

## Solid-Phase Synthesis of Chiral *N*-Acylethylenediamines and Their Use as Ligands for the Asymmetric Addition of Alkylzinc and Alkenylzinc Reagents to Aldehydes

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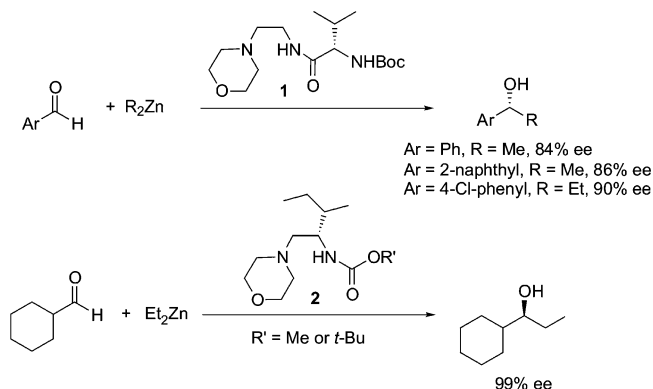
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A solid-phase procedure has been developed for the synthesis of chiral *N*-acylethylenediamine ligands. The ligands are obtained in good yield and purity, without the need for chromatography or other purification methods. Several new and previously reported ligands were prepared using this procedure. These compounds were examined as catalysts for the enantioselective addition of alkylzinc reagents to aldehydes. In all cases, the crude ligands from the solid-phase syntheses catalyzed the reactions with similar yields and stereoselectivities when compared to reactions using ligands that had been purified by standard methods. Preliminary studies were also performed with ligands **3a** and **3f** as catalysts for the addition of alkenylzinc reagents to aldehydes to give chiral allylic alcohols. Ligand **3f** was found to catalyze this addition reaction in up to 76% ee.

### Introduction

Combinatorial chemistry is becoming an important tool in the development of new catalysts for asymmetric reactions.<sup>1,2</sup> The methods of combinatorial chemistry have the potential to increase the efficiency by which successful chiral catalysts are discovered. However, to realize this goal several challenges must be met. First, ligands must be designed that can be assembled in a modular fashion. Second, the ligands need to be effective catalysts for a synthetically useful transformation. Third, an economical synthesis of the ligands has to be developed that allows for easy incorporation of diversity elements into the modular structure and that requires little or no purification of the final products. Finally, a high-throughput method must be available to evaluate the stereoselectivity of the catalyst library.

As part of our efforts to develop and screen libraries of enantioselective catalysts, we have recently reported two different types of modular ligands that catalyze the asymmetric addition of dialkylzinc reagents to aldehydes (Figure 1).<sup>3,4</sup> Both types of ligands incorporate an *N*-



**FIGURE 1.** Reactions catalyzed by 10 mol % of ligands **1** and **2**.

acylethylenediamine subunit that, upon deprotonation, provides a binding site for zinc. Ligand **1** includes a chiral center on an attached amino acid and was found to promote the reaction between  $\text{Me}_2\text{Zn}$  or  $\text{Et}_2\text{Zn}$  and a variety of aromatic aldehydes with up to 90% ee. Ligand **2**, which incorporates a chiral center on the ethylenediamine bridge, catalyzes the addition of  $\text{Et}_2\text{Zn}$  to cyclohexanecarboxaldehyde in 99% ee. These and other related ligands were prepared using standard solution-phase methods. In some cases, we found that it was necessary to recrystallize the ligand in order to obtain the highest % ee in the catalyzed reactions. For both types of ligands, amino acids provided the initial source of chirality.

We have also developed a high-throughput method for determining the enantiomeric excess of chiral alcohols<sup>5</sup>

<sup>†</sup> These two authors contributed equally to this work.

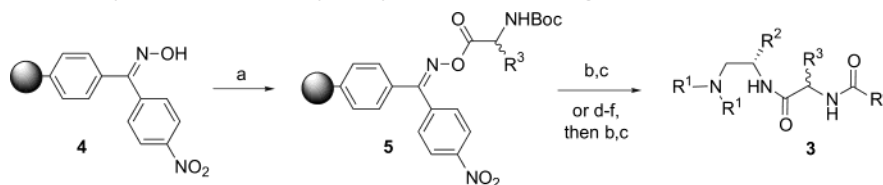
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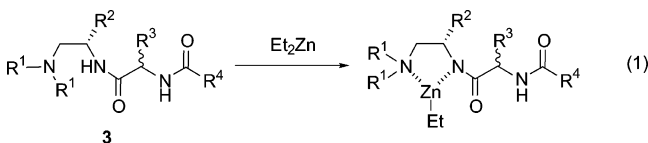
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SCHEME 1. Solid-Phase Synthesis of *N*-Acylethylenediamine Ligands<sup>a</sup>

<sup>a</sup> Reagents: (a) HBTU, DIEA, *N*-Boc-protected amino acid, DMF, double coupling; (b) diamines **6–9**, CH<sub>2</sub>Cl<sub>2</sub> or CH<sub>3</sub>CN; (c) isocyanate resin, CH<sub>2</sub>Cl<sub>2</sub>; (d) 25% TFA, CH<sub>2</sub>Cl<sub>2</sub>; (e) 10% DIEA, CH<sub>2</sub>Cl<sub>2</sub>; (f) R<sup>4</sup>COCl, 10% DIEA, CH<sub>2</sub>Cl<sub>2</sub>.

and allylic acetates.<sup>6</sup> This technique is called EMDee for an enzymatic method for determining enantiomeric excess. In this method, the products from a catalytic asymmetric reaction that are of unknown stereochemical composition are analyzed using an enzyme. The enzyme stereospecifically recognizes and processes only one of the two possible enantiomers in the sample. As a result, the rate of the enzyme-catalyzed reaction can be used to determine the % ee of the sample. This method and a variety of other methods that have been reported in the literature<sup>7,8</sup> provide useful tools for screening libraries of asymmetric catalysts.

In our current work, we are focusing on two of the remaining challenges in the development of such libraries. The first challenge is the design of an efficient synthesis that can be used to generate a large number of ligands in a parallel fashion and that does not require chromatographic purification of the final products. It is equally important to broaden the synthetic utility of the ligands by examining new reactions in which they function as enantioselective catalysts. To accomplish these goals, we have developed a solid-phase synthesis of the *N*-acylethylenediamine-based ligands and examined the crude ligands from this synthesis as catalysts for the enantioselective addition of alkylzinc reagents to aldehydes.<sup>9,10</sup> In all cases, we find that the crude ligands give similar yields and stereoselectivities when compared to those of ligands that have been purified by chromatography or recrystallization. We have also examined two of the ligands as enantioselective catalysts for the reaction between alkenylzinc reagents, generated via the Oppolzer method,<sup>11</sup> and aldehydes to yield chiral allylic alcohols. Finally, we have used the solid-phase protocol to synthesize ligands with the general structure **3** (eq 1) that are hybrids of ligands **1** and **2**.<sup>12</sup> These compounds



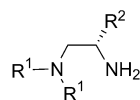
incorporate stereochemical elements on both the ethylenediamine bridge and on an attached amino acid. They have four potential diversity elements (R<sup>1</sup>–R<sup>4</sup>) that each can be easily modified in order to investigate their influence on the stereoselectivity of the catalyzed reactions. In analogy with previously reported ligands, we expect that compounds such as **3** will be deprotonated by alkylzinc reagents to give a zinc chelate as the catalytically active species. Although the zinc chelate

species shown in eq 1 is reasonable, it is only one of several possible chelate structures.

