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Effect of diphosphine ligands on ruthenium catalysed asymmetric hydrogenation of ketones

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Abstract

A series of diphosphines including those that are configurationally flexible were examined in the Ru(II) catalysed enantioselective hydrogenation of 1-acetonaphthone in the presence of a chiral diamine. These ligands were found to exert significant effects on both the activity and enantioselectivity of Ru(II)-diamine catalysts, with the ligand with the smallest bite angle yielding the lowest conversion and the one with largest bite angle yielding the lowest enantioselection.

Keywords: Diphosphines; Bite angles; Asymmetric hydrogenation; Ketones; Ruthenium catalysts; Diamines

1. Introduction

One of the most significant developments in asymmetric catalysis in recent years is the discovery by Noyori and co-workers of highly efficient ruthenium catalysts for enantioselective hydrogenation of ketones, a reaction leading to chiral alcohols and of great importance to the synthesis of a variety of natural and non-nature products [1]. In the Noyori catalyst, ruthenium is combined with a chiral diphosphine and a chiral diamine forming an octahedral complex, a typical example of the former being (*S*)- or (*R*)-Binap and that of the latter being (*S*,*S*)- or (*R*,*R*)-diphenylethylenediamine (Dpen). Noyori further showed that matching the chirality of diphosphines with that of a diamine is critical to high hydrogenation rates and enantioselectivities [1,2]. This matching in chirality can be put into practice by physically selecting the right enantiomers of Binap and Dpen, but can also be brought about chemically through asymmetric activation, in which a chirally dynamic diphosphine, such as 2,2′-bis(diphenylphosphino)-1,1′-biphenyl (Biphep), is employed and its chirality is induced by the coordinated chiral diamine [3]. However, aside from Binap and its derivatives, few other diphosphines have been reported for the Noyori catalyst systems [1a,4]. We herein present a brief report on how the choice of diphosphines may affect the outcome of ketone hydrogenation. Specifically we investigated the combination of Dppe, Dppp, Dppb, Dppf and Xantphos with Ru(II)-Dpen for the enantioselective hydrogenation of 1-acetonaphthone (Scheme 1).

These ligands have bite angles ranging from 85 to 112° [5]. The bite angles of diphosphines have been shown to be an important parameter in affecting catalyst activity and selectivity, although their effects have been rarely investigated in asymmetric hydrogenation [5,6]. Further, the chirality at the Dpen ligand might induce a chiral disposition of the phenyl rings at the phosphorus and stabilise a chiral

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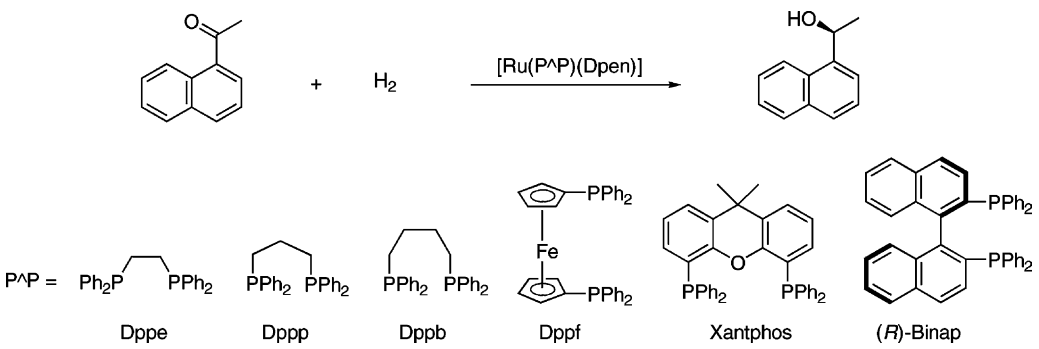
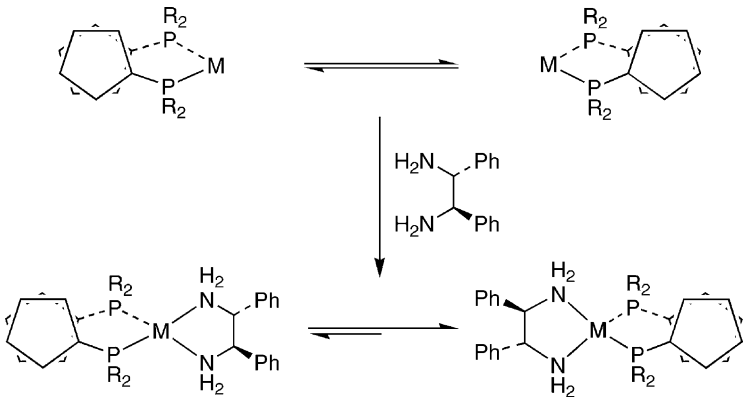


Scheme 1. Enantioselective ketone hydrogenation with Ru(II)-diphosphine-diamine catalysts.



