--- Supporting Information ---

Optimization and Multigram Scalability of a Catalytic Enantioselective Borylative Migration for the Synthesis of Functionalized Chiral Piperidines

You-Ri Kim, Dennis G. Hall*

Department of Chemistry, University of Alberta,
Edmonton, Alberta, T6G 2G2, Canada
dennis.hall@ualberta.ca

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1. General information and experimental details

1.1. General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. THF and toluene were purified using a MBraun MB SPS* solvent system. Dioxane was distilled over sodium. Diethyl ether (Et₂O) was distilled over sodium/benzophenone ketyl. Anhydrous chlorobenzene, cyclopentyl methyl ether (CPME), methyl tert-butyl ether (MTBE), dibutyl ether, 2-methyltetrahydrofuran (2-MeTHF), and diglyme were purchased from Sigma-Aldrich and used as received. N,N-Diisopropylethylamine (DIPEA) and N,N-dimethylaniline (DMA) were purchased from Sigma-Aldrich and distilled over potassium hydroxide prior to use. Pinacolborane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Oakwood Products and Sigma-Aldrich, respectively, and were used without further purification. 1-tert-Butoxycarbonyl-4-piperidone, 1-carbobenzoxy-4-piperidone, 1-benzyl-4-piperidone, and perfluorobutanesulfonyl fluoride (NfF) were purchased from Combi-Blocks Inc. and were used without further purification.

All aldehydes were purified by a bulb-to-bulb distillation under reduced pressure. Palladium(II) acetate, allylpalladium(II) chloride dimer, tris(dibenzylideneacetone)dipalladium(0), DPEphos, Taniaphos, and Walphos were purchased from Strem Chemicals. All other palladium catalysts and ligands were purchased from Sigma-Aldrich.

Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F₂₅₄ plates and visualized with UV light, p-anisaldehyde stain, and KMnO₄ stain. Flash column chromatography was performed on ultra-pure silica gel 230-400 mesh. Nuclear magnetic resonance (NMR) spectra were recorded on INOVA-400 or INOVA-500 instruments. The residual solvent protons (1H) and the solvent carbons (13C) were used as internal standards. 1H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; app s, apparent singlet; t, triplet; app t, apparent triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet. Reported J-values are deemed accurate within ± 0.3 Hz. NMR data were processed either using VnmrJ from Agilent Technologies or MestReNova from Mestrelab Research. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using electrospray ionization (ESI) method. Infrared spectra were obtained from a Nicolet Magna-IR machine with frequencies expressed in cm⁻¹. Optical rotations were measured using a 1 mL cell with a 1 dm length on a P.E. 241 polarimeter. Regioselectivity of alkenyl to allyl boronate and the diastereomeric ratios for chiral compounds were determined by integration of relevant signals on the crude 1H NMR spectra. The enantiomeric excess ratios for optically enriched compounds were determined using a HPLC Agilent instrument with a Chiralcel-OD or IB or IC column as specified in the following individual procedures.

1.2. Experimental details

Pinacolborane received in a bottle was transferred to a round bottom flask under a nitrogen atmosphere and
stored in a freezer. DIPEA and DMA were distilled over potassium hydroxide under a nitrogen atmosphere and stored in a refrigerator. Synthesized alkenyl nonaflates were transferred to vials after purification and stored in a refrigerator. Prior to the borylative migration reaction, pinacolborane, the base, and the alkenyl nonaflate were allowed to warm up to room temperature (ca. 20 min). Ultrapure (99.95+% Pd(OAc)$_2$ was used. All the phosphine ligands were checked for oxidation via ESI-ToF technique prior to use. Palladium and ligand were weighed out carefully and transferred to a reaction flask, which was evacuated and back-filled with nitrogen three times. Due to its instability to a prolonged exposure to air and silica gel, freshly-made crude allylic boronate 5 was filtered through a silica plug (silica gel to crude product, 100/1, w/w) very quickly (ca. 30 seconds) and subjected to the allylboration reaction directly after concentration of solvent. The major side product, alkenyl boronate, was removed during the purification of final products, α-hydroxyalkyl dehydropiperidines.

