Synthesis A. F. Kotthaus et al. PSP

Synthesis and Resolution of a Chiral Diamine: 2,2′-(Propane-2,2-diyl)dipyrrolidine

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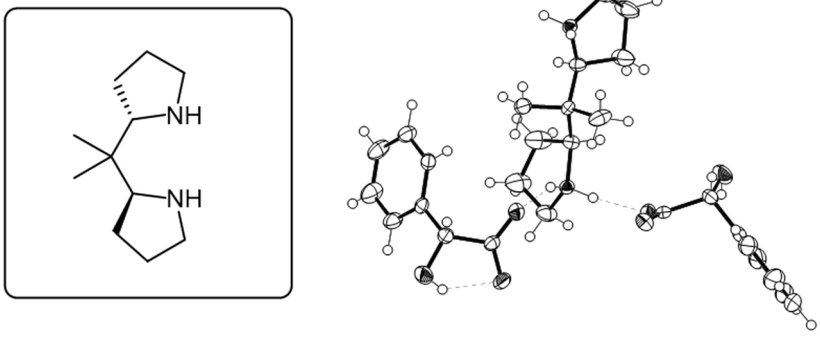

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Abstract A short and practical synthesis of a new chiral dipyrrolidine is presented. The three-step route includes a hydrogenation and a resolution with mandelic acid, which easily affords large quantities of the title compound.

Key words diamine, chiral, pyrrolidine, hydrogenation, resolution

Chiral diamines are present in a large number of naturally occurring molecules.[1] Recently, chiral diamines became also a leading motif in ligand design for asymmetric synthesis.[2] As summarized in Figure 1, the diamine structures most widely used as ligands in metal-catalyzed reactions are based on ethylenediamine (**1**), cyclohexanediamine (**2**), BINAM (**3**), sparteine (**4**), and 2,2′-bipyrrolidine (**5**).[3] In particular, fields like copper-catalyzed arylations,[4] oxidations,[5] and asymmetric deprotonations[6] have profited from readily available diamine compounds.

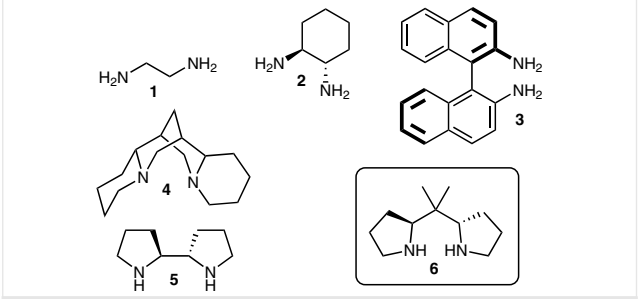
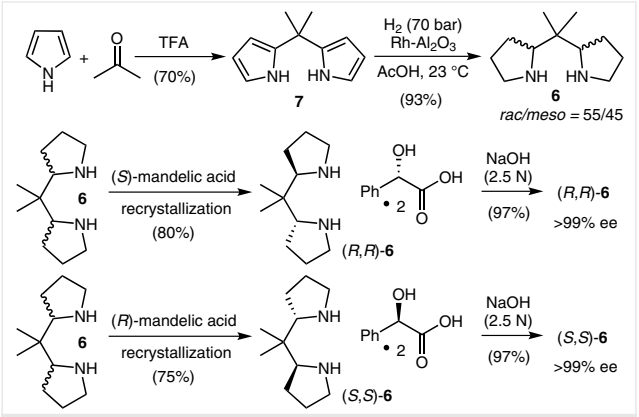


Figure 1 Diamine motifs

During our research aiming at Lewis base catalyzed hydrosilylations,[7] we became interested in chiral diamines with C_2-symmetry. While derivatives of the standard 2,2′-bipyrrolidine (**5**) were found to be excellent for our purposes, the related methylene-bridged 2,2′-dipyrrolidine core **6** was, to our surprise, unknown. We now describe a short and practical synthesis of this C_2-symmetrical dipyrrolidine unit, as shown in Scheme 1.



