Synthesis A. Vijayan et al. Review

Advances in Carbon–Element Bond Construction under Chan–Lam Cross-Coupling Conditions: A Second Decade

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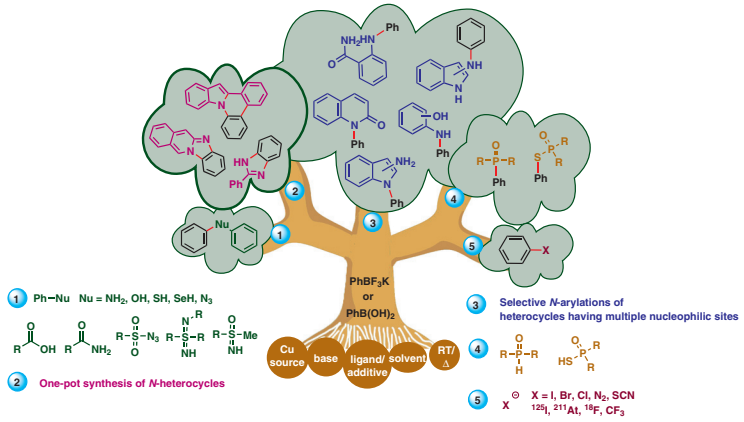
In memory of Siva Reddy



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Abstract Copper-mediated carbon–heteroatom bond-forming reactions involving a wide range of substrates have been in the spotlight for many organic chemists. This review highlights developments between 2010 and 2019 in both stoichiometric and catalytic copper-mediated reactions, and also examples of nickel-mediated reactions, under modified Chan–Lam cross-coupling conditions using various nucleophiles; examples include chemo- and regioselective N-arylations or O-arylations. The utilization of various nucleophiles as coupling partners together with reaction optimization (including the choice of copper source, ligands, base, and other additives), limitations, scope, and mechanisms are examined; these have benefitted the development of efficient and milder methods. The synthesis of medicinally valuable or pharmaceutically important nitrogen heterocycles, including isotope-labeled compounds, is also included. Chan–Lam coupling reaction can now form twelve different C–element bonds, making it one of the most diverse and mild reactions known in organic chemistry.

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Key words Chan–Lam coupling, C–O bond formation, C–N bond formation, N-arylation, copper-catalyzed, copper mediated

1 Introduction

Metal-mediated aromatic/heteroaromatic carbon–heteroatom bond-forming reactions have been used as an efficient protocol for the construction of (hetero)aryl motifs, which are ubiquitous in many natural products and pharmaceutically important compounds.[1] In addition, the construction of heteroaromatic building blocks for the synthesis of pharmaceuticals, crop protection chemicals, and materials in a site-selective manner is highly recognized by organic chemists. The discovery of novel and optimized catalytic systems for functionalizing reactants with multiple heteroatom sites using Cu-mediated coupling reactions is a great challenge for the synthetic community. The synthesis of complex systems using minimum synthetic operations via the selective N- or O-arylation of heteroaromatic molecules is promising in this regard.

During the past few decades, different groups have developed promising synthetic protocols for the formation of C–N or C–O bonds, which can overcome the drawbacks of the original Ullmann and Goldberg procedures.[2,3] The exploration of Pd-catalyzed amination reactions by Buchwald[4] and Hartwig[5] marked an era in the construction of a wide variety of aromatic amines, which cannot be accomplished through the reaction conditions previously reported. However, this strategy also has several limitations, such as sensitivity to air and moisture, relatively high tem-

Biographical Sketches

Ajesh Vijayan is a native of Aluva (Kerala), India. He obtained his B.Sc. degree in chemistry from Union Christian College, Aluva (Mahatma Gandhi University, Kottayam), in 2009 and his M.Sc. Degree in chemistry from Bharathiar University, Coimbatore in 2011. He did Ph.D. in organic chemistry at CSIR-NIIST, Thiruvananthapuram under the guidance of Dr. K. V. Radhakrishnan on the topic 'Construction of carbocycles and heterocycles utilizing the steric strain in heterobicyclic olefins'. Later, he joined Christ College, Irinjalakuda, Kerala as an Assistant Professor ADHOC. Currently, he is working as an Assistant Professor in the Department of Chemistry at CHRIST (Deemed to be University), Bengaluru, India.

Desaboini Nageswara Rao received his M.Sc. in organic chemistry from Osmania University, Hyderabad, India in 2009. He completed his Ph.D. degree in 2016 under the supervision of Prof. Parthasarathi Das at Indian Institute of Integrative Medicine (CSIR-IIIM), Jammu on the research topic 'Studies directed towards the formation of C–N and C–C bonds for the synthesis of novel nitrogenated heterocycles'. Soon after, he joined Piramal Discovery Solutions in Ahmedabad, India as a research scientist. Currently, he is working as a Post-doctoral Research Associate at the University of Massachusetts Medical School, USA in the laboratory of Prof. Celia A. Schiffer on antiviral drug discovery with avoiding drug resistance. Particularly on the design, synthesis, and their structure activity relationship studies for the discovery of more potent HCV (NS3/4A) and HIV-1 protease inhibitors against drug resistance pathogens using structure-based drug design approach.

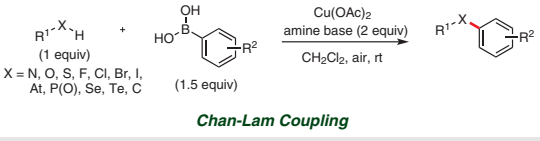
K. V. Radhakrishnan received his higher education (B.Sc. and M.Sc. degrees) from Christ College, Irinjalakuda, Kerala, India (University of Calicut). He completed his Ph.D. in synthetic organic chemistry from the University of Kerala in 1998 under the supervision of Dr. Vijay Nair at NIIST (CSIR), Trivandrum. Subsequently he held postdoctoral positions at Tohoku University, Sendai, Japan with Professor Yoshinori Yamamoto, Molecumetics Institute, Bellevue, WA, USA with Professor Michael Kahn, and NPG Research Institute, Raleigh, NC with Professor Bert Fraser-Reid. He joined the National Institute for Interdisciplinary Science and Technology (NIIST-CSIR), Trivandrum as Scientist in the Chemical Sciences and Technology Division in May 2002. Currently, he is the senior principal scientist and head of the organic chemistry section at NIIST. His research interests include sustainable utilization of abundant natural resources and screening of spices for activity against neurodegenerative diseases, innovative processes and technologies for agrochemicals, the development of novel synthetic methodologies utilizing pentafulvenes as synthons, synthetic carbohydrate chemistry, and transition-metal-catalyzed organic transformations towards pharmaceutically important molecules. To his credit, he has authored more than 113 research publications, 2 books, and 1 patent.

Patrick Y. S. Lam is currently a Distinguished Professor at Baruch S. Blumberg Institute (USA) and an Adjunct Professor at Drexel University College of Medicine (USA). He is also the president of Lam Drug Discovery Consulting, LLC (USA). He recently retired from a director position in the Discovery Chemistry Department of Bristol-Myers Squibb Co. He joined DuPont in 1984 and moved to BMS in 2001. He was the group leader/co-inventor responsible for the discovery of Eliquis®/Apixaban, a novel factor Xa anticoagulanton the market. Eliquis® is currently the top-selling small-molecule drug in the world (>$8B annual sales). Patrick is also internationally known as the co-discoverer of the powerful Chan–Lam coupling reaction. Patrick has presented >100 invited seminars worldwide. He has authored 103 papers/reviews/book chapters and is an inventor on 38 patents/patent applications. He received his Ph.D. from the University of Rochester (Dr. Louis Friedrich) and was a postdoctoral fellow in UCLA (Prof. Mike Jung and the late Prof. Don Cram, 1987 Nobel Laureate).

Parthasarathi Das received his Ph.D. in organic chemistry from CSIR-National Chemical Laboratory, University of Poona, India. Later, he continued his academic work as a post-doctoral fellow at Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA, USA, Department of Chemistry, Tohoku University, Sendai, Japan, and also at Institut für Organische Chemie, RWTH-Aachen, Aachen, Germany. He has also worked as Research Investigator at Dr. Reddy's Laboratories Ltd./Aurigene Discovery Technologies, Hyderabad, India and a Principal Scientist at Indian Institute of Integrative Medicine (CSIR), Jammu, India. Parthasarathi Das is currently an Associate Professor at Indian Institute of Technology (ISM) Dhanbad, India. His current research interests include medicinal chemistry, development of new synthetic tool and synthesis of biologically active natural products. He has received Chemical Research Society of India (CRSI) Bronze Medal, 2019 for his contribution to research in chemistry.

peratures, expensive palladium and ligands, a limited number of substrates, and so on. These drawbacks necessitated the demand for the invention of novel metal catalysts, and the Ullmann[6] and Goldberg[7] coupling reactions are among the more explored strategies.[8–10] To overcome these limitations, many researchers have tried various more reactive arylating reagents instead of aryl halides to develop milder reaction conditions involving organometalloids such as organobismuth, organolead, organostannane, and organosiloxane derivatives or hypervalent iodonium salts.

In 1998, research groups of Chan,[11] Evans,[12] and Lam[13] reported Cu-mediated heteroatom arylation reaction using arylboronic acids as coupling partners for the construction of C–N and C–O bonds. In addition to N- and O-based nucleophiles, sulfur, selenium, tellurium, and halogen nucleophiles are also suitable partners in these reactions. The use of copper salts and organoboron compounds are beneficial as they have several advantages, such as readily availability, low toxicity, etc. (Scheme 1). As the oxidation of Cu(II) complexes bearing electron-deficient aryl groups is challenging, arylboronic acids bearing electron-withdrawing substituents are poor substrates for the Chan–Lam reaction. The sensitivity to the electronic properties of the arylboronic acids, which imparts a limited substrate scope, and the use of a large amount of catalyst are areas that still need further improvement in these reactions.



Scheme 1 Chan–Lam cross-coupling reaction

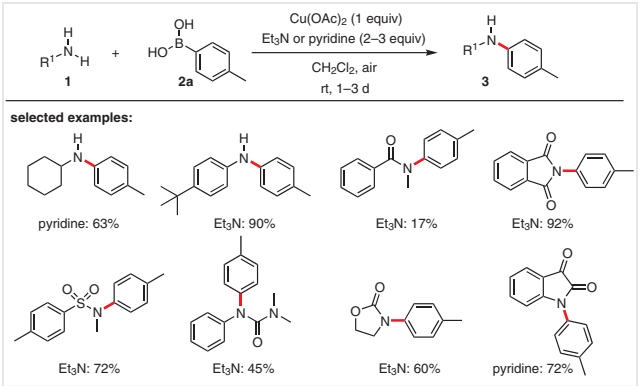
In order to overcome these limitations and their applications for the synthesis of aromatic or heteroaromatic building blocks, various research groups have developed various reaction conditions under modified Chan–Lam coupling conditions. In particular, recent developments of chemo- and regioselective N-arylations or O-arylations and synthesis of medicinally or pharmaceutically important heterocycles have been significant discoveries and are discussed in this review, which includes the construction of complex chemical scaffolds for synthetic methodology development. Proper mechanistic investigations including the choice of copper source, ligands, base, and other additives have benefitted the development of efficient and milder methods. The Chan–Lam coupling reaction is now capable of forming 12 different C–element bonds (C–N, C–O, C–S, C–P, C–F, C–C, C–Cl, C–Br, C–I, C–At, C–Se, and C–Te). This makes the Chan–Lam coupling reaction one of the most diverse mild reactions known in organic chemistry. This review concentrates mostly on publications starting from 2010, where our previous review[1h] ends. However, some historic significant work will also be discussed, in particular those not discussed in our 2011 *Synthesis* review.[1h] The present review covers all the 12 C–element bonds, including astatine, which is gaining importance for radiotherapy because of its unique properties.[14]

2 Construction of C–N and C–O Bonds

2.1 C–N Bond Formation

2.1.1 Original Discovery via Stoichiometric Copper-Mediated C–N Bond Formation

The N-arylation of a wide variety of NH-containing moieties, such as amines, amides, ureas, imides, sulfonamides and carbamates, with boronic acids **2** using a stoichiometric amount of copper reagent was first reported by Chan and co-workers (Scheme 2).[11]

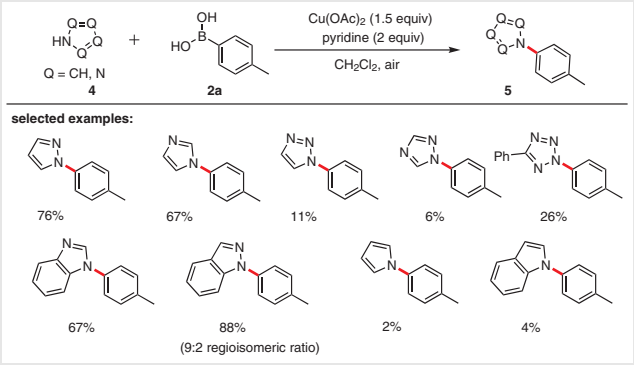


Scheme 2 Stoichiometric Cu-mediated C–N bond formation with various nitrogen nucleophiles

Lam and co-workers demonstrated that NH-containing heteroaromatics such as imidazoles, triazoles, tetrazoles, pyrazoles, benzimidazoles, and indazoles could also be used as coupling partners in this reaction; 2.0 equiv of arylboronic acid and 1.0 equiv of heteroarene were treated with 1.5 equiv anhydrous $Cu(OAc)_2$ and 2 equiv of pyridine as the base in the presence of 4 Å molecular sieves in air at room temperature for 2 days (Scheme 3).[13] Even though azoles such as triazoles and tetrazoles, which are electron-poor, pyrrole, and indole gave the corresponding products in low yields, pyrazoles and imidazoles gave good yields.

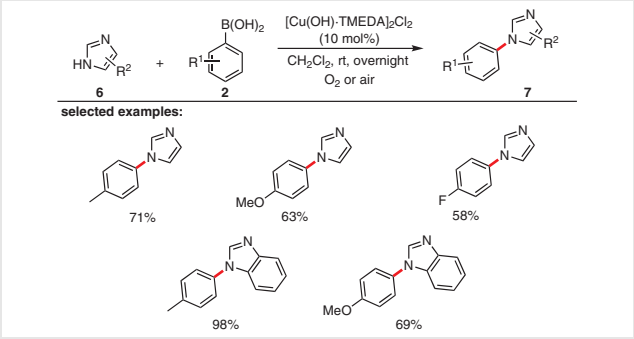
2.1.2 Copper-Catalyzed C–N Bond Formation

In 2001, the Collman group reported the synthesis of a wide range of *N*-arylimidazoles **7** in good to excellent yields by the reaction of arylboronic acids and imidazoles **6** using a novel binuclear bis-μ-hydroxocopper(II) complex $[Cu(OH)\cdot TMEDA]_2Cl_2$ (Scheme 4).[15] This procedure required



Scheme 3 Cu-mediated C–N bond formation with various azoles

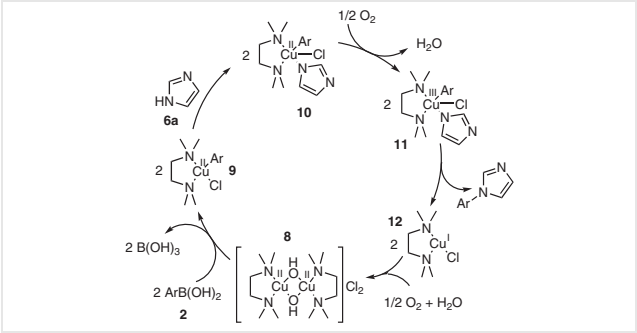
the use of 10 mol% catalyst and the ratio of imidazole/arylboronic acid was 1:2; the products were obtained in good to excellent yields and the use of stoichiometric amount of copper salts and amines was minimized.



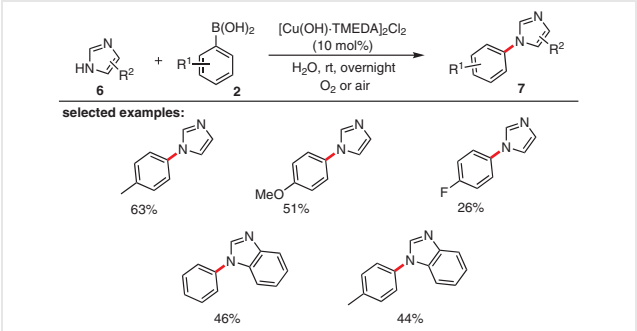
Scheme 4 [Cu(OH)·TMEDA]$_2$Cl$_2$-catalyzed N-arylation of azoles with arylboronic acids

A plausible mechanism for the formation of N-arylated products based on Evans' postulated mechanism via the coupling of arylboronic acids and phenols is shown in Scheme 5. In the initial step, the arylboronic acid **2** undergoes transmetalation with catalyst **8** to afford **9** which subsequently complexes with the imidazole **6** to form **10**. The Cu(II) in complex **10** is oxidized to Cu(III) by oxygen to form **11**. This is followed by reductive elimination to generate the products and complex **12** which regenerates the active catalyst. The formation of triarylboroxine and water from boronic acids can arylate H_2O which results in a competitive reaction between phenol and imidazole molecules to give lower yield of desired coupling products.

Next, in 2001, the Collman group reported the first example of the synthesis of *N*-arylimidazoles using [Cu(OH)·TMEDA]$_2$Cl$_2$ as the catalyst in water as the solvent (Scheme 6).[16] The yields are lower as compared with the reaction in dichloromethane, nevertheless the use of water as the solvent opens up the future arena of green chemistry and the arylation of the nucleophilic sidechains of peptides, proteins, and carbohydrates.

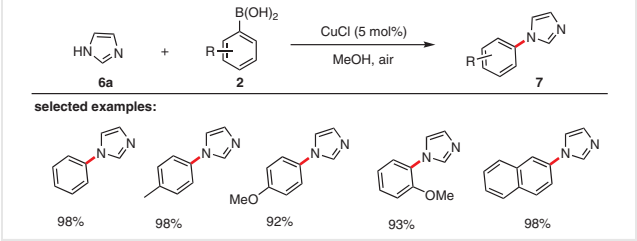


Scheme 5 Mechanism for the catalytic Cu-catalyzed N-arylation of azoles



Scheme 6 [Cu(OH)·TMEDA]$_2$Cl$_2$-catalyzed N-arylation of azoles with arylboronic acids in water

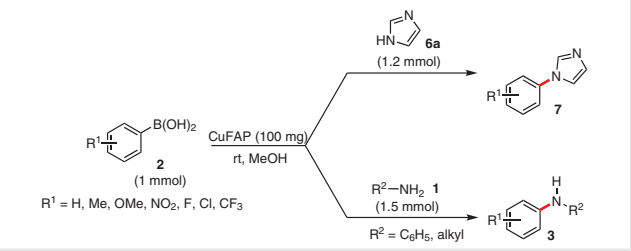
In 2004, Yu, Xie, and co-workers developed a useful method using only 5 mol% of simple CuCl with methanol as the solvent that gave the corresponding *N*-arylimidazoles in almost quantitative yields without the addition of base or ligand (Scheme 7).[17] Methanol was used for better solubility of CuCl, and it is interesting that methanol did not undergo O-arylation. This coupling reaction was also performed in a mixture of water and protic solvent to give *N*-arylimidazoles in high yields.



Scheme 7 CuCl-catalyzed N-arylation of imidazoles with arylboronic acids

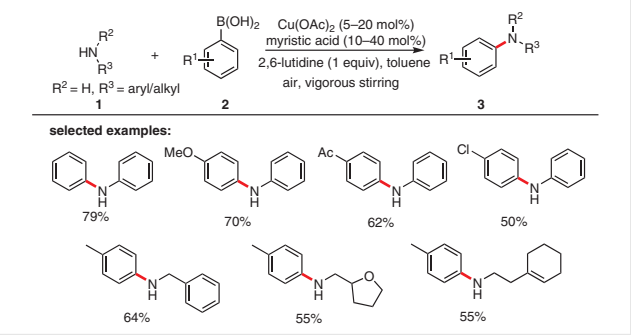
In 2006, Kantam and co-workers reported coupling of imidazoles and amines with arylboronic acids using copper-exchanged fluorapatite (CuFAP) in methanol at room temperature to give N-arylated imidazoles and amines in good to excellent yields (Scheme 8).[18] Screening a variety of

catalysts found that $Cu(OAc)_2$, CuI, and copper-exchanged hydroxyapatite (CuHAP) gave poor yields; CuFAP was the best catalyst and it could be reused a number of times with the same activity even after the fourth catalytic cycle. The catalyst CuFAP can be recovered from the reaction using simple filtration, and it was also confirmed using atomic absorption spectroscopy there is no leaching of copper from the reaction mixture.



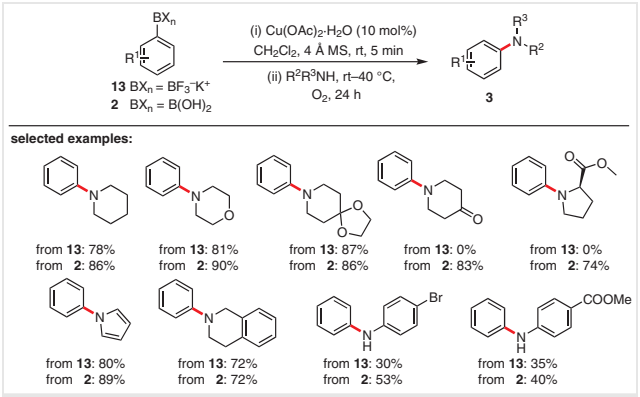
Scheme 8 CuFAP-catalyzed N-arylation of azoles and amines with arylboronic acids

The Buchwald group, in 2001, reported the reaction of amines with arylboronic acids using $Cu(OAc)_2$ as the catalyst, 2,6-lutidine as the base, and myristic acid as an additive at room temperature (Scheme 9).[19] The reaction was general to both aryl- and alkylamines and gave diarylamines and *N*-alkylanilines in good (58–91%) to moderate (50–64%) yields, respectively.



Scheme 9 $Cu(OAc)_2$-catalyzed N-arylation of amines with arylamines

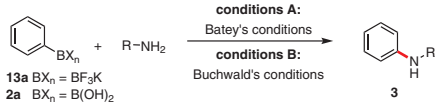
The coupling of anilines and both primary and secondary amines with arylboronic acids and aryltrifluoroborates using a catalytic amount of $Cu(OAc)_2{\cdot}H_2O$ was described by Batey and Quach in 2003 (Scheme 10).[20] This base- and ligand-free strategy worked with a wide variety of functional groups in the presence of oxygen at slightly elevated temperatures. The reaction was general to different boronic acids containing both electron-donating and electron-withdrawing substituents.

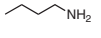
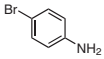


Scheme 10 Cu(II)-catalyzed N-phenylation of aliphatic amines, ammonium salts, and anilines

As the arylboronic acids are more solubility in dichloromethane than trifluoroborates, slightly greater yields were obtained with the former. Also, the presence of 4 Å molecular sieves was essential, and the *N*-dealkylated side product was not observed in the reaction. Comparing the conditions of Batey and Quach[20] (Table 1, conditions A; see Scheme 10) to those of the Buchwald group[19] (conditions B; see Scheme 9) shows that for aliphatic amines the yield of *N*-arylamines diminishes using the Buchwald conditions as the high concentration of copper in the reaction favors the formation of *N*-dealkylated side products (Table 1, entry 1). As the aryltrifluoroborates are insoluble in toluene, they failed to react under Buchwald's conditions (entries 1 and 2). To date, among the Chan–Lam reactions that use $Cu(OAc)_2$ catalysts, the conditions developed by Batey and Quach continue to be the best for the arylation of alkylamines in the literature.

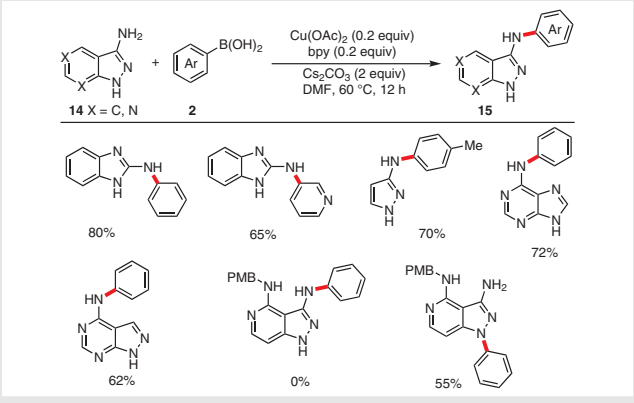
Table 1 Comparison of Cu(II)-Catalyzed Methods



Entry	R-NH_2	Conditions	Product	Yield (%)	
				From **13a**	From **2a**
1		A	**3a**	89	92
		B		0	47
2		A	**3b**	30	53
		B		0	91

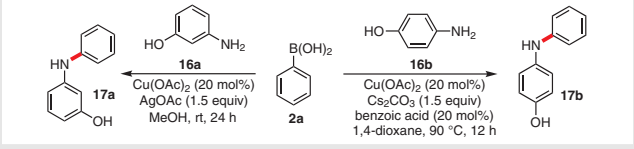
In 2016, our group reported the selective C–NH_2 arylation of various derivatives of C-amino-NH-azoles and 2-aminobenzimidazoles using Cu(II)-catalyzed coupling with arylboronic acids in the presence of 2,2′-bipyridine (bpy) and Cs_2CO_3 at 60 °C in DMF under air.[21] Many unexplored heteroaromatics with multiple nucleophilic sites such as 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and 9*H*-purin-6-amine

underwent the reaction smoothly to furnish the products without the protection of the diazole N–H bonds (Scheme 11). It is noteworthy that the reaction of PMB-protected 1*H*-pyrazolo[4,3-*c*]pyridine-3,4-diamine gave selective N-1 arylation due to steric crowding by the protecting group.



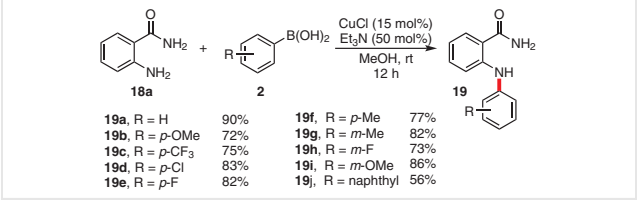
Scheme 11 Selective C–NH_2 arylation of C-amino-NH-azoles and 2-aminobenzimidazoles

We have examined the selective N-arylation of unprotected aminophenols using $Cu(OAc)_2$/AgOAc in methanol as the solvent at room temperature.[22] This open-flask chemistry was extended to 4-aminophenol derivatives albeit with the use of the $Cu(OAc)_2/Cs_2CO_3$ system with benzoic acid as an additive. These two novel Cu-mediated catalytic systems provided a robust protocol that tolerates many functional groups for the chemoselective N-arylation of aminophenols (Scheme 12). By employing density functional theory (DFT) calculations for a better overview of the reaction mechanism, we concluded that the O-arylation process has a higher overall barrier (39.99 kcal mol^{-1}) compared to the N-arylation process (18.87 kcal mol^{-1}) making the latter more kinetically and thermodynamically favorable.

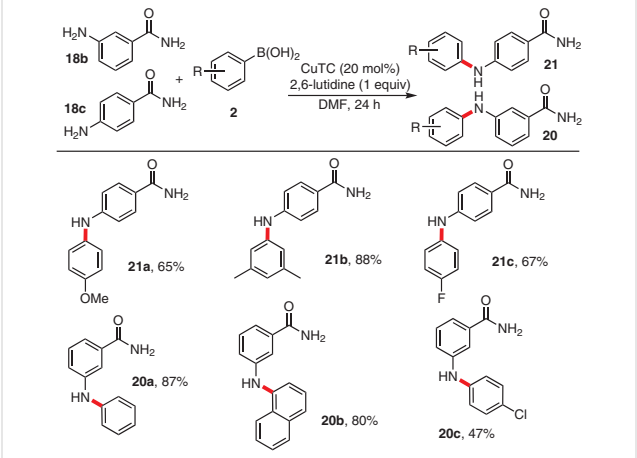


Scheme 12 Cu-catalyzed chemoselective N-arylation of aminophenols with phenylboronic acid

In 2017, Zhang, Xu, and co-workers developed the chemoselective N-arylation of unprotected aminobenzamides using Cu-catalyzed coupling with arylboronic acids under open-flask conditions.[23] Reactions between 2-aminobenzamides and arylboronic acids in methanol at room temperature under air for 12 hours using 15 mol% of CuCl as the catalyst and 0.5 equiv of triethylamine gave chemoselectively 2-(arylamino)benzamides (Scheme 13). The reaction was general with both electron-rich and electron-deficient arylboronic acids and also with a variety of substituted 2-aminobenzamides. The selective arylation of 3- or 4-aminobenzamides using this system was unsuccessful, however the use of copper thiophene-2-carboxylate (CuTC, 20 mol%), 2,6-lutidine (1.0 equiv), and DMF (1.0 mL) as the reaction system resulted in a Cu-catalyzed C–N cross-coupling reaction to give the corresponding 3-(arylamino)- or 4-(arylamino)benzamides (Scheme 14).

