Letter

Enantioselective, Aerobic Copper-Catalyzed Intramolecular Carboamination and Carboetherification of Unactivated Alkenes

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Enantioselective, Aerobic Copper-Catalyzed Intramolecular Carboamination and Carboetherification of Unactivated Alkenes

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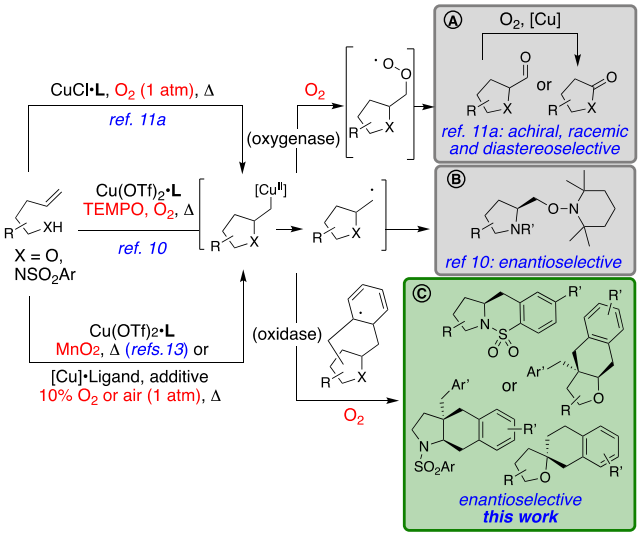
ABSTRACT: Reduction of waste is an important goal of modern organic synthesis. We report herein oxidase reactivity for enantioselective intramolecular copper-catalyzed alkene carboamination and carboetherification reactions where previously used stoichiometric MnO_2 has been replaced with oxygen. This substitution was risky as the reaction mechanism is thought to involve C–C bond formation via addition of alkyl carbon radicals to arenes. Such intermediates are also susceptible to C–O bond formation via O_2 addition. Control of absolute stereochemistry under aerobic conditions was also uncertain. The oxidative cyclization efficiencies appear to track with the ease of the radical addition to the arenes.

Oxygen is the most abundant element in the Earth's crust, and the third-most abundant element in the universe. It plays an essential role in biological processes such as cellular respiration, and is incorporated in a vast majority of biomolecules. It is also considered an ideal oxidant because of its low cost, high abundance, high atom economy, and the non-toxic character of its reaction byproducts. Consequently, much effort has been devoted to the study and understanding of aerobic processes designed by nature as well as the chemical industry.[1,2] In these processes, oxygen can act as either an oxidant that is reduced to water (oxidase-like activity), a reagent that is incorporated into the final product (oxygenase-like activity), or both.[3,4] The sustainable nature of aerobic oxidations can be further enhanced by developing catalytic reactions that rely on earth-abundant transition metals like copper.[3, 5-7]

Advances in copper-catalyzed alkene heterofunctionalization reactions that enable the synthesis of ethers and amine derivatives and that require either external oxidants or pre-oxidized reagents have been reported.[8] Stoichiometric oxidants and reagents that have been applied include MnO_2,[8a] hypervalent iodine reagents,[8b-g] Ag_2CO_3,[8d] *N*-fluorobenzenesulfonamide,[8c,h] hydroxylamines,[8i-k] diaziradinones,[8l] peroxides,[8m-o] and $K_2S_2O_8$.[8p] Several of these transformations are thought to involve carbon radical intermediates. The application of air or oxygen as stoichiometric oxidant in copper-catalyzed alkene heterofunctionalizations that do not incorporate the oxygen moiety into the product (oxidase function) are uncommon,[9] and enantioselective examples are even more rare.[10]

We recently explored aerobic copper-catalyzed oxygenase-like activity in the oxidative cyclization of alkenols and alkenyl sulfonamides.[11a] These reactions are thought to involve copper-catalyzed heterocyclization onto the alkene, homolysis of the resulting alkyl-Cu(II) bond, and oxidation of the subsequent primary radical intermediate with molecular oxygen to generate *N*-heterocyclic aldehydes, γ-lactams and γ-lactones (Scheme 1A).[11a] Copper halides, e.g. CuCl,[11a] or copper carboxylates[11b,c] are the most effective pre-catalysts reported for such transformations.



