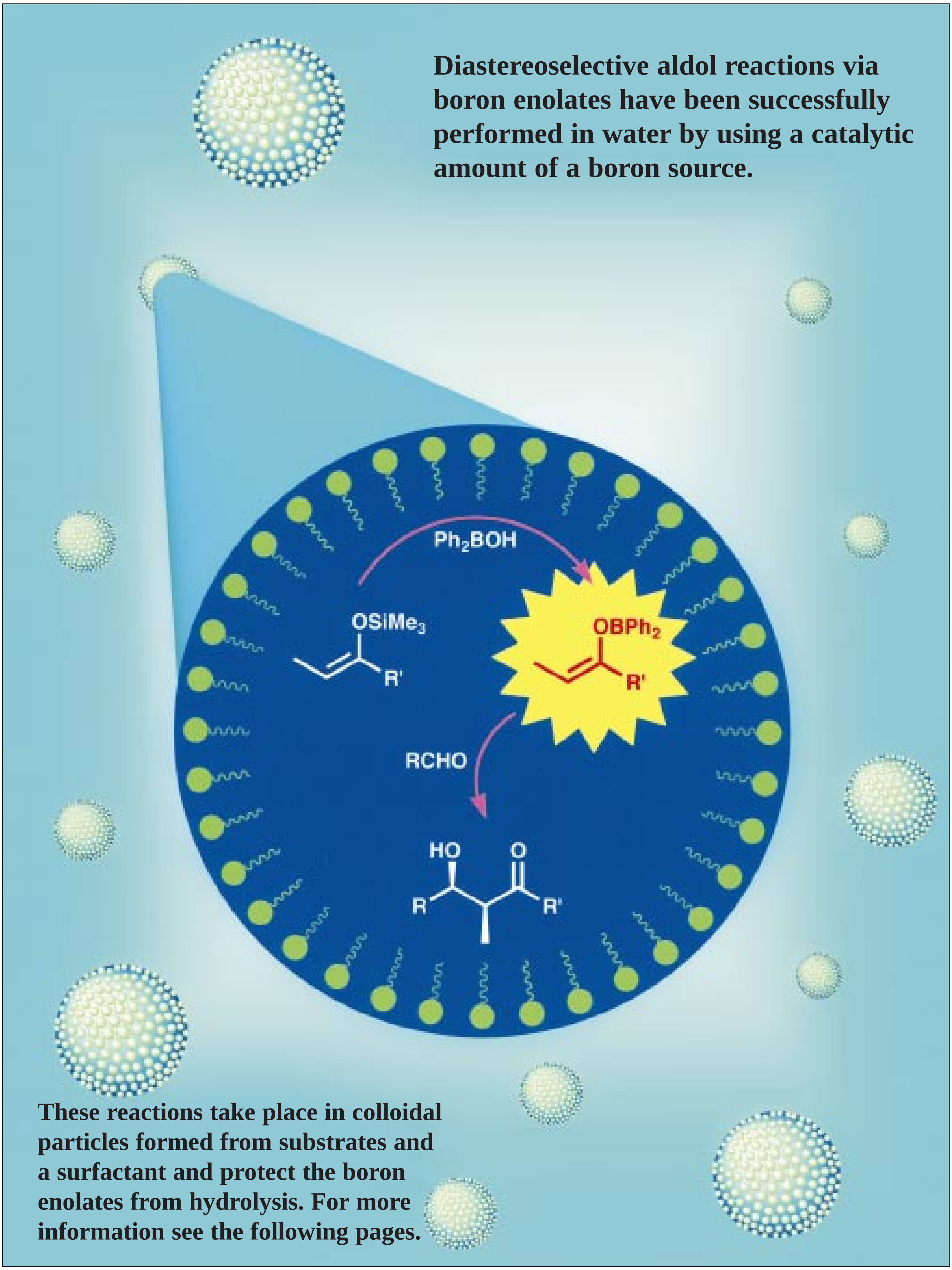


Diastereoselective aldol reactions via boron enolates have been successfully performed in water by using a catalytic amount of a boron source.

