A Highly Enantioselective Hydrogenation of Silyl Enol Ethers Catalyzed by Chiral Frustrated Lewis Pairs

Simin Wei and Haifeng Du*

Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

Ⓢ *Supporting Information*

ABSTRACT: Using a simple combination of tri-*tert*-butylphosphine and chiral borane generated *in situ* by the hydroboration of chiral diene with $HB(C_6F_5)_2$ as a frustrated Lewis pair catalyst, a highly enantioselective metal-free hydrogenation of silyl enol ethers was successfully realized to furnish a variety of optically active secondary alcohols in 93−99% yields with 88−>99% ee's.

Catalytic hydrogenation of unsaturated compounds with H_2 is one of the most useful reactions in both academia and industry, which has long been predominated by the transition-metal catalysis.[1] Recently, the advent of frustrated Lewis pair (FLP) chemistry provides an important approach for the metal-free homogeneous hydrogenation.[2,3] A wide range of unsaturated compounds, including imines,[4] *N*-heterocycles,[5] nitriles,[4a,c] alkenes,[6] alkynes,[7] arenes,[8] and anilines,[9] have been successfully hydrogenated with H_2 using either a stoichiometric or a catalytic amount of FLP catalysts. However, the direct hydrogenation of ketones to secondary alcohols under FLP catalysis still remains as an unsolved problem.[10] Using silyl enol ethers instead of ketones for the FLP catalysis is a clever detour to avoid the presence of incompatible free carbonyl groups. In 2008, Erker and co-workers described the first metal-free hydrogenation of silyl enol ethers **1** using bisphosphine and $B(C_6F_5)_3$ to give silyl protected secondary alcohols (Scheme 1).[11] In 2012, Paradies and co-workers reported a hydrogenation of silyl enol ether intermediates generated by hydrosilylation of enones using [2,2]-paracyclophane-derived
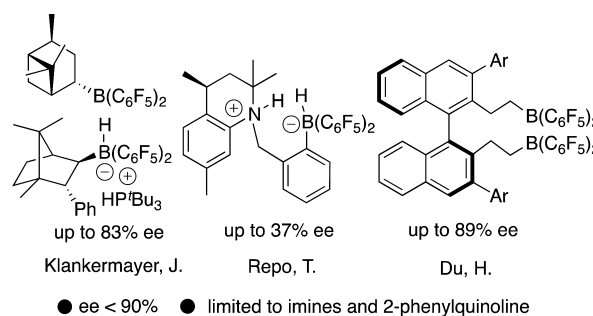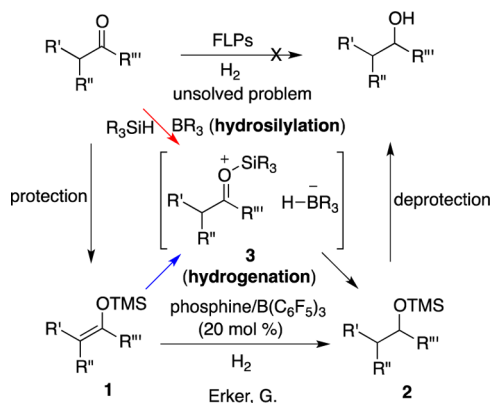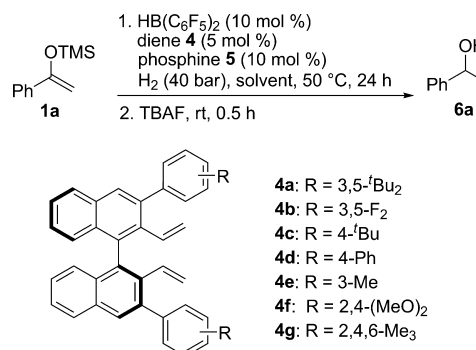
Scheme 1. FLP approaches to secondary alcohols

bisphosphine and $B(C_6F_5)_3$.[12] In these reactions, the FLP activates dihydrogen, and the phosphonium ion protonates the silyl enol ethers to yield intermediate **2**, which is also an intermediate for Piers-type hydrosilylation of ketones[13] (Scheme 1). It is noteworthy that silyl enol ethers belong to the very rare substrate class which can be hydrogenated with FLP but not metal catalysts. To obtain the highly desirable optically active secondary alcohols by FLP catalysis, the key issue is how to explore the asymmetric hydrogenation of silyl enol ethers.[14]

Despite the extremely rapid growth of FLP catalysis, the asymmetric reactions have been far less developed. In 2008, Klankermayer and co-workers reported the first FLP-catalyzed asymmetric hydrogenation of imines with 13% ee (Figure 1).[15a]

Figure 1. Representative chiral FLP catalysts for asymmetric hydrogenation with H_2.

