Biaryls

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Enantiodivergent Atroposelective Synthesis of Chiral Biaryls by Asymmetric Transfer Hydrogenation: Chiral Phosphoric Acid Catalyzed Dynamic Kinetic Resolution

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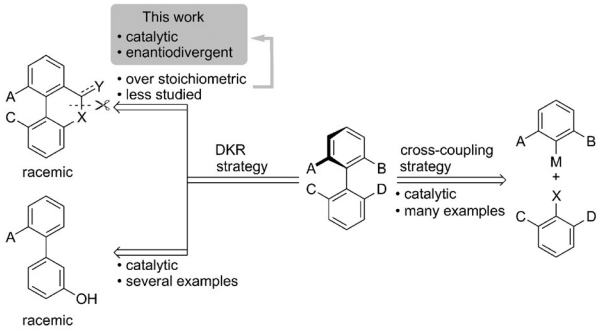
Abstract: *Reported herein is an enantiodivergent synthesis of chiral biaryls by a chiral phosphoric acid catalyzed asymmetric transfer hydrogenation reaction. Upon treatment of biaryl lactols with aromatic amines and a Hantzsch ester in the presence of chiral phosphoric acid, dynamic kinetic resolution (DKR) involving a reductive amination reaction proceeded smoothly to furnish both R and S isomers of chiral biaryls with excellent enantioselectivities by proper choice of hydroxyaniline derivative. This trend was observed in wide variety of substrates, and various chiral biphenyl and phenyl naphthyl adducts were synthesized with satisfactory enantioselectivities in enantiodivergent fashion. The enantiodivergent synthesis of synthetically challenging, chiral o-tetrasubstituted biaryls were also accomplished, and suggests high synthetic potential of the present method.*



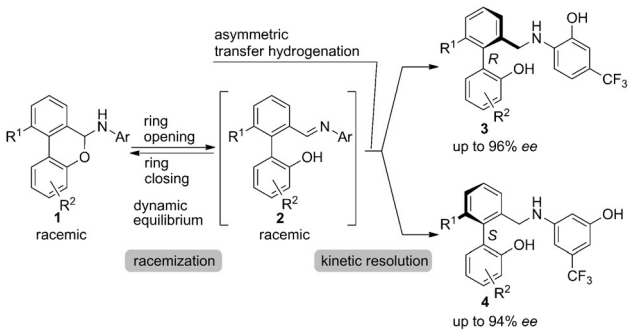
Scheme 1. Strategies for chiral biaryls.

Because of the broad utility of chiral biaryls,[1] much effort has been directed toward the development of novel methods for their asymmetric synthesis in recent years. The diastereo- and enantioselective coupling reaction of two aromatic rings has been extensively studied as the most straightforward method.[2]

A dynamic kinetic resolution (DKR) approach, starting from preformed racemic biaryls, is an alternative and effective tool for the asymmetric synthesis of chiral biaryls (Scheme 1). In 2010, Miller and co-workers reported an atroposelective asymmetric bromination, which utilized configurationally unstable monosubstituted biaryls as substrates, to give chiral *o*-trisubstituted biaryls with high enantioselectivities through peptide catalysis.[3] Quite recently, Miyaji, Asano, and Matsubara accomplished a chiral-urea-catalyzed asymmetric synthesis of 1-arylisoquinolines *N*-oxides on the basis of the same strategy.[4] Cross-coupling at the 2-position of the binaphthyl skeleton is also a viable DKR strategy, but a slightly high temperature is required because of the moderate configurational stability of the starting materials.[5]

Among the methods which use preformed racemic biaryls as substrates,[6] the asymmetric ring-opening strategy, reported by Bringmann et al.,[7] wherein biaryl lactones serve as a substrates, is reliable from a practical point of view, but it requires an excess amount of a chiral nucleophile. Its utility is demonstrated in several total syntheses of biologically active compounds.[8] The catalytic variant of the strategy is limited to the recent study by Yamada and co-workers wherein a chiral metal catalyst was used.[9] In this regard, the development of an effective catalytic method, in particular organocatalysis, is highly desired.[10]

We report herein a chiral phosphoric acid catalyzed DKR strategy for the asymmetric synthesis of chiral biaryls (Scheme 2).[11–13] A chiral phosphoric acid catalyzed asymmetric transfer hydrogenation reaction plays a crucial role in accomplishing the desired DKR strategy.[14] The ring-opening/ring-closing equilibrium between the biaryl *N*,*O*-acetal **1** and biaryl imine **2** (racemization), and the subsequent kinetic-resolution-type asymmetric transfer hydrogenation of **2**



Scheme 2. Enantiodivergent synthesis of chiral biaryls by chiral phosphoric acid catalyzed DKR strategy.

