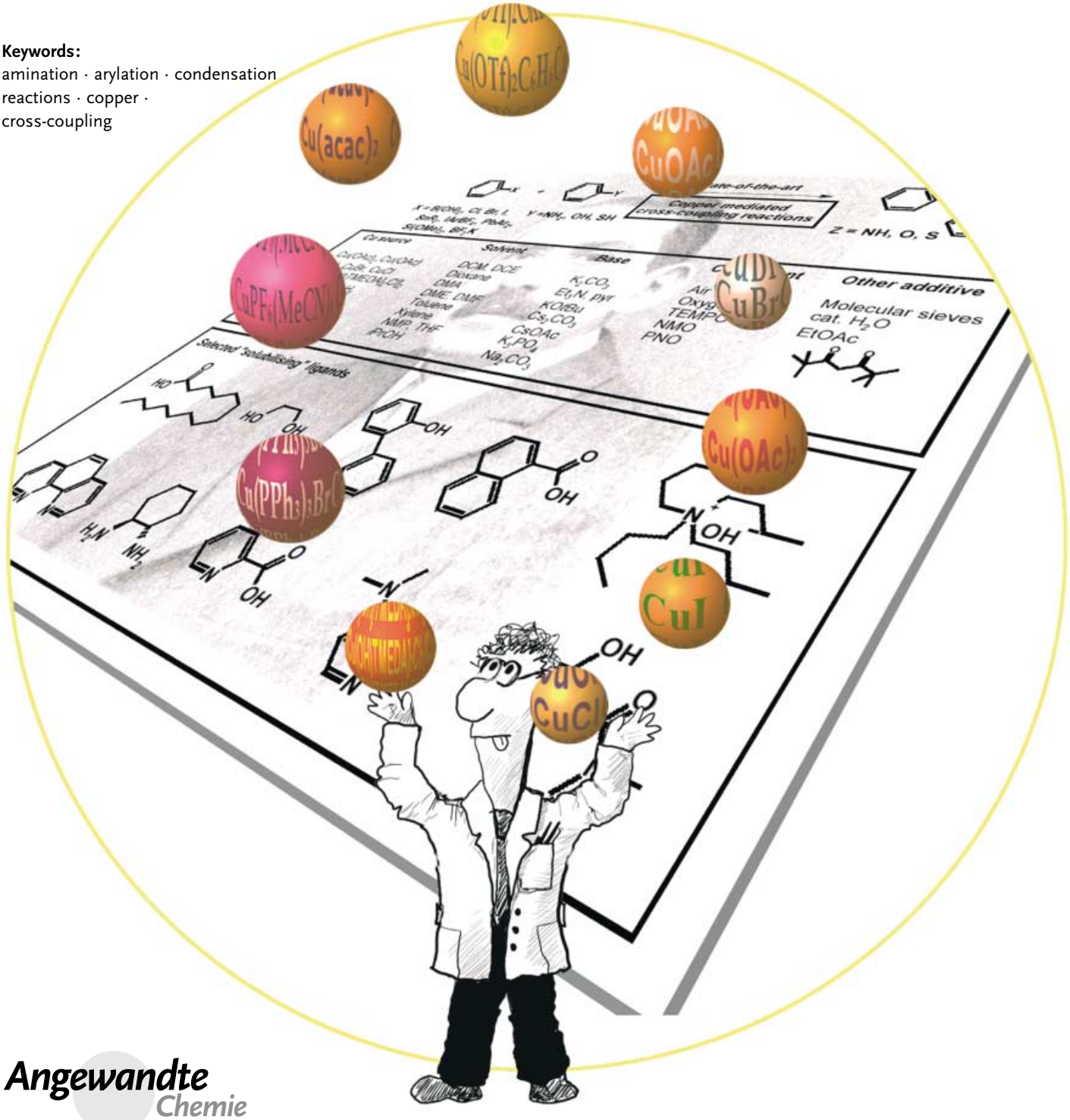
Ullmann Condensation

Modern Synthetic Methods for Copper-Mediated C(aryl)–O, C(aryl)–N, and C(aryl)–S Bond Formation

*Steven V. Ley and Andrew W. Thomas**

Keywords:
amination · arylation · condensation reactions · copper · cross-coupling



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The copper-mediated C(aryl)–N, C(aryl)–O, and C(aryl)–S bond formation is an important transformation and has been developed to include a wide range of substrates. This Review highlights the recent developments in the copper-mediated (both stoichiometric and catalytic) reactions of aryl boronic acids, aryl halides, iodonium salts, siloxanes, stannanes, plumbanes, bismuthates, and trifluoroborate salts as aryl donors. In particular, the recent introduction of boronic acids as reaction partners in both O- *and* N*-arylation has been a significant discovery and will occupy centre-stage in this review. Clear improvements can be obtained by the correct choice of copper source, base, ligands, and other additives. Mechanistic investigations should provide insight into the catalytically active species, which would aid in the development of milder, more-efficient methods.*

1. Introduction: The Legacy of the Past[1]

There is high demand for new methods to facilitate the synthesis of diaryl ethers, alkylaryl ethers, diaryl amines, alkylaryl amines, diaryl thioethers, and alkylaryl thioethers owing to their importance as structural motifs in a wide range of molecules with numerous and important applications. The classical copper-mediated Ullmann reaction (Figure 1) has

Figure 1. Fritz Ullmann, 1875–1939. Reproduced courtesy of the Library and Information Centre, Royal Society of Chemistry, from *Helv. Chim. Acta* **1939**, *23*, 94–100.

underpinned the research community when functionalities of these sorts are required. However, the harsh reaction conditions (high temperatures, strong bases, stoichiometric amounts of copper or copper salts, long reaction times) needed to effect these transformations, usually only in moderate yields, led to severe limitations in the general use of this reaction, especially on a large scale. Notable advances in the use of ultrasound[2] and use of alternative bases[3] required for the transformation have been reported, however these have not resulted in widespread popularity or use. Furthermore, activation of the aryl halide with a nitro group[4] or a triazene[5] has proven to be a valid method for diaryl ether synthesis with "copper phenoxides". However, removal of the

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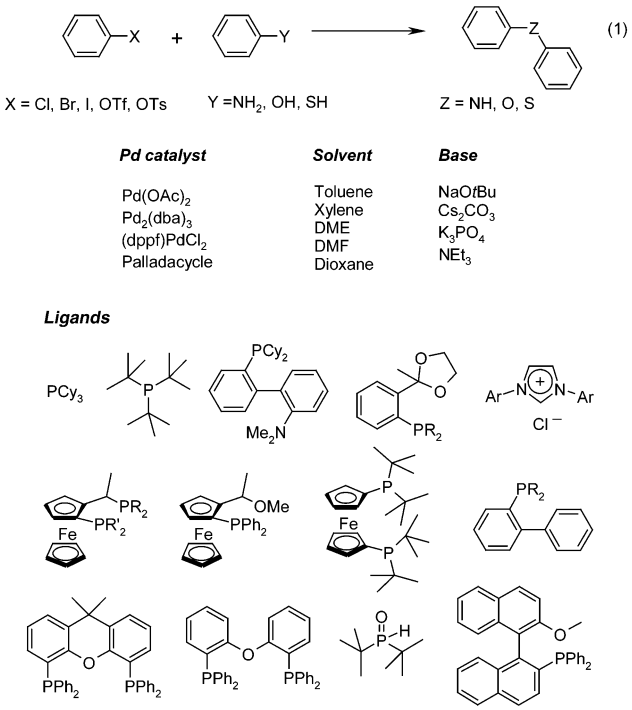
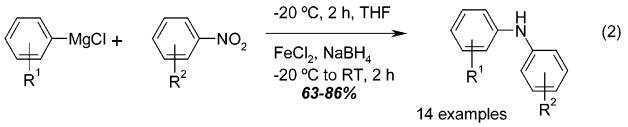
activating group by additional reaction steps renders these methods less efficient.

Current direct routes to form diaryl ethers, alkylaryl ethers, diaryl amines, alkylaryl amines, diaryl thioethers, and alkylaryl thioethers are, not surprisingly, mainly based on palladium-catalyzed reactions [Eq. (1)]. An extensive toolbox



of reaction variables allows the synthetic chemist to prepare a vast array of desired products in an efficient and practical manner, and a recent survey of palladium-mediated arylations using soft, non-organometallic nucleophiles has been compiled.[6]

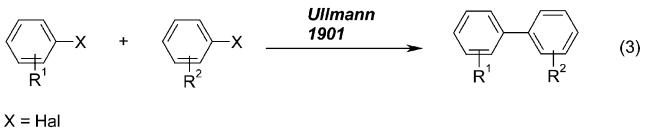
An interesting, novel, practical method for the synthesis of polyfunctionalized diaryl amines from the reaction of nitroarenes and functionalized aryl magnesium reagents (formed through Mg–halogen exchange from the corresponding aryl iodides or bromides with *i*PrMgCl) and has been developed by Knochel and Sapountzis [Eq. (2)].[7] Owing, in



part, to the recent emergence of this method, these reaction conditions are currently underdeveloped but do show great promise as a complementary route to prepare a range of diaryl amines, and interesting improvements are anticipated.

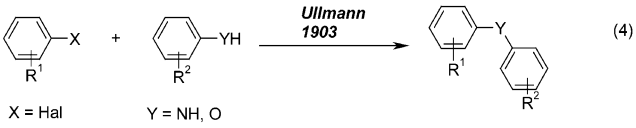
1.1. The Copper-Mediated Arylation Reaction Revisited: Reaction Nomenclature

Ullmann Reaction (synthesis of biaryl compounds): The formation of a C–C bond between two aryl units, which originate from two aryl halides, mediated by a copper species, although the transformation can be performed with various transition metals [Eq. (3)]. This transformation has recently



been reviewed in detail.[8] In this Review we associate Ullmann's name mainly with the synthesis of diaryl ethers and diaryl amines.

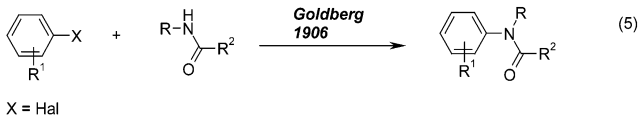
Ullmann Condensation Reaction (synthesis of diaryl ethers, diaryl amines, or diaryl thioethers): The formation of a C(aryl)–O, a C(aryl)–N, or a C(aryl)–S bond by the reaction of an aryl halide with a phenol, an aniline, or a thiophenol, respectively, mediated (originally catalytic) by a copper species [Eq. (4)].



Goldberg-Modified Ullmann Condensation Reaction: The copper-mediated (originally catalytic) formation of a C(aryl)–N bond after the reaction between an amide and an aryl halide [Eq. (5)].

Andrew Thomas earned his PhD under the guidance of Dr. R. Alan Aitken at the University of St. Andrews as a St. Leonard's College Fellow. He then spent two years as a postdoctoral student with Professor Steve V. Ley at the University of Cambridge as a Glaxo-Wellcome Research Fellow. In 1991 he moved to "Discovery Chemistry", F. Hoffmann-La Roche AG in Basel, Switzerland, and is currently a group leader and senior scientist in the central nervous system therapy area.

Steven V. Ley was appointed to the faculty at Imperial College in 1975 and made Head of Department in 1989. In 1992 he was appointed Professor of Organic Chemistry at the University of Cambridge and Fellow of Trinity College. He is Immediate Past President of the RSC and was made a CBE in January 2002. Steve's research involves the discovery and development of new synthetic methods and their application to biologically active systems. His group has reported the synthesis of over 90 target compounds in nearly 500 papers. In recognition of his work, he has been awarded 14 major prizes, most recently the Ernest Guenther Award.



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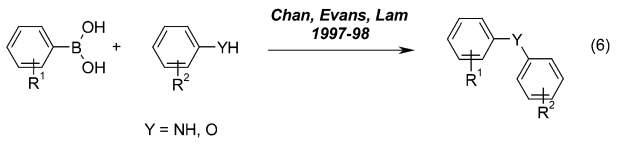
Chan–Evans–Lam-Modified Ullmann Condensation Reaction: The formation of a C(aryl)–O, a C(aryl)–N, or a C(aryl)–S bond by the reaction of an aryl boronic acid with a phenol, an aniline (or other N nucleophile), or thiophenol, respectively, mediated by a copper species [Eq. (6)].



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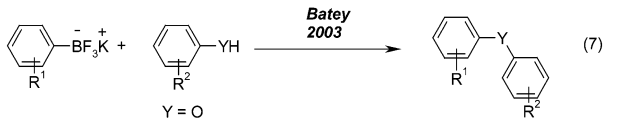
Batey-Modified Ullmann Condensation Reaction: The formation of a C(aryl)–O bond by the reaction of a phenol with a potassium aryltrifluoroborate mediated by a copper species [Eq. (7)].



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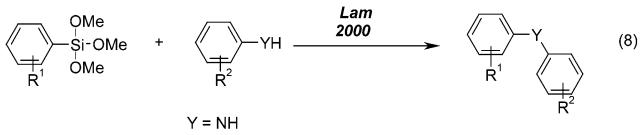
Lam-Modified Ullmann Condensation Reaction: The formation of a C(aryl)–O, a C(aryl)–N, or a C(aryl)–S bond by the reaction of an aryl siloxane with a phenol, an aniline (or other N nucleophile), or a thiophenol, respectively, mediated by a copper species [Eq. (8)].



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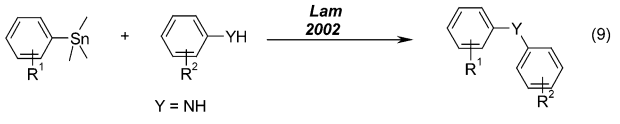
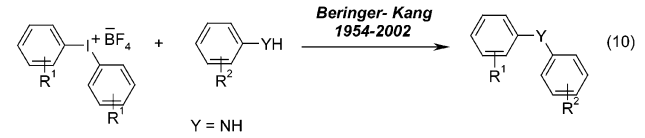
Lam Stannane-Modified Ullmann Condensation Reaction: The formation of a C(aryl)–O, a C(aryl)–N, or a C(aryl)–S bond by the reaction of an aryl stannane with a phenol, an aniline (or other N nucleophile), or a thiophenol, respectively, mediated by a copper species [Eq. (9)].



(9)

Beringer–Kang-Modified Ullmann Condensation Reaction: The formation of a C(aryl)–O, a C(aryl)–N, or a C(aryl)–S bond by the reaction of an aryl iodonium salt with a phenol, an aniline (or other N nucleophile), or a thiophenol, respectively, mediated by a copper species [Eq. (10)].

Avendano-Modified Ullmann Condensation Reaction: The formation of a C(aryl)–O, a C(aryl)–N, or a C(aryl)–S bond by the reaction of an aryl lead reagent with a phenol, an aniline (or other N nucleophile), or a thiophenol, respectively, mediated by a copper species [Eq. (11)].



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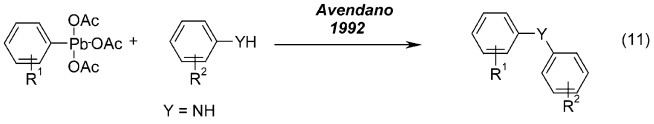

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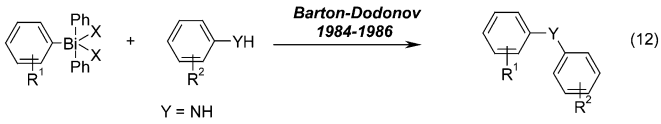
Barton-Modified Ullmann Condensation Reaction: The formation of a C(aryl)–O, a C(aryl)–N, or a C(aryl)–S bond by the reaction of an aryl bismuth reagent with a phenol, an aniline (or other N nucleophile), or a thiophenol, respectively, mediated by a copper species [Eq. (12)].



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Cross-Coupling Reactions: The reaction of organometallic reagents with organic electrophiles in the presence of group 8–10 metal catalysts, notably Ni and Pd complexes. This reaction is currently a popular method for a wide range of C–C, C–H, C–N, C–O, C–S, C–P, or C–M bond-forming processes.

Throughout the remainder of this Review we use the same terminology as Sir Derek Barton did in examining advances in the "arylation reaction".[9] Arylation in this context means replacement of an H atom on an heteroatom by an aryl group.

1.2. Following in the Footsteps of Success: Palladium-Mediated Strategies

Buchwald and co-workers[10] and Hartwig and co-workers[11] have endeavored to develop "user-friendly" palladium-mediated methods for C(aryl)–O and C(aryl)–N bond formation. This has been a very successful research program, as evidenced by the enormous popularity of these reactions, which has led to a fascinating number of potentially biologically active molecules that incorporate these structural motifs. Indeed, the vast amount of published material available describing a wide range of Pd-catalyzed methods, ligands, solvents, temperatures, and substrates has led to a toolbox of tunable reaction conditions whose scope should allow access to most target molecules that incorporate an aryl amine motif.

These research groups, and others, are continually providing important new advances and insight through iterative development of new catalytic methods, routinely using mechanistic investigations in the design cycle. Fu and co-

workers have also contributed significantly and have recently summarized the state of the art of palladium-catalyzed coupling reactions of aryl chlorides.[12]

1.3. Organization of this Review

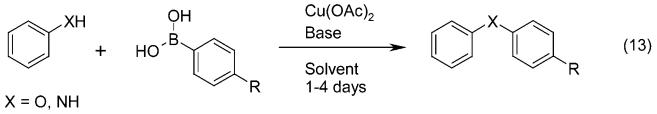
Each section of this Review presents the most recent developments in the formation of C(aryl)–N, C(aryl)–O, and C(aryl)–S bonds. Each section describes a class of aryl donor and is further subclassified by the nature of the two reaction partners, and then further elaborated in the development of the transformation, whether stoichiometric or catalytic in nature. In each section, a survey of the reaction scope is also shown schematically: these "visual tables" can be used as a quick reference guide to search for first-attempt reaction conditions for a planned transformation.

For clarity, in cases in which more than one aryl moiety is present in the product (attached to the same type of heteroatom used in the transformation), the unit that originates from the electrophile is colored in red.

The comprehensive Sections 2 and 3 (boronic acids and aryl halides as aryl donors, respectively) are concluded by drawing specific attention to the state of the art as well as briefly outlining current deficiencies.

2. Boronic Acids as the Aryl Donor: "A Long-Standing Problem Has Been Solved"[13]

Independent reports by the groups of Chan,[14] Evans,[15] and Lam[16] in 1998 revolutionized the copper-mediated heteroatom arylation reaction for the formation of C(aryl)–O and C(aryl)–N bonds [Eq. (13)]. In these key contributions, the groups successfully and simply devised new milder methods for the construction of these bonds. This Review describes the discovery and development of the transformation into a practical and reliable method, which can be used either stoichiometrically or catalytically and overcomes some of the deficiencies associated with the classical Ullmann and Goldberg arylation protocols.



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2.1. Starting Off: Why Boronic Acids? Why Cupric Acetate?

Chan's previous experiences using triarylbismuth[17] and the quest to introduce new aryl-transfer reagents as the electrophilic reaction partner in heteroatom–aryl bond construction using cupric acetate as a promoter led his group at DuPont to try a new combination of reagents. By replacing the palladium with a copper species (copper acetate) and the use of a boronic acid and a heteroatom donor, they discovered that these new conditions were ideal to effect an Ullmann condensation. At this point, there was little deliberation on the mechanistic rationale for these precise reaction conditions, although the outcome is of considerable importance.

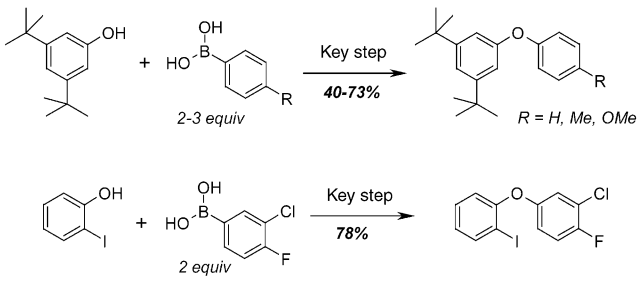
Chan and co-workers[18] first described a collection of *N*- and *O*-arylation transformations under novel reaction conditions as early as in June 1997, but only part of the work was disclosed at this meeting. However in the first publication[14] it was already demonstrated that this method with a boronic acid as the aryl donor was applicable to a wide range of nucleophilic reaction partners, including phenols (C(aryl)–O bonds) and amines, anilines, amides, imides, ureas, carbamates, and sulfonamides (C(aryl)–N bonds). The method quickly attracted interest and Evans and co-workers[15] were quick to exploit the process in an expedient formal synthesis of throxine; they also suggested a speculative mechanism analogous to that proposed by Barton for the amine arylation reaction. In the final of the back-to-back series of papers, Lam, Chan, and co-workers[16] also reported that aromatic heterocycles (imidazoles, pyrazoles, triazoles, tetrazoles, benzimidazoles, and indazoles) participate efficiently in this reaction mediated by copper acetate and using aryl boronic acids as the aryl donor.

The stage was now set, and the remainder of this section is focused on the development of these preliminary reaction conditions to effect these transformations, charting its emergence from a stoichiometric to a catalytic method. The scope of the reaction was expanded by incorporating different substrates, solvents, reaction temperatures, reaction times, as well as by the introduction of new "nontailored" ligands. These developments led to a potentially powerful new and general methodology for *O*- and *N*-arylation reactions. Efficient *S*-arylation involved overcoming challenges associated with thiol oxidations during the reaction process, and the successful work of Guy and co-workers and Liebeskind and co-workers is discussed in detail (Section 2.4).

2.2. Copper-Mediated C(aryl)–O Bond Formation

2.2.1. The Original Discovery: Stoichiometric Cu^{II} Methods

The simultaneous papers by the groups of Chan and Evans are important, as they set the standard for attracting the interest of the synthetic community: Both showed in detail the remarkable simplicity of the new reaction conditions. A mixture of the phenol (1 equiv), aryl boronic acid (2–3 equiv), anhydrous $Cu(OAc)_2$ (1–2 equiv), and Et_3N (2–3 equiv) in dichloromethane were stirred at room temperature for 1–2 days and then the product was isolated in good yield after chromatography (Scheme 1). These reaction conditions have therefore greatly improved the standard classic reaction protocols for the formation of diaryl ethers. Although Chan and co-workers described only four examples of the unoptimized synthesis of trisubstituted unsymmetrical diaryl ethers using only two phenolic substrates, they both underwent efficient cross-coupling with electronic-rich, electron-deficient, and *ortho*-substituted boronic acids. In these first examples, only Et_3N was used as the tertiary base along with either 1 or 2 equivalents of cupric acetate.



Scheme 1. Key step: $Cu(OAc)_2$ (1–2 equiv), Et_3N, CH_2Cl_2, room temperature.

2.2.2. *Molecular Sieves as Water Scavengers*

Evans and co-workers, on the other hand, who used the method to great effect for the synthesis of diaryl ether functionalities present in multifunctionalized macrocycles, further evaluated the scope and limitations of the new stoichiometric copper-mediated procedure (Table 1, [Eq. (14)]).

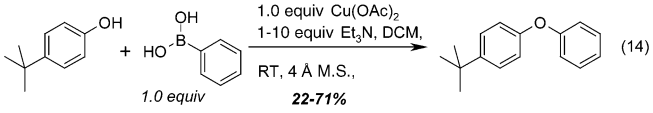


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Table 1: Reaction conditions for the *O*-arylation of phenols with aryl boronic acids [Eq. (14)].

Atmosphere	Et_3N [equiv]	$Cu(OAc)_2$ [equiv]	Yield [%]
Ar	1	1	22
Ar	10	1	34
air	1	1	41
air	10	1	71
O_2	5	1	71

They confirmed that the reaction conditions outlined above worked well in most cases. In fact they realized that $Cu(OAc)_2$ was an optimal Cu^{II} source and that the use of other copper salts, for example, $Cu(OPiv)_2$, $Cu(NO_3)_2$, $Cu(acac)_2$, and $Cu(OCOCF_3)_2$, gave inferior results and did not lead to the products of an arylation reaction. Neither did the use of $CuSO_4$, $CuCl_2$, or $Cu(ClO_4)_2$, and the use of $Cu(OTf)_2$ resulted in significant C–C bond formation. To allow the synthesis of more products with higher molecular complexity, milder conditions were sought. The reaction was monitored by GC–MS; it was shown that during the reaction, significant amounts of phenol and diphenyl ether were produced which may be due to the formation of water during the reaction. This water could be formed from the boronic acid, which forms the trimeric triaryl boroxine that may then participate in the reaction. Indeed this was found to be the case in independent experiments when using 0.33 equivalents of the boroxines. Investigations into the need for inert gas during the reaction also led to the observation that ambient atmospheric air or even oxygen offered a better reaction outcome, leading to more than double the yields observed under an argon atmosphere. Moreover, the addition of excess base to the reaction medium did not impede the reaction and may infer that this component plays a dual role as a base and as a participating ligand with a possible organocopper species in the reaction.

These observations then developed into a new *general* reaction procedure**:** A heterogeneous mixture of the phenol (1 equiv), aryl boronic acid (1–3 equiv), $Cu(OAc)_2$ (1–2 equiv), powdered molecular sieves (4 Å, amount not indicated) and Et_3N (5 equiv) in dichloromethane was stirred at room temperature for 18 h exposed to the atmosphere; the product was then isolated in good yield after chromatography. The use of molecular sieves resulted in a significant enhancement in the product yield. Notably, excess amounts of the aryl donor were still necessary (1–3 equiv) for higher-yielding reactions. Presumably the minimum amount of molecular sieves to be added should correspond to at least the amount of water that can be produced by the hydrolysis of the boronic acid during the reaction.

2.2.3. *Substrate Scope*

It was shown that all types of structurally and electronically diverse boronic acids and phenols, even *ortho*-substituted phenols, which had caused problems with previous procedures, underwent smooth reaction to afford products in near quantitative yields (Table 2, [Eq. (15)]).

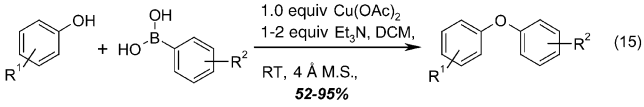

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Table 2: Substrate scope examined for the *O*-arylation of phenols with aryl boronic acids [Eq. (15)].

R^1	R^2	Et_3N [equiv]	Yield [%]
p-*t*Bu	H	1.5	95
p-*t*Bu	*p*-Me	2.0	87
p-*t*Bu	*p*-F	2.0	42
p-*t*Bu	*p*-OMe	2.0	85
p-*t*Bu	*m*-OMe	1.0	68
p-*t*Bu	*m*-NO_2	2.0	68
o-Cl	H	2.0	95
o-Cl	*p*-Me	1.0	70
o-Cl	*p*-F	2.0	61
o-OMe	H	1.0	92
o-OMe	*p*-Me	1.0	95
o-OMe	*p*-F	1.0	97
o-OMe	*p*-OMe	2.0	82
o-OMe	*o*-Me	1.0	52

2.2.4. *Applications: L-Thyroxine, (S, S)-Isodityrosine, Teicoplanin Aglycon, MMP Inhibitors*

The diaryl ether motif is abundant in a number of naturally occurring compounds, including important medicinal compounds such as vancomycin[19] and chloropeptins[20] as well as molecules of potential clinical use such as RA-I–IV,[21]

OF4949-I–IV,[22] piperazinomycin,[23] and K-13 (Figure 2).[24] However, the synthesis of this class of molecules currently relies on classical Ullmann condensation reactions between aryl halides and phenols.[25] This problem was addressed by Evans and co-workers, who further expanded the scope of these transformations whilst investigating the coupling of functionalized phenolic tyrosine derivatives **1**–**3** (Scheme 2, Table 3). In these reactions pyridine (2.0 equiv) was used as the base (in place of Et_3N) to afford the desired diaryl ethers **4**–**6**, respectively, in good to excellent yields with no apparent

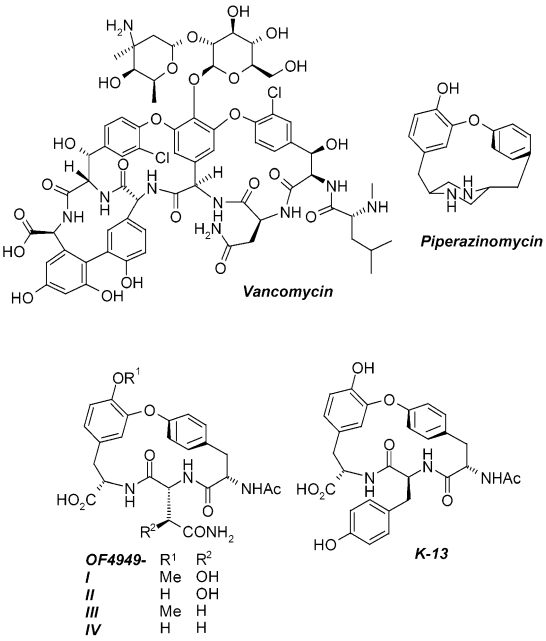
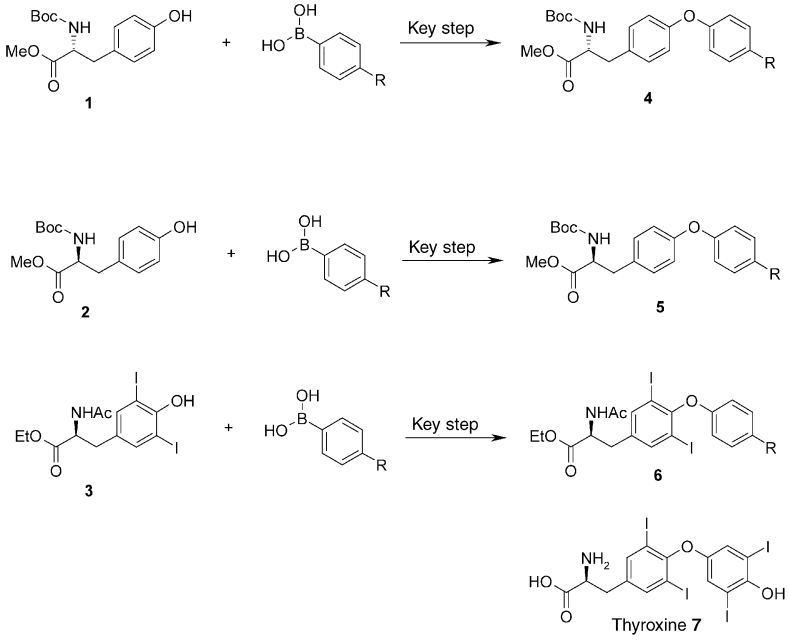


Figure 2. Selected examples of biologically active macrocyclic diaryl ethers.



Scheme 2. Key step: $Cu(OAc)_2$ (1 equiv) pyr and Et_3N, 4 Å molecular sieves, CH_2Cl_2, room temperature, time not specified.

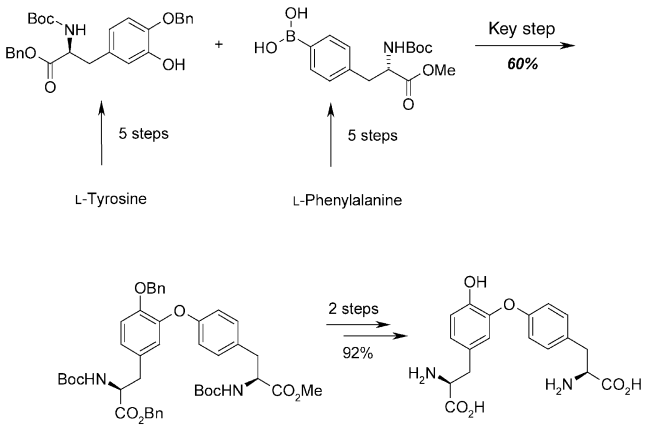
Table 3: Synthesis of diaryl ethers **4**–**6** in the $Cu(OAc)_2$-mediated arylation of phenols with aryl boronic acids (Scheme 2).

R	Compound	Yield [%]
H	**4a**	95
p-Me	**4b**	98
p-F	**4c**	97
p-OMe	**4d**	96
m-OMe	**4e**	97
m-NO_2	**4f**	98
o-Me	**4g**	98
o-OMe	**4h**	37
Cl	**4i**	7
p-Me	**5a**	81
p-OMe	**5b**	76
Me	**6a**	81
TBDMS	**6b**	84

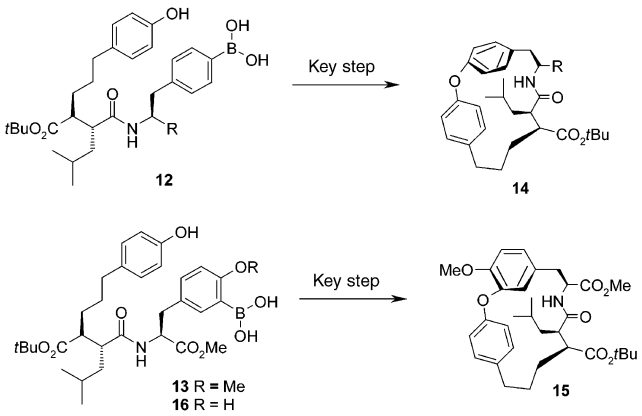
change in the integrity of the racemization-prone stereogenic centers. The only problems were found with *ortho*-methoxy and -chloro substituents on the boronic acid, and although no details were given, it is implied that some reactions in this series were more sluggish and needed a second equivalent of the boronic acid. It was shown that *ortho*-alkyl substitution was well-tolerated (Table 3, **4g**). In the synthesis of thyroxine (**7**), the impact of steric hindrance on the course of the reaction was crucial as two iodine atoms are present in the phenolic substrate *ortho* to the OH group. In the event a slight, but important, variation was required in the general reaction procedure in which a mixture of Et_3N/pyr (1:1, 5 equiv) was used to obtain the desired intermediate **6a** in 81% yield which was previously used by Hems and co-workers.[26] Furthermore, the silylated phenol **6b** was also prepared in 84% yield to demonstrate the generality of this method in the efficient synthesis of functionalized unsymmetrical diaryl ethers.

In these syntheses, the boronic acid was chosen as the aryl donor, and tyrosine derivatives were used as the phenolic partner. Jung and Lazarova,[27] however, demonstrated that the role of reaction partners can be reversed in a new efficient convergent total synthesis of (*S,S*)-isodityrosine starting from the two aromatic α-amino acids L-tyrosine and L-phenylalanine (Scheme 3).