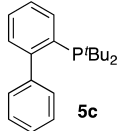**Scheme 2. Metal-Free Asymmetric Hydrogenation of Silyl Enol Ether 1a**

Table 1. Optimization of Reaction Conditions for Asymmetric Hydrogenation of Silyl Enol Ether 1a[a]
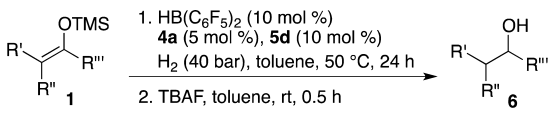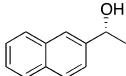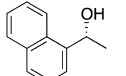
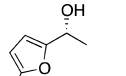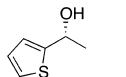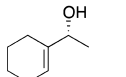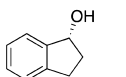| entry	diene 4	Phosphine 5	solvent	conv. (%)[b]	ee (%)[c]
1	4a	none	toluene	nr[d]	nd[e]
2	4a	Mes₃P 5a	toluene	nr[d]	nd[e]
3	4a	Cy₃P 5b	toluene	90	93
4	4a	5c (P^{t}Bu₂ biphenyl)	toluene	97	90
5	4a	^{t}Bu₃P 5d	toluene	>99	98
6	4a	5d	hexane	94	89
7	4a	5d	CH₂Cl₂	93	95
8	4a	5d	C₆H₅F	89	96
9	4a	5d	THF	nr[d]	nd[e]
10	4b	5d	toluene	>99	79
11	4c	5d	toluene	90	85
12	4d	5d	toluene	99	76
13	4e	5d	toluene	97	42
14	4f	5d	toluene	97	65
15	4g	5d	toluene	>99 (94)[f]	-94

[a]All reactions were carried out with silyl enol ether 1a (0.10 mmol), HB(C₆F₅)₂ (10 mol %), chiral diene 4 (5 mol %), phosphine 5 (10 mol %), and H₂ (40 bar) in solvent (0.05 mL) for 24 h, followed by removal of the TMS group with TBAF in solvent at room temperature for 0.5 h. [b]Determined by crude ¹H NMR. [c]Determined by chiral HPLC. [d]No reaction. [e]Not determined. [f]Isolated yield.

Soon, the ee was improved to 83% by the same group using the combination of chiral borane and phosphine.[15b] In 2011, Repo and co-workers employed chiral *ansa*-ammonium borates as catalysts to obtain up to 37% ee (Figure 1).[16] Very recently, our group employed the *in situ* generated chiral borane catalysts by the hydroboration of chiral dienes with Pier's borane[17] for the asymmetric hydrogenation of imines to give up to 89% ee (Figure 1).[18] Moreover, the hydrogenation of chiral imines using B(C₆F₅)₃ has also been reported by Stephan and co-workers.[19] Up to date, to the best of our knowledge, the ee for the FLP-catalyzed asymmetric hydrogenation is still less than 90%, and the substrate is limited to imines and 2-phenylquinoline.[20] Accordingly, the development of highly enantioselective reactions with a broad substrate scope is a challenging but important subject in this area. Herein, we report our preliminary results on the metal-free asymmetric hydrogenation of silyl enol ethers using phosphine and borane generated *in situ* from chiral diene as a FLP catalyst.

