

Diastereoselective Pyrrolidine Synthesis via Copper Promoted Intramolecular Aminooxygenation of Alkenes: Formal Synthesis of (+)-Monomorine

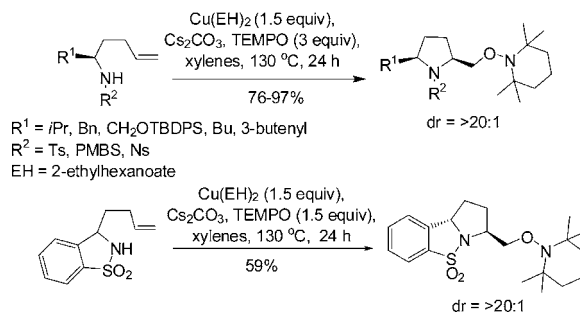
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ABSTRACT



The diastereoselectivity of the copper-promoted intramolecular aminooxygenation of various alkene substrates was investigated. α -Substituted 4-pentenyl sulfonamides favor the formation of 2,5-*cis*-pyrrolidines ($\text{dr} > 20:1$) giving excellent yields which range from 76–97% while γ -substituted substrates favor the 2,3-*trans* pyrrolidine adducts with moderate selectivity (ca. 3:1). A substrate whose N-substituent was directly tethered to the α -carbon exclusively yielded the 2,5-*trans* pyrrolidine. The synthetic utility of the method was demonstrated by a short and efficient formal synthesis of (+)-monomorine.

Pyrrolidine moieties are frequently found in biologically active molecules.¹ These include glycosidase inhibitors such as alexine² and australine,³ antiviral agents such as preussin,⁴ antileukemia agents such as harringtonine⁵ and crambescidin,⁶ and the angiotensin-converting enzyme (ACE) inhibitor ramipril.⁷ Due to the therapeutic importance of these

pyrrolidine alkaloids, considerable effort has been devoted to the stereoselective synthesis of substituted pyrrolidines.⁸ In this paper, we report a copper(II) promoted diastereoselective synthesis of disubstituted pyrrolidines via an intramolecular aminooxygenation of alkenes.

The intramolecular aminooxygenation of alkenes can be catalyzed and promoted using a number of reagents and catalysts, but few result in the stereoselective synthesis of pyrrolidines.^{9–12} Donohoe has reported a diastereoselective osmium-catalyzed aminohydroxylation that results in the synthesis of 2,5-*cis*-

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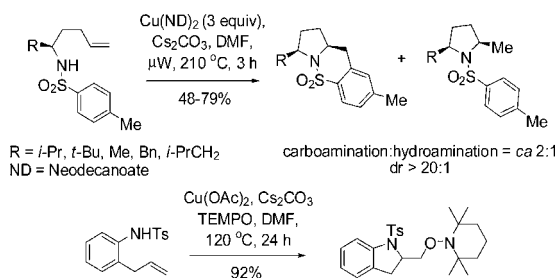
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pyrrolidines.^{9a} However, Donohoe's reaction requires two coordinating groups in the substrate, the sulfonamide nitrogen that forms the C–N bond and an additional vicinal alcohol, to achieve high diastereoselectivity.

The diastereoselective copper-promoted aminooxygenation reactions reported in this paper do not require additional coordinating groups to provide high levels of 2,5-*cis*-pyrrolidine selectivity. Furthermore, analysis of the conformational factors that control the diastereoselectivity in these reactions led to the development of a 2,5-*trans*-pyrrolidine selective reaction as well (*vide infra*).

Recent reports from our group showed that the copper(II)-promoted synthesis of 2,5-disubstituted pyrrolidines via intramolecular alkene carboamination occur in high diastereoselectivity with predominating *cis* stereochemistry (Scheme 1).^{13a} Mechanistic studies of these reactions^{13a} revealed a

Scheme 1. Copper(II) Promoted Diastereoselective Formation of 2,5-*cis*-Pyrrolidines and TEMPO Trapping of Radical Intermediate



pathway involving a primary carbon radical intermediate that was trapped efficiently with 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), a standard carbon radical trapping agent (Scheme 1).^{13b} These results led us to investigate the diastereoselectivity of this net alkene aminooxygenation reaction using substrates bearing substituents α as well as γ to the sulfonamide unit.