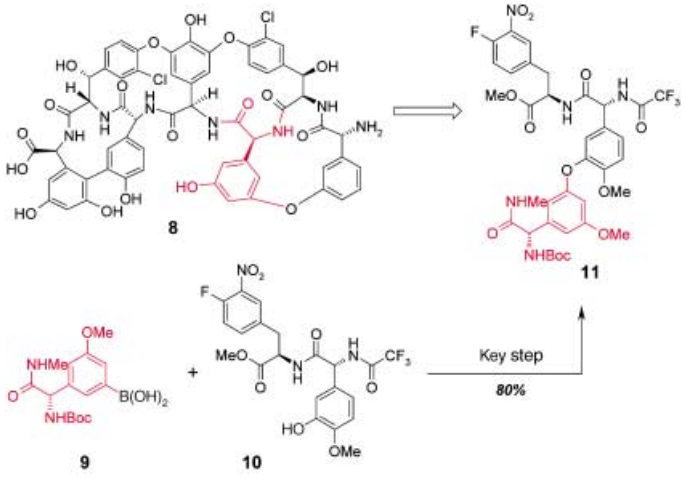
Evans and co-workers planned the total synthesis of the teicoplanin agylcon **8** based on the coupling reaction of the aryl boronic acid **9** and the phenol **10** (Scheme 4).[28] In the key transformation, the desired diaryl ether **11** was formed in 80% yield with no detection of epimerization at any of the three stereogenic centers under the previously optimized conditions using molecular oxygen as co-oxidant. An elegant collection of organic transformations, including two atropdiastereoselective nucleophilic aromatic substitution reactions (between a phenol and an aryl fluoride), led to completion of the synthesis of **8**.



Scheme 3. Key step: $Cu(OAc)_2$ (1 equiv), pyr, 4 Å molecular sieves, CH_2Cl_2, room temperature, 18 h.



Scheme 5. Key step: dilute conditions, $Cu(OAc)_2$ (amount not specified), Et_3N, CH_2Cl_2, room temperature, 48 h (note: no molecular sieves/no air or O_2).



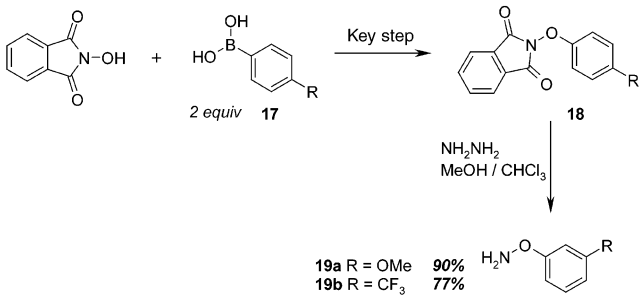
Scheme 4. Key step: $Cu(OAc)_2$, O_2, pyr, 4 Å molecular sieves, CH_2Cl_2, room temperature, time not specified.

2.2.5. *Intramolecular Coupling*

Decicco, Song, and Evans have extended the generality of this transformation to intramolecular *O*-arylation in their novel synthesis of a small series of inhibitors of the metalloproteinases collagenase 1 and gelatinases A and B (Scheme 5).[29] The key step relied on the development of a novel intramolecular macrocyclization in which a diaryl ether was formed by the reaction of the boronic acid function and the phenol group in precursors **12** and **13**; a pinacol boronate was not a suitable substrate. Stoichiometric amounts of $Cu(OAc)_2$ and Et_3N as base under dilute conditions (1 μM in CH_2Cl_2) afforded the desired products **14** and **15**, respectively, in good yields. One exception was the macrocyclization of the bisphenol boronic acid **16**, which only proceeded in a disappointing 5% yield. The resulting scaffolds were elaborated further to the target hydroxamic acids under standard reaction conditions to provide active ($K_i = 91$–5000 nM) matrix metalloproteinase (MMP) inhibitors.

2.2.6. **N-*Hydroxyimides as the Nucleophilic Reaction Partner***

Synthetic routes to *N*-aryl hydroxylamines are rare.[30] In response to this, Sharpless, Kelly and Petrassi recently extended the wide range of oxygen-centered nucleophiles that can participate in the copper-mediated arylation reaction; they investigated the coupling of *N*-hydroxyimides with a variety of boronic acids **17** under slightly modified conditions, with molecular sieves and ambient air in 1,2-dichloroethane (Scheme 6, Table 4).[31] It was shown that in the presence of base, preferably pyridine (1 equiv), all copper sources ($Cu(OAc)_2$, $Cu(OTf)_2$, CuCl, and $CuBr{\cdot}SMe_2$) resulted in the desired coupling products **18** in up to 98% yield. In fact, there was no direct correlation between the effectiveness of a specific salt or its oxidation state except that Cu, Cu(OAc), $CuCl_2$,and $Cu(OCOCF_3)_2$ were not suitable in effecting the transformation. The use of Et_3N resulted in lower yields (13–37%), and neither DMAP, DABCO, or Cs_2CO_3 were effective bases in the reactions. In line with earlier reports, electronically and structurally diverse substituents on the boronic acid are tolerated, and the only recorded exceptions were *ortho*-fluorine and *para*-boronic acid precursors (which can undergo oligomerization). Two examples of **18** were converted into the correspoding *O*-arylhydroxylamine **19** in good yields after hydrazinolysis in methanol (Scheme 6). The main limitations



Scheme 6. Key step: Cu salt (1 equiv), pyr, 4 Å molecular sieves, $C_2H_4Cl_2$, room temperature, 24–48 h.

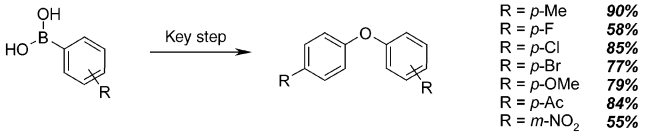
Table 4: $Cu(OAc)_2$-mediated arylation of aryl boronic acids with *N*-hydroxyphthalimide (Scheme 6).

Compound	R	Yield [%]
18a	H	90
18b	*p*-Br	73
18c	*p*-I	57
18d	*p*-OMe	37
18e	*p*-CH=CH_2	87
18f	*p*-CO_2Me	64
18g	*p*-CHO	52
18h	*p*-CN	66
18i	*p*-CF_3	65
18j	*p*-$B(OH)_2$	0
18k	*m*-*i*Pr	68
18l	*m*-F	65
18m	*m*-OMe	57
18n	*m*-CF_3	87
18o	*o*-OMe	60
18p	*o*-F	0
18q	*m*,*m*,-di-F	72

of the method are the requirement for 2 equivalents of the boronic acid and the incompatability of an *ortho*-heteroatom substituent or a second boronic acid functionality in the substrate.

2.2.7. One-Pot Preparation of Symmetrical Diaryl Ethers[32]

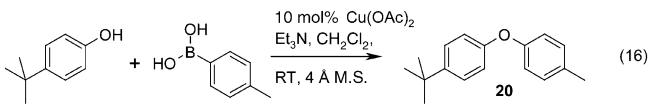
A recent extension of this coupling process involves the reaction of a phenol formed in situ (regioselective reaction of a boronic acid (1.0 equiv) with hydrogen peroxide (0.25 equiv)) followed by further reaction with the adduct boronic acid (2.0 equiv) in the presence of $Cu(OAc)_2$ (0.5 equiv) and Et_3N (3.0 equiv) in CH_2Cl_2. As Evans and co-workers found previously, the addition of molecular sieves to sequester the water formed during triarylboroxine formation was beneficial in terms of yield (Scheme 7). The reaction worked particularly well with electron-rich boronic acids (up to 90% yield), although satisfactory yields (> 55%) were obtained with electron-deficient boronic acids. No *ortho*-substituted boronic acids were reported.



Scheme 7. Symmetrical diaryl ether synthesis. Key step: $Cu(OAc)_2$ (0.5 equiv), H_2O_2, Et_3N, 4 Å molecular sieves, CH_2Cl_2, room temperature, overnight.

2.2.8. Catalytic Cu Methods: The Original Discovery

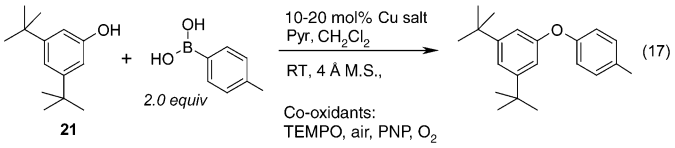
The potential for a catalytic variant was recognized early on in the synthesis of **20**. The use of less than stoichiometric amounts of $Cu(OAc)_2$ (10 mol%) in CH_2Cl_2, in the presence of Et_3N (5 equiv) under argon or oxygen, gave rise to product, albeit in low yield [Eq. (16)].[15] Unfortunately, no studies



(16)

profiting from this early observation followed until some time later.

Lam et al, however, improved on the catalytic version by employing a co-oxidant in the cross-coupling of the phenol **21** with *p*-tolylboronic acid [Eq. (17)].[33] Although the best

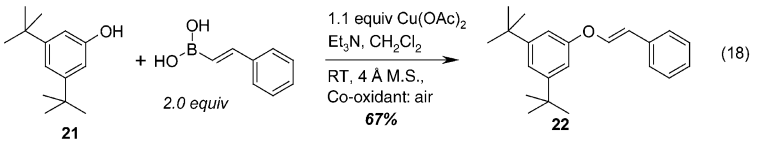


(17)

yields (79%) were obtained with oxygen as oxidant, it was possible to use TEMPO (1.1 equiv)/air, pyridinium *N*-oxide (1.1 equiv)/air, or $[\{Cu(\mu\text{-}OH)(tmeda)\}_2]Cl_2$/oxygen in the presence of $Cu(OAc)_2$ (20 mol%) as the Cu^{II} source. These reactions were best performed in refluxing CH_2Cl_2 using pyridine as base.

2.2.9. Styrylboronic Acids

As can be seen in the following sections, a variety of structurally diverse boronic acids function well in these transformations. In an interesting extension to the method, Lam et al. showed that a vinyl boronic acid could function well in the coupling reaction [Eq. (18)].[33] Although a



(18)

catalytic system was not successful, the electron-rich phenol **21** provided **22** in good yield when using $Cu(OAc)_2$ (stoichiometric) and Et_3N (2 equiv) as base under air as oxidant at room temperature. Dichloromethane was the optimal solvent of choice; DMF could also be used, but increasing the temperature to 50 °C led to inferior results.

2.3. Copper-Mediated C(aryl)–N Bond Formation

2.3.1. The Original Discovery: Stoichiometric Cu^{II} Methods

The simultaneously published original papers by Chan and co-workers and Lam and co-workers had a significant impact on establishing the substrate scope and preoptimal reaction conditions in the cross-coupling of aryl boronic acids and nitrogen nucleophiles.[14,16]

2.3.2. *Substrate Scope*

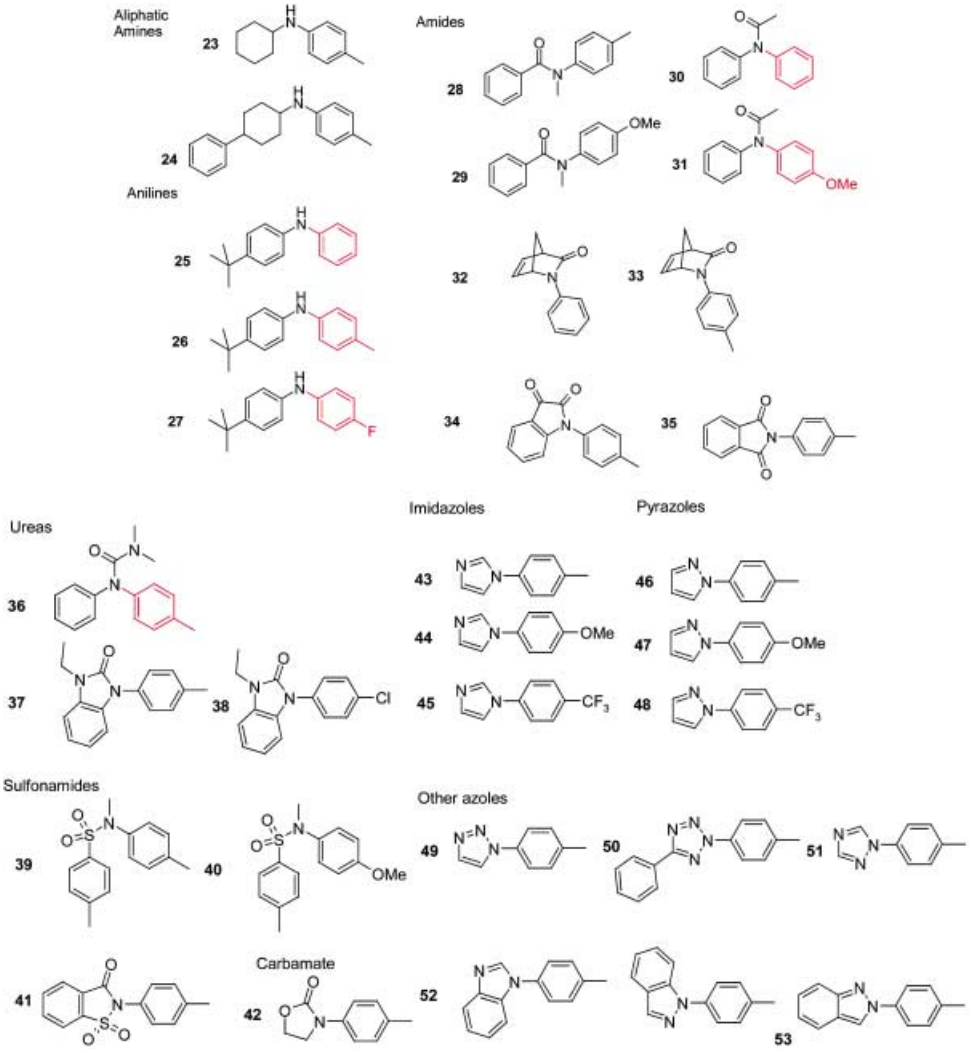
In the first[14] of the two communications, an impressive range of nucleophiles were successful, and suitable substrates for the reaction, which included amines, anilines, amides, imides, ureas, carbamates, sulfonamides, and aromatic heterocycles (imidazoles, pyrazoles, triazoles, tetrazoles, benzimidazoles, and indazoles) were reported. Table 5 and (Scheme 8) show the range of products **23**–**53** prepared by using a slightly modified form of the general reaction procedure. However, no true substrate trend emerged in these reactions, in contrast to the analogous process when bismuthates were employed as the aryl donor.

2.3.3. *Which Base Is Best?*

Much of the early base screening was carried out on the reaction with *p*-tolylboronic acid as aryl donor. For this limited substrate, it would appear that Et_3N was the best choice. In all the reactions investigated with N nucleophiles, the use of Et_3N as a base resulted in yields superior to those obtained with pyridine. However, for the preparation of

Table 5: $Cu(OAc)_2$-mediated arylation of aryl boronic acids with N nucleophiles (Scheme 8).

Compound	Base	*t* [h]	Yield [%]	Compound	Base	*t* [h]	Yield [%]
23	Et_3N	45	56	**37**	Et_3N	66	96
23	Pyr	45	63	**37**	Pyr	66	52
24	Et_3N	48	50	**38**	Et_3N	66	37
24	Pyr	48	74	**39**	Et_3N	65	72
25	Et_3N	48	58	**39**	Pyr	65	23
26	Et_3N	24	90	**40**	Et_3N	48	67
27	Et_3N	18	93	**41**	Et_3N	53	23
28	Et_3N	66	17	**41**	Pyr	53	92
28	Pyr	67	4	**42**	Et_3N	50	60
29	Et_3N	48	5	**43**	Pyr	48	72
30	Et_3N	48	59	**44**	Pyr	48	62
30	Pyr	48	4	**45**	Pyr	48	71
31	Et_3N	48	41	**46**	Pyr	48	76
32	Et_3N	64	12	**47**	Pyr	48	64
33	Et_3N	40	77	**48**	Pyr	48	45
34	Et_3N	65	53	**49**	Pyr	48	11
34	Pyr	65	72	**50**	Pyr	48	26
35	Et_3N	35	92	**51**	Pyr	48	6
35	Pyr	35	83	**52**	Pyr	48	67
36	Et_3N	47	45	**53** (4.5:1)	Pyr	48	88
36	Pyr	47	7				



Scheme 8. Initial array of *N*-arylated products formed. Key step: $Cu(OAc)_2$ (1–2 equiv), Et_3N or pyr (see Table 5), CH_2Cl_2, room temperature, 18–66 h.

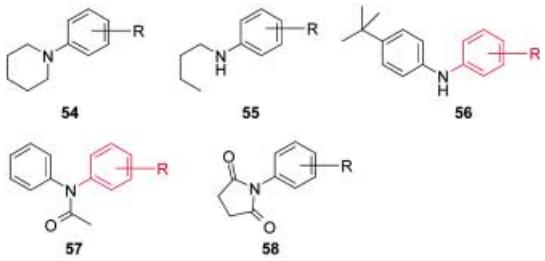
compounds **43–53** from the range of heteroarenes examined as nucleophiles, it appears that pyridine was the base of choice as no examples were recorded with the supposedly equally efficient Et_3N. For the tetrazole **50** NMO and DBU were studied as alternative bases, but were found to be less effective. It was also shown that in the slower reactions (with less-nucleophilic amines), substantial amounts of the phenol and symmetrical diaryl ethers were formed, even in the presence of molecular sieves.

2.3.4. Which Solvent Is Best?

An empirical order has been established for the solvent in terms of reaction yield:

$$CH_2Cl_2 \gg 1,4\text{-dioxane} = NMP = THF = DMF \gg > EtOAc = \text{toluene} = DMSO \gg \gg MeOH$$

Cundy and Forsyth presented several additional examples **54–58** and confirmed the capricious nature of the reaction: No substrate trend was observed in terms of the basicity of the amine and the sigma-donating effect of the aryl boronic acids (Scheme 9, Table 6).[34] In fact, on the basis of these findings



Scheme 9. Key step: $Cu(OAc)_2$ (1 equiv), Et_3N, CH_2Cl_2, room temperature, 48–72 h.

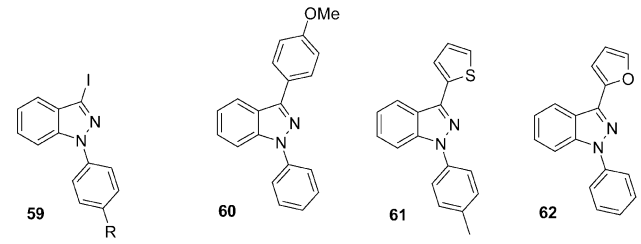
Table 6: $Cu(OAc)_2$-mediated arylation of aryl boronic acids with N nucleophiles.

Compound	Yield [%]						
	p-NMe_2	*p*-OMe	*o*-OMe	*p*-Me	H	*m*-CF_3	*m*-NO_2
54	–	82	14	58	–	–	11
55	–	39	17	43	6	21	n.d.[a]
56	n.d.	n.d.	–	56	42	10	< 10
57	11	n.d.	–	12	–	53	18
58	–	–	–	69	72	65	36

[a] Not determined.

and those of Chan and Lam, it could be concluded that the general reaction conditions had to be adapted for each substrate type in the *N*-arylation reaction. This is possibly best achieved by using a "Design of Experiment" (DoE) protocol.[35]

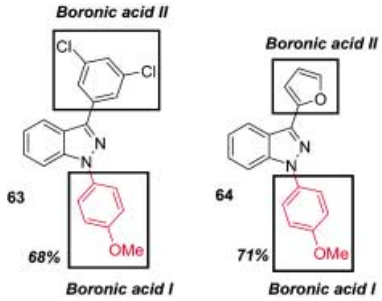
Rault and co-workers developed a regioselective copper-mediated *N*-arylation of 3-iodoindazole (Scheme 10) with four different boronic acids to form compounds of type **59–62** in good yields in only 1–2 h.[36] These results show a



Scheme 10. Key step: $Cu(OAc)_2$ (1.5 equiv), Et_3N, CH_2Cl_2, room temperature, 1–2 h.

remarkable rate enhancements for this particular substrate (3-iodoindazole) relative to that observed by the groups of Chan and Lam, who reported that indazoles were only *N*-arylated to completion after 48 h when using pyridine as base.[16]

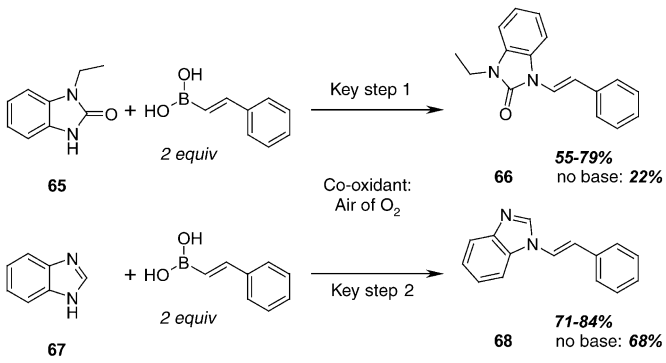
The efficient preparation of the 1,3-diaryl indazoles **63** and **64** from the 3-iodoindazole can be carried out in a one-pot process that combines two processes mediated by different catalysts (Scheme 11): The first process led to a surprisingly rapid *N*-arylation mediated by $Cu(OAc)_2$ (1 equiv), aryl boronic acid (1 equiv), Et_3N (3 equiv). A subsequent Suzuki reaction in the *same* reaction pot upon the simultaneous addition of $[Pd(PPh_3)_4]$ (5 mol%), $NaHCO_3$ (3 equiv) in DME, and the second boronic acid (1 equiv) gave the desired product. This is the first report of this sequence of reactions being performed in one pot with two catalysts efficiently functioning independently of one another. This strategy has enormous potential for the design and preparation of combinatorial libraries of compounds in which both N– and C–aryl moieties are fundamental features.



Scheme 11. Reagents and conditions: Boronic acid I (1 equiv), $Cu(OAc)_2$ (1 equiv), $[Pd(PPh_3)_4]$ (0.05 equiv), Et_3N, $NaHCO_3$, DME, room temperature, 1 h; then boronic acid II (1 equiv), 80°C, 3 h.

2.3.5. Not Only Aryl Boronic Acids React

In an interesting extension of the substrate scope of the reaction, it was shown that the aryl boronic acid reaction partner could be extended with a vinyl group. In the reaction



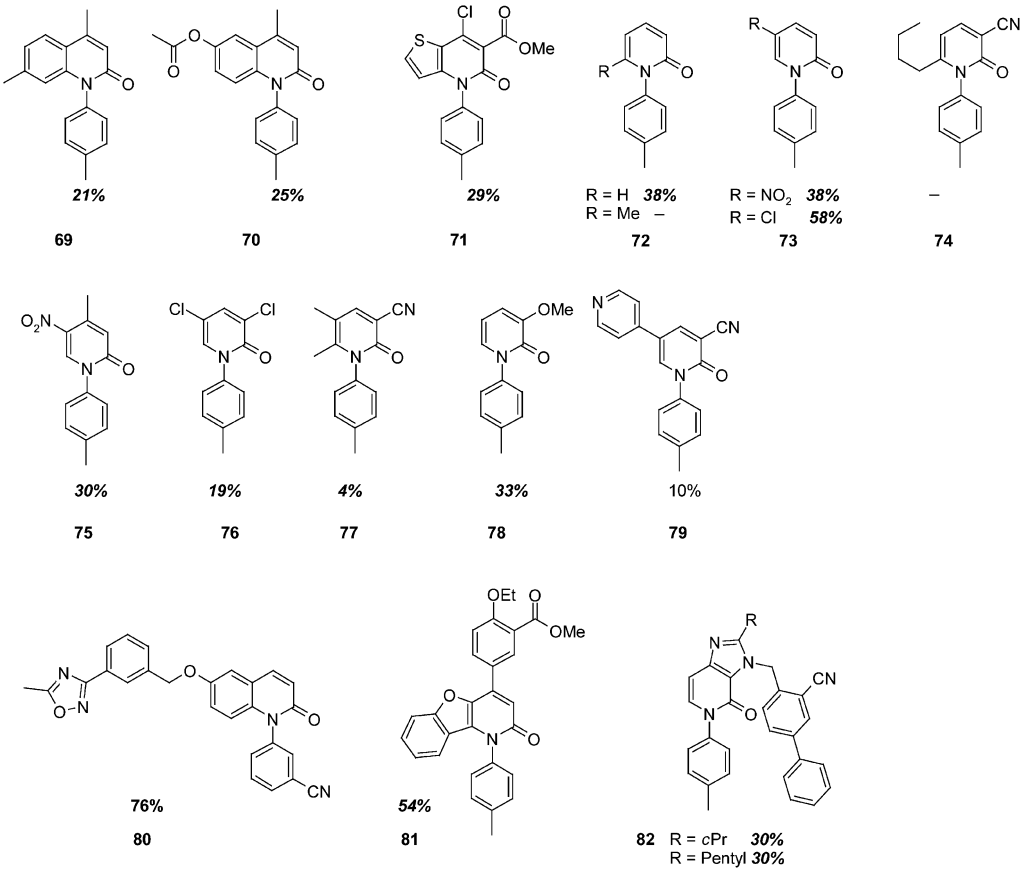
Scheme 12. Key step: 1) $Cu(OAc)_2$ (1.1 equiv), Et_3N, 4 Å molecular sieves, CH_2Cl_2, room temperature or 50 °C, 4 days; 2) $Cu(OAc)_2$ (1 equiv), pyr, 4 Å molecular sieves, CH_2Cl_2, room temperature, 4 days.

of the benzimidazolones and benzimidazoles, the best yields of the desired coupling products were obtained in the presence of stoichiometric amounts of $Cu(OAc)_2$ exposed to air (Scheme 12).[33] Interestingly, Et_3N was the base of choice for the substrate **65**, whereas pyridine was preferred in the cross-coupling of benzimidazole **67**. Both reactions proceeded best at room temperature, although in the case of **65** the yield was comparable at 50 °C. No explanation or comparison of bases were reported.

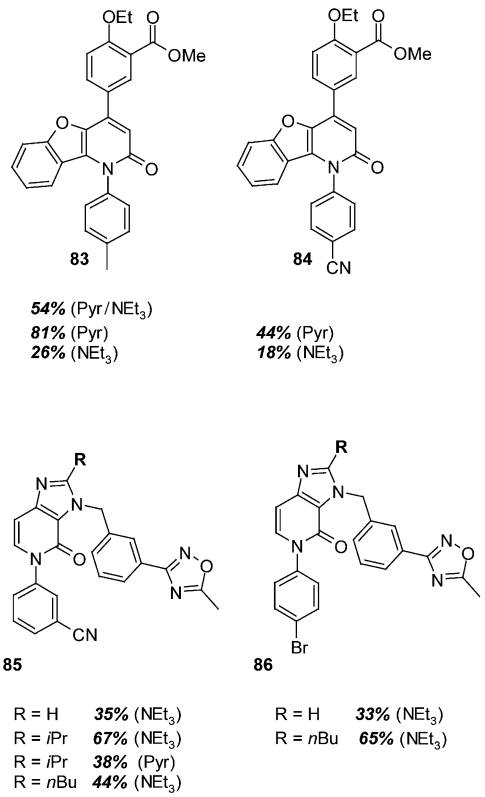
2.3.6. *Applications: Medicinal Chemistry and Solid-Phase Organic Synthesis*

Researchers at Merck showed that 2-pyridones were useful N nucleophiles in the arylation reaction with aryl boronic acids in a program dedicated towards the discovery of novel and potent Factor Xa inhibitors (Scheme 13).[37] Notably, in this transformation it was possible to selectively form the *N*-aryl product **69** with none of the corresponding *O*-arylated product being observed. Under different conditions (KO*t*Bu, DMF), a mixture of *N*-/*O*-arylated products (2:1) was observed. Interestingly, partly perhaps because there was no precedent for which base to use, Mederski et al. employed both Et_3N *and* pyridine in the reaction. No examples are given in which only one base was used. Scheme 13 shows the diverse range of substrates examined and products **69**–**82** formed. Again, there appears to be no general trend with respect to the impact of the electronic nature of the N nucleophiles; electron-poor and -rich systems behave similarly. However, in all cases, no trace of the aromatic *O*-arylated product was observed.

The acceptable to good yields of **83**–**86** were encouraging, as these were key molecular units in the quest for new Factor Xa inhibitors (Scheme 14). Further investigation showed that pyridine alone as base in these reactions offered the best yields for the benzo[3,2-*b*]pyridone moieties, but



Scheme 13. Key step: $Cu(OAc)_2$ (2 equiv), Et_3N *and* pyr, 4 Å molecular sieves, CH_2Cl_2, room temperature, 48 h.



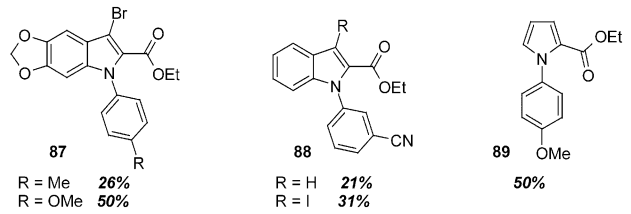
Scheme 14. Key step: $Cu(OAc)_2$ (2 equiv), Et_3N *and/or* pyr, 4 Å molecular sieves, CH_2Cl_2, room temperature, 48 h.

Et_3N proved to be the base of choice for the fused imidazolepyridone unit.

Moreover, Mederski et al. showed that indoles and pyrroles activated with an *ortho* carboxylate functional group were suitable N nucleophiles and they developed a general procedure for the formation of the products **87**–**89**, using pyridine as base (Scheme 15).

Potential MMP inhibitors that incorporate electron-deficient pyrrole scaffolds were constructed by using the stoichiometric $Cu(OAc)_2$ method described above by researchers at Pfizer.[38] In general these molecular motifs appear to be excellent substrates for *N*-arylation reactions, and in nearly all cases high yields of the products **90**–**95** were obtained (Scheme 16). However, the reaction times ranged from 2–13 days, but generally were in the 2-day range (Scheme 16). Heteroaryl boronic acids do not function well in this reaction: 3-pyridyl-, 2-thienyl-, and 2-furanylboronic acids all failed to give any of the desired product. This method was used to prepare a pivotal intermediate **95** for the synthesis of the MMP inhibitor AG3433, which is currently in preclinical trials.

The 3-pyrroleglyoxalates **96**, which lack the activating 2-acyl functionality, are not good substrates, whereas the 2-acetylpyrroles **97** react very well (Scheme 17). In each case, longer reaction times than those for the 2-formyl-3-glyoxalates

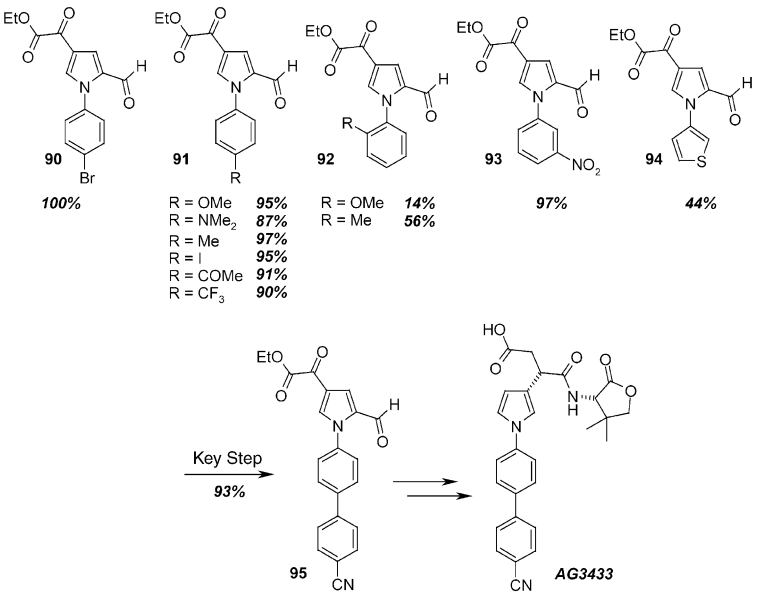


Scheme 15. Key step: $Cu(OAc)_2$ (2 equiv), pyr, 4 Å molecular sieves, CH_2Cl_2, room temperature, 48 h.

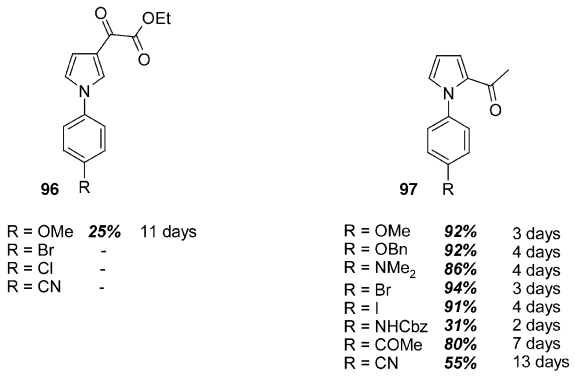
were required for complete conversion of reactants. This effect may be due to a possible chelating effect of the pyrrole N atom, the Cu complex, and the oxygen atom of the 2-carbonyl unit.

Amino acids and aminoesters are useful substrates for the Ullmann condensation reaction (see Section 3) with or without the use of solubilizing agents. Lam et al showed that the standard substrate *p*-tolylboronic acid couples smoothly with a range of 15 α-aminoesters (lipophilic examples and hence more soluble in the reaction medium) to form the *N*-arylated products in generally acceptable yields (Scheme 18).[39] Although the reactions required 1–2 days for complete conversion into product and the standard use of 2.0 equivalents of the boronic acid and stoichiometric amounts of copper acetate for optimum yields, the reactions were performed at room temperature. This represents a much milder alternative to the use of aryl halides as the electrophilic reaction partner. Furthermore, the reaction products were formed with almost complete retention of configuration for both enantiomers (94–99 % *ee*), which will ensure that this new method will continue to be an important method for the preparation of molecules of this type.

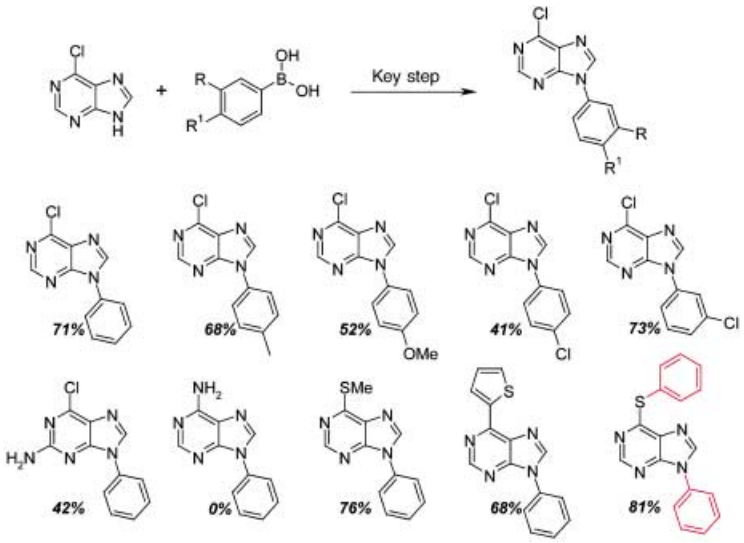
A rapid and direct synthesis of 9-aryl purines, which display diverse biological activities,[40] was sought, as standard



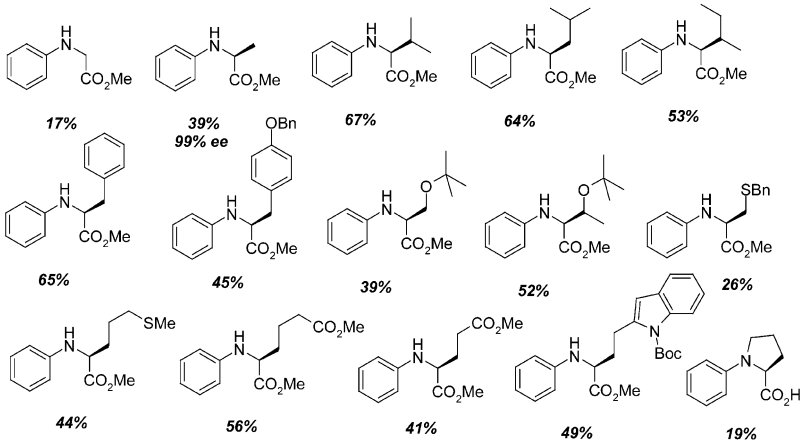
Scheme 16. Key step: $Cu(OAc)_2$ (1.5 equiv), pyr, air, CH_2Cl_2, room temperature, 3 days.



