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Large-Scale Synthesis of Singh's Catalyst in a One-Pot Procedure Starting from Proline

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Supporting Information

ABSTRACT: A practical one-pot procedure for the preparation of Singh's catalyst from either L-/D-proline or Boc-proline is described. The coupling partner, a chiral amino alcohol, can be prepared and used directly without purification from the corresponding amino acid ester. Moreover, a procedure for *tert*-butoxycarbonyl (Boc) group removal using concentrated HCl in MeOH−DCM was developed and utilized for the multigram-scale synthesis of Singh's catalyst.

INTRODUCTION

The use of chiral organocatalysts, purely organic and metal-free small molecules, has emerged as a highly efficient synthetic tool for enantioselective transformations (asymmetric organocatalysis) in a wide range of reactions.[1] Small chiral organocatalysts are generally nontoxic, stable, and fairly easy to design and synthesize from readily available chiral sources, such as natural amino acids and other chiral amines. Among them, proline-based chiral organocatalysts have been developed extensively and applied successfully in several reactions. Singh and co-workers have designed proline amide catalysts of type **1** (Scheme 1), bearing *gem*-diphenyl substituents at the β-carbon, which play a key role in providing high enantioselectivity in the direct aldol reaction of ketones with aldehydes.[2] The catalyst **1** has been proven to be one of the most effective organocatalysts for asymmetric direct aldol reactions of water-miscible ketones such as acetone with various aldehydes in aqueous medium.[3] Later, Gröger and Berkessel et al. reported the use of this catalyst **1** in a modular chemoenzymatic synthesis of all four stereoisomers of 1,3-diols through a combination of asymmetric organocatalysis and biocatalysis in a one-pot synthesis in aqueous reaction media (Scheme 1).[4] The catalyst **1**/*ent*-**1** was applied for the initial organocatalytic aldol reaction of acetone with aldehydes under solvent-free conditions. The compatibility of the organocatalyst **1** with the biocatalyst (ADH) allowed its direct use in the subsequent enzymatic reduction without the need for a workup step. Notably, high enantioselectivities were obtained when low catalyst loadings were used under kinetic control.[5] Furthermore, Wang et al. have successfully identified **1** as a catalyst for the aldol reaction of acetone with α-amino aldehydes in the synthesis of the antibiotic linezolid,[6] and for the aldol-lactonization of 2-formylbenzoic esters with ketones/aldehydes in a three-step synthesis of the natural product (*S*)-(−)-3-butylphthalide with a high level of enantioselectivity.[7]

As mentioned above, Singh's catalyst **1** was used very successfully in our work in asymmetric organocatalytic aldol reactions, especially in water as solvent or under solvent-free conditions.[4,5] To support our study, we needed a practical and reproducible procedure for the large-scale preparation of **1**. In the original method reported by Singh et al.,[2] a series of catalysts of type **1** were prepared from Boc-proline (**2**) and the corresponding diphenylamino alcohols **3** in a sequential two-step method, i.e. condensation and Boc-deprotection, with isolation of the intermediate from the condensation reaction, i.e. **4** (Scheme 2). We envisioned an alternative synthesis of **1** in a one-pot multistep synthesis to give an economical preparative method in which the reaction product from the initial step is used directly without purification for the next step (Scheme 3). In fact, Boc-L-proline (**2**) and the L-diphenylamino alcohol **3** are commercially available but rather expensive compared to the precursor L-proline (**5**) and the L-leucine ester **6**, respectively. Thus, the synthesis of **1** starting from easily accessible and cheap L-proline (**5**) and the L-leucine ester **6** in a one-pot transformation would offer an improved overall economy of the process. Herein, we report a practical one-pot procedure for the preparation of the Singh's catalyst **1** directly from either Boc-proline (**2**) or proline (**5**), and leucine methyl ester hydrochloride (**6**). Novel conditions for Boc group removal were also developed and utilized on multigram scale in the synthesis of **1**.

