Asymmetric Hydrogenation of 2,4-Dioxo Esters: Selective Synthesis of 2-Hydroxy-4-oxo Esters and Direct Access to Chiral 2-Hydroxy-4-butyrolactones

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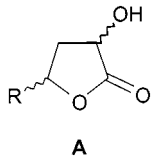
2,4-Dioxoesters **1a–c** are selectively converted into optically active 2-hydroxy-4-oxoesters **2a–c** by hydrogenation with chiral rhodium-aminophosphane-phosphinite catalysts (82–88% ee) or ruthenium-bisphosphane catalysts (52–67% ee). Direct one-pot hydrogenation of 2,4-dioxoesters **1a–c** to 2-hydroxy-4-butyrolactones **4a–c** proceeds in high yields; catalytic activities, chemo-, dia-, and enantioselectivities are strongly dependant upon the nature of the substrate and the catalyst.

Introduction

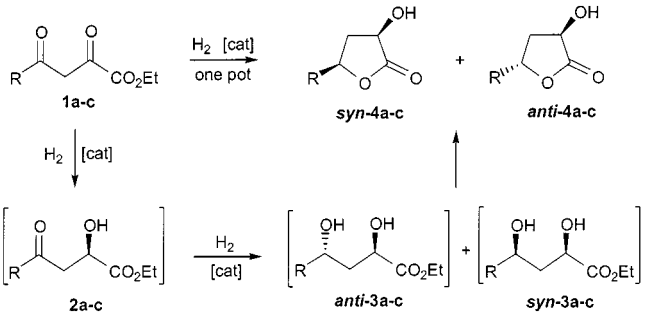
Significant attention has been focused in recent years on optically active α-hydroxy-γ-butyrolactones of type **A** (Scheme 1). Structures **A** bearing an alkyl R chain at the 4(γ)-position are well-identified hunger modulator substances[1] and key intermediates in the preparation of liquid crystals.[2] These compounds also proved to be useful chiral building blocks for the synthesis of biologically active molecules,[3] e.g., for the lactone portion of mevinic acids through simple homologation of the butyrolactone structure.[3a] Traditional stereoselective routes to γ-lactones **A** employ multistep procedures starting from natural chiral materials.[4] Enantiopure *syn*- and *anti*-α-hydroxy-γ-butyrolactones have been also prepared by diastereodivergent diamine-assisted deprotonation of chiral dicarbamates.[5] Generally speaking, many efforts in the last decades have been directed toward the development of simple asymmetric *catalytic* methods to produce optically active molecules from *achiral* reagents.[6] An interesting approach in this regard for the synthesis of γ-lactones **A** is the enzymatic reduction of easily available 2,4-dioxo acids;[7] however, enzymes reduce the α-keto function regioselectively to enantiopure 2-hydroxy-4-oxo acids leaving intact the γ-keto function, and *syn*-α-hydroxy-γ-butyrolactones are obtained by subsequent diastereoselective chemical reduction with DIBAL-H. In order to develop a direct, fully catalytic synthesis of γ-lactones **A**, we investigated a new procedure, the transition-metal-catalysed asymmetric hydrogenation of 2,4-dioxo esters (Scheme 2).

Highly enantioselective homogeneous catalysts based on rhodium− and ruthenium−diphosphane complexes have been developed for the asymmetric hydrogenation of simple keto esters and diketones.[8] Rhodium catalysts are very efficient for the hydrogenation of α-ketoesters (high catalytic activity under mild conditions, 90−99% ee),[9][10] but they are normally very poor for other types of keto compounds.[11] On the other hand, ruthenium complexes associated to atropisomeric bisphosphanes (BINAP, ...) or recently developed diphosphanes are outstanding catalysts for the hydrogenation of β-keto esters,[12] γ-keto esters,[13] diketones,[14] β,δ-diketo esters,[15] and also α-keto esters,[12g,16] although in the latter case more severe reaction conditions than with rhodium catalysts are required for reasonable activity. We have reported recently in a preliminary communication that ruthenium−diphosphane complexes are efficient catalyst precursors for the selective conversion of ethyl 2,4-dioxovalerate (**1a**) into the corresponding lactones (**4a**).[17] Here, we present a full account of this new process, through a systematic screening for the hydrogenation of 2,4-dioxo



A

Scheme 1



Scheme 2. One-pot asymmetric hydrogenation of α,γ-diketo esters **1a−c** (**1a**, R = Me; **1b**, R = *t*Bu; **1c**, R = 2-thienyl)

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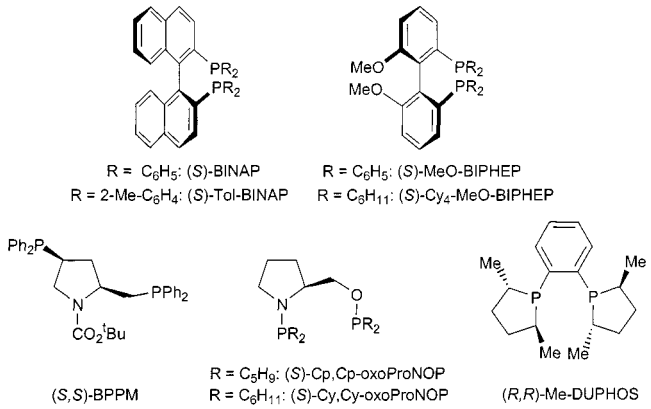

Scheme 3. Chiral ligands used in this study

esters **1a−c** (Scheme 2) with a variety of rhodium− and ruthenium−diphosphane catalyst precursors. It is shown that the performances, i.e., the degree of enantioselection and the catalytic activity, are highly dependent on the structures of the substrates, particularly bulkiness of the susbtituent; consequently, no generality in the choice of the optimal metal/ligand system is found. It is further shown that the reaction proceeds by the selective hydrogenation of the C-2 (α) keto group, which leads to the unprecedented catalytic synthesis of optically active 2-hydroxy-4-oxo esters **2a−c**. The results of this comparative study also gives some insight into the different coordination modes of 2,4-dioxo esters with rhodium and ruthenium species.

