Simple highly modular acyclic amine-catalyzed direct enantioselective additions of ketones to nitro-olefins

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Supporting Information

General. $^1$H NMR spectra were recorded on a Bruker AM-300 spectrometer for solution in CDCl$_3$ with tetramethylsilane (TMS) as internal standard; $^J$-values are in Hz. Nitro olefins except trans-$^\text{R}$-$^\text{S}$-nitrostyrene were prepared according to the literature.$^1$ Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel coated plates. Flash Column Chromatography was performed with Merck silica gel 60 (230-400 mesh) at increased pressure. The optical purities of the Michael adducts were determined by HPLC analysis using a chiral stationary phase column. The HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter ($\lambda = 589$ nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

General procedure for the conjugate addition of a ketone to a nitro-olefin

To a solution of catalyst (30 mol%) in solvents (1.0 mL) and H$_2$O (45 $\mu$L, 10 equiv.) was added the relevant ketone (0.75 mmol) and nitro-olefin (0.25 mmol). The resulting mixture was stirred for the time given in the tables. The reaction was quenched with brine and extracted with ethyl acetate (3x10 mL), the combined organic phase was dried over anhydride Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel/pentane: ethyl acetate = 10:1~4:1) to give the Michael products. The ee of the product was determined by chiral HPLC analysis. Relative ($^\text{syn}$) and absolute configuration of the product was determined by comparison with the known $^1$H-NMR data and optical rotation values. Compounds 3a, 3b, 3c, 3d, 3e, 3f and 3i are known.$^1$

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3a: a white solid: [α]$_D^{25}$ = +27.4 (c 0.5, CHCl$_3$). $^1$H NMR (CDCl$_3$, TMS, 400 MHz) δ = 7.40-7.10 (5H, m), 4.93 (1H, dd, J = 12.4, 4.4 Hz), 4.64 (1H, dd, J = 12.4, 9.6 Hz), 3.76 (1H, dt, J = 9.6, 4.4 Hz), 2.78-2.72 (1H, m), 2.52-2.32 (2H, m), 2.15-2.05 (1H, m), 1.84-1.48 (4H, m), 1.30-1.18 (1H, m). $^{13}$C NMR (CDCl$_3$, TMS, 100 MHz) δ = 211.90, 137.74, 128.93, 128.16, 127.77, 78.88, 52.53, 43.93, 42.73, 33.19, 28.51, 25.02. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 90/10, 0.5 mL/min, t$_R$ (major) = 19.45 min, t$_R$ (minor) = 22.82 min). MALDI-TOF MS: 270.1108; C$_{14}$H$_{17}$NO$_3$ (M+Na$^+$: calcld 270.1106).

3b: a white solid, [α]$_D^{25}$ = +39.2 (c 1.00, CHCl$_3$). $^1$H NMR (CDCl$_3$, TMS, 400 MHz) δ 7.83-7.75 (2H, m), 7.63 (1H, s), 7.51-7.45 (2H, m), 7.28 (1H, dd, J = 8.4, 1.8 Hz), 5.03 (1H, dd, J = 12.6, 4.5 Hz), 4.73 (1H, dd, J = 12.6, 9.9 Hz), 3.95 (1H, dt, J = 9.9, 4.5Hz), 2.84-2.73 (1H, m), 2.53-2.34 (2H, m), 2.10-2.03 (1H, m), 1.78-1.48 (4H, m), 1.33-1.19 (1H, m). $^{13}$C NMR (CDCl$_3$, TMS, 100 MHz) δ = 211.81, 135.07, 133.28, 132.76, 128.79, 127.73, 127.72, 127.59, 126.38, 126.11, 125.18, 78.79, 52.39, 44.03, 42.69, 33.23, 28.42, 24.93. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 90/10, 0.5 mL/min, t$_R$ (major) = 27.15 min, t$_R$ (minor) = 31.26 min).

