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Stereoselective Synthesis of Morpholines via Copper-Promoted Oxyamination of Alkenes

Fatima C. Sequeira and Sherry R. Chemler*

Department of Chemistry, The State University of New York at Buffalo, Buffalo, New York 14260, United States

schemler@buffalo.edu

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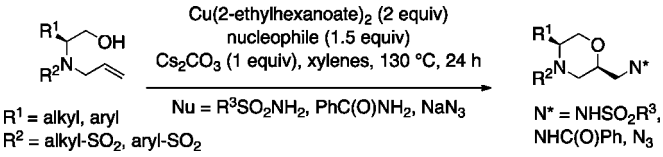
ABSTRACT



A new copper(II) 2-ethylhexanoate-promoted addition of an alcohol and an amine across an alkene (oxyamination) is reported. The alcohol addition is intramolecular, while coupling with the amine occurs intermolecularly. Several 2-aminomethyl morpholines were synthesized in good to excellent yields and diastereoselectivities.

The simultaneous addition of oxygen and nitrogen across an alkene (aminooxygenation, oxyamination) is a useful way to install the vicinal aminoalcohol moiety.[1] Vicinal amino alcohols are useful in a number of applications including catalysis and medicinal chemistry.[2] A number of reactions have been invented to enable this important transformation,[1] including those that construct a heterocycle in the process.[3] While the majority of ring-forming oxyaminations construct nitrogen heterocycles,[3a,b,d−k] few reports of oxygen heterocycle synthesis have appeared[3c,l] and only one of them is thought to initiate with addition of oxygen to the alkene.[3l] An alkyne oxyamination that likely initiates with intramolecular addition of the alcohol to the alkyne has recently been reported.[4]

We report herein a new copper(II) 2-ethylhexanoate-promoted alkene oxyamination reaction that provides 2-aminomethyl-functionalized morpholines in good to excellent yields and with generally high levels of diastereoselectivity. This reaction likely proceeds by initial addition of the alcohol moiety to the alkene (vide infra). Morpholines[5] are frequently found in bioactive compounds, thus new methods for their efficient and stereoselective synthesis are desirable. Substituted morpholines, in particular, are useful scaffolds and property-enhancing functional groups in drug discovery. In the past 20 years, a number of concise and inventive methods for the synthesis of variously substituted morpholines have been reported.[6] Despite their demonstrated utility in drug discovery,[7]

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(2) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875. (b) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561–2576.

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(5) Morpholine review:Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641.

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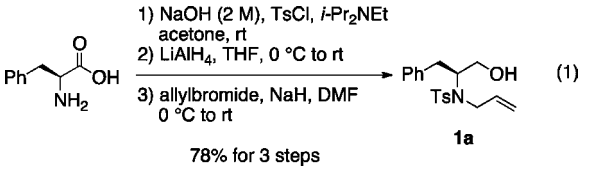
however, no direct methods for the synthesis of aminomethyl morpholines from alkenols have appeared.[6c]

We have recently reported that copper(II) carboxylates promote and catalyze intramolecular alkene aminooxygenation and diamination reactions.[8,9] In these reactions, nitrogen heterocycles are formed via a mechanism involving *cis*-aminocupration across the alkene.[3k] In these studies, all of the alkene substrates were tethered to amine nucleophiles. More recently, we have begun exploring copper-promoted and -catalyzed intramolecular additions of alcohols to alkenes.[10] Both carboetherification and hydroetherification reactions have been achieved where the reaction is thought to initiate with a *cis*-oxycupration of the alkene.[10] This paper describes an expansion of this method to the alkene oxyamination reaction, and both five- and six-membered ring oxygen-containing heterocycles have resulted (vide infra).

Our interest in the synthesis of morpholines led us to explore the copper(II) 2-ethylhexanoate-promoted cyclization/amination reactions of β-hydroxy-*N*-allylsulfonamide **1a**. Substrate **1a** was synthesized from L-phenylalanine in three steps and 78% overall yield as illustrated in eq 1.

