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Direct Synthesis of 2-Formylpyrrolidines, 2-Pyrrolidinones and 2-Dihydrofuranones via Aerobic Copper-Catalyzed Aminooxygenation and Dioxygenation of 4-Pentenylsulfonamides and 4-Pentenylalcohols

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Abstract

A new method for the direct conversion of 4-pentenylsulfonamides to 2-formylpyrrolidines and a 2-ketopyrrolidine has been developed. This transformation occurs via aerobic copper-catalyzed alkene aminooxygenation where molecular oxygen serves as both oxidant and oxygen source. The 2-formylpyrrolidines can further undergo oxidative carbon–carbon bond cleavage *in situ* upon addition of DABCO, providing 2-pyrrolidinones. These transformations have been demonstrated for a range of 4-pentenylsulfonamides. 4-Pentenylalcohols also undergo oxidative cyclization to form γ-lactones predominantly. The reaction is chemoselective, oxidizing one alkene in the presence of others, and is compatible with several functional groups. Application of these reactions to the formal syntheses of baclofen and (+)-monomorine was demonstrated.

Aerobic copper facilitated organic reactions provide practical solutions for the syntheses of a broad range of organic molecules and have been the subject of intensive research.[1] The range of copper oxidation states enables access to transformations that required both single and two-electron activation mechanisms. Molecular oxygen used in these reactions is often considered an ideal oxidant due to its low environmental impact and high atom economy. Significant natural abundance of copper and oxygen also make them better choices in comparison with more precious metal or organic oxidant combinations, especially when large-scale processes are involved. Unactivated alkenes are useful substrates that can be transformed via copper-catalyzed difunctionalization into a variety of *N*- and *O*-heterocycles.[2] In one of these approaches, we developed an aerobic aminooxyganation reaction leading to (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) adducts that can be subsequently converted to aldehydes (Scheme 1).[3]

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Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05680.

Experimental procedures and characterization of new compounds (PDF) NMR spectra (PDF)

Another strategy for the synthesis of *N*-heterocyclic aldehydes from alkenes includes aminohydroxylation/cyclization and subsequent oxidation of the resulting alcohol.[4] Related studies report aerobic Au- and Fe-catalyzed synthesis of oxazole aldehydes,[5] or aerobic Cu-catalyzed dehydrogenative amino-oxygenation affording nonenolizable *N*-heterocyclic aldehydes.[6] Electrochemical-chemical oxidation has also been used, producing 2-phenyl pyrrolidinyl and piperidinyl ketones from the corresponding phenyl-substituted unsaturated sulfonamides in the presence of DMSO.[7]

Herein, we disclose a direct transformation of 4-pentenyl sulfonamides into 2-formylpyrrolidines via aerobic copper catalyzed aminooxygenation. A slight modification of the reaction conditions leads to the synthesis of the corresponding γ-lactams or γ-lactones that previously were available from identical starting materials but required use of more expensive ruthenium,[8] osmium,[9] or gold catalysts.[10]

Although Cu-catalyzed alkene aminooxygenation reactions dependent on stoichiometric terminal oxidants like $PhI(OAc)_2$ or TEMPO have strong literature precedent,[11] few aerobic Cu-catalyzed aminoxygenations that use molecular oxygen as both reactant and terminal oxidant have been reported,[12] and none provide the aldehydes and lactams observed in this study (*vide infra*).

4-Pentenylsulfonamide **1a** was thus subjected to various Cu(I) and Cu(II) catalysts, ligands, additives and bases in $PhCH_3$ or $PhCF_3$ under oxygen atmosphere (1 atm, balloon) at 105–120 °C as illustrated in Table 1 (see Supporting Information for full optimization screen).

