Supporting Information

Sulfoximines as Ligands in Copper-Catalyzed Asymmetric Vinylogous Mukaiyama-Type Aldol Reactions

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General information: All experiments were carried out under Ar using standard Schlenk techniques. THF and toluene were dried and deoxygenated by standard procedures. Flash chromatography was carried out with Merck silica gel 60 (63-100 mesh). Analytical TLC was performed with Merck silica gel 60 F₂₅₄ plates, and the products were visualized by UV detection or by use of phosphomolybdic acid. Optical rotations measurements were carried out at RT, $\lambda = 589$ nm. NMR spectra (¹H: 400 MHz, ¹³C: 100 MHz) were recorded in CDCl₃ using TMS as internal standard and are reported in ppm. ¹H-NMR data are reported as: (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration, proton assignment). IR spectra were recorded as KBr pellet or film. Analytical HPLC measurements were carried out using a Chiralcel AD or OJ column (0.46 cm x 25 cm). Methyl pyruvate (**2a**), ethyl pyruvate (**2c**), and methyl benzoylformate (**2e**) were purchased from Aldrich. Benzyl pyruvate (**2b**) and isopropyl pyruvate (**2d**)^{1, 2} and silyl vinyl ketene acetals **5A**³ and **5B**⁴ were prepared according to literature procedures.

Analytical data of aldol products 6

(*R*)-*E*-5-Hydroxy-5-methyl-hex-2-enedioic acid 1-*tert*-butyl ester 6-methyl ester (6aA):

The product was prepared according to the general procedure (see footnote 13 in text) using methyl pyruvate (**2a**, 46 μ L, 0.5 mmol) and silyl vinyl ketene acetal **5A** (141 mg, 0.55 mmol). It was obtained as colorless oil in 85% yield (104 mg, 0.43 mmol) after flash chromatography (pentane/EtOAc: 4/1).

$[\alpha]_D^{20} = +2.3$ ($c = 1.2$, CHCl_3); $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 1.47$ (s, 3H, CH_3), 1.48 (s, 9H, *t*Bu), 2.53-2.60 (m, 2H, CH_2), 3.27 (s, 1H, OH), 3.80 (s, 3H, CH_3), 5.80 (d, $J = 15.7$ Hz, 1H, CH), 6.73-6.81 (m, 1H, CH) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 25.9$, 28.2, 42.6, 53.1, 74.2, 80.4, 126.8, 140.9, 165.2, 176.4 ppm; MS (70 eV, EI): m/z (%) = 245 (1) $[\text{M}+\text{H}^+]$, 188 (28), 171 (34), 129 (23), 111 (38), 86 (73), 57 (100); IR (film): $\tilde{\nu} = 3504$, 2935, 1713, 1123, 758 cm^{-1} ; HRMS (EI): m/z : calcd for $\text{C}_{12}\text{H}_{20}\text{O}_5 - \text{C}_4\text{H}_8 = \text{C}_8\text{H}_{12}\text{O}_5$: 188.0685; found 188.0685 $[\text{M}-\text{C}_4\text{H}_8]$.

The enantiomer ratio was determined by HPLC analysis using a Chiralcel AD column (flow rate 0.4 mL/min, heptane/*i*Pr-OH: 98/2, $\lambda = 230$ nm, 25 $^\circ\text{C}$); $t_r = 53.1$ min [major], $t_r = 57.6$ min [minor]; 92% ee (96% ee when the reaction is performed at -78 $^\circ\text{C}$).

Determination of the absolute configuration of 6aA

To a solution of compound **6aA** (200 mg, 0.82 mmol, 83% ee) in acetic acid (1.3 mL), pyridine (1.3 mL) was added dropwise. After 2 days, the solvent was evaporated, and the acetylated compound was separated from the starting material by flash chromatography (pentane/EtOAc: 4/1). The product (168 mg, 0.58 mmol, 72% yield) was dissolved in CCl_4 (6 mL), CH_3CN (6 mL), and distilled water (9 mL). To this mixture, a catalytic amount of $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ (5 mg) and NaIO_4 (618 mg, 2.9 mmol) was added. It was stirred overnight at room

temperature and then dichloromethane (10 mL) was added. The aqueous layer was acidified with HCl, and the layers were separated. Evaporation of the aqueous phase gave the crude acid, which was subsequently dissolved in dichloromethane (9 mL) and treated with oxalyl chloride (0.3 mL) and a catalytic amount of DMF. After stirring for 2 h at rt the solvent was removed under reduced pressure, the residue was taken up in THF (4.5 mL) and added to dry MeOH (4.5 mL) upon stirring. After a reaction period of 3 h the solution was concentrated. (*R*)-Dimethyl 2-acetocitramalate was obtained as colorless oil after flash chromatography (pentane/EtOAc: 5/1) in 30% yield over the two last steps (38 mg, 0.17 mmol). The absolute configuration of the obtained material was determined to be (*R*) by comparison of its optical rotation ($[\alpha]_{\text{D}}^{20} = +28.2$, $c = 1.1$, CHCl_3) with that reported one ($[\alpha]_{\text{D}}^{20} = +33.4$, $c = 1.0$, CHCl_3) for the (*R*)-enantiomer.⁵

