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Synthesis and application of chiral *N*,*N*′-dialkylated cyclohexanediamine for asymmetric hydrogenation of aryl ketones

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Abstract

Chiral *N*,*N*′-dialkylated cyclohexanediamine derived ligands have been synthesized and used in the asymmetric hydrogenation of aryl ketones. Optically active alcohols with up to 90% enantiomeric excess were obtained in high yields.

Keywords: Chiral diamine; Aryl ketone; Asymmetric hydrogenation; Ruthenium complex

Asymmetric hydrogenation has become increasingly popular for producing enantiomerically pure compounds in pharmaceutical and chemical industries [1]. In 1995 Noyori reported that ketones with no secondary binding functionality could be effectively hydrogenated in the presence of ruthenium catalysts [2]. These are based on a ruthenium metal centre bearing a chiral diphosphine and such as **1**–**4** and chiral diamine such as **5a**, **7**–**9** in the presence of a base (such as *t*-BuOK or KOH) (Fig. 1). The asymmetric hydrogenation of a wide range of unfunctionalised ketones now became possible, without the previous need to have a secondary binding group on the substrate.

A series of C_2-symmetric diphosphines such as BINAP **1** [3], HexaPHEMP **2** [4] and MeO-BIPHEP **3** [5], which gave high enantioselectivities in asymmetric hydrogenation, have been used in earlier studies. However, in contrast with chiral diphosphines, the chiral diamine has not been extensively studied as ligands to date [6]. In a quest to develop an accessible chiral diamine that forms catalytically active complexes with transition metals, having equal or improved activity and selectivity to equivalent complexes of known ones, we prepared a series of chiral diamine based on the (*R*,*R*)-1,2-diaminocyclohexane **5a** backbone (Fig. 2). Herein, we outline the synthesis and preliminary catalytic results associated with these ligands.

The route used to synthesise (*R*,*R*)-*N*,*N*′-dialkyl-1,2-diaminocyclohexane **5b**–**5e** is shown in Scheme 1. Enantiomerically pure (*R*,*R*)-1,2-diaminocyclohexane **5a** was converted into its (*R*,*R*)-*N*,*N*′-dimethyl analogs **5b** by reaction with ethyl chloroformate in the presence of sodium hydroxide, followed by reduction used LAH for 16 h in THF [7]. The (*R*,*R*)-*N*,*N*′-diethyl analog **5c** was prepared from the corresponding *N*,*N*′-diacetyl compound by

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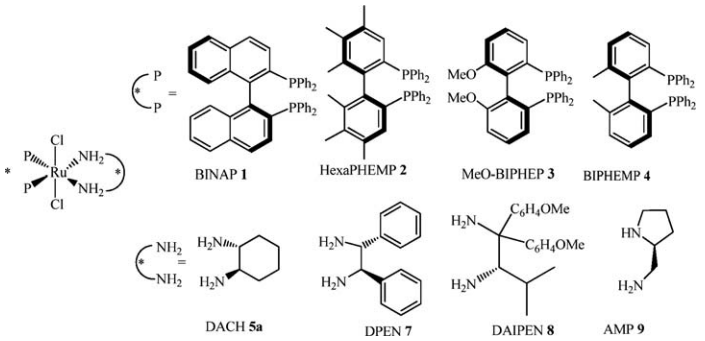


Fig. 1. Complexes used for ketone hydrogenation catalysts.

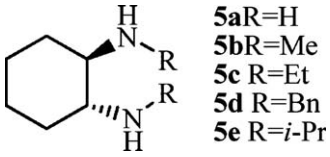
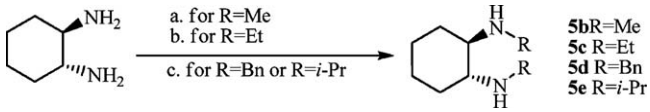


Fig. 2. Our chiral diamine.



