Diaryliodonium Salts in Organic Syntheses – A Useful Class of Compounds in Arylation Strategies

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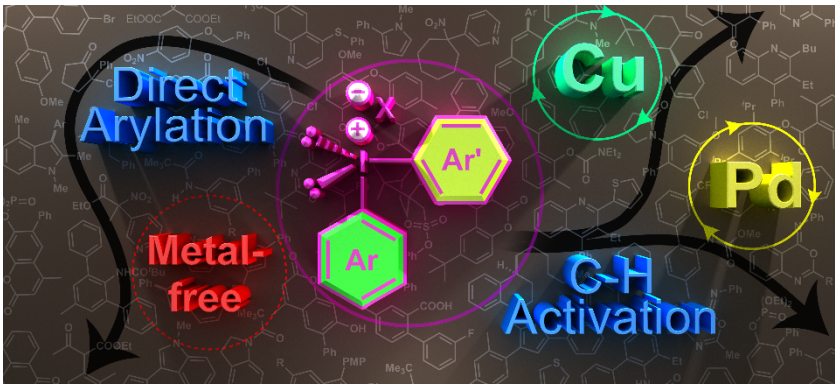

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Abstract This account aims to give a description of the usefulness of diaryliodonium salts in organic chemistry, including their synthesis and applications in the presence and absence of transition metal catalysts. Herein, we briefly summarize the structural properties and reactivity of diaryliodonium salts. We collected several applications of the hypervalent reagents including metal-free arylations of C, O, N and S nucleophiles. Synthesis and functionalization of aromatic and heteroaromatic systems via copper and palladium catalyzed transformations are also discussed in this account.

Key words arylation, diaryliodonium salts, hypervalent iodines, metal-free, copper-catalyzed, palladium-catalyzed, C-H activation, direct functionalization

1. Introduction

In the last decades, hypervalent iodine compounds have received great attention in organic syntheses[1] due to the fact that that they can be used as efficient reagents[2] in organic reactions. Their use provides efficient alternative to toxic heavy-metal-based oxidants and expensive organometallic catalysts for many organic transformations. Thus organic iodine(III) and iodine(V) derivatives are now routinely used in organic synthesis as reagents for various selective oxidative transformations of complex organic molecules. For example, Dess-Martin periodinane (DMP) is often used as mild oxidant of alcohol moieties[3] while 2-iodoxybenzoic acid (IBX) enables the oxidation of the benzylic position or the introduction of α, β-double bonds into carbonyl compounds.[4]

In contrast, diaryliodine(III)[5] reagents can be employed in reaction pathways that are similar to metal-catalyzed reactions. Owing to the highly electron-deficient nature of diaryliodonium salts at the iodine center and excellent leaving-group ability of the iodobenzene, they serve as versatile arylating agents with a variety of nucleophiles. Moreover, they also can

be used in sequential cyclizations for the synthesis of several important heterocyclic compounds.

2. Structural Properties and Reactivity

The first diaryliodonium salt was synthesized in 1894 by Meyer and Hartmann as an air- and moisture-stable compound.[6] Their structure consists of two aryl moieties connected to the iodine and an anion (X-) mostly halogen, triflate, tosylate or tetrafluoroborate (Figure 1a). Diaryliodonium salts with halide anion are less soluble in most organic solvents, while triflates and tetrafluoroborates have better solubility.

They are generally classified according to the *lambda* (λ) convention as λ^3-compounds,[7] where the iodine and two apical ligands (L) share a hypervalent bond (Figure 1b). The electron configuration of the iodine in hypervalent iodine compounds is not conventional. Instead of 8 electrons, 10 or 12 are located around the iodine center. The X-ray structures of these iodine(III) compounds show a T-shaped molecule geometry[8] (Ar–I–Ar is close to 90°). Iodine(III) compounds with two heteroatom ligands are believed to retain this T-shape also in solution.

Figure 1 a) General structure of diaryliodonium salts. b) T-shaped form determined by X-ray structure analysis.

The linear three-center, four-electron (*3c-4e*) bond in these types of compounds is highly polarized, and it is longer and weaker compared to a regular covalent bond. Due to the hypervalent property of this bond and the node in the nonbonding orbital of the hypervalent bond, iodine(III) compounds have electrophilic character which realizes in their excellent reactivity. As a consequence, the diaryliodonium salts can easily react with various nucleophiles. The high reactivity of aryliodonium salts in these reactions is explained by the “hyperleaving group ability” of the ArI group. For example, the leaving group ability of PhI from the corresponding iodonium compound is about 106 times greater than the triflate anion.[9] Iodine(III) compounds react with nucleophilic species (Nu^-) at iodine replacing one ligand. Then the substituted arene (ArNu) and iodoarene (ArI) form in a reductive elimination step (Scheme 1a). In metal-catalyzed reactions, diaryliodonium salts behave as more reactive versions of aryl iodides, by delivering an aryl moiety and the anion to the metal center in an oxidative addition manner. Then the formed aryl metal complex (ArMX) can enter into catalytic cycles to obtain versatile coupling products (Scheme 1b).[1]

Scheme 1 General reactivity of diaryliodonium salts in a) reactions with nucleophiles, b) metal-catalyzed reactions.

The use of symmetric diaryliodonium salts (Figure 1a, R^1=R^2) is generally preferable, to reduce selectivity problems in aryl-transfer reactions. However, this structural requirement limits the scope of the transformations. Aryl transfer from a diaryliodonium salt in the organic reactions is affected by steric and electronic properties of the rings. Considering these factors, a suitable non-transferable aryl group can be designed for the chemical transformations. With the aid of these types of aryl groups the number of available and applicable iodonium reagents can be expanded. The most frequently used non-transferable group called as “dummy-group” for metal-catalyzed reactions is the mesityl group.

3. Applications of Diaryliodonium Salts in Organic Syntheses

In the last decades, transformations including diaryliodonium salts become an important and widespread research field of organic syntheses. Thus, several applications have been developed such as metal-catalyzed cross-couplings, C-H activation, benzyne generation or dearomatization of phenols. Recently, diaryliodonium salts have been recognized as efficient electrophilic arylation reagents with a wide range of nucleophiles under both metal-free and metal-catalyzed conditions. In the following chapters we aim to summarize the arylation reactions performed in the presence of diaryliodonium salts with several nucleophilic systems (C, O, N and S nucleophiles). Chapter 3.1. includes the most efficient metal-free arylation methods, while in Chapter 3.2. several important transition metal-catalyzed transformations are collected.

3.1 Transition Metal-Free Arylations of Heteroatom and Carbon Nucleophiles

Functionalization of heteroatoms by alkylation and arylation is one of the most commonly used transformations in the pharmaceutical industry.[10] Utilization of diaryl iodonium salts in these reactions opens new possibilities to the access of the target compounds.

In 1953, Beringer et al. demonstrated that the diaryliodonium bromides are useful reagents for the phenylation of versatile organic and inorganic bases including alkoxides, phenoxides, benzoates, nitrites, sulfonamides, amines, sulfites, sulfinates and cyanides under relatively mild conditions.[11] These results provided a new research field in organic transformations. Since the first discoveries, several methodologies have been developed for carbon and

heteroatom arylations in the presence of diaryliodonium salts.

3.1.1. Arylation of Oxigen Nucleophiles

3.1.1.1 Arylation of Phenols

After the pioneering studies of Beringer,[11] the research group of Crowder[12] reported the preparation of diaryl ethers (**2**) by the S_N2 type[13] reaction of phenols (**1**) and diaryliodonium salts in aqueous media in presence of sodium hydroxide base (Scheme 2). The expected diaryl ethers were isolated in good yields (63-86%).

Scheme 2 O-arylation of phenols.

Olofsson and co-workers marked an era in metal-free arylations as they developed several reactions in the last decade. In 2011, they reported an *O*-arylation procedure for the preparation of diaryl ethers (**4**) from phenols (**3**) under mild conditions in short reaction time (Scheme 3).[14] The products were isolated in 72-99% yields with a number of diaryliodonium salts containing tetrafluoroborate or triflate anion. Sterically crowded, *ortho*-substituted phenol derivatives were also transformed to the desired products. The extended substrate scope of this transformation and the arylation of sulfonic acids were also demonstrated one year later.[15]

Scheme 3 Preparation of diaryl ethers by O-arylation.

Similar to Crowders's work,[12] Olofsson et al. also developed a metal-free synthesis of aryl ethers in aqueous media under mild conditions.[16] The reaction employs diaryliodonium salts and sodium hydroxide in water at low temperature. Both allylic, benzylic alcohols and phenols were active in the reaction and were transformed to the appropriate arylated products with good to excellent yields.

Gaunt et al. also developed a mild and transition metal-free counter-anion triggered electrophilic *O*-arylation strategy by using diaryliodonium fluorides.[17] A wide range of phenols (**5**) and diaryliodonium salts were compatible with this transformation which enabled a broad substrate scope of diaryl ethers (**6**) with high isolated yields (Scheme 4). The hydrogen bonding ability of fluoride enables the abstraction of proton, thus no additional strong base required for the transformation. The *O*-arylation process could be also initiated by the *in situ* combination of diphenyliodonium trifate and one equivalent of tetrabutyl ammonium fluoride (TBAF).

