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Chiral *N*-Acylethylenediamines as New Modular Ligands for the Catalytic Asymmetric Addition of Alkylzinc Reagents to Aldehydes

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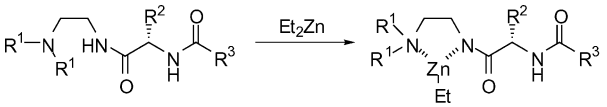
Chiral *N*-acylethylenediamines represent a new class of modular ligands for the catalytic asymmetric addition of alkylzinc reagents to aldehydes. The *N*-acylethylenediamine moiety serves as a metal binding site, while attached amino acids provide the source of chirality. Three sites of diversity on the ligands were optimized to enhance the enantioselectivity of the catalysts using an iterative optimization procedure. The most effective ligand, **4k**, was synthesized in a single reaction step from inexpensive and commercially available starting materials. This ligand (10 mol %) catalyzed the addition of Me_2Zn to 2-naphthaldehyde, benzaldehyde, and 4-chlorobenzaldehyde to give the corresponding alcohol products in 86%, 84% and 81% ee, respectively.

Introduction

Over the last several years, a number of investigators have been applying the techniques of combinatorial chemistry to problems in asymmetric catalysis.[1] One advantage of this strategy is that a large number of catalysts can be synthesized and screened for stereoselectivity in a relatively short period of time. As a result, combinatorial methods may help to increase the efficiency by which chiral catalysts are discovered.

If a large number of catalysts are to be screened, this approach requires a method for rapidly measuring the enantiomeric excess of a large number of chiral samples.[2] A variety of methods for doing so have been reported in the literature,[3] including an enzyme-based method that was developed in our own laboratories.[4] A second requirement is the design of ligands or catalysts that can be synthesized in a modular fashion. With modular ligands, many catalysts can be synthesized rapidly, and the structure of each of the subunits that make up the catalyst can be modified easily.

Here, we report on the synthesis of a new class of modular ligands that are based upon an *N*-acylethylenediamine core (eq 1). The *N*-acylethylenediamine structure



(1)

constitutes a metal binding site, while an attached amino acid provides a source of chirality.[5] Three subunits within the ligands, the tertiary amine (R^1), the amino acid side chain (R^2), and the acyl group on the N-terminus (R^3), can be modified to investigate their influence on the stereoselectivity of catalyzed reactions. We have initially applied these ligands to the asymmetric addition of alkylzinc reagents to aldehydes,[6,7] although in the long term, we envision that they may be applicable to a variety of other synthetic transformations that involve organometallic reagents. In analogy to the β-amino alcohol class of ligands, we expect that the *N*-acylethylenediamines will be deprotonated by diethylzinc to give a five-membered chelate in which the tertiary amine and the anion of the amide are coordinated to zinc.

Results and Discussion

The simple one- to three-step synthesis of the ligands is outlined in Scheme 1. This procedure allows easy

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(5) This ligand architecture is related to the wide variety of ligands that have been developed by Hoveyda and Snapper. For recent examples, see: (a) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690. (b) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018. (c) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276.

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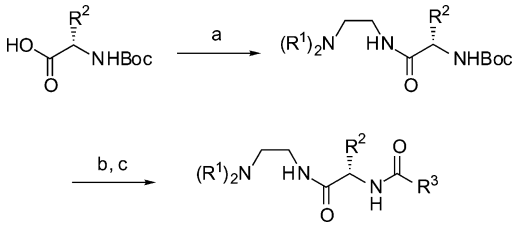
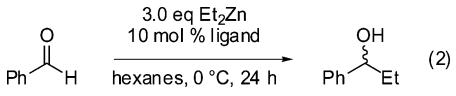
SCHEME 1[a]



[a] Reagents: (a) $(R^1)_2NCH_2CH_2NH_2$, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), diisopropylethylamine (DIEA); (b) TFA; (c) R^3COCl, triethylamine.

variation of all three diversity elements, R^1-R^3, within the ligands so that the enantioselectivity of the catalysts can be optimized using an iterative process. Boc-protected amino acids were first coupled to a variety of *N*,*N*-dialkylethylenediamines to yield the corresponding amides. To vary the R^3 substituent, the Boc protecting group was removed with trifluoroacetic acid, followed by coupling of the free amine with an acid chloride or a chloroformate to give the final ligands.

Ligand **4b**, which is based upon phenylalanine, was used to optimize the reaction conditions for the addition of alkylzinc reagents to aldehydes. Noncoordinating solvents such as hexanes and toluene gave both higher enantioselectivities and faster reactions when compared to coordinating solvents such as THF and Et_2O. The stereoselectivity of the reaction was mildly sensitive to temperature. With ligand **4b**, lowering the temperature of the reaction from 0 to −45 °C resulted in a modest increase in enantioselectivity from 54% to 63% ee. However, the reactions were significantly slower at the lower temperature. Equation 2 shows the final conditions

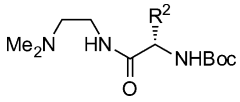


(2)

that were chosen for the alkylation reactions, which included 3 equiv of alkylzinc and 10 mol % ligand in hexanes at 0 °C.

We first examined how the amino acid side chain (R^2) of the ligands influence the stereoselectivity of the addition reaction, while the R^1 and R^3 groups were held constant as methyl and *tert*-butoxy, respectively (Table 1). Steric factors appear to play the dominant role in determining enantioselectivity in this series of ligands. Amino acid side chains that contain *β*-branching such as valine (**4a**) and cyclohexylglycine (**4c**), along with the unsubstituted aromatic ring of phenylalanine (**4b**), gave the highest % ee. Electron-donating (**4d**) or -withdrawing

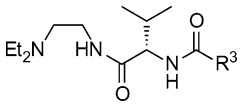
TABLE 1. Effect of Ligand R^2 Substituent on the Addition of Et_2Zn to Benzaldehyde[a]



ligand	amino acid	% ee[b]	% yield	ligand	amino acid	% ee[b]	% yield
4a	Val	55	75	**4f**[d]	Cha[e]	38	82
4b	Phe	54	79	**4g**	*t*-Leu	19	78[f]
4c	Chg[c]	48	82	**4h**[d]	*o*-Cl-Phe	18	83
4d	*t*-Bu-Tyr	39	82	**4i**[d]	Ala	12	78
4e[d]	*p*-NO_2-Phe	41	75	**4j**	*t*-Bu-Thr	6	88[f]

[a] Experiments performed in duplicate unless noted otherwise. [b] % ee of (*R*)-1-phenyl-1-propanol as measured by HPLC (Chiralcel OD). [c] Chg = cyclohexylglycine. [d] Based on one experiment. [e] Cha = cyclohexylalanine. [f] Reactions complete after 4 h.