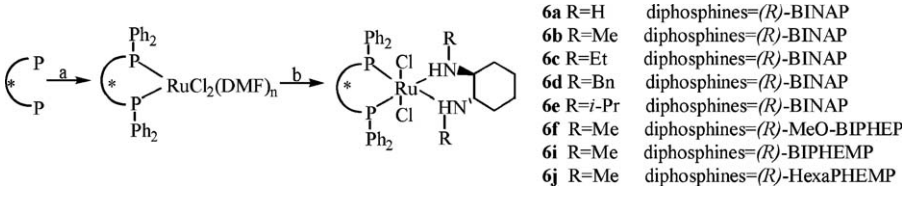
Scheme 1. Reagents and conditions: (a) (1) ClCOOEt, NaOH, toluene 25 °C; (2) LAH in THF 0 °C then Rf. 14 h, 72% yield. (b) (1) AcO_2, MeOH; (2) LAH in THF 0 °C then Rf. 14 h, 82% yield. (c) (1) PhCHO or $(CH_3)_2CO$, (2) $NaBH_4$, MeOH, **5d** 98 yield%, **5e** 90 yield%.

reduction with LAH in THF also [7]. The (*R*,*R*)-*N*,*N*′-dibenzyl and (*R*,*R*)-*N*,*N*′-diisopropyl analogs **5d**, **5e** was prepared through reductive amination with benzaldehyde and acetone [8].

A series of corresponding new ruthenium complexes were prepared according to literature methods [9], the precatalysts were readily prepared under inert conditions by reaction of $[RuCl_2C_6H_6]_2$ with a diphosphine in hot DMF followed by treatment with a diamine at room temperature yielding air stable, easily handled solids (Scheme 2). The corresponding ruthenium complexes of the DACH **5a** were also prepared for comparison.

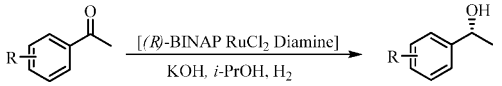
Parallel experiments were performed to make direct comparison between our catalysts and the reported ones under identical conditions with the same substrates. We first undertook comparative catalyst testing with each of these diamines and chose acetophenone as the model substrate and *trans*-$[RuCl_2(BINAP)(diamine)]$ as the precatalyst. The catalytic activities of these ruthenium complexes in the hydrogenation of acetophenone were tested in *i*-Pr-OH, with a substrate/catalyst/base ratio (S/C/B) of 3000/1/100, at 20 °C and under 30 bar of hydrogen (Table 1).

As is evident from Table 1, comparison of different diamines revealed that the *N*,*N*′-dimethyl-DACH **5b** and *N*,*N*′-diethyl-DACH **5c** showed similar activity but higher enantiomerical selectivity. The *N*,*N*′-dimethyl-DACH **5b** and *N*,*N*′-diethyl-DACH **5c** affords the product with 91% and 90% *ee* (Table 1, entries 2 and 3) and the DACH **5a** get 81%



Scheme 2. Reagents and conditions: (a) DMF and $[Ru(benzene)Cl_2]_2$ 100 °C, 25 min, (b) (*R*,*R*)-**5a**–**5e**, 25 °C, 5 h. The solvent DMF was removed by evaporation at 30 °C under reduced pressure.

Table 1
Asymmetric hydrogenation of acetophenone use different diamines



Entry	Complexes	R	Time (h)	Conc. (%)	*ee* (%)[a]
1	**6a**	H	3	85	81[b]
2	**6b**	H	3	83	91
3	**6c**	H	3	83	90
4	**6d**	H	3	69	78
5	**6e**	H	3	55	77
6	**6a**	H	12	99	82
7	**6b**	H	12	99	91
8	**6c**	H	12	99	90
9	**6d**	H	12	99	79
10	**6e**	H	12	95	78

[a] Reactions were run under 3 MPa H_2 and 20 °C in 50 mL magnetically stirred Parr pressure vessels and S/C/B 3000/1/100. Conversion and *ee*s were determined by GC analysis (Chirasil DEX-CB column), used (*S*)-1-phenylethanol as refer to determine the absolute configuration of product.
[b] Doherty et al. reported 84% *ee* [10]; J.P. Henschke reported 82% *ee* [4].