Scheme 17. Key step: $Cu(OAc)_2$ (1.5 equiv), pyr, air, CH_2Cl_2, room temperature, 2–11 days.



Scheme 19. Key step: Boronic acid (3 equiv), $Cu(OAc)_2$ (1.0 equiv), phen (2 equiv), CH_2Cl_2, 4 Å molecular sieves, air, room temperature, 4 days.

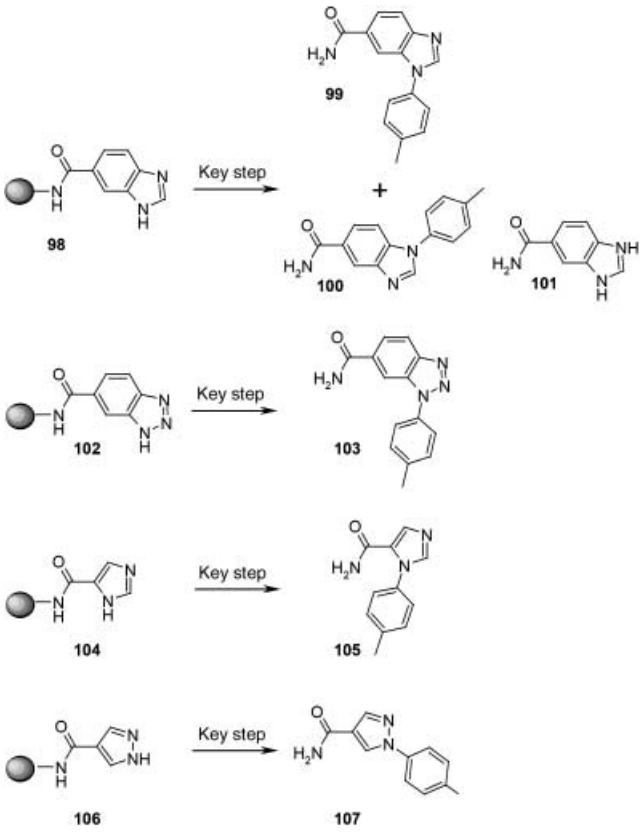


Scheme 18. Key step: Boronic acid (2 equiv), $Cu(OAc)_2$ (1.1 equiv), Et_3N (2 equiv), CH_2Cl_2, 4 Å molecular sieves, room temperature, 1–2 days.

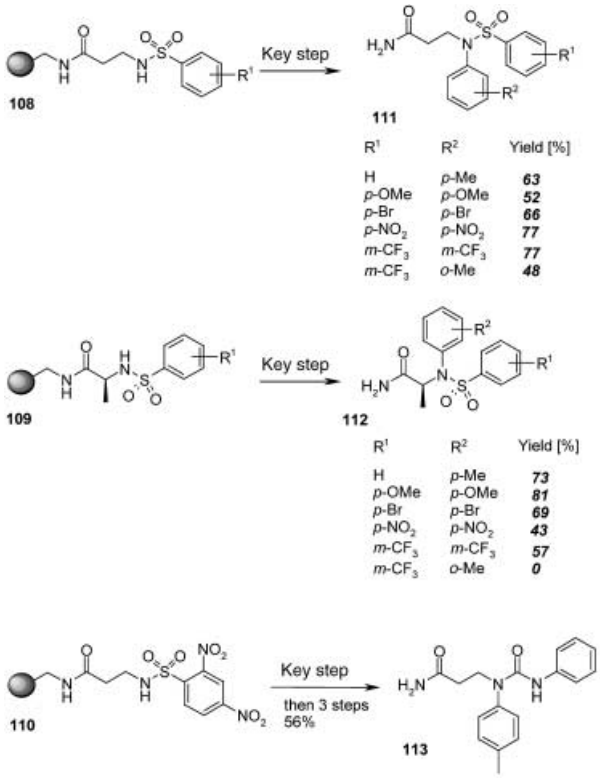
routes to molecules of this type involve cyclization strategies with the aryl unit already in place.[41] These strategies are not suitable for rapid exploration of structure–activity relationships (SAR). To meet these demands, Gunderson and Bakkestuen recently showed that purines react regio- and chemoselectively at N9, thus allowing the first direct access to the desired compounds in average to good yields (Scheme 19).[42] The use of 1,10-phenanthroline as a stoichiometric (see Section 3 for catalytic variant) ligand for the copper center proved optimal over the standard choices of Et_3N, pyridine and 2,2′-bipyridine, TMEDA and *N,N′*-diarylethanediimines, which had already shown promise in coupling reactions with aryl iodides (see Section 3).

The impact of solid-phase organic chemistry in academic and medicinal chemistry communities has been significant.[43] Combs et al. reported efficient examples of the solid-supported aryl and heteroaryl C–N cross-coupling reactions mediated by microwave irradiation: *p*-tolylboronic acid reacted with a range of solid-supported benzimidazoles, imidazoles, pyrazoles, and benzotriazoles (Scheme 20).[44] In preliminary experiments with the supported benzimidazole **98** and the *p*-tolylboronic acid, it was shown that the arylation reaction could not be driven to completion under standard conditions. However, with the aid of microwave irradiation from a domestic microwave oven, five heating, reagent addition, and agitation cycles allowed the reactions to proceed to completion (no benzimidazole (**101**) was observed after cleavage from the resin) and afforded the regioisomeric products **99** and **100** (56 % yield, 96 % pure). After establishing the route, a range of aryl and heteroaryl acids **102, 104**, and **106** were then attached to the PEG-supported amine to form an amide linker (apparently, polystyrene can also be employed as the support), and in each case the desired products **103, 105**, and **107** were obtained in good overall yields (56–64 %) and acceptable purities (73–96 %) after washing away excess reagents, cleavage with TFA, and purification by silica-gel chromatography. Notably, no *N*- or *O*-arylation of the amide linker was observed. The reaction could be performed in 96-well microtiter plates and thus lends itself well to the synthesis of libraries.

Combs and Rafalski also showed that solid-supported sulfonamides **108–110** can be used as the N nucleophile in copper-mediated *N*-arylation reactions (Scheme 21).[45] Optimization of the general protocol revealed that Et_3N as base, THF as solvent, and the use of molecular sieves was optimal (DIPEA, pyridine, and dichloromethane were explored as alternatives). As a result, a small array of products of type **111** and **112** were formed in good yields, even at room temperature. Importantly, no racemization was observed in compounds of type **112**. The study was extended to include Fukuyama's sulfonamide strategy involving *N*-arylation of



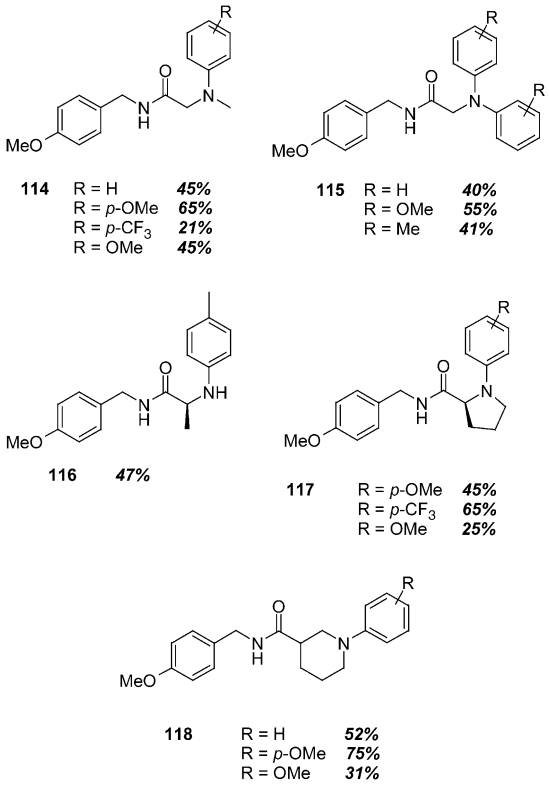
Scheme 20. Key step: Boronic acid (3 equiv), $Cu(OAc)_2$ (5 equiv), pyr/NMP, 80 °C, > 2 days; then optimized to: boronic acid (3 equiv), $Cu(OAc)_2$ (5 equiv), pyr/NMP, 4 Å molecular sieves, microwave heating (3 × 10 s 1000 W, 5 applications of reagents).



Scheme 21. Key step: Boronic acid (4 equiv), $Cu(OAc)_2$ (2 equiv), Et_3N, THF, 4 Å molecular sieves, repeat twice.

o,p-dinitroarylsulfonamides. In the event, copper(II)-mediated *N*-arylation followed by cleavage with *t*-butylamine to afford the amine and subsequent reaction with phenylisocyanate afforded **113** in 56% overall yield. Supported carbamates, amides, and ureas were also investigated as nucleophiles, but all failed to react under these reaction protocols.

The substrate scope of the solid-phase *N*-arylation reaction was also extended to include aliphatic secondary amines in a CNS-directed medicinal chemistry program at DuPont (Scheme 22).[46] The conditions previously optimized[41] for



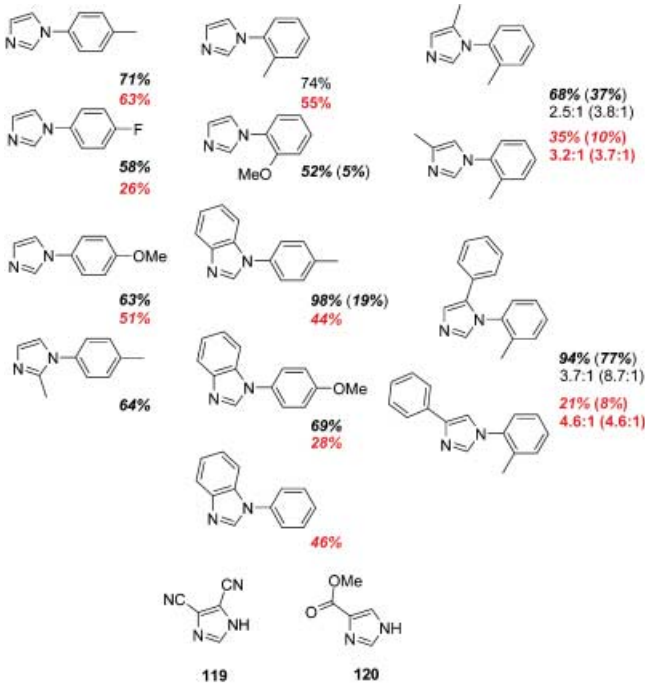
Scheme 22. Key step: Boronic acid (4 equiv), $Cu(OAc)_2$ (2 equiv), Et_3N, 4 Å molecular sieves, THF, repeat twice.

the *N*-arylation of supported sulfonamides (use of *powdered* molecular sieves) proved to be best for this class of substrate. The range of products **114**–**118** prepared demonstrates the scope and utility of the reaction; yields are representative of the *N*-arylation/cleavage/purification sequence. Notably, the primary amine **115** derived from glycine was bisarylated, and only traces of the monoarylated products were evident. However, in the case of α substitution (e.g. an alanine derivative) selective mono-*N*-arylation was predominant (e.g. to form **116**).

2.3.7. *Catalytic Cu^{II} methods*

In perhaps the most important development since the copper-mediated *N*-arylation of boronic acids, Collman and Zhong reported the catalytic version of this reaction.[47]

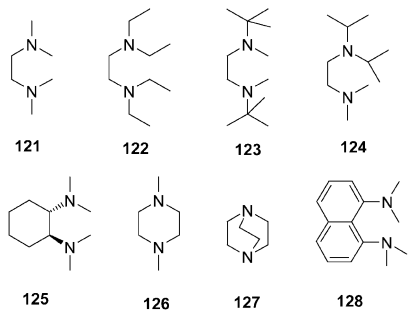
Imidazole was used as a standard N nucleophile with phenylboronic acid as the aryl donor. It was also shown that Cu^{II} alternatives in the form of [Cu(OH)Cl·tmeda] (formed in situ by the reaction of oxygen and the commercially available dimer $[\{Cu(OH)\cdot tmeda\}_2]Cl_2$) were potent catalysts. Several reaction parameters were optimized (amount of catalyst, aryl boronic acid, imidazole, solvent, time, atmosphere, molecular sieves), which resulted in an optimized general reaction procedure in which a mixture of aryl boronic acid (2 equiv), imidazole (1 equiv), $[\{Cu(OH)\cdot tmeda\}_2]Cl_2$ (10 mol%) in dichloromethane are stirred at room temperature overnight under oxygen. Scheme 23 shows the electronic and structural diversity in the boronic acids selected for this study. In all cases, reaction conditions were found that led to good to excellent yields (52–98%). Although benzimidazoles were also suitable substrates, the imidazoles **119**–**120** did not take part in the reaction.



Scheme 23. Key step: Boronic acid (2 equiv), $[\{Cu(OH)\cdot tmeda\}_2]Cl_2$ (10 mol%), O_2, CH_2Cl_2, room temperature, overnight. Yields in red for reactions in water.

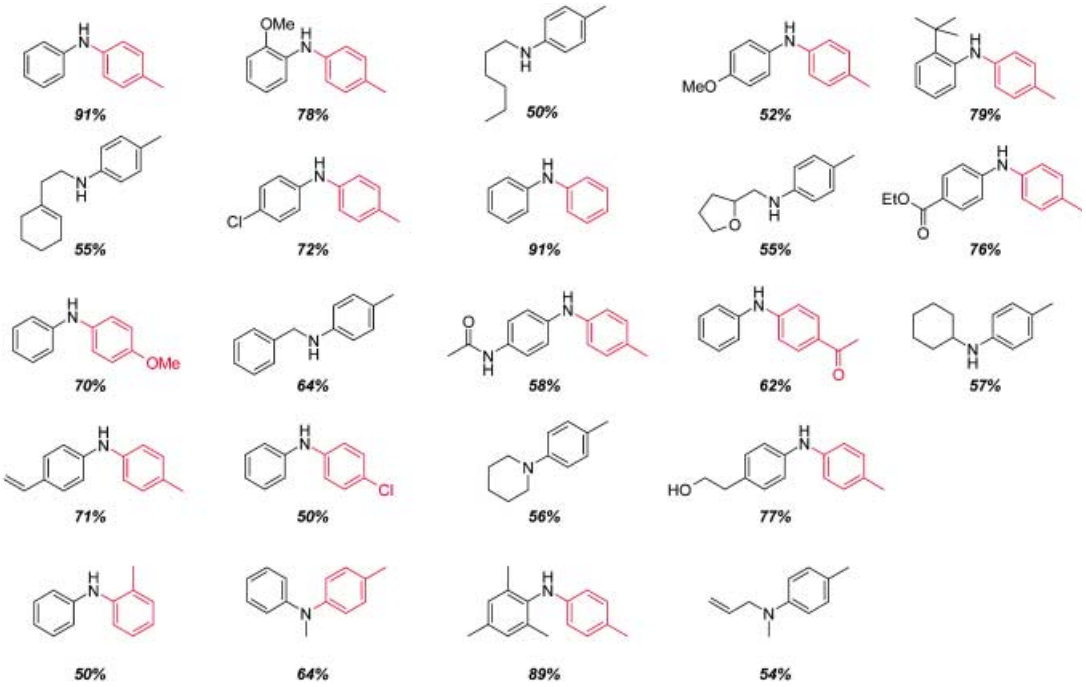
Environmentally friendly reaction procedures are fashionable, especially when performed in water.[48] Collman et al. studied exactly the above reaction with the same substrates and catalyst species, and reported the first examples of *N*-arylation of imidazoles in water.[49] The yields for the same products are shown in *red* in Scheme 23. This reaction system differs from the general reaction procedure only in the replacement of dichloromethane with water (2.5× dilution). Notably, the addition of phase-transfer catalysts offered no substantial benefit in terms of yield or reaction time. It was also shown that a neutral pH value for the reaction was optimal, as in both slightly acidic or basic media, the reaction yields were lower. The increased potential for water to intercept the putative reaction intermediates led to slightly lower yields for these transformations, but nevertheless in useful preparative amounts (26–63%).

Although perhaps the most efficient system for the arylation of imidazoles was discovered, Collman et al. attempted to make the route even better by closely investigating other copper catalysts and ligands.[50] The use of a commercially available μ-hydroxo Cu^{II} complex with the bidentate tmeda ligand was investigated first. This was followed by studies with other bidentate nitrogen ligands and counterions. In this report, a bidentate ligand **121**–**128** (Scheme 24) and a Cu^{I} salt (CuCl, CuBr, CuI, or CuOTf) in the presence of oxygen and water, were used to generates a Cu^{II} species that efficiently catalyzes the cross-coupling of imidazoles (and benzimidazoles) with aryl boronic acids. Although all ligands led to acceptable yields (19–68%), the most efficient ligand was tmeda (**121**).



Scheme 24. Key step: Boronic acid (2 equiv), $[\{Cu(OH)\cdot(\mathbf{121}–\mathbf{128})\}_2]Cl_2$ (10 mol%), O_2, CH_2Cl_2, room temperature, overnight.

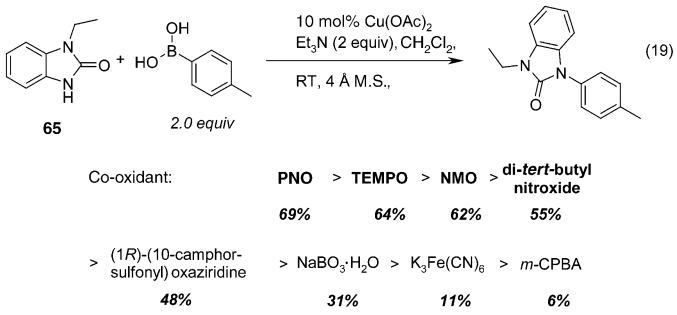
Building on these studies, further improvements to the catalytic variation of the boronic acid cross-coupling have been reported. Buchwald and Antilla, for example, developed a general reaction involving the use of catalytic $Cu(OAc)_2$ and myristic acid (n-$C_{13}H_{27}COOH$) as an additive along with stoichiometric amounts of 2,6-lutidine as base at room temperature. Substituted anilines as well as primary and secondary aliphatic amines reacted with a series of aryl boronic acids (Scheme 25).[51] Mainly *p*-tolylboronic acid was used in the optimization of the reaction, and in early observations it was shown by screening copper salts that $Cu(OAc)_2$, CuOAc, and Cu^{II} isobutyrate all efficiently catalyzed the reaction between aniline and phenylboronic acid, allowing conversions up to 55%. Vigorous stirring of the reaction mixture (which presumably allowed better oxygen uptake and hence an increased oxidative efficiency of a reduced copper intermediate in the reaction), allowed the complete cross-coupling of aniline derivatives when the reaction was performed in reaction flasks with large volumes (100 mL) relative to the amount of solvent (2 mL). It was discovered that the addition of a small amount of myristic acid enhanced the speed of the reactions, perhaps by rendering the copper species more soluble in the reaction medium.[52] Scheme 25 shows the range of products formed under these



Scheme 25. Key step: Boronic acid (1.5 equiv), $Cu(OAc)_2$ (5–20 mol%), myristic acid (10–40 mol%), air, 2,6-lutidine, toluene, room temperature, vigorous stirring, 24 h.

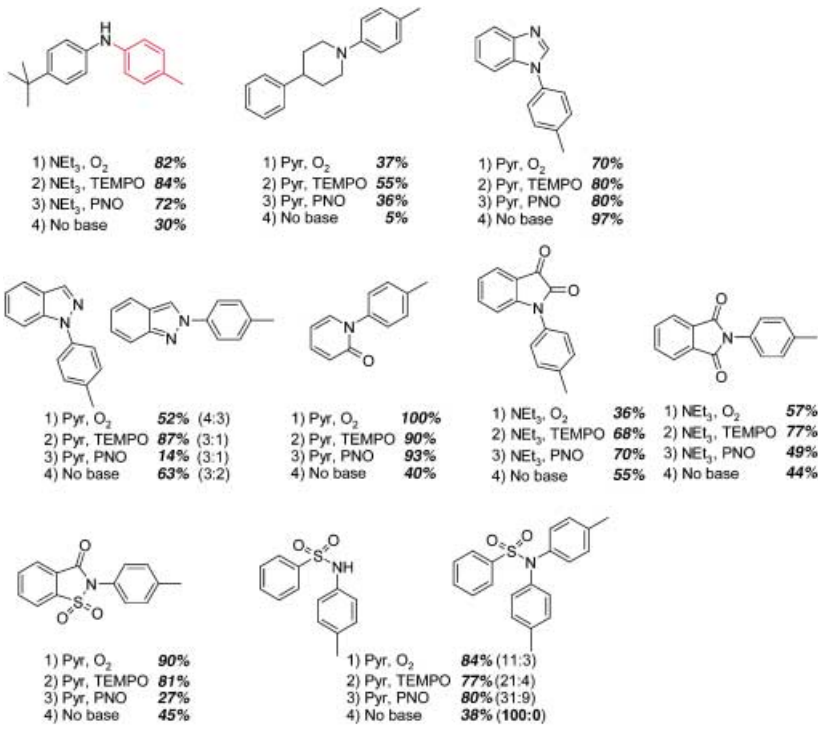
new conditions, demonstrating the versatility of this procedure. The reaction tolerates a wide range of electronically and structurally diverse substrates with other functionalities already incorporated in the products (e.g. alkene, ester, alcohol, acetamides), which did not interfere with the desired reaction pathway. In the reaction with primary amines, no bisarylated products were observed.

Lam et al. also reported an important alternative to this catalytic cross-coupling of aryl boronic acids and amines in the presence of $Cu(OAc)_2$ (10 mol%) and a co-oxidant additive (other than oxygen).[33] The best systems explored involved $Cu(OAc)_2$ and a combination of pyridine *N*-oxide (PNO) (1.1 equiv) and air, TEMPO (1.1 equiv) and air, or just oxygen. Most substrates reacted well, although no single catalytic system worked for *all* the substrates examined. The original study also screened NMO (62%), di-*tert*-butylnitroxide (55%), (1*R*)-(10-camphorsulfonyl)oxaziridine (48%), $NaBO_3{\cdot}H_2O$ (31%), $K_3Fe(CN)_6$ (11%), and *m*CPBA (6%) as co-oxidants in the *p*-tolylation of the benzimidazolone [Eq. (19)].

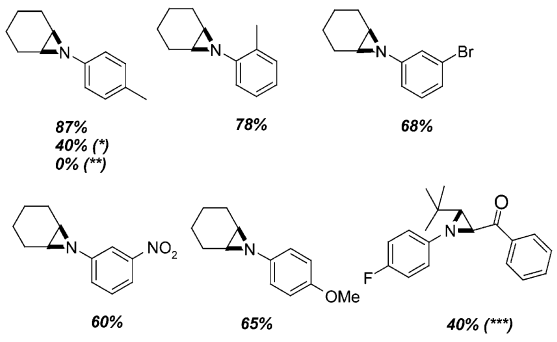


These investigations led to the following general reaction procedure: aryl boronic acid (2.0 equiv), the amine (1.0 equiv), $Cu(OAc)_2$ (0.1–0.2 equiv), PNO (1.1 equiv) or TEMPO (1.1 equiv), and Et_3N (2.0 equiv) or pyridine (2.0 equiv) and *powdered* molecular sieves were stirred under air at room temperature for 4 days. The range of substrates that work well in this transformation includes, benzimidazolones, isatins, phthalimides, piperidines, indazoles, anilines, pyridones, sulfonamides, saccharin, and benzimidazoles (Scheme 26). Although no general catalytic copper system works equally well for *all* substrates examined, choosing the best of the four systems leads to yields in the range 55–100%. The average yields for each of the four procedures in the presence of $Cu(OAc)_2$ (10 mol%) were: 1) 67% (O_2), 2) 75% (TEMPO/air), 3) 59% (PNO/air), and 4) 42%. A modified Collman catalytic system in the presence of $[\{Cu(OH){\cdot}tmeda\}_2]Cl_2$ (10 mol%)/oxygen was a less-efficient system, although it was best for benzimidazole derivatives.

Classic routes to *N*-arylated aziridines have not involved transition-metal-catalyzed *N*-arylation.[53] However, Yudin and co-workers recently showed that *N*-arylation is possible under the modifications of the Buchwald method. Both palladium- and copper-catalyzed routes were successful with a range of boronic acids (Scheme 27).[54]



Scheme 26. Key step: 1) Boronic acid (2 equiv), $Cu(OAc)_2$ (10 mol%), O_2, 4 Å molecular sieves, CH_2Cl_2, room temperature, 4 days; 2) boronic acid (2 equiv), $Cu(OAc)_2$ (10 mol%), TEMPO (1.1 equiv) and air, 4 Å molecular sieves, CH_2Cl_2, room temperature, 4 days; 3) boronic acid (2 equiv), $Cu(OAc)_2$ (10 mol%), PNO (1.1 equiv) and air, 4 Å molecular sieves, CH_2Cl_2, room temperature, 4 days; 4) boronic acid (2 equiv), $Cu(OAc)_2$ (10 mol%), $[\{Cu(OH)\cdot tmeda\}_2]Cl_2$, O_2, 4 Å molecular sieves, dichloromethane, room temperature, 4 days.



Scheme 27. Key step: Boronic acid (1.5 equiv), $Cu(OAc)_2$ (10 mol%), 2,6-lutidine (1 equiv), myristic acid (20 mol%), toluene, room temperature, 24 h; (*) with camphanic acid; (**) with 2-phenylbutyric acid; (***) at 50 °C, time not stated.

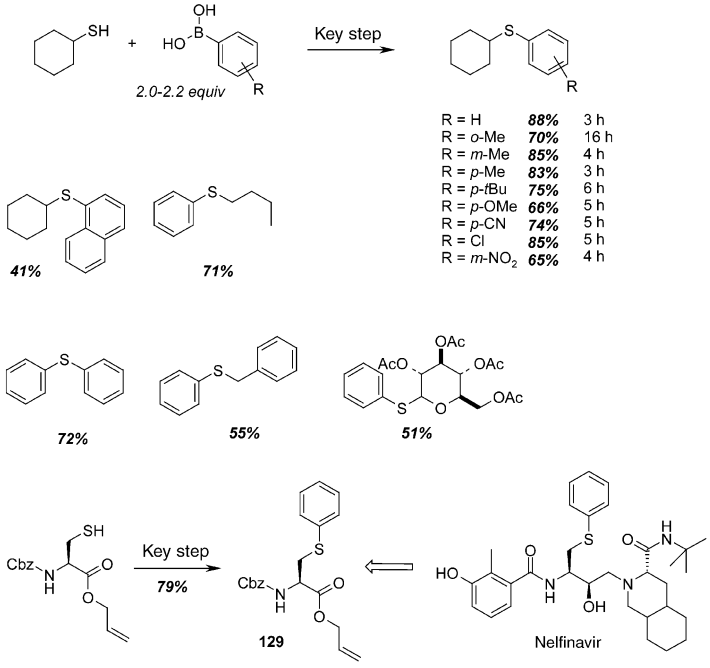
2.4. Copper-Mediated C(aryl)–S Bond Formation

2.4.1. The Original Stoichiometric Cu^{II} Methods and Their Substrate Scope

The need for better synthetic access to **129** led Guy and co-workers to explore a copper-mediated *S*-arylation of thiols (cysteine derivative) with phenylboronic acids in a formal synthesis of nelfinavir.[55] In a model study with cyclohexanethiol and *p*-tolylboronic acid, it was shown that under the conditions developed by the groups of Lam and Chan for *N*- and *O*-arylation reactions, the reactions were too slow for *S*-arylation because of significant disulfide formation as a result of competitive oxidation. However, it was shown that the reaction of a wide range of thiolate substrates with electronically and structurally diverse boronic acids proceeded well when heated to 155 °C in DMF to afford the desired cross-coupled products in good yields (Scheme 28). No racemization was observed during the synthesis of cysteine phenylsulfides. Unfortunately, tertiary thiols, thiolacetic acids, and α-methoxycarbonylthiolates did not react under these conditions.

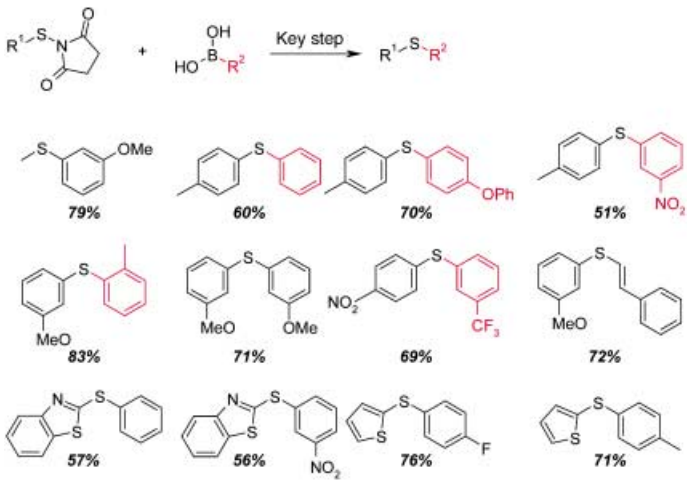
2.4.2. The Original Catalytic Cu^{I} Method

Improvements to this method were clearly needed and Liebeskind et al. reported a novel, interesting, mild, copper(I)-mediated strategy for the synthesis of thioethers in the absence of base. They proposed that the mechanism for alkylaryl sulfide formation does not parallel that of the *O* and *N* counterparts (see Section 11), but instead it is more likely that a Cu^{I}-mediated transformation takes place owing to the facile oxidation of thiols to disulfides by Cu^{II}.[56] This postulate was supported by the preparation of diphenylsulfide (74%) from the reaction between phenylboronic acid and Cu^{I}–3-methylsalicylate [CuMeSal]



Scheme 28. Key step: Boronic acid (2 equiv), $Cu(OAc)_2$ (1.5 equiv), pyr, 4 Å molecular sieves (75 wt%), DMF, reflux, argon, 2–16 h.

in DMA at 100 °C for 18 h. This result was particularly significant since it showed for the first time that *S*-arylation was possible under *non-basic* conditions. In fact the use of base (TBAF, K_2CO_3, NaOH, Et_3N, or pyridine) in the reaction actually impedes its progress. Accepting the empirical assumption that Cu^I is required in stoichiometric amounts (50 % is converted into the catalytically inactive Cu^I thiolate) led the investigators to develop a reaction protocol in which *N*-thioimides serve as the electrophilic sulfide source. In the reaction, a range of boronic acids (1.4 equiv) smoothly reacted with *N*-thioimides (1.0 equiv) in the presence of [CuMeSal] (20–30 mol %) in THF at 45–50 °C to afford the desired cross-coupled products in moderate to good yields of 51–79 % (Scheme 29). It was noted that disulfides can be used



Scheme 29. Key step: Boronic acid (1.4 equiv), CuMeSal (20–30 mol %), THF, 45–50 °C, 4–5 h. R = *p*-tolyl, *m*-methoxyphenyl, 2-benzothiazolyl, 2-thienyl.

efficiently in the reaction, although stoichiometric amounts of Cu^I are necessary. Alternative copper(I) carboxylates (CuOAc and CuTC; TC = [Cu^I–thiophene-2-carboxylate]) were effective in promoting the *S*-arylation, however CuCN, Cu_2O, and CuCl were not.

2.5. Reaction with Aryl Boronic Acids: Summary

When forming C(aryl)–O, C(aryl)–N, and C(aryl)–S bonds, the use of aryl boronic acids as the aryl donor is very much dependent on the oxidation state of the Cu catalyst. Cu^{II} salts are most commonly used, although it is not known for sure that Cu^{II} is the form of the active catalytic species during these processes. In nearly all reports with O, N, and S nucleophiles, $Cu(OAc)_2$ has proved to be the best source of Cu^{II} for the Chan, Evans, and Lam modifications of the Ullmann condensation reaction. The reactions are carried out with either Et_3N or pyridine as base in dichloromethane, and stirred vigorously to help with the uptake of oxygen. As the solubility of oxygen decreases at higher temperatures, the reactions are generally carried out at room temperature. These conditions seem to be critical to the success of the reaction with an impressive range of substrates. However, these reactions are generally slow (18 h–13 days to proceed to completion). As an exception, iodoindazoles react much quicker.

Although the reaction conditions in these powerful new methods are significant improvements over classical Ullmann condensation conditions, there is still room for improvement. The enhanced rates of reaction in the microwave-mediated process has only been shown for some solid-supported reactions of N nucleophiles. A parallel study with O and S nucleophiles has not yet been reported. In all cases, the use of excess aryl boronic acid is also a major limitation of the method. The reasons for this are discussed later (see Section 12). In general, the presence of molecular sieves results in better yields.

Catalytic variants of this transformation are possible and closely parallel the stoichiometric Cu^{II} route. These reactions rely on an efficient reoxidation of the active catalytic species involved in the reaction processes with molecular oxygen or other co-oxidants such as TEMPO. Again the reaction times are in excess of 24 h and rely on the use of excess aryl boronic acid. Additives such as myristic acid, which may aid solubilization of the Cu^{II} species, offer distinct advantages when used in combination with 2,6-lutidine and air or dioxygen. Collman et al. used [Cu(OH)Cl·tmeda] and related systems, which led to a considerable understanding of the catalytic process when employing Cu^I salts and a range of bidentate nitrogen-ligand systems. This has allowed environmentally benign variations of the reactions in water with air as reoxidant.

The reaction of sulfides with aryl boronic acids needed much more optimization as disulfide formation was a predominant reaction outcome with $Cu(OAc)_2$ under the standard conditions developed for O and N nucleophiles. Increasing reaction temperature to 155 °C, excluding air from the reaction, and use of DMF as solvent allowed the successful formation of C(aryl)–S bonds. The significant discovery by Liebeskind and co-workers, who used Cu^I (from [CuMeSal], CuOAc or CuTC) as the active catalytic species, showed that it was possible to form the desired *S*-arylated products from the reaction between excess aryl boronic acid and *N*-thioimides (as the *S* electrophile) under *nonbasic* conditions.

