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A Positional Scanning Approach to the Discovery of Dipeptide-Based Catalysts for the Enantioselective Addition of Vinylzinc Reagents to Aldehydes

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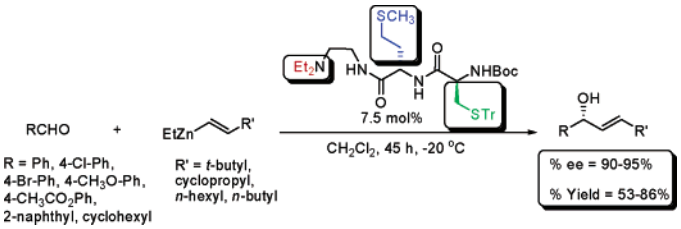

A combinatorial library of dipeptide *N*-acylethylenediamine-based ligands was synthesized by parallel solid-phase methods. These ligands were screened in crude form as catalysts for the asymmetric addition of vinylzinc reagents to aldehydes to give chiral allylic alcohols. Three sites of diversity on the ligands were optimized using a positional scanning approach. The optimized structure from the library, ligand **54**, was found to catalyze the formation of 10 different (*E*)-allylic alcohols with enantioselectivities ranging from 90% to 95% ee. This ligand was effective for both aromatic and α-branched aldehydes, and vinylzinc reagents derived from both bulky and straight chain terminal alkynes.

Introduction

Chiral allylic alcohols are an important class of compounds in synthetic organic chemistry.[1] They are versatile intermediates for the construction of more complex molecules because the stereochemistry of the alcohol functional group can be used to control the stereochemistry of subsequent reactions that are directed to the neighboring alkene. Two prominent methods for synthesizing chiral allylic alcohols are the asymmetric reduction of α,β-unsaturated ketones and the enantioselective addition of vinylzinc reagents to aldehydes. The later of these two methods provides an attractive option because a carbon−carbon bond is constructed concomitant with formation of the chiral secondary alcohol. In addition, organozinc reagents are versatile synthons since they are compatible with a wide variety of functional groups, and there is a great deal of precedent for their use in asymmetric catalytic reactions.[2]

Several research groups have recently reported catalysts for the asymmetric addition of vinylzinc reagents to aldehydes. For example, Walsh,[3] Chan,[4] and Soai[5] have each developed amino alcohol-based ligands for this reaction that show good to excellent stereoselectivities with a variety of substrates. Dahmen and Brase have reported a ketimine-based ligand,[6] and Tseng and Yang have reported an amino thiol-based ligand.[7] All of these investigators use Oppolzer's in situ method for generating the vinylzinc reagent.[8] In this method a terminal alkyne is treated with dicyclohexylborane to yield the corresponding vinylborane intermediate. This intermediate undergoes transmetalation with dimethylzinc or diethylzinc to produce the (alkyl)(vinyl)zinc species.

(1) For recent examples, see: (a) Smith, T. E.; Djang, M.; Velander, A. J.; Downey, C. W.; Carroll, K. A.; van Alphen, S. *Org. Lett.* **2004**, *6*, 2317. (b) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 588. (c) Takahashi, T.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2003**, *44*, 9219.

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Shair and co-workers used an amino alcohol ligand in stoichiometric quantities to control the addition of a vinylzinc reagent to an aldehyde during their enantioselective synthesis of (−)-longithorone A.[9] Wipf has developed an alternative method for generating vinylzinc reagents.[10] Hydrozirconation of an alkyne using Schwartz reagent generates a vinylzirconocene, which is then transmetalated with dimethylzinc. Wipf has used this procedure, in conjunction with an amino thiol ligand, to synthesize allylic alcohols in high ee.

Enantioselective catalysts are often discovered by an iterative, stepwise process wherein the structure of an initial catalyst candidate is modified, and the new catalyst is evaluated in the reaction of choice. These two steps are repeated until an optimal catalyst is obtained. Combinatorial chemistry has been shown to be a useful strategy for expediting the sometimes lengthy process of catalyst optimization. However, it requires that the catalyst be modular in its construction.[11,12] An ideal modular catalyst would incorporate several sites of diversity, would be easy to synthesize from inexpensive and readily available starting materials, would require no purification, and would reliably catalyze the formation of a synthetically useful product with high stereoselectivity and yield. One potential difficulty that arises in screening a relatively large library of chiral ligands (>1000 members) is that analysis of the reaction products can be time-consuming and tedious with the traditional serial methods that are most commonly used for measuring ee such as HPLC, GC, and NMR spectroscopy. However, recently a number of high throughput methods have been developed for measuring ee that could be very useful for evaluating libraries of catalysts, and therefore increase the efficiency by which highly enantioselective catalysts are discovered.[13]

We have reported that modular chiral *N*-acylethylenediamines are good catalysts for the addition of dialkylzinc reagents to aldehydes, yielding enantioenriched secondary alcohols.[14,15] The *N*-acylethylenediamine core was designed to form a five-membered zinc chelate between the tertiary amine and the anion of the neighboring amide (eq 1). This zinc binding mode is analogous to that

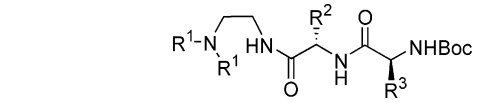
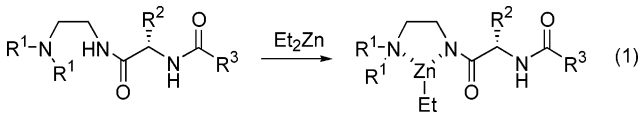


FIGURE 1. General structure of dipeptide *N*-acylethylenediamines.



(1)

which is observed for the β-amino alcohol class of ligands. Trivalent binding of the ligand to zinc is also reasonable. The amino acid that is attached to the *N*-acylethylenediamine provides a source of chirality.[16]

Here, we report the synthesis of a library of dipeptide *N*-acylethylenediamine ligands and their screening for the ability to catalyze the enantioselective addition of vinylzinc reagents to aldehydes (Figure 1). In contrast to our previous ligands (eq 1), we have incorporated a second amino acid into the ligand structure in order to exert a higher degree of stereochemical control over the catalyzed reaction. The ligands were synthesized in parallel using a solid-phase strategy, and were screened in crude form. We used the iterative optimization strategy to discover the most enantioselective catalyst in the library. During the optimization process three subunits within the ligands were varied: the alkyl groups on the tertiary amine (R^1), and the two amino acid side chains R^2 and R^3 (Figure 1). The optimal ligand from the library was re-synthesized by standard solution-phase methods. The purified ligand was then used to explore the scope of the addition reaction using a variety of vinylzinc reagents and aldehydes.

Results and Discussion

Solid-Phase Synthesis of the Ligands. We have developed an efficient synthesis of the ligands using a parallel solid-phase strategy that allows for easy variation of all three points of diversity.[17] In previous studies we have shown that the crude ligands that result from this synthesis are obtained in good purity without the need for chromatography. As a result, the crude and purified ligands catalyze reactions with similar yields and enantioselectivities. The solid-phase synthesis is shown in Scheme 1. Oxime resin **1** was treated with an *N*-Boc-

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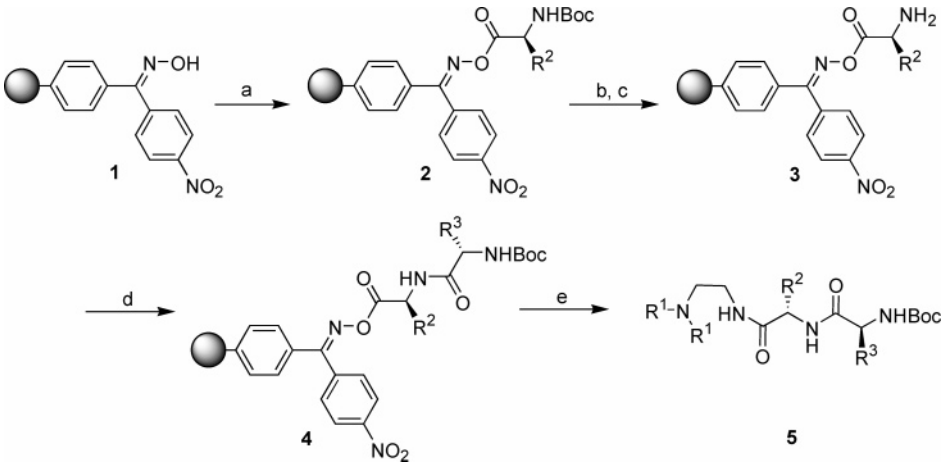
(18) Abbreviations: HBTU is *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; DIEA is diisopropylethylamine.

