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Incorporating azaheterocycle functionality in intramolecular aerobic, copper-catalyzed aminooxygenation of alkenes†

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Despite the maturity of alkene 1,2-difunctionalization reactions involving C–N bond formation, a key limitation across aminofunctionalization methods is incompatibility with substrates bearing medically relevant N-heterocycles. Using a cooperative ligand-substrate catalyst activation strategy, we have developed an aerobic, copper-catalyzed alkene aminooxygenation method that exhibits broad tolerance for β,γ -unsaturated carbamates bearing aromatic azaheterocycle substitution. The synthetic potential of this methodology was demonstrated by engaging a densely-functionalized vonoprazan analogue and elaborating an amino oxygenated product to synthesize a heteroarylated analogue precursor of the FDA-approved antibiotic chloramphenicol.

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Introduction

Alkene 1,2-aminofunctionalization is a powerful tool for synthetic chemists, rapidly constructing useful difunctionalized building blocks and targeted scaffolds.¹ This includes such transformations as diamination,² aminooxygenation,³ amino-halogenation,⁴ carboamination,⁵ and less commonly, aminoborylation,⁶ aminocyanation,⁷ aminophosphorylation⁸ and thioamination⁹ (Fig. 1A). While diverse inter- and intramolecular aminofunctionalization methods are available to construct a host of highly functionalized products, there is a notable lack of functional group tolerance in most methods with respect to substrates bearing N-heterocyclic scaffolds. Although several aminofunctionalization methods have shown isolated examples of N-heterocycle-bearing substrates,^{6,10} a method that demonstrates broad tolerance across a range of azaheterocycles has not yet been reported in the literature. These coordinating moieties can lead to catalyst poisoning, and reactions with substrates bearing these groups are prone to undesired side reactions under the oxidizing conditions typically necessary for alkene aminofunctionalization. This means that many otherwise useful methods cannot be confidently used in medicinal chemistry endeavors due to the lack of this medically relevant functionality in substrate scopes. This is consequential as over 85% of biologically active molecules contain at least one heterocycle,¹¹ and more than 75% of FDA approved therapeutics contain a nitrogen heterocycle.¹² Heterocycle incorporation into drug targets is often associated

with more beneficial therapeutic and pharmacokinetic properties.¹³ Thus, it is essential to develop methodologies that tolerate N-heterocyclic moieties to facilitate their application in the synthesis of biologically active compounds.

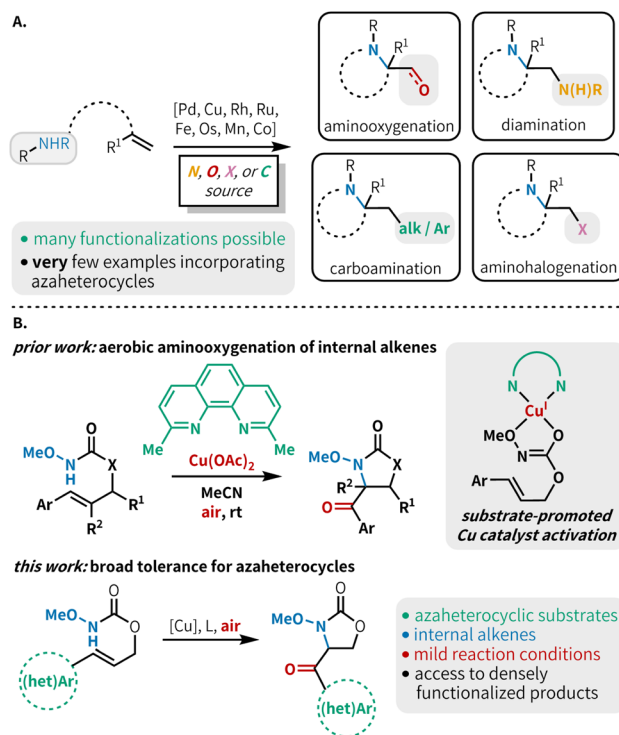


Fig. 1 (A) Overview of alkene aminofunctionalization strategies. (B) Our prior work: aminooxygenation of cinnamyl N-alkoxy carbamates featuring an atypical amidyl radical pathway. This work: alkene aminooxygenation of γ -heteroaryl- β,γ -unsaturated carbamates.

