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Enantioselective Addition of Vinylzinc Reagents to Aldehydes Catalyzed by Modular Ligands Derived from Amino Acids

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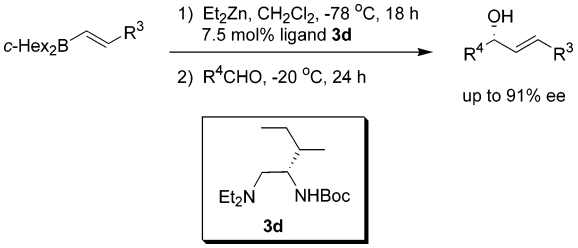

A series of *N*-acylethylenediamine-based ligands were synthesized from Boc-protected amino acids. The ligands were screened for the ability to catalyze the asymmetric addition of vinylzinc reagents to aldehydes. Three sites of diversity on the ligands were optimized for this reaction using a positional scanning approach. The optimized ligand **3d** was found to catalyze the formation of 15 different (*E*)-allylic alcohols with enantioselectivities that ranged from 52 to 91% ee and yields that ranged from 40 to 90%. This ligand was especially effective for the reaction of aromatic aldehydes with vinylzinc reagents derived from bulky terminal alkynes. Ligand **3d** catalyzed the addition of (*E*)-(3,3-dimethylbut-1-enyl)(ethyl)zinc to 2-naphthaldehyde to give (*R,E*)-4,4-dimethyl-1-(naphthalene-1-yl)pent-2-en-1-ol in 89% ee. The ee of this product could be increased to 97% through a single recrystallization.

Introduction

Reactions that form optically active secondary allylic alcohols represent a very useful class of catalytic enantioselective transformations. The resulting chiral allylic alcohols have many attractive features; they are important synthetic precursors[1] and they are found in numerous naturally occurring and biologically active compounds.[2] Two general approaches have been used to prepare chiral allylic alcohols: (a) the enantioselective reduction of α,β-unsaturated ketones and (b) the enantioselective addition of vinylzinc reagents to aldehydes. One advantage to the latter approach is that it generates a new C−C bond concomitant with formation of the chiral center.

Two methods have been developed for the dialkylzinc-promoted synthesis of chiral (*E*)-allylic alcohols. The first method, established by Wipf,[3] employs Cp_2ZrHCl (Schwartz's reagent)[4] to accomplish the (*E*)-selective hydrozirconation of terminal alkynes, yielding an organozirconium intermediate. Such organozirconium compounds are relatively unreactive toward electrophiles. However, they undergo smooth transmetalation with dialkylzinc reagents to give the corresponding vinylzinc species. After transmetalation, addition of an aromatic

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(3) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197−5200.

(4) (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333−340. (b) Labinger, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol 8, pp 667−702.

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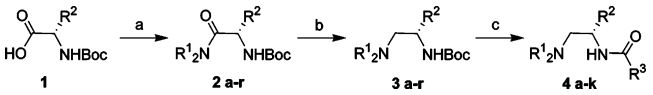
or aliphatic aldehyde and a chiral catalyst provides the (*E*)-allylic alcohol. Wipf and co-workers have used this method, in conjunction with a catalytic amount of a chiral amino-thiol ligand to provide (*E*)-allylic alcohols in high ee's.[5]

The second method, originally described by Oppolzer and Radinov,[6] begins with the regioselective hydroboration of a terminal alkyne to give a vinylborane. The vinylborane is transmetalated with dialkylzinc to yield a mixed (*E*)-alkeny(alkyl)zinc species. This vinylzinc species can be subsequently reacted with aldehydes in the presence of a ligand to provide chiral (*E*)-allylic alcohols. Oppolzer and Radinov developed several amino alcohol ligands that provide the desired chiral allylic alcohols in good enantioselectivities.[7] Other researchers have used the Oppolzer protocol, in conjunction with a variety of Lewis base ligands, to broaden the scope of the reaction. For example, Dahmen and Brase[8] have employed [2,2]paracyclophane hydroxyketimine ligands, Chan and co-workers[9] have employed an aromatic γ-amino alcohol, and Tseng and Yang[10] have used amino thiol ligands in this reaction. Walsh has developed Nugent's isoborneal-based β-amino alcohol ligand (−)-MIB[11] as a catalyst for the Oppolzer protocol. He has further elaborated the resulting chiral allylic alcohols into a number of products and synthetically useful intermediates including allylic amines,[12] α-amino acids,[12] γ-unsaturated β-amino acids,[13] hydroxyl enol ethers[14] and epoxy alcohols.[15]