Scheme 2. Asymmetric activation of the conformationally flexible Dppf by a chiral ligand.

conformation of the chelated diphosphines, and this induced chirality could lead to enhanced enantioselectivities in the hydrogenation using achiral phosphines. (For examples of improving asymmetric catalysis by combining chiral and achiral ligands, see [7].) The chiral arrangement of the phosphorus phenyl rings plays a key role in determining enantioselectivities in asymmetric catalysis by chiral diphosphines, but the chirality of the phenyl rings is usually transmitted by the chiral backbone of phosphines [8]. In the case of Dppf, an additional interesting dimension arises. Most of the reported metal Dppf complexes contain staggered Cp-P moieties, which can lead to the formation of two enantiomers of an equal ratio [9]. Upon the introduction of a chiral diamine such as (*R*,*R*)-Dpen, two diastereomers are formed, one of which could dominate and give rise to an active and enantioselective catalyst (Scheme 2).[1] The control of chirality of the Dppf ligand by Dpen is chemically similar to that involving Biphen; both Dppf and Biphen possess dynamic, potential axial chirality (for some recent examples, see [11]). In fact, Mikami has recently reported that Ni(II)-Dppf in the presence of a chiral diamine effects high ee's in the asymmetric ene reaction of ethyl glyoxylate with alkenes [11a].

2. Results and discussion

The hydrogenation reaction was effected by the catalyst formed by combining [$RuCl_2$(diphosphine)-

[1] Our work on the asymmetric activation of Dppf was first presented at the LCIC Fine Chemical Forum Meeting, September 2001. For our related work see [10].

$(DMF)_n$] with one equivalent of (*R*,*R*)-Dpen in DMF [12]. To ensure the formation of the pre-catalyst, [$RuCl_2$(diphosphine){(*R*,*R*)-Dpen}], (*R*,*R*)-Dpen was stirred at ambient temperature in DMF for 1 h with each of the Ru-diphosphine complex, which was generated by reacting [$RuCl_2$(benzene)]$_2$ with a diphosphine at 100 °C for 0.5 h in the same solvent. It should be stressed, however, that no further characterisation of these pre-catalysts were undertaken and hence their true nature could differ from that of [$RuCl_2$(diphosphine){(*R*,*R*)-Dpen}]. All the reactions were carried out with Ru:KO^{t}Bu:ketone = 1:6:500 (6.6 mmol of 1-acetonaphthone) at 10 bar H_2 and 20 °C for 3 h in 2-propanol. For comparison, (*R*)-Binap was also tested under the same conditions. Table 1 summarises the results obtained.

As can be seen from the table, the Ru-Dpen-diphosphine complexes display activities and enantioselectivities that vary significantly with the diphosphine ligands. The catalyst derived from Dppe, which has the smallest ligand bite angle, is the least active. Increasing the bite angle did result in higher conversions. However, the degree of increase in reaction rates with bite angles varies with ligands. Thus, while Dppp has a bite angle similar to that of Binap, the latter is much more effective in the hydrogenation, and the still larger bite angle in the case of Dppb does not lead to a higher conversion than Dppp. Xantphos having the largest bite angle is as active as Binap, but Dppf, with a bite angle of 96° larger that of Binap, yielded a lower conversion than the latter, although one needs keep in mind that Dppf is capable of adopting a wide range of bite angles [9]. Thus, it is clear that while a small bite angle is less effective in bringing about turnovers, the large variants do not necessarily lead to active catalysts. Regardless of bite angles, however, it appears from the table that arylphosphines yields more active catalysts than the alkylarylphosphines. It has recently been indicated that the key step in the Noyori catalyst system is the heterolysis of coordinated H_2 yielding Ru(II)-H and the high hydrogenation rates observed with the Noyori catalyst is a result of alkali metal cation coordination to the Ru-NR_2 amide moiety, which withdraws electron density from Ru(II) and hence enhances the acidity of Ru-H_2 [13]. Dppe with the smallest bite angle could lead to a more electron rich Ru(II) [5] thus reducing the acidity of Ru-H_2 and so the rate of H_2 heterolysis. The higher activity associated with the arylphosphines Xantphos and Binap corroborates this view, as these ligands are less basic than the first three ligands in Table 1. The lower activity with Dppf compared with Xantphos is probably due to it being more electron donating than the latter [14].

