RuCl₃/PPh₃: An Efficient Combination for the Preparation of Chiral 1,3-*anti*-Diols through Catalytic Hydrogenation

Olivier Labeeuw, Christophe Roche, Phannarath Phansavath,* and Jean-Pierre Genêt*

Laboratoire de Synthèse Sélective Organique et Produits Naturels UMR 7573 CNRS, ENSCP, 11 rue Pierre et Marie Curie, 75231 Paris Cedex 05, France

jean-pierre-genet@enscp.fr

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ABSTRACT



An efficient economical alternative to the commonly used Evans' reagent for the diastereoselective reduction of β -hydroxy ketones is reported. Thus, ruthenium-mediated hydrogenation of enantioenriched β -hydroxy ketones using RuCl₃ associated to achiral monophosphines allowed the preparation of a series of 1,3-*anti*-diols in good yields and with a high level of diastereoselectivity. A short screening of ligands pointed out PPh₃ as the most effective phosphine, and PCy₃ afforded the 1,3-diols with an unexpected moderate syn selectivity.

The stereoselective synthesis of 1,3-diols is of particular interest due to the prominence of this motif within many classes of natural products.¹ Among the procedures developed for the obtention of acyclic 1,3-diols,² metal hydride reduction of 1,3-diones³ and transition-metal-catalyzed hydrogenation reactions of 1,3-diketones⁴ and 3,5-dioxoesters⁵ have been reported. Apart from these methods, the diastereoselective reduction of β -hydroxy ketones is particularly attractive because both *syn*- and *anti*-1,3-diols can be prepared depending on the hydride reagents and the reaction conditions. The most commonly used methods for the reduction

to *syn*-diols involve either the Bu₃B/NaBH₄ combination developed by Narasaka and Pai⁶ or the modified Et₂BOMe/

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NaBH₄ system reported by Prasad.⁷ On the other hand, 1,3anti-diols are most usually prepared from the corresponding β -hydroxy ketones by reaction with the mild reducing agent, tetramethylammonium triacetoxyborohydride (commonly named Evans' reagent).⁸ Although good to excellent diastereoselectivities can be achieved with this method, the use of boron reagents remains prohibitive on a preparative scale due to economic and environmental concerns.

Herein, we report an operationally simple and waste-free method for diastereoselective hydrogenation⁹ of β -hydroxy-ketones into 1,3-*anti*-diols, using an inexpensive RuCl₃/ phosphine combination.¹⁰

Initial studies of the influence of reaction conditions were carried out with **1a** as the standard substrate and PPh₃ as a ligand. The hydrogenation reaction was first examined in methanol using 2 mol % of RuCl₃ and 4 mol % of PPh₃ (Table 1).

Table 1. Hydrogenation of $1a$ in the Presence of RuCl ₃ /PPh ₃ ^a							
BnO 1a (9	OH O F ↓	RuCl ₃ (2 n H ₂ (4-1	nol %), PF 00 bar), 2	⁹ h ₃ (4 mol 5-50 °C	%) BnO 2a	OH ∽nBu	
entry	solvent	time (h)	P (bar)	temp (°C)	$\begin{array}{c} \text{conversion} \\ (\%)^b \end{array}$	de (%) ^c	
1	MeOH	72	10	25	30	\mathbf{nd}^d	
2	MeOH	72	100	25	88	83	
3	MeOH	24	10	50	100	91	
4	MeOH	48	4	50	35	\mathbf{nd}^d	
5	CH_2Cl_2	24	10	50	61	44	
6	hexane	24	10	50	16	59	
7	toluene	24	10	50	10	62	

^{*a*} Conditions: **1a** (0.5 mmol), solvent (2 mL), RuCl₃ (10 μ mol), PPh₃ (20 μ mol). ^{*b*} Conversions were determined by ¹H NMR spectroscopy of the crude product. ^{*c*} de determined by HPLC analysis, chiralcel OD-H column, hexane/iPrOH 95:5, flow rate of 1 mL/min. An authentic sample of the 1,3-*anti*-diol **2a** was obtained by reduction of **1a** with Me₄NBH(OAc)₃, and an authentic sample of the 1,3-*syn*-diol was prepared by reduction with Et₂BOMe/NaBH₄. The identities of the diastereomers were established on the correspoding acetonides using the protocol reported by Rychnovsky.¹¹ ^{*d*} de not measured.

