Pergamon

Tetrahedron Letters, Vol. 36, No. 27, pp. 4801-4804, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00873-X

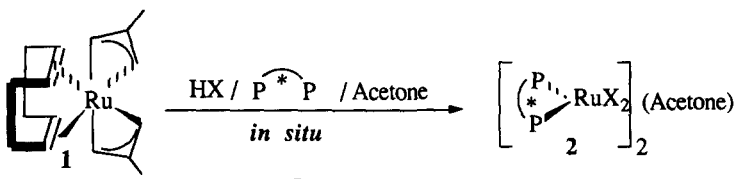
Practical Asymmetric Hydrogenation of β-Keto Esters at Atmospheric Pressure using Chiral Ru (II) Catalysts

J. P. Genêt*, V. Ratovelomanana-Vidal, M.C. Caño de Andrade, X. Pfister, P. Guerreiro, J. Y. Lenoir

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.

Key words: Asymmetric Hydrogenation, Chiral Ruthenium (II) Catalysts, β-keto esters, β-hydroxy esters, atmospheric pressure.
Abstract : New practical conditions of asymmetric hydrogenation of β-keto esters with chiral Ru(II) catalysts are described. It is now possible to carry out the reaction at **atmospheric pressure**. Under these conditions, β-keto esters are hydrogenated to β-hydroxy esters with excellent enantiomeric excesses (up to 99%) using chiral ruthenium (II) catalysts easily prepared *in situ* by treatment of commercially available (COD)Ru(2-methylallyl)$_2$ in the presence of the appropriate chiral ligands such as Binap, MeO-Biphep and Me-Duphos.

The first transition-metal catalysis using Binap-Ru complex in homogeneous phase for the enantioselective hydrogenation of β-keto esters was developed by Noyori and coworkers.[1] We have also recently developed a general synthesis[2a-e] of chiral diphosphine-ruthenium (II) catalysts preformed or prepared *in situ* from commercially available (COD)Ru(2-methylallyl)$_2$[2a,13] **1** (Scheme 1).

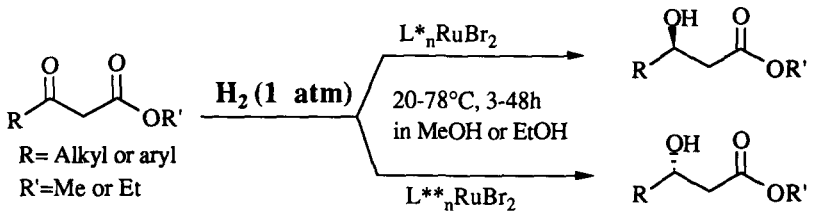


(P, * P) =Me-Duphos, Binap, MeO-Biphep, Biphemp

Scheme 1

These complexes have been found to be very effective homogeneous catalysts for asymmetric hydrogenation of various substrates such as β-keto esters[2c], cyclic β-keto esters[3] as well as 2-chloro 3-keto esters[4] with dynamic kinetic resolution. Recently, the enantioselective reduction of β-keto esters to β-hydroxy esters with chiral Ru (II) catalysts as the key step for the synthesis of various compounds such as carbacephem[5], Tetrahydrolipstatin[6] or (+)-Brefeldin A[7] was greatly used. To the best of our knowledge, all reports concerning such reductions required moderate to high pressure (35-100 atm[1,6b,8]). Only few asymmetric reactions were conducted under 3-4 atm hydrogen pressure with [(R)-Binap][*p*-cymene]$RuCl_2$[6a] or (R)-$(Binap)_2RuCl_2$,NEt_3[9] and more recently with cationic Ru (II) complexes.[10] It was of interest to find milder conditions particularly regarding hydrogen pressure. We report in this letter that our catalysts, prepared *in situ* from (COD)Ru(2-methylallyl)$_2$ **1**, are highly efficient for the asymmetric hydrogenation of β-keto esters

at **atmospheric hydrogen pressure** with high enantioselectivity. The catalysts $Ph_2P^*PPh_2RuBr_2$ ($Ph_2P^*PPh_2$=Binap, MeO-Biphep, Me-Duphos) are easily prepared from (COD)Ru(2-methylallyl)$_2$ **1**. [13] As we reported earlier [2e], the hydrogenation at 50-80°C under 6 to 20 atm of hydrogen was complete leading to the β-hydroxy esters in quantitative yield with high enantiomeric excesses. Interestingly, using our catalysts, satisfactory results were obtained at atmospheric hydrogen pressure. Our asymmetric hydrogenations were routinely carried out at a catalyst level of 2 mol% in methanol or ethanol (Scheme 2).



L* = (R)-Binap or (R)-MeO-Biphep

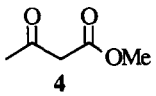
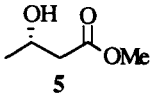
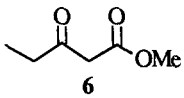
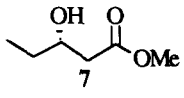
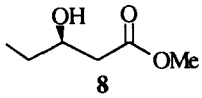
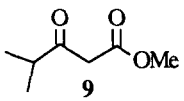
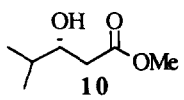
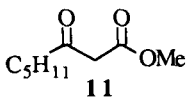
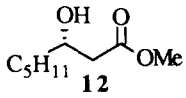
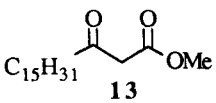
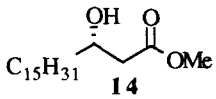
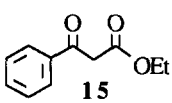
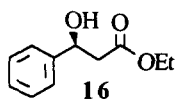
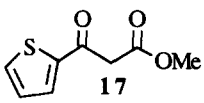
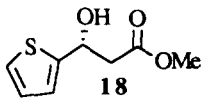
L** = (S)-Binap or (S)-MeO-Biphep

