Highly Enantioselective Rhodium-Catalyzed Hydrogenation of 2-(2-Methoxy-2-oxoethyl)acrylic Acid − A Convenient Access of Enantiomerically Pure Isoprenoid Building Blocks

Markus Ostermeier,[a] Bernhard Brunner,[a] Christian Korff,[a] and Günter Helmchen*[a]

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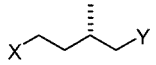
Asymmetric catalytic hydrogenation of 2-(2-methoxy-2-oxoethyl)acrylic acid (**5**) to give (2*S*)-4-methoxy-2-methyl-4-oxobutanoic acid [(*S*)-**6**] was studied. An enantiomeric excess of 99.7% *ee* was achieved with a catalyst formed in situ from $[Rh(COD)_2]BF_4$ and the chiral phosphite **L2** in 1,2-dichloroethane as solvent. In addition, enzyme-catalyzed semi-saponification of dimethyl 2-methylsuccinate was investigated. Mono ester (*S*)-**6** was transformed into a few compounds which can serve as C_5-building blocks in natural product syntheses.

Introduction

Enantiomerically highly enriched chiral C_5-compounds of type **A** are important building blocks for syntheses of terpenoid natural products; these syntheses often involve iterative coupling of C_5-units.



A

The formulas of a variety of compounds of type **A** are collected in Figure 1. Most often the lactones (*S*)-**A1** and (*S*)-**A2** were used, for example for syntheses of α-tocopherol,[1b,1c] vitamin K_1,[2] mammalian dolichols,[3] Archaea membrane lipids,[4] (*S*)-26-hydroxycholesterol[5] and (+)-invictolide.[6] Widely differing methods were employed for syntheses of these synthons. Lactones (*S*)-**A1**[1] and (*S*)-**A2**[1] as well as the bifunctional C_5-building blocks (*R*)- and (*S*)-**A3**[7] and (*S*)-**A4**[8] were prepared using asymmetric syntheses mediated by microorganisms. Lactone (*S*)-**A1**[9] and compound (*S*)-**A5**[4] were prepared from methyl (*R*)-3-hydroxy-2-methylpropanoate, obtained by microbial oxidation. Ethyl (*S*)-lactate served as starting material for the synthesis of the C_5-building block (*S*)-**A6**.[10] *de novo* Asymmetric catalysis, Rh-catalyzed asymmetric allylamine−enamine rearrangement, has been developed for synthesis of (*R*)- and (*S*)-**A7**.[11]

Hydrogenation of derivatives of low-cost 2-methylenesuccinic acid (**1**) has not served as basis of a useful method for

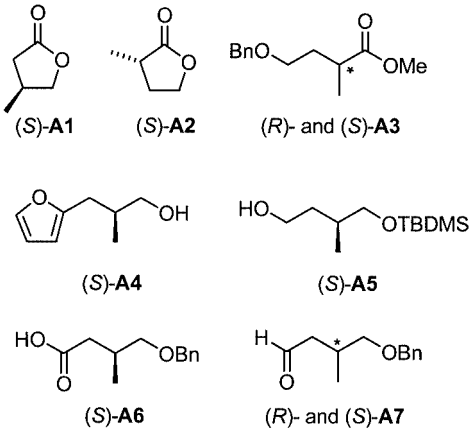
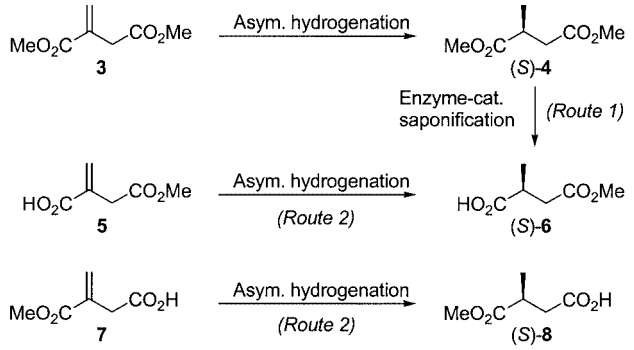


Figure 1. Known isoprenoid chiral C_5-building blocks

synthesis of an isoprenoid C_5-building block of type **A**. This is remarkable considering that 2-methylenesuccinic acid (itaconic acid) (**1**) and dimethyl 2-methylenesuccinate (**3**) belong to the standard substrates in the area of homogeneous asymmetric hydrogenation. We have now developed a simple and efficient procedure yielding mono ester **6** (Scheme 1) from 2-methylenesuccinic acid in high yield with enantiomeric purity of >99%. This mono ester can serve as convenient starting material for syntheses of many of the compounds listed in Figure 1.

Two straightforward strategies for syntheses based on 2-methylenesuccinic derivatives are described in Scheme 1. The first consists of catalytic hydrogenation of 2-methylenesuccinic acid (**1**) or dimethyl 2-methylenesuccinate (**3**) to give 2-methylsuccinic acid or dimethyl 2-methylsuccinate followed by enzyme-catalyzed semi-esterification or semi-saponification, respectively. The second involves asymmet-

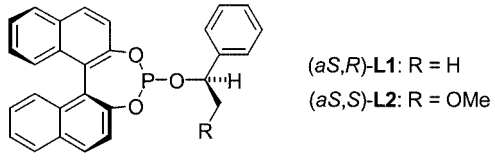
[a] Organisch-Chemisches Institut, Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
Fax: (internat.) +49-(0)6221-544205
E-mail: G.Helmchen@urz.uni-heidelberg.de



Scheme 1. Routes towards (*S*)-2-methylsuccinic acid mono-methyl ester

ric catalytic hydrogenation of 2-methylenesuccinic acid mono esters **5** or **7**. We have pursued both strategies.[12]

