Enantioselective Addition of Vinylzinc Reagents to 3,4-Dihydroisoquinoline *N*-Oxide

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ABSTRACT



Ligand 2a promotes the enantioselective addition of vinylzinc reagents to 3,4-dihydroisoquinoline *N*-oxide to yield chiral allylic hydroxylamines. With 0.1 equiv of the ligand, the product is obtained in up to 84% ee, whereas with 1.2 equiv of the ligand, the ee is increased to the 90–95% range with a variety of aliphatic, cyclic, and aromatic vinylzinc reagents. This method was used to synthesize the protected unnatural amino acid *N*-Cbz-D-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid in three steps from the allylic hydroxylamine.

Tetrahydroisoquinoline (THIQ) alkaloids, especially 1-substituted THIQs, are important synthetic targets because of their potent pharmacological properties.¹ Members of this family of alkaloids have diverse activities that include agonism of the β -adrenoceptor,² antagonism of D1 and NMDA receptors,³ inhibition of α -glucosidase,⁴ and neurotoxicity associated with Parkinson's disease.⁵ A majority of these compounds possess a chiral center at the C-1 position of the isoquinoline core, and stereoisomers at this position exhibit very different activities (Scheme 1). Thus, enantioselective synthesis of 1-substituted THIQs is an important goal in both synthetic and medicinal chemistry.

- (1) Chrzanowska, M.; Rozwadowska, M. D. Chem. Rev. 2004, 104, 3341–3370.
- (2) Nikulin, V. I.; Rakov, I. M.; De Los Angeles, J. E.; Mehta, R. C.; Boyd, L. Y.; Feller, D. R.; Miller, D. D. *Bioorg. Med. Chem.* **2006**, *14*, 1684–1697.
- (3) (a) Wanner, K. T.; Beer, H.; Höfner, G.; Ludwig, M. *Eur. J. Org. Chem.* **1998**, 2019–2029. (b) Gao, M.; Kong, D.; Clearfield, A.; Zheng, Q.-H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2229–2233.
- (4) Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. J. Am. Chem. Soc. 2004, 126, 187–193.
- (5) (a) Shinohara, T.; Takada, A.; Toda, J.; Terasawa, N.; Sano, T. *Heterocycles* **1997**, *46*, 555–565. (b) Nagatsu, T. *Neurosci. Res.* **1997**, *29*, 99–111 and references therein.

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Syntheses of THIQs most often employ the Pictet– Spengler reaction, which entails the intramolecular cyclization of an electron-rich aryl group onto an imine or iminium

Scheme 1. THIQ-Based Bioactive Structures and Enantioselective Approaches to 1-Substituted THIQs



A. Pictet-Spengler Approach



B. C_1 - C_{α} Connection Approach



ion electrophile. A number of diastereoselective syntheses of THIQs have been reported using this approach,¹ and Jacobsen has recently developed an enantioselective thioureabased catalyst for an acyl-Pictet—Spengler reaction.⁶ Other approaches to chiral THIQs include enantioselective addition of ketene silyl acetals to acylisoquinolines or nitrones,⁷ addition of alkynes to isoquinoline iminium ions,⁸ reaction of an allylsilane with 3,4-dihydro-6,7-dimethoxyisoquinoline catalyzed by chiral Cu(I) complexes,⁹ and the asymmetric hydrogenation of cyclic imines prepared by the Bischler—Napieralski reaction.¹⁰

An alternative approach that could provide efficient access to a wide variety of isoquinoline derivatives for biological screening is the catalytic enantioselective addition of organometallic reagents to the C-1 position of the isoquinoline ring system (the C_1-C_{α} connection, Scheme 1). Ukaji and Nakamura¹¹ described the synthesis of chiral THIQs with several organozinc reagents using tartrate ester or bisoxazoline ligands. These methods often give modest enantioselectivities or require stoichiometric amounts of the chiral controller. Here we report a convenient method to access chiral THIQs by the enantioselective addition of vinylzinc reagents to 3,4-dihydroisoquinoline N-oxide promoted by N-acylethylenediamine ligands. The reaction gives moderate to good enantioselectivities with 0.1 equiv of the chiral ligand and excellent enantioselectivities (90-95% ee) with 1.2 equiv of the ligand with a range of vinylzinc reagents.