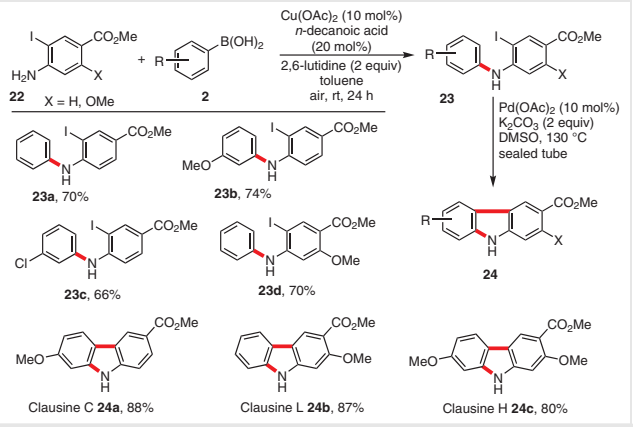


Scheme 13 Cu-catalyzed N-arylation of 2-aminobenzamides with arylboronic acids



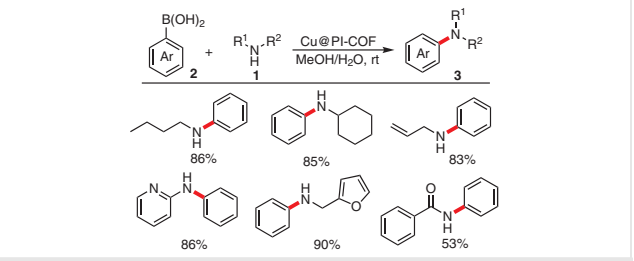
Scheme 14 Cu-catalyzed N-arylation of 3- or 4-aminobenzamides with arylboronic acids

We have developed (2014) an efficient route for the synthesis of methyl carbazole-3-carboxylates via the Cu-catalyzed N-arylation of methyl 4-amino-3-iodobenzoates with boronic acids to give methyl 4-(arylamino)-3-iodobenzoates which underwent Pd-catalyzed intramolecular C–H arylation to give the final product.[24] The synthesis of many naturally occurring carbazole alkaloids, such as clausine, glycozoline, and glycozolidal, and including the first reported total synthesis of 2,6-dioxygenated sansoakamine, were accomplished with this methodology. A variety of methyl 4-(arylamino)-3-iodobenzoates were synthesized using $Cu(OAc)_2$ and 2,6-lutidine as the catalytic system and *n*-decanoic acid as an additive in toluene under air (Scheme 15). These synthesized aryl(2-iodoaryl)amines underwent an intramolecular cyclization reaction to produce carbazole alkaloids using 10 mol% $Pd(OAc)_2$ as the catalyst and K_2CO_3 as the base in DMSO at 130 °C.



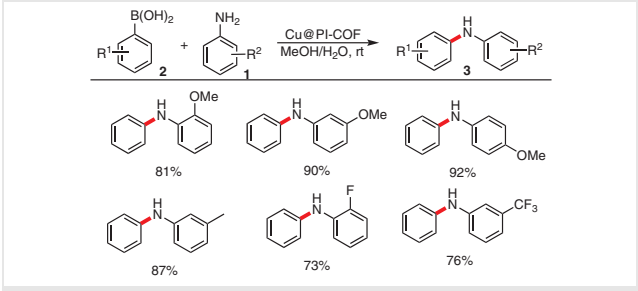
Scheme 15 Cu-catalyzed coupling of methyl 4-amino-3-iodobenzoates with boronic acids and subsequent Pd-catalyzed C–H arylation

In 2018, Zhang and co-workers explored the use of a copper embedded polyimide covalent organic framework (Cu@PI-COF) with a high thermal and chemical stability as an active heterogeneous catalyst for the Chan–Lam coupling reaction of arylboronic acids and amines.[25] The synthesis of Cu@PI-COF included heating a mixture of an equal molar ratio of pyromellitic dianhydride and melamine with to 325 °C for 4 hours followed by impregnating the synthesized PI-COF in a solution of $Cu(OAc)_2$ in EtOH at room temperature. Exploring the scope of the Cu@PI-COF-catalyzed coupling reaction showed that anilines with electron-donating groups gave good yields compared to those bearing electron-withdrawing ones (Schemes 16 and 17). A variety of arylboronic acids bearing electron-neutral, -donating, and -withdrawing groups underwent the reaction and furnished the desired products in good to excellent yields (Scheme 17). The scope of this reaction was checked with different amines, heteroarylamines and benzamides and arylboronic acids which furnished the corresponding cross-coupling products in excellent yields (Scheme 16). The catalyst is highly stable and can be reused eight times by recycling without any significant loss in its catalytic activity.

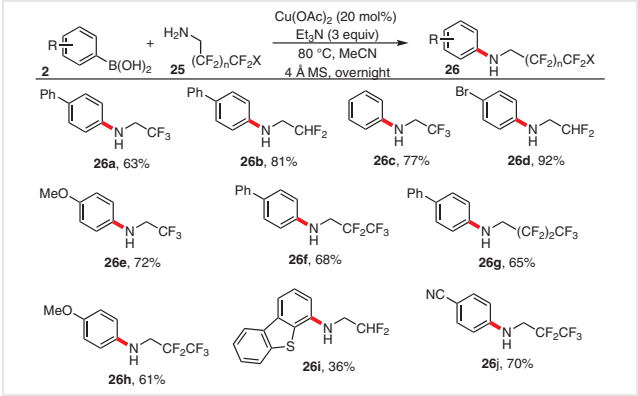


Scheme 16 Cu@PI-COF-catalyzed reaction of arylboronic acids and various amines

Also in 2018, Hu and co-workers reported the oxidative Chan–Lam coupling reaction of fluoroalkylamines with arylboronic acids to generate useful and interesting fluoroalkylamine-containing compounds (Scheme 18).[26] The use of inexpensive $Cu(OAc)_2$ as the catalyst and air as an oxidant effected good functional group tolerance which substantiates the strategy. The reactivity of four different fluoroalkylated amines proceeded as 2,2-difluoroethylamine > 2,2,2-trifluoroethylamine > pentafluoropropylamine ≈ heptafluorobutylamine.

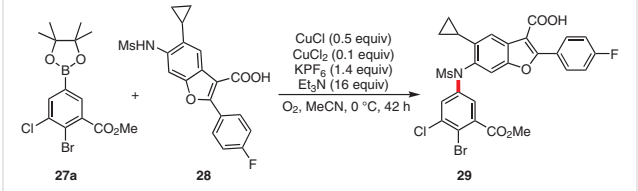


Scheme 17 Cu@PI-COF-catalyzed reaction of phenylboronic acids and aniline derivatives



Scheme 18 Cu-catalyzed coupling of fluoroalkylamines with arylboronic acids

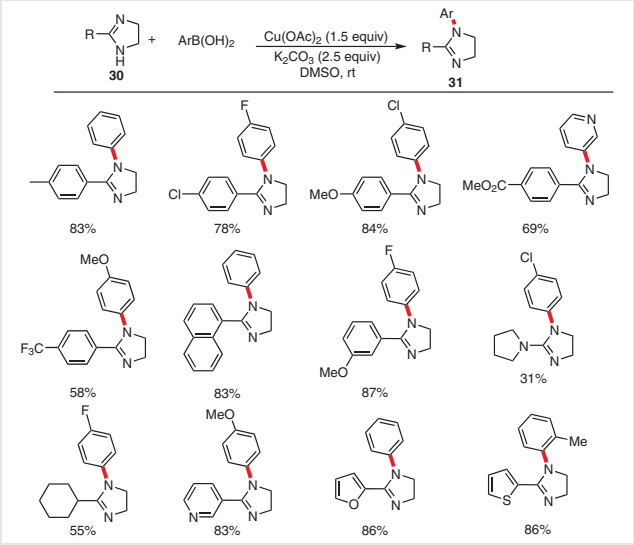
In 2019, Kowalski, Leitch, and co-workers reported the eight-stage synthesis of the boron-containing NS5B inhibitor GSK8175, which utilized a Chan–Lam coupling between a haloarylboronic acid pinacol ester and an *N*-arylmethanesulfonamide.[27a] A mixture of $CuCl/CuCl_2$ in conjunction with KPF_6 was used as the catalyst system for this transformation (Scheme 19). This route has a better 20% overall yield as compared to the previous route, which has an over-



Scheme 19 Chan–Lam coupling between a haloarylboronic acid pinacol ester and an aryl methanesulfonamide in the synthesis of GSK8175

all 10% yield involving 13 steps in a completely linear sequence.[27b]

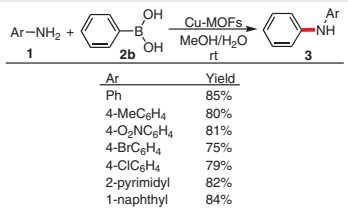
Krasavin and Dar'in reported (2016) the $Cu(OAc)_2$-promoted N-arylation of 2-imidazolines with arylboronic acids (Scheme 20).[28] Using a 1:2:1.5 molar ratio of the substrate/boronic acid/$Cu(OAc)_2$, as reported by Chan–Lam, the reaction was optimized to give the best yield in DMSO. Various 2-imidazolines bearing different substituents on the nitrogen and a number of boronic acids underwent the reaction smoothly to furnish *N*-aryl-2-imidazolines in moderate to good yields.



Scheme 20 $Cu(OAc)_2$-promoted N-arylation of 2-imidazolines with arylboronic acids

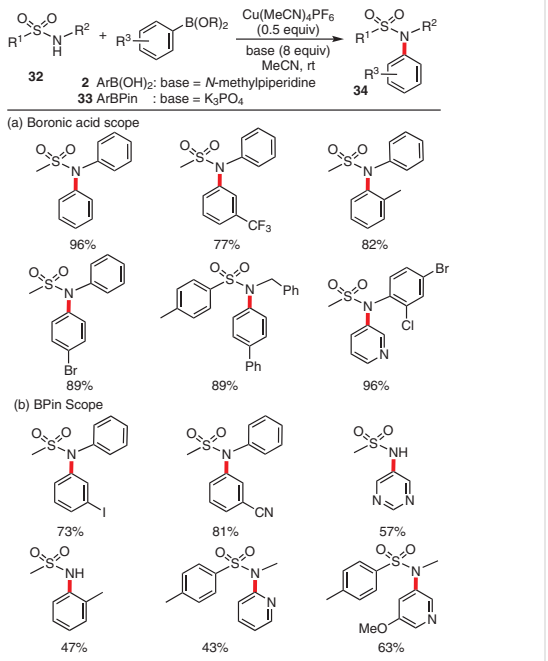
In 2017, Mokhtari, Naimi-Jamal, and co-workers reported the Chan–Lam coupling of arylboronic acids with arylamines using nanoporous $Cu_2(BDC)_2(4,4'\text{-bpy})$-MOF as the catalyst in the presence of air via a ball-milling strategy (Scheme 21).[29] The desired MOF was synthesized by solvent-free ball-milling a mixture of 1:1:0.5 ratio of $Cu(OAc)_2{\cdot}H_2O$, terephthalic acid, and 4,4′-bipyridine (4,4′-bpy) at room temperature which was analyzed by XRD that indicated mutually interpenetrating structure of a pair of three-dimensional frameworks. The optimized conditions used a 0.5:1 ratio of aniline and phenylboronic acid with $Cu_2(BDC)_2(4,4'\text{-bpy})$ as the catalyst in H_2O/MeOH (1:1) as the solvent. Different arylamines with electron-withdrawing and electron-releasing groups gave the corresponding *N*-arylanilines in good yields.

Leitch, Watson, and co-workers (2018) established the Chan–Lam N-arylation of primary and secondary *N*-arylsulfonamides at room temperature on a practical and large scale (Scheme 22).[30] After mechanistic studies, they selected $Cu(MeCN)_4PF_6$ as the catalyst to reduce the amount of H_2O present and competing ligating anions available (e.g., AcO^-) in the reaction mixture. The utilization of a stronger



Scheme 21 Nanoporous $Cu_2(BDC)_2(4,4'\text{-bpy})$-MOF-catalyzed coupling of arylboronic acids with arylamines

amine base, such as *N*-methylpiperidine, was crucial for the transformation of arylboronic acids. However, for arylboronic acid pinacol esters (ArBpin) substrates the base used was K_3PO_4 instead of an amine base due to catalyst inhibition by pinacol.

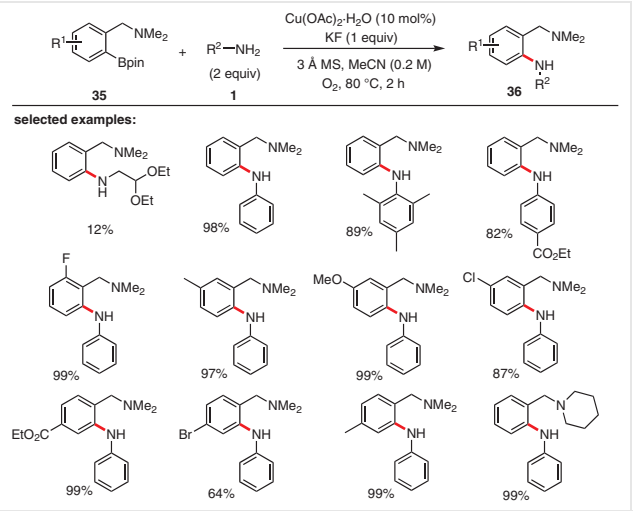


Scheme 22 $Cu(MeCN)_4PF_6$-catalyzed N-arylation of *N*-arylsulfonamides with arylboronic acids and arylboronic acid pinacol esters

In 2015, Clark and co-workers investigated the Cu-catalyzed coupling between 2-(aminomethyl)phenylboronate esters and arylamines using $Cu(OAc)_2$ under oxidative conditions to give *N*-aryl-2-(aminomethyl)anilines (Scheme 23).[31a] Homocoupling of the arylboronate ester was reported as a major side product in this reaction. In the absence of base, the *N*-aryl-2-(aminomethyl)anilines were formed with improved yield and increased selectivity over the homocoupled product. Both the boronate ester substrates and the aniline coupling partners bearing electron-donating and electron-withdrawing substituents were well tolerated under the reaction conditions. The reactivity of the boronate ester was enhanced by the presence of the adjacent

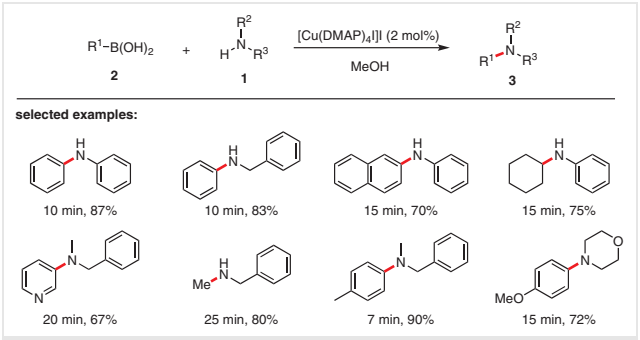
benzylamine moiety, which affected the competing rates of transmetalation in the catalytic cycles and thereby influencing the resulting product distribution.

Previous studies on Cu-mediated C–N bond-forming reactions have shown that the p*K*a of the N–H bond is an important factor in the rate of the coupling reaction, with more acidic substrates exhibiting faster reactivity. Alternatively, alkylamines may also undergo oxidative deamination under the Cu-mediated conditions, thus limiting the formation of the desired product. It was observed that the product distribution is related to the size of the counterion of the base. Alkylamines compared to arylamines generated different product distributions as the acidity and nucleophilicity of the amines are crucial factors toward the construction of desired diamines.[31b]



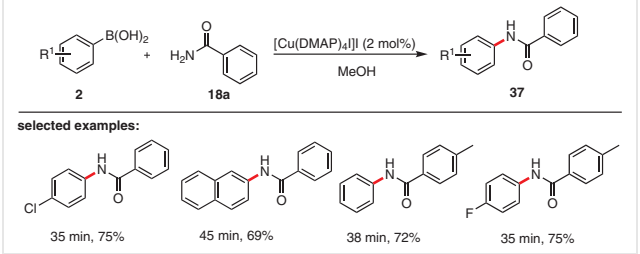
Scheme 23 $Cu(OAc)_2$-catalyzed reaction under oxidative conditions of 2-(aminomethyl)phenylboronate esters and arylamines

In 2016, Phukan and co-workers synthesized a novel square pyramidal copper complex, $[Cu(DMAP)_4I]I$ via the disproportionation reaction of CuI and DMAP in DMSO.[32] This catalyst was subsequently used in the Chan–Lam coupling reaction of arylboronic acids with either an amine, amide, azide (Section 2.1.3), or thiol (Section 3). The reaction of arylboronic acids with alkyl- and arylamines required the use of only 2 mol% $[Cu(DMAP)_4I]I$ in methanol at room temperature for a short time to give the N-arylated products in high yields (Scheme 24). In this rapid reaction the use of arylboronic acids with electron-withdrawing groups increased the reaction rate. This new protocol is important not only because of the excellent yields of amine substrates, but it may provide more information of the configuration of the copper reactive intermediate. More work needs to be done in this area of coordinated copper with known configuration.



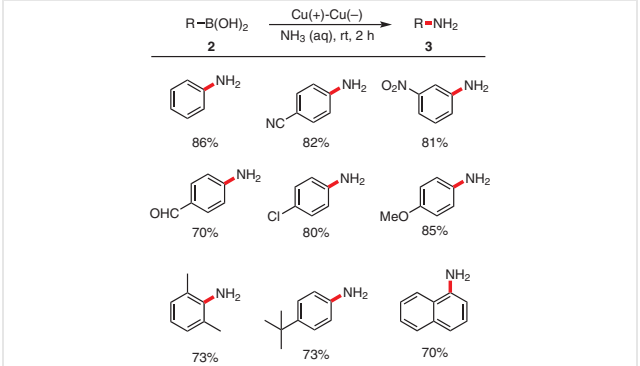
Scheme 24 $[Cu(DMAP)_4I]I$-catalyzed reaction of arylboronic acids with alkyl- and arylamines

The reaction was extended to different benzamides under the same optimized conditions (Scheme 25). However, the reaction with amides gave the corresponding products in lower yield and with a slower rate compared to that for amines.



Scheme 25 $[Cu(DMAP)_4I]I$-catalyzed reaction of arylboronic acids with benzamides

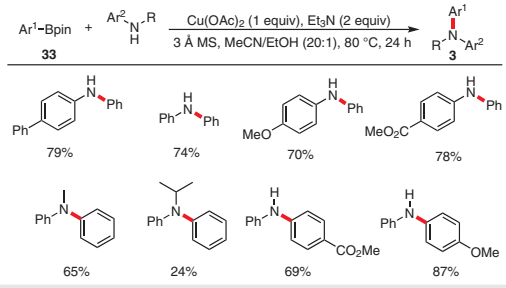
The electrosynthesis of arylamines and phenols from arylboronic acids in aqueous ammonia was explored by Huang and co-workers in 2013.[33] By changing the anode potential and the aqueous ammonia concentration, the synthesis of anilines and phenols can be achieved chemoselectively in an undivided cell. Cu foils served as the cathode and anode, whereas a Ag/AgCl electrode was chosen as the



Scheme 26 Electrochemical amination of arylboronic acids in aqueous NH_3

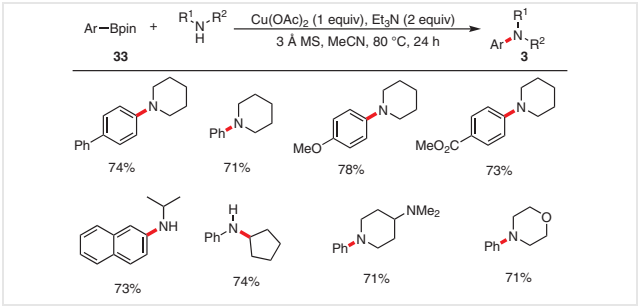
reference electrode. A variety of arylboronic acids bearing electron-donating or electron-withdrawing groups underwent the reaction chemoselectively to generate the arylamines in good yields (Scheme 26). The *N*-arylation of ammonia to give primary aniline is a very useful reaction.

Arylboronic acid pinacol esters are very useful reagents due to their ease of synthesis and improved stability compared to arylboronic acids, especially heteroarylboronic acids. However, there was only limited success in using arylboronic acid pinacol ester in Chan–Lam coupling reactions. In 2016, Watson and co-workers reported a breakthrough in the Chan–Lam coupling of arylboronic acid pinacol esters with alkyl- and arylamines using a mixed MeCN/EtOH solvent system.[34a] Careful optimization of the solvent ratio of MeCN/EtOH mixture to 20:1 was required as the use of EtOH as solvent in the reaction furnishes the corresponding ether product, and this solvent mix minimizes byproduct formation. Both arylboronic acid pinacol esters and arylamines bearing electron-donating or -withdrawing substituents were tolerated by this solvent mixture, which shows the broad functional group tolerance of this strategy (Scheme 27). Alkylamines underwent the reaction in MeCN, and EtOH was not necessary for this transformation (Scheme 28). Further careful mechanistic studies showed that excess amine and $B(OH)_3$ additives (to remove unproductive pinacol binding to the copper intermediate) are important. At 80 °C, arylboronic acid pinacol ester arylated anilines, amines, phenol, thiophenol sulfonamide, pyrrole, and indazole.[34b]

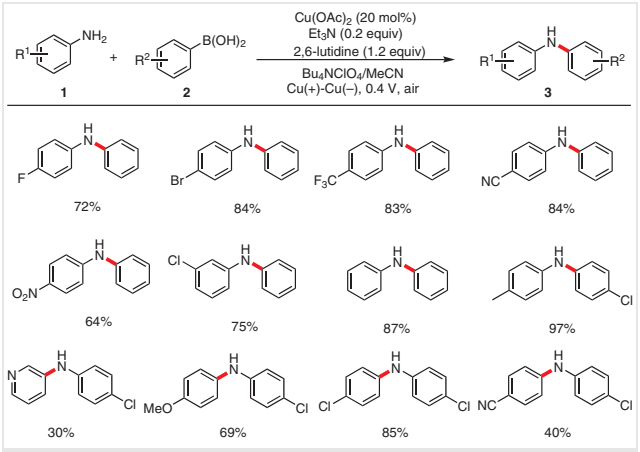


Scheme 27 $Cu(OAc)_2$-mediated reaction of arylboronic acid pinacol esters with arylamines

In 2019, Gale-Day and co-workers reported the electrochemical synthesis of a variety of *N*-arylanilines via the Chan–Lam coupling of anilines and arylboronic acids utilizing a dual copper anode/cathode system in the presence of Et_3N and air or oxygen (Scheme 29).[35] Anilines with electron-rich substituents or with *para*-halo groups reacted well, whereas those bearing electron-deficient groups gave moderate yields. A variety of arylboronic acids bearing both electron-withdrawing and -donating groups underwent the reaction smoothly to furnish the products in good to excellent yields.



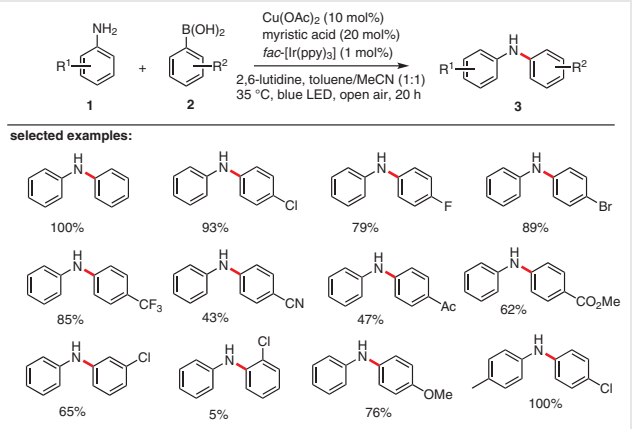
Scheme 28 $Cu(OAc)_2$-mediated reaction of arylboronic acid pinacol esters with alkylamines



Scheme 29 $Cu(OAc)_2$-catalyzed electrochemical reaction of boronic acids and anilines

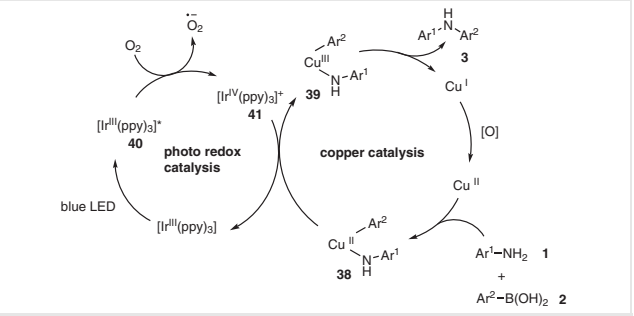
In 2015, the Kobayashi group developed the Cu(II)-catalyzed aerobic oxidative coupling reaction between arylboronic acids and aniline derivatives under visible-light-mediated photoredox catalysis (Scheme 30).[36] This synthetic protocol was even applied to arylboronic acids with electron-deficient groups. As the oxidation of Cu(II) in complexes with electron-withdrawing group substituted arylboronic acids was difficult, the reaction with these substrates was poor. However, to overcome this drawback and to oxidize Cu(II) to Cu(III), they utilized a combination of photoredox catalysis and copper. This reaction was more efficient in nitrile-based solvents. However, as removing benzonitrile is very difficult, they chose a 1:1 mixture of toluene and MeCN, which furnished *N*-arylanilines **3** in excellent yields. The presence of visible-light photo redox catalyst, copper catalyst, and blue LED radiation were found to be crucial for this reaction and was illustrated using controlled experiments.

A plausible mechanism for the reaction of anilines **1** and arylboronic acids **2** is illustrated in Scheme 31. Ligand exchange followed by transmetalation of the Cu catalyst with aniline **1** and arylboronic acid **2** produces the Cu amide **38**. At the same time, the light-induced metal-to-ligand charge

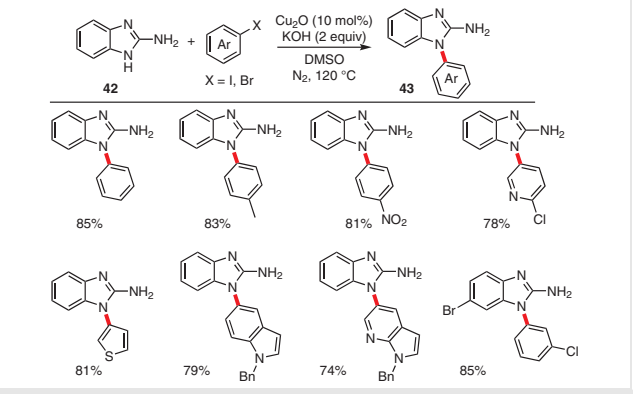


Scheme 30 Visible-light-mediated photoredox catalysis of anilines and arylboronic acids

transfer of [Ir(ppy)$_3$] furnishes the complex **40**, which on quenching with O_2 produces complex **41**. The complex **41** further oxidizes Cu(II) to Cu(III) and generates the Cu(III) intermediate **39**. The intermediate **39** undergoes reductive elimination to furnish *N*-arylaniline **3** and generates the catalyst Cu(I) which is subsequently oxidized to produce Cu(II) and continues the catalytic cycle.



Scheme 31 Mechanism for the visible-light-mediated Chan–Lam coupling reaction

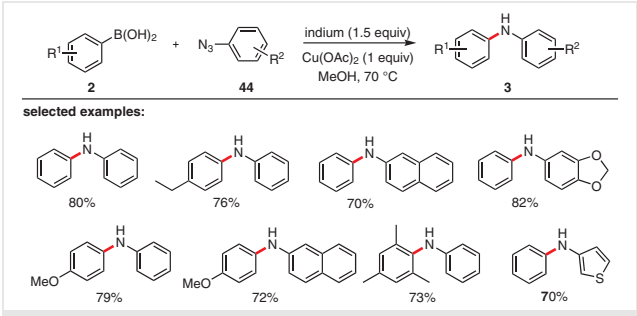


Scheme 32 Formation of 2-amino-1-arylbenzimidazoles by Cu-catalyzed reaction of 2-aminobenzimidazoles and aryl halides

Our group have also achieved the chemoselective N-arylation of the azole nitrogen by Cu-catalyzed coupling with aryl halides using catalytic Cu_2O and KOH in DMSO at 120 °C to give 2-amino-1-arylbenzimidazoles (Scheme 32).[37]

2.1.3 Coupling with Azides, Sulfoximines, and Sulfonediimines as Nitrogen Nucleophiles

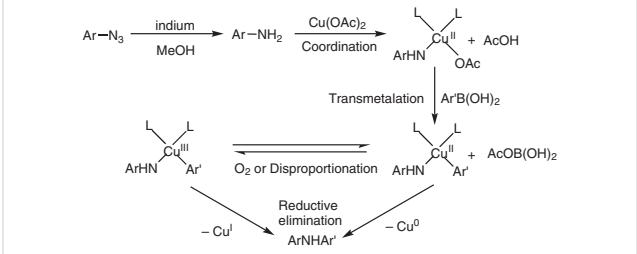
Reddy and co-workers first reported the N-arylation of aryl azides by Chan–Lam cross-coupling with arylboronic acids mediated by Cu(OAc)$_2$ and indium metal for the construction of *N*-arylanilines in 2011 (Scheme 33).[38] Optimization of the conditions showed that methanol was the best solvent, and the reaction did not proceed in the absence of Cu(OAc)$_2$ and indium metal. Examination of the scope of the reaction under the optimized conditions showed that aryl azides bearing substituents such as methoxy, ethyl, and 2,4,6-trimethylphenyl groups underwent the reaction smoothly. This reaction was unsuccessful if the azide is replaced by an aryl halide.



