New Expedient Route to Both Enantiomers of Nonproteinogenic α-Amino Acid Derivatives from the Unsaturated 2-Aza-Bicyclo Moiety

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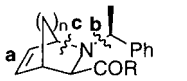
The influence of the reaction conditions on the catalytic hydrogenation of 2-aza-bicyclo hept-5-ene and oct-5-ene derivatives has been investigated. We found it possible to fully control the extent of allylic vs benzylic C−N hydrogenolysis by simple variations of H_2 pressure and acidity of the reaction medium. The use of the reaction pathways was demonstrated by the selective preparation of four categories of optically active α-amino acid derivatives. The strategy was also extended to the synthesis of enantiopure α-amino ketones.

Introduction

α-Amino acids, both natural and unnatural, play a central part in biology and chemistry.[1] They are the fundamental constituents of proteins and other biologically important compounds and one of the most frequently used sources of chiral starting materials for organic synthesis.[1a,2] In addition, amino acid derivatives have been widely used as chiral reagents,[1a] auxiliaries,[1a] and ligands for asymmetric catalysis.[3]

Although a few short routes to unnatural α-amino acids have been developed,[4] many preparations involve multistep reaction sequences giving rise to only one of the two enantiomers.[1b−c] Because of the divergent biological activity of the two forms, it is of importance that both enantiomers are readily available in optically pure form.

The diastereoselective aza-Diels−Alder reaction has been a useful tool for the preparation of several efficient chiral ligands used in various metal-catalyzed asymmetric transformations, including allylic oxidation,[5a] transfer hydrogenation,[5b] reduction of ketones,[5c] rearrangement of epoxides,[5d] diethylzinc addition to imines,[5e] and aldehydes.[5f] To form the different ligands, the aza-Diels−Alder adduct may be manipulated by hydrogenation of either the double bond selectively (bond **a**, Figure 1) or in concert with hydrogenolytic *N*-debenzylation (**a** and **b**, Figure 1). These reactions have been reported to run without difficulties,[5f,6] using H_2, Pd on carbon as catalyst, and EtOAc as solvent. However, we found that these conditions often gave rise to a byproduct that was identified as a ring-opened species resulting from allylic C−N cleavage (bond **c**, Figure 1). Because the byproduct formed is a useful α-amino acid derivative, we investigated the hydrogenolysis/hydrogenation to improve the reaction.



n = 1 or 2
R = EtO-, BnO-, Ph-

Figure 1.

We here report a method to obtain from one single substrate four different compounds as sole products. Particularly interesting is the α-amino ester, which after reduction to the amino alcohol could be used as a chiral building block, e.g., in ligand synthesis.

This new route for the synthesis of α-amino acid derivatives can produce both enantiomers as easily. The preparation, a three-step sequence, is easy to do, versatile, and cheap and may be done on a large scale. Using this protocol, it is also possible to obtain optically active α-amino ketones.

Results and Discussion

In Scheme 1, we present the products obtained after performing hydrogenolysis/hydrogenation of the Diels−Alder adduct **1**, of which both enantiomers are available on a multigram scale from cheap starting materials.[7] By

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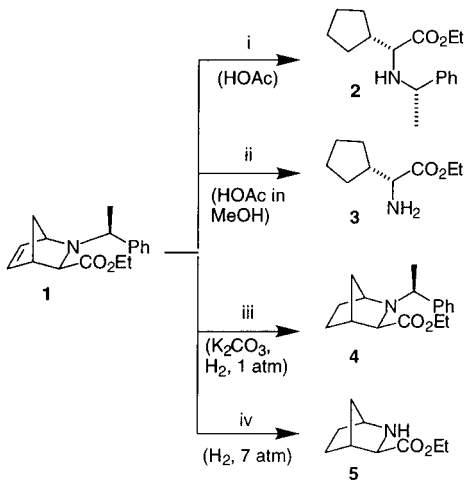
Scheme 1[a]



[a]Key: i) H_2 (1 atm), 5 % Pd/C (10 wt %), HOAc, rt, 98 % yield; ii) H_2 (1 atm), 5 % Pd/C (10 wt %), 10 equiv HOAc, MeOH, rt, 96 % yield; iii) H_2 (1 atm), 5 % Pd/C (10 wt %), 1 equiv K_2CO_3, EtOH, rt, >95 % yield; iv) H_2 (7 atm), 5 % Pd/C (20 wt %), EtOH, rt, 98 %.

varying the acidity and the hydrogen pressure in the reaction vessel, both the extent of hydrogenolysis/hydrogenation and the ratio between these two reactions can be controlled.

