Pergamon

Tetrahedron Letters, Vol. 38, No. 37, pp. 6603-6606, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01522-0

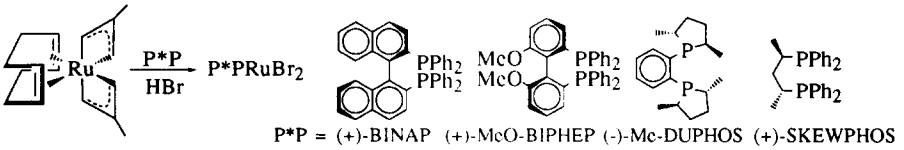
Skewphos-Ru(II) : An Efficient Catalyst for Asymmetric Hydrogenation of Functionalized Ketones

Delphine Blanc, Jean-Christophe Henry, Virginie Ratovelomanana-Vidal, Jean-Pierre Genêt

Laboratoire de Synthèse Organique, Associé au C.N.R.S., Ecole Nationale Supérieure de Chimie de Paris, 11 rue P. et M. Curie, 75231 Paris Cedex 05, France.

Abstract *: Asymmetric hydrogenation of prochiral keto groups with (S,S) and (R,R)- SkewphosRuBr$_2$ prepared in situ is described. Good enantiomeric excesses up to 95% were obtained.* © 1997 Elsevier Science Ltd.

It is now well established that homogeneous Ru(II)-catalyzed asymmetric hydrogenation is a highly efficient technology.[1] The development of new systems capable of catalyzing homogeneous asymmetric hydrogenation for a wide variety of prochiral substrates is highly desirable. The most commonly used P*PRuX$_2$ (figure 1) are those containing atropoisomeric chiral diphosphines[2,3] such as Binap **1** or MeO-Biphep **2**, etc... Having developed a general *in situ* preparation of chiral Ru(II)-catalysts[3], we found that bis(phospholane) ligands[4a] such as Me-DuPHOS **3** were efficient for the asymmetric hydrogenation of various prochiral olefins and keto groups.[3] This was extended to chiral bis(phospholane) ligand BPE[4b] that allowed highly enantioselective hydrogenation of β-keto esters. Less attention has been focused on Ru-Skewphos **4**[5] mediated hydrogenation although this 1,3-substituted diphosphine showed a high efficiency in rhodium asymmetric hydrogenation.[5a,6]



P*P = (+)-BINAP (+)-MeO-BIPHEP (-)-Me-DUPHOS (+)-SKEWPHOS

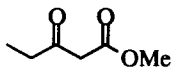
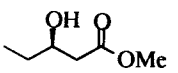
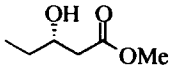
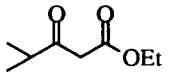
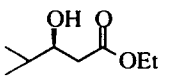
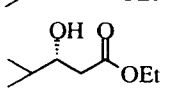
1 **2** **3** **4**

figure 1

In our preliminary studies, low enantioselectivities (22% e.e.) were obtained in the asymmetric hydrogenation of methyl acetoacetate carried out at 80°C under 20 atm hydrogen pressure with *(S,S)*-SkewphosRuBr$_2$ preformed in two steps.[3] Recently, Brunner et al. described that [Ru(C$_6$H$_6$)Cl$_2$]$_2$ complexed with Skewphos was an efficient catalyst for asymmetric hydrogenation of 2,4-pentanedione.[5c] Thus, we anticipated that the ruthenium-Skewphos mediated hydrogenation might be dependent of reaction conditions.

e-mail : genet@idf.ext.jussieu.fr

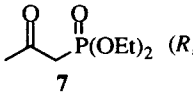
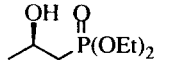
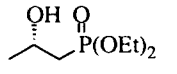
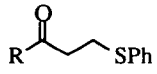
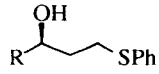
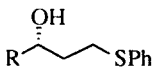
Table 1 : Asymmetric hydrogenation of β-keto esters with *(R,R)* and *(S,S)* Skewphos-Ru(II) catalysts

Entry	Substrate	Ligand[a]	Conditions			Product	Yield[b]	e.e[c]
			P (bars)	Temp. (°C)	Time (h)			
1	 **5**	(*R,R*)-Skewphos	10	30	24		100	89
2	"	(*S,S*)-Skewphos	10	30	24		100	89
3	 **6**	(*R,R*)-Skewphos	10	40	24		100	90
4	"	(*S,S*)-Skewphos	10	40	24		100	91

(a) Chiral Ru (II) catalyst (1% mol.). (b) Yields are determined by ^{1}H NMR (c) E. e. were determined by GC analysis (lipodex A, column)

