Metal-Free *O*- and *C*-Arylation with Diaryliodonium Salts

Erik Lindstedt

Academic dissertation for the Degree of Doctor of Philosophy in Organic Chemistry at Stockholm University to be publicly defended on Friday 12 May 2017 at 10.00 in Magnélisalen, Kemiska Övningslaboratoriet, Svante Arrhenius väg 16 B.

Abstract

This thesis concerns the development of metal-free applications using diaryliodonium salts. The first project describes an arylation protocol of allylic and benzylic alcohols in aqueous media. The method proceeds under mild conditions and the ether products were obtained in moderate to good yields. The methodology was also expanded to include arylation of phenols, giving diaryl ethers in good to excellent yields. In the second project, an arylation method that included a wider range of aliphatic alcohols was developed. The scope of accessible alkyl aryl ethers was studied and included a comparative study of phenylation and nitrophenylation of various alcohols. Finally, a formal metal-free synthesis of butoxycain was performed, illustrating the applicability of the developed method.

The third project focused on the limitations and side reactions occurring in Chapter 2 and 3. First, an approach to access symmetric diaryl ethers *via* arylation of hydroxide was presented. This reaction gave rise to a number of side products, which we hypothesized to originate from aryne-type intermediates. A mechanism for the formation of these side products was suggested, supported by trapping and deuterium labeling experiments.

Oxidation of the alcohol to the corresponding ketone was also observed and the mechanism of this interesting side reaction was investigated. The latter was suggested to proceed *via* an intramolecular oxidation without the involvement of radicals or arynes.

The fourth project covers a method to synthesize highly sterically congested alkyl aryl ethers *via* arylation of tertiary alcohols using diaryliodonium salts. The method displayed a broad scope of tertiary alcohols and was also suitable for fluorinated alcohols.

The final project detailed in this thesis deals with *C*-arylation with diaryliodonium salts, showcasing nitroalkanes as well as a nitro ester as suitable nucleophiles for metal-free arylation.

Keywords: *Hypervalent Iodine, Alkyl Aryl Ethers, Nitro Compounds, Alcohols, Diaryliodonium Salts.*

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Hur svårt kan det vara?

Lottie Lindstedt

Abstract

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List of Publications

This thesis is based on the following publications. The contribution by the author to each publication is clarified in Appendix B. Reprint permissions were made with the kind permission from the publisher, and are clarified in Appendix C. The first three chapters of the thesis are based on the author's licentiate thesis entitled "Synthesis of Aryl Ethers – Metal-Free Arylation of Alcohols using Diaryliodonium Salts", published 2015.

I. **Metal-Free Synthesis of Aryl Ethers in Water**
Erik Lindstedt, Raju Ghosh and Berit Olofsson*
Organic Letters, **2013**, *15*, 6070-6073

II. **Room Temperature, Metal-Free Arylation of Aliphatic Alcohols**
Raju Ghosh, Erik Lindstedt, Nazli Jalalian and Berit Olofsson*
ChemistryOpen, **2014**, *3*, 54-57

III. **Competing Pathways in *O*-Arylations with Diaryliodonium Salts – Mechanistic Insights**
Elin Stridfeldt,‡ Erik Lindstedt,‡ Marcus Reitti,‡ Jan Blid, Per-Ola Norrby and Berit Olofsson*
Manuscript in preparation

IV. **Mild Synthesis of Sterically Congested Alkyl Aryl Ethers**
Erik Lindstedt, Elin Stridfeldt and Berit Olofsson*
Organic Letters, **2016**, *18*, 4234-4237

V. **Metal-Free *C*-Arylation of Nitro Compounds with Diaryliodonium Salts**
Chandan Dey,‡ Erik Lindstedt‡ and Berit Olofsson*
Organic Letters, **2015**, *17*, 4554-4557

‡ These authors contributed equally.

Table of Contents

Abbreviations

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

3c-4e	3-center 4-electron
Ad	Adamantyl
DA	Diels-Alder
DIAD	Diisopropyl azodicarboxylate
DMEDA	*N*,*N*′-Dimethylethylenediamine
DPE	1,1-Diphenylethylene
dtbpy	Di-*tert*-butylpyridine
EBX	Ethynylbenziodoxolone
EDG	Electron-donating group
EWG	Electron-withdrawing group
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HTIB	[Hydroxy(tosyloxy)iodo]benzene, *Koser's reagent*
IUPAC	International Union of Pure and Applied Chemistry
L	Ligand
LG	Leaving group
NaHMDS	Sodium bis(trimethylsilyl)amide
nd	Not determined
Phen	Phenanthroline
S_NAr	Nucleophilic aromatic substitution
TBME	*tert*-Butyl methyl ether
TFE	2,2,2-Trifluoroethanol
TMB	1,3,5-Trimethoxybenzene
TMP	2,4,6-Trimethoxyphenyl

1 Introduction

Chemistry, possibly derived from the Greek word Chemia, meaning cast together, might have more relevance today than ever before. From the development of new materials to the food industry in form of efficient fertilizers, insecticides and excipients to a designed drug or a vaccine, chemistry is affecting everyone's life, every day. The desire to access highly decorated chemical structures has motivated many chemists to produce a great number of natural products and drugs. However, the need for new and more efficient methods in organic synthesis is still high to enable synthesis of molecules in a more economical and environmentally sustainable fashion.

1.1 Diaryliodonium salts

Hypervalent iodine chemistry is a research area of rapidly growing interest, probably due to the high reactivity, mild conditions and versatility of transformations that are associated with the field.[2] Diaryliodonium salts, or diaryl-λ^3-iodane (IUPAC standard), are a type of hypervalent iodine(III) reagents that were discovered in 1894 by Hartmann and Meyer.[3] Today these reagents can be easily synthesized *via* one-pot methods, starting from either another type of iodine(III) species, an aryl iodide or even elemental iodine.[4] The desired substitution pattern on the aryl moieties and the desired counterion of the diaryliodonium salt will determine which method that is most suitable. The syntheses usually proceed fast and efficiently, giving access to a broad spectrum of reagents, and the functional group tolerance is high. Many ways to depict a diaryliodonium salt can be found in the scientific literature. Figure 1a shows the historical depiction of the diaryliodonium salt as an ionic species, lacking the nowadays well-known T-shape characteristic. Throughout this thesis two structure types will be used, depending on the nature of the iodonium salt. Symmetric compounds will be depicted as in Figure 1b, to visualize the presence of a T-shaped structure, with the counterion associated to the iodine. Unsymmetric diaryliodonium salts will be represented as in Figure 1c, to illustrate that the counterion can be trans to either of the two aryl groups.

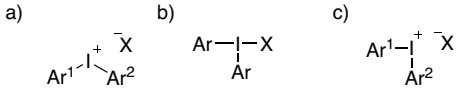
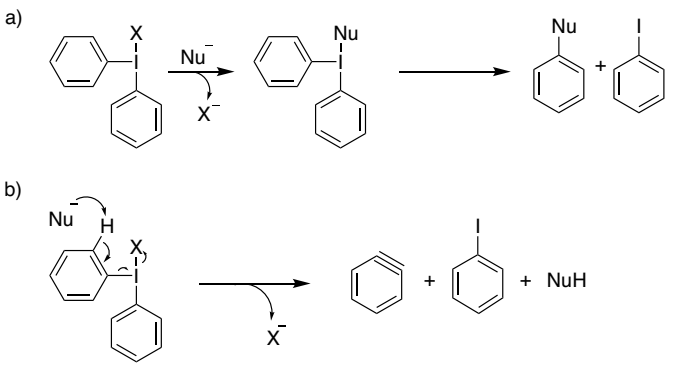


Figure 1. a) Historical ionic depiction of a general diaryliodonium salt. b) Symmetric diaryliodonium salt, the counterion X is associated to iodine. c) Unsymmetric diaryliodonium salt, 90° angle between the aryl groups.

1.1.1 Reactivity

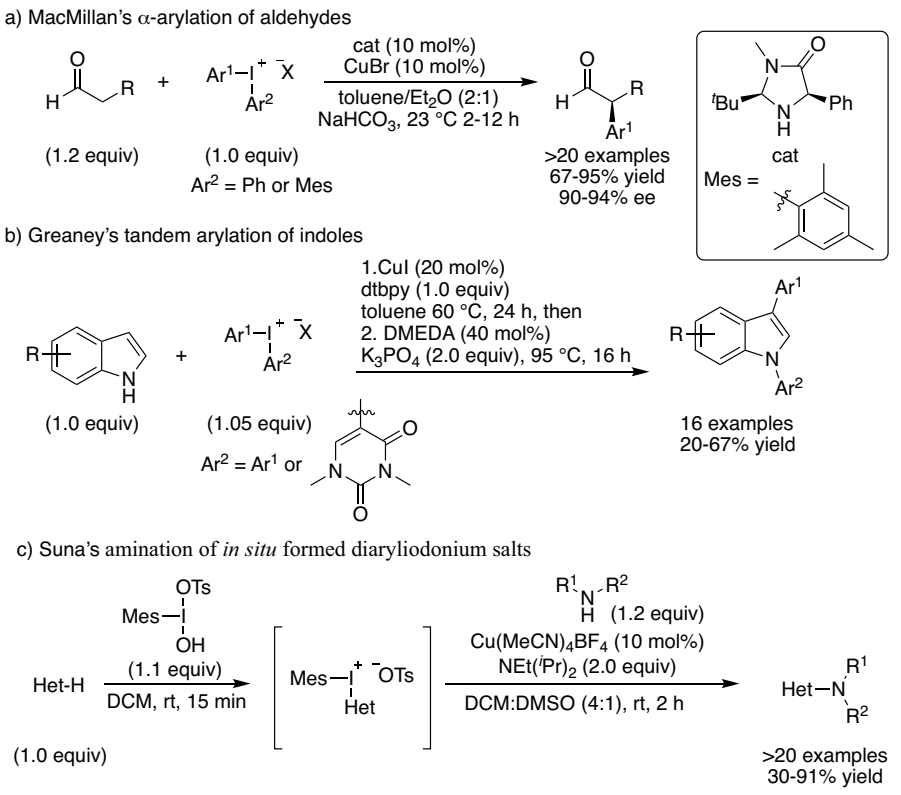
Diaryliodonium salts are bench-stable electrophilic arylating reagents that are highly reactive due to the hypervalent bond, and the inherent hyperleaving group in the form of an aryl iodide. Iodobenzene is a 10^6 times better leaving group than triflate, and has been named a "hypernucleofuge".[5] A nucleophile can interact with diaryliodonium salts *via* different pathways. The standard mechanism for metal-free applications is depicted in Scheme 1a. Initially, the nucleophile will undergo a ligand exchange with the counterion. This can occur either *via* an associative or a dissociative pathway, thus effectively forming a new T-shaped structure. This intermediate then undergoes a ligand coupling, driven by the release of iodobenzene, to form the desired product.[6] The counterion and the phenyl group trans to it resides in the apical positions and are part of the hypervalent 3-center 4-electron (3c-4e) bond. The phenyl group in the equatorial position (cis to the nucleophile), will undergo the ligand coupling. Another possible mechanism is through *ortho*-deprotonation to yield an aryne (Scheme 1b), which is discussed further in Chapter 4. There are other possible mechanisms as well, such as single electron transfer (SET) mechanism, which is common in reactions forming biaryls.[7]



Scheme 1. a) Ligand coupling mechanism for arylation with diaryliodonium salt. b) ortho-Deprotonation of a diaryliodonium salt.

1.1.2 Applications

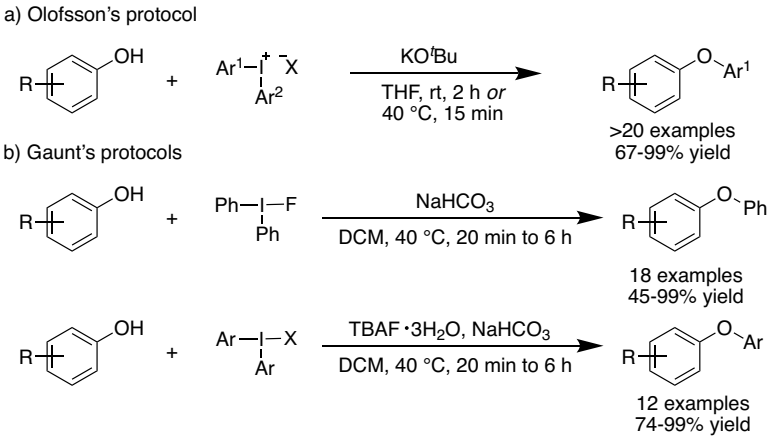
Diaryliodonium salts can undergo a wide range of transformations due to their inherent reactivity. Already in the 1950s Beringer reacted diaryliodonium salts with a number of organic and inorganic bases, such as alkoxides, phenoxides, nitrites, hydroxides and amines.[8] Today, there are numerous metal-free and transition metal-catalyzed methodologies available.[2a, 2b, 9] Some noteworthy examples of metal-catalyzed iodonium chemistry are presented in Scheme 2. MacMillan's elegant asymmetric α–arylation of aldehydes was achieved by combining organo- and copper catalysis with diaryliodonium salts (Scheme 2a).[10] Greaney and co-workers developed a sophisticated protocol, which utilized the *in situ* formed iodoarene to give a diarylated product (Scheme 2b).[11] Suna formed diaryliodonium salts *in situ* by mixing a heterocycle and a derivative of Koser's reagent (MesI[OH]OTs) (Scheme 2c). The addition of a copper catalyst and an amine resulted in *N*-arylated products with highly chemoselective transfer of the heteroaromatic moiety.[12] The scope was further developed to include the formation of diaryl ethers by applying the same strategy.[13]



Scheme 2. Selected examples of metal-catalyzed methodologies using diaryliodonium salts. dtbpy = Di-^{t}butylpyridine, DMEDA = N,N′-Dimethylethylenediamine.

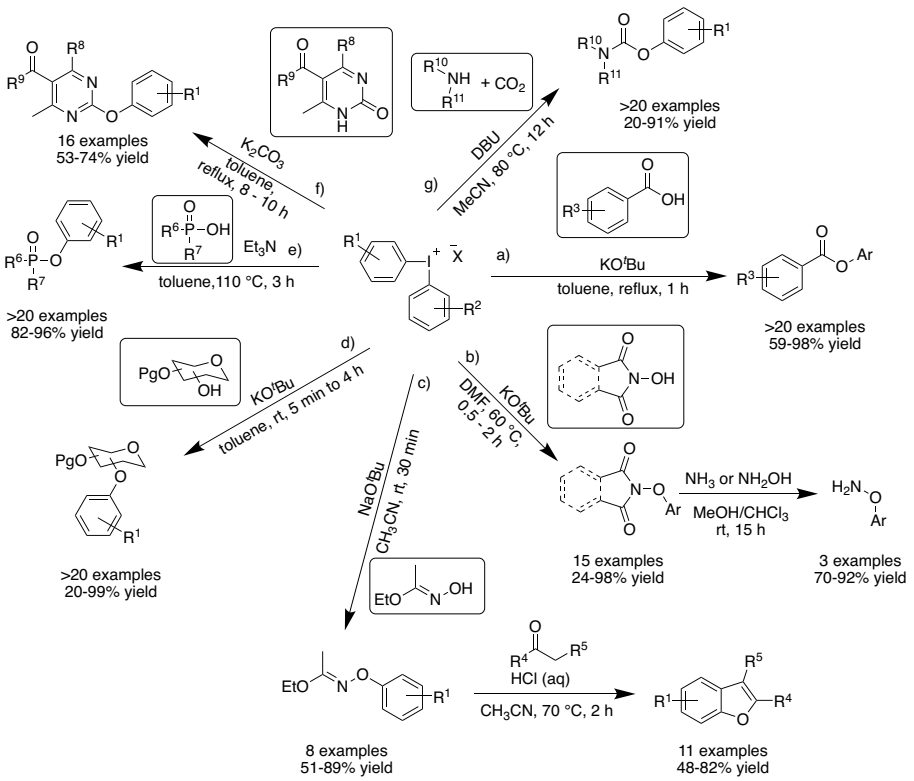
This thesis focuses on metal-free arylations using diaryliodonium salts. Creation of carbon-carbon bonds has always been an important goal within the organic chemistry community. Diaryliodonium salts have been used for metal-free *C*-arylation of esters,[14] malonates,[15] and silyl enol ethers[16] among other targets. Ochiai demonstrated an enantioselective α-arylation of β-keto esters,[17] and more recent contributions to the field include Gaunt's arylation of aldehydes to ketones using organocatalysis[18] and metal-free cross-coupling of aromatic compounds by Kita.[7, 19]

Diaryliodonium salts can also be applied in arylation of heteroatoms, such as nitrogen and oxygen nucleophiles.[9d] The Olofsson group has made significant contributions to the development of *O*-arylations with diaryliodonium salts. Several other groups have reported on the arylation of phenols, however these protocols required harsh conditions.[8, 20] Olofsson and co-workers recently developed the first general protocol (Scheme 3a).[21] The reactions were performed under mild conditions with short reaction times and has a broad scope. Later, Gaunt and co-workers utilized a strategy involving the fluoride of their iodonium salts to deprotonate the nucleophile (Scheme 3b).[22] This methodology was suitable in the synthesis of a number of diaryl ethers, and also applied in α-arylation of carbonyls.



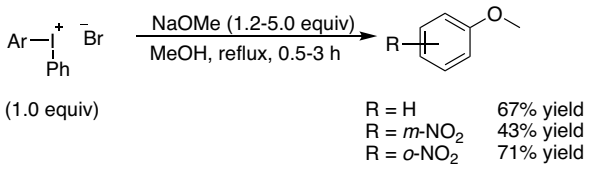
Scheme 3. Protocols for synthesis of diaryl ethers.

The Olofsson group has also developed methodology for the synthesis of aryl esters, which allowed formation of sterically congested products. However, the use of a weak nucleophile, carboxylate, required elevated temperature (Scheme 4a). [21b, 23] Later, arylated hydroxylamines were accessed in a similar manner (Scheme 4b),[24] a tactic that was further developed into a one-pot synthesis of benzofurans (Scheme 4c).[25] Recently, the methodology was modified to also include highly functionalized carbohydrates (Scheme 4d).[26] Yin has reported on metal-free arylation of phosphinic acids and other P(O)-OH compounds, a method that proceeded neatly with Et_3N as base, although requiring elevated temperature (Scheme 4e).[27] Arylation of masked phenols was demonstrated by Karade and co-workers, providing 2-aryloxy pyrimidine derivatives in good yields (Scheme 4f).[28] An elegant one-pot approach that furnished *O*-aryl carbamates was achieved by reacting an amine with carbon dioxide followed by arylation to form the oxygen-aryl bond (Scheme 4g).[29]



Scheme 4. Selected examples of metal-free O-arylation using Ar_2IX.

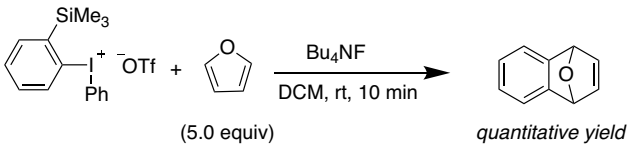
Several oxygen nucleophiles are suitable substrates for diaryliodonium salts, as depicted above. However, aliphatic alcohols have proven to be challenging to arylate. Nonetheless, Beringer demonstrated that this type of ether formation is feasible provided that an excess of methoxide is used (Scheme 5). However, the scope was very limited, and the reaction conditions rather harsh.[8]



Scheme 5. Arylation of methoxide by Beringer.

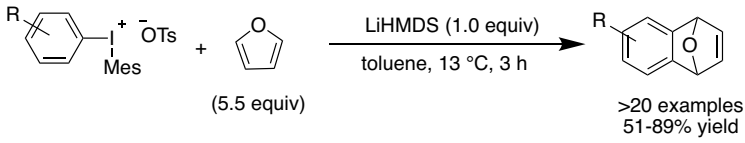
Mechanistic investigation on ether formation was performed by McEwen and co-workers.[30] The study was conducted by reacting a diaryliodonium salt with an alkoxide using the corresponding alcohol as solvent. They discovered that the addition of a radical trap or a co-solvent (toluene or hexane) increased the yield of the alkyl aryl ether. Oxidation of the alcohol to the corresponding ketone or aldehyde was observed, and was suggested to occur *via* a radical pathway.

Today, diaryliodonium salts are used also as precursors for arynes. Decomposition of diaryliodonium salts under harsh conditions was confirmed in early studies.[31] Kitamura designed diaryliodonium salts, exploiting this underlying reactivity, to control the formation of arynes. The approach was based on the leaving group ability of iodobenzene, together with trimethylsilyl (TMS) as a handle.[32] This method gave the desired benzyne intermediate in high yield, which then was used as a dienophile in a cycloaddition reaction with furan to give the desired product in quantitative yield (Scheme 6).



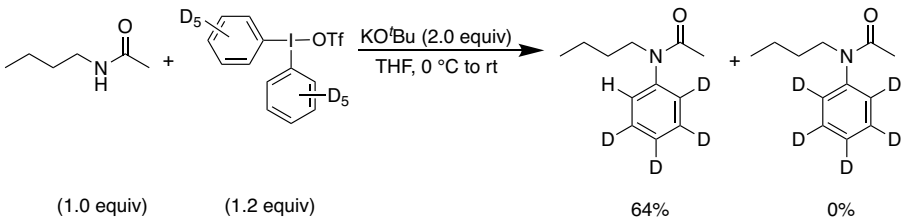
Scheme 6. Kitamura's diaryliodonium salt as a benzyne precursor.

This strategy has been developed further, *e.g.*, Stuart and co-workers recently presented a method in which arynes are formed under mild conditions, by employing aryl(mesityl)iodonium tosylates (Scheme 7).[33] Although the protocol is limited to furan as the diene, other reagents, such as benzyl azide and morpholine, can be employed as trapping agents as well.



Scheme 7. Generation of arynes from diaryliodonium salts to form cycloaddition products.

In another recent application, arynes were used to arylate secondary amides (Scheme 8).[34] The mechanism was investigated by using a fully deuterated diphenyliodonium salt, and protons were shown to be incorporated into the amide product in the *ortho*-position, suggesting that the arylation occurs *via* an aryne pathway rather than through ligand coupling.



