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Copper Catalyzed Enantioselective Intramolecular Aminooxygenation of Alkenes

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The catalytic asymmetric aminooxygenation of olefins is a very important process due to the significance of the products as building blocks in the synthesis of drugs and natural products.[1] The enantioselective *intermolecular* osmium-catalyzed aminohydroxylation developed by Sharpless and co-workers has proven to be an extremely useful method, as exemplified by its use in numerous syntheses of biologically active compounds.[2] Surprisingly, an enantioselective *intramolecular* olefin aminooxygenation, which would result in the direct synthesis of chiral nitrogen heterocycles, has not previously been reported. While regio- and diastereoselective intramolecular osmium-[3] and palladium-catalyzed[4] olefin aminooxygenation reactions have been reported, no successful ligand-based asymmetric variants have been disclosed.[5] Herein we report a novel and mechanistically distinct copper-catalyzed enantioselective intramolecular aminooxygenation of olefins.[5f] This method allows for the synthesis of chiral indolines and pyrrolidines, common components in biologically active molecules.

We recently reported an enantioselective copper-catalyzed intramolecular carboamination of olefins which results in the synthesis of chiral sultams.[6] Mechanistic analysis of the racemic, copper-promoted version of this reaction indicated the presence of a primary carbon radical species that was trapped with tetramethylaminopyridyl radical (TEMPO) in excellent yield (*cf* 1 → 2).[7] This process, signifying a net aminooxygenation reaction, inspired us to ascertain whether a catalytic enantioselective variant could be achieved.

Our study commenced by adding TEMPO (3 equiv) to the optimal catalytic enantioselective carboamination reaction conditions, which uses MnO_2 as stoichiometric oxidant (Table 1, entry 1). Upon further examination we found that TEMPO alone could be used for copper turnover [Cu(I) to Cu(II)]. As shown in Table 1, the yield and enantioselectivity both increased upon removal of additional oxidants (entry 3). A variety of other nitrogen protecting groups were also surveyed (Table 1, entries 4–6). The tosyl group proved superior to the unreactive methyl sulfonamide, benzamide and carbamate.

Our next objective was to identify an optimal ligand for asymmetric induction (Table 2). An early screen of commercially available bisoxazoline ligands revealed that the 5-phenyl substitution pattern is essential. Other aryl substituents such as 2-naphthalene,[8] as well as *cis* and *trans* 4,5-disubstituted phenyl bisoxazoline derivatives[9] were also examined. When used in slight excess, both antipodes of the 4,5-*cis*-diphenyl bisoxazoline ligand were optimal (entries 5 and 6).

The generality of the reaction was examined as shown in Table 3. *N*-Sulfonyl-2-allyl aniline substrates **1** cyclized in 57 – 97% yield providing indolines **2** in 50 – 91% ee. A variety of

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functional groups on the aniline were tolerated with the exception being a slight decrease in *ee* for the electron withdrawing nitrile **1i**.

The nature of the sulfonamide significantly effects the enantioselectivity where the tosyl was superior to the mesyl substrate **1b** (Table 1, entry 4) and the nosyl substrate **1k** (Table 3, compare entries 1,8, and 9). Worth noting, *ortho* substituted aniline derivatives (R = OMe, Cl) were unreactive.

The 4-pentenylamine substrates **3** cyclized in 74–97% yield providing pyrrolidines **4** in 75–92% ee (entries 10–16).[10] O_2 (1 atm) as a co-oxidant was necessary in order to drive these reactions to completion. The unsubstituted aliphatic substrate **3e**, nosylate **3f**, and the 1,1-disubstituted olefin substrate **5** all required higher catalyst loading in order to obtain an appreciable yield and *ee* (Table 3, entries 14–16). In the latter case, chiral tertiary amine **6** is formed in good enantioselectivity. The reaction of the nosylate **3f** (86% yield, 89% *ee*) is notable since this sulfonyl group is easier to remove than the corresponding tosylate.[11]

