Dipeptides from Methionine and *S*-Methylcysteine as Chiral Ligands for Asymmetric Michael Reactions

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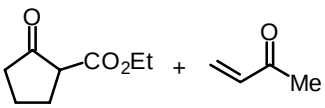
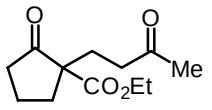
Abstract. Dipeptides derived from methionine and *S*-methylcysteine **3a**–**d** have been prepared and screened as chiral ligands in combination with 13 metal salts **4a**–**m** towards the catalysis of an asymmetric Michael reaction of a *β*-keto ester **1** with methyl vinyl ketone **2** resulting in an optimal *ee* of 18% achieved with $FeCl_3 \cdot 6\ H_2O$ **4c** as the metal salt.

The utilization of peptides as libraries of chiral ligands in a combinatorial search for asymmetric catalysts can be a successful approach [1]. In our group we are focusing on the application of polydentate thioether ligands [2] in the transition metal catalysis of asymmetric Michael reactions [3]. In this context we wish to report on our results in the screening of four dipeptides **3a**–**d** derived from methionine (MET) and *S*-methylcysteine (SMC) in combination with 13 metal compounds **4a**–**m** (Table 1) towards the catalysis of the Michael reaction of oxoester **1** with methyl vinyl ketone **2** to give the 1,5-dicarbonyl compound **5** bearing a quaternary stereocenter.



1 **2**

ligands **3a-d** | metal salts **4a-m**



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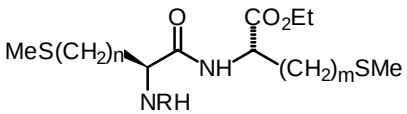

R = H: **3a-d**
R = Boc: **6a-d**

	n	m
a	1	1
b	1	2
c	2	1
d	2	2

Scheme 1 Metal catalyzed Michael reactions of donor **1** with acceptor **2**; *in situ*-formation of complexes of chiral ligands **3a**–**d** with metal salts **4a**–**m**

Results and Discussion

The dipeptide ethyl esters **3a**–**d** were prepared by a standard technique [4] (DCC–NEt_3, cat. DMAP) from *N*-Boc-SMC [5] and *N*-Boc-MET [6], *resp.* and the hydrochlorides of SMC–OEt [7] and MET–OEt [8], *resp.* Intermediate *N*-Boc-dipeptides **6a**–**d** (lettering like in **3a**–**d**) were deprotected with TFA–CH_2Cl_2 to furnish **3a**–**d** in very good overall yields.

All four ligands **3a**–**d** were separately screened together with each of the thirteen metal salts **4a**–**m** listed in Table 1 forming the catalytically active complexes in situ. Practically, 1.0 eq. of donor **1** was treated with 0.05 eq. of **4** and 0.075 eq. of the chiral ligands **3** in CH_2Cl_2 as solvent at room temperature. After equilibration (1 to 2 h) a small excess of the acceptor **2** (1.1 to 1.5 eq) was added, and after stirring the mixture overnight at room temperature all metal containing materials were removed by filtration over SiO_2. Analyses of the reaction mixtures and of the enantiomeric excess of **5** [9, 10] were performed by chiral GC. Conversions were usually at least greater than 10% with all compounds **4**, with Fe(III), Ni(II) and Co(II) (and some other single metal-ligand combinations) even greater than 95%. Moreover, it was checked that the ligand itself without any metal did not catalyze the conversion of **1** and **2** significantly.

