Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 3575–3580

TETRAHEDRON: *ASYMMETRY*

The preparation of enantiomerically pure cyclopropylalanine

Neil W. Boaz,* Sheryl D. Debenham, Shannon E. Large and Mary K. Moore

Research Laboratories, Eastman Chemical Company, PO Box 1972, Kingsport, TN 37662, USA

Received 24 June 2003; accepted 9 July 2003

Abstract—Single enantiomer cyclopropylalanine (>99.9% ee) and various derivatives were prepared using an asymmetric hydrogenation approach with a rhodium catalyst based on the methyl BoPhoz™ ligand. *N*-Boc cyclopropylalanine benzyl ester was the preferred derivative, as this material is ripe for further selective reaction and can be recrystallized to >99.5% enantiomeric excess.

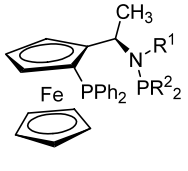
1. Introduction

Asymmetric hydrogenation is an efficient and attractive approach to a number of interesting single enantiomer materials, largely due to the ability to transform inexpensive starting materials such as olefins or ketones into higher value products. The area of asymmetric hydrogenation, and in particular the design and synthesis of novel ligands for these transformations, has been under intense investigation.[1] Although there are a number of materials available via asymmetric hydrogenation, the preparation of amino acid derivatives using this technology has long been of particular interest. Indeed, the first commercial application of asymmetric hydrogenation was the preparation by Knowles of L-DOPA.[2] The mechanism of this type of reaction has been thoroughly studied,[1b,3] and the central nature of this asymmetric hydrogenation reaction is indicated by the fact that virtually all new ligands prepared are tested for enantioselectivity in the hydrogenation of dehydroamino acid derivatives.

The continuing interest in unnatural amino acids is driven by their extensive use as key building blocks for a large variety of pharmaceutically active materials. The cyclopropyl group is also an important pharmacophore, and has found its way into a number of pharmaceutical agents. Cyclopropyl-substituted amino acids are an intriguing combination of these two functionalities. Of these, cyclopropylalanine has been incorporated into pharmaceutically active materials[4] despite the fact that the current syntheses of this amino acid in enantiomerically pure form are challenging.[4,5] None of the approaches to date have utilized asymmetric hydrogenation chemistry, presumably since cyclopropanecarboxaldehyde (CPCA), a key starting material for an efficient approach to the requisite dehydroamino acid, was not readily available. CPCA has recently become available to us by the sequential isomerization of 3,4-epoxybutene, a new material from Eastman Chemical Company.[6] The additional discovery of a new class of phosphine–aminophosphine ligands **1** (BoPhoz™ ligands, Fig. 1) as highly active and enantioselective ligands for the asymmetric hydrogenation of dehydroamino acids[7] spurred us to investigate the synthesis of single enantiomer cyclopropylalanine via asymmetric hydrogenation.

2. Results and discussion

The key variables for the synthesis of an amino acid using asymmetric hydrogenation are the amino and carboxyl substituents. The best combination of these



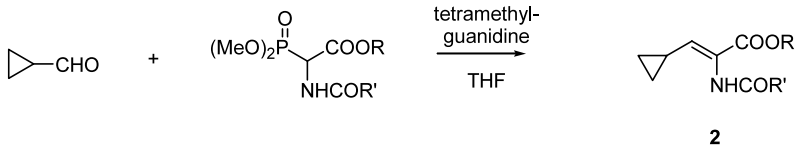
1

a: R^1 = H, R^2 = Ph
b: R^1 = CH_3, R^2 = Ph
c: R^1 = Et, R^2 = Ph
d: R^1 = n-Pr, R^2 = Ph
e: R^1 = CH_3, R^2 = cyc-C_6H_{11}

Figure 1.

