[(Bisphosphine) Ru(II) Diamine] Complexes in Asymmetric Hydrogenation: Expanding the Scope of the Diamine Ligand

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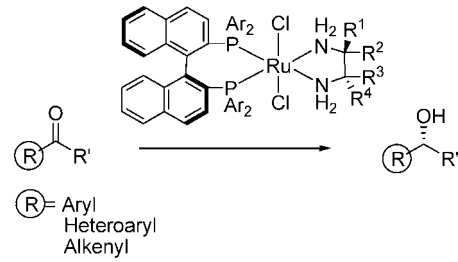
ABSTRACT

[(Bisphosphine) $RuCl_2$ (1,2-diamine)] complexes are powerful catalysts in the asymmetric hydrogenation of unfunctionalized ketones. We sought to expand the scope and applicability of these complexes by exploring changes to the diamine structural motif. Via introduction of 1,3- and 1,4-diamines, the catalytic activity was significantly altered such that new classes of ketones could be considered for [(bisphosphine) $RuCl_2$ (diamine)] asymmetric hydrogenation.

Introduction

The asymmetric catalytic hydrogenation of C=O bonds is now widely accepted in industry as one of the most cost-effective approaches to the synthesis of enantiomerically pure secondary alcohols.[1] Prof. Noyori pioneered this research in the 1980s with the application of BINAP–ruthenium catalysts for the hydrogenation of ketones with an ancilliary binding group.[2] However, by the mid-1990s, Noyori made a subsequent breakthrough in the catalytic asymmetric hydrogenation of unfunctionalized ketones by the combination of a ruthenium metal center bearing a chiral bisphosphine and a chiral diamine ligand (Scheme 1).[3]

Scheme 1



Such catalysts in 2-propanol in the presence of a base prove to be remarkably efficient in the asymmetric hydrogenation of a wide range of ketones. The efficiency of this catalyst system stems from the correct matching of the electronic and steric effects of the two moieties, the bisphosphine and the diamine ligands. These ligands craft the space around the ruthenium metal center and determine both reaction rates and selectivity. The source of the diamine effect was proposed to be the easy transfer of a proton from the amine to the carbonyl oxygen and a hydride from the ruthenium to the carbonyl carbon of the ketone.[4] This results in a unique second-coordination sphere reaction which Noyori has termed metal–ligand bifunctional catalysis. The replacement of the original BINAP ligands with other biaryl phosphines was the most obvious development of these catalysts, and this research was driven by a combination of scientific and intellectual property issues.[5] An increasingly large array of chiral bisphosphine ligands, many of them from commercial sources, has been available to researchers for many years.[6] Testing such ligands in combination with 1,2-diamine ligands for ketone asymmetric hydrogenation has been a natural consequence of Noyori's findings. Most of the new bisphosphines that have found success in these catalysts were based on a biaryl backbone. One noteworthy exception was the PhanePhos ligand, derived from a paracyclophane framework, which has proven to be remarkably efficient in combination with 1,2-diamines.[7] We have further developed the PhanePhos system to ParaPhos by

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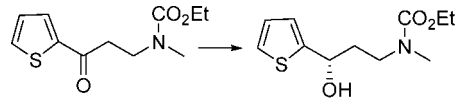
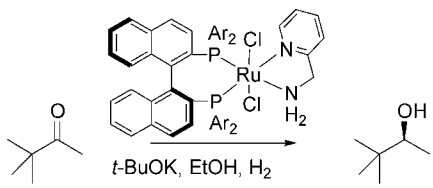
Scheme 2



(*R*)-TolBINAP-$RuCl_2$-(*1R,2R*)-DPEN 80.1% ee

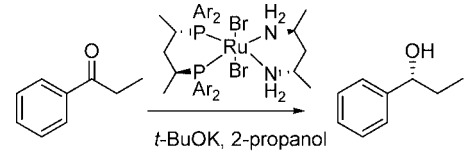
(*S*)-PhanePhos-$RuCl_2$-(*1R,2R*)-DPEN 93.4% ee

Scheme 3



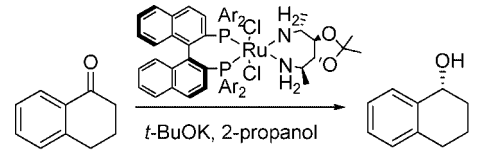
100%, 97% ee

Scheme 4



99%, 92% ee

Scheme 5



99.6%, 99%ee

increasing the electronic differential between the two rings.[8] The stereoselective formation of 3-hydroxy-(2-thienyl)propanamines using PhanePhos-$RuCl_2$-DPEN is a key step in the synthesis of Duloxetine (Scheme 2).[9]