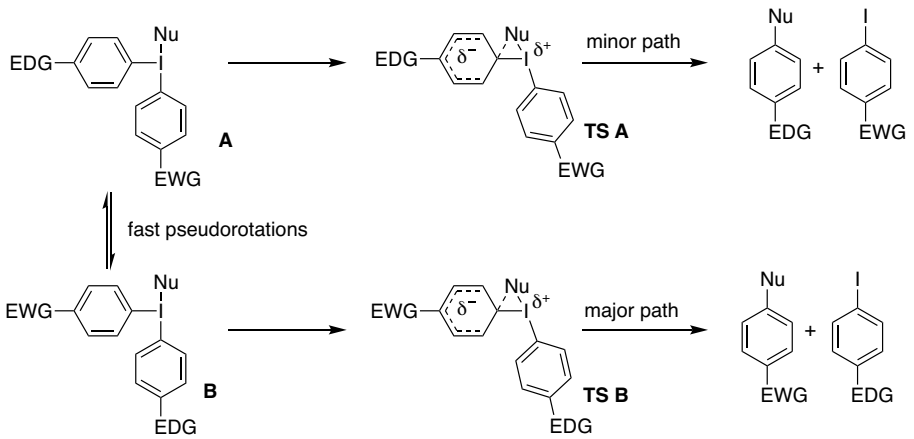
Scheme 8. Synthesis of aryl amides via an aryne pathway instead of ligand coupling.

It is possible to synthesize tertiary amides *via* a ligand coupling mechanism as well, as demonstrated by the groups of Olofsson and Adolfsson.[35] This method uses NaH as base and toluene as solvent. The mechanism was supported by the formation of single regioisomers of the amide products, and by the transfer of di-*ortho* substituted aryl groups that cannot form arynes.

The main drawback with diaryliodonium salts as reagents is the formation of stoichiometric amounts of aryl iodide as waste. Catalytic conditions are challenging to develop as the diaryliodonium salts are synthesized under acidic conditions,[4a-g] while the arylations are usually performed under basic conditions.

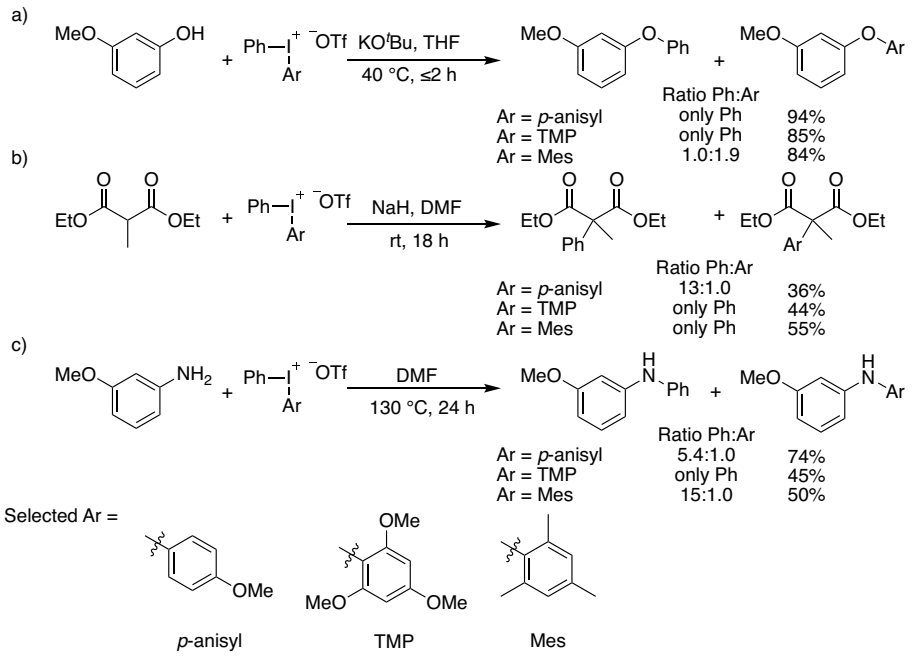
1.1.3 Chemoselectivity

As depicted in Figure 1, a diaryliodonium salt can either be symmetric ($Ar^1 = Ar^2$) or unsymmetric ($Ar^1 \neq Ar^2$). The main advantage of using a symmetric diaryliodonium salt is that only one possible product can be formed, *i.e.* one type of aryl group is transferred. Unsymmetric salts are often easier to prepare, and in addition, they may avoid the formation of stoichiometric amounts of precious aryl iodides as waste in reactions. The drawback of using unsymmetric diaryliodonium salts is the risk of forming two different products, since two different aryl groups can be transferred, as illustrated in Scheme 9. To understand this, the chemoselectivity among different nucleophiles needs to be investigated. It has been shown that it is the more electron-poor aryl group that is predominantly transferred.[36] This can be explained by the difference in the two possible transitions states (TS). The two intermediates **A** and **B** are in rapid equilibrium due to fast pseudorotations. This leads to two different TS, with **TS B** being lower in energy due to the stabilizing effect when an aryl moiety furnished with an electron-withdrawing group resides in the equatorial position. The product distribution is determined by the difference between **TS A** and **TS B** as predicted by the Curtin-Hammett principle.[6]



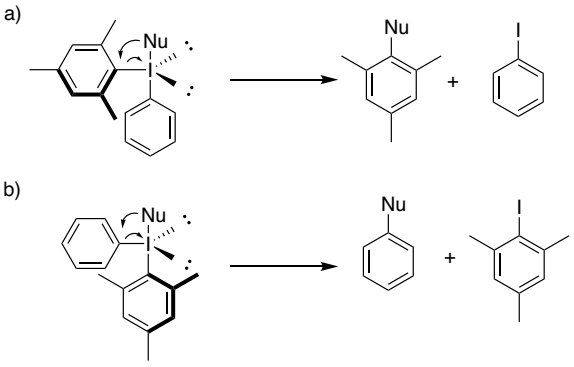
Scheme 9. Ochiai's chemoselectivity explanation for arylation of a nucleophile with an unsymmetric diaryliodonium salt.

A suitable "dummy" ligand on the diaryliodonium salt, *i.e.* an aryl moiety that is not transferred, should be more electron-rich than the other aryl group, thus favoring the transfer of the other ligand.[36] The Olofsson group demonstrated this type of preference for three nucleophiles in a thorough chemoselectivity study (Scheme 10),[37] and this was also supported by investigations by Togni[38] and Novak.[39]



Scheme 10. Chemoselectivity studies by Olofsson.

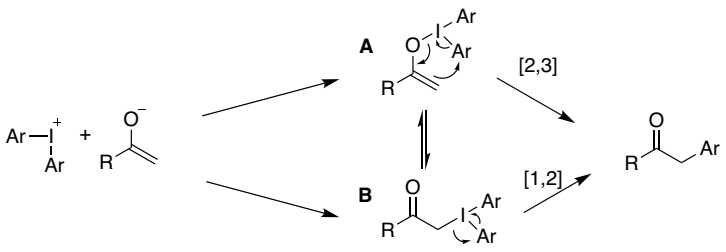
Another factor that can affect the chemoselectivity is the steric bulk in the *ortho*-positions on the aryl ligands. Studies have shown that the bulkier ligand often is transferred despite being the more electron-rich aryl group, *e.g.* mesityl(phenyl)iodonium salt will transfer the mesityl moiety (Scheme 11a, example in Scheme 10a). This trend is known as the *ortho*-effect.[40] The effect has sometimes been explained by steric repulsion between *ortho*-substituents in the apical aryl group and the iodine electron-pairs, disfavoring this intermediate (Scheme 11b). The energy difference of the two transition states decides the product distribution, and DFT calculations have been performed to understand this preference further.[37, 41]



Scheme 11. Arylation of a nucleophile using ortho-substituted diaryliodonium salt. a) Preferential transfer of the more sterically hindered aryl group – the ortho-effect. b) Transfer of the less sterically hindered aryl group.

This trend is clear for oxygen nucleophiles such as phenols[37] and carboxylic acids[23] but also in case of nitrogen nucleophiles such as amides[35] and nitrite.[42] Muñiz and co-workers recently utilized the *ortho*-effect to synthesize highly sterically congested precursors for anilines.[43] The opposite chemoselectivity has also been observed, *i.e.* where the less sterically hindered aryl group is transferred with higher selectivity than can be explained by electronic preferences. This often occurs under metal-catalyzed reactions, although through a different type of mechanism.[44] Under transition metal-free conditions the highly selective transfer of the less sterically hindered aryl group was coined the "anti-*ortho*-effect" by Olofsson (Scheme 10b) and this is dominant with carbon nucleophiles such as malonates.[37]

Arylation of malonates and other enolate equivalents can procced *via* two routes with transfer of the aryl group either to the *C*- or *O*-atom. Selectivity issues can be problematic to overcome and thus give rise to a mixture of products. Olofsson and Norrby performed a thorough mechanistic study of α-arylation of enolates using diaryliodonium salts.[45] The iodine can bind to either the oxygen or to the carbon of the enolate, giving rise to two intermediates (**A** and **B**) as depicted in Scheme 12. Calculations showed that **A** and **B** can interconvert rapidly, and that the transition state with the lowest energy was found for the [2,3]-rearrangement pathway from **A**. A recent study using NMR spectroscopy supported the formation of intermediates similar to **A**.[46]



Scheme 12. Arylation of enolates, selective C-arylation via two pathways.

Phenol dearomatization has been realized by Quideau and co-workers, utilizing that iodine can bind to either the *C* or *O* of a phenol.[47] The use of a protic, polar solvent with a low dielectric constant, such as ^{t}BuOH, gave preference to selective *C*-arylation for some substrates, instead of the more common aryl transfer to the oxygen atom to yield diaryl ethers.

1.2 Aryl ethers

1.2.1 Importance of aryl ethers

In Nature, the aryl ether bond is highly abundant, and selected examples of ethers are depicted in Figure 2. Aryl ethers can be found in both the natural dye berberine and in morphine. The ether bridge is also present in pesticides and it is prevalent in pharmaceuticals designed for many different targets and therapy areas. Roflumilast, which is used for treatment of chronic obstructive pulmonary disease contains two alkyl aryl ethers.[48] Fluoxetine, more commonly known as Prozac®, is an effective antidepressant agent,[49] and HS-10168, a new potent anti-tumor drug-candidate, both contain an alkyl aryl ether bridge.[50] A famous group of drugs is the family of proton pump inhibitors, including omeprazole, lanzoprazole, rabeprazole and pantoprazole, which all contain at least one alkyl aryl ether moiety.[51] Another potential drug candidate with an alkyl aryl ether moiety is fexinidazole, now in clinical trials for the treatment of visceral leishmaniasis (black fever). Aiming for the same target is DNDI-VL-2098, which also contains the ether motif, and where the sulfur moiety has been replaced by an additional ether moiety.[52] Furthermore, arylation and alkylation of heteroatoms belong to the top-ranked transformations performed by medicinal chemists.[53]

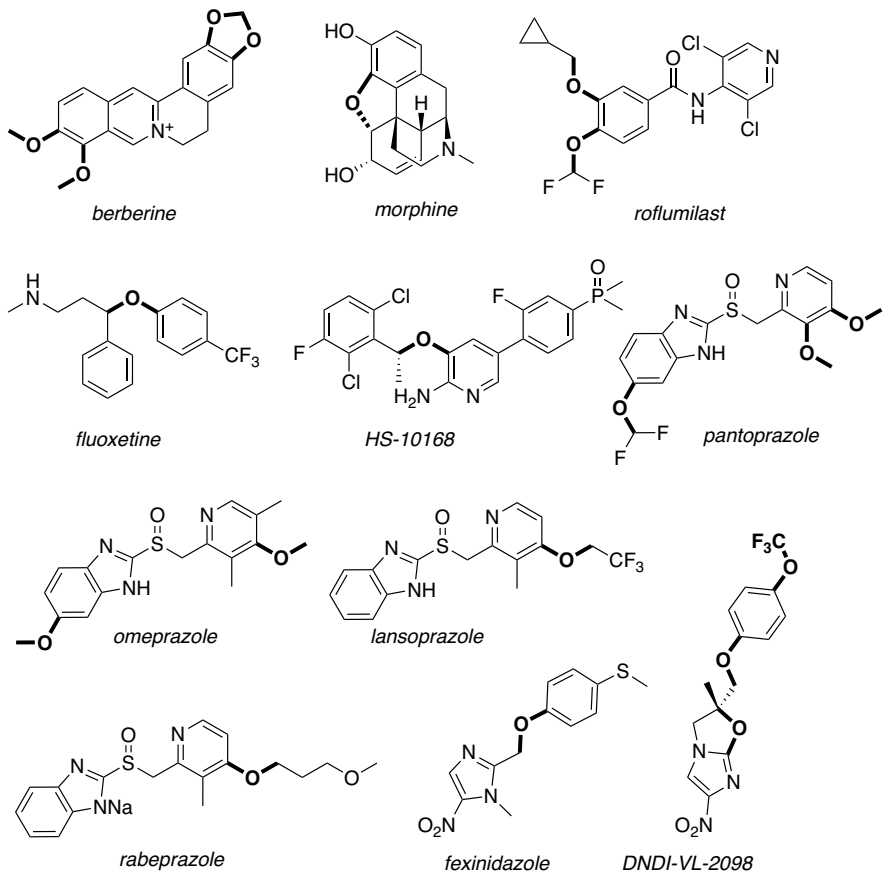
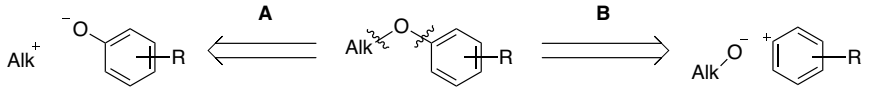


Figure 2. Examples of aryl ethers in Nature and pharmaceutical drugs.

1.2.2 Metal-free methodology

The formation of an alkyl aryl ether moiety can be viewed from two perspectives. It can originate from a phenol attacking an alkyl electrophile containing a good leaving group (Scheme 13A). Another possible route involves cleavage of the aryl oxygen bond. This means that the leaving group would be part of the aryl group, and the alkoxide would act as the nucleophile (Scheme 13B). In the latter design, an alkyl aryl ether with a stereocenter at the oxygen bridge would retain the configuration upon formation of the ether bond. Reported methodologies involving both pathways **A** and **B** are exemplified below have successfully been developed and therefore both strategies are exemplified below. The work presented in this thesis is only focused on the latter pathway, *i.e.* using alkyl alcohols as nucleophiles with an electrophilic aryl moiety.



Scheme 13. Retrosynthetic analysis of an alkyl aryl ether.

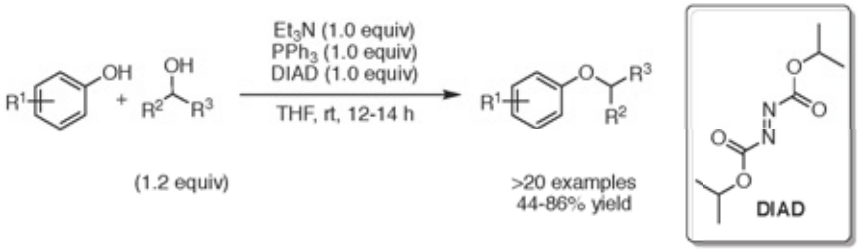
1.2.2.1 The Williamson ether synthesis

The Williamson ether synthesis is one of the first transformations taught to undergraduate students in organic chemistry. The reaction takes place between an alcohol and an alkyl halide to give an ether. Alkyl aryl ethers are obtained when phenols are used as nucleophiles. The reaction is suggested to occur *via* an S_N2 mechanism. The substrate scope is limited and primary alkyl halides are the most suitable as electrophiles. Secondary alkyl halides can also be employed, whereas tertiary substrates will mostly give elimination products.[54] One advantage of the Williamson procedure is the possibility to use weaker bases, such as carbonates, which stands in contrast to many other *O*-arylation reactions that require stronger basic conditions.[55]

1.2.2.2 Mitsunobu reaction

The Mitsunobu reaction is a powerful strategy for the formation of alkyl aryl ethers with a simultaneous inversion of a stereocenter and it is applied in a number of reported total syntheses.[56] The protocol requires several components, including a phosphine source, usually PPh_3, diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD), an alcohol as electrophile and a nucleophile. In the synthesis of alkyl aryl ethers, the nucleophile is a phenol. The reaction is mainly used for primary and

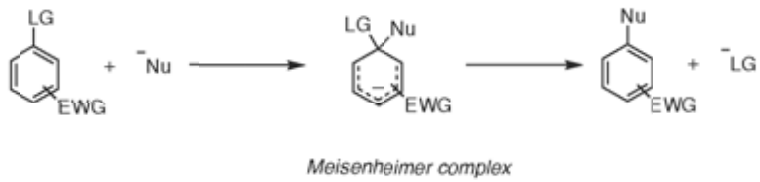
secondary alcohols,[57] due to the S_N2-type mechanism. A drawback of the reaction is the stoichiometric use of PPh_3, as well as DEAD/DIAD, which generates considerable amounts of waste.[56, 58] The reaction is tolerant to steric hindrance as bulky phenol substrates were applicable when sonication was used instead of conventional stirring.[59] Addition of Et_3N facilitate the formation of alkyl aryl ethers from secondary alcohols (Scheme 14).[60]



Scheme 14. The Mitsunobu reaction applied on secondary alcohols.

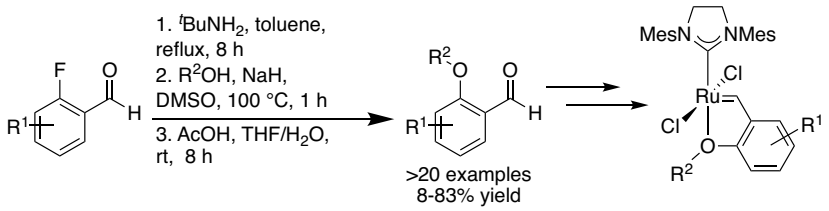
1.2.2.3 Nucleophilic aromatic substitution

A classic approach to form alkyl aryl ethers is to react an aryl halide with an alkoxide, commonly called nucleophilic aromatic substitution (S_NAr). The aryl halide is usually substituted with an electron-withdrawing group in the *ortho* or *para* position and the halide (LG) is generally a fluoride (Scheme 15). When the alkoxide attacks the arene, an intermediate known as a *Meisenheimer*-complex is formed. This is believed to be the rate-limiting step, rather than the cleavage of the carbon-fluoride bond, *i.e.* the release of the halide. The main drawback of this method is the requirement of an electron-withdrawing group, to facilitate the nucleophilic attack.[61]



Scheme 15. A general nucleophilic aromatic substitution reaction.

An advantage with the S_NAr reaction is the steric tolerance in the nucleophile, meaning that even tertiary alkoxides can undergo the reaction. This feature was used by Grubbs and co-workers in the development of novel ligands for olefin metathesis.[62] The key step to introduce the alkoxy side chain was performed with S_NAr chemistry, although the aldehyde had to be protected in order to avoid side product formation (Scheme 16). The ether products could subsequently be transformed into metathesis catalysts.

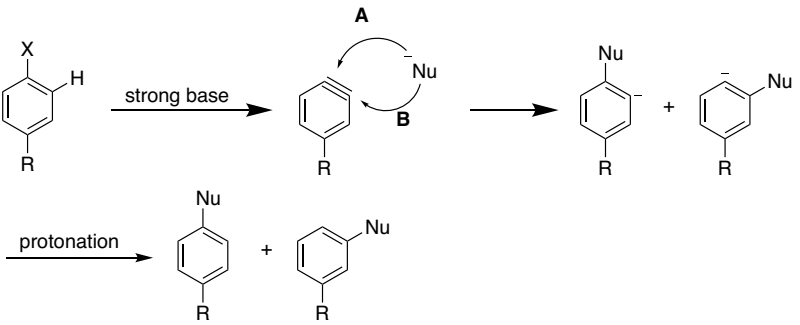


Scheme 16. Preparation of precursors for novel metathesis catalysts via S_NAr.

The S_NAr reaction has also recently been applied to decorate complex carbohydrates using a protocol that showed high regioselectivity.[63]

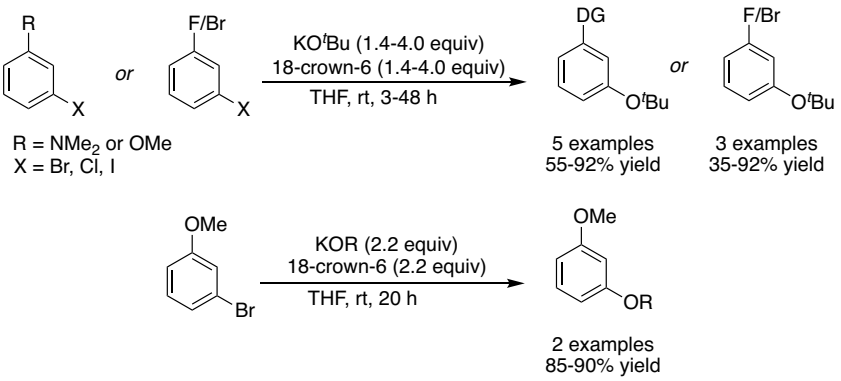
1.2.2.4 Aryne chemistry

Another strategy to access alkyl aryl ethers involves the use of arynes as highly reactive intermediates (Scheme 17). In order to form arynes, the aryl substrate must contain a good leaving group, with either a proton or a halide in an *ortho*-position to that group. The oxygen nucleophile will attack the aryne followed by protonation to yield the alkyl aryl ether. This methodology suffers from regioselectivity problems unless strong directing groups are used. Furthermore, harsh conditions are usually required to generate the arynes, and their inherent high reactivity often causes selectivity problems.[64]



Scheme 17. A general aryne mechanism.

Despite these issues several good methods have been developed. Recently Tilley and co-workers reacted arynes *in situ* by employing aryl halides and strong alkoxide bases, ultimately yielding alkyl aryl ethers (Scheme 18).[65] The addition of a crown ether (18-crown-6) allowed for the reaction to be performed at room temperature. The scope was rather limited to substrates containing directing groups, such as OMe and NMe_2, to control the regioselectivity.



Scheme 18. Aryne chemistry in the synthesis of alkyl aryl ethers.

1.2.3 Metal-catalyzed methodology

Most methodologies to form alkyl aryl ethers from alcohols involve the use of catalytic amounts of transition metals. This is a powerful approach and allows for the formation of many different ethers. The disadvantages with these methods include lower tolerance for steric hindrance in the aryl moiety, use of expensive ligands or harsh conditions,[66] and the risk of trace metals in the end-product.[67] Despite these drawbacks, the methods are widely used and developed further. The most commonly used transition metals are copper and palladium.