(19) See the Supporting Information for a complete listing of yields.

SCHEME 1. Solid-Phase Synthesis of *N*-Acylethylenediamine Dipeptide Ligands[a]



[a] Reagents: (a) HBTU, DIEA, *N*-Boc-amino acid, DMF, triple coupling; (b) 25% TFA, CH_2Cl_2; (c) 10% DIEA, CH_2Cl_2; (d) HBTU, DIEA, *N*-Boc-amino acid, DMF, double coupling; (e) *N*,*N*-dialkylethylenediamine, CH_2Cl_2.

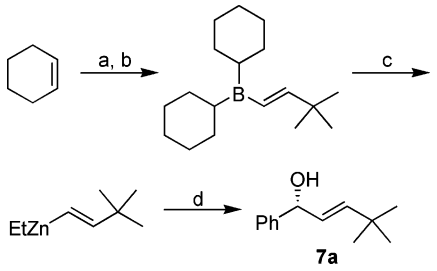
amino acid and HBTU to yield the resin-bound amino acid **2**.[18] The Boc protecting group was removed from compound **2** with TFA and the resulting free amine **3** was coupled with a second *N*-Boc-amino acid using HBTU to give dipeptide **4**. The dipeptide in compound **4** was displaced from the resin using a variety of *N*,*N*-dialkylethylenediamines. Excess diamine was then removed using an aqueous workup to give ligand **5**. The oxime resin **1** could be reused up to three times in this synthesis. However, the yield was reduced with each cycle.[19]

In preliminary studies, we used the solid-phase procedure to prepare ligand **6** in 84% yield and in good purity (Figure 2). The crude ligand catalyzed the addition of several vinylzinc reagents to benzaldehyde with moderate enantioselectivities (67−76% ee). A purified sample of this ligand catalyzed the formation of allylic alcohol **7a** in 65% ee, which is similar to the value that was obtained with the crude ligand (67% ee).

To further validate that the solid-phase synthesis provided ligands of acceptable purity, 10 library members were randomly selected and their purities estimated by ^{1}H NMR spectroscopy. These experiments showed that 7 of the 10 samples were >90% pure, while three samples were somewhat less pure (~80−85%).

Ligand Screening. Before we began screening the ligands, we first optimized the reaction conditions by varying a number of parameters including reagent stoichiometries and reaction times and temperatures. The standard set of reaction conditions that we settled on for the screening process is shown in Scheme 2. Borane−dimethyl sulfide complex was treated with 2 equiv of

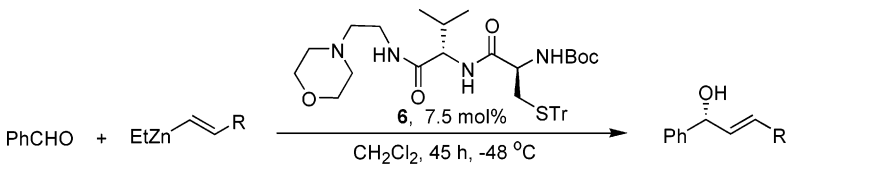
SCHEME 2. Reaction Conditions for Screening the Library of Ligands[a]



[a] Reagents: (a) BH_3·DMS, CH_2Cl_2, 2 h, 0 °C; (b) $(CH_3)_3CC{\equiv}CH$, 30 min, 0 °C to room temperature; (c) 7.5 mol % ligand, Et_2Zn, −78 °C, 18 h, CH_2Cl_2; (d) PhCHO, −20 °C, 24 h.

cyclohexene in CH_2Cl_2 to give dicyclohexylborane. Hydroboration of 3,3-dimethylbut-1-yne with dicyclohexylborane yielded the corresponding dicyclohexylvinylborane, which was transmetalated with Et_2Zn in the presence of 7.5 mol % of the ligand to give the vinylzinc reagent. Finally, benzaldehyde was added to the reaction mixture at −78 °C, followed by warming to −20 °C. The reaction was quenched after 24 h to yield allylic alcohol **7a**.

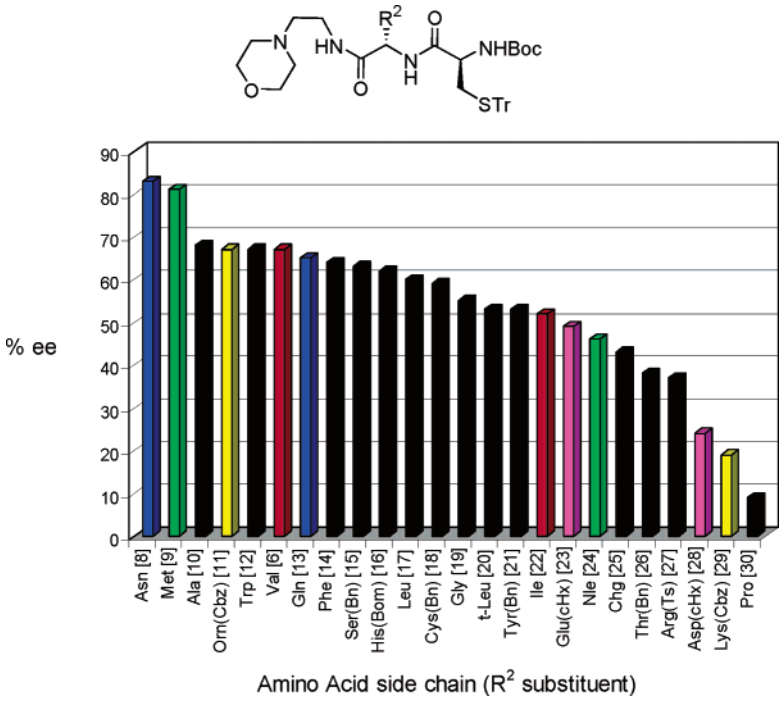
We began the positional scanning optimization process by holding the R^1 and R^3 substituents constant as $-(CH_2)_2O(CH_2)_2-$ and the side chain of Cys(Tr), respectively, while the R^2 position was varied in order to investigate its effect on the enantioselectivity of the addition reaction. We chose this specific starting point for the iterative optimization since our preliminary



7a: R = *tert*-Bu, 67% ee
7b: R = *n*-Bu, 76% ee
7c: R = *n*-C_6H_{13}, 73% ee

FIGURE 2. Enantioselective synthesis of allylic alcohols using crude ligand **6** from solid-phase synthesis.

CHART 1. Effect of Ligand R² Substituent on the Addition of Alkenylzinc to Benzaldehyde[a–d]



[a] All experiments performed in duplicate except for ligands **16**, **23**, and **28**, which were measured once. [b]Percent ee measured by HPLC (Chiralcel OD-H). [c]Absolute configuration was assigned as (*R*) by comparison of the optical rotation with the reported value, see ref 8a. [d]List of abbreviations: Orn = ornithine, Bom = benzyloxymethyl, cHx = cyclohexyl, Nle = norleucine, Chg = cyclohexylglycine.

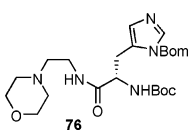
studies with ligand **6** (Figure 2) demonstrated that these particular substituents, with the side chain of Val at the R² position, gave moderate enantioselectivity. A total of 24 amino acid side chains were examined at the R² position (Chart 1). The identity of each ligand was confirmed by LC-MS, and its purity was estimated by TLC analysis. In all but one case these analyses showed that the desired products were produced by the solid phase synthesis in good purity. The only crude ligand that contained a significant number of side products was the His(Bom) ligand **16**. In addition to the desired material, we also observed two other major products. The first impurity was missing the His(Bom) amino acid, and was caused by failure of *N*-Boc-His(Bom) to couple with the resin. The second impurity was missing the Cys(Tr) amino acid, and was caused by the failed Boc deprotection of the resin-bound *N*-Boc-His(Bom). As a result, we resynthesized ligand **16** by standard solution-phase methods.[20] This was the only ligand that was screened in purified, rather than crude, form.

