One-Pot and Sequential Asymmetric Hydrogenation of β,δ-Diketoesters into Functionalized 1,3-Diols: From *anti*- to *syn*-Stereoselectivity

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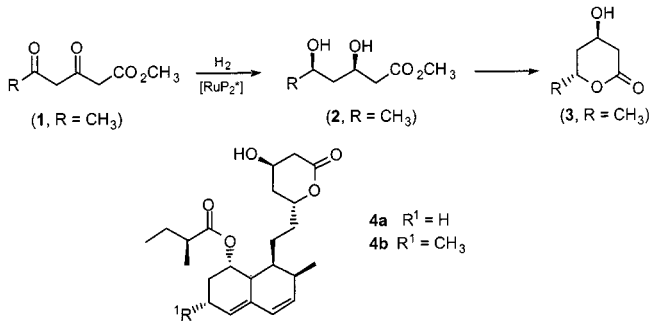
The asymmetric hydrogenation of methyl 3,5-dioxohexanoate (**1**) into mixtures of 3,5-dihydroxyesters (**2**) and 3-hydroxylactones (**3**) has been reinvestigated with a variety of ruthenium catalysts. Catalysts bearing diphosphanes which possess axial chirality such as (*S*)-MeO–Biphep give predominantly (3*R*,5*S*)-*anti*-**2** in up to 78% de and 95% ee, affording an efficient synthesis of (*S*)-6-methyl-5,6-dihydro-2-pyrone [(*S*)-**5**] in up to 95% enantiomeric excess. On the contrary, some Ru-{amidophosphane-phosphinite} complexes catalyze sluggishly the formation of *syn*-**2** in up to 92% de but with poor enantiomeric excesses. In all cases, methyl (*R*)-3-hydroxy-5-oxohexanoate [(*R*)-**11**] is the exclusive primary hydrogenation product, which can be isolated in high yields and enantiomeric excesses up to 78%. Further hydrogenation of enantiomerically enriched (*R*)-**11** in a separate experiment affords (3*R*,5*R*)-*syn*-**2** in high diastereomeric and enantiomeric excesses (up to 80% and 98%, respectively), provided a Ru-(*R*)-Binap-type catalyst is used.

Introduction

Saburi et al. suggested some years ago that if the hydrogenation of a β,δ-diketoester (such as **1**) could be successfully performed to yield an enantiomerically pure *syn*-3,5-dihydroxyester (**2**), it would provide a short and efficient access to hydroxylactones (**3**),[1][2] which are the key building blocks for the synthesis of inhibitors of HMG-coenzyme A reductase, such as compactin (**4a**)[3] and mevinolin (**4b**)[4] (Scheme 1). The requirements for the success of such a process are a high chemo-, enantio- and diastereoselectivity for the formation of *syn*-3,5-dihydroxyester **2**.



Scheme 1. Desired one-pot synthesis of chiral hydroxylactones and some target molecules

Chemoselectivity was not expected to be a crucial issue since β,δ-diketoesters involve, in the same molecule, partial structures of both β-diketone and β-ketoester, two kinds of functionalized carbonyl compounds which are efficiently hydrogenated by chiral ruthenium−diphosphane-type catalysts.[5][6] However, for the same reasons, the stereochemical outcome of the reaction was expected not to be simple. The conversion of a β,δ-diketoester such as **1** into the corresponding 3,5-dihydroxyester **2** obviously proceeds in two steps, and the stereochemistry of the hydrogenation of the remaining carbonyl group should be affected, not only by the chirality of the catalyst, but also by the chiral centre formed in the first hydrogenation. In particular, the hydrogenation of β-diketones is a typical example of such a double asymmetric induction, which leads selectively to almost enantiopure *anti*-1,3-diols.[5,6b] Indeed, Saburi et al. observed that the "one-pot" asymmetric hydrogenation of β,δ-diketoesters [Scheme 1; R = Me (**1**), Pr, $BnOCH_2$] using $\{RuCl_2[(S)$- or (R)-Binap$]\}_2 \cdot NEt_3$ as the catalyst precursor gave dominantly *anti*-3,5-dihydroxyesters. The monohydrogenation intermediate was neither isolated nor identified from the reaction mixture; however, the results of separate asymmetric hydrogenations conducted on enantiomerically pure *tert*-butyl 5-substituted 5-hydroxy-3-oxohexanoate (**8**),[7] one of the two possible intermediates, suggest that the hydrogenation of β,δ-diketoesters proceeds in fact via first selective hydrogenation of the C-3 (β) carbonyl group and subsequent hydrogenation of the C-5 (δ) carbonyl group, under *anti*-selective stereocontrol as for the hydrogenation of β-diketones.[5,6b]

We have reinvestigated this reaction with a variety of well-established and new ruthenium-based catalyst precursors using methyl 3,5-dioxohexanoate (**1**) as a model substrate. It is shown that some catalytic systems allow the so far unprecedented *syn*-diastereoselective formation of functionalized diol **2**, and that 3-hydroxy-5-oxohexanoate (**11**) is indeed always the exclusive primary hydrogenation product (Scheme 2). This intermediate can be isolated in high yields and fair enantiomeric excesses under smooth reaction conditions and when further hydrogenated in a separate experiment in the presence of a chiral catalyst with adequate configuration, *syn*-3,5-dihydroxyester **2** and *anti*-3-hydroxylac-

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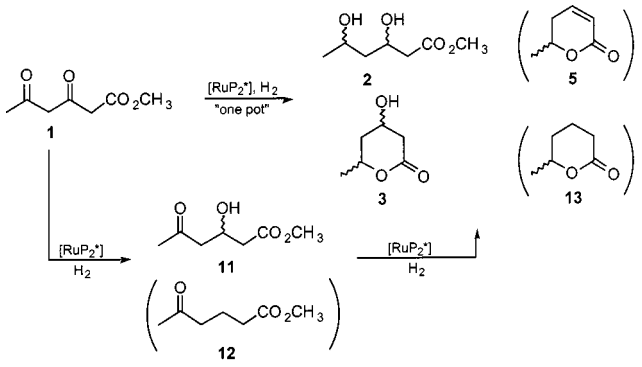
tone **3** can be prepared in interesting diastereomeric excesses and high enantiomeric excesses.



