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Aerobic Oxidation

Practical Aerobic Oxidations of Alcohols and Amines with Homogeneous Copper/TEMPO and Related Catalyst Systems[**]

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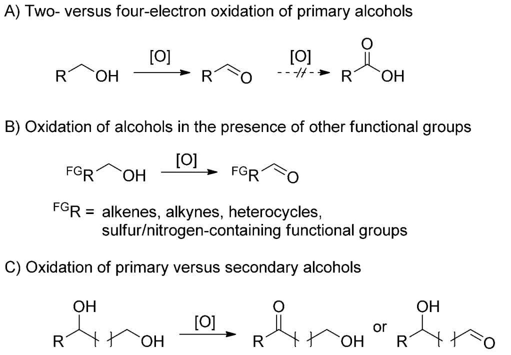
aerobic oxidation · alcohols · amines · copper · nitroxyl radicals

*Oxidations of alcohols and amines are common reactions in the synthesis of organic molecules in the laboratory and industry. Aerobic oxidation methods have long been sought for these transformations, but few practical methods exist that offer advantages over traditional oxidation methods. Recently developed homogeneous Cu/TEMPO (TEMPO = 2,2,6,6-tetramethylpiperidinyl-*N*-oxyl) and related catalyst systems appear to fill this void. The reactions exhibit high levels of chemoselectivity and broad functional-group tolerance, and they often operate efficiently at room temperature with ambient air as the oxidant. These advances, together with their historical context and recent applications, are highlighted in this Minireview.*

1. Introduction

Aldehydes and ketones are ubiquitous intermediates in the synthesis of pharmaceuticals, agrochemicals, and fine chemicals, and they are often prepared through alcohol oxidation. The target molecules for these applications commonly bear diverse functional groups, including amines, sulfur-containing groups, alkenes, and heterocycles. Therefore, effective alcohol oxidation reactions must exhibit one or more types of "chemoselectivity", such as A) oxidation of a primary alcohol to an aldehyde without overoxidation to the carboxylic acid, B) selective oxidation of an alcohol in the presence of other oxidizable and/or potentially inhibitory functional groups, and C) oxidation of one alcohol in preference to another within a diol or polyol (Scheme 1). Numerous stoichiometric reagents and catalytic oxidation methods have been developed to meet these requirements,[1] but there continues to be widespread interest in methods capable of using O_2 as an oxidant.[2] Aerobic oxidation methods, however, typically do not match the synthetic scope and utility of conventional alcohol oxidations, and they are rarely used in laboratory- or process-scale syntheses of complex molecules.

Herein, we survey Cu/TEMPO (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyl-*N*-oxyl) and related Cu/nitroxyl catalyst systems (Scheme 2), which have emerged as some of the most efficient catalysts available for aerobic alcohol oxidation.[3] They are often capable of using ambient air as the oxidant, they are compatible with both activated (allylic, benzylic, propargylic) and unactivated (aliphatic) alcohols, and their chemoselectivity and functional-group compatibility rival traditional alcohol oxidation methods. Recent mechanistic studies have provided the basis for significant expansion of the efficiency and scope of these reactions with sterically less hindered, bicyclic nitroxyl co-catalysts, such as ABNO (ABNO = 9-azabicyclo[3.3.1]nonane-*N*-oxyl; see Scheme 2). These methods offer numerous advantages over earlier Cu-catalyzed


A) Two- versus four-electron oxidation of primary alcohols

B) Oxidation of alcohols in the presence of other functional groups

C) Oxidation of primary versus secondary alcohols

Scheme 1. Chemoselectivity challenges encountered in alcohol oxidation reactions.

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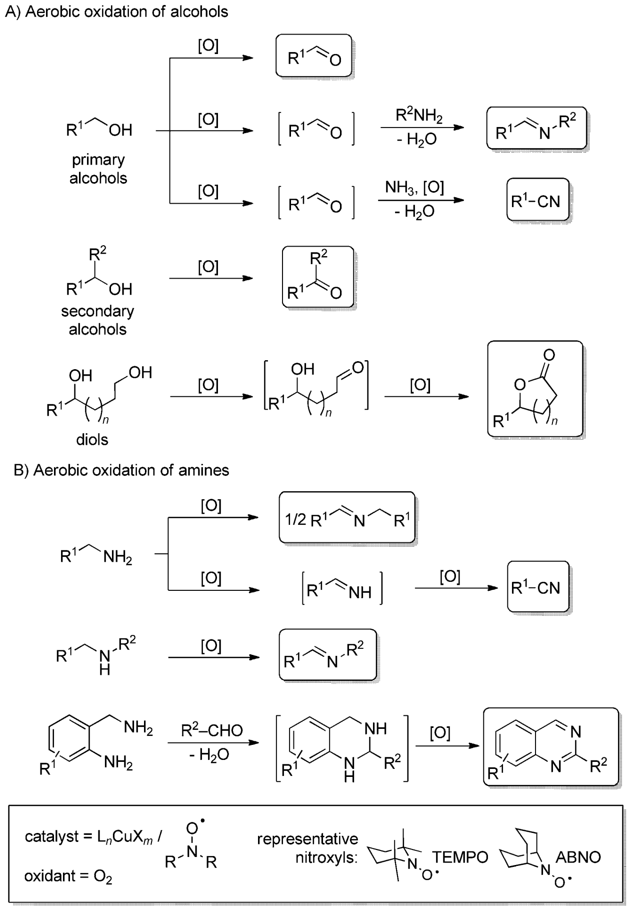
[**] TEMPO = 2,2,6,6-tetramethylpiperidinyl-*N*-oxyl.



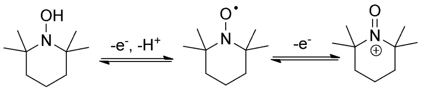
Scheme 2. Aerobic alcohol and amine oxidation reactions mediated by Cu/nitroxyl catalyst systems.

aerobic alcohol oxidation methods that lack nitroxyl co-catalysts.[4] Similar Cu/nitroxyl catalyst systems have also been identified for aerobic oxidation of amines (Scheme 2 B), with applications to the preparation of imines, nitriles, and unsaturated heterocycles. In addition, other variants of these reactions have been developed, including oxidations of diols to lactones and the oxidative coupling of alcohols and amines. Collectively, these methods represent some of the most versatile and accessible aerobic oxidation methods currently available to synthetic chemists.

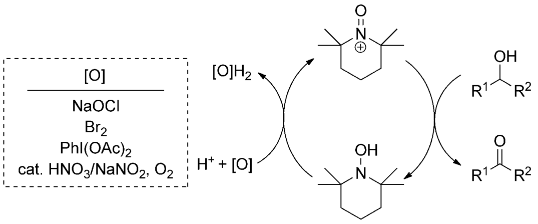
2. Copper/TEMPO-Catalyzed Aerobic Oxidation of Primary Alcohols

2.1. Nitroxyl Catalysts in Alcohol Oxidation

TEMPO is a well known, commercially available, stable nitroxyl radical.[5] One-electron oxidation of TEMPO affords an oxoammonium species (Scheme 3), which may be isolated and used as a stoichiometric oxidant.[6] Oxoammonium-mediated alcohol oxidation results in two-electron reduction of the oxoammonium species to afford a hydroxylamine (or hydroxylammonium species, depending on the pH value of the solution). Numerous methods have been developed to use catalytic quantities of TEMPO in combination with an inexpensive stoichiometric oxidant, such as sodium hypochlorite (NaOCl), bromine, or $PhI(OAc)_2$ (Scheme 4). One common protocol (the "Anelli oxidation") features catalytic TEMPO (or a TEMPO derivative) and bromide in a buffered organic/aqueous biphasic mixture, with NaOCl as the stoichiometric oxidant (Scheme 5).[7] Recent work by Iwabuchi[8] and others[9] has shown that bicyclic nitroxyl catalysts, such as ABNO, ketoABNO, AZADO, 1-methyl-AZADO, and 5-fluoro-AZADO (Scheme 6), can significantly enhance the efficiency and scope of these reactions. Alcohol oxidations



Scheme 3. Different TEMPO oxidation/protonation states.



Scheme 4. Hydroxylamine/oxoammonium mechanism for aerobic alcohol oxidation with diverse terminal oxidants.