2. Experimental procedure and spectral data for alkenyl nonaflates 8, 9, and 13

2.1. General procedure for the synthesis of alkenyl nonaflates 8, 9, and 13

N-Protected piperidone (10 mmol, 1.0 equiv) was dissolved in THF (50 mL) under a nitrogen atmosphere. The mixture was cooled in an ice-water bath (0 °C) and stirred for 5 min. DBU (1.8 mL, 12 mmol, 1.2 equiv) and perfluorobutanesulfonfyl fluoride (2.2 mL, 12 mmol, 1.2 equiv) were added respectively and the resulting solution was stirred for 10 min. The reaction was then allowed to warm up to rt and stirred for 16 h. The reaction was quenched with a slow addition of water (50 mL) and extracted with Et$_2$O (3 × 60 mL). The organic layers were combined and washed with brine (50 mL), dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo. The brown oil was then purified by flash column chromatography (25% Et$_2$O/pentane).

2.2. Spectral data for alkenyl nonaflates 8, 9, and 13

**tert-Butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (8)**

A colorless oil (4.6 g, 95% yield) was obtained according to the general procedure using 1-(tert-butoxycarbonyl)-4-piperidone (2.0 g, 10 mmol, 1.0 equiv) as a substrate. Spectral data correspond to that reported.$^1$ $^1$R$_f$ = 0.61 (15% EtOAc/hexane); $^1$H NMR (500 MHz, CDCl$_3$) δ (ppm) 5.76 (app s, 1 H), 4.04 (app s, 2 H), 3.62 (app s, 2 H), 2.43 (app s, 2 H), 1.46 (s, 9 H).
Benzyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (9)

A light-yellow oil (4.6 g, 89% yield) was obtained according to the general procedure using 1-carbobenzoxy-4-piperidone (2.3 g, 10 mmol, 1.0 equiv) as a substrate. \( R_f = 0.41 \) (15% EtOAc/hexane); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.39 – 7.32 (m, 5 H), 5.82 – 5.75 (m, 1 H), 5.16 (s, 2 H), 4.14 (app s, 2 H), 3.72 (app s, 2 H), 2.47 (app s, 2 H); \(^13\)C NMR (100 MHz, CDCl\(_3\), \(^{19}\)F decoupled, 60 °C) \( \delta \) (ppm) 155.1, 147.0, 136.5, 128.7, 128.3, 128.1, 115.8, 115.4, 114.5, 114.0, 108.7, 67.8, 42.1, 40.8, 28.2; \(^{19}\)F NMR (376 MHz, CDCl\(_3\), \(^1\)H decoupled, 60 °C) –80.8, –110.1, –120.6, –125.5; IR (Microscope, cm\(^{-1}\)) 3035, 2957, 1711, 1423, 1353, 1280; HRMS (ESI-ToF) for C\(_{17}\)H\(_{14}\)F\(_9\)N\(_2\)O\(_5\)S (M + Na\(^+\)): calcd. 538.0341; found 538.0337.

1-(Benzyl)-4-[(nonafluorobutanesulfonyloxy)-1,2,3,6-tetrahydropyridine (13)

