

Supporting Information

One-pot cross-double Mannich reaction of acetaldehyde catalyzed by a binaphthyl-based amino sulfonamide

Taichi Kano, Ryu Sakamoto, Yukako Yamaguchi, Ken-ichi Itoh and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University

Sakyo, Kyoto 606-8502, Japan

General Information. Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ¹H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane and dimethyl sulfoxide-D₆ as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quintet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ¹³C NMR spectra were recorded on a JEOL JNM-FX400 (100 MHz) spectrometer. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using a Daicel CHIRALPAK AD-H 4.6 mm × 25 cm column. The high-resolution mass spectra (HRMS) were performed on Applied Biosystems Mariner 8295 API-TOF workstation. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF₂₅₄, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230-400 mesh).

In experiments requiring dry solvents, tetrahydrofuran (THF) were purchased from Kanto Chemical Co. Inc. as “Dehydrated”. Chloroform (CHCl₃) was stored over 4Å molecular sieves. Acetaldehyde was distilled and stored under argon atmosphere at -17 °C. The following products are all known: axially chiral amino sulfonamide (*S*)-**1**,¹ ethyl (4-methoxyphenylimino)acetate,² *N*-protected imines were prepared according to the literature procedure.^{3,4} Other simple chemicals were purchased and used as such.

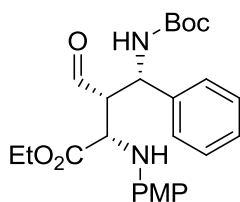
di-*tert*-Butyl ((1*S*,3*S*)-2-Formyl-1,3-diphenylpropane-1,3-diyl)dicarbamate (4**):** To a solution of *N*-Boc-protected imine **2a** (25.7 mg, 0.125 mmol) in acetaldehyde (250 μL) was added a chiral amino

sulfonamide (*S*)-**1** (2.7 mg, 0.00625 mmol) at 0 °C. After stirring for 3 h, the reaction mixture was evaporated and vacuumed. The residue and the additional catalyst (*S*)-**1** (2.7 mg, 0.00625 mmol) were dissolved in CHCl₃ (125 μL). To the mixture was added *N*-Boc-protected imine **2a** (38.6 mg, 0.1875 mmol) in CHCl₃ (125 μL) slowly over the course of 4 h with syringe pump at 0 °C. After stirring for 2 h, the reaction mixture was quenched with saturated NH₄Cl and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel to afford the double-Mannich adduct **4** (75% yield, 99% ee). Spectral data of **4** were in accordance with those previously reported.⁵

The relative and absolute configuration of **4** was determined as follows. The absolute configuration of the first Mannich adduct **3** was determined to be (*S*) based on the literature data.^{6,7} The relative stereochemistry of double-Mannich adduct **4** was assigned to be the *anti* configuration by comparison of the NMR spectra with the literature data.⁵ Based on these information, the absolute configuration of **4** obtained in the reaction catalyzed by (*S*)-**1** was determined to be (1*S*,3*S*).

General Procedure for the One-pot Double Mannich Reaction of Two Different Imines Catalyzed by (*S*)-1** (Table 2):** To a solution of *N*-Boc-protected imine (0.125 mmol) in acetaldehyde (250 μL) was added a chiral amino sulfonamide (*S*)-**1** (2.7 mg, 0.00625 mmol) at 0 °C. After stirring for 3 h, the reaction mixture was evaporated and vacuumed. The residue was dissolved in THF (1.25 mL). To the mixture were added (*S*)-**1** (2.7 mg, 0.00625 mmol) and ethyl (4-methoxyphenylimino)acetate **5** (38.8 mg, 0.1875 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was quenched with saturated NH₄Cl and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel to afford corresponding product.

