Stereoselective Reduction

Asymmetric Hydrogenation of Ketones Catalyzed by Ru^{II}–bicp Complexes**

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Enantiomerically pure secondary alcohols are among the most valuable key intermediates for the manufacture of pharmaceuticals and advanced materials. The simplest and most powerful way to produce chiral alcohols is the asymmetric hydrogenation of ketones.[1] The most general and efficient catalyst system for the enantioselective hydrogenation of a variety of simple ketones reported so far is Noyori's homochiral Xylbinap/daipen/Ru^{II} combination with *i*PrOH as the solvent and in the presence of *t*BuOK.[2] The high degree of enantioselectivity is a result of the synergistic effects of the chiral diphosphane and diamine ligands. The Ru complexes of the parent phosphane ligand of the series, binap (2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl), afford significantly lower selectivities in this reduction.[2] Studies have been reported showing that Noyori's homogeneous hydrogenation follows a nonclassical mechanism, whereby a hydride on the Ru center and a proton of the NH_2 ligand are transferred simultaneously to the C=O function through a six-membered pericyclic transition state.[2,3]

A few years ago Zhang et al. reported the synthesis of a new chiral 1,4-diphosphane, (2*R*,2′*R*)-bis(diphenylphosphanyl)-(1*R*,1′*R*)-dicyclopentane ((*R*,*R*)-bicp, **1a**) (Figure 1), and its application in asymmetric Rh- and Ru-catalyzed hydrogenations.[4] High enantioselectivities are observed for the Ru-catalyzed hydrogenation of acetophenones when a chiral diamine is also used as a ligand for the metal.[4b] One shortcoming for the general use of bicp as a ligand is that its original synthesis involves a hydroboration with Alpine-borane, which is available as only one isomer.[4] We have solved this problem by developing a different synthetic sequence that affords both bicp enantiomers.[5] Our synthetic procedure also allowed the preparation of new phosphane ligands in the bicp family (**1b**, **1d**, Figure 1). This paper describes a method to access either enantiomer of a secondary alcohol through a bicp/Ru^{II} reduction of the corresponding prochiral ketone and the appropriate solvent.

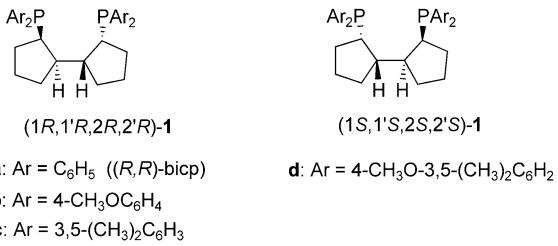


Figure 1. Chiral diphosphane ligands in the bicp family.

The initial studies carried out in our laboratory showed that [$RuCl_2${(*R*,*R*)-bicp}$(dmf)_n$] used in combination with an achiral 2-(alkylthio)amine such as 2-ethylthioaniline (**2a**, Figure 2) or an achiral diamine such as 4,5-dimethyl-1,2-phenylenediamine and *i*PrONa in *i*PrOH catalyzed the hydrogenation of various aryl alkyl ketones to give enantioselectivities similar to those achieved with chiral 1,2-diamines.[6] However, the selectivities obtained, between 70 and 80 % *ee*, were still less than satisfactory. For comparison, very low selectivities were obtained when [$RuCl_2${(*S*)-binap}(**2a**)] or [$RuCl_2${(*S*)-MeObiphep}(**2a**)] (MeObiphep = 6,6′-dimethoxy-2,2′-bis(diphenylphosphanyl)-1,1′-biphenyl) were used as catalysts.[6]

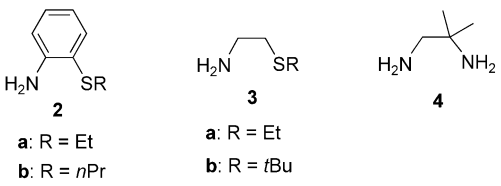
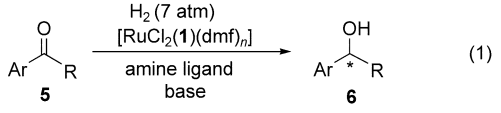


Figure 2. Achiral amine ligands.

