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A Continuously Regenerable Chiral Ammonia Borane for Asymmetric Transfer Hydrogenations

Qiwen Zhou,[a,b,c] Wei Meng,[a,c] Jing Yang,*[b] and Haifeng Du*[a]

Abstract: A novel chiral ammonia borane was designed and developed via the dehydrogenation of ammonia borane with chiral phosphoric acid, which was highly effective for the asymmetric transfer hydrogenation of imines and β-enamino esters to afford high levels of reactivities and enantioselectivies. Significantly, this chiral ammonia borane can be continuously regenerated during the transfer hydrogenation with the assistance of water and ammonia borane, which allowed as low as 0.1 mol % of chiral phosphoric acid to give satisfactory results. Notably, the role of chiral phosphoric acid is to produce the chiral ammonia borane.

Ammonia borane ($NH_3 \cdot BH_3$) has received substantial attention due to its unique features including low molecular weight, high hydrogen capacity, nice stability, and ready availability. Great progress has been achieved for its application as a solid hydrogen storage material.[1] In contrast, its use as the direct hydrogen source for reductions has been relatively less investigated.[2] Various metal-catalyzed or metal-free transfer hydrogenations have been reported.[3] Interestingly, Berke and co-workers discovered a catalyst-free transfer hydrogenation of aldimines with ammonia borane via concerted double hydrogen transfers (Figure 1). [4] However, asymmetric transfer hydrogenations with ammonia boranes have lagged behind. In 1984, Williams and co-workers utilized a chiral complex of ammonia borane and 18-crown-6 as a stoichiometric reagent for asymmetric reductions of ketones to give up to 67% ee (Figure 1).[5] Very recently, our group developed a frustrated Lewis pair (FLP)[6] of (*R*)-*tert*-butylsulfinamide and $HB(C_6F_5)_2$ for asymmetric transfer hydrogenations of imines[7] with ammonia borane as a hydrogen source for regeneration of the chiral FLP catalyst (Figure 1).[8] The development of highly efficient and enantioselective transfer hydrogenations is still in great demand.

Inspired by the work of Williams and Berke, it is highly probable and desirable to develop a regenerable chiral ammonia borane for asymmetric transfer hydrogenations. However, the formidable challenge lies in how to construct the chiral ammonia borane and how to make this chiral reagent continuously regenerable during the reaction process.

Chiral phosphoric acids (CPAs) have been widely used in the Brønsted acid catalysis.[9] In view of their strong acidity, we envision that the treatment of CPA **1** with ammonia borane is likely to lead a rapid release of H_2 to generate chiral ammonia boranes **2**, which further react with imines **3** to afford amines **4** and species **5**. CPA **1** is possibly regenerated by hydrolysis of species **5** to complete the reaction cycle (Scheme 1). Herein, we wish to report our preliminary results on this subject.

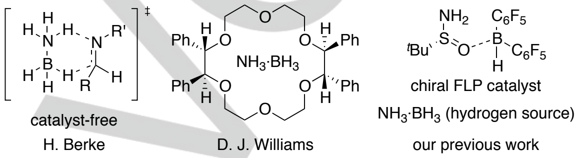
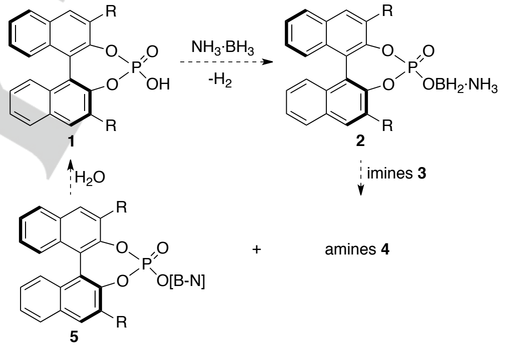
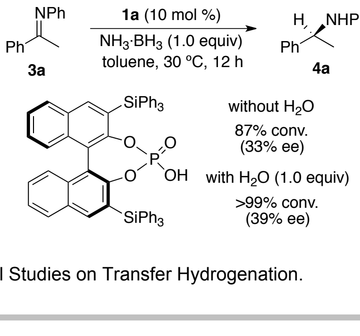


Figure 1. Examples with Ammonia Borane for Transfer Hydrogenations.



