DOI: 10.1002/adsc.200505246

Ru-(Phosphine-Oxazoline) Complexes as Effective, Industrially Viable Catalysts for the Enantioselective Hydrogenation of Aryl Ketones

Frédéric Naud,[a,*] Christophe Malan,[a] Felix Spindler,[a] Carsten Rüggeberg,[b] Andreas T. Schmidt,[b] Hans-Ulrich Blaser[a]

[a] Solvias AG, P. O. Box, 4002 Basel, Switzerland
Fax: (+41)-61-686-6311; e-mail: frederic.naud@solvias.com
[b] Rohner AG, Gempenstr. 6, 4133 Pratteln, Switzerland

Received: June 15, 2005; Accepted: October 13, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Complexes prepared *in* situ from $RuCl_2(PPh_3)_3$ and chiral phosphine-oxazoline ligands are effective catalysts for the hydrogenation of various aryl ketones with ees up to 99% and substrate to catalyst ratios of 10,000–50,000; the reaction tolerates high substrate concentrations and a pilot process has been developed for the hydrogenation of 3,5-bistrifluoromethyl acetophenone.

Keywords: aryl ketone hydrogenation; enantioselective hydrogenation; industrial catalysis; Ru-(phosphine-oxazoline) complexes

The enantioselective reduction of aryl ketones is an important transformation both from an academic/synthetic as well as an industrial point of view.[1] Besides biocatalytic and hydride reduction methods, two different effective hydrogenation methodologies have been developed: i) transfer hydrogenations, where the reducing agent is a hydrogen donor such as formic acid or isopropanol,[2] and ii) the catalytic addition of gaseous H_2 to the ArCO double bond.[3] Interestingly, with few exceptions the two methods require different types of catalysts.[4] While a few Ru complexes are able to reduce ArC=O groups with hydrogen as well as hydrogen donors, there is no catalytic system with high ees *and* high activity for both methods. In addition, an examination of systems able to catalyze aryl ketone reductions shows that most of the effective catalysts for hydrogenation as well as transfer hydrogenation have at least one ligand with an N–H function. Noyori has convincingly explained this observation by postulating the direct addition of the C=O bond to a H–Ru–N–H moiety to give the reduced substrate H–C–O–H and Ru=N without coordinating the carbonyl group to the Ru center.[3]

Chiral oxazoline-based ligands have attracted a lot of attention in the past decade due to their ease of preparation, their modularity and their favorable coordinating properties towards a large variety of metals. Indeed, high levels of enantioselectivities have been obtained for various catalytic reactions.[5] Of special interest to us were several Ru-phosphine-oxazoline complexes (see Figure 1) described by the groups of Helmchen,[6] Sammakia[7] and Uemura[8] which are able to transfer hydrogenate aryl ketones with ees > 95% using *i*-PrOH as reducing agent. Although attractive for its simplicity and high enantioselectivity, this method has a limited synthetic potential due to low ketone concentrations, low turnover numbers (TON = 1000) and erosion of ee at long reaction times.

Due to their very high enantioselectivity we were particularly interested in the ferrocene-based Ru complexes which can also be created *in situ* from $RuCl_2(PPh_3)_3$ with somewhat lower enantioselectivities but better activities.[7] During our studies with several aryl ketones under typical transfer hydrogenation conditions we surprisingly found that catalyst activity (expressed as turnover frequency, TOF, h^{-1}) and TONs increased significantly when the reaction was carried out

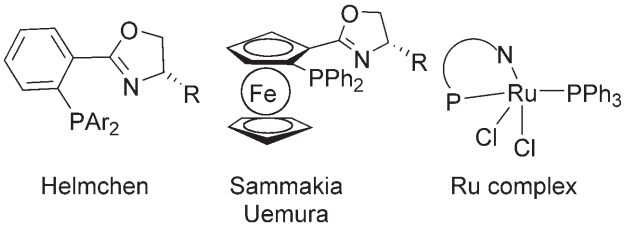

Figure 1. Structures of chiral ligands and Ru-complexes.

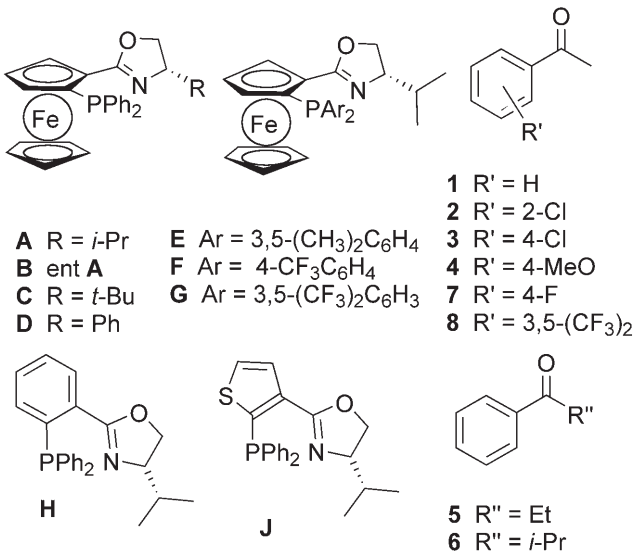

Figure 2. Structure of tested ligands and aryl ketones.