Scheme 2

Some examples of enantioselective hydrogenations using this procedure are given in Table 1. The hydrogenation of methyl-3-oxobutanoate **4** as a standard substrate was first tried. We were pleased to find that the β-keto ester **4** was reduced to (S)-hydroxybutyrate **5** with our chiral Ru (II) catalysts containing (S)-Binap, at 1atm of hydrogen and room temperature, with a good yield (80%) and high enantioselectivity (97% e.e., entry 1). Complete conversion was obtained at higher temperature (50°C). The enantioselective hydrogenation of methyl-3-oxopentanoate **6** using either (S)-Binap or (R)-MeO-Biphep proceeded smoothly with an extremely high enantiofacial discrimination (99% e.e.) leading respectively to the β-hydroxy esters **7** or **8** having the (R) or (S) absolute configuration (entries 2 and 3). Similarly, methyl-4-methyl-3-oxopentanoate **9** was quantitatively hydrogenated to **10** (entry 4) at 60°C with 97% e.e. Methyl-3-oxooctanoate **11** was hydrogenated quantitatively to **12** at 50°C in 5 hours with 97% e.e. using (S)-MeO-Biphep as ligand (entry 5) whereas methyl-3-oxooctadecanoate **13** having a longer alkyl chain required higher temperature (78°C). Under these conditions, the asymmetric hydrogenation proceeded smoothly leading quantitatively to **14** with 96% e.e.(entry 6). This study was then extended to β-keto esters having an aromatic chain, ethylbenzoylacetate **15** and methyl-3-oxo-3-(2-thiophenyl)propanoate **17** which were reduced respectively to the β-hydroxy esters **16** and **18** (96% and 87% e.e., entries 7 and 8). Interestingly, under these conditions, (R)-3-hydroxy-3-phenylpropionate **16** was obtained in a significant higher e.e. (96% e.e., entry 7) than described earlier[1] using (R)-MeO-Biphep as ligand. Furthermore, encouraging results were obtained for the reduction of **15** to **16** using (R)-Me-Duphos[14] as ligand (73% yield, 78% e.e.).

The interesting feature of our method resides on the easy accessibility of our chiral Ru (II) catalysts from commercially available (COD)Ru(2-Methylallyl)$_2$[2a,13] **1**. Moreover, our technique avoids the usual limitations of special apparatus such as stainless steel autoclave or Parr apparatus. The methodology described here compares favourably both with microbial and yeast-mediated transformations[12] to effect enantioselective reductions of β-keto esters and also with previous chemical transformations all requiring the use of pressure. This technique should be useful for most synthetic purposes.

Table 1 : Asymmetric Hydrogenation [a],[b] of β-keto esters using Ru (II) catalyst at atmospheric pressure

Entry	Substrate	Ligand	Conditions		Product	Yield	e.e.[c]
			Temp. °C	Time h			
1	 **4**	(S)-Binap	r. t.	48	 **5**	80	97
2	 **6**	(S)-Binap	50	3.5	 **7**	100	99
3		(R)-MeO-Biphep	50	48	 **8**	100	99
4	 **9**	(S)-Binap	60	48	 **10**	100	97
5	 **11**	(S)-MeO-Biphep	50	5	 **12**	100	97
6	 **13**	(S)-Binap	78	48	 **14**	100	96
7	 **15**	(R)-MeO-Biphep (R)-Me-Duphos	50 50	44 44	 **16**	82 73	96 78
8	 **17**	(S)-Binap	50	3	 **18**	100	87

(a)Chiral Ru (II) catalyst[2, 11] (2% mol).
(b)All hydrogenations were carried out in a Schlenk tube under 1 atm of hydrogen.
(c) Enantiomeric excesses were determined by GC analysis (Lipodex A column or DB 1701 column for (S)-(O-acetyl)lactyl esters).

Acknowledgements : We thank CNPq (Brazil) for a grant to M. C. Caño de Andrade and Elf Aquitaine for a grant to X. Pfister. We thank Dr. E. Broger and Dr. R. Schmid (Hoffman La Roche) for samples of (R)-(+)-MeO-Biphep = (R)-(+)-6,6'-Dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl and (S)-(-)-MeO-Biphep.

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11. Preparation *in situ* of the (P*P)RuBr$_2$: (S)-Binap (8 mg, 0.013 mmol.)and (COD)Ru(2-methylallyl)$_2$ (4 mg, 0.013 mmol) were placed in a 10 ml Schlenk tube and the vessel was purged with argon. 2 ml of anhydrous acetone (degassed by 3 cycles of vacuum/argon at r.t.) were added. To this suspension was added a solution of HBr (0.11 ml of a 0.29 M solution prepared by diluting 48% aq HBr in MeOH) and the suspension was stirred 30 min at r. t. A yellow solid precipitated. The mixture was evaporated under vacuum and the resulting catalyst was used immediatly for hydrogenation.
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(*Received in France* 14 *April* 1995; *accepted* 16 *May* 1995)