Catalytic Intramolecular Hydroamination of Substituted Aminoallenes by Chiral Titanium Amino-Alcohol Complexes

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Intramolecular hydroamination of aminoallenes is catalyzed by titanium complexes with a number of chiral amino alcohols. The ring-closing reaction of hepta-4,5-dienylamine at 110 °C with 5 mol % catalyst gives a mixture of 6-ethyl-2,3,4,5-tetrahydropyridine (14−33%) and both *Z*- and *E*-2-propenylpyrrolidine (67−86%). However, the ring-closing reaction of 6-methylhepta-4,5-dienylamine at 135 °C with 5 mol % catalyst gives exclusively 2-(2-methylpropenyl)pyrrolidine. The pyrrolidine products are obtained with enantiomeric excesses up to 16%.

Introduction

The organometallic chemistry of the early transition metals is dominated by complexes containing the cyclopentadienyl group (Cp) and its derivatives.[1] There is a growing interest in alternative ligands, such as amides,[2] alkoxides,[3] aryloxides,[4] sulfonamides,[5] and amidinates,[6] since the dramatically different steric and electronic environments they provide can result in novel reactivity of the resulting complexes.[7] Amide or mixed amide-alkoxide ligands show increased coordinative unsaturation relative to Cp complexes since both ligand types occupy only a single coordination site at the metal per donor atom. These ligands also provide highly tunable electronic and steric environments to a reactive metal center.

The hydroamination reaction (direct addition of an N−H bond across a C−C multiple bond) is one reaction that demonstrates how the development and study of new ligands can lead to better catalyst performance. This reaction is currently under wide investigation, as it is a highly atom economical method of synthesizing substituted amines. The hydroamination of alkenes and alkynes has been the subject of several comprehensive reviews,[8,9] including a review of enantioselective catalytic hydroamination of alkenes.[10]

The intermolecular hydroamination of alkynes and allenes has been carefully investigated by Bergman. Both stoichiometric and catalytic variants were initially examined with zirconocene bisamides.[11] Titanocene imido complexes react with alkenes or alkynes undergoing a reversible [2+2] cycloaddition to form the corresponding azametallacyclobutane or -butene.[12] This chemistry was used in a selective kinetic resolution of chiral allenes by a C_2-symmetric zirconium ethylene-bis-tetrahydroindenyl complex.[13] More recent evidence shows that the active catalyst undergoes a Cp/amide ligand exchange process;[14] theoretical calculations support the experimentally determined mechanism.[15] Other researchers have reported the use of titanocene,[16] organolanthanide,[17] and organoactinide[18] complexes as catalysts for the intermolecular hydroamination of alkynes. The f-block organometallic complexes have a

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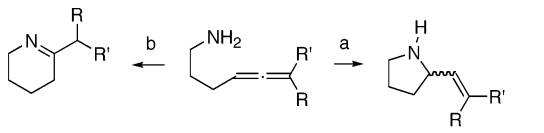
smiliar proposed mechanism to the group(IV) metals, proceeding through a four-centered transition state. In contrast, late metal-catalyzed hydroamination involves activation of the amine group by the metal to form a hydrido-amido complex with subsequent reactions taking place at either the M−H or M−N bond.[9,19] Recently, early metal complexes of a number of new ligands have been investigated including aryloxides,[20] amides,[21] pyrrolyl ligands,[22] guanidinates,[23] and imidos.[24]

The intramolecular hydroamination of aminoalkynes has also been catalyzed by titanium imido complexes prepared in situ from $CpTiCl_3$, $CpTiCl(NR_2)_2$, or $CpTiCl(CH_3)_2$. The reactions were used in the synthesis of a variety of natural products.[25] More recently, catalysts derived from $(CH_3)_2TiCl_2$(DME) have been described.[26] Other ligands that have been used for intramolecular hydroamination with early transition metals include sulfonamides,[27,28] amidates,[29] diketiminatos,[30] and amides.[31] Organolanthanide complexes catalyze this reaction as well.[32]

Chiral yttrium complexes with binaphtholate ligands catalyze the intramolecular hydroamination of aminoalkenes and can be used for the kinetic resolution of these substrates,[33] while chiral zirconium cationic complexes with aminophenol ligands catalyze the intramolecular hydroamination of alkenes with the highest ee yet reported (82%) for this reaction type.[34] Chiral lanthanide complexes with salicylaldimine[35] and binaphthyl diamine[36] ligands have recently been reported to catalyze the intramolecular hydroamination of alkenes. The enantiomeric excesses of these transformations range up to 61% for the salicylaldimine and 53% for the diamine.

Scheme 1



2a, R = R' = H **1a**, R = R' = H **3a**, R = R' = H
2b, R = CH_3, R' = H **1b**, R = CH_3, R' = H **3b**, R = CH_3, R' = H
2c, R = R' = CH_3 **1c**, R = R' = CH_3 **3c**, R = R' = CH_3

The intramolecular hydroamination of allenes is intermediate in difficulty between the reaction of alkynes and alkenes,[14] but has been the focus of less attention than the other reactions. The catalysis by silver, mercury, and palladium was described more than 20 years ago,[37] the catalysis by organolanthanide complexes has been studied at length by Marks and co-workers,[38,39] and Bergman recently investigated amide- and sulfonamide-derived catalysts for the intramolecular hydroamination of alkynes and allenes.[27,28]