Highly enantioselective hydrogenations of 2-methylenesuccinic acid and dimethyl 2-methylenesuccinate using chelate diphosphanes have often been reported.[13] Recently, excellent results were obtained with Rh complexes of conveniently available monodentate ligands[14] as catalysts. Outstanding results with respect to selectivity and reactivity were achieved by Reetz and Mehler with the monodentate phosphite **L1** as ligand prepared from BINOL via two simple steps.[15]



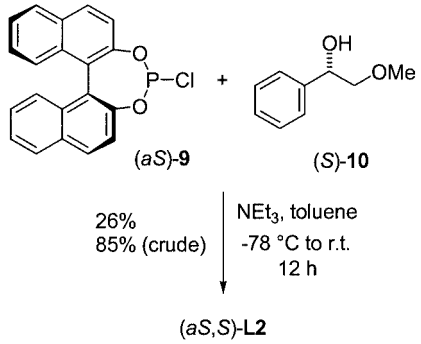
While asymmetric hydrogenation of substituted 2-methylenesuccinic acid mono esters, which are easily available via Stobbe condensation, was widely investigated,[16] there are only a few publications on the hydrogenation of 2-methylenesuccinic acid mono esters. Thus, using Rh-catalyzed hydrogenation with a bidentate PAMP-DuPHOS hybrid as ligand, J. M. Brown et al. have been able to prepare mono esters **6** and **8** with 94 and 95% *ee*, respectively,[17] and Berens has produced mono ester **6** with 95% *ee* using PrFerroTANE as ligand.[18] Despite of this rather high selectivity, these results do not suffice to fulfil requirements posed by syntheses of pharmaceuticals for which enantiomeric purities > 99% are usually required.

Our own work was based on the following considerations: (a) It was anticipated that ligand **L1** would also induce high enantioselectivity in the hydrogenation of a 2-methylenesuccinic mono ester. (b) The known mono ester **5**[19] appeared a particularly well suited starting material as it is crystalline and available in excellent yield by simple acid-catalyzed esterification. We were not able to meet our objectives with **L1**, however a simple change to the potentially hemilabile ligand **L2** in conjunction with optimization of the solvent were successful. The selection of **L2** was induced by our previous work on oxaphosphinane ligands.[20]

Results and Discussion

Enantioselective Rhodium-Catalyzed Hydrogenations

Ligand **L1** was prepared as described previously.[15] An analogous synthesis made **L2** readily available (Scheme 2). The requisite alcohol (*S*)-**10** was prepared from (*S*)-mandelic acid.[21] Reaction of (*S*)-**10** at −78 °C with phosphorous chloride **9**[22] (1.1 equivalents) in toluene in the presence of triethylamine gave crude ligand **L2** in excellent yield. Purity of ligand **L2**, assessed by ^{31}P NMR (singlet at δ = 151.54 ppm), was ca. 90%. This material was sufficiently pure for asymmetric hydrogenation. Nevertheless, it was purified by column chromatography, which caused partial decomposition, and recovery of the pure compound was low (26%).



Scheme 2. Preparation of phosphite **L2**

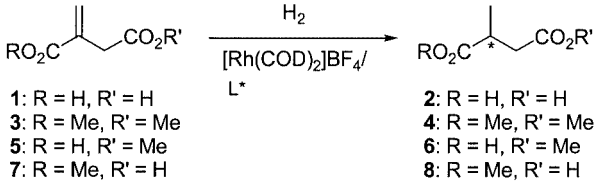
Precatalysts for asymmetric hydrogenation were prepared by reaction of $[Rh(COD)_2]BF_4$ with 2.2 equiv. of **L2** in CH_2Cl_2 at −78 °C or in 1,2-dichloroethane at −25 °C. After 20−30 min, the mixture was allowed to reach room temperature, and the resultant solution was used for hydrogenation. NMR spectroscopy (titration of $[Rh(COD)_2]BF_4$ with **L2** in CD_2Cl_2) and HR-FAB-MS showed remarkably clean formation of a single new species, a complex with molar ratio Rh/**L2** = 1:2 [^{31}P NMR: δ = 128.8 (d, $^1J_{P,Rh}$ = 254 Hz) ppm] if up to 2 equiv. of **L2** were used. Upon further addition of **L2**, signals of this complex diminished and vanished with > 3 equiv. of **L2**. Addition of $[Rh(COD)_2]BF_4$ to the mixture caused reformation of the 1:2 complex. Results achieved in hydrogenations of 2-methylenesuccinic acid (**1**), dimethyl 2-methylenesuccinate (**3**) as well as mono esters **5** and **7**, using complex $[Rh(COD)(L2)_2]BF_4$ as precatalyst, are described in Table 1 and Scheme 3. Hydrogenations were initially carried out with purified **L2**. Fortunately, identical results were obtained with crude **L2** (Table 2, Entry 5). For the particularly important substrate **5** excellent 97.3% *ee* were reached with dichloromethane as solvent. Further improvement resulted upon variation of the solvent: 98.3% *ee* with (trifluoromethyl)benzene[23] and 99.7% *ee* with 1,2-dichloroethane. Solvents EtOAc and THF gave rise to low selectivity. In contrast, selectivities of hydrogenations with substrate **7** were less effected by the solvent, and ligand **L1** was superior

to **L2**. Again, the best result, 98.8% *ee*, was obtained with 1,2-dichloroethane as solvent.

