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New one pot synthesis of a chiral α-hydroxy-γ-butyrolactone via sequential asymmetric hydrogenation of an α,γ-diketoester

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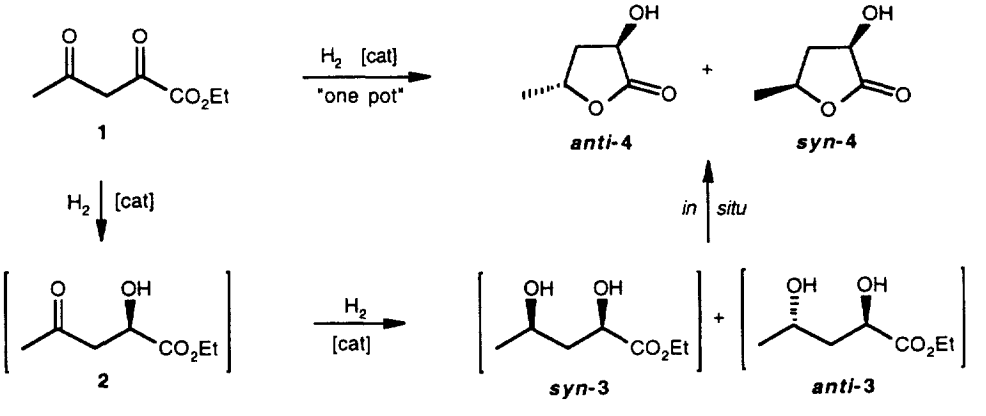
Abstract

The hydrogenation of ethyl 2,4-dioxovalerate in the presence of chiral rhodium or ruthenium catalysts provides direct access to 2-hydroxy-4-methyltetrahydrofuran-2-one **4** with *syn:anti* ratios of up to 84:16 and with up to 98% and 94% e.e. in the *syn* and *anti* form, respectively.

Optically active α-hydroxy-γ-butyrolactones of type **4** are attractive compounds as well-identified hunger modulators,[1a,b] and key chiral intermediates in the synthesis of various biologically active molecules[1c–e] and liquid crystals.[1f] To the best of our knowledge, all the existing methods for preparing α-hydroxy-γ-butyrolactones employ chiral natural starting materials and involve multistep procedures.[1] Our involvement in the past decade in the design and the applications of rhodium- and ruthenium-based asymmetric catalysts for the hydrogenation of prochiral ketones[2] has led us to investigate a new potential route to compounds **4**. We report herein our preliminary results on a direct, catalytic synthesis of optically active **4** using such methodology starting from the easily available α,γ-diketoester **1**.



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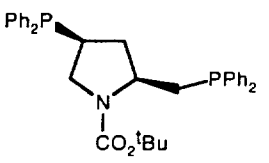
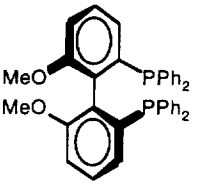
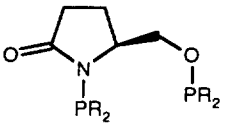


(*S,S*)-BPPM



(*S*)-MeO-BIPHEP



R = C_6H_{11}: (*S*)-Cy,Cy-oxoProNOP
R = C_5H_9: (*S*)-Cp,Cp-oxoProNOP

In this one pot procedure, both stereogenic centers are created in two successive hydrogenation steps leading to intermediates **2** and **3**,[3] followed by the in situ lactonization of **3** into **4**. Ethyl 2,4-dioxovalerate **1** was chosen as a model substrate for the evaluation of typical Rh- and Ru-diphosphine catalysts. Representative results are summarized in Table 1. Although most of the evaluated systems allow the selective conversion of **1** to the desired lactones **4**, large differences in the catalyst performance were observed. As a general trend, Ru systems proved to be more efficient in terms of enantioselectivity and above all of diastereoselectivity than Rh catalysts.

