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# Asymmetric Transfer Hydrogenations of 2,3-Disubstituted Quinoxalines with Ammonia Borane

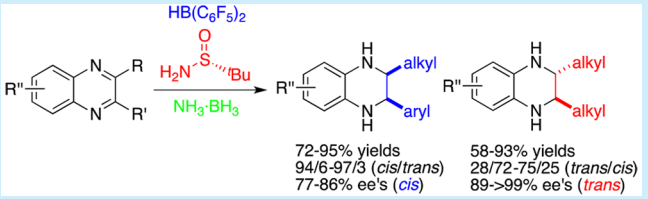
Songlei Li,[†,‡] Wei Meng,[†,‡] and Haifeng Du*[,†,‡]

[†]Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, CAS Research/Education Center for Excellence in Molecular Sciences, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

[‡]University of Chinese Academy of Sciences, Beijing 100049, China

Supporting Information

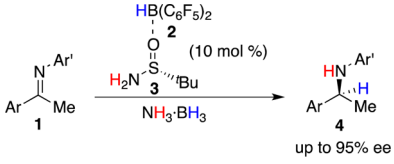
**ABSTRACT:** An asymmetric transfer hydrogenation of 2,3-disubstituted quinoxalines using a chiral frustrated Lewis pair of Piers' borane and (*R*)-*tert*-butylsulfinamide as the catalyst with ammonia borane as the hydrogen source has been successfully realized. For 2-alkyl-3-arylquinoxaline substrates, *cis*-tetrahydroquinoxalines were obtained as the predominant products in high yields with 77−86% ee. In contrast, *trans* isomers were often furnished as major products for the reactions of 2,3-dialkylquinoxalines with up to >99% ee.



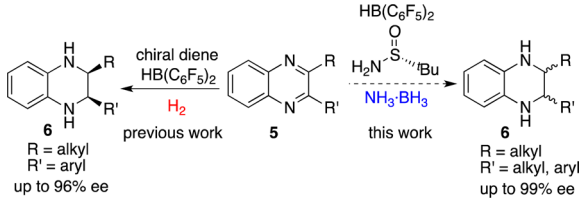



The chemistry of frustrated Lewis pairs (FLPs) has become one of the most important protocols for metal-free hydrogenations, and great progress on the catalyst and substrate diversity has been achieved in the past decade.[1,2] Significantly, a big step forward in asymmetric hydrogenation has also been made since Chen and Klankermayer reported the first example in 2008.[3,4] Chiral boron Lewis acid components or motifs in FLPs were usually employed for the asymmetric induction, which were synthesized either by the hydroboration of chiral alkenes with Piers' borane, $HB(C_6F_5)_2$,[5] or by the substitution reaction of $(C_6F_5)_nBCl_{3-n}$ with chiral organometallic reagents.[6] Recently, our group brought forth a practical strategy to access chiral boranes via an in situ hydroboration of chiral dienes or diynes.[7] Despite these advances, the use of readily available chiral Lewis bases for asymmetric hydrogenation has rarely been reported. In 2011, Stephan and co-workers reported a hydrogenation of imines using the combination of $B(C_6F_5)_3$ and (*S*,*S*)-DIOP to give 25% ee.[8] Very recently, our group developed a novel FLP of Piers' borane (**2**) and (*R*)-*tert*-butylsulfinamide[9] (**3**), which itself can release proton and hydride to the substrate and can be regenerated with ammonia borane as the hydrogen source (Scheme 1).[10,11] The asymmetric transfer hydrogenation of imines **1** was realized to give amine products **4** with up to 95% ee. The easy accessibility of this FLP makes it interesting to further explore its application in the asymmetric transfer hydrogenation of other unsaturated compounds.

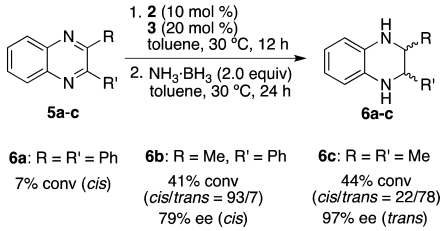
**Scheme 1. FLP-Catalyzed Transfer Hydrogenation of Imines with Ammonia Borane**




**Scheme 2. Chiral FLP-Catalyzed Asymmetric Hydrogenation of 2,3-Disubstituted Quinoxalines**




**Scheme 3. Initial Studies of the Asymmetric Transfer Hydrogenation of 2,3-Disubstituted Quinoxalines**




Catalytic asymmetric hydrogenation of quinoxalines and transfer hydrogenation also provide a straightforward approach for the synthesis of optically active tetrahydroquinoxalines, which are widely represented in biologically and medically