* Corresponding author. Tel.: 423-229-8105; fax: 423-224-7582; e-mail: nwboaz@eastman.com

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.07.007

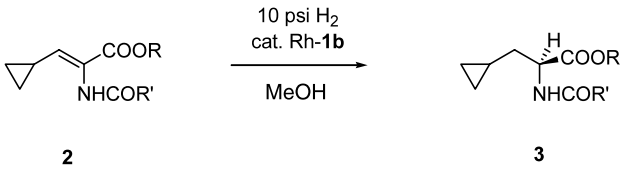


Scheme 1. Initial substrate synthesis.

two groups depends on a variety of factors including ease of synthesis, hydrogenation characteristics (enantioselectivity, rate, and throughput), ability to enhance to absolute enantiomeric purity, and ease and selectivity of protecting group removal. The key initial hurdle is obtaining high enantioselectivity in the asymmetric hydrogenation reaction. Thus, our initial investigation involved the preparation of a number of dehydrocyclopropylalanine derivatives for asymmetric hydrogenation screening.

There are several methods for the synthesis of dehydroamino acids. The most flexible approach in this case was the condensation of CPCA with a variety of appropriately substituted phosphonate reagents as pioneered by Schmidt.[8] Using the chemistry shown in Scheme 1 (as well as that described below for benzyl esters) we prepared a number of species **2** for hydrogenation screening with the rhodium complex of the BoPhoz™ ligands.

Our previous results have indicated that the rhodium complex of the methyl BoPhoz™ ligand **1b** is superior to all other BoPhoz™ ligands for dehydroamino acid hydrogenation enantioselectivity.[7] Thus, we examined the hydrogenations of substrates **2** as shown in Scheme 2 in THF with 1 mol% of a complex prepared in situ from **1b** and bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate under 10 psig of hydrogen. The results shown in Table 1 indicate that the methyl BoPhoz™ ligand **1b** affords high conversion to the desired product **3** with high enantioselectivity for a variety of amine and carboxyl protection schemes. The data suggest that while variation of the carboxyl substituent has minimal effect, the *N*-acetyl or *N*-Boc groups display decidedly higher enantioselectivity than the other amino substituents. The *N*-Boc substrates were preferred as they afford the highest enantioselectivities and are much more synthetically versatile.



Scheme 2. Asymmetric hydrogenation of **2**.

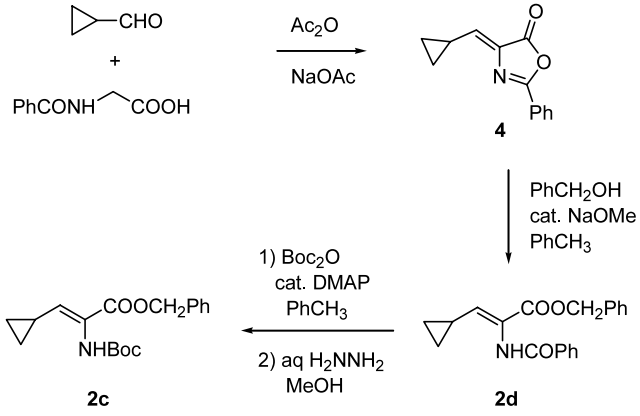
The choice of the most desirable substrate for further study and scale-up was thus largely predicated on the attractiveness of its preparation and the versatility of the carboxyl protecting groups.

Table 1. Asymmetric hydrogenation of dehydrocyclopropylalanine derivatives with (*R*)-methyl BoPhoz™ rhodium complex[a]

Compound	R	R′	Ee (%)	Conversion (%)
a	Me	Me	98.0	100
b	Me	*t*-BuO	97.8	99
c	$PhCH_2$	*t*-BuO	98.6	100
d	$PhCH_2$	Ph	92.0	100
e	H	Ph	95.0	96
f	Me	Ph	95.0	99
g	Me	$PhCH_2O$	94.2	98

[a] Reactions were run at 0.5 M in MeOH using 1 mol% catalyst for 1 h at 10 psig hydrogen.

