Aerobic Oxidations

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Copper-Catalyzed Aerobic Oxidative C–H Functionalizations: Trends and Mechanistic Insights

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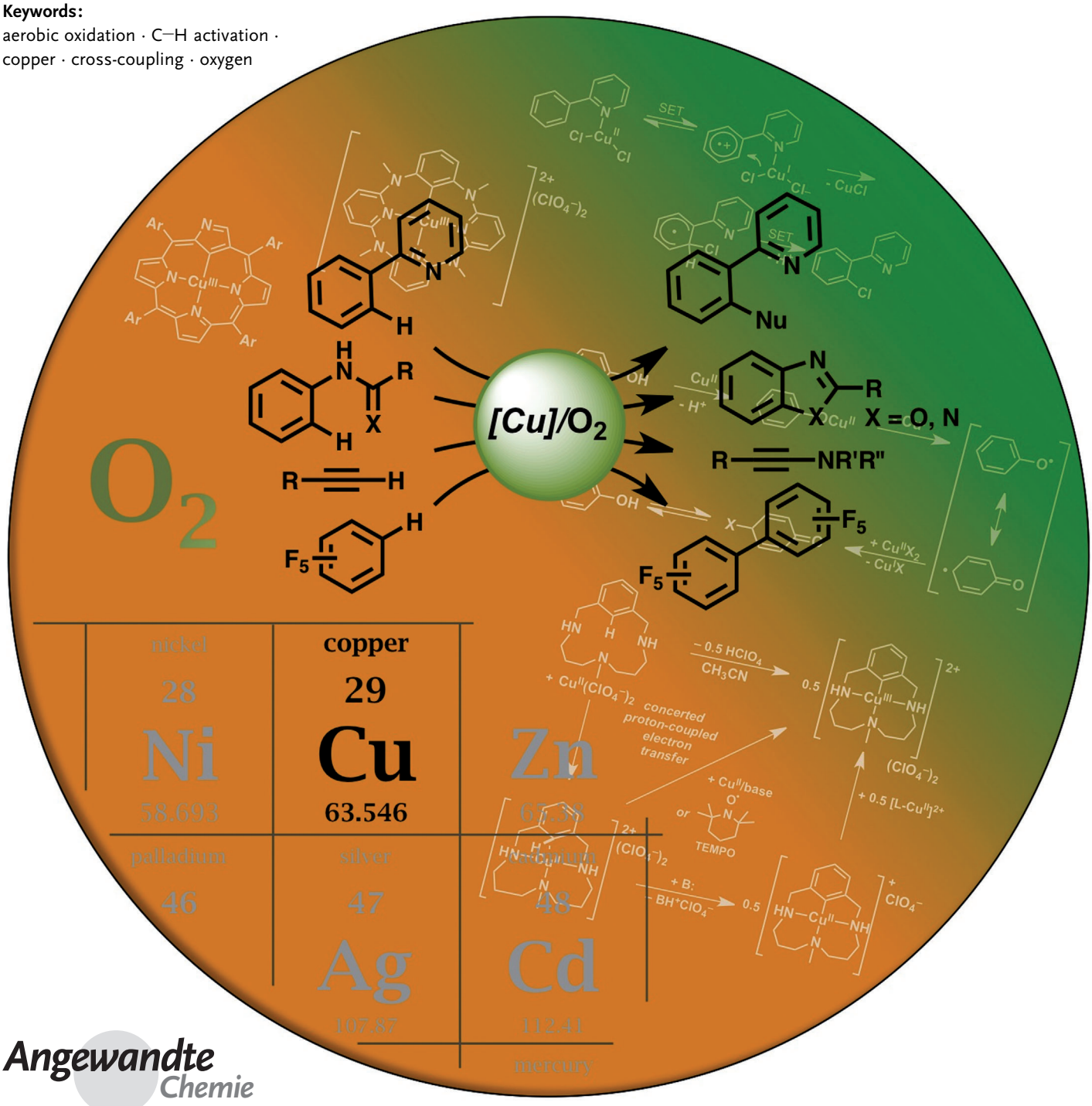

The selective oxidation of C–H bonds and the use of O_2 as a stoichiometric oxidant represent two prominent challenges in organic chemistry. Copper(II) is a versatile oxidant, capable of promoting a wide range of oxidative coupling reactions initiated by single-electron transfer (SET) from electron-rich organic molecules. Many of these reactions can be rendered catalytic in Cu by employing molecular oxygen as a stoichiometric oxidant to regenerate the active copper(II) catalyst. Meanwhile, numerous other recently reported Cu-catalyzed C–H oxidation reactions feature substrates that are electron-deficient or appear unlikely to undergo single-electron transfer to copper(II). In some of these cases, evidence has been obtained for the involvement of organocopper(III) intermediates in the reaction mechanism. Organometallic C–H oxidation reactions of this type represent important new opportunities for the field of Cu-catalyzed aerobic oxidations.

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1. Introduction and Historical Context

The selective oxidation of organic molecules is a topic of critical importance to laboratory and industrial chemical synthesis,[1] and oxidative functionalization of C–H bonds is one of the most challenging classes of oxidation reactions.[2] Molecular oxygen is the ideal oxidant because of its abundance, low cost and lack of toxic by-products, but aerobic oxidation methods often face significant limitations with respect to selectivity and scope. Radical-chain autoxidation reactions are used in the production of important commodity organic molecules, such as terephthalic acid and *tert*-butyl hydroperoxide, but such methods are intrinsically limited to substrates that undergo selective radical chemistry. Consequently, they find limited use in the synthesis of complex organic molecules, such as pharmaceuticals, or in laboratory-scale oxidations.

Within the field of homogeneous catalysis, palladium-catalyzed reactions are perhaps the most versatile methods for selective aerobic oxidation of organic molecules,[3] and they include methods ranging from alcohol oxidation to oxidative C–C, C–N and C–O bond formation. Advances in this field have occurred in parallel with a rapid growth in Pd-catalyzed methods for C–H oxidation;[4,5] however, many of the latter methods are not compatible with the use of O_2 as the stoichiometric oxidant. Instead, other oxidants, such as $PhI(OAc)_2$, benzoquinone, Cu^{II} or Ag^{I}, are required to achieve catalytic turnover. Mechanistic studies suggest that these oxidants are often required to promote reductive elimination of the product from the Pd center through the formation of high-valent intermediates.[6] New Pd catalyst systems may be capable of overcoming this limitation,[7] but another, complementary solution may involve the use of other transition-metal catalysts. In particular, recent advances in homogeneous copper catalysis highlight opportunities to achieve selective aerobic oxidative functionalization of C–H bonds.

Copper is found in the active site of many metalloenzymes that catalyze aerobic oxidation reactions. These enzymes include "oxygenases", which mediate oxygen-atom transfer to organic substrates, and "oxidases", which couple the reduction of O_2 to H_2O (or H_2O_2) to the oxidation of diverse substrates. The latter reactions range from outer-sphere oxidations (e.g., of lignin and Fe^{2+}) to the dehydrogenation of alcohols and amines. Extensive studies in the fields of mechanistic enzymology and bioinorganic chemistry have provided valuable insights into fundamental mechanisms of O_2 activation and substrate oxidation mediated by these enzymes.[8]

Independent of the biological reactions, the facile aerobic oxidation of Cu^{I} ions to Cu^{II} is widely recognized,[9] and a number of important synthetic Cu-catalyzed aerobic oxidation reactions exist, including industrial applications.[10] These include Glaser–Hay coupling of terminal alkynes (Scheme 1A);[11] oxidative polymerization of 2,6-dimethylphenol to produce polyphenylene oxide, a commodity-scale, high-temperature thermoplastic (Scheme 1B);[12] synthesis of 2,3,5-trimethyl-*p*-quinone, an intermediate in the commercial synthesis of vitamin E (Scheme 1C);[13] oxidative carbonylation of methanol to dimethycarbonate (Scheme 1D);[14] and numerous methods for aerobic alcohol oxidation (Scheme 1E).[15,16] Each of these examples formally corresponds to an "oxidase" reaction in which the formation of a new carbon-carbon or carbon-heteroatom bonds is coupled to the reduction of O_2. Despite this common feature, the mechanisms by which copper mediates the different substrate oxidation reactions exhibit considerable diversity.

Copper(II) is an effective one-electron oxidant, and it has been used in a number of oxidative-coupling reactions initiated by single-electron transfer from electron-rich organic molecules.[17] The oxidative dimerization of phenols and naphthols is a reaction that can be traced to the work of Pummerer in 1914,[18] in which the oxidative coupling of 2-

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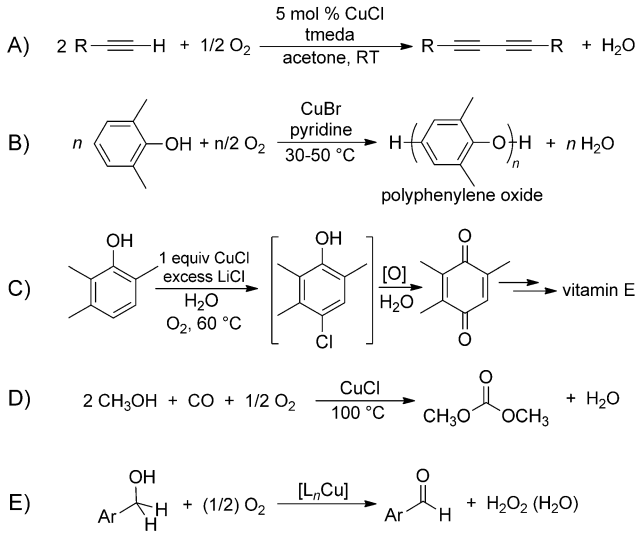
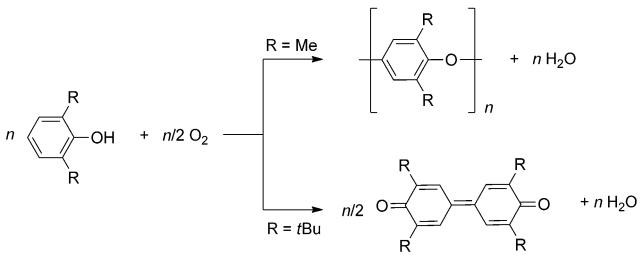


Scheme 1. Synthetic copper "oxidase" reactions.

naphthols was accomplished with silver oxide or potassium ferricyanide as a one-electron oxidant. Subsequently, analogous reactions were demonstrated with a wide range of other oxidants.[19] In 1959, Hay and co-workers reported that the oxidative polymerization of 2,6-disubstituted phenols could be accomplished by bubbling O_2 through a solution of a phenol derivative, 5 mol % copper(I) chloride and pyridine at room temperature.[12b,20] When substituents are small, as with 2,6-dimethylphenol, carbon-oxygen coupling occurs, allowing preparation of linear, high-molecular-weight polyphenylene oxide (Scheme 2, top pathway).[12] The presence of large



Scheme 2. Aerobic, oxidative polymerization or dimerization of 2,6-disubstituted phenols.

substituents leads to carbon-carbon coupling products (Scheme 2, bottom pathway). Substrates that lack *ortho* substituents form complex mixtures of *ortho* and *para* carbon-carbon and carbon-oxygen coupling products, in addition to the formation of quinone-like products.[21–23] *Ortho*-hydroxylation is often observed in phenol oxidations mediated by Cu/O_2/amine systems[24,25] suggesting that oxygenase-type reactivity can compete with the oxidase (oxidative-coupling) reactions. Overall, these observations are rationalized by mechanisms that involve the formation of phenoxyl radical intermediates, where the copper(I) species formed upon one-electron oxidation of the phenols can be reoxidized to copper(II) by molecular oxygen.

Single-electron-transfer (SET) mechanisms similar to those noted above explain many copper-mediated oxidation reactions, but other reactions are not readily rationalized by such mechanisms. The aerobic, oxidative dimerization of terminal alkynes (Scheme 1 A) was first reported in 1869 by Glaser, who obtained diphenyldiacetylene by treating copper(I) phenylacetylide with air.[26] Glaser coupling reactions, including their historical development, applications and mechanistic studies, are the subject of an excellent recent review.[11] Several points are worth repeating here. In 1937, Zalkind and Aizikovich found that copper(I) acetylides could be generated in situ,[27] and, in 1962, Hay reported that these reactions could be carried out with catalytic Cu, if the reaction was performed in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (tmeda) under an atmosphere of O_2.[28]

Despite the nearly 150-year history of this reaction, the mechanism remains poorly understood. Until the 1960s, mechanistic proposals typically featured the formation and coupling of alkynyl radicals. In situ deprotonation of the terminal alkyne could afford acetylides susceptible to one-electron oxidation by Cu^{II} to afford the alkynyl radicals. Subsequent kinetic studies, investigation of alkyne electronic effects, and consideration of the low activation barriers for these reactions[29] caused these proposals to be abandoned in favor of organometallic pathways. π-Complexation of the alkyne to Cu^{I} or Cu^{II}, for example, should facilitate deprotonation of the alkyne and formation of Cu-acetylide intermediates. The copper oxidation states involved in different steps of the mechanism remain unclear, and both Cu^{I} and Cu^{II} species have been proposed.[30] One widely accepted mechanism involves formation of dimeric copper(II) acety-

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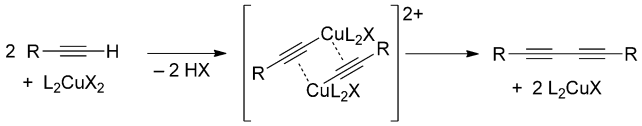
lides that undergo coupling of the alkynyl fragments to afford the diyne product (Scheme 3).[31]

The aerobic oxidative coupling of phenols and alkynes proceed with similar Cu catalysts under similar conditions; however, the above discussion suggests that the mechanisms for these reactions are quite different. This conclusion aligns with the observation that a variety of oxidants that promote



Scheme 3. Proposed mechanism for the Glaser reaction.

SET reactions promote the oxidative coupling of phenols,[21] whereas other transition metals that mediate the oxidative coupling of alkynes, such as Pd^{II} and Ni^{II}, typically employ organometallic pathways.[11] This divergence between single electron transfer and organometallic mechanisms provides a framework for the consideration of recent advances in copper-catalyzed aerobic C–H oxidation, and it underlies the organization of this review.

Section 2 surveys copper-based SET reactions that have been achieved with aerobic catalytic turnover. The content focuses on the different synthetic transformations, but it includes recent insights into the mechanisms of these reactions. Section 3 surveys reactions that qualitatively resemble organometallic C–H oxidation reactions catalyzed by Pd and other transition metals. The mechanisms for most of these reactions have not been fully elucidated, but the substrates tend not to be electron-rich molecules commonly associated with SET reactions, and in many cases they are highly electron-deficient. These features suggest that organometallic mechanisms may be involved.

The relevance of organocopper intermediates is even more plausible in light of recent insights into the formation and reactivity of organocopper(II) and -copper(III) complexes. The organometallic chemistry of Cu^{II} and Cu^{III} and its prospective role in catalytic oxidation reactions are considered in Section 4, together with possible mechanistic similarities between oxidative and non-oxidative Cu-catalyzed coupling reactions.

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The research summarized in this review includes material published through early June 2011, and emphasizes results from the past five years. Collectively, the recent advances in this area highlight a wealth of new opportunities to achieve selective aerobic oxidative functionalization of C–H bonds.

