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Practical Synthesis of Amides via Copper/ABNO-Catalyzed Aerobic Oxidative Coupling of Alcohols and Amines

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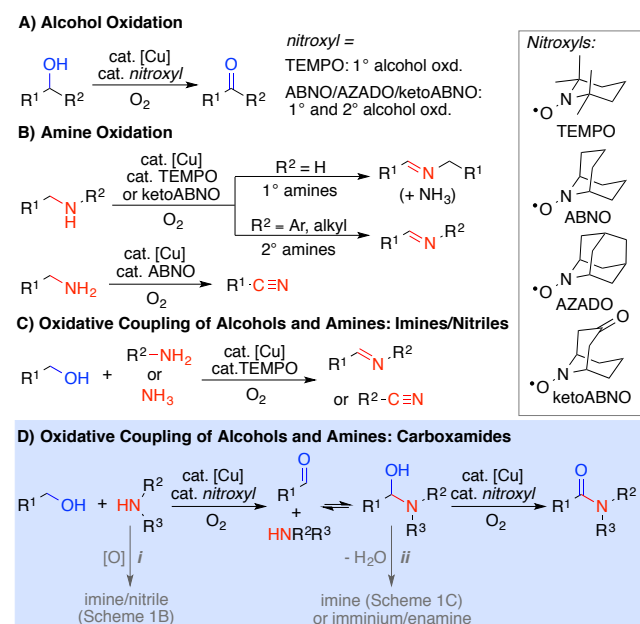
Supporting Information Placeholder

ABSTRACT: A modular Cu/ABNO catalyst system has been identified that enables efficient aerobic oxidative coupling of alcohols and amines to amides. All four permutations of benzylic/aliphatic alcohols and primary/secondary amines are viable in this reaction, enabling broad access to secondary and tertiary amides. The reactions exhibit excellent functional group compatibility and are complete within 30 min – 3 h at room temperature. All components of the catalyst system are commercially available.

In recent years, versatile Cu/nitroxyl catalysts have been developed for aerobic oxidation of alcohols and amines (Scheme 1).¹ Judicious choice of the copper and nitroxyl catalyst components and reaction conditions may be used to control product selectivity. For example, Cu/TEMPO catalysts (TEMPO = 2,2,6,6-tetramethyl-1-piperidine *N*-oxyl) achieve chemoselective oxidation of 1° alcohols,² even in the presence of unprotected 2° alcohols, whereas sterically less hindered bicyclic nitroxyls, such as ABNO (9-azabicyclo[3.3.1]nonane *N*-oxyl), enable efficient oxidation of both 1° and 2° alcohols (Scheme 1A).³ Similar tactics have been used to oxidize amines to imines⁴ or nitriles⁵ (Scheme 1B) and for regioselective lactonization of diols.⁶ Whereas Cu/TEMPO catalysts have been identified for the oxidative coupling of alcohols and amines to imines⁷ or nitriles⁸ (Scheme 1C), the highly appealing, complementary transformation involving oxidative coupling of alcohols and amines to carboxamides has been elusive (Scheme 1D).

Amides are among most important molecules in chemistry and biology, and extensive efforts have targeted new methods for amide bond formation.⁹ Important precedents exist for dehydrogenative or oxidative coupling of alcohols and amines to amides. Such methods must avoid side reactions, such as oxidation of amines to imines or nitriles, and/or condensation of amines with intermediate aldehydes to form imines or iminium ions/enamines (cf. Scheme 1D), which could represent dead ends or undergo decomposition. Some of the most effective examples include dehydrogenation routes with homogeneous Ru catalysts in the presence or absence of a hydrogen acceptor,^{10–12} and oxidative coupling with a Au-nanoparticle catalyst.^{13,14} The former methods primarily favor aliphatic alcohol coupling partners, operate at elevated temperatures (≥ 110 °C), and often generate H₂, which can limit functional group tolerance. The Au-nanoparticle catalyst is reported to have good scope, but the catalysts are not commercially available or otherwise accessible to synthetic chemists.¹⁵

Scheme 1. Cu/Nitroxyl-Catalyzed Aerobic Oxidation Reactions with Alcohol and/or Amine Substrates

