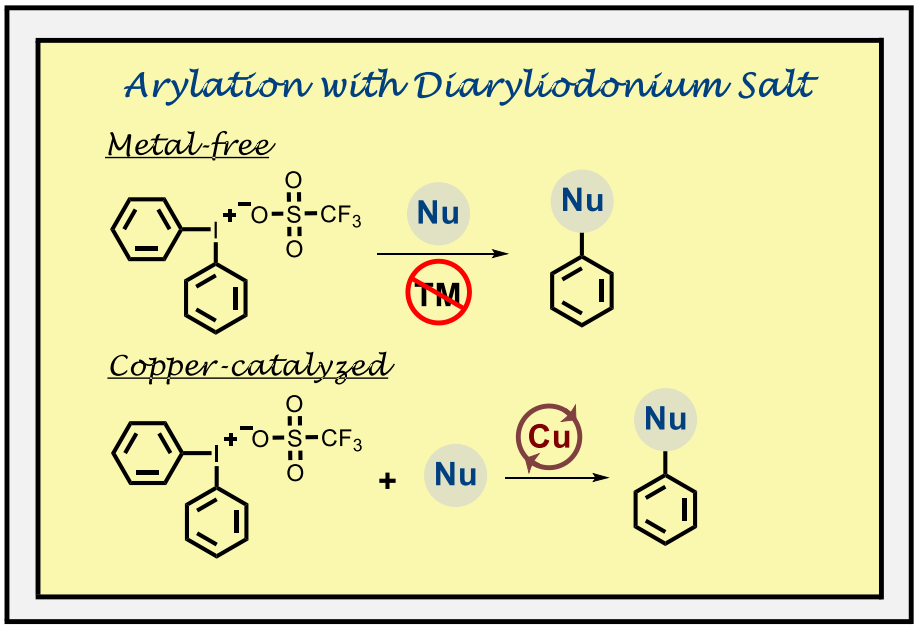
Chapter 1

General Introduction

"Diaryliodonium Salts: A Hypervalent Iodine(III) aryl-transferring reagent"

Abstract: Since Hartmann and Meyer discovered the first example of diaryliodonium salt in 1894, a new chapter originated in arylation chemistry. In the realm of arylation chemistry where aryl halides and arylboronic acids act as dominating arylating partners, this hypervalent iodine(III) arylating source is a new player in this field and has been exploring tremendously in the last two decades. Because of the unique feature of the diaryliodonium salts, it allows metal-free arylation and mild copper-catalyzed arylation with various nucleophiles.



1. Introduction

1.1 Brief Background of Hypervalent Iodine Chemistry

In general, hypervalent iodine chemistry describes the chemistry of organoiodine compounds possessing higher oxidation states on the iodine atom (especially +3 or +5) [1]. Iodine (symbol **I**) is one of the heaviest non-metals and non-radioactive element among the main group elements. This element was discovered by industrial chemist Bernard Courtois back in 1811 and later, J. L. Gay Lussac named this peculiar element as "iodine" in 1813 because of its violet colour appearance in the condensed state [2]. The word was derived from the Greek word "*ioeides*" which meant violet. In the periodic table, iodine has its position in the group 17 (halogen family) and period 5 with electronic configuration $[Kr]5s^2 4d^{10} 5p^5$. It has large atomic size, low electronegativity, and high polarizability, due to which the bonding pattern exhibited by iodine compounds is not almost similar with its lighter congeners. This unique bonding pattern, which can be observed in a wide range of polyvalent organoiodine compounds, and inorganic iodine compounds is known as "hypervalent iodine bond" [3]. The hypervalent bond is highly polarizable and longer than conventional covalent bond. Because of their distinguishing nature, the polyvalent iodine compounds having hypervalent bonding demonstrates special reactivity and some characteristic properties. These important iodine compounds possessing a hypervalent bond and exhibiting unique chemical reactivity can be called "hypervalent iodine reagents" (HIRs) and their chemistry have been recognized as hypervalent iodine chemistry (HIC).

Historically, the early development of HICs were identified during the period 1885-1900 [4]. In 1886, German Chemist C. Willgerodt synthesized the first hypervalent iodine compound **1**, i.e., "(dichloroiodo)benzene" while he was passing chlorine gas into a vessel containing ice-cold iodobenzene solution (Figure 1.1) [5]. Later, other well-known oxidizing HIRs, such as (diacetoxyiodo)benzene **2** [6] and 2-iodoxybenzoic acid **3** (IBX) [7] were too developed in 1892 and 1893 respectively along with several useful polyvalent iodine compounds. Similarly, the first report for the example of diaryliodonium salt **4** was published by C. Hartmann and V. Meyer in 1894 (Figure 1.1) [8]. The progress on synthesis of HIRs and their applications during this period were such that chemist Willgerodt published a comprehensive book on

HIC mentioning approximately 500 organoiodine reagents in 1914 [9]. In the current time, many of the hypervalent iodine compounds have been recognized as versatile and common laboratory reagents because of their mild reactivity, non-toxicity, and environmentally benign properties [10]. Owing to their similar reactivity pattern with transition-metal-based oxidants in many organic transformations [11], these HIRs are good alternatives to the toxic and expensive heavy transition-metals. As iodine is a non-toxic and inexpensive source, the hypervalent iodine chemistry has been much acknowledged from the perspective of sustainable and green chemistry [12].

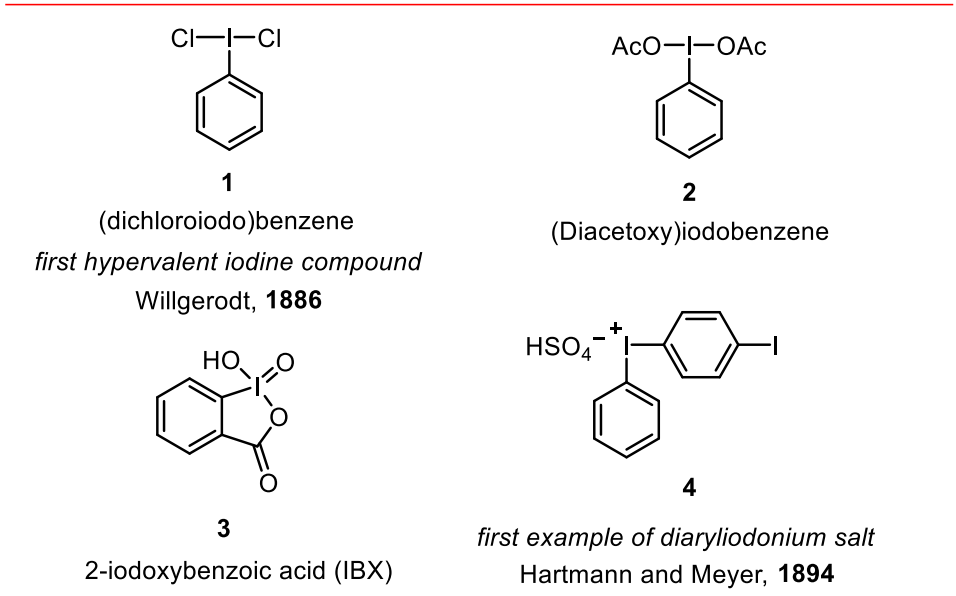


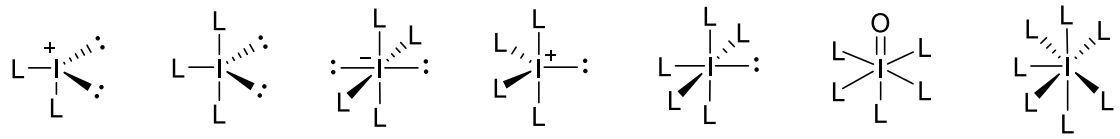
Figure 1.1 Examples of early reported hypervalent iodine compounds

1.2 Hypervalent Bonding and Important Iodine(III) Reagents

1.2.1 Classification

The presence of "hypervalent" species are quite common among the ions or molecules of the elements of groups 15–18, as summarized by J. I. Musher [13]. Hypervalent iodine compounds can be determined from the valence shell electron counting of the iodine centre, i.e., if there are more than eight electrons in the iodine valence shell, then the compound can be considered as a hypervalent iodine compound. Depending on the oxidation state of the iodine centre, the hypervalent iodine compounds can be found in the six different structural types **5-11** (Figure 1.2). The species **5** is iodonium ion and it cannot be considered as a hypervalent iodine compound, as the valence shell of iodine contains eight electrons. However, in the

salt form of species **5** in presence of an appropriate anion; the iodonium salt species is considered as a ten-electron hypervalent compound in modern literature [14]. Among the various types of hypervalent species, the two important classes are the iodine(III) and iodine(V) types of compounds. In literature, there are specific notations to represent these types of hypervalent iodine compounds. According to the Martin–Arduengo classification, the hypervalent iodine compounds can be designated with a code *N-X-L*, where N states the number of total valence electrons present around the valence shell of central atom X, and L states the number of sigma bonds between the various ligands and central atom [15]. However, in accordance with 1983 IUPAC recommendations, the new convention to designate iodine(III) and iodine(V) compounds are λ^3-iodanes and λ^5-iodanes respectively, where the representation λ^n signify the valence states (n) of the central atom [16].

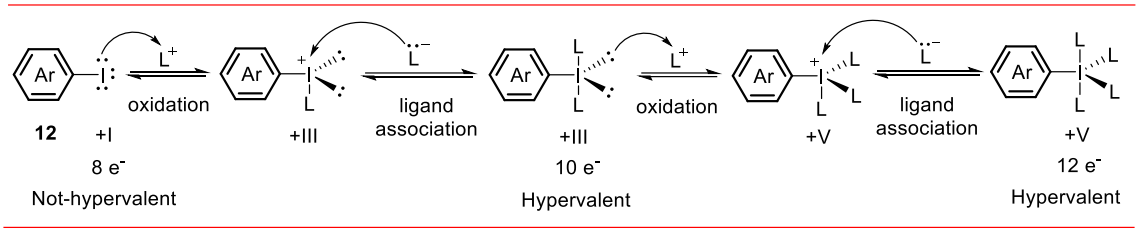


8-I-2	*10-I-3*	*12-I-4*	*10-I-4*	*12-I-5*	*14-I-6*	*14-I-7*
5	**6**	**7**	**8**	**9**	**10**	**11**

Figure 1.2 Structural types of polyvalent iodine species

1.2.2 General synthesis of hypervalent iodine species

Due to the characteristic atomic properties of iodine, the synthesis of hypervalent iodine species from non-hypervalent iodine compounds (I^2 or PhI) can be achieved by oxidation of the iodine centre with appropriate ligands (Scheme 1.1) [17]. Both λ^3-iodanes and λ^5-iodanes can be synthesized under a similar approach, however the reagents and applications of λ^3-iodanes are comparatively higher in comparison to λ^5-iodanes. Scheme 1.1 illustrates for aromatic iodide **12** as precursor of hypervalent iodine compounds, where L is ligand either derived from oxidising agent or an acidic solution source [18]. Like aryl iodide, other hypervalent iodine species with sp^2- and sp^3- carbons can be synthesized with similar protocols [19–20]. Depending on the iodine centre, oxidant utilized and ligand type, the reaction condition of the synthetic procedures can be different.



Scheme 1.1 Oxidative pathway for the formation of hypervalent iodine compounds

1.2.3 Molecular orbital bonding

The molecular orbital (MO) diagram for an aryl λ^3-iodane species ($ArIL_2$) can be explained from its geometry (Figure 1.3) [21]. In aryl λ^3-iodanes, the aryl group and the two ligands are generally found in T-shape (*pseudo*-trigonal pyramidal geometry), where two ligands reside in apical positions (*trans* to each other) [22]. The MO bonding pattern can be rationalized as the 5p orbital of iodine centre overlaps with the two appropriate orbitals derived from the ligands and forms a three-centre four-electron bond (3c-4e) bond [23]. The excellent electrophilicity of the hypervalent bond can be understood from the highest occupied molecular orbital (HOMO). The HOMO is non-bonding, and a node is present on the iodine centre of the HOMO. Due to this, the two electrons of the non-bonding MO reside more towards the ligands side and the iodine centre gains a partial positive charge. Therefore, the iodine centre acts as an electrophile.

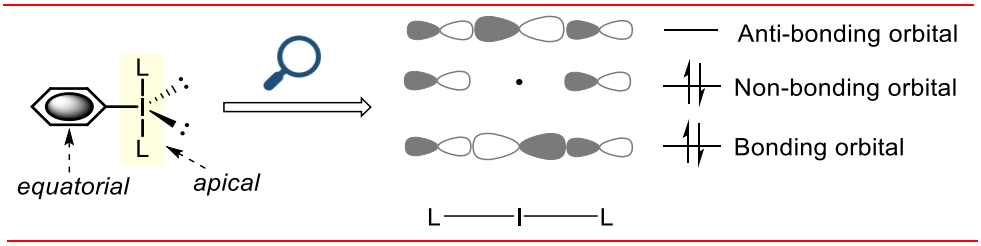


Figure 1.3 Depiction of molecular orbital diagram for 3c-4e L-I-L bond

1.2.4 Examples of iodine(III) compounds

Among the diverse examples of hypervalent iodine(III) reagents, the primary and significant categories are oxidizing reagents and group-transferring reagents (Figure 1.4). Compounds such as (diacetoxyiodo)benzene (**14**) (DIB or PIDA), bis(trifluoroacetoxy)iodobenzene (**15**) (BTI, PIFA) and [hydroxy(tosyloxy)iodo]benzene (HTIB or Koser's reagent) are very valuable reagents for oxidation chemistry [24], dearomatization of phenol scaffolds [24],

oxidative C-C coupling reactions [25], oxidative C-N coupling [26] etc. On the other hand, number of iodine(III) reagents are utilized as suitable choice for transferring groups like -N_3 (**16**) [27], -CF_3 (**17**) [28] and -CN (**18**) [29] from their benziodoxolone precursor (Figure 1.4). Along with them, other group-transferring reagents are diaryliodonium salts **19** (for aryl group), vinylbenziodoxolones **20** (for alkenyl group) [30] and enthynylbenziodoxolones **21** (for alkynyl group) [31] have become quite popular reagents for arylation, vinylation and ethynylation, respectively.

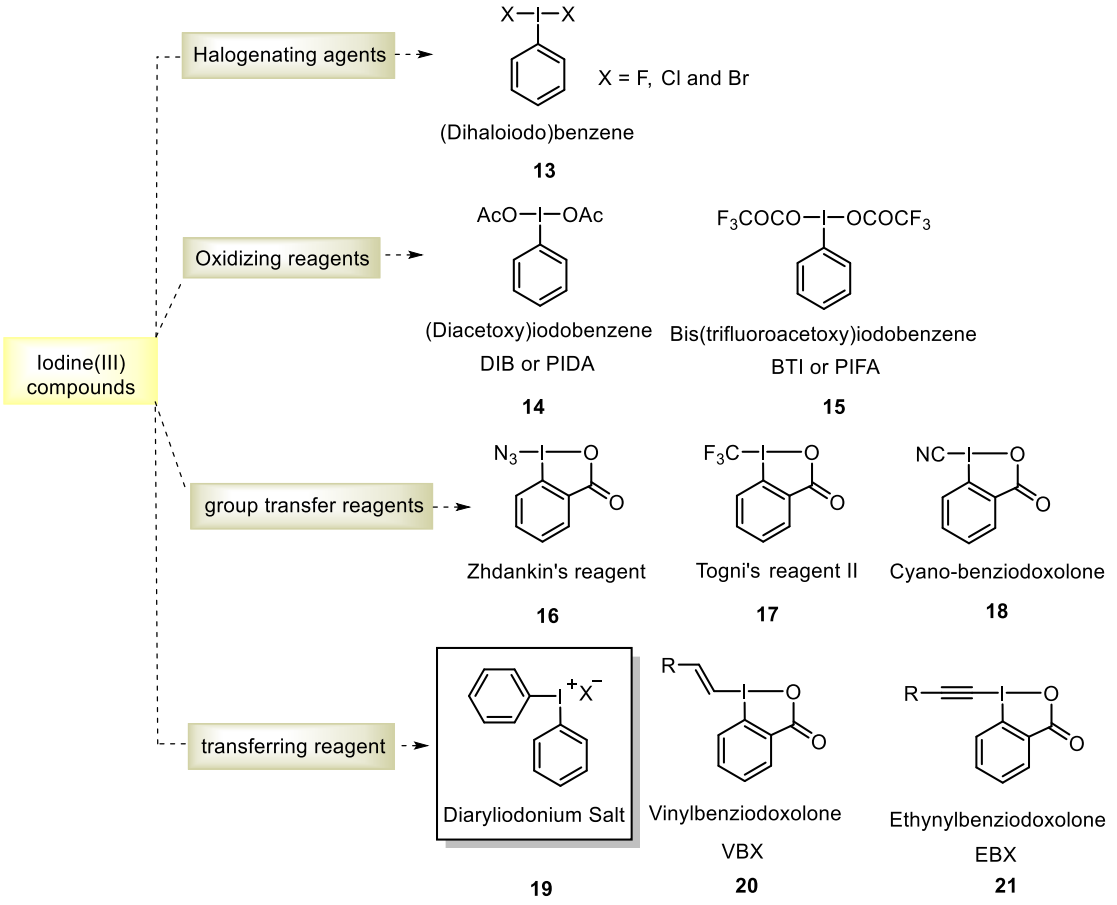


Figure 1.4 Examples of different types of iodine(III) reagents

The following discussion will be solely on chemistry of diaryliodonium salts. The discussion is focused on the types of diaryliodonium salts, synthesis of both symmetrical and unsymmetrical diaryliodonium salts and their application as arylating partner both in metal-free conditions and copper-catalyzed conditions with diverse carbon and hetero-atomic nucleophiles.