We recently demonstrated that *N*-acylethylenediaminebased ligands catalyze the enantioselective addition of vinylzinc reagents to aldehydes to give chiral allylic alcohols.¹² To extend the utility of these chiral ligands, we investigated whether a similar reactivity and selectivity could be obtained using other electrophiles. In particular, nitrones provide interesting opportunities because they are more reactive than most unactivated imines, and the resulting hydroxylamine products can be easily reduced to the corresponding chiral allylic amines.

Amino acids provide an inexpensive and readily available starting material for the preparation of chiral ligands.¹³ The *N*-acylethylenediamines, which are derived from amino acids,

are modular structures with three potential sites of diversity. The amino acid side chain provides the source of chirality. The tertiary amine and the carbamate, upon deprotonation of the carbamate N-H, could provide a bidentate coordination site for a metal. Both the alkyl groups on the tertiary amine and the acyl group on the primary amine can be varied to tune the steric and electronic environment surrounding the metal atom. As shown in Scheme 2, the *N*-acylethylene-



 $^{\it a}$ For R^2 = CH_2STrt, EDC and HOBt were used in place of HBTU in the first coupling step.

diamines were prepared by coupling Boc-protected amino acids with secondary amines to give the corresponding amides 1a-f.¹⁴ For *N*-BocCys(Trt), EDC and HOBt gave a significantly higher yield in the coupling reaction with morpholine when compared to HBTU. The amides were reduced with borane–THF, followed by cleavage of the resulting B–N bond with ethylenediamine to give ligands 2a-f. During the last step, we found that microwave heating gave higher yields and much shorter reaction times than conventional heating methods. This synthesis can be used to prepare a variety of ligands on a multigram scale.

The substrate for the addition reactions, 3,4-dihydroisoquinoline N-oxide, was prepared by the Na₂WO₄-catalyzed oxidation of 1,2,3,4-tetrahydroisoquinoline with H₂O₂.¹⁵ We used the method developed by Oppolzer to generate the vinylzinc reagents.¹⁶ In this procedure, terminal alkynes are first hydroborated with dicyclohexylborane to give (E)vinylboranes. Transmetalation with diethylzinc then yields the corresponding (E)-vinylzinc reagents. Our preliminary screening studies indicated the use of a modified Oppolzer procedure in which the vinylborane was slowly added via syringe pump to a cooled (-48 °C) solution of nitrone, diethylzinc, and the ligand in methylene chloride. Reactions were allowed to proceed for 24 h at this temperature. This inverse addition procedure increased both the yield and stereoselectivity of the reaction. Reactions that were performed with an excess of alkyne resulted in both alkynyl and vinyl addition to the nitrone. If the reaction was performed at higher temperatures (-20 °C), we began to

^{(6) (}a) Taylor, M. S.; Jacobsen, E. N. J. Am. Chem. Soc. **2004**, *126*, 10558–10559. For a Lewis acid-mediated Pictet–Spengler reaction, see: (b) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. J. Org. Chem. **1998**, *63*, 6348–6354. (c) Hino, T.; Nakagawa, M. *Heterocycles* **1998**, *49*, 499–531.

^{(7) (}a) Taylor, M. S.; Tokunaga, N. T.; Jacobsen, E. N. Angew. Chem., Int. Ed. **2005**, 44, 6700–6704. (b) Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. J. Am. Chem. Soc. **2002**, 124, 2888–2889.

⁽⁸⁾ Taylor, A. M.; Schreiber, S. L. Org. Lett. 2006, 8, 143-146.

⁽⁹⁾ Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. Org. Lett. 2006, 8, 1295–1297.

⁽¹⁰⁾ Morimoto, T.; Suzuki, N.; Achiwa, K. Tetrahedron: Asymmetry 1998, 9, 183–187.

^{(11) (}a) Ukaji, Y.; Shimuzu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. *Chem. Lett.* **1997**, *1*, 59–60. (b) Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 447–452. (c) Ukaji, Y.; Yoshida, Y.; Inomata, K. *Tetrahedron: Asymmetry* **2000**, *11*, 733–736.