These reactions were used successfully in a range of studies into the substrate scope, in natural product directed synthesis, as well as in medicinal chemistry directed programs, and it is anticipated that the use of these methods will continue to escalate.

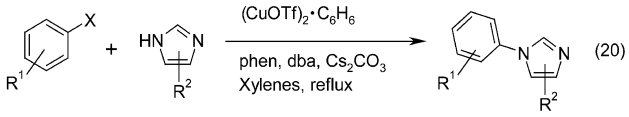
3. Aryl Halides as the Aryl donor: C(aryl)–N Bond Formation

The first *ipso* substitution of an aryl halide by a nucleophile was first reported in 1901 by Ullmann. It was shown that "Cu" can oxidatively insert into and thus polarize a carbon–halogen bond effectively. The polarized bond then undergoes further attack (either inter- or intramolecular) by a nucleophilic species, as was demonstrated in the early cases with phenoxides and aryl amines. Possible mechanisms of this Ullmann condensation reaction have already been reviewed.[57]

3.1. The Original Discovery: Catalytic Cu Methods and Substrate Scope

The groups of Buchwald and Hartwig pioneered a renaissance in the C(aryl)–heteroatom bond construction with their seminal contributions using palladium salts and "tailored ligands and bases" to cope with a broad range of heteroatom-containing substrates.

Since this time, Buchwald and co-workers have continued to make further important contributions to the introduction of a general Ullmann-type synthesis of diaryl amines [Eq. (20)].[58] Perhaps the first modern variant was

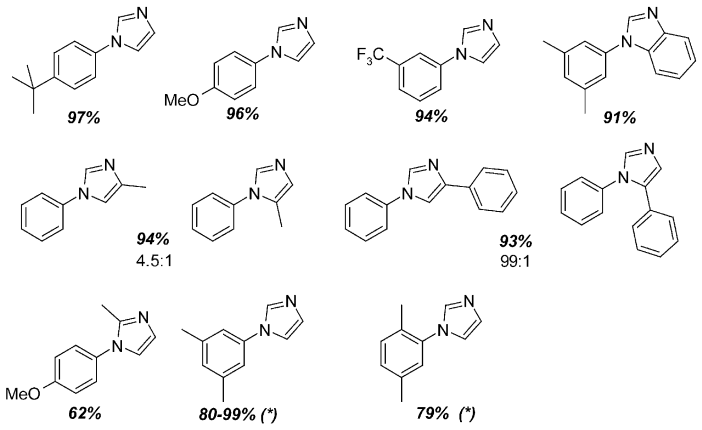


(20)

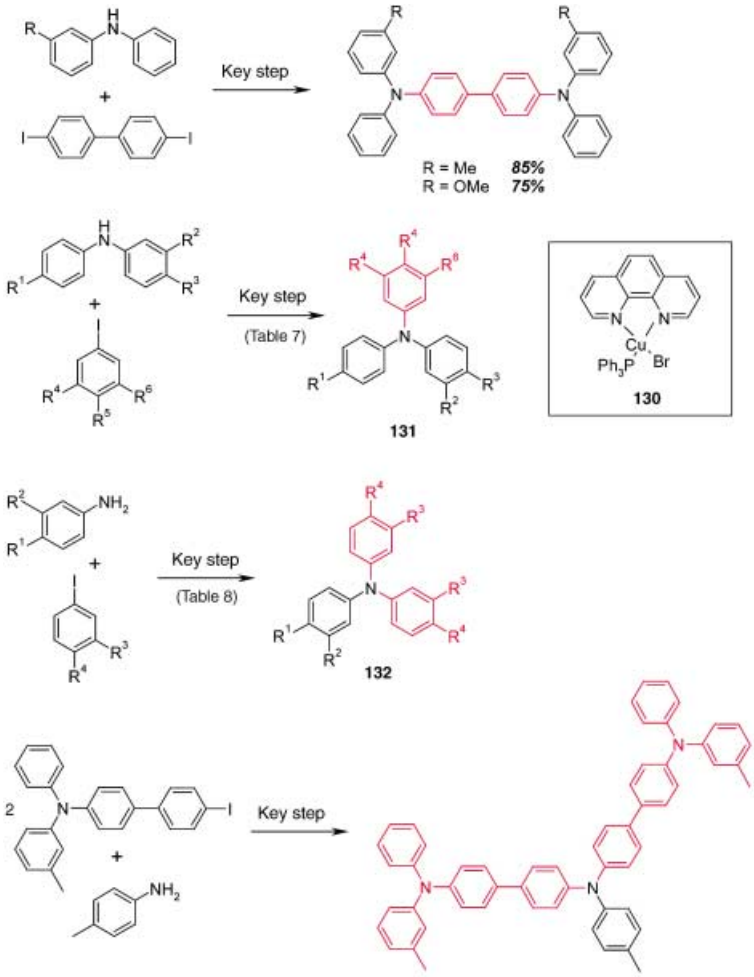
the report that $(CuOTf)_2$ can efficiently catalyze the reaction between imidazoles and aryl halides which revitalized this area of research, as reflected by the increasing number of reports in the scientific literature.

Although the reaction conditions used were certainly not yet general (100–125 °C in xylenes), it was clear that a new strategy for investigating improved catalytic systems had commenced. The use of catalytic amounts of $(CuOTf)_2 \cdot C_6H_6$ and the addition of stoichiometric amounts of 1,10-phenanthroline, *trans,trans*-dibenzylidineacetone, and Cs_2CO_3 (as base) were critical to the effectiveness and reproducibility of the imidazole arylation. Both electron-rich and electron-deficient aryl iodides and bromides reacted well, offering the desired products in near-quantitative yields (Scheme 30).

Goodbrand and Hu also used a similar system to prepare "hole-conducting" triaryl amines in the presence of [Cu(phen)(PPh_3)Br] (**130**) as an accelerating ligand (Scheme 31).[59] In this case, lower temperatures were



Scheme 30. Key step: Aryl iodide (2 equiv), imidazole (3 equiv), $(CuOTf)_2 \cdot C_6H_6$ (10 mol%), phen (2 equiv), dba (10 mol%), Cs_2CO_3, xylenes, 110–125 °C, 24–48 h; (*) from aryl bromide.



Scheme 31. Key step: Aryl iodide (1 equiv), diaryl amine (1 equiv), CuCl (4 mol%), phenanthroline (4 mol%), KOH, toluene, 125 °C, 4–5 h.

Table 7: Ligand-accelerated catalysis of the Ullmann condensation with CuCl and phenanthroline.

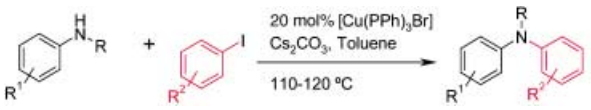
Compound	R^1	R^2	R^3	R^4	R^5	R^6	Yield [%]
131a	H	H	H	Me	H	Me	85
131b	H	OMe	H	H	Me	H	61
131c	Ph	Me	Me	OMe	H	H	80
131d	Ph	Me	Me	H	Ph	H	78
131e	Ph	Me	Me	Me	Me	H	80
131f	Ph	Me	Me	H	H	H	80
131g	H	Me	H	H	*p*-BrC_6H_4	H	80

Table 8: Ligand-accelerated catalysis of the Ullmann condensation with CuCl and phenanthroline.

Compound	R^1	R^2	R^3	R^4	Yield [%]
132a	H	H	H	Me	73
132b	Br	H	H	Me	85
132c	Br	H	Me	Me	83
132d	Me	Me	Me	Me	70
132e	Ph	H	Me	Me	83
132f	Br	H	H	Br	73

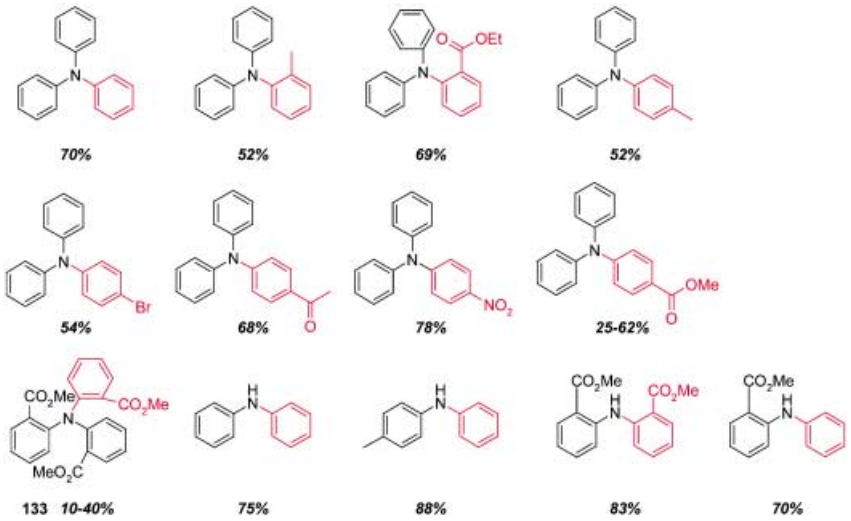
required when using catalytic CuCl and KOH as base. Some examples of the products formed are shown in Tables 7 and 8.

Venkataraman and co-workers also showed that a *soluble* copper(I) species can be used as a catalyst in the construction of C(aryl)–N bonds [Eq. (21)].[60] $[Cu(PPh_3)_3Br]$ is air-stable,



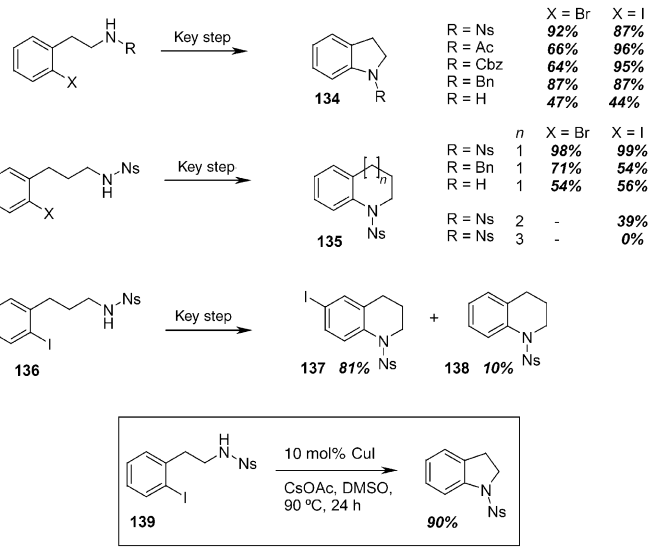
(21)

readily prepared from $CuBr_2$ and PPh_3 in methanol, and is soluble in a wide range of solvents, including THF, CH_2Cl_2, MeCN, $CHCl_3$, NMP, DMF, DMSO, toluene, and benzene. It is, however, insoluble in methanol, ethanol, and diethyl ether. A general reaction procedure followed, which included heating a mixture of the aryl iodide with the $[Cu(PPh_3)_3Br]$ catalyst (20 mol%) and Cs_2CO_3 at 120°C for 24–36 h. In general, the desired diaryl amines were obtained in good yields (Scheme 32). Importantly, the diaryl amines can be formed only if the amine, catalyst, and Cs_2CO_3 are preheated together at 110°C for 5 min prior to the addition of the aryl iodide. Of note was the successful preparation of **133**, which with an *ortho* ester functionality had eluded synthesis by modern palladium-catalyzed methods.



Scheme 32. Key step: Aryl iodide (1 equiv), diphenylamine (1 equiv), $[Cu(PPh_3)_3Br]$ (20 mol%), Cs_2CO_3 (1.5 equiv), toluene, 110–175°C, 24 h.

Fukuyama and co-workers used a novel combination of CuI (2.0 equiv) and CsOAc in an efficient intramolecular cyclization route to dihydroindoles **134** and tetrahydroquinolines **135**; reactions were usually complete after 1–24 h at temperatures ranging from room temperature to 90°C (Scheme 33).[61] This remarkably mild method signifies a breakthrough in the Ullmann condensation reactions at room temperature, although it should be noted that the reaction

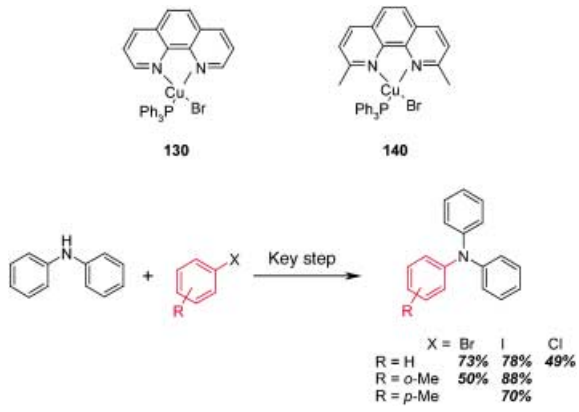


Scheme 33. Key step: CuI (2 equiv), CsOAc, DMSO, RT→90°C, 1–24 h.

required 2 equivalents of CuI and that the intermolecular variant failed. The scope of the reaction was established using both *o*-bromo- and *o*-iodophenethylamines and a small range of amino-protecting groups (Ac, Ns, Cbz, Bn). The intramolecular reaction was also successful with six- and seven-membered fused ring systems, but failed in the case of the eight-membered system. Remarkably, for substrate **136**, the desired product **137** was only accompanied by 10% of the deiodinated compound **138**—a distinct advantage over palladium-mediated methods. A catalytic system also provided product, although for the same substrate **139** the reaction times needed to be extended from 1 to 24 h.

Venkataraman used diaryl amines substrates to exploit the use of the air-stable and soluble Cu^I catalysts **130** and **140**.[62] The synthesis and characterization of these chemically well-defined, stable, and soluble copper(I) complexes was inspired by the fact *soluble* cuprous ions are proposed as the active catalytic species in Ullmann condensation reactions. In the first examples it was shown that the catalyst **140** is soluble in a wide range of solvents, including CH_2Cl_2, $CHCl_3$, toluene (warm), benzene, NMP, DMF and DMSO. However, it is insoluble in diethyl ether and hexane. The catalyst **140** was shown to be twice as fast as **130** in mediating *N*-arylations, and its use was demonstrated in the preparation of the triaryl amines shown (Scheme 34). Thus far, *N*-arylation of primary amines in the presence of **140** has not been reported.

The synthesis of triaryl amines (from aryl iodides and aryl amines) in a *one-pot* reaction was reported to proceed under

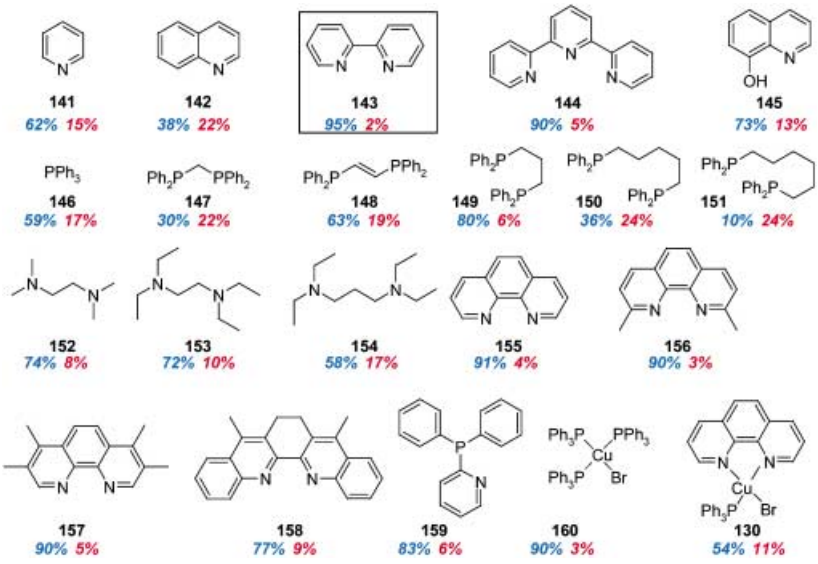


Scheme 34. Key step: [Cu(neocup)(PPh)$_3$Br] (**140**) (10 mol%), KO*t*Bu, toluene, 110°C, 6–36 h.

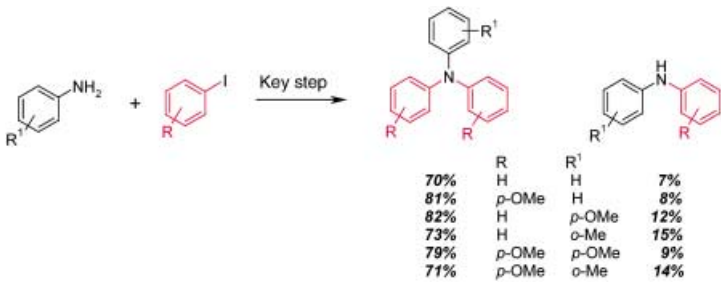
ligand-free Cu-catalyzed conditions in the presence of potassium *tert*-butoxide (Scheme 35).[63] The first system involved the reaction of an aryl amine, aryl halide (3 equiv), and CuI (5 mol% gave moderate turnover numbers of 30–40) in the presence of KO*t*Bu (3 equiv) in toluene at 135°C for 14 h which provided the desired triaryl amines in yields of 28–82%. Other bases (such as NaO*t*Bu, NaOMe, DBU, Cs_2CO_3, KOH, and $NaHCO_3$) were less effective. Best results were obtained with electron-rich aryl amines and aryl iodides; the *o*- or *p*-nitroaniline did not afford any triaryl amine.

A systematic study was undertaken on the mono- and bidentate chelating ligands **141**–**160** (Scheme 36). Their ability to form an active copper catalyst species with CuI and to form triphenylamine in the reaction of iodobenzene with aniline was investigated. Contrary to the results of Venkataram and co-workers,[62] it was shown that the PPh_3 ligand only accelerated the reaction when the PPh_3/Cu ratio was $>2:1$. Quinolines and pyridines were shown to be less efficient ligands. The most efficient chelating bisphosphanes was dppf; however, the diamino chelating ligands gave consistently better yields. 2,2′-Bipyridine (**143**) gave the highest yield and selectivity in favor of the triaryl amine. The yields of triphenylamine and diphenylamine are given in blue and red, respectively, for the representative ligand set (Scheme 36). Further investigation of a single-step transformation showed that the CuI/2,2′-bipyridine-catalyzed amination reaction with electron-rich aryl amines and aryl iodides proceeded with 100% conversion in excellent yields in only 3.5 h at 115°C.

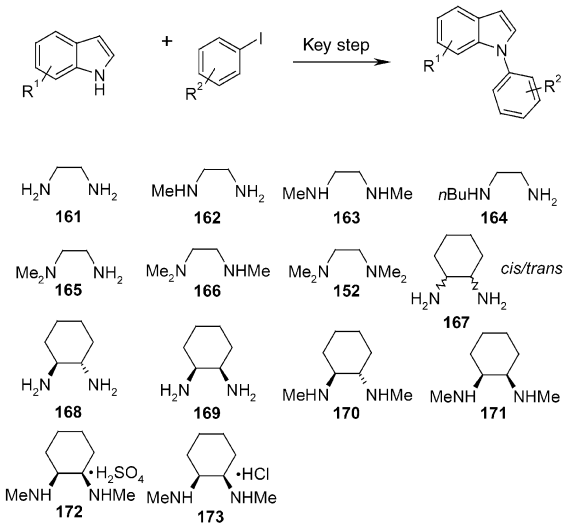
Buchwald and co-workers showed that the known copper-chelating diamine ligands **152** and **161**–**173** are efficient catalysts in the *N*-arylation of a range of substituted indoles (Scheme 37).[64] The desired products were obtained in yields up to 99% under the usual conditions (CuI (1–5 mol%), ligand (**161**–**173, 152**) (10–20 mol%), K_3PO_4 base, and preferably toluene as solvent at 110°C for 24 h). From these initial studies, **168** and **170** were shown to be the best ligands (Scheme 38). In studies with **170**, CuI and Cu^0 (bronze) were shown to be the most efficient copper sources. Copper(II)



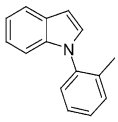
Scheme 36. Key step: Aryl halide (3 equiv), aryl amine (1 equiv), CuI (5 mol%), KO*t*Bu, toluene, 135°C, 14 h.



Scheme 35. Key step: Aryl halide (3 equiv), aryl amine (1 equiv), CuI (5 mol%), KO*t*Bu, toluene, 135°C, 14 h.



Scheme 37. Key step: Aryl iodide (1 equiv), indole (1 equiv), CuI (5 mol%), K_3PO_4, ligand **152** or **161**–**173**, toluene, 135°C, 14 h.



Ligand	Yield [%] 4 h	24 h	Ligand	Yield [%] 4 h	24 h
163	52	99	**168**	66	93
161	22	96	**169**	59	88
162	52	90	**170**	52	98
164	52	90	**171**	39	90
165	5	43	**172**	55	94
166	8	71	**173**	19	85
152	<1	2	**167**	41	80

Scheme 38. Key step: Aryl bromide (1.2 equiv), indole (1 equiv), CuI (5 mol%), K_3PO_4, ligand **152** or **161**–**173** (20 mol%), toluene, 110°C, 4–24 h.

sources such as $Cu(OAc)_2$, $CuCl_2$, and $Cu(OMe)_2$ were less efficient, but still suitable. In each case, arylation of the ligand was observed as a side reaction (up to 10%).

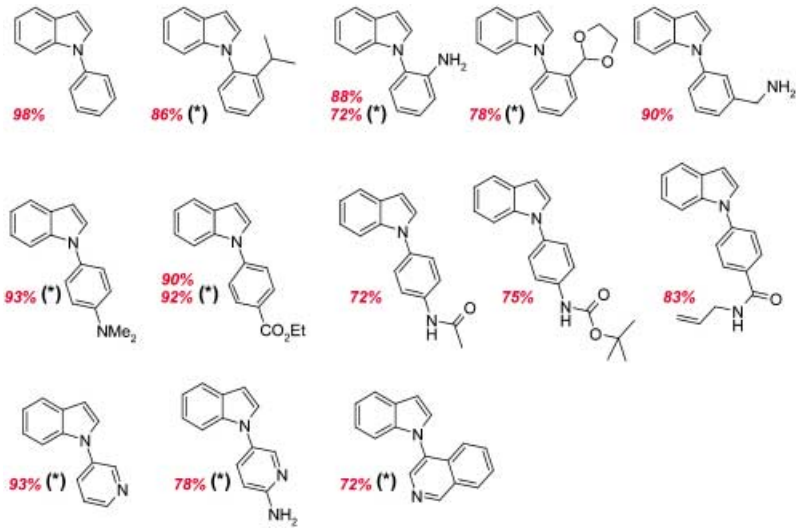
The generality of this transformation was shown with a wide range of functionally substituted indoles (Scheme 39) and aryl halides (Scheme 40) in the presence of ligands **168** (yields in blue) or **170** (yields in red). No reaction occurred with benzoic acids, phenols, or when both reaction partners were substituted at C2.

A variety of diol ligands, **174**–**185**, were assessed in the CuI-catalyzed amination of aryl iodides (Scheme 41).[65] The most efficient system involved a combination of CuI (5 mol%), ethylene glycol (**174**) (2 equiv), and K_3PO_4 base in 2-propanol at 80°C; the desired products were obtained in consistently high yields, without the need to protect the reaction from air or moisture.

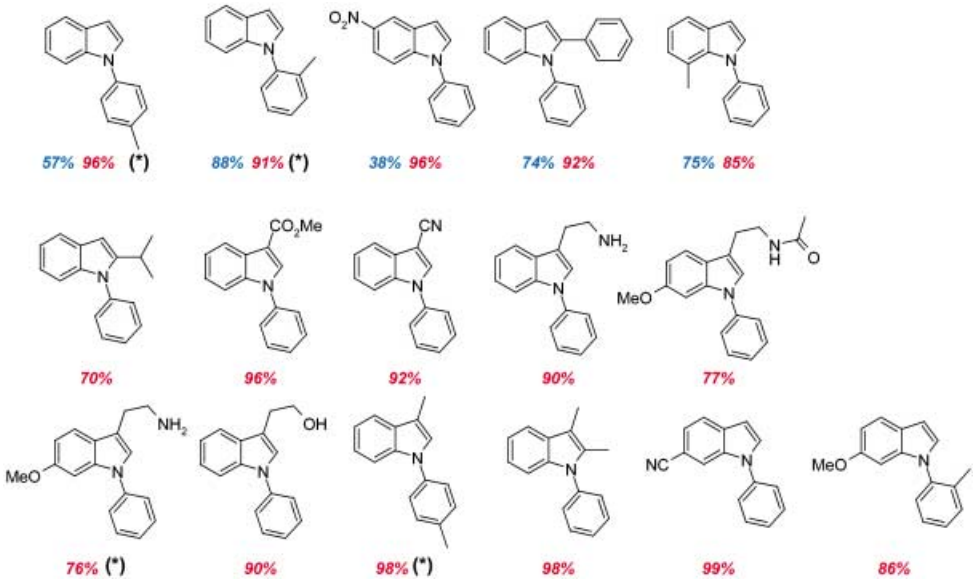
Alternative copper sources (CuBr, CuCl, and CuOAc) were possible, and Cs_2CO_3 could be used as base; however, larger amounts of the *O*-arylated ethylene glycol were formed. 2-Propanol was the best choice of solvent, butanol gave acceptable results, but toluene, dioxane, and DMF were much less effective.

Products from the reactions of benzylamine with a variety of substituted aryl iodides are shown in Scheme 42. A range of amines (primary and secondary aliphatic, as well as bi- and tri-functionalized) were also shown to be suitable substrates and all reacted selectively under these new conditions (Scheme 43). Interestingly, neither amides nor anilines are efficient substrates in these reactions.

Aryl bromides were also useful substrates. The products shown in Scheme 44 were formed in initial investigations with the phenol ligands **186a,b**. Driven by the goal to develop even better conditions for the *N*-arylation of primary alkyl amines under which only a stoichiometric amount of the aryl donor is used, Buchwald and co-workers examined a further range of anionic O-donor ligands (Scheme 45).[66] They concluded that

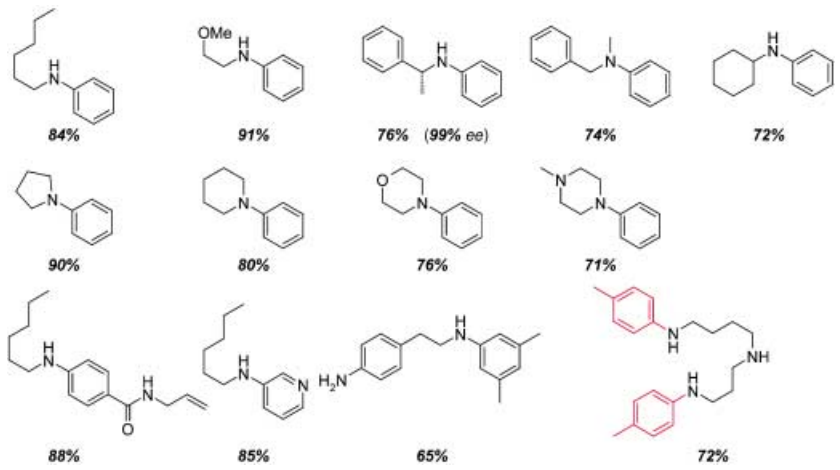


Scheme 40. Key step: Aryl iodide (1 equiv), indole (1.2 equiv), CuI (5 mol%), K_3PO_4, ligand **170** (20 mol%), toluene, 110°C, 24 h; (*) from aryl bromide.

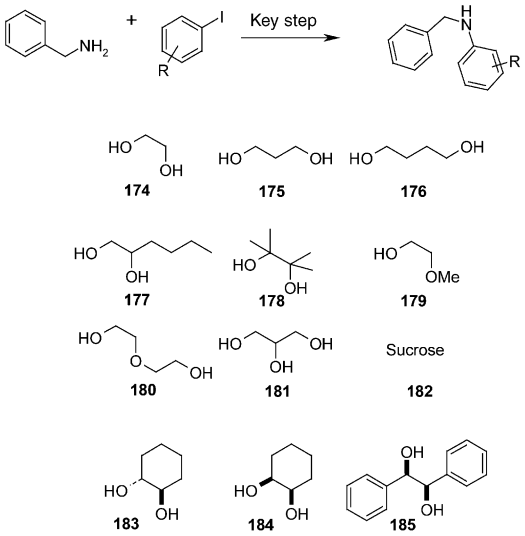


Scheme 39. Key step: Aryl iodide (1 equiv), indole (1.2 equiv), CuI (5 mol%), K_3PO_4, ligand **170** (20 mol%), toluene, 110°C, 24 h; (*) from aryl bromide.

the commercially available *N,N*-diethylsalicylamide (**187**) provided the best results in terms of yield and conversion. A range of products accessible through this method are shown in Scheme 46, including a variety of *ortho*-substituted and heteroaryl substrates, which normally pose significant challenges owing to their poor reactivity. A limitation of this new method is that secondary amines have provided poor results so far. Both K_3PO_4 and K_2CO_3 were found to be effective bases. However, the amine bases DBU or DABCO were inefficient. DMF was shown to be a better solvent than toluene, DME, dioxane, and Et_3N, although the reaction can also be run under solvent-free conditions. In this case, although the reaction mixture maintains its appearance as a solid throughout the reaction, a range of products were formed in good yields (shown in red in Scheme 46).

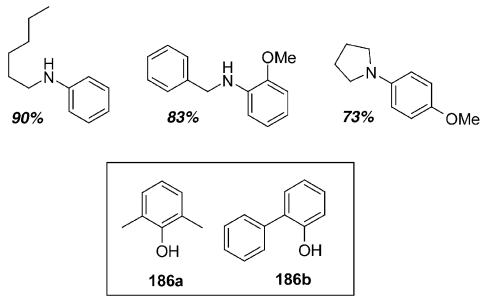


Scheme 43. Key step: Aryl iodide (1 equiv), amine (1.2 equiv), CuI (5 mol%), K_3PO_4, ethylene glycol (**174**) (200 mol%), *i*PrOH, 80°C, 12–40 h.

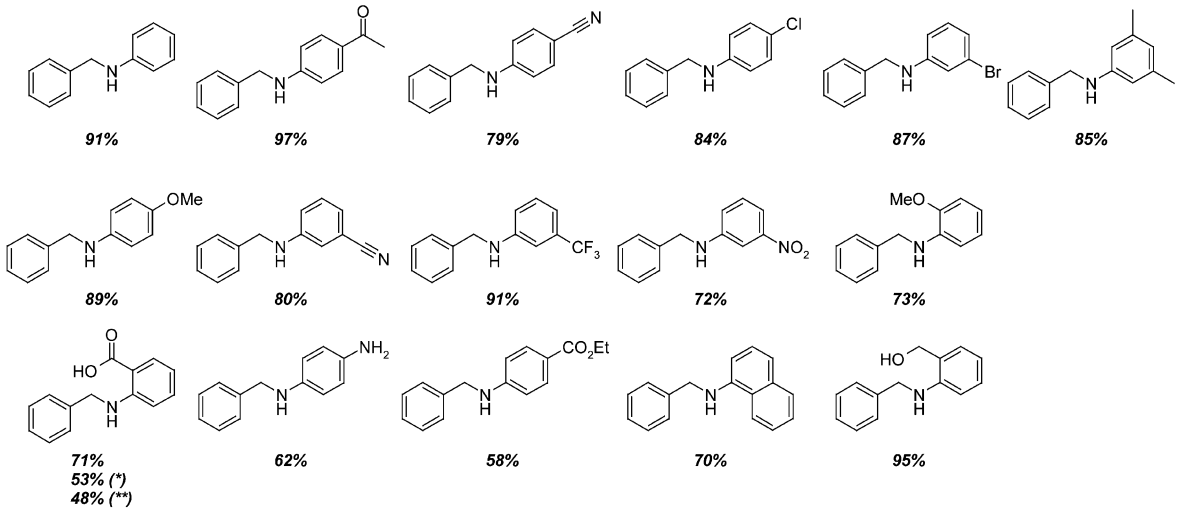


Scheme 41. Key step: Aryl iodide (1 equiv), benzylamine (1.2 equiv), CuI (10 mol%), K_3PO_4, ligand **174**–**185** (10–20 mol%), *i*PrOH, 80°C, 18 h.

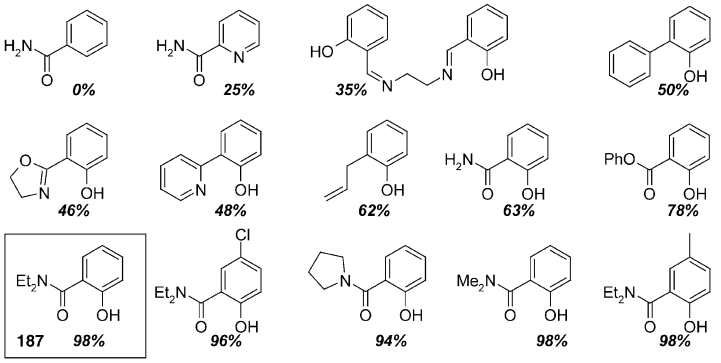
An intramolecular CuOAc-catalyzed amination of *o*-bromo- and *o*-chlorophenethylamines, in which the *N*-atoms are not protected, provided direct access to dihydroindoles and tetrahydroquinolines (Scheme 47, cf. Scheme 33). Aryl



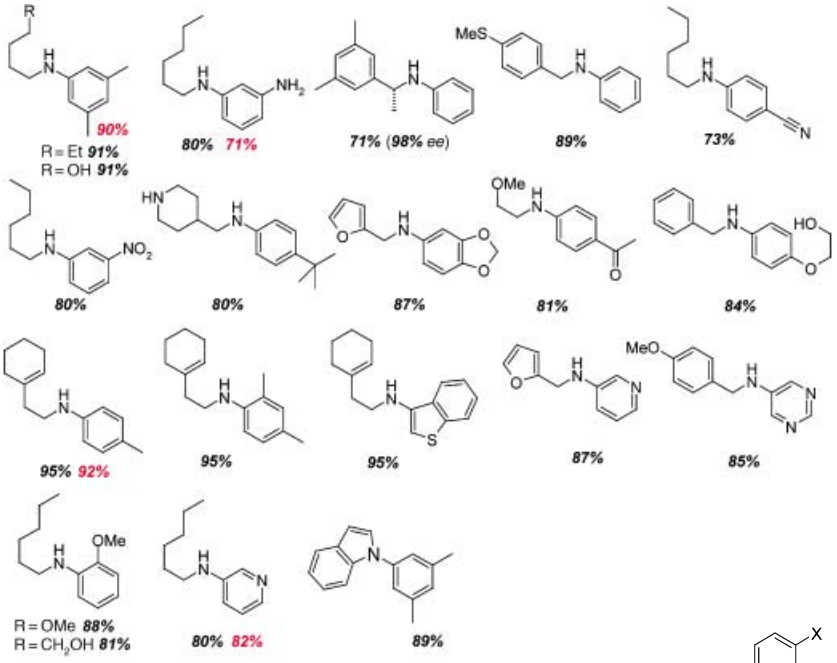
Scheme 44. Key step: Aryl bromide (1 equiv), amine (1.2 equiv), CuI (5 mol%), K_3PO_4, **186a** or **186b** (20 mol%), *n*HexNH_2, toluene, 100°C, 5–72 h.



