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Sterically encumbered chiral amino alcohols for titanium-catalyzed asymmetric intramolecular hydroamination of aminoallenes

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ABSTRACT

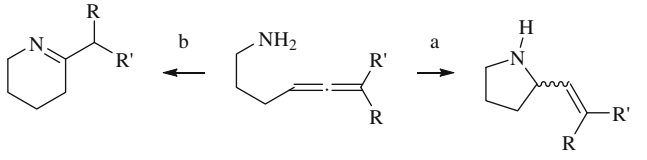
A variety of sterically encumbered amino alcohol ligands were prepared in a two-step modular synthesis. The titanium complexes of these ligands were prepared in situ and used as catalysts for hydroamination. The intramolecular hydroamination of 6-methyl-hepta-4,5-dienylamine at 135 °C with 5 mol % catalyst gave exclusively 2-(2-methyl-propenyl)-pyrrolidine with enantiomeric excesses up to 16%.

1. Introduction

The hydroamination reaction, which is the addition of an N–H bond across an unsaturated C–C bond, has been the subject of ever-increasing scrutiny due to its highly atom-economical formation of nitrogen-containing compounds of potential utility for industrial and pharmaceutical applications. The reaction is generally thermoneutral or slightly exothermic, but the reaction requires a catalyst due to the large electronic repulsion between the nitrogen and the unsaturated group.[1] Both inter- and intramolecular variations of the reaction have been reported for the hydroamination of olefins, alkynes, and allenes, and the field has been extensively reviewed.[1–7]

Catalysts for the reaction range from alkali metal bases,[8–11] early[12–16] and late[17,18] transition metal complexes, gold,[19–25] and lanthanide[6,26,27] complexes, but there has been a recent significant focus on the early metal catalysts due to their relatively lower air- and moisture sensitivity compared to lanthanide organometallics. Titanium, zirconium, and yttrium bisamide derivatives catalyze the intramolecular cyclization of aminoalkynes to give the imine product.[28,29] Neutral group IV amide,[30] amidate,[31] pyrrolyl,[32] and cyclopentadienyl complexes[33,34] are effective catalysts for the intramolecular hydroamination of unactivated olefins, as are cationic zirconocene and titanocene complexes.[35] Often, the substrates for the olefin cyclizations require gem dialkyl substitution that encourages preorganization via either a compression of the bond angle (the Thorpe–Ingold effect)[36] or raising the energy of the ground state (the 'reactive rotamer' effect).[37]

The hydroamination of allenes is thermodynamically more favorable than that of alkenes,[38,39] but leads to more complex product mixtures, and has therefore been less studied. Amidate complexes of titanium do catalyze the intermolecular reaction regioselectively for both aryl and alkylamines.[40] More interesting, from a product standpoint, is the intramolecular reaction, as the products are highly valuable nitrogen-containing heterocycles with a pendant vinyl group for further substitution (Scheme 1, 3a and 3b). The intramolecular cyclization by silver, mercury, palladium,[41–44] titanium,[45,46] and lanthanides is also known.[39,47,48]



2a, R = R' = CH_3
2b, R = CH_3, R' = H

1a, R = R' = CH_3
1b, R = CH_3, R' = H

3a, R = R' = CH_3
3b, R = CH_3, R' = H

Scheme 1.

The mechanism for the intramolecular hydroamination has been the subject of careful investigation. Lanthanide metal and cationic group IV metal catalysts react first to form a neutral or cationic amido complex which undergoes a 1,2-insertion reaction on the unsaturated carbon–carbon bond to form a metal alkyl complex.[39,47,48] The addition of a second equivalent of amine substrate leads to protonolysis of the alkyl and regeneration of the amido complex. In a closely related mechanism, neutral early metal complexes initially react with a substrate to form an imido complex (Scheme 2). A subsequent [2+2] cycloaddition with the unsaturated bond results in an azametallocycle that can be removed by protonation by the next equivalent of incoming amine.[45,46] Computational studies have helped to confirm and elaborate upon the

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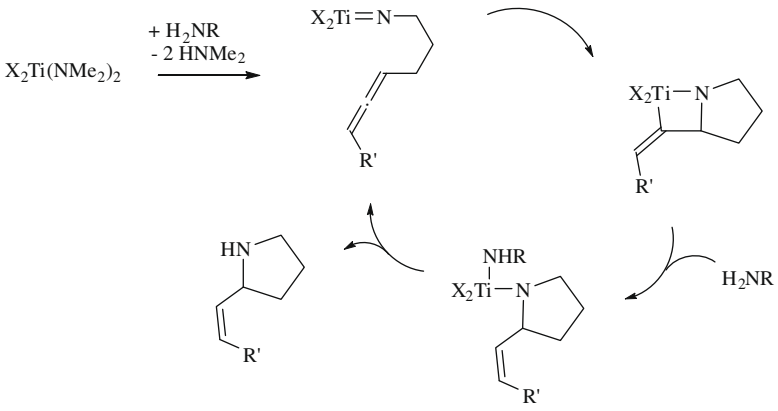
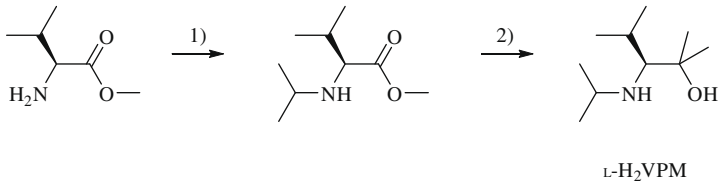


Scheme 2.



