

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

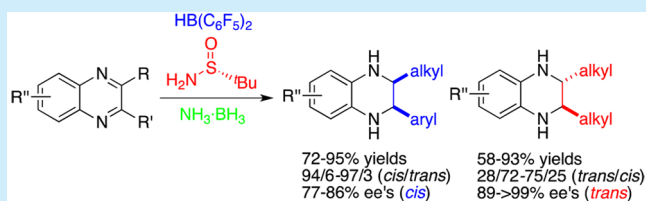
Songlei Li,^{†,‡} Wei Meng,^{†,‡} and Haifeng Du^{*,†,‡}

[†]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

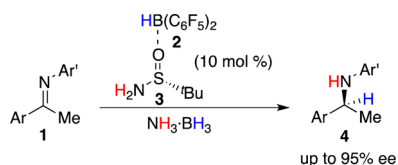
S Supporting Information

ABSTRACT: An asymmetric transfer hydrogenation of 2,3-disubstituted quinoxalines using a chiral frustrated Lewis pair of Piers' borane and (*R*)-*tert*-butylsulfonamide 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.

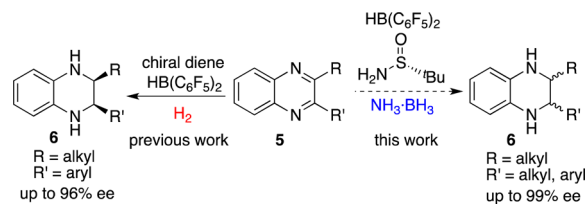


The chemistry of frustrated Lewis pairs (FLPs) has become one of the most important protocols for metal-free hydrogenations, and great progress on the catalyst and substrate diversity has been achieved in the past decade.^{1,2} Significantly, a big step forward in asymmetric hydrogenation has also been 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(C₆F₅)₂,⁵ or by the substitution reaction of (C₆F₅)_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(C₆F₅)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*-butylsulfonamide (**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

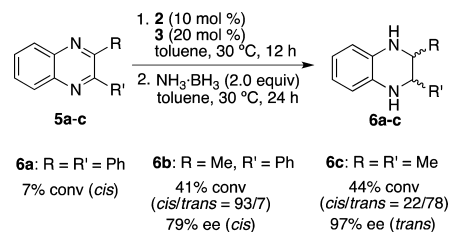
Scheme 1. FLP-Catalyzed Transfer Hydrogenation of Imines with Ammonia Borane



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

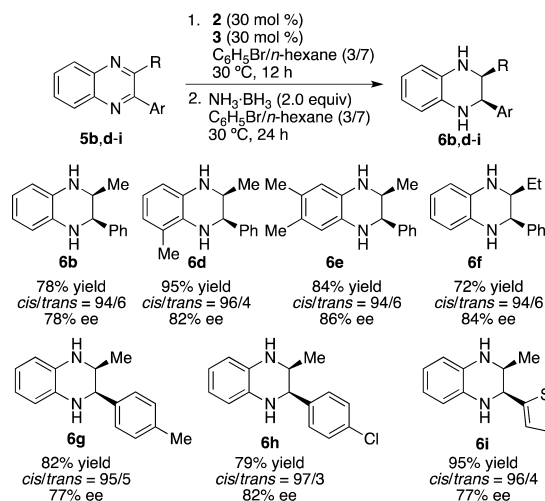


give amine products **4** with up to 95% ee. The easy accessibility of this FLP makes it interesting to further explore its application in the asymmetric transfer hydrogenation of other unsaturated compounds.

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

Received: March 28, 2017

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-arylquinoxalines 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(C₆F₅)₂ and (*R*)-*tert*-butylsulfonamide 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(C₆F₅)₂ (**2**) and 20 mol % (*R*)-*tert*-butylsulfonamide (**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

Table 1. Asymmetric Transfer Hydrogenation of 2,3-Dialkylquinoxalines^a

entry	product 6	yield (%) ^b	<i>trans/cis</i> ^c	ee (%) ^d (<i>trans</i>) ^d	ee (%) ^d (<i>cis</i>) ^d
1	6c : R = H	84 87 ^e	72/28 71/29 ^e	99 99 ^e	--
2	6j : R = F	72	64/36	98	23
3	6k : R = Cl	86	56/44	>99	<i>rac</i>
4	6l : R = Br	81	58/42	99	<i>rac</i>
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 = <i>c</i> -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	--

^aAll 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 CH₂Cl₂ (3.0 mL) at 30 °C. ^bIsolated yields. ^cDetermined by ¹H NMR analysis of the crude material. ^dDetermined by chiral HPLC. ^eThe reaction was run on a 1.0 mmol scale.

proceeded smoothly to give the desired products **6b,d–i** in 72–95% yield with 94:6–97:3 dr and 77–86% ee.

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 H₂.¹⁶ After a further optimization (Table S2), it was found that utilizing dichloromethane as the solvent and the combination of HB(C₆F₅)₂ (20 mol %) and (*R*)-*tert*-

butylsulfonamide (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(C₆F₅)₂ and (*R*)-*tert*-butylsulfonamide 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.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (21572231, 21502199, and 21521002).

