Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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*September 2014: The paragraphs above replace the section “Handling and Disposal of Hazardous Chemicals” in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*
One-pot Preparation of (S)-N-[(S)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl]pyrrolidine-2-carboxamide from L-Proline

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Checked by Takahiro Sakai and Keisuke Suzuki

Procedure

A. (S)-2-Amino-4-methyl-1,1-diphenylpentan-1-ol (2). (Note 1) A 1-L three-necked round-bottomed flask (Note 2), equipped with a 4.5-cm oval Teflon-coated magnetic stirring bar, is charged with L-leucine methyl ester hydrochloride (1, 9.10 g, 50 mmol, 1.0 equiv) (Notes 3 and 4). The flask is
equipped with a reflux condenser, fitted at the top with an argon balloon. Another neck is capped with a rubber septum and Et₂O (50 mL) (Note 5) is added to the flask via syringe. The remaining neck is equipped with a 100 mL dropping funnel. The reaction flask is cooled to 0–5 °C in an ice-water bath. By means of nitrogen pressure, the 3.0 M solution of phenylmagnesium bromide in Et₂O (83 mL, 250 mmol, 5.0 equiv) is transferred via an 18 gauge stainless cannula into the dropping funnel; this solution is added to the cold suspension of 1 over 10 min (Note 6). Upon completion of the addition, the reaction mixture is stirred for an additional 0.5 h in an ice-water bath and then overnight at room temperature (Note 7). The reaction mixture becomes a light yellow liquid mixed with white–brown precipitates. This heterogeneous mixture is cooled to 0–5 °C in an ice-water bath and cautiously quenched, with vigorous stirring, by slow addition of 10 wt% aqueous NH₄Cl (150 mL) (Note 8). Ethyl acetate (100 mL) (Note 9) is added and the ice-water bath is removed. The pH of the aqueous (lower) phase is adjusted to 7–8, as determined by pH paper, through addition of 4 M HCl (45–50 mL) in one portion. The resulting slurry is vigorously stirred until all solid dissolves (approximately 0.5 h) to give a clear two-phase mixture (Note 10). The mixture is then transferred to a 1-L separatory funnel using EtOAc (50 mL). The aqueous phase is separated and extracted with EtOAc (2 x 100 mL). The combined organic layers are washed with saturated NaHCO₃ solution (50 mL), water (50 mL) and brine (50 mL). The organic layer is dried over anhydrous MgSO₄ and filtered. The filtrate is concentrated by rotary evaporation (40 °C, 170 mmHg to 35 mmHg) (Note 11) and then further dried under vacuum (ca. 0.3 mmHg) at room temperature for 2–3 h. The title compound 2 is obtained as a pale yellow solid (12.2–12.9 g, 91–96%) (Notes 12 and 13) and used for the next step without further purification.