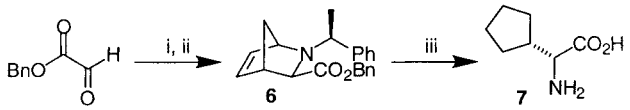
Addition of acetic acid to the reaction mixture accelerated the hydrogenolysis reaction, resulting in ring opening of the bicyclic structure to afford compound **2** or **3** (Scheme 1). When the reaction was carried out in neat HOAc, the protected amino ester **2** was obtained as the sole product, whereas addition of a cosolvent (10 equiv HOAc in MeOH) resulted in cleavage of the phenylethyl group on nitrogen to afford **3**. This observation was not further investigated, but there are several examples in the literature of unpredictable solvent effects in hydrogenolysis/hydrogenation reactions.[8a]

To ensure that the stereochemistry was preserved during the ring opening of the 2-azanorbornene **1**, the enantiomeric excess of the aminoester **3** was determined and found to be 99.3% ee (chiral GC, see Experimental Section). It should be noted that both enantiomers of **3** were readily available and were prepared in high optical purity when starting from either (*S*)- or (*R*)-phenylethylamine.

To avoid ring opening, the rate of hydrogenation of the C−C double bond needs to be greater than the rate of hydrogenolysis of the allylic C−N bond. This is because the substrate cannot undergo ring opening after reduction of the double bond has taken place (compare cleavage of an ordinary C−N bond with an allylic C−N bond).[8b] To completely suppress allylic C−N cleavage, EtOH was used as solvent instead of EtOAc because EtOAc might contain small amounts of acetic acid which could activate the allylic bond by protonation of the amine moiety. Also, to further reduce the risk of ring opening, 1 equiv of K_2CO_3 was added to increase the basicity of the reaction mixture.[8c] When performing a selective reduction of the olefin in the presence of a benzylamine function to obtain compound **4**[5f] (Scheme 1), the hydrogen pressure required was 1 atm. If the desired product was the debenzylated bicyclic amino ester **5**,[5e] the pressure was increased to 7 atm. When running the reaction at this elevated pressure, addition of K_2CO_3 can be excluded without any effect on the selectivity.

If the desired product is the amino acid and not the amino ester, the benzylic ester **6**, prepared from benzylglyoxal monohydrate and cyclopentadiene, is used (Scheme 2).[5a] With compound **6**, it is possible to perform both

Scheme 2[a]

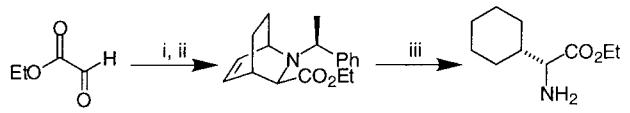


[a]Key: i) (*S*)-1-phenylethylamine, CH_2Cl_2, 0 °C; ii) TFA, BF_3•OEt_2, cyclopentadiene, -78 °C to rt, 83 %; iii) H_2 (7 atm), 20% $Pd(OH)_2$ /C (10 wt %),10 equiv HOAc, MeOH, rt, 98 % yield.

hydrogenolysis/hydrogenation and ester hydrogenolysis in one step, which furnishes the free amino acid **7** in excellent yield.

The described route for preparation of cyclopentylglycine ethyl ester **3** can be extended to synthesis of other α-amino esters by changing the diene in the aza-Diels−Alder reaction. Replacing cyclopentadiene with cyclohexadiene gives rise to the derivative **8**,[7] which after hydrogenolysis/hydrogenation results in cyclohexylglycine ethyl ester **9** (Scheme 3).