Scheme 1 Synthesis of the chiral dipyrrolidine **6**

We started the synthesis of dipyrrolidine **6** using a modified protocol by Neier and co-workers: Pyrrole and acetone were condensed in the presence of trifluoroacetic acid, yielding the dipyrrole **7** in 70% yield.[8] As the next step, the dipyrrole was converted to a mixture of *rac*- and *meso*-dipyrrolidine **6** in a ratio of 55:45 (by ^{1}H NMR). This hydrogenation was improved greatly over the partial one previously reported[9] by employing rhodium on activated alumina as the hydrogenation catalyst in acetic acid. The crude mixture of dipyrrolidines was obtained in almost quantitative yield, and the purity was sufficient for the subsequent resolution step. At this point, precipitation of the diamine mixture with (*S*)-mandelic acid and recrystallization from acetone–ethanol gave an 80% yield of the (*R*,*R*)-**6** (*S*)-man-

delic acid salt. Accordingly, the mother liquor from the resolution of the one enantiomer could be treated with (*R*)-mandelic acid to obtain the (*S*,*S*)-**6** salt.

The mandelic acid salts were simply treated with aqueous NaOH (2.5 N) to obtain the diamines **6** in pure form (Scheme 1). To determine the enantiomeric access of the diamine compounds, derivatization with benzoyl chloride was required. The corresponding diamides were then easily analyzed with chiral HPLC: Both diamine enantiomers were formed with an enantiopurity of >99% ee, and almost free of any residual *meso*-diastereomer.

As shown in Figure 2, the absolute configuration of the dipyrrolidine (*S*,*S*)-**6** was determined by an X-ray crystallographic analysis of the (*R*)-mandelic acid salt. The structure unequivocally proves that the (*R*)-mandelic acid crystallized with the (*S*,*S*)-**6** (see the Supporting Information for detailed X-ray crystal data).

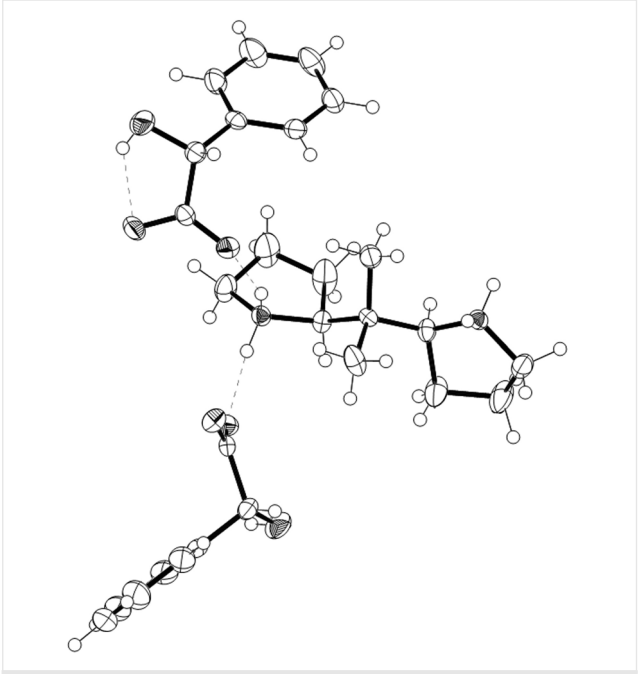
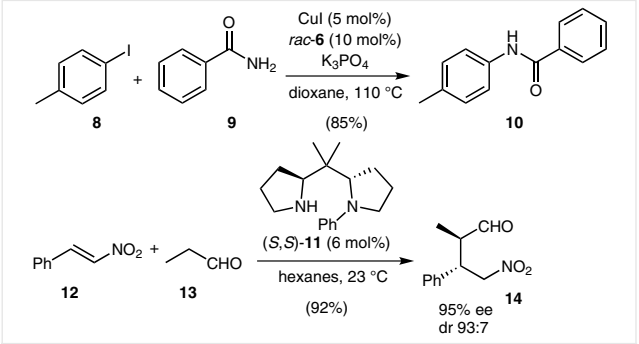


Figure 2 Crystal structure of the (*S*,*S*)-**6** salt; ellipsoids are drawn at 30% probability

We then briefly tested the chiral diamine in arbitrarily selected reactions: The copper-catalyzed formation of amide **10** through arylation was, for example, possible in the presence of racemic diamine **6** in 85% yield (Scheme 2).[10] The reaction of *trans*-β-nitrostyrene (**12**) with propanal (**13**) was efficiently catalyzed by amino catalyst **11**, derived from diamine (*S*,*S*)-**6** through arylation.[11,12] The nitro-containing product **14** was formed in 92% yield with a dr of 93:7 (*syn*/*anti*) and 95% ee.