Scheme 3. Reagents and conditions: (1) $NaHCO_3$/acetone/$NaBH(OAc)_3$ and (2) MeMgBr.

basic mechanistic picture described here for aminoallene substrates.[49,50]

As the cyclization of aminoalkene or -allene substrates results in the formation of a chiral nitrogen heterocycle, there has been much effort in further development of the asymmetric reaction. The first example of asymmetric hydroamination was reported for the cyclization of aminoolefins using a chiral lanthanide catalyst,[51] with enantioselectivities of up to 74%ee. Chiral lanthanocene catalysts can undergo epimerization under catalytic hydroamination conditions (presence of amine),[52] although high enantioselectivities can still be observed with equilibrium epimer ratios of 95:5.[53,54] Still, it is important to develop improved chiral ligands that are resistant to this process. The asymmetric intramolecular hydroamination of alkenes using lanthanide catalysts has been further optimized to give very high enantioselectivities ranging from 70% to 90%ee.[55,56] Ligands giving high enantioselectivities include those that are binaphthyl based,[57–60] or polydentate amide based.[61,62]

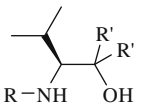
More recently, a variety of cyclopentadienyl and imido complexes of the early metals have been examined for asymmetric reactions. For the intramolecular reaction of aminoalkenes, group IV alkyl complexes with chelating bis-amidate ligands catalyze the enantioselective hydroamination/cyclization with enantioselectivities above 90%ee.[63,64] The corresponding zirconium amide complexes also catalyze the cyclization if the substrate has *gem*-dimethyl substitution. Chiral binaphtholate-derived yttrium complexes catalyze the asymmetric hydroamination of aminoalkenes with enantioselectivities up to 89%ee.[65–67] Chiral polydentate N,O-ligands on zirconium result in the cyclization of aminoalkenes with enantioselectivities of up to 82%ee.[68] Related chemistry using yttrium results in cyclizations with enantioselectivities in the 20–40%ee range.[69] Chiral yttrium amide complexes were used to investigate the cyclization of a variety of substrates, all with 2,2-dialkyl substitution; enantioselectivities were as high as 68%ee.[70] Group IV complexes with a variety of chiral bidentate ligands catalyze the hydroamination of aminaoalkenes enantioselectively. Zirconium diphosphinic amides were found to be the best catalysts, and the optimized reaction conditions gave yields of the cyclized product with enantioselectivies as high as 80%ee.[71] Progress on the asymmetric cyclization of aminoallenes has focused on the use of gold complexes with bulky chiral phosphine complexes, resulting in high enantioselectivities (70–90%ee).[72–74] In a related reaction, when starting with chiral allenes, catalysis with gold halides can yield products that retain their configuration.[75,76]

The first reported asymmetric intramolecular hydroamination of an allene by a titanium catalyst was reported by our group in 2004 using chiral titanium complexes with amino alcohol-derived ligands.[77] Herein, we report the results of the hydroamination using improved 'second generation' catalysts. We sought to improve our initial results through rational modification of our catalysts. Our 'first generation' catalysts were amino alcohols with primary alcohols and varied steric protection at nitrogen and the carbon alpha to the nitrogen. Due to the modular nature of the ligand design, it was straightforward to prepare new tertiary alcohol derivatives with altered steric environments at the carbon alpha to the oxygen (Fig. 1).

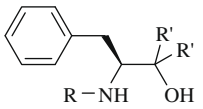
2. Results and discussion

2.1. 1. Synthesis of ligands

The ligands used in this study (Fig. 1) were prepared in a two-step procedure from the methyl esters of the respective amino acids such as valine (V) and phenylalanine (P). The ligands were prepared with substitution at the amino nitrogen with isopropyl (P), cyclohexyl, (C) or adamantyl (A) groups, and at the position α to the alcohol with methyl (M), butyl (B), or phenyl (P) groups. The synthesis and nomenclature is illustrated for L-H_2VPM (**V**alinol-*N*-**P**ropyl-di**M**ethyl, Scheme 3). First, the *N*-isopropyl group was added to the amino nitrogen (the free base is generated in situ by the addition of sodium bicarbonate) of valine methyl ester by reductive amination of the corresponding ketone, acetone in this case, with $NaBH(OAc)_3$ to give the intermediate.[78,79] Second, the ester was alkylated to the tertiary alcohol with methyl magnesium bromide to generate the desired ligand. A total of 17 new ligands were prepared for this study; the primary alcohol derivatives



L-H_2VPH(M, B, P), R = ^{i}Pr, R' = H (Me, ^{n}Bu, Ph)
L-H_2VCH(M, B, P), R = c-C_6H_{11}, R' = H (Me, ^{n}Bu, Ph)
L-H_2VAH (M, B, P), R = 2-Ad, R' = H (Me, ^{n}Bu, Ph)



L-H_2PPH(M, B, P), R = ^{i}Pr, R' = H (Me, ^{n}Bu, Ph)
L-H_2PCH(M, B, P), R = c-C_6H_{11}, R' = H (Me, ^{n}Bu, Ph)
L-H_2PAH(M, B, P), R = 2-Ad, R' = H (Me, ^{n}Bu, Ph)

Figure 1. Ligands used in this study (^{i}Pr = CCH$(CH_3)_2$, 2-Ad = 2-adamantyl; the ligands are named as illustrated for l-H_2VPM (**V**alinol-*N*-**P**ropyl-di**M**ethyl).

