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Highly Efficient New Catalysts for Enantioselective Transfer Hydrogenation of Ketones

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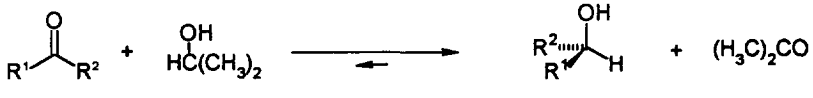
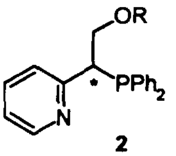
Abstract: *Transfer hydrogenations of alkyl aryl ketones as well as a representative dialkyl ketone with isopropanol catalyzed by Ru complexes of chiral phosphinooxazolines were found to proceed with excellent turnover at a substrate/catalyst mole ratio of 1000:1 to yield products with up to 94 % enantiomeric excess.*

Considerable effort has recently been devoted to the development of transition metal catalyzed transfer hydrogenations of ketones with isopropanol (Scheme 1). In view of the low cost of the reducing agent and operational simplicity this method appears an attractive supplement to catalytic hydrogenation with H_2. The work in this area up to 1991 was reviewed exhaustively[1]. Impressive levels of enantioselectivity have occasionally been achieved with Sm[2], Ir[3] and Ru[4] complexes, but the scope has been limited to a rather small set of aryl alkyl ketones or low turnover. In this communication we report a new highly selective and extremely active catalyst system which gives excellent results for aryl alkyl ketones, and for the first time also high turnover and promising enantioselectivity for dialkyl ketones.

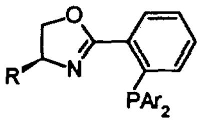
Scheme 1



Our work was induced by a recent report of Mathieu and co-workers[5] who showed for the complex $RuCl_2(PPh_3)_3$ (**1**) that replacement of PPh_3 by pyridinophosphines **2** is facile. Under conditions (co-activation with OH^-) previously worked out for catalyst **1** by Bäckvall and co-workers[6], resultant chelate complexes displayed unusually high activity (up to >100000 turnover/h) in reductions of both cycloalkanones and aryl alkyl ketones with 2-propanol. The high activity was believed to be related to the hemilabile ether arm. However, with nonracemic chiral ligands **2** no significant enantioselectivity could be induced. Considering this work, we found it surprising that a hemilabile group could lead to enhanced activity in an alcoholic reaction medium. In order to prove our point, we prepared a Ru complex with tentative stoichiometry [$RuCl_2$**3a**(PPh_3)] by reaction[7] of **1** with the phosphinooxazoline **3a**[8], without a hemilabile group. The ligand **3a** was initially chosen because it had served particularly well in asymmetric hydrosilylations of ketones[9].



2



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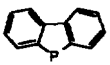
	R	PAr$_2$
3a	iPr	DBP
3b	iPr	PPh$_2$
3c	tBu	PPh$_2$

DBP =



In addition to the preformed complex, *in situ* catalysts were prepared from the parent complex **1** and ligands **3a**-**3c** (1.3 equiv). Results of the transfer reductions are displayed in Table 1.

The new complex [RuCl$_2$**3a**(PPh$_3$)], promoted with NaOH, showed excellent turnover in the reduction of alkyl phenyl ketones with isopropanol used in excess[10] (Table 1, entries 1, 11, 13). Enantioselectivities increased with the steric bulk of the alkyl substituent in the substrate and the oxazoline ligand. With isopropyl phenyl ketone the product displayed 92 %ee even after a reaction time of 30 min when 87 % conversion was reached (entry 15). This demonstrates that equilibration *via* oxidation of the alcohol is comparatively slow. Despite the steric bulk of this substrate, satisfactory levels of catalyst turnover are achieved. Selectivities obtained with the preformed catalyst and an *in situ* catalyst prepared from the same components were *grosso modo* the same. However, the preformed catalyst was distinctly more active (cf. entries 1 and 3).

With respect to reaction rates, the example of ethyl phenyl ketone is of particular interest as it allows a direct comparison with the corresponding catalyst derived from pyridinophosphine **2**: this induced 12 % conversion within 1 h (120 turnover/h)[5]; under otherwise identical reaction conditions, the complex of **3a** gave rise to 85 % conversion after 10 min (ca. 5000 turnover/h) (entry 12).