Table 1. Enantioselective hydrogenation of 2-methylenesuccinic acid (**1**), dimethyl 2-methylenesuccinate (**3**) and mono esters **5** and **7** using complexes $[Rh(COD)(\mathbf{L1})_2]BF_4$ or $[Rh(COD)(\mathbf{L2})_2]BF_4$ as precatalysts

Entry[a]	Ligand	Solvent	Substrate / % *ee* of product **1**	**3**	**5**	**7**
1	**L1**	CH_2Cl_2	74.7[b]	99.6	94.1	94.8
2	**L1**	$ClCH_2CH_2Cl$	65.8	99.0	97.5	98.8
3	**L2**	CH_2Cl_2	99.7	93.9	97.3	94.9
4	**L2**	EtOAc	99.2	19.2	47.7	92.2
5	**L2**	THF	98.6	28.6	22.9	94.9
6	**L2**	Toluene	75.5[c]	29.8	40.4	95.4
7	**L2**	$C_6H_5CF_3$	95.8[d]	77.0	98.3	96.0
8	**L2**	$ClCH_2CH_2Cl$	98.6	91.0	99.7	92.2

[a] Reaction conditions: 1.1 bar of H_2; 20 °C; 12 h; *c*(substrate) = 0.1 mol L^{-1}; molar ratio ligand/Rh = 2.2, molar ratio substrate/catalyst 200:1, catalyst preparation see text, reaction time 12 h. Conversion was 100% if not otherwise noted. Products with (*S*)-configuration were generated. For determinations of enantiomeric purities the crude reaction products were transformed with diazomethane into the methyl esters and these were analyzed by GC; column Chrompack-CP-γ-Cyclodextrin-TA (30 m × 0.25 mm), flow 60 mL h^{-1}, 70 °C: t_R[(*S*)-**4**] = 22.8 min, t_R[(*R*)-**4**] = 25.6 min. Absolute configurations were determined by comparison with known signs of optical rotations: ref.[30] [b] 66% conversion. [c] 88% conversion. [d] 51% conversion.



Scheme 3. Asymmetric hydrogenation of 2-methylenesuccinic acid and its derivatives. L* = chiral phosphite ligand, COD = cyclooctadiene

Table 2. Enantioselective hydrogenation of mono ester **5** in 1,2-dichloroethane using $[Rh(COD)\mathbf{L2}_2]BF_4$ as catalyst

Entry[a]	Ratio rhodium:substrate	Enantiomeric excess of **6** [% *ee*] (config.)
1	1:200	99.7 (*S*)
2	1:500	99.3 (*S*)
3	1:1000	99.3 (*S*)
4[b]	1:1000	99.3 (*S*)
5[c]	1:1000	99.3 (*S*)

[a] Reaction conditions: 1.1 bar of H_2; 20 °C, 12 h, solvent: 1,2-dichloroethane, *c*(substrate) = 0.1 mol L^{-1} molar ratio **L2**/Rh = 2.2, every case 100% conversion. Determinations of enantiomeric excess as described in Table 1. [b] *c*(**5**) = 0.7 mol L^{-1} (saturated solution). [c] Crude **L2** was used.

Next, the substrate/catalyst ratio was optimized. Complete hydrogenation of **5** to give **6** with 99.3% *ee* was possible with a **5**/Rh ratio of 1000:1 (Table 2, Entry 3). Hydrogenation of **5** in a saturated solution in 1,2-dichlorethane (ca. 0.7 mol l^{-1}) using crude **L2** proceeded with the same results (Table 2, Entry 5).

A standard reaction time of 12 h was used, however, with chloroalkanes as solvents complete hydrogenations required shorter time periods. As demonstrated by Figure 2, complete conversion was achieved for the hydrogenation of substrate **5** in 1,2-dichloroethane, using 0.1 mol % of $[Rh(COD)\mathbf{L2}_2]BF_4$ as catalyst, within 63 min. A turnover frequency of 952 h^{-1} is calculated from the data. Furthermore, all hydrogenations proceeded essentially without induction period.

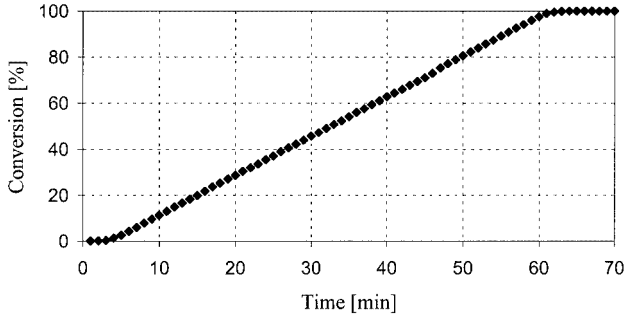


Figure 2. Hydrogen consumption in the asymmetric hydrogenation of **5** in 1,2-dichloroethane (1 bar H_2 pressure, catalyst 0.1 mol % $[Rh(COD)\mathbf{L2}_2]BF_4$, *c*(**5**) = 0.1 mol L^{-1})

In asymmetric hydrogenations with diphosphanes as ligands, increase of hydrogen pressure usually leads to decrease of enantioselectivity (examples: DIPAMP[24] or BINAP[25]). The data in Table 3, describing the dependence of enantioselectivity of the hydrogenation of **5** on pressure, demonstrate relatively low sensitivity of enantioselectivity in the case of the monodentate ligand **L2**.