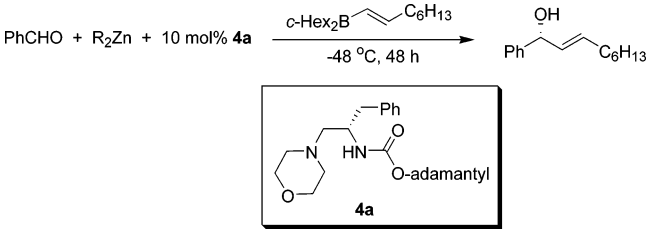
We have recently reported the synthesis of modular *N*-acylethylenediamine ligands with three sites of diversity and their use as asymmetric catalysts for the addition of dialkylzinc reagents to aldehydes.[16,17] We envision that these ligands, in analogy to amino alcohol-based ligands, react with organozinc reagents by deprotonation of the amide or carbamate N−H group to give a five-membered zinc chelate.[18] We have also described an efficient solid-phase synthesis of these chiral ligands.[19] In this report, we describe the application of the *N*-acylethylenediamine ligands to the enantioselective addition of vinylzinc reagents to aldehydes using the Oppolzer protocol.

SCHEME 1. Synthesis of Modular Amino Acid-Based Ligands[a−c]



[a] Reagents: (a) *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), diisopropylethylamine (DIEA), $(R^1)_2NH$, DMF, 55−96%; (b) (i) BH_3−THF, (ii) $H_2N(CH_2)_2NH_2$, 11−53%; (c) (i) TFA, (ii) R^3COX (X = Cl or F), DIEA, CH_2Cl_2, 48−99%. [b]For the specific structures of compounds **2a**−**r**, see the Supporting Information. [c]For the specific structures of compounds **3a**−**r** and **4a**−**k**, see Tables 2−4 and 6 and Scheme 2.

SCHEME 2



Results and Discussion

We began the synthesis of the ligands by coupling commercially available Boc-protected amino acids with a secondary amine to yield the corresponding amides **2** (Scheme 1). The amides were reduced with borane−THF to give the corresponding diamine as a complex with boron. The free diamine **3** was liberated by treating the complex with an excess of ethylenediamine in methanol solution and heating the reaction to 100 °C for 120 s using microwave irradiation. Finally, the Boc group was removed with TFA, and the resulting free amine was reacted with an acid chloride or a chloro- or fluoroformate to yield the corresponding amide or carbamate **4**.[20]

Other investigators who have developed catalysts for use in the Oppolzer protocol have employed a variety of different reaction conditions, including different temperatures for the transmetalation, the use of Me_2Zn or Et_2Zn, and several methods for the addition of reagents. Since so many different and conflicting conditions have been reported, we began our investigations by optimizing the reaction conditions for the *N*-acylethylenediamine class of ligands. In the first series of reactions, the vinylborane reagent obtained from 1-octyne was added to a solution of benzaldehyde, dialkylzinc and 10 mol % of ligand **4a** (Scheme 2). The reactions were allowed to proceed at −48 °C for 48 h, and then they were quenched with aqueous ammonium chloride solution and the ee was analyzed by chiral HPLC. At −48 °C, the reaction between dialkylzinc and benzaldehyde is much slower than the desired transmetalation/vinyl transfer reaction.

When Et_2Zn was employed as the transmetalating agent and the vinylborane was added quickly to the

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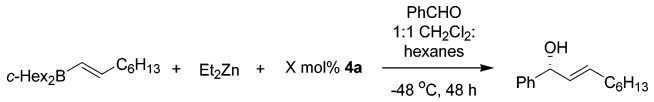
(18) The ^{1}H NMR spectrum of a mixture of diethylzinc and a related *N*-acylethylenediamine-based ligand shows disappearance of the NH protons and formation of ethane. See ref 17.

(19) Sprout, C. M.; Richmond, M. R.; Seto, C. T. *J. Org. Chem.* **2004**, *69*, 6666.

(20) For the synthesis and characterization of amides **2a**,**b**,**h**−**i** and ligands **3a**,**b**,**h**,**i**, and **4d**−**i**, see ref 16.

TABLE 1. Effect of Catalyst Loading on the % ee of (*R*,*E*)-1-Phenyl-2-nonen-1-ol[a]



entry	**4a** (mol %)	ee[b,c] (%)
1	2.5	9
2	5	26
3	7.5	48
4	7.5	66[d]
5	10	48
6	15	46

[a] All experiments performed in duplicate. [b] Absolute configuration assigned by comparison with literature values. [c] Determined by chiral HPLC (Chiralcel OD-H). [d] Reaction conducted in CH_2Cl_2 as the only solvent. *c*-Hex = cyclohexyl.