TABLE 2. Effect of Ligand R^3 Substituent on the Addition of Et_2Zn to Benzaldehyde[a]



ligand	R^3	% ee[b]	% yield	ligand	R^3	% ee[b]	% yield
1a	O-*t*-Bu	59	83	**1f**	CH_2NHBoc	28	43
1b[c]	*t*-Bu	53	82	**1g**	OMe	27	77
1c	adamantyl	42	72	**1h**[c]	4-Me-C_6H_5	22	63
1d	OCH_2-fluorenyl	37	82	**1i**	OBn	16	79[e]
1e	O-*i*-Bu	34	76[d]	**1j**[c]	4-NO_2-C_6H_5	9	48

[a] Experiments performed in duplicate unless noted otherwise. [b] % ee of (*R*)-1-phenyl-1-propanol as measured by HPLC (Chiralcel OD). [c] Based on one experiment. [d] Reaction run for 48 h. [e] Reaction run for 72 h.

(**4e**) substituents on Phe decreased the ee by approximately 15%, while a chloro substituent at the *ortho*-position (**4h**) resulted in a much larger decrease in enantioselectivity. Very large amino acid side chains, such as *t*-Leu (**4g**) and *t*-Bu-Thr (**4j**), and small side chains, such as Ala (**4i**), are also detrimental to the stereoselectivity of the alkylation reaction.

In the next stage of optimization, the R^3 substituent of the ligands was varied, while the R^2 position was held constant as the isopropyl side chain of valine and ethyl was chosen for the R^1 position (Table 2). Both carbamates and amides are well tolerated at R^3. Again, steric effects are the most important factor in determining enantioselectivity across this series of ligands. Compounds with the bulky Boc (**1a**) and pivaloyl amide (**1b**) groups gave the highest ee values in the alkylation reaction, while the ligands with adamantyl (**1c**) and fluorenyl (**1d**) groups were somewhat less stereoselective. Ligands with small aliphatic or aromatic groups at the R^3 position (**1e**−**j**) gave low stereoselectivity.

Equation 1 shows a bidentate binding mode between the zinc atom and a monoanionic ligand. However, we observe that the steric bulk of the R^3 substituent, which is remote from the site of catalysis, is important for determining stereoselectivity. This observation suggests the possibility that the dianionic form of the ligand could bind zinc in a tridentate fashion, as shown in Figure 1. Tridentate chelation would bring the R^3 substituent into closer proximity with the zinc atom and provides a

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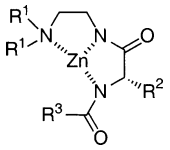
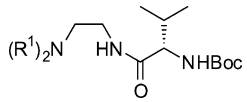


FIGURE 1. Possible trivalent binding mode of zinc to the ligands.

TABLE 3. Effect of Ligand R^1 Substituent on the Addition of Et_2Zn to Benzaldehyde[a]



ligand	R^1	% ee[b]	% yield	ligand	R^1	% ee[b]	% yield
4k	$-(CH_2)_2O(CH_2)_2-$	68	86	**4a**	Me	55	75
4l	$-(CH_2)_4-$	67	68	**4n**[c]	*n*-Bu	40	49
4m	$-(CH_2)_5-$	66	74	**4o**	*i*-Pr	30	93[d]
1a	Et	59	83				

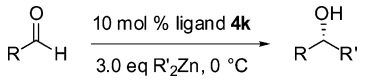
[a] Experiments performed in duplicate unless noted otherwise. [b] % ee of (*R*)-1-phenyl-1-propanol as measured by HPLC (Chiralcel OD). [c] Based on one experiment. [d] Reaction run for 43 h.

reasonable explanation for its influence on the stereoselectivity.[8] The use of tridentate or tetradentate ligands for zinc to promote the asymmetric alkylation of aldehydes has been described by several investigators, including Corey[9] and Polt.[10] An alternate explanation for the influence of the R^3 substituent is that bulky R^3 groups may restrict the population of amide bond rotamers in the ligands, and this may lead to an enhancement of stereoselectivity.

In the final round of optimization, we examined the influence of the tertiary amine component of the ligands (R^1) on stereoselectivity (Table 3). Ligands with a cyclic tertiary amine including morpholine (**4k**), pyrrolidine (**4l**), and piperidine (**4m**) were the most selective. The morpholine ring system appears as a common structural motif in a variety of other amino alcohol-based chiral ligands.[11,12] By contrast, noncyclic amines gave ee values that were approximately 10−30% lower than the cyclic analogues. The sterically hindered diisopropylamino analogue showed the lowest selectivity in this series.

Ligand **4k** gives the highest stereoselectivity for the addition of diethylzinc to benzaldehyde. Therefore, we have screened this ligand against a variety of other aldehydes using both diethylzinc and dimethylzinc (Table 4). Several trends have emerged from these experiments. First, the reactions with diethylzinc were significantly faster than reactions with dimethylzinc. Second, dimethylzinc generally gave products with higher ee values when compared to diethylzinc. The only exception to this trend is in the case of *trans*-cinnamaldehyde (entries 10 and 11), where the reaction with diethylzinc was more stereoselective. Third, the enantioselectivity with aromatic aldehydes was generally higher than with aliphatic aldehydes. Substrates including 2-naphthaldehyde, benzaldehyde, and 4-chlorobenzaldehyde react with dimethylzinc in the presence of ligand **4k** to give the corresponding alcohol product with 81−86% ee. Aliphatic aldehydes (entries 12, 14, and 15) and aromatic aldehydes with electron-donating substituents (entry 13) gave lower stereoselectivity. Finally, entry 7 shows that for the reaction between 4-chlorobenzaldehyde and dimethylzinc the enantioselectivity of the reaction can be increased from 77% to 90% ee by reducing the temperature of the reaction from 0 to −48 °C.

TABLE 4. Variation of Substrate and Dialkylzinc Reagent Using Optimized Ligand 4k[a]



entry	R	R′	ee %[b]	% yield[c]	entry	R	R′	ee %[b]	% yield[c]
1	2-naphthyl	Me	86	72	9	1-naphthyl	Et	24	89
2	2-naphthyl	Et	73	94	10	*trans*-PhCHCH	Me	25	24[e]
3	Ph	Me	84	68	11	*trans*-PhCHCH	Et	61	89
4	Ph	Et	68	84	12	$C(CH_3)_3$	Et	57[f]	7[g]
5	4-Cl-Ph	Me	81	77	13	4-MeO-Ph	Et	40	88
6	4-Cl-Ph	Et	77	100	14	cyclohexyl	Et	17[f]	81
7[d]	4-Cl-Ph	Et	90	79	15	$PhCH_2CH_2$	Et	0	78
8	1-naphthyl	Me	76	73					

[a] All experiments performed in duplicate. [b] % ee of (*R*)-alcohol as measured by HPLC (Chiralcel OD-H). [c] Reactions were allowed to proceed from 17 to 72 h. [d] Reaction performed at −48 °C for 72 h. [e] 30% conversion after 48 h. [f] Determined using the corresponding (*R*)-α-methoxy-α-trifluoromethylphenyl ester by ^{19}F NMR spectroscopy. [g] Neopentyl alcohol is a major side product in this reaction.

