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(R,R) DIPAMP-RUTHENIUM (II) (2-METHYLALLYL)$_2$: SYNTHESIS AND SELECTED USE IN ASYMMETRIC HYDROGENATION.

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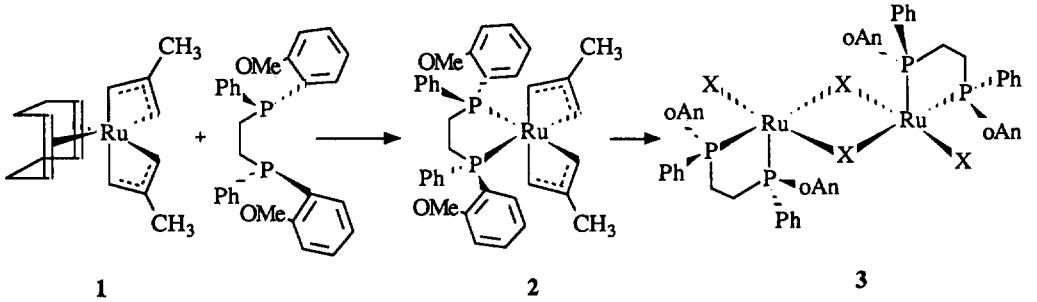
Key words : Asymmetric hydrogenation ; Catalysis ; Chiral ruthenium complexes ; DIPAMP.

Abstract : The synthesis of (R, R)DIPAMP ruthenium bis (2-methylallyl) **2** and halogeno derivative (R, R) DIPAMPRu_2X_2 **3** complexes is presented, which uses the easily available from $(COD)_2Ru$(2-methylallyl)$_2$ **1**. These new catalysts were found to be effective for asymmetric hydrogenation of both olefins and keto groups (35-80% ee).

Since the discovery of binuclear Ru_2Cl_4 (-) BINAP, NEt_3 in 1985,[2] a number of mononuclear BINAP-ruthenium catalysts, have been prepared from polymeric $(RuCl_2COD)_n$ and requires the presence of triethylamine in toluene reflux to cleave the halogeno-bridged structure.[3] These conditions are not suitable for tertiary biphosphines having the phosphorus atom as stereogenic center.[4] Although such homogeneous chiral catalysts are well known for most of the transition element especially with rhodium,[5] ruthenium derivatives containing chiral ligands with asymmetric phosphorus atom (e.g. PAMP, DIPAMP) are unkown. We have recently reported a mild and reliable synthesis of chiral ruthenium catalysts.[6] Reported therein are our results, which successfully permit the practical asymmetric synthesis of the new R,R DIPAMP-ruthenium II (2-methylallyl)$_2$ catalyst and its use in some selected asymmetric hydrogenation.

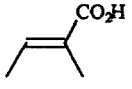
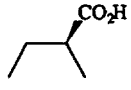
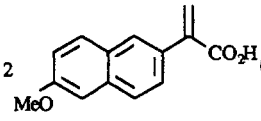
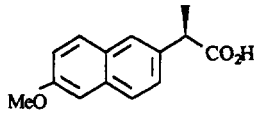
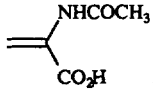
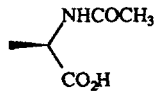
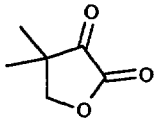
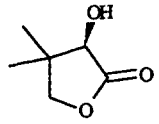
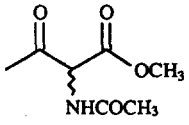
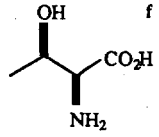


1 2 3

Scheme I : Preparation of DIPAMP-ruthenium complexes.

Addition of 1 equiv. of (R, R) DIPAMP (diphenylanisylmethyl phosphine)[7] to a degassed hexane solution of COD ruthenium (methylallyl)$_2$ **1** (COD = 1,5 cyclooctadiene) led at 45°C for 5 h after smooth displacement of the bounded COD ligand to the formation of an orange solution from which yellow powder of the formula (R,R) DIPAMP Ru (2-methylallyl) **2** could be isolated in 85% yield as shown in scheme I.

Table : Hydrogenation of olefins and ketones using (R, R) DIPAMP Ru complexes.[8]

Entry	Substrate (Complexe)		Conditions				Product	Yield	e.e
			Solvent	Press. atm.	Temp. °C	Time h			
1		(2)	MeOH	4	25	24		100	40[b]
2		(2)	THF	30	25	64		100	55[c]
3		(3)	EtOH/ THF 1/1	12	48	72		85	35[d]
4		(3)	toluene	100	50	64		35	80[e]
5		(3)	MeOH	100	25	68		45	43[g]

a) Hydrogenations were carried out in 0.5-1 M solution of the substrate in degassed solvent. Substrate / Ru-Catalysts : 100/1. Experimental conditions employing catalysts 2 and 3 are described in ref 8 b) Determined by H.P.L.C. analysis after conversion to the ester of (R)-(+)-α-(1-Naphtyl) ethylamine. c) Determined by H.P.L.C. analysis (Chiral AGP column, 100 x 4.0 mm,). d) Based on the rotation value $[\alpha]_D^{26}$ *+66 (c 2, H_2O) (S. M. Birbaum, L. Levintow, R. B. Kingsley, and J. P. Greenstein, J. Biol. Chem. 1952, 194 , 455. e) After distillation of the pantolactone, the ee were determined by H.P.L.C. analysis (Chiracel O.A. column, heptane : propanol-2 = 9:1). f) Obtained after hydrolysis of the hydrogenated product and treatment with propylene oxide.*

g) Determined by H.P.L.C. analysis (Chiralpak WH column, $CuSO_4$ 0.25 mM). Syn/Anti : 92/8, $ee_{(allothreonine)}$ *= 30%.*

