Pergamon

Tetrahedron Letters 43 (2002) 8059–8062

TETRAHEDRON LETTERS

N,N′-Dialkylated 1,2-diamine derivatives as new efficient ligands for $RuCl_2(PPh_3)_3$ catalyzed asymmetric transfer hydrogenation of aromatic ketones

Geon-Joong Kim,* Sang-Han Kim, Pong-Hyun Chong and Mi-Ae Kwon

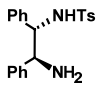
Department of Chemical Engineering, Inha University, Inchon 402-751, South Korea

Received 17 May 2002; revised 6 September 2002; accepted 12 September 2002

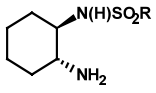
Abstract—Chiral *N,N′*-dialkylated cyclohexanediamine derivatives ligands have been synthesized and used in an asymmetric transfer hydrogenation of aryl ketones. Optically active alcohols with up to 93% enantiomeric excess were obtained in high yield.

During the last decade, considerable efforts have been devoted to the development of highly efficient catalysts for the hydrogen-transfer (H-transfer). An especially useful method is the catalytic transfer hydrogenation using 2-propanol[1] or $HCOOH/Et_3N$ mixture[2] as a hydride source and a chiral ruthenium catalyst complex bearing ligands. Among these, H-transfer from boiling isopropyl alcohol to ketones is particularly useful due to its simplicity and the many favorable properties of the reaction. Through the work in this area, many other chiral ligands[3] which are highly selective and extremely active have been achieved with Ru complexes.

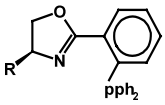
Chiral 1,2-diamine based Ru(II) complexes effectively promoted the reduction of acetophenone to give (*S*)-1-phenyl ethanol with excellent yield and very high ee% using 2-propanol as a hydrogen source.[4] The reaction rates and enantioselectivity are highly dependent on the electronic properties of substituents in phenyl rings as well as the bulkiness around the carbonyl moiety.



1



2



3

Langer and Helmchen[3] have reported that Ru complexes with chiral phosphinooxazolines are highly reactive and enantioselective in the H-transfer of aliphatic as well as aromatic ketones. Preformed $RuCl_2$(**3**)-$[P(C_6H_5)_3]_3$ acts as an extremely effective catalyst for reduction of acetophenone at 82°C. The degree of optical yield tends to increase with increasing of the size of alkyl groups in the ketone substrates.

