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Asymmetric Catalytic Hydrogenation of α -Ketoesters Using New Chiral Ru(II)(AMPP) Complexes

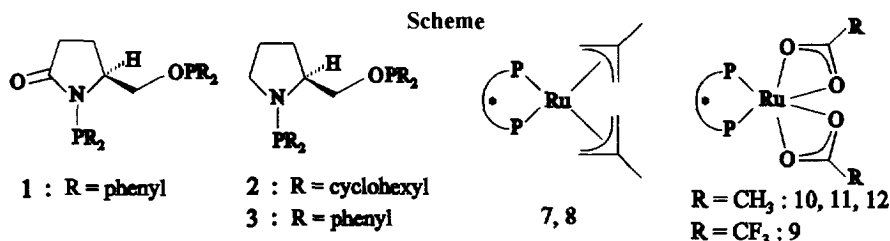
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Abstract : Chiral bidentate amino(amido)phosphinephosphinite ligands (AMPP) have been used to synthesise new ruthenium bismethylallyl $\text{Ru}(\text{AMPP})(\text{CH}_2\text{C}(\text{CH}_3)\text{CH}_2)_2$ and biscarboxylate $\text{Ru}(\text{AMPP})(\text{OCOR})_2$ ($\text{R} = \text{CH}_3$ or CF_3) complexes. These complexes act as efficient catalyst precursors for the homogeneous asymmetric hydrogenation of α -ketoesters with enantiomeric excesses up to 79%.

Optically active α -hydroxy esters represent an important class of building blocks for natural product synthesis¹. Among the many methods available for the preparation of these compounds, the asymmetric hydrogenation of α -ketoesters catalysed by soluble chiral rhodium(I) complexes has been extensively studied in the last two decades². However, less is known regarding the asymmetric catalytic hydrogenation of α -ketoesters with chiral ruthenium(II) catalysts³.

We have undertaken a study of the synthesis of ruthenium(II) complexes chelated by chiral amino(amido)phosphinephosphinite bisphosphines (AMPP) and their use in asymmetric hydrogenation of activated ketones. Thus, we previously reported that cationic $[\text{RuX}(\text{arene})(\text{AMPP})]\text{X}$ complexes were efficient precursors for the asymmetric catalytic hydrogenation of ketopantolactone⁴. These new chiral ruthenium precursors presented very good activities with moderate enantiomeric excesses (up to 42%).



Surprisingly, when trying to prepare the corresponding complexes with less basic AMPP ligands⁵, such as (S)-Ph,Ph-5-oxo-ProNOP 1, instead of (S)-Cy,Cy-ProNOP 2 or (S)-Ph,Ph-ProNOP 3 (Scheme), synthetic difficulties appeared. Therefore, we sought to extend our studies towards other easily accessible mononuclear ruthenium precursors. In this communication, we report on the synthesis and the characterisation of new chiral

Ru(II)(AMPP) complexes and on their use in the asymmetric hydrogenation of ketopantolactone **4**, ethyl pyruvate **5** and methyl benzoylformate **6**.

First, the AMPP ligands **1** and **3** were reacted with the easily accessible complex Ru(COD)(2-methylallyl)₂⁶ in hexane at 60°C for 5 hours under N₂⁷ to give the corresponding Ru(AMPP)(2-methylallyl)₂ complexes. Thus, after workup, Ru((S)-Ph,Ph-ProNOP)(2-methylallyl)₂ **7** and Ru((S)-Ph,Ph-5-oxoProNOP)(2-methylallyl)₂ **8** were isolated in 75-85% yields (ligand **2** did not react under these conditions). These air-sensitive Ru(II) complexes presented two sets of doublets in the ³¹P{¹H} NMR spectra, corresponding to two diastereomers (**7a** / **7b** and **8a** / **8b**) in different ratios depending on the ligand (Table 1). These diastereomers result from enantiomeric configuration of the methylallyl ligands. Similar observations have been made for P₂Ru(acac)₂ complexes⁸. In the reported complexes, we observe only two diastereomers whereas for other complexes four diastereomers are formed⁹. Second, our attention then turned to the synthesis of another type of catalyst of general formula : Ru(AMPP)(OCOCF₃)₂. Extensive efforts to isolate pure complexes by reaction of [Ru(COD)(OCOCF₃)₂]₂ with AMPP ligands were unsuccessful, except for **2**¹⁰. Therefore, we developed a convenient access to the mixture of diastereomers Ru((S)-Ph,Ph-ProNOP)(OCOCF₃)₂ **9a** / **9b**, which was obtained in good yield (85-95%) after reaction of Ru((S)-Ph,Ph-ProNOP)(2-methylallyl)₂ **7a** / **7b** with one equivalent of trifluoroacetic acid at -10°C in CH₂Cl₂ for 20 min under N₂ (Table 1). Finally, a third new family of complexes have been investigated through reaction of Ru(COD)(OCOCH₃)₂ with **1**, **2** and **3** in CH₂Cl₂ under nitrogen at room temperature for 14 hours¹⁰.

