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Asymmetric Hydrogenations One by One: Differentiation of up to Three β-Ketocarboxylic Acid Derivatives Based on Ruthenium(II)–Binap Catalysis[#]

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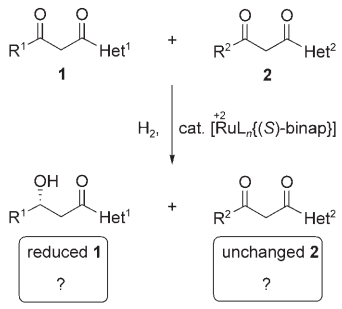
Dedicated to Professor Koichi Narasaka on the occasion of his retirement from Tokyo University

Abstract: Noyori-type reductions of pairs of β-ketoamides and β-ketoesters with elemental hydrogen (4 bar) proceeded substrate by substrate. When $Et_2NH_2^+[\{RuCl(S)\text{-binap}\}_2](\mu\text{-}Cl)_3^-$ was employed as a catalyst in a methanol or ethanol solution, the substrates were reduced at room temperature in the order β-ketopyrrolidide ≥ β-ketopiperidide ≥ β-keto(*N*,*N*-diethylamide) > β-keto(alkyl esters) > β-keto(oligofluoroalkyl esters). This is the first time that β-ketoamides have been reduced asymmetrically (91 to >98% *ee*) under such mild conditions. Monitoring the concentrations of these β-ketocarboxyl acid derivatives and their respective hydrogenation products over the course of time showed that the most electron-rich substrate is captured by the catalyst preferentially and exothermically; whether this occurs reversibly or irreversibly remains to be determined. The hydrogenation product is subsequently formed. The last transformation includes the rate-determining step. The combination of these events explains why starting from appropriate mixtures of substrates a "first-choice substrate" reacted from early on while the "second-choice substrate" stayed virtually untouched over an extended period of time and reacted no earlier than after the "first-choice substrate" had disappeared. From then onward, however, the "second-choice substrate" also reacted relatively rapidly.

Keywords: asymmetric synthesis · hydrogenation · kinetics · reduction

Introduction

Pairs of β-ketoesters **1** ($Het^1 = OR'$) and **2** ($Het^1 = OR''$) can be hydrogenated asymmetrically with considerable differences in the reaction rate using Noyori's method[2,3] and "$[\{RuCl_2(binap)\}_2]\cdot NEt_3$"[4,5] as a catalyst (Scheme 1): As we found,[6] β-ketoesters **1** with a relatively electron-rich substituent $Het^1 = OR'$ are hydrogenated completely on time scales, on which β-ketoesters **2** with a more electron-deficient substituent $Het^2 = OR''$ remain essentially untouched. Appropriate pairs of substrates contained, amongst others, $Het^1 = O\text{-}tBu/Het^2 = O\text{-}CH_2\text{-}CF_3$ or $Het^1 = O\text{-}CH_2\text{-}CF_3/Het^2 = O\text{-}CH(CF_3)_2$. Such kinetic differentiations become even more pronounced when β-ketoamides **1** ($Het^1 = NR'_2$) are included in the substrate mixtures as reported in the following: β-Ketopyrrolidides and β-ketopiperidides undergo asymmetric hydrogenation (AH) more than one order of magnitude faster than β-keto(alkyl esters) and up to two orders of magnitude faster than β-keto(oligofluoroalkyl esters).



Scheme 1. Differential Ru^{II}-catalyzed asymmetric hydrogenation of β-ketocarboxylic esters[2,3] and β-ketocarboxylic amides.[2b,7–11]

To date, AHs of β-ketoamides have been described only sporadically with reaction conditions invariably harsher than in the present study. *N*,*N*-Dimethyl acetoacetamide provided the corresponding β-hydroxyamide with 96% *ee* in the presence of in situ formed $RuBr_2$(*S*)-binap (63 bar H_2, room

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[#] See reference [1].

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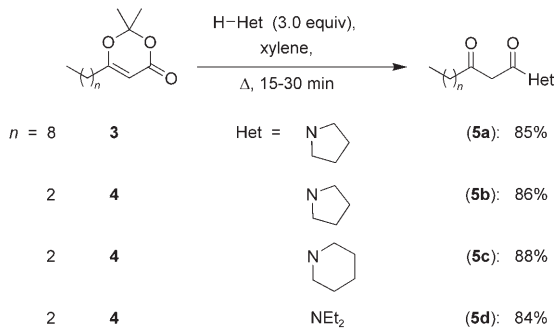
temperature).[2b,7] Secondary β-ketoamides susceptible to AH were limited to *N*-phenyl acetoacetamide [using "[{$RuCl_2$(binap)}$_2$]·NEt_3";[5] 30 bar H_2, 60 °C, >95 % *ee*][8] and *N*-methyl benzoylacetamide [using $RuCl_2$(*R*)-binap or $RuCl_2$(*S*)-binap; 14 bar H_2, 100 °C, >99.9 % *ee*][9] until a recent investigation showed that many *N*-methyl, *N*-benzyl, and other *N*-phenyl β-ketoamides react similarly in the presence of Ru complexes of the axially chiral bisphosphines SYNPHOS or DIFLUORPHOS (10 bar H_2, 50 °C, up to >99 % *ee*).[10] The only AH of a primary β-ketoamide of which we are aware entails acetoacetamide and (*S*,*S*)-bis-(*tert*-butylmethylphosphino)ethane-complexed $RuBr_2$, that is, a differently designed catalyst (6 bar H_2, 50 °C, 89 % *ee*).[11]

Results and Discussion

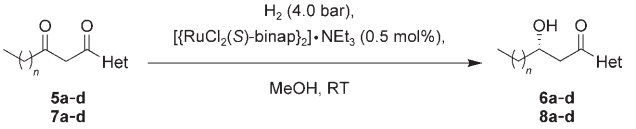
Our range of substrates consisted of β-ketoamides **5a–d** (see Scheme 2) and three of the previously studied β-ketoesters **7a–d**[6] (see Table 1). The β-ketoalkanoyl moieties of these compounds were not uniform. Instead, they were varied in order to establish a set of substrates distinguishable by non-coinciding gas–liquid chromatography (GLC) retention times of all the starting materials and hydrogenation products involved in the competing AHs which we undertook, starting either from pairs of substrates or even from a trio. In these experiments we were able to hydrogenate asymmetrically up to three of the tabulated β-ketocarboxylic acid derivatives one by one (see below).



Scheme 2. Synthesis of β-ketocarboxylic amides **5a–d**.

β-Ketoamides **5a–d** were obtained by aminolyses of dioxenones **3**[12] or **4**,[12] that is, employing an established strategy (Scheme 2).[13] In $CDCl_3$ solutions, we obtained keto/enol mixtures of 77:23–89:11 according to 400 or 500 MHz ^{1}H NMR spectroscopy. The keto form was identified by a 2-proton singlet for the C(=O)-CH_2-C(=O) moiety (δ = 3.46–3.52 ppm), the tautomeric enol by an OH (δ = 14.67–14.89 ppm) and an olefinic resonance (δ = 4.95–5.14 ppm). The syntheses of β-ketoesters **7a–d** are described elsewhere.[12]

Table 1. β-Hydroxyamides **6a–d** for GLC analysis prepared by AHs of β-ketoamides **5a–d** (AHs of β-ketoesters **7a–d** giving β-hydroxyesters **8a–d**: ref. [6]).



	n	Het	*t* [h]	Yield [%][a]	*ee* [%][b]
amides **5**,**6**					
a	8		24	97	96
b	2		24	97	>98
c	2		24	98	93
d	2	NEt_2	24	94	91
esters[6] **7**, **8**					
a	2	O-*t*Bu	8	95	98
b	4	O-Me	9	95	>98
c	2	O-CH_2-CF_3	16	97	96
d	8	O-$CH(CF_3)_2$	24	93	94

[a] Isolated yield after flash chromatography on silica gel.[15] [b] **6a**: Determined by HPLC;[17] **6b–d**: determined by GLC.[16]

In our standard set-up for AH (Table 1), methanol solutions (4.0 mL) of 0.5 mmol amounts of β-ketoamides **5a–d** were hydrogenated in the presence of 2.5 μmol (0.5 mol %) "[{$RuCl_2$(binap)}$_2$]·NEt_3",[5,14] that is, under the conditions already employed for the AHs of β-ketoesters **7a–d**.[6] After 24 h, workup by flash chromatography on silica gel[15] provided the corresponding (*S*)-hydroxyamides **6a–d** in very good yields (94–98 %). Their *ee* values ranged from >98 % (pyrrolidide **6b**) to 91 % (*N*,*N*-diethylamide **6d**) as determined by GLC[16] or HPLC.[17] Each AH was run under 4 bar H_2 pressure and none required heating. This is distinctly milder than any literature precedence.