We first investigated the aminooxygenation reaction of 4-pentenyl sulfonamide **1** using catalytic amounts of copper(II) salts (Table 1).^{11f,g} The use of the bisoxazoline ligand [(*R,R*)-Ph-box] gave better conversion than the 2,2'-dipyridyl ligand under catalytic conditions using O₂ (1 atm) (Table 1, entries 1 and 2). The (*R,R*)-Ph-box ligand and substrate **1** both favor formation of the C2(*S*) stereocenter (the reaction is matched).^{11f} We have previously used these conditions to catalyze the aminooxygenation reactions of slightly more reactive achiral substrates.^{11f,g} However, neither reaction of sulfonamide **1** went to completion. While the catalytic reaction shows promise (yield = 60%, Table 1, entry 2), its optimization is ongoing. On the other hand, we were able to rapidly identify a highly efficient and operationally simple reaction process by use of a slight excess (1.5 equiv) of a readily available and inexpensive copper(II) carboxylate, copper(II) 2-ethylhexanoate [Cu(EH)₂]. Because Cu(EH)₂ is neither very expensive nor toxic and since the reaction is

Table 1. Effects of Varying the Amount of Cu(R)₂, Ligand, Temperature, and Solvent^a

entry	R (equiv)	ligand (equiv)	solvent	temp (°C)	yield (%) ^b
1 ^c	OTf (0.2)	2,2'-dipyridyl (0.2)	xylenes	130	20 ^d
2 ^c	OTf (0.2)	(<i>R,R</i>)-Ph-box (0.2)	xylenes	130	60 ^d
3	EH (3)	–	DMF	160	80
4	EH (1.5)	–	DMF	160	40
5	EH (1.5)	–	xylenes	130	94
6 ^e	EH (1.5)	–	xylenes	130	78
7	EH (1.5)	–	xylenes	120	54 ^d
8	EH (1.5)	–	DMF	130	40 ^d
9	EH (1.5)	–	CF ₃ Ph	120	63 ^d
10	EH (1.0)	–	CF ₃ Ph	120	38 ^d
11	EH (1.0)	–	xylenes	130	68 ^d

^a All reactions were run in pressure tubes at 0.1 M w/r to **1**. ^b Yield refers to amount of product isolated after purification by flash chromatography on silica gel. ^c Reaction was run under O₂ (1 atm). ^d Remainder of the material is the starting olefin **1**. ^e Reaction was run using 1.5 equiv of TEMPO. EH = 2-ethylhexanoate, PMBS = *p*-methoxybenzenesulfonyl.

quite operationally simple, not requiring an O₂ atmosphere, we concluded that the stoichiometric reaction provides an acceptable solution until superior catalytic conditions are identified.

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Table 2. Diastereoselective Aminoxygenation of Alkenes^a

entry	substrate	product	yield (%) ^b (selectivity) ^d
1			94 (dr >20:1)
2			97 (dr >20:1)
3			96 (dr >20:1)
4			94 (dr >20:1)
5			97 (dr >20:1)
6			76 (dr >20:1)
7		 	80 ^c (trans: cis = 3:1)
8		 	88 ^c (trans: cis = 2:1)
9 ^e		 	57 ^f (20, dr >20:1) 20:21 = 7:1

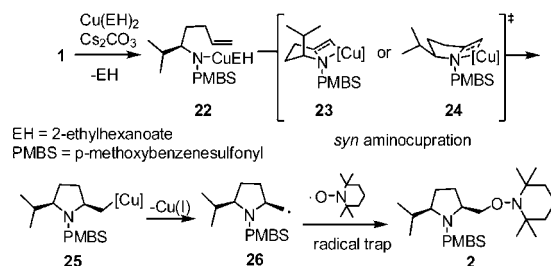
^a R = 2,2,6,6-tetramethylpiperidine, Reaction conditions: 1.5 equiv of Cu(EH)₂, 3 equiv of TEMPO, 1 equiv of Cs₂CO₃, xylenes (0.1 M), 130 °C, 24 h, pressure tube. ^b Yield refers to amount of product isolated upon purification by column chromatography on SiO₂. ^c Yield refers to the sum of the products isolated by chromatography on SiO₂. ^d Diastereomeric ratio was determined by analysis of the crude ¹H NMR spectrum. ^e Reaction was run at 140 °C. ^f Yield refers to amount of **20** isolated.