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proceeds to afford the chiral biaryls **3** and **4** with excellent enantioselectivities. A noteworthy feature of this reaction is that the atroposelectivity of the products was completely controlled by the choice in the hydroxyaniline derivative. Whereas use of the *o*-hydroxyaniline derivatives furnished chiral biaryls with excellent enantioselectivities in favor of the *R* isomer, use of the *m*-hydroxyaniline derivative reversed the atroposelectivity to furnish the *S* isomer of the biaryl in a highly enantioselective manner.

We selected **1** as a substrate for three reasons (Figure 1): 1) ease of ring opening to form the biaryl imine **2**; 2) high affinity of the resulting **2** to chiral phosphoric acids (CPA);

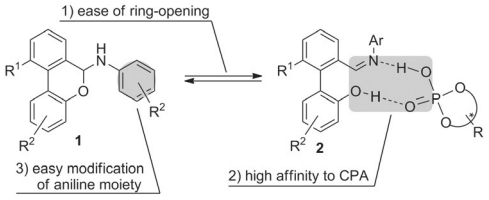
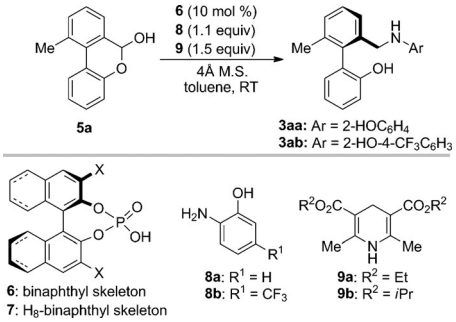


Figure 1. Three reasons for the substrate selection.

and 3) ease of modification of the aromatic ring of the aniline moiety, a feature which would strongly affect both reactivity and enantioselectivity. The selection of the transformation from **2** was also important to achieve the high selectivity. We envisaged that the transfer hydrogenation was suited for this purpose because of the high reliability of the chiral phosphoric acid catalysis.[15–17]

An initial trial was conducted under reductive amination conditions starting with the lactol **5a**, not **1a**, for streamline the screening of reaction conditions (catalysts and anilines): a solution of **5a** in toluene was treated with 1.1 equivalents of *o*-hydroxyaniline (**8a**) and 1.5 equivalents of the Hantzsch ester **9a** in the presence of 4 Å M.S. and 10 mol% of a phosphoric acid (Table 1). When TRIP (**6a**), which showed excellent catalytic performance in the asymmetric transfer hydrogenation of imines,[16,17] was employed, the transfer hydrogenation reaction proceeded smoothly to afford the biaryl **3aa** in 75% yield with 33% *ee* (entry 1). Catalysts bearing 9-anthryl groups (**6b**) and 2,4-$(CF_3)_2C_6H_3$ groups (**6c**) resulted in moderate selectivities (entries 2 and 3). The catalyst **6d**, having biphenyl groups, was also ineffective (entry 4). The catalyst **6e**, having $SiPh_3$ groups gave the desired adduct in 91% yield with 59% *ee* (entry 5). Motivated by the results, we examined the aryl moiety on the silyl group in detail. Gratifyingly, the catalyst **6f**, bearing Si(3-$FC_6H_4)_3$ groups, gave **3aa** with 73% *ee* (entry 6). Finally, we found that the key to achieving satisfactory enantioselectivity was the concentration of the reaction medium and the use of modified *o*-hydroxyaniline. When the concentration of the reaction medium was lowered from 0.1 to 0.01 M, and further to 0.005 M, the selectivity was improved to 81 and 84% *ee*, respectively (entries 7 and 8). Use of the CF_3-substituted *o*-hydroxyaniline derivative **8b** further improved the selectivity to give corresponding adduct **3ab** in 98% yield with 90% *ee* (entry 9). The absolute stereochemistry of **3a** was determined

