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The Preparation of Single Enantiomer 2-Naphthylalanine Derivatives Using Rhodium−Methyl *BoPhoz*-catalyzed Asymmetric Hydrogenation

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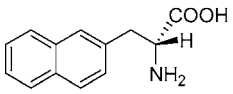
Abstract:

The single enantiomers of 2-naphthylalanine and *N-tert*-butoxycarbonyl 2-naphthylalanine were prepared from 2-naphthaldehyde. The sequence has been optimized and run on multikilogram scale, with the key step the asymmetric hydrogenation of methyl 2-acetamido-3-(2-naphthyl)propenoate using the rhodium complex of the methyl *BoPhoz* ligand, which proceeded smoothly at scale with 97.9% ee. Enhancement to >99.5% ee was achieved by crystallization of the methyl 2-amino-3-(2-naphthyl)propanoate methanesulfonic acid addition salt, the product of acidic deacylation of the hydrogenation product. This protocol for enantiomeric purity enhancement appears to be general for these types of amino acid derivatives. Subsequent transformations did not effect the enantiomeric purity, affording the desired products in >99.5% ee.

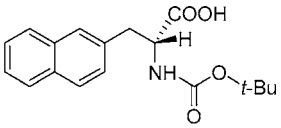
Introduction

Asymmetric hydrogenation is an efficient and attractive approach to single enantiomer materials, largely due to the ability to transform inexpensive achiral starting materials such as olefins or ketones into higher-value products with high enantioselectivity. 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 of L-DOPA by Knowles and co-workers.[2] We have recently reported the synthesis and utility of a new class of phosphine−aminophosphine ligands (*BoPhoz* ligands) that show exceedingly high enantioselectivities and activities for the asymmetric hydrogenation of dehydro-α-amino acid and itaconate derivatives, as well as high enantioselectivities and activities for the asymmetric hydrogenation of α-ketoesters.[3] We chose to demonstrate the scale-up potential of these ligands for the preparation of an unnatural amino acid.

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. Of particular interest are 2-naphthylalanine (2-amino-3-[2-naphthyl]propanoic acid, **1**) and especially the *N-tert*-butoxycarbonyl (*N*-Boc) derivative **2**. These materials, particularly **2** as it has advantages for solid-phase peptide synthesis, have found extensive use in the synthesis of a number of pharmaceutically useful agents, including luteinizing hormone-releasing factors,[4] somatostatin analogues,[5] growth hormone release stimulators,[6] advanced glycated end product (AGE) receptor modulators,[7] and NK1 tachykinin receptor antagonists.[8]



R-**1**



R-**2**

There have been a number of preparations of enantiomerically enriched *N*-Boc-2-naphthylalanine (as well as the parent amino acid), utilizing strategies involving enzymatic resolution,[4a−c,9] alkylation of a chiral enolate,[10] chiral phase-transfer alkylation,[11] and asymmetric hydrogenation.[12] The

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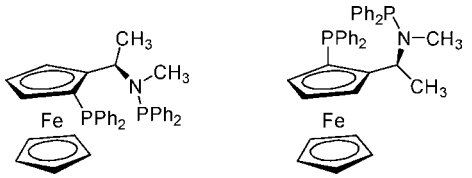
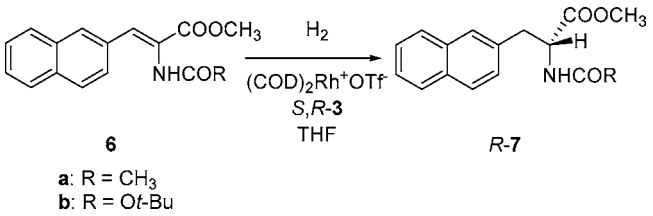
high enantioselectivities and activities for the asymmetric hydrogenation of dehydroamino acid derivatives using the rhodium complexes of the phosphine−aminophosphine (*BoPhoz*) ligands **3** suggested that a sequence incorporating this type of asymmetric hydrogenation might be a viable approach to prepare *N*-Boc-2-naphthylalanine (and also the native amino acid) efficiently and in absolute enantiomeric purity.