Synthesis of the Catalyst 1 Starting from Boc-proline (2). According to reported procedures,[2,8] Boc-L-proline (**2**) was condensed with the L-diphenylamino alcohol (*S*)-**3** via a mixed anhydride method using ethyl chloroformate or isobutyl chloroformate, as shown in Scheme 2. The resulting *N*-Boc proline amide (*S*,*S*)-**4** was purified by recrystallization and then subjected to Boc-deprotection by treatment with formic acid or TFA. After neutralization, workup, and recrystallization, the proline amide (*S*,*S*)-**1** was obtained in 82−83% yield. In our hands, the removal of the Boc group using formic acid or TFA resulted in the formation of side products (e.g., the *N*-formyl pyrrolidinyl derivative), leading to the lower yield of the desired (*S*,*S*)-**1**. Thus, an alternative method was needed that would provide **1** in high yield and high purity. We found that the use of a solution of HCl(g) in MeOH for the Boc-deprotection step

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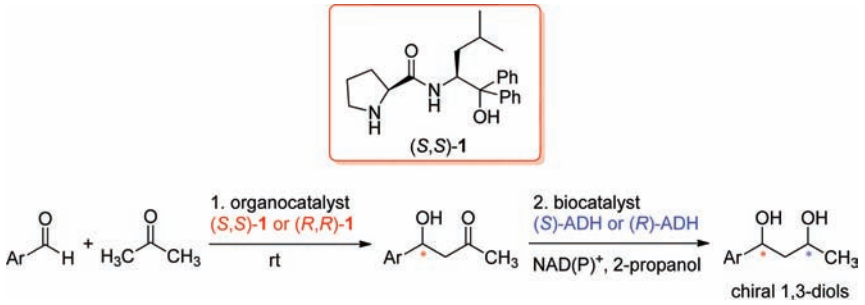
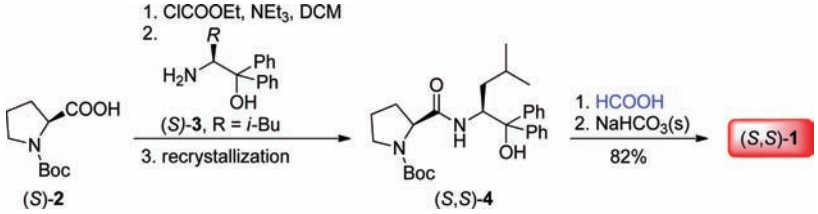
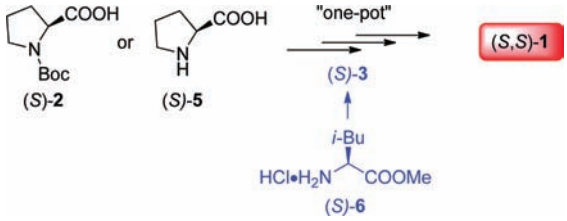
Scheme 1. Singh's catalyst 1 and its application in combined asymmetric organo- and biocatalytic reaction sequences.[4,5]



Scheme 2. Synthesis of the catalyst 1 as reported by Singh et al.[2]



Scheme 3. Synthesis of the catalyst 1 in a one-pot multistep synthesis starting from either Boc-proline (2) or proline (5)

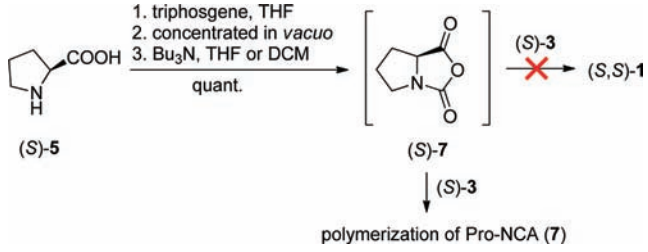


Scheme 4. Synthesis of the catalyst 1, starting from Boc-L-proline (2)

such a combination of the coupling of (*S*)-**2** with the pure amino alcohol (*S*)-**3** on a gram scale, using less expensive ethyl chloroformate, and a subsequent removal of the Boc group was achieved by adding a HCl(g)/MeOH solution directly to the reaction mixture. After a final neutralization and workup step, we were pleased to find that this procedure proceeded highly efficiently and led to the desired proline amide (*S,S*)-**1** in a very good yield of 95% after recrystallization.