Although the phosphonate chemistry in Scheme 1 can readily afford the *N*-Boc derivatives of **2**, this chemistry was deemed unattractive for scale-up due to the lengthy preparation of the phosphonate reagent and its atom inefficiency. Two other routes are generally used for dehydroamino acid preparation. The first involves the simple condensation of an amide or carbamate with an α-ketoester, but is disfavored due to the lack of ready availability of a cyclopropylpyruvate ester. The other standard approach to the preparation of dehydroamino acids is the Erlenmeyer condensation of an *N*-acylglycine with an aldehyde (CPCA in this case).[9] Unfortunately, this condensation is usually limited to aromatic aldehydes, as aliphatic aldehydes in general perform poorly.[10] However, cyclopropylcarbonyl compounds such as CPCA often react more like aromatic rather than aliphatic carbonyl species, and although the condensation of CPCA with *N*-acetylglycine afforded an intractable mixture, the similar condensation with hippuric acid afforded a moderate yield of the desired azlactone **4** (Scheme 3). This material was readily



Scheme 3. Optimized substrate synthesis.

purified and could be converted into a variety of esters **2** by reaction with the corresponding alkoxide. Although there are a number of good choices for the carboxyl derivative, we chose the benzyl ester. This group provides the most downstream versatility as it can be removed under either base hydrolytic or reductive conditions, both of which would differentiate it from the Boc group. This ester was readily formed by the reaction of **4** with benzyl alcohol in toluene using sodium methoxide catalysis. Conversion of the benzamido species to the desired *N*-Boc derivative was achieved using chemistry similar to that previously described for saturated amino acid derivatives.[11] Compound **2d** was reacted with di-*tert*-butyl dicarbonate using DMAP as catalyst to afford the mixed imide species **5**, which was treated directly with hydrazine to specifically cleave the benzoyl group and afford the desired *N*-Boc benzyl ester **2c**.

We investigated the asymmetric hydrogenation of **2c** with a variety of catalysts. We were surprised to find that this substrate is non-trivial to reduce with the rhodium complexes of a variety of available ligands. The results shown in Table 2 indicate that many commercially available ligands afford moderate enantioselectivity and often poor activity under our screening conditions. Of these ligands, only the DuPHOS species show results comparable to the methyl BoPhoz™ ligand (with Et DuPHOS affording slightly higher enantioselectivity).

Table 2. Asymmetric hydrogenation of benzyl *N*-Boc 3-cyclopropylpropenoate **2c**[a]

Ligand	Ee (%)	Conversion (%)
1b	98.6	100
(*S*,*S*)-Methyl DuPHOS	98.6	99
(*S*,*S*)-Ethyl DuPHOS	99.3	100
(*S*)-BINAP	55	41
(*R*,*R*)-DIOP	40	97
(*R*,*S*)-BPPFA	34	89
(2*S*,3*S*)-CHIRAPHOS	–	0
(*R*)-PROPHOS	81.8	5[b]
(*S*,*S*)-PHANEPHOS	5.0	51
(*R*,*S*)-Josiphos	86.8	81

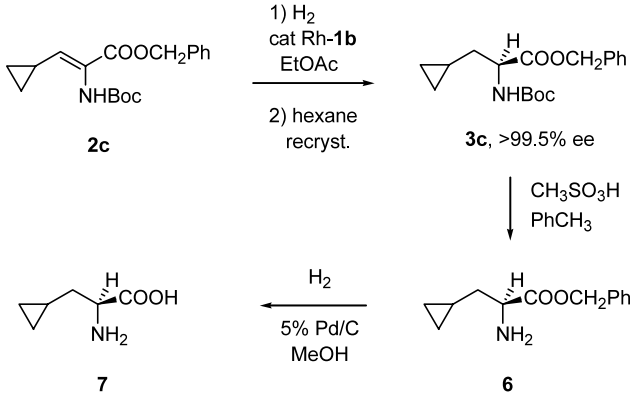
[a] Reactions were run at 0.5 M in THF using 1 mol% catalyst for 1 h at 10 psig hydrogen.
[b] Reaction was run for 6 h.

