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ASYMMETRIC HYDROGENATION OF ACTIVATED KETO COMPOUNDS CATALYZED BY NEW CHIRAL PERALKYL-AMPP RHODIUM COMPLEXES

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Summary : Readily available peralkyl aminophosphinephosphinite ligands (alkyl-AMPP*) give neutral rhodium complexes active for the catalytic reduction of some activated ketones under atmospheric hydrogen pressure at ambient temperature (ee = 80 %).

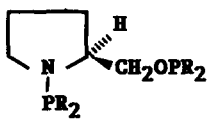
Asymmetric hydrogenation of ketones has been performed under rather drastic conditions on rhodium diphosphine catalysts in moderate optical yields[1].

Much better ee's have been obtained recently on ruthenium catalysts with functionalized ketones as substrates[2] and previous results on α-diketones have also proved that these bifunctionnal compounds exhibit a better ability to provide asymmetric alcohol derivatives[3]. This behavior has been confirmed by the use of peralkyl diphosphine ligands which enhances both activity and selectivity on rhodium catalysts[4].

We have found that we could get easily related alkyl compounds in only one simple reaction between a chiral aminoalcohol and a dialkyl chlorophosphine, in a modification of the procedure used to prepare aminophosphinephosphinite ligands[5] (AMPP*) :

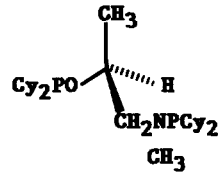
$$HO\overset{*}{C}HR_1\overset{*}{C}HR_2NHR_3 + 2P(R)_2Cl \xrightarrow{Et_3N} \underset{\text{alkyl-AMPP}^*}{P(R)_2O\overset{*}{C}HR_1\overset{*}{C}HR_2NP(R)_2R_3}$$

Among these new chelating ligands, some good results have been obtained with the following : (S)-Cy-ProNOP **1** ; (S)-Cp^S-ProNOP **2** ; (S)-Cy-isoAlaNOP **3** (Cy = cyclohexyl, Cp^S = cyclopentyl).



1 : R = Cy

2 : R = Cp^s



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As shown in Table 1, good enantioselectivities can be obtained with neutral AMPP* modified rhodium catalysts, during reduction of N-benzylbenzoylformamide and its p-OH substituted derivative :

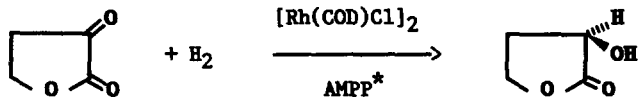
$$PhCOCONHBz + H_2 \xrightarrow[AMPP^*]{[Rh(COD)Cl]_2} Ph\overset{*}{C}H(OH)CONHBz$$

Table 1 : Asymmetric hydrogenation of α-ketoamides on $[Rh(COD)Cl]_2$-AMPP* catalysts.[a]

Substrate S	Ligand	S/Rh	$t_{1/2}$ (min)	Reaction Time (H)	ee(%)
$C_6H_5COCONHCH_2C_6H_5$	1	200	20	2	74(+)[d]
"	1	1000[b]	72	12	73(+)
"	2	200	5	0.5	79(+)
"	2	1000[b]	38	2	76(+)
"	3	200	16	1.5	75(-)
$p\text{-}OHC_6H_4COCONHCH_2C_6H_5$	1	200[c]	n.d.	6	66(+)[e]

[a] The catalysts are prepared either in situ from 1/2 $[Rh(COD)Cl]_2$ and 1 eq. of ligand 1-3 or isolated. Reactions were conducted with 12 mmol of substrate in 30 ml of anhydrous toluene under 1 atm. of H_2 at 20°C unless otherwise stated. [b] 15 ml of toluene were used. [c] A mixture of benzene and methanol (2/1) was used instead of toluene. [d] The reported optical rotation for the optically pure (S)-(+)-enantiomer of $Ph\overset{*}{C}H(OH)CONHCH_2Ph$ is lower than that we obtained, $[\alpha]_D^{26}=+82°$ (C 1.09, $CHCl_3$). [e] Determined on the basis of the optical rotation of the enantiomerically pure product $p\text{-}OHC_6H_4CH(OH)\overset{*}{C}ONHCH_2Ph$, isolated by repeated cristallisations, $[\alpha]_D^{20}=+53°$ (C 1,CH_3OH).

Applying these catalysts to α-ketoesters, more interesting results are found during the synthesis of chiral-2-hydroxy-3,3-dimethyl-γ-butyrolactone (pantolactone) from the corresponding ketone, as a very high substrate/catalyst ratio could be used without any loss of optical yield (Table 2).



Furthermore, according to the ligand used, both enantiomers could be formed with ee's as high as 77% (R(-)) with 2 and 80% (S(+)) with 3, like what was observed in Table 1 with the same ligands during N-benzylbenzoylformamide reduction.

Table 2 : Asymmetric hydrogenation of α-keto esters on $[Rh(COD)Cl]_2$-AMPP* catalysts.[a]

Substrate S	Ligand	S/Rh	$t_{1/2}$ (min)	Reaction Time (H)	ee(%)
o,p-$(CH_3O)_2C_6H_4COCOOC_2H_5$	1	100[b]	n.d.	15	56(-)[d]
"	2	100[b]	n.d.	15	64(-)
$CH_2C(CH_3)_2COCOO$	1	200	27	6	47(-)
"	2	200	19	1	76(-)
"	2	5000[c]	n.d.	2	76(-)
"	2	10000[c]	n.d.	3	77(-)
"	3	200	13	1.3	80(+)

[a] Conditions are the same as in Table 1. [b] 30 atm H_2. [c] Determined by ^{19}F NMR analysis of the Mosher ester derivatives[6]. [d] 50 atm, 70°C, 30 ml toluene. [e] Determined on the basis of the reported optical rotation for pure R-pantolactone $[\alpha]_D^{25}$=-50.7° (C 2.05 , H_2O)[7].

It has to be noticed that in this case, the ee's are not lowered upon increasing temperature and that substitution of the cyclohexyl groups on phosphorus by cyclopentyl moities greatly enhances both the activity and the enantioselectivity.

Due to the ease of preparation of alkyl AMPP* ligands and the good results here reported, active investigation is continuously under way and a detailed description will appear elsewhere.

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