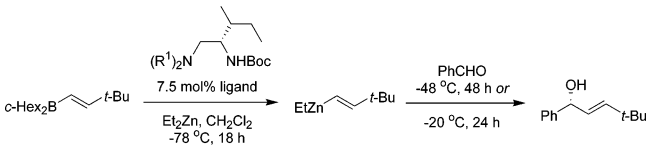
reaction mixture in a single portion, none of the desired allylic alcohol was detected. However, when the vinylborane was added slowly to the reaction over a period of 1 h by syringe pump, the product (*R*)-allylic alcohol was obtained in 26% ee. With Me_2Zn as the transmetalating agent, no product was observed with fast or slow addition of the vinylborane.

We next modified the order of addition of the reactants. The vinylzinc reagent was first prepared by reacting Me_2Zn or Et_2Zn with the vinylborane derived from 1-octyne in the presence of ligand **4a** at −78 °C for 1 h. Benzaldehyde was then added, and the reaction was incubated at −48 °C for 48 h and quenched. As before, reactions employing Me_2Zn did not yield any of the desired product. When Et_2Zn was used as the transmetalating agent, and benzaldehyde was added to the preformed vinylzinc reagent over 30 min by syringe pump, the product allylic alcohol was obtained in 20% ee. By contrast, when benzaldehyde was added quickly and in one portion to the vinyl(ethyl)zinc species, we obtained the allylic alcohol in 48% ee. As a result, we performed all subsequent reactions by adding the aldehyde in a single portion to a preformed solution of the mixed (alkenyl)(ethyl)zinc species and ligand.

We have also observed that the quality of the vinylzinc reagent and the subsequent ee of the reaction product are very sensitive to the temperature of the transmetalation reaction. Walsh and co-workers reported that the transmetalation reaction with Me_2Zn or Et_2Zn could be performed at 0 °C, which gave excellent enantioselectivities and yields of the desired products.[12] However, in our hands we found that warming the reaction mixture containing Et_2Zn, the vinylborane and ligand above −78 °C was not favorable. When the transmetalation reaction was allowed to warm from −78 to 0 °C over 1 h, the solution turned deep brown and the resulting alcohol, after addition of benzaldehyde, was formed in only 30% ee. Similar results were obtained when the reaction was warmed to −48 °C over an hour. When the transmetalation reaction was kept at −78 °C for 1 h, the solution remained colorless and the ee of the product was increased to 48%.

Finally, we examined the effect of catalyst loading on the formation of (*R*,*E*)-1-phenyl-2-nonen-1-ol (Table 1). The ee of the product increased from 9 to 48% as the catalyst was increased from 2.5 to 7.5 mol %. Beyond this point we did not observe a further increase in product ee with catalyst loading. Changing the solvent to 100% CH_2Cl_2 gave a further increase in enantioselectivity to 66% ee (entry 4). As a result, all further experiments were performed using a catalyst loading of 7.5 mol % and CH_2Cl_2 as the solvent.

TABLE 2. Effect of the Ligand Tertiary Amine on the Addition of Vinylzinc Reagent to Benzaldehyde[a]



entry	ligand	$N(R^1)_2$	ee (%) at −48 °C[b,c]	ee (%) at −20 °C[b,c]	yield[d] (%)
1	**3a**	$N(CH_2CH_2)_2O$	85	76	55
2	**3b**	$N(CH_2)_5$	86	82	61[e]
3	**3c**	$N(CH_2)_4$	91	88	61
4	**3d**	NEt_2	90	89	67
5	**3e**	NMe_2	89	78	54

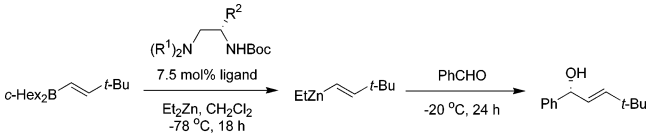
[a] All experiments performed in duplicate. [b] Absolute configuration assigned by comparison with literature values. [c] Determined by chiral HPLC (Chiralcel OD-H). [d] All yields are for reactions performed at −20 °C unless otherwise noted. [e] Yield for reaction performed at −48 °C. *c*-Hex = cyclohexyl.

With the conditions for the transmetalation, catalyst loading, and reagent addition in place, we began to optimize the structure of the modular ligands. We first investigated the effect of the tertiary amine on product ee by employing ligands derived from *N*-Boc-Ile that incorporated five different tertiary amine groups (Table 2). All of the ligands gave good enantioselectivities, with those containing the five-membered pyrrolidine ring and diethylamine (entries 3 and 4) providing the highest ee. Increasing the temperature of the reaction from −48 to −20 °C allowed us to decrease the reaction time from 48 to 24 h, although it resulted in a small decrease in enantioselectivity. Ligands **3c** and **3d** lost only 1−3% ee with the increase in temperature, while ligands **3a** and **3e** showed a larger erosion of product ee of 9 and 11%, respectively.

