JOC Notes

Modular Ligands Derived from Amino Acids for the Enantioselective Addition of Organozinc Reagents to Aldehydes

Meaghan L. Richmond and Christopher T. Seto*

Department of Chemistry, Brown University, 324 Brook Street, Box H, Providence, Rhode Island 02912

christopher_seto@brown.edu

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Abstract: A new series of modular chiral ligands that are derived from amino acids were prepared and tested for their ability to catalyze the asymmetric addition of alkylzinc reagents to aromatic and aliphatic aldehydes. The ligands contain a tertiary amine, an amino acid side chain, and a carbamate or amide functional group. One ligand, which was synthesized from Ile, catalyzes the addition of diethylzinc to cyclohexanecarboxaldehyde in 99% ee.

The design of catalysts for the asymmetric addition of organozinc reagents to aldehydes to give chiral secondary alcohols has been the focus of intensive research.[1] A large number of catalysts for this reaction have been developed that rely on either a Lewis acidic or Lewis basic strategy for catalyzing the reaction.[2]

We are interested in developing new modular chiral ligands for this reaction. In the long term, we envision that these modular ligands could serve as the basis for synthesizing libraries of catalysts[3] for reactions involving alkylzinc, as well as other organometallic reagents. This work will then be interfaced with a high-throughput strategy that we have developed recently for screening the enantiomeric excess of chiral secondary alcohols.[4]

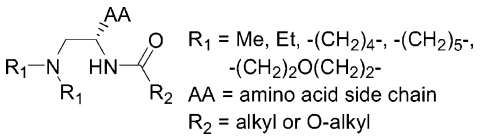

FIGURE 1. General design of ligands.

To gain quick access to a diversity of ligands, a modular system comprised of simple components is essential. Utilizing amino acids from the chiral pool allows for the easy incorporation of chirality into the ligands and opens the way for a number of straightforward chemical modifications. Amino acids have been used as the basis for a variety of catalyst systems,[5] and ligands that are based on proline,[6] valine,[7] tyrosine,[8] tryptophan,[9] serine,[10] and leucine[11] have been reported.

We imposed two important restrictions on the design of these new modular ligands. First, the components needed to be simple and readily available in order to facilitate preparation of a number of different analogues. Second, the reactions that are employed during their synthesis must be reliable, and they must be accomplished with a reasonable yield. The general structure of the ligands is illustrated in Figure 1. They are derived from L-amino acids and incorporate both a tertiary amine and a carbamate or amide functional group. This class of ligands mimics the very successful chiral β-amino alcohol-based ligands that have been developed by Soai and others.[1c] We have replaced the alcohol moiety of a β-amino alcohol with a carbamate or amide N−H group.[12,13] We reasoned that this would be an appropriate substitution because alcohol and carbamate protons have similar pK_a values.[14] Deprotonation of the carbamate provides, in conjunction with the tertiary amine, a good

(1) For comprehensive reviews, see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

(2) For selected reports, see: (a) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823−2824. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072. (c) Fitzpatrick, K.; Hulst, R.; Kellogg, R. M. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1861−1864. (d) Kang, J.; Lee, J. W.; Kim, J. I. *J. Chem. Soc., Chem. Commun.* **1994**, 2009−2010. (e) Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1991**, *47*, 8251−8258. (f) Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron*: *Asymmetry* **1998**, *9*, 4165−4173. (g) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99−101. (h) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233−6236. (i) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3651−3655. (j) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657−1660. (k) Paquette, L. A.; Zhou, R. *J. Org. Chem.* **1999**, *64*, 7926−7934. (l) Shi, M.; Sui, W.-S. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3319−3325. (m) Soai, K.; Hirose, Y.; Ohno, Y. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1473−1474.

(3) For selected reports, see: (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284−310. (b) Huttenloch, O.; Laxman, E.; Waldman, H. *Chem. Eur. J.* **2002**, *8*, 4767−4779. (c) Gilbertson, S. R.; Wang, X. *Tetrahedron* **1999**, *55*, 11609−11618. (d) Burguete, M. I.; Collado, M.; Garcia-Verdugo, E.; Vicent, M. J.; Luis, S. V.; von Keyserling, N. G.; Martens, J. *Tetrahedron* **2003**, *59*, 1797−1804. (e) Jacobsen, E. N.; Francis, M. B. *Angew. Chem., Int. Ed.* **1999**, *38*, 937−941. (f) Chataigner, I.; Gennari, C.; Piarulli, U.; Ceccarelli, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 916−918. (g) Cole, B. M.; Shimizu, K. D.; Kruger, C. A.; Harrity, J. P.; Snapper, M. L.; Hoveyda, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668−1671.