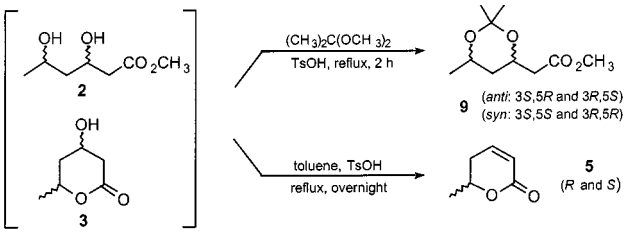
Scheme 2. Asymmetric hydrogenation of methyl 3,5-dioxohexanoate

Results and Discussion

Analytical Procedures

In order to investigate the reaction paths and the chemo- and stereoselectivity of the hydrogenation, different analytical procedures were used. As summarized in Scheme 2, the asymmetric hydrogenation of **1** leads to a relatively complex mixture of products. The analysis is hampered by the formation of side products (in parentheses), which are sometimes formed in significant amounts (vide infra). All of these products were unambiguously identified from their spectroscopic and analytical data after separation by column chromatography and, in some cases, from comparison with authentic samples (see Experimental Section). Quantitative GLC analysis of the crude reaction mixtures allowed the determination of the conversion of **1** and the respective selectivity for the primary hydrogenation products (**2**, **3**, **11**) and the side products (**5**, **12**, **13**).

For stereochemical features, Saburi's techniques were used with important additions. The relative stereochemistry of the hydrogenation products of **1** was determined after conversion of 3,5-dihydroxyesters **2** and 3-hydroxylactones **3** into the corresponding acetonides *anti*-**9** and *syn*-**9**, by treatment of small portions of the crude reaction mixtures with 2,2-dimethoxypropane (Scheme 3); the *syn:anti* diastereomer ratio of **9**, which corresponds to the diastereomer ratio of the parent 1,3-diols **2**, was determined by GLC analysis on an achiral column. GLC analysis of the same diastereomeric acetonides **9** on a *chiral* column allows the separation of the four enantiomers; this gives an additional confirmation of the *syn:anti* diastereomer ratio and, most importantly, the *individual* enantiomeric excesses for each of the diastereomers.[8] In previous work, only the *average* enantiomeric excess at the C-5 (δ) carbonyl group was attainable after conversion of mixtures of **2** and **3** into 6-methyl-5,6-dihydro-2-pyrone **5** by treatment with *para*-toluenesulfonic acid (TsOH) (Scheme 3), and either measurement of the optical purity of purified **5** or HPLC analysis after further derivatization. In this work, conversion of the whole reaction mixtures containing **2** and **3** into lactone **5**, and direct measurement of its enantiomeric excess by chiral GLC analysis, was used to confirm individual enantiomeric excesses of each diastereomer as described above; as expected, it was found in each case that, within experimental errors: ee(**5**) = [0.01 ×%(*syn*-**9**) ×%ee(*syn*-**9**)] + [0.01 ×%(*anti*-**9**) ×%ee(*anti*-**9**)]. Finally, the enantiomeric excess of the intermediary hydrogenation product (**11**) was assessed by chiral GLC analysis of the trifluoroacetate ester obtained by treatment of samples of the reaction mixtures with trifluoroacetic anhydride. With these analytical tools, the hydrogenation of β,δ-diketoester **1** was investigated.

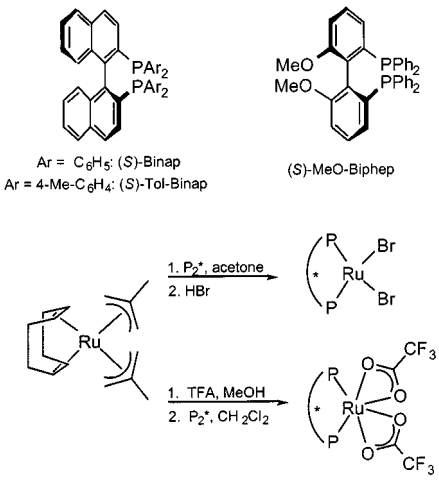


Scheme 3. Conversion of primary hydrogenation products to lactone and acetals

Asymmetric Hydrogenation of Methyl 3,5-dioxohexanoate (1) with Ruthenium Catalysts Bearing Chiral Atropisomeric Diphosphanes