Copper(II) 2-ethylhexanoate is more reactive than many copper carboxylates owing to its high solubility in organic solvents.^{13a,14} Among the solvents (DMF, xylenes, CF₃Ph) and temperatures (120–160 °C) surveyed, we found that xylenes at 130 °C provided the optimal yield (94%, Table 1, entry 5). Slightly more than 1 equiv of Cu(EH)₂ (1.5 equiv) was also required for optimal yield, and the reaction was complete within 24 h. Lower TEMPO amounts (1.5 equiv) gave slightly lower yield (entry 6), so the reactions were run using 3 equiv of TEMPO.

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Using the optimized reaction conditions (Table 1, entry 5), the reactions of a number of α and γ-substituted 4-pentenyl sulfonamides were examined (Table 2). Similar to the diastereoselectivity results in the analogous copper(II) promoted carboamination reaction of 4-pentenyl sulfonamides (Scheme 1), substrates **1**, **3**, **5**, **7**, and **9** generated the 2,5-*cis*-pyrrolidines **2**, **4**, **6**, **8**, and **10** in excellent yields with >20:1 selectivity (Table 2, entries 1–5). Gratifyingly, no hydroamination side products were observed in these reactions. The crystal structure of **2** indicated *cis* stereochemistry with an absolute configuration of C2(S), C5(R) (see Supporting Information).¹⁵ The relative configurations of pyrrolidines **4**, **6**, **8**, and **10** were assigned by analogy and by NOE experiments. Upon changing the nitrogen protecting group from tosyl (Ts) or *p*-methoxybenzenesulfonyl (PMBS) to 4-nitrophenyl sulfonyl (Ns), there was a slight decrease in the yield, but a high level of stereocontrol was still observed (Table 2, entry 6). The Ns group is usually more easy to remove.¹⁶ γ-Substituted 4-pentenyl sulfonamides **13** and **16** gave only moderate selectivity (3:1 for **13** and 2:1 for **16**) favoring the *trans* pyrrolidine adducts (Table 2, entries 7 and 8). Little difference between the electron-donating OMe and electron-withdrawing CF₃ benzyl substituents was observed. The relative configurations of the *cis* and *trans* isomers were assigned by X-ray crystallography and NOE experiments (see Supporting Information). The *trans* pyrrolidine is presumably favored due to equatorial placement of the γ-substituent in the cyclic transition state (see Supporting Information). It was not clear if substrate **19**, with an internal disubstituted olefin, would favor aminoxygenation (**20**) or oxidative amination (**21**). In the carboamination series^{13a} only **21** was obtained. To our delight, the aminoxygenation product **20** was isolated as the major product with >20:1 diastereoselectivity and 7:1 aminoxygenation:oxidative amination selectivity. The stereochemistry of **20** was determined by X-ray crystallography (see Supporting Information).¹⁵

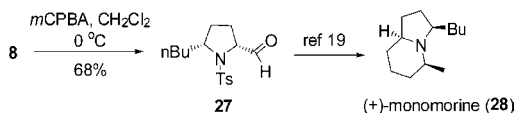
The mechanism illustrated in Scheme 2 provides a rationalization for the high degree of *cis* stereoselectivity observed in the aminoxygenation reaction of the α substituted substrates. It was reasoned that this reaction underwent a mechanism similar to the copper(II) promoted intramolecular carboamination reaction.^{13a} The first C–N bond is proposed to form in a stereoselective manner via *syn* aminocupration through the chairlike transition state **23** or possibly the boat-like transition state **24**, generating an

Scheme 2. Proposed Mechanism for the Formation of 2,5-*cis*-Pyrrolidine

unstable organocopper(II) species **25**. This organocopper(II) species then undergoes homolysis, forming a primary carbon radical intermediate which is trapped by the TEMPO radical,^{11f,13} forming the cis aminoxygenation product **2**.

