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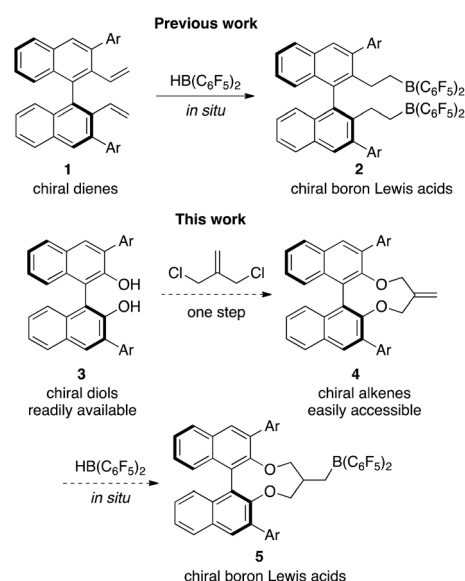# Asymmetric hydrogenation of imines with chiral alkene-derived boron Lewis acids†

Xiaoqin Liu,[a,b] Ting Liu,[a,b] Wei Meng*[a,b] and Haifeng Du (ID) *[a,b]

With the aim of developing easily accessible chiral Lewis acids for asymmetric hydrogenation, a variety of binaphthyl-based chiral alkenes were prepared in one step from the corresponding diols. Using the *in situ* generated chiral boron Lewis acids through the hydroboration of chiral alkenes with Piers' borane, metal-free asymmetric hydrogenations of imines were realized to furnish the desired amine products in high yields with up to 89% ee.

Asymmetric hydrogenation represents one of the most reliable and useful approaches for the synthesis of optically active molecules, and numerous well-known chiral transition-metal catalysts have been successfully developed.[1] However, metal-free asymmetric hydrogenations had not seen significant progress until the advent of frustrated Lewis pair (FLP) chemistry.[2] A wide range of unsaturated compounds have proven to be effective substrates for the FLP-catalyzed metal-free hydrogenation.[3] In particular, the asymmetric hydrogenation has also undergone an important step forward since the seminal work reported by Klankermayer and coworkers in 2008 with an α-pinene-derived chiral boron Lewis acid.[4] Several intra- or intermolecular chiral FLP catalysts have been subsequently developed for asymmetric hydrogenations of imines, enamines, and quinolines.[5,6] Less than 90% ee was obtained in the majority of cases. The access to these catalysts can be generally categorized into two protocols. One is the hydroboration of chiral alkenes with Piers' borane $HB(C_6F_5)_2$,[7] and the other is the substitution of boron chloride with chiral organometallic reagents. The preparation and purification of the chiral FLP catalyst still remain difficult due to the sensitivity of boron Lewis acids. The lack of highly effective and readily available

chiral catalysts undoubtedly presents an obstacle to the rapid progress of this lately emerging field.

To avoid the tedious purification of the sensitive boron Lewis acids, recently, our group developed a simple strategy for developing chiral boron Lewis acids **2** *in situ* without isolation by the hydroboration of binaphthyl-based chiral dienes **1** with $HB(C_6F_5)_2$ (Scheme 1). These chiral boron acids **2** were highly effective for the asymmetric hydrogenation of various unsaturated compounds, such as imines, silyl enol ethers, aromatic *N*-heterocycles and so on, to afford the corresponding products with high ee values.[8] Despite these advances, multiple steps were still required to access chiral dienes **1**. To explore more easily accessible chiral alkenes, we propose to synthesize chiral alkenes **4** *via* a one-step reaction of chiral binaphthols **3** with 3-chloro-2-(chloromethyl)prop-1-ene (Scheme 1). The cyclic structures of chiral alkenes **4** make them more rigid than chiral dienes **2**. Chiral boron Lewis acids **5** generated *in situ*

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†Electronic supplementary information (ESI) available: Procedure for the hydrogenation, characterization of products along with the NMR spectra. See DOI: 10.1039/c8ob02446d

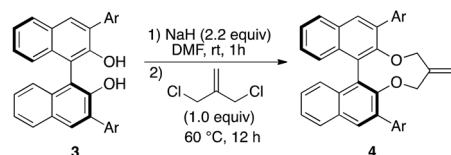Scheme 1 Our strategy for developing chiral boron Lewis acids.

from chiral alkenes **4** might be effective for asymmetric hydrogenations. Herein, we wish to report our preliminary results on this subject.

