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A Frustrated Lewis Pair Catalyzed Asymmetric Transfer Hydrogenation of Imines Using Ammonia Borane

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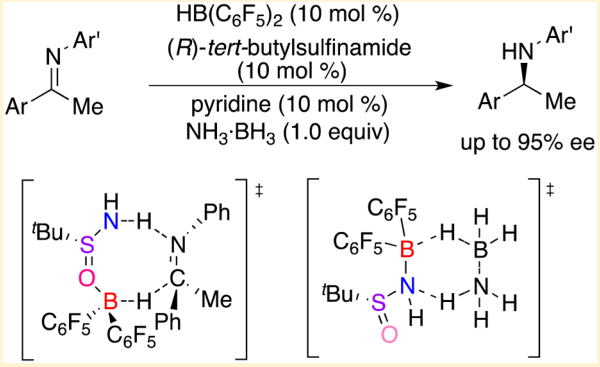
Supporting Information

ABSTRACT: Inspired by the zwitterion species generated from the splitting of H_2 by frustrated Lewis pairs, we put forward a novel frustrated Lewis pair by the combination of $H^{\delta-}$ and $H^{\delta+}$ incorporated Lewis acid and base together. Piers' borane and chiral *tert*-butylsulfinamide were chosen as the FLP, and a metal-free asymmetric transfer hydrogenation of imines was realized with high enantioselectivities. Significantly, with ammonia borane as hydrogen source, a catalytic asymmetric reaction using 10 mol % of Piers' borane, chiral *tert*-butylsulfinamide, and pyridine additive, has been successfully achieved to furnish optically active amines in 78−99% yields with 84−95% ee's. Experimental and theoretical mechanistic studies reveal an interesting 8-membered ring hydrogen transfer transition state and an expected regeneration of reactive species with ammonia borane. Accordingly, a plausible catalytic pathway for this reaction is depicted.



INTRODUCTION

The chemistry of frustrated Lewis pairs (FLPs) has experienced extremely rapid growth in the past decade and has become one of the most useful methodologies for the metal-free hydrogenations.[1,2] The H_2 splitting mechanism of FLPs involves an interaction between the vacant orbital of Lewis acid and the H−H σ-bonding orbital as well as a synergic interaction of the lone pair of Lewis base with the H−H σ^* antibonding orbital, generating proton and hydride, which can be transferred to unsaturated compounds (Figure 1). Since the first FLPs

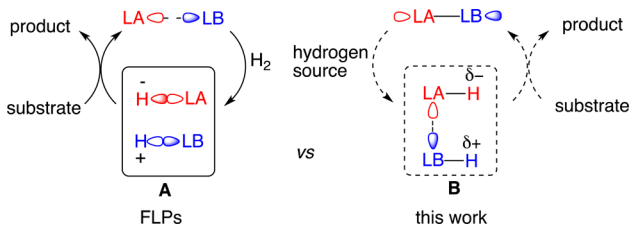


Figure 1. Our hypothesis for the FLP catalysis.

catalyzed metal-free hydrogenations reported by Stephan and co-workers in 2007,[3] a wide range of unsaturated compounds have been successfully hydrogenated under the catalysis of FLPs.[2] Significantly, in recent years, some important progresses have also been achieved for the challenging asymmetric hydrogenations.[4,5] As part of our general interest in exploring readily accessible FLPs, we developed an *in situ* borane generation strategy by the hydroboration of commercially available alkenes, chiral dienes, and chiral diynes with Piers' borane $HB(C_6F_5)_2$.[6] These boranes were highly effective for the stereoselective and/or enantioselective metal-free hydrogenations.[7]

Based on our previous work and inspired by the zwitterion species **A** containing both proton and hydride, we put forward a hypothesis to use species **B** instead of species **A** for the metal-free hydrogenation (Figure 1). In species **B**, $H^{\delta-}$ and $H^{\delta+}$ are originally incorporated in Lewis acid and base, respectively. After the hydrogen transfer, a covalent bond will form between Lewis acid and base. To realize this hypothesis, two key issues must be fulfilled: the matched Lewis pair without rapid releasing of H_2 itself and the regeneration of reactive species from the bonding Lewis acid and base with hydrogen sources. Moreover, the choice of effective chiral Lewis acid or base is also crucial for the asymmetric hydrogenation.