A yellow oil (4.3 g, 91% yield) was obtained according to the general procedure using 1-benzyl-4-piperidone (1.9 mL, 10 mmol, 1.0 equiv) as a substrate. \( R_f = 0.56 \) (15% EtOAc/hexane); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.35 – 7.27 (m, 5 H), 5.75 – 5.73 (m, 1 H), 3.64 (s, 2 H), 3.15 – 3.13 (m, 2 H), 2.73 (t, \( J = 5.7 \) Hz, 2 H), 2.46 – 2.45 (m, 2 H); \(^13\)C NMR (100 MHz, CDCl\(_3\), \(^{19}\)F Dec) \( \delta \) (ppm) 147.5, 137.7, 129.0, 128.5, 127.4, 117.1, 116.3, 114.2, 109.9, 108.5, 61.3, 50.5, 49.1, 28.4; \(^{19}\)F NMR (376 MHz, CDCl\(_3\), \(^1\)H decoupled) –80.8, –110.1, –121.1, –126.0; IR (Microscope, cm\(^{-1}\)) 3031, 2926, 2806, 1699, 1454, 1421; HRMS (ESI-ToF) for C\(_{16}\)H\(_{16}\)F\(_9\)NO\(_3\)S (M + H\(^+\)): calcd. 472.0623; found 472.0618.

3. Experimental procedure and spectral data for allylic boronate 5

3.1. Experimental procedure and spectral data for racemic allylic boronate, rac-5

tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2H)-carboxylate (rac-5)
Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and DPEPhos (18 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with N₂ three times. Et₂O (3 mL) was added and the mixture was stirred for 15 min. DIPEA (192 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and tert-butyl-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (8) (481 mg, 1.00 mmol, 1.00 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated in vacuo, followed by a quick filtration through a silica plug (100% Et₂O). The resulting mixture was concentrated in vacuo and purified by flash column chromatography (25% Et₂O/pentane) providing a colorless oil (155 mg, 56% yield). Spectral data correspond to that reported.² Regioselectivity of alkenyl to allyl boronic ester determined by integration of relevant signals on the crude ¹H NMR spectrum was 15:85.

3.2. Experimental procedure and spectral data for an optically enriched allylic boronate 5

(4S)-tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2H)-carboxylate (5)

Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and (+)-TANIAPHOS (23 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et₂O (3 mL) was added and the mixture was stirred for 30 min. DMA (140 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and tert-butyl-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (8) (481 mg, 1.00 mmol, 1.00 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated in vacuo, followed by a quick filtration through a silica plug (100% Et₂O). The resulting mixture was concentrated in vacuo and purified by flash column chromatography (25% Et₂O/pentane) providing a colorless oil (155 mg, 50% yield). Spectral data correspond to that reported.² Regioselectivity of alkenyl to allyl boronic ester determined by integration of relevant signals on the crude ¹H NMR spectrum was 1:4. R_f = 0.35 (25% Et₂O/pentane); ¹H NMR (500 MHz, CDCl₃) rotamers are present: δ (ppm) 6.84 – 6.71 (m, 1 H), 4.94 – 4.82 (m, 1 H), 3.58 – 3.53 (m, 2 H), 1.87 – 1.83 (m, 3 H), 1.47 (s, 9 H), 1.23 (s, 12 H).
4. Experimental procedure and spectral data for α-hydroxyalkyl dehydropiperidines

4.1. General procedure for the synthesis of racemic α-hydroxyalkyl dehydropiperidines

Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and DPEPhos (18 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et2O (3 mL) was added and the mixture was stirred for 15 min. DIPEA (192 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and alkenyl nonaflate (1.0 mmol, 1.0 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated in vacuo, followed by a quick filtration through a silica plug (100% Et2O). The resulting mixture was concentrated in vacuo and transferred to a pre-dried 5 mL round bottom flask using dry toluene (1 mL). The flask was flushed with nitrogen and aldehyde (1.1 mmol, 1.1 equiv) was added. The solution was stirred at rt under a nitrogen atmosphere for 3 or 16 h as specified in the following individual procedures. The mixture was purified directly by flash column chromatography.

