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Enantioselective Hydrogenation of 2'-Chloroacetophenone with ((R)-Binap)Ru(O_2CAr)$_2$ complexes : Influence of Carboxylate Ligands and Solvents

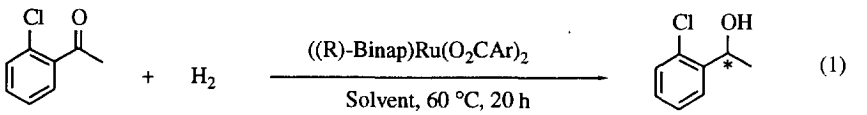
Henri Doucet, Pierre Le Gendre, Christian Bruneau,* Pierre H. Dixneuf,* Jean-Claude Souvie¶

Laboratoire de Chimie de Coordination Organique, URA CNRS 415, Campus de Beaulieu, Université de Rennes, F-35042 Rennes, France

¶Oril S. A., 13 rue Desgenetais, 76210 Bolbec, France

Abstract : New (Binap)Ru(carboxylate)$_2$ have been prepared and used for the enantioselective hydrogenation of 2'-chloroacetophenone. Both enantiomers of 2'-chlorophenylethanol can be selectively prepared with the same optically active catalyst precursor simply by changing the solvent, and the carboxylate groups have an influence on the enantioselectivity only in aprotic solvents.

Enantioselective hydrogenation of prochiral aromatic ketones into optically active secondary alcohols is a topic of current interest.[1,2] (Binap)ruthenium complexes have already been used successfully for the stereochemical control of the direct hydrogenation of functionalized ketones with molecular hydrogen.[3] The enantioselective reduction of carbonyl bonds of ketoamines[4a] or chloro β-ketoesters,[4b] has been performed with (Binap)Ru(acetate)$_2$ complexes, but very few studies have been devoted to the role of the achiral carboxylate ligands associated to the chiral Ru-diphosphine moiety.[5] We report the straightforward synthesis of a variety of new (Binap)ruthenium catalyst precursors containing substituted aromatic carboxylate ligands, and their influence on the enantioselectivity of the hydrogenation of 2'-chloroacetophenone in alcohols or aprotic solvents, without significant cleavage of the C-Cl bond, according to equation (1).

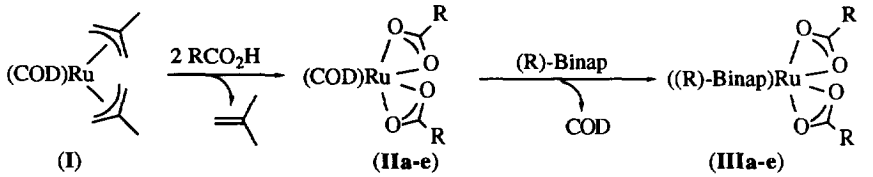


(1)

Several methodologies have been developed to prepare (diphosphine)Ru(carboxylate)$_2$ complexes, based on the utilization of [(COD)$RuCl_2$]$_n$[6] or [(arene)$RuCl_2$]$_2$[7] as starting materials. They proceed *via* preliminary coordination of the diphosphine and then elimination of chloride on treatment with sodium carboxylate. Another strategy starting from [(COD)$RuCl_2$]$_n$ involves its transformation into (COD)Ru(2-methylallyl)$_2$(**I**)[8,9] which provides an easy access to (COD)Ru(O_2CCF_3)$_2$ (**IIa**) on protonation of the methallyl ligand with trifluoroacetic acid. This latter complex can be used to generate (Binap)Ru(acetate)$_2$ on displacement of COD by the diphosphine followed by exchange of the trifluoroacetate group by sodium acetate or *vice-versa*.[9]