With respect to enantioselectivity, *ee*'s greater than 10% were only obtained with ligand **3d** (see Table 1). With **3b** and **3c** only two results were 10% *ee*. Ligand **3a** gave no *ee*'s exceeding 10%. Interestingly, in all cases the formation of the (–)-enantiomer ($CHCl_3$) as the major isomer was observed, which was assigned to be the *R*-compound [9b]. Although these results are not satisfying at all with respect to an asymmetric synthesis of **5**, they show two interesting trends which are providing a promising base for further investigations: Ligands **3a**–**d** are the first of all investigated in this field so far (including chiral phosphanes and oxazolines [11]), which

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give a selectivity significantly different from zero with Fe(III) as the center metal. In terms of ecological and economical considerations iron is an ideal metal for catalysis [12], however, in the oxidation state Fe(III) is – presumably due to 17 valence electrons (in an octahedron) – kinetically very labile and therefore not commonly applicable for enantioselective catalysis (and thus gives about zero *ee* with all other ligands investigated so far). Secondly, on the first view selectivities achieved with dipeptides **3a**–**d** seem to correlate with the constitutional distance of the thioether moieties. Best results were achieved with MET-MET-OEt (**3d**). This provides a field for further optimizations, *e.g.* application of tri- or other oligopeptides containing at least two MET units. Moreover, investigations on the utilization of Fe(III) in combination with oligopeptide ligands are subject of current work in our laboratory.

Table 1 List of investigated metal salts **4a**–**m** and best screening results obtained with ligands **3b**–**d**, numerical values are *ee*'s of the (*R*)-(–)-enantiomer of **5**; no entry: *ee*'s < 10%.

metal salt		ligand		
$MX_n \cdot x\ H_2O$		**3b**	**3c**	**3d**
$CrCl_3 \cdot 6H_2O$	**4a**	–	–	–
$Mn(OAc)_2 \cdot 4H_2O$	**4b**	–	–	11
$FeCl_3 \cdot 6H_2O$	**4c**	–	–	18
$Ni(OAc)_2 \cdot 4H_2O$	**4d**	–	–	13
$NiCl_2 \cdot 6H_2O$	**4e**	–	–	–
$Co(OAc)_2 \cdot 4H_2O$	**4f**	–	–	10
$CoCl_2 \cdot 6H_2O$	**4g**	–	10	–
$RhCl_3 \cdot 3H_2O$	**4h**	–	–	–
$Cu(OAc)_2 \cdot H_2O$	**4i**	–	–	12
AgOAc	**4j**	–	10	10
$ZnCl_2$	**4k**	–	–	–
$SnCl_2$	**4l**	10	–	–
$Pb(OAc)_2 \cdot 3H_2O$	**4m**	–	–	–

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Experimental

Column chromatography was accomplished with Merck silica gel (type 60, 0.063–0.200 mm) using *tert*-butyl methyl ether (MTB) and petroleum ether (*b.p.* 40–60 °C) (PE). – ^{1}H NMR: Bruker AM 400 (400 MHz). – ^{13}C NMR: Bruker AC 200 (50 MHz), assignments were made using DEPT experiments. – MS: Varian MAT 711 and MAT 955Q (high resolution). – IR: Nicolet Magna IR 750. – Optical rotations: Perkin Elmer Polarimeter 341. – Chiral GC analysis: HP 5890 II with FI detection and a Shimadzu C-R6A integrator, Macherey-Nagel column FS-LIPODEX E (25 m, 0.25 mm), nitrogen carrier gas. – All reagents used were commercially available. – The following compounds were prepared according to literature procedures: *N*-Boc-SMC [5], *N*-Boc-MET [6], SMC-OEt · HCl [7], MET-OEt · HCl [8].

Dipeptide Formation (General Procedure)

Amino acid ethyl ester hydrochloride (3.00 mmol, SMC-OEt · HCl: 599 mg, MET-OEt · HCl: 641 mg) was added portionwise to a solution of *N*-Boc amino acid (3.00 mmol, *N*-Boc-SMC: 706 mg, *N*-Boc-MET: 748 mg), DCC (3.00 mmol, 599 mg), DMAP (0.15 mmol, 18 mg), and NEt_3 (3.00 mmol, 303 mg) in CH_2Cl_2 (4 ml). The resulting suspension was stirred overnight at room temperature, then completely transferred onto a SiO_2 column (l = 10 cm, d = 3 cm), and the product was eluted with PE/MTB (1 : 5) to give the *N*-Boc dipeptide ethyl ester as a colorless oil in 90–97% yield.