Until recently, much less effort had been dedicated to the modification of the diamine ligand. Most phosphines have exclusively been used in conjunction with 1,2-diamines, with DPEN and DAIPEN[10] being favored.[3] We undertook a program of research to investigate the effect of other diamines in this catalyst system. The ultimate prize of this research is the development of catalysts with characteristics that depart more radically from those of the now well-established [(bisphosphine) Ru (1,2-diamine)] template and that expand the scope of the Noyori-type hydrogenation to include new classes of substrates. Our working hypothesis for this was that changing the ring size of the chelate between the diamine and metal center would alter the orientation of the NH group, thus potentially changing the hydrogen bond interaction with the ketone that is believed to occur in the catalytic cycle.[4] In this Account, we describe our efforts to develop ketone hydrogenation catalysts by combining ruthenium metal centers with 1,3- and 1,4-diamines with both P-Phos[11] and BINAP as the bisphosphine "partner ligand".

Development of the Diamine Ligand

While there has been a plethora of new mono- and bisphosphine ligands developed for the Ru catalysts,[6] surprisingly, there has been much less research focused on the development of new diamine partner ligands. Nevertheless, when the diamine component is altered, a significant difference in catalytic activity is observed. Research into the diamine moiety has taken three approaches.

(i) Changing the Nature of the Diamine Ligand. Replacement of one amino group with a pyridine has proven to be very successful.[12] In fact, the combination of aminomethylpyridine[13] (AMPY) with BINAP allows the asymmetric hydrogenation of *tert*-alkyl ketones with excellent activity and enantioselectivity (Scheme 3). This was the first example of the successful asymmetric hydrogenation of *tert*-alkyl ketones. Notably, the achiral aminopyridine does not result in an erosion of enantiomeric excess, and the stereochemical result is due to the chirality of the bisphosphine ligand.

This class of catalysts not only has overcome the notoriously poor reactivity of *tert*-alkyl ketones but also allows their use as catalysts under transfer hydrogenation conditions.[14] This duality of purpose is highly novel for [(biphosphine) $RuCl_2$ (diamine)] catalysts.

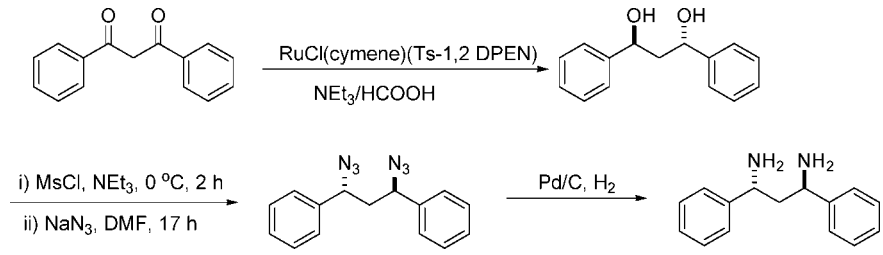
A thiol group has also successfully replaced one of the amino components.[15] Thus, the combination of an achiral amino thiol ligand (e.g., 2-ethylthioaniline) with the 1,4-bisphosphine ligand, BICP,[16] facilitates the asymmetric hydrogenation of ketones with excellent enantioselectivity and activity.

(ii) Increasing the Chain Length of the Diamine Ligand from 1,2 to the 1,3- and 1,4-Homologues. Independently of our research described below, Ikariya published the application of the bisphosphine (*S,S*)-Xyl-Skewphos in combination with the chiral 1,3-diamine (*R,R*)-1,3-diphenylpropanediamine (DPPN) in the asymmetric hydrogenation of propiophenone (Scheme 4).[17]

Noyori has exploited the combination of 1,4-diamines derived from tartaric acid and mannitol with BINAP to facilitate the Ru-catalyzed asymmetric hydrogenation of tetralones (Scheme 5) with excellent activity and selectivity.[18] Thus, the application of 1,4-diamine ligands has expanded the scope of the catalytic system to the hitherto less successful class of cyclic ketones.

(iii) Application of Nonracemic Diamine Ligands To Control the Stereochemical Outcome of the Asymmetric Hydrogenation. The extent to which the stereochemistry of one of the two moieties controls the conformation of the partner ligand is the object of intense research. Mikami's group has demonstrated that the chirality of the diamine ligands can determine the conformation of an achiral, flexible, biaryl-bisphosphine ligand.[19] Thus, when a pro-atropisomeric ligand such as BIPHEP[20] is applied with an enantiomerically pure diamine ligand, diastereomeric complexes may be formed in unequal amounts. Then, the major diastereoisomer may display a higher chiral efficiency than the minor isomer, resulting in moderate to excellent ee's (enantiomeric excesses). Ding's

Scheme 6



group has shown that very bulky achiral monophosphines can replace chiral bisphosphines, while the chirality of the catalysts is defined by the sole diamine ligand.[21] This somewhat unprecedented result achieved enantiomeric excesses higher than 90%.