1.2.3.1 Copper catalysis

Ullmann discovered in the early 1900s that diaryl ethers could be formed when a phenol was reacted with an aryl bromide in the presence of copper at elevated temperature.[68] The methodology was further explored and today a great number of protocols are available for ether synthesis.[69] Buchwald and co-workers developed a Cu-catalyzed system to access alkyl aryl ethers with the use of the ligand Me_4Phen (Scheme 19).[70] Aliphatic, benzylic, allylic and propargylic alcohols were tolerated, although the reaction required elevated temperature and prolonged reaction time to proceed. Moreover, tuning the

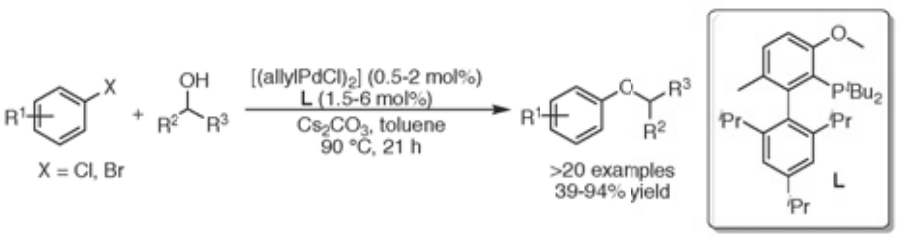
system enabled highly chemoselective *O*-arylation in the presence of *N*-nucleophiles.[71]

Scheme 19. Cu-catalyzed synthesis of alkyl aryl ethers.

The field of Cu-catalyzed ether formation is still progressing and ligand free copper-catalyzed ether synthesis has been realized, although with only two examples of alkyl aryl ethers in the scope.[72]

1.2.3.2 Palladium catalysis

The Pd-catalyzed methodology to form alkyl aryl ethers was pioneered by the contemporary work of the groups of Buchwald and Hartwig.[73] The main challenge with this approach was a competition between β-hydride elimination and reductive elimination. β-Hydride elimination leads to the undesired oxidation of the alcohol into the corresponding ketone or aldehyde, instead of the desired alkyl aryl ether. This issue has been resolved by employing bulky phosphine ligands on the metal.[74] The use of these types of ligands has broadened the scope from tertiary alcohols[75] to include primary and secondary alcohols (Scheme 20).[74b]



Scheme 20. Pd-catalyzed synthesis of alkyl aryl ethers using a bulky phosphine ligand.

1.3 Aim of the thesis

There are numerous methods to functionalize alcohols and to synthesize alkyl aryl ethers, however, the available protocols are all associated with certain limitations. One aim of this thesis is to develop methodology for aryl ether synthesis, and to address the lack of a general synthesis of aryl ethers under transition metal-free conditions, without the need of harsh conditions or excess reagents. This will be realized by employing diaryliodonium salts as electrophilic aryl group transfer agents. The more refined goal is to, in depth, understand the reaction between an alkoxide and a diaryliodonium salt, in order to achieve efficient synthetic protocols. Furthermore, the thesis seeks to broaden the arylation scope with this type of hypervalent iodine reagent and it will be fulfilled by *C*-arylation of nitro compounds. The formation of stoichiometric amounts of aryl iodide in the reaction is a drawback with diaryliodonium reagents. We aimed to address this with the use of unsymmetric diaryliodonium salts to avoid the formation of precious aryl iodides as waste, and by recovering the iodoarene after the reaction.

2 Arylation of Alcohols in Water (Paper I)

2.1 Introduction

When this project started, the Olofsson group had recently published methods for efficient preparation of diaryl ethers and aryl esters.[21, 23] However, no general protocol for arylation of aliphatic alcohols using diaryliodonium salt was available. The literature precedence was, as mentioned above, Beringer's initial arylation using harsh conditions,[8] a solvolysis study[76] and McEwen's mechanistic studies.[30] The aim was to develop an arylation without the previously encountered limitations of S_NAr and transition metal-catalyzed methodology. We envisioned a mild protocol with no requirement of excess reagents or ligands, that also would have good tolerance for steric hindrance and halide substituents on the aryl moiety.

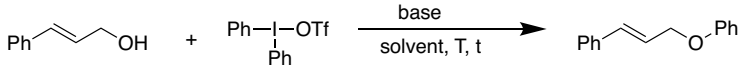
2.2 Results

2.2.1 Optimization

Cinnamyl alcohol (**1a**) was selected as the model substrate, which together with diphenyliodonium triflate (**2a-OTf**), gave ether **3a** in moderate yield when toluene was used as solvent and KO^{t}Bu as the base (Table 1, entry 1). Changing base to NaH slightly increased the yield of **3a** (entry 2), whereas the use of other organic solvents did not improve the outcome (entries 3-4). Surprisingly, the transformation proceeded in water with sodium hydroxide as base (entries 5). Since water is abundant in Nature it was intriguing to investigate the possibility to synthesize aryl ethers in aqueous media with an inexpensive base. An increase of the reaction temperature to 60 °C resulted in a significantly higher yield (entry 6), but further elevation of the temperature proved to be unproductive (entries 7-8). When the reaction was performed at ambient temperature only traces of **3a** could be detected (entry 9). Next, the amount of base was investigated and a 1:2 ratio of **1a** to NaOH seemed optimal

(entries 10-11). The reaction time could be reduced to 1 h (entry 12) and the cation of the hydroxide did not influence the reaction (entries 13-14). The addition of a radical trap did not alter the outcome of the reaction (entry 15). Additional screening concluded that the temperature could be lowered to 50 °C without any decrease in yield of **3a** (entry 16).

*Table 1. Optimization of synthesis of **3a**.*



1a (1.0 equiv) **2a-OTf** (1.2 equiv) **3a**

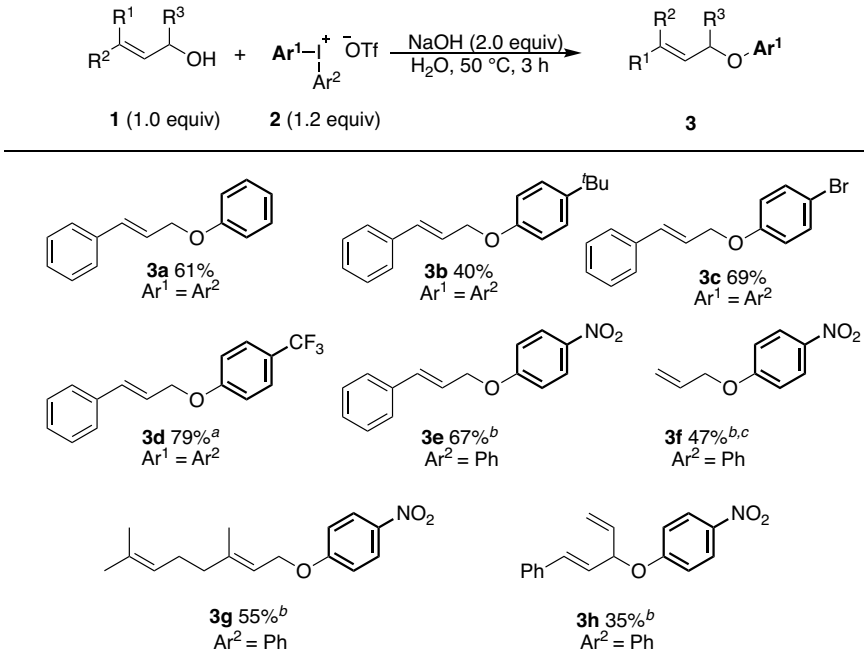
Entry	Solvent	Base	(equiv)	T (°C)	t (h)	Yield (%)[a]
1	toluene	KO^{t}Bu	1.2	40	4	38
2	toluene	NaH	1.2	40	6	46
3	DCM	NaH	1.2	40	2	29
4	THF	NaH	1.2	40	6	29
5	H_2O	NaOH	1.2	40	3	32
6	H_2O	NaOH	1.2	60	3	56
7	H_2O	NaOH	1.2	80	3	55
8	H_2O	NaOH	1.2	100	3	49
9	H_2O	NaOH	1.2	rt	3	3
10	H_2O	NaOH	2.0	60	3	64
11	H_2O	NaOH	5.0	60	3	65
12	H_2O	NaOH	2.0	60	1	63
13	H_2O	KOH	2.0	60	1	61
14	H_2O	LiOH	2.0	60	1	61
15[b]	H_2O	NaOH	2.0	60	3	64
16	H_2O	NaOH	2.0	50	3	62

Reaction conditions: **1a** (0.5 mmol) was dissolved in solvent (2.5 mL), then base was added at rt and after 10 min **2a-OTF** (1.2 equiv) was added, the reaction was thereafter submitted to a pre-heated oil bath for the indicated duration. [a] ^{1}H NMR yield using 4-anisaldehyde as internal standard. [b] 5 mol% 1,1-diphenylethylene (DPE) was added.

The moderate yield of **3a** can be explained by a competing oxidation of the alcohol to the corresponding aldehyde or carboxylic acid, as discussed in Chapter 4.

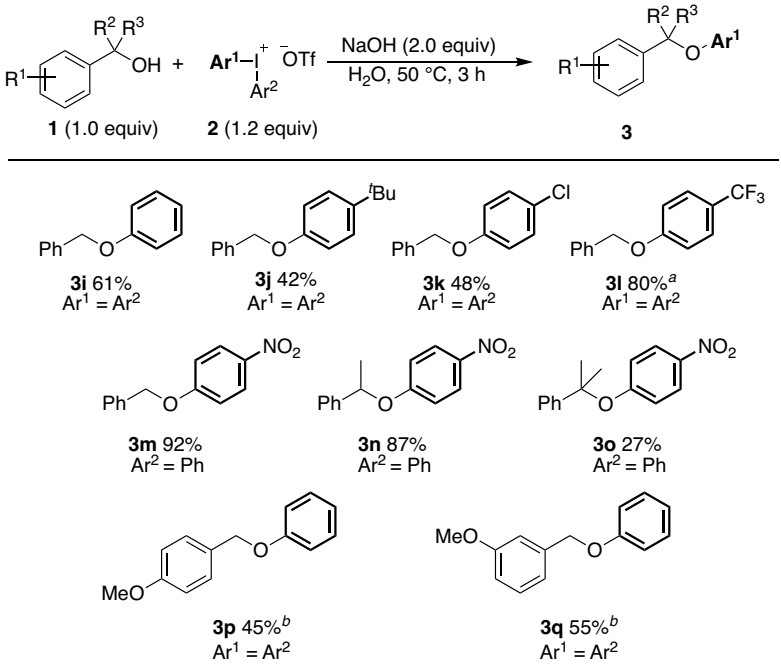
2.2.2 Substrate scope

With the optimized conditions at hand, the scope of arylation of allylic alcohols with various diaryliodonium salts was investigated (Scheme 21). The phenylated product **3a** was isolated in 61% yield. With an increased electron density of the diaryliodonium salt, the yield of the ether product (**3b**) was decreased. Halide substituted substrates are important since they are useful handles for further transformations and these substituents can be challenging for metal-catalyzed protocols. Thus, we were pleased to obtain the bromo-containing product **3c** in good isolated yield. **3c** also demonstrates the benefits of the methodology, as these types of products can be challenging for metal-catalyzed protocols.[74b] Fluoride containing compounds are frequently used in the field of medicinal chemistry,[77] and a CF_3-group on the diaryliodonium salt was well tolerated producing the ether **3d** in high yield. Employing the unsymmetric nitrophenyl(phenyl)iodonium salt **2e** gave ether **3e** with high chemoselectivity. Due to the electronic deficient, and hence, reactive nature of this diaryliodonium salt the reaction was performed at room temperature. Allyl alcohol was arylated to give **3f**, albeit in slightly lower yield despite the longer reaction time. This low yield can be explained by competing side reactions, such as diaryl ether formation, *vide infra*. Geraniol is an interesting natural product that underwent the transformation smoothly to give the desired ether **3g**. The evaluation of a secondary allylic alcohol led to a modest yield of the alkyl aryl ether **3h**.



*Scheme 21. Scope of allylic alcohol arylation. 0.5 mmol of **1**. [a] BF_4 instead of OTf. [b] Reaction performed at rt. [c] 22 h.*

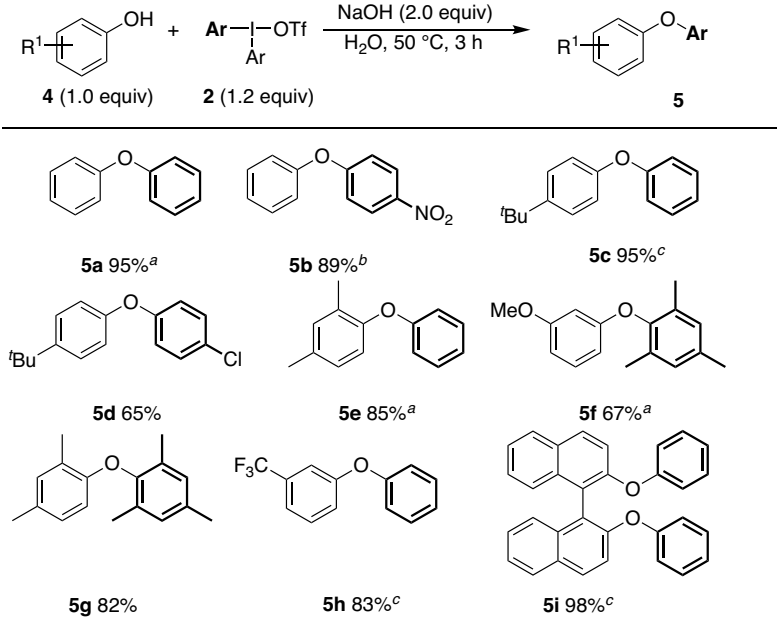
There was an interest to broaden the scope to other types of activated alcohols, and subjecting benzyl alcohol to the reaction conditions (Scheme 22), gave ether **3i** in a similar yield to **3a** (Scheme 21). Electron-donating substituents, such as *t*butyl, on the diaryliodonium salt resulted in a decreased yield (**3j**). The same observation was surprisingly made with slightly electron-withdrawing groups like chlorides, giving the ether **3k**. Employing more electron-deficient iodonium salts gave the alkyl ether **3l** in high yield, and **3m** in excellent yield. Nitrophenylation occurred smoothly even with a secondary alcohol (**3n**). It was possible to employ tertiary alcohols albeit the product **3o** was obtained in low isolated yield. Additionally, two different benzylic alcohols were submitted to the reaction conditions, however both increasing and decreasing the electronic density led to lower isolated yields of the aryl ethers (**3p**-**q**).



*Scheme 22. Arylation scope of benzylic alcohols using diaryliodonium salts. 0.5 mmol of **1**. [a] BF_4 was used instead of OTf. [b] Reaction temperature 60 °C.*

The next step was to compare the novel *O*-arylation conditions to the established protocol to arylate phenols, published by the Olofsson group.[21] The aim was to demonstrate the generality of arylation in aqueous media with inexpensive NaOH. The diphenyl ether **5a** was isolated in excellent yield within short reaction time (Scheme 23). Nitrophenylation occurred in a similarly high yield to give **5b** and additionally an electron-rich phenol underwent phenylation to give **5c**. Other phenols also reacted smoothly to give

products **5d-h**. Sterically hindered aryl groups could be transferred (**5f-g**), even to an *ortho*-substituted phenol (**5g**). An electron-deficient phenol underwent phenylation with ease to produce **5h** in high yield. BINOL was diarylated to give **5i** in almost quantitative yield upon prolonged reaction time.

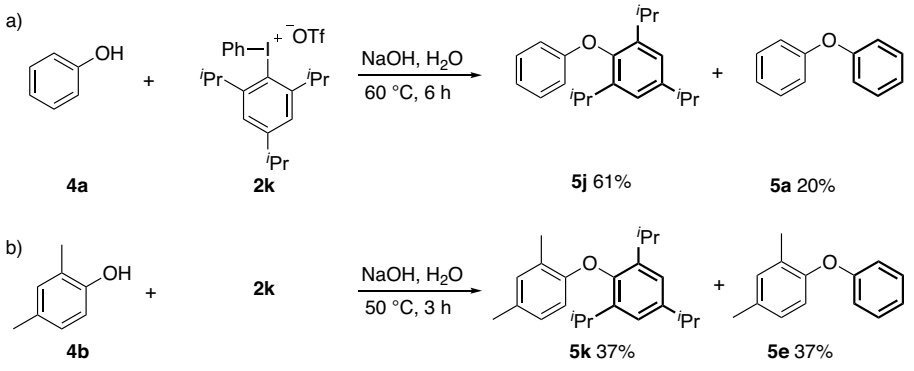


*Scheme 23. Arylation scope of phenols in water. The right aryl moiety (in bold) originates from the diaryliodonium salt. 0.5 mmol of **4**. [a] Reaction performed at 60 °C for 1 h. [b] Unsymmetric salt **2e** was used. [c] Reaction performed at 60 °C for 6 h. [c] 17.5 h.*

Phenols proved to be highly suitable substrates for arylations with diaryliodonium salt also in aqueous media, and the yields were generally higher than for the allylic and benzylic alcohols tested, see Scheme 21 and Scheme 22.

2.2.4 Chemoselectivity

As mentioned in section 1.1.3, the Olofsson group has previously performed an in-depth chemoselectivity study of three different nucleophiles, including arylation of phenols in THF as solvent.[37] The phenols were chemoselectively phenylated when the dummy aryl was substituted with a strongly electron-donating group such as a methoxy. Moreover, when mesityl(phenyl)iodonium triflate was used, the mesityl group was transferred in a 1.9:1.0 ratio, clearly demonstrating an *ortho*-effect (Scheme 10). The previously obtained results inspired us to investigate whether phenols would show the same kind of reactivity under aqueous conditions. Indeed, phenol (**4a**) was preferentially arylated with salt **2k** to give **5j** with minor amounts of phenylated **5a**, showing a strong *ortho*-effect (Scheme 24). Upon switching to the more sterically hindered nucleophile **4b**, the ratio of arylation versus phenylation changed to 1:1 displaying that steric and electronic factors in both the nucleophile and the diaryliodonium salt, influence the chemoselectivity.

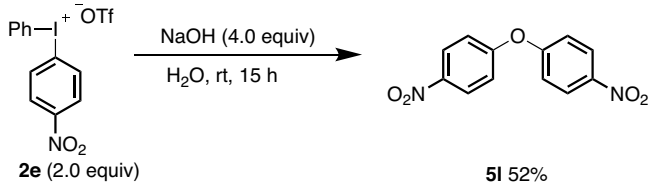


Scheme 24. Chemoselectivity study of phenols in water.

2.2.5 Challenges

A number of issues were discovered during the development of this methodology, which will be discussed in depth in the following chapters. The problems include the oxidation of the alcohol (up to 25%) to the corresponding aldehyde/ketone or carboxylic acid, and the scope limitation that only activated alcohols and electron-deficient diaryliodonium salts gave high yields. For example, phenylation of allyl alcohol gave no detectable product, and when a longer chain aliphatic allylic alcohol, *i.e.* geraniol was used, only around 25% impure product was obtained. Furthermore, a competing reaction was observed where the base was arylated. This was especially prominent with electron-deficient diaryliodonium salts. Under nitrophenylation of allyl

alcohol, the symmetric diaryl ether **5l** was the main side product, possibly originating from two sequential arylations of the hydroxide base. When hydroxide was reacted with **2e** without any added alcohol, the symmetric ether **5l** was indeed formed (Scheme 25).



Scheme 25. Double arylation of hydroxide to give a symmetric diaryl ether.

This particular transformation was studied further in an attempt to turn it into a more general method, which is discussed in Chapter 4.

2.3 Conclusions

A method to arylate allylic and benzylic alcohols in water using diaryliodonium salts has been developed. The scope was broader compared to S_NAr and benzyne chemistry, and the yields ranged from moderate to good. Phenols were arylated in good to excellent yields, also tolerating a broader scope of diaryliodonium salts compared to the arylation of allylic and benzylic alcohols. The chemoselectivity of phenols was studied in water and the same *ortho*-effect trend was observed as in organic solvent.

3 Synthesis of Alkyl Aryl Ethers (Paper II)

3.1 Introduction

Early in the previous project (Chapter 2), it was clear that unactivated aliphatic alcohols could not be arylated under the aqueous conditions used. The main reason for this was probably the high *p*Ka of these alcohols. Another protocol was therefore envisioned in organic solvent to ensure an environment in which any alcohol could be deprotonated. The literature precedence included our previous paper[78] and a copper-catalyzed monoarylation of diols,[79] besides the early mechanistic work by McEwen[30] and a few examples by Beringer.[8] Trace metals in the end-products can constitute a large concern in the pharmaceutical industry due to difficulties in purification.[67a] Moreover, the use of otherwise palladium and copper chemistry might be unsuitable for some transformations, owing to either high reaction temperature and long reaction time, or the use of expensive ligands.[70, 74a, 74b] The aim of this project was to use mild conditions and apply all kinds of aliphatic alcohols, in combination with electron-rich and electron-deficient diaryliodonium salts, to synthesize a broad range of alkyl aryl ethers.

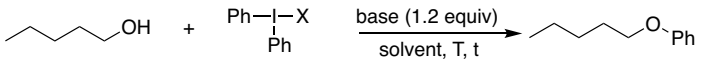
3.2 Results

3.2.1 Optimization

1-Pentanol (**1b**) and diphenyliodonium triflate (**2a-OTf**) were selected as model substrates, and toluene was used as starting solvent, since this solvent had worked well in previous projects in the Olofsson group. First the base was screened, and NaH was found to be better than NaOH (Table 2, entries 1-2). Three *tert*-butoxide bases were evaluated and the experiments revealed that the choice of cation had a big influence on the yield. Sodium was identified as optimal for this transformation (entries 3-5). Satisfyingly, the high yield was maintained also at lower temperature (compare entries 4 and 6). Furthermore, other organic solvents were less efficient than toluene (entries 6-9). To our delight, the reaction could be performed in shorter time and at room temperature with equally good results (entry 10). Addition of more **2a-OTf**

and base did not increase the yield (entry 11). The synthesis of the diaryliodonium salt is facilitated if several anions can be used. Therefore, three common counterions (X = OTf, OTs, BF_4) of **2a** were screened. Unfortunately, **2a-OTs** delivered the ether in a lower yield than **2a-OTf** (compare entries 10 and 12). To our surprise the same trend was seen with **2a-BF_4** (entry 13), which usually has a similar reactivity as **2a-OTf**.