The data were identical with those reported in the literature.⁵

¹H-NMR (400 MHz, CDCl_3): $\delta = 1.65$ (s, 3H), 2.07 (s, 3H), 2.87 (d, $J = 14.4$, 1H), 3.15 (d, $J = 14.4$ Hz, 1H), 3.73 (s, 3H), 3.74 (s, 3H) ppm; ¹³C-NMR (100 MHz, CDCl_3): $\delta = 21.0$, 22.6, 40.7, 51.9, 52.7, 77.7, 169.5, 169.9, 171.6 ppm.

(*R*)-*E*-5-Hydroxy-5-methyl-hex-2-enedioic acid 6-benzyl ester 1-*tert*-butyl ester (6bA):

The product was prepared according to the general procedure (see footnote 13 in text) using benzyl pyruvate (**2b**, 81 μL , 0.5 mmol) and silyl vinyl ketene acetal **5A** (141 mg, 0.55 mmol). It was obtained as colorless oil in 83% yield (133 mg, 0.42 mmol) after flash chromatography (pentane/EtOAc: 9/1).

$[\alpha]_{\text{D}}^{20} = +27.1$ ($c = 1.0$, CHCl_3); ¹H-NMR (400 MHz, CDCl_3): $\delta = 1.45$ (s, 3H, CH_3), 1.47 (s, 9H, *t*Bu), 2.49-2.63 (m, 2H, CH_2), 2.64 (br s, 1H, OH), 5.20 (s, 2H, CH_2), 5.75 (d, $J = 15.7$ Hz, 1H, CH), 6.73-6.81 (m, 1H, CH), 7.32-7.40 (m, 5H, Ar-H) ppm; ¹³C-NMR (100 MHz, CDCl_3): $\delta = 25.8$, 28.1, 42.4, 67.7, 74.0, 80.20, 126.8, 128.2, 128.5, 134.8, 140.6, 165.0, 175.7 ppm; MS (70 eV, EI): m/z (%) = 264 (4) [$\text{M}^+ - \text{C}_4\text{H}_8$], 129 (15), 111 (18), 91 (100), 86 (9), 57(38); IR (film): $\tilde{\nu} = 3767$, 2934, 1715, 1159, 987 cm^{-1} ; elemental analysis (%) calcd for $\text{C}_{18}\text{H}_{24}\text{O}_5$ (320.38): C 67.48, H 7.55; found: C 67.44, H 7.53.

The enantiomer ratio was determined by HPLC analysis using a Chiralcel AD column (flow rate 0.4 mL/min, heptane/*i*PrOH: 98/2, λ = 230 nm, 25 °C); t_r = 53.6 min [major], t_r = 62.1 min [minor]; 91% ee (97% ee when the reaction is performed at -78 °C).

(*R*)-*E*-5-Hydroxy-5-methyl-hex-2-enedioic acid 1-*tert*-butyl ester 6-ethyl ester (6cA):

The product was prepared according to the general procedure (see footnote 13 in text) using ethyl pyruvate (**2c**, 55 μ L, 0.5 mmol) and silyl vinyl ketene acetal **5A** (141 mg, 0.55 mmol). It was obtained as colorless oil in 81% yield (104 mg, 0.40 mmol) after flash chromatography (pentane/EtOAc: 9/1).

$[\alpha]_D^{20}$ = -3.3 (c = 1.2, CHCl_3); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 1.30 (t, J = 7.1 Hz, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.47 (s, 9H, *t*Bu), 2.49-2.63 (m, 2H, CH_2), 2.92 (br s, 1H, OH), 4.21-4.30 (m, 2H, CH_2), 5.80 (d, J = 15.4 Hz, 1H, CH), 6.73-6.81 (m, 1H, CH) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 14.2, 25.8, 28.1, 42.5, 62.1, 73.8, 80.2, 126.6, 140.8, 165.1, 175.8 ppm; MS (70 eV, EI): m/z (%) = 259 (1) [$\text{M}+\text{H}^+$], 129 (38), 111 (51), 86 (77), 57 (100); IR (film): $\tilde{\nu}$ = 3511, 2935, 1717, 1296, 1161 cm^{-1} ; elemental analysis (%) calcd for $\text{C}_{13}\text{H}_{22}\text{O}_5$ (258.31): C 60.45, H 8.58; found: C 60.41, H 8.27.