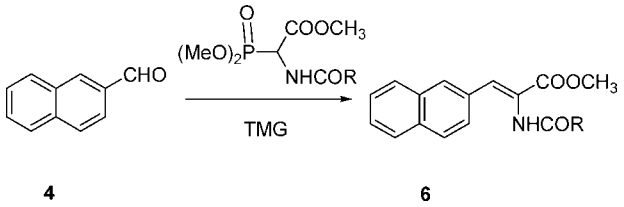
R,*S*-**3** *S*,*R*-**3**

Results and Discussion

The rhodium complexes of a number of ligands (including **3**) have been reported to afford 2-naphthylalanine derivatives in high enantioselectivities under screening conditions.[12,13] In selecting a particular ligand for preparative purposes, scalability factors can become very important, particularly if high enantioselectivity is routinely obtained and ee enhancement is possible. We chose to utilize the *BoPhoz* ligands **3** for our investigations, as in addition to high enantioselectivities, the ligand synthesis is readily scaled (either enantiomer), they have long shelf stability, are easy to use, and afford high turnover numbers and exceedingly high turnover frequencies.[3] Reaction screening with the rhodium complex of **3** indicated that either the *N*-acetyl or *N*-Boc substrates **6a** or **6b**, respectively, afforded the hydrogenation product **7** in high enantiomeric purity (**7a**, 98.1% ee; **7b**, 97.4% ee). The product stereochemistry was as expected, with ligand *R*,*S*-**3** affording the *S* enantiomers of the amino acids.[3] The sensitivity of the Boc derivative, particularly toward acidic media, suggested that its use might limit the options for downstream chemistry. In addition, the relatively expensive nature of the Boc anhydride reagent and the cumbersome nature of the preparation of the dehydroamino acid derivative[14] suggested that converting to this derivative at a late stage of the synthesis would be advantageous.



Although the initial preparation of the substrates **6** utilized rapid and versatile phosphonate chemistry as shown below,[15] the lengthy preparation of the phosphonate reagent and its atom inefficiency indicate that it is not advantaged for larger-scale preparation of any particular dehydroamino acid.



The preparative synthesis of the single enantiomers of **1** and **2** instead used a classical approach as shown in Scheme 1. This synthesis is described for the preparation of the *R* enantiomers of **1** and **2** using the rhodium complex of *S*,*R*-**3**, but the other enantiomers are equally available by using *R*,*S*-**3**.

The first step utilized the classical Erlenmeyer condensation, in general the most efficient preparative method for aryl-substituted dehydroamino acids.[16] In this case the chemistry involved the condensation of 2-naphthaldehyde with *N*-acetyl glycine using acetic anhydride as solvent and dehydrating agent (the excess was used to afford a fluid reaction mixture and minimize by-product formation) and sodium acetate as base at 100 °C to form the oxazol-5(4H)-one (azlactone) product **5** along with some highly colored impurities. Removal of these by-products was effected by trituration of the crude product with methanol (**5** is largely insoluble) at ambient temperature, affording the desired azlactone **5** as a pale-yellow solid in about 65% overall yield. The use of methanol for this re-slurry also avoids the necessity for complete drying of the product, as methanol is used as solvent for the next step.

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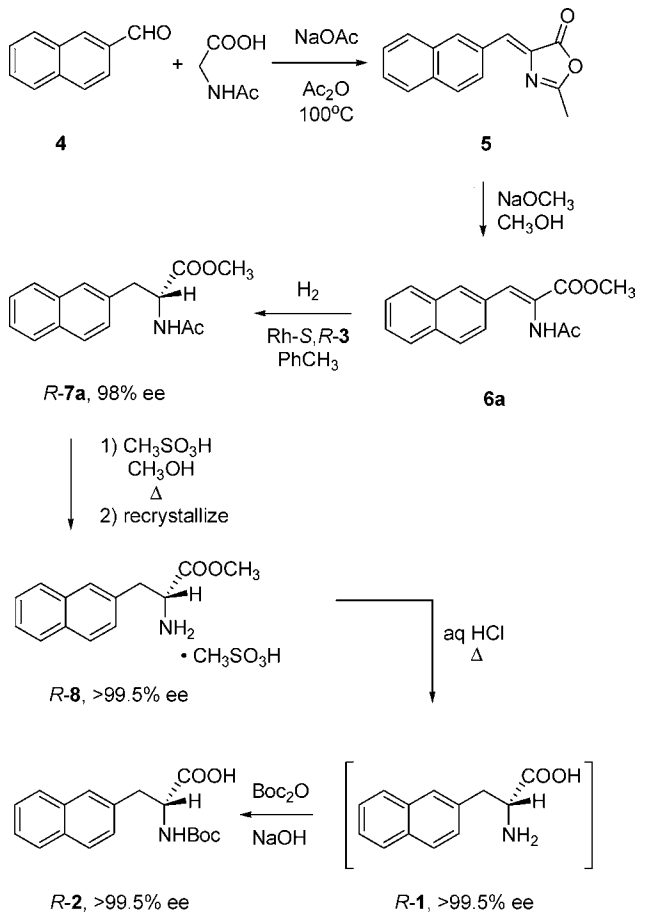
Scheme 1. **Synthetic sequence for the preparation of *N*-Boc *R*-2-naphthylalanine**



Conversion of the azlactone to the methyl ester **6a** was most conveniently performed using a catalytic amount of sodium methoxide in methanol. This reaction was very rapid, as evidenced by the conversion of a slurry of **5** in methanol to a homogeneous solution upon the addition of the catalyst. The methyl ester product partially precipitated from solution, and the addition of water completed the solid formation, affording the ester **6a** in 91% yield as a tan solid.

