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Supporting Information

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Direct, Highly Enantioselective Pyrrolidine Sulfonamide Catalyzed Michael Addition Reactions of Aldehydes to Nitrostyrenes

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General Information: Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence F_{254} indicator were used for thin-layer chromatography (TLC) analysis. ^{1}H and ^{13}C NMR spectra were recorded on Broker Advance 500, and tetramethylsilane (TMS) was used as a reference. Data for ^{1}H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for ^{13}C NMR are reported as ppm. Mass Spectra were obtained from the Ohio State University Mass Spectral facility.

Procedures for preparation of pyrrolidine trifluoromethanesulfonamide organocatalyst I.

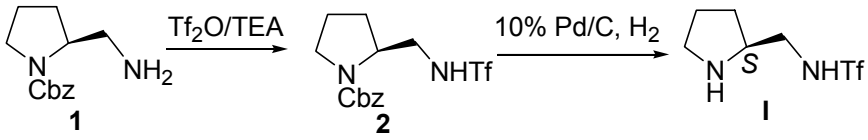
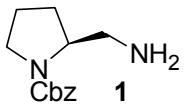
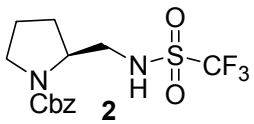


Figure. Synthesis of organocatalyst pyrrolidine trifluoromethanesulfonamide **I**.

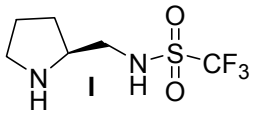


(*S*)-2-Aminomethyl-1-*N*-Cbz-pyrrolidine (1). Compound **1** is prepared according to the known procedures in 4 steps from *N*-Cbz-Proline.[1]



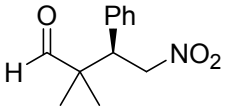
(*S*)-2-(Trifluoromethanesulfonylaminomethyl)-1-*N*-Cbz-pyrrolidine (2). To a solution of (*S*)-2-aminomethyl-1-*N*-Cbz-pyrrolidine (2.0 g, 8.55 mmol) and TEA

(1.43 mL, 10.3 mmol) in 40 mL of CaH_2 dried CH_2Cl_2 was added trifluoromethanesulfonic anhydride (1.6 mL, 9.4 mmol) dropwisely by a syringe pump over 1 h at 0 ˚C under N_2. The resulting solution was stirred for 4.5 h at room temperature, then diluted with 80 mL of CH_2Cl_2 and washed with 50 mL of 1*N* HCl aqueous solution. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (Ethyl Acetate/Hexane = 1/7) afforded a colorless oil in 76% yield (2.38 g, 6.50 mmol). $[\alpha]_D^{25}$ -27.7 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.68 (s, 1H; Ph), 7.10-7.39 (m, 5H; Ph), 5.15 (m, 2H; CH_2), 3.98-4.09 (m, 1H; CH), 3.24-3.57 (m, 4H; CH and CH_2), 2.12 (m, 1H; CH), 1.88 (m, 2H; CH_2), 1.67 (m, 1H; CH); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 157.7, 136.2, 128.8, 128.6, 128.5, 128.3, 68.0, 58.1, 49.9, 47.5, 30.0, 24.1; HRMS (FAB) calcd for $C_{14}H_{18}F_3N_2O_4S$ (M + 1) m/z 367.0939, found 367.0928.