Ammonia borane $NH_3{\cdot}BH_3$ is an ideal hydrogen source which has been intensively studied as hydrogen storage materials for its high storage capacity (19.6% weight H) and small molecular weight (30.87 g/mol).[8] Notably, ammonia borane is also widely used in synthetic chemistry as a reagent due to its stability and easy handling, which can provide both proton and hydride.[9] For example, with ammonia borane, Stephan and co-workers reported a FLPs catalyzed reduction of

Received: July 13, 2016
Published: September 8, 2016

DOI: 10.1021/jacs.6b07245
J. Am. Chem. Soc. 2016, 138, 12956−12962

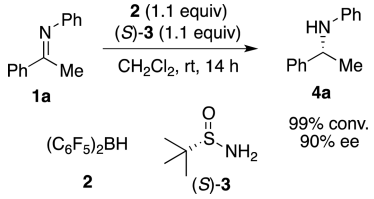
CO_2,[9a] Berke and co-workers described the hydrogenation of imines, polarized olefins, and carbonyl compounds,[9b−e] Kinjo, Hirao, and co-workers reported a 1,3,2-diazaphospholene-catalyzed transfer hydrogenation of N═N bond,[9g] and Liu, Luo, and co-workers reported a cobalt-catalyzed transfer hydrogenation of alkynes.[9i] Despite these advances, to the best of our knowledge, the asymmetric reduction reaction with ammonia borane as a hydrogen source has rarely been reported. In 1984, Williams and co-workers described an asymmetric reduction of imines with complexes of ammonia borane and chiral 18-crown-6 derivatives to give up to 67% ee.[10] The development of highly enantioselective reactions with ammonia borane is therefore a challenging and interesting subject.

Chiral *tert*-butylsulfinamide has a wide application as auxiliaries[11] or coordinating moieties in chiral ligands.[12] It possesses adjacent N, O, and S Lewis base centers, appropriate steric hindrance, and weak N−H acidity, which will well-fulfill the requirements of Lewis base in the proposed FLP. Piers' borane $HB(C_6F_5)_2$[13] is a suitable Lewis acid candidate due to its strong Lewis acidity, good hydride nucleophilicity, and appropriate steric hindrance. Herein, we wish to report our efforts on the asymmetric transfer hydrogenation[14] of imines using chiral *tert*-butylsulfinamide and Piers' borane as a FLP with ammonia borane as a hydrogen source.

RESULTS AND DISCCUSSION

Stoichiometric Asymmetric Transfer Hydrogenation of Imines. Initially, the transfer hydrogenation of imine **1a** was carried out using Piers' borane **2** (1.1 equiv) and (*S*)-*tert*-butylsulfinamide (**3**) (1.1 equiv) in CH_2Cl_2 at room temperature for 14 h (Scheme 1). To our pleasure, desired product **4a**

Scheme 1. Initial Study on the Asymmetric Transfer Hydrogenation of Imine

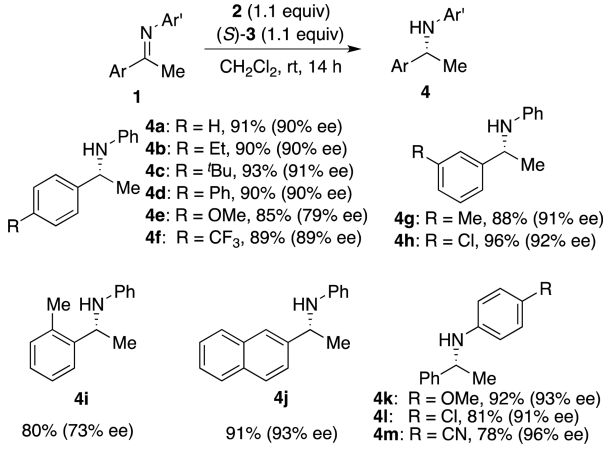


was obtained in a quantitative conversion with 90% ee. Using $BH_3{\cdot}SMe_2$ or catecholborane instead of Piers' borane led to racemic products. When a benzyl group was introduced to sulfinamide **3**, amine **4a** was obtained as a racemate in 86% conversion.

