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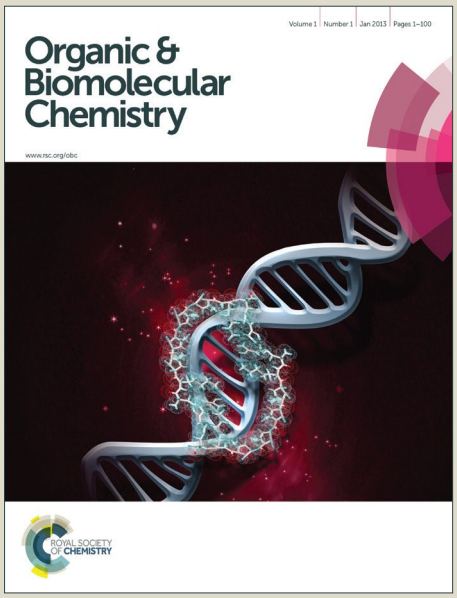

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A metal-free hydrogenation of 3-substituted 2*H*-1,4-benzoxazines

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A metal-free hydrogenation of 3-substituted 2*H*-1,4-benzoxazines has been successfully realized with 2.5 mol % of $B(C_6F_5)_3$ as catalyst to furnish a variety of 3,4-dihydro-2*H*-1,4-benzoxazines in 93-99% yields. Up to 42% ee was also achieved for the asymmetric hydrogenation with the use of chiral diene and $HB(C_6F_5)_2$.

Since the seminal discovery of frustrated Lewis pairs (FLPs) for their reversible activation of H_2 and application in the catalytic hydrogenation of imines,[1] the lately emerging chemistry of FLPs has witnessed an extremely rapid growth in the past decade.[2] A broad range of unsaturated compounds have proven to be effective substrates for the FLPs-catalyzed metal-free hydrogenations.[2] In particular, in recent several years, some significant advances have been made for the asymmetric hydrogenations with chiral FLP catalysts.[3,4] Imines derived from aldehydes or ketones with various amines were one type of most often studied substrates in this field, and numerous FLPs were efficient for their transformations.[5] Moreover, some imine analogues were also investigated for the hydrogenations. For example, in 2011, Stephan and co-workers reported a $B(C_6F_5)_3$-catalyzed metal-free hydrogenation of ethane-1,2-diimines.[6] Recently, our group described a highly *cis*-selective hydrogenation of vicinal diimines.[7] In 2014, Oestreich and Mohr reported a $B(C_6F_5)_3$-catalyzed hydrogenation of oxime ethers without cleavage of the N-O bond.[8] Very recently, the same group successfully extended the substrate scope to hydrazones.[9] Despite these advances, to the best of our knowledge, cyclic imines have seldom been employed for the FLPs-catalyzed hydrogenations, especially for the asymmetric reactions, which will produce highly desirable nitrogen-containing heterocycles.

3,4-Dihydro-2*H*-1,4-benzoxazines are important moieties widely present in biologically and medicinally active compounds such as Obscurinervidine, Niblinine, and Levofloxacin.[10] The hydrogenation of 2*H*-1,4-benzoxazines provides a powerful and straightforward approach for their synthesis. Great progress has been made for the transition-metal catalyzed hydrogenations and the organocatalytic asymmetric transfer hydrogenations.[11,12] However, the metal-free catalytic hydrogenation of the 3-substituted 2*H*-1,4-benzoxazines using H_2 has rarely been reported.

As part of our general interest in the metal-free FLP catalysis, we have developed an *in situ* borane generation strategy by the hydroboration of commercially available alkenes, chiral dienes, and chiral diynes with Piers' borane, which were highly effective for the stereoselective and/or enantioselective hydrogenations of imines, aromatic nitrogen-containing heterocycles, and silyl enol ethers.[13-15] In searching for novel substrates for the FLP catalysis, we devoted our efforts on the hydrogenation of 2*H*-1,4 benzoxazines. Herein, we wish to report our preliminary results on this subject.

