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Chiral Indoline Synthesis via Enantioselective Intramolecular Copper-Catalyzed Alkene Hydroamination

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Supporting Information

ABSTRACT: An enantioselective copper-catalyzed hydroamination/cyclization of *N*-sulfonyl-2-allylanilines for the synthesis of chiral 2-methylindolines is reported. Chiral 2methylindolines are important subunits in drugs and bioactive compounds. This method provides chiral *N*-sulfonyl-2methylindolines in up to 90% ee.

The enantioselective hydroamination/cyclization of aminoalkenes is an active topic of interest to organic and organometallic chemists.¹ The nitrogen heterocyclic products obtained in these reactions are commonly found as components of bioactive natural products and pharmaceutical agents. While a number of highly selective methods for the metal-catalyzed enantioselective hydroamination/cyclization of 4-pentenylamines have been developed,¹ few methods report use of 2-allylaniline-based substrates,^{1f-h} and the highest enantioselectivity reported for the synthesis of a 2-methylindoline via alkene hydroamination is 70% ee.^{1g} 2-Methylindolines can be found in bioactive molecules with diverse biological activities (e.g., Figure 1).²





The synthesis of chiral 2-methylindolines has been actively pursued,³ and resolutions are frequently used to obtain these compounds in optically enriched form.^{3b,c} The enantioselective hydrogenation of indoles has also been reported as a straightforward method for synthesizing chiral indolines, but the procedures often suffer from long reaction times, harsh reaction conditions, or limited substrate scope.^{3d,e} Herein is reported a complementary method for the synthesis of variously substituted chiral 2-methylindolines **2** from *N*-sulfonyl-2-allylanilines **1** with up to 90% ee, the highest selectivity yet reported for the enantioselective alkene hydro-amination/cyclization of 2-allylaniline derivatives (Scheme 1, vide infra).

Reports of copper(I) and copper(II) complexes catalyzing the racemic hydroamination of alkenes have previously



appeared.⁴ Copper(II) triflate catalyzed intra- and intermolecular hydroamination of alkenes with sulfonamides have been reported by Komeyama, Chan, and Hii, respectively, but these reactions are generally thought to be promoted by trace amounts of Brønsted acid generated under the reaction conditions.^{4a-c} A Cu(O-t-Bu)·Xantphos catalyzed hydroamination/cyclization of electron-rich amines has been reported where copper(I) is thought to directly activate the alkene (via aminocupration), but no enantioselective variant of this reaction has yet appeared.^{4d} The enantioselective copper(II)-catalyzed hydroamination/cyclization reaction reported herein is based on a family of alkene aminofunctionalization reactions we have recently developed.⁵ In these reactions, addition of the nitrogen and copper(II) across the alkene is thought to occur via a *cis* aminocupration transition state (Scheme 1).^{Sb,c} The





resulting organocopper(II) intermediate is unstable and suffers homolysis under the reaction conditions, generating a primary organic radical and copper(I). We have shown that the carbon radical can be trapped with (2,2,6,6-tetramethylpiperidin-1yl)oxyl radical (TEMPO) or undergo addition to various alkenes and arenes.⁵ We reasoned that atom transfer via H

Special Issue: Copper Organometallic Chemistry

Received: August 3, 2012 Published: August 27, 2012 atom abstraction from a good H atom donor, e.g. 1,4-cyclohexadiene,^{5d} would provide a net hydroamination product (Scheme 1). 5c

The enantioselectivity would be determined by the *cis*aminocupration step, and we have previously shown that the ligand (4R)-(+)-2,2'-isopropylidinebis(4-phenyl-2-oxazoline) ((R,R)-Ph-box) provides very good levels of asymmetric induction in such reactions.⁵ *N*-Tosyl-2-allylaniline (1a) was subjected to [Cu(R,R)-Ph-box](OTf)₂-catalyzed (20 mol %) cyclization in the presence of 1,4-cyclohexadiene (3 equiv) using MnO₂ (3 equiv) as the stoichiometric oxidant in toluene at 110 °C (eq 1). (The MnO₂ used in all reactions described



herein is activated, ca. 85%, <5 μ m, as supplied by a commercial vendor.) This reaction provided a 43:57 mixture of the desired hydroamination product **2a** along with the intramolecular carboamination product **3a**.^{5e} Chiral HPLC analysis of 2-methylindoline **2a** indicated it had been formed in 90% ee. Increasing the amount of 1,4-cyclohexadiene to 9 equiv resulted in only a slight decrease in the relative amount of carboamination product **3a** (result not shown).