Scheme 1. Strategy for Developing Regenerable Chiral Ammonia Boranes.

CPA **1a** (10 mol %) was initially subjected to the transfer hydrogenation of imine **3a** with ammonia borane in toluene (Scheme 2). It was pleased to find that the addition of water (1.0 equiv) could improve both reactivity and enantioselectivity. Imines **3b**-**e** with different *N*-protecting groups were further examined, and 3,5-di(trifluoromethyl)phenyl group (**3e**) proved to be the optimal one to give 79% ee (Scheme 3). CPAs **1b**-**f** were next evaluated for the transfer hydrogenation of imine **3e**. Substituents at the 3,3'-positions of binaphthyl frameworks had a large impact on the ee values. To our delight, 93% ee with 94% conversion was obtained with the use of CPA **1f** (Scheme 3).



Scheme 2. Initial Studies on Transfer Hydrogenation.

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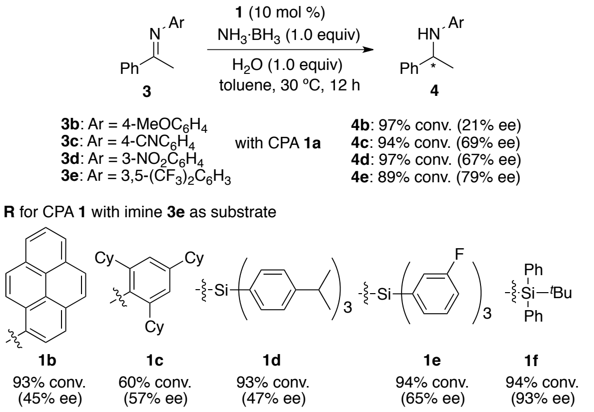


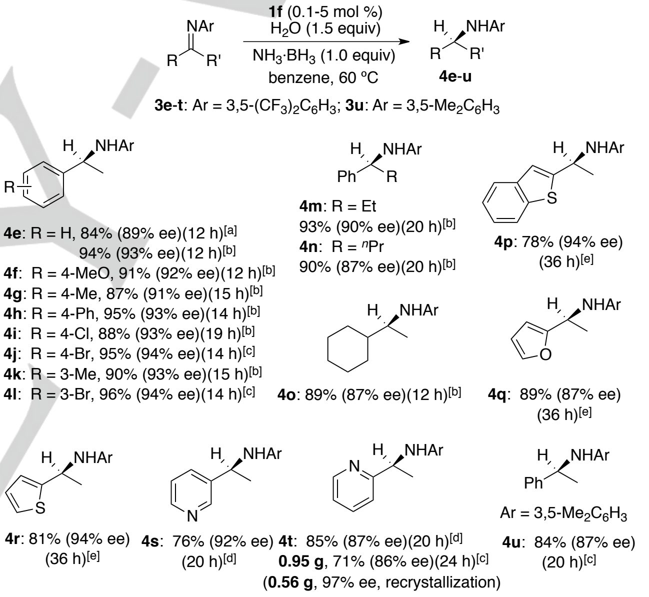
Scheme 3. Screen of Imines and Chiral Phosphoric Acids.

