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Oxidative Amide Coupling from Functionally Diverse Alcohols and Amines using Aerobic Copper/Nitroxyl Catalysis

Paige E. Piszel, Aristidis Vasilopoulos, and Shannon S. Stahl*

Abstract: The aerobic Cu/ABNO catalyzed oxidative coupling of alcohols and amines is highlighted here in the synthesis of amide bonds in diverse drug-like molecules (ABNO = 9-azabicyclo[3.3.1]nonane *N*-oxyl). The robust method leverages the privileged reactivity of alcohols bearing electronegative heteroatoms (O, F, N, Cl) in the β-position. The reaction tolerates over 20 unique functional groups and is demonstrated on a 15 mmol scale under air. Steric constraints of the catalyst allow for chemoselective amidation of primary amines in the presence of secondary amines. All catalyst components are commercially available, and the reaction proceeds under mild conditions with retention of stereocenters in both reaction partners, while producing only water as a by-product.

Amide coupling reactions account for 16% of all reactions performed in pharmaceutical syntheses.[1] Typical methods use stoichiometric coupling reagents to activate a carboxylic acid for nucleophilic attack by the amine coupling partner.[2] Several catalytic methods for amide coupling have been reported, but none yet exhibit the synthetic utility of methods that use stoichiometric coupling reagents. Recent efforts have explored catalytic methods for amide bond formation with reaction partners other than carboxylic acids.[3] Prominent examples include oxidative or dehydrogenative coupling of amines with primary alcohols, which often produce only water or H_2 as a by-product. In spite of the potential appeal of these reactions,[4] the precedents lack the functional-group compatibility, efficiency, or synthetic reliability needed to compete with traditional amide coupling methods. Herein, we demonstrate highly practical applications of Cu/ABNO-catalyzed aerobic oxidative coupling of primary alcohols and amines for the synthesis of diverse α-heteroatom-substituted amides (ABNO = 9-azabicyclo[3.3.1]-nonane *N*-oxyl).

Heteroatom-substituted amides and α-substituted derivatives, in particular (Figure 1), are an important class of molecules due to their prevalence in pharmaceuticals and related bioactive compounds.[5] For example, a recent survey of over 3500 pharmaceuticals revealed that the majority of alkyl amides feature an oxygen or nitrogen atom α, β, or γ to the carbonyl.[1b] The heteroatom linkage at these positions has a beneficial effect on bioactivity and/or pharmacological properties of the molecule due to changes in enzyme binding and solubility. In light of these considerations, new strategies to access such structures could have broad impact.

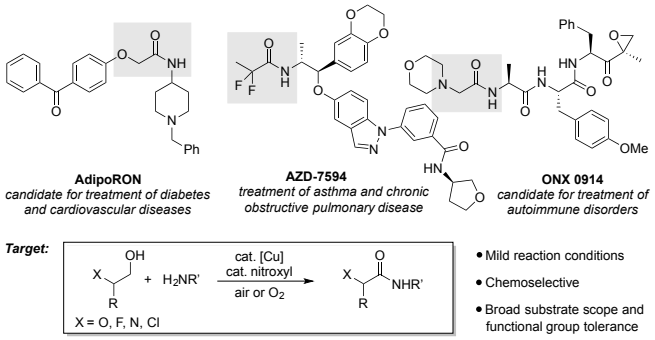
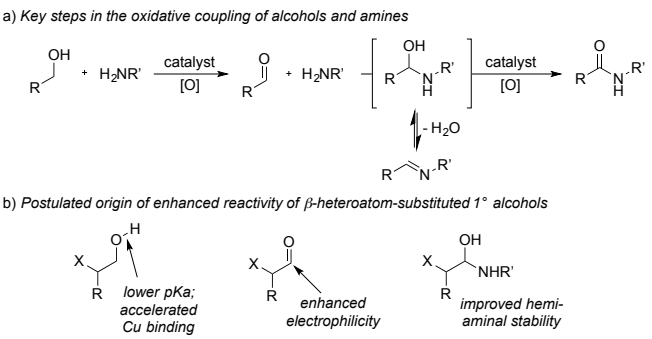


Figure 1: α-Heteroatom-substituted amides in pharmaceuticals and targeted strategy for their preparation.