Table 3. Dependence of the enantiomeric excess of **6**, obtained by asymmetric hydrogenation of **5**, on the pressure of H_2 using 1,2-dichloroethane as solvent and $[Rh(COD)\mathbf{L2}_2]BF_4$ as precatalyst

Entry[a]	Pressure (bar)	Enantiomeric excess of **6,** [% *ee*] (absol. config.)
1	20	98.6 (*S*)
2	40	97.9 (*S*)
3	60	97.3 (*S*)
4	80	97.0 (*S*)
5	100	96.7 (*S*)

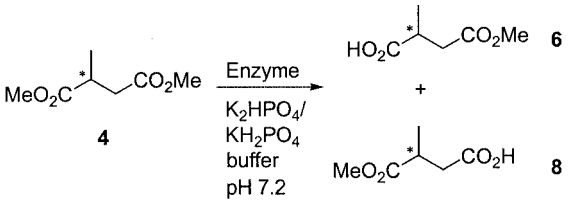
[a] Reaction conditions: 20 °C; 12 h; 1,2-dichloroethane; *c*(**5**) = 0.1 mol L^{-1}; molar ratio **L2**/Rh = 2.2, ratio substrate/catalyst = 200:1, every case 100% conversion. Determination of enantiomeric excess as described in Table 1.

While ligand **L2** gave rise to excellent enantioselectivities in hydrogenations of 2-methylensuccinic acid derivatives, re-

sults obtained with dehydroamino acids were not completely satisfactory.[26]

Enzyme-Catalyzed Semisaponification of Dimethyl 2-Methylsuccinate

Enzyme-catalyzed selective saponification of diester (*S*)-**4** (Scheme 4) appears an interesting route to mono ester (*S*)-**6**. It has been reported that kinetic resolution of *rac*-dimethyl 2-methylsuccinate (*rac*-**4**) catalyzed by porcine pancreatic lipase[27] or α-chymotrypsin[28] selectively yields mono ester (*S*)-**6** or (*S*)-**8**, respectively. Induced by these reports, both enzymes were used to catalyze the semisaponification of diester (*S*)-**4**, obtained by asymmetric hydrogenation. Surprisingly, both reactions proceeded with low regioselectivity and only mixtures of mono esters (*S*)-**6** and (*S*)-**8** were obtained (Table 4, Entries 5, 6). As a consequence, further screening with a variety of commercially available enzymes was carried out. As demonstrated by the data of Table 4, selectivity and reactivity of the saponification of (*S*)-**4** were generally low, excepting catalysis with a lipase from *Mucor javanicus* (*MJL*), which gave rise to completely selective formation of (*S*)-**6**. Saponification of racemic diester *rac*-**4** (conversion 40%) furnished mono ester (*S*)-**6** with only 36.5% *ee* (enantioselectivity $E = 2.3$).

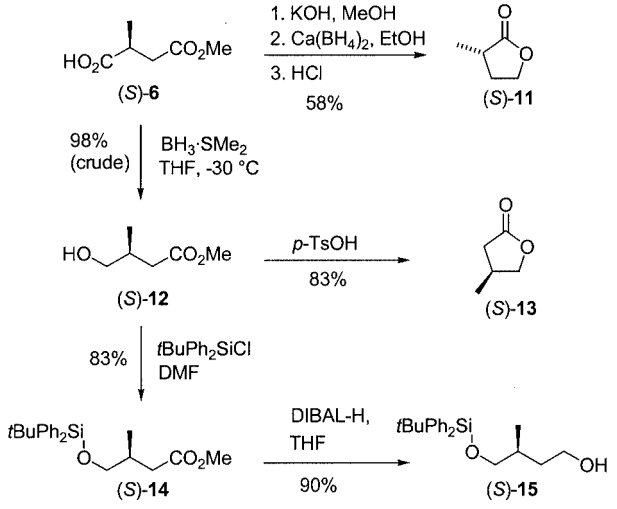


Scheme 4. Enzyme-catalyzed semisaponification of dimethyl 2-methylsuccinate

Table 4. Enzyme-catalyzed hydrolysis of diester (*S*)-**4** to give mono esters (*S*)-**6** and (*S*)-**8**

Entry	Enzyme	(*S*)-**8**/(*S*)-**6**	Conversion [%]
1	PPL (type I)	–	0
2	PS-C-Amano II	–	0
3	Novozyme 435	74:26	100
4	Chirazyme L7	68:32	100
5	PPL (type II)	50:50	100
6	α-Chymotrypsin	31:69	100
7	PS-C-Amano I	26:74	100
8	Esterase from hog liver	24:76	100
9	*Aspergillus niger* lipase	19:81	100
10	Chirazyme L1	14:86	100
11	*Mucor javanicus* lipase	0:100	100

According to these results, use of the enzymes listed in Table 4 does not allow regio- and enantioselective semisaponification of *rac*-**4**. The combination of sequential asymmetric hydrogenation of dimethyl 2-methylenesuccinate and *MJL* catalyzed semisaponification of the resultant (*S*)-**4** appears promising.



Scheme 5. Preparation of C_5-building blocks

Preparation of Hydroisoprene Synthons

Mono ester (*S*)-**6** was transformed via simple routes into a variety of synthetically important hydroisoprene equivalents (Scheme 5). Thus, selective reduction with $Ca(BH_4)_2$, prepared in situ from $CaCl_2$ and $NaBH_4$, and subsequent acidic workup gave lactone (*S*)-**11** in 58% yield. A more efficient access of a C_5-building block was selective reduction with BH_3·THF furnishing pure hydroxy ester (*S*)-**12** in essentially quantitative yield and treatment with a catalytic amount of *p*-TsOH to give lactone (*S*)-**13** in 83% yield. Silylation of (*S*)-**12** using conditions avoiding lactone formation gave ester (*S*)-**14** which was reduced with DIBAL-H to give alcohol (*S*)-**15**. From (*S*)-**15** numerous further C_5-building blocks can be obtained that are suitable for natural products syntheses.