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(5) For a recent review on amino acids and peptides as catalysts, see: Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481−2495.

(6) (a) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111−7115. (b) Yang, X.; Shen, J.; Da, C.; Wang, R.; Choi, M. C. K.; Yang, L.; Wong, K.-Y. *Tetrahedron*: *Asymmetry* **1999**, *10*, 133−138. (c) Cicchi, S.; Crea, S.; Goti, A.; Brandi, A. *Tetrahedron*: *Asymmetry* **1997**, *8*, 293−301. (d) List, B. *Tetrahedron* **2002**, *58*, 5537−5590.

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(8) Beliczey, J.; Giffels, G.; Kragl, U.; Wandrey, C. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1529−1530.

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(10) Sibi, M. P.; Chen, J.-X.; Cook, G. R. *Tetrahedron Lett.* **1999**, *40*, 3301−3304.

(11) Kawanami, Y.; Mitsuie, T.; Miki, M.; Sakamoto, T.; Nishitani, K. *Tetrahedron* **2000**, *56*, 175−178.

(12) (a) For a review of phosphonamides and sulfonamides as ligands for the enantioselective reduction of ketones, see: Zhang, J.; Zhou, H. B.; Xie, R. G. *Curr. Org. Chem.* **2002**, *6*, 865−890. (b) Rhyoo, H. Y.; Young-Ae, Y.; Park, H.-J.; Chung, Y. K. *Tetrahedron Lett.* **2001**, *42*, 5045.

(13) Dangel, B. D.; Polt, R. *Org. Lett.* **2000**, *2*, 3003−3006.

(14) Bordwell, F. G.; Zhang, X.-M. *J. Org. Chem.* **1994**, *59*, 6456−6458.

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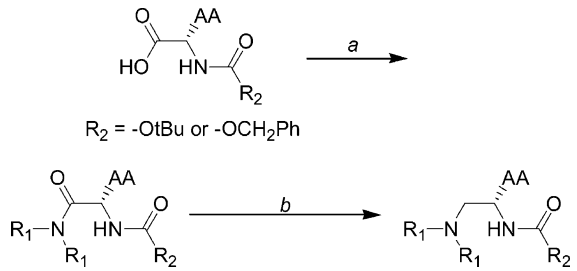
SCHEME 1. General Synthesis of Amino Acid Based Ligands[a]



[a] Key: (a) HBTU,[15] DIEA, $(R_1)_2NH$, DMF, 53−98%; (b) (i) BH_3−THF, (ii) $H_2N(CH_2)_2NH_2$, CH_3OH, 23−80%.

binding site for a metal atom such as zinc. The carbamate group also provides an additional site for diversity within the ligands. The results presented in this report serve as a proof of concept for this ligand class and demonstrate that they can be used to develop enantioselective reactions that proceed with good stereoselectivity.

The general synthesis of the ligands starting from *N*-Boc- or *N*-Cbz-protected amino acids is shown in Scheme 1.[16] The amino acids were coupled to five different secondary amines to give the corresponding amides. Reduction of the amides with BH_3−THF[17] gave the desired tertiary amines that were chelated to boron. The boron was removed with ethylenediamine to give the final ligands.

We first examined how the structure of the amino acid side chain affected enantioselectivity for the addition of Et_2Zn to benzaldehyde (Table 1). All of the ligands in this series (compounds **5a**−**g**) incorporated piperidine as the tertiary amine component, with a Boc group on the primary amine. Reactions were performed with 3 equiv of Et_2Zn in hexanes and 10 mol % of the catalyst at 4 °C for 24 h. Over this period, the benzaldehyde was completely consumed, and after workup, the product (*S*)-(−)-1-phenyl-1-propanol was isolated in satisfactory yield. Enantioselectivities ranged from 29 to 62% ee, with the *β*-branched side chains derived from isoleucine, valine, and cyclohexylglycine giving the highest ee. The larger steric bulk of the *tert*-leucine side chain (entry 7) resulted in significantly lower enantioselectivity.