Table 1: Examination of reaction conditions.[a]

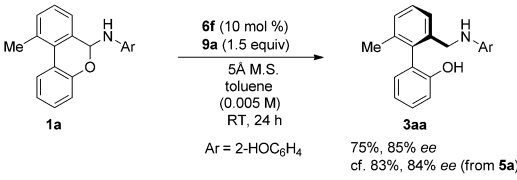


Entry	Catalyst (X)	Yield [%]	*ee* [%][b]
1	2,4,6-(*i*Pr)$_3$C$_6$H$_2$ (**6a**)	75	33
2	9-anthryl (**6b**)	80	30
3	2,4-(CF$_3$)$_2$C$_6$H$_3$ (**6c**)	86	47
4	4-PhC$_6$H$_4$ (**6d**)	74	13
5	SiPh$_3$ (**6e**)	91	59
6	Si(3-FC$_6$H$_4$)$_3$ (**6f**)	75	73
7[c,d]	Si(3-FC$_6$H$_4$)$_3$ (**6f**)	72	81
8[c,e]	Si(3-FC$_6$H$_4$)$_3$ (**6f**)	83	84
9[c,e,f]	Si(3-FC$_6$H$_4$)$_3$ (**6f**)	98	90

[a] Unless otherwise noted, all reactions were conducted with the lactol **5a** (0.10 mmol), hydroxyaniline **8a** (0.11 mmol), and Hantzsch ester **9a** (0.15 mmol) in the presence of 10 mol% **6** and 4 Å M.S. in toluene (1.0 mL) at room temperature. [b] Enantiomeric ratio was determined by HPLC analysis using a chiral stationary phase. [c] 5 Å M.S. was employed instead of 4 Å M.S. [d] 0.01 M. [e] 0.005 M. [f] 2-Amino-5-(trifluoromethyl)phenol (**8b**) was employed instead of **8a**. M.S. = molecular sieves.

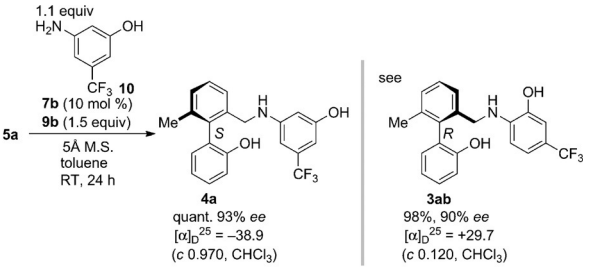
by X-ray crystallographic analysis (see the Supporting Information).[18]

Then, we carried out the reaction with the initially planned **1a** [Eq. (1)]. When **1a** was subjected to the reaction conditions (same as entry 8 in Table 1), **3aa** was obtained in 75% yield with 85% *ee*, which was almost identical to the result when **5a** was used as the substrate. Further examination was therefore conducted with **5** as the starting material, from a practical point of view.



(1)

Interestingly, excellent selectivity (93% *ee*) was also achieved when the *m*-hydroxyaniline derivative **10** was used in the presence of the hydrogenated binaphthyl-type phosphoric acid **7b** (see Table 1). bearing 9-anthryl groups (Scheme 3). The important feature here is that the adducts **3ab** and **4a** showed opposite signs in optical rotation values, and implied that atroposelectivity was controlled by the position of the hydroxy group of aniline. We confirmed the reversal of the atroposelectivity by transforming the analogues of **3** and **4** into a common compound (see the Supporting Information for details).



Scheme 3. Reaction with the *m*-hydroxyaniline **10**.

With the atropodivergent strategy for the synthesis of chiral biaryls in hand, a range of lactols were subjected to the reductive amination protocol (Figure 2). Various *o*-hydroxyaniline substituted biaryls (**3ab**, **3b**–**d**), having electron-donating groups (Me, *i*Pr) and an electron-withdrawing group (Cl) on the upper aromatic ring, were obtained with good to excellent enantioselectivities (77–94% *ee*). Biaryls bearing substituents on the lower aromatic ring were also found to be suitable substrates, thus affording the biaryls **3e**–**g** with excellent enantioselectivities (≥86% *ee*). This method was applicable to the enantioselective synthesis of aryl naphthalene derivatives (**3h**–**j**). The same tendency was also observed when **10** was employed, and the corresponding adducts (**4a**–**j**) were obtained with good to excellent enantioselectivities (up to 94% *ee*) in favor of the enantiomer, as confirmed by comparison of the optical rotations of the products.

