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Asymmetric hydrogenation of ketones catalyzed by a ruthenium(II)-indan–ambox complex†‡

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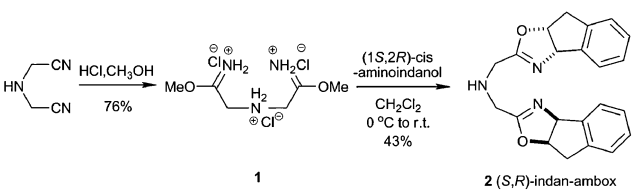
(*S*,*R*)-Indan–ambox ligand and its ruthenium(II) complex have been prepared and successfully applied to asymmetric hydrogenation of prochiral simple ketones. A wide range of unfunctionalized ketones are reduced by Ru(II)-indan–ambox catalyst with excellent enantioselectivities (up to 97% ee).

Enantioselective reduction of prochiral ketones *via* asymmetric catalysis is a powerful tool for stereo-controlled organic synthesis. It can provide a useful and convenient method to prepare chiral alcohols in the pharmaceutical, agricultural and synthetic chemistry.[1] In the past decade, asymmetric transfer hydrogenation and asymmetric hydrogenation both using transition metal complexes have been demonstrated to be the most effective strategies to achieve ketone reduction catalytically.[2] The milestone discoveries have been done by Noyori and Ikariya who developed the Ru-TsDPEN complexes as a highly effective catalyst system for asymmetric transfer hydrogenation of ketones and demonstrated the mechanistic insight of the metal–ligand bifunctional catalysis.[3] More extensive studies have been carried out based on the Ru-TsDPEN complex.[4] Recently, Grützmacher *et al.* synthesized rhodium(I) amide olefin complexes as active hydrogenation and transfer hydrogenation catalysts from tridentate ligands containing the "NH" moiety, and studied the heterolytic splitting of hydrogen by the rhodium(I) amide species.[5] The "NH effect" was also utilized in the design of Ru(II)-diphosphine–diamine complexes by Noyori and co-workers for direct hydrogenation of simple ketones and other ketonic substrates.[6] Prompted by this fundamental study, a few diphosphine ligands, such as PhanePhos,[7] P-Phos,[8] SDP ligand,[9] C_3*-TunePhos[10] were developed and proved to be effective for the ruthenium-catalyzed asymmetric hydrogenation of simple ketones.

In 1998, our group designed and synthesized the bis-(oxazolinylmethyl)amine (ambox) ligand, and successfully applied the *in situ*-generated Ru(II)-ph–ambox complex in the transfer hydrogenation of simple ketones achieving high enantioselectivities.[11] We also proved the "NH effect" in the chiral tridentate ambox ligand by control experiments. Thus, we attempted to apply the Ru complex of a similar but sterically more hindered indan–ambox ligand in direct asymmetric hydrogenation of simple ketones, especially aliphatic ketones. Because of lack of CH/π interaction, which acts as the direct origin of the enantiocontrol in Noyori and Ikariya's Ru(II)-η^6-arene-TsDPEN system, the enantioselective hydrogenation of aliphatic ketones has been a more challenging task than that of the aromatic counterparts.[12] Only Rh(I)-PennPhos[13] and Ru(II)-BINAP[6b,14] have achieved over 90% ee for the asymmetric hydrogenation of alkyl alkyl ketones. Here we report our achievements in the synthesis of a novel steric hindered tridentate ambox ligand and highly enantioselective asymmetric hydrogenation of a variety of aromatic and aliphatic ketones by using Ru(II)-indan–ambox catalyst.

The synthesis of the air-stable (*S*,*R*)-indan–ambox (bis[8,8a-dihydro-3aH-1-oxa-3aza-cyclopenta⟨α⟩inden-2-yl]methyl]amine) was achieved by condensation of the imidate salt of iminodiacetonitrile **1** with chiral *cis*-amino indanol[15] (Scheme 1). The catalyst was prepared by refluxing the indan–ambox ligand with $RuCl_2(PPh_3)_3$ in 2-propanol and subsequently removing the free PPh_3 generated from the coordination of the ligand to the metal precursor.