To determine if there was a difference between the pyrrolidine ring and the diethylamino group within the context of ligands derived from other amino acids, we prepared ligands based upon Phe and Val that contained these two tertiary amines. For the addition of (*E*)-(3,3-dimethylbut-1-enyl)(ethyl)zinc to benzaldehyde (Table 3), ligands that contained the diethylamino group (entries 2, 4, and 6) gave the same or in some cases significantly higher ee values for the product allylic alcohol when compared to ligands that contained the pyrrolidine ring (entries 1, 3, and 5). In addition, diethylamino-containing ligands **3d**, **3g**, and **3i** gave higher yields when compared to pyrrolidine-containing ligands **3c**, **3f**, and **3h**.

We next investigated the effect of the carbamate and amide groups of the ligand on the stereoselectivity of the reaction (Table 4). In the first series of reactions (entries 1−8), the amino acid side chain and the tertiary amine of the ligand were held constant as the side chain of Ile and morpholine, respectively. All of the modifications that we explored at the R^3 position of the ligands gave substantially lower enantioselectivities and yields when compared to ligand **3a**, which incorporates an O-*t*Bu

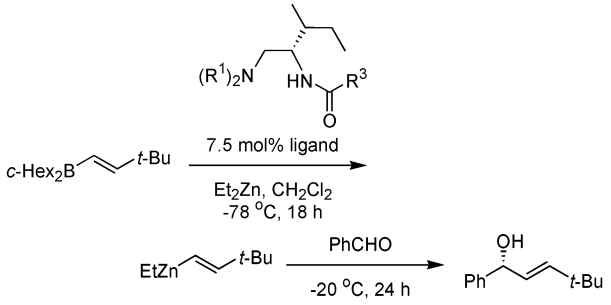
TABLE 3. Comparison between Diethylamino and Pyrrolidino Substituents on the Ligand[a]



entry	ligand	$N(R^1)_2$	R^2 = side chain of	ee[b,c] (%)	yield[d] (%)
1	**3c**	$N(CH_2)_4$	Ile	88	61
2	**3d**	NEt_2	Ile	89	67
3	**3f**	$N(CH_2)_4$	Phe	33	18
4	**3g**	NEt_2	Phe	59	56
5	**3h**	$N(CH_2)_4$	Val	35	40
6	**3i**	NEt_2	Val	87	56

[a] All experiments performed in duplicate. [b] Absolute configuration assigned by comparison with literature values. [c] Determined by chiral HPLC (Chiralcel OD-H). [d] All yields are for reactions performed at −20 °C. *c*-Hex = cyclohexyl.

TABLE 4. Effect of Ligand Carbamate and Amide Functional Groups on the Addition of Vinylzinc Reagent to Benzaldehyde[a]

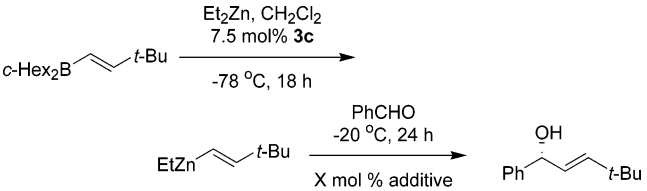


entry	ligand	$N(R^1)_2$	R^3	ee (%)[b,c]	yield (%)
1	**4b**	$N(CH_2CH_2)_2O$		42	40
2	**4c**	$N(CH_2CH_2)_2O$		46	36
3	**4d**	$N(CH_2CH_2)_2O$	OBn	23	40
4	**4e**	$N(CH_2CH_2)_2O$	OMe	16	36
5	**4f**	$N(CH_2CH_2)_2O$	O-*i*-Bu	19	46
6	**4g**	$N(CH_2CH_2)_2O$	*t*-Bu	0	28
7	**4h**	$N(CH_2CH_2)_2O$	adamantyl	0	33
8	**4i**	$N(CH_2CH_2)_2O$	O-adamantyl	78	44
9	**4j**	$N(CH_2)_4$	O-adamantyl	84	48
10	**4k**	NEt_2	O-adamantyl	86	48

[a] All experiments performed in duplicate. [b] Absolute configuration assigned by comparison with literature values. [c] Determined by chiral HPLC (Chiralcel OD-H). *c*-Hex = cyclohexyl.