We studied the GLC behavior of β-hydroxyamides **5a–d** while their syntheses according to the top moiety of Table 1 were underway. Before that we had explored the GLC properties of β-hydroxyesters **8a–d**.[6] Both data sets combined allowed to track the consumption of the starting materials and the formation of the respective products in the subsequent AHs by GLC.[18] The reactions were performed with substrates competing with one another in binary mixtures of a β-ketoamide and another β-ketocarboxylic acid derivative (Figures 1–4) or in a ternary mixture composed of β-ketoamide **5b** and β-ketoesters **7a** and **d** (Figure 5). The experimental procedures were identical with those specified in our β-ketoester study[6] except that ethanol was sometimes replaced by methanol as the solvent. Otherwise, we used alcoholic solutions (8.0 mL) of the dimeric Ru^{II} catalyst (2.5 μmol) and 0.5 mmol amounts of each β-ketocarboxylic acid derivative. In different terms, the starting concentration of "[{$RuCl_2$(binap)}$_2$]·NEt_3"[5] was uniformly 0.31 μM while the total substrate concentration changed: 0.188 M starting from the ternary mixture, 0.125 M starting from all binary

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substrate mixtures, and 0.067 M when monitoring the hydrogenation of pure **7a**. For the GLC analyses (details: Figure 1, footnote a) we took between 9 (Figure 1) and 22 100-μL samples (Figure 5) during the reaction.

Monitoring the progress with time of the AH of a 1:1 mixture of β-ketopyrrolidide **5b** and β-ketopiperidide **5c** revealed a bias in favor of the former (Figure 1): Only 48% **5b** but 61% **5c** were retrieved after 22 h. This suggested that AHs of β-ketoamides follow the same rate order as AHs of β-ketoesters: "the electron-richer the double-bonded oxygen atom of the carboxyl moiety, the faster the AH".[6] *O*=C-Pyrrolidyl is expected to be electron-richer than *O*=C-piperidinyl because *C*=C-pyrrolidyl is more nucleophilic than *C*=C-piperidinyl in the respective pairs of cyclopentene- and cyclohexene-based enamines.[20] A control experiment showed that the AH of *N*,*N*-diethyl-β-ketoamide **5d** is slightly slower than the AH of β-ketopyrrolidide **5b**. Consequently, we selected β-ketopyrrolidide **5b**, or in one case its chain-extended analogue **5a**, as the most reactive component in the following AH experiments.

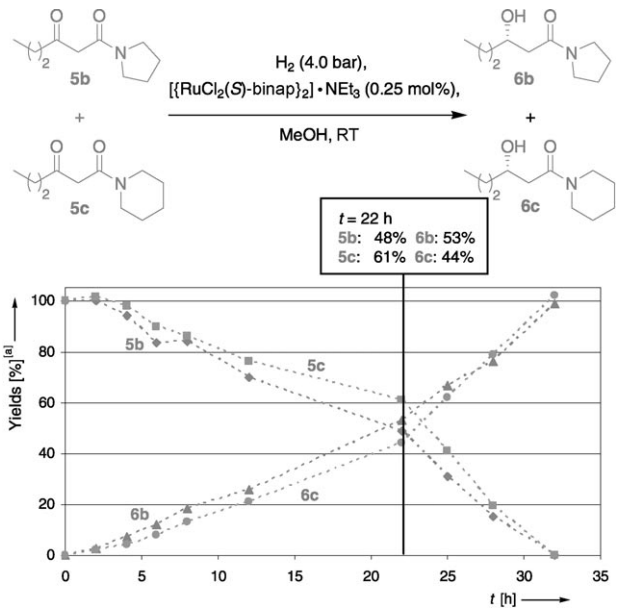

Figure 1. Progress with time of the AH reaction of a 1:1 (mol/mol) mixture of β-ketoamides **5b** and **5c**. [a] Yields monitored by interrupting the reaction at the indicated times, removing 100 μL from the mixture (and re-submitting it to AH conditions), and quantifying the amounts of reactants and products by GLC comparison (achiral capillary column)[18] with the respective reference peak, which was due to a known amount of biphenyl deliberately added to the reaction mixture at $t=0$ h. $t_{r,\mathbf{5b}}=15.7$, $t_{r,\mathbf{5c}}=18.6$, $t_{r,\mathbf{6b}}=22.0$, $t_{r,\mathbf{6c}}=26.8$, $t_{r,biphenyl}=4.6$ min [1 μL: 100 °C (45 min), $p(H_2)=60$ kPa].

Figures 2–4 and Scheme 3 describe the hydrogenation of 1:1 mixtures of a β-ketopyrrolidide and one of three electronically varied β-ketoesters. In each case the β-ketopyrrolidide reacted faster. In more detail we found:

- The differentiation between β-ketopyrrolidide **5b** and β-keto(*tert*-butyl ester) **7a** was good (Figure 2). After 16 h only 7% of the ketoamide but as much as 96% of the ketoester had not reacted. On the other hand as much as 93% hydroxyamide **6a** but only 2% hydroxyester **8a** were formed. When allowing the AH of this mixture to proceed for (just) another 4 h, both substrates were completely consumed and 99% hydroxyamide **6a** as well as 98% hydroxyester **8a** were obtained. Their *ee* values were >98 and 97%, respectively. Within the error limits of GLC detection,[18] these values are equivalent to the enantioselectivities of the respective single-compound hydrogenations (Table 1). Hence there is no indication that the presence of (*S*)-hydroxyamide **6b** determines the enantioselectivity of the AH **7a**→**8a**.

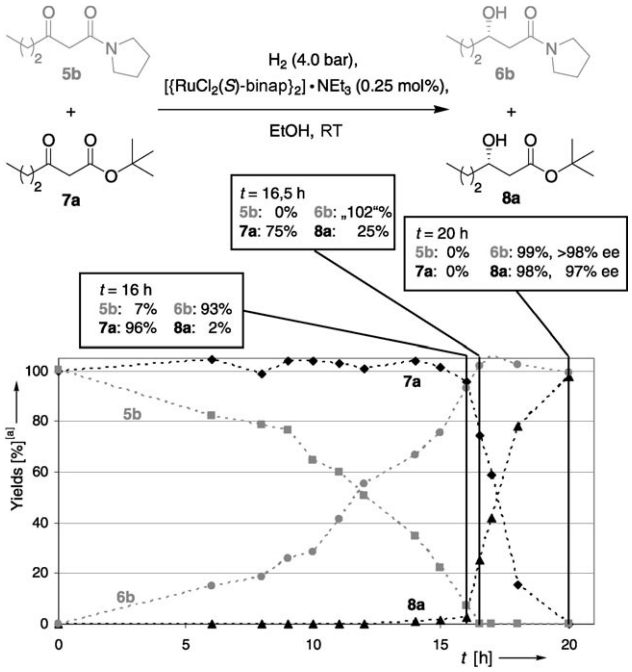

Figure 2. Progress with time of the AH of a 1:1 (mol/mol) mixture of β-ketoamide **5b** and β-ketoester **7a**. a) Yields determined as detailed in footnote [a] of Figure 1. $t_{r,\mathbf{5b}}=23.1$, $t_{r,\mathbf{6b}}=25.5$, $t_{r,\mathbf{7a}}=12.0$, $t_{r,\mathbf{8a}}=13.2$, $t_{r,biphenyl}=18.0$ min [1 μL, 55 °C (15 min) → 20 °C min^{-1} → 120 °C (10 min), $p(H_2)=60$ kPa].

- The AH differentiated between the β-ketopyrrolidide **5b** and the β-keto(trifluoroethyl ester) **7c** in a 1:1 mixture of these compounds more efficiently (Figure 3). After 17 h, only 3% of ketoamide **5b** remained unchanged while as much as 96% of the corresponding hydroxyamide **6b** had formed. In contrast, we detected none of hydroxyester **8c**, which meant that its precursor, that is, β-ketoester **7c**, had not reacted at all.[21] After another 12 h, the *two* hydrogenation products were present in nearly quantitative yields (**6b**: 99% *ee*; **8c**: 97% *ee*) and with the same enantiopurities (**6b**: >98% *ee*; **8c**: 97% *ee*) which were obtained for the respective single-compound AHs (Table 1: **6b**: >98%; **8c**: 96%). That is, like in the ex-

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periment shown in Figure 2, the presence of the faster-forming hydrogenation product (**6b**) was irrelevant for the degree of enantiocontrol in the slower hydrogenation (→**8c**).

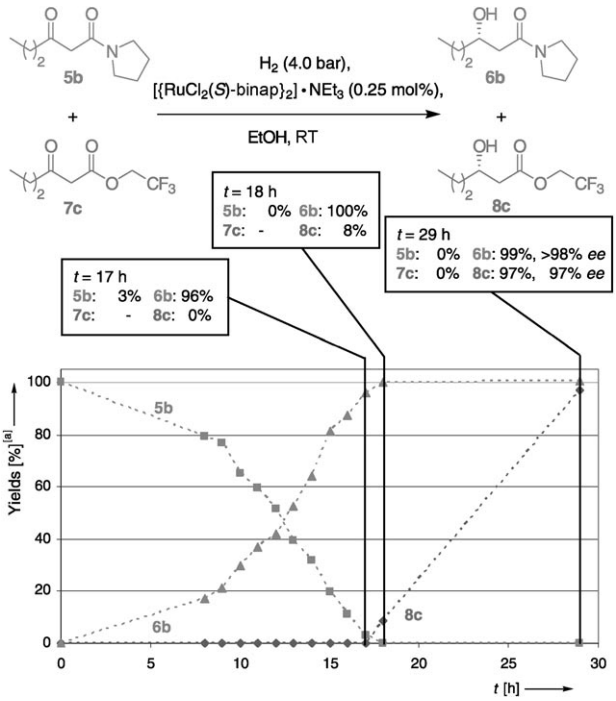


Figure 3. Progress with time of the AH of a 1:1 (mol/mol) mixture of β-ketoamide **5b** and β-ketoester **7c**. a) Yields determined as detailed in footnote [a] of Figure 1. $t_{r,\mathbf{5b}}$=24.5, $t_{r,\mathbf{6b}}$=26.5 min, trifluoroethyl ester **7c** not quantifiable because of partial ethanolysis (→**13**[22]) upon injection into the apparatus, $t_{r,\mathbf{8c}}$=11.2 min, $t_{r,\text{biphenyl}}$=20.1 min [1 μL, 35 °C (15 min) → 20 °C min^{-1} → 120 °C (20 min), $p(H_2)$=60 kPa].