Scheme 2 Selected reactions with diamine **6**

In summary, a new chiral diamine with C_2-symmetry was introduced. The short multigram synthesis provides the methylene-bridged dipyrrolidine in excellent enatiopurity through resolution. We encourage researchers to use this diamine core for all types of future efforts.

All reagents and solvents were purchased from commercial sources and were used as received. NMR spectra were recorded using a Bruker Avance 400 or a Bruker Avance III 600 spectrometer. All ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) using the solvent signal ($CDCl_3$: ^{1}H 7.26 ppm, ^{13}C 77.16 ppm; DMSO-d_6: ^{1}H 2.50 ppm, ^{13}C 39.52 ppm) as reference. Multiplicities are indicated with standard abbreviations. All coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded using ATR technique on a Bruker ALPHA FT-IR spectrometer. High-resolution mass spectra were obtained on a Bruker MicroTOF using ESI or APCI ionization methods. Low-resolution mass spectra were taken on an Agilent MSD-5975C using EI ionization. Single crystal X-ray diffraction studies were performed on an Oxford Diffraction Gemini Ultra diffractometer. Flash chromatography was performed with silica gel 43–60 µm (VWR Chemicals). TLC was performed on aluminum plates precoated with silica gel 60 F_{254} (Merck), and components were visualized by observation under UV light or by treating the plates with $KMnO_4$ or CAM (cerium ammonium molybdate in dil H_2SO_4) or ninhydrin (in EtOH). Enantiomeric purities were determined using chiral HPLC (Agilent 1200 series, Chiralpak IA or Chiralcel OD-H column with solvent mixtures consisting of heptane and *i*-PrOH).

2,2′-(Propane-2,2-diyl)di(1*H*-pyrrole) (7)

Trifluoroacetic acid (1.3 mL, 17 mmol) was slowly added to a vigorously stirred solution of pyrrole (95 mL, 1.37 mol) and acetone (12 mL, 0.163 mol) under an argon atmosphere. The temperature of the reaction mixture was maintained below 80 °C in a water bath. After 5 min, the reaction was quenched with aq NaOH (1.1 g in 1 mL H_2O, 28 mmol). Unreacted pyrrole and H_2O were removed by distillation at 40 mbar. The residue was then distilled to provide 19.8 g (70%) of the title compound as a colorless solid (bp 110–120 °C/~1 × 10^{-3} mbar); mp 56–59 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (s, 2 H), 6.58 (td, *J* = 2.7, 1.6 Hz, 2 H), 6.16 (dt, *J* = 3.4, 2.6 Hz, 2 H), 6.12 (ddd, *J* = 3.4, 2.7, 1.6 Hz, 2 H), 1.64 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.2, 117.2, 107.8, 103.9, 35.4, 29.4.

MS (EI, 70 eV): *m*/*z* (%) = 174 (18, M^+), 159 (64), 92 (100), 67 (22), 65 (30).

HRMS-APCI: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}N_2$: 175.1230; found: 175.1230.

The analytical and spectral data were in complete agreement with the previously published data.[8]

rac- and *meso*-2,2′-(Propane-2,2-diyl)dipyrrolidine (6)