2. C–H Oxidation Initiated by Single-Electron Transfer

A number of electron-rich substrates, in particular tertiary amines, enolates, phenols, and electron-rich arenes and heterocycles, are susceptible to one-electron oxidation. Many oxidants, including Cu^{II}, are capable of promoting oxidative coupling reactions with these substrates, initiated by single-electron transfer. Copper(II) is especially attractive as an oxidant in these reactions because, under appropriate conditions and with suitable substrates, the reactions can be carried out with catalytic Cu using ambient air or O_2 as the stoichiometric oxidant. Recent work has demonstrated this principle in the oxidative coupling reactions of electron-rich arenes, α-functionalization of tertiary amines and cyclic ethers, and reactions of stabilized enolates.

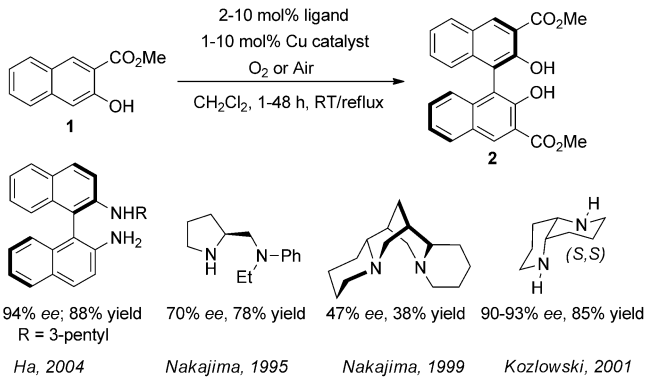
2.1. Homocouplings of Electron-Rich Arenes

Chiral 1,1′-bi-2-naphthol (binol) derivatives are a useful class of chiral ligands and auxiliaries, which may be accessed through oxidative homo- or cross-coupling of naphthols. This well-developed strategy capitalizes on the facile one-electron oxidation of phenols and naphthols, which can be accomplished using a number of different oxidants under relatively mild conditions.[21] Recent research efforts on oxidative binaphthol coupling have focused on replacing stoichiometric oxidants with catalytic methods using first-row transition metals, such as V,[32] Fe,[33] Mn,[34] and Cu,[35–41] in particular, for the formation of enantioenriched products through asymmetric catalysis.[32c–i,33a,c–d,36–39,41]

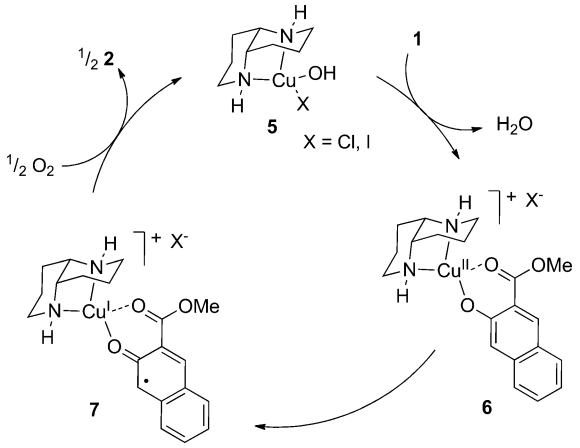
Copper-based procedures for the oxidative dimerization of naphthols and phenols have been studied extensively, and many of these methods are capable of using O_2 as the terminal oxidant (Scheme 4).[36–41] These reactions have been the subject of several previous reviews,[42] but the recent results presented here provide a valuable segue to some of the other results discussed herein.

Conditions for the aerobic, copper-catalyzed oxidative dimerization of naphthols are quite mild, commonly involving 1–10 mol% Cu catalyst loading, 2–10 mol% chiral amine ligand, and an O_2 or air atmosphere at ambient temperatures (Scheme 4). Though high yields and excellent *ee*'s have been obtained, the best results almost universally feature naphthol substrates containing a methyl ester substituent at the C3 position (e.g., **1**, Scheme 4).

Some of the highest yields and enantioselectivities to date have been achieved by Kozlowski and co-workers with a computationally designed 1,5-diaza-*cis*-decalin ligand.[38] Recently, this catalyst system has been applied in the aerobic copper-catalyzed enantioselective coupling of functionalized

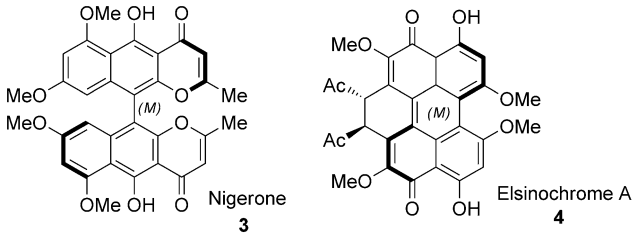


Scheme 4. Aerobic, copper-catalyzed, oxidative dimerization of naphthol derivatives using chiral amine ligands.



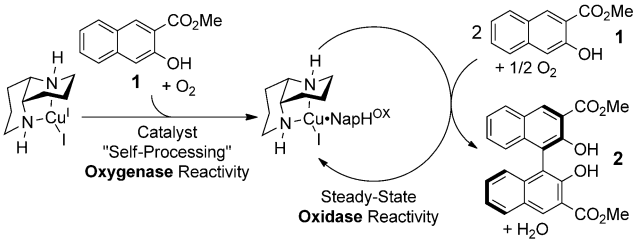
Scheme 5. Proposed mechanism for catalytic naphthol dimerization.

2-naphthols to prepare binaphthyl polymers[43] and homochiral biaryl natural products, such as nigerone (**3**) and elsinochrome A (**4**).[42f,44]



The prevailing mechanistic proposal for these reactions features formation of a Cu^{II}-naphthoxide (**6**) species that undergoes intramolecular electron transfer from the coordinated naphthoxide to Cu^{II} to form a Cu^{I}-naphthoxyl radical (**7**).[45] The chiral diamine ligand provides the basis for the enantioselective C–C coupling from this species. Details of the C–C coupling step are not well understood, but possibilities include attack of a second naphthol substrate on the naphthoxyl radical or bimolecular coupling of two Cu^{I}-naphthoxyl radicals. Evidence for binuclear Cu intermediates and their potential involvement in the C–C coupling step have been obtained from gas-phase studies of the reaction, catalyzed by [Cu(tmeda)(OH)]Cl.[45b,c] A simplified catalytic cycle featuring the diaza-*cis*-decalin ligand is shown in Scheme 5.

Copper(I) and copper(II) 1,5-diaza-*cis*-decalin complexes [(N_2)Cu] are effective pre-catalysts for aerobic oxidative coupling of naphthol substrates, but recent mechanistic studies by Kozlowski and Stahl reveal that these complexes are not the reactive form of the catalyst under steady-state conditions.[46] Rather, the active catalyst forms in a pre-steady-state self-processing step that involves oxygenation of the naphthol substrate, **1**, to form an oxygenated "cofactor", $NapH^{OX}$. The identity of this cofactor was not firmly established; however, orthoquinone derivatives of **1** were obtained under single-turnover conditions. Formation of $NapH^{OX}$ is correlated with a kinetic "burst" of O_2 consumption, after which the (N_2)Cu/$NapH^{OX}$ catalyst effects highly selective, steady-state oxidase reactivity (i.e., aerobic oxidative biaryl coupling) (Scheme 6). These observations implicate a striking similarity between this synthetic catalyst system and certain biological copper oxidases, such as copper amine oxidases (CAOs),[47] which also undergo preliminary oxidative self-processing to generate an oxygenated cofactor (e.g., topaquinone[48]) that is required for subsequent oxidase-type oxidation catalysis.

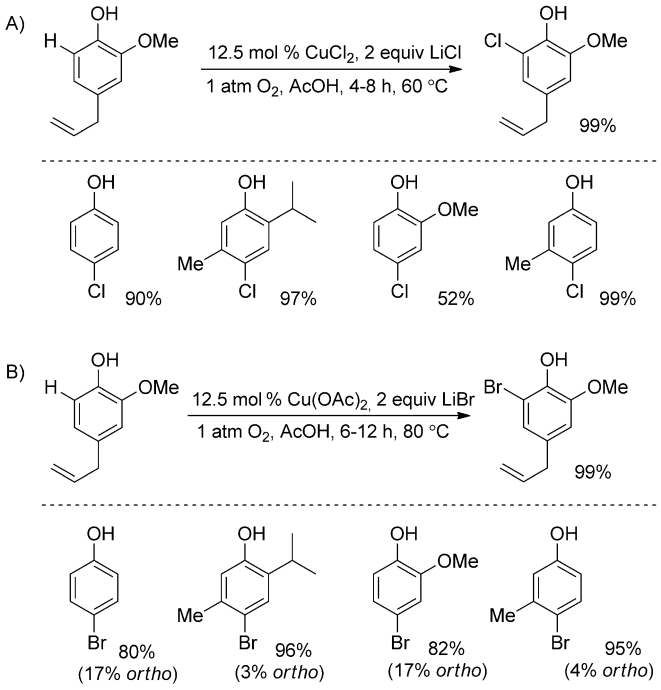


Scheme 6. Oxygenase vs. oxidase reactivity identified from mechanistic studies of Cu-catalyzed oxidative coupling of naphthol substrate, **1**.

2.2. Oxidative Bromination and Chlorination of Electron-Rich Arenes

The facile single-electron oxidation of phenols and other electron-rich arenes and heteroarenes has led to the development of copper-catalyzed halogenation protocols for these substrates.[49] Gusevskaya and co-workers reported a highly selective method for oxidative halogenation of phenols under aerobic copper-catalyzed conditions.[50] *Para*-chlorinated phenols could be obtained with high selectivity[51] using 12.5 mol% $CuCl_2$ and 2 equiv LiCl in AcOH under 1 atmosphere of O_2 (Scheme 7A). *Para*-brominated phenols were obtained with excellent selectivity and good yields under similar reaction conditions (12.5 mol% $Cu(OAc)_2$, 2 equiv LiBr, AcOH under 1 atm O_2) (Scheme 7B).[52]

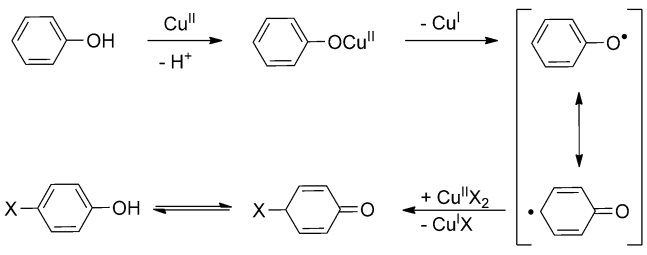
In both reactions, more-electron-rich phenols undergo oxidative halogenation with higher rates, and electron-



Scheme 7. Aerobic oxidative chlorination (A) and bromination (B) of phenols.

deficient substrates, such as *p*-nitrophenol, and non-phenolic arenes are unreactive. On the basis of these observations, the authors propose that high selectivity for monochlorination arises from the electron-withdrawing effect of a chlorine substituent, which deactivates the substrate toward further reaction. The phenolic OH group is proposed to be crucial to substrate activation. A detailed mechanism of these reactions is not known, but the proposed pathway features formation of a Cu^{II}-phenolate, followed by intramolecular electron transfer to afford a phenoxyl radical. Halogen-atom transfer to the *para* position of the phenoxyl radical by $CuCl_2$ or $CuBr_2$ and tautomerization of the dienone generates the *para*-halogenated phenol (Scheme 8).

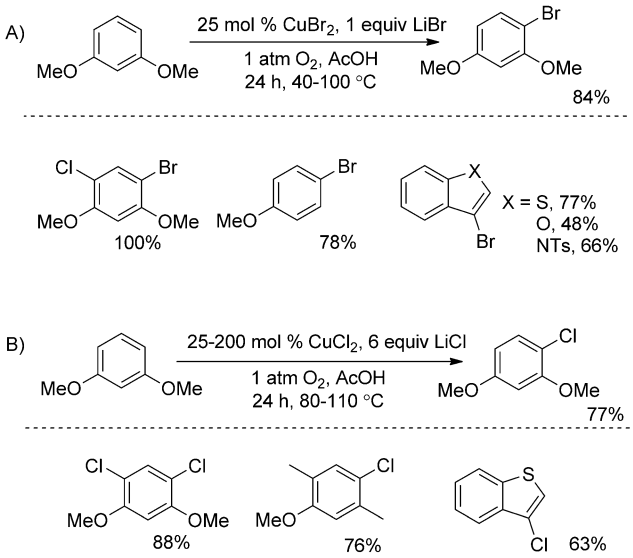
In subsequent studies, Gusevskaya demonstrated that anilines are also effective substrates for oxidative bromination.[53] Using conditions similar to those developed for the halogenation of phenols, they achieved bromination of unprotected anilines with high regioselectivity. Unlike phenol halogenation, however, monobrominated aniline products could undergo further bromination. Though aniline



Scheme 8. Proposed mechanism for the oxidative halogenation of phenols.

itself was an excellent substrate under these conditions, *N*-methyl aniline showed almost no reactivity. The chlorination of anilines proved to be much less effective than bromination; formation of *N*-acetylated byproducts competes with chlorination of the heterocycle.

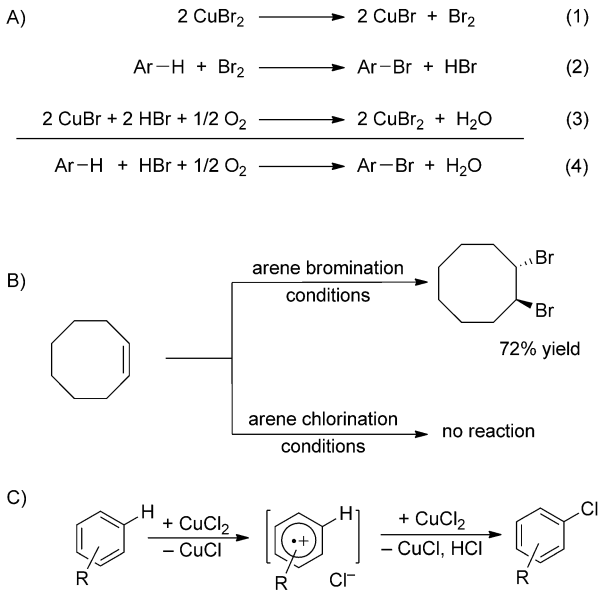
Stahl and co-workers reported a complementary copper-catalyzed method for the regioselective chlorination and bromination of electron-rich arenes that lack OH or NH groups.[54] Under conditions similar to those reported by Gusevskaya (25 mol% $CuBr_2$, 1 equiv LiBr, in AcOH under an O_2 atmosphere), regioselective monobromination of a range of electron-rich arenes and heteroarenes was achieved (Scheme 9A).[55] Arene chlorination was also achieved, but more forcing conditions were typically required (Scheme 9B).



Scheme 9. Representative copper-catalyzed oxidative bromination (A) and chlorination (B) reactions of electron-rich arenes.

Appropriate selection of the reaction conditions enabled selective mono- or di-halogenation of the arenes. Li and co-workers have reported a method for aerobic oxidative bromination of arenes, using 1 mol% $Cu(NO_3)_2$, and 1.1 equiv HBr at 100°C in water under air.[56] Excellent conversions and selectivities were achieved for a range of simple arenes, including toluene, anisole and cresole. The results by Stahl and Li reveal that substrate depronation to form a Cu^{II}-bound adduct, as in formation of a Cu^{II}-phenoxide or -anilide (cf. Scheme 8), is not a prerequisite to achieve oxidative halogenation of arenes.