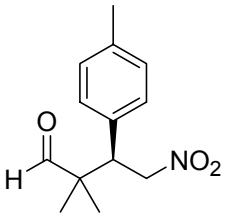


(*S*)-2-(Trifluoromethanesulfonylaminomethyl)pyrrolidine (I). A solution of (*S*)-2-(trifluoromethanesulfonylaminomethyl)-1-*N*-Cbz-pyrrolidine (0.794 g, 2.17 mmol) in 15 mL of MeOH was hydrogenated in the presence of 10% Pd/C (0.16 g) with a H_2 balloon at room temperature for 5 h. The catalyst was filtered through a pad of celite and washed with 2 × 20 mL of MeOH. The filtrate was concentrated *in vacuo* to give a white solid (>95% purity) in 93% yield (0.469 g, 2.02 mmol). The product was crystallized in MeOH to give a crystal, which was used for catalyzing reactions. $[\alpha]_D^{25}$ + 10.5 (*c* = 1.0 in CH_3OH); ^{1}H NMR (500MHz, CD_3OD, TMS): δ = 3.47 (m, 1H; CH), 3.08-3.28 (m, 4H; CH and CH_2), 1.86-2.02 (m, 3H; CH and CH_2), 1.61-1.68 (m, 1H; CH); ^{13}C NMR (125 MHz, CD_3OD, TMS): δ = 123.5 (q, $^2J(C, F)$ = 325 Hz), 122.2, 63.7, 46.4, 28.5, 24.7; HRMS (FAB) calcd for $C_6H_{12}F_3N_2O_2S$ (M + 1) *m/z* 233.0572, found 233.0580.

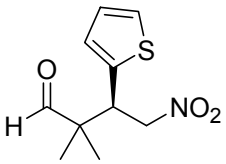
Typical Procedure for Michael Addition Reaction: To a vial containing *iso*-butyraldehyde (0.20 mL, 2.19 mmol), and 1.0 mL of dry isopropyl alcohol was added catalyst pyrrolidine sulfonamide **I** (10 mg, 0.044 mmol) at 0°C. The mixture was vigorously stirred for 15 min, and then *trans*-*β*–nitrostyrene (33 mg, 0.219 mmol) was added. After 4.5 d stirring, TLC analysis indicated completion of the reaction. After reaction mixture was concentrated under reduced pressure, the resulting residue was then purified by silica gel chromatography (ethyl acetate/hexane = 1/30 to 1/5) and fractions were collected and concentrated *in vacuo* to provide a clear oil (41 mg, 0.186 mmol, 85%). Relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR, ^{13}C NMR, chiral HPLC analysis, and optical rotation values. Compounds reported in Table 2, entries 1[2], 4[3], 5[3], 8[4], and 11[5] are known.



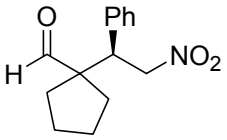
(*R*)-2,2-Dimethyl-4-nitro-3-phenylbutanal[2] (Table 2, entry 1): The title compound was prepared according the typical procedure, as described above in 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 9.53 (s, 1H; CHO), 7.35-7.19 (m, 5H; Ph), 4.85 (dd, ^{2}J(H,H) = 13.0 Hz, ^{3}J(H,H) = 11.5 Hz, 1H; CH), 4.69 (dd, ^{2}J(H,H) = 13.0 Hz, ^{3}J(H,H) = 4.0 Hz, 1H; CH), 3.78 (dd, ^{3}J(H,H) = 11.5 Hz, ^{3}J(H,H) = 4.0 Hz, 1H; CH), 1.14 (s, 3H; CH_3), 1.01 (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 204.4, 135.6, 129.3, 128.9, 128.4, 76.5, 48.7, 48.4, 21.9, 19.1; HPLC (Chiralpak AS-H, *i*-Propanol/Hexane = 10/90, flow rate 0.5 mL/min, λ = 254 nm): t_{minor} = 22.2 min, t_{major} = 23.0 min, ee = 90%.



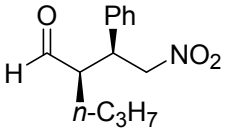
(*R*)-2,2-Dimethyl-4-nitro-3-p-tolylbutanal (Table 2, entry 2): The title compound was prepared according the typical procedure, as described above in 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 9.53 (s, 1H; CHO), 7.13 (d, ^{3}J(H,H) = 8.0 Hz, 2H; Ph), 7.07 (d, ^{3}J(H,H) = 8.0 Hz, 2H; Ph), 4.82 (dd, ^{2}J(H,H) = 12.5 Hz, ^{3}J(H,H) = 11.5 Hz, 1H; CH), 4.67 (dd, ^{2}J(H,H) = 13.0 Hz, ^{3}J(H,H) = 4.0 Hz, 1H; CH), 3.74 (dd, ^{3}J(H,H) = 11.5 Hz, ^{3}J(H,H) = 4.0 Hz, 1H; CH), 2.32 (s, 3H; CH_3), 1.13 (s, 3H; CH_3), 1.00 (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 204.6, 138.1, 132.4, 129.6, 129.1, 76.6, 48.4, 21.8, 21.2, 19.1; HPLC (Chiralcel OD-H, *i*-Propanol/Hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_{minor} = 15.1 min, t_{major} = 10.4 min; $[\alpha]_D$ = +25.4 (*c*=0.5 in $CHCl_3$), ee = 90%.