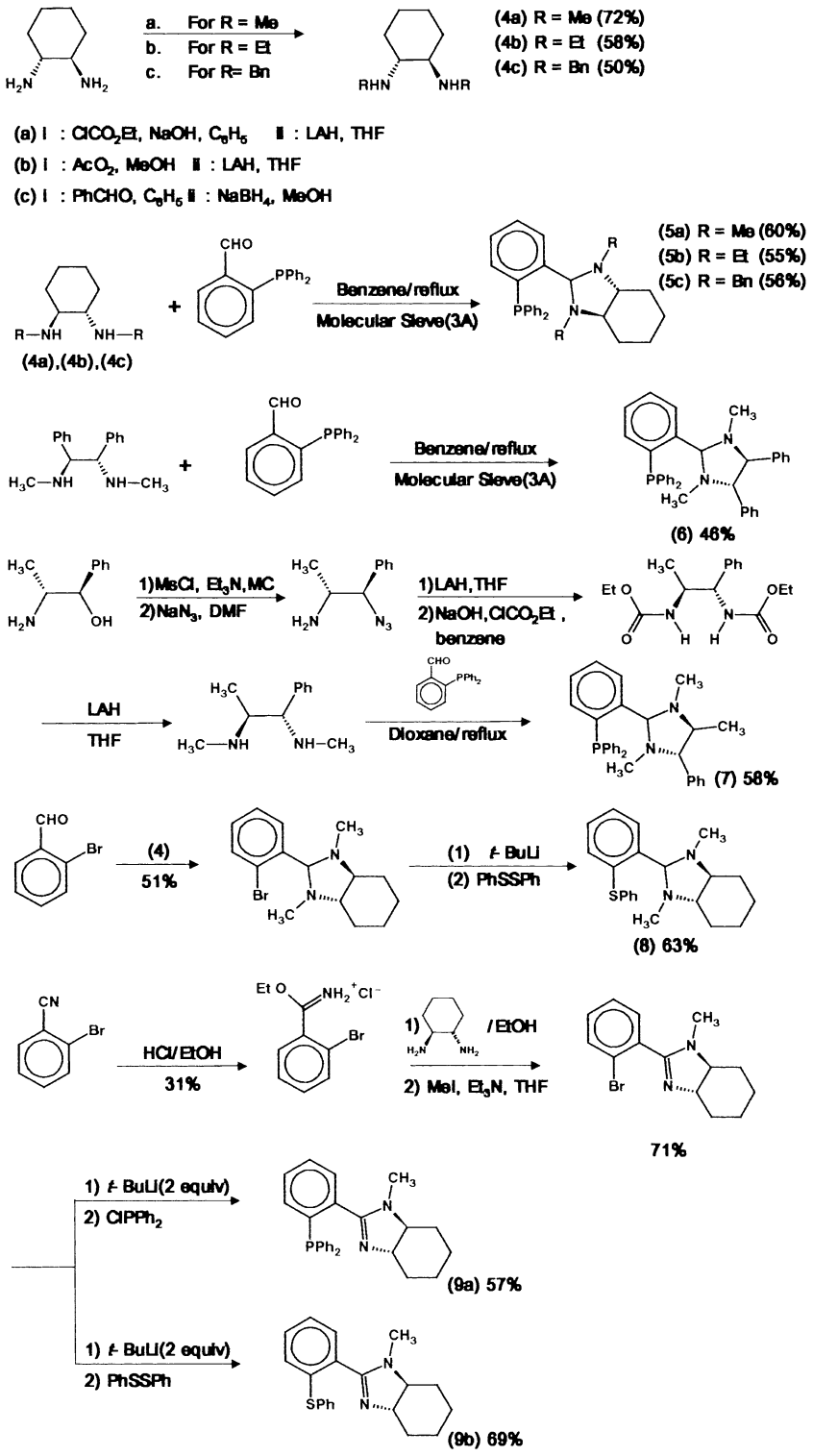
In fact, $RuCl_2[P(C_6H_5)_3]_3$ is known as an excellent catalyst for olefin hydrogenation, but very poor for carbonyl hydrogenation. Chowdhury and Backvall[5] have reported that $RuCl_2[P(C_6H_5)_3]_3$ catalyses efficient transfer hydrogenation of ketones by 2-propanol with very high turnover frequency, but no hydrogenation occurs in the absence of bases such as NaOH. Okuma et al.[6] have investigated that the combined effects of diamine and KOH accelerate the carbonyl hydrogenation.

However, the chiral imidazolidine ligands have never been applied in the reduction of ketones using 2-propanol. With the aim of exploiting the imidazolidines, we synthesized new chiral imidazolidines from optically active (1*R*,2*R*)-(+)-*N,N′*-dialkylcyclohexane-1,2-diamines. Herein we report the application of the imidazolidines as a ligand to the Ru-catalyzed asymmetric H-transfer of aryl ketones. This communication also describes the preparation of the new imidazolidines possessing a five-membered backbone.

Scheme 1 shows the method to synthesize the phosphinoimidazolidines and thioimidazolidines. Enantiomerically pure (*R,R*)-1,2-diaminocyclohexane was converted to its *N,N′*-dialkyl analogs of type (**4a**–**4c**). (*R,R*)-*N,N′*-Dimethyl-1,2-diamino cyclohexane (**4a**) was synthesized by the reaction of (*R,R*)-1,2-diamino cyclohexane with ethyl chloroformate in the presence of NaOH, followed by lithium aluminum hydride (LAH) reduction in anhy-

* Corresponding author. Tel.: +82-32-860-7472; fax: +82-32-872-0959; e-mail: kimgj@inha.ac.kr

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)01962-7



Scheme 1.

drous THF. In addition, for the synthesis of (**5a**), commercially available (1*R*,2*R*)-(+)-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**4a**) could be chosen as a starting auxiliary. The *N*,*N*′-diethyl analog (**4b**) was prepared from the corresponding *N*,*N*′-diacetyl compound by reduction with LAH in THF also. (*R*,*R*)-*N*,*N*′-Diacetyl-1,2-diaminocyclohexane was synthesized by the reaction of (*R*,*R*)-1,2-diaminocyclohexane with acetic anhydride in methanol. The *N*,*N*′-dibenzyl-1,2-diamino cyclohexane (**4c**) was obtained through reductive amination of (*R*,*R*)-1,2-diaminocyclohexane with benzaldehyde, followed by reduction with $NaBH_4$ at room temperature for 6 h.

Chiral phosphinoimidazolidine ligands can be readily synthesized by condensation of *N*-alkylated diamine derivatives (**4a**–**4c**) and 2-diphenylphosphino benzaldehyde in refluxing benzene.