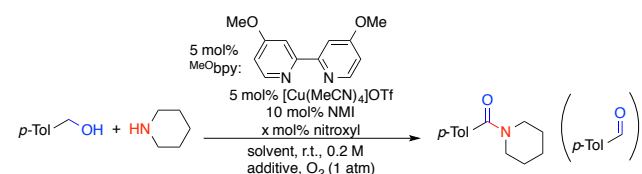


Cu/nitroxyl-catalyzed oxidation reactions operate efficiently under mild conditions, often reaching completion within a few hours at room temperature, and the catalyst components are readily available from commercial sources. If these features could be replicated for oxidative amidation, the reactions would have important advantages over precedents, while also providing an appealing alternative to traditional acylation-based coupling methods. Here, we report the development of Cu/ABNO catalyst systems that achieve this goal.

Previous reports show that Cu/nitroxyl-catalyzed alcohol oxidation is possible in the presence of unprotected amines,^{3a,b} suggesting that side-reaction *i* in Scheme 1D should not be a significant problem. On the other hand, formation of imines via Cu/TEMPO-catalyzed coupling of alcohols and amines⁷ raised concern that side reaction *ii* in Scheme 1D could present an obstacle to amide formation. The hemiaminal hydroxyl group is more hindered than the initial 1° alcohol. Therefore, we speculated that use of a sterically less-hindered nitroxyl co-catalyst might enable oxidation of the hemiaminal intermediate in preference to the competing dehydration pathway *ii*.

Our initial studies focused on the reaction between a benzylic alcohol and a 2° amine (4-methylbenzyl alcohol and piperidine, Table 1), in order to limit the number of possible side reactions. Imine formation is not possible with 2° amines, and formation of enamines via tautomerization of an iminium species is not possible with benzylic alcohols. Use of our previously disclosed conditions for 2° alcohol oxidation,^{3a} with 4,4'-dimethoxy-2,2'-bipyridine (Me^obpy) and *N*-methylimidazole (NMI) as ligands and ABNO as the nitroxyl, led to formation of aldehyde as the sole product (Table 1, entry 1). Use of 1 atm O₂ rather than air as the source of oxidant afforded amide in 26% yield (entry 2), and increasing the ABNO loading from 1 to 3 mol% led to a further increase in amide yield (56%, entry 3).¹⁶ Inclusion of 3Å molecular sieves led to excellent yields in both MeCN (90%) and THF (89%) (entries 4 and 5), but near-quantitative yield (98%) was obtained in CH₂Cl₂ (DCM) (entry 6).¹⁷ The role of molecular sieves is not yet clear.¹⁸ Two other commercially available unhindered nitroxyls, ketoABNO and AZADO (2-azaadamantane-*N*-oxyl), displayed inferior or similar performance to ABNO (entries 7 and 8). The lower cost of ABNO relative to AZADO prompted us to proceed with ABNO. In contrast, use of the sterically hindered nitroxyl TEMPO resulted in only a modest yield of amide (entry 9). These optimized conditions successfully generated amide with air as the oxidant; however, a somewhat lower yield was observed and longer reaction time was required (entry 10; see Supporting Information for further details).

Table 1. Benzylic Alcohols and 2° Amines: Optimization of the Reaction Conditions^a



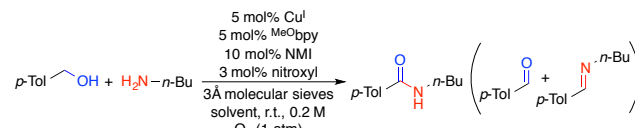
entry	nitroxyl (mol %)	additive	solvent	conv. (%)	amide (%) ^b	aldehyde (%) ^b
1 ^c	ABNO (1)	-	MeCN	>99	<1	96
2	ABNO (1)	-	MeCN	>99	26	68
3	ABNO (3)	-	MeCN	>99	56	39
4	ABNO (3)	3Å mol. sieves	MeCN	>99	90	9
5	ABNO (3)	3Å mol. sieves	THF	>99	89	9
6 ^d	ABNO (3)	3Å mol. sieves	DCM	>99	98	<1
7	ketoABNO (3)	3Å mol. sieves	DCM	>99	55	26
8	AZADO (3)	3Å mol. sieves	DCM	>99	98	<1
9	TEMPO (3)	3Å mol. sieves	DCM	>99	50	50
10 ^e	ABNO (3)	3Å mol. sieves	DCM	>99	75	16

^a1.0 mmol scale, O₂ balloon, 1.1 equiv. amine. Reactions were allowed to run for 10 h to ensure maximum conversion. ^bCalibrated ¹H NMR yields using dimethyldiphenylsilane as an internal standard. ^cReaction was run under ambient air instead of an O₂ balloon. ^dThis reaction was also run on a 10 mmol scale: 91% calibrated ¹H NMR yield; reaction time: 1 h. ^eReaction was run open to air.