We now show a general access to a variety of (Binap)Ru(O_2CAr)$_2$ catalysts (**III**) in four steps from $RuCl_3.xH_2O$ *via* (**I**) and (**II**), and with the advantage of introducing the optically active ligand in the last step (eq. 2). Thus, the treatment of (COD)Ru(2-methylallyl)$_2$ (**I**) with 2 equivalents of aromatic carboxylic acid in THF at 40 °C for 20 h under an inert atmosphere of nitrogen led to (COD)Ru(O_2CAr)$_2$ (**IIb-e**) after smooth elimination of isobutene. After removal of the solvent and drying, complexes (**IIb-e**) could be isolated in 80-90% yield. Subsequent addition of 1 equivalent of (R)-Binap in a THF-diethylether mixture and stirring at 40 °C for 20 h afforded (**IIIb**)[7] in 90% yield and the new catalyst precursors (**IIIc-e**) in 85, 70, and 90% isolated yields respectively, after displacement of the

coordinated 1,5-cyclooctadiene. ^{1}H, ^{13}C, ^{31}P NMR and IR spectra were in good agreement with the expected formulas and elemental analysis were satisfactory. The new complexes (**IIIc-e**) were found to catalyze the asymmetric hydrogenation of 2'-chloroacetophenone (Table 1).



(I) (IIa-e) (IIIa-e) (2)

(**IIa**) : R= CF_3
(**IIb**) : R = Ph (90%)
(**IIc**) : R = 2,6-difluorophenyl (85%)
(**IId**) : R= 4-methoxyphenyl (80%)
(**IIe**) : R= 2,6-dimethoxyphenyl (90%)

(**IIIa**) : R= CF_3
(**IIIb**) : R = Ph (90%)
(**IIIc**) : R = 2,6-difluorophenyl (85%)
(**IIId**) : R= 4-methoxyphenyl (70%)
(**IIIe**) : R= 2,6-dimethoxyphenyl (90%)

Hydrogenation in methanol :

Table 1 : Hydrogenation of 2'-Chloroacetophenone in Methanol with ((R)-Binap)Ru($O_2CAr)_2$ (III)

Catalyst precursor	Yield of (+)-2'-chlorophenylethanol (%)	e. e. (%)
((R)-Binap)Ru($O_2CPh)_2$ (**IIIb**)	97	87
((R)-Binap)Ru(2,6-difluorobenzoate)$_2$ (**IIIc**)	94	85
((R)-Binap)Ru(4-methoxybenzoate)$_2$ (**IIId**)	97	78
((R)-Binap)Ru(2,6-dimethoxybenzoate)$_2$ (**IIIe**)	95	85
((R)-Binap)Ru($O_2CCF_3)_2$ (**IIIa**)	94	85

General conditions : 2'-chloroacetophenone (6.5 mmole), catalyst 0.013 mmol, H_2 : 100 bar, S/C = 500, MeOH (10 ml), 60 °C, 20 h.

In the presence of ((R)-Binap)Ru($O_2CAr)_2$ catalyst precursors (**IIIb-e**), the total conversion of 2'-chloroacetophenone at 60 °C for 20 h under 100 bar H_2 pressure led to (+)-2'-chlorophenylethanol as the major product. The enantiomeric excesses of (+)-2'-chlorophenylethanol obtained with these catalyst precursors were located in the range 85-87% except 78% with (**IIId**), which revealed a weak influence of the carboxylate ligand on the enantioselectivity of the reaction. With each catalyst precursor (**IIIb-e**), a small amount of acetophenone (3-6%) was formed, which was not hydrogenated under our catalytic conditions, showing that the presence of the halogen in 2'-chloroacetophenone was essential for the hydrogenation of the C=O bond. Under similar conditions but at 50 °C, the formation of acetophenone was less important (4% with (**IIIc**)) indicating that the C-Cl bond cleavage was temperature dependent. It is noteworthy that the carbon-halogen bond cleavage was much more effective with 2'-bromoacetophenone which gave 15% and 7% of acetophenone at 60 °C and 25 °C respectively, under 50 bar of H_2 in the presence of ((R)-Binap)Ru($O_2CCF_3)_2$ (**IIIa**) as catalyst precursor. The choice of methanol was important as under our typical experimental conditions, the hydrogenation of 2'-chloroacetophenone in the presence of ((R)-Binap)Ru($O_2CCF_3)_2$ (**IIIa**) in EtOH and ^{i}PrOH only gave 45 and 25% conversion of the ketone, respectively.