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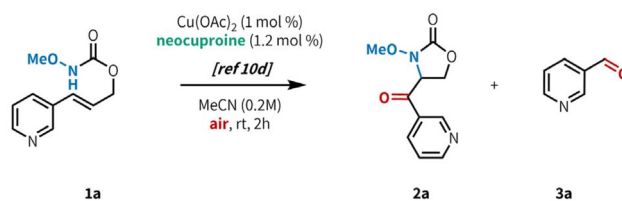
Among the many aminofunctionalization variants, alkene aminooxygenation is an excellent strategy to access 1,2-aminoalcohols and 1,2-aminocarbonyls, which are prevalent functional motifs within building blocks for the construction of bioactive compounds (Fig. 1A).¹⁴ Seminal reports detail the use of transition metal catalysts, often paired with a stoichiometric oxidant for catalyst turnover, and/or as a source of oxygen functionality.¹⁵ Recent reports have demonstrated an attractive alternative approach, using molecular oxygen to serve the dual role of oxidant and source of oxygen functionality; this approach also avoids the generation of stoichiometric byproducts and expensive reagents.^{3h,10d,16} Advantageously, aerobic aminooxygenation methods are typically mediated by earth-abundant metals such as Mn,¹⁷ Co,¹⁷ and Cu.¹⁸ Despite these notable advances in aerobic transition metal-catalyzed alkene aminooxygenation, typically monosubstituted or 1,1-disubstituted alkenes are used. Further, the incorporation of N-heteroaromatic substitution in substrates for these reactions is scarce.

Our lab recently developed an aerobic, copper-catalyzed aminooxygenation method for internal alkenes in the synthesis of 4-benzoyl-oxazolidin-2-ones from cinnamyl N-alkoxy carbamates (Fig. 1B).^{10d} This reaction occurs under mild conditions, uses low catalyst loadings, and operates under an ambient atmosphere at room temperature. Our mechanistic findings were consistent with C–N bond formation proceeding *via* an amidyl radical cyclization pathway, as opposed to the aminometallation mechanism that is commonly observed in other transition metal-catalyzed alkene aminofunctionalizations.^{3c,16a,19} This mechanistic divergence was made possible through chelation of the substrate to the copper

metal center, triggering a rapid reduction of Cu(II) to Cu(I) and subsequent generation of a potent one-electron copper oxidant. We hypothesized that the preference for O-binding of the substrate and the mild reaction conditions would allow for efficient reactivity in the presence of N-heterocyclic substituents. Herein, we report the successful implementation of this strategy through the synthesis of a variety of carbonyl-linked, heteroaryl-oxazolidin-2-ones (Fig. 1B). This method is compatible with a broad range of 5- and 6-membered N-heterocycles, including those containing multiple heteroatoms.

In our initial investigations (Table 1), we applied our previously published conditions to the reaction with 3-pyridyl substituted allyl carbamate **1a**, and found that amino-oxygenated product **2a** was formed in 54% yield (entry 1). Similar Cu sources bearing acetate counterions performed well (entries 3–4), but a slight improvement in yield was found when using CuTC (entry 4, 59%). It is worth noting that while the original conditions from our previous report worked well in this case, Cu(OAc)₂ is highly sensitive to trace impurities in the starting material. Indeed, in that report we tested several azaheterocycle-containing substrates and found them all to be unreactive under those conditions.^{10d} In contrast, CuTC is much more robust to minor impurities, giving us more consistent reactivity. Model substrate **1a** reacted well even at 1 mol% loading of CuTC (entry 5), but 5 mol% loading gave better results across a wider range of substrates (Fig. 2, see below).²⁰ Base and acid additives both hindered the reaction (entries 6–7). Further increasing catalyst loading to 20 mol% did not provide any benefit (entry 8), furnishing **2a** in a slightly diminished yield (42%). Increasing the reaction temperature (entry 9) led to decomposition of the reaction components,