The intramolecular reaction of substituted hexa-4,5-dienylamines (**1a**−**1c**) can proceed by one of two pathways (Scheme 1) to give either the achiral tetrahydropyridine (**2a**−**2c**) or the chiral α-vinylpyrrolidine (**3a**−**3c**). Late metal catalysts (Ag, Hg, Pd)[37] give exclusively pyrrolidine **3** via pathway a, while lanthanide catalysts can be tuned to give a mixture of products but convert 1,3-disubstituted aminoallenes (R = alkyl, R′ = H) exclusively to the pyrrolidine.[38,39] Titanium amides (such as $Ti(NMe_2)_4$ or titanium sulfonamides) give almost exclusively the cyclic imine product, with less than 10% of **3**. The corresponding zirconium sulfonamides favor the formation of the pyrrolidine product with regioselectivities that depend on the substitution of the allene: when R = Et and R′ = H, a 4:1 product distribution favoring **3** is observed, but when R = Et and R′ = Me (a trisubstituted aminoallene), **3** is favored by 11:1.[27,28] The proposed mechanistic step crucial for determining the product distribution is the [2+2] cycloaddition reaction to form an azametallacyclobutane from a metal imido species (Scheme 2).[27,28]

We have been developing the chemistry of a family of readily prepared N-,O-donor ligands shown in Chart

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Scheme 2

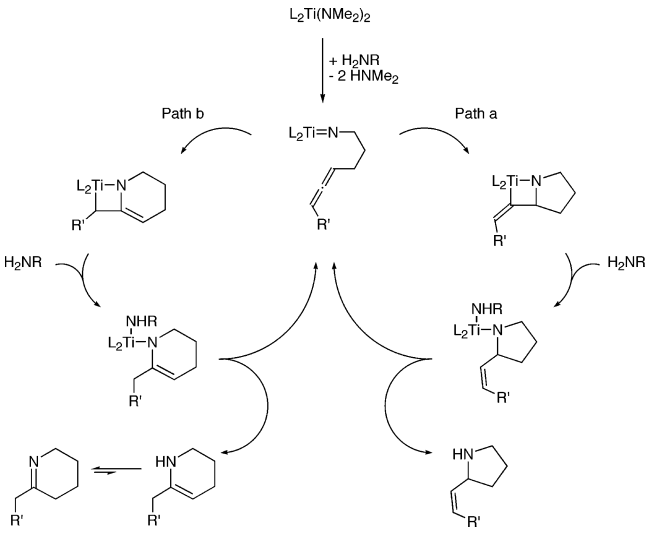
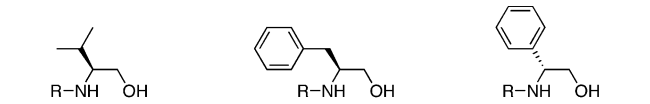


Chart 1. Ligands Used in This Study (^{i}Pr = CH(CH$_3$)$_2$, 2-Ad = 2-adamantyl)



L-H_2ValPrO, R = ^{i}Pr
L-H_2ValCyO, R = c-C_6H_{11}
L-H_2ValAdO, R = 2-Ad

L-H_2PhePrO, R = ^{i}Pr
L-H_2PheCyO, R = c-C_6H_{11}
L-H_2PheAdO, R = 2-Ad

D-H_2PhgPrO, R = ^{i}Pr
D-H_2PhgCyO, R = c-C_6H_{11}
D-H_2PhgAdO, R = 2-Ad

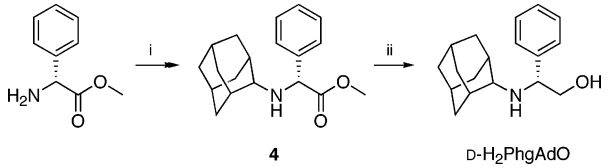
1. These ligands are prepared in a few steps from the chiral amino acids valine (Val), phenylalanine (Phe), and phenylglycine (Phg).[40] We have found that amino acids are ideal precursors since a large body of literature exists on selective protection/deprotection strategies for the amino acids,[41,42] allowing them to be readily modified in a few well-precedented steps. The steric properties of the ligands are readily modified by changing either N-alkyl or side chain alkyl groups, and the synthesis of titanium complexes with these π-donor ligands is a straightforward extension of known pathways. Although others have prepared well-defined chiral amido-alkoxide complexes with titanium,[5] the procedures we have developed are highly modular and general in scope, allowing wide flexibility in sterics and electronics for future ligands.

We originally set out to synthesize titanium complexes with these ligands for use in stoichiometric transformations, but discovered that they were competent catalysts for the intramolecular hydroamination of aminoallene **1a**. We envisioned these catalysts could be used in the asymmetric catalytic hydroamination of di- and tridisubstituted aminoallenes **1b** and **1c** and therefore initiated a study to investigate this reaction in more detail.

Results and Discussion

The ligands used in this study (Chart 1) were prepared in a two-step procedure from the methyl (or ethyl) esters of the respective amino acids, as illustrated for

Scheme 3[a]



4 D-H_2PhgAdO

[a] Reagents and conditions: (i) adamantanone/NaBH(OAc)$_3$, (ii) LiAlH$_4$.

D-H_2PhgAdO (Scheme 3). First, the *N*-alkyl group was added to the methyl ester of phenylglycine by reductive amination of the corresponding ketone with NaBH(OAc)$_3$ to give **4**.[43] Second, the ester was reduced to the alcohol with LiAlH$_4$ to generate the desired ligand.[40]

The three valine and phenylalanine ligands shown in Chart 1 have the opposite absolute configuration than the three phenylglycine-derived ligands shown. The synthesis of the opposite enantiomers of the two largest ligands (L-H_2PhgAdO and D-H_2PheAdO) was also completed.

The enantiomeric purity of the ligands was determined by NMR contact shift experiments.[44] The addition of 1 and 2 equivalents of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol to the appropriate valine- and phenylalanine-derived ligands resulted in clear shifting of about 0.1 ppm per equivalent of the proton NMR resonances of the ligand hydrogens due to the formation of transient diastereomeric complexes. No splitting of the resonances into two sets of peaks was observed, indicating that the ligands were enantiomerically pure. However, it is possible that the splitting of the peaks was too small to be resolved. Therefore, a 1:1 mixture of D- and L-enantiomers of the H_2PheAdO and H_2ValCyO was examined by the same technique. Clear splitting of the peaks was observed, indicating that the original samples were in fact enantiomerically pure.