B. (S)-N-[(S)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl]pyrrolidine-2-carboxamide (5). A 500-mL, oven-dried three-necked round-bottomed flask, equipped with a 4.5-cm oval Teflon-coated magnetic stir bar, is charged with L-proline (6.34 g, 55 mmol, 1.1 equiv) (Note 14). One neck of the flask is fitted with an argon balloon, and a second neck is equipped with a thermometer for measuring the internal temperature. The flask is charged with dichloromethane (120 mL) and the third neck capped with a rubber septum (Note 14). Di-tert-butyl dicarbonate (12.5 mL, 54.4 mmol, 1.1 equiv) is added by means of a syringe in one portion (Note 15). The resulting suspension is cooled to 0–5 °C using an ice-water bath. Triethylamine (27.0 mL, 194 mmol, 3.9 equiv) (Note 16) is added via a
syringe over approximately 5 min. After completion of the addition, the ice-water bath is removed and the suspension is stirred at room temperature for 1 h. The reaction mixture becomes homogeneous as the proline reacts with Boc₂O to afford the intermediate N-Boc protected proline. The reaction mixture is then cooled to 0 °C in an ice-water bath. Ethyl chloroformate (5.0 mL, 53 mmol, 1.1 equiv) is added dropwise over 5 min by means of a syringe. During the addition, a white precipitate of triethylammonium hydrochloride is formed. Upon completion of the addition, the resulting slurry is stirred at 0 °C for an additional 0.5 h. The crude solid 2 is then added in one portion via a solid addition funnel. Dichloromethane (20 mL) (Note 14) is used to rinse the residue on the addition funnel into the reaction flask. After the addition is complete, the resulting milky suspension is stirred vigorously at 0 °C for 1 h and then allowed to warm to room temperature overnight (Note 17). The reaction mixture is then concentrated by rotary evaporation (40 °C, 100 mmHg) to dryness, providing the crude N-Boc proline amide 4 as a pale yellow solid. Dichloromethane (40 mL) and methanol (80 mL) are then added to the crude 4, followed by dropwise addition of 12 N HCl (20 mL, ca. 240 mmol) (Note 18). After the addition, the flask is placed in an oil bath (50–55 °C) and the resulting slurry is vigorously stirred for 5 h. During this time, the slurry becomes homogeneous after 1.5 h as 4 is converted to the 5•HCl salt. After the reaction is complete (Note 19), the resulting solution is concentrated by rotary evaporation (45 °C, 70 mmHg) until most of MeOH is removed, and the residue solidifies. The resulting solid is suspended in H₂O (100 mL) and EtOAc (200 mL) at 0–5 °C in an ice-water bath. The aqueous (lower) phase is adjusted to pH 8–9 with 6 M NaOH (35 mL). The ice-water bath is removed and the slurry is vigorously stirred at room temperature for 0.5 h. The resulting slurry of 5 (Note 20) is transferred to a 1-L separatory funnel using EtOAc (150 mL) to aid the transfer. After separation of the organic layer, the aqueous phase is extracted with EtOAc (2 x 100 mL). The combined organic layers are washed with 1 M NaOH (50 mL), H₂O (2 x 50 mL) and brine (50 mL), dried over MgSO₄, and filtered to give a pale-yellow solution (Note 21). The filtrate is concentrated by rotary evaporation (40 °C, 150 mmHg to 40 mmHg) (Note 22) and then further dried under vacuum (0.3 mmHg) at room temperature for 1–2 h, to give the crude product 5 as a white–pale yellow solid (14.9–18.0 g) (Note 23). The crude product is dissolved in EtOAc (11 mL per gram of crude 5) at reflux (Note 24), and the product is allowed to crystallize at room temperature overnight. The resulting crystals are collected by suction filtration on a Büchner funnel, washed with 50 mL
of ice-cold 5% EtOAc in hexane, and then air-dried to constant weight to provide the title compound 5 as a white crystalline solid (7.6–8.4 g, 42–46% based on 1) (Notes 25 and 26).

Notes

1. The submitters recorded the following: To insure complete The checkers used phenylmagnesium bromide purchased from Sigma-Aldrich, 3.0 M in Et₂O solution. The submitters reported that the Grignard reagent was prepared using the following procedure, which was not checked: A 500-mL, oven-dried three-necked round-bottomed flask (Note 2), is equipped with a 4-cm oval Teflon-coated magnetic stir bar, a 125 mL pressure-equalizing addition funnel placed on the middle neck of the reaction flask, and a reflux condenser fitted at the top with an in-line oil bubbler connected to an argon line. The third neck is fitted with a glass stopper. The flask is purged with argon and an atmosphere of argon is maintained during the reaction. The flask is charged with dry magnesium turnings (6.1 g, 250 mmol, 5.0 equiv), and stirring is initiated to activate the magnesium surface. After stirring for 15 min, anhydrous Et₂O (50 mL) (Note 5) is added via the addition funnel. A solution of bromobenzene (39.3 g, 250 mmol, 5.0 equiv) (Note 3) in anhydrous Et₂O (100 mL) was transferred into the addition funnel and added dropwise. The clear reaction mixture becomes cloudy within 5 min, and soon thereafter begins to reflux and turns brown. The dropwise addition is continued for 45 min, at a rate to sustain a gentle reflux. After completion of the addition, the residue is rinsed from the addition funnel into the reaction flask with dry Et₂O (10 mL). The reaction mixture is then heated for 0.5 h using a warm-water bath of 45–50 °C. At this time, only a trace of magnesium metal is visible, and the solution has a dark brown, cloudy appearance. The flask is then removed from the warm-water bath, and the reaction mixture is stirred at room temperature for an additional 0.5–1 h.