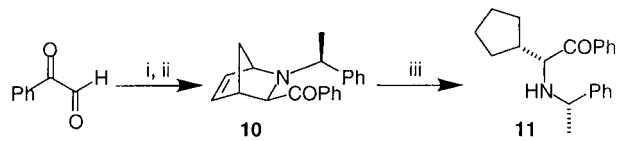
Scheme 3[a]



[a]Key: i) (*S*)-1-phenylethylamine, CH_2Cl_2, 0 °C; ii) TFA BF_3•OEt_2, cyclohexadiene, -78 °C to rt, 31 %; iii) H_2 (1 atm), 5% Pd/C (10 wt %),10 equiv HOAc, MeOH, rt, 93 % yield.

Our new approach to α-amino esters can also be used in the synthesis of chiral α-amino ketones. In Scheme 4,

Scheme 4[a]



[a]Key: i) (*S*)-1-phenylethylamine, CH_2Cl_2, 0 °C; ii) TFA, BF_3•OEt_2, cyclopentadiene, -78 °C to rt, 42%; iii) H_2 (1 atm), 5 % Pd/C (10 wt %), HOAc, rt, 97 % yield.

the preparation of the α-amino phenyl ketone **11** from the 2-azanorbornyl adduct **10** is outlined. α-Amino ketones have, like amino acids, proven to be useful chiral building blocks in asymmetric synthesis.[9]

The amino ester **5** obtained by hydrogenolysis/hydrogenation of the 2-azanorbornyl derivative in acidic reaction medium (10 equiv HOAc in MeOH) can easily be transformed into the corresponding amino alcohol by reduction with $LiAlH_4$. This amino alcohol has proved to be a valuable building block for the preparation of chiral

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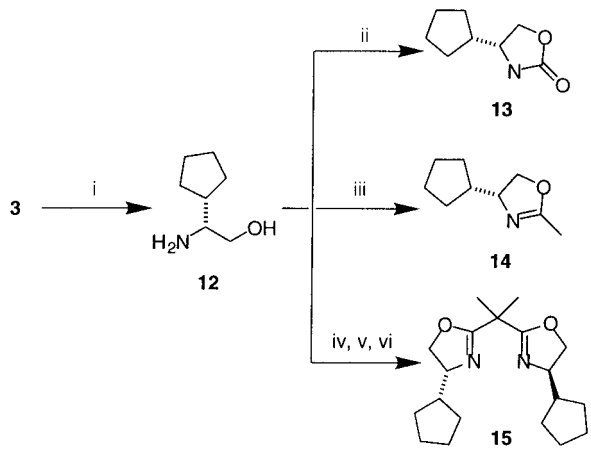
Scheme 5[a]



[a] Key: i) $LiAlH_4$, THF, 0 °C, 98 % yield; ii) Et_3N, $COCl_2$ in toluene, CH_2Cl_2, rt, 96 % yield; iii) acetimidoethylether hydrochloride, CH_2Cl_2, 0 °C to rt, 70 %; iv) 2,2-dimethyl malonyldichloride, Et_3N, CH_2Cl_2 , 0 °C to rt; v) $SOCl_2$, benzene, reflux; vi) 0.5 M NaOH/MeOH, reflux. Overall yield 75 % (iv to vi).

auxiliaries and ligands for use in asymmetric synthesis. Some examples of its applications are shown in Scheme 5.

Conclusions

In this paper, we report on a simple route to optically pure α-amino acid derivatives, including amino esters and amino ketones. By this route, both enantiomeric forms of the derivatives are readily available in high optical purity.

Experimental Section

General Comments. For general experimental information, see refs 10 and 5d. All reactions were run under N_2, using dry glassware. Pd/C was purchased from Lancaster Chemical Co. or Aldrich Co. ^1H and ^{13}C NMR spectra are for $CDCl_3$ solutions. GC analysis was performed on a Varian 3400 capillary gas chromatograph using a CP-Chirasil-Dex CB (25 m/0.25 mm i.d.) column under isothermic conditions, with N_2 (7 atm) as carrier gas and a flame ionization detector. Mass spectra were recorded using a Finnigan MAT GCQ PLUS system.