## Results and Discussion

The solid-phase protocol that we have developed for the synthesis of the ligands is shown in Scheme 1. It begins with coupling of a Boc-protected amino acid to an oxime-functionalized resin to give intermediate **5**.<sup>13</sup> To optimize and quantitate the yield of this step, we coupled Boc-Val-OH to the oxime resin under a variety of conditions and then cleaved the amino acid from the solid support using methanol and DBU to give Boc-Val-OMe.<sup>14</sup> Single or double coupling reactions using DIC, DMAP, HOBt, and Boc-Val-OH gave unsatisfactory yields. By contrast, a double coupling procedure using HBTU provided Boc-Val-OMe in 72% yield. This coupling procedure was used in subsequent syntheses of the ligands.

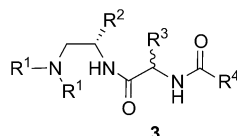
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- 6:  $R^1 = -(CH_2)_2O(CH_2)_2-$ ,  $R^2 = H$   
 7:  $R^1 = -(CH_2)_5-$ ,  $R^2 = H$   
 8:  $R^1 = Et$ ,  $R^2 = H$   
 9:  $R^1 = -(CH_2)_2O(CH_2)_2-$ ,  
 $R^2 = sec\text{-butyl}$

**FIGURE 2.** Structures of diamines used in the synthesis of the *N*-acylethylenediamine ligands.

**TABLE 1.** Solid-Phase Synthesis of Ligands **3a–l**



lig- and	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup> = amino acid side chain	R <sup>4</sup>	reaction condi- tions <sup>a</sup>	% yield
<b>3a</b>	$-(CH_2)_2O(CH_2)_2-$	H	L-Val	O- <i>t</i> -Bu	1	86
<b>3b</b>	$-(CH_2)_2O(CH_2)_2-$	H	L-Phe	O- <i>t</i> -Bu	1	73
<b>3c</b>	$-(CH_2)_5-$	H	L-Val	O- <i>t</i> -Bu	1	88
<b>3d</b>	Et	H	L-Val	O- <i>t</i> -Bu	1	92
<b>3e</b>	Et	H	L-Val	<i>t</i> -Bu	1	73
<b>3f</b>	$-(CH_2)_2O(CH_2)_2-$	H	L-Val		1	84
<b>3g</b>	$-(CH_2)_2O(CH_2)_2-$	<i>s</i> -Bu	L-Val	O- <i>t</i> -Bu	2	62
<b>3h</b>	$-(CH_2)_2O(CH_2)_2-$	<i>s</i> -Bu	D-Val	O- <i>t</i> -Bu	3	83
<b>3i</b>	$-(CH_2)_2O(CH_2)_2-$	<i>s</i> -Bu	L-Phe	O- <i>t</i> -Bu	2	69
<b>3j</b>	$-(CH_2)_2O(CH_2)_2-$	<i>s</i> -Bu	D-Phe	O- <i>t</i> -Bu	2	64
<b>3k</b>	$-(CH_2)_2O(CH_2)_2-$	<i>s</i> -Bu	L-Ala	O- <i>t</i> -Bu	2	65
<b>3l</b>	$-(CH_2)_2O(CH_2)_2-$	<i>s</i> -Bu	D-Ala	O- <i>t</i> -Bu	2	59

<sup>a</sup> Reaction conditions for displacement of the ligand from the solid support with diamines **6–9** (step b in Scheme 1 and step e in Scheme 2): (1) CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, (2) CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, (3) CH<sub>3</sub>CN, 80 °C.

Six different Boc-protected amino acids were coupled to the oxime resin: D- and L-Val, D- and L-Phe, and D- and L-Ala. The resin-bound amino acid was then cleaved from the solid support using an excess of the *N,N*-dialkylethylenediamines **6–8** (Figure 2) at 25 °C to give ligands **3a–d** (Table 1). After the reactions were complete, the remaining *N,N*-dialkylethylenediamine was scavenged with an isocyanate resin. Examination of the <sup>1</sup>H and <sup>13</sup>C NMR spectra of the ligands, without further purification, showed that the desired products were obtained in essentially pure form, with only trace impurities.<sup>15</sup> In all cases, the yield for the solid-phase syntheses was similar to or better than the yield that is obtained through standard solution-phase methods.<sup>4</sup>

The solid-phase synthesis can be modified to allow variation at the R<sup>4</sup> position of the ligands. For example, ligand **3e** was prepared by treating intermediate **5** (Scheme 1) with TFA to remove the Boc group, followed by reaction of the free amine with pivaloyl chloride to

give the corresponding amide. Cleavage of this amide from the solid support with diamine **8** and scavenging of the excess diamine gave ligand **3e** in 73% overall yield (Table 1). Additional amino acids can also be incorporated to further extend the ligand architecture (Scheme 2). After loading the oxime resin **4** with Boc-L-Val-OH and subsequently removing the Boc protecting group with TFA, the resin-bound amine **11** was treated twice with Boc-L-Cys(Trt)-OH under HBTU coupling conditions. Displacement of the ligand was performed using diamine **6**. Removal of excess diamine was accomplished with an aqueous workup to provide ligand **3f** in 84% yield.

Reaction of intermediate **5** (Scheme 1) with chiral diamine **9**<sup>3</sup> gave ligands **3g–l** that incorporate two stereocenters. We found that, unlike diamines **6–8**, the more sterically hindered diamine **9** required heating at reflux in methylene chloride to effect both efficient displacement of the amino acid from the resin and scavenging of the residual diamine with isocyanate resin after the reaction was complete. Other investigators have noted similar difficulty in displacing peptides from an oxime resin using  $\alpha$ -branched nucleophiles.<sup>16,17</sup> The reaction between diamine **9** and resin-bound Boc-D-Val was particularly problematic and required heating at 80 °C in acetonitrile to obtain a good yield of ligand **3h**.

The solid-phase procedure can be further modified to synthesize the carbamate-containing ligand **13** (Scheme 3). The oxime resin was double coupled using methyl chloroformate in the presence of DIEA and DMAP to give intermediate **14**. This compound was reacted with an excess of diamine **9** in refluxing acetonitrile to give, after scavenging of the remaining diamine with isocyanate resin, ligand **13** in excellent yield and purity.

The crude ligands that resulted from the solid-phase syntheses were examined as enantioselective catalysts for the addition of dialkylzinc reagents to aldehydes (Table 2). The % ee of the alcohol products from these reactions were compared to the results of similar reactions performed using ligands that had been purified by chromatography or recrystallization. We found that the two sets of reactions gave comparable enantioselectivities. Many of the reactions gave essentially identical % ee values using crude and purified ligands (entries 2, 3, and 5), while the largest decrease of 9% ee was observed with ligand **3e** (entry 6). The results shown in entries 2 and 14 illustrate that the solid-phase ligands can catalyze the dialkylzinc addition with good enantioselectivity. Yields for the reactions catalyzed by a majority of the ligands (entries 1–6, 8, 12–14) range from good to excellent.

