Mechanistic Analysis and Optimization of the Copper-Catalyzed Enantioselective Intramolecular Alkene Aminooxygenation

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S *Supporting Information*

ABSTRACT: The catalytic asymmetric aminooxygenation of alkenes provides an efficient and straightforward approach to prepare chiral vicinal amino alcohols. We have reported a copper(II)-catalyzed enantioselective intramolecular alkene aminooxygenation, using (2,2,6,6-tetramethylpiperidin-1-yl)-oxyl (TEMPO) as the oxygen source, which results in the synthesis of chiral indolines and pyrrolidines. Herein we disclose that kinetics studies indicate the reaction is first order both in substrate and the $[Cu(R,R)$-Ph-bis(oxazoline)]OTf$_2$ catalyst and zero order in TEMPO. Furthermore, kinetic isotope effect studies support that the *cis*-aminocupration step, the addition of N—Cu across the alkene, is the rate-limiting step. Subsequent formation of a carbon radical intermediate and direct carbon radical trapping with TEMPO is the indicated mechanism for the C—O bond formation as suggested by a deuterium labeling experiment. A ligand screen revealed that C(4)-phenyl substitution on the bis(oxazoline) is optimal for high asymmetric induction. The size of the substrate's *N*-sulfonyl group also influences the enantioselectivity of the reaction. The preparative-scale catalytic aminooxygenation reaction (gram scale) was demonstrated, and an unexpected dependence on reaction temperature was uncovered on the larger scale reaction.
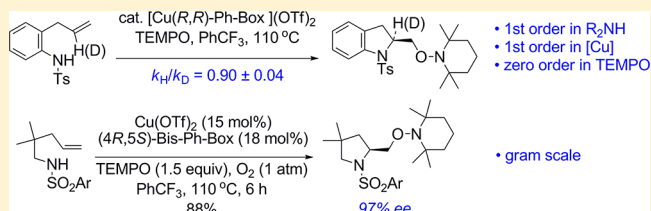
INTRODUCTION

The catalytic asymmetric aminooxygenation of alkenes provides straightforward access to chiral vicinal amino alcohols, which are valuable intermediates used in the synthesis of catalysts and ligands as well as biologically active molecules.[1] Sharpless and co-workers reported the first catalytic enantioselective *inter-molecular* aminohydroxylation, catalyzed by osmium, which has proven to be an extremely useful method, as exemplified by its use in numerous syntheses of biologically active compounds.[2] More recently, Yoon and co-workers have developed copper-[3] and iron-catalyzed[4] protocols for the enantioselective inter-molecular aminooxygenation of styrenes and dienes as less expensive and less toxic transition-metal-catalyst alternatives. Enantioselective aminooxygenation of α,β-unsaturated aldehydes catalyzed by chiral pyrrolidines has also been reported recently.[5] The development of catalytic enantioselective *intramolecular* alkene aminooxygenation protocols, however, has been more rare.

A number of regio- and diastereoselective intramolecular transition-metal-[6−11] and nonmetal-promoted[12] olefin amino-oxygenation reactions have been reported over the years. In 2008, our group reported the first catalytic enantioselective intramolecular alkene aminooxygenation.[10a,b] Our method makes use of (2,2,6,6-tetramethylpiperdin-1-yl)oxyl (TEMPO) as both the oxidant and oxygen source. A preliminary report of a new enantioselective copper-catalyzed reaction that uses PhI(OAc)$_2$ as both the stoichiometric oxidant and oxygen source has since appeared.[11b] A stoichiometric chiral hypervalent iodine-promoted aminooxygenation reaction has also been reported.[12g] Our copper-catalyzed amino-oxygenation reaction provides direct access to 2-(hydroxy-methyl)indoline and pyrrolidine derivatives with very good levels of enantioselectivity (eqs 1 and 2). We have subsequently
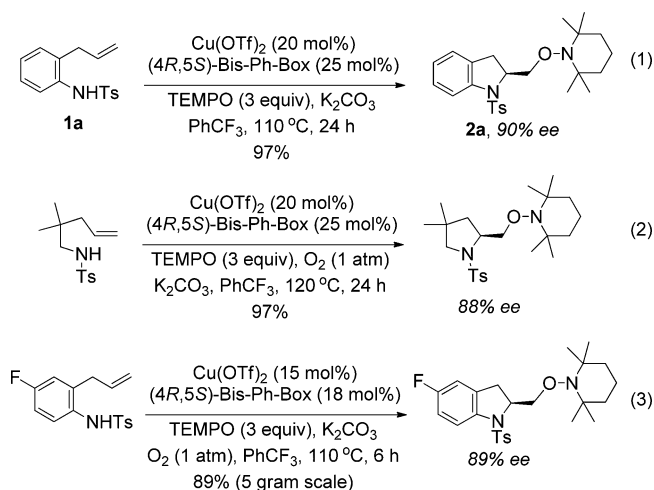
demonstrated that the chiral indoline-forming reaction could be further optimized for catalyst loading and conducted on a multigram scale (eq 3).[10b] We found, however, that we were not immediately able to scale-up the pyrrolidine-forming reaction (eq 2) using our published method[10a] and the lessons we had learned in the indoline synthesis scale-up study (eq

3).[10b] Herein we report our successful optimization and scale-up of the chiral pyrrolidine-forming aminooxygenation reaction, which draws on knowledge we gleaned during a detailed mechanistic analysis of the enantioselective reaction. We report herein a mechanistic analysis of the enantioselective reaction using kinetics, kinetic isotope effects, and isotopic labeling experiments.

■ RESULTS AND DISCUSSION

Experimental Mechanistic Study. *Reaction Kinetics.* Our previously reported copper(II)-catalyzed enantioselective intramolecular alkene aminooxygenation conditions involved use of a slight excess of the (4R,5S)-Bis-Ph-Box ligand and K_2CO_3 as base (Table 1, entry 1).[10a] We reexamined the reaction

Table 1. Conditions for Reaction Kinetics Optimization[a]
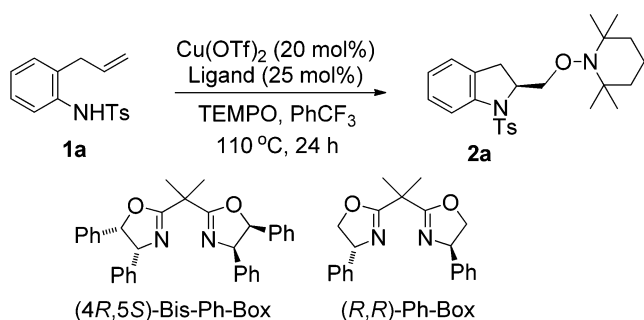
entry	ligand	base	yield[b] (%)	ee[c] (%)
1	(4R,5S)-Bis-Ph-Box	K_2CO_3	97	90
2	(R,R)-Ph-Box	K_2CO_3	90	88
3	(R,R)-Ph-Box	NBu_4OAc	98	<5
4	(R,R)-Ph-Box	2,6-di-*tert*-butyl-4-methyl-pyridine	75	87
5	(R,R)-Ph-Box		87	88
6[d]	(R,R)-Ph-Box		88	87

[a]$Cu(OTf)_2$ (20 mol %), (R,R)-Ph-Box (25 mol %) and $PhCF_3$ (0.07 M w/r to **1a**) were combined in a pressure tube and heated to 60 °C for 2 h. Substrate **1a** (1 equiv, 0.139 mmol), TEMPO (3 equiv), and K_2CO_3 (1 equiv) were added. The reaction mixture was heated to 110 °C for 24 h. [b]Yield (%) refers to amount of isolated **2a** after purification by flash chromatography on SiO_2. [c]Enantiomeric excesses were determined by chiral HPLC analysis. [d]The reaction was run using 20 mol % of (R,R)-Ph-Box. OTf = trifluoromethanesulfonyl.