Table 1. Optimization of Reaction Conditions.[a]

Entry	**1f** [mol %]	Solvent	H_2O [equiv]	Temp. [°C]	Conv. [%][b]	Ee [%][c]
1	10	Toluene	1.0	30	94	93
2	10	*n*-Hexane	1.0	30	52	88
3	10	CH_2Cl_2	1.0	30	98	89
4	10	PhCl	1.0	30	96	92
5	10	Benzene	1.0	30	>99	93
6	10	THF	1.0	30	58	81
7	10	Toluene	0	30	67	81
8	10	Toluene	0.5	30	62	89
9	10	Toluene	1.5	30	>99	93
10	10	Toluene	2.0	30	>99	93
11	10	Toluene	5.0	30	>99	93
12	5	Toluene	1.5	60	95	93
13	2.5	Toluene	1.5	60	94	93
14	2.5	Benzene	1.5	60	>99	93
15	1.0	Benzene	1.5	60	98	93
16	0.5	Benzene	1.5	60	97	93
17	0.1	Benzene	1.5	60	89	90
18	0.1	Benzene	1.5	80	95	89
19[d]	0.5	Benzene	1.5	60	48	93

[a] All reactions were carried out with imine **3e** (0.10 mmol) in solvent (0.5 mL) for 12 h. [b] Determined by crude ^1H NMR. [c] The ee was determined by chiral HPLC. [d] $NH_3{\cdot}BH_3$ (0.5 equiv) was used.

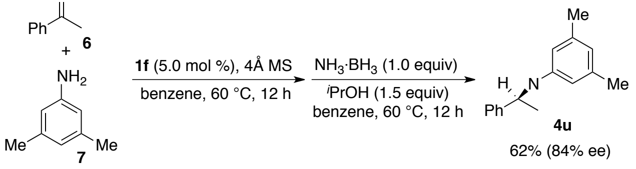
The reaction conditions for transfer hydrogenations of imine **3e** with CPA **1f** were subsequently optimized. Various solvents gave moderate to high conversions with 81-93% ee's (Table 1, entries 1-6). Toluene and benzene were more suitable solvents. Significantly, the amount of water had a large influence on both reactivity and enantioselectivity (Table 1, entries 1, 7-11). Without water, only 67% conversion with 81% ee was obtained (Table 1, entry 7). In contrast, with 1.5 equivalent of water, a quantitative conversion with 93% ee was afforded (Table 1, entry 9). Further increasing the amount of water gave similar results (Table 1, entries 10 and 11). When the CPA loading was reduced to 5 or 2.5 mol %, slightly lower conversions were obtained without loss of any enantioselectivities (Table 1, entries 12 and 13). Notably, the CPA loading can be lowered to 0.1 mol % with benzene as solvent at 60 °C to give amine **4e** in 89% conversion with 90% ee (Table 1, entries 14-17). Further raising the temperature to 80 °C gave a slightly higher conversion (Table 1, entry 18). Reducing the amount of ammonia borane to 0.5 equivalent gave 48% conversion. It suggests that only one hydride of chiral ammonia borane is likely utilized in the transfer hydrogenation (Table 1, entries 16 vs 19).



Scheme 4. Asymmetric Transfer Hydrogenation of Imines, CPA **1f** Loading: [a] 0.1 mol %. [b] 0.5 mol %. [c] 1.0 mol %. [d] 3.0 mol %. [e] 5.0 mol %.