N-(tert-Butyloxycarbonyl)-S-methylcysteinyl-S-methylcysteine ethyl ester (**6a**)

R_f (SiO_2, PE/MTB 1: 5) = 0.52. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.26 (t, J = 7.1 Hz, 3H; CH_3), 1.42 (s, 9H; $3CH_3$), 2.08 (s, 3H; SCH_3), 2.13 (s, 3H; SCH_3), 2.82–2.99 (m, 4H; $2SCH_2$), 4.19 (q, J = 7.1 Hz, 2H; OCH_2), 4.26–4.32 (m, 1H; NCH), 4.74 (td, J = 7.6 Hz, J = 5.3 Hz, 1H; NCH), 5.45 (d, br., J = 7.2 Hz, 1H; NH), 7.25 (d, br., J = 7.5 Hz, 1H, NH). – ^{13}C (^{1}H) NMR ($CDCl_3$, 50 MHz): δ/ppm = 14.01 (CH_3), 15.77 (CH_3), 16.13 (CH_3), 28.18 (CH_3), 36.21 (CH_2), 36.33 (CH_2), 51.92 (CH), 53.36 (CH), 61.77 (CH_2), 80.33 (C), 155.20 (C=O), 170.26 (C=O), 170.54 (C=O). – IR (ATR): $\tilde{\nu}$/cm^{-1} = 3306 (s), 2978 (m), 2921 (m), 1741 (s), 1715 (s), 1661 (vs), 1516 (vs), 1367 (m), 1249 (m), 1167 (s), 1024 (m), 866 (m). – MS (EI, 70 eV), *m/z* (%): 380 (1) [M^+], 307 (12) [M^+ – *t*-BuO], 263 (70) [M^+ – *t*-BuOCONH$_2$], 216 (68) [*t*-BuOCONC(CH_2SMe)CO$^+$], 146 (91) [$MeSCH_2CCO_2Et^+$], 117 (94) [*t*-BuOCONH$_2^+$], 101 (52) [*t*-BuOCO$^+$], 90 (93) [$MeSCH_2CHNH_2^+$], 61 (59) [$MeSCH_2^+$], 57 (100) [*t*-Bu$^+$]. – $[\alpha]_D^{RT}$ = +2.1 (c 4.8 g/l, $CHCl_3$). – $C_{15}H_{28}N_2O_5S_2$ (380.52): Mol. mass calcd. 380.1440, found 380.1447 (HRMS).

N-(tert-Butyloxycarbonyl)-S-methylcysteinylmethionine ethyl ester (**6b**)

R_f (SiO_2, MTB) = 0.60. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.25 (t, J = 7.2 Hz, 3H; CH_3), 1.43 (s, 9H; $3CH_3$), 1.93–2.03 (m, 1H), 2.06 (s, 3H; SCH_3), 2.08–2.20 (m, 1H), 2.13 (s, 3H; SCH_3), 2.46–2.50 (m, 2H), 2.80 (dd, J = 13.9 Hz, J = 6.7 Hz, 1H), 2.90 (dd, J = 13.9 Hz, J = 5.8 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H; OCH_2), 4.21–4.25 (m, 1H; NCH), 4.62 (td, J = 7.5 Hz, J = 5.1 Hz, 1H; NCH), 5.41 (d, br., J = 6.5 Hz, 1H; NH), 7.05 (d, br., J = 7.6 Hz, 1H; NH). – ^{13}C (^{1}H) NMR ($CDCl_3$, 50 MHz): δ/ppm = 14.05 (CH_3), 15.35 (CH_3), 15.86 (CH_3), 28.19 (CH_3), 29.75 (CH_2), 31.59 (CH_2), 36.29 (CH_2), 49.33 (CH_2), 53.50 (CH_2), 61.61 (CH_2), 80.37 (C), 155.24 (C=O), 170.48 (C=O), 171.28 (C=O). – IR (ATR): $\tilde{\nu}$/cm^{-1} = 3313 (s), 2978 (m), 2919 (m), 1738 (s), 1714 (s), 1661 (vs), 1519 (vs), 1446 (m), 1367 (s), 1250 (s), 1166 (vs), 1022 (s), 865 (m). – MS (EI, 70 eV), *m/z* (%): 395 (4) [M + H$^+$], 338 (7) [M^+ – *t*-BuH], 321 (8) [M^+ – *t*-BuO], 277 (58) [$EtO_2CCH(NHCO_2t\text{-Bu})(CH_2)_2SMe^+$], 264 (22) [$EtO_2CCH(NHCO_2t\text{-Bu})CH_2SH_2^+$], 203 (100) [$M^+$ – *t*-BuOCOH –$MeSCH_2CHNH_2$], 90 (17) [$MeSCH_2CHNH_2^+$], 57 (34) [*t*-Bu$^+$]. – $[\alpha]_D^{RT}$ = +6.0 (c 2.0 g/l, $CHCl_3$). – $C_{16}H_{30}N_2O_5S_2$