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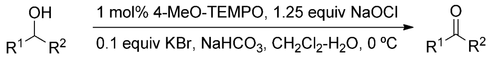
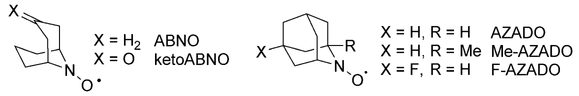
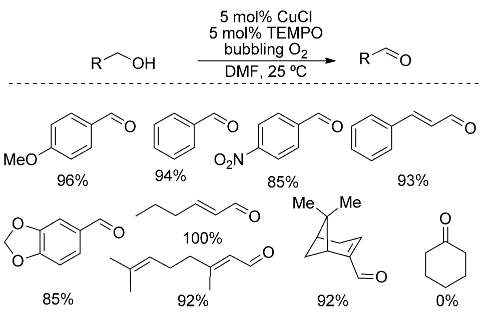


Scheme 5. Commonly used TEMPO/bleach "Anelli oxidation" conditions for the conversion of alcohols to carbonyl compounds.



Scheme 6. Bicyclic nitroxyl derivatives that significantly expand the efficiency and scope of nitroxyl-catalyzed alcohol oxidation reactions. AZADO = 2-azaadamantane-*N*-oxyl.



Scheme 7. Aerobic oxidation of activated alcohols by CuCl/TEMPO in DMF reported by Semmelhack.[21]

using TEMPO and related catalysts are widely used in laboratory and industrial syntheses, and they are the focus of a recent comprehensive *Organic Reactions* article by Bobbitt, Brückner, and Merbouh.[10]

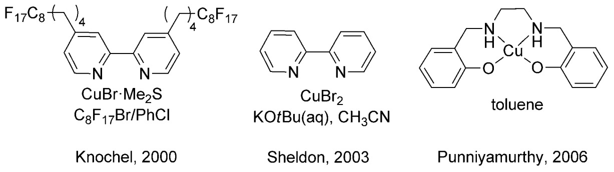
Considerable effort has been made to identify co-catalysts for the regeneration of the oxoammonium species with O_2 as the terminal oxidant. An important development in this area is the identification of $NaNO_2$, HNO_3, and other NO_x sources that participate in a dioxygen-coupled NO/NO_2 redox cycle and enable transition-metal-free aerobic oxidation of alcohols. Such methods were first developed for TEMPO-based alcohol oxidation,[11] however, the bicyclic nitroxyl catalysts (see Scheme 6) again show significant advantages in these reactions.[12]

Aerobic alcohol oxidation with nitroxyl catalysts has also been achieved by using transition-metal salts (e.g. Mn,[13] Fe,[14] Co,[15] and Ce),[16] polyoxometallates,[17] or metalloenzymes (laccase)[18] as co-catalysts.[19] Among these, the reactions with Cu co-catalysts have been the most extensively studied and exhibit particularly broad scope and synthetic utility. Mechanistic studies have shown that the reaction does not proceed through the classical hydroxylamine/oxoammonium cycle shown in Scheme 4, but involves a cooperative pathway with one-electron redox chemistry at Cu and TEMPO. These synthetic and mechanistic developments are the focus of the discussion below.

2.2. Copper/Nitroxyl Catalyst Systems for the Aerobic Oxidation of Primary Alcohols

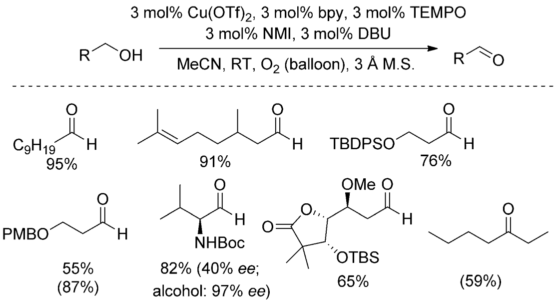
The use of Cu/nitroxyl catalysts for aerobic oxidation of alcohols was first reported in 1966, when Brackman and Gaasbeek showed that di-*tert*-butylnitroxide significantly promotes the oxidation of methanol to formaldehyde by phenanthroline/Cu^{II} complexes in basic methanol solutions.[20] This work was overlooked by synthetic chemists until it was highlighted in 2004 in a review on nitroxyl radicals by Sheldon and Arends.[2b] The first exploration of the synthetic scope of Cu/nitroxyl-catalyzed aerobic alcohol oxidation was reported by Semmelhack in 1984.[21] Catalytic CuCl and TEMPO in DMF mediates the oxidation of numerous activated primary alcohols (i.e., allylic and benzylic; Scheme 7). Aliphatic alcohols are much less reactive and stoichiometric quantities of copper and TEMPO were required to oxidize these substrates under the reported conditions. The enhanced reactivity of activated alcohols is evident in many of the other Cu/TEMPO catalyst systems that have been reported in recent years, many of which probe the role of different copper sources, ligands, and/or reaction conditions.[22] Systems that use ionic liquids,[23] fluorous biphasic solvents,[24] and supported reaction components (e.g., polymer-supported nitroxyls,[25] ancillary ligands,[26] and metal–organic frameworks[27]) have also been reported.

In 2000, Knochel and co-workers described fluorous biphasic reaction conditions, in which $CuBr{\cdot}Me_2S$ and a perfluoroalkyl-substituted bipyridine ligand could promote the aerobic oxidation of alcohols (Scheme 8).[24a] This catalyst system was the first to show broad utility with aliphatic alcohols. Some reactivity toward aliphatic alcohols was also observed with a Cu/salen catalyst system reported by Punniyamurthy, albeit under relatively forcing conditions (100 °C, 7 mol% TEMPO, 21–25 h).[28] In 2003, Sheldon and co-workers described a catalyst system, consisting of $CuBr_2$/bpy/TEMPO/KO*t*Bu (5 mol% each; bpy = 2,2′-bipyridine) in acetonitrile/H_2O as the solvent, capable of promoting the oxidation of benzylic and allylic alcohols in ≤ 5 h at room temperature with ambient air as the source of O_2.[29] Selective oxidation of 1-octanol to 1-octanal was successful, but required a higher temperature and a longer reaction time (40 °C, 24 h).

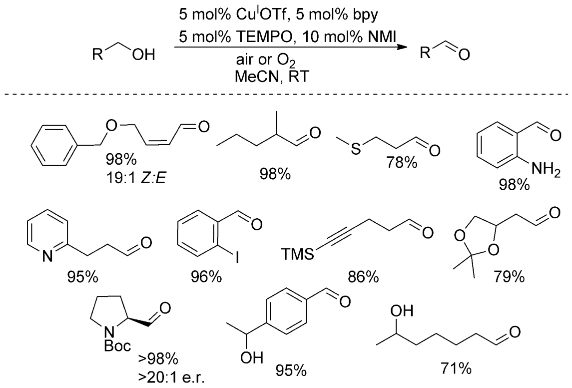


Scheme 8. Ligand, Cu source, and solvent used in early Cu/TEMPO catalyst systems capable of oxidizing aliphatic alcohols.[24a,b,29,28]

The groups of Koskinen (Scheme 9)[30] and Stahl (Scheme 10)[31] subsequently developed two related catalyst systems that exhibit broad synthetic utility for the oxidation of primary alcohols to aldehydes, including aliphatic substrates. The catalyst system developed by Kumpulainen and Koskinen



Scheme 9. Aerobic oxidation of aliphatic alcohols with bpy/Cu^{II}/NMI/DBU/TEMPO reported by Koskinen (GC yields in parentheses). NMI = *N*-methylimidazole, DBU = 1,8-diazabicycloundec-7-ene.[30]



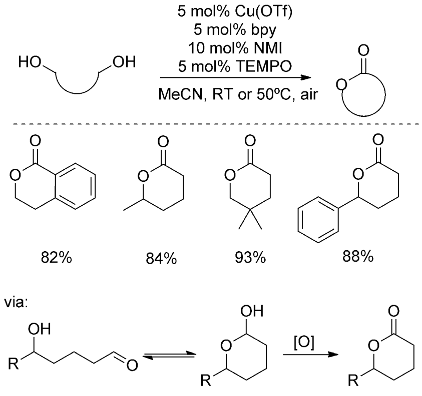
Scheme 10. Aerobic oxidation of aliphatic alcohols with bpy/Cu^{I}/NMI/TEMPO reported by Stahl.[31]

features Cu(OTf)$_2$/bpy/TEMPO, two heterocyclic bases, *N*-methylimidazole (NMI) and 1,8-diazabicycloundec-7-ene (DBU), and 3 Å molecular sieves (M.S.). The oxidation of a number of aliphatic alcohols was achieved at room temperature within 1–5 h under an atmosphere of pure O_2 (Scheme 9). Oxidation of Boc-protected valinol resulted in substantial epimerization of the stereocenter adjacent to the aldehyde probably arising from the presence of DBU, which is a relatively strong organic base (pK_a DBU-H$^+$ = 24 in MeCN). Nevertheless, the reaction tolerates alkenes, ethers, esters, and protected amines and alcohols. Variations of this catalyst system, differing in the identity of the organic base (among NMI, DBU, and 4-(*N*,*N*-dimethylamino)pyridine (DMAP)), showed excellent activity in the aerobic oxidation of allylic and benzylic alcohols.