Results and Discussion

Hydrogenation of Ethyl 2,4-Dioxovalerate (1a)

Hydrogenation of **1a** was first investigated in the presence of rhodium catalysts. Representative results are reported in Table 1. In toluene or dichloromethane as solvent,[18] all the systems tested catalyse the chemoselective one-pot transformation of **1a** into γ-lactone **4a** as a mixture of *syn* and *anti* diastereomers. GLC monitoring revealed that the reaction proceeds by the route outlined in Scheme 2. The first step consists of the hydrogenation of the α-keto function of **1a** to yield ethyl 2-hydroxy-4-oxovalerate (**2a**); the other possible monohydrogenation regioisomer, ethyl 2-oxo-4-hydroxyvalerate, was never detected. Such a high regioselectivity for the α-keto function is directly in line with previous studies which have shown that the rate of hydrogenation of a carbonyl group by neutral rhodium catalysts is greatly enhanced by the presence of an α-alkoxycarbonyl moiety.[10] In a second step, **2a** is further hydrogenated to 2,4-dihydroxy ester **3a**, which exists as a mixture of *syn* and *anti* diastereomers. With a significantly active catalyst, intermediate **2a** can be selectively obtained in good yield by carrying out the hydrogenation at 20°C (entry 8). At 60°C, subsequent hydrogenation of **2a** to **3a** starts before the first step is complete. Under these conditions, in situ lactonization of **3a** to **4a** proceeds relatively fast, so that the **3a**/**4a** ratio in aliquot samples is typically lower than 20:80.

Despite a common mechanistic pathway, large differences in the catalyst performance are observed depending to the nature of the diphosphane and the X ligand present in the rhodium precursor. Commercially available chiral diphosphanes bearing diphenylphosphanyl residues (Scheme 3) lead to sluggish catalysts, especially for the second hydrogenation step, and poor selectivities (entries 1−3). A more basic ligand with dicyclohexylphosphanyl residues increases the overall rate, especially when a trifluoroacetato rhodium precursor is used, but de′s and ee′s for **4a** are very low (entries 3−5). The best rhodium systems are based on aminophosphane-phosphinite ligands derived from (*S*)-2-(hydroxymethyl)-5-pyrrolidinone and were developed in our laboratory for the hydrogenation of α-keto esters[10] (entries 6−14). Optimization experiments showed that important parameters for catalytic activity are (i) presence of cyclopentyl (Cp) groups vs. cyclohexyl (Cy) groups at the phosphorus moieties of the AMPP ligand (compare entries 6 and 9), and (ii) a high catalyst concentration (entries 9, 10). The in situ combination of $[Rh(COD)Cl]_2$ with (*S*)-Cp,Cp-oxoProNOP affords **4a** in 91% yield with up to 73% and 86% ee′s in the *syn* and *anti* form, respectively, but with a ca. 50:50 *syn*/*anti* ratio. Actually, the first hydrogenation step proceeds in fair to good enantioselectivity, as evidenced by the ee′s for **2a** which are in the typical range observed for the hydrogenation of aliphatic α-keto esters with Rh-AMPP catalysts (70−86% ee, Table 1);[10][19] however, rhodium catalysts are not diastereoselective at all for the second step. Variation of the nature of the solvent, or replacement of the chloro ligand in the rhodium precursor by various carboxylato ligands, including optically active α-methoxy-α-trifluoromethylphenyl acetate (MTPA), has little effect on activity and selectivities (entries 11−14).

In view of the inherent inefficiency of rhodium catalysts to promote the diastereoselective formation of γ-lactone **4a**, we next investigated ruthenium-based systems. Significant results are summarized in Table 2. GLC monitoring of the experiments showed that the reaction in the presence of ruthenium species in CH_2Cl_2 proceeds by the same route as with rhodium catalysts (Scheme 2). In particular, **2a** is also the only monohydrogenation intermediate observed, and it can be isolated in high yields (but fair ee′s) in the first stage of the reaction (entries 4 and 6). In situ lactonization of intermediate **3a** to γ-lactone **4a** proceeds faster than with Rh/toluene systems and the **3a**/**4a** ratio in aliquot samples is typically lower than 5:95. All the ruthenium catalysts tested are more than 99% chemoselective for the formation of compounds **2a**, **3a**, and **4a**. As expected in light of diastereoselective hydrogenations of β-hydroxy ketones reported by Noyori et al.,[12b,c] ruthenium catalysts favour the formation of *anti* diol **3a** and thus of the *syn* diastereomer of **4a**. This trend, observed with a simple *achiral* catalyst (entry 1), is even more pronounced with chiral Ru catalysts bearing chelating atropisomeric bisphosphanes, which afford *syn*-**4a** in 65−70% de and 96−98% ee (entries 2−8). The reaction is optimally carried out with 0.5 mol-% of

Table 1. Rhodium-catalysed asymmetric hydrogenation of ethyl 2,4-dioxovalerate (**1a**)[a]