conditions to identify an optimal protocol for reaction kinetics. Because of the low solubility of K_2CO_3 in CF_3Ph, we needed to find an alternative base to enable optimal reaction kinetics studies. We also reexamined use of the commercially available (R,R)-Ph-Box ligand for further protocol simplification. Gratifyingly, we found that the use of the (R,R)-Ph-Box ligand gave us comparable yield and enantioselectivity (Table 1, entry 2). In screening soluble bases, we found that use of NBu_4OAc gave high yield but no enantioselectivity (<5%, Table 1, entry 3). This base was previously used in our study of the reaction kinetics of the copper(II) 2-ethylhexanoate promoted intramolecular alkene aminooxygenation reaction.[13] Use of 2,6-di-*tert*-butyl-4-methylpyridine as base provided the indoline **2a** in 87% ee and 75% yield (Table 1, entry 4). We next ran the reaction in the absence of additional base and found that sulfonamide **1a** cyclized efficiently to form **2a** in 87% yield and 88% ee (entry 5). We also found that the reaction proceeds

efficiently without using a slight excess of the (R,R)-Ph-Box ligand, relative to $Cu(OTf)_2$ (Table 1, entry 6). We hypothesized that $[(R,R)\text{-Ph-Box}]Cu](OTf)_2$ is the active catalyst species in the aminooxygenation reaction; thus, in order to keep an accurate 1:1 ratio between the Cu and the (R,R)-Ph-Box ligand we ran the kinetics experiments using the reaction conditions in Table 1, entry 6. Small-scale reactions with 2-allylaniline derived substrates such as **1a** [<70 mg (ca. 0.240 mmol) **1a**] do not require the use of O_2 for copper turnover; the soluble TEMPO radical serves both as copper oxidant and oxygen atom source (vide infra). This simplified our kinetics study by reducing a reagent (O_2) to monitor. On larger scale and with less reactive substrates, O_2 (1 atm), is necessary for copper turnover as the reactions do not go to completion without it.[10a,b]

Kinetic Order of the Reaction. We determined the kinetic order of the aminooxygenation reaction by monitoring the disappearance of substrate **1a** using high performance liquid chromatography (see the Experimental Section for details). The kinetic order of substrate **1a** was established under pseudo-first-order conditions (excess TEMPO). Loss of **1a** showed a linear decrease of the natural logarithm of its concentration with time, indicating first-order rate dependence (Figure 1).
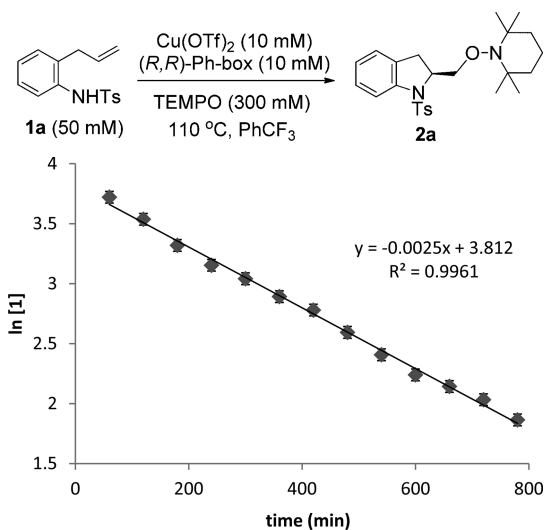
Figure 1. Plot of ln[**1a**] (mM) versus time (min) showing first-order kinetics in substrate **1a**.

After we established the order in substrate **1a**, we determined the dependence in the catalyst (Cu−L) and TEMPO concentration. We obtained the observed rate constant, k_{obs} from plots of ln[**1a**] against time at varying catalyst (2.5−20.4 mM) and TEMPO (150 and 300 mM) concentrations. We found that at constant Cu−L concentration, no significant change in k_{obs} was observed when the TEMPO concentration was doubled (see the Experimental Section for the kinetic data). Thus, we concluded that the aminooxygenation reaction has zero order kinetic dependence in TEMPO.

To determine the order in catalyst, we plotted $ln(k_{obs})$ against $ln[Cu−L]$ (Figure 2). The plot gave a linear relationship with slope equal to the order of the catalyst, which is found to be 0.99 ± 0.02, consistent with first-order kinetic behavior. In these experiments, reactions were run up to 80−90% conversion for higher catalyst loadings (20−40 mol % or 10−20 mM). We observed that at low catalyst loadings (5−
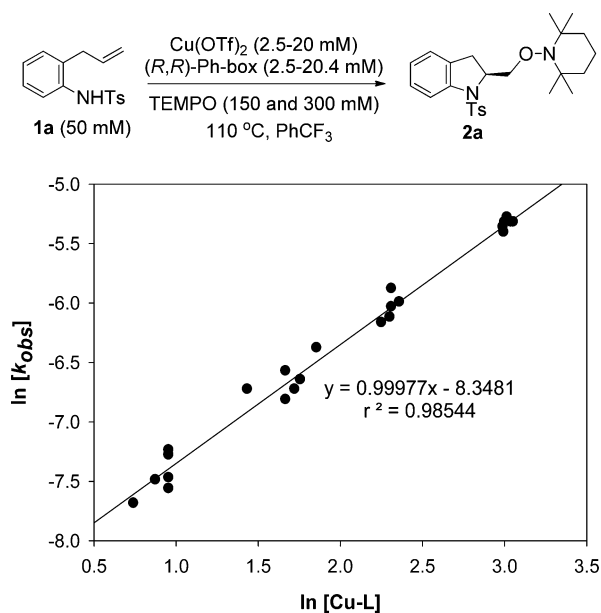
Figure 2. Plot of $\ln(k_{obs})$ against $\ln[Cu-L]$ showing first-order dependence on the catalyst concentration. The order in Cu−L was obtained from the slope of the plot, 0.99 ± 0.02.

10 mol % or 2.5−5 mM) the reaction tails off at 40−60% conversion, presumably due to catalyst decomposition, therefore, initial reaction rates were measured for these catalyst loadings (see the Supporting Information for details).

On the basis of the observed rate law ($-d[\mathbf{1a}]/dt = k_{obs}[\mathbf{1a}][Cu-L]$), we proposed the catalytic cycle shown in Scheme 1. The $[(R,R)\text{-Ph-Box})Cu](OTf)_2$ complex is the

proposed active catalyst species that coordinates with substrate **1a** to form the nitrogen−copper(II) intermediate **3**. The existence of an analogous $R_2N-Cu(II)$ intermediate has been previously supported by electron paramagnetic resonance spectroscopy (EPR)[13a] and is reasonably invoked in this reaction mechanism as a heteroatom such as R_2NH should readily displace a triflate anion from a copper(II) complex. It is noteworthy that the TEMPO anion [the result of the reoxidation of copper(I)] or trace TEMPOH[14] from excess TEMPO can also serve as a base to sequester the triflic acid formed during substrate-catalyst complexation (hence the realization that K_2CO_3 is not always necessary). This complex then undergoes *cis*-aminocupration via transition state **A** to give rise to the alkylorganocopper(II) species **4**. In the proposed transition state **A**, the substrate's N-substituent is *trans* to the nearest phenyl group of the oxazoline. This proposed transition state is consistent with the observed first-order dependence on both substrate **1a** and catalyst. The *cis*-aminocupration mechanism for this catalytic reaction is further invoked in analogy to that of the copper(II)-carboxylate promoted aminooxygenation that gives similar diastereoselectivity trends in 2,5-disubstituted pyrrolidine-forming reactions.[10c,d,13] The alkyl organocopper(II) species **4** readily homolyzes to provide the carbon radical intermediate **5**, giving off copper(I). The carbon radical species is quickly trapped by TEMPO to form the enantiomerically enriched aminooxygenation product **2a**. Copper(I) is then reoxidized by TEMPO to form the reactive copper(II) species and complete the catalytic cycle.

Kinetic Isotope Effects (KIE). For the rate-limiting step analysis, we investigated primary and secondary kinetic isotope effects (k_H/k_D). We determined the primary kinetic isotope effect by treating substrates **1a** and **1a-1-[D]** with our catalytic

