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Copper-Catalyzed Enantioselective Hydroalkoxylation of Alkenols for the Synthesis of Cyclic Ethers

Dake Chen,

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

Ilyas A. Berhane,

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

Sherry R. Chemler

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

Abstract

The copper-catalyzed enantioselective intramolecular hydroalkoxylation of unactivated alkenes for the synthesis of tetrahydrofurans, phthalans, isochromans, and morpholines from 4- and 5-alkenols is reported. The substrate scope is complementary to existing enantioselective alkene hydroalkoxylation and is broad with respect to substrate backbone and alkene substitution. The asymmetric induction and isotopic labeling studies support a polar/radical mechanism involving enantioselective oxycupration followed by C–[Cu] homolysis and hydrogen atom transfer. Synthesis of the antifungal insecticide furametpyr was accomplished.

Graphical Abstract

Corresponding Author: Sherry R. Chemler – Chemistry Department, State University of New York at Buffalo, Buffalo, New York 14260, United States; schemler@buffalo.edu.

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Supporting Information

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Experimental procedures and HPLC traces; NMR spectra of new compounds; X-ray structures of **6a** and **10** (PDF)

Accession Codes

CCDC 1978103 and 1992008 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The hydroalkoxylation (or hydroetherification) of alkenes, both intermolecular^{1–3} and intramolecular,^{4–12} has engaged the efforts of numerous research groups over the past several decades.^{13,14} Acyclic and cyclic ethers and esters, compounds that can be made by this transformation, have demonstrated broad utility from fuel additives² to moieties of bioactive small molecules.^{15–21} The synthesis of enantioenriched ethers is particularly relevant to the latter application. The catalytic enantioselective alkene hydroalkoxylation has presented a contemporary challenge, and notable solutions have emerged. In this regard, a number of enantioselective cyclizations of alcohols onto electron-deficient alkenes (oxa-Michael reactions), catalyzed by chiral Brønsted acids, have been reported.^{14,22–27} An enantioselective protonation/cyclization onto electron-rich enol ethers²⁸ has also been achieved. Reports of transition metal catalyzed enantioselective hydroalkoxylations of allenes have also appeared.^{29–35} Conversely, few effective solutions for the catalytic enantioselective hydroalkoxylation of electronically neutral alkenes have been identified (Scheme 1). Reports of transition metal catalyzed enantioselective intramolecular hydroetherifications include the titanium-catalyzed cyclization of 2-allylphenols (Scheme 1a),³⁶ the copper(I)-catalyzed cyclization of 2,2-diphenyl-4-pentenol (single substrate, 71% ee),³⁷ a cobalt-catalyzed cyclization of 2,2-disubstituted-4-pentenols (Scheme 1b),⁸ and an intermolecular iridium-catalyzed coupling of alkenes with phenols (single substrate, 36% ee).³⁸ An enantioselective mercury-promoted hydroalkoxylation that employs stoichiometric amounts of a chiral mercury catalyst has also been reported.³⁹ Thus, far, the scope of the intramolecular enantioselective transition metal catalyzed methods has been limited to terminal alkene substrates for the formation of chiral five-membered rings (Scheme 1a and 1c). A highly enantioselective intramolecular hydroalkoxylation catalyzed by a chiral imidophosphate Brønsted acid has recently been reported for the cyclization of 1,1-disubstituted alkenols (Scheme 1c).⁴⁰ Other enantioselective metal-free strategies, such as enzyme-catalyzed alkene protonation⁴¹ and photo-catalytic chiral ion paired C–O bond formation,⁴² have been reported for specific substrates with varying degrees of enantioselectivity. Herein we report the enantioselective intramolecular hydroalkoxylation of a range of 4- and 5-alkenols catalyzed by chiral copper(II) bis(oxazoline) complexes (Scheme 2b).

We have disclosed the copper(II)-catalyzed enantioselective carboetherification of alkenols involving net C–O and C–C bond formation across the alkene (Scheme 2a).^{43–46} These carboetherifications were demonstrated primarily for the synthesis of tetrahydrofurans, spirocyclic tetrahydrofurans, and phthalans. The C–O bond formation is thought to occur by alkene oxycupration⁴⁴ while the C–C bond formation, either intramolecular or intermolecular, is proposed to occur by addition of a carbon radical intermediate to an unsaturated moiety. The existence of a carbon radical (e.g., **II**, Scheme 2) was supported, in part, by observation of C–H bond formation upon addition of 1,4-cyclohexadiene, a well-known hydrogen atom transfer (HAT) reagent.^{43,47,48} 1,4-Cyclohexadiene (C₆H₈) is an attractive hydrogen-atom donor due to its low molecular weight, and its favorable hydrogen-atom donor kinetics (BDE = 76 kcal/mol, aromaticity driving force).^{47,48} Herein is reported development of this protocol to target enantioselective alkene hydroalkoxylation.