Although this material appeared quite pure by NMR and GC, there were small amounts of impurities present that were anathema for the asymmetric hydrogenation reaction using the rhodium complex of ligand **3**. When industrially useful low loadings of catalyst were used, these impurities resulted in virtually complete catalyst inactivation and no reaction. The offending impurities were readily removed by charcoal treatment in acetone at ambient temperature, although it required a large amount of both acetone (10 mL/g of crude **6a**) and carbon (0.75 g/g of crude **6a**) for effective impurity removal and product recovery. Purified **6a** was most efficiently recovered by distillation of the majority of the acetone from the filtrate (resulting in a slurry of purified **6a)** and dilution of this reduced solution with approximately three volumes of water. The product **6a** was obtained with up to 91% recovery on laboratory scale using this protocol, resulting in an overall yield of **6a** from **4** of 54%. The recoveries were slightly lower at kilo-scale, affording an overall yield to **6a** of 42%.

Table 1. **Solvent screening for the asymmetric hydrogenation of 6a to *R*-7a using the rhodium complex of *S,R*-3[a]**

entry	solvent	substrate concentration (M)	ee (%)	conversion (%)
1	methanol	0.19[b]	97.2	99.6
2	methanol	0.37	94.8	87.9
3	acetone	0.19[b]	97.0	99.3
4	acetone	0.37	97.0	100
5	toluene	0.19	97.8	100
6	toluene	0.37	97.4	100
7	ethyl acetate	0.19	97.2	100
8	ethyl acetate	0.37	97.2	100
9	TCE[c]	0.19	97.6	99.9
10	TCE[c]	0.37	97.4	99.7

[a] All reactions were run at S:C molar ratio of 250:1 for 1 h at ambient temperature and were initially slurries (except where indicated) that became homogeneous as the reaction progressed. [b] Initial reaction mixture was homogeneous. [c] TCE is tetrachloroethylene.

The (in)solubility characteristics of **6a** caused concern for the ability to perform an efficient asymmetric hydrogenation reaction at reasonable concentration. Thus, the hydrogenation was screened using the rhodium complex of *S,R*-**3** in a variety of solvents at two concentrations. The results are shown in Table 1 and indicate that a number of solvents performed well for this reaction, despite the limited solubility of the substrate. Toluene was chosen as the solvent for further investigation, as it afforded the best overall results.

Further optimization of this hydrogenation in toluene indicated a rapid and highly enantioselective reaction with a turnover frequency of up to 19 200 catalyst turnovers per hour. The reaction was complete well within 1 h and afforded up to 98.3% ee at a catalyst loading of 0.04 mol % (S:C, 2500:1). The hydrogenation was scaled up to 22-L scale in toluene using 0.05 mol % loading (S:C, 2000:1) of the rhodium complex of *S,R*-**3**, and resulted in smooth hydrogenation, affording the desired product *R*-**7a** with complete conversion and high enantioselectivity (97.9% ee). The initial run required extended reaction time, but eventually afforded complete conversion with a moderate exotherm to about 33 °C. Modifying the equipment in subsequent runs to allow subsurface hydrogen addition greatly increased the reaction rate (the exotherm remained the same), indicating that mass transfer limitations were the cause of the slow rate of the first run.

The hydrogenation product *R*-**7a** can be isolated in 96% yield (and the ee enhanced) by crystallization from a toluene/heptane mixture. This afforded *R*-**7a** with >99% ee that possessed a negative optical rotation, indicating that it was the *R* enantiomer based on literature data.[13a,17] Unfortunately, *R*-**7a** tends to solidify into large masses rather than crystallize, resulting in material that would be difficult to isolate on large scale. Instead, the solvent was removed, and the crude product was submitted directly to the next step.

The fourth step of the sequence involved removal of the *N*-acetyl group. Both this step and the ester hydrolysis are performed under acidic conditions and in principle could be run concurrently. However, amine salt *R*-**8**, the product of

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methanolic methanesulfonic acid acetyl solvolysis of **7a**, is a highly tractable solid that could be readily recrystallized to absolute enantiomeric purity. This type of behavior was also observed for several other species similar to **8** that we have investigated. The initial recrystallization protocol used refluxing *n*-propanol as the solvent, and under laboratory conditions afforded *R*-**8** with >99.5% ee in 70% yield. Under the extended reflux that would occur upon scale-up of the recrystallization it was noted that there was significant transesterification of the methyl ester to the *n*-propyl ester, which caused difficulties during the crystallization. Instead, the product was isolated by diluting the cooled methanolic reaction mixture with two volumes each of 2-propanol and heptane to afford *R*-**8** in 90% yield with >99% ee. This material was recrystallized under a similar protocol from refluxing methanol (2 mL/g of **6**) by cooling to ambient temperature and dilution with two volumes each of 2-propanol and heptane, resulting in 92% recovery of *R*-**8** (83% overall yield) with >99.5% ee.