2. Glassware was oven-dried (110 °C) before use.

3. The checkers used the following reagents in step A as received: L-leucine methyl ester hydrochloride (Tokyo Chemical Industry Co., Ltd., >98.0%). The submitters used the following reagents in step A: L leucine methyl ester hydrochloride (Alfa Aesar-Johnson Matthey Co., 99%).
4. The submitters recorded the following: To insure complete and clean conversion, L-leucine methyl ester hydrochloride (1) must be milled and/or delumped to a fine powder using a pestle and mortar and dried under vacuum (<0.1 mmHg, 2 h, 50 °C) prior to use. The checkers used commercial L-leucine methyl ester hydrochloride without pretreatment.

5. The checkers used anhydrous diethyl ether (Kanto Chemical Co., Inc., dehydrated, >99.5%), which was purified under argon by a solvent purifying unit (Wako Pure Chemical Industries, Ltd.). The submitters used anhydrous diethyl ether (Acros, 99%) that was freshly distilled under argon from Na/benzophenone.

6. Initially, the reaction is highly exothermic due to the Grignard reagent reacting with HCl resulting in the ether boiling. However, by slowly adding the Grignard reagent to the cooled suspension of 1, this exotherm is easily controlled. The checkers added the Grignard reagent dropwise during 10 min. When half amount of Grignard reagent was added, the temperature had increased to 25 °C from 5 °C. Subsequently, the temperature gradually decreased to 17 °C.

7. The reaction is monitored by TLC; the checkers used the following analytical conditions. An aliquot (ca. 0.02 mL) is quenched by addition to saturated NH₄Cl (0.5 mL) and EtOAc (0.5 mL). The EtOAc layer was analyzed by TLC on silica gel with 1:9 MeOH/CH₂Cl₂ as eluent and visualization with phosphomolybdic acid. The starting material and product have the following Rₚ values: 1 as a free amine (0.62); 2 (0.55) on Merck TLC Plate 60 F₂⁵₄.

8. The checkers noted that the addition of NH₄Cl solution is initially violent. When the first 50 mL of NH₄Cl solution was added carefully, the mixture solidified and the internal temperature rose to 35 °C from 6 °C. After the mixture was cooled in an ice bath to stop the boiling of diethyl ether, 100 mL of NH₄Cl was added dropwise over 5 min and the mixture became a yellow slurry.

9. For workup in steps A and B and for recrystallization, the checkers used ethyl acetate (Kanto Chemical Co., Inc., >99.5%). The submitters used ethyl acetate (tech. grade, BCD), which was distilled prior to use.

10. The submitters recorded the following: the addition of aqueous HCl can result in the formation of the 2•HCl salt, which is not soluble in the two-phase mixture. After vigorous stirring at ca. pH 8, 2•HCl is converted to 2, resulting in dissolution of the solid, and giving a clear two-phase mixture. If the aqueous phase is not sufficiently basic, 4 M NaOH was added to adjust the pH.
11. The pressure should be lowered gradually in order to prevent bumping, since a precipitate of 2 is formed during the concentration. **CAUTION:** Benzene, formed during the quench of the excess phenylmagnesium bromide, is evaporated during the concentration.

12. Pure (S)-2-amino-4-methyl-1,1-diphenylpentan-1-ol (2) can be obtained by recrystallization from EtOAc and has the following physical and spectroscopic properties: colorless crystals; mp 134–137 °C; [α]D20 = 91.6 (c 1.00, CHCl3); 1H NMR (CDCl3, 600 MHz) δ: 0.87 (d, J = 6.4 Hz, 3 H), 0.89 (d, J = 6.4 Hz, 3 H), 1.06–1.11 (m, 1 H), 1.27 (ddd, J = 14.3, 10.4, 3.8 Hz, 1 H), 1.54–1.59 (m, 1 H), 2.31 (brs, 3 H), 3.98 (d, J = 10.4 Hz, 1 H), 7.14–7.19 (m, 2 H), 7.27 (t, J = 7.4 Hz, 2 H), 7.31 (t, J = 7.7 Hz, 2 H), 7.48 (d, J = 6.8 Hz, 2 H), 7.61 (d, J = 7.6 Hz, 2 H); 13C NMR (CDCl3, 150 MHz) δ: 21.3, 24.0, 25.3, 39.4, 54.5, 79.1, 125.5, 125.8, 126.3, 126.6, 128.0, 128.4, 144.5, 147.1; IR (ATR): 3337, 3264, 2953, 2866, 1586, 1490, 1469, 1448, 1384, 1181, 1057, 1005, 903, 743 (s), 695 (s), 639 cm–1; Anal. Calcd. for C18H23NO: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.36; H, 8.82; N, 5.15.

