

Review

# Diaryliodoniums Salts as Coupling Partners for Transition-Metal Catalyzed *C*- and *N*-Arylation of Heteroarenes

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**Abstract:** Owing to the pioneering works performed on the metal-catalyzed sp2 C–H arylation of indole and pyrrole by Sanford and Gaunt, *N*– and *C*-arylation involving diaryliodonium salts offers an attractive complementary strategy for the late-stage diversification of heteroarenes. The main feature of this expanding methodology is the selective incorporation of structural diversity into complex molecules which usually have several C–H bonds and/or N–H bonds with high tolerance to functional groups and under mild conditions. This review summarizes the main recent achievements reported in transition-metal-catalyzed *N*– and/or C–H arylation of heteroarenes using acyclic diaryliodonium salts as coupling partners.

**Keywords:** diaryliodonium salts; arylation; heteroarenes; palladium; copper; iridium; visible light; tandem; domino; atom-economical

### 1. Introduction

Diaryliodonium salts are air- and moisture-stable, non-toxic, easy to handle and commercially available or easy to prepare [1–8]. During the last decade, noteworthy improvement in the synthesis and use of diaryliodonium salts has been reported [9–21]. Owing to their electron-deficient nature at the iodine center and to the excellent leaving-group ability of the iodoarene, diaryliodonium salts are frequently employed as aromatic electrophiles in aryl transfer processes [22–38]. Seminal contributions from the Pike, Olofsson, Kita and Stuart groups highlighted the efficiency and the selectivity of this aforementioned reaction. Diaryliodonium salts appear as fairly appealing electrophilic arylating reagents as well as precursors for positron emission tomography (PET) [39,40]. They are powerful intermediates for the synthesis of a broad range of radiofluorinated synthons and clinically relevant PET tracers [41–56]. Since the pioneering works on the palladium- and copper-catalyzed arylation of sp2 C–H indoles reported respectively by Sanford [57] and Gaunt groups [58], *N*– and *C*–arylation involving diaryliodonium salts offer a highly complementary strategy for the synthesis and derivatization of heteroarenes (Scheme 1). Indeed, several methodologies have been developed for carbon and heteroatom arylations in the presence of acyclic diaryliodonium salts.

The synthesis of bis-arylated compounds from this late-stage functionalization strategy represents an appealing approach, notably in drug discovery, and provides more options for the incorporation of structural diversity into heterocycles having several C–H bonds [59]. In most intermolecular iodonium arylation reactions to date, a symmetric aryliodonium salt or a non-symmetric bearing a hyper nucleofuge ("dummy" group) such as TMB (2,4,6-trimethoxyphenyl), Mes (2,4,6-methylphenyl) or TRIP (2,4,6-tri*iso*propylphenyl) was used as a coupling partner liberating the aryliodide as a by-product. Sparse examples of attractive tandem/domino C–H and *N*–H reactions, avoiding waste, have also



been reported. Here we focused on recent developments in metal-catalyzed  $C_{sp2}$ - and N-arylation of heteroarenes using acyclic diaryliodonium salts as coupling partners over the past 10 years. Mechanism details, usually involving "high-valent" organometallic palladium, copper or iridium intermediates, are given when they are discussed by the authors but are not fully covered here.



Scheme 1. C-H or N-H arylation of heteroarenes with diaryliodonium salts.

#### 2. Metal-Catalyzed sp2 C-H Arylation of Heteroarenes

#### 2.1. Palladium-Catalyzed C-H Arylation

In 2006, Sandford and co-workers were the first to report the regioselective Pd-catalyzed arylation of indoles and pyrroles with symmetrical diaryliodonium salts at the C2–H site under mild conditions [57]. Using IMesPd(OAc)<sub>2</sub> as a catalyst (IMes=1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene), free and *N*-methyl heterocycles were selectively 2-arylated through an electrophilic indole or pyrrole palladation followed by a subsequent oxidative arylation with the diaryliodonium salt involving a Pd<sup>II/IV</sup> pathway. The direct palladium-catalyzed phenylation of an indole-derived metal-organic framework (MOF) at C2 and the arylation of 2,5-disubstituted pyrroles at C3 were further reported by Glorius [60] and Sanford [61] respectively. From a general point of view, site-selective arylation of indole derivatives has attracted much attention in the last decade as a straightforward strategy for late-stage functionalization of these valuable *N*-bearing scaffolds [62–65].

Following these preliminary studies, one example of palladium-catalyzed C–H arylation of *N*-benzyl-3-pivaloylindole was recently reported by Shi and co-workers who have developed a regiocontrolled C–H arylation of indoles at the C4 and C5 positions (see, Part 2.2. Copper-Catalyzed C–H Arylation) by switching the additive and the solvent [66] (Scheme 2). The palladium-catalyzed C4 and C5 arylation of the indole scaffold with diaryliodonium triflates took place using a versatile pivaloyl group as the directing group. The additive and the solvent were found to have a significant role in determining the site selectivity of the palladium-catalyzed phenylation reaction. Nevertheless, the scope of the reaction was done with various iodoarenes as coupling partners instead of aryliodonium salts. In this context, the suggested catalytic cycle to account for the selectivity of the palladium-catalyzed arylation reactions was restricted to the use of iodoarenes as arylating reagents.



**Scheme 2.** Site-selective phenylation of *N*–benzyl-3-pivaloylindole depending on the additive and the solvent of the reaction. DCM: dichloromethane; HFIP: hexafluoro*iso*propanol or trifluoroethanol.

Very recently, McGlacken and co-workers described the synthesis of phenyl(mesityl)-iodonium triflate and its application in the direct palladium-catalyzed C2–H arylation of indole [67] dedicated to a collaborative laboratory experiment undertaken by undergraduate chemistry students at University College Cork in Ireland and Technische Universität Wien in Austria. The phenylation reaction of the NH-free indole was performed under base-free conditions using Pd(OAc)<sub>2</sub> as the catalyst in ethyl acetate as the solvent at 50 °C for 1 h (Scheme 3) and gave the 2-phenylindole with an average yield of 30%.



**Scheme 3.** Palladium-catalyzed direct C2–H arylation of indole with phenyl(Mes)iodonium triflate. Mes: 2,4,6-methylphenyl.

Since the introduction of an aryl group drastically improves the intrinsic photophysical properties of the indole motif, some examples of palladium-mediated C–H bond arylation have been designed on tryptophan derivatives and more challenging tryptophan-containing peptides [68,69]. In 2015, Fairlamb developed the synthesis of 2-aryl-tryptophans using Pd(OAc)<sub>2</sub> in the presence of unsymmetrical diaryliodoniums composed of the sterically hindered mesityl group in ethylacetate as the solvent under mild conditions (Scheme 4a) [68]. The strategy was successfully extended to small tryptophan-containing dipeptides TfaGlyTrp-OMe and Tfa-LeuTrp-OMe (Scheme 4a) and to two peptides containing a C– terminal alanine residue (Ac-AlaTrpAla–OH and AcSerGlyTrpAla–OH) which had proved problematic with oxidative conditions such as Cu–mediated arylation (Scheme 4b).