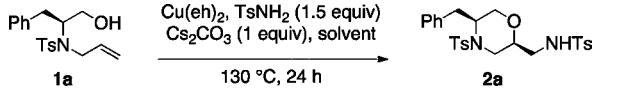


(1)

Upon treatment with copper(II) 2-ethylhexanoate (3 equiv) in the presence of $TsNH_2$, β-hydroxy-*N*-allylsulfonamide **1a** underwent oxyamination to provide morpholine **2a** as a single diastereomer (>20:1 dr) in 45% yield (Table 1, entry 1). Bouyed by this promising initial result, we optimized the product yield and copper(II) loading in this reaction (Table 1). Copper(II) 2-ethylhexanoate [$Cu(eh)_2$] was chosen as the copper(II) source as it is very soluble in nonpolar organic solvents where analogous alkene difunctionalization reactions tend to perform well.[3i–k,10]

In this reaction, we found that the higher boiling xylenes proved to be a better solvent than $PhCF_3$ at 130 °C, the temperature these reactions performed best at (Table 1, entries 1–3). We found the copper(II) loading could be reduced from 3 to 2 equiv without diminishing the isolated yield (Table 1, compare entries 3 and 4). Decreasing the copper(II) loading to 1.5 equiv resulted in diminished conversion (Table 1, entry 5).

Table 1. Optimization of the Alkene Oxyamination[a]



entry	equiv of $Cu(eh)_2$	solvent	yield (%)[b]
1[c]	3	$PhCF_3$	45[d]
2	3	$PhCF_3$	50[d]
3	3	xylenes	85
4	2	xylenes	87
5	1.5	xylenes	50[d]
6[c]	2	xylenes	80[d]

[a] Conditions: Substrate **1a** (0.116 mmol) in solvent (0.1 M) was treated with the specified amount of $Cu(eh)_2$, Cs_2CO_3 (1 equiv), and $TsNH_2$ (1.5 equiv) at 130 °C for 24 h unless otherwise noted. Only one diastereomer (dr >20:1) was observed by ^1H NMR. [b] Isolated yield unless otherwise noted. [c] Reaction run at 120 °C. [d] Percent conversion based on ^1H NMR analysis of the crude mixture. The remainder of the material balance is starting substrate. $Cu(eh)_2$ = copper(II) 2-ethylhexanoate.

Lowering the reaction temperature from 130 to 120 °C resulted in lower conversion, as well (Table 1, compare entries 4 and 6). No conversion to product was observed under conditions where a catalytic amount of Cu(2-ethylhexanoate)$_2$ (20 mol %) and a stoichiometric amount of MnO_2 (3 equiv) was used as oxidant under otherwise optimal reaction conditions (130 °C in xylenes). We have previously used MnO_2 successfully in analogous reactions to turnover catalytic amounts of Cu(II).[8,9c,10]

Using the optimized reaction conditions (Table 1, entry 4), we examined the copper(II)-promoted oxyamination reaction of a number of β-hydroxy-*N*-allylsulfonamides (Table 2, entries 1–8). Alkyl, phenyl, silyloxymethyl, and benzylsulfidomethyl substituents were all tolerated in the reaction, albeit the sulfide's conversion was lower (Table 2, entry 5) and the phenyl-substituted substrate **1i** (Table 2, entry 8) gave a comparably lower diastereoselectivity (dr = 6:1). *N*-Nosyl- and *N*-mesyl-containing substrates **1g** and **1h** reacted with similar efficiencies as the *N*-tosyl substrate **1a** (Table 2, entries 6 and 7).

