Tuning diastereoselectivity with the solvent: the asymmetric hydrogenation of simple and functionalized 1,3-diketones with ruthenium(amidophosphine–phosphinite) catalysts

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Spectacular solvent effects in the asymmetric hydrogenation of methyl 3,5-dioxohexanoate (**3**) and 2,4-pentanedione (**5**) have been observed using Ru[(*S*)-Ph,Ph-oxoProNOP]X_2 complexes (X = η^3-C_4H_7, **IIa**; CF_3CO_2, **IIb**; (*R*)-MTPA, **IIc**) as catalyst precursors. β-Diketones **3** and **5** are respectively reduced to the corresponding β-diols **4** and **6**. In both cases, an almost complete reversal in the diastereoselectivity of the reaction is observed when changing the solvent from CH_2Cl_2 (*syn*-**4** in up to 92% de; *meso*-**6** in up to 84% de) to a 1 : 1 CH_2Cl_2–CH_3OH mixture (*anti*-**4** and *anti*-**6** in up to 84% de). The extent of this solvent effect is much less marked with Ru-atropisomeric diphosphine catalysts.

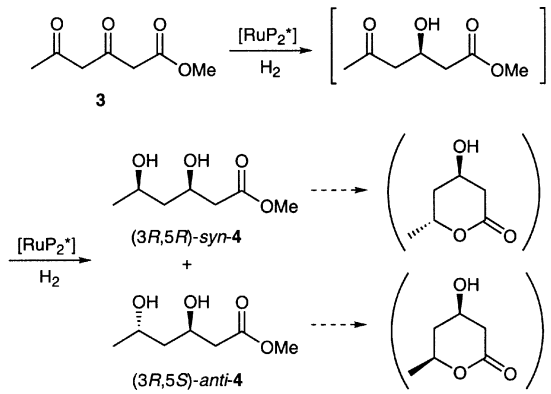
1. Introduction

Catalytic asymmetric hydrogenation of 1,3-dicarbonyl systems mediated by Ru-diphosphine complexes is a highly efficient tool in organic synthesis for the production of chiral functionalized alcohols or diols, as useful synthons.[1] Intensive and successful developments have been made in this field in the last decade, essentially by investigating the reactivity of new functionalized ketones[2] and by optimizing the catalyst performance through tuning of the chiral diphosphine and the ruthenium precursor.[1c,d] Another parameter that is known to influence the outcome of some of these processes is the nature of the solvent. A classical example is the dynamic kinetic resolution of β-ketoesters with epimerizable substituents at the α position.[1,3] In this process, diastereoselectivities are always more efficient when the reductions are performed in CH_2Cl_2 compared to a protic solvent such as methanol. High *syn* diastereomer formation is attributed to a transition state that is stabilized by hydrogen bonding between the amide hydrogen and ester moiety. Protic solvents would no longer stabilize the hydrogen bonding in the transition state, which results in dismal diastereoselectivities.[1,3] Investigations on solvent effects in the asymmetric hydrogenation of functionalized ketones are indeed very rare and have been almost exclusively carried out with catalysts based on atropisomeric bisphosphines. In this note, we wish to report on related, even more marked solvent effects in the asymmetric hydrogenation of 1,3-dicarbonyl systems in the presence of ruthenium(amidophosphine-phosphinite) catalysts.

2. Results and discussion

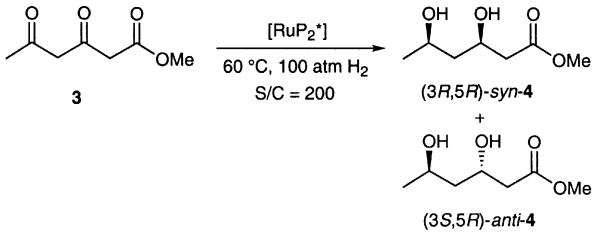
The first series of examples is concerned with the asymmetric hydrogenation of methyl 3,5-dioxohexanoate (**3**). This model reaction is aimed at evaluating a simple one-pot access to *syn*-3,5-dihydroxyesters (*i.e.*, *syn*-**4**; Scheme 1), which are key building blocks for the synthesis of important inhibitors of HMG-coenzyme A reductase.[4] Saburi *et al.*[5] have first investigated this reaction with {$RuCl_2$[(*S*)-BINAP]}$_2$·NEt_3 (**I**) as catalyst precursor in methanol and shown that, despite excellent chemoselectivity for the desired products,† it gives predominantly *anti*-diol **4** in *ca.* 60% de; the corresponding enantiomeric excess could not be determined accurately. In a recent thorough reinvestigation of this reaction in which we set up efficient analytical tools,[6] we have found that carrying out the reaction with this catalyst precursor in CH_2Cl_2 instead of CH_3OH allows a slight improvement of both diastereoselectivity (from 52% to 72% de) and enantioselectivity (from 87 to 92% ee) for *anti*-(3*R*,5*S*)-**4** (Table 1). Related catalyst precursors such as $RuBr_2$[(*S*)-TolBINAP] and $RuBr_2$[(*S*)-MeO-BIPHEP] afford slightly improved performance (with respect to **I**) in terms of stereoselectivity [up to 78% de and 95% ee for *anti*-(3*R*,5*S*)-**4** in CH_2Cl_2], but exhibit basically the same solvent dependence. In fact, the extent of this solvent effect on the stereoselective outcome of the asymmetric hydrogenation of **3** with Ru-atropisomeric diphosphine systems remains rather limited (*ca.* −20 points in de from CH_2Cl_2 to CH_3OH), a trend that compares well with the aforementioned example of dynamic kinetic resolution.

