Ru-BICP-Catalyzed Asymmetric Hydrogenation of Aromatic Ketones

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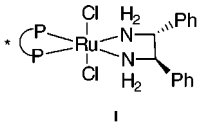
Introduction

The design and synthesis of effective enantioselective catalysts for hydrogenation of simple ketones remains a challenging problem.[1] Recently, Noyori[2] disclosed a ternary catalyst system consisting of Ru-BINAP−chiral diamine−KOH, which is highly efficient in the asymmetric hydrogenation of a variety of simple ketones lacking a secondary coordinating functional group. We have developed rhodium complexes with a conformationally rigid, electron-rich bidentate phosphine ligand (PennPhos)[3] as highly enantioselective catalysts for hydrogenation of both aryl alkyl and dialkyl ketones. In a related study, we have designed and synthesized a new conformationally rigid 1,4-bisphosphine, (2*R*,2′*R*)-bis(diphenylphosphino)-(1*R*,1′*R*)-dicyclopentane (BICP). Rh-BICP gives excellent enantioselectivity upon asymmetric hydrogenation of 2-(acylamino)acrylic acids.[4] Prompted by these encouraging results, we were interested in exploring the Ru-BICP-catalyzed hydrogenation of simple ketones using Noyori's protocol (Scheme 1). Our experimental results on a Ru-BICP catalytic system indicate an important finding of possible multipoint interactions between a chiral chelating diamine and acetylthiophene derivatives.

Results and Discussion

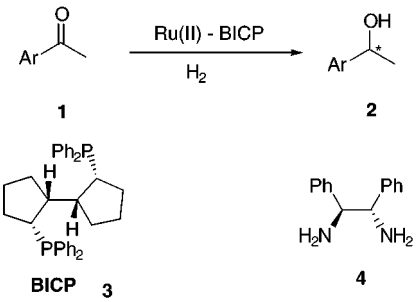
We have prepared several Ru-BICP complexes and probed their catalytic activity and enantioselectivity for hydrogenation of simple ketones. The Ru-BICP precatalyst (**I**, Figure 1) was prepared by combining $RuCl_2$[(*R*,*R*)-BICP](TMEDA) with 1 equiv of (*R*,*R*)-1,2-diphenylethylenediamine in 2-propanol. [Ru(η^6-cymene)Cl_2]$_2$, [Ru(η^6-benzene)Cl_2]$_2$, and [(COD)$RuCl_2$]$_n$ all can be used to prepare $RuCl_2$[(*R*,*R*)-BICP](TMEDA) according to a literature procedure.[5] Alternatively, $RuCl_2$(*R*,*R*)-BICP[6] can



I

Figure 1.

Scheme 1



be synthesized by reacting [Ru(η^3-methyl-allyl)$_2$(COD)] with BICP in acetone, followed by addition of 2 equiv of methanolic HCl. The catalyst precursor made from this $RuCl_2$[(*R*,*R*)-BICP] recipe in combination with 1 equiv of (*R*,*R*)-1,2-diphenylethylenediamine is also suitable for asymmetric hydrogenation of aromatic ketones. In this work, we typically used $RuCl_2$[(*R*,*R*)-BICP](TMEDA) made from the [Ru(η^6-cymene)Cl]$_2$ precursor for catalytic reactions because it has higher activity toward hydrogenation of ketones.

We chose acetophenone as a typical substrate and the hydrogenation reaction was performed in 2-propanol under 60 psi of H_2 at room temperature with 0.2 mol % of catalyst. The Ru−BICP catalyst was generated in situ from three components: $RuCl_2$[(*R*,*R*)-BICP](TMEDA), (*R*,*R*)-1,2-diphenylethylenediamine and KOH (molar ratio 1:1:2). Under these conditions, hydrogenation of acetophenone gave 1-phenylethanol in 72% ee. Varying the solvent or H_2 pressure had only a small effect on the enantioselectivity. At −20 °C, a slightly higher ee (78%) was obtained. The match of the steric environment of the chiral diamine with that of the chiral bisphosphine BICP is important for achieving high enantioselectivity, which is consistent with Noyori's observation.[2] For example, combination of (*S*,*S*)-1,2-diphenylethylenediamine and $RuCl_2$[(*R*,*R*)-BICP](TMEDA) resulted in only 36% ee upon hydrogenation of acetophenone. Switching from (*R*,*R*)-1,2-diphenylethylenediamine to (*R*,*R*)-1,2-cyclohexanediamine gave lower enantioselectivity (57% ee).