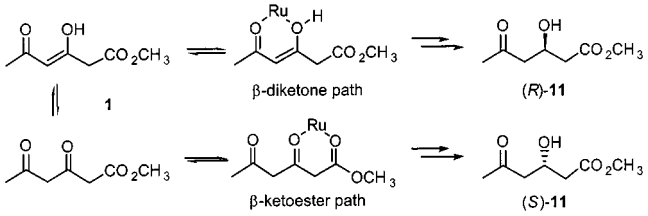
We first investigated the reaction in the presence of Ru-Binap type catalysts by extending the study from Saburi's precursor, i.e. $\{RuCl_2[(S)\text{-Binap}]\}_2{\cdot}NEt_3$, to other diphosphanes which possess axial chirality as well as other complexes (Scheme 4). The most significant results are reported in Table 1. The hydrogenation with $\{RuCl_2[(S)\text{-Binap}]\}_2{\cdot}NEt_3$ in methanol as the solvent was carried out as a reference (entry 2); the results found are consistent with those previously reported, although the enantiomeric excess for lactone **5** is slightly higher (88 vs. 78%). The individual enantiomeric excesses determined for each diastereomer, which turned out to be identical in this case, confirm the enantiomeric excess for **5**. Attempts were conducted to improve the performances of this catalyst system by varying the reaction conditions and, in particular, the nature of the solvent (entries 3, 4). The most interesting result in this way has been obtained with dichloromethane, in which the reaction proceeds at a similar rate, but with a better diastereo- and enantioselectivity for *anti*-dihydroxyester **2**. With the aim of increasing further the selectivities for this compound, we examined other related catalyst precursors such as trifluoroacetato−ruthenium and dibromo−ruthenium complexes, readily prepared according to Heiser's[9] and Genêt's[10] procedures, respectively (Scheme 4). It turned out that none of these systems is really more efficient than $\{RuCl_2[(S)\text{-Binap}]\}_2{\cdot}NEt_3$; only $RuBr_2[(S)\text{-MeO-Biphep}]$ exhibits a higher diastereo- and enantioselectivity, but at the expense of catalytic activity and chemoselectivity (entry 6). In fact, this catalyst precursor induces the formation of a noticeable amount of methyl 5-oxohexanoate (**12**). GLC monitoring and sequential hydrogenation experiments (vide infra) suggest that this side product arises from the hydro-

genolysis of the primary hydrogenation product, i.e., methyl 5-oxo-3-hydroxyhexanoate (**11**).



Scheme 4. Chiral atropisomeric diphosphanes and associated catalyst precursors used in this study

Indeed, analysis of aliquot samples established that, for all of the catalysts investigated in this study, the first step of the process consists in the hydrogenation of the C-3 (β) carbonyl group of **1** to yield **11**; the other possible monohydrogenation regioisomer, i.e., methyl 3-oxo-5-hydroxyhexanoate, was never detected. Under the standard reaction conditions, compound **11** enters in competition with **1** towards the catalyst as soon as it is formed, and it is therefore not possible to isolate it in combined good yield and selectivity. This goal was achieved by carrying out the reaction at room temperature in CH_2Cl_2 (which proved not to be possible in CH_3OH) and carefully monitoring the reaction by GLC. Representative examples are given in Table 1 (entries 7−11). The enantiomeric excesses of **11** obtained with (*S*)-catalysts are moderate and range typically from 60 to 80% in the (*R*)-enantiomer. These values highlight interesting issues about the mechanistic pathway. Actually, it is known that the



Scheme 5. Possible competitive chelation modes of **1** onto a Ru-(*S*)-Binap type catalyst

hydrogenation of simple β-ketoesters and β-diketones with Ru-Binap-type catalysts yield the corresponding secondary alcohols in high enantioselectivity (95−99% ee).[5][6] The moderate enantiomeric excesses obtained for **11** show that, for **1**, like for other multifunctionalized ketones,[6b] there is a competitive ligation of functionalities to the Ru atom (Scheme 5). Because of the enolic structure of **1**[11] and the high final *anti* diastereoselectivity, it is reasonable to assume that the hydrogenation of the C-3 (β) carbonyl group of **1** arises mainly from a β-diketone chelated intermediate, which gives preferentially the (*R*)-enantiomer of **11** in the case of a Ru-(*S*)-Binap type catalyst. On the contrary, the hydrogenation of simple β-ketoesters with Ru-(*S*)-Binap catalysts is known to lead to the corresponding (*S*)-β-hydroxyesters.[6] These two chelation modes have, in fact, opposite directions for the final stereoselectivity at C-3, and the β-diketone/β-ketoester control ratio in the case of **1** can be roughly estimated to 80/20. It is noteworthy that this ratio does not necessarily account for the competitive chelation modes of **1** onto the Ru species, as kinetic issues of subsequent elementary steps of the catalytic cycle (e.g. H_2 oxidative addition, H transfer) should also be taken into account.[12]

Asymmetric Hydrogenation of Methyl 3,5-dioxohexanoate (1) with Ru-AMPP Catalysts

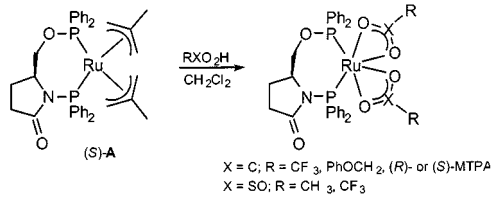
We also investigated the catalytic precursor properties of some ruthenium complexes of an amidophosphane-phos-

Table 1. Asymmetric hydrogenation of methyl 3,5-dioxohexanoate (**1**) with Ru-Binap-type catalyst precursors[a]