Entry	Rhodium catalyst[b]	Time (h)	**1a** conv	**2a** sel	ee[c]	**4a** sel	*syn*/*anti*	ee[d]
1	RhCl[(*R,R*)-Me-DUPHOS]	136	9	81	17	19	46:54	nd
2	RhCl[(2*S*,4*S*)-BPPM]	67	100	63	60	26	54:46	58/64
		331	100	11	66	89	55:45	57/64
3	RhCl[(*S*)-MeO-BIPHEP]	138	100	82	78	18	54:46	79/53
4	RhCl[(*S*)-Cy_4MeO-BIPHEP]	137	97	46	28	44	46:54	0/50
5	Rh(TFA)[(*S*)-Cy_4MeO-BIPHEP]	119	97	8	28	73	44:56	0/55
6	RhCl[(*S*)-Cy,Cy-oxoProNOP]	84	100	81	70	18	65:35	80/60
7	Rh(TFA)[(*S*)-Cy,Cy-oxoProNOP]	86	100	45	80	47	48:52	80/86
		166	100	3	nd	92	48:52	80/86
8[e]	RhCl[(*S*)-Cp,Cp-oxoProNOP]	24	92	95	86	1	nd	nd
9	RhCl[(*S*)-Cp,Cp-oxoProNOP]	19	99	64	78	23	42:58	73/86
		70	100	3	nd	91	44:56	73/86
10[f]	RhCl[(*S*)-Cp,Cp-oxoProNOP]	23	99	11	nd	61	41:59	72/84
		43	100	0	–	91	44:56	72/86
11[f,g]	RhCl[(*S*)-Cp,Cp-oxoProNOP]	43	100	1	-	82	43:57	75/84
12	Rh(TFA)[(*S*)-Cp,Cp-oxoProNOP]	26	100	39	80	56	45:55	72/87
		165	100	4	nd	96	45:55	72/87
13	Rh[(*R*)-MTPA][(*S*)-Cp,Cp-oxoProNOP]	44	92	42	82	49	49:51	73/81
		140	100	4	nd	92	49:51	73/81
14	Rh[(*S*)-MTPA][(*S*)-Cp,Cp-oxoProNOP]	39	92	54	83	32	44:56	70/83
		179	100	< 1	nd	> 99	47:53	74/83

[a] Toluene, 60°C, 50 atm H_2, [**1a**]/[P]/[Rh] = 200:2.2:1, [Rh] = 0.6−1.4 mmol·L^{-1} unless otherwise stated. Conversion (mol-%) of **1a** and selectivities (ee, de;%) for **2a** and **4a** were determined by quantitative GLC analysis; diol **3a** accounts for the balance. – [b] Catalyst generated in situ from the appropriate precursor $[Rh(COD)X]_2$ (X = Cl, TFA or MTPA) and 2.2 equiv. of the diphosphane ligand. – [c] In all cases, the configuration of the prevailing enantiomer of **2a** is (*R*), as established from the specific rotation.[7] – [d] Enantiomeric excess of *syn*-**4a** and *anti*-**4a**, respectively. The configuration of the prevailing enantiomer for *syn*-**4a** and *anti*-**4a** is (2*R*,4*S*) and (2*R*,4*R*), respectively, as established from the specific rotations.[5] – [e] *T* = 20°C. – [f] [Rh] = 3.2 mmol·L^{-1}. – [g] Solvent: CH_2Cl_2.

$[RuBr_2\{(S)$-MeO-BIPHEP$\}]$ at 80°C, leading to *syn*-**4a** in 84% GLC yield and 98% ee (entry 6). Commercially available $[RuCl_2\{(S)$-BINAP$\}]_2 \cdot NEt_3$ is an active, although slightly less enantioselective catalyst (entry 2). Deviation from the optimal temperature (80°C) results in lower de′s (entries 4 and 5, 6, and 7), while a ligand bearing dicyclohexylphosphanyl moieties proved inefficient (entry 8).

Hydrogenation of Ethyl 2,4-Dioxo-5,5-dimethylhexanoate (1b)

To probe the influence of steric effects, we investigated the hydrogenation of 2,4-dioxoester **1b** bearing a *tert*-butyl group at the γ-keto function. Representative results are summarized in Table 3. As shown for **1a**, the reaction of **1b**

Table 2. Ruthenium-catalysed asymmetric hydrogenation of ethyl 2,4-dioxovalerate (**1a**)[a]

Entry	Ruthenium catalyst	Time[b] (h)	**1a** conv	**2a** sel	ee[c]	**4a** sel	*syn*/*anti*	ee[d]
1	$RuCl_2(PPh_3)_3$	63	100	17	0	83	73:27	0/0
2	$\{RuCl_2[(S)$-BINAP$]\}_2$ NEt_3	13	100	8	nd	92	83:17	94/75
		23	100	0	nd	>99	83:17	96/77
3	$RuBr_2[(S)$-BINAP]	13	100	72	75	28	81:19	96/66
		37	100	36	80	64	85:15	96/66
4	$RuBr_2[(S)$-TolBINAP]	2.5	100	>99	67	<1	–	–
		21	100	0	–	>99	83:17	94/87
5[e]	$RuBr_2[(S)$-TolBINAP]	13.5	100	12	nd	87	80:20	92/77
6	$RuBr_2[(S)$-MeO-BIPHEP]	3	99	94	72	3	73:27	nd
		17	100	29	nd	71	83:17	98/87
		39	100	0	–	>99	84:16	98/87
7[f]	$RuBr_2[(S)$-MeO-BIPHEP]	65	100	6	nd	93	78:22	97/94
		157	100	0	–	>99	79:21	96/93
8	$RuBr_2[(S)$-Cy_4MeO-BIPHEP]	30	15	>99	39	0	–	–

[a] CH_2Cl_2, 80°C, 100 atm H_2, [**1a**]/[Ru] = 200:1, [Ru] = 1.8 mmol·L^{-1} unless otherwise stated. Conversion and selectivities: see Table 1. – [b] Non-optimized time. – [c] In all cases, the configuration of the prevailing enantiomer of **2a** is (*R*), as established from the specific rotation.[7] – [d] Enantiomeric excess of *syn*-**4a** and *anti*-**4a**, respectively. The configuration of the prevailing enantiomer for *syn*-**4a** and *anti*-**4a** is (2*R*,4*S*) and (2*S*,4*S*), respectively, as established from the specific rotations.[5] – [e] *T* = 110°C. – [f] *T* = 60°C.