The enantiomer ratio was determined by HPLC analysis using a Chiralcel AD column (flow rate 0.4 mL/min, heptane/*i*PrOH: 98/2, λ = 230 nm, 25 °C); t_r = 41.3 min [major], t_r = 51.0 min [minor]; 91% ee (97% ee when the reaction is performed at -78 °C).

(*R*)-*E*-5-Hydroxy-5-methyl-hex-2-enedioic acid 1-*tert*-butyl ester 6-isopropyl ester (6dA):

The product was prepared according to the general procedure (see footnote 13 in text) using isopropyl pyruvate (**2d**, 53 μ L, 0.5 mmol) and silyl vinyl ketene acetal **5A** (141 mg, 0.55 mmol). It was obtained as colorless oil in 58% yield (79 mg, 0.29 mmol) after flash chromatography (pentane/EtOAc: 9/1).

$[\alpha]_D^{20} = -3.0$ ($c = 1.2$, CHCl_3); $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 1.27$ (d, $J = 2.2$ Hz, 3H, CH_3), 1.28 (d, $J = 2.2$ Hz, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.47 (s, 9H, $t\text{Bu}$), 2.48-2.61 (m, 2H, CH_2), 5.05-5.11 (m, 2H, CH_2), 5.80 (d, $J = 15.4$ Hz, 1H, CH), 6.73-6.81 (m, 1H, CH) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 21.7, 25.8, 42.5, 69.9, 73.7, 80.2, 126.6, 140.8, 165.1, 175.3$ ppm; MS (70 eV, EI): m/z (%) = 216 (21) $[\text{M}^+-\text{C}_4\text{H}_8]$, 185 (9), 157 (38), 129 (51), 111 (57), 86 (79), 57 (100); IR (film): $\tilde{\nu} = 3498, 2980, 1717, 1262, 1161$ cm^{-1} ; HRMS (EI): m/z : calcd for $\text{C}_{14}\text{H}_{24}\text{O}_5-\text{C}_4\text{H}_8 = \text{C}_{10}\text{H}_{10}\text{O}_5$: 216.0998; found 216.0998 $[\text{M}-\text{C}_4\text{H}_8]$.

The enantiomer ratio was determined by HPLC analysis using a Chiralcel AD column (flow rate 0.4 mL/min, heptane/ $i\text{PrOH}$: 98/2, $\lambda = 230$ nm, 25 °C); $t_r = 32.8$ min [major], $t_r = 39.7$ min [minor]; 91% ee (99% ee when the reaction is performed at -78 °C).

(S)-E-5-Hydroxy-5-phenyl-hex-2-enedioic acid 1-*tert*-butyl ester 6-methyl ester (6eA):

The product was prepared according to the general procedure (see footnote 13 in text) using methyl benzoylformate (**2e**, 71 μL , 0.5 mmol) and silyl vinyl ketene acetal **5A** (141 mg, 0.55 mmol). It was obtained as colorless oil in 88% yield (135 mg, 0.44 mmol) after flash chromatography (pentane/EtOAc: 9/1).

$[\alpha]_D^{20} = -8.9$ ($c = 1.2$, CHCl_3); $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 1.45$ (s, 9H, $t\text{Bu}$), 2.84-2.89 (m, 1H, CH_2), 3.03-3.09 (m, 1H, CH_2), 3.78 (s, 3H, CH_3), 5.83 (d, $J = 15.7$ Hz, 1H, CH), 6.73-6.80 (m, 1H, CH), 7.25-7.38 (m, 3H, Ph), 7.55-7.58 (m, 2H, Ph) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 28.2, 42.3, 53.5, 77.9, 80.4, 125.3, 126.9, 128.1, 128.4, 141.0, 140.9, 165.3, 174.4$ ppm; MS (70 eV, EI): m/z (%) = 307 (1) $[\text{M}+\text{H}^+]$, 165 (99), 105 (100), 86 (22), 57 (29); IR (film): $\tilde{\nu} = 3665, 2977, 1713, 1654, 1256, 1157, 919$ cm^{-1} ; elemental analysis (%) calcd. for $\text{C}_{17}\text{H}_{22}\text{O}_5$ (306.36): C 66.65, H 7.24; found: C 66.58, H 7.17.

The enantiomer ratio was determined by HPLC analysis using a Chiralcel AD column (flow rate 0.4 mL/min, heptane/ $i\text{Pr-OH}$: 98/2, $\lambda = 230$ nm, 20 °C); $t_r = 77.0$ min [minor], $t_r = 90.5$ min [major]; 89% ee (93% ee when the reaction is performed at -78 °C).