- The differentiations between β-ketopyrrolidides **5a** or **b** and β-keto(hexafluoroisopropyl ester) **7d** by time-controlled AHs were almost perfect (Figure 4, Scheme 3); this was true irrespective of whether the acyl substituents had equal chain lengths (that is, 2×decanoyl, Figure 4) or not (that is, butyroyl vs decanoyl, Scheme 3). When amide **5a** competed with ester **7d** in the hydrogenation (Figure 4), the former disappeared completely after 30 h and a 99% yield of its reduction product **6a** was detected by GLC. Concomitantly, the hexafluoroisopropyl ester was almost completely retained (95% **7d** retrieved after in situ transesterification leading to methyl ester **15**[22]) and no more than 2% of its reduction product **8d** were found. The related competition between pyrrolidide **5b** and hexafluoroisopropyl ester **7d** for the Noyori reductant was run on a preparative scale (Scheme 3). Workup after 26 h by flash chromatography on silica gel[15] allowed to isolate two compounds. These were the newly formed hydroxyamide **6b** (94% yield, >98% *ee*) and none of ketoamide **5b** from the late fractions and recovered ketoester **7d** (94% yield) and none of the corresponding hydroxyester **8d** from the early fractions.

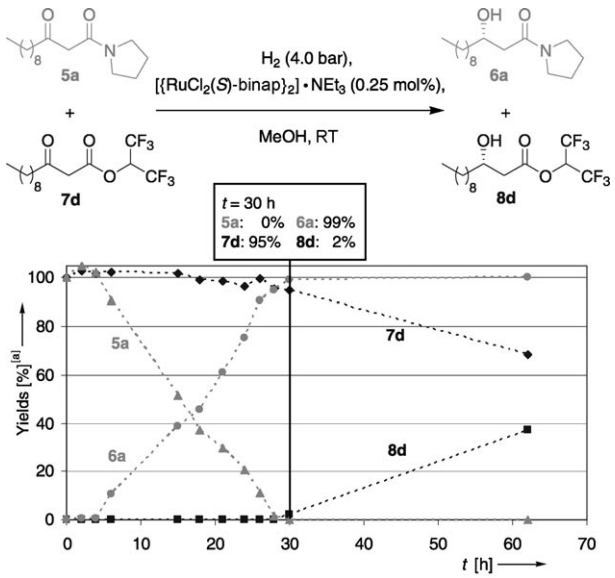
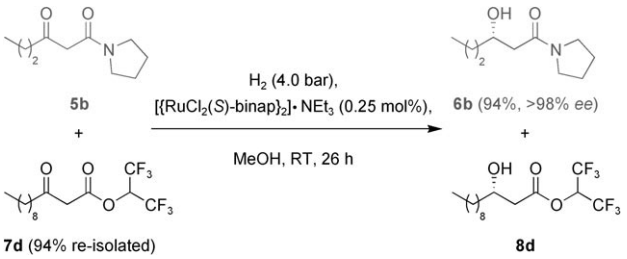


Figure 4. Progress with time of the AH of a 1:1 (mol/mol) mixture of β-ketoamide **5a** and β-ketoester **7d**. a) Yields determined as detailed in footnote [a] of Figure 1. $t_{r,\mathbf{5a}}$=31.1, $t_{r,\mathbf{6a}}$=34.0 min, hexafluoroisopropyl ester **7d** quantified as its methanolysis product **15**[22] ($t_{r,\mathbf{15}}$=21.4 min) formed in the GLC apparatus, $t_{r,\mathbf{8d}}$=14.4, $t_{r,\text{biphenyl}}$=4.5 min [1 μL, 100 °C (20 min) → 20 °C min^{-1} → 180 °C (20 min), $p(H_2)$=60 kPa].



Scheme 3. Preparative-scale substrate-selective AH of a 0.5 mmol: 0.5 mmol mixture of β-ketoamide **5b** and β-ketoester **7d**.

Figure 5 displays our most impressive substrate-differentiating AH reactions. Three β-ketocarboxylic acid derivatives R-C(=O)-CH_2-C(=*O*)-Het competed for the reductant. The reaction proceeded more efficiently the greater the +M effect of the substituent Het. Ketopyrrolidide **5b** took the lead, that is, was consumed completely when the reaction mixture was probed for the 14th time 17 h 20 min after the hydrogenation started. At this moment in time, keto(*tert*-butyl ester) **7a** had scarcely reacted (→ 6% **8a** besides 95% unreacted **7a**) but none of keto(hexafluoroisopropyl ester) **7d** (100% retrieved as methyl ester **15** after transesterification in the GLC apparatus[22]). 21 h 30 min after starting the hydrogenation, GLC analysis of the 20th sample revealed that the AH of keto(*tert*-butyl ester) **7a** was practi-

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cally over, delivering 95% of the corresponding hydroxyester **8a** besides 2% residual starting material **7a**. None of the keto(hexafluoroisopropyl ester) **7d** (95% retrieved after in situ transesterification as mentioned above) had started yet to pick up hydrogen as evidenced by the absence of reduction product **8d** in the gas chromatogram. Probing the reaction mixture 32 h after the start of the experiment showed that the fluorinated ketoester **7d** finally had begun to react, 72% thereof remaining[22] and 26% **8d** having been formed. After 66 h, the values were 54 and 44%, respectively.

Figure 5 suggests that the AH of the 1:1:1 mixture of β-ketocarboxylic acid derivatives **5b**, **7a**, and **7d** approached a halt before the latter reacted to half as much as if hydrogenated in the absence of competing substrates (→93% **8d**[6]). This was not too surprising considering two factors: 1) The initial concentrations of ester **7d** and catalyst dimer "$[\{RuCl_2(binap)\}_2]\cdot NEt_3$"[5] in the competition experiment were half of what they were using the single substrate. 2) The competition experiment was interrupted 22 times for

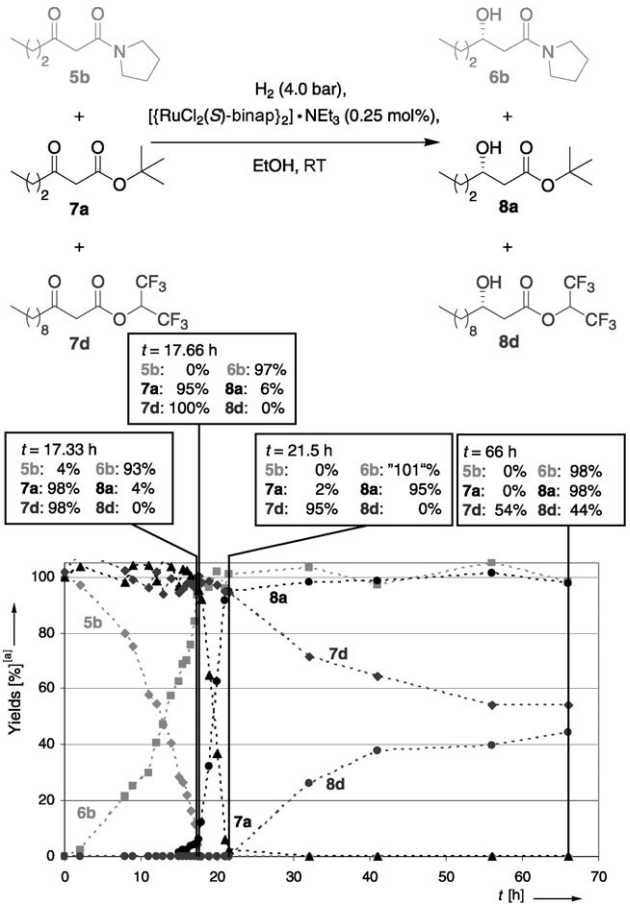

Figure 5. Progress with time of the AH of a 1:1:1 (mol/mol/mol) mixture of β-ketoamide **5b**, β-ketoester **7a**, and β-ketoester **7d**. a) Yields determined as detailed in footnote [a] of Figure 1. $t_{r,5b}$=23.1, $t_{r,6b}$=25.1, $t_{r,7a}$=12.0 min, hexafluoroisopropyl ester **7d** quantified as its ethanolysis product **14**[22] ($t_{r,14}$=30.0 min) formed in the GLC apparatus, $t_{r,8a}$=13.4 min, $t_{r,8d}$=22.5, $t_{r,biphenyl}$=18.4 min [1 μL, 55°C (15 min) → 20°C min^{-1} → 120°C (15 min), $p(H_2)$=60 kPa].

data analysis, which probably compromised the catalyst's activity.

We excluded the latter in two additional AH reactions of the β-ketopyrrolidide **5b**/β-ketoester **7a**/β-ketoester **7d** mixture. These hydrogenations proceeded without interfering sampling beyond the previously explored time range, namely for 72 and 90 h. After these times we analyzed the amounts of all substrate/product pairs involved by GLC. In the reaction terminated after 72 h, 0% **5b**/97% **6b**, 0% **7a**/98% **8a**, and only 23% **7d**[22] besides 79% **8d** were found. The AH, which had run for 90 h, delivered 0% **5b**/96% **6b**, 0% **7a**/97% **8a**, and just 11% **7d**[22] besides 86% **8d**. These increased conversions and the results of Figure 5 combined mean that it is possible to hydrogenate three β-ketocarboxylic acid derivatives asymmetrically one after the other.