Chiral alkenes **4a–l** with diverse substituents at the 3,3'-positions were easily prepared in 38–89% yields *via* the reaction of chiral diols **3** and sodium hydride followed by treating with 3-chloro-2-(chloromethyl)prop-1-ene (Scheme 2). With these chiral alkenes in hand, the asymmetric hydrogenation of imine **6a** was chosen to evaluate the catalytic abilities of the *in situ* generated chiral boron Lewis acids from alkenes **4**. As shown in Table 1, all the reactions proceeded smoothly and cleanly to afford amine **7a** in quantitative conversions. However, only low to moderate ee values were obtained (entries 1–12). Chiral alkene **4i** bearing 3,5-di-*tert*-butylphenyl groups gave a promising 60% ee (entry 9).

The reaction conditions with chiral alkene **4i** were further optimized. Solvents were found to have an obvious impact on the enantioselectivity, and *p*-xylene gave a slightly better ee (Table 1, entries 13–21). The concentration also had an influence on the reactivity, and a dilute reaction solution resulted
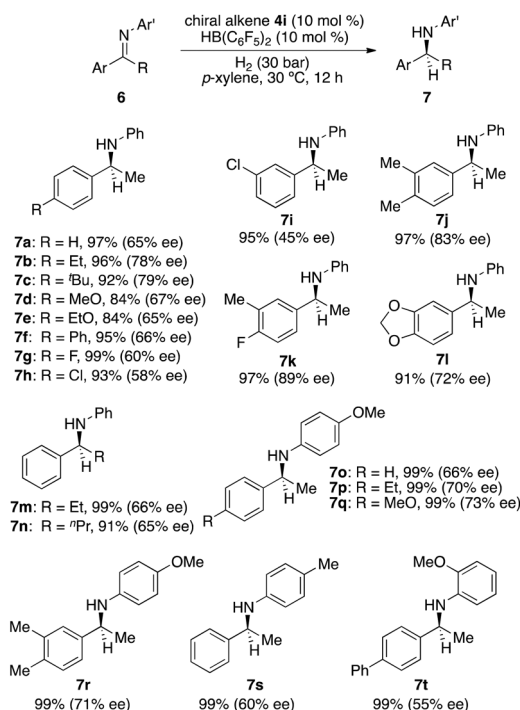
in a lower conversion (Table 1, entries 22 *vs*. 23). Lowering the temperature to 0 °C with toluene as the solvent led to a sharp drop of reactivity (Table 1, entry 24).

Under the optimal reaction conditions, various imines **6a–t** were next subjected to metal-free asymmetric hydrogenations. As shown in Scheme 3, both electron-withdrawing and -donating substituents on the phenyl groups were well tolerated to

Scheme 3 Asymmetric hydrogenations of imines.

Scheme 2 Synthesis of chiral alkenes **4**.

Table 1 Evaluation of chiral alkenes and optimization of reaction conditions[a]

Entry	Alkene **4**	Solvent	ee[b] (%)	Entry	Alkene **4**	Solvent	ee[b] (%)
1	**4a**	Toluene	4	13	**4i**	CH_2Cl_2	52
2	**4b**	Toluene	10	14	**4i**	n-C_6H_{12}	42
3	**4c**	Toluene	8	15	**4i**	c-C_6H_{12}	41
4	**4d**	Toluene	10	16	**4i**	o-Xylene	60
5	**4e**	Toluene	2	17	**4i**	p-Xylene	65
6	**4f**	Toluene	5	18	**4i**	Mesitylene	59
7	**4g**	Toluene	16	19	**4i**	C_6H_5F	58
8	**4h**	Toluene	18	20	**4i**	C_6H_5Cl	58
9	**4i**	Toluene	60	21	**4i**	C_6H_5Br	53
10	**4j**	Toluene	37	22[c]	**4i**	p-Xylene	64
11	**4K**	Toluene	33	23[d]	**4i**	p-Xylene	61
12	**4l**	Toluene	10	24[e]	**4i**	Toluene	50