Scheme 1. Proposed Mechanism for the Copper(Ii)-Catalyzed Enantioselective Intramolecular Aminooxygenation of Alkenes
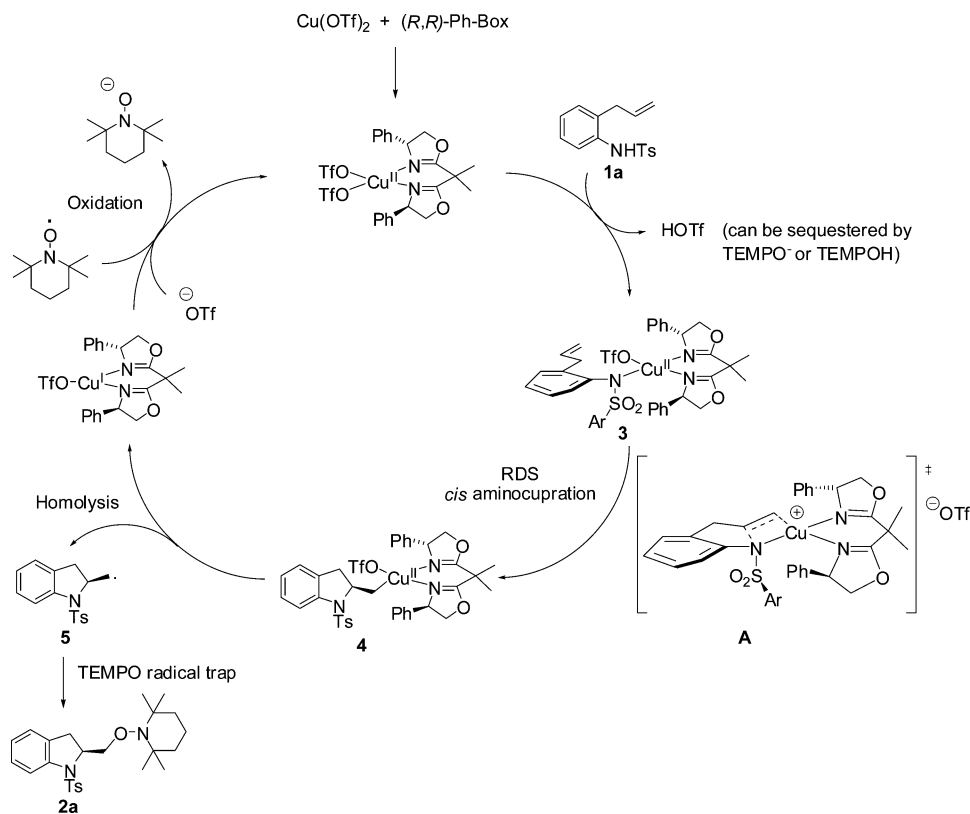
reaction conditions and comparing the rate constants of each reaction (see the Supporting Information for details). The primary kinetic isotope effect that was observed ($k_H/k_D = 0.96 \pm 0.2$) is not significant compared to the maximum theoretical KIE of 8.5 based on ν_{NH} of 3100 cm^{-1} (25 °C) (eqs 4 and 5).[15,16] This result implies that the amine deprotonation in the conversion of **1a** to **3**, Scheme 1, is not rate-limiting.


$$k_H/k_D = 0.96 \pm 0.2$$
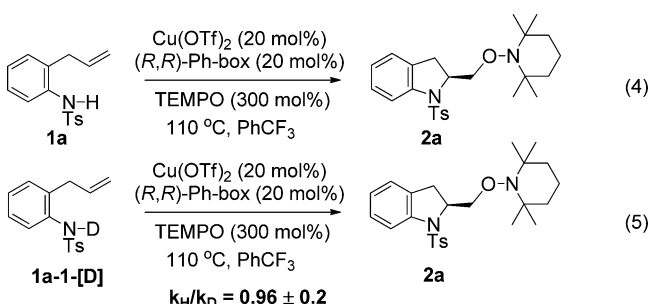
We determined the secondary kinetic isotope effect by subjecting a mixture of substrates **1a** and alkene labeled **1a-2-[D]** to the catalytic conditions under partial conversion and by analyzing the isotopic ratio before and after the reaction (see the Supporting Information for details). An inverse secondary kinetic isotope effect was observed ($k_H/k_D = 0.90 \pm 0.04$) (eq 6).[17] An inverse secondary kinetic isotope effect is consistent

$$k_H/k_D = 0.90 \pm 0.04$$
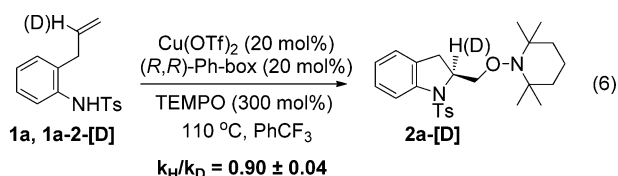
with a change from C(sp^2) to C(sp^3) in the rate-determining step of a reaction.[17] This result is consistent with the inverse kinetic isotope effect we observed in the analogous copper(II) carboxylate promoted intramolecular aminooxygenation of **1a** ($k_H/k_D = 0.90 \pm 0.03$).[13] These studies support the *cis*-aminocupration step as the enantioselectivity-determining step of the reaction.

Mechanism for C−O Bond Formation. When we treated the deuterioalkene **6-[D]** with the catalytic aminooxygenation reaction conditions under partial conversion, 79% of the 1:1 mixture of diastereomers of the aminooxygenation product **7-[D]** and 15% of the starting alkene with retained alkene geometry were isolated (eq 7). Based on these observations, we

1:1 mixture of diastereomers
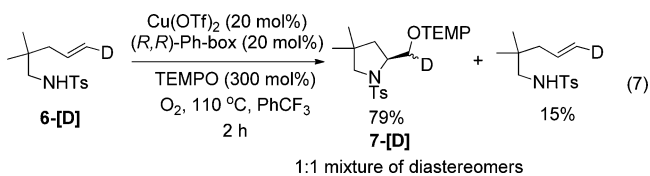
concluded that the reaction most likely proceeds via direct capture of an sp^2-hybridized carbon radical intermediate with TEMPO[18−21] (Scheme 1). The complete retention of the geometry of the isolated alkene indicates that the N−C bond formation is not reversible after C−Cu homolysis in this reaction. It is interesting to note that TEMPO completely outcompetes O$_2$ as the carbon radical trapping agent in this reaction. Similar relative reactivity, however, has been previously observed in reactions of carbon radicals generated

from organomercury hydrides.[19] It would have been difficult to predict the observed relative reactivity using independently determined rate constants reported for the reaction of carbon radicals with TEMPO and O$_2$, respectively.[18b,c] It is likely the concentration of O$_2$ at 110 °C in PhCF$_3$ is very low, contributing to the result.

Based on these labeling studies, we were also able to eliminate other mechanistic alternatives such as the potential formation of alkyl copper(III) complex via oxidation of an alkyl copper(II) with TEMPO followed by reductive elimination. Concerted reaction processes were also ruled out as possible mechanisms for this transformation. For example, a TEMPO-coordinated copper complex could facilitate a concerted two-electron electrophilic addition[22,23] and cyclization of the sulfonamide amine to the alkene, forming an alkylcopper(III) intermediate which could subsequently undergo reductive elimination. Alternatively, an oxoammonium ion [O=NR$_2$]$^+$ formed from oxidation of TEMPO by Cu^{II} could also initiate a concerted electrophilic addition/cyclization mechanism. In these other mechanistic possibilities, however, one diastereomer of **7-[D]** would be expected.

Effect of Ligand Substituent on Enantioselectivity. The effect of the ligand substituents on the reaction enantioselectivity was next examined. An early screen of the bis(oxazoline) ligands revealed that *cis*-diphenyl substitutions on the 4- and 5-positions gave optimal ee.[10a,b] We found that commercially available ligands with alkyl substituents [e.g., (S,S)-*t*-Bu-Box, (S,S)-*i*Pr-Box, and (R,R)-Bn-Box] were less reactive and gave lower enantioselectivity (Table 2, entries 1−3). We also investigated the effect of adding a substituent on the phenyl group of the bis(oxazoline). Electron-donating groups such as -OMe on the 4-position of the phenyl ring gave comparable yield and % ee to the parent phenyl substituent (Table 2, compare entry 4 to entry 9), while electron-withdrawing groups (i.e., −CF$_3$) gave a slightly lower yield and a significant decrease in % ee (entry 5). 3,5-Dimethylphenyl substitution rendered the catalyst much less reactive as seen by the lower yield, and the selectivity was also diminished (entry 6). 4-*tert*-Butylphenyl substitution, however, gave comparable yield and % ee (entry 7).