Of particular significance is the possibility that a dialkyl ketone of considerable steric bulk such as cyclohexyl methyl ketone can be reduced with a rate similar to that of propiophenone (cf. entries 16, 17). Enantioselectivity giving rise to a product of near 60 %ee is vastly superior to previous results for transfer reductions of purely aliphatic ketones, but considerable improvement is necessary.

In conclusion, ruthenium complexes of chiral phosphinooxazolines have been demonstrated to extremely efficiently catalyze the transfer hydrogenation of both purely aliphatic as well as alkyl aryl ketones to give secondary alcohols of high enantiomeric purity. The reaction displays surprising indifference to the steric bulk of the substrate which indicates extremely broad scope. Currently, vigorous efforts are being directed towards probing a variety of substrates and ligands as well as kinetic resolutions and reductions of chiral ketones (double asymmetric induction). Further efforts are devoted to characterization of the catalytically active species.

Table 1. Enantioselective Transfer Hydrogenations of Ketones Catalyzed by Phosphinooxazoline-ruthenium Complexes (temp. 82 °C, S/C = 1000)[10].

Entry	Substrate		Catalyst[a]	Reaction Time	Conversion[b]	% ee
	R^1	R^2		[min]	[%]	(Config.)[b]
1	Ph	CH_3	[RuCl$_2$**3a**(PPh$_3$)]	1	71	87 (*R*)
2				3	80	78 (*R*)
3			[RuCl$_2$(PPh$_3$)$_3$] + **3a**	1	9	91 (*R*)
4				30	37	88 (*R*)
5				60	49	86 (*R*)
6			[RuCl$_2$(PPh$_3$)$_3$] + **3b**	5	24	94 (*R*)
7				30	74	86 (*R*)
8				60	83	73 (*R*)
9			[RuCl$_2$(PPh$_3$)$_3$] + **3c**	30	81	85 (*R*)
10				60	84	79 (*R*)
11	Ph	CH_2CH_3	[RuCl$_2$**3a**(PPh$_3$)]	4	50	91 (*R*)
12				10	85	87 (*R*)
13	Ph	$CH(CH_3)_2$	[RuCl$_2$**3a**(PPh$_3$)]	4	56	93 (*R*)
14				10	74	93 (*R*)
15				30	87	92 (*R*)
16	cyclohexyl	CH_3	[RuCl$_2$**3a**(PPh$_3$)]	2	70[c]	60 (*S*)[c]
17			[RuCl$_2$(PPh$_3$)$_3$] + **3b**	60	88[c]	58 (*S*)[c]

[a] The + sign indicates use of an *in situ* catalyst prepared from the components given (m.r. = 1:1.3).

[b] Conversions and enantioselectivities were determined by gas chromatography (GLC) (Chrompack Permethyl β-CD, 50 m x 0.25 mm); retention times: acetophenone 8.9 min, (*R*)-1-phenylethanol 14.1 min, (*S*)-1-phenylethanol 17.9 min (100 °C); propiophenone 15.1 min, (*R*)-1-phenylpropanol 42.1 min, (*S*)-1-phenylpropanol 47.7 min (100 °C); 2-methyl propiophenone 10.5 min, (*R*)-2-methyl-1-phenylpropanol 34.6 min, (*S*)-2-methyl-1-phenylpropanol 36.8 min (110 °C). Absolute configurations were determined by comparing optical rotations of isolated alcohols with reference data from the literature.

[c] Conversion was determined by removal of the catalyst by filtration of samples of the reaction mixture through silica gel and GLC analysis; for determination of the enantioselectivity acetates were formed by removing the solvent *in vacuo*, dissolving the residue in pyridine and addition of 3 equiv of acetic anhydride and a catalytic amount of 4-dimethylaminopyridine; after extractive work-up the samples were analyzed by GLC (Chrompack Permethyl β-CD, 50 m x 0.25 mm); retention times: cyclohexyl methyl ketone 8.9 min, (*S*)-O-acetyl-1-cyclohexylethanol 13.9 min, (*R*)-O-acetyl-1-cyclohexylethanol 17.9 min (100 °C). The absolute configuration was determined by comparing optical rotations of the isolated alcohol with reference data from the literature.