2,2′-(Propane-2,2-diyl)di(1*H*-pyrrole) (**7**; 19.5 g, 112 mmol) was dissolved in AcOH (350 mL). Then, 5% Rh on activated alumina (1.95 g, 0.95 mmol Rh) was added, and the reaction mixture was placed in an autoclave. After flushing the apparatus with H_2 for 5 min, the mixture was stirred for 18 h under H_2 atmosphere (70 bar) at r.t. The catalyst was removed by filtration over Celite and the filtrate was concentrated in vacuo. The residue was dissolved in aq 2.5 N NaOH (pH >12), and the mixture was extracted with Et_2O (3 ×). The combined organic extracts were dried (K_2CO_3) and the solvent was removed under reduced pressure. The crude product (yellow oil) contained a mixture of *rac*- and *meso*-2,2′-(propane-2,2-diyl)dipyrrolidine (**6**; 19.0 g, max. 93%, ratio 55:45 by ^{1}H NMR) and was pure enough for the subsequent resolution step.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.98–2.87 (m), 2.83–2.72 (m), 1.81 (br s), 1.70–1.57 (m), 1.48–1.36 (m), 0.84 (s, CH_3 *meso*), 0.82 (s, CH_3 *rac*), 0.77 (s, CH_3 *meso*).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 67.3, 66.1, 47.2, 47.1, 38.5, 38.2, 26.7, 26.5, 25.9, 25.7, 21.0, 20.5, 17.5.

(*R*,*R*)-2,2′-(Propane-2,2-diyl)di(pyrrolidin-1-ium) Bis[(*S*)-hydroxy(phenyl)]acetate

To a hot (oil bath 90 °C) and vigorously stirred solution of crude *rac*- and *meso*-2,2′-(propane-2,2-diyl)dipyrrolidine (**6**; 19 g, max. 104 mmol) in acetone (50 mL), was added (*S*)-mandelic acid (31.7 g, 208 mmol) in one portion. After 1 min, the oil bath was removed, and the solution was cooled down to r.t. and then to 0 °C in an ice bath (1 h). The colorless precipitate was collected by suction and was washed with acetone (3 ×) [the mother liquor was saved for the recovery of the (*S*,*S*)-2,2′-(propane-2,2-diyl)dipyrrolidine, see below]. The filter residue was suspended in EtOH (60 mL) and refluxed for 2 h. Then, acetone (60 mL) was added slowly and the solution was cooled down to r.t. and then to 0 °C in an ice bath (1 h). After suction, the solid was washed with acetone (3 × 30 mL) and purified twice, as detailed above, to provide 11.22 g (80% based on the isomer content, >99% ee, >99:1 dr) of the title compound as colorless needles; mp 185–186 °C.

The enantiomeric excess was determined after derivatization with benzoyl chloride by chiral HPLC [Chiralpak IA, heptane–*i*-PrOH 7:3, 0.8 mL/min, t_R (*meso*) = 8.3 min, t_R (*S*,*S*) = 10.4 min, t_R (*R*,*R*) = 16.6 min].

IR (ATR): 3408, 3382, 2972, 2950, 2894, 2724 (br), 2407 (br), 1636, 1345, 1324, 1058, 739 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.41–7.34 (m, 4 H), 7.31–7.23 (m, 4 H), 7.24–7.16 (m, 2 H), 6.10 (br s, 6 H), 4.71 (s, 2 H), 3.34–3.26 (m, 2 H), 3.00–2.93 (m, 2 H), 2.91–2.82 (m, 2 H), 1.85–1.74 (m, 4 H), 1.68–1.56 (m, 4 H), 0.86 (s, 6 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 174.9, 142.6, 127.5, 126.5, 126.3, 73.2, 64.9, 45.1, 36.1, 25.4, 24.5, 20.6.

HRMS-ESI: *m*/*z* [M – 2 × mandelic acid + H]$^+$ calcd for $C_{11}H_{23}N_2$: 183.1856; found: 183.1856.

