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P-chiral β-aminophosphine oxides vs. β-aminophosphines as auxiliaries for ruthenium catalysed enantioselective transfer hydrogenation of arylketones

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Abstract

Enantiopure P-chiral β-aminophosphine oxides and the corresponding β-aminophosphines have been synthesised and used as chiral auxiliaries in ruthenium catalysed asymmetric transfer hydrogenation of arylketones producing optically active alcohols up to 80% ee. Both types of auxiliaries provide comparable induction levels but the β-aminophosphine oxide ligands induce higher catalytic activities generally. In some experiments, when changing the *achiral* arene ligand in the catalyst precursor, a peculiar reversal of the product configuration was observed.

Keywords: Ruthenium; Transfer hydrogenation; Chirality; Ketone; Alcohol; Phosphine oxide

1. Introduction

Asymmetric hydrogen transfer using alcohols as the hydrogen source appears to be an especially valuable method for the reduction of prochiral substrates into optically active compounds because of the easy set up of the experiments [1]. Ketones have been reduced with high levels of efficiency and enantioselectivity in the presence of ruthenium [2], iridium [3], and rhodium [4] catalysts. Very efficient catalytic systems have been developed for ruthenium associated to aminophosphines [5], aminoalcohols [6], monotosylated-1,2-diamines [7], and diamines [8].

Recently, we have demonstrated that asymmetric transfer hydrogenation of alkylarylketones could be achieved efficiently in the presence of chiral β-aminophosphine oxides [9]. We have found that the ligands containing a P-chiral alkylarylphosphinoyl moiety in their structure proved to be the most efficient. We sought to undertake a systematic study to compare the properties of the above chiral β-aminophosphine oxides and the corresponding P-chiral β-aminophosphines obtained by the reduction of the P-chiral alkylarylphosphinoyl moiety. However, the above-mentioned ligands could not be converted into the corresponding P-chiral aminophosphines. Thus, new ligands bearing a reducible chiral phosphinoyl group were sought.

Here we report the synthesis and use in asymmetric transfer hydrogenation of two new P-chiral aminophosphine oxide ligands and their corresponding P-chiral aminophosphines. This time the former has borne a readily reducible methylphenylphosphinoyl group, which was meant to secure their easy conversion into the corresponding phosphines. These new ligands also bear a secondary NH functionality, which appears to be essential to obtain good activity [2]. The selected ligands enable us to compare the efficiency of P-chiral aminophosphine oxide vs. P-chiral aminophosphine in the asymmetric transfer hydrogenation of the ketones studied.

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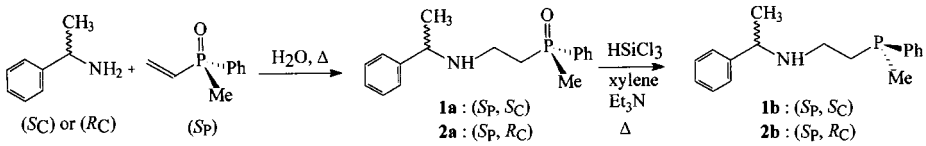
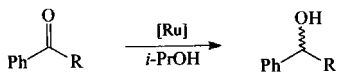


Scheme 1.

2. Results and discussion

The optically pure diastereomeric β-aminophosphine oxides S_P,S_C-**1a** and S_P,R_C-**2a** were prepared by the reaction of (S_P)-vinylmethylphenylphosphine oxide with (S_C)- and (R_C)-1-phenylethylamine, respectively, following our previously reported protocol (Scheme 1) [9,10]. The oxides **1a** and **2a** were then reduced stereoselectively under standard conditions using $HSiCl_3$ in the presence of triethylamine [11]. Under these conditions, the inversion of configuration at phosphorus is routinely observed [12].[1] This step provided the corresponding P-chiral aminophosphines S_P,S_C-**1b** and S_P,R_C-**2b** in quantitative yields (Scheme 1). Importantly, no loss of the optical purity was observed during this process. The oxidation of **1b** and **2b** by means of H_2O_2 in chloroform, known to occur with a clean retention of configuration [13], provided *ent*-**2a**(R_P,S_C) and *ent*-**1a**(R_P,R_C), respectively, which accordingly exhibited specific rotations equal in magnitude and opposite in sign to those recorded for **2a** and **1a**. This correlation confirmed unequivocally the optical purity and the assigned absolute configuration of phosphines **1b** and **2b**.[2]



