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Generation of Self-Supported Noyori-Type Catalysts Using Achiral Bridged-BIPHEP for Heterogeneous Asymmetric Hydrogenation of Ketones

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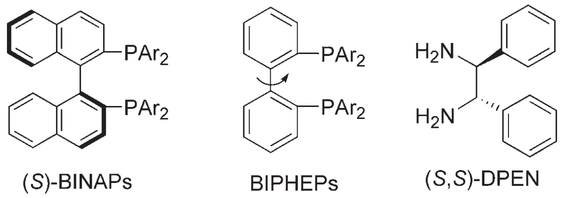
Abstract: The programmed assembly strategy has been applied to the generation of self-supported Noyori-type catalysts for asymmetric hydrogenation of ketones by spontaneous hetero-coordination of an achiral bridged diphosphine and chiral bridged diamine ligands with Ru^{II} metal ions. The immobilized catalyst demonstrates good enantioselectivity and activity in the heterogeneous catalysis of the hydrogenation of aromatic ketones and can be recovered and recycled for 4 times without obvious loss of selectivity and activity.

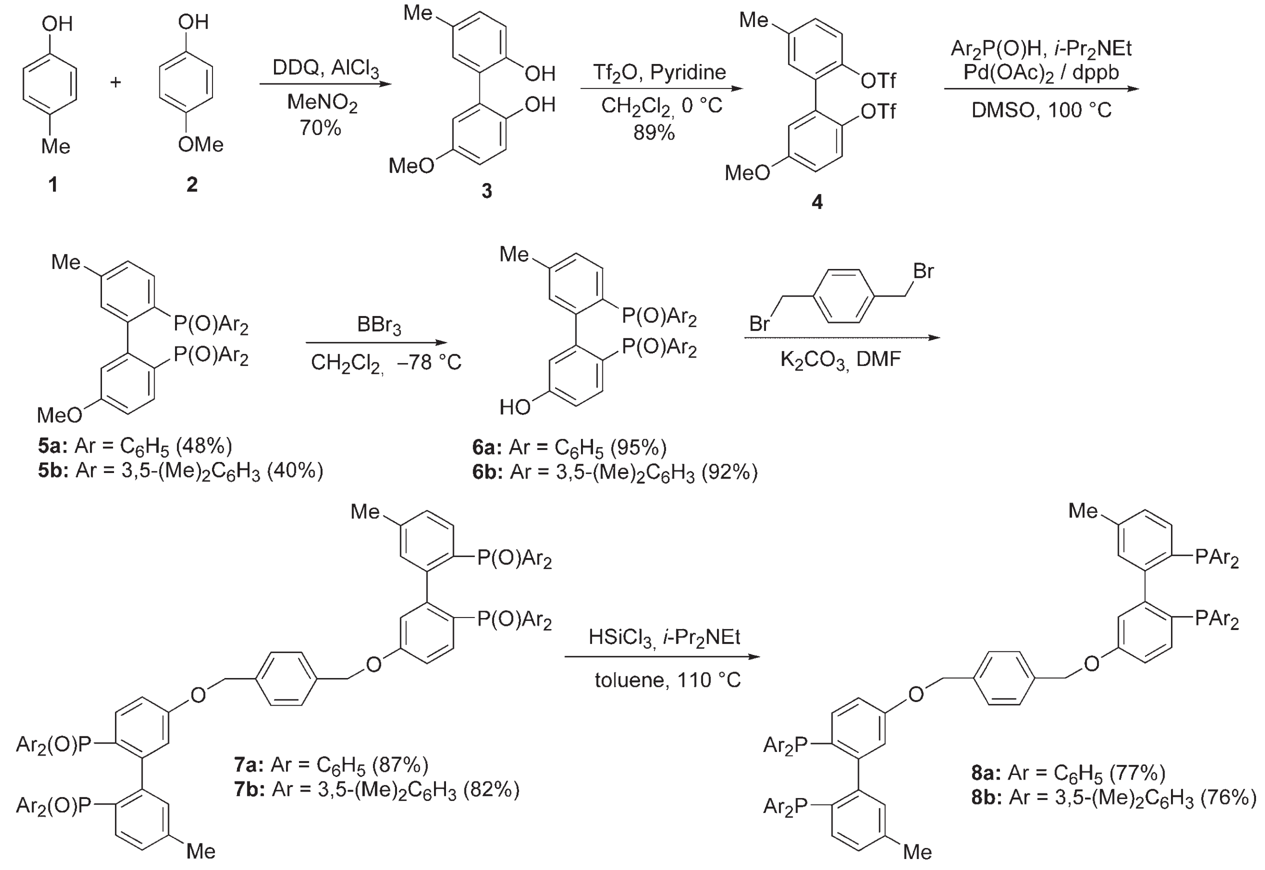
Keywords: achiral ligands; asymmetric catalysis; hydrogenation; immobilization; ketones