Parameters impacting the enantioselective copper-catalyzed hydroalkoxylation of tertiary alkenol **1a** are illustrated in Table 1. A screen of ligands and temperature (Table 1, entries 2–6) identified (*S,S*)-*t*-Bu-Box (**L4**) and 120 °C as optimal, providing **2a** in 97% isolated yield and 99% ee (Table 1, entry 6). Application of (*S,S*)-*i*-Pr-Box (**L3**) gave **2a** with 83% ee, the next highest selectivity (Table 1, entry 3). Lowering the catalyst loading from 20 mol % to 15 mol % diminished the yield (79% isolated) without diminishing the selectivity (97% ee) (Table 1, entry 7). 1,2-Dichloroethane (DCE) and toluene were acceptable reaction solvents, but gave lower levels of conversion (Table 1, entries 8 and 9). When the reaction was performed in the absence of K₂CO₃ (1 equiv), **2a** was still formed but in 77% isolated yield (99% ee) (Table 1, entry 10). Oxidants other than MnO₂ were briefly explored (Table 1, entries 11–13). Use of Ag₂CO₃ (1 equiv) as a stoichiometric oxidant resulted in an 82% isolated yield of **2a** in 99% ee. Use of air (1 atm) resulted in 5% of **2a** formed. Application of air as an oxidant in the absence of K₂CO₃ resulted in higher conversion (12% of **2a**), but a considerable amount of starting **1a** still remained. Under the optimal conditions (Table 1, entry 6), the reaction could be run on 1 mmol scale without significant loss of efficiency or selectivity (Table 1, entry 14). Other hydrogen atom donors were briefly explored. Use of γ -terpinene led to diminished conversion to product (Table 1, entry 15). Conversely, 9,10-dihydroanthracene proved to be an excellent hydrogen atom donor and **2a** was obtained in high yield and enantioselectivity (Table 1, entry 16).⁴⁹ Isopropanol, which has previously been used as a hydrogen atom donor,⁵⁰ was ineffective in this reaction but did not substantially inhibit formation of the carbaoetherification adduct **2** (Table 1, entry 17).

The scope of the enantioselective hydroalkoxylation of a range of 4-alkenols was examined (Scheme 3). The optimal reaction conditions (Table 1, entry 6) give 2,2,5-trisubstituted tetrahydrofuran **2a-H** from alkenol **1a** in 98% yield and 99% ee. Alkenol **1a** provided tetrahydrofuran **2a-D** in similar yield and enantioselectivity (85% yield, 96% ee) when 9,10-dihydroanthracene-9,9,10,10-d₄ (>95%) was applied as an atom transfer reagent⁵¹ under otherwise identical conditions. This conversion serves as an isotopic labeling experiment to support the proposed carbon radical H/D atom transfer mechanism (Scheme 2 and vide infra). 2,2,5,5-Tetrasubstituted tetrahydrofuran **2b**, which originated from enantioselective hydroetherification of a 1,1-disubstituted alkene, was formed with high efficiency and selectivity (81% yield, 97% ee). A range of highly enantioenriched phthalans **2c–2f** originating from differently substituted tertiary 2-vinylbenzyl alcohols were formed in excellent yields. (*E*)-1,2-Diaryl alkene variants (stilbenes) of these benzyl alcohols also reacted to form **2g–2j** in good yields, while the enantioselectivity ranged from very good to moderate, with a decrease observed for the electron-poor *p*-CF₃ styrene product **2i**. The lower enantiomeric excess of **2i** might indicate a competing racemic pathway, perhaps an electronically driven decrease in HAT rate that enables ring opening to an alkoxy radical and racemic reclosure.⁴³ 1,1-Disubstituted alkenes converted to 1,1,3,3-tetrasubstituted phthalans **2j** and **2k** in excellent yields and moderate (64%) to excellent (92%) enantioselectivity, respectively. Phenols were unreactive in this transformation (not shown).