Conclusions

In summary, we have developed a new class of modular ligands that consist of an *N*-acylethylenediamine metal-binding moiety coupled to an amino acid that serves as a source of chirality. Three sites within the ligands were varied in order to optimize enantioselectivity. This process resulted in the valine-based ligand **4k**, which catalyzes the addition of dimethylzinc to benzaldehyde, 2-naphthaldehyde, and 4-Cl-benzaldehyde with reasonable enantioselectivity. Our future work will involve the development of libraries of chiral ligands that are based upon the *N*-acylethylenediamine motif in order to improve further their stereoselectivity and to investigate their application to other reactions.

Experimental Section

Synthesis of Ligands 4a−o, 1a, 1d, and 1i. General Procedure. To the appropriate *N*-protected amino acid (1.5 equiv) were added HBTU (2.2 equiv), DIEA (3.0 equiv), and enough DMF to dissolve all the solids. After stirring for 5 min, the appropriate *N*,*N*-dialkylethylenediamine (1.0 equiv) was added. The reaction was stirred at room temperature for 1 h and then diluted with H_2O. The aqueous phase was then extracted with EtOAc and the organic phase washed with H_2O and brine. The organic layer was dried over Na_2SO_4, the solvent removed, and the crude product purified by column chromatography.

[1-(2-(Dimethylamino)ethylcarbamoyl)-2-methylpropyl]-carbamic Acid *tert*-Butyl Ester 4a. Compound **4a** was

(8) When 2 equiv of diethylzinc are added to a solution of ligand **4k** in toluene-d_8, the ^1H NMR spectrum shows the disappearance of both of the NH protons and formation of ethane.

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prepared as described above from Boc-Val-OH (0.570 g, 2.62 mmol) and *N*,*N*-dimethylethylenediamine (0.432 mL, 3.94 mmol). Chromatography (0.7:6.3:93 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.159 g, 0.553 mmol, 21%): mp 88−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (br s, 1 H), 5.15 (br d, 1 H), 3.89 (dd, J = 8.7, 6.3 Hz, 1 H), 3.33 (dt, J = 5.9, 5.6 Hz, 2 H), 2.41 (dt, J = 6.1, 1.9 Hz, 2 H), 2.22 (s, 6 H), 2.10 (m, 1 H), 1.45 (s, 9 H), 0.94 (dd, J = 11.6, 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 156.4, 80.4, 60.6, 58.3, 45.2, 36.5, 31.3, 28.7, 19.6, 18.3; HRMS-ESI (M + H^+) calcd for $C_{14}H_{30}N_3O_3$ 288.2287, found 288.2294; $[\alpha]_D^{25}$ = +1.4 (c = 1.0, $CHCl_3$).

[1-(2-(Dimethylamino)ethylcarbamoyl)-2-phenylethyl]-carbamic Acid *tert*-Butyl Ester 4b. Compound **4b** was prepared as described above from Boc-Phe-OH (0.725 g, 2.73 mmol) and *N*,*N*-dimethylethylenediamine (0.500 mL, 4.56 mmol). Chromatography (1:9:90 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.708 g, 2.11 mmol, 77%): mp 113−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.21 (m, 5 H), 6.19 (br s, 1 H), 5.18 (br s, 1 H), 4.31 (d, J = 6.7 Hz, 1 H), 3.23 (t, J = 10.3 Hz, 2 H), 3.10 (dd, J = 13.5, 6.0 Hz, 1 H), 3.02 (m, 1 H), 2.29 (m, 1 H), 2.23 (m, 1 H), 2.13 (s, 6 H), 1.43 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 155.6, 137.3, 129.7, 129.0, 127.2, 80.3, 57.7, 56.4, 45.3, 39.6, 36.9, 28.7; HRMS-ESI (M + H^+) calcd for $C_{18}H_{30}N_3O_3$ 336.2287, found 336.2281; $[\alpha]_D^{25}$ = +15 (c = 1.0, $CHCl_3$).

[Cyclohexyl-(2-(dimethylamino)ethylcarbamoyl)-methyl]carbamic Acid *tert*-Butyl Ester 4c. Compound **4c** was prepared as described above from Boc-Chg-OH (0.302 g, 1.17 mmol) and *N*,*N*-dimethylethylenediamine (0.219 mL, 1.99 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.213 g, 0.650 mmol, 71%): mp 112−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (br s, 1 H), 5.17 (br d, 1 H), 3.87 (dd, J = 8.5, 6.7 Hz, 1 H), 3.33 (dt, J = 5.9, 5.5 Hz, 2 H), 2.40 (dt, J = 6.0, 2.2 Hz, 2 H), 2.22 (s, 6 H), 1.73−1.65 (m, 5 H), 1.44 (s, 9 H), 1.28−0.96 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 156.2, 80.0, 59.9, 58.1, 45.5, 41.2, 37.1, 30.1, 28.7, 26.5, 26.4; HRMS-ESI (M + H^+) calcd for $C_{17}H_{34}N_3O_3$ 328.2600, found 328.2601; $[\alpha]_D^{25}$ = +9.6 (c = 1.0, $CHCl_3$).

[2-(4-*tert*-Butoxyphenyl)-1-(2-(dimethylamino)ethylcarbamoyl)ethyl]carbamic Acid *tert*-Butyl Ester 4d. Compound **4d** was prepared as described above from Boc-Tyr(*tert*-Bu)-OH (0.349 g, 1.04 mmol) and *N*,*N*-dimethylethylenediamine (0.171 mL, 1.55 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.245 g, 0.601 mmol, 60%): mp 76−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 8.4 Hz, 2 H), 6.92 (d, J = 7.7 Hz, 2 H), 6.27 (br s, 1 H), 5.16 (d, J = 6.3 Hz, 1 H), 4.28 (d, J = 7.2 Hz, 1 H), 3.24 (m, 2 H), 3.00 (t, J = 6.4 Hz, 2 H), 2.28 (m, 2 H), 2.14 (s, 6 H), 1.42 (s, 9 H), 1.34 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 155.7, 154.6, 132.0, 130.1, 124.6, 80.3, 78.8, 57.9, 56.4, 45.4, 38.8, 37.1, 29.2, 28.7; HRMS-ESI (M + H^+) calcd for $C_{22}H_{38}N_3O_4$ 408.2862, found 408.2861; $[\alpha]_D^{25}$ = +13 (c = 1.1, $CHCl_3$).