Initially, the asymmetric hydrogenation of silyl enol ether 1a under H₂ (40 bar) at 50 °C in toluene was investigated using a chiral borane catalyst generated *in situ* by the hydroboration of chiral diene 4a (5 mol %) with HB(C₆F₅)₂ (10 mol %) (Scheme 2). However, we found that chiral borane itself cannot catalyze this reaction (Table 1, entry 1). The combination of

Table 2. Asymmetric Hydrogenation of Silyl Enol Ethers[a]

entry	product (6)	yield (%)[b]	ee (%)[c,d]
1	6a: R = H	98	98
2	6b: R = 4-Et	97	97
3	6c: R = 4-Cl	97	>99
4	6d: R = 4-F	93	95
5	6e: R = 3-MeO	97	>99
6	6f: R = 3-Cl	94	99
7	6g: R = 2-MeO	97	>99
8	6h: R = 2-F	97	>99
9	6i: R = 3,4-Me₂	97	>99
10	6j: R = 3,4-(CH₂)₄	98	96
11	6k	99	99
12	6l	98	98
13	6m: R = H	97	88
14	6n: R = Me	94	89
15	6o	97	97
16	6p	98	99
17	6q	98	99

[a]Reactions were carried out with silyl enol ether 1 (0.30 mmol), HB(C₆F₅)₂ (10 mol %), chiral diene 4a (5 mol %), tri-*tert*-butylphosphine (5d) (10 mol %) and H₂ (40 bar) in toluene (0.15 mL) for 24 h, followed by removal of the TMS group with TBAF in toluene at room temperature for 0.5 h. [b]Isolated yield. [c]Ee was determined by chiral HPLC. [d]Absolute configuration was determined by comparing the optical rotation with the reported one.

chiral borane and Mes$_3$P (**5a**) was also not effective for this reaction (Table 1, entry 2). To our pleasure, with the addition of alkyl-substituted phosphines **5b−d**, the reactions can proceed smoothly, and after being treated with TBAF to remove the TMS group, the desired secondary alcohol **6a** was obtained in 90->99% conversion with 90−98% ee (Table 1, entries 3−5). Tri-*tert*-butylphosphine (**5d**) proved to be the best Lewis base (Table 1, entry 5). Subsequently, solvents were found to have an obvious influence on both reactivity and enantioselectivity (Table 1, entries 5−9). Toluene seems to be a suitable solvent. A variety of chiral dienes **4b−g**[18,21] were next examined for this asymmetric hydrogenation (Scheme 2). All these reactions went well to give product **6a** in 90->99% conversion with 42−94% ee (Table 1, entries 10−15). The substituents on the 3,3′-positions of binaphthyl frameworks can largely affect the enantioselectivity. Significantly, when chiral diene **4g** bearing mesityl groups at the 3,3′-positions was used, alcohol **6a** with a reverse absolute configuration was obtained in 94% yield with 94% ee (Table 1, entry 15).

A variety of silyl enol ethers was subjected to the metal-free asymmetric hydrogenations with the use of chiral diene **4a** (5 mol %), HB(C$_6$F$_5$)$_2$ (10 mol %), and tri-*tert*-butylphosphine (**5d**) (10 mol %). All these reactions went cleanly to give the desired products **6a−q** in 93−99% yields with 88->99% ee's (Table 2, entries 1−17). Both electron-donating and -withdrawing substituents on the phenyl group were well tolerant for this reaction (Table 2, entries 1−10). Silyl enol ethers prepared from 1-acetonaphthone and 2-acetonaphthone were also effective substrates to give 98−99% ee's (Table 2, entries 11 and 12). The hydrogenation of 2-acetylfurans derived silyl enol ethers gave relatively lower ee's (Table 2, entries 13 and 14). But 2-acetylthiophene derived enol ether gave an excellent ee (Table 2, entry 15). Interestingly, 1-acetylcyclohexene derived silyl enol ether can also be hydrogenated in 98% yield and 99% ee (Table 2, entry 16). The hydrogenation of cyclic silyl enol ether gave the desired product **6q** in 98% yield with 99% ee (Table 2, entry 17).