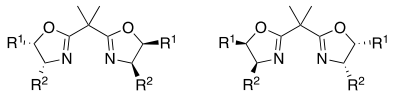
Scheme 1. Copper-catalyzed difunctionalization of alkenes

Our attempts to render our aminooxygenation reaction enantioselective using chiral bis(oxazoline) ligands (Figure 1) met with promising, yet limited success (ca. 45% ee).[11a] The poor enantioselectivity was disappointing because, prior to this oxygenase work, we had developed a highly enantioselective intramolecular aminooxygenation reaction using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as the

radical trap, [Cu(4*R*,5*S*)-Ph-Box](OTf)$_2$ as catalyst and O_2 as stoichiometric oxidant (Scheme 1B).[10] We hypothesized that TEMPO radical served as an intermediary oxidant between Cu(I) and O_2, effecting turnover to Cu(II), since the copper-catalyzed aminooxygenation worked well (at small scale) with excess TEMPO in the absence of O_2[10] and related aerobic [Cu]-catalyzed oxidative aminations are aided by catalytic TEMPO.[12]

Concurrently, we developed a series of enantioselective copper-catalyzed intramolecular carboamination and carboetherification reactions using manganese(IV) oxide (MnO_2) as stoichiometric oxidant (bottom of Scheme 1).[13] In 2007, we reported the enantioselective carboamination of alkenes towards sultams.[13a] In this reaction the primary carbon radical adds to the aromatic ring of the *N*-tosyl group and, after rearomatization, leads to a sultam. A similar concept was used in the synthesis of hexahydro-1*H*-benz[*f*]indoles.[13b] Related hexahydronaphtho[2,3-*b*]furans were obtained via doubly intramolecular carboetherication of alkenes.[13c,d] While this latter reaction was primarily explored in its racemic variant,[13c] a few examples suggested the enantioselective potential of this transformation.[13d] More recently, an enantioselective intramolecular carboetherication of 1,1-disubstituted alkenes towards spirocyclic ethers was disclosed.[13e]

In our initial investigation with the [Cu(*R,R*)-Ph-Box](OTf)$_2$ catalyzed enantioselective alkene carboamination, for the formation of chiral sultams, MnO_2 was identified as the best oxidant for optimal yield and enantioselectivity.[13a] Use of O_2 as oxidant led to very poor reactivity in this system. Related enantioselective copper-catalyzed alkene diamination reactions have also been developed where MnO_2 was also employed.[14] Interestingly, while (*t*-BuO)$_2$ was an effective oxidant for a related copper-catalyzed alkene diamination reaction, the products were racemic.[14] Additionally, use of copper(II) carboxylates as precatalyst with (*R,R*)-Ph-Box also resulted in racemic product formation in our carboamination and carboetherification reactions.[13a,13c] Thus, we conclude both the copper(I/II) counterion [OTf versus Cl or OC(O)R] and the stoichiometric oxidant [MnO_2 or O_2/TEMPO versus (*t*-BuO)$_2$] are important factors that impact product enantioselectivity. Based on our aminooxygenations involving TEMPO and O_2 (Scheme 1B), we were optimistic that if good turnover efficiency could be achieved with O_2 as sole oxidant, then under such conditions an enantioselective alkene aminofunctionalization could also be developed. However, in the absence of TEMPO, enantioselectivity with use of O2 as sole oxidant was not a foregone conclusion as it or its byproducts could potentially coordinate to the copper center and disrupt the enantioselectivity-determining step.



R^1, R^2 = H: **L1**
R^1 = H, R^2 = Ph: **L2**
R^1, R^2 = Ph: **L3**
R^1 = H, R^2 = Bn: **L4**

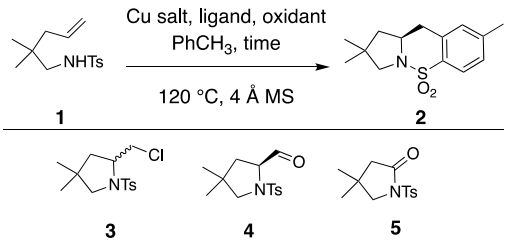
R^1, R^2 = Ph: **L5**
R^1 = H, R^2 = *t*-Bu: **L6**
R^1 = H, R^2 = *i*-Pr: **L7**

