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$RuCl_3/PPh_3$: An Efficient Combination for the Preparation of Chiral 1,3-*anti*-Diols through Catalytic Hydrogenation

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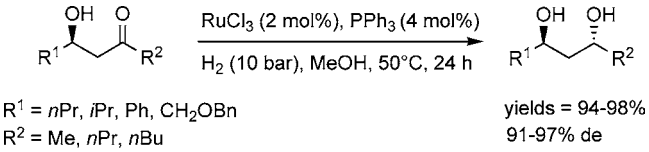
ABSTRACT



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 $RuCl_3$ 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 PPh_3 as the most effective phosphine, and PCy_3 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-diones[3] and transition-metal-catalyzed hydrogenation reactions of 1,3-diketones[4] and 3,5-dioxoesters[5] 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 $Bu_3B/NaBH_4$ combination developed by Narasaka and Pai[6] or the modified Et_2BOMe/

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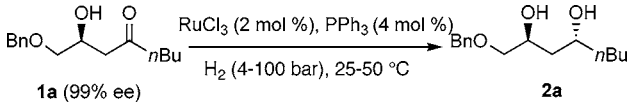
$NaBH_4$ system reported by Prasad.[7] On the other hand, 1,3-*anti*-diols are most usually prepared from the corresponding β-hydroxy ketones by reaction with the mild reducing agent, tetramethylammonium triacetoxyborohydride (commonly named Evans' reagent).[8] Although good to excellent diastereoselectivities 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 hydrogenation[9] of β-hydroxyketones into 1,3-*anti*-diols, using an inexpensive $RuCl_3$/phosphine combination.[10]

Initial studies of the influence of reaction conditions were carried out with **1a** as the standard substrate and PPh_3 as a ligand. The hydrogenation reaction was first examined in methanol using 2 mol % of $RuCl_3$ and 4 mol % of PPh_3 (Table 1).

Table 1. Hydrogenation of **1a** in the Presence of $RuCl_3/PPh_3$[a]



1a (99% ee) **2a**

entry	solvent	time (h)	*P* (bar)	temp (°C)	conversion (%)[b]	de (%)[c]
1	MeOH	72	10	25	30	nd[d]
2	MeOH	72	100	25	88	83
3	MeOH	24	10	50	100	91
4	MeOH	48	4	50	35	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

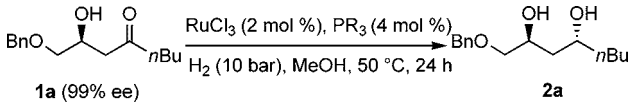
[a] Conditions: **1a** (0.5 mmol), solvent (2 mL), $RuCl_3$ (10 μmol), PPh_3 (20 μmol). [b] Conversions were determined by ^{1}H NMR spectroscopy of the crude product. [c] de determined by HPLC analysis, chiralcel OD-H column, hexane/iPrOH 95:5, flow rate of 1 mL/min. An authentic sample of the 1,3-*anti*-diol **2a** was obtained by reduction of **1a** with $Me_4NBH(OAc)_3$, and an authentic sample of the 1,3-*syn*-diol was prepared by reduction with $Et_2BOMe/NaBH_4$. 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 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 $RuCl_3/PR_3$



1a (99% ee) **2a**

entry	phosphine[a]	θ (°)[b]	pK_a[b]	conversion (%)[c]	de (%)[d]
1	PPh_3	145	2.73	100	91 (anti)
2	$P(p\text{-}MeC_6H_4)_3$	145	3.84	80	90 (anti)
3	$P(p\text{-}MeOC_6H_4)_3$	145	4.59	77	89 (anti)
4	$P(p\text{-}ClC_6H_4)_3$	145	1.03	100	74 (anti)
5	$P(m\text{-}MeC_6H_4)_3$	148	3.30	78	90 (anti)
6	$P(o\text{-}MeC_6H_4)_3$	178	−[e]	5−10	nd[f]
7	PPh_2Cy	153	5.05	50	83 (anti)
8	$PPhCy_2$	162	−[e]	30	23 (anti)
9	PCy_3	170	9.70	75	27 (syn)

[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 ^{1}H 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 $P(p\text{-}MeC_6H_4)_3$, $P(p\text{-}MeOC_6H_4)_3$, and $P(m\text{-}MeC_6H_4)_3$ afforded high diastereoselectivities albeit lower conversions (77−80% conversion, 89−90% de, entries 2, 3, and 5), whereas $P(o\text{-}MeC_6H_4)_3$ led to very poor conversion presumably due to the higher steric hindrance (entry 6). On the other hand, the less electron-rich phosphine $P(p\text{-}ClC_6H_4)_3$ 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 $P(p\text{-}MeC_6H_4)_3$ and $P(p\text{-}MeOC_6H_4)_3$, the diastereoselectivity of the hydrogenation (89−90% de) remains similar to that obtained with PPh_3. On the contrary, a less basic