Synthesis of the Catalyst 1 Starting from Proline (5). Having succeeded in performing a one-pot multistep synthesis of **1** from **2**, we further aimed at a multigram-scale synthesis of **1** starting from cheap L-proline (**5**), ideally without isolation of any intermediates. The in situ generation of *N*-protected proline was required for this purpose. We first attempted the desired transformation via the reactive intermediate proline-*N*-carboxyanhydride (Pro-NCA, **7**, Scheme 5), which has been

Scheme 5. Attempted synthesis of (*S,S*)-1 via Pro-NCA (7)



successfully used in the synthesis of small peptides,[9] and in the preparation of chiral α,α-diaryl-2-pyrrolidinemethanols.[10] Ideally, the anhydride **7** could provide **1** in a single operation, by coupling with the amino alcohol **3** and concomitant decarboxylation. As outlined in Scheme 5, L-proline (**5**) was converted quantitatively to the anhydride (*S*)-**7** by reaction with triphosgene in THF, followed by the addition of tributylamine to affect cyclization. The resulting homogeneous solution of (*S*)-**7** was used immediately for the coupling step. Unfortunately, all attempts to condense (*S*)-**7** and (*S*)-**3** failed. In all cases, we observed the polymerization of (*S*)-**7**, while (*S*)-**3** remained unchanged. Upon addition of (*S*)-**7** to a (*S*)-**3** solution at 0 °C, the evolution of gas (CO_2) occurred rapidly to afford a white solid. A trace of (*S,S*)-**1** could be detected when the reaction was performed at a temperature as low as −40 °C. At lower temperature, no conversion to the desired product occurred. It appears that (*S*)-**3** mainly acts as a polymerization initiator in the known base-catalyzed polymerization of Pro-NCA (**7**).[11] This assumption is also supported by the order of amine nucleophilicities (determined by kinetic experiments) according to which secondary amines are 10^2−10^3 times more nucleophilic than typical primary alkyl amines.[12]

Consequently, we considered suitable *N*-protection of proline as the crucial factor for success in the coupling reaction with (*S*)-**3**. We therefore focused our attention to the in situ generation of Cbz- or Boc-protected proline, which could be readily deprotected in the final step.[13] In particular, we examined the generation of the mixed anhydride intermediates **9** by sequentially reacting L-proline with different reagents as

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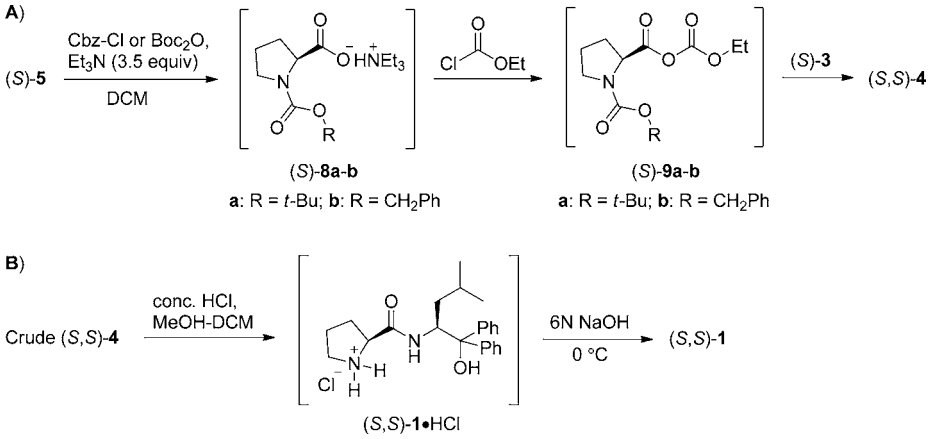
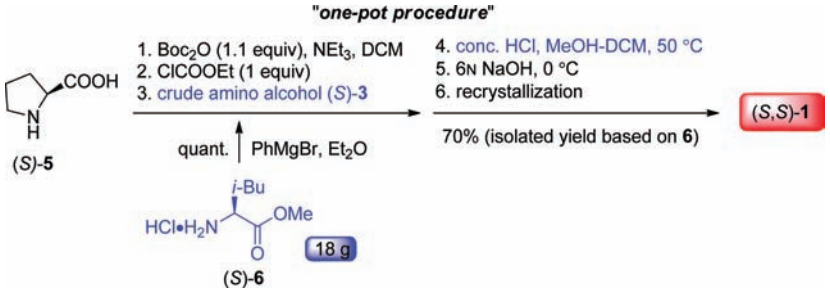
Scheme 6. In situ preparation of the mixed anhydride (*S*)-9 (A) and the removal of the Boc group from the crude (*S,S*)-4 using conc. HCl (B)



