Asymmetric Catalysis

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Discrimination of β-Ketoesters by Ruthenium(II)–Binap-Catalyzed Asymmetric Hydrogenation**

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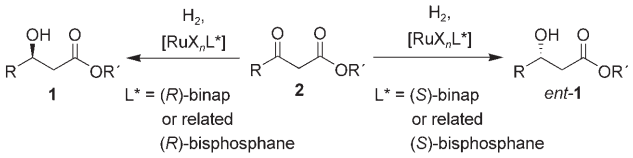
Dedicated to Professor Ivars Kalwinsch on the occasion of his 60th birthday

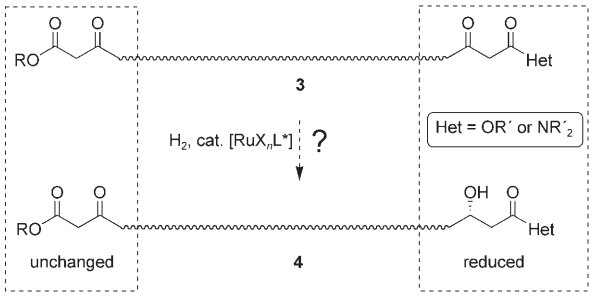
Since the pioneering work of Noyori and co-workers,[1] Ru^{II} complexes of enantiomerically pure atropisomers of 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (binap) have become the standard catalysts for the asymmetric hydrogenation (AH) of β-ketoesters **2** (Scheme 1).[2] β-Hydroxyesters **1** or their enantiomers *ent*-**1** are formed in excellent yields and with rigorously controlled and unambiguously predictable absolute configurations.[3] Such reductions may be conducted with as little as 0.01 mol% of the catalyst and on scales of milligrams, moles,[4] 240-kg batches,[5] or tons of the substrate.[6]



Scheme 1. Ru^{II}-catalyzed AH of β-ketoesters **2** controlled by enantiomerically pure bisphosphane ligands.[1–3]

Other Ru^{II} complexes inspired by the original [RuX_2-(binap)] catalysts formed in situ and described by Noyori and co-workers[1,7] have been developed to improve the reduction.[8] Many early AH reactions of β-ketoesters suffered from the requirement of temperatures of up to 100 °C and/or hydrogen pressures of up to 100 bar.[7] In contrast, contemporary AH reactions of β-ketoesters can be performed at temperatures as low as room temperature, at hydrogen pressures as low as 1 bar, and with standard glassware.[9] AH reactions of β-ketoesters have not only been studied from a methodological point of view, but have also been used widely as an entry into natural product synthesis.[10]

In an ongoing project, we needed to differentiate two structurally different β-ketocarboxylic acid moieties within an intermediate of generic structure **3** (Scheme 2). We wondered whether such a species could be tailored such that one keto group could be hydrogenated asymmetrically while the other remained inert. To the best of our knowledge, the substituent dependence of the rate of AH of β-ketoesters and β-ketoamides has not been recorded.[11] Consequently, we decided to gather the first pertinent data. To this end we studied intermolecularly rather than intramolecularly competing AH reactions because of the readier accessibility of the requisite substrates, namely mono(β-ketocarboxylic acid) derivatives.



Scheme 2. Asymmetric monohydrogenation of bis(β-ketocarboxylic acid) derivatives **3** as a means of terminus differentiation.

For our investigation of the AH of β-ketoesters[12] and β-ketoamides, we chose substrates with chain lengths such that the ensuing AH reactions could be monitored by GC for any substrate mixture. The substrates selected by these criteria were the sterically and electronically varied β-ketoesters **5a–d**[13,14] (Table 1) and three *N*,*N*-dialkyl β-ketoamides.[15] In the presence of "[{$RuCl_2$((*S*)-binap)}$_2$]·NEt_3",[16,17] up to three of these compounds could be hydrogenated one by one. Herein we describe the AH of binary mixtures of the β-ketoesters **5a–d** with concomitant kinetic differentiation of their constituents. Related experiments that include the AH of β-ketoamides are reported separately.[15]

Each of the β-ketoesters **5a–d** (0.5 mmol) was hydrogenated as a solution in methanol (4.0 mL) at room temperature in excellent yield (93–97%) and with excellent enantioselectivity (94–98% *ee*) in the presence of the catalyst "[{$RuCl_2$((*S*)-binap)}$_2$]·NEt_3" (2.5 μmol, 0.5 mol%)[18] (Table 1). This complex is arguably the most practical isolable

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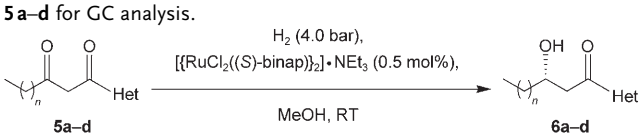
Table 1: Reference β-hydroxyesters **6a–d** prepared by AH of β-ketoesters **5a–d** for GC analysis.