When the pure phenylglycine-derived ligands were examined by this technique, splitting of the peaks was observed, indicating partial racemization during their synthesis. The D-enantiomers of H_2PhgPrO, H_2PhgCyO, and H_2PhgAdO were obtained in enantioenriched form, with enantiomeric excesses of up to 64, 65, and 82% respectively, while L-H_2PhgAdO was obtained in optically pure form. The degree of racemization is not reproducible but presumably occurs during the harsh LiAlH$_4$ reduction conditions during the second step of the synthesis. The phenylglycine-derived methyl esters have a potentially reactive benzylic hydrogen that may be abstracted during the reaction (Scheme 3, compound **4**). Treating the pure L-H_2PhgAdO with LiAlH$_4$ in THF for several days did not result in racemization. Attempts to examine the optical purity of the esters by the chiral shift NMR technique gave very small contact shifts. Additional experiments are underway in order to optimize the optical purity of the phenylglycine-derived ligands.

An initial screening of the catalytic activity was carried out with the unsubstituted aminoallene hexa-4,5-dienylamine (Scheme 1, compound **1a**). Addition of

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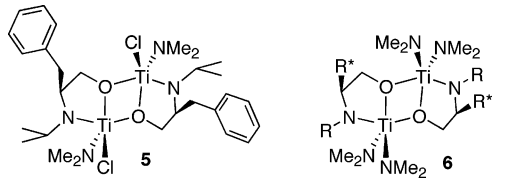
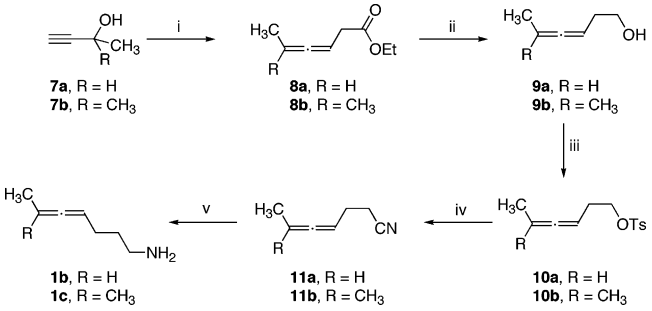
Chart 2. Structures of Reported (5) and Proposed (6) Titanium Complexes



Scheme 4[a]



[a] Reagents and conditions: (i) triethylorthoacetate/Me_3CCO_2H, (ii) $LiAlH_4$, (iii) TsCl/pyridine, (iv) NaCN/DMSO, (v) $LiAlH_4$.

1 equiv of H_2PhePrO to $TiCl(NMe_2)_3$ gives the dimeric complex $[TiCl(NMe_2)(PhePrO)]_2$ (Chart 2, compound **5**).[40] Addition of 10 mol % of this to a solution of the allene gave exclusively the previously reported[38] tetrahydropyridine product via pathway b within 2 h at 75 °C. Encouraged by the initial results, we prepared the methyl- and dimethyl-substituted aminoallenes **1b** and **1c** in order to investigate the ability of the ligand set to produce the pyrrolidine product and to determine whether the reaction was enantioselective.

The allene substrates were prepared by a modification of the original procedures (Scheme 4).[28,45] The propargylic alcohol **7** (3-butyne-2-ol or 2-methyl-3-butyne-2-ol) was converted to the allene ethyl ester **8** by an ortho ester Claisen rearrangement. The ester was reduced with $LiAlH_4$, and the resulting alcohol **9** was converted to the tosylate **10**. Substitution with a cyanide group followed by another reduction step afforded either hepta-4,5-dienylamine **1b** or 6-methylhepta-4,5-dienylamine **1c**. The proton NMR spectra of the aminoallene products were identical to those originally reported.[38,46]

We prepared titanium precatalyst complexes in situ by mixing stock solutions of the desired ligand (ca. 0.06 M) with stock solutions of $Ti(NMe_2)_4$ (ca. 0.09 M) in benzene-d_6. Although we have been unable to isolate these precatalysts in pure form due to their high solubility and oily nature, we believe them to have a similar dimeric structure to our previously reported complexes on the basis of their similar NMR spectra (Chart 2). The catalytic reaction was initiated by adding a stock solution of the appropriate aminoallene (ca. 1.5 M). To rule out catalysis by particulate matter from the molecular sieves, a control experiment was carried out without $Ti(NMe_2)_4$ or the ligand; no conversion to product was observed under catalysis conditions.

Scheme 5

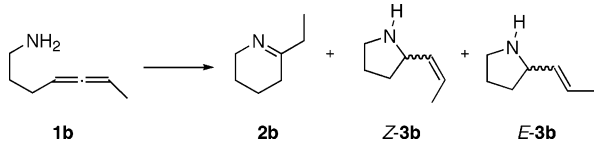


Table 1. Hydroamination of Hepta-4,5-dienylamine 1b at 110 °C with in Situ Catalysts (5 mol % catalyst)

			yield (%)[a]				
entry	ligand	*t*/h	**2b**	*Z*-**3b**	ee[b]	*E*-**3b**	ee[b]
1	L-H_2ValPrO	48	20	41	1	39	4
2	L-H_2ValCyO	91	19	41	0	41	5
3	L-H_2ValAdO	94	24	40	0	36	5
4	L-H_2PhePrO	22	33	34	6	33	4
5	L-H_2PheCyO	22	32	33	8	35	5
6	L-H_2PheAdO	43	22	42	7	36	16
7	D-H_2PheAdO	22	23	42	10[c]	35	13[c]
8	D-H_2PhgPrO	24	20	50	2	30	4
9	D-H_2PhgCyO	24	20	48	0	32	4
10	D-H_2PhgAdO	22	14	53	5[c]	33	8[c]
11	L-H_2PhgAdO	22	18	51	11	31	15
12	none	134[d]	22	47	0	31	0

[a] Relative amount of imine:5-exo determined by NMR, ±2%. [b] Of the benzamide derivative, determined by GC, ±2%. [c] Enantiomer with lower R_f favored. [d] Ca. 95% conversion.