Heterogenization of homogeneous chiral catalysts has been an important topic in the area of asymmetric catalysis in the past decades.[1] Recently, we have demonstrated a conceptually new strategy, i.e., a "self-supporting" approach, for the immobilization of homogeneous catalysts through self-assembly of chiral multitopic ligands and metal ions without the use of any support.[2,3] On the basis of this strategy, the chiral multitopic ligand can spontaneously form a chiral environment inside the cavities of or on the surface of the solids for enantioselective control of the reaction, and the metal ions act as the catalytically active centers. For example, self-supported Noyori-type catalysts generated by spontaneous hetero-coordination of bridged BINAP [BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] and bridged 1,2-diarylethylenediamine ligands with Ru(II) metal ions exhibited excellent enantioselectivity and activity in the heterogeneous catalysis of the hydrogenation of aromatic ketones and could be recovered and recycled for at least 7 times without obvious loss of selectivity and activity.[3e] In asymmetric catalysis, the common practice for construction of chiral catalysts is the use of enantiopure ligands to coordinate with catalytically active metal ions.[4] On the other hand, the pioneering works reported by Brown, Yamamoto, Faller and Mikami demonstrated that asymmetric catalysis could also be achieved by using racemic or achiral ligands on the basis of the chiral poisoning[5] or asymmetric activation concept,[6] obviating the use of expensive enantiopure chiral ligands. Research by Mikami and Noyori showed the feasibility of a combinatorial use of pro-atropisomeric BIPHEP [BIPHEP: 2,2′-bis(diphenylphosphino)-1,1′-biphenyl] ligands and an enantiopure diamine DPEN (DPEN: 1,2-diphenylethylenediamine) (Scheme 1) with Ru(II) to generate Noyori-type catalysts. The resulting complexes demonstrated good to excellent enantioselectivities in the catalysis of hydrogenation of ketones.[6c] Inspired by Mikami and Noyori's discovery, herein we report on the generation of self-supported catalysts by assembly of achiral bridged diphosphine and chiral bridged diamine with Ru(II) metal ion on the basis of our self-supporting strategy[2,3e] for heterogeneous asymmetric catalysis of the hydrogenation of aromatic ketones.

The bridged bis-BIPHEP-type ligands **8a** and **8b** were designed to possess a conformationally flexible 1,4-phenylene-bis-methoxy linker assembled at the 4′-position of BIPHEP backbones. As shown in Scheme 2, the multitopic ligand **8a** was synthesized