(VPH, VCH, VAH, PPH, PCH, and PAH) were reported previously.[77,80] Although it was possible to prepare the phenyl derivatives for most of the ligands, it is still not possible to prepare the VPP ligand. *N*-Isopropyl-valine methyl ester did not react cleanly with either commercial PhMgBr or PhLi, or with freshly prepared PhMgBr; the same batches of alkylating agent did react cleanly with other starting materials to generate the phenyl derivatives of those ligands. All reactions that failed proceeded to give multiple products that could not be conclusively identified by NMR or IR spectroscopy. The reason for the failed synthesis of this ligand is unknown.

As reported previously for the first generation ligands of valine and phenylalanine,[77] no evidence was observed for the racemization of the ligands during their synthesis. The addition of one and two equivalents of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol to the appropriate valine- and phenylalanine-derived ligands resulted in the shifting of the ligand hydrogen signals due to the formation of transient diastereomeric complexes, but no splitting of the resonances into two sets of peaks was observed, indicating that the ligands were enantiomerically pure.

2.2. Catalytic intramolecular hydroamination with titanium complexes of amino alcohols

We reported the first titanium-catalyzed asymmetric intramolecular hydroamination of aminoallene substrates in 2004.[77] When hepta-4,5-dienylamine **1b** (Scheme 1) was used as the substrate, all three possible products (*Z*- and *E*-5-*exo* pyrrolidine **3b** and tetrahydropyridine **2b**) were observed by ^{1}H NMR spectroscopy. On the other hand, when 6-methyl-hepta-4,5-dienylamine **1a** was used as the substrate, only the pyrrolidine product **3a** was observed. To simplify the analysis, catalytic hydroamination of only substrate **1a** was carried out with the new catalysts. The allene substrate was prepared as previously described from 2-methyl-3-butyne-2-ol.[46,77,81]

The catalytic cyclization of substrate **1a** with the various titanium catalysts was carried out in benzene-d_6 in high-pressure NMR tubes. Titanium precatalyst complexes were prepared 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 dimeric structure similar to those previously reported complexes based on their similar NMR spectra.[80,82] The catalytic reaction was initiated by adding a stock solution of the appropriate aminoallene (ca. 1.5 M). Catalysis by particulate matter from the molecular sieves used to dry the ligand solutions was ruled out by a control experiment.[77] This reaction can be carried out at either 135 °C or 110 °C, but is significantly slower at 110 °C (presumably due to the steric bulk of the allene); all catalyses were therefore carried out at the higher temperature. The amino alcohol-based catalysts are again significantly faster than Ti$(NMe_2)_4$ as reported previously; the reaction was determined to have reached completion by ^{1}H NMR spectroscopy after approximately 18 h. All reactions exclusively formed the 5-*exo* pyrrolidine **3a** quantitatively by NMR spectroscopy.

Livinghouse and Lee reported the use of the chiral resolving agent (*R*)-(*O*)-acetylmandelic acid for the determination of the enantiomeric excess of hydroamination products by NMR spectroscopy.[66] The product amine and the benzene-d_6 were separated from the catalyst solution by vacuum transfer, and 1 equiv of (*R*)-(*O*)-acetylmandelic acid was added. The NMR spectrum revealed a distinct diastereomeric splitting of the doublet for the pyrrolidine product at 5.3 ppm with a baseline resolution. Integration of the peaks allowed for the determination of the percent of each stereoisomer, although the absolute stereochemistry of the isomers remains to be determined. All ligands show modest but reproducible enantioselectivities of up to 16% (Table 1). In several cases, enantiomeric excesses were determined by preparing benzamide derivatives of the catalysis products and then separating them on a chiral GC column (Chiraldex β-DM) as described previously;[77] enantioselectivity was found to be the same by both methods within error (±2%).

The enantioselectivity of the hydroamination reaction broadly correlates with the sterics of the ligand, with the phenylalanine-derived ligands showing higher enantioselectivities than the valine-derived ligands. However, the desired increase in selectivity due to increased substitution at the alkoxy carbon was not realized (compare first generation ligands, entries 1, 5, 9, 13, 17, and 21 with the other entries in the table). The valine-derived ligands generally show very low enantioselectivity, with the best ligand being VAB (entry 11, 10%ee). The phenylalanine-derived ligands behaved more consistently; increased steric bulk at the alkoxy

Table 1
Hydroamination of 6-methyl-hepta-4,5-dienylamine at 135 °C with in situ catalysts (5 mol % catalyst)

Entry	L	ee[a] (%)
1	VPH	4[b]
2	VPM	−2[c]
3	VPB	5
4	VPP	—
5	VCH	4[b]
6	VCM	−1[c]
7	VCB	1
8	VCP	5
9	VAH	5[b]
10	VAM	2
11	VAB	10
12	VAP	0
13	PPH	2[b]
14	PPM	−4[c]
15	PPB	3
16	PPP	16
17	PCH	6[b]
18	PCM	−1[c]
19	PCB	−5[c]
20	PCP	16
21	PAH	15[b]
22	PAM	−2[c]
23	PAB	1
24	PAP	7

[a] By chiral shift NMR spectroscopy using (*R*)-(*O*)-acetylmandelic acid.[66]
[b] Data from Ref. 77.
[c] Enantiomer with opposite configuration favored.

carbon increased the enantioselectivity (entries 16 and 20, 16%ee). However, increasing the steric bulk of the best ligand from our prior study (entry 21) resulted in a loss of selectivity (entries 22–24).