As shown in Chart 1, the side chains of Asn (ligand **8**) and Met (ligand **9**) provide the highest enantioselectivities in this series with ee values for the standard reaction of 83% and 81%, respectively.[21] Several comparisons within this data set are worth examining. For example, the side chain of Nle is the same length as the side chain of Met; however, the Nle ligand (**24**) gives much lower enantioselectivity at 46% ee (green bars). This result suggests that the sulfur atom in Met is critical for determining the stereoselectivity of ligand **9**. In a number of cases, changing the length of the side chain by a single methylene unit has a significant impact on enantioselectivity. This can be seen in the comparisons of Orn(Cbz) **11** (67% ee) and Lys(Cbz) **29** (19% ee) (yellow bars), Asn **8** (81% ee) and Gln **13** (65% ee) (blue bars), Glu(cHx) **23** (49% ee) and Asp(cHx) **28** (24% ee) (purple bars), and Val **6** (67% ee) and Ile **22** (52% ee) (red bars). These comparisons suggest that the length of the side chain also plays an important role in determining enantioselectivity.

Two characteristics of this data set indicate that the R³ substituent, although it is remote from the putative zinc binding site, has a dominant influence on stereoselectivity when compared to R².[22] For example, the Gly ligand (**19**) and the *t*-Leu ligand (**20**) gave very similar enantioselectivities (55% vs 53% ee), even though the size of their side chains (H vs *t*-Bu) are drastically different. In addition, ligands **6** and **10**–**16** all gave reasonable enantioselectivities (>60% ee), even though their side chains are very different in structure.

After completing the first round of screening, we chose the side chain of Met as the optimal group for the R² position (ligand **9**). We selected Met over Asn because this choice avoids the need for the side chain protecting group on Asn that is necessary to prevent dehydration of the amide to the corresponding nitrile.[23] We have found

(20) TLC of the crude product from the attempted solid-phase synthesis of ligand **16** indicated three major spots, and LC-MS analysis (ESI) showed three major peaks at *m/z* 488, 576, and 833, which correspond to the structures respectively.



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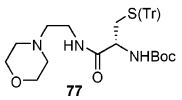

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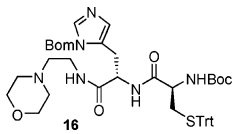

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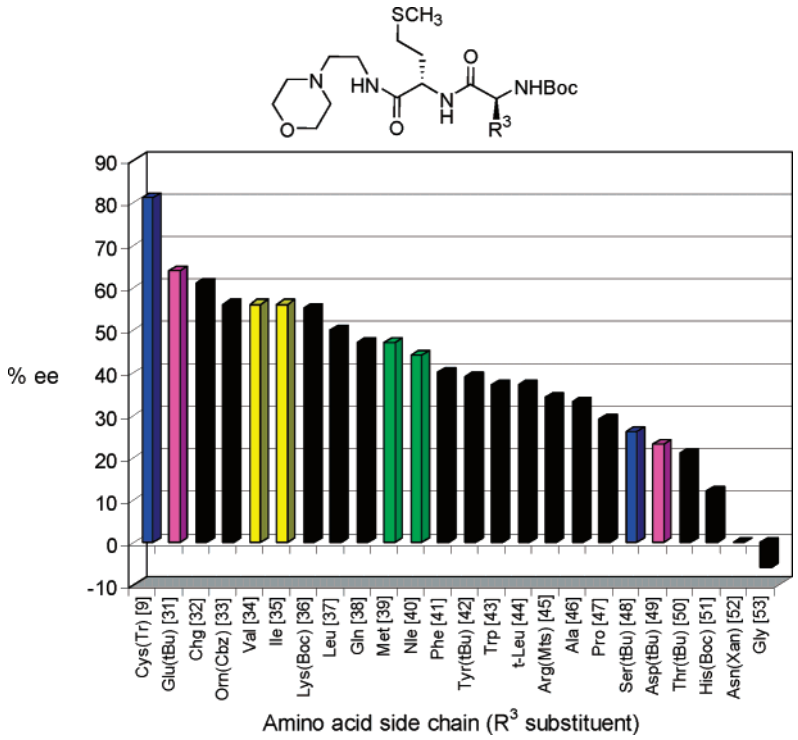
(21) See the Supporting Information for a numerical table of all screening results.

(22) Similar results for other dipeptide-based ligands have been reported elsewhere. See ref 16a.

CHART 2. Effect of Ligand R^3 Substituent on the Addition of Alkenylzinc to Benzaldehyde[a–d]



[a] All experiments performed in duplicate. [b]Percent ee measured by HPLC (Chiralcel OD-H). [c]Absolute configuration was assigned as (*R*), except for Gly (**53**), which was assigned as (*S*), by comparison to the known HPLC retention times for each enantiomer of allylic alcohol **7a**. [d]List of abbreviations: Mts = mesitylene-2-sulfonyl, Xan = xanthyl.

that as long as ligand **9** was stored under an atmosphere of nitrogen, we do not observe evidence of significant air oxidation of the Met thioether group.

In the second stage of the iterative optimization, we evaluated 24 amino acid side chains at the R^3 position of the ligands, while the R^1 and R^2 positions were held constant as $-(CH_2)_2O(CH_2)_2-$ and the side chain of Met, respectively (Chart 2). In this series, all of the ligands were obtained from the solid-phase synthesis in satisfactory yield and purity. The ligand containing Asn(Xan) **52** was not soluble in CH_2Cl_2, and no allylic alcohol product was isolated from reactions using this ligand. The ligand with the side chain of Cys(Tr) (**9**) at the R^3 position emerged as the most enantioselective catalyst by a fairly wide margin. In contrast to the first round of optimization, only one other ligand (**31**) gave an ee value >60%. The very large side chain of Cys(Tr) appears to be important for controlling the stereochemistry of the catalyzed reaction. For example, ligand **48** that incorporates the side chain of Ser(*t*-Bu) at the R^3 position gave a much lower ee value (26%) (blue bars). Even though Cys and Ser are similar in structure, the trityl protecting group is significantly larger than *t*-Bu.

In this series, changing the length of the amino acid side chain by a single methylene unit provided no difference in the ee values for the pair Val (**34**) and Ile (**35**) (yellow bars). By contrast, Glu(*t*-Bu) and Asp(*t*-Bu) (ligands **31** and **49**) gave ee values that differ by 41% (purple bars).

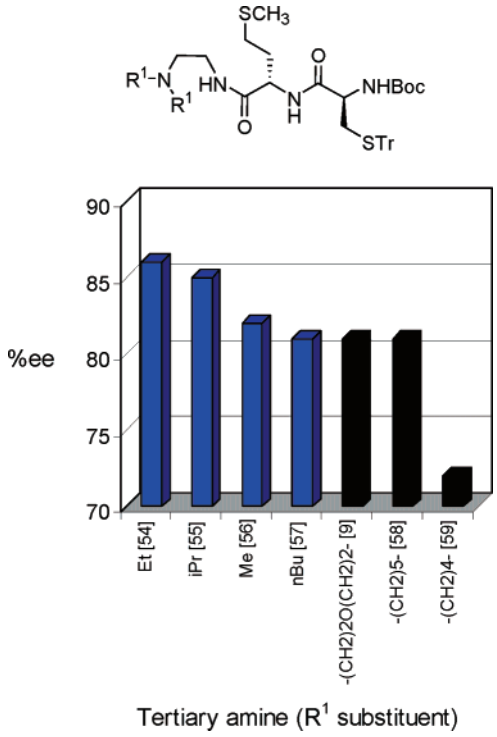
Ligands with the side chains of Met (**39**) and Nle (**40**) at the R^3 position gave similar ee values, indicating that the sulfur atom in Met at R^3 plays no significant role in controlling stereochemistry (green bars). Interestingly, the Gly containing ligand **53** showed a slight preference for catalyzing the formation of the (*S*)-allylic alcohol. This is the opposite sense of asymmetric induction than we have observed for all of the other ligands, and provides further support for the idea that the side chain of Cys(Tr) at the R^3 position plays a dominant role in controlling the stereoselectivity of the ligands shown in Chart 1.