A range of primary alcohols also underwent copper-catalyzed hydroalkoxylation in good yields (Scheme 3). The primary alcohols suffered from competitive oxidation to their respective aldehyde under the standard conditions using MnO₂ as a stoichiometric oxidant

(see e.g., **2p**, Scheme 3), however, so the milder oxidant, Ag₂CO₃, was applied instead. The enantioselective hydroalkoxylation/cyclization of 2,2-diphenyl-4-pentenol to 2-methyl-4,4-diphenyltetrahydrofuran **2l** was challenged by a competing intramolecular carboetherification process (as in Scheme 2a) under the otherwise optimal hydroalkoxylation conditions. Fortunately, an 82% yield of the desired **2l** was obtained when the 1,4-cyclohexadiene loading was increased to 5 equiv. The 1,2-disubstituted alkenol, (*E*)-2,2-diphenyl-5-phenyl-4-pentenol, cyclized efficiently under standard conditions to give tetrahydrofuran **2m**. Both reactions occurred with moderate enantioselectivity. 2-Indanyl-4-pentenol cyclized to give tetrahydrofuran **2n** efficiently (93% yield) but in a 65% ee. The related, predominantly (*E*) (*E*:*Z* = 78:22), 2-indanyl-5-methyl-4-pentenol cyclized to give 2-ethyltetrahydrofuran **2o** in 93% ee. A 64:36 *E*/*Z* 2-indanyl-5-methyl-4-pentenol sample gave **2o** in 84% ee, indicating the *E* alkene is more selective than the *Z*. (*E*)-5-Aryl-4-pentenols underwent the hydroetherification to produce 2-benzyl tetrahydrofurans **2p** and **2q** in moderate levels (ca. 50% ee) of enantioselectivity while the reaction of (*Z*)-5-phenyl-4-pentenol resulted in racemic **2p**. Tetrahydrofuran **2r** and phthalan **2s** were produced in good yields but low enantioselectivity from their respective alkenol substrates.

The enantioselective hydroalkoxylation was also extended to the synthesis of 3-methylisochromans **4** (Scheme 4a). A steric matching between ligand and substrate quickly became apparent. Primary benzyl alcohols **3a** and **3e** gave **4a** and **4e** with 82% and 68% ee, respectively when (*S,S*)-*t*-Bu-Box was applied as the chiral ligand, and in lower enantioselectivity when (*S,S*)-*i*-Pr-Box was used. Chroman **4e** was formed in higher enantioselectivity and conversion when DCE was applied as solvent instead of PhCF₃. Tertiary benzyl alcohols **4b–d** efficiently cyclized to give 1,1-dialkyl-3-methylisochromans **4b–4d** with high enantioselectivity. These sterically demanding alcohols paired best with the less sterically demanding ligand; e.g., **4d** was formed in much higher enantioselectivity when (*S,S*)-*i*-Pr-Box was applied as a chiral ligand (96% ee) instead of (*S,S*)-*t*-Bu-Box (72% ee). A carboxylic acid substrate, 6-allyl-2-methoxybenzoic acid, gave *O*-methylmellein,⁵² **4f**, in moderate yield and low enantioselectivity under these conditions. The enantioselective synthesis of morpholines **6** from *N*-allyl amino alcohols **5** was also feasible (Scheme 4b). Terminal alkenes **5a** and **5b** gave 2-methylmorpholines **6a** and **6b** in excellent enantioselectivity using (*S,S*)-*t*-Bu-Box. The (*S,S*)-*i*-Pr-Box ligand performed better in the synthesis of morpholines **6c–e** from 1,1-disubstituted alkene **5c** and (*E*)-1,2-disubstituted alkenes **5d** and **5e**, although the enantioselectivity ranged from poor (**6c**) to moderate and good (**6d** and **6e**). When the (*S,S*)-*t*-Bu-Box ligand was applied for the synthesis of **6e**, the selectivity remained excellent (90% ee) but the isolated yield was significantly diminished (29%).

The proposed catalytic cycle for the conversion of **1** to **2** is illustrated in Scheme 5. Coordination of alcohol **1** to the [Cu(II)] catalyst gives intermediate **III**. *Cis*-oxycupration via **TS-A** gives organocopper(II) species **IV**. **TS-A** leads to the major enantiomer of **2**; it minimizes steric interactions between the ligand and C(1) of the alkenol. These sterics are more pronounced for tertiary alkenols, which can rationalize the selectivity trend that tertiary alkenols react with higher enantioselectivity than primary alkenols. Homolysis of the C–Cu(II) bond of **IV** then gives alkyl radical **V** and [Cu(I)]. Hydrogen atom abstraction from

1,4-cyclohexadiene by radical **V** gives **2**, and oxidation of both the cyclohexadienyl radical to benzene and [Cu(I)] back to [Cu(II)] by the stoichiometric oxidant (Ag₂CO₃ or MnO₂) completes the catalytic cycle (Scheme 5).