Table 1 Optimization screening. Yields correspond to quantitative NMR results using 1,3,5-trimethoxybenzene as an internal standard and are an average of three runs. Reaction conditions: **1a** (0.200 mmol), Cu source (10.0–40.0 μmol), 2,9-dimethyl-1,10-phenanthroline (neocuproine) (12.0–44.0 μmol), MeCN (1.0 mL, 0.2 M), open vial, rt, 2 h. Cu(OAc)₂ = copper(II) acetate, Cu(EH)₂ = copper(II) 2-ethylhexanoate, CuTC = copper(I) thiophene-2-carboxylate, PivOH = pivalic acid



Entry	Changes to conditions	Yield 2a	Yield 3a	Recovered 1a
1	None	54%	12%	0%
2 ^a	5 mol% Cu(OAc) ₂	50%	11%	0%
3 ^a	5 mol% Cu(EH) ₂	51%	10%	0%
4 ^a	5 mol% CuTC	59%	13%	0%
5	1 mol% CuTC	59%	12%	0%
6 ^a	As in entry 4, 1 eq. K ₂ CO ₃ added	0%	3%	61%
7 ^a	As in entry 4, 1 eq. PivOH added	0%	0%	>95%
8 ^b	20 mol% CuTC	2%	10%	0%
9 ^a	5 mol% CuTC, 70 °C	3%	8%	42%
10 ^b	20 mol% CuTC, 70 °C	4%	8%	41%

^a 6 mol% of neocuproine was used. ^b 24 mol% of neocuproine was used.