[1-(2-(Dimethylamino)ethylcarbamoyl)-2-(4-nitrophenyl)ethyl]carbamic Acid *tert*-Butyl Ester 4e. Compound **4e** was prepared as described above from Boc-Phe(*p*-NO_2)-OH (0.356 g, 1.15 mmol) and *N*,*N*-dimethylethylenediamine (0.214 mL, 1.95 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a yellow solid (0.243 g, 0.639 mmol, 56%): mp 117−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, J = 6.9, 1.8 Hz, 2 H), 7.40 (dd, J = 7.0, 1.7 Hz, 2 H), 6.52 (br s, 1 H), 5.33 (d, J = 8.5 Hz, 1 H), 4.39 (dd, J = 14.9, 7.2 Hz, 1 H), 3.21 (m, 4 H), 2.31 (m, 2 H), 2.13 (s, 6 H), 1.40 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 155.6, 147.3, 145.3, 130.7, 124.0, 80.7, 57.8, 55.8, 45.3, 39.2, 37.1, 28.6; HRMS-ESI (M + H^+) calcd for $C_{18}H_{29}N_4O_5$ 381.2138, found 381.2126; $[\alpha]_D^{25}$ = +3.4 (c = 1.0, $CHCl_3$).

[2-Cyclohexyl-1-(2-(dimethylamino)ethylcarbamoyl)-ethyl]carbamic Acid *tert*-Butyl Ester 4f. Compound **4f** was prepared as described above from Boc-Cha-OH (0.198 g, 0.728 mmol) and *N*,*N*-dimethylethylenediamine (0.120 mL, 1.09 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.160 g, 0.468 mmol, 65%): mp 64−66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (br s, 1 H), 4.96 (br d, 1 H), 4.14 (m, 1 H), 3.35 (dt, J = 5.9, 5.4 Hz, 2 H), 2.45 (t, J = 6.0 Hz, 2 H), 2.27 (s, 6 H), 1.83−1.64 (m, 7 H), 1.46 (s, 9 H), 1.34−1.27 (m, 4 H), 0.95 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 155.9, 80.2, 58.1, 52.8, 45.5, 40.8, 37.1, 34.5, 34.0, 33.1, 28.7, 26.8, 26.7, 26.5; HRMS-ESI (M + H^+) calcd for $C_{18}H_{36}N_3O_3$ 342.2757, found 342.2749; $[\alpha]_D^{25}$ = −12 (c = 1.1, $CHCl_3$).

[1-(2-(Dimethylamino)ethylcarbamoyl)-2,2-dimethyl-propyl]carbamic Acid *tert*-Butyl Ester 4g. Compound **4g** was prepared as described above from Boc-*t*-Leu-OH (0.078 g, 0.337 mmol) and *N*,*N*-dimethylethylenediamine (0.044 mL, 0.404 mmol). Chromatography (30:70 MeOH/CH_2Cl_2) of the crude material yielded a yellow solid (0.055 g, 0.182 mmol, 54%): mp 127−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (br s, 1 H), 5.34 (d, J = 9.1 Hz, 1 H), 3.82 (d, J = 9.4 Hz, 1 H), 3.34 (m, 2 H), 2.43 (m, 2 H), 2.23 (s, 6 H), 1.44 (s, 9 H), 0.99 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 156.2, 79.9, 62.8, 57.9, 45.4, 36.9, 35.0, 28.7, 27.0; HRMS-ESI (M + H^+) calcd for $C_{15}H_{32}N_3O_3$ 302.2444, found 302.2439; $[\alpha]_D^{25}$ = +15 (c = 0.81, $CHCl_3$).

[2-(2-Chlorophenyl)-1-(2-(dimethylamino)ethylcarbamoyl)ethyl]carbamic Acid *tert*-Butyl Ester 4h. Compound **4h** was prepared as described above from Boc-Phe(2-Cl)-OH (0.319 g, 1.06 mmol) and *N*,*N*-dimethylethylenediamine (0.198 mL, 1.81 mmol). Chromatography (gradient of 0.5:4.5:95 to 0.8:7.2:92 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.258 g, 0.697 mmol, 66%): mp 132−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 1 H), 7.27 (m, 1 H), 7.19 (m, 2 H), 6.24 (br s, 1 H), 5.25 (d, J = 7.3 Hz, 1 H), 4.43 (dd, J = 15.0, 7.4 Hz, 1 H), 3.21 (m, 4 H), 2.31 (m, 1 H), 2.22 (m, 1 H), 2.13 (s, 6 H), 1.38 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 155.6, 135.4, 134.8, 132.0, 129.9, 128.7, 127.3, 80.3, 57.8, 55.0, 45.4, 37.3, 37.1, 28.7; HRMS-ESI (M + H^+) calcd for $C_{18}H_{29}N_3O_3Cl$ 370.1897, found 370.1882; $[\alpha]_D^{25}$ = +11 (c = 1.0, $CHCl_3$).

[1-(2-(Dimethylamino)ethylcarbamoyl)ethyl]-carbamic Acid *tert*-Butyl Ester 4i. Compound **4i** was prepared as described above from Boc-Ala-OH (2.02 g, 10.7 mmol) and *N*,*N*-dimethylethylenediamine (1.76 mL, 16.0 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.360 g, 1.39 mmol, 22%): mp 61−64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (br s, 1 H), 5.14 (br s, 1 H), 4.15 (t, J = 6.9 Hz, 1 H), 3.34 (m, 2 H), 2.45 (t, J = 6.0 Hz, 2 H), 2.25 (s, 6 H), 1.45 (s, 9 H), 1.36 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 155.8, 80.3, 58.1, 50.6, 45.5, 37.1, 28.7, 19.2; HRMS-ESI (M + H^+) calcd for $C_{12}H_{26}N_3O_3$ 260.1974, found 260.1986; $[\alpha]_D^{25}$ = −11 (c = 3.5, $CHCl_3$).