 ^{(12) (}a) Sprout, C. M.; Richmond, M. L.; Seto, C. T. J. Org. Chem.
 2005, 70, 7408-7417. (b) Richmond, M. L.; Seto, C. T. J. Org. Chem.
 2005, 70, 8835-8840.

⁽¹³⁾ Vicario, J. L.; Badía, D.; Carrillo, L.; Etxebarria, J. *Curr. Org. Chem.* **2003**, *7*, 1775–1792.

⁽¹⁴⁾ Richmond, M. L.; Seto, C. T. J. Org. Chem. 2003, 68, 7505-7508.

^{(15) (}a) Murahashi, S.-I.; Shiota, T.; Imada, Y. Org. Synth. **1998**, 9, 632–637. (b) Murahashi, S. I.; Shiota, T. Tetrahedron Lett. **1987**, 28, 6469–

^{6472.} (16) Oppolzer, W.; Radinov, R. N. Helv. Chim. Acta 1992, 75, 170– 173.

observe small amounts of products from ethyl and cyclohexyl addition. Finally, because the yield and stereoselectivity appeared to depend on the amount of ligand present in the reaction, subsequent screening studies were performed using 1.2 equiv of the ligand.

With optimized reaction conditions in hand, we next examined how the ligand structure influenced the yield and ee of the allylic hydroxylamine product (Table 1). In terms

 Table 1. Effect of Ligand Structure on Addition of Vinylzinc

 Reagents to 3,4-Dihydroisoquinoline N-Oxide



entry	ligand	\mathbb{R}^1	R ² = side chain of	yield (%) ^a	ее (%) ^b
1	2a	$-(CH_2)_2O(CH_2)_2-$	Chg	74	95
2	2b	$-CH_2)_2O(CH_2)_2-$	Ile	68	95
3	2c	$-(CH_2)_2O(CH_2)_2-$	Phe	60	84
4	2d	$-(CH_2)_2O(CH_2)_2-$	Cys(Trt)	72	90
5	2e	$-(CH_2)_5-$	Chg	63	90
6	2f	$-\mathrm{CH}_{2}\mathrm{CH}_{3}-$	Chg	58	72

 a Isolated yield. b Measured by HPLC (Chiralcel OD-H). Cy = cyclohexyl, Chg = cyclohexylglycine.

of stereoselectivity, comparison of ligands 2a-d (entries 1–4) demonstrated that β -branched amino acid side chains were optimal. Ligands derived from cyclohexylglycine and isoleucine both gave the product in 95% ee. Ligands with less bulky substituents that lack β -branching, such as the benzyl side chain of Phe, reduced the ee to 84%. Side chains with a sterically demanding group more distal from the chiral

Table 2. Effect of Ligand Loading on the Enantioselectivity ofthe Addition of a Vinylzinc Reagent to 3,4-Dihydroisoquinoline*N*-Oxide



center, such as CH_2STrt (ligand 2d), gave an intermediate level of enantioselectivity.

With entries 1, 5, and 6, we examined the influence of the tertiary amine. Ligands that incorporated cyclic amines, such as those derived from morpholine and piperidine, were preferred over noncyclic analogues (2f). Because the yield of the reaction with ligand 2a was higher than that with 2b, we chose 2a as the optimized structure for further experiments.

The data in Table 2 show that both the yield and ee of the reaction correlate with the equivalent of ligand **2a**. As **2a** is increased from 0.1 to 1.2 equiv, the yield increases from 60 to 74% and the ee increases from 84 to 95%. We have found that, although the highest levels of enantioselectivity are observed with 1.2 equiv of the ligand, in practice the ligand can be isolated from the reaction by chromatography and recycled up to three times without erosion of product ee.

To investigate the scope of this reaction, we prepared seven vinylzinc reagents and reacted them with 3,4-dihydroisoquinoline *N*-oxide in the presence of either 0.1 or 1.2 equiv of ligand 2a. As shown in Table 3, using 1.2 equiv of 2a,

Table 3. Enantioselective Addition of Vinylzinc Reagents to3,4-Dihydroisoquinoline N-Oxide