With the side chains of Met and Cys(Tr) as the optimal groups for the R^2 and R^3 positions, respectively, we began the final round of optimization at the R^1 position (Chart 3). Noncyclic alkyl groups on the tertiary amine generally gave higher stereoselectivities, with values ranging from 81% to 86% ee for ligands **54** (diethyl), **55** (diisopropyl), **56** (dimethyl), and **57** (di-*n*-butyl) (blue bars). In contrast, the cyclic tertiary amines including morpholine **9**, piperidine **58**, and pyrrolidine **59** were less effective with ee values in the range of 72−81% (black bars). Among the three cyclic amines, the dominant factor in determining stereoselectivity was ring size. The six-membered ring in ligands **9** and **58** (81% and 81% ee) gave significantly higher enantioselectivity when compared to the five-membered ring in ligand **59** (72% ee). TLC analysis of crude ligand **57** indicated that the desired product was contaminated with a significant amount of *N*,*N*-dibutylethylenediamine that was not removed during the aqueous workup procedure. As a result, this ligand was purified by chromatography before screening.[24]

(23) It is well-known that asparagine can dehydrate during peptide couplings. Therefore, we chose the xanthyl protecting group for the side chain of Asn to avoid this problem. This protecting group was subsequently removed during Boc deprotection. See: Shimonishi, Y.; Sakakibara, S.; Akabori, S. *Bull. Chem. Soc. Jpn*. **1962**, *35*, 1966.

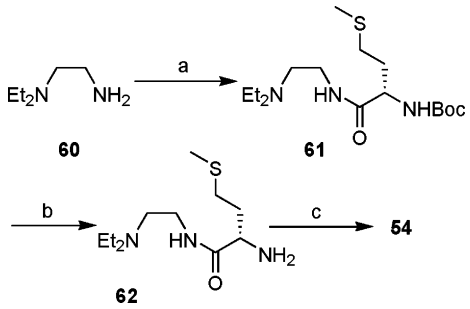
(24) Isocyanate scavenging resin was also found ineffective at removing the excess diamine.

CHART 3. Effect of Ligand R[1] Substituent on the Addition of Alkenylzinc to Benzaldehyde[a–c]



[a] All experiments performed in duplicate. [b]Percent ee measured by HPLC (Chiralcel OD-H). [c]Absolute configuration was assigned as (*R*) by comparison to the known HPLC retention times for each enantiomer of allylic alcohol **7a**.

SCHEME 3. Solution-Phase Synthesis of the Optimized Dipeptide Ligand 54[a]



[a] Reagents: (a) HBTU, DIEA, *N*-Boc-Met, DMF; (b) TFA, CH_2Cl_2; (c) HBTU, DIEA, *N*-Boc-Cys(Tr), DMF.

We have also examined one diastereomer of ligand **54** that had the opposite absolute configuration at the R^3 position. This compound gave allylic alcohol **7a** in 42% ee (*S*) in the screening reaction (data not shown). This result again suggests that the R^3 stereocenter is the key factor in determining the sense of asymmetric induction.

Compound **54** provided the highest degree of stereoselectivity from the ligands in the library, and this compound was re-synthesized on a larger scale using solution-phase methods (Scheme 3). *N*,*N*-Diethylethylenediamine (**60**) was coupled to *N*-Boc-Met to yield amide **61**. The Boc group was removed using TFA and the resulting free amine **62** was coupled to *N*-Boc-Cys(Tr) to give ligand **54** in a 36% overall yield for the three-step sequence. The final product was purified by chromatography prior to its use as a catalyst in subsequent reactions.

Purified ligand **54** (7.5 mol %) catalyzed the formation of (*R*,*E*)-4,4-dimethyl-1-phenylpent-2-en-1-ol (**7a**) in 92% ee and 49% yield (entry 2, Table 1). Increasing the catalyst loading to 10 mol % increased the ee to 94% (entry 1), while lower catalyst loadings consistently increased the yield and maintained the enantioselectivity above 90% ee (entries 3 and 4). Only when the catalyst loading was decreased to 1% was there a significant drop in ee (entry 5).[25] Lowering the reaction temperature to −48 °C decreased the reaction rate and boosted the ee to 93% (entry 6), while raising the temperature to +4 °C (entry 7) increased the yield and had little effect on the ee. Decreasing the reaction time of the boron/zinc transmetalation reaction to 1 h and doubling the amount of vinylzinc reagent were both successful at increasing the yield of the product, but both resulted in lower ee values (entries 8 and 9, respectively).

Changing the solvent to diethyl ether increased the yield but reduced the ee by 4% (entry 10), while the nonpolar solvents hexanes and toluene gave much lower enantioselectivities (entries 11 and 12).[26] Exchanging Et_2Zn for Me_2Zn and using a mixed solvent system of CH_2Cl_2/toluene increased both the yield and ee value by a small margin. However, by using a fresh bottle of Me_2Zn, the yield could be further improved to 80% with a 93% ee (compare entries 2, 13, and 14).[27] The most reproducible results, in terms of both yield and ee, were obtained using 7.5 mol % of the ligand, fresh Me_2Zn as the transmetalating reagent, a mixed solvent system of CH_2Cl_2/toluene (2:1), and a reaction temperature of −20 °C (entry 14). This set of conditions was used in further studies to investigate the scope of the reaction.

It should be noted that vinylzinc reagents do add to benzaldehyde in the absence of a ligand. As a result, there is a nonstereoselective background reaction that competes with the ligand-catalyzed reactions. Ligands that both accelerate the reaction and have high inherent stereoselectivity will give allylic alcohol products with high ee. However, ligands that have low stereoselectivity or ligands that do not significantly accelerate the reaction, even though they are highly stereoselective, will both result in products with low ee.

The data shown in Table 2 demonstrate that the reaction catalyzed by ligand **54** is remarkably tolerant to changes in the structure of the vinylzinc reagent. The reaction can accommodate both branched (entries 1, 2, and 5) and straight chain (entries 3 and 4) substituents on the alkene without a large loss in stereoselectivity.

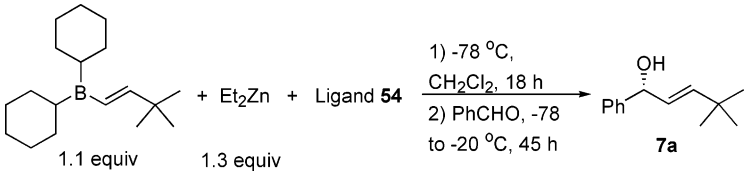
The two reactions with cyclopropyl and *n*-butyl substituents (entries 2 and 4) gave somewhat lower yields of the expected allylic alcohol products when compared to the other reactions. Analysis of the products showed an impurity in each reaction. These impurities were identified as compounds **65** and **66**, which were isolated in 19% and 13% yield, respectively (Figure 3).[28] We

(25) A similar increase in yield with an accompanying decrease in catalyst loading has been reported elsewhere. See ref 6.

(26) Other solvents were explored including CCl_4, $ClCH_2CH_2Cl$, and $Cl_2CHCHCl_2$, but all gave lower enantioselectivities when compared to methylene chloride.

(27) The lower yield when using an older bottle of Me_2Zn was likely caused by a diminished concentration of active Me_2Zn in the bottle. Dahmen and Brase have reported that Me_2Zn gave improved enantioselectivity when compared to Et_2Zn for the addition of the vinylzinc reagent derived from *tert*-butylethyne. See ref 6.