After these initial studies, we carried out a comprehensive investigation on the asymmetric hydrogenation of ketone **5a** [Eq. (1)] and observed unexpected solvent effects on the



(1)

a: Ar = 4-$CF_3C_6H_4$, R = CH_3OCH_2
b: Ar = C_6H_5, R = CH_3OCH_2
c: Ar = 3-ClC_6H_4, R = $C_6H_5C(O)NHCH_2$
d: Ar = 3,5-$(CF_3)_2C_6H_3$, R = CH_3
e: Ar = C_6H_5, R = nC_3H_7
f: Ar = 4-FC_6H_4, R = CH_3
g: Ar = 4-$CH_3OC_6H_4$, R = CH_3
h: Ar = 2-$CH_3C_6H_4$, R = CH_3
i: Ar = 3-$CH_3C_6H_4$, R = CH_3
j: Ar = 2-(5-chlorothienyl), R = CH_3
k: Ar = 2-(5-bromothienyl), R = CH_3
l: Ar = 2-thienyl, R = $(CH_3)_2NCH_2CH_2$

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enantioselectivity. These observations ultimately led us to optimize conditions to achieve excellent selectivities. The results of selected hydrogenation experiments with **5a** are listed in Table 1. When the hydrogenation of **5a** was carried out in MeOH using $[RuCl_2\{(R,R)\text{-}\mathbf{1a}\}(dmf)_n]$ in combination with 2-ethylthioethylamine (**3a**) (Figure 2) as a catalyst and *t*BuONa as a base, the *R* enantiomer of **6a** was obtained with 80% *ee* (Table 1, entry 1). Changing the solvent from MeOH to EtOH resulted in the opposite enantiomer of **6a** (*S*) in 53% *ee*. In *i*PrOH the selectivity was very low (8% *ee* of (*R*)-**6a**) (Table 1, entry 2). It has been reported previously that the rate of the hydrogenation can be affected by changing the alcohol solvent,[3b] but to our knowledge this is the first example of a reversal of the configuration of the product by simply changing the solvent from methanol to ethanol. When *tert*-butylthioethylamine (**3b**) (Figure 2) was used as the amine ligand, (*S*)-**6a** was obtained predominantly in all alcohol solvents (MeOH, *i*PrOH, *i*BuOH, EtOH, and *n*BuOH) at room temperature, but the enantioselectivities in EtOH and *n*BuOH were significantly higher (Table 1, entries 4–7). Thus, while (*S*)-**6a** was obtained in 61% *ee* when *i*PrOH was used as the solvent (Table 1, entry 5), the enantioselectivity rose to 90% *ee* when the hydrogenation was carried out in *n*BuOH (Table 1, entry 7). The enantioselectivity achieved in the hydrogenation of **5a** in *n*BuOH was further enhanced when the experiment was conducted at a lower temperature. Thus, when **5a** was hydrogenated in *n*BuOH at −10°C using Ru/(*R*,*R*)-**1a**/**3b** (molar ratio of substrate to catalyst = 500) as the catalyst and *t*BuONa as the base, (*S*)-**6a** was obtained in 96% *ee* (Table 1, entry 8). (*S*)-**6a** is a precursor for the synthesis of a second generation CCR5 receptor antagonist (HIV entry inhibitor).[7] The change of the diphosphane ligand to the more hindered (*S*,*S*)-**1d** (Figure 1) gave (*R*)-**6a** in a similar selectivity (97% *ee*, Table 1, entry 10).

Table 1: Asymmetric hydrogenation of 2-methoxy-4′-trifluoromethylacetophenone (**5a**) catalyzed by Ru/**1** complexes.[a]