From a preparative point of view, the present findings and their predecessors[6] call for three extensions: 1) Testing whether Ru^{II}-based AH catalysts containing enantiopure bisphosphines other than binap[23] allow for even subtler kinetic differentiations of β-ketocarboxylic acid derivatives; 2) effecting mono-AHs of unsymmetric achiral bis(β-ketocarboxylic acid derivatives) for accessing tetra- or higher functionalized enantiomerically pure building blocks for synthesis; 3) extending the scope of substrate-selective Ru^{II}– or Rh^{I}–binap catalyzed AHs to unsaturated compounds different from β-ketocarboxylic acid derivatives. These topics are currently under scrutiny in our laboratory.

From a mechanistic point of view, the concentration versus time profiles of our AHs of substrate *mixtures* (Figures 2–5 here, Figures 3–5 in ref. [6]) reveal several unusual features for competition experiments:

- Substrate mixtures are not consumed proportional to the inherent reactivities of their constituents.
- When the substrate differentiation is good, a "first-choice substrate" undergoes hydrogenation while the other substrate remains, or the other substrates remain, inert.
- Only when the "prior-choice substrate" has been consumed, the "next-choice substrate" starts to react.
- Once started, the "next-choice substrate" reacts to completion within a time-span similar to that in the absence of a faster-reacting substrate.

Figure 6 confirms these observations by tracing the concentration changes with time of the substrate/product pair β-keto(*tert*-butyl ester) **7a**/β-hydroxy(*tert*-butyl ester) **8a** during four AHs: a) when pure **7a** was the substrate; b) when **7a** was the faster reacting constituent of a 1:1 mixture with β-keto(hexafluoroisopropyl ester) **7d**; c) when **7a** was the more slowly reacting component in a 1:1 mixture with β-ketopyrrolidide **5b**; and d) when **7a** was the second-most reactive substrate in a ternary mixture with β-ketopyrrolidide **5b** and β-keto(hexafluoroisopropyl ester) **7d**.[24] Graphs a) and b) are inconspicuous. However, curves c) and d) exhibit sharp bends between initial sections, which are perfectly horizontal, and subsequent sections, which ascend or descend steeply. Clearly, these features don't allow the charac-

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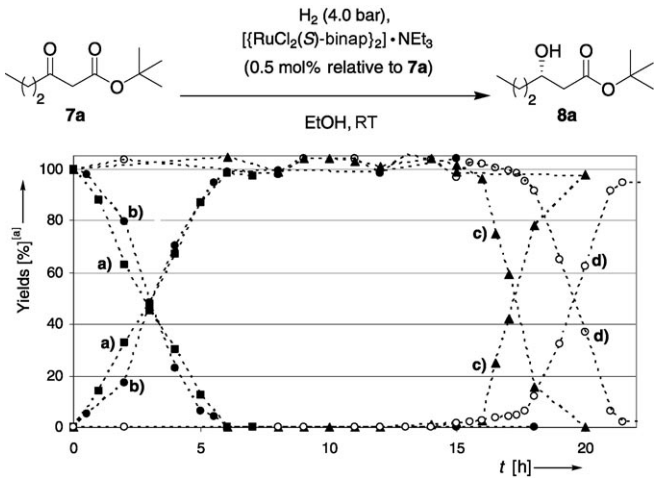

Figure 6. Consumption of β-keto(*tert*-butyl ester) **7a** with time (descending curves) accompanied by formation of β-hydroxy(*tert*-butyl ester) **8a** with time (ascending curves) while hydrogenating the former in EtOH asymmetrically a) by itself (■), b) in a 1:1 (mol/mol) mixture with β-keto(hexafluoroisopropyl ester) **7d** (●; excerpt from Figure 4 of ref. [6]), c) in a 1:1 (mol/mol) mixture with β-ketopyrrolidide **5b** (▲; excerpt from Figure 2 of the present communication), and d) in a 1:1:1 (mol/mol/mol) mixture with β-ketopyrrolidide **5b** and β-keto(hexafluoroisopropyl ester) **7d** (open circles; excerpt from Figure 5 of the present communication). Starting concentrations were [any substrate]$_0$ = 0.5 mmol/8.0 mL EtOH and [catalyst dimer] = 2.5 μmol/8.0 mL EtOH.

terization of such hydrogenations by an overall rate constant or by a half-reaction time.

The unusual concentration of **7a** versus time plots c) and d) in Figure 6 and similar curves for other "second-choice" substrates imply that selectivity and reactivity of our AHs result from a subtle combination of steps:

- Substrate selection preferentially affects the most electron-rich constituent of a mixture, making it the "first-choice substrate".
- The rate-determining step follows. It occurs only under the condition that a substrate has been selected. Otherwise it remains elusive.
- Accordingly, in a mixture of substrates reacting with sufficient bias, the "first-choice substrate" delivers the product from early on. In the meantime the "second-choice substrate" stays inert. It starts delivering product only after the "first-choice substrate" has been nearly fully consumed.
- Differently expressed: The more efficiently a substrate is selected, the sooner AH of its C=O bond begins. To the best of our knowledge, nothing alike has been recognized to date.[3]

Figure 7 shows four prototype energy profiles A–D for the conversion of our mixtures of substrates, hydrogen, and the catalyst into the respective products and the re-formed catalyst. Energy profiles A and C would agree with our results while profiles B and D would be at odds. This is because only according to energy profiles A or C the onset of the reaction of the "second-choice substrate" would be delayed as long as the "first-choice substrate" is processed. The delaying effect is due to different reasons in energy profiles A versus C. If pathway A of Figure 7 applies, the reactants deliver two intermediates **I** and **I′**, respectively, reversibly and exothermically. As long as the "first-choice substrate" is present, the reaction passes exclusively through intermediate **I**, thereafter exclusively through intermediate **I′**. Notwithstanding that, both phases of the reaction could display more or less the same gross reaction rate. If pathway C of Figure 7 were true, intermediates **I** and **I′** would emerge from exothermic but irreversible reactions. In the case illustrated, intermediate **I** thereby arises from the "first-choice

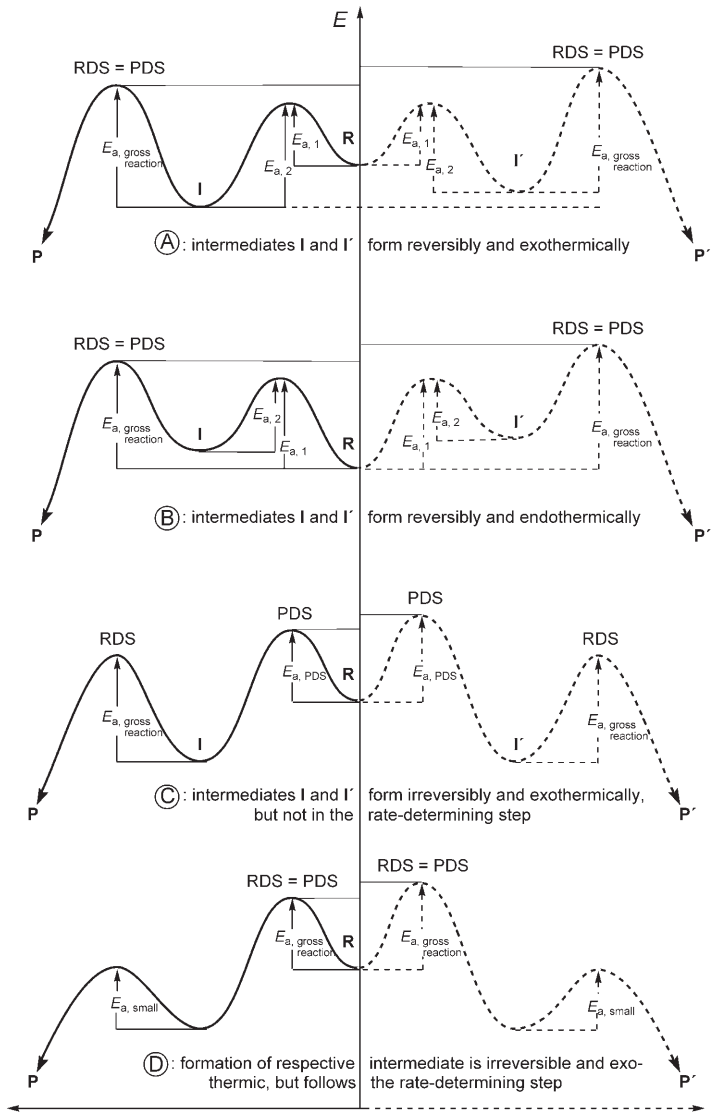

Figure 7. Simplified energy profiles for the selective AH of a "first-choice" β-ketocarboxylic acid derivative (reaction coordinate from right to left) in the presence of a "second-choice" competitor (reaction coordinate from left to right): reactants (R), products (P, P′), product-determining step (PDS), rate-determining step (RDS), lowest-energy intermediate (I, I′) before RDS. Profiles A or C explain our observations while profiles B or D are in conflict.