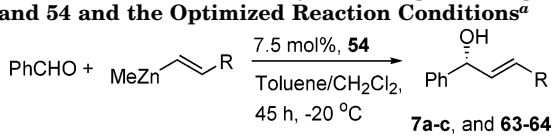
TABLE 1. Optimization of Reaction Conditions Using Purified Ligand 54[a]



entry	ligand (mol %)	temp (°C)	solvent	% yield[b]	% ee[c]
1[d]	10	−20	CH_2Cl_2	45	94
2	7.5	−20	CH_2Cl_2	49	92
3	5.0	−20	CH_2Cl_2	84	92
4[d]	2.5	−20	CH_2Cl_2	67	90
5	1.0	−20	CH_2Cl_2	73	61
6[e]	7.5	−48	CH_2Cl_2	47	93
7[d]	7.5	+4	CH_2Cl_2	56	92
8[f]	7.5	−20	CH_2Cl_2	77	88
9[g]	7.5	−20	CH_2Cl_2	71	91
10	7.5	−20	Et_2O	64	88
11	7.5	−20	hexanes	38	83
12	7.5	−20	toluene	63	77
13[h]	7.5	−20	CH_2Cl_2:toluene (2:1)	54	93
14[h,i]	7.5	−20	CH_2Cl_2:toluene (2:1)	80	93

[a] All experiments performed in duplicate. [b] Isolated yields. [c] Percent ee of (*R*)-allylic alcohols as measured by HPLC (Chiralcel OD-H). [d] Reactions run for 21 h. [e] Reactions run for 74 h. [f] 1 h transmetalation. [g] 2.6 equiv of Et_2Zn and 2.2 equiv of vinylborane reagent. [h] Used 1.3 equiv of Me_2Zn in toluene instead of Et_2Zn. [i] Fresh bottle of Me_2Zn.

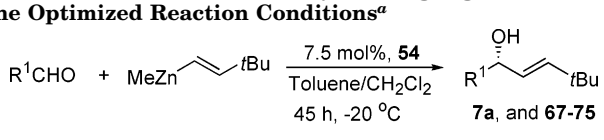
TABLE 2. Variation of Alkenylzinc Reagent Using Ligand 54 and the Optimized Reaction Conditions[a]



entry	allylic alcohol	% yield[b]	% ee[c,d]
1	**7a**: R= *tert*-butyl	80	93
2	**63**: R= cyclopropyl	55	92
3	**7c**: R= *n*-hexyl	63	91
4	**7b**: R= *n*-butyl	53	90
5	**64**: R= cyclohexyl	66	89

[a] All experiments performed in duplicate. [b] Isolated yields. [c] Percent ee of allylic alcohols as measured by HPLC (Chiralcel OD-H). [d] Absolute configuration was assigned as (*R*) by comparison of the optical rotations with the reported values, see refs 3a and 8a.

TABLE 3. Variation of Aldehyde Using Ligand 54 and the Optimized Reaction Conditions[a]



entry	allylic alcohol	% yield[b]	% ee[c]
1	**67**: R^1 = 4-ClPh	86	95
2	**68**: R^1 = 4-BrPh	74	95
3	**69**: R^1 = 4-CH_3CO_2Ph	84	94
4	**7a**: R^1 = Ph	80	93
5	**70**: R^1 = cyclohexyl	56[d]	93[e]
6	**71**: R^1 = 4-CH_3OPh	60	91
7	**72**: R^1 = 2-naphthyl	83	91
8	**73**: R^1 = $PhCH_2CH_2$	62[d]	83
9	**74**: R^1 = *trans*-PhCHCH	67[d]	79
10	**75**: R^1 = 1-naphthyl	72	62

[a] All experiments performed in duplicate. [b] Isolated yields. [c] Percent ee of allylic alcohols as measured by HPLC (Chiralcel OD-H). [d] Reactions run for 57 h. [e] Determined using the corresponding (*R*)-α-methoxy-α-trifluoromethylphenyl ester by ^{19}F NMR spectroscopy.

examined the absolute configuration of allylic alcohol **65**, and found that it was racemic. This result suggests that these products were formed during the reaction or product isolation procedure by an S_N1-like allylic rearrangement process.

To further probe the scope of the reaction, we examined the addition of (*E*)-(3,3-dimethylbut-1-enyl)(methyl)zinc to a variety of different aldehydes (Table 3). Aromatic and α-branched aliphatic aldehydes provided the (*E*)-allylic alcohols in 91−95% ee (entries 1−7). Benzaldehyde substituted with electron-withdrawing groups at the *para* position gave the highest ee values of 94−95% (entries 1−3). Electron-donating substituents such as a methoxy group were also tolerated giving 91% ee (entry 6). 2-Naphthaldehyde gave 91% ee (entry 7), while its isomer 1-naphthaldehyde gave only 62% ee (entry 10). Less sterically demanding aldehydes such as 3-phenylpropanal and *trans*-cinnamaldehyde (entries 8 and 9) gave somewhat lower ee values.

In general, electron-poor aldehydes gave the highest yields of the allylic alcohol product, with yields ranging from 72% to 86% (entries 1−4, 7, and 10). By contrast, less activated aldehydes gave somewhat lower yields (56−67% yield for entries 5, 6, 8, and 9). Overall, the data

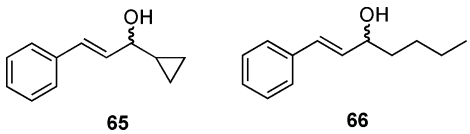


FIGURE 3. Allylic rearrangement products.

(28) (a) Olah, G. A.; Spear R. J. *J. Am. Chem. Soc.* **1975**, *97*, 1546. (b) Minami, T.; Shikita, S.; So, S.; Nakayama, M.; Yamamoto, I. *J. Org. Chem.* **1988**, *53*, 2937.

that are presented in Tables 2 and 3 demonstrate that ligand **54** can accommodate a broad range of structural changes in both the aldehyde and vinylzinc components of the reaction, while providing good yields of the desired products with ee values that are at synthetically useful levels.

Conclusions

We have described the synthesis and evaluation of a 52-membered library of modular dipeptide *N*-acylethylenediamine-based ligands. The ligands were synthesized using a parallel solid-phase strategy, and they were screened, in crude form, for the ability to catalyze the enantioselective addition of vinylzinc reagents to aldehydes. The catalyst structure was optimized using a positional scanning approach. Three rounds of optimization were performed to sequentially identify the best structure for the R^2, R^3, and R^1 positions of the catalyst. This process led us to identify ligand **54** as a highly enantioselective catalyst for the desired transformation. This ligand catalyzes the addition of both branched and linear vinylzinc reagents to benzaldehyde in 89−93% ee, and in up to 80% yield. It also catalyzes the addition of (*E*)-(3,3-dimethylbut-1-enyl)(methyl)zinc to aromatic and α-branched aliphatic aldehydes in 91−95% ee, and up to 86% yield.

We are pursuing these studies in two directions. First, we are examining these ligands as asymmetric catalysts for a variety of other synthetic transformations. Second, we are planning to construct and screen the full 2880-membered library that is represented by the catalysts in this report. These catalysts incorporate 24 possible amino acids side chains at the R^2 and R^3 positions, and 5 possible substituents at the R^1 position. This screening effort will require a high throughput method for measuring the ee of the products,[13] and has the potential to reveal cooperative interactions among the three diversity sites of the catalyst. Such cooperative interactions may have a profound influence on catalyst stereoselectivity.

Experimental Section

General Procedure for the Solid-Phase Synthesis of the Dipeptide Ligands. Variation at R^2: Ligands 6 and 8−30. Oxime resin (0.156 g, 0.140 mmol) was loaded by treating it with a DMF (1.5 mL) solution containing the appropriate *N*-Boc-amino acid (0.420 mmol), HBTU (0.420 mmol), and DIEA (0.12 mL, 0.70 mmol). The reaction mixture was shaken for 23 h at room temperature and subsequently washed with DMF (5 × 3 mL). The above procedure was repeated twice and the resin was washed with CH_2Cl_2 (5 × 3 mL). The resin was treated with a 25% solution of TFA in CH_2Cl_2 (2 mL) and shaken for 2 h at room temperature. The resin was then washed with CH_2Cl_2 (5 × 2 mL), followed by 10% DIEA in CH_2Cl_2 (5 × 2 mL), and DMF (2 × 3 mL). A solution of *N*-Boc-Cys(Tr)-OH (0.200 g, 0.420 mmol), HBTU (0.159 g, 0.420 mmol), and DIEA (0.12 mL, 0.70 mmol) dissolved in DMF (1.5 mL) was added to the resin and the mixture was shaken for 2 h at room temperature. The resin was then washed with DMF (5 × 3 mL) and the coupling procedure was repeated a second time, followed by washes with DMF (5 × 3 mL) and CH_2Cl_2 (7 × 2 mL). The resin was then treated with 2-morpholin-4-ylethylamine (0.055 mL, 0.42 mmol) in CH_2Cl_2 (2 mL) and shaken for 15 h at room temperature. The reaction mixture was filtered and the resin was washed with CH_2Cl_2 (6 × 3 mL). The filtrates were combined, washed twice with H_2O, and dried over Na_2SO_4, and the solvent was removed. The crude ligands were used without further purification. In several cases, residual DMF was removed from the crude ligands via azeotropic distillation with heptane.