We next investigated how the tertiary amine component of the ligands affected stereoselectivity while the side chain derived from valine was held constant (Table 2). Ligands that contained the six-membered ring of either morpholine or piperidine gave the highest enantioselectivities, while pyrrolidine and smaller amines such as dimethylamine were less stereoselective. To confirm that *β*-branched side chains were optimal, even in the presence of the morpholine group, we examined ligands **6a** and **7a**−**d** (Table 3). In this series, the side chain of isoleucine (entry 1) again gave the highest enantioselectivity.

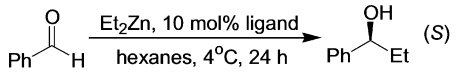
With both the tertiary amine and the amino acid side chain optimized, we next examined the effect of the

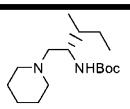
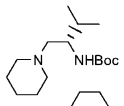
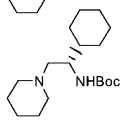
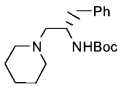
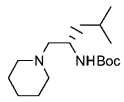
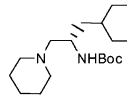
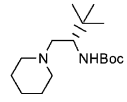
(15) HBTU is *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.

(16) For a detailed description of the synthesis of ligands **5**−**8**, see the Supporting Information.

(17) Roseke, R. W.; Weitl, F. L.; Prasad, K. U.; Thompson, R. M. *J. Org. Chem.* **1976**, *41*, 1260−1261.

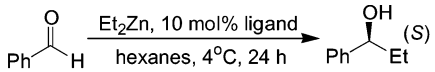
TABLE 1. Addition of Diethylzinc to Benzaldehyde Using Ligands 5a−g

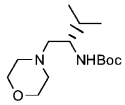
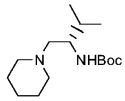
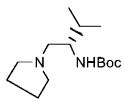
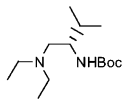
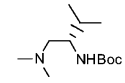


Entry	Ligand	Ligand Structure	Yield (%)	ee (%)[a, b]
1	**5a**		87	62
2	**5b**		69	60
3	**5c**		83	59
4	**5d**		74	46
5	**5e**		69	44
6	**5f**		85	44
7	**5g**		73	29

[a] Absolute configuration assigned by comparison to literature values. [b] Determined by chiral HPLC (Chiralcel OD-H).

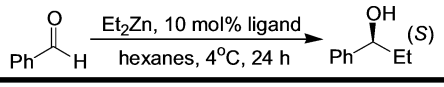
TABLE 2. Effect of Tertiary Amine on the Addition of Diethylzinc to Benzaldehyde

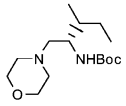
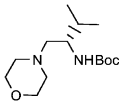
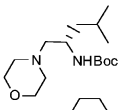
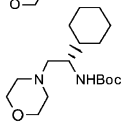
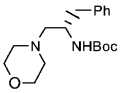


Entry	Ligand	Ligand Structure	Yield (%)	ee (%)[a, b]
1	**6a**		85	68
2	**5b**		69	60
3	**6b**		91	41
4	**6c**		82	36
5	**6d**		81	21

[a] Absolute configuration assigned by comparison to literature values. [b] Determined by chiral HPLC (Chiralcel OD-H).

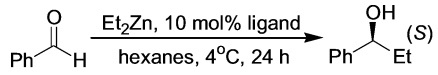
TABLE 3. Optimatization of the Alkyl Side Chain in the Additon of Diethylzinc to Benzladehyde

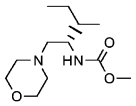
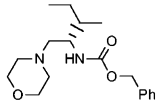
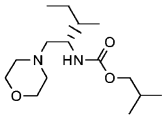
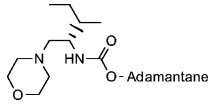
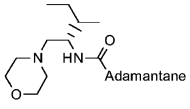
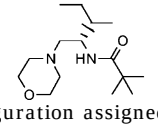


Entry	Ligand	Ligand Structure	Yield (%)	ee (%)[a, b]
1	**7a**		73	70
2	**6a**		85	68
3	**7b**		90	56
4	**7c**		87	51
5	**7d**		87	46

[a] Absolute configuration assigned by comparison to literature values. [b] Determined by chiral HPLC (Chiralcel OD-H).