These reactions take place in colloidal particles formed from substrates and a surfactant and protect the boron enolates from hydrolysis. For more information see the following pages.

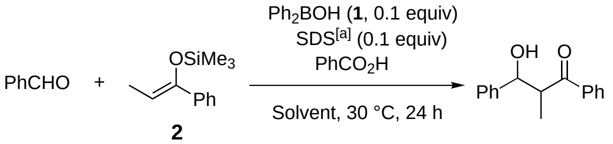
Catalytic Use of a Boron Source for Boron Enolate Mediated Stereoselective Aldol Reactions in Water[**]

Yuichiro Mori, Kei Manabe, and Shū Kobayashi*

Boron enolate chemistry has been well-established and several useful reactions using boron enolates have been developed. However, stoichiometric amounts of boron sources such as dialkylboron triflates have been required in all cases so far reported. Herein, we disclose the first example of the catalytic use of a boron source in boron enolate mediated stereoselective aldol reactions.[1] Interestingly, the reactions proceed in water without using any organic solvents.

Recently, we reported the use of Lewis acid surfactant combined catalysts (LASCs) in organic synthesis in water.[2] LASCs create colloidal particles of approximately 1 μm diameter with organic materials in water, and useful synthetic reactions such as aldol, allylation, Mannich, and Michael reactions were shown to proceed smoothly in the presence of a LASC. In the course of our investigations to improve the reaction system, we tested various compounds which might act as better catalysts in water. We chose the Mukaiyama aldol reaction as a model reaction. After screening various catalysts, we found diphenylborinic acid (Ph_2BOH, **1**),[3, 4] which is stable in water, was an effective catalyst in the presence of sodium dodecyl sulfate (SDS) as a surfactant.[5] We then examined a reaction of benzaldehyde with the silyl enolate **2** in water (Table 1). While the reaction proceeded very slowly in the presence of 0.1 equivalents of **1** and SDS (Table 1, entry 1), a dramatic improvement of the yield was observed when benzoic acid was added to this system (entry 2). To our surprise, the diastereoselectivity (*syn*/*anti*) of the product was much higher than that of the previously reported LASC system.[6] In the presence of SDS only (entry 3), or in the presence of benzoic acid and SDS (without **1**, entry 4), the desired adducts were obtained in low yields with low diastereoselectivities. In the presence of **1** and benzoic acid (without SDS), high *syn* selectivity was obtained, albeit the yield was low (entry 5). The best yield and selectivity were obtained when **1** (0.1 equiv), SDS (0.1 equiv), and benzoic acid (0.01 equiv) were used at 0 °C (entry 6). Note that the use of water as a solvent is essential in this reaction. The reaction proceeded sluggishly in organic solvents such as dichloromethane and diethyl ether (entries 7, 8). Much lower yield than that in water was obtained under neat conditions (entry 9).

Table 1. Mukaiyama aldol reaction using **1** in water.



Entry	Solvent	$PhCO_2H$ [equiv]	Yield [%]	*syn*/*anti*
1	H_2O	–	trace	–
2	H_2O	0.01	90	92/8
3[b]	H_2O	–	2	53/47
4[b]	H_2O	0.01	27	58/42
5[c]	H_2O	0.01	4	91/9
6[d]	H_2O	0.01	93	94/6
7	Et_2O	0.01	trace	–
8	CH_2Cl_2	0.01	trace	–
9	–	0.01	24	90/10

[a] Sodium dodecyl sulfate. [b] Without **1**. [c] Without SDS. [d] 0 °C.