Scheme 33 Cu(OAc)$_2$/indium metal mediated coupling of arylboronic acids and aryl azides

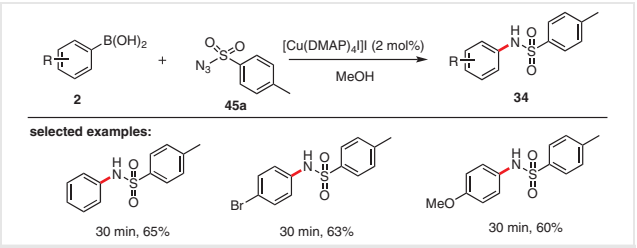
Mechanistically, in the first step, the aryl azides are converted into arylamines with indium metal, and this is followed by N-arylation with the arylboronic acid (Scheme 34).[38]

The work by Phukan and co-workers (see Sections 2.1.2 and 3) using the novel square pyramidal copper complex [Cu(DMAP)$_4$I]I also utilized this catalyst for the Chan–Lam



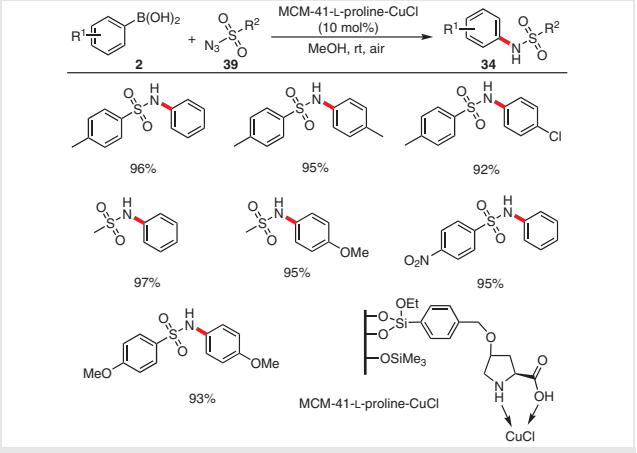
Scheme 34 Proposed mechanism for the Cu(OAc)$_2$/indium metal mediated coupling of arylboronic acids and aryl azides

coupling of arylboronic acids with tosyl azide to give *N*-arylsulfonamides in moderate yields (Scheme 35).[32]



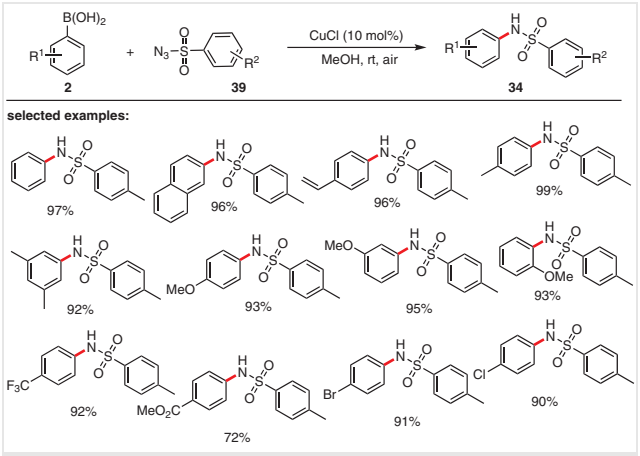
Scheme 35 Cu-catalyzed coupling of arylboronic acids with tosyl azide

Cai and co-workers developed a L-proline-functionalized MCM-41-immobilized copper(I) complex [MCM-41-L-proline–CuCl] catalyzed heterogeneous Chan–Lam coupling reaction of sulfonyl azides with arylboronic acids under open-air conditions without the aid of base or additive that gave a variety of *N*-arylsulfonamides (Scheme 36).[39] The new heterogeneous MCM-41-L-proline–CuCl utilized readily available and cheap starting materials and can be used up to 8 times with the same catalytic activity by recovering it from the reaction mixture by simple filtration. The optimized conditions used 10 mol% of MCM-41-L-proline–CuCl as the catalyst with methanol as the solvent at room temperature for 4 hours. The reaction of tosyl, arenesulfonyl, or methanesulfonyl azides with various arylboronic acids bearing electron-donating as well as electron-withdrawing substituents gave *N*-aryl and *N*-methylsulfonamides in excellent yields (87–97%) in 2–6 hours.



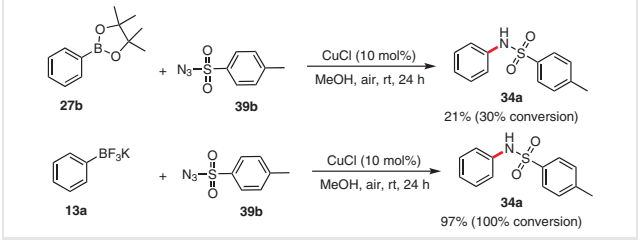
Scheme 36 MCM-41-L-proline–CuCl-catalyzed coupling of arylboronic acids with sulfonyl azides

In 2014, Kim and co-workers developed a novel method using sulfonyl azides **39** as nitrogen nucleophiles with various arylboronic acids using CuCl as the catalyst in the absence of a base or ligand at room temperature, in a mild and efficient coupling reaction that gave a variety of *N*-arylsulfonamides (Scheme 37).[40]



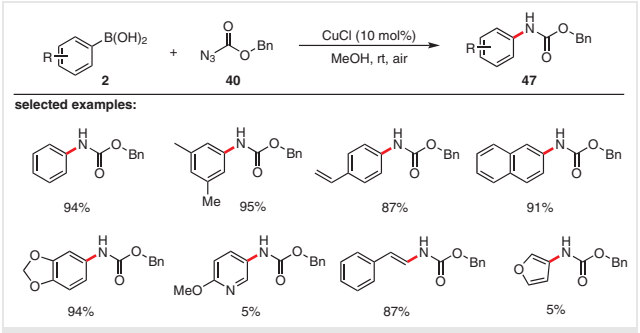
Scheme 37 $Cu(OAc)_2$-catalyzed N-arylation of sulfonyl azides with arylboronic acids

To examine the generality of the reaction, the reaction of sulfonyl azides with various phenylboronic acid derivatives was performed (Scheme 38).[40] The reaction of tosyl azide (**39b**) with potassium trifluoro(phenyl)borate (**13a**) gave *N*-tosylaniline (**34a**) in a maximum yield of 97% after 15 hours and 100% conversion, but the reaction with phenylboronic acid pinacol ester (**27b**) gave **34a** in 21% yield with 30% conversion.



Scheme 38 $Cu(OAc)_2$-catalyzed N-arylation of sulfonyl azides with different aryl donors

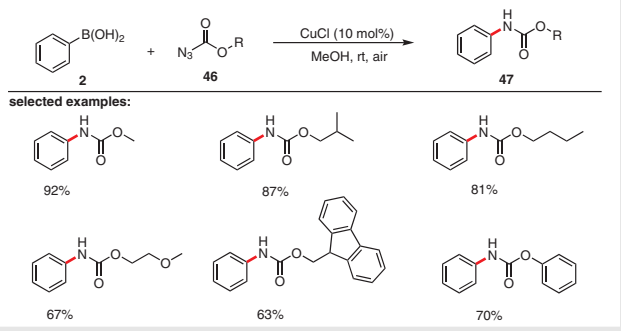
In 2015, Kim and co-workers reported the CuCl-catalyzed reaction of azidoformates and arylboronic acids gave *N*-arylcarbamates **46** (Scheme 39).[41] Arylboronic acids with



Scheme 39 CuCl-catalyzed N-arylation of benzyl azidoformate with arylboronic acids

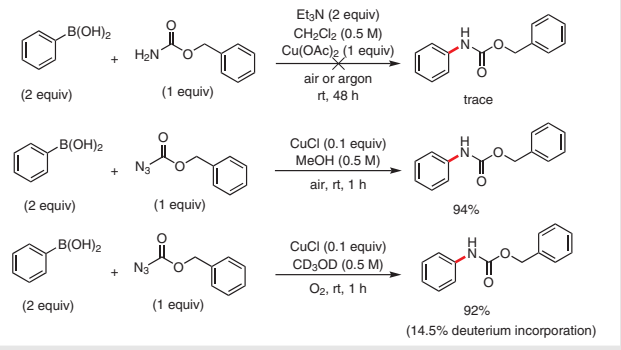
both electron-donating and electron-neutral substituents furnished benzyl *N*-arylcarbamates in good yields in the absence of a base or ligand at room temperature .

The generality of the reaction was also examined using phenylboronic acid and a variety of azidoformates **46**; generally the reactions readily proceeded at room temperature to yield alkyl and phenyl *N*-phenylcarbamates **47** in moderate to excellent yields (Scheme 40).[41]



Scheme 40 CuCl-catalyzed N-arylation of various azidoformates with phenylboronic acid

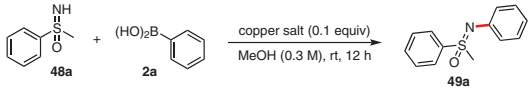
To understand the reaction mechanism better, several control experiments were performed (Scheme 41). These results highlighted the unique necessity of the azidoformate functionality, and also a 14.5% deuterium incorporation in the final product proved that both the solvent and the boronic acid can act as a proton source.



Scheme 41 Control experiments for the CuCl-catalyzed N-arylation of azidoformates with arylboronic acids

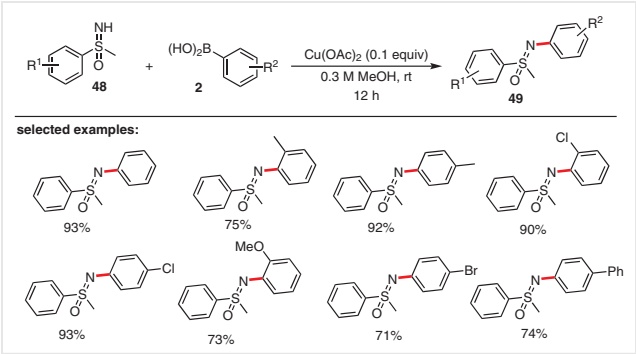
Bolm and co-workers reported a mild and simple N-arylation of sulfoximines (sulfoximides) by the $Cu(OAc)_2$-catalyzed coupling of NH-sulfoximines with arylboronic acids in the absence of base or heating.[42] Optimization experiments were performed with sulfoximine **48a** and phenylboronic acid (**2a**), and the results of the effect of various copper salts are summarized in Table 2. Among them, anhydrous $Cu(OAc)_2$ as catalyst gave the highest yield for the reaction.

Table 2 Effect of Various Copper Salts on the Reaction of a Sulfoximine and Phenylboronic Acid



Entry	Copper salt	Yield (%) of **49a**
1	CuI	85
2	CuCl	55
3	$CuSO_4$	91
4	$Cu(OAc)_2·H_2O$	87
5	$Cu(OAc)_2$	93

The reaction was efficient with different commercially available arylboronic acids and various sulfoximines under the optimized conditions (Scheme 42). Good to excellent results were achieved with *para*- and *ortho*-substituted boronic acids, irrespective of the electronic nature of the substituent of the boronic acid.



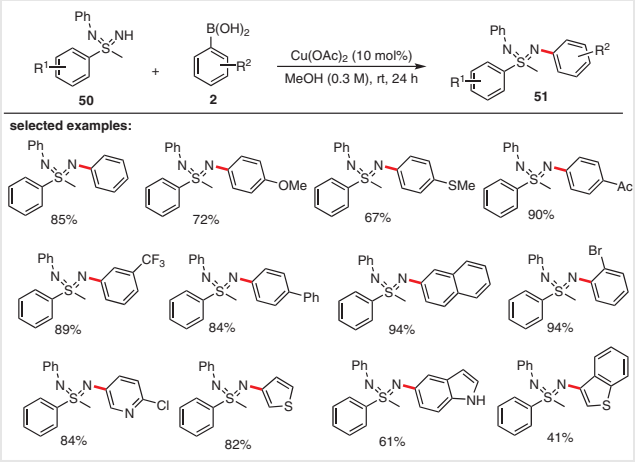
Scheme 42 $Cu(OAc)_2$-catalyzed N-arylation of sulfoximines with arylboronic acids

In 2013, Bolm and co-workers reported the Cu-catalyzed C–N cross-coupling of sulfonediimines with boronic acids to give a variety of *N*,*N*′-disubstituted sulfonediimines, including *N*-(hetero)aryl and *N*-alkenyl sulfonediimines in good to excellent yields (Scheme 43, Figure 1).[43] Optimization of the conditions with a variety of Cu(I) and Cu(II) salts and solvents showed that only anhydrous $Cu(OAc)_2$ and anhydrous methanol were effective, the remainder furnished the products in poor yields. The presence of a significant amount of oxygen and water was crucial for the transformation. In the presence of argon, the product was obtained in low yield (64%) with incomplete conversion. However, the use of a $CaCl_2$-drying tube for the removal of moisture increased the yield of the desired product **47** to 85%.

Bolm and co-workers also reported the palladium-catalyzed coupling of NH-sulfonediimines using aryl bromides to give the N-arylated products in high yields.[44] However,

the construction of *N*,*N*′-disubstituted moieties using this method has various drawbacks, such as the use of costly palladium, poor substrate scope, glove box usage, use of harsh conditions such as high temperature, and so on.

To check the substrate scope of the optimized $Cu(OAc)_2$-catalyzed reaction,[43] the reaction of *S*-methyl *N*,*S*-diphenyl sulfonedimine (**50**; R^1 = H) was performed with different boronic acids to give *N*,*N*′-disubstituted products **51** in good to excellent yields (Scheme 43).



Scheme 43 $Cu(OAc)_2$-catalyzed N-arylation of sulfonediimines with arylboronic acids

The optimized reaction conditions were applicable to alternatively substituted sulfonediimines (Figure 1).[43] In general, good yields of *N*-phenylated products were synthesized when *S*-alkyl *S*-aryl sulfonediimines were reacted with phenylboronic acid derivatives.

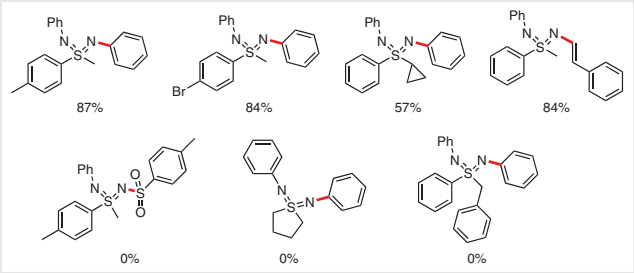
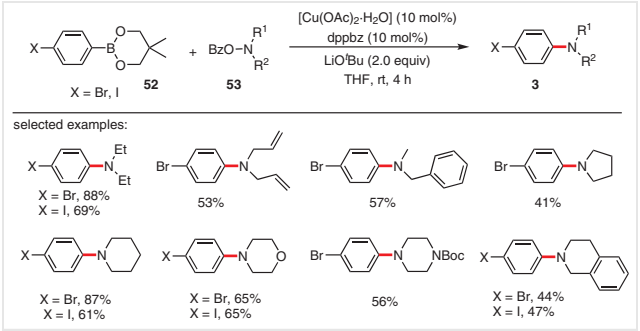


Figure 1 $Cu(OAc)_2$-catalyzed N-arylation of different sulfonediimines with arylboronic acids

In 2014, the Battula[45] and Arvidsson[46] groups independently reported efficient and low-cost Cu-catalyzed systems for the N-arylation of sulfonimidamides. The Battula group used 10 mol% $Cu(OAc)_2$ in methanol in the absence of base at room temperature to successfully introduce various aryl, heteroaryl, and cyclopropyl groups, while the Arvidsson group used 100 mol% $Cu(OAc)_2$ with Et_3N as the base in acetonitrile at room temperature to successfully introduce various aryl and heteroaryl groups in both cases in good to excellent yields.

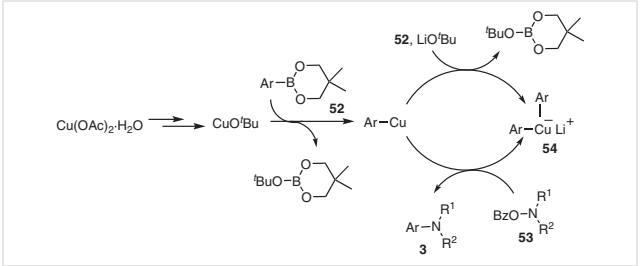
2.1.4 Coupling with *N*,*N*-Dialkylhydroxylamines

In 2012, Miura, Hirano, and co-workers reported the Cu-catalyzed N-arylation of hydroxylamines with arylboronic acids to give *N*-arylamines (Scheme 44).[47] The hydroxylamines were generally secondary acyclic amines and the arylboronic acid pinacol or neopentylglycol esters (neop) were substituted with I, Cl, Br, CO_2Me, COPh, and CHO. Arylboronates bearing electron-donating groups and electron-withdrawing groups underwent the amination smoothly. The strategy was even extended toward the preparation of heteroarylamines like 2- and 3-thienylamines. Attempts to use alkylboronates such as butylboronic acid neopentylglycol ester were unsuccessful. Acyclic amines bearing *N*,*N*-diethyl, *N*,*N*-diallyl, *N*-benzyl-*N*-methyl substituents were compatible under standard reaction conditions.



Scheme 44 Cu-catalyzed amination of arylboronates with various hydroxylamines

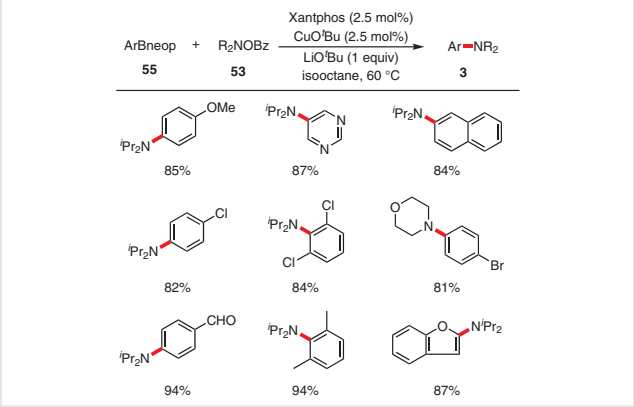
The mechanism proposed for the amination is shown in Scheme 45. Initially, the Cu(II) catalyst is reduced to Cu(I) forming CuO^tBu, which reacts with the neopentylglycol boronate **52** to form the monoarylcopper. This is followed by the generation of diarylcuprate **54** by the reaction of



Scheme 45 Plausible reaction mechanism for the Cu-catalyzed amination of arylboronates with various hydroxylamines

monoarylcopper with boronate using LiO^{t}Bu; **54** reacts with the hydroxylamine **53** to generate the product **3** and the monoarylcopper to continue the reaction.

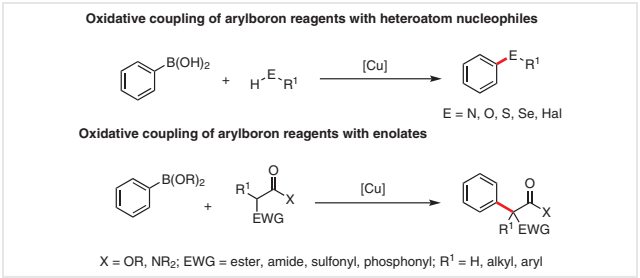
Also in 2012, Lalic and co-workers reported the synthesis of sterically hindered anilines in high yields via the Chan–Lam cross-coupling reaction of *O*-benzylhydroxylamines with (hetero)arylboronic acid neopentylglycol esters using XantphosCu-O^{t}Bu, formed in situ from $(CuO^tBu)_4$ and Xantphos in toluene (Scheme 46), in the presence of LiO^{t}Bu in concentrated isooctane solution.[48] Various aryl- and heteroarylboronic esters underwent the reaction smoothly with a variety of electrophiles, such as *N*-(benzyloxy)morpholine, -pyrrole, and -piperazine. For the reaction of *ortho*-substituted boronic esters with less hindered electrophiles, replacing LiO^{t}Bu with CsF was beneficial in improving the yield.



Scheme 46 Cu-catalyzed reaction of *O*-benzylhydroxylamines with aryl- and heteroarylboronic acid neopentylglycol esters

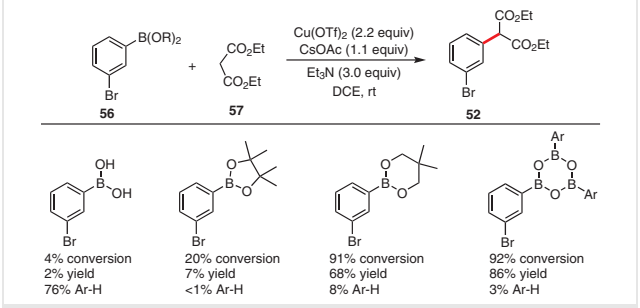
2.1.5 Enolate Coupling with sp^3-Carbon Nucleophiles

In 2016, Lundgren and co-workers reported the arylation of active methylene species via oxidative methods. Functionalized arylboronic acid esters were coupled with a variety of stabilized sp^3-nucleophiles mediated by $Cu(OTf)_2$ under mild reaction conditions (rt to 40 °C).[49a] Quaternary centers were generated by using substrates like tertiary malonates and amido esters (Scheme 47). This mild enolate Chan–Lam reaction is chemoselective in the presence of halogen electrophiles, such as haloarylboron reagents, and thus complements traditional cross-coupling and SNAr protocols. Furthermore, the generality extends to activated methylene substrates such as phosphonyls, amides, and sulfonyls, which have not been reported to undergo Hurtley-type reaction conditions (Schemes 48 and 49).[49b] This method could overcome the drawbacks of the oxidative arylation strategies employing organoboron reagents and activated methylenes that require the use of $Pb(OAc)_4$ and Hg additives in stoichiometric amounts.[49c]

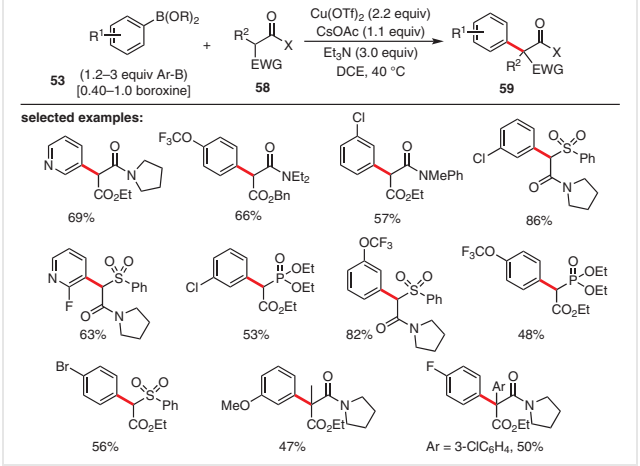


Scheme 47 Chan–Lam coupling of arylboron reagents with enolates

Other reactions such as homocoupling, protodeborylation, and acetoxylation were also observed, which furnished the minor side products in the coupling reaction. The reaction of diethyl malonate with 3-bromophenylboronic acid and 3-bromophenylboronic acid pinacol ester was poor and gave diethyl 2-(3-bromophenyl)malonate (**42**) in 2% and 7% yield, respectively whereas 3-bromophenylboronic acid neopentylglycol ester gave **42** in 68% yield and, surprisingly, arylboroxine gave **42** in 86% yield (Scheme 48).[49]



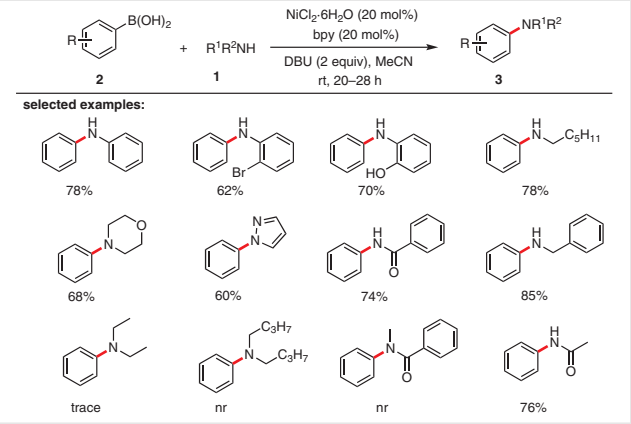
Scheme 48 Enolate Chan–Lam coupling: effect of arylboronic acid



Scheme 49 Cu-mediated oxidative arylation of arylboroxines with sp^3-nucleophiles

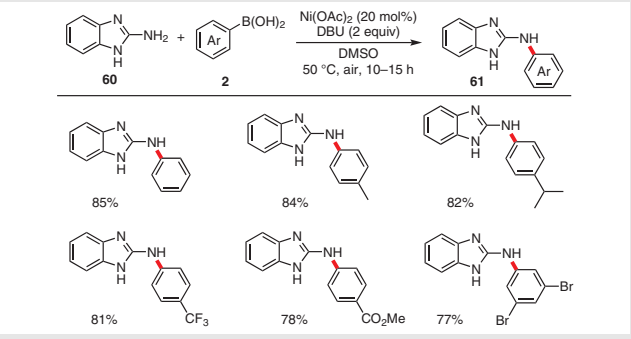
2.1.6 Nickel-Catalyzed Chan–Lam Coupling

In 2012, nickel was used as a catalyst for the first time in the Chan–Lam couple by Singh and co-workers. They developed a Ni-catalyzed N-arylation using the reaction of arylboronic acids with amines, amides, and N-heterocycles with 20 mol% $NiCl_2·6H_2O$ and 20 mol% bpy as the catalyst and DBU as the base in acetonitrile at room temperature under atmospheric conditions (Scheme 50).[50] This method was successful with various boronic acids irrespective of their nature. The reaction was also performed on a larger scale (20 mmol, gram) giving the product in 70% yield, showing that it is suitable for industrial applications.



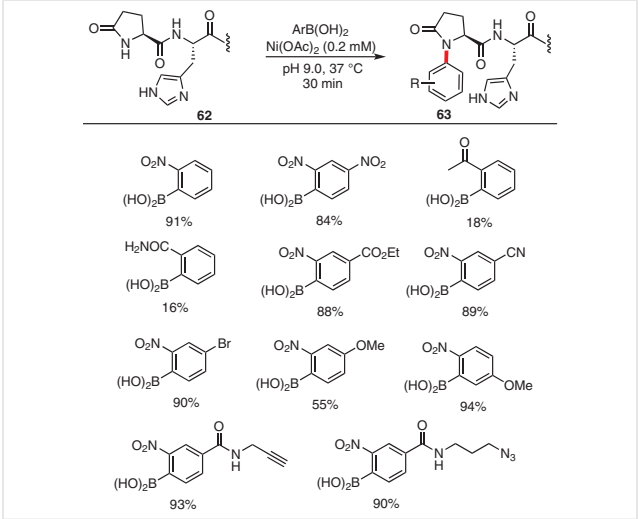
Scheme 50 Ni-catalyzed N-arylation of phenylboronic acids with nitrogen nucleophiles

We have developed a facile one-pot Ni-catalyzed coupling reaction strategy for the selective N-arylation of the primary amine ($C–NH_2$) group of 2-aminobenzimidazoles using boronic acids under ligand-free conditions (Scheme 51).[37] The reaction of diverse 2-aminobenzimidazoles and phenylboronic acids was examined under the optimized conditions for the Ni-catalyzed coupling reaction, which used 20 mol% $Ni(OAc)_2$ and 2.0 equiv DBU as the base in DMSO at 50 °C. This was the first report of a Ni-catalyzed selective $C–NH_2$-arylation in such substrates with multiple reactive nucleophilic sites.



Scheme 51 Formation of 2-(arylamino)benzimidazoles by Ni-catalyzed reaction of 2-aminobenzimidazoles and arylboronic acids

In 2019, Ball and co-workers reported the nickel-promoted pyrrolidone N–H arylation of pyroglutamate-histidine sequences using 2-nitroarylboronic acids under mild aqueous conditions (Scheme 52).[51a] The synthetic procedures utilizing copper catalysts cause serious selectivity concerns as they furnish histidine-directed products at both internal and pyroglutamate sites.[51b] The presence of *ortho* π-conjugated electron-deficient groups, such as the nitro group, was required in the arylboronic acids to generate the N-arylation product in good yields.