Conversion of the methyl ester of **8** to the native amino acid **1** could be performed under either acidic or basic hydrolysis conditions. Basic hydrolysis was a much faster reaction, but resulted in a small but unacceptably significant amount of racemization (ca. 1% loss of ee). Acidic hydrolysis of *R*-**8** in dilute hydrochloric acid left the chiral center untouched. Neutralization afforded the amino acid *R*-**1** as a highly pure white precipitate in 98% yield and >99.5% ee. Subsequent conversion to the Boc derivative under literature reaction conditions (triethylamine, methanol, sodium hydroxide)[18] afforded the desired product *R*-**2** as an intractable thick oil, which only grudgingly crystallized in an overall 75% yield (two steps).

In the hopes of obtaining higher overall efficiency and better morphology for **2**, these last two steps were telescoped into one pot. Thus, after acidic hydrolysis to afford *R*-**1**, excess sodium hydroxide was added followed by di-*tert*-butyl dicarbonate to form the *N*-Boc derivative *R*-**2** under Schotten−Baumann conditions. This reaction proceeded exceedingly well, and acidification of the reaction mixture afforded *R*-**2** as a free-flowing white solid that precipitated directly from the reaction mixture. It was generally advisable to reslurry this material in water to remove small amounts of water-soluble salts that were occluded in the product cake. Filtration and drying afforded *R*-**2** in 97% overall yield for the two steps in the lab and 93% upon scale-up.

Analysis of this final product for chemical purity was performed by reverse-phase HPLC, and afforded >98% purity (area percent) in all cases. The enantiomeric purity was assessed by conversion of *R*-**2** to *N*-Boc-2-naphthylalanine methyl ester (*R*-**9**) under nucleophilic conditions (CH_3I, $KHCO_3$, acetone, 50 °C, quantitative yield) and chiral HPLC analysis. All batches prepared afforded >99.5% ee for *R*-**2**, indicating no loss of enantiomeric purity during the functional group transformations from *R*-**8**.

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Conclusions

The single enantiomers of 2-naphthylalanine and *N*-*tert*-butoxycarbonyl 2-naphthylalanine were prepared using a rhodium−methyl *BoPhoz*-catalyzed hydrogenation of dehydroamino acid derivative **6a** as the key stereoselective step. The asymmetric hydrogenation proceeded particularly smoothly during scale-up with a commercially relevant high substrate-to-catalyst ratio as a result of the ease of use and stability of the ligand **3** and complexes prepared from it. This hydrogenation rapidly afforded the desired product with complete conversion, high yield, and excellent enantioselectivity due to the high turnover frequency and stereoselectivity of the methyl *BoPhoz*−rhodium complex. The downstream chemistry proceeded smoothly to the desired products, with enhancement to absolute enantiomeric purity conveniently afforded by simple recrystallization of ammonium methanesulfonate intermediate **8**. Subsequent conversion to the desired products proceeded without loss of enantiomeric purity.

Experimental Section

General Methods. All solvents were used as received from Burdick and Jackson except where indicated. All reagents were used as received from Aldrich Chemical Co. 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 Waters Model 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. Chiral HPLC was performed on a Hewlett-Packard 1050 HPLC with UV detection. Reverse-phase HPLC was performed on a Hewlett-Packard 1100 HPLC with UV detection. Optical rotations were determined on a Rudolph Research Autopol III polarimeter. Melting points are uncorrected.

***Z*-2-Methyl-4-(naphthalen-2-ylmethylene)oxazol-5(4H)-one (5).** Acetic anhydride (17.275 L, 183 mol, 10 equiv) was added to a 50-L round-bottom flask with mechanical stirrer, condenser, and thermowell. *N*-acetylglycine (4.304 kg, 36.7 mol, 2 equiv), anhydrous sodium acetate (3.014 kg, 36.7 mol, 2 equiv), and 2-naphthaldehyde (**4**, 2.87 kg, 18.4 mol) were added. The mixture was heated to 100 °C (no exotherm noted) to afford a homogeneous solution and was held for 12 h to consume 99.3% of **4** (GC analysis). The mixture was allowed to cool to 87 °C and transferred while hot to a 72-L round-bottom flask with a mechanical stirrer, addition funnel, and a thermowell in an ice−water cooling bath. The mixture was cooled to below 30 °C, and water (2.3 L) was added slowly in portions over 4 h such that the temperature of the reaction mixture remained below 40 °C (maximum observed temperature was 28 °C). At this point 22 L of water was added rapidly, resulting in an exotherm to 38 °C. The mixture was cooled to below 30 °C and then stirred for 1 h. The solid was isolated by filtration and washed

with 30 L of water followed by 5 L of methanol. The resulting solid was dried on the nutsche for 8 h, then dried in a vacuum oven at ambient temperature under a nitrogen purge to afford 6.045 kg of crude **5**. ^{1}H NMR ($CDCl_3$) δ 8.404 (s, 1H); 8.38−8.34 (m, 1H); 7.94−7.83 (m, 3H); 7.59−7.50 (m, 2H); 7.307 (s, 1H); 2.449 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 168.0; 166.1; 134.5; 133.9; 133.3; 132.8; 131.6; 131.1; 129.3; 128.7; 128.2; 127.9; 127.8; 126.8; 15.8. HRMS *m*/*z* calcd for $C_{15}H_{12}NO_2$ ($M + H^+$) 238.0868, found 238.0865. GC (Chirasil L-Valine [Varian] 25 m × 0.25 mm i.d., film thickness 0.12 μm, 100 °C, 5 min; 100−175 °C, 10°/min; 175 °C, 17.5 min): t_R (**4**) 8.9 min, t_R (**5**) 26.4 min.