Next we studied the enantioselective synthesis of *o*-tetrasubstituted biaryls. Interestingly, the substrate **5k** was observed as a ring-opened form, hydroxy aldehyde, and no appreciable peaks of the lactol were observed by ^{1}H NMR spectroscopy,[19] although the equilibrium was largely shifted toward **5a** (lactol/hydroxy aldehyde = 10:1). The same situation holds for the corresponding imine derivative **2k**, and only the imine form was observed. These observations suggest that the rate of the interconversion of the enantiomers of **5k** and **2k** would be slow. As expected, subjecting **5k** to the optimum reaction conditions delivered the adducts **3k** and **4k** in excellent chemical yields, albeit with low enantioselectivities (≤11% *ee* with 1.5 equiv of **9**; Scheme 4).

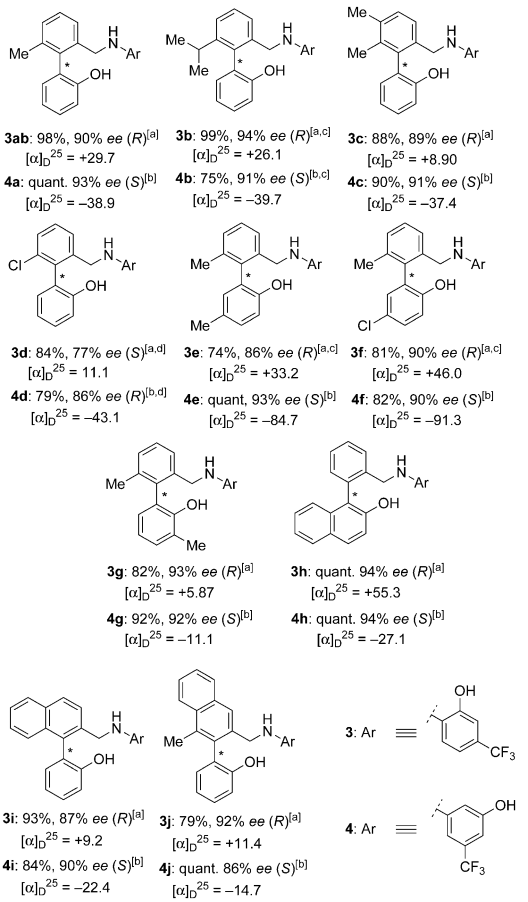
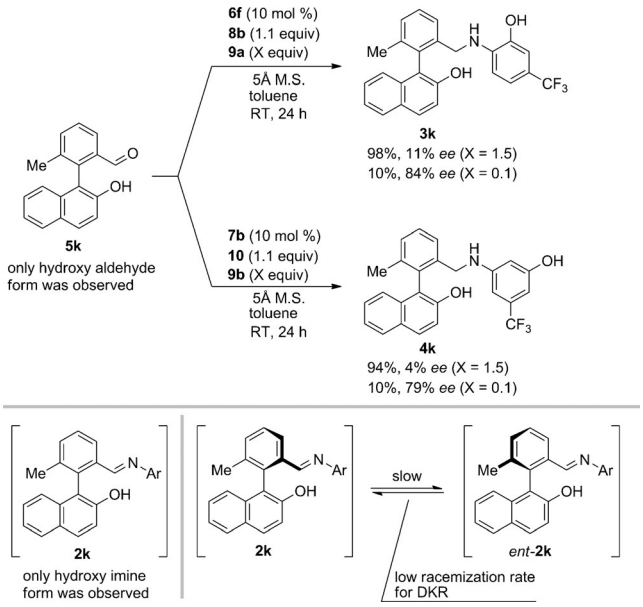