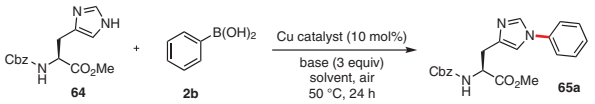


Scheme 52 Ni(II)-promoted pyrrolidone N–H arylation of pyroglutamate-histidine sequences using arylboronic acids

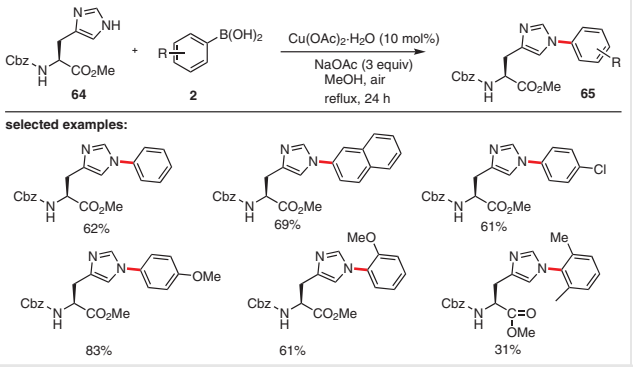
2.1.7 Coupling with Amino Acids

In 2010, the Campagne group utilized Chan–Lam cross-coupling reaction conditions for the N-arylation of Cbz-protected histidine (Scheme 53).[52] Protected histidines were directly functionalized with arylboronic acids to give the corresponding *N*(τ)-arylhistidines in moderate to good yields under mild conditions. They first examined various methods for the metal-catalyzed transformation of protected histidines to synthesize *N*(τ)-(hetero)arylhistidine derivatives including recent variants of the Buchwald–Hartwig and Ullmann coupling and Cu-catalyzed cross-coupling from aryllead triacetates but none proved successful. Moving to the Chan–Lam–Evans cross-coupling reaction had a dramatic influence on the reaction outcome. The optimized conditions used $Cu(OAc)_2·H_2O$ as the catalyst in methanol under open-air conditions in the presence of 3 equiv of NaOAc as the base (Table 3). No improvement in the product yield was observed without the use of a base.

Table 3 Optimization of Reaction Conditions



Catalyst (10 mol%)	Conditions (50 °C, 24 h)	Additive	Isolated yield (%)
$Cu(OTf)_2$	CH_2Cl_2, air	–	n.r.
CuBr	CH_2Cl_2, air	–	26
$Cu(OAc)_2·H_2O$	MeOH, air	–	31
$Cu(OAc)_2·H_2O$	MeOH, air	–	44
$Cu(OAc)_2·H_2O$	MeOH, air	NaOAc (3 equiv)	62
$Cu(OAc)_2·H_2O$	MeOH, air	KF (3 equiv)	40
$Cu(OAc)_2·H_2O$	MeOH, air	4 Å MS	27
$Cu(OAc)_2·H_2O$	MeOH, N_2	NaOAc (3 equiv)	n.r.



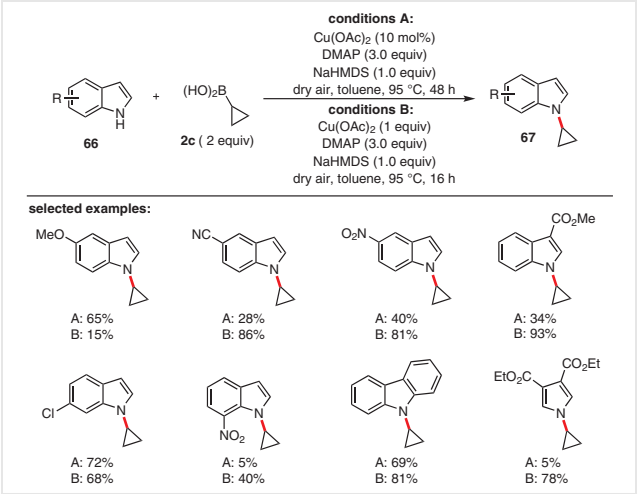
Scheme 53 $Cu(OAc)_2·H_2O$-catalyzed coupling of Cbz-protected histidine with various boronic acids

The optimized conditions were used in the reaction of Cbz-protected histidine with various arylboronic acids to give *N*(τ)-arylhistidines in moderate to good yields (Scheme 53). This reaction was successful with arylboronic acids containing either electron-donating or withdrawing groups.

2.1.8 Coupling with Alkylboron Reagents

Even though it is challenging to introduce a cyclopropyl group into indoles, pyrroles, and amides, Gagnon and co-workers successfully achieved the cyclopropylation of cyclic amides and azoles in 2007.[53] This pioneering work utilized a triscyclopropylbismuth reagent with $Cu(OAc)_2$, and the reaction proceeded in good yields with broad substrate scope. A few issues with this reaction are reagent availability and atom efficiency: the triscyclopropylbismuth reagent is not commercially available and cannot be stored for a long time, and two cyclopropyl substituents on bismuth remain unaffected in the transformation.

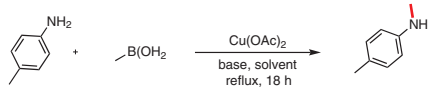
In 2008, Tsuritani and co-workers developed the Cu-mediated coupling reaction of cyclopropylboronic acid with indoles, pyrroles, and carbazoles and cyclic amides using catalytic or stoichiometric $Cu(OAc)_2$, DMAP, and NaHMDS at 95 °C under an oxygenated atmosphere (Scheme 54).[54] Various functional groups were tolerated.



Scheme 54 $Cu(OAc)_2$-mediated reaction of cyclopropylboronic acid with indoles and pyrroles

In 2009, Cruces and co-workers reported a new method for the selective monomethylation of anilines by the Cu(II)-promoted coupling of anilines and methylboronic acid to give *N*-methylanilines in high yields (Scheme 55).[55] This is the first reported example of the use of methylboronic acid in a Chan–Lam coupling reaction and is a new approach to the selective monomethylation of anilines. It is necessary to incubate the substrate with the copper reagent before the addition of methylboronic acid. Screening a variety of Cu(I)

Table 4 Optimization of the Reaction Conditions for the N-Methylation of 4-Methylaniline

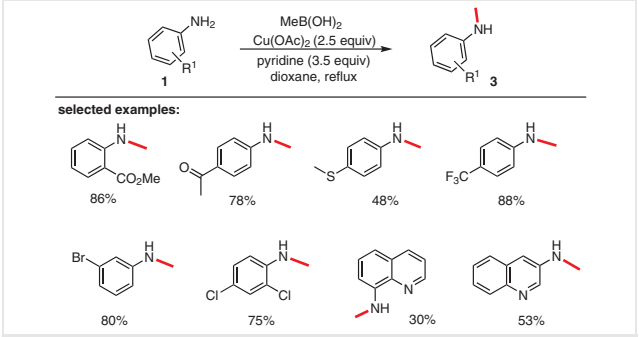


Entry	Base	Solvent	Yield (%)
1	pyridine	CH_2Cl_2	9
2	pyridine	DCE	23
3	pyridine	THF	29
4	pyridine	xylenes	33
5	pyridine	DMF	24
6	pyridine	MeCN	37
7	pyridine	dioxane	53
8	DIPEA	dioxane	21
9	Et_3N	dioxane	42

and Cu(II) salts showed $Cu(OAc)_2$ to be the best catalyst for this transformation; the Pd-catalyzed reaction, as well as the use of other copper salts, were unsuccessful. The use of a variety of solvents at different temperatures was examined (Table 4).

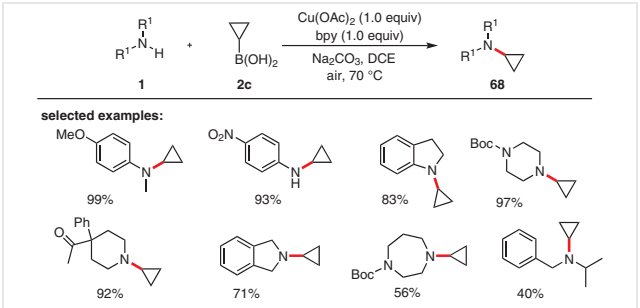
Use of excess base was not a crucial factor for the transformation as conversions with 3 and 5 equiv of pyridine were similar. However, the reaction mainly depended on the ratio of boronic acid and copper salt. Maximum yields were obtained when a mixture of the aniline, 2.5 equiv of $Cu(OAc)_2$, and pyridine in dioxane was incubated for 10–15 minutes, and then 2.5 equiv of methylboronic acid were added. This order of addition was crucial as it lowered the yield of dimethylated amine.

Both electron-deficient and -rich anilines underwent the reaction smoothly, showing good functional group tolerance (Scheme 55). Anilines bearing *ortho* substituents also produced monomethylated products but required a longer reaction time due to steric hindrance. Anilines with a ketone or ester group, which are problematic in reductive amination reactions, also gave the corresponding products. The reaction was shown to be general to other substituted anilines.

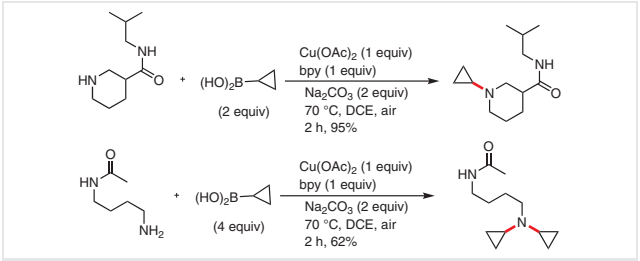


Scheme 55 $Cu(OAc)_2$-mediated monomethylation of anilines with methylboronic acid

In 2010, Zhu, Neuville, and Benard reported the reaction of anilines and primary and secondary aliphatic amines with cyclopropylboronic acid in dichloroethane in the presence of $Cu(OAc)_2$ (1 equiv), 2,2′-bipyridine (1 equiv), and Na_2CO_3 or $NaHCO_3$ (2 equiv) under air atmosphere to give the corresponding *N*-cyclopropyl derivatives in good to excellent yields (Scheme 56).[56] Anilines having electron-donating and -withdrawing groups participate in this reaction to afford *N*-cyclopropylanilines in good to excellent yields. The N-cyclopropylation of various cyclic secondary amines such as *N*-monoacylated/arylated piperazines, isoindoline, piperidine, and *N*-Boc-1,4-diazepine was also achieved using this protocol. It is interesting to note that 1-(2,5-dimethylphenyl)piperazine was successfully converted into 1-cyclopropyl-4-(2,5-dimethylphenyl)piperazine in 75% yield. Chemoselective cyclopropylation of amines was also developed by using these optimized reaction conditions (Scheme 57).

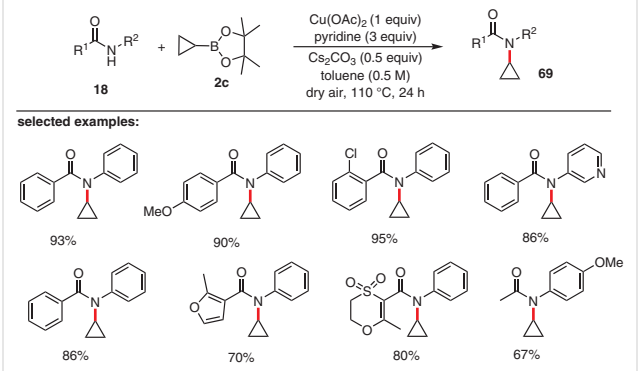


Scheme 56 Cu-mediated cyclopropylation of anilines and aliphatic amines with cyclopropylboronic acid



Scheme 57 Chemoselective Cu-mediated cyclopropylation of amide-substituted amines with cyclopropylboronic acid

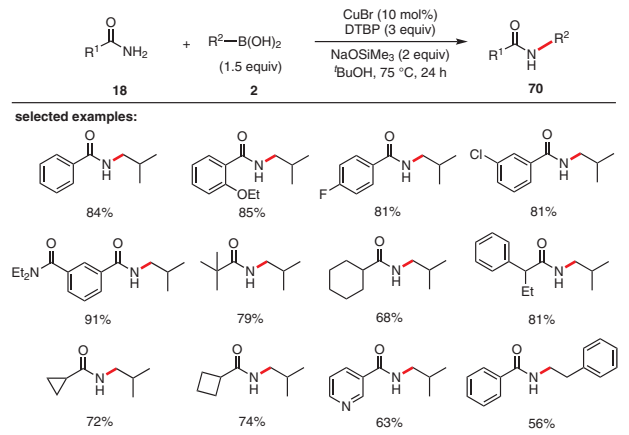
In 2013, Taillefer and co-workers explored the N-cyclopropylation of poor nucleophiles, such as aromatic and aliphatic secondary acyclic amides, using a simple and cheap copper system.[57] Treatment of acyclic *N*-alkyl- and *N*-arylamides with cyclopropylboronic acid pinacol ester under the optimized reaction conditions of 1 equiv of $Cu(OAc)_2$, 3 equiv of pyridine, 0.5 equiv of Cs_2CO_3 in toluene at 100 °C in dry air gave tertiary *N*-alkyl- and *N*-aryl-*N*-cyclopropylamides in good to excellent yields (Scheme 58); these compounds constitute a wide family of biologically active com-



Scheme 58 $Cu(OAc)_2$-promoted *N*-cyclopropylation of various secondary amides with cyclopropylboronic acid pinacol ester

pounds. In devising the optimal conditions the use of several oxidants other than the dioxygen from dry air such as pyridine *N*-oxide (PINO) or 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) was examined but no improvement in the yield was observed. On the other hand, performing the reaction under an inert atmosphere of N_2 led to a dramatic decrease in the yield.

In 2013, Watson and co-workers reported the first Chan–Lam coupling of alkylboronic acids with primary amides (Scheme 59).[58] The Cu-catalyzed coupling of amides with alkylboronic acids used $NaOSiMe_3$ as a mild base and di-*tert*-butyl peroxide (DTBP) as the oxidant and gave *N*-monoalkylamides in good to very good yields. This transformation was possible even with amides containing β-hydrogen atoms using the alkylboronic acid only in slight excess. This alkyl C–N cross-coupling has been shown to be the best facile and simple strategy for the synthesis of secondary amides.



Scheme 59 Cu-catalyzed coupling of amides with alkylboronic acids

As the alkylboronic acids were difficult to prepare and the functional group tolerance of the reaction limited, in 2016 Watson and co-workers reported the oxidative Cu-catalyzed cross-coupling of both primary and secondary alkylboronic esters with a variety of primary amides using appropriate diketimine ligands.[59] Copper catalysts were developed based on two new diketimine (NacNac) ligands (Figure 2) that easily coupled both primary and secondary alkylboronic acid pinacol esters. Optimization studies revealed that the primary boronic esters underwent coupling using ligand L3 whereas the anisidine-derived ligand L2 furnished the products with secondary boronic esters containing minimal rearranged products. The scope and generality of various substituted primary alkylboronic esters with primary amides is shown in Scheme 60, while those of different secondary alkylboronic esters with primary amides are shown in Scheme 61.

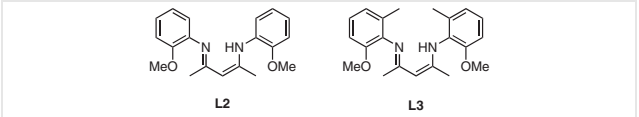
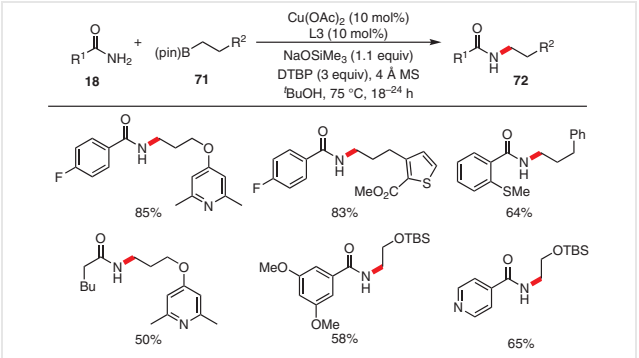
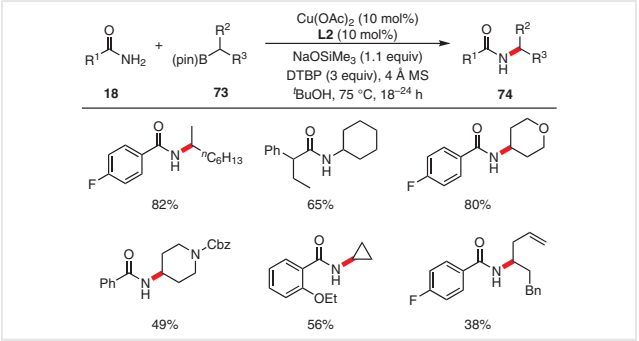


Figure 2 Diketimine (NacNac) ligands



Scheme 60 Cu-catalyzed reaction of primary alkylboronic esters with primary alkylamides

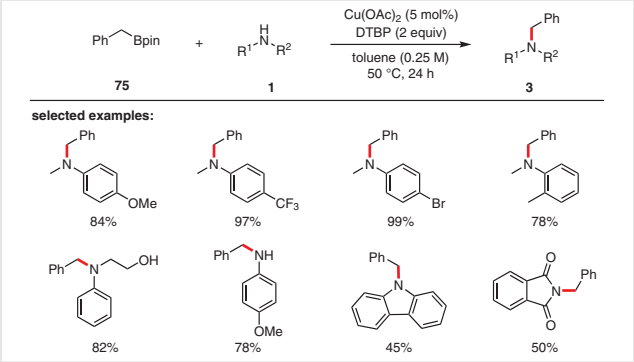


Scheme 61 Cu-catalyzed reaction of primary alkylboronic esters with secondary alkylamides

In 2013, Kuninobu and Sueki reacted amines with alkylboronic acid pinacol esters in the presence of a catalytic amount of $Cu(OAc)_2$ and di-*tert*-butyl peroxide to give alkylated amines in good to excellent yields (Scheme 62).[60] This reaction used stable boronates as substrates, and the addition of a strong base is not necessary. This reaction is a rare example of the catalytic alkylation of amines and has potential applicable to the synthesis of useful compounds such as tyrosine kinase antagonist lavendustin and folic acid antagonist methotrexate.

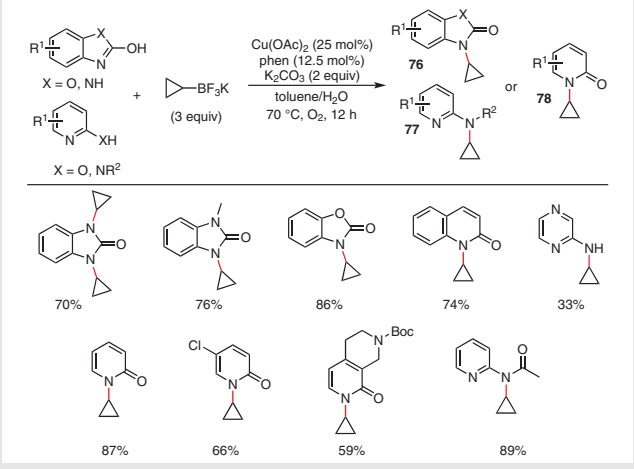
An examination of the suitability of alkylborane reagents showed that benzylboronic acid pinacol ester, even when containing electron-withdrawing or -donating groups, was more reactive than *B*-benzyl-9-borabicyclo-[3.3.1]nonane and borate. The reaction was extended to both primary and secondary alkylboronic acid pinacol esters also to alkyl groups containing base-sensitive groups such as cyano and ethoxycarbonyl. The $Cu(OAc)_2$ and di-

tert-butyl peroxide system was also used for the alkylation of phenols with alkylboronic acid pinacol esters to give alkyl aryl ethers (see Section 2.2.2).



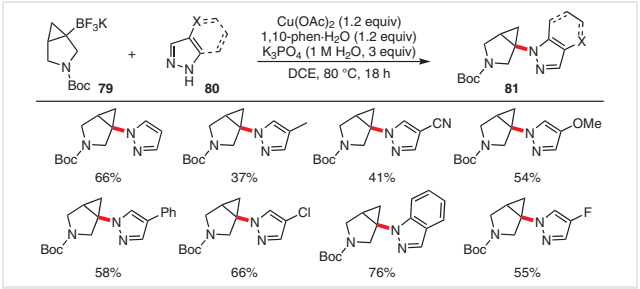
Scheme 62 $Cu(OAc)_2$-catalyzed reaction of amines with alkylboronic acid pinacol esters

In 2018, McAlpine, Engle, and co-workers reported the N-cyclopropylation of nitrogen-containing heterocycles using potassium cyclopropyltrifluoroborate and catalyzed by $Cu(OAc)_2$ and 1,10-phenanthroline and employing 1 atm of O_2 as the terminal oxidant (Scheme 63).[61] The use of more stable potassium cyclopropyltrifluoroborate, 1 atm O_2 as the terminal oxidant, bidentate ligands such as 1,10-phenanthroline and a 3:1 ratio of toluene/H_2O dramatically improved the efficiency of the reaction and improved reproducibility. These reaction conditions are not generally effective in promoting N-cyclopropylation of nitrogen nucleophiles such as unprotected, N-Boc, and N-Ac anilines. Nevertheless, three classes of aza-heterocycles such as 2-pyridones, 2-aminopyridines, and 2-hydroxybenzimidazoles were reactive substrates using this method (Scheme 63).



Scheme 63 $Cu(OAc)_2$/phen catalyzed N-cyclopropylation

In 2017, Harris and co-workers reported the Chan–Lam coupling of tertiary potassium 3-Boc-3-azabicyclo-[3.1.0]hexan-1-yltrifluoroborate with various 1,2-diazoles mediated by $Cu(OAc)_2$, phenanthroline monohydrate ligand, and K_3PO_4 to give 1-heteroaryl-3-azabicyclo-[3.1.0]hexanes containing a C-tertiary heteroarylamine (Scheme 64).[62] The reaction of a range of substituted pyrazoles proceeded in moderate to good yields while 1*H*-indazole gave the N-1 substituted product in high yield, but other nitrogen heterocycles, amides, sulfonamides, and phenol gave very poor yields.



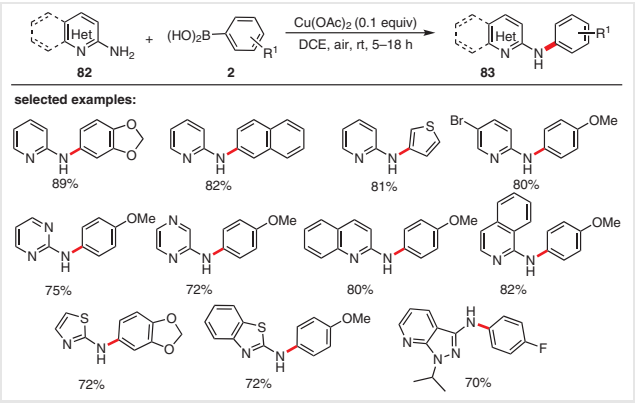
Scheme 64 $Cu(OAc)_2$/phenanthroline monohydrate -mediated coupling of potassium 3-Boc-3-azabicyclo[3.1.0]hexan-1-yltrifluoroborate with various 1,2-diazoles

2.1.9 Coupling with Electron-Deficient Heteroarylamines

In 2013, Das and co-workers reported the ligand- and base-free Cu-catalyzed N-arylation of electron-deficient 2-amino-N-heterocycles with arylboronic acids at ambient temperature in air to give a wide range of 2-(arylamino)-N-heterocycles with potential bioactivity (Scheme 65).[63]

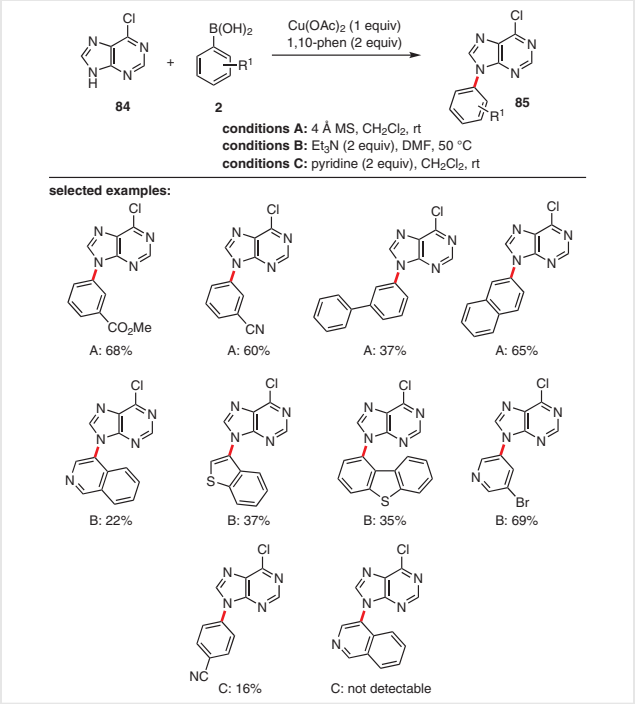
In the Chan–Lam coupling, electron-rich N-nucleophiles tends to give better results, but the presence of a chelating nitrogen atom in can also significantly influence the product yield. The reaction of 2-amino-substituted heterocycles, such as 2-amino-substituted pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, thiazole, and benzothiazole, with electronically diverse boronic acids using 10 mol% $Cu(OAc)_2$ in DCE with air as the oxidant gave the corresponding products in good to excellent yields, and the only noticeable difference was observed in the reaction times. The generality of the reaction was shown by the reaction of 5-bromo-2-aminopyridine, which is otherwise difficult to react under palladium-catalyzed amination reactions. The reaction was further extended to pharmaceutically important heterocyclic pyrazolopyridines such as 1-alkyl-substituted 1*H*-pyrazolo[3,4-*b*]pyridin-3-amine.

In 2015, Wu and co-workers also developed a similar method for the N-arylation of 2-amino-N-heterocycles by using arylboronic acids with $Cu(OAc)_2 \cdot H_2O$ as the active catalyst.[64]



Scheme 65 Cu-catalyzed N-arylation of 2-amino-N-heterocycles with arylboronic acids

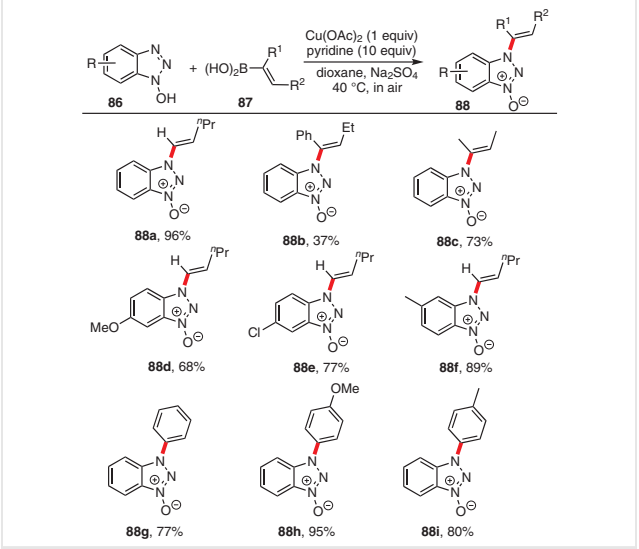
In 2014, Pochet and co-workers reported the $Cu(OAc)_2$-mediated synthesis of 9-(hetero)aryl purine derivatives using 6-chloropurine and arylboronic acids (Scheme 66).[65] The coupling reaction of sterically demanding (hetero)arylboronic acids was successfully performed by optimizing the reaction conditions in terms of base and solvent. Target adenine derivatives were then obtained from the coupling products.



Scheme 66 Cu-catalyzed N-arylation of 6-chloropurine with arylboronic acids

They developed three different conditions: Conditions A: $Cu(OAc)_2$ (1 equiv), (hetero)arylboronic acid (3 equiv), and 1,10-phenanthroline (2 equiv) in 4 Å MS in CH_2Cl_2 as solvent at room temperature. Conditions B: $Cu(OAc)_2$ (1 equiv), (hetero)arylboronic acid (3 equiv), 1,10-phenanthroline (2 equiv), and Et_3N (2 equiv) in DMF as solvent at 50 °C . Conditions C: $Cu(OAc)_2$ (1 equiv) and (hetero)arylboronic acid (3 equiv), 1,10-phenanthroline (2 equiv), and pyridine (2 equiv) in CH_2Cl_2 as solvent at room temperature. The described two-step procedure provides simple and rapid access to original adenine fragments, which are valuable starting points for fragment-based screening applications, as well as for further chemical diversification into potential therapeutic agents.

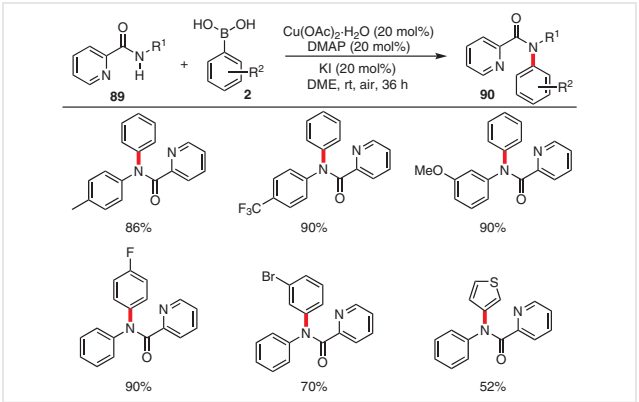
Mo and co-workers reported the N-vinylation or N-arylation of *N*-hydroxybenzotriazoles by Cu-mediated coupling with alk-1-enyl- or arylboronic acids to give 1-alk-1-enyl- or 1-arylbenzotriazole 3-oxides, respectively (Scheme 67).[66] Treating HOBt derivatives and various substituted boronic acids with 1.0 equiv $Cu(OAc)_2$, 6 equiv of Na_2SO_4, and 10.0 equiv pyridine in dioxane at 40 °C provided 1-alk-1-enylbenzotriazole 3-oxides in good to excellent yields. This Cu-mediated coupling reaction was also generalized to N-arylation using arylboronic acids bearing various electron-rich and electron-deficient groups in the *ortho*-, *meta*-, and *para*-positions to give 1-arylbenzotriazole-3-oxides in excellent yields.