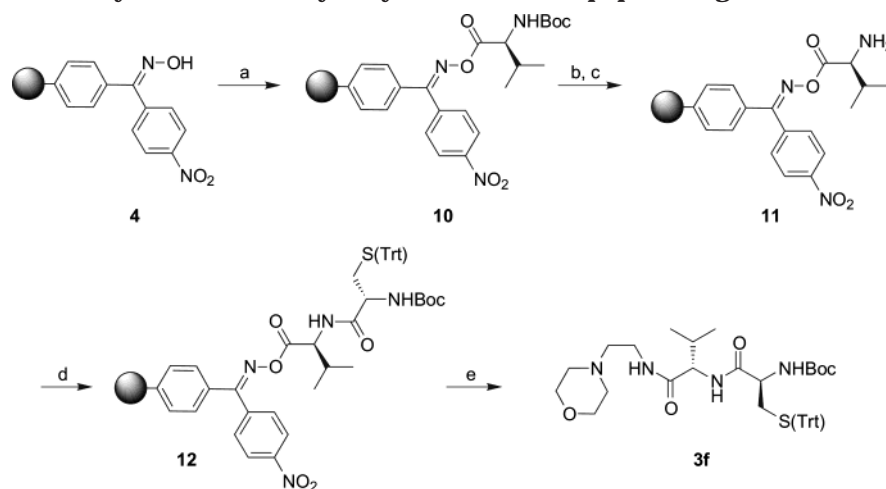
Because we observe similar % ee values using crude ligands from the solid-phase synthesis and purified ligands, we believe that the solid-phase protocol will be useful for synthesizing large libraries of chiral ligands. For such libraries, the % ee values obtained during screening of the crude ligands will provide a clear indication of the stereoselectivity that would be observed with purified ligands. Thus, highly enantioselective catalysts that are discovered through the library screening process will have a high probability of remaining

(14) Abbreviations: HBTU, *O*-(benzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate; DIEA, diisopropylethylamine; DIC diisopropylcarbodiimide; HOBT, 1-hydroxybenzotriazole; DMAP, 4-(dimethylamino)pyridine; TFA, trifluoroacetic acid; DBU 1,8-diazabicyclo[4.5.0]undec-7-ene.

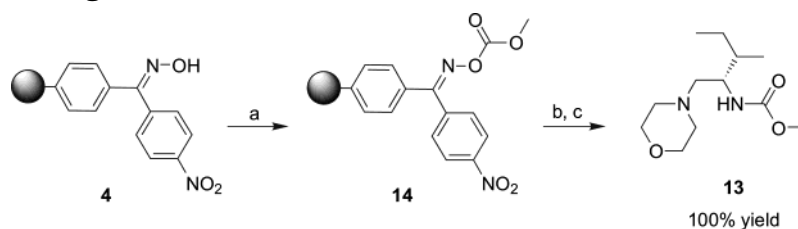
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SCHEME 2. Solid-Phase Synthesis of *N*-Acylethylenediamine Dipeptide Ligand **3f**<sup>a</sup>

<sup>a</sup> Reagents: (a) HBTU, DIEA, *N*-Boc-Val-OH, DMF, triple coupling; (b) 25% TFA, CH<sub>2</sub>Cl<sub>2</sub>; (c) 10% DIEA, CH<sub>2</sub>Cl<sub>2</sub>; (d) HBTU, DIEA, *N*-Boc-Cys(Trt)-OH, DMF, double coupling; (e) diamine **6**, CH<sub>2</sub>Cl<sub>2</sub>.

SCHEME 3. Synthesis of Ligand **13**<sup>a</sup>

<sup>a</sup> Reagents: (a) CH<sub>3</sub>OCOCl, DMAP, DIEA, CH<sub>2</sub>Cl<sub>2</sub>, double coupling; (b) diamine **9**, CH<sub>3</sub>CN, reflux; (c) isocyanate resin, CH<sub>2</sub>Cl<sub>2</sub>.

TABLE 2. Use of Ligands **3a–l** and **13** as Catalysts for the Addition of Dialkylzinc Reagents to Aldehydes<sup>a</sup>

		R		R'		% ee	
		R		R'		crude ligand from solid-phase synthesis <sup>b,c</sup>	
entry	ligand	R	R'	config of alcohol		purified ligand <sup>b,c</sup>	
1	<b>3a</b>	Ph	Et	<i>R</i>	60 (83)	68 (86)	
2	<b>3a</b>	Ph	Me	<i>R</i>	84 (85) <sup>d</sup>	84 (68) <sup>d</sup>	
3	<b>3b</b>	Ph	Et	<i>R</i>	23 (89) <sup>e</sup>	25 (86) <sup>e</sup>	
4	<b>3c</b>	Ph	Et	<i>R</i>	61 (89)	66 (74)	
5	<b>3d</b>	Ph	Et	<i>R</i>	58 (83)	59 (83)	
6	<b>3e</b>	Ph	Et	<i>R</i>	44 (86)	53 (82)	
7	<b>3f</b>	Ph	Et	na	nr		
8	<b>3g</b>	Ph	Et	<i>R</i>	18 (81)		
9	<b>3h</b>	Ph	Et	<i>S</i>	24 (52)		
10	<b>3i</b>	Ph	Et	<i>R</i>	16 (58)		
11	<b>3j</b>	Ph	Et	<i>S</i>	29 (48)	30 (54)	
12	<b>3k</b>	Ph	Et	na	0 (73) <sup>e</sup>		
13	<b>3l</b>	Ph	Et	<i>S</i>	27 (82)		
14	<b>13</b>	cyclo-hexyl	Et	<i>S</i>	94 (100) <sup>f</sup>	99 (93) <sup>f</sup>	

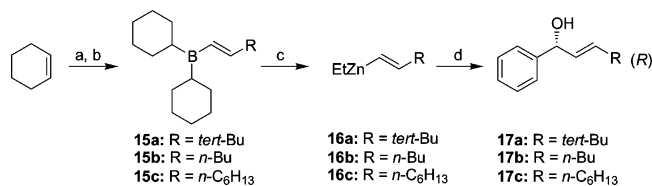
<sup>a</sup> Experiments performed in duplicate unless noted otherwise. <sup>b</sup> % ee measured by HPLC (Chiralcel OD-H). <sup>c</sup> Values in parentheses are the % yield. <sup>d</sup> Reaction run for 65 h. <sup>e</sup> Based on one experiment. <sup>f</sup> % ee measured by <sup>19</sup>F NMR of the (*S*)-MPTA ester. na = not applicable. nr = no reaction.

“hits” when they are examined in purified form. The converse is also true. Catalysts that show poor stereoselectivity in the screening process are not likely to be highly selective when purified.