Scheme 4 Preparation of diaryl ethers with diaryliodonium fluorides.

3.1.1.2. Arylation of Aliphatic Alcohols

In 1975, McEwen et al. published an etherification reaction by using diphenyliodonium tetrafluoroborate salt and sodium ethoxide in which complex reaction mixture was formed.[18] The use of 1,1-diphenylethylene (DPE) as additive solved the selectivity problem of the radical process and only the desired *O*-arylated product was obtained in 77% yield.

In 2014, the Olofsson group has developed a practical method for the *O*-arylation of aliphatic alcohols[19] (**7**) (Scheme 5). Iodonium salts containing electron-withdrawing groups such as NO_2, CN, CF_3 could be efficiently utilized in the transformation. Primary alcohols proved to be the best reaction partners, but also secondary, benzylic and allylic alcohols were successfully transformed in the reaction and several novel alkyl-aryl ethers (**8**) have been synthesized.

Scheme 5 *O*-arylation of aliphatic alcohols.

Very recently, Stuart and co-workers reported a base mediated chemoselective synthesis of alkyl-aryl ethers[20] (**10**) starting from the reaction of aliphatic alcohols (**9**) and unsymmetric aryl-mesityliodonium bromides (Scheme 6). Primary, secondary, tertiary, allylic, and benzylic aliphatic alcohols were all suitable substrates for the transformation. In their procedure they used sodium hydride as a base and the reactions were performed in *tert*-butyl methyl ether (TBME) at 50 °C.

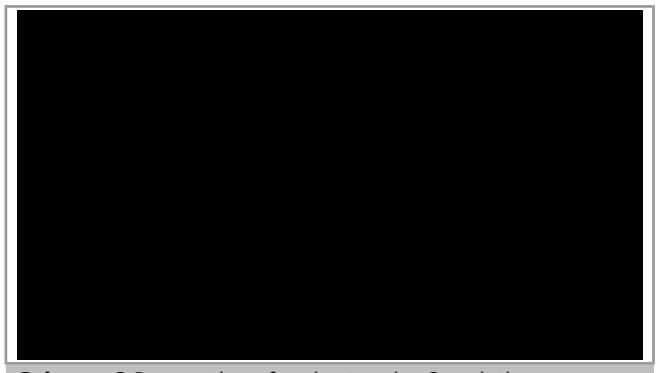
Scheme 6 *O*-arylation of alkyl and alkenyl alcohols.

N-Aryloximides[21] (**13**, **14**) can be also synthesized with the aid of iodonium salts under transition-metal-free conditions via *O*-arylation of N-hydroxysuccinimides (**11**) and *N*-hydroxyphtalimides (**12**) in excellent yields in short reaction times (Scheme 7). Several products were synthesized by using both symmetric and unsymmetric iodonium salts. In case of phtalimide derivatives (**12**), the obtained chemoselectivity showed that the most electron deficient aryl group, i. e. the phenyl group was transferred with high or complete selectivity and both trimethoxyphenyl and thienyl groups were ideal as nontransferable „dummy" groups.

Scheme 7 *O*-arylation of *N*-hydroxyphtalimides and *N*-hydroxysuccinimides.

3.1.1.3. Arylation of Acids

With the utilization of diaryliodonium salts sterically crowded aryl esters (**16**) can be synthesized from carboxylic acids (**15**).[22] The transformation was suitable for both aromatic and aliphatic substrates and the transformation provided the desired esters in good yield in short reaction times (Scheme 8).



Scheme 8 Preparation of aryl esters by *O*-arylation.

Sulfonic acids were also suitable starting materials for the appropriate sulfonester synthesis.[15] In the presence of a bulky base, sulfonic acids (**17**) could be transformed to the corresponding sulfonates (**18**) in a short reaction time in refluxing toluene (Scheme 9).

Scheme 9 Arylation of sulfonic acids by diaryliodonium triflate.

3.1.2. Arylation of Nitrogen Nucleophiles

3.1.2.1. *N*-Arylation of Amines and Amides

In the last few years, a large number of methodology developments were reported focusing to transition metal-free functionalization of nitrogen nucleophiles. In 2007, Carroll and Wood published a transition-metal-free *N*-arylation for the synthesis of diarylamines[23] (**20**) using anilines (**19**) and diphenyliodonium trifluoroacetate (Scheme 10). The reactions were conducted in dimethylformamide at high temperature. The presence of electron-withdrawing groups such as nitro group on the aniline moiety decreased the yields, while anilines equipped with electron-donating groups were transformed to the desired products in good to high yields.

Another approach for the *N*-arylation with the aid of diaryliodonium salts was demonstrated by Wang et al.[24] They demonstrated that the arylation of hydroxylamines (**21**) proceeded smoothly at room temperature in the presence of cesium carbonate (Scheme 11) and the desired products (**22**) were isolated in good to excellent yields.

Scheme 11 *N*-arylation of hydroxylamines with diaryliodonium salts.

The *N*-arylation of non-aromatic systems such as alkyl-amides is also possible with the utilization of diaryliodonium salts. Very recently, Olofsson's group reported a metal-free *N*-arylation method for secondary acyclic amides[25] (**23**) using diaryliodonium salts and sodium hydride as a base at room temperature (Scheme 12). The methodology has a wide scope regarding the *N*-arylated products (**24**), ensures excellent yields, avoids harsh conditions[26] and solves regioselectivity problems observed earlier in this type of transformation.[27]

Scheme 12 *N*-arylation of acylic amides at room temperature.

The metal-free *N*-arylation of *ortho*-acyl anilines (**25**) for the synthesis of acridine derivatives (**26**) was recently described by Chen et al.[28] The reactions were conducted in 1,2-dichloroethane (DCE) at 130 °C (Scheme 13). The usefulness of transformation was demonstrated on several examples which provided the desired products in good to high yields. According to the reported mechanism, the reactions undergoes by a tandem arylation/ *Friedel-Crafts* reaction mechanism.

Scheme 14 Synthesis of acridines via *N*-arylation.

3.1.2.2. *N*-Arylation of Heterocycles

Very recently, the metal-free *N*-arylation of pyrazole derivatives (**27**) was developed in our research group[29] utilizing a wide range of diaryliodonium salts. Aqueous conditions were used at room temperature and the desired *N*-arylated pyrazoles (**28**) were obtained in good to high yields (Scheme 14) in very short reaction time (20 min. - 6 h). Chemoselectivity studies revealed that the transfer of the sterically more hindered and more electron deficient aryl group from the iodonium salt is preferable.

Scheme 14 Transition metal-free *N*-arylation of pyrazoles.

Also this year, Riedmüller et al. described the synthesis of *N*-arylated of indolines[30] (**31**) using diaryliodonium salts as electrophilic arylating reagents. Without the use of any additional additives, the desired products could be obtained in up to 85% isolated yield (Scheme 15). With a few examples, the developed procedure was extended on heteroaromatic substrates such as 1H-benzotriazoles (**30**) for the construction of 2-arylated benzotriazole derivatives (**32**).

Scheme 15 Synthesis of *N*-arylated indolines with diaryliodonium salts.

3.1.3. Arylation of Sulfur Nucleophiles

The metal-free arylation of sulfur nucleophiles with diaryliodonium salts has known for a long time in organic syntheses. The first transformation was published in 1947 by Sandin[31] and co-workers in which the reactions of diphenyliodonium chlorides with thioglycolic acid (**33**), thiophenol and cysteine were studied (Scheme 16). However, *S*-phenylthioglicolic acid (**34**) was isolated only in 21% yield.

Scheme 16 *S*-arylation of thioglycolic acid with diphenyliodonium chloride.

In 2001, Huang et al. reported the preparation of diaryl sulfides (**36**) using benzenethiolates (**35**) and polymer bounded diaryliodonium salts.[32] The synthesis of different diaryl ethers was also achieved using sodium phenolate derivatives as starting materials. The reactions were performed in dimethylformamide at 100 °C (Scheme 17) and various diaryl sulfides were isolated in 67-76% yield.

Scheme 17 Preparation of diaryl sulfides with polymeric iodonium salt.

In 2006, the S-arylation of n-hexyl thiolate (**37**) and n-hexyl-phenyl sulfides[33] (**38**) using diaryliodonium triflates was reported by Krief et al. The transformation of thiolate took place in the absence of transition metal catalyst in dimethyl sulfoxide and provided the desired product (**39**) in high yield (Scheme 18). It is of note that the synthesis of sulfonium salt from sulfides and diaryliodonium salts required the presence of copper triflate catalyst.

Scheme 18 Arylation of *n*-hexyl thiols and *n*-hexyl-phenyl sulfides via *S*-arylation.

