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Dynamic Kinetic Resolution of Cyclic β-Ketoesters with Preformed or Prepared *in situ* Chiral Diphosphine-Ruthenium (II) Catalysts

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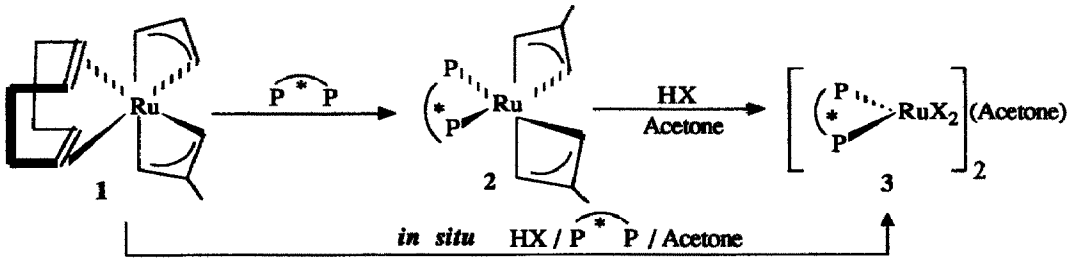
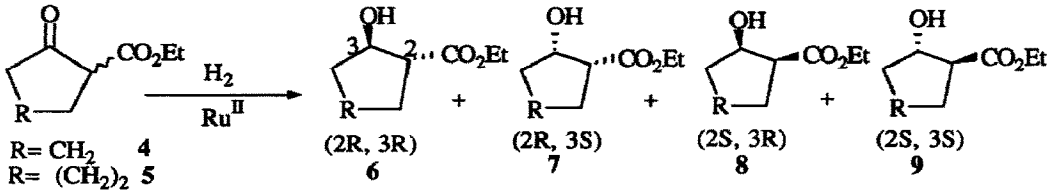
Key Words: Asymmetric Hydrogenation, Chiral Ruthenium Catalysts, β-Hydroxy Esters
Abstract: The reduction of racemic β-keto esters having the tetralone structure by chiral ruthenium(II) catalysts is realized with an ideal kinetic dynamic resolution. Remarkably, high *anti* selectivity approaching 100% and enantioselectivity (up to 97%) using atropisomeric ligands are obtained. The trans β-hydroxy esters thus available are useful starting materials for production of enantiomerically pure compounds.

Asymmetric hydrogenation using the BinapRu(η^2-O_2CCH_3)$_2$ has been introduced by Noyori and Takaya[1] and [BinapRuCl$_2$]$_2$NEt$_3$ by Ikariya and Saburi[2]. These catalysts have found wide application in asymmetric hydrogenation with outstanding performances[3].We have also discovered a new class of mononuclear chiral Ru^{II} catalysts : (P*P)Ru(η_3-2-methylallyl)$_2$[4]. Our synthetic general method allows the production of ruthenium complexes from a wide variety of diphosphines including diphosphines having chirality at the phosphorus atom such as Dipamp [5]. This synthesis uses the very easily accessible (cod)Ru(η_3-2-methylallyl)$_2$[6] **1** complex as starting material. These complexes (P*P)Ru(η_3-2-methylallyl)$_2$ **2** have shown high efficiency in asymmetric hydrogenation. They are suitable for the preparation of chiral (P*P)RuX$_2$ **3** bearing a whole set of chiral diphosphines (e.g. P*P=DIOP, CBD, BINAP, BIPHEMP, CHIRAPHOS, PROPHOS, DIMPC, BPPM, BDPP, etc) and previously used in a powerful dynamic kinetic resolution of 2-acylamino-3-oxo butyrates[7]. In addition, we have found[8] (scheme 1) that it was also possible to prepare these same catalysts **3** directly ***in situ*** from (cod)Ru(η_3-2-methylallyl)$_2$ **1** by adding in acetone at room temperature 1-1.3 equiv. of the appropriate chiral ligand in the presence of HBr. These complexes can be used as crude catalysts and this procedure allows a rapid screening of chiral ligands in Ruthenium-mediated reactions.