13. The submitters report that the amount of 2 present in the crude product can be determined by 1H NMR (400 MHz) analysis using methyl cinnamate as an external standard and using the CH resonances of methyl cinnamate (6.44 ppm) and 2 (3.98 ppm). Sample preparation: a mixture of the crude 2 (15 mg) and methyl cinnamate (8 mg) is dissolved in CDCl3 (0.6 mL). Biphenyl (3-6%) is typically observed as the by-product (GC-MS). This does not affect the reaction in the next step.

14. The checkers used the following reagents and solvents in step B: L-proline (Tokyo Chemical Industry Co., Ltd., >99.0%), di-tert-butyl dicarbonate (Boc₂O, Wako Pure Chemical Industries, Ltd., >97%), ethyl chloroformate (Wako Pure Chemical Industries, Ltd., >95%), anhydrous CH₂Cl₂ (Kanto Chemical Co., Inc., dehydrated, >99.5%), which was purified under argon by solvent purifying unit (Wako Pure Chemical Industries, Ltd.), CH₂Cl₂ (Nacalai Tesque, Inc., 99.5%), MeOH (Nacalai Tesque, Inc., 99.8%), 35% HCl (Koso Chem.). The submitters used the following reagents and solvents in step B: L-proline (BioChemica AppliChem, 99%), di-tert-butyl dicarbonate (Boc₂O, Acros, 97%), ethyl chloroformate (Acros, 99%, AcroSeal®), anhydrous CH₂Cl₂ (Acros, 99.8%, extra dry over molecular sieves, stabilized, AcroSeal®), CH₂Cl₂ (Acros, 99.8%), MeOH (VWR BDH Prolabo, 99.9%), 37% HCl (BASF).
15. Prior to the transfer by syringe, Boc$_2$O is melted by warming the container in a warm-water bath (35-40 °C).
16. Triethylamine (Sigma-Aldrich, 99.5%) was freshly distilled under an argon atmosphere from CaH$_2$ prior to use.
17. The checkers monitored the progress of the reaction with the following analytical conditions: TLC on silica gel with 1:9 MeOH/CH$_2$Cl$_2$ as eluent and visualization with phosphomolybdic acid. The starting material and product have the following $R_f$ values: 2 (0.60); 4 (0.70) on Merck TLC Plate 60 F$_{254}$.
18. The addition of 12 M HCl by pipette is slightly exothermic. The flask turns warm and fumes are evolved.
19. The reaction progress can be monitored by TLC; the checkers used the following analytical conditions: An aliquot (ca. 0.02 mL) was quenched by addition to 1 M NaOH (0.5 mL) and EtOAc (0.5 mL). The EtOAc layer was analyzed by TLC on silica gel with 1:9 MeOH/CH$_2$Cl$_2$ as eluent and visualization with phosphomolybdic acid. The starting material and product have the following $R_f$ values: 4 (0.63); 5 (0.19) on Merck TLC Plate 60 F$_{254}$.
20. Since 5 is sparingly soluble in EtOAc, the conversion of 5•HCl to 5 proceeded via a slurry-to-slurry transformation. After the extraction process, 5 has a solubility in EtOAc of ca. 1 g/40 mL.