Figure 1. Bis(oxazoline) ligands used in this study

The use of stoichiometric MnO_2 as oxidant contributes negatively to the E-factor of these reactions,[15] which would be a drawback were these reactions performed on large scale. Given our recent promising results in the oxygenase-type aminooxygenations,[11a] we decided, then, to reinvestigate molecular oxygen as stoichiometric oxidant for enantioselective copper-catalyzed carboamination and carboetherification reactions (Scheme 1C).[16]

Our initial investigation into copper-catalyzed oxidase-type reactions focused on the conversion of 4-pentenylsulfonamide **1** to sultam **2**. Under O_2 (1 atm) we had previously observed that either aldehyde **4** or γ-lactam **5** could be formed preferentially using CuCl as pre-catalyst, where the preference for **4** or **5** largely depended on the presence or absence of ligand, e.g. the achiral bis(oxazoline), **L1** (Table 1, entries 1 and 2).[9a] By comparison, the reaction catalyzed by Cu(OTf)$_2$•**L1** under O_2 provided ca. 25% of **4**, 18% of **5**, 57% of substrate **1** and trace sultam **2** (Table 1, entry 3). We speculated that the amount of sultam **2** could be further enhanced by lowering the O_2 concentration from 100% to ca. 21% (air) or 10%. Lowering the O_2 concentration should kinetically disfavor the intermolecular reaction of the carbon radical intermediate with oxygen, while maintaining oxygen facilitated oxidation of copper(I) to copper(II) that is necessary for catalytic turnover. This concept was examined under a variety of conditions employing both achiral and chiral ligands (Table 1).

Table 1. Optimization for carboamination, sultam 2[a]



entry	Cu salt	L	oxidant	time (h)	products, yield (%)	ee **2** (%)
1[11a]	CuCl (20 mol%)	--	100% O_2	5	**4**: 62	n.a.
2[11a]	CuCl (20 mol%)	**L1**	100% O_2	20	**4**: 20[b]; **5**: 80[b]	n.a.
3[11a]	Cu(OTf)$_2$ (20 mol%)	**L1**	100% O_2	20	**4**: 25[b]; **5**: 18%[b]; **1**: 57%[b]; trace **2**[b]	n.a.
4	CuCl (15 mol%)	L1	10% O_2 in N_2	7	**2**: 63%	n.a.
5	CuCl (20 mol%)	**L1**	air	24	**1**[b]: 9, **2**[b]: 44, **3**: 17	n.a.
6[c]	CuCl (20 mol%)	**L1**	air	24	**2**: 50, **3**: 18	n.a.

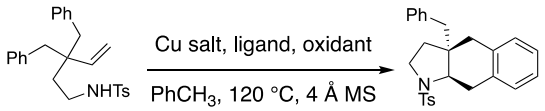
7[c]	CuCl (15 mol%)	**L1**	none	17	mostly **1**	n.a.
8[d]	CuCl (15 mol%)	**L1**	10% O_2 in N_2	7	**1**: 89, **3**: 5	n.a.
9[c]	CuCl (15 mol%)	**L2**	10% O_2 in N_2	22	**1**[b]: 49, **2**[b]: 23, **3**[b]: 8, **4**[b]: 16	29
10	$Cu(OTf)_2$ (20 mol%)	**L3**	dried air	24	**1** (no reaction)	n.a.
11	CuCl (20 mol%)	**L3**	dried air	24	**2**: 56, **3**: 18, **4**: 5	29
12[e]	CuCl (20 mol%) + AgOTf (40 mol%)	**L3**	dried air	24	**2**[b]: 27, **1**[b]: 54, **4**: 4	89

[a] Ligand (**L**) loading = 1.1 x copper salt loading. Reactions run on 0.19 mmol of **1** in $PhCH_3$ (0.1 M w/r to **1**). Yields are of isolated products unless otherwise noted. [b]Yields are estimated based on NMR ratio. [c] Solvent = $PhCF_3$ (0.1 M w/r to **1**). [d] K_2CO_3 (1 equiv) was included in the reaction. [e] 4% of the corresponding 2-hydroxymethyl-*N*-sulfonylpyrrolidine was also obtained.