A variety of imines **1a−m** were next subjected to the stoichiometric asymmetric transfer hydrogenations. As shown in Scheme 2, all these reactions proceeded smoothly to furnish products **4a−m** in 78−96% yields with 73−96% ee's. Both electron-withdrawing and -donating substituents at the *para*- and *meta*- positions were well-tolerant, but *ortho*-substituted imine **1i** gave an obvious lower yield and ee. Imines **1k−m** with different protecting groups on the nitrogen atoms were also effective substrates.

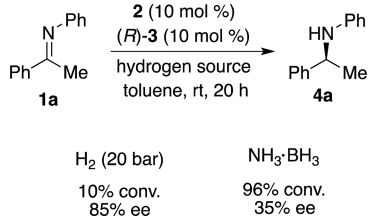
Catalytic Asymmetric Transfer Hydrogenation of Imines. After accomplishment of the stoichiometric reaction, we further devoted our efforts to the catalytic asymmetric transformation. The transfer hydrogenation of imine **1a** was re-examined using Piers' borane **2** (10 mol %) and (*R*)-*tert*-butylsulfinamide **3** (10 mol %) in toluene with H_2 (20 bar) and

Scheme 2. Asymmetric Transfer Hydrogenation of Imines Using FLPs



ammonia borane (1.0 equiv) as hydrogen sources, respectively (Scheme 3). Only 10% conversion was obtained with H_2.

Scheme 3. Catalytic Asymmetric Transfer Hydrogenation of Imine with Hydrogen Sources



Further raising the temperature to 100 °C and the H_2 pressure to 60 bar led a similar conversion, which suggests that H_2 was not an effective hydrogen source for the regeneration of reactive species. In contrast, the reaction with ammonia borane as a hydrogen source went well to give amine **4a** in 96% conversion with a dramatic loss of enantioselectivity, indicating that there were other pathways involved besides the chiral catalyst-controlled transformation.

To avoid these side reactions, further optimization of reaction conditions was conducted. Increasing the amount of sulfinamide **3** from 10 to 20 mol % resulted in a higher ee (Table 1, entry 1). Both solvents and reaction concentration had impacts on the enantioselectivities, and toluene was the optimal solvent (Table 1, entries 1−6). Interestingly, subjecting ammonia borane 12 h later to the reaction mixture of imine **1a**, **2**, and **3** gave a little higher ee than that of the addition of all materials in one portion (Table 1, entry 6 vs 7). A possible explanation is that this process inhibited the racemic reaction of imine with ammonia borane catalyzed by free Piers' borane **2**. The protecting groups on the nitrogen atoms were also investigated, and 4-CNC_6H_4 protecting group gave 78% ee (Table 1, entries 8−10). The ee can be improved to 83% at the concentration of 0.05 M (Table 1, entry 11). The effect of additives (10 mol %) was subsequently studied (Table 1, entries 12−15). It is noteworthy that 90% ee was obtained with pyridine as an additive (Table 1, entry 12). Significantly, the loading amount of **3** can be reduced to 10 mol % without any loss of ee value (Table 1, entry 15). Overall, the reaction of imine **1m** using 10 mol % Piers' borane **2**, sulfinamide **3**, and

DOI: 10.1021/jacs.6b07245
J. Am. Chem. Soc. 2016, 138, 12956−12962

Table 1. Optimization of Reaction Conditions[a]