Table 1 summarizes the hydrogenation results with aryl alkyl ketones under the optimized conditions. Substitution on the 4′-position of the benzene ring with electron-withdrawing groups has only a small effect on the enantioselectivity (73−76% ee, entries 1−3). Variation of the structure of the alkyl groups on the ketones causes major changes in the observed enantioselectivity (76% ee, entry 1, 79% ee, entry 5, 26% ee, entry 6). A change in the steric environment on the aromatic ring also results in a big difference in the activity and enantioselectivity of this catalytic system. For example,

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (d) Fehring, V.; Selke, R. *Angew. Chem., Int. Engl. Ed.* **1998**, *37*, 1827. For early examples of direct asymmetric hydrogenation, see: (e) Bakos, J.; Tóth, I.; Heil, B.; Markó, L. *J. Organomet. Chem.* **1985**, *279*, 23. (f) Chan, A. S. C.; Landis, C. R. *J. Mol. Catal.* **1989**, *29*, 165. (g) Zhang, X.; Taketomi, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 3318.

(2) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (b) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Engl. Ed.* **1998**, *37*, 1703 and references therein.

(3) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang X. *Angew. Chem., Int. Engl. Ed.* **1998**, *37*, 1100.

(4) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799.

(5) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1.

(6) Genêt, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; Caño De Andrade, M. C.; Darses, S.; Galopin, C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 675.

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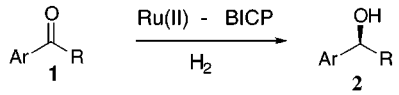
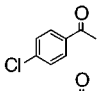
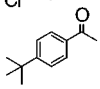
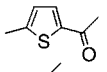
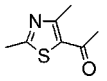
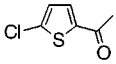
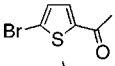
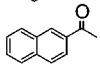
Table 1. Enantioselective Hydrogenation of Simple Aromatic Ketones Catalyzed by a BICP-Ru(II) Complex−Chiral Diamine−KOH System[a]



Entry	Ketone	Product	conv.%[b]	ee %[b]	config.[c]	Entry	Ketone	Product	conv.%[b]	ee %[b]	config.[c]
1		2a	100	76	*S*	10		2j	100	74	*S*
2		2b	100	74	*S*						
3		2c	100	73	*S*	11		2k	100	93[d]	*S*
4		2d	100	74[e]	*S*	12		2l	92	91[d]	*S*
5		2e	100	79	*S*	13		2m	38	92[d]	*S*
6		2f	100	26	*S*	14		2n	65	90[d]	*S*
7		2g	100	67	*S*	15		2o	90	89[d]	*S*
8[f]		2h	100	83	*S*	16		2p	88	88[d]	*S*
9		2i	100	41	*S*	17		2q	86	86[d]	*S*

a: Reactions were carried out at rt using 2M solution of substrate (5mmol) in 2-propanol for 24h. [(R,R)-diphenylethylenediamine was used as the chiral diamine, (R,R)-BICP was the chiral phosphine ligand. Substrate:Ru(II):diamine:KOH = 500:1:1:2 *b*: Determined by GC analysis using a β-DEX 120 column *c*: Determined by sign of optical rotation *d*: the reaction run at -30°C for 48h *e*: Determined by GC analysis using a γ-DEX 225 column *f*: The reaction run at -20° C for 48h.

2,4,6-trimethyl acetophenone cannot be reduced under the aforementioned reaction conditions, while hydrogenation of 1′-acetonaphthone (**2j**) and 2′-acetonaphthone (**2i**) afforded alcohol products with significantly different enantioselectivities (entries 9 and 10). Compared with Noyori's Ru-BINAP hydrogenation system, the results obtained with the Ru-BICP catalyst for hydrogenation of aromatic ketones are lower by 10−20% ee.

Upon further examination of the hydrogenation system, we have uncovered some surprising results for hydrogenation of 2-acetylthiophene and its derivatives. Under the optimized conditions, 2-acetylthiophene was hydrogenated in 93% ee at −30 °C (84% ee at room temperature), which is significantly higher than the result obtained with acetophenone (78% ee, −30 °C). An array of 2-acetylthiophene derivatives can also be reduced with high enantioselectivity (entries 12−16). Hydrogenation of 3′-acetylthiophene, however, proceeded with lower enantioselectivity (86% ee, entry 17).