Methyl 2-Acetamido-3-(2-naphthyl)propenoate (6a). Methanol (17 L) was charged to a 50-L round-bottom flask, and crude **5** (6.045 kg, 18.4 mol maximum) prepared above was added. The mixture was stirred for 30 min, filtered on a nutsche, and washed two times with 4 L of methanol. The solids were dried on the nutsche for 3 h and then added to 12 L of methanol cooled to 15 °C in a 72-L round-bottom flask with a mechanical stirrer, a thermowell, and an addition funnel. A 25% solution of sodium methoxide in methanol (160 mL, 0.70 mol mmol, 0.04 equiv based on **2**) was added to the slurry of **5** slowly over 1 h such that the temperature remained below 30 °C (maximum observed 27 °C). A homogeneous solution was observed after the addition. The reaction mixture was allowed to stir at 21 °C for 1 h at which point TLC analysis (1:4 ethyl acetate:heptane) indicated a small amount of residual **5**. Additional 25% sodium methoxide (25 mL, 0.004 mol, 0.0002 equiv) was added, and the mixture was stirred at 23−25 °C for 1 h to complete the reaction (TLC analysis). The stirrer was slowed to minimum speed, and the reaction mixture was cooled to 15 °C. Cold water (24 L, prepared by mixing 16 L of water with 8 kg of ice) was added over 4 h to maintain the temperature below 20 °C (maximum observed 17.2 °C) resulting in a large amount of tan precipitate. The mixture was cooled to 15 °C and stirred for 1 h, and the solid was collected by filtration on a nutsche and washed with 8 L of water. The solid was dried on the filter for 12 h and then in a vacuum oven at 40 °C under a nitrogen purge for 1 day to afford 3.108 kg (63% from **4**) of crude **6a** as a tan powder. Acetone (35 L) was charged to a 50-L round-bottom flask with a mechanical stirrer and condenser. The crude **6a** (3.108 kg) was added, and the mixture was heated to 50 °C and stirred until a homogeneous solution was obtained. Activated carbon (Darco; 2.33 kg, 0.75 g/g of **6a**) was added, and the mixture was heated to reflux (54 °C) and stirred for 1 h. The mixture was cooled to below 30 °C, and the charcoal was removed by vacuum filtration into a 72-L flask with a mechanical stirrer and a distillation head. The carbon was washed with 15 L of acetone, and the cake was pulled dry. The solution was distilled at atmospheric pressure (head temperature ca. 56 °C) until 36 L of acetone was removed. The reaction mixture was cooled to 38 °C, and half of the mixture was transferred to the original (cleaned) 50-L flask, and each portion was cooled to below 30 °C. The product was precipitated by adding 35 L of water to each flask, resulting in an exotherm (heat of mixing) to about 35 °C. The mixtures were each cooled to below 30 °C, filtered onto a single nutsche, and washed with 20 L of water. The solids were dried on the nutsche for 12 h, then dried in a vacuum oven with nitrogen purge at 45 °C for 2.5 days (until there was no residual moisture) to afford 2.062 kg (66% recovery, 42% overall yield from **4**) of **6a** as a white powder, mp 153−154 °C. ^{1}H NMR (DMSO-d_6) δ 9.773 (s, 1H); 8.170 (s, 1H); 7.95−7.91 (m, 3H); 7.779 (d, 1H, J = 8.79 Hz); 7.58−7.55 (m, 2H); 7.335 (s, 1H); 3.738 (s, 3H); 2.051 (s, 3H).^{13}C NMR (DMSO-d_6) δ 169.5; 165.6; 133.0; 131.1; 130.9; 130.1; 128.4; 128.0; 127.5; 127.1; 126.9; 126.6; 126.4; 52.2; 22.5. HRMS *m*/*z* calcd for $C_{16}H_{16}NO_3$ ($M + H^+$) 270.1130, found 270.1133. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.59; H, 5.92; N, 5.11. GC (Chirasil L-Valine [Varian] 25 m × 0.25 mm i.d., film thickness 0.12 μm, 200 °C isothermal): t_R (**6a**) 23.3 min.