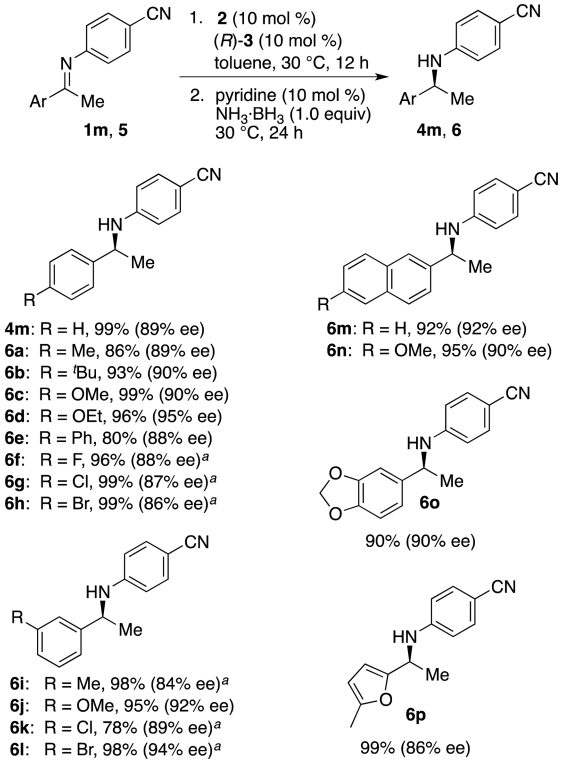
entry	imine	method	additive	solvent	conc. (M)	conv. (%)[b]	ee (%)[c]
1	**1a**	A		toluene	0.1	>99	56
2	**1a**	A		hexane	0.1	56	42
3	**1a**	A		mesitylene	0.1	97	51
4	**1a**	A		C_6H_5F	0.1	>99	43
5	**1a**	A		CH_2Cl_2	0.1	>99	42
6	**1a**	A		toluene	0.2	>99	60
7	**1a**	B		toluene	0.2	>99	69
8	**1k**	B		toluene	0.2	>99	69
9	**1l**	B		toluene	0.2	>99	74
10	**1m**	B		toluene	0.2	>99	78
11	**1m**	B		toluene	0.05	90	83
12	**1m**	C	pyridine	toluene	0.05	96	90
13	**1m**	C	Et_3N	toluene	0.05	95	89
14	**1m**	C	aniline	toluene	0.05	83	67
15[d]	**1m**	C	pyridine	toluene	0.05	87	91
16[d,e]	**1m**	C	pyridine	toluene	0.05	99	92

[a]All reactions were carried out with imines (0.10 mmol), Piers' borane **2** (0.01 mmol), (*R*)-*tert*-butylsulfinamide **3** (0.02 mmol), and ammonia borane (0.10 mmol) at room temperature for 24 h according to the following methods: (A) All materials were subjected in one portion. (B) Imine, **2**, and **3** were subjected and stirred for 12 h before addition of ammonia borane. (C) Imine, **2**, and **3** were subjected and stirred for 12 h before addition of ammonia borane and additive (10 mol %). [b]Determined by crude ^{1}H NMR. [c]Determined by chiral HPLC. [d](*R*)-*tert*-Butylsulfinamide **3** (0.01 mmol) was used. [e]At 30 °C.

pyridine was carried out at 30 °C to produce amine **4m** in 99% conversion with 92% ee (Table 1, entry 16).

Under optimal conditions, the substrate scope was studied for the catalytic asymmetric transfer hydrogenations. As shown in Scheme 4, a variety of imines **1m** and **5a**–**p** were suitable substrates to furnish the desired products in 78–99% yields with 84–95% ee's. Both electron-withdrawing and -donating substituents were well-tolerated. Imine **5p** containing 2-furyl

Scheme 4. Asymmetric Transfer Hydrogenation of Imines[a]

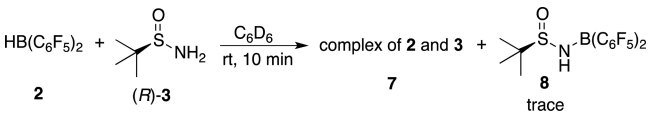


[a]With 20 mol % of **2** and **3**.

was also effective for this reaction to give the corresponding product **6p** in 99% yield with 86% ee.

Mechanistic Study. The interesting results for the transfer hydrogenation of imines encouraged us to investigate the mechanism by experiments and theoretical calculations. An NMR study on the mixture of Piers' borane **2** and sulfinamide **3** in C_6D_6 showed that complex **7** was formed completely with a trace amount of dehydrogenation product **8** (Scheme 5). Notably, the dehydrogenation process was slow, and a 60% conversion was observed after 18 h, which well fulfills the requirement of our hypothesis.