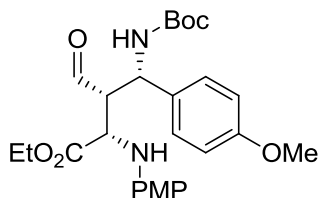
Ethyl (2*S*,3*R*,4*S*)-4-((*tert*-Butoxycarbonyl)amino)-3-formyl-2-((4-methoxyphenyl)amino)-4-phenyl-



butanoate (Table 2, entry 1): $[\alpha]_D^{24} = 25.3$ (*c* 1.1, CHCl₃, 99% ee), ¹H NMR (400 MHz, CDCl₃) δ 9.77 (1H, s, CHO), 7.44-7.41 (2H, m, ArH), 7.36-7.32 (3H, m, ArH), 6.74-6.70 (2H, m, ArH), 6.62 (1H, d, *J* = 9.9 Hz, NH), 6.47 (2H, d, *J* = 8.9 Hz, ArH), 5.82-5.79 (1H, m, NH), 4.32 (1H, d, *J* = 11.4 Hz, ArCH), 4.05 (2H, q, *J* = 7.1 Hz, CH₂CH₃), 3.86-3.78 (1H, m, CHCHO), 3.74 (4H, app s, OCH₃ and CHCO₂Et), 1.40 (9H, s, C(CH₃)₃), 1.14 (3H, t, *J* = 7.1 Hz, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 200.9, 172.5, 155.2, 153.9, 140.9, 139.1, 129.1, 127.9, 126.2, 117.4, 80.0, 61.6, 58.5, 56.4, 55.6, 52.5, 28.3, 13.9; IR (neat) 3354, 2978, 1717, 1514, 1244, 1167, 1030, 735 cm⁻¹; HRMS (ESI-TOF)

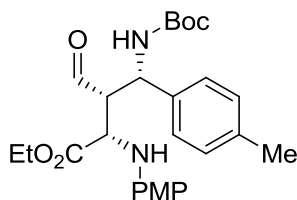
Calcd. for $C_{25}H_{32}N_2NaO_6$: 479.2153 ($[M + Na]^+$), Found: 479.2175 ($[M + Na]^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, retention time; 54.5 min (major) and 58.7 min.

Ethyl (2*S*,3*R*,4*S*)-4-((*tert*-Butoxycarbonyl)amino)-3-formyl-4-(4-methoxyphenyl)-2-((4-methoxyphenyl)amino)butanoate (Table 2, entry 2): $[\alpha]_D^{24} = 93.2$ (*c* 0.5, $CHCl_3$, 99% ee), 1H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s, CHO), 7.26 (2H, d, *J* = 8.7 Hz, ArH), 6.94 (2H, d, *J* = 8.7 Hz, ArH), 6.73 (2H, d, *J* = 8.9 Hz, ArH), 6.57 (1H, br, NH), 6.52 (2H, d, *J* = 8.9 Hz, ArH), 5.74-5.71 (1H, m, NH), 4.33 (1H, d, *J* = 11.4 Hz, ArCH), 4.06 (2H, q, *J* = 6.9 Hz, CH_2CH_3),

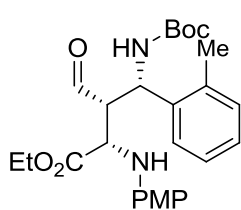


3.89-3.77 (1H, m, $CHCHO$), 3.84 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.65 (1H, m, $CHCO_2Et$), 1.40 (9H, s, $C(CH_3)_3$), 1.14 (3H, t, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 172.5, 159.2, 155.2, 153.9, 140.9, 131.1, 127.3, 117.4, 114.6, 114.5, 80.0, 61.6, 58.6, 56.4, 55.6, 55.4, 52.1, 28.3, 14.0; IR (neat) 3358, 2930, 1715, 1512, 1246, 1167, 1032, 829 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $C_{26}H_{34}N_2NaO_7$: 509.2258 ($[M + Na]^+$), Found: 509.2268 ($[M + Na]^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 4/1, flow rate = 0.5 mL/min, retention time; 30.1 min and 39.1 min (major).

Ethyl (2*S*,3*R*,4*S*)-4-((*tert*-Butoxycarbonyl)amino)-3-formyl-2-((4-methoxyphenyl)amino)-4-(*p*-tolyl)butanoate (Table 2, entry 3): $[\alpha]_D^{24} = 39.6$ (*c* 0.88, $CHCl_3$, 99% ee), 1H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, s, CHO), 7.26-7.16 (4H, m, ArH), 6.73 (2H, d, *J* = 8.2 Hz, ArH), 6.58 (1H, d, *J* = 9.2 Hz, NH), 6.51 (2H, d, *J* = 8.5 Hz, ArH), 5.76-5.73 (1H, m, NH), 4.32 (1H, d, *J* = 11.4 Hz, ArCH), 4.05 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 3.88 (1H, m, $CHCHO$), 3.75 (3H, s, OCH_3), 3.76 (1H, br, $CHCO_2Et$), 2.38 (3H, s, $ArCH_3$), 1.39 (9H, s, $C(CH_3)_3$), 1.13 (3H, t, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 172.5, 155.2, 153.9, 140.9, 137.5, 136.1, 129.8, 126.1, 117.5, 114.6, 80.0, 61.6, 58.6, 56.4, 55.6, 52.4, 28.3, 21.1, 14.0; IR (neat) 3363, 2978, 1714, 1512, 1244, 1167, 1030, 741 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $C_{26}H_{34}N_2NaO_6$: 493.2309 ($[M + Na]^+$), Found: 493.2307 ($[M + Na]^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, retention time; 36.8 min and 45.4 min (major).