1,3-Diamine Ligands

1,3-Diphenylpropanediamine (DPPN). The attention of our research group was initially focused on the development of the 1,3-analogue of DPEN.[22] The synthesis of 1,3-diphenylpropanediamine (DPPN) was accomplished by standard transformations (Scheme 6).[23]

Both P-Phos and BINAP were chosen as the bisphosphine partner ligands for the preparation of the Noyori-type ruthenium catalysts, due to both the excellent enantioselectivities achieved with DPEN[11] and the experience developed in our group on the use of such phosphine ligands (Figure 1).

Single-crystal X-ray analysis of [(*R*)-Xyl-P-Phos $RuCl_2$ (*S,S*)-DPPN]-**1b** showed that when coordinated to ruthenium, the DPPN assumes a six-membered ring with a λ conformation with the phenyl substituents oriented in the equatorial direction.[22] This is not dissimilar to the conformation assumed by the DPEN ligand in the analogous complex [(*S*)-Xyl-P-Phos $RuCl_2$ (*S,S*)-DPEN] (the reversal of stereochemical descriptors from DPPN to DPEN makes the two complexes quasi-enantiomers).[24] The Xyl-P-Phos ligand also adopts a λ seven-membered chelate with the xylyl moieties adopting axial and equatorial arrangements.

Preliminary experimental results revealed that rapid and highly enantioselective catalytic hydrogenation of acetophenone was achieved using catalyst **1b**. In fact, this new class of complexes exhibited characteristics similar to those of the analogous DPEN complexes: high activity and stereoselectivity were associated with the use of Xyl-P-Phos. Moreover, the similar behavior of the 1,2- and 1,3-diamine catalysts is in agreement with the very similar

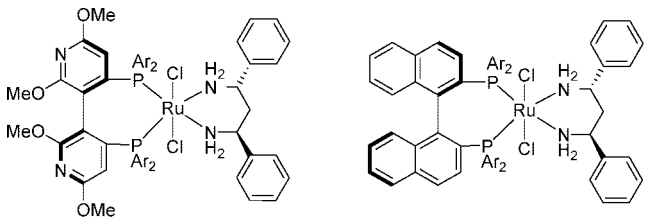


FIGURE 1. Bisphosphine $RuCl_2$ DPPN complexes.

Scheme 7

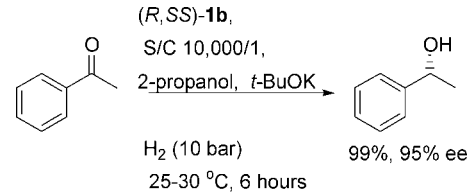
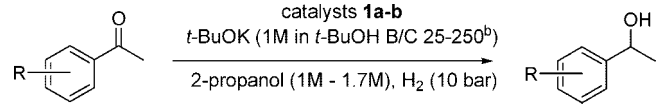


Table 1. Hydrogenation of Aromatic Ketones Using Catalysts 1a–b[a]



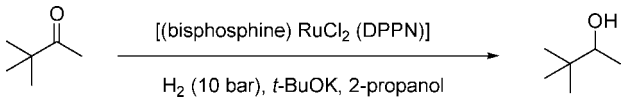
ketone	catalyst	S/C[c]	ee (%)[d]
R = H	(*R,SS*)-**1a**	1000	36(*S*)
R = H	(*R,SS*)-**1b**	1000	95(*S*)
R = H	(*S,SS*)-**1b**	1000	69(*R*)
R = H	(*S,RR*)-**1b**	2500	95(*R*)
R = H	(*S,RR*)-**1b**	10000	95(*R*)
R = *p*-F	(*S,RR*)-**1b**	2500	95(*R*)
R = *p*-OMe	(*S,RR*)-**1b**	2500	97(*R*)
R = *m*-Me	(*S,RR*)-**1b**	2500	96(*R*)
R = *o*-Me	(*R,SS*)-**1b**	1000	86(*S*)
R = *o*-OMe	(*R,SS*)-**1b**	1000	84(*S*)
R = 3,5-CF3	(*S,RR*)-**1b**	1000	95(*R*)

[a] Reaction conditions: 2–5 mmol of substrate, 25 °C. Reaction times of 2–24 h to obtain 100% conversion. [b] Molar ratio of base to catalyst. [c] Molar ratio of substrate to catalyst. [d] The conversion and ee were determined by chiral gas chromatography (Chrompack Chirasil-DEX CB column). The absolute configuration was determined by comparison of the retention time with literature data.

crystallographic properties of the two catalysts.[24] The hydrogenation of acetophenone using (*R,SS*)-**1b** at a molar substrate to catalyst (S/C) ratio of 1000 under 10 bar of H_2 in 2-propanol with *t*-BuOK gave greater than 99% conversion in less than 2 h with 95% ee of the *S* alcohol.