[2-*tert*-Butoxy-1-(2-(dimethylamino)ethylcarbamoyl)-propyl]carbamic Acid *tert*-Butyl Ester 4j. Compound **4j** was prepared as described above from Boc-Thr(*t*-Bu)-OH (0.372 g, 1.35 mmol) and *N*,*N*-dimethylethylenediamine (0.223 mL, 2.03 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.216 g, 0.625 mmol, 46%): mp 65−67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (br s, 1 H), 5.68 (d, J = 5.0 Hz, 1 H), 4.12−4.08 (m, 2 H), 3.35 (dt, J = 6.5, 5.3 Hz, 2 H), 2.41 (m, 2 H), 2.24 (s, 6 H), 1.46 (s, 9 H), 1.25 (s, 9 H), 1.05 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 156.0, 79.9, 75.3, 67.3, 58.9, 58.0, 45.5, 37.4, 28.8, 28.6, 18.1; HRMS-ESI (M + H^+) calcd for $C_{17}H_{36}N_3O_4$ 346.2706, found 346.2697; $[\alpha]_D^{25}$ = +38 (c = 3.4, $CHCl_3$).

[2-Methyl-1-[2-morpholin-4-ylethylcarbamoyl)propyl]-carbamic Acid *tert*-Butyl Ester 4k. Compound **4k** was prepared as described above from Boc-Val-OH (1.02 g, 4.69 mmol) and 2-morpholin-4-ylethylamine (0.681 mL, 5.19 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (1.18 g, 3.58 mmol, 76%, mp 92−95 °C). It was found that in some instances the material that was purified by chromatography required recrystallization from EtOAc/hexanes to provide a colorless ligand that produced the highest ee values for the dialkylzinc addition to aldehydes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (br s, 1 H), 5.11 (d, J = 7.2 Hz, 1 H), 3.89 (dd, J = 8.7, 6.3 Hz, 1 H), 3.72 (t, J = 4.5 Hz, 4 H), 3.38 (m, 2 H), 2.48 (m, 6 H), 2.11 (m, 1 H), 1.45 (s, 9 H), 0.95 (t, J = 7.4 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 156.2, 80.1, 67.3, 60.4, 57.2, 53.7, 36.0, 31.5, 28.7, 19.6, 18.4; HRMS-ESI (M + H$^+$) calcd for $C_{16}H_{32}N_3O_4$ 330.2393, found 330.2408; $[\alpha]_D^{25} = -3.8$ (c = 1.0, $CHCl_3$).

[2-Methyl-1-[2-pyrrolidin-1-ylethylcarbamoyl)propyl]-carbamic Acid *tert*-Butyl Ester 4l. Compound **4l** was prepared as described above from Boc-Val-OH (0.515 g, 2.37 mmol) and 2-pyrrolidin-1-yl-ethylamine (0.451 mL, 3.56 mmol). Chromatography (0.7:6.3:93 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a yellow solid (0.263 g, 0.839 mmol, 35%): mp 98−103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (br s, 1 H), 5.18 (br d, 1 H), 3.88 (dd, J = 8.7, 6.3 Hz, 1 H), 3.38 (dt, J = 6.4, 5.3 Hz, 2 H), 2.63 (dt, J = 6.1, 1.5 Hz, 2 H), 2.55 (br s, 4 H), 2.09 (m, 1 H), 1.79 (m, 4 H), 1.44 (s, 9 H), 0.94 (dd, J = 10.0, 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 156.3, 80.1, 60.4, 54.9, 54.2, 38.3, 31.5, 28.7, 23.8, 19.6, 18.3; HRMS-ESI (M + H$^+$) calcd for $C_{16}H_{32}N_3O_3$ 314.2444, found 314.2450; $[\alpha]_D^{25} = +3.9$ (c = 0.33, $CHCl_3$).

[2-Methyl-1-(2-piperidin-1-ylethylcarbamoyl)propyl]-carbamic Acid *tert*-Butyl Ester 4m. Compound **4m** was prepared as described above from Boc-Val-OH (1.07 g, 4.92 mmol) and 2-piperidin-1-ylethylamine (1.05 mL, 7.39 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (1.137 g, 3.47 mmol, 70%, mp 91−93 °C). It was found that in some instances the material that was purified by chromatography required recrystallization from EtOAc/hexanes to provide a colorless ligand that produced the highest ee values for the dialkylzinc addition to aldehydes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (br s, 1 H), 5.15 (d, J = 6.8 Hz, 1 H), 3.88 (dd, J = 8.1, 6.1 Hz, 1 H), 3.42 (m, 2 H), 2.59 (m, 6 H), 2.10 (m, 1 H), 1.64 (m, 4 H), 1.52 (m, 2 H), 1.46 (s, 9 H), 0.96 (t, J = 7.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 156.4, 80.4, 60.6, 57.7, 54.7, 36.0, 31.3, 28.7, 25.8, 24.1, 19.5, 18.4; HRMS-ESI (M + H$^+$) calcd for $C_{17}H_{34}N_3O_3$ 328.2600, found 328.2597; $[\alpha]_D^{25} = +2.0$ (c = 2.5, $CHCl_3$).

[1-(2-(Dibutylamino)ethylcarbamoyl)-2-methylpropyl]-carbamic Acid *tert*-Butyl Ester 4n. Compound **4n** was prepared as described above from Boc-Val-OH (0.930 g, 4.28 mmol) and *N*,*N*-dibutylethylenediamine (1.35 mL, 6.42 mmol). Chromatography (0.4:3.6:96 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.721 g, 1.94 mmol, 45%): mp 43−46 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (br s, 1 H), 5.07 (d, J = 6.4 Hz, 1 H), 3.88 (m, 1 H), 3.56−3.46 (m, 2 H), 3.02 (m, 2 H), 2.84 (br s, 4 H), 2.13 (m, 1 H), 1.57 (m, 4 H), 1.46 (m, 9 H), 1.37 (m, 4 H), 0.96 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 156.5, 80.6, 60.8, 55.0, 54.1, 36.5, 30.9, 28.7, 27.5, 20.5, 19.6, 18.3, 14.1; HRMS-ESI (M + H$^+$) calcd for $C_{20}H_{42}N_3O_3$ 372.3226, found 372.3216; $[\alpha]_D^{25} = 0.0$ (c = 4.0, $CHCl_3$).

[1-(2-(Diisopropylamino)ethylcarbamoyl)-2-methylpropyl]carbamic Acid *tert*-Butyl Ester 4o. Compound **4o** was prepared as described above from Boc-Val-OH (0.627 g, 2.89 mmol) and *N*,*N*-diisopropylethylenediamine (0.750 mL, 4.30 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.880 g, 2.56 mmol, 89%): mp 114−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (br s, 1 H), 5.08 (d, J = 8.5 Hz, 1 H), 3.95 (dd, J = 8.4, 5.8 Hz, 1 H), 3.35 (m, 2 H), 3.20 (t, J = 6.2 Hz, 2 H), 2.78 (m, 2 H), 2.17 (m, 1 H), 1.44 (s, 9 H), 1.12 (d, J = 6.6 Hz, 12 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 156.2, 80.3, 60.4, 49.8, 44.8, 38.2, 31.1, 28.7, 20.5, 19.7, 18.0; HRMS-ESI (M + H$^+$) calcd for $C_{18}H_{38}N_3O_3$ 344.2913, found 344.2912; $[\alpha]_D^{25} = -0.73$ (c = 3.4, $CHCl_3$).