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substrate" at the expense of intermediate **I′**. Accordingly, as long as **I** can be formed the catalyst brings about essentially nothing but the reaction via **I** giving product **P**. The reaction via **I′** giving **P′** would come into effect when the "first-choice substrate" has disappeared, that is, when no more of **I** can be formed. Nonetheless, thereafter the "second-choice substrate" could (but need not) react with about the same gross reaction rate as its predecessor.

Beyond the framework of the more general energy profiles A or C of Figure 7, a particular observation still awaits interpretation: How is it possible that during AHs of mixtures containing β-ketopyrrolidide **5b** and β-keto(*tert*-butyl ester) **7a**, compound **5b** takes the lead over **7a** but nonetheless needs about three times longer until being fully consumed (cf. Figures 2, 5). Starting from energy profiles A and C of Figure 7, lowering the energy of intermediate **I** versus the energy of intermediate **I′** creates two modified profiles, which are depicted as energy profiles A′ and C′ of Figure 8. Each of them agrees perfectly with the selectivities and hydrogenation rates in question.

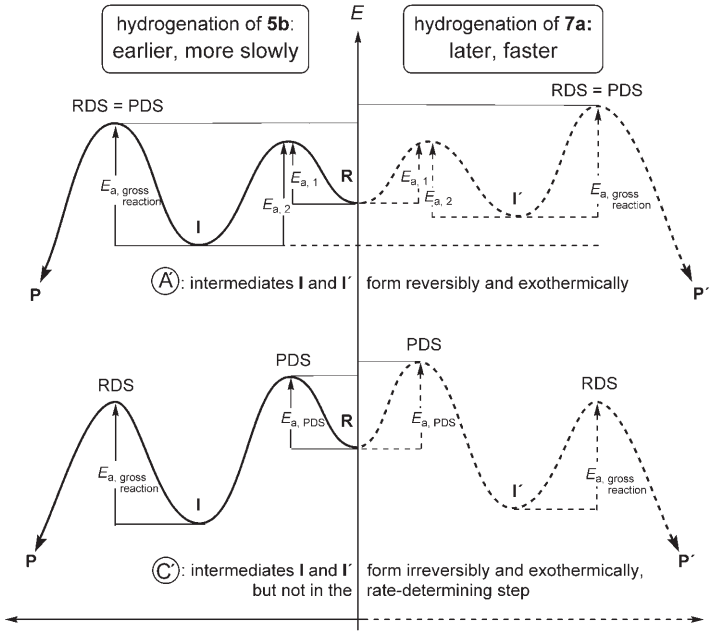
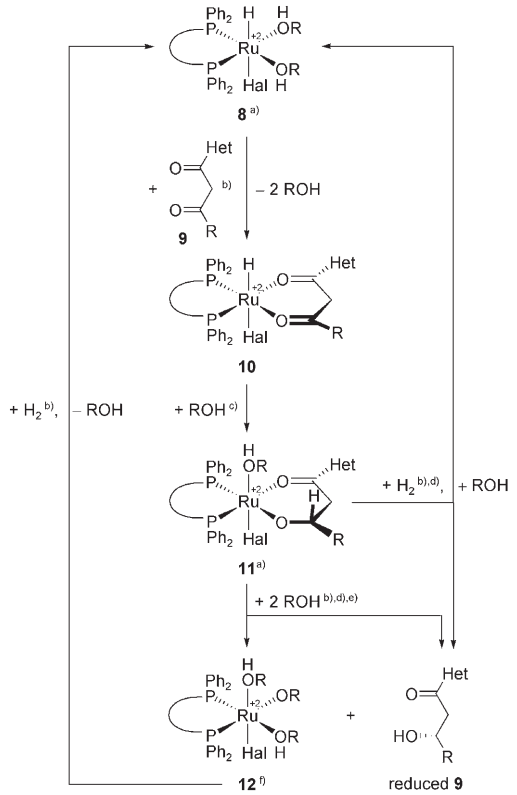


Figure 8. Analysis of the selective AH of "first-choice" β-ketoamide **5b** (reaction coordinate from right to left) in the presence of "second-choice" β-ketoester **7a** (reaction coordinate from left to right). Energy profiles A and C from Figure 7 adapted (→ A′, C′) such as to explain why the net-conversion of "second-choice" substrate **7a** is faster than that of "first-choice" substrate **5b** in the experiments of Figures 2 and 5. For captions see Figure 7.

We would like to attribute our preceding analysis to specific elementary reactions. Unfortunately, too little is actually known about the mechanism of AHs of β-ketoesters let alone of β-ketoamides, to the extent that such a mechanism is not at all mentioned in a first-hand 2004 review.[25] Nonetheless two variations of the putative catalytic cycle of such AHs have been published[26,27] (Scheme 4). They comprise



Scheme 4. Catalytic cycle of $RuHal_2$(*S*)-binap-catalyzed AHs of β-ketocarboxylic esters (Het = OR′) combined from ref. [26] (ROH = MeOH, Hal = Cl) and ref. [27] (ROH = EtOH, Hal = Br); dimer dissociation omitted for the sake of clarity. a) Stereostructure not specified in ref. [26]; b) if ligand dissociation precedes ligand association, a 16-e⁻ species would be an intermediate; c) if hydroruthenation precedes ligand binding, a 16-e⁻ species would be an intermediate; d) product release as suggested in ref. [27]; e) product release as suggested in ref. [26]; f) stereostructure different in ref. [27].

three[27] or four[26,27] octahedral Ru^{II} complexes as recurring intermediates (unless there are more): Hydrido-complex **8**, possibly its alkoxy precursor **12**, Ru^{II} complex **10** of the substrate, and Ru^{II} complex **11** of the product. Interpreting energy profiles A and C of Figure 7 in the terms of Scheme 4, the substrate-selecting step appears to be ligand exchange between hydrido-complex **8** and the most electron-rich, that is, Lewis-basic β-ketocarboxylic acid derivative **9** in the reaction mixture. The newly obtained hydrido-complex **10** would be relatively long-lived, thereby representing a "resting state" of the catalyst. Complex **10** would be expected to be consumed in the rate-determining step. We suggest that the latter is the hydroruthenation **10**→**11**. Liberation of the product ("reduced **9**") accompanied by or followed by restoration of complex **8** would allow the next substrate molecule to enter the catalytic cycle.

Conclusion

In summary we discovered that the rates of [{$RuCl_2$(binap)}$_2$]·NEt_3-catalyzed AHs of β-ketocarboxylic acid de-

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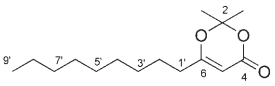
rivatives R-C(=O)-CH_2-C(=O)-Het depend significantly on the nature of Het: The more electron-rich the C(=O)-Het moiety, the faster the onset of the respective hydrogenation. This substituent dependence made it possible to hydrogenate β-keto(pyrrolidides) very enantioselectively while several β-ketoesters stayed untouched initially but reacted subsequently. We even hydrogenated a mixture of three β-ketocarboxylic acid derivatives selectively one by one. In these competitions a typical "first-choice substrate" delivered product from early on while the "second-choice substrate" was unaffected unless the "first-choice substrate" substrate had disappeared. This switch from an initially inert mode to a reactive mode means that for these AHs selectivity and reactivity are determined in different steps. Substrate selection, in one or more than one step, provides an intermediate, which may form reversibly or irreversibly but must be more stable than the reactants. This intermediate proceeds toward the hydrogenated product through the rate-determining step. As soon as the latter materializes, its rate is independent from whether the substrate under consideration was "first" or "second choice".

Experimental Section

General information: All reactions were performed in oven-dried (110 °C) glassware under N_2. Products were purified by flash chromatography[15] [eluents in brackets; volume of each collected fraction (mL)/column diameter (cm): 10/2, 20/3, 20/4 50/5, 80/6; which fractions contained the isolated product is indicated in each description as "#*xx–yy*"] on Merck silica gel 60 (0.040–0.063 mm). Yields refer to analytically pure samples. ^{1}H NMR [$CHCl_3$ ($\delta=7.26$) or TMS as internal standard in $CDCl_3$]: Varian Mercury VX 300 and Bruker AM 400. ^{13}C NMR [$CDCl_3$ ($\delta=77.10$) or TMS as internal standard in $CDCl_3$]: Bruker AM 400. Assignments of ^{1}H and ^{13}C NMR resonances refer to the IUPAC nomenclature except within substituents (where primed numbers are used). Combustion analyses: E. Hickl, Institut für Organische Chemie und Biochemie, Universität Freiburg. IR spectra: Perkin–Elmer Paragon 1000. Optical rotations were measured with a Perkin–Elmer polarimeter 341 MC at 589 nm and 20 °C and were calculated according to the Drude equation {$[\alpha]_D=(\alpha_{exptl}\times 100)/(c\times d)$}; rotational values are the average of five measurements of α_{exptl} in a given solution of the respective sample.

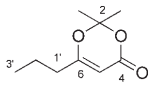
GLC and HPLC analyses: See refs. [16–18].