The catalytic hydroamination of hepta-4,5-dienylamine **1b** with various titanium catalysts was carried out in benzene-d_6 in high-pressure NMR tubes (J. Young tubes) at 110 °C with 5 mol % catalyst. The reaction was monitored periodically by NMR spectroscopy and was found to be complete after a period of approximately 24 h (Scheme 5). The reaction was sluggish at 75 °C, taking several days to reach 95% completion, but gave an almost identical product distribution.[47] All three possible products were observed by NMR spectroscopy. The *Z*- and *E*-5-exo pyrrolidine products **3b** were favored over imine **2b** with regioselectivities ranging from 2:1 to 4:1 (Table 1). The product ratios were determined by comparison with known spectra.[38] These results are comparable with the results obtained from zirconium sulfonamide catalysts with the ethyl-substituted allene (Scheme 1, R = Et, R′ = H), while related titanium sulfonamide catalysts favor the formation of the imine.[28] The *Z*/*E* ratio for the 5-exo product is relatively low, ranging from 1:1 to 1.5:1. While the small valine-derived ligands (entries 1−3) give a 1:1 ratio, the most sterically encumbered phenylglycine ligands (entries 8−11) give ratios on the order of 1.5:1. Zirconium sulfonamide catalysts with related substrates give ratios on the order of 20:1,[28] while organolanthanide catalysts give a 7:1 ratio for the same substrate.[38] $Ti(NMe_2)_4$ was found to be a significantly slower catalyst for this reaction (entry 12), requiring 134 h to reach 95% conversion.

The enantiomeric excess (ee) of each of the two 5-exo products was determined by making the corresponding benzamide derivatives and separating by GC on a chiral stationary phase (Chiraldex B-DM).[47] The adamantyl-substituted ligands (entries 3, 6, 7, 10, and 11) give the highest ee values of up to 16%. The catalysts derived from the D-enantiomers of the ligands (entries 7−10) show a selectivity for the opposite enantiomer for both

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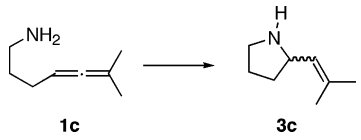
(47) Additional information about the catalytic reactions carried out at 75 °C is in the Supporting Information.

Scheme 6



1c **3c**

Table 2. Hydroamination of 6-Methylhepta-4,5-dienylamine 1c at 135 °C with in Situ Catalysts (5 mol % catalyst)

entry	ligand	*t*/h	ee[a]
1	L-H_2ValPrO	18	4
2	L-H_2ValCyO	18	4
3	L-H_2ValAdO	17	5
4	L-H_2PhePrO	16	2
5	L-H_2PheCyO	16	6
6	L-H_2PheAdO	20	15
7	D-H_2PheAdO	22	3[b]
8	D-H_2PhgPrO	17	3
9	D-H_2PhgCyO	15	4
10	D-H_2PhgAdO	15	10[b]
11	L-H_2PhgAdO	22	12
12	none	67[c]	0

[a] Of the benzamide derivative, determined by GC, ±2%. [b] Enantiomer with lower R_f favored. [c] Only ca. 95% conversion.

Z and *E* products. While modest, the ee values correlate with the sterics of the ligand and are higher for the *E* than the *Z* isomer. These results can be rationalized using a steric argument. Since the methyl group should be closer to the metal center during the formation of the *E* isomer (Scheme 2), the *Z* isomer should form preferentially. However, the increased steric congestion leads to higher ee values for the *E* product.

The catalytic cyclization of 6-methylhepta-4,5-dienylamine **1c** with the various titanium catalysts was also carried out in benzene-d_6 in high-pressure NMR tubes (Scheme 6). This reaction was significantly slower at 110 °C (presumably due to the increased sterics of the allene) but was complete after approximately 18 h at 135 °C. The amino-alcohol-based catalysts are again significantly faster than $Ti(NMe_2)_4$. All catalysts formed exclusively the 5-exo product **3c**, unlike the zirconium sulfonamide catalysts with a related trisubstituted allene substrate (Scheme 1, R = Et, R′ = Me), which yielded a detectable (ca. 9%) amount of the imine product.[27,28] The pyrrolidine product was converted to the sulfonamide derivative, and the proton NMR spectrum of this product matched that of the literature compound prepared by a different method.[48]

The enantiomeric excess (ee) of each of the pyrrolidine products was determined by making the corresponding benzamide derivatives and separating by GC on a chiral stationary phase (Chiraldex B-DM). The ee values again correlate with the sterics of the ligand and are highest for the adamantyl-substituted ligands (entries 3, 6, 7, 10, and 11) with ee values of up to 15% (Table 2). The catalysts derived from the D-enantiomers of the ligands (entries 7−10) again show some selectivity for the production of the opposite enantiomer of the product.

Conclusions

We have prepared a variety of sterically varied chiral amino alcohol ligands via a modular two-step synthesis. The titanium complexes of these ligands catalyze the intramolecular hydroamination of di- and trisubstituted hexa-4,5-dienylamines and show an improved selectivity for the formation of pyrrolidines over other titanium- and zirconium-based catalysts. The pyrrolidines are formed with low enantioselectivity. Experiments are currently underway to determine if either isolated or in situ prepared imidos are catalytically active species as seen in related group IV catalysis.[27,28] We are also investigating the cause of the dramatic rate acceleration of our ligands relative to $Ti(NMe_2)_4$ through computational and experimental means.