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[7] Under argon, a solution of 288 mg (0.30 mmol) of RuCl$_2$(PPh$_3$)$_3$ and 112 mg (0.30 mmol) of **3a** in 7 ml of dry toluene was stirred at rt. After 14 h the solvent was completely removed *in vacuo* and the residue was recrystallized from chloroform/hexane to give 192 mg (79 %) of the catalyst as black needles (mp. 165-178 °C). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.69 [d, J = 6.6 Hz, 3H, CH(C$\underline{H}_3$)$_2$], 0.93 [d, J = 6.7 Hz, 3H, CH(C$\underline{H}_3$)$_2$], 2.05 [m$_c$, 1H, C$\underline{H}$(CH$_3$)$_2$], 4.54 (t, J = 8.6 Hz, 1H, OCH$_A$H$_B$), 4.85 (dd, J = 8.6 Hz, J = 10.2 Hz, 1H, OCH$_A$H$_B$), 5.12 (dd, J = 8.6 Hz, J = 8.3 Hz, CHN=), 6.45 (dd, J = 7.5 Hz, J = 8.2 Hz, 1H, Ar-H), 6.54 (d, J = 3.6 Hz, 1H, Ar-H), 7.01-7.08 (m, 7H, Ar-H), 7.19-7.36 (m, 13H, Ar-H), 7.51 (t, J = 7.5 Hz, 1H, Ar-H), 7.62 (d, J = 7.7 Hz, 1H, Ar-H), 7.78 (d, J = 8.0 Hz, 1H, Ar-H), 7.87 (t, J = 8.2 Hz, 1H, Ar-H), 8.18 (dd, J = 3.9 Hz, J = 3.5 Hz, 1H, Ar-H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 17.84 [q, CH(CH$_3$)$_2$], 23.06 [q, CH(CH$_3$)$_2$], 32.34 [d, CH(CH$_3$)$_2$], 70.74 (t, OCH$_2$), 75.07 (d, CHN=), 120.18, 120.28, 120.99 (s, C-Ar), 121.08, 127.26, 127.38, 127.84, 127.98 (d, C-Ar), 128.76. 128.89 (s, C-Ar), 129.56, 130.18, 130.65, 130.85 (d, C-Ar), 130.96 (s, c-Ar), 131.57, 131.67 (d, C-Ar), 132.20, 133.18, 133.33 (s, C-Ar), 133.74, (d, C-Ar), 134.95, 134.30 (s, C-Ar), 134.58, 1324.71 (d, C-Ar), 140.27, 141.65 (s, C-Ar), 163.03 (s, C=N). ^{31}P NMR (81.02 MHz, CDCl$_3$): δ = 44.1 ($J_{P,P}$ = 38 Hz), 80.9 ($J_{P,P}$ = 38 Hz).

[8] Preparation of phosphinooxazolines: M. Peer, J.C. de Jong, M. Kiefer, Th. Langer, H. Rieck, H. Schell, P. Sennhenn, J. Sprinz, H. Steinhagen, B. Wiese, G. Helmchen, *Tetrahedron*, in print, and work of other groups cited therein.

[9] Th. Langer, G. Helmchen, to be published.

[10] Typical procedure for the transfer reduction: Under an atmosphere of argon, 0.010 mmol of [RuCl$_2$(PPh$_3$)$_3$] and 0.013 mmol of **3** or 0.010 mmol of the isolated complex [RuCl$_2$**3a**(PPh$_3$)] were dissolved by heating to reflux in 5 ml of degassed, dry 2-propanol (bp of *i*PrOH = 82 °C) for 30 min. Then a solution of 10.0 mmol of the ketone in 3 ml of degassed, dry 2-propanol was added and the solution was refluxed for 15 min. The reaction was started by addition of a solution of 10 mg (0.25 mmol) of NaOH in 2 ml of degassed, dry 2-propanol and refluxed.

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