(1*R*,3*R*,4*S*)-2-[(1*S*)-Phenylethyl]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic Acid Ethyl Ester (1).[11] Compound **1** was prepared via an aza-Diels−Alder reaction after a literature procedure.[7] All of the physical and spectroscopic data for compound **1** were in complete agreement with the reported data for its enantiomer,[11] except the sign of the optical rotation.

(2*R*)-Cyclopentyl-*N*-[(1*S*)-phenylethyl]-glycine Ethyl Ester (2). A solution of amino ester **1** (1.0 g, 3.7 mmol) in acetic acid (50 mL) was stirred under H_2 (1 atm) at room temperature overnight in the presence of 5% Pd/C (0.10 g). The reaction mixture was filtered through a pad of Celite, and the filter was washed with MeOH, which was removed in vacuo. The residue was dissolved in CH_2Cl_2 and triethylamine (10:1, 50 mL) and washed with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford **2** (1.0 g, 98%) as a colorless oil. An analytical amount was purified by flash chromatography (deactivated silica, pentane/Et_2O: 9/1): R_f 0.75 (pentane/ Et_2O, 8:2); $[\alpha]^{25}_D$ −8.2 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) 3330, 1723; ^1H NMR (300 MHz) δ 1.19 (3 H, t, *J* = 7.2 Hz), 1.31 (3 H, d, *J* = 6.6 Hz), 1.35−1.81 (9 H, m), 1.99−2.04 (1 H, m), 3.12 (1 H, d, *J* = 8.1 Hz), 3.70 (1 H, q, *J* = 6.6 Hz), 3.95−4.06 (2 H, m), 7.20−7.33 (5 H, m); ^{13}C NMR (75.3 MHz) δ 14.3, 22.6, 25.1, 25.3, 28.9, 29.5, 43.5, 57.0, 60.2, 63.7, 126.8, 127.0, 128.3, 145.8, 175.9; MS (GC) *m*/*z* (rel intensity) 276 ($M + H^+$, 15), 202 (100), 105 (54), 98 (63). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.29; H, 9.06; N, 4.87.

(2*R*)-Cyclopentyl Glycine Ethyl Ester (3).[12] A solution of **1** (2.5 g, 9.2 mmol) and acetic acid (5.3 mL, 92 mmol) in MeOH (100 mL) was stirred under H_2 (1 atm) for 3 h at room temperature in the presence of 5% Pd/C (0.25 g). The catalyst was removed by filtration through a pad of Celite, which was washed with MeOH. After concentration in vacuo, the residue was dissolved in CH_2Cl_2 and triethylamine (10:1, 50 mL) and washed with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to afford **3** (1.5 g, 96%) pure by ^1H NMR. An analytically pure sample was prepared by flash chromatography (deactivated silica, pentane/EtOAc, 3:1). The enantiomeric purity of (**3**) was determined to 99.3% ee using chiral GC analysis: (110 °C) t_r (R) = 29.57 min, t_r (S) = 32.64 min; R_f 0.60 (pentane/EtOAc, 3:2); $[\alpha]^{25}_D$ −10.2 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) 3384, 1726; ^1H NMR (300 MHz) δ 1.27 (3 H, t, *J* = 7.2 Hz), 1.30−1.77 (10 H, m), 2.01−2.13 (1 H, m), 3.28 (1 H, d, *J* = 7.2 Hz), 4.13 (2 H, q, *J* = 7.2 Hz); ^{13}C NMR (75.3 MHz) δ 14.2, 25.3, 25.5, 28.4, 29.1, 44.3, 58.3, 60.6, 175.9; MS (GC) *m*/*z* (rel intensity) 172 ($M + H^+$, 12), 98 (100), 81 (86), 79 (28). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.24; H, 9.78; N, 8.05. The *S*-enantiomer has the same physical and spectroscopic data, except for the sign of the optical rotation.