Various nitrogen nucleophiles were explored as summarized in Table 2, entries 9–15. Sulfonamide nucleophiles including the easily desulfonylated nosyl and 2-trimethylsilylethylsulfonamide generally performed well (Table 2, entries 9–12), but the reaction with methanesulfonamide gave a lower conversion and the copper(II) loading had to be increased to 4 equiv for a reasonable isolated yield (Table 2, entry 11). The benzamide nucleophile also underwent the coupling; however, increased copper(II) loading (3–4 equiv) was critical to obtaining

(6) (a) Lai, J.-Y.; Shi, X.-X.; Gong, Y.-S.; Dai, L.-X. *J. Org. Chem.* **1993**, *58*, 4775–4777. (b) Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826–6832. (c) Wilkinson, M. C. *Tetrahedron Lett.* **2005**, *46*, 4773–4775. (d) Lanman, B. A.; Myers, A. *Org. Lett.* **2004**, *6*, 1045–1047. (e) Dave, R.; Sasaki, N. A. *Org. Lett.* **2004**, *6*, 15–18. (f) Pedrosa, R.; Andres, C.; Mendiguchia, P.; Nieto, J. *J. Org. Chem.* **2006**, *71*, 8854–8863. (g) Leathen, M. L.; Rosen, B. R.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 5107–5110. (h) Chowdhury, C.; Mukherjee, S.; Das, B.; Achari, B. *J. Org. Chem.* **2009**, *74*, 3612–3615. (i) Ghorai, M. K.; Shukla, D.; Das, K. *J. Org. Chem.* **2009**, *74*, 7013–7022. (j) Albanese, D.; Landini, D.; Penso, M.; Tagliabue, A.; Carlini, E. *Org. Process. Res. Dev.* **2010**, *14*, 705–711. (k) Bornholdt, J.; Felding, J.; Kristensen, J. L. *J. Org. Chem.* **2010**, *75*, 7454–7457. (l) Ritzen, B.; Hoekman, S.; Verdasco, D. D.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2010**, *75*, 3461–3464. (m) Bera, S.; Panda, G. *ACS Comb. Sci.* **2012**, *14*, 1–4. (n) Lu, Z.; Stahl, S. S. *Org. Lett.* **2012**, *14*, 1234–1237. (o) O'Reilly, M. C.; Lindsley, C. W. *Org. Lett.* **2012**, *14*, 2910–2913. (p) Gharpure, S. J.; Prasad, J. V. K. *J. Org. Chem.* **2011**, *76*, 10325–10331.

(7) Ancliff, R. A.; Cook, C. M.; Eldred, C. D.; Gore, P. M.; Harrison, S. T.; Judd, D. B.; Keeling, S. E.; Lewell, X. Q.; Mills, G.; Robertson, G. M.; Swanson, S.; Walker, A. J.; Wilkinson, M. U.S. Patent Appl. 7,622,464 (Glaxo Group Limited), Nov. 24, 2009.

(8) Chemler, S. R. *J. Organomet. Chem.* **2011**, *696*, 150–158.

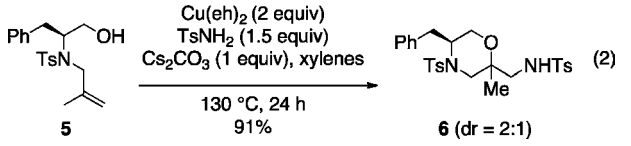
(9) (a) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250–11251. (b) Zabawa, T. P.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 2035–2038. (c) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6365–6368.

(10) Miller, Y.; Miao, L.; Hosseini, A.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149–12156.

a good diastereomeric ratio (Table 2, entries 13 and 15 and see Supporting Information for diastereoselectivity as a function of copper loading). Sodium azide could also be used as nucleophile under the higher copper(II) loading conditions (Table 2, entry 14). Anilines failed to function as the amine component in these reactions (no reaction observed, reactions not shown).

While most of the examples provide 2,5-disubstituted morpholines **2**, a brief examination using 2-substituted substrate **3** indicated that 2,6-disubstituted morpholines **4** can also be synthesized, albeit the reaction temperature had to be raised to 150 °C to obtain moderate conversion (Table 2, entry 16).

