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Synthesis of New Chiral Arene Ruthenium(II) Aminophosphinephosphinite Complexes and Use in Asymmetric Hydrogenation of an Activated Keto Compound

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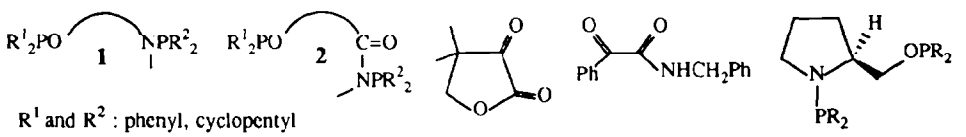
Abstract : The easy access to new arene-ruthenium(II)bisphosphine complexes bearing aminophosphine phosphinite ligands is presented. The complexes were prepared in two steps from $[RuX_2(arene)]_2$ under mild conditions and were found to be effective precursors for the asymmetric hydrogenation of dihydro-4,4-dimethyl-2,3-furandione giving the corresponding pantolactone with up to 42% enantiomeric excess.

The asymmetric hydrogenation catalysed by transition metal complexes bearing chiral bisphosphine ligands provides a useful tool for preparing optically active organic compounds and has been the subject of numerous investigations.[1] Thus, many rhodium complexes chelated by chiral bisphosphines have been reported as efficient catalysts which show high to almost complete enantioselectivity for the hydrogenation of functionalized olefins and ketones.[2] Recently, it has been found that the extensively studied BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphtyl) could also be used for the "Ru(II)" catalysed hydrogenations.[3] In fact, (BINAP)Ru(II) complexes are outstandingly efficient catalysts in the asymmetric hydrogenation of various substrates.[4] Surprisingly, however, much fewer studies on the related ruthenium complexes with other chiral bisphosphines have been undertaken.[2d,4c,5]

We have had an ongoing interest in the synthesis of easily accessible chiral bisphosphines and their application in asymmetric catalysis.[6] Thus, the syntheses of chiral amino(amido)phosphinephosphinite ligands (AMPP) bearing either identical or different substituents on the amino(amido)phosphine and phosphinite residues (general formula **1** and **2**) have been presented.[7] The mixed ligands have been found the most active and selective for the hydrogenation of dihydro-4,4-dimethyl-2,3-furandione (ketopantolactone) (**3**) and N-benzylphenylglyoxamide (**4**).[7c] Hence, we set out to extend the preceding chemistry to the synthesis of related ruthenium precursors and their use in enantioselective hydrogenation. Our first results on their synthesis and application to asymmetric hydrogenation of ketone **3** are described below.



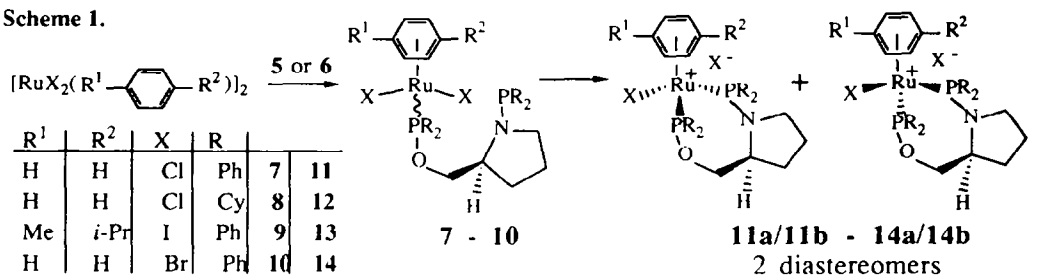
R^1 and R^2 : phenyl, cyclopentyl or cyclohexyl