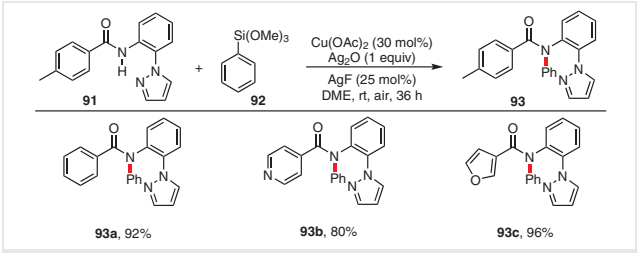
Scheme 67 Cu-mediated coupling of *N*-hydroxybenzotriazoles with alk-1-enyl- or arylboronic acids

Baidya and co-workers explored the chelation-assisted Cu-catalyzed cross-coupling of bidentate amides with arylboronic acids to give unsymmetrical amides in high yields (Scheme 68).[67] The catalyst system used $Cu(OAc)_2{\cdot}H_2O$ with DMAP as the base and KI as an additive in DME under open-air conditions at room temperature. This reaction was adapted for the reaction of bidentate amides with phenyl(trimethoxy)silanes using $Cu(OAc)_2$, Ag_2O, and AgF in DMSO at 80 °C for 24 hours (Scheme 69). The generality of

this reaction was further extended with 1-(2-aminophenyl)pyrazole and aminophenyloxazoline bidentate auxiliaries. It is interesting to note that arylboronic acids containing both electron-rich as well as electron-deficient groups generated the N-arylated products, and *ortho* C–H arylation was not seen under these conditions.



Scheme 68 Chelation-assisted Cu-catalyzed cross-coupling of bidentate amides with arylboronic acids



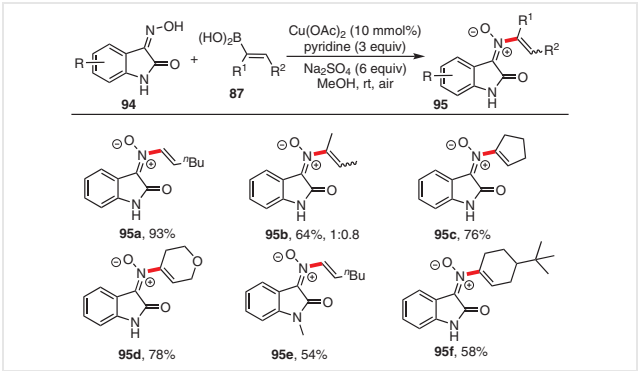
Scheme 69 Chelation-assisted Cu-catalyzed cross-coupling of bidentate amides with phenyl(trimethoxy)silane

In 2017, Mo and co-workers reported that 3-(hydroxyimino)indolin-2-ones underwent Cu-catalyzed selective cross-coupling reaction with alk-1-enylboronic acids to furnish (*E*)-*N*-(alk-1-enyl)oxindole nitrones under mild conditions (Scheme 70).[68] They demonstrated that mono-N-vinylation could be achieved using catalytic copper salt whereas 2.0 equiv of copper salt generated double N-vinylation products. The synthesized nitrones were cyclized to spirooxindoles under thermal conditions in toluene at 120–140 °C (Scheme 71).

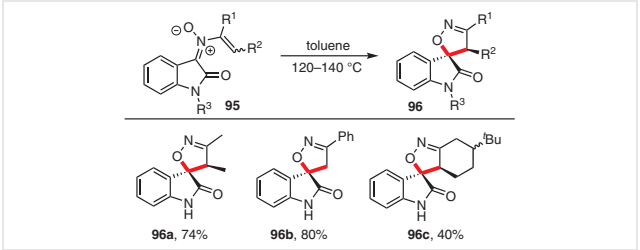
2.1.10 Selective C–N Bond Formation for the Synthesis of Heterocycle-Containing Compounds

In 2014, Das and co-workers reported the Cu(II)-catalyzed sequential N-arylation of C-amino-NH-azoles with (hetero)arylboronic acids (Figure 3).[69]

The N-arylation of cyclic amidines, such as 2-aminobenzimidazole, 3-aminoindazoles, and 3-aminopyrazolopyridine, using transition-metal catalysts is very difficult as



Scheme 70 Cu-catalyzed N-vinylation of 3-(hydroxyimino)indolin-2-ones with alk-1-enylboronic acids



Scheme 71 Thermal reaction of (*E*)-*N*-(alk-1-enyl)oxindole nitrones to form spirooxindoles

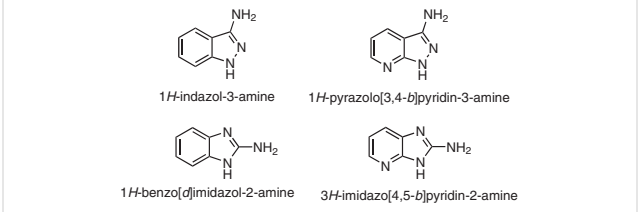
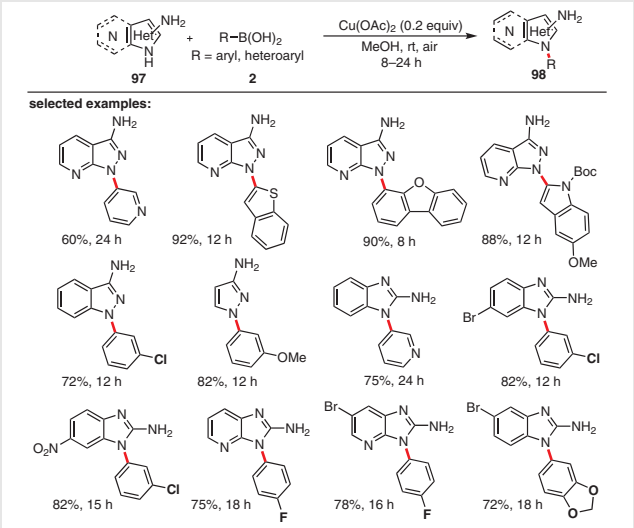


Figure 3 (Hetero)arene-fused C-amino-NH-azoles

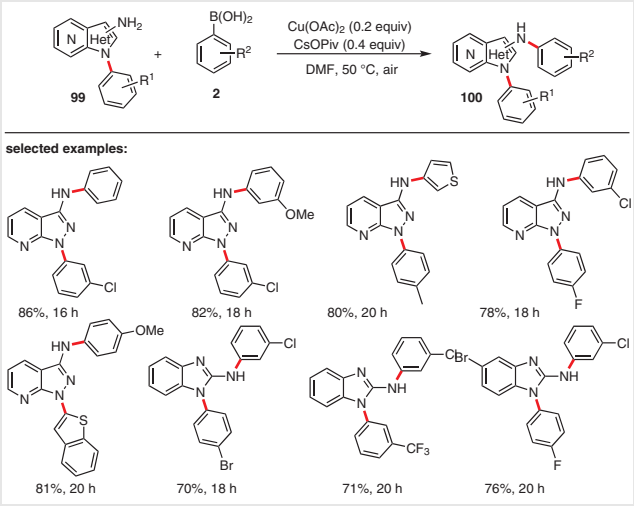
they coordinate to the active metal centers. Das and coworkers developed an efficient strategy to first give N-aryl-C-aminoazoles and then N-aryl-C-(arylamino)azole derivatives using various (hetero)arylboronic acids in a one-pot or two steps (Schemes 72 and 73). Using this method, for the first time, even substrates with two different nucleophilic sites, such as pyrazolopyridine and pyridoimidazole, were successfully transformed (Scheme 73).

Mechanistic studies showed that the [Ar–Cu(II)–Nu] complex is oxidized to [Ar–Cu(III)–Nu] in the presence of O_2 (air), which further undergoes reductive elimination to form the product [Ar-azole(Nu)]. Oxygen also helps in the regeneration of the catalyst.

In 2013, Neuville and Li used a three-component system with arylboronic acids, amines, and cyanamides for the Cu-catalyzed formation of *N*,*N*′,*N*″-trisubstituted aryl guanidines (Scheme 74).[70] The catalyst system used $CuCl_2·2H_2O$ as the catalyst and K_2CO_3 as the base in the presence of 2,2′-



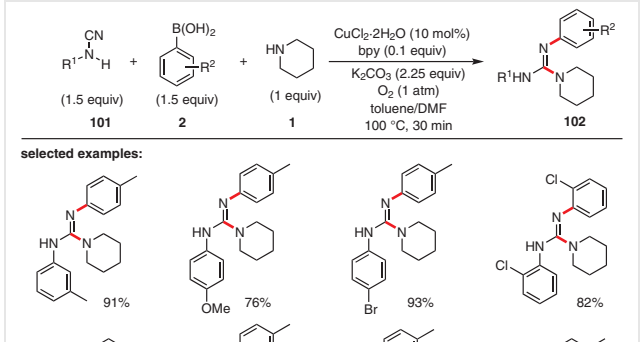
Scheme 72 Cu-catalyzed N-arylation of C-amino-NH-azoles with (hetero)arylboronic acids



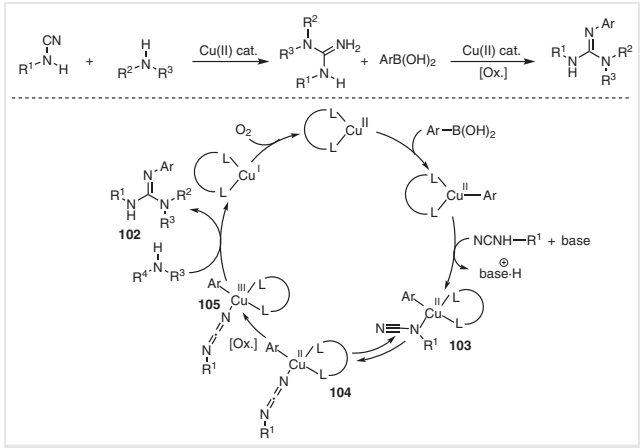
Scheme 73 Cu-catalyzed C–NH_2-arylation of N-aryl-C-[(hetero)arylamino]azoles with (hetero)arylboronic acids

bipyridine and oxygen (1 atm). These structures are prevalent in many pharmaceuticals such as Relenza (antiviral), famotidine (antiulcer), and clonidine (anesthetic R_2 adrenoceptor agonist). This strategy can also be extended toward the synthesis of heterocyclics, such as benzimidazoles or quinazolines.

A plausible mechanism for this transformation is illustrated in Scheme 75. In the initial step, the Cu(II) complex undergoes transmetalation with boronic acid, which coordinates to the deprotonated cyanamide to form complex **103**, which then tautomerizes to generate diimide complex **104** that is oxidized to Cu(III) complex **105** by either O_2 or Cu(II). Even though the reductive elimination of this complex **105** can generate the carbodiimide, this was not observed in the reaction. Thus, it is proposed that complex **105** undergoes nucleophilic addition by the amine **1** followed by reductive elimination to generate the product **102** and regenerate the Cu(I) catalyst. The Cu(I) species is oxidized to Cu(II) to continue the catalytic cycle.



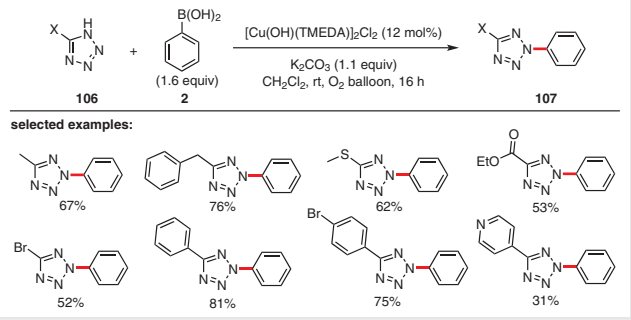
Scheme 74 Cu-catalyzed reaction of the three-component system of arylboronic acids, amines, and cyanamides



Scheme 75 Mechanism of the Cu-catalyzed reaction of the three-component system of arylboronic acids, amines, and cyanamides

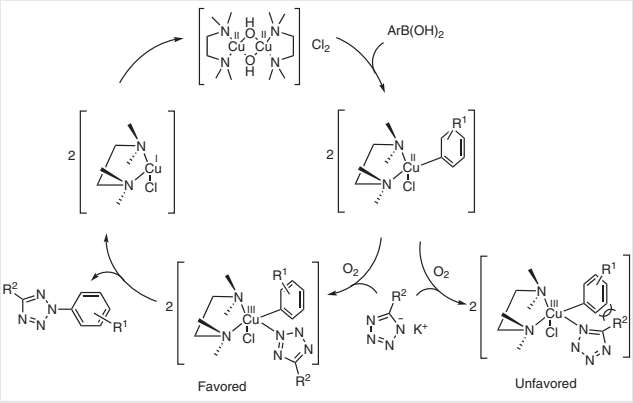
In 2014, Onaka, Maegawa, and co-workers developed a mild and regioselective 2-arylation of 5-substituted tetrazoles with various arylboronic acids using $[Cu(OH)(TMEDA)]_2Cl_2$ to generate 2,5-disubstituted tetrazoles (Scheme 76). This is the first report of a highly regioselective arylation of 5-alkyltetrazoles.[71]

A similar mechanism to that of the Collman group (Scheme 5)[15,16] was proposed for this transformation (Scheme 77). In the initial step, the transmetalation of Cu(II) with arylboronic acid followed by the coordination of tetrazole results in the formation of a Cu(III) complex in the presence of oxygen. Even though the reaction of imidazoles



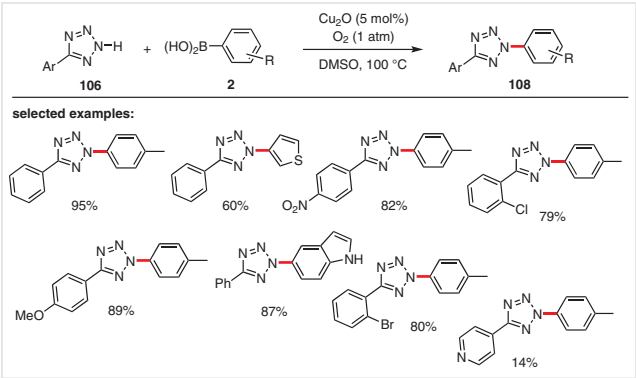
Scheme 76 $[Cu(OH)(TMEDA)]_2Cl_2$-catalyzed 2-arylation of 5-substituted tetrazoles with various arylboronic acids

using the same catalyst was performed by the Collman group, the reaction with tetrazole was unsuccessful. As the nucleophilicity of tetrazoles is different from imidazoles, the addition of K_2CO_3 was found to be crucial to carry out the reaction. Due to steric repulsion of the aryl group with the substituent on the 5-position, coordination of tetrazole at N-2 is more favored than at N-1. This complex undergoes reductive elimination to furnish the product and regenerates the Cu(II) catalyst.



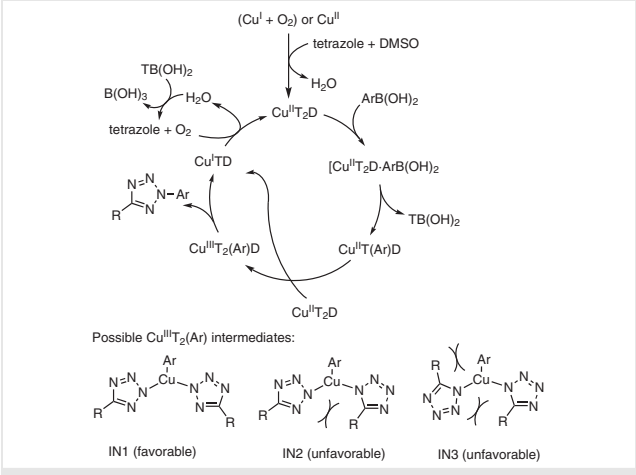
Scheme 77 Mechanism for the $[Cu(OH)(TMEDA)]_2Cl_2$-catalyzed 2-arylation of 5-substituted tetrazoles

In 2014, Han and co-workers reported the Chan–Lam reaction by simply stirring 5-aryl-*H*-tetrazoles with arylboronic acids using 5 mol% of either Cu(I) or Cu(II) catalyst in the presence of O_2 in DMSO as solvent at 100 °C to give 2,5-disubstituted tetrazoles easily and regioselectively in high to excellent yields (Scheme 78).[72] Tetrazole and DMSO play a significant role in the regeneration of the active catalyst in addition to serving as reactant and solvent, respectively. The Cu(II) complex formed via the oxidation of Cu(I) species by oxygen undergoes oxidative amination to form $[CuT_2D]$ complex [T = tetrazole; D = DMSO]. This is the active complex that generates arylCu(III) and Cu(I) species from which the product is formed by Cu(III) species.



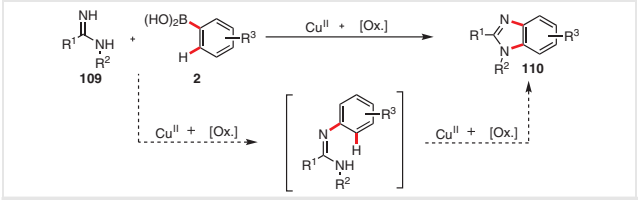
Scheme 78 Cu-catalyzed coupling of various tetrazoles with boronic acids

The steric repulsion in the $[Cu(III)T_2(Ar)]$ intermediate plays a crucial role in the regioselective synthesis of 2,5-disubstituted tetrazoles. Among the three isomers IN1, IN2, and IN3 (Scheme 79), the least steric hindrance is observed in IN1, in which the Cu–N bond is generated at the N-2 position. Large steric repulsion in the isomers IN2 and IN3 due to the bond formation at N-1 position restricts the formation of these intermediates in the reaction. Thus the 1,5-disubstituted product is not observed in the reaction.

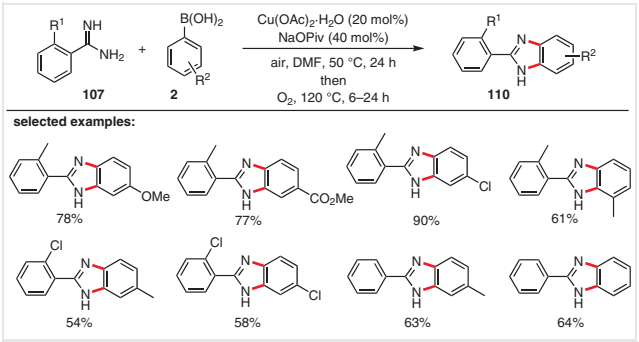


Scheme 79 Proposed reaction mechanism of Cu(I)- and Cu(II)-catalyzed direct coupling of tetrazole and boronic acid

The $Cu(OAc)_2$-catalyzed mono-N-arylation reaction of amidines **109** using arylboronic acids **2** in the presence of NaOPiv to give N^2-arylamidines was reported by Zhu and co-workers in 2012 (Scheme 80). Slight modification of the reaction conditions by increasing the temperature to 120 °C in the presence of O_2, resulted in an intramolecular C–H functionalization of the N^2-arylamidines to generate benzimidazoles (Scheme 81).[73]

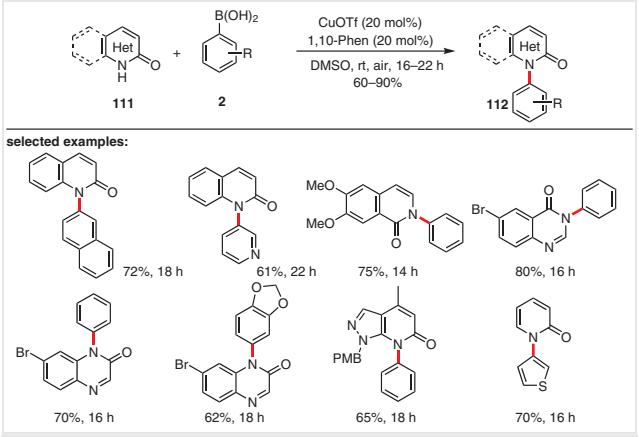


Scheme 80 Mono-N-arylation reaction of amidines and intramolecular C–H functionalization of the resulting N^2-arylamidines



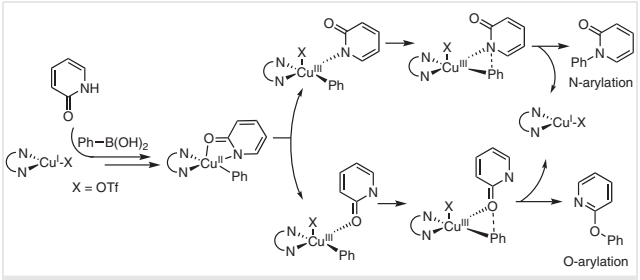
Scheme 81 Cu-catalyzed synthesis of benzimidazoles from primary amidines

In 2016, Das and co-workers reported a base-free, open-flask, mild strategy for the N-arylation of tautomerizable N-heterocycles with various arylboronic acids using CuOTf as the catalyst and 1,10-phenanthroline as the ligand (Scheme 82).[74] The reaction was found to be controlled both kinetically and thermodynamically as determined by the density functional methods. The N-arylation of 1,3-benzoxazol-2(3*H*)-one gave 3-aryl-1,3-benzoxazol-2(3*H*)-ones (15 examples) that were further transformed to various naturally occurring oxygenated carbazole alkaloids (e.g., clausenine, clauraila A, clausenal).



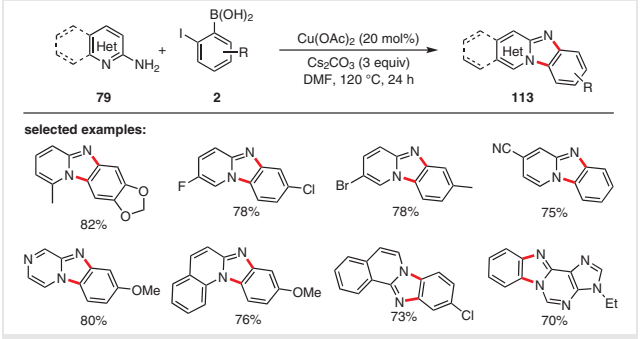
Scheme 82 CuOTf/1,10-phen-catalyzed N-arylation of tautomerizable N-heterocycles with arylboronic acids

The selectivity in the N-arylation of pyridin-2(1*H*)-one was explained both thermodynamically and kinetically by energy calculations (Scheme 83). The overall energy barrier required for N-arylation is 10.50 kcal/mol, which is 5.10 kcal/mol less than that for O-arylation (15.60 kcal/mol).

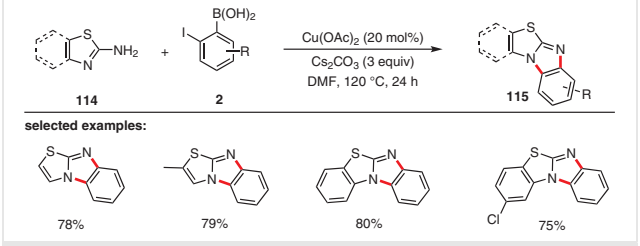


Scheme 83 Possible catalytic pathway for the selective N-arylation of pyridin-2(1*H*)-one

In 2015, Das and co-workers reported the synthesis of various benzimidazole-fused heterocycles via a Cu(II)-catalyzed, inter/intramolecular C–N bond-forming reaction.[75] The one-pot reaction of 2-aminoheteroarenes and 2-iodoarylboronic acids furnished a wide range of benzimidazole-fused N-heteroarenes, such as benzimidazo[1,2-*a*]quinolines, benzo[4,5]imidazo[2,1-*b*]thiazoles, pyrido[1,2-*a*]benzimidazole, benzimidazo[1,2-*a*]pyrazine, etc. (Schemes 84 and 85). The Chan–Lam type coupling was subsequently followed by an Ullmann-type reaction in this novel cascade protocol for C–N bond formation.

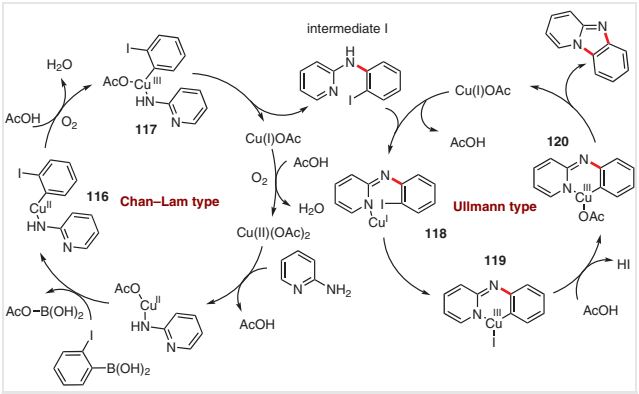


Scheme 84 Synthesis of pyrido[1,2-*a*]benzimidazoles and derivatives



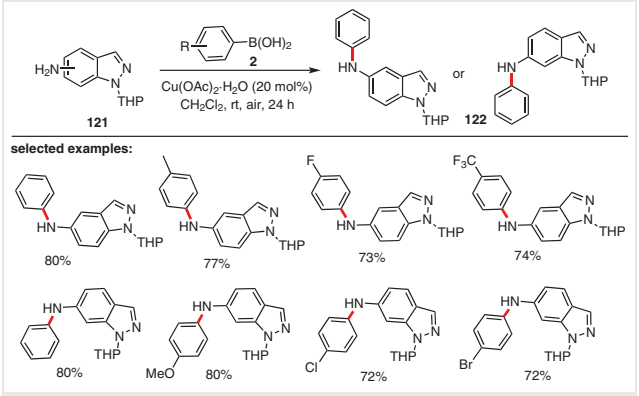
Scheme 85 Synthesis of benzo[*d*]thiazolo[3,2-*a*]imidazole and benzo[4,5]imidazo[2,1-*b*]thiazoles

In the first step (Scheme 86), Cu(II) coordinates to 2-aminopyridine and undergoes transmetalation with $PhB(OH)_2$ to form **116**. Then **116** is oxidized to **117**, a Cu(III) complex, by O_2 and it undergoes reductive elimination to form an *N*-arylated product (Intermediate I). Intermediate I can coordinate with Cu(I) to generate **118**, which undergoes oxidative addition with aryl halide to form **119**. Complex **120** is formed from **119**, which further undergoes reductive elimination to form benzo[4,5]imidazo[1,2-*a*]pyridine, the cyclized product, and regenerates the Cu(I) species. This Cu(I) species is oxidized by O_2 to Cu(III), which continues the catalytic cycle.



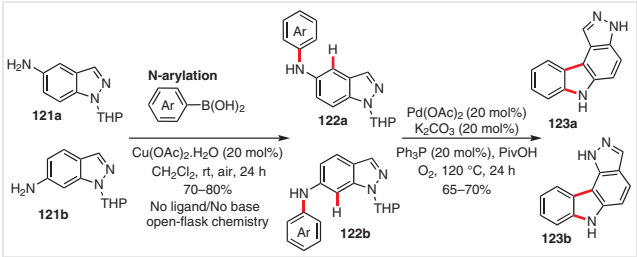
Scheme 86 Mechanism for the formation of pyridobenzimidazoles

Also in 2015, Das and co-workers reported the Cu(II)-catalyzed reaction of 5- and 6-aminoindazoles with arylboronic acids to give 5- and 6-(arylamino)-substituted indazoles (Scheme 87).[76] These (arylamino)indazoles were converted into pyrazole-fused carbazoles by Pd(II)-catalyzed cross-dehydrogenative coupling (CDC). Various polyheterocycles such as 1,6-dihydropyrazolo[4,3-*c*]carbazoles and 3,6-dihydropyrazolo[3,4-*c*]carbazoles were synthesized using this combined N-arylation/C–H arylation strategy (Scheme 88). Quantum chemical analysis was performed to

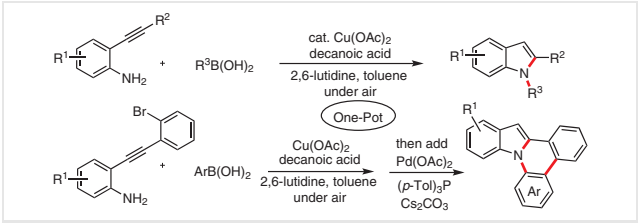


Scheme 87 Cu-catalyzed arylation of 5- and 6-aminoindazoles with arylboronic acids

better understand the regioselectivity and to trace the potential energy surface of the entire reaction upon 5-(arylamino)indazole conversion into the corresponding carbazole.