Employing CuCl•**L1** as pre-catalyst,[11a] we were delighted to find we could obtain racemic sultam **2** in moderate to good yields both under air (filling headspace of a pressure tube) and 10% oxygen in nitrogen (balloon, 1 atm) atmosphere (Table 1, entries 4-6). It should be noted that at lower reaction temperatures the amount of aldehyde **4** increases (not shown). A control experiment was also performed to verify whether oxygen is necessary for reaction completion (entry 7). Post-reaction TLC indicated mostly starting material, while traces of sultam **2** and chloride **3** were also visible in the crude NMR spectrum. In addition, when the aerobic reaction was performed in the presence of K_2CO_3 (1 equiv), little conversion was observed (entry 8). It is likely K_2CO_3 impedes the reaction by sequestering the required protons for the conversion of O_2 to H_2O. Switching to the chiral ligand (*R,R*)-Ph-Box, **L2** (see Figure 1 for structure), one of the ligands optimal for the previously reported anaerobic (MnO_2 oxidant) copper-catalyzed alkene carboamination conditions[13a] resulted in poor reactivity and enantioselectivity (entry 9). Additionally, carboamination was accompanied by competitive reactions: aminochlorination **3** as well as aminooxygenation **4**. We investigated copper(II) triflate, the optimal copper source for many of the enantioselective alkene difunctionalizations we had developed under anaerobic conditions and those where TEMPO was used as co-oxidant under aerobic conditions (Scheme 1). Unfortunately, no conversion was observed even when copper(II) triflate was combined with (4*R*,5*S*)-bis-Ph-Box, **L3**, a frequently superior chiral ligand[17] with better solubility in organic solvents (entry 10). (We note that the organic soluble $Cu(CH_3CN)_4PF_6$ had demonstrated low conversion of **1** to **4** in our previous study, so it was not applied here.[11a]) After switching back to copper(I) chloride, we observed improved reactivity with **L3**, however, the enantioselectivity was still low (entry 11). We hypothesize that the chloride diminishes asymmetric induction, perhaps by serving as an extra ligand on [Cu] in the enantioselectivity-determining aminocupration step.[8a] We speculated that silver triflate could sequester chloride and therefore minimize aminochlorination **3**, and possibly increase enantioselectivity. Indeed, we found that the addition of AgOTf (40 mol%) to the carboamination reaction (Table 1, entry 12) resulted in 27% yield of sultam **2**, formed in 89% ee. The remainder of the material was primarily substrate **1** (54%). Despite the fact that only good reactivity or high enantioselectivity could be achieved for this system, the copper turnover under aerobic carboamination conditions was established.

We hypothesized that substrates that could undergo the product-forming C–C bond formation (carbon radical addition to pendant arene) more readily might display better reactivity under the aerobic conditions. The anaerobic copper-catalyzed carboamination towards fused ring *N*-heterocycles (cf. **6** → **7**) exhibited excellent yields and enantioselectivity and was compatible with a wide range of functional groups.[13b] Therefore, it was reasonable to develop an aerobic variant of the carboamination reaction for alkenes **6**. To our delight, a racemic reaction using CuCl•**L1** under air provided the product with quantitative yield (Table 2, entry 1). Following this result, a series of chiral copper complexes were tested under the same conditions. A summary of these experiments is presented in Table 2.

Table 2. Optimization of aerobic carboamination of alkenes towards fused ring *N*-heterocycles[a]



