

Stereoselective Copper-Catalyzed Intramolecular Alkene Aminooxygenation: Effects of Substrate and Ligand Structure on Selectivity

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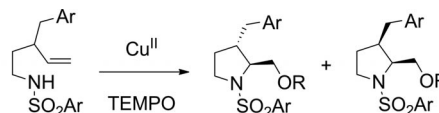
Keywords: Copper / Alkenes / Aminooxygenation / Pyrrolidine / Cyclic urea

A new protocol for diastereoselective copper-catalyzed intramolecular alkene aminooxygenation, which provides methyleneoxy-functionalized disubstituted pyrrolidines and five-membered cyclic ureas from the corresponding γ -alkenyl sulfonamides and *N*-allylureas, is reported. In addition, some

success was achieved in enantioselective desymmetrizations reactions. We discovered that the level of enantioselectivity and diastereoselectivity could be tuned by choice of copper(II) ligands and substrate *N*-substituent.

Introduction

Recent advances in metal-catalyzed intramolecular amino functionalization of unactivated alkenes (carboamination,^[1] diamination,^[2] aminooxygenation,^[3] amino-halogenation^[4]) have rendered these reactions practical synthetic strategies for the efficient, straightforward and stereoselective synthesis of nitrogen heterocycles.^[5] Metals that catalyze these processes include Au, Pd, Os, Ni and Cu, with Cu being the least expensive and one of the most versatile.^[1–5] We recently reported a diastereoselective copper(II)-promoted intramolecular alkene aminooxygenation protocol that provides 2,5-disubstituted pyrrolidines in high yields and high levels of diastereoselectivity and 2,3-disubstituted pyrrolidines in high yield and moderate selectivity (Scheme 1).^[6] These reactions are thought to involve carbon radical intermediates and use (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO) as the oxygen atom source. The resulting TEMPO adducts (Scheme 1) can be converted into the corresponding synthetically useful alcohol or aldehyde intermediates.^[3a,6] While this copper-promoted protocol, which uses commercially available copper(2-ethylhexanoate)₂ (1.5 equiv.), is operationally simple and high-yielding, we sought an environmentally more benign method that would use copper in catalytic rather than stoichiometric quantities. Herein is reported the successful development of a high-yielding copper-catalyzed diastereoselective alkene aminooxygenation method that uses O₂ (1 atm) as the stoichiometric oxidant.



Previous work: Cu(EH)₂ (1.5 equiv.), *trans/cis* = 2–3:1

This work: Cu(OTf)₂·bisoxazoline (20 mol-%), O₂, *trans/cis* = 6–14:1

Scheme 1. Copper-promoted and copper-catalyzed intramolecular alkene aminooxygenation reactions. EH = 2-ethylhexanoate, R = 2,2,6,6-tetramethylpiperidinyl.

During substrate and catalyst screening (vide infra), we found that we could further optimize the diastereoselectivity of the reactions with choice of ligand and *N*-substituent (e.g., Scheme 1). We have also investigated enantioselective desymmetrization reactions, and we have expanded the scope of the alkene aminooxygenation reaction to include *N*-allylurea substrates (vide infra).

Results and Discussion

Catalytic reaction conditions were screened with *meso*-sulfonamide **1a** (Table 1). When **1a** was subjected to catalytic amounts of Cu(OTf)₂ (20 mol-%) complexed with 2,2-bis[(4*R*)-4-phenyl-2-oxazolin-2-yl]propane [(*R*)-Ph-box, 25 mol-%] in the presence of TEMPO (300 mol-%) and O₂ (1 atm, balloon) in PhCF₃ at 120 °C for 24 h, 83% of 2,5-*cis*-pyrrolidine **2a** (*dr* > 20:1) was obtained (Entry 1, Table 1). Unfortunately, enantioselective desymmetrization with this *meso* substrate was not achieved (< 5% *ee*). Since achieving a catalytic diastereoselective process was still a worthy goal, we simplified the ligand by removing its phenyl substituents.^[1a] Reaction with the resulting complex of Cu(OTf)₂ (20 mol-%) and the unsubstituted bis(oxazoline) ligand **3** (25 mol-%) resulted in good yield (77%, Entry 2, Table 1) but occurred with a surprising reduction

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Table 1. Catalytic reaction optimization.^[a]