Entry	Ligand	Amine	S/C	Solv.	*T* [°C]	Conv. [%][b]	*ee* [%][c]
1	(*R*,*R*)-**1a**	**3a**	200	MeOH	RT	>99	80 (*R*)
2	(*R*,*R*)-**1a**	**3a**	200	*i*PrOH	RT	>99	8 (*R*)
3	(*R*,*R*)-**1a**	**3a**	200	EtOH	RT	>99	53 (*S*)
4	(*R*,*R*)-**1a**	**3b**	200	MeOH	RT	>99	53 (*S*)
5	(*R*,*R*)-**1a**	**3b**	200	*i*PrOH	RT	>99	61 (*S*)
6	(*R*,*R*)-**1a**	**3b**	200	EtOH	RT	>99	87 (*S*)
7	(*R*,*R*)-**1a**	**3b**	200	*n*BuOH	RT	>99	90 (*S*)
8[d]	(*R*,*R*)-**1a**	**3b**	500	*n*BuOH	−10	>99	96 (*S*)
9	(*R*,*R*)-**1a**	**3b**	1000	*n*BuOH	−10	98	95 (*S*)
10	(*S*,*S*)-**1d**	**3b**	500	*n*BuOH	−10	>99	97 (*R*)
11	(*R*,*R*)-**1a**	**2a**	200	MeOH	RT	>99	83 (*R*)
12	(*R*,*R*)-**1a**	**2a**	200	EtOH	RT	>99	83 (*R*)
13	(*R*,*R*)-**1a**	**2a**	200	*i*PrOH	RT	>99	74 (*R*)
14	(*R*,*R*)-**1a**	**4**	200	MeOH	RT	25	70 (*R*)
15	(*R*,*R*)-**1a**	**4**	200	EtOH	RT	>99	85 (*R*)
16	(*R*,*R*)-**1a**	**4**	200	*i*PrOH	RT	>99	57 (*R*)

[a] Unless otherwise stated, reactions were carried out with 0.5 mmol **5a** and 7 atm H_2 pressure for 15 h. The catalyst was formed in situ by the addition of $[RuCl_2(\mathbf{1})(dmf)_n]$ solution in the corresponding solvent, amine (molar ratio of substrate to amine = 50) and base (molar ratio of substrate to base = 25) to the reaction mixture. [b] The yields were determined by ^{1}H NMR and GC analysis. [c] The *ee* values were determined by chiral GC with γ-DEX 225 column. The absolute configurations were determined using authentic samples. [d] The reaction was carried out with 1 mmol **5a**. The yield of the product isolated by column chromatography was 99%.

The strong solvent effect seen with 2-alkylthioethylamines was not observed when a 2-alkylthioaniline or a 1,2-diamine is used as an amine ligand. For example, with **2a** (*R*)-**6a** was obtained in 83% *ee* in both MeOH and EtOH and in 74% *ee* in *i*PrOH (Table 1, entries 11–13). Note that this is the opposite enantiomer to that achieved with **3b** as the amine ligand.

Taking into account the solvent effect observed for **5a**, asymmetric hydrogenations of various ketones [Eq. (1)] were performed. Table 2 shows the optimized results obtained with Ru complexes of the parent ligand and those obtained with the ligand from the bicp family (Figure 1) giving the highest *ee*. Three amines, **2b**, **3b**, and **4** (Figure 2), emerged as the amine ligands of choice to be used in combination with Ru/**1** for highly enantioselective carbonyl reductions. As catalyst components, they are complementary to each other, as each of them is efficient for asymmetric reduction of a different structural type of ketone substrate.

The amine **3b** is the best ligand for the asymmetric hydrogenations of α-functionalized ketones (**5a–c**). The selectivities obtained in the asymmetric hydrogenation of **5b** were analogous to those observed for the structurally similar **5a** (Table 2, entries 1 and 2). The asymmetric hydrogenation of ketone **5c** using $[RuCl_2\{(R,R)\text{-}\mathbf{1a}\}(dmf)_n]$ (molar ratio of substrate to catalyst = 1000) in combination with **3b** and *t*BuONa in *n*BuOH at room temperature afforded the corresponding *S* alcohol (**6c**) in a quantitative yield with 96% *ee* (Table 2, entry 3). (*R*)-**6c** is a building block for the preparation of a very potent β3-adrenergic receptor agonist[8] and can be obtained by using (*S*,*S*)-**1a**[5] as the diphosphane ligand. In the hydrogenation of ketone **5c** the parent ligand **1a** leads to better selectivities than the more substituted **1d** (Table 2, entry 4).