Hoover and Stahl noticed significant improvement in catalytic activity upon using a copper(I) source, rather than copper(II). Cu^I salts with a non-coordinating anion (e.g., Cu^{I}OTf) were particularly effective, and the CuOTf/bpy/TEMPO/NMI catalyst system was effective in the oxidation of benzylic, allylic, propargylic, and aliphatic alcohols under ambient air.[31,32] Most of the reactions were performed at room temperature, although selected aliphatic alcohols required heating to 50 °C to achieve complete conversion. The operational simplicity of these conditions is complemented by a very broad substrate scope (Scheme 10). Numerous common functional groups, including aryl halides, anilines, nitrogen and sulfur heterocyles, and sulfides, are tolerated. NMI is a considerably weaker base than DBU (pK_a NMI-H$^+$ = 14.3 in MeCN), and the use of NMI as the sole organic base probably provides the basis for selective oxidation of (*Z*)-allylic alcohols without *cis–trans* isomerization of the base-sensitive enal and retention of enantioselectivity in the oxidation of *N*-Boc-protected prolinol. Like most other Cu/TEMPO catalyst systems, secondary alcohols showed poor reactivity; however, this feature was exploited to achieve selective oxidation of several diols that contain both primary and secondary alcohols, resulting in near-exclusive formation of the aldehyde products.

2.3. Copper/Nitroxyl-Catalyzed Aerobic Oxidation of Primary Alcohols in Tandem or Sequential One-Pot Reactions

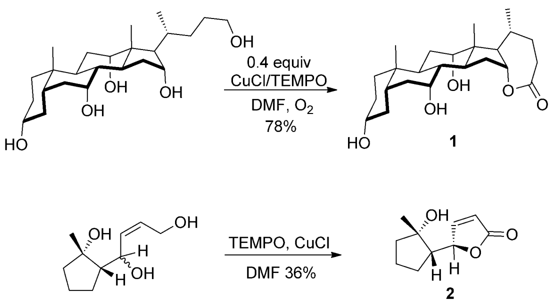
The mild reaction conditions associated with Cu/TEMPO-catalyzed alcohol oxidation make these reactions well suited for tandem or sequential reactions with an aldehyde intermediate. One implementation of this concept is the lactonization of diols. As an extension of the selective oxidation of diols, Hoover and Stahl showed that a number of 1,5-diols undergo lactonization. The reaction selectivity is controlled by the reactivity of the respective alcohols, including primary versus secondary, benzylic versus aliphatic, and primary alcohols in different steric environments (Scheme 11).[31]



Scheme 11. Cu/TEMPO-catalyzed aerobic lactonization of diols.[31]

The strong steric sensitivity of the reaction is highlighted by the last example in Scheme 11, in which the lactone arises from selective oxidation of a primary aliphatic alcohol, rather than an electronically activated secondary benzylic alcohol.

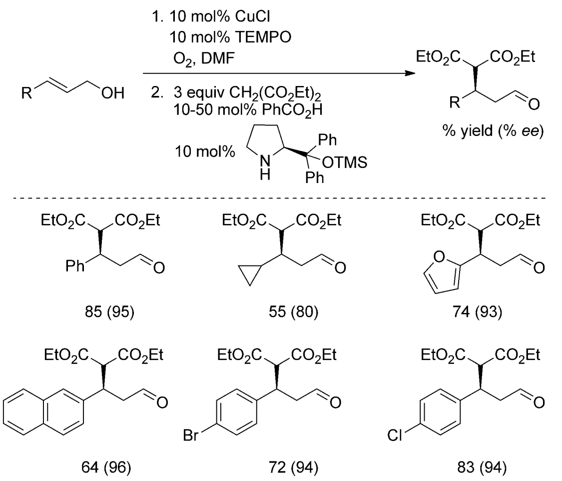
Cu/TEMPO-mediated lactonization of polyols has been implemented in the synthesis of more complex molecules (Scheme 12). Nonappa and Maitra prepared the steroidal lactone **1** by selective oxidation of the primary alcohol in the presence of several unprotected secondary alcohols.[33] This reaction employed Semmelhack-type conditions (0.4 equiv CuCl/TEMPO),[21] but it seems well suited for implementation with one of the more recent aerobic catalyst systems that show good reactivity with aliphatic alcohols, as in Scheme 11.



Scheme 12. Synthetic applications of Cu/TEMPO-catalyzed aerobic lactonization reactions.[33,34]

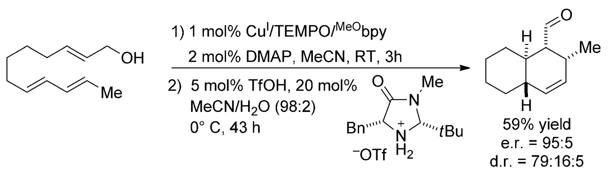
In a related application, the terpenoid precursor **2** was prepared by Cu/TEMPO-mediated oxidation of the allylic primary alcohol; in situ cyclization with the proximal secondary alcohol and further oxidation afforded the desired lactone.[34]

Jang et al. showed that Cu/TEMPO-catalyzed oxidation of allylic alcohols could be performed in sequence with enantioselective organocatalytic Michael additions, without isolation of the intermediate aldehyde (Scheme 13).[35] Christmann and co-workers prepared (E)-α,β-unsaturated aldehydes selectively from a mixture of (Z)- and (E)-allylic alcohols with a catalyst system consisting of CuOTf/^{MeO}bpy/TEMPO/DMAP (^{MeO}bpy = 4,4′-dimethoxy-2,2′-bipyridine). DMAP was found to be effective as an alternative to NMI as a co-catalyst and was sufficiently basic to promote *cis–trans* isomerization of the enal product. This reactions was also implemented in a one-pot alcohol oxidation/enantioselective organocatalytic Diels–Alder sequence (Scheme 14).[36]



Scheme 13. Alcohol oxidation/conjugate addition, developed by Jang.[41]

Masson and Jhu showed that alcohols, rather than aldehydes, could be used in Passerini three-component coupling reactions by performing the in situ alcohol oxidation with a Cu/TEMPO catalyst system.[37] The groups of Porco[38] and Mehta[39] have used the Semmelhack catalyst system (see Scheme 7) to achieve selective oxidation of primary allylic alcohols en route to epoxyquinols and related molecules. One example, shown in Scheme 15, highlights the use of alcohol oxidation in tandem with [4+2] and [4+4] dimerization reactions to access epoxyquinoid dimers.[38b] Selective oxidation of the primary allylic alcohol was accomplished without a need to protect the secondary allylic alcohol. Attempts to perform alcohol oxidation with MnO_2 or Dess–Martin periodinane led to a mixture of alcohol oxidation products. Cu/TEMPO-based alcohol oxidation reactions have also been used in numerous other syntheses of natural products and complex molecules.[40]