**Scheme 4.** (a) Palladium-catalyzed direct C2–H phenylation of tryptophane amino acids and dipeptides derivatives with phenyl(Mes)iodonium triflate. (b) Direct C2–H phenylation of two peptides containing a C– terminal alanine residue.

Li and co-workers described in 2018 a palladium-catalyzed C2 arylation of Fmoc-L-tryptophan using symmetrical and unsymmetrical diaryliodonium triflates with good chemoselectivities [69].

In the case of unsymmetrical iodine(III) compounds containing a 1,3,5-tri*iso*propylphenyl unit (Trip) as a dummy group, the smaller group was transferred selectively. Aryliodoniums bearing electron-withdrawing or electron-donating groups at the para position exhibited good reactivity, except the *p*-nitrophenyl derivative (Scheme 5a). The expected arylated compounds were obtained in yields ranging from 16% to 82% without the loss of stereochemical integrity. It could be noted that chlorine and bromide substituents were well-tolerated whereas the sterically congested 2- and 2,4,6-substituted iodonium salts provided lower yields. The observed reactivity with a favored transfer of more electron-rich or least bulky aryl group is consistent with the trends in chemoselectivity in the presence of a transition-metal catalyst. The proposed mechanism is in agreement with the biaryl formation through a Pd<sup>II/IV</sup> catalytic cycle involving a coordination of the Fmoc-Trp-OH amino acid to the Pd(TFA)<sub>2</sub> and subsequent C–H activation to form a seven-membered palladacycle (Scheme 5b). After the oxidation by the aryliodane of the Pd(II) intermediate to the Pd(IV) species, the reductive elimination provided the desired products and the Pd(II) catalyst was regenerated.



**Scheme 5.** (a) scope of the direct C2–H arylation of Fmoc-Trp–OH amino acid with various diaryliodoniums. (b) Plausible mechanism of the palladium-catalyzed C2–H arylation of Fmoc-Trp–OH. TRIP: 1,3,5-tri*iso*propylphenyl.

Although decarboxylative cross-coupling reactions are not covered in this review, it is worth mentioning a recent report from the group of Kumar who described the synthesis of 2-arylindoles from indole-3-carboxylic acid and diaryliodoniums under base- and ligand-free conditions [70].

Heterogeneous catalytic systems were also developed for the selective arylation of 5-membered ring heterocycles using diaryl- $\lambda^3$ -iodanes. In 2014, Bäckvall and Olofsson described the selective C2 arylations of both *N*–H indoles and *N*-protected indoles with various diaryliodonium salts in water under mild conditions [71]. Evaluation of the counteranion revealed that the reactions with

tetrafluoroborate are more efficient than those with tosylate or triflate anions, probably due to its weakly coordinating ability to the palladium center. The desired products were obtained thanks to a powerful heterogeneous catalytic system based on recyclable Pd nanoparticles supported on amino-functionalized mesocellullar foam, Pd<sup>0</sup>-AmP-MCF, in high yields (Scheme 6). Even if this catalyst is reusable, the dispersion of Pd species away from the nanoclusters to the aminopropyl groups on the MCF results in a gradual decrease in activity at each catalytic cycle.



**Scheme 6.** Heterogeneous nanopalladium catalyzed-C2 selective arylation of indoles. MCF: mesocellullar foam.

A similar ligand- and additive-free reaction using *N*-methylindole was published by Wan in which C2-selective arylation was achieved by using a reusable solid Pd catalyst and water as a solvent [72]. These environmentally benign and robust reactions were carried out with diaryliodonium triflates employing ordered mesoporous materials to support a reusable solid Pd catalyst (Pd/11.5ODDMA-MP, ODDMA = octadecyldimethyl[3-(trimethoxysilyl)propyl]ammonium chloride) (Scheme 7). The study was successfully extended to *N*-H indole and benzofuran but with reverse selectivity in the case of benzothiophene (C2:C3 < 1:99). Both hot filtration tests and mercapto-functionalized silica as a selective trapping agent demonstrated the undetected leaching of Pd in the liquid phase—a huge benefit notably in the synthesis of pharmaceuticals. The authors explained the high catalytic performance by the well-dispersed Pd nanoparticles as well as the electron-rich environment stabilized by the *N*-containing functional groups and the uniform mesopores.



**Scheme 7.** Selective C2 arylation of indoles and benzofuran using Pd/11.5ODDMA-MP. ODDMA: octadecyldimethyl[3-(trimethoxysilyl)propyl]ammonium chloride.

Very recently, Vaccaro also reported an efficient procedure for the selective C2-arylation of indole derivatives using palladium-containing metal-organic-frameworks (Pd@MOF) as a heterogeneous Pd catalyst and biomass-derived solvent ( $\gamma$ -valerolactone, GVL) as a reaction medium, ensuring reduced metal leaching and improvement of the catalyst-recyclability (Scheme 8) [73]. The high yields and excellent site-selectivity were triggered by the presence of the MOF (UiO-66-BTeC, (Zr<sub>6</sub>O<sub>4</sub>(OH)<sub>4</sub>(BDC)<sub>4.75</sub>(BTeC)<sub>1.25</sub>) as a structural formula with BDC (terephthalate) and BTeC (1,2,4,5-benzenetetracarboxylate), with increasing the activity of Pd(OAc)<sub>2</sub> compared to homogeneous conditions.



**Scheme 8.** Eco-friendly Pd@UiO-66-BTeC catalyzed selective C2 arylation of various indoles in bioderived  $\gamma$ -valerolactone. BTeC: 1,2,4,5-benzenetetracarboxylate.

Palladium-catalyzed C3–H arylation of thiophenes was then investigated by Glorius to design a streamlined synthetic route to various substituted  $\beta$ –arylated thiophenes with notable functional group tolerance [74]. Several 4- or 5-monosubstituted thiophenes or 2,5/4,5-dimethylated thiophenes were successfully selectively arylated at C3 using diphenyliodonium tetrafluoroborate or unsymmetrical iodonium salts and 5 mol% of Pd/C in ethanol at 60 °C (Schemes 9 and 10). The reaction was found to be tolerant to water and air. The mild reaction conditions using a widely available heterogeneous catalytic system were applied to various heteroarenes including furan, benzofurans, benzothiophenes and *N*–*H* indole useful for materials or biological applications. Expected C3–phenylated benzothiophene derivatives were obtained in good yields and high selectivity (>99:1) whereas the C2–phenylated benzofuran and indole were isolated in moderate yields.



**Scheme 9.** Direct C3–H arylation of 2-*n*-butylthiophene with various diaryliodoniums [ArI(TRIP)]BF<sub>4</sub> or OTf.



**Scheme 10.** Thiophene scope in the direct C3–H phenylation with diphenyliodonium tetrafluoroborate salt as a coupling partner.

The selective arylation of thiophene and benzothiophene derivatives at the C3–position was described by McGlacken using an impregnated palladium on magnetite as a catalyst and diphenyliodonium tetrafluoroborate as an electrophilic arylating reagent (Scheme 11) [75].