The importance of the correct combination of bisphosphine and diamine ligands was demonstrated as the (*S,SS*)-**1b** catalyst gave only 69% ee in the hydrogenation of acetophenone under identical conditions. The practical utility of catalyst **1b** was demonstrated with the hydrogenation of acetophenone at a S/C ratio of 10 000, using catalyst (*S,RR*)-**1b** (Scheme 7). Acetophenone was smoothly converted to the *R* alcohol in 95% ee with an average TOF of 1400 h^{-1}. A brief survey of ring-substituted aromatic ketones using catalyst **1b** also gave excellent selectivities irrespective of the presence of electron donating or withdrawing substituents at the para or meta positions (Table 1). The use of catalyst (*S,RR*)-**1b** resulted in the asymmetric hydrogenation of the highly electron deficient

Table 2. Asymmetric Hydrogenation of Pinacolone Using Catalysts Containing DPPN[a]



catalyst	S/C[b]	B/C[c]	conversion (%)	ee (%)[d]
(*R*)Xyl-BINAP-RuCl2-(*R*,*R*)Dpen	1000	25	30	11
(*R*,*SS*)-**1b**	1000	25	46	65
(*R*,*SS*)-**1b**	500	500	100	62
(*R*,*SS*)-**1b**	500	10	75	71
(*R*,*SS*)-**2b**	1000	25	48	60
(*R*,*SS*)-**2b**	500	25	39	55
(*R*,*SS*)-**2b**	500	10	100	74
(*R*,*SS*)-**2a**	500	25	40	64
(*R*,*SS*)-**2a**	500	10	100	68

[a] Reaction conditions: 2–5 mmol of substrate, 25 °C. Reaction times of 6–24 h. [b] Molar ratio of substrate to catalyst. [c] Molar ratio of base to catalyst. [d] The conversion and ee were determined by chiral gas chromatography (Chrompack Chirasil-DEX CB column).

3,5-bis(trifluoromethyl)acetophenone to give the corresponding *R* alcohol in 95% ee, which is a precursor for the synthesis of potent NK1 receptor antagonists.[25]

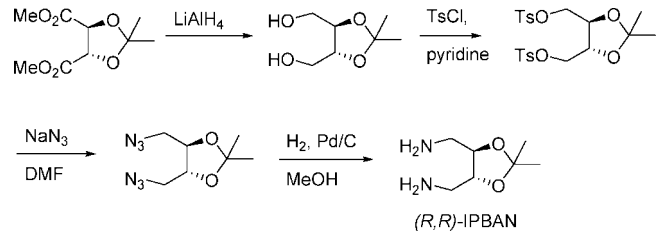
Substituents in the ortho position, however, were not tolerated so well and resulted in a lower ee. The importance of the Xyl-P-Phos ligand was also outlined as a significantly lower enantiomeric excess was obtained using the parent P-Phos catalyst **1a**.

This class of catalysts was then tested in the hydrogenation of pinacolone. [(Bisphosphine) $RuCl_2$ (1,2-diamines)] catalysts are generally found to be poorly active in the asymmetric hydrogenation of pinacolone. This was assumed to be due to the steric bulk about the ketone. The application of [(*R*)-Xyl-BINAP $RuCl_2$ (*R*,*R*)-DPEN] for this ketone hydrogenation gave only 30% conversion with just 11% ee. Much better results, in terms of both activity and enantioselectivity, were achieved when the DPPN ligand was applied, both with the P-Phos and with the BINAP families of ligands (Table 2). Under otherwise identical conditions, the catalyst derived from Xyl-BINAP and DPPN, (*R*,*SS*)-**2b**, gave a moderate conversion of 48% but with a dramatically enhanced enantiomeric excess of 60%. Full conversions could be achieved by tailoring the reaction conditions, but the enantioselectivity of the reaction was limited to ca. 74%. These results have only been surpassed by the introduction of AMPY ligands with $RuCl_2$ (bisphosphine) catalysts.[12,26]

1,4-Diamines

Noyori's research group[18] and our research group[27] independently focused on the use of 1,4-diamines derived from the tartaric acid backbone. 1,4-Diamine ligands would form a seven-membered chelate with the metal center. This is directly analogous to many phosphine ligands that, upon coordination, also exist as seven-membered chelates. Three such phosphorus ligands successfully used in Rh-catalyzed hydrogenations have been DIOP,[28] SK-PHOS,[29] and BPPM.[30] It was with this in mind that we sought to prepare structurally similar diamines.