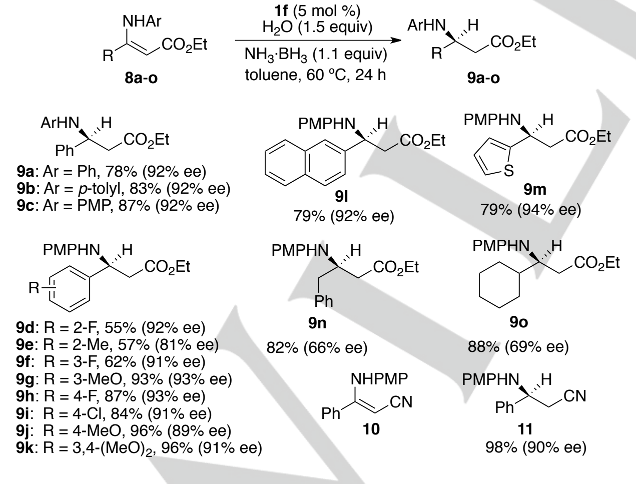
A variety of imines **3e**-**u** were subjected to asymmetric transfer hydrogenations under the optimal reaction conditions (Scheme 4). All these reactions proceeded smoothly to give the corresponding products **4e**-**u** in 76-96% yields with 87-94% ee's. The absolute configuration was tentatively assigned as *S* according to X-ray structure of compound **4h** (see Supporting Information).[10] 1-Cyclohexylethanone-derived imine **4o** gave a promising 87% ee. Imines **3p**-**r** bearing *O*- or *S*-heterocycles were suitable substrates to give amine products **4p**-**r** in 78-89% yields with 87-94% ee's. Notably, the transfer hydrogenation of imines **3s** and **3t** containing pyridinyl groups with 3 mol % of CPA **1f** gave amines **4s** and **4t** in high yields with 92% and 87% ee, respectively. The reaction of imine **3t** can be carried out in gram-scale with 1 mol % of CPA **1f** to afford the desired product

4t in 71% yield with 86% ee. After a recrystallization in the mixture of water and methanol, the ee was further improved to 97%. Moreover, imine **3u** with 3,5-dimethylphenyl *N*-protecting group was an effective substrate to give amine **4u** in 84% yield with 87% ee. Remarkably, a reductive amination of acetophenone (**6**) and 3,5-dimethylaniline (**7**) using 5 mol % of CPA **1f** with 4Å molecular sieves and isopropanol instead of water, can be successfully realized in a sequent one pot manner to give the desired product **4u** in 62% yield with 84% ee (Scheme 5).



Scheme 5. A Reductive Amination in Sequent One Pot Manner.

To extend the usage of this regenerable chiral ammonia borane, a variety of β-enamino esters **8a**-**o** were examined for the asymmetric transfer hydrogenation under a slightly modified reaction conditions (Scheme 6).[11] To our pleasure, all these reactions went smoothly to afford β-amino esters **9a**-**o** in 55-96% yields with 66-94% ee's. *N*-protecting groups had little impact on the enantioselectivity (**9a**-**c**). Both electron-withdrawing and donating substituents on the phenyl group were well tolerated for this reaction (**9d**-**k**). β-enamino esters **8n**-**o** bearing benzyl and cyclohexyl group were also effective substrates to give high yields but relatively lower ee's. Moreover, β-enamino cyanide **10** was a highly reactive substrate for this reaction to afford β-amino cyanide **11** in 98% yield with 90% ee.



Scheme 6. Asymmetric Transfer Hydrogenation of β-Enamino Esters and Cyanide.

Preliminary studies were conducted for a better insight into this reaction. H_2 was released rapidly when CPA **1f** was treated with ammonia borane (1.0 equiv), to give chiral ammonia borane **2f** cleanly (Figure 2b). A stoichiometric reaction of **2f** and imine **3e** resulted in the appearance of several P-signals which was attributed to the production of different [N-B] species (Figure 2c). Treating this mixture with water, most of these signals were converted to that of CPA **1f**, but some weak signals still left (Figure 2d). Subsequent addition of ammonia borane led a simple signal of chiral ammonia borane **2f** (Figure 2e). These results indicate that chiral ammonia borane is a reactive species, and both water and ammonia borane can efficiently promote its complete regeneration from a messy mixture.