4.2. General procedure for the synthesis of optically enriched α-hydroxyalkyl dehydropiperidines

Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and (+)-TANIAPHOS (23 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et2O (3 mL) was added and the mixture was stirred for 30 min. DMA (140 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and alkenyl nonaflate (1.0 mmol, 1.0 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated in vacuo, followed by a quick filtration through a silica plug (100% Et2O). The resulting mixture was concentrated in vacuo and transferred to a pre-dried 5 mL round bottom flask using dry toluene (1 mL). The flask was flushed with nitrogen and aldehyde (1.1 mmol, 1.1 equiv) was added. The solution was stirred at rt under nitrogen for 3 or 16 h. The mixture was purified directly by flash column chromatography.

4.3. Spectral data for optically enriched α-hydroxyalkyl dehydropiperidines

(R)-tert-Butyl 2-[(R)-hydroxy(p-tolyl)methyl]-5,6-dihydropyridine-1(2H)-carboxylate (7)

The title compound (7) was synthesized by the general procedure using tert-butyl-4-(nonafluorobutysulfonyl)oxy)-5,6-dihydropyridine-1(2H)-carboxylate (8) (481 mg, 1.00 mmol, 1.00 equiv) and p-tolualdehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a colorless oil (213 mg, 70% yield) after flash column chromatography (50% Et2O/pentane). Rf = 0.50 (20% EtOAc/hexane); [α]20D + 135.0 (c 1.00, CHCl3); 1H NMR (400 MHz, CDCl3) rotamers are present: δ
The title compound was obtained as a colorless oil (258 mg, 70% yield) after flash column chromatography (50% EtOAc/pentane). The IR (Microscope, cm⁻¹) 3040, 2969, 2929, 1652, 1592, 1454; HRMS (EI-MS) for C_{15}H_{19}BrNO_3: calcd. 368.0856; found 368.0850; HPLC (Chiralcel OD): 3.8% i-PrOH/hexane, 6 °C, 0.5 mL/min, λ = 210 nm, Tr_major = 19.6 min, Tr_minor = 17.3 min; 92% ee; >96% de.

(R)-tert-Butyl 2-[(R)-hydroxy(3-phenylpropyl)methyl]-5,6-dihydropyridine-1(2H)-carboxylate (18)