Scheme 1

The Ru-catalyzed asymmetric reduction of racemic 2-substituted keto esters is a powerful synthetic tool. Use of BinapRu^{II} complex allowed selective formation of one stereoisomer among the four possible isomers. Using preformed (P*P)RuBr$_2$ catalysts, this so-called dynamic kinetic resolution [3,9] has simultaneously been discovered by us [7]. Thus, it was of interest to investigate, using our complexes, the stereoselectivity of this process from racemic cyclic 2-substituted-3-oxo carboxylic esters .We report the asymmetric hydrogenation of 2-(ethoxycarbonyl)cyclopentanone **4**, 2-(ethoxycarbonyl)cyclohexanone) **5** .The reduction should in principle provide a mixture of the four possible stereoisomers **6, 7, 8, 9** (scheme 2). A study as summarized in Table 1 has revealed that the stereochemical course of the reduction with (P*P)RuX$_2$ was noticeably influenced by the structures of the substrates and reaction conditions. Inspection of the data on the catalyzed reduction by Ruthenium complexes bearing (R,R)-cbd and (S,S)-chiraphos ligands revealed that under 100 atm of hydrogen pressure and 1% of catalyst, the racemic substrate **4** was reduced quantitatively to **6** and **9** with a trans selectivity (71 to 72%) and poor to moderate enantioselectivities (10% and 40% e.e., respectively entries 1-2). Under the same conditions, with the *in situ* (R)-binapRuBr$_2$, the hydrogenation of **4** proceeded with 92% trans selectivity giving **6** with high chiral recognition (85% e.e., entry 3).



Scheme 2

Using a lower pressure of hydrogen (20 atm.) at 80°C for 2h, the preformed (R)-binapRuBr$_2$ afforded **6** with high enantioselectivity (94% e.e.) in 50% yield (entry 4).

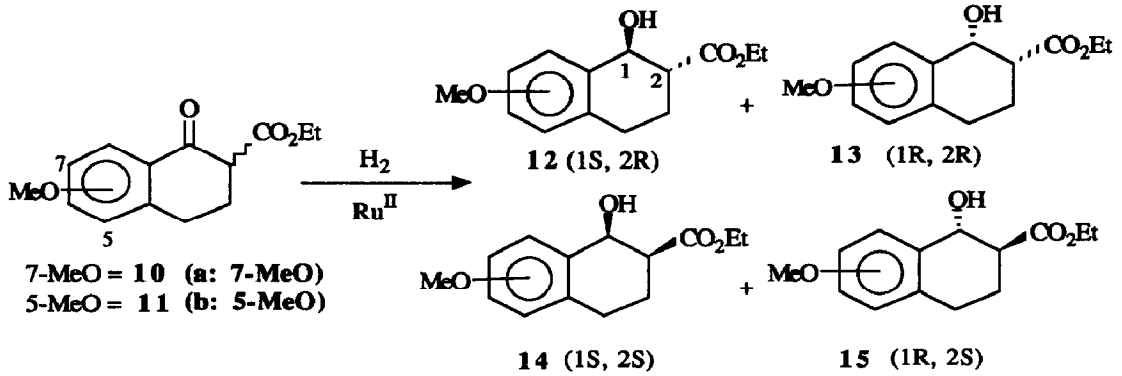
Table 1 Hydrogenation of 2-(ethoxycarbonyl)cyclanones **4** and **5** with Ru(II) Catalysts

Entry	Substrate	Catalyst (%)	Conditions (a)			Yield (%)	d.e.(b) (%)	e.e.(trans) (%)	e.e.(cis) (c) (%)
			Press atm.	Temp. °C	Time h	(a)			
1	4	(R,R)-cbd Ru(all)$_2$ (1)	100	80	48	100	72(trans)	10(R, R)	11(S, R)
2	4	(S,S)-chiraphosRuBr$_2$ (1)	100	20	48	100	71 (trans)	40(S, S)	34(R, S)
3	4	*in-situ* (R)-binapRuBr$_2$ (1)	100	80	48	100	92(trans)	85(R, R)	23(S, R)
4	4	(R)-binapRuBr$_2$ (1)	20	80	2	50	94(trans)	94(R, R)	95(S, R)
5	5	(R)-binapRuBr$_2$ (1)	20	80	2	100	8(cis)	97(R, R)	88(R, S)
6	5	(S)-binapRuBr$_2$ (1)	20	80	3	100 (d)	47(trans)	91(S, S)	82(S, R)

a) Reactions were carried out in MeOH ; (b) The diastereoisomeric excesses were mesured by G.C. analysis (OV 1701 column) ; (c) e.e. determined by G.C.(OV 1701 column) analysis of (L) Lactic Acid O-acetyl ester ;(d) Hydrogenation carried out in CH_2Cl_2.