21. The submitters noted a yellow to yellow-brown solution might be obtained if a lower grade of MeOH and CH$_2$Cl$_2$ were used for the deprotection step. In that case, it is advisable to filter the solution through a pad of silica (5 g) in a sintered glass funnel using EtOAc (200 mL) to rinse the filter cake. This serves to remove the base-line impurities prior to recrystallization in order to obtain an optimal yield of the pure product.
22. The pressure should be lowered gradually in order to prevent bumping as a precipitate of 5 is formed during the concentration.
23. The submitters recorded an alternative procedure: The filtered EtOAc solution is concentrated by rotary evaporation (40 °C, 150 mmHg) to a volume of ca. 250 mL, to give an off-white slurry of the crude product. The slurry is then heated at reflux for dissolution of the solid and left at room temperature for crystallization.
24. The submitters observed the formation of side products upon long reflux of 5 in EtOAc. However, the recrystallization of 5 from EtOAc provided the best crystalline 5 compared to recrystallization from other solvents (e.g. MeOH, EtOH, CH$_2$Cl$_2$, MTBE).
25. (S)-N-[(S)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl]pyrrolidine-2-carboxamide (5) is obtained as a single isomer (by $^1$H and $^{13}$C NMR) and has the following physical and spectroscopic properties: mp 197–199 °C; $[\alpha]_D^{20}$ $-51.6$ (c 1.00, CHCl$_3$) lit.$^{2a}$; $[\alpha]_D^{25}$ $-46$ (c 1.2, CHCl$_3$); $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$: 0.86 (d, $J$ = 6.7 Hz, 3 H), 0.91 (d, $J$ = 6.5 Hz, 3 H), 1.19–1.25 (m, 2 H), 1.42–1.49 (m, 2 H), 1.54–1.59 (m, 3 H), 1.86–1.92 (m, 2 H), 2.56 (dt, $J$ = 10.0, 6.1 Hz, 1 H), 2.82 (dt, $J$ = 9.9, 6.4 Hz, 1 H), 3.48 (dd, $J$ = 9.3, 4.2 Hz, 1 H), 4.58 (t, $J$ = 9.8 Hz, 1 H), 5.45 (br. s, 1 H), 7.12 (t, $J$ = 7.3 Hz, 1 H), 7.18 (t, $J$ = 7.4 Hz, 1 H), 7.24 (t, $J$ = 7.5 Hz, 2 H), 7.30 (t, $J$ = 7.6 Hz, 2 H), 7.55 (t, $J$ = 7.6 Hz, 4 H), 7.94 (d, $J$ = 8.0 Hz, 1 H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$: 21.5, 23.8, 25.3, 25.7, 30.4, 37.5, 46.9, 56.5, 60.2, 80.8, 125.6, 125.7, 126.3, 126.5, 127.8, 128.1, 145.1, 146.5, 175.9; IR (ATR): 3466, 3275, 3069, 2955, 2868, 1634, 1513, 1494, 1100, 1060, 885, 744 (s), 700 (s); Anal. Calcd for C$_{23}$H$_{30}$N$_2$O$_2$: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.55; H, 7.98; N, 7.74. The checkers established the enantiomeric purity of 5 thus obtained by conversion into (+) and (−)-MTPA amides.$^{10}$ Several sets of diagnostic peaks are observed without cross-over, proving the enantiomeric purity of the final product 5. MTPA amide derived from (+)-MTPACl: $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$: 0.90 (d, $J$ = 6.9 Hz, 3 H, (C$_3$H$_7$)$_2$CH-), 1.07 (d, $J$ = 6.4 Hz, 3 H, (CH$_3$)$_2$CH-)), 3.60 (s, 3 H, CH$_3$O-); MTPA amide derived from (−)-MTPACl: $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$: 0.89 (d, $J$ = 6.6 Hz, 3 H, (CH$_3$)$_2$CH-)), 0.98 (d, $J$ = 6.4 Hz, 3 H, (CH$_3$)$_2$CH-)), 3.70 (s, 3H, CH$_3$O-).