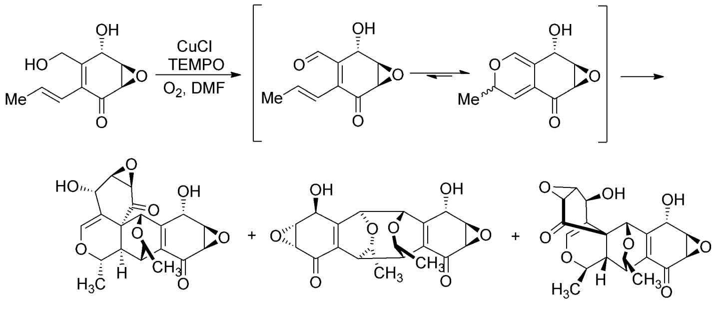


Scheme 14. One-pot allylic alcohol oxidation/Diels–Alder cyclization demonstrated by Christmann.[36]

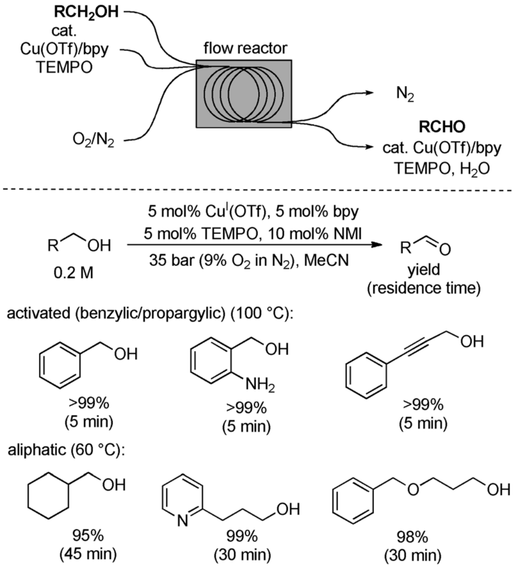
Tandem reactions initiated by Cu/nitroxyl-catalyzed oxidations of amines, as well as oxidative coupling reactions of alcohols and amines, will be discussed further below (see Sections 5.2 and 6). These applications, together with the reactions described in this section, highlight the significant potential utility of Cu/nitroxyl-based methods in organic chemical synthesis.

2.4. Toward Scalable Copper/TEMPO-Catalyzed Aerobic Alcohol Oxidation Reactions.

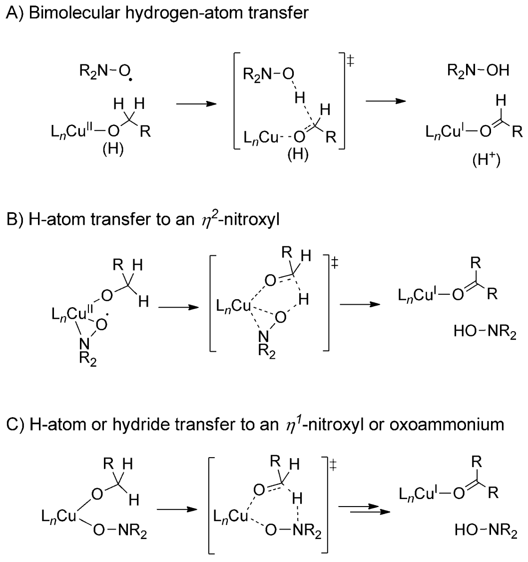
The optimized conditions for Cu/TEMPO-catalyzed alcohol oxidation with ambient air at room temperature are very convenient for lab-scale reactions. The efficiency and synthetic scope of these reactions potentially also make them attractive for large-scale applications; however, the flash point of acetonitrile is well below room temperature (2 °C) and large volumes of acetonitrile under air or O_2 represent a significant safety hazard. One way this issue can be addressed is to operate the reactions outside the O_2/CH_3CN flammability limits.[41] Root and Stahl recently reported a scalable application of this concept using a continuous flow reactor developed by Johnson and co-workers at Eli Lilly.[42,43] The reactions were performed by passing solutions of the catalyst and alcohol with dilute oxygen gas (9% O_2 in N_2; 35 bar total pressure) through a stainless steel tube reactor maintained at 100 °C (Scheme 16). Near-quantitative yields of aldehydes from activated alcohols could be obtained with reactor residence times as low as 5 min, and benzyl alcohol oxidation was demonstrated on a 100 g scale. Aliphatic alcohols reacted more slowly (as expected, see Ref. [31]) and the reaction temperature had to be lowered to 60 °C to minimize overoxidation of the aliphatic aldehydes to carboxylic acids under the reaction conditions (carboxylic acids inhibit catalytic turnover, resulting in incomplete conversion of the starting alcohol). Near-quantitative yields of the aliphatic aldehydes could be obtained with 30–45 min resi-



Scheme 15. Alcohol oxidation/6π-electrocyclization/cycloadditon sequence employed in the synthesis of epoxyquinoid molecules.[38b]



Scheme 16. Continuous flow method for Cu/TEMPO-catalyzed aerobic alcohol oxidation.[42]



Scheme 17. Mechanistic pathways proposed for Cu^{II}/TEMPO-mediated alcohol oxidation.

dence times. These results are significantly better than analogous reactions with a homogeneous Pd catalyst reported earlier using the same reactor.[43] A $Pd(OAc)_2$/pyridine catalyst used in the latter application required residence times from 2.5–4.5 h, was not compatible with primary aliphatic alcohols (over oxidation to the acid led to catalyst poisoning), and exhibited very limited functional-group tolerance.

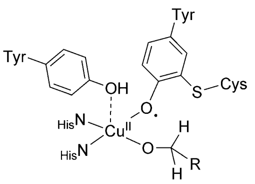
3. Mechanism of Copper/TEMPO-Catalyzed Aerobic Oxidation of Primary Alcohols

The mechanism of Cu/TEMPO-catalyzed alcohol oxidation reactions has both fundamental and practical implications. The involvement of three open-shell reagents (Cu^{II}, TEMPO, and O_2) in a two-electron oxidation of a closed-shell organic molecule raises fundamental questions about the electronic coupling between individual reaction partners and the nature of redox steps involving these species. The origin of electronic effects that favor the oxidation of activated alcohols over aliphatic alcohols, and steric effects that favor the oxidation of primary over secondary alcohols, have important practical implications for the development of new catalysts. Insights into some of these issues have been gained, but a number of questions remain unanswered and results from different studies remain to be reconciled.

In their 1966 study of methanol oxidation by (phen)Cu^{II}/di-*tert*-butylnitroxyl, Brackman and Gaasbeek proposed that the nitroxyl species abstracts a hydrogen atom from a Cu^{II}-coordinated methanol molecule (Scheme 17 A).[20a] Loss of the H atom was proposed to occur in concert with the reduction of Cu^{II} to Cu^{I} and formation of the formaldehyde. Inhibition of the reaction by $NaOCH_3$ was interpreted as support for the reaction of a methanol ligand, rather than methoxide, and evidence against a hydride-transfer pathway.

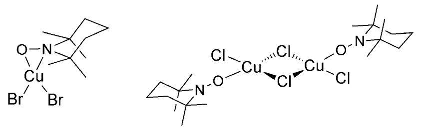
In 1984, Semmelhack and co-workers proposed a two-electron oxoammonium/hydroxylamine redox cycle, mediated by $Cu^{I/II}$ and O_2. This mechanism resembles that of TEMPO-catalyzed alcohol oxidation with other terminal oxidants (see Scheme 4), but it was not studied in detail, and the Brackman/Gaasbeek results were not considered. Contel, Fish, and co-workers studied a fluorous biphasic Cu/TEMPO system,[24c,d] and a loss of EPR signals during the reaction was interpreted in favor of an oxoammonium pathway, although β-hydride elimination from a Cu–alkoxide was also considered. Semmelhack et al. supported their proposal by noting that the $E^{1/2}$ of the $CuCl_2$/CuCl redox couple is 370 mV higher than the TEMPO/$TEMPO^+$ potential; however, the Cu^{II}/Cu^I potential is strongly solvent dependent. Whereas their catalytic reactions were performed in DMF, the electrochemical potentials were measured in acetonitrile. Stahl and co-workers recently showed that the Cu^{II}/Cu^I potential in DMF is lower than the TEMPO/$TEMPO^+$ potential, providing evidence against an oxoammonium-based mechanism.[44]