group at R^3 (Table 2, entry 1). Even ligands with additional stereocenters such as (*R*)- or (*S*)-menthyl carbamates **4b** and **4c** did not change the absolute stereochemistry of the products or improve the ee. The only exception to this trend is ligand **4i** with an *O*-adamantyl group at R^3 (entry 8). Ligands **3a** and **4i** both incorporate bulky carbamate groups, and gave similar ee values in the catalyzed reaction (76% vs 78% ee). As

TABLE 5. Effect of Poly(ethylene glycol) Additives on the Reaction of Vinylzinc Reagents with Benzaldehyde[a]



entry	additive	additive (mol %)	ee[b,c] (%)
1	none		88
2	MPEG	1	79
3	MPEG	2.5	78
4	MPEG	5	84
5	DiPEG	1	81
6	DiPEG	2.5	78
7	DiPEG	5	80

[a] All experiments performed in duplicate. [b] Absolute configuration assigned by comparison with literature values. [c] Determined by chiral HPLC (Chiralcel OD-H). *c*-Hex = cyclohexyl.

we observed previously for the addition of Et_2Zn to aldehydes,[16] amides such as **4g** and **4h** catalyze the reaction but give racemic products (entries 6 and 7).

We also examined changes to the tertiary amine component of ligand **4i** (entries 8−10). The ee values for adamantyl carbamates **4i**−**k** follow the same trend as was observed for the *tert*-butyl carbamates **3a**, **3c** and **3d** (Table 2). These comparisons provide a further indication that the adamantyl and *tert*-butyl carbamates fulfill a similar role within these catalysts.

Bolm[21] and Dahmen[22] have examined the effects of MeOPEG (poly(ethylene glycol) monomethyl ether, MW 2000) and DiMPEG (poly(ethylene glycol) dimethyl ether, MW 2000) on the enantioselective reaction of organozinc reagents with aldehydes. In many cases, addition of 1−10 mol % of these additives increases the ee of the reaction by approximately 3−6%. These additives also allow lower catalyst loadings to be used without a significant decrease in the enantioselectivity. One of the reactions investigated by Bolm was the arylation of aldehydes using a mixture of BPh_3 and Et_2Zn. These reagents undergo exchange reactions to give an equilibrium mixture of organozinc species that includes Ph_2Zn and PhZnEt. Since Ph_2Zn is the more reactive aryl transfer reagent, Bolm has suggested that the additives influence the stereoselectivity of the reaction by coordinating to this more reactive species. This coordination reduces the rate of the uncatalyzed addition of Ph_2Zn to the aldehyde. As a result, the enantioselectivity of the overall reaction increases because the competing nonstereoselective reaction pathway is closed down.

These observations have prompted us to examine the effects of MeOPEG and DiMPEG as additives for the addition of vinylzinc reagents to aldehydes using ligand **3c** (Table 5). In all cases, addition of the additive decreased the stereoselectivity of the reaction. For (vinyl)(alkyl)Zn reagents, ^1H NMR studies have shown that at −65 °C the mixed organozinc species is favored over dialkylzinc and divinylzinc species. As the temperature is increased, the equilibrium shifts even further toward

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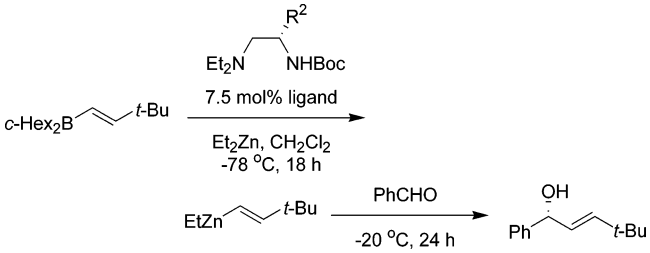
TABLE 6. Optimization of the Amino Acid Side Chain of the Ligands[a,b]



entry	ligand	R^2 = side chain of	ee (%)[c–e]	yield (%)
1	**3d**	Ile	89	67
2	**3g**	Phe	68	56
3	**3i**	Val	87	56
4	**3j**	Tle	57	29
5	**3k**	Leu	52	47
6	**3l**	Cha	51	37
7	**3m**	Chg	73	51
8	**3n**	Ala	55	58
9	**3o**	Nle	63	70
10	**3p**	Dph	50	50
11	**3q**	D-2-Nal	65 (*S*)	58
12	**3r**	Met	52	64