When the reaction was run at room temperature, conversions were incomplete under either low or high pressures of hydrogen (10 or 100 bar, respectively, entries 1 and 2). Full

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conversion was actually achieved at 50 °C and under 10 bar of hydrogen pressure (entry 3). Under these conditions, high anti diastereoselectivity (91% de) was obtained. Decreasing the hydrogen pressure to 4 bar afforded low conversion (entry 4).

A short screening of solvents showed that MeOH was the solvent of choice for the hydrogenation reaction in terms of both conversion and selectivity because, using the optimized reaction parameters, we obtained low conversions and unsatisfactory diastereomeric excesses in CH_2Cl_2 , hexane, or toluene (entries 5–7).

To increase the selectivity of the reaction, we next focused our attention on the influence of the monophosphine ligands in the hydrogenation of **1a** using various phosphines under the optimized conditions (Table 2).

Table 2. Hydrogenation of 1a in the Presence of RuCl ₃ /PR ₃								
BnO, MBu RuCl ₃ (2 mol %), PR ₃ (4 mol %) H ₂ (10 bar), MeOH, 50 °C, 24 h								
1a (99% ee) 2a								
		θ		conversion	de			
entry	$phosphine^{a}$	(°) <i>b</i>	$pK_a{}^b$	(%) ^c	(%) ^d			
1	PPh ₃	145	2.73	100	91 (anti)			
2	$P(p-MeC_6H_4)_3$	145	3.84	80	90 (anti)			
3	$P(p-MeOC_6H_4)_3$	145	4.59	77	89 (anti)			
4	$P(n C C_{a} H_{i})_{a}$	145	1 0 2	100				
-	1 p - 0 1 0 6 1 14 / 3	140	1.05	100	74 (anti)			
5	$P(m-MeC_6H_4)_3$	$140 \\ 148$	3.30	78	74 (anti) 90 (anti)			
5 6	$P(m-MeC_6H_4)_3$ $P(o-MeC_6H_4)_3$	143 148 178	3.30	$78 \\ 5-10$	74 (anti) 90 (anti) nd ^f			
5 6 7	$P(m-MeC_6H_4)_3$ $P(o-MeC_6H_4)_3$ PPh_2Cy	145 148 178 153	$ \begin{array}{r} 1.03 \\ 3.30 \\ -^{e} \\ 5.05 \end{array} $	$78 \\ 5-10 \\ 50$	74 (anti) 90 (anti) nd ^f 83 (anti)			
5 6 7 8	$P(m-MeC_6H_4)_3$ $P(m-MeC_6H_4)_3$ $P(o-MeC_6H_4)_3$ PPh_2Cy $PPhCy_2$	143 148 178 153 162	$ \begin{array}{r} 1.03 \\ 3.30 \\ -^{e} \\ 5.05 \\ -^{e} \\ \end{array} $	78 5-10 50 30	74 (anti) 90 (anti) nd ^f 83 (anti) 23 (anti)			

^{*a*} In the absence of phosphine, no reduction was observed. ^{*b*} Values of cone angles (θ) and pK_a are taken from the literature.¹² ^{*c*} Conversions were determined by ¹H NMR spectroscopy of the crude product. ^{*d*} de determined by HPLC analysis. ^{*e*} Unknown. ^{*f*} de not measured.

