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Asymmetric Synthesis | *Hot Paper* |

Dynamic Kinetic Resolution Approach for the Asymmetric Synthesis of Tetrahydrobenzodiazepines Using Transfer Hydrogenation by Chiral Phosphoric Acid

Kosaku Horiguchi,[a] Eri Yamamoto,[b] Kodai Saito,[a, c] Masahiro Yamanaka,[b] and Takahiko Akiyama*[a]

Abstract: Asymmetric synthesis of tetrahydrobenzodiazepines was achieved by transfer hydrogenation of dihydrobenzodiazepines with benzothiazoline having a hydrogen-bonding donor substituent by means of a newly synthesized chiral phosphoric acid. This method was applicable to various racemic dihydrobenzodiazepines to give the corresponding products in good yields with excellent diastereoselectivities and enantioselectivities taking advantage of the dynamic kinetic resolution. Furthermore, the effect of bulky substituent at 3,3′-position on the catalyst and hydrogen-bonding donor substituent on benzothiazoline was fully elucidated by the theoretical study.

Enantiomerically pure compounds are key components of pharmaceuticals and agrochemicals. Thus, the development of new methods for the asymmetric synthesis of chiral skeletons has captured the attention of synthetic organic chemists. Although kinetic resolution is one of the representative methods for the preparation of chiral compounds,[1] this method gives a maximum chemical yield of 50% for a particular enantiomer. On the other hand, dynamic kinetic resolution (DKR) has proven to be a more versatile strategy in terms of chemical yield, theoretically allowing the stereodivergent transformation of both enantiomers of a racemic substrate into a single enantiomer of a target molecule up to 100%.[2] Although DKR of alcohols could be achieved by either chemical[3] or chemoenzymatic approaches,[4] catalytic non-enzymatic methodologies for the DKR of amines are much less developed than those of alcohols. The development of DKR of amines is, thus, in high demand.[5]

[a] *K. Horiguchi, Dr. K. Saito, Prof. Dr. T. Akiyama*
Department of Chemistry, Gakushuin University
1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588 (Japan)
E-mail: takahiko.akiyama@gakushuin.ac.jp

[b] *E. Yamamoto, Prof. Dr. M. Yamanaka*
Department of Chemistry, Rikkyo University
3-34-1 Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501 (Japan)

[c] *Dr. K. Saito*
Present address: Department of Chemistry, Keio University
Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522 (Japan)

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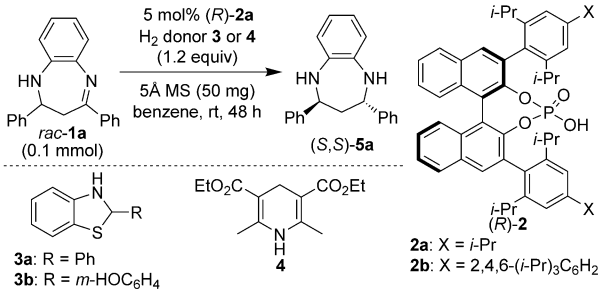
Nitrogen-containing cyclic chiral molecules with multiple stereogenic centers have attracted much attention in recent years. Benzodiazepine derivatives, in particular, possess unique seven-membered cyclic chiral centers, and the biological activities of these compounds have shown several promising functions.[6] Although the asymmetric synthesis of 1,5-benzodiazepines[7] has been investigated by organocatalyzed transfer hydrogenation[7a] and transition-metal-catalyzed hydrogenation,[7b] highly stereoselective synthesis of these structures is extremely important, and the mechanism, in particular the theoretical study, has not yet been fully investigated.

The organocatalyzed enantioselective transfer hydrogenation (ATH) of carbon–nitrogen double bonds has been recognized as one of the most reliable approaches to give chiral amines.[8] We have recently developed chiral phosphoric-acid-catalyzed ATH of a range of ketimine derivatives using benzothiazoline as a hydrogen donor.[9,10] Tuning the 2-substituent of benzothiazoline improved both reactivity and enantioselectivity. Based on these properties, we envisioned that the choice of the 2-substituent of benzothiazoline might serve as a new strategy to control the enantioselectivity of ATH of other complex molecules, thus extending the application of this combination of chiral phosphoric acid with benzothiazoline. Herein, we report the highly stereoselective ATH of dihydrobenzodiazepines involving the DKR process, in which a newly synthesized chiral phosphoric acid was employed in conjunction with benzothiazoline bearing a hydrogen-bonding donor substituent. The necessity of the precise hydrogen-bonding interaction in the transition state of this ATH was elucidated by theoretical studies.