5,6	*n*	Het	*t* [h]	Yield [%][a]	*ee* [%][b]
a	2	O*t*Bu	8	95	98
b	4	OMe	9	95	>98
c	2	OCH_2CF_3	16	97	96
d	8	$OCH(CF_3)_2$	24	93	94
–	–	NR_2		Ref. [15]	

[a] Yield of the isolated product after flash chromatography on silica gel.[21]. [b] Determined by GC.[22]

catalyst for AH reactions,[19] as it can be handled in air, stored under an inert atmosphere for several months, and used at 40–80 °C and a hydrogen pressure of 3.4 bar if activated by a strong acid.[20] We performed our hydrogenation reactions under the same low pressure even at room temperature and in the absence of an acid.

The AH reactions summarized in Table 1 provided us with the *S*-configured β-hydroxyesters **6a–d**. These were required as reference compounds for monitoring the progress with time of the hydrogenation experiments undertaken subsequently (Figures 2–5). In the latter experiments we used the same catalyst (2.5 μmol, 0.25 mol%) at unaltered (ambient) temperature and a hydrogen pressure of 4 bar. We used ethanol (8.0 mL) as the solvent, and no longer methanol, because of better reproducibility and shorter reaction times. Moreover, we hydrogenated 1:1 mixtures of two of the aforementioned β-ketoesters (each 0.5 mmol) rather than a single compound. In other words, both the catalyst concentration and the concentration of a given β-ketoester amounted to half of what they were in the single-substrate experiments of Table 1, whereas the total β-ketoester concentration was unchanged.

Each of the time-dependent AH reactions was run in a discontinuous manner. That is, the hydrogen atmosphere (4 bar) was exchanged for dry argon (1 bar) before a 100-μL sample of the reaction mixture was taken for analysis, and the remaining mixture was then resubjected to the AH conditions. In this manner, we collected between 7 (Figure 3) and 12 (Figure 4) samples during the hydrogenation of a pair of competing substrates. The quantities of the β-ketoester(s) still present in the reaction mixture and the β-hydroxyester(s) already formed were determined by GC (for an example, see Figure 1).[23] Comparison of the peaks due to the components in question[24] with a reference peak due to previously added biphenyl allowed us to determine absolute rather than only relative yield values. The plots of yield versus time thus obtained are shown in Figures 2–5.

When we hydrogenated a 1:1 (mol/mol) mixture of the β-keto(*tert*-butyl ester) **5a** and the β-keto(methyl ester) **5b**, the former reacted slightly faster (Figure 2). This reactivity order is contrasteric. We explained the rate effect in terms of the slightly greater Lewis basicity of the C(=O)O*t*Bu group relative to that of the C(=O)OMe group. This explanation

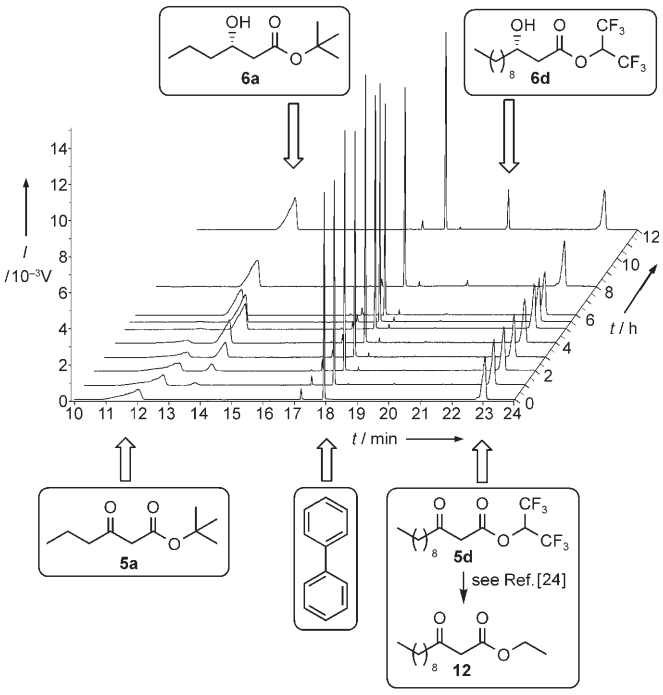


Figure 1. Gas–liquid chromatograms documenting the progress with time of the AH of the β-ketoester mixture shown in Figure 4.