In terms of enantioselectivity, the three alkylarylphosphines produced similar results, although the ee value with Dppp is slightly higher, suggesting that the remote (*R*,*R*)-Dpen is not capable of inducing a stable chiral conformation at the phosphine chelates. Dppf yielded a still higher ee than Dppp, but much lower than that obtained with Binap. The ee value with Dppf could be further increased to 70% when the reaction temperature was lowered to −20 °C. The higher ee value with Dppf could result from the asymmetric activation by (*R*,*R*)-Dpen discussed earlier. If so, the chirality induction at Dppf by Dpen would appear less effective than using modified Biphep and Dpen; the latter gave ee's up to 84% in the same reaction at 28 °C [3]. This is probably due to the greater flexibility of Ru-Dppf than Ru-Biphep moieties. Indeed, in the asymmetric ene reaction catalysed by $[Ni(Dppf)(diamine)]^{2+}$ aforementioned, chiral diamines, more rigid and with larger bite angles than Dpen, were necessary for higher conversions as well as higher ee's [11c]. The most striking observation is made with Xantphos, which yielded an ee value of

Table 1
Effect of diphosphine on the enantioselective hydrogenation of 1-acetonaphthone by Ru(II)-[(*R*,*R*)-Dpen] catalysts[a]

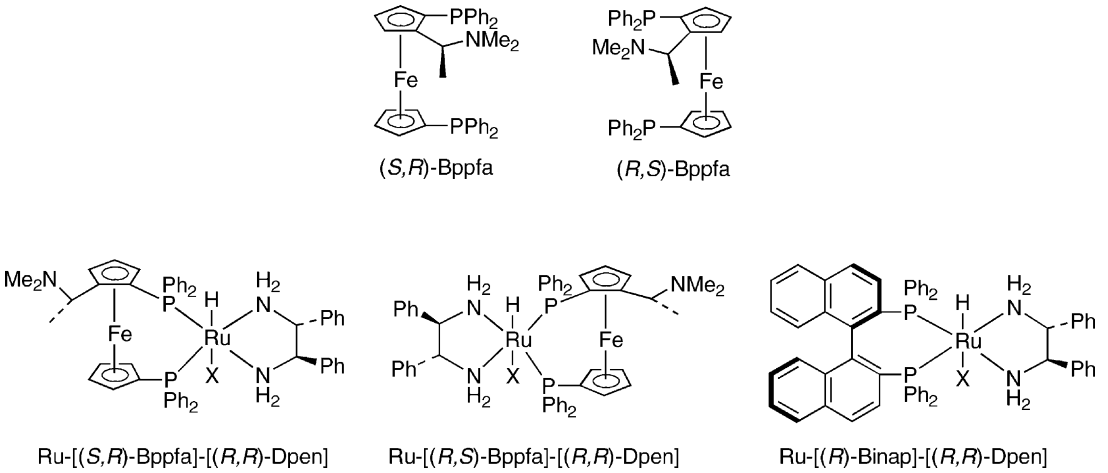
Diphosphine	Conversion (%)[b]	ee (%)[b]	β (°)[c]
Dppe	21	57	85
Dppp	76	56	91
Dppb	66	61	98
Dppf	93	65	96
Xantphos[d]	>99	27	112
(*R*)-Binap	>99	98	92

[a] The reactions were performed with Ru:KO^{t}Bu:ketone = 1:6:500 (ketone = 1-acetonaphthone, 6.6 mmol) at 10 bar H_2 and 20 °C for 3 h in 5 ml of 2-propanol. Prior to the hydrogenation, the solvent and the reaction mixture were degassed.

[b] Determined by GC equipped with a chiral column, Chrompack Chirasil-Dex CB (25 m × 0.25 mm). (*S*)-1-(1-Naphthyl)ethanol was the major enantiomer in all the reactions except for Xantphos.