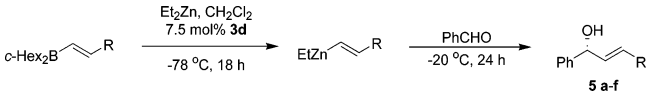
[a] All experiments performed in duplicate. [b] Abbreviations: Cha = cyclohexylalanine, Chg = cyclohexylglycine, Nle = norleucine, Dph = diphenylalanine, D-2-Nal =D-3-(2-naphthyl)alanine, *c*-Hex = cyclohexyl. [c] Absolute configuration assigned by comparison with literature values. [d] Determined by chiral HPLC (Chiralcel OD-H). [e] All ligands provided the product with the (*R*) configuration unless otherwise noted.

the mixed species.[6] Thus, addition of the additives does not result in an improvement in stereoselectivity. In addition, the additives may act as weak achiral Lewis basic ligands that slightly accelerate the nonstereoselective reaction between the vinylzinc reagent and aldehyde.

The final step in the optimization of the modular ligands involved variation of the amino acid side chain that is attached to the ethylenediamine scaffold (Table 6). A series of ligands were synthesized containing a diethylamino group at the tertiary amine position, and a Boc group on the primary amine. Ligands with β-branched alkyl groups such as the side chains of Ile (**3d**), Val (**3i**), and cyclohexylglycine (**3m**) provide the highest ee values for the catalyzed reaction. Other sterically less demanding side chains give lower enantioselectivities. In addition, the side chain of *tert*-leucine (**3j**), which is larger than Ile, results in a ligand that is too bulky to promote the reaction with high stereoselectivity. All of the catalysts except for **3q** were derived from L-amino acids, and gave the (*R*)-allylic alcohol as the major product. Since **3q** was derived from D-2-naphthylalanine, the product from the reaction catalyzed by this ligand had the (*S*)-configuration.

Ligand **3d** emerged as the best ligand in this class from our screening studies. As a result, we examined the scope of the reactions catalyzed by this ligand by first varying the structure of the vinylzinc reagent (Table 7). Using the optimized set of reaction conditions, **3d** catalyzed the addition of (*E*)-(3,3-dimethylbut-1-enyl)(ethyl)zinc, formed from *tert*-butylacetylene and dicyclohexylborane, to benzaldehyde in 89% ee. The reaction is sensitive to the size of the vinylzinc reagent. Using cyclohexylacetylene, the ee value drops to 73%. Lower values were obtained with

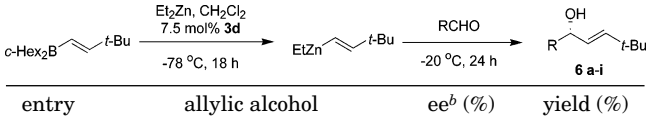
TABLE 7. Variation of the Vinylzinc Reagent Using Ligand 3d[a]



entry	allylic alcohol	ee[b] (%)	yield (%)
1	**5a**, R = *tert*-butyl	89	67
2	**5b**, R = cyclohexyl	73	51
3	**5c**, R = CH_2CH_2Ph	67	48
4	**5d**, R = *n*-hexyl	65	49
5	**5e**, R = *n*-butyl	60	40
6	**5f**, R = cyclopropyl	52	51

[a] All experiments performed in duplicate. [b] Determined by chiral HPLC (Chiralcel OD-H). *c*-Hex = cyclohexyl.

TABLE 8. Variation of Aldehydes Using Ligand 3d[a]



entry	allylic alcohol	ee[b] (%)	yield (%)
1	**6a**, R = 4-chlorophenyl	91	86
2	**6b**, R = 2-naphthyl	89	90
3	**6b**, R = 2-naphthyl	97	59[c]
4	**6c**, R = 4-bromophenyl	89	71
5	**5a**, R = phenyl	89	67
6	**6d**, R = 4-methylbenzoate	86	81
7	**6e**, R = 4-methoxyphenyl	81	54
8	**6f**, R = 1-naphthyl	70	81
9	**6g**, R = *trans*-CH=CHPh	67	68
10	**6h**, R = $PhCH_2CH_2$	67	63
11	**6i**, R = cyclohexyl	39[d]	33

[a] All experiments performed in duplicate. [b] Determined by chiral HPLC (Chiralcel OD-H). [c] Purified alcohol from entry 2 was recrystallized once from hexanes. [d] Determined using the corresponding (*R*)-α-methoxy-α-trifluoromethylphenyl ester by ^{19}F NMR spectroscopy.

vinylzinc reagents derived from other less sterically demanding alkynes.