We further optimized the reaction with the optimal ligand as shown in Table 2, entries 8−14. When the copper and ligand [(4R,5S)-Bis-Ph-Box] loadings were further lowered to 15 and 18 mol %, respectively, the starting alkene **1a** was recovered (entry 12). However, in the presence of O$_2$ the reaction goes to completion (Table 2, entries 8, 13, and 14). Advances in transition-metal-catalyzed reactions that use O$_2$ as an oxidant have been reported recently.[24] O$_2$ has been recognized as an attractive oxidant both in academic and industry due to its low expense and environmental impact. We next found that the reaction time could be reduced from 24 to 6 h (entries 8, 13, and 14).[10b] Our kinetics experiments indicated that the aminooxygenation of **1a** using the [Cu(R,R)-Ph-Box]OTf$_2$ catalyst (20 mol %) was almost complete after 12 h (see the Supporting Information, Figure S-2). That we were able to reduce the reaction time even further in Table 2, entry 9, indicates that the reaction goes even faster in the presence of O$_2$ (1 atm) and K$_2$CO$_3$. We observed that at the lower catalyst loading the (4R,5S)-Bis-Ph-Box ligand gave higher yield and % ee than the (R,R)-Ph-Box ligand (compare entries 10 and 13). Finally, since we were no longer using TEMPO as the sole oxidant, we were also able to reduce the TEMPO loading to 1.5 equiv (entry 14). We believe O$_2$ serves as the terminal oxidant

Table 2. Ligand Screening, Optimization with Time, TEMPO and Catalyst Loading[a]

(4R,5S)-Bis-Ph-Box
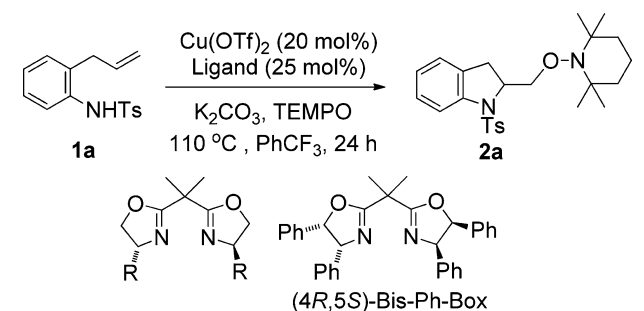
entry	ligand	yield[b] (%)	ee[c] (%) (config)
1	(S,S)-t-Bu-Box	30[d]	11 (R)
2	(S,S)-iPr-Box	57[d]	72 (R)
3	(R,R)-Bn-Box	20[d]	62 (S)
4	(S,S)-4-MeOPh-Box	85	86 (R)
5	(R,R)-4-CF₃Ph-Box	75	<5
6	(S,S)-3,5-di-Me-Ph-Box	51[d]	81 (R)
7	(S,S)-4-t-Bu-Ph-Box	85	91 (R)
8[e]	(S,S)-4-t-Bu-Ph-Box	95	90 (R)
9[f]	(R,R)-Ph-Box	90	88 (S)
10[e]	(R,R)-Ph-Box	82[d]	83 (S)
11[f]	(4R,5S)-Bis-Ph-Box	97	90 (S)
12[g]	(4R,5S)-Bis-Ph-Box	80[d]	86 (S)
13[e]	(4R,5S)-Bis-Ph-Box	95	91 (S)
14[e,h]	(4R,5S)-Bis-Ph-Box	92	90 (S)

[a]Conditions: Cu(OTf)₂ (20 mol %), bis(oxazoline) ligand (25 mol %), TEMPO (3 equiv), K₂CO₃, PhCF₃ (0.07 M wrt 1a), 110 °C, 24 h. [b]Yield (%) refers to amount of isolated 2a after purification by flash chromatography on SiO₂. [c]Enantiomeric excesses were determined by chiral HPLC analysis. [d]The remainder of the material is the starting olefin 1a. [e]The reaction was run using 15 mol % of Cu(OTf)₂ and 18 mol % of ligand under O₂ (1 atm) for 6 h. [f]The reaction was run for 6 h. [g]The reaction was run using 15 mol % of Cu(OTf)₂ and 18 mol % of ligand for 6 h. [h]1.5 equiv of TEMPO was used.

when it is present, oxidizing TEMPO-H back to TEMPO radical in the presence of K₂CO₃.[25] TEMPO radical is the oxidant of [Cu(I)] to [Cu(II)] in all cases, and little reaction occurs in the absence of TEMPO under O₂ atmosphere under catalytic conditions (not shown). We have observed that the presence of O₂ (1 atm) is necessary for the aminooxygenation reaction to go to completion when it is performed on larger scale[10b] and when using the less reactive N-pentenylsulfonamide substrates,[10a] even at lower scale. The need for O₂ appears to be tied to the reactivity of the substrate, and we speculate that if the aminooxygenation reaction does not occur relatively rapidly, a competitive process that diminishes the amount of TEMPO radical (e.g., autoxidation, 2TEMPO + H⁺ → [R₂N═O]⁺ + TEMPOH) can occur,[25] thereby impeding a productive reaction.

Effect of N-Substituent on Enantioselectivity. We next examined the effect of the size of the N-sulfonyl group on the level of enantioselectivity of the reaction. We have previously shown in catalytic desymmetrization reactions of meso β-substituted 4-pentenyl sulfonamides that the use of a sterically demanding aryl sulfonyl group (i.e., 3,5-di-tert-butylbenzene-sulfonyl) increases the reaction selectivity.[10c] (Substitution ortho to the sulfonyl decreases reactivity and selectivity, not shown.) Similarly, we obtained high enantioselectivity in our catalytic enantioselective aminooxygenation reaction with the

use of bulky substituents both with the 2-allylaniline-derived substrates (up to 92%, Table 3, entries 3 and 4) and the 4-

Table 3. Effect of N-Substituent on Enantioselectivity[a]

entry	substrate	product	yield (%)[b]	ee (%)[c]
1	**1a**, R = Ts	**2a**	90	88
2	**1b**, R = Ms	**2b**	50[d]	63
3	**1c**, R = 3,5-di-t-Bu-C₆H₃SO₂	**2c**	89	91
4	**1d**, R = 3,5-di-t-Bu-4-MeOC₆H₂SO₂	**2d**	85	92
5[e]	**6a**, R = Ts	**7a**	88	88
6[e]	**6b**, R = 3,5-di-t-Bu-C₆H₃SO₂	**7b**	92	96
7[e]	**6c**, R = 3,5-di-t-Bu-4-MeOC₆H₂SO₂	**7c**	94	97

[a]Conditions: Cu(OTf)₂ (20 mol %), (R,R)-Ph-Box (25 mol %), TEMPO (3 equiv), K₂CO₃, PhCF₃ (0.07 M wrt substrate), 110 °C, 6 h. [b]Yield (%) refers to amount of isolated 2 after purification by flash chromatography on SiO₂. [c]Enantiomeric excesses were determined by chiral HPLC analysis. [d]The remainder of the material is the starting olefin 1b. [e]Reaction was run under O₂ (1 atm, balloon).
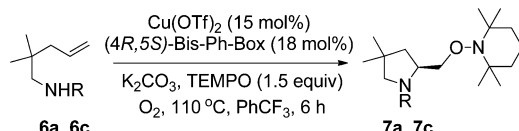
pentenylamine-derived substrates (up to 97%, Table 3, entries 6 and 7). We have previously reported that use of the more easily removable nosyl group in this reaction led to a decrease in reactivity and selectivity.[10a] We found the enantioselective aminooxygenation reaction efficiency and selectivity to be highest with substrates that have carbon chain alkyl substitution (mono or bis) as the parent N-tosyl-4-pentenylamine reacts poorly in this reaction (yield typically is <50%, substrate can suffer decomposition, not shown).

Enantiomeric excess for each product was determined by chiral HPLC. In the cases of products 2c, 7b, and 7c, the enantiomers were inseparable by chiral HPLC. Reduction of the O–N bond of each product with zinc in the presence of saturated aqueous NH₄Cl and methanol at 90 °C furnished the respective alcohols 8 and 9, whose enantiomeric ratios could be determined by chiral HPLC (eqs 8 and 9).
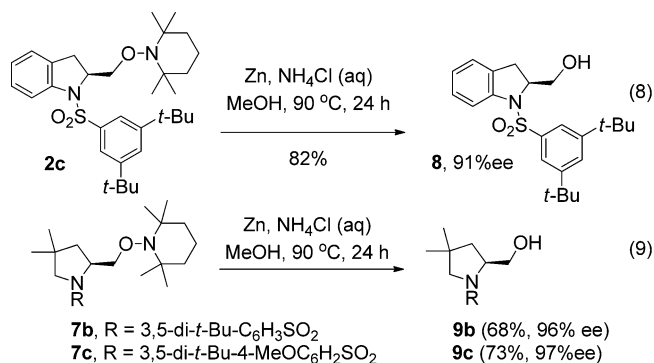
Scale-up of the Pyrrolidine-Forming Aminooxygenation Reaction. We next sought to establish if the enantioselective alkene aminooxygenation reaction of a 4-pentenylamine-derived sulfonamide could be performed on gram scale. We recently demonstrated that the catalytic enantioselective aminooxygenation reaction of N-tosyl-2-allyl-4-fluoroaniline could be run on multigram scale using 15 mol % of Cu(OTf)$_2$, 18 mol % of (4R,5S)-Bis-Ph-Box, and 3 equiv of TEMPO and heating the reaction in PhCF$_3$ to 110 °C under O$_2$ (1 atm) for 6 h (vide supra, eq 3).[10b] The chiral indoline product was prepared on a 5 g scale and with high enantioselectivity. In that study, use of the (4R,5S)-Bis-Ph-Box ligand was essential for enabling catalyst loading reduction to 15 mol %.[10b] In the process of scaling up the reaction of 2,2-dimethyl-4-pentenylsulfonamide **6a**, we found that the protocol we reported in 2008 for the enantioselective aminooxygenation of this substrate[10a] was significantly less efficient on a larger scale (250 mg, 19% yield, Table 4, entry 1). When we lowered