Scheme 7. Preparation of (*S,S*)-1 on 100 mmol scale in a one-pot procedure



outlined in Scheme 6(A). We found that the in situ generation of Boc-protected proline, (*S*)-**8a**, using Boc_2O (97% purity, 1.1 equiv) in the presence of NEt_3 (3.5 equiv), followed by treatment with ethyl chloroformate (1 equiv) resulted in the clean formation of the mixed anhydride (*S*)-**9a**. The subsequent coupling reaction with (*S*)-**3** led to the *N*-Boc proline amide (*S,S*)-**4** in high purity. It is worthwhile noting that the carboxylate group of (*S*)-**8a** does not significantly react with Boc_2O, even when it is present in an excess of 2 equiv. In contrast, if (*S*)-**8a** was not formed quantitatively in the first step, the remaining proline reacted with ethyl chloroformate, leading to its undesired *N*-ethyl carbamate. It should also be noted that the *N*-Cbz anhydride **9b** could be cleanly formed when purified Cbz-protected proline was used but not in a one-pot procedure using Cbz-Cl. This is probably due to the reagent Cbz-Cl, which is typically contaminated to some extent with benzyl chloride (formed upon storage even for shorter periods of time and at low temperatures).[14]

With an operationally simple and efficient coupling procedure in hand, we then focused on the development of novel conditions for Boc group removal, to be utilized in the large-scale synthesis of **1**. For this purpose, we envisaged the use of commercially concentrated HCl, more practical and convenient than the use of gaseous HCl. Gratifyingly, we found that the Boc group of (*S,S*)-**4** in the crude product still containing triethylammonium chloride could be deprotected using conc. HCl in a mixture of MeOH/DCM (2:1), as shown in Scheme 6(B). The conversion proceeded via a slurry-to-homogeneous transformation. It should be mentioned that the reaction was sluggish and did not go to completion when only MeOH was used as a single solvent. On 10 mmol scale, by using ~12 equiv of conc. HCl, the deprotection was complete after stirring at rt for 15 h to give (*S,S*)-**1**·HCl in high purity according to NMR analysis. While these results were very encouraging, we wanted to avoid the use of a large excess of HCl. Furthermore, the reaction did not reach completion in a reasonable time on the larger scale. We felt that the process needed to be more consistent if it was going to be used on larger scale. We therefore examined the reaction on 50 mmol scale at 50 °C. The most consistent results were obtained when ~5 equiv of conc. HCl (20 mL) was used in a mixture of MeOH/DCM of 80:40 mL. The deprotection was complete within 6–7 h, yielding the protonated proline (*S,S*)-**1**·HCl in high purity. After neutralization with 6 N NaOH and workup, the crude product was purified by a final recrystallization to furnish (*S,S*)-**1**.

The procedure described above was implemented on 100 mmol scale in a one-pot procedure, starting from L-proline (**5**) and the crude amino alcohol (*S*)-**3**, obtained quantitatively from the reaction of the L-leucine ester (*S*)-**6** and PhMgBr (5 equiv).[15] As illustrated in Scheme 7, L-proline (**5**) was first converted to the mixed anhydride (*S*)-**9a** and then condensed with the crude amino alcohol (*S*)-**3**. After concentration under reduced pressure, the resulting crude (*S,S*)-**4** was stirred in a mixture of conc. HCl/MeOH/DCM (40:160:80 mL) at 50 °C for 7 h to afford (*S,S*)-**1**·HCl. Subsequent neutralization, workup, and recrystallization furnished the desired (*S,S*)-**1** in 70% isolated yield based on the L-leucine ester (*S*)-**6**. Using the same procedure, (*R,R*)-**1** could be synthesized starting from D-proline and (*R*)-**3** instead.