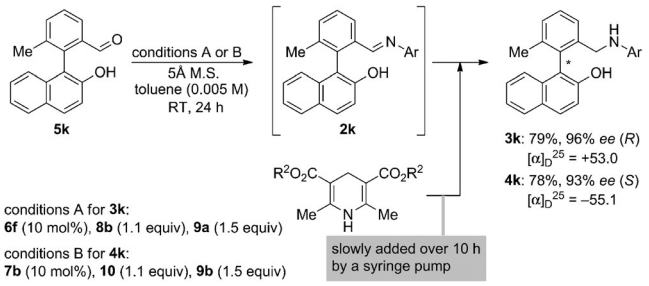
Figure 2. Substrate scope. [a] Reaction conditions A: **6f** (10 mol%), **8b** (1.1 equiv), **9a** (1.5 equiv), 5 Å M.S., toluene (0.005 M), RT, 24 h. [b] Reaction conditions B: **7b** (10 mol%), **10** (1.1 equiv), **9b** (1.5 equiv), 5 Å M.S., toluene (0.005 M), RT, 24 h. [c] 0 °C, 48 h. [d] 40 °C, 24 h.



Scheme 4. Attempt to synthesize *o*-tetrasubstituted biaryls.

Gratifyingly, use of 0.1 equivalents of **9** resulted in the formation of **3k** and **4k** in 84 and 79% *ee*, respectively. These results imply that the slow addition of small portions of the Hantzsch ester, which was indispensable for the requisite racemization of the imine, markedly improve the enantioselectivity. As expected, the slow addition of a toluene solution of 1.5 equivalents of **9** with a syringe pump over 10 hours afforded **3k** and **4k** with excellent enantioselectivities with both hydroxyanilines (Scheme 5).

Figure 3 illustrates rationalization of the asymmetric induction mechanism of the reaction. The key to achieving excellent selectivity is twofold: 1) prominent kinetic resolution in the asymmetric transfer hydrogenation of **2**, and 2) appropriate reaction rate difference between the equilibrium of **2** and *ent*-**2**, and the transfer hydrogenation.[20,21] The asymmetric transfer hydrogenation of the imines **2** and the



Scheme 5. Asymmetric synthesis of *o*-tetrasubstituted biaryls by DKR strategy.

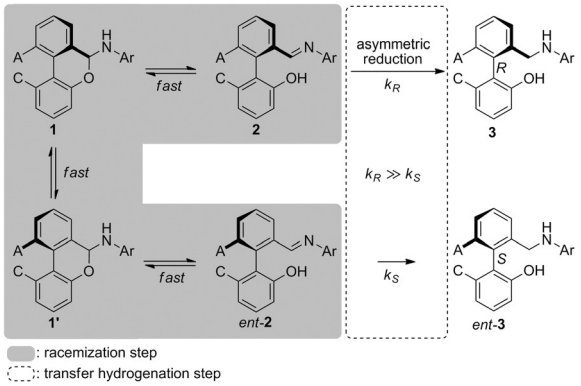


Figure 3. Proposed asymmetric induction mechanism.

subsequent rapid supply of the consumed isomer through the interconversion route occurred faster than transfer hydrogenation to imines, thereby affording the desired biaryls **3** with excellent enantioselectivities.

In summary, we have developed a strategy for the enantiodivergent synthesis of chiral biaryls by means of chiral phosphoric acid. Two interesting features are underscored: 1) the atroposelective synthesis of chiral biaryls by the chiral phosphoric acid catalyzed DKR approach, and 2) the accomplishment of the enantiodivergent synthesis by a proper choice in hydroxyaniline derivatives. Investigations aimed at clarifying the role of the position of the hydroxy group will be reported in due course.

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Keywords: biaryls · enantioselectivity · hydrogenation · kinetic resolution · organocatalysis

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Angew. Chem. **2016**, *128*, 11814–11818

[1] For recent reviews on axially chiral biaryls, see: a) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384; *Angew. Chem.* **2005**, *117*, 5518; b) O. Baudoin, *Eur. J. Org. Chem.* **2005**, *2005*, 4223; c) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193; d) K. Tanaka, *Chem. Asian J.* **2009**, *4*, 508; e) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563; f) G. Ma, M. P. Sibi, *Chem. Eur. J.* **2015**, *21*, 11644; g) P. Loxq, E. Manoury, R. Poli, E. Deydier, A. Labande, *Coord. Chem. Rev.* **2016**, *308*, 131.