Several examples of the aldol reactions are shown in Table 2. In all cases, the reactions proceeded smoothly in the presence of **1** (0.1 equiv), SDS (0.1 equiv), and benzoic acid (0.01 equiv) to afford the corresponding adducts in good yields. When (*Z*)-3-trimethylsiloxy-2-pentene was used, the highest diastereoselectivity (*syn*/*anti* = 96/4 and 97/3) was obtained (entries 1 and 8). In all cases, high *syn* selectivity was observed when *Z*-enolates were used (*syn*/*anti* = 90/10 – 97/3). Not only aromatic aldehydes but also α,β-unsaturated and aliphatic aldehydes gave high *syn* selectivity. Although lower diastereoselectivity was observed when *E*-enolates were used (entries 2 and 10), reverse diastereoselectivity was observed when both stereoisomers of the silyl enolate derived from *tert*-butyl thiopropionate were used (entries 4 and 5).

The high *syn* selectivity observed in these reactions is remarkable because lower diastereoselectivities are obtained in the Lewis acid catalyzed Mukaiyama aldol reactions in water. For the metal-catalyzed aldol reactions of aldehydes with silyl enolates only two reaction mechanisms are known. One is the Lewis acid mechanism,[7] and the other involves a metal enolate as a reaction intermediate generated by silicon – metal exchange.[8] In the present reaction system, the latter mechanism can explain the results more clearly. That the diastereoselection was reversed by using the stereoisomers of the silyl enolate derived from *tert*-butyl thioester (Table 2, entries 4 and 5) supports the hypothesis because this type of reversal was also observed in the traditional boron enolate mechanism which involves a chairlike six-membered transition state. Furthermore, the trend that *anti* selectivity is poorer than *syn* selectivity in our reactions is also found in the traditional boron enolate mediated aldol reactions.[9] Thus, we proposed a mechanism which involved a boron enolate as a reaction intermediate (the boron enolate mechanism, Scheme 1). The mechanism is based on the hypothesis that **1** can react with a silyl enolate to form the corresponding boron enolate under the reaction conditions.[10] When a *Z*-enolate was used, an aldehyde and the boron enolate would react via a chairlike six-membered transition state to give the *syn* aldol product. The B–O bond of the initial aldol product **5** is presumed to be easily cleaved by hydrolysis, and **1** can be

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[**] This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. Y. M. thanks the JSPS fellowship for Japanese Junior Scientists.

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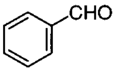
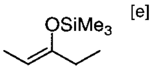
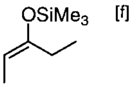
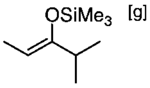
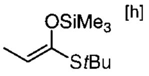
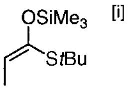
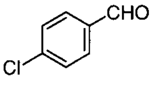
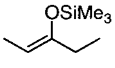
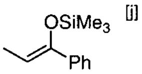
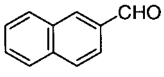
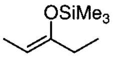
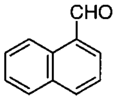
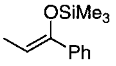
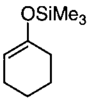
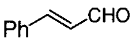
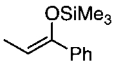
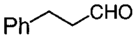
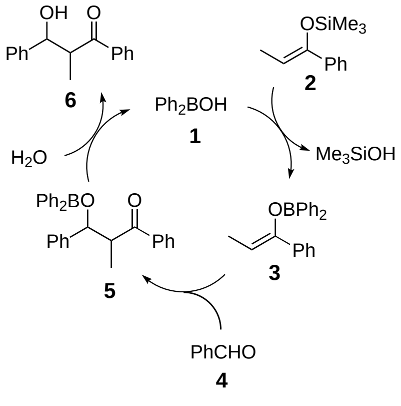
Table 2. Mukaiyama aldol reactions using **1** in water.[a]

Entry	Substrate		Yield [%]	*syn*/*anti*
1[b]		 [e]	60	96/4
2[b]		 [f]	72	53/47
3[b]		 [g]	72	95/5
4[b,c]		 [h]	62	96/4
5[b,c]		 [i]	84[k]	39/61
6[b]			51	95/5
7		 [j]	92	90/10
8[b]			74	97/3
9			80	92/8
10			79	47/53
11[d]			76	91/9
12			61	92/8