More interesting are the results obtained for this reaction with some Ru(amidophosphine-phosphinite) complexes (hereafter denoted as Ru-AMPP) developed in our group (Scheme 2).[7] Indeed, the catalytic species produced from these precursors proved to have a much more versatile behavior with respect to the nature of the solvent, allowing in certain cases an almost complete reversal in the diastereoselectivity of



Scheme 1 Asymmetric hydrogenation of methyl 3,5-dioxohexanoate **3** (for clarity only half of the stereoisomers are represented)

Table 1 Hydrogenation of methyl 3,5-dioxohexanoate (**3**)

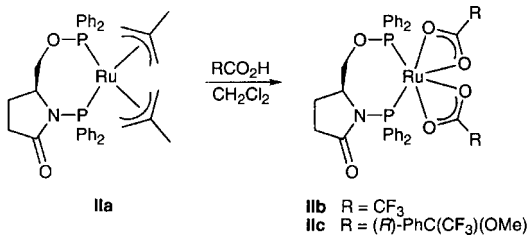


Catalyst	Solvent	t/h[a]	Yield **4**[b]	*syn* : *anti* **4**[b]	ee *syn*-**4**[b]	ee *anti*-**4**[b]
I	CH_2Cl_2	91[c]	96	14 : 86	22 (*S*, *S*)	92 (*R*, *S*)
	MeOH	23	96	24 : 76	87 (*S*, *S*)	87 (*R*, *S*)
IIa	CH_2Cl_2	238	49[d]	61 : 39	14 (*R*, *R*)	29 (*S*, *R*)
	CH_2Cl_2–MeOH (9 : 1)	166	74	42 : 58	33 (*R*, *R*)	55 (*S*, *R*)
	CH_2Cl_2–MeOH (1 : 1)	113	78	10 : 90	nd	nd
IIb	CH_2Cl_2	24	>99	68 : 32	34 (*R*, *R*)	60 (*S*, *R*)
	CH_2Cl_2–MeOH (1 : 1)	93	88	14 : 86	11 (*R*, *R*)	12 (*S*, *R*)
IIc	CH_2Cl_2	18	>98	96 : 4	5 (*R*, *R*)	nd
	CH_2Cl_2–MeOH (1 : 1)	169	72	8 : 92	12 (*R*, *R*)	5 (*S*, *R*)

[a] Non-optimized time for total conversion of **3**. [b] Yield (mol %), *syn* : *anti* ratio and respective enantiomeric excesses of **4** as determined by GLC analysis of crude reaction mixtures and corresponding acetonides. Letters in parentheses refer to the absolute configuration of the prevailing enantiomer at C-3 and C-5, respectively. [c] S/C = 500. [d] The monohydrogenation product at C-3 was formed in 51% yield and 8% ee (*R*).

the reaction. The readily attainable precursor {Ru[(*S*)-Ph,Ph-oxoProNOP](η³-C_4H_7)$_2$} (**IIa**) and its dicarboxylato derivatives {Ru[(*S*)-Ph,Ph-oxoProNOP](O_2CCF_3)$_2$} (**IIb**) and {Ru[(*S*)-Ph,Ph-oxoProNOP][(*R*)-MTPA]$_2$} (**IIc**) [(*R*)-MTPA) = (*R*)-α-methoxy-α(trifluoromethyl)phenylacetate], both prepared according to the procedure of Heiser *et al.*,[8] are representative examples of this unusual behavior. In pure CH_2Cl_2, all of these complexes induce the formation of *syn*-rich mixtures of diol **4** (Table 1); the reaction that proceeds sluggishly with a poor de in the presence of **IIa** is significantly accelerated with **IIb** and **IIc** with the latter complex leading to a much better diastereoselectivity. In a 1 : 1 (v/v) CH_2Cl_2–CH_3OH mixture, the same catalyst precursors lead this time to the diastereoselective formation of *anti*-**4** in 72–84% de. Although it must be pointed out that the presence of CH_3OH in the reaction medium also induces a decrease of the reaction rate and some side reactions at the expense of chemoselectivity (*i.e.*, dehydration-hydrogenation, acetal formation, *etc.*, which hampers the study of these reactions in pure methanol with Ru-AMPP systems, in contrast to Ru-atropisomeric diphosphine systems),‡ the most striking feature is undoubtedly the reversal in the diastereocontrol of the reaction. The extent of this solvent effect is particularly important in the case of complex **IIc**, for which the diastereomeric excess switches from 92% for *syn*-**4** in CH_2Cl_2 to 84% for *anti*-**4** in a 1 : 1 CH_2Cl_2–CH_3OH mixture. As shown in the case of **IIa** this effect can be modulated with the methanol content.