Experimental Section

General Procedures. All reagents were obtained from commercial suppliers and were purified by standard methods[49] or used as received. Solvents were purified by distillation from sodium/benzophenone or by passage through a column of activated alumina[50] and stored under nitrogen. All air- and/or moisture-sensitive compounds were manipulated under an atmosphere of nitrogen using standard Schlenk techniques, or in a glovebox (MBraun UNIlab). Microanalyses were performed by Desert Analytics (Tucson, AZ). Mass spectra were obtained at the Mass Spectrometry Facility, University of California, Riverside, CA. All NMR spectra were recorded at ambient temperature on a Brüker Avance 400 spectrometer. Chemical shifts (δ) are given in ppm relative to TMS and were determined by reference to the residual ^{1}H and ^{13}C solvent resonances. Carbon assignments were made using DEPT experiments. Melting points were taken on a Meltemp melting apparatus and are uncorrected. Polarimetry was carried out using a Perkin-Elmer 141 instrument with a sodium lamp (589 nm). Ligands L-H_2PhePrO (L-*N*-isopropylphenylalanol) and L-H_2PheCyO (L-*N*-cyclohexylphenylalanol) were prepared as previously described.[40] Hepta-4,5-dienylamine (**1b**) and 6-methylhepta-4,5-dienylamine (**1c**) were prepared by slight modification of the published procedures[28,45] and were dried (CaH_2) and stored over 4 Å sieves.[38] Methyl and ethyl esters of the amino acids were prepared by standard techniques.[42] Optical purities were determined by NMR shift experiments as previously described using (*S*)-(+)-2,2,2-trifluroro-1-(9-anthryl)-ethanol.[40,44]

Typical Procedure A for the Synthesis of *N*-Alkyl Amino Acid Alkyl Esters. To the L-valine ethyl ester hydrochloride (7.9 g, 44 mmol) and sodium bicarbonate (3.71 g, 44.1 mmol, 1 equiv) was added THF (150 mL) under an atmosphere of nitrogen. The mixture was allowed to stir for 1 h before acetone (3.8 mL, 51 mmol, 1.2 equiv), sodium triacetoxy borohydride (9.34 g, 44.1 mmol, 1 equiv), and acetic acid (3.7 mL, 65 mmol, 1.5 equiv) were added. After being stirred for 2 days under an atmosphere of nitrogen, the reaction was quenched with 10% acetic acid in methanol (100 mL). The solution was concentrated by rotary evaporation, and equal amounts of water and ethyl acetate were added (~75 mL each). The aqueous layer was brought to a pH of 12 with the addition of sodium hydroxide. This layer was then separated and washed with ethyl acetate. The organic layers were washed with brine and dried over magnesium sulfate, and the solvents were removed by rotary evaporation to give L-*N*-isopropylvaline ethyl ester as a thick yellow oil (5.25 g, 28.1 mmol, 64%). The oil was purified by vacuum distillation.

L-*N*-Isopropylvaline Ethyl Ester. Bp: 30−34 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.9 (m, 6H), 0.095 (d,

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3H, J = 6.0 Hz), 1.0 (d, 3H, J = 6.0 Hz), 1.2 (t, 3H, J = 7.1 Hz), 1.5 (s, 1H (NH)), 1.8 (m, 1H), 2.6 (sept, 1H, J = 6.2 Hz), 3.0 (d, 1H, J = 5.6 Hz), 4.1 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1 (C), 65.2 (CH), 60.6 (CH_2), 47.7 (CH), 32.1 (CH), 24.3 (CH_3), 22.5 (CH_3), 19.4 (CH_3), 19.1 (CH_3), 14.7 (CH_3). MS (GC/MS): *m*/*z* (%): 188 (100) [MH^+]. HRMS (NH_3/CI): calcd for $C_{10}H_{22}NO_2$ 188.1651, found 188.1657. Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 64.09; H, 11.07; N, 7.21. $[\alpha]_D$ (*c* 0.03950 g·mL $^{-1}$, EtOAc): −20.9°.

L-*N*-Cyclohexylvaline Methyl Ester. Yield: 6.85 g, 89%. Bp: 60−65 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.9 (m, 6H), 1.0−1.8 (m, 11H), 2.2 (m, 1H), 3.1 (m, 1H), 3.7 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8 (C), 64.7 (CH), 55.9 (CH), 51.7 (CH_3), 34.6 (CH_2), 33.2 (CH_2), 32.2 (CH), 26.5 (CH_2), 25.4 (CH_2), 25.0 (CH_2), 19.5 (CH_3), 19.1 (CH_3). MS (DCI/NH_3): *m*/*z* (%): 214 (100) [MH^+]. HRMS (DCI/NH_3): calcd for $C_{12}H_{24}NO_2$ 214.1807, found 214.1814. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.21; H, 11.11; N, 6.53. $[\alpha]_D$ (*c* 0.03007 g·mL^{-1}, EtOAc): −40°.

L-*N*-(2-Adamantyl)valine Methyl Ester. Yield: 1.46 g, 55%. Bp: 79 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, 3H, J = 6.4 Hz), 0.97 (d, 3H, J = 6.8 Hz), 1.4−2.2 (m, 15H), 2.6 (s, 1H), 3.0 (d, 1H, J = 6.8 Hz), 3.7 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1 (C), 65.1 (CH), 60.8 (CH), 51.7 (CH_3), 38.4 (CH_2), 38.0 (CH_2), 37.3 (CH_2), 34.7 (CH), 32.4 (CH), 31.9 (CH_2), 31.4 (CH_2), 28.22 (CH), 28.19 (CH), 20.1 (CH_3), 19.2 (CH_3). One CH carbon not observed. MS (GC/MS, 40 eV): *m*/*z* (%) 266 (5) [MH^+]. HRMS (DEI/CI-NH_3): calcd for $C_{16}H_{28}NO_2$ 266.21200, found 266.21198. Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.44; H, 10.22; N, 5.42. $[\alpha]_D$ (*c* 0.02084 g·mL^{-1}, EtOAc): −36.0°.