Cu/nitroxyl catalyst systems have been identified as highly effective catalyst systems for aerobic alcohol oxidation,[6,7] and we recently demonstrated that analogous catalyst systems could support aerobic oxidative coupling of alcohols and amines.[4o] The latter reactions, however, were subject to many of the synthetic limitations noted above. The oxidative amidation begins with alcohol oxidation to the aldehyde, followed by trapping by an amine to form a hemiaminal, which is then oxidized further to the corresponding amide (Scheme 1a). Insights from mechanistic studies of Cu/nitroxyl-catalyzed alcohol oxidation[8] suggested that β-heteroatom-substituted primary alcohols could be a privileged substrate class for oxidative coupling due to their enhanced acidity (e.g., the aqueous pK_a values for EtOH, ethylene glycol, and trifluoroethanol are 15.9,[9] 15.1,[10] and 12.4,[11] respectively). The previous studies showed that more acidic alcohols undergo more rapid oxidation, owing to their more favorable reaction with the Cu^{II}–hydroxide intermediate.[8b] For example, competition studies showed that electron-deficient benzyl alcohol derivatives undergo more rapid oxidation than electron-rich analogs. In addition, the aldehyde intermediate with an α-heteroatom substituent will have enhanced electrophilicity that will promote formation of a hemiaminal and disfavor formation of an imine (Scheme 1b),[12] which is not an intermediate in amide



Scheme 1. (a) General mechanism for the oxidative coupling of alcohols and amines to prepare amides. (b) Basis for enhanced reactivity of β-heteroatom-substituted alcohols in catalytic Cu/nitroxyl-catalyzed oxidative amidation.

[*] P. E. Piszel, A. Vasilopoulos, Prof. S. S. Stahl
Department of Chemistry
University of Wisconsin-Madison
Madison, WI 53706 (USA)
E-mail: stahl@chem.wisc.edu