Scheme 11. C3-arylation of thiophenes and benzothiophene using heterogeneous catalysis.

This attractive approach using heterogeneous catalysis was successfully extended to benzofuran and indole derivatives with diphenyliodonium tetrafluoroborate or unsymmetrical iodine(III) compounds containing a 1,3,5-tri*iso*propylphenyl unit (TRIP) as a dummy group. After heating at 60 °C in ethanol for 24 h, the C2–arylated products were isolated in moderate to high yields (Scheme 12). The deactivation of the catalyst was observed probably because of the adsorbance of iodine on the surface of the Pd catalyst. It could be noted that C2–phenylation of benzofuran and indole was previously reported in 2012 by Zhang, using Pd(OAc)<sub>2</sub> as a catalyst [76].



Scheme 12. Selective C2-arylation of benzofuran and indoles under mild conditions.

Recently, diaryliodonium salts have been shown to promote the synthesis of various aryl butenolides, widely found in biologically active lactones, following a palladium-catalyzed  $\gamma$ -arylation of silyloxy furan derivatives (Scheme 13) [77,78]. The reactions were carried out at room temperature using Pd(OAC)<sub>2</sub> (5 mol%) and 1,2-Bis(diphenylphosphino)benzene (dppbz) as bidentate phosphine ligand in the presence of NaOAc (0.8 equivalent) as an additive. The optimization studies revealed that the use of dichloromethane (DCM) as a solvent ruled out the undesired proto-desilylation as well as the precipitation of palladium and the diaryliodonium salt being the limiting reagent. The use of symmetrical diaryliodonium salt led to the corresponding arylated butenolides in a yield ranging from 13% to 90% whereas unsymmetrical coupling partners gave the corresponding products in lower yields (5%–61%). The methyl group on the butenolide drastically affected the efficiency of the reaction and the arylation of  $\gamma$ -methyl silyloxy furan derivatives suffered from reduced yields. The authors hypothesized a mechanism based on the reaction of the hypervalent iodine reagent with the catalyst in which the aryl group is transferred selectively to generate the palladium intermediate. Subsequent C–H activation affords the Pd(IV) species which leads to the arylated product after reductive elimination (Scheme 13b).



**Scheme 13.** (a) Scope of Pd-catalyzed  $\gamma$ -arylation of silyloxy furans with unsymmetrical aryl(mesityl)iodonium hexafluorophosphates. (b) palladium-catalyzed  $\gamma$ -arylation reaction by coupling silyloxy furans and aryl(Mes)iodonium salts. DCM: dichloromethane; dppbz: 1,2-Bis(diphenylphosphino)benzene.

The Pd(II)-catalyzed C4–selective arylation of isoquinolone using symmetrical diaryliodonium tetrafluoroborates was reported by Hong [79]. The reaction was conducted with Pd(OPiv)<sub>2</sub> (10 mol%) as a catalyst in DME at 120 °C for 24 h and the high regioselectivity was consistent with an electrophilic palladation pathway involving a Pd(II/IV) catalytic cycle (Scheme 14) [80]. A radical mechanism was ruled out since the addition of a scavenger in the reaction mixture did not affect the reaction. The authors suggested that the reaction was initiated by electrophilic palladation before deprotonation by the pivalate ligand to generate the C4–palladated intermediate. Oxidation of the palladated species afforded the Pd(IV) complex with diaryliodium salts as oxidants. Finally, C–C bond formation was done by a reductive elimination from the hypervalent palladium center (Scheme 14b). The optimization studies revealed that both the efficiency of the arylation and the C4–regioselectivity were enhanced using diaryliodonium salts as the coupling partners.



**Scheme 14.** (a) Base- and ligand-free C4 selective arylation of isoquinolinones with symmetrical diaryliodonium tetrafluoroborates. (b) Proposed mechanism for C4 arylation of isoquinolinones.

Very recently, Kumar and co-workers reported a site-selective palladium-catalyzed CH arylation of quinolin-4(1H)-ones using diaryliodonium Salts [81]. Driven by the design of substrate-controlled site-selective reactions, the authors described an elegant C3–, C5– and C8–selective arylation by the utilization of an intrinsic directing group (Scheme 15a) [82,83]. The regioselective keto-directed C5 arylation of quinolin-4(1H)-one was conducted using 5 mol% Pd(OAc)<sub>2</sub> as a catalyst in AcOH at 100 °C for 6 h and various unsymmetrical aryl-(mesityl) iodonium triflates, leading to a wide range of 5-arylquinolin-4(1H)-ones in high yields (Scheme 15b). Selective C8 arylation was obtained under the same reaction conditions by using *N*-hydroxy as an intrinsic directing group, whereas C3 phenylated quinolones were reached by switching the reaction solvent from acetic acid to 1,4-dioxane, followed by the addition of silver carbonate (Scheme 15a). The suggested mechanism for C5 and C8 arylation involved a coordination between the oxygen atom of the keto or hydroxy group to the  $Pd^{II}$  metal leading to cyclopalladation species through the activation of the C-H bond of C5 or C8 position. The oxidative addition of diaryliodonium triflates generated Pd<sup>IV</sup> intermediates and the reductive elimination produced C5/C8 arylated products. For C3 arylation, initial electrophilic palladation of N-alkyl or benzyl-quinolin-4(1H)-one followed by a classical oxidative addition of diaryliodonium triflate to the Pd<sup>II</sup> intermediate afforded arguably Pd<sup>IV</sup> species which upon reductive elimination lead concomitantly to the C3-arylated product and the release of the Pd catalyst regenerated by the silver carbonate.





**Scheme 15.** (a) substrate- and solvent-controlled site-selective phenylation of quinolin-4(1H)-one derivatives using Pd(OAc)<sub>2</sub> as a catalyst. (b) Scope of the C5 arylation using various unsymmetrical aryl-(mesityl) iodonium triflates.

Very recently, Pd-catalysed C8 arylation of quinoline-*N*-oxides by reaction with diaryliodonium salts as an arylating agent has been developed by Sharma and co-workers [84]. The reaction of quinoline-*N*-oxide and aryl(mesityl)iodonium triflates was performed using 5 mol% Pd(OAc)<sub>2</sub> as a catalyst in AcOH at 100 °C for 12 h (Scheme 16a). The proposed plausible reaction pathways for C8 arylation of quinoline-*N*-oxide involved the coordination of the oxygen atom of *N*-oxide group to the Pd<sup>II</sup> metal followed by a C–H insertion to generate a palladacycle. The oxidative addition of (aryl)(mesityl)iodonium salt to the cyclopalladation species furnished the high valent Pd(IV) intermediate. C8–arylated quinoline-*N*-oxides were produced after reductive elimination with the regeneration of the Pd(II) species to complete the catalytic cycle (Scheme 16b).