Table 2. Optimization of phenylation of 1-pentanol.



1b (1.0 equiv) **2a** (1.2 equiv) **3r**

Entry	Solvent	X	Base	T (°C)	t (h)	Yield (%)[a]
1	toluene	OTf	NaOH	80	2.0	47
2	toluene	OTf	NaH	80	2.0	75
3	toluene	OTf	LiO^{t}Bu	80	2.0	45
4	toluene	OTf	NaO^{t}Bu	80	2.0	80
5	toluene	OTf	KO^{t}Bu	80	2.0	62
6	toluene	OTf	NaO^{t}Bu	40	2.0	80
7	DCM	OTf	NaO^{t}Bu	40	2.0	70
8	THF	OTf	NaO^{t}Bu	40	2.0	24
9	H_2O	OTf	NaOH	40	2.0	0[b]
10	toluene	OTf	NaO^{t}Bu	rt	0.5	81
11[c]	toluene	OTf	NaO^{t}Bu	rt	0.5	81
12	toluene	OTs	NaO^{t}Bu	rt	0.5	50
13	toluene	BF_4	NaO^{t}Bu	rt	0.5	67
14	toluene	OTf	NaH	40	5.0	75
15[d]	toluene	OTf	NaH	40	5.0	45
16[e]	toluene	OTf	NaO^{t}Bu	rt	0.5	74
17	THF	OTf	NaO^{t}Bu	40	0.75	29
18[e]	THF	OTf	NaO^{t}Bu	40	0.75	58

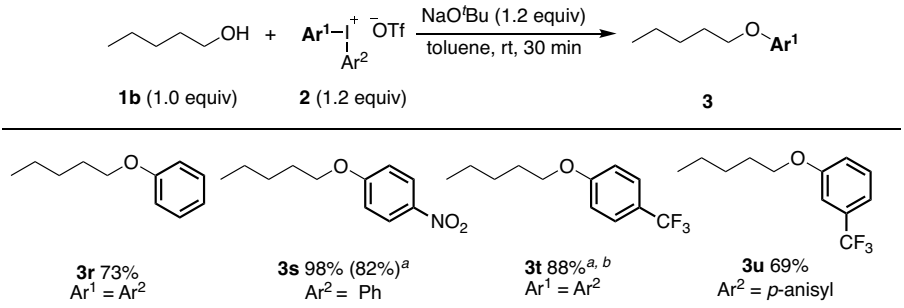
Reaction conditions: Base (0.6 mmol, 1.2 equiv) was dissolved in solvent (2.5 mL), then **1b** (0.5 mmol, 1.0 equiv) was added dropwise at 0 °C. After 15 min at rt **2a** (0.6 mmol, 1.2 equiv) was added at 0 °C, the reaction mixture was then stirred for the indicated time. [a] ^{1}H NMR yield using 4-anisaldehyde as internal standard. [b] No reaction [c] **2a** (2.0 equiv), NaO^{t}Bu (2.0 equiv). [d] 15-crown-5 (1.2 equiv) was added. [e] DPE (1.0 equiv) was added.

The reaction could also be performed with high yield using NaH at 40 °C, although with prolonged reaction time and the addition of a crown-ether lowered the yield of product **3r** (entries 14-15). To check whether the transformation involved radicals, the radical scavenger DPE was added, albeit without any major effect on the outcome in toluene (entry 16). However, when the same trap was added to an otherwise low yielding reaction performed in THF, the yield increased drastically (entries 17-18), indicating a side reaction in certain solvents. The low yield and effect of a radical trap in THF was

surprising, since phenols undergoes arylation smoothly in this solvent.[21] This suggests that the difference in *p*Ka between alcohols and phenols is not the only factor affecting the arylation outcome, but that there is probably a side reaction occurring, which would be a possible explanation to the different reactivity between the nucleophiles.

3.2.2 Substrate scope

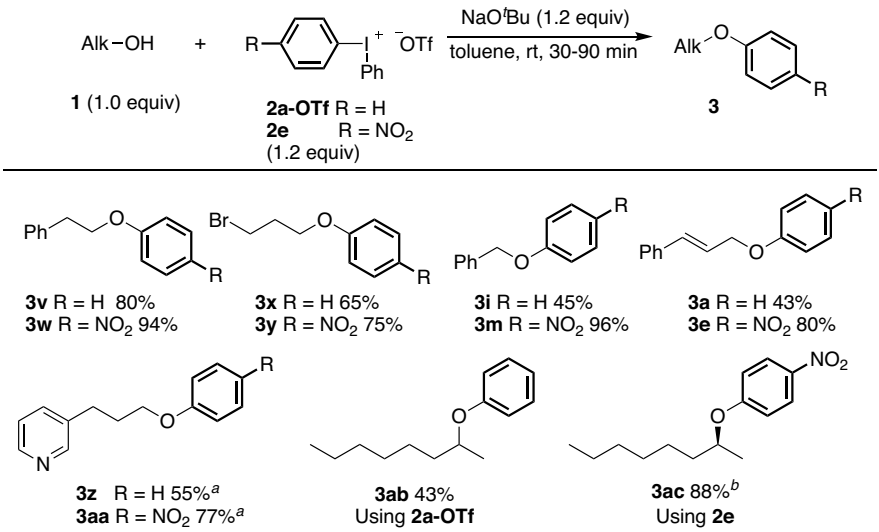
With the optimized conditions at hand, the arylation scope of the model substrate 1-pentanol (**1b**) was evaluated (Scheme 26). The phenylated product **3r** was isolated in 73% yield (Table 2, entry 10). The use of the unsymmetric electron-deficient salt **2e** delivered ether **3s** chemoselectively in almost quantitative yield. We observed the formation of a side product in trace amounts, which was nitrophenylation of NaO^{t}Bu (**3ad**, Scheme 28). This side reaction could be avoided by employing NaH as base, however, at the expense of decreased yield of ether **3s**. Electron-poor diaryliodonium salts were generally suitable, and a *para*-CF_3 substituted aryl moiety was successfully introduced (**3t**). This result also shows that tetrafluoroborate could be used as anion with this type of electron-deficient salt (**2d**). To further demonstrate the chemoselectivity of the arylation, ether **3u** was synthesized using the unsymmetric salt **2i**, with an anisyl as the dummy ligand. Reactions with more electron-rich diaryliodonium salts resulted in complex mixtures of products. This is discussed in depth in the next chapter of this thesis (Chapter 4).



*Scheme 26. Arylation of 1-pentanol using different diaryliodonium salts. 0.5 mmol of **1b**.*
[a] NaH was used as base. [b] BF_4 was used instead of OTf.

Next, different alcohols were tested under the developed conditions and a comparative study was performed between phenylation using **2a-OTf**, and nitrophenylation using salt **2e** (Scheme 27). 2-Phenylethanol was phenylated in good yield (**3v**) and the more reactive **2e** delivered **3w** in almost quantitative yield. A bromo-substituted alcohol was smoothly transformed into **3x** and **3y**. These types of ethers may be challenging to access using other types of methodologies due to the leaving group ability of the bromide.

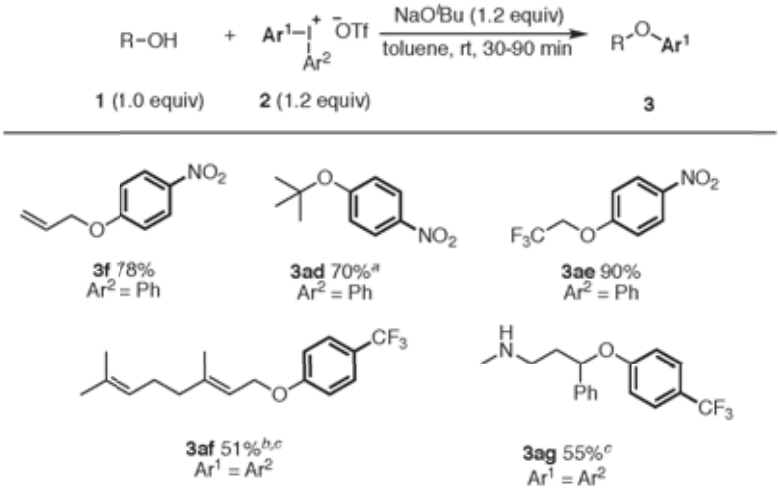
Benzyl alcohol and cinnamyl alcohol were phenylated in roughly 20% lower yield compared to the aqueous conditions (**3i** and **3a**, compare with results in Section 2.2.2, Scheme 21 and Scheme 22). Pleasingly, when applying salt **2e**, the ethers **3m** and **3e** were isolated in good to excellent yields. A pyridyl moiety was tolerated on the alcohol, upon slightly increased temperature (**3z** and **3aa**). Arylation of a secondary alcohol was also successful, with the yield of phenylated **3ab** in the same range as **3i** and **3a**. Salt **2e** efficiently provided ether **3ac** upon arylation of (S)-2-octanol, without racemization of the stereocenter. This is a clear advantage compared to, for instance the Williamson ether synthesis or the Mitsunobu reaction, which both can give an inversion of the stereocenter at the best.[54, 56]



*Scheme 27. Phenylation and nitrophenylation of aliphatic alcohols, using a symmetric and unsymmetric diaryliodonium salt. 0.5 mmol of **1**. [a] Reaction performed at 40 °C. [b] 93% ee in acylated starting material, 92.5% ee in **3ac**.*

The scope was further explored using various alcohols (Scheme 28). Allyl alcohol was successfully nitrophenylated into **3f**. As stated earlier for **3s** in Scheme 26, a competition reaction with the base occurred when 1-pentanol was reacted with **2e**. NaO^{t}Bu was hence submitted to the reaction conditions in the absence of alcohol substrate, and was indeed arylated in good yield (**3ad**). This is the first example of a synthetically useful coupling between a tertiary alcohol and a diaryliodonium salt, as far as we know. 2,2,2-Trifluoroethanol (TFE) underwent the reaction smoothly, delivering ether **3ae** in excellent yield. Geraniol was easily decorated with a CF_3-aryl moiety (**3af**). The efficiency of the developed protocol was illustrated with a one-step synthesis of the anti-depressing agent fluoxetine (**3ag**), from the

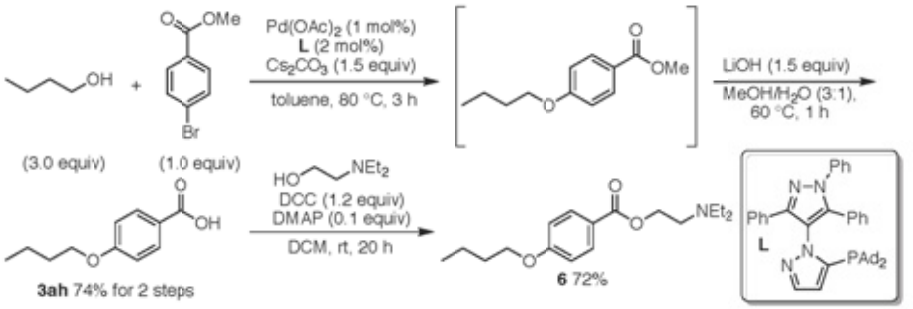
commercially available unprotected aminoalcohol. No competing *N*-arylation was detected, and the ether product (**3ag**) was isolated in 55% yield.



Scheme 28. Synthesis of alkyl aryl ethers. 0.5 mmol of 1. [a] *In the absence of R-OH.* [b] *NaH was used as base.* [c] *BF_3 was used instead of OTf.*

3.2.3 Formal synthesis of butoxycain

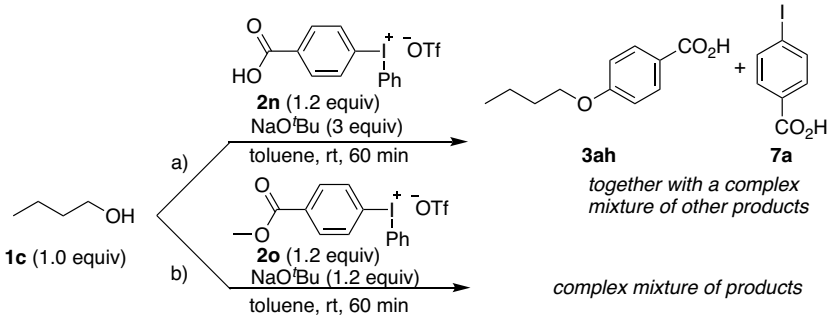
To demonstrate the usefulness of the methodology it was desirable to apply our method in the synthesis of a natural product or a pharmaceutical. Beller had previously developed a metal-catalyzed synthesis of the local anesthetic butoxycain (**6**) (Scheme 29).[74a] Their strategy involved a palladium-catalyzed coupling as the first step, followed by hydrolysis to form ether **3ah**, without a purification in between. A DCC-mediated esterification finished the synthesis and delivered butoxycain (**6**) in 53% overall yield.



Scheme 29. Beller's synthesis of butoxycain.

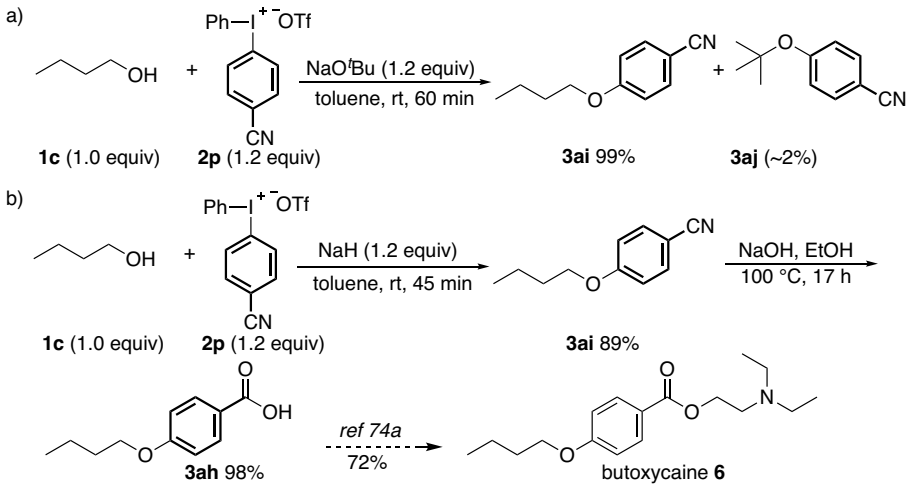
Butoxycain was identified as a good target to demonstrate the potential of metal-free synthesis, thus avoiding any trace transition metals in the final

product. In the first approach, the ether **3ah** was identified as a straightforward intermediate (Scheme 30a). Diaryliodonium salt **2n** contains a highly electron-withdrawing aryl group,[80] which should be chemoselectively transferrable to yield **3ah**. Unfortunately, the addition of 1-butanol (**1c**) to salt **2n** yielded an inseparable mixture of the desired ether **3ah** and the side product **7a**. The corresponding ester-functionalized diaryliodonium salt **2o** was then synthesized (Scheme 30b), but this salt afforded a complex mixture upon reaction with **1c**.



Scheme 30. Initial approach to synthesize butoxycain.

Fortunately, carboxylic acids can be accessed from several derivatives, including hydrolysis of nitriles. Hence, diaryliodonium salt **2p** was reacted with **1c** and produced the desired alkyl aryl ether **3ai** in excellent yield although with traces of **3aj** (Scheme 31a). The ethers (**3ai** and **3aj**) could not be separated using flash chromatography. To solve the problem NaH was used as the base and pure product **3ai** was obtained in high yield (Scheme 31b). This could then be hydrolyzed to **3ah** in almost quantitative yield and completing the metal-free formal synthesis of butoxycain.



Scheme 31. Formal synthesis of butoxycain a) using standard conditions, b) using NaH as base.

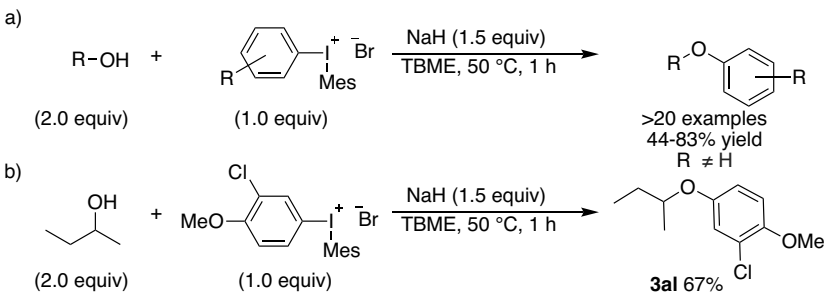
3.3 Conclusions

A metal-free method to access alkyl aryl ethers has been developed. The reactions were performed at room temperature using only a slight excess of diaryliodonium salt and base. Primary aliphatic alcohols were phenylated in moderate to good yields, and nitrophenylated in excellent to quantitative yields. Secondary alcohols required electron-deficient diaryliodonium salts as coupling partners to react smoothly. The lack of steric tolerance both on the diaryliodonium salt and alcohol is a drawback, and the low tolerance towards electron-donating substituents on the diaryliodonium salts is noticeable. The methodology was successfully applied in the synthesis of fluoxetine and a metal-free formal synthesis of the local analgesic butoxycain.

4 Mechanistic Insights in *O*-Arylation with Diaryliodonium Salts (Paper III)

4.1 Background

Although two different methods to synthesize alkyl aryl ethers had been developed, there still was no general procedure for arylation of alcohols tolerating electron-donating groups on the diaryliodonium salt. The main issues associated with this transformation are oxidation of the alcohol to the corresponding aldehyde or ketone and formation of side products inseparable from the desired ether. These two factors have been observed during the previous investigations (Chapter 2 and 3). Consequently, this resulted in mainly arylation of primary alcohols with only a few examples of secondary alcohols. Diphenyliodonium triflate (**2a-OTf**) or electron-deficient diaryliodonium salts have preferentially been used in those cases.[78, 81] Stuart and co-workers recently developed a method in which secondary alcohols were arylated using unsymmetric aryl(mesityl)iodonium bromides, surprisingly utilizing the mesityl as a dummy group (Scheme 32a).[82] Despite the prevalently high yields of the alkyl aryl ethers, only electron-poor aryl groups were tolerated. The most electron-rich salt was applied in the synthesis of ether **3al**, and this aryl moiety is still considered to be electron-deficient (Scheme 32b).[80]

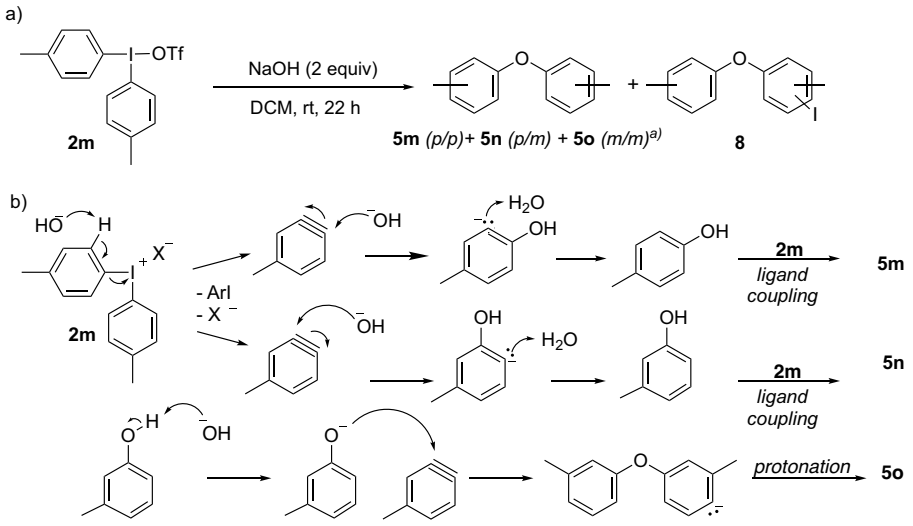


Scheme 32. Arylation of aliphatic alcohols by Stuart and co-workers. a) General protocol. b) The most electron-rich diaryliodonium salt used in the study. TBME = ^{t}Butyl methyl ether.

Phenols show an entirely different type of reactivity compared to aliphatic alcohols in arylations with diaryliodonium salts and are regarded as optimal *O*-nucleophiles. While synthesis of diaryl ethers from phenols and diaryliodonium salts is well known,[8, 21b] the synthesis of symmetric diaryl ethers by double arylation of hydroxide is rarely seen. Synthesis of phenols, *i.e.* arylation of hydroxide using diaryliodonium salts, have only been reported a few times, and not in a general manner.[8] During the arylation of activated alcohols in water, a side reaction was detected that originated from arylation of the hydroxide base (Scheme 25) probably facilitated by the electron-withdrawing group on the diaryliodonium salt (**2e**). Therefore, an investigation of this transformation was initiated, using one electron-neutral and one more electron-rich diaryliodonium salt (Ph_2IOTf, **2a-OTf** and *para*-$tolyl_2IOTf$, **2m**, respectively). The aim was to synthesize phenols *in situ* by arylation of hydroxide and then arylate the formed nucleophile to produce diaryl ethers. This chapter focuses on mechanistic studies with both hydroxide and aliphatic alcohols as nucleophiles.