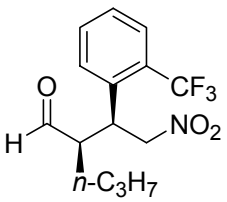
(*R*)-2,2-Dimethyl-4-nitro-3-(thiophen-2-yl)butanal (Table 2, entry 3): The title compound was prepared according the typical procedure, as described above in 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 9.54 (s, 1H; CHO), 7.26-6.92 (m, 3H; Ph), 4.73-4.67 (m, 2 H; CH_2), 4.14 (dd, ^{2}J(H,H) = 10.8 Hz, ^{3}J(H,H) = 4.0 Hz, 1H; CH), 1.21 (s, 3H; CH_3), 1.09 (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 192.8, 138.1, 129.6, 129.2, 125.2, 59.9, 30.9, 25.7, 24.2; HPLC (Chiralcel OD-H, *i*-Propanol/Hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_{minor} = 19.8 min, t_{major} = 11.4 min; $[\alpha]_D$ = +54.1 (*c*= 1.0 in $CHCl_3$), ee = 89%.



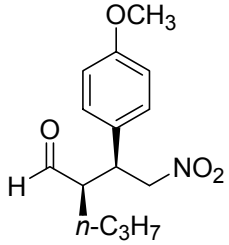
1-((*R*)-2-Nitro-1-phenylethyl)cyclopentanecarbaldehyde[3] (Table 2, entry 4): The title compound was prepared according the typical procedure, as described above in 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 9.49 (s, 1H; CHO), 7.33-7.19 (m, 5H; Ph), 4.96 (dd, ^{2}J(H,H) = 13.5 Hz, ^{3}J(H,H) = 11.5 Hz, 1H; CH), 4.70 (dd, ^{2}J(H,H) = 13.5 Hz, ^{3}J(H,H) = 4.0 Hz, 1H; CH), 3.70 (dd, ^{3}J(H,H) = 11.5 Hz, ^{3}J(H,H) = 4.0 Hz, 1H; CH), 2.07-2.02 (m, 1H; CH), 1.90-1.86 (m, 1H; CH), 1.68-1.51 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 204.6, 136.6, 129.019, 129.002, 128.3, 77.6, 60.5, 49.5, 32.8, 31.7, 25.0, 24.9; HPLC (Chiralcel OD-H, *i*-Propanol/Hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_{minor} = 14.6 min, t_{major} = 10.5 min; $[\alpha]_D$ = -7.2 (*c*=3.8 in $CHCl_3$), ee = 93%.



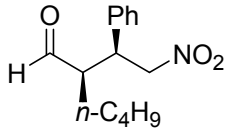
(*R*)-2-[(*S*)-2-Nitro-1-phenylethyl]pentanal[3] (Table 2, entry 5): The title compound was prepared according the typical procedure, as described above in 99% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 9.71 (d, ^{3}J(H,H) = 3.0 Hz, 1H; CHO), 7.35-7.17 (m, 5H; Ph), 4.72-4.63 (m, 2H), 3.80-3.75 (m, 1H; CH), 2.73-2.68 (m, 1H; CH), 1.49-1.11 (m, 4H), 0.80 (t, ^{3}J(H,H) = 7.5 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 203.4, 137.0, 129.3, 128.4, 128.2, 78.6, 54.0, 43.4, 29.7, 20.0, 14.1; HPLC (Chiralcel OD-H, *i*-Propanol/Hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_{minor} = 10.9 min, t_{major} = 12.9 min; $[\alpha]_D$ = +51.2 (*c*=0.5 in $CHCl_3$), ee = 97%.