Under these conditions, varying amounts of aldehyde **2a** and lactam **3a** were formed. From this screen, we concluded that the copper source, ligand choice, and presence or absence of base have the most important impact on reactivity and selectivity. Only CuCl and CuCN enabled full conversion (Table 1, entries 5–9), but use of CuCN required longer reaction time (~40 vs ~20 h) and higher temperature (120 vs 105 °C) compared to CuCl. The higher reactivity of CuCl might be explained by it relatively lower activation energy in end-on O_2 coordination via a di-μ-chloro complex.[13] Application of CuCl as a catalyst for aerobic oxidative C–C bond cleavage in the synthesis of lactones from hemiketals has recently been demonstrated.[14] Using CuCl alone allowed formation of aldehyde **2a** as a major product (Table 1, entries 8 and 9). When CuCl or CuCN is combined with bis(oxazoline) ligand **L**, the major product is lactam **3a** (Table 1, entries 5 and 6). Surprisingly, use of other bidentate ligands lowers both reactivity and selectivity (Table 1, entries 10 and 11). High selectivity toward lactam **3a** can also be achieved by addition of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO). This can be done after the first step of the reaction, when formation of aldehyde **2a** is complete (disappearance of **1a** monitored by TLC, Table 1, entry 7). In this case, for most substrates, use of ligand is not necessary (Table 2, conditions A). Use of DABCO likely accelerates deprotonation of the aldehyde, which was shown to be the rate-determining step in a related study on Cu-catalyzed C–C oxidative cleavage of aldehydes to ketones.[15]

We employed the optimal lactam synthesis conditions (Table 1, entries 5, 7, and ligand free conditions A in Table 2) in the syntheses of several γ-lactams (Table 2).

The reaction is compatible with both aliphatic and aromatic substituents at positions 1, 2 and 3 of the 4-pentenylsulfonamides and affords the products with moderate to good yields. The reaction works for 4-chlorophenylpentenyl sulfonamide **1f**, which is an intermediate in the synthesis of baclofen, a skeletal muscle relaxant (Scheme 2).[8b] Additionally, the reaction is compatible with another alkene present in the molecule leading to chemoselective formation of lactams **3c** and **3e**. This chemoselectivity would be challenging to access via the alternative Ru-based approach. *N*-Tosyl-2-allylaniline did not provide much of the corresponding lactone under cyclization/oxidation conditions A, Table 2 (complex mixture obtained, not shown).

Using similar conditions, the method can be extended to the synthesis of γ-lactones from unsaturated alcohols (Table 3). When allylbenzene derivative **4b′** was used, the γ-lactone **5b** was obtained, which suggests isomerization of the double bond under these conditions.

We next investigated the possibility that aldehyde **2a** was an intermediates in the formation of lactam **3a**. Submitting **2a** to the reaction condition resulted in formation of **3a** (see Scheme 4, *vide infra*, for a related experiment). This observation was consistent with a reaction kinetic profile that shows initial increase of aldehyde concentration that is later consumed in the lactam formation (Figure 1).

Performing the reaction without ligand or base present is sufficient to prevent excessive lactam formation and to obtain the aldehyde in moderate to good yields (Table 1, entries 8 and 9). Ligand free conditions were tested for a variety of alkenes and proved their applicability to substrates containing another double bond (**2c** and **2e**), chloride (**2f**), thioether (**2n**), ether (**2o**, **2p**, and **2i**), nitro group (**2g**) and furan (**2r**). The selectivity and stereochemistry of the major product depend on the substitution position of the 4-pentenylsulfonamide. A single diastereomer (*cis*) was observed in the crude ^{1}H NMR spectra of 2,5-pyrrolidines (dr > 20:1) (Table 4).

Poor diastereoselectivity (up to dr = 2:1) was found for 3,5-pyrrolidines **2s** and **2f**. Moderate diastereoselectivity (dr ~ 5:1) favoring *trans* products **2t** and **2j** was observed for 3,5-pyrrolidines. These stereochemical patterns are similar to those previously reported by us for Cu-catalyzed alkene aminoxygenation/cyclization using a TEMPO/O_2 oxidative system.[16] Use of the (*R*)-(+)-2,2′-isopropylidenebis(4-phenyl-2-oxazo-line) ligand gave **2a** in a promising 25% yield and 44% ee (not shown, see Supporting Information for details). *N*-Tosyl-2-allylaniline provided aldehyde **2u** in a modest 35% yield. Transformation of an internal alkene into ketone **2v** was possible with addition of ligand **L**; however, full conversion was not achieved. In all of these reactions, the remainder of mass can be accounted for by some formation of lactam **3** (as in Table 2), some formation of the corresponding amino chloride, amino alcohol and carboamination product, and in some instances starting material (see Supporting Information for details).