Scheme 5. NMR Study on the Mixture of 2 and 3



The interaction of Piers' borane **2** and sulfinamide **3** may lead to three possible isomers (Figure 2). Their thermodynamic

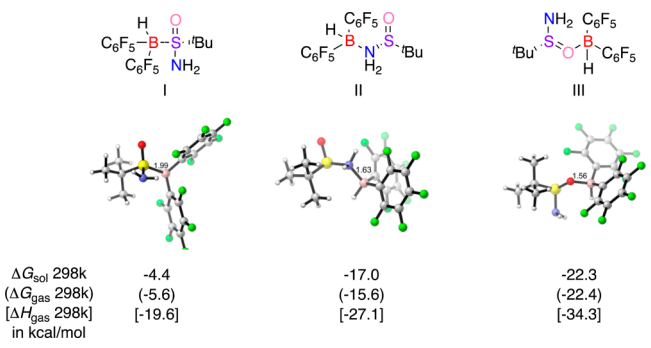


Figure 2. Thermodynamic stabilities of complexes **7**. Selected bond distances are given in Å; relative Gibbs free energies and enthalpies calculated at 298.15 K and 1.0 atm in toluene (with respect to that of the reactants) are given.

DOI: 10.1021/jacs.6b07245
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stabilities are tested utilizing M06-2X method[15] on the 6-31G(d) level.[16] It is indicated that in the toluene solution the formation of corresponding complexes **7** is exothermic in terms of enthalpy. After taking the solvent effects into consideration, the computed free energies of B/S (**I**) and B/N (**II**) species are −4.4 and −17.0 kcal/mol, respectively, and that of the B/O coordinated species **III** lies 5.3 kcal/mol below, indicating the preference of forming the B/O complex (Figure 2). The B−O distance is 1.56 Å, which is longer than the single bond (1.50 Å)[17] but shorter than the sum of corresponding van der Waals radius (3.41 Å).[18] A quantitative Laplacian bond order analysis,[19] which is a definition of covalent bond order rather than total bond order and noncovalent interactions thus have no contribution, depicts that the bond order of B−O is 0.041, suggesting a primary contribution of coordinate bonding. Moreover, the electrostatic potential computation also supports the preference of forming the B/O complex (see Figure S3).

To explore the possible reactive species, the reaction process of imine **1a** with Piers' borane **2** (1.0 equiv) and sulfinamide **3** (1.0 equiv) in C_6D_6 was monitored by ^{11}B NMR spectroscopy (Figure 3). It was found that the signal for complex **7** gradually

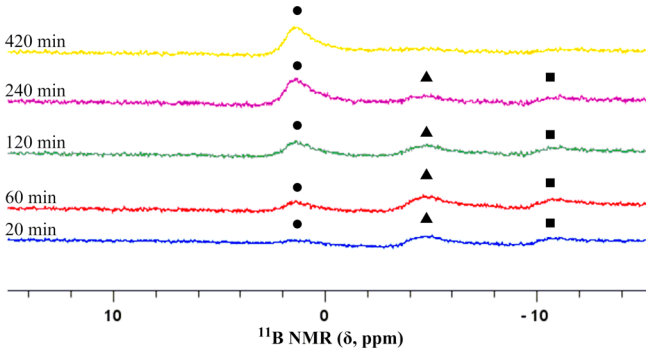


Figure 3. NMR study on stoichiometric reaction of imine **1a** (0.05 mmol), $HB(C_6F_5)_2$ **2** (0.05 mmol), and (*R*)-*tert*-butylsulfinamide **3** (0.05 mmol) in C_6D_6 (0.5 mL) at room temperature: ●, compound **8** (δ = 1.3 ppm); ▲, complexes **7** (δ = −4.8 ppm); and ■, complexes of $HB(C_6F_5)_2$ **2** and imine (δ = −11.2 ppm).

decreased, while the signal for compound **8** gradually increased with extension of time, which indicates that complex **7** is likely a reactive species and that compound **8** is generated from the reaction of imine and complex **7**. Moreover, a complex of imine **1a** and Piers' borane **2** was also observed, which may lead a racemic reaction.