Our initial study began with acetophenone (**3a**) as the model substrate and a brief screening of the ruthenium complex's performance in different solvents. Under 30 atm of H_2, dichloromethane could give high enantioselectivity but only moderate conversion (Table 1, entry 3). Whereas, switching to polar protic solvents such as methanol, ethanol and 2-propanol, good ee values (>99% ee) were observed (Table 1, entries 4–6). However, only in 2-propanol was the ketone substrate fully converted to the desired product (Table 1, entry 6). Subsequently, the pressure effect on the enantioselectivity as well as the reaction rate was tested when the hydrogen pressure was reduced to 5 atm, and the results showed that the milder reaction condition gave slightly higher ee value (95% ee; Table 1, entry 9). Furthermore, the control experiment without the presence of base revealed the key role of base as the co-catalyst, as the hydrogenation reaction did not even



Scheme 1 Synthesis of (*S*,*R*)-indan–ambox.

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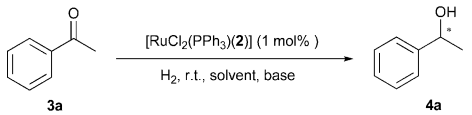
‡ Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b927028k

Table 1 Ru-catalyzed asymmetric hydrogenation of acetophenone **3a**[a]



Entry	Solvent	Base	H_2 (atm)	Conv.[b] (%)	Ee[c] (%)
1	Toluene	^{t}BuOK (2.5 eq.)	30	71	59 (*R*)
2	THF	^{t}BuOK (2.5 eq.)	30	78	67 (*R*)
3	CH_2Cl_2	^{t}BuOK (2.5 eq.)	30	42	95 (*R*)
4	MeOH	^{t}BuOK (2.5 eq.)	30	62	92 (*R*)
5	EtOH	^{t}BuOK (2.5 eq.)	30	56	95 (*R*)
6	^{i}PrOH	^{t}BuOK (2.5 eq.)	30	>99	94 (*R*)
7	^{i}PrOH	None	5	n.r.[d]	n.a.[e]
8	^{i}PrOH	^{t}BuOK (1 eq.)	5	53	82 (*R*)
9	^{i}PrOH	^{t}BuOK (2.5 eq.)	5	>99	95 (*R*)
10	^{i}PrOH	^{t}BuOK (10 eq.)	5	>99	94 (*R*)
11	^{i}PrOH	^{i}PrONa (2.5 eq.)	5	>99	94 (*R*)
12	^{i}PrOH	KOH (2.5 eq.)	5	>99	93 (*R*)

[a] The reactions were carried out with 0.4 mmol of substrate in 2 mL of solvent in the presence of 1 mol% of Ru catalyst for 12 h. [b] The conversions were determined by GC. [c] The enantiomeric excesses (configuration indicated in parentheses) were determined by chiral GC. The absolute configuration was determined by comparison of the retention times with the reported data (see ESI). [d] n.r. = no reaction. [e] n.a. = not analyzed.

slightly proceed when the base was absent (Table 1, entry 7). Also in comparison, much lower conversion was obtained when the amount of base was insufficient (only 1 equiv.; Table 1, entry 8). Moreover, further changing the inorganic base from ^{i}PrONa to ^{t}BuOK or KOH (all 2.5 equiv.; Table 1, entries 9–12), did not significantly affect the hydrogenation results.

Although the similar Ru(II)-ph–ambox system could also catalyze the transfer hydrogenation of simple ketone substrates[10] with comparable enantioselectivity results, it was proven that the reduction in this study was a direct asymmetric hydrogenation (AH) with H_2 and the asymmetric transfer hydrogenation (ATH) pathway was completely suppressed in the H_2 atmosphere. The key evidences are: (a) the same ketone substrates were quantitatively hydrogenated at a much higher reaction rate (r.t., 12 h) than by asymmetric transfer hydrogenation (ATH). The ATH catalyzed by Ru(II)-Ph–ambox usually needed at least 24 h to reach the same level of conversion at room temperature. (b) In this study, when applying up to 10 equiv. of base in the hydrogenation using the same catalyst, no significant ee erosion was observed (Table 1, entry 10). In sharp contrast, it was proven that using 1 equiv. base was critical in ATH for achieving high ee values. (c) Under 30 atm of H_2, in THF rather than 2-propanol, the hydrogenation of acetophenone still proceeded with 78% conversion although with much lower ee (Table 1, entry 2). These observations of the asymmetric hydrogenation pathway of this reaction were in accordance with the studies of the bifunctional catalysis performance of a Cp*Ru(II)-P,N-ligand system in ATH and AH by Ikariya *et al.*,[16] and also with the mechanistic scenario investigated by Noyori *et al.*[17]