Entry	Catalyst Precursor	solvent	temp. (°C)	time[b] (h)	**11** sel	ee	**2** + **3** sel	*syn*:*anti*[c]	ee *syn*[c]	ee *anti*[c]	**5** ee[d]	Side Products sel
1	$RuCl_2(PPh_3)_3$	CH_2Cl_2	60	88	10	0	87	21/79	0	0	0	**5** (2), **12** (1)
2	$[RuCl_2((S)\text{-Binap})]_2.NEt_3$	MeOH	50	23	4	nd	96	24/76	87 (*S*,*S*)	87 (*R*,*S*)	88 (*S*)	-
3	$[RuCl_2((S)\text{-Binap})]_2.NEt_3$	CH_2Cl_2	60	91[e]	3	nd	96	14/86	22 (*S*,*S*)	92 (*R*,*S*)	84 (*S*)	**5** (1)
4	$[RuCl_2((S)\text{-Binap})]_2.NEt_3$	MeOH/ ^{i}PrOH	60	62	17	69 (*R*)	80	20/80	30 (*S*,*S*)	87 (*R*,*S*)	78 (*S*)	**5** (2), **12** (1)
5	$RuBr_2((S)\text{-Tol-Binap})$	CH_2Cl_2	60	136	27	nd	73	13/87	2 (*S*,*S*)	93 (*R*,*S*)	84 (*S*)	-
6	$RuBr_2((S)\text{-MeO-Biphep})$	CH_2Cl_2	60	97	7	nd	86	11/89	78 (*S*,*S*)	95 (*R*,*S*)	95 (*S*)	**5** (1), **12** (6)
7	$RuCl_2(PPh_3)_3$	CH_2Cl_2	50	2[f]	85	0	14	nd	0	0	0	**5** (1)
8	$[RuCl_2((S)\text{-Binap})]_2.NEt_3$	CH_2Cl_2	20	29[g]	97	78 (*R*)	3	nd	-	-	-	-
9	$[RuCl_2((S)\text{-Binap})]_2.NEt_3$	^{i}PrOH	60	89	92	69 (*R*)	8	nd	-	-	-	-
10	$RuBr_2((S)\text{-Tol-Binap})$	CH_2Cl_2	40	40[f]	96	78 (*R*)	4	nd	-	-	-	-
11	$RuBr_2((S)\text{-MeO-Biphep})$	CH_2Cl_2	40	47	96	74 (*R*)	4	nd	-	-	-	-

[a] Reactions were conducted under 100 atm H_2; [**1**]/[Ru] = 200:1, [Ru] = ca. 1 mmol·l^{-1}. Conversion (mol-%) of **1** and selectivities (sel, ee, de;%) for the products were determined by quantitative GLC analysis (see Experimental). − [b] Non optimized time for total conversion of **1**. − [c] *syn*:*anti* ratio and enantiomeric excesses of 3,5-dihydroxyesters **2** as determined by GLC analysis of acetonides **9**. The letters into brackets refer to the absolute configuration of the prevailing enantiomer at C-3 and C-5, respectively. − [d] Enantiomeric excess of **5** determined by GLC analysis after dehydration of crude reaction mixtures. − [e] [**1**]/[Ru] = 500:1. − [f] Conversion of **1** = 97%. − [g] Conversion of **1** = 94%.

phinite (AMPP) ligand; i.e., (*S*)-Ph,Ph-oxoProNOP. Previous studies in our group have shown that {Ru[(*S*)-Ph,Ph-oxoProNOP](methylallyl)$_2$} [(*S*)-**A**, Scheme 6] and its bis(trifluoroacetato) analogue, {Ru[(*S*)-Ph,Ph-oxoProNOP)(TFA)$_2$}, catalyze (sluggishly) the hydrogenation of β-ketoesters with moderate to good enantioselectivities (75−85% ee).[13] In the present study, we sought to observe peculiarities due to the unusual P(O)/P(N) feature present in AMPP ligands and for that, we examined a variety of catalysts prepared ex situ by protonolysis of (*S*)-**A** with some carboxylic and sulfonic[14] acids (Scheme 6) (see Experimental Section).



Scheme 6. Chiral Ru-{Amidophosphane-phosphinite} catalyst precursors used in this study

The most striking feature among the results reported in Table 2 is the propensity of Ru-[(*S*)-Ph,Ph-oxoProNOP] catalysts to promote the formation of *syn*-rich mixtures of 3,5-dihydroxyesters **2**. This tendency is observed with the bis(methylallyl) complex (*S*)-**A** and all of its dicarboxylato derivatives, provided the reaction is carried out in dichloromethane or in 1,2-dichloroethane. In a 1:1 (v/v) methanol/dichloromethane mixture, the above catalyst precursors induce the selective formation of *anti*-**2**, accompanied by noticeable amounts of side products (see for representative examples, entries 2 and 6).[15][16][17] The best results in terms of diastereoselectivity for the *syn*-3,5-dihydroxyesters are obtained with (*S*)-**A** itself (entry 1), and above all with the ruthenium complexes prepared from (*S*)-**A** and (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)- and (*S*)-MTPA; entries 8 and 9, respectively]. The combination of Ru(η^3-C_4H_7)$_2$[(*S*)-Ph,Ph-oxoProNOP] with (*R*)-MTPA (1:4) proved to be remarkably active and diastereoselective but the enantiomeric excess was extremely poor. This turned out to be a general trend for all the Ru-AMPP catalytic systems investigated, the highest enantiomeric excess for *syn*-**3** reaching only a modest 40% (entry 4). This poor final enantioselectivity for the 3,5-dihydroxyesters stems from the incapability of the Ru-[(*S*)-Ph,Ph-oxoProNOP] catalysts to promote enantioselectively the first hydrogenation at the C-3 (β) carbonyl group; indeed, GLC analysis of some aliquot samples revealed that the enantiomeric excesses of **11** typically range between 5 and 15% (*R*). This significant decrease in the enantioface discrimination of the chiral Ru-AMPP species going from simple β-ketoesters (75−85% ee) to β,δ-diketoester **1** is assumed to arise from the aforementioned competitive ligation of functionalities (Scheme 5). As described below, when an enantiomerically enriched sample of **11** is hydrogenated with a Ru-AMPP catalyst such as (*S*)-**A**, much better enantiomeric excesses with comparable, good diastereoselectivity for *syn*-**3** are obtained.