(*S*,*S*)-2,2′-(Propane-2,2-diyl)di(pyrrolidin-1-ium) Bis[(*R*)-hydroxy(phenyl)]acetate

The mother liquors (taken from the resolution of the other enantiomer) were concentrated in vacuo and then dissolved in aq 2.5 N NaOH (pH >12). This solution was extracted with Et_2O (3 × 100 mL), dried (K_2CO_3), and the solvent was removed under reduced pressure. The recovered material (14.0 g, max. 77 mmol) was dissolved in acetone (45 mL) and heated to reflux using an oil bath (90 °C). Then, (*R*)-mandelic acid (23.4 g, 154 mmol) was added in one portion and stirred vigorously for 1 min before the oil bath was removed. The solution was cooled down to r.t. and then to 0 °C in an ice bath (1 h). The colorless precipitate was collected by suction and washed with acetone (3 ×). The filter residue was suspended in EtOH (60 mL) and refluxed for 2 h. Then, acetone (60 mL) was added slowly and the solution was cooled down to r.t. and then to 0 °C in an ice bath (1 h). After suction, the solid was washed with acetone (3 × 30 mL) and purified again, as detailed above, to provide 10.5 g (75% based on the isomer content, >99% ee, >99:1 dr) of the title compound as colorless needles; mp 185–186 °C.

The enantiomeric excess was determined after derivatization with benzoyl chloride by chiral HPLC [Chiralpak IA, heptane–*i*-PrOH 7:3, 0.8 mL/min, t_R (*meso*) = 8.3 min, t_R (*S*,*S*) = 10.4 min, t_R (*R*,*R*) = 16.6 min].

IR (ATR): 3408, 3381, 2971, 2951, 2894, 2723 (br), 2410 (br), 1636, 1345, 1324, 1058, 739 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.41–7.36 (m, 4 H), 7.30–7.23 (m, 4 H), 7.22–7.16 (m, 2 H), 6.21 (br s, 6 H), 4.71 (s, 2 H), 3.34–3.26 (m, 2 H), 3.00–2.93 (m, 2 H), 2.90–2.82 (m, 2 H), 1.85–1.74 (m, 4 H), 1.68–1.56 (m, 4 H), 0.86 (s, 6 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 174.9, 142.6, 127.5, 126.5, 126.3, 73.2, 64.9, 45.1, 36.1, 25.4, 24.5, 20.6.

HRMS-ESI: *m*/*z* [M – 2 × mandelic acid + H]$^+$ calcd for $C_{11}H_{23}N_2$: 183.1856; found: 183.1855.

(*R*,*R*)-2,2′-(Propane-2,2-diyl)dipyrrolidine [(*R*,*R*)-6]

(*R*,*R*)-2,2′-(Propane-2,2-diyl)di(pyrrolidin-1-ium) bis[(*S*)-hydroxy(phenyl)]acetate (1.50 g, 3.08 mmol) was dissolved in aq 2.5 N NaOH (pH >12) and extracted with Et_2O (4 × 5 mL). The combined organic phases were dried (K_2CO_3) and then concentrated in vacuo to provide 550 mg (97%) of the title compound as a colorless liquid; $[\alpha]_D^{25}$ +17.6 (*c* 1.00, MeOH).

IR (ATR): 3289, 2959, 2869, 1466, 1385, 1080, 1052, 802, 557 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.01–2.88 (m, 4 H), 2.84–2.72 (m, 2 H), 1.86 (br s, 2 H), 1.71–1.59 (m, 6 H), 1.52–1.35 (m, 2 H), 0.83 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 66.1, 47.1, 38.2, 26.5, 25.9, 20.5.

MS (EI, 70 eV): *m*/*z* (%) = 182 (4, M^+), 113 (17), 96 (56), 81 (19), 70 (100), 56 (12).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{23}N_2$: 183.1856; found: 183.1853.

(*S*,*S*)-2,2′-(Propane-2,2-diyl)dipyrrolidine [(*S*,*S*)-6]

(*S*,*S*)-2,2′-(Propane-2,2-diyl)di(pyrrolidin-1-ium) bis[(*R*)-hydroxy(phenyl)]acetate (1.50 g, 3.08 mmol) was dissolved in aq 2.5 N NaOH (pH >12) and extracted with Et_2O (4 × 5 mL). The combined organic phases were dried (K_2CO_3) and then concentrated in vacuo to provide 550 mg (97%) of the title compound as a colorless liquid; $[\alpha]_D^{25}$ –17.8 (*c* 1.00, MeOH).

IR (ATR): 3287, 2959, 2869, 1466, 1385, 1080, 1052, 804, 557 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.00–2.89 (m, 4 H), 2.83–2.73 (m, 2 H), 1.81 (br s, 2 H), 1.72–1.58 (m, 6 H), 1.52–1.36 (m, 2 H), 0.83 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 66.1, 47.1, 38.2, 26.5, 25.9, 20.5.