This aminooxygenation was performed on gram scale (3.4 mmol) providing aldehyde **2q** in 61% yield. Aldehyde **2q** is an intermediate in the synthesis of (+)-monomorine (Scheme 2).[17] This modification reduced our previous formal synthesis of that trail pheromone by one step.[16a] We hypothesize that the reaction starts with oxidation of copper(I) to copper(II) by

O_2. Copper(II)-catalyzed alkene *cis*-aminocupration then affords an unstable organocopper(II) intermediate **II** that undergoes C–Cu homolysis to give primary radical **III** (Scheme 3).[3] The radical reacts with molecular oxygen and leads to formation of aldehyde **2a**.

Aldehyde **2a** can either be isolated or, in the presence of *in situ* formed hydroxide or external base (DABCO) is transformed into copper(II) enolate **VI**. Reaction of the enolate with molecular oxygen gives peroxy intermediate **VIII** and then **I**X.[18] Oxidative C–C bond cleavage then occurs to form lactam **3a** and carbon monoxide. The CO was detected by mass spectrometry. In addition, we performed labeling studies with oxygen-18 to detect the source of oxygen in the final products (Scheme 4). In agreement with the proposed mechanism, we observed labeled lactam **3a′** and labeled carbon monoxide. These studies do not support formation of carbon monoxide from C–C bond cleavage of the 2-formylpyrrolidine carbonyl via an acyl radical[15] but rather are consistent with a mechanism involving cyclic peroxo intermediates **VIII** and **IX**.[18]