[a] Conditions: silyl enolate (1.5 equiv), **1** (0.1 equiv), $PhCO_2H$ (0.01 equiv), SDS (0.1 equiv), H_2O (aldehyde: 167 mM), 30 °C, 4–24 h. [b] Silyl enolate (3.0 equiv). [c] 0 °C. [d] $PhCO_2H$ (0.1 equiv). [e] $Z/E = >99/<1$. [f] $Z/E = 19/81$. [g] $Z/E = 96/4$. [h] $Z/E = 2/98$. [i] $Z/E = 97/3$. [j] $Z/E = >99/<1$. [k] 72 h.



Scheme 1. Proposed boron enolate mechanism.

regenerated. In this mechanism, benzoic acid[11] may accelerate the Si–B exchange step, which is thought to be a rate-determining step.

To obtain information about the mechanism, kinetic studies were undertaken. The rate of disappearance of silyl enolate **2** was examined (Figure 1a). It was found that the rate was independent of the reactivity of the aldehydes. The reactivity of the aldehydes (benzaldehyde (more reactive), cyclohexanecarboxaldehyde (less reactive, 34% yield under the conditions of Figure 1)) has no significant effect on the disappearance rate of **2**. Furthermore, the amount of **2** also decreased at the same rate when no aldehyde was added to the reaction system. In addition, the rate was found to be dependent only on the amount of **2**, following first-order kinetics ($k = 3.0 \times 10^{-4}\ s^{-1}$, Figure 1b). These facts support the boron enolate mechanism rather than the Lewis acid mechanism, because the reactivity and the absence of the aldehyde are presumed to affect the rate of disappearance of the silyl enolate in the Lewis acid mechanism. In our mechanism, the aldol-addition step should be very fast because of the instability of the boron enolate in water. The results of the kinetic studies suggest the Si–B exchange step, not the aldol-addition step, is the rate-determining step because the rate depends only on the amount of the remaining silyl enolate.[12] The formed boron enolate would react rapidly with an aldehyde or be hydrolyzed to form the corresponding ketone. The cleavage of the B–O bond of the initial aldol product **5** should be fast because of the acidity of the reaction media (pH ≈ 4). Thus, the boron enolate mechanism is much more likely than the Lewis acid mechanism. As far as we know, this is the first example of the formation of boron enolate using a catalytic amount of a boron source.

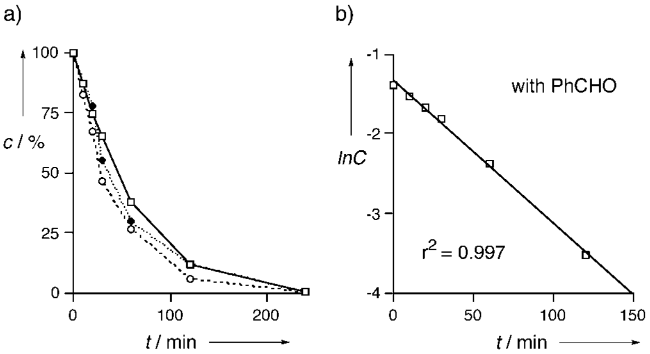


Figure 1. Changes of the amount of **2** during the reactions using **1** as a catalyst in water with □: benzaldehyde, ◆: cyclohexanecarboxaldehyde, ○: no aldehyde, *C*: Concentration of **2** in water ($mol\,L^{-1}$). Conditions: **2** (1.5 equiv), **1** (0.1 equiv), $PhCO_2H$ (0.1 equiv), SDS (0.1 equiv), H_2O (aldehyde: 167 mM), 30 °C. The amount of **2** was determined by HPLC (acetophenone was used as an internal standard). See text for further details

In summary, we have found that highly diastereoselective aldol reactions via boron enolates have been successfully performed in water using a catalytic amount of a boron source. The reactions proceed smoothly in water at ambient temperature while traditional boron aldol reactions need lower temperature and strictly anhydrous conditions. Water is used as the sole solvent, and thus should lead to environmentally friendly systems. Further investigations to improve the yield and selectivity and to clarify the detailed mechanism of these reactions are now in progress.

