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Supporting Information

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Highly Enantioselective Conjugate Reduction of ß,ß-Disubstituted a,ß-Unsaturated Nitriles**

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Experimental

General Methods. Toluene was distilled from sodium benzophenone ketyl under nitrogen. $Cu(OAc)_2$. Hydrosilanes and other commercial substrates were purchased from Aldrich and used as received. Nitrile substrates (**1a-1f**) were prepared from the corresponding ketones with diethyl cyanomethylphosphonate by the literature procedure.[1] All reactions were carried out under a nitrogen atmosphere, in an oven-dried Schlenk tube and run two or more times. Flash chromatography was performed on silica gel from Merck (70–230 mesh). All ^1H NMR spectra were obtained on Varian Mercury 400 systems and reported parts per million (ppm) downfield from tetramethylsilane. ^{13}C NMR spectra are reported in ppm referenced to deuteriochloroform (77.2 ppm). Infrared spectra (IR) were obtained on Nicolet 205 FT-IR and are recorded in cm^{-1}. HPLC analyses were performed on a Varian Prostar.

Preparation of a,ß-unsaturated nitriles. NaH (15 mmol, 360 mg) was placed in an oven-dried 250 mL two-neck round bottom flask. THF (40 mL) were added under nitrogen. The reaction mixture was cooled and diethyl cyanomethylphosphonate (12 mmol, 1.89 mL) was added dropwise with stirring at 0 °C. The solution was stirred at room temperature for 1 h until gas evolution had ceased. And then, ketone (10mmol) was added to the yellow solution dropwise, maintained below 25 ℃. During the addition, a gummy precipitate appeared. The solution was stirred at room temperature until no starting material was detected by TLC. The reaction mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The product was purified by silica gel chromatography.

[1] W. S. Wadsworth, W. D. Emmons, *J. Am. Chem. Soc*. **1961**, *83*, 1733- 1738.

(*E*)-3-Phenyl-but-2-enenitrile (1a).[2] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.45- 7.37 (m, 5H), 5.60 (q, *J* = 1.1 Hz, 1H), 2.46 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 159.9, 138.3, 130.4, 129.0, 126.0, 117.8, 95.8, 20.6; IR (neat): 3062, 2980, 2213, 1609, 1495, 1380 cm^{-1}.

(*Z*)-3-Phenyl-but-2-enenitrile (1a).[2] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.55- 7.40 (m, 5H), 5.40 (q, *J* = 1.5 Hz, 1H), 2.29 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 161.1, 138.0, 130.0, 128.8, 127.2, 117.8, 95.7, 25.1; IR (neat): 3057, 2954, 2214, 1611, 1494, 1378 cm^{-1}.

(*E*)-3-(4-Chloro-phenyl)-but-2-enenitrile (1b).[3] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.37- 7.36 (m, 4H), 5.59 (q, *J* = 1.1 Hz, 1H), 2.44 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 158.4, 136.7, 136.5, 129.2, 127.3, 117.5, 96.2, 20.6; IR (neat): 3063, 2922, 2212, 1607, 1590, 1444, 1379, 734, 692, 550 cm^{-1}.

(*E*)-3-p-Tolyl-but-2-enenitrile (1c). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.35 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.58 (q, *J* = 1.1 Hz, 1H), 2.44 (d, *J* = 1.1 Hz, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 159.6, 140.8, 135.4, 129.7, 125.9, 118.1, 94.7, 21.7, 20.5; IR (neat): 3129, 2918, 2204, 1642, 1598, 1441, 1380, 804 cm^{-1}.

(*E*)-3-Phenyl-pent-2-enenitrile (1d).[3] Colorless oil; ^{1}H NMR (400MHz, $CDCl_3$): d = 7.39- 7.24 (m, 5H), 5.50 (s, 1H), 2.89 (q, *J* = 7.5 Hz, 2H), 1.13 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 166.5, 137.4, 130.2, 129.1, 126.5, 117.6, 95.2, 27.7, 13.8; IR (film): 3059, 2981, 2213, 1603, 1465, 1445, 1378, 760, 693 cm^{-1}.

(*Z*)-4-Methyl-3-phenyl-pent-2-enenitrile (1e).[4] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.45- 7.20 (m, 5H), 5.24 (s, 1H), 3.33 (sept, *J* = 7.0 Hz, 1H), 1.24 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 172.2, 138.9, 129.1, 128.5, 127.2, 117.0, 94.6, 34.9, 21.6; IR (film): 3056, 2975, 2214, 1683, 1596, 1463, 1365, 765, 697 cm^{-1}.