The chiral diazide was obtained from norephedrine and the reduction of diazide to corresponding diamine was accomplished by treating the former with LAH in boiling THF for 16 h. The *N*,*N*′-dimethylated diamine derivative was prepared in the same manner as described above. A chiral phosphinoimidazolidine (**7**) was prepared by condensation of *N*,*N*′-dimethylated diamine with 2-diphenylphosphino benzaldehyde in refluxing dioxane.

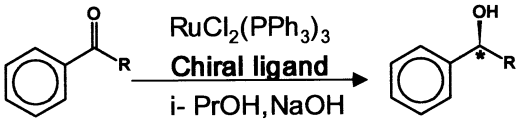
Treatment of *o*-bromobenzaldehyde with chiral dialkyl cyclohexane-1,2-diamine derivatives yielded the bromoimidazolines and these compounds were treated with *tert*-butyllithium at −78°C in THF under argon and allowed to react with diphenyl disulfide furnishing the chiral thioimidazolidine (**8**). The ligand (**9b**) was prepared in the same manner as the procedure reported in literature.[7]

To examine the catalytic efficiency of **4a**–**9b** as chiral ligands for the ruthenium-catalyzed transfer hydrogenation, the chiral Ru catalyst precursors were prepared in situ by heating a mixture of $RuCl_2(PPh_3)_3$ and ligands **4a**–**9b** in dry 2-propanol to reflux. For a given ruthenium precursor, $RuCl_2(PPh_3)_3$ is very air-sensitive and readily spoiled by moisture, so all H-transfer procedures were proceeded under N_2. Transfer hydrogenation started by addition of a substrate and a base (NaOH, KOH or sodium isopropoxide) in dry 2-propanol.

As shown in Table 1, the reactions with $RuCl_2(PPh_3)_3$, promoted with NaOH, proceeded remarkably both in terms of enantioselectivity and reactivity. A range of alkyl phenyl ketones was reduced to secondary alcohols with a high yield and a satisfactory ee (%). The enantioselectivity and the reactivity are strongly dependant on the structure of imidazolidines. New phosphinoimidazolidine ligands **5a**–**5c** and **7** are proved to be very efficient in terms of enantioselectivity for the transfer hydrogenation of alkyl aryl ketones. It appears that the imidazolidines of *N*-methylated diamine derivatives that are sterically less hindered at the nitrogen gave much better results in enantioselectivity than those of *N*-benzylated diamine derivatives. In the case of ligand **5a**, the product displayed 81% ee with acetophenone when 99% conversion was reached. The transfer hydrogenation of propiophenone catalyzed by the imidazolidine **5a**–$RuCl_2(PPh_3)_3$–NaOH system gave the corresponding alcohol in 89% ee. Enantioselectivities increased with the bulkiness of the alkyl substituent adjacent to the carbonyl group in the substrate. It is known that high-yield H-transfer of α-tetralone, which has low oxidation potential, is difficult under equilibrium conditions with 2-propanol as a hydrogen donor.[3,8] In contrast, α-tetralone was reduced to tetralol with 93% ee in the presence of Ru complex of chiral phosphino-imidazolidine (**5a**).

The phosphinoimidazolidine (**5b**) synthesized from *N*,*N*′-diethyl-1,2-diaminocyclohexane (**4b**) affords the

Table 1. Asymmetric transfer hydrogenation of ketones catalyzed by a chiral $RuCl_2(PPh_3)_3$ complex in 2-propanol



Entry	Ligand	Substrate	S/Ru/L mole ratio	Time (h)	Conv.[a] (%)	% ee[a]
1	**4a**	Acetophenone	50/1/1.5	3	>99	56
2	**4a**	Propiophenone	50/1/1.5	3	>99	67
3	**4a**	Acetophenone	500/1/1.5	6	81	44
4	**4a**	Propiophenone	500/1/1.5	6	90	53
5	**4a**	Tetralone	50/1/1.5	3	>99	71
6	**4a**	Propiophenone	50/1/1.5	3	92	30
7	**5a**	Acetophenone	50/1/1.5	3	>99	81
8	**5a**	Propiophenone	50/1/1.5	3	>99	89
9	**5a**	Tetralone	50/1/1.5	3	>99	93
10	**5b**	Propiophenone	50/1/1.5	3	>99	86
11	**5b**	Tetralone	50/1/1.5	3	>99	88
12	**5c**	Propiophenone	50/1/1.5	3	>99	75
13	**6**	Acetophenone	50/1/1.5	5	90	48
14	**6**	Propiophenone	50/1/1.5	5	85	54
15	**7**	Propiophenone	50/1/1.5	3	98	85
16	**8**	Propiophenone	50/1/1.5	3	>99	77
17	**8**	Tetralone	50/1/1.5	3	>99	74
18	**9a**	Propiophenone	50/1/1.5	3	>99	81
19	**9a**	Tetralone	50/1/1.5	3	>99	86
20	**9b**	Propiophenone	50/1/1.5	3	91	71
21	**9b**	Tetralone	50/1/1.5	3	87	73

[a] Determined by GC analysis. S: substrate, Ru: $RuCl_2(PPh)_3$, L: ligand. Reaction temperature: 82°C (bp of 2-propanol).