In summary, using the combination of tri-*tert*-butylphosphine (**5d**) and borane formed by the *in situ* hydroboration of chiral diene **4a** with HB(C$_6$F$_5$)$_2$ as a FLP catalyst, a highly enantioselective metal-free hydrogenation of silyl enol ethers has been successfully realized for the first time to furnish a variety of optically active secondary alcohols in 93−99% yields with 88->99% ee's. The readily accessible chiral boranes from chiral dienes and the diverse combination with Lewis bases make them a promising class of FLP catalysts for the metal-free asymmetric hydrogenation. Further efforts on the development of highly enantioselective hydrogenations of other unsaturated compounds using the *in situ* borane generation strategy are underway in our laboratory.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedure for the metal-free catalytic asymmetric hydrogenation of silyl enol ethers, characterization of silyl enol ethers and products, and data for the determination of enantiomeric excesses along with the NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
haifengdu@iccas.ac.cn

Notes
The authors declare no competing financial interest.

REFERENCES

(1) (a) de Vries, J. G.; Elsevier, C. J. *The Handbook of Homogeneous Hydrogenation*; Wiley-VCH: Weinheim, 2007. (b) Ertl, G.; Knözinger, H.; Shcüth, F.; Weitkamp, J. *Handbook of Heterogeneous Catalysis*; Wiley-VCH. Weinheim, 2008.

(2) For a seminal work, see: Welch, G. C.; Juan, R. R. S.; Masuda, J. D.; Stephan, D. W. *Science* 2006, 314, 1124−1126.

(3) For leading reviews, see: (a) Stephan, D. W. *Org. Biomol. Chem.* 2008, 6, 1535−1539. (b) Stephan, D. W. *Dalton Trans.* 2009, 3129−3136. (c) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* 2010, 49, 46−76. (d) Soós, T. *Pure Appl. Chem.* 2011, 83, 667−675. (e) 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, 12338−12348. (f) Stephan, D. W. *Org. Biomol. Chem.* 2012, 10, 5740−5746. (g) Erker, G. *Pure Appl. Chem.* 2012, 84, 2203−2217. (h) Paradies, J. *Synlett* 2013, 24, 777−780. (i) Paradies, J. *Angew. Chem., Int. Ed.* 2014, 53, 3552−3557. (j) Liu, Y.; Du, H. *Acta Chim. Sin.* 2014, 72, 771−777.

(4) For selected examples, see: (a) Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem., Int. Ed.* 2007, 46, 8050−8053. (b) Spies, P.; Schwendemann, S.; Lange, S.; Kehr, G.; Fröhlich, R.; Erker, G. *Angew. Chem., Int. Ed.* 2008, 47, 7543−7546. (c) Chase, P. A.; Jurca, T.; Stephan, D. W. *Chem. Commun.* 2008, 1701−1703. (d) Sumerin, V.; Schulz, F.; Atsumi, M.; Wang, C.; Nieger, M.; Leskelä, M.; Repo, T.; Pyykkö, P.; Rieger, B. *J. Am. Chem. Soc.* 2008, 130, 14117−14119. (e) Jiang, C.; Blacque, O.; Berke, H. *Chem. Commun.* 2009, 5518−5520. (f) Rokob, T. A.; Hamza, A.; Stirling, A.; Pápai, I. *J. Am. Chem. Soc.* 2009, 131, 2029−2036. (g) Axenov, K. V.; Kehr, G.; Fröhlich, R.; Erker, G. *J. Am. Chem. Soc.* 2009, 131, 3454−3455. (h) Axenov, K. V.; Kehr, G.; Fröhlich, R.; Erker, G. *Organometallics* 2009, 28, 5148−5158. (i) Erös, G.; Mehdi, H.; Pápai, I.; Rokob, T. A.; Király, P.; Tárkányi, G.; Soós, T. *Angew. Chem., Int. Ed.* 2010, 49, 6559−6563. (j) Zhao, L.; Li, H.; Lu, G.; Huang, F.; Zhang, C.; Wang, Z.-X. *Dalton Trans.* 2011, 40, 1929−1937. (k) Farrell, J. M.; Hatnean, J. A.; Stephan, D. W. *J. Am. Chem. Soc.* 2012, 134, 15728−15731.