The synthetic utility of this method is illustrated for the enantioselective synthesis of (*R*)-furametpyr (Limber), and its (+)-enantiomer could be correlated to the (*R*)-configuration for the first time (Scheme 6).¹⁵ Furametpyr, a tetrahydroiso benzofuran carboxamide, has been used as a fungicide to control sheath blight in rice crops in Japan.^{53,54} Although the enantiomers have been separated by chiral chromatography^{15,16} and individually studied,¹⁵ the absolute configuration of each enantiomer, as correlated with its respective optical rotation sign, has not previously been assigned. A previous six-step racemic synthesis of furametpyr started from 4-acetaminophthalide.¹⁶ Our synthesis of (*R*)-(+)-furametpyr was also accomplished in six steps and is enantioselective (Scheme 6). Conversion of methyl 3-bromo-2-methylbenzoate **7** to phosphonium bromide **8** followed by Wittig olefination and Grignard addition provided alkenol **1t**. Copper-catalyzed enantioselective hydroalkoxylation provided bromophthalan **2t** in 97% yield and 97% ee. Buchwald–Hartwig coupling⁵⁵ of **2t** with amide **9** provided (*R*)-(+)-furametpyr (**10**) in 60% yield.

In conclusion, we have developed a copper-catalyzed enantioselective hydroalkoxylation for a range of aliphatic 4- and 5-alkenols. On the whole, this method and the prior art (summarized in Scheme 1) support enantioselective hydroalkoxylation as a competitive approach for enantioenriched cyclic ether synthesis.⁵⁶ Efforts to elucidate a more nuanced mechanistic analysis that can better rationalize electronic and steric effects on reactivity and selectivity are underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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a) Hintermann and co-workers

b) Shigehisa and co-workers

c) List and co-workers

Scheme 1. Catalytic Enantioselective Hydroalkoxylations of Unactivated Alkenes^a^aL*, R* = chiral ligand.

a) **Our prior work:** [Cu]-catalyzed alkene *carboetherifications*

b) **This work:**
hydroalkoxylation

•aliphatic alcohols

•terminal alkenes,
1,1-disubstituted,
1,2-disubstituted

enantioselective [Cu]-catalyzed hydroalkoxylation of unactivated alkenes

tetrahydrofurans, phthalans, isochromans, morpholines

Scheme 2.

Copper-Catalyzed Carboetherification and Projected Hydroalkoxylation

Scheme 3. Alkenol Hydroetherification Scope^a

Reaction conditions from Table 1, entry 6 for tertiary alcohol substrates and entry 11 for primary alcohol substrates were applied. ^b9,10-Dihydroanthracene was used instead of 1,4-cyclohexadiene. ^c9,10-Dihydroanthracene-9,9,10,10-d₄ was used instead of 1,4-cyclohexadiene. 10% of the corresponding carboetherification adduct was also obtained. ^d5 equiv of 1,4-cyclohexadiene was used due to competitive intramolecular carboetherification (giving a known⁴³ [3.2.1]-bicyclic ether, as in Scheme 2a). ^eMnO₂ instead of Ag₂CO₃ was used, 38% of the corresponding aldehyde of **1** was obtained. The transferred H atom is illustrated on **2b** and **2j** for clarity.

Scheme 4. Synthesis of Isochromans and Morpholines

Reaction conditions from Table 1, entry 11 were applied but with the (*S,S*)-*i*-Pr-Box (**L3**).

^bReaction was run with (*S,S*)-*t*-Bu-Box (**L4**). ^cReaction was run at 105 °C with MnO₂ (2.6 equiv). ^dReaction was run in DCE, 105 °C.

Scheme 5.
Proposed Hydroalkoxylation Catalytic Cycle

Scheme 6.

Enantioselective Synthesis of (R)-(+)-Furametpyr

Table 1.