In conclusion, we developed the first direct method of transforming 4-pentenylsulfonamides into 2-formylpyrrolidines, a reaction that can occur in high diastereoselectivity and provide useful heterocyclic intermediates. A slight change of cleavage to access the corresponding lactams and lactones. This work extends the scope of aerobic oxidative organic transformations and provides insight into further potential reaction developments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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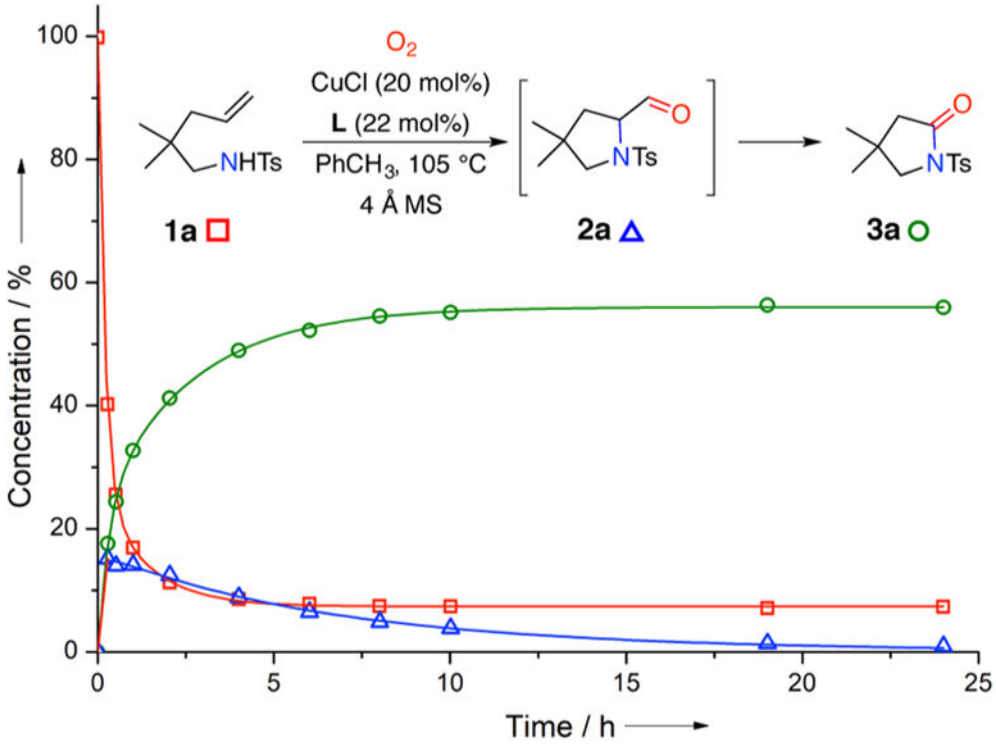
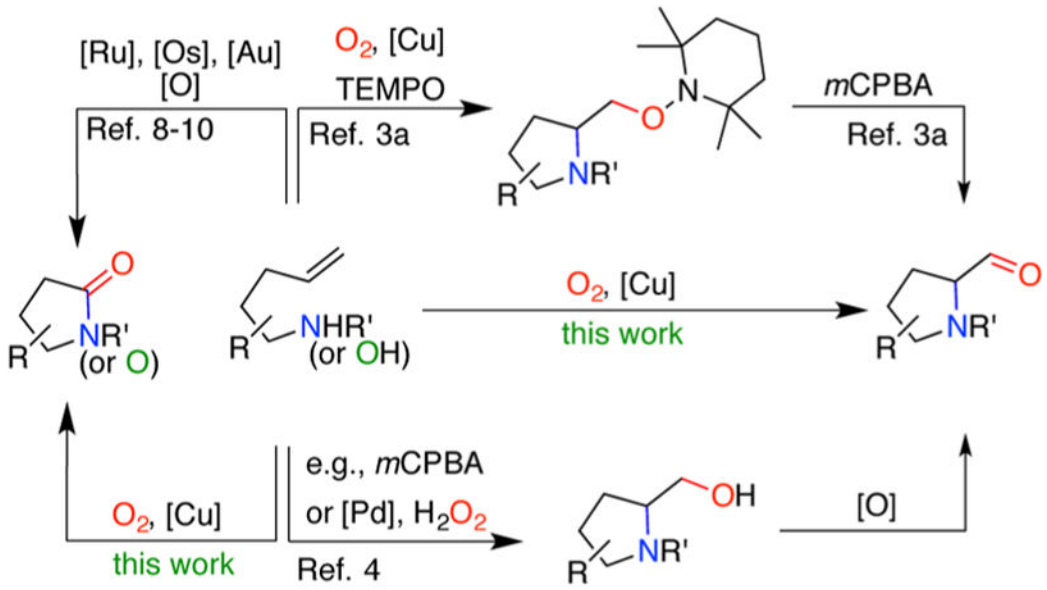
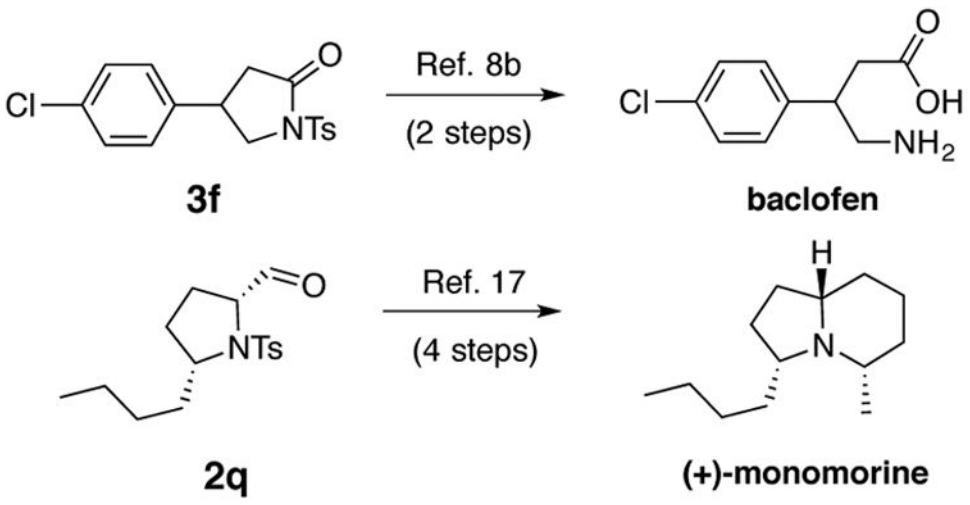


