Transition Metal-Mediated Direct C–H Arylation of Heteroarenes Involving Aryl Radicals

Hélène Bonin,a,* Mathieu Sauthier,a and François-Xavier Felpinb,*

a Université de Lille, UMR CNRS 8181, Unité de Catalyse et Chimie du Solide, USTL–ENSCL, BP 90108, 59652 Villeneuve d’Ascq cedex, France
Fax: (+33)-320-436-585; phone: (+33)-320-434-893; e-mail: helene.bonin@univ-lille1.fr

b Université de Nantes, UFR Sciences et Techniques, UMR CNRS 6230, CEISAM, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France
Fax: (+33)-251-125-402; phone: (+33)-251-125-422; e-mail: fx.felpin@univ-nantes.fr

Received: September 25, 2013; Revised: November 18, 2013; Published online: January 31, 2014

Abstract: This review gives an overview of the generation of aryl radicals, mediated by transition metals, and their use for the C–H arylation of heteroarenes. The different sources of aromatic derivatives able to generate aryl radicals via a metal-assisted reduction or oxidation are discussed, with a critical view of the developed systems. The radical arylations of nitrogen-, oxygen- or sulfur-containing heterocycles are then described and mechanistic considerations are discussed as well.

1 Introduction

The metal-catalyzed direct C(sp²)–H arylation of heterocycles has attracted considerable attention as such an approach saves a pre-functionalization step of the heterocyclic structure.[1] The activation of the heteroarene moiety, usually consisting in a halogenation, borylation or stannylation step, proved to be sometimes perilous due to the higher sensitivity toward both acidic and basic conditions compared to more robust arenes. The numerous direct C–H arylation methodologies developed during the past years have changed the way chemists draw up synthetic routes and opened the door to higher molecular diversity.[2] Most direct C(sp²)–H arylation processes are initiated through an oxidative addition of a transition metal including Pd,[3] Ru,[4] Fe,[5] and Cu[6] onto a haloarene for the most representative ones, followed by a metal-mediated C–H bond activation. However, the high inertness of the C–H bond requires, in most cases, rather elevated temperatures as well as elaborate ligands. On the other hand, the metal-mediated C(sp²)–H arylation of heteroarenes involving aryl radicals has recently emerged as a promising alternative, allowing processes at room temperature and under relatively simple experimental conditions. Although this approach has been known for a long time with the work of Meerwein,[7] it only recently turned out to be efficient with the development of novel catalytic systems. This review aims to provide a picture of the actual state-of-the-art involving the arylation of heteroarenes or by extension, olefin-containing heterocycles, with aryl radicals generated by transition metals. Depending on the nature of the reagent, the aryl radical formation mechanism might obviously be different. Whereas iodonium salts, aromatic halides and diazonium salts have to be reduced to generate the corresponding aryl radicals, their formation from arylhydrazines and boronic acids requires the use of oxidants. It should be noted that transition metal-free approaches have also shown promising results and readers interested by this field can find excellent recent reviews on this topic.[8] We also excluded from this review any non-transition metal-mediated arylation processes involved in a radical chain mechanism with Bu₃SnH, (Me₃Si)₃SiH as well as SmI₂. This field of research has been already reviewed by Vaillard and Studer.[9]
2 Generation of Aryl Radicals using a Reductant

2.1 Phenyliodonium Salts

Diarylodonium salts have recently emerged as highly reactive, non-toxic synthetic intermediates. These salts are usually more reactive than their corresponding aromatic halides, due to the excellent leaving group ability of the aryl iodide. Even though they have been mostly used for transition metal-catalyzed carbon-carbon cross-coupling reactions, many other applications have been developed over the past few years: racemic or enantioselective arylation of carbonyl compounds, metal-free electrophilic arylation of heteroatom-containing nucleophiles, photochemical polymerization, etc. Direct C–H aylations of arenes and heteroarenes involving hypervalent iodide derivatives have been recently reported with or without transition metal catalysts.

Diarylodonium salts are considered as mild oxidants [for example, $E^\text{0}/2\text{u} (\text{Ph}_2\text{IPF}_6) = 0.04 \text{ V vs. NHE}$] able to generate aryl radicals in the presence of a reductant or by photodecomposition. They represent an important source of radicals for various applications such as photoinitiated cationic polymerization or electrochemical grafting on glassy carbon surfaces. An interesting property of radicals arising from diarylodonium salts is that they can be generated at room temperature, allowing the use of mild reaction conditions. Based on this principle, Sanford developed a new strategy, merging Pd-catalyzed C–H functionalization and visible-light photocatalysis, to produce biaryls at a remarkably low temperature.

François-Xavier Felpin was born in Villefranche-sur-Saône (France) in 1977. He received his Ph.D. degree in 2003 from the University of Nantes under the supervision of Prof. Jacques Lebreton working on the synthesis of alkaloids. After his Ph.D., he held a post-doctoral position with Prof. Robert S. Coleman at The Ohio State University working on the synthesis of mitomycin. In 2004 he joined the University of Bordeaux 1 as assistant professor and he received his habilitation in 2009. In fall of 2011 he moved to the University of Nantes where he was promoted to full professor. His research interests include heterogeneous and homogenous sustainable catalysis as well as medicinal chemistry.
the room temperature photoredox-catalyzed arylation of various heteroarenes with diaryliodonium salts. They combined the use of a ruthenium catalyst $[\text{Ru(bpy)}_3\text{Cl}_2]·6\text{H}_2\text{O}$ with blue LED light ($460 ± 15$ nm) to generate the radical. The reaction conditions were optimized for the arylation of $N$-methylpyrrole with diphenyliodonium salt; highest yields being obtained using 50 equiv. of $N$-methylpyrrole and 1 mol% of Ru catalyst at $25^\circ\text{C}$ for 12 h in acetonitrile (Scheme 1).

The amount of catalyst could be decreased to 0.05 mol%, but the reaction time had to be increased to 36 h. The counterion of the diphenyliodonium salt showed an influence on reaction yields. The trifluoromethanesulfonate and hexafluorophosphate derivatives gave the highest yield (84%), while tetrafluoroborate, trifluoroacetate or bromide derivatives led to about 70% yield. Using the optimized conditions, the authors subsequently investigated the scope of the reaction. The C–H arylation of $N$-methylpyrrole was first examined with various substituted symmetrical diaryliodonium salts. Higher yields were obtained in the presence of electron-withdrawing substituents, even at the ortho-position (Scheme 2). This trend is due to the increasing redox potentials of electron-poor aromatic rings. The reaction is regioselective, since pyrrole was arylated only at C-2, as well as chemoselective, since halide groups on the aryl moiety were tolerated.

When unsymmetrical diaryliodonium salts were used, the authors noticed that the less hindered aryl group was preferentially transferred. However, only arylmesityliodonium salts were tested, and the unreactive mesityl group is not only hindered but also electron-rich so that the electronic properties of the mesityl group might be predominant over the steric hindrance to explain this reactivity. Arylated $N$-methylpyroles were thus obtained after radical couplings with unsymmetrical iodonium derivatives, albeit with lower yields than those obtained with the corresponding

![Scheme 1](image1.png)

Scheme 1. Optimized conditions for the arylation of $N$-methylpyrrole with diphenyliodonium salt catalyzed by a ruthenium photoredox catalyst.