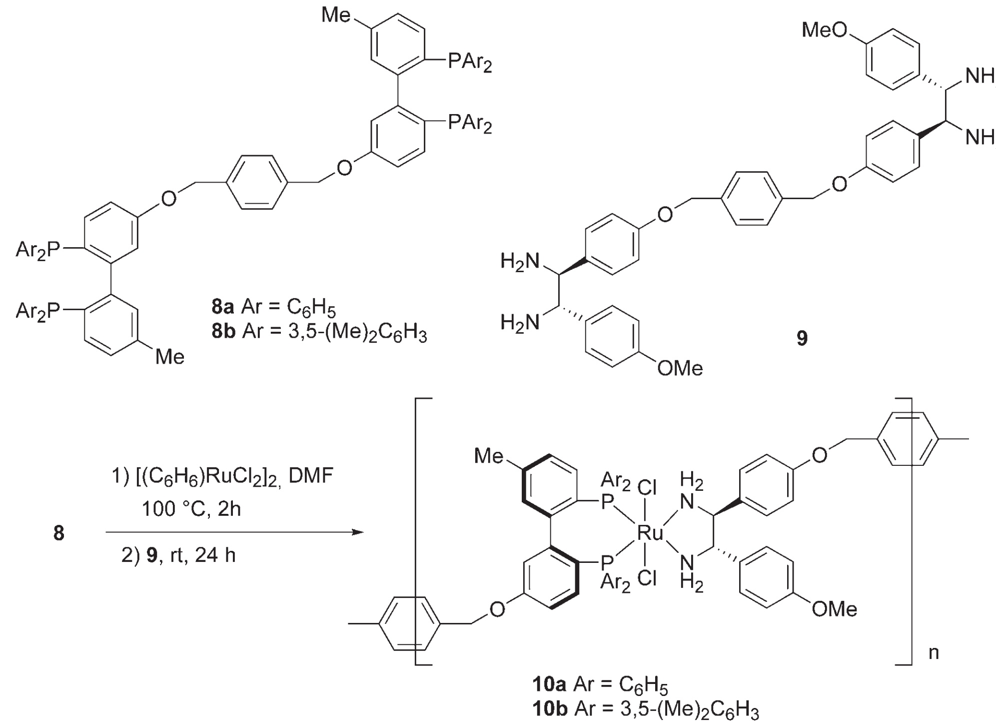
Scheme 1. BINAP, BIPHEP and DPEN.



Scheme 2. Synthesis of Bridged BIPHEP **8a–b**.

from the cheap starting materials 4-methoxylphenol (**1**) and 4-methylphenol (**2**) in six steps. Oxidative cross-coupling of **1** with **2** by DDQ (DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in the presence of $AlCl_3$ afforded 2,2′-biphenol **3**[7] which, upon treatment with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of Et_3N, yielded its ditriflate derivative **4** in good yield. Pd-catalyzed phosphinoylation of **4** with $Ph_2P(O)H$ proceeded smoothly in DMSO at 100 °C to afford the corresponding bisphosphine oxide **5a** in 48 % yield. Demethylation of **5a** with BBr_3 at −78 °C provided phenol derivative **6a** in 95 % yield. The coupling of **6a** with 1,4-xylylene dibromide in the presence of anhydrous K_2CO_3 resulted in the formation of the bridged bisphosphine oxide **7a** in 87 % yield. Subsequent reduction of **7a** with trichlorosilane afforded the target ligand **8a** in 77 % yield (Scheme 2). Ligand **8b**, a structural analogue of **8a** with bulkier di(3,5-xylyl)phosphino moieties in the BIPHEP units, was synthesized by following a similar procedure.

The self-supported catalysts **10a** and **b** were prepared by reacting the bridged bis-BIPHEP ligands **8a** and **b** with $[(C_6H_6)RuCl_2]_2$ in DMF at 80 °C, followed by treatment of the resulting reddish brown solution with 1 equivalent of bridged bis-DPEN **9**[3e] (Scheme 3). After removal of the solvent under vacuum, the resulting brown solids were washed with 2-propanol three times to afford catalysts **10a** and **b** in nearly quantitative yields. These assembled catalysts were found to be completely insoluble in 2-propanol (as shown for **10b** in Figure 1a). Elemental C/H/Cl/N/P analysis of the resulting solids were consistent with the composition of the expected structure **10**. Moreover, the solid-state ^{31}P NMR (^{31}P CP/MAS) spectral data (see Figure S2 in Supporting Information) of the free ligand 2,2′-bis[di(3,5-xylphosphino)-5-methyl-5′-methoxy]-1,1′-biphenyl (−21.5 ppm), an authentic sample of monomeric complex ($RuCl_2${2,2′-bis[di(3,5-xylphosphino)]-5-methyl-5′-methoxy-1,1′-biphenyl}[(*S,S*)-1,2-bis-(4-methoxyphenyl)ethylenediamine]) (43.6 ppm) and the assembled polymeric catalyst **10b** (43.2 ppm) clearly indicate that the selective formation of hetero-ligands complex has occurred exclusively in the assembly of two different multi-topic ligands **8b** and **9** with Ru(II) ions. The FT-IR spectra (see Figure S3 in Supporting Information) of the free ligand **9** [ν(N–H) = 3376, 3252 cm^{-1}], the monomeric complex ($RuCl_2${2,2′-bis[di(3,5-xylphosphino)]-5-methyl-5′-methoxy-1,1′-biphenyl}[(*S,S*)-1,2-bis-(4-methoxyphenyl)ethylenediamine]) [ν(N–H) = 3328, 3259 cm^{-1}], and the assembled polymeric catalyst **10b**