More industrially relevant conditions were then investigated with the rhodium complex of the methyl BoPhoz™ ligand **1b**. We were particularly interested in the kinetics of this transformation, as there was some concern that the sterically hindered Boc substituent of **2c** would render it sluggish in its reactivity. It was not particularly surprising that this asymmetric hydrogenation was significantly slower than that of an *N*-acetyl species such as methyl 2-acetamidocinnamate.[7] However, the exceedingly high intrinsic reactivity of the rhodium complex of the methyl BoPhoz™ ligand for the hydrogenation of dehydroamino acid derivatives is more than sufficient to overcome the large steric nature of the Boc substituent of **2c**. Thus, we observed an initial rate of reaction of over 9100 catalyst turnovers per hour in methanol (our usual preferred solvent) at a substrate to catalyst ratio of 1000:1, affording **3c** with 96.4% ee. We also performed a solvent screen of reactivity and selectivity for this transformation, and found that ethyl acetate is preferred over methanol for this reaction, as under the same reaction conditions it afforded a similar rate (8300 catalyst turnovers per hour) and improved enantioselectivity (98.4% ee). Reactions at a higher substrate to catalyst ratio preferable for scale-up (e.g. 2500:1) afforded similar turnover frequencies with slight diminution of enantiomeric purity (97.6% ee).

The final criterion for an effective synthesis of cyclopropylalanine is the ability to enhance the enantiomeric purity to high levels. We examined a number of solvents to determine if the hydrogenation product **3c** could be recrystallized to enantiomeric purity, and found that recrystallization from hexane afforded material of >99.5% ee.

The absolute configuration of this material was originally inferred by the elution order of the enantiomers on chiral GC. However, it was important to unequivocally determine the absolute configuration of the products, and this was most readily ascertained by conversion to the native amino acid, which also allowed us to examine how readily derivative **3c** could be selectively deprotected.

As shown in Scheme 4, the *t*-butyl carbamate of **3c** could be readily removed by simple treatment with methanesulfonic acid in toluene. Neutralization and aqueous isolation afforded the benzyl ester **6** in 99% yield. This material was hydrogenated under mild conditions using 5% palladium on carbon to hydrogenolyze the benzyl ester and afford the amino acid **7**, which could be readily recrystallized from an ethanol/water mixture (83% yield). The hydrogenation conditions did not hydrogenolyze the cyclopropyl ring. The examination of the specific rotation of **7** derived from the asymmetric hydrogenation of **2c** using (*R*)-methyl BoPhoz™ ligand and comparison to literature values indicated that these conditions afforded the (*S*)-enan-



Scheme 4. Synthesis of (*S*)-cyclopropylalanine.

tiomer of **3c**.[5d,f] The enantiomeric purity of **7** was also of concern to determine whether any racemization occurred during the deprotection reactions. This was accomplished by conversion of **7** to **3b** by sequential treatment with di-*tert*-butyl dicarbonate ($NaOH/H_2O$) and trimethylsilyldiazomethane (MeOH). Chiral GC examination of **3b** thus produced indicated that the deprotection sequence afforded **7** with >99.9% ee.

3. Conclusions

We have developed an efficient and effective synthesis of the single enantiomers of cyclopropylalanine and various derivatives in high enantiomeric purity. The material is derived from cyclopropanecarboxaldehyde, a readily available epoxybutene derivative. The synthesis proceeds via the asymmetric hydrogenation of the corresponding dehydroamino acid derivative using a rhodium complex of the methyl BoPhoz™ ligand **1b**. The *N*-Boc benzyl ester of cyclopropylalanine was chosen for scale-up due to synthetic ease and downstream versatility.

4. Experimental

4.1. General methods

All solvents were used as received from Burdick and Jackson except where indicated. All reagents were used as received from Aldrich Chemical Company except where indicated. Bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate was obtained from Alfa Aesar. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were obtained on a Varian Gemini-300 Spectrometer. Mass spectral data were collected on a Micromass Autospec Magnetic Double Focusing Mass Spectrometer using field desorption ionization techniques. High resolution mass spectra were run by positive ion electrospray on a Micromass LCT Time of Flight mass spectrometer in positive ion mode. Gas chromatography was performed on a Hewlett–Packard 6890 gas chromatograph with flame ionization detection. Optical rotations were determined on a Rudolph Research Autopol III polarimeter. Melting points are uncorrected.