By contrast, the reduction of 2-(ethoxycarbonyl)cyclohexanone **5** in methanol using the same preformed BinapRu catalyst proceeded with poor diastereoselectivity to give (cis/trans 56 : 44) with a high enantioselectivity up to 97% e.e. (entry 5). Under the same conditions in dichloromethane, the reverse selectivity was observed with (S)-binapRuBr$_2$ (trans/cis 76 : 23) and with high enantioselectivity (up to 91%

e.e., entry 6). The efficiency of this powerful dynamic kinetic resolution was profoundly affected by the nature of the substrate skeleton[9]. Using this new technology, we then investigated the hydrogenation of racemic β-keto esters containing the tetralone structure (e.g. 7-methoxy and 5-methoxy-2-(ethoxycarbonyl) tetralones **10** and **11** (scheme 3). This asymmetric hydrogenation should in principle provide a mixture of **12, 13, 14, 15.**



Scheme 3

Table 2 Hydrogenation of Tetralones with Ru(II) complexes

Entry	Catalyst	Conditions [a]			Yield	d.e.[b]	e.e.(trans)	e.e.(cis)[c]
		Press. atm.	Temp. °C	Time h				
10								
1	(R,R)-diopRuBr$_2$ (2)	50	25	48	100	93(trans)	25(S, R)	79(S, S)
2	(S,S)-chiraphosRuBr$_2$ (1.5)	100	25	48	100	>99(trans)	57(S, R)	57(S, S)
3	*in-situ* (R)-binapRuBr$_2$ (3)	10	80	48	100	95(trans)	83(S, R)	17(S, S)
4	*in-situ* (R)-binapRuBr$_2$ (3)	10	80	48	95 [d]	97(trans)	96(S, R)	68(S, S)
5	[RuCl$_2$(R)-binap]$_2$NEt$_3$ (3)	10	80	48	90	87(trans)	87(S, R)	74(S, S)
6	*in-situ* (R)MeO-biphepRuBr$_2$ (3)	10	80	48	85	97(trans)	95(S, R)	19(S, S)
7	*in-situ* (S)-binapRuBr$_2$ (1)	10	80	48	93	93(trans)	86(R, S)	81(R, R)
11								
8	(S,S)-chiraphosRuBr$_2$ (1.6)	100	25	48	100	>99(trans)	54(S, R)	38(S, S)
9	(S)-binapRuBr$_2$ (2)	10	25	48	60	97(trans)	92(R, S)	13(R, R)
10	(S)-binapRuBr$_2$ (1.4)	5	80	6	100	96(trans)	88(R, S)	43(R, R)

(a) All reactions were carried out in MeOH except entry 4 ; (b) The d.e. were mesured by G.C. analysis (OV 1701 column).(c) e.e. determined by G.C.(OV 1701 column) and analysis of (L) Lactic Acid O-acetyl ester[10] ; (d) Hydrogenations carried out in CH_2Cl_2.

However, we found that under 10-100 atm of H_2 using dibromide ruthenium complexes (1-3%) preformed or prepared *in situ* and bearing four different chiral ligands (R,R)-diop, (S,S)-chiraphos, Binap and MeO-Biphep in methanol, racemic tetralone **10** was hydrogenated with very high *anti* diastereo selectivity (96-100%) to give **12** or **15**. However the enantiofacial discrimination was dramatically affected by the nature of the catalyst (table 2). The (R,R)-diopRuBr$_2$ catalyst was the less effective (25% e.e. **12a**) compared to (S,S)-

chiraphos (57% e.e. **12a**), (R)-binap (83% e.e. **12a**), (S)-binap (86% e.e. **15a**) and (R)-MeOBiphep (95% e.e. **12a**) (entries 1, 2, 3, 6, 7 respectively). A very high diastereoselectivity and a enantiofacial discrimination (87% e.e. **12a**) were also observed with the Ru_2Cl_4(R)-binap$_2$,NEt_3 complex (entry 5). However, it was established that higher efficiency was generally obtained in dichloromethane giving the *anti* product. By changing the solvent from methanol to dichloromethane, no significant increase of diastereoselectivity was observed (entry 4). The 5-methoxy 2-(ethoxycarbonyl) tetralone **11** was hydrogenated in methanol using (S,S)-chiraphosRuBr$_2$ catalyst. As pointed out with compound **10**, the trans (2S, 3R) alcohol **12b** was the major product obtained with 54% e.e. (entry 8). The hydrogenation of **11** with (S)-binapRuBr$_2$ gave **15b** with 92% e.e. (entry 9).