![Scheme 2](image2.png)

Scheme 2. Radical arylation of $N$-methylpyrrole with various symmetrical diaryliodonium salts.

![Scheme 3](image3.png)

Scheme 3. Radical arylation of $N$-methylpyrrole with various unsymmetrical diaryliodonium salts.
ing symmetrical salts (Scheme 3). Electron-withdrawing substituents on the aryl moiety increased the reaction yields.

The C–H arylation with diaryliodonium salts was then extended to other electron-poor and electron-rich heteroarenes, such as pyrrole, substituted pyrroles, furan, thiophene, benzofuran, benzothiophene and pyrazine. It is worth noting that no protection of the nitrogen was required for the couplings with pyrrole or substituted pyrroles. Electron-rich heteroarenes coupling with electron-deficient aryl radicals provided heterobiaryls in higher yields. Whatever the nature of the heteroarene, the monoarylation only occurred at C-2 with good to excellent yields. The amount of heteroarene could be reduced to 10 equivalents without a noticeable reduction in the yields. The methodology was also applied to electron-deficient arenes with moderate to good yields (Scheme 4).

Finally, the mechanism of the reaction was examined and preliminary investigations were reported.

![Scheme 4. Radical arylation of various heteroarenes with di-(4-acetylphenyl)iodonium triflate.](image-url)

When the arylation of N-methylpyrrole with diphenyliodonium triflate is conducted in the presence of the radical trapping TEMPO, the isolated yield of arylated pyrrole decreases significantly from 81% to 22%, while the TEMPO-trapped O-aryl intermediate is isolated in 17% yield. These observations support the hypothesis of a radical mechanism (Scheme 5).

Tosibu and Chatani recently reported the room temperature, visible light-mediated arylation of heteroarenes using an iridium photoredox catalyst with various symmetrical diaryliodonium salts.[20b] Under the optimized conditions the radical arylation of pyridine, pyrazine, pyrimidine, N-methylpyrrole or NH-free pyrrole, imidazole and thiophene with diphenyliodonium hexafluorophosphate led to the formation of the desired products in moderate to good yields (Scheme 6).

Heteroarenes were used as both solvent and reactant in a large excess (~40 equiv.). The best yields were obtained using pyrrole and pyrimidine (63–88%) while other heterocycles gave coupling products in lower yields (33–55%). The arylation occurred exclusively α to the heteroatom, except with pyridine and pyrazine which led to a mixture of regioisomers. The arylated adducts were isolated in higher yields with electron-poor diaryliodonium salts (68–76%) than with electron-rich ones (0–61%). A reaction mechanism, starting from a single-electron transfer (SET) of the excited Ir(III)* catalyst to the iodonium salt, is described by the authors (Scheme 7, path a). A singu-
lar reactivity was observed, however, with N-methylpyrrole, since the reaction could surprisingly be successfully conducted in the presence of white LED light but without a photoredox catalyst. The 2-phenyl adduct was isolated in a non-negligible yield of 54% at room temperature under these conditions. The authors suggested the generation of a charge-transfer complex (CTC), whose formation is supported by the observation of a new band in the UV-vis spectrum of a mixture of pyrrole and diphenyliodonium hexafluorophosphate. The excitation of the CTC generates the aryl radical and the pyrrole radical cation, which recombine to form the 2-arylated pyrrole cation. Its rearomatization by loss of a proton generates the arylated adduct (Scheme 7, path b). Both mechanisms are thus complementary in the arylation of N-methylpyrrole with diaryliodonium salts. However, the formation of the aryl radical by SET seems to be predominant with electron-rich diaryliodonium salts, since yields of arylated pyroles are much lower in the absence of the photoredox catalysts (see yields in parenthesis in Scheme 7), while the CTC formation prevails for the electron-poor iodonium salts.

Only two examples of transition metal-catalyzed arylation of heteroarenes with diaryliodonium salts have been published until now. The arylated products were isolated with moderate to excellent yields, but improved methodologies using equimolar amounts of reactants are still highly desired. Even though the production of aryl iodide as by-product might be considered as a limitation, its purification and recycling can be envisaged.

### 2.2 Aromatic Halides

Aromatic halides are among the most commonly used reagents in organic chemistry, especially for the construction of carbon-carbon bonds. A wide variety of halogenated starting materials is commercially available, and many efforts have been made to develop new methodologies to activate the less reactive but less expensive chloride derivatives. The transition metal-catalyzed cross-couplings of electrophilic aryl halides with nucleophilic organometallic reagents, known as the Suzuki–Miyaura, Stille, Hiyama or Kumada–Corriu reactions,[21] are among the most powerful existing methods for the synthesis of (hetero)biaryls. More recently, the direct arylation of aromatic compounds by C–H activation with aryl halides has emerged as a very attractive atom-economical method, especially for the synthesis of heterobiar- yls, directly from the heteroarenes, such as furans, thiophenes, pyrroles, oxazoles, thiazoles, etc.[22]

Different methods have been used to generate aryl radical from aryl halides, including visible-light irradiation,[23] electrochemical reduction[24] or activation by
organic derivatives, such as potassium tert-butyl oxide or silicon derivatives. The transition metal-mediated radical C–H arylation of (hetero)arenes has the advantage of requiring only a catalytic amount of radical initiator, but it usually requires several equivalents of a strong base and a very large excess of (hetero)arene. Iridium, cobalt, nickel, and iron catalysts have been used to carry out the direct C–H arylation of unactivated arenes with good to excellent yields, starting from aryl iodides, bromides and even chlorides, although with lower yields in the latter case.

Li and Hua described the first transition metal-mediated radical arylation of electron-poor pyridine using an Au(I) catalyst. The reaction was examined with pyrazine as well, but mechanistic investigations using 1,2-dihydroxybenzene as radical inhibitor showed that a radical pathway was probably not involved with this substrate. The optimization of the reaction conditions was done with pyrazine, and the same conditions could be applied to pyridine. Among the different Au(I) catalysts and bases tested, the combination of PCy₃AuCl and t-BuOK proved to be the best. t-BuOK alone is able to generate aryl radicals from aryl halides, but when the reaction was carried out without the Au catalyst, the yield dropped dramatically. It is worth noting that the reaction is highly base dependent since t-BuOK is the only base that led to the formation of the desired product. The reaction with pyridine required a 5 mol% catalyst loading, a moderate to high temperature (60–100°C) as well as a large excess of pyridine (~25 equiv.) and led to mixtures of 2-, 3- and 4-arylpyridines with moderate yields, the ortho-derivative being always the major compound (Scheme 8).

The reaction is sensitive to steric hindrance, since the isolated yield of arylpyridine was 26% when 2-bromotoluene was used, whereas it increases to 48% with 4-bromotoluene. When electron-poor 1-bromo-4-chlorobenzene was used, the reaction temperature had to be decreased to 60°C to avoid the formation of the 1-chloro-tert-butoxybenzene side-product. Finally, use of 2-bromo-6-chlorotoluene led to the exclusive formation of the corresponding 2-arylpyridine, albeit in a low yield.