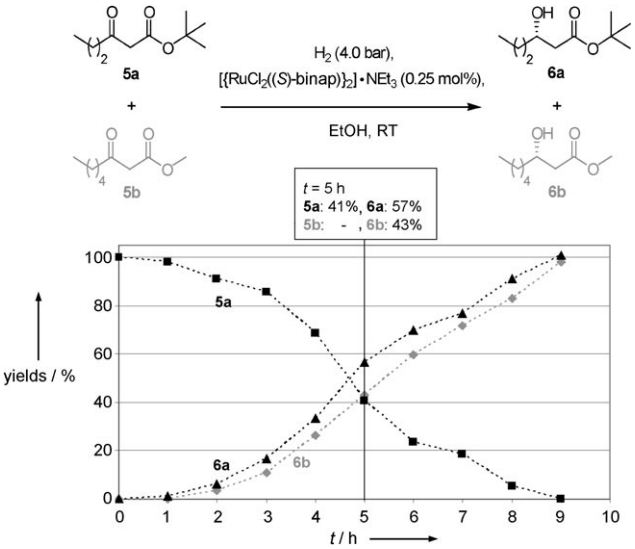


Figure 2. Progress with time of the AH of a 1:1 (mol/mol) mixture of β-ketoesters **5a** and **5b**; ■ **5a**, ▲ **6a**, ◆ **6b**. The progress was monitored by interrupting the reaction at the indicated times, removing an aliquot from the mixture (which was then resubmitted to AH conditions), and quantifying the amounts of reactants and products by GC (achiral capillary column)[23] by comparison with the reference peak. The reference was biphenyl, a known amount of which had been added to the reaction mixture at $t = 0$ h. t_R(**5a**) = 12.2 min, t_R(**6a**) = 13.6 min, t_R(**6b**) = 19.4 min, t_R(biphenyl) = 27.3 min (1 μL, 55 °C (25 min)/20 K min^{-1}→120 °C, $p(H_2)$ = 60 kPa); the methyl ester **5b** was not quantifiable in this way because of partial ethanolysis to **10** upon injection into the GC apparatus.[24]

implied that if the difference in the Lewis basicities of the C(=O)–Het moieties in two β-ketocarboxylic acid derivatives R^1–C(=O)CH_2C(=O)–Het^1 and R^2–C(=O)CH_2C(=O)–Het^2 was greater than for Het = O*t*Bu versus OMe, the difference in the AH rates of the respective substrates should be greater. This expectation was corroborated by the distinctly better kinetic differentiation of the constituents of a 1:1 mixture of the β-keto(*tert*-butyl ester) **5a** and the β-keto(trifluoroethyl ester) **5c** through AH (Figure 3): After 6 h, most of the *tert*-butyl ester had disappeared (6% remaining) as a result of the