Scheme 8



2,3-*O*-Isopropylidenebutane-1,4-diamine (IPBAN). The diamine IPBAN was synthesized via a literature procedure from tartaric acid (Scheme 8).[31]

The IPBAN was then reacted with the Ru (bisphosphine) complexes of the P-Phos and BINAP families (Figure 2).

The complex [(*S*)-BINAP $RuCl_2$ (*R*,*R*)-IPBAN] [(*S*,*RR*)-**4a**] was analyzed by X-ray crystallography.[26] As expected, the diamine forms a seven-membered chelate with a λ configuration. The BINAP ligand adopts a δ seven-membered chelate, and the phenyl moieties adopt axial and equatorial arrangements. A comparison of the bond angles around the Ru center of (*S*,*RR*)-**4a** and the [(*R*)-TolBINAP $RuCl_2$ (DPEN)][32] complex shows that while P–Ru–P angles are similar, the N–Ru–N bite angle is much larger in the case of (*S*,*RR*)-**4a** (92° vs 78°). These new complexes were then tested for their efficacy in catalysis. Application with acetophenone under standard hydrogenation conditions gave rather disappointing results in terms of enantioselectivity (Table 3). Nevertheless, there were some interesting observations made.

Surprisingly, for the hydrogenation of acetophenone, the catalysts bearing the less sterically demanding P-Phos ligand gave better results than the catalysts bearing the Xyl-P-Phos ligand. Moreover, a very limited bisphosphine/diamine matching/mismatching effect was detected, with both diastereoisomers of the catalyst (*S*,*RR*)-**3a** and (*R*,*RR*)-**3a** providing very similar levels of enantioselectivity (75% ee vs 81% ee). The finding that the same catalysts gave higher selectivity in the hydrogenation of a hindered substrate *o*-methoxyacetophenone (93% ee) prompted us to study the use of this class of catalysts in the hydrogenation of bulky substrates such as isobutyrophenone (Table 4).

We were surprised that a far superior stereoselectivity was observed in the hydrogenation of the more sterically demanding isobutyrophenone as compared with acetophenone with catalysts **3a** and **4b**. Moreover, these

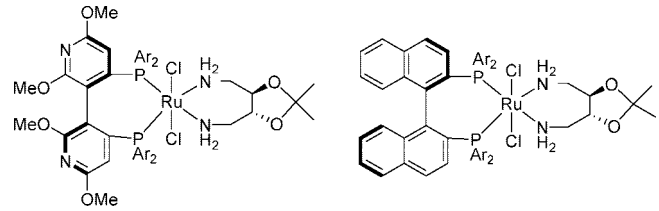
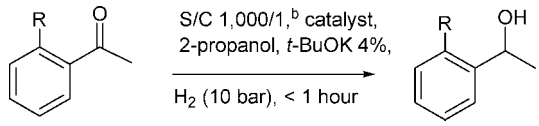


FIGURE 2. [(Bisphosphine) $RuCl_2$ (IPBAN)] complexes.

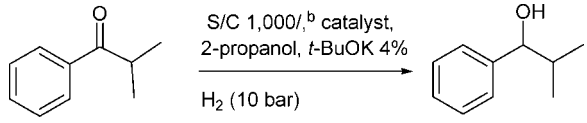
Table 3. Hydrogenation of Acetophenone with (Bisphosphine) Ru (IPBAN) Catalysts[a]



R	catalyst	conversion (%)[c]	ee (%)[c]
R = H	(*R*,*RR*)-**3a**	100	75(*R*)
R = H	(*S*,*RR*)-**3a**	100	81(*S*)
R = H	(*R*,*RR*)-**3b**	100	55(*S*)
R = H	(*S*,*RR*)-**3b**	100	51(*R*)
R = H	(*S*,*RR*)-**4b**	100	70(*R*)
R = H	(*S*,*RR*)-**4b**	100	85(*S*)
R = H	(*R*,*RR*)-**4c**	100	34(*S*)
R = H	(*S*,*RR*)-**4c**	100	64(*R*)
R = OMe	(*S*,*RR*)-**4a**	100	93

[a] Reaction conditions: 2–5 mmol of substrate, 25 °C. [b] Molar ratio of substrate to catalyst. [c] The conversion and ee were determined by chiral gas chromatography (Chrompack Chirasil-DEX CB column). The absolute configuration was determined by comparison of the retention time with literature data.