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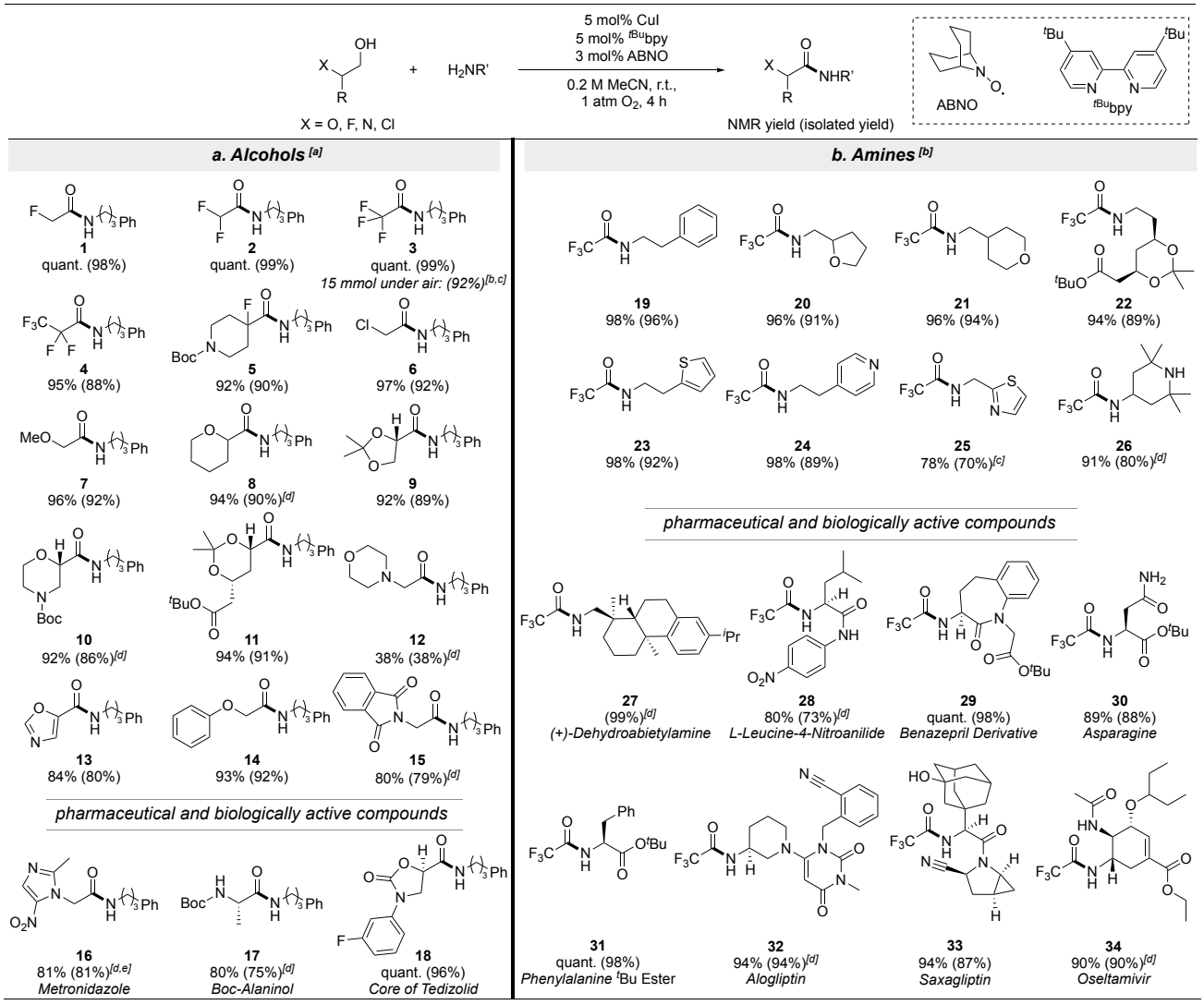
formation. Improved reactivity in these fundamental steps should allow these methods to be particularly effective for the preparation of pharmaceutically relevant α-heteroatom-substituted amides.

The present study was initiated by testing the oxidative amidation of tetrahydropyran-2-methanol with 3-phenylpropylamine. Screening of multiple conditions and catalyst compositions revealed that use of CuI/^{t}Bubpy (4,4'-di-*tert*-butyl-2,2'-bipyridine) in combination with ABNO in MeCN produced the desired amide **8** (Scheme 2) in 94% yield under O_2 (see Supporting Information for full screening data). While an improved yield was obtained with pure O_2 as the source of oxidant, a yield of 77% was still retained with air as the oxidant. This simplified 3-component catalyst system provided the starting point to evaluate the scope and functional group tolerance of the method with other alcohols and amines.

A variety of β-heteroatom-substituted alcohols were tested in the oxidative coupling reaction with 3-phenylpropylamine (Scheme 2a). Relevant β-heteroatom-substituted alcohol starting materials are readily available from glycol derivatives, amino alcohols, and halohydrins. Five β-fluorinated alcohols (**1**-**5**) were coupled under the optimized conditions, and each coupling resulted in >90% yield of the corresponding amide product. The trifluoroethanol-derived product **3** was prepared in a 15 mmol scale reaction using ambient air as the oxidant (92% isolated yield). A number of other noteworthy results were obtained from these reactions. The mild conditions allowed for preservation of the Boc protecting group on the piperidine in **5**. A high yield was retained when using β-chloroethanol (**6**) as the substrate, indicating that the amidation outcompetes S_N2 displacement of a primary alkyl chloride. In contrast, β-bromoethanol was not an effective substrate due to competing S_N2 reactivity. (The latter result and other examples of unsuccessful substrates are documented in the Supporting Information; see Tables S9 and S10). Alcohols with alkyl ethers, aryl ethers, and acetonides at the β position also were converted effectively to the corresponding amide products (**7**, **8**, **9**, **11**, **14**). Boc-protected 2-(*S*)-morpholinemethanol afforded the corresponding amide in 92% yield (**10**). β-Nitrogen containing alcohols are more challenging substrates, possibly reflecting their reduced electron-withdrawing effect and/or deleterious chelation of the Cu center and inhibition