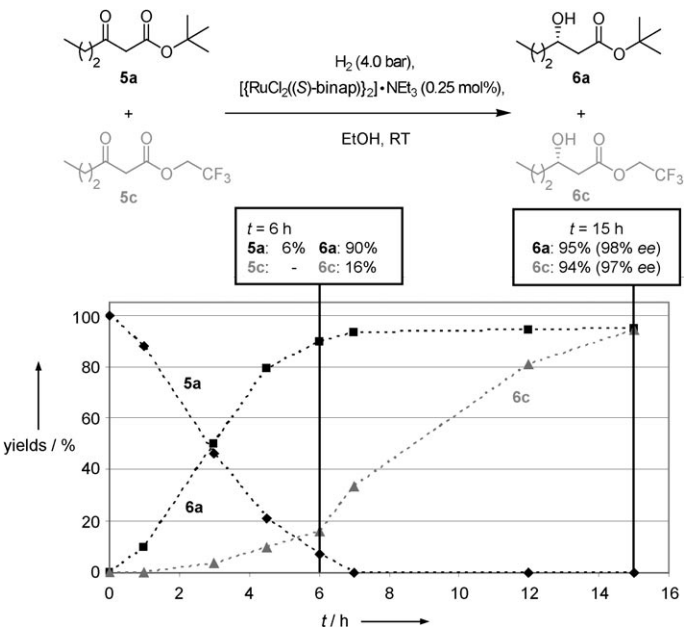


Figure 3. Progress with time of the AH of a 1:1 (mol/mol) mixture of β-ketoesters **5a** and **5c**; ◆ **5a**, ■ **6a**, ▲ **6c**. The yields were determined as detailed in Figure 2. t_R(**5a**) = 21.1 min, t_R(**6a**) = 22.2 min, t_R(**6c**) = 11.2 min, t_R(biphenyl) = 28.6 min (1 μL, 35 °C (15 min)/ 20 K min^{-1}→60 °C (10 min)/20 K min^{-1}→200 °C, $p(H_2)$ = 60 kPa); the trifluoroethyl ester **5c** was not quantifiable in this way because of partial ethanolysis to **11**[24] upon injection into the GC apparatus.

formation of the corresponding hydroxyester **6a** in 90% yield. After the same time, the hydroxy(trifluoroethyl ester) **6c** was detected by GC in only 16% yield. After 15 h, the β-keto(trifluoroethyl ester) **5c** had been consumed completely to afford the β-hydroxyester **6c** in 94% yield with 97% *ee*. This result shows that the enantioselectivity of the transformation to give **6c** is unaffected by the presence of the *S*-configured β-hydroxy(*tert*-butyl ester) **6a** in the reaction mixture.

We reinforced the differentiation between electron-rich and electron-poor ester moieties in the hydrogenation of a 1:1 mixture of the β-keto(*tert*-butyl ester) **5a** and the β-keto(hexafluoroisopropyl ester) **5d** (Figure 4). After 6 h, the *tert*-butyl ester **5a** had disappeared completely, whereas the hexafluoroisopropyl ester was essentially preserved ("102" % of **5d** remained—as the artifact **12**[24]—according to GC). The corresponding hydroxy(*tert*-butyl ester) **6a** had formed in almost quantitative yield (98% by GC), whereas the hydroxy(hexafluoroisopropyl ester) **6d** had not formed at all.

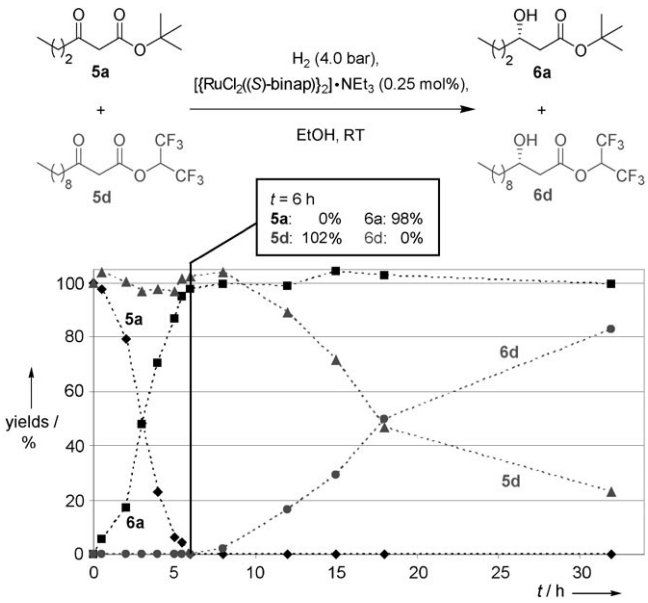
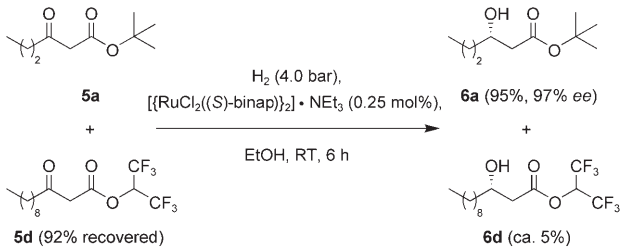


Figure 4. Progress with time of the AH of a 1:1 (mol/mol) mixture of β-ketoesters **5a** and **5d**; ◆ **5a**, ▲ **5d**, ■ **6a**, ● **6d**. The yields were determined as detailed in Figure 2. t_R(**5a**) = 12.1 min; the hexafluoroisopropyl ester **5d** was quantified as its ethanolysis product **12**[24] formed in the GC apparatus (t_R(**12**) = 23.0 min); t_R(**6a**) = 13.5 min, t_R(**6d**) = 19.9 min, t_R(biphenyl) = 17.9 min (1 μL, 55 °C (15 min)/ 20 °C min^{-1}→140 °C (10 min), $p(H_2)$ = 60 kPa); see Figure 1 for the corresponding chromatograms.