The typical disadvantages of all these kind of transformations are the relatively low yields or moderate functional group tolerance. The Sanford research group solved these problems and developed a novel transition-metal-free acid-mediated synthesis of diaryl and alkyl-aryl sulfides[34] (**42**) from thiols and thioethers (**41**) with high functional group tolerance in good to excellent yields (Scheme 19).

Additionally, the arylation of lithium sulfonates is possible in a direct approach,[35] or from in-situ generated metal-sulfinates as it was demonstrated by Manolikakes and coworkers.[36]

Scheme 19 Preparation of diaryl and alkyl-aryl sulfides with diaryliodonium salt.

3.1.4. Arylation of Inorganic Anions

By the decomposition of diaryliodonium salts different functional groups can be introduced to the aromatic ring in a pseudo S_N2-type fashion. The alkyne-azide click chemistry has an increasing importance in bioorganic chemistry, thus there is a need for widening the availability of useful azidation methods. Symmetric and bicyclic iodonium salts and zwitterions can be converted to azides with the aid of NaN_3.[37,38] Choosing a suitable dummy aryl group, such as cyclophanes, the target aromatic substrate can be azidated selectively.[39] Cyclic diaryliodonium tetrafluoroborates are shown to undergo reaction with N_3^-, NO_2^-, and Br^- as well.[40] By far the most studied inorganic nucleophile is the fluoride ion. The extensive

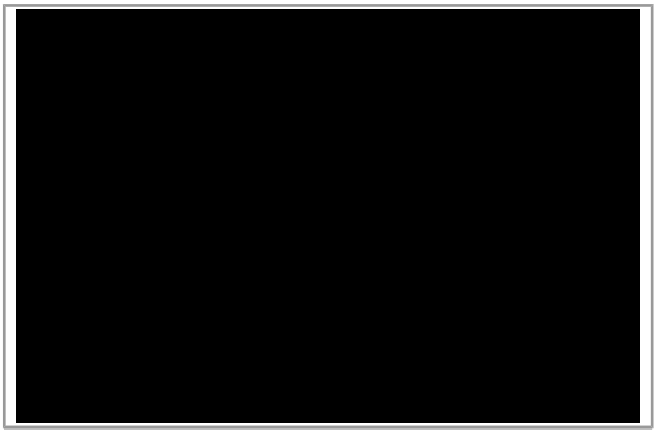
application of positron emission tomography in medicine[41] enhances the need of fast methods introducing fluoride to complex organic molecules. The good balance in stability and reactivity of iodonium compounds, such as ylides and diaryliodonium salts enables reaction times fast enough to use them in radiochemistry. This topic was reviewed earlier by Zhdankin,[42] and others.[43,44] Similarly arylation of iodide is also possible.[45]

3.1.5 Arylation of Carbon Nucleophiles

3.1.5.1 Electron-rich Heterocycles

After Beringer's work,[11] *C*-arylation strategies using diaryliodonium salts under transition metal-free conditions were underdeveloped. However, in recent years these progresses have received considerable attention, therefore the arylation of several aromatic and heteroaromatic systems were achieved. In 2010, Kita and co-workers reported direct transition-metal-free arylation of electron-rich aromatic compounds[46] with diaryliodonium salts.

In 2011, Ackermann's group reported the *C3*-arylation of indoles[47] (**43**) and pyrroles in the absence of metal catalyst and additives using diaryliodonium salts in dimethylformamide at high temperature (Scheme 20). *N*-protected and free indole derivatives were also suitable substrates for the transformation, and easily converted to the desired products (**44**). In case of 2,3-unsubstituated indole derivatives, the direct arylation provided also a small amount of *C2*-arylated side products.



Scheme 20 Direct *C3*-arylation of indoles.

In 2012, *C*-arylation of different aryl moieties including substituted pyrroles (**45**), pyridine (**46**), pyrazine (**47**) and benzene derivatives (**48**) in the absence of transition-metal catalysts was reported by Yu et al.[48] (Scheme 21).

Scheme 21 Direct arylation of arenes and *N*-heteroarenes.

As a general feature of the reaction *N*-protected and free pyrrole derivatives were suitable for the reaction. In case of six-membered rings, *C*-arylation of pyrimidine ring provided isomers (**50**), while reactions of pyridazine and benzene derivatives provided selectively the desired arylated products (**51**, **52**).

3.1.5.2. Arylation of carbonyl and nitro compounds

The metal-free arylation of silyl-enol ethers (**53**) with iodonium salts provide α-arylated carbonyl compounds[49] as it was reported by Koser in 1991. The reactions were conducted in tetrahydrofuran at low temperature and the α-arylated products (**54**) were isolated in 20-88% yield (Scheme 22). In this transformation the activation of silyl ether was initiated by the fluoride counterion of the iodonium salt.

Scheme 22 Arylation of silylenol ethers.

Carbonylation of alkyl malonates (**55**) and alkyl β-keto esters (**56**) under metal-free conditions was developed by Oh et. al.[50] Sodium hydride base and dimethylformamide solvent were used in the reaction (Scheme 23). The study draws attention to the usefulness of suitable dummy groups. If 2,4,6-trimethoxyphenyl-phenyl iodonium salt was used for the synthesis of alkyl-aryl β-keto esters (**58**), the presence of the non-transferable trimethoxyphenyl group enabled a selective phenylation as the less hindered and less electron deficient aryl group transferred.

Scheme 23 Arylation of malonates and *β*-keto esters.

The first enantioselective transition metal-free arylation of cyclohexanones (**59**) was described by Olofsson and Aggarwal in 2005.[51] Their methodology applies Simpkin's base to generate the nucleophilic enolate intermediate (Scheme 24). The presence of bulky substituents on the *C4* carbon of the cyclohexanone ring was necessary to reach good enantioselectivity for the appropriate arylated products (**60**). To demonstrate the power of this transformation, it was utilized in the short total synthesis of (-)-epibatidine.

Scheme 24 Transition metal-free arylation of cyclohexanones; on the way to (-)-epibatidine

C2-arylation of quinone systems (**61**, **62**) using diaryliodonium salts was developed by Wang et al.[52] In the ligand-free transformation sodium hydroxide was used as a base and the reactions were conducted in refluxing dichloroethane (Scheme 25).

Scheme 25 *C2*-arylation of quinones and naphtoquinones.

The products (**63**, **64**) were isolated in good yields when the aryl groups of the iodonium salt contained electron donating groups, while the presence of electron-withdrawing groups had deleterious effect on the transformation and the expected products were isolated in lower yields. Based on the radical trapping experiments the reaction was proposed to undergo via radical mechanism.

Scheme 26 Synthesis of 3-aryl-4(1*H*)quinolones via C-arylation.

Recently, the *C*-arylation of *β*-ketocarboxylic acids was developed by Manetsch et al.[53] The functionalization of ethyl acetoacetate (**63**) with diaryliodonium salts in dimethylformamide in the presence of potassium tert-butoxide occurred at 25 °C (Scheme 26). The appropriate arylated products (**64**) were transformed to 3-aryl-4(1*H*)quinolones (**65**) via Conrad-Limpach reaction in two subsequent reaction steps. The method has been also applied for the synthesis of antimalarial compound ELQ-300, which is currently in preclinical development phase.

A few months ago, the metal-free *C*-arylation of nitro compounds[54] was published by Olofsson's group using diaryliodonium salts. The reaction proceeds in high yields without the need for excess reagents and can be extended to *α*-arylation of

nitrocycloalkanes (**66**) and nitroesters (**67**) (Scheme 27).

Scheme 27 Metal-free *C*-arylation of nitrocycloalkanes and nitroesters.

3.2. Synthesis and Functionalization of Aromatic and Heteroaromatic Molecules with Diaryliodonium Salts in the Presence of Copper and Palladium Catalysts

Numerous transition metal-catalyzed reactions of diaryliodonium salts were developed in the last decade. Amongst the metals, palladium and copper catalysts are used most frequently for the arylations of aromatic, heteroaromatic and non-aromatic systems. In the following chapters we summarize the copper and palladium catalyzed reactions of diaryliodonium salts with various substrates.

3. 2. 1. C-H functionalizations by Copper Catalyzed C-H Arylations

Functionalization of aromatic and heteroaromatic systems via copper catalyzed C-H activation[55] is an important and intensively studied area of current organic chemistry. Diaryliodonium salts can be efficiently used in copper catalyzed oxidative arylations of aromatic and heteroaromatic substrates. In 2008, Gaunt and co-workers demonstrated that Cu(I) or Cu(II) catalyst could be oxidized in the presence of diaryl-iodine(III) reagent to form a highly electrophilic arylcopper(III) intermediate.[56] The generation of this aromatic electrophile equivalent species (**70**) enables the functionalization of aromatic C-H bonds via C-H arylation processes (Scheme 28).

Scheme 28 Generation of Ar-Cu(III) intermediate and utilization in C-H arylations.