Sheldon et al. revisited Semmelhack's Cu/TEMPO-catalyzed alcohol oxidation reaction in 2003.[45] They measured kinetic isotope effects (KIEs) through intramolecular competition with [D_1]-*p*-methoxybenzyl alcohol (i.e., ArCHD-OH), and determined a Hammett correlation with *para*- and *meta*-substituted benzyl alcohols. The results were compared to analogous data for alcohol oxidation mediated by $TEMPO^+Cl^-$, a Ru/TEMPO-based catalyst system believed to operate through an organometallic β-hydride elimination pathway,[19b] galactose oxidase (GOase),[46] and a small-molecule GOase mimic.[47] Differences between the Cu/TEMPO and the $TEMPO^+Cl^-$ and Ru/TEMPO systems provided evidence against oxoammonium and organometallic alcohol oxidation pathways, while quantitative similarities between the KIEs and Hammett ρ values for Cu/TEMPO, GOase, and the GOase mimic led the authors to conclude that these systems mediate alcohol oxidation by a similar mechanism. GOase features a Cu^{II} center with coordinated tyrosyl radical ligand (Scheme 18), and the proposed alcohol oxidation mechanism involves H-atom transfer from an alkoxide ligand to the oxyl radical.[46] Sheldon and co-workers suggested that Cu/TEMPO acts as a GOase mimic, in which TEMPO coordinates to Cu^{II} as an η^2 ligand prior to abstracting a hydrogen atom from a bound alkoxide (Scheme 17B), and this mechanism has also been proposed by Sheldon et al. for (bpy)Cu/TEMPO catalyst systems.[29]



Scheme 18. Structural representation of the active site of galactose oxidase with the galactose substrate present as an alkoxide ligand.

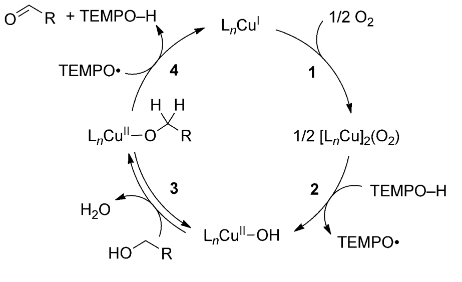
Cu/TEMPO complexes have been crystallographically characterized, with examples including both η^1- and η^2-coordinated TEMPO (Scheme 19).[48] These complexes are EPR silent, which suggests a strong coupling between the unpaired electrons of Cu^{II} and the nitroxyl ligand. Structures of this type have been investigated by DFT computational methods to probe the nature of the hydrogen transfer to a coordinated nitroxyl group.[49] Both radical (H atom) and hydride-transfer pathways have been proposed, and mechanisms involving H transfer to the nitrogen and oxygen atom of a coordinated nitroxyl have been considered. In the most compelling study to date, Baerends and co-workers identified a low-energy pathway for intramolecular hydride transfer from a Cu–alkoxide to an η^1-O-coordinated nitroxyl ligand (Scheme 17C).[49d] These studies employed a model piperidyl-*N*-oxyl that lacks the steric effects of TEMPO, and the results remain to be reconciled with experimental data, such as the first-order dependence of the reaction on the concentration of TEMPO[50] (see below).



Scheme 19. Examples of crystallographically characterized Cu–TEMPO complexes.

Koskinen[30] and Stahl[50] have carried out kinetic studies of their respective (bpy)Cu/TEMPO-catalyzed alcohol oxidation reactions, and Stahl also reported an independent comparative kinetic and mechanistic study of the catalytic reactions reported by Semmelhack, Sheldon, Koskinen, and Stahl (see Schemes 7–10).[44] Several observations demonstrate clearly that the (bpy)Cu/TEMPO-catalyzed alcohol oxidation does not involve an oxoammonium pathway: 1) different KIEs are observed for (bpy)Cu/TEMPO- and $TEMPO^+$-mediated alcohol oxidation (similar to Sheldon's observations with the Semmelhack system), 2) the Cu^{II}/Cu^I $E^{1/2}$ is too low under the reaction conditions to oxidize TEMPOH or TEMPO to the oxoammonium species, and 3) $TEMPO^+$-mediated alcohol oxidation was shown to be kinetically incompetent to account for the fast reaction rates observed with the (bpy)Cu/TEMPO catalysts.[44,50]

The mechanistic study of Stahl and co-workers provides the basis for the simplified catalytic mechanism in Scheme 20 (see the original report for a more elaborate discussion).[50] Aerobic oxidation of Cu^I and TEMPOH affords a Cu^{II}-OH species and TEMPO (steps 1 and 2). This sequence explains why a strong base, such as KO*t*Bu or DBU, is not required when a Cu^I salt is used as the catalyst source (see Scheme 10): the base (L_nCu^{II}-OH) is generated upon reduction of O_2. As noted above, this feature has beneficial implications in the oxidation of base-sensitive substrates. The oxidation of the alcohol proceeds through the formation of a pre-equilibrium of a Cu^{II}–alkoxide species (step 3) followed by hydrogen-



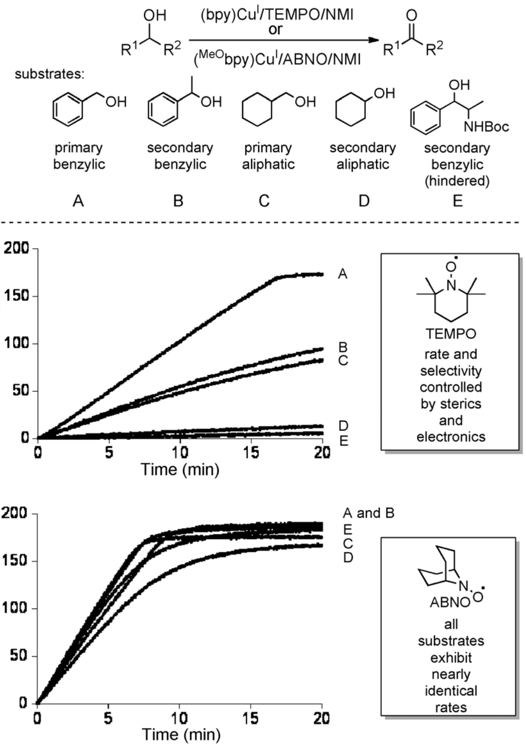
Scheme 20. Mechanism of (bpy)Cu/TEMPO-catalyzed alcohol oxidation deduced by Stahl and co-workers.[50,52]

atom transfer to TEMPO (step 4). Details of the H-atom transfer step could not be discerned from these studies, but a first-order dependence on [TEMPO] was observed in reactions of aliphatic alcohols and no evidence was obtained for an interaction between TEMPO and Cu^{II} under the reaction conditions.[50,51] These observations are consistent with a bimolecular H-atom transfer step, similar to that proposed by Brackman and Gaasbeek (Scheme 17 A); however, mechanisms involving the rate-limiting coordination of TEMPO to Cu^{II} followed by rapid H-atom transfer cannot be excluded on the basis of available evidence.

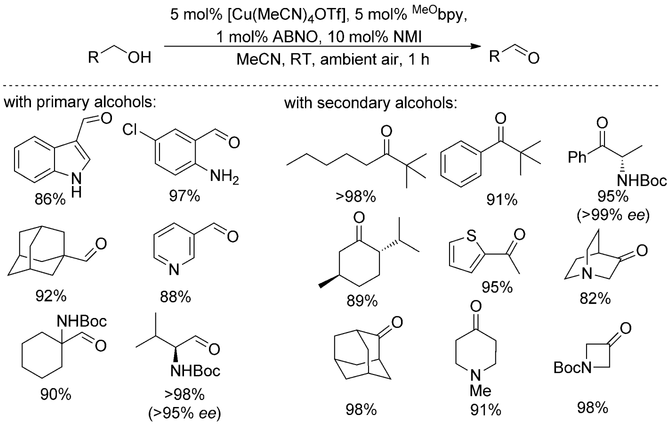
The latter studies provide important insights into the origin of the reactivity difference between activated and aliphatic alcohols.[50] Benzylic alcohols exhibit faster rates and no kinetic dependence on [alcohol] or [TEMPO]. A rate dependence on [Cu] and [O_2] suggests that the aerobic oxidation of the Cu catalyst (step , Scheme 20) is the turnover-limiting step of the reaction. In contrast, aliphatic alcohols react more slowly and the rate exhibits a saturation dependence on [alcohol] and a first-order dependence on [TEMPO]. These observations had a direct impact on the development of a new Cu/nitroxyl catalyst systems, described in the next section.[52]