Scheme 42. Key step: Aryl iodide (1 equiv), benzylamine (1.2 equiv), CuI (5 mol%), K_3PO_4, ethylene glycol (**174**) (200 mol%), *i*PrOH, 80°C, 5–72 h; (*) from aryl bromide; (**) from aryl chloride.



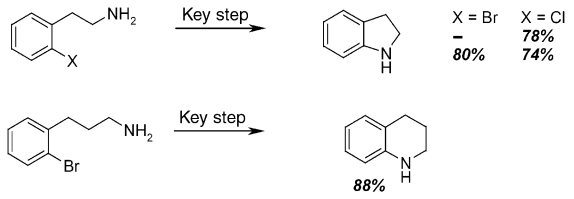
Scheme 45. Range of ligands used in the reaction between 5-bromo-*m*-xylene and *n*HexNH$_2$.



Scheme 46. Key step: Aryl iodide (1 equiv), Amine (1.5 equiv), CuI (5 mol%), K_3PO_4, **177** (20 mol%), DMF, 90°C, 18–22 h; yields in red solvent-free, 100°C, 18–22 h.

bromides were the best substrates, but aryl chlorides also reacted even though longer reaction times were required. When CuI was used as catalyst the yield was much lower, which implies that the solubilizing effect of the preformed CuOAc is responsible for this pronounced effect.

Under conditions similar to those in Scheme 41 (CuI (2.5 mol%), K_3PO_4 (2 equiv), $HO(CH_2)_2OH$ (1 equiv) in *i*PrOH at 75°C), the selective *N*-arylation of amino alcohols (1.2 equiv) with aryl iodides proceeded in good yields (Scheme 48).[67] A general reaction procedure was developed in which the amino alcohol is the limiting reagent and reacts with the aryl iodide in the presence of CuI (2.5 mol%) and NaOH (2 equiv) in DMSO/H_2O (2:1) or *i*PrOH at 90°C. It was also possible to use

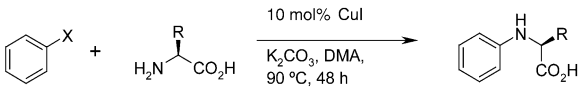


Scheme 47. Key step: CuOAc (5 mol%), K_3PO_4 (200 mol%), **177** (20 mol%), DMF, 35–100°C, 12–48 h.

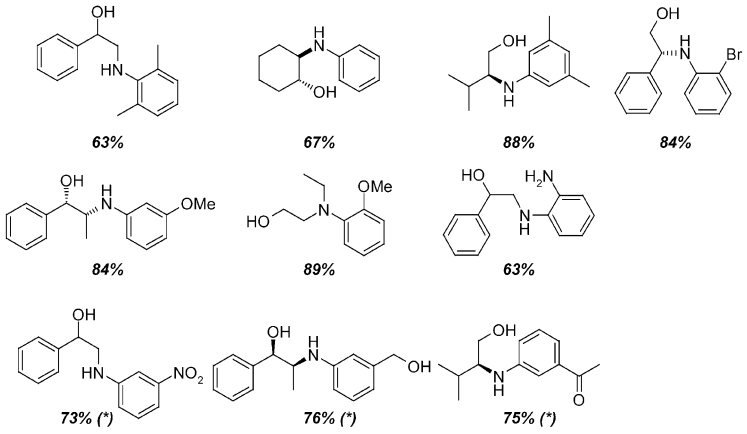
the aryl iodide as the limiting reagent, hence sparing the more valuable chiral material. K_3PO_4 can be used as the base instead of NaOH. In both systems, the reaction times were in the 16-h range and only the *N*-arylated product was formed. These protocols offer complementary approaches to epoxide aminolysis, and offer new strategies in planning stereoselective routes to enantiopure arylated β-amino alcohols.

A general *N*-arylation coupling reaction of α-amino acids with aryl halides has also been reported [Eq. (22)].[68]

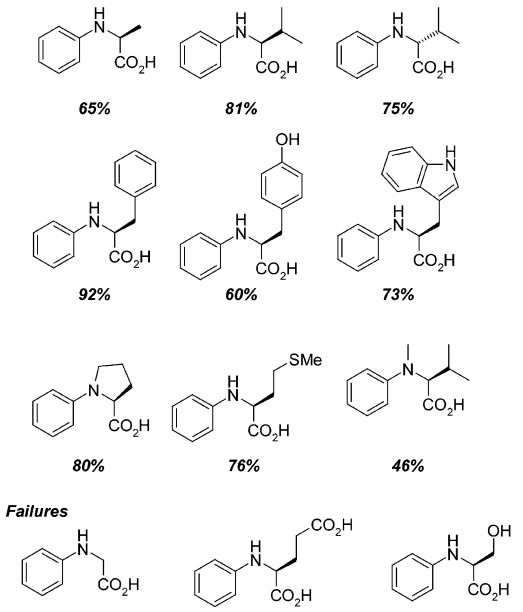
The accelerating affect induced by α-amino acids has allowed Ullmann-type condensations to be carried out at temperatures significantly lower than those under classic experimental conditions. A systematic study of a variety of amino acids (Schemes 49–51) as well as different aryl halides and copper ion sources allowed the formation of a wide range of products.



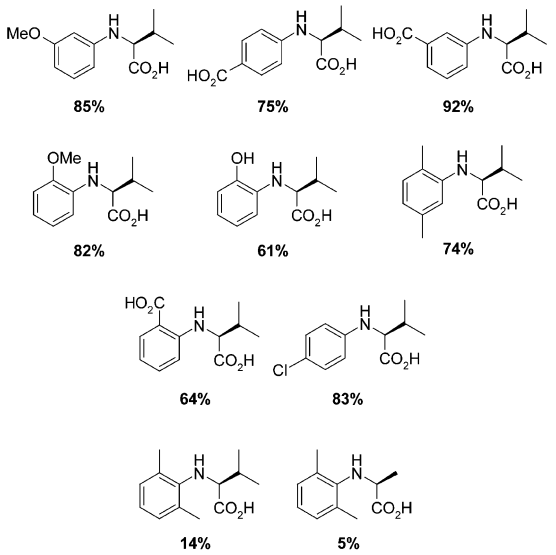
(22)



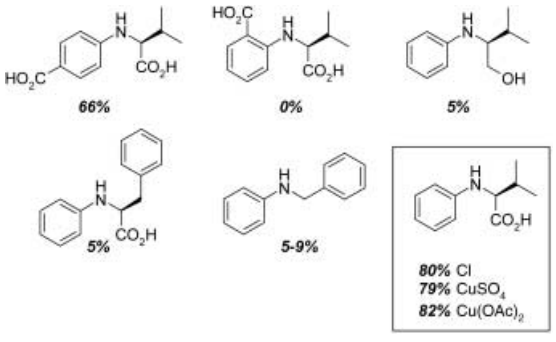
Scheme 48. Key step: Aryl iodide (1.2 equiv), amino alcohol (1 equiv), CuI (2.5 mol%), NaOH, DMSO/H_2O (2:1) or *i*PrOH, 90°C, 15–17 h; (*) aryl iodide (1.2 equiv), amino alcohol (1 equiv), CuI (2.5 mol%), K_3PO_4, ethylene glycol (**174**) (100 mol%), *i*PrOH, 75°C, 16 h.



Scheme 49. Key step: Aryl halide (1 equiv), amino acid (1 equiv), CuI (10 mol%), K_2CO_3 (150 mol%), DMA, 90°C, 48 h.



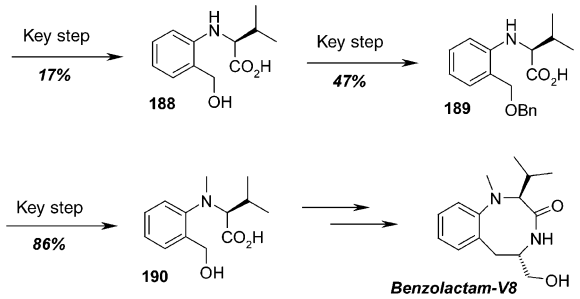
Scheme 50. Key step: Aryl halide (1 equiv), amino acid (1 equiv), CuI (10 mol%), K_2CO_3 (150 mol%), DMA, 90–110°C, 48 h.



Scheme 51. Key step: Aryl halide (1 equiv), amino acid (1 equiv), CuI (10 mol%), K_2CO_3 (150 mol%), DMA, 75°C, 24–48 h.

3.1.1. Application to the Total Synthesis of Molecules of Potential Pharmaceutical Interest

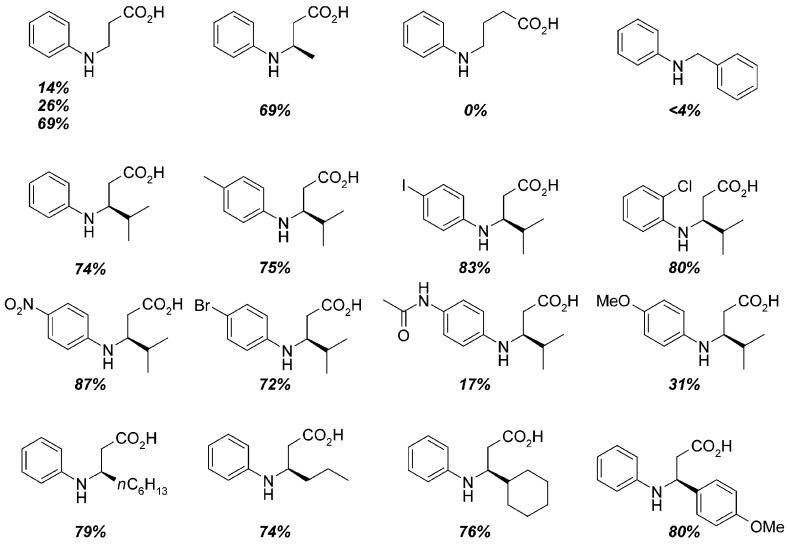
The above-mentioned conditions (see Schemes 49–51) were applied in three copper-mediated strategies in which *o*-iodobenzoic acid derivatives were used as aryl donors in coupling reactions with L-valine to afford the key intermediates **188–190**. Further elaboration with standard reactions allowed an efficient total synthesis of benzolactam-V8 (Scheme 52).



Scheme 52. Key step: Aryl halide (1 equiv), amino acid (1 equiv), CuI (10 mol%), K_2CO_3 (150 mol%), DMA, 90°C, 48 h.

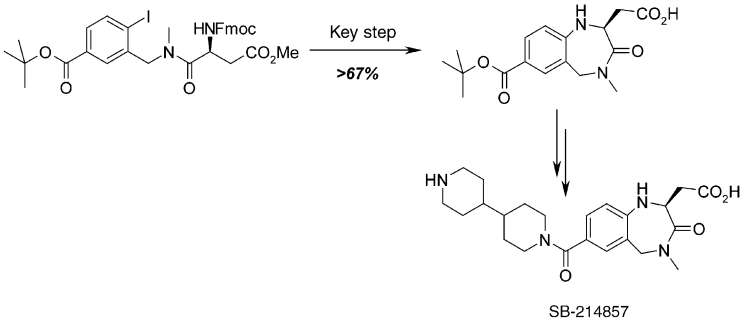
A survey of amino acids revealed that β-amino esters were also useful substrates for the CuI-catalyzed coupling reaction with a variety of aryl halides. Higher yields were obtained with aryl iodides after shorter reaction times at lower temperatures than with aryl bromides; aryl chlorides did not react. During the reaction, the ethyl esters were efficiently cleaved in situ to reveal the desired acidic products (Scheme 53).

An intramolecular version of this transformation evolved and was used in a facile synthesis of SB-214857. A β-amino



Scheme 53. Key step: Aryl halide (1 equiv), amino acid (1 equiv), CuI (10 mol%), DMF (250 mol%), H_2O (cat.), 90–110°C, 48 h.

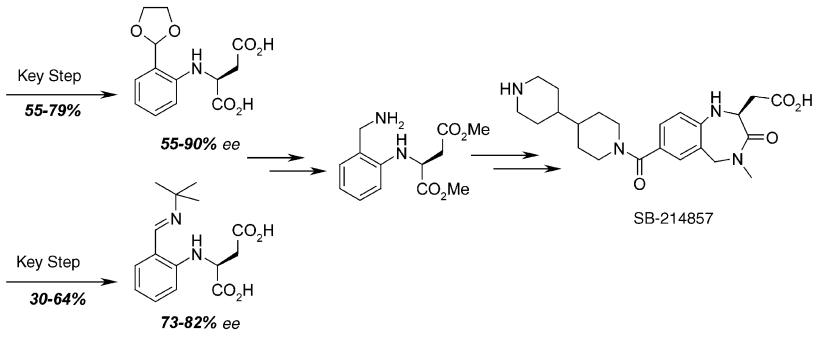
acid was used to accelerate the CuI-catalyzed key intramolecular *N*-arylation reaction, which proceeded in >67% yield (Scheme 54).[69a] No racemization was observed, in contrast to the original aryl fluoride displacement reaction in which 5% racemization was detected.



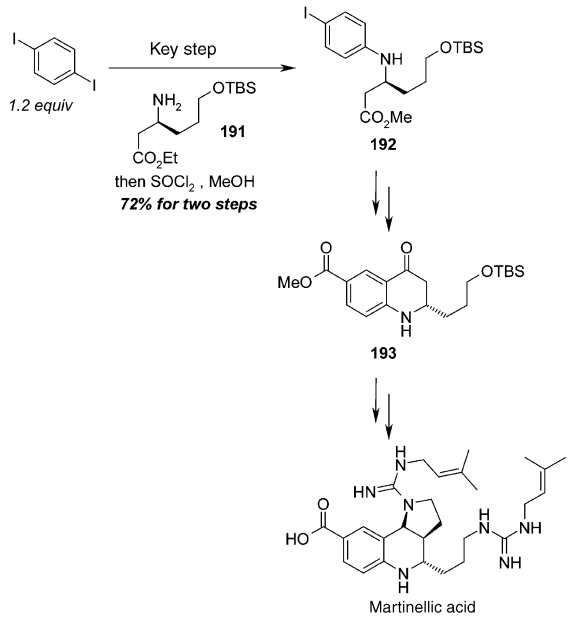
Scheme 54. Key step: CuI (10 mol%), DMF (250 mol%), H_2O (cat.), 90°C, 48 h.

In parallel, Hayes and co-workers examined a similar synthetic strategy to allow efficient access to SB-214857.[69b] The work described above established that there was a tendency for the amino acids with α-hydrophilic substituents to react poorly under the conditions used. It was proposed that the poor reaction outcome may be in part due to the low solubility of this substrate in the reaction medium, and therefore a method was sought to solubilize the substrates. Upon the addition of tetrabutylammonium hydroxide, aspartic acid (which failed to react under the conditions described above, Scheme 49) pleasingly provided access to the desired products, albeit in modest yield, in the presence of CuI in either MeCN, DMF, or DMA (Scheme 55). To improve on these early promising results, a range of copper catalysts were screened. It was shown that the catalytic efficiency was mainly influenced by the oxidation state of copper ($Cu^0 > Cu^I > Cu^{II}$). However, the best system was an unusual combination of Raney copper (19 mol%) mixed with Cu_2O (1 mol%), which was used to prepare lotrifiban SB-214857 (Scheme 55). Notably, the enantiomeric purity tends to decrease with increasing reaction time.

Ma et al. also demonstrated that 1,4-diiodobenzene is a good electrophile in the arylation reaction with the β-amino



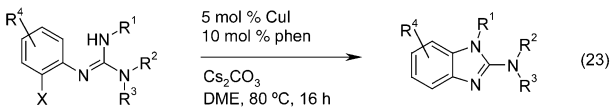
Scheme 55. Key step: Aryl bromide (1 equiv), aspartic acid (1 equiv), Raney copper (19 mol%), Cu_2O (1 mol%), tetrabutylammonium hydroxide (40% aq., 200 mol%), MeCN, reflux, 18 h.



Scheme 56. Key step: CuI (10 mol%), K_2CO_3 (300 mol%), DMF, H_2O (cat.), 100°C, 48 h.

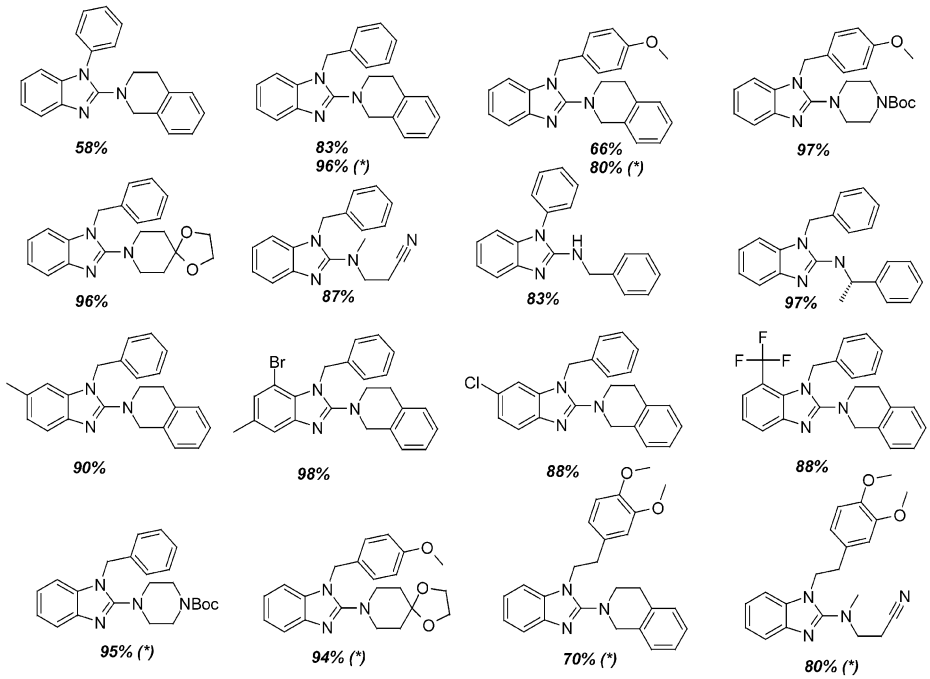
ester **191**. No diamination was observed. Although the reaction times were long (2 days), the product was obtained in good yield (>72%) on a >10-g scale. The product **192** was used as a key intermediate en route to **193**, which was then converted into the natural product martinellic acid (Scheme 56).[70]

An efficient intramolecular aryl guanidinylation reaction allows access to a number of 2-aminobenzimidazoles [Eq. (23)].[71]



(23)

A direct comparison of a CuI/phenanthroline catalytic system with a palladium-mediated reaction protocol showed that the optimized copper-catalyzed system was superior in terms of yield and selectivity, and a wide range of products were formed in good to excellent yields (Scheme 57). Another comparison between copper- and palladium-catalyzed systems was reported by Buchwald and co-workers, who described a facile route to 6-aminoimidazo[1,2-*a*]pyridines from an aryl iodide substrate (Scheme 58).[72] Again, a copper-catalyzed (Scheme 38, CuI (5–15 mol%), **174**, K_3PO_4)[65] proved to be of significant synthetic use, although in some cases the reaction temperature had to be optimized (85–112°C). Scheme 58 shows a range of products obtained in the copper- and palladium-mediated syntheses (yields shown in black and red, respectively).

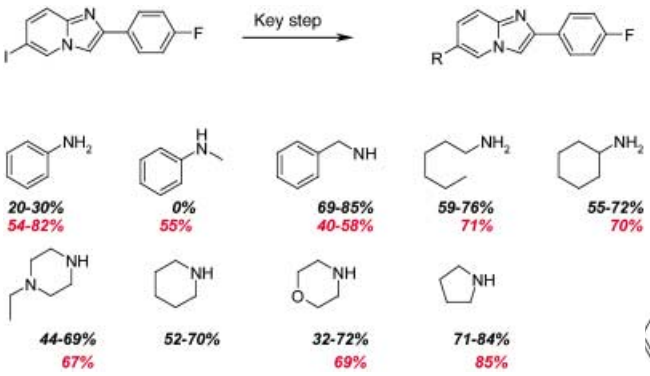


Scheme 57. Key step: CuI (5 mol%), Cs_2CO_3 (2 equiv), phenanthroline (10 mol%), DME, 80°C, 16 h; (*) from aryl iodide.

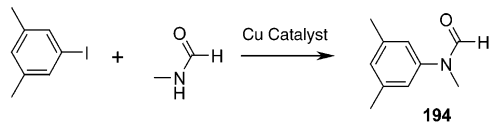
ligands was also performed. When *n*-hexylamine was used as solvent, the product was obtained in near-quantitative yield. This study also revealed that the inexpensive racemic *trans*-1,2-cyclohexanediamine (**168**) in the presence of a base (K_3PO_4, K_2CO_3, Cs_2CO_3, or NaO*t*Bu) in combination with CuI comprised a general and efficient protocol for the *N*-arylation of a variety of amides with aryl and heteroaryl iodides and bromides.

3.2.1. *Choice of Copper Source*

For the formation of **194**, a range of readily available copper sources were screened, which revealed that Cu^0 (bronze), CuCl, CuSCN, Cu_2O, $CuCl_2$, $CuSO_4 \cdot 5H_2O$, $Cu(OAc)_2$, and $Cu(acac)_2$ were suitable alternatives to CuI [Eq. (25)]. Although in the following investigations only CuI was examined in detail,



Scheme 58. Key step: N nucleophile (1.1 equiv), CuI (5–15 mol%), $HOCH_2CH_2OH$ (200 mol%), K_3PO_4, *i*PrOH, 85–112°C, 20–48 h.



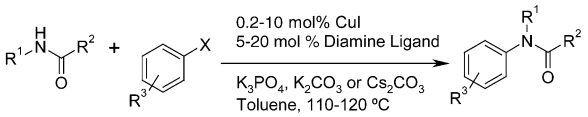
(25)

it can be assumed that for most of the transformations these other reagents can be used as alternatives.

3.2. N-*Arylation of Amides: Improvements in the Goldberg-Modified Ullmann Condensation Reaction*

Buchwald and co-workers have made major contributions to the copper-catalyzed amidation of aryl halides [Eq. (24), Schemes 59–63].[73–75]

These studies confirmed that bidentate chelating ligands such as **168** and **170** have an accelerating effect on these transformations. A systematic screening of



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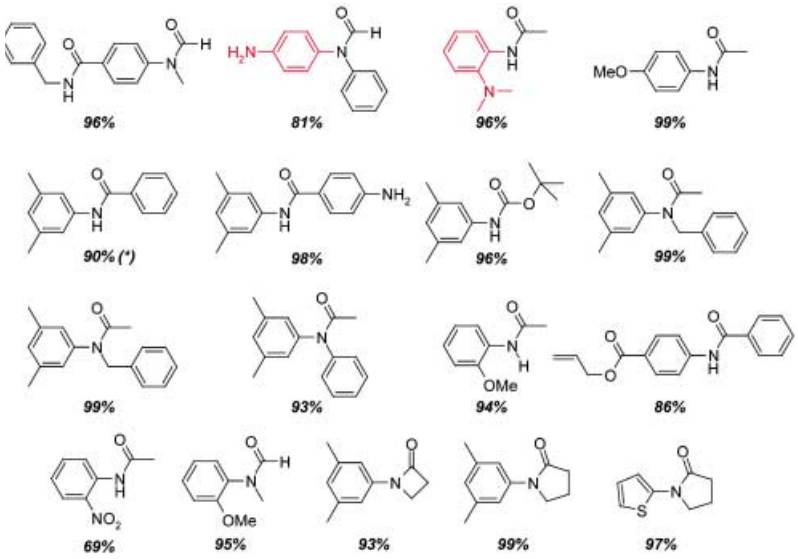
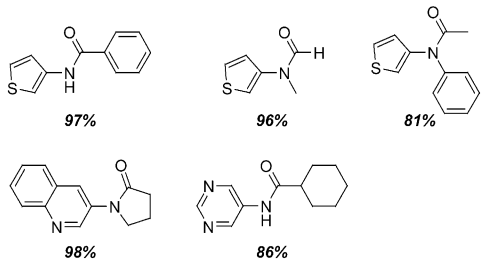
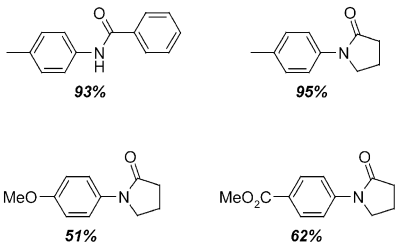


Scheme 59. Key step: Aryl iodide (1 equiv), amide (1 equiv), CuI (10 mol%), **168** (10 mol%), K_3PO_4, dioxane, 90–110°C, 23 h. (*) Aryl iodide (1 equiv), amide (1 equiv), CuI (10 mol%), **168** (5 mol%), Cs_2CO_3 (2 equiv), dioxane, room temperature, 46 h.



Scheme 60. Key step: Aryl bromide (1 equiv), amide (1 equiv), CuI (1–10 mol%), **168** (10 mol%), K_3PO_4, dioxane, 110°C, 15–24 h.

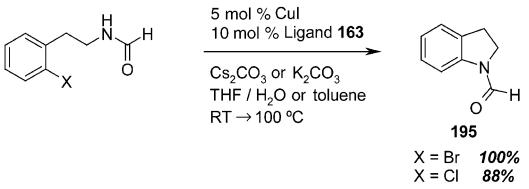


Scheme 62. Key step: Aryl chloride (1 equiv), amide (1 equiv), CuI (5 mol%), **170** (11 mol%), K_3PO_4, dioxane, 110–130°C, 23 h.

An interesting relationship between the pK_{HA} values of the amide and the base was observed: for enhanced yields, the pK_{HA} value of the base should be lower than that of the amide substrate. Further studies on the effect of chelating and nonchelating ligands on the stability constant for the catalytically active copper–amine species are clearly needed since working guidelines for the use and design of these catalytic systems are required.

Aryl chlorides were also used as electrophilic arylation partners, although ligand **170** was the best choice (Scheme 62). A variety of other *N* nucleophiles efficiently reacted with aryl iodides and in each case only one isomer was formed (Scheme 63).

The room-temperature intramolecular aryl amidation reaction with an aryl chloride or bromide was also developed which afforded **195** in yields of 88 and 100%, respectively [Eq. (26)]. This striking result parallels the outcome from palladium-mediated strategies in which the intramolecular amidation reaction is more facile. In the absence of the ligand, no reaction occurs.



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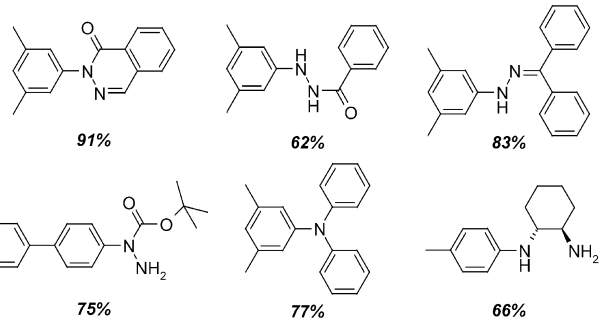
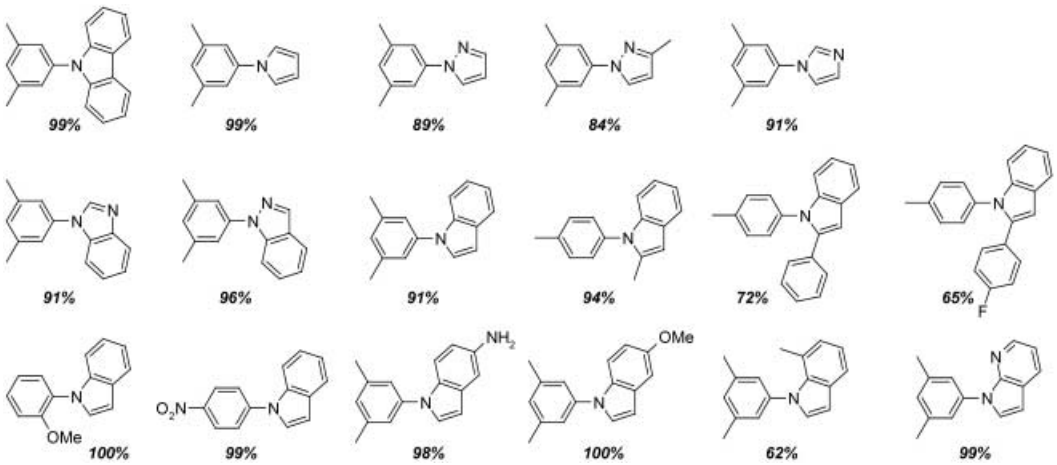
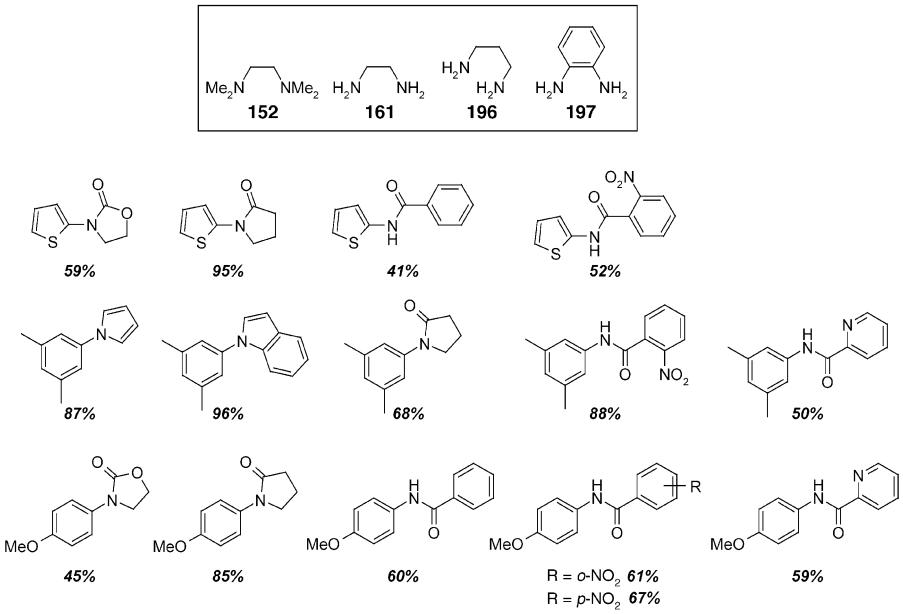


Scheme 63. Key step: Aryl iodide (1 equiv), Aza-nucleophile (1 equiv), CuI (1–20 mol%), **168** or **170** (10 mol%), K_2CO_3, K_3PO_4, Cs_2CO_3 or NaO*t*Bu, dioxane, 110°C, 24 h.

Kang et al. demonstrated that the cross-coupling of primary and secondary amides as well as carbamates with heteroaryl halides was most efficient in the presence of CuI/**161** (10 mol%) and K_3PO_4 base (Scheme 64).[75] These studies also showed that a range of other diamines were suitable ligands (e.g. **152, 196, 197**) in combination with the correct base to affect the amidation of iodothiophene, 3,5,-dimethyliodobenzene, and *p*-methoxyiodobenzene in 45–96% yields.



Scheme 61. Key step: Aryl iodide (1 equiv), azole (1.2 equiv), CuI (10 mol%), 168 (10 mol%), K_3PO_4, dioxane, 110°C, 24 h.



Scheme 64. Key step: Aryl iodide (1 equiv), amide (1.2 equiv), CuI (10 mol%), **161** (10 mol%), K_3PO_4, dioxane, 110°C, 24 h.

Padwa and co-workers also recently exploited these routes in a ligand-free arylation of thiopheno and furano halides to prepare a range of 2- and 3-amido-substituted thiophenes and furans after their reactions with a variety of amides and carbamates (Scheme 65). Thiazole was also examined and afforded the desired product in 58% yield.[76]

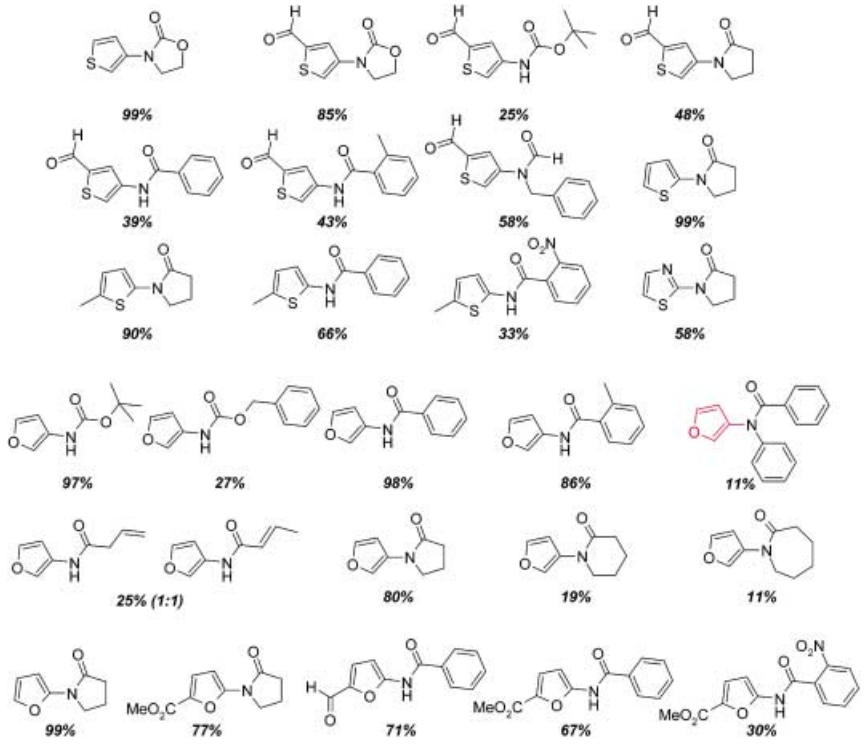
3.2.2. *Enhancing Reaction Rates by Microwave Irradiation*

Lange et al used the amidation of aryl bromides in a key strategic step in the efficient syntheses of *N*-aryl piperazinones, piperazinediones, and 3,4-dihydroquinolinones (Scheme 66).[77] In each case, the substrates were combined with CuI (10 mol%) and K_2CO_3 base in NMP and exposed to microwave irradiation to afford the desired products very rapidly (20–40 min) in good yields.