Scheme 2. Substrate scope of alcohols and amines for aerobic Cu/ABNO catalyzed α-heteroatom-substituted amide formation. Reactions at 0.5 mmol scale. Calibrated ^{1}H NMR yields using dimethyldiphenylsilane as an internal standard. ^{tBu}bpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine, ABNO = 9-Azabicyclo[3.3.1]nonane *N*-oxyl. [a] 1 equiv alcohol with 1.1 equiv amine. [b] 1 equiv amine with 1.5 equiv alcohol. [c] Under air. [d] Catalyst loading: 10 mol% CuI, 10 mol% ^{tBu}bpy, and 6 mol% ABNO. [e] DMF used as solvent.

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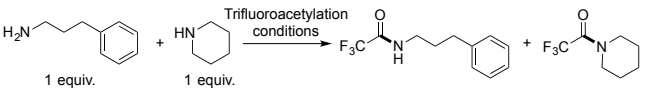
of catalytic turnover.[7b] Despite this challenge, tertiary amine (**12**) was isolated in modest yield. Acylation of the β-nitrogen atom, including conversion to a phthalimide (**15**) or Boc-protected amino alcohol (**17**), led to product formation in high-yield. Similarly, alcohols bearing β-heteroaromatic rings, oxazole (**13**) and imidazole (**16**), formed the amidation product in 80% and 81% isolated yields, respectively. The β-oxazolidinone of an alcohol fragment in tedizolid (**18**) was well tolerated under the optimal conditions. The antibiotic metronidazole is insoluble in acetonitrile (**16**); however, conducting the reaction in DMF led to an 81% yield of the desired product.[13]

After assessing the alcohol substrate scope, we explored different amine coupling partners (Scheme 2b). We elected 2,2,2-trifluorethanol (TFE) as the coupling partner for coupling with different amines, resulting in formation of the corresponding trifluoroacetamide derivative.[14] An initial set of substrates (**19-26**) was selected to probe the compatibility of various functional groups, while a second set features an expanded set of functional groups within specific pharmaceutically relevant molecules (**27-34**). Functional groups in the first set include oxygen-containing groups (ethers, *t*Bu ester, and acetonide **19-22**), and aromatic heterocycles (thiophene, pyridine, and thiazole **23-25**), all of which formed the desired amide product in very good-to-excellent yields. The catalyst system favors reaction with the primary amine over the sterically encumbered secondary amine, leading to formation of **26**. The reaction tolerated a primary amide[15] and a free tertiary alcohol (**30** and **33**; 89% and 94% yields, respectively), showing that this protocol could have advantages over the use of trifluoroacetic anhydride, which can lead to competitive functionalization of other groups in a molecule.[16] Compatible functional groups evident from reactions with the second set of molecules include nitriles, alkenes, nitro groups, imides, cyclopropyl rings, and lactams. The effectiveness of the reaction with substrates as complex as the anti-diabetic drugs alogliptin (**32**) and saxagliptin (**33**) and antiviral oseltamivir (**34**), all of which underwent oxidative coupling in >90% yield, shows that this oxidative coupling strategy represents a compelling complement, and in some cases may be superior, to traditional amide coupling reactions.[17]