In summary baker's yeast and various strains reduced such β-keto esters to optically pure **cis** β-hydroxy esters [10,11]. The approach outlined in this paper is a powerful method for the stereoselective synthesis of **trans** β-hydroxyesters, allows the production of each enantiomer from (R) and (S)-binap catalyst with high enantioselectivity and offers new opportunities for the preparation of enantiomerically pure[12] materials.

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References and notes

1. a) Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566-569 ; b) Mashina, K.; Kusano, K. H. ; Ohta, T.; Noyori, R.; Takaya, H.*J. Chem. Soc. Chem Commun.* **1989**, 1208-1210 ; c) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Org. Chem.* **1992**, *57*, 4053-4054.
2. a) Ikariya, T.; Ischii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S.*J. Chem.Soc. Chem. Commun.* **1985**, 922-924.
3. For reviews see a) Noyori, R.; Kitamura, M. in Modern Synthetic Methods Ed. R. Scheffold, Spinger Verlag, **1989**, *128* ; b) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187-208 ; c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345-350 ; d) Noyori, R. *Science* **1990**, *248*, 1194 ; e) Organic Synthesis in Japan Past, Present and Future, Noyori, R. , Ed Tokyo Kagaku Dozin, **1992**, 301 and for some leading references see also : a) Heiser, B.; Broger, E. A.; Crameri, Y.*Tetrahedron : Asymmetry*, **1991**, *2*, 51-62.; b) Mezzetti, A.; Consiglio, G.; *J. Chem. Soc. Chem. Commun.* **1991**, 1675-1677.
4. Genêt, J. P.; Mallart, S.; Pinel, C.; Jugé, S.; *Tetrahedron : Asymmetry* ,**1991**, *2*, 43-46 .
5. Genêt, J. P.; Pinel, C.; Mallart, S.; Caihlol, N.; Laffitte, J. A. *Tetrahedron Lett.* **1992**, *33*, 5343-46.
6. This material will be available from Janssen Chimica.
7. a) Genêt J.P.; Mallart, S.; Jugé, S. Brevet Français n° 8911159 (August 1989) ; b) Genêt, J. P.; Pinel, C.; Mallart, S.; Jugé, S.; Thorimbert, S.; Laffitte, J. A.*Tetrahedron : Asymmetry* **1991**, *2*, 555-567.
8. 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.
9. a) Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.;Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Takemoti, T.; Kumobayashi ,H., *J. Am. Chem. Soc.* **1989**, *111*, 9134-9135 ; b) Kitamura, M.; Okhuma, T.; Tokunaga, M.; Noyori,R. *Tetrahedron : Asymmetry*, **1990**, *1*, 1-4 ; c) Mashima, K; Matsumara, Y.; Kusano, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Chem. Soc. Chem. Commun.* **1991**, 609-610 ; d) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144-152.
10. Azerad, R.; Buisson, D.; Cecchi, R.; Guizzi, U.; Laffitte, J. A. , French Patent 9300529.
11. a) Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1986**, *23*, 2631-2634 ; b) Seebach, D.; Roggo, S.; Maetzke, T.; Braunschweiger, H.; Cercus, J.; Krieger, M. *Helv. Chim. Acta.* **1987**, *70*, 1605-1615.
12. Preparation of ***in situ*** catalysts [P*PRuX$_2$]$_2$ **3**: (cod)Ru(η_3-2-methylallyl)$_2$ complex **1** and the chiral diphosphine (1.2 equiv) were dissolved in 1ml degassed acetone and 2.2 equiv. of HX in methanol (X=Cl, Br, I) were slowly added. The resulting orange solution was stirred for 1/2 hour, the solvent was removed under reduced pressure to give complexes which were used directly as hydrogenation catalysts.

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