We next explored the hydroamination reactions of N-mesyl-2-allylaniline (1b), which cannot undergo the intramolecular carboamination reaction, and N-(3,5-di-tert-butyl-4-methoxybenzenesulfonyl)-2-allylaniline (1c), where intramolecular carboamination is minimized due to steric hindrance on the arylsulfonyl group (Table 1). The data in Table 1 indicate that the N-mesyl substrate 1b readily converts to the indoline product **2b** in good yield (Table 1, entries 1-12). A number of reaction conditions such as temperature, time, amount of 1,4cyclohexadiene, the presence or absence of 4 Å molecular sieves, and catalyst loading were examined. We found that the reaction time could be reduced from 24 to 8 h (Table 1, compare entries 1 and 2 to entries 3 and 4) and the reaction temperature could be lowered to 90 °C at 20 mol % [Cu(R,R)-Ph-box](OTf)₂ loading (Table 1, entries 4-6). We found that flame-dried 4 Å molecular sieves were beneficial to the reaction selectivity and reproducibility (Table 1, compare entries 6 and 8 and additional trials not shown), and 2,6-di-tert-butyl-4methylpyridine was a better base than K₂CO₃ (Table 1, compare entries 6 and 9). We were able to reduce the catalyst loading to 15 mol % $[Cu(R,R)-Ph-box](OTf)_2$, but the temperature had to be increased to 100 °C for optimal conversion at 8 h (Table 1, compare entries 10 and 11). Thus, the optimal conditions are 15 mol % $[Cu(R,R)-Ph-box](OTf)_{2}$ 2,6-di-tert-butyl-4-methylpyridine (1 equiv) as base, and 3 equiv of 1,4-cyclohexadiene at 100 °C for 8 h to give a 73% yield of 2 $>90^{d} (70:30)^{h}$

 $>90^{d} (77:23)^{h}$

 $80^d (81:19)^h$

72 $(94:6)^h$

nd

nd

86

nd

Table 1. Optimization of the Hydroamination^a

110

100

110

110

13

14

 15^b

 $16^{b,f}$

1c

1c

10

1c

$ \begin{array}{c} \text{NH} \\ \text{O}_2 S, R \\ \text{1b, } R = Me \\ \text{1c, } R = 3,5-di-tert- \end{array} $		(OTf) ₂ (20 mol%), (<i>R</i> , <i>R</i>)-Ph-box (25 mol%) -cyclohexadiene (3 equiv), MnO ₂ (3 equiv) ,6-di- <i>tert</i> -butyl-4-methylpyridine (1 equiv) PhCH ₃ , 4 Å mol. sieves, temp, time -butyl-4-methoxybenzene			2b 2c
entry	substrate	temp (°C)	time (h)	yield (%)	ee (%)
$1^{b,c}$	1b	110	24	>95 ^d	nd
2^{c}	1b	110	24	>95 ^d	nd
3	1b	120	8	>95 ^d	nd
4	1b	110	8	77 (>95 ^{d})	81
5	1b	100	8	77	80
6	1b	90	8	77	77
7	1b	80	8	61 ^{<i>d</i>}	nd
8 ^c	1b	90	8	74	73
9^e	1b	90	8	56 (89^d)	76
10 ^f	1b	90	8	90 ^d	nd
11^{f}	1b	100	8	$73 (>95^d)$	77
12^g	1b	90	8	50 ^d	nd