Since 2-arylbenzothiazole derivatives are attractive building blocks for various drug molecules, their synthesis via a palladium-catalyzed C–H arylation in the presence of diaryliodonium salts has been developed [76,85]. The reactions are catalyzed by palladium bromide in the presence of cesium carbonate and 1,3-bis(diphenyphosphino)propane (dppp) as a ligand and are conducted at reflux in acetonitrile for 24 h (Scheme 17a). Studying the effect of diaryliodonium salt on the reaction revealed that tetrafluoroborate salts led to the expected product in higher yield and steric hindrance affected the course of the reaction. Unsymmetrical diaryliodonium tetrafluoroborates bearing a 2,6-dimethylphenyl group as a dummy group gave exclusively the expected arylated compounds. The reaction pathway involving a Pd(II/IV) catalytic cycle through an oxidative addition of the diaryl iodine(III) salt to PdBr<sub>2</sub> is the most plausible mechanism. The highly electrophilic Pd(IV)-aryl intermediate, generated by the cleavage of the hypervalent iodine aryl bond, reacted with benzothiazole to give the corresponding Pd(IV)-heteroaryl intermediate which could release concomitantly the C2–arylated compound and the Pd(II) catalyst after reductive elimination (Scheme 17b).



**Scheme 16.** (a) Scope of the C8 arylation of various quinoline-*N*-oxides with aryl(mesityl)iodonium triflates. (b) Plausible mechanism of palladium-catalyzed C8 arylation.



**Scheme 17.** (a) C2 arylation of benzothiazole derivatives with diaryliodonium tetrafluoroborates. (b) Possible mechanism for C2 arylation of benzothiazoles with PdBr<sub>2</sub> and dppp = L as a catalytic system.

advantages such as reduction of the synthetic steps and no production of stoichiometric amount of toxic by-products are provided by using domino arylations of imidazopyridine derivatives. In this context, a palladium-catalyzed direct arylation of 2-phenylimidazo[1– $\alpha$ ]pyridine using diphenyliodonium triflate as a coupling partner was described by Wang et al. [89]. The screening of the reaction conditions revealed that using K<sub>2</sub>CO<sub>3</sub> as the base and Pd(OAc)<sub>2</sub> (10 mol%) as a catalyst in DMF at 100 °C for 24 h led to the selective C3–phenylation in 91% (Scheme 18). On the other hand, when the reactions were carried out in acetic acid in the presence of K<sub>2</sub>HPO<sub>4</sub> instead of carbonate, a domino arylation process took place. This one-pot synthesis approach gave easy access to a family of phenanthro-imidazopyridine-fused heteropolycycles.



**Scheme 18.** C3–selective arylation versus domino arylation of 2-phenylimidazo $[1-\alpha]$ pyridine.

#### 2.2. Copper-Catalyzed C–H Arylation

The first copper catalysis system, based on electrophilic metalation of indole, that enables site-selective sp2 C–H bond arylation at C3 was reported by Gaunt and co-workers [58]. The authors hypothesized that a Cu(III)-aryl intermediate, a highly electrophilic d8-configured metal species, is generated from the in situ oxidation of the Cu(I) catalyst and undergoes Friedel–Crafts-type arylation at the most nucleophilic position of the indole. C2–arylated indoles were also synthesized through a C3 to C2 migration of the C–Cu bond promoted by an *N*-acetyl group on indole derivatives. Four years later, MacMillan [90] and Reisman [91] reported independently the synthesis of pyrroloindoline derivatives via a copper-catalyzed C3–H arylation-cyclisation cascade with diaryliodonium salts. In 2014, the C2 arylation of tryptophol (Scheme 19) and tryptophan derivatives using Cu(OTf)<sub>2</sub> or Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> (10 mol%) as a catalyst and diaryliodonium triflates as coupling partners was reported by You [92]. One example of C2 alkenylation was also described and led to the expected vinyl product with an 80% yield. It could be noted that, under these reaction conditions, substrates with 4-Cl or 5-OMe substituents afforded the C2 arylation products among the dearomatization products derived from the C3 arylation of tryptophol derivatives and subsequent cyclization.

In 2016, Shi et al. disclosed the first regioselective arylation at the C6 position of indoles bearing a N-P(O)tBu<sub>2</sub> (TBPO)-directing group in combination with diaryliodonium triflates [93]. The direct arylation was performed ligandless using CuO (10 mol%) in 1,2-dichloroethane (DCE) at 80 °C for 12 h (Scheme 20a). These optimized reaction conditions discarded the competitive arylation of indole at C2 and C7 positions providing the desired C6–arylated products in high yields. The mechanism of the Cu(II)–catalyzed C6–H arylation was suggested to be initiated with the disproportionation of Cu<sub>2</sub>O. The key to the success of this rewarding selectivity was the formation of a metallacycle at C7 position due to the steric hindrance from the *N*-protecting group. The aryl group was transferred to the C6 position via the Heck-type four-membered-ring transition state followed by a base-assisted E2-type elimination providing the arylated compounds and the regeneration of the catalyst (Scheme 20b). The authors also proved the suitability of the TBPO-directing group by its cleavage with LiAlH<sub>4</sub> in dioxane at room temperature to give the corresponding arylated unprotected indole.



R<sup>2</sup> = H, Me, F, Cl, Br

**Scheme 19.** C2 arylation of tryptophol derivatives with symmetrical diaryliodonium triflates at room temperature.



R<sup>1</sup> = H, 3-Me, 3-CI, 3-I, 3-CO<sub>2</sub>Me, 3-(CH<sub>2</sub>)<sub>3</sub>CO<sub>2</sub>Me, 4-Me, 4-Br, 4-CI, 4-F, 4-CH=CH-Ph, 5-OMe R<sup>2</sup> = H, 2-Me, 3-Me, 3-Br, 3-CF<sub>3</sub>, 3,4-diOMe, 4-Me, 4-Me, 4-Ph, 4-F, 4-CI, 4-Br, 4-I, 4-CF<sub>3</sub>, 4-Ac, 4-CO<sub>2</sub>Et



Scheme 20. (a) Synthesis of various C6 arylated indoles via a selective copper-catalyzed C–H arylation using removable steric hindered TBPO-directing group. (b) Proposed catalytic cycle for the copper-catalyzed C6–arylation of *N*–TBPO-indoles involving aryl-CuIII species. DCE: 1,2-dichloroethane; TBPO: N–P(O) $tBu_2$ .

Following their studies on regiocontrolled direct arylation of indole without prefunctionalization, the same group reported the challenging site-selective C5 arylation of indoles [66]. Of the widely reported selective metal-catalyzed C2 and C3–H functionalization of indole derivatives, much less

research has dealt with the selective C–H arylation on the benzene core restricted to C6 and C7 positions. However, this structural motif is of great interest owing to its many applications in drug discovery. The introduction of a pivaloyl at C3 as a removable directing group has been used as a reliable strategy to ensure direct C5 selectivity. The authors drill down the directing groups to point out the crucial role of the pivaloyl substituent. Indoles bearing less encumbered substituents at C3 position (formyl, acetyl or *iso*butyryl) afforded the expected C5–phenylated products in lower yields. The role of pivaloyl moiety appears to be crucial for promoting the Heck-type four-membered-ring transition state by coordination to the Cu(III) intermediates. The C5 selectivity was gained with diaryliodonium triflates as coupling partners and copper(I) thiophene-2-carboxylate (CuTc) in the presence of 2,6-di-*tert*butylpyridine (dtpby) as a base in dichloromethane at 40 °C for 12 h (Scheme 21a). In the suggested catalytic cycle, the reaction may proceed first through an oxidative addition of the aryl(Mes)iodonium triflate to CuTc to afford a "high-valent" CuIII intermediate, which could be coordinated to the oxygen of the pivaloyl group. The next step is an aryl migration to the C5 position followed by an E2-type elimination providing the concomitant formation of the arylated indole and the regeneration of the copper catalyst (Scheme 21b).