R = Me: **3**; Et: **4**; *i*-Pr: **5**

[Ru] = (**A** or **B**) + chiral ligand + KOH
Ru / ligand / KOH = 1 : 2 : 5
A [Ru(*p*-cymene)Cl2]2
B [Ru(hexamethylbenzene)Cl2]2

Scheme 2.

The obtained ligands were then examined in the ruthenium catalysed transfer hydrogenation of arylketones **3**–**5** to the corresponding chiral alcohols (Scheme 2). The Ru catalysts were prepared by heating the precursor $[RuCl_2(arene)]_2$ (**A**: arene = *p*-cymene, **B**: hexamethylbenzene) with two equivalents of the ligand in *i*-PrOH at 80°C during 20 min. The catalytic reactions were carried out following the procedure described previously [9]. The results are summarised in Table 1.

The examination of the results indicates clearly that with each of the tested ligands, the best enantioselectivity was achieved in the reduction of *i*-butyrophenone (**5**) and when $[RuCl_2(hexamethylbenzene)]_2$ (**B**) was used as the catalyst precursor.[3] The highest ees (80–78%) were reached with aminophosphine ligands **1b** and **2b** although it should be noted that with the corresponding aminophosphine oxides **1a** and **2a** only a slightly lower level of induction was observed (65–76%). In the context of the four best results (entries 6, 12, 18, and 24), it could be reasonably argued that the absolute configuration of the product is governed by the carbon centred chirality of the amine residue regardless of the configuration and the oxidation level of the phosphine part of the ligand used. Intriguingly, however, when the arene ligand in the catalyst precursor was changed from hexamethylbenzene to *p*-cymene in those *i*-butyrophenone reductions, a dramatic decrease of catalyst activity as well as of the resulting ee was observed (entries 5, 11, 17, and 23). In addition, in the two cases involving phosphine oxide ligands, this deteriorating effect was also accompanied by the reversal of the configuration of the major alcohol produced (entries 5 and 17). It thus appears that the nature of the achiral ligand can also play a crucial role in the asymmetric transfer hydrogenations, as it was already reported for other substrates [14].

For acetophenone (**3**) and propiophenone (**4**) reductions, the *p*-cymene catalyst precursor **A** proved more suitable than **B** and for both substrates similar ees were obtained. Again, the above-mentioned reversal of configuration was observed here (entries 10 vs. 9 and 22 vs. 21) and it is difficult to trace a clear-cut correlation between the ligand and the product chiralities. How-

[1] The inversion of the spatial arrangement of the groups around phosphorus in the reduction step does not require a change of the descriptor of the absolute configuration. As a matter of fact, in the process, the oxygen ligand of the highest priority is replaced by a lone pair of the lowest priority, according to the Cahn–Ingold–Prelog system.

[2] Selected physical properties: **1a**: ^{31}P-NMR ($CDCl_3$) $\delta = 36.1$ ppm, $[\alpha]_D = +27.3$ (*c* 5.3, $CHCl_3$)[10]; **1b**: ^{31}P-NMR ($CDCl_3$) $\delta = -40$ ppm, $[\alpha]_D = -5.6$ (*c* 3.2, $CHCl_3$); **2a**: ^{31}P-NMR ($CDCl_3$) $\delta = 36.1$ ppm, $[\alpha]_D = -56.1$ (*c* 3.2, $CHCl_3$)[11]; **2b**: ^{31}P-NMR ($CDCl_3$) $\delta = -40$ ppm, $[\alpha]_D = -24.3$ (*c* 3.4, $CHCl_3$).