Entry	Ligand or catalyst	Solvent	Temp. [°C]	Yield [%] ^[b]	<i>dr</i> (<i>cis/trans</i>) ^[c]
1	(<i>R</i>)-Ph-box	CF ₃ Ph	120	83	>20:1 ^[d]
2	3	CF ₃ Ph	120	77	4:1
3	4	CF ₃ Ph	120	8 ^[e]	14:1
4	4	xylene	130	20 ^[e]	14:1
5	Cu(EH) ₂	xylene	120	90	>20:1
6	Cu(EH) ₂	xylene	110	65 ^[e]	>20:1
7 ^[f]	Cu(EH) ₂	xylene	120	56 ^[e]	>20:1

ligands

(*R*)-Ph-box

3 R = H

4 R = CH₃

[a] All reactions were run under O₂ (1 atm) at 0.1 M with respect to **1a**. [b] Yield refers to amount of product isolated after purification by flash chromatography on silica gel. [c] Diastereomeric ratio was determined by analysis of the crude ¹H NMR spectrum. [d] **2a**, < 5% *ee*. [e] The remainder of the material is the starting olefin **1a**. [f] The reaction was run by using 10 mol-% Cu(EH)₂; EH = 2-ethylhexanoate, OTf = trifluoromethanesulfonyl.

in diastereoselectivity (*dr* = 4:1). Reaction with the complex of Cu(OTf)₂ and 4,4,4',4'-tetramethylbis(oxazoline) **4** resulted in increased diastereoselectivity (*dr* = 14:1) but substantial reduction in yield (Entry 3, Table 1). Increasing the temperature provided only a slight increase in yield (Entry 4, Table 1). This marginal success with bis(oxazoline) ligands led us to re-investigate the use of Cu(2-ethylhexanoate)₂, but in catalytic quantity (20 mol-%). Gratifyingly, under such catalytic conditions (with 1 atm O₂) we were delighted to obtain both high yield and high diastereoselectivity at 120 °C (90% yield, *dr* > 20:1, Entry 5, Table 1). Further reduction in catalyst loading or reaction temperature resulted in decreased yield (Entries 6 and 7, Table 1).

The optimized catalytic conditions (Entry 5, Table 1) provide **2a** in comparable yield and diastereoselectivity as our previously reported^[6] conditions with the same substrate that use stoichiometric amounts (1.5 equiv.) of Cu(EH)₂ promoter.

We performed the Cu(EH)₂-catalyzed aminooxygenation reaction on a variety of α -substituted 4-pentenyl sulfonamides (Table 2), and uniformly high yields and diastereoselectivities were observed. The 2,5-*cis* diastereomer is highly favored for substrates where the R¹ and R² substituents are not tethered directly to one another (Entries 1–8, Table 2). In contrast, upon tethering the two substituents in a ring, the 2,5-*trans*-pyrrolidine was favored (Entry 9,

Table 2. Scope of the diastereoselective intramolecular aminooxygenation of α -substituted 4-pentenyl sulfonamides;^[a] Ns = 4-nitrobenzenesulfonyl, PMBS = *p*-methoxybenzenesulfonyl.

Entry	Substrate	Product ^[a]	Yield ^[b] [%]
1 ^[c]	1b , R ¹ = <i>i</i> Pr, R ² = PMBS	2b	80
2 ^[c]	1c , R ¹ = Me, R ² = Ts	2c	94
3 ^[c]	<i>ent</i> - 1d , R ¹ = Bu, R ² = Ts	<i>ent</i> - 2d	86
4 ^[c]	1e , R ¹ = CH ₂ OTBDPS, R ² = Ts	2e	90
5 ^[c]	1f , R ¹ = Bn, R ² = Ts	2f	80
6 ^[c]	1g , R ¹ = CH ₂ CH ₂ CH=CH ₂ , R ² = Ns	(±)- 2g	50
7	1h , R ¹ = CH ₂ CH ₂ CH=CH ₂ , R ² = SO ₂ Bn	(±)- 2h	70
8	1i , R ¹ = CH ₂ CH ₂ CH=CH ₂ , R ² = 3,5-di- <i>t</i> BuC ₆ H ₃ SO ₂	(±)- 2i	93
9 ^[d]	 (±)-1j	 (±)-2j	70