4.2. Preparation of 4-cyclopropylmethylene-2-phenyl-4*H*-oxazol-5-one 4

A 72 L flask fitted with a condenser, mechanical stirrer, addition funnel, and thermocouple was charged with acetic anhydride (19 L; 201 mol; 6 equiv.), sodium acetate (4.14 kg; 50.5 mol; 1.5 equiv.), and *N*-benzoylglycine (hippuric acid, 6.0 kg, 33.5 mol) under an inert atmosphere. CPCA (7.56 L; 101 mol; 3 equiv.) was added via the addition funnel over 40 min to the mixture at 25°C. Once the addition was complete, the reaction mixture was heated to 110°C. After 1.5 h, the reaction was cooled to 50°C. Volatile materials (24 L) were removed by vacuum distillation. Toluene (39 L) was added and the mixture was stirred for 1 h and washed with water (3×30 L). The organic solution was concentrated by distillation of ca. 20 L of toluene (white precipitate formed as toluene was removed). The remaining thick slurry was filtered, washed with toluene, and dried to afford 2.35 kg (33%) of azlactone **4** as an off-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09–8.07 (m, 2H); 7.60–7.46 (m, 3H); 6.17–6.13 (d, 1H, $J=10.8$ Hz); 2.46–2.35 (m, 1H); 1.29–1.23 (m, 2H); 0.96–0.91 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 165.9; 161.7; 145.4; 134.3; 132.7; 128.8; 127.8; 125.8; 110.7; 13.5; 11.1. HRMS calcd for $C_{13}H_{12}NO_2$ $(M+H)^+$: 214.0898, found: 214.0868.

4.3. Preparation of 2-benzoylamino-3-cyclopropylacrylic acid benzyl ester 2d

To a 5 L jacketed 3-neck flask was added azlactone **4** (343 g; 1.61 mol), toluene (3.5 L) and benzyl alcohol (172 g; 1.6 mol; 1 equiv.) at ambient temperature. Sodium methoxide (8.6 g; 0.16 mol; 0.1 equiv.) was added to the slurry at 25°C. After 1 h much solid had precipitated and NMR analysis indicated complete consumption of starting material. The solid was filtered, washed with toluene, and dried to afford **2d** as a white amorphous solid (441 g; 85%), mp 130–132°C, which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90–7.85 (m, 2H), 7.61–7.25 (m, 3H), 6.27–6.24 (d, 1H, $J=11.1$ Hz), 5.19 (s, 2H), 1.83–1.57 (m, 1H), 1.05–1.02 (m, 2H), 0.72–0.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 177.0; 164.5; 144.5; 128.6; 128.4; 128.2; 127.3; 67.1; 65.3; 44.4; 12.6; 8.9. HRMS calcd for $C_{20}H_{20}NO_3$ $(M+H)^+$: 322.1443, found: 322.1460. Anal. calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.52; H, 5.91; N, 4.11.

4.4. Preparation of 2-*tert*-butoxycarbonylamino-3-cyclopropylacrylic acid benzyl ester 2c

A 5 L three-neck jacketed flask with a mechanical stirrer and thermocouple thermowell was charged with enamide **2d** (260 g, 0.81 mol) and DMAP (19.8 g; 0.16 mol; 0.2 equiv.). Toluene (2.0 L) was added and the slurry was stirred at 20°C. Di-*tert*-butyl dicarbonate (200 g; 0.92 mol; 1.13 equiv.) was added to the solution, which resulted in the evolution of carbon dioxide and a temperature drop to 17°C. The reaction mixture was stirred at ambient temperature for 17 h at which point TLC analysis indicated no **2d**. The solution was cooled to 10°C and methanol (250 mL) was added. The mixture was further cooled to 3°C and 55% aqueous hydrazine hydrate (200 mL; 3.5 mol; 4.4 equiv.) was added over 1 h such that the temperature remained below 5°C. The solution was cooled to 3°C for 3 h and warmed to 7°C for 1 h, then diluted with ethyl acetate (500 mL) and washed with water (2×1 L). The organic layer was washed with 0.5N HCl (2×1L), saturated $NaHCO_3$ (2×800 mL), dried over Na_2SO_4 and concentrated. The crude product was crystallized from hot methanol by cooling to ambient temperature to afford two crops of **2c** as a white solid (227 g; 87%). This material was recrystallized from hot ethyl acetate (454 mL; 2 mL/g) by cooling overnight to 4°C to afford 136 g (52%) of **3c**, mp 92–94°C, which was highly active for asymmetric

