Direct Catalytic Asymmetric *Anti*-Selective Mannich-type Reactions

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Supporting Information

**General.** $^1$H NMR spectra were recorded on a Bruker AM-300 spectrometer and CDCl$_3$ as the solvent and with tetramethylsilane (TMS) as the internal standard; $J$-values are in Hz. The commercially obtained reagents were used without further purification. All the 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 products 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.

**Typical procedure for the chiral amine 1 catalyzed direct asymmetric *anti*-selective Mannich-type reaction.**

In a typical experiment, the aldehyde 2 (1.5 mmol) and N-*$p$-methoxyphenyl-$\alpha$-iminoglyoxylate (0.5 mmol) were added to a round-bottomed flask charged with diphenylprolinol 1 (10 mol %) and 1 mL CH$_3$CN or CHCl$_3$. After being stirred for the time and temperature shown in the Tables, the reaction mixture was poured into H$_2$O (10 mL), extracted with EtOAc (15 mL $\times$ 3), dried with Na$_2$SO$_4$, and evaporated in *vacuo*. Purification by silica gel chromatography (ethyl acetate/pentane mixtures) gave the $\beta$-formyl amino acids 3.

**Typical procedure for the chiral amine 1 catalyzed direct asymmetric *anti*-selective Mannich-type reaction in H$_2$O.**

In a typical experiment, the aldehyde 2 (1.5 mmol) and N-*$p$-methoxyphenyl-$\alpha$-iminoglyoxylate (0.5 mmol) were added to a round-bottomed flask charged with diphenylprolinol 1 (10 mol %) and 200 $\mu$L H$_2$O. After being stirred for the time and temperature shown in the Tables, the reaction was quenched by addition of EtOAc (15 mL) and dried with Na$_2$SO$_4$. Next, filtration and evaporation of the EtOAc in *vacuo* and purification by silica gel chromatography (ethyl acetate/pentane mixtures) gave the $\beta$-formyl amino acids 3.
Ethyl-(2S,3R)-3-formyl-2-(4-methoxyphenylamino)-4-methylpentanoate 3a:

![Structure 3a]

Light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.74 (d, $J = 3.3$ Hz, 1H, CHO), 6.77 (d, $J = 8.9$ Hz, 2H, ArH), 6.66 (d, $J = 8.9$ Hz, 2H, ArH), 4.35 (d, $J = 7.8$ Hz, 1H, CHNHPMP), 4.15 (q, $J = 6.9$ Hz, 1H, OCH$_2$CH$_3$), 4.01 (bs, 1H, NH), 3.73 (s, 3H, OCH$_3$), 2.63-2.57 (m, 1H, RCHCHO), 2.18-2.02 (m, 1H, CHCH(CH$_3$)$_2$), 1.21 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): 203.2, 172.8, 153.2, 140.4, 115.9, 114.8, 61.3, 59.6, 57.2, 55.6, 32.7, 21.2, 19.2, 14.1; HPLC: (Daicel Chiralpak AS, $i$-hexane / $i$-PrOH = 97:3, flow rate: 0.5 mL/min, $\lambda$ = 254 nm): major isomer: $t_R = 24.52$ min; minor isomer: $t_R = 39.12$ min.; $[\alpha]_D^{25} = -35.1$ (c = 0.92, CHCl$_3$); MALDI-TOF MS: 294.1701; C$_{16}$H$_{24}$NO$_4$ (M+H$^+$: calcd 294.1700).

Ethyl-(2S,3R)-3-formyl-2-(4-methoxyphenylamino)octanoate 3b:

![Structure 3b]

Light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.66 (d, $J = 2.5$ Hz, 1H, CHO), 6.78 (d, $J = 8.9$ Hz, 2H, ArH), 6.66 (d, $J = 8.9$ Hz, 2H, ArH), 4.33 (d, $J = 7.1$ Hz, 1H, CHNHPMP), 4.27 (q, $J = 7.2$ Hz, 2H, OCH$_2$CH$_3$), 4.01 (bs, 1H, NH), 3.75 (s, 3H, OCH$_3$), 2.74 (m, 1H, RCHCHO), 2.13-1.31 (m, 9H, CH$_2$), 1.23 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): 202.9, 172.7, 153.5, 140.7, 116.3, 115.0, 61.7, 58.6, 55.8, 53.9, 31.9, 27.4, 25.3, 22.6, 14.4, 14.2; HPLC: 95%ee (Daicel Chiralpak AS, $i$-hexane / $i$-PrOH = 97:3, flow rate: 0.5 mL/min, $\lambda$ = 254 nm): major isomer: $t_R = 27.51$ min; minor isomer: $t_R = 35.21$ min.; $[\alpha]_D^{25} = -3.5$ (c = 1.0, CHCl$_3$).