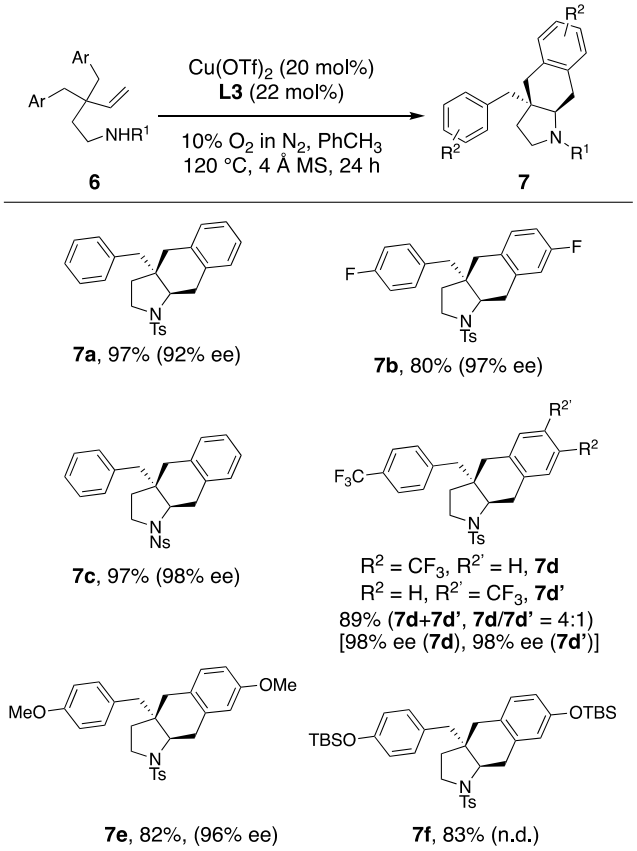
6a **7a**

entry	Cu salt	L	oxidant	yield **7a** (%)	ee (%)
1	CuCl (20 mol%)	**L1**	air	97	n.a.
2	CuCl (20 mol%)	**L4**	air	ca. 73	<5
3	CuCl (20 mol%)	**L5**	air	ca. 67	-45
4	$Cu(OTf)_2$ (20 mol%)	**L1**	air[b]	ca. 76[c]	n.a.
5	$Cu(OTf)_2$ (20 mol%)	**L2**	air[b]	68[c]	87
6	$Cu(OTf)_2$ (20 mol%)	**L3**	air[b]	97	93
7	$Cu(OTf)_2$ (20 mol%)	**L3**	10% O_2 in N_2	97	92
8	$Cu(OTf)_2$ (15 mol%)	**L3**	10% O_2 in N_2	93	95
9	$Cu(OTf)_2$ (10 mol%)	**L3**	10% O_2 in N_2	89	94

[a] Ligand (**L**) loading = 1.1 x Cu salt loading. Reactions run on 0.19 mmol of **6a** at 0.1 M. [b]Dried air. [c]Unreacted **6a** (about 25%) was also obtained.

Chiral ligands that enabled good reactivity, i.e., (*R,R*)-Bn-Box, **L4** and (4*S*,5*R*)-bis-Ph-Box, **L5**, offered no or poor enantioselectivity when combined with CuCl (entry 2 and 3). The reactivity of the catalytic system based on an achiral box ligand suffered somewhat, once chloride was replaced with triflate (97% vs. 76% yield). Surprisingly, the opposite was true for chiral ligands, where great improvement of reactivity and, particularly, enantioselectivity was observed (entries 5–9). Using **L3**, we were able to achieve the same level of yields and enantiomeric excesses as in the original MnO_2-based protocol.[13a] It is also worth mentioning that because of the increased lipophilicity of [Cu]•**L3** complex (in comparison to [Cu]•**L2**), the more expensive trifluorotoluene solvent, used in the original studies, could be replaced with less polar toluene. While running the reaction under air was convenient from the operational point of view and did not result in unwanted oxygenase-like activity (which would result in aldehydes or alcohols), performing the reaction on a larger scale could present a challenge due to the flammability risk associated with exposing toluene to oxygen at elevated temperatures.[18] To address this problem, we lowered the oxygen concentration to the level below limiting oxygen concentration for toluene in similar conditions (10% oxygen in nitrogen).[18] This change did not affect the reaction, leading to the most optimal conditions for aerobic carboamination towards fused-ring heterocycles (entry 7). We could also lower the catalyst loading from 20 to 15 mol% and even 10 mol% without diminishing selectivity and minimally diminishing efficiency (entries 8–9). The scope of this aerobic copper-catalyzed enantioselective carboamination reaction was explored as illustrated in Chart 1.