Table 3. Asymmetric hydrogenation of ethyl 2,4-dioxo-5,5-dimethylhexanoate (**1b**)[a]

Entry	Catalyst	Time[b] (h)	**2b** sel	ee[c]	**4b** sel	*syn*/*anti*	ee[d]
1	$RuCl_2(PPh_3)_3$	65	>99	0	0	–	–
2	$\{RuCl_2[(S)\text{-BINAP}]\}_2 \cdot NEt_3$	12	>99	52 (+)	0	–	–
		35	95	56 (+)	3	72:28	nd
3	$RuBr_2[(S)\text{-TolBINAP}]$	15	>99	39 (+)	0	–	–
		64	87	35 (+)	13	86:14	88 (−)
4	$RuBr_2[(S)\text{-MeO-BIPHEP}]$	21	98	49 (+)	2	nd	nd
		160	91	47 (+)	9	87:13	72 (−)
5	$RhCl(PPh_3)_3$	234	>99	0	0	–	–
6	$RhCl[(R)\text{-Cy,Cy-oxoProNOP}]$	17	>99	88 (−)	0	–	–
		157	94	87 (−)	6	50:50	60 (−)
7	$Rh(TFA)[(S)\text{-Cp,Cp-oxoProNOP}]$	38	>99	48 (+)	0	–	–
		93	>99	49 (+)	0	–	–
8	$RhCl[(S)\text{-Cp,Cp-oxoProNOP}]$	23	98	82 (+)	2	nd	nd
		88	88	83 (+)	12	32:68	97 (+)
9[e]	$RhCl[(R)\text{-Cp,Cp-oxoProNOP}]$	25	78	74 (−)	22	31:69	97 (−)
		163	19	96 (−)	81	30:70	97 (−)

[a] Unless otherwise stated, Rh systems: toluene, 60°C, 50 atm H_2, [**1b**]/[Rh] = 50:1, [Rh] = 0.5−4.0 mmol·L^{-1}; Ru systems: CH_2Cl_2, 80°C, 100 atm H_2, [**1b**]/[Ru] = 50:1, [Ru] = 1.8 mmol·L^{-1}. Conversion and selectivities: see Table 1. − [b] Non-optimized time for 100% conversion of **1b**. − [c] The absolute configuration of (+)-**2b** is assumed to be (*R*); see Note [20]. − [d] Enantiomeric excess of *anti*-**4b**. − [e] T = 90°C.

also proceeds via corresponding intermediate **2b** (Scheme 2); however, hydrogenation of **2b** proved to be much more difficult than that of **2a** (compare entries 1 of Tables 2 and 3). As a matter of fact, all the ruthenium and rhodium catalysts investigated for this reaction allow the easy synthesis of **2b**, without any contamination by dihydrogenated products. Enantiomeric excesses for **2b** obtained with chiral ruthenium catalysts are lower than those observed for **2a** (39−52% vs. 67−72% ee), suggesting that the R group of **1** is within the coordination sphere and thus that **1** forms a chelate with Ru through the two keto functions.[12] On the contrary, chlororhodium-AMPP catalysts afford **2b** in ee′s as high as 88% (entry 6),[20] a typical value almost unaffected by the nature of the R group,[19] which suggests that **1** is monocoordinated to the Rh centre through the α-keto group.[10b] Lactones **4b** are produced very slowly with ruthenium catalysts; with 2 mol-% of the most active system found, **4b** is formed after 64 h at 80°C in only 13% as a 86/14 mixture of *syn* and *anti* diastereomers (entry 3). Surprisingly, better yields of **4b** are obtained with chlororhodium−AMPP catalysts (entries 6−9), although catalytic activities are still low and require a higher operating temperature. Thus, the in situ combination of $[Rh(COD)Cl]_2$ with (*R*)-Cp,Cp-oxoProNOP in toluene at 60°C affords **4b** in only 12% yield with a *syn*/*anti* ratio of 32:68 and 97% ee for *anti*-**4b** (entry 8), but by carrying out the reaction at 90°C over a longer time, **4b** is formed in 81% yield with the same de and ee (entry 9). With Rh-AMPP catalysts, going from R = Me (**1a**) to R = *t*Bu (**1b**) results logically in a decrease of catalytic activity and an increase of dia- and enantioselectivity; however, it is not clear why this change affects the activity of ruthenium catalysts much more than that of rhodium catalysts.

Hydrogenation of Ethyl 2,4-Dioxo-4-(2-thienyl)butyrate (1c)

To probe the influence of electronic effects, we investigated the hydrogenation of 2,4-dioxoester **1c** bearing a γ-ketoaryl group (Table 4). Formation of the corresponding intermediates **2c** and **3c** to yield γ-lactones **4c** was also observed with both ruthenium and rhodium catalysts. Chemoselective transformation of **1c** to intermediate **2c** is easily carried out under mild conditions (entries 4,5 and 9); ee′s of **2c** follow the same trend as the one observed for **2b**, i.e., a significant decrease (with respect to **2a**) with ruthenium catalysts (27−52% ee) and an almost steady value with Rh-AMPP catalysts (82% ee), which is consistent with the afore-mentioned hypotheses on coordination of **1** to the metal centres. Catalytic activities for the hydrogenation of **1c** to γ-lactones **4c** are intermediate between those observed for the hydrogenation of **1a** and **1b** under comparable reaction conditions. A striking difference is the poor chemoselectivity of ruthenium catalysts. Indeed, ca. 25−30% of **2c** is systematically converted into various by-products, of which ethyl 2-hydroxy-4-(2-thienyl)butyrate (**5c**), the γ-keto hydrogenolysis product of **2c**, accounts for more than 50%. HPLC monitoring showed that the minor enantiomer of **2c** is preferably consumed (see for instance entry 3). α-Hydroxy ester **5c** is typically recovered in 20−30% ee. In the presence of rhodium catalysts, less than 2% of by-products are formed. Conversion of **2c** into **3c** proceeds relatively fast in contrast to in situ lactonization of **3c** into **4c** (entries 6 and 7). Diastereoselectivities and enantioselectivities for **4c** are similar to those found with the same catalysts for the hydrogenation of **1a** and testify again to the inef-

ficiency of rhodium catalysts to promote the diastereoselective formation of γ-lactones **4**.