Table 4. Hydrogenation of Isobutyrophenone with (Bisphosphine) Ru (IPBAN) Catalysts[a]



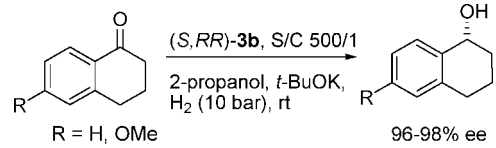
catalyst	conversion (%)[c]	ee (%)[c]
(*S*,*RR*)-**3a**	100	97(*S*)
(*S*,*SS*)-**3a**	100	95(*S*)
(*S*,*rac*)-**3a**	100	96(*S*)
(*rac*,*SS*)-**3a**	100	9
(*S*,*SS*)-**4b**	100	94(*S*)
(*S*,*RR*)-**4b**	100	97(*S*)
(*S*,*rac*)-**4b**	100	95(*R*)
(*R*,*RR*)-**3b**	100	46(*R*)
(*S*,*RR*)-**3b**	100	75(*S*)

[a] Reaction conditions: 2–5 mmol of substrate, 25–30 °C, 3 h. [b] Molar ratio of substrate to catalyst. [c] The conversion and ee were determined by chiral gas chromatography (Chrompack Chirasil-DEX CB column). The absolute configuration was determined by comparison of the retention time with literature data.

results also exceeded those obtained when DPEN-containing catalysts were applied. Regardless of the stereochemistry of the diamine ligand, high selectivity was obtained (95–97% ee) for catalyst **3a**. The catalyst bearing the racemic diamine (*S*,*rac*)-**3a** produced the same activity and selectivity (96% ee). Very similar results were obtained using the Tol-BINAP-based catalyst **4b**. In stark contrast, the Xyl-P-Phos derivative **3b** gave disappointing selectivities. Moreover, it would appear that with catalyst **3b** there is a bisphosphine/diamine matching/mismatching interaction.

The experimental results for the hydrogenation reactions with complexes **3a** and **4b** suggest that the chiral bisphosphine dictates the stereochemical outcome of the hydrogenation reaction and that the 1,4-diamine is implicated in the increased activity observed for isobutyrophenone. The fact that the different diastereoisomers of the catalysts showed very similar reaction rates combined with NMR analysis of the synthesis of the ruthenium precatalysts tends to exclude a mechanism of selective

Scheme 9



activation of one of the two diastereoisomers. At this point, we postulate that the 1,4-diamine, being more flexible than the analogous 1,2- and 1,3-diamines, assumes a conformation dictated by the chirality of the phosphine ligand while still remaining capable of participating in a bifunctional hydrogenation mechanism. Moreover, when a catalyst prepared using racemic P-Phos and the chiral IPBAN was tested, virtually no stereoinduction was observed. The reduced stereoselectivity observed with **3b** can also be rationalised in that the increased steric bulk of the xylyl groups for Xyl-P-Phos impacts on the potential conformation that can be adopted by the IPBAN ligand. This then influences the stereocontrol of the hydrogenation reaction.

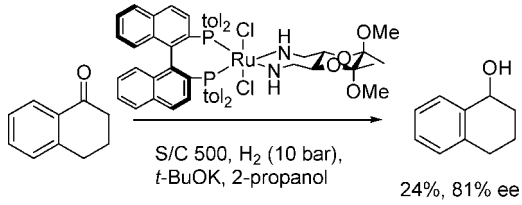
Around the time of this research, Noyori reported the IPBAN and IPHAN (derived from mannitol) diamine ligands and their application in the asymmetric hydrogenation of substituted tetralones.[18] Noyori found that whereas the less sterically congested IPBAN was more active in the hydrogenation reaction, the stereoselectivity was lower than that found for the IPHAN (90% ee vs 99% ee). We have examined the same reaction replacing the BINAP bisphosphines with the Xyl-P-Phos ligand and found that in combination with IPBAN, (*S*,*RR*)-**3b** gave an enhanced ee for the asymmetric hydrogenation of tetralone (96% ee) (Scheme 9).

In Noyori's research, the absolute stereochemistry of the diamine was relatively unimportant. However, he found that 1,4-diaminobutane gave a very poor conversion (11% yield, 52% ee, S/C 1000) and suggested that the rigidity of the acetonide ring on the backbone of the diamine ligand confers a degree of stability to the catalytically active species. It may be possible to draw a correlation between this result and recent work carried out by Morris et al.[4d] In their investigation of the catalytic pathway, they observed that the application of ethylene diamine resulted in complex decomposition via dehydrogenation of the diamine ligand. In fact, a 1,4-diazabutadiene-ligated RuH complex was isolated and analyzed. The crystal structure of the complex indicated that the diimine (HN=CHCH=NH) forms a bridging $\eta^2;\eta^4$ ligand between two $RuH(PPh)_3$ fragments.