Both the key role of the base as the co-catalyst in our study and the "NH effect" studied by Noyori *et al.*, based upon experimental data and detailed theoretical calculations[12] could help us to understand the mechanism of this catalysis. In a similar way that the Ru(II)-η^6-arene–TsDPEN active species is formed, the catalytically active Ru dihydride complex **7** is generated with the facilitation of two equivalents of base and H_2. Hence the hydridic Ru–H and the protic N–H moiety from the ambox ligand can work in a synergetic fashion as a bifunctional catalyst by forming a six-membered pericyclic ring transition state. After reducing the ketone substrate, the catalytic species can be regenerated dominantly by the heterocleavage of H_2 under the hydrogenation atmosphere (Fig. 1). The crucial role of the N–H moiety could also be demonstrated by substituting the NH with NCH_2Ph. Under the same optimized conditions for the acetophenone hydrogenation, the Ru complex prepared from the substituted ligand **8** only gave 66% conversion and 25% ee.[18] Our mechanistic hypothesis is in agreement with the mechanistic studies on Ru-η^6-arene–TsDPEN catalyst systems for the hydrogenation of simple ketones.[17] However, the major difference is that the origin of enantioselectivity in this study mainly comes from the steric interaction of the substrate and the rigid C_2-symmetric scaffold of the ambox ligand rather than a CH/π interaction (Fig. 2).

We also investigated the scope of ketone substrates including a series of substituted acetophenone derivatives and aliphatic ketones. With 1 mol% of Ru-indan–ambox catalyst, the ketone substrates could be reduced smoothly with good to excellent enantioselectivities under the optimized conditions (Table 2). Higher catalytic capability of the catalyst was also explored when 0.1 mol% catalyst converted 97% of acetophenone to (*R*)-phenylethanol under the same mild conditions without any ee erosion (95% ee, entry 2). As shown in Table 2, substrates containing an *ortho* substituent on the phenyl ring in the R group gave the highest enantioselectivities (up to 97% ee; entries 3–5, 13), since the *ortho*-substituted R group has larger steric bulk and thus a better steric differentiation from R^1 (Me). However, substituents capable of chelating to the metal could decrease the reactivity of the catalyst (82% conversion; entry 5). Substrates containing electron-withdrawing groups such as Cl or F group were hydrogenated successfully but with lower ee values (Table 2, entries 7, 10, 11). When R^1 is changed to larger alkyl groups such ethyl, isopropyl, cyclopropyl groups, the enantioselectivities slightly decrease and the conversions also decrease to 80%. We also tried to extend the substrate scope to more challenging substrates such as alkyl alkyl ketones (entries 18–20). Notably, the hydrogenation of cyclohexyl methyl ketone gave 95% ee, which to our best knowledge is the best ee result for this alkyl alkyl substrate (entry 18).

In conclusion, a new chiral tridentate indan–ambox ligand was synthesized and has formed a highly enantioselective ruthenium catalyst for direct hydrogenation of unfunctionalized

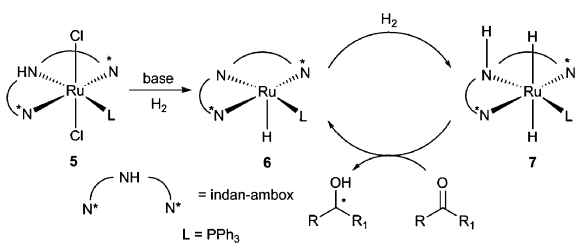


Fig. 1 Proposed mechanism of metal–ligand bifunctional catalysis.

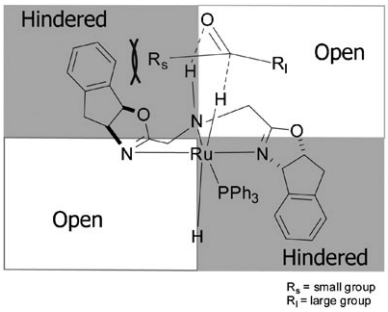
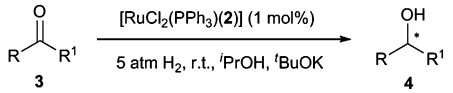


Fig. 2 Proposed transition state of the six-membered pericyclic ring.