hydrogenation. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.26 (m, 5H), 6.07–6.04 (d, 1H, $J=10.8$ Hz), 5.92 (bs, 1H), 5.18 (s, 2H), 1.76–1.66 (m, 1H), 1.45 (s, 9H), 1.03–0.97 (m, 2H), 0.66–0.63 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 164.1; 153.9, 143.4; 135.9, 128.4; 128.3; 124.4, 110.9; 80.3; 66.9; 28.3; 11.7; 8.8. HRMS calcd for $C_{18}H_{24}NO_4$ $(M+H)^+$: 318.1705, found: 318.1726. Anal. calcd for $C_{18}H_{23}NO_3$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.05; H, 7.38; N, 4.26.

4.5. Kinetic analysis and preparation of (*S*)-2-*tert*-butoxycarbonylamino-3-cyclopropylpropionic acid benzyl ester 3c

(*R*)-*N*-Methyl-*N*-diphenylphosphino-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **1b** (14.7 mg; 0.024 mmol; 1.2 equiv. based on Rh) and bis(1,5-cyclooctadienyl)rhodium trifluoromethanesulfonate (9.4 mg; 0.02 mmol) were combined and 2.0 mL of argon-degassed methanol was added. The solution was stirred for 15 min. To a Fisher–Porter bottle was added enamide **2c** (3.17 g; 10.0 mmol) and 10 mL of ethyl acetate. The mixture was stirred and degassed with an argon stream for 5 min. A pressure head was attached and the mixture was evacuated and filled with helium ten times. The rhodium complex solution of **1b** prepared above (1.0 mL; 0.01 mmol; 0.001 equiv.) was added to the bottle and the reaction mixture was evacuated and filled with helium ten times and hydrogen five times. The bottle was pressurized to 45 psig of hydrogen, sealed and stirred vigorously. The time course of the reaction was followed by the pressure change in the bottle using a pressure sensor, and uptake ceased after about 20 min. The vessel was filled and evacuated with helium five times, then the contents were removed and concentrated to afford 3.20 g of a pale red oil which showed 100% conversion to **3c** with an enantiomeric purity of 98.4% ee. The extent of conversion was correlated with the observed pressure change. Graphical analysis over the first 40% of the reaction indicated a catalyst turnover frequency of 8300 catalyst turnovers per hour. The oil was dissolved in hexane (6.4 mL; 2 mL/g) and chilled to 4°C for 1 h to afford a small amount of flocculent red precipitate. This was clarified and the filtrate was cooled to 4°C overnight to afford a white solid. The precipitate was collected, washed with hexane, and air-dried to afford **3c** (2.69 g; 84%), mp 54–55°C, with an enantiomeric purity of >99.5% ee. Chiral GC [CP-Chirosil-Val (Varian) 175°C isothermal, 15 psig He column pressure]: $t_R=15.23$ (minor), $t_R=15.89$ (major). ^{1}H NMR ($CDCl_3$) δ 7.41–7.30 (m, 5H), 5.13–5.12 (m, 1H), 5.02 (s, 2H), 1.70–1.60 (m, 2H), 1.45 (s, 9H), 0.69–0.61 (m, 1H), 0.42–0.39 (m, 2H), 0.02–0.01 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 172.8, 155.4, 135.6, 128.7, 128.5, 128.4, 79.9, 67.1, 54.2, 37.5, 28.5, 7.1, 4.4. HRMS calcd for $C_{18}H_{26}NO_4$ $(M+H)^+$: 320.1862, found: 320.1876. Anal. calcd for $C_{18}H_{25}NO_3$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.49; H, 7.99; N, 4.13. $[\alpha]_D^{24}$ −22.5 (*c* 1.04, CH_3OH).