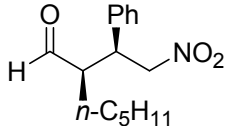
(*R*)-2-[(*S*)-1-(2-(Trifluoromethyl)phenyl)-2-nitroethyl]pentanal (Table 2, entry 6): The title compound was prepared according the typical procedure, as described above in 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 9.76 (d, ^{3}J(H,H) = 3.0 Hz, 1H; CHO), 7.73 (d, ^{3}J(H,H) = 8.0 Hz, 1H; Ph), 7.59 (t, ^{3}J(H,H) = 7.5 Hz, 1H; Ph), 7.45 (t, ^{3}J(H,H) = 8.0 Hz, 1H; Ph), 7.37 (d, ^{3}J(H,H) = 7.5 Hz, 1H; CH), 4.80 (dd, ^{2}J(H,H) = 13.0 Hz, ^{3}J(H,H) = 7.5 Hz, 1H; CH), 4.66 (dd, ^{2}J(H,H) = 13.0 Hz, ^{3}J(H,H) = 5.0 Hz, 1H; CH), 4.17-4.14 (m, 1H; CH), 2.95-2.93 (m, 1H; CH), 1.60-1.20 (m, 4H), 0.81 (t, ^{3}J(H,H) = 7.5 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 203.0, 136.3, 132.6, 129.4 (q), 128.0, 126.9, 125.1, 123.0, 77.8, 54.0, 38.6, 30.3, 20.1, 13.9; HPLC (Chiralcel OD-H, *i*-Propanol/Hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_{minor} = 8.6 min, t_{major} = 10.1 min; $[\alpha]_D$ = +31.4 (*c*=1.0 in $CHCl_3$), ee = 94%.



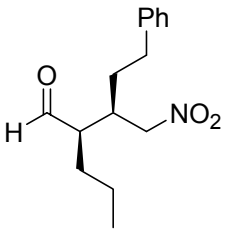
(*R*)-2-[(*S*)-1-(4-Methoxyphenyl)-2-nitroethyl]pentanal (Table 2, entry 7): The title compound was prepared according the typical procedure, as described above in 86% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 9.69 (d, ^{3}J(H,H) = 3.0 Hz, 1H; CHO), 7.08 (d, ^{3}J(H,H) = 8.5 Hz, 2H; Ph), 6.86 (d, ^{3}J(H,H) = 8.5 Hz, 2H; Ph), 4.66 (dd, ^{2}J(H,H) = 13.0 Hz, ^{3}J(H,H) = 5.0 Hz, 1H; CH), 4.60 (dd, ^{2}J(H,H) = 13.0 Hz, ^{3}J(H,H) = 10.0 Hz, 1H; CH), 3.78 (s, 3H; CH_3), 3.75-3.71 (m, 1H; CH), 2.66-2.65 (m, 1H; CH), 1.49-1.29 (m, 4H), 0.80 (t, ^{3}J(H,H) = 7.5 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 203.6, 159.4, 129.2, 128.7, 114.7, 78.8, 55.4, 54.1, 42.6, 29.6, 20.0, 14.1; HPLC (Chiralcelk OD-H, *i*-Propanol/Hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_{minor} = 18.4 min, t_{major} = 21.5 min; $[\alpha]_D$ = +41.7 (*c*=2.0 in $CHCl_3$), ee = 99%.



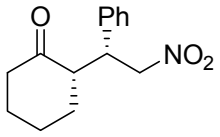
(*R*)-2-[(*S*)-2-Nitro-1-phenylethyl]hexanal[4] **(**Table 2, entry 8**)**: The title compound was prepared according the typical procedure, as described above in 94% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 9.71 (d, ^{3}J(H,H) = 3.0 Hz, 1H; CHO), 7.36-7.17 (m, 5H; Ph), 4.73-4.62 (m, 2H), 3.80-3.75 (m, 1H; CH), 2.72-2.67 (m, 1H; CH), 1.53-1.11 (m, 6H), 0.78 (t, ^{3}J(H,H) = 7.0 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 203.5, 137.0, 129.3, 128.4, 128.2, 78.6, 54.1, 43.4, 28.7, 27.2, 26.7, 13.8; HPLC (Chiralcel OD-H, *i*-Propanol/Hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_{minor} = 10.4 min, t_{major} = 11.8 min; $[\alpha]_D$ = +52.4 (*c*=0.5 in $CHCl_3$), ee = 99%.