Table 2 Asymmetric hydrogenation of ketones **3** by Ru-indan–ambox[a]



3 **4**

Entry	R	R^1	Conv.[b] (%)	Ee[c] (%)
1	C_6H_5	Me	>99	95 (*R*)
2[d]	C_6H_5	Me	97	95 (*R*)
3	*o*-MeC_6H_4	Me	>99	97 (*R*)
4	*o*-ClC_6H_4	Me	>99	92 (*R*)
5	*o*-$MeOC_6H_4$	Me	82	93 (*R*)
6	*m*-MeC_6H_4	Me	>99	95 (*R*)
7	*m*-ClC_6H_4	Me	>99	81 (*R*)
8	*m*-$MeOC_6H_4$	Me	>99	90 (*R*)
9	*p*-MeC_6H_4	Me	>99	93 (*R*)
10	*p*-ClC_6H_4	Me	>99	80 (*R*)
11	*p*-FC_6H_4	Me	>99	83 (*R*)
12	*p*-$MeOC_6H_4$	Me	>99	92 (*R*)
13	1-Naphthyl	Me	>99	94 (*R*)
14	2-Naphthyl	Me	>99	87 (*R*)
15	C_6H_5	Et	>99	93 (*R*)
16	C_6H_5	^{i}Pr	95	91 (*R*)
17	C_6H_5	Cyclopropyl	80	92 (*R*)
18	Cyclohexyl	Me	>99	95 (*R*)
19	^{t}Bu	Me	45	42 (*R*)
20	^{i}Pr	Me	>99	65 (*R*)

[a] The reactions were carried out with 0.4 mmol of substrate in 2 mL of solvent in the presence of 1 mol% of Ru catalyst at r.t. for 15 h unless otherwise specified. Substrate/base = 20. [b] The conversions were determined by GC. [c] The enantiomeric excesses (configuration indicated in parentheses) were determined by chiral GC. [d] 0.1% Catalyst loading.

aryl alkyl and aliphatic ketones. The tunable nature of this ligand leaves a great potential for broadening the ketone substrate scope, especially for pure aliphatic ketones. Further investigation of ambox ligand system and its application in other asymmetric reactions will be reported in due course.

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Notes and references

1 (*a*) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; (*b*) T. Ohkuma and R. Noyori, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Springs, Berlin, vol. 1, ch. 6, 1999, pp. 199–246; (*c*) T. Ohkuma, M. Kitamura and R. Noyori, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley, New York, 2nd edn, 2000, ch. 1, pp. 1–110; (*d*) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029.

2 (*a*) R. Noyori and T. Ohkuma, *Angew. Chem., Int. Ed.*, 2001, **40**, 40; (*b*) R. Noyori, *Adv. Synth. Catal.*, 2003, **345**, 15; (*c*) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97; (*d*) M. J. Palmer and M. Wills, *Tetrahedron: Asymmetry*, 1999, **10**, 2045; (*e*) S. Gladiali and E. Alberico, *Chem. Soc. Rev.*, 2006, **35**, 226; (*f*) T. Ikariya and A. J. Blacker, *Acc. Chem. Res.*, 2007, **40**, 1300.

3 (*a*) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 7562; (*b*) J.-X. Gao, T. Ikariya and R. Noyori, *Organometallics*, 1996, **15**, 1087; (*c*) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 2521; (*d*) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 285.

4 (*a*) X. Li, X. Wu, W. Chen, F. E. Hancock, F. King and J. Xiao, *Org. Lett.*, 2004, **6**, 3321; (*b*) X. Wu, X. Li, F. King and J. Xiao, *Angew. Chem., Int. Ed.*, 2005, **44**, 3407; (*c*) D. S. Matharu, J. E. D. Martins and M. Wills, *Chem.–Asian J.*, 2008, **3**, 1374; (*d*) F. K. Cheung, A. M. Hayes, J. Hannedouche, A. S. Y. Yim and M. Wills, *J. Org. Chem.*, 2005, **70**, 3188.