Scheme 3. Preparation of self-supported catalysts **10a-b**

[ν(N–H) = 3331, 3259 cm^{-1}]also support the conclusion mentioned above.[8b] SEM images showed that the solids were composed of micrometer particles (Figure 1b) and the powder X-ray diffraction (PXD) pattern (see Figure S1 in Supporting Information) indicated their non-crystalline nature.

The self-supported catalysts **10a** and **b** were then examined for the heterogeneous catalysis of the enantioselective hydrogenation of aromatic ketones. As shown in Table 1, all the hydrogenation reactions were carried out in 2-propanol at 25 °C for 24 h in the presence of *t*-BuOK under 40 atm of H_2, with complete conversions observed for all substrates. While catalyst **10a** promoted the hydrogenation of acetophenone (**11a**) to afford **12a** with only a moderate *ee* (46.2 %, entry 1), the enantioselectivity of the same reaction with catalyst **10b** was dramatically enhanced to 83.2 % (entry 2). As a comparison, the control experiment using the homogeneous counterpart of **10b**, ($RuCl_2$\{2,2′-bis-[di(3,5-xylylphosphino)]-5-methyl-5′-methoxy-1,1′-biphenyl\}[(*S,S*)-1,2-bis-(4-methoxyphenyl)ethylenediamine]), resulted in a slightly lower *ee* in **12a** (entry 3). Subsequently, the catalyst **10b** was tested for the catalytic hydrogenation of a variety of aromatic ketones **11b–f**, affording the corresponding secondary alcohols (**12b–f**) with enantioselectivities ranging from 71.9 % to 86.9 % *ee*. For the reaction of 1-acetonaphthone, the heterogenized catalyst **10b** affords the hydrogenation product **12b** with a lower *ee* than that of its homogeneous counterpart (entry 4 vs. entry 5). The reactions of three methyl-substituted acetophenones gave rise to the hydrogenation products in different *ee* values depending on the position of methyl substituent on the phenyl ring (entries 6, 7 and 8). With electron-deficient 4′-chloroacetophenone as substrate, only 71.9 % *ee* of the product was obtained (entry 9). These observations suggest that the catalytic behavior of **10b** is sensitive to the structures of both the supramolecular assembly and the substrates.

It is obvious that the enantioselectivities achieved in the hydrogenation of ketones with the present heterogeneous catalysts **10a** and **b** composed of chirally flexible biphenylphosphane liagnds **8a** and **b** are lower than those obtained with chiral BINAP-containing heterogeneous catalysts.[3e] This might be explained using Mikami's mechanistic Scheme outlined on the basis of ^{1}H NMR study of the monomeric complex of DM-BIPHEP/$RuCl_2$/(*S,S*)-DPEN. It was found that in Mikami's system a maximum of 3:1 ratio of matched (*S*)-DM-BIPHEP/$RuCl_2$/(*S,S*)-DPEN to mismatched (*R*)-DM-BIPHEP/$RuCl_2$/(*S,S*)-DPEN catalyst diastereomers could be observed in solution under the optimized conditions.[6f] While the higher enantioselectivity can be expected with the major diastereomeric complex, the minor mismatched species would deteriorate the enantioselection of the catalysis.[6e] Such a kind of incomplete asymmetric induction may also occur in the formation of the present heterogeneous catalysts containing conformationally flexible bisphosphine ligands, which accordingly lead to relatively lower enantioselectivities in the cat-