We also performed the synthesis of (*R,R*)-**1** from Boc-D-proline on 25 mmol scale using the procedure described in Scheme 7 starting from step 2. For this purpose, D-leucine was first converted to the D-leucine ester (*R*)-**6** by treatment with

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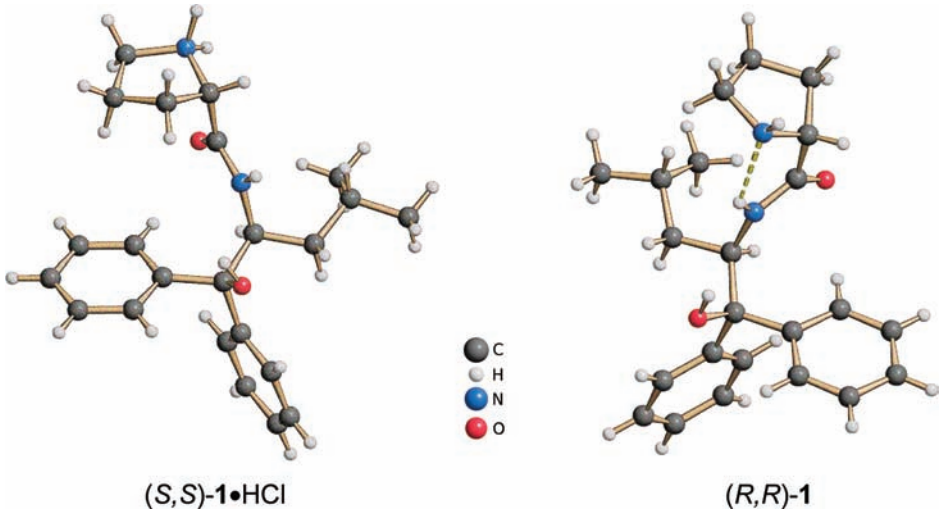

Figure 1. X-ray crystal structures of (*S*,*S*)-**1**·HCl (left, chloride anion is omitted for clarity), and (*R*,*R*)-**1** (right).

thionyl chloride in MeOH at reflux for 3 h.[16] Subsequent reaction with PhMgBr (5 equiv)[17] afforded the desired (*R*)-**3** which was used directly without purification for the condensation with Boc-D-proline. After purification by recystallization with EtOAc, (*R*,*R*)-**1** was obtained in 72% based on D-leucine (89% yield calculated from the crude product by NMR analysis).

Furthermore, we were able to characterize the structure of the catalyst **1** by X-ray crystallography in both the protonated form as (*S*,*S*)-**1**·HCl, and the free proline amide form of (*R*,*R*)-**1**, as depicted in Figure 1. These two crystal structures show differences in mainly in the positioning of the proline's pyrrolidine ring. There is an intramolecular hydrogen bond between the proline's N-atom and the amide-NH in the free proline amide (*R*,*R*)-**1**, whereas the protonated N-atom of proline in the (*S*,*S*)-**1**·HCl salt points away from the amide-NH bond, presumably to minimize steric hindrance.

In conclusion, we have developed an efficient and practical one-pot procedure for the synthesis of proline amide organocatalysts, in particular Singh's catalyst **1**, starting from either proline or Boc-proline. This synthetic strategy can be applied to large laboratory scale, and can potentially be extended to technical synthesis. One of the key features is the removal of the Boc-group using concentrated HCl in MeOH/DCM as a clean and convenient protection method.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 400, a Bruker DRX 500 or a Bruker Avance II 600 spectrometer at ambient temperature and are referenced to the solvent used. IR spectra were measured on a Shimadzu IRAffinity-1 instrument. Optical rotations were measured on a Perkin-Elmer 343 Plus polarimeter. Melting points were determined on a Büchi apparatus and are uncorrected.