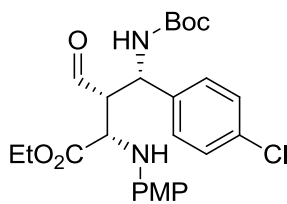


Ethyl (2*S*,3*R*,4*S*)-4-((*tert*-Butoxycarbonyl)amino)-3-formyl-2-((4-methoxyphenyl)amino)-4-(*o*-tolyl)butanoate (Table 2, entry 4): $[\alpha]_D^{24} = 29.7$ (*c* 0.8, $CHCl_3$, 99% ee), 1H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s, CHO), 7.38-7.12 (4H, m, ArH), 6.80-6.76 (2H, m, ArH), 6.69 (1H, d, *J* = 9.2 Hz, NH), 6.63



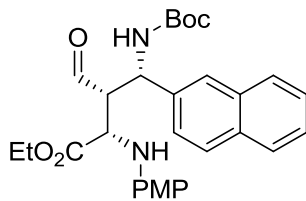
(2H, d, $J = 8.9$ Hz, ArH), 5.91-5.88 (1H, m, NH), 4.43 (1H, d, $J = 11.6$ Hz, ArCH), 4.04 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 3.87 (1H, app d, $J = 9.9$ Hz, CHCHO), 3.76 (3H, s, OCH_3), 3.61 (1H, br, CHCO_2Et), 2.52 (3H, s, ArCH_3), 1.38 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.11 (3H, t, $J = 7.1$ Hz, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 200.7, 172.5, 155.1, 153.8, 140.8, 137.5, 134.6, 131.3, 127.9, 126.5, 126.2, 117.1, 114.6, 80.0, 61.6, 56.3, 55.9, 55.6, 49.9, 28.3, 19.2, 13.9; IR (neat) 3365, 2978, 1717, 1513, 1368, 1242, 1165, 1036 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{NaO}_6$: 493.2309 ($[\text{M} + \text{Na}]^+$), Found: 493.2307 ($[\text{M} + \text{Na}]^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, retention time; 32.7 min and 35.1 min (major).

Ethyl (2S,3R,4S)-4-((tert-Butoxycarbonyl)amino)-4-(4-chlorophenyl)-3-formyl-2-((4-methoxyphenyl)amino)butanoate (Table 2, entry 5):



$[\alpha]_D^{24} = 28.8$ (c 1.0, CHCl_3 , 98% ee), ^1H NMR (400 MHz, CDCl_3) δ 9.75 (1H, s, CHO), 7.40 (2H, d, $J = 8.7$ Hz, ArH), 7.29 (2H, d, $J = 8.2$ Hz, ArH), 6.75 (2H, d, $J = 8.7$ Hz, ArH), 6.66 (1H, d, $J = 8.9$ Hz, NH), 6.51 (2H, d, $J = 8.7$ Hz, ArH), 5.77-5.73 (1H, m, NH), 4.34 (1H, d, $J = 11.6$ Hz, ArCH), 4.06 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 3.85-3.78 (1H, m, CHCHO), 3.75 (3H, s, OCH_3), 3.66 (1H, m, CHCO_2Et), 1.39 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.14 (3H, t, $J = 7.1$ Hz, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 200.4, 172.2, 155.1, 154.0, 140.6, 137.9, 133.8, 129.3, 127.6, 117.4, 114.7, 80.3, 61.7, 58.2, 56.2, 55.6, 52.2, 28.3, 14.0; IR (neat) 3362, 2978, 1713, 1512, 1491, 1241, 1165, 1028 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $\text{C}_{25}\text{H}_{31}\text{ClN}_2\text{NaO}_6$: 513.1763 ($[\text{M} + \text{Na}]^+$), Found: 513.1758 ($[\text{M} + \text{Na}]^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, retention time; 48.1 min and 60.1 min (major).