(394.54): Mol. mass calcd. 395.1674 ($C_{16}H_{31}N_2O_5S_2$), found 395.1675 (M + H^+, HRMS).

N-(tert.-Butyloxycarbonyl)methionyl-S-methylcysteine ethyl ester (**6c**)

R_f (SiO_2, PE/MTB 1 : 5) = 0.46. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.11 (t, J = 7.1 Hz, 3H; CH_3), 1.26 (s, 9H; $3CH_3$), 1.73–1.84 (m, 2H; CH_2), 1.92 (s, 3H; SCH_3), 1.93 (s, 3H; SCH_3), 2.41 (t, J = 7.0 Hz, 2H; SCH_2), 2.72–2.82 (m, 2H; SCH_2), 4.03 (q, J = 7.1 Hz, 2H; OCH_2), 4.20–4.26 (m, 1H; NCH), 4.60 (dt, J = 7.7 Hz, J = 5.4 Hz, 1H; NCH), 5.62 (d, br., J = 8.1 Hz, 1H; NH), 7.26 (d, br., J = 6.6 Hz, 1H; NH). – ^{13}C (^{1}H) NMR ($CDCl_3$, 50 MHz): δ/ppm = 13.93 (CH_3), 14.99 (CH_3), 15.97 (CH_3), 28.12 (CH_3), 29.87 (CH_2), 31.56 (CH_2), 36.01 (CH_2), 51.59 (CH), 53.16 (CH), 61.60 (CH_2), 79.80 (C), 155.23 (C=O), 170.31 (C=O), 171.38 (C=O). – IR (ATR): $\tilde{\nu}$/cm^{-1} = 3310 (s), 2978 (m), 2919 (m), 1742 (s), 1713 (s), 1662 (vs), 1520 (vs), 1444 (m), 1392 (m), 1367 (s), 1305 (m), 1250 (s), 1204 (s), 1168 (vs), 1047 (m), 1027 (m), 863 (m). – MS (EI, 70 eV), *m/z* (%): 394 (2) [M^+], 338 (10) [M^+ – *t*-BuH], 320 (26) [M^+ – *t*-BuOH], 264 (86) [$EtO_2CCH(NHCO_2t$-Bu)CH_2SMe + H^+], 164 (45) [$EtO_2CCH(NH_3)CH_2SMe^+$], 147 (49) [$MeSCH_2CCO_2Et$ + H^+], 118 (52) [*t*-$BuOCONH_3^+$], 104 (71) [$MeS(CH_2)_2CHNH_2^+$], 61 (85) [$MeSCH_2^+$], 57 (100) [*t*-Bu^+]. – $[\alpha]_D^{RT}$ = + 6.0 (c 3.7 g/l, $CHCl_3$). – $C_{16}H_{30}N_2O_5S_2$ (394.56): Mol. mass calcd. 394.1596, found 394.2599 (HRMS).