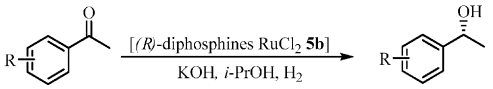
ee (Table 1, entry 1). The results showed that the DACH substituted by alkyl provided a slight improvement in selectivity over DACH **5a** themselves. It appears that the *N*,*N*′-dimethylated diamine derivatives **5b** that are sterically less hindered at the nitrogen gave slightly better results in enantioselectivity than those of *N*,*N*′-dibenzylated diamine derivatives **5d** and *N*,*N*′-diisopropyl derivatives **5e**. The *N*,*N*′-dimethylated diamine **5b** and *N*,*N*′-diethylated diamine **5c** get 91% and 90% *ee* (Table 1, entries 2 and 3), whereas the complexes obtained from *N*,*N*′-dibenzyldiamine **5d** and *N*,*N*′-diisopropyldiamine **5e** affords 77% and 78% *ee*, respectively (Table 1, entries 4 and 5).

Different complexes were synthesized by using different diphosphine ligands and *N*,*N*′-dimethyl-DACH **5b**. The catalytic activities of these ruthenium complexes in the hydrogenation of acetophenone were tested too. The results showed almost no difference in the enantiomerical selectivity (Table 2).

With the optimal reaction conditions in hand, complexes **6b** were used in the hydrogenation of a series of acetophenones derivatives (Table 3, entries 1–9). A range of alkyl phenyl ketones was reduced to secondary alcohols with a high yield and a satisfactory *ee*%. The excellent enantioselectivities *ee* were observed. The best result was hydrogenation of *o*-bromoacetophenone (Table 3, entry 6), in which the conversion to products was >99% with 99% *ee*. The *o*-chloroacetophenone (Table 2, entry 7) and *o*-trifluromethylacetophenone (Table 2, entry 5) could get better *ee* at 96%.

In summary, a series of chiral *N*,*N*′-dialkylated cyclohexanediamine derivatives were synthesized and used to produce the corresponding new ruthenium complexes, which were applied in catalysts hydrogenation of aryl ketones.

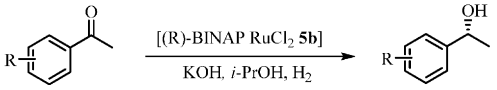
Table 2
Asymmetric hydrogenation of acetophenone use different diphosphines



Entry	Complexes	R	Time (h)	Conc. (%)	*ee* (%)[a]
1	**6b**	H	12	99	91
2	**6f**	H		99	89
3	**6i**	H		99	87
4	**6j**	H		99	92

[a] Reactions were run under 3 MPa H_2 and 20 °C in 50 mL magnetically stirred Parr pressure vessels and 12 h. S/C/B 3000/1/100. Conversion and *ee*s were determined by GC analysis (Chirasil DEX-CB column). Used (*S*)-1-phenylethanol as refer to determine the absolute configuration of product.

Table 3
The results of hydrogenation of different acetophenones derivatives



Entry	Complexes	R	Conc. (%)	*ee* (%)
1	**6b**	H	99	91
2		*p*-CH_3O	99	91
3		*p*-CF_3	99	90
4		*o*-CH_3O	99	92
5		*o*-CF_3	99	97
6		*o*-Br	99	99
7		*o*-Cl	99	96
8		*o*-F	99	94
9		*o*-OH	30	87

Reactions were run under 3 MPa H_2, 20 °C in 50 mL magnetically stirred Parr pressure vessels and in 12 h. S/C/B 3000/1/100. Conversion and *ee*s were determined by GC analysis (Chirasil DEX-CB column).

In all cases studied, *N*,*N*′-dialkyl-DACH performed as well as or better than the DACH complexes. Further synthesis of chiral imidazolidines and their application to asymmetric catalysis are underway in our laboratory.

Acknowledgments

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