To prove the free radical mechanism, the authors carried out the reaction using bromobenzene and pyridine in the presence of 10 mol% of the radical inhibitor 1,2-dihydroxybenzene, and the desired phenylpyridine could not be detected under these conditions. However, the mechanism of the aryl radical formation was not detailed.

The Ni-catalyzed C–H arylation of electron-deficient pyridine was described with various aryl bromides. The optimized reaction conditions used a combination of 5 mol% of bis(cyclopentadienyl)-nickel and PPh₃, with one equivalent of t-BuOK, in pyridine (60 equiv.) at 100°C for 12 h. The reaction temperature was higher than that required for the arylation of benzene and naphthalene with the corresponding aryl bromides. With these conditions in hand, mixtures of 2-, 3- and 4-arylpyridines could be isolated with good yields (Scheme 9). Due to the presence of 3- and 4-substituted pyridines, the arylation mechanism seems to proceed through a radical pathway rather than ortho-metallation that would lead to the exclusive formation of the 2-substituted adduct. The observed ratios differing from that observed with the Au-catalyzed radical arylation, the authors considered that the mechanism is more complex and might not be proceeding only via a radical pathway.

Scheme 8. Gold-catalyzed radical arylation of pyridine with aryl bromides.

Scheme 9. Nickel-catalyzed radical arylation of pyridine with aryl bromides.
Finally, Chan et al. recently reported the C–H arylation of both electron-rich and electron-poor heteroarenes with aryl halides catalyzed by a cobalt(II) porphyrin.[32] The optimization of the reaction conditions was not detailed, but authors used a catalytic amount of 5 mol% of cobalt(II)-tetrakis-4-anisylphorphyrinato dianion, combined with 10 equivalents of KOH and t-BuOH and a large excess of heteroarene (100 equivalents) serving both as reactant and solvent, at 200°C (Scheme 10). Under these conditions, 2-arylated furans or pyrroles were obtained in good yields (50–70%) with short reaction times (15–60 min). As usually observed for coupling reactions with aromatic halides, yields were higher and reaction times shorter when iodide derivatives were used instead of bromides. The scope of the reaction was thus extended using aryl iodides. It is worth noting that the reaction was regioselective since only 2-arylated products were isolated, as well as chemoselective since no competing reaction was observed at the nitrogen-free atom. Pyrrole reacted faster than furan and consistently led to the formation of arylated products in higher yields.

In contrast to the regioselective arylation of pyrrole and furan, the arylation of thiophene and pyridine led to a mixture of isomers (Scheme 11).

The formation of two isomers for the thiophene arylation was explained by the stabilization of the radical intermediate. Due to the available d orbital of the sulfur atom which can participate in mesomeric forms, the 3-aryltiolphenium radical intermediate can indeed be stabilized by resonance, whereas this phenomenon is not possible with oxygen- or nitrogen-containing 5-membered rings (Scheme 12).

Concerning the mechanism, authors suggested a homolytic aromatic substitution (HAS), as described by Curran and Studer for the organocatalytic C–H arylation of arenes and heteroarenes.[8a] Competition reactions with an equimolar mixture of benzene and a heteroarene (pyridine, furan, thiophene and pyrrole) showed that the radical consistently reacted faster with electron-richer substrates, demonstrating the electrophilic nature of aryl radicals. The SOMO-HOMO energy level difference was also examined for different substrates and confirmed the electrophilic nature of the radical. Based on these data, Chan et al. proposed the mechanism shown in Scheme 13.

The wide variety of commercially available substituted aryl iodides or bromides makes them promising candidates for the synthesis of arylated heteroarenes. A quite high catalyst loading is, however, required for their reduction into the corresponding aryl radical. The development of more efficient catalysts seems thus to be essential to make the use of aromatic halides even more attractive for these arylation, espe-
cially to reduce the reaction temperature as well as the amount of base and heteroarene.

2.3 Arenediazonium Salts

Arenediazonium salts are well known species discovered at the end of the 19th century by Peter Griess who worked on dyes and pigments. They can be classified as “super-electrophiles” and highly reactive aryl halide surrogates. They have been frequently exploited for transformations involving aryl cations, they have attracted much more interest as aryl halide substitutes for palladium-catalyzed coupling reactions including Heck[34] and Suzuki-type[35] transformations.

However, depending on the reaction conditions, diazonium ions can also follow a homolytic pathway. Indeed, are known aryl radical precursors through homolytic C=N bond cleavage.[36] The high redox potential of these species (E_{red} > 0.5 V vs. NHE) allows rapid electron transfer processes from a reducing agent capable of supplying a single electron. Electron-withdrawing substituents on the aryl moiety increase the redox potential of diazonium salts, favoring thereby, the homolytic C=N bond cleavage. Electrochemical,[37] photo-induced[38] and metal-catalyzed reductions are the main pathways for generating aryl radicals from diazonium salts. The role of the counterion in the redox process has not been rationalized nor thoroughly studied although one can expect that it does not act as a spectator regarding the reaction outcome.

A number of transformations involving aryl radicals generated from diazonium salts has been developed for many years and includes the Sandmeyer,[39] Pschorr,[40] Gomberg–Bachmann[41] and Meerwein reactions. The Meerwein reaction,[7] a copper-catalyzed redox transformation between diazonium ions and olefins, can be formally classified as a C-H arylation since the products are usually synthetically equivalent to those obtained through a Pd-catalyzed Heck reaction. However, the generally low efficiency of the Meerwein reaction precluded its development from further synthetic relevant applications. It has been essentially studied with acrylates, methyl vinyl ketones and styrenes as olefinic partners under copper(II) chloride catalysis in aqueous conditions.[42] Alternatively, the use of stoichiometric amount (2–3 equiv.) of Fe(II) and Ti(III) as reducing metals has been successfully reported for the arylation of various olefins.[43] More recently, Kürig et al. reported visible-light mediated arylations with Ru(bpy)_3Cl_2 as catalyst,[44] while arylation of heteroarenes under metal-free photocatalyzed reactions were also successful.[45]

On the other hand, the C-H arylation of heteroarenes following a Meerwein-type reaction has been much less explored, although a few successful approaches should be mentioned.

In their seminal publication,[7] Meerwein and co-workers reported the arylation of coumarins under a copper-catalyzed process. Under the optimized con-

Scheme 13. Mechanism of the cobalt-catalyzed arylation of heteroarenes with aryl halides.
ditions equimolar amounts of coumarin and diazonium chlorides were mixed in aqueous acetone at room temperature in the presence of a rather high copper loading (30 mol%) (Scheme 14). As diazonium salts having a chloride counterion are very unstable in their dry form, an in situ preparation was preferred. However, in this case, aqueous HCl was used as a solvent and the use of an excess of NaOAc as a base was required to buffer the reaction media. Although rather synthetically useful yields (40–50%) were obtained with para-substituted electron-deficient diazonium salts, ortho-substituted, neutral and electron-rich diazonium salts were much less reactive. This result reflects the easier homolytic C–N bond cleavage of electron-poor diazonium salts due to higher redox potentials.