Methyl *R*-2-Acetamido-3-(2-naphthyl)propionate (*R*-7a). To a 22-L drop-bottom pressure vessel with an addition port and a gas inlet dip tube was charged 16.5 L of toluene. Purified **6a** (2.062 kg, 7.66 mol) was added slowly with stirring to avoid clumping of the solid. The resulting slurry was degassed with argon for 30 min using the dip tube. During this time a catalyst solution was prepared by combining ligand *S,R*-**3** (2.81 g, 4.6 mmol, 0.0006 equiv) and bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (1.79 g, 3.8 mmol, 0.0005 equiv) in 50 mL of argon-degassed methanol. After the degassing of the reaction mixture was complete, the headspace of the vessel was pressurized with 15 psig of argon and vented three times. The headspace was pressurized with 2 psig of argon, and the catalyst solution was added via a gastight syringe. The vessel was then pressurized to 15 psig with hydrogen, vented, and then held under a constant 15 psig hydrogen pressure with subsurface hydrogen introduction (via the dip tube) and the reaction was followed by hydrogen uptake using a mass flowmeter. After about 1.5 h the mixture became homogeneous during which time an exotherm to 33 °C was noted. The reaction was stirred under hydrogen for a total of about 6 h. Chiral GC analysis of the reaction mixture indicated >99.9% conversion to *R*-**7a** with 97.9% ee. The resulting solution of *R*-**7a** was taken directly to the next step. On small scale, the product could be isolated by solvent removal and recrystallized from toluene/heptane to afford *R*-**7a** in >95% yield with >99% ee, mp 95−96 °C. ^{1}H NMR ($CDCl_3$) δ 7.85−7.75 (m, 3H); 7.553 (s, 1H); 7.47 (m, 2H); 7.218 (d, 1H, J = 8.52 Hz); 6.01 (br s, 1H); 4.966 (q, 1H, J = 6.04 Hz); 3.727 (s, 3H); 3.314 (dd, 1H, J = 5.77, 13.74 Hz); 3.244 (dd, 1H, J = 6.04, 14.01 Hz); 1.973 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 172.3; 169.9; 133.6; 133.5; 132.5; 128.3; 128.1; 127.7; 127.6; 127.3; 126.3; 125.8; 53.3; 52.4; 38.1; 23.0. HRMS *m*/*z* calcd for $C_{16}H_{18}NO_3$ ($M + H^+$) 272.1287, found 272.1283. Chiral GC (Chirasil L-Valine [Varian] 25 m × 0.25 mm i.d., film thickness 0.12 μm, 185 °C isothermal, 15 psig He): t_R(*R*-**7a**) 15.5 min, t_R(*S*-**7a**) 16.0 min. Chiral HPLC (250 × 4.6 mm Chiralpak AD-H, 90:10 hexane:2-propanol, 1 mL/min, λ = 254 nm): t_R (*R*-**7a**) 13.2 min, t_R (*S*-**7a**) 16.2 min. $[\alpha]^{24}_D = -35.3$ (*c* 1.00, ethanol); $[\alpha]^{24}_D =$

−104.7 (*c* 0.99, $CHCl_3$), indicating the *R* enantiomer of **7a**.[13a,17]

Methyl *R*-2-Amino-3-(2-naphthyl)propionate Methanesulfonic Acid Addition Salt (*R*-8). The toluene solution of crude *R*-**7a** (7.66 mol maximum) was added to a 50-L flask with a mechanical stirrer, stripping head, and addition funnel. The solvent was stripped at 60 mm vacuum by heating in stages from 50 to 114 °C until no further distillate was removed. The residual material was cooled to 40 °C at which point it solidified. Methanol (3.85 L) was added and the material was dissolved by stirring while slowly lowering the stirrer paddle from the top of the liquid. Methanesulfonic acid (1.103 kg, 11.5 mol, 1.5 equiv) was added over 50 min so that the temperature of the solution remained below 60 °C. The mixture was heated to reflux (68 °C) for 72 h to afford complete consumption of **7a** by TLC analysis (2:1 ethyl acetate:heptane).[19] The reaction mixture was cooled to 31 °C, and 2-propanol (7.685 L) and heptane (7.685 L) were added to complete the precipitation. The mixture was stirred while cooling to below 28 °C, at which point the solid was isolated by filtration and washed with 2 L of 2-propanol and 2 L of heptane. The product was air-dried on the nutsche for 6 h, then added to 4 L of methanol in a 50-L flask with a mechanical stirrer, thermowell, and condenser, and washed in with 200 mL of methanol. The mixture was heated to reflux for 15 min to afford a homogeneous solution and then cooled to 33 °C. 2-Propanol (9 L) and heptane (9 L) were added to complete the precipitation of **8**, and the mixture was cooled to 30 °C and stirred for 1 h. The solid was isolated by filtration and washed sequentially with 1 L of 2-propanol and 1 L of heptane. The solid was air-dried for 2 h on the nutsche and then dried in a vacuum oven at ambient temperature under a nitrogen purge to afford 2.082 kg (84% overall from **6a**) of *R*-**8a**, mp 197−198 °C, that possessed 99.9% ee as determined by conversion to the corresponding acetamide **7a** and chiral GC analysis.[20] ^{1}H NMR (DMSO-d_6) δ 8.442 (br s, 3H); 7.93−7.86 (m, 3H); 7.758 (s, 1H); 7.53−7.51 (m, 2H); 7.381 (dd, 1H, J = 1.37, 8.52 Hz); 4.437 (t, 1H, J = 6.59 Hz); 3.699 (s, 3H); 3.276 (d, 2H, J = 6.59 Hz); 2.324 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 169.4; 133.0; 132.3; 128.2; 128.2; 127.6; 127.5; 127.4; 126.2; 126.0; 53.3; 52.7; 39.7; 36.1. HRMS *m*/*z* calcd for $C_{14}H_{16}NO_2$ (M-CH_3SO_3) 230.1181, found 230.1187. Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89; N, 4.30. Found: C, 55.63; H, 5.92; N, 4.19. $[\alpha]^{25}_D$ = +2.2 (*c* 1.03, H_2O).