Asymmetric Hydrogenation of Enantiomerically Enriched Methyl (*R*)-3-hydroxy-5-oxohexanoate [(*R*)-11]

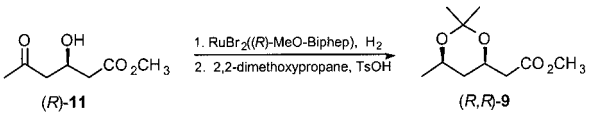
As described previously, we were able to isolate the primary intermediate of the hydrogenation process (**11**) in good yields and fair enantiomeric excesses. Because the stereochemical outcome of the hydrogenation reaction depends, not only, on the chiral catalyst but also on the chiral centre formed in the primary stage, it was worth evaluating some combinations which are not favoured in one-pot experiments. Thus, we next investigated the hydrogenation of enantiomerically enriched (*R*)-**11** under the same conditions as those employed for the hydrogenation of **1** with various catalysts. In particular, for chiral catalysts, it is of obvious interest to focus on catalysts modified by ligands having an opposite configuration to the one which leads to the prevailing enantiomer of **11** used in the experiment. The usual analytical procedures were used to determine the conversion and the different selectivities (Scheme 7). The most significant results are summarized in Table 3.

As expected, achiral catalysts do not direct the reaction towards the *syn* diastereomer (entries 1−3), but rather to *anti*-**2** or ca. 50/50 mixtures. It is noteworthy that the afore-

Table 2. Asymmetric hydrogenation of methyl 3,5-dioxohexanoate (**1**) with Ru-AMPP catalyst precursors[a]

Entry	Catalyst Precursor[e]	time[b] (h)	**11** sel	**2** + **3** sel	*syn*:*anti*[c]	ee *syn*[c]	ee *anti*[c]	**5** ee[d]	Side Products sel
1[f]	(*S*)-**A**	235	<1	>99	87/13	14 (*R*,*R*)	29 (*S*,*R*)	22 (*R*)	-
2[g]	(*S*)-**A**	113	0	78	10/90	nd	nd	5 (*S*)	**5** (15), **13** (7)
3	(*S*)-**A** + CF_3CO_2H	23	0	>99	65/35	33 (*R*,*R*)	59 (*S*,*R*)	43 (*R*)	-
4[h]	(*S*)-**A** + CF_3CO_2H	138	0	97	72/28	40 (*R*,*R*)	70 (*S*,*R*)	51 (*R*)	**5** (3)
5[i]	(*S*)-**A** + CF_3CO_2H	17	6	94	64/36	34 (*R*,*R*)	63 (*S*,*R*)	48 (*R*)	-
6[g]	(*S*)-**A** + CF_3CO_2H	93	0	88	14/86	11 (*R*,*R*)	12 (*S*,*R*)	10 (*R*)	**12** (12)
7	(*S*)-**A** + $PhOCH_2CO_2H$	137	43	56	68/32	13 (*R*,*R*)	55 (*S*,*R*)	21 (*R*)	**5** (1)
8	(*S*)-**A** + (*R*)-MTPA	18	0	>98	96/4	< 5 (*R*,*R*)	nd	<2 (*R*)	-
9	(*S*)-**A** + (*S*)-MTPA	63	2	92	92/8	5 (*R*,*R*)	42 (*S*,*R*)	7 (*R*)	**5** (6)
10	(*S*)-**A** + CH_3SO_3H	17	0	72	23/77	28 (*S*,*S*)	10 (*S*,*R*)	8 (*R*)	**5** (9), **12** (10), **13** (9)
11	(*S*)-**A** + CF_3SO_3H	118[j]	5	9	nd	nd	nd	nd	**12** (86)

[a] Unless otherwise stated, reactions were conducted in CH_2Cl_2 at 60°C under 100−130 atm H_2; [**1**]/[Ru] = 200:1, [Ru] = ca. 1 mmol.l^{-1}. Conversion and selectivities: see Table 1. − [b],[c],[d] See Table 1. − [e] Catalyst pre-prepared by addition of 4 mol equiv. of acid to catalyst precursor (*S*)-**A**. − [f] P = 155 atm. − [g] Solvent: CH_2Cl_2/MeOH (1:1). − [h] T = 20°C. [i] Solvent: $(CH_2Cl)_2$. − [j] Conversion of **1** = 88%.



Scheme 7. Stereoselective hydrogenation of methyl (*R*)-3-hydroxy-5-oxohexanoate

mentioned hydrogenolysis by-product **12** is formed in higher amounts than during the corresponding one-pot experiment (compare Table 1, entry 1 and Table 3, entry 1); this observation confirms that the formation of **12** is subsequent to that of **11**, which could be prevented by lowering the concentration of **11** in the reaction medium. The hydrogenations of a 66% ee sample of (*R*)-**11** using trifluoroacetato-Ru complexes bearing (*R*)-atropisomeric ligands led to the formation of (3*R*,5*R*)-*syn*-**2** in high diastereomeric excesses (up to 80%) and fair enatiomeric excesses (entries 4−6). Similar stereoselectivities were obtained with the trifluoroacetato derivative of the Ru-AMPP complex (*S*)-**A**, although this proved to be significantly better in terms of activity than the previous catalyst precursors (entry 10). On the other side, dibromo-Ru complexes bearing (*R*)-atropisomeric ligands, although somewhat less chemoselective than their trifluoroacetato analogues, led to (3*R*,5*R*)-*syn*-**2** in lower diastereomeric excesses but very high enantiomeric excesses (96−98%) (entries 7−9). As it proved to be also for the one-pot experiments, $RuBr_2$[(*R*)-MeO-Biphep] is the most efficient catalyst precursor for this sequential hydrogenation, leading to (3*R*,5*R*)-*syn*-**2** in ca. 70% yield and 97% ee from a 59% ee sample of (*R*)-**11**.[18]