The photo-Meerwein arylation of a five-fold excess of coumarin with benzenediazonium tetrafluoroborate has been described, on a single example, using [Ru(bpy)], as photocatalyst and visible light in DMSO as solvent.[44a] Under these conditions, a much improved yield was obtained compared to the procedure described by Meerwein (63% vs. 26%). This elegant chemistry has been very recently extended to the surface patterning of cellulose.[44b] Indeed, coumarin-functionalized cellulose sheets were grafted with 4-methoxybenzenediazonium tetrafluoroborate using a visible light (455 nm) photocatalyzed Meerwein arylation. The use of a photomask to pattern the cellulose sheets produced a writing observable by the naked eye.

Besides coumarin, furans and thiophenes have been the most studied heteroarenes as substrates for the Meerwein arylation. The C-5 arylation of furans bearing formyl,[46] acetyl,[47] carboxylic[48] and other groups[49] at C-2 have been described as privileged structures, due to their good reactivity with arenediazonium salts and the suppression of unwanted C-2/C-5 diarylation processes. Obushak and co-workers have extensively studied these kinds of couplings (> 45 examples). The arylations were typically conducted in a mixture of aqueous HCl and acetone with an equimolar amount of diazonium salts and furans in the presence of copper(II) chloride as copper source at room temperature. Contrary to the original conditions reported by Meerwein, a base was not required with these heterocycles although aqueous HCl was used for the in situ preparation of the diazonium salt. It is, however, rightful to question the potential influence of a base and a detailed study for a deeper understanding of its role would be helpful, especially for acid-sensitive substrates. In most cases, synthetically useful yields, considered as rather high for the Meerwein arylation (40–70%), were obtained with 2-CO2Me-, 2-COCH 3- and 2-CO 2H-substituted furans (Scheme 15). The authors noticed a lower reactivity for arenediazonium salts bearing electron-donor substituents, a trend which was, however, not always reflected by the yields reported. The arylation of 2-acetylfuran provided 2,5-diarylfurans as unusual side-products upon in situ deacetylation as previously observed.[50] It is interesting to note that all examples reported by Obushak and co-workers were run on a multi-gram scale (0.2 mol) highlighting the scalability and the robustness of this transformation.

Although the role of the counterion associated to the diazonium function has not been extensively studied, Obushak and co-workers reported on a single example, describing for the arylation of furfural, its strong influence on the reaction yield (Table 1).[51] The use of commercially available 4-nitrobenzenediazonium tetrafluoroborate was preferable to in situ generated 4-nitrobenzenediazonium chloride and sul-

Scheme 14. Cu-catalyzed Meerwein arylation of coumarin with diazonium salts.
fate (entry 1 vs. entries 2 and 3). Although this trend might not be general to other diazonium salts and/or heterocycles, it could reflect the peculiar role of the counterion. Moreover, a closer look at the results reported by this group suggested that the influences of the catalyst and counterion are strongly and thinly tied (entries 1 and 2 vs. entries 4 and 5). Contrary to their previous reports, they reported that aqueous DMSO was superior to aqueous acetone or water as solvent media.

Studies directed at the improvement of the reaction have been scarce and this point should stimulate further innovative catalytic systems.

Recent studies showed that reaction yields could be significantly improved, providing that a stoichiometric amount of copper(I) chloride was used as reductant, under water-only conditions for the coupling of diazonium chlorides with furfural (Scheme 16). These results suggest that the search for a more robust catalyst, having a higher turnover number should definitively improve the Meerwein arylation, especially for heterocyclic structures. Although examples working with electron-rich diazonium salts were not provided, it should be noted that ortho-substituted aryls were well tolerated.

When an excess of the heteroarene moiety (5 equiv.) was used with TiCl$_4$ (2 equiv.) as reducing agent, excellent yields of the corresponding arylfuran were obtained (Scheme 17). Interestingly, the use of pure water as solvent allows a control of the monoarylation at C-2 of furan due to the insolubility of the diarylated congener. The use of an organic solvent considerably increased the formation of unwanted diarylated product. The extension of these reaction conditions directed at the improvement of the reaction have been scarce and this point should stimulate further innovative catalytic systems.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Counterion $X^-$</th>
<th>$[Cu]$</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_4^-$</td>
<td>CuCl$_2$</td>
<td>75–80</td>
</tr>
<tr>
<td>2</td>
<td>CI$^-$</td>
<td>CuCl$_2$</td>
<td>50–60</td>
</tr>
<tr>
<td>3</td>
<td>HSO$_4^-$</td>
<td>CuCl$_2$</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>BF$_4^-$</td>
<td>Cu(OAc)$_2$</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CI$^-$</td>
<td>Cu(OAc)$_2$</td>
<td>61–66</td>
</tr>
</tbody>
</table>

Table 1. Arylation of 2-furfural with 4-nitrobenzene diazonium salts.
Obushak and co-workers observed that 2-thiophenecarbaldehydes\[^{54}\] and 2-acetylthiophene\[^{55}\] displayed a lower reactivity (20–55%, Scheme 18) toward the radical arylation with arenediazonium salts, under copper-catalyzed reaction conditions, than did their corresponding furan congeners (compare Scheme 15 with Scheme 18). It should be noted that a similar trend was previously briefly communicated during the preparation of compounds having potential fluorescent properties.\[^{56}\] Although modest yields were usually obtained, when a catalytic amount of copper and an equimolar amount of heterocycles were used, the Meerwein reaction remains attractive due to the simplicity of the experimental conditions and the inexpensive reagents and catalyst required. A screening of solvents showed that an organic-aqueous medium was required for optimal results, with DMSO being superior to acetone, acetonitrile and DMF as the organic solvent. The reaction was consistently fully regioselective at C-5 for all cases studied, the 4-nitrobenzenediazonium chloride being the only exception to this trend, giving 27% of the C-3 arylated product.

Applications of the Meerwein arylation of furans and thiophenes for the preparation of high value compounds are rare. In the search for H\(_2\) receptor histamine antagonists, a series of arylated furans, obtained through the Meerwein methodology, has been described, with albeit limited success.\[^{57}\] On the other hand, organic materials incorporating an arylfuran or thiophene skeleton prepared via a Meerwein approach and displaying fluorescent properties have been reported a few years ago.\[^{58}\]

The C–H arylation of maleimide was studied by Rondestvedt in the middle of 1950s (Scheme 19).\[^{59}\] In most cases, the crude product appeared to be a mixture of the expected 3-arymaleimide along with the 3-aryl-4-chlorosuccinimide. However, the latter was easily converted into the former by a simple base-mediated treatment with 2,6-lutidine or 2,4,6-collidine. Sodium acetate was used as a buffer additive bringing the solution to pH 3, due to the excess of...
HCl used for the diazonium salt preparation. Although yields were rather modest (20–50%), a surprising effect was observed with electron-rich diazonium salts. Indeed, while diazonium salts bearing electron-donating substituents usually displayed a low reactivity, Rondestvedt observed an inverse phenomenon with maleimide, leading to a prominent side diarylation process. This unusual behavior has not been clearly rationalized and should stimulate further investigations. As a note is the surprising compatibility of the free NH function with diazonium salts that allows protecting group-free arylations.