5 (*a*) P. Maire, T. Büttner, F. Breher, P. L. Floch and H. Grützmacher, *Angew. Chem., Int. Ed.*, 2005, **44**, 6318; (*b*) T. Zweifel, J.-V. Naubron, T. Büttner, T. Ott and H. Grützmacher, *Angew. Chem., Int. Ed.*, 2008, **47**, 3245.

6 (*a*) H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya and R. Noyori, *Angew. Chem., Int. Ed.*, 1998, **37**, 1703; (*b*) T. Ohkuma, M. Koizumi, K. Muñiz, G. Hilt, C. Kabuto and R. Noyori, *J. Am. Chem. Soc.*, 2002, **124**, 6508; (*c*) C. A. Sandoval, T. Ohkuma, K. Muñiz and R. Noyori, *J. Am. Chem. Soc.*, 2003, **125**, 13490.

7 M. J. Burk, W. Hems, D. Herzberg, C. Malan and A. Zanotti-Gerosa, *Org. Lett.*, 2000, **2**, 4173.

8 (*a*) J. Wu, H. Chen, W.-H. Kwok, R.-W. Guo, Z.-Y. Zhou, C.-H. Yeung and A. S. C. Chan, *J. Org. Chem.*, 2002, **67**, 7908; (*b*) J. Wu, J.-X. Ji, R.-W. Guo, C.-H. Yeung and A. S. C. Chan, *Chem.–Eur. J.*, 2003, **9**, 2963.

9 J.-H. Xie, L.-X. Wang, Y. Fu, S.-F. Zhu, B.-M. Fan, H.-F. Duan and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2003, **125**, 4404.

10 W. Li, X. Sun, L. Zhou, G. Hou, S. Yu and X. Zhang, *J. Org. Chem.*, 2009, **74**, 1397.

11 Y. Jiang, Q. Jiang and X. Zhang, *J. Am. Chem. Soc.*, 1998, **120**, 3817.

12 R. Noyori, M. Yamakawa and S. Hashiguchi, *J. Org. Chem.*, 2001, **66**, 7931.

13 Q. Jiang, Y. Jiang, D. Xiao, P. Cao and X. Zhang, *Angew. Chem., Int. Ed.*, 1998, **37**, 1100.

14 T. Ohkuma, C. S. Sandoval, R. Srinivasan, Q. Lin, Y. Wei, K. Muñiz and R. Noyori, *J. Am. Chem. Soc.*, 2005, **127**, 8288.

15 For the application of *cis*-aminoindanol in asymmetric synthesis and catalysis, see: (*a*) E. Didier, B. Loubinoux, G. M. Ramos Tombo and G. Rihs, *Tetrahedron*, 1991, **47**, 4941; (*b*) A. K. Ghosh, S. Fidanze and C. H. Senanayake, *Synthesis*, 1998, 937; (*c*) N. J. Gilmore, S. Jones and M. P. Muldowney, *Org. Lett.*, 2004, **6**, 2805; (*d*) M. Bandini, P. G. Cozzi, L. Negro and A. Umani-Ronchi, *Chem. Commun.*, 1999, 39; (*e*) I. Gallou and H. Senanayake, *Chem. Rev.*, 2006, **106**, 2843; (*f*) C. H. Senanayake, D. Krishnamurthy and I. Gallou, in *Handbook of Chiral Chemicals*, ed. D. Ager, CRC, Boca Raton, FL, 2nd edn, 2006, pp. 319–343.

16 (*a*) M. Ito and T. Ikariya, *Chem. Commun.*, 2007, 5134; (*b*) M. Ito, A. Sakaguchi, C. Kobayashi and T. Ikariya, *J. Am. Chem. Soc.*, 2007, **129**, 290; (*c*) M. Ito, A. Osaku, C. Kobayashi, A. Shiibashi and T. Ikariya, *Organometallics*, 2009, **28**, 390.

17 T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, C. Sandoval and R. Noyori, *J. Am. Chem. Soc.*, 2006, **128**, 8724.

18 Similar studies of the *N*-substituting effect on the performance of Ru-Ph–ambox in transfer hydrogenation were carried out in ref. 11.