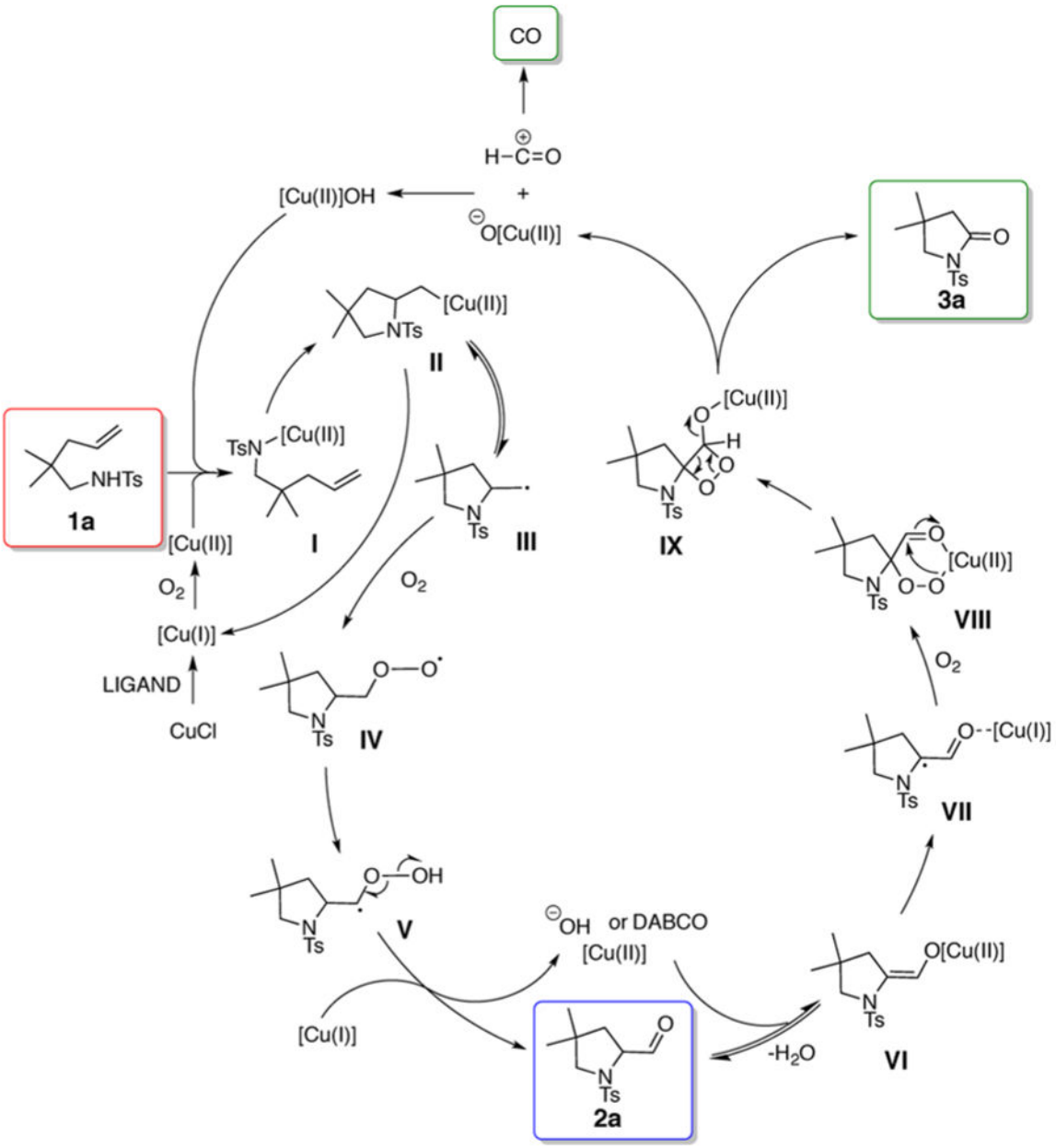
Figure 1.
Kinetic profile of aminooxygenation/oxidative C–C bond cleavage.