Using this strategy Gaunt et al. developed a new site-selective Cu-catalyzed C-H bond functionalization process which enables the selective arylation of indoles in either the *C3* or *C2* position under mild conditions (Scheme 28 and 29).[54] Utilization of the sterically hindered triisopropylphenyl-substituted diaryliodonium salt enabled the versatile synthesis of *C3*-arylated indole derivatives (**72**) with excellent selectivity and in good yields (Scheme 29).

Scheme 29 Selective *C3*-arylation of indoles.

The authors speculated that the arylation of indole took place through a migration of the Cu(III)-aryl group from *C3* to *C2*. The migration can be controlled by the nature of the group attached to the nitrogen atom. While free (NH)- and N-alkylindoles (**71**) delivered the *C3*-arylated product (**72**) (Scheme 29), *N*-acetylindoles (**73**) afforded the *C2* isomer (74) (Scheme 29). According to the mechanism, the oxidative addition of the diaryl-iodine(III)reagent to the Cu(I) salt could generate the electrophilic Cu(III)-aryl intermediate (**70**) which can attack at the *C3* position of the indole ring. Rearomatization followed by reductive elimination provided the *C3*-arylated product (**72**). In the case of N-acetylindoles (**73**), the carbonyl oxygen of the acetyl group can coordinate to the copper and may steer the Cu(III) species to *C2* position. The experiments supported the mechanistic sights as a wide range of electronically diverse *N*-acetylindole derivatives worked well in the process,

delivering the *C2*-arylated products (**74**) in good yields (Scheme 30).

Scheme 30 Formation of Ar-Cu(III) intermediate and *C2*-arylation via aryl group migration.

Very recently, Modha and Greaney developed a copper catalyzed atom economical procedure for the tandem C-H and N-H arylation of indoles. In their procedure the aryliodide sideproduct of the C-H functionalization was utilized in the copper catalyzed N-arylation step.[57]

In 2009, Phipps and Gaunt reported the *meta*-selective copper catalyzed arylation of pivalanilides[58] (**75**) using diphenyliodonium triflates and borates. The reaction was conducted in dichloroethane and copper(II) triflate was used as catalyst. The desired *meta*-arylated products were isolated in 11-93% yield (Scheme 31). The reaction was proposed to undergo via the formation of highly active arylcopper(III) intermediate. The carbonyl group is indeed responsible for the selectivity of this reaction. The oxygen atom of the acetyl group coordinates to the *ortho* position, while the arylcopper(III) species will be formed at the *meta* position.

Scheme 31 *Meta*-selective copper catalyzed arylation of pivalanilides.

Rearomatization and deprotonation followed by reductive elimination would provide *meta*-substituated products (**76**). Theoretical and experimental studies by DFT calculations suggest that *meta*-arylated products are formed via a *Heck*-like four-membered-ring transition state through a Cu(III)-Ph intermediate.[5859]

Other studies of this research group revealed, that the addition of transition metal is not always crucial for this kind of reaction. The products could be obtained at elevated temperatures without adding copper, albeit in lower yields, what might indicate a more complicated mechanistic profile. As an extension, further developments were performed by Gaunt and the copper catalyzed *meta*-selective direct arylation of *α*-aryl carbonyl compounds[60] was reported. Diaryliodonium triflates containing EDG and EWG groups were both tolerated in the reaction.

The copper mediated α-arylation of carbonyl compounds was described first by Stang, as early as 1997, but the need of equivalent copper and the low yields were significant drawback of the procedure.[61] The catalytic enantioselective *α*-arylation of aldehydes[62] and silyl enol ethers[63] were also carried out by MacMillan et al. In 2011, the Gaunt's group also reported a C-H arylation procedure in which the enantioselective *α*-arylation of N-acyloxazolidinones[64] with copper(II)-bisoxazoline catalysts and diaryliodonium salts was achieved.

In 2012, a new approach to alkene (**77**) arylation using diaryliodonium salts and copper catalysis was developed by Gaunt and co-workers (Scheme 32).[65] Formation of two alkene isomers was observed (**78** and **79**) and the selectivity was influenced by the structure of the alkene and the iodonium salt. Preliminary studies showed that a carbocation-type mechanism was operated in these reactions.

Scheme 32 Alkene arylation with diaryliodonium salts and copper catalysts.

3. 2. 2. Copper Catalyzed Cyclization of Unsaturated Compounds with Diaryliodonium Salts Utilizing Copper Catalysts

Arylation and functionalization of unsaturated systems such as alkenes, alkynes and nitriles with the utilization of iodonium salt in the presence of copper catalysts enables the construction of diverse heterocyclic skeletons. Thanks to this fact, in the last few years several methods have been developed for the synthesis of complex heterocyclic compounds. According to the mechanism of the transformations discussed in the followings, the transformations are proposed to undergo via the formation of highly active arylcopper(III) species which can activate triple bonds or generate carbocationic species from alkynes and nitriles.

In 2013, a new copper catalyzed *endo*-selective oxyarylation and oxyvinylation of allylic amides[66] (**80**) was developed by Gaunt and co-workers. The procedure enables the arylation of allylic amides both with diaryl- and vinyl(aryl)iodonium triflates in the presence of CuTC (TC = thiophene-2-carboxylate) catalyst (Scheme 33). The developed reaction is tolerant to a wide range of functional groups and provides easy access to a broad selection of *endo*-oxazine products (**81**) in high yields and excellent diastereoselectivity.

Scheme 33 Copper catalyzed oxyarylation and oxyvinylation of allylic amides.

In the same year, Gaunt et al. reported the copper catalyzed carboarylation of alkynes[67] (**82**) via the formation of vinyl cations formed in the reaction of the triple bond and the arylcopper(III) species.

Scheme 34 Copper catalyzed arylation of functionalized alkynes.

The electron-rich alkynes were converted to complex tetrasubstituted alkenes (**83**) under mild conditions in high yields, while copper(I) chloride was utilized as the catalyst of the transformation (Scheme 34).

In 2014, the copper catalyzed alkene and alkyne arylation strategies were extended for the synthesis of carbocyclic compounds[68] such as tetraline (**86**) and cyclopentene (**87**) derivatives in cascade reactions utilizing diaryliodonium salts as coupling partners. The CuTC-catalyzed reactions were performed in dichloromethane at 70 °C (Scheme 35).

Scheme 35 Copper catalyzed arylation of functionalized alkenes and alkynes.

The mechanism of the transformation includes a 1,2-hydride shift, carbocation formation and a subsequent *Friedel-Crafts*-type reaction to provide tetralins (**86**) from alkenes (**84**) through a classical carbocation-type pathway. In contrast, the cyclopentene (**87**) formation is notable for a concerted 1,5- hydride shift process in case of internal alkynes (**85**) that retains stereochemical information at the site of the carbocation-type intermediate (Scheme 36).

Scheme 1 Carbocation-induced 1,2- and 1,5-hydride shift processes for the construction of tetraline and cyclopentene derivatives.

The concept of aromatic electrophile generation via the intermediacy of Cu(III) species was presented previously on several examples.[54-67] Utilizing this concept, several syntheses of diverse heterocyclic skeletons were developed in the last few years in our and other laboratories. The copper catalyzed synthesis of new oxazoline derivatives (**89**) from propargyl amides (**88**) and diaryliodonium salts was recently developed by our research group.[69] In this transformation copper chloride was used as a catalyst for the arylation-ring closure sequence to obtain the desired oxazoline derivatives (Scheme 37). The reaction includes a *5-endo-dig* cyclization step in which the incoming aryl group originated from the iodonium salt is in *cis* position to the oxygen atom of the oxazoline ring. The cyclization occurs selectively and only the formation of one geometric isomer was observed, which suggest the coordination of the arylcopper intermediate from the inner sphere of the triple bond.

Scheme 37 Copper catalyzed synthesis of oxazolines.

The intramolecular aryl-etherification of alkoxy alkynes[70] (**90**) for the synthesis of oxo-heterocycles (**91**) via cleavage of a stable C-O bond was recently developed by Chen et al. In this transformation diaryliodonium hexafluorophosphates were utilized as arylating agents and 10 mol% $Cu(OTf)_2$ was used as catalyst (Scheme 38). The reaction was proposed to undergo via vinylcopper(III) intermediate.

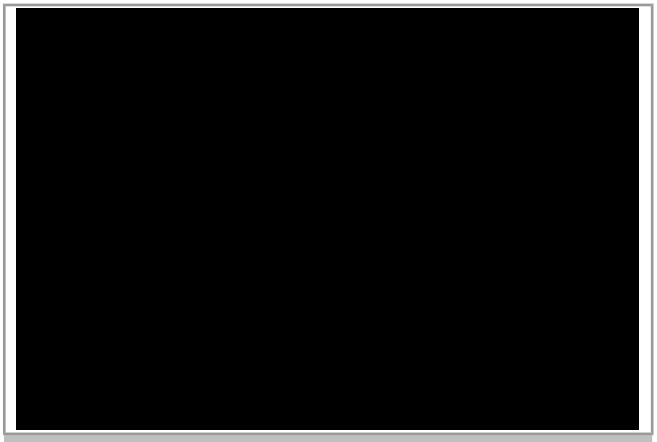
Scheme 38 Copper catalyzed intramolecular aryl-etherification of alkoxy alkynes.