Conclusion

An enantiomeric excess of 99.7% *ee* was achieved for the asymmetric catalytic hydrogenation of 2-(2-methoxy-2-oxoethyl)acrylic acid (**5**) to give (2*S*)-4-methoxy-2-methyl-4-oxobutanoic acid [(*S*)-**6**], using a catalyst formed in situ from $[Rh(COD)_2]BF_4$ and the chiral phosphite **L2**. The choice of the solvent 1,2-dichloroethane was crucial for high selectivity. Enzyme-catalyzed semi-saponification of dimethyl 2-methylsuccinate was investigated using a wide variety of enzymes. A high degree of regioselectivity was only found for *Mucor javanicus* lipase. Mono ester (*S*)-**6** can be transformed in good yield into C_5-building blocks, i. a. (3*S*)-3-methyldihydrofuran-2(3*H*)-one [(*S*)-**11**], that are useful for natural product syntheses.

Experimental Section

General Remarks: Reagents, including (piperidinomethyl)polystyrene, were purchased from Aldrich or Fluka. Hydrogen of grade

5.0 from Messer-Griesheim was used for hydrogenations. Enzymes were purchased from the following suppliers: novozyme from Novo Nordisk, PPL type I and II, α-chymotrypsin, hog liver esterase, *Aspergillus niger* lipase and *Mucor javanicus* lipase from Sigma−Aldrich/Fluka, PS-C-Amano I and II (*Pseudomonas cepacia)* from Amano Enzyme, Chirazyme L1 and L7 from Roche Molecular Biochemicals. Substrates **5**[19] and **7**[29] were prepared according to the literature. Reactions in dry solvents were carried out under argon atmosphere using standard Schlenk techniques. Thin-layer chromatography was performed on pre-coated TLC-plates (Polygram Sil G/UV_{254}, Macherey−Nagel); I_2 vapour, $KMnO_4$ or molybdatophosphoric acid solutions were used for visualization. For column chromatography Macherey−Nagel silica gel grade 60 (0.04−0.063 mm) was used. Melting and boiling points are uncorrected. NMR spectra were recorded at 300.13 MHz (^{1}H), 75.47 MHz (^{13}C) and 121.50 MHz (^{31}P) with a Bruker Avance AC-300 or a Bruker Avance DRX-300 instrument. Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in ppm downfield from TMS as internal standard. ^{31}P NMR chemical shifts refer to H_3PO_4 as external standard. Signals are quoted as s (singlet), d (doublet), br. (broad) and m (multiplet). Optical rotations were measured with a Perkin−Elmer P 241 polarimeter. Mass spectra were performed with a Joel JMS 700 (FAB) or a ZAB 2F (EI) instrument. Hydrogenations under pressure were performed in a 250 mL autoclave (Roth). GC analyses were performed using a Hewlett−Packard HP 5890 series II instrument equipped with Chrompack CP-γ-cyclodextrin-TFA column (30 m × 0.25 mm) [FID, carrier gas He (60 mL/min)]. Autotitration experiments were performed with a Metrohm Dosimat 665 equipped with an Impulsomat 614 and a pH-Meter 654.

(*aS*,*S*)-4-[(1*S*)-2-Methoxy-1-phenylethoxy]dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]-dioxaphosphepine (L2): A solution of (*aS*)-2,2′-binaphthol (3.15 g, 11.0 mmol) in dry THF (5.0 mL) was added dropwise to a stirred suspension of (piperidinomethyl)polystyrene (7.50 g, ca. 22 mmol) and PCl_3 (1.15 mL, 13.2 mmol) in dry toluene (40 mL). The reaction mixture was stirred at room temperature for 12 h and then filtered. The filtrate was concentrated in vacuo to yield crude (*aS*)-4-chlorodinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepine (3.41 g, 9.7 mmol, 88%) as a colorless solid, which was sufficiently pure for the subsequent reaction [^{31}P NMR ($CDCl_3$): one peak at δ = 179.68 ppm]. An aliquot (1.14 g, 3.25 mmol) was dissolved in dry toluene (7 mL) and triethylamine (360 mg, 3.54 mmol) was added. The resultant solution was cooled to −78 °C and dropwise treated with a solution of alcohol (*S*)-**8** (450 mg, 2.95 mmol) in dry toluene (1 mL). The reaction mixture was stirred at −78 °C for 1 h and then at room temperature for 12 h, then filtered through a short pad (2 cm) of celite and concentrated in vacuo. The crude product (1.17 g, 85%) was 90% pure according to ^{31}P NMR (peaks of impurities at 3.7, 4.1, 13.6 and 144.4 ppm). It nevertheless gave excellent results in hydrogenation experiments. A pure sample was obtained by rapid column chromatography (silica, petroleum ether/EtOAc, 19:1) as a colorless solid (355 mg, 0.76 mmol, 26%). M.p. (softening point) 58−60 °C. $[\alpha]_D^{20}$ = 381 (*c* = 0.78, $CHCl_3$). ^{1}H NMR (CD_2Cl_2): δ = 3.43 (s, 3 H, CH_3), 3.59 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2), 5.46 (dt, *J* = 9.2, *J* = 6.0 Hz, 1 H, CH), 6.90 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, Ar-H), 7.21−7.49 (m, 11 H, Ar-H), 7.55 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H, Ar-H), 7.84 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H, Ar-H), 7.91−7.98 (m, 2 H, Ar-H), 8.02 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (CD_2Cl_2): δ = 59.00 (q, OCH_3), 76.67 (dd, $^2J_{C,P}$ = 18.0 Hz, Ph*C*HCH$_2$), 76.86 (dd, $^3J_{C,P}$ = 3.5 Hz, CH_2), 121.88 (dd, $J_{C,P}$ = 2.1 Hz, Ar-C), 122.21 (d, Ar-C), 122.83 (ds, $J_{C,P}$ = 2.1 Hz, Ar-C), 124.30 (ds, $J_{C,P}$ = 4.8 Hz, Ar-C), 124.95 (d, Ar-C), 125.14 (d, Ar-C), 126.18 (2 × d, 2 × Ar-C), 126.31 (2 × d, 2 × Ar-C), 126.76 (d, Ar-C), 126.83 (d, Ar-C), 126.89 (d, Ar-C), 128.37 (d, Ar-C), 128.46 (2 × d, 2 × Ar-C), 128.52 (2 × d, 2 × Ar-C), 129.55 (d, Ar-C), 130.38 (d, Ar-C), 131.20 (s, Ar-C), 131.66 (s, Ar-C), 132.51 (ds, $^2J_{C,P}$ = 1.4 Hz, Ar-C), 132.83 (ds, $^2J_{C,P}$ = 2.1 Hz, Ar-C),138.46 (ds, $^3J_{C,P}$ = 2.8 Hz, Ph-C_{ipso}), 147.62 (ds, $^2J_{C,P}$ = 2.1 Hz, Ar-C), 148.05 (ds, $^2J_{C,P}$ = 4.5 Hz, Ar-C) ppm. ^{31}P NMR (CD_2Cl_2, 121.495 MHz): δ = 151.54 ppm. HRMS (FAB+) [M^+ + H] ($C_{29}H_{24}O_4P$): calcd. 467.1412; found 467.1370.