Preliminary mechanistic studies by Stahl and co-workers into these reactions suggest that bromination and chlorination occur through different pathways (Scheme 10). The bromination reactions turn red-brown, and the disproportionation of $CuBr_2$ into CuBr and Br_2 has been described under similar conditions.[57] Accordingly, the arene bromination reactions could proceed through electrophilic bromination by in situ generated Br_2. Molecular oxygen will reoxidize CuBr to $CuBr_2$ in the presence of LiBr (Scheme 10A). In support of this proposal, exposure of cyclooctene to the arene bromina-



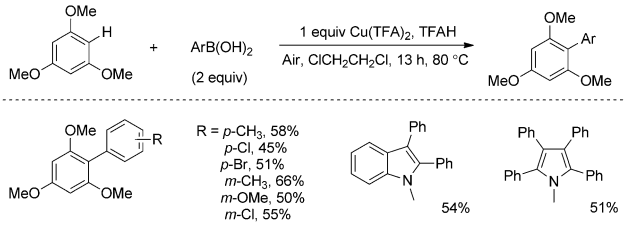
Scheme 10. Proposed mechanism for electrophilic bromination of electron-rich arenes (A), divergent outcomes for the reaction of cyclooctene under the arene bromination and chlorination reaction conditions (B), and proposed SET mechanism for oxidative chlorination of electron-rich arenes (C).

tion conditions resulted in the formation of *trans*-1,2-dibromocyclooctane in 75% yield (Scheme 10B). The disproportionation of $CuCl_2$ into CuCl and Cl_2 is much less favorable, and chlorination of cyclooctene was not observed under the arene chlorination conditions (Scheme 10B). In light of these observations, an SET mechanism was suggested for the arene chlorination reactions (Scheme 10C).[17] An arene radical-cation formed in this step could undergo chlorination of the ring through reaction with $CuCl_2$ and loss of a proton.

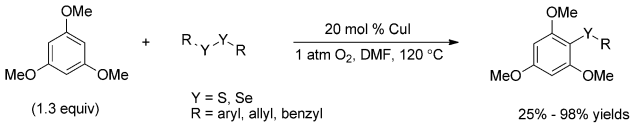
2.3. Other Oxidative C–H Functionalization Reactions of Electron-Rich Arenes

Electron-rich arenes and heteroarenes have been shown to undergo other C–H functionalization reactions. Itami and co-workers reported the arylation of electron-rich arenes with boronic acids using 1 equiv $Cu(TFA)_2$ (TFA = trifluoroacetate) under aerobic conditions at 80 °C.[58] The reaction was selective for formation of cross-coupled products; no homocoupled products arising from the trimethoxybenzene or boronic acid reagents were observed. Reactions with nitrogen heterocycles led to products arising from multiple C–H arylations (Scheme 11).

Trimethoxybenzene also underwent oxidative C–S coupling with disulfides in the presence of 20 mol% CuI, in DMF under O_2 (Scheme 12).[59] Substituted phenyl, allyl, and benzyl disulfides were used to thiolate 1,3,5-trimethoxybenzene in variable yields. Aryl thioethers were obtained with 1,2,4-trimethoxybenzene and 1,3-dimethoxybenzene, but the yields were relatively low, and other electron rich arenes were not effective. Examples of mono- and diselenylation of trimethoxybenzene in 70 and 30% yields, respectively, with



Scheme 11. Arylation of trimethoxybenzene and nitrogen heterocycles with aryl boronic acids.



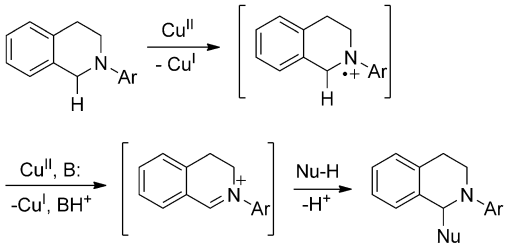
Scheme 12. Oxidative functionalization of trimethoxybenzene with disulfides and diselenides.

diphenylselenide were also reported. The synthetic scope of these reactions was rather limited, but they represent an intriguing example of C–S and C–Se coupling under aerobic conditions.

2.4. α-Functionalization of Tertiary Amines

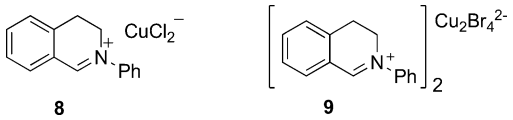
Tertiary amines are electron rich and susceptible to one-electron oxidation. This reactivity has been used to enable the oxidative functionalization of C–H bonds adjacent to tertiary amines with Ru,[60] Fe,[61] and Cu[62] catalysts, typically with oxidants such as *tert*-butylhydroperoxide (TBHP) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Li and co-workers pioneered the development of many different methods within this class of "cross dehydrogenative coupling" reactions, and have written several recent reviews in this area.[63] Recently, a number of these reactions have been shown to be amenable to aerobic catalytic turnover, and these will be the subject of the following discussion. The mechanistic principles that establish when O_2 can be used as an oxidant, rather than TBHP, DDQ or other oxidants, have not yet been established.

These reactions are believed to be initiated by SET from a tertiary amine to form an amine radical-cation (Scheme 13). Subsequent loss of a hydrogen atom (or H^+ and an electron) from the α-position, which is often a benzylic position,



Scheme 13. Proposed mechanism for α-functionalization of tertiary amines.

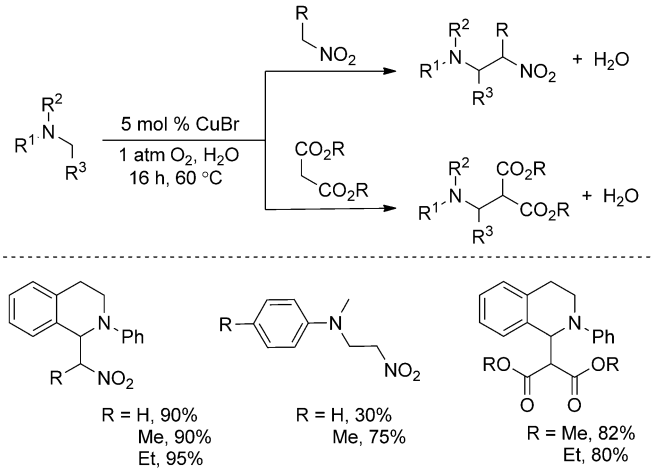
generates an iminium ion that is susceptible to attack by a wide range of soft nucleophiles. Klussmann and co-workers have recently obtained X-Ray crystal structures of tetrahydroisoquinolinium cuprates having dichlorocuprate and $(Cu_2Br_4)^{2-}$ counterions, **8** and **9**, resulting from oxidation of



8 **9**

the tetrahydroisoquinoline by $CuCl_2$ and CuBr, respectively, in the presence of O_2.[64] Both iminium species react smoothly with added nucleophiles to give expected cross-coupling products. A similar ionic crystal structure was obtained from related studies where DDQ was used as the oxidant instead of Cu/O_2.[65]

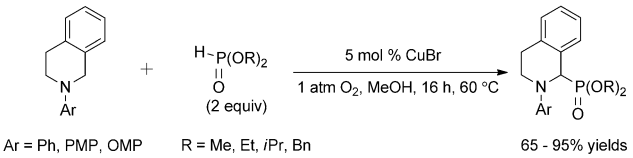
Li and co-workers described the coupling of stabilized carbon nucleophiles with *N*-phenyl-1,2,3,4-tetrahydroisoquinoline.[66] The reaction utilized 5 mol% CuBr at 60 °C in H_2O under ambient air (Scheme 14). Various nitroalkanes served



Scheme 14. Aerobic Cu-catalyzed oxidative cross-dehydrogenative coupling (CDC) reaction.

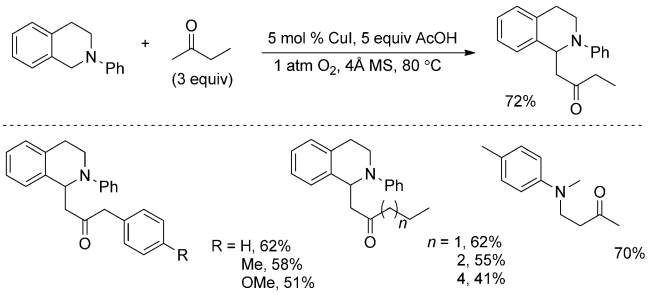
as competent substrates, though over-alkylation, in the case of *N*,*N*-dimethyl anilines, was a problem. Dialkyl malonate derivatives were effective nucleophiles in reactions with *N*-phenyltetrahydroisoquinoline as well as cyclic benzyl ethers.[67]

Li and co-workers reported the aerobic phosphonation of 2-aryl tetrahydroisoquinolines to afford α-aminophosphonates.[68] With diethyl phosphonate and *N*-phenyltetrahydroisoquinoline, a variety of copper salts (CuBr, $CuBr_2$, CuOTf, CuCl, CuI) catalyzed C–P bond formation under an O_2 atmosphere in excellent yields (Scheme 15). Dimethyl-, diisopropyl-, and dibenzyl-phosphonates were also effective coupling partners. In addition to *N*-phenyltetrahydroisoquinoline, *N*-*p*-methoxyphenyl and *N*-*o*-methoxyphenyl derivatives could be used.



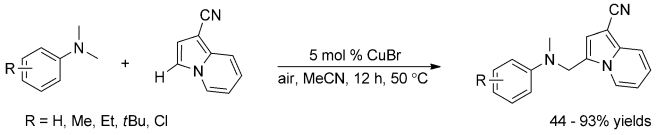
Scheme 15. Oxidative synthesis of α-aminophosphates from tertiary benzylamines.

Guo, Tan, and co-workers reported the reaction of tetrahydroisoquinolines with simple methyl ketones using 5 mol% CuI and 4 Å molecular sieves at 80 °C under O_2 (Scheme 16).[69] Aliphatic ketones and aryl methyl ketones are competent substrates; however, unsymmetrical ketones, such as 2-butanone, can lead to a mixture of regioisomeric products.



Scheme 16. Oxidative functionalization of tetrahydroisoquinolines with methyl ketones.

Zhang and co-workers reported the copper-catalyzed oxidative coupling of *N*,*N*-dimethylanilines with heteroarenes using 5 mol% CuBr in MeCN at 50 °C under air (Scheme 17).[70] A range of methoxy- and nitrile-substituted indolizines underwent cross-coupling under these conditions.

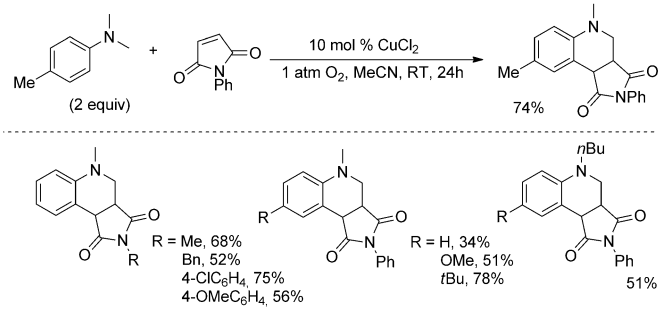


Scheme 17. CDC reaction between *N*,*N*-dimethylaniline and substituted indolizines.

Indoles, too, were acceptable substrates, though mixtures of products of mono- and bis-heteroarylation products of *N*,*N*-dimethylaniline were obtained. Only a small number of simple *N*,*N*-dimethylanilines were explored, and the presence of substituents on the aniline were found to have a significant impact on reaction yield.

Finally, Miura and co-workers have reported an oxidation/cycloaddition reaction involving *N*,*N*-dimethylanilines and *N*-substituted maleimides.[71] A mixture of maleimide and 2.0 equiv *N*,*N*-dimethylaniline were treated with 10 mol%

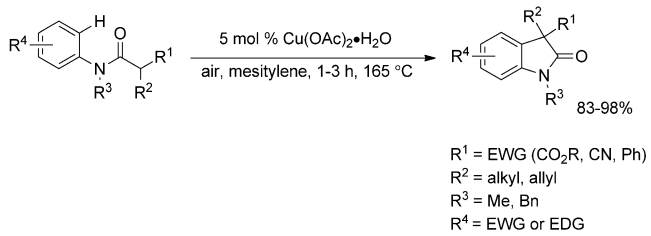
$CuCl_2$ in MeCN at room temperature under an O_2 balloon for 24 h, affording the corresponding tetrahydroquinoline in moderate yields (Scheme 18). Malonitrile was also an effective coupling partner.



Scheme 18. Tandem oxidation-cycloaddition of *N*,*N*-dimethylanilines with maleimides.

2.5. Reactions of Amide-Enolates

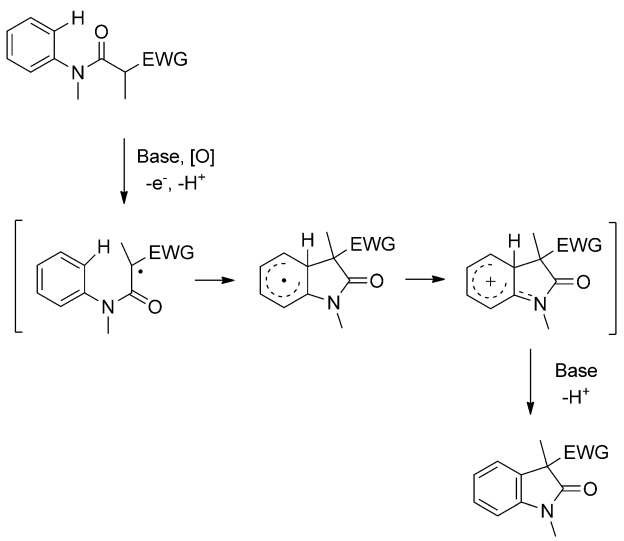
A number of important examples of stoichiometric oxidative coupling reactions of enolates with stoichiometric Cu^{II} salts have been reported;[72,73] however, these reactions are not typically amenable to aerobic catalytic turnover. Two groups have recently described copper-mediated C–H oxidation routes for the synthesis of oxindoles from anilides.[74] Taylor and co-workers reported the Cu-catalyzed cyclization of anilides to form 3,3-disubstituted oxindoles using 5 mol% $Cu(OAc)_2{\cdot}H_2O$ in refluxing mesitylene under air (Scheme 19).[74a] Yields were best when R^1 was an electron-withdrawing group.



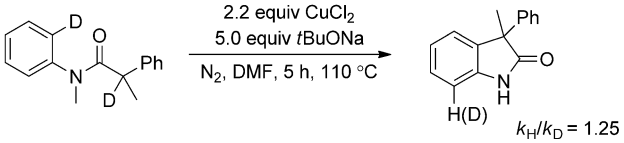
Scheme 19. Cyclization of anilides to give oxindoles.