[2] For selected examples of chiral biaryls by biaryl coupling reactions, see: a) Y. Uozumi, Y. Matsuura, T. Arakawa, Y. M. A. Yamada, *Angew. Chem. Int. Ed.* **2009**, *48*, 2708; *Angew. Chem.* **2009**, *121*, 2746; b) H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2009**, *131*, 6082; c) S. Huang, T. B. Petersen, B. H. Lipshutz, *J. Am. Chem. Soc.* **2010**, *132*, 14021; d) X. Shen, G. O. Jones, D. A. Watson, B. Bhayana, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 11278; e) H. Egami, K. Matsumoto, T. Oguma, T. Kunisu, T. Katsuki, *J. Am. Chem. Soc.* **2010**, *132*, 13633; f) T. Yamamoto, Y. Akai, Y. Nagata, M. Suginome, *Angew. Chem. Int. Ed.* **2011**, *50*, 8844; *Angew. Chem.* **2011**, *123*, 9006; g) K. Yamaguchi, J. Yamaguchi, A. Studer, K. Itami, *Chem. Sci.* **2012**, *3*, 2165; h) Y. Zhou, S. Wang, W. Wu, Q. Li, Y. He, Y. Zhuang, L. Li, J. Pang, Z. Zhou, L. Qiu, *Org. Lett.* **2013**, *15*, 5508; i) G. Xu, W. Fu, G. Liu, C. H. Senanayake, W. Tang, *J. Am. Chem. Soc.* **2014**, *136*, 570; j) Y. Zhou, X. Zhang, H. Liang, Z. Cao, Y. Zhao, X. He, S. Wang, J. Pang, Z. Zhou, Z. Ke, L. Y. Qiu, *ACS Catal.* **2014**, *4*, 1390.

[3] a) J. L. Gustafson, D. Lim, S. J. Miller, *Science* **2010**, *328*, 1251; See also: b) K. T. Barrett, S. J. Miller, *J. Am. Chem. Soc.* **2013**, *135*, 2963; c) M. E. Diener, A. J. Metrano, S. Kusano, S. J. Miller, *J. Am. Chem. Soc.* **2015**, *137*, 12369.

[4] R. Miyaji, K. Asano, S. Matsubara, *J. Am. Chem. Soc.* **2015**, *137*, 6766.

[5] a) A. Ros, B. Estepa, P. Ramírez-López, E. Álvarez, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2013**, *135*, 15730; b) V. Bhat, S. Wang, B. M. Stoltz, S. C. Virgil, *J. Am. Chem. Soc.* **2013**, *135*, 16829; See also: c) D.-W. Gao, Q. Gu, S.-L. Yu, *ACS Catal.* **2014**, *4*, 2741; d) P. Ramírez-López, A. Ros, B. Estepa, R. Fernández, B. Fiser, E. Gómez-Bengoga, J. M. Lassaletta, *ACS Catal.* **2016**, *6*, 3955.

[6] The asymmetric desymmetrization is also an important strategy for asymmetric synthesis of chiral biaryls from preformed C_s-symmetric biaryls. See: a) T. Hayashi, S. Niizuma, T. Kamikawa, N. Suzuki, Y. Uozumi, *J. Am. Chem. Soc.* **1995**, *117*, 9101; b) T. Matsumoto, T. Konegawa, T. Nakamura, K. Suzuki, *Synlett* **2002**, 0122; c) K. Okuyama, K. Shingubara, S. Tsujiyama, K. Suzuki, T. Matsumoto, *Synlett* **2009**, 941; d) Q. Perron, A. Alexakis, *Adv. Synth. Catal.* **2010**, *352*, 2611; e) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 3964; f) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *Chem. Sci.* **2013**, *4*, 4235; g) T. Osako, Y. Uozumi, *Org. Lett.* **2014**, *16*, 5866; h) R. J. Armstrong, M. D. Smith, *Angew. Chem. Int. Ed.* **2014**, *53*, 12822; *Angew. Chem.* **2014**, *126*, 13036; i) K. Mori, M. Kobayashi, T. Itakura, T. Akiyama, *Adv. Synth. Catal.* **2015**, *357*, 35; j) J. Graff, E. Lastawiecka, L. Guénée, F. Leroux, A. Alexakis, *Adv. Synth. Catal.* **2015**, *357*, 2833.