L-Proline (99%, BioChemica AppliChem), Boc-L-proline (>99%, BACHEM Biochemica GmbH), Boc-D-proline (>99%, NovaBiochem), L-leucine methyl ester hydrochloride and D-leucine (99%, Alfa Aesar-Johnson Matthey Co.), Boc_2O (97%, Acros or ≥98%, Fluka) were purchased from the suppliers indicated and used as received. Ethyl chloroformate (99%) was purified prior to use: shaken with sat. aq. Na_2CO_3 (three times), aq. 50% $CaCl_2$ (three times), and brine (twice), then dried with Na_2SO_4 and redistilled using an efficient fractionating column at atmospheric pressure under Ar atmosphere. Et_2O was freshly distilled from Na/benzophenone. NEt_3 and CH_2Cl_2 were freshly distilled from CaH_2.

Synthesis of (*S*,*S*)-1. *Procedure A: Synthesis Starting from L-Boc-proline.* A dry, 250-mL Schlenk flask containing L-Boc-proline (2.583 g, 12 mmol) was fitted with a mechanical stirrer, argon inlet tube, and flushed with argon. Anhydrous CH_2Cl_2 (50 mL) was added, and the solution was cooled to 0 °C, followed by the addition of Et_3N (1.68 mL, 12 mmol. The reaction mixture was then treated with ethyl chloroformate (1.14 mL, 12 mmol) and stirred at 0 °C for 30 min, resulting in the formation of triethylammonium hydrochloride as a white precipitate. A solution of the pure (*S*)-**3** (2.694 g, 10 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise. After the addition was complete, the reaction mixture was stirred at 0 °C to room temperature overnight. To the resulting white slurry of the crude *N*-Boc-proline amide (*S*,*S*)-**4** was added a solution of HCl(g) in MeOH (48 mL, 1.25 M, 60 mmol). A clear colorless solution was obtained and stirred at rt overnight. The resulting solution of the (*S*,*S*)-**1**·HCl salt was evaporated under reduced pressure and diluted with EtOAc (60 mL). The mixture was made slightly basic (pH 8−9) with 1 N KOH (~60 mL) with vigorous stirring to give (*S*,*S*)-**1**. After separation of the organic layer, the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with 1 N KOH, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo, affording (*S*,*S*)-**1** as a white solid in quantitative yield. After recrystallization from EtOAc, (*S*,*S*)-**1** was obtained as a white crystalline solid [3.482 g, 95% yield based on (*S*)-**3**].

Procedure B: Synthesis Starting from L-Proline. A dry, 1-L three-necked flask containing dry Mg turnings (12.16 g, 500 mmol), fitted with a mechanical stirrer, dried reflux condenser, argon inlet tube, and a 250-mL pressure-equalized addition funnel, was flushed with argon and charged with anhydrous Et_2O (100 mL). A solution of bromobenzene (79.30 g, 505 mmol) in dry Et_2O (200 mL) was placed into the addition funnel and added slowly and dropwise over a 2.0−2.5 h period. After completion of the addition, the mixture was warmed to 40 °C and aged for 0.5 h to complete the reaction. The resulting brown solution of PhMgBr was cooled to 0 °C in an ice bath and a bent flask containing (*S*)-**6** (18.026 g, 99 mmol) as dry fine powder was fitted to a side neck of the reaction flask. By rotation and tapping, the solid (*S*)-**6** was gradually added to the

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solution under vigorous stirring. After the addition was complete, the reaction mixture was stirred at 0 °C for 30 min and then at rt for 15 h to give a light-yellow liquid mixed with a white precipitate. The resulting heterogeneous mixture was cooled to 0 °C and quenched by the slow addition of saturated NH_4Cl (300 mL), resulting in vigorous evolution of gas. The mixture was then diluted with EtOAc (200 mL) and H_2O (100 mL) and partitioned. After separation of the organic layer, the aqueous phase (pH 7−8) was extracted with EtOAc. The combined organic layers were washed with sat. $NaHCO_3$, H_2O, and brine, were dried over Na_2SO_4 and evaporated to dryness in vacuo. The crude product was obtained as a pale-yellow solid (27.212 g) containing (*S*)-**3** in quantitative yield together with a small amount of biphenyl as a byproduct (by NMR and GC−MS analysis), and used for the next step without further purification.