In 2013, a novel copper catalyzed oxidative ring closure strategy was developed in our laboratory for the construction of benzoxazines[71] (**93**) from 2-ethynylanilides (**92**) and diaryliodonium salts (Scheme 39). The transformation which enables a versatile synthesis of benzoxazine derivatives includes an unusual *6-exo-dig* cyclization step by the formation of new C-C and C-O bonds. The synthesis of benzoxazine derivatives was also achieved in our laboratory by utilization of copper on iron catalyst[72] used previously in our group for the construction of pyrazole derivatives.[73] This easily removable catalyst provides

the product in similar efficiency compared to the homogeneous catalytic version.

Scheme 39 Synthesis of benzoxazines by copper catalyzed oxidative arylation.

In 2015, the methodology was extended on aromatic nitriles (**94**) equipped with amido function in *ortho* position for the synthesis of imino-benzoxazine[74] derivatives (**95**). With this reaction we demonstrated that the carbon-nitrogen triple bond can also be activated similarly to carbon-carbon triple bond. In these transformation copper(II) triflate was used as copper source in dichloromethane or ethyl acetate solvent. The latter one could be used, as an environmentally and industrially more acceptable alternative to halogenated solvents, frequently used in hypervalent iodonium chemistry (Scheme 40).



Scheme 40 Synthesis of iminobenzoxazines by copper catalyzed oxidative arylation.

Recently, phenantridine[75] derivatives were synthesized by Li et al. via cascade annulation of diaryliodonium salts and nitriles. Copper(II) triflate was used as catalyst and the reactions were performed at high temperature (150 °C). This example also demonstrates the activation of nitrile moiety using diaryliodonium salt in the presence of copper catalysts.

The potential of nitrile activation was explored and extended by Chen and co-workers. The activation of a nitrile group in the presence of a carbon-carbon triple bond with copper catalyst and iodonium salts enables the construction of various heterocycles. Utilizing this strategy, the synthesis of diverse heterocyclic skeletons such as quinolones,[76] quinazolines[77] and tetrahydroacridines[78] has been described recently by Chen. These transformations were performed in dichloroethane at 120 °C. The synthesis of quinoline derivatives (**96**) were demonstrated on several examples with good to excellent yields (Scheme 41).

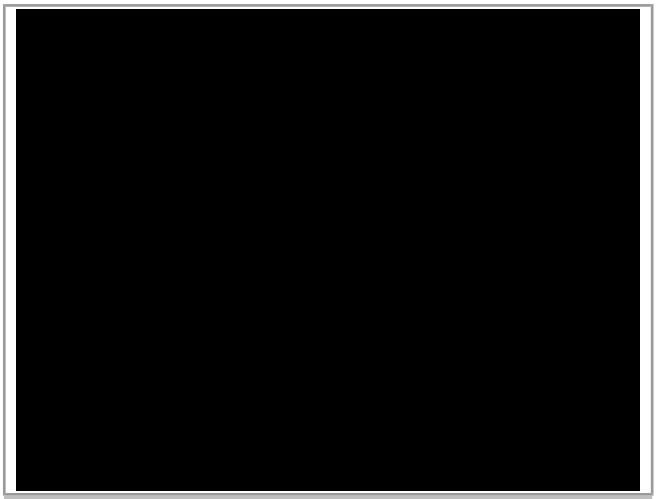
Scheme 41 Synthesis of quinolines by copper catalyzed oxidative arylation.

The authors also reported the plausible mechanism for the transformations in which the formation of aryl-copper(III) intermediate (**70**) was proposed. This key intermediate supposedly activates the nitrile function to generate iminium cation, which interacts with the alkyne moiety and forms vinyl cation. The electrophilic species induces intramolecular aromatic electrophilic substitution providing the appropriate heterocyclic systems such as quinoline (**96**) and quinazoline (**97**) derivatives (Scheme 42).

Scheme 42 Synthesis of heterocycles quinolines and quinazolines via the formation of Ar-Cu(III) intermediate.

Activation of nitrile moiety in the presence of acetylene function in copper catalyzed arylations was also studied by us. A novel synthesis of chromeno[*4,3*-

b]quinolines[79] (**99**) was developed in our group. The procedure is based on the copper catalyzed oxidative ring closure of arylpropynyloxy-benzonitriles (**98**) with diaryliodonium salts. The reactions were conducted in ethyl acetate while copper(I) chloride was used as a catalyst (Scheme 43). The overall transformation includes two sequential cyclizations which are accompanied by the formation of new C-C and C-N bonds. As a plausible mechanism, the reaction may proceed via the formation of arylcopper(III) species, which activates the nitrile function and the resulted iminium cation induces intramolecular triple bond activation and electrophilic substitution to give the condensed heterocyclic system.



Scheme 43 Synthesis of chromenoquinolines by copper catalyzed arylation.

3.3. Palladium Catalyzed Arylations

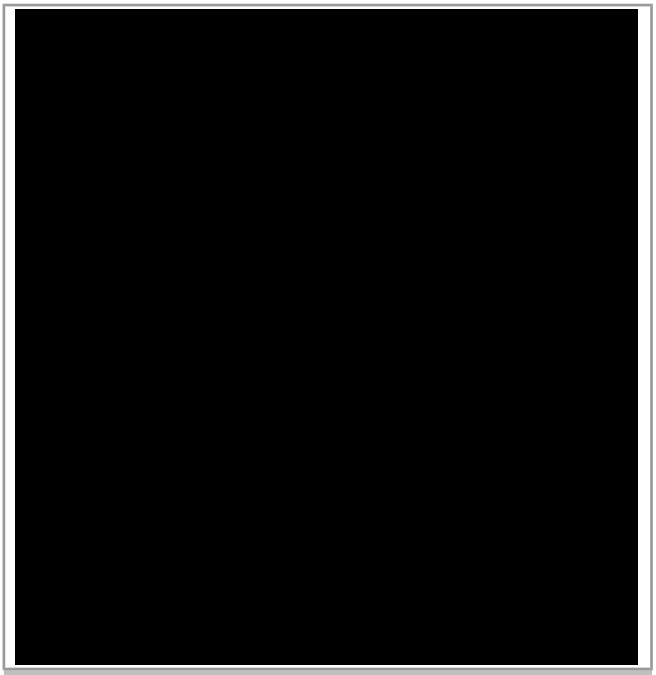
Similarly to the copper catalyzed arylations the palladium catalyzed reactions of diaryliodonium salts evolved in the last decade. Compared to other transition metals (Rh, Ru, Ir, Ag, Au) the utilization of palladium catalyst significantly came into the focus of organic transformations. This chapter is aimed to highlight the palladium catalyzed C-H activation reactions of arenes and heteroarenes.

The palladium catalyzed direct arylation of aromatic systems has short history. These transformations have been developing since the year of 2000. This topic can be divided into two major groups considering the direction of the C-H activation in the catalytic process: 1. Electrophilic palladation and arylation; 2. Directing group assisted C-H bond activation and arylation. However, in this account we do not discuss the palladium catalyzed cross-coupling-like arylations, oxidations and other couplings utilizing hypervalent iodine reagents are involved. It is important to note, the remarkable results on these topics have already been excellently reviewed earlier by others.[80]

3.2.3.1. Electrophilic Palladation and Arylation

From mechanistic point of view, it is important to focus to the electronic properties of the substrate and especially the palladium catalyst. Regarding this issue, the key palladation step can be significantly enhanced by the increased electron-deficiency of the catalyst during the C-H activation of aromatic systems.

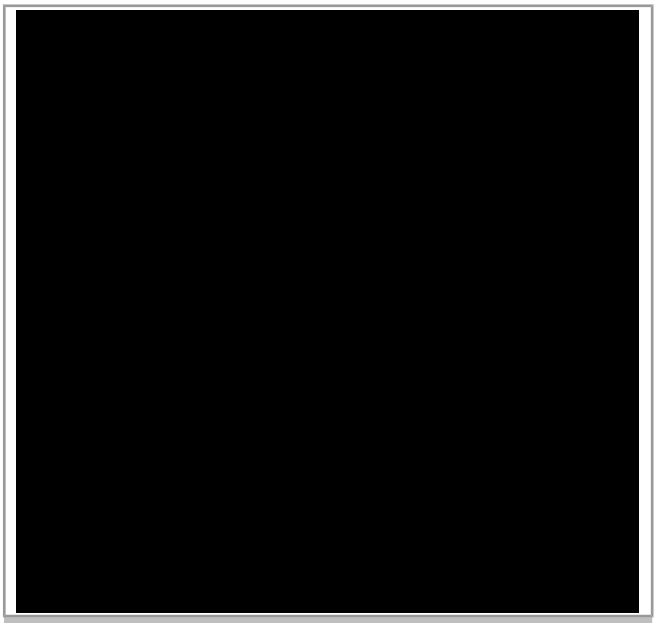
In 2006 M. S. Sanford and coworkers developed a procedure which enables the palladium catalyzed *C2* arylation of indoles (Scheme 44).[81] They utilized symmetric diaryliodonium salts as powerful arylating agents. In most cases, the arylation can be performed at room temperature, in acetic acid as a solvent.