Table 4. Scaling-up of the Catalytic Aminooxygenation Reaction of Aliphatic Substrates

entry	substrate	amount substrate (mg, mmol)	yield[a] (%)	ee[b] (%)
1[c]	**6a**, R = Ts	50, 0.19	97	88
1[c]	**6a**, R = Ts	250, 0.93	19[d]	85
2[e]	**6a**, R = Ts	250, 0.93	88[f]	86
3	**6a**, R = Ts	250, 0.93	95	90
4	**6c**, R = 3,5-di-t-Bu-4-MeOC$_6$H$_2$SO$_2$	300, 0.76	89	95
5	**6c**, R =3,5-di-t-Bu-4-MeOC$_6$H$_2$SO$_2$	1000, 2.53	88	97

[a]Yield (%) refers to amount of isolated **7** after purification by flash chromatography on SiO$_2$. [b]Enantiomeric excesses were determined by chiral HPLC analysis. [c]The reaction was run at 120 °C using 3 equiv of TEMPO. [d]80% of the starting alkene **6a** was recovered. [e]The reaction was run at 110 °C using 3 equiv of TEMPO. [f]9% of the starting alkene **6a** was recovered.

the temperature to 110 °C, a substantial increase in isolated yield was observed (entry 2). The isolated yield of **7a** was further improved when the TEMPO loading was decreased to 1.5 equiv (entries 3 and 4). We believe the temperature effect is related to a catalyst decomposition process that can occur under the reaction conditions. We believe TEMPO may be involved in the catalyst decomposition process and also the decomposition of some substrates (e.g., the less reactive N-tosyl-4-pentenylamine, see the Discussion). When [Cu(4R,5S)-Bis-Ph-Box]OTf$_2$ was subjected to heating in the presence of TEMPO and O$_2$ but absence of substrate, a new compound, clearly derived from the ligand, appeared in the ^{1}H NMR spectrum of the crude mixture (see the Supporting Information for spectra). We speculate that the ligand may undergo oxidation at its benzylic positions. Attempted isolation/purification of the ligand mixture, unfortunately, failed. We believe, however, that the development of a more stable ligand for this aminooxygenation reaction could enable further lowering of the catalyst loading in future investigations.

With the current optimized conditions in hand, we ran a gram-scale reaction using substrate **6c** since it gave us the highest enantioselectivity (Table 3, entry 7). Sulfonamide **6c** cyclized efficiently on gram scale to form the pyrrolidine **7c** in good yield and excellent ee (Table 4, entry 5). We have demonstrated that the TEMPO adducts **7** can be reduced to the corresponding alcohol or oxidized to the corresponding aldehyde without erosion of enantiopurity.[10]

CONCLUSIONS

We have reported a mechanistic study of the copper(II)-catalyzed enantioselective intramolecular aminooxygenation of alkenes which involved reaction kinetics, kinetic isotope effects and deuterium-labeling studies. The reaction kinetics showed first-order dependence in the sulfonamide substrate and the copper−bis(oxazoline) complex and zero order in TEMPO. We also observe a secondary kinetic isotope effect for the alkene addition step. The reactions kinetics and observed secondary kinetic isotope effect are consistent with the cis-aminocupration being the rate-limiting step. Isotopic labeling studies indicate that the C−O bond formation occurs via direct carbon radical trapping with TEMPO. This deuterium labeling study also helps rule out other possible concerted reaction processes. This study is distinct from our previous study of the copper(II) 2-ethylhexanoate promoted aminooxygenation reaction where 1/2 order kinetics in both substrate and [copper] was observed.[13] The different kinetics are explained by the structure of the starting copper complexes: a [Cu(bisoxazoline)]OTf$_2$ complex is monomeric while Cu(II) 2-ethylhexanoate exists initially as a dimer. The copper-catalyzed enantioselective aminooxygenation mechanism (Scheme 1) also shares a number of similarities with the copper(II) carboxylate promoted aminooxygenation reaction.[13] In both cases, the cis-aminocupration was the most likely rate-determining step, and the C−O bond formation was determined to occur via direct carbon radical trap. These mechanistic studies will serve as the experimental basis for follow up molecular modeling calculations that can shed light on the detailed three-dimensional transition states that determine the reaction enantioselectivity.

In this study, we were able to improve the enantioselectivity of the aminooxygenation reaction (up to 97% ee) with the use of a bulky N-substituent (i.e., 3,5-di-t-Bu-4-MeOC$_6$H$_2$SO$_2$). We have shown that the reaction can be efficiently catalyzed with the use of several chiral bis(oxazoline) ligands [(S,S)-4-t-Bu-Ph-Box, (R,R)-Ph-Box, (4R,5S)-Bis-Ph-Box]. Our newly optimized reaction conditions require lower catalyst (15 mol % Cu(OTf)$_2$ and 18 mol % bisoxazoline ligand) and TEMPO (1.5 equiv) loadings, less time (6 h), lower temperature, and use of environmentally benign O$_2$ as the stoichiometric oxidant. The practicality of this protocol was further demonstrated on a gram scale reaction. This study should aid in the practical application of this useful copper-catalyzed enantioselective alkene amino-oxygenation reaction in organic synthesis and drug discovery.

EXPERIMENTAL SECTION

General Experimental Information. Reagents were used out of the bottle as purchased from the supplier without further purification unless otherwise specified. Solvents were purified using a commercial solvent filtration system. PhCF$_3$ can generally be used out of the bottle as supplied but can be further dried by distillation over CaH$_2$. ^{1}H NMR spectra were recorded in CDCl$_3$ at 500 MHz. ^{13}C NMR spectra were recorded in CDCl$_3$ at 75 MHz. Spectra are reported in ppm

relative to residual chloroform (7.26 ppm for ^{1}H NMRs and 77.0 ppm for ^{13}C NMRs). IR spectra were obtained neat, and characteristic peaks are reported in wavenumbers, cm^{-1}. High-resolution mass spectra were obtained using ESI (double-focusing magnetic sector). Optical rotations were obtained using a polarimeter fitted with a micro cell with a 100 mm path length. Melting points are reported as uncorrected. Cu(OTf)$_2$ was used as purchased but handled in a dry atmosphere (glovebox). Moisture can lower % yield and % ee. Sulfonamides **1a−d** were synthesized as previously reported.[10,26] Characterization data for indolines **2a** and **2b** have been previously reported.[10a] Sulfonamides **6a** and **6b** were synthesized as previously reported.[10,27] Characterization data for pyrrolidine **7a** has been reported.[10a] The synthesis of sulfonamide **6-[D]** and the characterization data for indolines **7-[D]** have been reported.[10a,13]

Chiral Bis(oxazoline) Ligands. The (*R*,*R*)-Ph-Box, (*S*,*S*)-*t*-Bu-Box, (*S*,*S*)-*i*-Pr-Box, and (*R*,*R*)-Bn-Box ligands were purchased from commercial sources. The (4*R*,5*S*)-di-Ph-Box ligand was synthesized as previously reported.[10b] The remaining ligands were synthesized from their respective chiral amino alcohols using the procedure reported by Evans and co-workers.[28,29] The amino alcohols were prepared either from the reduction of the commercially available amino acid[30] or following Sharpless' asymmetric aminohydroxylation method[31,32] from the corresponding substituted styrene. The substituted styrene was either commercially available or was readily prepared using the procedure reported by Denmark and Butler.[33,34] The synthesis and characterization data of the (*R*,*R*)-4-*t*-Bu-Ph-Box, (*R*,*R*)-4-MeO-Ph-Box, and (*S*,*S*)-4-CF$_3$-Ph-Box ligands have been reported.[35,36]

(S,S)-3,5-Di-Me-Ph-Box. The known (2*S*)-2-amino-2-[3,5-(dimethyl)phenyl]ethan-1-ol precursor was obtained using Sharpless' method[31] (96% ee). The amino alcohol was converted to the (*S*,*S*)-3,5-di-Me-Ph-Box ligand,[28,29] which was obtained as a colorless oil:[36] ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.89 (s, 2H), 6.86 (s, 4H), 5.16 (dd, *J* = 10.0, 8.0 Hz, 2H), 4.63 (dd, *J* = 10.0, 8.5 Hz, 2H), 4.16 (t, *J* = 7.5 Hz, 2H), 2.26 (s, 12H), 1.68 (s, 6H).