Although the exact nature of this higher selectivity with 2-acetylthiophene derivatives is unclear, we hypothesize that the multipoint interactions between the sulfur atom and the acetyl group and the NH groups of the chiral diamine may be important. Noyori has proposed that the NH group on a chiral chelating diamine plays an important role in the so-called metal−ligand bifunctional hydrogenation catalyst (Figure 2). A six-membered ring transition state for ketone reduction is a reasonable model, where a ketone does not coordinate to

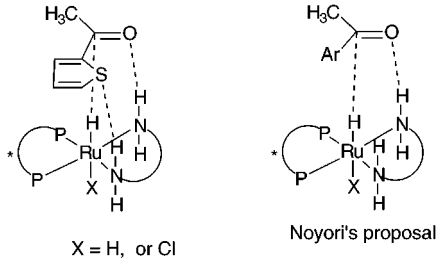


Figure 2.

the Ru center.[1c,2b] This new hypothesis is interesting, and further study will focus on illustrating the nature of the possible control element.

In conclusion, a Ru-BICP−chiral−diamine−KOH catalyst system is effective for hydrogenation of aromatic ketones, especially 2-acetylthiophene derivatives. Multipoint interactions between the substrate and the catalyst might be responsible for high enantioselectivity in reduction of 2-acetylthiophene derivatives.

Experimental Section

General Information. All operations were carried under a N_2 atmosphere in a glovebox. $[Ru(cymene)Cl_2]_2$,[7] 1,2-diphenylethylenediamine,[8] BICP,[4] and Ru(η^3-methyl-allyl)$_2$(COD)[9] were

(7) Bennett, M. A.; Huang, T.; Matheson, T. W.; Smith, A. K. *Inorg. Synth.* **1982**, *21*, 74.

prepared according to literature procedures. 2-Propanol was distilled from magnesium and stored under N_2 atmosphere. Ketones were distilled before use. GC analyses were carried on a Helwett-Packard 6890 gas chromatograph with a 30-m Supelco β-DEX 120 column or a γ-DEX 225 column.

General Procedure for Preparation of $RuCl_2$-[(*R*,*R*)-BICP](TMEDA).[5] To a solution of *N*,*N*,*N*,*N*-tetramethylethylenediamine (4.5 mL) were added 27.5 mg (0.045 mmol) of $[Ru(cymene)Cl_2]_2$ and a 0.1 M toluene solution of BICP ligand (1 mL, 0.1 mmol), and the solution was heated in a sealed Schlenk tube at 100 °C for 10 min. A red solution was formed, and the solution was then cooled to about 50 °C. After the solvent was removed under vacuum, the resulting orange solid was collected and used in the next step without further purification.

General Procedure for Hydrogenation of Aromatic Ketones Catalyzed by the BICP-Ru(II) Complex−1,2-Diphenylethylenediamine−KOH System. The $RuCl_2$−[(*R*,*R*)-BICP](TMEDA) complex (0.09 mmol) was dissolved in 13.5 mL of 2-propanol. To 1.5 mL of this solution was added a 0.01 M 2-propanol solution of 1,2-diphenylethylenediamine (1 mL, 0.01 mmol) and a 0.1 M 2-propanol solution of KOH (0.22 mL, 0.022 mmol). The resulting mixture was stirred at room temperature for 30 min, and then the ketone (5.0 mmol) was added. After being stirred for 2 min, the solution was transferred to a Parr autoclave, and hydrogenation was carried out at room temperature under 60 psi of hydrogen for 24 h. Hydrogen was carefully vented, and the residue was passed through a short silica gel column eluting with diethyl ether to remove the catalyst and give desired products. Enantiomeric excesses and reaction conversions were measured by gas chromatography. The absolute configuration of products was determined by comparing the observed rotation with the reported value.[2a,10]

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Supporting Information Available: The detailed procedure for determination of enantiomeric excesses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Pini, D.; Iuliano A.; Rosini, C.; Salvadori, P. *Synthesis* **1990**, 1023.
(9) Genêt, J. P.; Pinel, C.; Ratovelomanana-Vidal V.; Mallart, S.; Pfister, X.; Caño De Andrade; M. C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 665.
(10) Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Poli, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1607.