These results were extended to the β-ketophosphonate 7 and the phenylthio ketones **8** and **9** using (*R,R*) and (*S,S*)-Skewphos (table 2). All reactions were carried out under 30 bars and room temperature. Under these conditions, diethyl 2-oxopropylphosphonate **7** was quantitatively reduced using the two enantiomers of Skewphos with 95% and 94% of optical purities (entries 5 and 6). In the case of functionalized ketones **8** and **9** bearing a sulfur group, the hydrogenation of 4-phenylthio-2-butanone **8** and 5-phenylthio-3-pentanone **9** performed with (*R,R*) and (*S,S*)-Skewphos afforded (*R*) and (*S*)-4-phenylthio-2-butanol[8] with 92% and 94% e.e. (entries 7 and 9) and (*R*) and (*S*)-5-phenylthio-3-pentanol with 88% and 95% of enantioselectivity (respectively entries 8 and 10).

Table 2 : Asymmetric hydrogenation of β-keto phosphonate and phenylthio sulfides.

Entry	Substrate	Ligand[a]	Conditions			Product	Yield[b]	ee[c]
			P (bars)	Temp. (°C)	Time (h)			
5	 **7**	(*R,R*)-Skewphos	30	r.t.	60		100	95
6	"	(*S,S*)-Skewphos	30	r.t.	60		100	94
		(*R,R*)-Skewphos						
7	**8**-R = Me		30	r.t.	30		97	92
8	**9**-R = Et		30	r.t.	30		96	88
		(*S,S*)-Skewphos						
9	**8**-R = Me		30	r.t.	30		100	94
10	**9**-R = Et		30	r.t.	30		100	95

(a) Chiral Ru (II) catalyst (1 to 2% mol.). (b) Yields are determined by ^{1}H NMR (c) E. e. were determined by GC analysis (Megadex 5 column).

Indeed, careful studies in the asymmetric hydrogenation of methyl acetoacetate as standard substrate demonstrated that adequate choice of conditions (temperature, pressure) were required to obtain high enantioselectivities (figure 2).

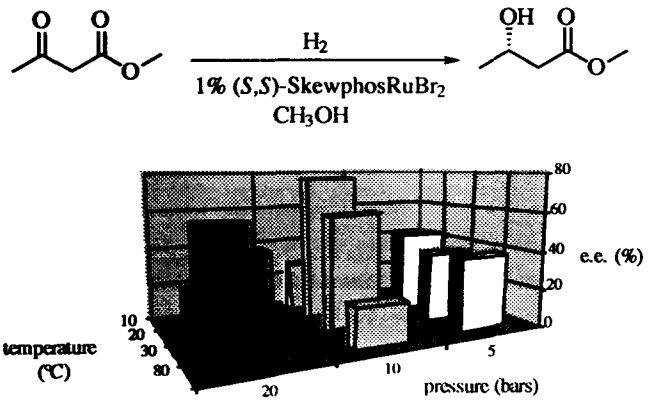
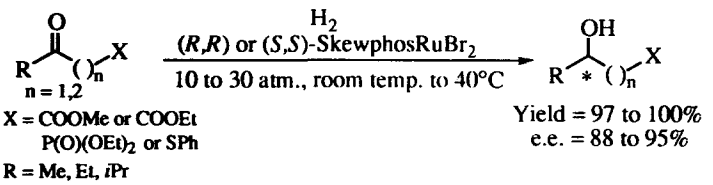


figure 2

As shown in figure 2, enantiomeric excess of (*S*)-β-hydroxybutyrate is highly dependent on the reaction temperature. An increase in enantioselectivity was observed by lowering the temperature and when the hydrogenation was performed under 20 atm of hydrogen pressure, the best selectivity was reached at room temperature (e.e. 58%). At lower pressure (10 bars), the same temperature effect is observed with a maximum selectivity of 77% at 25°C although under 5 bars, the hydrogenation reaction proceeded with fair enantioselectivity whatever the temperature. This spectacular temperature effect may be due to conformationnal effect of the catalyst.[7] Therefore under these optimized conditions, the (*R*,*R*) and (*S*,*S*)-SkewphosRuBr$_2$ catalysts prepared[3] ***in situ*** from CodRu(2-methylallyl)$_2$ were highly efficient for homogeneous asymmetric hydrogenation of a wide range of functionalized keto groups (scheme 1).