***R*-2-Naphthylalanine (*R*-1).** Methanesulfonate salt *R*-**8** (>99.7% ee; 1.00 g, 3.07 mmol) was combined with 3 M HCl (2.05 mL, 6.14 mmol, 2.0 equiv). The mixture was heated to 95 °C for 22 h to consume virtually all of **8** according to TLC analysis (neutralized sample, triethylamine-deactivated plate, 2:1 ethyl acetate:heptane). The reaction mixture was cooled to ambient temperature, and sodium hydroxide (2 M, 4.6 mL, 9.2 mmol, 3 equiv) was added to afford a solution with a small amount of precipitate. The pH of the mixture was found to be ca. 12, and it was acidified to pH 6 by the addition of 86 μL (1.5 mmol) of acetic acid, resulting in the precipitation of a large amount of white solid. The reaction mixture was stirred at ambient temperature for 2 h, filtered, and washed with water. The resulting white solid was dried in a vacuum oven at ambient temperature with a nitrogen purge to afford 650 mg (98%) of *R*-**1** which was 99.8% ee (determined by sequential conversion to *R*-**2** and *R*-**9** as indicated below and analysis by chiral HPLC). ^{1}H NMR (NaOD/D_2O) δ 7.86−7.81 (m, 3H); 7.683 (s, 1H); 7.54−7.45 (m, 2H); 7.390 (d, 1H, J = 8.52 Hz); 3.60−3.55 (m, 1H); 3.159 (dd, 1H, J = 5.49, 13.73 Hz); 2.938 (dd, 1H, J = 7.97, 13.46 Hz). ^{13}C NMR (NaOD/D_2O) δ 185.0; 138.9; 135.9; 134.7; 130.7; 130.6; 130.4; 130.4; 130.3; 129.1; 128.5; 60.1; 43.9. HRMS *m*/*z* calcd for $C_{13}H_{14}NO_2$ (M + H^+) 216.1025, found 216.1037. $[\alpha]^{25}_D$ = +14.9 (*c* 0.43, 0.04 M HCl). The positive rotation indicates the *R* enantiomer of **1**.[17]

***N*-Boc-*R*-2-naphthylalanine (*R*-2).** Water (14.89 L) was added to a 50-L round-bottom flask with a mechanical stirrer, thermowell, and condenser. Aqueous hydrochloric acid (3 M, 4.27 L, 12.8 mol, 2.0 equiv) was added. Methanesulfonate salt *R*-**8** (2.082 kg, 6.4 mol) was added, and the mixture was stirred to afford a homogeneous solution. The mixture was heated to 95 °C for 12 h at which point ^{1}H NMR analysis of an aliquot indicated >99% conversion of **8** to **1**.[21] The reaction mixture was cooled to 40 °C and transferred to a 72-L round-bottom flask (in a cooling bath) equipped with a mechanical stirrer, thermowell, addition funnel, and condenser. The mixture was cooled to 33 °C, and 50% sodium hydroxide (2.66 kg, 33.25 mol, 5.2 equiv) was added over 2 h. Di-*tert*-butyl dicarbonate (Boc anhydride; 1.676 kg, 7.7 mol, 1.2 equiv) was added over 1 h such that the temperature remained below 35 °C (maximum observed 34.9 °C). The reaction mixture was cooled to below 30 °C, the cooling was removed, and the mixture was stirred for 6 h and then analyzed by ^{1}H NMR to indicate >99% conversion of **1** to **2**.[22] HCl (3 M, 4.685 L, 14.1 mol, 2.2 equiv) was added slowly over 6 h, resulting in the precipitation of a solid (but not much observable gas evolution). The mixture was stirred for 1 h and was checked and found to be acidic (pH 1−2). The solid was isolated by filtration, washed with 1.1 L of water, and dried on the nutsche for 12 h. Water (12.5 L) was added to the flask and the contents of the nutsche were added. The heterogeneous mixture was stirred for 30 min and filtered, and the product cake was washed

(19) The reaction time can be signficantly shortened by performing the reaction under pressure above the boiling point of the solvent (reaction times as short as 40 min have been observed using a microwave reactor at 115 °C). These types of facilities were unavailable to us during scale-up.