We have also examined ligands **3f–l**, which contain two stereogenic centers, as catalysts for the addition of diethylzinc to benzaldehyde. However, none of these ligands catalyzed the reaction with significant enantioselectivity. In the case of ligand **3f** no reaction occurred. This result may be caused by the insolubility of the ligand in hexanes, which was used as the solvent for the addition reaction. If we examine the absolute configuration of the alcohol products that are obtained using ligands **3g–l**, we find that the sense of stereochemical induction in the catalyzed reaction is controlled by the stereochemistry of the side chain on the attached amino acid of the ligand (*R*<sup>3</sup> position, Table 1), not by the chirality of the alkyl group on the ethylenediamine bridge (*R*<sup>2</sup> position, Table 1). Comparison of the results using ligands **3a**, **3b**, and **3g–3j** shows that when *R*<sup>3</sup> is of the *S* configuration (ligands **3a**, **3b**, **g**, and **i**), the (*R*)-alcohol is the predominate product. Conversely, when *R*<sup>3</sup> has the *R* configuration (ligands **3h** and **3j**), the (*S*)-alcohol is the predominate product. The only exception to this trend is ligand **3k**, which shows no stereoselectivity in the catalyzed reaction.

To broaden the overall utility of the *N*-acylethylenediamine ligands, we have performed a preliminary examination of two of these compounds as potential catalysts for the asymmetric addition of alkenylzinc reagents to aldehydes to yield chiral allylic alcohols. Several investigators, including Oppolzer,<sup>11</sup> Walsh,<sup>18</sup> and

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**SCHEME 4. Enantioselective Synthesis of Allylic Alcohols Using Ligands **3a** and **3f**<sup>a</sup>**


<sup>a</sup> Reagents: (a) BH<sub>3</sub>·DMS, CH<sub>2</sub>Cl<sub>2</sub>, 2 h, 0 °C; (b) RC≡CH where R = *t*-Bu, *n*-Bu, or *n*-C<sub>6</sub>H<sub>13</sub>, 30 min, 0–25 °C; (c) 7.5 mol % ligand **3a** or **3f**, Et<sub>2</sub>Zn, –78 °C, 18 h, CH<sub>2</sub>Cl<sub>2</sub>; (d) PhCHO, –48 °C, 48 h.

**TABLE 3. % ee Values of Allylic Alcohol Products from the Reaction of Alkenylzinc Reagents with Benzaldehyde Catalyzed by Ligands **3a** and **3f** (Scheme 4)<sup>a</sup>**

entry	ligand	R <sup>b</sup>	% ee	
			crude ligand from solid-phase synthesis <sup>c</sup>	purified ligand <sup>c</sup>
1	<b>3a</b>	<i>t</i> -Bu	59	54
2	<b>3a</b>	<i>n</i> -Bu	36	
3	<b>3a</b>	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	41 <sup>d</sup>	
4	<b>3f</b>	<i>t</i> -Bu	67	65
5	<b>3f</b>	<i>n</i> -Bu	76 <sup>e</sup>	
6	<b>3f</b>	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	73 <sup>d</sup>	

<sup>a</sup> Experiments performed in duplicate unless noted otherwise. <sup>b</sup> Refers to the R group in compounds **17a–c**. <sup>c</sup> % ee measured by HPLC (Chiralcel OD-H). <sup>d</sup> The absolute configuration was assigned by comparison of the optical rotation with the reported values of the related compounds (*R*)-1-phenyl-hept-2-ene-1-ol and (*S*)-4,4-dimethyl-1-phenyl-pent-2-en-1-ol (see refs 1 and 2 in Supporting Information). <sup>e</sup> Based on one experiment.

Chan,<sup>19</sup> have developed amino alcohol based catalysts for this reaction that show good to excellent stereoselectivities. Brase has examined chiral paracyclophane-containing catalysts,<sup>20</sup> and Wipf and co-workers have developed aminothiols catalysts for use with alkenylzinc reagents that are generated via the corresponding alkenyl zirconocene species.<sup>21</sup> Scheme 4 shows the procedure that we employed using the *N*-acylethylenediamine-based ligands. Reaction of 2 equiv of cyclohexene with borane–dimethyl sulfide complex gave dicyclohexylborane. This compound was used to hydroborate three different terminal alkynes to give the vinylboranes **15a–c**. Transmetalation of the vinylboranes with diethylzinc gave alkenylzinc intermediates **16a–c**, which were then treated with benzaldehyde in the presence of 7.5 mol % of the ligand to yield allylic alcohols **17a–c**.

Table 3 shows the results from these alkene transfer reactions using ligands **3a** and **3f**. Both ligands are effective catalysts for this reaction, and in all cases the (*R*)-allylic alcohol was the predominant product. A comparison of the results using ligand **3a** as a catalyst for the reaction of benzaldehyde with alkylzinc reagents (Table 2) and alkenylzinc reagents (Table 3) shows that the ligand promotes both of these reactions with the same sense of stereochemical induction, with (*R*)-alcohols as the major product in both cases. The enantioselectivities observed using ligand **3a** are only moderate, and range

from 36% to 59% ee. Ligand **3f** gives somewhat higher stereoselectivities, with allylic alcohol products that range from 67% to 76% ee. Although the *N*-acylethylenediamine-based ligands do not yet give high stereoselectivity in the alkyenylation of aldehydes, the structures of the ligands are not yet optimized. However, these preliminary results show that ligand **3f** gives a promising degree of stereoselectivity and suggest that further variation of the amino acid components of the ligand is likely to lead to improved asymmetric catalysts for this reaction. A library-based approach could be ideal for performing this type of optimization process. A comparison of the % ee values obtained using crude ligands that come directly from the solid-phase synthesis with purified ligands (Table 3, entries 1 and 4) shows similar results for both sets of reactions. This observation provides further evidence that the solid-phase synthesis protocol that we have developed yields ligands that are directly suitable for screening purposes and do not require purification.

## Conclusion

In summary, we have developed a solid-phase synthesis of our recently reported class of modular chiral *N*-acylethylenediamine ligands. The synthetic route utilizes an oxime resin to activate *N*-protected amino acids, followed by displacement of the amino acid with either a commercially available achiral *N,N*-dialkylethylenediamine or a synthesized chiral diamine. An isocyanate-based scavenging resin was used to remove the excess diamine. This procedure provided ligands in good yield and purity that did not require further purification. By modification of the *N*-terminus of the amino acid, this procedure can generate ligands that incorporate up to four different diversity sites. The ligands, in crude form, are suitable for use as catalysts for the addition of both alkylzinc and alkenylzinc reagents to aldehydes. For the reactions using alkylzinc reagents, high enantioselectivities are observed for specific ligands. For the alkenylzinc reactions, we have obtained allylic alcohol products in up to 76% ee. Our future work will use this solid-phase protocol to synthesize a library of *N*-acylethylenediamine-based ligands. This library will be screened to discover optimal catalysts for the alkyenylation of aldehydes and other synthetically useful transformations.