While the reaction catalyzed by **3d** is fairly limited in terms of the vinylzinc reagent, it is much more tolerant of variations of the aldehyde (Table 8). Electron poor benzaldehyde derivatives gave ee values that range from 86 to 91% and yields in the range of 67−86% (entries 1 and 4−6). 2-Naphthaldehyde is also a good substrate for the reaction, giving the corresponding allylic alcohol **6b** in 89% ee. The ee of this product could be improved to 97% by a single recrystallization from hexanes. The electron-rich 4-methoxybenzaldehyde (entry 7) gave a lower ee (81%) and yield (54%) when compared to its electron poor counterparts. The use of aliphatic (entries 10 and 11) and other aldehydes also gave lower stereoselectivities.

Conclusion

In summary, we have synthesized and screened a series of chiral *N*-acylethylenediamine ligands for the ability to catalyze the asymmetric addition of vinylzinc reagents to aldehydes. The modular structure of these ligands allowed for easy modification of three diversity sites. Ligand **3d** was found to catalyze the addition of (*E*)-(3,3-dimethylbut-1-enyl)(ethyl)zinc to a variety of aromatic aldehydes to yield chiral (*E*)-allylic alcohols in 81−91% ee and 54−90% yield. In addition, the ee of

allylic alcohol **6b** was improved from 89 to 97% ee through a single recrystallization from hexanes. We are currently exploring these ligands as asymmetric catalysts for other synthetically useful transformations.

Experimental Section

General Procedure for the Synthesis of Amides 2c−g and 2j−r. The Boc-protected amino acid (1 equiv) was suspended or dissolved in dry DMF. To this solution were added DIEA (2 equiv) and HBTU (1.5 equiv). After the mixture was stirred at rt for 1 h, the appropriate secondary amine (1.1 equiv) was added and the reaction was allowed to stir for 1 h. The reaction was quenched by the addition of 1 N HCl. The mixture was extracted with EtOAc, and the organic phase was washed with 1 N HCl and brine and dried ($MgSO_4$). The solvent was removed, and purification was performed by flash column chromatography.

Amide 2c. Amide **2c** was prepared as described above from Boc-Ile-OH (0.571 g, 2.4 mmol) and pyrrolidine (0.220 mL, 2.6 mmol). Purification (EtOAc/hexanes 5:28) gave a yellow oil (0.520 g, 1.85 mmol, 78%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (m, 6 H), 1.14 (m, 1 H), 1.44 (s, 9 H), 1.56−1.72 (m, 1 H), 1.83−1.99 (m, 4 H), 3.39−3.59 (m, 4 H), 3.68−3.73 (m, 1 H), 4.28 (dd, J = 9.4, 7.2 Hz, 1 H), 5.24 (d, J = 9.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 156.2, 79.8, 56.8, 47.1, 46.2, 38.4, 29.4, 28.7, 24.6, 15.9, 11.7; IR (neat) 3436, 3287, 2971, 2878, 1707, 1636, 1503, 1449, 1366, 1250, 1171, 1044, 1019, 917, 878, 817, 754 cm^{-1}; HRMS-ESI (M + H$^+$) calcd for $C_{15}H_{29}N_2O_3$ 285.2178, found 285.2186; $[\alpha]^{24}_D$ = +1.43 (c = 0.77, $CHCl_3$).

General Procedure for the Synthesis of Ligands 3c−g and j−r. To a solution of the amide (1 equiv) dissolved in anhydrous THF was slowly added 1.8 M BH_3 in THF (4 equiv). The reaction was stirred at rt for 18 h, cooled to 0 °C, and carefully quenched (evolution of H_2 gas!) with methanol. The solvent was removed, and the residue was redissolved in methanol. To this solution was added ethylenediamine (4 equiv), and the solution was heated by microwave irradiation for 120 s at 100 °C. The methanol was removed, and the residue was dissolved in water and extracted with CH_2Cl_2. The organic phase was washed with water, dried (Na_2CO_3), and concentrated. The crude product was purified by flash column chromatography.

Ligand 3c. Amide **2c** (0.506 g, 1.8 mmol) was reduced as described above with 1.8 M BH_3 (4.0 mL, 7.1 mmol) followed by boron exchange with ethylenediamine (0.475 mL, 7.1 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $NH_4OH/CH_3OH/CH_2Cl_2$) gave a yellow oil (0.250 g, 0.925 mmol, 51%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (m, 6 H), 1.09 (m, 1 H), 1.43 (s, 10 H), 1.75 (s, 5 H), 2.34 (dd, J = 12.3, 4.7 Hz, 1 H), 2.45−2.57 (m, 4 H), 3.63 (s, 1 H), 4.72 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 79.3, 56.6, 54.7, 53.9, 37.7, 28.8, 25.4, 23.9, 15.2, 12.4; IR (neat) 3378, 2962, 2875, 2791, 1681, 1517, 1454, 1385, 1363, 1247, 1172, 1058 cm^{-1}; HRMS-FAB (M + Na$^+$) calcd for $C_{15}H_{30}N_2O_2Na$ 293.2205, found 293.2210; $[\alpha]^{24}_D$ = +18.3 (c = 1.25, $CHCl_3$).