4. Improved Aerobic Alcohol Oxidation with Bicyclic Nitroxyl Derivatives

Stahl and co-workers expanded on the mechanistic studies described above by testing different nitroxyl derivatives, with the hope of achieving faster rates with aliphatic alcohols and/or broader substrate scope.[52] They examined TEMPO analogues with different redox potentials and sterically less-hindered bicylic nitroxyl derivatives (ABNO, ketoABNO, and AZADO) as co-catalysts in combination with CuOTf/bpy/NMI. Reactions with benzylic and aliphatic primary and secondary alcohols show the dramatic effect of replacing TEMPO with ABNO under similar, but independently optimized, conditions (Scheme 21). Specifically, the Cu/TEMPO conditions show significantly different rates for different classes of alcohols, with the following trends: primary benzylic > primary aliphatic/secondary benzylic ≫ secondary aliphatic/sterically hindered secondary benzylic. In contrast, the Cu/ABNO catalyst systems exhibited nearly identical rates with all classes of alcohols. The observations suggest that replacement of TEMPO with ABNO significantly increases the rate of the alcohol oxidation step (step 4, Scheme 20) and the overall reaction rate is controlled by an alcohol-independent step, such as the aerobic oxidation of Cu^{I} (step 1, Scheme 20). This conclusion is suppported qualitatively by the beneficial effect of an electron-rich bpy ligand (^{MeO}bpy) and the ability to lower the ABNO loading from 5 to 1 mol % without affecting the rate. The optimized Cu/ABNO catalyst system shows excellent reactivity with a broad range of activated and aliphatic primary and secondary alcohols, including those bearing diverse functional groups and stereocenters adjacent to the aldehyde group in the product (Scheme 22). The good reactivity with secondary alcohols undoubtedly reflects the smaller steric profile of the bicyclic ABNO structure relative to TEMPO, although the precise origin of the steric effect remains to be resolved.

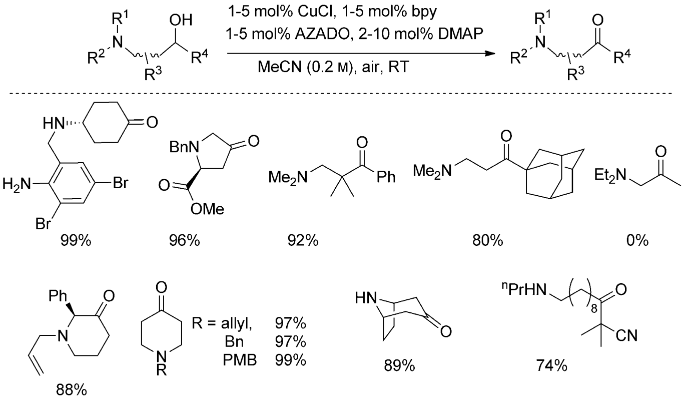


Scheme 21. Rate comparison of five different alcohols with Cu^{I}/TEMPO and Cu^{I}/ABNO alcohol oxidation systems. Data adapted from Ref. [52]. See Schemes 10 and 22 for more details of the reaction conditions.



Scheme 22. A Cu/ABNO catalyst system effective with diverse primary and secondary alcohols under ambient conditions, reported by Stahl.[52]

Iwabuchi and co-workers recently reported a complementary study with Cu/AZADO and related catalyst systems, focused on chemoselective oxidation of alcohols within substrates that bear unprotected primary, secondary, and tertiary amine substituents (Scheme 23).[53] The Cu/AZADO method was shown to be superior to several conventional

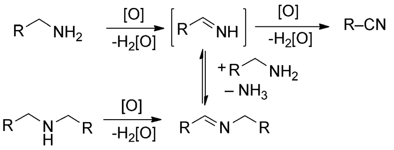


Scheme 23. A Cu/AZADO catalyst system for selective oxidation of diverse amine-containing alcohol substrates under ambient conditions, reported by Iwabuchi.[53]

alcohol oxidation reagents and methods (e.g., pyridinium chlorochromate, Swern, Dess–Martin periodinane, and tetrapropylammonium perruthenate) for a selection of substrates of this type. The results highlight the distinct reactivity of Cu/nitroxyl catalyst systems relative to oxoammonium reagents and catalytic methods, as the latter are often incompatible with unprotected amines. The chemoselectivity of the reaction may be rationalized by the higher acidity of the O-H of the alcohol relative to the N-H of the amines, which promotes the formation of a Cu–alkoxide (see Scheme 20), which is activated for hydrogen-atom transfer to the nitroxyl. The methods in Schemes 22 and 23 are among the most efficient and general alcohol oxidation methods reported to date, even when considering non-aerobic methods, and they provide a powerful complement to the Cu/TEMPO-based methods, which show high selectivity for the oxidation of primary alcohols (see Schemes 9 and 10).

5. Copper/Nitroxyl-Catalyzed Aerobic Oxidation of Amines

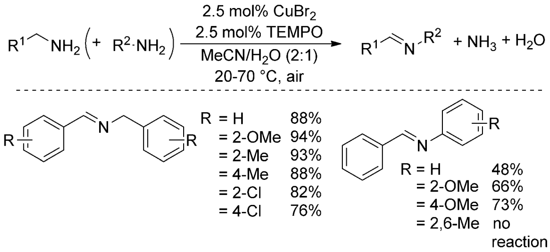
The reactions outlined in the previous section show that alcohols can be oxidized in the presence of amines. Meanwhile, several groups have independently developed methods for the Cu/nitroxyl-catalyzed oxidation of amines to imines and nitriles (Scheme 24), as well as unsaturated nitrogen heterocycles (see below). In some cases, analogous Cu-catalyzed aerobic oxidation reactions (i.e., in the absence of nitroxyls) have been reported,[54] but the use of a nitroxyl co-catalyst enables faster rates, milder reaction conditions, and broader substrate scope.



Scheme 24. Amine oxidation pathways and products.

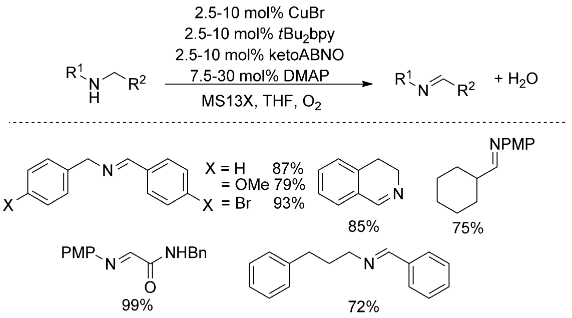
5.1. Oxidation of Primary and Secondary Amines to Form Imines, Nitriles, and Unsaturated Heterocycles

In 2012, the groups of Kerton[55] and Kanai[56] independently reported methods for the Cu/nitroxyl-catalyzed aerobic oxidation of primary and secondary amines. In the Kerton report,[55] reactions were mostly limited to sterically unhindered, primary benzylic amines, and they led to homocoupled imines through the condensation of an amine substrate with the initially formed primary imine. In the presence of electron-rich and/or sterically unhindered anilines, selective cross-coupled imine products could be obtained (Scheme 25), and electron-rich anilines underwent homocoupling to the corresponding azo compounds in the absence of benzyl amine.



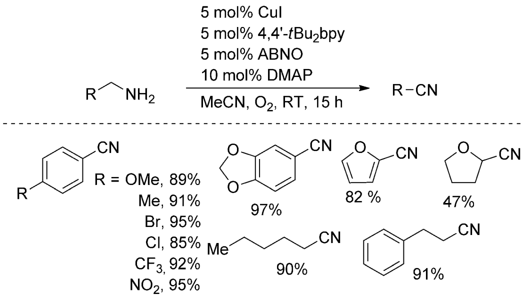
Scheme 25. Cu/TEMPO-catalyzed oxidation of primary benzylic amines resulting in imine formation, developed by Kerton.[55]

Kanai and co-workers developed a different catalyst system that uses ketoABNO, rather than TEMPO, as the co-catalyst.[56] They achieved similar homocoupling reactions of primary benzylic amines, including α-methylbenzylamine, which was not effective under the Kerton conditions. The smaller steric profile of ketoABNO relative to TEMPO probably accounts for the broader scope of this catalyst system. For example, this catalyst system achieved aerobic oxidation of secondary amines to the corresponding imines (Scheme 26). While the reactivity favors benzylic substrates, a number of other substrates were effective, such as PMP-substituted aliphatic amines.