[1-(2-(Diethylamino)ethylcarbamoyl)-2-methylpropyl]-carbamic Acid *tert*-Butyl Ester 1a. Compound **1a** was prepared as described above from Boc-Val-OH (5.00 g, 23.0 mmol) and *N*,*N*-diethylethylenediamine (4.85 mL, 34.5 mmol). Chromatography (0.7:6.3:93 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (6.88 g, 21.8 mmol, 95%): mp 78−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (br s, 1 H), 5.13 (d, J = 7.9 Hz, 1 H), 3.88 (dd, J = 8.2, 6.1 Hz, 1 H), 3.40 (m, 2 H), 2.71 (m, 6 H), 2.10 (m, 1 H), 1.45 (s, 9 H), 1.09 (t, J = 7.2 Hz, 6 H), 0.95 (dd, J = 10.3, 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 156.3, 80.3, 60.6, 52.4, 47.3, 36.8, 31.2, 28.7, 19.6, 18.3, 11.5; HRMS-ESI (M + H$^+$) calcd for $C_{16}H_{34}N_3O_3$ 316.2600, found 316.2600; $[\alpha]_D^{25} = -0.57$ (c = 3.5, $CHCl_3$).

[1-[2-(Diethylamino)ethylcarbamoyl)-2-methylpropyl]-carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester 1d. Compound **1d** was prepared as described above from Fmoc-Val-OH (0.804 g, 2.37 mmol) and *N*,*N*-diethylethylenediamine (0.50 mL, 3.55 mmol). Chromatography (0.4:3.6:96 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.908 g, 2.07 mmol, 88%): mp 109−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.4 Hz, 2 H), 7.62 (d, J = 7.3 Hz, 2 H), 7.41 (t, J = 7.4 Hz, 2 H), 7.35 (t, J = 6.7 Hz, 2 H), 6.62 (br s, 1 H), 5.60 (d, J = 8.7 Hz, 1 H), 4.40 (m, 2 H), 4.23 (t, J = 7.0 Hz, 1 H), 3.99 (dd, J = 8.4, 6.7 Hz, 1 H), 3.35 (t, J = 4.5 Hz, 2 H), 2.59 (m, 6 H), 2.13 (m, 1 H), 1.00 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 156.8, 144.3, 144.2, 141.7, 129.2, 128.1, 127.5, 125.6, 125.5, 121.4, 120.4, 120.2, 67.5, 61.0, 51.8, 47.6, 47.4, 47.0, 37.1, 31.7, 19.5, 18.5, 12.1, 11.9; HRMS-ESI (M + H$^+$) calcd for $C_{26}H_{36}N_3O_3$ 438.2757, found 438.2753; $[\alpha]_D^{25} = -7.2$ (c = 1.0, $CHCl_3$).

[1-(2-(Diethylamino)ethylcarbamoyl)-2-methylpropyl]-carbamic Acid Benzyl Ester 1i. Compound **1i** was prepared as described above from Cbz-Val-OH (0.894 g, 3.56 mmol) and *N*,*N*-diethylethylenediamine (0.750 mL, 5.34 mmol). Chromatography (0.6:5.4:94 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.725 g, 2.07 mmol, 58%): mp 104−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 6.68 (br s, 1 H), 5.47 (br d, 1 H), 5.11 (s, 2 H), 3.96 (dd, J = 8.3, 6.1 Hz, 1 H), 3.37 (dt, J = 5.6, 5.2 Hz, 2 H), 2.63 (m, 6 H), 2.11 (m, 1 H), 1.05 (t, J = 7.1 Hz, 6 H), 0.96 (dd, J = 9.7, 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 156.9, 136.6, 129.0, 128.6, 128.4, 67.4, 61.1, 52.0, 47.1, 36.8, 31.5, 19.6, 18.3, 11.6; HRMS-ESI (M + H$^+$) calcd for $C_{19}H_{32}N_3O_3$ 350.2444, found 350.2440; $[\alpha]_D^{25} = +2.6$ (c = 0.93, $CHCl_3$).

Synthesis of Ligands 1b, 1c, 1e, 1 g, 1h, and 1j. General Procedure. Ligand **1a** was treated with CF_3CO_2H (10 equiv) in CH_2Cl_2 at 0 °C and allowed to warm to room temperature. The reaction was monitored by TLC (1.5:13.5:85 30% aqueous NH_4OH/MeOH/CH_2Cl_2), and after the disappearance of starting material, the reaction was diluted with CH_2Cl_2 followed by rotary evaporation. The crude material was dissolved in EtOAc and treated with small aliquots of saturated aqueous Na_2CO_3 until the aqueous layer tested basic. The aqueous layer was further extracted with fresh EtOAc and the combined organic layers were dried over Na_2SO_4. The crude material was used immediately upon isolation, without further purification unless otherwise noted. The crude free amine from ligand **1a**, 2-amino-*N*-(2-(diethylamino)ethyl)-3-methylbutyramide, (1.0 equiv) was dissolved in EtOAc and treated with DIEA (1.2−3.6 equiv) followed by the appropriate acid chloride or chloroformate (1.0 equiv). After a few hours the reaction was quenched with H_2O and extracted into EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The crude product was then purified by column chromatography.

***N*-(2-(Diethylamino)ethyl)-2-(2,2-dimethylpropionylamino)-3-methylbutyramide 1b.** Compound **1b** was prepared as described above using 2,2-dimethylpropionyl chloride (0.079 mL, 0.64 mmol) and 2-amino-*N*-(2-(diethylamino)ethyl)-3-methylbutyramide (0.125 g, 0.581 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.133 g, 0.44 mmol, 76%): mp 123−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (br s, 1 H), 6.34 (d, J = 8.3 Hz, 1 H), 4.25 (dd, J = 8.4, 6.4 Hz, 1 H), 3.34 (m, 2 H), 2.56 (m, 6 H), 2.11 (m, 1 H), 1.24 (s, 9 H), 1.04 (t, J = 7.1 Hz, 6 H), 0.95 (dd, J = 6.8, 2.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 171.5, 58.5, 51.7, 46.9, 39.3, 37.0, 31.9, 28.0, 19.5, 18.6, 11.9; HRMS-ESI (M + H$^+$) calcd for $C_{16}H_{34}N_3O_2$ 300.2651, found 300.2657; $[\alpha]_D^{25} = -9.0$ (c = 2.8, $CHCl_3$).