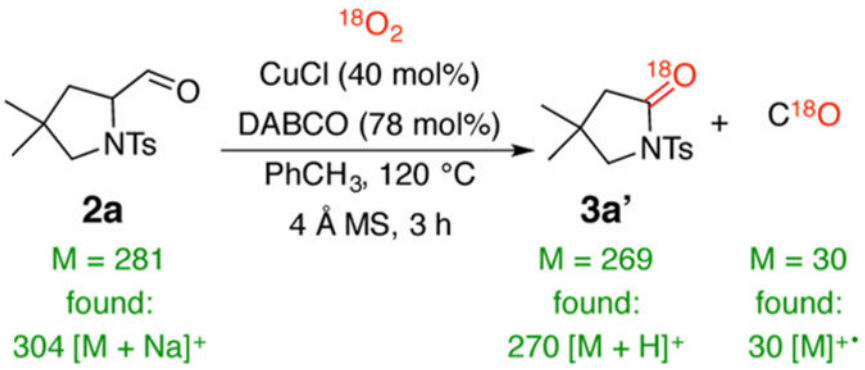
Scheme 1.
Aminooxygenation of Alkenes/Oxidative C–C Bond Cleavage



Scheme 2.
Formal Syntheses of Baclofen and (+)-Monomorine



Scheme 3.
Proposed Mechanism of Aminooxygenation/Oxidative C–C Bond Cleavage



Scheme 4.
Mechanistic Investigation

Table 1

Optimization of the Reaction Conditions

Entry	Cu salt (20 mol%)	Ligand/base	Product[a]		
			1a	2a	3a
1[b]	$Cu(OTf)_2$	Bis(oxazoline) (**L**)	57	25	18
2[b]	CuI	**L**	41	0	59
3[b]	CuBr	**L**	45	16	39
4[b]	CuCN	**L**	47	6	47
5[c]	CuCN	**L**	6	6	88 (62)
6[b]	CuCI	**L**	0	20	80
7[d]	CuCI	**L** + DABCO	9	0	91 (66)
8[b]	CuCI	–	0	77	23
9[c]	CuCI	–	0	91	9
10[e]	CuCI	1,10-phenanthroline	65	10	25
11[e]	CuCI	2,2′-bipyridine	39	22	39

[a]Relative ratio based on crude ^{1}H NMR analysis (isolated percent yield).

[b]Reaction run in $PhCH_3$ at 105 °C for ca. 20 h.