We recently reported a significant breakthrough in this field with the copper-catalyzed C–H arylation of pyrroles with in situ generated arenediazonium salts under neutral conditions. When we started our studies, the metal-catalyzed arylation of pyrroles with diazonium salts was unknown since their high nucleophilicity strongly favored the addition over the diazonium function, leading to the corresponding azo compound. This unwanted process was even reinforced in the acidic conditions required for the Meerwein arylation (pH < 3). We reasoned that an N-protecting group decreasing the nucleophilicity of the pyrrole would disfavor the azo formation. In the same time, the development of neutral conditions would also be useful for conserving the integrity of acid-sensitive pyrroles. Toward this end, we took inspiration from our publications on metal-catalyzed transformations involving arenediazonium salts, where we reported unprecedented mild and neutral condition through in situ activation of anilines.

We modulated the nucleophilicity of the pyrrole with the evaluation of electron-withdrawing N-protecting groups including carbamates (CO₂-t-Bu, CO₂Me), sulfonate (Ts) and amide (COPh). From these optimization studies, we learned that strongly electron-withdrawing groups such as Ts and COPh deactivated too much the heterocycle, thereby, decreasing the reaction yield while carbamates realized a good balance. The drop of reaction yields with electron-deficient pyrroles might reflect the electrophilic character of aryl radicals. Arenediazonium salts were generated in situ from an equimolar amount of aniline, t-BuONO and MeSO₃H. We had previously observed that the nature of the counterion surrounding the diazonium cation greatly influenced the reaction outcome, and we observed that sulfonates were anions of choice for Pd-catalyzed Heck-type reactions. Although mechanisms involved were likely very different for copper-catalyzed reactions, a similar behavior was observed in this study, since the use of commercially available diazonium tetrafluoroborates considerably hampered reaction yields. In order to trap MeSO₃H generated during advancement of the reaction and thereby exclude any acid-mediated azo side-products, we selected CaCO₃ as a mild base. The copper source proved to be crucial for obtaining good reaction yields. Indeed, with CuCl₂, traditionally used in the Meerwein-type arylation, significant amounts of aryl chlorides were observed due to the trapping of chlorine by highly reactive aryl radicals. To avoid diarylation side-products at C-2/C-5, a slight excess of the pyrrole moiety was required. These optimized conditions proved to be very efficient with a variety of anilines, giving yields significantly higher than those usually encountered for the Meerwein arylation of heterocycles (Scheme 20). The process was compatible with a variety of substituents including esters, ethers, nitriles, nitro, ketones and halogens, revealing the mild conditions used in this study. The pyrrole moiety can even react with unusual anthraquinones and heteroarene nuclei in very synthetically useful yields.

The mechanism of the Meerwein reaction is still the subject of a debate, more than 70 years after its discovery. Meerwein’s classical conditions involve aqueous acetone as solvent and CuCl₂ as catalyst. It is usually admitted that CuCl₂ is reduced into CuCl by acetone, providing chloroacetone as by-product.
Then, CuCl reduces the diazonium salt into an aryl radical with concomitant loss of nitrogen. Whilst this mechanism could be acceptable in many cases, it cannot explain why in acetone-free solvents, e.g., water, acetonitrile or NMP, the reaction still takes place nor why using directly CuCl tends to be less efficient than starting with CuCl₂. On the other hand, the formation of an arenediazonium tetrachlorocuprate(II) has been suggested when starting from CuCl₂ and arenediazonium chlorides, but this complex was not reduced by acetone.

In 2009, another mechanism was proposed and involved the reduction of CuCl₂ into CuCl by the olefinic substrate giving a radical cation. Then copper(I) chloride reduces the arenediazonium salt and the generated aryl radical reacts with the olefin. In the same year this mechanism was criticized, since apparently nitrogen cannot be eliminated by reduction of the diazonium salt in the ground singlet state. Instead, it was postulated that tetrachlorocuprate plays a key role in the formation of the diazonium salt in a triplet state. In that framework, we underlined that the latter previous theoretical work relied on a quite low level of theory (investigation of molecular orbitals with semi-empirical approaches), and did not provide any reaction path (no transition states have been located). On top of that, it cannot explain why Cu(OAc)₂ gave identical and even sometimes better results.

On the basis of literature precedents and with the complement of our experimental observations, a catalytic cycle was proposed (Scheme 21).

The Cu(I)-catalyzed homolytic dediazoniation of the diazonium salt A provides the corresponding aryl radical B, quickly intercepted by the heteroarene C. The radical intermediate D is likely oxidized by Cu(II) species into the corresponding cation E which upon deprotonation provides the expected coupling products. With the support of labelled experiments we suggested that a base, such a carbonate (CaCO₃), could facilitate the deprotonation of the pyrrolo cation E, diminishing, thereby, undesirable pathways.

Although the metal-catalyzed arylation of heterocycles with arenediazonium salts had been discovered a long time ago by Hans Meerwein, relatively few studies have been undertaken to improve the original...
experimental conditions. We have, however, recently showed that the nature of the diazonium salt as well as the pH of the media could have a significant impact on the reaction outcome. The simplicity of the experimental procedures as well as the high reactivity of diazonium salts, allowing for mild conditions, make this transformation of high synthetic value. There is, however, still room for improvement to design catalytic systems with high turnover numbers, and working with diversely decorated heterocycles.

3 Generation of Aryl Radicals using an Oxidant

3.1 Arylhydrazines

Arylhydrazines, known for their genotoxicity and carcinogenicity,[67] have been mainly used for the synthesis of heterocycles such as indoles,[68] indazoles[69] or pyrazoles,[68b,70] as well as electrochemical grafting onto carbon or metal surfaces.[71] Another recent application is their utilization as arylating agent for the palladium-catalyzed C–C coupling with heteroarenes[72] or alkenes[73] via a C–N bond cleavage.

Arylhydrazines are reductants easily oxidized by oxygen or metallic oxidizing agents such as mercury, lead, copper, manganese or iron salts, to generate the corresponding aryl radicals via the formation of unstable diazenes. Their oxidation was initially developed for the synthesis of biaryls from arylhydrazines and aromatic solvents, albeit with moderate yields, using stoichiometric amounts of silver oxide[74] or lead(IV) acetate.[75] More recently, manganese derivatives have emerged as powerful oxidants for free-radical generation from arylhydrazines. For instance, the group of Demir reported the reaction of phenylhydrazines with benzene with high yields, using 3 equivalents of manganese triacetate either preformed[76] or in situ generated from a KMnO₄/CH₃COOH mixture.[77] More recently, Heinrich et al. extended the scope of this reaction to the synthesis of 2-aminobi-phenyls from arylhydrazines and anilines, by exploiting the strong directing effect of the free unprotected amino group.[78] Finally, the environmentally-friendly oxidative arylation of thiophene and furan,[81] using the conditions optimized earlier for the arylation of arenes.[76] Only the 2-substituted furan and thiophene were isolated, demonstrating the regioselectivity of the radical reaction. The scope of the reaction was then extended to electron-rich and electron-poor substituted phenylhydrazines in moderate to good yields (22–70%), usually higher for thiophene derivatives (Scheme 24). The lowest yields were obtained for the arylation of furan with electron-rich 4-methoxyphenylhydrazine (30%) and electron-poor pentafluorophenylhydrazine (22%), whereas the sterically-hindered 2-bromophenylhydrazine led to the corresponding arylated furan or thiophene with good

![Scheme 22. First radical arylation of heteroarenes with arylhydrazines.](image)

![Scheme 23. Mechanism of the arylation of heteroarenes with arylhydrazines.](image)
yields (~60%). It has to be noticed, however, that a high temperature and a large excess of manganese acetate (3 equiv.) as well as heteroarene (~200 equiv.), used as both reactant and solvent, are required.