At the outset, we studied ATH of **1a** with (*R*)-TRIP[11] **2a** in the presence of **3a** as a model reaction (Table 1, entry 1, see the Supporting Information for details). The reaction proceeded slowly to give (*S*,*S*)-**5a**[12] in 8% yield with a 2.4:1 diastereomeric ratio and 88% *ee*. Surprisingly, use of benzothiazoline **3b** bearing a 3-hydroxyphenyl moiety dramatically improved both yield and diastereomeric ratio to 90% and 7.6:1, respectively, with an increase of *ee* to 96% (entry 2). This result showed that DKR is operative in the ATH, including racemization of the original stereogenic center at the 2-position of the substrate.[13,14] The use of Hantzsch ester **4** in place of benzothiazoline exhibited an efficient and enantioselective hydrogenation, but with low diastereoselectivity (entry 3). Remarkable improvement of diastereoselectivity was observed when (*R*)-**2b** bearing a more bulky 3,3′-substituent was employed (*trans*/*cis*

Table 1. Examination of reaction conditions.



Entry	3 or 4	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	**3a**	8	2.4/1	88
2	**3b**	90	7.6/1	90
3	**4**	quant.	1.1/1	>99
4[d]	**3b**	76	>99/1	>99
5[d]	**4**	quant.	1.1/1	>99
6[d,e]	**3b**	94[f]	>99/1	>99

[a] Yields were determined by NMR spectroscopy. [b] d.r. (*trans*/*cis*) values were determined by NMR analysis of crude products. [c] Determined by chiral HPLC analysis. [d] (*R*)-**2b** was used. [e] **3b** (1.4 equiv) and 5 Å MS (200 mg) were used. [f] Isolated yield.

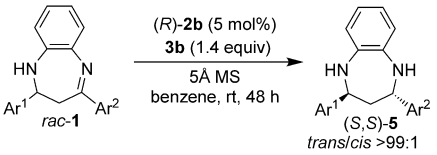
>99:1, entry 4). Diastereoselectivity was not affected by the combined use of (*R*)-**2b** with Hantzsch ester **4** (entry 5). The use of a larger amount of 5 Å MS and **3b** led to significant increase in yield (94%, entry 6).

We explored the scope of the transfer hydrogenation of 2,4-diaryl-dihydrobenzodiazepine derivatives **1** using **3b** and (*R*)-**2b** (Table 2). A range of C_2-symmetric 2,4-diaryl-tetrahydrobenzodiazepines were obtained in good yields with excellent enantioselectivities (entries 1–9). Next, we explored the reactions by using substrates bearing different aryl groups at the 2,4-positions, which had not been employed by the previous asymmetric hydrogenation approaches.[7b] Substrates **1j–l** containing trifluoromethyl and methoxy groups at 2- or 4-positions were all tolerated to give **5j** and **l** in high yields with excellent stereoselectivities. The introduction of a functional group on the fused phenylene ring also led to excellent stereoselective transfer hydrogenation, giving **5m** and **n** in good yields with excellent stereoselectivities. *N*-Methylated **1o** provided access to **5o**. Use of **3b**-D for this reaction resulted in the formation of **5a**-D in 80% yield with 99% *ee*.[15,16]

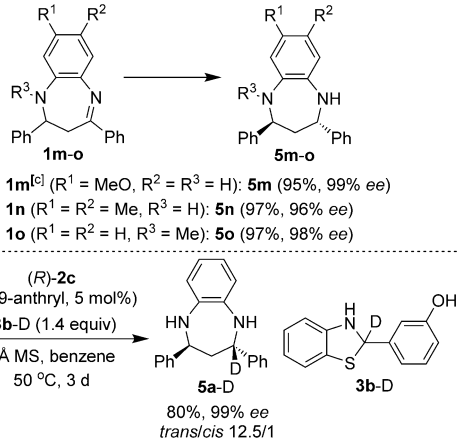
As an extension of this work, we investigated the ATH of benzodiazepine **6a**.[7b] When **6a** was subjected to the same reaction conditions using 2.4 equivalents of **3b**, we isolated **5a** in 85% yield with slightly higher stereoselectivities (*trans*/*cis* >99:1, >99% *ee*). Interestingly, when this reaction was performed for a shorter reaction time, **1a** was recovered in low yield in racemic form. This result confirmed that the faster second hydrogenation step is the stereochemically determining step. The scope of the reaction is summarized in Scheme 1. Unfortunately, alkyl-substituted substrate **6q** gave no conversion.

To elucidate mechanism of the racemization process in the present DKR, we tried to trap the reaction intermediate. Treat-

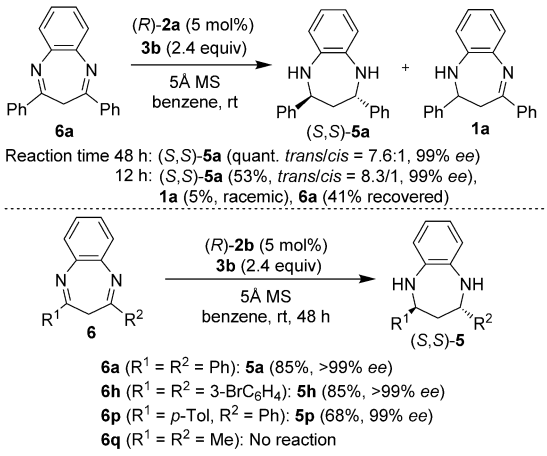
Table 2. Substrate scope.