N-(2-Allylphenyl)-3,5-di-tert-butylbenzenesulfonamide (1c). *o*-Allylaniline[37] (120 mg, 0.90 mmol, 1 equiv) was dissolved in dry CH$_2$Cl$_2$ (4.5 mL), and the solution was treated with 3,5-di-*tert*-butylbenzene sulfonyl chloride[38,39] (286 mg, 0.99 mmol, 1.1 equiv) and Et$_3$N (0.38 mL, 2.7 mmol, 3 equiv). The mixture was stirred at room temperature overnight, washed with 1 N HCl (5.0 mL), and extracted with CH$_2$Cl$_2$ (3 × 8 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Flash chromatography of the resulting crude product on SiO$_2$ (0−5% EtOAc in hexanes) afforded sulfonamide **1c** (200 mg, 58% yield) which matches the previously reported characterization data:[27] ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.56 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.43 (s, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.5, 1H), 6.41 (s, 1H), 5.66 (m, 1H), 5.06 (dd, *J* = 10.0, 1.5 Hz, 1H), 4.87 (dd, *J* = 17.5, 1.5 Hz, 1H), 2.73 (d, *J* = 6.5 Hz, 2H), 1.25 (s, 18H).

N-(2-Allylphenyl)-3,5-di-tert-butyl-4-methoxybenzenesulfonamide (1d). The procedure for the synthesis of **1c** was followed except that 3,5-di-*tert*-butyl-4-methoxybenzenesulfonyl chloride[38,39] was used.[26] Sulfonamide **1d** was obtained as a white solid (310 mg, 60% yield). Its spectral properties matched the reported values:[26] ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.52 (d, *J* = 8.5 Hz, 1H), 7.48 (s, 2H), 7.25 (t, *J* = 7.5, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.40 (s, 1H), 5.66 (m, 1H), 5.06 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.90 (dd, *J* = 17.0, 1.5 Hz, 1H), 3.66 (s, 3H), 2.80 (d, *J* = 6.5 Hz, 2H), 1.31 (s, 18H).

(S)-1-((3,5-Di-tert-butylphenyl)sulfonyl)-2-(((2,2,6,6-tetramethyl-piperidin-1-yl)oxy)methyl)indoline (2c). Cu(OTf)$_2$ (7.5 mg, 0.021 mmol, 0.2 equiv) and (*R*,*R*)-Ph-Box (0.32 mL of 0.08 M solution, 0.026 mmol, 0.25 equiv) were combined and stirred in CF$_3$Ph (0.48 mL) under Ar for 2 h at 60 °C in a 100 mL round-bottom flask equipped with magnetic stir bar. The blue-green solution was cooled to rt and was treated with sulfonamide **1c** (40 mg, 0.104 mmol, 1 equiv), TEMPO (48.6 mg, 0.311 mmol, 3 equiv), K$_2$CO$_3$ (14.3 mg, 0.104 mmol, 1 equiv), and CF$_3$Ph (0.70 mL). The reaction mixture was heated to 110 °C for 6 h. Filtration of the cooled solution through

a SiO$_2$ plug (with Et$_2$O washing) and removal of the solvent in vacuo afforded the crude product. Purification via flash chromatography on silica gel (0−5% Et$_2$O in hexanes gradient) gave the TEMPO adduct **2c** (50 mg, 89% yield) as a white solid: mp 100−105 °C; [α]$^{19}_D$ = 66.0 (*c* = 1.15, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.40 (s, 2H), 7.20 (m, 1H), 7.00 (d, *J* = 5.0 Hz, 2H), 4.25 (m, 1H), 3.99 (dd, *J* = 9.0 Hz, 3.5 Hz, 1H), 3.93 (dd, *J* = 8.0 Hz, 6.5 Hz, 1H), 2.72 (d, *J* = 15.5 Hz, 1H), 2.49 (dd, *J* = 15.5 Hz, 10.0 Hz, 1H), 1.22−1.38 (m, 6H), 1.18 (s, 18H), 1.14 (s, 3H), 1.10 (s, 3H), 0.96 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 151.8, 142.3, 136.8, 133.1, 127.2, 126.6, 124.8, 124.4, 121.0, 117.8, 78.8, 60.9, 59.9, 39.5, 35.0, 33.0, 31.6, 31.2, 31.0, 19.9, 19.7, 17.0; IR (neat, thin film) ν 2965, 2870, 1598, 1478, 1461, 1360, 1360, 1314, 1247, 1170, 1024, 788, 758, 705, 622, 600 cm^{-1}; HRMS (ESI) calcd for [M + H]$^+$ C$_{32}$H$_{49}$O$_3$N$_2$S$_1$ 541.3458, found 541.3461.

(S)-(1-((3,5-Di-tert-butylphenyl)sulfonyl)indolin-2-yl)methanol (8). The enantiomers of the TEMPO adduct **2c** were inseparable so the enantiomeric excess was determined using the free alcohol **8**. Following the reported procedure for the reduction of TEMPO,[10] **2c** (30 mg, 0.06 mmol, 1 equiv) was stirred in methanol (1.5 mL) in a pressure tube, and then aqueous NH$_4$Cl (1.5 mL) was added followed by Zn dust (157 mg, 2.4 mmol, 40 equiv). The reaction mixture was heated to 90 °C for 24 h and was then cooled to room temperature and filtered through Celite. Purification of the crude product via flash chromatography (20% ethyl acetate in hexanes) gave 82% yield of *N*-protected amino alcohol **8** (18.0 mg) which is a white solid: mp 40−45 °C; [α]$^{19}_D$ = 140.6 (*c* = 1.35, CHCl$_3$), ee = 91%, determined by HPLC [Regis (*S*,*S*) Whelk, 5% IPA/hexane, 1.0 mL/min, λ = 254 nm, *t*(major) = 15.00 min, *t*(minor) = 13.33 min]; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.53 (s, 1H), 7.39 (s, 2H), 7.24 (d, *J* = 6.5 Hz, 1H), 7.03 (m, 2H), 4.23 (m, 1H), 3.68 (d, *J* = 6.0 Hz, 2H), 2.55 (d, *J* = 9.5 Hz, 2H), 2.17 (s, 1H), 1.22 (s, 18H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.0, 141.5, 136.2, 132.5, 127.7, 127.0, 125.3, 124.9, 121.1, 118.3, 65.3, 63.5, 35.0, 31.1, 31.0; IR (neat, thin film) ν 3541, 2963, 2869, 1593, 1476, 1461, 1349, 1243, 1171, 1095, 1039, 958, 760 cm^{-1}; HRMS (ESI) calcd for [M + Na]$^+$ C$_{23}$H$_{31}$O$_3$N$_1$Na$_1$S$_1$ 424.1917, found 424.1925.

(S)-1-((3,5-Di-tert-butyl-4-methoxyphenyl)sulfonyl)-2-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)indoline (2d). Sulfonamide **1d** was converted to indoline **2d** using the procedure described for the aminooxygenation reaction of **1c** to **2c**. The TEMPO adduct **2d** was obtained as a white solid (46 mg, 85% yield): mp 80−83 °C; [α]$^{20}_D$ = 66.8 (*c* = 2.0, CHCl$_3$); ee = 92%, determined by HPLC [Regis (*S*,*S*) Whelk, 0.4% IPA/hexane, 0.5 mL/min, λ = 254 nm, *t*(major) = 30.56 min, *t*(minor) = 24.74 min]; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 2H), 7.19 (t, *J* = 7.0 Hz, 1H), 7.02 (m, 2H), 4.25 (m, 1H), 4.00 (m, 1H), 3.92 (m, 1H), 3.62 (s, 3H), 2.77 (d, *J* = 15.5 Hz, 1H), 2.55 (dd, *J* = 15.5 Hz, 9.0 Hz, 1H), 1.38−145 (m, 6H), 1.26 (s, 6H), 1.16 (s, 3H), 1.13 (s, 3H), 0.95 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 163.4, 144.8, 142.4, 133.1, 131.5, 127.3, 125.5, 124.8, 124.4, 117.8, 78.8, 64.5, 60.8, 59.9, 39.5, 35.9, 33.1, 31.7, 31.6, 29.6, 19.8, 17.0; IR (neat, thin film) ν 2966, 2871, 1603, 1479, 1462, 1406, 1359, 1256, 1227, 1170, 1128, 1007, 883, 794, 759, 707, 665 cm^{-1}; HRMS (ESI) calcd for [M + H]$^+$ C$_{33}$H$_{51}$O$_4$N$_2$S$_1$ 571.3564, found 571.3583.