Experimental Section

A typical experimental procedure: aldehyde (0.25 mmol) and silyl enolate (0.375 mmol) were added successively at 30 °C to a stirred white suspension of diphenylborinic acid (0.025 mmol), benzoic acid (0.0025 mmol), and SDS (0.025 mmol) in water (1.5 mL). After 24 h, saturated aq. $NaHCO_3$ (5 mL) and brine (5 mL) were added, and the mixture was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. The aldol product was purified by preparative thin layer chromatography (TLC; SiO_2, ethyl acetate/hexane = 1/3).

Received: March 27, 2001 [Z16861]

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[1] For boron-mediated aldol reactions, see: a) B.-M. Kim, S. F. Williams, S. Masamune in *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 239–268; b) W. Fenzl, R. Köster, *Liebigs Ann. Chem.* **1975**, 1322–1338; c) T. Inoue, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174–178; d) D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111; e) S. Masamune, S. Mori, D. Van Horn, D. W. Brooks, *Tetrahedron Lett.* **1979**, *19*, 1665–1668.

[2] For LASC-mediated carbon–carbon bond forming reactions in water, see: a) S. Kobayashi, T. Wakabayashi, *Tetrahedron Lett.* **1998**, *39*, 5389–5392; b) S. Otto, J. B. F. N. Engberts, J. C. T. Kwak, *J. Am. Chem. Soc.* **1998**, *120*, 9517–9525; c) K. Manabe, S. Kobayashi, *Synlett* **1999**, 547–548; d) K. Manabe, S. Kobayashi, *Tetrahedron Lett.* **1999**, *40*, 3773–3776; e) S. Kobayashi, Y. Mori, S. Nagayama, K. Manabe, *Green Chem.* **1999**, 175–177; f) K. Manabe, Y. Mori, S. Nagayama, K. Odashima, S. Kobayashi, *Inorg. Chim. Acta* **1999**, *296*, 158–163; g) K. Manabe, Y. Mori, S. Kobayashi, *Tetrahedron* **1999**, *55*, 11203–11208; h) Y. Mori, K. Kakumoto, K. Manabe, S. Kobayashi, *Tetrahedron Lett.* **2000**, *41*, 3107–3111; i) K. Manabe, Y. Mori, T. Wakabayashi, S. Nagayama, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 7202–7207.

[3] Ph_2BOH can be easily prepared from its ethanolamine ester, see: G. E. Coates, J. G. Livingstone, *J. Chem. Soc.* **1961**, 4909–4911.

[4] Ph_2BOH was used for the generation of a boron enolate from ethoxyacetylene, see: M. Murakami, T. Mukaiyama, *Chem. Lett.* **1982**, 241–244.

[5] Anionic surfactants are effective, see the Supporting Information.

[6] When a Lewis acid (for example, $Sc(O_3SOC_{12}H_{25})_3$) was used in water, the diastereoselectivity was *syn*/*anti* = 49/51 (substrates: aldehyde **4** and silyl enolate **2**), see: refs. [2a,i].

[7] Diarylborinic acids with electron-withdrawing substituents at their aryl groups are known to function as Lewis acids for Mukaiyama aldol reactions in dichloromethane, see: K. Ishihara, H. Kurihara, H. Yamamoto, *Synlett* **1997**, 597–599.