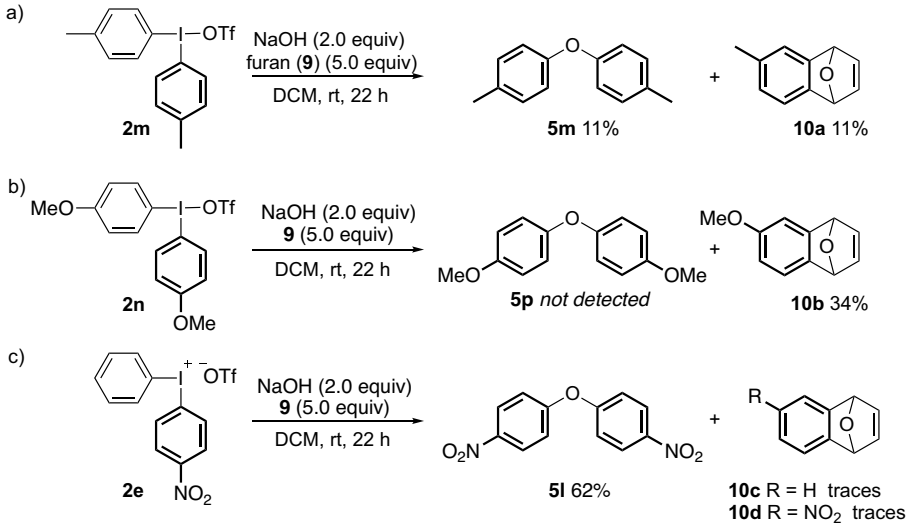
4.2 Arylation of hydroxide

Initially, various solvents were screened at different temperatures, and it was found that at elevated temperatures (>60°C) water was a suitable solvent, whereas dichloromethane was better at room temperature. However, with salt **2m** the desired ether **5m** could not be isolated from the complex product mixture (Scheme 33a). Not only were the regioisomers **5m-o** formed, but there were also some indications that iodine had been incorporated forming products **8** (*vide infra*). It was postulated that the ethers **5n** and **5o** are formed *via* aryne intermediates as depicted in Scheme 33 and Scheme 1b, and the major product ether **5m** could be formed *via* arynes or *via* ligand coupling mechanism. It is known that diaryliodonium salts can form arynes, although harsh conditions are usually required.[31c, 31d] Under the course of this study, Stuart and co-workers published the first method to synthetically use arynes from diaryliodonium salts lacking an *ortho*-TMS group (Scheme 7).[33]



*Scheme 33. a) Arylation of hydroxide. b) Suggested mechanisms for formation of regioisomers **5m-o**.*

Arynes are known to participate in cycloaddition reactions and act as dienophiles in Diels-Alder (DA) reactions.[83] Therefore, furan (**9**) was added to a reaction between **2m** and NaOH as a cycloaddition partner, and the DA adduct **10a** was indeed formed (Scheme 34a). Fortunately, also the diaryl ether **5m** was formed and could now be isolated as a single regioisomer. Since both **5m** and **10a** were formed, we conjectured that there could be a competition between the ligand coupling and the *ortho*-deprotonation *i.e.* aryne formation. To verify this hypothesis, the electron-rich diaryliodonium salt **2n** was submitted to the reaction conditions together with **9**. Diaryl ether **5p** was not detected and the DA adduct **10b** was isolated in 34% yield, indicating that increased electron density on the diaryliodonium salt disfavors the ligand coupling and assists the aryne pathway (Scheme 34b). It should be noted that ether **5p** can be synthesized in high yield (86%) by arylation of 4-methoxyphenol,[21b] illustrating that the hydroxide arylation is the difficult step. Reaction with the electron-poor diaryliodonium salt **2e** gives opposite results and the desired diaryl ether (**5l**) is formed as a single regioisomer with only traces of the DA adducts **10c** and **10d** (Scheme 34c).

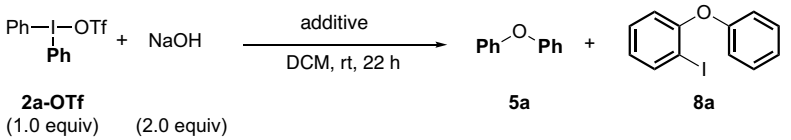


Scheme 34. Competing reactions of ligand coupling and aryne formation with diaryliodonium salts with different electronic properties.

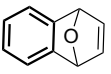
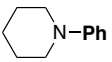
Ph_2IOTf (**2a-OTf**) was selected as the model substrate to avoid problems with regioisomeric products in the continued investigation of the competition between *ortho*-deprotonation and ligand coupling (Table 3). Under our standard conditions in DCM, diphenyl ether (**5a**) was formed in 40% yield together with 25% of the iodo-containing ether **8a** (Table 3, entry 1). It was hypothesized that ether **8a** was formed *via* an aryne-type pathway, while **5a** could be formed both *via* ligand coupling and aryne pathway. The addition of furan to the reaction lowered the yield of **5a** and furthermore decreased the amount of **8a**, indicating that the latter is indeed formed *via* an aryne pathway (entry 2) and that **5a** might originate from this mechanism. The DA adduct **10c** was isolated in a similar amount as the desired ether **5a**.

Amines are known to react well with arynes,[83] and are considered to be challenging to ligand couple with diaryliodonium salts under transition metal-free conditions.[84] Hence, piperidine (**11**) was added as an alternative aryne trap (entry 3), and ether **5a** was formed in a similar yield as in entry 2, this time without impurities since **8a** was not detected. In conclusion, piperidine proved to be a more efficient aryne trap than furan, since only substoichiometric amounts of the amine was sufficient to suppress formation of **8a** completely, thus avoiding the difficult separation.

*Table 3. Trapping of arynes in reactions with **2a-OTf**.*

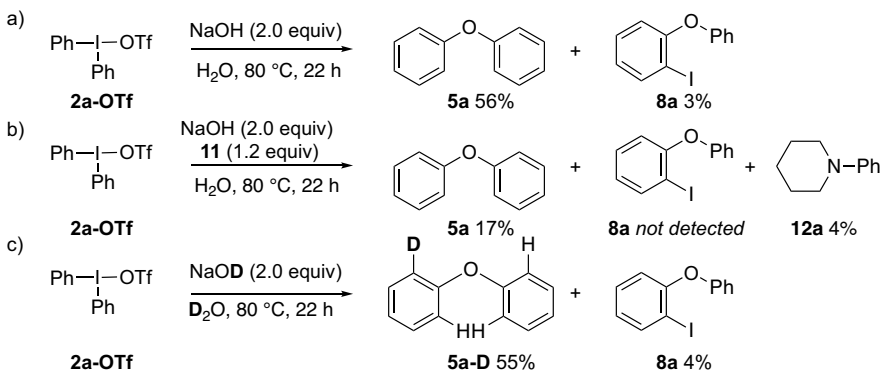


2a-OTf (1.0 equiv) (2.0 equiv) **5a** **8a**

Entry	Additive		equiv	5a (%)[a]	8a (%)[a]	Other products (%)[b]
1	-			40	25	-
2		**9**	5.0	23	2	 **10c** 20
3		**11**	0.5	27	-	 **12a** 26

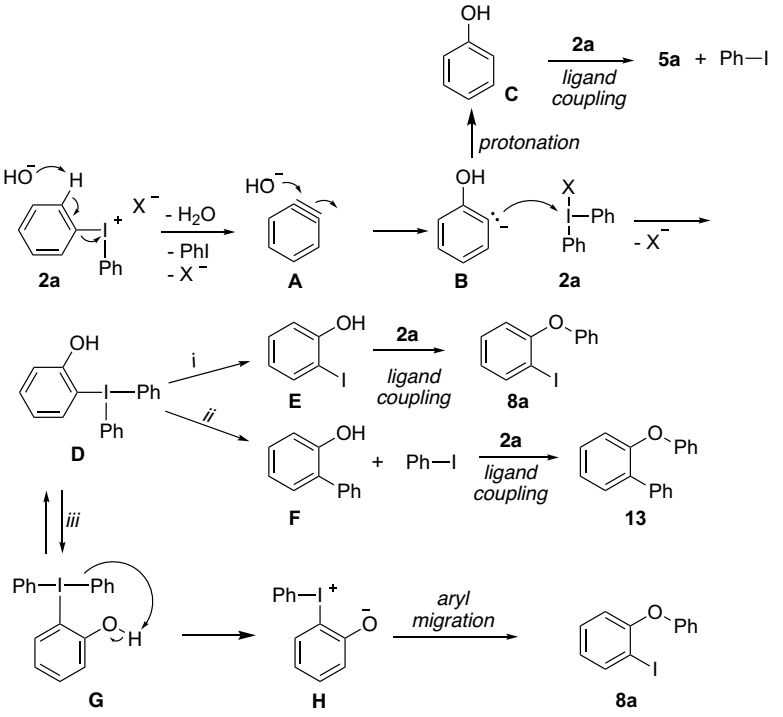
Reaction conditions: NaOH (1.6 mmol, 2.0 equiv) was dissolved in DCM (4.0 mL), then the additive followed by **2a-OTf** (1.0 equiv) were added. [a] Isolated as a mixture. [b] Isolated yield.

The reaction was also studied in water at elevated temperature (Scheme 35). Diphenyl ether (**5a**) was isolated in 56% yield with only minor amount of iodoether **8a** at 80 °C (Scheme 35a). The addition of piperidine as aryne trap severely suppressed the formation of product **5a**, and gave 4% of the *N*-arylated product **12a**, while iodoether **8a** could not be detected (Scheme 35b). Interestingly, when the reaction was performed in D_2O using NaOD as the base, the resulting ether **5a-D** had deuterium incorporated in one *ortho*-position (Scheme 35c). The ^{1}H NMR spectrum suggested that approximately 1 out of 4 *ortho*-protons had been exchanged, and this correlates well to the suggestion that one part of the ether is formed *via* an aryne pathway, and the other arylation proceeds *via* a ligand coupling. This also converge well with our report that phenols are suitable nucleophiles for diaryliodonium salts, and that the products are formed regiospecifically, excluding aryne pathways.[21, 78]



Scheme 35. Phenylation of hydroxide in water.

Although the iodoether **8a** is formed only in minor amount when the arylation is performed in water, it supports the presence of benzyne. We suggest that iodoether **8a** forms according to the mechanism depicted in Scheme 36. Initial *ortho*-deprotonation of **2a** is driven by the release of iodobenzene. The formed benzyne (**A**) can be attacked by a hydroxide to give the anionic intermediate **B**, which then can be protonated to the corresponding phenol **C**. This undergoes ligand coupling with **2a** to give the desired ether **5a**. Alternatively, anion **B** can attack another molecule of **2a** and form the triaryl intermediate **D**.[85] This species can then collapse into iodophenol **E** (*i*) or Ph-phenol **F** (*ii*), followed by ligand coupling to give **8a** and **13**, respectively. The mechanism for the collapse of **D** to **E** is unclear. If it would procced *via* ligand coupling it would also produce the corresponding biphenyl, which has not been detected in similar amounts as **8a**. A more plausible formation of **8a** starts from **D**, which is in equilibrium with triaryl **G** via pseudorotations (*iii*). **G** will undergo an internal proton transfer from the phenolic hydrogen to a phenyl ligand and this would give the zwitterion **H**, which after aryl migration forms **8a**.[86] By use of GC-MS all of the ether products mentioned have been observed, and the major products (**5a** and **8a**) can also be observed by ^{1}H NMR. Protonation of **B** probably occurs rapidly in aqueous media, which explains the low amount of iodoether **8a** in reaction using water as solvent.



Scheme 36. Suggested mechanisms for formation of side products.

There are other possible mechanisms to form *ortho*-iodinated ethers. For example by attack of a species like **B** on an iodoarene, which would form a negatively charged complex.[87] This possibility was investigated by addition of an external iodoarene in excess to the reaction between NaOH and **2a-OTf** in DCM, which did not alter the crude ratio between **5a** and **8a**, reducing the probability for this type of mechanism.

4.3 Arylation of aliphatic alcohols

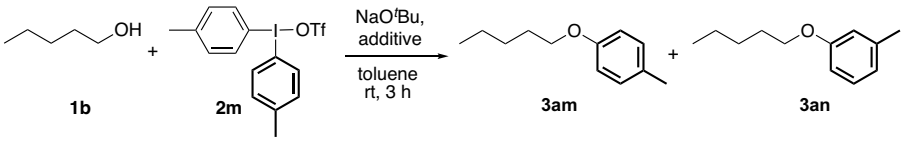
As previously stated the arylation of aliphatic alcohols using diaryliodonium salts is challenging. McEwen and co-workers performed mechanistic studies on the transformation and found that ethanol was oxidized as a side reaction, and proposed a radical pathway for the process. The authors claimed that no evidence for arynes as intermediates for product formation could be detected.[30b] Today, the field of hypervalent iodine has evolved and new mechanistic insights have been brought to light.[37-38, 45, 88] Sluggish reactions were experienced when applying substituted diaryliodonium salts in the previously described projects (Chapter 2 and Chapter 3). Regioisomeric mixtures of products were obtained, especially when bromo and methyl substituted diaryliodonium salts were used in toluene as solvent. It was desirable to understand these observations and an area of interest to continue to investigate was the use of electron-rich diaryliodonium salts as substrates for arylation with aliphatic alcohols.

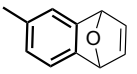
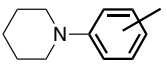
4.3.1 Electron-rich diaryliodonium salts

1-pentanol (**1b**) and salt **2m** were selected as a model substrates as the diaryliodonium salt **2m** was easy to follow with ^{1}H NMR and the alcohol was used as the standard substrate in a former study (Chapter 3). Submitting salt **2m** to the previously developed reaction conditions (Table 2) resulted in a mixture of two regioisomers, with the *para* isomer (**3am**) as major and the *meta* isomer (**3an**) as the minor product (Table 4, entry 1). Since furan (**9**) operated as an aryne trap in the arylation of hydroxide, it was evaluated as trap here too, and the DA adduct **10a** was indeed formed (entry 2). Unfortunately, the ethers **3am** and **3an** were still formed as a regioisomeric mixture. The addition of piperidine as an aryne trap was then explored and finally the alkyl aryl ether **3am** could be isolated as a single regioisomer (entry 3). Piperidine (**11**) was shown to be the most efficient trap among several evaluated amines, such as piperazine, morpholine, 2,6-dimethylpiperidine and 2,2,6,6-tetramethylpiperidine. In an effort to avoid the formation of arynes various conditions were also evaluated, including different temperatures and equivalents of amine, base and salt **2m**, as well as changing the addition order of the reagents. Unfortunately, no further improvement to obtain **3am** as a

single regioisomer was achieved. Efforts to avoid external alkoxide bases were made, but use of only piperidine as base yielded no detectable product (entry 4). Neither did other organic bases such as DBU. The alcohol probably needed to be deprotonated for a reaction to occur, and therefore attempts were made with NaHMDS. The idea was to use a strong amine base to deprotonate the alcohol, and that the protonated base then would act as an aryne trap. Sadly, this was not successful, and two ethers (**3am** and **3an**) were formed in a regioisomeric mixture (entry 5). This was also confirmed by Stuart and co-workers since they applied LiHMDS as base for formation of arynes from unsymmetric diaryliodonium salts.[33]

*Table 4. Arylation of 1-pentanol using an electron-rich diaryliodonium salt (**2m**).*



Entry	Additive (equiv)	Yield 3am + 3an (%)[a]	Ratio *p*/*m*	Other products yield (%)[a]
1	-	51	4:1	-
2	**9** (5.0)	36[b]	nd[c]	 9 **10a**
3	**11** (0.5)	27	only **3am**	 **12b** (*p*) + **12c** (*m*) 13
4[d]	**11** (1.2)	-	-	-
5[d]	NaHMDS (1.2)	51	4:1	-

Reaction conditions: 1-pentanol (0.5 mmol) and base (1.2 equiv) were stirred in toluene for 15 min before addition of additive followed by **2m** (1.2 equiv). [a] Isolated yields. [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene (TMB) as internal standard. [c] The ratio could not be determined, **3am** as major product. [d] No NaO^{t}Bu was added, additive was used as base.

Effective traps of the reactive arynes have been identified, but up to this date, we have been unable to suppress the formation of these species. Therefore, the scope of the reaction was not further evaluated, due to the low isolated yield of the desired alkyl aryl ethers. New insights to the field of hypervalent iodonium chemistry suggests that the role of the counterion of the diaryliodonium salt may affect the outcome more than previously realized.[84]

4.3.2 Oxidation of the aliphatic alcohol

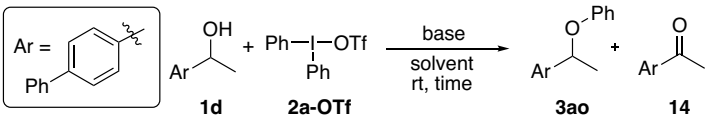
As mentioned earlier an oxidation of the alcohol to the corresponding ketone or aldehyde has been observed, which lowered the yield of the desired alkyl aryl ether. This was seen both in the aqueous conditions and in organic solvents. With primary alcohols oxidation to the carboxylic acids may occur in some cases. [78, 81] One aim has been to unravel the underlying mechanism for this peculiar transformation. This side reaction is interesting due to that diaryliodonium salts are generally not considered as oxidizing reagents. This separates diaryliodonium salts and other iodine(III) species with two carbon ligands from other types of hypervalent iodine reagents, which are commonly used as oxidizers in various transformations.[2a]

Possible mechanistic pathways for the observed alcohol oxidation could involve either arynes, radicals, external or internal deprotonation. Initial studies were performed with benzyl alcohol and 1-phenylethanol, however, some of the formed products were volatile, leading to uncertainty in the data. Therefore, an alcohol with relatively high molecular weight was selected as a model substrate (**1d**). To simplify analysis, **2a-OTf** was chosen as the diaryliodonium salt. Firstly, the conditions used in the arylation of aliphatic alcohols[81] (see Chapter 3) was evaluated with alcohol **1d** and salt **2a-OTf**, and indeed was the oxidized product, the ketone **14** formed as the major product along with only 21% of arylated product **3ao** (Table 5, entry 1). The addition of piperidine (**11**) as an aryne trap did not significantly lower the formation of ketone **14**, but decreased the yield of ether **3ao** (entry 2).

Stuart reported that benzyl alcohol underwent arylation with only traces of oxidation of the alcohol.[82] However, when alcohol **1d** was submitted to Stuart's conditions (Scheme 32) using **2a-OTf**, the ketone **14** was still formed as the major product (entry 3). Additionally, the use of Stuart's counterion and dummy ligand (Mes(Ph)IBr) gave similar results (entry 4). Not only did the ketone **14** form as the major product but a mixture of ethers originating from unselective transfer of both aryl groups was observed (entry 4). This clearly demonstrates that Stuart's conditions are not a solution to the oxidation problem.

THF was selected as solvent when different radical traps were evaluated, as toluene itself is known to act as a radical trap from previous studies by McEwen.[30a] Also, we did not observe any major effect when DPE was added to a reaction in toluene in the previous study (Chapter 3). While the yield of ether **3ao** increased upon addition of the radical scavengers DPE and TEMPO, the oxidation remained at a similar level (entries 5-7). This suggests that neither ether formation nor oxidation proceeds *via* a radical pathway, but that other side products might indeed be formed *via* radicals in this solvent.

Table 5. Investigation of the oxidation mechanism.

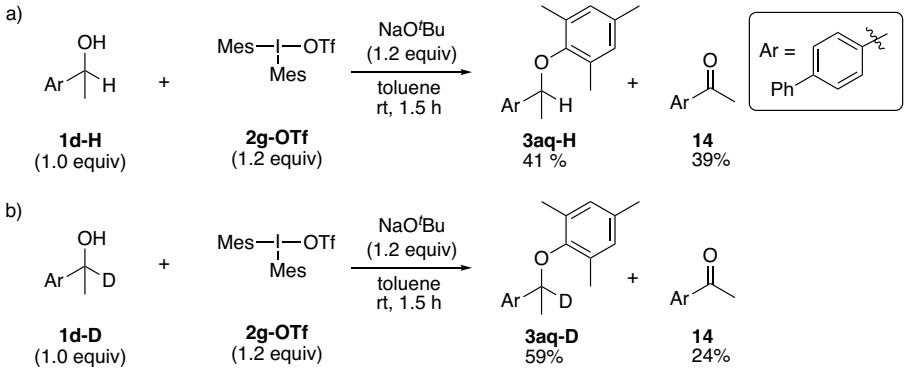


1d **2a-OTf** **3ao** **14**

Entry	Solvent	Base	Additive (1.2 equiv)	3ao (%)[a]	14 (%)[a]
1	toluene	NaO^{t}Bu	-	21	60
2	toluene	NaO^{t}Bu	piperidine (**11**)	14	54
3[b]	TBME	NaH	-	30	53
4[b,c]	TBME	NaH	-	11[d]	65
5	THF	NaO^{t}Bu	-	10	31
6	THF	NaO^{t}Bu	DPE	21	39
7	THF	NaO^{t}Bu	TEMPO	24	43

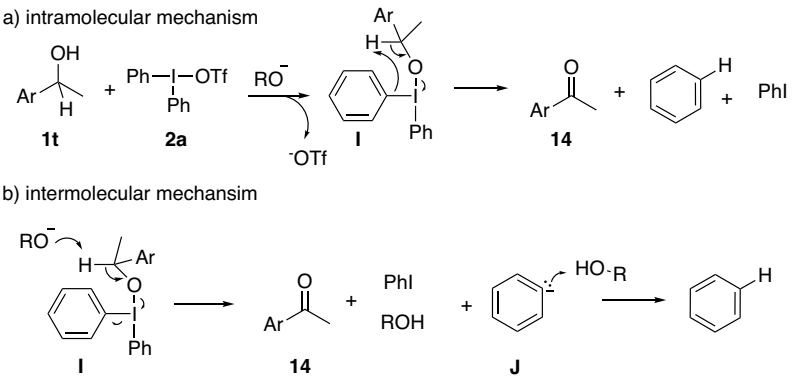
Reaction conditions in toluene and THF: **1d** (1.0 equiv, 0.2 mmol) was dissolved in the indicated solvent (2 mL), then NaO^{t}Bu (1.2 equiv) was added, after 15 min the additive followed by **2a-OTf** (1.2 equiv) were added and the reaction was performed at rt for 3 h.
In TBME: NaH (0.75 mmol, 1.5 equiv) was added to a vial, to which **1d** (1 mmol, 2.0 equiv) dissolved in TBME (2.5 mL) was added, and after 15 min salt **2** (1.0 equiv, 0.5 mmol) was added, the reaction was performed at 50 °C for 1 h. [a] ^{1}H NMR yield using TMB as internal standard. [b] Isolated yields. [c] With Mes(Ph)IBr instead of **2a-OTf**. [d] The mesityl was transferred in 6%, total ether yield 17%.

Next, we wished to investigate in more detail whether arynes were involved in the oxidation process. By blocking all *ortho*-positions with methyl groups it was ensured that arynes could not form. Hence, Mes_2IOTf (**2g-OTf**) was submitted to the reaction with **1d-H**, delivering ether **3aq-H** and ketone **14** in similar quantities (Scheme 37a). This rules out the involvement of arynes in the oxidation process. Interestingly the yield of the oxidation product was decreased in favor of ligand coupling, but the total yield of **3aq-H** and **14** corresponds well to the use of **2a-OTf** (compare with Table 5, entry 1). Employing a deuterated alcohol (**1d-D**) changed the ratio between ether **3aq-D** and ketone **14** (Scheme 37b) compared to when **1d-H** was used. It shows that the ratio of ligand coupling to oxidation is highly dependent on the substrate.