4.6. Preparation of (*S*)-2-*tert*-butoxycarbonylamino-3-cyclopropylpropionic acid benzyl ester 3c

(*R*)-*N*-Methyl-*N*-diphenylphosphino-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **1b** (36.7 mg; 0.060 mmol; 1.2 equiv. based on Rh) and bis(1,5-cyclooctadienyl)rhodium trifluoromethanesulfonate (23.4 mg; 0.05 mmol) were combined and 5.0 mL of argon-degassed methanol was added. The solution was stirred for 15 min. To a Fisher–Porter bottle was added enamide **2c** (31.74 g; 100 mmol) and 50 mL of ethyl acetate. The mixture was stirred and degassed with an argon stream for 5 min. A pressure head was attached and the mixture was evacuated and filled with helium ten times. The rhodium complex solution of **1b** prepared above (4.0 mL; 0.04 mmol; 0.0004 equiv.) was added to the bottle and the reaction mixture was evacuated and filled with helium ten times and hydrogen five times. The bottle was pressurized to a constant 45 psig of hydrogen and stirred vigorously. A mild exotherm (to ca. 30°C) was noted as the reaction commenced, which subsided to room temperature over about 1.5 h. After 3 h the reaction vessel was sealed and no pressure change was noted. The vessel was filled and evacuated with helium five times, then the contents were removed and concentrated. Hexane (ca. 20 mL) was added and the mixture was concentrated once more to afford 32.04 g of a pale red oil which showed 99.9% conversion to **3c** with an enantiomeric purity of 97.6% ee. The oil was dissolved in hexane (48 mL; 1.5 mL/g) and held at ambient temperature for 2 h to afford a flocculent red precipitate. This was removed by filtration and washed with hexane (16 mL; 0.5 mL/g of **3c**). Seed crystals were added to the filtrate and crystallization began immediately. The mixture was cooled to 4°C overnight to afford a white solid. The precipitate was collected, washed with hexane, and air-dried to afford **3c** (29.88 g; 94%) with an enantiomeric purity of >99.5% ee.

4.7. Preparation of *S*-2-amino-3-cyclopropylpropionic acid benzyl ester 6

N-Boc benzyl ester **3c** (2.0 g; 6.3 mmol) was dissolved in 6 mL of toluene and methanesulfonic acid (0.49 mL; 1.2 equiv.) was added. Vigorous gas evolution was immediately noted which lasted for about 15 min. After the bubbling had ceased a precipitate was formed over about 2 h, at which time **3c** had been completely consumed according to NMR analysis. Ethyl acetate (10 mL) and 2N sodium hydroxide (10 mL) were added and the mixture was stirred for 5 min to afford two homogeneous layers. The layers were separated and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic solution was dried with magnesium sulfate and concentrate to afford 1.36 g (99%) of **6** as a pale tan oil. ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 5H), 5.18 (d, 1H, $J=12.4$ Hz), 5.13 (d, 1H, $J=12.4$ Hz), 3.60 (t, 1H, $J=6.0$ Hz); 1.73 (s, 2H); 1.70–1.50 (m, 2H), 0.76–0.70 (m, 1H), 0.49–0.42 (m, 2H), 0.09–0.04 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 175.8, 135.8, 128.6, 128.4, 126.8, 66.7, 55.1, 39.7, 28.5, 7.3, 4.4, 4.2. HRMS

calcd for $C_{13}H_{18}NO_2$ $(M+H)^+$: 220.1338, found: 220.1361. $[\alpha]_D^{24}$ +5.6 (*c* 1.0, CH_3OH).