3c: a white solid: [α]$_D^{25}$ = +22.7 (c 1.00, CHCl$_3$). $^1$H NMR (CDCl$_3$, TMS, 400 MHz) δ 7.08 (2H, d, J = 8.8 Hz), 6.83 (2H, d, J = 8.8 Hz), 4.91 (1H, dd, J = 12.4, 4.8 Hz), 4.57 (1H, dd, J = 12.4, 9.6 Hz), 3.77 (3H, s), 3.71 (1H, dt, J = 9.6, 4.8 Hz), 2.69-2.60 (1H, m), 2.48-2.32 (2H, m), 2.11-2.03 (1H, m), 1.88-1.50 (4H, m), 1.28-1.17 (1H, m). $^{13}$C NMR (CDCl$_3$, TMS, 100 MHz) δ = 212.01, 158.98, 129.49, 129.12, 114.26, 79.05, 55.16, 52.63, 43.16, 42.66, 33.08, 28.46, 24.95. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 90/10, 0.5 mL/min, t$_R$ (major) = 23.81 min, t$_R$ (minor) = 30.07 min).
**3d**: a yellow viscous liquid: $[\alpha]_D^{25} = +34.5$ (c 1.00, CHCl$_3$). $^1$H NMR (CDCl$_3$, TMS, 400 MHz) $\delta = 8.20$ (2H, d, $J = 8.8$ Hz), 7.38 (2H, d, $J = 8.8$ Hz), 4.98 (1H, dd, $J = 13.2$, 4.4 Hz), 4.69 (1H, dd, $J = 13.2$, 10.0 Hz), 3.92 (1H, dt, $J = 10.0$, 4.4 Hz), 2.75-2.67 (1H, m), 2.52-2.34 (2H, m), 2.14-2.09 (1H, m), 1.84-1.55 (4H, m), 1.30-1.18 (1H, m). $^{13}$C NMR (CDCl$_3$, TMS, 100 MHz) $\delta = 210.76, 147.46, 145.51, 129.29, 124.08, 77.95, 52.21, 43.73, 42.70, 33.16, 28.26, 25.08$. The ee of the product was determined by chiral HPLC analysis (Chiralpak OJ column, isohexane/2-propanol = 80/20, 0.5 mL/min, $t_R$ (major) = 101.45 min, $t_R$ (minor) = 93.69 min).

**3e**: a white solid: $[\alpha]_D^{25} = +11.8$ (c 1.00, CHCl$_3$). $^1$H NMR (CDCl$_3$, TMS, 400 MHz) $\delta = 7.33-7.25$ (3H, m), 7.15 (2H, $J = 6.8$ Hz), 4.94 (1H, dd, $J = 12.4$, 4.8 Hz), 4.61 (1H, dd, $J = 12.4$, 9.6 Hz), 3.97-3.81 (5H, m), 3.09-3.01 (1H, m), 2.74-2.65 (1H, m), 2.44 (1H, ddd, $J = 14.0$, 5.2, 3.6 Hz), 2.06-2.01 (1H, m), 1.98 (1H, dt, $J = 13.2$, 5.2 Hz), 1.68 (1H, ddd, $J = 13.2$, 5.6, 3.6 Hz), 1.54 (1H, t, $J = 13.2$ Hz). $^{13}$C NMR (CDCl$_3$, TMS, 100 MHz) $\delta = 210.32, 137.23, 128.99, 128.19, 127.86, 106.98, 78.87, 64.76, 64.50, 48.12, 43.38, 39.27, 38.57, 35.02$. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 80/20, 0.5 mL/min, $t_R$ (major) = 17.68 min, $t_R$ (minor) = 27.81 min).