*Scheme 37. Mesitylation of alcohol **1d**; oxidation occurs without aryne formation.*

We had speculated in two mechanisms, similar to pathways for oxidation using iodine(V) reagents (Scheme 38).[89] After initial ligand exchange to form T-shape intermediate **I**, the oxidation can occur in an intramolecular fashion releasing ketone **14**, iodobenzene and benzene in the process (Scheme 38a). The alternative is an intermolecular mechanism, in which an external base will deprotonate the benzylic proton, which results in the formation of a ketone (**14**) and intermediate **J** that then quickly will be protonated to give benzene (Scheme 38b). Dilution of the reaction with **1d-H** led to a slight decrease of oxidized product **14**, whereas increased amount of base did not affect the oxidation process. The experimental results indicate that the internal mechanism is the more probable.



Scheme 38. Proposed oxidation mechanisms, a) intramolecular mechanism, b) intermolecular mechanism.

DFT calculations support the experimental results, and predict the internal mechanism to be favored over the external deprotonation. The details of the calculations are further discussed in paper III.[ii]

[ii] DFT calculations performed by Marcus Reitti.

Based on the results above, we suggest that the main pathway for oxidation neither involves radical nor arynes, but probably is an intramolecular mechanism similar as for oxidations using iodine(V) reagents.

4.4 Conclusions

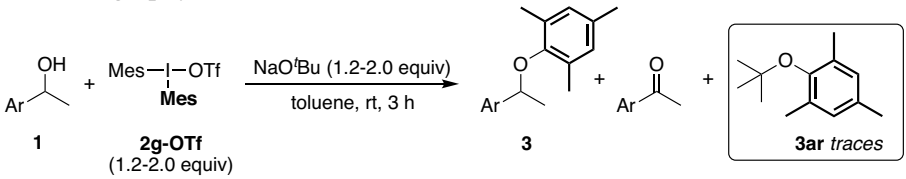
Several mechanistic aspects of reactions between diaryliodonium salts and *O*-nucleophiles have been discussed. For hydroxides, the main limitation was the competing *ortho*-deprotonation *i.e.* the energetically favorable aryne formation. This led to regioisomeric mixtures of products, and the ligand coupling that would give a phenol is probably the challenging step in the reaction. This has been shown in organic solvents as well as in water, by either trapping of arynes or incorporation of deuterium. For aliphatic alcohols, the main limitations were the incompatibility with electron-donating diaryliodonium salts as well as competing oxidation of the alcohol. The desired alkyl aryl ether could be isolated as a single isomer with piperidine as additive.

The oxidation was suggested to proceed in an intramolecular fashion, with the benzylic proton being shuffled to one of the aryl ligands, releasing the aryl iodide, an arene and ketone. More research needs to be conducted in order to find ways to avoid the formation of arynes instead of trapping them, as well as possibly design iodonium salts that favors the ligand coupling over the alcohol oxidation.

5 Synthesis of Sterically Congested Alkyl Aryl Ethers (Paper IV)

5.1 Background

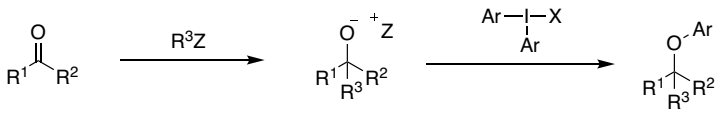
During the investigation of the oxidation of secondary alcohols (Chapter 4) a side product was detected when salt **2g-OTf** was used. NaO^{t}Bu, was employed as the base and competed with the secondary alcohol to undergo ligand coupling with **2g-OTf** (Scheme 39). This gave two alkyl aryl ethers, the desired ether **3** and traces of **3ar**, often inseparable from each other by column chromatography.



*Scheme 39. Detection of tertiary alkyl aryl ether **3ar**.*

This competition was not observed for all secondary aliphatic alcohol and could be avoided by changing base to NaH, although the yields were suffering. The traces of the tertiary alkyl aryl ether **3ar** had seized our interest. This type of structure is challenging to synthesize with conventional methods due to the steric hindrance on both the aryl and alcohol moiety. Metal-catalyzed protocols can be efficient but are sensitive towards steric hindrance in the aryl part and require high temperatures and long reaction times.[74a, 74b, 90] Pd-catalyzed protocols can use *tert*-butoxide as nucleophile, however, examples with two *ortho*-substituents on the aryl halide are rare.[90b, 91] On the other hand, metal-free methods *e.g.* the Mitsunobu reaction tolerate high steric congestion on the aryl part, but are mainly limited to primary and secondary alcohols as coupling partners.[56, 58] S_NAr methodology usually demands an electron-withdrawing group on the aromatic ring for the reaction to proceed.[61b] Thus, the possibility of combining steric hindrance in both the alcohol and an electron-rich aryl part was very interesting. The mesityl group was the most sterically hindered aryl ligand that had been transferred from a diaryliodonium salt to an alcohol (Scheme 39), to our knowledge.

This new system would also have the benefit of not suffering from the side reactions observed in previous projects,[78, 81] since oxidation of the tertiary alcohol is not plausible and aryne formation is impossible in fully *ortho*-substituted diaryliodonium salts. It was envisioned that the reaction set-up would allow investigation of how the counterion of the diaryliodonium salt and of the alkoxide affected the ligand coupling, without interfering side reactions such as oxidation and aryne formation. The aims of this project were therefore 1) to correlate the reaction outcome depending on the anion (X^-) of the diaryliodonium salt and the cation (Z^+) of the chosen alkoxide in different solvents, and 2) to develop a general method for arylation of tertiary alcohols. A long-term goal in the Olofsson group has also been to develop efficient one-pot syntheses,[25a, 42, 92] thus an underlying aim of this project was to form alkoxides *via* a nucleophilic addition to an aldehyde or ketone followed by *in situ* arylation of the formed alkoxide using a diaryliodonium salt (Scheme 40). To achieve this sequential one-pot reaction, the development of conditions for arylation of lithium alkoxides was of interest, due to the vast number of available R-Li reagents.



Scheme 40. Envisioned formation of an alkoxide via nucleophilic addition to a carbonyl and subsequent in situ arylation. Z = Li, Na, K, MgX.

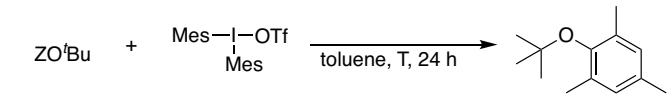
5.2 Results

5.2.1 Screening of reaction conditions

The selection of diaryliodonium counterions (X) was based on commonly used anions in previous *O*-arylation protocols,[21b, 78, 81-82] and consequently OTs, OTf, BF_4 and Br were chosen. Toluene has successfully been applied by the Olofsson group in several *O*-arylations and was, therefore, the first solvent to be screened together with **2g-OTf** (Table 6). KO^{t}Bu gave the desired tertiary alkyl aryl ether **3ar** in good yield (entry 1), and NaO^{t}Bu gave ether **3ar** in slightly decreased yield (entry 2). Lithium proved to be more challenging, although elevated temperature slightly increased the yield (entries 3-4). Fortunately, diluting the reaction mixture and performing the reaction at high temperature gave ether **3ar** in similar yield as with KO^{t}Bu (entry 5 and 1). Diluting the reaction mixture at lower temperatures decreased the yield of ether **3ar** (entries 6-7), so to allow for ether formation with lithium as cation, the reaction had to be diluted and performed at elevated temperature.

Hence, our focus shifted to use NaO^{t}Bu or KO^{t}Bu as nucleophiles, and the use of lithium alkoxides was cancelled.

*Table 6. Initial screening of the synthesis of tertiary alkyl aryl ether **3ar**.*



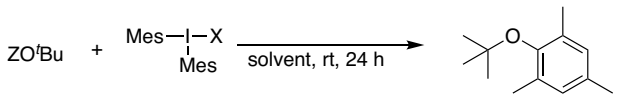
(1.0 equiv) **2g-OTf** (1.0 equiv) **3ar**

Entry	Z	M	T (°C)	Yield (%)[a]
1	K	0.2	rt	62
2	Na	0.2	rt	53
3	Li	0.2	rt	10
4	Li	0.2	110	25
5	Li	0.05	110	64
6	Li	0.05	rt	12
7	Li	0.05	70	47

Reaction conditions: ZO^{t}Bu (0.2 mmol, 1.0 equiv) and **2g-OTf** (1.0 equiv) were added to a vial, before toluene (1 or 4 mL) was introduced. [a] ^{1}H NMR yield using TMB as internal standard.

The solvents were selected on a similar literature basis as the counterions X. Further investigations in more polar solvent like MeCN led to only traces of product **3ar** with both OTs and OTf as counterions (Table 7, entries 1-2). The results were the same for all combinations of cations and anions in this solvent, however in Table 7 only two combinations are shown. The yields in THF were low (entries 3-4) and this corresponds well to the results obtained during the phenylation of primary alcohols (Section 3.2.1, Table 2). Stuart recently presented the arylation of secondary aliphatic alcohols in a bulkier ether, TBME.[82] Gratifyingly, applying this solvent improved the yields for all the counterions tested (entries 5-9). As shown by the previous reactions in toluene (Table 6), nonpolar solvents may be more suitable for this kind of transformation, thus pentane was tested. This gave the desired ether **3ar** in high yield with all diaryliodonium counterions (Table 6, entries 10-14). Moreover, increasing the amount of NaO^{t}Bu from one to two equivalents allowed the reaction time to be shortened and the product **3ar** was formed in 91% yield (entry 15). The impact of concentration was investigated, but did not show any improvement and the results are therefore omitted here.

Table 7. Mesitylation of tert-butoxide.



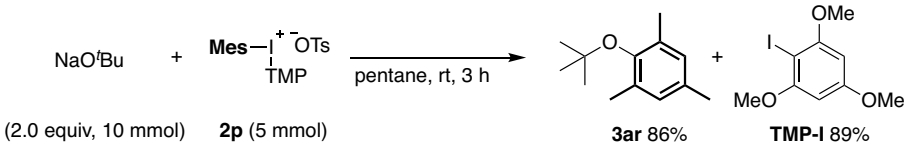
(1.0 equiv) **2g** (1.0 equiv) **3ar**

Entry	Z	X	Solvent	Yield (%)[a]
1	Na	OTf	MeCN	-
2	Na	OTs	MeCN	-
3	Na	OTf	THF	6
4	Na	OTs	THF	<5
5	Na	OTf	TBME	54
6	Na	OTs	TBME	56
7	Na	Br	TBME	57
8	Na	BF_4	TBME	79
9	K	BF_4	TBME	54
10	Na	BF_4	Pentane	73
11	K	BF_4	Pentane	70
12	Na	OTf	Pentane	62
13	Na	Br	Pentane	73
14	Na	OTs	Pentane	67
15	Na	BF_4	Pentane	91[b]

Reaction conditions: See Table 6. [a] ^{1}H NMR yield using TMB as internal standard. [b] 1 h reaction time, NaO^{t}Bu (2.0 equiv).

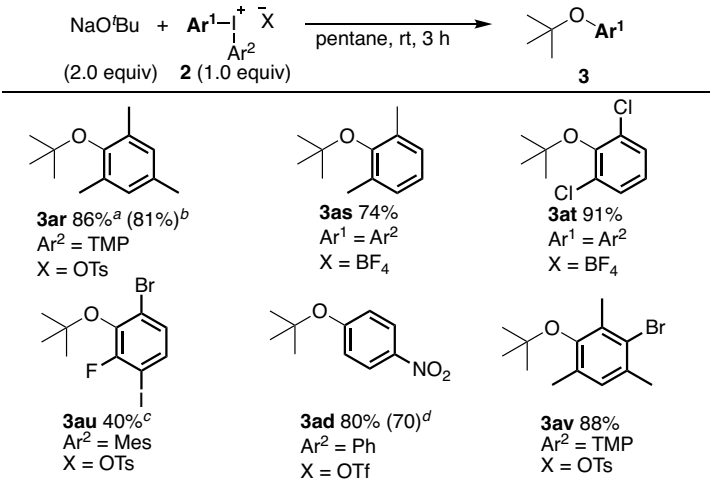
5.2.2 Aryl scope

The scope and limitations of the NaO^{t}Bu arylation protocol was investigated in pentane. We wished to use unsymmetric diaryliodonium salts if possible, since the synthesis of Mes_2IBF_4 (**2g-BF$_4$**) is a somewhat low yielding with the current methods available[4d, 4e] and requires an anion exchange from OTs or OTf to BF_4. As stated in Section 1.1.3 the electronic properties of the dummy ligand in the unsymmetric salt is of high importance. The dummy in this project needed to be electron-rich, and have both *ortho*-positions blocked to avoid formation of arynes, and hence 2,4,6-trimethoxyphenyl (TMP) was suitable. This ligand has also been used by other groups and has been demonstrated in a chemoselectivity study to be an efficient dummy with *O*-nucleophiles (Scheme 10).[37] Gratifyingly, the unsymmetric diaryliodonium salt **2p** could be synthesized in a higher yield. Reacting the salt **2p** with NaO^{t}Bu chemoselectively delivered ether **3ar** in high yield with similar amounts of TMP-I (Scheme 41). The success with TMP as dummy ligand can simplify the isolation of the alkyl aryl ether since the polarity of TMP-I is higher than *e.g.* Mes-I, which facilitates the separation by column chromatography.



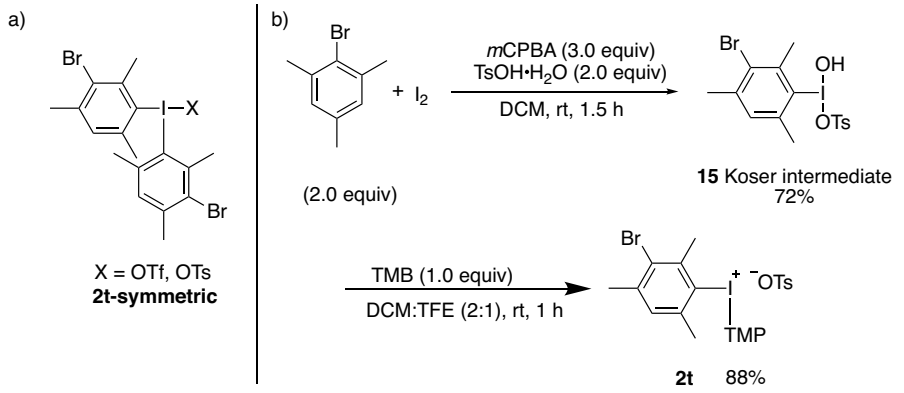
*Scheme 41. Chemoselective large-scale synthesis of **3ar**.*

The scope using commercial NaO^{t}Bu was further explored with various symmetric and unsymmetric diaryliodonium salts (Scheme 42). **3ar** was isolated in slightly lower yield using symmetric **2g-BF$_4$**, and another symmetric salt **2q** gave **3as** in good yield. Electron-withdrawing groups on the salt **2r** delivered the product **3at** in high yield. As discussed above, Stuart used a mesityl as dummy in their synthesis of alkyl aryl ethers.[82] Unfortunately, the mesityl group was not a suitable dummy to chemoselectively transfer the more electron-deficient aryl group in salt **2s** under our conditions. Fortunately, we found that toluene as solvent gave the desired ether **3au** in both higher yield and ratio compared to the corresponding reaction in pentane. Using toluene and longer reaction time allowed for **3au** to be isolated in an acceptable yield. Ether **3au** is interesting due to the three different halide substituents, making it easy to derivatize. To compare the newly developed conditions (Table 7) for tertiary alkoxides to previous conditions (Table 2), NaO^{t}Bu was submitted to the highly reactive salt **2e** and the ether **3ad** could be isolated in higher yield than in toluene (see Section 3.2.2, Scheme 28). Ether **3av** was also formed with high chemoselectivity and this further demonstrates the utility of TMP as dummy ligand.



*Scheme 42. Arylation of NaO^{t}Bu with symmetric and unsymmetric diaryliodonium salts. 0.5 mmol of **2**. [a] 5 mmol of **2p**. [b] Yield when Mes$_2$IBF$_4$ was used. [c] Toluene, 24 h, crude ^{1}H NMR ratio of **3au**:**3ar** 2.8:1.0. [d] In toluene, see Section 3.2.2.*

Access to ether **3av** required some minor optimization of the standard salt synthesis protocols.[4a, 4c-e] Initially, efforts to form the corresponding symmetric diaryliodonium salt (Scheme 43a) starting from iodine and arene were made but gave low yields (<15%). Therefore, the unsymmetric diaryliodonium salt **2t** was synthesized (Scheme 43b). First, the Koser-type (HTIB) intermediate **15** was synthesized from iodine and bromomesitylene,[93] followed by the addition of TMB which delivered the salt **2t** in a high yield.

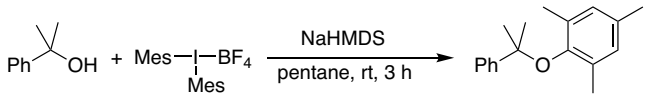


*Scheme 43. Synthesis of diaryliodonium salt **2t**.*

5.2.3 Alcohol scope

To further expand the scope and investigate the possible limitations of the methodology, various alcohols were to be used as substrates. For convenience, 2-phenylpropan-2-ol (**1e**), was selected as model substrate instead of *t*butanol, since **1e** is a solid at room temperature. Consequently, the addition of a base was required for the reaction to occur. The standard alkoxide bases (NaO*t*Bu and KO*t*Bu) would be in equilibrium with substrate **1e** and compete to perform ligand coupling with the diaryliodonium salt, and stronger bases were therefore evaluated. After initial attempts with NaH and $NaNH_2$, NaHMDS turned out to be a suitable base, giving the desired ether **3aw** in high yield (Table 8, entry 1). Increased equivalents of the base (entries 2-4) or the diaryliodonium salt (entry 5) did not prove to be beneficial for the reaction.

Table 8. Optimization data for arylation of tertiary alcohols.

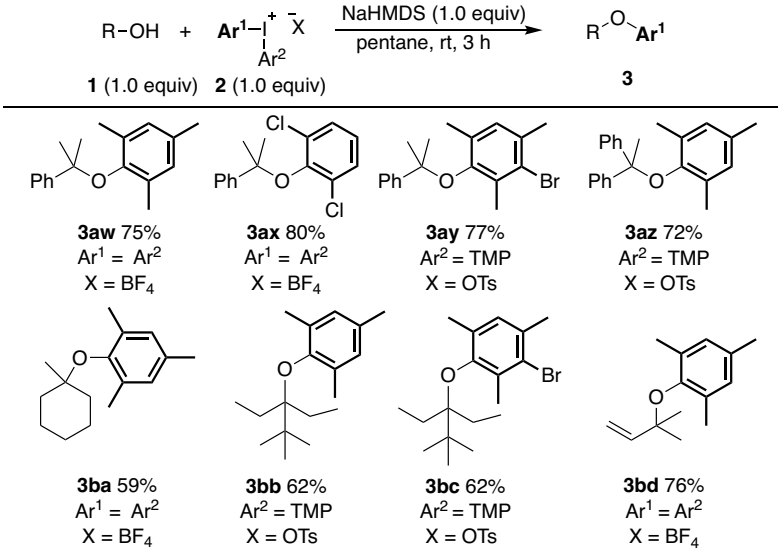


1e (1.0 equiv) **2g-BF_4** **3aw**

Entry	NaHMDS (equiv)	Mes_2IBF_4 (equiv)	Yield (%)[a]
1	1.0	1.0	75[b]
2	1.5	1.0	34
3	1.5	1.5	66
4	2.0	1.0	11
5	2.0	2.0	70[b]

Reaction conditions: **1e** (0.2 mmol, 1.0 equiv) was dissolved in pentane (1.0 mL), NaHMDS (1.0 equiv) was added and after 10 min **2g-BF_4** (1.0 equiv) was added. [a] ^{1}H NMR yield using TMB as internal standard. [b] Isolated yields, 0.5 mmol scale.

The scope of tertiary alcohols with sterically congested salts were investigated using NaHMDS as base (Scheme 44). The model alcohol **1e** could be mesitylated in good yield into product **3aw**, also electron-withdrawing groups on the iodonium part were well tolerated giving ether **3ax** in slightly better yield. The highly chemoselective formation of **3ay** proved once again TMP as a suitable dummy ligand in unsymmetric salts. Changing substrate from **1e** to an alcohol with two phenyl groups delivered the product **3az** in comparable yield as **3aw**, however the triphenyl substituted alcohol did not yield the corresponding ether product under similar conditions. Cyclic, as well as acyclic tertiary alkyl alcohols were tolerated, with only a slight drop in yields (**3ba-3bc**). Furthermore, when an allylic alcohol was subjected to the conditions, the mesitylated ether **3bd** was easily isolated in a good yield.

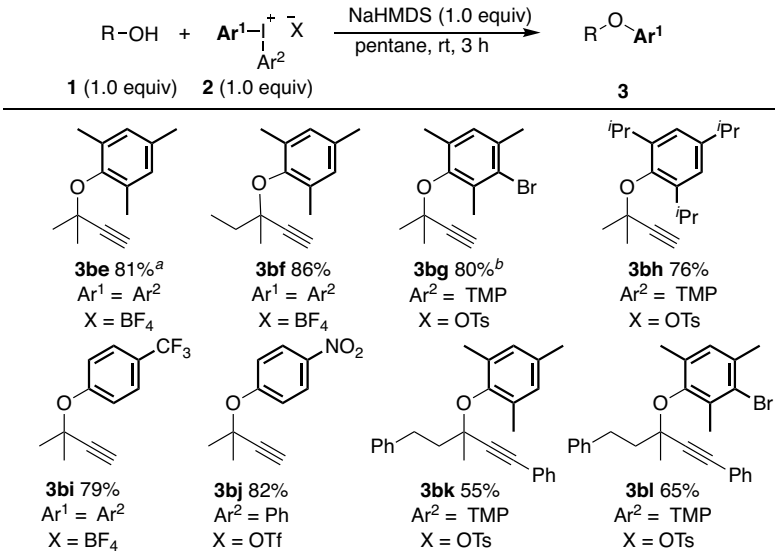


*Scheme 44. Arylation of tertiary alcohols with di-ortho-substituted diaryliodonium salts. 0.5 mmol of **1**.*

Propargylic alcohols are interesting due to their versatile use in different transformations. Tertiary aryl propargylic ethers are usually synthesized *via* substitution reactions, starting from phenols and a good leaving group on the propargylic part. However, this can lead to racemization through an S_N1 type of mechanism.[94] Recently, primary propargylic alcohols were arylated using diaryliodonium salts.[95] Aryl propargylic ethers can be ring-closed to give chromenes, which are precursors to biologically active coumarines.[96] The alkyne group can also undergo a broad range of different synthetic steps. It was therefore of interest to examine whether propargylic alcohols could be suitable substrates under our conditions (Scheme 45). This succeeded very well and substrates with both internal and terminal alkynes underwent the reaction smoothly to give products **3be-3bl**. The tolerance for a terminal non-protected alkyne (**3be-3bj**) allows for further transformations without additional deprotection steps. The reaction was easily scalable and ether **3bg** was produced chemoselectively in good yield. Gratifyingly, even the highly sterically hindered triisopropyl phenyl group could be transferred with excellent chemoselectivity, furnishing ether **3bh** in 76% yield.