Entry	1	Ar[1]	Ar[2]	5	Yield [%][a]	*ee* [%][b]
1	**1a**	Ph	Ph	**5a**	94	>99
2	**1b**	4-FC_6H_4	4-FC_6H_4	**5b**	67	>99
3	**1c**	4-ClC_6H_4	4-ClC_6H_4	**5c**	91	99
4	**1d**	4-BrC_6H_4	4-BrC_6H_4	**5d**	90	>99
5	**1e**	*p*-Tol	*p*-tol	**5e**	96	99
6	**1f**	*m*-tol	*m*-tol	**5f**	89	99
7	**1g**	3-ClC_6H_4	3-ClC_6H_4	**5g**	71	>99
8	**1h**	3-BrC_6H_4	3-BrC_6H_4	**5h**	75	>99
9	**1i**	2-thienyl	2-thienyl	**5i**	74	99
10	**1j**	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	**5j**	quant.	99
11	**1k**	Ph	4-$CF_3C_6H_4$	**5j**	quant.	>99
12	**1l**	PMP	Ph	**5l**	quant.	>99

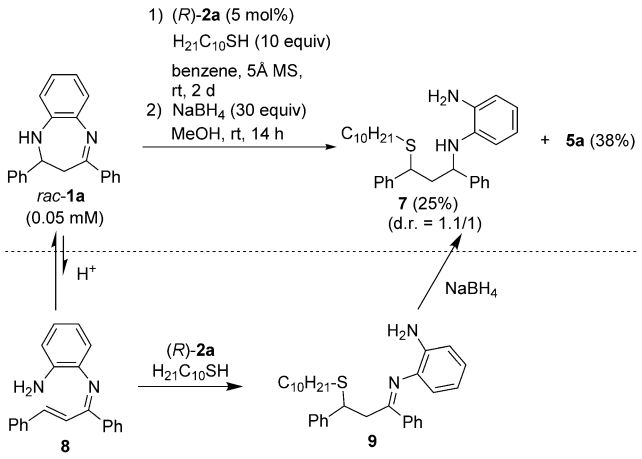


[a] Yields were determined by NMR spectroscopy. [b] d.r. (*trans*/*cis*) values were determined by NMR analysis of crude products. [c] Determined by chiral HPLC analysis. [d] (*R*)-**2b** was used. [e] **3b** (1.4 equiv) and 5 Å MS (200 mg) were used. [f] Isolated yield.



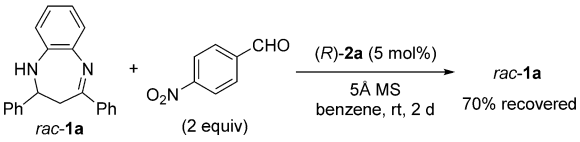
Scheme 1. Reaction of benzodiazepines (isolated yields are given; d.r. was determined by NMR analysis of the crude product; *ee* was determined by chiral HPLC analysis).

ment of *rac*-**1a** with decanethiol (10 equiv) in the presence of phosphoric acid (*R*)-**2a**, and subsequent treatment with $NaBH_4$ gave aminothiol **7** in 25% yield. Sulfide **7** was considered to be formed by thia-Michael reaction of decanethiol to **8**, which was obtained by *retro*-aza-Michael reaction of **1a** followed by reduction with $NaBH_4$ (Scheme 2).[17] This result suggests that **1a** was racemized by the sequential *retro*-Michael/Michael addition reaction.



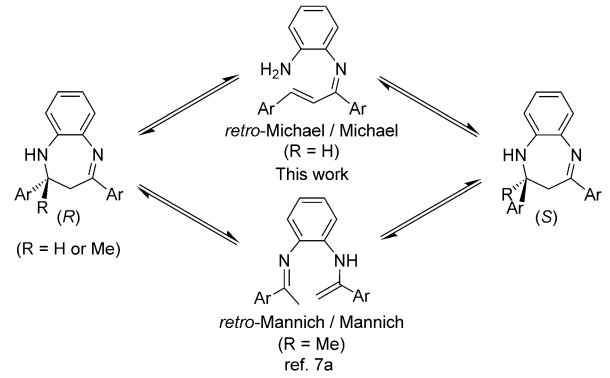
Scheme 2. Reaction of dihydrobenzodiazepine with thiol.

Gong and co-workers had reported phosphoric-acid-catalyzed asymmetric synthesis of dihydrobenzodiazepines through DKR process,[7a] and proposed that the starting material racemized by the sequential *retro*-Mannich/Mannich reactions.[18] Upon treatment of *rac*-**1a** with *p*-nitrobenzaldehyde in the presence of (*R*)-**2a**, *rac*-**1a** was recovered in 70% yield without formation of scrambling product (Scheme 3). These results clearly show that the racemization of benzodiazepine derivatives proceeded by *retro*-Michael/Michael reactions (R = H) different from the mechanism of Gong (*retro*-Mannich/Mannich reactions; R = Me; Scheme 4).



Scheme 3. Reaction of dihydrobenzodiazepine with aromatic aldehyde.