General Procedure for the Synthesis of Ligands 4a−c and j−k. To the Boc-protected precursor (1 mmol) was added trifluoroacetic acid (1 mL) at rt, and the reaction was stirred for 1 h. The TFA was removed by rotary evaporation, the residue was diluted with water, and the pH was adjusted to pH 10 with 10% aqueous KOH. The aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL), the organic layers were combined and dried (Na_2CO_3), and the solvent was removed by rotary evaporation. The residue was redissolved in anhydrous CH_2Cl_2 (3 mL), and DIEA (1.5 mmol) was added. The reaction was cooled to 0 °C, the appropriate fluoroformate, chloroformate or acid chloride (1.1 mmol) was added, and the solution was warmed to rt and stirred for 1 h. The reaction was diluted with CH_2Cl_2, washed with water (2 × 10 mL) and brine (1 × 10 mL), and dried (Na_2CO_3). The solvent was removed by rotary evaporation, and the crude product was purified by flash column chromatography.

Ligand 4a. (*S*)-*tert*-Butyl 1-morpholino-1-oxo-3-phenylpropan-2-ylcarbamate **7**[16] (1.05 g, 3.3 mmol) was deprotected and transformed to **4a** as described above using DIEA (0.900 mL, 4.9 mmol) and adamantyl fluoroformate (0.713 g, 3.6 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $NH_4OH/CH_3OH/CH_2Cl_2$) gave a white solid (1.30 g, 3.27 mmol, 99%): mp 124−127 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.72 (s, 6 H), 2.16 (s, 6 H), 2.22 (s, 3 H), 2.30 (m, 2 H), 2.44 (m, 4 H), 2.84 (dd, J = 13.5, 6.3 Hz, 1 H), 2.94 (dd, J = 13.6, 5.3 Hz, 1 H), 3.83 (t, J = 4.6 Hz, 4 H), 3.95 (s, 1 H), 4.63 (s, 1 H), 7.19−7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8, 138.2, 130.1, 128.7, 126.7, 79.6, 67.4, 61.5, 54.1, 48.6, 42.1, 39.2, 36.6, 31.2; IR (neat) 3332, 2909, 2855, 1680, 1537, 1455, 1265, 1115, 1065 cm^{-1}; HRMS-FAB (M + Na$^+$) calcd for $C_{24}H_{34}N_2O_3Na$ 421.2467, found 421.2468; $[\alpha]^{24}_D$ = +15.9 (c = 1.75, $CHCl_3$).

Representative Procedure for the Addition of Vinylzinc Reagents to Aldehydes. To an oven-dried vial were added dry CH_2Cl_2 (2.5 mL) and neat BH_3·DMS complex (0.260 mL, 2.74 mmol). The solution was cooled to 0 °C, and cyclohexene (0.550 mL, 5.40 mmol) was added. The reaction was stirred for 2 h, during which time a white precipitate formed. After 2 h, 3,3-dimethyl-1-butyne (0.360 mL, 2.95 mmol) was added, and the reaction was slowly warmed to rt. After addition of the alkyne, the white precipitate dissolved. However, in a few cases when the precipitate did not dissolve, the reaction yielded the product with a lower ee than expected. An aliquot of the above solution (0.735 mL) was transferred to a vial pre-loaded with ligand **3c** (0.0104 g, 0.038 mmol). The reaction was cooled to −78 °C and a 1 M solution of diethylzinc in CH_2Cl_2 was added (0.640 mL, 0.640 mmol). After 18 h at −78 °C, benzaldehyde (0.050 mL, 0.49 mmol) was added in one portion, and the reaction was slowly warmed from −78 to −20 °C. After 24 h, the reaction was carefully quenched with saturated NH_4Cl solution (0.50 mL). The reaction was extracted with ether, and the organic phase was washed with 1 N HCl (2 × 1 mL), H_2O (1 × 1 mL), saturated $NaHCO_3$ solution (2 × 1 mL), and brine (1 × 1 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAC/hexanes 1:9) to yield 4,4-dimethyl-1-phenylpent-2-en-1-ol (0.057 g, 0.30 mmol, 61%).

Supporting Information Available: HPLC column conditions and retention times for all allylic alcohol products; structures for amides **2a−r**; complete experimental details; ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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