The 1,1-disubstituted alkene **5** also underwent efficient conversion, giving the highly substituted morpholine **6** in 91% yield, albeit as a 2:1 diastereomeric mixture (eq 2).

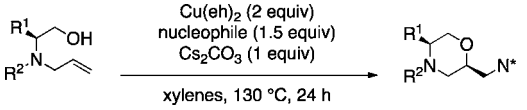


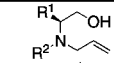
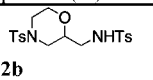
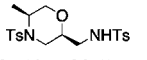
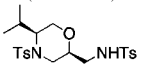
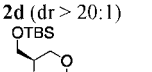
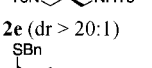
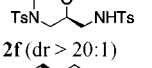
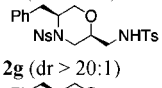
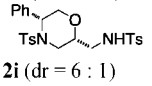
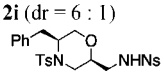
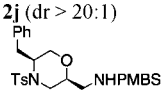
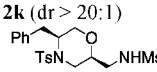
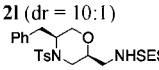
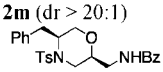
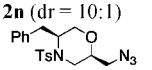
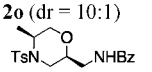
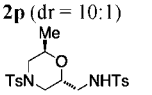
The relative stereochemistry of the major diastereomer of morpholine **2n** was assigned as 2,5-*cis* by X-ray crystallography (Figure 1). All other 2,5-disubstituted morpholine (major) products were assigned by analogy. The relative stereochemistry of the 2,6-*trans*-disubstituted morpholine **4** was assigned by NOE (see Supporting Information).

In the absence of an amine nucleophile, dioxygenation of the alkene occurs to give a 1:1 mixture of 2-ethylhexanoic esters **7** (Scheme 1). Saponification of this ester mixture provided the 2-hydroxymorpholine **8** as a single diastereomer (dr = >20:1), confirming that the diastereomeric mixture originated from the ester configuration.

A proposed mechanism that accounts for the observed diastereoselectivity is illustrated in Scheme 2. Coordination of alcohol **1a** to the copper(II) 2-ethylhexanoate dimer in the presence of Cs_2CO_3 likely results in monomer **9**. This first step is an analogy to similar reactions of the copper(II) carboxylate with alkenylsulfonamides and the copper(II) ligation is undefined as either one or two carboxylates may be attached at the copper center.[3k] Thermally promoted *cis*-oxycupration via transition state **A** then provides the unstable organocopper(II) intermediate **10**. The diastereoselectivity is rationalized by a chairlike transition state where the vicinal tosyl and benzyl substituents adopt pseudoaxial positions,[11] much like in the final product **2** (e.g., Figure 1). Intermediate **10** then undergoes C−Cu(II) homolysis to give carbon radical **11**.[3k,10] Recombination of the radical with a [Cu(II)] in the presence of $TsNH_2$ then gives an organocopper(III) intermediate **12** that can undergo reductive elimination to form the C−N bond of **2a**.[9] In the absence of amine nucleophile, a carboxylate ligand is transferred, giving the dioxygenated product **7** (Scheme 1).

Table 2. Morpholine Synthesis Scope[a]