Conclusion

The chemoselective hydrogenation of 2,4-dioxo esters **1** into optically active 2-hydroxy-4-oxo esters **2** is best achieved with rhodium-AMPP catalysts, which afford good ee′s, independent of the nature of the R substituent at the γ-keto function. On the contrary, the R substituent affects strongly the catalyst performance for the direct preparation of chiral α-hydroxy-γ-butyrolactones **4**, which is a major limitation of this new synthetic procedure. Ruthenium-bisphosphane complexes are very efficient catalyst precursors for the preparation of the simple, methyl-substituted α-hydroxy-γ-butyrolactone *syn*-**4a** in high yields and ee′s; however, for 2,4-dioxo esters bearing a bulky alkyl substituent or an aryl substituent, these catalysts are either not chemoselective or sluggish or both. In this case, rhodium-AMPP catalysts offer an alternative leading to *anti*-α-hydroxy-γ-butyrolactones **4** in fair to good yields and ee′s, but with poor de′s. Diastereomers of **4** can naturally be separated by chromatography. However, it is also worth mentioning that catalyst precursor RhCl(Cy,Cy-oxoProNOP) leads, for the three substrates **1a−c**, to larger amounts of *syn*-**4** than the corresponding cyclopentyl-substituted Rh-AMPP systems, indicating that diastereoselectivity could be improved by tuning of the $-PR_2$ moieties of the chiral AMPP ligand. Work in this direction is underway in our laboratory.

Experimental Section

General: All the catalytic reactions were performed under anaerobic conditions with standard Schlenk techniques. Hydrogenation solvents were distilled from sodium benzophenone ketyl (toluene) or CaH_2 (CH_2Cl_2), and degassed before use. − NMR spectra were recorded on a AC-300 Bruker spectrometer at ambient temperature; chemical shifts are reported in ppm downfield from TMS and coupling constants are reported in Hz. − Mass spectra were performed with a Finnigan Mat at 70 eV. − GLC analyses were performed on a Chrompack apparatus equipped with a FID and a BPX5 (25 m × 0.32 mm, SGE) or a chiral Cydex-B (25 m × 0.32 mm, SGE) column. HPLC analyses were carried out on a Shimadzu apparatus equipped with a UV detector and a Chiralcel OD (5 × 250 mm, DAICEL) column. − Optical rotations were measured on a Perkin−Elmer polarimeter in a 1-dm cell. IR bands are expressed in wave number (cm^{-1}).

Materials: Ethyl 2,4-dioxovalerate (**1a**, Acros), ethyl 2,4-dioxo-5,5-dimethylhexanoate (**1b**, Maybridge), and ethyl 2,4-dioxo-4-(2-thienyl)butyrate (**1c**, Maybridge) were used as received. AMPP ligands were synthesized according to literature.[10] Me-DUPHOS, BPPM, BINAP, TolBINAP, $RuCl_2(PPh_3)_3$, $RhCl(PPh_3)_3$, and $[RuCl_2\{(S)\text{-BINAP}\}]_2 \cdot NEt_3$ were purchased from Strem and Fluka. MeO-BIPHEP and Cy_4-MeO-BIPHEP were graciously made available by Hoffman La Roche Co. $[Rh(COD)(MTPA)]_2$ complexes were prepared by the same procedure as for $[Rh(COD)(TFA)]_2$,[21] by reaction of $[Rh(COD)(OMe)]_2$ with (*S*)- or (*R*)-[MTPA]H. Rh-AMPP[10] and $RuBr_2$(diphosphane)[12f] catalyst precursors were prepared according to literature.

Asymmetric Hydrogenations: In a typical experiment (Table 2, entry 6), a solution of **1a** (820 mg, 5.2 mmol) in CH_2Cl_2 (8 mL) was degassed by two freeze-thaw cycles and then added under nitrogen to a solution of $[RuBr_2\{(S)\text{-MeO-BIPHEP}\}]$ (22 mg, 0.026 mmol) in CH_2Cl_2 (7 mL). The resulting solution was transferred to a 100-mL stainless steel autoclave equipped with a magnetic stirrer bar. Hydrogen (99%, Air Liquide) was introduced (100 bar), the reactor was heated to 80°C by circulating thermostated water in the double wall, and stirring was started. The reaction was monitored by quantitative GLC analysis (BPX5 column) of some aliquots. After the desired reaction time, the autoclave was cooled to room temperature, hydrogen was removed and the solution was concentrated under vacuum. The crude oily residue was chromatographed on silica (Merck, 60) with heptane/ethyl acetate (4:1) as eluant to give analytically pure (2*R*,4*S*)-*syn*-**4a** (0.42 g, 70% yield, 98% ee).

NMR Characterization of Hydrogenation Products: ^1H- and ^{13}C-NMR analyses were performed on isolated products separated by

Table 4. Asymmetric hydrogenation of ethyl 2,4-dioxo-4-(2-thienyl)butyrate (**1c**)[a]