Scheme 26. Cu/ketoABNO-catalyzed oxidation of secondary amines, developed by Kanai.[56] MS13X = 13X molecular sieves, PMP = *para*-methoxyphenyl.

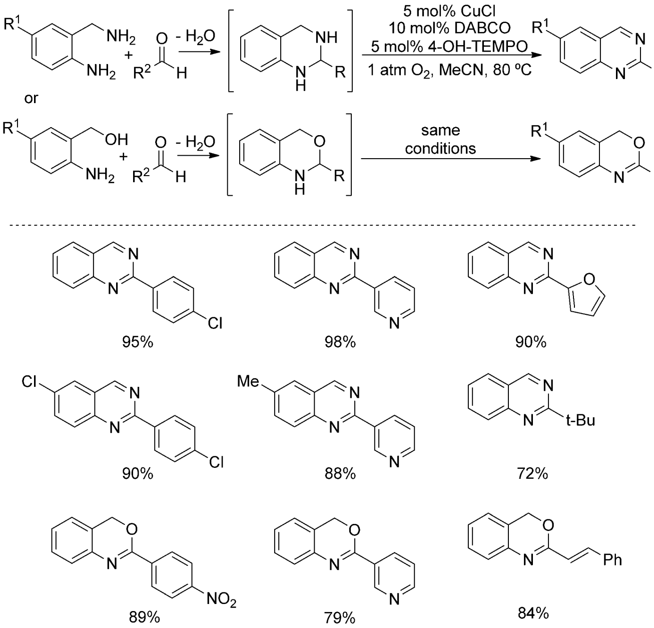
Kim and Stahl reported a catalyst system that enables the selective oxidation of benzylic and aliphatic primary amines to nitriles, with minimal formation of the imine homocoupling product (Scheme 27; see Scheme 24).[57] ABNO was used as the nitroxyl co-catalyst, and the reaction proceeds efficiently at room temperature with a variety of allylic, benzylic, and aliphatic substrates (Scheme 27). The similarity between this catalyst system and that reported by Kanai for the formation of imines is noteworthy, and shows how minor changes in reaction conditions and/or ligand architecture can alter the product selectivity. Use of acetonitrile as the solvent was found to be an important factor in order to achieve the selective formation of nitriles.



Scheme 27. Cu/ABNO catalyzed oxidation of primary amines to nitriles, reported by Stahl.[57]

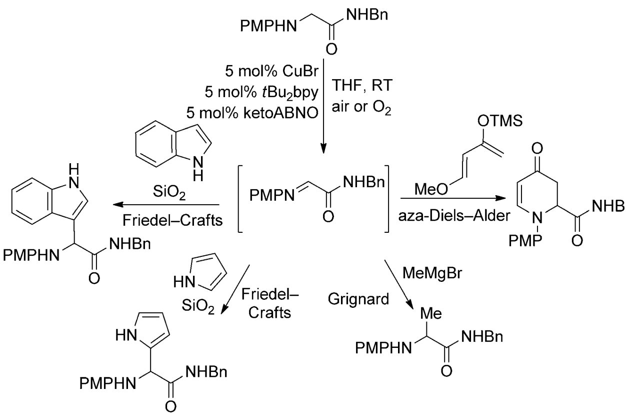
5.2. Copper/Nitroxyl-Catalyzed Aerobic Oxidation of Amines in Tandem or Sequential One-Pot Reactions.

Copper/nitroxyl-catalyzed amine oxidation reactions have been incorporated within tandem reaction sequences. Han and co-workers showed that 2-aminobenzyl amines and alcohols could undergo in situ condensation with aldehydes, followed by the oxidation of the secondary amine(s) to afford the corresponding quinazoline and 4*H*-3,1-benzoxazine heterocycles (Scheme 28).[58] The catalyst system was adapted from an alcohol oxidation catalyst developed earlier by Sekar and co-workers.[22h] The second oxidation step involved in the conversion of dihydroquinazoline to quinazoline is fast and may not require a catalyst.

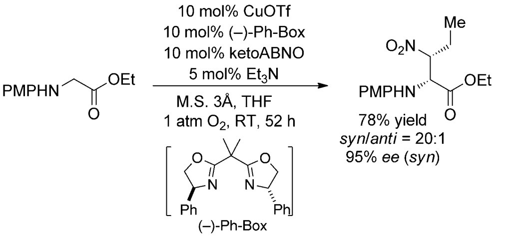


Scheme 28. Condensation/amine oxidation sequence for the synthesis of quinazolines and 4*H*-3,1-benzoxazines, developed by Han.[58]

Kanai and co-workers showed that imines arising from the Cu/ketoABNO-catalyzed oxidation of secondary amines are effective substrates for subsequent, in situ coupling reactions.[56] Examples include the sequential Grignard addition and tandem Friedel–Crafts addition, the aza-Diels–Alder cycloaddition, and the Strecker reaction (Scheme 29). Perhaps the most noteworthy demonstration involves the tandem amine oxidation/nitroalkane addition with a Cu catalyst system employing a chiral bisoxazoline ligand, (−)-Ph-Box (Scheme 30). The resulting product is obtained in excellent diastereo- and enantioselectivity. Collectively, these reactions represent an impressive class of “cross-dehydrogenative coupling” reactions.[59]



Scheme 29. Tandem amine oxidation/addition reactions developed by Kanai.[56]

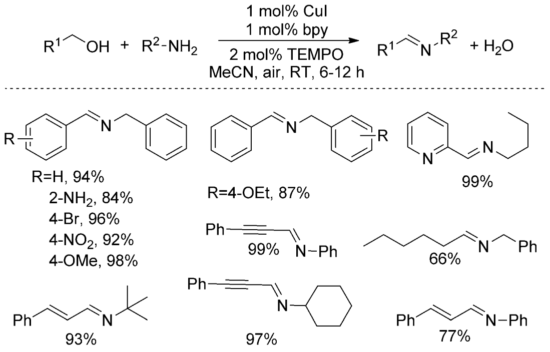


Scheme 30. Amine oxidation followed by an enantioselective aza-Henry reaction employing a single chiral Cu^I complex.

6. Oxidative Coupling Reactions of Alcohols and Amines

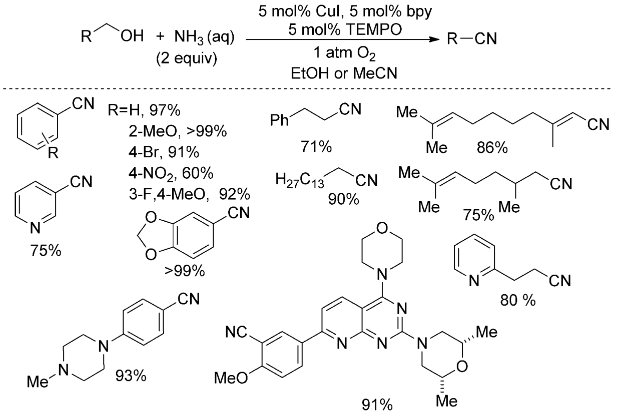
Alcohols are typically more readily available starting materials than amines. Recent studies by a number of groups have shown that Cu/nitroxyl catalyst systems enable the efficient formation of imines, nitriles, and nitrogen heterocycles through the aerobic oxidative coupling of alcohols and amines. Such reactions exploit the apparent chemoselectivity of the Cu/nitroxyl system for alcohol over amine oxidation (see Section 4).

Xu and co-workers reported an efficent method for the preparation of imines from primary alcohols and amines at room temperature under ambient air (Scheme 31).[60] Benzyl, cinnamyl, and phenylpropargyl alcohols were especially effective coupling partners for a range of aliphatic and benzylic amine and aniline derivatives. Two aliphatic alcohols were shown to react effectively, although difficult isolation of the resulting imine complicated determination of the yield. Ideally, labile products of this type would not need to be isolated, and future work focused on in situ transformations of the products could significantly enhance the synthetic utility. 2-Pyridylmethanol is a challenging substrate for Cu/TEMPO alcohol oxidation to the aldehyde (see Scheme 10),[31] but it undergoes efficient oxidative coupling under the reaction conditions of Scheme 31. This observation may suggest that the amine substrate minimized the inhibitory effect of the potentially chelating pyridyl substituent.