The formation of the aryl radical was explained by the formation of the unstable phenyldiazeno intermediate after two successive Mn(III)-mediated oxidations (Scheme 25). The continuation of the mechanism was not described, but one can assume that the attack of the radical on the heteroarene generates only the corresponding 2-arylated 3-radical intermediate, whose stability is greater than that of the 2-radical intermediate. This radical is probably oxidized by a third equivalent of Mn(III) to generate the corresponding cation, followed by the rearomatization of the arene concomitant with the loss of H⁺.

Finally, Heinrich et al. developed a manganese-mediated regioselective radical C–H arylation of anilines with arylhydrazines and reported, in this paper, one example of arylation of furan (Scheme 26).[79] MnO₂ was used as oxidant, with the hydrochloride salt of 4-chlorophenylhydrazine (to enhance its stability) and 40 equivalents of furan, leading to the exclusive formation of the 2-(4-chlorophenyl)furan in a yield similar to that obtained by Demir with manganese-(III) acetate.[81] The reaction mechanism is not mentioned but is probably similar to that described by Demir.[81]

Only a few examples of radical arylation of heteroarenes with arylhydrazines have been published until now, probably due to the moderate yields of arylated products and the amount of both oxidizing agent and heteroarene required. The development of new methodologies might thus be useful, for instance, to extend the scope to nitrogen derivatives, such as pyrroles or indoles, and to make more attractive the use of arylhydrazines as aryl radical source.

3.2 Arylboronic Acids

Arylboron derivatives are highly stable, non-toxic compounds, than can be easily synthesized, especially by electrophilic trapping with trialkyl borates of organometallic compounds[82] or C–H borylation.[83] A wide variety of derivatives is thus commercially available. They have been extensively used as coupling partners in the transition metal-catalyzed Suzuki–Miyaura cross-coupling reactions, and much progress has been achieved to carry out reactions under very mild conditions and with short reaction times, even when challenging partners are used.[84]

Arylboronic acids as well as potassium aryltrifluoroborates are known to decompose into aryl radicals through a single-electron transfer in the presence of an oxidant. Aryl radicals deriving from boronic acids were initially generated by

**Scheme 24.** Mn(III)-mediated arylation of thiophene and furan by protonated phenylhydrazines.

**Scheme 25.** Mechanism of the Mn(III)-mediated arylation of thiophene and furan by phenylhydrazines.

**Scheme 26.** Arylation of furan with 4-chlorophenylhydrazine catalyzed by manganese oxide.
manganese(III) and used for the C–H arylation of benzene. Whatever the source of Mn(III), either Mn(OAc)₃ or a KMnO₄/AcOH mixture, 3 equivalents of oxidant and a large excess of refluxing benzene, used as both solvent and reactant, were required. It is worth noting that arylboronic esters were unreactive toward oxidation. Later on, the combination of an organic oxidant with a catalytic amount of transition metal has been used for the radical arylation of quinones and biaryls. For instance, Baran et al. developed a new synthesis of fluorenones through intramolecular radical cyclisation, using 0.2 equivalent of AgNO₃ and 3 equivalents of K₂S₂O₈ as radical initiators, whereas Shirakawa and Hayashi rather used a 10 mol% Fe(III)/10 mol% phenanthroline/2 equiv. (t-BuO)₂ mixture for the oxidative coupling of boronic acids with arenes.

Demir et al., who had reported the Mn(III)-mediated radical arylation of heteroarenes with arylhydrazines in 2002, extended their methodology to arylboronic acids as radical source, using the optimized conditions previously reported. Aryl radicals were generated by reaction with Mn(OAc)₃, and trapped with furan or thiophene, used as both solvent and reactant (> 300 equiv.), to produce exclusively the corresponding 2-arylated heteroarenes (Scheme 27). Various electron-rich and electron-poor heterocycles were used as model substrates for the optimization of the reaction conditions (Scheme 29).

Among the different oxidants tested, such as Ce(IV), Cu(II), Fe(III), Ag(I) and V(V), Mn(OAc)₃, compared to that obtained with arylhydrazines could be noticed. It is worth noting that 2-, 3- and 4-formylbenzeneboronic acids led to the formation of the corresponding 2-arylated thiophene and furan adducts without any oxidation side-product being isolated. No mechanism was detailed in this publication.

A few years later, the same group published the Mn(III)-mediated radical arylation of thiophene with arylboronic acids under 800 W microwave irradiation in the presence of zeolite, using Mn(OAc)₃ or KMnO₄/AcOH systems. The exact procedure was, however, not clearly detailed, since the temperature was not reported and the exact role of the zeolite not described. Reaction yields were higher than those previously reported under traditional heating, but a larger excess of thiophene was used (> 600 equiv.) and the scope was rather limited (Scheme 28). Electron-rich, electron-poor and heteroarylboronic acids led to the corresponding heterobiaryls in good to excellent yields (65–95%). No oxidation side-product was isolated when 3-formyl-4-methoxybenzeneboronic acid was used. Finally, when the reaction was carried out in furan instead of thiophene, the desired aryalted adducts could not be isolated.

A more efficient microwave-promoted, Mn(III)-mediated C–H arylation of heteroarenes with arylboronic acids was published almost at the same time by the group of Guchhait. The single-electron transfer oxidative radical cross-coupling could be carried out with electron-rich as well as electron-poor heterocycles thanks to the microwave activation. Phenylboronic acid and electron-deficient pyridine were chosen as model substrates for the optimization of the reaction conditions (Scheme 29).
proved to be the most efficient, and 3 equivalents were required since all attempts to use it in a catalytic amount with a co-oxidant failed. However, the large excess of heteroarene, usually used as both solvent and reactant, could be reduced to only 10 equivalents in the presence of EtOH as solvent. Under these conditions, the reaction, carried out at 170°C, was complete in less than 10 min. The importance of the activation by microwaves was demonstrated by the high yield of arylated adduct (78%) and low yield of homo-coupling side-product (4%) (Scheme 29), whereas the same compounds were isolated respectively in 28% and 26% yields when using a conventional heating method. Finally, addition of a base to increase the reactivity of the aryl moiety resulted in a lower yield of 2-phenylpyridine (46%) and a higher yield of biphenyl (18%).

The scope of the reaction was then explored, and a wide variety of both electron-rich and electron-deficient heteroarenes underwent successful arylation with phenylboronic acid: thiophene, furan, N-methylpyrrole, thiazole, benzofuran, benzothiazole, pyridine, pyrimidine, quinolone and isoquinoline (Scheme 30). Whatever the heteroarene, the arylation exclusively occurred to the heteroatom, even with pyridine or thiophene.

Various para-substituted arylboronic acids, and even 4-pyridineboronic acid, also led to the formation of the 2-arylated furan adducts in modest yields (43–65%) (Scheme 31).

