-rich \(Ar^2\) groups, e.g. \(p\)-OPh and \(p\)-OMe, as these reactions led to competing oxidation of the substrate.

Scheme 52. Substrate scope of salts \(35\), \(36\). [a] Upon completion of reaction, TfOH (2.0 equiv) was added and the reaction was stirred for 30 min at rt. [b] Reaction of mesitylene (1.1 equiv) with isolated \(33\). [c] Anisole (1.1-3.0 equiv) present from the start of the reaction in the absence of TFE, reaction time 16 h. [d] Synthesized from (2-iodophenyl)phenyl ether.

5.6 Applications of aryloxy-diaryliodonium salts

The synthetic utility of salt \(35a\text{-}OTf\) was demonstrated by chemoselective transfer of the valuable ether moiety to a range of \(C\)- and heteroatom nucleophiles under metal-free conditions (Scheme 53). \(O\)-arylation of both benzoic acid\([69a]\) and phenol\([73]\) was proficient, giving products \(37a,b\) in good yield. Even weaker nucleophiles, such as nitrocyclopentane, could be employed in the \(C\)-\(C\) bond construction to afford \(37c\) with complete chemoselectivity.\([109]\) \(S\)-arylation\([110]\) with thioamides and the heterocyclic 2-mercabenzothiazole was achieved in good to excellent yield (\(37d,e\)). Late-
stage $N$-functionalization of $35a$-OTf by nitration[111] proceeded in 98% yield (37f), also allowing for efficient isolation of the iodoarene 1c in quantitative yield. Recovery of the byproduct is an important atom economy improvement of these LC-arylations, as this enables accessibility of the iodoarene for further transformations.

Scheme 53. Transition metal-free arylations with salt 35a-OTf.
5.7 Conclusion

In summary, broad synthetic utility of the ortho-iododiaryl-amines 8 and ethers 12 was demonstrated in various downstream functionalizations. A range of C-I diversifications was achieved by classical Pd- and Cu-catalyzed cross couplings to deliver complex and structurally diverse diarylamines. The feasibility for smooth transformations of the key functional groups by dehalogenation and NO$_2$-reduction were demonstrated in excellent yields. Furthermore, the diarylation strategy was utilized in a three-step route to attain the drug molecule NMP-7, providing a complement to the literature route with the advantages of increased flexibility and sustainability due to reduced purification steps.

Two methods for one-pot preparations of oxygen-bridged cyclic diaryliodonium salts 32 and acyclic aryloxy-diaryliodonium salts 35 were developed, starting from the diaryl ethers 12. By careful regulation of the reaction conditions, complete selectivity in the formation of either the cyclic or acyclic product was achieved. Both methods proved compatible with ethers of varied electronic properties, where a broader synthetic adaptability was realized for the acyclic salts 35. As oxygen-bridged cyclic iodonium salts are highly scarce in literature and no previous reactivity studies with unsymmetric analogous are available, the model cyclic salt was evaluated in reactions with various nucleophiles under literature conditions. These salts proved most efficient under metal catalysis and could be employed in a series of atom economical transformations to afford both mono- and difunctionalized products. Enhanced reactivity was displayed by the acyclic salts, enabling their versatile utilization in metal-free O-, C-, S- and N- arylation with complete chemoselective transfer of the diaryl ether moiety. All functionalized products described in this chapter except NMP-7, 34a and 37f are novel and represent an expansion of the unexplored chemical space.
6. Concluding remarks

The novel reactivity of a new class of diaryliodonium salts has been developed and investigated in this thesis. To address the current limitations in the field concerning the poor atom economy in Ar₂IX arylations, the iodonium salts were designed to allow simultaneous transfer of both aryl groups onto external nucleophiles in one single step. The counterion of the Ar₂IX constitutes the only formal waste of the reaction, as the diarylation also proceeds with retention of the iodine atom into the final products. The core of the strategy builds on the unprecedented S_N_Ar reactivity enabled by the unique design of these new reagents and represents a conceptual expansion of iodine(III) chemistry.

The second chapter concerned the synthesis and design of the new ortho-fluorinated diaryliodonium salts. Certain limitations within the literature protocols for Ar₂IX synthesis had to be addressed to attain a broad scope of diaryliodonium salts with one electron-deficient S_N_Ar ligand in combination with either a highly electron-rich or electron-poor second aryl group. To this end, updated protocols were developed, allowing for efficient preparation of ortho-fluorinated diaryliodonium salts with diverse functionalities and electronic properties.

In the third chapter, the reactivity of the fluorinated salts was explored in the development of N- and O-diarylation protocols for aliphatic amines, ammonia, anilines and water. Extensive synthetic flexibility was demonstrated as over 100 examples of novel diaryl- and triarylamines as well as diaryl ethers were prepared in generally high yields. The mild conditions enabled impressive functional group tolerance, rendering the methodology applicable in the late-stage functionalizations of pharmaceuticals and natural products. Thorough mechanistic studies supported the unprecedented reactivity of the new salts, which in combination with nucleophiles underwent a cascade reaction initiated by an S_N_Ar arylation followed by an intramolecular aryl transfer.

In the fourth chapter the diarylation strategy was combined with the structural diversification of cyclic aliphatic amines in the development of a one-pot sequential arylation/ring-opening protocol. A new class of previously inaccessible amino-functionalized diaryliodonium salts was prepared by an S_N_Ar reaction between cyclic aliphatic amines and the ortho-fluorinated
iodonium salts. These $N$-functionalized salts were utilized in the synthesis of densely functionalized diarylamines, by undertaking intramolecular aryl transfer to afford cyclic ammonium salts in situ, which upon reaction with external nucleophiles underwent deconstructive $C-N$ functionalizations.