8

8

8

8

^aConditions: Cu(OTf)₂ (20 mol %) and (R,R)-Ph-box (25 mol %) were stirred for 2 h at 60 °C in dry toluene in a sealed tube under Ar. The cooled solution was diluted with dry toluene (0.1 M total concentration with respect to 1) and was treated with sulfonamide 1b (0.237 mmol) or 1c (0.120 mmol), 2,6-di-tert-butyl-4-methylpyridine (1 equiv), MnO₂ (3 equiv), 1,4-cyclohexadiene (3 equiv), and 4 Å flame-dried molecular sieves (20 mg/mL) under Ar and was heated in the sealed tube for 8 h unless otherwise noted. Filtration through Celite and flash chromatography on SiO₂ afforded the isolated product unless otherwise noted. The percent ee was determined by chiral HPLC. ^b5 equiv of 1,4-cyclohexadiene was used. ^cNo molecular sieves were used. ^dPercent conversion (NMR) given. ^eK₂CO₃ (1 equiv) was used instead of 2,6-di-tert-butyl-4-methylpyridine. ^f15 mol % Cu- $(OTf)_2$ and 19 mol % (*R*,*R*)-Ph-box were used. ^{*g*} γ -Terpinine was used instead of 1,4-cyclohexadiene. ^hRatio of hydroamination (2c) to carboamination (3c) as determined by analysis of the crude ¹H NMR spectrum. nd = not determined.

methylindoline **2b** in 77% ee (Table 1, entry 11). We attempted to use γ -terpinene as a hydrogen atom source (Table 1, entry 12) under conditions otherwise identical with those of Table 1, entry 6, and found that this commonly available natural product could transfer a hydrogen atom but was less efficient than 1,4-cyclohexadiene.

The hydroamination reaction of N-arylsulfonyl-2-allylaniline 1c, a hindered analogue of N-tosyl-2-allylaniline (1a), was next investigated. The hope was the enantioselectivity could be increased, relative to the reaction of 1b (note that the hydroamination of 1a occurs with 90% ee, eq 1, vide supra) without reducing the hydroamination yield due to competing carboamination. When substrate 1c was subjected to the reaction conditions (110 °C, 20 mol % Cu[(R,R)-Ph-box]OTf₂, and 3 equiv 1,4-cyclohexadiene; Table 1, entry 13), >90% conversion was achieved but the hydroamination reaction was accompanied by formation of the corresponding carboamination product 3c (hydroamination/carboamination 70/30). When the temperature was decreased, the ratio improved but the reaction did not go to completion (Table 1, entry 14). Increasing the amount of 1,4-cyclohexadiene to 5 equiv and running the reaction at 110 °C provided a tolerable

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hydroamination/carboamination ratio of 94/6, where the reaction went to completion (Table 1, entry 15). This reaction provided the highest isolated yield (72%) of **2c**, which was formed in 86% ee. Reduction of the catalyst loading to 15 mol % led to an increased formation of the undesired carboamination product (Table 1, entry 16).

The reaction enantioselectivity as a function of time was briefly examined (not shown) to ascertain if enantioenrichment could be lost due to reversible hydroamination.^{4c} In such a scenario, the reaction enantioselectivity could be higher in the initial hours of the reaction. Running substrate 1b under the same conditions as in Table 1. entry 11 but for only 3 h led to a 30% isolated yield of 2b (the rest being substrate 1b) in 67% ee. This indicates that the reaction is not more selective in its early stages and the observed enantioselectivity is nearly within experimental error of Table 1, entry 11 for the detection method (\pm 5% ee for chiral HPLC). We also ran a control experiment using the same conditions as Table 1, entry 11 but without $Cu[(R,R)-Ph-box]OTf_2$ (not shown). This control reaction gave 8% conversion of 1b to 2b, indicating there is a degree of uncatalyzed background reaction that can lead to racemic product.

