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Ferrocene-based aminophosphine ligands in the Ru(II)-catalysed asymmetric hydrogenation of ketones: assessment of the relative importance of planar versus carbon-centred chirality

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Abstract—Several ferrocene-based aminophosphine ligands have been prepared and shown to be effective in the Ru(II)-catalysed asymmetric hydrogenation of ketones. The enantioselectivity is mainly determined by the carbon-centred chirality of the ligands but the planar chirality is also important such that (R_C,S_{Fc})- or (S_C,R_{Fc})- are the matched chiralities.

1. Introduction

The asymmetric hydrogenation of simple ketones catalysed by ruthenium complexes formed from chiral diphosphine and diamine ligands provides the most efficient process for the production of optically active secondary alcohols, which, in turn, are some of the most valuable intermediates for the manufacturing of pharmaceuticals and advanced materials. Precatalysts of the type *trans*-RuXY(PAr_2-Q-PAr_2)(NH_2-Q-NH_2) (X = Y = Cl;[1,2] X = H, Y = BH_4;[3] X = H, Y = Cl;[4] X = H, Y = H[5]), in which ruthenium is combined with a chiral diphosphine (PAr_2-Q-PAr_2) and a chiral diamine (NH_2-Q-NH_2) ligand, to form an octahedral complex, have been used successfully in such asymmetric hydrogenations. The high degree of enantioselectivity was considered to be the result of the synergistic effect of the chiral diphosphane and diamine ligands. Alternatively, Ru(II) complexes composed of racemic BINAP or chirally flexible diphosphane ligands in the presence of enantiopure diamine,[6] or of Ru(II) complexes of enantiopure diphosphane in combination with an inexpensive achiral amine,[7] have been used to good effect. Even Ru(II) complexes of achiral diphosphane[8] or achiral triaryl phosphine[9] in combination with enantiopure amine, have been employed in the asymmetric hydrogenation of ketones. Very recently, Morris and co-workers reported complexes of the type *trans*-RuHCl(PPh_2-Q-NH_2)$_2$ and RuHCl(PPh_2-Q-NH_2)(BINAP) (where aminophosphine PPh_2-Q-NH_2 is derived from amino acids or norephedrine), which are active precatalysts for the hydrogenation of ketones and imines to alcohols and amines, respectively, in the presence of an alkoxide base.[10]

As part of our studies on the design and synthesis of new ferrocene-based chiral ligands for asymmetric catalysis,[11] we have developed a very simple, highly stereoselective and modular synthesis of ferrocene-based P-chiral phosphine ligands. Herein, we report the preliminary results of ferrocene-based aminophosphine ligands for the construction of Ru(II) complexes and their use as catalysts in the asymmetric hydrogenation of ketones. The interplay of carbon-centred and planar chirality was found to be important in the catalytic reaction.

2. Results and discussion

We anticipated that a ligand of type **1** could react easily with [$RuCl_2$(benzene)]$_2$ to form complex **2**, which should be an active precatalyst for the asymmetric hydrogenation of ketones. Furthermore, as the ligands are sterically demanding, the catalysts might accomplish higher stereoselectivity in asymmetric reactions.

In order to investigate the influence of R, R^1 and Ar on activity and enantioselectivity, we first synthesised a series

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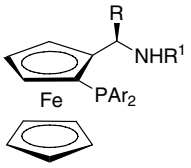

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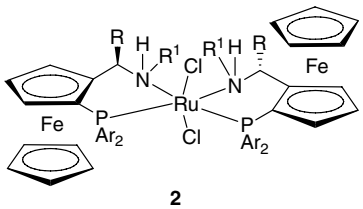