[a] All the reactions were carried out with imine **6a** (0.1 mmol), chiral alkene **4** (0.01 mmol), and $HB(C_6F_5)_2$ (0.01 mmol) in the solvent (0.5 mL) at 30 °C under H_2 (30 bar) for 12 h to afford amine **7a** in quantitative conversions unless otherwise noted. [b] The ee was determined by chiral HPLC. [c] 0.25 mL solvent was used. [d] 1.0 mL solvent gave 79% conversion. [e] The reaction was run at 0 °C for 18 h to give 29% conversion.

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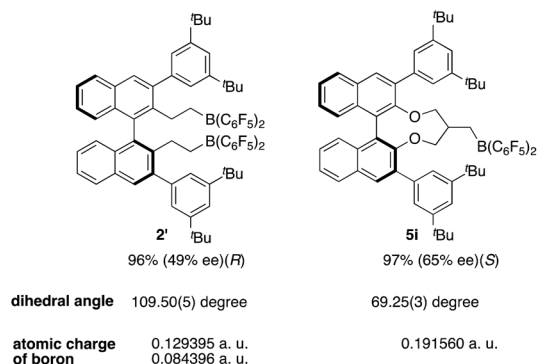*Org. Biomol. Chem.*, 2018, **16**, 8686–8689 | **8687**

Fig. 1 A comparison of two boron Lewis acids.

afford the corresponding amines **7a–i** in 84–99% yields with 45–79% ee values. The hydrogenation of imines **6j–l** bearing substituents at *p*- and *m*-positions gave amines **7j–l** in 91–97% yields with 72–89% ee values. Imines **6m** and **6n** were suitable substrates to furnish the desired products **7m** and **7n** with 66% and 65% ee, respectively. Moreover, imines **6o–t** with *p*-methoxylphenyl, *p*-methylphenyl, or *o*-methoxylphenyl groups as the *N*-protecting groups were also effective substrates for the metal-free asymmetric hydrogenation to give amines **7o–t** in high yields with 55–73% ee values.

A comparison of chiral boron Lewis acids derived from chiral diene and chiral alkene **4i** with the same substituents at the 3,3′-positions was conducted for the asymmetric hydrogenation of imine **6a**. Chiral boron Lewis acid **2′** gave 49% ee in favor of *R* absolute configuration, while **5i** gave 65% ee in favor of *S* absolute configuration (Fig. 1). Preliminary theoretical studies were carried out to clarify some differences between chiral boron Lewis acids **2′** and **5i** utilizing the M06-2X method[9] at the 6-31G(d) level.[10] The dihedral angles for **2′** and **5i** were 109.50(5) and 69.25(3) degrees, respectively. ADCH (atomic dipole moment corrected Hirshfeld population)[11] analysis showed that atomic charges of borons are 0.191560 a.u. for **5i**, 0.129395 and 0.084396 a.u. for **2′**, respectively, which indicates that chiral boron Lewis acid **5i** possesses a stronger Lewis acidity. The detailed asymmetric induction process is still not clear at present and awaits further mechanistic study.

Conclusions

In summary, a variety of readily available chiral alkenes were prepared in one step from chiral binaphthols. Using chiral boron Lewis acids generated *in situ* by the hydroboration of chiral alkenes with Piers' borane, a metal-free asymmetric hydrogenation of imines has been successfully realized, to give a variety of optically active amines in 84–99% yields with 45–89% ee values. Further efforts on searching for more effective chiral catalysts, exploring the mechanism, and expanding the application of these chiral boron Lewis acids in other asymmetric reactions are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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