(R)-E-5-Hydroxy-5-methyl-hex-2-enedioic acid 1-ethyl ester 6-methyl ester (6aB):

The product was prepared according to the general procedure (see footnote 13 in text) using methyl pyruvate (**2a**, 46 μ L, 0.5 mmol) and silyl vinyl ketene acetal **5B** (100 mg, 0.55 mmol). It was obtained as colorless oil in 68% yield (73 mg, 0.34 mmol) after flash chromatography (pentane/EtOAc: 9/1).

$[\alpha]_D^{20} = +1.7$ ($c = 1.5$, CHCl_3); $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 1.28$ (d, $J = 7.1$ Hz, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.53-2.66 (m, 2H, CH_2), 3.80 (s, 3H, CH_3), 4.16-4.21 (m, 2H, CH_2), 5.88 (d, $J = 15.7$ Hz, 1H, CH), 6.85-6.92 (m, 1H, CH) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) $\delta = 14.2, 25.9, 42.5, 53.0, 60.3, 74.0, 124.9, 142.1, 165.7, 176.2$ ppm; MS (70 eV, EI): m/z (%) = 217 (3) $[\text{M}+\text{H}^+]$, 171 (17), 157 (18), 114 (100), 111, (60), 86 (66), 68 (25); IR (film): $\tilde{\nu} = 2927, 1724, 1215, 759$ cm^{-1} ; elemental analysis (%) calcd. for $\text{C}_{10}\text{H}_{16}\text{O}_5$ (216.23): C 55.55, H 7.46; found: C 55.48, H 7.30.

The enantiomer ratio was determined by HPLC analysis using a Chiralcel OJ column (flow rate 0.4 mL/min, heptanes/*i*PrOH: 98/2, $\lambda = 230$ nm, 25 $^\circ\text{C}$); $t_r = 59.1$ min [major], $t_r = 64.9$ min [minor]; 97% ee (99% ee when the reaction is performed at -78 $^\circ\text{C}$).

Table S1. Investigation of the Effect of Various Counterions in the Test Reaction to Give **6aA**^a

entry	CuX_2	yield (%) ^b	ee (%) ^c
1	$\text{Cu}(\text{OTf})_2$	75	92 (<i>R</i>)
2	$\text{Cu}(\text{ClO}_4)_2$	26	71 (<i>R</i>)
3	$\text{Cu}(\text{PF}_6)_2$	20	—
4	$\text{Cu}(\text{OAc})_2$	12	—
5	$\text{Cu}(\text{SO}_4)$	4	—
6	$\text{Cu}(\text{SbF}_6)_2$	—	—

^a Reaction conditions: **2a** (0.50 mmol), **5A** (0.55 mmol), $\text{CF}_3\text{CH}_2\text{OH}$ (0.6 mmol), CuX_2 (0.05 mmol), aminosulfoximine **1j** (0.05 mmol), Et_2O , rt, 12 h. ^b After column chromatography. ^c The enantiomer ratios were determined by HPLC using a chiral column (Chiralcel AD); the absolute configuration was determined by correlating **6aA** with (*R*)-2-acetocitromalate (see above).

Table S2. Effect of the Temperature and the Catalyst Loading in the Test Reaction to Give **6aA**^a

entry	catalyst (mol %)	temp. (° C)	reaction time (h)	yield (%) ^b	ee (%) ^c
1	10	RT	12	75	92 (<i>R</i>)
2	10	−78	12	80	92 (<i>R</i>)
3	10	RT	5	85	92 (<i>R</i>)
4	5	RT	5	64	90 (<i>R</i>)
5	1	RT	5	60	86 (<i>R</i>)

^a Reaction conditions: **2a** (0.50 mmol), **5A** (0.55 mmol), CF₃CH₂OH (0.6 mmol), Cu(OTf)₂, aminosulfoximine **1j** (equimolar with respect to copper salt), Et₂O, 12 h. ^b After column chromatography. ^c The enantiomer ratios were determined by HPLC using a chiral column (Chiralcel AD); the absolute configuration was determined by correlating **6aA** with (*R*)-2-acetocitromalate (see above).

References

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¹H NMR 400 MHz PR279-3 ¹³C NMR 400 MHz PR279-3

¹H NMR 400 MHz PR275C ¹³C NMR 400 MHz PR275C

¹H NMR 400 MHz PR275B

¹³C NMR 400 MHz PR275B

13C NMR 400 MHz PR289B

¹H NMR 400 MHz PR265D ¹³C NMR 400 MHz PR265D