The proposed mechanism begins with single-electron oxidation of the amide-enolate moiety by Cu^{II}, followed by cyclization, oxidation, and aromatization (Scheme 20). Consistent with this mechanism, an earlier stoichiometric study by Kündig and co-workers revealed the presence of a secondary isotope effect of 1.25, which the authors suggest indicates that C–H bond cleavage is not involved in the rate-determining step (Scheme 21).[74b]

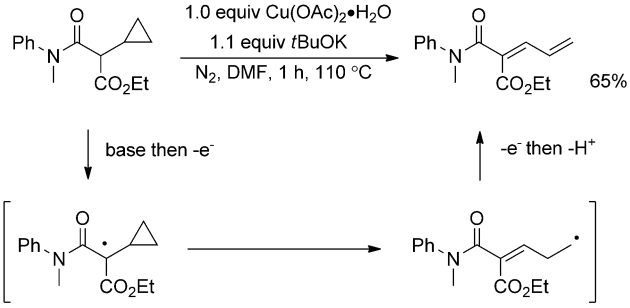
A subsequent stoichiometric study was carried out by Taylor and co-workers in which the anilide substrate contained a cyclopropyl radical probe (Scheme 22).[74c] Oxindole products were not detected in this case. Instead, the dienyl anilide was produced, resulting from the radical fragmentation of the cyclopropyl substituent and further supporting the likelihood of a radical amide-enolate intermediate.



Scheme 20. Proposed mechanism involving a radical amide-enolate.



Scheme 21. Intramolecular competition experiment reveals a secondary isotope effect.



Scheme 22. Radical probe experiment suggests SET-initiated mechanism.

2.6. Summary of Cu-Catalyzed C–H Oxidation Reactions Initiated by SET

Each of the reactions highlighted in Section 2 is consistent with a mechanistic pathway wherein a Cu^{II} catalyst mediates the one-electron oxidation of an electron-rich substrate (naphthols, phenols, methoxyarenes, tertiary amines, or enolates) followed by reaction of the oxidized intermediate with a suitable nucleophile, before or after loss of another electron. In many of these transformations, copper is one of several viable oxidants capable of promoting the reaction.

However, copper is appealing as a reagent because of its low cost and toxicity and, perhaps more importantly, because the Cu^{I} byproduct of these SET steps is capable of undergoing efficient oxidation to Cu^{II} in the presence of O_2. Much work remains to understand the mechanism of these reactions, particularly with respect to understanding the factors that will enable undesirable stoichiometric oxidants, such as Cu^{II} or DDQ, to be replaced with catalytic Cu in combination with O_2.

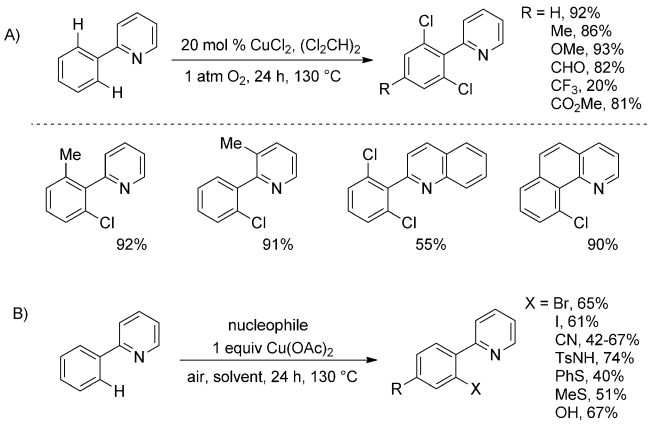
3. C–H Oxidations that Resemble Organometallic Reactions

Over the past five years, a number of copper-catalyzed aerobic oxidation reactions have emerged that resemble organometallic C–H oxidation reactions mediated by 2nd and 3rd row transition metals. In most cases, mechanisms have not been established; however, the reactions employ substrates that are electronically neutral or electron-deficient and, therefore, differ from classical substrates for SET-initiated reactions. Several early studies provided a foundation for the ensuing developments in this area: Yu reported chelate-directed oxidative C–H functionalization reactions of 2-phenylpyridine;[75] the groups of Buchwald and Nagasawa developed oxidative annulation reactions of *N*-aryl amidines and amides for the synthesis of 2-substituted benzimidazoles and benzoxazoles, respectively;[76,77] Stahl described the oxidative amidation of terminal alkynes;[78] and Daugulis reported "aromatic Glaser–Hay" reactions for the homocoupling of electron-deficient arenes and heteroarenes.[79] These reports provide the basis for the four general reaction classes surveyed below: 1) chelate-directed C–H oxidation reactions, 2) oxidative annulation reactions, 3) heterofunctionalization reactions of alkynes and electron-deficient (hetero)arenes, and 4) homo- and cross-coupling reactions of electron-deficient arenes.

3.1. Chelate-Directed C–H Oxidation Reactions

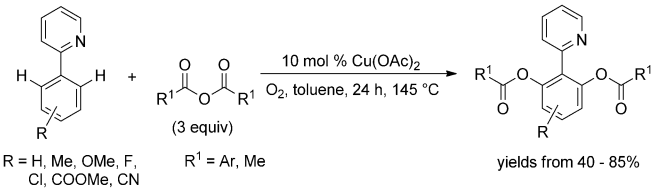
In 2006, Yu and co-workers reported a Cu^{II}-catalyzed chelate-directed oxidative functionalization of 2-phenylpyridine derivatives.[75] Their report largely focused on *ortho*-chlorination reactions and demonstrated that a variety of 2-arylpyridines could be chlorinated in the presence of 20 mol% $CuCl_2$ in $Cl_2CHCHCl_2$, under 1 atm O_2 at 130°C (Scheme 23 A). The solvent serves as an in situ source of the chloride nucleophile. High yields of monochlorinated products could be obtained when the pyridyl-directing group was *ortho*-substituted, and monosubstitution could be additionally improved by reducing the reaction temperature and time.

Bromination of the arene ring was achieved by using $Br_2CHCHBr_2$ as a solvent instead of tetrachloroethane and by switching the copper source to $Cu(OAc)_2$. Use of 1 equiv of $Cu(OAc)_2$ and a range of different nucleophiles enabled diverse functional groups to be introduced into the aryl ring (Scheme 23 B). The hydroxylation reaction was run under anaerobic conditions with $H_2{}^{18}O$, and a lack of label incorporation into the product prompted the authors to propose that the reaction proceeds through $Cu(OAc)_2$-mediated acetoxylation of the arene. Subsequent in situ hydrolysis of the acetate affords the phenol. The reaction could be carried out with catalytic $Cu(OAc)_2$ (10 mol%) by performing the reaction in a mixture of acetic acid and acetic anhydride, resulting in formation of the aryl acetate product.



Scheme 23. Cu-catalyzed chlorination of 2-phenylpyridine derivatives (A) and Cu^{II}-promoted functionalization of 2-phenylpyridine with various nucleophiles (B).

Cheng and co-workers subsequently expanded upon these results in the acyloxylation of 2-arylpyridines with a range of alkyl and aryl anhydrides.[80] The reaction conditions featured 10 mol% $Cu(OAc)_2$ in toluene under O_2 at 145°C (Scheme 24), and a range of mono- and di-acetoxylated 2-arylpyridines were accessed in this manner. In a subsequent

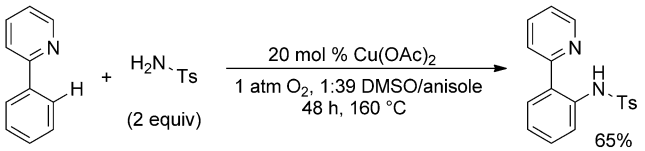


Scheme 24. Pyridyl-directed acyloxylation of 2-phenylpyridine.

study, the acyloxylation of 2-phenylpyridine was accomplished using acyl chlorides, which can undergo in situ formation of anhydrides.[81] The procedure is similar to that for anhydrides, but employs 2 equiv of acyl chloride, 20 mol% $Cu(OAc)_2$, and 2 equiv KO*t*Bu in toluene under O_2 at 145°C for 48 h. The latter protocol enables access to an expanded scope of aryl acyloxylated products due to the broad availability of acyl chloride reagents.

Concurrent with the original study of Yu, Chatani and co-workers reported chelate-directed amination of 2-phenylpyridine derivatives with aniline using stoichiometric $Cu(OAc)_2$.[82,83] Ohno and co-workers later described the use of tetrahydropyrimidine rather than pyridine as a directing group to achieve *ortho* hydroxylation and amidation (with $BocNH_2$ and $TsNH_2$) using stoichiometric $Cu(OAc)_2$.[84] Nicholas and co-workers recently reported conditions for

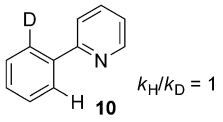
the catalytic amidation of 2-phenylpyridine, using 20 mol% $Cu(OAc)_2$ under 1 atm O_2 in DMSO/anisole (1:39) at 160°C for 48 h. (Scheme 25).[85] Modest catalytic turnover numbers were observed (from 1.2 to 3.3 turnovers; yields from 26–65%) in the amidation/amination of 2-phenylpyridine with several sulfonamides, carboxamides, and *p*-nitroaniline.

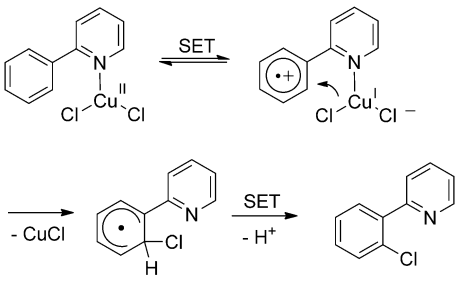


Scheme 25. Catalytic amidation of 2-phenylpyridine.

Related reactions employing oxidants other than O_2 have been reported, including the amidation of 2-phenylpyridine and indole derivatives with di-*tert*-butylperoxide, and methylthiolation of 2-phenylpyridines with dimethylsulfoxide as the source of methylthiolate and $K_2S_2O_8$ as the oxidant.[86] Yao and co-workers reported an oxidative C–H halogenation of pyrazole-3,5-dicarboxylic acid using stoichiometric $CuCl_2$, KOH, and halide salts.[87] After 3 days at 160°C, halogenated pyrazoles were isolated as Cu^{II} coordination complexes; halogenation is proposed to benefit from a directing effect by pendant carboxylates.[88]

These reactions qualitatively resemble Pd-catalyzed chelate-directed C–H functionalization reactions,[4c] but preliminary mechanistic insights suggest the reactions proceed by a different mechanism. Yu and co-workers noted that Cu-catalyzed chlorination reactions in Scheme 23A exhibit a first-order dependence on substrate and $CuCl_2$ and that electron-withdrawing groups lower the rate of the reaction. No deuterium kinetic isotope effect was observed in an intramolecular competition experiment with substrate **10**. The lack of isotopic sensitivity in the C–H cleavage step contrasts observations from Pd-catalyzed reactions. On the basis of these results, Yu and co-workers propose that the reactions are initiated by a SET step (Scheme 26), similar to those described in Section 2 of this review (cf. Scheme 10C). Intramolecular chloride transfer to a radical-cation intermediate is proposed to occur, followed by another SET step and loss of a proton to afford the chloroarene product. The Cu^{II} catalyst can be regenerated by oxidation of Cu^{I} by O_2. A mechanism initiated by electrophilic activation of the arene was not considered in this work, but also could explain the available results.

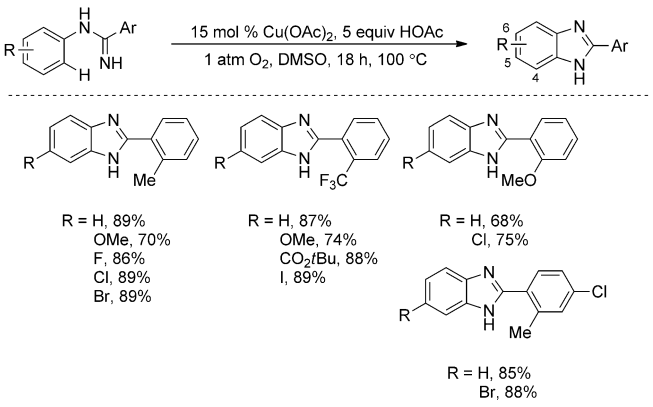




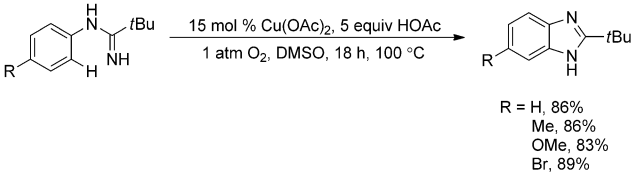
Scheme 26. Proposed mechanism for pyridyl-directed monochlorination of 2-phenylpyridine.

3.2. Oxidative Annulation Reactions

Buchwald and co-workers described the aerobic oxidative cyclization of amidines to give benzimidazoles using 15 mol% $Cu(OAc)_2$ and 5 equiv AcOH at 100°C in DMSO under a dioxygen atmosphere (Scheme 27).[76] Cyclization was tolerant of both electron-donating and electron-withdrawing substituents, including halogen substituents. Best yields were obtained with substrates that afforded 5- and 6- substituted benzimidazoles; low conversions were obtained for reactions leading to 4-substituted and 4,6-disubstituted products. For reasons that are not clear, amidines with aryl groups lacking *ortho*-substitution showed little conversion to the desired benzimidazole. *N*-methyl-2-phenylbenzimidazoles could be prepared by slight modification of the reaction conditions, and 2-*tert*-butyl-benzimidazoles were also accessible (Scheme 28).

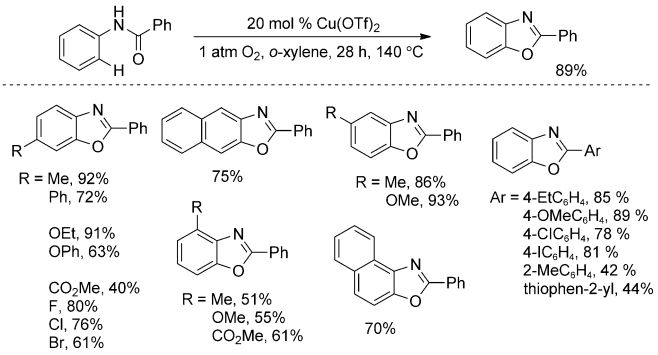


Scheme 27. Synthesis of 2-arylated benzimidazoles.



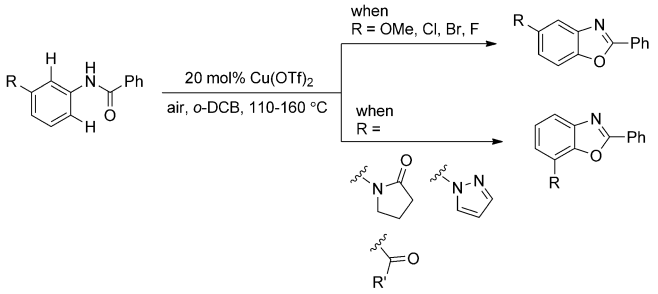
Scheme 28. Synthesis of 2-*tert*-butylbenzimidazoles.

The Nagasawa group reported a similar protocol for the preparation of benzoxazoles.[77] Various benzanilides underwent cyclization to the desired benzoxazole products in high yields using 20 mol% $Cu(OTf)_2$ at 140°C in *o*-xylene under an oxygen atmosphere (Scheme 29).



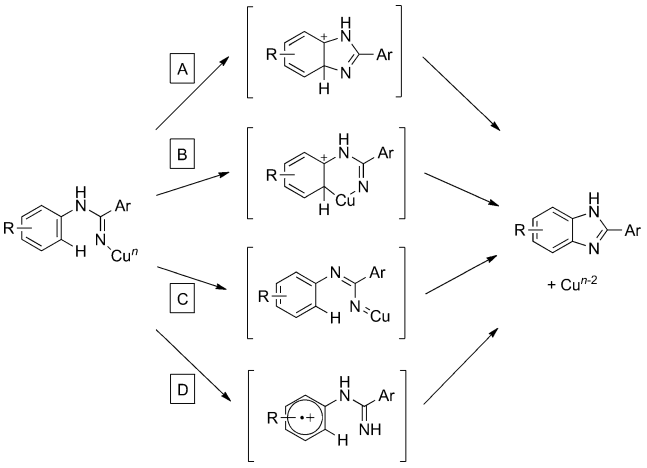
Scheme 29. Synthesis of 2-arylated benzoxazoles from anilides.