MS (EI, 70 eV): *m*/*z* (%) = 182 (4, M^+), 113 (16), 96 (59), 81 (21), 70 (100), 56 (14).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{23}N_2$: 183.1856; found: 183.1857.

N-(4-Methylphenyl)benzamide (10)

A 4 mL vial was charged with benzamide (73 mg, 0.6 mmol, 1.2 equiv), K_3PO_4 (222 mg 1.05 mmol, 2.1 equiv), and CuI (4.76 mg, 0.025 mmol, 5 mol%). *p*-Iodotoluene (109 mg, 0.5 mmol, 1 equiv) and *rac*-**6** (9 mg, 0.05 mmol, 10 mol%), dissolved in 1,4-dioxane (0.5 mL), were added to the mixture and the reaction mixture was stirred at 110 °C for 24 h under an argon atmosphere. The mixture was diluted with EtOAc (1–2 mL), filtered through a short pad of silica gel, and washed with EtOAc (5–10 mL). The filtrate was concentrated under reduced pressure to provide the crude product, which was purified by column chromatography (cyclohexane–EtOAc 90:10) to afford 90 mg (85%) of **10** as a white solid; R_f = 0.54 (cyclohexane–EtOAc 1:1 [UV]).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.87–7.83 (m, 2 H), 7.57–7.50 (m, 3 H), 7.49–7.43 (m, 2 H), 7.16 (d, *J* = 8.1 Hz, 2 H), 2.34 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 165.8, 135.5, 135.3, 134.4, 131.8, 129.7, 128.9, 127.1, 120.5, 21.0.

MS (EI): *m*/*z* (%) = 211.1 (10), 106.1 (9), 105.1 (100), 77.1 (72), 51.1 (20).

The analytical and spectral data were in complete agreement with the previously published data.[13]

(2*S*)-1-Phenyl-2-{2-[(2*S*)-pyrrolidin-2-yl]propan-2-yl}pyrrolidine [(*S*,*S*)-11]

(*S*,*S*)-2,2′-(Propane-2,2-diyl)dipyrrolidine [(*S*,*S*)-**6**; 150 mg, 0.823 mmol), bromobenzene (95 µL, 0.905 mmol), and KO*t*-Bu) (146 mg, 95%, 1.23 mmol) were suspended in xylene (5 mL) and heated for 45 min to 210 °C in a microwave reactor. After the mixture was cooled down to r.t., the solids were filtered off and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2–MeOH–25% aq NH_3 93:5:2) to yield 119 mg (56%) of the title compound as a colorless oil; $[\alpha]_D^{25}$ +13.6 (*c* 1.365, EtOH).

IR (ATR): 3354, 3057, 2961, 2869, 1595, 1501, 1474, 1361, 1319, 1292, 1156, 1077, 991, 960, 745, 693, 524 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.17 (m, 2 H), 6.90–6.86 (m, 2 H), 6.67 (tt, *J* = 7.1, 1.1 Hz, 1 H), 4.07 (dd, *J* = 8.3, 1.7 Hz, 1 H), 3.63–3.57 (m, 1 H), 3.35–3.26 (m, 1 H), 3.01–2.87 (m, 2 H), 2.82–2.76 (m, 1 H), 2.09–1.96 (m, 1 H), 1.96–1.56 (m, 6 H), 1.54–1.43 (m, 1 H), 0.91 (s, 3 H), 0.84 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.4, 128.7, 116.2, 114.1, 65.2, 63.7, 52.8, 47.1, 43.0, 26.8, 26.8, 26.2, 24.9, 21.2, 20.6.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{27}N_2$: 259.2169; found: 259.2172.