Despite high and versatile diastereoselectivities, Ru-AMPP systems afford poor enantiomeric excesses. The highest ees so far obtained for *syn*-**4** and *anti*-**4** reach only a modest 40% and 60%, respectively, considering also that these values could not be combined with high des. This general trend for Ru(Ph,Ph-oxoProNOP) catalysts stems from their incapability to enantioselectively promote the first hydrogenation at the C-3



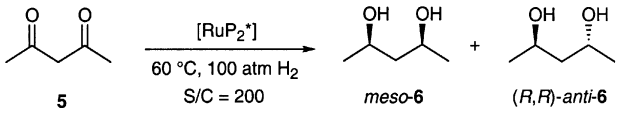
Scheme 2 Chiral Ru(amidophosphine-phosphinite) catalyst precursors used in this study

(β) carbonyl group; this was clearly evidenced by GLC analysis of some aliquot samples, which revealed that ees of methyl 3-hydroxy-5-oxohexanoate (*i.e.*, the sole intermediary monohydrogenation product formed) typically range between 5 and 15%. The ineffective enantioface differentiation of chiral Ru-AMPP species is assumed to arise from a competitive ligation of the functionalities of **3** onto the Ru center. The two chelation modes, β-ketoester/β-diketone (also taking into account the very likely involvement of β-ketoenol tautomers), may have in fact opposite directions for the final stereoselectivity at C-3.[1c,5,6] In this regard, it is noteworthy that Ru-AMPP systems such as **IIa** hydrogenate simple β-ketoesters in 75–85% ee.[9]

Considering the above arguments, we investigated the asymmetric hydrogenation of a simple β-diketone. Ru-catalyzed hydrogenations of symmetrical 1,3-diketones with various ligands such as BINAP, MeO-BIPHEP, SKEWPHOS and Me-DuPHOS are well-known to afford the *anti* diols in very high diastereo- and enantiomeric excesses.[1,10] Representative results obtained in the case of 2,4-pentanedione (**5**) with Ru(Ph,Ph-oxoProNOP) systems **IIa–c** are summarized in Table 2. The latter reveal rather similar trends as those found for the asymmetric hydrogenation of **3**. In fact, in pure CH_2Cl_2, the three Ru systems induce the formation of *meso*-rich mixtures of diol **5**; the bis(methylallyl) and di(trifluoroactetato) precursors **IIa** and **IIb** afford only poor des while *meso*-**5** is formed in up to 84% de in the presence of the MTPA complex **IIc**. Interestingly, ees as high as 93% can be reached in this solvent using catalyst precursor **IIb**, which also proved the most efficient in terms of reaction rate. In a 1 : 1 CH_2Cl_2–CH_3OH mixture, systems **IIa–c** lead this time to the diastereoselective formation of *anti*-**5** in 74–84% de, but with poor ees. This low final enantioselectivity is ascribed again to the inefficiency of the first hydrogenation step that proceeds in *ca.* 20% ee (see Table 2). Thus, with respect to the solvent effect, this second series of experiments reveal the same atypical behavior of Ru-AMPP catalysts.

In conclusion, we have shown that some Ru(Ph,Ph-oxoProNOP) complexes, such as the remarkable {Ru[(*S*)-Ph,Ph-oxoProNOP][(*R*)-MTPA]$_2$} (**IIc**), can induce the diastereoselective formation of either a *syn*-diol or an *anti*-diol just by modifying the nature of the solvent. As aforementioned, related solvent effects on the diastereoselectivity of the asymmetric hydrogenation of epimerizable β-ketoesters with Ru-

Table 2 Hydrogenation of 2,4-pentanedione (**5**)