Focusing on the second hydrogenation step, DFT calculations[19] of (*R*)-**2a**-catalyzed ATH of **1a** by using **3b** were carried out to elucidate the major factors for controlling the stereochemistry. Based on the previously reported theoretical study of the phosphoric acid catalysis,[20,21] a dicoordinated model of the transition state (TS) was predicted. As a preliminary study, various transition structures corresponding to two absolute configurations of **3b** (*R* and *S*, **TS1r** and **TS1s**), the enantiofacial selection of **1a** [leading to (*S*,*S*) and (*R*,*R*) enantiomers of **5**, **TS1α** and **TS1β**], and three coordination modes between (*R*)-**2a** and **1a** (**TS1_A**, **TS1_B**, and **TS1_N**, Figure 1a) were compared (see the Supporting Information). After exploring those diastereomeric TSs, four types of TSs were found to be energetically more favored for each enantiomer of **5** (Figure 1b). In both **TS1_A** and **TS1_B**, **3b** interacts with the phosphoric acid moiety of (*R*)-**2a** through the two-point hydrogen bonds at the NH and *m*-OH groups (**TS1_A**: naphtholic oxygen; **TS1_B**: phosphoryl oxygen). Depending on the coordination modes A and B, **3b** is oriented perpendicular and parallel to the phosphate moiety (e.g., O-P-O plane) in **TS1_A** and **TS1_B**, respectively. For **TS1_A**, therefore, (*S*)-**3b** is only fitted into the chiral space constructed by the 3,3′-substituents of (*R*)-**2a**.[22] In contrast, two types of diastereomeric **TS1_B** (**TS1_B** and **TS1_B′**) having different relative orientations of **1a** and **3b** exist there due to the lack of coordination of **1a** on the phosphoric acid moiety. It was noted that both **TS1αs_A** and **TS1αs_N** leading to the major (*S*,*S*)-**5a** are relatively more stable than the other diastereomeric TSs. On the other hand, both **TS1βs_A** and **TS1βs_B** leading to the minor (*R*,*R*)-**5a** are located in a similar



Scheme 4. Racemization pathway of dihydrobenzodiazepine derivatives.

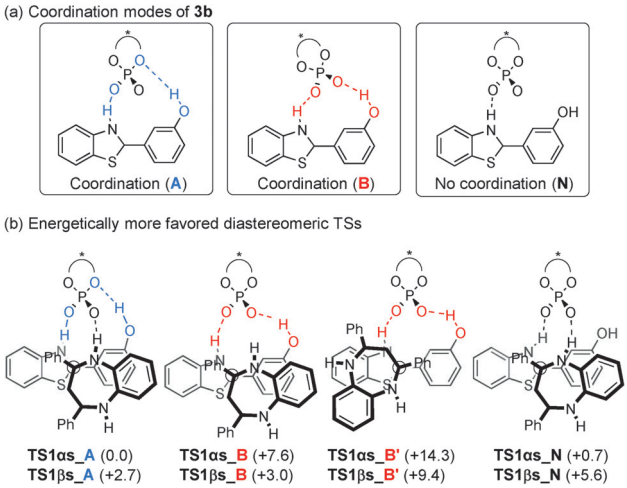


Figure 1. (a) Coordination modes between (*R*)-**2a** and **1a** and (b) diastereomeric TS structures of **TS1αs** and the relative energies [kcal mol^{-1}] of both **TS1αs** and **TS1βs**.

energy level, albeit 2.7 and 3.0 kcal mol^{-1} less stable, respectively, than the most stable **TS1 αs_A**. These computational results are qualitatively consistent with the experimentally observed high enantioselectivity of (*S*,*S*)-**5 a**.[23]

Structural analysis of **TS1 αs_A**, **TS1 αs_N**, **TS1 βs_A**, and **TS1 βs_B** allowed us to obtain deep insights into the stereocontrol. **TS1 αs_A** and **TS1 αs_N** have no unfavorable steric interactions when the preferred ring-flipped conformation of **1 a** is located in the empty upper right-hand quadrant (Figure 2).[24] Both **TS1 αs_A** and **TS1 αs_N** are stabilized by the attractive interaction between (*R*)-**2 a** and **3 b** through the OH/O and OH/π hydrogen bonds, respectively. The *m*-OH group of **3 b** plays a key role in fixing the orientation in the chiral space and stabilizing the TS through the multipoint hydrogen bond.