(1*S*,3*R*,4*R*)-2-[(1*S*)-Phenylethyl]-2-aza-bicyclo[2.2.1]heptane-3-carboxylic Acid Ethyl Ester (4).[5f] Pd/C (5%, 50 mg) and K_2CO_3 (0.25 g, 1.8 mmol) were added to a solution of **1** (0.50 g, 1.8 mmol) in EtOH (10 mL). The reaction mixture was stirred under H_2 (1 atm) at room temperature for 1 h. The catalyst was removed by filtration through a thin pad of Celite, and the filtrate was concentrated in vacuo to afford **4** (0.46 g, >95% yield) as a white solid. All of the physical and spectroscopic data for compound **4** were in complete agreement with the reported data for its enantiomer,[5f] except for the sign of the optical rotation.

(1*S*,3*R*,4*R*)-2-Aza-bicyclo[2.2.1]heptane-3-carboxylic Acid Ethyl Ester (5).[5e] Compound **5** was prepared using a literature procedure, and all of the physical and spectroscopic data were in complete agreement with the reported data.[5e]

(1*R*,3*R*,4*S*)-2-[(1*S*)-Phenylethyl]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic Acid Benzyl Ester (6).[5a] Compound **6** was prepared using a literature procedure, and all of the physical and spectroscopic data were in complete agreement with the reported data for its enantiomer,[5a] except for the sign of the optical rotation.

(2*R*)-Cyclopentyl Glycine (7).[13] A solution of **6** (0.10 g, 0.31 mmol) in acetic acid (0.18 mL, 3.1 mmol) and MeOH (5 mL) was stirred under H_2 (7 atm) for 24 h at room temperature in the presence of 20% $Pd(OH)_2$/C (0.01 g). The catalyst was removed by filtration through a thin pad of Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and Et_3N (10:1, 10 mL) and extracted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to afford **7** (0.04 g, 98%). All the physical and spectroscopic data were in complete agreement with the reported data.[13]

(1*R*,3*R*,4*S*)-2-[(1*S*)-Phenylethyl]-2-aza-bicyclo[2.2.2]oct-5-ene-3-carboxylic Acid Ethyl Ester (8).[7] Compound **8** was

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prepared using a literature procedure.[7] (*S*)-1-Phenylethylamine (10 mL, 79 mmol) was added to a solution of ethylglyoxylate (10 g, 75 mmol) in dry CH_2Cl_2 (100 mL) containing activated molecular sieves (30 g) at 0 °C, and the mixture was stirred for 1 h. The reaction mixture was cooled to −78 °C, and trifluoroacetic acid (6.0 mL, 79 mmol), $BF_3{-}OEt_2$ (9.9 mL, 79 mmol), and cyclohexadiene (6.3 g, 79 mmol) were added. The reaction mixture was allowed to slowly reach room temperature and was stirred for 48 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. After filtration and extraction with CH_2Cl_2, the organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (deactivated silica, pentane/EtOAc, 20:1) to afford **8** (6.9 g, 31%) as a colorless oil. All the physical and spectroscopic data were in complete agreement with the reported data.[7]

(2*R*)-Cyclohexyl Glycine Ethyl Ester (9).[14] The product was prepared following the same procedure as described above for **3** to afford **9** (0.4 g, 93%) as a colorless oil. An analytical amount was purified by flash chromatography (deactivated silica, pentane/ether, 1:1): R_f 0.25 (pentane/Et_2O, 1:1); $\eta_D^{24} = 1.4641$; $[\alpha]_D^{25} = -31.0$ (*c* 0.50, $CHCl_3$); IR (film, cm^{-1}) 3450−3200, 1732; ^1H NMR (200 MHz) δ 0.90−1.18 (5 H, m), 1.22 (3 H, t, $J = 7.0$ Hz) 1.40−1.78 (8 H, m), 3.19 (1 H, d, $J = 4.8$ Hz), 4.12 (2 H, q, $J = 7.0$); ^{13}C NMR (50.2 MHz) δ 14.1, 25.9, 26.0, 26.1, 27.6, 29.5, 42.0, 59.5, 60.4, 175.6; MS (GC) *m*/*z* (rel intensity) 186 ($M + H^+$, 13), 112 (100), 95 (84), 67 (30).