1.3 Diaryliodonium Salts

As mentioned above, diaryliodonium salts **19** (DISs) are one of the important hypervalent iodine(III) reagents, and it is generally considered as a 8-I-2 hypervalent iodine species (according to Figure 1.2). The general representation of the diaryliodonium salts is Ar^1Ar^2X, where both Ar^1 and Ar^2 are characteristic carbon ligands (aryl groups) and X is negatively charged counterion (Figure 1.5). DISs are air- and moisture- stable compounds and are mostly known as mild, stable, easily synthesizable, storable, and non-toxic arylating precursors in modern organic chemistry [32]. Though this compound has been known for more than 100 years and early applications of it were accomplished during the 1950-1960s period [33], diaryliodonium salts have been tremendously applauded as an arylating partner both in metal-free [34] and transition-metal-catalyzed reaction conditions [35].

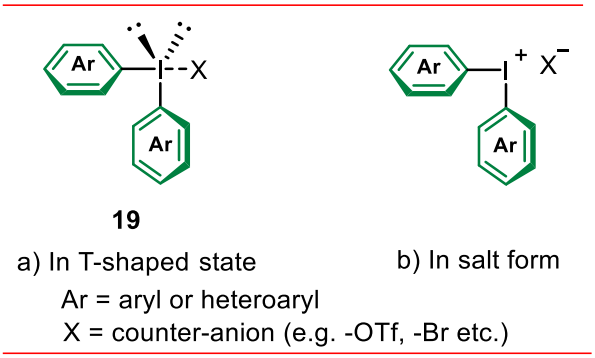


Figure 1.5 General representation of diaryliodonium salts

1.3.1 Structure and types of diaryliodonium salts

According to the IUPAC nomenclature, diaryliodonium salt can also be named as diaryl-λ^3-iodane, however the common name (i.e., diaryliodonium salt) is still in use. In the solid state, diaryliodonium salts with counter-anions such as halides and tetrafluoroborates exhibit dimeric structures showcasing iodine–counteranion secondary bonding (Figure 1.6a) [36]. The coordination around the iodine centre is square planar and the bond angle of C-I-C of the Ar_2I^+ moiety is approximately 90°. Though, diaryliodonium salts is considered as hypervalent iodine species, but the hypervalent bond distance I···X is quite longer than conventional hypervalent bond of iodine(III) compounds. Due to this, the iodine centre of diaryliodonium salts possesses partial positive charge. For example, the secondary bond distance of I···Cl in case of Ph_2ICl is not similar like the hypervalent I–Cl bond length of 2.47 Å in $PhICl_2$

[37]. A similar observation was noticed for the compound (2-methylphenyl)(2-methoxyphenyl)iodonium chloride from its single-crystal X-ray structure (Figure 1.6b) [38].

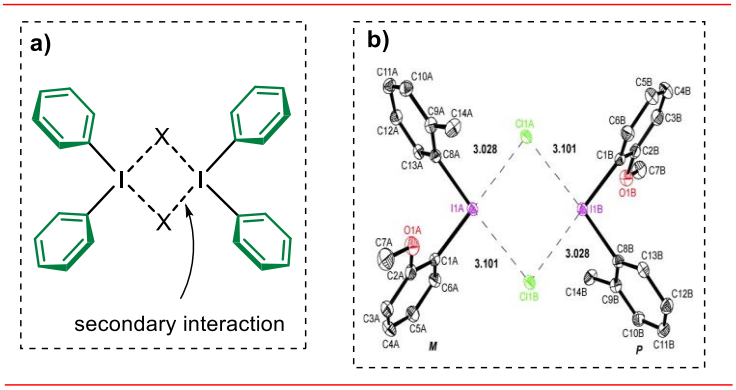


Figure 1.6 a) Representative crystal structure of Ph_2IX in dimeric state, and b) X-ray crystal structure of dimeric 2-methylphenyl(2′-methoxyphenyl)iodonium chloride

Depending on the substituents on the aryl moieties of diaryliodonium salts (Figure 1.7), diaryliodonium salts can be of two types: i) symmetrical iodonium salts (Ar^1=Ar^2) **22**, where either the functional groups on the aryl rings (or the their position of the substituents are same) or the aryl moieties (arene) are similar (naphthyl-naphthyl or thionyl-thionyl etc.); ii) unsymmetrical iodonium salts (Ar^1≠Ar^2) **23**, when a) the functional groups on the aryl rings are different; b) the positions of similar substituents are not identical; and c) the arene rings are not similar. Depending on type of diaryliodonium salt, the reactivity of each case differs with different nucleophiles [32].

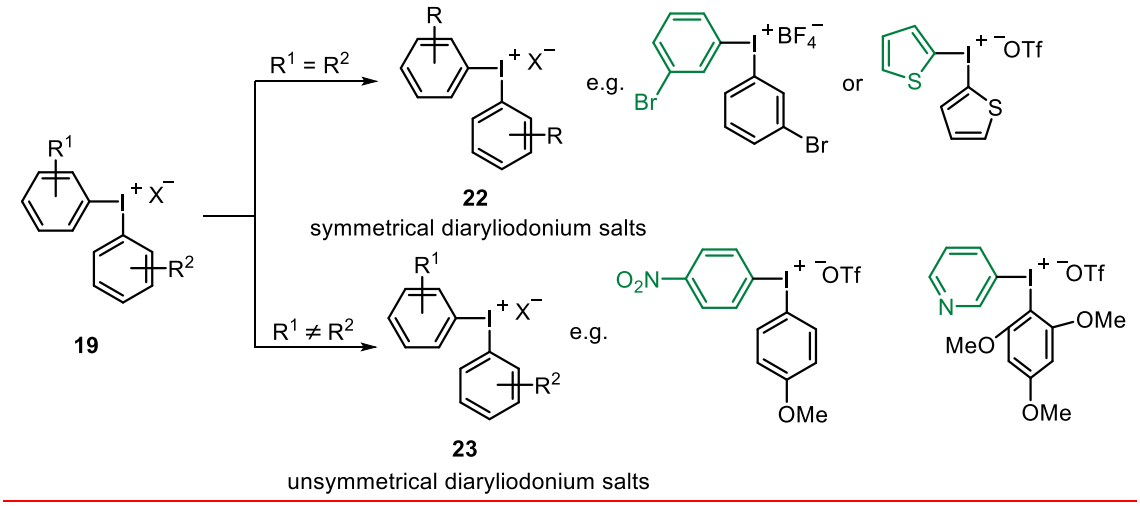
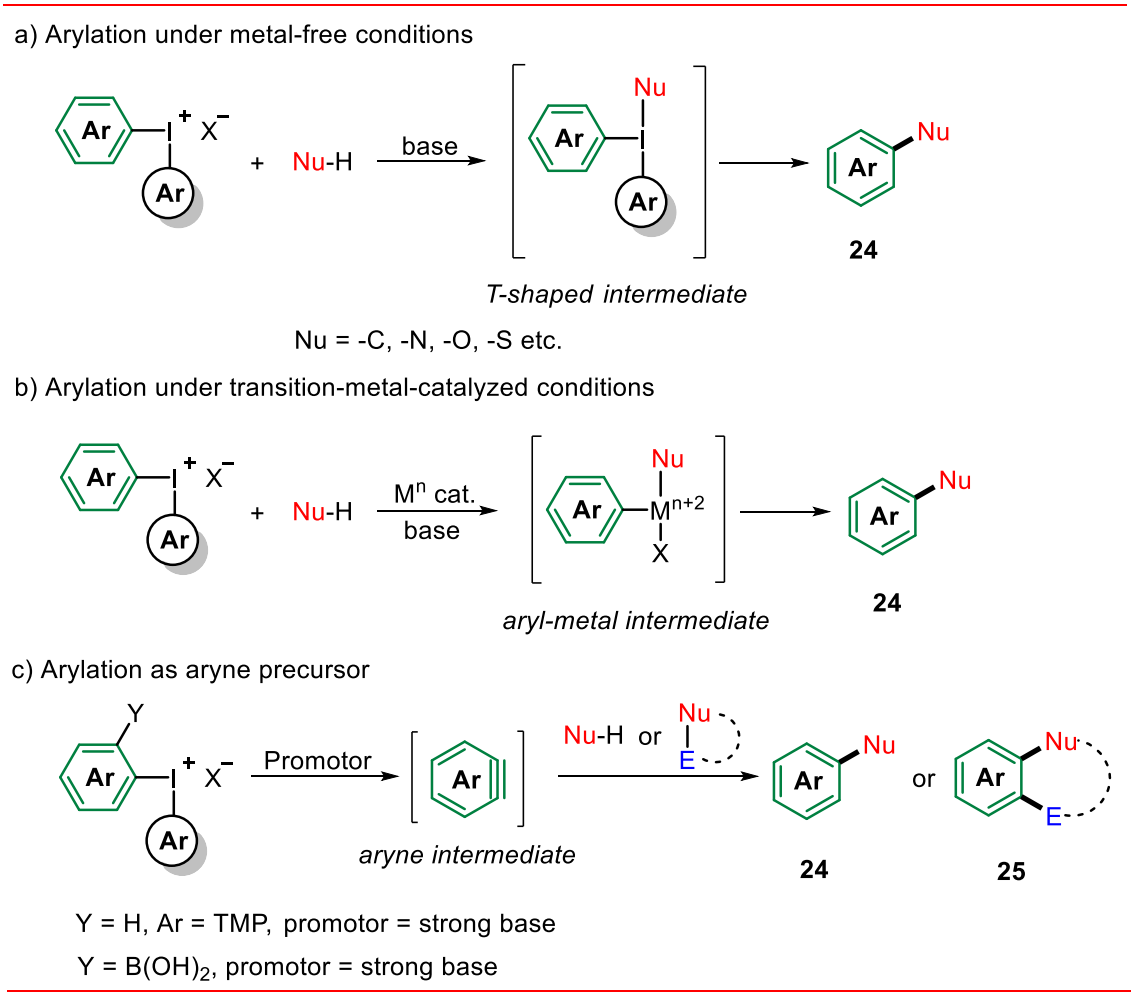


Figure 1.7 Different types of diaryliodonium salts

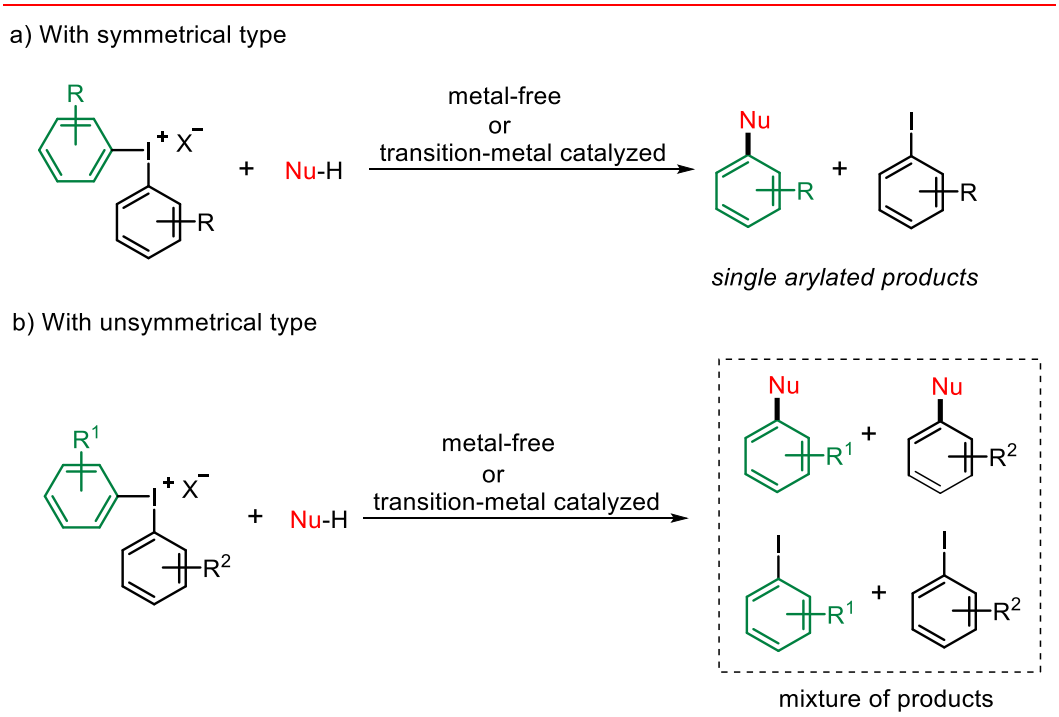
1.3.2 General reactivity of diaryliodonium salts

Due to the inherent electrophilicity on the iodine atom of diaryliodonium salt, this aryl-transferring reagent easily reacts with a suitable nucleophile (Nu) and affords the arylated product of the nucleophile (Nu-Ar). Another driving force of this reagent to act as an excellent arylating precursor is the higher leaving group affinity of the ArI moiety [39]. In the arylation reactions, diaryliodonium salts can participate differently depending on the reactions, a) metal-free conditions, b) transition-metal catalyzed conditions, and c) as an aryne precursor. (Scheme 1.2) [32,40]. In metal-free conditions, the nucleophile reacts with diaryliodonium salt either in presence of base or without any base (Scheme 1.2a) and provides the arylated product **24**. As all nucleophiles are not compatible for metal-free coupling, diaryliodonium salt has been utilized as a suitable arylating partner under transition- metal catalyzed reaction (Scheme 1.2b). The transition-metal catalyzed arylation reactions with



Scheme 1.2 General application of diaryliodonium salt as aryl source

diaryliodonium salts are mild and operationally simple in comparison to other arylating partners such as aryl halides or aryl boronic acids. Apart from being utilized as an arylating partner under metal-free and transition-metal catalyzed conditions, diaryliodonium salts can also be employed as an aryne precursor and are applicable in arylation reactions with diverse dienophiles and nucleophiles (Scheme 1.2c) [41]. As diaryliodonium salts can be utilized as an effective arylating partner, the reactivities and their applications vary with types of the iodonium salts [42]. Symmetrical iodonium salts own similar reactive aryl rings, therefore they undergo easy conversion to the arylated products by incorporating any one of the two aryl rings (Scheme 1.3a). However, unsymmetrical iodonium salt provides a mixture of arylated products and overall atom-economy is much less. Both aryl rings in unsymmetrical iodonium salts can be different with respect to electronical and steric factors, because of which the selectivity of arylation with unsymmetrical iodonium salt is less (Scheme 1.3b).