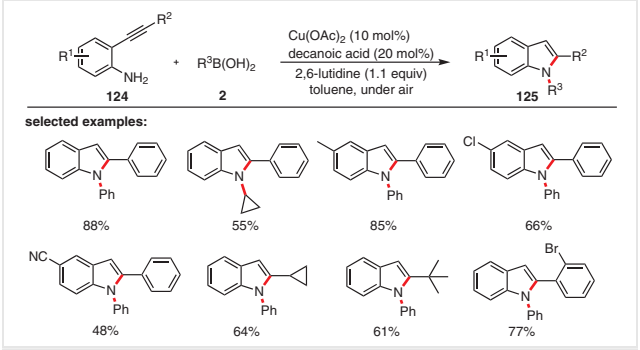


Scheme 88 Cu-catalyzed N-arylation and Pd-catalyzed C–H arylation to give pyrazolo-carbazoles



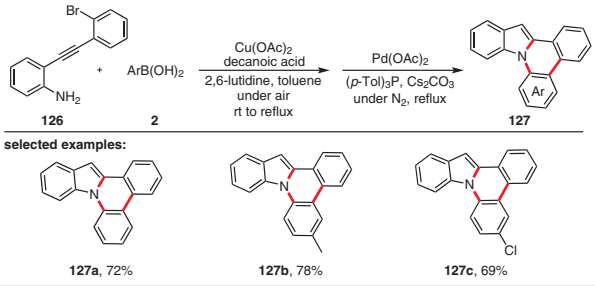
Scheme 89 Cu(II)-catalyzed domino coupling/cyclization of 2-alkynylanilines and alkyl- and arylboronic acids

In 2014, Wang, Lv, and co-workers developed a method for the direct assembly of 1,2-disubstituted indoles via Cu(II)-catalyzed domino coupling/cyclization process (Scheme 89).[77] The reaction of 2-alkynylanilines and alkyl- and arylboronic acids catalyzed by $Cu(OAc)_2$ with 2,6-lutidine as a base and decanoic acid as an additive under aerobic conditions gave 1,2-disubstituted indoles (Scheme 90). The reaction of 2-(2-bromophenylethynyl)anilines with arylboronic acids under these conditions gave 1-aryl-2-(2-bromophenyl)-1*H*-indoles that underwent intermolecular Pd-catalyzed C(sp^2)–H arylation by addition of $Pd(OAc)_2$, (p-Tol)$_3$P, and Cs_2CO_3 under nitrogen without isolation of



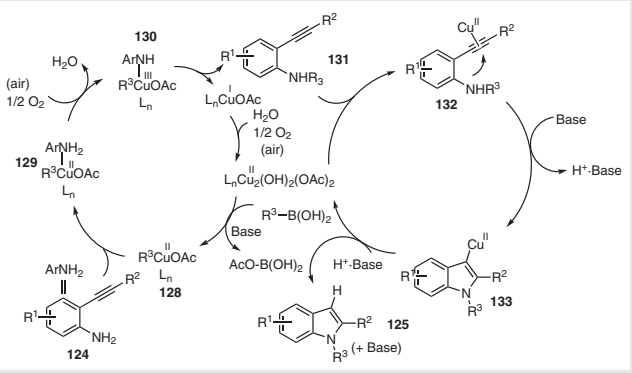
Scheme 90 One-pot Cu(II)-catalyzed domino coupling/cyclization to give 1,2-disubstituted indoles

the indole intermediate to give indolo[1,2-*f*]phenanthridines in a one-pot synthesis (Scheme 91). Polycyclic indole derivatives were also synthesized using this method.



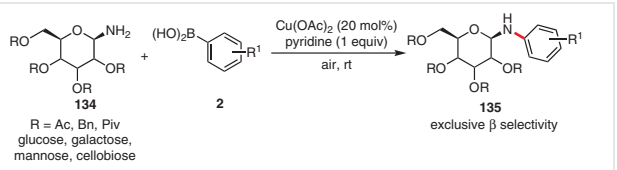
Scheme 91 One-pot Cu(II)-catalyzed domino coupling/cyclization followed by intramolecular Pd-catalyzed C(sp^2)–H arylation to give indolo[1,2-*f*]phenanthridines

A possible mechanism for the coupling/annulation under aerobic conditions was proposed (Scheme 92). The $L_nCu^{II}_2(OH)_2(OAc)_2$ complex undergoes transmetalation with boronic acid promoted by base (such as 2,6-lutidine) to afford R–Cu(II) species **128**. This is followed by the generation of Cu(II) complex **129** via the coordination of the complex **128** to aniline **124**, which is subsequently oxidized by oxygen to Cu(III) complex **130**. Final reductive elimination generates the product **131** and the Cu(I) complex. This Cu(I) complex is oxidized to Cu(II) and this activates the alkyne by coordinating with the C≡C bond giving **132**. Finally, the intramolecular cyclization of **132** followed by protonolysis gives the product **125** and regenerates the active catalyst.



Scheme 92 Mechanism for the Cu(II)-catalyzed domino coupling/cyclization to give 1,2-disubstituted indoles

In 2013, Alami, Messaoudi, and co-workers reported an efficient stereoselective $Cu(OAc)_2$ and pyridine catalyzed method for the N-arylation of glycosylamines with substituted arylboronic acids at room temperature under air to furnish aryl *N*-glycosides with exclusive β-selectivity (Scheme 93).[78] One of the most important subfamilies of *N*-glycosides is (hetero)aryl *N*-glycosides, whose derivatives

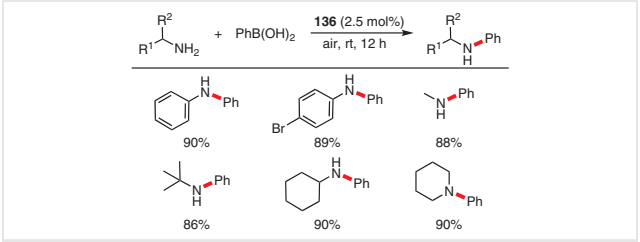


Scheme 93 Cu-catalyzed N-arylation of glycosylamines with substituted arylboronic acids

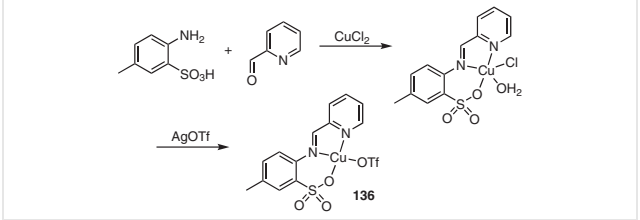
show promising biological activities, including antiviral and anticancer properties.

2.1.11 Using Sulfonato-imino Copper(II) Complexes

In 2017, Schaper and Hardouin Duparc reported the efficient Chan–Lam coupling of various amines or anilines, including sterically hindered examples, with phenylboronic acid using sulfonato-imino copper(II) complexes under mild conditions without the need of an external base or ligand to give *N*-alkyl- or *N*-arylanilines (Scheme 94).[79] The imino-sulfonate copper complex with chloride as the counteranion was prepared in a one-step reaction using commercially available starting materials; this complex underwent anion-exchange with AgOTf furnishing complex **136** with triflate as the counteranion (Scheme 95). As complex **136** remains active under aqueous conditions, it was used in the synthesis of *N*-methylaniline using aqueous methylamine and phenylboronic acid. In this reaction, it was only necessary to optimize temperature and time, and typical side reactions, such as deboronation and homocoupling, were absent.



Scheme 94 Imino-sulfonate copper complex catalyzed reaction of amines and anilines with phenylboronic acid

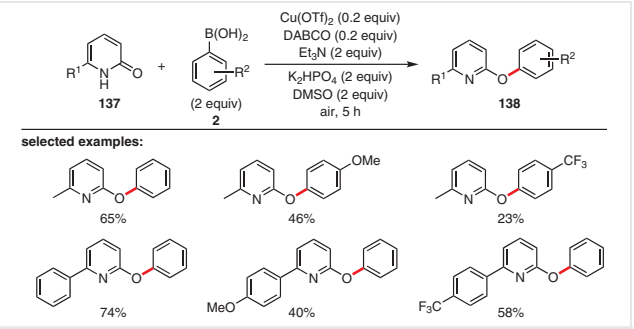


Scheme 95 Formation of imino-sulfonate copper complexes

2.2 C–O Bond Formation

2.2.1 Coupling with (Hetero)arylboron Reagents

In 2013, Luo, Hu, and co-workers used the Cu-catalyzed reaction of 6-substituted pyridin-2(1*H*)-ones and arylboronic acids in the synthesis of O-arylated pyridin-2(1*H*)-ones (Scheme 96).[80] Using the optimum conditions with 20 mol% of $Cu(OTf)_2$ as the catalyst, DABCO as the ligand, Et_3N as the base, and K_2HPO_4 as an additive for 5 hours at 50 °C gave O-arylated pyridin-2(1*H*)-ones in up to 81% yield.



Scheme 96 $Cu(OTf)_2$/DABCO-catalyzed reaction of 6-substituted pyridin-2(1*H*)-ones and arylboronic acids

On the basis of the mechanism of the Chan–Lam coupling reaction and further experiments, they identified two crucial factors for the regioselectivity (Figure 4): 1. the steric hindrance of DABCO catalyst system, which restricts the generation of the N–Cu(II) intermediate, and 2. steric hindrance by the 6-substituent, such as methyl.

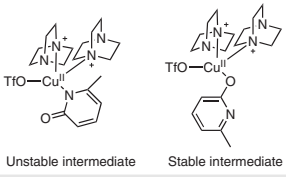
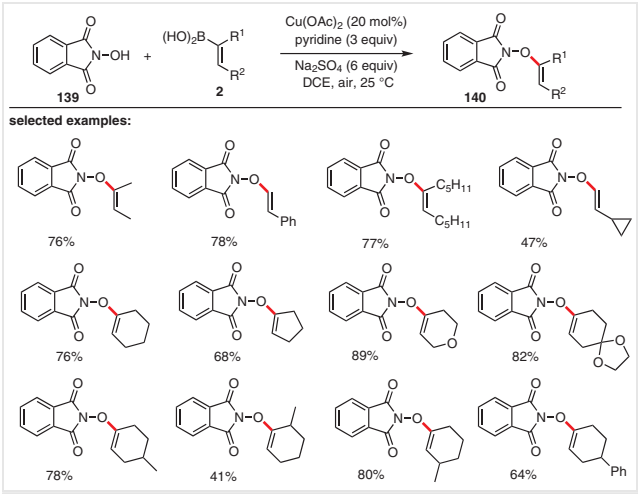


Figure 4 Plausible intermediates for the explanation of regioselectivity of C–O bond formation

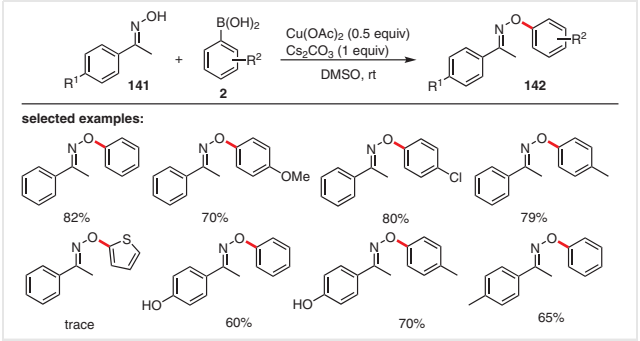
Although the Cu-mediated arylation of *N*-hydroxyphthalimide with arylboronic acids has been previously reported,[81a], the corresponding process for vinylation was unknown. In 2012, Anderson and co-workers reported the of *N*-hydroxyphthalimide with 2 equiv of alk-1-enylboronic acid under the optimized conditions using $Cu(OAc)_2$ as the catalyst, 3 equiv of pyridine as the base, and 4 equiv of Na_2SO_4 in DCE and O_2 (Scheme 97).[81b] The use of 2 equiv of alk-1-enylboronic acid, air, and halogenated solvents all played a significant role in the reaction.

In 2012 in a more efficient alternative to existing protocols, Bora and co-workers used Chan–Lam coupling of aryloximes and arylboronic acids for the synthesis of arylox-



Scheme 97 $Cu(OAc)_2$-catalyzed reaction of *N*-hydroxyphthalimide with alk-1-enylboronic acids

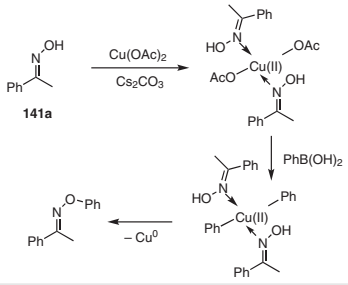
ime ethers (Scheme 98).[82] The optimized reaction conditions utilized $Cu(OAc)_2$ as the catalyst and Cs_2CO_3 as the base in DMSO at room temperature for 5 hours. The use of Cs_2CO_3 has several advantages, such as increased product yields with shorter reaction times, smaller amounts of reagents, easy workup, and clean and mild reaction conditions.



Scheme 98 $Cu(OAc)_2$-catalyzed coupling of acetophenone oximes with arylboronic acids

The mechanism for the $Cu(OAc)_2$-mediated construction of *O*-aryloxime ether from oximes in the presence of inorganic bases has not yet been reported. Lam and co-workers have investigated the formation of a deep blue copper complex from an insoluble mixture of $Cu(OAc)_2$ and CH_2Cl_2 on the addition of amine-based substrates.[83] Using DMSO as solvent increased the yield as $Cu(OAc)_2$ is soluble in DMSO.

Bora and co-workers proposed a mechanism that includes the coordination of $Cu(OAc)_2$ to oxime followed by transmetalation with $PhB(OH)_2$ (Scheme 99).[82] The product oxime ether is produced by the reductive elimination of this complex.

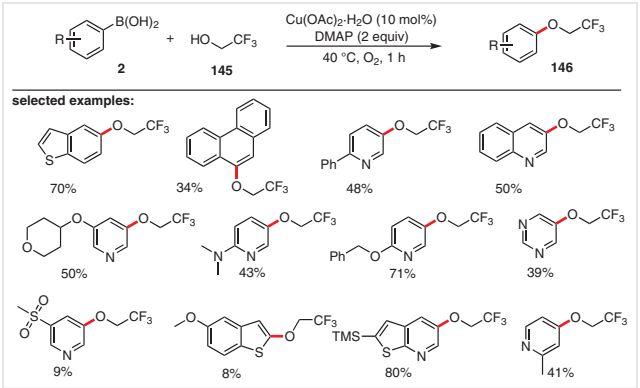


Scheme 99 Mechanism for the $Cu(OAc)_2$-catalyzed coupling of acetophenone oximes with phenylboronic acid

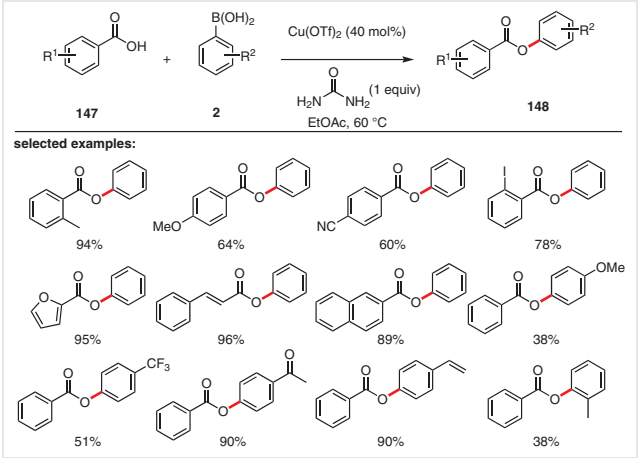
The reaction between **141a** and $Cu(OAc)_2$ was carried out to check the involvement of the Cu(II) complex; IR spectroscopic studies of the resulting complex showed that it contains the OH group and this indicates that it is the nitrogen atom of the oxime group that coordinates to the metal and this was also confirmed by IR data. All other evidence, such as mass spectroscopic analysis, the formation of the product using a preformed Cu(II) complex, and formation of the deep blue solution on stirring **141a**, **2**, $Cu(OAc)_2$, and Cs_2CO_3 all support the formation of the copper complex. The formation of the Cu(II) complex was not affected by the presence or absence of the base.

In 2014, Gagnon and co-workers reported $Cu(OAc)_2$-mediated O-arylation reaction of phenols and trivalent organobismuthanes to give highly functionalized diaryl ethers (Scheme 100).[84] Various phenols bearing different functional groups and a variety of organobismuth reagents reacted under these simple reaction conditions. By using an oxygen atmosphere, the amount of catalyst used in the reaction can be significantly minimized (conditions B). The N-arylation of pyridin-2(1*H*)-ones was also reported using conditions A.

2,2,2-Trifluoroethyl ethers have gathered attention as pharmaceuticals and polymer materials; the trifluoromethoxy group confers metabolic stability and lipophilicity, hence their synthesis is of interest.[85a] Methods for the synthesis of trifluoroethyl ethers have frequently included harsh reaction conditions, such as elevated temperatures, activated substrates, limited applicability, and use of DMSO or the toxic solvent HMPA. For example, in 1985 Suzuki and co-workers reported the construction of aryl 2,2,2-trifluoroethyl ethers using the CuI-assisted reaction of aryl iodides and sodium 2,2,2-trifluoroethoxide in HMPA at 90–100 °C.[85b] In 2015, Zou, Wu, and co-workers developed a Cu-catalyzed coupling of 2,2,2-trifluoroethanol with various (hetero)arylboronic acids under mild conditions to give (hetero)aryl 2,2,2-trifluoroethyl ethers in moderate to good yields (Scheme 101).[86] The optimal conditions used $Cu(OAc)_2{\cdot}H_2O$ as catalyst and DMAP as base and ligand in 2,2,2-trifluoroethanol as solvent at 40 °C for 1 hour in the presence of O_2.

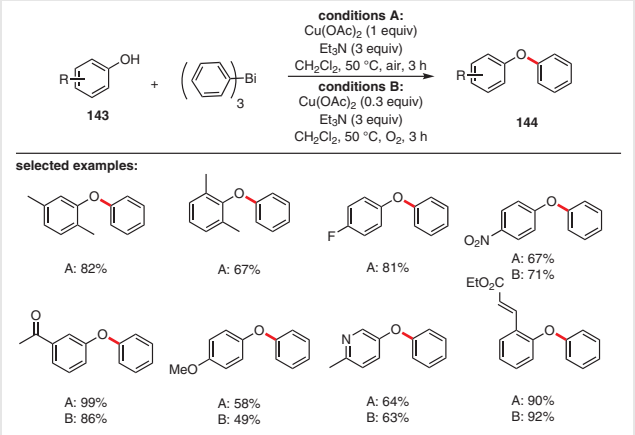


Scheme 101 $Cu(OAc)_2$-catalyzed cross-coupling of trifluoroethanol with (hetero)arylboronic acids



Scheme 102 $Cu(OTf)_2$/urea-catalyzed coupling of carboxylic acids with phenylboronic acids

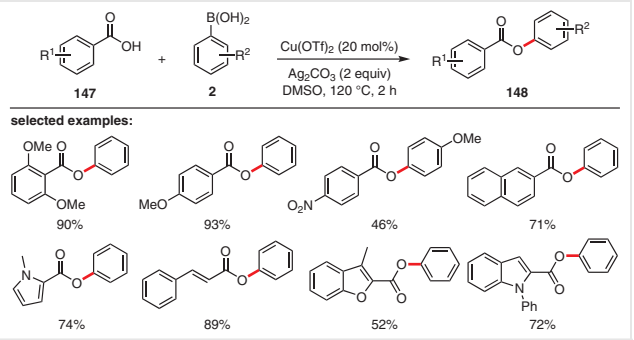
In 2010, Cheng and co-workers reported the first example utilizing carboxylic acids as an O-donor in the Chan–Lam coupling. The $Cu(OTf)_2$-mediated coupling of carboxyl-



Scheme 100 $Cu(OAc)_2$-mediated O-arylation reaction of phenols and trivalent organobismuthanes

ic acids, such as benzoic, cinnamic, phenylacetic, furan-2-carboxylic, and naphthoic acid, and phenylboronic acids gave esters (Scheme 102).[87] Substitution on both the benzoic acids (Me, OMe, CN, halo, NO_2, and OH) and phenylboronic acids (Me, OMe, Cl, vinyl, Ac, CF_3, CO_2Me) gave the ester products in moderate to good yields. The optimized catalyst system used 40 mol% of $Cu(OTf)_2$ with 1 equiv of urea as the ligand in EtOAc solvent at 60 °C in the presence of air.

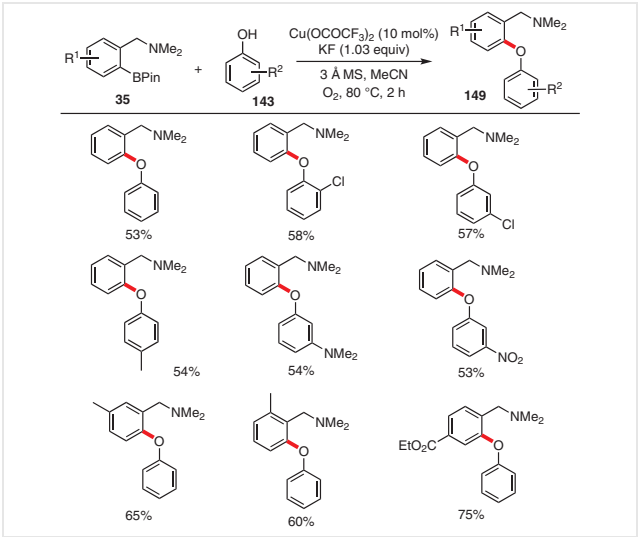
An alternative synthesis of esters using $Cu(OTf)_2$ as the catalyst with Ag_2CO_3 as a promoter in DMSO at 120 °C for 2 hours was reported in 2011, by Liu and co-workers (Scheme 103).[88] The scope of carboxylic acid extended to 2,6-disubstituted benzoic acids, heteroarenecarboxylic acids, cinnamic acids, and electron-rich and electron-poor substituted benzoic acids, while both electron-rich and electron-poor boronic acids were tolerated. Yields were generally in the range 60–95%.



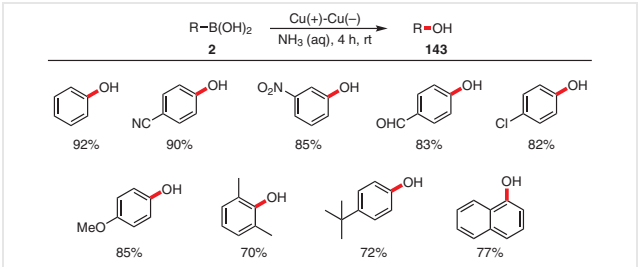
Scheme 103 $Cu(OTf)_2/Ag_2CO_3$-catalyzed coupling of carboxylic acids with phenylboronic acids

In 2016, Clark and co-workers used the Cu-catalyzed etherification of *ortho*-[(dimethylamino)methyl]phenylboronic acid pinacol esters with phenols to give aryl 2-[(dimethylamino)methyl]phenyl ethers (Scheme 104).[89] This is similar to their amination work described in Section 2.1.2 (Scheme 23).[31a] Various substituted arylboronate esters and phenols underwent the reaction smoothly to furnish the product in moderate to high yields. It was observed that during a competition reaction between phenol and aniline, phenol was highly favored over aniline. A simple boronate ester, 2-(pinacolboryl)toluene lacking the pendant (dimethylamino)methyl group gave only 5% conversion to the corresponding ether; thus the pendant (dimethylamino)methyl group activates the boronate ester toward coupling.

In 2013, Huang and co-workers synthesized phenols from arylboronic acids using electrochemical techniques by modulating potential and ammonia concentration (Scheme 105).[33] By keeping the concentration of aqueous ammonia at 0.13 M, various boronic acids chemoselectively gave the corresponding phenols in good yields (see also Scheme 26 in Section 2.1.2).



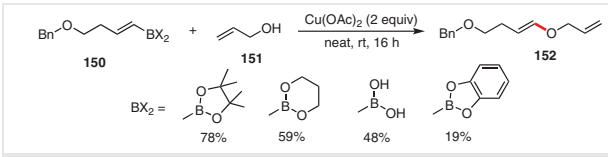
Scheme 104 Cu-catalyzed etherification of *ortho*-[(dimethylamino)-methyl]phenylboronic acid pinacol esters with phenols



Scheme 105 Electrochemical hydroxylation of arylboronic acids in aqueous NH_3

2.2.2 Coupling with Alkyl- and Alkenylboron Reagents

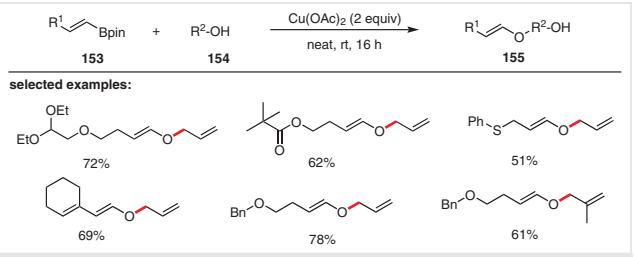
Vinyl ethers are ubiquitous structural moieties which are difficult to synthesize using direct O-alkylation methods of enolates. Some indirect methods developed include the carbonyl alkenylation using Tebbe reagent, etherification using selenium, vinyl ether exchange catalyzed by acid or metal, alcohol addition to alkynes, etc.[90a–d] However, these methods have different drawbacks, such as the use of strong acid or base, less functional group tolerance, uncontrolled stereochemistry, etc. In this regard, in 2010 Merlic and co-workers developed the $Cu(OAc)_2$-mediated synthesis of vinyl ethers using the coupling of vinylboronic acid



Scheme 106 $Cu(OAc)_2$-mediated coupling of vinylboronic acid esters with aliphatic alcohols

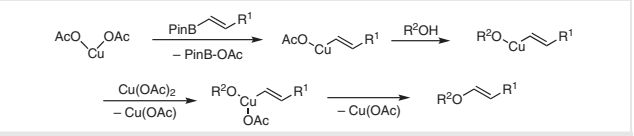
esters with aliphatic alcohols (Scheme 106).[90e] Vinylboronic acid pinacol esters such as **150** gave the highest yields, whereas other boronate esters, boronic acids, boroxines, and boranes provided lower yields.

Various aliphatic and allylic alcohols were employed in this coupling reaction (Scheme 107).[90e] Even groups sensitive to acidic, basic, oxidative, nucleophilic, and radical conditions are compatible with this reaction.



Scheme 107 Cu-catalyzed coupling of vinylboronic acid pinacol esters and alcohols

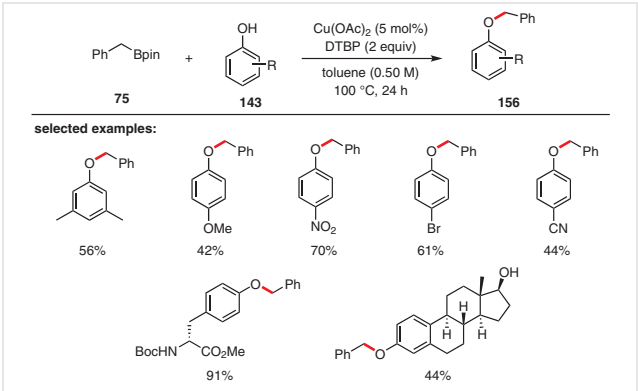
It is proposed that the reaction takes place by a modified Chan–Lam mechanism (Scheme 108).[90e] The mechanism involves transmetalation, ligand exchange from $Cu(OAc)_2$, disproportionation, which also explains the need for excess $Cu(OAc)_2$ and the absence of copper metal formation, and reductive elimination. As alkoxy(vinyl)copper is easily oxidized compared to acetoxy(vinyl)copper, the former undergoes disproportionation, and vinyl acetate side products are not formed in the reaction.



Scheme 108 Mechanism of the Cu-catalyzed coupling of vinylboronic acid pinacol esters and alcohols

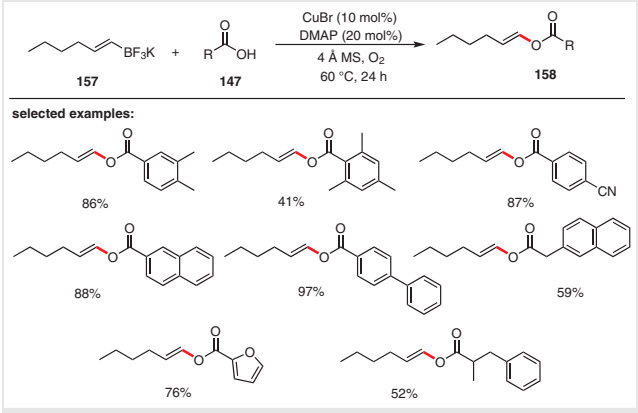
In 2013, Kuninobu and Sueki developed a method for the benzylation of aromatic and aliphatic alcohols by the reaction of phenols with benzylboronic acid pinacol ester (Scheme 109).[60] This cross-coupling reaction used $Cu(OAc)_2$ as the catalyst in the presence of di-*tert*-butyl peroxide and gave alkyl and aryl benzyl ethers in good to excellent yields. In this reaction di-*tert*-butyl peroxide played a crucial role. See also Section 2.1.8 for the amines with alkylboronic acid pinacol esters using this catalyst system.