The results in Table 1 demonstrate that (Binap)Ru(carboxylate)$_2$ complexes can find efficient applications for the hydrogenation of halogenated aromatic ketones, and that the modification of the catalyst precursor (**IIIa**) by replacement of the aliphatic trifluoroacetate ligands by aromatic carboxylates in (**IIIb-e**) under otherwise identical

conditions leads to similar results for the enantioselective hydrogenation of 2'-chloroacetophenone, e. g. total conversion of the aromatic ketone, comparable enantioselectivities and only a slight C-Cl bond cleavage. These results compete well with those observed by Noyori with a ((S)-Binap)-ruthenium complex associated to a chiral diamine.[1]

Hydrogenation in aprotic solvents

Table 2 : Hydrogenation of 2'-Chloroacetophenone in Aprotic Solvents

Catalyst Precursor	Solvent	Yield of 2'-chlorophenylethanol (%)	Enantiomers (%)		e. e. (%)
			(+)	(-)	
((R)-Binap)Ru(O_2CCF_3)$_2$ **(IIIa)**	methanol	94	92.5	7.5	85
((R)-Binap)Ru(4-methoxybenzoate)$_2$ **(IIId)**	"	97	89	11	78
((R)-Binap)Ru(O_2CCF_3)$_2$ **(IIIa)**	toluene	100	37	63	26
((R)-Binap)Ru(2,6-difluorobenzoate)$_2$ **(IIIc)**	"	100	25	75	50
((R)-Binap)Ru(O_2CPh)$_2$ **(IIIb)**	"	100	20	80	60
((R)-Binap)Ru(4-methoxybenzoate)$_2$ **(IIId)**	"	100	16.5	83.5	67
((R)-Binap)Ru(O_2CPh) **(IIIb)**	hexane	100	16	84	68
((R)-Binap)Ru(O_2CPh) **(IIIb)**	ether	100	19	81	62

General conditions : 2'-chloroacetophenone (6 mmol), catalyst (0.012 mmol), H_2 : 100 bar, S/C = 500, 60 °C, 20 h.

As the influence of the alcohol was important on the catalytic activity (MeOH >> EtOH > ^{i}PrOH), we investigated the feasability of the hydrogenation in aprotic solvents. The data in Table 2 show that the catalytic hydrogenation of 2'-chloroacetophenone can be carried out in toluene, hexane or diethylether, and clearly reveal the drastic effect of the solvent on the enantioselectivity of the hydrogenation. By contrast with the use of alcohol, (-)-2'-chlorophenylethanol was the major enantiomer in aprotic solvents. In addition, the influence of the carboxylate ligand was important as enantioselectivities of 26, 50, 60 and 67% were respectively observed in toluene when trifluoroacetate, 2,6-difluorobenzoate, benzoate and 4-methoxybenzoate were associated to (R)-Binap in complexes **(IIIa)**, **(IIIc)**, **(IIIb)** and **(IIId)**, respectively. Moreover, no cleavage of the C-Cl bond took place under these experimental conditions.

The mechanism of hydrogenation of aromatic ketones in aprotic solvents is obviously very different from that involved in protic solvents ; the carboxylate ligand has a strong effect which indicates that at least one of these ligands remains coordinated and no proton arising from the solvent is expected to participate in the reduction process. Electronic rather than steric effects of the substituents of the aromatic ring seem to be responsible for the differences of enantioselectivity observed.[10] Such a reversal of the enantioselectivity according to the solvent, as exemplified by the use of catalyst **(IIId)** in MeOH or toluene (Table 2), has just been noticed in a rhodium-catalyzed asymmetric hydrogenation of the carbon-carbon double bond of a menthyl *N*-benzoylamidocinnamate for the synthesis of (S)-amino esters.[11] These results suggest that the best profit of an optically active catalyst should be reached by changing both solvent and ancillary ligands.