D-*N*-Isopropylphenylglycine Methyl Ester. Yield: 7.44 g, 75%. Bp: 96 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (d, 3H, J = 4.8), 1.08 (d, 3H, J = 4.8 Hz), 2.0 (s, NH), 2.8 (sept, 1H, J = 6.2 Hz), 3.7 (s, 3H), 4.5 (s, 1H), 7.4 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3 (C), 138.9 (C), 129.1 (CH), 128.4 (CH), 127.7 (CH), 63.3 (CH), 52.6 (CH_3), 46.6 (CH), 23.3 (CH_3), 23.1 (CH_3). MS (DCI, NH_3): *m*/*z* 208 (100) [MH^+]. HRMS (DCI, NH_3): calcd for $C_{12}H_{18}NO_2$ 208.1338, found 208.1345. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.61; H, 8.25; N, 6.76. $[\alpha]_D$ (*c* 0.03338 g·mL^{-1}, EtOAc): −80.7°.

D-*N*-Cyclohexylphenylglycine Methyl Ester. Yield: 9.03 g, 84%. Bp: 107−114 °C, <1 mm Hg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.0−2.0 (m, 10H), 2.1 (s, NH), 2.4 (m, 1H), 3.7 (s, 3H), 4.5 (s, 1H), 7.3−7.4 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4 (C), 139.2 (C), 129.0 (CH), 128.3 (CH), 127.7 (CH), 62.8 (CH), 54.8 (CH), 52.5 (CH_3), 33.9 (CH_2), 33.7 (CH_2), 26.4 (CH_2), 25.20 (CH_2), 25.19 (CH_2). MS (DCI, NH_3): *m*/*z* 248 (100) [MH^+]. HRMS (DCI, NH_3): calcd for $C_{15}H_{22}NO_2$ 248.1651, found 248.1641. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.16; H, 8.32; N, 5.72. $[\alpha]_D$ (*c* 0.02732 g·mL^{-1}, EtOAc): −60.5°.

D-*N*-(2-Adamantyl)phenylglycine Methyl Ester. Yield: 2.74 g, 72%. Mp: 102.5−106 °C, <1 mm Hg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.3−2.1 (m, 14H), 2.7 (s, 1H), 3.7 (s, 3H), 4.5 (s, 1H), 7.2−7.4 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7 (C), 139.6 (C), 128.9 (CH), 128.1 (CH), 127.8 (CH), 63.0 (CH), 60.1 (CH), 52.5 (CH_3), 38.3 (CH_2), 37.8 (CH_2), 37.7 (CH_2), 32.8 (CH), 32.6 (CH), 31.7 (CH_2), 28.2 (CH), 28.1 (CH). One CH_2 was not observed. MS (CI, NH_3): *m*/*z* 300 (100) [MH^+]. HRMS (CI, NH_3): calcd for $C_{19}H_{26}NO_2$ 300.1963, found 300.1964. Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.31; H, 8.70; N, 4.61. $[\alpha]_D$ (*c* 0.00900 g·mL^{-1}, EtOAc): −54.0°.

L-*N*-(2-Adamantyl)phenylglycine Methyl Ester. Yield: 6.89 g, 97%. The ^{1}H NMR spectrum matched that of the D-enantiomer.

L-*N*-(2-Adamantyl)phenylalanine Methyl Ester. Yield: 6.20 g, 92%. Bp: 133−134 °C, <1 mm Hg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.3−1.9 (m, 14H), 2.6 (s, 1H), 2.9 (dd, 1H, J_1 = 8.0 Hz, J_2 = 13.9 Hz), 3.0 (dd, 1H, J_1 = 6.0 Hz, J_2 = 13.4 Hz), 3.6 (t, 1H, J = 7.0 Hz), 3.7 (s, 3H), 7.2 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2 (C), 138.3 (C), 129.6 (CH), 128.7 (CH), 126.9 (CH), 60.7 (CH), 60.6 (CH), 51.9 (CH_3), 40.7 (CH_2), 38.3 (CH_2), 38.0 (CH_2), 37.5 (CH_2), 34.2 (CH), 31.8 (CH_2), 31.3 (CH), 31.2 (CH_2), 28.1 (CH), 28.0 (CH). MS (DCI, NH_3): *m*/*z* 314 (100) [MH^+]. HRMS (DCI, NH_3): calcd for $C_{20}H_{28}NO_2$ 314.2120, found 314.2126. Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.64; H, 8.47; N, 4.68. $[\alpha]_D$ (*c* 0.01378 g·mL^{-1}, EtOAc): −10.75°.

D-*N*-(2-Adamantyl)phenylalanine Methyl Ester. Yield: 4.66 g, 91%. The ^{1}H NMR spectrum matched that of the L-enantiomer.

Typical Procedure B for the Synthesis of the Ligands. L-*N*-Isopropyl valine ethyl ester (3.277 g, 17.5 mmol) was dissolved in anhydrous THF (100 mL) under an atmosphere of nitrogen. Lithium aluminum hydride (3 g, 80 mmol) was added, and the solution was stirred overnight in a 63 °C oil bath. Ether (300 mL) was then added to the solution, followed by the dropwise addition of water (3 mL), 15% sodium hydroxide (3 mL), and water (9 mL). The white precipitate was removed by vacuum filtration and rinsed with ethyl acetate. The filtrate was washed with 1 M sodium hydroxide and brine. The organic layer was dried over magnesium sulfate and filtered. The solvent was removed by rotary evaporation to give a colorless oil, which was purified by vacuum distillation (1.74 g, 12.0 mmol, 68.5%).

L-*N*-Isopropylvalinol (L-H_2ValPrO). Bp: 32−33 °C, <1 mm Hg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, 3H, J = 6.8 Hz), 0.94 (d, 3H, J = 6.8 Hz), 1.02 (d, 3H, J = 6.4 Hz), 1.06 (d, 3H, J = 6.4 Hz), 1.7 (m, 1H), 2.4 (m, 1H), 2.9 (m, 1H), 3.2 (dd, 1H, J_1 = 6.8 Hz, J_2 = 10.4), 3.5 (dd, 1H, J_1 = 4.6 Hz, J_2 = 10.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.4 (CH), 61.0 (CH_2), 46.7 (CH), 30.0 (CH), 24.0 (CH_3), 23.7 (CH_3), 19.7 (CH_3), 18.5 (CH_3). MS (GC/MS, 40 eV): *m*/*z* (%) 146 (7) [MH^+]. HRMS (GC/MS, 40 eV): calcd for $C_8H_{20}NO$ 146.1545, found 146.1543. Anal. Calcd for $C_8H_{19}NO$: C, 66.16; H, 13.19; N, 9.64. Found: C, 66.04; H, 13.24; N, 9.78. $[\alpha]_D$ (*c* 0.02118 g·mL^{-1}, EtOAc): 12.65°.