entry	substrate	nucleophile	product (dr)[b]	yield[c]
1	 **1b**, R^1 = H; R^2 = Ts	$TsNH_2$	 **2b**	80%
2	**1c**, $R^1 = CH_3$, R^2 = Ts	$TsNH_2$	 **2c** (dr > 20:1)	73%
3	**1d**, R^1 = i-Pr, R^2 = Ts	$TsNH_2$	 **2d** (dr > 20:1)	82%
4	**1e**, $R^1 = CH_2OTBS$, R^2 = Ts	$TsNH_2$	 **2e** (dr > 20:1)	72%
5	**1f**, $R^1 = CH_2SBn$, R^2 = Ts	$TsNH_2$	 **2f** (dr > 20:1)	42%
6	**1g**, R^1 = Bn, R^2 = Ns	$TsNH_2$	 **2g** (dr > 20:1)	83%
7	**1h**, R^1 = Bn, R^2 = Ms	$TsNH_2$	 **2h** (dr > 20:1)	73%
8	 **1i**	$TsNH_2$	 **2i** (dr = 6 : 1)	67%
9	**1a**, R^1 = Bn; R^2 = Ts	$NsNH_2$	 **2j** (dr > 20:1)	82%
10	**1a**	$PMBSNH_2$	 **2k** (dr > 20:1)	82%
11[d]	**1a**	$MsNH_2$	 **2l** (dr = 10:1)	43%
12	**1a**	$SESNH_2$	 **2m** (dr > 20:1)	98%
13[d]	**1a**	$PhC(O)NH_2$	 **2n** (dr = 10:1)	87%
14[d]	**1a**	NaN_3	 **2o** (dr = 10:1)	53%
15[e]	**1c**	$PhC(O)NH_2$	 **2p** (dr = 10:1)	73%
16[f]	 **3**	$TsNH_2$	 **4** (dr > 20:1)	52%

[a] Same conditions as Table 1, entry 4, unless otherwise noted. [b] Diastereoselectivity obtained by analysis of the crude ^1H NMR spectra. [c] Isolated yields. [d] Reaction was run using 4 equiv of $Cu(eh)_2$. [e] Reaction was run using 3 equiv of $Cu(eh)_2$. [f] Reaction was run at 150 °C.

(11) The SO_2R group of sulfonamides in six-membered rings prefers to be equatorial except when adjacent to a carbon bearing an alkyl substituent, presumably due to mimimization of $A_{1,3}$-strain: (a) Modarresi-Alam, A. R.; Amirazizi, H. A.; Bagheri, H.; Rijanzadeh, H.-R.; Kleinpeter, E. *J. Org. Chem.* **2009**, *74*, 4740–4746. (b) Toumieux, S.; Compain, P.; Martin, O. R.; Selkti, M. *Org. Lett.* **2006**, *8*, 4493–4496. (c) Ragoussi, M.-E.; Walker, S. M.; Piccanello, A.; Kariuki, B. M.; Horton, P. N.; Spencer, N.; Snaith, J. S. *J. Org. Chem.* **2010**, *75*, 7347–7357.

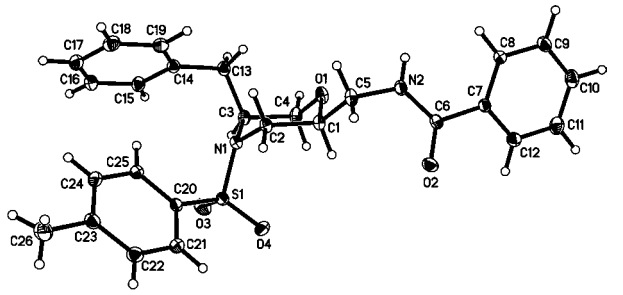
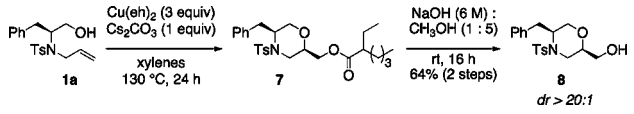
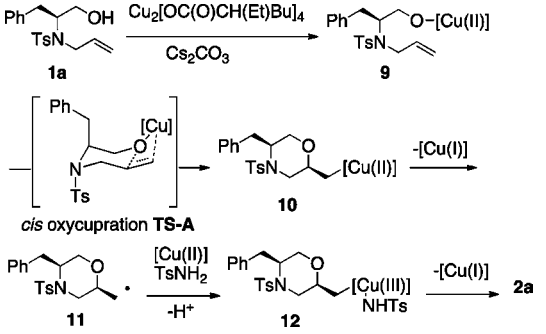


Figure 1. X-ray crystallography structure of 2,5-*cis*-**2n**.