To a suspension of L-proline (11.515 g, 100 mmol) and Boc_2O (22.961 g, 105 mmol) in dry CH_2Cl_2 (200 mL) was slowly added Et_3N (45.0 mL, 324 mmol) at 0 °C. The cooling bath was removed, and the reaction mixture was stirred at rt for 1 h. During this time the mixture became homogeneous as proline reacted with Boc_2O to afford the intermediate *N*-Boc proline (*S*)-**8a**. Then, the reaction mixture was cooled to 0 °C and treated with ethyl chloroformate (9.50 mL, 100 mmol), resulting in the formation of triethylammonium hydrochloride as a white precipitate. Upon completion of the addition, the resulting slurry was stirred for an additional 30 min. The crude solid of (*S*)-**3** (99 mmol) was then added in portions by means of a funnel (rinsing with dry CH_2Cl_2). Upon completion of the addition, the reaction mixture was stirred at 0 °C to room temperature overnight, followed by evaporation of volatiles under reduced pressure to provide the crude *N*-Boc proline amide (*S*,*S*)-**4** as a pale-yellow solid. MeOH (160 mL) and CH_2Cl_2 (80 mL) were then added to the crude (*S*,*S*)-**4**, followed by slow addition of conc. HCl (40 mL). The resulting slurry was heated to 50 °C and stirred for 7 h. During this time, the mixture became homogeneous (after ∼2.5 h). After the reaction was complete (TLC analysis), the resulting solution of the (*S*,*S*)-**1**·HCl salt was evaporated under reduced pressure and diluted with H_2O (200 mL) and EtOAc (300 mL). The mixture was cooled to 0 °C and made slightly basic (pH 8−9) with 6 N NaOH (∼70 mL), with vigorous stirring, to give (*S*,*S*)-**1**. Since (*S*,*S*)-**1** was only partially soluble in EtOAc, the conversion of (*S*,*S*)-**1**·HCl to (*S*,*S*)-**1** proceeded via a slurry-to-slurry transformation. After separation of the organic layer, the aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with 1 N NaOH, H_2O, and brine and were dried over Na_2SO_4. The solution was filtered through a short pad of silica and concentrated in vacuo to afford (*S*,*S*)-**1** as a pale-yellow solid. After purification by recrystallization from EtOAc, (*S*,*S*)-**1** was obtained as a white crystalline solid [25.457 g, 70% yield based on (*S*)-**6**].

(*S*)-2-Amino-4-methyl-1,1-diphenylpentan-1-ol, (*S*)-3. Prepared from (*S*)-**6** according to procedure B and purified by recrystallization from EtOAc to give (*S*)-**3** as white crystals; mp 126.5−128.5 °C; $[\alpha]^{20}_D$ −97.7 (*c* 1.0, $CHCl_3$) [lit.:[18] mp 136−138 °C; $[\alpha]^{25}_D$ −96.6 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.60 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.46 (d, *J* = 7.4 Hz, 2H, Ar*H*), 7.30 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.26 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.24−7.13 (m, 2H, Ar*H*), 4.24 (bs, 1H, O*H*), 3.97 (dd, *J* = 10.2, 1.7 Hz, 1H, NC*H*), 1.62−1.52 [m, 1H, C*H*(CH_3)$_2$], 1.25 (ddd, *J* = 14.1, 10.3, 3.8 Hz, 1H, CHC*H*H′CH), 1.19 (bs, 2H, NH_2), 1.10−1.02 (m, 1H, CHCH*H*′CH), 0.88 (d, *J* = 6.5 Hz, 3H, CH_3), 0.85 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): 147.2 (Ar*C*), 144.5 (Ar*C*), 128.4 (Ar*C*H), 128.0 (Ar*C*H), 126.6 (Ar*C*H), 126.3 (Ar*C*H), 125.8 (Ar*C*H), 125.5 (Ar*C*H), 79.0 (*C*−OH), 54.4 (*C*HNH$_2$), 39.4 (*C*H$_2$), 25.3 [*C*H(*C*H$_3$)$_2$], 24.1 (*C*H$_3$), 21.3 (*C*H$_3$); IR (ATR): ν 3339, 3265, 2955, 2866, 1637, 1599, 1586, 1508, 1491, 1468, 1449, 1385, 1182, 1057, 1005, 901, 743 (s), 694 (s), 638 cm^{-1}; Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.28; H, 8.50; N, 5.06.