Scheme 44 Phenylation of diverse indoles and pyrroles.

Interestingly, the screen of potential catalyst revealed that the more stabilizing ligands improve the catalytic performance, albeit in a longer reaction time. For this reason *IMes*$Pd(OAc)_2$ [*IMes* = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene] were applied as catalyst. The C-C coupling is feasible, and works excellently both with free indoles and its *N*-protected derivatives.

In 2011, Sanford reported a palladium catalyzed C-H arylation of 2,5-disubstituted pyrroles (Scheme 45).[82] The utility of the transformation was demonstrated (19 examples), including free or *N*-alkyl pyrroles and application of several symmetric iodonium salts as coupling partners. The presence of electron-withdrawing substituents on the aromatic rings of the diaryliodonium salts has deleterious effect on the arylation, but electron-donating groups and halogens were tolerated.



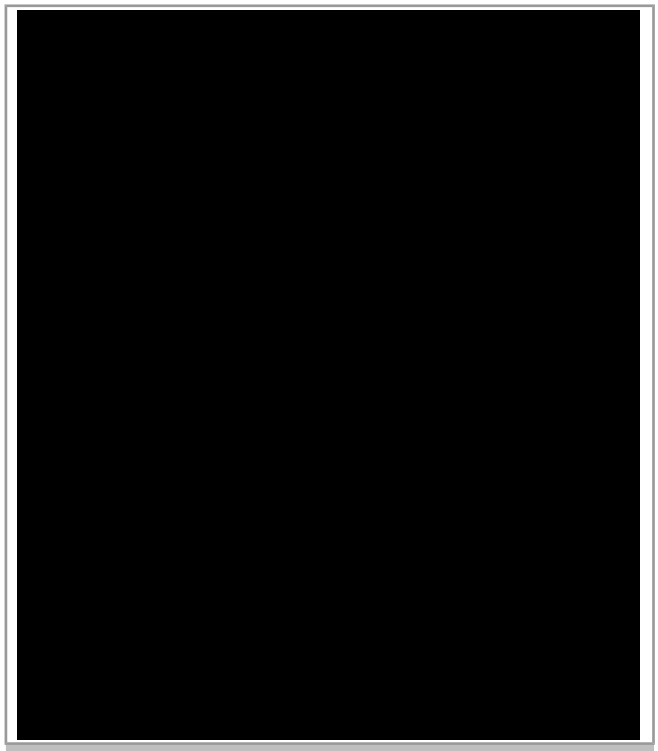
Scheme 45 Palladium catalyzed electrophilic arylation of substituted pyrroles.

Recently, a novel *C2*-selective arylation of indoles with heterogeneous nanopalladium catalyst using symmetrical and unsymmetrical iodonium salts was developed by Bäckvall and Oloffson.[83]

The C-H activation on benzofuran, benzothiophene, benzothiazole and benzimidazole have been reported by Zhang (Scheme 46).[84] The direct electrophilic palladation occur in the *C2* position of the heterocyclic substrate and provides the arylated product in moderate yields. Interestingly, *N*-phenylbenzimidazole and benzoxazole did not undergo in this arylation process.

Scheme 46 Phenylation of heteroaromatic compounds.

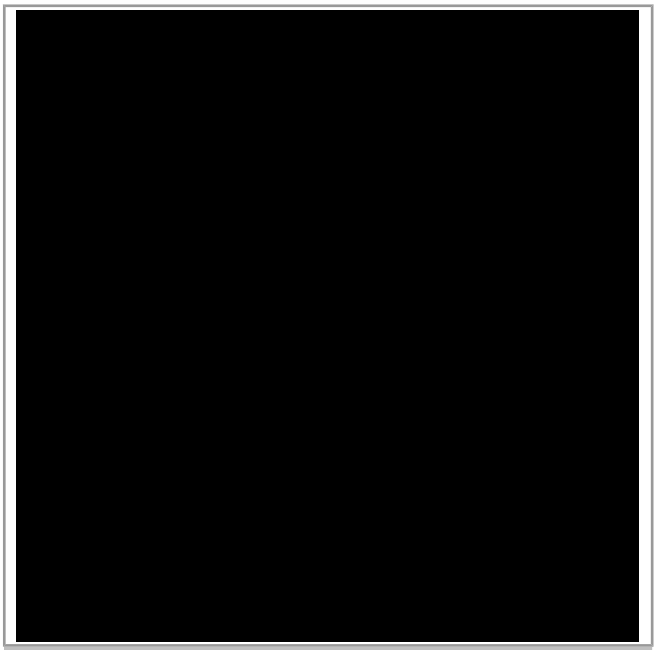
The direct arylation of thiophene, benzothiophene, indole, benzofuran and furan derivatives have also been investigated in thorough study by Glorius (Scheme 47).[85]



Scheme 47 Pd/C catalyzed C-H functionalization of heteroarenes.

The C-C bond formation was achieved using heterogeneous Pd/C catalyst without any ligand or additive. Practically, the arylation of thiophenes and benzothiophenes were completely *C3*-selective, but remarkably the N and O containing heterocycles underwent in exclusive *C2*-arylation. Under mild reaction conditions, the presence of halogen substituents (F, Cl, Br), electron-donating and electron-withdrawing functional groups were tolerated well. The chemo- and regioselectivity of this transformation were also demonstrated in this publication by application on more complex molecules.

The application of cyclic diaryliodonium salts (**111**) offers possibility for the synthesis of multi-substituted fused rings. In these transformations the biaryl moiety of iodonium salt remains the part of the aryl annulated product. With the utilization of this strategy phenanthrenes were synthesized[86] and other multi-component cascade reactions exclusively provided methylidenefluorenes.[87] Nevertheless, dibenzocarbazoles (**112**) were prepared via palladium catalyzed dual C-H functionalization of indoles (Scheme 48).[88]



Scheme 48 Synthesis of dibenzocarbazoles via dual C-H activation.

In a single operation two C-C bonds can be formed at position *C2* and *C3* of indole. The optimized conditions allowed the annulation in wide range of *N*-alkyl indoles (**110**). The reaction was found to be robust, insensitive to air and moisture. The indole substrates bearing substituents in position 4, 5 or 6 reacted smoothly in this double C-H activation manner. Electron-withdrawing substituents were tolerated, but in these cases the products were isolated in modest yields even at elevated temperature.

Very recently, a palladium catalyzed C-H bond activation cascade reaction was developed by Jana and coworkers for the synthesis of dibenzo-fused carbazoles (**115**) from easily accessible 2-arlyindoles and excess symmetrical diaryliodonium salts (Scheme 49).[89] Beyond the demonstration of the synthetic utility of the transformation, the exciting mechanism has also been discussed by the authors. It was supposed that the reaction includes several mechanistic steps such as *C3* electrophilic palladation of the indole ring, remote C-H activation, “through-space” 1,4-palladium migration, *ortho*-arylation of phenyl ring, 1,2-palladium migration, 1,2-aryl shift and finally the intramolecular cross-dehydrogenative coupling at the *C2* position. Utilizing this arylating method, 32 compounds were isolated in moderate to good yields. Regarding the compatibility of the functional groups with the reaction conditions it was demonstrated that alkyl groups and other electron-donating group, such as methoxy were tolerated as well as the presence of halogens (F, Cl, Br).

Scheme 49 Triple C-H activation to access dibenzo[*a,c*]carbazoles.

In 2011, a study was reported by Sanford on palladium catalyzed direct arylation of naphthalene derivatives (Scheme 50).[90] It was shown that by tuning of the properties of the catalyst (**118**) utilized in the transformation resulted remarkable 71:1=α:β selectivity. The chemoselectivity of C-H phenylation was investigated using different arenes for the transformation, and the regioisomeric ratio of the products was determined.

Scheme 50 α-Arylation of naphthalene and the proposed mechanism.

The optimized conditions yielded 5 pure α-, β-arylated naphthalenes also. On the basis of additional experiments, a mechanism was proposed, which was based on Pd(II)/Pd(IV) catalytic cycle. Similarly, palladium catalyzed C-H activation followed C-I dual activation reactions of coumarines has been reported by Han and Wang, very recently. The coumarines were condensed with aryl rings in position *C4* and *C5* and

30 examples of substituted 4,5-benzocoumarins were isolated.[91]

Arylation of arenes with iodonium salts was reported by Greaney et. al. (Scheme 51).[92] This procedure allowed the direct synthesis of substituted biphenyl derivatives, starting from simple alkylbenzenes. The arylation can be easily performed in trifluoroacetic acid using equivalent amount of symmetric diaryliodonium salts and 5 mol% of *Hermann-Beller* palladium catalyst (**120**). The reaction afforded the desired products mainly in good yields in the presence of electron-withdrawing and –donating groups on the hypervalent iodine reagents.