The amine **3b** was also a very efficient ligand for the asymmetric hydrogenation of 3,5-bis(trifluoromethyl)acetophenone [**5d** in Eq. (1)]. The use of $[RuCl_2\{(S,S)\text{-}\mathbf{1d}\}(dmf)_n]$ (molar ratio of substrate to catalyst = 1000) in combination with **3b** and *t*BuONa in *n*BuOH at −10°C gave the corresponding *S* alcohol (**6d**) in 93–94% *ee* (Table 2, entry 6). The *R* enantiomer of this alcohol, which can be obtained by using (*R*,*R*)-**1d**,[5] is a precursor for the synthesis of potent NK_1 receptor antagonists.[9] The enantioselectivity obtained with our system is the same as that obtained with

Table 2: Asymmetric hydrogenation of ketones **5b–l** catalyzed by Ru/**1** complexes.[a]

Entry	Ketone	Ligand	Amine	S/C	Solv.	*T* [°C]	Conv. [%][b]	*ee* [%][c]
1	**5b**	(*R*,*R*)-**1a**	**3b**	500	*n*BuOH	−10	>99	93 (*S*)
2	**5b**	(*S*,*S*)-**1d**	**3b**	500	*n*BuOH	−10	>99	96 (*R*)
3[d]	**5c**	(*R*,*R*)-**1a**	**3b**	1000	*n*BuOH	RT	>99	96 (*S*)
4	**5c**	(*S*,*S*)-**1d**	**3b**	500	*n*BuOH	RT	>99	93 (*R*)
5	**5d**	(*R*,*R*)-**1a**	**3b**	1000	*n*BuOH	−10	>99	89 (*R*)
6[e]	**5d**	(*S*,*S*)-**1d**	**3b**	1000	*n*BuOH	−10	>99	93 (*S*)
7	**5d**	(*S*,*S*)-**1d**	**2b**	1000	EtOH	RT	>99	90 (*R*)
8	**5e**	(*R*,*R*)-**1a**	**2b**	500	EtOH	RT	>99	90 (*S*)
9	**5e**	(*S*,*S*)-**1d**	**2b**	500	EtOH	RT	>99	91 (*R*)
10	**5f**	(*R*,*R*)-**1a**	**2b**	1000	EtOH	RT	>99	87 (*S*)
11	**5f**	(*S*,*S*)-**1d**	**2b**	1000	EtOH	RT	>99	90 (*R*)
12	**5g**	(*R*,*R*)-**1a**	**2b**	500	EtOH	RT	>99	88 (*S*)
13	**5g**	(*S*,*S*)-**1d**	**2b**	500	EtOH	RT	>99	90 (*R*)
14	**5h**	(*R*,*R*)-**1a**	**2b**	500	EtOH	RT	>99	76 (*S*)
15	**5h**	(*R*,*R*)-**1c**	**2b**	500	EtOH	RT	>99	87 (*S*)
16	**5i**	(*R*,*R*)-**1a**	**2b**	500	EtOH	RT	>99	88 (*S*)
17	**5i**	(*R*,*R*)-**1c**	**2b**	500	EtOH	RT	>99	93 (*S*)
18	**5j**	(*R*,*R*)-**1a**	**4**	200	EtOH	RT	>99	94 (*S*)
19	**5k**	(*R*,*R*)-**1a**	**4**	200	EtOH	RT	96	94 (*S*)
20[f]	**5l**	(*R*,*R*)-**1a**	**4**	2000	EtOH	RT	>99	96 (*S*)

[a] Unless otherwise stated, reactions were carried out with 0.5 mmol **5** and 7 atm H_2 pressure for 15 h. The catalyst was formed in situ by the addition of $[RuCl_2(\mathbf{1})(dmf)_n]$ solution in the corresponding solvent, amine (molar ratio of substrate to amine = 50), and base (molar ratio of substrate to base = 25) to the reaction mixture. [b] The yields were determined by ^{1}H NMR and GC analysis. [c] The *ee* values were determined by chiral GC with a γ-DEX 225 column. The absolute configurations were determined using authentic samples or by comparison of the sign of optical rotation and the retention times with those in the literature.[4b,6,9a,11] [d] The yield of the product isolated by column chromatography was 99%. The *ee* was determined by chiral HPLC using a Chiracel OD-H 150×4.6-mm column. [e] The reaction was carried out with 1 mmol **5d**. The product was isolated by column chromatography (99%). [f] The reaction was carried out with 5.5 mmol **5l**, molar ratio of substrate to amine = 100, and molar ratio of substrate to base = 50. The yield of the product isolated after column chromatography was 90%. The *ee* was determined by chiral HPLC using a Chiracel OD 250×4.6-mm column.