DFT calculation is next conducted for the stoichiometric asymmetric transfer hydrogenation. As shown in Figure 4, (*R*)-*tert*-butylsulfinamide **3** complexes with Piers' borane **2** to form complex **7** with a reaction enthalpy of −34.3 kcal/mol in gas phase and a reaction free energy of −22.3 kcal/mol in toluene, which indicates that this process is thermodynamically favorable. Then, complex **7** binds with imine **1a**, and hydrogen transfer occurs via a 8-membered ring transition state **TS1** to generate amine **4a** and compound **8**, which is very similar to the concerted mechanism involving a six-membered transition state in the transfer hydrogenation of imines with ammonia borane reported by Berke and co-workers.[9b] A 1.5 kcal/mol energy difference between **TS1**-(*S*) and **TS1**-(*R*) predicts a 86% ee favored for (*S*)-isomer, which is in good accordance with the experiment result (90% ee). An atoms-in-molecules (AIM) analysis[20] shows that there involve some weak interactions, for example, H−F interactions between hydrogens

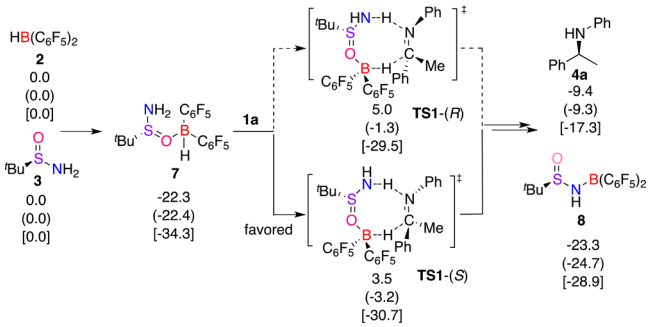


Figure 4. DFT calculated reaction profile for the stoichiometric asymmetric transfer hydrogenation of imines. Relative Gibbs free energies and enthalpies are calculated at 298.15 K and 1.0 atm in toluene.

of Me or *t*-Bu and fluorines of C_6F_5 in **TS1** (for detailed analysis, see Supporting Information). Moreover, the $\pi-\pi$ stacking between Ph and C_6F_5 is also likely to exist. These weak interactions make the conformations of **TS1** rigid enough for the enantiofacial discrimination despite the fact that the *t*-Bu group is remote from the C═N bond.

A ^{11}B NMR study was carried out by treating compound **8** with 1 equiv of ammonia borane in C_6D_6. As shown in Figure 5,

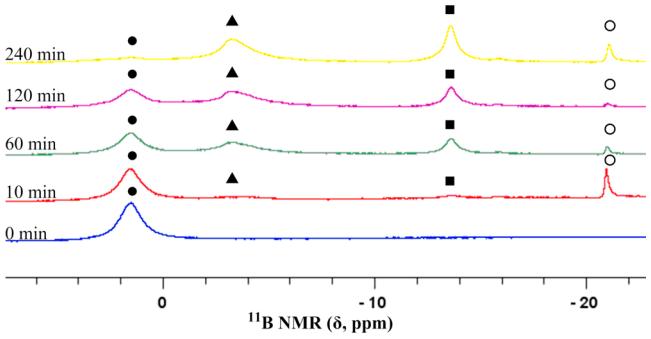


Figure 5. NMR study on reaction of ammonia borane (0.05 mmol) with **8** (0.05 mmol) in C_6D_6 at room temperature: ●, compound **8** (δ = 1.5 ppm); ▲, complexes **7** (δ = −3.4 ppm); ■, undetermined compounds; and ○, ammonia borane (δ = −21.0 ppm).

the signal of compound **8** gradually decreased, and the signal of complex **7** gradually increased with extension of time, which suggests that species **7** can be regenerated by the reaction of compound **8** with ammonia borane. Further DFT computational study indicates that the reaction of compound **8** with ammonia borane occurs in a concerted mechanism involving six-membered transition state **TS-1** with an activating Gibbs free energy of 14.4 kcal/mol (Figure 6). The B/N complex is formed and then converted to more stable B/O complex **7**. The calculation agrees with the observation on ^{11}B NMR spectra.