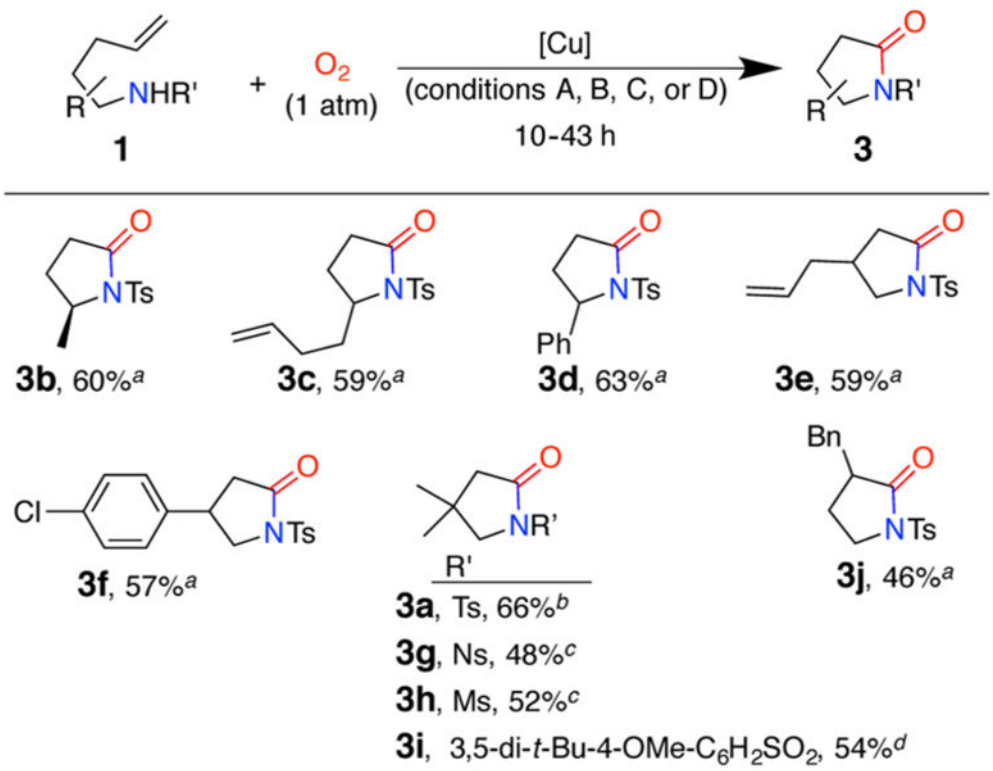
[c]Reaction run in $PhCH_3$ at 120 °C for 41 h (entry 5) and 5 h (entry 9).

[d]Reaction run in $PhCF_3$ at 120 °C for 8 h, 15 mol % of CuCl, 17 mol % of **L** and 40 mol % of DABCO (added after 5 h) were used.

[e]Reaction run in $PhCF_3$ at 105 °C for 22 h. Ligands were complexed with [Cu] for 2 h at 60 °C prior to addition of reagents.

Table 2

Reaction Scope for Synthesis of 2-Pyrrolidinones



[a]Conditions A: 1. CuCl (20 mol %), $PhCH_3$, 105 °C, 4 Å MS (reaction times 5–16 h, see Supporting Information for each reaction); 2. +DABCO (40 mol %) for 3–10 h.

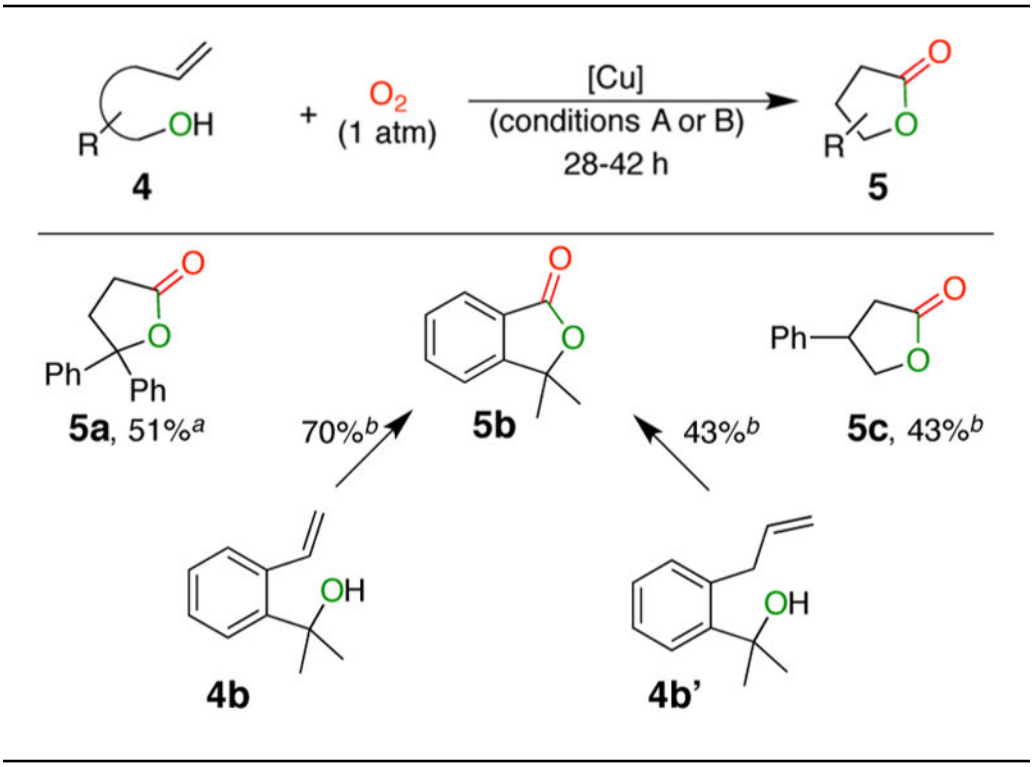
[b]Conditions B: 1. CuCl (15 mol %), **L** (17 mol %), $PhCF_3$, 120 °C, 4 Å MS for 5 h; 2. +DABCO (40 mol %) for 3 h.