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phosphine such as P(*p*-ClC$_6$H$_4$)$_3$ 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, PPh$_2$Cy, PPhCy$_2$, and PCy$_3$. 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$_2$Cy, the formal exchange of a phenyl ring by a cyclohexyl group led to a decrease in diastereoselectivity (from 91% de for PPh$_3$ to 83% de for PPh$_2$Cy, anti isomer, entries 1 and 7). Furthermore, a considerable decrease of diastereoselectivity was observed when switching from PPh$_2$Cy to PPhCy$_2$ (from 83 to 23% de, anti isomer, entries 7 and 8). Even more remarkable is the reversal of stereoselectivity observed with PCy$_3$ 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 PPh$_3$, PPh$_2$Cy, PPhCy$_2$, and PCy$_3$ is best visualized in Figure 1. Such a significant decrease in selectivity upon moving from PPh$_3$ to PCy$_3$ is unclear at present.

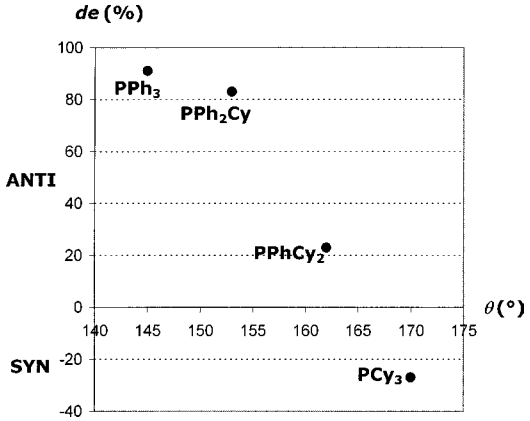
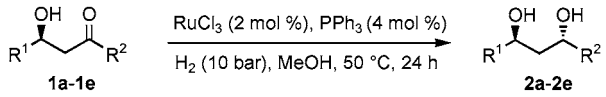


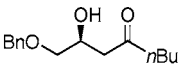
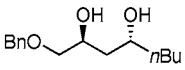
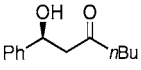
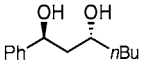
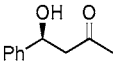
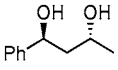
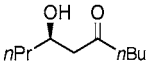
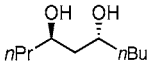
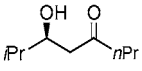
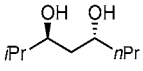
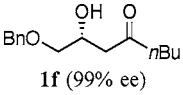
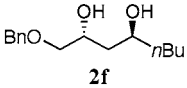
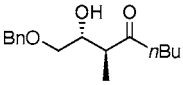
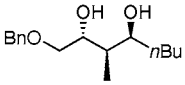
Figure 1. Correlation between the cone angles and the diastereoselectivity of the catalytic hydrogenation with PPh$_3$, PPh$_2$Cy, PPhCy$_2$, and PCy$_3$.

Achiral diphosphines have been used as well in the hydrogenation reaction of compound **1a**. However, the RuCl$_3$/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)Br$_2$] 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 RuCl$_3$/PPh$_3$-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 RuCl$_3$/PPh$_3$



Entry	Substrate **1**	Product **2**	yield (%)	de[a] (*anti*) (%)
1	 **1a** (99% ee)	 **2a**	96	91[b] (88)[c]
2	 **1b** (95% ee)	 **2b**	94	96[b] (92)[c]
3	 **1c** (95% ee)	 **2c**	95	97[b] (80)[c]
4	 **1d** (99% ee)	 **2d**	95	97[d] (92)[c]
5	 **1e** (98% ee)	 **2e**	98	94[d]
6	 **1f** (99% ee)	 **2f**	95	89[b]
7	 **1g** (99% ee)	 **2g**	99	94[b]

[a] For the determination of the de, samples of diastereomerically enriched 1,3-*syn*-diols **2** were prepared by reduction of **1** with Et$_2$BOMe/NaBH$_4$. [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 **2a**−**g** have been prepared through this procedure.[15] High yields were obtained in the hydrogenation of β-hydroxy ketones **1a**−**e**

(13) For preparation of the [Ru(P*P)Br$_2$] complexes using chiral diphosphines, see: Genet, J.-P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Caño de Andrade, M. C.; Laffite, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 665.

(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 $RuCl_3/PPh_3$-mediated hydrogenation afforded the 1,3-*anti*-diols with comparable selectivities (entries 1, 2, and 4) or even significantly higher de's (97% vs 80%, entry 3).

(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 $RuCl_3$ (2.1 mg, 10 μmol) and PPh_3 (5.2 mg, 20 μmol). 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.

In conclusion, we have shown that monodentate achiral phosphine ligands can be used efficiently for the ruthenium-catalyzed diastereoselective hydrogenation of β-hydroxy ketones. This catalytic procedure, involving the $RuCl_3/PPh_3$ 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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