		1.2 equiv of $\mathbf{2a}^{a}$		0.1 equiv of $\mathbf{2a}^{b}$	
entry	R (product)	yield (%) ^c	ee (%)	yield (%) ^c	ee (%)
1	tert-butyl (3a)	69	93	61	41
2	<i>n</i> -butyl (3b)	66	94	66	80
3	cyclopropyl (3c)	79	94	77	72
4	cyclohexyl (3d)	62	94	63	64
5	$CH_2CH_2Ph\left(\mathbf{3e}\right)$	74	95	60	84
6	Ph (3f)	74	90	81	71
7	$4\text{-MeO-Ph}\left(\boldsymbol{3g}\right)$	85	92	74	75

^{*a*} Reactions performed using 2.4 equiv of Et₂Zn. ^{*b*} Reactions performed using 1.3 equiv of Et₂Zn. ^{*c*} Isolated yield.

we obtained excellent ee values with a range of aliphatic, cyclic, and aromatic vinylzinc reagents. For catalytic reactions using 0.1 equiv of the chiral ligand, good enantio-selectivities in the range of 71-84% ee were obtained with five of the nucleophiles. However, vinylzinc reagents derived from cyclohexylacetylene and *tert*-butylacetylene gave poor enantioselectivities.

To highlight the utility of this method and to confirm the absolute configuration of the allylic hydroxylamine products, we performed a short synthesis of the unnatural amino acid *N*-Cbz-D-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (*N*-Cbz-D-Tiq). This conformationally constrained amino acid has been used in the design of thrombin inhibitors and to

enhance the biological activities and stabilities of peptides and peptidomimetics.¹⁷ The ee of hydroxylamine **3f** was increased from 90% to 96% by recrystallization from hexanes, which removes racemic **3f** from the sample as a crystalline solid. Reduction of the hydroxylamine with Zn/ AcOH followed by protection of the free amine with CbzCl afforded **4** in 67% yield over the two steps (Scheme 3).¹⁸



Oxidative cleavage of the alkene with $RuCl_3$ and $NaIO_4$ gave *N*-Cbz-D-Tiq in 61% yield.¹⁹ The absolute configuration of the product was confirmed by comparing the sign of its specific optical rotation with a value from the literature.²⁰ Thus, ligand **2a** catalyzes the addition of vinylzinc reagents to the *si* face of the nitrone C=N double bond. This procedure represents a significant improvement over reported syntheses of D-Tiq, which require separation of the racemic compound by recrystallization of a diastereomeric salt.²⁰

In summary, we have developed a new method for the addition of vinylzinc reagents to 3,4-dihydroisoquinoline *N*-oxide using chiral *N*-acylethylenediamine ligands. This method should be applicable to the asymmetric synthesis of tetrahydroisoquinoline alkaloids and derivatives of the conformationally constrained amino acid Tiq. Our current work is directed toward broadening the scope of the process through the use of other nucleophiles and gaining a better understanding of the reaction's mechanism and basis for stereoselectivity.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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^{(17) (}a) Shuman, R. T.; Rothenberger, R. B.; Campbell, C. S.; Smith,
G. F.; Gifford-Moore, D. S.; Gesellchen, P. D. J. Med. Chem. 1993, 36,
314-319. (b) Shuman, R. T.; Rothenberger, R. B.; Campbell, C. S.; Smith,
G. F.; Gifford-Moore, D. S.; Paschal, J. W.; Gesellchen, P. D. J. Med. Chem.
1995, 38, 4446-4453.

^{(18) (}a) Merino, P.; Franco, S.; Lafuente, D.; Merchan, F.; Revuelta, J.; Tejero, T. *Eur. J. Org. Chem* **2003**, *15*, 2877–2881. (b) Cong, X.; Liao, Q. J.; Yao, Z. J. *J. Org. Chem.* **2004**, *69*, 5314–5321.

^{(19) (}a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. J. Org. Chem. **1981**, 46, 3936–3938. (b) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. J. Am. Chem. Soc. **2002**, 124, 12225–12231.

⁽²⁰⁾ Observed for compound 5: $[\alpha]^{24}_{D} = -24.8^{\circ}$ (c = 0.5, MeOH). Literature value: $[\alpha]^{24}_{D} = -40.1^{\circ}$ (c = 1.0, MeOH). Bajusz, S.; Mohai, L.; Feher, A.; Lavich, J.; Szell, G.; Veghelyi, B. PCT Int. Appl. WO 9312091 A1 930624, 1993 (36 pp).