[c]Conditions C: CuCN (20 mol %), **L** (22 mol %), $PhCH_3$, 120 °C, 4 Å MS for 41 h.

[d]Conditions D: 1. CuCl (20 mol %), **L** (22 mol %), $PhCF_3$, 105 °C, 4 Å MS for 17 h; 2. +DABCO (34 mol %) for 3 h. Ligands were complexed with [Cu] for 2 h.

Table 3

Reaction Scope for Synthesis of 2-Dihydrofuranones

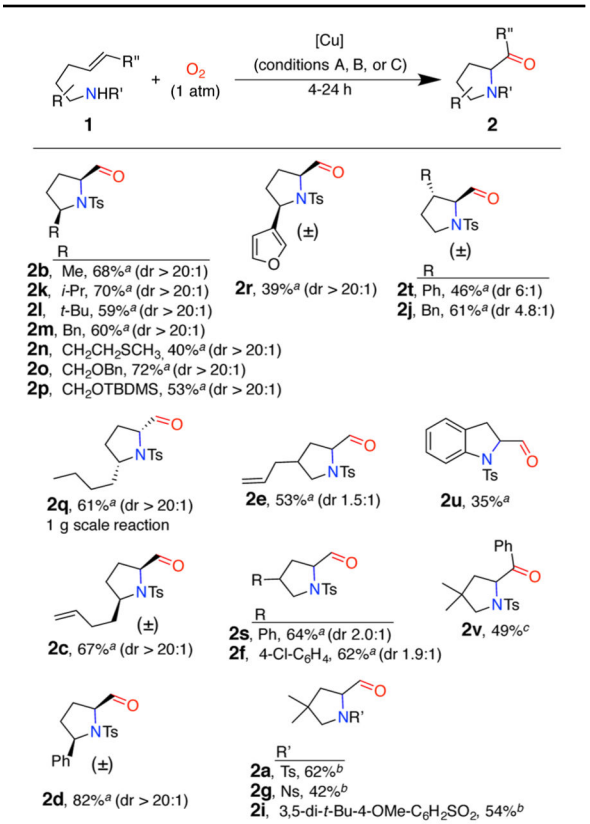


[a]Conditions A: CuCN (20 mol %), **L** (22 mol %), $PhCH_3$, 120 °C, 4 Å MS.

[b]Conditions B: CuCl (15 mol %), **L** (17 mol %), $PhCF_3$, 120 °C, 4 Å MS. See Supporting Information for individual reaction times.

Table 4

Reaction Scope for Synthesis of 2-Formylpyrrolidines and 2-Ketopyrrolidine



[a] Conditions A: CuCl (20 mol %), $PhCH_3$, 105 °C, 4 Å MS.

[b] Conditions B: CuCl (20 mol %), $PhCH_3$, 120 °C, 4 Å MS.

[c] Conditions C: CuCl (15 mol %), **L** (17 mol %), $PhCF_3$, 120 °C, 4 Å MS. See Supporting Information for individual reaction times.