Table 2. Effects of base and ruthenium source on asymmetric transfer hydrogenation of propiophenone with 2-propanol

Entry	Ligand	Base	Ru(II)	Temp. (°C)	Time (h)	Conv.[a] (%)	% ee[a]
1	**4a**	KOH	A	82	3	>98	67
2	**4a**	Na–isopropoxide	A	82	1	>98	66
3	**4a**	NaOH	A	25	6	No reaction	–
4	**4a**	NaOH	A	82	3	>98	67
5	**4a**	NaOH	B	82	3	>98	53
6	**9a**	NaOH	B	82	3	>98	74
7	**9b**	NaOH	B	82	3	85	67

[a] Ruthenium source; A = $RuCl_2(PPh_3)_3$, B = $[RuCl_2(p\text{-cymene})]_2$, S/Ru/L mole ratio = 50/1/1.5.

hydrogenated product of propiophenone with 86% ee (entry 10), whereas that obtained from *N*,*N*′-dibenzyldiamine compound (**4c**) affords 75% ee (entry 12). The phosphino imidazolidine (**7**) catalyzed the reduction of propiophenone in 2-propanol to afford the corresponding alcohol in 85% ee.

The reaction rate was relatively slow and the values of ee% decreased with the prolonged reaction time, when the substrate/Ru complex ratio was high (entries 3 and 4). As can be seen in Table 1, the higher enantioselectivity was obtained when 2 mol% ruthenium source and 3 mol% ligand were employed. The high enantiomeric excess of product was maintained consistently throughout the reaction until completion in our system. The preformed complex catalyst prepared by the reaction of $RuCl_2(PPh_3)_3$ and ligands **5a**–**9b** in dry toluene showed distinctly improved reactivity. With respect to reaction rates, the rate obtained on the preformed catalyst was about 20 times faster than that obtained over the catalyst prepared in situ.

The effects of ruthenium and base source on the selectivity were investigated and the results are summarized in Table 2. The chiral Ru complexes were prepared in situ by heating a mixture of Ru(II) source and chiral dimethyl cyclohexane diamine derivatives ligand. A model reaction using propiophenone showed that the combined system consisting of $RuCl_2(PPh_3)_3$ and ligands **4a**–**9b** gave slightly higher enantioselectivities than $[RuCl_2(p\text{-cymene})]_2$. In addition, the rate of reaction was influenced by the source of base. Sodium isopropoxide played improved roles for reactivity, while the enantioselectivity was independent on the kinds of base.

In conclusion, ruthenium complexes of chiral phosphinoimidazolidines have been demonstrated to catalyze the transfer hydrogenation of alkyl aryl ketones efficiently to give secondary alcohols of high enantiomeric purity. Further synthesis of chiral imidazolidines and their application to asymmetric catalysis are underway in our laboratory.

Acknowledgements

This work was supported by grant No. 2000-1-30700-002-3 from the Basic Research Program of the Korea Science & Engineering Foundation.

References

1. (a) Spogliarich, R.; Zassinovich, G.; Kaspar, J.; Graziani, M. *J. Mol. Catal.* **1982**, *16*, 359; (b) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051; (c) de Graauw, C. F.; Peters, J. A.; van Bekkum, P. H.; Huskens, J. *Synthesis* **1994**, 1007.
2. (a) Watanabe, Y.; Ohta, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2441; (b) Brunner, H.; Leitner, W. *J. Organomet. Chem.* **1990**, *387*, 209.
3. (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562; (b) Langer, T.; Helmchen, G. *Tetrahedron Lett.* **1996**, *37*, 1381; (c) Püntener, K.; Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8165; (d) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232.
4. (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916; (b) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199; (c) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 2101.
5. (a) Chowdhury, R. L.; Backvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1991**, *1*, 1063; (b) Yang, H.; Alvarez, M.; Lugan, N.; Mathieu, R. *J. Chem. Soc., Chem. Commun.* **1995**, 1721.
6. Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417.
7. Morimoto, T.; Tachibana, K.; Achiwa, K. *Synlett* **1997**, 783.
8. Hach, V. *J. Org. Chem.* **1973**, *38*, 293.