Adamantane-1-carboxylic Acid [1-(2-(Diethylamino)-ethylcarbamoyl)-2-methylpropyl]amide 1c. Compound **1c** was prepared as described above using adamantane-1-carbonyl chloride (0.437 g, 2.20 mmol) and 2-amino-*N*-(2-(diethylamino)-ethyl)-3-methylbutyramide (0.473 g, 2.20 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.210 g, 0.556 mmol, 25%): mp 150−210 °C dec; ^{1}H NMR (300 MHz, CDCl3) δ 6.93 (br s, 1 H), 6.33 (br d, 1 H), 4.27 (dd, J = 8.5, 6.4 Hz, 1 H), 3.36 (m, 2 H), 2.61 (m, 6 H), 2.09 (m, 1 H), 2.06 (m, 3 H), 1.91 (m, 6 H), 1.73 (d, J = 2.4 Hz, 6 H), 1.06 (t, J = 7.2 Hz, 6 H), 0.94 (t, J = 6.6 Hz, 6 H); ^{13}C NMR (75 MHz, CDCl3) δ 178.3, 171.9, 58.2, 51.7, 46.8, 41.2, 39.7, 39.6, 37.1, 36.9, 36.7, 31.8, 28.6, 28.5, 19.7, 18.5, 11.3; HRMS-ESI (M + H$^+$) calcd for $C_{22}H_{40}N_3O_2$ 378.3121, found 378.3127; $[\alpha]_D^{25} = -2.9$ (c = 4.7, $CHCl_3$).

[1-(2-(Diethylamino)ethylcarbamoyl)-2-methylpropyl]-carbamic Acid Isobutyl Ester 1e. Compound **1e** was prepared as described above using isobutyl chloroformate (0.142 mL, 1.09 mmol) and 2-amino-*N*-(2-(diethylamino)ethyl)-3-methylbutyramide (0.473 g, 2.20 mmol). Chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a white solid (0.102 g, 0.323 mmol, 30%): mp 85−88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (br s, 1 H), 5.34 (br d, 1 H), 3.95 (dd, J = 8.8, 6.2 Hz, 1 H), 3.85 (d, J = 6.7 Hz, 2 H), 3.33 (dt, J = 6.8, 5.1 Hz, 2 H), 2.55 (m, 6 H), 2.10 (m, 1 H), 1.92 (m, 1 H), 1.02 (t, J = 7.1 Hz, 6 H), 0.95 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 157.2, 71.7, 60.8, 51.7, 47.0, 37.0, 31.6, 28.4, 19.6, 19.4, 18.3, 12.0; HRMS-ESI (M + H$^+$) calcd for $C_{16}H_{34}N_3O_3$ 316.2600, found 316.2598; $[\alpha]_D^{25} = -2.1$ (c = 1.0, $CHCl_3$).

[1-(2-(Diethylamino)ethylcarbamoyl)-2-methylpropyl]-carbamic Acid Methyl Ester 1g. Ligand **1a** (0.760 g, 2.41 mmol) was treated with CF_3CO_2H in CH_2Cl_2 at 0 °C. After the reaction was complete, the organic layer was washed with saturated Na_2CO_3, and the solvent was removed by rotary evaporation. Chromatography (1.5:13.5:85 30% aqueous NH_4-OH/MeOH/CH_2Cl_2) gave the intermediate free amine 2-amino-*N*-(2-(diethylamino)ethyl)-3-methylbutyramide as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (br s, 1 H), 3.33 (dt, J = 6.3, 5.9 Hz, 2 H), 3.21 (d, J = 4.1 Hz, 1 H), 2.57 (m, 6 H), 2.26 (m, 1 H), 1.50 (br s, 2 H), 1.03 (t, J = 7.2 Hz, 6 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 60.8, 51.9, 47.4, 36.0, 31.5, 20.1, 16.6, 10.7; HRMS-ESI (M + H$^+$) calcd for $C_{11}H_{26}N_3O$ 216.2076, found 216.2078.

Compound **1g** was prepared as described above using 1.1 equiv of methyl chloroformate (0.127 mL, 1.65 mmol) and 2-amino-*N*-(2-(diethylamino)ethyl)-3-methylbutyramide (0.322 g, 1.50 mmol), yielding an amorphous solid (0.231 g, 0.845 mmol, 57%) without the need for further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (br s, 1 H), 5.35 (d, J = 7.7 Hz, 1 H), 3.94 (dd, J = 8.4, 6.4 Hz, 1 H), 3.68 (s, 3 H), 3.33 (m, 2 H), 2.57 (m, 6 H), 2.10 (m, 1 H), 1.02 (t, J = 7.1 Hz, 6 H), 0.95 (dd, J = 10.2, 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 157.4, 60.8, 52.7, 51.6, 47.0, 37.1, 31.6, 19.6, 18.2, 12.1; HRMS-ESI (M + H$^+$) calcd for $C_{13}H_{28}N_3O_3$ 274.2131, found 274.2138; $[\alpha]_D^{25} = -9.1$ (c = 1.0, $CHCl_3$).

***N*-[1-(2-(Diethylamino)ethylcarbamoyl)-2-methylpropyl]-4-methylbenzamide 1h.** Compound **1h** was prepared as described above using 4-methylbenzoyl chloride (0.189 mL, 1.43 mmol) and 2-amino-*N*-(2-(diethylamino)ethyl)-3-methylbutyramide (0.307 g, 1.43 mmol). Chromatography (0.5:4.5: 95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded an amorphous solid (0.0918 g, 0.275 mmol, 19%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2 H), 7.22 (d, J = 8.0 Hz, 2 H), 6.98 (m, 2 H), 4.40 (dd, J = 7.9, 7.1 Hz, 1 H), 3.91 (br s, 1 H), 3.38 (dt, J = 6.0, 5.7 Hz, 2 H), 2.67 (m, 6 H), 2.38 (s, 1 H), 2.19 (m, 1 H), 1.02 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 167.9, 142.6, 131.4, 129.6, 127.5, 59.7, 52.1, 47.2, 36.8, 31.8, 21.9, 19.6, 19.0, 11.5; HRMS-ESI (M + H$^+$) calcd for $C_{19}H_{32}N_3O_2$ 334.2495, found 334.2488; $[\alpha]_D^{25} = +30$ (c = 0.45, $CHCl_3$).