3,5-Di-tert-Butyl-N-(2,2-dimethylpent-4-en-1-yl)benzenesulfonamide (6b). 2,2-Dimethylpent-4-en-1-amine[41,42] (250 mg, 2.2 mmol, 1 equiv) was stirred in dry CH$_2$Cl$_2$ (12 mL), and 3,5-di-*tert*-butylsulfonyl chloride[38,39] (770 mg, 2.4 mmol, 1.1 equiv) was added followed by Et$_3$N (0.93 mL, 6.6 mmol, 3 equiv). The reaction mixture was stirred at room temperature overnight, washed with 1 N HCl (10 mL), and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by flash chromatography of the resulting crude product on SiO$_2$ (0−5% EtOAc in hexanes) gave sulfonamide **6c** (480 mg, 53% yield) as a colorless oil:[27] ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 (s, 2H), 7.59 (s, 1H), 5.66 (m, 1H), 4.91−4.96 (m, 2H), 2.69 (d, *J* = 6.5 Hz, 2H), 1.93 (d, *J* = 7.5 Hz, 2H), 1.31 (s, 18H), 0.84 (s, 3H); ^{13}C NMR (75 Hz, CDCl$_3$) δ 152.0, 139.1, 134.2, 126.5, 121.0, 117.7, 52.7, 44.0, 35.1, 34.0, 31.2, 24.7; IR (neat) ν 3279, 3076, 2964, 2873,

1639, 1598, 1466, 1410, 1359, 1324, 1313, 1247, 1161, 1070, 993, 922, 876, 831, 749, 704, 592 cm^{-1}; HRMS (ESI) calcd for [M + Na]$^+$ C$_{21}$H$_{35}$O$_2$N$_1$Na$_1$S$_1$ 388.2281, found 388.2275.

3,5-Di-tert-butyl-N-(2,2-dimethylpent-4-en-1-yl)-4-methoxybenzenesulfonamide (6c). 2,2-Dimethyl-4-pentenamine (1.00 g, 8.83 mmol) was dissolved in CH$_2$Cl$_2$ (44 mL) and was treated with 3,5-di-*tert*-butyl-4-methoxybenzenesulfonyl chloride[38,40] (2.95 g, 9.27 mmol) and Et$_3$N (3.7 mL, 26.5 mmol). The solution was stirred for 2 days at rt and then was quenched with H$_2$O and extracted with CH$_2$Cl$_2$ (2×). The combined organic extracts were washed with 1 N HCl and brine and then were dried over MgSO$_4$. The solution was filtered, and the volatiles were removed in vacuo. Chromatography on silica gel (0−10% EtOAc in hexanes gradient) afforded sulfonamide **6c** as a white solid (2.5 g, 72% yield): mp 95−98 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.71 (s, 2H), 5.68 (m, 1H), 4.96−5.01 (m, 2H), 4.37 (s, 1H), 3.70 (s, 3H), 2.73 (d, *J* = 6.5 Hz, 2H), 1.93 (d, *J* = 7.0 Hz, 2H), 1.43 (s, 18H), 0.85 (s, 6H); ^{13}C NMR (75 Hz, CDCl$_3$) δ 163.2, 145.1, 134.2, 133.6, 125.6, 117.8, 64.5, 52.7, 44.1, 36.1, 34.0, 31.7, 24.8; IR (neat) ν 3266, 2963, 2871, 1639, 1453, 1407, 1327, 1255, 1227, 1163, 1116, 1066, 1004, 928, 886, 756, 710, 592 cm^{-1}; HRMS (ESI) calcd for [M + H]$^+$ C$_{22}$H$_{38}$O$_3$N$_1$S$_1$ 396.2567, found 396.2569.

(S)-1-((1-((3,5-Di-tert-butylphenyl)sulfonyl)-4,4-dimethylpyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (7b). In a 100 mL round-bottom flask equipped with magnetic stir bar were added Cu(OTf)$_2$ (7.9 mg, 0.022 mmol, 0.2 equiv), (*R,R*)-Ph-Box (0.34 mL of 0.08 M solution, 0.027 mmol, 0.25 equiv), and CF$_3$Ph (0.46 mL). The mixture was heated and stirred under Ar for 2 h at 60 °C. The blue-green solution was then cooled to room temperature, and sulfonamide **6b** (40 mg, 0.109 mmol, 1 equiv), TEMPO (48.6 mg, 0.327 mmol, 3 equiv), K$_2$CO$_3$ (14.3 mg, 0.109 mmol, 1 equiv), and CF$_3$Ph (0.8 mL) were added. The flask was then fitted with a glass side arm adapter tapered to connect a short rubber vacuum hose through which the O$_2$ balloon was connected. The reaction mixture was heated to 110 °C for 6 h and then was cooled to room temperature and filtered through a SiO$_2$ plug (with Et$_2$O washing). The solvent was removed in vacuo to afford the crude product which was then purification by flash chromatography on silica gel (0−5% Et$_2$O in hexanes gradient). The TEMPO adduct **7b** was obtained as a white solid (52.1 mg, 92% yield): mp 90−95 °C; [α]$^{21}_D$ = −68.4 (*c* = 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.65 (s, 2H), 7.60 (s, 1H), 4.25 (dd, *J* = 8.5 Hz, 4.0 Hz, 1H), 3.86 (t, *J* = 8.5 Hz, 1H), 3.62 (m, 1H), 3.14 (AB quartet, *J* = 10.5 Hz, Δν = 20.6 Hz, 2H), 1.73 (d, *J* = 7.5 Hz, 2H), 1.46 (m, 6H), 1.34 (s, 18H), 1.25 (s, 3H), 1.14 (s, 3H), 1.06 (s, 6H), 1.04 (s, 3H), 0.40 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 151.9, 137.0, 126.4, 121.5, 79.8, 61.6, 59.7, 58.0, 44.4, 39.6, 37.4, 35.0, 33.0, 31.2, 26.4, 25.8, 20.1, 17.1; IR (neat, thin film) ν 2963, 2873, 1598, 1466, 1351, 1246, 1165, 1110, 1039, 755, 704, 625 cm^{-1}; HRMS (ESI) calcd for [M + H]$^+$ C$_{30}$H$_{53}$O$_3$N$_2$S$_1$ 521.3771, found 521.3784.

(S)-1-((1-((3,5-Di-tert-butylphenyl)sulfonyl)-4,4-dimethylpyrrolidin-2-yl)methanol (9b). The enantiomeric excess of **7b** was determined using the free alcohol. Compound **9b** was obtained as a colorless oil using the same method as in the conversion of **2c** to **8** (17 mg, 68% yield): [α]$^{22}_D$ = −20.6 (*c* = 1.25, CHCl$_3$), ee =96%, determined by HPLC [Chiralpak AD-RH, 50% H$_2$O/CH$_3$CN, 0.5 mL/min, λ = 254 nm, *t*(major) = 20.58 min, *t*(minor) = 17.82 min]; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.67 (s, 2H), 7.63 (s, 1H), 3.80 (dd, *J* = 12.0 Hz, 3.0 Hz, 1H), 3.69 (dd, *J* = 12.0 Hz, 4.5 Hz, 1H), 3.57 (m, 1H), 3.16 (AB quartet, *J* = 10.5 Hz, Δν = 22.7 Hz, 2H), 1.61 (dd, *J* = 7.5 Hz, 1.5 Hz, 2H), 1.34 (s, 18H), 0.99 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.2, 136.3, 126.8, 121.5, 65.8, 62.3, 62.2, 43.3, 36.9, 35.1, 31.2, 26.0, 25.3; IR (neat, thin film) ν 3504, 2961, 2873, 1598, 1466, 1340, 1247, 1162, 1114, 1066, 1036, 968, 791, 756, 707, 631, 592 cm^{-1}; HRMS (ESI) calcd for [M + Na]$^+$ C$_{21}$H$_{35}$O$_3$N$_1$Na$_1$S$_1$ 404.2230, found 404.2226.

(S)-1-((1-((3,5-Di-tert-butyl-4-methoxyphenyl)sulfonyl)-4,4-dimethylpyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (7c). Sulfonamide **6c** was converted to pyrrolidine **7c** using the procedure described for the conversion of **6b** to **7b**. The TEMPO adduct **7c** was obtained as a white solid (52 mg, 94% yield): mp 140−145 °C; [α]$^{21}_D$ = −64.1 (*c* = 2.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 (s,

2H), 4.24 (dd, *J* = 12.5 Hz, 3.0 Hz, 1H), 3.84 (t, *J* = 8.0 Hz, 1H), 3.67 (s, 3H), 3.63 (m, 1H), 3.12 (AB quartet, *J* = 10.5 Hz, Δν = 20.6 Hz, 2H), 1.74 (m, 2H), 1.50−1.58 (m, 6H), 1.43 (s, 18H), 1.15 (s, 3H), 1.06 (s, 6H), 1.04 (s, 3H), 0.41 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 163.2, 144.8, 131.6, 125.9, 79.9, 64.6, 61.5, 59.7, 58.1, 44.5, 39.6, 37.4, 36.0, 33.2, 31.7, 26.4, 25.7, 20.0, 17.1; IR (neat, thin film) ν 2955, 2874, 1471, 1453, 1405, 1349, 1253, 1225, 1165, 1125, 1042, 1008, 967, 920, 885, 812, 757, 710, 632, 595 cm^{-1}; HRMS (ESI) calcd for [M + H]$^+$ C$_{31}$H$_{55}$O$_4$N$_2$S$_1$ 551.3877, found 551.3887.