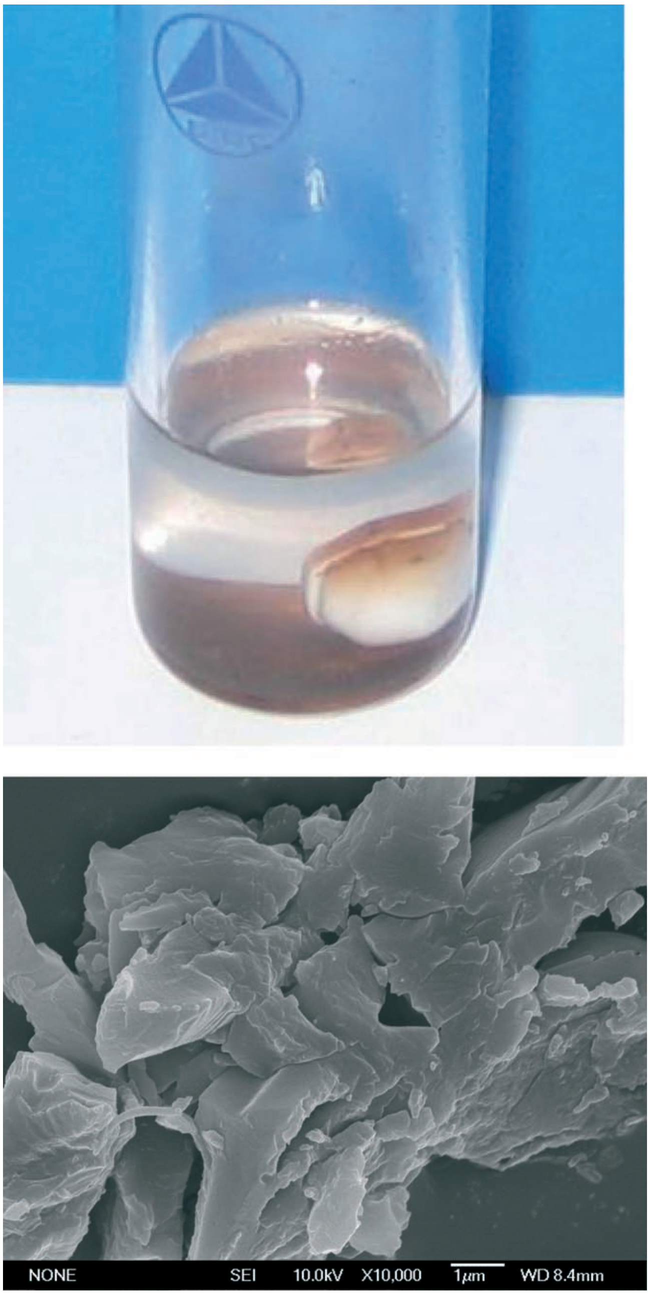
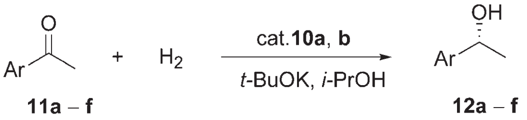


Figure 1. (a) Self-supported chiral Ru(II) catalyst **10b** (brown solids at the bottom of the reactor) in 2-propanol. (b) SEM image of the self-supported Ru catalyst **10b**. The scale bar indicates 1 μm.

alysis. This limitation may possibly be overcome by judicious choice of the achiral bisphosphine ligands with complete asymmetric induction in the catalyst formation.[9b,c]

The inductively coupled plasma atomic emission spectrometric analysis (ICP-AES) of supernatant of the catalyst indicated that no detectable Ru was leached into the organic phase (< 0.1 ppm). When the supernatant of catalyst **10b** in 2-propanol was used as catalyst, the hydrogenation of acetophenone (**11a**) did not occur at all, confirming the heterogeneous nature of the present catalytic system. On the basis of this finding, the recovery and the reusability of catalyst **10b** were then examined in the hydrogenation of **11a**. After the completion of the hydrogenation, the separation of the catalyst and product could be achieved by simple filtration under an argon atmosphere. The recovered solid catalyst was recharged with solvent, base and substrate for the next run of hydrogenation. As shown in Table 2, the self-supported catalyst could be reused four times in the hydrogenation without obvious loss of enantioselectivities and catalytic activities.