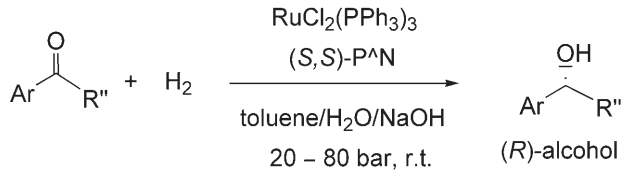

Figure 3. Reaction conditions for hydrogenation.

Table 1. Effect of ligand and ketone structure on ee.[a]

	1	2	3	4	5
A	**98.1**	94.7	95.8	95.0	**98.4**
C	95.8	93.6	94.9	95.6	**98.3**
D	**98.5**	92.9	96.6	97.5	**99.3**
E	97.2	90.2	96.4	95.7	**98.0**
F	95.0	94.3	94.1	*84.4*	96.2
G	92.9	93.2	91.9	*88.4*	93.7
H	*86.7*	*72.6*	*36.7*	*82.4*	91.6
J	96.9	90.7	95.0	95.3	96.2

[a] Reaction conditions: 0.01 mmol ligand and $RuCl_2(PPh_3)_3$; 2 mmol substrate; 2 mL toluene; 1 mL 1 molar aqueous NaOH; 80 bar; room temperature; reaction time 1 h.

under hydrogen pressure while ees were affected only slightly. We therefore investigated the effect of ligand and ketone structure as well as of other reaction parameters on catalyst performance in more detail. Here we describe a new technology which allows the hydrogenation of various aryl ketones with ees up to 99% without erosion at substrate to catalyst (S/C) ratios of 10,000–50,000, tolerates high substrate concentrations and has been scaled up to the pilot level.

Since enantioselective catalysts often have high specificity, we not only prepared a number of different ligands but tested these systematically on several aryl ketones. Phosphine-oxazolines are modular ligands which are stable towards hydrogenation and can easily be varied both on the phosphine and the oxazolines moieties. Besides the ferrocenyl-based derivatives, we also prepared and tested ligands with an aryl and heteroaryl backbone. Selected ligands as well as the investigated ketones are depicted in Figure 2.

The test hydrogenation reactions were carried out with catalysts prepared *in situ* from $RuCl_2(PPh_3)_3$ and the appropriate ligand under the conditions shown in Figure 3. Instead of the usual *i*-PrOH/*i*-PrOK solution we used a technically more practical toluene/aqueous NaOH mixture which gives a similar catalyst performance. Under these reaction conditions, GLC analysis did not show any by-products due to base-catalyzed condensation. A hydrogen pressure of 80 bar was used in most tests but it was later shown that pressures as low as 20 bar afford the same catalytic performance.

The influence of ligand and ketone structure on catalyst performance is summarized in Table 1 (ee) and Figure 4 (conversion after 1 h) and needs few comments. As already observed for the transfer hydrogenation,[7,8] the performance of the Ru complexes does not depend very much on the substituent R of the oxazolidine. We find that the same holds true for the nature of the phosphine substituents. In general, the enantioselectivities are better than 90% ee and in some cases are >98% (**bold**). For most substrates ee values as well as the conversions vary only a few percent when R (compare **A** with **C** and **D**) or Ar are changed (compare **A** with **E**–**G**). Interestingly, the replacement of the ferrocenyl moiety by an aryl or heteroaryl group also has a surprisingly small effect on the catalyst performance. With the exception of the commercially available ligand **H** which gives significantly lower ees, ligand **J** as well as two other heteroaryl based ligands (results see Supporting Information) have few values below 90% (*underlined italic*). However, as Figure 4 clearly shows, the conversion after 1 h with these ligands was consistently lower than with ligands **A**–**G** which in almost all cases was close to 100%. Regarding the effect of the substrate structure we cannot see a clear trend for the activity of the catalysts but it seems that substituents at the aryl ring generally lower the enantioselectivity anywhere from a few percent for ligands **A**–**E** to up to 60% for the other ligands. Substrate **6** (ee 97.2%) and 3-acetyl thiophene **9** (ee 93.9%) were also tested using ligand **A** but in both cases, catalyst activity was very low. Changing the methyl group in acetophenone to Et or even *i*-Pr (substrates **5** and **6**, respectively) does not affect enantioselectivity very much but, as expected, conversions after 1 h are significantly lower.