General Procedure for Asymmetric Hydrogenations, Determination of Enantiomeric Excess: A solution of **L1** or **L2** (2.20 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise to a cooled (−78 °C) solution of [Rh(COD)$_2$]BF_4 (406 mg, 1.0 mmol) in dry CH_2Cl_2 (30 mL). The mixture was stirred at −78 °C for 20 min and then at room temperature for 20 min. Aliquots of the resultant yellow solution of [Rh(COD)(**L2**)$_2$]BF_4 were used for hydrogenations. This procedure was used for the hydrogenations described in Table 1. For reactions described in Table 2 and 3 and Figure 2, the same procedure was carried out except that 1,2-dichloroethane was used as solvent and the initial mixture was cooled to −25 °C.

For hydrogenation, a Schlenk tube was charged with 0.5 mmol of substrate and a stir bar. Then five vacuum/argon cycles and five vacuum/hydrogen cycles were carried out and 5 mL of anhydrous, deoxygenated solvent and an appropriate amount the precatalyst solution were added. The Schlenk tube was then connected to the hydrogen reservoir and hydrogenation was allowed to proceed at room temperature under a hydrogen pressure of 1.1 bar for 12 h.

For determination of the enantiomeric excess, the reaction mixture was concentrated in vacuo and, except in the case of **4**, the residue was treated with a solution of diazomethane in diethyl ether until the yellow color persisted. For removal of the catalyst, the solution was passed through a short plug of silica which was washed with diethyl ether. Enantiomeric excess was determined by GC; column: Chrompack CP-γ-cyclodextrin-TA (30 m × 0.25 mm), flow: 60 mL·h^{-1}, column temp.: 70 °C, t_R[(*S*)-**4**] = 22.8 min, t_R[(*R*)-**4**] = 25.6 min. Absolute configuration was determined via the sign of the optical rotation.[30]

(2*S*)-4-Methoxy-2-methyl-4-oxobutanoic Acid [(*S*)-6]: The precatalyst was prepared by dropwise adding a solution of **L2** (0.694 mmol, 324 mg) in dry 1,2-dichloroethane (2 mL) to a cooled (−25 °C) solution of [Rh(COD)$_2$]BF_4 (121 mg, 0.347 mmol) in dry 1,2-dichloroethane (3 mL). The mixture was stirred at −25 °C for 20 min and for 20 min at room temperature. Hydrogenation of **5** (50.00 g, 346.9 mmol) was carried out according to the general procedure using 1,2-dichloroethane (500 mL). After 12 h, the mixture was transferred into a distillation apparatus equipped with a 20 cm Vigreux column. The solvent was distilled off at ambient pressure and the residue was distilled in vacuo (80 °C/4.4 mbar) to yield 48.35 g (95%) of (*S*)-**6**, colorless liquid. $[\alpha]_D^{20}$ = −10.8 (*c* = 3.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.25 (d, $^3J_{H,H}$ = 7.4 Hz, 3 H, CCH_3), 2.42 (dd, $J_{H,H}$ = 16.7, $J_{H,H}$ = 6.1 Hz, 1 H, CH_2), 2.74 (dd, $J_{H,H}$ = 16.9, $J_{H,H}$ = 8.1 Hz, 1 H, CH_2), 2.89−3.02 (m, 1 H, CH), 3.68 (s, 1 H, OCH_3), 9.88 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.79 (q, CCH_3), 35.63 (d, CH), 37.06 (t, CH_2), 51.79 (q, OCH_3), 172.18 (s, *C*O_2CH_3), 181.24 (s, CO_2H) ppm. MS (CI) [M + H^+] ($C_6H_{11}O_4$): *m*/*z* = 147.1. $C_6H_{11}O_4$ (146.14) calcd. C 49.31, H 6.90, found C 49.25, H 6.88.

