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Chiral β-aminophosphine oxides as ligands for ruthenium assisted enantioselective transfer hydrogenation of ketones

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Abstract

Enantiopure β-aminophosphine oxide ligands have been synthesized and used in asymmetric transfer hydrogenation of ketones. Optically active alcohols are obtained in high yields and with up to 84% enantiomeric excess.

1. Introduction

There has recently been much interest in asymmetric catalytic transfer hydrogenation of ketones using 2-propanol as the hydrogen donor for preparation of enantiomerically pure secondary alcohols.[1,2] Catalytic systems with various levels of efficiency have emerged which involve ruthenium complexes modified by various di- or tridentate ligands, i.e., diamines,[3] amino alcohols,[4] diureas,[5] amidates,[6] oxazoline/amines[7] and phosphine/amines.[8] It is worth noting that among the most efficient catalysts developed so far, the presence of a primary or secondary amine moiety is crucial for a catalytic activity.[2,9]

We have had an ongoing interest in the synthesis and use of optically active ligands in asymmetric catalysis, especially diphosphines and related chiral modifiers.[10] To date, all our studies have featured one or two phosphorus(III)-end groups for the ligands which are quite sensitive towards oxygen when not coordinated to a metallic center. On the other hand, some of us are making efforts towards the synthesis of functionalized P-chiral phosphine oxide derivatives.[11] Although the synthetic aspect to P-chiral phosphine oxides has been investigated,[12] to the best of our knowledge the use of such derivatives as ligands in asymmetric catalysis has not so far been reported. Moreover, even the use of achiral phosphine oxide based ligands has scarcely been reported.[13] We have been attracted by hybrid ligands where one

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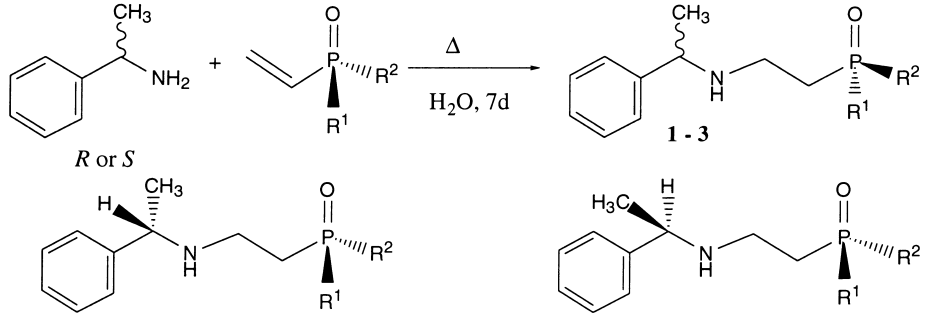
end would be a chiral phosphine oxide and the other an amine, both connected by an appropriate spacer. In fact, such ligands are expected to exhibit potential activity for asymmetric catalysis as they should have the combined properties of their components.[13] Thus, we sought to develop the chemistry of these optically active phosphine oxides including the construction of mixed chiral β-aminophosphine oxide ligands.

In this communication, we present our preliminary results on the synthesis and use of P-chiral β-amino phosphine oxides in asymmetric catalysis and report the first example of ruthenium-catalyzed enantioselective transfer hydrogenation of aryl ketones involving such ligands.

2. Results and discussion

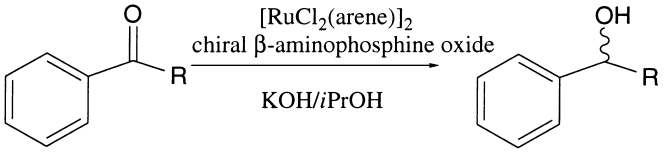
As shown in Scheme 1, diphenylvinylphosphine oxide and (*R*)-*tert*-butylphenylvinylphosphine oxide[14] were reacted with a 5–10 molar excess of the pertinent enantiomer of 1-phenylethylamine in water (closed ampule, 110°C, 7 days) and yielded the desired β-aminophosphine oxides **1**–**3** practically quantitatively.[15] After the extractive workup ($CHCl_3$), and removal of the excess of amines under reduced pressure, the crude oxides **1**–**3** were finally purified by column chromatography (silica gel, chloroform:acetone, 3:1).[16]



1 (S_C) R^1=R^2=Ph
2 (R_P, S_C) R^1=*t*Bu R^2=Ph
3 (R_P, R_C) R^1=*t*Bu R^2=Ph

Scheme 1.

These ligands were then examined in the asymmetric transfer hydrogenation of arylketones **4**–**6** to the corresponding alcohols (Scheme 2). The catalysts were generated in situ prior to hydrogen transfer by heating a mixture of either $[RuCl_2(p\text{-cymene})]_2$ **A** or $[RuCl_2(\text{hexamethylbenzene})]_2$ **B**[17] with the appropriate ligand (2 equiv. vs Ru) at 80°C for 20 min in dry 2-propanol. During this period, the color changed from orange to deep red. A 2-propanol solution of the substrate followed by KOH was then added to the mixture. The results are summarized in Table 1.



4 R=Me
5 R=Et
6 R=*i*Pr

Scheme 2.