Enol esters are diverse and prevalent structural moieties in a number of natural products, pharmaceuticals, and polymers. In 2013, Batey and co-workers reported a mild non-decarboxylative CuBr and DMAP-catalyzed cross-coupling reaction of potassium alk-1-enyltrifluoroborates with carboxylic acids at 60 °C in the presence of oxygen and 4Å MS for the regioselective and stereospecific preparation of (*E*)- or (*Z*)-enol esters (Scheme 110).[91a] Various potassium



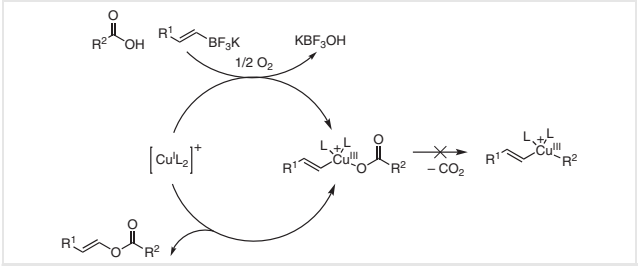
Scheme 109 $Cu(OAc)_2$-catalyzed reaction between benzylboronic acid pinacol esters and aromatic and aliphatic alcohols

(*E*)- and (*Z*)-alkenyltrifluoroborates, such as hex-1-enyl, oct-1-enyl, 3-(benzyloxy)prop-1-enyl, styryl, and prop-1-enyl, were used with benzoic, heteroarenecarboxylic and alkanoic acids. The reactions of carboxylic acids with alk-1-enyl or aryl halides and organometalloid derivatives for the generation of C–O bonds often suffer from various drawbacks, such as poor yields, the use of excess metal or catalysts, and elevated temperatures, but Batey and co-workers developed a mild protocol without the use of stoichiometric metal additives.



Scheme 110 CuBr/DMAP-catalyzed cross-coupling of carboxylic acids with potassium (*E*)-trifluoro(hex-1-enyl)borate

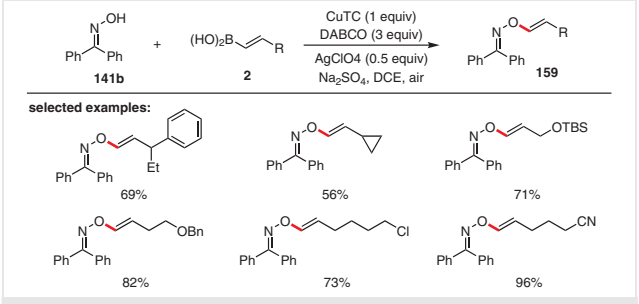
The stereospecificity of this transformation was examined by performing the reaction of potassium (*Z*)-trifluoro(prop-1-enyl)borate (*Z*/*E* ratio 18:1) with benzoic acid or its salts bearing both electron-withdrawing and -donating groups. ^{1}H NMR of the products showed that all the prop-1-enyl benzoates were generated with high *Z*-selectivity. Thus, a mechanism similar to earlier reports[91b] was also proposed for this transformation, including transmetalation and reductive elimination of the copper catalyst (Scheme 111).



Scheme 111 Mechanistic overview of enol acetate formation

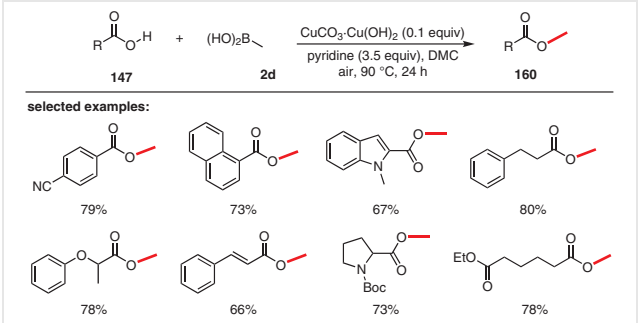
In 2013, Anderson and co-workers reported the Cu-mediated thermal [1,3]-rearrangement of benzophenone *O*-alk-1-enyloximes to give α-imino aldehydes.[92] The benzophenone *O*-alk-1-enyloximes were synthesized by C–O bond coupling between alk-1-enylboronic acids and benzophenone oximes (Scheme 112). The α-imino aldehydes were used in the Horner–Wadsworth–Emmons olefination to give γ-imino-α,β-unsaturated esters.

The reaction of benzophenone oxime with various substituted alk-1-enylboronic acids took place under the optimum conditions using 1 equiv of CuTC, 0.5 equiv of $AgClO_4$, and 3 equiv of DABCO as the base; the addition of a silver salt played a significant role in the yield of the products and its counterion also influenced the transformation.



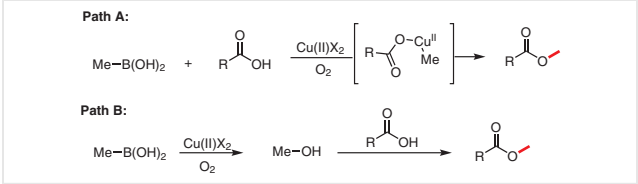
Scheme 112 CuTC/$AgClO_4$-mediated reaction of benzophenone oxime with alk-1-enylboronic acids

In order to replace toxic electrophilic alkylating reagents, in 2015 Gorin and co-workers reported the oxidative coupling of alkylboronic acids with oxygen nucleophiles. O-Alkylation with boronic acid is still rare, though Chan–Lam coupling is widely used in the arylation of heteroatom nucleophiles. The Cu-catalyzed non-decarboxylative methylation of carboxylic acids with methylboronic acid under aerobic conditions with no additional oxidant gave methyl esters in good yields (Scheme 113).[93] Isotope-labeling studies revealed an oxidative cross-coupling mechanism, similar to that proposed for the Chan–Lam arylation, where the methyl group is transferred to the substrate from the boronic acid. Optimization of the solvent found both chlorobenzene and dimethyl carbonate (DMC) to be effective; dimethyl carbonate was selected for use as a nontoxic, green solvent. The optimum catalyst was $CuCO_3{\cdot}Cu(OH)_2$.



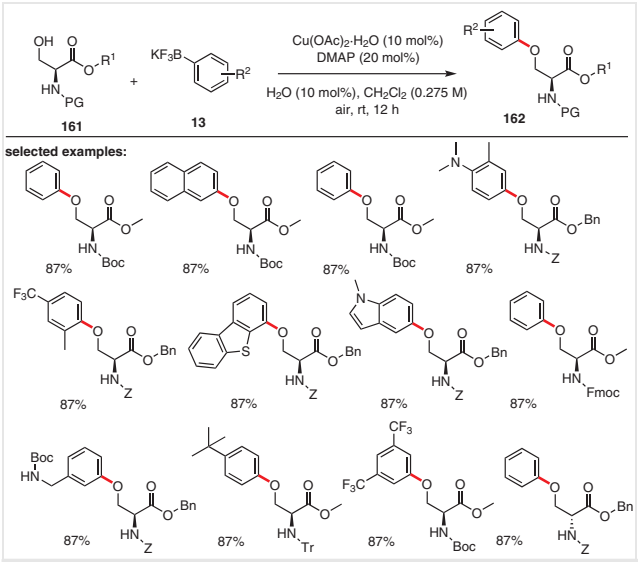
Scheme 113 Cu-catalyzed esterification of carboxylic acids with methylboronic acid

Two possible reaction mechanisms emerged; there was only one previous report of the aerobic Cu-catalyzed Chan–Lam alkylation with methylboronic acid, see Section 2.1.8.[55] In the first, O-methylation may proceed similarly to Chan–Lam O-arylation (Scheme 114, path A). According to Stahl and co-workers,[94] the carboxylic acid undergoes ligand exchange with the copper complex followed by the transmetalation with methylboronic acid. Reductive elimination followed by oxidation generates the product and active Cu(II) catalyst. In the second mechanism, methanol is formed by the oxidation of methylboronic acid, and it reacts with the carboxylic acid to give the methyl ester (Scheme 114, path B).



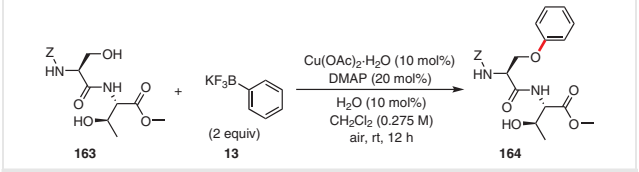
Scheme 114 Two possible reaction mechanisms for the Cu-catalyzed esterification carboxylic acids with methylboronic acid

The O-arylation of L-serines is usually performed by nucleophilic aromatic substitution, which uses strong bases (NaH and KHMDS) and 1-fluoro-2-nitrobenzene substrates.[95a] Other methods include the Mitsunobu reaction, which furnishes product, albeit in poor yields, and also uses triphenylphosphine as the reagent.[95b] In 2014, Molander and Khatib reported the Cu(II)-catalyzed O-arylation of β-hydroxy-α-amino acid substrates serine and threonine (Scheme 115).[95c] A wide variety of protected [Boc, Cbz (Z), Tr, and Fmoc] serine and threonine derivatives underwent the reaction smoothly with various (hetero)arylboronic acids and potassium (hetero)aryltrifluoroborates under open flask conditions.



Scheme 115 Cu(II)-catalyzed O-arylation of L-serine derivatives with potassium (hetero)aryltrifluoroborates

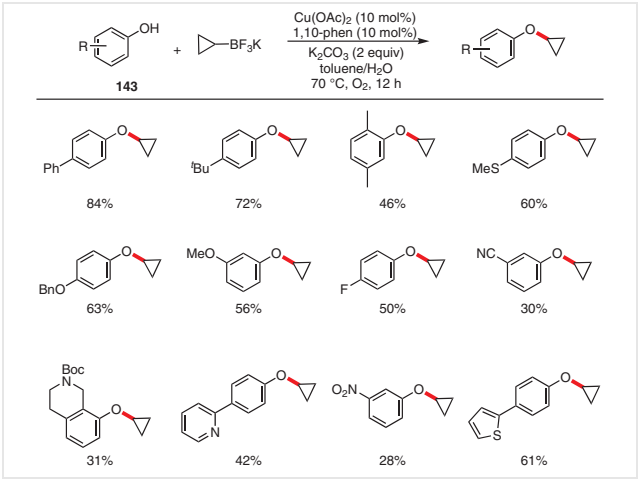
The reaction of potassium trifluoro(phenyl)borate (**13**) with Z-L-Ser-L-Thr-OMe (**163**) gave a single mono O-arylated product **164** in 22% yield (Scheme 116). This was also supported by mass spectrometric analysis, which confirmed the selective arylation at the L-serine site.



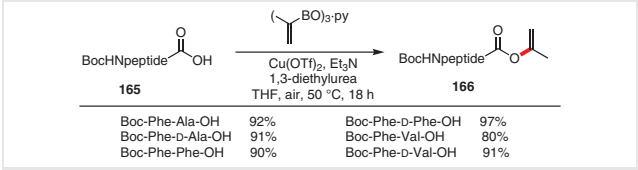
Scheme 116 Selective O-arylation of Z-L-Ser-L-Thr-OMe with potassium trifluoro(phenyl)borate

In 2018, McAlpine, Engle, and co-workers reported the O-cyclopropylation of phenols using potassium cyclopropyltrifluoroborate and catalyzed by $Cu(OAc)_2$ and 1,10-phenanthroline and employing 1 atm of O_2 as the terminal oxidant (Scheme 117).[61] Phenols with diverse functional groups, differing electronic properties, and varied substitution patterns reacted smoothly to furnish the desired product in moderate to high yields.

In 2019 Van Maarseveen and Steemers developed the Cu(II)-mediated enol esterification of peptide carboxylic acids with triisopropenylboroxine·pyridine complex using $Cu(OTf)_2$ as the catalyst, with triethylamine as the base, and 1,3-diethylurea as an additive for the synthesis of C-terminal dipeptide isopropenyl esters (Scheme 118).[96] A variety of amino acid and dipeptide nucleophiles were coupled stereoselectively with these peptide esters in the presence of pyrazole/DBU as the catalyst in high yield and purity.



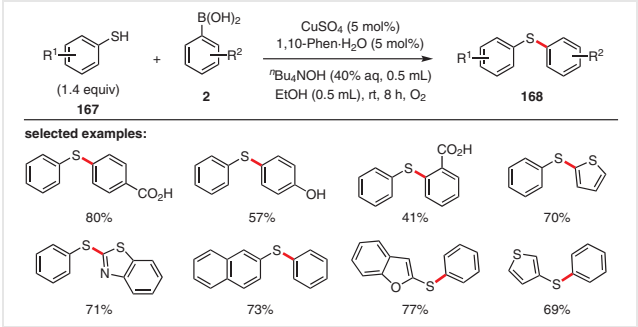
Scheme 117 $Cu(OAc)_2$/phen-catalyzed O-cyclopropylation of phenols with potassium cyclopropyltrifluoroborate



Scheme 118 Cu(II)-mediated enol esterification of peptide carboxylic acids with triisopropenylboroxine·pyridine complex

3 C–Element (Element = S, P, C, F, Cl, Br, I, Se, Te, At) Bond Formation under Modified Chan–Lam Conditions

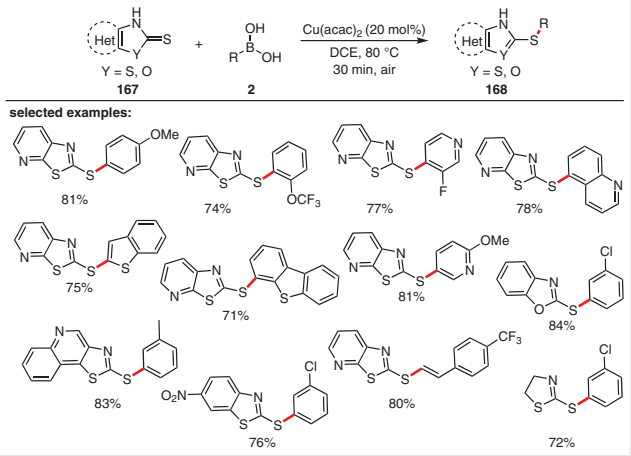
The first report on the coupling of alkanethiols with arylboronic acids was in 2000 by Guy and co-workers, they used $Cu(OAc)_2$ as the catalyst with pyridine as the base in DMF,[97] then in 2002 Liebeskind and co-workers reported the coupling of *N*-alkyl or *N*-arylthiosuccinimides with boronic acids catalyzed by copper(I) 3-methylsalicylate (CuMeSal) to give sulfides under mild conditions.[98]



Scheme 119 $CuSO_4$-catalyzed S-arylation of thiols using (hetero)arylboronic acids

In 2012, Feng and co-workers developed the $CuSO_4$-catalyzed S-arylation of thiols using (hetero)arylboronic acids with 1,10-phen·H_2O as the ligand, EtOH as solvent, and oxygen as the oxidant to give aryl (heteroaryl) sulfides (Scheme 119).[99]

In 2016, Muthusubramanian and co-workers reported the Cu(II)-catalyzed C–S cross-coupling of thiazolidine-2-thiones with boronic acids using $Cu(acac)_2$ in DCE to give azole sulfides under base-, ligand-, and additive-free conditions and requiring shorter reactions times (Scheme 120); one example of the corresponding reaction of an oxazolidine-2-thione was reported.[100] Azole sulfides find applications in the biological, pharmaceutical, and materials fields.

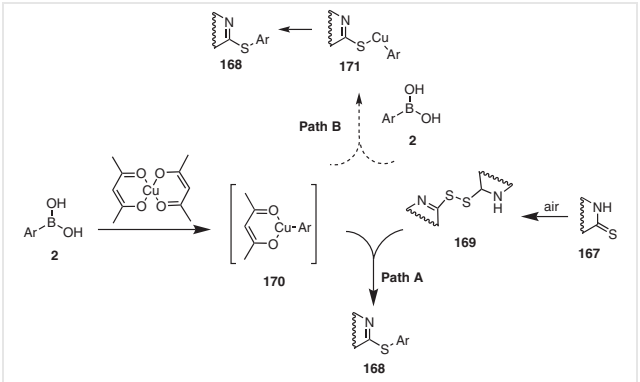


Scheme 120 Cu(II)-catalyzed C–S cross-coupling of thiazolidine-2-thiones with boronic acids

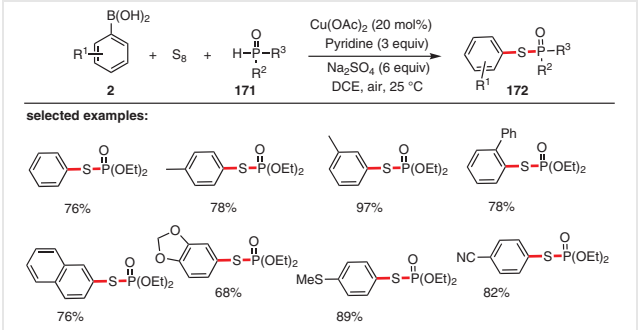
Mechanistically, it is proposed that the thioamide system is readily oxidized to give disulfide **169** stimulated by the Cu(II) reagent in the presence of air. The arylboronic acid then reacts with $Cu(acac)_2$ in a transmetalation step to form Cu(II) intermediate **170**, which reacts with disulfide **169** to give **168** (Scheme 121, path A). As an alternative possible mechanism, disulfide **169** and intermediate **170** may undergo transmetalation with the arylboronic acid to generate intermediate **171**, which ultimately delivers aryl sulfide **168** (Scheme 121, path B).

The first multicomponent reaction (MCR) was explored by Zhao and co-workers in 2016, which involved arylboronic acids, elemental sulfur, and P(O)H compounds. This method provided an efficient protocol for the one-pot synthesis of *S*-aryl phosphorothioates and *S*-aryl phosphorodithioates in excellent yields, which can be easily adapted to a large-scale preparation (Scheme 122).[101]

In addition to the phosphorothiolation of arylboronic acids, this strategy was used to synthesize phosphorothiolated phenylalanine, estrone, and nucleotide analogues, which have tremendous potential to be used for various biological activities (Figure 5).



Scheme 121 Mechanism of the Cu(II)-catalyzed C–S cross-coupling of thiazolidine-2-thiones with boronic acids



Scheme 122 $Cu(OAc)_2$-catalyzed multicomponent reaction phosphorothiolation of arylboronic acids

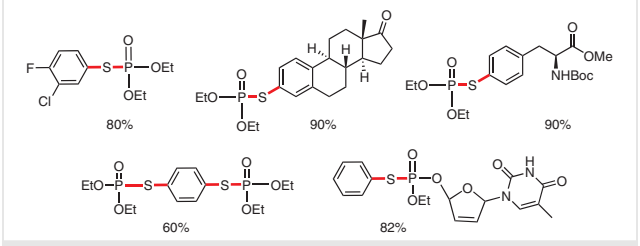
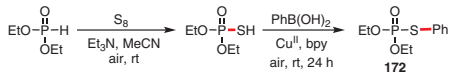


Figure 5 $Cu(OAc)_2$-catalyzed multicomponent reaction phosphorothiolation to give highly functionalized targets

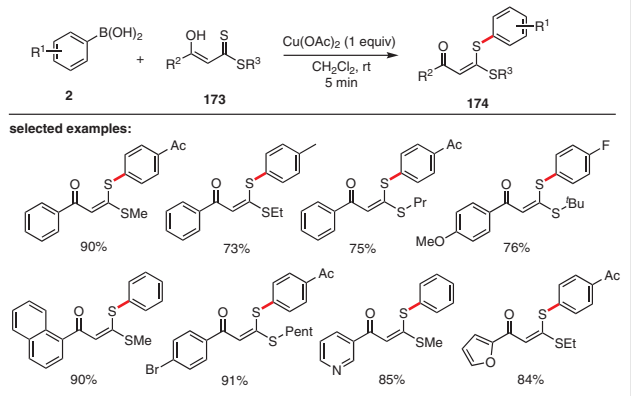
The role of sulfur in this synthetic protocol was examined. A complicated reaction mixture was generated by the reaction of sulfur with $PhB(OH)_2$ for 20 hours, and adding diethyl *H*-phosphonate to this mixture afforded only a trace amount of the product **172**, implying that diaryl disulfide and benzenethiol intermediates are not responsible for the reaction. ^{31}P NMR experiments showed that the active phosphorothiolating reagent is *S*-hydrogen phosphorothioate and that Et_3N is critical to its formation. ^{31}P NMR experiments also indicated the formation of the C(aryl)–S–P bond and that the reaction was complete after 24 hours. Based on this information the proposed mechanism is shown in Scheme 123. The reaction of elemental sulfur with *H*-phosphonate gives *S*-hydrogen phosphorothioate,

which undergoes $Cu(OTf)_2$-catalyzed reaction with phenylboronic acid to generate the phosphorothioated product **172**.



Scheme 123 Mechanistic pathway for the $Cu(OAc)_2$-catalyzed multicomponent reaction phosphorothiolation

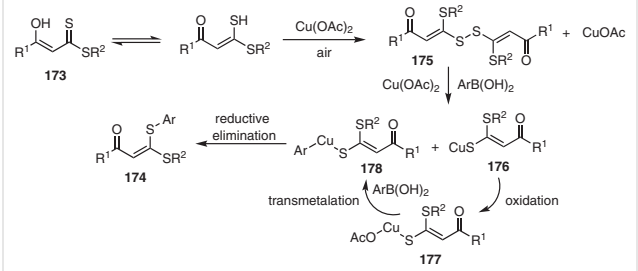
In 2015, Singh and co-workers developed a Cu(II)-mediated regioselective method for the S-arylation of α-enolic dithioesters with arylboronic acids to give α-oxoketene *S*,*S*-acetals (Scheme 124).[102] The reaction was performed in the absence of a base or a ligand at room temperature in the presence of O_2 and under neutral conditions. The striking features of this novel one-pot strategy include short reaction times (5 min), good to excellent yields, and highly selective C=S functionalization. The α-oxoketene *S*,*S*-acetals furnished in this reaction can be utilized for the generation of a number of carbocycles and heterocycles, which can find various applications in pharmaceutical and polymer industries.



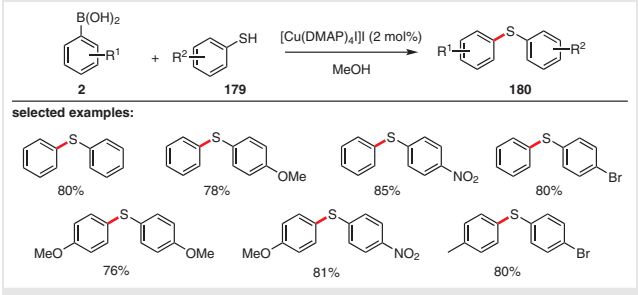
Scheme 124 $Cu(OAc)_2$-mediated S-arylation of α-enolic dithioesters with arylboronic acids

The proposed mechanism is outlined in Scheme 125. The thioenol form of the dithioester **173** dimerizes to the disulfide species **175** in the presence of $Cu(OAc)_2$, with the reduction of Cu(II) to Cu(I). Disulfide species **175** undergoes Chan–Lam coupling in the presence of arylboronic acid and Cu(I) and Cu(II) to generate the Cu(I) *S*,*S*-acetal complex **176** and Cu(II) *S*,*S*-acetal complex **178**. The dithioacetal–Cu(I) complex **176** is oxidized to dithioacetal–Cu(II) complex **177**, which undergoes transmetalation with arylboronic acid to produce **178**. Finally, intermediate **178** undergoes reductive elimination to give α-oxoketene *S*,*S*-acetals **174**.

Phukan and co-workers also utilized the novel square pyramidal copper complex $[Cu(DMAP)_4I]I$ that they had used for the formation of *N*-arylamines (Section 2.1.2) and *N*-arylsulfonamides (from azides, Section 2.1.3) for the formation of the Chan–Lam coupling of arylboronic acids with thiols to give diaryl sulfides (Scheme 126).[32] This complex successfully catalyzed the C–S cross-coupling reaction and the rate and yield of the reaction increased when thiols bearing electron-withdrawing groups were used. Only 2 mol% of the copper catalyst was required for the reaction in methanol at room temperature within a short time. However, the time required for the S-arylation of thiols (35–65 minutes for 9 examples) was longer than that required for N-arylation of amines (5–20 minutes for 26 examples, 40–75 minutes for 3 examples).



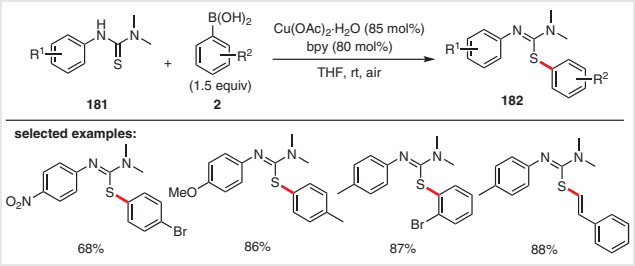
Scheme 125 Mechanism for the $Cu(OAc)_2$-mediated S-arylation of α-enolic dithioesters with arylboronic acids



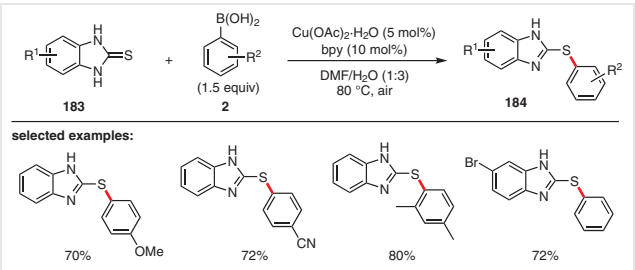
Scheme 126 $[Cu(DMAP)_4I]I$-catalyzed S-arylation of thiols with boronic acids

In 2018–2019, Dong and co-workers explored several new ways of C–S bond formation via Chan–Lam coupling.[103,104] Thioureas were efficiently S-arylated at room temperature using arylboronic acids catalyzed by $Cu(OAc)_2$ with 2,2′-bipyridine as the ligand to form *S*-arylisothioureas in very good yields (Scheme 127).[104a] A variety of functional groups on the *N*-aryl-*N*′,*N*′-dimethylthiourea and arylboronic acid reagents were tolerated, in particular 2-bromophenylboronic acid gave the corresponding S-(2-bromophenyl)isothiourea in 87% yield. Styrylboronic acids were also used as the boronic acid.

This chemistry was further applied to cyclic 1,3-dihydro-2*H*-benzimidazole-2-thiones to provide chemoselectively the useful 2-(arylthio)benzimidazoles (Scheme 128).[104b] It is interesting to note that the chemoselectivity was achieved by the addition of water, this provides a heterogeneous medium that slows down the reaction to



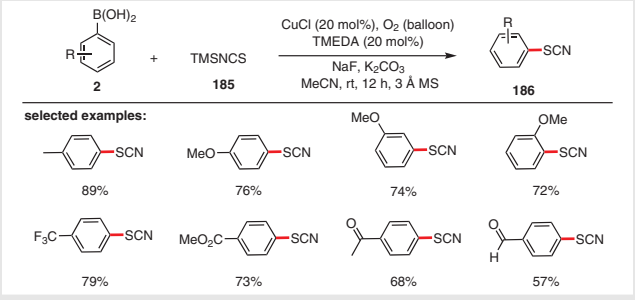
Scheme 127 $Cu(OAc)_2$/bpy-catalyzed S-arylation of thioureas with aryl- and styrylboronic acids



Scheme 128 $Cu(OAc)_2$/bpy-catalyzed chemoselective S-arylation of 1,3-dihydro-2*H*-benzimidazole-2-thiones with arylboronic acids

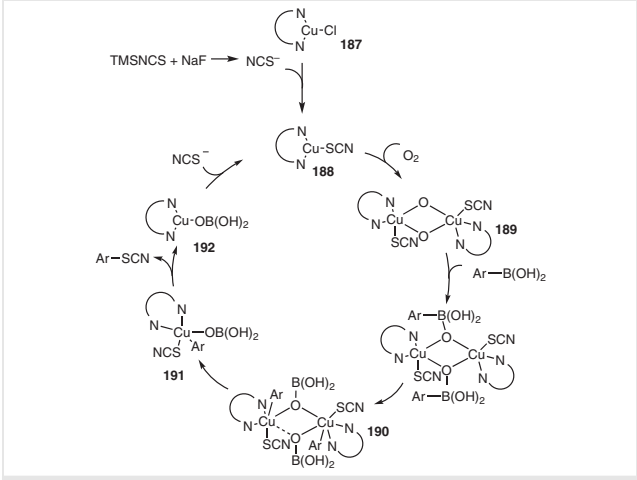
achieve the selectivity, but it was necessary to increase the reaction temperature to 80 °C.