The title compound was synthesized by the general procedure using tert-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (8) (481 mg, 1.00 mmol, 1.00 equiv) and 2-bromobenzaldehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a yellow oil (222 mg, 70% yield) after flash column chromatography (25% EtOAc/pentane). Spectral data correspond to that reported.² R_F = 0.65 (50% EtOAc/hexane); ²H NMR (400 MHz, CDCl_3, 60 °C) δ (ppm) 7.28 – 7.15 (m, 5 H), 5.96 – 5.93 (m, 1 H), 5.68 – 5.66 (m, 1 H), 4.41 – 4.37 (m, 1 H), 4.16 – 4.06 (m, 1 H), 3.72 – 3.68 (m, 1 H), 3.02 – 2.97 (m, 1 H), 2.93 – 2.88 (m, 1 H), 2.80 – 2.76 (m, 1 H), 2.21 – 2.17 (m, 1 H), 2.15 – 2.14 (m, 1 H), 1.95 – 1.89 (m, 1 H), 1.49 (s, 9 H); ¹³C NMR (100 MHz, CDCl_3, 60 °C) δ (ppm) 156.0, 140.7, 132.7, 129.1, 129.0, 128.0, 127.7, 124.7, 123.3, 80.3, 75.1, 57.5, 38.2, 28.4, 24.8; IR (Microscope, cm⁻¹) 3427, 3028, 2976, 2929, 1670, 1592, 1454; HRMS (EI-MS) for C_{17}H_{19}BrNO_3: calcd. 368.0856; found 368.0850; HPLC (Chiralcel OD): 3.8% i-PrOH/hexane, 6 °C, 0.5 mL/min, λ = 210 nm, Tr_major = 26.5 min, Tr_minor = 19.3 min; 90% ee; >96% de.
The title compound (19) was synthesized by the general procedure using tert-butyl-4-(nonafluorobutyloxyl)-5,6-dihydropyridine-1(2H)-carboxylate (8) (481 mg, 1.00 mmol, 1.00 equiv) and 4-pyridinecarboxaldehyde (104 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 3 h. The product was obtained as a colorless oil (206 mg, 71% yield) after flash column chromatography (100% EtOAc). Rf = 0.27 (100% EtOAc); [α]D20 = +131.6 (c 1.07, CHCl3); 1H NMR (400 MHz, DMSO-d6) rotamers are present: δ (ppm) 8.48 – 8.47 (m, 2 H), 7.25 – 7.23 (m, 2 H), 5.91 – 5.88 (m, 1 H), 5.71 – 5.68 (m, 1 H), 4.77 (app t, J = 4.8 Hz, 1 H), 4.52 – 4.41 (m, 1 H), 3.94 – 3.68 (m, 1 H), 2.71 – 2.62 (m, 1 H), 1.94 – 1.83 (m, 2 H), 1.33 – 1.21 (m, 9 H); 1H NMR (400 MHz, DMSO-d6, 80 °C) δ (ppm) 8.48 (d, J = 5.8 Hz, 2 H), 7.25 (d, J = 5.8 Hz, 2 H), 5.89 – 5.88 (m, 1 H), 5.71 – 5.68 (m, 1 H), 5.45 – 5.43 (m, 1 H), 4.78 (app t, J = 4.8 Hz, 1 H), 4.51 (app s, 1 H), 3.87 – 3.83 (m, 1 H), 2.64 – 2.57 (m, 1 H), 1.96 – 1.91 (m, 1 H), 1.83 – 1.78 (m, 1 H), 1.32 (s, 9 H); 13C NMR (100 MHz, DMSO-d6, 80 °C) δ (ppm) 153.6, 151.0, 148.6, 126.7, 124.6, 121.8, 78.3, 72.5, 56.3, 37.2, 27.6, 23.7; IR (Microscope, cm⁻¹) 3402, 3189, 2976, 2929, 1691, 1603, 1477, 1455; HRMS (ESI-ToF) for C27H26N2O3 (M + H)+: calcd. 391.1703; found 391.1707; HPLC (Chiralcel IC): 50% i-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, Tmajor = 6.3 min, Tminor = 14.2 min; 94% ee; >96% de.

The title compound (20) was synthesized by the general procedure using tert-butyl-4-(nonafluorobutyloxyl)-5,6-dihydropyridine-1(2H)-carboxylate (8) (481 mg, 1.00 mmol, 1.00 equiv) and 4-quinolinecarboxaldehyde (173 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 3 h. The product was obtained as a colorless oil (245 mg, 72% yield) after flash column chromatography (100% EtOAc). Rf = 0.44 (100% EtOAc); [α]D20 = +51.4 (c 1.56, CHCl3); 1H NMR (500 MHz, DMSO-d6) rotamers are present: δ (ppm) 8.85 – 8.82 (m, 1 H), 8.26 – 8.11 (m, 1 H), 8.04 – 7.98 (m, 1 H), 7.74 – 7.71 (m, 1 H), 7.59 – 7.50 (m, 2 H), 5.98 – 5.80 (m, 2 H), 5.69 – 5.60 (m, 2 H), 4.71 – 4.59 (m, 1 H), 3.99 – 3.95 (m, 1 H), 3.18 – 3.12 (m, 1 H), 1.93 – 1.86 (m, 2 H), 1.30 – 0.67 (m, 9 H); 1H NMR (500 MHz, DMSO-d6, 115 °C) δ (ppm) 8.83 (d, J = 4.4 Hz, 1 H), 8.21 (d, J = 8.4 Hz, 1 H), 8.02 (d, J = 8.4 Hz, 1 H), 7.70 (dt, J = 7.6, 0.91 Hz, 1 H), 7.56 – 7.51 (m, 2 H), 5.92 – 5.89 (m, 1 H), 5.75 – 5.72 (m, 1 H), 5.59 (app t, J = 4.5 Hz, 1 H), 5.39 (app s, 1 H), 4.74 (app s, 1 H), 3.85 – 3.84 (m, 1 H), 2.73 (br s, 1 H), 2.01 – 1.93 (m, 1 H), 1.83 – 1.80 (m, 1 H), 1.12 (s, 9 H); 13C NMR (125 MHz, DMSO-d6, 115 °C) δ (ppm) 153.5, 149.0, 147.5, 147.4, 129.1, 127.9, 126.5, 125.7, 125.2, 125.0, 123.1, 119.0, 77.9, 69.4, 56.0, 36.9, 27.2, 23.5; IR (Microscope, cm⁻¹) 3405, 3180, 3041, 2976, 2930, 1687, 1477;
HRMS (ESI-ToF) for \( C_{20}H_{25}N_{2}O_3\) (M + H)^+: calcd. 341.1860; found 341.1863; HPLC (Chiralcel IC): 50% \( t\)-PrOH/hexane, 20 °C, 0.5 mL/min, \( \lambda = 280\) nm, \( T_{\text{major}} = 6.1\) min, \( T_{\text{minor}} = 13.2\) min; 90% ee; >96% de.