## Experimental Section

**Solution-Phase Synthesis of (1*S*)-[1-(2-Morpholin-4-yl-ethylcarbamoyl)-2-phenyl-ethyl]carbamic Acid *tert*-Butyl Ester **3b**.** To Boc-Phe-OH (0.460 g, 1.73 mmol) were added HBTU (1.45 g, 3.82 mmol), DIEA (0.91 mL, 5.20 mmol), and enough DMF to dissolve all of the solids. After 5 min of stirring, 2-morpholin-4-yl-ethylamine (0.273 mL, 2.08 mmol) was added. The reaction mixture was stirred at 25 °C for 1 h and then diluted with H<sub>2</sub>O. The aqueous phase was then extracted with EtOAc, and the organic phase was washed with H<sub>2</sub>O and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, the solvent was removed, and the crude product was purified by column chromatography (0.5:4.5:95 30% aqueous NH<sub>4</sub>OH/MeOH/CH<sub>2</sub>-Cl<sub>2</sub>) to yield compound **3b** as a white solid (0.444 g, 1.18 mmol, 68%): mp 109–111 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.31 (m, 1 H), 7.22 (m, 4 H), 6.07 (br s, 1 H), 5.19 (br s, 1 H), 4.28 (m, 1 H), 3.60 (m, 4 H), 3.23 (m, 2 H), 3.11 (dd, *J* = 13.4, 6.0 Hz, 1 H), 2.97 (dd, *J* = 13.3, 8.4 Hz, 1 H), 2.33 (m, 6 H), 1.44 (s, 9

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H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.2, 155.7, 137.4, 129.7, 129.0, 127.2, 80.4, 67.2, 56.8, 56.6, 53.4, 39.7, 35.7, 28.7; IR (neat) 3298, 2966, 1704, 1660, 1523, 1454, 1365, 1246, 1168, 1118, 1022  $\text{cm}^{-1}$ ; HRMS-ESI ( $\text{M} + \text{H}^+$ ) calcd for  $\text{C}_{20}\text{H}_{32}\text{N}_3\text{O}_4$  378.2393, found 378.2393;  $[\alpha]_D^{25} = +13$  ( $c = 0.94$ ,  $\text{CHCl}_3$ ).

**Solid-Phase Synthesis of Ligands 3a–d. General Procedure.** To the appropriate *N*-Boc amino acid (3.0 equiv) were added HBTU (3.0 equiv), DIEA (4.0 equiv), and enough DMF to dissolve all of the solids. The DMF solution was added to the oxime resin (1.0 equiv), and the reaction mixture was shaken for 3 h. The resin was then washed with DMF ( $4 \times 3$  mL), and the coupling procedure was repeated a second time, followed by washes with DMF ( $5 \times 3$  mL) and  $\text{CH}_2\text{Cl}_2$  ( $6 \times 3$  mL). The resin was suspended in 3–5 mL of  $\text{CH}_2\text{Cl}_2$ , and the appropriate *N,N*-dialkylethylenediamine (2.25–3.00 equiv) was added at 25 °C. After the reaction mixture was shaken for 15 h, isocyanate resin (3.75–6.00 equiv) was added at 25 °C, and shaking was continued for an additional 6 h. The reaction mixture was filtered, the filtrate was collected, and the solvent was removed. The crude ligands were used without further purification. In several cases, residual DMF was removed from the crude ligand via azeotropic distillation with heptane. Spectroscopic characterization of ligands **3a,c**, and **d** matched the previously reported values.<sup>4</sup> Spectroscopic characterization of ligand **3b** matched the data listed above.

**(1*S*)-[2-Methyl-1-(2-morpholin-4-yl-ethylcarbamoyl)-propyl]carbamate *tert*-Butyl Ester 3a.** Ligand **3a** was prepared as described above from oxime resin (0.200 g, 0.180 mmol), Boc-Val-OH (0.117 g, 0.540 mmol), and 2-morpholin-4-yl-ethylamine (0.072 mL, 0.550 mmol), yielding a white solid (0.051 g, 0.155 mmol, 86%).

**(1*S*)-[1-(2-Morpholin-4-yl-ethylcarbamoyl)-2-phenylethyl]carbamate *tert*-Butyl Ester 3b.** Ligand **3b** was prepared as described above from oxime resin (0.217 g, 0.196 mmol), Boc-Phe-OH (0.128 g, 0.587 mmol), and 2-morpholin-4-yl-ethylamine (0.025 mL, 0.440 mmol), yielding a yellow-brown solid (0.054 g, 0.143 mmol, 73%).

**(1*S*)-[2-Methyl-1-(2-piperidin-1-yl-ethylcarbamoyl)-propyl]carbamate *tert*-Butyl Ester 3c.** Ligand **3c** was prepared as described above from oxime resin (0.215 g, 0.194 mmol), Boc-Val-OH (0.130 g, 0.598 mmol), and 2-piperidin-1-yl-ethylamine (0.062 mL, 0.437 mmol), yielding a yellow solid (0.056 g, 0.170 mmol, 88%).

**(1*S*)-[1-(2-(Diethylamino)ethylcarbamoyl)-2-methylpropyl]carbamate *tert*-Butyl Ester 3d.** Ligand **3d** was prepared as described above from oxime resin (0.215 g, 0.194 mmol), Boc-Val-OH (0.130 g, 0.598 mmol), and *N,N*-diethylethylenediamine (0.061 mL, 0.437 mmol), yielding a white solid (0.056 g, 0.178 mmol, 92%).

**(2*S*)-*N*-(2-(Diethylamino)ethyl)-2-(2,2-dimethyl-propionylamino)-3-methylbutyramide 3e.** Ligand **3e** was prepared by first loading oxime resin (0.421 g, 0.379 mmol) with Boc-Val-OH (0.247 g, 1.14 mmol) using the general procedure described above for the synthesis of ligands **3a–3d**. After Boc-Val-OH was coupled to the resin, the resin was treated with 25% TFA (20 equiv, 0.581 mL) in  $\text{CH}_2\text{Cl}_2$ , and the mixture was shaken for 2 h at 25 °C. The resin was washed with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 2$  mL) followed by 10% DIEA in  $\text{CH}_2\text{Cl}_2$  ( $3 \times 1$  mL). The resin was then treated with 2,2-dimethyl-propionyl chloride (0.103 mL, 0.835 mmol) in 2 mL of 10% DIEA in  $\text{CH}_2\text{Cl}_2$ , shaken for 22 h, and washed with  $\text{CH}_2\text{Cl}_2$  ( $6 \times 3$  mL). The resin was treated with *N,N*-diethylethylenediamine (0.16 mL, 1.14 mmol) in  $\text{CH}_2\text{Cl}_2$  and shaken for 16 h, and the excess diamine was scavenged using isocyanate resin (0.857 g, 1.52 mmol) at 25 °C for 6 h. The reaction mixture was filtered, the filtrate was collected, and the solvent was removed to yield compound **3e** as a white solid (0.0833 g, 0.278 mmol, 73%). The ligand was used without further purification. Spectroscopic characterization of the crude ligand matched that of previously reported values.<sup>4</sup>