Table 1. Enantioselective hydrogenation of aromatic ketones **11a–f** under the catalysis of **10a** and **b**.[a]



Entry	Catalyst	Ar in **11**	*ee* [%] of **12**[b]
1	**10a**	Ph (**11a**)	46.2 (*R*)
2	**10b**	Ph (**11a**)	83.2 (*R*)
3	[c]	Ph (**11a**)	82.1 (*R*)
4	**10b**	1-naphthyl (**11b**)	77.7 (*R*)
5	[c]	1-naphthyl (**11b**)	85.1 (*R*)
6	**10b**	2′-Me-C_6H_4 (**11c**)	81.4 (*R*)
7	**10b**	3′-Me-C_6H_4 (**11d**)	86.9 (*R*)
8	**10b**	4′-Me-C_6H_4 (**11e**)	74.9 (*R*)
9	**10b**	4′-Cl-C_6H_4 (**11f**)	71.9 (*R*)

[a] All reactions were carried out at 25 °C under 40 atm pressure of H_2 at a substrate concentration of 1.5 M with substrate/catalyst/*t*-BuOK = 1000/1/20 for 24 h. The conversions of the substrates were determined by ^{1}H NMR to be > 99 %.

[b] Determined by chiral GC. The absolute configuration of the products was determined by the sign of optical rotation.

[c] Catalyst: ($RuCl_2${2,2′-bis[di(3,5-xylphosphino)]-5-methyl-5′-methoxy-1,1′-biphenyl}[(*S*,*S*)-1,2-bis(4-methoxyphenyl)ethylenediamine]).

Table 2. Recycling and reuse of the self-supported catalysts **10b** in enantioselective hydrogenation of **11a**.[a]

Run	1	2	3	4	5
Conv. [%]	> 99	> 99	> 99	97	82
ee [%]	83.6	82.7	83.1	79.1	73.2

[a] All of the reactions were carried out under the experimental conditions of entry 2 in Table 1.

In summary, hetero-combination of two different multi-topic ligands (i.e., the conformationally flexible achiral bridged bis-BIPHEP-type ligands and the chiral bridged bis-DPEN) with Ru metal ions was used to generate self-supported chiral Ru catalysts, which exhibited good activity and enantioselectivity for the hydrogenation of some aromatic ketones. The extension of this strategy to the development of practical catalysts for asymmetric hydrogenation using achiral bis- or monophosphine ligands[9] is underway in this laboratory.

Experimental Section

Typical Procedure for Heterogeneous Asymmetric Hydrogenation of Ketones using Self-Supported Catalyst 10b and Catalyst Recycle

To a mixture of the Ru complex **10b** (4.2 mg, 3.0 μmol based on Ru) and potassium *tert*-butoxide (6.8 mg, 60 μmol) in a test tube were added acetophenone (0.36 g, 3.0 mmol) and anhydrous 2-propanol (2 mL) under argon. The test tube was placed in a stainless steel autoclave, and the autoclave was sealed under N_2 before purging with hydrogen for 6 times. The autoclave was then charged with hydrogen (40 atm), and the reaction mixture was stirred at room temperature for 24 h. The remaining hydrogen was released slowly and the catalyst was recovered by filtration through a cannula under N_2. The solid catalyst was washed with anhydrous degassed 2-propanol and then was recharged with substrate, potassium *tert*-butoxide and 2-propanol for next run of the hydrogenation. After removal of solvent from the filtrate under the reduced pressure, the residue was submitted to ^{1}H NMR analysis to assess the conversion of the starting materials. The enantiomeric excesses of the products were determined by chiral GC.