Effect of Reaction Conditions on the Enantioselective Hydroalkoxylation^a

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;"> <p>1a</p> </div> <div style="text-align: center; margin: 0 20px;"> <p>Cu(OTf)₂ (20 mol%), L (25 mol%)</p> <p>H-atom donor [H] (3 equiv)</p> <hr style="width: 100%;"/> <p>K₂CO₃ (1 equiv), oxidant [O],</p> <p>4 Å MS, 120 °C, 24 h</p> </div> <div style="text-align: center;"> <p>2a</p> </div> </div>						
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>Ligands:</p> <p>L1, R¹, R², R³ = H, achiral Box</p> <p>L2, (<i>R,R</i>)-Ph-Box, R¹ = Ph; R², R³ = H</p> <p>L3, (<i>S,S</i>)-<i>i</i>-Pr-Box, R¹, R³ = H; R² = <i>i</i>-Pr</p> <p>L4, (<i>S,S</i>)-<i>t</i>-Bu-Box, R¹, R³ = H; R² = <i>t</i>-Bu</p> <p>L5, (<i>4R,5S</i>)-bis-Ph-Box, R¹, R³ = Ph; R² = H</p> </div> <div style="width: 45%;"> <p>H-atom donors:</p> <p>C₆H₈: 1,4-cyclohexadiene </p> <p>C₁₄H₁₂: 9,10-dihydroanthracene </p> <p>C₁₀H₁₆: γ-terpinene </p> </div> </div>						
entry	L*	[O]	[H]	solvent	2a (%) ^b	ee (%) ^c
1	L1	MnO ₂	C ₆ H ₈	PhCF ₃	52	-
2 ^{de}	L2	MnO ₂	C ₆ H ₈	PhCF ₃	85	-76
3	L3	MnO ₂	C ₆ H ₈	PhCF ₃	71	83
4 ^e	L4	MnO ₂	C ₆ H ₈	PhCF ₃	46	99
5	L5	MnO ₂	C ₆ H ₈	PhCF ₃	80	-71
6	L4	MnO ₂	C ₆ H ₈	PhCF ₃	97	99
7 ^f	L4	MnO ₂	C ₆ H ₈	PhCF ₃	79	97
8 ^e	L4	MnO ₂	C ₆ H ₈	DCE	52	97
9 ^g	L4	MnO ₂	C ₆ H ₈	PhCH ₃	57	98
10 ^h	L4	MnO ₂	C ₆ H ₈	PhCF ₃	77	99
11	L4	Ag ₂ CO ₃	C ₆ H ₈	PhCF ₃	82	99
12	L4	air	C ₆ H ₈	PhCF ₃	5	nd
13 ^h	L4	air	C ₆ H ₈	PhCF ₃	12	98
14 ⁱ	L4	MnO ₂	C ₆ H ₈	PhCF ₃	86	98

Ligands: **L1**, $R^1, R^2, R^3 = \text{H}$, achiral Box**L2**, (*R,R*)-Ph-Box, $R^1 = \text{Ph}$; $R^2, R^3 = \text{H}$ **L3**, (*S,S*)-*i*-Pr-Box, $R^1, R^3 = \text{H}$; $R^2 = i\text{-Pr}$ **L4**, (*S,S*)-*t*-Bu-Box, $R^1, R^3 = \text{H}$; $R^2 = t\text{-Bu}$ **L5**, (*4R,5S*)-bis-Ph-Box, $R^1, R^3 = \text{Ph}$; $R^2 = \text{H}$ **H-atom donors:** C_6H_8 : 1,4-cyclohexadiene $\text{C}_{14}\text{H}_{12}$: 9,10-dihydroanthracene $\text{C}_{10}\text{H}_{16}$: γ -terpinene

entry	L*	[O]	[H]	solvent	2a (%) ^b	ee (%) ^c
15	L4	MnO ₂	C ₁₀ H ₁₆	PhCF ₃	61	nd
16	L4	MnO ₂	C ₁₄ H ₁₂	PhCF ₃	95	98
17 ^j	L4	MnO ₂	<i>i</i> -PrOH	PhCF ₃	<5	nd

^a Unless otherwise noted, all reactions were run in sealed tubes with dry solvent at 0.1 M w/r to alkenol **1a**, 20 mol % Cu(OTf)₂, 25 mol % ligand, 3 equiv hydrogen atom donor source, 1 equiv K₂CO₃, 4 Å mol. sieves and with either MnO₂ (260 mol %, <5 μ, 85% MnO₂ by weight), Ag₂CO₃ (100 mol %), or air (1 atm) at 120 °C.

^b Isolated yields of **2a** following flash chromatography on silica gel are reported.

^c % ee was determined by chiral gas chromatography (CP-Chirasil-Dex CB column).

^d Taken from ref 43.

^e Reaction run at 100 °C.

^f 15 mol % [Cu] and 18 mol % **L4** was used.

^g Reaction run at 110 °C.

^h No K₂CO₃ was used.

ⁱ 1 mmol (**1a**) scale.

^j 60% conversion to the respective carboetherification product was observed. nd = not determined.