26. The submitters reported that concentration of the mother liquors and recrystallization from EtOAc (100 mL) afforded an additional 2 g (11%) of 5 of slightly lower purity ($^1$H NMR).

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should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011 www.nap.edu). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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Discussion

Proline-based chiral organocatalysts have been developed extensively and applied successfully in several reactions.\(^2\) Singh and co-workers have designed proline amide catalysts of type 5, bearing \(\text{gem-diaryl}\) substituents at the \(\beta\)-carbon, which play a key role in providing high enantioselectivity in the direct aldol reaction of ketones with aldehydes.\(^3\) Catalyst 5 has proven to be one of the most effective organocatalysts for asymmetric direct aldol reactions of water-miscible ketones such as acetone with various aldehydes and reactive ketones, especially in aqueous reaction media or under solvent-free conditions.\(^3,4,5\)

In the original method reported by Singh \textit{et al.},\(^3\) a series of catalysts of type 5 were prepared from Boc-proline and the corresponding diphenylamino alcohols 2 in a sequential two-step method, i.e. condensation and Boc-deprotection, with isolation of the intermediate from the condensation reaction, i.e. 4. As the first step, Boc-L-proline was condensed with the L-diphenylamino alcohol 2 via a mixed anhydride method using ethyl chloroformate\(^3\) or \(\text{iso-butyl\ chloroformate,}^6\) affording 4. The final Boc-deprotection step was conducted by treatment of 4 with formic acid\(^3\) or TFA,\(^6\) furnishing 5 in 82–83% yield after recrystallization. In our hands, the removal of the Boc group using formic acid or TFA resulted in the formation of significant amounts of side products (e.g. the \(\text{N-formyl pyrrolidinyl\ derivative)\). As a consequence, the purification of the resulting crude product by recrystallization led to a significantly lower yield of the desired 5. Furthermore, this method starts from Boc-proline and pure
diphenylamino alcohol 2 which are commercially available but rather expensive compared to their precursors proline and leucine methyl ester hydrochloride (1), respectively.

In summary, we have developed an economical and practical one-pot multistep synthesis in which the reaction product from the initial step is used directly without purification for the next step, thus affording 5 directly from proline. Moreover, the chiral amino alcohol 2, as the coupling partner, can be prepared and used directly without purification from the corresponding amino acid ester 1. For the direct coupling process of proline with 2, the Boc-protected proline is first generated in situ from proline and Boc₂O (1 equiv). Successive treatment with ethyl chloroformate and the amino alcohol 2 yields the N-Boc proline amide 4. Subsequent removal of the Boc-group using concentrated HCl in MeOH-CH₂Cl₂ as a clean, reliable and convenient deprotection method is another key feature of the procedure presented herein.

References

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Appendix

Chemical Abstracts Nomenclature (Registry Number)

Magnesium turning; (7439-95-4)
Bromobenzene; (108-86-1)
L-Leucine methyl ester hydrochloride; (7517-19-3)
L-Proline; (147-85-3)
Di-tert-butyl dicarbonate; (24424-99-5)
Triethylamine; (121-44-8)
Ethyl chloroformate; (541-41-3)
Albrecht Berkessel obtained his Ph.D. with Professor Waldemar Adam at the University of Würzburg in 1985. Later on, he joined the research group of Professor Ronald Breslow at Columbia University, New York. His habilitation at the University of Frankfurt/Main (associated to Professor Gerhard Quinkert) was completed in 1990. In 1992, he became Associate Professor at the University of Heidelberg. Since 1997, he is a Full Professor of Organic Chemistry at the University of Cologne. His research interests center around various aspects of catalysis, such as mechanism and method development, both in metal-based catalysis and organocatalysis, biomimetic and medicinal chemistry.

Wacharee Harnying (born 1975 in Thailand) completed her undergraduate education in Chemistry in 1996 at Khon Kaen University. She then moved to Mahidol University and completed her M.Sc. (Organic Chemistry) in 2000 under supervision of Professor Manat Pohmakotr. From 2000 to 2007, she served as a lecturer at Khon Kaen University. In parallel, she pursued a PhD (2001-2004) at RWTH-Aachen, Germany, under guidance of Professor Dieter Enders. In 2008-2009, she was a postdoctoral fellow of the Alexander von Humboldt-Foundation at the University of Cologne (Germany) with Professor Albrecht Berkessel, where she is now holding the position of a senior researcher.

Nongnaphat Duangdee was born in 1974 in Thailand. She received her Bachelor’s Degree in Chemistry from Khon Kaen University in 1996. Since 1997, she joined the Department of Science Service (DSS, Thailand) where she worked as analytical chemist until 2009. In the meantime, she obtained her M.Sc. (Organic Chemistry) under the supervision of Professor Manat Pohmakotr at Mahidol University in 2002. In 2009, she began her doctoral studies in the group of Professor Albrecht Berkessel at Cologne University (Germany), investigating organocatalytic asymmetric aldol reactions with ketone acceptors, and she obtained her Ph.D. in 2013.
Takahiro Sakai was born in Niigata, Japan. He received his B. Sc. degree in 2010, and M. Sc. in 2013 at Kanazawa University under the supervision of Prof. Yutaka Ukaji. In the same year, he joined the research group of Prof. Keisuke Suzuki at the Tokyo Institute of Technology to pursue his Ph. D.
(S)-2-Amino-4-methyl-1,1-diphenylpentan-1-ol 2
(S)-2-Amino-4-methyl-1,1-diphenyloctan-1-ol 2
(S)-N-[(S)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl]pyrrolidine-2-carboxamide 5
(S)-N-[(S)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl]pyrrolidine-2-carboxamide 5