As a matter of fact, the performance of Rh catalysts varies largely upon the nature of the diphosphine (entries 1–6). Among the numerous chiral ligands investigated, including several outstanding diphosphines, only a few afforded quite interesting results.[4] The best Rh systems found so far are based on amidophosphine–phosphinite (AMPP) ligands developed in our group, i.e. (*S*)-Cy,Cy-oxoProNOP and (*S*)-Cp,Cp-oxoProNOP.[2] Under optimized reaction conditions (entry 5), the combination of (*S*)-Cp,Cp-oxoProNOP with $[Rh(COD)Cl]_2$ affords **4** in 91% yield with up to 74% and 85% e.e.s in the *syn* and *anti* form respectively, but with a ca. 50:50 *syn:anti* ratio. The results with Rh catalysts clearly demonstrate that the first hydrogenation step of **1** to the corresponding α-hydroxy-γ-ketoester **2** proceeds enantioselectively, in direct line with our previous studies,[2b] while the second hydrogenation to diol **3** is almost completely unselective and also requires about 10 times longer than the first one. The replacement of the chloro ligand by a trifluoroacetato ligand in the rhodium precursor only slightly affects the activity and the selectivities (compare entries 3/4 and 5/7), and it has so far been impossible to significantly improve the diastereoselectivity, even with optically active carboxylato ligands.

Much better results were obtained with Ru catalysts having atropisomeric bis(diarylphosphino) ligands (entries 7–11). Most of the evaluated systems allow the whole dihydrogenation–lactonization process to proceed cleanly at 60–80°C in CH_2Cl_2 giving virtually quantitative yields of lactones **4** in reasonable times. Most interestingly, both reductions are strictly controlled by the catalyst, so that significantly increased (with respect to Rh catalysts) d.e.s up to 68% and e.e.s up to 98% for the *syn* diastereomer are obtained. Thus, when the reaction is carried out in the presence of 0.5 mol% of $RuBr_2$(*S*)-MeO-BIPHEP[5] at 80°C, *syn*-**4** is produced in 84% yield and 98% e.e. (entry 10).[6] Decreasing the reaction temperature to 60°C results in a slightly lower d.e., while the e.e. of *anti*-**4** increases to 94% (entry 11). Other adequate, but somewhat less enantioselective catalysts for this reaction include $RuBr_2$(*S*)-TolBINAP and commercially available $RuCl_2$(*S*)-BINAP·$(NEt_3)_2$ (entries 7 and 9), while $RuBr_2$(*S*)-BINAP was found to be sluggish (entry 8).

Such an improvement of d.e.s with Ru–BINAP type catalysts is not surprising in light of diastereoselective hydrogenations of β-hydroxy-ketones previously reported by Noyori et al.[7] The inefficiency of Rh systems for controlling the second reduction probably arises from the lack of chelation of intermediate **2** onto the metal center. As a consequence, not only the d.e.s are significantly lower with Rh, but also a reversal of enantioselectivity for *anti*-**4** is observed in the second hydrogenation step going from Rh- to Ru-(*S*)-MeO-BIPHEP systems (entries 2 and 10).

Current investigations are directed towards both the enhancement of diastereo- and enantioselectivities,

Table 1
Asymmetric hydrogenation of ethyl 2,4-dioxovalerate (**1**)[a]