Attempts were made with non-*ortho* blocked diaryliodonium salts such as **2a-OTf**, **2b** and **2c**, however, these gave rise to a mixture of products, probably derived from aryne intermediates (see discussion in Chapter 4). On the other hand, the use of electron-deficient *para*-substituted diaryliodonium

salts allowed for the desired ether formation. This was demonstrated by the synthesis of ethers **3bi** and **3bj**, which were isolated as single regioisomers. A substrate containing an internal alkyne was submitted to the reaction conditions with two different diaryliodonium salts (**2t** and **2p**) and gave ethers **3bk** and **3bl** in moderate yields. Attempts to synthesize the products **3bk** and **3bl** in sequential one-pot reactions from the corresponding ketone were made, as depicted in Scheme 40. Nucleophilic alkynylation of the ketone, followed by the addition of **2t** or **2p** however failed to give the desired ether product in any synthetically useful yields. The challenging step was probably the coupling with the diaryliodonium salt, as the alcohol could be isolated after the reaction.

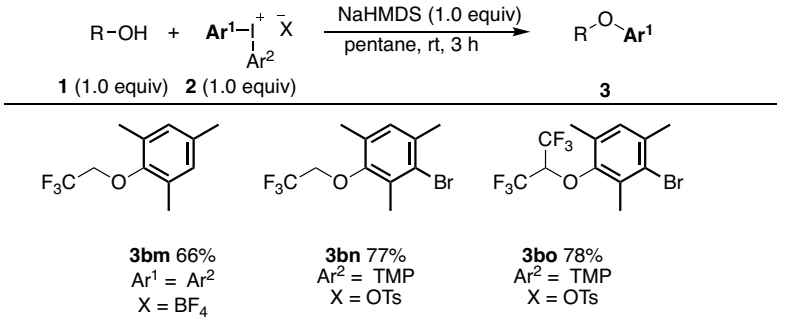


*Scheme 45. Arylation of tertiary propargylic alcohols. 0.5 mmol of **1**. [a] 1 mmol scale. [b] 2 mmol scale.*

In order to expand the scope, it was desirable to also include arylation of primary and secondary alcohols with *ortho*-blocked salts to the planned general protocol. Unfortunately, this proved to be challenging. Benzyl alcohol, 1-phenylethanol, and 1-pentanol were submitted to the reaction conditions but the desired alkyl aryl ethers were not formed in any satisfactory yields, exposing the limitation of the methodology. Employing primary and secondary alcohols substituted with EWGs, thus with a lower *p*Ka and more similar to phenols,[iii] the reaction proceeded as for the tertiary alcohols (Scheme 46). TFE could be mesitylated in moderate yield (**3bm)** and

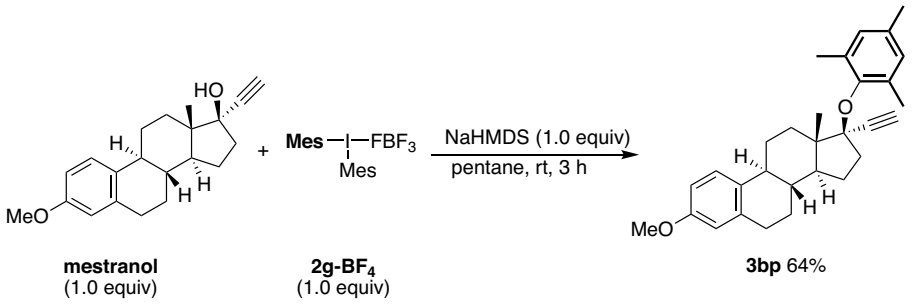
[iii] According to Evan's *p*Ka table for inorganic and organic bases; MeOH 27.9, ^{t}BuOH 29.4, PhOH 18.0, TFE 23.5, HFIP 18.2.[97] Values are in DMSO.

arylated in higher yield using salt **2t** to give ether **3bn**. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) was well tolerated and smoothly gave ether **3bo**. Access to this type of fluorinated substrates that are easy to functionalize can be of high interest for example in the pharmaceutical industry.[77]



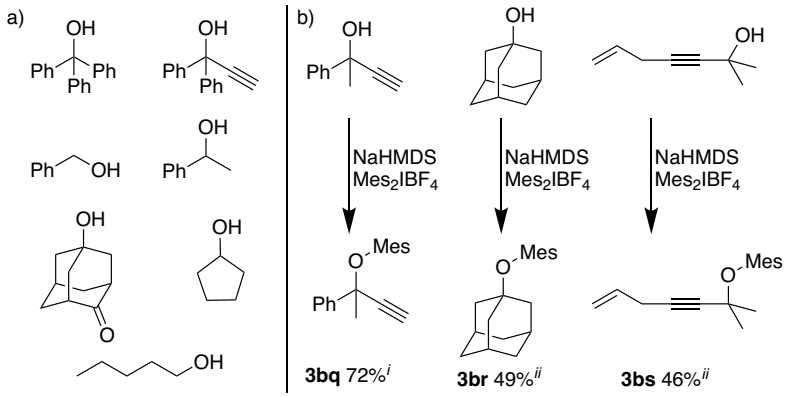
*Scheme 46. Arylation of primary and secondary fluorinated alcohols. 0.5 mmol of **1**.*

The prodrug mestranol is an estrogen-type steroid commonly used as a contraceptive. The methyl oxygen bond (O-Me) is cleaved in the body to form the biologically active drug.[98] We decided to arylate mestranol as a proof of concept of the steric bulk tolerated in the methodology. Without any further optimization, the mesitylated ether **3bp** was isolated in 64% yield (Scheme 47). Derivatization of complex molecules is important since it gives access to novel products with potentially interesting biological activity.



Scheme 47. Mesitylation of mestranol.

As mentioned throughout the chapter some alcohols were found to be unsuitable for arylation, and several alcohols gave rise to complex mixtures of unidentified side products. These limitations are summarized in Scheme 48a-b. For example, the ether product **3bq** was formed in 72% yield according to ^{1}H NMR, but could not be isolated without impurities.



Scheme 48. a) Examples of incompatible alcohols, b) examples of substrates which were successfully arylated but difficult to purify using flash chromatography. [i] *^{1}H NMR yield using TMB as internal standard.* [ii] *Isolated with unknown impurities.*

5.3 Conclusion

A number of novel, sterically congested alkyl aryl ethers have been successfully synthesized. The steric bulk tolerated on both the alcohols and the diaryliodonium salts exceeds previously reported methods and the main limitation is related to the use of electron-rich diaryliodonium salts lacking *ortho*-substituents. The method was suitable for tertiary propargylic, allylic, benzylic as well as cyclic and acyclic aliphatic alcohols. Primary and secondary alcohols with sufficiently low *p*Ka could undergo arylation. To demonstrate the applicability of the developed methodology on a more complex substrate, the prodrug mestranol was successfully mesitylated and isolated. The reaction was sensitive towards the cation of the alkoxide, with potassium and sodium being superior to lithium, making sequential *in situ* formation and subsequent arylation of alkoxides challenging. While reactions with NaO^{t}Bu and KO^{t}Bu proceeded well at room temperature, the lithium reagent required dilution and elevated temperature.

It would be interesting to expand the scope further and investigate the limit of sterically congested the diaryliodonium salts that are still able to perform the ligand coupling. Diaryliodonium salts with *ortho*-^{t}butyl groups or even bulkier substituents would definitely be exciting to evaluate.

It should be mentioned that after the development of this methodology but before the publication of this work, the mesityl group was transferred to a carbohydrate using Mes_2IOTf.[26] This method was also developed within the Olofsson laboratory.

6 *C*-Arylation of Nitro Compounds (Paper V)

6.1 Introduction

Construction of new C-C bonds is the foundation of organic chemistry, yet it remains challenging. Even though there are reliable methods to build up the carbon skeleton of a molecule available today, most rely on precious transition metals to catalyze them, thus there is still room for improvement. Commonly used nucleophiles for new carbon-carbon bonds are enolates and their derivatives. Generally, these have been applied in metal-catalyzed reactions,[99] but also in metal-free applications, for instance with hypervalent iodine.[100] The group of Oh developed a metal-free α-arylation of malonates[15] and Ochiai enantioselectively α-arylated β-keto esters using chiral iodonium salts.[17] In Aggarwal's and Olofsson's total synthesis of epibatidine, the asymmetric α-arylation of a ketone using a diaryliodonium salt was a key step.[101] Combining metal catalysis and diaryliodonium salts can be highly effective, as demonstrated by MacMillan's α-arylation of aldehydes (see Scheme 2).[10] Moreover, the groups of MacMillan and Gaunt have performed enantioselective α-arylation of carbonyls using copper-catalysis.[102] Recently, an elegant chiral Lewis acid-catalyzed α-arylation of oxindoles was developed.[103]

Nitroalkanes have the versatile NO_2 moiety, which can be transformed into many other interesting functionalities.[104] They have similar properties as stabilized carbonyl derivatives and can act as nucleophiles with suitable electrophiles.[105] Nitroalkanes have been *C*-arylated using palladium-catalyzed methodology, but the substrate scope focuses on nitromethane and primary nitroalkanes, with limited examples of more substituted nitroalkanes.[106] Secondary nitroalkanes have been *C*-arylated with a stoichiometric amount of toxic heavy metals such as lead, mercury[107] and thallium.[108] Arylation has also been performed with bismuth(V) reagents, which generates plenty of waste.[109] There are a few reports of arylations of nitroalkanes using diaryliodonium salts, all starting from nitronates and include a very limited substrate scope.[110] Therefore, the goal was to develop an easily operated, general procedure for *C*-arylation of nitro compounds and then explore the chemoselectivity using unsymmetric diaryliodonium salts.

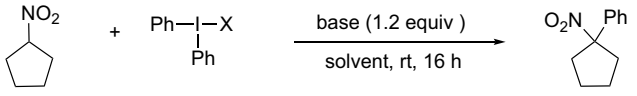
Since the aforementioned palladium-catalyzed methodology already has a broad scope for primary nitroalkanes, the aim was to establish methodology that would focus on secondary nitroalkanes.

6.2 *C*-Arylation of nitroalkanes

6.2.1 Optimization

After some initial reactions with various nitroalkanes, nitrocyclopentane (**16a**) was chosen as the model substrate for optimization. Selection of **16a** was based on the following; a) it is commercially available and b) the low volatility of both the starting material and the expected product, which simplifies the purification and analysis step. The solvent was the first parameter to be screened and DME proved to be superior to the other solvents that were tested (Table 9, entries 1-4). Next, different bases were evaluated and KO^{t}Bu gave product **17a** in the highest yield (entries 4-9). Finally, four of the most commonly used counterions of salt **2a** were also assessed, and OTf and BF_4 outperformed OTs and PF_6 (entries 4 and 10-12).

*Table 9. Optimization of phenylation of nitrocyclopentane (**16a**).*



16a (1.0 equiv) **2a** (1.0 equiv) **17a**

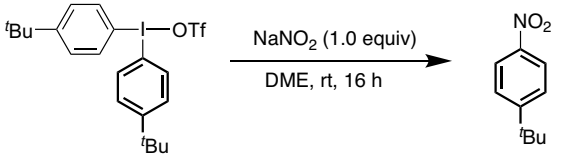
Entry	X	Solvent	Base	Yield (%)[a]
1	OTf	toluene	KO^{t}Bu	78
2	OTf	2-MeTHF	KO^{t}Bu	79
3	OTf	DMF	KO^{t}Bu	76
4	OTf	DME	KO^{t}Bu	94 (89)[b]
5	OTf	DME	NaH	52
6	OTf	DME	Et_3N	32
7	OTf	DME	KOH	63
8	OTf	DME	NaO^{t}Bu	85
9	OTf	DME	LiO^{t}Bu	52
10	PF_6	DME	KO^{t}Bu	80[b]
11	BF_4	DME	KO^{t}Bu	88[b]
12	OTs	DME	KO^{t}Bu	68[b]

Reaction conditions: **16a** (0.2 mmol, 1.0 equiv) and base (1.2 equiv) was stirred in solvent indicated (1.0 mL), after 10 min **2a** (0.2 mmol, 1.0 equiv) was introduced. [a] ^{1}H NMR yield using TMB as internal standard. [b] Isolated yield.

6.2.2 Side product formation

A nitroarene was sometimes detected in trace amount when reacting different salts with the nitroalkanes, possibly arising from nitration[8] instead of nitroalkylation of the diaryliodonium salt. The side product formation was more dominant when six-membered ring nitroalkanes were used compared to five-membered ones. A brief investigation of how to avoid the formation of the side product was undertaken. Different radical traps and stabilizers of the DME were tested to elucidate the mechanism behind the side product, but without any definite conclusions. Different solvent mixtures were also screened, however DME proved most beneficial for the *C*-arylation of nitroalkanes.

Submission of $NaNO_2$ together with salt **2b** under the optimized conditions yielded the nitrated product **18** (Scheme 49), which indicates that nitration is possible under the reaction conditions. Since the nitrated product **18** usually did not form, we continued to evaluate the scope of the methodology. The nitration reaction was subsequently developed within the Olofsson group to a general procedure.[42]

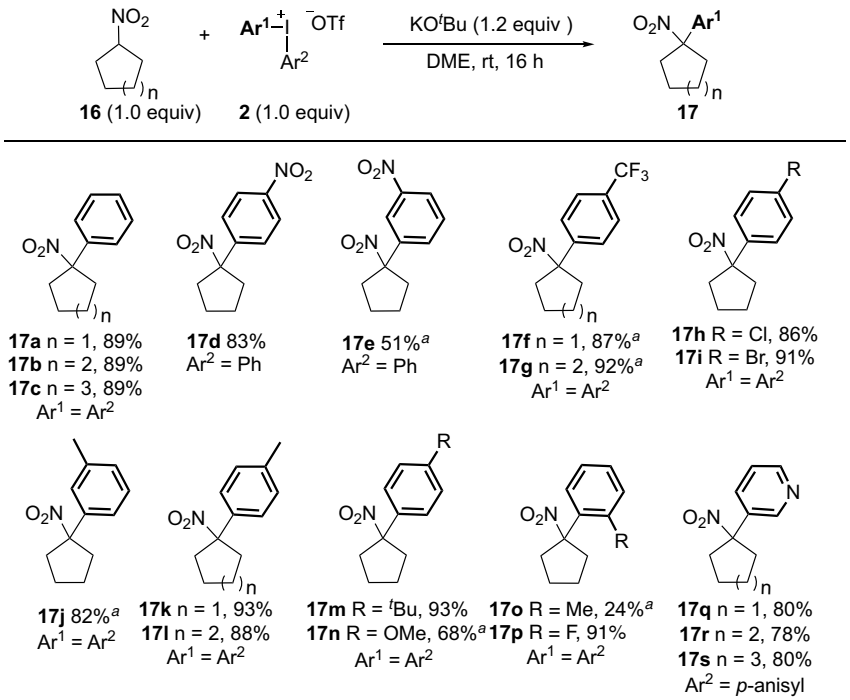


*Scheme 49. Formation of nitrated product **18**.*

6.2.3 Substrate and salt scope

With the optimized conditions at hand, the scope of the reaction with various cyclic nitroalkanes **16** and diaryliodonium salts **2** was evaluated (Scheme 50). As detailed in the optimization section, nitrocyclopentane (**16a**) was phenylated in good yield to give product **17a**, but also larger ring sizes were tolerated and delivered products **17b-c** in equally high yields. Electron-withdrawing substituents on the diaryliodonium salt were assessed next (**17d-i**). The *para*-nitrophenyl group was easily transferred (**17d**), while the *meta*-nitrophenyl product **17e** was formed in a much lower yield. The popular CF_3-group was efficiently introduced and gave products **17f-g** in high yields. Fortunately, both chloro- and bromo-containing aryl groups were well suitable for the reaction (**17h-i**), and this allows for further transformations.

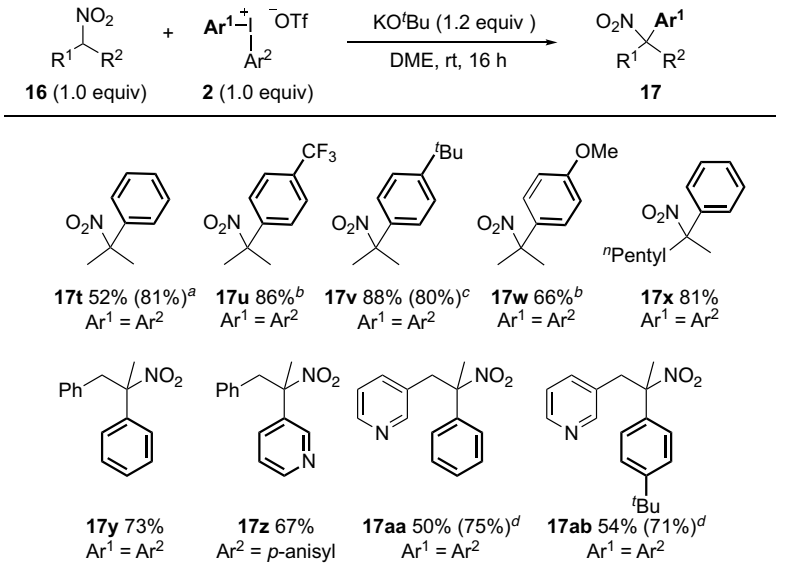
Electron-donating groups on the diaryliodonium salts delivered the desired products in good yields (**17j-n**), except for the diaryliodonium salt containing an *ortho*-methyl group (**17o**). The product **17o** was isolated in low yields and efforts to react **16a** with even more sterically hindered Mes_2IOTf (**2g-OTf**) were low yielding. This demonstrates the lack of steric tolerance for this type of reaction, which is a limitation of the scope. However, an *ortho*-fluoro substituent was well tolerated and smoothly produced **17p** in excellent yield. Heteroaromatic moieties are in high demand, especially in the pharmaceutical industry. As a proof of concept, the pyridyl moiety was thus transferred chemoselectively in high yields to give products **17q-s**, using an anisyl dummy group, *vide infra*.



*Scheme 50. Arylation of cyclic nitroalkanes. 0.4 mmol of **16**. [a] BF_4 was used instead of OTf.*

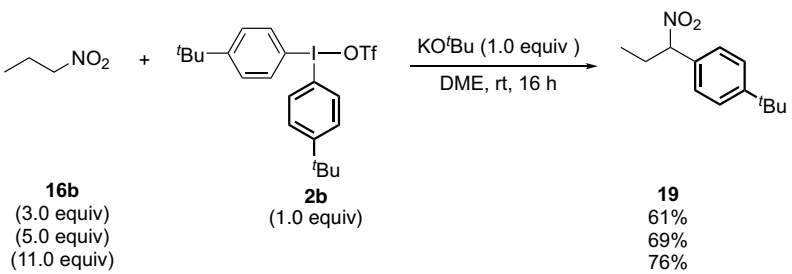
The intention was to expand the methodology by also including acyclic nitroalkanes in the scope (Scheme 51). Initially, phenylated 2-nitropropane **17t** was isolated in a disappointingly low yield (52%). This might be due to high volatility of the product and indeed, formation of **17t** in high yield was confirmed by ^{1}H NMR analysis using an internal standard. Electron-poor aryl groups were easily transferred (**17u**), as well as electron-rich ones (**17v-w**). The protocol was suitable for scale-up (**17v**), and the corresponding iodoarene was easily recovered. Longer aliphatic chains were tolerated giving products **17x-ab**. These results indicate that steric hindrance in the nitroalkane part is

not a hindrance for the ligand coupling to occur. A pyridyl moiety showed to be compatible also with the acyclic substrates, both as the transferred aryl group (**17z**) and as part of the nitroalkane (**17aa-ab**).



*Scheme 51. Arylation of secondary acyclic nitroalkanes. 0.4 mmol of **16**. [a] ^{1}H NMR yield using 1,4-dimethoxybenzene as internal standard. [b] BF_4 was used instead of OTf. [c] 5 mmol. [d] Based on recovered **16**.*

Subsequently, the possibilities to functionalize primary nitroalkanes were briefly evaluated (Scheme 52). It was possible to isolate the monoarylated product **19** in good yield by using an excess of 1-nitropropane (**16b**). Applying the standard conditions from Table 9 afforded both mono and diarylation. Since arylation of primary nitroalkanes is extensively covered by Pd-catalyzed methodology,[106d] which also requires an excess of nitroalkane, this example will serve as a proof of principle and the scope was not further evaluated.



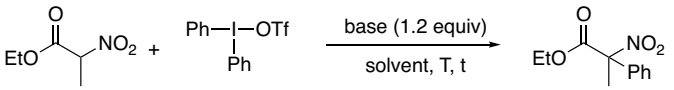
Scheme 52. Monoarylation of 1-nitropropane using excess of nitroalkane.

6.3 α-Arylation of nitro ester

Synthetic chemists are often interested in compounds that are easy to functionalize and therefore can be transformed into a various number of derivatives. Nitro esters belong to this group, as these compounds can be transformed into a plethora of different valuable and biologically active products, including amino alcohols and amino acids.[111] Recently, Waser and co-workers developed an efficient α-alkynylation of nitro esters using EBX.[112] However, it is still a challenge to α-arylate a nitro ester to form a quaternary α-carbon.