This new hydrogenation catalyst containing ligand **A** was also applied under industrially more relevant conditions. Three model reactions (substrates **1**, **3** and **7**) were carried out with S/C ratios of 10,000 to 50,000. The selected results presented in Table 2 show that technically

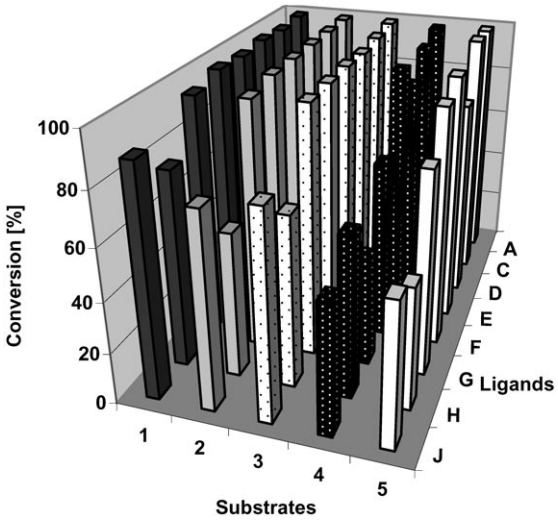

Figure 4. Effect of ligand and ketone structure on conversion (reaction conditions see Table 1).

feasible TONs and TOFs can be obtained with several substrates. The reaction can be run at very high concentrations (entries 2 and 3), even though reaction times increase significantly, there is no ee erosion (compare entries 1 and 3). The isolated [$RuCl_2$(**A**)(PPh_3)] complex gives the same performance as the *in situ* prepared catalyst (compare entries 5 and 6).

Furthermore, starting with substrate **8** we developed a technical process for the production of 3,5-$(CF_3)_2$-phenyl ethanol, a chiral building block for an NK-1 receptor antagonist.[9] Details will be published elsewhere, here we will only briefly describe our most important findings. Since a limited ligand screening showed again only small variations in ee (91–95%), ligand **A** was chosen for further development. The following parameters were investigated and optimized: Nature and quantity of the base (aqueous NaOH was clearly superior, weaker bases were not suitable), temperature (only 85% ee at 75 °C, see entry 8), isolated *vs. in situ* formed catalyst (an induction period was often observed for the isolated complex but otherwise with the same catalyst performance) and purity of the substrate which turned out to be the most important parameter affecting TON and TOF. S/Cs of up to 50,000 were possible but required very long reaction times and gave somewhat lower ees (see entry 10). The optimized process was run twice with 140 kg of substrate in a 4 m^3 hydrogenation reactor with an S/C ratio of 20,000 at 20 bar and 25 °C. The ee values were 95 and 96%, respectively, and full conversion was reached after 15 h.

In conclusion, we have shown that Ru-(phosphine-oxazoline) complexes are not only highly selective transfer hydrogenation catalysts but are also very effective for the hydrogenation of aryl ketones using H_2 with ees of 95–99% and TONs of up to 50,000. This compares well with several recently published catalysts for aryl ketone hydrogenation such as Ru/phanephos/dpen[10] or Ru/p-phos/dpen[11] which are also able to hydrogenate various aryl ketones with high ees as well as high TONs and TOFs.

In contrast to the catalyst system described by Noyori or the cited analogues thereof, the Ru-(phosphine-oxazoline) complexes do not contain an N–H group. Since the hydrogenation of the oxazoline is very unlikely under these conditions, this means that the pathway involving reaction of the C=O bond with an H–Ru–N–H moiety cannot be operative. While there is no experimental evidence, a plausible alternative is a classical C=O coordination-insertion mechanism.[12] The function of the indispensable strong base could be to assist the heterolytic activation of H_2 typical for ruthenium catalysts. The effect of the substrate and ligand structure on the catalyst performance is relatively small both for the various phosphine-oxazolines as well as for the aryl alkyl ketones. Since analogues of $RuCl_2(PPh_3)_3$ or of isolated

Table 2. Effect of various parameters on the performance of **A**/$RuCl_2(PPh_3)_3$.