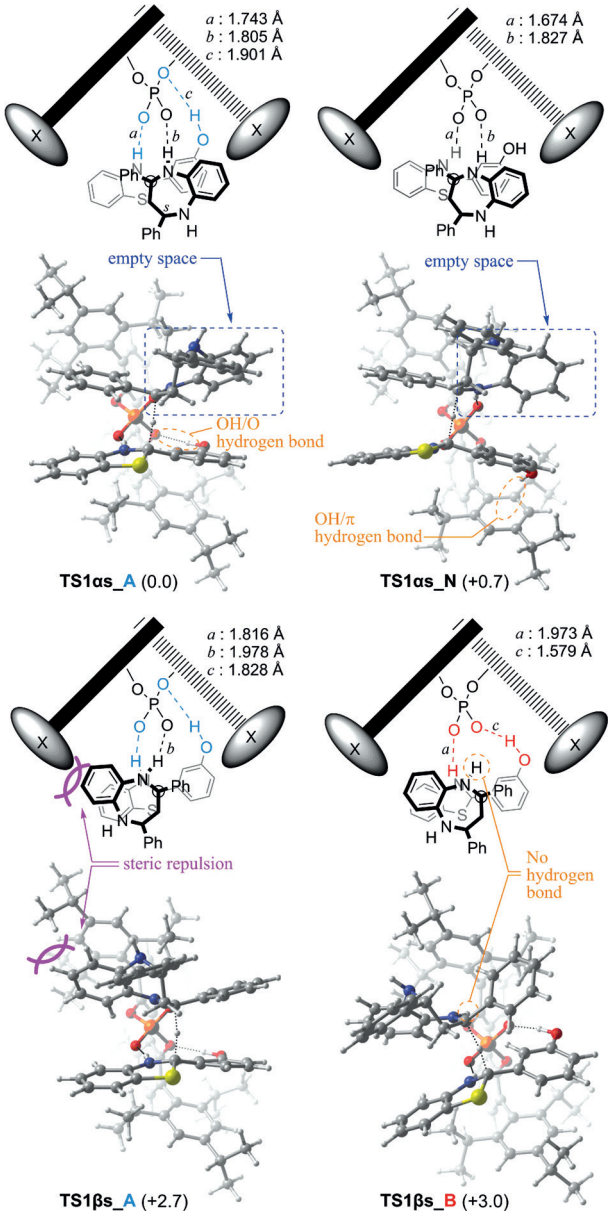


Figure 2. Schematic representations and 3D structures of **TS1 αs_A**, **TS1 αs_N**, **TS1 βs_A**, and **TS1 βs_B**. The relative energies [kcal mol^{-1}] are shown in parentheses.

On the other hand, the phenylene moiety of **1 a** has serious steric repulsion with the 3,3′-substituent of (*R*)-**2 a** to destabilize **TS1 βs_A**. In spite of the loss of steric repulsion between **1 a** and (*R*)-**2 a**, **TS1 βs_B** is also destabilized by the absence of the NH/phosphoryl oxygen hydrogen bond. The 3,3′-substituent effect of (*R*)-**2 b** achieving higher diastereoselectivity than (*R*)-**2 a** was also addressed. Although a beneficial effect of bulky *para*-substituent at the 3,3′-substituent on stereoselectivity in chiral phosphoric acid catalysis had been documented, such remote stereocontrol of the 3,3′-substituent had not been elucidated.[25] The energy difference between the energetically favored and competitive diastereomeric TSs (**TS1 αs_A** and **TS1 γs_A**) is significantly larger for (*R*)-**2 b** (3.1 kcal mol^{-1}) than (*R*)-**2 a** (0.4 kcal mol^{-1}), which is in good agreement with the experimental results. The deeper chiral space constructed by the 3,3′-biaryl substituents in (*R*)-**2 b** enables the control of stereoselectivity at the remote site (highlighted in green, Figure 3). The terminal aryl substituent of (*R*)-**2 b** induces steric repulsion with the Ph group of **1 a** to significantly destabilize **TS1 γs_A**. These computational studies fully explained the origin of the high enantioselectivity, as well as the remote control of high diastereoselectivity in the (*R*)-**2 a** and (*R*)-**2 b** catalyzed ATH of **1 a** using **3 b**.

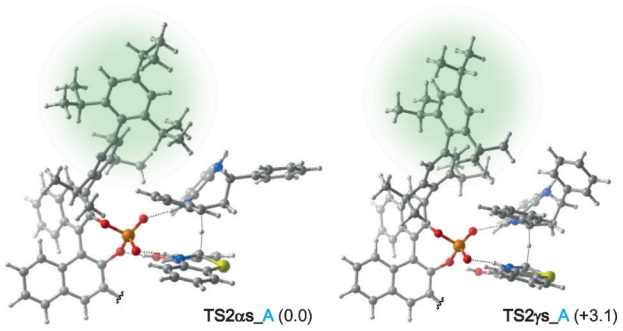


Figure 3. Partial 3D structures of **TS2 αs_A** and **TS2 γs_A**. The relative energies [kcal mol^{-1}] are shown in parentheses.

In conclusion, we have developed highly efficient method for the construction of 1,5-tetrahydrobenzodiazepines based on organocatalyzed transfer hydrogenation of dihydrobenzodiazepines involving the DKR process. The salient features are 1) DKR of cyclic amines was promoted by chiral phosphoric acid; 2) 2-substituent of benzothiazoline specifically enhanced the efficiency of this DKR; 3) high remote stereocontrol was achieved by newly synthesized chiral phosphoric acid catalyst; and 4) the unique effect of the substituent of benzothiazoline and chiral phosphoric acid was rationalized by the DFT study to be hydrogen-bonding network, formed between the catalyst and hydrogen donor. Further investigation of the mechanism and applications to the synthesis of more complex molecules are underway in our laboratory.