(S)-Benzy1 2-[(S)-hydroxy(p-tolyl)methyl]-5,6-dihydropyridine-1(2H)-carboxylate (12)

The title compound (12) was synthesized by the general procedure (modification: use of (−)-TANIAPHOS instead of (+)-TANIAPHOS) using benzyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (9) (515 mg, 1.00 mmol, 1.00 equiv) and \( p\)-tolualdehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a colorless oil (202 mg, 60% yield) after flash column chromatography (50% EtO/pentane). \( R_f = 0.41\) (20% EtOAc/hexane); \( [\alpha]^{20}_D = -109.1\) (c 0.32, CHCl\(_3\)).

\( ^{1}H\) NMR (500 MHz, CDCl\(_3\)) \( \delta\) (ppm) 7.38 – 7.31 (m, 5 H), 7.31 – 7.12 (m, 4 H), 5.89 – 5.82 (m, 1 H), 5.41 – 5.38 (m, 1 H), 5.23 – 5.11 (m, 2 H), 4.70 – 4.67 (m, 2 H), 4.22 – 3.46 (m, 1 H), 3.03 – 2.83 (m, 1 H), 2.34 (s, 3 H), 2.23 – 2.20 (m, 1 H), 1.97 – 1.93 (m, 1 H); \( ^{1}H\) NMR (400 MHz, CDCl\(_3\), 65 °C) \( \delta\) (ppm) 7.39 – 7.29 (m, 5 H), 7.23 (app d, \( J = 7.9\) Hz, 2 H), 7.14 (app d, \( J = 7.9\) Hz, 2 H), 5.89 – 5.84 (m, 1 H), 5.36 – 5.34 (m, 1 H), 5.18 (s, 2 H), 4.68 – 4.66 (m, 2 H), 4.21 – 4.16 (m, 1 H), 2.98 – 2.90 (m, 1 H), 2.35 (s, 3 H), 2.27 – 2.17 (m, 1 H), 1.97 – 1.90 (m, 1 H); \( ^{13}C\) NMR (100 MHz, CDCl\(_3\), 65 °C) \( \delta\) (ppm) 156.8, 138.3, 137.8, 136.9, 129.2, 128.6, 128.1, 128.0, 127.1, 124.9, 76.2, 67.6, 58.7, 38.0, 24.8, 21.2; IR (Microscope, cm\(^{-1}\)) 3438, 3031, 2921, 1697, 1515, 1431, 1391; HRMS (ESI-ToF) for \( C_{21}H_{23}NNaO_3\) (M + Na)^+: calcd. 360.1570; found 360.1567; HPLC (Chiralcel IB): 5% \( t\)-PrOH/hexane, 20 °C, 0.5 mL/min, \( \lambda = 210\) nm, \( T_{\text{major}} = 15.8\) min, \( T_{\text{minor}} = 18.9\) min; 90% ee; >96% de.
5. Copies of $^1$H NMR spectra for known compounds