In 2015, Hu and co-workers reported the efficient CuCl-catalyzed oxidative cross-coupling reaction of substituted arylboronic acids with trimethylsilyl isothiocyanate under oxygen atmosphere to give aryl thiocyanates (Scheme 129).[105]



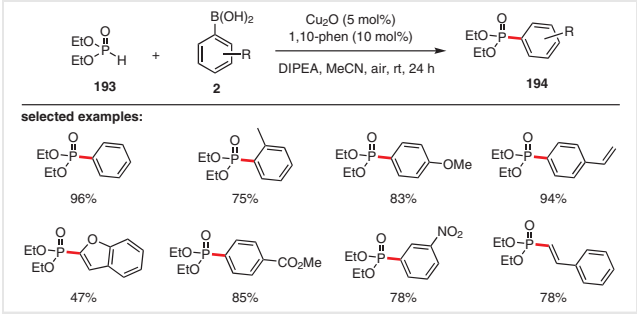
Scheme 129 CuCl-catalyzed aerobic oxidative thiocyanation of arylboronic acids with TMSNCS

The proposed mechanism is given in Scheme 130. In the initial step, LCu(I)Cl **187** undergoes exchange with the NCS^- anion to give LCu(I)SCN **188**, which is oxidized to the bis(μ-oxo)dicopper(III) complex **189** by oxygen; coordination of the diamine ligand TMEDA (L) is crucial as electron density on the Cu is increased by its presence. Bis(μ-oxo)dicopper(III) complex **189** reacts with two molecules of arylboronic acid, and an aryl group is further transferred to the Cu atom to form **190**, which generates two molecules of unstable Cu(III) complex **191**. Subsequent reductive elimination of **191** generates the product aryl thiocyanate and LCu(I)–$OB(OH)_2$ **192**. The formed **192** undergoes further exchange with the NCS^- anion to form LCu(I)SCN **188** to complete the catalytic cycle.



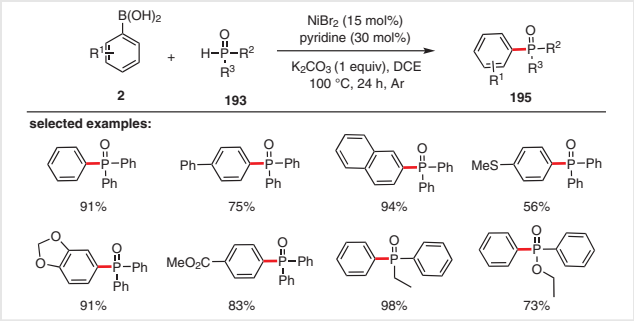
Scheme 130 Mechanism for thiocyanation of arylboronic acids with TMSNCS

In 2011, Fang, Zhao and co-workers reported the Chan–Lam coupling between *H*-phosphonate diesters and boronic acids catalyzed by Cu_2O and 1,10-phenanthroline for the construction of arylphosphonates (Scheme 131).[106]



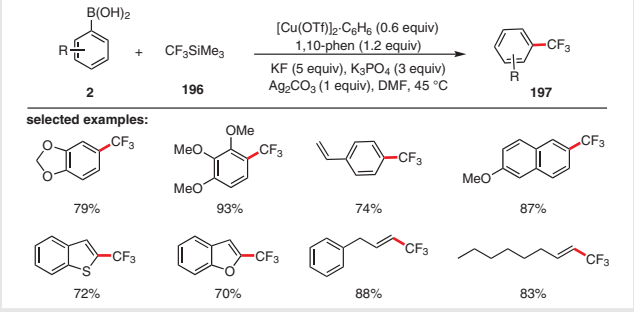
Scheme 131 Cu_2O/1,10-phen-catalyzed cross-coupling of arylboronic acids with H-phosphonate diester

In 2013, Gao and co-workers reported the Ni-catalyzed cross-coupling of a variety of functionalized arylboronic acids with *H*-phosphites, *H*-phosphine oxides, and *H*-phosphinate esters to give various arylphosphorus compounds; good to excellent yield of triarylphosphine oxides were formed (Scheme 132).[107] This strategy provided a generalized and substantial tool for the synthesis of arylphosphorus compounds and is the first example of a Ni-catalyzed C–P bond-forming reaction utilizing P(O)H substrates and arylboronic acids. The optimized conditions used $NiBr_2$ as the catalyst, pyridine as an additive, and K_2CO_3 as the base and gave triarylphosphine oxides in up to 99% yield.



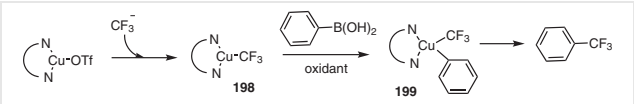
Scheme 132 Ni-catalyzed coupling of arylboronic acids with P-nucleophiles

In 2010, Qing and Chu reported the Cu-catalyzed coupling of trimethyl(trifluoromethyl)silane (Me_3SiCF_3) with aryl- and alkenylboronic acids to give (trifluoromethyl)-substituted arenes and alkenes (Scheme 133).[108a] The optimized conditions used $[Cu(OTf)_2]\cdot C_6H_6$ (0.6 equiv), 1,10-phen (1.2 equiv), CF_3SiMe_3 (5.0 equiv), KF (5.0 equiv), K_3PO_4 (3.0 equiv), and Ag_2CO_3 (1.0 equiv) in DMF at 45 °C. A wide range of functional groups were tolerated on the arene and alkene component. This oxidative trifluoromethylation resulted in the incorporation of the trifluoromethyl group into highly functionalized organic molecules. However, the $[Cu(OTf)]_2\cdot C_6H_6$ used in this reaction is highly air-sensitive, and a nitrogen-filled glovebox is required. Also, stoichiometric amounts of trimethyl(trifluoromethyl)silane ($TMSCF_3$; 5 equiv) and Ag_2CO_3(1 equiv) were required.



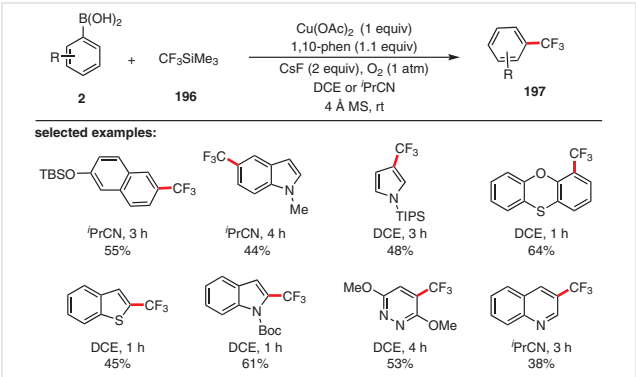
Scheme 133 Cu-catalyzed coupling of Me_3SiCF_3 with aryl- and alkenylboronic acids

The proposed mechanism is shown in Scheme 134 based on an earlier report on the trifluoromethylation of terminal alkynes.[108b] Complex **198** undergoes transmetalation with the arylboronic acid to form aryl(trifluoromethyl)copper **199**. The diamine ligand increases the electron density on the Cu atom and stabilizes the intermediate **199**, which undergoes reductive elimination to generate the product.



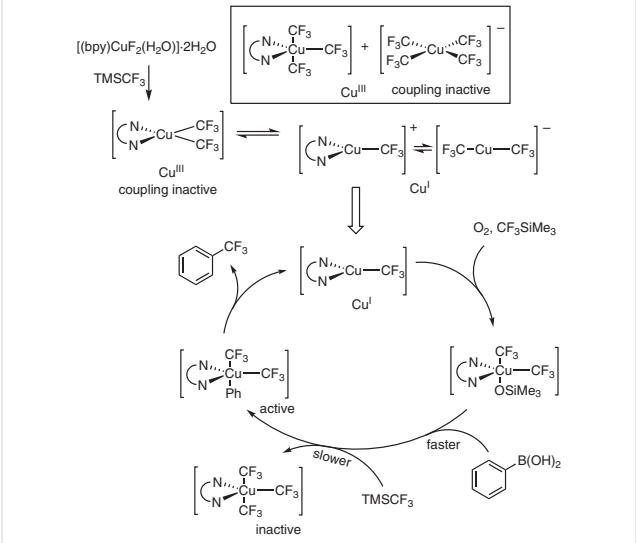
Scheme 134 Mechanism for the Cu-catalyzed coupling of Me_3SiCF_3 with aryl- and alkenylboronic acids

In 2011, Buchwald and co-workers also reported the Cu-mediated trifluoromethylation of (hetero)arylboronic acids at room temperature for short reaction times (1–4 h) to give a wide range of (trifluoromethyl)arenes containing a variety of functional groups (Scheme 135).[109]



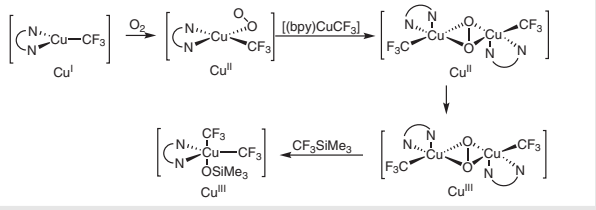
Scheme 135 Cu-catalyzed coupling of Me_3SiCF_3 with (hetero)arylboronic acids

In 2014, Grushin and co-workers reported an efficient oxidative trifluoromethylation of phenylboronic acid with trimethyl(trifluoromethyl)silane catalyzed by $[(bpy)CuF_2(H_2O)]\cdot 2H_2O$ in DMF at room temperature for 15 minutes to give (trifluoromethyl)benzene in >95% yield method.[110] This reaction only occurs under aerobic conditions. A well-defined mechanism justifies this transformation, as shown in Scheme 136. In the first step, $TMSCF_3$ undergoes trifluoromethylation with $[(bpy)CuF_2(H_2O)]\cdot 2H_2O$



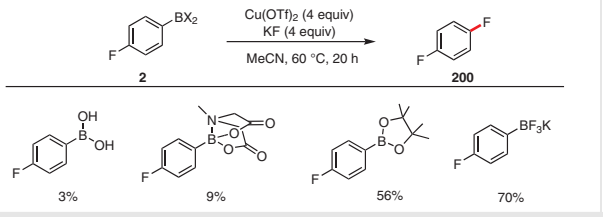
Scheme 136 $[(bpy)CuF_2(H_2O)]\cdot 2H_2O$-catalyzed oxidative trifluoromethylation of phenylboronic acid with $TMSCF_3$

to form [(bpy)Cu(CF_3)$_2$], which spontaneously disproportionates into two Cu(III) ([Cu(CF_3)$_4$]$^-$ and [(bpy)Cu(CF_3)$_3$]) and two Cu(I) ([(bpy)Cu(CF_3)] and [Cu(CF_3)$_2$]$^-$) complexes. The Cu(III) complexes generated in the reaction are stable and unreactive throughout the coupling. [Cu(CF_3)$_2$]$^-$ is in equilibrium with [(bpy)Cu(CF_3)] and serves as the active catalyst for Ph–CF_3 bond formation. Thus, the role of oxygen was found to be crucial for the reaction as trifluoromethylation of PhB(OH)$_2$ will not happen with [(bpy)Cu(CF_3)$_2$]. Details are shown in Scheme 137.



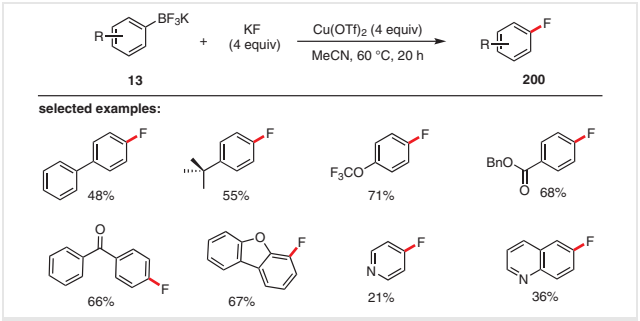
Scheme 137 Air oxidation of [(bpy)Cu(CF_3)] in the presence of TMSCF_3 leading to [(bpy)Cu(CF_3)$_2$(OTMS)]

In 2013, Sanford and co-workers developed the Cu(OTf)$_2$-mediated fluorination of (hetero)aryltrifluoroborates with KF to give aryl fluorides.[111] Evaluation of 4-fluorophenylboron substrates by reaction with 4 equiv KF, 4 equiv of Cu(OTf)$_2$ in MeCN at 60 °C for 20 hours found that potassium trifluoro(phenyl)boronate gave the best yield (70%) (Scheme 138). This method tolerates potassium (hetero)aryltrifluoroborates with a wide range of functional groups under mild reaction conditions (Scheme 139). In this transformation, Cu is used as a mediator for aryl–F coupling and also as an oxidant to generate the Cu(III)(aryl)(F) intermediate.

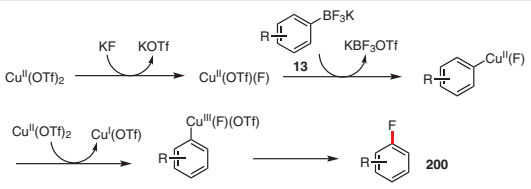


Scheme 138 Cu(OTf)$_2$-mediated fluorination of 4-fluorophenylboron substrates with KF

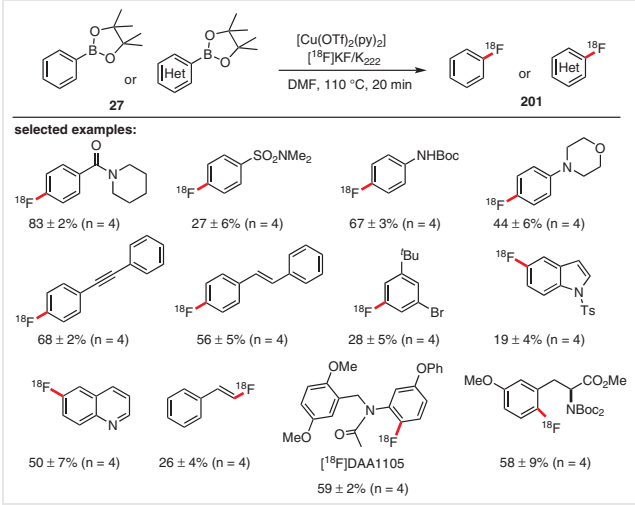
The proposed mechanism is given in Scheme 140. As the reaction was performed at 60 °C for 24 hours, this indicates the low activation barrier required for C–F coupling. The disproportion reaction involving the oxidation of the aryl(fluoro)Cu(II) intermediate (1 equiv) using Cu(OTf)$_2$ (1 equiv) generates the corresponding Cu(III) species leading to the final fluoroarene product **200**. As Cu(OTf)$_2$ is a strongly oxidizing Cu source, it is more effective in this transformation, and the reduction in the number of equivalents from 2 to 1 decreased the yield of the reaction to 15% illustrating the dual role played by copper in this reaction.



Scheme 139 Cu(OTf)$_2$-mediated fluorination of (hetero)aryltrifluoroborates with KF

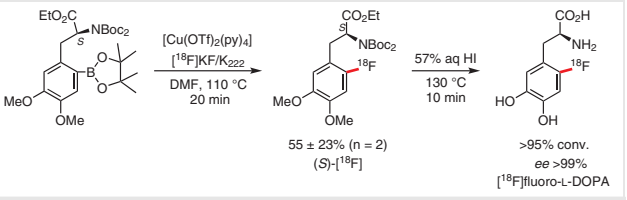


Scheme 140 Mechanism for the Cu(OTf)$_2$-mediated fluorination of (hetero)aryltrifluoroborates with KF



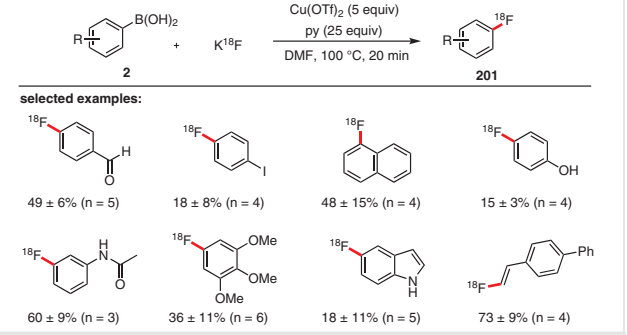
Scheme 141 Cu-mediated ^{18}F fluorination of (hetero)arylboronic acid pinacol esters with [^{18}F]fluoride; n = number of repeats

In 2014, Gouverneur and co-workers reported the unprecedented nucleophilic ^{18}F fluorination of a broad range of (hetero)arylboronic acid pinacol esters with [^{18}F]KF/K_{222} in the presence of the commercially available copper complex [Cu(OTf)$_2$(py)$_4$] (Scheme 141).[112] This strategy was applied to arenes with both electron-donating and electron-withdrawing groups with a variety of functional groups, and can be used in the synthesis of translocator protein (TSPO) PET ligand [^{18}F]DAA1106 and 6-[^{18}F]fluoro-L-DOPA, 6-[^{18}F]fluoro-m-tyrosine (Scheme 142).[112]



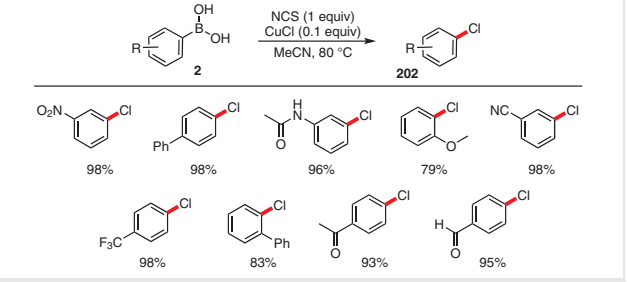
Scheme 142 Radiosynthesis of 6-[^{18}F] fluoro-L-DOPA from [^{18}F]fluoride; n = number of repeats

In 2015, Sanford and co-workers developed a protocol to synthesize [^{18}F]FPEB, a PET radiotracer for quantifying metabotropic glutamate 5 receptors by the copper-mediated radiofluorination of vinyl- and arylboronic acids with K^{18}F (Scheme 143).[113] This method exhibits high functional group tolerance and is effective for the radiofluorination of a range of electron-deficient, electron-neutral, and electron-rich aryl-, heteroaryl-, and vinylboronic acids.

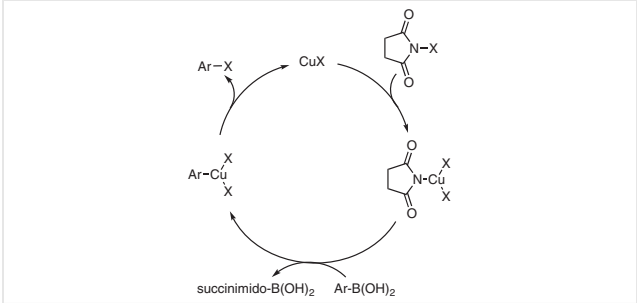


Scheme 143 Cu-mediated radiofluorination of vinyl- and arylboronic acids with K^{18}F; n = number of repeats

Hynes and co-workers reported the conversion of arylboronic acids into aryl chlorides via a mild and efficient Cu(I)-catalyzed boron–chloride exchange (chlorodeboronation) reaction (Scheme 144).[114] The optimal conditions of this low-metal-loading method used 0.1 equiv of CuCl and 1 equiv of NCS in MeCN; it was effective for both electron-rich and electron-deficient substituted arylboronic acids. Mechanistically, it is proposed that a Cu(III) complex is generated via the oxidative addition of the Cu(I) halide with the corresponding *N*-halosuccinimide (Scheme 145). Subsequent transmetalation with boron generates an Ar–Cu(X)$_2$ species followed by reductive elimination to afford the aryl chloride product.

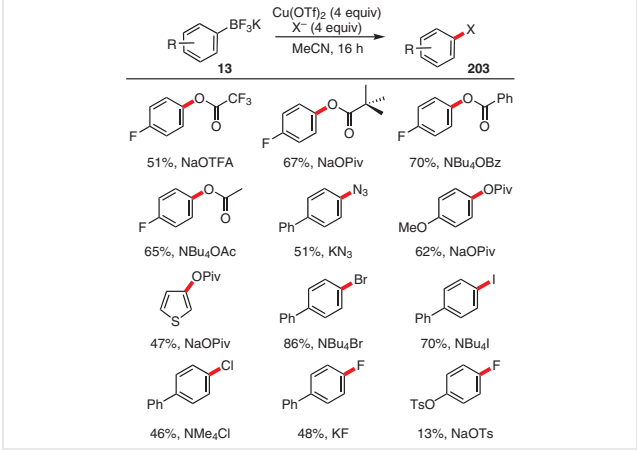


Scheme 144 CuCl-catalyzed boron–chloride exchange of arylboronic acids



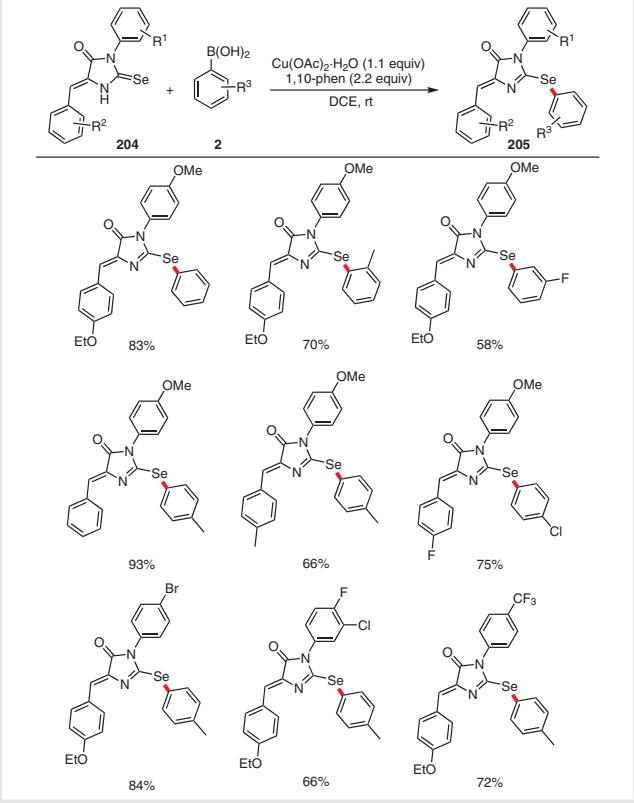
Scheme 145 Mechanism of the CuCl-catalyzed boron–chloride exchange of arylboronic acids

In 2016, Sanford and co-workers developed a facile strategy to construct C–O, C–N, and C–halogen bonds by the Cu-mediated functionalization of potassium (hetero)aryltrifluoroborates with tetrabutylammonium or alkali metal salts (Scheme 146).[115] This versatile reaction requires mild conditions and proceeds well with carboxylate, halide, and azide salts. The corresponding esters were synthesized using alkanoate and arenecarboxylate salts, such as trifluoroacetate, acetate, propanoate, pivalate, and benzoate salts. The optimized conditions for tetraalkylammonium halide salts required 4 equiv of both Cu(OTf)$_2$ and the nucleophile at room temperature in acetonitrile for 16 hours and gave the corresponding chloro, bromo-, and iodoarenes, whereas fluorination was performed with KF at 60 °C (Scheme 139).[111] Employing potassium azide as an efficient nucleophile in this transformation generated valuable aryl azides in moderate yields.



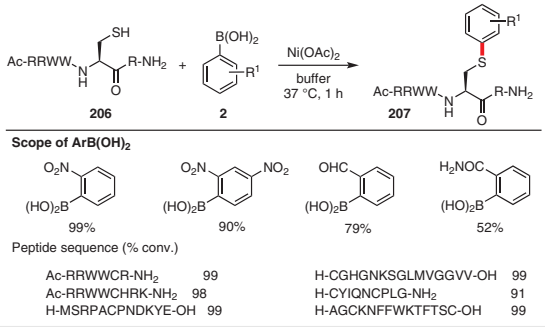
Scheme 146 Copper-mediated functionalization of potassium (hetero)aryltrifluoroborates

In 2019, Finko and co-workers reported the selective Se-arylation of 2-selenohydantoins using arylboronic acids under base-free mild conditions (Scheme 147).[116] The strategy was used in the synthesis of novel 3-substituted 5-arylidene-2-(arylseleno)imidazolin-4-ones in high yields. The starting 2-selenohydantoins were synthesized by converting selenoureas into the corresponding 3-substituted 2-selenohydantoins which then underwent Knoevenagel reaction with the aldehyde present in the reaction mixture. The optimum conditions used 1.1 equiv $Cu(OAc)_2{\cdot}H_2O$ as catalyst and 2.2 equiv of 1,10-phenanthroline as a ligand in DCE at room temperature in an open flask for 2–6 hours. A wide range of arylboronic acids underwent the arylation reaction to furnish the products in moderate to excellent yields.



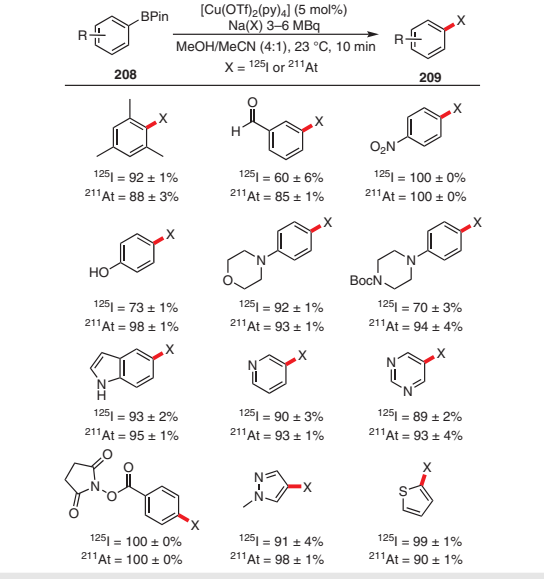
Scheme 147 $Cu(OAc)_2{\cdot}H_2O$/1,10-phen-catalyzed Se-arylation of 2-selenohydantoins using arylboronic acids

In 2019, Ball and co-workers reported an operationally simple S-arylation reaction of cysteine residues using 2-nitro-substituted arylboronic acids promoted by a simple nickel(II) salt (Scheme 148).[117] Fast reaction rates were achieved in purely aqueous media with excellent selectivity toward cysteine residue. Investigating the reaction of IL-8 inhibitor containing a single cysteine residue as a model peptide with 2-nitrophenylboronic acid in the presence of a variety of metal salts, such as Ni(II), Cu(II), and Co(II), identified Ni(II) as the best catalyst because of its superior reaction kinetics that helped in avoiding cysteine oxidation and histidine-directed amide N–H modification which is known for copper. A variety of cysteine-containing peptides reacted rapidly with phenylboronic acids bearing electron-deficient substituents in the 2-position.



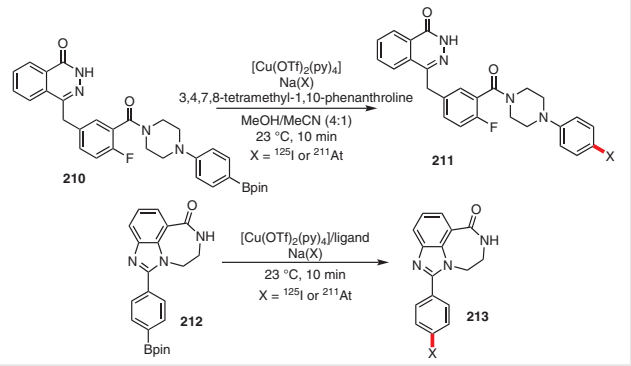
Scheme 148 Ni(II)-promoted S-arylation reaction of cysteine residues using 2-nitro-substituted arylboronic acids

In 2018, Makvandi, Mach, and co-workers reported the first approach to the synthesis of astatinated (^{211}At) and iodinated (^{125}I) compounds under modified Chan–Lam cross-coupling conditions using arylboronic acid pinacol esters with $Cu(pyridine)_4(OTf)_2$ as a catalyst in just 10 minutes at room temperature (Scheme 149);[118] this is an efficient and nontoxic protocol that eliminates the traditional need for toxic organotin reagents. The reaction conditions are applicable to a broad range of (hetero)arylboronic reagents with varying steric and electronic properties.



Scheme 149 Cu(II)-promoted ^{125}I and ^{211}At radiolabeling of boronic esters

This protocol was successfully applied to the late-stage installation of radioactive astatine (^{211}At) and iodine (^{125}I) in drug molecules for the development of α-emitting radiotherapeutics. As an example, the late-stage astatination and iodination of anticancer PARP-1 inhibitors provides a practical and environmentally friendly approach to developing α-emitting radiotherapeutics (Scheme 150).



Scheme 150 Cu(II)-promoted ^{125}I and ^{211}At radiolabeling of PARP-1 inhibitors

4 Conclusions

Copper-promoted Chan–Lam cross-coupling chemistry has come a long way since its invention in 1998. In this review, the recent developments in Cu-catalyzed carbon–heteroatom bond formation by using modified Chan–Lam coupling conditions are described. The limitations, scope, and applications of this method are greatly improved for various substrates and with optimization of the Cu catalyst, ligand, base, and solvent, these methods were successfully applied to the formation of various C–X bonds. Optimized reaction conditions are also discussed in terms of their substrate scope and mechanisms.[119] The Chan–Lam coupling reaction is now capable of forming twelve C–element bonds (C–N, C–O, C–C, C–S, C–P, C–F, C–Cl, C–Br, C–I, C–At, C–Se, and C–Te,). This makes the Chan–Lam coupling reaction the most diverse mild reaction known in organic chemistry.

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