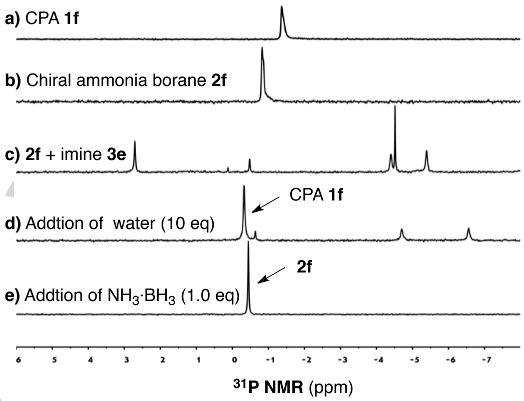
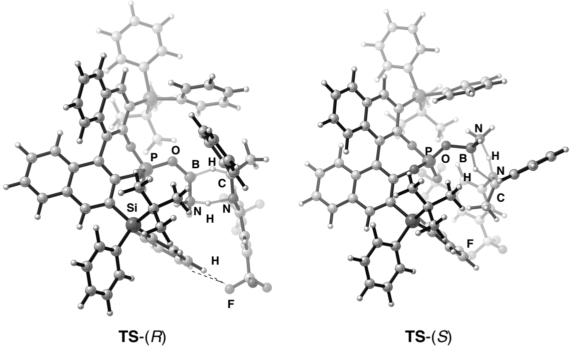


Figure 2. ^{31}P NMR Studies on the Transfer Hydrogenation (in benzene at room temperature).

The hydrogen transfer between chiral ammonia borane **2f** and imine **3e** was investigated by DFT calculations. Concerted 6-membered ring transition states **TS**-(*R*) and **TS**-(*S*) were located at the M06-2X/6-31G(d,p) level (Figure 2). A 1.7 Kcal/mol activation enthalpy difference in the gas phase predicts a 93% ee favored for (*S*)-isomer. It is highly consistent with the experimental result. For imine **3u**, the corresponding transition states were also located, which predicts a similar ee to the obtained one (see Supporting Information). Moreover, DFT calculation suggests that both water and ammonia borane can cleavage the O-B bond to regenerate CPA **1f** (see Supporting Information). But water seems to be a major contributor according to the obtained experimental results.



TS-(*R*) $\Delta\Delta H^{\neq}_{act} = 28.3$ Kcal/mol

TS-(*S*) $\Delta\Delta H^{\neq}_{act} = 26.6$ Kcal/mol

Figure 3. DFT Calculation for the Hydrogen Transfer Process.

Based on the experimental and theoretical mechanistic results, a plausible reaction cycle is outlined in Figure 4. CPA **1** quickly reacts with ammonia borane to release H_2 and form chiral ammonia borane **2**. Double hydrogen transfers occur via a concerted 6-membered ring transition state **TS**-(*S*) to produce amine **4** and species **5** (several [N-B] species). A followed hydrolysis of species **5** through a 4-membered ring transition state **TS1** regenerates CPA **1,** which further reacts with ammonia borane to reform the reactive chiral ammonia borane.

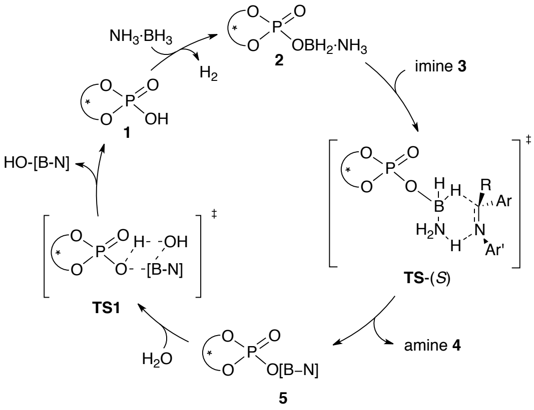


Figure 4. Plausible Reaction Cycle.

In summary, a novel and regenerable chiral ammonia borane was developed via a H_2 releasing reaction of ammonia borane and chiral phosphoric acid, which was a highly effective reductive reagent for asymmetric transfer hydrogenations. A wide range of amines and β-amino esters were obtained in 55-96% yields with 66-94% ee's. Significantly, this chiral ammonia borane can be efficiently and continuously regenerated during the transfer hydrogenation with the assistance of water and ammonia borane, which allowed as low as 0.1 mol % of chiral phosphoric acid to give satisfactory reactivities and enantioselectivities. Notably, herein, chiral phosphoric acid played a role as a simple Brønsted acid to generate the reactive chiral ammonia borane. Mechanistic studies suggest that the hydrogen transfer between chiral ammonia borane and imine occurs via a concerted 6-membered ring transition state. The unique features of this chiral ammonia borane make it a potentially useful chiral reagent for other asymmetric transfer hydrogenations.