Scheme 1. Dioxygenation in the Absence of Amine Nucleophile



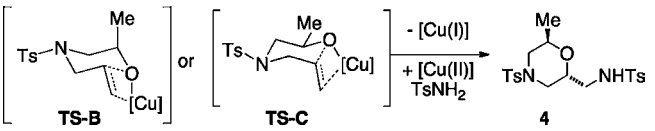
Scheme 2. Proposed Oxyamination Reaction Mechanism



It is possible that some of the amine nucleophiles could coordinate to the copper(II) prior to oxycupration, which may explain the dependence of the reaction diastereoselectivity on the amount of copper(II) 2-ethylhexanoate promoter in the reaction with benzamide. Such coordination could also explain why anilines fail to couple with **1a** via oxyamination. (Under the reaction conditions, aniline might complex too tightly with $Cu(eh)_2$ and render it unreactive.) Alternatively, the rate of C−N bond-forming reductive elimination (e.g., from **12**, Scheme 2) is likely different with different amine nucleophiles and could effect the observed reaction diastereoselectivity (by allowing ring opening and unselective ring closing when slow).[10]

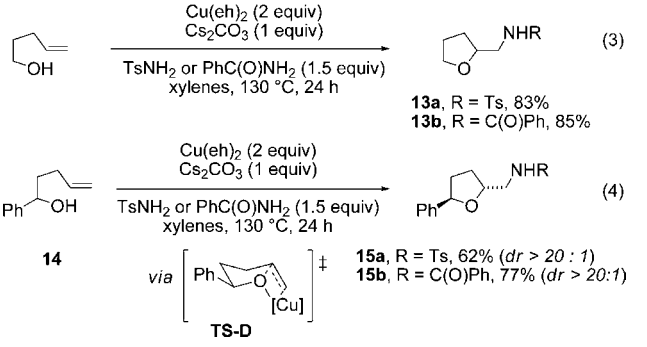
The 2,6-*trans*-diastereoselectivity observed in morpholine **4** can be rationalized by either **TS-B** or **TS-C**, where either the methyl or the alkene substituent must adopt a pseudoaxial position on the chairlike transition state (Scheme 3). The reaction of the α-methyl-substituted alcohol **3** was less

Scheme 3. Rationalization of 2,6-*trans*-Selectivity



efficient than that of **1a**, and the temperature of the reaction had to be raised to 150 °C for increased conversion, indicating steric demands proximal to the oxycupration bond formation in **TS-B** or **TS-C** decrease reactivity.

The synthesis of 2-aminomethyltetrahydrofurans was briefly examined. 4-Pentenol underwent oxyamination with $TsNH_2$ and $PhC(O)NH_2$, providing tetrahydrofurans **13a** and **13b** in 83 and 85% yield, respectively (eq 3). 1-Phenyl-4-pentenol **14** underwent oxyamination with $TsNH_2$ or $PhC(O)NH_2$ to provide the 2,5-*trans*-tetrahydrofurans **15** with >20:1 diastereoselectivity (eq 4), presumably via **TS-D**.



In summary, a new method for the stereoselective synthesis of oxygen-containing heterocycles via alkene oxyamination has been developed. This method offers direct entry into aminomethyl-functionalized morpholines and tetrahydrofurans and is a significant extension of copper(II)-promoted alkene difunctionalization chemistry both in the oxyamination transformation and in the ability to synthesize morpholines. Use of these new synthons in drug discovery should now be facile.

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Note Added after ASAP Publication. Reference 6p was added and this paper was reposted on August 17, 2012.

Supporting Information Available. Procedures and characterization data, NMR spectra for all new products, and cif data for **2n**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.