The formation of the intermediate aryl radical was demonstrated, for the reaction between furan or thiophene with phenylboronic acid, since 20 mol% of TEMPO as radical scavenger caused a dramatic decrease of the reaction yield.

The first room-temperature direct radical C–C/H arylation of pyridines and electron-deficient heteroarenes with arylboronic acids was developed by Baran using an inorganic oxidant, namely K₂S₂O₈, in combination with a catalytic amount of silver(I) nitrate. It is worth noting that, in this procedure, the heteroarene is the limiting reagent. The optimization of the conditions was not detailed, but authors used 1 equiv. of trifluoroacetic acid, to generate in situ the protonated heterocycle, in combination with 1.5 equiv. of aryloboric acid, 3 equiv. of K₂S₂O₈, 0.2 equiv. of AgNO₃ in a biphasic 1:1 DCM/H₂O mixture (Scheme 32). The protonation of the heterocycle was not essential but improved both reaction rates and conversions, probably by reducing the electron density of the pyridine C-2 and enhancing its electrophilicity. The reactions could be carried out in open flasks. The C–H arylation of 4-tert-butylypyridine with various aryloboric acids proceeded in moderate to good yields. Electron-rich aryloboric acids exhibited a higher reactivity and shorter reaction times, whereas electron-poor

\[
\text{Scheme 29. Arylation of pyridine with phenylboronic acid mediated by Mn(OAc)₃ under microwave irradiation (optimized conditions).}
\]

\[
\text{Scheme 30. Mn(III)-mediated arylation of various heteroarenes by phenylboronic acid under microwave irradiation.}
\]

\[
\text{Scheme 31. Mn(III)-mediated arylation of furan by various aryloboric acids under microwave irradiation.}
\]
boronic acids required the addition of additional K$_2$S$_2$O$_8$/AgNO$_3$ to drive the reaction to completion. The presence of electron-donating ortho-substituents was tolerated but led to the formation of the arylated adducts in low yields.

The reaction with 4-methylphenylboronic acid displays a broad scope with respect to electron-deficient heteroarenes with yields ranging from 30% to 96%, but a lack of regioselectivity was observed for most substrates, the 2- and 4-arylated adducts being predominant (Scheme 33). It was, however, chemoselective since the presence of halide substituents was tolerated. Electron-withdrawing substituents enhance the reactivity to the detriment of the selectivity. Electron-rich heteroarenes such as indole or imidazole did not undergo successful arylation.

A mechanism was proposed for the radical arylation, starting with the disproportionation of the persulfate anion into sulfate dianion and sulfate radical ion. The reaction between the radical ion and the boronic acid generates the aryl radical involved in the homolytic aromatic substitution. The silver catalyst plays two roles in the catalytic cycle. Silver(I) species reduces S$_2$O$_8^{2-}$/HCO$_2$ into SO$_4^{2-}$/HCO$_2$, and the generated silver(II) oxidizes the radical cation pyridine intermediate (Scheme 34). The reaction fails if a stoichiometric amount of silver(II) is used instead of K$_2$S$_2$O$_8$, or in the absence of silver(I), demonstrating the importance of SO$_4^{2-}$ as oxidant.

The same group reported later on an intramolecular version of this K$_2$S$_2$O$_8$/AgNO$_3$-catalyzed arylation, starting from potassium trifluoroborates, and leading
to the formation of fluorenones.\cite{88} One example of arylation of a pyridine derivative is described, and a mixture of 2- and 4-arylated adducts was isolated in good overall yields (Scheme 35). Dichloromethane was substituted by trifluorotoluene, and a temperature of 60°C was required.

The room-temperature C–H arylation of heteroarenes with arylboronic acids catalyzed by K$_2$S$_2$O$_8$/AgNO$_3$ was then extended by Mai and Li to pyridine and pyrazine N-oxides.\cite{92} The methodology was applied to these particular substrates, since Baran’s conditions required the use of 1 equivalent of trifluoroacetic acid to block the nitrogen atom of pyridine. Whilst a number of parameters was evaluated in the optimization studies including the metal, oxidant and solvent, the slightly modified Baran’s conditions remained the most efficient for the arylation of pyridine N-oxide (Scheme 36).

The scope of the reaction was successfully extended to various pyridine and pyrazine N-oxides with substituted arylboronic acids (Scheme 37). Pyrazine N-oxides led to the arylated adduct in higher yields (80–87%) than the corresponding pyridine derivatives. The same reaction with pyrazine led to a yield as low as 30%. It is worth noting that the arylation occurred exclusively at the 2-position of the pyridine or pyrazine.

The postulated mechanism is the same as the one proposed by Baran earlier. To support the formation of the aryl radical intermediate, the authors carried out the reaction in the presence of 2 equivalents of TEMPO as a radical scavenger, and noted that only a trace amount of the arylated pyridine could be detected.

Very recently, Patel and Flowers examined the mechanism of the cross-coupling of arylboronic acids with pyridines using kinetic and spectroscopic methods, in order to improve the catalytic system and broaden the substrate scope of the reaction.\cite{93} 4-Tri fluoromethylpyridine and p-tolylboronic acid were chosen as model substrates for this study (Scheme 38).

It was noticed that the use of degassed solvent and the exclusion of oxygen from the reaction were important factors to reach a higher yield of arylated pyr-
idine. A kinetic study allowed them to determine the rate order for each substrate: 1 for AgNO\(_3\) and pyridine derivative, 0 for K\(_2\)S\(_2\)O\(_8\) (but 1 for the more soluble Na\(_2\)S\(_2\)O\(_8\)) and, more surprisingly, −0.5 for the boronic acid, indicating an overall decrease in reaction rate when the boronic acid concentration increases. The first order observed for pyridine compared to the negative one observed for the boronic acid suggested a mechanism more complicated than the one starting from oxidation of the boronic acid to form the radical, followed by its addition onto pyridine. The authors thus investigated the possible formation of a pyridine-silver(I) complex using \(^1\)H NMR studies. The spectra of pyridine, pyridine and 1 equivalent of TFA or AgNO\(_3\), as well as a mixture pyridine/TFA/AgNO\(_3\) 1:1:1 in D\(_2\)O were compared, and showed an equilibrium complexation between the pyridine derivative and silver(I). In order to confirm this hypothesis, reactions with stoichiometric amounts of boronic acid and silver nitrate, with or without pyridine, were carried out. Almost 60\% of para-tolyloboronic acid was converted into toluene in the presence of pyridine, whereas the conversion decreased to 15\% only in the absence of pyridine. It had been shown that aromatic boronic acids react with silver(I) salts in ammoniacal solution to form the corresponding arene, boric acid and Ag\(_2\)O.[94] The higher conversion of para-tolyloboronic acid into toluene in the presence of pyridine suggested thus that a pyridine-silver(I) complex is likely involved, in the same way, in the homolytic deboronation of para-tolyloboronic acid and this complex is degraded to pyridine and inactive Ag\(_2\)O. The use of an additive capable of preventing the formation of this catalytically inactive Ag\(_2\)O, such as HNO\(_3\), allowed the isolation of 2-tolyl-4-trifluoromethylpyridine in an excellent 90\% yield (vs. 76\% with Baran’s conditions), with only 10 mol\% AgNO\(_3\) and 2 equivalents of K\(_2\)S\(_2\)O\(_8\).