A metal free hydrogenation of 1,4-benzoxazines **1a** using $B(C_6F_5)_3$[16] (10 mol %) under H_2 (10 bar) in toluene at room

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Electronic Supplementary Information (ESI) available: Procedure for the metal-free hydrogenation of 1,4-benzoxazines and the asymmetric reaction, characterization of the substrates and products along with the NMR spectra. See DOI: 10.1039/x0xx00000x

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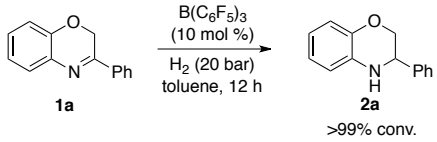
temperature was conducted initially. As shown in Scheme 1, this reaction went smoothly to give the desired product **2a** in a quantitative conversion. Various reaction conditions were next optimized. 5 mol % of $B(C_6F_5)_3$ was effective enough for this reaction (Table 1, entry 1). Further reducing the catalyst loading to 2.5 mol % gave a slight lower conversion (Table 1, entry 2). But no reaction occurred at room temperature or 50 °C with 1 mol % of catalyst (Table 1, entry 3). Raising the temperature to 50 °C, a complete conversion of 1,4-benzoxazine **1a** was obtained with only 2.5 mol % of $B(C_6F_5)_3$ (Table 1, entry 4). The reaction under H_2 (10 bar) gave product **2a** in 85% conversion (Table 1, entry 6). Solvents were found to influence this reaction largely, and toluene was an optimal solvent (Table 1, entries 4, 7-11).



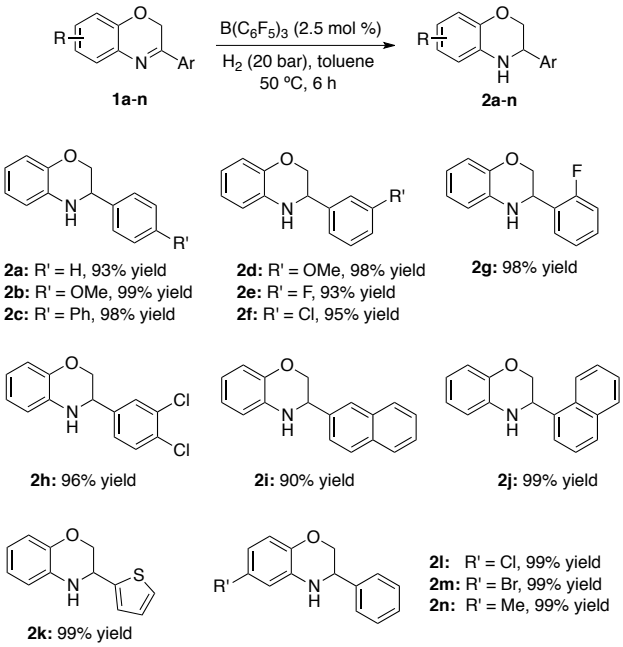
Scheme 1 Metal-free hydrogenation of 1,4-benzoxazine **1a**.

Table 1 Optimization of reaction conditions [a]

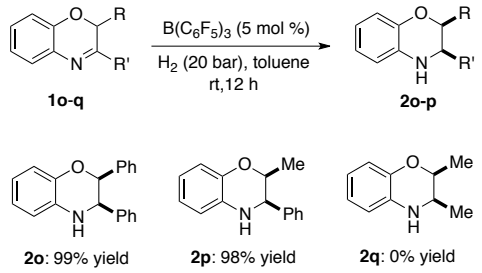
Entry	$B(C_6F_5)_3$ (mol %)	Solvent	Temp (°C)	Time (h)	Conv (%)[b]
1	5.0	Toluene	25	6	>99
2	2.5	Toluene	25	24	84
3	1.0	Toluene	25	24	NR[c]
4	2.5	Toluene	50	6	>99
5	1.0	Toluene	50	24	NR[c]
6[d]	2.5	Toluene	50	6	85
7	2.5	C_6H_5F	50	6	92
8	2.5	C_6H_5Cl	50	6	90
9	2.5	CH_2Cl_2	50	6	83
10	2.5	THF	50	6	5
11	2.5	Hexane	50	6	78

[a] All the reactions were carried out with 1,4-benzoxazine **1a** (0.10 mmol) in solvent (1.0 mL) under H_2 (20 bar) unless otherwise noted. [b] The conversion was determined by crude ^{1}H NMR. [c] No reaction. [c] H_2 (10 bar).