The highest yields were reported for *meta*- or *para*-substituted benzanilides, while *ortho*-substituted substrates gave lower yields. Electron-withdrawing substituents resulted in lower conversion, with recovered starting material reported in some cases. Regioselectivity of *meta*-substituted benzanilides exclusively favors the least sterically hindered position, resulting in 2,5-disubstituted benzoxazoles. However, when the *meta*-substituent is a pyrrolidinone, benzoyl, acetyl or other directing group, the reaction exclusively forms the more sterically hindered 2,7-disubstituted benzoxazoles (Scheme 30).[89]



Scheme 30. Directing-group effect on benzoxazole cyclization regiochemistry.

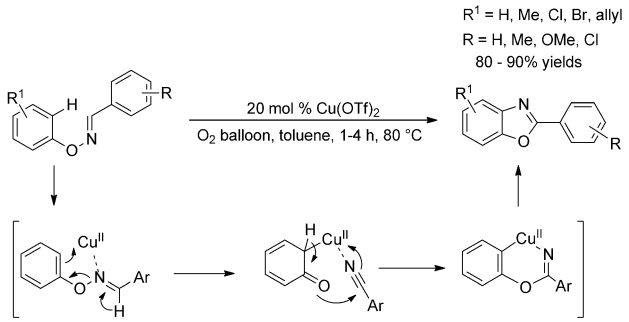
The mechanism for benzoxazole and benzimidazole formation is still uncertain. Buchwald postulated three possible mechanisms for oxidative annulation, each originating with coordination of the pendant amidine to the Cu center (Scheme 31). Pathway A involves attack of the arene π-system on the Cu-coordinated amidinate ligand, followed by rearomatization to produce benzimidazole. In pathway B, addition of the arene π-system to the Cu center affords an organocopper intermediate, which can then undergo aromatization and reductive elimination to produce desired product. Pathway C involves generation of a Cu-nitrene species that inserts into the arene C–H bond. The Cu is proposed to be in the +2 or +3 oxidation state, although no information is provided into specific redox steps. Both Buchwald and Nagasawa note that the reactions proceed more rapidly with electron-rich substrates. Nagasawa also reported the lack of a deuterium isotope effect in an intramolecular competition study with a mono-*ortho*-deuterated substrate. On the basis of these observations, Nagasawa suggests that Buchwald's electrophilic metalation pathway (Pathway B, Scheme 31) is the most reasonable mechanism for the reaction. An SET mechanism (cf. Scheme 26) is also consistent with the reported data; however, this mechanism was not considered in these initial reports (Pathway D, Scheme 31).



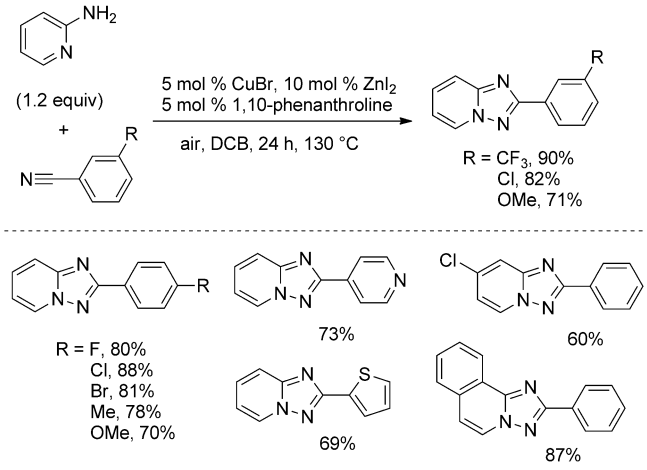
Scheme 31. Proposed mechanisms considered for benzoxazole/benzimidazole formation.

Punniyamurthy and co-workers have recently reported an alternative strategy for the preparation of benzoxazoles by rearrangement of bisaryloxime ethers using 20 mol% $Cu(OTf)_2$ under O_2 in toluene at only 80 °C (Scheme 32).[90] Though the substrate scope is abbreviated relative to the method reported by Nagasawa, the reaction conditions are much more mild. Punniyamurthy suggests a mechanism beginning with N–O bond scission followed by rearrangement to a copper-containing metallacycle and reductive elimination, possibly through a Cu^{III} intermediate.

Nagasawa and Ueda reported a copper-catalyzed tandem addition/oxidative cyclization reaction leading to the formation of 1,2,4-triazoles. Aryl nitriles were coupled to substituted 2-aminopyridines with 5 mol% CuBr, 5 mol% 1,10-



Scheme 32. Rearrangement of aryl oximes to give 2-aryl benzoxazoles.

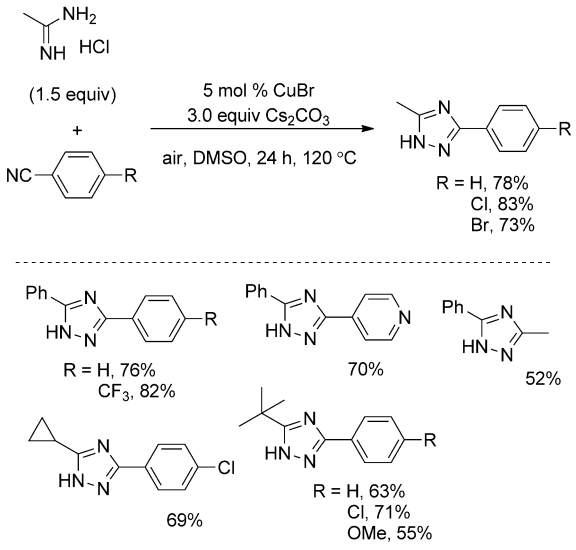


Scheme 33. Tandem addition-oxidative coupling of aminopyridines with aryl nitriles.

phenanthroline, and 10 mol% ZnI_2 in dichlorobenzene at 130 °C under O_2 atmosphere (Scheme 33).[91]

Mechanistically, the reaction is suggested to proceed through addition of the 2-amino group to the nitrile to form an *N*-2-pyridylamidine, followed by copper-catalyzed oxidative N–N coupling. The oxidative cyclization of a pre-formed amidine proceeds smoothly in the absence of zinc, implying that ZnI_2 assists only in amidine formation. Also, cyclization can also be achieved using stoichiometric $Cu(OAc)_2$ under an argon atmosphere, suggesting that molecular oxygen is only involved in the reoxidation of Cu^I to complete the catalytic cycle. The authors do not speculate on the mechanism of N–N bond formation.

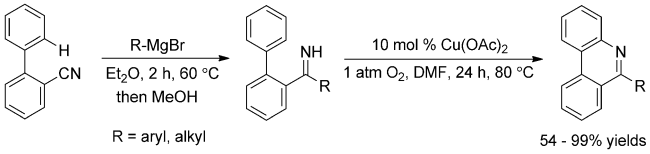
A modified procedure, employing 5 mol% CuBr, 3 equiv Cs_2CO_3 in DMSO with an air atmosphere at 120 °C, enabled the addition and oxidative cyclization of aryl nitriles with amidines to give 1*H*-1,2,4-triazoles. In all instances, electron-deficient benzonitriles gave best yields (Scheme 34). Bao and



Scheme 34. Oxidative coupling and cyclization of aryl nitriles with amidines.

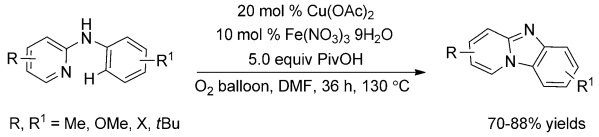
colleagues have developed a similar strategy for the preparation of benzimidazoles and quinazolines. Their cascade strategy begins with C–N bond formation between carbodiimides and various amines, followed by $Cu(OAc)_2/O_2$-catalyzed oxidative annulation to give desired product.[92]

Another tandem strategy, developed by Chiba and co-workers, involves the one-pot, two-step synthesis of phenanthridine derivatives from biaryl-2-carbonitriles.[93] Initial Grignard addition to biaryl nitrile substrates (followed by addition of MeOH) was shown to produce N–H imine intermediates, which, upon treatment with 10 mol% $Cu(OAc)_2$ in DMF under O_2, undergo intramolecular C–H amination to give annulated products in high yields (Scheme 35).



Scheme 35. One pot synthesis of phenanthridines from biaryl-2-nitriles.

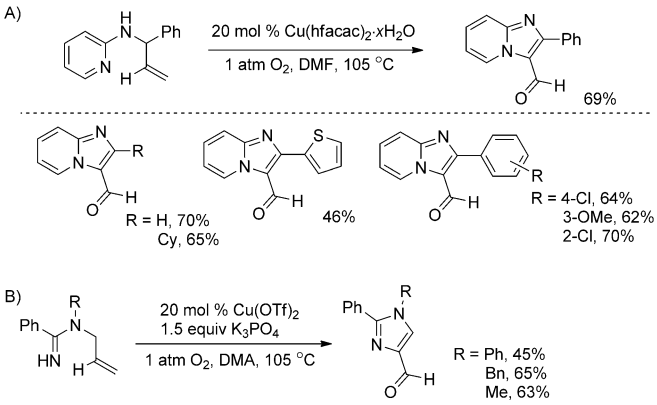
Zhu and co-workers demonstrated the oxidative annulation of *N*-aryl-2-aminopyridines using 20 mol% $Cu(OAc)_2$, with 10 mol% $Fe(NO_3)_3 \cdot 9H_2O$, and 5 equiv PivOH in DMF under O_2 at 130 °C (Scheme 36).[94] Without Fe^{III}, the product yield is diminished from 88% to 58%, even when Cu loading is increased to 2 equiv.[95]



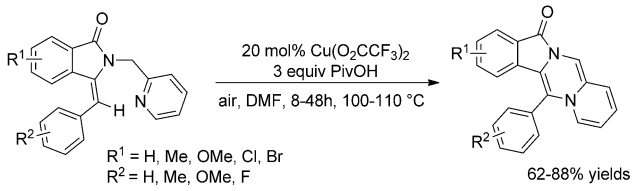
Scheme 36. Oxidative annulation of *N*-aryl-2-aminopyridines.

Zhu and co-workers have subsequently extended this method from arene C–H bonds to vinyl C–H bonds; however, instead of obtaining the expected oxidative amination products, aminooxygenation products were observed.[96] Using 20 mol% copper(II) hexafluoroacetylacetonate (hfacac) in DMF under O_2 at 105 °C, a range of imidazo[1,2-*a*]pyridine-3-carbaldehydes were formed from simple acyclic precursors (Scheme 37 A). Addition of iron nitrate, which proved essential in the previous study, had no beneficial effect on yield in this case. With slight modification of the reaction conditions, 1,2-disubstituted imidazole-4-carbaldehydes could be similarly obtained (Scheme 37 B).

Fu and co-workers have developed a similar strategy for the intramolecular oxidative amination of vinylic C–H bonds.[97] By treating substituted 3-benzylidene-2-pyridin-2-ylmethyl-2,3-dihydro-isoindol-1-ones with 20 mol% $Cu(O_2CCF_3)_2$ and 3 equiv PivOH in DMF at 100–110 °C under air for 8–48 h, ring-closed *N*-heterocycles could be obtained in good yields (Scheme 38). Substrates containing electron-



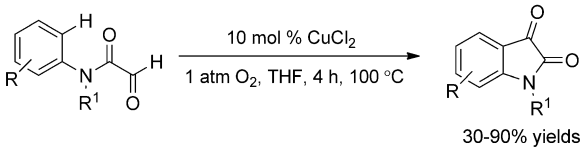
Scheme 37. Aminooxygenation for preparation of imidazo[1,2-a]pyridine carbaldehydes, and imidazole carbaldehydes.



Scheme 38. Intramolecular oxidative amination of vinyl C–H bonds.

donating groups led to slightly higher yields than those containing electron-withdrawing substituents, and the reaction was tolerant of C-Cl/Br bonds.

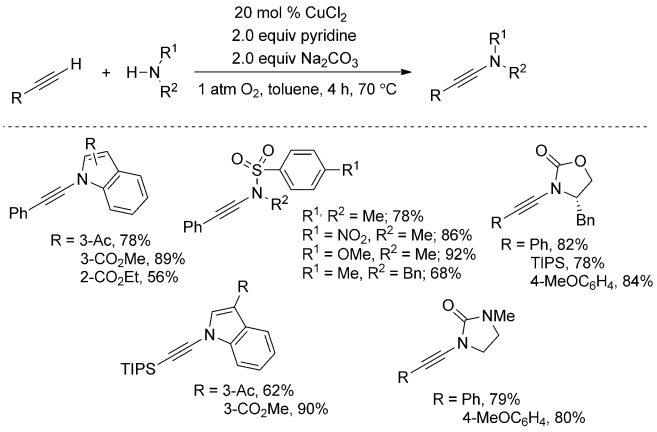
Finally, Li and co-workers reported an aerobic, copper-catalyzed oxidative C–H acylation procedure for the preparation of indoline-2,3-diones.[98] *N*-methyl-2-oxo-*N*-phenylacetamide could be cyclized in 90% yield using 20 mol% $CuCl_2$ and 1 atm O_2 in THF at 100 °C (Scheme 39). A range of *N*- and aryl-substituted substrates could be cyclized, with electron-rich substrates affording higher yields than electron-deficient substrates.



Scheme 39. Aerobic, copper-catalyzed synthesis of indoline-2,3-diones.

3.3. Hetero-Functionalization of Terminal Alkynes and Electron-Deficient Heteroarenes

In 2008, Stahl and co-workers reported the oxidative coupling of terminal alkynes with a wide range of nitrogen nucleophiles using 20 mol% $CuCl_2$, 2 equiv of Na_2CO_3 and 2 equiv of pyridine in toluene under an O_2 atmosphere (Scheme 40).[78] The use of excess amine nucleophile (5 equiv) minimized the quantity of Glaser alkyne homocoupling byproduct. Screening results showed that $Cu(OAc)_2$ is also an effective catalyst, and a respectable yield of the ynamide

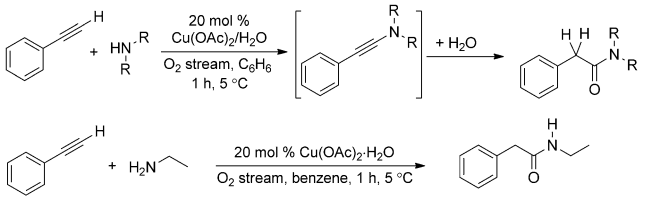


Scheme 40. Aerobic copper-catalyzed synthesis of ynamides from terminal alkynes.

(69%) can be obtained with a 1:1 stoichiometry of alkyne and amine under catalytic conditions. Cyclic carbamate, amide, and urea nucleophiles, as well as substituted indoles and *N*-alkyl benzenesulfonamides, were all good coupling partners. Effective substrates all had a pK_a between 15–23 (DMSO), although not all nitrogen nucleophiles within this pK_a range were effective. For example, acyclic nucleophiles other than sulfonamides exhibited poor reactivity. Terminal alkynes substituted with aryl, alkyl, and silyl groups were effective, with electron-rich alkynes being the most effective.