Scheme 3. Preparative-scale selective AH of the β-ketoester mixture shown in Figure 4 using 0.5 mmol of each reactant.

We subjected the same 1:1 mixture of **5a** and **5d** to another AH experiment (Scheme 3). Under otherwise identical conditions, the reaction was interrupted just once, after 6 h. We subjected the mixture obtained to workup and isolated the three components detectable by TLC at this point in time by flash chromatography on silica gel.[21] What resulted was in complete accordance with the graphs in Figure 4: None of the β-keto(*tert*-butyl ester) **5a** was found, but the β-hydroxy(*tert*-butyl ester) **6a** was isolated in 95% yield along with 92% of the β-keto(hexafluoroisopropyl ester) **5d** and a small quantity of the β-hydroxy(hexafluoroisopropyl ester) **6d** (no more than 5% yield).

Finally, the kinetic differentiation of β-ketoesters by AH was extended to an almost selective hydrogenation of the β-keto(trifluoroethyl ester) **5c** in the presence of the β-keto(hexafluoroisopropyl ester) **5d** (Figure 5). After 10 h, the reaction of the fairly electron-deficient trifluoroethyl

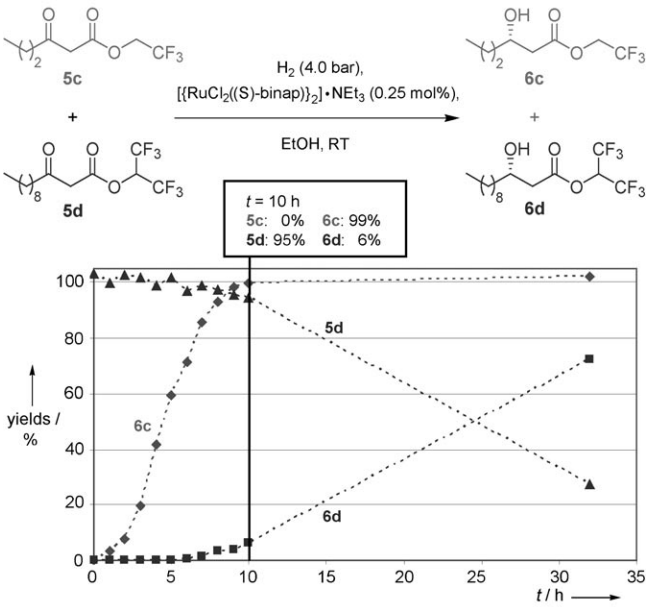


Figure 5. Progress with time of the AH of a 1:1 (mol/mol) mixture of β-ketoesters **5c** and **5d**; ▲ **5d**, ▲ **5d**, ◆ **6c**, ■ **6d**. The yields were determined as detailed in Figure 2. The trifluoroethyl ester **5c** was not quantifiable because of partial ethanolysis to **11**[24] upon injection into the GC apparatus; the hexafluoroisopropyl ester **5d** was quantified as its ethanolysis product **12**[24] formed in the GC apparatus (t_R(**12**) = 24.7 min); t_R(**6c**) = 11.1 min, t_R(**6d**) = 21.7 min, t_R-(biphenyl) = 19.9 min (1 μL, 35 °C (15 min)/20 °C min^{-1}→140 °C (20 min), $p(H_2)$ = 60 kPa).

ester **5c** had reached completion to furnish the corresponding hydroxyester **6c** in 99 % yield. In contrast, as much as 95 % of the competing hexafluoroisopropyl ester **5d** remained, with the hydroxyester derivative **6d** formed in just 6 % yield.

We have detailed herein the sequential asymmetric hydrogenation of β-ketoesters in mixtures. In particular, we found that the rate of [{$RuCl_2$((*S*)-binap)}$_2$]·NEt_3-catalyzed AH of β-ketoesters RC(=O)CH_2C(=O)OR′ depends on the electronic nature of the substituent OR′. The present data suggest that the more Lewis basic the C(=O)OR′ moiety is, the faster the hydrogenation is. This kind of substituent dependence extends to the AH of β-ketoamides, as reported elsewhere along with the implications of our findings in terms of the mechanism of the AH of β-ketocarboxylic acid derivatives.[15]

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[13] See the Supporting Information for the preparation of β-ketoesters **5a**–**d**.