The substrate scope was subsequently investigated by subjecting a variety of 1,4-benzoxazines **1a**-**n** into the metal-free hydrogenations. As shown in Scheme 2, all these reactions proceeded efficiently to furnish 3,4-dihydro-2*H*-1,4-benzoxazines **2a**-**n** in 93-99% yields. Electron-withdrawing and donating substituents at the *para*- and *meta*-positions of phenyl groups were well tolerant. Naphthyl and thienyl substituted 2*H*-1,4-benzoxazines **1i**-**k** were also suitable substrates for this reactions. When employing 1,4-benzoxazines **1i**-**n** with substituents at the 6-positions as substrates, the desired products **1l**-**n** can be obtained in 99% yield. Interestingly, 3,4-disubstituted 1,4-benzoxazines **1o** and **1p** were effective substrates to give the corresponding *cis* products **2o** and **2p** as single isomers (Scheme 3). The structure of **2o** was determined by the X-ray diffraction (Figure 1). However, 2,3-dimethyl 2*H*-1,4-benzoxazine **1q** was an inert substrate for this transformation, which might be attributed to the relatively less bulky steric hindrance.



Scheme 2 Metal-free hydrogenation of 1,4-benzoxazines.



Scheme 3 Metal-free hydrogenation of 3,4-disubstituted 1,4-benzoxazines.

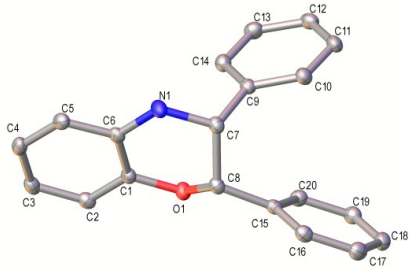


Figure 1 X-ray structure of compound **2o**.

With these results in hand, we moved on our attention to the asymmetric reactions, and a variety of chiral dienes

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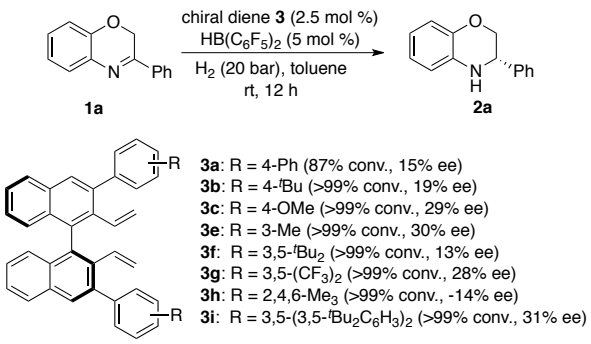
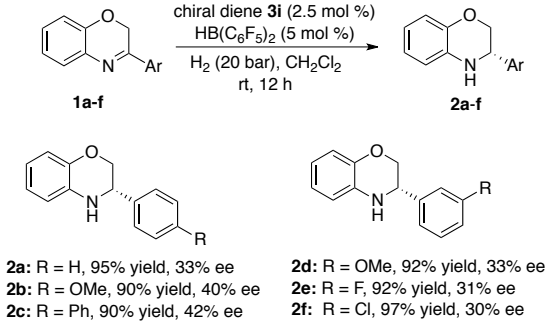
3a-**i** were evaluated for the asymmetric hydrogenation of 1,4-benzoxazine **1a** at room temperature. As shown in Scheme 4, all these reactions went with high reactivities, but gave disappointing ee's. Chiral diene **3i** bearing bulky substituents at 3,3'-positions gave a slightly higher ee. After a simple optimization, CH_2Cl_2 was a better solvent. 1,4-Benzoxazines **1a**-**f** were then subjected to this asymmetric hydrogenation, and products **2a**-**f** were obtained in 90-97% yields with 30-42% ee's (Scheme 5).



Scheme 4 Evaluation of chiral dienes for asymmetric hydrogenation.



Scheme 5 Metal-free asymmetric hydrogenation of 1,4-benzoxazines.

Conclusions

In summary, a frustrated Lewis pair catalyzed metal-free hydrogenation of 1,4-benzoxazines has been successfully realized with 2.5 mol % of $B(C_6F_5)_3$ under a mild condition to furnish a variety of 3,4-dihydro-2*H*-1,4-benzoxazines in 93-99% yields. For 3,4-disubstitued 1,4-benzoxazines, *cis*-products were obtained as single isomers. Using chiral borane catalysts generated *in situ* by the hydroboration of chiral dienes with $HB(C_6F_5)_2$, a preliminary attempt for the asymmetric hydrogenation gave 30-42% ee's. Further efforts on searching for more effective chiral FLPs for the asymmetric hydrogenations are underway in our laboratory.

Acknowledgements

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

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