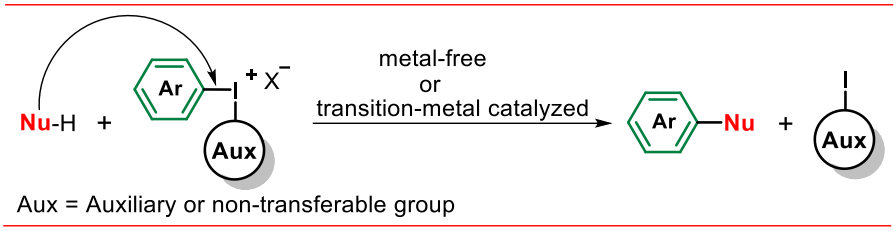


Scheme 1.3 Arylation products with symmetrical and unsymmetrical types

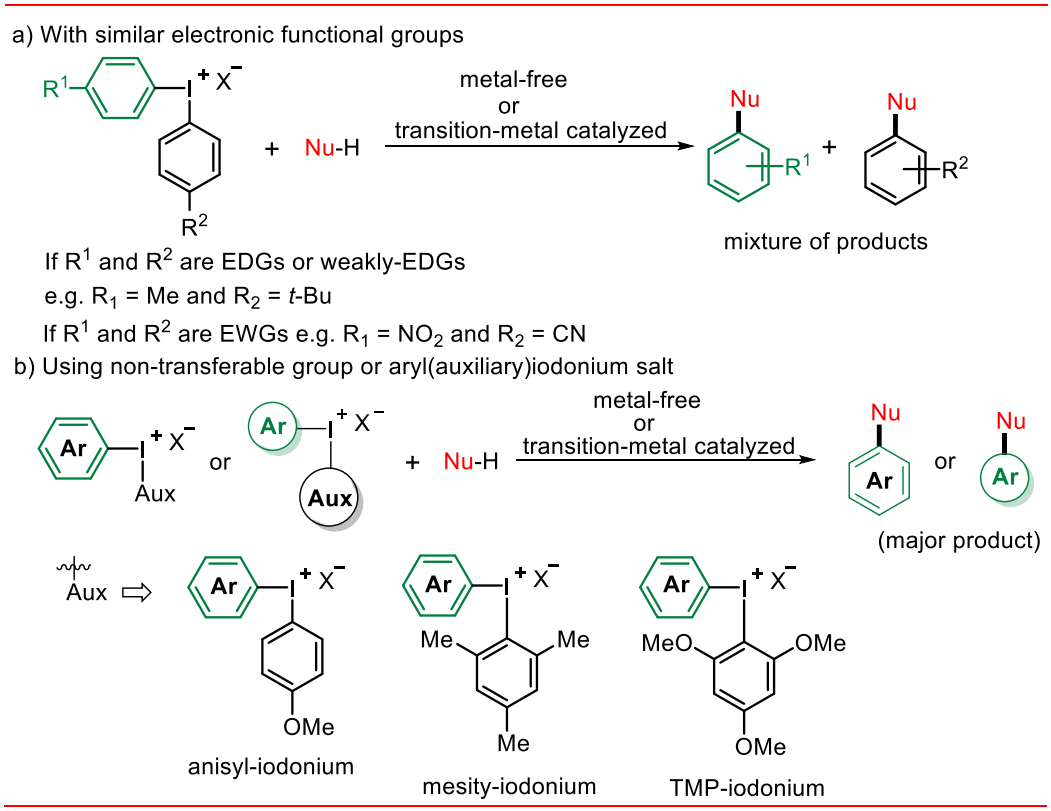
1.4 Unsymmetrical Diaryliodonium Salts with "dummy ligands"

The arylation methods with symmetrical iodonium salts are desirable as it prevents selectivity problems. However, when the starting materials (aryl iodides) are

expensive or aryl groups possess either electron-rich or electron-withdrawing functional groups, the synthetic route to achieve that corresponding symmetrical iodonium salt is difficult and overall cost is high [43]. Therefore, it is always useful if the unsymmetrical diaryliodonium salt possesses one non-transferable aryl group (the leaving group Ar-I in the arylation step) and the incoming nucleophile can be arylated selectively with the desired aryl moiety by eliminating the non-transferable aryl iodide group (Scheme 1.4). This selective arylation from an unsymmetrical iodonium salt possessing a non-transferable aryl group is basically controlled by electronic and steric factors. The non-transferable aryl group is also known as "dummy ligands" or "auxiliary". The study of selective transfer of specific aryl moiety from an unsymmetrical iodonium salt is known as chemoselective arylation.



Scheme 1.4 General chemoselective arylation with aryl(auxiliary)iodonium salt



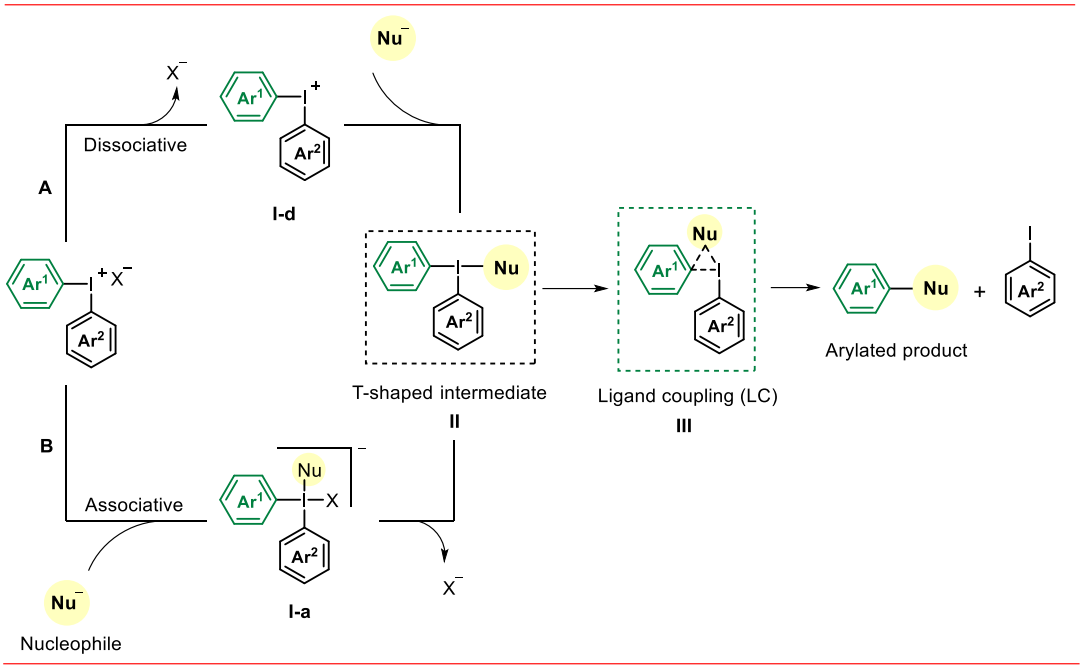
Scheme 1.5 Different auxiliaries for chemoselective arylation

The general rule for selection of dummy ligand in metal-free arylation reactions is that the dummy ligand must be more electron-rich in comparison to the other aryl part. If the unsymmetrical iodonium salt possesses aryl rings of electronically comparative aryl groups {both aryl groups are either electron-donating (ED) or electron-withdrawing (EW)}, then the arylation reaction shows mixture of products (Scheme 1.5a) [44]. So far, a good choice for auxiliary in unsymmetrical iodonium salts are anisyl (An), mesityl (Mes), and 2,4,6-trimethoxyphenyl (TMP), where the aryl group is either very electron-rich or both electron-rich and *ortho*-substituted. Anisyl- and TMP-iodonium salts are well-explored as effective arylating partners under metal-free conditions for diverse hetero-atomic nucleophiles (Schemes 1.5, b&d) [45-46]. On the other hand, sterically controlled mesityl-iodonium salts are suitable in copper-catalyzed arylation methods (Scheme 1.5c) [47]. In addition to metal-free conditions, some reports are found for TMP-iodonium salts where it has been explored as a versatile arylating partner in copper-catalyzed conditions too [48].

1.5 General Mechanism and Explanation for Chemoselective Arylation

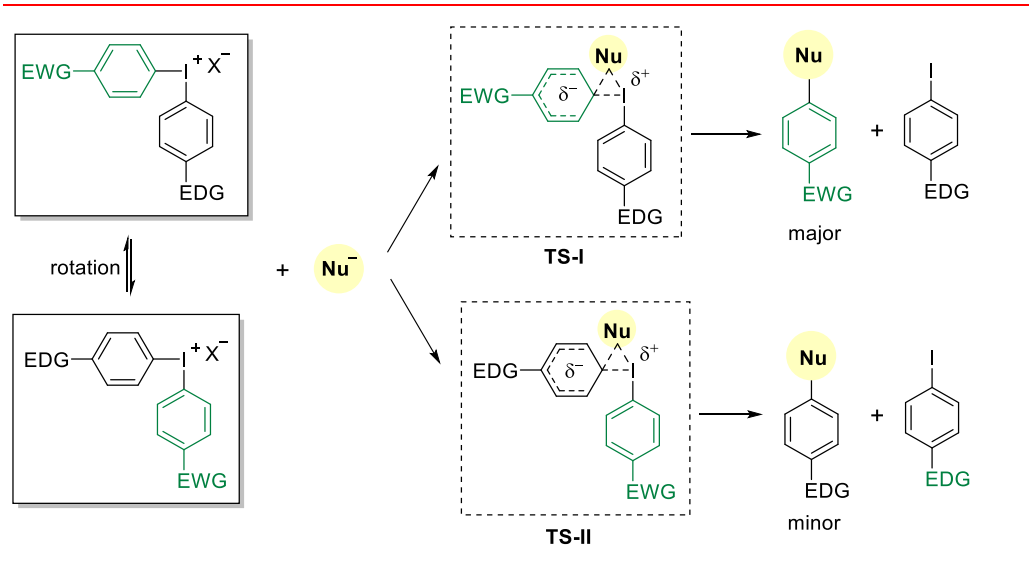
1.5.1 Under metal-free conditions

As mentioned in Scheme 1.2, the nucleophile initiates the reaction by forming a T-shaped intermediate (Ar_2I-Nu). The iodonium salt can follow two pathways for the formation of T-shaped intermediate: A) dissociative pathway, the attached counter-anion of the iodonium salt departs to form species **I-d** (Scheme 1.6) before the approach of the nucleophile; or B) the nucleophile coordinates with iodine(III) centre to form four-coordinated species **I-a**, and later the anion leaves to obtain the T-shaped species **II**. Muniz's group and Onomura's group independently isolated the T-coordinated species-II and the structure was further validated with single crystal X-ray analysis [49-50]. They isolated the species by reacting the corresponding nucleophiles with diphenyliodonium salt. From the T-shaped intermediate, the desired arylated product could be obtained *via* ligand coupling step. This step is very important, as depending on the electronic and steric factor of the aryl moieties; the selectivity of the arylation is different in case of unsymmetrical iodonium salts [51-52].



Scheme 1.6 General arylation mechanism under metal-free route

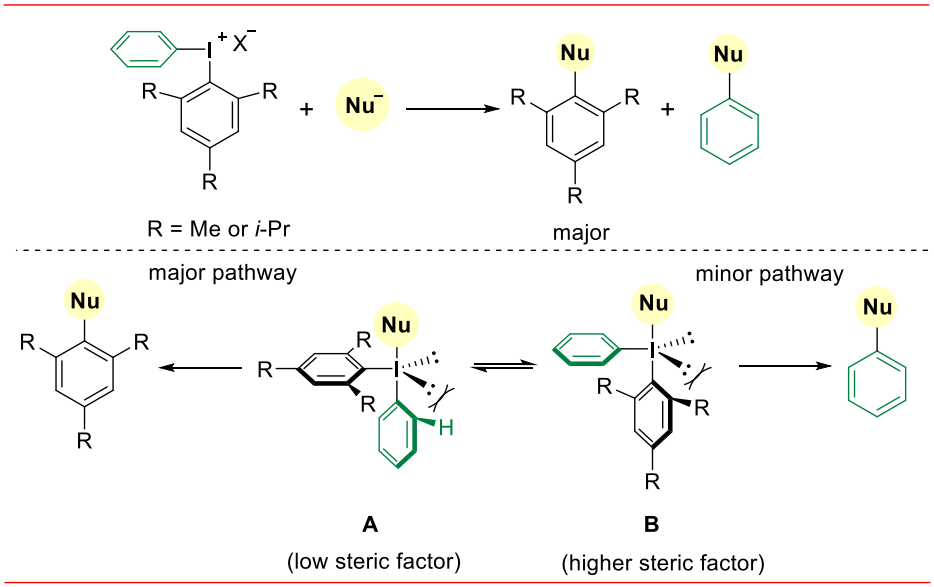
Due to the fast equilibrium through Berry pseudo-rotation [53], the unsymmetrical iodonium salts can produce two T-shaped intermediates. As mentioned in Scheme 1.5, the electronic factors play a crucial role and always an electron-deficient aryl moiety always prefers to transfer for arylation if the other aryl part is electron-rich, like in case of anisyl- and TMP-iodonium salts. An electronic model can easily explain the selectivity pattern in case of these types of auxiliaries [54]. In the ligand coupling stage (Scheme 1.7), both **TS-I** and **TS-II** can be rationalized since a partial positive



Scheme 1.7 Influence of electronic factors in selective arylation

charge is generated on the iodine centre and a partial negative charge is developed simultaneously on the equatorial aryl ring during the approach of the nucleophile at the *ipso*-carbon [55]. In case of **TS-I**, the EWG bearing aryl ring can stabilize the TS and therefore, this pathway possess more selectivity. However, the EDG aryl group is least sufficient to stabilize the developed partial negative charge in the **TS-II** and prefers to leave as a leaving group.

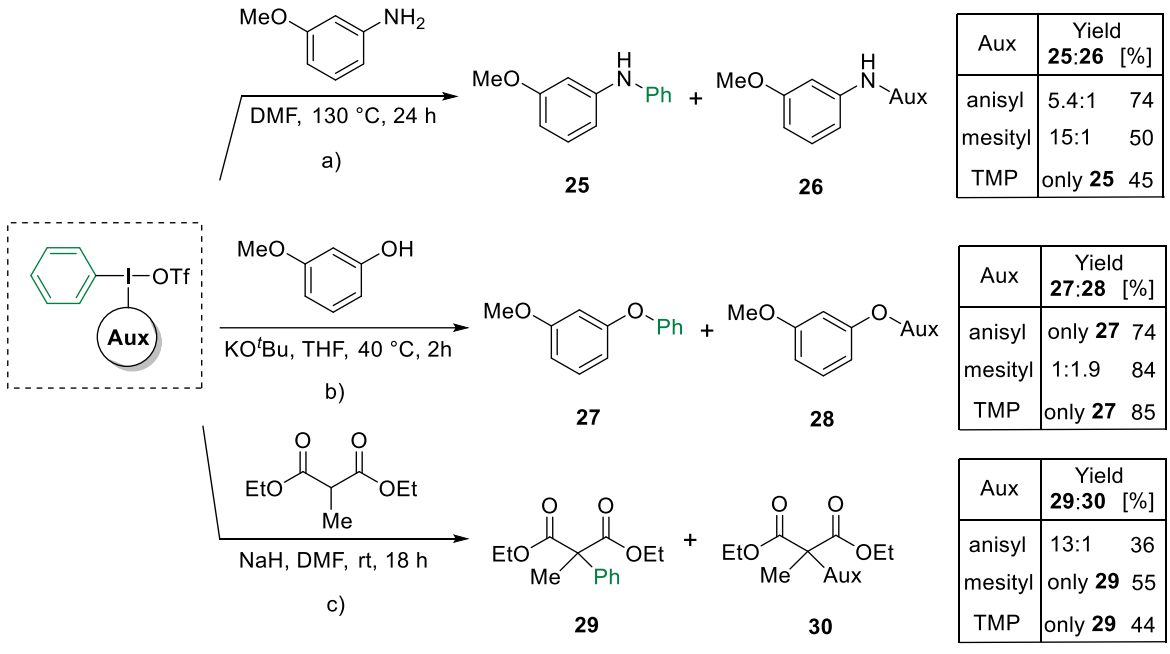
In case of unsymmetrical iodonium salts having *ortho*-substituted aryl groups (mesityl or *o*-tolyl), the nucleophile prefers to undergo selective arylation with the *ortho*-substituted aryl ring, despite the aryl ring being electron-rich. This trend of selectivity can be explained *via* the steric effect developed during the reaction mechanism and the phenomenon is also known as "*ortho effect*" [56]. Because of possible pseudo-rotation, the T-shaped intermediate in this case can be either A or B (Scheme 1.8). In B, the *ortho*-substituted aryl group is in apical position and the steric hindrance between the iodine lone pairs and *ortho*-substituent is much higher in comparison to the scenario in A. Due to this steric factor, the hindered aryl ring resides mostly in the equatorial position and become more accessible to undergo arylation with the nucleophile.