Chart 1. Reaction scope of aerobic enantioselective arboamination of *N*-(4-pentenyl)arylsulfonamides[a]

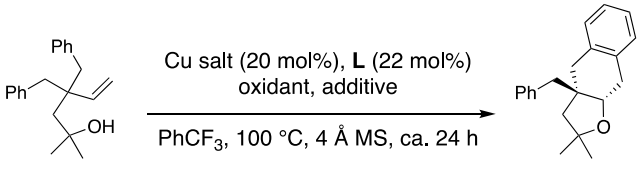


[a]Conditions from Table 2, entry 7 were used.

The reaction is compatible with both electron withdrawing and electron donating substituents on both the aromatic ring that serves as radical acceptor and the sulfonamide arene (Ts and Ns). This carboamination protocol gave yields and selectivities comparable to the conditions that previously employed MnO_2 as oxidant.[13b] Additionally, product **7f** was generated for the first time to illustrate the compatibility of synthetically useful silyl ethers in this transformation. The enantiomers of **7f** were inseparable using several chiral HPLC methods, so the % ee of **7f** was not obtained, unfortunately.

We next expanded our enantioselective aerobic copper-catalyzed investigations to intramolecular carboetherication of alkenols to access fused-ring ethers.[13c,d] Since the analogous enantioselective anaerobic (using MnO_2 oxidant) alkene carboetherifications had required (*S,S*)-*t*-Bu-Box, **L6**, for optimal enantioselectivity in our previous studies (limited to 3 examples),[13d] reaction conditions were reinvestigated for the aerobic process using alkenol **8a** (Table 3).

Table 3. Optimization of aerobic carboetherification of alkenes towards fused ring *O*-heterocycles[a]



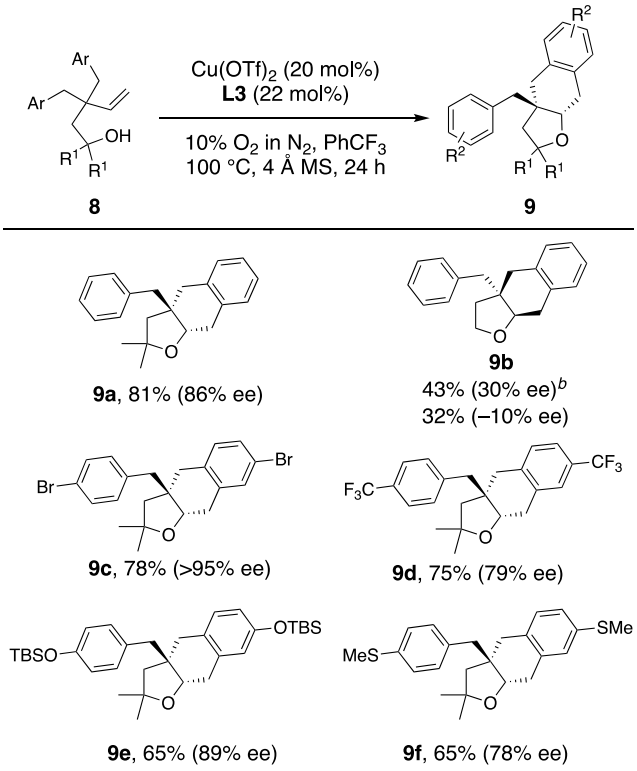
entry	Cu salt	L	oxidant	additive	yield (%)	ee (%)
1	CuCl	**L6**	air	none	32	<5
2	CuCl	**L6**	air[b]	AgOTf (40 mol%)	40	-62
3	CuCl	**L2**	air[b]	AgOTf (40 mol%)	65	90
4	CuCl	**L2**	air[b]	AgOTf (30 mol%)	70	90
5	CuCl	**L2**	air[b]	AgOTf (20 mol%)	51	89
6	CuCl	**L2**	air[b]	none	30	85
7	$Cu(OTf)_2$	**L6**	air[b]	none	30[c]	-67
8	$Cu(OTf)_2$	**L2**	air[b]	none	55	90
9	$Cu(OTf)_2$	**L3**	air[b]	none	81	87
10	$Cu(OTf)_2$	**L3**	10% O_2 in N_2	none	81	86
11[d]	$Cu(OTf)_2$	**L3**	10% O_2 in N_2	none	60	85

[a]Ligand (**L**) loading = 1.1 x Cu salt loading. Reactions run on 0.19 mmol of **8a** at 0.1 M. [b]Dried air. [c] 52% of **8a** was recovered. [d]Reaction run in toluene.