N-(tert.-Butyloxycarbonyl)methionylmethionine ethyl ester (**6d**)

R_f (SiO_2, PE/MTB 1 : 5) = 0.48. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.16 (t, J = 7.2 Hz, 3H; CH_3), 1.31 (s, 9H; $3CH_3$), 1.77–2.08 (m, 4H), 1.96 (s, 3H; SCH_3), 1.97 (s, 3H; SCH_3), 2.39 (t, J = 7.5 Hz, 2H; SCH_2), 2.45 (t, J = 7.2 Hz, 2H; SCH_2), 4.07 (q, J = 7.1 Hz, 2H; OCH_2), 4.20–4.24 (m, 1H; NCH), 4.53 (td, J = 7.8 Hz, J = 5.1 Hz, 1H; NCH), 5.52 (d, br., J = 7.9 Hz, 1H; NH), 7.12 (d, br., J = 7.5 Hz, 1H; NH). – ^{13}C (^{1}H) NMR ($CDCl_3$, 50 MHz): δ/ppm = 13.92 (CH_2), 14.94 (CH_3), 15.16 (CH_3), 28.09 (CH_3), 29.61 (CH_2), 29.81 (CH_2), 31.33 (CH_2), 31.41 (CH_2), 51.36 (CH), 53.12 (CH), 61.35 (CH_2), 79.77 (C), 155.32 (C=O), 171.43 (C=O), 171.43 (C=O). – IR (ATR): $\tilde{\nu}$/cm^{-1} = 3310 (s), 2978 (m), 1918 (m), 1741 (vs), 1660 (vs), 1524 (vs), 1445 (s), 1392 (m), 1367 (s), 1299 (m), 1250 (s), 1168 (vs), 1025 (m), 863 (m). – MS (EI, 70 eV), *m/z* (%): 408 (3) [M^+], 352 (10) [M + H^+ – *t*-Bu], 334 (26) [M^+ – *t*-BuOH], 278 (84) [$EtO_2CCH(NHCO_2t$-Bu)$(CH_2)_2$ SMe + H^+], 178 (58) [$EtO_2CCH(NH_3)(CH_2)_2SMe^+$], 104 (90) [$MeS(CH_2)_2CHNH_2^+$], 61 (100) [$MeSCH_2^+$]. – $[\alpha]_D^{RT}$ = + 7.3 (c 4.5 g/l, $CHCl_3$). – $C_{17}H_{32}N_2O_5S_2$ (408.58): Mol. mass calcd. 408.1753, found 408.1754 (HRMS).

Deprotection (General Procedure)

An amount of 2.5–3.0 mmol of the *N*-Boc dipeptide ethyl ester **6** was dissolved in CH_2Cl_2 (5 ml), TFA (2 ml) was added, and the resulting solution was stirred overnight at room temperature, and finally, all volatile materials were removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 ml), $NaHCO_3$ (5 ml, saturated aqueous solution) was added, and the suspension was treated with $NaHCO_3$ (solid) until the pH was greater than 8. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (three times 2 ml), the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 (MeOH) to give the dipeptide ethyl ester **3** as a colorless oil in 90–95% yield.

S-Methylcysteinyl-S-methylcysteine ethyl ester (**3a**)