General Procedure for Enzyme-Catalyzed Saponifications: The enzyme (ca. 200 mg) was added to a solution of dimethyl (2*S*)-2-methylsuccinate (*S*)-**4** (500 mg, 3.13 mmol) in 1 N aqueous KH_2PO_4/K_2HPO_4 buffer (5 mL, pH 7.2). The pH was kept at 7.2 by addition of 1 N NaOH solution, using an autotitrator, until

2.8 mL were consumed [corresponding to 90% conversion of (*S*)-**4**]. The mixture was then filtered through celite and the filtrate extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried (Na_2SO_4) and concentrated in vacuo to give unchanged ester (*S*)-**4**. The aqueous layer was acidified with 2 N H_2SO_4 until pH 2 was reached and then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo to yield a mixture of half esters (*S*)-**6** and (*S*)-**8**. Their ratio was determined by ^{1}H NMR spectroscopy.

For determination of the enantiospecificity of the hydrolysis catalyzed by *Mucor javanicus* lipase (*MJL*), racemic **4** was hydrolyzed as described above, except that the reaction was stopped at 40% conversion. Determination of the enantiomeric excess was carried out as described above.

(3*S*)-3-Methyldihydrofuran-2(3H)-one [(*S*)-11]: A cold solution (0 °C) of mono ester (*S*)-**6** (1.00 g, 6.85 mmol) in methanol (3.5 mL) was treated with 2 M aqueous KOH solution (3.4 mL, 6.85 mmol). After 15 min the solution was concentrated and the residue dried in vacuo. The residual oil was dissolved in ethanol (30 mL) and the solution was cooled in an ice bath. Powdered anhydrous $CaCl_2$ (1.92 g, 17.3 mmol) was added and the suspension was stirred for 15 min. Then a suspension of $NaBH_4$ (1.03 g, 24.7 mmol) in ethanol (10 mL) was added and the mixture was stirred at room temperature for 12 h. The mixture was cooled to 0 °C and acidified (pH, 1) with 3 M HCl. After 30 min the mixture was extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by Kugelrohr distillation (90 °C, 0.6 mbar) to yield lactone (*S*)-**11** as colorless, volatile oil (405 mg, 58%). $[\alpha]_D^{20} = -20.1$ (c = 2.0, EtOH), ref.[1a] $[\alpha]_D^{20} = -22.9$ (c = 2, EtOH). ^{1}H NMR ($CDCl_3$): δ = 1.22 (d, ^3J = 7.4 Hz, 3 H, CH_3), 1.81−1.93 (m, 1 H, CHC*H*H), 2.35−2.43 (m, 1 H, CHCH*H*), 2.50−2.60 (m, 1 H, CH), 4.13 (dt, ^3J = 7.4, ^2J = 9.2 Hz, 1 H, C(*H*H)O], 4.28 (dt, ^3J = 2.7, ^2J = 9.0 Hz, 1 H, C(H*H*)O] ppm. ^{13}C NMR ($CDCl_3$): δ = 14.98 (q, CH_3), 30.53 (t, CH*C*H$_2$), 33.97 (d, CH), 66.12 (t, *C*H$_2$O), 180.05 (s, CO) ppm. HRMS (EI) [M^+] ($C_5H_8O_2$): calcd. 100.0524; found 100.0523. $C_5H_8O_2$ (100.12) calcd. C 59.98, H 8.05, found C 59.69, H 8.04.

Methyl (3*S*)-4-Hydroxy-3-methylbutanoate [(*S*)-12]: $BH_3{\cdot}SMe_2$ (25.7 mL, 257 mmol) was added dropwise to a cold (−30 °C) solution of (*S*)-**6** (30.00 g, 205.5 mmol) in dry THF (150 mL). The mixture was warmed to 0 °C over a period of 1.5 h. After 0.5 h methanol (50 mL) was added and volatiles were removed in vacuo. This procedure was repeated twice. The resultant (*S*)-**12** (27.11 g, 98%), a colorless liquid, was pure according to ^{1}H NMR and was used without further purification for the next steps. ^{1}H NMR ($CDCl_3$): δ = 0.95 (d, ^3J = 6.6 Hz, 3 H, CCH_3), 1.79 (br. s, 1 H, OH), 2.10−2.23 (m, 1 H, CH), 2.24 (dd, ^2J = 14.7, ^3J = 6.6 Hz, 1 H, CHC=O), 2.43 (dd, ^2J = 14.7, ^3J = 6.2 Hz, 1 H, CHC=O), 3.43 (dd, ^2J = 10.7, ^3J = 6.6 Hz, 1 H, C*H*OH), 3.55 (dd, ^2J = 10.7, ^3J = 5.2 Hz, 1 H, C*H*OH), 3.66 (s, 3 H, OCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.69 (q, C*C*H$_3$), 33.02 (d, CH), 38.28 (t, *C*H$_2$C=O), 51.55 (q, OCH_3), 67.55 (t, CH_2OH), 173.84 (s, C=O) ppm. HRMS (FAB+) [$M^+ - H_2O$] ($C_6H_{10}O_2$): calcd. 114.0681; found 114.0687; [M^+ − MeOH] ($C_5H_8O_2$): calcd. 100.0524; found 100.0520.

(4*S*)-4-Methyldihydrofuran-2(3*H*)-one [(*S*)-13]: A mixture of (*S*)-**12** (9.00 g, 68.1 mmol) and *p*TsOH·H_2O (20 mg, 0.11 mmol) was stirred for 15 min and then fractionally distilled in vacuo (88−90 °C/55 mbar) to yield (*S*)-**13** (5.2 g, 84%), colorless oil. $[\alpha]_D^{20} = -24.8$ (c = 4.35, MeOH), ref.[1a] $[\alpha]_D^{20} = -24.7$ (c = 4, MeOH; 97.2% *ee*). ^{1}H NMR ($CDCl_3$): δ = 1.14 (d, ^3J = 6.6 Hz, 3 H, CH_3), 2.11 (dd, ^2J = 20.1, ^3J = 10.5 Hz, 1 H, CHC=O), 2.57−2.74 (m, 2 H, CHC=O and CH), 3.84 (dd, ^2J = 8.8, ^3J = 6.3 Hz, 1 H, CHO), 4.39 (dd, ^2J = 8.8, ^3J = 7.4 Hz, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.90 (q, CH_3), 33.36 (d, CH), 36.10 (t, *C*H$_2$C=O), 74.65 (t, CH_2O), 177.21 (s, C=O) ppm. HRMS (EI) [M^+] ($C_5H_8O_2$): calcd. 100.0524; found 100.0520. $C_5H_8O_2$ (100.12) calcd. C 59.98, H 8.05, found C 59.73, H 8.04.