**Scheme 21.** (a) Scope of the C5 arylation of indoles bearing a removeable pivaloyl directing group at C3. (b) Plausible mechanism for the copper-catalyzed C5 arylation of indoles. dtpby: 2,6-di-*tert*butylpyridine.

Even if a catalytic cycle involving CuI/CuIII intermediates is often described, site-selective arylation mechanisms of *N*-protected indoles and the exact role of the directing groups is still a

matter of debate. For this reason, combined density functional theory (DFT) and mass spectroscopic studies were then conducted by Shi and Wu [94]. Density functional theory (DFT) calculations suggested that all the site-selective C–H arylations proceed through a Heck-like mechanism involving a four-membered ring. The calculated free energies of the transition structures and the conducted mass spectroscopy investigations are in agreement with the experimental results, indicating that the observed regioselectivity depends on the electronic or the chelation effects in the Heck-like pathway. Neutral Heck-like transition state is favored with a weak directing group such as acetyl and the electronic effects dictate the C2 selectivity, while C5 and C6 arylations proceed through a cationic Heck-like pathway in which a favorable six-membered chelation between the oxygen atom on the directing group (DG) and the electron-deficient Cu<sup>III</sup> center is suggested (Scheme 22).



**Scheme 22.** Activation free energies of neutral and cationic Heck-like transition states of site-selective C–H arylation of indoles with various directing groups (DG).

In 2014, Kumar et al. described the synthesis of relevant C2–arylated azaheterocycles bearing two or three heteroatoms (e.g., oxadiazoles, thiadiazoles, benzoxazoles and benzothiazoles) as privileged scaffolds of interest for medicinal chemists using a copper-catalyzed C–H activation [95]. In this context, 2-substituted 1,3,4-oxadiazole derivatives were treated with diaryliodonium triflates in the presence of *t*BuOLi (3 equiv) as a base and CuBr (20–30 mol%) at room temperature in DMSO for 10–15 min (Scheme 23).



**Scheme 23.** Synthesis of 2,5-diaryl-1,3,4-oxadiazoles and thiadiazoles analogues through a copper-catalyzed C–H arylation.

The reaction was successfully extended to the synthesis of various 2-arylbenzoxazoles as attractive synthetic targets displaying potent biological activities. Applying these optimized conditions to

benzothiazole failed to produce the desired arylated product [96]. After the screening of the reaction conditions, the promoting effect of microwave activation was demonstrated by the successful C2–H arylation of benzothiazole at 130 °C in dioxane (Scheme 24). Di(2-thienyl)iodonium tosylate was also found to be an efficient cross-coupling partner affording the corresponding 2-heteroarylbenzothiazole with a 78% yield.



Scheme 24. C2-H arylation of benzothiazole using symmetrical diaryliodonium salts.

Recently, Martin and co-workers have reported that silvloxy furans could react with unsymmetrical diaryliodonium salts in the presence of Cu(OTf)<sub>2</sub> complexed with 2,2'-*iso*propylidenebis-4-phenyl-2-oxazoline (PhBox) ligand as the catalytic system in DCM at rt to give selectively the corresponding  $\gamma$ -aryl butenolides (Scheme 25) [77]. The reactions were conducted under mild conditions with a low catalyst loading but the yields remained low for  $\alpha$ - and  $\gamma$ -methyl silvloxy furans. A range of aryl(mesityl)iodonium hexafluoroborates underwent coupling with silvloxy furans, affording arylated butenolides in moderate yield. This complementary strategy gives access to various arylated butenolides as fairly appealing building blocks for the synthesis of bioactive molecules.





#### 2.3. Iridium-Catalyzed C-H Arylation and Visible-light mediated photoredox catalysis

The first iridium(III)-catalyzed arylation using diaryliodonium salts was reported by Hong in 2015 [79]. The authors reported the C8 site-selective arylation of isoquinolone using symmetrical diaryliodonium tetrafluoroborates in the presence of  $[IrCp*Cl_2]_2$  and AgSbF<sub>6</sub> as a ligand in AcOH at 100 °C for 24 h (Scheme 26a). The introduction of a phenyl bearing an electron-poor or electron-donating substituent did not affect the reaction efficiency and the corresponding C8-arylated isoquinolone derivatives were obtained in yields ranging from 57% to 93%. Thiophene could also be readily introduced at C8 with 67% yield. C8 arylations proceeded through a chelation between the oxygene atom on the pyridinone and the electron-deficient Ir(III) center leading to an iridacycle complex, followed by its oxidation by the hypervalent iodine reagent to afford highly oxidated aryl-Ir(V) intermediate (Scheme 26b).



R<sup>1</sup> = H, 6-Me, 6-OMe, 6-Cl, 6,7-diOMe, R<sub>2</sub> = H, Me, Bn R<sup>3</sup> = H, 2-F, 3-Me, 3,5-diMe, 3,4,5-triOMe, 3-CF<sub>3</sub>, 3-F, 3-Br, 3-NO<sub>2</sub>, 4-Me, 4-tBu, 4-Ph, 4-OMe, 4-F, 4-Cl, 4-Br, 4-CF<sub>3</sub>, 4-CO<sub>2</sub>Me, 4-SO<sub>2</sub>Me



**Scheme 26.** (a) C8–H selective arylation of isoquinolinones with various diaryliodonium tetrafluoroborates in AcOH. (b) Suggested reaction pathway of iridium-catalyzed selective C8 arylation.

Yuan then described one example of Cp\*Ir(III)-catalyzed C2–H arylation of 1-(pyrimidin-2-yl)-1H-indole with diphenyliodonium triflate as a coupling partner [97]. The role of pyrimidine as a directing group appears to be crucial for promoting the C2–indole irradiation by coordination to the Ir(III) species. The reaction was performed using a low catalyst loading, AgNTf<sub>2</sub> as a ligand in the presence of pivaloic acid and a 4 Å molecular sieve as a key additive for the efficiency of the phenylation reaction (Scheme 27).