R_f (SiO_2, MeOH) = 0.76. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.25 (t, J = 7.2 Hz, 3H; CH_3), 1.87 (s, br., 2H; NH_2), 2.06 (s, 3H; SCH_3), 2.08 (s, 3H; SCH_3), 2.65 (dd, J = 13.7 Hz, J = 8.9 Hz, 1H; SCHH), 2.85–2.99 (m, 3H; SCHH, SCH_2), 3.52 (dd, J = 8.9 Hz, J = 3.8 Hz, 1H; NCH), 4.14–4.20 (m, 2H; OCH_2), 4.72 (td, J = 8.2 Hz, J = 5.6 Hz, 1H; NCH), 8.13 (d, br., J = 7.8 Hz, 1H; NH). – ^{13}C (^{1}H) NMR ($CDCl_3$, 50 MHz): δ/ppm = 14.00 (CH_3), 15.15 (CH_3), 16.04 (CH_3), 36.36 (CH_2), 39.34 (CH_2), 51.30 (CH), 53.24 (CH), 61.60 (CH_2), 170.63 (C=O), 173.42 (C=O). – IR (ATR): $\tilde{\nu}$/cm^{-1} = 3358 (m), 3314 (m), 2980 (m), 2918 (s), 1738 (s), 1671 (vs), 1505 (s), 1427 (m), 1371 (m), 1341 (m), 1325 (m), 1305 (m), 1250 (m), 1197 (s), 1028 (m), 859 (m). – MS (EI, 70 eV), *m/z* (%): 281 (10) [M + H^+], 264 (22) [M^+ – NH_2], 90 (100) [$MeSCH_2CHNH_2^+$]. – $[\alpha]_D^{RT}$ = – 29.3 (c 13.6 g/l, $CHCl_3$). – $C_{10}H_{20}N_2O_3S_2$ (280.40): Mol. mass calcd. 281.0994 (for $C_{10}H_{21}N_2O_3S_2$), found 281.0996 (M + H^+, HRMS).

S-Methylcysteinylmethionine ethyl ester (**3b**)

R_f (SiO_2, MeOH) = 0.62. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.24 (t, J = 7.1 Hz, 3H; CH_3), 1.79 (s, 2H; NH_2), 1.89–1.98 (m, 1H), 2.04 (s, 3H; SCH_3), 2.06 (s, 3H; SCH_3), 2.05–2.17 (m, 1H), 2.46 (t, J = 7.7 Hz, 2H; SCH_2), 2.65 (dd, J = 13.6 Hz, J = 8.5 Hz, 1H; SCHH), 2.94 (dd, J = 13.6 Hz, J = 3.7 Hz, 1H; SCHH), 3.51 (dd, J = 8.6 Hz, J = 3.7 Hz, 1H; NCH), 4.16 (q, J = 7.1 Hz, 2H; OCH_2), 4.61 (td, J = 7.9 Hz, J = 5.1 Hz, 1H; NCH), 7.98 (d, br., J = 8.1 Hz, 1H; NH). – ^{13}C (^{1}H) NMR ($CDCl_3$, 50 MHz): δ/ppm = 14.02 (CH_3), 15.29 (CH_3), 15.37 (CH_3), 29.87 (CH_2), 31.79 (CH_2), 39.51 (CH_2), 51.15 (CH), 53.32 (CH), 61.43 (CH_2), 171.62 (C=O), 173.39 (C=O). – IR (ATR): $\tilde{\nu}$/cm^{-1} = 3358 (m), 3306 (m), 2979 (m), 2817 (s), 1737 (vs), 1669 (vs), 1509 (vs), 1437 (s), 1373 (m), 1198 (s), 1024 (m), 862 (m). – MS (EI, 70 eV), *m/z* (%): 294 (1) [M^+], 277 (8) [M^+ – NH_3], 233 (10) [M^+ – $MeSCH_2^+$], 159 (18) [M^+ – $MeSCH_2$ – CO_2Et – H], 90 (100) [$MeS(CH_2)_2CHNH_2^+$], 61 (16) [$MeSCH_2^+$]. – $[\alpha]_D^{RT}$ = – 21.3 (c 3.8 g/l, $CHCl_3$). – $C_{11}H_{22}N_2O_3S_2$ (294.42): Mol. mass calcd. 294.1072, found 294.1072 (HRMS).