Scheme 1.8 *Ortho*-effect of sterically hindered unsymmetrical iodonium salt

For instance, Olofsson and co-workers reported a detailed study on the chemoselective arylation of various unsymmetrical iodonium salts (auxiliaries i.e., anisyl, mesityl and TMP) with some useful nucleophilic centres (C, N and O

nucleophiles) [57]. The complete selectivity of arylation of unsymmetrical iodonium salt is not solely controlled by electronic and steric factors of iodonium salts, but it also depends on the nature of the nucleophilic centre. In case of aniline derivatives (Scheme 1.9a), the selective phenylation was observed from the iodonium salts containing auxiliaries such as anisyl and TMP and selectivity can be explained from electronic factors. But the *ortho*-effect with mesityl-iodonium salts was not completely exclusive. In contrast, phenolic nucleophiles demonstrated arylation of mesityl group in case of mesityl-iodonium salt and in case of anisyl- and TMP-iodonium salts, it showed selective *O*-phenylation as major product. Surprisingly, an opposite result was observed while using malonate as nucleophile with mesityl-iodonium salts, where the sterically congested mesityl group underwent arylation. This phenomenon is called the anti-*ortho* effect.



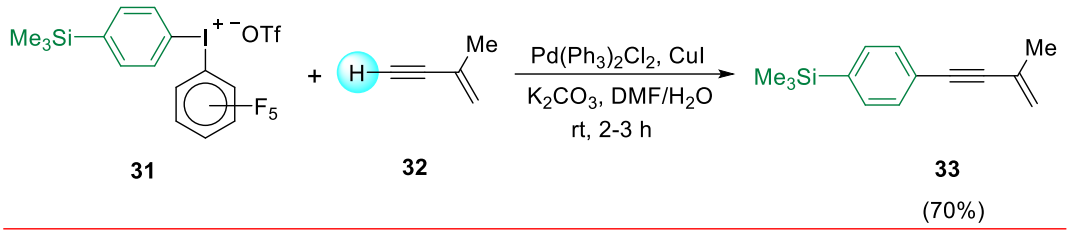
Scheme 1.9 Olofsson's chemoselective arylation study

1.5.2 Under copper-catalyzed conditions

In copper-catalyzed methods for arylation with diaryliodonium salts (mentioned in scheme 1.2b), the mechanistic route is not similar to the metal-free conditions. The T-shaped intermediate (shown in the earlier discussion) has no relevance in metal-catalyzed arylation methods. Instead, the formation of high-valent aryl-Cu(III) species is vital [58] and thus, selectivity patterns for unsymmetrical iodonium salts

with auxiliaries are quite different. From existing literature [59], the general trend of aryl selectivity under copper-catalyzed route: the electron-rich Ar substituents have higher selectivity over the electron-deficient Ar group from an unsymmetrical iodonium salt.

For example, Stang and co-workers demonstrated a methodology of alkyne-iodonium coupling of unsymmetrical iodonium salt **31** having both EDG and EWG, where the ED aryl group with trimethylsilyl group (TMS) selectively transferred to afford the product **33** (Scheme 1.10) [60].



Scheme 1.10 Selective arylation under metal-catalyzed conditions

Another opposite trend of chemoselectivity in copper-catalyzed reaction conditions is observed with (mesityl)(aryl)iodonium salts or mesityl-iodonium salts, (Ar(Mes)IX) [61-64]. The phenomenon is known as anti-*ortho* effect, where the other functionalized aryl groups easily transfer to the nucleophile, unlike that the transfer of sterically hindered mesityl group to the nucleophile under metal-free conditions.

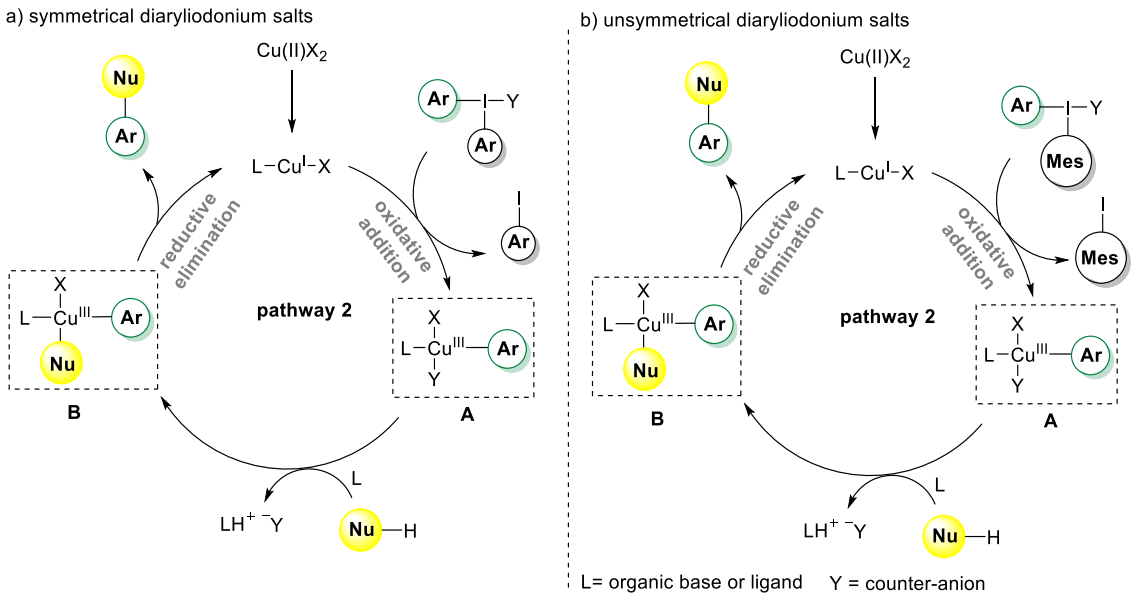
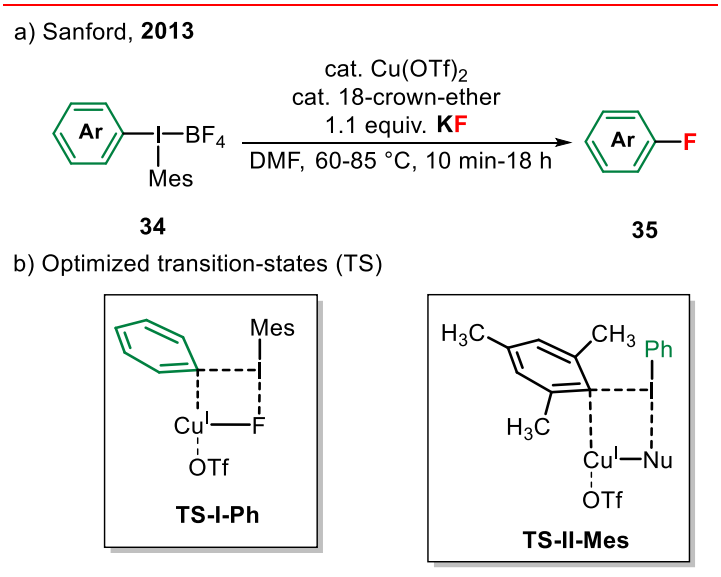


Figure 1.8 General mechanism for copper-catalyzed arylation

The general mechanism of copper- catalyzed arylation with diaryliodonium salts is illustrated in Figure 1.8. In both the cases, the mechanism is proceeded *via* the Cu^{I}/Cu^{III} catalytic cycle. The Cu(I) catalyst reacts with the diaryliodonium (Ar^1Ar^2X) salt and undergoes an oxidative addition to form highly electrophilic $Cu^{III}(Ar)$-species [65]. In presence of a nucleophile (Nu), the nucleophile generates the intermediate $Cu^{III}(Ar)(Nu)$ by reacting with aryl-Cu^{III} species and later, reductive elimination produces Ar-Nu product. In case of symmetrical type, there is only a single choice for arylation.

Further, the selective arylation from Ar(Mes)IX was explained by Sanford and co-workers using both experimental and density functional theory (DFT) investigations [66]. They reported a method for Cu-catalyzed fluorination using KF as fluoride source from unsymmetrical iodonium salts, $[Ar(Mes)I]BF_4$ (Scheme 1.11). As mentioned in their DFT study, the transition state **TS-I-Ph** is one of the crucial steps in their plausible mechanistic pathway (Scheme 1.10). They observed significant enhancement of energy in the transition state **TS-II-Mes** by 2.6 kcal/mol in comparison to **TS-I-Ph** because of the unfavourable steric hindrance experienced between the Cu atom and 2,6-dimethyl group of mesityl.



Scheme 1.11 Sanford's fluorination method using $Ar(Mes)IBF_4$

1.6 Synthesis of Diaryliodonium Salts

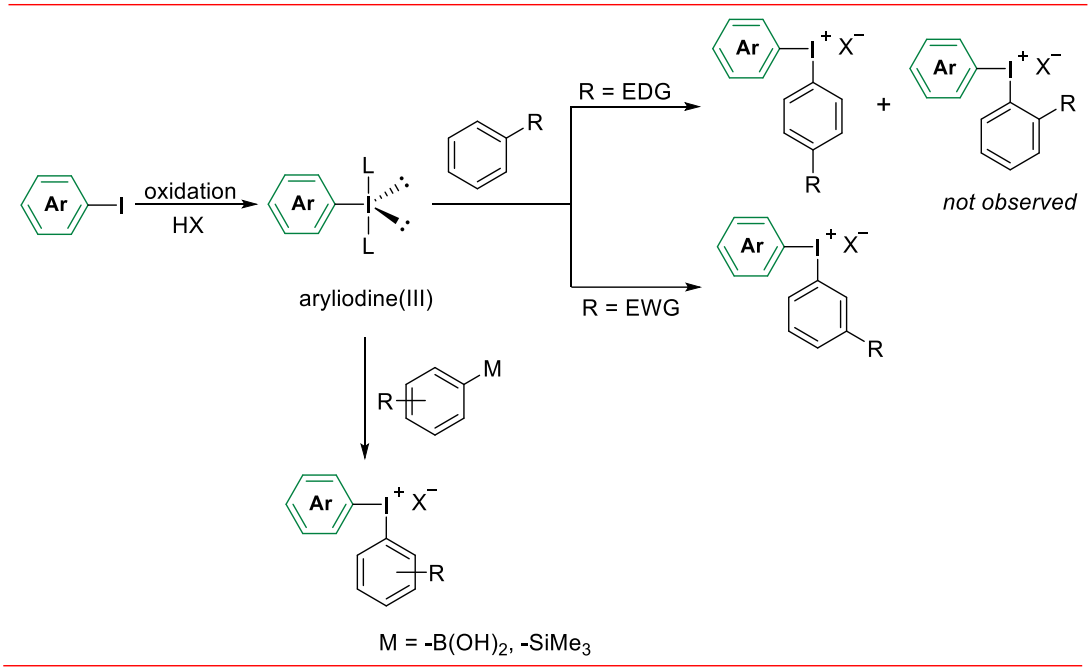
Till date, numerous methods have been developed for the synthesis of both symmetrical and unsymmetrical diaryliodonium salts. However, the following three approaches are usually noticed:

i. From aryl iodides and arenes: Relevant for symmetrical and unsymmetrical iodonium salts

ii. Using both aryl iodides and arylating organometallic reagent (aryl boronic acid, aryl silane, aryl stannane etc.): This method is applicable for both symmetrical and unsymmetrical iodonium salts. Arylboronic acids are preferable compared to the corresponding silanes and stannanes due to their high reactivity and low toxicity.

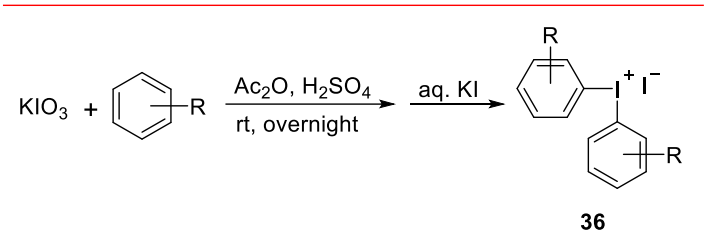
iii. Directly from iodine (I_2) and arenes: Especially for symmetrical types

Among the all reported methods, the formation of *in-situ* aryliodine(III) compounds or species is common in most cases [67]. In general, the aryl iodide is converted to iodine(III) species with appropriate oxidant under acidic or neutral conditions, followed by an electrophilic aromatic substitution (EAS) with suitable arenes or arylboronic acids leading to the formation of diaryliodonium salts (Scheme 1.12). The counter-anion generally comes from the acidic solution used and later, it can be exchanged with another desirable counter-anion. While utilizing arenes as coupling partners, electron-donating (ED) arenes are always preferred as it can easily undergo the EAS mechanism. Though ED arenes can interact with the iodine(III) centre *via ortho*- or *para*- position, the incorporation *via para*-position is mostly noticed. Reaction with electron-withdrawing (EW) arenes is less efficient for EAS mechanism and therefore, EW arenes are rarely used. If an unsymmetrical iodonium salt is to be designed with an EW aryl group, it is always desirable to choose the EW aryl fragment from corresponding aryl iodide to synthesize the aryliodine(III) compound, followed by EAS with an ED arene. When aryl boronic acids are utilized as coupling partners in replacement of arene, the choice of synthesis both symmetrical and unsymmetrical iodonium is broad in scope and arylboronic acids having *ortho*-, *meta*- and *para*-substituents can be applied in regiospecific manner. This synthetic route is mostly used for symmetrical types. Though the protocol is wider in scope, the approach is not economical as it involves both aryl iodides and aryl boronic acids.



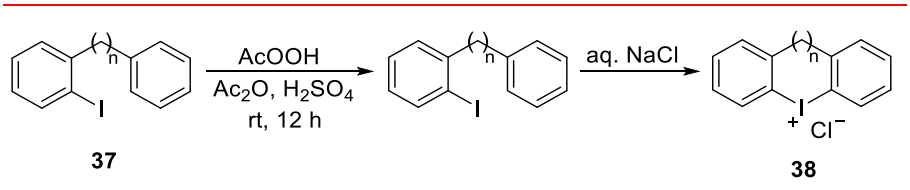
Scheme 1.12 General pathways for the synthesis of diaryliodonium salts

The earlier methods for synthesis of diaryliodonium salts involved either two- or three steps. However, the one-pot synthesis from aryl iodide is the most economical approach. In 1953, Beringer et al. developed a one-pot protocol for the synthesis of symmetrical iodonium salts **36** using potassium iodate both as oxidant and iodine source (Scheme 1.13) [68].



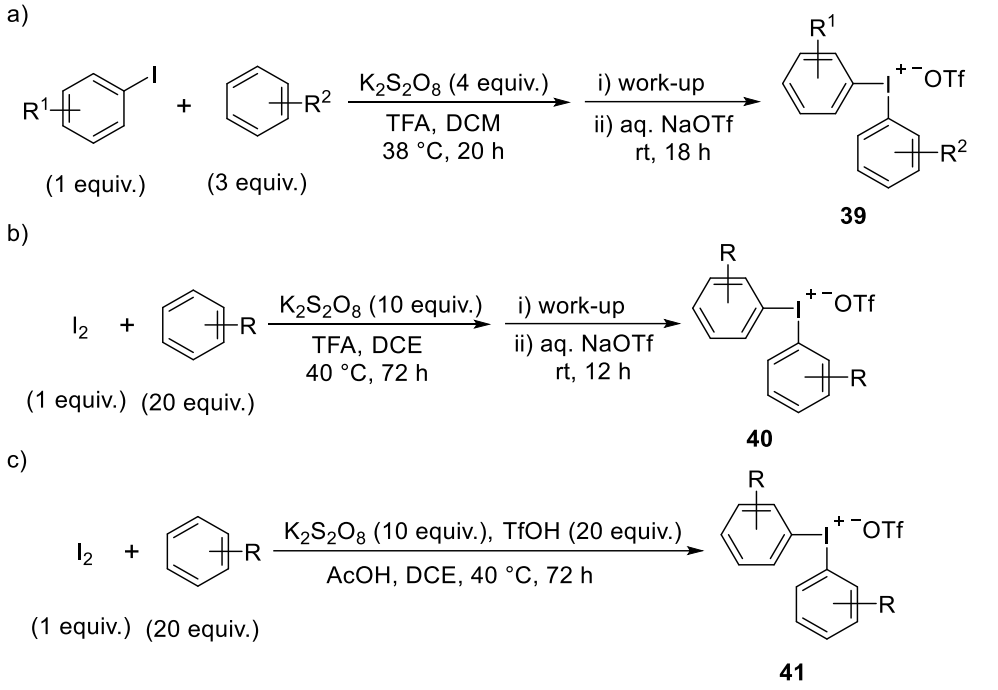
Scheme 1.13 Beringer's method for symmetrical diaryliodonium iodide

Similarly, Sandin and co-workers used peracetic acid as oxidant to synthesize cyclic iodonium salts **38** from 2-iodobiphenyl and similar analogues **37** (Scheme 1.14) [69].