5 *meso*-**6** (*R*,*R*)-*anti*-**6**

Catalyst	Solvent	t/h[a]	Yield **6**[b]	*meso* : *anti* **6**[b]	ee *anti*-**6**[b]
IIa	CH_2Cl_2	172	62[c]	57 : 43	46 (*R*, *R*)
	CH_2Cl_2–MeOH (1 : 1)	148	>99	13 : 87	16 (*S*, *S*)
IIb	CH_2Cl_2	24	>99	60 : 40	93 (*R*, *R*)
	CH_2Cl_2–MeOH (1 : 1)	24	>99	12 : 88	20 (*R*, *R*)
IIc	CH_2Cl_2	49	49[d]	92 : 8	86 (*R*, *R*)
	CH_2Cl_2–MeOH (1 : 1)	48	84[e]	8 : 92	14 (*R*, *R*)

[a] Non-optimized time for total conversion of **5**, unless otherwise stated. [b] Yield (mol %), *syn* : *anti* ratio and enantiomeric excess of **6** as determined by GLC analysis. [c] 2-Hydroxy-4-pentanone was formed in 38% yield and 18% ee (*R*). [d] Conversion of **5** = 66%; 2-hydroxy-4-pentanone was formed in 17% yield and 23% ee (*R*). [e] 2-Hydroxy-4-pentanone was formed in 16% yield and 28% ee (*R*).

BINAP type catalysts have been discussed in terms of stabilization of a transition state through hydrogen bonding between the amide hydrogen and ester moiety.[1,3] Such an explanation could account also for our results in the asymmetric hydrogenation of β,δ-diketoester **3**, as one can consider a similar interaction between the β-OH group and the ester moiety in the monohydrogenated intermediate. Nonetheless, this is a very unlikely hypothesis considering that both asymmetric hydrogenations of diketones **3** and **5** exhibit the same solvent effects, that is a reversal in diastereoselectivity, and that such an intramolecular interaction cannot exist in the case of **5**. An important, still open issue in our opinion is the exact nature of catalytic species involved in ruthenium-catalyzed hydrogenation of ketones and the influence of the solvent nature on it. We assume that the unusual features brought by the N–P and O–P bonds confer to Ru-AMPP species an even greater versatility compared to catalysts based on traditional C–P chiral diphosphines.

3. Experimental

General techniques and materials

All the catalytic reactions were performed under anaerobic conditions using standard Schlenk techniques. Hydrogenation solvents were distilled from magnesium methoxide (methanol) or CaH_2 (CH_2Cl_2), and degassed before use. 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 × 0.32 mm, SGE) column. Methyl 3,5-dioxohexanoate (**3**) was prepared by the reported method.[11] 2,4-Pentanedione was purchased from Aldrich and distilled before use. $\{RuCl_2[(S)\text{-BINAP}]\}_2 \cdot NEt_3$ (**I**) was purchased from Strem. Ru[(*S*)-Ph,Ph-oxoProNOP](methylallyl)$_2$ (**IIa**) was synthesized according to the reported procedure.[7] Catalyst precursors of the type Ru[(*S*)-Ph,Ph-oxoProNOP](OCOR)$_2$ were generated *ex situ* using the same procedure as described by Heiser *et al.*:[8] a solution of **IIa** in the reaction solvent (CH_2Cl_2 or CH_2Cl_2–CH_3OH) 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 min 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. *Ex situ* generated and preformed catalyst precursors led to identical results in terms of activity and stereoselectivity.

Asymmetric hydrogenations

A solution of diketone (2.4 mmol) in CH_2Cl_2 or a CH_2Cl_2–CH_3OH mixture (10 mL) was degassed by two freeze-thaw cycles and then added under nitrogen to a solution of the catalyst precursor (0.012 mmol Ru) in the same solvent (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.

Analytical procedures

Chemo-, diastereo- and enantioselectivities for the hydrogenation products of methyl 3,5-dioxohexanoate (**3**) were determined as described in ref. 6. In particular, des and ees were determined by GLC analysis of the corresponding acetonides of *syn*-**4** and *anti*-**4** (*syn*-**9** and *anti*-**9**, respectively), obtained by treatment of the final oily mixture with 2,2-dimethoxypropane in the presence of *para*-toluenesulfonic acid. Yield, diastereo- and enantioselectivities for the hydrogenation products of 2,4-pentanedione (**5**) were determined by GLC analysis. The absolute configuration of the prevailing enantiomer of *anti*-**6** was established from the optical rotation.

Notes and references

† As shown in Scheme 1, the 3,5-dihydroxyesters *syn*-**4** and *anti*-**4** are converted *in situ* to the corresponding *anti*- and *syn*-hydroxylactones, respectively; the dihydroxyesters **4** and these lactones are equivalent synthons.

‡ Other solvents were also investigated using **IIb** as catalyst precursor for the hydrogenation of **3**. 1,2-Dichloroethane gave identical results, in terms of reactivity and selectivity, as dichloromethane. In toluene and methyl acetate, the reaction proved to be very sluggish and no significant diastereo- and enantioselectivity were observed. When the reaction was carried out in pure 2-propanol, unidentified products were also formed.

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