L-*N*-Cyclohexylvalinol (L-H_2ValCyO). Yield: 2.49 g, 91%. Bp: 71−73 °C, <1 mm Hg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, 3H, J = 6.8 Hz), 0.94 (d, 3H, J = 6.8 Hz), 1.0−1.2 (m, 5H), 1.5 (m, 1H), 1.6−1.9 (m, 5H), 2.5 (m, 2H), 3.2 (m, 1H), 3.5 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.30 (CH), 61.29 (CH_2), 54.9 (CH), 34.9 (CH_2), 43.8 (CH_2), 30.2 (CH), 26.5 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 20.0 (CH_3), 18.8 (CH_3). MS (CI/NH_3): *m*/*z* (%) 186 (100) [MH^+]. HRMS (CI/NH_3): calcd for $C_{11}H_{24}NO$ 186.1858, found 186.1853. Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.16; H, 12.56; N, 7.86. $[\alpha]_D$ (*c* 0.04335 g·mL^{-1}, EtOAc): 0.484°.

L-*N*-(2-Adamantyl)valinol (L-H_2ValAdO). Yield: 1.28 g, 98%. Bp: 89 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, 3H, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz), 1.5−2.0 (m, 15H), 2.5 (m, 1H), 2.8 (s, 1H), 3.3 (dd, 1H, J_1 = 4.4 Hz, J_2 = 10.4 Hz), 3.5 (dd, 1H, J_1 = 4.4 Hz, J_2 = 10.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.0 (CH), 60.9 (CH_2), 59.8 (CH), 38.3 (CH_2), 37.8 (CH_2), 33.6 (CH), 33.0 (CH), 31.9 (CH_2), 31.8 (CH_2), 29.7 (CH), 28.0 (CH), 27.9 (CH), 20.1 (CH_3), 18.6 (CH_3). One CH_2 was not observed. MS (CI/NH_3): *m*/*z* (%) 238 (100) [MH^+]. HRMS (CI/NH_3): calcd for $C_{15}H_{28}NO$ 238.2171, found 238.2163. Anal. Calcd for $C_{15}H_{27}NO$: C,75.90; H, 11.46; N, 5.90. Found: C, 75.87; H, 11.14; N, 5.85. $[\alpha]_D$ (*c* 0.01125 g·mL^{-1}, EtOAc): −2.5°.

L-*N*-(2-Adamantyl)phenylalanol (L-H_2PheAdO). Yield: 1.57 g, 89%. Mp: 59−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2 (m, 5H); 3.5 (dd, 1H, J_1 = 4.0 Hz, J_2 = 10.4 Hz); 3.3 (m, 1H), 2.9 (m, 1H); 2.7 (m, 3H); 1.8 (m, 5H); 1.6 (m, 6H); 1.5 (m, 2H); 1.4 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1 (C); 129.6 (CH); 128.9 (CH); 126.8 (CH); 63.4 (CH_2); 59.1 (CH); 57.5 (CH); 39.2 (CH_2); 38.2 (CH_2); 38.1 (CH_2); 38.0 (CH_2); 33.3 (CH); 32.8 (CH); 31.8 (CH_2); 31.4 (CH_2); 28.0 (CH); 27.8 (CH). MS

(DCI/NH_3): *m*/*z* (%) 286 (100) [MH^+]. HRMS (DCI/NH_3): calcd for $C_{19}H_{28}NO$ 286.2171, found 286.2180. Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91. Found: C, 80.06; H, 9.80; N, 4.90. $[\alpha]_D$ (*c* 0.0637 g·mL^{-1}, EtOAc): −6.56°.

D-*N*-(2-Adamantyl)phenylalanol (D-H_2PheAdO). Yield: 3.45 g, 89%. $[\alpha]_D$ (*c* 0.00672 g·mL^{-1}, EtOAc): +5.9°. The ^1H NMR spectrum matched that of the L-enantiomer.

D-*N*-Isopropylphenylglycinol (D-H_2PhgPrO). Yield: 0.589 g, 85%. Mp: 75−76.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (d, 3H, J = 6.4 Hz), 1.05 (d, 3H, J = 6.0 Hz); 2.7 (sept, 1H, J = 6.1 Hz); 3.5 (dd, 1H, J_1 = 8.8 Hz, J_2=10.6 Hz); 3.7 (dd, 1H, J_1 = 4.6 Hz, J_2 = 10.6 Hz); 3.9 (dd, 1H, J_1 = 4.6 Hz, J_2 = 9.0 Hz); 7.3 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8(C), 129.0 (CH), 127.8 (CH), 127.4 (CH), 67.1 (CH_2), 61.9 (CH), 46.0 (CH), 24.7 (CH_3), 22.7 (CH_3). MS (DCI, NH_3): *m*/z (%) 180 (24) [MH^+]. HRMS (GC/MS, NH_3): calcd for $C_{11}H_{18}NO$ 180.1388, found 180.1392. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.46; H, 9.52; N, 7.82. $[\alpha]_D$ (*c* 0.02441 g·mL^{-1}, EtOAc): −89.6°.