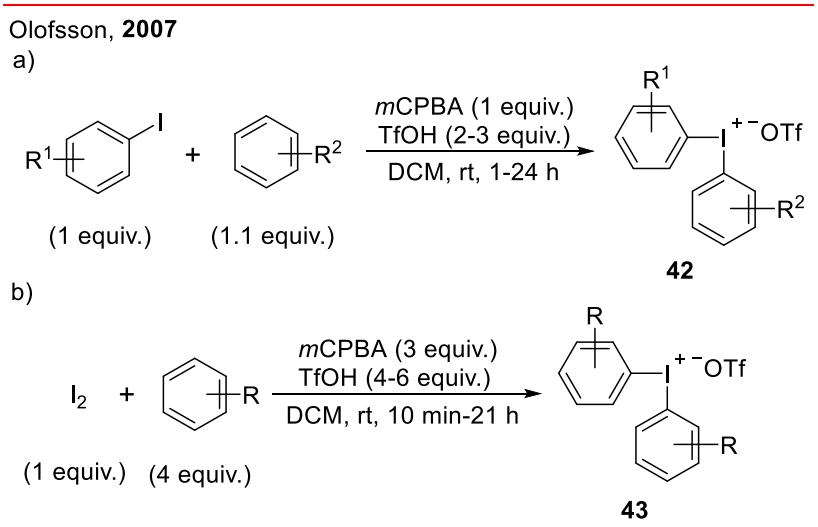


Scheme 1.14 Sandin's method for cyclic iodonium salts

Although, many reports were developed during that period by utilizing various oxidant, Kitamura's group and Olofsson's group independently developed a series of efficient one-pot methods to access iodonium salts. Kitamura and co-workers utilized potassium persulfate and trifluoroacetic acid, followed by anion-exchange to obtain the iodonium triflate salts (Scheme 1.15) [70]. The limitations of this method were the requirement of excess reagents and resistance towards electron-deficient aryl iodides.



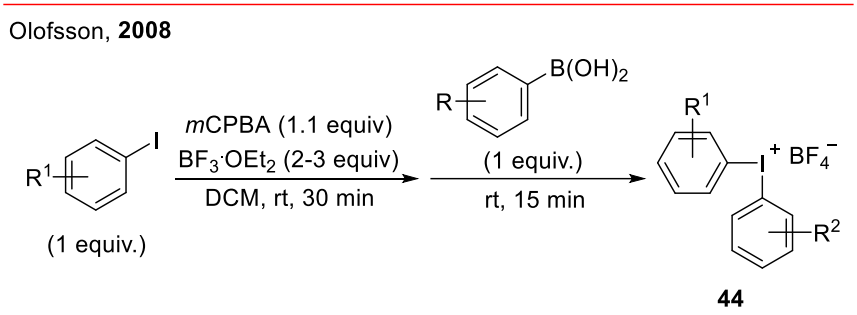
Scheme 1.15 Kitamura's one-pot methods



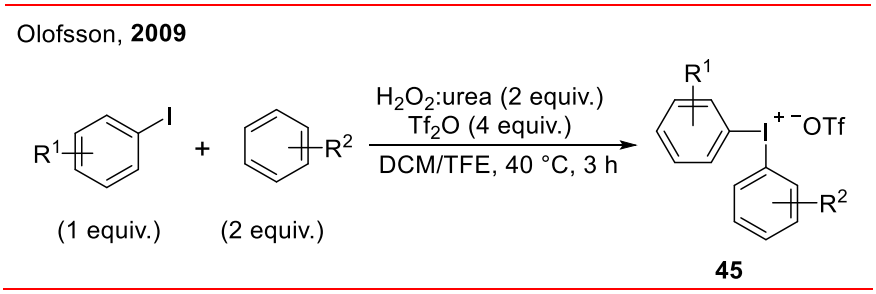
Scheme 1.16 Olofsson's first report on diaryliodonium salts

Subsequently, Olofsson and co-workers published a cost-effective and versatile method from aryl iodide and arenes where they applied *meta*-chloroperbenzoic acid (*m*-CPBA) in combination with triflic acid (Scheme 1.16a) [71-72]. The methodology was extended to synthesize symmetrical iodonium salts directly from iodine and electron-rich arenes (Scheme 1.16b).

Due to overoxidation of ED aryl iodide in presence of triflic acid, the same group developed another methodology with a milder acid, *p*-toluenesulfonic acid (TsOH) *via in-situ* formation of Koser's reagent, followed by anion-exchange method to give the desired counter-anion [73]. The regiospecific method was developed using aryl boronic acid as coupling partners and this methodology was extremely useful to synthesize symmetrical iodonium salts with *ortho*- and *meta*-substituents (Scheme 1.17) [74]. Another useful protocol was developed using urea-hydrogen peroxide as the environmentally benign oxidizing agent (Scheme 1.18) [75].

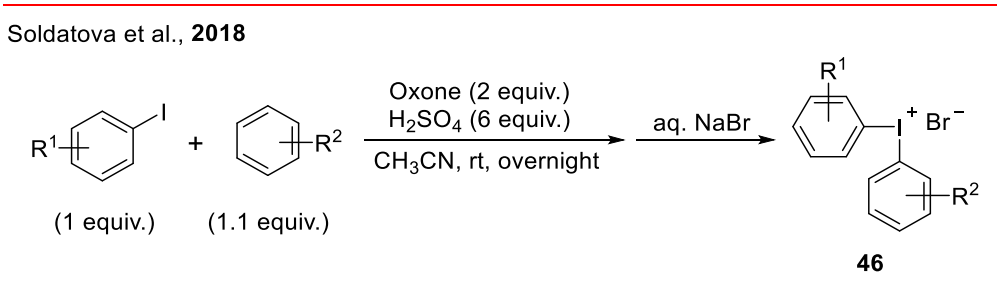


Scheme 1.17 Regiospecific method with aryl iodides and arylboronic acids



Scheme 1.18 Urea-hydrogen peroxide as oxidizing agent

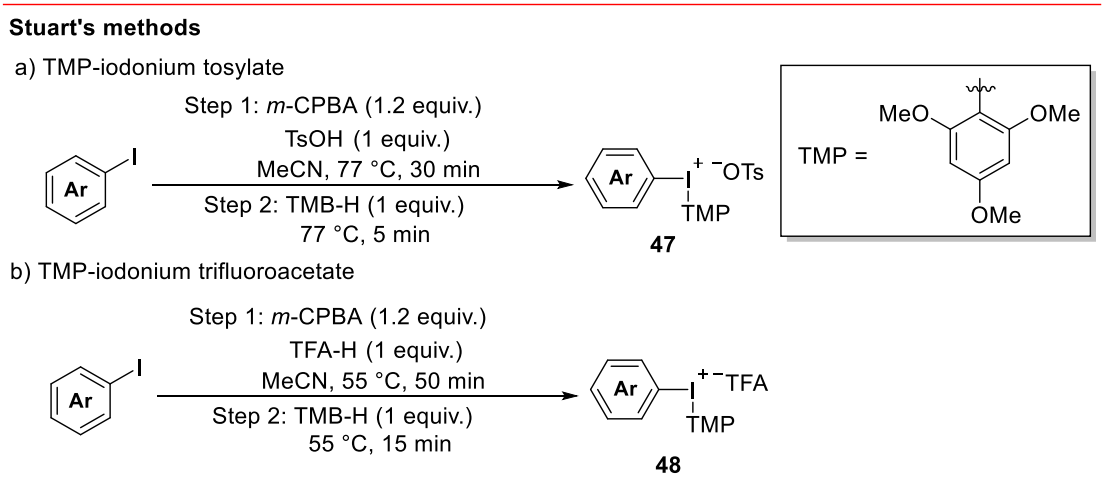
In 2018, Soldatova et al. introduced another methodology using oxone as oxidizing agent and this method provided the synthesis of diaryliodonium bromide **46** having identical or non-identical aryl rings (Scheme 1.19) [76].



Scheme 1.19 Utilizing oxone as oxidizing agent for diaryliodonium bromide

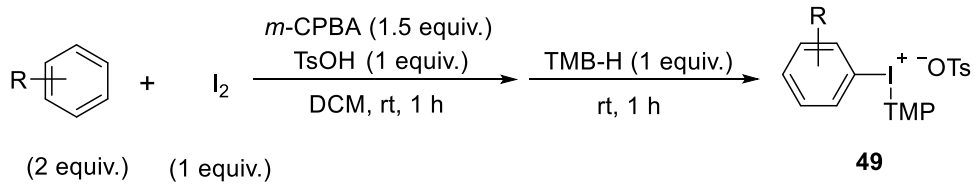
Auxiliary based unsymmetrical iodonium salts containing anisyl (An)- and mesityl (Mes)-iodonium salts can be synthesized mostly utilizing the scheme 1.16(a), however, modifications were required for better yields.

Stuart and co-workers reported an excellent modified protocol for one-pot access to unsymmetrical iodonium salt having 2,4,6-trimethoxyphenyl (TMP) auxiliary. Their group published two consecutive methods for the synthesis of TMP-iodonium salts with two different counter-anions: one containing tosylate (OTs) (Scheme 1.20a) [77] and another containing trifluoroaceate (TFA) (Scheme 1.20b) [78-79].



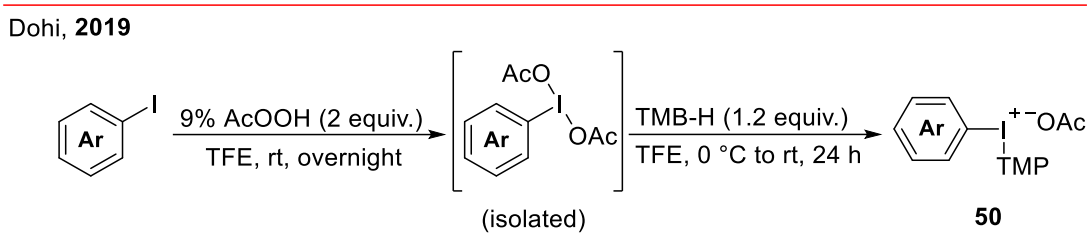
Scheme 1.20 Stuart's one-pot methods for TMP-iodonium salts

Subsequently, Olofsson's group developed a direct route from arenes and I_2 for the synthesis of TMP-iodonium salts (Scheme 1.21). This method could easily convert the ED arenes into unsymmetrical iodonium salt; however, earlier methodologies using the I_2-arene were generally utilized for symmetrical salts [80].



Scheme 1.21 Olofsson's method for TMP-iodonium salts from I_2-arenes

Dohi and co-workers reported another efficient method for TMP-iodonium salts having acetate as a counter-anion, a new version of TMP-iodonium salts (Scheme 1.22). This two-step procedure required isolation of the intermediate (diacetoxyiodo)arene [81].



Scheme 1.22 Synthesis of TMP-iodonium acetate

1.7 Metal-Free Arylation Methods with Diaryliodonium Salts

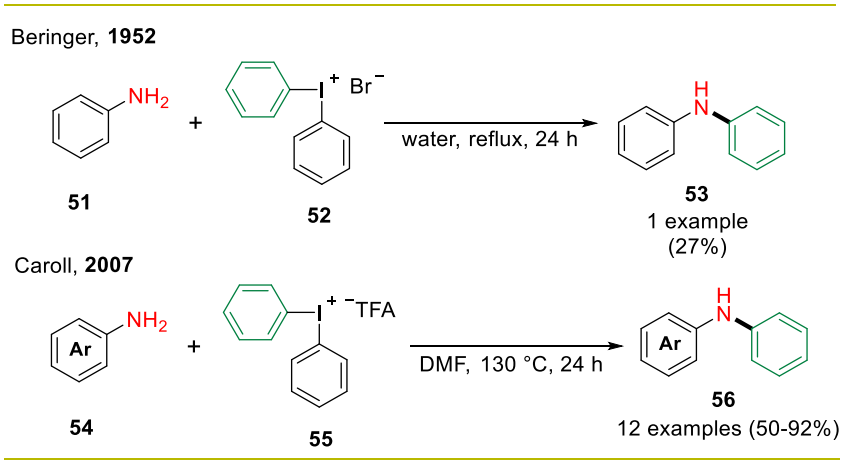
Pioneered by Beringer back in 1950s, the applications of diaryliodonium salt for arylation reactions with diverse nucleophiles have been in use for more than 90 years [33]. As earlier methods by Beringer were mostly in refluxing condition under water or methanol and exhibited limited scope for aryl substrates, now-a-days arylation studies are concerned with utilization of efficient unsymmetrical iodonium salts with proper auxiliary and mild reaction conditions. As my thesis work focuses on arylation of heteroatomic nucleophiles, the following discussion highlights the important methodologies using both symmetrical and unsymmetrical iodonium salt.

1.7.1 Arylation of Nitrogen Nucleophiles

1.7.1.1 *N*-arylation of amines

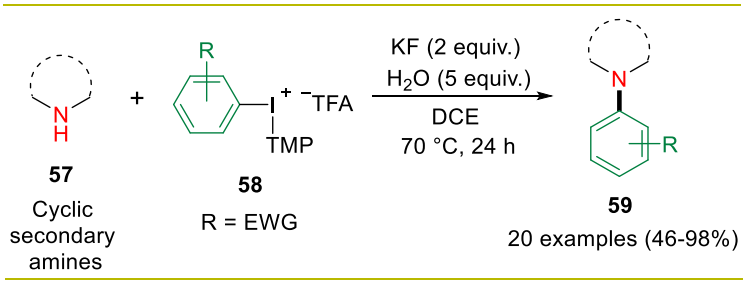
In 1952, Beringer and co-workers mentioned that diphenyliodonium bromide would be used for *N*-arylation of aniline, piperidine and dimethylamine under harsh conditions (Scheme 1.23) [33]. Later, Caroll and Wood published a base-free method where they demonstrated substantial examples of anilines **55** for *N*-arylation with diphenyliodonium trifluoroacetate. In addition, the electronic and steric effect of the

unsymmetrical iodonium salts having anisyl- and mesityl-auxiliaries were studied (as mentioned in scheme 1.9) [82]. Recently, the same methodology was revisited in a mechanochemical version under much mild conditions [83].



Scheme 1.23 Early reports on *N*-arylation of anilines

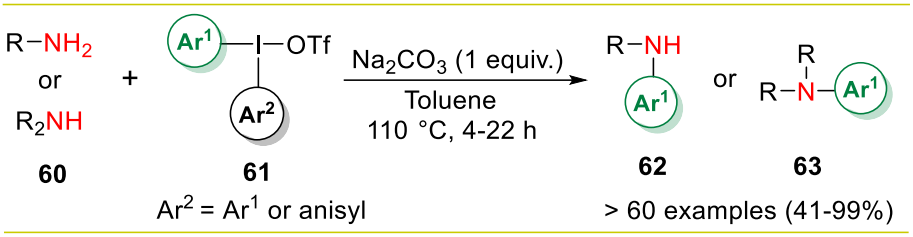
Stuart and co-workers achieved a breakthrough by providing a highly efficient chemoselective arylation method for *N*-arylation of secondary cyclic amines (Scheme 1.24). The method solely utilized unsymmetrical iodonium salts i.e., TMP-iodonium salts in presence of KF as an additive [84]. Though the mechanism of reaction was not fully understood, it was speculated that the hydrogen-bond formation between the amine N-H and fluoride anion could have assisted the mild activation of amine.