(2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanal (14)

Propanal (242 µL, 3.35 mmol, 10 equiv) was added to a suspension of (*S*,*S*)-**11** (5 mg, 0.02 mmol, 0.06 equiv) and *trans*-β-nitrostyrene (**12**; 50 mg, 0.335 mmol, 1 equiv) in *n*-hexane (1 M). The reaction mixture was stirred at r.t. for 5 h. Then aq 1 N HCl (1 mL) was added and extracted with Et_2O (3 × 0.75 mL). The combined organic extracts were dried ($MgSO_4$) and then concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane–EtOAc, 10 to 30% EtOAc) to yield 64 mg (92%) of the desired aldehyde as a colorless oil; *syn*/*anti* = 93:7 (by ^{1}H NMR of the crude mixture), 95% ee (*syn*).

The enantiomeric excess was determined by HPLC [Chiralcel OD-H, heptane–*i*-PrOH 9:1, 1.0 mL/min, t_R (*syn* major) = 29.9 min, t_R (*syn* minor) = 21.0 min].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (d, *J* = 1.7 Hz, 1 H), 7.36–7.26 (m, 3 H), 7.19–7.14 (m, 2 H), 4.79 (dd, *J* = 12.7, 5.5 Hz, 1 H), 4.68 (dd, *J* = 12.7, 9.3 Hz, 1 H), 3.81 (td, *J* = 9.1, 5.5 Hz, 1 H), 2.82–2.72 (m, 1 H), 1.00 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.3, 136.7, 129.2, 128.3, 128.2, 78.2, 48.6, 44.2, 12.3.

The analytical data were in complete agreement with the previously published data.[14]

Supporting Information

Supporting information for this article is available online at https://doi.org /10.1055/s-0036-1589023.

References

(1) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580.
(2) (a) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140. (b) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.
(3) (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13. (b) Jin, J.; Li, X.; Huang, Y.; Wu, F.; Wan, B. *Chem. Eur. J.* **2010**, *16*, 8259. (c) Jia, X.; Lin, A.; Mao, Z.; Zhu, C.; Cheng, Y. *Molecules* **2011**, *16*, 2971. (d) Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem.* **2006**, *71*, 1523. (e) Jiang, X.; Gandelman, M. *J. Am. Chem. Soc.* **2015**, *137*, 2542. (f) Scarborough, C. C.; McDonald, R. I.; Hartmann, C.; Sazama, G. T.; Bergant, A.; Stahl, S. S. *J. Org. Chem.* **2009**, *74*, 2613. (g) Breuning, M.; Hein, D.; Steiner, M.; Gessner, V. H.; Strohmann, C. *Chem. Eur. J.* **2009**, *15*, 12764. (h) Li, X.; Schenkel, L. B.; Kozlowski, M. C. *Org. Lett.* **2000**, *2*, 875.
(4) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684.
(5) (a) Cussó, O.; Garcia-Bosch, I.; Ribas, X.; Lloret-Fillol, J.; Costas, M. *J. Am. Chem. Soc.* **2013**, *135*, 14871. (b) White, M. C.; Chen, M. S. *Science* **2007**, *318*, 783.
(6) Carbone, C.; O'Brien, P.; Hilmersson, G. *J. Am. Chem. Soc.* **2010**, *132*, 15445.
(7) Wagner, C.; Kotthaus, A. F.; Kirsch, S. F. *Chem. Commun.* **2017**, 53, 4513.
(8) Journot, G.; Neier, R.; Stoeckli-Evans, H. *Acta Crystallogr., Sect. E* **2010**, *66*, o392.
(9) Journot, G.; Neier, R.; Stoeckli-Evans, H. *Acta Crystallogr., Sect. C* **2012**, *68*, o119.
(10) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.
(11) For the arylation protocol, see: Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, *5*, 3515.
(12) (a) Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 719. (b) Seebach, D.; Sun, X.; Sparr, C.; Ebert, M.-O.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta* **2012**, *95*, 1064.

(13) Liu, J.; Liu, Q.; Yi, H.; Qin, C.; Bai, R.; Qi, X.; Lan, Y.; Lei, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 502.

(14) (a) Petruzziello, D.; Gualandi, A.; Grilli, S.; Cozzi, P. G. *Eur. J. Org. Chem.* **2012**, 6697. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. (c) Betancort, J. M.; Barbas, C. F. III *Org. Lett.* **2001**, *3*, 3737.