Experimental Section

A typical procedure for the reaction of *rac*-**1a** is described. A magnetic stirrer and powdered 5 Å MS (200 mg) were placed in a round-bottom flask (10 mL) under nitrogen atmosphere. The 5 Å MS were then dried with a heat gun under reduced pressure, and the round-bottom flask was refilled with nitrogen. Compound *rac*-**1a** (29.8 mg, 0.0999 mmol), phosphoric acid (*R*)-**2b** (5.37 mg, 5.00 μmol), and benzothiazoline **3f** (32.1 mg, 0.140 mmol) were added to the round-bottom flask successively under nitrogen atmosphere at room temperature. Benzene (2 mL) was added to the round-bottom flask. After being stirred for two days at room temperature, the mixture was filtered over Celite pad (washed with CH_2Cl_2), the filtrate was concentrated under reduced pressure, and the residue was purified by preparative thin-layer chromatography on silica gel (AcOEt/hexane 1:10) to give 28.2 mg (0.0939 mmol, 94%, >99% *ee*, *trans*/*cis* >99:1) of (*S*,*S*)-**5a**.

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Keywords: dynamic kinetic resolution · heterocycles · hydrogenation · organocatalysis · stereoselective synthesis

[1] For reviews on kinetic resolutions, see: a) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.* **2005**, *44*, 3974–4001; *Angew. Chem.* **2005**, *117*, 4040–4069; b) E. Fogassy, M. Nogradi, D. Kozma, G. Egri, E. Palovics, V. Kiss, *Org. Biomol. Chem.* **2006**, *4*, 3011–3030; c) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 1613–1666.

[2] For reviews of dynamic kinetic resolution, see: a) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291–8327; b) H. Pellissier, *Tetrahedron* **2008**, *64*, 1563–1601; c) H. Pellissier, *Tetrahedron* **2011**, *67*, 3769–3802.

[3] For review of DKR based on nonenzymatic approaches, see: a) R. Noyori, M. Takunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56; b) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 659–676.

[4] For reviews on DKR based on enzymatic or chemoenzymatic approaches, see: a) J. H. Lee, K. Han, M.-J. Kim, J. Park, *Eur. J. Org. Chem.* **2010**, 999–1015; b) P. Hoys, V. Pace, A. R. Alcántara, *Adv. Synth. Catal.* **2012**, *354*, 2585–2611; c) F. F. Huerta, A. B. E. Minidis, J.-E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321–331; d) H. Stecher, K. Faber, *Synthesis* **1997**, 1–16; e) A. Kamal, M. A. Azhar, T. Krisnaji, M. S. Malik, S. Azeeza, *Coord. Chem. Rev.* **2008**, *252*, 569–592.

[5] Examples of nonenzymatic DKR of amines, see: a) J.-H. Xie, S. Liu, W.-L. Kong, W.-J. Bai, X.-C. Wang, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2009**, *131*, 4222–4223; b) D.-W. Wang, X.-B. Wang, D.-S. Wang, S.-M. Lu, C.-B. Yu, Y.-G. Zhou, *J. Org. Chem.* **2009**, *74*, 2780–2787; c) M. Rueping, T. Theissmann, S. Raja, J. W. Bata, *Adv. Synth. Catal.* **2008**, *350*, 1001–1006; d) Q.-S. Guo, D.-M. Du, J. Xu, *Angew. Chem. Int. Ed.* **2008**, *47*, 759–762; *Angew. Chem.* **2008**, *120*, 771–774; e) T. Wang, L.-G. Zhou, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu, A. S. C. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 9878–9891; f) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8909–8911; g) L. Shi, Z.-S. Ye, L.-L. Cao, R.-N. Guo, Y. Hu, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 8286–8289; *Angew. Chem.* **2012**, *124*, 8411–8414; h) M.-W. Chen, X.-F. Cai, Z.-P. Chen, L. Shi, Y.-G. Zhou, *Chem. Commun.* **2014**, *50*, 12526–12529.

[6] For recent examples, see: a) G. Grossi, M. D. Braccio, G. Roma, V. Ballabeni, M. Tognolini, F. Calcina, E. Barocelli, *Eur. J. Med. Chem.* **2002**, *37*, 933–944; b) A. Matsuhisa, H. Koshio, K. Sakamoto, N. Taniguchi, T. Yatsu, A. Tanaka, *Chem. Pharm. Bull.* **1998**, *46*, 1566–1579; c) W. Nawrocka, B. Sztubab, A. Opolskic, J. Wietrzykc, M. W. Kowalskad, T. Glowiakd, *Arch. Pharm. Med. Chem.* **2001**, *334*, 3–10; d) D. J. Lauffer, M. D. Mullican, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1225–1227; e) K. Vandyck, M. D. Cummings, O. Nyanguile, C. W. Boutton, S. Vendeville, D. McGowan, B. Devogelaere, K. Amssoms, S. Last, K. Rombauts, A. Tahri, P. Lory, L. Hu, D. A. Beauchamp, K. Simmen, P. Raboisson, *J. Med. Chem.* **2009**, *52*, 4099–4102.