Ethyl (2S,3R,4S)-4-((tert-Butoxycarbonyl)amino)-3-formyl-2-((4-methoxyphenyl)amino)-4-(naphthalen-2-yl)butanoate (Table 2, entry 6):



$[\alpha]_D^{24} = 49.5$ (c 0.62, CHCl_3 , 99% ee), ^1H NMR (400 MHz, CDCl_3) δ 9.82 (1H, s, CHO), 7.91 (1H, d, $J = 8.5$ Hz, ArH), 7.87 (1H, dd, $J = 5.9, 3.7$ Hz, ArH), 7.81-7.78 (2H, m, ArH), 7.52 (2H, dd, $J = 6.2, 3.3$ Hz, ArH), 7.47 (1H, dd, $J = 8.6, 1.6$ Hz, ArH), 6.79 (1H, d, $J = 8.9$ Hz, NH), 6.67 (2H, d, $J = 8.7$ Hz, ArH), 6.48 (2H, d, $J = 8.9$ Hz, ArH), 5.97-5.93 (1H, m, NH), 4.38 (1H, d, $J = 11.4$ Hz, ArCH), 4.03 (2H, q, $J = 7.3$ Hz, CH_2CH_3), 3.85-3.79 (2H, m, CHCHO , CHCO_2Et), 3.72 (3H, s, OCH_3), 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.11 (3H, t, $J = 7.0$ Hz, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 200.7, 172.4, 155.3, 153.9, 140.8, 136.6, 133.4, 132.9, 129.2, 128.0, 127.7, 126.7, 126.3, 125.3, 124.0, 117.4, 114.6, 80.2, 61.6, 58.4, 56.4, 55.6,

52.9, 28.3, 14.0; IR (neat) 3361, 2978, 1715, 1512, 1242, 1165, 1030, 735 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $\text{C}_{29}\text{H}_{34}\text{N}_2\text{NaO}_6$: 529.2309 ($[\text{M} + \text{Na}]^+$), Found: 523.2305 ($[\text{M} + \text{Na}]^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, retention time; 52.3 min and 65.0 min (major).

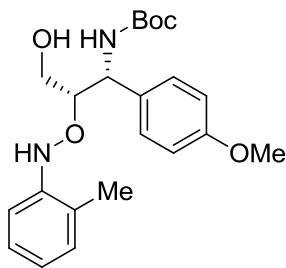
Table S1 Effects of additive in the Asymmetric Aminoxylation of **7** Catalyzed by (*S*)-**1**^a

Entry	Additive	Yield (%) ^b
1	none	27
2	PhCHO (1 equiv)	33
3	PhCHO (5 equiv)	47
4	CCl_3CHO (5 equiv)	n.r.

^a The reaction of aldehyde **7** (0.1 mmol) with 1-methyl-2-nitrosobenzene (0.1 mmol) was carried out in the presence of (*S*)-**1** (0.005 mmol) and an additive in CHCl_3 (50~100 μL) at 0 °C for 2 h. ^b Isolated yield after reduction with NaBH_4 .

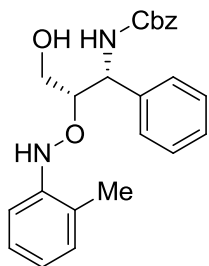
General Procedure for the Asymmetric One-pot Mannich Reaction-Aminoxylation Catalyzed by (*S*)-1**:** To a solution of *N*-protected imine (0.125 mmol) in acetaldehyde (250 μL) was added a chiral amino sulfonamide (*S*)-**1** (2.7 mg, 0.00625 mmol) at 0 °C. After stirring for 3 h, the reaction mixture was evaporated and vacuumed. The residue was dissolved in CHCl_3 (62.5 μL). To the mixture were added (*S*)-**1** (2.7 mg, 0.0625 mmol), 1-methyl-2-nitrosobenzene (15.1 mg, 0.125 mmol) and benzaldehyde (62.5 μL , 0.625 mmol) at 0 °C. The mixture was stirred for 2 h. To the reaction mixture was then added MeOH (1.0 mL) and NaBH_4 (14 mg, 0.375 mmol) at 0 °C. After 30 min of stirring at 0 °C, the reaction mixture was quenched with 1N HCl and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel to afford corresponding product.