Scheme 51 Electrophilic arylation of unactivated benzene derivatives.

Substituents in *para* (**121j-o**) and *meta* (**121d-i**) positions to the iodine were tolerated well, but *ortho* (**121a-c**) position provided only lower yields. The unsymmetric substrates resulted mixture of isomers in different ratio (**121p-t**).

Very recently, the Pd/C catalyzed C-H arylation of polyaromatic hydrocarbons (PAH) such as triphenylene, anthracene, pyrene, phenanthrene and fluoranthene also have been reported by Glorius.[93]

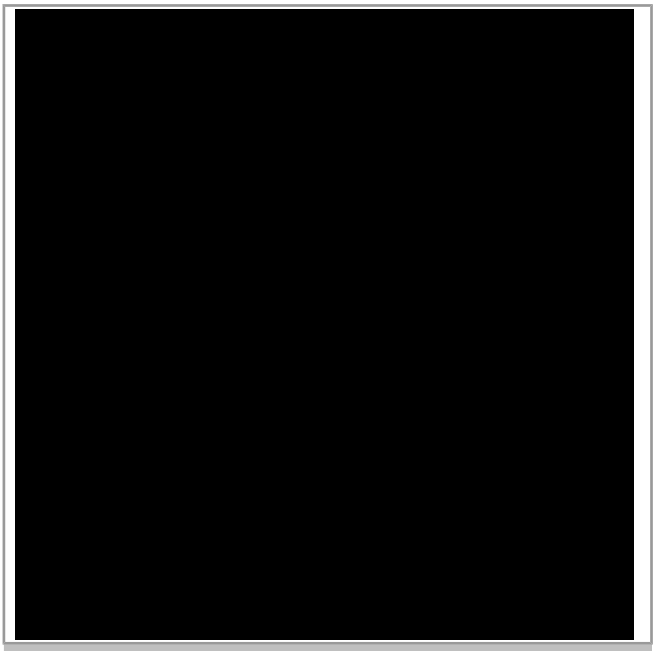
3.2.3.2. Directing group Assisted C-H Bond Activation and Arylation

In this section we discuss the set of C-H bond activation reactions which have been implemented under the aid of directing functional groups utilizing diaryliodonium salts. In general, the heteroatom of the directing group coordinates to the electrophilic palladium center. The formed dative bond directs the catalyst to the favorable conformation and allows the cleavage the *ortho* sp^2 C-H bond selectively.[94]

Scheme 52 Pivalamide phenylation with iodonium salt by Daugulis et. al.

In 2005 Daugulis et. al. reported an example of anilide ortho-arylation using the C-H activation methodology (Scheme 52).[95] The reaction of 4-methylpivalanilide (**122**) with excess diphenyliodonium tetrafluoroborate (**123**) underwent smoothly in presence of 5 mol% palladium(II) acetate catalyst and gave interestingly the sterically crowded 2,6-diarylated product (**124**) in 79% isolated yield.

In 2005, diverse directing group assisted *ortho*-arylation reactions were reported by Sanford et. al. (Scheme 53).[96] The mechanism of this palladium catalyzed oxidative C-H activation was also investigated.[97] Initially, the monophenylation of diverse heterocycles including pyridines (**125**), quinolones (**126**), pyrrolidinones (**128**), and oxazolidinones (**129**) were investigated using $[Ph_2I]BF_4$. The substrates containing effective directing group permit the regioselective *ortho*-arylation. In the presence of various functional groups such as ethers, amides, ketones, aldehydes or halides the transformation proceeds in moderate to good yields. There are some examples of phenylation of unactivated arenes with electron-donating and electron-withdrawing substituents. The reaction of *meta* substituted arenes resulted in a single regioisomeric product. Installation of diverse aryl groups with unsymmetrical $[MesIAr]BF_4$ salts was achieved as an extension of the reaction.

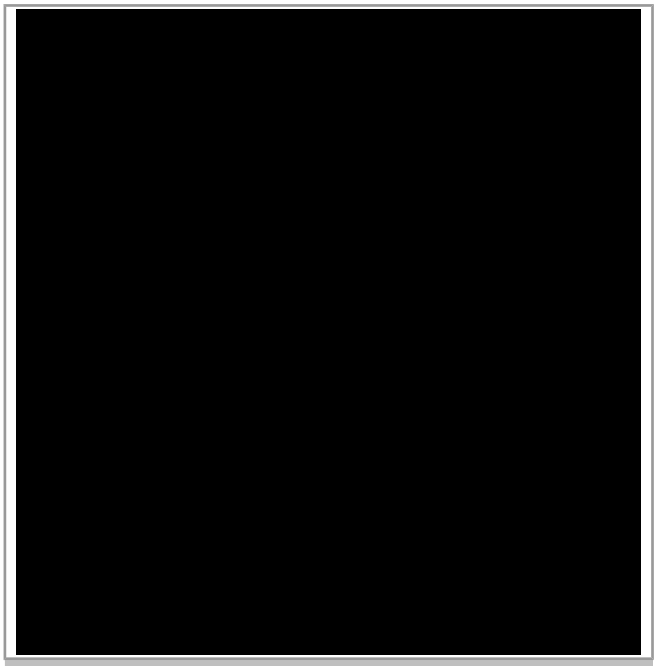


Scheme 53 Palladium catalyzed phenylation of C-H bonds.

The advent of photoredox chemistry greatly influenced on C-H activation reactions. In this co-operative photoredox and transition metal catalyzed coupling, the regioselectivity resolved by C-H activation and the photoredox chemistry contribute efficiently to the reactivity. The process starts in close proximity of photosensitizers with an electron transfer (SET) to the stable, non-activated compounds. The visible photons indirectly generate the desired, reactivated radicals from symmetrical diaryliodonium salts. In 2012, another example was reported by Neufeldt and Sanford, in which the C-H activation was merged with dual photoredox catalysis efficiently (Scheme 54.). [98]

Scheme 54 Pd/Ir-catalyzed phenylation.

The regioselective *ortho*-arylation of aromatic substrates was performed under mild conditions in methanol, at room temperature. *N*-aryl amides (**133**, **134**), benzamides (**136**), oxime ethers (**137**), aldoxime and ketoxime were used as a directing group to facilitate C-H arylation in moderate yields.



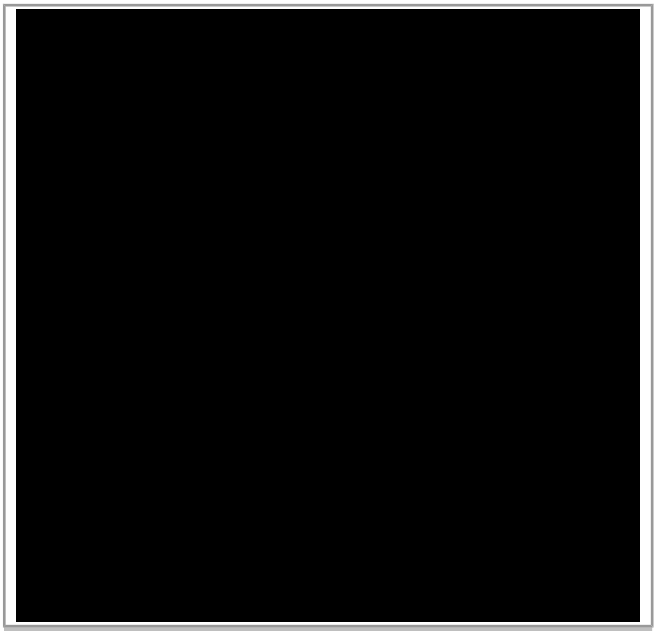
Scheme 55 Solvent-free catalytic *ortho*-arylation of carbamates and anilides.

However, *N*,*N*-disubstituted benzamide provided the product (**136c**) in poor yield. Various diaryliodonium salts were evaluated and high yields were obtained in case of electron-neutral substituents. The sterically hindered mesityl group from the iodonium salt could be transferred only in low yield.

Palladium catalyzed C-H activation of arylcarbamates (**140**) was carried out first by Bedford, Mitchell and Webster in 2009.[99] The reported results revealed the opportunity of a step-economical arylation of phenol derivatives in a solvent-free method using microwave irradiation. One year later, the authors presented a synthetically expanded new procedure to perform the arylation of aromatic carbamates. Under different reaction conditions a selective functionalization of amides (**139**), arylcarbamates (**141h**) and free phenols (**141a-g**) were achieved (Scheme 55).[100] Under the solvent-free approach, the reaction of *N*,*N*-diethyl carbamates underwent with mesitylaryliodonium salts [MesIAr]OTf and provided the corresponding mono-arylated free phenol products in excellent yield. The amide functional group retained without any change.