[14] Satisfactory ^{1}H NMR, ^{13}C NMR, and IR spectra were obtained for all new compounds (except **5c** and **5d**, the ^{13}C NMR spectra of which were not recorded, as the compounds exist as keto/enol mixtures), and correct combustion analytical data were obtained for all new compounds (except **5d**, **6c**, **6d**, for which only HRMS data were obtained).

[15] R. Kramer, R. Brückner, *Chem. Eur. J.*, DOI: 10.1002/chem.200700527.

[16] For the first preparation of this complex, see: S. Ikariya, Y. Ishii, H. Kawano, T. Arai, M. Saburi, S. Yoshikawa, S. Akutagawa, *J. Chem. Soc. Chem. Commun.* **1985**, 922 – 924.

[17] "[{$RuCl_2$((*S*)-binap)}$_2$]·NEt_3" is $Et_2NH_2^+$[{RuCl((*S*)-binap)}$_2$(μ-Cl)$_3$]$^-$ (L. DiMichele, S. A. King, A. W. Douglas, *Tetrahedron: Asymmetry Tetrahedron Asym.* **2003**, *14*, 3427 – 3430), that is, isostructural with $Et_2NH_2^+$[{RuCl((*R*)-*p*-MeO-binap)}$_2$(μ-Cl)$_3$]$^-$ (T. Ohta, Y. Tonomura, K. Nozaki, H. Takaya, M. Mashima, *Organometallics* **1996**, *15*, 1521 – 1523) and $Et_2NH_2^+$[{RuCl(1,2-bis(diphenylphosphanyl)benzene)}$_2$(μ-Cl)$_3$]$^-$ (K. Mashima, T. Nakamura, Y. Matsuo, K. Tani, *J. Organomet. Chem.* **2000**, *607*, 51 – 56).

[18] "[{$RuCl_2$((*S*)-binap)}$_2$]·NEt_3"[17] was prepared from commercially available [Ru(cod)Cl_2], (*S*)-binap, and NEt_3 by the procedure in Ref. [9c] in 50–55% yield (lit.:[9c] 75%).

[19] For the first use of [{$RuCl_2$((*S*)-binap)}$_2$]·NEt_3[17] for the AH of a β-ketoester, see Ref. [1a].

[20] See Ref. [9a,c]; a) D. F. Taber, P. B. Deker, L. J. Silverberg, *J. Org. Chem.* **1992**, *57*, 5990 – 5994; b) D. F. Taber, Y. Wang, *J. Am. Chem. Soc.* **1997**, *119*, 22 – 26; c) for acid effects on the AH of methyl acetoacetate under the catalysis of [$RuCl_2$((*S*)-binap)(*p*-cymene)], see: A. Wolfson, I. F. J. Vankelecom, S. Geresh, P. A. Jacobs, *J. Mol. Catal. A* **2004**, *217*, 21 – 26.

[21] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923 – 2925.

[22] The *ee* values of β-hydroxyesters **6a**–**d** were determined by GC on a chiral phase (with a Carlo Erba Instruments HRC 5160 Mega Series apparatus with a heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin/OV 1701 column, 25 m × 0.25 mm); **6a** (90 °C, $p(H_2)$ = 90 kPa): t_R(*S* enantiomer) = 14.7 min, t_R(*R* enantiomer) = 15.8 min (determined with racemic material); **6b** (100 °C, $p(H_2)$ = 90 kPa): t_R(*S* enantiomer) = 9.6 min, t_R(*R* enantiomer) = 10.1 min (determined with racemic material); **6c** (90 °C, $p(H_2)$ = 80 kPa): t_R(*S* enantiomer) = 12.3 min, t_R(*R* enantiomer) = 12.9 min; **6d** (95 °C, $p(H_2)$ = 80 kPa): t_R(*S* enantiomer) = 159.4 min, t_R(*R* enantiomer) = 166.2 min.

[23] GC analysis on an achiral phase was performed with a Carlo Erba Instruments ICU 600 GC 6000 Vega Series apparatus with a dimethylpolysiloxane column (J&W Scientific, SE-30, 25 m × 0.33 mm). Details of temperature and time are specified in the captions of Figures 2–5).

[24] Ethanolysis of β-ketoesters **5b**–**d** during GC analysis (a) and in separate deliberate experiments (b): a) Heat (250 °C) in the injection chamber of the GC apparatus; incomplete conversions of **5b** and **c**, complete conversion of **5d**; b) EtOH, reflux, 1 h; **11**: trace, **12**: 91%. An authentic specimen of ethyl ester **10** was prepared by a crossed Claisen condensation (75% yield).