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Keywords: asymmetric transfer hydrogenation • ammonia borane • chiral phosphoric acid • chiral ammonia borane • water

[1] For leading reviews, see: a) F. H. Stephens, V. Pons, R. T. Baker, *Dalton Trans.* **2007**, 2613-2626; b) T. B. Marder, *Angew. Chem. Int. Ed.* **2007**, *46*, 8116-8118; *Angew. Chem.* **2007**, *119*, 8262-8264; c) C. W. Hamilton, R. T. Baker, A. Staubitz, I. Manners, *Chem. Soc. Rev.* **2009**, *38,* 279-293; d) A. Staubitz, A. P. M. Robertson, I. Manners, *Chem. Rev.* **2010**, *110*, 4079-4124; e) Z. Huang, T. Autrey, *Energy Environ. Sci.* **2012**, *5*, 9257-9268; f) A. Rossin, M. Peruzzini, *Chem. Rev.* **2016**, *116*, 8848-8872.

[2] a) R. O. Hutchins, K. Learn, B. Nazer, D. Pytlewski, A. Pelter, *Org. Prep. Proced. Int.* **1984**, *16*, 335-372; b) A. Staubitz, A. P. M. Robertson, M. E. Sloan, I. Manners, *Chem. Rev.* **2010**, *110,* 4023-4078; c) O. Songis, C. S. J. Cazin, *Synlett* **2013**, *24*, 1877-1881.

[3] For selected examples, see: a) Y. Jiang, O. Blacque, T. Fox, C. M. Frech, H. Berke, *Organometallics* **2009**, *28*, 5493-5504; b) G. Ménard, D. W. Stephan, *J. Am. Chem. Soc.* **2010**, *132*, 1796-1797; c) C. C. Chong, H. Hirao, R. Kinjo, *Angew. Chem. Int. Ed.* **2014**, *53*, 3342-3346; *Angew. Chem.* **2014**, *126*, 3410-3414; d) S. Fu, N.-Y. Chen, X. Liu, Z. Shao, S.-P. Luo, Q. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 8588-8594; e) Q. Zhou, L. Zhang, W. Meng, X. Feng, J. Yang, H. Du, *Org. Lett.* **2016**, *18*, 5189-5191.

[4] a) X. Yang, L. Zhao, T. Fox, Z.-X. Wang, H. Berke, *Angew. Chem. Int. Ed.* **2010**, *49*, 2058-2062; *Angew. Chem.* **2010**, *122*, 2102-2106; b) X. Yang, T. Fox, H. Berke, *Chem. Commun.* **2011**, *47*, 2053-2055; c) X. Yang, T. Fox, H. Berke, *Org. Biomol. Chem.* **2012**, *10*, 852-860; d) X. Yang, T. Fox, H. Berke, *Tetrahedron* **2011**, *67*, 7121-7127; For a review, see: e) X. Yang, Z. Xie, J. He, L. Yu, *Chin. J. Org. Chem.* **2015**, *35*, 603-609.

[5] B. L. Allwood, H. Shahriari-Zavareh, J. F. Stoddart, D. J. Williams, *J. Chem. Soc., Chem. Commun.* **1984**, 1461-1464.