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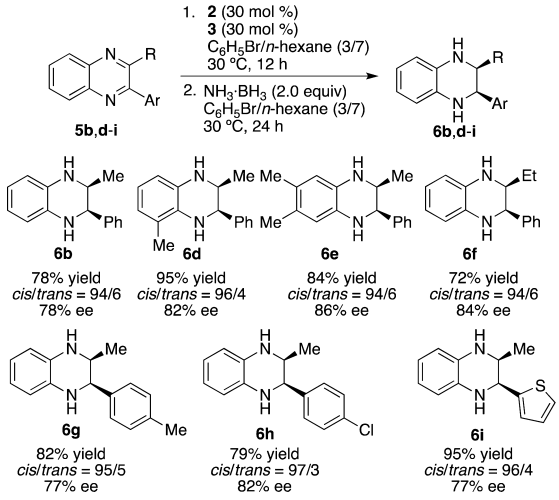
**Scheme 4. Asymmetric Transfer Hydrogenation of 2-Alkyl-3-arylquinoxalines**

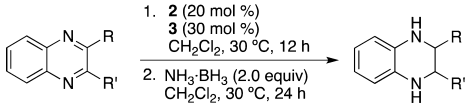


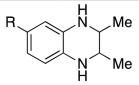
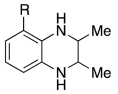
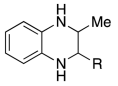
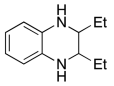
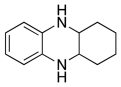
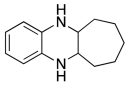
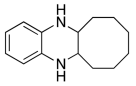

active compounds.[12,13] In comparison with the well-established methodologies for the reactions of 2-substituted quinoxalines,[14] only very few examples have been reported for the asymmetric hydrogenation of 2,3-disubstituted quinoxalines. In 2011, Fan and co-workers described the first asymmetric hydrogenation of 2,3-dialkylquinoxalines using a chiral ruthenium catalyst to give the desired products with *trans* selectivity and up to 99% ee.[15] In 2015, our group reported a highly *cis*-selective and enantioselective hydrogenation of 2-alkyl-3-arylquinoxlines employing a chiral borane catalyst generated by the in situ hydroboration of chiral dienes with Piers' borane (Scheme 2).[16] However, 2,3-diaryl- or dialkylquinoxalines were inert for this catalytic system. Herein we report our efforts on the asymmetric transfer hydrogenation of 2,3-disubstituted quinoxalines with ammonia borane using the combination of $HB(C_6F_5)_2$ and (*R*)-*tert*-butylsulfinamide as a chiral FLP catalyst (Scheme 2).

The tolerable substituents of quinoxalines for the FLP-catalyzed transfer hydrogenation were initially investigated. 2,3-Disubstituted quinoxalines **5a**−**c** were subjected to the asymmetric transfer hydrogenation with ammonia borane (2.0 equiv) at 30 °C in toluene using 10 mol % $HB(C_6F_5)_2$ (**2**) and 20 mol % (*R*)-*tert*-butylsulfinamide (**3**). As shown in Scheme 3, the reaction of 2,3-diphenylquinoxaline (**5a**) was sluggish and give only a small amount of product **6a** with *cis* selectivity. Meanwhile, 2-methyl-3-phenylquinoxaline (**5b**) proved to be a more reactive substrate, giving the corresponding product **6b** in 41% conversion with high *cis* selectivity and 79% ee. Notably, the *trans* isomer of **6c** was furnished with 97% ee as the major product when 2,3-dimethylquinoxaline (**5c**) was employed as the substrate. These preliminary results indicate that 2-alkyl-3-aryl- and 2,3-dialkylquinoxalines likely are suitable substrates for the current asymmetric transfer hydrogenation.

The reaction conditions for the asymmetric transfer hydrogenation of 2-methyl-3-phenylquinoxaline (**5b**) were optimized to further improve the reactivity and enantioselectivity (Table S1 in the Supporting Information). With a catalyst loading of 30 mol % and a mixture of bromobenzene and *n*-hexane (3/7 v/v) as the solvent, the product **6b** was obtained in 88% conversion with 94:6 dr and 82% ee (Table S1, entry 6). Under the optimal reaction conditions, a variety of 2-alkyl-3-arylquinoxalines **5b**,**d**−**i** were next examined for the asymmetric transfer hydrogenation. As shown in Scheme 4, all of these reactions proceeded smoothly to give the desired products **6b**,**d**−**i** in 72−95% yield with 94:6−97:3 dr and 77−86% ee.