3 **4**

R = Ph : **5**
Cy : **6**

The accessibility to cationic [RuX(arene)(AMPP)]X (arene = benzene, *p*-cymene, X= Cl, Br, I) using the standard procedure of Takaya and al.[8] ([RuX_2(arene)]$_2$, EtOH, temp.) was explored and gave unsatisfactory results. In fact, our ligands partially degrade in hot ethanol to the amine free phosphinite ligand. Other, attempts to synthesise Ru(AMPP)$(OOCCH_3)_2$ and Ru(AMPP)$(OOCCF_3)_2$[9,10] precursors starting from polymeric [$RuCl_2$(COD)]$_n$ (COD : 1,5-cycloctadiene) gave rise to a complex mixture of species.[4c, 5b, 5i] In this context, we developed a specific synthesis of [RuX(arene)(AMPP)]X that could be used for sensitive ligands under mild and reliable conditions. Thus, the dimeric benzene complex [$RuCl_2(C_6H_6)$]$_2$[11], placed in suspension in THF, was reacted with the ligand (S)-ProNOP (**5**) (2.6 equiv.) and the peralkylated (S)-Cy-ProNOP (**6**) (2.1 equiv.) at 60 °C for 3 hours to give orange-red coloured solutions (scheme 1). Workup gave the complexes $RuCl_2(C_6H_6)$((S)-ProNOP) (**7**) and $RuCl_2(C_6H_6)$((S)-Cy-ProNOP) (**8**) as orange powders in 85-95% yields.[12] Complexes 7 and **8** exhibited single PN and PO ^{31}P NMR resonances (ppm, THF, 112.8, PO ; 49.9, PN for **7** ; 143.2, PO ; 55.0, PN for **8**) consistent with a monocoordination of the diphosphine through the PO moiety. No bridged species ([$RuCl_2(C_6H_6)$]$_2$(μ-P_2*)) and no cationic complexes ([$RuCl(C_6H_6)(P_2$*)]Cl) were observed in the above reaction conditions.[5k] Complexes RuI_2(*p*-cymene)((S)-ProNOP) (**9**) and $RuBr_2(C_6H_6)$((S)-ProNOP) (**10**) where similarly synthesised in 85-95% yield[12] starting from [RuI_2(*p*-cymene)]$_2$[8,13] and [$RuBr_2(C_6H_6)$]$_2$[11] and 2.6 equiv. of ligand **5**.

Scheme 1.



R^1	R^2	X	R		
H	H	Cl	Ph	**7**	**11**
H	H	Cl	Cy	**8**	**12**
Me	*i*-Pr	I	Ph	**9**	**13**
H	H	Br	Ph	**10**	**14**

Then, our attention was turned to the conversion of the monohapto species to the corresponding cationic chelated complexes. Thus, after dissolution in acetonitrile, complex **8** was heated at 60 °C for 4 hours. The colour of the mixture changed from deep red to clear orange. Simultaneously, the reaction was followed by ^{31}P NMR and showed the disappearance of the OP and NP resonances of **8** and the growing of two AB quartets of unequal intensities. The observed ^{31}P resonances were attributed to two diastereomeric complexes [RuCl(C_6H_6)((S)-Cy-ProNOP)]Cl (**12a/12b**) produced in 90:10 ratio resulting from enantiomeric configurations of the ruthenium atom (^{31}P NMR, ppm, THF, major **12a** : 155.7, d, $OPCy_2$, 100.3, d, $NPCy_2$, $J_{(P-P)}$ 31.5Hz ; minor **12b** : 161.3, d, $OPCy_2$, 108.3, d, $NPCy_2$, $J_{(P-P)}$ 35.4Hz). After workup, the mixture **12a/12b** was isolated in 90% yield as an orange powder. Similarly, complex **9** was converted to a mixture of two diastereomers [RuI(*p*-cymene)((S)-ProNOP)]I (**13a/13b**). Complexes 7 and **10** were converted to mixtures of diastereomers **11a/11b** [RuCl(C_6H_6)((S)-ProNOP)]Cl and **14a/14b** [RuBr(C_6H_6)((S)-ProNOP)]Br respectively through stirring in isopropanol at room temperature for 24 hours.[14] Complexes **11** to **14** could be synthesised in one step in their chelating solvent (acetonitrile or isopropanol) but the reaction was less selective and showed poor reproducibility. The exact structure of the major diastereomers has not been clarified owing to non-availability of single crystals suitable for X-ray crystallography.

Next, the diastereomeric mixtures of cationic ruthenium complexes were applied in the enantioselective hydrogenation of **3**. Hydrogenations were carried at room temperature and at 60 °C under an initial H_2 pressure of 60 bar. The substrate **3** was hydrogenated with low to fair enantioselectivity (3-42%) to the corresponding optically active pantolactone. Selected results are summarised table 1.