2,2-Dimethyl-6-nonyl-1,3-dioxin-4(2*H*)-one (3):[12] At room temperature trifluoroacetic acid (15.8 mL, 23.5 g, 206 mmol, 15 equiv) was added to a

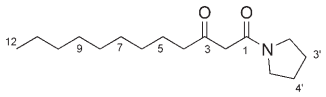


mixture of *tert*-butyl 3-oxododecanoate[28] (3.73 g, 13.8 mmol), acetone (4.1 mL, 55 mmol, 4.0 equiv), and trifluoroacetic anhydride (7.7 mL, 12 g, 55 mmol, 4.0 equiv). After stirring for 24 h, the mixture was neutralized with pH 7 buffer (Na_2HPO_4/KH_2PO_4, 450 mL) and extracted with CH_2Cl_2 (1×200 mL, 4×100 mL). The combined organic extracts were dried with $MgSO_4$ and the volatiles were evaporated under reduced pressure. The residue was submitted to flash chromatography (5 cm, cyclohexane/ethyl acetate 10:1) to afford the title compound (#7–24, 2.23 g, 64 %) as a yellow oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta=0.88$ (t, 3H, $J_{9',8'}=6.8$ Hz, 9′-H_3), 1.23–1.37 (m, 12H, 3′-H_2, 4′-H_2, 5′-H_2, 6′-H_2, 7′-H_2, 8′-H_2), 1.54 (br tt, 2H, $J_{2',3'}=J_{2',1'}=7.5$ Hz, 2′-H_2), 1.68 [s, 6H, 2-$(CH_3)_2$], 2.21 (t, 2H, $J_{1',2'}=7.5$ Hz, 1′-H_2; signal broadened by unresolved $^4J_{1',5}$ coupling), 5.23 (s, 1H, 5-H; signal broadened by unresolved $^4J_{5,1'}$ coupling); ^{13}C NMR (100.6 MHz, $CDCl_3$ internal standard in $CDCl_3$; small peak of contaminant at $\delta=77.3$): $\delta=14.1$ (C-9′), 22.7, 29.0, 29.3, 29.4, and 31.9 (C-3′, C-4′, C-5′, C-6′, C-7′, C-8′)*,**, 25.1 [2-$(CH_3)_2$]**, 25.8 (C-2′)**, 33.7 (C-1′)**, 93.2 (C-5)**, 106.3 (C-2), 161.5 (C-6), 172.2 (C-4); *five resonances for six nuclei, but probably the signal at $\delta=29.27$ belongs to two nuclei because it exhibits twice the intensity as the other four peaks; **distinguishable by a C,H-correlation spectrum; IR (film): $\tilde{\nu}=3000$, 2925, 2855, 1730, 1635, 1465, 1435, 1390, 1375, 1270, 1250, 1205, 1180, 1015, 900, 810 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{26}O_3$ (254.4): C 70.83, H 10.30; found: C 70.98, H 10.27.

2,2-Dimethyl-6-propyl-1,3-dioxin-4(2*H*)-one (4):[12,29] At room temperature trifluoroacetic acid (25.6 mL, 333 mmol, 15 equiv) was added to a mixture of β-keto(*tert*-butyl ester) **7a** (5.06 g, 27.2 mmol), acetone (8.0 mL, 108 mmol, 4.0 equiv), and trifluoroacetic anhydride (15.1 mL, 108 mmol, 4.0 equiv). After stirring for 24 h, the mixture was neutralized with pH 7 buffer (Na_2HPO_4/KH_2PO_4, 450 mL) and extracted with CH_2Cl_2 (1×200 mL, 4×100 mL). The combined organic extracts were dried with $MgSO_4$ and the volatiles were evaporated under reduced pressure. The residue was submitted to flash chromatography (5 cm, cyclohexane/ethyl acetate 10:1) to afford the title compound (#32–42, 2.23 g, 81 %) as a yellow oil. ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta=0.97$ (t, 3H, $J_{3',2'}=7.4$ Hz, 3′-H_3), 1.59 (tq, 2H, $J_{2',1'}=J_{2',3'}=7.4$ Hz, 2′-H_2), 1.68 [s, 6H, 2-$(CH_3)_2$], 2.20 (t, 2H, $J_{1',2'}=7.5$ Hz, 1′-H_2), 5.23 (s, 1H, 5-H).

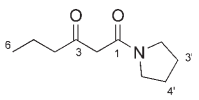


3-Oxododecanoic acid pyrrolidide (5a): A solution of dioxinone **3** (1.5 g, 5.9 mmol) and pyrrolidine (1.0 mL, 12 mmol, 2.0 equiv) in xylene



(20 mL) was heated under reflux for 30 min. After addition of more pyrrolidine (0.5 mL, 6 mmol, 1.0 equiv) the mixture was stirred under reflux for another 15 min. The solvent was evaporated and the residue was submitted to flash chromatography (4 cm, cyclohexane/ethyl acetate 3:1) to give **5a** (#22–42, 1.35 g, 85 %) as colorless oil and 78:22 keto/enol mixture {as determined by averaging the intensity ratios of the following pairs of signals: $\delta=2.17$ [t, 2H of this tautomer, $J_{4,5}=7.7$ Hz, 4-H_2 (enol-**5a**)] vs $\delta=2.57$ [t, 2H of this tautomer, $J_{4,5}=7.5$ Hz, 4-H_2 (keto-**5a**)]}; ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta=0.872$ [t, 3H of this tautomer, $J_{12,11}=6.9$ Hz, 12-H_3 (keto-**5a**)] superimposed by 0.875 [t, 3H of this tautomer, 12-H_3 (enol-**5a**); $J_{12,11}$ coupling insufficiently resolved due to overlap with aforementioned signal], 1.21–1.36 [m, 12H of both tautomers, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2 (keto-**5a** and enol-**5a**)], 1.52–1.62 [m, 2H of both tautomers, 5-H_2 (keto-**5a** and enol-**5a**)], 1.83–1.99 [m, 4H of both tautomers, 3′-H_2 and 4′-H_2 (keto-**5a** and enol-**5a**)], 2.17 [t, 2H of this tautomer, $J_{4,5}=7.7$, 4-H_2 (enol-**5a**)], 2.57 [t, 2H of this tautomer, $J_{4,5}=7.5$ Hz, 4-H_2 (keto-**5a**)], 3.41, 3.48 [2×t, 4H of both tautomers, $J_{2',3'}=6.8$, $J_{5',4'}=6.8$ Hz, respectively, 2′-H_2, 5′-H_2 (keto-**5a** and enol-**5a**)] superimposed by 3.46 [s, 2H of this tautomer, 2-H_2 (keto-**5a**)], 4.95 [s, 1H of this tautomer, 2-H (enol-**5a**)], 14.67 [br s, 1H of this tautomer, 3-OH (enol-**5a**)]; IR ($CDCl_3$): $\tilde{\nu}=2955$, 2930, 2875, 2865, 1715, 1640, 1585, 1490, 1480, 1450, 1370, 1345, 1255, 1230, 1190, 1170, 1115, 945, 915 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{29}NO_2$ (267.4): C 71.86, H 10.93, N 5.24; found: C 71.99, H 10.64, N 5.08.

3-Oxohexanoic acid pyrrolidide (5b): A solution of dioxinone **4** (1.5 g, 8.9 mmol) and pyrrolidine (1.5 mL, 18 mmol, 2.0 equiv) in xylene (30 mL) was heated under reflux for 15 min. After addition of more pyrrolidine (0.75 mL, 0.64 g, 9 mmol, 1.0 equiv), the mixture was stirred under reflux for another 15 min. The solvent was evaporated and the residue was submitted to flash chromatography (4 cm, cyclohexane/ethyl acetate 4:1) to give **5b**



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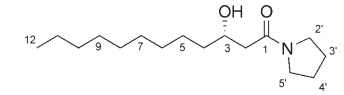
(#33–59, 1.41 g, 86%) as colorless oil and 77:23 keto/enol mixture {as determined by averaging the intensity ratios of the following pairs of signals: $\delta = 2.16$ [t, 2H of this tautomer, $J_{4,5} = 7.9$ Hz, 4-H_2 (enol-**5b**)] vs $\delta = 2.57$ [t, 2H of this tautomer, $J_{4,5} = 7.3$ Hz, 4-H_2 (keto-**5b**)]}. ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 0.92$ [t, 3H of this tautomer, $J_{6,5} = 7.4$ Hz, 6-H_3 (keto-**5b**)] superimposed by 0.95 [t, 3H of this tautomer, $J_{6,5} = 7.5$ Hz, 6-H_3 (enol-**5b**)], 1.618 [qt, 2H of this tautomer, $J_{5,6} = J_{5,4} = 7.4$ Hz, 5-H_2 (enol-**5b**)], 1.625 [qt, 2H of this tautomer, $J_{5,6} = J_{5,4} = 7.4$ Hz, 5-H_2 (keto-**5b**)], 1.92 [m, 4H of both tautomers, 3′-H_2, 4′-H_2 (keto-**5b**) and (enol-**5b**)], 2.16 [t, 2H of this tautomer, $J_{4,5} = 7.9$ Hz, 4-H_2 (enol-**5b**)], 2.57 [t, 2H of this tautomer, $J_{4,5} = 7.3$ Hz, 4-H_2 (keto-**5b**], 3.37–3.52 [m, 4H of both tautomers, 2′-H_2, 5′-H_2 (keto-**5b**) and (enol-**5b**)] superimposed by 3.46 [s, 2H of this tautomer, 2-H_2 (keto-**5b**)], 4.96 [s, 1H of this tautomer, 2-H, (enol-**5b**)], 14.67 [brs, 1H of this tautomer, 3-OH (enol-**5b**)]; IR ($CDCl_3$): $\tilde{\nu} = 3690$, 2970, 2935, 2880, 1720, 1630, 1480, 1450, 1370, 1345, 1297, 1230, 1190, 1170, 1125, 925, 890 cm^{-1}; elemental analysis calcd for $C_{10}H_{17}NO_2$ (183.3): C 65.54, H 9.35, N 7.64; found: C 65.22, H 9.48, N 7.80.