3. Conclusions

We have prepared a series of chiral amino alcohol ligands via a modular 2-step synthesis. The steric environment of the ligands was changed in a rational fashion using methyl, butyl, and phenyl substitution at the alkoxy carbon. The titanium complexes of the amino alcohol ligands catalyze the intramolecular hydroamination of 6-methyl-hepta-4,5-dienylamine, forming exclusively the pyrrolidine product. The pyrrolidines are formed with low enantioselectivity, up to 16% ee, but no obvious trends between the steric environment provided by the ligand and the enantioselectivity were observed.

4. Experimental

4.1. General

All reagents were obtained from commercial suppliers and purified by standard methods[83] or used as received. Solvents were purified by distillation from sodium/benzophenone or by passage through a column of activated alumina (Innovative Technology PS-400-5-MD) 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 glove box (MBraun UNIlab). Microanalyses were performed by Columbia Analytical Services (Tucson, AZ). Mass spectra were obtained at the Mass Spectrometry Facility, California Institute of Technology. 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. Melting points were taken on a Meltemp melting apparatus and are uncorrected. Polarimetry was carried out using a JASCO P1010 instrument. Ligand precursors were prepared as previously described.[77,80] 6-Methyl-hepta-4,5-dienylamine **1c** was prepared by slight modification of the published procedures,[46,81] and was dried (CaH_2) and stored over 4 Å sieves.[47,48]

4.2. Typical procedure 1 for synthesis of new amino alcohol ligands: L-*N*-isopropyl-dimethyl valinol (L-H_2VPM)

L-*N*-Isopropyl-valine methyl ester (2.8338 g, 16.36 mmol)[77] was dissolved in dry THF (100 mL) in a 500 mL round-bottomed flask under an atmosphere of nitrogen. The reaction vessel was cooled to −78 °C and 1.4 M solution of methyl magnesium bromide in THF (46.73 mL, 65.42 mmol) was added dropwise via syringe. The solution was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched by the slow addition of saturated ammonium chloride solution (30 mL) and water (30 mL). The solution was separated, and the aqueous layer washed with ether. The organic layers were combined, washed with saturated sodium chloride solution, and dried over magnesium sulfate. The solvents were removed by rotary evaporation to give a yellow oil (2.4368 g, 14.06 mmol, 86% yield). The oil was purified by flash chromatography (10% ethyl acetate, 0.5% triethylamine, hexane). Bp 63 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, 3H, J = 6.8 Hz), 1.02 (s, 3H), 1.04 (d, 3H, 8.4 Hz), 1.08 (d, 3H, 6.3 Hz), 1.10 (d, 3H, 5.6 Hz), 1.22 (s, 3H), 1.84 (d of sept, 1H, J_1 = 6.8 Hz, J_2 = 2.4 Hz), 2.34 (d, 1H, J = 2.4 Hz), 2.97 (sept, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 71.1, 68.2, 48.5, 29.2, 28.3, 25.5, 24.5, 23.1, 17.9, 14.6. HRMS (EI+) calcd for $C_{10}H_{22}NO$ (MH^+-H_2): 172.1701, found: 172.1693; Calcd for $C_{10}H_{24}NO$ (MH^+): 174.1852, found: 174.1859. $[\alpha]_D$ = 24.3 (c 5.49, EtOAc).

4.3. L-*N*-Isopropyl-dibutyl valinol (L-H_2VPB)

L-H_2VPB was prepared according to typical procedure 1 starting from L-*N*-isopropyl-valine methyl ester (1.245 g, 7.18 mmol)[77] to give a yellow oil (1.7474 g, 6.8 mmol, 94% yield). The oil was purified by vacuum distillation. Bp 120–122 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.95 (m, 8H), 1.1–1.2 (m, 8H), 1.3–1.5 (m, 14H), 1.9 (dsept, J_1 = 2.4 Hz, J_2 = 7.6 Hz, 1H), 2.5 (d, J = 2.4 Hz, 1H), 2.9 (sept, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 18.11, 23.3, 23.93, 24.15, 24.58, 25.23, 26.12, 26.17, 28.54, 35.92, 37.07, 48.96, 64.39, 74.48 (one carbon not observed). Anal. Calcd for $C_{16}H_{35}NO$: C, 74.64; H, 13.7; N, 5.44. Found: C, 74.32; H, 13.61; N, 5.44. HRMS (EI+) calcd for $C_{16}H_{36}NO(MH^+)$: 258.2797, found: 258.2790. $[\alpha]_D$ = +17.8 (c 2.485, EtOAc).

4.4. L-*N*-Cyclohexyl-dimethyl valinol (L-H_2VCM)

L-H_2VCM was prepared according to typical procedure 1 starting from L-*N*-cyclohexyl-valine methyl ester (1.4150 g, 6.63 mmol)[77] to give an impure yellow oil (1.5129 g, 7.1 mmol, 107% yield). The oil was purified by flash chromatography (8% ethyl acetate, 0.5% triethylamine, hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.9255 (d, 3H, J = 6.8), 1.011 (s, 3H), 1.060 (d, 3H, J = 7.2) 1.202 (s, 3H), 1.559–1.920 (br m, 11H), 2.363 (d, 1H, J = 2.8), 2.551 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 71.41, 68.10, 57.05, 35.29, 34.45, 29.42, 28.60, 26.66, 25.85, 25.56, 25.28, 24.83, 18.28. Anal. Calcd for $C_{13}H_{27}NO$: C, 73.18; H, 12.56; N, 6.56. Found: C, 72.83; H, 12.78; N, 6.55. HRMS(EI):calcd for $C_{13}H_{28}NO$: 214.2171, found: 214.2178. $[\alpha]_D$ = +28.6 (c 2.885, EtOAc).