Acknowledgements

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References

[1] For comprehensive reviews, see: a) *Chiral Catalyst Immobilization and recycling*, (Eds.: D. E. de Vos, I. F. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**; b) C. E. Song, S. Lee, *Chem. Rev.* **2002**, *102*, 3495; c) Q. Fan, Y.-M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, *102*, 3385; d) D. E. de Vos, M. Dams, B. F. Sels, P. A. Jacobs, *Chem. Rev.* **2002**, *102*, 3615; e) N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217; f) D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345; g) D. Rechavi, M. Lemaire, *Chem. Rev.* **2002**, *102,* 3467; h) L. Pu, *Chem. Rev.* **1998**, *98*, 2405; i) S. Bräse, F. Lauterwasser, R. E. Ziegert, *Adv. Synth. Catal.* **2003**, *345*, 869.

[2] For a highlight, see: a) L.-X. Dai. *Angew. Chem.* **2004**, *116*, 5846; *Angew. Chem. Int. Ed.* **2004**, *43*, 5726; for recent reviews, see: b) K. Ding, *Pure. Appl. Chem.* **2006**, *78*, 293; c) K. Ding, Z. Wang, X. Wang, Y. Liang, X. Wang, *Chem. Eur. J.* **2006**, *12*, 5188.

[3] For recent examples, see: a) S. Takizawa, H. Somei, D. Jayaprakash, H. Sasai, *Angew.Chem.* **2003**, *115*, 5889; *Angew. Chem. Int. Ed.* **2003**, *42*, 5711; b) H. Guo, X. Wang, K. Ding, *Tetrahedron Lett.* **2004**, *45*, 2009; c) X. Wang, K. Ding, *J. Am. Chem. Soc.* **2004**, *126*, 10524; d) X. Wang, X. Wang, H. Guo, Z. Wang, K. Ding, *Chem. Eur. J.* **2005**, *11*, 4078; e) Y. Liang, Q. Jing, X. Li, L. Shi, K. Ding, *J. Am. Chem. Soc.* **2005**, *127*, 7694; f) X. Wang, L. Shi, M. Li, K. Ding, *Angew. Chem.* **2005**, *117*, 6520; *Angew. Chem. Int. Ed.* **2005**, *44*, 6362; g) H. Y. Peng, C. K. Lam, T. C. W. Mak, Z. W. Cai, W. T. Ma, Y. X. Li, H. N. C. Wong, *J. Am. Chem. Soc.* **2005**, *127*, 9603; h) T. Harada, M. Nakatsugawa, *Synlett* **2006**, 321; i) S. Ishida, T. Hayano, H. Furuno, J. Inanaga, *Heterocycles*, **2005**, *66*, 645; j) L. Shi, X. Wang, C. A. Sandoval, M. Li, Q. Qi, Z. Li, K. Ding, *Angew. Chem.* **2006**, *118*, 4214; *Angew. Chem. Int. Ed.* **2006**, *45*, 4108.

[4] For comprehensive reviews on asymmetric catalysis see, for example: a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis* Wiley-Interscience, New York, **1994**; b) *Catalytic Asymmetric Synthesis* 2nd edn., (Ed.: I. Ojima), Wiley-VCH, New York, **2000**; c) *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen; A. Pfaltz; H. Yamamoto), Springer, Berlin, **1999**, Vol. I-III; d) *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH, New York, **2001**; e) G. Lin, Y. Li, A. S. C. Chan, *Principles and Applications of Asymmetric Synthesis* Wiley-VCH, Weinheim, **2002**.