The absolute configuration was assigned by conversion of **2a** and **4e** to their corresponding known chiral *N*-tosyl amino alcohols (Scheme 1 and supporting information). The observed stereochemistry is consistent with a proposed transition state model where the substrate's N-substituent is *trans* to the nearest oxazoline's phenyl groups (Scheme 1).[6,12] The TEMPO adduct **4a** was converted to the aminoalcohol[13] **7** and oxidized to aldehyde[14] **8** without diminished enantioselectivity (Scheme 1). Furthermore, removal of the tosyl group followed by TEMPO reduction provided the known chiral amino alcohol **9**.[15]

This aminooxygenation method provides efficient access to a variety of chiral pyrrolidines and indolines of interest to synthetic organic and medicinal chemists. Its further optimization and application towards the syntheses of such compounds is underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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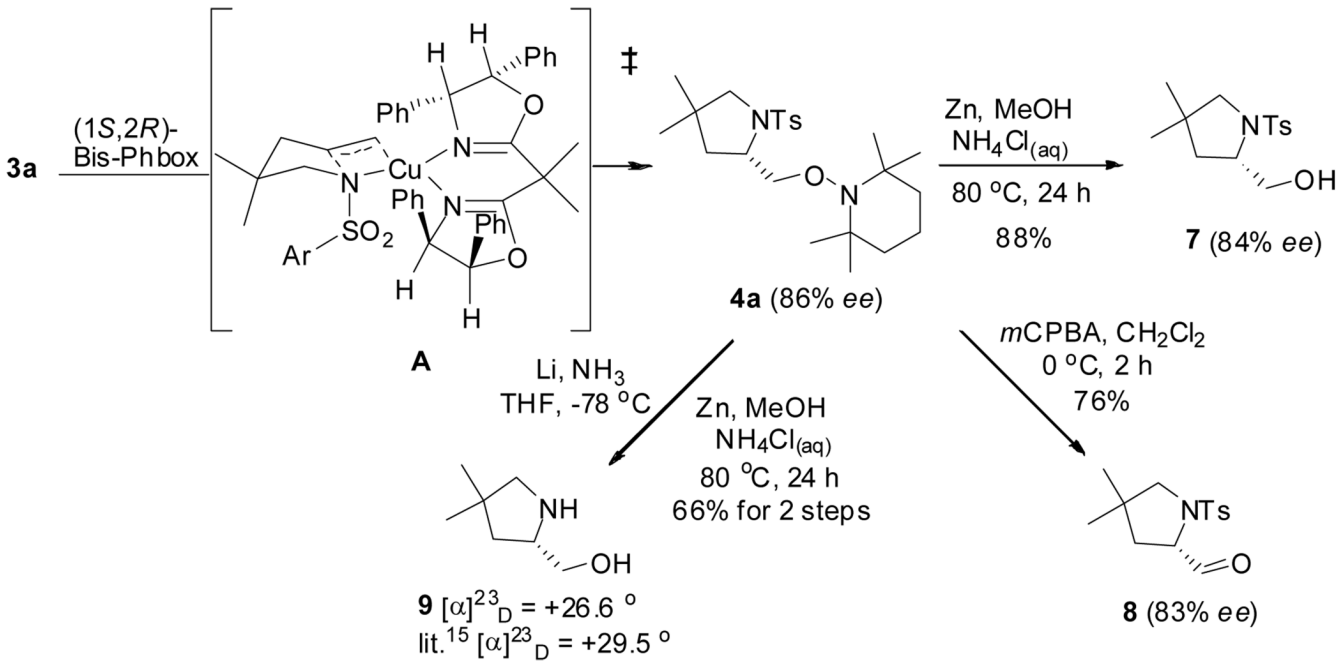
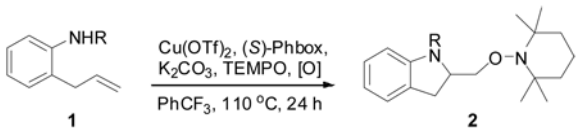


Scheme 1.
Transition state model and TEMPO functionalization

Table 1

Oxidant and *N*-substituent screen[a]