Corey's oxazaborolidine-catalyzed borane reduction of **5d**.[9] When the hydrogenation of **5d** was carried out in EtOH using the same enantiomer of the diphosphane ligand **1d** as above (molar ratio of substrate to catalyst = 1000), but with another nonchiral (alkylthio)amine instead of **3b**, **2b** (Figure 2), the opposite *R* enantiomer of **6d** was obtained again with high *ee* (90% *ee*, Table 2, entry 7).

For ketones **5e–i** (mono *para*-, *ortho*-, and *meta*-substituted acetophenones without functional groups in α-position to the carbonyl function), **2b** (Table 2) was the amine ligand that combined with Ru/**1d**, and *t*BuONa in EtOH gave the highest enantioselectivities (90–93% *ee*). The substituent at the sulfur atom in the 2-(alkylthio)aniline ligand **2** was varied extensively for each ketone, and the highest enantioselectivities were achieved with **2b**. The enantioselectivities obtained in the reductions of ketones **5e–i** in EtOH were only 1–2% higher than those achieved with *i*PrOH as the solvent.

For the heteroaromatic ketones **5j–l** (Table 2, entries 18–20) containing thienyl substituents, the highest enantioselectivities (94–96% *ee*) were obtained in EtOH with Ru/**1a**/**4** complexes in the presence of *t*BuONa. The more substituted diphosphane ligands **1c**,**d** gave selectivities lower than those achieved with the parent ligand **1a**. When the 2-thienyl ketone **5l**, which possesses a β-dimethylamino group, was hydrogenated with the Ru/(*R*,*R*)-**1a**/**4** complex as a catalyst (molar ratio of substrate to catalyst = 2000), (*S*)-**6l** was obtained in 96% *ee* and 99% yield (90% yield after column chromatography) (Table 2, entry 20). This amino alcohol is an intermediate for the synthesis of (*S*)-duloxetine, a potent inhibitor of serotonine- and norepinephrine-uptake carriers.[10] For comparison, (*S*)-**6l** was obtained in 92% *ee* with the Ru/(*R*)-Xylbinap/(*R*,*R*)-daipen catalyst system with the same molar ratio of substrate to catalyst.[11] We believe our process is advantageous since it uses the parent bicp ligand and the relatively inexpensive achiral amine ligand **4** rather than Xylbinap and daipen. In addition the molar ratio of substrate to catalyst in our process can be further increased by carrying out the reaction in a 1:1 mixture of EtOH and *i*PrOH. In this way full conversion and selectivities of 93–94% *ee* were obtained with molar ratio of substrate to catalyst = 4000. Furthermore, EtONa can be used instead of *t*BuONa without affecting the yield or the selectivity, thus reducing the number of the components in the reaction mixture.

At this point, the mechanism of the hydrogenation reactions reported here and the solvent effects are not fully understood. To gain some insight into the factors influencing the hydrogenation reactions, we carried out experiments with higher H_2 pressure (10 atm). The enantioselectivities observed were the same as those achieved with 7 atm H_2 pressure. Hydrogenations using *t*BuOLi or *t*BuOK as the base instead of *t*BuONa did not reveal any cation effect on the enantioselectivity. Lastly, experiments were performed in which each of the commercially available chiral alcohols **6e** was used in the hydrogenation reaction mixture instead of the corresponding ketone **5e**. No loss of enantiopurity was observed, thus ruling out reversible transfer hydrogenation. Full mechanistic studies are still being carried out and will be reported in due course.

In summary, a new catalyst system comprising Ru/**1** complexes in combination with inexpensive nonchiral 2-(alkylthio)amine or 1,2-diamine and an alkoxide as a base for the highly enantioselective hydrogenation of a variety of aryl ketones has been developed. The hydrogenation tolerates various substituents including CH_3O, NHCOPh, $N(CH_3)_2$, F, Cl, Br, and CF_3. The new catalyst system is of great practical potential because of the low cost and availability of the achiral auxiliary amine ligand used.[12]

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Keywords: asymmetric hydrogenation · bicp ligands · phosphanes · ruthenium

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[12] The Supporting Information includes the procedures for preparing the precatalyst and conducting the asymmetric hydrogenation, and detailed analytical methods for determining the *ee* values.