[6] For leading reviews, see: a) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46-76; *Angew. Chem.* **2010**, *122*, 50-81; b) T. Soós, *Pure Appl. Chem.* **2011**, *83*, 667-675; b) J. Paradies, *Angew. Chem. Int. Ed.* **2014**, *53*, 3552-3557; *Angew. Chem.* **2014**, *126*, 3624-3629; c) L. Shi, Y.-G. Zhou, *ChemCatChem* **2015**, *7*, 54-56; d) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2015**, *54*, 6400-6441; *Angew. Chem.* **2015**, *127*, 6498-6541; e) D. W. Stephan, *J. Am. Chem. Soc.* **2015**, *137*, 10018-10032; f) D. W. Stephan, *Acc. Chem. Res.* **2015**, *48*, 306-316; g) D. W. Stephan, *Science* **2016**, *354*, aaf7229; h) W. Meng, X. Feng, H. Du, *Acc. Chem. Res.* **2018**, *51*, 191-201.

[7] For selected reviews on asymmetric reduction of imines, see: a) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713-1760; b) Q.-A. Chen, Z.-S. Ye, Y. Duan, Y.-G. Zhou, *Chem. Soc. Rev.* **2013**, *42*, 497-511; c) J. H. Schrittwieser, S. Velikogne, W. Kroutil, *Adv. Catal. Synth.* **2015**, *357*, 1655-1685; d) M. Wills, *Top Curr. Chem.* **2016**, *374*, 14-49; e) B. Li, J.-B. Sortais, C. Darcel, *RSC Adv.* **2016**, *6*, 57603-57625; f) A. M. F. Phillips, A. J. L. Pombeiro, *Org. Biomol. Chem.* **2017**, *15*, 2307-2340; for recent examples on the metal-free asymmetric reduction of imines, see: g) V. N. Wakchaure, P. S. J. Kaib, M. Leutzsch, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 11852-11856; *Angew. Chem.* **2015**, *127*,12019-12023; h) D. Enders, A. Rembiak, B. A. Stöckel, *Adv. Synth. Catal.* **2013**, *355*, 1937-1942; i) M. R. Adams, C.-H. Tien, R. McDonald, A. W. H. Speed, *Angew. Chem. Int. Ed.* **2017**, *56*, 16660-16663; *Angew. Chem.* **2017**, *129*,16887-16890.

[8] a) S. Li, G. Li, W. Meng, H. Du, *J. Am. Chem. Soc.* **2016**, *138*, 12956-12962; b) S. Li, W. Meng, H. Du, *Org. Lett.* **2017**, *19*, 2604-2606.

[9] For selected reviews, see: a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999-1010; b) M. Terada, *Chem. Commun.* **2008**, 4097-4112; c) M. Terada, *Synthesis* **2010**, 1929-1982; d) J. Yu, F. Shi, L.-Z. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156-1171; e) M. Rueping, J. Dufour, F. R. Schoepke, *Green Chem.* **2011**, *13*, 1084-1105; f) C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498-2518.

[10] CCDC-1813490 contains the supplementary crystallographic data for **4h**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] For leading reviews on asymmetric reduction of enamino esters, see: a) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753-819; b) A. Weickgenannt, M. Oestreich, *ChemCatChem* **2011**, *3*, 1527-1529; c) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Soc. Rev.* **2012**, *41*, 4126-4139.

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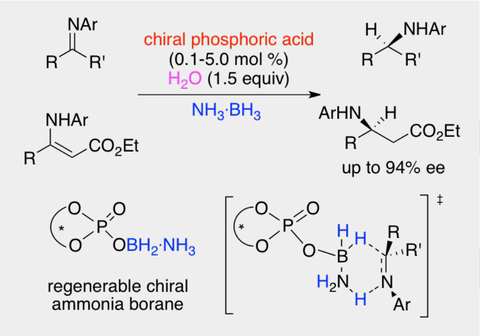
COMMUNICATION

A novel chiral ammonia borane was developed for asymmetric transfer hydrogenations to give high levels of yields and ee's. Significantly, this chiral ammonia borane can be continuously regenerated during the reaction with the assistance of water and ammonia borane, which allowed as low as 0.1 mol % of chiral phosphoric acid to give satisfactory results.



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