(1*R*,3*R*,4*S*)-3-Benzoyl-2-[(1*S*)-phenylethyl]-2-azabicyclo-[2.2.1]hept-5-ene (10). Compound **10** was prepared using a literature procedure.[7] (*S*)-1-Phenylethylamine (2.0 mL, 16 mmol) was added to a solution of phenylglyoxal monohydrate-(2.0 g, 15 mmol) in dry CH_2Cl_2 (15 mL) containing activated molecular sieves (10 g) at 0 °C, and the mixture was stirred for 1 h. The reaction mixture was cooled to −78 °C, and trifluoroacetic acid (1.2 mL, 16 mmol), $BF_3{-}OEt_2$ (2.0 mL, 16 mmol) and cyclopentadiene (1.3 mL, 16 mmol) were added. The reaction mixture was allowed to slowly warm to room temperature overnight. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. After filtration and extraction with CH_2Cl_2 (3 × 50 mL), the combined organic phases were dried ($MgSO_4$)and concentrated in vacuo. The residue was purified by flash chromatography (deactivated silica, pentane/Et_2O, 99:1 to 4:1) to afford **10** as the major diastereomer (2.0 g, 42%, 6:1 diastereomeric ratio of exo isomers): R_f 0.45 (Et_2O/pentane, 1:4); mp 111−112 °C; $[\alpha]^{25}_D + 10.1$ (*c* 1.00, CH_2Cl_2); IR ($CDCl_3$, cm^{-1}) 3680, 3601, 1711, 1691; ^1H NMR (400 MHz) δ 1.40 (1 H, d, $J = 8.0$ Hz), 1.46 (3 H, d, $J = 6.8$ Hz), 2.19 (1 H, d, $J = 8.4$ Hz), 2.84 (1 H, s), 3.15 (1 H, q, $J = 6.4$ Hz), 3.19 (1 H, s), 4.40 (1 H, s), 6.36 (1 H, dd, $J = 5.6$ Hz, $J = 2.0$ Hz), 6.5 (1 H, m), 6.94 (1 H, m), 7.05 (2 H, t, $J = 7.6$ Hz), 7.20−7.40 (7 H, m); ^{13}C NMR (75.3 MHz) δ 22.7, 44.6, 49.3, 62.7, 64.2, 66.9, 127.0, 127.4, 127.9, 128.0, 128.1, 132.1, 133.6, 136.1, 137.2, 145.1, 201.1; MS (EI) *m*/*z* (rel intensity) 304 ($M + H^+$, 4), 198 (66), 105 (100), 94 (49). Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.21; H, 6.87; N, 4.78.

(2*R*)-Cyclopentyl-1-phenyl-2-[(1*S*)-phenylethylamino]-ethanone (11). The product was prepared following the same procedure as described above for **2**, to afford **11** (0.5 g, 97%) as white crystals. An analytical amount was purified by flash chromatography (deactivated silica, pentane/Et_2O, 99:1): R_f 0.30 (pentane/ether, 99:1); $[\alpha]_D^{25} = -36.5$ (*c* 0.60, EtOAc); IR (film, cm^{-1}) 3300, 1676; ^1H NMR (200 MHz) δ 1.15−1.70 (7 H, m), 1.36 (3 H, d, $J = 6.4$ Hz), 1.95−2.20 (3 H, m), 3.72 (1 H, q, $J = 6.4$ Hz,), 4.18 (1 H, d, $J = 5.8$ Hz), 7.05−7.60 (8 H, m), 7.77 (2 H, app. d, $J = 8.6$ Hz); ^{13}C NMR (50.2 MHz) δ 23.0, 25.0, 25.3, 27.9, 29.5, 43.9, 57.3, 62.8, 126.8, 126.9, 128.1, 128.3, 128.6, 132.9, 137.0, 146.1, 204.6; MS (GC) *m*/*z* (rel intensity) 308 ($M + H^+$, 3), 105 (100), 79 (53); HRMS calcd for $C_{21}H_{25}NO$ 307.1936, found 307.1935.