D-*N*-Cyclohexylphenylglycinol (D-H_2PhgCyO). Yield: 1.00 g, 86%. Mp: 115−118 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.1−2.0 (m, 10H), 2.4 (m, 1H), 3.4 (dd, 1H, J_1 = 8.8 Hz, J_2 = 10.4 Hz), 3.7 (dd, 1H, J_1 = 4.8 Hz, J_2 = 10.4 Hz), 3.9 (m, 1H), 7.3 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0 (C), 129.0 (CH), 127.8 (CH), 127.3 (CH), 67.1 (CH_2), 61.4 (CH), 53.9 (CH), 35.2 (CH_2), 33.5 (CH_2), 26.5 (CH_2), 25.4 (CH_2), 25.0 (CH_2). MS (DCI/NH_3): *m*/*z* (%) 220 (100) [MH^+]. HRMS (DCI/NH_3) calcd for $C_{14}H_{22}NO$ 220.1701, found 220.1697. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.78; H, 9.44; N, 6.45. $[\alpha]_D$ (*c* 0.01031 g·mL^{-1}, EtOAc): −91.157°.

D-*N*-(2-Adamantyl)phenylglycinol (D-H_2PhgAdO). Yield: 1.70 g, 80%. Mp: 95−97 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.5−2.0 (m, 14H), 2.7 (s, 1H), 3.5 (dd, 1H, J_1 = 9.2 Hz, J_2 = 10.4 Hz), 3.7 (dd, 1H, J_1 = 4.6 Hz, J_2 = 10.6 Hz), 3.9 (dd, 1H, J_1 = 4.8 Hz, J_2 = 9.2 Hz), 7.3 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9 (C), 129.0 (CH), 127.8 (CH), 127.3 (CH), 67.1 (CH_2), 61.6 (CH), 59.0 (CH), 38.3 (CH_2), 38.1 (CH_2), 37.4 (CH_2), 34.5 (CH), 32.0 (CH_2), 31.7 (CH_2), 31.2 (CH), 28.1 (CH), 28.0 (CH). MS (DCI/NH_3): *m*/*z* (%) 272 (100) [MH^+]. HRMS (DCI/NH_3) calcd for $C_{18}H_{26}NO$ 272.2014, found 272.2022. Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.75; H, 9.05; N, 5.22. $[\alpha]_D$ (*c* 0.00649 g·mL^{-1}, EtOAc): −70.0°.

L-*N*-(2-Adamantyl)phenylglycinol (L-H_2PhgAdO). Yield: 3.241 g, 85%. $[\alpha]_D$ (*c* 0.00562 g·mL^{-1}, EtOAc): +58.0°. The ^1H NMR spectrum matched that of the D-enantiomer.

General Procedure for Chiral Shift Studies. Chiral shift studies were performed for all ligands using this procedure. L-H_2ValCyO (0.020 g, 0.11 mmol) was dissolved in $CDCl_3$ (ca. 0.75 mL) and examined by ^1H NMR spectroscopy. (*S*)-(+)-2,2,2-Trifluoro-1-(9-anthryl)ethanol (0.030 g, 0.11 mmol) was added to the solution, which was then reexamined. Additional shift reagent (0.030 g, 0.11 mmol) was added, and a final spectrum was taken.

Typical Procedure C for the Hydroamination of Hepta-4,5-dienylamine 1b. Inside the glovebox deuterated benzene (300 μL), $Ti(NMe_2)_4$ (65 μL of a 0.0908 M solution, 5.9×10^{-3} mmol), and L-H_2PheAdO (110 μL of a 0.056 M solution, 6.2×10^{-3} mmol) were combined in a medium-walled J. Young tube, and an NMR spectrum was taken. Hepta-4,5-dienylamine (**1c**, 100 μL of a 1.20 M solution, 0.12 mmol, 20 equiv) was added, and a second spectrum was taken. The tube was placed in a 110 ± 1 °C oil bath and monitored by ^1H NMR until the reaction reached completion. The *E*/*Z* ratios were determined by comparison with known spectra.[38] The reaction mixture was quenched with 2-propanol (1 mL) and diluted with ether (3 mL). To one-half of the solution were added benzoyl chloride (8 μL, 0.07 mmol) and triethylamine (20 μL, 0.14 mmol). After stirring at room temperature for 1 h, water (2 mL) and ether (2 mL) were added, layers were separated, and the organic layer was washed with brine. The crude benzamide was injected on the GC capillary column (Chiraldex B-DM, 30 m × 0.25 μm, 100 °C, 8 min, 1 °C/min to 180 °C, 180 °C 15 min). The two enantiomers of each of the *E* (retention times of 77.3 and 77.8 min) and *Z* (retention times of 78.3 and 78.7 min) isomers were resolved.

Typical Procedure D for the Hydroamination of 6-Methylhepta-4,5-dienylamine 1c. Inside the glovebox deuterated benzene (48 μL), $Ti(NMe_2)_4$ (98 μL of a 0.0862 M solution, 8.5×10^{-3} mmol), and L-H_2PheAdO (150 μL of a 0.056 M solution, 8.4×10^{-3} mmol) were combined in a medium-walled J. Young tube, and an NMR spectrum was taken. 6-Methylhepta-4,5-dienylamine (**1b**, 104 μL of a 1.621 M solution, 0.169 mmol, 20 equiv) was added, and a second spectrum was taken. The tube was placed in a 135 ± 1 °C oil bath and monitored by ^1H NMR until the reaction reached completion. The reaction mixture was quenched with 2-propanol (1 mL) and diluted with ether (3 mL). To one-half of the solution were added benzoyl chloride (9 μL, 0.08 mmol) and triethylamine (20 μL, 0.14 mmol). After stirring at room temperature for 1 h, water (2 mL) and ether (2 mL) were added, the layers were separated, and the organic layer was washed with brine. The crude benzamide was injected on the GC capillary column (Chiraldex B-DM, 30 m × 0.25 μm, 100 °C, 8 min, 1 °C/min to 180 °C, 180 °C 15 min). The two enantiomers were separated with retention times of 82.3 and 82.7 min.

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Supporting Information Available: Full preparative details for all new compounds and results for the catalytic hydroamination of **1b** at 75 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

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