Scheme 1.24 Stuart's metal-free *N*-arylation of cyclic amines

As the Stuart's method is very selective for cyclic secondary amines, the Olofsson group reported a transition-metal free arylation method for both primary and secondary amines (Scheme 1.25) [85]. The explored amines were wider in scope, including primary amine (aliphatic and aromatic) and secondary amines (acyclic and cyclic). The used diaryliodonium salts were mostly symmetrical iodonium salts and

unsymmetrical anisyl-iodonium salts. Broad scope of both ED and EW aryl groups were explored.

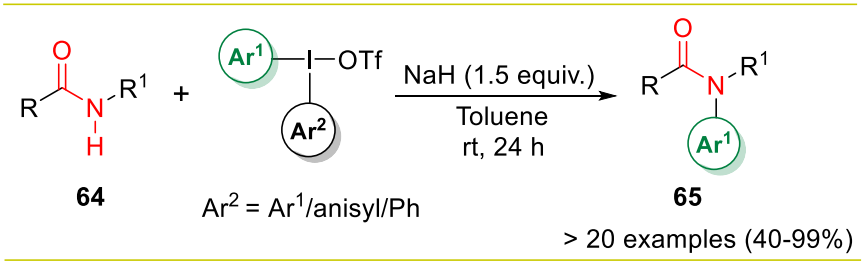


Scheme 1.25 Olofsson's method for *N*-arylation of primary and secondary amines

Apart from these reports, methodologies were developed with diaryliodonium salts as a facile arylating partner for *N*-arylation of the other substituted amines like ammonia, tertiary amines, DABCO etc. [86-90].

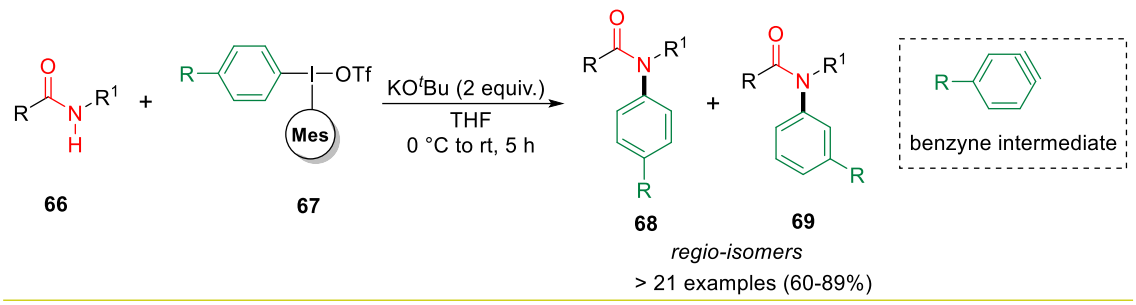
1.7.1.2 *N*-arylation of amides and imides

Even though some early reports were known for metal-free arylation of amides [91-92], Olofsson's group published a mild and metal-free *N*-arylation method for secondary acyclic amides (Scheme 1.26) using sodium hydride as base [93]. In their report, the aryl scope was explored mostly from symmetrical iodonium salts, and few EW aryl groups were incorporated utilizing anisyl- and phenyl- as auxiliaries. The mechanism of the reaction obeyed the formation of conventional T-shaped intermediate.



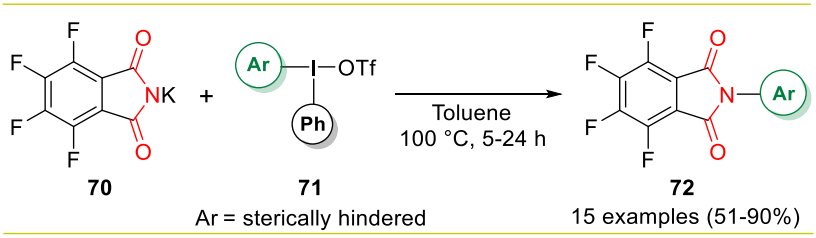
Scheme 1.26 Olofsson's method for *N*-arylation of amides

Shortly after, Wang mentioned a similar method for the *N*-arylation of secondary amides from the unsymmetrical aryl(mesityl)iodonium salts at room temperature (Scheme 1.27) [94]. They used KO^{t}Bu as base and observed the formation of regiomers of *N*-arylated products **60** and **61**. The formation of benzyne intermediate in the reaction mechanism was proved experimentally by showcasing the cycloaddition product with furan.



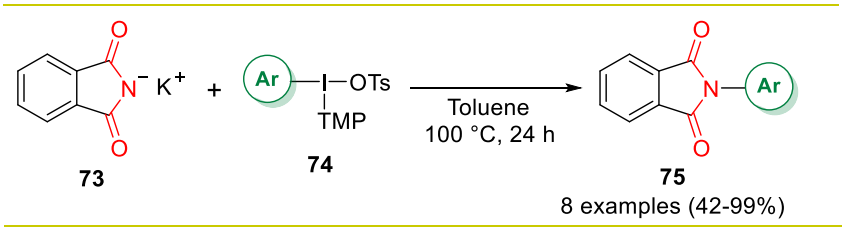
Scheme 1.27 Diaryliodonium salts as benzyne precursor for *N*-arylation of amides

In 2016, Muñiz and co-workers came up with a method for C-N bond formation between potassium tetrafluorophthalimide and unsymmetrical iodonium salt containing sterically hindered aryl rings (Scheme 1.28) [49]. The *ortho*-effect of unsymmetrical iodonium salts was demonstrated very vividly in this, as the bulky aryl group was incorporated. The method allowed the synthesis of sterically hindered *N*-arylated imide and subsequently, the deprotection led to the access of 2,6-disubstituted anilines, which are pharmaceutically relevant building blocks.



Scheme 1.28 Synthesis of sterically hindered *N*-arylated substituted phthalimide

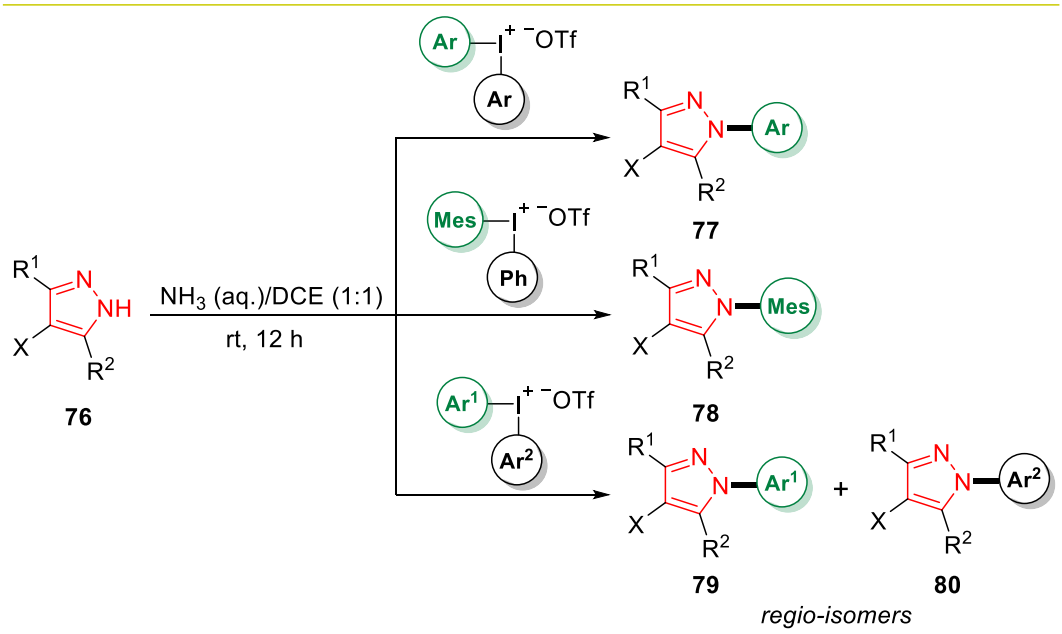
Stuart's group also published a protocol using unsymmetrical TMP-iodonium salts as an arylating partner for *N*-arylation of phthalimide (Scheme 1.29) [95]. The methodology demonstrated efficient chemoselective transfer of both electron-deficient and sterically encumbered aryl groups from the aryl (TMP)iodonium tosylates.



Scheme 1.29 Utilizing TMP-iodonium salt for *N*-arylation phthalimide

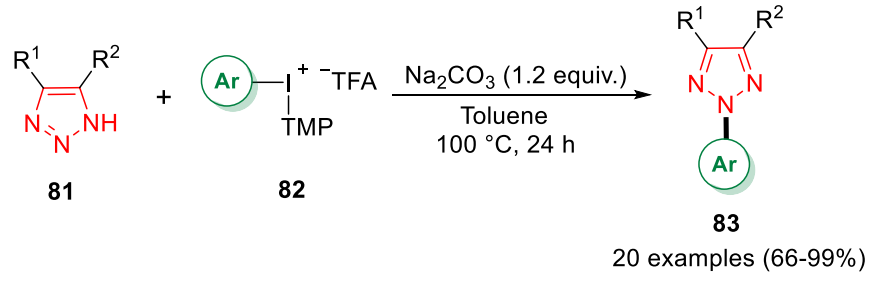
1.7.1.3 *N*-arylation of heterocycles

The metal-free strategies for *N*-arylation have been developed with various *N*-heterocycles too. The development was based on the implementation of symmetrical and aryl(auxiliary)iodonium salts [96-97]. In 2015, the Novak group introduced a straightforward protocol for *N*-arylation of symmetrical pyrazoles under mild and metal-free conditions (Scheme 1.30) [98]. The study included detailed analysis on the chemoselective arylation pattern of various unsymmetrical iodonium salts. The general *ortho*-effect of mesityl-iodonium salts prevailed and afforded *N*-mesitylated pyrazoles **78**. Moreover, various symmetrical iodonium salts were explored to demonstrate the arylation scope.



Scheme 1.30 *N*-arylation of symmetrical pyrazoles with diaryliodonium salts

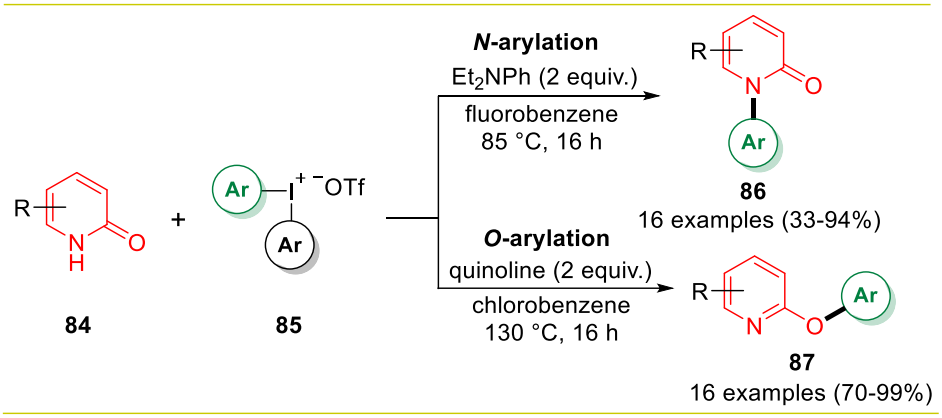
1,2,3-triazoles having a free N-H was transformed to the corresonding N^2-aryl-1,2,3-triazoles by Prakash and co-workers utilizing aryl(TMP)iodonium trifluoroacetate



Scheme 1.31 N^2-arylation of 1,2,3-triazoles

under mild basic conditions (Scheme 1.31) [99]. The methodology was highly regioselective and applicable to diverse 1,2,3-triazoles and iodonium salts. The mechanistic insights of the regioselectivity were further described by DFT investigations.

Onomura and co-workers published base-dependent switchable *N*- and *O*-arylation methods of pyridin-2-ones with diaryliodonium salts (Scheme 1.32) [50]. Selective *N*-arylation products required *N,N*-diethylaniline in fluorobenzene and trace amounts of *O*-arylated products were formed too. The T-shaped intermediate showing N-I bonding was isolated from the reaction between pyridin-2-one and diphenyliodonium triflate.

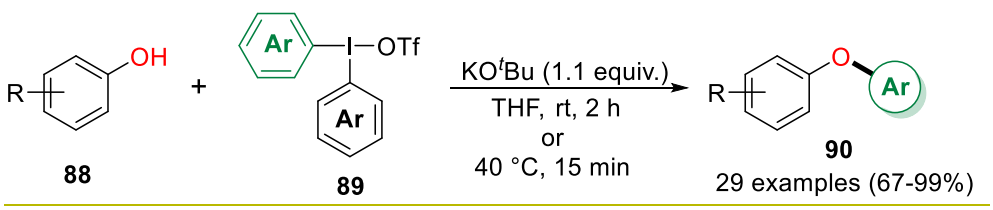


Scheme 1.32 *N*- and *O*-arylation of pyridin-2-ones

1.7.2 Arylation of Oxygen Nucleophiles

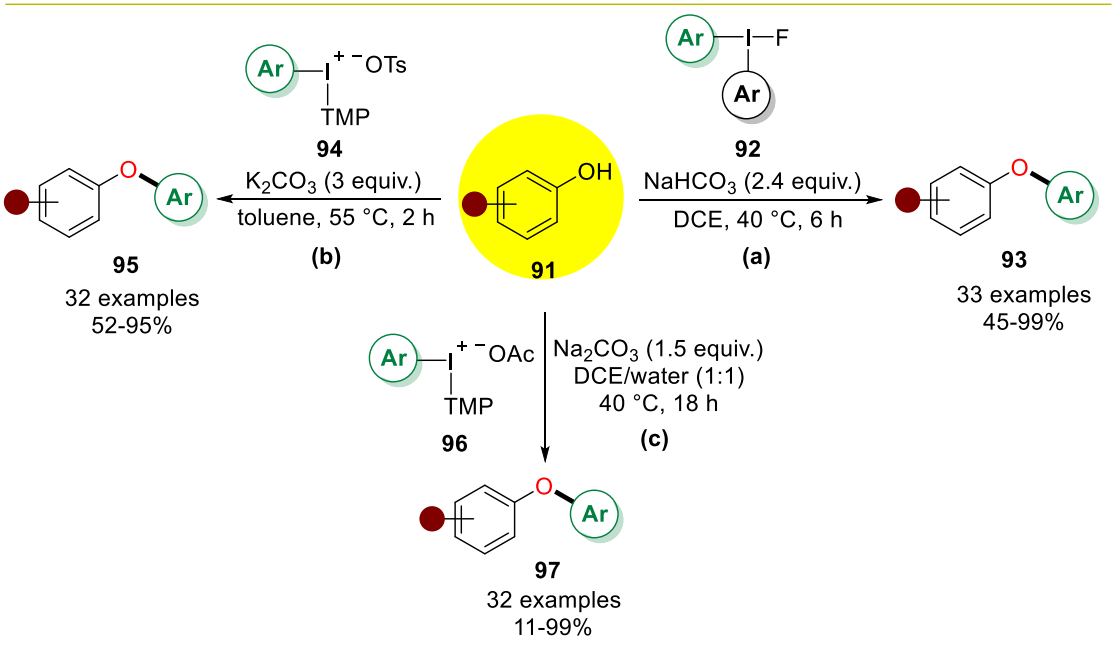
1.7.2.1 *O*-arylation of phenols

Beringer applied diphenyliodonium bromide with phenoxide anion under refluxing methanol and reported first example of diaryliodonium salt-based *O*-arylation of phenol in 1952 [33]. After the seminal reports on the synthetic procedures of the diaryliodonium salts, Olofsson's group reported a quick and high-yielding *O*-arylation method for phenol with symmetrical diaryliodonium salts (Scheme 1.33) [100]. The arylation method was demonstrated with a series of substituted phenols



Scheme 1.33 *O*-arylation of phenol by Olofsson's method

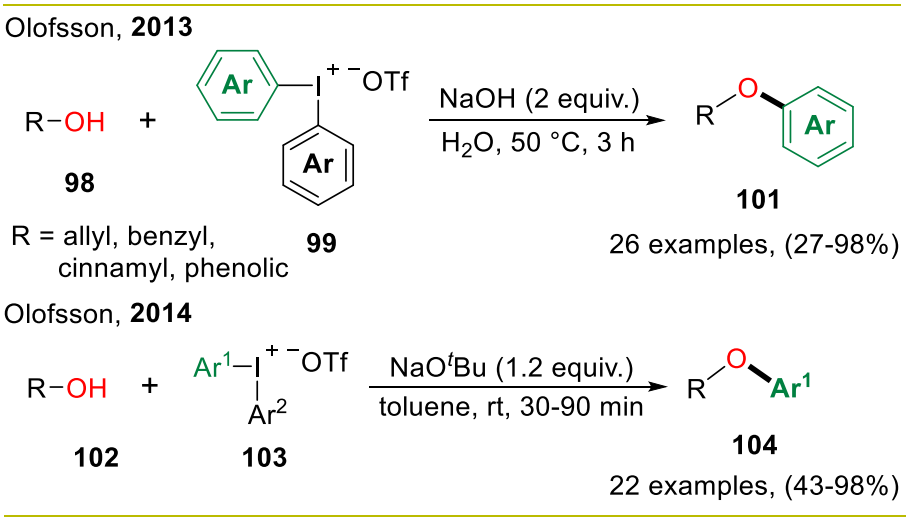
and diverse functionalized aryl moieties. Even chiral amino acids possessing phenolic scaffolds were exemplified and the arylation underwent without any racemization. Later, few other reports were developed based on counter-anion effects and selection of auxiliary of unsymmetrical iodonium salts. Gaunt's group improvised the symmetrical iodonium salt-based method with the influence of fluoride counter-anion and facilitated the reaction with a very weak base, $NaHCO_3$ (Scheme 1.34a) [101]. Stuart and co-workers used aryl(TMP)iodonium tosylates and developed the *O*-arylation method for phenol derivatives (Scheme 1.34b) [102]. The most recent method in this field was described by Dohi's group where they utilized newly discovered TMP-iodonium acetate (Scheme 1.34c) [103]. The methodology proposed that both TMP group and acetate counter-anion cooperatively assisted to enhance the electrophilicity of the iodonium salt towards phenol nucleophile.