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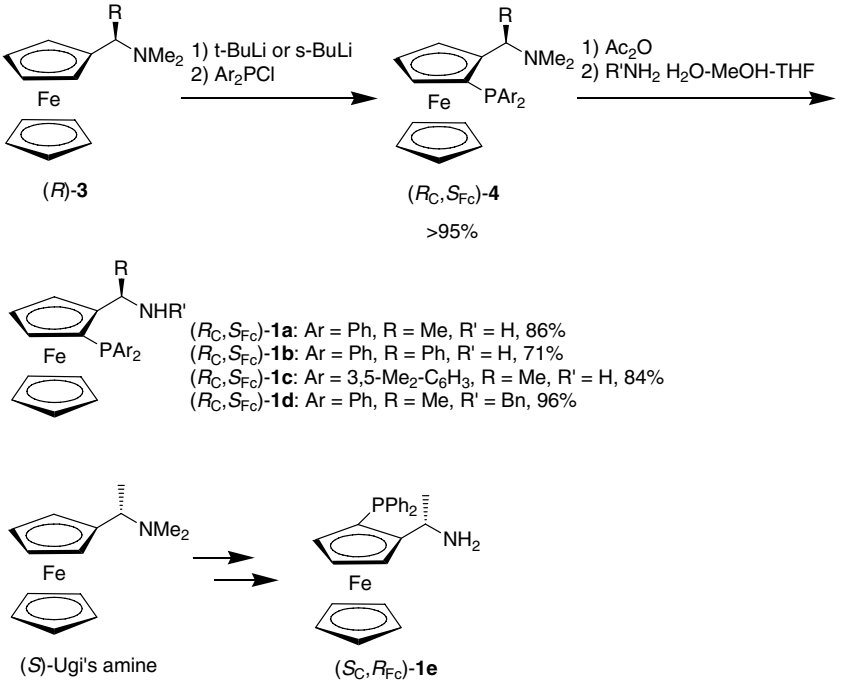
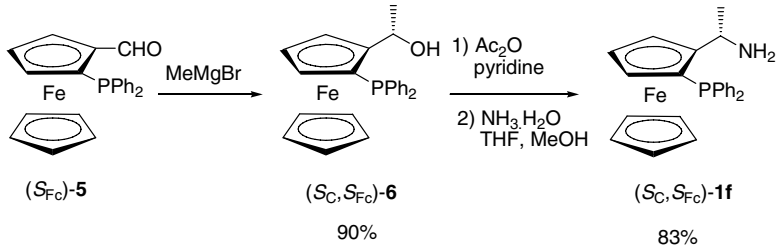
of type **1** ligands from the readily available (*R*)-amines (*R*)-**3**[12] (Scheme 1). Highly diastereoselective *ortho*-lithiation of amines (*R*)-**3** followed by treatment with $ClPAr_2$ gave compounds **4**, which have the (R_C,S_{Fc})-configuration. After reaction of **4** with Ac_2O at 100 °C, followed by treatment with a large excess of ammonia or amine in a mixture of water, methanol and THF at 60 °C, the dimethylamino group of **4** was substituted by either a primary or a secondary amino group to form ligand **1**. In the literature,[13] compounds **4** were prepared by lithiation of amines **3** with *n*-BuLi followed by reaction with $ClPAr_2$. However, we found that amines **3** could not be lithiated completely with *n*-BuLi and hence the yields of compounds **4** were unsatisfactory. Replacement of *n*-BuLi with *sec*-BuLi or *tert*-BuLi led to compounds **4** in very high yield (normally >95%). Similarly, the enantiomer of (R_C,S_{Fc})-**1a**, (S_C,R_{Fc})-**1e** was prepared from (*S*)-Ugi's amine (Scheme 1). The diastereomer of both (R_C,S_{Fc})-**1a** and (S_C,R_{Fc})-**1e**, (S_C,S_{Fc})-**1f** was prepared from easily available (S_{Fc})-α-(diphenylphosphino)ferrocenecarboxaldehyde **5**[18] (Scheme 2). Thus, the reaction of (S_{Fc})-**5** with MeMgBr gave product in 95% yield with a ratio of 9:1 for the (S_C,S_{Fc})/(R_C,S_{Fc}) diastereomers.[11b,19] Recrystallisation from hexane gave the pure diastereomer (S_C,S_{Fc})-**6** in 73% yield. Esterification of **6** with Ac_2O in the presence of pyridine, followed by treatment with a large excess of aqueous ammonia solution in a mixture of methanol and THF at 60 °C gave (S_C,S_{Fc})-**1f**.

1,2-Disubstituted ferrocenyl ligands have both planar and central chiralities. Hence, in other transformations, one or both elements of chirality influenced the outcome of the reaction. Kumada found that planar chirality is a decisive factor for exerting control over the enantiomeric excess and absolute configuration in a Ni-catalysed Grignard cross-coupling reaction.[14] Sammakia reported similar results in an asymmetric copper-catalysed conjugated addition of Grignard reagents to enones with chiral ferrocenyl phosphine oxazoline ligands.[15] In some other examples, the effect of planar chirality is not as apparent. Dai found that carbon-centred chirality played a decisive role in a hydrogen transfer reaction with a phosphine-oxazoline ferrocenyl ligand.[16] Furthermore, Dai examined the role of the planar chirality of S,N and Se,N bidentate ligands in palladium catalysed allylic alkylation,[17] and found that the absolute configuration and enantiomeric excess were governed mainly by the C-centred chirality, but that the planar chirality was also important. Hence we were most interested in assessing the role of planar and central chiralities of ligands **1** in the Ru-catalysed asymmetric hydrogenation of ketones.