General Procedure for the Solid-Phase Synthesis of the Dipeptide Ligands. Variation at R^3: Ligands 31−53. Oxime resin (2.75 g, 2.47 mmol) was loaded by treating it with a DMF (30 mL) solution containing *N*-Boc-Met-OH (1.85 g, 7.42 mmol), HBTU (2.91 g, 7.67 mmol), and DIEA (2.15 mL, 12.4 mmol). The reaction mixture was shaken for 23 h and subsequently washed with DMF (3 × 30 mL). The above procedure was repeated twice and the resin was washed sequentially with DMF (5 × 30 mL), CH_2Cl_2 (5 × 30 mL), and CH_3OH (3 × 30 mL), then dried under vacuum (0.3 mmHg) for 15 h. Using a portion of the dried resin (0.187 g, 0.146 mmol), the *N*-Boc protecting group on Met was removed, and the free amine was coupled with the appropriate *N*-Boc-amino acid (0.438 mmol) using the procedure described above for the synthesis of ligands **8**−**30**. The immobilized dipeptide was then treated with 2-morpholin-4-ylethylamine (0.055 mL, 0.42 mmol) in CH_2Cl_2 (2 mL) and shaken for 15 h at room temperature. The reaction mixture was filtered and the resin was washed with CH_2Cl_2 (6 × 3 mL). The filtrates were combined, washed twice with H_2O, and dried over Na_2SO_4, and the solvent was removed. The crude ligands were used without further purification.

General Procedure for the Solid-Phase Synthesis of the Dipeptide Ligands. Variation at R^1: Ligands 54−59. Oxime resin (0.188 g, 0.169 mmol) was loaded by treating it with a DMF (1.5 mL) solution containing *N*-Boc-Met-OH (0.127 g, 0.508 mmol), HBTU (0.199 g, 0.525 mmol), and DIEA (0.15 mL, 0.84 mmol). The reaction mixture was shaken for 23 h at room temperature and subsequently washed with DMF (5 × 3 mL). The above procedure was repeated twice and the resin was washed with CH_2Cl_2 (5 × 3 mL). The resin was treated with a 25% solution of TFA in CH_2Cl_2 (2 mL) and shaken for 2 h at room temperature. The resin was then washed with CH_2Cl_2 (5 × 2 mL), followed by 10% DIEA in CH_2Cl_2 (5 × 2 mL), and finally DMF (2 × 3 mL). A solution of *N*-Boc-Cys-(Tr)-OH (0.235 g, 0.508 mmol), HBTU (0.199 g, 0.525 mmol), and DIEA (0.15 mL, 0.84 mmol) dissolved in DMF (1.5 mL) was added to the resin and shaken for 3 h at room temperature. The resin was washed with DMF (5 × 3 mL) and the coupling procedure was repeated a second time, followed by washes with DMF (5 × 3 mL) and CH_2Cl_2 (7 × 2 mL). The resin was finally treated with the appropriate diamine (0.51 mmol) in CH_2Cl_2 (2 mL) and shaken for 14 h at room temperature. The reaction mixture was filtered and the resin washed with CH_2Cl_2 (6 × 3 mL). The combined filtrates were washed with H_2O (3 × 5 mL) and brine (1 × 5 mL) and dried over Na_2SO_4, then the solvent was removed. The crude ligands were used without further purification.

Solution-Phase Synthesis of (*S*)-(+)-[1-(2-Diethylaminoethylcarbamoyl)-3-methylsulfanylpropyl]carbamic Acid *tert*-Butyl Ester, Carbamate 61. To *N*-Boc-Met-OH (1.80 g, 7.20 mmol) was added HBTU (8.19 g, 21.6 mmol), DIEA (6.27 mL, 36.0 mmol), and DMF (20 mL). After the mixture was stirred for 5 min, *N*,*N*-diethylethylenediamine (2.02 mL, 14.4 mmol) was added. The reaction mixture was stirred at room temperature for 5 h and then diluted with H_2O. The aqueous phase was extracted with EtOAc (60 mL) and the organic phase was washed with H_2O (5 × 50 mL) and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, the solvent was removed, and the crude product was purified by column chromatography (0.5:4.5:95 30% aqueous NH_4OH/MeOH/CH_2Cl_2) to yield compound **61** as a pale brown viscous oil (1.89 g, 5.43 mmol, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (br s, 1 H), 5.26 (d, J = 7.4 Hz, 1 H), 4.26 (dd, J = 13.7, 6.8 Hz, 1 H), 3.30 (m, 2 H), 2.56 (m, 8 H), 2.11 (s, 3 H), 2.07 (m, 1 H), 1.92 (m, 1 H), 1.44 (s, 9 H), 1.02 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 155.8, 80.3, 53.9, 51.7, 47.1, 37.3, 32.5, 30.6, 28.7, 15.6, 12.1; IR (neat) 3300, 2970, 2921, 2813, 1701, 1656, 1524, 1447, 1388, 1366, 1291, 1248, 1170

cm^{-1}; HRMS-FAB (M + Na$^+$) calcd for $C_{16}H_{33}N_3O_3SNa$ 370.2140, found 370.2136; $[\alpha]^{25}_D$ +2.6 (*c* 2.5, $CHCl_3$).

(*S*)-(−)-2-Amino-*N*-(2-diethylaminoethyl)-4-methylsulfanylbutyramide, Amine 62. Carbamate **61** (1.89 g, 5.43 mmol) was treated with TFA (8.4 mL, 110 mmol) in CH_2Cl_2 (25 mL) at room temperature for 2 h. The excess TFA and solvent was removed by rotary evaporation and the residue was dissolved with EtOAc (75 mL) and washed with half saturated aqueous $NaHCO_3$ (4 mL). The organic layer was dried over Na_2SO_4, the solvent was removed, and the crude product was purified by column chromatography (gradient of 1:9:90 to 2:18:80 30% aqueous NH_4OH/MeOH/CH_2Cl_2) to yield compound **62** as a colorless oil (1.18 g, 4.78 mmol, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (br s, 1 H), 3.49 (dd, J = 8.2, 4.7 Hz, 1 H), 3.33 (m, 2 H), 2.60 (m, 8 H), 2.14 (m, 1 H), 2.11 (s, 3 H), 1.83 (br s, 2 H), 1.81 (m, 2 H), 1.05 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 54.7, 52.2, 47.4, 37.1, 34.6, 31.1, 15.7, 12.0; IR (neat) 3302, 2967, 2915, 2812, 1650, 1518 cm^{-1}; HRMS-FAB (M + H$^+$) calcd for $C_{11}H_{26}N_3OS$ 248.1797, found 248.1794; $[\alpha]^{24}_D$ −12 (*c* 1.5, $CHCl_3$).

(−)-{1-[1-(2-Diethylaminoethylcarbamoyl)-3-methylsulfanyl-(*S*)-1-propylcarbamoyl]-2-tritylsulfanyl-(*R*)-1-ethyl}carbamic Acid *tert*-Butyl Ester, Ligand 54. To *N*-Boc-Cys(Tr)-OH (4.43 g, 9.55 mmol) was added HBTU (3.80 g, 10.0 mmol), amine **62** (1.18 g, 4.78 mmol), DMF (27 mL), and DIEA (2.50 mL, 14.3 mmol). The reaction mixture was stirred at room temperature for 2 h and then diluted with H_2O (50 mL). The aqueous phase was extracted with EtOAc (70 mL) and the organic phase was washed with H_2O (2 × 50 mL) and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, the solvent was removed, and the crude product was purified by column chromatography (gradient of 0.4:3.6:96 to 1:9:90 30% aqueous NH_4OH/MeOH/CH_2Cl_2) to yield compound **54** as a white solid (1.81 g, 2.62 mmol, 55%): mp 109−111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 6 H), 7.34−7.22 (m, 9 H), 7.02 (br s, 2 H), 4.79 (d, J = 5.5 Hz, 1 H), 4.47 (dd, J = 12.9, 7.5 Hz, 1 H), 3.83 (dd, J = 11.6, 6.1 Hz, 1 H), 3.36 (br s, 2 H), 2.75 (br s, 6 H), 2.53 (m, 2 H), 2.12 (m, 1 H), 2.07 (s, 3 H), 2.00 (m, 1 H), 1.44 (s, 9 H), 1.11 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 171.0, 155.9, 144.2, 129.5, 128.2, 127.0, 80.9, 67.3, 54.1, 53.0, 52.2, 47.1, 36.5, 33.2, 30.3, 30.1, 28.2, 15.1, 10.8; IR (film) 3290, 3057, 2973, 2929, 1713, 1676, 1640, 1515, 1492, 1444, 1367, 1246, 1167, 845, 744, 701 cm^{-1}; HRMS-FAB (M + H$^+$) calcd for $C_{38}H_{53}N_4O_4S_2$ 693.3508, found 693.3495; $[\alpha]^{24}_D$ −4.5 (*c* 0.99, $CHCl_3$).