**[1-[2-Methyl-1-(2-morpholin-4-yl-ethylcarbamoyl)-(S)-1-propylcarbamoyl]-2-tritylsulfanyl-(R)-1-ethyl]-carbam-**

**ic Acid *tert*-Butyl Ester 3f.** Ligand **3f** was prepared by first loading oxime resin (0.160 g, 0.144 mmol) with a DMF (1.5 mL) solution containing Boc-Val-OH (0.0939 g, 0.432 mmol), HBTU (0.164 g, 0.432 mmol), and DIEA (0.125 mL, 0.718 mmol). The reaction mixture was shaken for 23 h and subsequently washed with DMF ( $5 \times 3$  mL). The above procedure was repeated twice, and the resin was washed with  $\text{CH}_2\text{Cl}_2$  ( $5 \times 3$  mL). The resin was treated with 25% TFA in  $\text{CH}_2\text{Cl}_2$  (2 mL) and shaken for 2 h at 25 °C. The resin was then washed with  $\text{CH}_2\text{Cl}_2$  ( $5 \times 2$  mL), followed by 10% DIEA in  $\text{CH}_2\text{Cl}_2$  ( $5 \times 2$  mL) and finally DMF ( $2 \times 3$  mL). A solution of Boc-Cys(Trt)-OH (0.200 g, 0.432 mmol), HBTU (0.164 g, 0.432 mmol), and DIEA (0.125 mL, 0.718 mmol) dissolved in DMF (1.5 mL) was added to the resin and shaken for 2 h at 25 °C. The resin was then washed with DMF ( $5 \times 3$  mL), and the coupling procedure was repeated a second time, followed by washes with DMF ( $5 \times 3$  mL) and  $\text{CH}_2\text{Cl}_2$  ( $10 \times 3$  mL). The resin was finally treated with 2-morpholin-4-yl-ethylamine (0.042 mL, 0.320 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) and shaken for 15 h at 25 °C. The reaction mixture was then filtered and washed with  $\text{CH}_2\text{Cl}_2$  ( $6 \times 3$  mL). The filtrates were combined, washed twice with  $\text{H}_2\text{O}$ , and dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvent provided the crude product as a white solid (0.082 g, 0.121 mmol, 84%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 (d,  $J = 8.3$ , 1.1 Hz, 6 H), 7.34–7.22 (m, 9 H), 6.49 (br s, 2 H), 4.76 (br d, 1 H), 4.17 (dd,  $J = 8.3$ , 5.9 Hz, 1 H), 3.80 (br s, 1 H), 3.70 (br s, 4 H), 3.33 (m, 2 H), 2.71 (m, 1 H), 2.61 (dd,  $J = 12.4$ , 5.4 Hz, 1 H), 2.44 (br s, 6 H), 2.25 (m, 1 H), 1.43 (s, 9 H), 0.92 (d,  $J = 6.8$  Hz, 3 H), 0.88 (d,  $J = 6.9$  Hz, 3 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.91, 170.87, 156.0, 144.7, 129.9, 128.5, 127.4, 81.0, 67.7, 67.2, 59.0, 57.4, 54.2, 53.7, 36.2, 33.6, 30.5, 28.7, 19.6, 17.9; IR (neat) 3299, 3057, 2964, 1714, 1698, 1647, 1516, 1494, 1450, 1366, 1245, 1169, 1118, 1016  $\text{cm}^{-1}$ ; HRMS-FAB ( $\text{M} + \text{Na}^+$ ) calcd for  $\text{C}_{38}\text{H}_{50}\text{N}_4\text{O}_5\text{SNa}$  697.33996, found 697.3378;  $[\alpha]_D^{25} = -9.2$  ( $c = 1.7$ ,  $\text{CHCl}_3$ ).

**(1*S*)-1-((S)-1-Methyl-propyl)-(2-morpholin-4-ylethyl)amine 9.** [(1*S*)-1-((S)-1-Methyl-propyl)-(2-morpholin-4-yl-ethyl)]carbamate *tert*-butyl ester (1.00 g, 3.5 mmol), prepared as previously described,<sup>3</sup> was treated with TFA (5.4 mL, 70 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) at 25 °C for 1 h. The excess TFA was removed by rotary evaporation, and the residue was treated with DOWEX Monosphere 550A ion-exchange resin (30 mL) in methanol (100 mL) and allowed to stir overnight. Removal of the solvent gave compound **9** as a viscous pale yellow oil (0.615 g, 3.3 mmol, 95%). As an alternate workup procedure, after the TFA is removed, the residue can be diluted with water and the pH adjusted to pH 10 with 10% aqueous KOH. The aqueous solution may then be extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 10$  mL), the organic layers combined and dried ( $\text{Na}_2\text{CO}_3$ ), and the solvent removed by rotary evaporation to yield compound **9**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.71 (m, 4 H), 2.82 (m, 1 H), 2.58 (m, 2 H), 2.32 (m, 2 H), 2.19 (m, 2 H), 1.67 (br s, 2 H), 1.49 (m, 1 H), 1.35 (m, 1 H), 1.20 (m, 1 H), 0.90 (m, 6 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  67.6, 63.3, 54.5, 51.7, 39.4, 25.6, 15.4, 12.0; HRMS-FAB ( $\text{M} + \text{H}^+$ ) calcd for  $\text{C}_{10}\text{H}_{23}\text{N}_2\text{O}$  187.1810, found 187.1815;  $[\alpha]_D^{25} = +48.8$  ( $c = 1.46$ ,  $\text{CHCl}_3$ ).

**Solid-Phase Synthesis of Ligands 3g–l. General Procedure.** To the appropriate *N*-Boc amino acid (3.0 equiv) was added HBTU (3.0 equiv), DIEA (4.0 equiv), and enough DMF to dissolve all of the solids. The DMF solution was added to the oxime resin (1.0 equiv), and the reaction mixture was shaken for 3 h. The resin was then washed with DMF ( $4 \times 3$  mL), and the coupling procedure was repeated a second time and shaken for 15 h, followed by washes with DMF ( $5 \times 3$  mL) and  $\text{CH}_2\text{Cl}_2$  ( $6 \times 3$  mL). The resin was transferred into a round-bottom flask and suspended in  $\text{CH}_2\text{Cl}_2$  (5–10 mL). Diamine **9** (2.0 equiv) was added, and the reaction was heated at 40 °C under  $\text{N}_2$  with stirring for 24 h. Isocyanate resin (3 equiv) was then added, and the reaction mixture was heated at 40 °C with stirring for an additional 14 h. The reaction mixture was filtered, the filtrate was collected, and the solvent

was removed. The crude ligands were used without further purification.