The reaction conditions identified for this benzyl alcohol/2° amine reaction were then tested for a benzyl alcohol/1° amine (*n*BuNH₂) reaction (Table 2). Only a low yield of amide was obtained (31%), with imine generated as the major product (Table 2, entry 1). Speculating that the sterically less bulky 1° amine might coordinate more strongly to Cu and inhibit the catalyst, we explored other Cu^I sources. Both CuI and CuCl afforded higher yields (82 and 87%; entries 2 and 3). Upon changing the solvent to THF, quantitative yield was obtained with CuCl (entry 4). In the absence of molecular sieves, imine

was the major product (entry 5), while use of TEMPO led to a mixture of aldehyde and imine (entry 6).

Table 2. Benzylic Alcohols and 1° Amines: Optimization of the Reaction Conditions^a

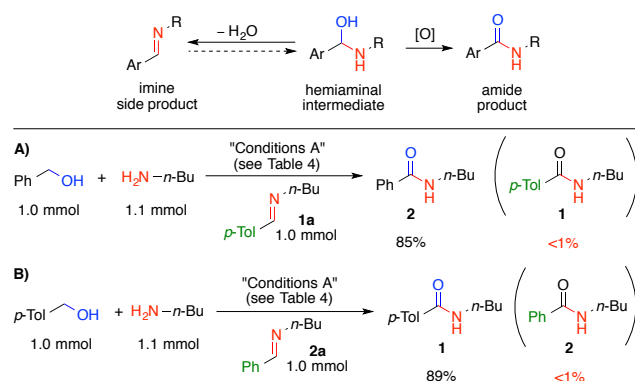


entry	Cu(I)	solvent	nitroxyl	conv. (%)	amide (%) ^b	aldehyde (%) ^b	imine (%) ^b
1	[Cu(MeCN) ₄]OTf	DCM	ABNO	>99	31	17	44
2	CuI	DCM	ABNO	>99	82	7	4
3	CuCl	DCM	ABNO	>99	87	6	6
4 ^c	CuCl	THF	ABNO	>99	99	<1	<1
5 ^d	CuCl	THF	ABNO	>99	2	2	90
6	CuCl	THF	TEMPO	>99	<1	50	50

^a1.0 mmol scale, O₂ balloon, 1.1 equiv. amine. Reactions were allowed to run for 10 h to ensure maximum conversion. ^bCalibrated ¹H NMR yields using dimethyldiphenylsilane as an internal standard. ^c2-MeTHF affords a comparable yield. ^dWithout 3Å molecular sieves.

In reactions of benzylic alcohols and 1° amines, imines are potential side-products, or they could equilibrate with the hemiaminal intermediate via reaction with water under the reaction conditions (Scheme 2). In order to test the role of imines in these reactions, we investigated the oxidative coupling of benzyl alcohol and *n*-butylamine in the presence of one equivalent of *N*-butyl-(4-methylbenzyl)imine **1a**. The sole amide product obtained from this reaction was derived from benzyl alcohol; none of the 4-methylbenzamide **1** was observed (Scheme 2A). The analogous outcome was observed in the reaction of 4-methylbenzyl alcohol with *n*-butylamine, which was performed in the presence of benzylimine **2a**. Only the 4-methylbenzamide **2** was observed (Scheme 2B). These results reveal that imine formation is irreversible under the reaction conditions and that productive amide formation arises from direct oxidation of the hemiaminal intermediate (cf. Scheme 1D).