1 2

entry	R	oxidant	yield[b] (%)	%ee[c]
1	**1a**, R = Ts	MnO_2 (3 eq)	71	72
2	**1a**	O_2 (1 atm)	96	81
3	**1a**	-	97	83
4	**1b**, R = SO_2Me	-	NR	-
5	**1c**, R = Bz	-	NR	-
6	**1d**, R = Cbz	-	NR	-

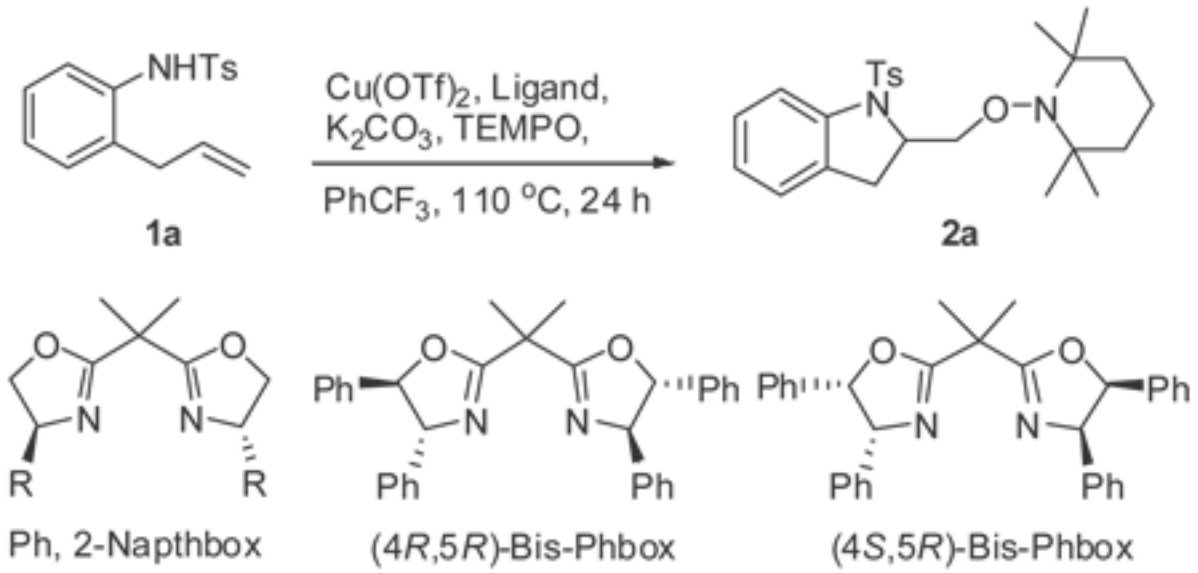
[a] Conditions: $Cu(OTf)_2$ (0.2 equiv) and ligand (0.2 equiv) were combined, dissolved in $PhCF_3$ (0.07 M w/r to 1) and heated at 50 °C for 2 h. Substrate **1** (1 equiv), oxidant, TEMPO (3 equiv) and K_2CO_3 (1 equiv) were added. The reaction was heated at 110 °C for 24 h.

[b] Yield refers to amount of isolated **2** after purification by flash chromatography on SiO_2.

[c] Enantiomeric excesses were determined by chiral HPLC analysis [Chiralcel (S,S) Whelk]. NR = No reaction.

Table 2

Chiral ligand screen[a]