■ REFERENCES

- (1) For a seminal work, see: Welch, G. C.; San Juan, R. R.; Masuda, J. D.; Stephan, D. W. *Science* **2006**, *314*, 1124.
- (2) For reviews, see: (a) Kenward, A. L.; Piers, W. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 38. (b) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46. (c) Soós, T. *Pure Appl. Chem.* **2011**, *83*, 667. (d) Erker, G. *Pure Appl. Chem.* **2012**, *84*, 2203. (e) Paradies, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3552. (f) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 6400. (g) Stephan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 10018. (h) Stephan, D. W. *Acc. Chem. Res.* **2015**, *48*, 306. (i) Stephan, D. W. *Science* **2016**, *354*, aaf7229.
- (3) Chen, D.; Klankermayer, J. *Chem. Commun.* **2008**, 2130.
- (4) For reviews, see: (a) Liu, Y.; Du, H. *Huaxue Xuebao* **2014**, *72*, 771. (b) Feng, X.; Du, H. *Tetrahedron Lett.* **2014**, *55*, 6959. (c) Shi, L.; Zhou, Y.-G. *ChemCatChem* **2015**, *7*, 54.
- (5) (a) Parks, D. J.; Spence, R. E. v. H.; Piers, W. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 809. (b) Parks, D. J.; Piers, W. E.; Yap, G. P. A. *Organometallics* **1998**, *17*, 5492.
- (6) For selected examples, see: (a) Chen, D.; Wang, Y.; Klankermayer, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 9475. (b) Sumerin, V.; Chernichenko, K.; Nieger, M.; Leskelä, M.; Rieger, B.; Repo, T. *Adv. Synth. Catal.* **2011**, *353*, 2093. (c) Lindqvist, M.; Borre, K.; Axenov, K.; Kótai, B.; Nieger, M.; Leskelä, M.; Pápai, I.; Repo, T. *J. Am. Chem. Soc.* **2015**, *137*, 4038. (d) Süssle, L.; Hermeke, J.; Oestreich, M. *J. Am. Chem. Soc.* **2016**, *138*, 6940. (e) Ye, K.-Y.; Wang, X.; Daniliuc, C. G.; Kehr, G.; Erker, G. *Eur. J. Inorg. Chem.* **2017**, *2017*, 368.
- (7) (a) Liu, Y.; Du, H. *J. Am. Chem. Soc.* **2013**, *135*, 6810. (b) Wei, S.; Du, H. *J. Am. Chem. Soc.* **2014**, *136*, 12261. (c) Ren, X.; Li, G.; Wei, S.; Du, H. *Org. Lett.* **2015**, *17*, 990. (d) Zhang, Z.; Du, H. *Org. Lett.* **2015**, *17*, 2816. (e) Zhang, Z.; Du, H. *Org. Lett.* **2015**, *17*, 6266. (f) Ren, X.; Du, H. *J. Am. Chem. Soc.* **2016**, *138*, 810.
- (8) Stephan, D. W.; Greenberg, S.; Graham, T. W.; Chase, P.; Hastie, J. J.; Geier, S. J.; Farrell, J. M.; Brown, C. C.; Heiden, Z. M.; Welch, G. C.; Ullrich, M. *Inorg. Chem.* **2011**, *50*, 12338.
- (9) For reviews, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.
- (10) Li, S.; Li, G.; Meng, W.; Du, H. *J. Am. Chem. Soc.* **2016**, *138*, 12956.
- (11) For selected examples using ammonia borane as a hydrogen source, see: (a) Ménard, G.; Stephan, D. W. *J. Am. Chem. Soc.* **2010**, *132*, 1796. (b) Yang, X.; Zhao, L.; Fox, T.; Wang, Z.-X.; Berke, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 2058. (c) Yang, X.; Fox, T.; Berke, H. *Chem. Commun.* **2011**, *47*, 2053. (d) Chong, C. C.; Hirao, H.; Kinjo, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 3342. (e) Fu, S.; Chen, N.-Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588. (f) Zhou, Q.; Zhang, L.; Meng, W.; Feng, X.; Yang, J.; Du, H. *Org. Lett.* **2016**, *18*, 5189.
- (12) For reviews, see: (a) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171. (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357. (c) Kuwano, R. *Heterocycles* **2008**, *76*, 909. (d) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557. (e) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498.
- (13) For selected examples, see: (a) Jacobsen, E. J.; Stelzer, L. S.; Belonga, K. L.; Carter, D. B.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D. *J. Med. Chem.* **1996**, *39*, 3820. (b) Sikorski, J. A. *J. Med. Chem.* **2006**, *49*, 1. (c) Eary, C. T.; Jones, Z. S.; Gronenberg, R. D.; Burgess, L. E.; Mareska, D. A.; Drew, M. D.; Blake, J. F.; Laird, E. R.; Balachari, D.; O'Sullivan, M.; Allen, A.; Marsh, V. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2608. (d) Borrok, M. J.; Kiessling, L. L. *J. Am. Chem. Soc.* **2007**, *129*, 12780.
- (14) For selected examples, see: (a) Murata, S.; Sugimoto, T.; Matsuura, S. *Heterocycles* **1987**, *26*, 763. (b) Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955. (c) Tang, W.; Xu, L.; Fan, Q.-H.; Wang, J.; Fan, B.; Zhou, Z.; Lam, K.-H.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 9135. (d) Chen, Q.-A.; Wang, D.-S.; Zhou, Y.-G.; Duan, Y.; Fan, H.-J.; Yang, Y.; Zhang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 6126. (e) Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2012**, *134*, 2442. For examples of transfer hydrogenations, see: (f) Rueping, M.; Tato, F.; Schoepke, F. R. *Chem. - Eur. J.* **2010**, *16*, 2688. (g) Shi, F.; Tan, W.; Zhang, H.-H.; Li, M.; Ye, Q.; Ma, G.-H.; Tu, S.-J.; Li, G. *Adv. Synth. Catal.* **2013**, *355*, 3715.
- (15) Qin, J.; Chen, F.; Ding, Z.; He, Y.-M.; Xu, L.; Fan, Q.-H. *Org. Lett.* **2011**, *13*, 6568.
- (16) Zhang, Z.; Du, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 623.