[7] a) Z.-Y. Han, H. Xiao, L.-Z. Gong, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3729–3732; b) Z.-Y. Ding, F. Chen, J. Qin, Y.-M. He, Q.-H. Fan, *Angew. Chem. Int. Ed.* **2012**, *51*, 5706–5710; *Angew. Chem.* **2012**, *124*, 5804–5808; Other asymmetric syntheses of 1,5-benzodiazepine derivatives, see: c) M. Rueping, E. Merino, R. M. Koenigs, *Adv. Synth. Catal.* **2010**, *352*, 2629–2634; d) X. Fu, J. Feng, Z. Dong, L. Lin, X. Liu, X. Feng, *Eur. J. Org. Chem.* **2011**, 5233–5236; e) X. Chen, Y. Zheng, C. Shu, W. Yuan, B. Liu, X. Zhang, *J. Org. Chem.* **2011**, *76*, 9109–9115; f) K. Gao, B. Wu, C.-B. Yu, Q.-A. Chen, Z.-S. Ye, Y.-G. Zhou, *Org. Lett.* **2012**, *14*, 3890–3893.

[8] For selected reviews on organocatalyzed ATH, see: a) C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498–2518; b) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2010**, 852–865; c) C. Wang, X. Wu, J. Xiao, *Chem. Asian J.* **2008**, *3*, 1750–1770; d) S. G. Ouellet, A. M. Walji, D. W. C. MacMillan, *Acc. Chem. Res.* **2007**, *40*, 1327–1339; e) S. J. Connon, *Org. Biomol. Chem.* **2007**, *5*, 3407–3417; f) J. G. de Vries, N. MrŠic, *Catal. Sci. Technol.* **2011**, *1*, 727–735.

[9] For reviews of chiral phosphoric acid, see: a) Z.-P. Yang, W. Zhang, S.-L. You, *J. Org. Chem.* **2014**, *79*, 7785–7798; b) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva, *Org. Biomol. Chem.* **2010**, *8*, 5262–5276; c) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047–9153; d) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; e) M. Terada, *Synthesis* **2010**, 1929–1982; f) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395–456; g) Y. Su, F. Shi, *Chin. J. Org. Chem.* **2010**, *30*, 486–498; For seminal works of chiral phosphoric acid, see: h) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568; *Angew. Chem.* **2004**, *116*, 1592–1594; i) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

[10] Our group has recently developed chiral Brønsted acid catalyzed transfer hydrogenation of imines using benzothiazoline derivatives as hydrogen donor, see: a) C. Zhu, T. Akiyama, *Org. Lett.* **2009**, *11*, 4180–4183; b) C. Zhu, T. Akiyama, *Adv. Synth. Catal.* **2010**, *352*, 1846–1850; c) C. Zhu, T. Akiyama, *Synlett* **2011**, 1251–1254; d) A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180–8183; *Angew. Chem.* **2011**, *123*, 8330–8333; e) K. Saito, T. Akiyama, *Chem. Commun.* **2012**, *48*, 4573–4575; f) C. Zhu, T. Akiyama, *Tetrahedron Lett.* **2012**, *53*, 416–418; g) T. Sakamoto, K. Mori, T. Akiyama, *Org. Lett.* **2012**, *14*, 3312–3315; See also: h) D. Enders, J. X. Liebich, G. Raabe, *Chem. Eur. J.* **2010**, *16*, 9763–9766; i) C. Zhu, J. R. Falck, *ChemCatChem* **2011**, *3*, 1850–1851; j) C. Zhu, K. Saito, M. Yamanaka, T. Akiyama, *Acc. Chem. Res.* **2015**, *48*, 388–398.

[11] a) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424–7427; *Angew. Chem.* **2005**, *117*, 7590–7593; b) G. Adair, S. Mukherjee, B. List, *Aldrichimica Acta* **2008**, *41*, 31–39.

[12] Absolute configuration of **2a** was determined to be (*S*,*S*) by the comparison of the sign of optical rotation and the retention time of HPLC analysis; see Ref. [7b].

[13] Because we could not prepare **1a** in enantio-enriched form, we could not study the kinetics of racemization process of **1a**.

[14] Although crossover experiment was carried for the elucidation of the reaction mechanism, no crossover was observed in the reaction of **1m** with **1b** or **e** under the optimized conditions.

[15] Reaction of **1a** with **3b**-D using the optimized catalyst (*R*)-**2b** gave lower yield (44%, 97% *ee*, d.r. 17.7/1).

[16] Reaction of the substrate reported in Ref. [7a] under the optimized conditions gave much lower conversion (<10% yield).

[17] When this reaction was carried out in the absence of phosphoric acid and 5 Å MS, no ring-opening product was obtained, but **5a** was obtained quantitatively. As an acidic reagent, 5 Å MS was reported to work, see: N. Asakura, T. Hirokane, H. Hoshida, H. Yamada, *Tetrahedron Lett.* **2011**, *52*, 534–537.