2-Amino-(2*R*)-cyclopentyl-ethanol (12). A solution of **3** (1.4 g, 8.0 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.91 g, 24 mmol) in dry THF at 0 °C, and the mixture was stirred for 10 min under N_2. The ice bath was removed, and the reaction mixture was stirred for 3 h at room temperature and then quenched following a literature procedure,[15] affording **12** as white crystals in 98% yield (1.0 g). An analytical amount was recrystallized (*tert*-butyl methyl ether) for characterization: R_f 0.40 (pentane/acetone, 4:1); mp 61−62 °C; $[\alpha]^{25}_D$ −12.0 (*c* 0.15, EtOH); IR (KBr, cm^{-1}) 3352, 3251, 1622; ^1H NMR (400 MHz) δ 1.05−1.35 (2 H, m), 1.45−1.92 (10 H, m), 2.60 (1 H, m), 3.25 (1 H, app. t, $J = 9.4$ Hz), 3.64 (1 H, dd, $J = 6.8$, 3.6 Hz); ^{13}C NMR (100.4 MHz) δ 25.1, 25.5, 29.4, 29.8, 44.4, 57.9, 66.0; MS (GC) *m*/*z* (rel intensity) 130 ($M + H^+$, 1), 98 (89), 81 (100), 79 (56). Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.78; N, 10.84. Found: C, 65.20; H, 11.85; N, 10.97. The *S*-enantiomer has the same experimental data, except for the sign of the optical rotation.

(4*R*)-Cyclopentyl-oxazolidin-2-one (13). Triethylamine (3.1 mL, 22 mmol) and a 1.9 M solution of phosgene in toluene (5.1 mL, 9.8 mmol) were added to a solution of **12** (0.63 g, 4.9 mmol) in dry CH_2Cl_2 (30 mL), and the mixture was stirred under N_2 for 1 h. The reaction was quenched with 1 M NaOH (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with 1 M HCl (40 mL) and saturated aqueous NaCl (40 mL) and dried ($MgSO_4$). Concentration in vacuo afforded **13** (0.73 g, 96%) as white crystals, pure by ^1H NMR. An analytical amount was purified by flash chromatography (deactivated silica, pentane/EtOAc, 2:3): R_f 0.30 (pentane/EtOAc, 2:5); mp 115−116 °C; $[\alpha]^{25}_D$ +22.4 (*c* 0.25, EtOH); IR (KBr, cm^{-1}) 3281, 1750, 1722; ^1H NMR (200 MHz) δ 1.05−1.30 (2 H, m), 1.55−1.90 (6 H, m), 2.01 (1 H, m), 3.71 (1 H, m), 4.08 (1 H, dd, $J = 8.4$, 6.4 Hz), 4.46 (1 H, t, $J = 8.4$ Hz), 5.41 (1 H, s); ^{13}C NMR (100.4 MHz) δ 25.1, 25.2, 28.1, 29.0, 44.5, 56.9, 69.4, 160.5; MS (GC) *m*/*z* (rel intensity) 156 ($M + H^+$, 7), 97 (18), 85 (100), 58 (30). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.02. Found: C, 62.04; H, 8.23; N, 8.79.

