

# Rapid Fluorescent Screening for Bifunctional Amine-Acid Catalysts: Efficient Syntheses of Quaternary Carbon Containing Aldols under Organocatalysis

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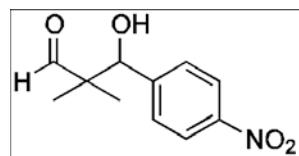
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## Supporting Information

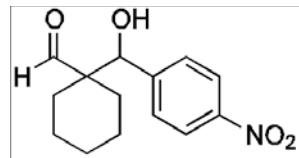
**General.** Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdc acid in ethanol followed by heating. Flash column chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm). <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on Varian Inova-399 and Mercury-300. Chemical shifts are given in *d* relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in CDCl<sub>3</sub> as solvent at room temperature, TMS served as internal standard (*d* = 0 ppm) for <sup>1</sup>H NMR, and CDCl<sub>3</sub> was used as internal standard (*d* = 77.0) for <sup>13</sup>C NMR. High-resolution mass spectra were recorded on an Ion Spec Fourier Transform Mass Spectrometer using dihydrobenzoic acid (DHB) as the matrix.

**The direct aldol reaction of *α,α*-dialkylaldehyde **7a** with *p*-nitrobenzaldehyde (**8a**) (Table 1, entry 4):** *p*-Nitrobenzaldehyde (**8a**, 0.5 mmol) was dissolved in anhydrous DMSO (0.5 mL) and isobutyraldehyde (**7a**, 0.6 mmol) was added. To the mixture acetic acid (0.125 mmol) and pyrrolidine (0.025 mmol) were added. After stirring for 2 h at room temperature, the reaction mixture was directly purified by flash column chromatography (silica gel 10 g, hexanes/ethyl acetate = 70/30) afforded the aldol product **9a** (96% yield).

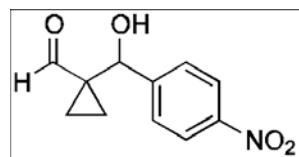
The stereochemistry of **9d** and **9e** was deduced by  $^1\text{H}$  NMR analysis according to the literature. See, Yamago, S.; Machii, D.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2098-2106. The stereochemistry of **9f** was determined by NOESY analysis after derivatization to 5-(4-isopropylbenzyl)-2,2,5-trimethyl-4-(4-nitrophenyl)[1.3]dioxane.



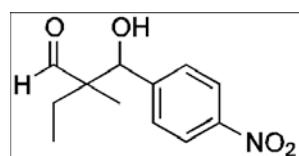
**3-Hydroxy-2,2-dimethyl-3-(4-nitrophenyl)propionaldehyde (9a):**  $R_f = 0.24$  (hexane:AcOH = 70:30);  $^1\text{H}$  NMR (300 MHz)  $\delta = 0.99$  (s, 3H, -CH<sub>3</sub>), 1.05 (s, 3H, -CH<sub>3</sub>), 2.97 (s, 1H, -OH), 5.03 (s, 1H, -CHOH), 7.48 (d,  $J = 8.4$  Hz, 2H), 8.18 (d,  $J = 8.4$  Hz, 2H), 9.59 (s, 1H, -CHO);  $^{13}\text{C}$  NMR (75 MHz)  $\delta = 15.7, 20.0, 50.8, 76.1, 123.0, 128.3, 146.8, 147.4, 205.6$ ; MALDI-FTMS: Calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>4</sub> (MNa<sup>+</sup>): 246.0737, found: 246.0746; ESI-MS 224 (MH<sup>+</sup>), 246 (MNa<sup>+</sup>).



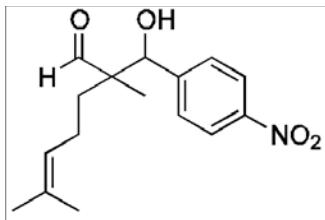
**1-[Hydroxy-(4-nitrophenyl)methyl]cyclohexanecarbaldehyde (9b):**  $R_f = 0.24$  (hexane:AcOH = 70:30);  $^1\text{H}$  NMR (400 MHz)  $\delta = 0.80-1.40$  (m, 5H), 1.50-1.80 (m, 3H), 1.90-2.10 (m, 1H), 2.10-2.25 (m, 1H), 2.60 (brs, 1H, -OH), 4.78 (s, 1H, -CHOH), 7.43 (d,  $J = 8.8$  Hz, 2H), 8.18 (d,  $J = 8.8$  Hz, 2H), 9.72 (s, 1H, -CHO);  $^{13}\text{C}$  NMR (100 MHz)  $\delta = 22.1, 22.5, 25.3, 27.1, 29.4, 53.9, 78.6, 123.1, 128.4, 147.2, 147.5, 207.9$ ; ESI-MS 298 ([M+Cl]<sup>-</sup>).