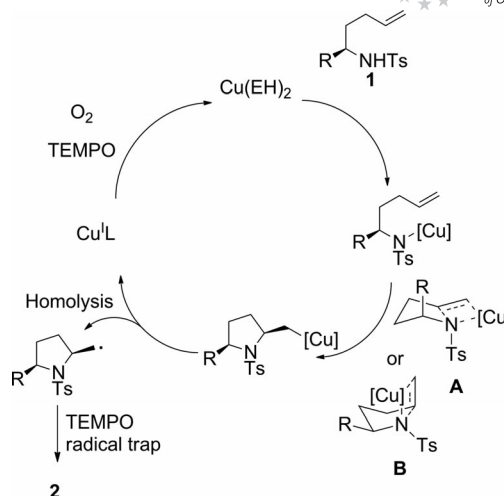
[a] Refer to Table 1, Entry 5 for reaction conditions. [b] Yield refers to amount of product isolated after purification by column chromatography on SiO₂. Diastereomeric ratio was determined by analysis of the crude ¹H NMR spectrum. [c] Reaction was run at 130 °C. [d] 1.5 equiv. of TEMPO was used.

Table 2). The relative placement of these two groups in the aminocupration cyclization transition state is proposed to account for the difference in diastereoselectivity of the two substrate types.^[6]

The *meso* substrate **1i** functionalized with the bulky 3,5-di-*tert*-butylphenylsulfonyl group also gave **2i** in < 5% *ee* in an attempted enantioselective desymmetrization reaction with the Cu(OTf)₂·(*R*)-Ph-box catalyst (reaction not shown).

The proposed catalytic cycle is illustrated in Scheme 2. Upon copper(II) complexation, the resulting N–Cu intermediate undergoes *syn* aminocupration through transition state **A** or **B** to generate the 2,5-*cis*-pyrrolidine. In these transition states, interaction between the adjacent SO₂Ar and R groups are minimized. The resulting organocupper(II) species readily undergoes C–Cu homolysis to form the primary radical, which is rapidly trapped with TEMPO. The Cu^I complex is re-oxidized by TEMPO in the presence of O₂, thereby regenerating the Cu^{II} catalyst.

We next investigated the catalytic diastereoselective reactions of β- and γ-monosubstituted 4-pentenylsulfonamides (Table 3). Under conditions A, Cu(EH)₂ (20 mol-%), was used as the catalyst. Under conditions B, Cu(OTf)₂ (20 mol-%) complexed to bis(oxazoline) **3** (25 mol-%) was used as the catalyst. The *trans* diastereomers of the 2,3-disubstituted pyrrolidines **6** were formed as the major products from γ-substituted 4-pentenylsulfonamides **5**, and the *cis* diastereomers of the 2,4-disubstituted pyrrolidines **8** were formed as the major products from β-substituted 4-pentenylsulfonamides **7**. In all cases, conditions B gave superior

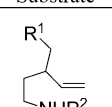
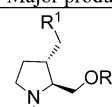
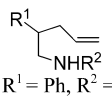
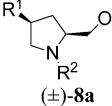


Scheme 2. Proposed alkene aminooxygenation catalytic cycle.

diastereoselectivities. We also observed an increase in diastereoselectivity in changing the *N*-substituent from tosyl to 3,5-di-*tert*-butylphenylsulfonyl (compare Entry 6 to 10 and Entry 16 to 18, Table 3).

We reinvestigated the possibility of a catalytic enantioselective desymmetrization reaction with the *meso*-β-allyl-4-pentenylsulfonamides **7b** and **7c** (Scheme 3). In this case, although the diastereoselectivity was modest (2–2.5:1), enantioselective desymmetrization was achieved. Notably, the *N*-(3,5-di-*tert*-butylphenylsulfonyl)-2,4-*cis*-pyrrolidine **8c** was produced in 98% *ee*. When compared to the 75% *ee*

Table 3. Diastereoselective aminooxygenation of β- and γ-substituted 4-pentenylsulfonamides; R³ = 2,2,6,6-tetramethylpiperidine.