***tert*-Butyl ((1*R*,2*S*)-3-Hydroxy-1-(4-methoxyphenyl)-2-((*o*-tolylamino)oxy)propyl)carbamate (**8a**):** $[\alpha]_{\text{D}}^{24} = -28.3$ (*c* 1.2, CHCl_3 , 99% ee), ¹H NMR (400 MHz, CDCl_3) δ 7.52 (1H, br, ONH), 7.29-7.26 (2H, m, ArH), 7.11 (1H, t, *J* = 7.6 Hz, ArH), 7.04 (2H, t, *J* = 8.0 Hz, ArH), 6.91-6.86 (3H, m, ArH), 5.26 (1H, br, NH), 5.15 (1H, br, ArCH), 4.05 (1H, dd, *J* = 11.0, 5.0 Hz, CHONH), 3.87-3.71 (5H, m, OCH_3 , CH_2OH), 3.17 (1H, br, OH), 2.10 (3H, s, ArCH_3), 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$); ¹³C NMR (100 MHz, CDCl_3)



δ 159.2, 156.4, 145.9, 131.3, 130.1, 128.0, 126.8, 123.5, 122.0, 114.5, 114.2, 85.7, 80.1, 62.5, 55.3, 53.5, 28.3, 16.8; IR (neat) 3414, 2976, 1694, 1512, 1248, 1169, 1036, 762 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{NaO}_5$: 425.2047 ($[\text{M} + \text{Na}]^+$), Found: 425.2047 ($[\text{M} + \text{Na}]^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 4/1, flow rate = 0.5 mL/min, retention time; 28.4 min (major) and 31.1 min.

Benzyl ((1*R*,2*S*)-3-Hydroxy-1-phenyl-2-((*o*-tolylamino)oxy)propyl)carbamate (8b): $[\alpha]_{\text{D}}^{24} = -21.0$



(*c* 0.9, CHCl_3 , 99% ee), ^1H NMR (400 MHz, CDCl_3) δ 7.43 (1H, br, NHCH), 7.40-7.25 (10H, m, ArH), 7.10-6.98 (3H, m, ArH), 6.88 (1H, t, $J = 7.4$ Hz, ArH), 5.58 (1H, br, NH), 5.25 (1H, br, ArCH), 5.14-5.07 (2H, m, $\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$), 4.13 (1H, dd, $J = 11.2, 4.8$ Hz, CHONH), 3.83-3.74 (2H, m, CH_2OH), 2.96 (1H, br, OH), 2.07 (3H, s, ArCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 145.7, 138.9, 136.2, 130.2, 129.0, 128.6, 128.2, 128.1, 128.0, 126.90, 126.86, 123.6, 122.2, 114.5, 85.6, 67.2, 62.5, 54.9, 16.8; IR (neat) 3397, 2359, 1699, 1512, 1246, 1049, 741 cm^{-1} ; HRMS (ESI-TOF) Calcd. for $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_4$: 407.1965 ($[\text{M} + \text{H}]^+$), Found: 407.1955 ($[\text{M} + \text{H}]^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 4/1, flow rate = 0.5 mL/min, retention time; 40.7 min and 57.4 min (major).

References

- (1) (a) T. Kano, Y. Yamaguchi, O. Tokuda and K. Maruoka, *J. Am. Chem. Soc.*, 2005, **127**, 16408.
(b) T. Kano, Y. Yamaguchi and K. Maruoka, *Chem. Eur. J.*, 2009, **15**, 6678.
- (2) K. Juhl, N. Gathergood and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 2995.
- (3) (a) A. G. Wenzel and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 12964.
(b) J. Song, Y. Wang and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 6048.
- (4) A. L. Tillman, J. Ye and D. J. Dixon, *Chem. Commun.*, 2006, 1191.
- (5) C. Chandler, P. Galzerano, A. Michrowska and B. List, *Angew. Chem., Int. Ed.*, 2009, **48**, 1978.
- (6) T. Kano, Y. Yamaguchi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2009, **48**, 1838.
- (7) J. W. Yang, C. Chandler, M. Stadler, D. Kampen and B. List, *Nature*, 2008, **452**, 453.