[c] Taken from [5].

[d] (*S*,*S*)-Dpen was used and the major enantiomer product was *R* configured.



Scheme 3. Ru(II) complexes of (*R*,*R*)-Dpen and chiral diphosphines.

only 27%. This must result from the rigid backbone of the ligand, which prevents the phenyl rings from adopting a chiral arrangement under the influence of (*R*,*R*)-Dpen and hence leads to a low face selection towards the ketone.

In an attempt to reduce the flexibility of the coordinated Dppf, we also examined two modified Dppf ligands in the hydrogenation (Scheme 3). The combination of (*S*,*R*)-Bppfa with Ru(II)-(*R*,*R*)-Dpen indeed afforded an increased ee value of 80%, but using the opposite enantiomer (*R*,*S*)-Bppfa led to a much lower value of 28% [15].[2] This may not be surprising. By comparing the Ru(II) complex of Bppfa with that of (*R*)-Binap that produces an excellent ee when combined with (*R*,*R*)-Dpen (Table 1), one may expect that (*S*,*R*)-Bppfa matches (*R*,*R*)-Dpen in chirality and hence should provide a catalyst with an better enantioselectivity (Scheme 3). In all cases, the *S*-configured alcohol was favoured. While the increased enantioselectivity obtained with (*S*,*R*)-Bppfa could be due to restricted twisting of the two Cp-P moieties, the contribution of the central and planner chirality of Bppfa may also play a role. Bppfa displays a bite angle of 99° [16].

In summary, the diphosphines examined in this study have a significant effect on both the activity and enantioselectivity of Ru(II)-Dpen catalysts in ketone hydrogenation, with the ligand with the smallest bite angle yielding the lowest conversion and the one with largest bite angle yielding the lowest enantioselection. The higher activity associated with the arylphosphines is probably due to their lower basicity, while the low enantioselectivity observed with Xantphos can be attributed to its rigid structure. In all the cases, (*R*,*R*)-Dpen as a potential chiral activator is not capable of effectively transmitting its chirality to the phenyl rings of achiral diphosphines or inducing significant axial chirality at the conformationally flexible Dppf.

3. Experimental

$[RuCl_2(benzene)]_2$ and all the diphosphines, except Xantphos which was purchased from Strem, were obtained from Aldrich. 1-Acetonaphthone was purchased from Lancaster and used after degassing. The hydrogenation product was analysed by a Varian CP-3380 GC equipped with a Chrompack Chirasil-Dex CB (25 m × 0.25 mm) column.

The catalyst precursors, $[RuCl_2(diphosphine)(Dpen)]$, were prepared using a reported procedure [12] that was slightly modified. In a typical preparation, $[RuCl_2(benzene)]_2$ (25 mg, 0.05 mol) and a diphosphine (0.1 mmol) were dissolved in degassed DMF (5 ml) in a Schlenk under argon. The mixture

[2] (*R*,*S*)-Bppfa = (*R*)-*N*,*N*-dimethyl-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine (see [15]).

was heated with stirring at 100 °C (80 °C for Dppf) for 0.5 h. After cooling to ambient temperature, (*R*,*R*)-Dpen (23 mg, 0.11 mol) was added, and the mixture was stirred for 1 h. Following the removal of the solvent under vacuum, the residue was dissolved in small volume of CH_2Cl_2. A powder solid resulted upon precipitation with Et_2O. After washing with Et_2O and drying, the solid was used for the hydrogenation.

A typical hydrogenation reaction was carried out as follows. An autoclave containing a glass liner was charged with [$RuCl_2$(diphosphine){(*R*,*R*)-Dpen}] (0.01 mmol), 2-propanol (5 ml) and KO^tBu in 2-propanol (0.6 ml, 0.1 M) under argon followed by 1-acetonaphthone (850 mg, 5.0 mmol). The reaction mixture was then degassed with 10 bar H_2 for three times, and finally the autoclave was pressurised to 10 bar with H_2. After stirring for 3 h at 20 °C, the H_2 was carefully released. The reaction mixture was diluted with Et_2O and passed through a short column of silica gel before being subjected to GC analysis [carrier gas: helium, 25 psi, column temperature: 160 °C, injection temperature: 250 °C, split ratio: 100/1, retention time $t_R = 10.4$ min (*S*), 11.4 min (*R*)].

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