4.8. Preparation of *S*-2-amino-3-cyclopropylpropionic acid 7

Benzyl ester **6** (1.00 g; 4.6 mmol) was dissolved in 10 mL of methanol in a Parr bottle and 5% palladium on carbon (50 mg; 5 wt%) was added. The reaction mixture was shaken under 40 psig hydrogen at 50°C for 3 h and then cooled to ambient temperature. The reaction mixture was filtered through Celite, eluted with hot methanol, and concentrated to afford 0.58 g (98%) of **7** as a white solid. The crude product was dissolved in 6 mL of refluxing water, diluted with 45 mL of ethanol, and cooled to 4°C overnight to afford 491 mg (83%) of **7** as a glistening white solid. ^{1}H NMR (NaOD in D_2O) δ 3.20 (t, 1H, $J=6.0$ Hz); 1.50–1.38 (m, 1H), 1.35–1.29 (m, 1H); 0.58–0.54 (m, 1H), 0.32–0.30 (m, 2H), –0.02 to –0.04 (m, 2H). ^{13}C NMR (NaOD in D_2O+DMSO-d_6) δ 184.9, 58.0, 40.9, 8.5, 5.2, 5.0. Anal. calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.90; H, 8.51; N, 10.78. $[\alpha]_D^{24}$ –12.8 (*c* 0.50, H_2O) [Lit.[5d] $[\alpha]_D$ –12.7 (*c* 0.50, H_2O)], $[\alpha]_D^{24}$ +14.5 (*c* 0.51, H_2O/2 M NaOH) [Lit.[5d] $[\alpha]_D$ +13.4 (*c* 0.50, H_2O/2 M NaOH)].

Acknowledgements

The authors thank Mr. W. Dell Nottingham and Mr. Matthew Elliot for scale-up assistance, Mr. James D. Little for high resolution mass spectral analyses, and Ms. Ellen F. Yeary for combustion analyses.

References

1. For recent reviews, see: (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp. 1–110; (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfalz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. I, pp. 121–182.
2. (a) Knowles, W. S.; Sabacky, M. J. US Patent 4124533, 1978; (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952 and references cited therein.
3. (a) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746–1754; (b) Chua, P. S.; Roberts, N. K.; Bosnich, B.; Okrasinski, S. J.; Halpern, J. *J. Chem. Soc., Chem. Commun.* **1981**, 1278–1280; (c) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952–5954; (d) Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838–840; (e) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 8055–8057.
4. (a) Wehner, V.; Flohr, S.; Blum, H.; Ruetten, H.; Stilz, H. U. PCT Int. Appl. WO 0311288, 2003; (b) Lynch, C. L.; Hale, J. J.; Budhu, R. J.; Gentry, A. L.; Mills, S. G.; Chapman, K. T.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; Demartino, J. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3001–3004; (c) Hanson, G. J.; Chen, B. B.; Baran, J. S. U.S. Patent 5268391, 1993; (d) Christensen, J. V.; Kristensen, E. PCT Int. Appl. WO 0176636, 2001; (e) Wehner, V.; Stilz, H. U.; Schmidt, W.; Seiffge, D. PCT Int. Appl. WO 0069831, 2000.
5. (a) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322–3327; (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656–673; (c) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415; (d) Hamon, C.; Rawlings, B. J. *Synth. Commun.* **1996**, *26*, 1109–1115; (e) Chenault, H. K.; Dahmer, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 6354–6364; (f) Ohta, T.; Nakajima, S.; Sato, Z.; Aoki, T.; Hatanaka, S.; Nozoe, S. *Chem. Lett.* **1986**, 511–512.
6. (a) Monnier, J. R.; Muehlbauer, P. T. US Patent 4897498, 1990; (b) Phillips, G. W.; Falling, S. N.; Godleski, S. A.; Monnier, J. R. US Patent 5315019, 1994; (c) Nolen, T. R.; Falling, S. N.; Hitch, D. M.; Miller, J. L.; Terrill. D. L. US Patent 5681969, 1997; (d) Liang, S.; Price, T. W. US Patent 5633410, 1997.
7. Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421–2424.
8. (a) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53–60; (b) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487–490.
9. Carter, H. E. In *Organic Reactions*; Adams, R.; Bachman, W. E.; Fieser, L. F.; Johnson, J. R.; Snyder, H. R., Eds.; John Wiley and Sons: New York, 1946; Vol. 3, pp. 198–239.
10. Ref. 9, p. 206.
11. (a) Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054–7057; (b) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424–2426; (c) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *J. Chem. Soc., Chem. Commun.* **1985**, 1317.