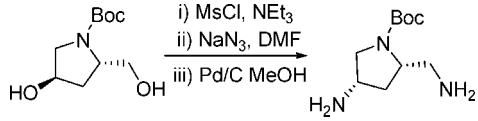
We explored the possibility of replacing the acetonide group with a dioxane acetal protecting group. (2*R*,3*R*,5*S*,6*S*)-2,3-Dimethoxy-2,3-dimethyl-5,6-diaminomethyl-1,4-dioxane [(*R*,*R*,*S*,*S*)-DAMDO] was prepared via a procedure published by Ley et al.[33] The corresponding complex [(*S*)-TolBINAP-$RuCl_2$ (*R*,*R*,*S*,*S*)-DAMDO] was synthesised and tested in the asymmetric hydrogenation of tetralone (Scheme 10).

Results from the catalysis experiments indicated that the hydrogenation started rapidly but then appeared to

Scheme 10



Scheme 11



stop. This suggests that the active Ru hydride species decomposed under the reaction conditions. Although the actual mode of decomposition is not known, it must be related to the electronic and steric properties of the dioxane acetal and further underlines the correlation between the diamine backbone and catalytic activity.

3-Amino-5-aminomethyl-Boc-pyrrolidine AABPY. The degree to which a 1,4-diamine ligand will influence the activity and selectivity of a [(bisphosphine) $RuCl_2$ (diamine)] catalyst is inexorably linked to the structure of the diamine. Whereas the tartrate-derived ligands (IPBAN and DAMDO) are reminiscent of the DIOP bisphosphine,[28] we were also attracted to diamines analogous to BPPM bisphosphines.[30] The synthesis of (*R,R*)-AABPY was based on the commercially available *trans*-diol (Scheme 11). Ganesh[34] has reported the synthesis of these diamines for use as analogues that stabilize DNA duplexes and triplexes.

The preparation of [(bisphosphine) $RuCl_2$ (diamine)] complexes by reaction of (*R,R*)-AABPY with (P-Phos) $RuCl_2$ and (BINAP) $RuCl_2$ was carried out (Figure 3).

It was anticipated that the pyrrolidine framework would increase the rigidity of the ligand, and we were interested in determining how this might affect the catalysis. Acetophenone and its derivatives were initially examined for activity and selectivity. Table 5 outlines the results obtained from the hydrogenation experiments.

While this class of catalysts is certainly active under the hydrogenation conditions, the observed enantioselectivity was modest. A comparison between the stereoselectivities attained for the P-Phos complexes with IPBAN and AABPY does highlight some notable aspects. The hydrogenation of acetophenone with the IPBAN complex **3b** gave the corresponding alcohol in 51–55% ee, whereas the analogous complex with AABPY, (*R,SS*)-**5**, gave an enhanced enantioselectivity of 84%. It would also appear

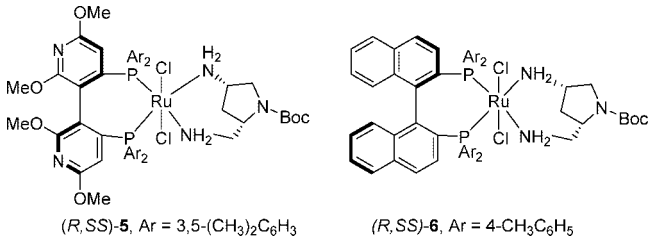
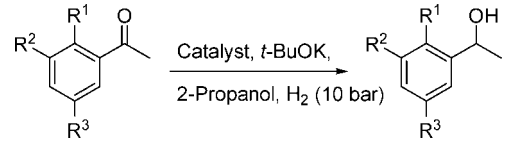


FIGURE 3. [(Bisphosphine) $RuCl_2$ (AABPY)] complexes.