(−)-[1-(2-Morpholin-4-ylethylcarbamoyl)-2-(3-benzyloxymethyl-3*H*-imidazol-4-yl)-(*S*)-1-ethyl]carbamic Acid *tert*-Butyl Ester, Carbamate 76. To *N*-Boc-His(Bom)-OH (0.309 g, 0.824 mmol) was added HBTU (0.938 g, 2.47 mmol), DIEA (0.72 mL, 4.1 mmol), and DMF (5 mL). After the mixture was stirred for 5 min, 2-morpholin-4-ylethylamine (0.22 mL, 1.7 mmol) was added. The reaction was stirred at room temperature for 3 h, then diluted with 50 mL of H_2O. The aqueous phase was extracted with EtOAc (75 mL), and the organic phase was washed with H_2O (2 × 50 mL) and 25 mL of brine. The organic layer was dried over Na_2SO_4, the solvent was removed, and the crude product was purified by column chromatography (gradient of 0.2:1.8:98 to 0.7:6.3:93 30% aqueous NH_4OH/MeOH/CH_2Cl_2) to yield compound **76** as a colorless oil (0.215 g, 0.441 mmol, 54%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 7.37 (m, 5 H), 6.90 (s, 1 H), 6.40 (br s, 1 H), 5.36 (m, 3 H), 4.56 (m, 2 H), 4.40 (dd, J = 14.5, 7.1 Hz, 1 H), 3.64 (t, J = 4.6 Hz, 4 H), 3.26 (m, 2 H), 3.09 (m, 2 H), 2.35 (m, 6 H), 1.45 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 155.7, 138.8, 136.4, 129.8, 129.2, 128.8, 128.6, 127.6, 80.6, 77.6, 73.5, 70.5, 67.3, 57.0, 54.3, 53.6, 36.0, 28.7, 27.7; IR (neat) 3302, 2969, 2929, 2860, 2808, 1708, 1669, 1519, 1498, 1453, 1366, 1250, 1168, 1117 cm^{-1}; HRMS-FAB (M + H$^+$) calcd for $C_{25}H_{37}N_5O_5Na$ 510.2692, found 510.2680; $[\alpha]^{24}_D$ −7.5 (*c* 1.1, $CHCl_3$).

(*R*)-(−)-1((*S*)-3-(1-(benzyloxymethyl)-1*H*-imidazol-5-yl)-1-(2-morpholinoethylamino)-1-oxopropan-2-ylamino)-1-oxo-3-(tritylthio)propan-2-ylcarbamic Acid *tert*-Butyl Ester, Ligand 16. Carbamate **76** (0.215 g, 0.441 mmol) was treated with TFA (0.68 mL, 8.8 mmol) in CH_2Cl_2 (5 mL) at room temperature for 2 h. The excess TFA was removed by rotary evaporation and the residue was dissolved in EtOAc (100 mL) and washed with half saturated aqueous $NaHCO_3$ (10 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed to yield the crude amine (0.112 g, 0.289 mmol, 66%). To the crude amine (0.112 g, 0.289 mmol) was added *N*-Boc-Cys(Tr)-OH (0.268 g, 0.579 mmol), HBTU (0.329 g, 0.868 mmol), and enough DMF to dissolve all the solids. After the solution was stirred for 5 min, DIEA (0.25 mL, 1.5 mmol) was added. The reaction was stirred at room temperature for 3 h, then diluted with 50 mL of H_2O. The aqueous phase was extracted with EtOAc (75 mL), and the organic phase was washed with H_2O (2 × 50 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, the solvent was removed, and the crude product was purified by column chromatography (0.7:6.3:93 30% aqueous NH_4OH/MeOH/CH_2Cl_2) to yield compound **16** as a yellow solid (0.161 g, 0.193 mmol, 67%): mp 79−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 7 H), 7.30 (m, 9 H), 7.22 (m, 3 H), 6.84 (s, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 6.40 (br s, 1 H), 5.34 (m, 2 H), 4.78 (d, J = 6.5 Hz, 1 H), 4.65 (m, 1 H), 4.54 (m, 2 H), 3.81 (br d, J = 4.9 Hz, 1 H), 3.61 (t, J = 4.5 Hz, 4 H), 3.25 (m, 1 H), 3.16 (m, 2 H), 3.02 (dd, J = 15.2, 8.1 Hz, 1 H), 2.74 (dd, J = 12.6, 6.6 Hz, 1 H), 2.59 (dd, J = 12.9, 5.2 Hz, 1 H), 2.29 (m, 6 H), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.9, 155.8, 144.6, 138.9, 136.5, 129.9, 129.7, 129.1, 128.8, 128.6, 127.43, 127.37, 81.0, 77.7, 73.5, 70.5, 67.7, 67.2, 57.1, 54.1, 53.6, 52.7, 36.2, 34.0, 28.6, 27.1; IR (film) 3292, 2974, 2931, 2860, 2814, 1706, 1658, 1494, 1445, 1366, 1248, 1166, 1116, 746, 700 cm^{-1}; HRMS-FAB (M + Na$^+$) calcd for $C_{47}H_{56}N_6O_6SNa$ 855.3880, found 855.3895; $[\alpha]^{24}_D$ −5.6 (*c* 2.0, $CHCl_3$).

Optimized Conditions for Alkenylzinc Addition to Aldehydes. A flame-dried vial was cooled to 0 °C and BH_3−DMS (0.31 mL, 3.3 mmol) in CH_2Cl_2 (3 mL) was added, followed by cyclohexene (0.67 mL, 6.6 mmol). This solution was stirred at 0 °C for 2 h and appeared as a white cloudy solution. Next, the alkyne (1.2 equiv, 3.6 mmol) was added and the reaction was warmed to room temperature for 30 min yielding a clear stock solution of vinylborane. Ligand **54** (13 mg, 0.019 mmol) was combined with 2.0 M Me_2Zn (0.16 mL, 0.32 mmol) in toluene at room temperature for 5 min, then cooled to −78 °C, and the vinylborane stock solution was added (approximately 0.37 mL or 1/12 the stock solution volume depending on the alkyne used). After the reaction was stirred for 18 h at −78 °C, the appropriate aldehyde (0.25 mmol) was added and the reaction was surrounded with dry ice and placed in a −20 °C freezer for 48 h. The reaction was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. The organic layer was washed with aqueous 1 N HCl (1 × 5 mL) and saturated aqueous $NaHCO_3$ (1 × 5 mL). The solvent was removed and the product was purified by column chromatography (8:92 EtOAc:hexanes).

(*R*,*E*)-(−)-1-(4-Chlorophenyl)-4,4-dimethylpent-2-en-1-ol, Allylic Alcohol 67. 95% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes at 1.0 mL/min and detection at 219 nm), t_R = 61.4 min for (*R*) and t_R = 75.6 min for (*S*); $[\alpha]^{25}_D$ −56 (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (br s, 4 H), 5.78 (dd, J = 15.6, 0.6 Hz, 1 H), 5.50 (dd, J = 15.6, 7.0 Hz, 1 H), 5.12 (d, J = 7.0 Hz, 1 H), 1.89 (br s, 1 H), 1.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 142.3, 133.5, 128.9, 127.9, 127.3, 75.1, 33.3, 29.8; HRMS-EI (M$^+$) calcd for $C_{13}H_{17}ClO$ 224.0968, found 224.0979.