(*R*)-2-((*S*)-2-Nitro-1-phenylethyl)heptanal (Table 2, entry 9)**:** The title compound was prepared according the typical procedure, as described above in 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.70 (d, ^{3}J(H,H) = 3.0 Hz, 1H; CHO), 7.36-7.17 (m, 5H; Ph), 4.73-4.62 (m, 2H; CH_2), 3.80-3.75 (m, 1H; CH), 2.72-2.67 (m, 1H; CH), 1.53-1.08 (m, 8H), 0.80 (t, ^{3}J(H, H) = 7.5 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 203.4, 137.0, 129.3, 128.4, 128.2, 78.7, 54.1, 43.4, 31.8, 27.5, 26.3, 22.4, 14.0; HPLC (Chiralcel OD-H, *i*-Propanol/Hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_{minor} = 9.7 min, t_{major} = 11.0 min; $[\alpha]_D$ = +59.0 (c = 2.0, $CHCl_3$), ee = 97%.



(*R*)-2-((*S*)-1-nitro-4-phenylbutan-2-yl)pentanal (Table 2, entry 10**):** The title compound was prepared according the typical procedure, as described above in 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 9.67 (s, 1H; CHO), 7.31-7.14 (m, 5H; Ph), 4.53 (dd, ^{2}J(H,H) = 12.5 Hz, ^{3}J(H,H) = 7.0 Hz, 1H; CH); 4.46 (dd, ^{2}J(H,H) = 12.5 Hz, ^{3}J(H,H) = 6.5 Hz, 1H; CH), 2.69-2.61 (m, 3H), 2.55-2.50 (m, 1H; CH), 1.80-1.65 (m, 3H), 1.45-1.30 (m, 3H), 0.94 (t, ^{3}J(H,H) = 6.5 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 202.9, 140.4, 128.6, 128.1, 126.3, 52.0, 36.5, 33.0, 30.9, 27.5, 20.7, 14.0. HPLC (Chiralcel OD-H, *i*-Propanol/Hexane = 8/92, flow rate 0.5 mL/min, λ = 254 nm), t_{major} = 40.5 min, t_{minor} = 44.2 min; ee = 22%.



(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclohexanone[5] (Table 2, entry 11): The title compound was prepared according the typical procedure, as described above in 96% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.34-7.16 (m, 5H; Ph), 4.94 (dd, ^{2}J(H,H) = 12.5 Hz, ^{3}J(H,H) = 4.5 Hz, 1H; CH), 4.63 (dd, ^{2}J(H,H) = 12.5 Hz, ^{3}J(H,H) = 10.0 Hz, 2H; CH_2), 3.78-3.74 (m, 1H; CH), 2.75-2.64 (m, 1H; CH), 2.47-2.30 (m, 2H; CH_2), 2.10-2.00 (m, 1H; CH), 1.77-1.55 (m, 3H), 1.26-1.22 (m, 1H; CH); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 212.1, 138.0, 129.1, 128.4, 128.0, 79.1, 52.7, 44.1, 42.9, 33.4, 28.7, 25.2; HPLC (Chiralpak AS-H, *i*-Propanol/Hexane = 25/75, flow rate 1.0 mL/min, λ = 254 nm): t_{minor} = 7.9 min, t_{major} = 12.2 min; $[\alpha]_D$ = -17.3 (*c*=2.0 in $CHCl_3$), ee = 97%.

Reference:

[1] R. M. Burch, R. J. Patch, B. G. Shearer, J. J. Perumattam, K. J., Natalie, Jr., (Nova Pharmaceutical Corp., USA), WO 9203415, 1992.
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