[18] They examined the racemization process by the reaction of starting material with electron-deficient acetophenone derivative.

[19] All TSs were computed at the M05–2X/6–31G*//ONIOM(B3LYP:HF) level. Computational details are given in the Supporting Information.

[20] a) Y. Shibata, M. Yamanaka, *J. Org. Chem.* **2013**, *78*, 3731 – 3736; b) K. Saito, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 11740 – 11743; c) K. Saito, K. Horiguchi, Y. Shibata, M. Yamanaka, T. Akiyama, *Chem. Eur. J.* **2014**, *20*, 7616 – 7620.

[21] Selected examples of theoretical study of chiral phosphoric acid catalysis: a) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, *129*, 6756 – 6764; b) L. Simón, J. M. Goodman, *J. Am. Chem. Soc.* **2008**, *130*, 8741 – 8747; c) T. Marcelli, P. Hammar, F. Himo, *Chem. Eur. J.* **2008**, *14*, 8562 – 8571; d) M. Yamanaka, T. Hirata, *J. Org. Chem.* **2009**, *74*, 3266 – 3271; e) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819 – 13825; f) N. Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 15301 – 15310; g) L. Simón, J. M. Goodman, *J. Org. Chem.* **2010**, *75*, 589 – 597; h) C. Zheng, Y.-F. Sheng, Y.-X. Li, S.-L. You, *Tetrahedron* **2010**, *66*, 2875 – 2880; i) T. Hirata, M. Yamanaka, *Chem. Asian J.* **2011**, *6*, 510 – 516; j) L. Simón, J. M. Goodman, *J. Org. Chem.* **2011**, *76*, 1775 – 1788; k) M. Yamanaka, M. Hoshino, T. Katoh, M. Mori, T. Akiyama, *Eur. J. Org. Chem.* **2012**, *24*, 4508 – 4514; l) M. N. Grayson, S. C. Pellegrinet, J. M. Goodman, *J. Am. Chem. Soc.* **2012**, *134*, 2716 – 2722; m) F. Shi, G.-J. Xing, Z.-L. Tao, S.-W. Luo, S.-J. Tu, L.-Z. Gong, *J. Org. Chem.* **2012**, *77*, 6970 – 6979; n) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 3964 – 3970; o) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *Chem. Sci.* **2013**, *4*, 4235 – 4239; p) H. Wang, P. Jain, J. C. Antilla, K. N. Houk, *J. Org. Chem.* **2013**, *78*, 1208 – 1215; q) K. Kanomata, Y. Toda, Y. Shibata, M. Yamanaka, S. Tsuzuki, I. D. Gridnev, M. Terada, *Chem. Sci.* **2014**, *5*, 3515 – 3523; r) M. Terada, T. Komuro, Y. Toda, T. Korenaga, *J. Am. Chem. Soc.* **2014**, *136*, 7044 – 7057; s) C. Liu, P. Han, M. Tang, *Comput. Theor. Chem.* **2014**, *1050*, 39 – 45; t) J. Pous, T. Courant, G. Bernadat, B. I. Iorga, F. Blanchard, G. Masson, *J. Am. Chem. Soc.* **2015**, *137*, 11950 – 11953; u) N. Momiyama, K. Funayama, H. Noda, M. Yamanaka, N. Akasaka, S. Ishida, T. Iwamoto, M. Terada, *ACS Catal.* **2016**, *6*, 949 – 956.

[22] Although **TS_N** has similar structural features to **TS_A**, no additional coordination of *m*-OH group reduces the structural requirement for the chiral space. Therefore, in **TS_N**, the diastereomeric TSs are located for each absolute configuration of **3b**.

[23] Based on the **TS1α** and **TS1β**, the diastereomeric TSs (**TSγ**) leading to the *meso* isomer (*S*,*R*)-**5a** were also compared. The relative energy difference between the competitive diastereomeric TSs (**TSα** and **TSγ**) is significantly decreased (within 1 kcal mol^{-1}) in agreement with the lower diastereoselectivity experimentally obtained by (*R*)-**2a**. See the Supporting Information.

[24] Details of the ring-flipped conformations of **1a** are given in Supporting Information.

[25] Examples of remote control of stereoselectivity by the bulky substituent at the *para*-position at the aryl substituent on stereoselectivity in BINOL-based chiral phosphoric acids, see: a) P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chem. Int. Ed.* **2008**, *47*, 2411 – 2413; *Angew. Chem.* **2008**, *120*, 2445 – 2447; b) X. Cheng, R. Goddard, G. Buth, B. List, *Angew. Chem. Int. Ed.* **2008**, *47*, 5079 – 5081; *Angew. Chem.* **2008**, *120*, 5157 – 5159; c) C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246 – 9247; d) X. Cheng, S. Vellalath, R. Goddard, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 15786 – 15787; e) C. H. Cheon, H. Yamamoto, *Org. Lett.* **2010**, *12*, 2476 – 2479; f) M. Sai, H. Yamamoto, *J. Am. Chem. Soc.* **2015**, *137*, 7091 – 7094.

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