***N*-[1-(2-(Diethylamino)ethylcarbamoyl)-2-methylpropyl]-4-nitrobenzamide 1j.** Compound **1j** was prepared as described above using 4-nitrobenzoyl chloride (0.192 mL, 1.04 mmol) and 2-amino-*N*-(2-(diethylamino)ethyl)-3-methylbutyramide (0.223 g, 1.04 mmol). Chromatography (0.7:6.3:93 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded a yellow solid (0.157 g, 0.431 mmol, 42%): mp 89−94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (dt, J = 8.9, 2.1 Hz, 2 H), 8.00 (dt, J = 8.9, 2.1 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 1 H), 6.68 (br s, 1 H), 4.47 (dd, J = 8.4, 6.7 Hz, 1 H), 3.36 (m, 2 H), 2.56 (m, 6 H), 2.20 (m, 1 H), 1.03 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 165.6, 150.0, 140.2, 128.8, 124.2, 59.5, 51.5, 46.9, 37.2, 32.3, 19.5, 18.9, 12.0; HRMS-ESI (M + H$^+$) calcd for $C_{18}H_{29}N_4O_4$ 365.2189, found 365.2193; $[\alpha]_D^{25} = +36$ (c = 1.5, $CHCl_3$).

{[1-(2-(Diethylamino)ethylcarbamoyl)-2-methylpropylcarbamoyl]methyl}carbamic Acid *tert*-Butyl Ester 1f. 2-Amino-*N*-(2-(diethylamino)ethyl)-3-methylbutyramide (0.180 g, 0.83 mmol) was coupled to Boc-glycine (0.122 g, 0.695 mmol) using the general procedure used to synthesize ligands **4a**−**o**. Chromatography (0.7:6.3:93 30% aqueous NH_4OH/MeOH/CH_2Cl_2) of the crude material yielded **1f** as a white solid (0.024 g, 0.064 mmol, 9%): mp 127−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, J = 8.7 Hz, 1 H), 6.59 (br s, 1 H), 5.24 (br s, 1 H), 4.26 (dd, J = 8.7, 6.4 Hz, 1 H), 3.89 (dd, J = 16.8, 5.8 Hz, 1 H), 3.79 (dd, J = 16.8, 5.6 Hz, 1 H), 3.32 (m, 2 H), 2.55 (m, 6 H), 2.12 (m, 1 H), 1.47 (s, 9 H), 1.03 (t, J = 7.2 Hz, 6 H), 0.95 (dd, J = 6.7, 5.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 169.7, 156.4, 80.7, 58.8, 51.6, 47.0, 44.8, 37.1, 31.7, 28.7, 19.5, 18.4, 12.0; HRMS−FAB (M + Na$^+$) calcd for $C_{18}H_{36}N_4O_4Na$ 395.2634, found 395.2628; $[\alpha]_D^{25} = -3.1$ (c = 2.4, $CHCl_3$).

General Procedure for Et_2Zn Addition to Aldehydes. To an oven-dried vial was added the ligand (0.06 mmol) followed by a 1.0 M solution of Et_2Zn in hexanes (1.8 mmol). The solution was allowed to stir for 10 min at room temperature and then cooled to 0 °C followed by the addition of benzaldehyde (0.60 mmol). After 24 h the reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extractions were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered through a plug of SiO_2, and concentrated in vacuo. The crude alcohol was analyzed without further purification by chiral HPLC (Chiralcel OD or OD-H).

(*R*)-1-Phenyl-1-propanol: 68% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5: 2.5) at 1.0 mL/min and detection at 219 nm), t_R = 12.4 min for (*R*) and t_R = 14.0 min for (*S*).[13]

(*R*)-1-Phenyl-1-ethanol: 84% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detection at 219 nm), t_R = 12.5 min for (*R*) and t_R = 16.3 min for (*S*).[14]

(*R*)-1-(1′-Naphthyl)-1-propanol: 24% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol

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(97.5:2.5) at 1.0 mL/min and detection at 219 nm), t_R = 21.2 min for (*S*) and t_R = 43.7 min for (*R*).[13]

(*R*)-1-(1′-Naphthyl)-1-ethanol: 76% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detection at 219 nm), t_R = 27.5 min for (*S*) and t_R = 44.0 min for (*R*).[14]

(*R*)-1-(2′-Naphthyl)-1-propanol: 73% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detection at 219 nm), t_R = 23.2 min for (*S*) and t_R = 25.9 min for (*R*).[13]

(*R*)-1-(2′-Naphthyl)-1-ethanol: 86% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:ethanol (95.0:5.0) at 0.5 mL/min and detection at 219 nm), t_R = 25.8 min for (*S*) and t_R = 27.5 min for (*R*).[14]

(*R*)-1-Phenylpent-1-(E)-en-3-ol: 61% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detection at 219 nm), t_R = 18.7 min for (*R*) and t_R = 31.3 min for (*S*).[13]

(*R*)-4-Phenyl-4-but-3-(E)-en-2-ol: 25% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detection at 219 nm), t_R = 25.0 min for (*R*) and t_R = 44.2 min for (*S*).[15]

(*R*)-1-Phenyl-3-pentanol: 0% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detection at 219 nm), t_R = 13.8 min for (*R*) and t_R = 21.0 min for (*S*).[16]

(*R*)-1-Cyclohexyl-1-propanol: 17% ee by ^{19}F NMR analysis of the (*R*)-MTPA ester; $[\alpha]_D^{23} = +1.5$ (*c* =1.84, $CHCl_3$) {lit.[13] $[\alpha]_D^{24} = -6.39$ (*c* = 1.05, $CHCl_3$) for 97% ee (*S*)}.

(*R*)-1-(4′-Methoxyphenyl)-1-propanol: 40% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detection at 219 nm), t_R = 16.7 min for (*R*) and t_R = 19.7 min for (*S*).[13]

(*R*)-1-(4′-Chlorophenyl)-1-propanol: 77% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detection at 219 nm), t_R = 10.6 min for (*S*) and t_R = 11.3 min for (*R*).[13]

(*R*)-1-(4′-Chlorophenyl)-1-ethanol: 81% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detection at 219 nm), t_R = 12.2 min for (*S*) and t_R = 13.2 min for (*R*).[17]

(*R*)-2,2-Dimethylpentan-3-ol: 57% ee by ^{19}F NMR analysis of the (*R*)-MTPA ester; $[\alpha]_D^{23} = +1.2$ (*c* =5.35, $CHCl_3$) {lit.[18] $[\alpha]_D^{22} = -32.6$ (*c* = 2.38, $CHCl_3$) for 98% ee (*S*)}.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds and HPLC column conditions/retention times for all alcohol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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