**Scheme 27.** Cp\*Ir(III)-catalyzed C2–H phenylation of 1-(pyrimidin-2-yl)-*1H*-indole with diphenyliodonium triflate.

Of the widely reported metal-catalyzed C–H arylation, much less research has dealt with diaryliodonium salts acting as sources for aryl radicals. From this point of view, photoredox chemistry involving radical intermediates is discussed here. Since the breakdown of Sanford in 2012 who reported

a photoredox palladium/iridium-catalyzed C–H arylation with diaryliodonium reagents under mild conditions [98], support for the feasibility of these photocatalytic reactions with heteroarenes is provided by few reports [99–104]. Room-temperature, visible-light photocatalysis-promoted transformations of diaryliodonium salts were described by Chatani in 2013 [99]. The arylations were performed at room temperature under visible-light irradiation provided by a white LED light ( $\lambda = 400-700$  nm) in the presence of [Ir(ppy)2(bpy)]PF<sub>6</sub> (ppy: 2-phenylpyridine, bpy: 2,2'-bipyridine) to generate aryl radicals from diaryliodonium salts. Under these optimized conditions, electron-deficient heteroarenes such as pyridine and diazines as well as electron-rich heteroarenes were successfully arylated using symmetrical diaryliodonium salts (Scheme 28). The main limitations of this strategy are the required large excess of heteroarene used as a solvent and the lack of regioselectivity. It is also noteworthy that this exquisite visible-light-mediated arylation can be realized in the absence of a photocatalyst with pyrrole via a colored charge-transfer complex.



**Scheme 28.** Scope of the Ir(III)-photocatalyzed arylation of heteroarenes using symmetrical diaryliodonium salts.

Visible-light-promoted anylation usually proceeds by a SET (single electron transfer) reaction from a photoexcited catalyst, to give the aryl radical intermediate which is selectively added to the heteroarene to generate radical intermediate, which leads to a cationic intermediate through another SET reaction and a regenerated photocatalyst. Finally, the cationic intermediate losses one proton to give the desired arylated products.

Visible-light-promoted Ir(III)-photoredox catalysis for C3–selective direct arylation of 2-pyridones at ambient temperature using diaryliodoniums was reported by Miura and Hirano as an elegant eco-friendly and safe process [101]. The screening of the reaction conditions has shown that both visible light and the Ir(ppy)<sub>3</sub> catalyst were crucial for the reaction efficiency. The selective C3 arylations of 2-pyridinone derivatives were performed in the presence of KOAc in CH<sub>3</sub>CN at room temperature with symmetrical diaryliodonium or unsymmetrical aryl(mesityl)iodonium triflates (Scheme 29a). Even if the dummy group was not transferred, the yields were still lower with unsymmetrical diaryliodanes. The authors suggested a single electron transfer (SET) from the active photoexcited \*Ir(III) species to the diaryliodonium salts providing the formation of the aryl radical and an Ir(IV) complex (Scheme 29b). Its subsequent addition to the pyridinone produces the allylic radical intermediate which is prone to oxidation by Ir(IV), generating both the cationic intermediate and the Ir(III) photocatalyst. The final deprotonation led to the expected 3-aryl-2-pyridinones. Under this photoredox catalysis, pyridinones bearing an electron-donating substituent led to poor yield of the corresponding C3–phenylated compound maybe because of the SOMO/LUMO interaction between nucleophilic phenyl radical and the  $\pi$ -deficient heterocycle.



**Scheme 29.** (a) Synthesis of various C3–aryl-2-pyridinones as attractive targets for medicinal chemistry under visible-light-promoted Ir(III) catalysis. (b) Plausible photochemical pathway involved in the reaction of diaryliodonium triflates with 2-pyridinones.

#### 3. Metal-Catalyzed N-H Arylation of Heteroarenes

The use of diaryliodonium salts in the *N*-arylation reaction of heteroarenes opens new possibilities to access the target compounds in eco-friendlier and cheaper process [105]. In addition, the *N*-arylated azoles have received considerable attention as key structural motifs of various bioactive molecules [106] and as ligands in synthetic chemistry [107]. In 2000, Lee and co-workers reported the first copper-catalyzed *N*-arylation of various azoles with hypervalent iodonium compounds in the presence of carbonate as a base under mild conditions [108]. Fifteen years later, Suna described a few examples of copper-catalyzed *N*-arylation of azole derivatives using an in-situ-generated unsymmetrical diaryliodane derived from anisole [109]. Imidazole, 1,2,4-triazole and tetrazole derivatives possessing more acidic N–H bonds were arylated with moderate to good yields using a Cu(MeCN)<sub>4</sub>BF<sub>4</sub> catalyst in the presence of a Hunig's base (DIPEA: di*iso*propylethylamine) in acetonitrile/DMSO: 1/4 as the solvent for 30 h at 40 °C or 40 h at 50 °C (Scheme 30a). Reactions conducted with *N*-containing heteroarenes having less acidic N–H bonds such as indoles failed to produce the desired compounds under these optimized conditions. The higher efficiency of the catalyst than that observed with the Cu(II) complex suggests that the Cu-catalyzed amination of unsymmetrical diaryliodonium salts with azoles proceeds through a Cul/CuIII catalytic cycle (Scheme 30b).



**Scheme 30.** (a) Cu(I)-catalyzed *N*–H arylation of azole derivatives using *p*OMe-Ph(TRIP)IOTs as an electrophilic arylating reagent. (b) Suggested mechanism for copper-catalyzed *N*–arylation of azoles. DIPEA: di*iso*propylethylamine.

As a complement to common imidazole *N*–arylation strategies [110], Shafir and Lledós reported the challenging synthesis of *N*1–aryl-5-iodoimidazoles by a selective copper-catalyzed intramolecular aryl migration [111]. Imidazolyl aryliodonium acetates were first generated from imidazole and aryliodine(III) diacetates, before undergoing an iodine-to-nitrogen aryl transfer in the presence of a low Cu(OTf)<sub>2</sub> catalyst loading to produce the desired molecules (Scheme 31). The structure of the 5-iodoimidazolyl- $\lambda^3$ -iodanes were confirmed by X-Ray crystallography analysis and a DFT calculation corroborated the lower energy for these isomers and suggested a Wheland-type intermediate. Both the efficiency and the selectivity of the aryl migration were improved using a fluorinated solvent (HFIP: hexafluoro*iso*propanol or trifluoroethanol) and a catalytic amount of *N*–methylbenzimidazole as an additive. The authors hypothesized the formation of a copper-heterocyclic additive complex showing higher solubility in HFIP could play a role in the favored intramolecular pathway. The reaction was initiated by a bond formation between a Cu<sup>I</sup>OTf fragment and *N*1, before an aryl transfer from iodide to copper providing a Cu<sup>III</sup>-aryl intermediate. Subsequent reductive elimination produced the *N*1–arylcompounds. Furthermore, the targeted *N*1–aryl-5-iodoimidazole products were useful precursors for the synthesis of higher valuable compounds by further derivatization.





R = H, 2-Me, 2,4,6-triMe, 2-Br, 3-OMe, 3-Br, 4-Me, 4-Ph, 4-OMe, 4-OCF<sub>3</sub>, 4-Cl S = Solvent

Scheme 31. Intramolecular copper-catalyzed aryl migration of imidazoyl aryliodonium acetates.