Entry	Catalyst	Time[b] (h)	**2c** sel	ee[c]	**3c** sel	**4c** sel	*syn*/*anti*	ee[d]
1[e]	$RuCl_2(PPh_3)_3$	62	58	0	<1	10	63:37	0
2[e]	$RuBr_2$[(*S*)-TolBINAP]	62	46	75 (+)	<1	29	62:38	4 (+)
3[e]	$RuBr_2$[(*R*)-MeO-BIPHEP]	0.2[h]	>99	52 (−)	0	<1	−	−
		0.5[i]	97	56 (−)	0	<1	−	−
		22	89	65 (−)	0	3	nd	nd
		87	74	72 (−)	0	3	nd	nd
		136	40	92 (−)	0	13	64:36	20 (−)
4[f]	$RuBr_2$[(*S*)-MeO-BIPHEP]	4	99	40 (+)	0	<1	−	−
5[f]	$\{RuCl_2[(S)\text{-BINAP}]\}_2 \cdot NEt_3$	2	99	27 (+)	0	<1	−	−
6	$RhCl(PPh_3)_3$	99	90	0	<1	9	60:40	0
7	RhCl[(*R*)-Cy,Cy-oxoProNOP]	97	6	nd	41	53	66:34	nd
		163	1	60 (−)	25	74	61:39	77 (−)
8	RhCl[(*S*)-Cp,Cp-oxoProNOP]	8	52	76 (+)	27	21	35:65	nd
		36	4	73 (+)	30	66	37:63	83 (+)
		118	<1	nd	18	82	40:60	83 (+)
9[g]	RhCl[(*S*)-Cp,Cp-oxoProNOP]	3	97	82 (+)	<1	1	−	−

[a] See Table 3. − [b] Non-optimized time for 100% conversion of **1c**. − [c] The absolute configuration of (+)-**2c** is assumed to be (*R*); see Note [20]. − [d] Enantiomeric excess of *anti*-**4c**. − [e] By-products, including **5c**, accounts for the balance. − [f] $T = 60°C$. − [g] $T = 40°C$. − [h] Conversion of **1c**: 48%. − [i] Conversion of **1c**: 83%.

column chromatography. Assignment of resonances was confirmed when necessary by ^{13}C-detected ^{13}C-^{1}H HETCOR experiments (gem and alpha coupling) and/or ^{1}H-^{1}H COSY experiments. The assignment of relative stereochemistry of γ-butyrolactones *syn*-**4b**/*anti*-**4b** and *syn*-**4c**/*anti*-**4c** was made unambiguously on the basis of ^{1}H-NMR data, as reported for α-hydroxy-γ-butyrolactones **4a**[22] and 3-hydroxy-5-phenyltetrahydrofuran-2-one (**A**, R = Ph, Scheme 1),[7] considering (i) the deshielding effect of the OH group *cis* to the 5-C*H*(R) and (ii) the larger dispersion of the resonances of 4-C*HH* in the *syn* isomer.

***anti*-3-Hydroxy-5-methyltetrahydrofuran-2-one (*anti*-4a):**[5][22] $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 177.8 (*C*OO), 75.2 (*C*HMe), 67.5 (*C*HOH), 37.2 (CH_2), 21.2 (CH_3).

***syn*-3-Hydroxy-5-methyltetrahydrofuran-2-one (*syn*-4a):**[5][22] $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 177.9 (*C*OO), 73.7 (*C*HMe), 68.9 (*C*HOH), 38.7 (CH_2), 20.8 (CH_3).

Ethyl 2-Hydroxy-4-oxo-5,5-dimethylhexanoate (2b): Colourless oil. ^{1}H NMR: δ 4.49 (m, 1 H, C*H*OH), 4.26 (q, ^{3}J = 7.1, 2 H, CH_2CH_3), 3.3 (s br, 1 H, OH), 3.04 (d, ^{3}J = 4.6, 2 H, CH_2), 1.30 (t, ^{3}J = 7.1, 3 H, CH_2CH_3), 1.17 (s, 9 H, *t*Bu). − $^{13}C\{^{1}H\}$ NMR: δ 213.7 (C=O), 173.9 (COO), 67.1 (CHOH), 61.6 (CH_2CH_3), 44.0 (*C*Me$_3$), 40.3 (CH_2), 26.0 [C(*C*H$_3$)$_3$], 14.0 (CH_2CH_3). MS (EI) *m*/*z* (%): 202 [M$^+$] (8), 145 [M$^+$ − *t*Bu] (24), 129 [M$^+$ − CO_2Et] (11), 117 [M$^+$ − *t*BuCO] (42), 85 [*t*BuCO] (30), 57 [*t*Bu] (100). − HRMS, $C_{10}H_{18}O_4$: calcd. 202.1205; found 202.1183. $[\alpha]_D^{20}$ (*c* = 0.7, acetone) = +13.6 (83% ee, assumed in (*R*) enantiomer). − IR (neat): ṽ 1731 (vs), 1705 (vs).

***anti*-3-Hydroxy-5-tertiobutyltetrahydrofuran-2-one (*anti*-4b):** White crystals. ^{1}H NMR: δ 4.45 (dd, ^{3}J = 6.1 and 8.4, 1 H, C*H*OH), 4.38 (dd, ^{3}J = 5.4 and 8.1, 1 H, C*H*t*Bu*), 2.32 (ddd, ^{3}J = 5.4 and 8.4, ^{2}J = 13.9, 1 H, C*H*H *cis* to OH), 2.19 (ddd, ^{3}J = 6.1 and 8.1, ^{2}J = 13.9, 1 H, C*H*H *trans* to OH), 0.93 (s, 9 H, *t*Bu). − $^{13}C\{^{1}H\}$ NMR: δ 177.4 (COO), 86.5 (*C*H*t*Bu), 68.0 (CHOH), 34.1 (*C*Me$_3$), 31.1 (CH_2), 24.9 [C(*C*H$_3$)$_3$]. − MS (EI) *m*/*z* (%): 103 (11), 84 (5), 70 (52), 57 [*t*Bu] (100). − HRMS, $C_8H_{14}O_3$: calcd. 158.0943; found 158.0903. − $[\alpha]_D^{20}$ (*c* = 0.8, acetone) = +59.0 (97% ee).