Entry	Substrate	P [bar]	S/C	Time [h]	Conversion [%]	ee [%]	TOF [h^{-1}]	Comments
1	**1**	80	10,000	1	98	98.5	9,800	50 mmol/18 mL toluene
2	**1**	80	10,000	6	98	98.5	1,633	50 mmol/no toluene
3	**1**	80	50,000	78	99	99.0	635	250 mmol/2 mL toluene
4	**3**	20	20,000	1	92	96.2	18,400	
5	**7**	20	20,000	19	100	96.0	1,050	
6[a]	**7**	20	20,000	19	99	97.4	1,040	
7[a]	**8**	20	500	1	100	95.0	500	2.34 mmol
8[a, b]	**8**	20	500	1	100	85.0	500	2.34 mmol
9[a]	**8**	20	10,000	2.3	100	96.0	4,500	586 mmol/1.44 L toluene/60 mL NaOH
10[a]	**8**	20	50,000	92	99	94.3	500	3.75 mol/0.35 L toluene/150 mL NaOH
11	**8**	20	20,000	15	100	96.0	1,660	547 mol; 4000-L reactor

Reaction conditions: In situ catalyst with ligand **A** and $RuCl_2(PPh_3)_3$; 100 mmol substrate; 9–12 mL toluene; 1 mL 1 molar aqueous NaOH; 25 °C.
[a] Isolated $RuCl_2$(**A**)(PPh_3) complex.
[b] At 75 °C.

$[RuCl_2(PN)(PPh_3)]$ complexes with phosphines other than PPh_3 are not easily accessible, the effect of this auxiliary ligand has not yet been investigated.

To the best of our knowledge this is the first system which can both transfer hydrogenate and hydrogenate aryl ketones with high ee *and* high efficiency and also the first industrial catalytic process with an oxazoline based ligand.

Experimental Section

Ligands **A**–**D** were prepared as described in ref.[8b] and **J** as described in ref.[13] For the preparation of ligands **E**–**G** see Supporting Information, ligand **H** is available from Strem. The catalyst precursor $RuCl_2(PPh_3)$ was prepared according to ref.[8a]

General Hydrogenation Procedure

The catalyst is prepared *in situ* by allowing 0.1 mmol of ligand and 0.1 mmol of $[RuCl_2(PPh_3)_3]$ in 20 mL of toluene to react for 2 h under reflux. The catalyst solution is transferred to the inertized mini-autoclave and the substrate and the base are subsequently added. The autoclave is sealed and pressurized with hydrogen to the desired pressure. The reaction is started by switching on the stirrer. When the hydrogenation time has elapsed, the stirrer is switched off and the autoclave is ventilated. Conversion and ee are determined *via* GC analysis on a Beta-Dex 110 column (for details see Supplementary Information).

Acknowledgements

We thank Andrea Holderer, Oanh Mai-Huynh, Stefan Modin, Thomas Stebler and Horatio Tagliente for skillful laboratory work, and Prof. L. Tietze for ligand samples.

References

[1] a) T. Ohkuma, M. Kitamura, R. Noyori in: *Catalytic Asymmetric Synthesis*, 2nd edn, (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**, p. 1; b) T. Ohkuma, R. Noyori in E. N. Jacobsen, H. Yamamoto, A. Pfaltz (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Berlin, **1999**, p 199.

[2] a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97; b) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry* **1999**, *10*, 2045; c) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, *92*, 1051.

[3] R. Noyori, T. Ohkuma, *Angew. Chem. Int. Ed*. **2001**, *40*, 40.

[4] V. Rautenstrauch, X. Hoang-Cong, R. Churlaud, K. Abdur-Rashid,, R. H. Morris, *Chem. Eur. J.* **2003**, *9*, 4954.

[5] a) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151; b) O. B. Sutcliffe, M. R. Bryce, *Tetrahedron: Asymmetry* **2003**, *14*, 2297; c) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336.

[6] T. Langer, G. Helmchen, *Tetrahedron Lett.* **1996**, *37*, 1381.

[7] T. Sammakia, E. L. Stangeland, *J. Org. Chem.* **1997**, *62*, 6104.

[8] a) Y. Nishibayashi, I. Takei, S. Uemura, M. Hidai, *Organometallics* **1999**, *18*, 2291; b) Y. Arikawa, M. Ueoka, K. Matoba, Y. Nishibayashi, M. Hidai, S. Uemura, *J. Organomet. Chem.* **1999**, *572*, 163.

[9] K. B. Hansen, J. R. Chilenski, R. Desmond, P. N. Devine, E. J. J. Grabowski, R. Heid, M. Kubryk, D. J. Mathre, R.Varsolona, *Tetrahedron: Asymmetry* **2003**, *14*, 3581.

[10] D. Chaplin, P. Harrison, J. P. Henschke, J. C. Lennon, G. Meek, P. Moran, C. J. Pilkington, J. A. Ramsden, S. Watkins, A. Zanotti-Gerosa, *Org. Process Res. Devel*. **2003**, *7*, 89.

[11] J. Wu, J.-X. Ji, R. Guo, C.-H. Yeung, A. S. C. Chan, *Chem. Eur. J.* **2003**, *9*, 2963.

[12] S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248,* 2201.

[13] L. Tietze, J. K. Lohmann, *Synlett* **2002**, *12*, 2083.