Entry	Substrate	Major product	Conditions ^[a]	Yield [%] ^[b] (<i>dr</i>) ^[c]
1			A	78 (3:1)
2			B	70 (6:1)
	5a , R ¹ = <i>o</i> -MeOC ₆ H ₄ , R ² = Ts	(±)- 6a		
3	5b , R ¹ = <i>m</i> -F ₃ CC ₆ H ₄ , R ² = Ts	(±)- 6b	A	82 (2:1)
4			B	75 (5:1)
5	5c , R ¹ = Ph, R ² = Ts	(±)- 6c	A	84 (3:1)
6			B	96 (8:1)
7	5d , R ¹ = Ph, R ² = Ms	(±)- 6d	A	85 (2.4:1)
8			B	80 (6:1)
9	5e , R ¹ = Ph, R ² = 3,5-di- <i>t</i> BuC ₆ H ₃ SO ₂	(±)- 6e	A	76 (3:1)
10			B	83 (14:1)
11	5f , R ¹ = Ph, R ² = Ns	(±)- 6f	A	80 (3:1)
12			B	91 (12.5:1)
13			A	60 (1:1)
14			B	90 (8:1)
	7a , R ¹ = Ph, R ² = Ts	(±)- 8a		
15	7b , R ¹ = CH ₂ CH=CH ₂ , R ² = Ts	(±)- 8b	A	68 (1:1)
16			B	87 (4:1)
17	7c , R ¹ = CH ₂ CH=CH ₂ , R ² = 3,5-di- <i>t</i> BuC ₆ H ₃ SO ₂	(±)- 8c	A	70 (1:1)
18			B	81 (7:1)

[a] Reaction conditions: A: Cu(EH)₂ (20 mol-%), O₂ (1 atm, balloon), K₂CO₃ (1 equiv.), TEMPO (3 equiv.), xylenes, 120 °C, 24 h. B: Cu(OTf)₂ (20 mol-%), bis(oxazoline) **3** (25 mol-%), K₂CO₃ (1 equiv.), TEMPO (300 mol-%), CF₃Ph, O₂ (1 atm, balloon), 120 °C (oil-bath temp.), 24 h. [b] Yield refers to the sum of the products isolated by chromatography on SiO₂. [c] Diastereomeric ratio was determined by analysis of the crude ¹H NMR spectrum.

served in reactions with the *meso* substrate **1a** (e.g. Table 1, Entry 1). Transition state **C** (substrate **7c**) may be more favorable than transition state **A** (substrate **1a**) since the α -substituent in TS **A** is in an axial position. We are currently investigating this further with molecular modeling calculations.

Experimental Section

Representative Procedures for Catalytic Diastereoselective Aminooxygenation of Alkenes

1-[(2*S*,5*S*)-5-Methyl-1-tosylpyrrolidin-2-yl]methoxy-2,2,6,6-tetramethylpiperidine (2c**):** Table 2, Entry 2. Sulfonamide **1c** (40 mg, 0.158 mmol, 1 equiv.), Cu(EH)₂ (11 mg, 0.032 mmol, 0.2 equiv.), TEMPO (74 mg, 0.474 mmol, 3 equiv.), K₂CO₃ (22 mg, 0.158 mmol, 1 equiv.) and xylenes (1.6 mL) were combined in a 100 mL round-bottom flask equipped with a magnetic stir bar. The flask was fitted with a glass side-arm adapter tapered to connect to a short rubber vacuum hose, through which O₂ (balloon) was introduced. The reaction mixture was heated to 120 °C and stirred for 24 h. The cooled solution was filtered through an SiO₂ plug, with Et₂O washing. Concentration in vacuo and flash chromatography on SiO₂ (5% EtOAc in hexanes) afforded disubstituted pyrrolidine **2c** (61 mg, 94%) as a white solid. The diastereoselectivity (> 20:1) was determined from the crude ¹H NMR spectrum. The *cis* stereochemistry of **2c** was assigned by NOE experiments. Data for *cis*-**2c**: M.p. 121–125 °C. [α]_D²⁰ = –63.9° (*c* = 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 7.72 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 3.90 (dd, *J* = 9.0, 3.5 Hz, 1 H), 3.84 (t, *J* = 8.0 Hz, 1 H), 3.72 (m, 1 H), 3.62 (m, 1 H), 2.41 (s, 3 H), 1.91 (m, 1 H), 1.67–1.55 (m, 3 H), 1.50–1.43 (m, 6 H), 1.36 (d, *J* = 6.0 Hz, 3 H), 1.18 (s, 3 H), 1.16 (s, 3 H), 1.09 (s, 3 H), 1.08 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 143.1, 135.0, 129.5, 127.6, 78.6, 60.0, 57.4, 39.6, 32.9, 32.5, 27.3, 22.8, 21.4, 20.2, 17.0 ppm. IR (neat, thin film): $\tilde{\nu}$ = 2976, 2931, 2877, 1591, 1460, 1351, 1261, 1211, 1161, 1098, 1052, 957, 812, 663 cm^{–1}. HRMS (ESI): calcd. for C₂₂H₃₇N₂O₃S [M + H]⁺ 409.2519; found 409.2522.