***syn*-3-Hydroxy-5-tertiobutyltetrahydrofuran-2-one (*syn*-4b):** White crystals. ^{1}H NMR: δ 4.52 (dd, ^{3}J = 8.5 and 11.2, 1 H, C*H*OH), 4.09 (dd, ^{3}J = 5.1 and 11.2, 1 H, C*H*t*Bu*), 2.51 (ddd, ^{3}J = 5.1 and 8.5, ^{2}J = 12.4, 1 H, C*H*H trans to OH), 1.98 (ddd, ^{3}J = 11.2 and 11.2, ^{2}J = 12.4, 1 H, C*H*H cis to OH), 0.96 (s, 9 H, *t*Bu). − $^{13}C\{^{1}H\}$ NMR: δ 177.3 (COO), 84.1 (*C*H*t*Bu), 69.0 (CHOH), 33.4 (*C*Me$_3$), 32.2 (CH_2), 24.9 [C(*C*H$_3$)$_3$]. − MS (CI, NH_3): 159 [MH$^+$], 176 [M + NH_4^+]. − MS (EI, 70 eV) as for *anti*-**4b**. − $[\alpha]_D^{20}$ (*c* = 0.2, acetone) = +2.5 (ee n.d.).

Ethyl 2-Hydroxy-4-(2-thienyl)-4-oxobutyrate (2c): Colourless oil. ^{1}H NMR: δ 7.72 (dd, *J* = 1.0 and 3.8, 1 H, H thienyl), 7.63 (dd, *J* = 1.0 and 4.9, 1 H, H thienyl), 7.17 (m, 1 H, H thienyl), 4.65 (m, 1 H, C*H*OH), 4.20 (q, ^{3}J = 7.1, 2 H, CH_2CH_3), 3.36 (m, 2 H, CH_2), 1.27 (t, ^{3}J = 7.1, 3 H, CH_2CH_3). − $^{13}C\{^{1}H\}$ NMR: δ 190.1 (C=O), 173.5 (COO), 143.5 (C-2 thienyl), 134.4 (CH thienyl), 132.6 (CH thienyl), 128.2 (CH thienyl), 67.3 (CHOH), 61.9 (CH_2CH_3), 42.7 (CH_2), 14.0 (CH_2CH_3). − MS (CI, NH_3) *m*/*z* (%): 111 ($C_4H_3SCO^+$, 40), 229 [MH$^+$] (100), 246 [M + NH_4^+] (60). − HRMS, $C_{10}H_{12}O_4S$: calcd. 228.0456; found 228.0466. − IR (neat): ṽ 1730 (vs), 1645 (vs). − $[\alpha]_D^{20}$ (*c* = 0.5, acetone) = +13 (82% ee, assumed in (*R*) enantiomer).

Ethyl 2,4-Dihydroxy-4-(2-thienyl)butyrate (mixture of *syn*-3c and *anti*-3c). − Isomer 1: ^{1}H NMR, selected signals: δ 5.25 (dd, ^{3}J = 2.9 and 9.3, 1 H, C*H*Ar), 4.49 (dd, ^{3}J = 3.3 and 8.9, 1 H, C*H*OH), 4.25 (q, ^{3}J = 7.1, 2 H, CH_2CH_3), 2.40−2.30 (C*H*H), 2.20−2.10 (CH*H*), 1.30 (t, ^{3}J = 7.1, 3 H, CH_2CH_3). − $^{13}C\{^{1}H\}$ NMR: δ 174.6 (COO), 147.9 (C-2 thienyl), 124.1 (CH thienyl), 123.2 (CH thienyl), 67.8 (CHOH), 66.3 (CHOH), 61.5 (CH_2CH_3), 42.4 (CH_2), 13.8 (CH_2CH_3).

Isomer 2: ^{1}H NMR, selected signals: δ 5.32 (dd, ^{3}J = 4.1 and 9.0, 1 H, C*H*Ar), 4.35 (dd, ^{3}J = 3.7 and 8.3, 1 H, C*H*OH), 4.25 (q, ^{3}J = 7.1, 2 H, CH_2CH_3), 2.40−2.10 (CH_2), 1.30 (t, ^{3}J = 7.1, 3 H, CH_2CH_3). − $^{13}C\{^{1}H\}$ NMR: δ 174.3 (COO), 147.4 (C-2 thienyl), 124.3 (CH thienyl), 123.6 (CH thienyl), 69.0 (CHOH), 67.4 (CHOH), 61.5 (CH_2CH_3), 42.4 (CH_2), 13.8 (CH_2CH_3). − HRMS, $C_{10}H_{14}O_4S$: calcd. 230.0613; found 230.0610.

***anti*-3-Hydroxy-5-(2-thienyl)tetrahydrofuran-2-one (*anti*-4c):** ^{1}H NMR: δ 7.34 (dd, *J* = 1.2 and 5.1, 1 H, H-5 thienyl), 7.08 (dd, *J* = 0.9 and 1.7, 1 H, H thienyl), 6.97 (m, 1 H, H thienyl), 5.88 (dd, ^{3}J = 3.8 and 7.7, 1 H, C*H*Ar), 4.66 (dd, ^{3}J = 8.0 and 8.0, 1 H, C*H*OH), 2.70−2.58 (m, 2 H, CH_2). − $^{13}C\{^{1}H\}$ NMR: δ 177.0 (COO), 141.3 (C-2 thienyl), 127.0−126.0 (CH thienyl), 75.0 (*C*HAr), 67.2 (CHOH), 37.9 (CH_2). − MS (CI, NH_3) *m*/*z* (%): 111 [$C_4H_3SCO^+$] (100), 185 [MH$^+$] (100), 202 [M + NH_4^+] (60). − HRMS, $C_8H_8O_3S$: calcd. for 184.0194; found 184.0184.