Alkynyl chloride byproducts were isolated from the reaction mixture, suggesting that C–N bond formation may originate through an alkynyl chloride intermediate, but, when alkynyl chlorides were subjected to the reaction conditions, little conversion to the ynamides was observed. The authors invoked a simplified mechanism involving the sequential activation of alkyne C–H and nucleophile N–H groups at a Cu^{II} center, followed by C–N bond formation to give ynamide product. Details of the C–N coupling process and aerobic reoxidation of the catalyst were not addressed.

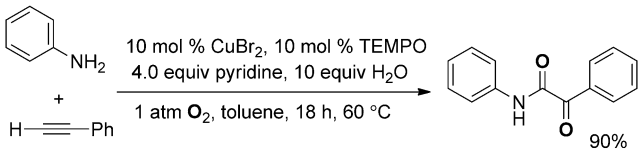
This reactivity expands upon an early report by Peterson in 1968, who described the oxidative coupling of phenylacetylene with simple secondary amines.[99] Dimethylamine, diethylamine, and piperidine were reported to react with phenylacetylene in the presence of 20 mol% $Cu(OAc)_2$-H_2O in benzene under a steady stream of oxygen (Scheme 41). Isolation of the products is complicated by the reactivity of these products toward hydrolysis, which forms the corresponding *N*,*N*-dialkylamides. When primary amines, such as



Scheme 41. Ynamidation of phenylacetylene with simple secondary and primary amines.

ethylamine, were used as the nitrogen nucleophile, *N*-ethyl-2-phenylacetamide was obtained instead of the ynamide. In some cases the amide product may be desired;[100] however, the ability to stop at the intermediate ynamide expands the synthetic versatility of the reactions.

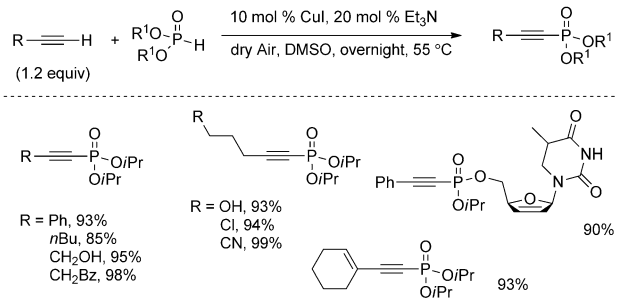
Jiao et al. reported an aerobic copper-catalyzed ynamination reaction with concomitant dioxygenation of the alkyne using 10 mol% $CuBr_2$, 10 mol% TEMPO, and 4 equiv pyridine in toluene and water under an O_2 atmosphere (Scheme 42).[101] This tandem amination-diketonization was



Scheme 42. Tandem ynamidation-diketonization reaction.

effective with both electron-rich and electron-deficient alkynes and with a variety of anilines. Electron-deficient anilines performed more efficiently, and halo-substituted anilines were partially compatible with the reaction conditions, affording products in low yields. The reaction is performed with 10 equiv H_2O, but ^{18}O-labeling studies revealed that both oxygen atoms in the diketone come from O_2, and not H_2O. Under the reaction conditions, oxidative coupling of the anilines was also observed, forming *trans*-1,2-diphenyldiazene; this reactivity was the subject of a later independent report.[102]

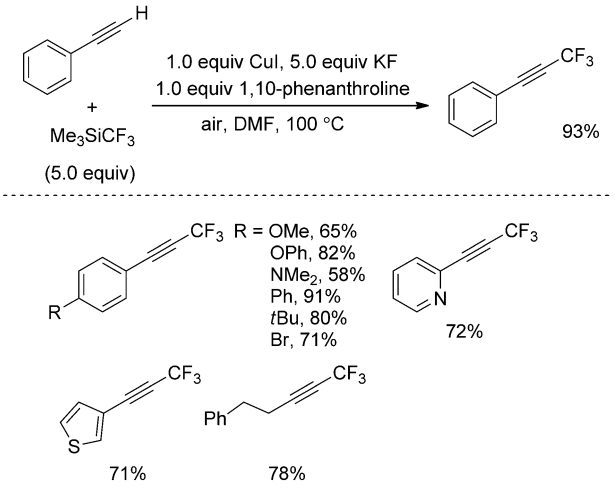
Other alkyne heterofunctionalization reactions have also been developed. Han and co-workers reported the oxidative phosphonation of terminal alkynes under aerobic conditions.[103] Using 10 mol% CuI or $Cu(OAc)_2$, 2 equiv Et_3N or Et_2NH, in DMSO under dry air, *H*-phosphonates could be coupled to terminal alkynes to yield alkynylphosphonates in excellent yields (Scheme 43). A wide range of terminal alkynes could be used, including aliphatic, aryl, and highly



Scheme 43. Synthesis of alkynylphosphonates.

functionalized alkynes, giving high yields of desired alkynylphosphonate diethyl, diisopropyl, dibutyl, and dibenzyl esters. Interestingly, only very small quantities (10%) of Glaser dimerization products are formed under these reaction conditions. When oxygen was excluded from the reaction mixture, hydrophosphorylation occured to give alkenylphosphorus compounds.[104] The authors reported that a copper acetylide precipitates at the beginning of the reaction and disappears over the course of the reaction. Subjection of the Cu-acetylide to the reaction conditions was reported to give both alkynylphosphonate and Glaser diyne coupling products. If coordination of *H*-phosphonate to copper acetylide is fast relative to the reaction of copper acetylide with oxygen, formation of Glaser products can be minimized.

Qing et al. reported the oxidative trifluoromethylation of alkynes using 1 equiv Cu^I, 1 equiv phenanthroline, and 5 equiv Me_3SiCF_3 in DMF under air atmosphere.[105] A range of aryl alkynes, and a few aliphatic alkynes, were trifluoromethylated using this procedure in good-to-excellent yields (Scheme 44). When O_2 was used instead of air, Glaser alkyne dimers were the sole product. The authors speculate that this effect arises from the quenching of a $CuCF_3$ species in the presence of high concentrations of O_2.

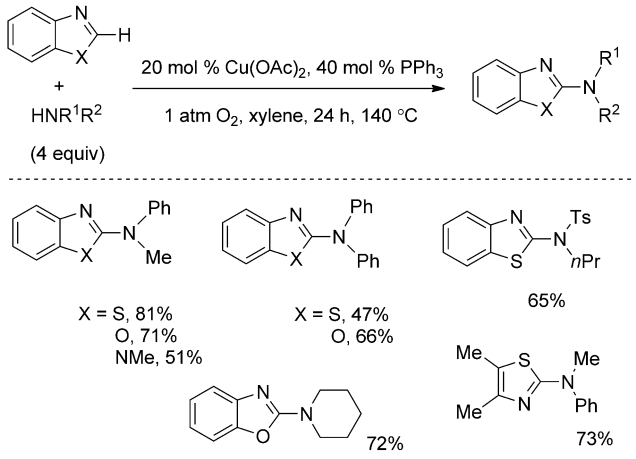


Scheme 44. Aerobic copper-mediated trifluoromethylation of alkynes.

Alkynes, heteroaromatics, and electron-deficient arenes share very similar C–H bond acidities. For example, the pK_a values of pentafluorobenzene, benzoxazole, benzothiazole, and phenylacetylene are 21, 24, 27, and 28.8, respectively. Reactions across these classes of molecules show remarkable similarities, and a number of oxidative heterofunctionalization reactions of electron-deficient heteroaromatics and arenes analogous to those described for alkynes have also been developed.[106]

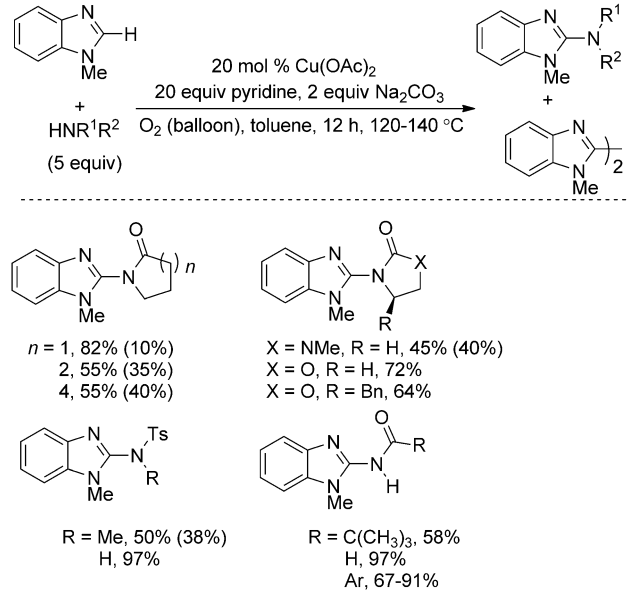
In 2009, Mori and co-workers reported conditions for the oxidative intermolecular coupling of benzothiazole with *N*-methylaniline with 20 mol% $Cu(OAc)_2$, 40 mol% PPh_3, 4 equiv NaOAc, at 140 °C in xylenes under an O_2 atmosphere (Scheme 45).[107] The substrate scope encompassed benzoxazoles and benzimidazoles, and aromatic and some aliphatic amines were effective in the amination reactions.

Shortly after the report by Mori, Schreiber and co-workers reported a similar procedure for the preparation of 2-aminobenzimidazoles, using 20 mol% $Cu(OAc)_2$ and 2 equiv Na_2CO_3, with pyridine as an additive in toluene.[108] Homocoupling of the heteroarene was observed as a byproduct



Scheme 45. Synthesis of 2-aminobenzimidazoles, oxazoles, and thiazoles.

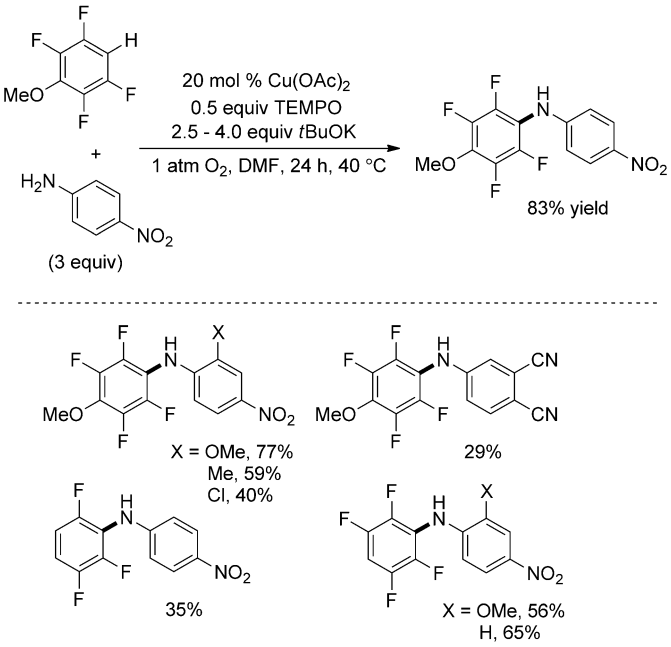
under many conditions, but could be suppressed by the use of 5 equiv of the nitrogen nucleophile. Under these conditions various cyclic amide, urea, and carbamate nucleophiles afforded the desired aminobenzimidazoles (Scheme 46). *N*-Methylbenzenesulfonamide was also an effective nucleophile; however, other acyclic secondary amide derivatives



Scheme 46. Synthesis of 2-aminobenzimidazoles.

were not effective. In contrast, a number of primary amides were successful in the reactions. Other aromatic and heterocyclic C–H bonds were also investigated; benzothiazole, oxazole derivatives, and 1,2,4,5-tetrafluorobenzene derivatives were included in the substrate scope.

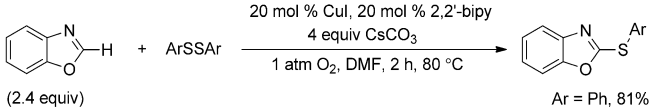
Subsequently, Su and colleagues described the C–H amination of perfluorinated arenes as well as heteroarenes with simple nitroanilines using 20 mol % $Cu(OAc)_2$, 2–3 equiv *t*BuOK, 50 mol % TEMPO, under O_2 in DMF.[109] In reactions



Scheme 47. C–H amination of electron-deficient arenes.

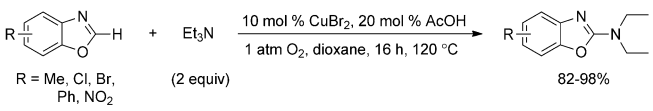
with electron-deficient arenes (Scheme 47), a number of tetra- and pentafluoroarenes underwent coupling with various electron-deficient anilines. In the absence of a Cu catalyst, nucleophilic aromatic substitution of a fluoro group by the amine nucleophile was observed. The C–H amination of benzoxazoles and benzothiazoles can be carried out using the same conditions, albeit at slightly higher temperature. Though the substrate scope is limited to amination with simple nitroaniline derivatives, this reaction proceeds under milder conditions than the earlier methods developed by Mori and Schreiber.

Other heterocoupling reactions of electron deficient arenes and alkynes have also been reported. For example, polyfluoroarenes and electron-deficient arenes will undergo aerobic, copper-catalyzed sulfoximation.[110] Fukuzawa and colleagues showed that benzoxazoles could also be thiolated with aryl disulfides using 20 mol % CuI, 20 mol % 2,2′-bipyridine, and 4 equiv Cs_2CO_3 in DMF under an O_2 atmosphere (Scheme 48).[111] Huang and co-workers have shown that tertiary amines can be used in the amination of



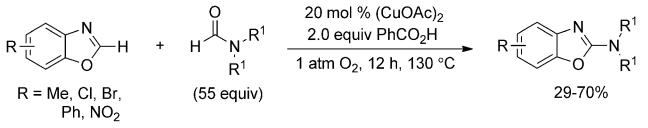
Scheme 48. Thiolation of benzoxazole.

benzoxazole in the presence of 20 mol % $CuBr_2$ and 10 mol % AcOH under O_2 to give *N*,*N*-dialkyl-2-aminobenzoxazoles (Scheme 49).[112] The latter reactions presumably arise from oxidative degradation of the tertiary amine to a secondary amine, followed by oxidative coupling of the benzoxazole with the secondary amine. Finally, Li, Duan and co-workers have demonstrated that the amination of benzoxazoles can be



Scheme 49. Oxidative amination of benzoxazole using tertiary amines.

accomplished using *N*,*N*-dialkyl formamides, through net decarbonylation of the formamide and coupling with the resulting secondary amine (Scheme 50).[113]

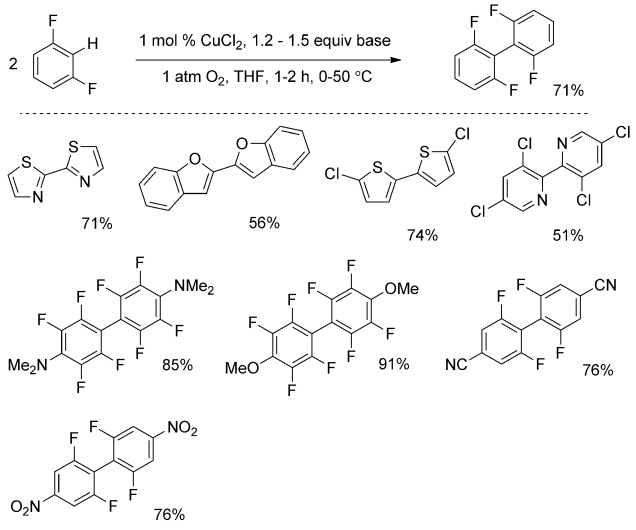


Scheme 50. Oxidative amination of benzoxazole using formamides.