When the best ligand in the related anaerobic studies,[13d] **L6**, was combined with copper(I) chloride, a racemic mixture of **9a** was obtained (Table 3, entry 1). Addition of silver triflate dramatically improved enantioselectivity (to 62% ee, entry 2). The same level of reactivity and enantioselectivity was observed when copper(II) triflate was used (entry 7). It appears, however, that in this particular reaction, the bis(oxazoline) ligand has more effect on enantioselectivity than the copper source, as comparable values of ee (85%–90%) were obtained with CuCl (entry 6), CuCl/AgOTf (entries 3–5), and $Cu(OTf)_2$ (entry 8) when the ligand was **L2**. These data could mean that the alcohol substrate is more effective at displacing the chloride, compared to the sulfonamide. An improvement of reactivity was achieved with the more lipophilic (4*R*,5*S*)-bis-Ph-Box, **L3**, whose use resulted in 81% yield and 87% ee (entry 9). Changing the oxidant from air to 10% oxygen in nitrogen had virtually no effect on the reaction (entry 10), and it was used as a safe oxidant in studies exploring the substrate scope of this transformation (Chart 2).

Changing from a tertiary alcohol substrate, producing **9a**, to a primary alcohol substrate, producing **9b**, resulted in diminished enantioselectivity, though **L6** gave superior results to **L3** (Chart 2). The alcohol sterics were also important to the enantioselectivity in the anaerobic copper-catalyzed carboetherification variant.[13d] Both electron-donating and electron-withdrawing arene substituents were compatible, including substrates with more readily activated groups such as bromide **9c** and silyl ether **9e** (both functionalities are newly demonstrated herein for this carboetherification reaction). While the aryl substituents did impact the enantioselectivity, (±10% ee) there was no clear trend.

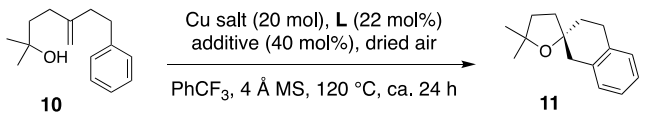
Chart 2. Reaction scope of aerobic enantioselective carboetherification of alkenols[a]



[a]Conditions: Table 3, entry 10. [b]**L6** was used.

The aerobic copper-catalyzed enantioselective synthesis of spirocyclic ethers[13e] was explored next. Aerobic spirocyclization was deemed feasible upon successful conversion of alkenol **10** to spirocycle **11** catalyzed by CuCl•**L1** (Table 4, entry 1). Re-optimization of the enantioselective carboetherification, however, was required because the conditions optimal for the fused-ring synthesis [Table 3, entry 10, use of $Cu(OTf)_2$•**L3**] did not provide any spirocycle **11**, but rather produced a hydroetherification/cyclization product (Table 4, entry 2). Application of a hindered pyridine base (1 equiv) as additive (to sequester any strong acid, e.g. HOTf) led to minimal conversion to a mixture of hydroetherification and spirocycle products (ca. 5%, Table 4, entry 3). Fortunately, changing to (*R,R*)-Ph-Box, **L2**, led to 29% isolated **11** albeit in 22% ee (Table 4, entry 4). More encouragingly, changing to (*S,S*)-*t*-Bu-Box, **L6**, provide 30% of **11** in 72% ee (Table 4, entry 5). Given the poor yields, use of the potentially more robust pre-catalyst CuCl was investigated further. While the CuCl•**L2** pre-catalyst, in the presence of AgOTf additive gave a much improved 81% yield of **11**, it was practically racemic (Table 4, entry 6). Further screening revealed that use of CuCl•**L6**/AgOTf could give spirocycle **11** in 30% isolated yield in 90% ee. Although the remainder of the mass was largely starting **10**, longer reaction time under these conditions did not lead to higher yields (Table 4, entry 10). Use of the less sterically hindered (*S,S*)-*i*-Pr-Box, **L7**, did not improve conversion either (Table 4, entry 11).