**(((1S)-1-((S)-1-Methyl-propyl)-2-morpholin-4-yl-ethyl-carbamoyl)-(S)-2-propyl-methyl]carbamic Acid tert-Butyl Ester 3g.** Ligand **3g** was prepared as described above from oxime resin (0.384 g, 0.346 mmol), Boc-Val-OH (0.225 g, 1.04 mmol), and diamine **9** (0.129 g, 0.691 mmol), yielding a white solid (0.083 g, 0.216 mmol, 62%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.02 (br s, 1 H), 5.13 (d, *J* = 7.7 Hz, 1 H), 4.01 (m, 1 H), 3.84 (dd, *J* = 8.9, 6.9 Hz, 1 H), 3.64 (br s, 4 H), 2.52 (m, 2 H), 2.09 (m, 4 H), 2.10 (m, 1 H), 1.73 (m, 1 H), 1.44 (s, 9 H), 1.38 (m, 1 H), 1.10 (m, 1 H), 0.93 (m, 12 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 171.8, 156.2, 80.1, 67.2, 60.9, 58.9, 54.2, 50.3, 37.3, 31.1, 28.7, 25.6, 19.7, 18.4, 15.1, 12.2; IR (neat) 3323, 2961, 1684, 1644, 1525, 1249, 1177 cm<sup>-1</sup>; HRMS–FAB (*M* + *H*<sup>+</sup>) calcd for C<sub>20</sub>H<sub>40</sub>N<sub>3</sub>O<sub>4</sub> 386.3019, found 386.3014; [α]<sub>D</sub><sup>25</sup> = +2.5 (*c* = 1.3, CHCl<sub>3</sub>).

**(((1S)-1-((S)-1-Methyl-propyl)-2-morpholin-4-yl-ethyl-carbamoyl)-(R)-2-propylmethyl]carbamic Acid tert-Butyl Ester 3h.** Oxime resin (0.302 g, 0.27 mmol) was suspended in dry DMF (3 mL), and to this solution were added Boc-D-Val-OH (0.177 g, 0.81 mmol), DIEA (0.190 mL, 1.1 mmol), and HBTU (0.320 g, 0.81 mmol). After the solution was shaken for 3 h, the resin was washed with DMF (10 × 5 mL), and the coupling procedure was repeated. After the second coupling, the resin was washed with DMF (10 × 5 mL), followed by washing with CH<sub>2</sub>Cl<sub>2</sub> (20 × 5 mL). The resin was transferred to a round-bottom flask and suspended in dry CH<sub>3</sub>CN (10 mL). Diamine **9** (0.110 g, 0.59 mmol) was dissolved in CH<sub>3</sub>CN (0.5 mL) and was added to the resin. The solution was brought to reflux for 24 h and then cooled to 40 °C. Isocyanate resin (0.402 g, 0.96 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) were added to the reaction, and it was maintained at 40 °C with stirring for 24 h. The reaction mixture was cooled and filtered through a fine glass fritted Buchner funnel with water aspiration, and the resin was washed with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The filtrate was collected, and the solvent removed to yield a white solid (0.877 g, 0.23 mmol, 84%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.36 (s, 1 H), 5.16 (s, 1 H), 4.10 (m, 1 H), 3.91 (m, 1 H), 3.73 (s, 4 H), 2.62–2.39 (m, 5 H), 2.16 (m, 1 H), 1.71 (s, 1 H), 1.44 (s, 9 H), 1.26 (m, 1 H), 1.10 (m, 1 H), 0.94 (m, 12 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 172.2, 156.3, 80.2, 66.8, 60.9, 58.5, 53.9, 49.8, 37.4, 31.0, 28.7, 25.5, 19.8, 18.3, 15.4, 12.2; IR (neat) 3326, 2961, 2931, 2871, 2810, 1709, 1659, 1522, 1456, 1366, 1172, 1118, 1010 cm<sup>-1</sup>; HRMS–FAB (*M* + *H*<sup>+</sup>) calcd for C<sub>20</sub>H<sub>40</sub>N<sub>3</sub>O<sub>4</sub> 386.3019, found 386.3017; [α]<sub>D</sub><sup>25</sup> = +21.9 (*c* = 2.2, CHCl<sub>3</sub>).

**(((1S)-1-((S)-1-Methyl-propyl)-2-morpholin-4-yl-ethyl-carbamoyl)-(S)-1-phenylmethyl-methyl]carbamic Acid tert-Butyl Ester 3i.** Ligand **3i** was prepared as described above from oxime resin (0.366 g, 0.406 mmol), Boc-Phe-OH (0.324 g, 1.22 mmol), and diamine **9** (0.151 g, 0.812 mmol), yielding a white solid (0.122 g, 0.282 mmol, 69%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.31 (m, 3 H), 7.25 (m, 2 H), 5.99 (br s, 1 H), 5.04 (br s, 1 H), 4.34 (dd, *J* = 15.1, 7.2 Hz, 1 H), 3.94 (br s, 1 H), 3.59 (br s, 4 H), 3.08 (m, 2 H), 2.37 (br s, 2 H), 2.27 (br m, 4 H), 1.75 (br m, 1 H), 1.44 (s, 9 H), 1.35 (m, 1 H), 1.03 (m, 1 H), 0.90 (t, *J* = 7.2 Hz, 3 H), 0.82 (d, *J* = 6.8 Hz, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 171.5, 155.8, 137.4, 129.9, 129.0, 127.2, 80.5, 66.7, 58.5, 56.4, 53.9, 50.1, 38.4, 37.1, 28.7, 25.3, 15.2, 12.2; IR (neat) 3318, 2964, 1681, 1650, 1524, 1455, 1390, 1370, 1170 cm<sup>-1</sup>; HRMS–FAB (*M* + *Na*<sup>+</sup>) calcd for C<sub>24</sub>H<sub>39</sub>N<sub>3</sub>O<sub>4</sub>–Na 456.2838, found 456.2852; [α]<sub>D</sub><sup>25</sup> = –1.2 (*c* = 0.42, CHCl<sub>3</sub>).

**(((1S)-1-((S)-1-Methyl-propyl)-2-morpholin-4-yl-ethyl-carbamoyl)-(R)-1-phenylmethyl-methyl]carbamic Acid tert-Butyl Ester 3j.** Ligand **3j** was prepared as described above from oxime resin (0.334 g, 0.371 mmol), Boc-D-Phe-OH (0.294 g, 1.11 mmol), and diamine **9** (0.138 g, 0.742 mmol), yielding a white solid (0.104 g, 0.239 mmol, 64%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.30 (m, 3 H), 7.23 (m, 2 H), 6.53 (br s, 1 H), 5.36 (br s, 1 H), 4.41 (dd, *J* = 14.9, 7.3 Hz, 1 H), 4.09 (br s, 1 H), 3.78 (m, 4 H), 3.10 (d, *J* = 7.4 Hz, 2 H), 2.71 (br s, 2 H), 2.58 (br s, 2 H), 2.45 (br s, 1 H), 2.42 (br s, 1 H), 1.58 (m,

1 H), 1.43 (m, 1 H), 1.39 (s, 9 H), 0.97 (m, 1 H), 0.87 (t, *J* = 7.0 Hz, 3 H), 0.74 (d, *J* = 6.1 Hz, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 172.0, 155.9, 137.3, 129.8, 129.0, 127.2, 80.4, 66.3, 58.4, 56.7, 53.6, 49.3, 38.8, 37.6, 28.7, 25.4, 15.2, 12.1; IR (neat) 3307, 2963, 2931, 2871, 1698, 1653, 1522, 1455, 1366, 1249, 1170, 1118, 1018 cm<sup>-1</sup>; HRMS–FAB (*M* + *Na*<sup>+</sup>) calcd for C<sub>24</sub>H<sub>39</sub>N<sub>3</sub>O<sub>4</sub>–Na 456.2838, found 456.2831; [α]<sub>D</sub><sup>25</sup> = +17 (*c* = 1.3, CHCl<sub>3</sub>).