**Table 1. Asymmetric Transfer Hydrogenation of 2,3-Dialkylquinoxalines**[a]




| entry | product **6** | yield (%)[b] | *trans*/*cis*[c] | ee (%) (*trans*)[d] | ee (%) (*cis*)[d] |
|---|---|---|---|---|---|
| |  | | | | |
| 1 | **6c**: R = H | 84 | 72/28 | 99 | -- |
| | | 87[e] | 71/29[e] | 99[e] | -- |
| 2 | **6j**: R = F | 72 | 64/36 | 98 | 23 |
| 3 | **6k**: R= Cl | 86 | 56/44 | >99 | *rac* |
| 4 | **6l**: R = Br | 81 | 58/42 | 99 | *rac* |
| 5 | **6m**: R = Me | 84 | 75/25 | 99 | 12 |
| 6 | **6n**: R = OMe | 58 | 69/31 | 99 | 46 |
| |  | | | | |
| 7 | **6o**: R = Cl | 78 | 55/45 | 99 | 56 |
| 8 | **6p**: R = Me | 85 | 72/28 | 99 | 55 |
| |  | | | | |
| 9 | **6q**: R = Et | 75 | 60/40 | 98 | 19 |
| 10 | **6r**: R = $^n$Pr | 72 | 58/42 | 98 | 39 |
| 11 | **6s**: R = $^i$Pr | 63 | 53/47 | 93 | 40 |
| 12 | **6t**: R = $^n$Bu | 85 | 60/40 | 98 | 37 |
| 13 | **6u**: R = *c*-hexyl | 67 | 50/50 | 89 | 6 |
| 14 | **6v**: R = benzyl | 76 | 65/35 | 97 | 35 |
| |  | | | | |
| 15 | **6w** | 72 | 50/50 | 99 | -- |
| |  | | | | |
| 16 | **6x** | 78 | 28/72 | 93 | -- |
| |  | | | | |
| 17 | **6y** | 78 | 29/71 | 99 | -- |
| |  | | | | |
| 18 | **6z** | 93 | 59/41 | >99 | -- |

[a]All of the reactions were carried out with quinoxaline (0.30 mmol), **2** (0.06 mmol), **3** (0.09 mmol), and ammonia borane (0.60 mmol) in $CH_2Cl_2$ (3.0 mL) at 30 °C. [b]Isolated yields. [c]Determined by $^1$H NMR analysis of the crude material. [d]Determined by chiral HPLC. [e]The reaction was run on a 1.0 mmol scale.

The asymmetric transfer hydrogenation of 2,3-dimethylquinoxaline (**5c**) with ammonia borane intrigued us because **5c** was inert for the previously reported asymmetric hydrogenation with $H_2$.[16] After a further optimization (Table S2), it was found that utilizing dichloromethane as the solvent and the combination of $HB(C_6F_5)_2$ (20 mol %) and (*R*)-*tert*-



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butylsulfinamide (30 mol %) as the catalyst can afford tetrahydroquinoxaline **6c** in 84% conversion with 72:28 dr and 99% ee (Table S2, entry 6). Under the same reaction conditions, a variety of 2,3-dialkylquinoxalines **5c,j−w** were subjected to the asymmetric transfer hydrogenation, which furnished the desired products **6c,j−w** in 58−86% yield with 50:50−75:25 dr and 89−99% ee for the *trans* isomers (Table 1, entries 2−15). Unfortunately, the ee for the *cis* isomers were much lower (Table 1, entries 2−14). Because of the ring strain, the transfer hydrogenation of quinoxalines **5x** and **5y** gave *meso* isomers as major products (Table 1, entries 16 and 17). Interestingly, high ee's can be still obtained for the *trans* isomers. When quinoxaline **5z** bearing a larger ring was used, tetrahydroquinoxaline **6z** in favor of the *trans* isomer was obtained in 93% yield with >99% ee (Table 1, entry 18).

In summary, a metal-free asymmetric transfer hydrogenation of 2,3-disubstituted quinoxalines with ammonia borane as the hydrogen source using a chiral frustrated Lewis pair of $HB(C_6F_5)_2$ and (*R*)-*tert*-butylsulfinamide as the catalyst has been successfully achieved. High *cis* selectivities and 77−86% ee's were obtained for the reactions of 2-alkyl-3-arylquinoxalines. Interestingly, when 2,3-dialkylquinoxalines were employed as substrates, the desired products were obtained in 58−93% yield with 28:72−75:25 dr (*trans*:*cis*) and 89−99% ee. Further efforts on searching for novel chiral FLPs and exploring their applications in asymmetric hydrogenation and transfer hydrogenation 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/acs.orglett.7b00935.

Procedure for the asymmetric transfer hydrogenation, characterization of products, and data for the determination of enantiomeric excesses along with the NMR spectra (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*haifengdu@iccas.ac.cn

### ORCID

Wei Meng: 0000-0002-1555-3738

Haifeng Du: 0000-0003-0122-3735


### Notes

The authors declare no competing financial interest.

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