Scheme 1.34 Other methods for *O*-arylation of phenols

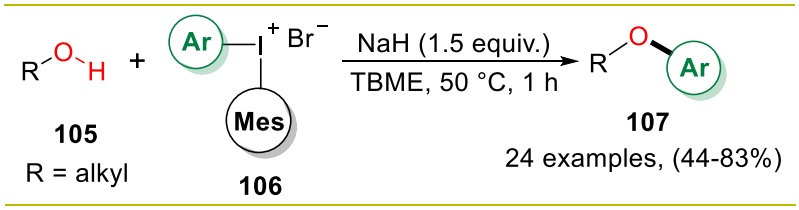
1.7.2.2 *O*-arylation of alcohols

Like phenol, the Olofsson group published two seminal reports on *O*-arylation of alcohols (benzylic, allylic, cinnamylic etc.). These reports implemented only symmetrical iodonium salts as major aryl precursors (Scheme 1.35a,b) [104-105]. In addition, they reported another robust protocol for the synthesis of sterically congested alkyl aryl ethers by implementing both bulky alcohols and aryl(auxiliary)iodonium salts [106].



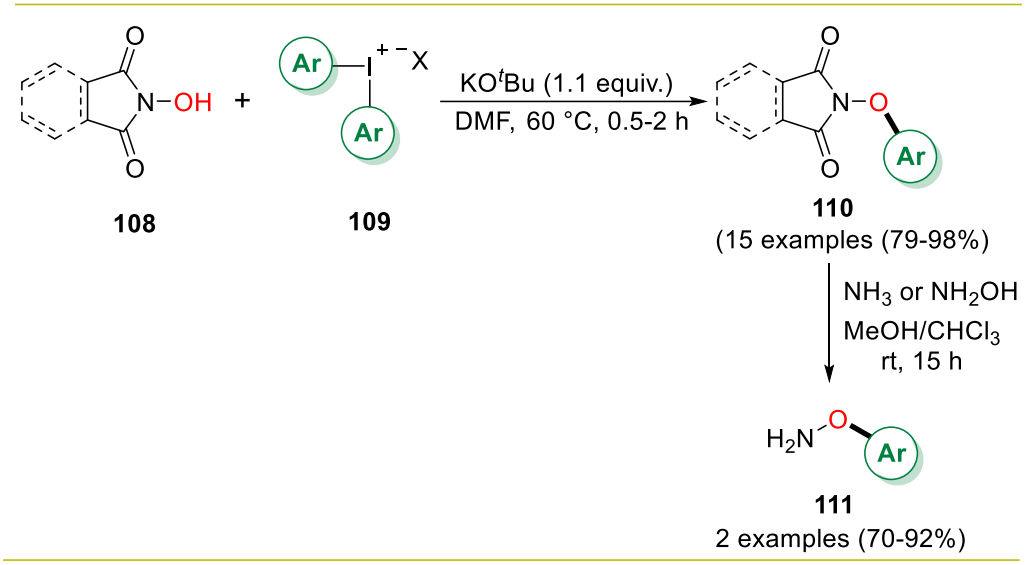
Scheme 1.35 *O*-arylation of various alcohols with diaryliodonium salts

The aryl(mesityl)iodonium bromide was explored by Stuart group to access diverse industrially important alkyl-aryl ethers (Scheme 1.36) [107]. The methodology was operationally simple and exhibited excellent chemoselective arylation from mesityl-iodonium salts. The synthetic utility of the method was further illustrated with the synthesis of bio-active ether fragment of pioglitazone, an ingredient for antidiabetic.



Scheme 1.36 Stuart's method with aryl(mesityl)iodonium bromide

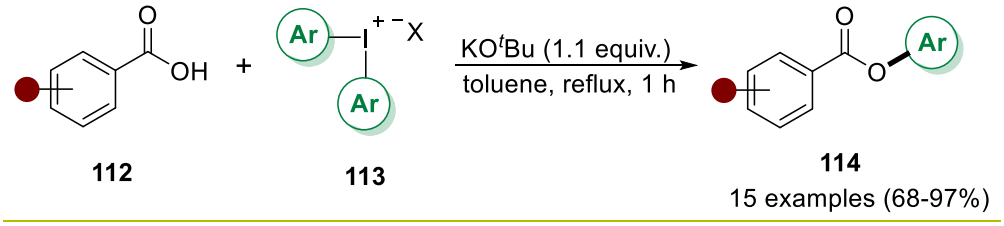
The mild and metal-free *O*-arylation method was further established with *N*-hydroxyimides by Olofsson's group too [108]. The major scope of arylation was discussed with symmetrical iodonium salts. In addition, the chemoselective arylation pattern of various unsymmetrical iodonium salts was also systematically mentioned. The method demonstrated synthetic usefulness to access aryloxyamines **110** after hydrolysis of the *O*-arylated products **111** (Scheme 1.37).



Scheme 1.37 *O*-arylation of *N*-hyroxysuccinimide and *N*-hydroxyphthalimide

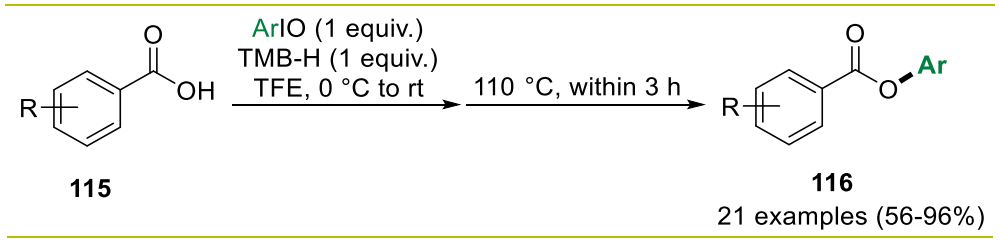
1.7.2.3 *O*-arylation of carboxylic acids

During the period of their synthesis and application of diaryliodonium salts, Olofsson's group investigated the *O*-arylation of carboxylic acid, and they published a metal-free and indirect approach to obtain aryl esters without performing amidation of carboxylic acid (Scheme 1.38) [109]. The protocol was explored with both aliphatic and aryl carboxylic acid scaffolds and symmetrical iodonium salts were used to establish arylation scope.



Scheme 1.38 Symmetrical iodonium salt-based *O*-arylation of carboxylic acid

The Dohi group later devised an indirect protocol by using iodosoarenes (ArIO) as arylating source and 1,3,5-trimethoxybenzene as promotor for the *in-situ* synthesis



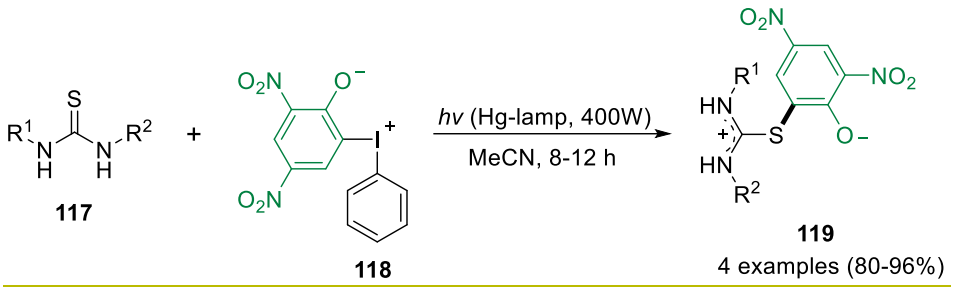
Scheme 1.39 Unsymmetrical iodonium salt-based *O*-arylation of carboxylic acid

of unsymmetrical iodine(III)-species followed by *O*-arylation of carboxylic acids (Scheme 1.39) [110]. Both EDG and EWG containing iodosoarenes were easily executed under the reaction conditions and provided highly functionalized aryl esters.

1.7.3 Arylation of Sulphur Nucleophiles

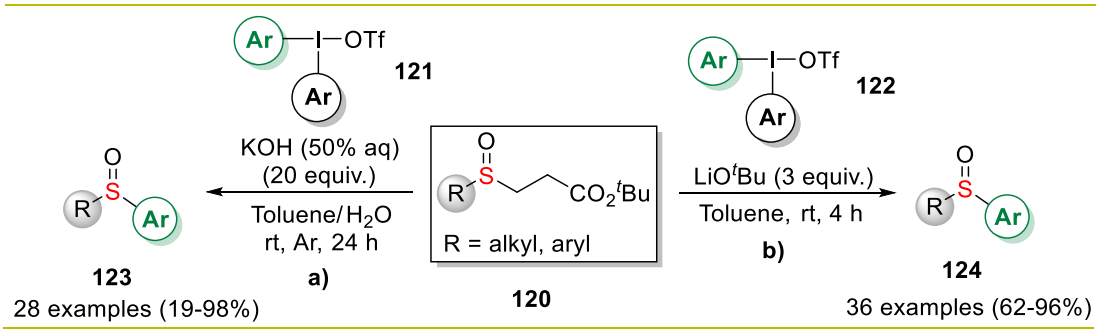
Sulphur nucleophiles are highly reactive and many metal-free protocols to obtain *S*-arylation with diaryliodonium salts have been reported. Important literature on previous methods of metal-free *S*-arylation of thiols with diaryliodonium salts are related to my work in chapter 3 of this thesis and has been discussed there.

In 1989, Varvoglis and co-workers utilized oxidodiaryl iodonium zwitterions with substituted thiourea derivatives and *S*-arylation of the iodonium salt generated thiourenium zwitterions (Scheme 1.40) [111].



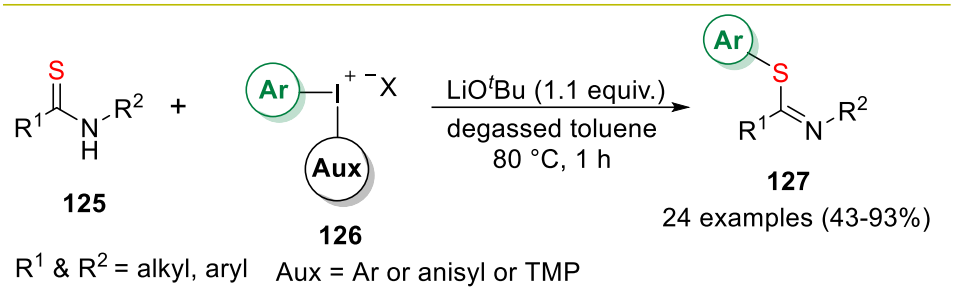
Scheme 1.40 Ding's method for *S*-arylation of aryl thioureas

Bolm's group and Zhang's group independently published *S*-arylation of sulfenate anion with diaryliodonium salts (Scheme 1.41a&b) [112-113]. In both the methodologies, the sulfenate anion was generated *in-situ* from β-sulfinyl esters with their corresponding basic conditions and synthesized a library of *S,S*-diaryl and *S*-alkyl *S*-aryl sulfoxides.



Scheme 1.41 *S*-arylation of sulfenates

Olofsson's group developed a method for synthesis of aryl thioimidates by reacting secondary thioamides with diaryliodonium salts in a transition-metal free approach (Scheme 1.42) [114]. The synthetic procedure allowed selective *S*-arylation in case of acyclic secondary amides. However, *N*-arylation was observed in case of cyclic secondary thioamide.



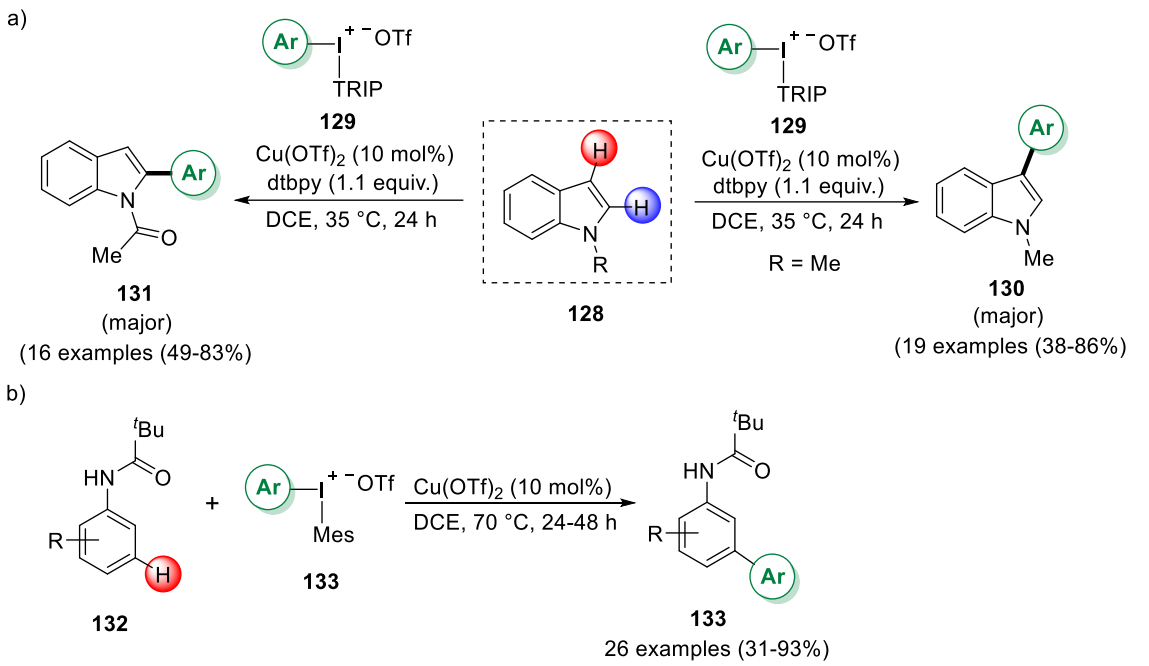
Scheme 1.42 Chemoselective *S*-arylation of thioamides

1.8 Copper-Catalyzed Arylation Methods with Diaryliodonium Salts

The reactivity of the nucleophilic site generally determines the choice of arylation methodology. Copper-catalysed methods with diaryliodonium salts have been explored as effective methodologies for nucleophiles, which are non-reactive under metal-free conditions. This section only highlights some important early and present developments under copper-catalysis, as two chapters (chapters 4 & 5) in this thesis address arylation methods with copper-catalysis and diaryliodonium salt.