***syn*-3-Hydroxy-5-(2-thienyl)tetrahydrofuran-2-one (*syn*-4c):** ^{1}H NMR: δ 7.39 (dd, *J* = 1.2 and 5.1, 1 H, H-5 thienyl), 7.15 (d, *J* = 2.0, 1 H, H-3 thienyl), 7.00 (m, 1 H, H-4 thienyl), 5.58 (dd, ^{3}J = 5.2 and 11.1, 1 H, C*H*Ar), 4.67 (dd, *J* = 8.0 and 11.5, 1 H, C*H*OH), 3.03 (m, 1 H, C*H*H), 2.45−2.30 (m, 1 H, CH*H*). − $^{13}C\{^{1}H\}$ NMR: δ 177.0 (COO), 140.0 (C-2 thienyl), 127.0−126.0 (CH thienyl), 73.4 (*C*HAr), 68.6 (CHOH), 39.1 (CH_2). − MS (CI, NH_3) and HRMS as for *anti*-**4c**.

Ethyl 2-Hydroxy-4-(2-thienyl)butyrate (5c): ^{1}H NMR: d 7.12 (m, 1 H, H thienyl), 6.91 (m, 1 H, H thienyl), 6.82 (m, 1 H, H thienyl), 4.25 (q, ^{3}J = 7.1, 2 H, CH_2CH_3), 4.20 (m, 1 H, C*H*OH), 3.00 (m, 2 H, ArCH_2), 2.25−1.90 (m, 2 H, CH_2CHOH), 1.27 (t, ^{3}J = 7.1, 3 H, CH_2CH_3). − $^{13}C\{^{1}H\}$ NMR: δ 174.6 (COO), 143.4 (C-2 thienyl), 126.6 (CH thienyl), 124.3 (CH thienyl), 122.9 (CH thienyl), 69.2 (CHOH), 61.3 (CH_2CH_3), 35.7 (CH_2), 24.8 (CH_2), 13.7 (CH_2CH_3). − MS (CI, NH_3) *m*/*z* (%): 111 [$C_4H_3SCH_2CH_2^+$] (80), 215 [MH$^+$] (80), 232 [M + NH_4^+] (100).

Determination of Enantio- and Diastereoselectivities: Ee′s and de′s of the hydrogenation products of **1a**−**c** were determined by GLC or HPLC analysis. For this purpose, racemic samples of **2a**−**c** and *syn*/*anti*-**4a** were prepared by hydrogenation of the corresponding 2,4-dioxoester with $RuCl_2(PPh_3)_3$. Racemic samples of *syn*/*anti*-**4b** and *syn*/*anti*-**4c** were prepared by reduction of the corresponding 2,4-dioxoester with $NaBH_4$ in EtOH. The retention times for the hydrogenation products of **1a** are (Cydex−B, 110°C, 0.55 bar H_2): (*R*)-**2a**, t_R = 12.8 min; (*S*)-**2a**, t_R = 13.4 min; *syn*-(2*S*,4*R*)-**4a**, t_R = 13.1 min; *syn*-(2*R*,4*S*)-**4a**, t_R = 14.1 min; *anti*-(2*S*,4*S*)-**4a**, t_R = 16.8 min; *anti*-(2*R*,4*R*)-**4a**, t_R = 17.8 min; (BPX5, 90°C, 0.2 bar N_2): **2a**, t_R = 7.2 min; **3a**, t_R = 7.6 and 8.2 min; *syn*-**4a**, t_R = 3.5 min; *anti*-**4a**, t_R = 3.9 min. Hydrogenation products of **1b** (Cydex−B, 120°C, 0.7 bar H_2): (−)-**2b**, t_R = 14.4 min; (+)-**2b**, t_R = 15.1 min; *syn*-**4b** (both enantiomers), t_R = 22.5 min; *anti*-(−)-**4b**, t_R = 27.0 min; *anti*-(+)-**4b**, t_R = 31.1 min. (BPX5, 115°C, 0.2 b N_2): **2b**, t_R = 7.2 min; *syn*-**4b**, t_R = 4.1 min; *anti*-**4b**, t_R = 4.8 min. Hydrogenation products of **1c** (BPX5, 140 to 160°C, 5°C/min, 0.2 bar N_2): **2c**, t_R = 11.5 min; **3c**, t_R = 10.3 and 10.6 min; *anti*-**4c**, t_R = 6.6 min; *syn*-**4c**, t_R = 6.9 min; **5c**, t_R = 5.0 min. (Chiralcel OD, hexane/2-propanol 80:20, 1 mL/min, UV detector 254 nm): (−)-**2c**, t_R = 11.1 min; (+)-**2c**, t_R = 12.3 min; *anti*-(−)-**4c**, t_R = 17.4 min; *anti*-(+)-**4c**, t_R = 20.9 min; **5c**, 5.4 and 6.0 min.

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[18] Experiments conducted with preformed or in situ generated cationic Rh catalysts in alcohol solvent led to either significant amounts of unidentified by-products ([Rh(COD){(*S,S*)-BPPM}][ClO_4] or [Rh(COD){(*R*)-Cy,Cy-oxoProNOP}][ClO_4], MeOH, 60°C, 50 bar H_2) or unsatisfactory enantio- and diastereoselectivities ([Rh(COD){(*S,R*-JOSIPHOS}][BF_4], EtOH, 60°C, 50 bar H_2).

[19] Asymmetric hydrogenation of **1a** to **2a** with Rh-AMPP catalysts proceeds with similar enantioselectivity to that of ethyl pyruvate into ethyl lactate (80–86% ee′s in the (*R*) enantiomer with a (*S*)-R,R-oxoProNOP ligand).[10] This fact suggests that **1a** is reduced rather as the keto form than the enol form.

[20] The absolute configuration of (+)-**2b** and (+)-**2c** is assumed to be (*R*), from the following arguments: (i) our studies on the hydrogenation of a variety of aliphatic α-ketoesters catalysed by neutral Rh-(*S*)-R,R-oxoProNOP (R = Cy or Cp) complexes have shown that these ligand systems induce systematically the (*R*) configuration for the α-hydroxyester;[10] this trend also applies to the hydrogenation of **1a** to **2a**. (ii) (*R*)-**2a** has also a positive specific rotation; see ref.[7]

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