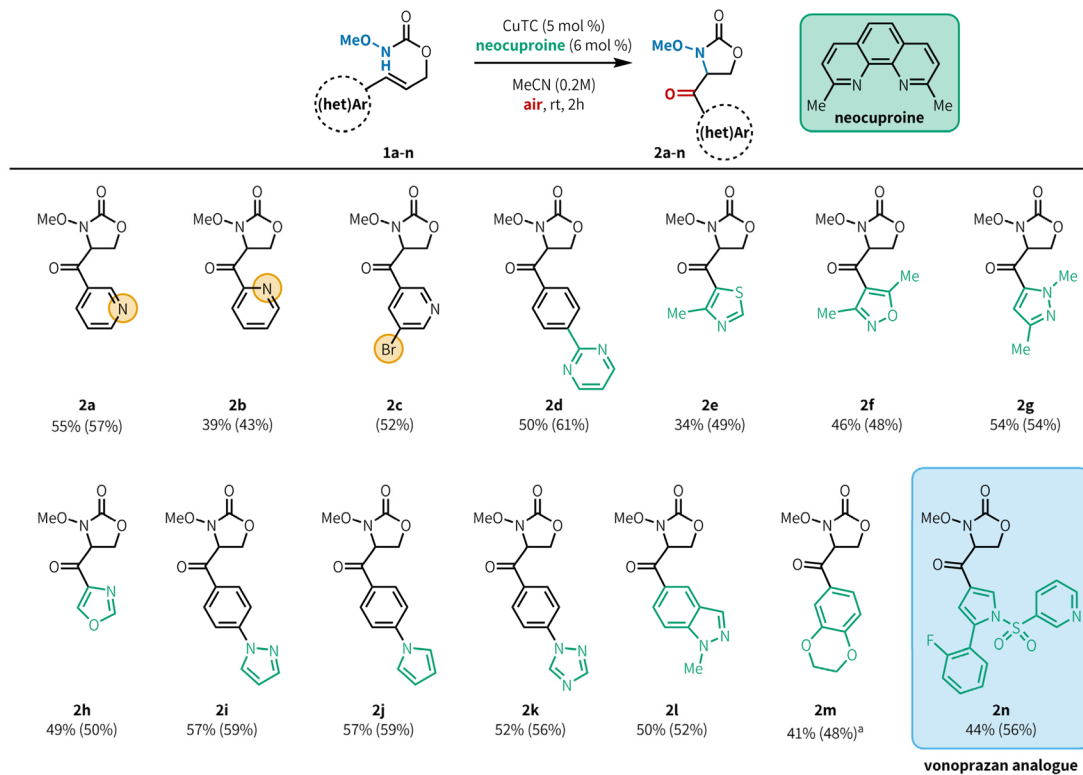


Fig. 2 Substrate scope. Yields correspond to isolated products and are averages of three runs at 0.500 mmol scale. Quantitative NMR yields in parentheses, determined using 1,3,5-trimethoxybenzene as internal standard. Reaction conditions: **1** (0.500 mmol), CuTC (25.0 μmol), neocuproine (30.0 μmol), MeCN (0.2 M), rt, 2 h, 70 °C. CuTC = copper(I) thiophene 2-carboxylate.

presumably from overoxidation. Similar results were observed when increasing both temperature and catalyst loading (entry 10). Investigation into ligand structure–reactivity relationships revealed 2,9-dimethyl-1,10-phenanthroline (neocuproine) was optimal, consistent with our previous studies.^{10d,20} Other 1,10-phenanthroline ligands bearing alkyl substitution adjacent to the nitrogen centers (*i.e.* *ortho*) showed similar results, in addition to 2,2′-bipyridyl ligands bearing 6,6′-dialkyl substitution.²⁰

With optimized conditions in hand, we evaluated the scope of heteroaryl alkenes in the reaction (Fig. 2). Model product **2a** was isolated in 55% yield at 0.500 mmol scale. The position of the pyridine nitrogen relative to the tether did not substantially impact the reaction, with 2-pyridyl substitution providing **2b** in 39% yield, and synthetically versatile bromide substituents were well tolerated (**2c**, 52%). Pyrimidines were effective as substituents on phenyl rings (**2d**, 50%), although product yields were poor when the pyrimidine was directly attached to the alkene.²⁰ This method is also compatible with a variety of 5-membered azaheterocycles, including thiazole (**2e**, 34%), isoxazole (**2f**, 46%), pyrazole (**2g**, 54%), and oxazole (**2h**, 49%). Substrates bearing arenes with heteroaromatic substitution are also effective in this reaction (**2i–2k**, 52–57%). We had previously demonstrated that protected indoles were compatible with aerobic amino-oxygenation;^{10d} under our revised conditions, the related but more challenging indazole **2l** is also a good substrate (50%). Oxygen-containing heterocycles can also be employed,^{10d}

exemplified by benzodioxine **2m** (41%), although elevated temperatures were required for efficient reaction of this substrate within 2 h. Notably, a precursor compound in the synthesis of the ulcer medication vonoprazan could be elaborated to generate analogue **1n**, which underwent the desired amino-oxygenation. Product **2n** was isolated in reasonable yield (44%) showcasing this method's tolerance for densely functionalized, drug-like substrates. Some heterocycles bearing reactive C–X bonds, such as α -halopyridines, were not compatible in the reaction. The primary limitation of this method was our ability to access the substrate; substrates containing azaheterocycles such as imidazole, pyrroles, pyrazoles, halopyrimidines, and pyrrolopyridine were incompatible with the substrate synthesis and were unable to be tested in the amino-oxygenation reaction.²⁰