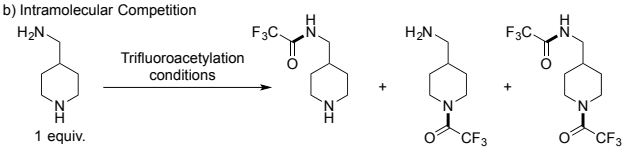
The chemoselective functionalization of the primary amine over the secondary amine in substrate **26** prompted us to explore this issue further.[18] Cu/nitroxyl catalyst systems show good sterically controlled selectivity in oxidations of two different alcohols,[7b,19] owing to the closed 6-membered transition state involved in the H-transfer between bound alkoxide and nitroxyl ligands.[20] We reasoned that analogous selectivity could be achieved in reactions of hemiaminals derived from primary and secondary amines due to the steric differences between these intermediates. A competition experiment between 3-phenylpropylamine and piperidine in the presence of 1 equiv of TFE exhibited >15:1 selectivity for the primary amine (94% yield) over the secondary amine (Scheme 3a). In contrast, use of traditional trifluoroacetylation conditions with trifluoroacetic anhydride (TFAA)[21] resulted in low selectivity (primary:secondary ≤ 2:1), again favoring reaction with the primary amine. These results were then extended to the reaction of 4-(aminomethyl)piperidine (Scheme 3b). Chemoselective trifluoroacetylation of the primary amine was again achieved with the Cu/ABNO catalyst system (primary:secondary > 30:1, with very little difunctionalization; 64% yield). Traditional trifluoroacetylation conditions with TFAA exhibited poor selectivity, with preferential formation of the difunctionalized product.

a) Intermolecular Competition



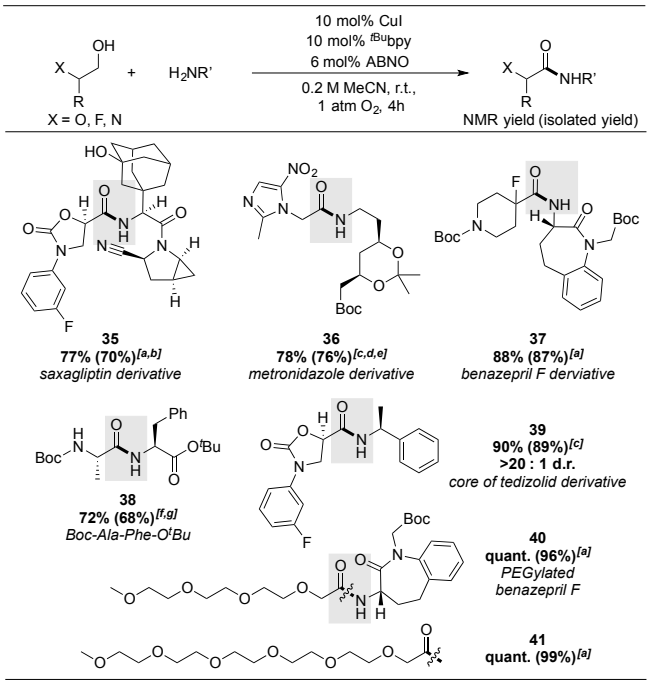
Trifluoroacetylation Conditions:	*2° amide*	*3° amide*
TFAA, DBU, DCM [a]	66%	34%
TFAA, TMG, MeCN [b]	53%	34%
Cu/ABNO [c]	***94%***	*6%*

b) Intramolecular Competition



Trifluoroacetylation Conditions:	*2° amide*	*3° amide*	*di-functionalized*
TFAA, DBU, DCM [a]	16%	3%	29%
TFAA, TMG, MeCN [b]	30%	3%	33%
Cu/ABNO [c]	***64%***	*1%*	*2%*

Scheme 3. Intermolecular (a) and Intramolecular (b) competition experiments between a primary and secondary amine under optimized conditions and using typical trifluoroacetylation protocols. [a] 1 equiv TFAA, 1.5 equiv DBU, DCM (0.6 M), 0 °C to rt, overnight. [b] 1 equiv TFAA, 1.5 equiv TMG, MeCN (0.6 M), 0 °C to rt, overnight. [c] 1 equiv TFE, 10 mol% CuI, 10 mol% $^{t\text{Bu}}$bpy, 6 mol% ABNO, MeCN (0.2 M), air, rt, 4 h. TFAA = trifluoroacetic acid, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, TMG = 1,1,3,3-Tetramethylguanidine, TFE = 2,2,2-trifluoroethanol.