Table 1
Transfer hydrogenation of arylketones in the presence of ruthenium catalysts[a]

Entry	Ligand	Substrate	Ru precursor	Time (h)	Conv. (%)[b]	ee (%)[c]	Conf.[d]
1	**1**	**4**	**A**	18 (25)	22 (22)	34 (34)	*R*
2[e]		**4**	**A**	1 (4)	31 (87)	15 (10)	*R*
3[e]		**5**	**A**	1 (17)	17 (90)	11 (3)	*R*
4[e]		**6**	**A**	1 (18)	11 (22)	0	-
5	**2**	**4**	**A**	0.5	93	50	*R*
6[e]		**4**	**A**	0.25	91	36	*R*
7		**5**	**A**	1	70	35	*R*
8		**6**	**A**	1	63	28	*S*
9		**4**	**B**	1	95	45	*R*
10		**5**	**B**	1	96	10	*R*
11		**6**	**B**	1	85	84	*R*
12	**3**	**4**	**A**	1	93	43	*S*
13		**5**	**A**	1	81	30	*S*
14		**6**	**A**	1	36	15	*S*

[a]Reactions were carried out by using 2 mmol of the substrate in 20 mL *i*PrOH at 20 °C unless otherwise stated in the presence of either complex **A** $[RuCl_2(p\text{-cymene})]_2$, or **B** $[RuCl_2(\text{hexamethylbenzene})]_2$, (substrate/Ru = 100), the ligand (ligand/Ru : 1) and KOH (0.1 mmol). For details about the preparation procedure see the text. [b]The progression of the reaction was monitored by GC analysis with a Chiraldex capillary column. [c]Determined by GC analysis with a Chiraldex capillary column. [d]Absolute configurations were determined by comparing the sign of the optical rotations with the literature ones. [e]Reactions performed at 60 °C.

The first catalytic system investigated was composed of a combination of the precursor **A** and the aryl-substituted ligand **1**, presenting a single carbon centered chirality. At room temperature, transfer hydrogenation to acetophenone **4** occurred slowly with a modest enantioselectivity (34% ee, entry 1) and stopped at 22% conversion. At 60°C, the rate remained low (31% after 1 h) and the enantiomeric excess dropped (entry 2 vs 1). In the same way, transfer hydrogenation with ligand **1** to ketones **5** and **6** occurred with poor conversions and a decrease of the ee along with the time is also observed (entries 3 and 4). The results obtained with ligand **1** suggest a decomposition of the enantioselective active species during the catalysis at 60°C. Interestingly, the reaction rate could be enhanced by changing the nature of the substituents on the phosphorus atom. Thus, replacing a phenyl moiety by a *tert*-butyl group induced an increase of the conversion and the reaction could be carried out at room temperature (entries 5, 7 and 8). An increase of the enantioselectivity was observed as well (at room temperature from 34 to 50% ee, entry 1 vs 5, at 60°C, from 15 to 36 ee%, entry 2 vs 6). However, it has to be noted that in addition to the substituent change, a second chiral element, phosphorus centered, was present in **2** when compared to **1**.

As observed, the reaction rate is also dependent on the steric properties of the substrates. This point is illustrated by the results obtained upon variation of the alkyl group of the ketone, the *iso*-propylphenylketone leading to sluggish catalysis (entries 4, 8 and 14). This trend was further confirmed when a similar catalysis was performed with PhCO*t*Bu (4.5 h, 35% conversion, 22% ee). Enantioselectivities also relied upon the nature of this alkyl group. For example, lower ees were always observed for the *iso*-propyl substituted substrate **6** (entries 4 and 8).

The general trend given above for *p*-cymene based catalysts was not followed by the complex bearing

the hexamethylbenzene unit. Indeed, a surprisingly higher enantioselectivity was reached for the most hindered substrate **6** (entry 11). Moreover, even in the presence of the diastereomeric ligand **3**, the induction remained quite good for that substrate as 60% ee were observed with a 62% conversion over 1 h. That specific trend has not been rationalized so far. Nevertheless, we may attribute the major contribution to both the activity and the enantioselectivity to the phosphine oxide moiety. The presence of an alkyl group on the phosphorus atom is essential in two respects. First, an enhancement of the coordination ability of the oxygen atom of the P=O is expected. Second, the stereogenicity at the phosphorus atom induced a consequent increase in the level of enantioselection. These features strongly support the participation, eventually through coordination, of phosphine oxide during the catalytic cycle of the ruthenium complexes.

We therefore sought to spectroscopically identify the behaviour of the chiral phosphine oxide ligands in the presence of ruthenium complexes as coordinated P=O exhibit distinctive ^{31}P NMR and IR features[18] possibly under catalytic conditions. Thus, ligand **2** and **A** were combined in 2-propanol in a NMR tube. The ^{31}P NMR spectrum of the mixture provided a single signal at 52.2 ppm which is also the chemical shift for the free ligand. Consequently, there is no real evidence for a P=O coordination. Hence, the initial color change, i.e., from clear orange to deep red, attributed to the dimer cleavage most probably by the amino group of the ligand. A subsequent addition of KOH led to a darkening of the mixture. Nevertheless, the ^{31}P NMR remained unchanged. Next we carefully examined the IR spectra obtained from the above mixtures as the P=O moiety is most readily distinguished through the change in frequency of the P=O stretching vibration. Unfortunately, the above experiments provided no clear evidence for coordination–chelation of the hemilabile ligands through the P=O end.

Although the contribution of the chiral P=O moiety in these ligands have been shown via this study, there is no evidence for some coordination of this group on the metal. Further studies are in progress to explain the improvement of both activity and enantioselectivity related to this P=O end group and to extend the use of these new ligands in other asymmetric catalytic reactions.

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16. Selected physical properties: **1**: mp: 176–177°C, ^{31}P NMR ($CDCl_3$) δ=32.0 ppm, $[\alpha]_D$= −24.0 (*c* 2.5, $CHCl_3$). **2**: mp 69.5–71°C, ^{31}P NMR ($CDCl_3$) δ=49.0 ppm, $[\alpha]_D$= −56.6 (*c* 2.5, $CHCl_3$). **3**: semisolid, ^{31}P NMR ($CDCl_3$) δ=49.0 ppm, $[\alpha]_D$= +30.6 (*c* 2.5, $CHCl_3$).
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