As previously mentioned, comparable asymmetric hydrogenations have been carried out by Saburi et al. on the other regioisomer; i.e., *tert*-butyl 5-hydroxy-3-oxohexanoate (**8**).[1][7] The reaction of enantiopure (*R*)-**8** with a Ru-(*R*)-Binap catalyst gave dominantly the corresponding (3*R*,5*R*)-*syn*-dihydroxyester, but in only 20% diastereomeric excess. Noyori also reported that the hydrogenation of enantiopure (*R*)-2-hydroxy-4-pentanone (the intermediate in the hydrogenation of β-diketones) with a Ru-(*S*)-Binap catalyst led to isomeric *anti* and *syn* diols in 15:85 ratio.[6b] In our experiments, the fair enantiomeric excesses obtained in the hydrogenation of **11** with $Ru(TFA)_2L_2$ precursors and the moderate diastereomeric excesses obtained with $RuBr_2L_2$ complexes are most likely due, at least in part, to the limited enantiomeric purity of **11**.

Conclusion

The most striking result of this systematic study is that some ruthenium[19] complexes associated with an amido-phosphane-phosphinite ligand induce the highly diastereoselective formation of *syn*-dihydroxyester **2**. Although the catalytic activity and above all the enantioselectivity are poor, this is the first example of a one-pot catalytic synthesis of a functionalized *syn*-1,3-diol; recent results in our group show that this system is also effective for the diastereoselective conversion of β-diketones into simple *syn*-1,3-diols. Also, the asymmetric hydrogenation of an enantiomerically enriched β-hydroxy-δ-ketoester offers an attractive entry to the *syn*-dihydroxyesters; this alternative procedure leads to either high enantiomeric excesses or diastereomeric excesses, the combination of both being in part hampered by the enantiomeric purity of the starting material which is initially produced via selective hydrogenation of the β,δ-diketoester. Further investigations in this direction are currently under way

Experimental Section

General: All the catalytic reactions were performed under anaerobic conditions using standard Schlenk techniques. Hydrogenation solvents were distilled from magnesium alkoxide (methanol, 2-propanol), CaH_2 (CH_2Cl_2, $ClCH_2CH_2Cl$) or sodium benzophenone ketyl (toluene), 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 flame ionization detector and a BPX5 (25 m × 0.32 mm, SGE) or a chiral Cydex-B (25 m ×

Table 3. Asymmetric hydrogenation of optically active methyl 3-hydroxy-5-oxohexanoate (**11**) with Ru-Binap type catalyst precursors[a]

Entry	Catalyst Precursor	**11** ee[e]	time[b] (h)	**11** conv	**2** + **3** sel	*syn*:*anti*[c]	ee *syn*[c]	ee *anti*[c]	**5** ee[d]	Side Products sel
1	$RuCl_2(PPh_3)_3$	66 (*R*)	138	>99	80	20/80	42 (*R*,*R*)	61 (*R*,*S*)	37 (*S*)	**5** (2), **12** (15), **13** (3)
2[f]	Rh/C	66 (*R*)	40	54	99	50/50	55 (*R*,*R*)	67 (*R*,*S*)	<5	−
3[f]	Ru/C	66 (*R*)	23	96	99	52/48	60 (*R*,*R*)	67 (*R*,*S*)	<5	**5** (1)
4	$Ru(TFA)_2$((*R*)-Binap)	66 (*R*)	21	>99	98	90/10	75 (*R*,*R*)	70 (*R*,*S*)	70 (*R*)	**12** (2)
5	$Ru(TFA)_2$((*R*)-Tol-Binap)	67 (*R*)	21	100	98	81/19	67 (*R*,*R*)	63 (*R*,*S*)	45 (*R*)	**12** (2)
6	$Ru(TFA)_2$((*R*)-MeO-Biphep)	67 (*R*)	22	96	99	86/14	72 (*R*,*R*)	36 (*R*,*S*)	61 (*R*)	**5** (1)
7	$RuBr_2$((*R*)-Binap)	59 (*R*)	25	89	90	55/45	96 (*R*,*R*)	19 (*R*,*S*)	45 (*R*)	**5** (1), **12** (7), **13** (2)
8	$RuBr_2$((*R*)-Tol-Binap)	67 (*R*)	23	>99	93	58/42	98 (*R*,*R*)	23 (*R*,*S*)	53 (*R*)	**5** (1), **12** (5), **13** (1)
9	$RuBr_2$((*R*)-MeO-Biphep)	59 (*R*)	25	100	95	72/28	97 (*R*,*R*)	32 (*S*,*R*)	79 (*R*)	**5** (1), **12** (2), **13** (2)
10	(*S*)-**A** + CF_3CO_2H	59 (*R*)	3	100	96	80/20	74 (*R*,*R*)	4 (*S*,*R*)	64 (*R*)	**5** (4)

[a] Unless otherwise stated, reactions were conducted in CH_2Cl_2 at 60°C under 100 atm H_2; [**11**]/[Ru] = 50:1, [Ru] = ca. 0.8 mmol.l^{-1}. − [b] Non optimized time. − [c],[d] See Table 1. − [e] Enantiomeric purity of purified starting material. − [f] Solvent: MeOH; T = 80°C.