4.5. L-*N*-Cyclohexyl-dibutyl valinol (L-H_2VCB)

L-H_2VCB was prepared according to typical procedure 1 starting from L-*N*-cyclohexyl-valine methyl ester (2.7038 g, 12.6 mmol)[77] to give an impure yellow oil (2.8638 g, 9.6 mmol, 80.2% yield). The product was purified via flash column chromatography (5% EtOAc, 0.1% Et_3N, hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.809 (d, 1H, J = 6.8 Hz), 0.926 (td, J_1 = 1.4 Hz, J_2 = 5.6 Hz, 4H), 0.979 (d, 2H, J = 6.8), 1.061 (d, 2H, J = 7.2 Hz) 1.27–1.98 (br m, 25H), 2.555 (m, 2H), 3.128 (d, J = 5.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 74.575, 64.155, 57.317, 37.127, 35.821, 35.050, 34.325, 28.511, 26.456, 26.162, 26.125, 25.719, 25.236, 25.068, 24.123, 23.907, 18.149, 14.563 (one carbon not observed). Anal. Calcd for $C_{19}H_{39}NO$: C, 76.70; H, 13.21; N, 4.71. Found: C, 76.20; H, 13.34; N, 3.74. HRMS (EI+) calcd for $C_{19}H_{40}NO$ (MH^+): 298.3110, found: 298.3115. $[\alpha]_D$ = +19.3 (c 1.985, EtOAc).

4.6. L-*N*-Cyclohexyl-diphenyl valinol (L-H_2VCP)

L-H_2VCP was prepared according to typical procedure 1 starting from L-*N*-cyclohexyl-valine methyl ester (1.415 g, 6.64 mmol)[77] to give a light yellow solid (2.0583 g, 6.10 mmol, 92% yield). The solid was recrystallized from boiling ethanol. Mp 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.6 (d, J = 6.8 Hz, 3H), 0.83–0.86 (m, 4H), 1.0 (d, 6.8 Hz, 3H), 1.5–1.8 (m, 6H), 2.1 (sept, 1H), 3.6 (d, J = 2.0 Hz, 1H), 7.15–7.18 (m, 2H), 7.26–7.30 (m, 4H), 7.5 (m, 2H), 7.6 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 23.5, 25.7, 25.8, 26.4, 28.9, 35.2, 34.4, 35.2, 55.4, 65.2, 78.4, 126.5, 127.5, 128.2, 128.3, 146.2, 149.5 (two additional aromatic carbons appear to overlay at 126.5 ppm). Anal. Calcd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 81.83; H, 9.09; N, 4.34. HRMS (EI+) calcd

for $C_{23}H_{32}NO$: 338.2484, found: 338.2499. $[\alpha]_D = -42.3$ (*c* 2.23, CH_2Cl_2).

4.7. L-*N*-Adamantyl-dimethyl valinol (L-H_2VAM)

L-H_2VAM was prepared according to typical procedure 1 starting from L-*N*-adamantyl-valine methyl ester (1.7266 g, 6.565 mmol)[77] to give a yellow oil (1.0613 g, 3.998 mmol, 60.9%). This was then purified with flash column chromatography (5% EtOAc, 0.5% Et_3N, hexanes). The final product was a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.869$ (br s, 1H), 2.358 (d, 1H, $J = 2.4$ Hz), 2.055–1.537(m, 15H) 1.220 (s, 3H), 1.079 (d, 3H, $J = 7.2$ Hz), 1.063 (s, 3H), 0.953 (d, 3H, $J = 7.2$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ =71.271, 69.089, 61.755, 38.190, 37.847, 37.158, 34.204, 31.477, 31.361, 31.284, 28.711, 27.985, 27.651, 25.172, 24.365, 17.49 (one carbon not observed). Anal. Calcd for $C_{17}H_{31}NO$: C, 76.92; H, 11.77; N, 5.28. Found: C, 77.04; H, 11.92; N, 5.18. $[\alpha]_D = +26.05$ (*c* 4.78, EtOAc).

4.8. L-*N*-Adamantyl-dibutyl valinol (L-H_2VAB)

L-H_2VAB was prepared according to typical procedure 1 starting from L-*N*-adamantyl-valine methyl ester (1.3583 g, 5.118 mmol)[77] to give a yellow oil (1.5847 g, 4.533 mmol, 88.6%). This was then purified with flash column chromatography (3% EtOAc, 0.5% Et_3N, hexane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$–0.94 (m, 12H), 1.052 (d, $J = 7.2$ Hz, 3H), 1.2–2.2 (m, 24H) 2.503 (d, 1H, $J = 2.4$ Hz), 2.806 (br s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 75.10$, 66.20, 62.75, 60.98, 38.79, 38.40, 37.84, 37.28, 36.09, 34.60, 32.32, 32.07, 31.86, 28.56, 28.18, 26.42, 26.37, 25.44, 24.36, 24.13, 21.65, 18.16, 14.78. Anal. Calcd for $C_{23}H_{43}NO$: C, 79.02; H, 12.40; N, 4.01. Found: C, 78.71; H, 12.17; N, 4.02. HRMS(EI): calcd for $C_{23}H_{44}NO$: 350.3423, found: 350.3428. $[\alpha]_D = +22.2$ (*c* 3.745, EtOAc).