Ethyl-(2S,3R)-3-formyl-2-(4-methoxyphenylamino)butanoate 3c:

![Structure 3c]
Light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.73 (d, $J$ = 1.3 Hz, 1H, CHO), 6.78 (d, $J$ = 8.9 Hz, 2H, ArH), 6.66 (d, $J$ = 8.9 Hz, 2H, ArH), 4.35 (d, $J$ = 8.8 Hz, 1H, CHNHPMP), 4.15 (m, 1H, OCH$_2$CH$_3$), 4.09 (bs, 1H, NH), 3.74 (s, 3H, OCH$_3$), 2.91-2.85 (m, 1H, RCHCHO), 1.23 (t, $J$ = 7.2 Hz, 3H, OCH$_2$CH$_3$), 1.17 (d, $J$ = 7.2 Hz, 3H, CHCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): 201.9, 171.8, 153.2, 140.1, 115.6, 114.9, 61.6, 58.6, 55.7, 48.5, 14.2, 9.9; HPLC: 95%ee (Daicel Chiralpak AS, $i$-hexane / $i$-PrOH = 97:3, flow rate: 0.5 mL/min, $\lambda$=254 nm): major isomer: $t_R$ = 50.21 min; minor isomer: $t_R$ = 67.01 min.; $[\alpha]_{D}^{25}$ = -29.8 (c = 1.0, CHCl$_3$).

**Ethyl-(2S,3R)-3-benzyloxy-3-formyl-2-(4-methoxyphenylamino)propionate 3d:**

Light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.71 (bs, 1H, CHO), 7.38-7.34 (m, 5H, ArH), 6.78 (d, $J$ = 8.9 Hz, 2H, ArH), 6.60 (d, $J$ = 8.9 Hz, 2H, ArH), 4.80 (d, $J$ = 11.8 Hz, 1H, ArH), 4.61 (d, $J$ = 12.5 Hz, 1H), 4.27 (d, $J$ = 1.9 Hz, 1H), 4.17-4.03 (m, 3H), 3.75 (s, 3H, OCH$_3$), 1.16 (t, $J$ = 7.2 Hz, 3H, OCH$_2$CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): 200.6, 170.9, 153.6, 140.6, 136.7, 128.8, 128.6, 128.5, 128.2, 115.6, 114.9, 83.1, 73.7, 61.8, 60.1, 55.8, 14.3; HPLC: (Daicel Chiralpak ODH, $i$-hexane / $i$-PrOH = 97:3, flow rate: 0.5 mL/min, $\lambda$=254 nm): major isomer: $t_R$ = 25.71 min; minor isomer: $t_R$ = 30.01 min.; $[\alpha]_{D}^{25}$ = -4.2 (c = 1.0, CHCl$_3$).

**Ethyl-(2S,3R)-3-formyl-2-(4-methoxyphenylamino)-4-phenyl-butanoate 3e:**
Light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.74 (bs, 1H, CHO), 7.31-7.22 (m, 5H, ArH), 6.76 (d, $J = 8.7$ Hz, 2H, ArH), 6.56 (d, $J = 8.7$ Hz, 2H, ArH), 4.22 (d, $J = 4.8$ Hz, 1H, CHNHPMP), 4.17-4.12 (m, 2H, OCH$_2$CH$_3$), 3.75 (s, 3H, OCH$_3$), 3.30 (m, 1H, RCHCHO), 3.14 (dd, $J = 13.4, 7.6$ Hz, 1H, PhCH$_2$CH), 2.94 (dd, $J = 13.4, 7.6$ Hz, 1H, PhCH$_2$CH), 1.20 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): 202.0, 172.3, 153.4, 140.3, 138.2, 129.4, 128.9, 128.6, 127.0, 116.1, 115.0, 61.9, 57.5, 55.8, 55.6; HPLC: (Daicel Chiralpak AS, i-hexane / i-PrOH = 97:3, flow rate: 0.5 mL/min, $\lambda$=254 nm): major isomer: $t_R = 48.71$ min; minor isomer: $t_R = 53.81$ min.; $\left[\alpha\right]_D^{25} = -3.3$ (c = 1.0, CHCl$_3$).

**Preparation of catalyst 1:**

![Image](image.png)

The commercially available $\alpha,\alpha$-diphenyl-2-pyrrolidinemethanol (1g, 3.95 mmol) was readily protected with TMSOTf (1.1 g, 5.1 mmol) in the presence of TEA (0.51 g, 5.1 mmol) in CH$_2$Cl$_2$ (20 mL) at 0 ºC. The reaction was stirred at room temperature for 17 h and quenched with water (10 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3x15 mL). The combined organic extracts were stirred with NaHCO$_3$ for 15 minutes, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo after filtration. Purification with silica gel column chromatography (EtOAc:pentane-1.7→1.3) furnished 10 as a thick oil (99%, 1.3 g). Catalyst 12 was prepared by the same procedure.

**1:** $^1$H NMR (CDCl$_3$, 400 MHz): δ (ppm) -0.03 (s, 9H), 1.53-1.71 (m, 4H), 2.81-2.93 (m, 2H), 4.09 (t, $J = 7.0$ Hz, 1H), 7.22-7.53 (m, 10H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ (ppm): 2.4, 25.1, 28.0, 47.3, 65.5, 83.3, 126.8, 127.0, 128.0, 129.0, 146.0, 147.0.