Ligand **1** reacted with $[Ru(benzene)Cl_2]_2$ in DMF at 100 °C for 10 min followed by removal of DMF in vacuo to give the precatalyst **2** as yellow crystals. In the presence of *t*-BuOK in *i*-propanol, some of precatalysts **2** displayed high reactivity and moderate to good enantioselectivity in the hydrogenation of 1-acetonaphthone (Table 1). Thus, the complete hydrogenation of 1-acetonaphthone to (*R*)-1-naphthylethanol in 66.7% ee occurred in less than 3 h at room temperature under an H_2 pressure of 20 bar in the presence of precatalyst **2a** (0.1 mol %), generated from (R_C,S_{Fc})-**1a** (entry 1). Similarly, precatalyst **2e**, the enantiomer of **2a**, prepared from (S_C,R_{Fc})-**1e**, gave (*S*)-1-naphthylethanol in 66.5% ee (entry 5). Replacement of the methyl

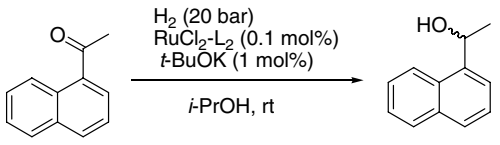


Scheme 1.



Scheme 2.

Table 1. Asymmetric hydrogenation of 1-acetonaphthone catalysed by various Ru-complexes[a]



Entry	Ligand	Precatalyst	Time (h)	Conv. (%)	ee[b] (%)
1	(R_C,S_{Fc})-**1a**	**2a**	3	100	66.7 (*R*)
2	(R_C,S_{Fc})-**1b**	**2b**	3	88	44.3 (*R*)
3	(R_C,S_{Fc})-**1c**	**2c**	3	100	78.7 (*R*)
4	(R_C,S_{Fc})-**1d**	**2d**	4	3.7	20.5 (*R*)
5	(S_C,R_{Fc})-**1e**	**2e**	3	100	66.5 (*S*)
6	(S_C,S_{Fc})-**1f**	**2f**	3	56	16.4 (*S*)
7	(R_C,S_{Fc})-**1a**		3	100	66.5 (*R*)[c]
8	(R_C,S_{Fc})-**1c**		3	100	78.9 (*R*)[c]

[a] Reaction conditions: 5 mmol of substrate, 0.005 mmol of **2**, 0.05 mmol of *t*-BuOK, 3 mL of *i*-PrOH, room temperature and H_2 pressure of 20 bar.
[b] Determined by GC using Chrompack Chirasil-Dex CB (25 m × 0.25 mm).
[c] Catalyst **2** was prepared in situ by reaction of ligand **1** with [Ru(benzene)Cl_2]$_2$ in *i*-PrOH at room temperature for 15 min.

group in **1a** with phenyl group, (R_C,S_{Fc})-**1b**, lowered both the reactivity and enantioselectivity (entry 2). In contrast, and mimicking Noyori's precatalysts of the type *trans*-RuXY(PAr_2-Q-PAr_2)(NH_2-Q-NH_2),[1–5] the introduction of 3,5-dimethyl groups to *P*-phenyl rings, (R_C,S_{Fc})-**1c**, significantly increased the enantioselectivity to 78.7% ee (entry 3). Substitution of one hydrogen atom of the amino group in **1a** with a benzyl group, (R_C,S_{Fc})-**1d**, dramatically lowered both reactivity and enantioselectivity (entry 4).

Carbon-centred chirality plays the decisive role in the Ru(II)-catalysed asymmetric hydrogenation of ketones a ligand **1**. Thus, in the presence of precatalyst **2f**, generated from ligand (S_C,S_{Fc})-**1f**, hydrogenation of 1-acetonaphthone gave (*S*)-1-naphthylethanol in only 16.4% ee and 56% conversion under the standard reaction conditions (entry 6 vs entry 1 and entry 5). While the atom-centred chirality is the main governing factor, the planar chirality is also important, and (R_C,S_{Fc})- or (S_C,R_{Fc})-**1** is the ligand with matched C-centred and planar chiralities. The matching of planar and central chiralities is essential for obtaining high asymmetric induction and also demonstrates the importance of planar chirality.

Finally, precatalyst **2** is very easy to form and, in this respect, is quite different from the formation of Noyori's precatalysts of the type *trans*-$RuCl_2$(PAr_2-Q-PAr_2)-(NH_2-Q-NH_2).[1,2] Thus, precatalyst **2**, generated in situ by stirring a mixture of ligand **1** and [Ru(benzene)Cl_2]$_2$ in *i*-PrOH for 15 min at room temperature, gave the same results as using the prepared precatalyst **2** (entry 7 and entry 8 vs entry 1 and entry 3). The easy formation of precatalyst **2** indicates a possibility of finding a better catalyst in a combinatorial manner, using two different aminophosphine ligands. The concept of using two different chiral monodentate phosphine ligands for asymmetric catalysis, which was first proposed by us,[20] has been confirmed successfully by other groups.[21]

3. Conclusion

In conclusion, ferrocene-based aminophosphine ligands have been shown to be effective in the Ru(II)-catalysed asymmetric hydrogenation of ketones. The enantioselectivity is mainly determined by the C-centred chirality of the ligands but the planar chirality is also important, and (R_C,S_{Fc})- or (S_C,R_{Fc})- is the matched combination of chiralities. Studies are currently under way in order to obtain highly enantioselective ligands by modification of Ar on phosphorus and R on carbon.

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