(*E*)-3-o-Tolyl-but-2-enenitrile (1g). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.24- 7.03 (m, 4H), 5.23 (q, *J* = 1.1 Hz, 1H), 2.36 (d, *J* = 1.1 Hz, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 163.5, 140.5, 134.1, 130.9, 128.8, 127.1, 126.2, 117.0,

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[2] T. Nishimura, Y. Nishiguchi, Y. Maeda, S. Uemura, *J. Org. Chem.* **2004**, *69*, 5342- 5347.

[3] C.-Q. Zhao, X. Huang, *Synth. Commun.* **1996**, *26*, 3607- 3611.

[4] a) F. F. Fleming, B. C. Shook, *J. Org. Chem.* **2002**, *67*, 3668- 3672; b) G. Jones, R. F. Maisey, *Chem. Commun.* **1968**, 543- 545.

99.3, 23.4, 20.2; IR (film): 2218 cm^{-1}. The stereochemical assignment was made on the basis of the small allylic coupling constant (J = 1.1 Hz) of the olefinic hydrogen compared with that of the other isomer (J = 1.5 Hz).[4b]

(*E*)-3-Pyridin-2-yl-but-2-enenitrile (1f). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): d = 8.61 (m, 1H), 7.77- 7.24 (m, 3H), 6.45 (s, 1H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 157.1, 153.9, 149.7, 137.1, 124.8, 120.8, 117.9, 98.7, 18.8; IR (neat): 3061, 2964, 2211, 1691, 1617, 1434, 1379 cm^{-1}; Anal. Calcd for $C_9H_8N_2$, C 74.98, H 5.59, N 19.43. Found C 74.99, H 5.46, N 19.50. The (*E*)-isomer was assigned by a nuclear Overhauser enhancement (NOE) study; irradiation of the methyl hydrogens at d 2.50 gave a 0% enhancement of the olefin hydrogen. Based on this observation, the stereochemistry of the isomer was as indicated.

General Procedure for the 1,4-reduction of a,ß-unsaturated nitriles using $Cu(OAc)_2$ and (*S,R*)-Josiphos. $Cu(OAc)_2$ (2.72 mg, 0.015 mmol) and Josiphos ligand (8.92 mg, 0.015 mmol) were placed in an oven-dried Schlenk tube and PMHS (0.12 mL, 2 mmol) and toluene (0.5 mL) were added under nitrogen. The reaction mixture was stirred for 5 min at 0 ? and then, a,ß-unsaturated nitrile (0.5 mmol) was added, followed by *t*BuOH (0.191 mL, 2.0 mmol). The reaction tube was washed with toluene (0.5 mL), sealed, and stirred until no starting material was detected by TLC. The reaction mixture was quenched with water and transferred to a round bottom flask with an aid of Et_2O (10 mL), and NaOH (2.5 M, 1.2 mL) was added. The biphasic mixture was stirred vigorously for 0.5 h. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The product was purified by silica gel chromatography or Kugelrohr distillation.

(*S*)-3-Phenyl-butyronitrile (Table 1, entry 4). The title compound was isolated as a colorless oil in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.35- 7.21 (m, 5H), 3.15 (m, 1H), 2.61 (dd, J = 16.7 Hz, 6.4 Hz, 1H), 2.54 (dd, J = 16.7 Hz, 7.5 Hz, 1H), 1.45 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) d = 143.2, 129.0, 127.5, 126.7, 118.8, 36.9, 26.8, 21.1; IR (neat): 3029, 2968, 2246, 1602, 1453, 1381 cm^{-1}; The ee (97% ee) was measured by chiral HPLC on a OD-H column (IPA:HEX = 5:95, 0.5 mL/min): (*S*) isomer t_r = 21.4 min and (*R*) isomer t_r = 23.7 min. The stereochemical assignment was made by comparison with the optical rotation of the corresponding ester derivative.[5]

[5] D. H. Appella, Y. Moritani, R. Shintani, E. M. Ferreira, S. L. Buchwald, *J. Am. Chem .Soc.* **1999**, *121*,

$[a]_D^{20}$ = +21.99° (c =0.74, $CHCl_3$).

3-(4-Chloro-phenyl)-butyronitrile (Table 2, entry 1). The title compound was isolated as a colorless oil in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.31- 7.16 (m, 4H), 3.14 (m, 1H), 2.59 (dd, *J* = 15.6 Hz, 5.7 Hz, 1H), 2.53 (dd, *J* = 15.6 Hz, 6.0Hz, 1H), 1.43 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 141.6, 133.2, 129.1, 128.1, 118.4, 36.3, 26.7, 21.0; IR (neat): 2968, 2931, 2246, 1653, 1494, 1456, 1381, 826, 556 cm^{-1}; The ee (97% ee) was measured by chiral HPLC on a OD-H column (IPA:HEX = 5:95, 0.5 mL/min); major isomer t_r = 21.8 min and minor isomer t_r = 23.5 min.