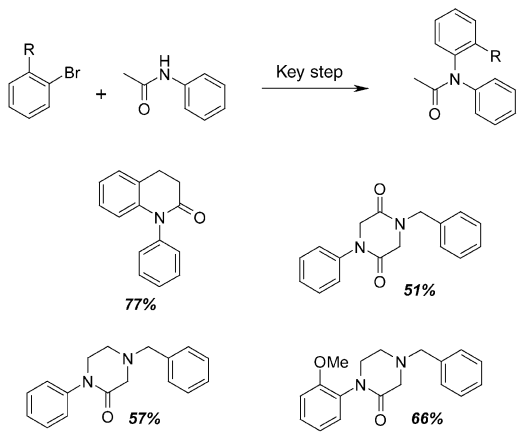
3.2.3. N-*Aminoamides as Substrates*

Acyl hydrazides are also suitable substrates under slightly modified conditions with CuI and Cs_2CO_3 in combination with phenanthroline (Schemes 67 and 68).[78] Consistently high yields were obtained with long reaction times (24 h), although the temperatures were reduced to 80°C [Eq. (27)]. In these series of examples, a remarkably wide range of functional groups (enolizable ketones, primary and phenolic OH, aniline NH_2, ester, and cyano) was tolerated.

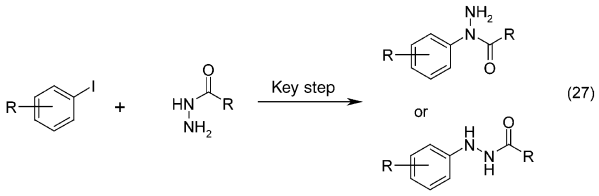
The transformation described above was found to be completely regioselective, and the *N*-Boc hydrazine reacted



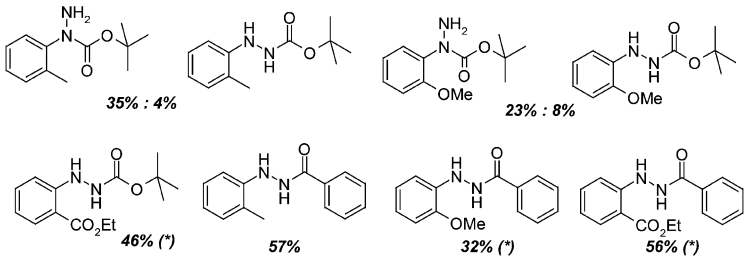
Scheme 65. Key step: Thiophene halide or furan halide (1 equiv), amide (1.2 equiv), (10 mol% CuI), K_2CO_3 (430 mol%), dioxane, 110°C, 24 h.



Scheme 66. Key step: Aryl bromide (1.5 equiv), Amide (1 equiv), CuI (10 mol%), K_2CO_3 (100 mol%), NMP, microwave irradiation (250 W), 190 °C, 20–40 min.

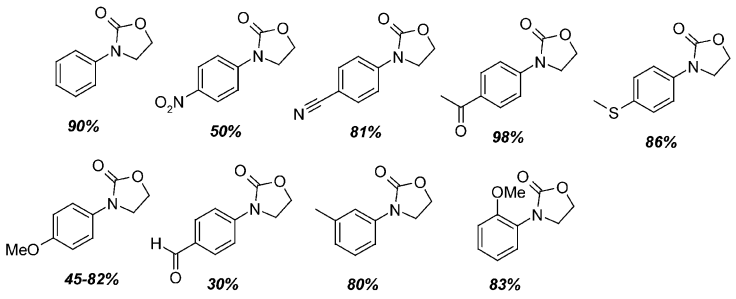


exclusively with *meta*- and *para*-substituted aryl iodides (Scheme 67). When using *ortho*-substituted aryl iodides as the electrophile, a poorer regioselectivity was observed. In the absence of ligand, there was a complete loss of regioselectivity. The use of benzoic hydrazide afforded regioselectively the *N*′-arylated products regioselectively in moderate to good yields (Scheme 68).

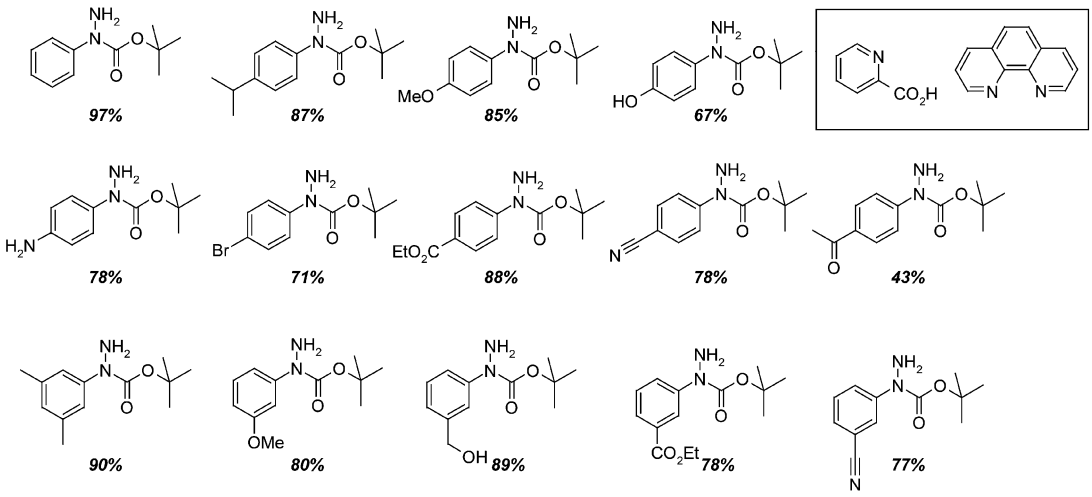


Scheme 68. Key step: Aryl iodide (1 equiv), hydrazide (1.2 equiv), CuI (1–5 mol%), **130** (10–20 mol%), Cs_2CO_3 (1.4 equiv), DMF, 80 °C, 21 h; (*) with picolinic acid.

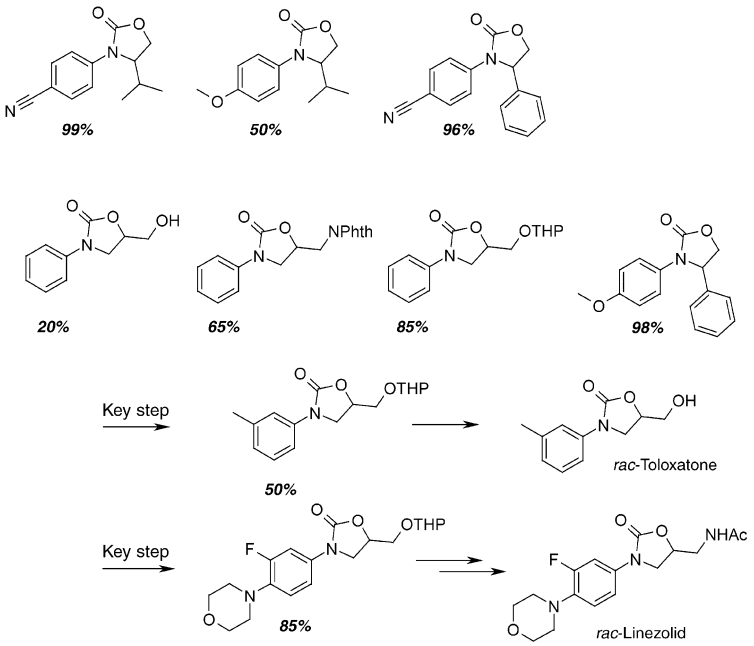
Oxazolidinones are excellent substrates in the *N*-arylation reaction and allow access to a range of substituted *N*-aryl oxazolidinones after some optimization of the conditions previously reported by Buchwald and co-workers (Scheme 69; recrystallized CuI (3 mol%), freshly distilled (±)-**168** (10 mol%), K_2CO_3 (200 mol%)).[79] Substituted oxazolidinones also reacted well, and Trehan and co-workers also used this method in an efficient synthesis of racemic linezolid and toloxatone (Scheme 70).



Scheme 69. Key step: Aryl bromide (1 equiv), CuI (3 mol%), **168** (10 mol%), K_2CO_3 (2 equiv), dioxane, 110 °C, 15 h.



Scheme 67. Key step: Aryl iodide (1 equiv), hydrazide (1.2 equiv), CuI (1–5 mol%), phenanthroline (10–20 mol%), Cs_2CO_3 (1.4 equiv), DMF, 80 °C, 21 h. In box: applied ligands.

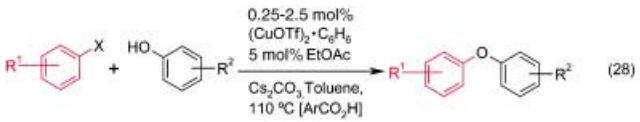


Scheme 70. Key step: Aryl bromide (1 equiv), CuI (3–5 mol%), **168** (10 mol%), K_2CO_3 (2 equiv), dioxane, 110°C, 15 h.

4. Aryl Halides as the Aryl Donor: C(aryl)–O Bond Formation

4.1. The Original Discovery: Catalytic Cu Methods and Substrate Scope

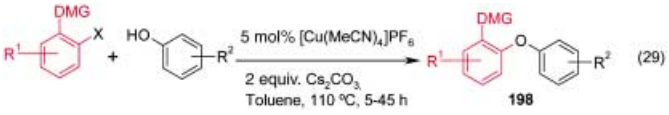
The introduction of cesium carbonate as a base by Buchwald and co-workers for the Ullmann arylation reaction has led to much better procedures for the synthesis of diaryl ethers from a variety of phenols and aryl bromides or iodides [Eq. (28)].[80] Reaction times were in the range of 12–26 h, and ethyl acetate was necessary as a catalytic additive in the reactions.



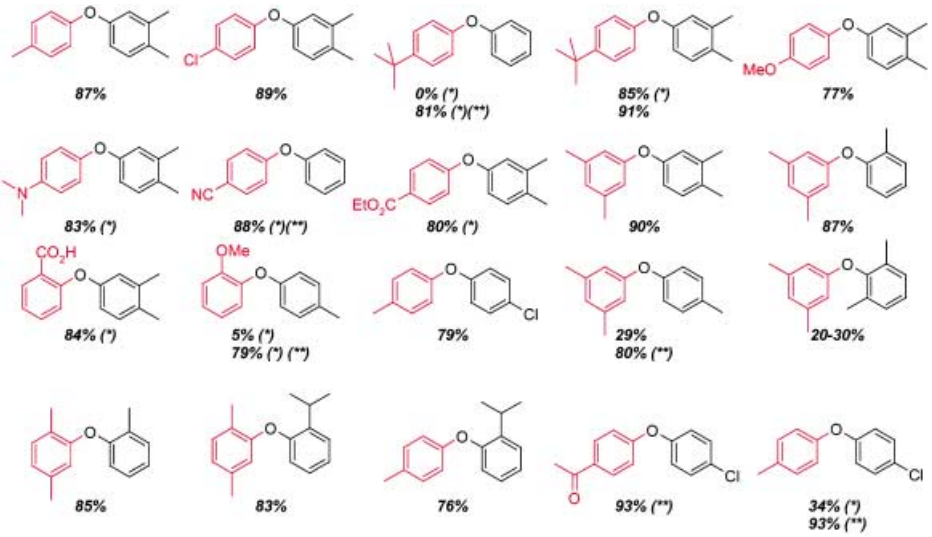
A variety of copper sources, namely $(CuOTf)_2{\cdot}C_6H_6$, CuCl, CuBr, CuI, $CuBr_2$, and $CuSO_4$, displayed similar efficiencies (Scheme 63). Interestingly, less reactive phenols required an equimolar amount of 1-napthoic acid (presumably to solubilize the copper–phenoxide complex or the cesium phenoxide), and molecular sieves greatly facilitated the transformation, presumably by enhancing the reactivity of the system. Under these new conditions, the Ullmann condensation between unactivated aryl halides and less reactive or hindered phenols was now possible (Scheme 71).

The 2-hydroxy-2′-methoxydiphenyl ether framework present in verbenachalcone was assembled through the copper-catalyzed coupling of the 2-benzyloxybromobenzene derivative with a 2-methoxyphenol (Scheme 72). An alternative disconnection using a 2-bromoanisole derivative as the electrophile failed.[81]

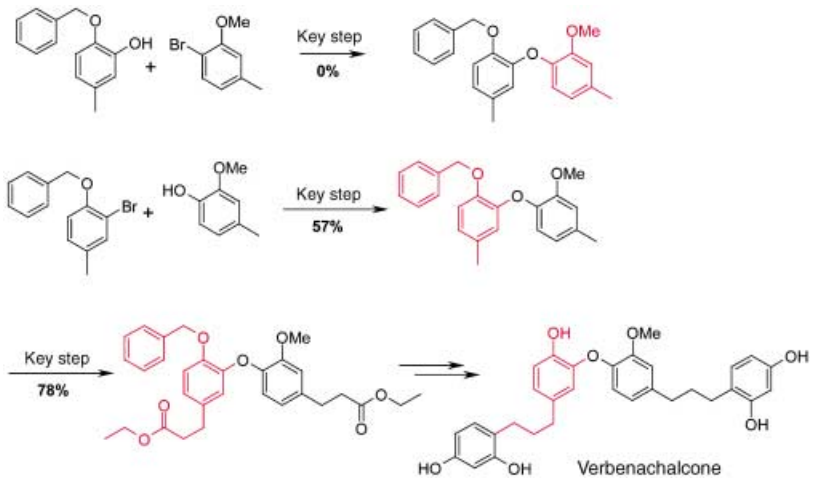
Snieckus and co-workers elegantly used a directed *ortho* and remote metalation concept to prepare a series of 1,2,3-contiguous aromatic substitution patterns for compounds of type **198** [Eq. (29)].[82]



The methodology employed the catalytic (5 mol%) use of $[CuPF_6(MeCN)_4]$ instead of the air-sensitive $(CuOTf)_2{\cdot}C_6H_6$



Scheme 71. Key step: Aryl iodide (1 equiv), phenol (1.4–2 equiv), $(CuOTf)_2{\cdot}C_6H_6$ (2.5 mol%), Cs_2CO_3 (1.4 equiv), EtOAc (5 mol%), toluene, 110°C, 12–26 h; (*) from aryl bromide; (**) with 1-naphthoic acid (1 equiv) and 5 Å molecular sieves.

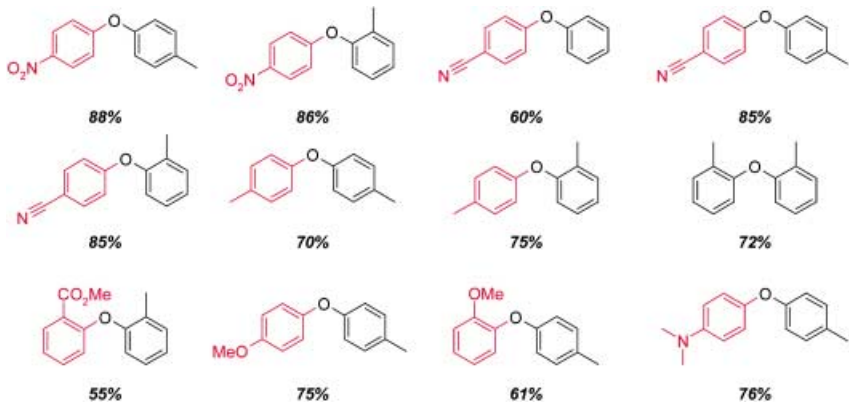


Scheme 72. Key step: Aryl bromide (1.1 equiv), $(CuOTf)_2$·PhMe (2.5 mol%), Cs_2CO_3 (1.1 equiv), Pyr, 110°C, 24 h.

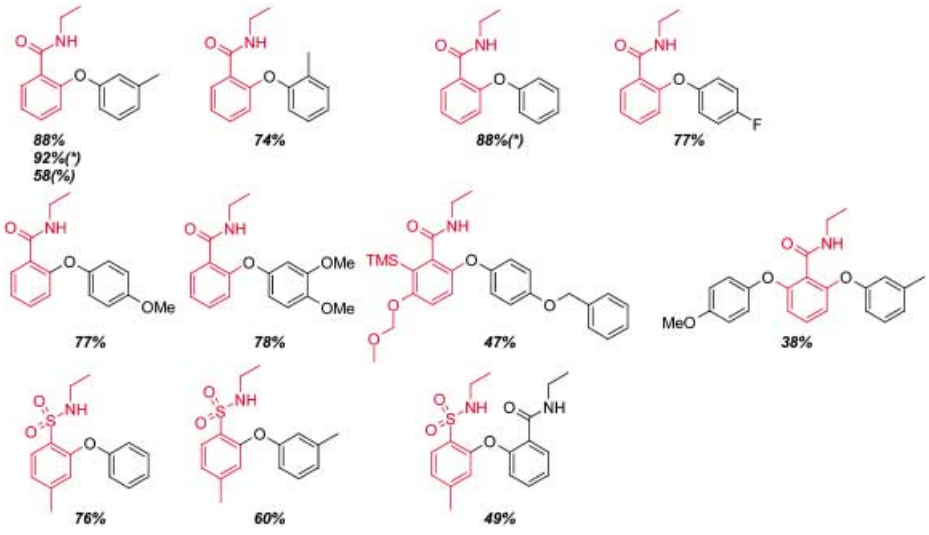
along with Cs_2CO_3 in boiling toluene or xylenes. This protocol allowed the preparation of a range of products (Scheme 73) from aryl iodides, bromides, and even secondary chloro benzamides, which are reported to be poor substrates for the Ullmann condensation. Thiophenols and benzylamines were also found to be suitable substrates.

$[Cu(PPh_3)_3Br]$ is an easy-to-prepare air-stable copper(I) catalyst and was found to be a suitable catalyst for the synthesis of diaryl ethers from electron-rich aryl bromides and electron-rich phenols in the presence of Cs_2CO_3 in NMP (Scheme 74).[83] With 5 mol% catalyst, long reactions times were required (up to 48 h) to provide the products in good to excellent yields. However, the reaction times could be decreased to 24 h by increasing the catalyst concentrations to 20 mol% or even to stoichiometric amounts. Efficient stirring of the reaction mixture was obligatory, and the reactions did not proceed when using K_2CO_3, KO*t*Bu, or DMAP, or when using toluene as solvent.

The choice of protecting group for the aniline in the synthesis of *p*-aminomethoxy derivatives was crucial for the Ullmann reaction of 2-fluoro-4-iodoaniline.[84] Unprotected aniline, methylacetamide, methylcarbamate, phthalate, or benzophenone imine all failed to provide any trace of



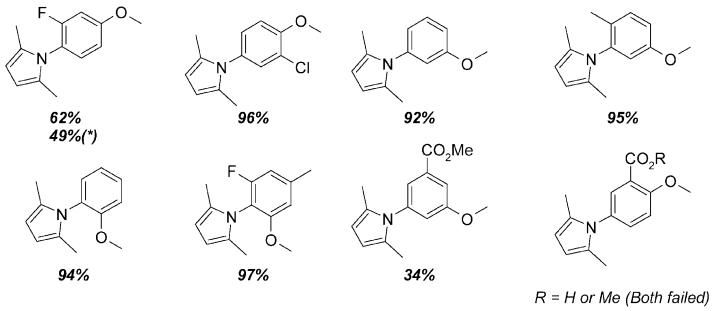
Scheme 74. Key step: Aryl halide (1 equiv), phenol (1 equiv), $[Cu(PPh_3)_3Br]$ (20 mol%), Cs_2CO_3, NMP, 100°C, 17–24 h.



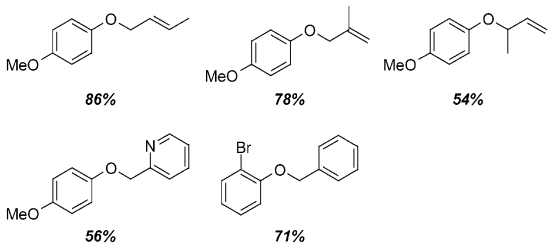
Scheme 73. Key step: Aryl halide (1 equiv), phenol (1.2–1.5 equiv), $[Cu(MeCN)_4]PF_6$ (5 mol%), Cs_2CO_3, toluene or xylene, reflux, 5–45 h.

the desired products. However, protection with a 2,5-dimethylpyrrole unit followed by methoxylation with NaOMe/MeOH in the presence of CuI or CuCl (15 mol%) as catalyst gave the desired products in good yields (Scheme 75).

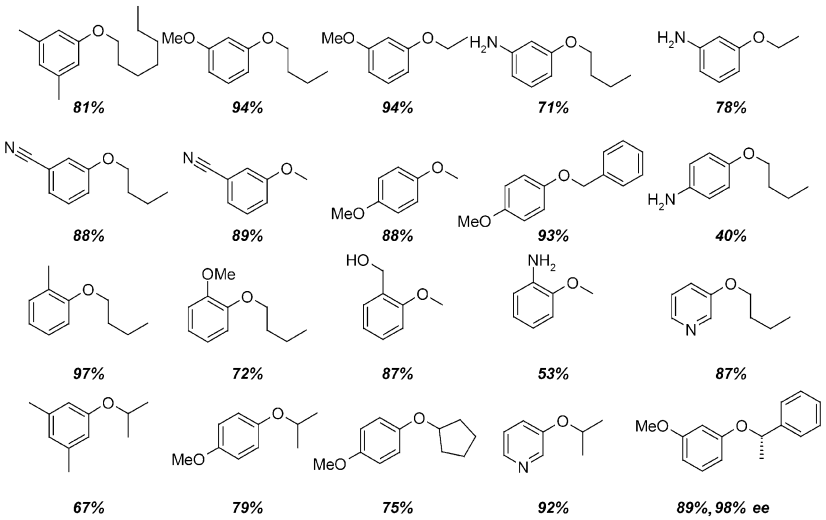
Buchwald and co-workers also demonstrated that alkoxide bases can be replaced during the coupling of aryl iodides with aliphatic alcohols by using neat alcohol in the presence of catalytic amounts of CuI and phenanthroline with cesium carbonate as base (Scheme 76).[85] The range of products shown in Scheme 77 demonstrates the use of alcohol as solvent; with more valuable alcohols, 2 equivalents were used in the presence of toluene as solvent.



Scheme 75. Key step: Aryl iodide, CuCl (15 mol%), NaOMe (3 equiv), MeOH/DMF (3:1), 80°C, 4 h; (*) from aryl bromide.



Scheme 77. Key step: Aryl iodide (1 equiv), alcohol (2 equiv), CuI (10 mol%), phenanthroline (20 mol%), Cs_2CO_3 (1.4–2 equiv), toluene, 110°C, 22–38 h.

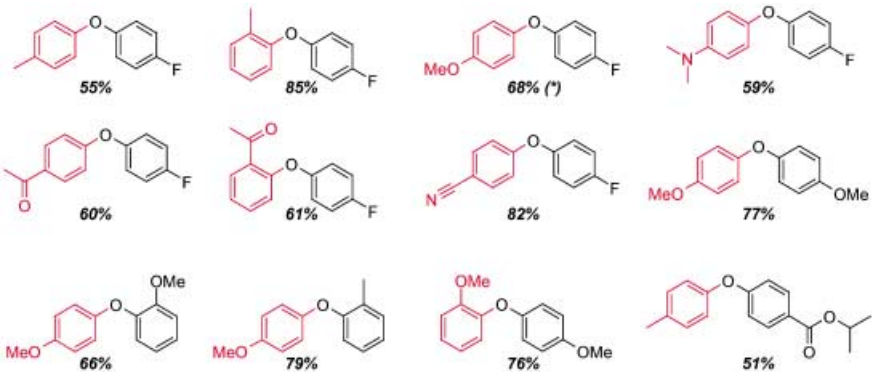


Scheme 76. Key step: Aryl iodide (1 equiv) in alcohol, CuI (10 mol%), **155** (20 mol%), Cs_2CO_3 (1.4–2.0 equiv), 110°C, 18–24 h.

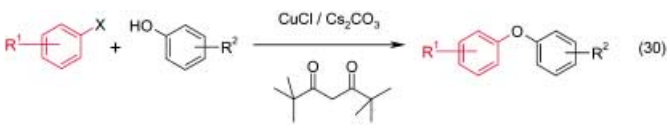
4.2. Enhancing Reaction Rates by Additives

In another recent development in the synthesis of diaryl ethers by an Ullmann condensation reaction, it was found that rate enhancements (10–15-fold) could be obtained by using 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) as an additive along with CuCl as catalyst and Cs_2CO_3 as base [Eq. (30)].[86]

The reason behind the accelerating effect of this ligand is still unclear, but interestingly this ligand works best with Cs_2CO_3, and no accelerating effect was observed with other bases. The optimum amount of TMHD was found to be 25 mol%. 8-Hydroxyquinoline, 2-aminopyridine, and 1,10-phenenthroline **155** were possible alternative ligands. In addition, the use of acetylacetone offered only small rate enhancements. It was proposed that the diketone (TMHD) exists mainly as the diketo tautomer under the reaction conditions and forms a co-complex with the copper(I)–phenolate species which equilibrates rapidly and hence accelerates the rate-determining step. A range of products formed under these conditions are shown in Scheme 78.

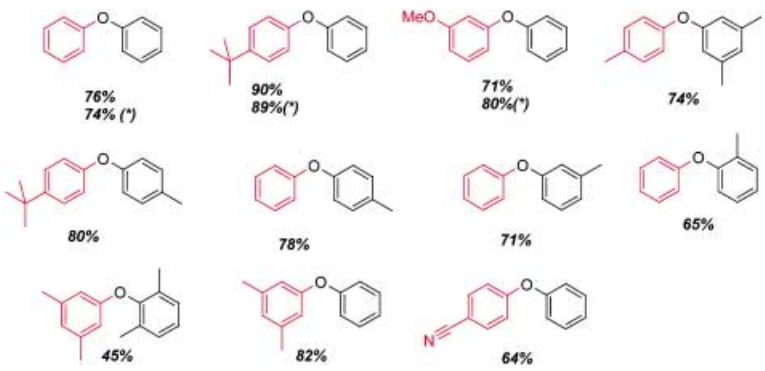


Scheme 78. Key step: Aryl bromide (1 equiv), phenol (2 equiv), CuCl (50 mol%), TMHD (10 mol%), NMP, 120°C, 4 h; (*) from aryl iodide.



4.3. Enhancing Reaction Rates by Microwave Irradiation

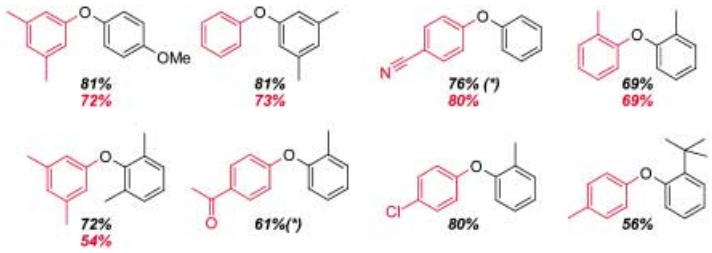
An operationally simplistic protocol using microwave irradiation and based on the conventional thermally induced protocol developed by Buchwald and co-workers was used by He and Wu for the reaction of aryl bromides and iodides with a range of phenols (Scheme 79).[87] The reaction appears to be general with respect to the electronic nature of both reaction partners, although so far only CuI has been examined as the copper catalyst. Aryl chlorides do not need to react under these conditions; even after 14 h at 195°C under microwave irradiation, mainly starting materials were recovered unchanged.



Scheme 79. Key step: Aryl bromide (1 equiv), phenol (2 equiv), CuI (10 mol%), Cs_2CO_3 (2 equiv), NMP, microwave heating, 195 °C, 2 h; (*) from aryl bromide.

4.4. Enhancing Reaction Rates with Phosphazene Bases

Palomo et al. have developed an efficient method for the coupling of aryl halides with phenols in the presence of P_4-*t*Bu base in combination with Cu^I salts in dioxane or toluene.[3] CuBr proved to be the best Cu^I source, but CuCl, CuI, and $(CuOTf)_2{\cdot}C_6H_6$ were also possible. A catalytic version with CuBr (20 mol%) was also established (Scheme 80, yields given in red) but no reaction was observed when Cu^{II} salts were used.



Scheme 80. Key step: Aryl iodide (1 equiv), phenol (2 equiv), CuBr (200 mol%), P_4-*t*Bu (2 equiv), toluene or dioxane, reflux, 16–20 h; (*) from aryl bromide.

5. Aryl Halides as the Aryl Donor: C(aryl)–S Bond Formation

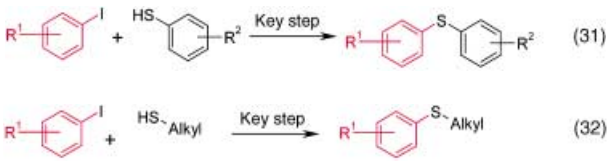
5.1. Phosphazene Bases and Cu^I Catalysis

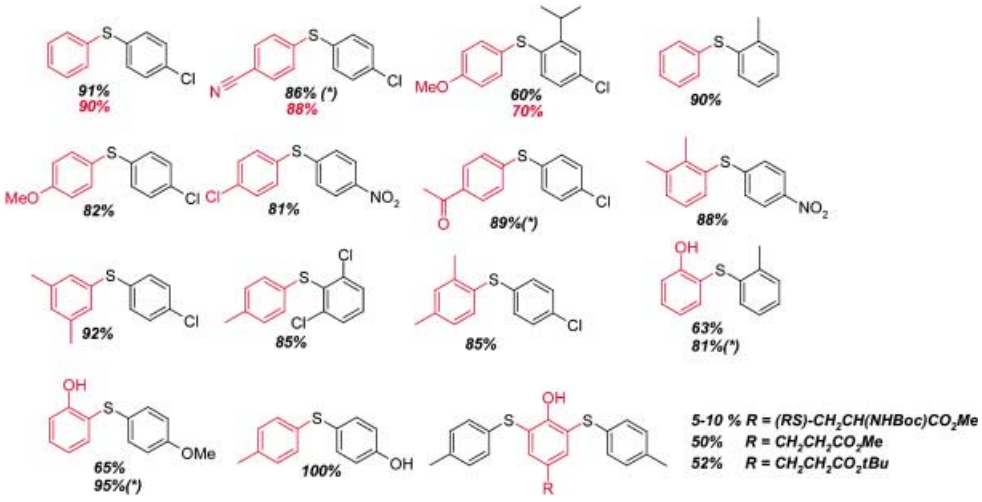
Palomo et al. also used the P_2-Et base (the P_4-*t*Bu base was ineffective) in combination with catalytic amounts of CuBr (20 mol%) to prepare a range of diaryl sulfides in good yields (Scheme 81).[88] Chemoselectivity was observed with dihalo aryl-donor substrates; aryl chlorides do not react at all. As thiophenol is much more reactive than phenol, selective reaction of the sulfur atom was observed in the catalytic version of the reaction. Higher yields were obtained when CuBr was used in stoichiometric amounts. Notably, DBU was an efficient alternative to the phosphazene base, although longer reaction times were required (yields given in red).

5.2. Catalytic Cu^I Methods and Substrate Scope

Transition-metal-mediated C(aryl)–sulfur bond formation is a much less studied transformation.[89] A variety of diaryl sulfides and arylalkyl sulfides have been prepared under the new conditions in the presence of CuI (10 mol%), neocuproine (10 mol%), and NaO*t*Bu base in toluene [Eq. (31) and Eq. (32)].[90]

Under other conditions, especially when Cs_2CO_3 was used as base, significant amounts of the disulfides were formed. It was also shown that [Cu(neocuproine)(PPh_3)Br] (**140**)





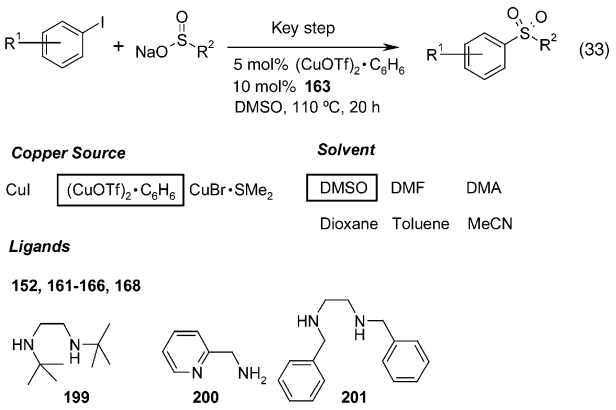
Scheme 81. Key step: Aryl iodide (1 equiv), thiophenol (2 equiv), CuBr (20 mol%), P_2-Et (2 equiv), toluene, reflux, 4–6 h; (*) from aryl bromide.

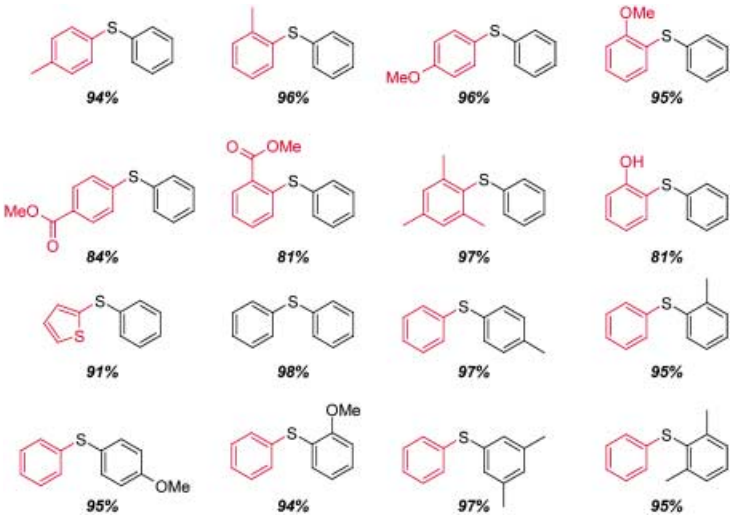
afforded the desired products in yields up to 50%, but was much less efficient overall than CuI/neocuproine/NaO*t*Bu (Scheme 82). K_3PO_4 was also a suitable base for the reaction; Et_3N and K_2CO_3 were not. Alkyl thiolates were also useful nucleophiles in this process (Scheme 83).

Buchwald and co-workers introduced an alternative method for the same transformation which is reported to be experimentally simple, highly general, and displays an exceptional level of functional-group tolerance.[91] The system relies on an optimized copper(I)-catalyzed coupling of aryl iodides with aromatic and alkane thiols in the presence of CuI (5 mol%), K_2CO_3 (2 equiv), and **174** (2 equiv) in 2-propanol at 80°C under argon. Schemes 84–86 show the formidable range of products that can be formed in high yields under these relatively mild conditions.