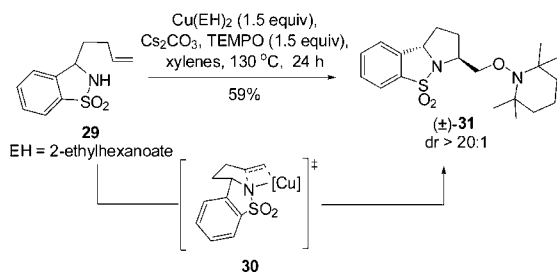
To demonstrate the synthetic utility of the method, we performed a short and efficient formal synthesis of (+)-monomorine (**28**). (+)-Monomorine is an indolizidine alkaloid that is known to be a trail pheromone of a health hazard pharaoh ant *Monomorium pharaonis* L.¹⁷ Along with the other indolizidine alkaloids, (+)-monomorine has been the target of many organic chemists for some time. As a result, a number of different ways of synthesizing it have been reported.¹⁸ Particularly relevant to this study was the synthesis reported by Bäckvall and co-workers¹⁹ wherein they used aldehyde **27** as an intermediate in their synthesis of (+)-monomorine. Utilizing our method, aldehyde **27** was synthesized in 6 steps and 40% overall yield. Our route to **27** is 3 steps shorter than Bäckvall's approach. The 2,5-*cis*-pyrrolidine **8** was formed from substrate **7** in 94% yield and high selectivity (>20:1) (Table 2, entry 4). Substrate **7** was readily synthesized from commercially available D-norleucine (see Supporting Information). The TEMPO adduct **8** was oxidized to aldehyde **27** using *m*CPBA in 68% yield (Scheme 3).²⁰ We have previously also demonstrated that dissolving metal reduction can chemoselectively reveal one or both of the free amine and free alcohol functionalities.^{11f}

Scheme 3. Formal Synthesis of (+)-Monomorine



On the basis of the proposed transition state for the α substituted 4-pentenyl sulfonamides (Scheme 2), we predicted that if the N-substituent was directly tethered to the α -carbon (e.g., substrate **29**), the reaction would occur via transition state **30**, which places the α -substituent in a pseudoequatorial position, thereby favoring the formation of the 2,5-*trans* pyrrolidine adduct (Scheme 4). When sulfonamide **29** was subjected to the optimized reaction conditions

Scheme 4. Diastereoselective Aminooxygenation of Sulfonamide **29** Forming the *trans* Pyrrolidine **31**



for this copper(II) promoted aminooxygenation, it produced the *trans* pyrrolidine **31** in poor yield but with high diastereoselectivity (>20:1). We hypothesized that addition of excess TEMPO (3 equiv) caused the decomposition of the starting material via benzylic oxidation. When the amount of TEMPO was decreased to 1.5 equiv, we were able to increase the yield to 59% with the same level of selectivity. The *trans* configuration of pyrrolidines **31** was confirmed by X-ray crystallography (Figure 1).¹⁵ We have previously demonstrated that the SO₂ moiety in sultams such as **31** can be removed by dissolving metal reduction.^{13a,21}

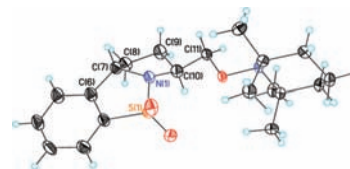


Figure 1. Crystal structure of **31**.

In conclusion, we have developed a high yielding route for the synthesis of disubstituted pyrrolidines via the intramolecular copper promoted aminooxygenation of alkenes. These reactions afford the 2,3-*trans*-pyrrolidines in moderate selectivity and both the 2,5-*cis*- and 2,5-*trans*-pyrrolidines in excellent diastereoselectivity. The efficiency of this approach was demonstrated with the formal synthesis of (+)-monomorine. More efforts to apply this method to the total synthesis of interesting biologically active nitrogen heterocycles and further investigations into substrate scope and catalytic methods are currently underway.

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Supporting Information Available: Procedures and characterization data and NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) CCDC 696031 (**2**), 711960 (**17**), 714177 (**20**), and 704323 (**31**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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