In 2010 Liu and co-workers published the palladium catalyzed C-H arylation of phenol esters (Scheme 56).[101] In most cases the pure arylated esters (**143**) have been prepared in good to excellent yields. Interestingly, during the reaction process certain substrates controllably provided the free phenol products (**144**). With systematic optimizations 10 mol % palladium(II) acetate or pivalate catalyst, 10 mol% triflic acid and acetic anhydride or pivalic anhydride additives proved to be applicable for the efficient catalytic transformation. However, the utilization of bulkier palladium(II) pivalate and Piv_2O composition ensured higher yields. $[Ph_2I]OTf$ has been used as

phenylating agent, but in the other hand, different aryl functionalities installed by utilizing [MesIAr]OTf unsymmetrical iodonium salts. The reaction tolerates well the presence of both electron-withdrawing and electron-donating functional groups.



Scheme 56 *Ortho* C-H activation and arylation of phenol esters.

In 2013 Zhou et. al. presented a novel synthetic tool for the arylation of aromatic carboxylic acids (**145**) using mesitylaryliodonium salts. The palladium catalyzed C-H *ortho*-arylation of benzoic acids was performed in water at 100 °C (Scheme. 57).[102]

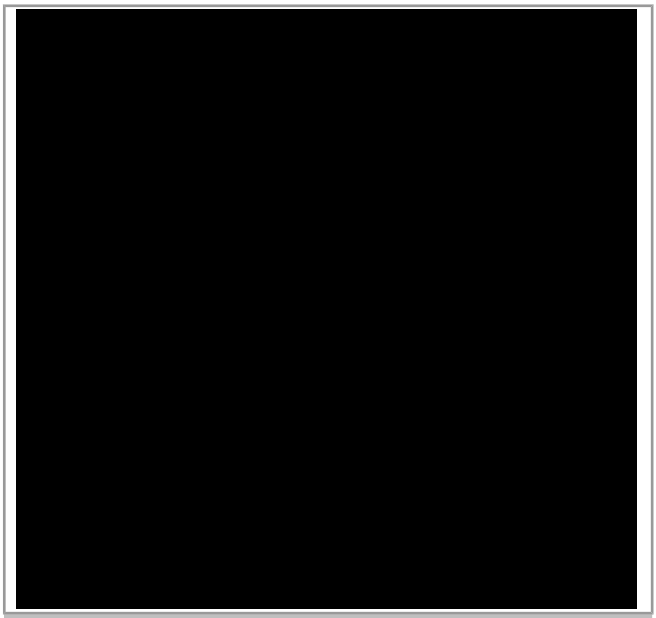
Scheme 57 Palladium catalyzed C-H *ortho*-arylation of benzoic acids.

Generally, this method provided smoothly the differently substituted monoarylated benzoic acid derivatives (**146**) with high efficiency. Noteworthy, the F, Cl and Br substituents on the aromatic ring of the acid were tolerated as well as on the installed aryl group, but the highly electron-deficient functional groups such as CF_3 had deleterious effect on the C-H activation.

Recently, Li and co-workers developed a versatile palladium catalyzed direct C-H activation process for the *ortho* arylation of aromatic carbamates (Scheme 58).[103] Under mild reaction conditions the carbamates (**147**) were arylated in the *ortho* position using palladium(II) acetate as catalyst and symmetrical diaryliodonium tetrafluoroborate salts as arylating agents. Compared to the chemically similar phenol carbamates, the aniline carbamates did not decompose in acidic reaction media. Most substrates provided regioselectively the desired products at different reaction temperature in good to excellent yields. Notably, electron-deficient aniline carbamates gave generally moderate to good yields. Interestingly, in a sequential reaction setup both *ortho* C-H bonds could be activated and the appropriate diarylated *N*-phenyl carbamates (**148y**) were isolated.

Scheme 58 Palladium catalyzed C-H activation/arylation of anilide carbamates.

Although, the use of directing groups has become a widespread strategy for *ortho*-selective C-H activation and functionalization, there is a great driving force in development of more practical and effective directing groups. Instead of carboxylic derivatives, Lee and co-workers took advantage of possibilities afforded by the phosphoramidate functional group (Scheme 59).[104] In these *ortho*-arylation reactions mainly diphenyliodonium triflate and other symmetric iodonium salts were used as reagents.

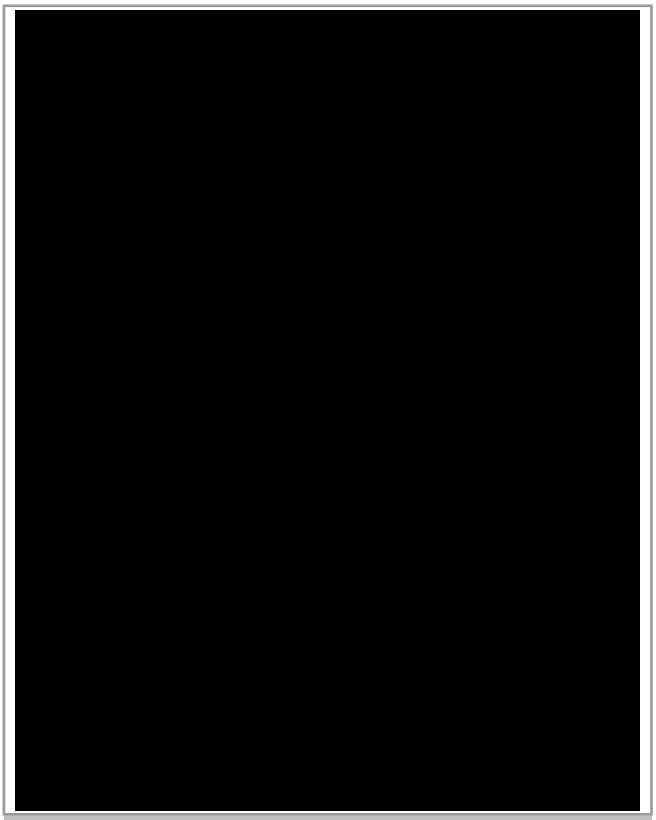


Scheme 59 Phosphoramidate directed *ortho*-arylation at room temperature.

Numerous substrates were arylated in wide variety, using the optimized reaction conditions. In this transformation the bulky phenyl (**150x,y**), *tert*-butyl (**150h**) substituted compounds underwent mono-phenylation. Ethers (**150f-k, r, v**), esters and benzylic CH functionalities (**150c**) were tolerated well. *N*-aryl-*N*-alkyl phosphoramidates (**150n-q**) proceeded smoothly to give the corresponding *ortho*-arylated products.

Simultaneously with the previous example, in 2013 two research groups (Kang et. al.[105] and Kim et. al.[106]) presented independently the innovative arylation of aryl phosphates (Scheme 60). The two reaction conditions marginally differ from each other, but these methods demonstrated their robust nature. The application of diverse symmetrical [Ar_2I]OTf and unsymmetrical [MesIAr]OTf hypervalent iodonium salts allowed broad and versatile arylation of mono- and disubstituted aryl phosphates in *ortho* position. Furthermore, the transformation was also applicable to more complex bicyclic aromatic compounds.

Recently, Yang et al. reported a palladium catalyzed C–H activation and arylation of (diisopropylphosphoryl)biphenyl skeleton derivatives by the direction of $P(O)R_2$ functional group (Scheme 61).[107] A series of polyaromatic monophosphorus compounds have been synthesized and transformed into trivalent phosphorous compound by reduction. After this treatment these directing groups become applicable in transition-metal catalyzed cross-coupling reactions as phosphane ligands. The scope of the arylation and limitations has been investigated.



Scheme 60 Organophosphates directed regioselective arylation of arenes.

Different directing groups were examined, where R is cyclohexyl (**156b**), *tert*-butyl (**156c**) or phenyl (**156d**) and the desired products were obtained in moderate yields. The phenylation proceed smoothly to give the corresponding products if *ortho*-, *meta*- or *para*-positioned electron-donating (methyl, methoxy) substituents are connected to the diisopropylphosphoryl biphenyls. The presence of Cl (**156k, p**) and CF_3 (**156l**) were also tolerated. Considerably, different hypervalent iodine reagents were evaluated as arylating agents.

Scheme 61 Palladium catalyzed $P(O)R_2$ directed C–H arylation.

4. Conclusion

In this account we aimed to give a brief insight into the chemistry performed with one member of the family of hypervalent reagents. We can conclude that, diaryliodonium salts gained several applications in organic synthesis in the last decade. The unique chemical properties of the compound class make them useful reagents, and their utilization opened new synthetic possibilities in organic chemistry. It has been demonstrated that the hypervalent diaryliodonium reagents serve as excellent aryl sources for the functionalization of aromatic and heteroaromatic systems both in the presence and absence of transition metal catalyst. Moreover, with the exploitation of their electrophilic character cyclization of unsaturated acyclic compounds can be achieved to construct novel and versatile carbocyclic and heterocyclic frames. The existing methodologies not only ensures easy access to arylated organic species, but offer new mechanistic possibilities for the design of novel transformations on the field of metal free and transition metal catalyzed reactions in the future.

Acknowledgment

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