Scheme 2. Experiments Demonstrating that Imine Formation is Irreversible under the Reaction Conditions



Following this identification of reaction conditions for benzylic alcohols, we turned our attention to aliphatic alcohols. Initial testing of 3-phenyl-1-propanol with a 1° and 2° amines (*n*BuNH₂ and pyrrolidine) revealed that the two conditions identified for benzylic alcohols are largely ineffective. Quantitative conversion of the alcohol was observed together with complex product mixtures, including

unidentified side products (Table 3, entries 1–2 and 5–6). Tris(2-pyridylmethyl)amine (TPA) has been studied extensively as a ligand for Cu in the context of stoichiometric Cu/O₂ experiments to mimic Cu-oxidase and Cu-oxygenase reactivity.^{19,20} To our knowledge, however, it has not been tested in Cu/nitroxyl catalyzed aerobic oxidation reactions. Preliminary tests showed that TPA enables successful reactivity with aliphatic alcohols. A combination of TPA and CuCl in THF was identified as an effective catalyst system for the reaction of 3-phenyl-1-propanol with *n*-butylamine (85% yield, entry 4). Replacing CuCl with [Cu(MeCN)₄OTf] resulted in only <5% yield (entry 3). Use of the TPA/CuCl/THF system in the reaction between 3-phenyl-1-propanol and the 2° amine pyrrolidine was not successful (entry 7). In this case, a good yield of amide (77%) was achieved by using CuCN as the Cu source, together with 2.5 equiv. of the amine (entry 8).

Table 3. Aliphatic Alcohols and Amines: Identification of Reaction Conditions Using the Ligand TPA^a

5 mol% Cu^I
x mol% ligand(s)
3 mol% ABNO
3 Å molecular sieves
solvent, r.t., 0.2 M
O₂ (1 atm)

entry	amine	Cu(I)	ligand(s) (mol %)	solvent	conv. (%) ^b	yield (%) ^{b,c}
1	H ₂ N- <i>n</i> -Bu	CuCl	MeO b py (5); NMI (10)	THF	>99	56
2	H ₂ N- <i>n</i> -Bu	[Cu(MeCN) ₄ OTf]	MeO b py (5); NMI (10)	DCM	>99	<5
3	H ₂ N- <i>n</i> -Bu	[Cu(MeCN) ₄ OTf]	TPA (5)	THF	66	<5
4 ^d	H ₂ N- <i>n</i> -Bu	CuCl	TPA (5)	THF	>99	85
5	pyrrolidine	CuCl	MeO b py (5); NMI (10)	THF	>99	<5
6	pyrrolidine	[Cu(MeCN) ₄ OTf]	MeO b py (5); NMI (10)	DCM	>99	<5
7	pyrrolidine	CuCl	TPA (5)	THF	>99	<5
8	pyrrolidine	CuCN	TPA (5)	THF	>99	40 (77^{d,e})

^a1.0 mmol scale, O₂ balloon, 1.1 equiv. amine. Reactions were allowed to run for 10 h to ensure completion. ^bCalibrated ¹H NMR yields using dimethyldiphenylsilane as an internal standard. ^cGenerally, mass balances = product yields, due to undesired aldehyde side reactions that form reactive imines/enamines. ^d2-MeTHF affords a comparable yield. ^e2.5 equiv. pyrrolidine.

With the complementary sets of conditions identified in Tables 1–3 (cf. bold entries in each table), we examined the substrate scope (Table 4). Reactions with benzylic alcohols and 1° amines are insensitive to electronic variations of the benzylic alcohol (**1**, **3**, **4**). Heterocycle-derived benzylic alcohols containing pyridine, benzothiophene, and furan are tolerated (**5–8**), as are α -branched amine substrates (**9** and **10**). The chiral benzylic amine (**10**) couples with no erosion of enantiomeric purity. Aniline and an allylic alcohol are also suitable amine and alcohol coupling partners, respectively (**11** and **12**). Similarly impressive scope was observed with benzylic alcohols and secondary amines. Electronically varied (**13–15**) benzylic alcohols, including an example with an *ortho* methyl group (**16**), and heterocycle-containing substrates (**17** and **19**) are well-tolerated. Acyclic 2° amines are effective substrates (**18–21**), as is an allylic alcohol (**22**). Limitations were encountered when the amine reaction partner had too much steric bulk. For example, 2-methylpyrrolidine (**23**) and *t*-butylamine (**24**) are not viable substrates. In reactions of aliphatic alcohols, unbranched derivatives (**25** and **26**) as well as β -branched alcohols (**27–29**) undergo successful coupling with 1° amines. The latter group includes the sterically hindered neopentanol substrate (cf. **28**). The mildness of the reaction conditions is evident in the oxidative coupling of a branched, enantiomerically pure chiral alcohol, which affords