3-Oxohexanoic acid piperidide (5c): A solution of dioxinone **4** (0.98 g, 5.8 mmol) and piperidine (1.2 mL, 0.99 g, 12 mmol, 2.0 equiv) in xylene (25 mL) was heated under reflux for 15 min. After adding more piperidine (0.6 mL, 0.5 g, 6 mmol, 1.0 equiv) the mixture was stirred under reflux for another 15 min. The solvent was evaporated and the residue was submitted to flash chromatography (4 cm, cyclohexane/ethyl acetate 3:1) to give **5c** (#23–36, 1.01 g, 88%) as a colorless oil and 89:11 keto/enol mixture {as determined by averaging the intensity ratios of the following pairs of signals: $\delta = 2.16$ [t, $J_{4,5} = 7.5$ Hz, 4-H_2 (enol-**5c**)] vs $\delta = 2.54$ [t, $J_{4,5} = 7.3$ Hz, 4-H_2 (keto-**5c**)] and $\delta = 3.52$ [s, 2-H_2 (**5c**)] vs 5.14 [s, 2-H, (enol-**5c**)]}. ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 0.92$ [t, 3H of this tautomer, $J_{6,5} = 7.5$ Hz, 6-H_3 (keto-**5c**)] superimposed by 0.95 [t, 3H of this tautomer, $J_{6,5} = 7.4$ Hz, 6-H_3 (enol-**5c**)], 1.52–1.68 [m, 8H of both tautomers, 5-H_2, 3′-H_2, 4′-H_2, 5′-H_2 (keto-**5c** and enol-**5c**)], 2.16 [t, 2H of this tautomer, $J_{4,5} = 7.5$ Hz, 4-H_2 (enol-**5c**)], 2.54 [t, 2H of this tautomer, $J_{4,5} = 7.3$ Hz, 4-H_2 (keto-**5c**)], 3.35 [m, 2H of this tautomer, 2′-H_2^* (keto-**5c**)], 3.44–3.51 [m, 4H of this tautomer, 2′-H_2, 6′-H_2 (enol-**5c**)], 3.52 [s, 2H of this tautomer, 2-H_2 (keto-**5c**)], 3.57 [m, 2H of this tautomer, 6′-H_2* (keto-**5c**)], 5.14 [s, 1H of this tautomer, 2-H, (enol-**5c**)], 14.87 [brs, 1H of this tautomer, 3-OH (enol-**5c**)]; *interchangeable; IR ($CDCl_3$): $\tilde{\nu} = 3480$, 2935, 2860, 1720, 1635, 1585, 1485, 1445, 1385, 1255, 1230, 1185, 1140, 1125, 1020, 955, 855 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{19}NO_2$ (197.3): C 66.97, H 9.71, N 6.96; found: C 66.88, H 9.77, N 7.10.

3-Oxohexanoic acid *N,N*-diethylamide (5d): A solution of the dioxinone **4** (1.1 g, 6.5 mmol) and diethylamine (1.4 mL, 0.95 g, 13 mmol, 2.0 equiv) in xylene (10 mL) was heated under reflux for 15 min. The solvent was evaporated and the residue was submitted to flash chromatography (4 cm, cyclohexane/ethyl acetate 10:1 → fraction 15, 8:1 → fraction 30, 6:1 → fraction 40, 3:1) to afford unconsumed dioxinone **4** (#31–38, 299 mg, 27%) and β-ketoamide **5d** [#42–48, 740 mg, 61% (84% based on recovered starting material)] as a slightly yellow oil and 77:23 keto/enol mixture {as determined by averaging the intensity ratios of the following pairs of signals: $\delta = 0.92$ [t, 3H of this tautomer, $J_{6,5} = 7.5$ Hz, 6-H_3 (keto-**5d**)] vs 0.96 [t, 3H of this tautomer, $J_{6,5} = 7.4$ Hz, 6-H_3 (enol-**5d**)] and $\delta = 2.16$ [t, 2H of this tautomer, $J_{4,5} = 7.6$ Hz, 4-H_2 (enol-**5d**)] vs 2.57 [t, 2H of this tautomer, $J_{4,5} = 7.2$ Hz, 4-H_2 (keto-**5d**)] and $\delta = 3.48$ [s, 2H of this tautomer, 2-H_2 (keto-**5d**)] vs 5.05 [s, 1H of this tautomer, 2-H, (enol-**5d**)]}.- ^{1}H NMR (499.9 MHz, $CDCl_3$): $\delta = 0.92$ [t, 3H of this tautomer, $J_{6,5} = 7.5$ Hz, 6-H_3 (keto-**5d**)], 0.96 [t, 3H of this tautomer, $J_{6,5} = 7.4$ Hz, 6-H_3 (enol-**5d**)], 1.14, 1.17 [2×t, 6H of both tautomers, $J_{2',1'} = 7.2$, $J_{2'',1''} = 7.2$ Hz, respectively, 2′-H_3 and 2″-H_3 (keto-**5d** and enol-**5d**)], 1.63 [tt, 2H of both tautomers, $J_{5,4} = J_{5,6} = 7.4$ Hz, 5-H_2 (keto-**5d** and enol-**5d**)], 2.16 [t, 2H of this tautomer, $J_{4,5} = 7.6$ Hz, 4-H_2 (enol-**5d**)], 2.57 [t, 2H of this tautomer, $J_{4,5} = 7.2$ Hz, 4-H_2 (keto-**5d**)], 3.29, 3.39 [q, 4H of both tautomers, $J_{1',2'} = 7.2$, $J_{1'',2''} = 7.1$ Hz, respectively, 1′-H_2 and 1″-H_2 (keto-**5d** and enol-**5d**)], 3.48 [s, 2H of this tautomer, 2-H_2 (keto-**5d**)], 5.05 [s, 2-H, 1H of this tautomer, (enol-**5d**)], 14.89 [brs, 1H of this tautomer, 3-OH (enol-**5d**)]; IR ($CDCl_3$): $\tilde{\nu} = 3690$, 2970, 2935, 2905, 2875, 2250, 1715, 1630, 1590, 1490, 1465, 1440, 1405, 1380, 1365, 1315, 1270, 1220, 1190, 1150, 1100, 1075, 950 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{19}NO_2$ (185.3): C 64.83, H 10.34, N 7.56; found: C 64.58, H 10.60, N 7.46.

Asymmetric hydrogenation ("AH") of β-ketoamides 5a–d (general procedure): "[{$RuCl_2$(*S*)-binap}$_2$]·NEt_3"[5] was added to a degassed solution of the respective β-ketoamide in MeOH. The resulting mixture was stirred in a glass autoclave under H_2 (4.0 bar) at room temperature for 24 h. After the autoclave had been vented, the solvent was evaporated and the residue was purified by flash chromatography.

(3*S*)-3-Hydroxydodecanoic acid pyrrolidide (6a): Compound **6a** was prepared by AH according to the general procedure using β-ketoamide **5a**



(133.7 mg, 0.5 mmol) and "[{$RuCl_2$(*S*)-binap}$_2$]·NEt_3"[5] (4.2 mg, 2.5 μmol, 0.5 mol%) in MeOH (4.0 mL). Flash chromatography (2.0 cm, CH/EE 1:1) of the crude hydrogenation product provided β-hydroxyamide **6a** (#23–35, 170 mg, 97%) as colorless oil. $[\alpha]_D^{20} = +34.3$ ($c = 1.03$, $CHCl_3$); 96% *ee* (by chiral HPLC[17]); ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 0.85$ (t, 3H, $J_{12,11} = 7.0$ Hz, 12-H_3), 1.19–1.58 (m, 14H, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2), 1.79–1.98 (m, 4H, 3′-H_2, 4′-H_2), AB signal ($\delta_A = 2.24$, $\delta_B = 2.41$, 2H, $J_{AB} = 16.4$ Hz, in addition split by $J_{A,3} = 9.5$, $J_{B,3} = 2.5$ Hz, 2-H_2), 3.31–3.49 (m, 4H, 2′-H_2, 5′-H_2), 4.00 (dddd, 1H, $J_{3,2\text{-H(A)}} = 9.7$, $J_{3,4\text{-H(A)}} = 7.3$, $J_{3,4\text{-H(B)}} = 4.7$, $J_{3,2\text{-H(B)}} = 2.5$ Hz, 3-H), 4.42 (brs, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.1$ (C-12), 22.7, 25.6, 29.4, 29.61, 29.65, 29.68, 31.9, 36.6 (C-4, C-5, C-6, C-7, C-8, C-9, C-10, C-11)*, 24.4, 26.0 (C-3′, C-4′)*, 40.7 (C-2)*, 45.5, 46.6 (C-2′, C-5′)*, 68.1 (C-3)*, 171.5 (C-1); *distinguished by a C,H-correlation spectrum; IR ($CDCl_3$): $\tilde{\nu} = 3420$, 2955, 2925, 2870, 2855, 1625, 1455, 1340, 1275, 1255, 1225, 1195, 1170, 1085, 1065, 915, 860 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{31}NO_2$ (269.4): C 71.33, H 11.60, N 5.20; found: C 71.19, H 11.32, N 5.00.