Then, compound **8** (10 mol %) was subjected to the reaction of imine **1a** with sulfinamide **3** (10 mol %) and ammonia borane (1.0 equiv). As shown in Scheme 6, amine **4a** was obtained in a quantitative conversion with 72% ee agreeing with the previous result (69% ee, Table 1, entry 7), which demonstrates that complex **7** can be regenerated from compound **8** and serve as an active species. Compound **9**, a dimer of compound **8**, can be observed in the catalytic reaction despite its very limited amount. The X-ray structure of compound **9** (Figure 7) provides an additional clue for the determination of the structure of compound **8**. When

DOI: 10.1021/jacs.6b07245
J. Am. Chem. Soc. 2016, 138, 12956−12962

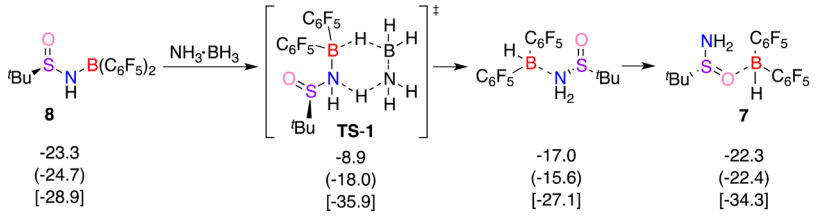
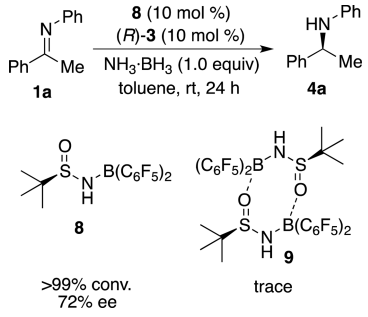


Figure 6. DFT computation on the reaction of **8** with ammonia borane. Free energies and enthalpies are calculated at 298.15 K and 1.0 atm in toluene.

Scheme 6. Control Experiments on Reduction of Imine 1a



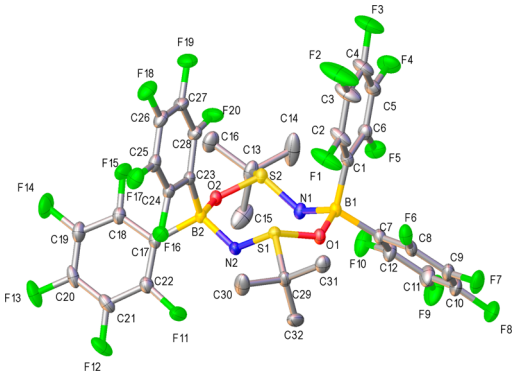


Figure 7. X-ray structure of **9**.

compound **9** was subjected to this reaction, no desired product was observed, which indicates that compound **9** cannot react with ammonia borane due to its stability (Scheme 6).

The possibility that compound **8** plays a role as a chiral Brønsted acid catalyst is also investigated by the DFT computation. As shown in Figure 8, by treating complex **10** with ammonia borane, a concerted and asynchronous hydrogen transfer occurs via a 6-membered ring transition state **TS2** with an activating Gibbs free energy of 29.0 kcal/mol. The 0.5 kcal/mol energy difference between **TS2**-(*R*) and **TS2**-(*S*) predicts 40% ee in favor of (*S*)-isomer, which is much lower than the experimental result. Notably, compound **8** can react with ammonia borane to generate complex **7**, which will further diminish the possibility of compound **8** as a Brønsted acid catalyst. Moreover, as a Lewis base, the pyridine additive might also partially inhibit this low enantioselective pathway by a competitive interaction with compound **8**. Overall, although this Brønsted acid catalysis pathway cannot be completely precluded at the current stage, it is not likely to be a major pathway for the catalytic reaction.