The product ($[\alpha]_D^{20}$ = - 43.5 (c 0.23, toluene), was washed by degassed hexane and characterized by ^1H, ^{13}C, ^{31}P, IR and elemental analyses.[9] In addition, this catalyst can be used for the synthesis of derivatives of general formula (R, R) DIPAMP Ru X_2) (X = Br, I) by treatement of **2** with the corresponding hydracid. This air-sensitive Ru (P-P) complexe with P-P = (R, R) DIPAMP reveals an AB pattern in the ^{31}P (^1H) NMR spectra which is consistent with a bridged structure.[10]

These new chiral ruthenium catalysts were found to catalyze asymmetric hydrogenation of both olefins and keto groups. A diverse selection is provided in the table. This new chiral bis-allyl ruthenium complex **2** was found to catalyze hydrogenation of trisubstitued double bond. The tiglic acid was hydrogenated quantitatively under mild conditions (4 atm. at R.T.) with a modest enantioselection (40% ee, entry 1). The precursors of naproxen and alanine were also hydrogenated at R.T. in good yield (85 - 100 %) with 55% and 35% ee respectively (entries 2 and 3). The asymmetric hydrogenation of ketopantoyl lactone to pantolactone, key intermediate of pantothenic acid,[11] was carried out with DIPAMP Ru X_2 catalyst **3** at 100 atm. and 50°C with a significant enantiomeric excess up to 80% (entry 4). The hydrogenation of 2-acylamino-3-oxobutyrates with **3** (100 atm., 25° C, 64 h) afforded after hydrolysis the L-threonine. A very high syn preference is seen (syn/anti : 92/8) with a moderate enantioface discrimination (45% ee) (entry 5). Noteworthy, the racemisation of stereogenic center C_2 is faster than hydrogenation and an useful dynamic kinetic resolution is achieved here, with this ruthenium complex bearing chiral ligand such as DIPAMP.[12]

In conclusion we have prepared the first mononuclear chiral ruthenium complex with chirality at the phosphorus atom. The fair to significant enantiomeric excesses induced by this new chiral mononuclear ruthenium complex are encouraging, considering the fact that a large number of new chiral phosphorus ligands with the chirality at the stereogenic phosphorus center are now easily available[7] and this work is currently in progress.

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4) DIPAMP racemizes under these conditions (toluene, reflux, 10 hrs).

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7) The two enantiomers of DIPAMP are synthesized in large scale in our laboratory : Jugé, S.; Stéphan, M. ; Laffitte, J.A. and Genêt, J.P. *Tetrahedron Lett.*, **1990**, *31*, 635.

8) Experimental conditions for high pressure hydrogenations of the illustrated substrates and ruthenium catalysts **2** and **3** : To a small autoclave, are added in dry and degassed solvents the keto or olefin derivative and catalyst (1 mol %). The autoclave is pressure-flushed with hydrogen (3 times) pressurized and heated to the desired levels. After hydrogenation completed, solvent was evaporated and products were purified. For determination of enantiomeric excesses see table.

9) NMR (ppm, C_6D_6) : ^1H (250MHz) 8.11-6.5 (18H, m, arom.) ; 3.4 (4H, m, CH_2P) ; 2.92 (6H, s, CH_3O) ; 2.31 (6H, s, CH_3) ; 2.22 (2H, d, J_{PH} = 2Hz, C*H*-Ru) ; 1.7 (2H, s, C*H*-Ru) ; 1.1 (2H, dd, J_{HH} = 15Hz, J_{PH} = 5Hz, C*H*-Ru) ; 0.25 (2H, d, J_{HH} = 15Hz, C*H*-Ru) ; ^{13}C (62 MHz) : 159.9-110.6 (m, arom.) ; 96.1 (s, *C*-CH_3) ; 54.0 (s, CH_3-O) ; 44.3 (s, CH_2-Ru) ; 42.4 (d, J_{CP}=25Hz, CH_2-Ru) ; 32.5 (dd, J_{CP1}= J_{CP2}= 27 Hz, CH_2-P) ; 26.6 (s, CH_3) ; ^{31}P (100 MHz, ref. H_3PO_4 85%) 85. IR (cm^{-1}, Nujol) : 1460, 1380, 1240, 800, 750. MS : DCI, m/e = 671, 615, 559. m.p : 183°-185°C (decomp.). Anal. Calcd for $C_{36}H_{42}O_2P_2$ (found) ; C,64.57 (64.84) ; H, 6.29 (6.40) ; P, 9.27 (8.48), Ru, 15.1 (15.3).

10) James, B.R. ; Pacheco, A. ; Rettig, S.J. ; Thorburn, I.S. ; Ball, R. G. and Ibers, J.A. , *J.Mol.Cat.* ; **1987**, *41*, 147 and references cited therein.

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12) a) With Chiraphos-Ru complex we observed the same diastereoselectivity (syn/anti : 93/7) with fairly higher enantioselectivity ($ee_{threonine}$ = 85%), Genêt, J.P. ; Pinel, C. ; Mallart, S. ; Jugé, S. ; Thorimbert, S. and Laffitte, J.A. ; *Tetrahedron : Asymmetry*, **1991**, *2*, 555 ; b) Noyori, R. ; Ikeda, T. ; Ohkuma, T. ; Widhalm, M. ; Kitamura, M. ; Takaya, H. ; Akutagawa, S. ; Sayo, N. ; Saito, T. ; Taketomi, T. and Kumobayashi, H. ; *J. Am. Chem. Soc.* , **1989**, *111*, 9134.

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