In the final chapter, the applicability of the ortho-iodo diaryl products from chapter 3 was explored as aromatic building blocks in various post-synthetic modifications. The retained iodine substituents enabled straightforward downstream functionalizations to afford products with enhanced complexity, including preparation of the drug-molecule NMP-7. Two protocols for preparation of oxygen-bridged cyclic and acyclic diaryliodonium salts were developed as well, demonstrating additional applicability in chemoselective functionalizations of carbon and heteroatom nucleophiles.

In summary, the work of this thesis represents an expansion of the field of atom economical applications of diaryliodonium salts under metal-free conditions. These discoveries unveil a range of synthetic transformations that address the significance of sustainable arylation strategies. Future studies will be focused on expanding the diarylation methodology to other nucleophiles, where encouraging results already have been obtained with carbon nucleophiles. We also aim to further elucidate the details of the reaction mechanism as the nature of the second arylation step is currently unknown. We anticipate that this arylation proceeds either by a direct nucleophilic ipso-substitution of the iodine via a five-membered cyclic transition state similar to those of iodonium ylides or by pre-coordination to the iodine prior to the aryl migration.

Furthermore, as protocols for preparation of complex diaryliodonium salts with oxidation sensitive substituents are lacking, we also envision the possibility of preparing such diaryliodonium salts by exploiting the unique $S_{N}Ar$ reactivity of the fluorinated/EWG-bound Ar$_2$IX. By varying the position of the leaving group on the $S_{N}Ar$ aryl, a diverse scope of previously inaccessible Ar$_2$IX is envisaged by incorporation of various external nucleophiles.
Appendix A – Contribution list

The author’s contribution to the work discussed in this thesis:

I. Advancements in the synthesis of diaryliodonium salts: updated protocols

I synthesized the salts described in this thesis under Method A, B and C and wrote the major part of the manuscript. Shobhan Mondal synthesized the salts of Method D and wrote the corresponding part of the manuscript. Berit Olofsson designed and supervised the study and assisted in the writing of the manuscript.

II. Diarylation of N- and O-nucleophiles through a metal-free cascade reaction

I initiated the project and conducted the optimization and substrate scope studies of the aliphatic amines, ammonia and water. I performed the experimental mechanistic studies, designed and executed the total synthesis of the drug molecule NMP7. I conducted the downstream functionalizations of the aliphatic amines and diaryl ethers. I wrote the major part of the supporting information and assisted in the preparation of the manuscript. David Bulfield conducted the optimization and substrate scope studies for the anilines, the computational mechanistic studies, wrote parts of the manuscript and the supporting information. Gabriella Kervefors supervised me during the start of the project. Nibadita Purkait performed the proof-of-concept experiment with aliphatic amines. Berit Olofsson designed and supervised the study, and wrote parts of the manuscript.

III. A one-pot cascade protocol for diarylation of amines and water

I performed all the experiments and wrote the protocol. Berit Olofsson designed the study and assisted in the writing of the protocol.
IV. Synthesis of complex diarylamines through a ring-opening difunctionalization via ammonium salts

I performed all the experiments and contributed to the overall design of the study. I wrote the major part of the manuscript and the full supporting information. Berit Olofsson designed and supervised the study and wrote parts of the manuscript.

V. Synthesis of cyclic and acyclic ortho-aryloxy diaryliodonium salts for chemoselective functionalizations

I initiated and finished the project. I performed the optimization studies for the cyclic diaryliodonium salts and conducted the major part of the application studies of both the cyclic and acyclic diaryliodonium salts. I performed parts of the substrate scope evaluation with both the cyclic and acyclic salts. I wrote the supplementary information and the results and discussion section of the manuscript, as well as supervised the master student Niels Knippenberg. Niels Knippenberg contributed largely to the substrate scope- of both the cyclic and acyclic diaryliodonium salts and took part in the screening of conditions for applications of the cyclic salts. Berit Olofsson designed and supervised the study and wrote parts of the manuscript.
Appendix B – Reprint permissions

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**Paper I:** E. Linde, S. Mondal, B. Olofsson, *Adv. Synth. Catal.* **2023**, *365*, DOI:10.1002/adsc.202300354. © 2023 The authors. Advanced Synthesis & Catalysis published by Wiley-VHC GmbH. This is an open access article published under a Creative Commons Attribution (CC BY-NC 4.0) license, which gives permission to reproduce the material freely.

**Paper II:** E. Linde, D. Bulfield, G. Kervefors, N. Purkait and B. Olofsson. *Chem* **2022**, *8*, 850-865. © 2022 The authors. Chem published by Elsevier Inc. This is an open access article published under a Creative Commons Attribution (CC BY 4.0) license, which gives permission to reproduce the material freely.

**Paper III:** E. Linde and B. Olofsson, *STAR protocols* **2022**, *3*, 101700. © 2022 The authors. STAR protocols published by Elsevier Inc. This is an open access article published under a Creative Commons Attribution (CC BY 4.0) license.

**Paper IV:** E. Linde and B. Olofsson, *ChemRxiv* **2023**, DOI:10.26434/chemrxiv-2023-5pzhz © 2023 The authors via a Creative Commons Attribution license (CC BY 4.0).


Parts of Schemes 13, 17, 18, 19, and 36 are very similar to the published versions, which we retain copyright of.

Schemes 13, 17, 18, 19 are taken from Paper I.
Scheme 36 is taken from Paper IV.
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References