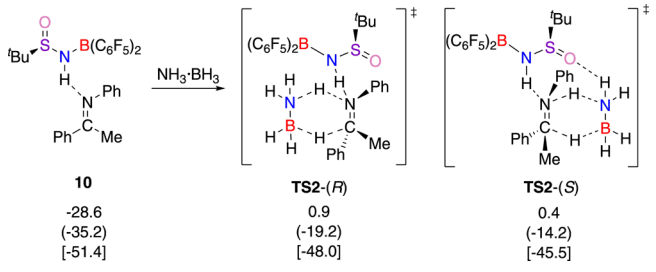
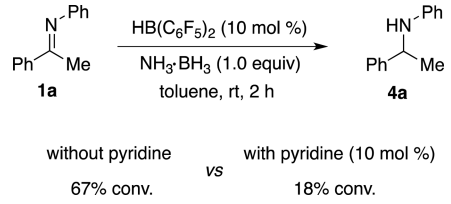


Figure 8. DFT computation on the acid-catalyzed reduction. Free energies and enthalpies are calculated at 298.15 K and 1.0 atm in toluene.

An NMR study indicates that a complex of pyridine with Piers' borane **2** can be formed rapidly. Control experiments were next conducted to explore the possible role of pyridine additive. As shown in Scheme 7, without pyridine additive, 67% conversion was obtained in 2 h. In sharp contrast, in the presence of pyridine (10 mol %), only 18% conversion was obtained. One possible role of pyridine is to trap free Piers' borane and inhibit the racemic reaction.

Scheme 7. Control Experiments on the Role of Pyridine Additive



Based on the experiment results and the fact that complex **7** can be generated when compound **8** and ammonia borane coexist, the mechanism with complexes **7** as reactive species is preferred. A probable catalytic pathway is outlined as shown in Figure 9. Piers' borane **2** and sulfinamide **3** form a complex **7** (our proposed FLP), which binds with imines followed by the hydrogen transfer via a 8-membered ring transition state **TS** to generate amine product and compound **8**. Complex **7** is regenerated by the reaction of compound **8** with ammonia borane to complete a catalytic cycle.

CONCLUSIONS

A metal-free asymmetric transfer hydrogenation of imines using a combination of Piers' borane and chiral *tert*-butylsulfinamide as a novel frustrated Lewis pair has been realized to furnish the desired products in high yields with up to 95% ee. Significantly, a further step on the catalytic transformation has been successfully achieved using Piers' borane (10 mol %), chiral *tert*-butylsulfinamide (10 mol %), and pyridine additive (10 mol %) with ammonia borane as hydrogen source. A variety of optically active amines were obtained in 78−99% yields with 84−95% ee's. Notably, this work represents the first highly

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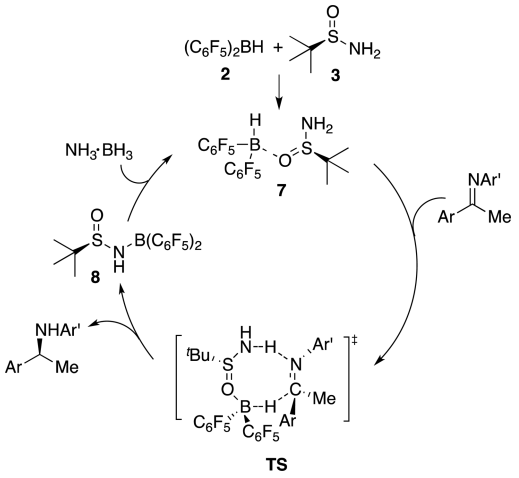

Figure 9. Plausible catalytic pathway.

enantioselective reaction using ammonia borane as hydrogen source. Mechanistic studies by experiments and theoretical calculations indicate that Piers' borane can complex with chiral *tert*-butylsulfinamide to form a reactive FLP, which binds with imine substrates to lead hydrogen transfer via a 8-membered ring transition state to produce amines. Furthermore, the resulting dehydrogenation product of Piers' borane and chiral *tert*-butylsulfinamide reacts with ammonia borane to regenerate the reactive FLP. We believe that the current work will be of broad synthetic and mechanistic interest for chemists. Further efforts on the application of this novel frustrated Lewis pair for other asymmetric transfer hydrogenations are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07245.

Procedure for transfer hydrogenation of imines and experimental mechanistic study, computational details and data for DFT calculations, determination of enantiomeric excesses, and characterization of products along with NMR spectra (PDF)

Crystallographic informatino file for compound **9** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (21222207, 21572231, and 21521002).

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J. Am. Chem. Soc. 2016, 138, 12956−12962