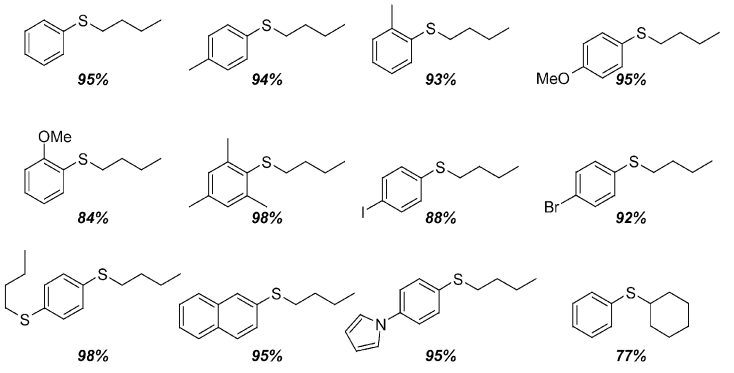
Baskin and Wang have reported a new reaction sequence for the preparation of a range of methylaryl and diaryl sulfones from aryl iodides and the corresponding sulfinic acid salts after screening a range of conditions [Eq. (33)].[92a]

This method tolerates a wide range of functional groups (Scheme 87). The utility of this methodology will rely heavily on efficient access to sulfinic acid salts.[92b] The scope of the reaction is further limited by the fact that aryl bromides do not react.





Scheme 82. Key step: CuI (10 mol%), **156** (10 mol%), NaO*t*Bu, toluene, 110°C, 18–22 h.

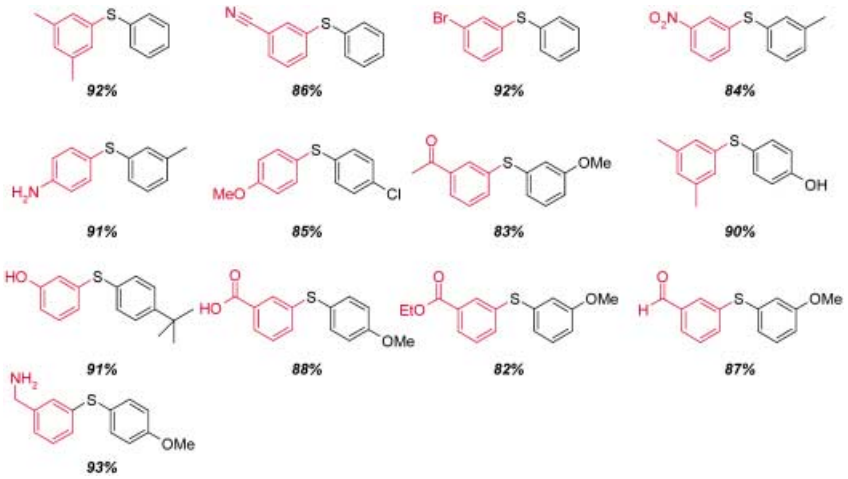


Scheme 83. Key step: CuI (10 mol%), **156** (10 mol%), NaO*t*Bu, toluene, 110°C, 18–20 h.

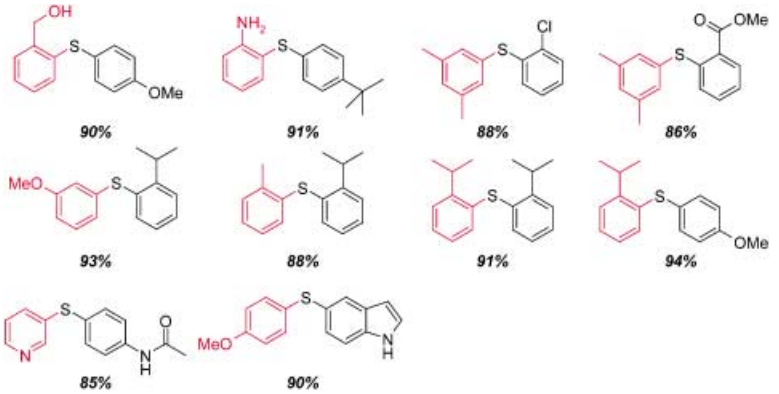
5.3. Aryl Halides as Aryl Donors: Summary

When forming C(aryl)–O, C(aryl)–N, and C(aryl)–S bonds with aryl halides as the aryl donor, the oxidation state of the Cu in the precatalyst plays a decisive role. In general, Cu^I gives the best results, and nearly all recent improvements on the classic Ullmann method have examined the catalytic variation in the presence of Cu^I salts. The first copper-catalyzed method ($(CuOTf)_2/Cs_2CO_3$/phenanthroline) led to numerous studies of different ligand/catalyst/base combinations in the quest for the "holy grail" of room-temperature Ullmann condensation reactions, which so far have not been developed. Thus far it appears that catalytic CuI together with phenanthroline is optimal for a range of substrates, especially when KO*t*Bu is used as base, although reaction temperatures are usually still in excess of 120°C. The discovery of ethylene glycol and *N,N*-diethylsalicylamide as copper ligands is particularly important in C(aryl)–N bond formation. Fewer studies have been carried out on new ligand systems for the related C(aryl)–O and C(aryl)–S bond formation. Important contributions include the use of phosphazene bases to effect both C(aryl)–O and C(aryl)–S bond formation. Microwave irradiation has been shown to enhance the reaction rates of C(aryl)–O bond formation. TMHD as an additive can significantly enhance reaction rates by up to 15-fold. Both concepts need to be further investigated. These reaction processes have been used successfully in several studies into substrate scope, natural product synthesis, as well as in medicinal chemistry.

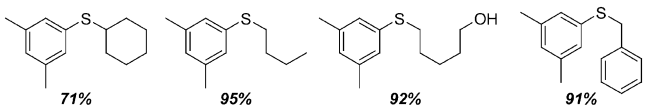
In general, the current state-of-the-art in modern variants of the classic Ullmann condensation has not reached the goal of being able to perform these intermolecular transformations at temperatures less than 80–100°C, apart from one isolated example by



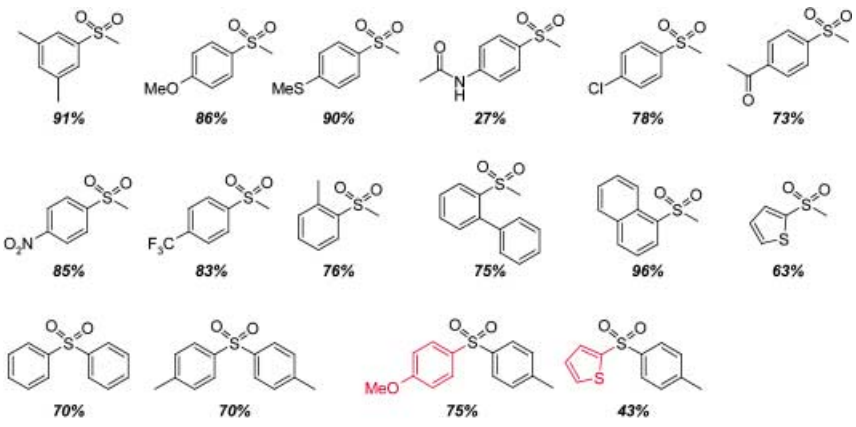
Scheme 84. Key step: Aryl iodide (1 equiv), ArSH (1 equiv), CuI (5 mol%), $HOCH_2CH_2OH$ (**174**) (200 mol%), K_2CO_3, *i*PrOH, 80°C, 18–22 h.



Scheme 85. Key step: Aryl iodide (1 equiv), ArSH (1 equiv), CuI (5 mol%), $HOCH_2CH_2OH$ (**174**) (200 mol%), K_2CO_3, *i*PrOH, 80°C, 18–22 h.



Scheme 86. Key step: Aryl iodide (1 equiv), ArSH (1 equiv), CuI (5 mol%), $HOCH_2CH_2OH$ (**174**) (200 mol%), K_2CO_3, *i*PrOH, 80°C, 18–22 h.

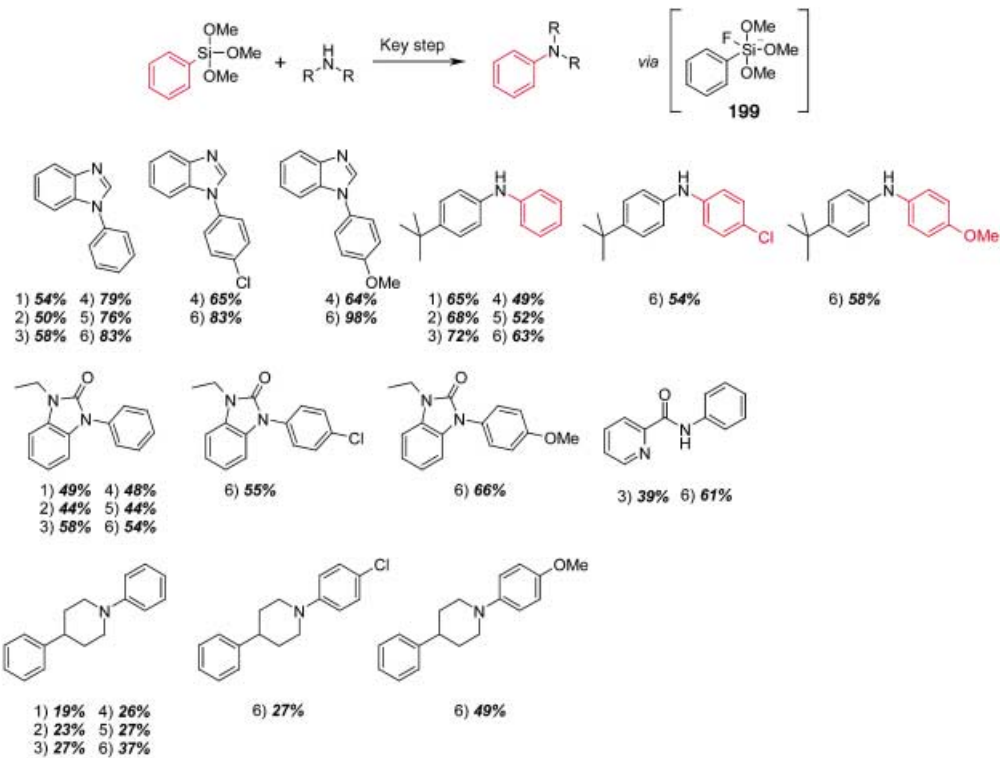


Scheme 87. Key step: Aryl iodide (1 equiv), sodium sulfinate (1.2 equiv), $(CuOTf)_2{\cdot}C_6H_6$ (5 mol%), air, DMSO, 110°C, 20 h.

Buchwald and co-workers for the Goldberg-modified Ullmann condensation reaction.[73] Strikingly, however, Fukuyama and co-workers have shown that intramolecular C(aryl)–N bond formation at room temperature was successful when using 2 equivalents of Cu salt.[61] The key to this mild method relies on the use of CuI and CsOAc, which presumably form CuOAc in situ. The fact that this catalytic system is much less efficient in intermolecular reactions reflects the accelerating effect described by Ma and co-workers on the intermolecular amination of α-and β-amino acids with aryl halides. Buchwald and co-workers recently showed that CuOAc can be used catalytically in a similar intramolecular reaction with *N,N*-diethylsalicylamide as ligand, although the reaction needs higher temperatures for aryl bromides (35–40°C) and aryl chlorides (50–100°C). The range of aryl donors used in the modern Ullmann condensation reaction encompasses aryl iodides, bromides, and chlorides but so far no investigations with pseudohalides (ArOTf, ArONf, etc) have been reported.

6. Aryl Siloxanes as the Aryl Donor: C(aryl)–Heteroatom Bond Formation

The hypervalent siloxane species **199**, which is generated in situ, is an excellent reagent for the one-pot arylation of a suitable N nucleophile in the presence of cupric acetate at room temperature exposed to that atmosphere. This was the first room-temperature *N*-arylation of an aryl iodide in the *absence* of a strong base. The rate of reactions were found to be one order of magnitude quicker than the corresponding reactions with the boronic acids, and no further base, ligand, or molecular sieves were necessary (Scheme 88).[93–94] A one-pot version of the C–N cross-coupling of aryl iodides with a range of amines was also possible. Essentially, the reaction proceeded well with most N nucleophiles, except for piperidine derivatives, and gave yields in excess of 50%. A catalytic version was possible when using 10 mol% of $[\{Cu(OH){\cdot}tmeda\}_2]Cl_2$, and was used for the efficient (69%) phenylation of benzimidazole with phenyltrimethoxysiloxane albeit at 50°C.

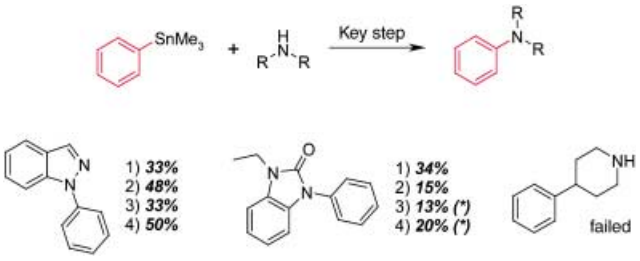


Scheme 88. Key step: 1) $Cu(OAc)_2$ (1.1 equiv), TBAF (2 equiv), pyr (2 equiv), CH_2Cl_2, air, room temperature; 2) with Et_3N; 3) no base; 4) in DMF; 5) with Et_3N in DMF; 6) no base in DMF.

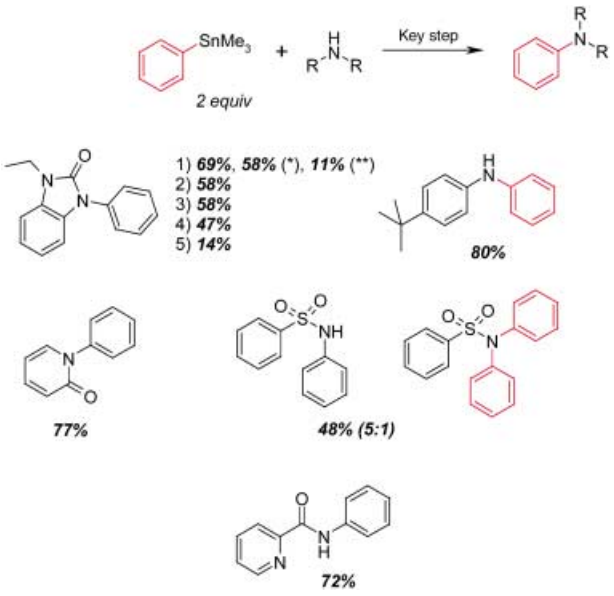
7. Aryl Stannanes as the Aryl Donor: C(aryl)–Heteroatom Bond Formation

In the search for alternative arylating reagents, Lam et al. also demonstrated the use of commercially available aryl stannanes as electrophiles in the copper(II) acetate mediated *N*-arylation (Scheme 89).[95] However, the yields are modest and in some cases the reaction completely fails. In most cases, even after prolonged heating, homocoupling was a major side reaction. Changing the copper source to CuCl resulted in a similar outcome, but, remarkably, the reaction could be effected at room temperature.

An improvement to these modest results soon followed, and it was found that the addition of TBAF to the reaction mixture resulted in enhanced yields in the reaction of benzimidazolones with the fluorophilic phenylstannane. As is the case with the siloxanes, it can be postulated that the addition of fluoride anion can lead to the formation of the hypervalent stannane anion, which accelerates the transmetalation step. Other fluoride sources such as CsF and TASF were also suitable, but pyridinium fluoride was not. A range of products accessible under these conditions are shown in Scheme 90.



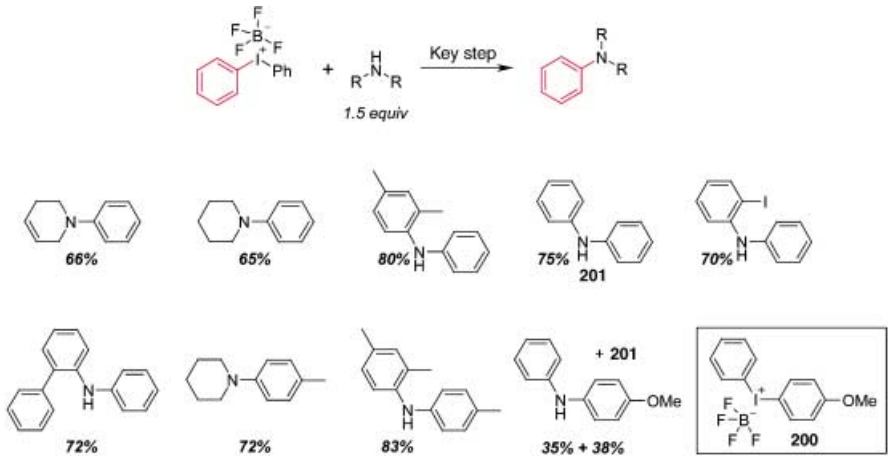
Scheme 89. Key step: 1) $Cu(OAc)_2$ (1.5 equiv), pyr (2 equiv), dioxane, 80 °C, 2 days; 2) $Cu(OAc)_2$ (1.5 equiv), Et_3N (2.0 equiv), dioxane, 80 °C, 2 days; 3) CuCl (5 equiv), pyr (2 equiv), dioxane, room temperature, 2 days; 4) CuCl (5 equiv), pyr (2 equiv), dioxane, room temperature, 2 days; (*) at 80 °C.



Scheme 90. Key step: 1) $Cu(OAc)_2$ (1.1 equiv), TBAF (2 equiv), CH_2Cl_2, room temperature, 2 days; 2) with TBAF and Et_3N; 3) CsF; 4) TASF; 5) with Et_3N; (*) in DMF; (**) in 1,4-dioxane.

8. Iodonium Salts as the Aryl Donor: C(aryl)–Heteroatom Bond Formation

The copper-catalyzed or noncatalytic *N*-arylation of aryl iodonium salts has been known for some time.[96] However, a new milder method employing CuI (10 mol%) and Na_2CO_3 (2 equiv) in CH_2Cl_2 at room temperature allows the *N*-arylation of a number of piperidines and anilines (Scheme 91).[97] In general, the yields of the reactions are good (65–83%), and the reaction times are short (< 6 h). Na_2CO_3 is a better base than K_2CO_3 and Cs_2CO_3, and alkoxides bases such as NaOMe and NaO*t*Bu are ineffective. CuBr and $CuCl_2$ were less effective than CuI. Interestingly, when the unsymmetrical iodonium salt **200** was used, the two aryl groups competitively participated in the transfer of the aryl unit in a 1:1 ratio to give a mixture of **201** and the expected product. This is in line with the observations of Barton and co-workers with unsymmetrical aryl bismuth reagents.

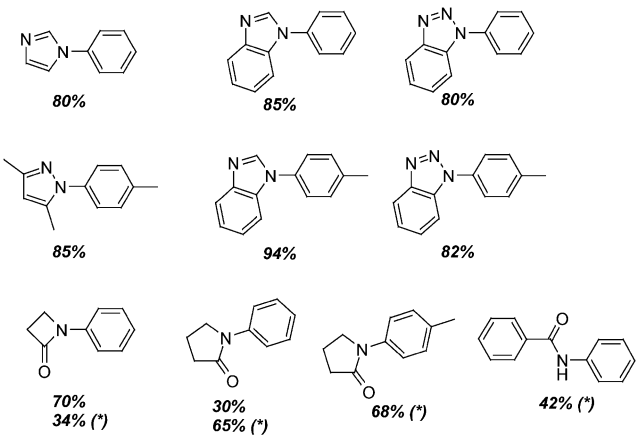


Scheme 91. Key step: CuI (10 mol%), Na_2CO_3 (2 equiv), CH_2Cl_2, room temperature, 6 h.

The procedure was extended to a range of azole derivatives, including imidazole, benzimidazole, benzotriazoles, and a pyrazole. $Cu(acac)_2$ was the preferred catalyst, but the reactions only proceeded to completion at 50 °C (Scheme 92). Furthermore, cyclic secondary amides and benzamide were efficient substrates and provided the desired products under the same reaction protocol, although in these cases CuI was a better catalytic copper ion source.

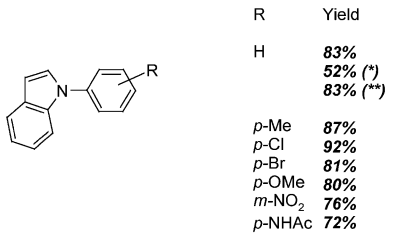
Zhou and Chen later extended the scope of the nucleophiles to indoles. Their catalytic system involved CuI (10 mol%) and K_2CO_3 (3 equiv) in DMF, although much higher temperatures (140–150 °C) were required to afford the desired products in good yields after 6–7 h (Scheme 93).[98]

Tetrazoles (in the form of sodium salts) are also suitable nucleophilic reaction partners in the *N*-arylation of diaryl iodonium salts (Scheme 94).[99] It was observed that in the presence of [Cu^{II}–phenylcyclopropyl carboxylate], the desired coupling product **202** was formed in 35% yield after 18 h at 80 °C; **203** was not observed. The use of a Pd^0 catalyst reduced the reaction times to 6 h. However, mixtures of



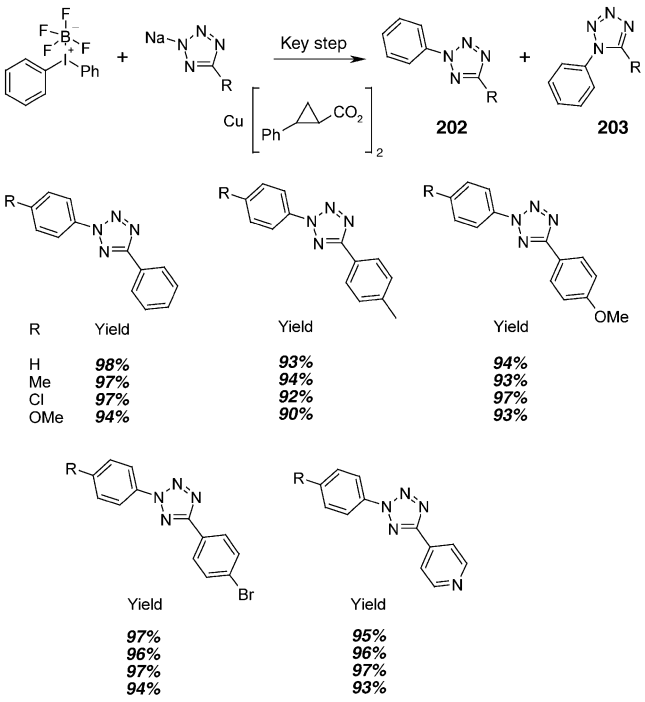
Scheme 92. Key step: $Cu(acac)_2$ (5 mol%), K_2CO_3 (2 equiv), toluene, 50 °C, 6 h; (*) with CuI (10 mol%).

isomers were formed. It was shown that the positive synergistic effects of the two catalysts (Cu^{II} enhances selectivity and Pd^0 leads to better yields) could be combined: When the sodium salt of 5-phenyltetrazole was treated with $Ar_2I^+BF_4^-$ at reflux in *t*BuOH for 8 h in the presence of both Cu^{II} and $[Pd(dba)_2]$, all products were formed in near-quantitative yields as only one isomer. Scheme 94 shows that a range of electron-donating or electron-withdrawing substituents on both the aryl tetrazoles and iodonium moiety are tolerated. Aryl iodides and bromides were examined as suitable electrophiles, but all conditions examined proved to be ineffective.



Scheme 93. Key step: CuI (10 mol%), K_2CO_3 (3 equiv), DMF, 140–150 °C, 6–7 h; (*) with $Cu(OAc)_2$; (**) with $Cu(acac)_2$.

However, the nucleophile species could be changed, and the use of the stannylated tetrazole **204** with either diaryl iodonium salt **205** or **206** resulted in selective arylation in yields of 72 and 75%, respectively, for the 2,5-disubstituted tetrazoles in the presence of $Cu(OAc)_2$ (1.1 equiv) in CH_2Cl_2 at room temperature for 8 h. Products successfully formed under these conditions are shown in Scheme 95.[100] Aryl halides, aryl bismuth reagents, and aryl boronic acids were not suitable aryl donors.



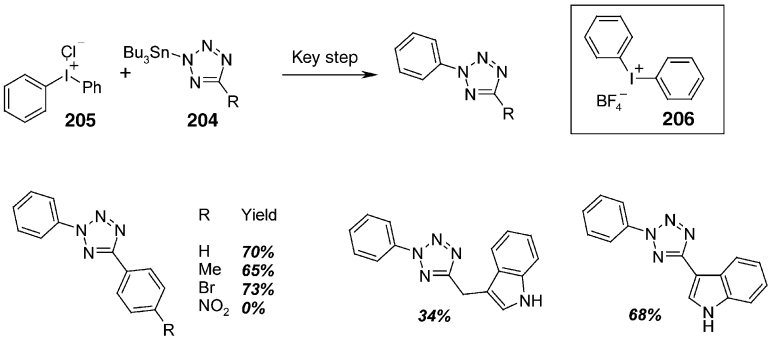
Scheme 94. Key step: [Cu^{II}–phenylcyclopropyl carboxylate] (5 mol%), *rac*-binap/[Pd(dba)$_2$] (5 mol%), *t*BuOH, 80°C, 8 h.

9. Aryl Lead(IV) Triacetates as the Aryl Donor: C(aryl)–Heteroatom Bond Formation

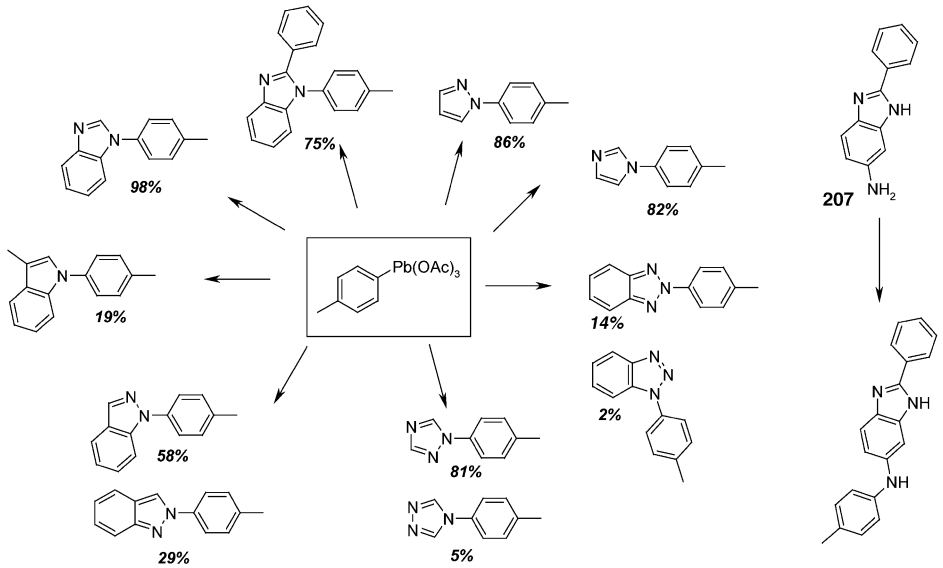
Barton and co-workers previously reported that indoles and carbazoles failed to react under their standard procedure for the arylation of aromatic amines.[104] However, Avendano and co-workers showed that imidazoles, pyrazoles, indazoles, and benzimidazoles were all suitable substrates for *N*-arylation with *p*-tolyllead triacetate (1.1–1.5 equiv) as the aryl donor with the copper catalyst [Cu(OAc)$_2$] in stoichiometric amounts (Scheme 96).[101–102] 1,2,4-Triazole was a poor substrate, but it was shown that the sodium salt reacted much better under the same conditions to afford only one regioisomer in high yield. In a chemoselectivity study, it was shown that the aminobenzimidazole **207** reacted solely at the N atom of the aniline group, although the product was only isolated in 50% yield.

10. Pentavalent Organobismuth Reagents as the Aryl Donor: C(aryl)–Heteroatom Bond Formation

David and Thieffry first showed that triphenylbismuth diacetate was capable of donating a phenyl moiety in the monoarylation of glycols.[103] The original conditions proved to be extremely capricious (solvent specific, need for thermal and photochemical activation, long induction times). Barton and co-workers as well as Dodonov and Gushchin independently reported that the aryl transfer from triarylbismuth diacetates to alcohols proceeded much more smoothly (room temperature, 15 min, various solvents) in the presence of



Scheme 95. Key step: Cu(OAc)$_2$ (1.2 equiv), CH_2Cl_2, room temperature, 8 h.

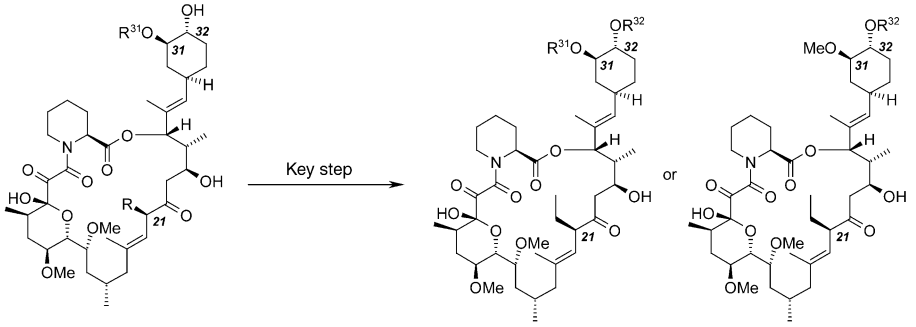


Scheme 96. Key step: Cu(OAc)$_2$ (1.2 equiv), CH_2Cl_2, 4–48 h.

catalytic amounts of copper acetate.[104] Over the last 20 years, the arylation of heteroatoms with aryl bismuthates has become standard and was recently reviewed by Finet et al.[105] As a result, we only discuss the most recent advances in synthesis and application to natural products.

10.1. C(aryl)–O Bond Formation

The natural product ascomycin and its derivative L-683,742 were arylated by researchers at Merck when searching for novel immunosuppresive macrolides similar to FK-506 (Scheme 97).[106] The key arylation reaction worked best under the conditions shown to selectively transfer one aryl group to the secondary alcohol group at C32, albeit in modest yields. In the case of L-683,742, a 1:1 mixture of mono- and diarylated product was formed. Enhanced levels of activity were observed with the simple phenyl ethers and led the team to perform the aryl-transfer reaction with functionalized bismuth derivatives (Table 9).

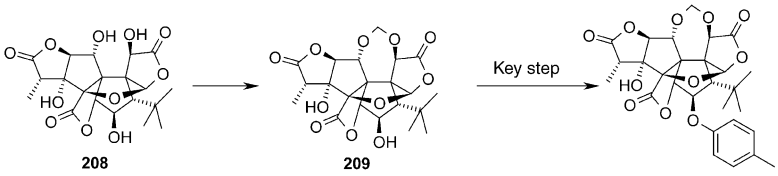


Scheme 97. Key step: $Cu(OAc)_2$ (amount not stated), $BiAr_3(OAc)_2$, peracetic acid (1–1.2 equiv), AcOH, THF/CH_2Cl_2, room temperature.

Table 9: Preparation of derivatives of FK-506 and ascomycin-related macrolides (Scheme 97).

R^{32}	Yield [%]
phenyl	42
2-naphthyl	18
5-indolyl	10
N-methyl-5-indolyl	50
3,5-di-$(CF_3)C_6H_3$	46
p-$CF_3C_6H_4$	51
m-MeC_6H_4	42
p-MeC_6H_4	42
p-$MeSC_6H_4$	14
m-$MeOC_6H_4$	62
p-$MeOC_6H_4$	18
p-$Me_2NC_6H_4$	17
m-OHC_6H_4	34
p-OHC_6H_4	65

Finet and co-workers attempted the selective arylation of the ginkgolide tetrahydroxy compound **208**. Under the standard conditions, only a complex mixture of products was formed. However, protection of the hydroxy groups at C1 and C10 with a methylenedioxy bridge to afford the diol **209** allowed the introduction of the *p*-tolyl moiety at the relatively less-hindered hydroxy functional group at C7, albeit in only 21% yield (Scheme 98).[107]

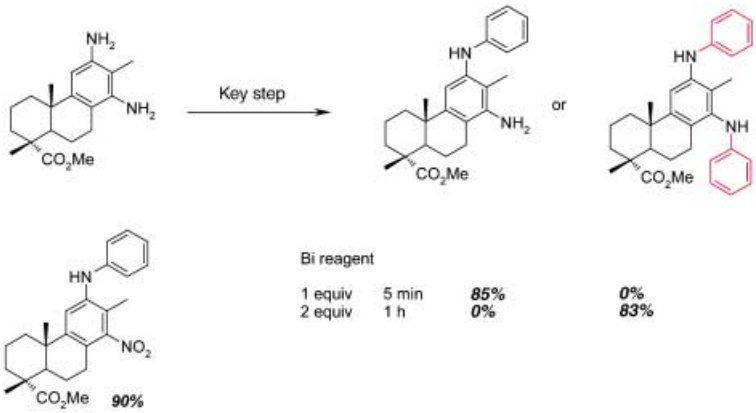


Scheme 98. Key step: $Cu(OAc)_2$ (cat.), $Bi(p\text{-Me-Ar})_3(OAc)_2$, DMAP, CH_2Cl_2, room temperature.

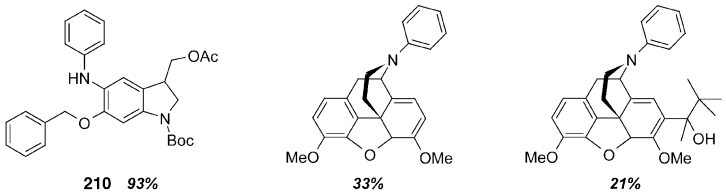
10.2. C(aryl)–N Bond Formation

Selective monoarylation of dehydroabietate derivatives was possible at room temperature in only 5 minutes when using $Cu(Piv)_2$ in catalytic amounts with triphenylbismuth diacetate as the aryl donor (Scheme 99).[108] The di-*N*-arylated product was exclusively formed in good yield in the presence of 2 equivalents of the aryl donor.

In the quest for novel cytotoxic compounds based on the aminoindoline scaffold,[109] an aniline was selectively monoarylated in high yield to give **210**. It was also shown that morphine alkaloids could be efficiently arylated at the N atom (Scheme 100).[110]

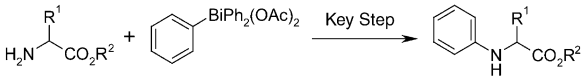


Scheme 99. Key step: $Cu(OPiv)_2$ (cat.), $BiPh_3(OAc)_2$, CH_2Cl_2, room temperature.