4.9. L-*N*-Adamantyl-diphenyl valinol (L-H_2VAP)

^{l}-H_2VAP was prepared according to typical procedure 1 starting from L-*N*-adamantyl-valine methyl ester (1.74 g, 6.56 mmol)[77] to give an impure yellow solid (2.6657 g, 6.85 mmol, 104% yield). The solid was recrystallized from boiling hexane. Mp 177–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.68$ (d, $J = 6.8$ Hz, 3H), 1.04 (d, $J = 6.8$ Hz, 3H), 1.1–1.9 (14H), 2.1 (m, 2H), 3.6 (d, $J = 1.6$ Hz, 1H), 7.16–7.17 (m, 2H), 7.25–7.30 (m, 4H), 7.56 (d, 2H), 7.66 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.5$, 23.7, 27.8, 29.1, 31.8, 31.8, 32.0, 33.8, 38.1, 38.1, 38.2, 60.5, 67.1, 78.6, 126.5, 126.5, 126.7, 128.2, 128.3, 146.3, 149.5. (two carbon signals not observed). Anal. Calcd for $C_{27}H_{35}NO$: C, 83.24; H, 9.06; N, 3.60. Found: C, 83.03; H, 9.85; N, 3.65. HRMS (EI+) calcd for $C_{27}H_{36}NO$: 390.2797, found: 390.2792. $[\alpha]_D = -34.3$ (*c* 2.21, CH_2Cl_2).

4.10. L-*N*-Isopropyl-dimethyl phenylalanol (L-H_2PPM)

L-H_2PPM was prepared according to typical procedure 1 starting from L-*N*-isopropyl-phenylalanine methyl ester (1.78 g, 8.06 mmol)[77] to give an impure yellow oil in greater than quantitative yield. The oil could be purified by vacuum distillation (0.7624 g, 3.44 mmol, 43%). Bp 97–98 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.71$ (d, $J = 6.0$ Hz, 3H), 0.84 (d, $J = 6.0$ Hz, 3H), 1.1 (s, 3H), 1.2 (s, 3H), 2.18 (sept, $J = 6.0$ Hz, 1H), 2.4 (dd, $J_1 = 9$ Hz, $J_2 = 15$ Hz, 1H), 2.6 (dd, $J_1 = 4.5$ Hz, $J_2 = 10$ Hz, 1H), 3.0 (dd, $J_1 = 4.5$ Hz, $J_2 = 14$ Hz, 1H), 7.2 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.5$, 24.0, 24.5, 27.5, 39.8, 48.2, 66.6, 71.0, 126.7, 128.9, 129.4, 140.5. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.39; H, 10.33; N, 6.10. HRMS(FAB):calcd for $C_{14}H_{24}NO$: 222.1858, found: 222.1853. $[\alpha]_D = -20.9$ (*c* 5.705, EtOAc).

4.11. L-*N*-Isopropyl-dibutyl phenylalanol (L-H_2PPB)

L-H_2PPB was prepared according to typical procedure 1 starting from L-*N*-isopropyl-phenylalanine methyl ester (1.69 g, 7.63 mmol)[77] to give a yellow oil (2.16 g, 7.07 mmol, 93%). The oil can be purified by vacuum distillation under an atmosphere of nitrogen. Bp 110–118 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.68$ (d, $J = 6.0$ Hz, 3H), 0.83 (d, $J = 6.00$ Hz, 3H), 0.92–0.94 (m, 6H), 1.4–1.6 (m, 12H), 2.1 (sept, $J = 6.0$ Hz, 1H), 2.3 (dd, $J_1 = 10.4$ Hz, $J_2 = 13.6$ Hz, 1H), 2.8 (dd, $J_1 = 3.6$ Hz, $J_2 = 10.4$ Hz, 1H), 3.0 (dd, $J_1 = 3.6$ Hz, $J_2 = 13.6$ Hz, 1H), 7.2 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.6$, 14.6, 23.5, 23.9, 24.1, 25.9, 26.0, 36.2, 36.7, 39.3, 48.6, 63.4, 73.7, 126.7, 128.8, 129.5, 140.7 (one aliphatic carbon not observed). Anal. Calcd for $C_{20}H_{35}NO$: C, 78.63; H, 11.55; N, 4.58. Found: C, 78.28; H, 11.61; N, 4.42. HRMS (FAB):calcd for $C_{20}H_{36}NO$: 306.2797, found: 306.2798. $[\alpha]_D = +1.1$ (*c* 5.49, EtOAc).