0.32 mm, SGE) column. Optical rotations were measured on a Perkin−Elmer polarimeter in a 1-dm cell. IR spectra are expressed by wavenumber (cm^{-1}).

Materials: Methyl 3,5-dioxohexanoate (**1**) was prepared by the reported method.[20] (*R*)- and (*S*)-Binap, (*R*)- and (*S*)-Tol-Binap, Ru(COD)(methylallyl)$_2$, {RuCl$_2$[(*S*)-Binap]}$_2$·NEt$_3$ and RuCl$_2$(PPh$_3$)$_3$ were purchased from Acros and Strem. The catalyst precursors Ru(TFA)$_2$(L$_2$)[9] and RuBr$_2$(L$_2$)[10] bearing chiral atropisomeric diphosphanes were prepared according to literature methods. AMPP ligands (*S*)- and (*R*)-Ph,Ph-oxoProNOP[21] and the corresponding complexes Ru[(*S*)- or (*R*)-Ph,Ph-oxoProNOP](methylallyl)$_2$[22] [(*S*)-**A** and (*R*)-**A**] were synthesized according to reported procedures.

Catalyst precursors of the type Ru[(*S*)-Ph,Ph-oxoProNOP](X)$_2$ (X = OCOR or OSO$_2$R) were generated ex situ using the same procedure as described by Heiser.[9] A solution of (*S*)-**A** in the reaction solvent (CH$_2$Cl$_2$ or CH$_2$Cl$_2$/CH$_3$OH) was cooled to −78°C and the appropriate acid (4.5 mol equiv.) was gently added via syringe. The reaction mixture was stirred for 10 minutes at low temperature, and then allowed to warm to room temperature. After additional stirring for 0.5−1 h, the solution was directly used for a catalytic experiment.

Asymmetric Hydrogenations of Dioxoester 1 for Screening Purposes: In a typical experiment (Table 1, entry 6), a solution of **1** (0.37 g, 2.4 mmol) in CH$_2$Cl$_2$ (10 mL) was degassed by two freeze−thaw cycles and then added under nitrogen to a solution of RuBr$_2$[(*S*)-MeO-Biphep] (10 mg, 0.012 mmol) in CH$_2$Cl$_2$ (10 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 60°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 completion, the autoclave was cooled to room temperature, hydrogen was vented and the solution was concentrated under vacuum to give an oily residue.

Determination of Chemoselectivities: Chemoselectivities were determined by direct GLC analysis of the crude reaction mixture using a BPX5 column (25 m × 0.32 mm; 90°C iso, 0.2 bar N$_2$). The retention times are as follows: **1** (diketoester and enol form), t_R = 5.0 and 7.1 min; {*syn*-**2** + *anti*-**2**}, t_R = 11.1 min (immediate dehydration occurred in the chromatograph injector to form CH$_3$CH(OH)CH$_2$CH=CHCO$_2$CH$_3$, as revealed by GC/MS); *syn*-**3**, t_R = 19.2 min; *anti*-**3**, t_R = 20.5 min; **5**, t_R = 4.1 min; **11**, t_R = 8.1 min; **12**, t_R = 4.4 min; **13**, t_R = 4.7 min.

The identity of all of the compounds issued from the hydrogenation of **1** was formally established by isolation of the latter by column chromatography and comparison of their ^{1}H- and ^{13}C-NMR and GC/MS data with those reported in the literature.[1]

Methyl 5-Oxohexanoate (12):[23] ^{1}H NMR (CDCl$_3$): δ = 3.66 (s, 3 H, C*H*$_3$OCO), 2.50 (t, ^3J = 7.1, 2 H, C*H*$_2$CO), 2.34 (t, ^3J = 7.1, 2 H, C*H*$_2$COO), 2.13 (s, 3 H, C*H*$_3$CO), 1.88 (tt, ^3J = 7.1 and 7.1, 2 H, C*H*$_2$). − ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 207.9 (*C*O), 173.2(*C*OO), 51.1 (COO*C*H$_3$), 42.0 (*C*H$_2$CO), 32.6 (*C*H$_2$COO), 29.5 (*C*H$_3$CO), 18.4 (*C*H$_2$). − MS (CI, NH$_3$): 145 [MH$^+$], 162 [M + NH$_4^+$]. − MS (EI) (*m*/*z*,%): 144 [M$^+$] (2), 112 (20), 85 (22), 74 (34), 43 (CH$_3$CO, 100).

6-Methyl-tetrahydropyran-2-one (13):[24] ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 172.0 (*C*OO), 77.0 (*C*H(O)), 29.5 (*C*H$_2$), 29.2 (*C*H$_2$), 21.6 (*C*H$_2$), 18.5 (*C*H$_3$). − MS (CI, NH$_3$): 115 [MH$^+$], 132 [M + NH$_4^+$].

Determination of Diastereo- and Enantioselectivities: For this purpose, the final mixture containing dihydroxyesters **2** and lactones **3** was converted into the corresponding acetonides *syn*-**9** and *anti*-**9**, by refluxing a small portion of the oily mixture (ca. 20 mg) for 2 h in 2,2-dimethoxypropane (5 mL) in the presence of *para*-toluenesulfonic acid (2 mg). The authenticity of acetals **9** was confirmed from their ^{1}H- and ^{13}C-NMR data.[1]

The resulting solution was first analysed by GLC on a BPX5 column (25 m × 0.32 mm; 90°C iso, 0.2 bar N$_2$); the retention times for *syn*-**9** and *anti*-**9** are t_R = 11.0 min and t_R = 9.8 min, respectively.