Scheme 4. Synthesis of complex molecules using bioactive coupling partners in Cu/ABNO catalyzed alcohol-amine coupling. Reactions at 0.5 mmol scale. [a] 1.1 equiv of alcohol used. [b] 5 mol% CuI, 5 mol% $^{t\text{Bu}}$bpy, and 3 mol% ABNO. [c] 1.1 equiv of amine used. [d] DMF used as solvent. [e] Catalyst loading doubled. [f] 1.5 equiv of amine used. [g] 15 mol% CuI, 15 mol% $^{t\text{Bu}}$bpy, and 9 mol% ABNO.

Finally, we sought to demonstrate that the coupling method could be effective for cases in which both coupling partners exhibit significant molecular complexity (Scheme 4). Reactions of this type lack precedent among prior oxidative amidation methods.

Each of the examples in Scheme 4 feature reactions in which both reaction partners contain two or more heteroatom substituents. Noteworthy examples include amide coupling with saxagliptin, as the resulting amide product contains 10 unique heteroatoms (**35**). Formation of a dipeptide was achieved via the coupling of a *t*Bu-ester amino acid with an *N*-Boc-protected amino alcohol (**38**).

Polyethylene glycols (PEGs) are a prominent class of β-heteroatom-substituted alcohols, and PEGylation of pharmaceuticals can lead to enhanced pharmacological properties by changing their solubility or membrane permeability.[22,23] The Cu/ABNO-catalyzed method proved to be effective in coupling mPEG–OH units with benazepril F,[24] affording excellent product yields in both cases (**40**, **41**).

The results described herein demonstrate that the Cu/ABNO catalyst system exhibits broad scope and synthetic utility for the oxidative coupling of alcohols and amines to form amides. The reactions take advantage of the unique activating properties of β-heteroatom-substituted alcohols to afford pharmaceutically important α-substituted amides. The reaction yields, even with complex substrates, are commonly >90%, suggesting that these methods represent an important complement to traditional amide coupling methods. For example, the efficiency and chemoselectivity evident in the trifluoroacetylation of primary amines suggests that this method offers an appealing alternative to methods that use trifluoroacetic anhydride. More broadly, these methods could find extensive use in medicinal chemistry, enabling rapid diversification of simple building blocks or core structures containing a primary alcohol or amine. And, the lack of requirement for a stoichiometric coupling reagent offers potential advantages in large scale amide coupling reactions.

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Conflict of interest:

The authors declare no conflict of interest.

Keywords: amide coupling • copper • homogeneous catalysis • aerobic oxidation • cross-coupling

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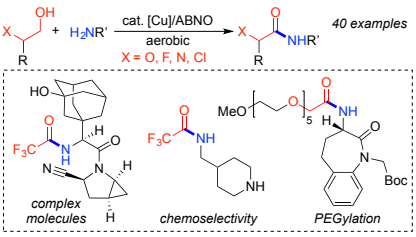
Cu/ABNO-catalyzed oxidative amidation is shown to be highly effective in the cross coupling of complex alcohols and amines. The reactions exploiting the unique reactivity of β-heteroatom-substituted alcohols to enable access to diverse products with pharmaceutically relevant functional groups.



*P. E. Piszel, A. Vasilopoulos, S. S. Stahl**

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Oxidative Amide Coupling from Functionally Diverse Alcohols and Amines using Aerobic Copper/Nitroxyl Catalysis