(4*R*)-Cyclopentyl-2-methyl-4,5-dihydro-oxazole (14). The oxazoline was prepared using a method developed by A. I. Meyers et al.[16] To a solution of acetimidoethyl ether hydrochloride[17] (0.21 g, 1.7 mmol) in dry CH_2Cl_2 (4 mL) was added the amino alcohol **12** (0.20 g, 1.6 mmol) dissolved in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C and then allowed to slowly reach room temperature. After 7 h, the reaction was quenched by pouring the solution into ice water (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **14** (0.17 g, 70% yield) as a colorless oil. An analytical sample was purified by flash chromatography (pentane/EtOAc, 8:2), using deactivated silica: R_f 0.36 (pentane/EtOAc, 3:2); $[\alpha]^{21}_D = +19.9$ (*c* 0.89, CH_2Cl_2); IR (film, cm^{-1}) 3401, 2361, 1677, 1386; ^1H NMR (400 MHz) δ 1.12−1.25 (1 H, m), 1.27−1.41 (1 H, m), 1.46−1.73 (5 H, m), 1.77−1.93 (2 H, m), 1.94 (3 H, d, $J = 1.3$ Hz), 3.85 (1 H, t, $J = 7.9$ Hz), 3.92 (1 H, ddq, $J = 9.1$, 7.9, 1.3 Hz), 4.24 (1 H, dd, $J = 9.1$, 7.8 Hz); ^{13}C NMR (100.4 MHz) δ 13.9, 25.3, 25.4, 29.0, 29.5, 45.1, 71.0, 71.5, 164.4; MS (EI) *m*/*z* (rel intensity) 153 (M^+, <1), 121 (22), 105 (100), 103 (10), 77 (25); HRMS calcd for $C_9H_{15}NO$ 153.1154, found 153.1155.

2,2-Isopropylidenebis-[((4*R*)-cyclohexyl)-4,5-dihydro-oxazole] (15).The ligand was prepared using a three-step literature procedure.[18] To a solution of cyclopentylglycinol (0.50 g, 3.9 mmol) and Et_3N (1.4 mL, 9.7 mmol) in CH_2Cl_2 (10 mL)

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was added via cannula at 0 °C 2,2-dimethylmalonyldichloride (0.33 g, 1.9 mmol) dissolved in 5 mL of CH_2Cl_2. The reaction mixture was allowed to reach room temperature (over 20 min) after which it was diluted with CH_2Cl_2 (40 mL) and washed with 1 M HCl (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were washed with a saturated solution of $NaHCO_3$ (15 mL) and saturated aqueous NaCl (15 mL). After drying with $MgSO_4$, the mixture was filtered and concentrated under reduced pressure to afford the diamidodiol (0.68 g, 1.9 mmol). The crude product was used in the following step without further purification.

To a cooled (0 °C) solution of the diamidodiol (0.68 g, 1.9 mmol) in benzene (10 mL) was added $SOCl_2$ (0.83 mL, 11 mmol). The reaction mixture was heated at reflux for 19 h and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and concentrated to afford the dichloride as a white solid (0.74 g, 1.9 mmol). The dichloride was used without further purification.

The dichloride (0.74 g, 1.9 mmol) was dissolved in a 0.5 M solution of NaOH in MeOH (15 mL, 7.5 mmol). The mixture was heated to reflux and after 3 h concentrated in vacuo. The resulting solid was dissolved in CH_2Cl_2 and washed with a mixture of water and saturated aqueous NaCl (1:1, 25 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield crude product **15** (0.45 g, 1.4 mmol, 75% overall yield from cyclopentylglycinol) as a colorless oil. An analytical sample was purified by flash chromatography (pentane/EtOAc, 4:1) using deactivated silica: R_f 0.23 (pentane/EtOAc, 1:1); $[\alpha]^{21}_D = +119.9$ (*c* 0.97, CH_2Cl_2); IR (film, cm^{-1}) 3000−2800, 2216, 1658, 1452; ^{1}H NMR (400 MHz) δ 1.18−1.34 (4 H, m), 1.50 (6 H, s), 1.42−1.80 (12 H, m), 1.98 (2 H, dpent, J = 8.1, 6.8 Hz), 3.94 (2 H, dd, J = 8.0, 7.0 Hz), 4.05 (2 H, dt, J = 9.4, 7.0 Hz), 4.22 (2 H, dd, J = 9.4, 8.0 Hz); ^{13}C NMR (100.4 MHz) δ 24.4, 25.4, 25.5, 28.4, 28.8, 38.6, 44.7, 70.0, 71.4, 163.8; MS (EI) *m*/*z* (rel intensity) 319 (M^++1, 1), 249 (56), 181 (82), 137 (100), 91 (30). Anal. Calcd for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50; N, 8.80 Found: C, 71.89; H, 9.21; N, 9.09.

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