The same mixture of *syn*-**9** and *anti*-**9** was then subjected to a GLC analysis using a chiral column Cydex-B (25 m × 0.32 mm; 90°C iso, 0.75 bar H$_2$); the retention times were as follows: (3*R*,5*S*), t_R = 15.2 min; (3*S*,5*R*), t_R = 16.5 min; (3*R*,5*R*), t_R = 17.0 min; (3*S*,5*S*), t_R = 17.5 min.[8] TsOH was converted in 2,2-dimethoxypropane to a product eluted at t_R = 16.1 min.

In parallel, the final mixture containing dihydroxyesters **2** and lactone **3** was converted into lactone **5** by refluxing a small portion of the oily mixture (ca. 20 mg) for 2 h in toluene (5 mL) in the presence of *para*-toluenesulfonic acid (2 mg). The resulting solution was directly analyzed by GLC on a chiral column Cydex-B (25 m × 0.32 mm; 90°C iso, 0.75 bar H$_2$); the retention times for (*S*)-**5** and (*R*)-**5** were t_R = 10.3 min and t_R = 10.8 min, respectively. The validity of this analysis was assessed with racemic samples, and scalemic samples of **5** prepared with catalysts of opposite configuration. The enantiomeric excesses determined by polarimetry on purified **5** are consistent with the chiral GLC analysis, but the latter proved to be much easier to perform and more reliable.

The enantiomeric excess of the primary hydrogenation product (**11**) was determined on the trifluoroacetate derivative: trifluoroacetic anhydride (3 drops) was added to an aliquot sample of the crude reaction mixture, the solution was stirred at room temperature for ca. 10 min, and then subjected to a GLC analysis using a chiral column Cydex-B (25 m × 0.32 mm; 95°C iso, 0.75 bar H$_2$); the retention times were as follows: (*S*)-TFA-**11**, t_R = 10.5 min; (*R*)-TFA-**11**, t_R = 10.7 min.

Synthesis of Methyl (*S*)-3-Hydroxy-5-oxohexanoate (11) via Selective Hydrogenation of 1: In a typical experiment, [Ru(COD)(methylallyl)$_2$] (41 mg, 0.13 mmol) and (*R*)-Tol-Binap (87 mg, 0.13 mmol) were dissolved in acetone (15 mL). To this solution was added a methanol solution of HBr (0.3 M, 1.0 mL, 2.2 equiv). The resulting solution was stirred at room temperature for 30 min and volatiles were removed under vacuum to give a brown residue. A solution of **1** (4.05 g, 25.6 mmol) in CH$_2$Cl$_2$ (50 mL) was degassed by two freeze-thaw cycles and added under nitrogen to the brown residue {RuBr$_2$[(*R*)-Tol-Binap]}. The resulting solution was then transferred to a 100 mL-stainless steel autoclave equipped with a magnetic stirrer bar. Hydrogen was introduced (100 bar), the reactor was heated to 40°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 5.5 h, the autoclave was cooled to room temperature and hydrogen was vented. GLC analysis of the crude solution showed that 96% of **1** was converted and that the selectivity of **11** was 84% [75% ee (*S*)]. The crude solution was concentrated under vacuum to give an oily residue which was separated by chromatography on silica using ethyl acetate/heptane (2:3) as eluent. The purest fractions were collected and concentrated under vacuum to give analytically pure **11** [1.8 g, 45% yield, 75% ee (*S*)]. Anal. C$_7$H$_{12}$O$_4$: calcd. for C, 52.49; H, 7.55; found C, 52.9; H, 7.2. − ^{1}H NMR (CDCl$_3$): δ = 4.43 (m, 1 H, C*H*OH), 3.66 (s, 3 H, C*H*$_3$OCO), 3.45 (d, ^3J = 3.8, 1 H, O*H*),

2.64 (d, ^3J = 7.3, 1 H, C*H*HCO), 2.63 (d, ^3J = 5.1, 1 H, CH*H*CO), 2.48 (d, ^3J = 6.8, 1 H, C*H*HCOO), 2.47 (d, ^3J = 6.1, 1 H, CH*H*COO), 2.15 (s, 3 H, CH_3CO). – $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 208.1 (*C*O), 172.0 (*C*OO), 64.1 (*C*HOH), 51.6 (COO*C*H_3), 49.0 (*C*H_2CO), 40.4 (*C*H_2COO), 30.5 (*C*H_3CO). – MS (CI, NH_3) *m/z* (%): 160 [M^+] (100), 161 [MH^+] (70), 178 [M + NH_4^+] (65). – $[\alpha]_D^{20}$ (*c* 1.1, $CHCl_3$) = −10.0° [75% ee (*S*)].

Asymmetric Hydrogenation of β-Hydroxy-δ-oxoester 11: The hydrogenation of **11** was carried out under similar conditions to those used for the hydrogenation of **1**, using samples prepared as described above. The selectivities were determined by the procedures described above.

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[19] Attempts to perform the hydrogenation of **1** with rhodium-based catalysts led to poor results. For instance, the in situ combination $[Rh(COD)Cl]_2$/(*S*)-Cy_4-MeO-Biphep (1:2.2; [**1**]/Rh = 200) in toluene at 60°C under 50 atm H_2 gave after 47 h a 55/45 mixture of *syn*-**2**/*anti*-**2** (100% conversion, 99% combined selectivity into **2** and **3**), with 4% ee (3*R*,5*R*) and 54% ee (3*S*,5*R*), respectively; lactone **5** was then recovered in 25% ee (*R*).
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