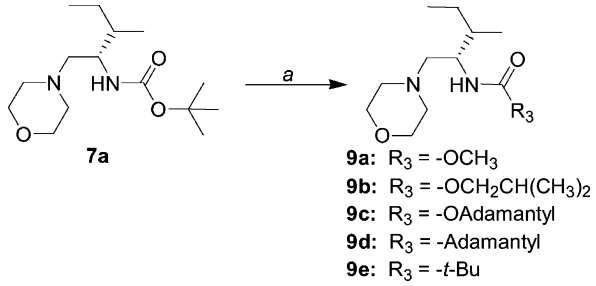
TABLE 4. Effect of Carbamate and Amide Funtionalities on the Addition of Diethylzinc to Benzaldehyde



Entry	Ligand	Ligand Structure	Yield (%)	ee (%)[a, b]
1	**9a**		66	80
2	**8**		63	72
3	**9b**		70	71
4	**9c**		74	69
5	**9d**		90	25
6	**9e**		79	26

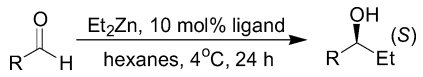
[a] Absolute configuration assigned by comparison to literature values. [b] Determined by chiral HPLC (Chiralcel OD-H).

SCHEME 2. Synthesis of Ligands 9a−e[a]



[a] Key: (a) (i) TFA, (ii) R_3COX (X = Cl or F), DIEA, CH_2Cl_2, 48−80%.

TABLE 5. Addition of Diethylzinc to Aldehydes Using Ligands 7a and 9a



entry	R	ligand	Yield (%)	ee[a] (%)
1	1-naphthyl	**7a**	70	53[b]
2	2-naphthyl	**7a**	73	70[b]
3	trans-cinnamyl	**7a**	68	64[b]
4	hydrocinnamyl	**7a**	72	81[b]
5	cyclohexyl	**7a**	78	99[c]
6	$CH_3(CH_2)_4$	**7a**	81	83[d]
7	1-naphthyl	**9a**	79	64[b]
8	2-naphthyl	**9a**	94	76[b]
9	trans-cinnamyl	**9a**	98	58[b]
10	hydrocinnamyl	**9a**	74	72[b]
11	cyclohexyl	**9a**	93	99[c]
12	$CH_3(CH_2)_4$	**9a**	79	74[d]

[a] Absolute configuration assigned by comparison to literature values. [b] Determined by chiral HPLC (Chiralcel OD-H). [c] Determined by ^{19}F NMR of the (*S*)-MPTA ester. [d] Determined by chiral HPLC (Chiralcel OD-H) of the corresponding phenyl carbamate.

carbamate or amide functional group on the stereoselectivity of the alkylation reaction. Several carbamates and amides were synthesized as illustrated in Scheme 2. The Boc-protecting group on ligand **7a** was removed with TFA, followed by reaction of the resulting primary amine with the appropriate acid chloride or chloro- or fluoroformate to give compounds **9a**−**e**.

Table 4 shows the results of the alkylation reaction with these ligands. Carbamates **7a** (Table 3, entry 1), **8**, **9b**, and **9c** all gave similar stereoselectivity with ee values that range from 69 to 72%. Interestingly, the smaller methyl carbamate of **9a** consistently gave the highest stereoselectivity with 80% ee. By contrast, replacement of the carbamate functional group with amides (entries 5 and 6) resulted in a significant decrease in enantioselectivity.

Finally, we examined the utility of ligands **7a** and **9a** for the alkylation of a variety of other aromatic and aliphatic aldehydes (Table 5). In all of the reactions, the aldehyde was completely consumed after 24 h. 1- and 2-naphthylaldehyde and *trans*-cinnamaldehyde gave ee values that ranged from 53 to 76%. However, the ligands generally gave higher stereoselectivities with aliphatic aldehydes. In particular, alkylation of cyclohexanecarboxaldehyde using either ligand **7a** or **9a** yielded (*S*)-1-cyclohexyl-1-propanol in 99% ee.

In summary, we have developed a new class of modular ligands that are derived from amino acids for the enan-

tioselective addition of diethylzinc to aromatic and aliphatic aldehdyes. These ligands can be synthesized in two to three simple steps from readily available and inexpensive starting materials. This work paves the way for the synthesis and evaluation of larger libraries of ligands that are based upon the same general structure.

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Supporting Information Available: Experimental details and characterization data, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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