(*S*)-3-*p*-Tolyl-butyronitrile (Table 2, entry 3).[6] The title compound was isolated as a colorless oil in 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.24- 7.07 (m, 4H), 3.12 (m, 1H), 2.56 (dd, *J* = 16.7 Hz, 6.4 Hz, 1H), 2.52 (dd, *J* = 16.7 Hz, 7.5 Hz, 1H), 2.32 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 140.3, 137.1, 129.6, 126.5, 118.8, 36.5, 26.8, 21.4, 21.1; IR (neat): 3023, 2924, 2874, 2246, 1654, 1458, 816.28 cm^{-1}; The ee (95% ee) was measured by chiral HPLC on a OD-H column (IPA:HEX = 5:95, 0.5 mL/min); (*S*) isomer t_r = 17.1 min and (*R*) isomer t_r = 19.6 min. $[a]_D^{20}$ = -4.56° (c =0.99, Hexane).

3-Phenyl-pentanenitrile (Table 2, entry 4). The title compound was isolated as a colorless oil in 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.35- 7.13 (m, 5H), 2.85 (m, 1H), 2.60 (d, *J* = 7.0 Hz, 2H), 1.94- 1.84 (m, 1H), 1.81- 1.70 (m, 1H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 141.7, 128.9, 127.5, 127.3, 118.8, 44.2, 28.3, 25.2, 12.3; IR (neat): 3029, 2965, 2930, 2245, 1602, 1494, 1453, 1381, 760, 701 cm^{-1}; The ee (98% ee) was measured by chiral HPLC on a OD-H column (IPA:HEX = 5:95, 0.5 mL/min); major isomer t_r = 18.6 min and minor isomer t_r = 21.8 min.

4-Methyl-3-phenyl-pentanenitrile (Table 2, entry 5). The title compound was isolated as a colorless oil in 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.34- 7.17 (m, 5H), 2.75- 2.61 (m, 3H), 2.1 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 141.3, 128.8, 127.9, 127.4, 119.1, 49.5, 32.4, 22.8, 21.1, 20.8; IR (neat): 3029, 2961, 2245, 1602, 1493, 1453, 1388, 771, 702 cm^{-1}; The ee (99% ee) was measured by chiral HPLC on a OD-H column (IPA:HEX = 5:95, 0.5 mL/min); major isomer t_r = 16.5 min and minor isomer t_r = 22.8 min.

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[6] K. Mori, *Tetrahedron: Asymmetry* **2005**, *16*, 685- 692.

3-*o*-Tolyl-butyronitrile (Table 2, entry 6). The title compound was isolated as a colorless oil in 92% yield by using (*R*,*S*)-Josiphos as the ligand; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.24- 7.01 (m, 4H), 3.42 (m, 1H), 2.59 (dd, *J* = 16.7 Hz, 6.0 Hz, 1H), 2.52 (dd, *J* = 16.7 Hz, 7.9 Hz, 1H), 2.35 (s, 3H) 1.42 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 141.4, 135.3, 130.9, 127.2, 126.8, 124.9, 119.0, 32.1, 25.7, 20.9, 19.8; IR (neat): 2246 cm^{-1}; The ee (98% ee) was measured by chiral HPLC on a OD-H column (IPA:HEX = 10:90, 0.5 mL/min); minor isomer t_r = 17.3 min and major isomer t_r = 27.1 min.

3-Pyridin-2-yl-butyronitrile (Table 2, entry 7). The title compound was isolated as a colorless oil in 96% yield; ^{1}H NMR (400 MHz, $CDCl_3$): d = 8.57 (d, *J* = 4.4 Hz, 1H), 7.68-7.64 (m, 1H), 7.27-7.17 (m, 2H), 3.31 (m, 1H), 2.84 (dd, *J* = 16.7 Hz, 6.4 Hz, 1H), 2.74 (dd, *J* = 16.7 Hz, 7.1 Hz, 1H), 1.46 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d = 161.6, 149.6, 136.9, 122.4, 121.9, 119.2, 38.4, 24.4, 20.6; IR (neat): 3010, 2970, 2246, 1591, 1474, 1435, 1375 cm^{-1}; Anal. Calcd for $C_9H_{10}N_2$, C 73.94, H 6.89, N 19.16. Found C 74.00, H 6.91, N 19.02; The ee (65% ee) was measured by chiral HPLC on a AS-H column (IPA:HEX = 10:90, 0.5 mL/min); minor isomer t_r = 24.8 min and major isomer t_r = 28.5 min.