Table 4. Optimization of aerobic carboetherification of alkenol towards spirocyclic ethers[a]



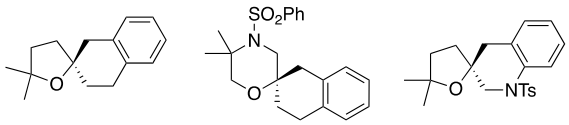
10 **11**

entry	Cu salt	L	Additive	yield (%)	ee (%)
1	CuCl	**L1**	none	22	n.a.
2	$Cu(OTf)_2$	**L3**	none	not obtained[b]	n.a.
3	$Cu(OTf)_2$	**L3**	2,6-di-*t*-Bu-4-methylpyridine	trace	n.a.
4	$Cu(OTf)_2$	**L2**	none	29	-22
5	$Cu(OTf)_2$	**L6**	none	30[c]	72
6	CuCl	**L2**	AgOTf	81	-10
7	CuCl	**L3**	AgOTf	not obtained[b]	n.a.
8	CuCl	**L6**	none	n.d.	-2
9	CuCl	**L6**	AgOTf	32	90
10[d]	CuCl	**L6**	AgOTf	33	79
11	CuCl	**L7**	AgOTf	26	70

[a]Ligand (**L**) loading = 1.1 x Cu salt loading. Reactions run on 0.19 mmol of **10** at 0.1 M. [b]A racemic hydroetherification/cyclization product (ca. 50%) was obtained. [c] 48% of starting **10** was recovered. [d] Reaction time was 48 h.

Although no conditions delivering both high reactivity and enantioselectivity were found, the conditions from Table 4, entry 9 were used for other alkenes to expand the substrate scope of the reaction (Chart 3).[13e] Aerobic carboetherication for formation of a six-membered ring is also feasible: morpholine **12** was obtained in 40% isolated yield along with 28% of the recovered starting alkenol. Bis-heterospirocycle **13** was formed in similar yield and excellent enantioselectivity.

Chart 3. Reaction scope of aerobic enantioselective spirocyclization of alkenols[a]



11, 32% (90% ee) **12**, 40% (69% ee) **13**, 42% (90% ee)

[a]Conditions: Table 4, entry 9

Extension of the methodology to intermolecular C-C bond forming reactions, such as addition of the carbon radical intermediate to styrenes,[13d] has thus far been limited by the proclivity of the radical acceptor styrenes to undergo oxidation to aldehydes and ketones under the copper-catalyzed aerobic conditions.[19] Further efforts to achieve intermolecular carboetherification under aerobic conditions are being made.

In conclusion, an aerobic protocol for copper-catalyzed enantioselective carboamination and carboetherication of alkenes has been developed. The efficiency and selectivity of the reactions vary with copper pre-catalyst, chiral ligand, and substrate structure. For fused-ring heterocycle synthesis, the reaction offers high yields and enantioselectivity and uses industrially-friendly 10% oxygen in nitrogen as an oxidant and Cu(OTf)2 as pre-catalyst.[18] This methodology can be extended towards the synthesis of sultams and spirocyclic ethers although the efficiencies of these processes are lower. For these less efficient transformations, the CuCl/AgOTf-based pre-catalyst is more effective, likely due to its higher stability in a reaction that creates water as a byproduct. Under the aerobic conditions, the copper catalyst likely becomes inactive over time, so a more stable catalyst, and substrates that react with higher rate, positively impact the efficiency of the reaction. This research adds new reactions to a growing arsenal of aerobic transformations and provides access to chiral saturated heterocycles potentially useful in medicinal chemistry endeavors.

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Notes

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ABBREVIATIONS

Ar = aryl
Bn = benzyl
ee = enantiomeric excess
HPLC = high-performance liquid chromatography
i-Pr – isopropyl
Me = methyl
MS = molecular sieves
n.d. = not determined
n.a. = not applicable
NMR = nuclear magnetic resonance
Ns = *p*-nitrobenzenesulfonyl
Ph = phenyl
TBS = *tert*-butyldimethylsilyl
t-Bu = *tert*-butyl
TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl
Tf = trifluoromethylsulfonyl
TLC = thin layer chromatography
Ts = *p*-toluenesulfonyl

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures and characterization of new compounds (PDF)

NMR spectra (PDF)

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