entry	Catalyst system[b]	temp	time[c]	**2**		**4**		
		(°C)	(h)	sel (%)	ee (%)[d]	sel (%)	*syn:anti*	ee (%)[e]
1	[RhCl((2*S*,4*S*)-BPPM)]	60	162	46	64	49	54 / 46	57 / 64
2	[RhCl((*S*)-MeO-BIPHEP)]	60	138	82	78	18	54 / 46	79 / 53
3	[RhCl((*S*)-Cy,Cy-oxoProNOP]	60	84	81	70	18	65 / 35	80 / 60
4	[Rh(TFA)((*S*)-Cy,Cy-oxoProNOP)]	60	86	45	80	47	48 / 52	80 / 86
			166	3	nd	92	48 / 52	80 / 86
5[f]	[RhCl((*S*)-Cp,Cp-oxoProNOP)]	60	43	0	-	91	44 / 56	72 / 86
6	[Rh(TFA)((*S*)-Cp,Cp-oxoProNOP)]	60	26	39	80	56	45 / 55	72 / 87
			165	4	nd	96	45 / 55	72 / 87
7	$RuCl_2$(*S*)-BINAP.$(NEt_3)_2$	80	23	0	-	>99	83 / 17	96 / 77
8	$RuBr_2$(*S*)-BINAP	80	13	72	75	28	81 / 19	96 / 66
9	$RuBr_2$(*S*)-TolBINAP	80	21	0	-	>99	83 / 17	94 / 87
10	$RuBr_2$(*S*)-MeO-BIPHEP	80	39	0	-	>99	84 / 16	98 / 87
11	$RuBr_2$(*S*)-MeO-BIPHEP	60	65	6	nd	93	78 / 22	97 / 94
			157	0	-	>99	79 / 21	96 / 93

[a]Rh systems: toluene, 50 atm H_2, [**1**]/[P]/[Rh] = 200:2.2:1, [Rh] = 0.6–1.4 mmol/l unless otherwise stated. Ru systems: CH_2Cl_2, 100 atm H_2, [**1**]/[Ru] = 200:1, [Ru] = 1.8 mmol/l. Conversion of **1** and selectivities (e.e., d.e.) for **2** and **4** were determined by quantitative GLC analysis (BPX5 and chiral β-Cyclodex-permethylated columns); Diol **3** accounts for the balance. [b]Rh catalysts were generated *in situ* from the appropriate precursor $[Rh(COD)X]_2$ (X = Cl or TFA = trifluoroacetato) and 2.2 equiv of the diphosphine ligand; $RuBr_2P_2$ type catalysts were synthesized according to literature.[5] [c]Non optimized time for 100% conversion of **1**. [d]In all cases, the configuration of the prevailing enantiomer of **2** is *R*, as established from the specific rotation.[8] [e]E.e. (chiral GLC) of *syn*-**4** and *anti*-**4**, respectively; The configuration of the prevailing enantiomer for *syn*-**4** is always 2*R*,4*S* and for *anti*-**4** either 2*R*,4*R* (entries 1–6) or 2*S*,4*S* (entries 7–11), as established from the specific rotations.[9] [f][Rh] = 3.0 mmol/l.

and the reactivity of higher α,γ-diketoesters to widen the applicability of this new procedure for the synthesis of targeted α-hydroxy-γ-butyrolactones and related molecules.

Acknowledgements

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3. Ethyl 2-hydroxy-4-oxo-valerate **2** is the only monohydrogenated intermediate observed with both Rh and Ru systems. In situ lactonization of **3** to **4** proceeds relatively quickly under the reaction conditions, so that the relative amount of **3** with respect to **4** in aliquot samples is typically lower than 20% for Rh systems, and lower than 5% with Ru catalysts.
4. Toluene was found to be the most appropriate solvent for neutral Rh catalysts. Significant amounts of unidentified heavy products are formed when the reaction is carried out in methanol using cationic Rh catalysts of the type [Rh(diphosphine)(COD)][ClO_4].
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6. In a typical experiment (entry 10), a degassed solution of **1** (820 mg, 5.2 mmol) in CH_2Cl_2 (8 ml) was added under nitrogen to a solution of $RuBr_2$(*S*)-MeO-BIPHEP (22 mg, 0.026 mmol) in CH_2Cl_2 (7 ml). The solution was transferred to a 100 ml stainless steel autoclave equipped with a magnetic stir bar, which was then pressurized with 100 atm of H_2 and warmed to 80°C. After completion of the reaction (quantitative and chiral GLC monitoring), the autoclave was cooled to room temperature, degassed, and the solution concentrated under vacuum. The oily residue was chromatographed on silica (heptane:ethyl acetate=4:1) to afford pure samples of *syn*- and *anti*-lactones **4** (overall yield: 0.49 g, 81%), which were characterized by ^1H, ^{13}C NMR and MS.
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