$^1$H NMR of compound 8 (CDCl$_3$, 500 MHz)

$^1$H NMR of compound 5 (CDCl$_3$, 400 MHz)
$^1$H NMR of compound 18 (CDCl$_3$, 400 MHz, 60 °C)
6. Copies of $^1$H and $^{13}$C NMR spectra for new compounds

$^1$H NMR of compound 9 (CDCl$_3$, 500 MHz)

$^{13}$C NMR of compound 9 (CDCl$_3$, 100 MHz, $^{19}$F decoupled, 60 °C)
$^{19}$F NMR of compound 9 (CDCl$_3$, 100 MHz, $^1$H decoupled, 60 °C)

$^1$H NMR of compound 13 (CDCl$_3$, 500 MHz)
$^{13}$C NMR of compound 13 (CDCl$_3$, 100 MHz, $^{19}$F decoupled, 60 °C)

$^{19}$F NMR of compound 13 (CDCl$_3$, 100 MHz, $^1$H decoupled)
$^1$H NMR of compound 7 (CDCl$_3$, 400 MHz)

$^1$H NMR of compound 7 (CDCl$_3$, 400 MHz, 65 °C)
$^{13}$C NMR of compound 7 (CDCl$_3$, 100 MHz, 60 °C)

$^1$H NMR of compound 17 (CDCl$_3$, 400 MHz, 65 °C)
$^{13}$C NMR of compound 17 (CDCl$_3$, 100 MHz, 65 °C)

$^1$H NMR of compound 19 (DMSO-$d_6$, 400 MHz)
$^1$H NMR of compound 19 (DMSO-\textit{d}$_6$, 400 MHz, 80 °C)

$^{13}$C NMR of compound 19 (DMSO-\textit{d}$_6$, 100 MHz, 80 °C)
$^1$H NMR of compound 20 (DMSO-$d_6$, 400 MHz)

$^1$H NMR of compound 20 (DMSO-$d_6$, 400 MHz, 115 °C)
\textsuperscript{\textit{13}C} NMR of compound 20 (DMSO-d\textsubscript{6}, 100 MHz, 115 °C)

\textit{1}H NMR of compound 12 (CDCl\textsubscript{3}, 500 MHz)
$^1$H NMR of compound 12 (CDCl$_3$, 400 MHz, 65 °C)

$^{13}$C NMR of compound 12 (CDCl$_3$, 100 MHz, 65 °C)
7. HPLC chromatograms for enantiomeric excess measurements

**Signal 1: DAD1 C, Sig=210,8 Ref=360,100**

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
<th>%</th>
</tr>
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<tbody>
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<td>#</td>
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<td>[min]</td>
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<td>[mAU]</td>
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Totals: 1.76788e4 370.98163

**Compound rac-7**

![Compound rac-7](image_url)

**Signal 1: DAD1 C, Sig=210,8 Ref=360,100**

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
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Totals: 1.82719e4 315.91970

**Compound 7**

![Compound 7](image_url)
Signal 1: DAD1 A, Sig=210.8 Ref=360,100

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %
1 18.503 BB 0.8022 2.93236e4 522.92322 49.8967
2 25.418 BB 1.1548 2.94451e4 373.89606 50.1033

Signal 1: DAD1 A, Sig=210.8 Ref=360,100

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %
1 19.287 MM 0.9569 2.22074780 38.68064 4.7387
2 26.482 MM 1.4230 4.46435e4 522.87378 95.2613

Totals : 4.68643e4 561.55442
Note: HPLC chromatogram of the above racemate was referenced from our group's former student, Stephanie Lessard.2
8. References