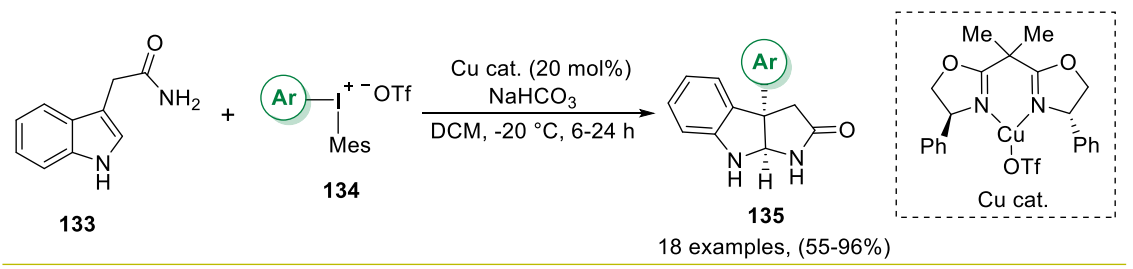
1.8.1 C-H Arylation

In 2008, Gaunt and co-workers pioneered the combination of diaryliodonium salts under Cu(II)-catalysis for C-H functionalization (Scheme 1.43). The free N-H or N-Me indoles delivered chemoselective arylation from TRIP-iodonium salts at C3-position of the indole. However, acetyl-protected indoles showed site-selective arylation at C2-position (Scheme 1.43a) [65]. Another ground-breaking work by Gaunt's group was *meta*-arylation of aniline derivatives by utilizing the reactivity of Cu(III)-aryl species (Scheme 1.43b) [115]. The carbonyl-protected aniline derivatives exhibited unique reactivity, and *meta*-C-H bond activation proceeded *via* dearomatizing oxy-cupration. Subsequently, this research group contributed many significant C-H functionalization methods of important organic building blocks [116-119].



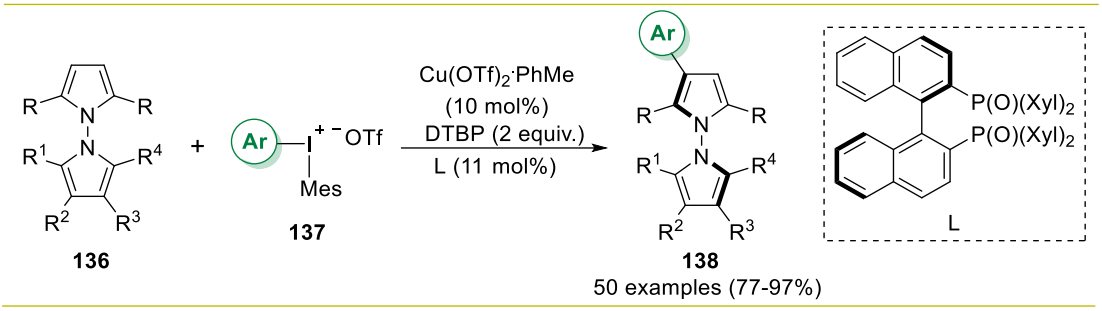
Scheme 1.43 a) C-H arylations of indoles, and b) *m*-arylation of aniline derivatives

In 2012, McMillan's group extended the application of Cu(III)-aryl moiety and synthesized C(3)-aryl pyrroloindoline skeletal from indole acetamide derivatives (Scheme 1.44) [120]. The methodology was performed under asymmetric copper catalysis and the arylation method featured in an enantioselective approach.



Scheme 1.44 Enantioselective synthesis of C(3)-aryl pyrroloindoline scaffolds

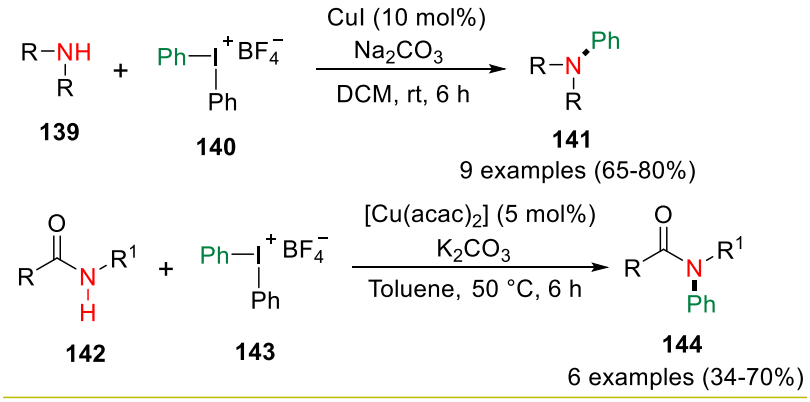
Recently, Xu et al. described an asymmetric approach to achieve arylation of bipyrroles using copper-catalysis and chiral bis(phosphine) dioxides ligand (Scheme 1.45) [121]. As mentioned in the report [122], the formation of chiral Cu-phosphine oxide environment is essential prior to the oxidative addition between diaryliodonium salt and copper catalyst (as discussed in scheme 1.8) to achieve asymmetric arylation. Later, the chiral Cu(I) results in highly electrophilic chiral Ar-Cu(III) species.



Scheme 1.45 Copper-catalyzed desymmetric arylation of bipyrroles

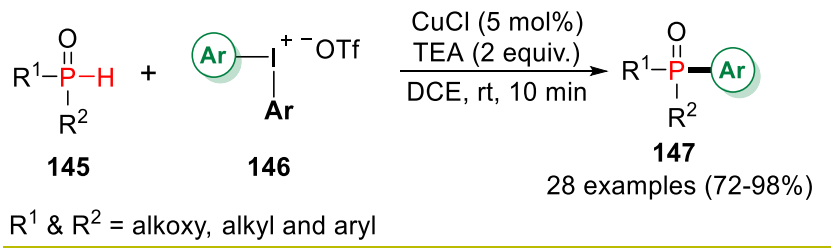
1.8.2 Hetero-atom Arylation

In 2000, Kang and co-workers utilized diaryliodonium salts and accomplished copper-catalysed arylation methods for amines, azoles, and amides (Scheme 1.46) [123]. The catalytic conditions were different depending on the nitrogen nucleophile.



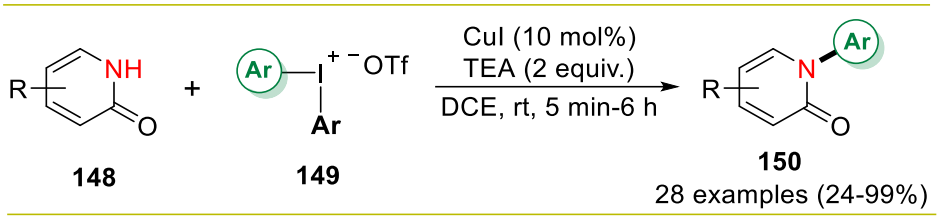
Scheme 1.46 Kang's Cu-catalyzed methods for *N*-arylations

The *P*-arylation of *H*-phosphonates and diarylphosphine oxides with diaryliodonium salts were reported under copper-catalyzed conditions (Scheme 1.47) [124]. The chemoselectivity pattern of unsymmetrical iodonium salts was well-studied and the symmetrical types used in this study were prepared from direct arenes, without any aryl iodides.



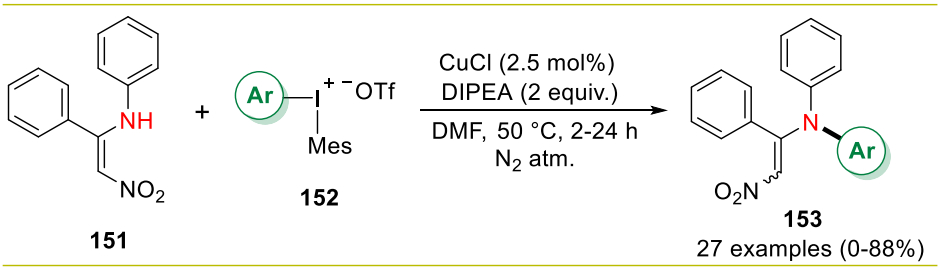
Scheme 1.47 Copper-catalysed *P*-arylation with symmetrical iodonium salts

In 2016, Kim and co-workers developed a copper-catalyzed method for *N*-arylation of 2-pyridones at room temperature (Scheme 1.48) [125]. The method was highly selective towards *N*-arylation, however some substrates exhibited *O*-arylation as the major product. The practical utility of the method was demonstrated through the synthesis of Pirfenidone, an antifibrotic agent for idiopathic pulmonary fibrosis (IPF).



Scheme 1.48 *N*-arylation of 2-pyridones under copper-catalysis

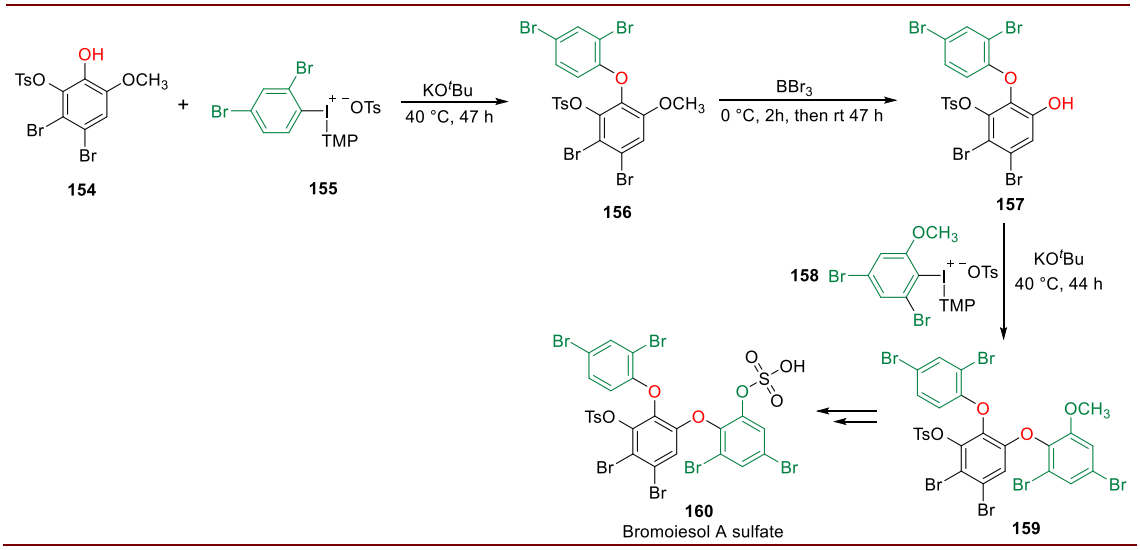
Novak's group utilized aryl(mesityl)iodonium salts for *N*-arylation of biologically relevant nitroenamines scaffolds (Scheme 1.49) [126]. The formed *N*-arylated products were obtained as a mixture of *E* and *Z* isomers, the ratio varied depending on the electronic and steric effect of both the reagents.



Scheme 1.49 Copper-catalyzed *N*-arylations of nitroenamines

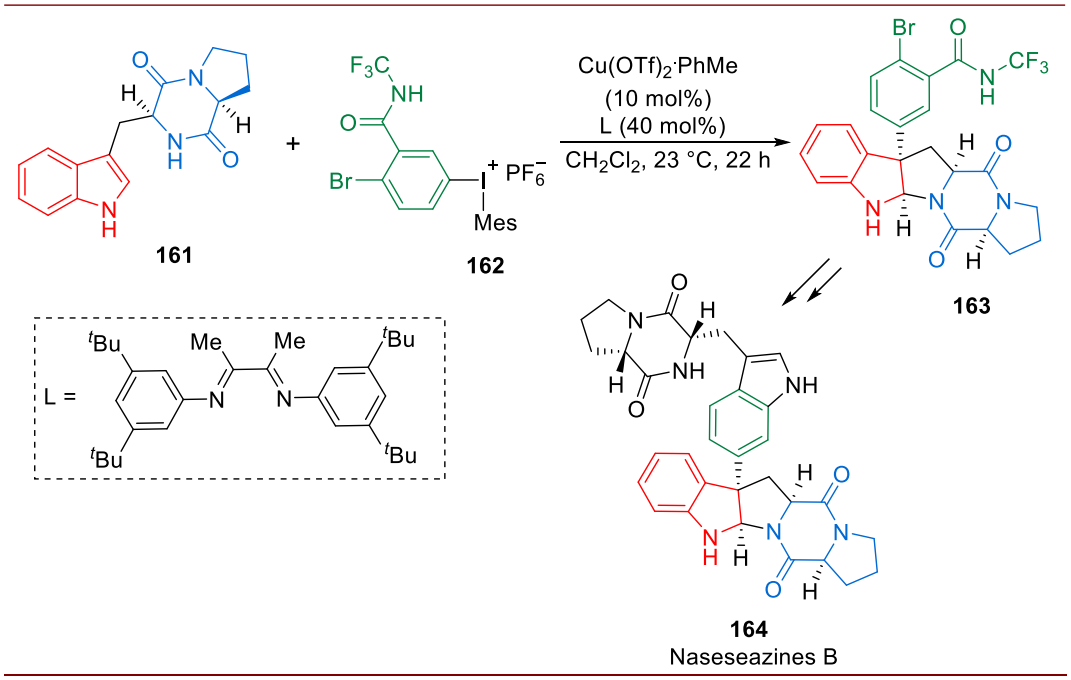
1.9 Applications of Diaryliodonium Salts in Total Synthesis

The synthetic utility of arylation methods based on diaryliodonium salts have been extended for the synthesis of many natural products and pharmaceutically active molecules [127-131]. Suenaga and co-workers developed a route for the synthesis of bromoiesol-A sulfate (anti-trypanosomal), with the application of aryl(TMP)iodonium salts under metal-free conditions (Scheme 1.50) [132]. Because of the presence of the bromide groups on the aryl rings, the regioselective synthesis of this crowded aryl ether would be complicated in transition-metal catalyzed arylation methods. In this report, they explored Stuart's method for synthesis of diaryliodonium salts.



Scheme 1.50 Utilizing diaryliodonium salts to access bromoiesol A sulfate

In 2013, the Reisman group highlighted a diastereoselective synthesis of natural product (+)- Naseseazine B, a pyrroloindoline alkaloid, where they demonstrated copper-catalyzed site-selective *C*-arylation with aryl(Mes)iodonium salts (Scheme 1.51) [133]. In addition, a series of synthetically challenging arylated pyrroloindolines were synthesized from diketopiperazines precursors using chiral Cu(II)-ligand catalytic pathway.



Scheme 1.51 Reisman's approach for the synthesis of Naseseazine B

1.10 Thesis overview and Objectives

Diaryliodonium salts have been recognized as an effective and versatile arylating with a diversity of nucleophiles under both metal-free and copper-catalyzed conditions. With no doubts, the metal-free arylation methods with diaryliodonium salts are always more appreciable, as metal-free procedures avoid the use of any transition-metals and provide a sustainable approach towards the synthesis of pharmaceutical molecules. However, copper-catalyzed methods in combination with diaryliodonium salts also deliver a wide in this field because of their unprecedented C-H and other heteroatomic arylation methodologies. Nevertheless, many important nucleophiles in heterocylic molecules still require detailed investigation to obtain facile arylation protocols and counter previous harsh reaction methodologies. To extend the chemical space of diaryliodonium salts, the following objectives are investigated during this thesis work:

i) The first two experimental chapters of the thesis aims to highlight the application of diaryliodonium salts for *N*- and *S*-arylations of tetrazoles and heterocylic thiols respectively under metal-free route. The earlier approaches for *N*-arylation of tetrazoles were mostly transition-metal based. Therefore, we are interested in utilizing symmetrical and unsymmetrical iodonium salts for *N*-arylation of tetrazoles under transition-metal free condition. Similarly, many reports on *S*-arylation of thiols were known with diaryliodonium salts, but we intend to extend the utilization of unsymmetrical TMP-iodonium salts with previously less-explored heterocylic thiols.

ii) The subsequent experimental chapters explore the heterocylic N–H nucleophiles, where the reactivity of these nucleophiles is not compatible with metal-free conditions. The discussed copper-catalyzed methods in these chapters investigate the chemoselective arylation with unsymmetrical iodonium salts and identified the suitable aryl(auxiliary)iodonium salt. The wider scope of aryl moieties from diaryliodonium salts aims to study in those nucleophiles.

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