(*R*,*E*)-(−)-1-(4-Bromophenyl)-4,4-dimethylpent-2-en-1-ol, Allylic Alcohol 68. 95% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes at 1.0 mL/min and detection at 219 nm), t_R = 67.1 min for (*R*) and t_R = 98.5 min for (*S*); $[\alpha]^{25}_D$ −57 (*c* 2.2, $CHCl_3$); mp 45−46 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 2 H), 5.80 (dd, J = 15.5, 0.8 Hz, 1 H), 5.52 (dd, J = 15.6, 6.9 Hz, 1

H), 5.12 (d, J = 6.8 Hz, 1 H), 2.03 (s, 1 H), 1.04 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 142.4, 131.5, 127.9, 126.9, 121.2, 74.8, 32.9, 29.4; HRMS-FAB (M + H^+) calcd for $C_{13}H_{18}$BrO 269.0541, found 269.0535.

(*R*,*E*)-(−)-Methyl-4-(1-hydroxy-4,4-dimethylpent-2-enyl)-benzoate, Allylic Alcohol 69. 94% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (95:5) at 1.0 mL/min and detection at 219 nm), t_R = 13.1 min for (*S*) and t_R = 14.9 min for (*R*); $[\alpha]^{25}_D$ −67 (*c* 2.6, $CHCl_3$); mp 52−53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.3 Hz, 2 H), 7.41 (d, J = 8.0 Hz, 2 H), 5.78 (dd, J = 15.4, 0.6 Hz, 1 H), 5.50 (dd, J = 15.6, 7.2 Hz, 1 H), 5.18 (d, J = 6.4 Hz, 1 H), 3.88 (s, 3 H), 2.28 (d, J = 2.4 Hz, 1 H), 1.00 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 148.7, 144.5, 129.9, 129.2, 126.9, 126.2, 75.2, 52.2, 33.1, 29.5; HRMS-FAB (M + Na^+) calcd for $C_{15}H_{20}O_3Na$ 271.1310, found 271.1302.

(*S*,*E*)-(+)-1-Cyclohexyl-4,4-dimethylpent-2-en-1-ol, Allylic Alcohol 70. 93% ee by ^{19}F NMR analysis of the (*R*)-MTPA ester; $[\alpha]^{24}_D$ +3.8 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (d, J = 15.7 Hz, 1 H), 5.37 (dd, J = 15.7, 7.5 Hz, 1 H), 3.78 (t, J = 7.0 Hz, 1 H), 1.88 (m, 1 H), 1.75 (m, 2 H), 1.66 (m, 2 H), 1.37 (m, 1 H), 1.28−1.07 (m, 4 H), 1.03 (s, 9 H), 0.93 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 126.5, 78.4, 44.2, 33.3, 30.0, 29.24, 29.16, 27.0, 26.6, 26.5; HRMS-FAB (M + Na^+) calcd for $C_{13}H_{24}ONa$ 219.1725, found 219.1730.

(*R*,*E*)-(−)-1-(4-Methoxyphenyl)-4,4-dimethylpent-2-en-1-ol, Allylic Alcohol 71. 91% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detection at 219 nm), t_R = 24.6 min for (*R*) and t_R = 31.4 min for (*S*); $[\alpha]^{25}_D$ −21 (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, J = 6.7, 2.0 Hz, 2 H), 6.91 (dd, J = 6.7, 2.1 Hz, 2 H), 5.80 (dd, J = 15.6, 0.9 Hz, 1 H), 5.58 (dd, J = 15.6, 6.7 Hz, 1 H), 5.14 (d, J = 6.6 Hz, 1 H), 3.82 (s, 3H), 1.88 (br s, 1 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 143.5, 136.2, 127.9, 127.6, 114.2, 75.3, 55.7, 33.3, 29.9; HRMS-FAB (M + Na^+) calcd for $C_{14}H_{20}O_2Na$ 243.1361, found 243.1368.

(*R*,*E*)-(−)-4,4-Dimethyl-1-naphthalen-2-ylpent-2-en-1-ol, Allylic Alcohol 72. 91% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99.5:0.5) at 1.0 mL/min and detection at 219 nm), t_R = 68.7 min for (*R*) and t_R = 75.2 min for (*S*); $[\alpha]^{25}_D$ −52 (*c* 1.0, $CHCl_3$); mp 77−79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (m, 4 H), 7.49 (m, 3H), 5.88 (dd, J = 15.6, 0.7 Hz, 1 H), 5.66 (dd, J = 15.6, 6.8 Hz, 1 H), 5.35 (d, J = 6.8 Hz, 1 H), 2.01 (br s, 1 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 141.3, 133.8, 133.3, 128.6, 128.4, 128.1, 127.5, 126.5, 126.2, 125.0, 75.9, 33.4, 29.9; HRMS-EI (M^+) calcd for $C_{17}H_{20}O$ 240.1514, found 240.1510.

(*S*,*E*)-(−)-6,6-Dimethyl-1-phenylhept-4-en-3-ol, Allylic Alcohol 73. 81% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detection at 219 nm), t_R = 22.7 min for (*S*) and t_R = 44.6 min for (*R*); $[\alpha]^{24}_D$ −7.5 (*c* 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 2 H), 7.20 (m, 3 H), 5.70 (dd, J = 15.7, 0.7 Hz, 1 H), 5.42 (dd, J = 15.7, 7.0 Hz, 1 H), 4.10 (dt, J = 6.8, 6.6 Hz, 1 H), 2.71 (m, 2H), 1.88 (m, 2 H), 1.58 (br s, 1 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 142.4, 128.9, 128.8, 127.9, 126.2, 73.1, 39.3, 33.2, 32.2, 29.9; HRMS-FAB (M + Na^+) calcd for $C_{15}H_{22}ONa$ 241.1568, found 241.1569.

(*S*,1*E*,4*E*)-(+)-6,6-Dimethyl-1-phenylhepta-1,4-dien-3-ol, Allylic Alcohol 74. 80% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (90:10) at 1.0 mL/min and detection at 219 nm), t_R = 6.9 min for (*S*) and t_R = 11.0 min for (*R*); $[\alpha]^{24}_D$ +1.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 2 H), 7.36 (m, 2H) 7.25 (m, 1 H), 6.61 (d, J = 15.9 Hz, 1 H), 6.27 (dd, J = 15.9, 6.3 Hz, 1 H), 5.79 (dd, J = 15.7, 0.9 Hz, 1 H), 5.51 (dd, J = 15.7, 6.7 Hz, 1 H), 4.79 (m, 1 H), 1.69 (d, J = 3.5 Hz, 1 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 137.2, 131.7, 130.5, 129.0, 128.1, 126.9, 126.4, 74.3, 33.4, 29.9; HRMS-EI (M^+) calcd for $C_{15}H_{20}O$ 216.1514, found 216.1520.

(*R*,*E*)-(+)-4,4-Dimethyl-1-naphthalen-1-ylpent-2-en-1-ol, Allylic Alcohol 75. 64% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detection at 219 nm), t_R = 27.7 min for (*S*) and t_R = 43.9 min for (*R*); $[\alpha]^{26}_D$ +23 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 1H), 7.90 (m, 1 H), 7.82 (d, J = 8.3 Hz, 1 H), 7.67 (d, J = 7.0 Hz, 1H), 7.52 (m, 3H), 5.95 (dd, J = 15.7, 0.7 Hz, 1 H), 5.91 (d, J = 6.0 Hz, 1 H), 5.77 (dd, J = 15.7, 6.2 Hz, 1 H), 2.04 (br s, 1 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 139.3, 134.3, 131.1, 129.1, 128.7, 126.9, 126.3, 126.0, 125.8, 124.3, 123.9, 72.8, 33.4, 29.8; HRMS-FAB (M + Na^+) calcd for $C_{17}H_{20}ONa$ 263.1412, found 263.1406.

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Supporting Information Available: Full experimental details; ^{1}H and ^{13}C NMR spectra for all new compounds; HPLC column conditions/retention times for all allylic alcohol products; yields for all ligands synthesized by the solid phase; tabular listings of ligand screening results. This material is available free of charge via the Internet at http://pubs.acs.org.

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