4.12. L-*N*-Isopropyl-diphenyl phenylalanol (L-H_2PPP)

L-H_2PPP was prepared according to typical procedure 1 starting from L-*N*-isopropyl-phenylalanine methyl ester (1.28 g, 5.79 mmol) to give a yellow solid (2.02 g, 5.87 mmol, 101%). The solid was recrystallized from boiling hexane. Mp 110–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.402$ (d, $J = 6.0$ Hz, 3H), 0.623 (d, $J = 6.4$ Hz, 3H), 1.847 (sept, $J = 6.0$ Hz, 1H), 2.188 (dd, $J_1 = 14.0$ Hz, $J_2 = 10.4$ Hz, 1H), 2.954 (dd, $J_1 = 2.4$ Hz, $J_2 = 14.0$ Hz, 1H), 3.905 (dd, $J_1 = 2.8$ Hz, $J_2 = 10.8$ Hz, 1H), 7.2–7.4 (m, 11H), 7.6–7.7 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.6$, 24.4, 38.8, 47.6, 64.0, 78.2, 126.4, 126.5, 126.8, 126.9, 127.0, 128.5, 128.6, 129.0, 129.7, 140.1, 145.8, 148.2. Anal. Calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.25; H, 8.03; N, 4.07. HRMS (EI+) calcd for $C_{24}H_{28}NO$: 346.2171, found: 346.2154. $[\alpha]_D = +3.6$ (*c* 5.00, EtOAc).

4.13. L-*N*-Cyclohexyl-dimethyl phenylalanol (L-H_2PCM)

L-H_2PCM was prepared according to typical procedure 1 starting from L-*N*-cyclohexyl-phenylalanine methyl ester (1.90 g, 7.29 mmol)[77] to give an impure yellow oil. The oil could be purified by vacuum distillation (0.8178 g, 3.13 mmol, 43%). Bp 121–127 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.4$–1.1 (m, 5H), 1.12 (s, 3H), 1.24 (s, 3H), 1.4–1.8 (m, 6H), 2.38 (dd, $J_1 = 9.9$ Hz, $J_2 = 13.7$ Hz, 1H), 2.66 (dd, $J_1 = 4.0$ Hz, J_2 9.9 Hz, 1H), 3.00 (dd, $J_1 = 4.0$ Hz, $J_2 = 13.7$ Hz, 1H), 7.2 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.5$, 25.0, 25.4, 26.3, 27.6, 34.4, 34.5, 39.7, 56.4, 66.4, 71.1, 126.7, 128.8, 129.5, 140.4. Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.94; H, 10.28; N, 5.26. HRMS(EI):calcd for $C_{17}H_{28}NO$: 262.2171, found: 262.2170. $[\alpha]_D = -8.6$ (*c* 5.945, EtOAc).

4.14. L-*N*-Cyclohexyl-dibutyl phenylalanol (L-H_2PCB)

L-H_2PCB was prepared according to typical procedure 1 starting from L-*N*-cyclohexyl-phenylalanine methyl ester (1.50 g, 5.75 mmol)[77] to give a yellow oil (1.96 g, 5.67 mmol, 99%). The oil was purified by vacuum distillation. Bp 148–152 °C, <1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.75$–1.0 (m, 9H), 1.3–1.6 (m, 19H), 1.8 (br m, 1H), 2.36 (dd, $J_1 = 10.4$ Hz, $J_2 = 13.6$ Hz, 1H), 2.82 (dd, $J_1 = 3.6$ Hz, $J_2 = 10.4$ Hz, 1H), 2.97 (dd, $J_1 = 13.6$ Hz, $J_2 = 3.6$ Hz, 1H), 7.2 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.6$, 22.7, 23.9, 24.1, 25.0, 25.5, 25.9, 26.3, 34.3, 34.4, 36.2, 36.7, 37.8, 39.2, 56.8, 63.3, 73.8, 126.7, 128.9, 129.5, 140.6. Anal. Calcd for $C_{23}H_{39}NO$: C, 79.94; H, 11.38; N, 4.05. Found: C, 79.30; H, 11.12; N, 3.68. HRMS

(EI+) calcd for $C_{23}H_{40}NO$: 346.3110, found: 346.3120. $[\alpha]_D$ = +9.4 (*c* 5.205, EtOAc).

4.15. L-*N*-Cyclohexyl-diphenyl phenylalanol (L-H_2PCP)

L-H_2PCP was prepared according to typical procedure 1 starting from L-*N*-cyclohexyl-phenylalanine methyl ester (1.74 g, 6.64 mmol)[77] to give a yellow solid (2.43 g, 6.32 mmol, 95%). The solid was recrystallized from boiling ethanol. Mp 100–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.6–0.9 (m, 4H), 1.2–1.4 (m, 7H), 2.20 (dd, J_1 = 10.3 Hz, J_2 = 14.4 Hz, 1H), 2.95 (dd, J_1 = 2.8 Hz, J_2 = 14.0 Hz, 1H), 3.98 (dd, J_1 = 2.8 Hz, J_2 = 10.8 Hz, 1H), 7.3 (m, 11H), 7.6 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 25.5, 26.2, 33.3, 35.0, 38.6, 55.0, 63.5, 78.1, 126.4, 126.5, 126.8, 126.9, 126.9, 128.4, 128.6, 129.0, 129.6, 140.2, 145.8, 148.2. Anal. Calcd for $C_{27}H_{31}NO$: C, 84.11; H, 8.18; N, 3.63. Found: C, 83.80; H, 8.24; N, 3.65. HRMS (EI+): calcd for $C_{27}H_{32}NO$: 386.2484, found: 386.2494. $[\alpha]_D$ = +5.6 (*c* 2.885, EtOAc).