3.4. Homo- and Cross-Coupling Reactions of Terminal Alkynes and Electron-Deficient Arenes

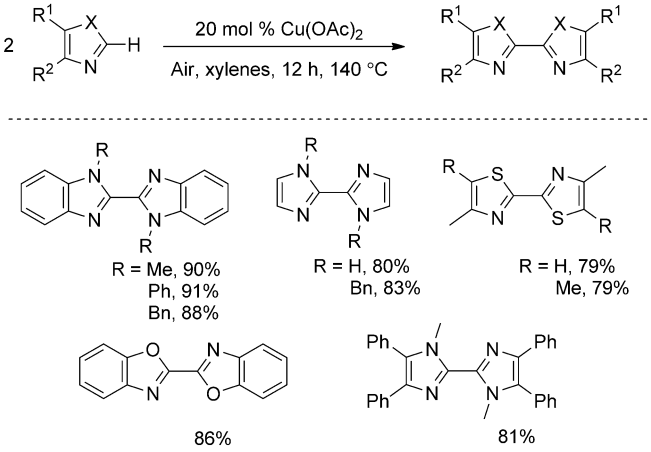
The similarity in C–H bond acidity between alkynes and electron-deficient arenes appears to provide the basis for a number of oxidative coupling reactions that resemble the Glaser–Hay reaction. Daugulis and co-workers reported an aerobic copper-catalyzed method for the homocoupling of electron-deficient (hetero)aromatics, termed "aromatic Glaser–Hay" reactions.[79] Using only 1–3 mol% $CuCl_2$ and a Zn/Mg amide base in THF at room temperature under an O_2 atmosphere, good yields of arene homodimers could be obtained (Scheme 51). The reaction exhibited good tolerance of functional groups. Cross-coupling reactions were not examined in this report.[114]

Bao recently reported an aerobic $Cu(OAc)_2$-mediated homo- and cross-coupling reaction at the 2-position of a range of azoles.[115] The homocoupling reactions were achieved with



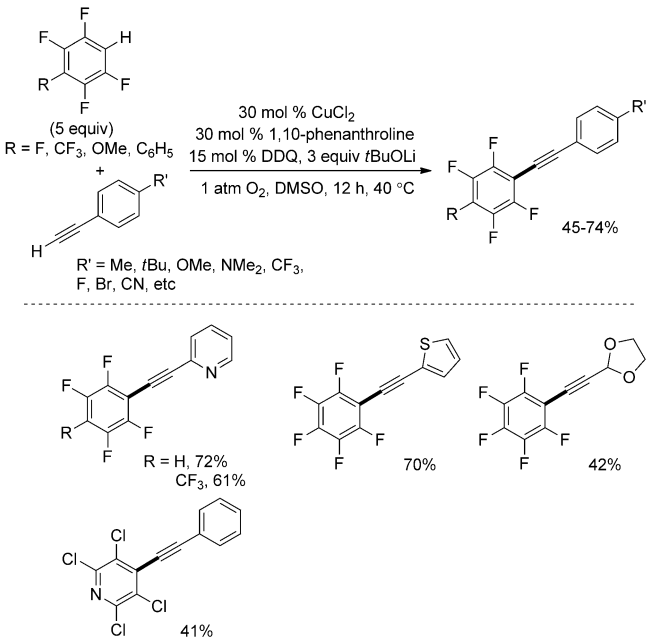
Scheme 51. Aerobic oxidative copper-catalyzed homodimerization of functionalized arenes.

20 mol% $Cu(OAc)_2$ in xylenes at 140 °C under an air or O_2 atmosphere. This method was applied to the oxidative homocoupling of imidazoles, benzimidazoles, thiazoles, oxadiazoles and benzoxazoles (Scheme 52). Moderate yields of cross-coupling products could be obtained, but the selectivity was not high. Generally, not more than 50–60% yields were achieved for cross-coupling products.



Scheme 52. Aerobic oxidative copper-catalyzed dimerization of 2-*H* azoles, oxazoles, and thiazoles.

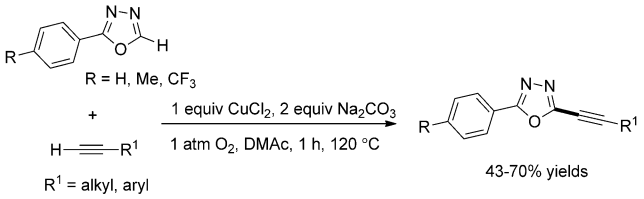
Su, Hong and co-workers described oxidative cross-coupling reactions of terminal alkynes with electron-deficient arenes and heteroarenes (Scheme 53).[116] The reactions employed 3 equiv of *t*BuOLi, 30 mol% $CuCl_2$, 30 mol% 1,10-phenanthroline, and 15 mol% DDQ in DMSO with O_2 as the oxidant at 40 °C. Excess fluoroarene (5 equiv) was used to enhance the cross-coupling selectivity. When Brønsted bases weaker than *t*BuO^- were used, such as $NaHCO_3$ and



Scheme 53. Sonagashira-type aryl-alkynyl coupling reaction.

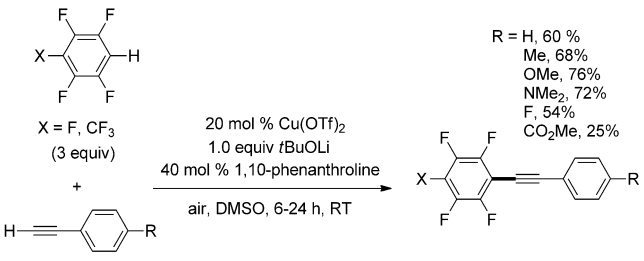
K_3PO_4, Glaser dimerization products dominated. The addition of catalytic DDQ also improved the reaction by suppressing diyne formation. The mechanistic origin of this effect is not understood, and other quinones did not exhibit a similar effect. Under these conditions, pentafluorobenzene could be coupled to a variety of simple arylalkynes; both electron-rich and electron-deficient alkynes were effective. Other polyfluorinated aromatics could be coupled to terminal alkynes as well. Di- and trifluoroarenes were unreactive, presumably due to the difference in acidity of the aryl C–H bonds and phenylacetylene.

In a concurrent study, Miura and co-workers reported the aerobic cross-coupling of terminal alkynes with heteroarenes.[117] The 2-position of 1,3,4-oxadiazoles could be functionalized with a range of terminal alkynes using 1 equiv $CuCl_2$ and 2 equiv Na_2CO_3 in *N*,*N*′-dimethylacetamide under 1 atm O_2. When run under air the reaction was sluggish; no reaction occurred under N_2. Oxazoles, too, could be coupled to terminal alkynes in slightly lower yields using a similar procedure, which required increased temperatures and the use of DMSO as a solvent. Electron-rich alkynes were more effective substrates than electron-deficient alkynes, which is attributed to the increased rate of alkyne dimerization with electron-poor alkynes. Aliphatic alkynes and alkynes bearing heterocyclic substituents were also fine coupling partners (Scheme 54) in each of these reactions.



Scheme 54. Aerobic copper-mediated oxidative coupling of coupling of alkynes and azoles.

Immediately thereafter, Miura et al. reported methods for the oxidative coupling of polyfluorobenzenes with arylalkynes using 20 mol% $Cu(OTf)_2$, 40 mol% 1,10-phenanthroline, and 1 equivalent Li*O*t*Bu in DMSO at room temperature under air (Scheme 55).[118] Once again, electron-rich arylalkynes gave higher yields than electron-poor derivatives; use of the latter substrates led to significant formation of diyne byproducts. This study also described a Ni-catalyzed method for aerobic oxidative coupling of alkynes and azoles.



Scheme 55. Cu-catalyzed oxidative coupling of polyfluorinated arenes and arylalkynes.

3.5. Summary of C–H Oxidations that Resemble Organometallic Reactions

This section has highlighted a number of oxidative C–H functionalization reactions with substrates that are electronically neutral or electron-deficient, properties not typically associated with SET reactions mediated by Cu^{II}. The similarity between some of these reactions and those mediated by Pd and Rh (e.g., chelate-directed C–H functionalizations and annulation reactions in Sections 3.1 and 3.2) make it tempting to propose an electrophilic C–H activation pathway by the Cu center, followed by organometallic functionalization of a Cu–C bond. Preliminary mechanistic insights, however, do not necessarily support such a pathway. For example, the lack of deuterium isotope effects from intramolecular competition experiments seem more consistent with electrophilic activation of the arene π-system or SET-initiated C–H functionalization. Further studies will be needed to clarify the mechanisms of these reactions. Sections 3.3 and 3.4 highlight a wealth of new C–H oxidation reactions involving substrates with acidic C–H bonds. These reactions closely resemble Glaser–Hay couplings; however, they employ substrates and achieve transformations for which the Glaser–Hay analogy was not previously recognized. The mechanisms of these reactions are not well understood, but they seem almost certain to proceed through organometallic intermediates, presumably involving Cu in the +2 or +3 oxidation states. Some insights can be gleaned from recent fundamental studies of the organocopper chemistry.

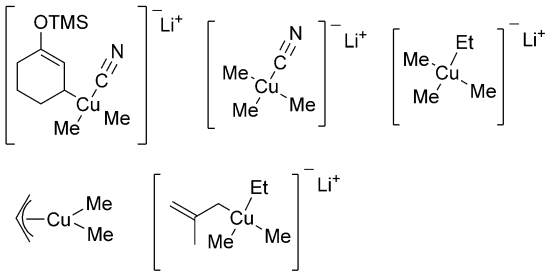
4. Organometallic Copper Chemistry Relevant to C–H Oxidation Reactions

The organometallic chemistry of Cu^{II} and Cu^{III} is still in a nascent stage of development, but a number of advances in recent years have important implications for the chemical reactions described above. Organocopper(III) intermediates have been widely proposed in non-oxidative Cu-mediated reactions, with prominent examples including conjugate additions and nucleophilic substitution reactions mediated by Cu^{I} organocuprates[119] and Ullmann-type coupling reactions of aryl halides.[120] In contrast, the role of organocopper species in Cu-catalyzed oxidative coupling reactions has received much less consideration.

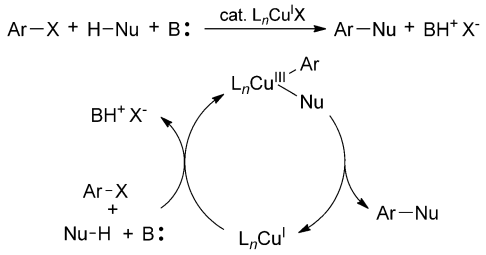
4.1. Survey of High-Valent Organocopper Complexes in Non-Oxidative Reactions

Experimental characterization of organocopper(III) intermediates in the reactions of cuprates were reported for the first time in 2007 by Bertz and Ogle[121,122] and Gschwind,[123] using low-temperature NMR techniques. Subsequent work has led to spectroscopic characterization of a number of related reactive intermediates (Scheme 56).[124]

Ullmann-type cross-coupling reactions of aryl halides are commonly proposed to proceed through a Cu^{I}/Cu^{III} catalytic cycle (Scheme 57),[120,125] analogous to the well-established

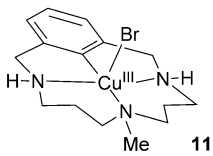


Scheme 56. Examples of organocopper(III) species observed using low-temperature NMR spectroscopy.



Scheme 57. Simplified mechanism commonly proposed for Ullmann-type cross-coupling reactions.

Pd^0/Pd^{II} cycle for Pd-catalyzed cross-coupling reactions. The involvement of arylcopper(III) intermediates in these reactions was recently challenged[126] and defended[127] on the basis of DFT computational studies. In addition, the first direct experimental evidence for the involvement of a Cu^{III} intermediate in an Ullmann-type coupling reactions was reported by Ribas and Stahl in 2010, using a macrocyclic aryl-halide substrate.[128] Aryl–Cu^{III}–halide species were independently synthesized and characterized by X-ray crystallography, and they were shown to undergo reversible reductive elimination/oxidative addition of the aryl halide at the Cu center. Aryl–Cu^{III}–Br species **11** was directly detected by NMR and UV-visible spectroscopy as an intermediate in an Ullmann-type coupling reaction with pyridone as a nitrogen nucleophile.



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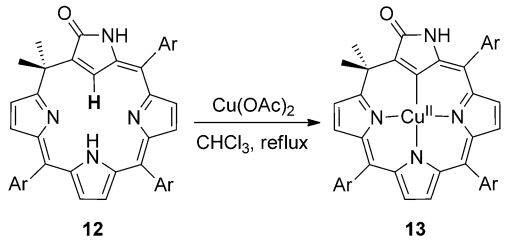
4.2. Formation of Organocopper(II) and Copper(III) Complexes through Cu^{II}-Mediated C–H Activation

Many of the Cu-catalyzed aerobic oxidation reactions described in this review can be carried out under anaerobic conditions by employing Cu^{II} as a stoichiometric reagent. This observation, together with the thermodynamic stability of the +2 oxidation state of copper in the presence of molecular oxygen, suggests that C–H activation steps in the catalytic reactions will be initiated by Cu^{II}. Consequently, the ensuing discussion will emphasize the formation of organocopper species originating from Cu^{II}. Organometallic C–H activation reactions mediated by Cu^{I} and Cu^{III}, relevant to other (non-aerobic) catalytic reactions, have been discussed elsewhere.[129–133]

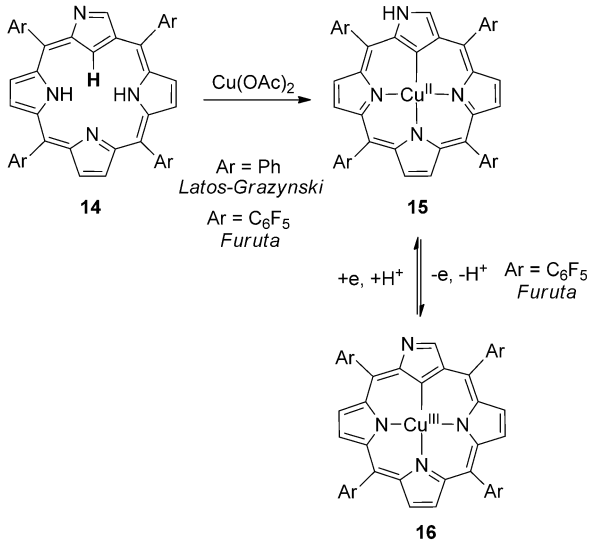
A number of organocopper(II) and copper(III) complexes have been synthesized and crystallographically characterized in recent years,[134–140] and these results provide a useful starting point for the consideration of such intermediates in Cu-catalyzed oxidation reactions. Several of these complexes have been prepared by Cu^{II}-mediated activation of a C–H bond within a macrocycle. Starting in 2000, the groups of Latos-Grażyński[136] and Otsuka and Furuta[137] reported a number of organocopper(II) and copper(III) complexes derived from N- and O-confused porphyrins. The first crystallographically characterized example of an organocopper(II) complex, reported by Furuta and co-workers in 2001,[137b] was obtained by direct metalation of the ligand by $Cu(OAc)_2$ (**13**, Scheme 58).[141] Similarly, N-confused porphyrins, **14**, with *meso*-aryl groups (aryl = Ph, C_6F_5) undergo metalation in the presence of $Cu(OAc)_2$ to afford the corresponding macrocyclic organocopper(II) complexes **15**.[136a,137d,e] The pentafluorophenyl derivative of **15** was later shown to undergo oxidation to organocopper(III) derivative **16**, coupled with the loss of the N–H proton, upon treatment with a chemical oxidant (DDQ) (Scheme 59).[137e] The reverse reaction was accomplished by the reaction of **16** with a reductant (*p*-toluenesulfonylhydrazide).