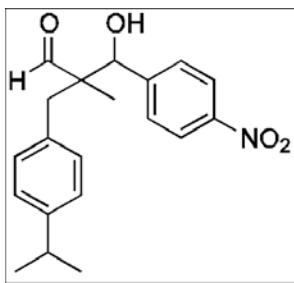
**1-[Hydroxy-(4-nitrophenyl)methyl]cyclopropanecarbaldehyde (9c):**  $R_f = 0.13$  (hexane:AcOH = 70:30);  $^1\text{H}$  NMR (400 MHz)  $\delta = 0.94-1.06$  (m 1H), 1.16-1.38 (m, 3H), 3.13 (d,  $J = 4.6$  Hz, 1H, -OH), 5.24 (d,  $J = 4.6$  Hz, 1H, -CHOH), 7.57 (d,  $J = 8.8$  Hz, 2H), 8.21 (d,  $J = 8.8$  Hz, 2H), 8.77 (s, 1H, -CHO);  $^{13}\text{C}$  NMR (75 MHz)  $\delta = 10.1, 11.8, 37.7, 71.3, 123.3, 127.5, 147.3, 147.6, 201.0$ ; ESI-MS 244 (MNa<sup>+</sup>), 220 ([M-H]<sup>-</sup>), 256 ([M+Cl]<sup>-</sup>).



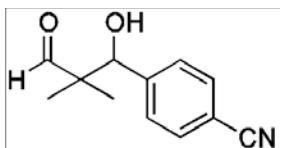
**2-[Hydroxy-(4-nitrophenyl)methyl]-2-methylbutyraldehyde (9d):**  $R_f = 0.22$  (hexane:AcOH = 70:30);  $^1\text{H}$  NMR (300 MHz, diastereomer mixtures)  $\delta = 0.80-0.95$  (m, 3H, -CH<sub>3</sub>), 1.01 (anti) and 1.05 (syn) (s, 3H, -CH<sub>3</sub>), 1.21-2.00 (m, 2H, -CH<sub>2</sub>), 2.80 (brs, 1H, -OH), 5.00 (syn) and 5.08 (anti) (s, 1H, -CHOH), 7.48 (d,  $J = 8.7$  Hz, 2H), 8.16 (syn) and 8.18 (anti) (d,  $J = 9.0$  and 8.4 Hz, 2H), 9.63 (anti) and 9.64 (syn) (s, 1H, -CHO); ESI-MS 237 (MH<sup>+</sup>).



**2-[Hydroxy-(4-nitrophenyl)methyl]-2,6-dimethylhept-5-enal (9e):**  $R_f = 0.41$  (hexane:AcOH = 70:30);  $^1\text{H}$  NMR (400 MHz, diastereomer mixtures)  $\delta = 1.04$  (anti) and 1.06 (syn) (s, 3H, -CH<sub>3</sub>), 1.10-1.75 (m, 2H, -CH<sub>2</sub>), 1.56 (s, 3H, -CH<sub>3</sub>), 1.66 (s, 3H, -CH<sub>3</sub>), 1.80-2.05 (m, 2H, -CH<sub>2</sub>), 2.86 (brs, 1H, -OH), 4.90-5.05 (m, 1H, -CH=), 5.00 (syn) and 5.09 (anti) (s, 1H, -CHOH), 7.50 (d,  $J = 8.6$  Hz, 2H), 8.20 (d,  $J = 8.6$  Hz, 2H), 9.66 (anti) and 9.68 (syn) (s, 1H, -CHO); ESI-MS 292 (MH<sup>+</sup>), 314 (MNa<sup>+</sup>), 326 ([M+Cl]<sup>-</sup>).



**3-Hydroxy-2-(4-isopropylbenzyl)-2-methyl-3-(4-nitrophenyl)propionaldehyde (9f):**  $R_f = 0.40$  (hexane:AcOH = 70:30);  $^1\text{H}$  NMR (300 MHz, diastereomer mixtures)  $\delta = 0.97$  (anti) and 1.04 (syn) (s, 3H, -CH<sub>3</sub>), 1.21 (syn) and 1.22 (anti) (d,  $J = 6.9$  and 7.2 Hz, 6H, 2X-CH<sub>3</sub>), 2.54 (syn) and 2.68 (anti) (d,  $J = 13.5$  and 13.5 Hz, 1H), 2.74-3.20 (m, 2H, -CH, -OH), 2.97 (anti) and 3.38 (syn) (d,  $J = 13.5$  and 13.5 Hz, 1H), 4.97 (anti) and 5.05 (syn) (s, 1H, -CHOH), 6.90-7.04 (m, 2H), 7.06-7.16 (m, 2H), 7.45 (anti) and 7.51 (syn) (d,  $J = 9.0$  and 8.7 Hz, 2H), 8.12-8.22 (m, 2H), 9.54 (syn) and 9.72 (anti) (s, 1H, -CHO); MALDI-FTMS: Calcd for C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub> (MNa<sup>+</sup>): 364.1519, found: 364.1515.



**3-Hydroxy-2,2-dimethyl-3-(4-cyanophenyl)propionaldehyde (9g):**  $R_f = 0.20$  (hexane:AcOH = 70:30);  $^1\text{H}$  NMR (400 MHz)  $\delta = 0.96$  (s, 3H, -CH<sub>3</sub>), 1.04 (s, 3H, -CH<sub>3</sub>), 3.80 (brs, 1H, -OH), 4.97 (s, 1H, -CHOH), 7.44 (d,  $J = 8.4$  Hz, 2H), 7.63 (d,  $J = 8.4$  Hz, 2H), 9.62 (s, 1H, -CHO);  $^{13}\text{C}$  NMR (100 MHz)  $\delta = 15.5, 19.7, 50.7, 76.3, 111.5, 118.6, 128.2, 131.6, 145.1, 205.9$ ; ESI-MS 202 ([M-H]<sup>-</sup>), 238 ([M+Cl]<sup>-</sup>).