**3f**: a white solid: $^1$H NMR (CDCl$_3$, TMS, 400 MHz) $\delta = 7.31-7.14$ (5H, m), 4.67 (1H, dd, $J = 8.4$, 12.0 Hz), 4.61 (1H, dd, $J = 4.8$, 12.0 Hz), 3.71-3.64 (1H, m), 2.69 (1H, dq, $J = 8.4$, 7.2 Hz), 2.23 (3H, s), 0.98 (3H, d, $J = 7.2$ Hz). $^{13}$C NMR (CDCl$_3$, TMS, 100 MHz) $\delta = 210.75, 137.42, 129.02, 127.98, 127.95, 78.40, 49.06, 45.83, 29.17, 15.91$. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 99/1, 0.9 mL/min, $t_R$ (major) = 23.24 min, $t_R$ (minor) = 29.74 min).
O
\[\text{NO}_2\]
S
\[\text{3g: a white solid: } [\alpha]_D^{25} = +28.7^\circ \text{ (c 1.0, CHCl}_3\text{). } ^1\text{H NMR (CDCl}_3\text{, TMS, 400 MHz) } \delta = 7.37-7.17 (5\text{H, m}), 4.75 (1\text{H, dd, } J = 12.4, 4.4 \text{ Hz}), 4.62 (1\text{H, dd, } J = 12.4, 9.6 \text{ Hz}), 3.76 (1\text{H, dt, } J = 10.4, 4.4 \text{ Hz}), 3.07-2.92 (3\text{H, m}), 2.88-2.75 (2\text{H, m}), 2.63-2.56 (1\text{H, m}), 2.48-2.41 (4\text{H, m}). ^{13}\text{C NMR (CDCl}_3\text{, TMS, 100 MHz) } \delta = 209.49, 136.47, 129.28, 128.27, 128.13, 78.58, 54.95, 44.48, 43.45, 35.08, 31.55. \text{ The ee of the product was determined by chiral HPLC analysis (Chiralpak AS column, isohexane/2-propanol = 50/50, 0.5 mL/min, } t_R (\text{major}) = 16.40 \text{ min, } t_R (\text{minor}) = 18.52 \text{ min).} \]
O
\[\text{NO}_2\]
O
\[\text{3h: a white solid: } [\alpha]_D^{25} = +30.2^\circ \text{ (c 1.0, CHCl}_3\text{). } ^1\text{H NMR (CDCl}_3\text{, TMS, 400 MHz) } \delta = 7.34-7.17 (5\text{H, m}), 4.93 (1\text{H, dd, } J = 12.8, 4.8 \text{ Hz}), 4.64 (1\text{H, dd, } J = 12.8, 10.4 \text{ Hz}), 4.14 (1\text{H, m}), 3.86-3.75 (2\text{H, m}), 3.70 (1\text{H, ddd, } J = 11.6, 8.8 \text{ Hz}), 2.88 (1\text{H, dddd, } J = 10.4, 8.8, 5.6, 1.2 \text{ Hz}), 2.67 (1\text{H, dddd, } J = 14.0, 10.0, 6.4, 1.2 \text{ Hz}), 2.56 (1\text{H, dt, } J = 14.0, 4.0 \text{ Hz}). ^{13}\text{C NMR (CDCl}_3\text{, TMS, 100 MHz) } \delta = 207.32, 136.21, 129.18, 128.23, 127.87, 78.64, 71.52, 68.92, 53.20, 42.91, 41.26. \text{ The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 70/30, 0.5 mL/min, } t_R (\text{major}) = 16.50 \text{ min, } t_R (\text{minor}) = 27.55 \text{ min).} \]
O
\[\text{NO}_2\]
O
\[\text{3i: a white solid (2:1 dr (anti-isomer:syn-isomer*)): } ^1\text{H NMR (CDCl}_3\text{, TMS, 400 MHz) } \delta = 8.42-7.16 (5\text{H+2.5H*, m}), 5.03 (0.5\text{H*, dd, } J = 7.7, 13.14 \text{ Hz}), 4.83 (1\text{H, dd, } J = 6.2, 13.5 \text{ Hz}), 4.74 (0.5\text{H*, dd, } J = 7.1, 13.4 \text{ Hz}), 4.65 (1\text{H, dd, } J = 8.2, 13.2 \text{ Hz}), 4.52 (0.5\text{H*, m}), 4.40 (1\text{H, m}), 4.03 (0.5\text{H*, m}), 3.86-3.80 (1\text{H, m}), 3.73 (1\text{H+0.5H*, m}), 2.17 (1.5\text{H*, s}), 2.08 (3\text{H, s}). ^{13}\text{C NMR (CDCl}_3\text{, TMS, 100 MHz) } \delta = 208.2, 206.5, 137.4, 134.0, 129.6, 129.2, 128.9, 128.7 (2\text{C}), 128.2, 78.9, 76.3, 47.2, 46.0, 26.7, 25.7. \text{ The ee of the product was determined by chiral HPLC analysis (Chiralpak OJ column, hexane/2-propanol = 70/30, 0.5 mL/min, } t_{R, \text{anti}} (\text{minor}) = 28.89 \text{ min, } t_{R, \text{anti}} (\text{major}) = 34.86 \text{ min, } t_{R, \text{syn}} (\text{major}) = 42.26 \text{ min, } t_{R, \text{anti}} (\text{minor}) = 52.59 \text{ min).} \]

**General procedure for the preparation of amino acid amides:**

A stirred solution of Boc-protected α-amino acid (5 mmol) in 30 mL dichloromethane is cooled down to -15 °C and neutralized with NMM (N-methyl morpholine, 5 mmol). Next, isobutyl chlorocarbonate (5 mmol) was added. After 20 minutes of stirring a solution of the corresponding amine (5 mmol) in 10 mL dichloromethane was added. The mixture is
stirred at -15 °C for 1 hour and is next allowed to warm up to room temperature. TLC using AMC stain monitored the reaction progress. At the completion, wash the reaction mixture was extracted with 1N HCl (3×20 mL), 1N Na2CO3 (3×20 mL), and brine (30 mL). The organic layer was dried with sodium sulphate. The product was checked with TLC and NMR, in most case it was pure enough for next step. If not, the product was purified by silica-gel column chromatography.

To a solution of protected amide (5 mmol) in 10mL CH2Cl2, TFA (5 mL) in 10 mL CH2Cl2 was added under Argon atmosphere. The reaction mixture was stirred for 1.5 hours. The reaction was checked by TLC and NMR analyses. At the completion of deprotecting, the solvent was removed in vacuum. Then methanol and water was added to the residue, the resulting mixture was treated with ammonia solution (25% NH3) to be basic, extracted with CH2Cl2 (3×10 mL). The organic layer was dried Na2SO4. The combined filtrates were evaporated under reduced pressure to give the amino amides.