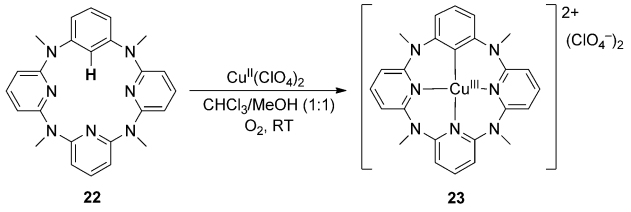
12 **13**

Scheme 58. First crystallographically characterized organocopper(II) and its preparation through C–H metalation.

In 2002, Ribas, Llobet, Stack and co-workers reported a different Cu^{II}-mediated C–H activation mechanism.[138a] Reaction of the macrocyclic arene **17** with 1 equiv $Cu^{II}(ClO_4)_2$ in acetonitrile at room temperature resulted in formation of 0.5 equiv of aryl–Cu^{III} species **18** and 0.5 equiv of a ligated Cu^{I} product **19** (Scheme 60). Evidence was provided for formation of an arene C–H agostic complex **20** prior to C–H activation, and insights into the CH···Cu^{II} interaction were recently provided through pulsed-EPR spectroscopic studies and DFT computational methods.[142] The C–H activation step was initially proposed to proceed through a base-assisted electrophilic activation of the arene C–H bond by Cu^{II} (**20** → **21**). A subsequent Cu^{II}-disproportionation reaction between the aryl–Cu^{II} species **21** and another equivalent of the ligated Cu^{II} species **20** would afford the 1:1 product ratio of **18** and **19** (Scheme 60). Recently, however, a thorough kinetic and mechanistic study provided evidence that formation of the aryl–Cu^{III} complex **18** proceeds through concerted proton-coupled electron transfer (PCET) directly from **20**. Additional support for this mechanism, which represents a novel



Scheme 59. C–H metalation of N-confused porphyrins to afford well-defined organocopper(II) species, and the reversible formation of an organocopper(III) derivative (Ar = C_6F_5).



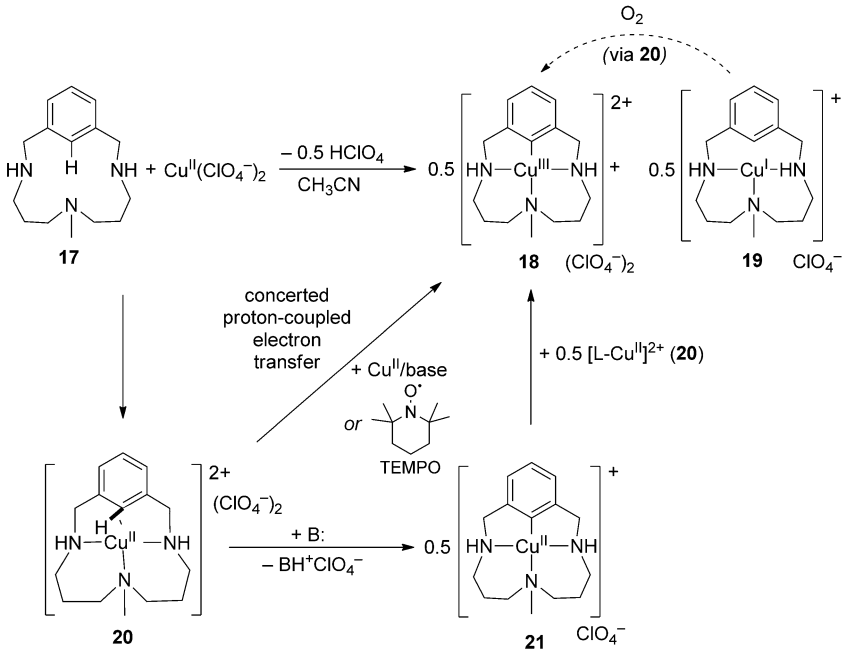
Scheme 61. Synthesis of a macrocyclic aryl–Cu^{III} complex under aerobic conditions.

could be obtained by performing the reaction under an aerobic atmosphere. Stahl and Ribas made similar observations in the aerobic synthesis of aryl–Cu^{III} complex **18**. The beneficial effect of O_2 in these reactions can be rationalized by the ability of O_2 to promote the oxidation of Cu^{I} that forms upon disproportionation of Cu^{II} (i.e., Scheme 60, **19**→**20**→**18**).

4.3. Reactivity of Organocopper(III) Complexes and Cu-Catalyzed C–H Oxidations

The fundamental insights into Cu^{II}-mediated C–H activation reactions described above have been complemented recently by systematic reactivity studies of organometallic copper(III) complexes.[130,140,143–145] This work includes the first direct evidence for the involvement of an aryl–Cu^{III} intermediate in a Cu-catalyzed C–H oxidation reaction.[146]

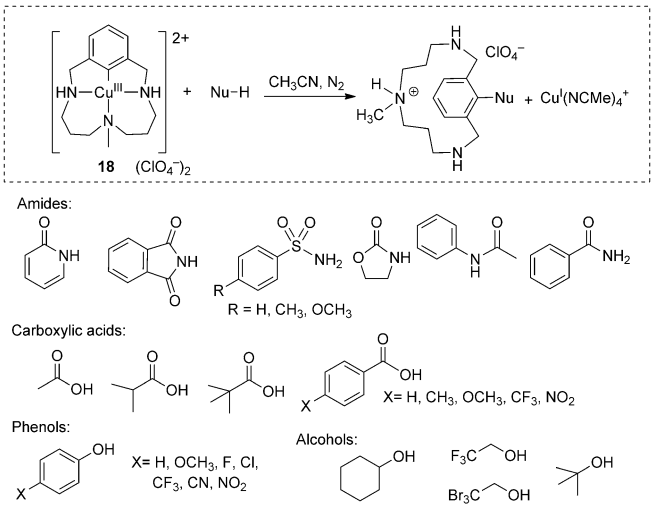
In 2008, Huffman and Stahl reported the reaction of a number of different nitrogen nucleophiles with the triazamacrocyclic aryl-Cu^{III} complex **18**, which closely resembles high-valent Cu intermediates proposed in oxidative[147] and non-oxidative[120] Cu-catalyzed coupling reactions. The reactions proceed readily from room temperature to 50 °C, even in the absence of base and despite the stabilizing effect of the macrocyclic ligand. These observations highlight the innate reactivity of organocopper(III) species relative to isoelectronic Pd^{II} complexes. The reaction exhibited bimolecular reaction kinetics, and no intermediate was observed in the reaction. The reactions were faster with more-acidic nucleophiles, implicating proton loss as a key step prior to C–N bond formation (Scheme 62). In a later study carried out jointly by Stahl and Ribas groups,[144] analogous reactions with oxygen nucleophiles were investigated. Carboxylic acids and phenols reacted considerably more rapidly than the nitrogen nucleophiles, and spectroscopic evidence was obtained for the formation of adducts between the nucleophile and aryl–Cu^{III} that precede C–O bond formation. Wang and co-workers demonstrated similar



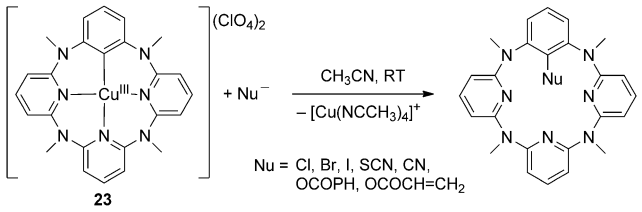
Scheme 60. Possible mechanistic pathways for disproportionation of Cu^{II} macrocycle **20** to give aryl–Cu^{III} **18** and Cu^{I}–macrocycle **19**.

route to reactive aryl–Cu^{III} species, was obtained from the reaction of **20** with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO).[143]

Wang and co-workers subsequently reported the reaction of Cu^{II} with another macrocyclic arene substrate.[140] The azacalix[1]arene[3]pyridine **22** reacts with $Cu^{II}(ClO_4)_2$ to afford the aryl–Cu^{III} complex **23** (Scheme 61). An important observation from this study was the improved yields of **23** that



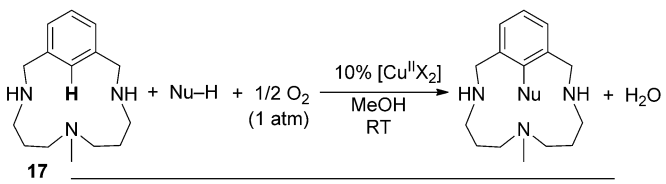
Scheme 62. Reductive elimination from macrocyclic aryl–Cu^{III} complex **18** to form new C–Nu bonds (Nu–H = amide, carboxylic acid, phenol, alcohol).

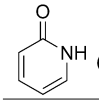


Scheme 63. Reductive elimination from macrocyclic aryl–Cu^{III} complex **23**.

reactions with the macrocyclic aryl–Cu^{III} complex **23**. A diverse scope of anionic nucleophiles reacted very efficiently to afford the C_{aryl}–Nu coupling products (Scheme 63).[140]

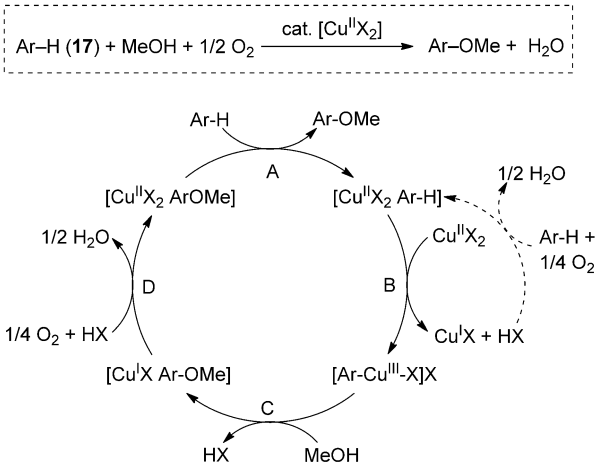
Stahl and Ribas recently demonstrated that the macrocyclic arene **17** can undergo catalytic C–H oxidation under 1 atm O_2 with 10 mol% $Cu(ClO_4)_2$ or $CuBr_2$ (Scheme 64).[146] Kinetic and spectroscopic analysis of the methoxylation reaction, employing simultaneous O_2-uptake methods and UV-visible spectroscopy, provided direct evidence for the formation and disappearance of an aryl–Cu^{III}–Br intermedi-



Nu–H	10% $Cu(ClO_4)_2 \cdot 6\,H_2O$	10% $CuBr_2$
MeOH (solvent)	72%	81%
 (5 equiv)	77%	84%

Scheme 64. Cu-catalyzed aerobic oxidative C–H functionalization of arene **17**.

ate in the reaction. These and related observations from the catalytic reactions, together with independent studies of the formation and reaction of the aryl–Cu^{III} intermediate, provide the clearest mechanistic insights to date into a Cu-catalyzed aerobic C–H oxidation reaction. The proposed mechanism (Scheme 65) is initiated by complexation of the macrocyclic



Scheme 65. Proposed catalytic cycle for Cu-catalyzed aerobic oxidative methoxylation of arene **17**.

arene to Cu^{II} (step A), followed by C–H activation through Cu^{II} disproportionation to give the aryl–Cu^{III} intermediate (step B) (cf. Scheme 60). Subsequent reaction of the aryl–Cu^{III} with methanol results in formation of the methoxylated arene and Cu^I (step C) (cf. Scheme 62). Rapid reoxidation of Cu^I to Cu^{II} by O_2 (step D) completes the catalytic cycle; the same aerobic reoxidation of Cu^I occurs in the stoichiometric synthesis of the aryl–Cu^{III} complex (dashed arrows).

The catalytic cycle in Scheme 65 exhibits distinct similarities to the Cu^I/Cu^{III} catalytic cycle commonly proposed for Ullmann-type coupling reactions. (cf. Scheme 57). Aryl–Cu^{III} species can form through oxidative addition of aryl halides to Cu^I in Ullmann-type reactions, whereas the analogous aryl–Cu^{III} intermediate arises here from a Cu^{II}-disproportionation C–H activation process (cf. Scheme 60). Subsequent reductive elimination from the aryl-Cu^{III} intermediate accounts for product formation in both the oxidative and non-oxidative reactions.

This organometallic mechanism for C–H oxidation of an arene represents an intriguing alternative to SET mechanisms commonly proposed for Cu-catalyzed oxidative coupling reactions. Steps B and C of the mechanism in Scheme 65 involve loss of a proton from the Ar–H and MeO–H coupling partners. This feature may explain the observation that many Cu-catalyzed oxidative coupling reactions, such as those in Sections 3.3 and 3.4, utilize substrates with acidic C–H bonds (alkynes, fluoroarenes, electron-deficient heterocycles). Despite the extensive history of Glaser–Hay reactions of alkynes, alkynyl–Cu^{III} intermediates have never been proposed, to our knowledge; however, the results summarized here suggest that such a pathway might be viable.

5. Summary and Outlook

This review highlights the broad array of Cu-catalyzed aerobic C–H oxidation reactions that have been developed in recent years, and it also clarifies key challenges that lie ahead. The emphasis of the content above on synthetic advances largely reflects the relatively poor mechanistic understanding of many of these reactions. For example, many SET-based oxidative coupling reactions are not yet capable of using O_2 as the oxidant. The factors that control the success or failure of different oxidants in these reactions are not well understood. In addition, the vast majority of the reactions discussed here represent "oxidase"-type reactions, but oxygen-atom-transfer ("oxygenase") reactions were also noted (see Schemes 6, 37, and 42). Recent studies of fundamental Cu/O_2 reactivity have largely focused on work relevant to enzymatic and bioinorganic chemistry. Elucidating principles of Cu/O_2 reactivity relevant to important synthetic transformations could provide an important foundation for expanding the scope of useful aerobic oxidation reactions.

This review was generally divided into Cu-catalyzed aerobic oxidation reactions initiated by SET from the substrate to Cu^{II} and those that resemble organometallic C–H oxidation reactions. The line dividing these two reaction classes is not especially clear, however, and the importance of organocopper chemistry in aerobic oxidation reactions remains an open question. The reactions that provide direct evidence for an organometallic mechanism generally feature macrocyclic substrates that impose rather significant constraints on the reaction pathway. As the field expands, it will be important to begin bridging the gap between experimental model studies of the type described in Section 4, and the synthetically useful catalytic oxidation reactions. Despite the uncertainties that exist, the organometallic aerobic oxidation pathways supported by recent studies are quite exciting because they represent a significant departure from classical Cu-catalyzed oxidative coupling mechanisms, and they offer new modes of reactivity that could enable new types of synthetic transformations. If the rapid pace of advances in this field over the past five years is a representative guide, it seems reasonable to expect that these challenges will be addressed and many new opportunities in Cu-catalyzed aerobic C–H oxidation will be realized.

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