[5] For recent reviews on this topic, see: a) J. W. Faller, A. R. Lavoie, J. Parr, *Chem. Rev.* **2003**, *103*, 3345; b) P. J. Walsh, A. E. Lurain, J. Balsells, *Chem. Rev.* **2003**, *103*, 3297; for examples of chiral poisoning, see: c) N. W. Alcock, J. M. Brown, P. J. Maddox, *J. Chem. Soc., Chem. Commun.* **1986**, 1532; d) K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 789; e) J. W. Faller, J. Parr, *J. Am. Chem. Soc.* **1993**, *115*, 804; f) J. W. Faller, D. W. Sams, X. Liu, *J. Am. Chem. Soc.* 1996, 118, 1217; g) K. Mikami, Y. Yusa, T. Korenaga, *Org. Lett.* **2002**, *4,* 1643.

[6] For comprehensive reviews on asymmetric activation, see: a) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki, R. Angelaud, *Angew. Chem.* **2000**, *112*, 3676; *Angew. Chem. Int. Ed.* **2000**, *39,* 3532; b) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, S. Matsukawa, *Acc. Chem. Res.* **2000**, **33**, 391; for a more recent review, see**:** c) K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369; for leading examples of asymmetric activation, see: d) K. Mikami, S. Matsukawa, *Nature* **1997**, *385*, 613; e) T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 1086; f) K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham, R. Noyori, *Angew. Chem.* **1999**, *111*, 517; *Angew. Chem. Int. Ed.* **1999**, *38*, 495; g) K. Mikami, T. Korenaga, T. Ohkuma, R. Noyori, *Angew. Chem.* **2000**, *112*, 3854; *Angew. Chem. Int. Ed.* **2000**, *39*, 3707; h) A. Ishii, V. A. Soloshonok, K. Mikami, *J. Org. Chem.* **2000**, *65*, 1597; i) K. Mikami, K. Aikawa, Y. Yusa, *Org. Lett.* **2002**, *4,* 95; j) K. Mikami, K. Aikawa, T. Korenaga, *Org. Lett.* **2001**, *3*, 243; k) K. Mikami, K. Aikawa, *Org. Lett.* **2002**, *4*, 99; l) J. Hao, M. Hatano, K. Mikami, *Org. Lett.* **2000**, *2*, 4059; m) K. Mikami, K.

Aikawa, Y. Yusa, M. Hatano, *Org. Lett.* **2002**, *4*, 91; n) K. Ding, A. Ishii, K. Mikami, *Angew. Chem.* **1999**, *111*, 519; *Angew. Chem. Int. Ed.* **1999**, *38*, 497; o) K. Mikami, R. Angelaud, K. Ding, A. Ishii, A. Tanaka, N. Sawada, K. Kudo, M. Senda, *Chem. Eur. J.* **2001**, *7*, 730; p) K. Mikami, H. Kakuno, K. Aikawa, *Angew. Chem.* **2005**, *117*, 7423; *Angew. Chem. Int. Ed.* **2005**, *44*, 7257; q) K. Mikami, S. Kataoka, K. Aikawa, *Org. Lett.* **2005**, *7*, 5777; r) T. Korenaga, K. Aikawa, M. Terada, S. Kawauchi, K. Mikami, *Adv. Synth. Catal.* **2001**, *343*, 284; s) K. Aikawa, K. Mikami, *Angew. Chem.* **2003**, *115*, 5613; *Angew. Chem. Int. Ed.* **2003**, *42*, 5455; t) K. Aikawa, K. Mikami, *Angew. Chem.* **2003**, *115*, 5616; *Angew. Chem. Int. Ed.* **2003**, *42*, 5458.

[7] G. Sartori, R. Maggi, F. Bigi, M. Grandi, *J. Org. Chem.* **1993**, *58*, 7271.

[8] For pioneering works on asymmetric hydrogenation of ketones, see: a) R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa; *J. Am. Chem. Soc.* **1987**, *109*, 5856; b) T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529.

[9] a) Q. Jing, X. Zhang, J. Sun, K. Ding, *Adv. Synth. Catal.* **2005**, *347*, 1193; b) Q. Jing, C. A. Sandoval, Z. Wang, K. Ding, *Eur. J. Org. Chem.* **2006**, 10.1002/ejoc.200600299; c) K. Mikami, K. Wakabayashi, K. Aikawa, *Org. Lett.* **2006**, *8*, 1517.