(3*S*)-3-Hydroxyhexanoic acid pyrrolidide (6b): Compound **6b** was prepared by AH according to the general procedure using β-ketoamide **5b** (91.5 mg, 0.5 mmol) and "[{$RuCl_2$(*S*)-binap}$_2$]·NEt_3"[5] (4.2 mg, 2.5 μmol, 0.5 mol%) in MeOH (4.0 mL). Flash chromatography (2.0 cm, CH/EE 1:2) of the crude hydrogenation product provided β-hydroxyamide **6b** (#9–20, 90.2 mg, 97%) as colorless oil. $[\alpha]_D^{20} = +42.9$ ($c = 1.17$, $CHCl_3$); >98% *ee* (by chiral GLC[16]); ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 0.94$ (t, 3H, $J_{6,5} = 7.1$ Hz, 6-H_3), 1.34–1.61, 1.83–2.01 (2×m, 8H, 4-H_2, 5-H_2, 3′-H_2, 4′-H_2), AB signal ($\delta_A = 2.27$, $\delta_B = 2.43$, 2H, $J_{AB} = 16.3$ Hz, in addition split by $J_{A,3} = 9.7$ Hz, $J_{B,3} = 2.5$ Hz, 2-H_2), 3.33–3.51 (m, 4H, 2′-H_2, 5′-H_2), 4.05 (m_c, 1H, 3-H), 4.41 (brs, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.1$ (C-6), 18.8, 24.4, 26.2, 38.7 (C-4, C-5, C-3′, C-4′)*, 40.7 (C-2)*, 45.6 and 46.6 (C-2′, C-5′)*, 67.8 (C-)*, 171.5 (C-1); *distinguished by a C,H-correlation spectrum; IR ($CDCl_3$): $\tilde{\nu} = 3445$, 2960, 2935, 2875, 1620, 1455, 1345, 1310, 1280, 1255, 1230, 1190, 1175, 1135, 1115, 1075, 1045, 940, 910, 890, 850 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{19}NO_2$ (187.3): C 64.83, H 10.34, N 7.56; found: C 64.52, H 10.33, N 7.64.

(3*S*)-3-Hydroxyhexanoic acid piperidide (6c): Compound **6c** was prepared by AH according to the general procedure using β-ketoamide **5c** (98.5 mg, 0.5 mmol) and "[{$RuCl_2$(*S*)-binap}$_2$]·NEt_3"[5] (4.2 mg, 2.5 μmol, 0.5 mol%) in MeOH (4.0 mL). Flash chromatography (2.0 cm, CH/EE 1:1) of the crude hydrogenation product provided β-hydroxyamide **6c** (#10–

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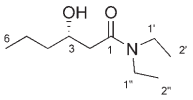
24, 97 mg, 98 %) as colorless oil. $[\alpha]_D^{20} = +44.4$ ($c = 1.15$, $CHCl_3$); 93 % *ee* (by chiral GLC[16]); ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 0.94$ (t, 3H, $J_{6,5} = 7.1$ Hz, 6-H_3), 1.33–1.69 (m, 10H, 4-H_2, 5-H_2, 3′-H_2, 4′-H_2, 5′-H_2), AB signal ($\delta_A = 2.29$, $\delta_B = 2.47$, 2H, $J_{AB} = 16.3$ Hz, in addition split by $J_{A,3} = 9.7$, $J_{B,3} = 2.4$ Hz, 2-H_2), 3.37, 3.56 (2 × m, 4H, 2′-H_2, 6′-H_2), 4.03 (m, 1H, presumably interpretable as dddd, $J_{3,2\text{-H(A)}} = J_{3,4\text{-H(A)}} = 9.6$, $J_{3,4\text{-H(B)}} = 4.8$, $J_{3,2\text{-H(B)}} = 2.3$ Hz, 3-H), 4.30 (d, 1H, $J_{OH,3} = 2.4$ Hz, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.1$ (C-6), 18.8, 24.5, 25.6, 26.4, 38.6 (C-4, C-5, C-3′, C-4′, C-5′)*, 39.3 (C-2)*, 42.5, 46.4 (C-2′, C-6′)*, 67.8 (C-3)*, 171.0 (C-1); *distinguished by a C,H-correlation spectrum; IR ($CDCl_3$): $\tilde{\nu} =$ 3410, 2935, 2860, 1620, 1445, 1250, 1220, 1140, 1125, 1015, 850 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{21}NO_2$ (197.3): C 66.29, H 10.62, N 7.03, C 66.22, H 10.53, N 6.80.

(3*S*)-3-Hydroxyhexanoic acid *N*,*N*-diethylamide (6d): Compound **6d** was prepared by AH according to the general procedure using β-ketoamide **5d** (93 mg, 0.5 mmol) and "[{$RuCl_2$(*S*)-binap}$_2$]·NEt_3"[5] (4.2 mg, 2.5 μmol, 0.5 mol %) in MeOH (4.0 mL). Flash chromatography (2.0 cm, CH/EE 2:1) of the crude hydrogenation product provided β-hydroxyamide **6d** (#12–20, 88 mg, 94 %) as a colorless oil. $[\alpha]_D^{20} = +38.3$ ($c = 1.07$, $CHCl_3$); 91 % *ee* (by chiral GLC[16]); ^{1}H NMR (400.1 MHz, TMS): $\delta = 0.93$ (t, 3H, $J_{6,5} = 7.1$ Hz, 6-H_3), 1.12, 1.17 (2 × dd, 6H, $J_{2',1'\text{-H(A)}} = J_{2',1'\text{-H(B)}} = 7.1$, $J_{2'',1''\text{-H(A)}} = J_{2'',1''\text{-H(B)}} = 7.1$ Hz, respectively, 2′-H_3 and 2″-H_3), 1.33–1.60 (m, 4H, 4-H_2, 5-H_2), AB signal ($\delta_A = 2.28$, $\delta_B = 2.47$, 2H, $J_{AB} = 16.2$ Hz, in addition split by $J_{A,3} = 9.6$ Hz, $J_{B,3} = 2.3$ Hz, 2-H_2), 3.21–3.45 [m, 4H, presumably interpretable as two overlapping AB signals ($\delta_A = 3.27$, $\delta_B = 3.30$, $J_{AB} = 14.7$ Hz, in addition split by $J_{A,2'} = 7.1$ Hz, $J_{B,2'} = 7.1$ Hz, 1′-H_2) and ($\delta_A = 3.36$, $\delta_B = 3.39$, $J_{AB} = 13.8$ Hz, in addition split by $J_{A,2''} = 7.1$ Hz, $J_{B,2''} = 7.1$ Hz, 1″-H_2), 1′-H_2 and 1″-H_2], 4.02 (m, 1H, 3-H), 4.43 (br d, 1H, $J_{OH,3} = 2.4$ Hz, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.1$, 14.1 and 14.2 (C-6, C-2′, C-2″), 18.9, 38.7, 39.1, 40.2, 42.0 (C-2, C-4, C-5, C-1′ and C-1″), 68.0 (C-3), 172.1 (C-1); IR ($CDCl_3$): $\tilde{\nu} = 3460$, 2980, 2935, 2875, 1620, 1485, 1465, 1450, 1440, 1385, 1250, 1220, 1150, 1110, 1075, 1045, 935, 880 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{21}NO_2$ (187.3): C 64.13, H 11.30, N 7.48; found: C 63.88, H 11.28, N 7.21.



Acknowledgements

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[17] The *ee* value of β-hydroxyamide **6a** was determined by chiral HPLC (Chiralpak AD-H, *n*-heptane/EtOH 85:15, 0.8 mL min^{-1}, 20 °C isotherm, 212 nm): $t_{r,S\text{ enantiomer}} = 9.6$ min, $t_{r,R\text{ enantiomer}} = 11.4$ min (determined with racemic material).

[18] Achiral GLC analyses were performed with a Carlo Erba Instruments ICU 600 GC 6000 Vega Series apparatus on a dimethylpolysiloxane column (J&W Scientific, SE-30, 25 m × 0.33 mm); *T* and *t* details specified in the captions of Figures 1–6.

[19] Expressed differently, the total substrate concentration was 0.188 M starting from the ternary mixture, 0.125 M starting from all binary substrate mixtures, and 0.067 M when monitoring the hydrogenation of pure **7a**. The starting concentration of "[{$RuCl_2$(binap)}$_2$]·NEt_3"[5] was 0.31 μM in all kinetic investigations.

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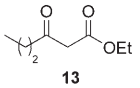
[21] We could not cross-check this assumption by retrieving the full amount of substrate **5c** in the reaction mixture because it was unstable under our GLC analysis conditions.[22]

[22] GLC analyses[18] of each mixture containing β-ketoester **7c** or β-ketoester **7d** evidenced partial (→ **13**) or complete alcoholysis (→ **14**,



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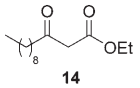

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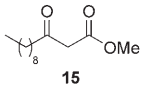

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→ **15**) of these species in the injection chamber (250 °C) of the GLC apparatus (representative details: footnote 25 of ref. [6]).

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[24] Curves c) vs d) show that the onset of the conversion **5a**→**6a** occurred with a time-lag of ca. 2 h. Similarly, pyrrolidide **5b** in the 1:1 mixture with ester **7a** was completely consumed after 16.5 h (Figure 2) but in the 1:1 mixture with ester **7c** after 17 h not yet (Figure 3). The most likely explanation for these small discrepancies appears to be weighing errors of the catalyst: 4.2 mg thereof were weighed in a 10 mL round-bottom flask.

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