A comparison of various triarylphosphines has first been studied (entries 1–6). Phosphines such as $P(p-MeC_6 H_4)_3$, $P(p-MeOC_6 H_4)_3$, and $P(m-MeC_6 H_4)_3$ afforded high diastereoselectivities albeit lower conversions (77–80% conversion, 89–90% de, entries 2, 3, and 5), whereas $P(o-Me C_6 H_4)_3$ led to very poor conversion presumably due to the higher steric hindrance (entry 6). On the other hand, the less electron-rich phosphine $P(p-ClC_6H_4)_3$ yielded complete conversion but lower diastereomeric excess (74% de, entry 4). For phosphines bearing the same cone angle value (145°), an increase of the pK_a values has no effect on the diastereoselectivity (entries 1–3). Indeed, for basic phosphines such as $P(p-MeC_6H_4)_3$ and $P(p-MeOC_6H_4)_3$, the diastereoselectivity of the hydrogenation (89–90% de) remains similar to that obtained with PPh₃. On the contrary, a less basic

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phosphine such as $P(p-ClC_6H_4)_3$ afforded a lower diastereomeric excess (74% de, entry 4).

The hydrogenation reaction of compound **1a** was also examined with monophosphines bearing one or more alkyl substituents, namely, PPh₂Cy, PPhCy₂, and PCy₃. Given the steric hindrance brought by the cyclohexyl group, the reduction of 1a with the aforementioned phosphines afforded the corresponding diol with only moderate conversions, up to 75% (entries 7–9). In the case of PPh_2Cy , the formal exchange of a phenyl ring by a cyclohexyl group led to a decrease in diastereoselectivity (from 91% de for PPh₃ to 83% de for PPh₂Cy, anti isomer, entries 1 and 7). Furthermore, a considerable decrease of diastereoselectivity was observed when switching from PPh₂Cy to PPhCy₂ (from 83 to 23% de, anti isomer, entries 7 and 8). Even more remarkable is the reversal of stereoselectivity observed with PCy₃ because in this case the 1,3-syn-diol was the major product of the reaction (27% de for the 1,3-syn-diol, entry 9). From these data, an increase in the cone angle values results in a decrease of the diastereoselectivity.

A correlation between the cone angles and the stereochemical issues of the hydrogenation reactions of compound **1a** with PPh₃, PPh₂Cy, PPhCy₂, and PCy₃ is best visualized in Figure 1. Such a significant decrease in selectivity upon moving from PPh₃ to PCy₃ is unclear at present.



Figure 1. Correlation between the cone angles and the diastereoselectivity of the catalytic hydrogenation with PPh₃, PPh₂Cy, PPhCy₂, and PCy₃.

Achiral diphosphines have been used as well in the hydrogenation reaction of compound **1a**. However, the RuCl₃/diphosphine combination failed to afford complete conversion owing to the lower activity of the relevant ruthenium complex. The hydrogenation reactions of **1a** were therefore conducted under the above-mentioned standard conditions using the more active [Ru(PP)Br₂] complexes,¹³ prepared in situ from commercially available (COD)Ru(2-

methylallyl)₂ and the diphosphine. Thus, using dppe (1,2-bis(diphenylphosphino)ethane) or dppb (1,4-bis(diphenylphosphino)butane) as achiral diphosphines, the reaction proceeded quantitatively and delivered the corresponding 1,3-anti-diols with good diastereoselectivities (91% de in both cases).

Finally, in an attempt to establish the scope of the RuCl₃/ PPh₃-promoted hydrogenation, a series of β -hydroxy ketones **1a**-**g** bearing various substitution patterns were synthesized.¹⁴ These compounds were subjected to hydrogenation reactions under the established standard conditions, and good to high diastereoselectivities were achieved (Table 3). Thus,