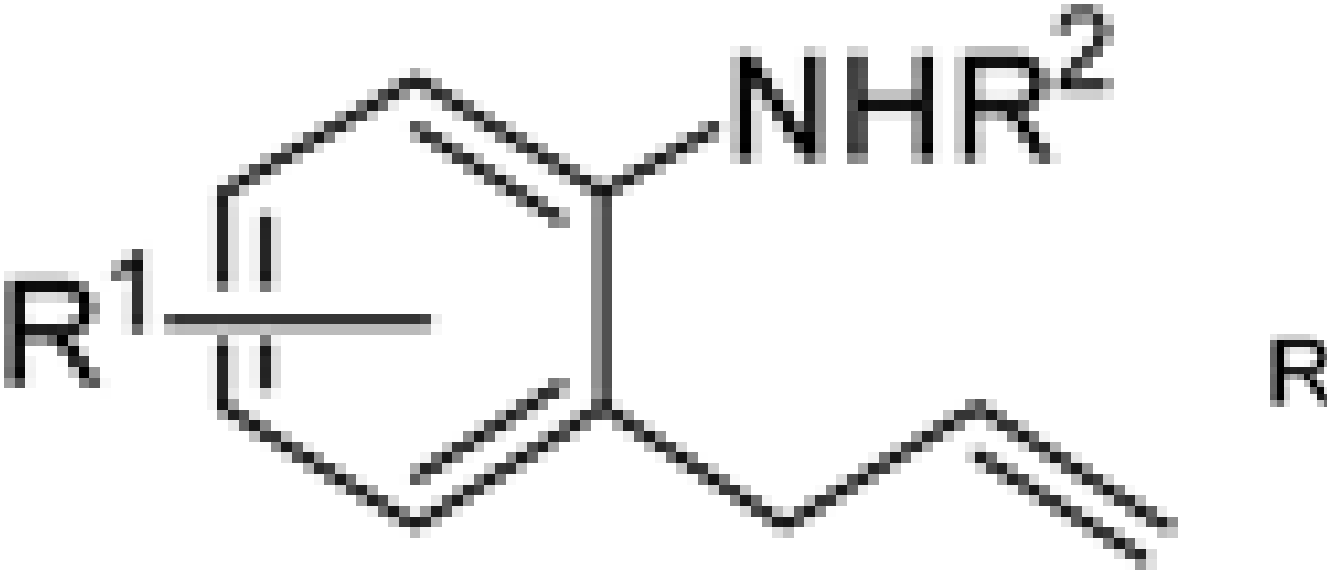
entry	ligand(equiv)	yield[b] (%)	%ee(config)[c]
1	R = (*S*,*S*)-Phbox (0.2)	97%	83% (*R*)
2	R = (*S*,*S*)-2-Napthbox (0.2)	47%	43% (*R*)
3	R = (4*R*,5*R*)-Bis-Phbox (0.2)	97%	77% (*S*)
4	R = (4*S*,5*R*)-Bis-Phbox (0.2)	97%	88% (*S*)
5	R = (4*R*,5*S*)-Bis-Phbox (0.25)	97%	84% (*R*)
6	R = (4*S*,5*R*)-Bis-Phbox (0.25)	97%	90% (*S*)