Table 4. Substrate Scope for Cu/ABNO-Catalyzed Aerobic Synthesis of Amides from Alcohols and Amines^a

cat. Cu^I/ligand
3 mol% ABNO
3 Å molecular sieves
solvent, r.t., 0.2 M
O₂ (1 atm), 30 min–3 h

Conditions:
(A): 5% CuCl/MeO**b**py, 10% NMI, THF
(B): 5% [Cu(MeCN)₄OTf]/MeO**b**py, 10% NMI, DCM

(C): 5% CuCl/TPA, THF
(D): 5% CuCN/TPA, THF

Yields and conditions for products 1–37:
1: 91% (A), **3**: 85% (A), **4**: 95% (A)
5: 96% (A), **6**: 98% (A), **7**: 82% (A)
8: 85% (A), **9**: 93% (A)^b, **10**: 87% (B)^c, **11**: 73% (B)^d
12: 70% (A)^d, **13**: 96% (B)^e, **14**: 91% (B), **15**: 94% (B)^f, **16**: 93% (B)^d, **17**: 79% (B)
18: 93% (B), **19**: 83% (B), **20**: 71% (B)^b, **21**: 71% (B)^b
22: 84% (B)^d, **23**: <1% (A or B), **24**: <1% (A or B), **25**: 80% (C)
26: 82% (C), **27**: 78% (C), **28**: 71% (C), **29**: 65% (C)^c
30: 79% (C), **31**: 80% (C), **32**: 79% (C)^f, **33**: 70% (D)
34: 32% (D), **35**: 68% (D), **36**: 85% (B)^f, **37**: 66% (D)

^a1.0 mmol scale, O₂ balloon, isolated yields. Conditions A, B, C: 1.1 equiv. amine. Conditions D: 2.5 equiv. amine. ^bDouble catalyst loading: 10% Cu^I, 10% MeO**b**py, 20% NMI, 6% ABNO. ^cProduct ee: >99%. ^dTriple catalyst loading: 15% Cu^I, 15% MeO**b**py, 30% NMI, 9% ABNO. ^eUsing conditions A: 77% yield (calibrated ¹H NMR yield). ^f2.5 equiv. amine.

the corresponding amide **29** with no stereochemical erosion. This observation indicates the amine substrate reacts selectively with the intermediate aldehyde, without epimerizing the adjacent stereocenter. Efforts to form peptide bonds using this method have yielded poor results (see Supporting Information, Section VI). These reactions will be the focus of future catalyst development efforts. Amide products containing α -ether and α -fluoro substituents are readily accessed (**30–31**), and amines with a nitrile substituent and with α -branching are also effective (**32–33**). Secondary amines are the most challenging class of reaction partners with aliphatic alcohols under these oxidative conditions, matching observations made previously with the Au nanoparticle catalyst systems.^{13c} This challenge appears to reflect formation of unstable iminium ions or enamines in reactions of aliphatic alcohols and 2° amines. While piperidine couples in low yield (**34**), the 5- and 4-membered ring substrates pyrrolidine (**35**) and azetidine (**36**), couple in good yields. These observations

are consistent with the expected less-favorable iminium/enamine formation with the smaller cyclic amines. A similar rationale accounts for the successful coupling of piperidine and cyclopropylmethanol (**37**).

Overall, these results highlight the utility of new Cu^I/nitroxyl catalyst systems for aerobic oxidative coupling of alcohols and amines to amides. The unusually mild reaction conditions (room temperature) and catalytic efficiency (30 min – 3 h reaction times) is matched by excellent functional group compatibility and broad substrate scope. These favorable features combine with the commercial availability of the catalyst components to offer a highly appealing strategy for amide bond formation.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and compound characterization data. This material is available free of charge via the internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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(19) Zhang, C. X.; Kaderli, S.; Costas, M.; Kim, E.-i.; Neuhold, Y.-M.; Karlin, K. D.; Zuberbühler, A. D. *Inorg. Chem.* **2003**, *42*, 1807–1824.

(20) $\text{Cu}^{\text{II}}\text{-O}_2$ adducts have been proposed in Cu/nitroxyl catalyzed reactions: Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 2357–2367.