[7] For Bringmann's asymmetric ring-opening methodology, see: a) G. Bringmann, T. Hartung, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 761; *Angew. Chem.* **1992**, *104*, 782; b) G. Bringmann, J. Kraus, M. Breuning, S. Tasler, *Synthesis* **1999**, 525; c) G. Bringmann, S. Tasler, R.-M. Pfeifer, M. Breuning, *J. Organomet. Chem.* **2002**, *661*, 49; d) G. Bringmann, M. Breuning, P. Henschel, J. Hinrichs, *Org. Synth.* **2002**, *79*, 72.

[8] For representative examples of application of the asymmetric ring-opening strategy to the total synthesis of natural products, see: a) G. Bringmann, J. Hinrichs, T. Pabst, P. Henschel, K. Peters, E.-M. Peters, *Synthesis* **2001**, 0155; b) G. Bringmann, D. Menche, *Angew. Chem. Int. Ed.* **2001**, *40*, 1687; *Angew. Chem.* **2001**, *113*, 1733; c) G. Bringmann, D. Menche, J. Kraus, J. Mühlbacher, K. Peters, E.-M. Peters, R. Brun, M. Bezabih, B. M. Abegaz, *J. Org. Chem.* **2002**, *67*, 5595; d) K. Ohmori, M. Tamiya, M. Kitamura, H. Kato, M. Ohrui, K. Suzuki, *Angew. Chem. Int. Ed.* **2005**, *44*, 3871; *Angew. Chem.* **2005**, *117*, 3939; e) M. Tamiya, K. Ohmori, M. Kitamura, T. Arai, H. Kato, M. Oorui, K. Suzuki, *Chem. Eur. J.* **2007**, *13*, 9791.

[9] a) T. Ashizawa, S. Tanaka, T. Yamada, *Org. Lett.* **2008**, *10*, 2521; b) T. Ashizawa, T. Yamada, *Chem. Lett.* **2009**, *38*, 246; c) S. Kikuchi, T. Tsubo, T. Ashizawa, T. Yamada, *Chem. Lett.* **2010**, *39*, 594; d) K. Nushiro, S. Kikuchi, T. Yamada, *Chem. Lett.* **2013**, *42*, 165.

[10] During preparation of the manuscript, Wang and co-workers have reported the catalytic atroposelective synthesis of chiral biaryls by chiral-thiourea-catalyzed ring opening of biaryl lactones. C. Yu, H. Huang, Y. Zhang, W. Wang, *J. Am. Chem. Soc.* **2016**, *138*, 6956.

[11] For selected examples of control of axial chirality by organocatalysts, see: a) S. Brandes, M. Bella, A. Kjarsgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1147; *Angew. Chem.* **2006**, *118*, 1165; b) S. Shirakawa, X. Wu, K. Maruoka, *J. Am. Chem. Soc.* **2012**, *134*, 916; c) S. Shirakawa, S. Liu, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 14200; *Angew. Chem.* **2013**, *125*, 14450; d) S. Lu, S.-B. Poh, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 11041; *Angew. Chem.* **2014**, *126*, 11221; e) G. Ma, J. Deng, M. P. Sibi, *Angew. Chem. Int. Ed.* **2014**, *53*, 11818; *Angew. Chem.* **2014**, *126*, 12012; f) S. Shirakawa, S. Liu, S. Kaneko, *Chem. Eur. J.* **2016**, *11*, 330; g) S. Shirakawa, X. Wu, S. Liu, K. Maruoka, *Tetrahedron* **2016**, *72*, 5163; h) J.-W. Zhang, J.-H. Xu, D.-J. Cheng, C. Shi, X.-Y. Liu, B. Tan, *Nat. Commun.* **2016**, DOI: 10.1038/ncomms10677; See also: i) H. Gao, Q.-L. Xu, C. Keene, M. Yousufuddin, D. H. Ess, L. Kürti, *Angew. Chem. Int. Ed.* **2016**, *55*, 566; *Angew. Chem.* **2016**, *128*, 576.