(20) Methanesulfonate **8** (8.1 mg, 0.025 mmol) was slurried in 1 mL of dichloromethane, and triethylamine (11 μL, 0.079 mmol, 3.1 equiv) was added to afford a homogeneous solution. Acetic anhydride (6 mL, 0.064 mmol, 2.5 equiv) was added and the mixture was allowed to sit for 1 h. The mixture was diluted with 3 mL of ethyl acetate, then washed with 3 M HCl (1 mL) and saturated sodium bicarbonate (1 mL). The solution of **7a** thus generated was dried (magnesium sulfate) and analyzed directly by either chiral GC or HPLC to determine the ee.

(21) A sample of the reaction mixture (150 μL) was concentrated at reduced pressure, dissolved in D_2O, and concentrated once more. The resulting material was analyzed by ^{1}H NMR in D_2O by comparing the integration of the product peak (one proton) at 4.37 ppm with the starting material peak (three protons) at 3.75 ppm to determine the conversion.

(22) A sample of the reaction mixture (0.20 mL) was concentrated at reduced pressure, dissolved in D_2O, and concentrated once more. The resulting material was analyzed by ^{1}H NMR in D_2O by comparing the integration of the product peak (one proton) at 4.25 ppm with the starting material peak (one proton) at 3.55 ppm to determine the conversion.

with 2 L portions of water until the pH of the wash was above 3 (total 5 washes). The product was air-dried on the nutsche for 2 h and then dried at 50 °C in a vacuum oven with nitrogen purge until no moisture remained to afford 1.868 kg (93%) of *R*-**2** which was >99% chemically pure and >99.5% ee as determined by conversion to the methyl ester *R*-**9** and chiral HPLC analysis (see below), mp 91−93 °C. The NMR spectrum indicates two isomers, syn and anti rotamers of the carbamate. ^{1}H NMR ($CDCl_3$) major isomer δ 7.82−7.86 (m, 3H); 7.631 (s, 1H); 7.47−7.44 (m, 2H); 7.319 (d, 1H, J = 8.52 Hz); 5.018 (br d, 1H, J = 7.42 Hz); 4.663 (br q, 1H, J = 7.14 Hz); 3.39−3.33 (m, 1H); 3.24−3.17 (m, 1H); 1.381 (br s, 9H). minor isomer δ 7.82−7.86 (m, 3H); 7.631 (s, 1H); 7.47−7.44 (m, 2H); 7.319 (d, 1H, J = 8.52 Hz); 6.42 (m, 1H); 4.66 (m, 1H); 3.1−3.0 (m, 2H); 1.177 (br s, 9H). ^{13}C NMR (DMSO-d_6) δ 173.6; 155.4; 135.7; 133.0; 131.8; 127.6; 127.5; 127.4; 127.4; 127.3; 125.9; 125.4; 78.0; 55.1; 36.7; 28.1. FDMS: m/z 314.109 ($M - H^+$). HRMS m/z calcd for $C_{18}H_{22}NO_4$ ($M + H^+$) 316.1549, found 316.1568. HPLC (150 × 4.6 mm Aquasil C18, 5 μ, 70:30 0.1% aqueous H_3PO_4:acetonitrile; 20 min, 5:95 0.1% aqueous H_3PO_4:acetonitrile, 10 min, 1.0 mL/min, λ = 225 nm): t_R 10.4 min. $[\alpha]^{25}_D = -17.3$ (c 1.04, $CHCl_3$).

Methyl *N*-Boc-*R*-2-naphthylalanine (*R*-9). *N*-Boc-*R*-2-naphthylalanine (*R*-**2**) (100 mg, 0.32 mmol) was dissolved in 2 mL of acetone. Potassium hydrogen carbonate (50 mg, 0.50 mmol, 1.6 equiv) was added followed by iodomethane (50 μL, 0.80 mmol, 2.5 equiv). The mixture was heated to reflux for 12 h, then cooled to ambient temperature. The reaction mixture was diluted with ethyl acetate, washed with aqueous sodium bicarbonate (10 mL), 2 M sodium thiosulfate (5 mL), and water (10 mL). The organic layer was dried with magnesium sulfate and concentrated to afford 0.11 g of *R*-**9** (99%) which was 99.7% ee by chiral HPLC analysis. ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 3H); 7.586 (s, 1H); 7.45 (m, 2H); 7.26 (m, 1H); 5.000 (br d, 1H, J = 7.14 Hz); 4.677 (q, 1H, J = 6.87 Hz); 3.713 (s, 3H); 3.35−3.15 (m, 2H); 1.399 (s, 9H). Chiral HPLC (250 mm × 4.6 mm Chiralpak AD-H, 97:3 hexane:2-propanol, 1 mL/min, λ = 254 nm): t_R (*R*-**9**) 34.0 min, t_R (*S*-**9**) 36.8 min.

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