(*R*)-2-Amino-4-methyl-1,1-diphenylpentan-1-ol, (*R*)-3. Prepared from (*R*)-**6** according to procedure B, and purified by recrystallization from EtOAc to give (*R*)-**3** as white crystals; mp 127−129 °C; $[\alpha]^{20}_D$ +100.0 (*c* 1.0, $CHCl_3$); Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.29; H, 8.51; N, 5.11.

(*S*)-*N*-((*S*)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl)pyrrolidine-2-carboxamide, (*S*,*S*)-1. White crystals (recrystallization from EtOAc); mp 184−186 °C; $[\alpha]^{20}_D$ −49.7 (*c* 1.0, $CHCl_3$) [lit.:[2] mp 184−187 °C; $[\alpha]^{25}_D$ −45.9 (*c* 1.2, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.94 [d, *J* = 8.2 Hz, 1H, C(O)N*H*CH], 7.53 (t, *J* = 6.8 Hz, 4H, Ar*H*), 7.28 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.22 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.16 (t, *J* = 7.3 Hz, 1H, Ar*H*), 7.10 (t, *J* = 7.3 Hz, 1H, Ar*H*), 5.41 (bs, 1H, O*H*), 4.59 [t, *J* = 9.3 Hz, 1H, C(O)NHC*H*CH], 3.49 [dd, *J* = 9.2, 4.8 Hz, 1H, C(O)C*H*NH], 2.81 (dt, *J* = 10.1, 6.8 Hz, 1H, NHC*H*H′CH$_2$), 2.56 (dt, *J* = 10.3, 6.2 Hz, 1H, NHCH*H*′CH$_2$), 2.03 (bs, 1H, N*H*), 1.91−1.80 (m, 2H, CHCH_2CH), 1.59−1.50 [m, 1H, C*H*(CH_3)$_2$], 1.49−1.36 (m, 2H, CH$_2$CH_2CH), 1.27−1.15 (m, 2H, CH$_2$CH_2CH$_2$), 0.90 (d, *J* = 6.5 Hz, 3H, CH_3), 0.84 (d, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): 175.9 [*C*(O)NH], 146.6 (Ar*C*), 145.1 (Ar*C*), 128.2 (Ar*C*H), 127.9 (Ar*C*H), 126.6 (Ar*C*H), 126.4 (Ar*C*H), 125.7 (Ar*C*H), 125.6 (Ar*C*H), 80.9 (*C*-OH), 60.3 [C(O)NHC*H*], 56.9 [*C*HC(O)], 47.0 (NHCH_2), 37.3 [*C*H$_2$CHC(O)], 30.5 (CH$_2$CH$_2$CH), 25.7 (CH$_2$CH$_2$CH$_2$), 25.4 [*C*H(CH$_3$)], 23.8 (*C*H$_3$), 21.5 (*C*H$_3$); IR (ATR): ν 3464, 3343, 3275, 2967, 2870, 1636, 1512, 1493, 1447, 1144, 1101, 1059, 885, 745 (s), 700 (s), 640 cm^{-1}; Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.35; H, 8.27; N, 7.60.

(*R*)-*N*-((*R*)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl)pyrrolidine-2-carboxamide, (*R*,*R*)-1. White crystals (recrystallization from EtOAc); mp 185−187 °C; $[\alpha]^{20}_D$ +50.9 (*c* 1.0, $CHCl_3$); Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.37; H, 8.25; N, 7.62.

CCDC 842976 and CCDC 842977 contain the supplementary crystallographic data for this paper [compounds (*S*,*S*)-**1**·HCl and (*R*,*R*)-**1**]. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Supporting Information

IR and NMR spectra of (*S*)-**4**, (*S*,*S*)-**1**, the intermediate (*S*)-**9a**, and the crude products obtained in the course of the synthesis according to procedures A and B. This material is available free of charge via the Internet at http://pubs.acs.org.

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