Table 1. Enantioselective hydrogenation of **3** [a]

run	precursor	solvent	T (°C)	conv. (%) [b]	ee (%) [c]
1	Rh(Cp-oxo-ProNOP)[d]	$PhCH_3$	rt	100	96
2	**12**	CH_2Cl_2	rt	29	6
3	**11**	CH_2Cl_2	60	100	33
4	**11**	CH_2Cl_2	rt	47	41
5	**11**	CH_2Cl_2/EtOH[e]	rt	50	42
6	**11**	EtOH	60	100	21
7	**14**	CH_2Cl_2	60	71	26
8	RuBINAP[f]	CH_2Cl_2	rt	26	43
9	RuBINAP	EtOH	60	100	10
10	RuBINAP	EtOH	rt	10	82
11	**13**	EtOH	60	100	6
12	**7**	THF	rt	6	3

[a] Reactions were carried out by using 6.10^{-3} M of recrystallized substrate dissolved in the specified solvent. Substrate/Ru : 200/1. A stainless steel autoclave was used and an initial pressure of hydrogen of 60 bar. [b] Conversions were determined by GC. The reaction times were not optimised and all reactions runned for 14 hours. [c] determined by GC analysis (FS-cyclodex beta-I/P) on the isolated product. The mixture of unreacted **3** and the product or the product alone when the conversion was 100% were isolated in > 95% yield. All the hydrogenation products are (R). [d] Precursor $[RhCl(Cp\text{-}oxo\text{-}ProNOP]_2$[7c], reaction time 72 min, H_2 1 bar, substrate/Rh : 200/1. [e] 1:1 ratio. [f] $[RuCl(C_6H_6)((+)\text{-}(R)\text{-}BINAP)]Cl$.[8]

The asymmetric induction decreased significantly when (S)-Cy-ProNOP was used as the ligand (run 2) compared to (S)-ProNOP (run 4). This behaviour is opposite to what was observed with rhodium based catalysts.[7] This suggest that with more "acidic" ligands, one might expect an increase of enantioselectivity. The hydrogenation does not take place at room temperature and at 1 bar of H_2. The chirality induced in the product (R) is the same as that obtained by the "Rh(AMPP)" analogues (using the same AMPP enantiomers).[7] A decrease of temperature induces a higher enantioselectivity (runs 3 and 4). It is unclear if only one of each diastereomeric pair is responsible for the asymmetric hydrogenation reaction as the reaction is done with the mixture of diastereomeric precursors. So far we have been unable to separate them or to obtain the mixtures with different ratios. A comparison with precursor $[RuCl(C_6H_6)((R)\text{-}BINAP)]Cl$ (runs 4 and 8) showed that in CH_2Cl_2, ProNOP ligand and BINAP induce equivalent selectivities. But in presence of EtOH this induction becomes significantly different (runs 5 and 10). With precursor **7**, a monohapto species, only a very low activity and selectivity are observed (run 12).

In summary, this is the first report on the synthesis of $Ru(II)X_2(arene)(P_2^*)$ precursors bearing monohapto chiral bisphosphines. More, our method allows the production of cationic $[Ru(II)X(arene)(P_2^*)]X$ complexes under mild conditions. So far, the presented ligands showed only moderate selectivities for the asymmetric hydrogenation of **3**. Future reports will focus on the synthesis of ruthenium complexes bearing other AMPP ligands and on their use in asymmetric hydrogenation of other activated ketones and olefins.[15]

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12. Complexes **7** to **10** were characterised by ^{1}H, ^{13}C and ^{31}P NMR. Typical ^{31}P $\{^{1}H\}$ NMR data at 121 MHz are (ppm, all resonances are sharp singlets) : **9** (THF) 105.9 ($OPPh_2$), 42.7 ($NPPh_2$) ; **10** (*i*-PrOH) 107.2 ($OPPh_2$), 46.4 ($NPPh_2$).
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15. F. Hapiot, F. Agbossou and A. Mortreux, manuscript in preparation.

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