The absolute stereochemistry of *N*-mesyl-2-methylindoline (**2b**; 77% ee), initially assigned *R* by analogy to other Cu[(R,R)-Ph-box]OTf₂ catalyzed reactions we have reported with substrates **1**,⁵ was confirmed by removal of the mesyl group by treatment with sodium bisaluminumhydride (Red-Al) in refluxing xylenes (eq 2). (Removal of the arylsulfonyl group



of **2c** is best performed as previously described.^{Sf}) The optical rotation of the 2-methylindoline was compared to the known value for (S)-2-methylindoline $(4)^{3b}$ and found to be of the opposite sign, establishing the configuration of our major product as *R*. 2-Methylindoline (4) is a key intermediate in the synthesis of the clinically used diuretic indapamide; thus, methods for the enantioselective synthesis of this compound and analogues thereof are useful.^{2a}

The hydroamination reactions of various N-sulfonyl-2allylanilines 1 were examined under the optimal reaction conditions (Table 1, entry 11 for N-mesyl substrates 1d,e and Table 1, entry 15 for N-arylsulfonyl substrates 1f-j and N-SES substrate 1k), as illustrated in Scheme 2. Yields of the isolated hydroamination products are given along with the hydroamination (HA) to carboamination (CA) ratios (based on analysis of the crude ¹H NMR) of substrates with Narylsulfonyl groups. The hydroaminations of substrates 1f,g were run for 24 h, and the reaction of 1g was run with 3 equiv of 1,4-cyclohexadiene (reactions performed prior to reaction time optimization). The N-mesyl-2-allylanilines 1d,e gave the respective indolines in 76% and 73% ee, while the N-SES substrate 1k gave indoline 2k in 72% ee. The N-arylsulfonyl-2allylanilines 1c,f-j gave higher levels of enantioselectivity, but the yields were somewhat eroded by formation of the competing carboamination products 3. We observed that anilines 1c (Table 1) and 1i (containing H and Me aniline substituents, respectively) gave higher ratios of hydroamination

Scheme 2. Scope of the Enantioselective Indoline Synthesis^a



^{*a*}Ar = 3,5-di-*tert*-butyl-4-methoxybenzene, Ms = methanesulfonyl, SES = 2-trimethylsilylethylsulfonyl. The percent yield refers to amount of pure isolated indoline 2. HA = hydroamination product (2), and CA = carboamination product (3); the ratio was obtained by analysis of the crude ¹H NMR spectrum. Reactions of R₂NMs substrates were performed at 100 °C with 15 mol % [Cu]; reactions of R₂NSO₂Ar and R₂NSES substrates were performed at 110 °C with 20 mol % [Cu]. nd = not determined. Enantiomers could not be separated by chiral HPLC.

to carboamination (3, Figure 2) than did the anilines 2f-h,j (functionalized with MeO, Cl, Br, and CN aniline substituents).



Figure 2. Carboamination side products.

Nevertheless, moderately good yields of the hydroamination products can be obtained in all cases and the enantioselectivities of the *N*-arylsulfonyl hydroamination products range from 84 to 89%. Indoline products **2c**,**g**–**j** were isolated as solids; therefore, further enantiomeric enrichment of these compounds via recrystallization can in principle be achieved.^{5g,i}

In summary, we have developed the first copper-catalyzed enantioselective alkene hydroamination/cyclization. The method provides an expedient route to enantioenriched 2methylindolines, compounds of value in medicinal chemistry and drug design. This chiral 2-methylindoline synthesis method is competitive with other reported methods.³ The N-sulfonyl-2allylaniline substrates 1 can be synthesized in two to three steps,⁵ and the hydroamination reaction uses a commercially available, amino acid derived chiral ligand and a widely available copper(II) salt. The hydrogen atom source, 1,4-cyclohexadiene, has a low molecular weight, is relatively inexpensive, and produces a volatile byproduct. This enantioselective intramolecular alkene hydroamination provides the highest enantioselectivity yet reported for the hydroamination of 2allylaniline-derived substrates, and several of the products are crystalline; thus, the enantiomeric excesses of such products can

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in principle be even further enhanced. Further reaction optimization and expansion of the substrate scope are underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Text and figures giving full experimental details, characterization data, and NMR spectra for all new compounds and chiral HPLC traces for all chiral products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Author Contributions

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the National Institutes of Health (GM078383) for support of this work.

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