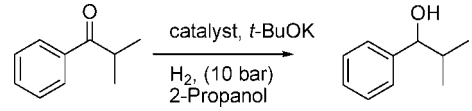
Table 5. Asymmetric Hydrogenation of Acetophenone with (Bisphosphine) $RuCl_2$ (AABPY)[a]



ketone	catalyst	S/C[b]	conversion (%)[c]	ee (%)[c]
$R^1 = R^2 = R^3 = H$	(*R,SS*)-**5**	2500	100	84(*S*)
$R^1 = R^2 = R^3 = H$	(*S,SS*)-**5**	2500	100	57(*R*)
$R^1 = R^2 = R^3 = H$	(*S,SS*)-**6**	2500	100	64(*S*)
$R^1 = R^2 = R^3 = H$	(*R,SS*)-**6**	1000	100	20
R^1 = OMe; $R^2 = R^3 = H$	(*S,SS*)-**5**	1000	100	42(*S*)
R^1 = OMe; $R^2 = R^3 = H$	(*R,SS*)-**5**	1000	100	76(*S*)
R^1 = Me; $R^2 = R^3 = H$	(*R,SS*)-**5**	1000	100	74(*R*)
R^1 = H; $R^2 = R^3$ = CF3	(*R,SS*)-**5**	1000	98	91

[a] Reaction conditions: 2–5 mmol of substrate, 25–30 °C, 0.5–24 h. [b] Molar ratio of substrate to catalyst. [c] The conversion and ee were determined by chiral gas chromatography (Chrompack Chirasil-DEX CB column). The absolute configuration was determined by comparison of the retention time with literature data.

Table 6. Asymmetric Hydrogenation of Isobutyrophenone with (Bisphosphine) $RuCl_2$ (AABPY)[a]



catalyst	S/C[b]	conversion (%)[c]	ee (%)[c]
(*R,SS*)-**5**	1000	98	40
(*S,SS*)-**5**	1000	98	19
(*S,SS*)-**6**	1000	98	80

[a] Reaction conditions: 2–5 mmol of substrate, 25–30 °C, 0.5–24 h. [b] Molar ratio of substrate to catalyst. [c] The conversion and ee were determined by chiral gas chromatography (Chrompack Chirasil-DEX CB column).

that for this catalyst, there is an observed bisphosphine/diamine matching/mismatching effect with the (*S,SS*)-**5**, resulting in the formation of the opposite enantiomer in only 57% ee. The more sterically demanding *o*-methoxyacetophenone, however, gave only a moderate enantioselectivity. Nevertheless, we were pleased to find that the electron deficient bis(trifluoromethyl)acetophenone was efficiently and stereoselectively hydrogenated to the corresponding alcohol in 91% ee. This compares very favorably with the analogous reaction with 1,2-diamine ligand [(*R*)-Xyl-P-Phos $RuCl_2$ (*R,R*)-DPEN], which achieved an enantiomeric excess of only 60% for the same substrate under identical reaction conditions.

Considering the superior enantioselectivites that were achieved for the hydrogenation of isobutyrophenone with the IPBAN-ligated ruthenium complexes, we were interested in exploring the effect of the AABPY diamine ligand (Table 6). The commercial availability of the *trans*-4-hydroxy-L-proline in only one diastereomeric form unfortunately meant that for this diamine ligand we could not fully assess the influence of the chirality of the diamine on the stereochemical output of the reaction.

The [Xyl-P-Phos $RuCl_2$ AABPY] complex **5** gave a disappointing enantioselectivity (40% ee). This is much

lower than the result obtained with the IPBAN-containing complex **3b** (75% ee). However, while the TolBINAP complex **6** gave a much better enantioselectivity (80%), it still did not match that achieved by the analogous complex with IPBAN (94–97% ee).

Catalysts **5** and **6** were further examined in the hydrogenation of tetralone. For this substrate, these catalysts displayed very poor activity with conversions of only 5–15% being observed at a S/C ratio of 500.

Conclusions

When we commenced this research, little work had been published on developing the scope of the diamine in catalysts of the type [(bisphosphine) $RuCl_2$ (diamine)]. The parent 1,2-diamino structural motif can be extended to include a range of chiral 1,2-diamines, from DPEN to DAIPEN to DACH, in tailoring the reactivity and selectivity of the catalyst, and in many cases, the diamines can be used interchangeably. The 1,3-diamine, DPPN, displayed a reactivity and selectivity similar to those of the 1,2-diamines except in the case of pinacolone reduction where vastly improved activities and selectivities were observed. The DPPN ligand can now be considered as a viable alternative to the 1,2-systems, expanding the catalyst toolbox. When the diamines were extended to the 1,4-homologue, a more complex catalytic system evolved where the structural properties of this class of diamines played a profound role in the activity and selectivity of the catalyst. The application of IPBAN ligands with $RuCl_2$ (P-Phos) has allowed for new classes of ketones to be readily reduced, namely, cyclic ketones such as tetralones and hindered aromatic ketones such as isobutyrophenone.

Research into the diamine component of Noyori-type catalysts is still in its infancy. The nature and role of diamines other than those of the 1,2-class have not yet been well defined. Nevertheless, the significance of these catalysts in the formation of enantiopure secondary alcohols will ensure that further research into the development of both the bisphosphine and diamine will continue for some time to come.

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