*Methionyl-S-methylcysteine ethyl ester (**3c**)*

R_f (SiO_2, MeOH) = 0.61. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.18 (t, J = 7.1 Hz, 3H; CH_3), 1.53 (s, br., NH_2), 1.63–1.73 (m, 1H), 1.91–2.06 (m, 1H), 1.99 (s, 2H; SCH_3), 2.02 (s, 3H; SCH_3), 2.47–2.56 (m, 2H; SCH_2), 2.80 (dd, J = 13.9 Hz, J = 6.5 Hz, 1H; SCHH), 2.87 (dd, J = 13.9 Hz, J = 5.0 Hz, 1H; SCHH), 3.44 (dd, J = 8.0 Hz, J = 4.8 Hz, 1H; NCH), 4.10 (q, J = 7.1 Hz, 2H; OCH_2), 4.64 (td, J = 8.1 Hz, J = 5.9 Hz, 1H; NCH), 7.86 (d, br., J = 8.1 Hz, 1H; NH). – ^{13}C (^{1}H) NMR ($CDCl_3$, 50 MHz): δ/ppm = 13.83 (CH_3), 14.95 (CH_3), 15.80 (CH_3) 30.17 (CH_2), 33.79 (CH_2), 36.15 (CH_2), 51.03 (CH), 53.85 (CH), 61.37 (CH_2), 170.56 (C=O), 174.38 (C=O). – IR (ATR): $\tilde{\nu}$/cm^{-1} = 3316 (s), 2979 (m), 2917 (s), 1738 (s), 1669 (vs), 1506 (vs), 1199 (s), 1029 (s). – MS (EI, 70 eV), *m/z* (%): 294 (28) [M^+], 220 (22) [M^+ – $MeSCH_2CH$], 164 (29) [$MeSCH_2CH(NH_3)CO_2Et^+$], 147 (38) [$MeSCH_2CO_2Et^+$], 131 (76) [$MeS(CH_2)_2CH(NH)CO^+$], 104 (100)

[$MeS(CH_2)_2CHNH_2^+$], 61 (90) [$MeSCH_2^+$], 56 (86) [$NHCH(CH_2)_2^+$]. – $[\alpha]_D^{RT} = -9.9$ (c 7.5 g/l, $CHCl_3$). – $C_{11}H_{22}N_2O_3S_2$ (294.42): Mol. mass calcd. 294.1072, found 294.1077 (HRMS).

Methionylmethionine ethyl ester (**3d**)

R_f (SiO_2, MeOH) = 0.61. – ^1H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.22 (t, J = 7.1 Hz, 1H; CH_3), 1.55 (s, br., 2H; NH_2), 1.67–1.76 (m, 1H), 1.88–1.98 (m, 1H), 2.00–2.14 (m, 2H), 2.03 (s, 3H; SCH_3), 2.04 (s, 3H; SCH_3), 2.38–2.50 (m, 2H; SCH_2), 2.50–2.62 (m, 2H; SCH_2), 3.46 (dd, J = 8.1 Hz, J = 4.8 Hz, 1H; NCH), 4.14 (q, J = 7.2 Hz, 2H; OCH_2), 4.59 (td, J = 8.1 Hz, J = 5.1 Hz, 1H; NCH), 7.75 (d, br., J = 8.1 Hz, 1H; NH). – ^{13}C (^1H) NMR ($CDCl_3$, 50 MHz): δ/ppm = 13.99 (CH_3), 15.11 (CH_3), 15.34 (CH_3), 29.89 (CH_2), 30.41 (CH_2), 31.71 (CH_2), 33.94 (CH_2), 51.11 (CH), 54.01 (CH), 61.36 (CH_2), 171.66 (C=O), 174.48 (C=O). – IR (ATR): $\tilde{\nu}$/cm^{-1} = 3309 (m), 2978 (m), 2915 (s), 1735 (vs), 1658 (vs), 1507 (vs), 1439 (s), 1273 (m), 1193 (vs), 1023 (s), 859 (s). – MS (EI, 70 eV), *m/z* (%): 308 (52) [M^+], 234 (38) [$M^+ - MeSCH_2CH$], 178 (56) [$MeS(CH_2)_2CH(NH_3)CO_2Et^+$], 171 (90) [$M^+ - MeSCH_2 - MeS - Et$], 131 (78) [$MeS(CH_2)_2CH(NH)CO^+$], 104 (98) [$MeS(CH_2)_2CHNH_2^+$], 61 (100) [$MeSCH_2^+$], 56 (94) [$NHCH(CH_2)_2^+$]. – $[\alpha]_D^{RT}$ = +13 (c 3.6 g/l, $CHCl_3$). – $C_{12}H_{24}N_2O_3S_2$ (308.45): Mol. mass calcd. 308.1228, found 308.1223 (HRMS).