4.16. L-*N*-Adamantyl-dimethyl phenylalanol (L-H_2PAM)

L-H_2PAM was prepared according to typical procedure 1 starting from L-*N*-adamantyl-phenylalanine methyl ester (0.542 g, 1.73 mmol)[77] to give an impure yellow oil (0.336 g, 1.07 mmol, 62%). The oil was purified by column chromatography (15% EtOAc, hexanes). Mp 100–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ =1.161 (s, 3H), 1.236 (s, 3H), 1.3–1.8 (m, 12H), 1.8–1.9 (br m, 2H), 2.165 (br s, 1H), 2.440 (dd, J_1 = 13.7 Hz, J_2 = 9.6 Hz, 1H), 2.655 (dd, J_1 = 9.6 Hz, J_2 = 4.0 Hz, 1H), 3.012 (dd, J_1 = 4.0 Hz, J_2 = 13.7 Hz, 1H), 7.2–7.3 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 23.1, 24.6, 27.7, 27.9, 31.6, 32.0, 32.1, 37.4, 38.2, 39.8, 61.5, 67.9, 71.4, 77.4, 126.7, 128.8, 129.4, 140.5. Anal. Calcd for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.09; H, 9.92; N, 4.46. $[\alpha]_D$ = +0.2 (*c* 2.435, EtOAc).

4.17. L-*N*-Adamantyl-dibutyl phenylalanol (L-H_2PAB)

L-H_2PAB was prepared according to typical procedure 1 starting from L-*N*-adamantyl-phenylalanine methyl ester (3.758 g, 11.48 mmol)[77] to give a dark yellow oil in more than quantitative yield (5.1 g). The product could be purified by column chromatography (10% ethyl acetate, 0.5% NEt_3 in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.8–1.0 (m, 6H), 1.2 - 1.7 (m, 25H), 1.95 (br m, 1H), 2.01 (br s, 1H), 2.40 (dd, J_1 = 10.0 Hz, J_2 = 13.6 Hz, 1H), 2.79 (dd, J_1 = 3.6 Hz, J_2 = 10.0 Hz, 1H), 3.01 (dd, J_1 = 3.6 Hz, J_2 = 13.6 Hz, 1H), 7.2–7.3 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7, 129.5, 128.8, 126.7, 74.2, 64.9, 61.9, 39.3, 38.2, 38.1, 37.4, 36.8, 36.2, 34.2, 32.1, 31.6, 27.9, 27.8, 26.1, 26.0, 24.2, 23.9, 14.7, 14.6 (1 aliphatic carbon not observed). MS: (DCI) *m/z*: 398 [MH^+] calculated for $C_{27}H_{44}NO$: 398.3423, found: 398.3416. Anal. calcd for $C_{27}H_{43}NO$: C, 81.55; H, 10.90; N, 3.52. Found: C, 82.07; H, 10.73; N, 3.69. $[\alpha]_D$ = +9.9 (*c* 5.23, EtOAc).

4.18. L-*N*-Adamantyl-diphenyl phenylalanol (L-H_2PAP)

L-H_2PAP was prepared according to typical procedure 1 starting from L-*N*-adamantyl-phenylalanine methyl ester (1.43 g, 4.57 mmol)[77] to give a yellow solid (2.06 g, 4.70 mmol, 103%). The solid was recrystallized from boiling ethanol. Mp 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.6 (br d, 1H), 0.9 (br d, 2H), 1.0 (br d, 1H), 1.3–1.7 (m, 11H), 2.284 (dd, J_1 = 10.8 Hz, J_2 = 14.0 Hz, 1H), 2.941 (dd, J_1 = 2.8 Hz, J_2 = 14.4 Hz, 1H), 3.973 (dd, J_1 = 3.2 Hz, J_2 = 11.2 Hz, 1H), 7.3 (m, 11H), 7.7 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5, 27.7, 30.5, 31.1, 31.5, 33.9, 37.9, 38.0, 38.2, 38.5, 59.5, 64.3, 77.9, 126.2, 126.3, 126.4, 126.9, 127.0, 128.4, 128.6, 129.1, 129.7, 140.2, 146.0, 148.6. Anal. Calcd for $C_{31}H_{35}NO$: C, 85.08; H, 8.06; N, 3.20. Found: C, 84.90; H, 8.13; N, 3.21. HRMS (EI+) calcd for $C_{31}H_{36}NO$: 438.2797, found: 438.2815. $[\alpha]_D$ = +4.1 (*c* 4.90, EtOAc).

4.19. Typical procedure 2 for catalytic hydroamination

Hydroamination was carried out with 5% catalyst loading. Solutions of ligands (~0.050 M) and aminoallene (~1.6 M) in C_6D_6 were dried over molecular sieves overnight and stored at −35 °C when not in use. Solutions of titanium tetrakisdimethylamide (~1.2 M) in C_6D_6 were also prepared. In the glove box, the titanium tetrakisdimethylamide solution (70 μL, 6.0×10^{-3} mmol) ligand (120 μL, 6.0×10^{-3} mmol), and deuterated benzene (110 μL) were combined in a J. Young NMR tube, and an NMR spectrum was acquired, showing the formation of dimethylamine as the ligand displaces two of the dimethylamide ligands. Next, aminoallene solution (100 μL, 0.120 mmol) was added, and the tube was placed into a heated oil bath. The progress of the reaction was monitored periodically by NMR spectroscopy. After completion of the reaction, the volatiles from the reaction were vacuum transferred to a new tube containing (*R*)-(*O*)-acetylmandelic acid (14.6 mg, 75 μmol). An NMR spectrum revealed diastereomeric splitting of the doublet at 5.3 ppm with baseline separation. The two doublets were integrated, the percent of each isomer was calculated, and the enantiomeric excess was determined.

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