 Table 3.
 Diastereoselective Hydrogenation of Compounds

 1a-f in the Presence of RuCl₃/PPh₃
 Old

 Old
 Old
 Old

J J	0 RuCl ₃ (2 m	nol %), PPh ₃ (4 mol %)	$R^1 \xrightarrow{OH} R^2$ 2a-2e	
R ¹ 1a	R ² H ₂ (10 bar), MeOH, 50 °C, 24 h		
Entry	Substrate 1	Product 2	yield (%)	de ^a (anti) (%)
1	он о	он он	96	91 ^{<i>b</i>}
	BnOnBu 1a (99% ee)	BnOnBu2a		(88) ^c
2	он о	он он	94	96 ^b
	Ph	Ph nBu 2b		(92) ^c
3	OH O ∎	он он	95	97^b
	Ph 1c (95% ee)	Ph 2c		(80) ^c
4	OH O	он он	95	97 ^d
	<i>n</i> Pr <i>n</i> Bu 1d (99% ee)	nPr nBu 2d		(92) ^c
5	он о _ , , , , , , , , , , , , , , , , , , ,	OH OH 	98	94 ^d
	<i>P</i> r ² * <i>n</i> Pr 1e (98% ee)	iPr ² ⁿ Pr 2e		
6	OH O BnO、 ス 人 _		95	89 ^b
	1f (99% ee)	2f		
7	BnO nBu	BnO	99	94 ^{<i>b</i>}
	1g (99% ee)	2g		

^{*a*} For the determination of the de, samples of diastereomerically enriched 1,3-*syn*-diols **2** were prepared by reduction of **1** with Et₂BOMe/NaBH₄. ^{*b*} de determined by HPLC analysis. ^{*c*} de obtained after reduction of **1** with tetramethylammonium triacetoxyborohydride. ^{*d*} de determined by GC analysis on the corresponding Mosher diesters.

a series of variously substituted 1,3-*anti*-diols $2\mathbf{a}-\mathbf{g}$ have been prepared through this procedure.¹⁵ High yields were obtained in the hydrogenation of β -hydroxy ketones $1\mathbf{a}-\mathbf{e}$

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⁽¹⁴⁾ Compounds 1a-g were prepared from the corresponding enantiomerically pure β -hydroxyesters, through addition of alkyllithium reagents on the related Weinreb amides.

bearing phenyl or benzyloxy groups as well as linear and branched alkyl substituents (entries 1-5). The diastereoselectivities observed for the corresponding 1,3-anti-diols were uniformly high (91–97% de). Starting from β -hydroxy ketone 1f, the enantiomer of 1a, the corresponding anti-diol 2f was obtained in high yield and, as could be expected, with comparable diastereoselectivity (89% de, entry 6 vs 91% de, entry 1). The presence of a methyl substituent in the α position had no effect on the hydrogenation reaction because high anti selectivity was obtained in the reduction of compound 1g (94% de, entry 7). For comparison, a number of β -hydroxy ketones have also been reduced using tetramethylammonium triacetoxyborohydride. In all cases, the RuCl₃/PPh₃-mediated hydrogenation afforded the 1,3-antidiols with comparable selectivities (entries 1, 2, and 4) or even significantly higher de's (97% vs 80%, entry 3).

In conclusion, we have shown that monodentate achiral phosphine ligands can be used efficiently for the rutheniumcatalyzed diastereoselective hydrogenation of β -hydroxy ketones. This catalytic procedure, involving the RuCl₃/PPh₃ combination, is highly preparative in nature, avoids the use of expensive tetramethylammonium triacetoxyborohydride, and tolerates varied hydroxyketone structures. This method should be an interesting alternative to boron reagents for the preparation of 1,3-*anti*-diols and is particularly suitable for large-scale reactions.

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Supporting Information Available: Complete spectroscopic data for compounds **2a**–**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹⁵⁾ Typical procedure for the hydrogenation reaction: hydroxyketone 1 (0.5 mmol) was purged by three vacuum/argon cycles, dissolved in degassed methanol (2 mL), and transferred via cannula to a round-bottomed tube containing a degassed mixture of RuCl₃ (2.1 mg, 10 μ mol) and PPh₃ (5.2 mg, 20 μ mol). The reaction vessel was placed in a stainless steel autoclave which was purged with hydrogen and pressurized to 10 bar. The autoclave was heated to 50 °C by circulating thermostated water in the double wall, and magnetic stirring was started as soon as the required temperature was reached. After stirring for 24 h, the autoclave was cooled to room temperature. Hydrogen was vented, and the reaction mixture was concentrated in vacuo.