Methyl (3*S*)-4-{[*tert*-Butyl(diphenyl)silyl]oxy}-3-methylbutanoate [(*S*)-14]: *tert*-Butyldiphenylsilyl chloride (38.80 g, 141.5 mmol) was added dropwise to a solution of crude (*S*)-**12** (17.00 g, 128.6 mmol), prepared as described above, and imidazole (13.13 g, 192.9 mmol) in anhydrous DMF (100 mL). After 3 h the reaction mixture was treated with water (50 mL) and extracted with diethyl ether (3 × 120 mL). The combined organic layers were washed once with 1 M HCl (100 mL) and sat. $NaHCO_3$ solution (100 mL) and dried with Na_2SO_4. The solvent was removed in vacuo and the residue purified by column chromatography (silica, petroleum ether/Et_2O 9:1; TLC: R_f = 0.58) to yield ester (*S*)-**14** as a colorless oil (16.2 g, 83%). $[\alpha]_D^{20} = -4.9$ (c = 3.7 $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.93 (d, ^3J = 6.5 Hz, 3 H, CHC*H*$_3$), 1.03 [s, 9 H, SiC(C*H*$_3$)$_3$], 2.12 (dd, ^2J = 14.3, ^3J = 8.12 Hz, 1 H, C*H*$_2$COO), 2.21 (m, 1 H, C*H*CH$_3$), 2.58 (dd, ^2J = 14.3, ^3J = 4.7 Hz, 1 H, C*H*$_2$COO), 3.43 (dd, ^2J = 9.8, ^3J = 6.3 Hz, 1 H, C*H*$_2$OSi), 3.53 (dd, ^2J = 9.8, ^3J = 5.2 Hz, 1 H, C*H*$_2$OSi), 3.63 (s, 3 H, CO_2CH_3), 7.61−7.64 (m, 10 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.63 (q, CH*C*H$_3$), 19.29 [s, Si*C*(CH$_3$)$_3$], 26.83 [q, SiC(*C*H$_3$)$_3$], 33.02 (d, CH), 38.05 (t, *C*H$_2$CO$_2$), 51.38 (q, CO$_2$*C*H$_3$); 68.08 (t, *C*H$_2$OSi), 127.63 (d, Ph-C), 129.59 (d, Ph), 133.71 (s, Ph-C$_{ipso}$), 135.60 (d, Ph), 173.64 (s, CO_2) ppm. HRMS (FAB+) [M^+ + H] ($C_{22}H_{31}O_3Si$): calcd. 371.2042; found 371.2031. $C_{22}H_{30}O_3Si$ (370.56) calcd. C 71.31, H 8.16, found C 71.16, H 8.16.

(3*S*)-4-{[*tert*-Butyl(diphenyl)silyl]oxy}-3-methylbutan-1-ol [(*S*)-15]: A 1 M solution of diisobutylaluminum hydride in toluene (108 mL, 107.9 mmol) was slowly added to a cold (−78 °C) solution of ester (*S*)-**14** (16.00 g, 43.2 mmol) in anhydrous THF (80 mL). After 2 h the reaction mixture was warmed to −20 °C and was then stirred for 1 h. Then 1 M aqueous NH_4Cl solution (60 mL) was added, and the reaction mixture was allowed to reach room temperature. The reaction mixture was extracted with ethyl acetate (3 × 75 mL), and the combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica, petroleum ether/EtOAc, 4:1; TLC: R_f = 0.22) to yield (*S*)-**15** as a colorless oil (13.32 g, 90%). $[\alpha]_D^{20} = -2.0$ (c = 2.3 $CHCl_3$), ref.[31] $[\alpha]_D^{20} = 4.7$ (c = 3.3 $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.88 (d, ^3J = 6.8, 3 H, CHC*H*$_3$), 1.04 [s, 9 H, SiC(C*H*$_3$)$_3$], 1.44−1.56 (m, 1 H, CH$_2$C*H*$_2$CH) 1.60−1.74 (m, 1 H, CH$_2$C*H*$_2$CH), 1.75−1.87 (m, 1 H, C*H*CH$_3$), 3.44−3.55 (m, 2 H, CHSi), 3.59−3.76 (m, 2 H, HOCH$_2$), 7.33−7.70 (m, 10 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.19 (q, CH*C*H$_3$), 19.22 [s, Si*C*(CH$_3$)$_3$], 26.83 [q, SiC(*C*H$_3$)$_3$], 33.27 (d, CH), 37.35 (t, CH$_2$*C*H$_2$CH), 61.19 (t, HOCH$_2$), 69.25 (t, CH$_2$OSi), 127.65 (d, Ph), 129.65 (d, Ph), 133.53 (s, PhC$_{ipso}$), 135.66 (d, Ph) ppm. HRMS (FAB+) [M^+ + H] ($C_{21}H_{31}O_2Si$): calcd. 343.2093; found 343.2106. $C_{21}H_{30}O_2Si$ (342.55) calcd. C 73.63, H 8.83, found C 73.55, H 8.83.

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