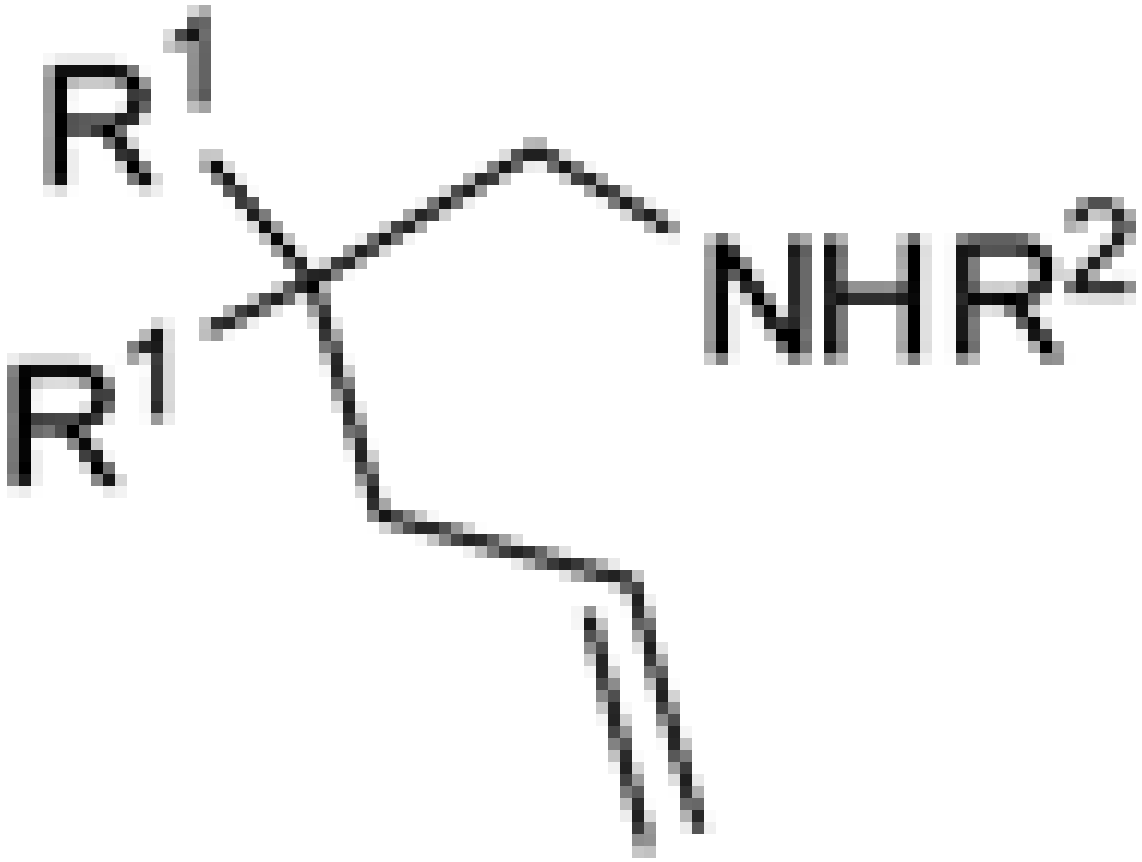
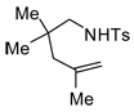
[a]Conditions: $Cu(OTf)_2$ (0.2 equiv) and ligand were combined, dissolved in $PhCF_3$ (0.07 M w/r to **1a**) and heated at 50 °C for 2 h. Substrate **1a** (1 equiv), TEMPO (3 equiv) and K_2CO_3 (1 equiv) were added. The reaction was heated at 110 °C for 24 h.

[b,c]Same as Table 1.

Table 3

Scope of Enantioselective Aminooxygenation with (1*S*,2*R*)-Bis-Phbox ligand[a]

entry	substrate
	
1	**1a**, R^1 = H, R^2 = Ts
2	**1e**, R^1 = *p*-F, R^2 = Ts
3	**1f**, R^1 = *p*-Cl, R^2 = Ts
4	**1g**, R^1 = *p*-OMe, R^2 = Ts
5	**1h**, R^1 = *p*-Me, R^2 = Ts
6	**1i**, R^1 = *p*-CN, R^2 = Ts
7	**1j**, R^1 = *m*-OMe, R^2 = Ts
8	**1k**, R^1 = H, R^2 = Ns
9	**1b**, R^1 = H, R^2 = Ms

entry	substrate
	
10[b]	**3a**, R^1 = Me, R^2 = Ts
11[b]	**3b**, R^1 = Ph, R^2 = Ts
12[b]	**3c**, R^1 = $-CH_2O(Si(tBu)_2)OCH_2-$, R^2 = Ts
13[b]	**3d**, R^1 = $-CH_2O(CH_3)_2OCH_2-$, R^2 = Ts
14[c]	**3e**, R^1 = H, R^2 = Ts
15[c]	**3f**, R^1 = Me, R^2 = Ns
	
16[c]	**5**

[a] Conditions: $Cu(OTf)_2$ (0.2 equiv) and ligand (0.25 equiv) were combined, dissolved in $PhCF_3$ (0.07 M w/r to substrate) and heated at 50 °C for 2 h. Substrate (1 equiv), TEMPO (3 equiv) and K_2CO_3 (1 equiv) were added. The reaction was heated at 110 °C for 24 h.

[b] Reaction was run at 120 °C under O_2 (1 atm).

[c] 0.4 equiv of $Cu(OTf)_2$ and 0.5 equiv of ligand were used.

[d] Yield refers to amount of isolated product after purification by flash chromatography on SiO_2.

[e] Enantiomeric excess were determined by chiral HPLC analysis. Each reaction was run at least 2 times.

[f] A range of 86–90% *ee* was obtained.