One of the most important challenges in C–H or *N*–H activation of heteroarenes is to find the catalytic system that enables the reaction to occur at one of the many C–H or *N*–H bonds [112,113]. Following their pioneering study on Pd(II) and Cu(II) salts that co-catalyzed *N*1-arylation of 1*H*-1,2,3-benzotriazoles [114] and *N*2–arylation of 5-aryltetrazoles [115], Beletskaya and coworkers reported a catalyst-controlled site-selective *N*-phenylation of benzotriazoles using Ph<sub>2</sub>IOTs in the presence of copper or palladium as the catalyst source (Scheme 32) [116,117]. The authors investigated how to steer the reaction to selectively produce the *N*1 or *N*2–phenyl isomer using aryliodonium salts by tweaking the catalyst system [118,119]. The regioselective *N*1–phenylation of benzotriazole derivatives readily occured with K<sub>2</sub>CO<sub>3</sub> as the base in the presence of CuI as a catalyst at room temperature or with a Pd/Al<sub>2</sub>O<sub>3</sub> heterogeneous system, whereas *N*2–phenylation was reached using CuI and [Cu<sub>2</sub>(TMEDA)<sub>2</sub>(OH)<sub>2</sub>]Cl<sub>2</sub> as both the base and complexing additive that could react first with the benzotriazoles to form complexes leaving the *N*2–atom available for reaction with the diphenyliodonium salt.



Scheme 32. Catalyst-controlled site-selective N-phenylation of benzotriazoles.

2-substituted-2*H*-indazoles have been recognized as biologically privileged structures, exhibiting a wide range of biological properties such as anticancer activities. Reflecting this, their challenging synthesis under mild conditions was reported by Pan in 2018 [120]. Compared to the previously described C–N cross-coupling reaction starting from 1*H* indazoles, the use of hypervalent iodine reagent under the catalysis of copper led to *N*2 arylation in high selectivity. The solvent effects strongly

affected the selectivity since polar protic solvents lead to no reaction or poor selectivity whereas polar aprotic solvents provide higher N2 selectivity. The reactions were mainly conducted under base-free conditions using CuCl (5 mol%) as a catalyst in DCM or THF at 50 °C for 12 h and were tolerant to a wide range of functional groups such as sensitive nitrile, aldehyde, ester or phenol (Scheme 33a). In the case of ortho-substituted aryliodonium triflates, the aryl transfer was not selective and the 2-mesityl-2*H*-indazole was isolated among the expected products. It could be noted that the selectivity could be switched for N1 by the addition of NaOEt into the reaction mixture. DFT calculations suggested that the complex involving 1*H* indazole is the most stable and could not be isomerized without an external base, which explains the selectivity. A plausible mechanistic pathway suggested the in situ formation of a small amount of CuOTf could react with the diaryliodonium salt to produce the Cu(III)-aryl species. The further coordination of N1 to the copper(III) center followed by a reductive elimination produces the N2–arylated indazoles (Scheme 33b).





More recently, Dohi described the copper(I)-catalyzed *N* arylation of benzimidazole and imidazole derivatives with aryl(2,4,6-trimethoxyphenyl)iodonium triflates. In this study, the TMP auxiliary group proved to be a powerful non-transferable group leading to higher reactivity of the iodonium salt than the hindered mesityl auxiliary [121–124]. *N*-arylbenzimidazoles and imidazoles were obtained by reaction of the corresponding *N*–H azoles with aryl(TMP)iodonium triflates at 50 °C in toluene or DCM in the presence of CuOAc as the catalyst and NEt<sub>3</sub> as a base (Scheme 34). Unfortunately, unsymmetrical benzimidazoles led to a mixture of *N*1– and *N*3–phenylated compounds in equivalent

ratio. One example of *N*–phenylation of pyrazole was also reported providing *N*–phenylpyrazole with a 97% yield.



**Scheme 34.** CuOAc-catalyzed *N*-arylation of benzimidazole and imidazole derivatives using aryl(TMP)iodonium triflates.

The attractive synthesis of the high valuable N,N'-disubstituted indigos from direct N-functionalization of the parent indigo dye is highly desirable. N,N'-diarylated indigos are appealing targets able to undergo efficient E–Z photoisomerization to maximize the light-induced activity modulation. Indeed, these newly designed indigo-red-shifted photoswitches are expected to have a huge impact on the development of applications in both life and material sciences. From this point of view, a reaction utilizing hypervalent iodine reagents in C–N bond formation of indigo was found by Jacquemin and Hecht in 2017 [125]. A copper-catalyzed cross-coupling reaction with electron-deficient diaryliodonium salts was conducted using copper chloride as a catalyst and K<sub>3</sub>PO<sub>4</sub> as a base in DCM at rt or 40 °C and N,N'-diarylated products were isolated in low yields (Scheme 35). Nevertheless, electron-withdrawing N-aryl substituents allowed long thermal half-lives of the Z-isomers, which are appealing for biomedical applications, as well as argued for the compounds' absorption in the red and photoisomerization ability with 660 nm light.



**Scheme 35.** Synthesis of *N*,*N*′-diarylated indigos as tailored targets for red-light photoswitches starting from indigo dye.

In his pioneering paper in 2005, Zhou reported the first copper-catalyzed arylation of uracil derivatives with diaryliodonium salts to afford *N*-monoarylated or  $N^1$ , $N^3$ -diarylated products with high selectivity under mild conditions [126]. In 2017, Hong and Park reported an orthogonal reactivity modulation of 2-arylquinazolin-4(3*H*)-ones in which a transition-metal catalyst-controlled reactivity enabled access to *N*-arylation or annulative extension reactions [127]. The site-selective derivatizations of this privileged alkaloid scaffold represent an extremely attractive step-economic route to provide various analogues. The unmasked 2-phenylquinazolin-4(3*H*)-one reacts with diphenyliodonium triflate in the presence of CuI complexed with a quinoline-based ligand as the catalytic system in DMF at 130 °C to give the corresponding *N*-phenylated product with a 93% yield (Scheme 36).



**Scheme 36.** Synthesis of an attractive analogue of alkaloid via a copper-catalyzed *N*–phenylation of the.2-phenylquinazolin-4(3*H*)-one.

Progress in this area has been also achieved by Kim in which the author demonstrated the first selective copper(I)-catalyzed *N*-arylation of 2-pyridinone derivatives with symmetrical diaryliodonium salts and its application to the straightforward synthesis of an antifibrotic drug [128]. The reactions were carried out at room temperature or at 50 °C in the presence of 10 mol% of copper chloride and trimethylamine as a base in toluene (Scheme 37). A wide range of substituted aryl groups were successfully introduced selectively on various pyridinone derivatives showing the versatility of these described reactions. In the case of 6-methyl and 6-phenylpyridin-2-ones, a mixture of *N*-arylated and O-arylated products was obtained. The reaction was also successfully applied to fused 2-pyridinones and pyridazinone providing the expected arylated compounds in good to excellent yields.