Scheme 31. Oxidative coupling of primary alcohols with amines to generate imines, developed by Xu.[60]

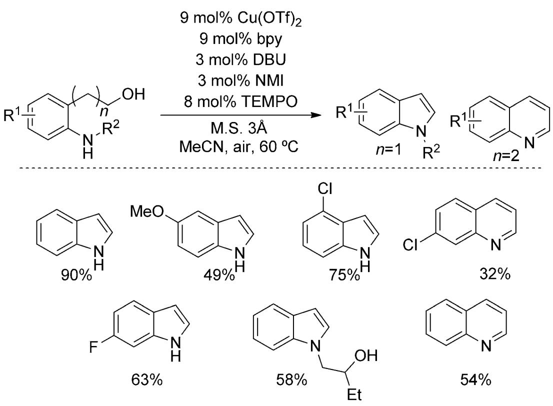
The oxidative coupling of alcohols (or aldehydes) and ammonia provides an efficient route to nitriles. In 1966, Gaasbeek et al. noted that (phen)Cu/di-*tert*-butylnitroxl converts methanol and ammonia to HCN,[20] but they did not explore this reactivity with other alcohols. In 1989, Capdevielle and co-workers reported a Cu-catalyzed aerobic oxidation method for the conversion of aromatic aldehydes and ammonia to nitriles, in the absence of a nitroxyl co-catalyst.[61,62] In 2013, the groups of Tao,[63] Huang,[64] Stahl,[57] and Muldoon[65] independently reported catalytic methods for the conversion of primary alcohols to nitriles, by employing Cu/TEMPO catalyst systems in the presence of aqueous ammonia. The method reported by Huang and co-workers is the most versatile, enabling conversion of both activated and aliphatic alcohols to nitriles (Scheme 32). Like other Cu/nitroxyl oxidation methods, it shows broad functional group compatibility and often may be carried out at room temperature. Aromatic nitriles are especially versatile intermediates, and several benzonitrile derivatives were converted further, without isolation, into an aryl tetrazole, imidazoline, oxazoline, thiazoline, and triazolopyridine by traditional protocols.[64]



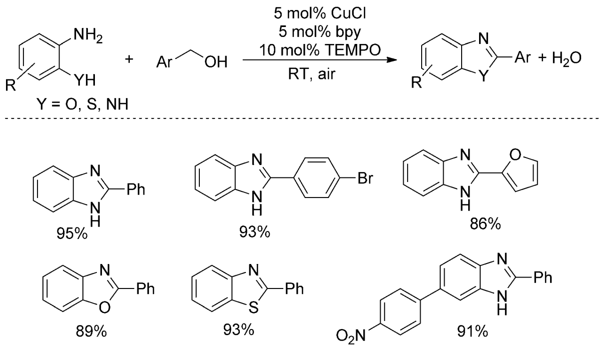
Scheme 32. Preparation of aliphatic, aromatic, and allylic nitriles from primary alcohols, developed by Huang.[64]

Tao employed a different Cu source and solvent (Cu(NO_3)$_2$ and DMSO) at 80 °C, and converted a wide range of benzylic and allylic alcohols and aldehydes to the corresponding nitriles. Stahl identified conditions similar to those of Tao and applied them to several benzylic alcohols. Muldoon observed that NaOH accelerated the reactions and identified conditions for the conversion of aryl aldehydes to nitriles with air as the source of O_2. At elevated pressures of dilute O_2 (8 % O_2 in N_2), it was possible to lower the catalyst loading to 1 mol %.[65]

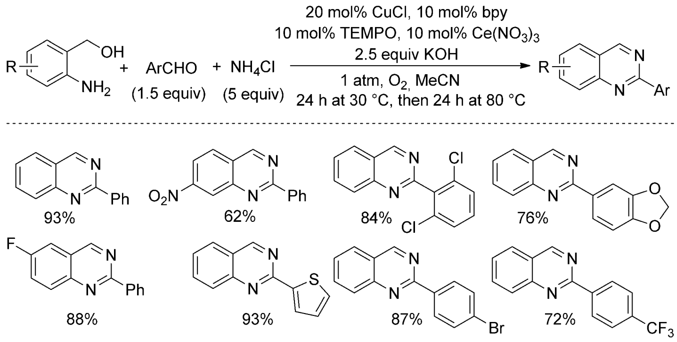
Intra- and intermolecular oxidative coupling reactions of alcohols and amines can be used to prepare unsaturated heterocycles. Muldoon and co-workers reported one of the first applications of this concept in the oxidation of hydroxyalkyl-substituted anilines, leading to the formation of indoles and quinolines (Scheme 33).[66] An indole bearing an unprotected secondary alcohol substituent could be prepared,



Scheme 33. Alcohol oxidation/amine condensation to afford indoles and quinolines, reported by Muldoon.[66]



Scheme 34. Synthesis of benzimidazoles, benzoxazoles, and benzothiazoles through oxidative coupling of aromatic alcohols with *ortho*-amino anilines, phenols, and thiophenols, reported by Lu.[64]



Scheme 35. Three-component synthesis of quinazolines from 2-aminobenzyl alcohols, an aryl aldehyde, and ammonium chloride, reported by Wu.[68]

highlighting the low reativity of secondary alcohols under Cu/TEMPO oxidation conditions (see Schemes 10 and 11).

Facile oxidation of benzylic alcohols to benzaldehydes provided the basis for additional oxidative coupling routes to aromatic heterocycles (Schemes 34 and 35). The reaction of phenylene diamine with aromatic alcohols was developed by Lu and co-workers under solvent-free conditions with CuCl, bpy, and TEMPO to afford 2-arylbenzimidazoles (Scheme 12).[67] The method was also adapted for the preparation of benzoxazoles and benzothiazole products. And, finally, Wu and co-workers prepared quinazolines through a three-component oxidative coupling of 2-aminobenzyl alcohol, aryl aldehyde, and ammonium chloride reagents (Scheme 35).[68] The reaction proceeds through the formation of the benzaldehyde followed by the condensation of the three components and oxidation of the heterocyclic ring.

7. Summary and Outlook

The development of aerobic oxidation reactions for chemical synthesis has been a long-standing goal in organic chemistry, but practical methods, suitable for widespread adoption in the laboratory have been elusive. The Cu/TEMPO and related catalyst systems described here exhibit a level of practicality that appear to address this challenge. Their scope, selectivity, efficiency, and synthetic predictability rival or exceed that of many conventional oxidation methods commonly used in synthetic organic chemistry. The use of ambient air as the oxidant, reaction conditions at room temperature, and common organic solvents, such as acetonitrile, add a level of convenience that removes common barriers associated with lab-scale use of aerobic oxidation reactions. Furthermore, the fast rates and readily available reagents make these reactions ideal targets for large-scale applications. Future work focusing on the identification of lower-cost catalyst components and new catalysts that are effective at a lower loading will further enhance their use on a large scale.

The intimate coupling of Cu^{I}/Cu^{II} and TEMPOH/TEMPO redox processes shows a mechanistic paradigm similar to that of galactose oxidase, whereby two one-electron redox partners mediate efficient two-electron oxidation of an organic molecule. Such pathways represent a powerful strategy for the use of first-row transition metals as alternatives to commonly used noble-metal catalysts. Nevertheless, several aspects of the mechanism remain unresolved (see Section 3), and future studies will be needed to gain further insights that can guide the development of new catalyst systems.

Researchers have only begun to realize the synthetic scope and utility of these catalyst systems. The majority of the work thus far has focused on simple dehydrogenation reactions, such as the oxidation of alcohols to carbonyl compounds and amines to imines and nitriles. The reactions highlighted in Sections 2.3, 5.2, and 6 demonstrate that these catalyst systems can be readily implemented in tandem and sequential one-pot transformations that provide efficient routes to substituted heterocycles and other molecules from simple precursors. Reactions of this type hold significant promise for the use in medicinal chemistry and applications where rapid access to diverse structure types is sought. The further discovery and creative implementation of multicomponent/tandem reactions employing catalyst systems of the type described here are inevitable and will be facilitated by the development of improved catalyst systems.

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