[3] This favourable substrate–catalyst matching was already observed in our previous study involving analogous aminophosphine oxide ligands. See Ref. [9].

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

Entry	Chiral ligand	Substrate	Ru precursor	Time (h)	Conversion (%) [b]	ee (%) [b]	Configuration [c]
1	**1a**	**3**	**A**	1	95	55	*R*
2		**3**	**B**	0.1	93	50	*R*
3		**4**	**A**	3	94	53	*R*
4		**4**	**B**	0.25	95	0	–
5		**5**	**A**	24	22	8	*S*
6		**5**	**B**	3	93	76	*R*
7	**1b**	**3**	**A**	17	95	57	*S*
8		**3**	**B**	1.5	93	49	*S*
9		**4**	**A**	24	85	57	*S*
10		**4**	**B**	2.5	65	9	*R*
11		**5**	**A**	24	74	13	*R*
12		**5**	**B**	17	92	80	*R*
13	**2a**	**3**	**A**	3	91	39	*S*
14		**3**	**B**	0.25	91	22	*S*
15		**4**	**A**	3	92	34	*S*
16		**4**	**B**	1	97	16	*S*
17		**5**	**A**	17	48	5	*R*
18		**5**	**B**	3	93	65	*S*
19	**2b**	**3**	**A**	4	93	23	*S*
20		**3**	**B**	4	71	19	*S*
21		**4**	**A**	17	71	18	*S*
22		**4**	**B**	17	57	43	*R*
23		**5**	**A**	3	44	6	*S*
24		**5**	**B**	43	83	78	*S*

[a] Reactions were carried out by using 2 mmol of the substrate in 20 ml *i*-PrOH at 20°C 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: 2) and KOH (0.1 mmol).
[b] The conversions of the substrate and the ees were monitored by GC analysis using a Chirasildex capillary column.
[c] Absolute configurations were determined by comparing the sign of the optical rotations with those of the literature.

ever, the carbon centred chirality seems to dominate in the phosphine oxide ligands (entries 1–6 vs. 13–18) whereas for the phosphine ones, this tendency is less pronounced (entries 7–12 vs. 19–24).

The catalyst activities in the studied hydrogen transfer reactions were generally much higher for the phosphine oxide ligands **1a** and **2a** than for the phosphine ligands **1b** and **2b**. For example, under identical conditions, transfer hydrogenation of acetophenone **3** with the system $[RuCl_2(p\text{-cymene})]_2$–**1a** led to 95% conversion and 55% ee within 1 h whereas with **1b** as the chiral auxiliary, the same 95% conversion and 57% ee was achieved only after a 17 h period (entries 1 vs. 7). This higher catalyst activity can be explained by the inherent hemilabile character [15] of the phosphine oxide ligands which can generate an open coordination site at ruthenium more easily, thus allowing a faster substrate complexation. The tendency observed above when considering the outcome of the chirality at phosphorous in the sense of enantioselection can also illustrate the hemilabile properties of the phosphine oxides. Indeed, the chirality at phosphorous presents a greater influence and dictates in most cases the configuration of the product for the most coordinating ligand, e.g. the phosphines, whereas using the phosphine oxides, the latter is much more governed by the carbon configuration within the ligand frame.

3. Conclusions

In summary, we have shown that the P-chiral aminophosphine oxides constitute an interesting source of precursors for the synthesis of P-chiral aminophosphines, which are valuable chiral ligands for the asymmetric catalysis. For the ruthenium catalysed transfer hydrogenation of ketones, the latter are, however, less efficient than their parent P-chiral aminophosphine oxides. We have indeed demonstrated that the use of readily available and air-stable P-chiral β-aminophosphine oxides as chiral ligands in ruthenium catalysed asymmetric transfer hydrogenation of ketones results in the formation of efficient catalytic systems which yield products of high enantiomeric purity. We are still unable to definitely prove that the phosphine oxide moiety of those ligands really coordinate to the ruthenium centre but the recent results published by Faller and coworkers [15] suggest strongly that such coordination can be effective. Studies in this direction are in progress.

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