**(((1S)-1-((S)-1-Methyl-propyl)-2-morpholin-4-yl-ethyl-carbamoyl)-(S)-1-methyl-methyl]carbamic Acid tert-Butyl Ester 3k.** Ligand **3k** was prepared as described above from oxime resin (0.342 g, 0.380 mmol), Boc-Ala-OH (0.216 g, 1.14 mmol), and diamine **9** (0.142 g, 0.762 mmol), yielding a white solid (0.088 g, 0.247 mmol, 65%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.10 (br s, 1 H), 5.06 (br s, 1 H), 4.16 (m, 1 H), 4.04 (br s, 1 H), 3.69 (br s, 4 H), 2.52 (br s, 2 H), 2.38 (br s, 4 H), 1.72 (m, 1 H), 1.64 (m, 1 H), 1.46 (s, 9 H), 1.38 (d, *J* = 7.0 Hz, 3 H), 1.10 (m, 1 H), 0.93 (m, 6 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 173.0, 155.9, 80.4, 66.9, 59.0, 54.0, 50.6, 50.1, 37.5, 28.7, 25.4, 18.6, 15.3, 12.2; IR (neat) 3309, 2966, 2932, 2874, 1697, 1656, 1524, 1455, 1366, 1249, 1169, 1118 cm<sup>-1</sup>; HRMS–FAB (*M* + *Na*<sup>+</sup>) calcd for C<sub>18</sub>H<sub>35</sub>N<sub>3</sub>O<sub>4</sub>Na 380.2525, found 380.2539; [α]<sub>D</sub><sup>25</sup> = –6.0 (*c* = 3.1, CHCl<sub>3</sub>).

**(((1S)-1-((S)-1-Methyl-propyl)-2-morpholin-4-yl-ethyl-carbamoyl)-(R)-1-methyl-methyl]carbamic Acid tert-Butyl Ester 3l.** Ligand **3l** was prepared as described above from oxime resin (0.334 g, 0.371 mmol), Boc-D-Ala-OH (0.210 g, 1.11 mmol), and diamine **9** (0.138 g, 0.742 mmol), yielding a white solid (0.079 g, 0.220 mmol, 59%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.53 (br s, 1 H), 5.26 (br s, 1 H), 4.18 (m, 1 H), 4.10 (m, 1 H), 3.78 (br s, 4 H), 2.69 (br s, 2 H), 2.49 (m, 4 H), 1.66 (m, 1 H), 1.50 (m, 1 H), 1.47 (s, 9 H), 1.39 (d, *J* = 7.1 Hz, 3 H), 1.10 (m, 1 H), 0.94 (t, *J* = 7.1 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 173.7, 155.9, 80.4, 66.1, 58.8, 53.6, 51.0, 49.0, 37.9, 28.7, 25.3, 18.8, 15.5, 12.0; IR (neat) 3305, 2965, 1708, 1659, 1518, 1450, 1367, 1246, 1168 cm<sup>-1</sup>; HRMS–FAB (*M* + *Na*<sup>+</sup>) calcd for C<sub>18</sub>H<sub>35</sub>N<sub>3</sub>O<sub>4</sub>Na 380.2525, found 380.2524; [α]<sub>D</sub><sup>25</sup> = +34 (*c* = 0.70, CHCl<sub>3</sub>).

**Solid-Phase Synthesis of [(1S)-1-((S)-1-Methyl-propyl)-(2-morpholin-4-yl-ethyl)]carbamic Acid Methyl Ester 13.** To prewashed (3 × 5 mL CH<sub>2</sub>Cl<sub>2</sub>) oxime resin (0.452 g, 0.410 mmol) were added DMAP (0.014 g, 0.102 mmol) and DIEA (0.285 mL, 1.64 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). Enough CH<sub>2</sub>Cl<sub>2</sub> was added to suspend the resin, methyl chloroformate (0.95 mL, 1.23 mmol) was added, and the reaction was shaken for 3 h at 25 °C. The resin was washed with CH<sub>2</sub>Cl<sub>2</sub> (10 × 5 mL), and the loading step was repeated. The resin was again washed with CH<sub>2</sub>Cl<sub>2</sub> (20 × 5 mL) and then transferred to a round-bottom flask. The resin was suspended in CH<sub>3</sub>CN (10 mL). Diamine **9** (0.169 g, 0.900 mmol) was dissolved in CH<sub>3</sub>CN (0.5 mL) and added to the resin. The reaction was brought to reflux for 24 h and then cooled to 40 °C before the isocyanate resin (0.616 g, 1.48 mmol) was added. After 24 h of stirring at 40 °C, the reaction was cooled and filtered through a fine glass fritted Buchner funnel with water aspiration, and the resin was washed with large amounts of CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was collected, and the solvent was removed to yield a yellow oil (0.100 g, 0.410 mmol, 100%). Spectroscopic characterization of ligand **13** matched previously reported data.<sup>3</sup>

**General Procedure for Et<sub>2</sub>Zn Addition to Aldehydes.** To an oven-dried vial was added the ligand (0.06 mmol) followed by a 1.0 M solution of Et<sub>2</sub>Zn in hexanes (1.8 mmol). The solution was stirred for 10 min at 25 °C and cooled to 0 °C, and then benzaldehyde (0.60 mmol) was added. After 18 h, the reaction was quenched first with saturated aqueous NH<sub>4</sub>Cl and then with 1 N HCl (2 mL), and then it was extracted with Et<sub>2</sub>O (2 × 5 mL). The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> solution (5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered through a plug of silica gel, and concentrated in vacuo. The crude alcohol was analyzed without further purification by HPLC (Chiralcel OD-H) using an eluent of 97.5% hexanes/2-propanol running at 1.0 mL/min.

**General Procedure for Reaction of Alkenylzinc Reagents to Aldehydes.** An oven-dried vial was cooled to 0 °C, and borane–dimethyl sulfide complex (0.55 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.25 mL) was added, followed by cyclohexene (1.1 mmol). This solution was stirred at 0 °C for 2 h. Next, the alkyne (0.55 mmol) was added, and the reaction was warmed to room temperature for 30 min. To this solution was added the ligand (0.038 mmol), and the reaction was cooled to –78 °C. A 1.0 M solution of Et<sub>2</sub>Zn in CH<sub>2</sub>Cl<sub>2</sub> (0.625 mmol) was added to the solution. After 18 h at –78 °C, benzaldehyde (0.50 mmol) was added, and the reaction was warmed to –48 °C for 48 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and diluted with diethyl ether. The organic layer was washed with 1 N HCl (3 × 2 mL), water (2 mL), saturated aqueous NaHCO<sub>3</sub> (2 × 2 mL), and brine (2 mL) and was dried (MgSO<sub>4</sub>). The

solvent was removed, and purification was performed by column chromatography (9:1 hexanes/EtOAc).

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

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