(S)-(1-((3,5-Di-tert-butyl-4-methoxyphenyl)sulfonyl)-4,4-dimethylpyrrolidin-2-yl)methanol (9c). The enantiomeric excess of **7c** was determined using the free alcohol. Compound **9c** was obtained as colorless oil using the same procedure as in the conversion of **2c** to **8** (16 mg, 73% yield): [α]$^{22}_D$ = −19.3 (*c* = 1.0, CHCl$_3$), ee =97%, determined by HPLC [Chiralpak AD-RH, 40% H$_2$O/CH$_3$CN, 0.75 mL/min, λ = 254 nm, *t*(major) = 9.61 min, *t*(minor) = 8.35 min]; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.71 (s, 2H), 3.80 (dd, *J* = 12.0 Hz, 3.0 Hz, 1H), 3.69 (m, 1H), 3.67 (s, 3H), 3.58 (m, 1H), 3.19 (AB quartet, *J* = 11.0 Hz, Δν = 24.4 Hz, 2H), 1.60−1.63 (m, 2H), 1.44 (s, 18H), 1.00 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 163.6, 145.2, 130.9, 125.9, 65.8, 64.6, 62.4, 62.2, 43.3, 36.9, 36.0, 31.7, 29.6, 26.0, 25.3; IR (neat, thin film) ν 3503, 2961, 2873, 1576, 1465, 1406, 1337, 1254, 1226, 1162, 1123, 1065, 1034, 1006, 967, 885, 795, 756, 632, 596 cm^{-1}; HRMS (ESI) calcd for [M + H]$^+$ C$_{22}$H$_{38}$O$_4$N$_1$S$_1$ 412.2516, found 412.2517.

(S)-1-((1-((3,5-Di-tert-butyl-4-methoxyphenyl)sulfonyl)-4,4-dimethylpyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (7c) (Gram Scale). To an oven-dried 250 mL round-bottom flask equipped with magnetic stir bar were added Cu(OTf)$_2$ (137 mg, 0.38 mmol, 0.15 equiv), (*4R,5S*)-Bis-Ph-Box (222 mg, 0.46 mmol, 0.18 equiv), and CF$_3$Ph (30.0 mL). The solution was heated and stirred for 2 h at 60 °C under Ar atmosphere. The blue-green solution was cooled to room temperature and was treated with sulfonamide **6c** (1.0 g, 2.53 mmol, 1 equiv), TEMPO (593 mg, 3.8 mmol, 1.5 equiv), K$_2$CO$_3$ (349 mg, 2.53 mmol, 1 equiv), and an additional 6.0 mL of CF$_3$Ph. The reaction mixture was heated to 110 °C for 6 h under O$_2$ (1 atm) and was then cooled to room temperature and filtered through a SiO$_2$ plug (with Et$_2$O washing). Removal of the solvent in vacuo afforded the crude product. Purification via flash chromatography on SiO$_2$ (0−5% Et$_2$O in hexanes) gave the TEMPO adduct **7c** (1.23 g, 88% yield). Enantioselectivity (97% ee) was determined using the amino alcohol **9c**.

Mechanistic Analysis of C−O Bond Formation.
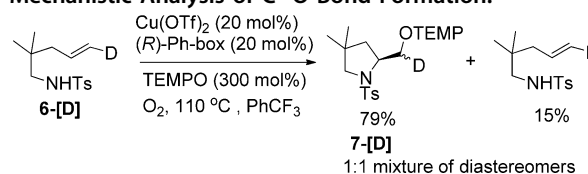
Cu(OTf)$_2$ (5.4 mg, 0.015 mmol, 0.20 equiv) and (*R,R*)-Ph-Box (0.20 mL of 0.08 M solution, 0.016 mmol, 0.20 equiv) were heated and stirred in CF$_3$Ph (0.31 mL) for 2 h at 60 °C in a 100 mL round-bottom flask equipped with magnetic stir bar. Upon being cooled to room temperature, the reaction mixture was treated with deuterated substrate **6-[D]**[13b] (20 mg, 0.075 mmol, 1 equiv), TEMPO (35.2 mg, 0.23 mmol, 3 equiv), and CF$_3$Ph (0.60 mL). An O$_2$ balloon was connected to the flask with the use of a glass side arm adapter connected to a short rubber vacuum hose. The reaction mixture was heated in an oil bath at 110 °C for 2 h and then was cooled to room temperature, diluted with Et$_2$O, and filtered through a plug of silica gel with Et$_2$O. Removal of the solvent in vacuo afforded the crude product. Purification by flash chromatography on silica gel (5−10% EtOAc in hexanes) gave compound **7-[D]** (22 mg, 70% yield) and the unscrambled starting material (4.5 mg, 22% yield). The crude ^{1}H NMR spectrum showed two −C*H*D-OTEMP protons at 4.20 and 3.87 ppm, respectively, each integrating as 0.5 H, which indicates the presence of a 1:1 mixture of diastereomers. This result is consistent with the analysis of the previously reported C−O bond formation of the copper(II)-promoted aminooxygenation reaction of alkene.[13] Data

for compound **7-[D]** matches the previously reported characterization:[10a,13] [1H] NMR (500 MHz, CDCl$_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.17 (m, 0.5H), 3.85 (m, 0.5H), 3.68 (m, 1H), 3.13 (ABq, $\Delta\nu_{AB}$ = 18.5 Hz, J = 10.4 Hz, 2H), 2.43 (s, 3H), 1.78−1.75 (m, 2H), 1.45−1.42 (m, 4H), 1.20 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 1.06 (s, 6H), 0.55 (s, 3H).

Catalyst Decomposition Study. Three separate solutions were prepared following the procedure below. Cu(OTf)$_2$ (10 mg, 0.028 mmol, 1 equiv) and (4R,5S)-Bis-PhBox (16 mg, 0.033 mmol, 1.2 equiv) were heated and stirred in CF$_3$Ph (2.7 mL) for 2 h at 60 °C in a 10 mL round-bottom flask equipped with magnetic stir bar. The solution was cooled to room temperature and was treated with TEMPO (88 mg, 0.56 mmol, 20 equiv). The first solution was stirred at room temperature for about 15 min, the second and third solutions were heated to 110 and 120 °C for 6 h, respectively. The cooled solution was filtered through Celite (with Et$_2$O washing), and the filtrate was washed with saturated aqueous Na$_2$EDTA (2 × 3 mL). The organic layer was dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo to afford the crude product. [1H] NMR spectra of the three crude materials were obtained.

General Procedure for Kinetics Experiments. Cu(OTf)$_2$ and (R,R)-Ph-Box were heated and stirred in CF$_3$Ph under argon for 2 h at 60 °C in an oven-dried 10 mL round-bottom flask equipped with magnetic stir bar and sealed with septa. The solution was cooled to rt and treated with substrate **1a** and TEMPO. The reaction mixture was heated to 110 °C using a temperature regulated oil bath. It was taken out of the oil bath every hour and a 20 μL aliquot was collected using a gastight syringe. The aliquots collected were dried under vacuum and the residue was dissolved in 200 μL acetonitrile. The samples were analyzed using HPLC in a Microsorb-MV 100 C8 column by gradient elution (65−100% CH$_3$CN in H$_2$O). Calibration plots for substrate **1a** and the TEMPO adduct **2a** were used to calculate the concentrations of **1a** and **2a** as a function of time.

Reactions were run up to 80−90% conversion for higher catalyst loading (20−40 mol % or 10−20 mM). We observed that at low catalyst loading (5−10 mol % or 2.5−5 mM) reactions do not go to completion, and the rate tails off at 40−60% conversion presumably due to catalyst decomposition. Therefore, initial reaction rates were measured for these catalyst loadings.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, kinetic studies, kinetic isotope effect studies, and characterization data for all reactions and products, including [1H] NMR and [13C] NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ NOTE ADDED AFTER ASAP PUBLICATION

Figure 1 was incorrect in the version published ASAP on December 28, 2012; the correct version reposted on January 3, 2013.