Scheme 1

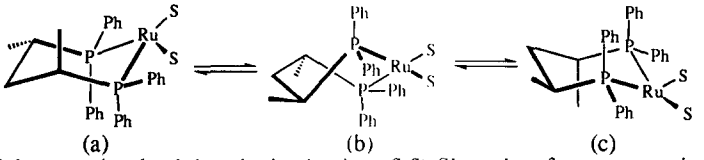
As shown in Table 1, some β-keto esters were quantitatively hydrogenated under 30°C or 40°C and 10 bars of hydrogen pressure to secondary alcohols with high chemical yields and satisfactories e.e.'s. Asymmetric hydrogenation was extended to methyl 3-oxopentanoate **5** (entries 1 and 2) leading to the two β-hydroxyesters enantiomers with a 89% enantiomeric excess. A good selectivity was also obtained for the asymmetric hydrogenation of ethyl 4-methyl-3-oxopentanoate **6** affording (*R*) and (*S*)-ethyl-4-methyl-3 hydroxypentanoate, respectively with 90% and 91% of enantioselectivity (entries 3 and 4).

In summary, asymmetric syntheses of optically enriched alcohols were achieved with good enantiomeric excesses up to 95% using both enantiomers of SKEWPHOS. A general orientation of the enantioselectivity is observed allowing a general prediction of the absolute configuration of the alcohols by the appropriate choice of SKEWPHOS.

Acknowledgement : We thank Dr P. Savignac for sample of β-keto phosphonates.

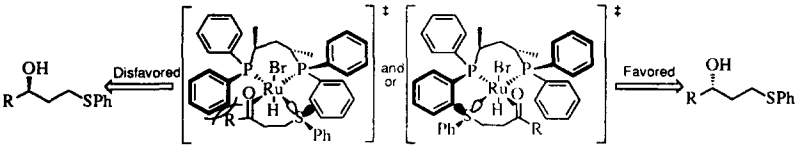
References

1. Noyori , R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97-102. Genêt J. P. *in Reductions in Organic Synthesis in A.C.S. symposium series 641*, **1996**, pp 31-51. Genêt, J. P. *Acros Chim. Acta* **1995**, *1*, 4-9. Noyori, R. *Asymmetric Catalysis Synthesis*, J. Wiley, N. Y. **1994.** Takaya, H.; Ohta, T.; Noyori, R. *Catalytic Asymmetric Synthesis* , I. Ojima, N.Y. **1993**. Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345-350.
2. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R.; *J. Am. Chem. Soc.* **1980**, *102*, 7932-7934. Schmid R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure and Appl. Chem*, **1996**, *68*, 131-138.Schmid, R.; Foricher, J. Cereghetti, M.; Schönholzer, *Helv. Chim. Acta* **1991**, *74*, 370-388. Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, H.-J. Hansen, *Helv. Chim. Acta* **1988**, *71*, 897-929.
3. a) Genêt, J.-P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S; Pfister, X.; Caño de Andrade, M. C.; Laffitte, J.A. *Tetrahedron:Asymmetry* **1994**, *5*, 665-674. b) Genêt, J.-P.; Pinel, C.; Ratovelomanana-Vidal, V. ; Mallart, S.; Pfister, X.; Bischoff, L.; Caño de Andrade, M.C.; Darses, S.; Galopin, C.; Laffitte, J.A. *Tetrahedron : Asymmetry* **1994**, *5*, 675-690. d) Tranchier, J.-P., Ratovelomanana-Vidal, V., Genet, J.-P.; Tong, S.; Cohen, T. *Tetrahedron Lett.* **1997**, *38*, 2951-2954.
4. a) Burk, M. J.; Harper, T. G. P.; Kalberg, C. S.; *J. Am. Chem. Soc.* **1995**, *117*, 4423-4424. b) Burk, M. J., Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125-10131.
5. Both enantiomers of Skewphos (also named BDPP : 2,4-bis(diphenylphosphino)pentane) are commercially avalaible. For some syntheses of SKEWPHOS, see a) MacNeil, P. A.; Roberts, N. K.; Bosnish, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273-2280. b) Bakos, J.; Toth, I.; Heil, B.; Marko, L. *J. Organomet. Chem*, **1985**, *279*, 23-29. c) Brunner, H.; Terfort, A. *Tetrahedron : Asymmetry* **1995**, *6*, 919-922.
6. Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett*, **1992**, 169-178.
7. According to Bosnich's group, by comparison with rhodium chemistry and catalytic hydrogenation of dehydroaminoacids, the Ru-catalyst may adopt a six membered chelate system for which the chelate ring is stabilized in a chiral skew conformation (b) with both methyl groups in a preferred equatorial disposition rather than the two chair conformation (a) and (c) having one destabilizing axially disposed methyl group and the phenyl groups which are not disposed in a chiral array in respect to ruthenium center.



(a) (b) (c)

8. The sense of the enantioselectivity obtained using (*S,S*)-Skewphos for asymmetric hydrogenation of phenyl thiosulfides could be explained by the preferred transition state where interactions between the phenyl group of the Skewphos and the alkyl chain of the keto group are minimized.



(*Received in France* 20 *June* 1997; *accepted* 22 *July* 1997)