Table 1 : ³¹P{¹H} NMR characteristics for ruthenium complexes 7-12^a

Complexes ^b	δ , ppm	J(P,P') Hz	a / b ^c
Ru((S)-Ph,Ph-ProNOP)(2-methylallyl) ₂ 7a / 7b	7a : 155.7(d, P-O), 95.2(d, P-N) 7b : 138.3(d, P-O), 109.3(d, P-N)	38 31	50 / 50
Ru((S)-Ph,Ph-5-oxo-ProNOP)(2-methylallyl) ₂ 8a / 8b	8a : 173.7(d, P-O), 103.4(d, P-N) 8b : 161.3(d, P-O), 114.0(d, P-N)	30 36	90 / 10
Ru((S)-Ph,Ph-ProNOP)(OCOCF ₃) ₂ 9a / 9b	9a : 171.1(d, P-O), 137.2(d, P-N) 9b : 162.2(d, P-O), 135.4(d, P-N)	57 57	60 / 40
Ru((S)-Cy,Cy-ProNOP)(OCOCH ₃) ₂ 10a / 10b	10a : 189.9(d, P-O), 152.6(d, P-N) 10b : 181.5(d, P-O), 161.4(d, P-N)	40 42	85 / 15
Ru((S)-Ph,Ph-ProNOP)(OCOCH ₃) ₂ 11a / 11b	11a : 162.7(d, P-O), 123.3(d, P-N) 11b : 158.2(d, P-O), 122.3(d, P-N)	46 46	70 / 30
Ru((S)-Ph,Ph-5-oxoProNOP)(OCOCH ₃) ₂ 12a / 12b	12a : 159.7(d, P-O), 115.4(d, P-N) ^d 12b : 147.6(d, P-O), 87.8(d, P-N) ^d	58 57	90 / 10

a) In CDCl₃ unless otherwise noted, referenced to external H₃PO₄ (85% in D₂O) b) Mixture of diastereomers

c) Diastereomeric ratio. (d) In CD₂Cl₂.

Accordingly, the mixture of diastereomeric bidentate complexes Ru((S)-Cy,Cy-ProNOP)(OCOCH₃)₂ **10a** / **10b**, Ru((S)-Ph,Ph-ProNOP)(OCOCH₃)₂ **11a** / **11b**, and Ru((S)-Ph,Ph-5-oxo-ProNOP)(OCOCH₃)₂ **12a** / **12b** were isolated in 85-95% yields (Table 1)¹¹.

The complexes prepared have been applied in asymmetric hydrogenation of ketopantolactone **4**, ethylpyruvate **5** and methylbenzoylformate **6**. Some catalytic results are summarised in Table 2.

Table 2 : Asymmetric Hydrogenation of α -ketoesters ^a.

Run	Substrate	Complex	Reaction time (h)	T (°C)	Conversion ^b (%)	ee ^c (%)
1	4	7a / 7b	60	20	95	40 (R)
2	4	8a / 8b	60 ^d	20	100	79 (R)
3	4	8a / 8b	19	60	100	68 (R)
4	4	9a / 9b	17	20	17	14 (R)
5	4	10a / 10b	17	20	30	<1 (S)
6	4	11a / 11b	17	20	26	15 (R)
7	4	12a / 12b	15	20	32	65 (R)
8	5	8a / 8b	60	20	72	11 (S)
9	5	8a / 8b	16	96	100	63 (R)
10	5	12a / 12b	16	96	98	42 (R)
11	6	8a / 8b	60	20	37	22 (R)
12	6	8a / 8b	16	96	89	48 (R)
13	4	13a / 13b ^e	14	20	29	6 (R)
14	4	14a / 14b ^f	14	20	50	50 (R)

(a) Hydrogenations were carried out under 50 bar of H₂ in a stainless steel autoclave in the presence of 0.05 M solution of the substrate in degassed CH₂Cl₂ (15ml); Substrate / Ru = 150 / 1. (b) determined by GC analysis (FS-cyclodextrine.beta-l/P) on the isolated product. (c) measured by HPLC analysis (Chiralcel OD column, hexane : 2-propanol = 90 : 10, 1 ml / min). (d) 12% conversion in 15 hours. (e) **13a** / **13b** = [RuCl(C₆H₆)((S)-Cy,Cy-ProNOP)]Cl (diastereomeric ratio = 90 / 10). (f) **14a** / **14b** = [RuCl(C₆H₆)((S)-Ph,Ph-ProNOP)]Cl (diastereomeric ratio = 90 / 10).

We observe that the highest enantiomeric excess is obtained when the hydrogenation of substrate **4** is conducted in the presence of the mixture of precursors **8a** / **8b** (run 2). Analysis of these results suggests the following. First, when the phosphorus atom is substituted by phenyl (run 6) rather than by cyclohexyl groups (run 5), we observe an increase in the selectivity (from 1 to 15% ee). This had already been mentioned for the previously reported arene ruthenium precursors⁴. Second, the amido residue of ligand **1** allows concomitant increase of rigidity and decrease of electron density (at least on the N-P moiety) leading thus to the most efficient Ru(II)AMPP catalysts studied so far (run 2 vs. run 1). The benefit of a pyrrolidinone structure had already been reported for Rh(I)-AMPP catalysts¹².

Complexes Ru(AMPP)(2-methylallyl)₂ are slightly more selective (run 2) than acetato complexes (run 7), but less active (12% conversion for **8a** / **8b** compared to 32% for **12a** / **12b** for a reaction time of 15 hours). This is attribute to the rate of elimination of the non-phosphine participant ligands which conducts to the catalytic species. Therefore, we observed that activities and enantioselectivities are influenced by the nature of these ligands.

Finally, according to the substrate, asymmetric induction is highly dependent upon the temperature. With substrate **4**, the level of enantioface discrimination increased by decreasing the reaction temperature (runs 2 and 3) whereas with substrates **5** and **6** an increase of the temperature is necessary to enhance the ee (run 8 vs. run 9, run 11 vs. run 12). A plausible explanation of this phenomenon might be that an increase of temperature could be necessary to bring the substrates to the *S-cis* geometry which is required for the chelation of the α -ketoester to ruthenium¹³.

In summary, this study has demonstrated the ready accessibility of Ru(AMPP) methylallyl and carboxylate complexes and their efficiency in the hydrogenation of α -ketoesters. Chemical properties of these complexes regarding the mechanism and the hydrogenation of β -ketoesters and olefins will be reported in the future⁹.

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