Experimental

Synthesis of new chiral ruthenium carboxylate complexes. All manipulations were carried out under an inert atmosphere using Schlenk techniques. All solvents were dried and distilled under argon before use. Commercial aromatic acids were used without further purification. (COD)Ru(η^3-methylallyl)$_2$ was synthetized according to reported methods. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded from a Bruker AC 300 spectrometer and the IR

spectrometer used was a Nicolet 205 FTIR. Elemental analysis were performed by "Le Service Central d'Analyses du CNRS" at Vernaison.

(Binap)Ru(2-6-difluorobenzoate)$_2$ (**IIIc**) : IR : ν (KBr) cm^{-1} : 1623 (C=O); ^{31}P NMR ($CDCl_3$): δ_P : 65.60 (s, PPh_2); ^{1}H NMR ($CDCl_3$): δ_H : 6.45-7.92 (m, 32 H, aromatic protons); ^{13}C NMR ($CDCl_3$): δ : 111.30-162.31 (m, aromatic carbons), 175.79 (s, OCOAr); $[\alpha]_D^{20}$ = +641 (c = 0.5, toluene); Elemental analysis : calculated : C : 67.12, H : 3.69, P : 5.97, F : 7.32; Found C: 66.69, H : 3.77, P : 5.80, F : 7.18.

(Binap)Ru(4-methoxybenzoate)$_2$ (**IIId**) : IR : ν (KBr) cm^{-1} : 1620 (C=O); ^{31}P NMR ($CDCl_3$): δ_P : 65.23 (s, PPh_2); ^{1}H NMR ($CDCl_3$): δ_H : 3.76 (s, 6 H, OCH_3), 6.20-8.00 (m, 40 H, aromatic protons); ^{13}C NMR ($CDCl_3$): δ : 55.26 (s, OCH_3), 112.71-162.56 (m, aromatic carbons), 182.16 (s, OCOAr); $[\alpha]_D^{20}$ = +744 (c = 0.5, CH_2Cl_2); Elemental analysis : calculated : C : 70.24, H : 4.52, P : 6.03; Found C : 70.32, H : 4.48, P : 5.95.

(Binap)Ru(2-6-dimethoxybenzoate)$_2$ (**IIIe**) : IR : ν (KBr) cm^{-1} : 1600 (C=O); ^{31}P NMR (CD_2Cl_2): δ_P : 65.01 (s, PPh_2); ^{1}H NMR (CD_2Cl_2): δ_H : 3.40 (s, 12 H, OCH_3), 6.36-7.95 (m, 38 H, aromatic protons); ^{13}C NMR (CD_2Cl_2): δ : 56.01 (s, OCH_3), 104.36-157.77 (m, aromatic carbons), 184.00 (s, OCOAr); $[\alpha]_D^{20}$ = +586 (c = 0.5, CH_2Cl_2); Elemental analysis : calculated : C : 68.57, H : 4.64, P : 5.70; Found C: 68.27, H : 4.64, P : 5.80.

General procedure for hydrogenation of 2'-chloroacetophenone. A 125 ml stainless steel autoclave equipped with a mechanical stirrer was charged under inert atmosphere successively with the substrate, the solvent and the catalyst. The autoclave was carefully flushed with hydrogen and pressurized with 100 bar of hydrogen. Hydrogenations were carried out under the experimental conditions given in Table 1 and 2. The reaction mixture was analyzed by gas chromatography for the determination of the conversion of the ketone, and a sample was submitted to ^{1}H NMR after treatment with Mosher chloride.[12]

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