R<sup>1</sup> = H, 2,4,6-triMe, 3-Br, 3-Me-5-NO<sub>2</sub>, 3,5-diBr, 4-OMe, 5-Me, 5-CO<sub>2</sub>Me, 5-NO<sub>2</sub>, 5-Br, 6-Me, 6-Ph R<sup>2</sup> = H, Me, *t*Bu, OCF<sub>3</sub>, F, Cl, Br, CO<sub>2</sub>Me

**Scheme 37.** Selective *N*–arylation of 2-pyridinones with symmetrical diaryliodonium salts under mild conditions.

Quaternized *N*-heteroarenes have also received considerable attention as important structural units with application in materials science. Several advantages such as reduction of the synthetic steps and late-stage functionalization are provided by using the direct quaternarization protocol. Due to their ability as promising new material, Baumgartner and co-workers studied the design of new  $\pi$ -conjugated ring-fused phosphaviologens salts through the direct quaternization of 2,7-diazadibenzophosphole oxide with diaryliiodonium triflates and hexafluorophosphates [129]. The *N*,*N*-bisarylation of phosphoryl-bridged 4,4'-bipyridine proceeded using Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (8 mol%) as a catalyst in DMF at 100 °C or 40 °C for the heteroaryliodonium hexafluorophosphate (Scheme 38). Both electron-rich and electron-poor diaryliodonium salts were viable and the sterically less hindered aromatic moieties were preferentially transferred to pyridine derivatives. This alternative method provided a practical strategy for preparing *N*,*N*'-bisarylated phosphaviologens as well as *N*,*N*'-bis(*p*-fluorophenyl)bipyridinium ditriflate by converting the parent 4,4'-bipyridine in yields ranging from 61% to 95%.



**Scheme 38.** Synthesis of  $\pi$ -conjugated ring-fused phosphaviologens salts through the direct quaternization of 2,7-diazadibenzophosphole oxide with diaryliodonium salts.

#### 4. Atom-Economical Tandem N-H/CH Arylation of Heteroarenes

Atom-economical strategies using hypervalent iodanes through domino or tandem processes represent an extremely attractive approach to avoid the waste of aryl iodide side-product [35,36]. The development of cascade reactions allowing the multiple formation of bonds starting from simple substrates in a single transformation consisting of at least two steps is a fairly appealing issue. In this context, sustainable processes have been developed such as tandem reactions involving a second step that enables the capture of the in-situ-generated aryl iodide side-compound. Even if tandem reactions including various sequences combining oxidation reactions or nucleophilic additions are widespread [130], tandem catalytic couplings on heteroarenes are really sparse and still remain a great challenge. Although decarboxylative cross-coupling reactions are not covered in this review, it is worth mentioning two recent reports from the group of Zhang who reported the tandem  $\pi$ -extended decarboxylative annulation [131,132]. Significant achievements have been reported by Greaney in the last 5 years, who was the first to describe tandem N-/N-, C-/N- and N-/C- arylation starting from unprotected heteroarenes and acyclic diaryliodoniums [133]. In 2015, Greaney and co-workers conducted a sequential diversification approach on indoles with symmetrical and unsymmetrical diaryliodonium triflates [134]. This strategy enabled the rapid installation of various aryl substituents at C3 and N- positions without extra synthetic steps and contributed to structural diversification. In order to merge both the CH and NH arylation processes, the reaction proceeded using copper iodide as a catalyst in dioxane as universal solvent in the presence of a stoichiometric amount of symmetrical diaryliodonium triflates. Using stepwise addition of bases and ligand to complete one-pot sequential arylation reactions, 1,3-bisarylated indoles were isolated in good yields ranging from 41% to 67% (Scheme 39). The successful tandem arylation was also extended to aryl-uracil iodonium triflates by switching the solvent to toluene and reducing the reaction temperature of the second step. Under these optimized conditions, a range of N-dimethyluracil-3-arylindoles were synthetized in moderate yields along with small amounts of C3-arylated products.





Cul (20 mol%)

Scheme 39. Copper-catalyzed tandem C-/N- arylation of indole derivatives using diaryliodonium salts.

Inspired by their first strategy for synthesis of indoles, a similar very powerful domino process using *N*-heterocycles was published by the same group in 2017 [135]. Notwithstanding the importance of multiaryl-substituted pyrazoles, the sequential *N*-H/C-H direct arylation approach based on readily available unsubstituted pyrazoles constituted an attractive choice for the one-pot synthesis of these privileged motifs [136]. Nevertheless, the strategy was slightly different from the former one since the second arylation took place on the introduced aryl group instead of the pyrazole core that acted as a directing group for subsequent ortho C-H arylation. The first metal-free *N*-arylation serves as a stepping stone on the way to the ruthenium-catalyzed C-H arylation of generated *N*-arylpyrazole derivatives (Scheme 40). The selective C-H mono-arylation was reached using cumbersome pyrazoles or diaryliodonium salts over competing the diarylated products. Treatment of pyrazole derivatives or triazole with unsymmetrical diaryliodonium triflates led to the diarylated compounds with excellent selectivity exhibiting a noteworthy steric and electronic differentiation.



Scheme 40. Atom-efficient domino N-/C-arylation of pyrazoles using diaryliodonium triflates.

A similar powerful domino process using *N*-heterocycles was recently published by Kong and Li who focused their interest on developing straightforward methods to prepare polyarylated imidazoles via copper-catalyzed domino di/tri-arylation [137]. The main feature was the formation of imidazolium salts also recycling the residual counter anion of the diaryliodoniums thus providing a high atom-economical process. The domino reactions were carried out using *N*-alkyl or *N*-aryl-imidazoles or benzimidazoles in the presence of one equivalent of basic Cu<sub>2</sub>O in DMF at 120 °C for 20 h (Scheme 41a). In addition, an excellent selectivity was observed with unsymmetrical diaryliodonium salts as coupling partners, where less sterically hindered aryls transferred first. Their attention turned finally to investigating how they might steer the reaction to produce pentaaryl imidazolium salts from simple unprotected azoles and diaryliodonium tetrafluoroborates. Driven by the design of new challenging polyarylimidazoliums, a rewarding domino triarylation including *N*-arylation, *N*-quaternarization and C-arylation was developed in one pot (Scheme 41b).



**Scheme 41.** (a) Synthesis of various imidazolium and benzimidazolium salts by copper-catalyzed domino N–/C–arylation reactions. (b) Copper-catalyzed domino triarylation of N–H imidazole and benzimidazole derivatives.

#### 5. Conclusions

Late-stage C–H or *N*–H arylation of heteroarenes is a powerful tool for incorporating some diversification into these highly valuable scaffolds, especially in drug discovery. The striking feature of air- and moisture-stable diaryliodonium salts is their ability to facilitate metal-catalyzed C–H functionalization. The use of diaryliodonium salts as versatile *N*– or C–arylating reagents provides rapid and streamlined access to various analogues of relevant heteroaryl compounds. Many reactions were conducted under mild conditions at room temperature or were not water and air sensitive. Homogeneous and heterogeneous catalytic systems have been developed during the last decade to improve both the efficiency and the scope of the reaction. The main drawback with diaryliodonium salts is the formation of a stoichiometric amount of aryl iodide as a waste, which is undesirable from atom-efficiency points of view. This disadvantage is overcome by recent advances in exquisite tandem or domino arylation reactions providing a straightforward eco-friendly strategy by recycling waste.

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