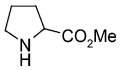
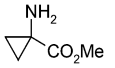
210 93% 33% 21%

Scheme 100. Key step: $Cu(OAc)_2$ (cat.), $Ph_3Bi(OAc)_2$, CH_2Cl_2, room temperature



Scheme 101. Key step: Cu (cat.), $Ph_3Bi(OAc)_2$, CH_2Cl_2, room temperature

Table 10: *N*-arylation of amino acid derivatives with triarylbismuth diacetates as aryl donors (Scheme 101)

R^2	R^1	Yield [%]
H	Et	81
$PhCH_2$	$PhCH_2$	80
$PhCH_2O_2CCH_2$	$PhCH_2$	50
$PhCH_2O_2CCH_2$	$PhCH_2$	58
3-Indolylmethyl	Me	66
(*S*)-*i*Pr	Me	85–92
(*S*)-*i*Bu	Me	86
(*R*)-Ph	Me	92
		61
		94

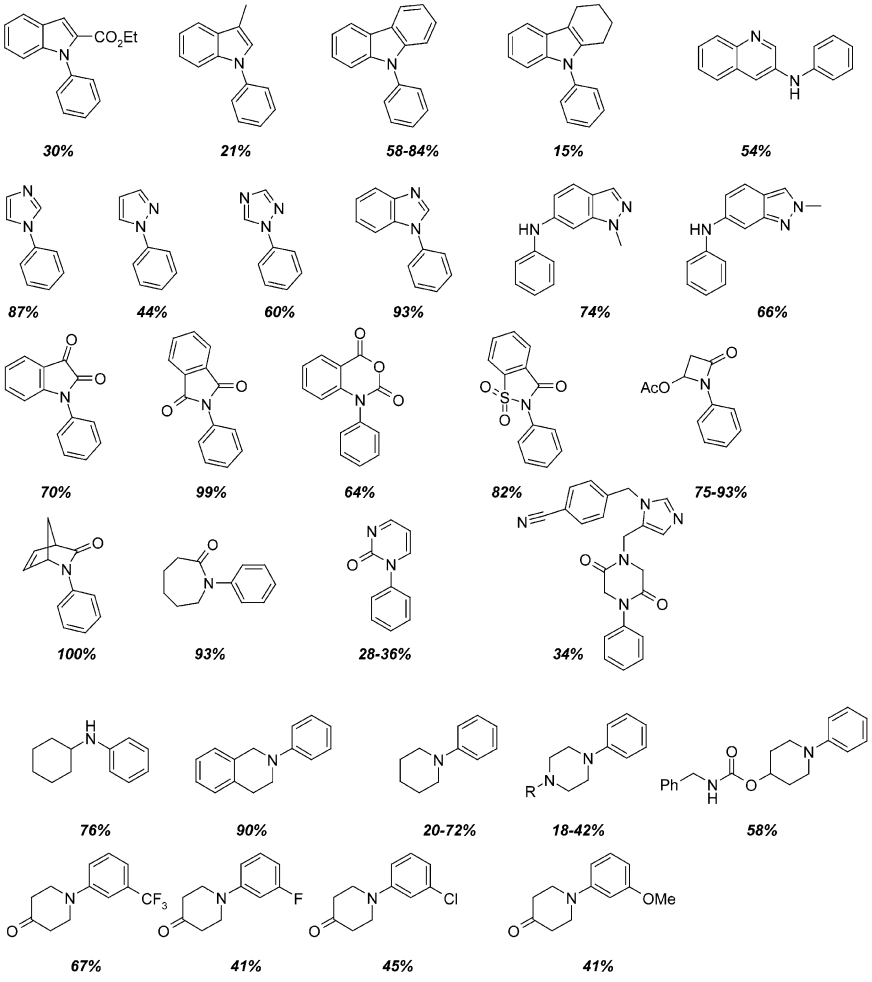
Barton and co-workers had already shown that α-amino acids were not useful aryl acceptors from triaryl bismuth diacetate, but their corresponding esters were indeed efficient substrates (Scheme 101, Table 10).[111] Recently, it was found that the addition of Et_3N has a dramatic effect and increases the yield to 94% for the cyclopropylamino acid derivative.[112]

As can be seen from Table 10, the monoarylation product was formed predominant in all cases when using 1 equivalent of the bismuth reagent. However, if the diarylated product was desired, then 1.5–2 equivalents were needed. The arylation reaction proceeded well for glycine or valine (14 days reaction time). However, for phenylalanine, even after extended reaction times, the diarylated product could not be formed in yields greater than 8%. Notably, no racemization was detected, thus offering a significant advantage over the corresponding palladium-mediated transformation in which full racemization of the products was reported.[113]

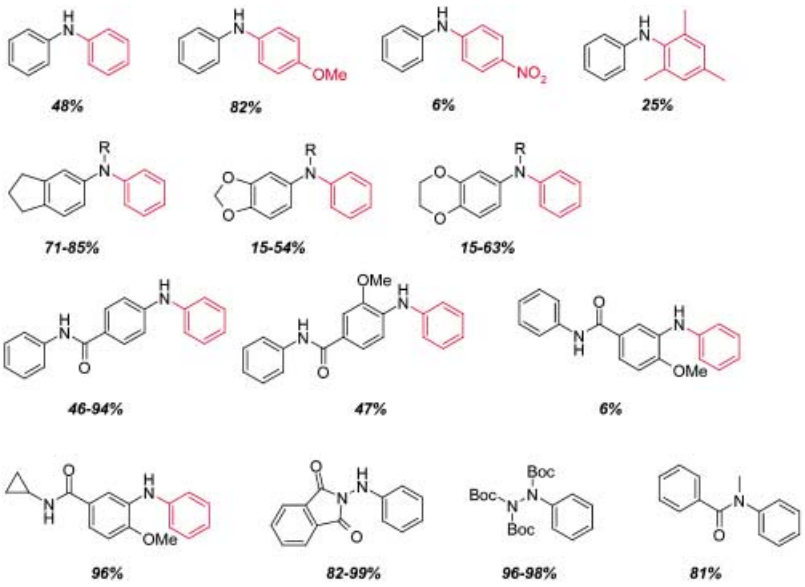
A range of heterocyclic (Scheme 102) and nonheterocyclic (Scheme 103) products were formed under these standard conditions.[17,114–128] These substrates were, in general, the first true exploration of the substrate scope of copper-catalyzed heteroatom-arylation reactions, as can be witnessed in the similarity between the schemes in earlier sections.

11. Pentavalent Organotrifluoroborate Reagents as the Aryl Donor: C(aryl)–N Bond Formation

Batey and Quach have developed a novel protocol for the Cu^{II}-mediated etherification of alcohols (1 equiv) under essentially neutral conditions in the presence of air- and moisture-stable potassium alkenyl and aryl trifluoroborate salts (2 equiv) at room temperature.[129] The optimized reaction procedure involves catalytic amounts of $Cu(OAc)_2$



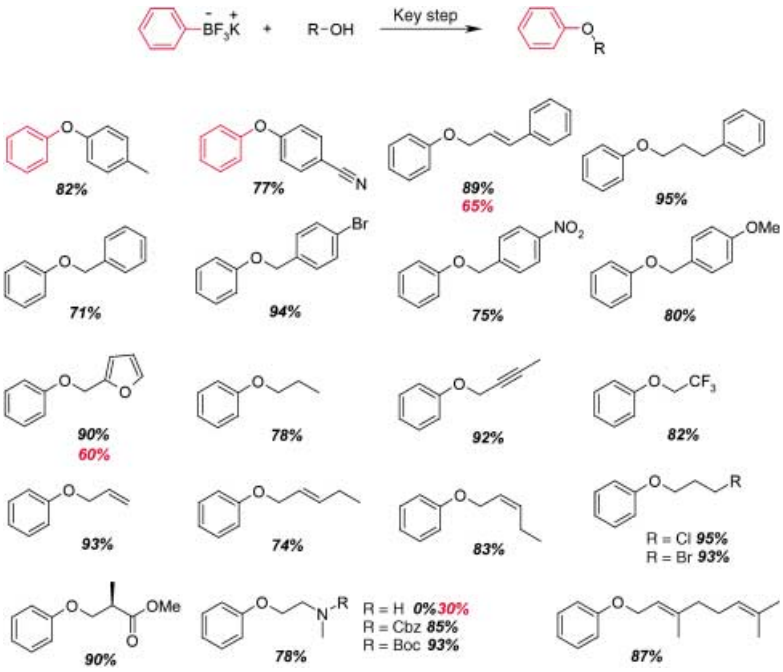
Scheme 102. Key step: $Cu(OAc)_2$, Ar_3Bi, Et_3N or pyr, CH_2Cl_2, room temperature.



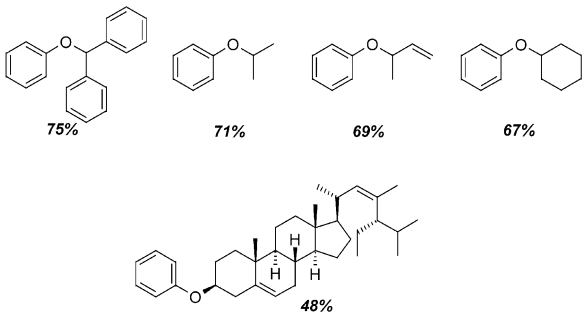
Scheme 103. Key step: $Cu(OAc)_2$, Ph_3Bi, Et_3N or pyr, CH_2Cl_2, room temperature.

(10 mol%) with DMAP (20 mol%) as a ligand in the presence of oxygen and molecular sieves. A variety of aliphatic primary and secondary alcohols as well as phenols are suitable reaction partners, thus displaying a broad functional-group tolerance (Schemes 104 and 105). A comparison between the efficiency of these reagents with that of the aryl boronic acids (yields given in red) revealed that the organotrifluoroborate salts give higher yields. However, although standard methods to prepare these salts are known,[130] increased commercial availability is required for this method to attract more widespread use.

A range of secondary alcohols also participate in the reaction, although tertiary alcohols do not react under the previously optimized conditions (Scheme 105). Moreover, the nature of the electrophilic reaction partner is important, and the electron-rich 4-methoxyphenyltrifluoroborate gave the best results, whereas the electron-deficient 4-acetylphenyltrifluoroborate did not afford any product when treated with 2-furfuryl alcohol (Scheme 106). Alkenyl trifluoroborate salts were also found to be effective reaction partners, but alkyl trifluoroborate derivatives did not react, presumably as a result of the low efficiency of transmetalation with Cu salts.



Scheme 104. Key step: Potassium aryl trifluoroborate (2 equiv), alcohol (1 equiv), $Cu(OAc)_2 \cdot H_2O$ (10 mol%), DMAP (20 mol%), O_2, 4 Å molecular sieves, CH_2Cl_2, room temperature, 24 h.

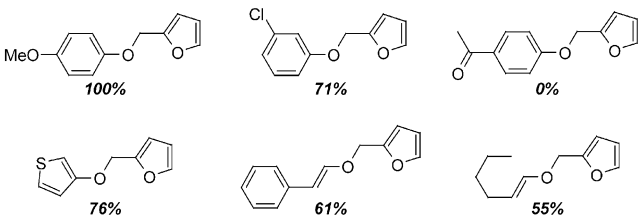


Scheme 105. Key step: Potassium aryl trifluoroborate (2 equiv), alcohol (1.0 equiv), $Cu(OAc)_2H_2O$ (10 mol%), DMAP (20 mol%), O_2, 4 Å molecular sieves, CH_2Cl_2, room temperature, 24 h.

12. Mechanistic Considerations for the Copper-Mediated Heteroatom-Arylation Reaction

The mechanism of the Ullmann arylation of alcohols has not been well-established.[131] As most studies devoted to the use of this reaction are synthetically driven, only themes and proposals for the mechanistic rationale have been discussed, some which are relatively speculative in nature. In general, much still has to be done for all types of metal-mediated C–heteroatom bond formation, including all Group 8–10 metals. Hartwig already commented that "In general, catalytic organometallic chemistry that forms carbon–heteroatom bonds is less developed than that forming C–C bonds and is less well understood".[11a]

As can be seen from the many examples in this Review, copper sources are diverse, but, in general, the most universal starting copper source is a Cu^{I} or Cu^{II} species. It seems most likely that Cu^{II} is not the catalytic species in the reaction. Furthermore, it has been ascertained that radical mechanisms are ruled out as the reactions are not inhibited when radical scavenger additives (such as 1,1-diphenylethylene) are included. For copper-mediated C(aryl)–heteroatom bond formation, the original investigations and proposals by



Scheme 106. Key step: Potassium aryltrifluoroborate (2 equiv), alcohol (1.0 equiv), $Cu(OAc)_2H_2O$ (10 mol%), DMAP (20 mol%), O_2, 4 Å molecular sieves, CH_2Cl_2, room temperature, 24 h.

Lockhardt[132] and by Barton et al.[133] dealing with the intermediacy of hypervalent copper(III) species during the reactions of diaryl iodonium salts and pentavalent bismuth reagents are the most prevailing mechanistic suggestions.

Aryl donors can be as follows:

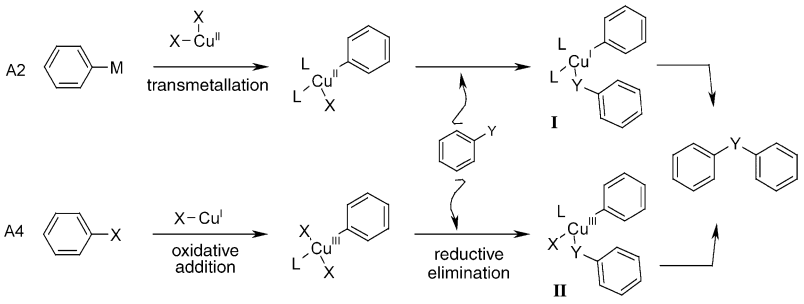
A1 = Hypervalent reagents (Sb^{5+}, Pb^{4+}, I^{3+})
A2 = Low-valent organometallic reagents (Bi^{3+}, B^{4+}, Si^{4+}, Sn^{4+}), stoichiometric in copper
A3 = Low-valent organometallic reagents with a co-oxidant, catalytic in copper
A4 = Aryl halides (I, Br, Cl), no examples of F, or pseudohalides OTf, ONf, etc.

A1: The mechanism involved in the transfer of an aryl moiety to X (X = heteroatom) has been rationalized with the following steps (Scheme 107):

1) Cu^{II} reduced to Cu^{I} by a nucleophile.
2) Cu^{I} species **I** forms **II**, another Cu^{I} species, by ligand exchange.
3) Oxidative addition to the Cu^{I} species **II** forms a Cu^{III} species.
4) The latter undergoes reductive elimination of the product, and the active catalytic species **I** is regenerated.

A2: Evans speculated that the paths of A2 and A4 intersect at the plausible aryl copper phenoxide intermediates, which are both capable of forming the observed diaryl ether products by reductive elimination (Scheme 108). The unresolved issue is whether the oxidation state of the intermediate is Cu^{I} or Cu^{III} or indeed an equilibrium (or disproportionation) controlled by the reduction potential of the Cu couple. It was later shown that the presence of an oxidizing atmosphere (air, oxygen, or co-oxidant) improves the process of the arylation reaction and lends some substantial supporting evidence that perhaps **I** can be oxidized to **II** prior to the reductive elimination.

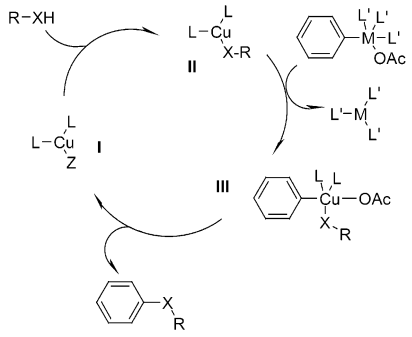
1) Transmetalation of boronic acid and copper catalyst.
2) N nucleophile coordinates to Cu^{II}: reduction potential of the Cu^{III}/Cu^{II} couple decreases
3) Oxygen oxidizes Cu^{II} to Cu^{III} (putative) ready for reductive elimination.
4) Product eliminated and Cu^{I} species ready to regenerate catalytic species.



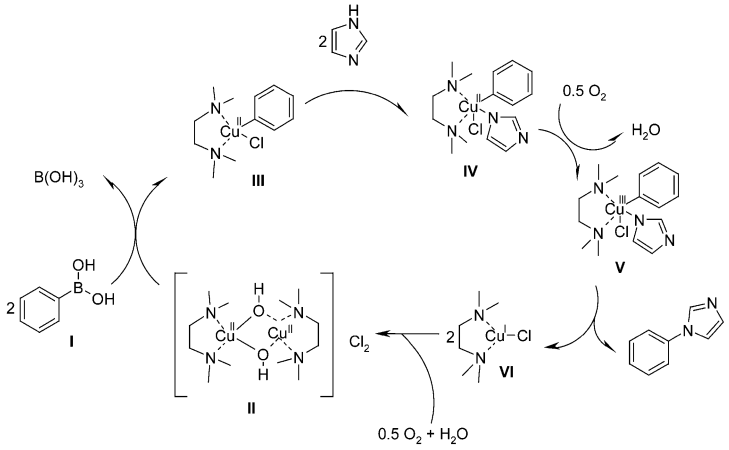
Scheme 108. Plausible mechanism for the copper-catalyzed arylation with class A2 and A4 reagents. M = $B(OH)_2$, $BiAr_2(OAc)_2$, or $SnBu_3$; X = Cl, Br, I; Y = NH, O.

A3: Building on this proposal, Collman and Zhong[47] have proposed the follow catalytic cycle for the coupling of imidazole with aryl boronic acids (Scheme 109). Although, as yet, no experimental evidence exists for any of the putative steps, the hypothesis can be supported.[134] The individual steps may include:

1) Transmetalation of the aryl boronic acid **I** with the catalyst **II**, generating the Cu^{II} species **III**.
2) Coordination of the imidazole nucleophile to give **IV**.
3) Oxidation of **IV** to **V** in the presence of oxygen or air.
4) Reductive elimination of the desired product and oxidation to regenerate the active bis-μ-hydroxo Cu^{II} catalytic species **II** via **VI**.

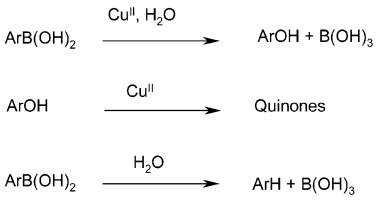


Scheme 107. Catalytic cycle for the copper-catalyzed arylation with polyvalent reagents. Y = NH,O; L, Z = exchangeable ligands; M = polyvalent center.



Scheme 109. Catalytic cycle for the arylation of imidazole with phenylboronic acid and $[\{Cu(\mu\text{-}OH)(tmeda)\}_2]Cl_2$ as catalyst.

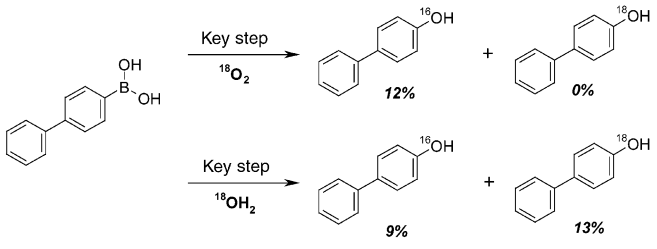
During these processes (catalytic or stoichiometric), possible side reactions do occur and are shown in Scheme 110). These explain why the use of >1 equivalent



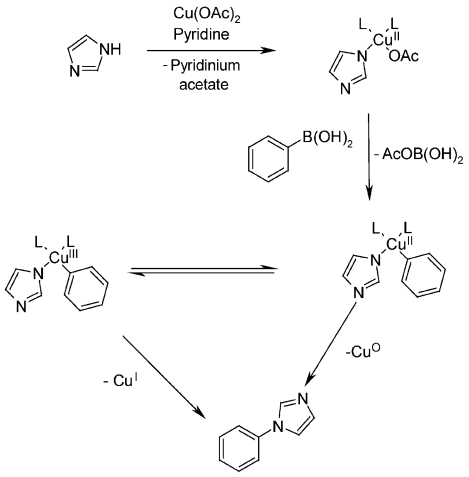
Scheme 110. Possible side reactions in the arylation of imidazole with aryl boronic acids.

of the boronic acid is necessary. Furthermore, during the oxidation of Cu^{II} to Cu^{III}, hydrogen peroxide is produced, which can decrease the yields of the reaction as a result of a reaction with the aryl boronic acid. This may also explain why >1 equivalent of the aryl boronic acid results in enhanced yields.[135] Moreover, the aryl boronic acid can form triaryl boroxines[136] and in doing so forms water, which can be removed from the reaction by molecular sieves. Evans and co-workers postulated that phenolic products are formed as a result of the competitive arylation of water formed during the reaction process. Lam and co-workers conducted oxygen isotope incorporation studies to validate Evans's hypotheses.[39] The use of $^{18}O_2$ demonstrated that the phenols are not formed from atmospheric oxygen, which suggests that the phenol is formed from water produced during the reaction. Indeed, when $H_2{}^{18}O$ was used, the isotope label was incorporated into the biphenylphenol product, as shown (Scheme 111). An alternative proposal follows the sequence: a) coordination and deprotonation; b) transmetalation; c) oxidation or disproportionation; and d) reductive elimination (Scheme 112).

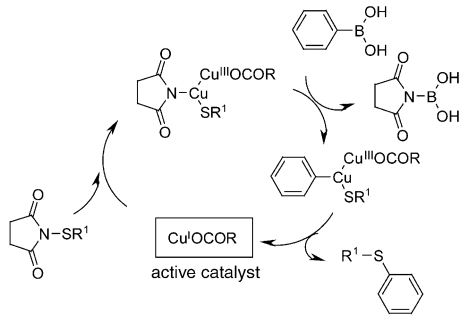
Liebeskind et al. have reported a novel, interesting, mild, non-base copper(I)-mediated strategy for the synthesis of thioethers. They proposed that the mechanism for alkylaryl sulfide formation does not parallel that of the O and N (see Section 11) counterparts but instead, it is more likely that a Cu^{I}-mediated transformation takes place (due to the facile oxidation of thiols to disulfides by Cu^{II}).[56] This postulate was supported by the preparation of diphenylsulfide (74%) from the reaction between phenylboronic acid and Cu^{I}–3-methylsalicylate (CuMeSal) in DMA at 100°C for 18 h (Section 2.4.2). A possible mechanism for the copper-catalyzed coupling of boronic acids and *N*-thioimides proceeds through a reversible oxidative addition of the *N*-thioimide to Cu^{I} followed by transmetalation from boron to copper. Regeneration of the active catalytic Cu^{I} species is viable through carbon–sulfur bond reductive elimination to afford the observed thioether product. Again, the postulated mechanism proceeds through Cu^{I} and Cu^{III} intermediates (Scheme 113).



Scheme 111. Oxygen-isotope-incorporation studies: Under the conditions for the Ullmann reaction, ^{18}O from $H_2{}^{18}O$ is incorporated into phenol derivatives.



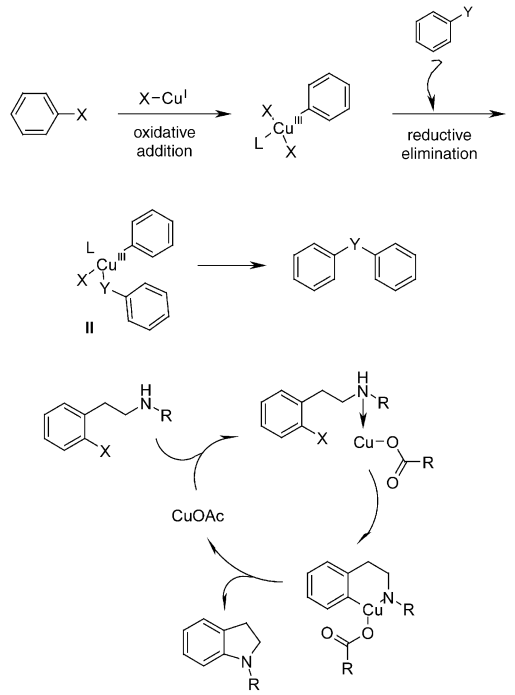
Scheme 112. Alternative mechanism for the copper-catalyzed arylation of imidazole with aryl boronic acids.



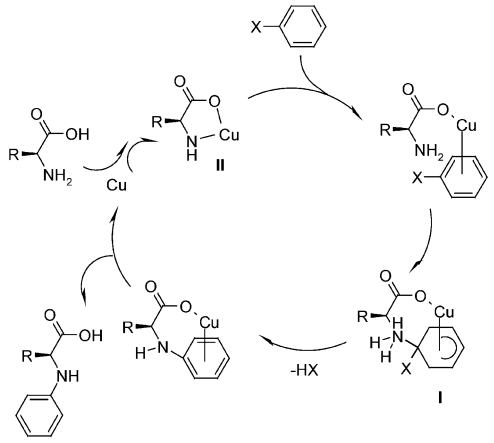
Scheme 113. Plausible catalytic cycle for the copper-catalyzed arylation of *N*-thioimides with boronic acids.

A4: The Ullmann reaction may proceed as shown in Scheme 114, and an intramolecular variant is also given. A possible reaction mechanism was proposed which proceeds via the air-sensitive CuOAc. This was not cross-checked by adding the commercially available material as a control. Interestingly, another advantage over the palladium-mediated reaction was noted in which a *meta*-iodo substrate did indeed produce the desired product and not only a product formed from the oxidative addition of copper to the aryl iodide.[61]

The nature of the carboxylate ligand has a significant accelerating effect on the heteroatom arylation reaction. Ma and co-workers proposed a catalytic cycle (Scheme 115) based on some underlying principles. A mechanistic rational



Scheme 114. Plausible mechanism for the copper-catalyzed Ullmann reaction with aryl halides as aryl donors. Reductive elimination releases the coupling product. X = Cl, Br, I; Y = NH, O.



Scheme 115. Catalytic cycle for the copper-catalyzed *N*-arylation of amino acids.

discussing the accelerating effects of α-, β-, and γ-amino acids has been proposed. α-Amino acids can chelate copper ions through the amine and acid functionalities, and since the π complex mechanism is a common proposal for the mechanism of the Ullmann condensation, the intermediate **I** is proposed to form as follows:

1) Formation of the amino acid–Cu^{I} salt **II**.
2) π Complex formation with an aryl halide.
3) Intramolecular S_NAr reaction to form **I** as a transition-state intermediate.
4) Elimination of HX (base-mediated) to form the π complex copper salt of the desired *N*-arylated product.

A similar mechanism has been proposed for β-amino acids.

13. Summary and Outlook

The copper-mediated C(aryl)–O, C(aryl)–N, and C(aryl)–S bond formation is a powerful reaction used routinely for the preparation of a wide variety of compounds ranging from simple to complex molecular targets. Leading contributions have clearly been the use of aryl boronic acids as the aryl donor, which react efficiently in the presence of Cu^{II} sources such as $Cu(OAc)_2$ at room temperature to form products of the Ullmann condensation reaction. When using aryl halides as the aryl donor, major progress has been made in the presence of Cu^{I} sources, in particular CuOAc in combination with chelating and/or solubilizing ligands in approaching the ultimate goal of a room-temperature Ullmann condensation reaction. So far, this goal has only been reached in the intramolecular transformation.

In general it is apparent from a synthetic perspective that the recent discoveries described in this Review have had a considerable impact in organic synthesis. This is represented by the increasing amount of publications in the areas encompassing a) substrate design, b) optimization of reaction conditions, bases, additives, time, solvent, c) nature of the copper species involved, and d) introduction of new ligands, paralleling to a small extent the progress made in the corresponding palladium-mediated arylation reactions. However, in the Pd-mediated field, today's state-of-the-art has been the incorporation of iterative design cycles in the use and developmental design of new ligands to offer the synthetic chemists a bountiful toolbox of opportunities for the synthesis of a wide range of targets. To continue the initial rapid progress of the copper-mediated arylation, still relatively in its infancy, it is imperative to apply many of the principles precedented in the palladium-mediated work. Despite many important contributions and significant progress, many challenges remain. To meet these, many more mechanistic studies have to be performed to shed more light on the copper species involved during the reactions, including identifying the substrate/ligand/catalyst intermediates.

However, with few exceptions, most of the work carried out thus far reports yields after chromatographic purification and in some case yields judged by GC are presented. For this process to be used more widely in industry, it is prudent to encourage the reporting of ICP analyses of the copper residues within final products to give an adequate indication of product purity. In particular, for a major impact on industry, higher turnover numbers of the catalytic cycles must be established and new and effective supported ligand/catalyst combinations are necessary. Clearly, the low cost price [Pd = \$1000 per ounce; Cu = \$0.1 per ounce] of copper relative to palladium offers a distinct financial advantage on an industrial scale.

Many substrates fail to react under some of the reaction conditions, and the choice of reaction conditions is still open to trial and error attempts. Improvement in both scope and the mildness of the reaction conditions are necessary for all of the methods described above. Owing to the increased amount of research work being conducted in this field, major steps to solve these challenges should emerge in the near future. The continued development and discovery of new and efficient

aryl-transfer reagents[137] is also essential to keep pace with competing methods[138] to prepare the usual products from C(aryl)–O, C(aryl)–N, and C(aryl)–S bond formation.

Addendum

Further improvements, novel applications, and new classes of Ullmann condensation reactions are continually appearing in the literature. The latest developments are described below.

Snapper, Hoveyda, and co-workers used a $Cu(OAc)_2$-mediated formation of a macrocyclic diaryl ether as a key step in the stereoselective total synthesis of the anti-HIV agent chloropeptin I.[139] The reaction was carried out under dilute conditions with 10 equivalents of Et_3N. Methanol (10 equiv) was used as an additive to increase the solubility of the copper salt and in situ formation of the dimethylboronate. Takeya and co-workers investigated the use of a variety of bases and copper ligands in a similar diaryl ether formation, as a significant amount of protodeborylated products was formed. In the synthesis of two cycloisodityrosines, the use of DMAP allowed respectable yields (35–56%) of the desired products (free from epimerization), with less than 6% of the side product formed under dilute reaction conditions.[140]

Sagar et al. reported the synthesis of symmetrical diaryl ethers through the arylation of phenols generated in situ from boronic acids.[141] Their method is complementary to that of Petasis and co-workers.[32] The products were all formed in high yields using water (rather than H_2O_2 previously used) as a key additive (10–12 equiv) with $Cu(OAc)_2$ and Et_3N.

Kabalka and Guchhait have reported the room temperature synthesis of diprotected monosubstituted hydrazine derivatives by the reaction of *t*-butyl carbazates and aryl boronic acids in the presence of CuCl with pyridine as base and air as co-oxidant.[142]

The introduction of deanol (2-(*N,N*-dimethylamino)ethanol) as a solvent for the amination of aryl halides by Twieg and co-workers is significant. A wide range of substrates, copper salts, additive contents, and reaction temperatures were studied.[143]

Ma et al. elegantly used *N*-methylglycine and L-proline as accelerating ligands in the formation of aryl amines. The reaction temperatures used (40–90 °C) are some of the lowest reported to date to effect the Ullmann condensation of aryl halides.[144] Under these conditions and with *N,N*-dimethylglycine·HCl salt (instead of *N*-methylglycine or L-proline), a range of diaryl ethers were prepared at only 90 °C from aryl bromides or iodides and substituted phenols.[145]

Wu et al. used microwave radiation to effect the amination of a number or azole substrates with (*S*)-1-(3-bromophenyl)-ethylamine as the electrophile in the presence of CuI (10 mol%) with K_2CO_3 in NMP as solvent.[146] Under the same conditions, Wu and He effected the *N* arylation of a number of sulfonamides with aryl bromides and iodides,[147] as well as *S* arylation of a thiophenols with aryl bromides and iodides.[148]

Buchwald and co-workers compared the regioselective arylation of difunctionalized nucleophiles with copper and palladium catalysts, which lead to complementary products:[149] Aniline derivatives with carbamoyl, indolyl, or aliphatic amino functions are arylated at the nitrogen atom of the aniline function in the presence of palladium catalysts. When copper catalysts are used, mainly the other functional group is arylated. Although outside the scope of this Review, the reaction conditions developed initially by Buchwald and co-workers for the arylation of amides has proven to be general for the amidation of vinyl halides, providing rapid access to a wide range of enamides in good yields.[150] Miyashita and co-workers recently reported the total synthesis of scytophcin C in which a crucial terminal amidation of a vinyl iodide was used at an advanced stage.[151] Under the Buchwald-modified Goldberg amidation conditions, the desired coupling product was formed in 85% yield.

Pellon Comdom and Docampo Palacious have shown that water can be used as the solvent in the copper- and ultrasound-mediated preparation of 2-carboxy-substituted diphenyl ethers.[152]]

Heaney and co-workers have illustrated the desymmetrization of resorcinol with 3-benyloxyiodobenzene as a substrate with a range of alcohol donors under previously developed conditions (CuI, 1,10-phenanthroline, Cs_2CO_3).[154]

Again, although outside the scope of this Review, the reaction conditions developed initially by Lam and co-workers for the arylation of NH and OH substrates with aryl boronic acids has proven to be general, and the use of vinyl boronic acids provided rapid access to a wide range of products in good yields. Both stoichiometric and catalytic reactions (with or without co-oxidants) were developed for $Cu(OAc)_2$- and base-mediated *O* and *N* vinylation. The range of products formed were then elaborated as protecting groups or as substrates for ring-closing metathesis or for Simmons–Smith cyclopropanations.[154]

This Review has dealt with *O, N*, and *S* arylations, but other C(aryl)–heteroatom bond formations are possible. Recently, the introduction of copper-mediated methods for the formation of C(aryl)–Se bonds was demonstrated by Gujadhur and Venkataraman, who effected the Cu^I-mediated cross-coupling of aryl iodides with phenylselenol.[155] The best reaction conditions involved the use of CuI (10 mol%), neocuproine, and NaO*t*Bu (or K_2CO_3) as base in toluene at 100 °C. Recently, Taniguchi and Onami showed that unsymmetrical diaryl selenides can be formed from aryl iodides and diphenyl selenides in the presence of Cu_2O and Mg under neutral conditions.[156] Beletskaya et al. used a complimentary approach with $Bu_3SnSeAr$ and aryl bromides to prepare unsymmetrical diaryl selenides.[157] Buchwald and co-workers[158] and Venkataraman and Van Allen[159] reported improved conditions for copper-catalyzed C–P bond formations from aryl and vinyl iodides.

Abbreviations

Ac	acetyl
acac	acetylacetone
Bn	benzyl

Boc	*tert*-butoxycarbonyl
cat.	catalytic
Cbz	benzyloxycarbonyl
CNS	Central Nervous System
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N,N*-diisopropylethylamine
DMA	dimethylacetamide
DME	1,2,-dimethoxyethane
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
Fmoc	9-fluorenylmethyl
ICP	inductively coupled plasma
*m*CPBA	*m*-chloroperoxybenzoic acid
NMO	4-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrolidinone
Ns	2-nitrobenzenesulfonamide
PEG	poly(ethylene glycol)
phen	phenanthroline
Piv	pivaloyl
pyr	pyridine
P_2-Et	1-ethyl-2,2,4,4,4-pentakis(dimethylamino)-2Λ^5-catenadi(phosphazene)
P_4-*t*Bu	1-*tert*-butyl-2,2,4,4,4-pentakis(dimethylamino)-2Λ^5-catenadi(phosphazene)
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEMPO	tetramethylpiperidinyloxy
TFA	trifluoroacetic acid
tmeda	tetramethylethylenediamine
TMHD	2,2,6,6-tetramethylheptane-3,5-dione

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