To showcase the synthetic utility of our aerobic amino-oxygenation method, we synthesized a heteroaryl analogue precursor of the amphenicol antibiotics, which includes FDA-approved therapeutics chloramphenicol and thiamphenicol. Amino-oxygenation product **2i** was selected by analogy to the chloramphenicol structure (Fig. 3). Preparation of **2i** *via* aerobic amino-oxygenation scaled readily to 5.0 mmol, proceeding in identical yield to the scope investigation scale (0.500 mmol), and the reaction was performed in an open beaker (57% yield, 826 mg). Reduction with NaBH₄ fashioned alcohol **4** in 68% yield. Subsequent N–O cleavage with SmI₂ generated free carbamate **5** (57%), which underwent base mediated ring



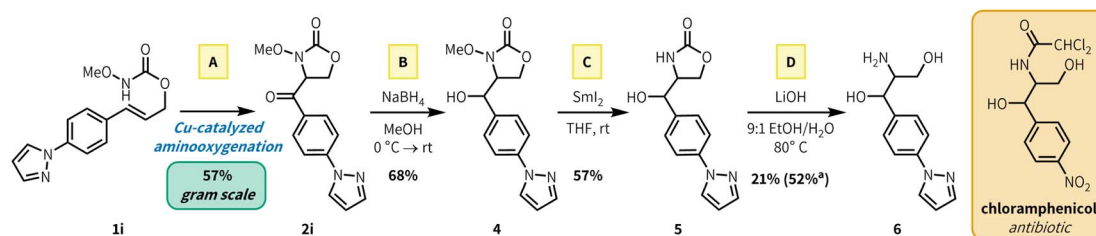


Fig. 3 Synthesis of amphenicol antibiotic analogues. Reaction conditions: (A): **1i** (1.37 g, 5.00 mmol, 1.0 equiv.) CuTC (47.7 mg, 0.250 mmol, 0.05 equiv.), neocuproine (62.5 mg, 0.300 mmol, 0.06 equiv.), MeCN (25 mL, 0.2 M), rt, open beaker, 2 h. (B): **2i** (318 mg, 1.11 mmol, 1.0 equiv.), NaBH₄ (46.0 mg, 1.1 equiv.), MeOH (0.2 M), 0 °C → rt, 1 h. (C): **4** (180 mg, 0.622 mmol, 1.0 equiv.), SmI₂ (0.1 M in THF) (50 mL, 5.0 mmol, 8.0 equiv.), THF (16 mL, 0.4 M), rt, 2 h. (D): **5** (40.0 mg, 0.154 mmol, 1.0 equiv.), LiOH·H₂O (19.4 mg, 0.462 mmol, 3.0 equiv.), 16 h.^aQNMR yield using 1,3,5-trimethoxybenzene as internal standard.

opening in 52% yield (21% isolated) to generate heteroarylated amphenicol analogue **6**. Subsequent *N*-acetylation of free amines in the presence of alcohols has been reported in previous chloramphenicol syntheses.²¹

Conclusions

By employing the catalytic strategy of substrate-promoted catalyst activation, we have developed an operationally simple, mild, and efficient approach to use *N*-heteroaryl alkene substrates in copper-catalyzed alkene aminooxygenation. This method displays broad compatibility across a diverse range of heteroaromatic groups that has not previously been demonstrated in alkene aminofunctionalization reactions. Further, the practicality and applicability of our strategy to the synthesis of drug-like compounds shows promise for its adoption in the rapid preparation of valuable α -amino-oxygenated motifs for diverse synthetic applications.

Data availability

The data supporting this article, including experimental procedures, additional reaction screening data, and full compound characterization, have been included as part of the ESI.†

Author contributions

E. M. D. and S. M. P. conceived of and designed the project. E. M. D. and N. T.-L. conducted all the experimental work, and all authors analyzed the data and discussed the results. E. M. D. and S. M. P. wrote the manuscript with support from all authors. S. M. P. directed the research.

Conflicts of interest

There are no conflicts to declare.

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