Almost no reaction occurred when the developed protocol for arylation of nitroalkanes was applied to nitro ester **20** and salt **2a-OTf** (Table 10, entry 1). The yield increased at elevated temperature (entry 2) and when the solvent was changed to toluene (entries 3-4). Exchanging the alkoxide base to Cs_2CO_3 further improved the yield (entries 4-5), and the reaction time could be shortened from 16 h to 6 h (entry 6).

*Table 10. Optimization of α-arylation of nitro ester **20**.*

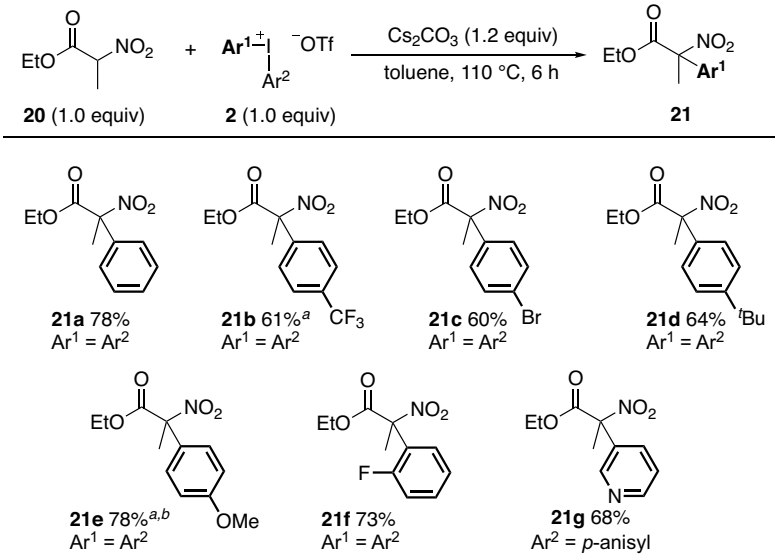


20 (1.0 equiv) **2a-OTf** (1.0 equiv) **21a**

Entry	Solvent	Base	Time (h)	T (°C)	Yield (%)[a]
1	DME	KO^{t}Bu	16	rt	6
2	DME	KO^{t}Bu	16	50	58
3	toluene	KO^{t}Bu	16	50	65
4	toluene	KO^{t}Bu	16	110	70
5	toluene	Cs_2CO_3	16	110	78
6	toluene	Cs_2CO_3	6	110	78

Reaction conditions: **20** (1.0 equiv, 0.2 mmol) and base (1.2 equiv) were stirred in indicated solvent (1.0 mL) for 1 h at rt, then **2a-OTf** (1.0 equiv) was added, and the reaction mixture was stirred at rt for 1 h, then at the indicated temperature and reaction time. [a] Isolated yields.

When the optimized conditions were applied (Scheme 53), both electron-deficient and electron-rich diaryliodonium salts smoothly arylated **20** to yield the products **21b-c** and **21d-e**, respectively. This transformation also proved sensitive towards steric hindrance in the diaryliodonium salts, as seen for the nitroalkanes. Fortunately, an *ortho*-fluoride substituent was well tolerated, giving α-arylated product **21f** in good yield. A pyridyl moiety could be transferred with high chemoselectivity (**21g**), opening up possibilities to access a range of interesting heteroaromatic amino acids in only a few synthetic steps.

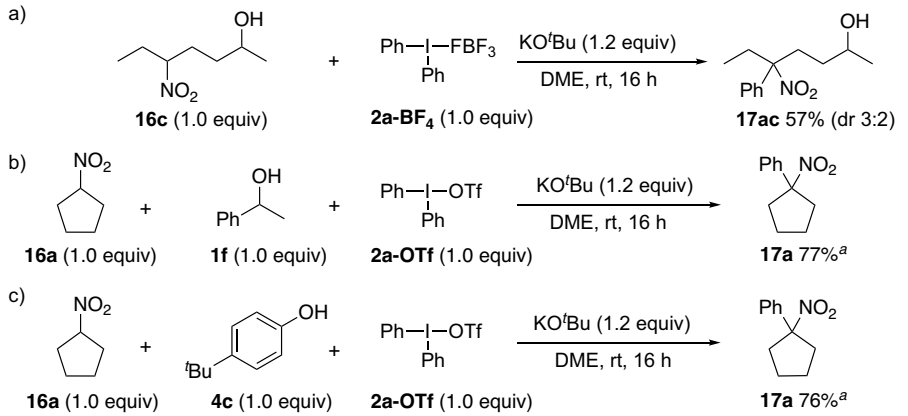


*Scheme 53. Scope for α-arylation of nitro ester **20** using diaryliodonium salts. 0.2 mmol of **20**. [a] BF_4 was used instead of OTf. [b] Reaction time 16 h.*

6.4 Chemoselectivity

Having demonstrated a broad scope for arylation of both nitroalkanes (**16**) and nitro ester **20**, it was of interest to further evaluate the functional group tolerance of the methodology established for *C*-arylation. This could be explored by competitive arylation experiments, combining other easily arylated substrates, such as phenols and alcohols, in the same reaction as a nitroalkane. Therefore, substrate **16c** containing both a secondary aliphatic alcohol and a nitro group was synthesized.[113] When **16c** was subjected to our optimized conditions only *C*-arylation was observed and neither oxidation nor *O*-arylation were detected (Scheme 54a). Driven by this success, the benzylic alcohol **1f** was added to the reaction with nitrocyclopentane (**16a**) to

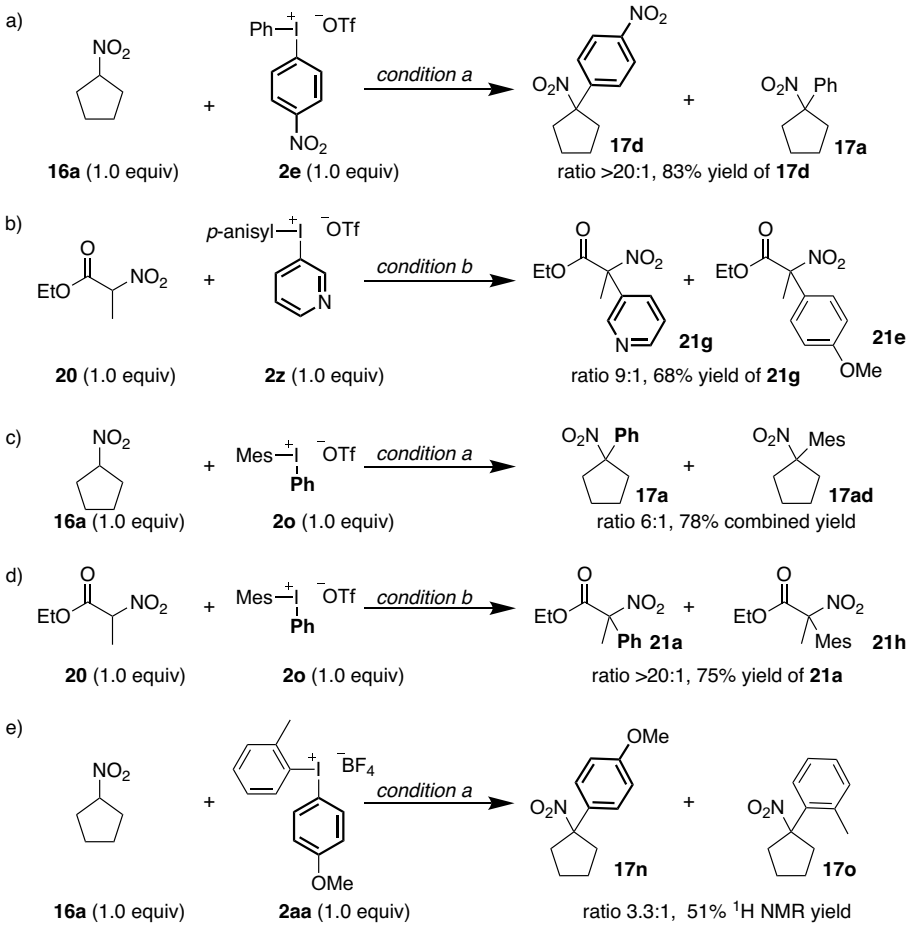
perform a competition experiment, and this resulted in formation of only the *C*-phenylated product **17a** (Scheme 54b). The nitroalkane **16a** was preferentially phenylated even in the presence of phenol **4c** (Scheme 54c), indicating that a late stage *C*-arylation could be possible in larger molecules containing OH-groups. The difference in *p*Ka between **16a** and **4c** in aprotic solvents is probably the reason behind the observed high chemoselectivity.



Scheme 54. Chemoselective C-arylation of nitro compounds in presence of OH-groups. [a] *^{1}H NMR yield using TMB as internal standard.*

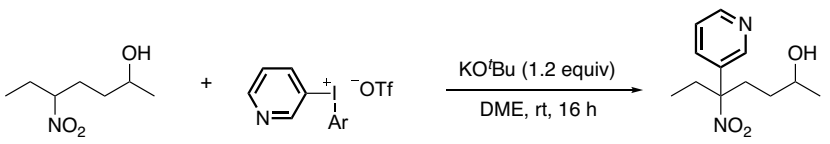
The chemoselectivity was also investigated with regards to the electrophile using unsymmetric diaryliodonium salts. Some results previously presented with focus on yield and functional groups are discussed here in terms of the chemoselectivity of the diaryliodonium salt. In Section 1.1.3 the use of symmetric or unsymmetric diaryliodonium salts are discussed, and two suitable dummy ligands for *C*-nucleophiles are anisyl or mesityl (Scheme 10c). When the diaryliodonium salt is substituted with a highly electron-withdrawing group, even a phenyl moiety can serve as a dummy group. This was demonstrated with salt **2e**, where the transfer of the *para*-nitrophenyl group was preferred, generating product **17d** with a ratio greater than 20:1 (Scheme 55a). With nitro ester **20** and salt **2z**, the electronic control was shown with anisyl as dummy group, favoring the transfer of the pyridyl moiety to obtain **21g** over **21h** in a 9:1 ratio (Scheme 55b). Under metal-free *C*-arylation conditions, the less sterically hindered group is usually transferred, which the Olofsson group has coined as the "anti-*ortho*-effect".[37] This was demonstrated here for both nucleophiles **16a** and **20** (Scheme 55c-d) with salt **2o**. With nitro ester **20** the preference for phenyl group transfer is impressing high, with a ratio between **21a** and **21h** ratio of 20:1. It was anticipated that the electronic effects will override the *ortho*-effect, and it was desirable to investigate if a sterically hindered aryl moiety would favor the more electron-rich group, thus salt **2aa** was synthesized. Surprisingly, the

transfer of the more electron-rich aryl moiety was favored (Scheme 55e). This is a rare example of this type of chemoselectivity.[114]



Scheme 55. Chemoselectivity study of C-arylation of nitro compounds. The major product is highlighted. Condition a: KO^{t}Bu (1.2 equiv), DME, rt, 16 h. Condition b: Cs_2CO_3 (1.2 equiv), toluene, 110 °C, 6 h. ^{1}H NMR yield using TMB as internal standard.

To further demonstrate the chemoselectivity, substrate **16c** with possibility for both *C*- and *O*-arylation was treated with unsymmetric diaryliodonium salts carrying either mesityl (**2ab**) or anisyl (**2z**) as dummy group. Gladly, in both cases, only the pyridyl moiety was transferred with high chemoselectivity to produce selectively the *C*-arylated product **17ae**, albeit in moderate yield (Scheme 56).



16c
(1.0 equiv)

2ab Ar = Mes
2z Ar = *p*-anisyl
(1.0 equiv)

17ae
with **2ad** = 39% yield
with **2ab** = 41% yield

Scheme 56. Selective C-arylation and chemoselective transfer of a pyridyl group. 0.4 mmol of ***16c****.*

6.5 Conclusion

A highly efficient method to *C*-arylate nitro compounds has been developed. The methodology required no excess reagents and the majority of reactions were performed at ambient temperature. Nitroalkanes have been chemoselectively phenylated in the presence of highly active functional groups, and also to be arylated with high chemoselectivity using unsymmetric diaryliodonium salts.

There is a great potential to continue this project with related substrate classes, in order to access highly decorated carbon skeletons.

7 Concluding Remarks

In this thesis, three methods to access aryl ethers have been presented. The common denominator was diaryliodonium salts, which enabled the reactions to proceed under mild conditions without the need for excess material, fulfilling parts of the aim of the thesis. It was demonstrated that water could be used as the solvent for arylations of allylic and benzylic alcohols. Performing the reactions in toluene allowed for the formation of alkyl aryl ethers at room temperature. The methodology was suitable to prepare biologically active aryl ethers, as demonstrated by the synthesis of fluoxetine and a formal synthesis of butoxycain. Oxidation was observed as a side reaction, and the mechanism of this was investigated. This resulted in a proposal of a mechanism similar to the one for iodine(V) reagents. The incompatibility between the substrates and electron-rich iodonium salts was scrutinized, with the main challenge being a competing *ortho*-deprotonation of the aryl group instead of the ligand coupling. The resulting aryne intermediates were trapped with furan, which gave Diels-Alder adducts. The use of piperidine as additive allowed for isolation of a single regioisomer of the alkyl aryl ether instead of a mixture.

Sterically congested alkyl aryl ethers have been synthesized, and steric hindrance was tolerated on both the alcohol and diaryliodonium salt. Cyclic, acyclic, benzylic, allylic and propargylic tertiary, as well as primary and secondary fluorinated alcohols were suitable substrates, in combination with a strong base. The methodology was applied to *O*-arylate the prodrug mestranol.

Nitro compounds were demonstrated to be suitable substrates to undergo *C*-arylation with diaryliodonium salts. Two general protocols were developed, the first at room temperature for secondary cyclic and acyclic nitroalkanes, yielding a broad spectrum of products. The second method was developed for nitro esters and required elevated temperature. The chemoselectivity for both types of nitro compounds was investigated, and found to correlate well to other carbon nucleophiles. It was found that the arylation of nitroalkanes followed the anti-*ortho*-effect, with a favored transfer even of a more electron-rich aryl group over a sterically hindered one.

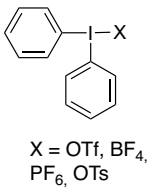
This aim of this thesis was to develop metal-free applications for *O*-arylations of alcohols using diaryliodonium salts, and to understand the mechanisms behind. The work described herein is by far not the full story, but hopefully it can be used as a stepping-stone towards a general method covering all types of diaryliodonium salts and alcohols to make ethers.

8 Populärvetenskaplig Sammanfattning på Svenska

Kemi påverkar varje människas vardag, varje dag. Från jordbruksprodukter och nya material till framställning av läkemedel. Denna industri kräver ständigt nya verktyg för att kunna bygga ihop molekyler på ett mer effektivt och miljövänligt vis. Hypervalenta jodföreningar kan vara gröna alternativ till tungmetaller. Diaryljodoniumsalter är en typ av hypervalenta jodreagens som kan användas under milda betingelser, och därmed kan miljöfarliga reagens undvikas. I denna avhandling har övergångsmetallfria metoder för att syntetisera alkylaryletrar utvecklats. Syftet har varit att hitta en generell metod, där alla möjliga alkoholer kan aryleras med diaryljodoniumsalter, och därmed utvidga möjligheterna för världens kemister att bygga nya molekyler. I kapitel 2 och 3 beskrivs två nya metoder för att framställa alkylaryletrar, i den första används vatten som lösningsmedel medan den andra är mer generell för olika typer av alifatiska alkoholer. I kapitel 4 undersöks mekanismen bakom begränsningen för metoderna som presenteras i kapitel 2 och 3. Kapitel 5 beskriver en syntesväg för etrar med steriskt hinder på båda sidor av eterbryggan. I tidigare metoder har oftast bara hinder på ena sidan av syret varit möjligt. Kapitel 6 byter fokus till arylering av kolnukleofiler, och metoder för att framställa arylerade nitroföreningar beskrivs. Selektiviteten undersöks i detalj och inkluderar många exempel på nya föreningar som kan syntetiseras.

9 Appendix A – Diaryliodonium Salts

This appendix shows the structures of all diaryliodonium salts that were mentioned in the text, in order of appearance. All diaryliodonium salts used in this thesis were synthesized according to published procedures[4a-e] or modified protocols, except for **2a-PF$_6$** that was purchased from a commercial supplier.



X = OTf, BF_4, PF_6, OTs

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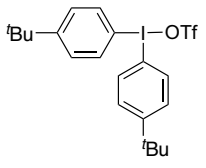

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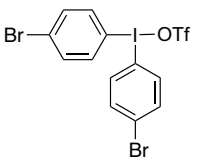

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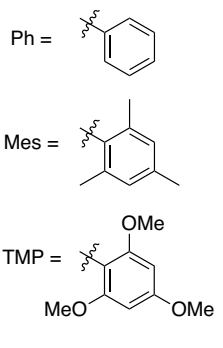

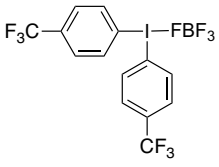

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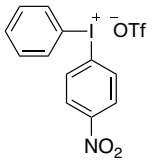

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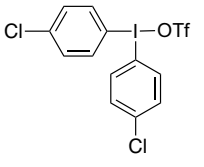

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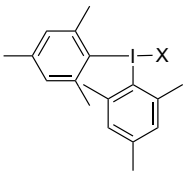

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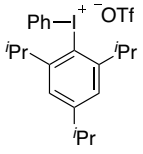

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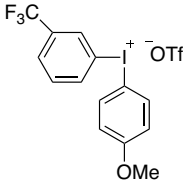

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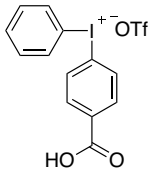

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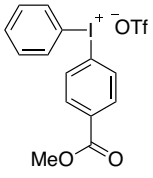

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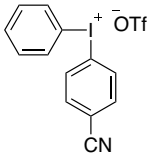

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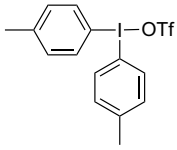

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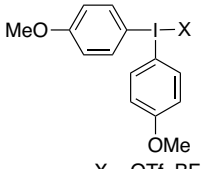

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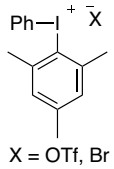

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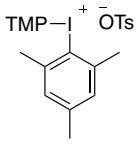

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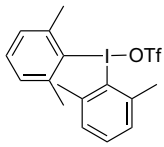

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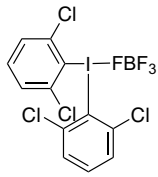

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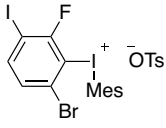

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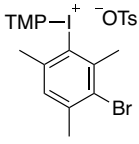

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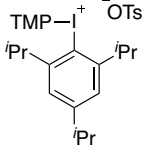

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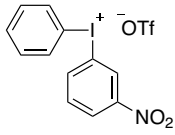

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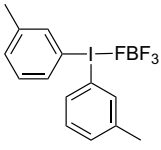

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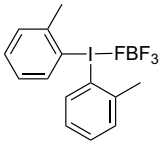

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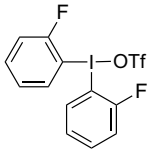

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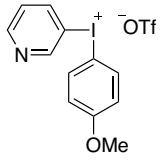

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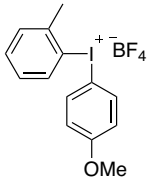

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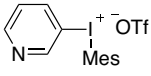

2ab

10 Appendix B – Contribution List

The author's contribution to projects **I-V**

I. Shared the experimental work with Dr. Raju Ghosh. Performed the major part of the optimization and the scope. Took part in writing of the article and wrote parts of the supporting information.

II. Shared the experimental work with Dr. Raju Ghosh. Performed a minor part of the optimization and the scope. Wrote a minor part of the supporting information.

III. Shared the experimental work with Elin Stridfeldt and Marcus Reitti. Performed studies on the formation of diaryl ethers *in situ* and on arylation of primary alcohols using electron-rich diaryliodonium salts, as well as the oxidation mechanism. Wrote parts of the manuscript and parts of the supporting information.

IV. Initiated the study together with Elin Stridfeldt. Performed the major part of the optimization and 90% of the scope. Synthesized a majority of the diaryliodonium salts and starting materials used in the project. Wrote a major part of the article and a major part of the supporting information.

V. Shared the experimental work with Dr. Chandan Dey. Performed half of the optimization, and half of the scope on the aliphatic nitroalkanes. Performed a major part of the chemoselectivity experiments. Wrote parts of the article and parts of the supporting information.

11 Appendix C – Reprint Permissions

Reprint permissions were kindly granted for each publication by the following publisher:

Metal-Free Synthesis of Aryl Ethers in Water
Erik Lindstedt, Raju Ghosh and Berit Olofsson*
Org. Lett. **2013**, *15*, 6070–6073

Room Temperature, Metal-Free Arylation of Aliphatic Alcohols
Raju Ghosh, Erik Lindstedt, Nazli Jalalian and Berit Olofsson*
ChemistryOpen, **2014**, *3*, 54-57

Mild Synthesis of Sterically Congested Alkyl Aryl Ethers
Erik Lindstedt, Elin Stridfeldt and Berit Olofsson*
Org. Lett. **2016**, *18*, 4234-4237

Metal-Free *C*-Arylation of Nitro Compounds with Diaryliodonium Salts
Chandan Dey,[‡] Erik Lindstedt[‡] and Berit Olofsson*
Org. Lett. **2015**, *17*, 4554–4557

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Per-Ola Norrby – for the guidance during my master work, and for always asking questions.

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Joel Malmgren – Thanks for the guidance and help, for all fun activities and so on!

Elin Stridfeldt – En lång resa och det har varit tacksamt att veta att du alltid har varit på SU en månad längre! Det har varit väldigt roligt att doktorera samtidigt som dig.

MARCUS REITTI – En äkta ängel! Thank you for all the good times, and especially for your patience, and for not going crazy in the office…

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To my conference companions – *Anuja*, *Joel*, *Marcus*, *Elin*, *Erik, Chandan*, *Marin*, *Iris*… Thanks for all the adventures and fun times!

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All the people at *Medicinal Chemistry, AstraZeneca, Mölndal*, especially *Michael Kossenjans*. Thank you for giving me the opportunity to work in your group, I really had fun!

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