(±)-*cis*- and (±)-*trans*-{3-Benzyl-1-[(3,5-di-*tert*-butylphenyl)sulfonyl]pyrrolidin-2-yl]methoxy-2,2,6,6-tetramethylpiperidine (*cis*-6e** and *trans*-**6e**):** Table 3, Entry 10. Cu(OTf)₂ (7.0 mg, 0.019 mmol, 0.2 equiv.) and bis(oxazoline) **3** (4.3 mg, 0.024 mmol, 0.25 equiv.) were allowed to complex in CF₃Ph (0.7 mL) in a 100 mL round-bottomed flask at 60 °C for 2 h. The heat was removed, and the resulting room-temperature solution was treated with TEMPO (44 mg, 0.282 mmol, 3 equiv.), K₂CO₃ (13 mg, 0.094 mmol, 1 equiv.) and a solution of sulfonamide **5e** (40 mg, 0.094 mmol, 1 equiv.) in CF₃Ph (0.3 mL). The reaction mixture was heated to 120 °C (oil-bath temp.) under O₂ (1 atm, balloon, see above) for 24 h. Filtration of the cooled solution through an SiO₂ plug (washed with Et₂O) and removal of the solvent in vacuo afforded the crude product. Purification by flash chromatography on SiO₂ (5% EtOAc in hexanes) gave a 14:1 *trans/cis* mixture of pyrrolidines **6e** (46 mg, 83% yield). The diastereomers were further separated by HPLC (5% EtOAc in hexanes); (±)-*cis*-**6e** eluted first.

Major Pyrrolidine (±)-*trans*-6e**** was obtained as a clear, colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.72 (s, 2 H), 7.67 (s, 1 H), 7.19 (t, *J* = 7.0 Hz, 2 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 6.83 (d, *J* = 7.5 Hz, 3.96 (dd, *J* = 9.0, 3.5 Hz, 1 H), 3.84 (dd, *J* = 9.5, 8.0 Hz, 1 H), 3.46 (m, 1 H), 3.36 (m, 2 H) 2.49 (m, 1 H), 2.29 (dd, *J* = 14.0, 7.0 Hz, 1 H), 1.89 (m, 1 H), 1.76 (dd, *J* = 13.5, 8.5 Hz, 1 H), 1.40–1.49 (m, 6 H), 1.36 (s, 18 H), 1.27 (m, 1 H), 1.18 (s, 3 H), 1.15

(s, 3 H), 1.08 (s, 3 H), 1.00 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 152.1, 139.6, 136.7, 128.5, 128.3, 126.6, 126.1, 121.7, 78.8, 63.4, 59.8, 47.8, 43.4, 39.5, 39.1, 35.1, 33.1, 33.0, 31.3, 29.1, 20.3, 20.1, 17.0 ppm. IR (neat, thin film): $\tilde{\nu}$ = 2965, 2870, 1599, 1475, 1348, 1160, 1137, 1116, 1049, 757, 701 cm^{–1}. HRMS (ESI) calcd. for C₃₅H₅₅O₃N₂S [M + H]⁺ 583.3928; found 583.3941.

Minor Pyrrolidine (±)-*cis*-6e**** was obtained as a clear, colorless oil: ¹H NMR (500 MHz): δ = 1.95 (m, 1 H), 1.82 (m, 1 H), 1.64 (m, 1 H), 1.46–1.49 (m, 6 H), 1.35 (s, 18 H), 1.33 (s, 3 H), 1.26 (s, 3 H), 1.16 (s, 3 H), 1.11 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 151.9, 140.5, 137.0, 128.4, 128.3, 126.5, 126.0, 121.4, 77.8, 62.0, 60.1, 59.6, 47.5, 43.7, 39.8, 35.5, 35.0, 33.4, 32.8, 31.2, 30.3, 20.4, 17.0 ppm. IR (neat, thin film): $\tilde{\nu}$ = 2964, 2366, 1599, 1454, 1348, 1246, 1166, 1030, 751, 701 cm^{–1}. HRMS (ESI) calcd. for [M + H]⁺ C₃₅H₅₅O₃N₂S: 583.3928; found 583.3938.

Supporting Information (see footnote on the first page of this article): Complete experimental details and spectroscopic data for all new compounds.

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