Another important point is the identity of the species oxidizing the arylboronic acid. Baran and others suggested that the SO\(_4\)^{2−} intermediate was the oxidizing agent but one cannot rule out the role of the Ag(II) species, as suggested by Kochi for the homolytic decarboxylation of carboxylic acids using a Ag(I)/persulfate system.[95] The arylation was thus
carried out in the presence of 6 equivalents of allyl acetate which is known as a radical trap for \( \text{SO}_4^- \), but no impact on reaction yield was observed, indicating that arylboronic acid is more likely oxidized by Ag(II). Authors also suggested that boron “ate” derivatives might be more susceptible to single-electron oxidation than trigonal boron species, and a solvent or a pyridine molecule might interact with the boron atom to facilitate the process.

Based on these data, the authors proposed a mechanism (Scheme 39) involving the formation of the pyridine-silver(I) complex, followed by the oxidation of silver(I) into silver(II). This complex oxidizes the boronic acid or the “ate” complex to form the aryl radical that add to the radicophile pyridinium.

Yu et al. described the first iron-mediated arylation of nitrogen heterocycles with arylboronic acids using a methodology inspired from the work of Baran, but replacing \( \text{AgNO}_3 \), by cheaper and non-toxic iron(II) sulfide. The reaction is, however, not catalytic anymore since one equivalent of FeS was required, and longer reaction times were necessary (40 h instead of 12 h). No optimization study was described nor was any attempt made to use a catalytic amount of iron(II). Substituted pyridines, mostly bearing electron-withdrawing groups at C-3 or C-4, were successfully arylated with various arylboronic acids (Scheme 40). The reaction was not regioselective, however, since mixtures of products were isolated in most cases, but it was chemoselective since halide substituents on the arylboronic acid or on the pyridine ring were tolerated. Yields were higher with electron-rich arylboronic acids (80–97%) than with electron-poor derivatives (41–78%). The presence of an electron-donating group at C-4 of pyridine led to the formation of the 2-arylated adduct exclusively, albeit in lower yields (36–68%). Other nitrogen-containing heterocycles could be arylated as well. Pyrimidine underwent arylation in very high yield (93%), whereas pyrazine, quinoline, quinoxaline, pyridazine, thiazole or benzothiazole were less reactive (17–53%). Imidazole, pyrrole, indole, benzoxazole, caffeine and quinine were unreactive.

The mechanism of the reaction was investigated using a radical scavenger, and only a trace amount of 4-cyano-2-phenylpyridine was detected when the reaction of 4-cyanopyridine and phenylboronic acid was carried out in the presence of 2 equiv. of TEMPO. The authors proposed thus a reaction mechanism quite similar to that described by Baran. However, in the light of the work previously discussed (Scheme 38), one cannot rule out another reaction pathway. Moreover, the mechanism is described as a catalytic cycle with the regeneration of the initial Fe(II) species, whereas 1 equiv. of FeS is required to achieve good yields (Scheme 41).

Finally, Singh and Vishkarma improved the iron(II)-mediated radical C–H arylation of electron-deficient heteroarenes with arylboronic acid by reducing the iron(II) quantity to a catalytic amount. The optimization of the conditions, using pyrazine and phenylboronic acid as model substrates in the presence of 1 equiv. of trifluoroacetic acid (Scheme 42), started by varying the nature of the metal catalyst. Fe(acac)\(_2\) proved to be the best among several Fe,
Mn, Ag or Cu salts tested, with an optimal amount of 20 mol%. Several peroxides were tested as oxidants but none of them gave better results than K$_2$S$_2$O$_8$. The solvent system proved to be an important parameter as well, since the biphasic DCM/H$_2$O system greatly enhanced the yield of 2-phenylpyrazine. Due to the immiscibility of dichloromethane and water, the authors tested the use of the phase-transfer catalyst tetrabutylammonium bromide (TBAB) that led to the formation of the desired product in an improved 84% yield. The reaction could be carried out at room temperature in an open flask, making the reaction easy to handle under very mild conditions.

Under the optimized conditions, the scope of the reaction with pyrazine was investigated and extended to a wide variety of arylboronic acids (Scheme 43).

Whatever the nature and the position of substituents on the aryl moiety, ortho-, meta-, para-electron-donating or electron-withdrawing groups, 2-arylated pyrazines were exclusively isolated in moderate to good yields (30–86%). As already observed in the previous methodologies, the reaction is chemoselective, since halide substituents are tolerated. Dimethylpyrazine gave the corresponding product in a lower yield than that observed with the non-substituted pyrazine (64% vs. 86%). Heteroarylboronic acids were also tested but led to the corresponding arylated adducts in very low yields (0–15%), even after prolonged reaction times.

The substitution of phenylboronic acid by potassium phenyltrifluoroborate led to the formation of the 2-phenylpyrazine in 78% yield, whereas only 30% yield could be isolated when the reaction was carried out with the phenylboronic acid pinacol ester (Scheme 44).

The reactivity of various arylboronic acids towards quinoxalines was investigated as well, and 2-monoarylated adducts could be isolated in synthetically useful yields (45–65%), (Scheme 45). The reaction of 2-
methylquinoxaline with \( p \)-tolylboronic acid led to the coupling product in a much lower yield (45% vs. 65%).

Finally, other electron-deficient heteroarenes, such as pyridines, quinoline and isoquino- 
lane were coupled with arylboronic acids, and led exclusively to the arylation \( \alpha \) to the nitrogen atom furnishing adducts in moderate yields yet (Scheme 46).

The presence of an electron-donating substituent on the aryl moiety of the boronic acid only slightly increases the yields of arylated pyridine or quinoline. The authors used TEMPO as radical scavenger to demonstrate the involvement of radical intermediates. The addition of TEMPO drastically decreased the yield of 2-phenylpyrazine, even though no value was reported.

Based on the developed methodology, the authors described the short synthesis of the bioactive natural product botryllazine A (Scheme 47). The 5-step synthesis includes the radical arylation of 2,3-dimethylpyrazine.

Boronic acids are very promising arylating agents in radical reactions with heteroarenes, mainly due to their wide commercial availability and their tolerance
to sensitive functional groups. They can be oxidized under very mild conditions and with easy-to-carry-out protocols, using simple, cheap and non-toxic metallic catalysts, such as iron, to generate aryl radicals. The scope of the reaction with catalytic amounts of iron has been, however, limited to nitrogen heteroarenes, whereas a stoichiometric amount of manganese was used with oxygen- or sulfur-containing heterocyclic compounds. Nevertheless, new iron-based systems have been developed for the generation of these radicals. Unpredictable regioselectivity[96] as well as modest yields are still recurrent issues with radical chemistry, but some works described in this review clearly demonstrate that upon a deep mechanistic understanding impressive improvements can be achieved.

Acknowledgements

The authors are thankful to the “Université de Nantes”, the “Université de Lille”, the “CNRS”, and the “Région Pays de la Loire” in the framework of a “Recrutement sur poste stratégique” for the funding. FXF is member of the “Institut Universitaire de France”.

References