[12] For chiral phosphoric acid catalyzed asymmetric synthesis of chiral biaryls, see: a) G.-Q. Li, H. Gao, C. Keene, M. Devonas, D. H. Ess, L. Kürti, *J. Am. Chem. Soc.* **2013**, *135*, 7414; b) C. K. De, F. Pesciaioli, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 9293; *Angew. Chem.* **2013**, *125*, 9463; c) Y.-H. Chen, D.-J. Cheng, J. Zhang, Y. Wang, X.-Y. Liu, B. Tan, *J. Am. Chem. Soc.* **2015**, *137*, 15062; See also Refs. [6e,f,i].

[13] For a recent review on organocatalytic asymmetric synthesis of chiral biaryls, see: G. Bencivenni, *Synlett* **2015**, 1916.

[14] For asymmetric synthesis of chiral BINAMs by asymmetric kinetic-resolution-type transfer hydrogenation by means of chiral phosphoric acid, see: D.-J. Cheng, L. Yan, S.-K. Tian, M.-Y. Wu, L.-X. Wang, Z.-L. Fan, S.-C. Zheng, X.-Y. Liu, B. Tan, *Angew. Chem. Int. Ed.* **2014**, *53*, 3684; *Angew. Chem.* **2014**, *126*, 3758.

[15] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; *Angew. Chem.* **2004**, *116*, 1592; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356; For reviews on chiral phosphoric acid catalysis, see: c) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; d) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; e) S. J. Connon, *Angew. Chem. Int. Ed.* **2006**, *45*, 3909; *Angew. Chem.* **2006**, *118*, 4013; f) M. Terada, *Chem. Commun.* **2008**, 4097; g) M. Terada, *Synlett* **2010**, 1929; h) A. Zamfir, S. Schenker, M. Freund, S. M. Tsogoeva, *Org. Biomol. Chem.* **2010**, *8*, 5262; i) M. Terada, *Curr. Org. Chem.* **2011**, *15*, 2227; j) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539; k) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047. See also references cited therein.

[16] For pioneering work on chiral phosphoric acid catalyzed transfer hydrogenation, see: a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781; b) S. Hoffmann, A. Seayad, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424; *Angew. Chem.* **2005**, *117*, 7590; c) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84.

[17] Our group has recently developed chiral Brønsted acid catalyzed transfer hydrogenation of imines using benzothiazoline derivatives as hydrogen donors. See: a) C. Zhu, T. Akiyama, *Org. Lett.* **2009**, *11*, 4180; b) K. Saito, K. Horiguchi, Y. Shibata, M. Yamanaka, T. Akiyama, *Chem. Eur. J.* **2014**, *20*, 7616; c) C. Zhu, K. Saito, M. Yamanaka, T. Akiyama, *Acc. Chem. Res.* **2015**, *48*, 388; See Also: d) C. Zhu, J. R. Falck, *ChemCatChem* **2011**, *3*, 1850.

[18] CCDC 1445244, 1445245 contains the supplementary crystallographic data of compounds **s18** and **s19** (see the Supporting Information for details). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[19] Bringmann and co-workers reported that the configurational stability of tetrasubstituted biaryl-type hydroxy aldehyde was relatively high to suppress the required smooth racemization, see: a) G. Bringmann, T. Hartung, *Liebigs Ann. Chem.* **1994**, 313; b) G. Bringmann, B. Schöner, K. Peters, E.-M. Peters, H. G. von Schnering, *Liebigs Ann. Chem.* **1994**, 439; c) G. Bringmann, M. Breuning, *Synlett* **1998**, 634; d) G. Bringmann, M. Breuning, H. Endress, D. Vitt, *Tetrahedron* **1998**, *54*, 10677; e) G. Bringmann, D. Vitt, J. Kraus, M. Breuning, *Tetrahedron* **1998**, *54*, 10691, and see also refs. [7b,c].

[20] The effect of the lowering concentration is twofold: 1) the suppression of the background reaction, and 2) decreasing the reaction rate of transfer hydrogenation.

[21] Treatment of **5k** with 0.50 equiv of **10** and 0.55 equiv of **9b** under the optimal reaction conditions afforded **4k** in 48% with 5% *ee*, which clearly shows that kinetic resolution was not observed in the formation step of imine.

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