Ethyl 2-(3-oxobutyl)cyclopentanone-2-carboxylate (5) (General Procedure)

Metal salt **4** (0.017 mmol, 5 mol%), chiral ligand **3** (0.025 mmol, 7.5 mol%) and oxoester **1** (52 mg, 0.33 mmol) were dissolved in CH_2Cl_2 (0.5 ml). After stirring for 1 h at room temperature methyl vinyl ketone (**2**) (30 µl, 0.37 mmol) was added, and the mixture was stirred overnight at room temperature. Subsequently, the mixture was diluted with MTB (1 ml) and directly transferred on a SiO_2 column (3 cm), and the product was eluted with PE/MTB 1 : 1 (R_f = 0.25). The product mixture was analyzed by chiral GC, isotherm elution (130 °C), enantiomers of **5**: t_R = 30.3 min [(+)-enantiomer] and 32.4 min [(–)-enantiomer].

References

[1] a) M. S. Sigman, E. N. Jacobsen, J. Am. Chem. Soc. **1998**, *120*, 4901; b) K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, Angew. Chem. **1997**, *109*, 1782; Angew. Chem. Int. Ed. Engl. **1997**, *36*, 1781; c) M. B. Francis, N. S. Finney, E. N. Jacobsen, J. Am. Chem. Soc. **1996**, *188*, 8983

[2] a) J. Christoffers, Liebigs Ann./Recueil **1997**, 1353; b) J. Christoffers, U. Rößler, Tetrahedron: Asymmetry **1998**, *9*, 2349

[3] a) K. Yamada, T. Arai, H. Sasai, M. Shibasaki, J. Org. Chem. **1998**, *63*, 3666; b) Review: M. Shibasaki, H. Sasai, T. Arai, Angew. Chem. **1997**, *109*, 1290; Angew. Chem. Int. Ed. Engl. **1997**, *36*, 1236; c) N. End, L. Macko, M. Zehnder, A. Pfaltz, Chem. Eur. J. **1998**, *4*, 818; d) Review: J. Leonard, E. Diez-Barra, S. Merino, Eur. J. Org. Chem. **1998**, 2051

[4] A. Q. Lyons, L. D. Pettit, J. Chem. Soc., Dalton Trans. **1984**, 2305

[5] M. Medal, Acta Chem. Scand. B **1986**, *B40*, 250

[6] J. Jiang, K. K. Schumacher, M. M. Joullie, F. A. Davis, R. E. Reddy, Tetrahedron Lett. **1994**, *35*, 2121

[7] J. G. Wilson, L. A. Cohen, J. Am. Chem. Soc. **1963**, *85*, 560

[8] E. Booth, V. C. E. Burnop. W. E. Jones, J. Chem. Soc. **1944**, 666

[9] The asymmetric synthesis of **5** was reported three times before: a) H. Wynberg, R. Helder, Tetrahedron Lett. **1975**, 4057; b) Y. Tamai, A. Kamifuku, E. Koshiishi, S. Miyano, Chem. Lett. **1995**, 957; c) H. Sasai, E. Emori, T. Arai, M. Shibasaki, Tetrahedron Lett. **1996**, *37*, 5561

[10] For full spectral data of **5** see: J. Christoffers, J. Chem. Soc., Perkin Trans. 1 **1997**, 3141

[11] J. Christoffers, A. Mann, U. Rößler, unpublished results

[12] Review: J. Christoffers, Eur. J. Org. Chem. **1998**, 1259

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