[8] The examples of catalytic use of metals for generating metal enolates from silyl enolates in stereoselective aldol reactions have been reported, see: a) G. A. Slough, R. G. Bergman, C. H. Heathcock, *J. Am. Chem. Soc.* **1989**, *111*, 938–949; b) M. Sodeoka, K. Ohrai, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 2648–2649; c) J. Krüger, E. M. Carreira, *J. Am. Chem. Soc.* **1998**, *120*, 837–838; d) O. Fujimura, *J. Am. Chem. Soc.* **1998**, *120*, 10032–10039.

[9] Y. Li, M. N. Paddon-Row, K. N. Houk, *J. Org. Chem.* **1990**, *55*, 481–493.

[10] The examples of the generation of boron enolates from silyl enolates using stoichiometric amounts of boron sources in organic solvents have been reported, see: a) I. Kuwajima, M. Kato, A. Mori, *Tetrahedron Lett.* **1980**, *21*, 4291–4294; b) M. Wada, *Chem. Lett.* **1981**, 153–156.

[11] Various Brønsted acids are effective, see the Supporting Information.

[12] The reaction also showed first-order dependence with respect to the catalyst combination (**1**-SDS-$PhCO_2H$ (1:1:0.1)), see the Supporting Information.

CH/π Attraction: The Origin of Enantioselectivity in Transfer Hydrogenation of Aromatic Carbonyl Compounds Catalyzed by Chiral η^6-Arene-Ruthenium(II) Complexes[**]

Masashi Yamakawa, Issaku Yamada, and Ryoji Noyori[*]

In asymmetric catalysis using chiral transition metal complexes, metal ligands generally affect the stability of stereodetermining transition states (TSs) by exerting electronic influences on metallic centers and also by through-space interactions with the assembled substrates. In our enantioselective asymmetric transfer hydrogenation of aryl alkyl ketones[1–3] or [1-^{2}H]benzaldehydes[4] by using 2-propanol or formic acid, we intuitively selected $Ru^{II}(\eta^6\text{-arene})$ catalysts that possess a chiral 2-amino alcohol or related auxiliary. A theoretical study has now revealed that the enantioselectivity originates not only from the chiral geometry of the five-membered chelate ring but also from the CH/π attractive interaction[5] between the η^6-arene ligand and the carbonyl aryl substituent, instead of conventional nonbonded repulsion. This TS stabilization is reminiscent of the origin of *endo* selectivity in the Diels–Alder reaction that is based on an attractive secondary interaction between nonreacting sites.[6]

A combined system of $[RuCl\{(R,R)\text{-}YCH(C_6H_5)CH(C_6H_5)NH_2\}(\eta^6\text{-arene})]$ (Y = O or NTs) and an alkaline base in 2-propanol catalyzes transfer hydrogenation of aromatic ketones or aldehydes to give the corresponding *R* alcohols with fair to excellent enantiomeric purity.[1–4] The real reducing complex is $[RuH\{(R,R)\text{-}YCH(C_6H_5)CH(C_6H_5)NH_2\}(\eta^6\text{-arene})]$.[2c, 7, 8] The general stereochemical outcome[1–4] prompted us to study the TS structures by hybrid density functional theory-based (DFT) calculations.[9, 10]

Transfer hydrogenation of carbonyl substrates with **1** occurs by a novel metal–ligand bifunctional catalysis[1, 2c, 7, 8] (Scheme 1). The hydridic Ru–H and protic $N\text{–}H_{ax}$ in the 18e complex **1** are transferred simultaneously to the C=O bond in **2** to form the 16e complex **3** and alcohol **4**. The process is reversible. The chiral complex (*R*,*R*)-**1** reacts with **2** preferentially via "proximal" TS *Si*-**5** instead of "distal" *Re*-**5**, giving *R*-enriched **4**. The calculation for the reaction of (*R*,*R*)-**1** (η^6-arene = C_6H_6) and benzaldehyde at the RMP2/BS-II//B3LYP/LANL2DZ level[10] indicated that 1) the hydrogen

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[**] This work was financially supported by a Grant-in-Aid for Scientific Research (No. 07CE2004) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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