(5) For selected examples, see: (a) Geier, S. J.; Chase, P. A.; Stephan, D. W. *Chem. Commun.* 2010, 46, 4884−4886. (b) Erös, G.; Nagy, K.; Mehdi, H.; Pápai, I.; Nagy, P.; Király, P.; Tárkányi, G.; Soós, T. *Chem.—Eur. J.* 2012, 18, 574−585. (c) Liu, Y.; Du, H. *J. Am. Chem. Soc.* 2013, 135, 12968−12971.

(6) For selected examples, see: (a) Schwendemann, S.; Tumay, T. A.; Axenov, K. V.; Peuser, I.; Kehr, G.; Fröhlich, R.; Erker, G. *Organometallics* 2010, 29, 1067−1069. (b) Greb, L.; Oña-Burgos, P.; Schirmer, B.; Grimme, S.; Stephan, D. W.; Paradies, J. *Angew. Chem., Int. Ed.* 2012, 51, 10164−10168. (c) Inés, B.; Palomas, D.; Holle, S.; Steinberg, S.; Nicasio, J. A.; Alcarazo, M. *Angew. Chem., Int. Ed.* 2012, 51, 12367−12369. (d) Reddy, J. S.; Xu, B.-H.; Mahdi, T.; Fröhlich, R.; Kehr, G.; Stephan, D. W.; Erker, G. *Organometallics* 2012, 31, 5638−5649. (e) Greb, L.; Daniliuc, C.-G.; Bergander, K.; Paradies, J. *Angew. Chem., Int. Ed.* 2013, 52, 5876−5879. (f) Hounjet, L. J.; Bannwarth, C.; Garon, C. N.; Caputo, C. B.; Grimme, S.; Stephan, D. W. *Angew. Chem., Int. Ed.* 2013, 52, 7492−7495. (g) Wang, Y.; Chen, W.; Lu, Z.; Li, Z. H.; Wang, H. *Angew. Chem., Int. Ed.* 2013, 52, 7496−7499. (h) Greb, L.; Tussing, S.; Schirmer, B.; Oña-Burgos, P.; Kaupmees, K.; Lõkov, M.; Leito, I.; Grimme, S.; Paradies, J. *Chem. Sci.* 2013, 4, 2788−2796.

(7) For selected examples, see: (a) Xu, B.-H.; Kehr, G.; Fröhlich, R.; Wibbeling, B.; Schirmer, B.; Grimme, S.; Erker, G. *Angew. Chem., Int.*

Ed. **2011**, *50*, 7183−7186. (b) Chernichenko, K.; Madarász, Á.; Pápai, I.; Nieger, M.; Leskelä, M.; Repo, T. *Nat. Chem.* **2013**, *5*, 718−723.

(8) Segawa, Y.; Stephan, D. W. *Chem. Commun.* **2012**, *48*, 11963−11965.

(9) Mahdi, T.; Heiden, Z. M.; Grimme, S.; Stephan, D. W. *J. Am. Chem. Soc.* **2012**, *134*, 4088−4091.

(10) For leading reviews on transition-metal-catalyzed asymmetric hydrogenation of ketones, see: (a) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3069. (c) Klinger, F. D. *Acc. Chem. Res.* **2007**, *40*, 1367−1376. (d) Morris, R. H. *Chem. Soc. Rev.* **2009**, *38*, 2282−2291. (e) Wang, Z.; Cheng, G.; Ding, K. *Chem. Rev.* **2009**, *109*, 322−359. (f) Yoshimura, M.; Tanaka, S.; Kitamura, M. *Tetrahedron Lett.* **2014**, *55*, 3635−3640.

(11) Wang, H.; Fröhlich, R.; Kehr, G.; Erker, G. *Chem. Commun.* **2008**, 5966−5968.

(12) Greb, L.; Oña-Burgos, P.; Kubas, A.; Falk, F. C.; Breher, F.; Fink, K.; Paradies, J. *Dalton Trans.* **2012**, *41*, 9056−9060.

(13) For selected examples, see: (a) Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, *118*, 9440−9441. (b) Parks, D. J.; Blackwell, J. M.; Piers, W. E. *J. Org. Chem.* **2000**, *65*, 3090−3098. (c) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5997−6000.

(14) For leading references on metal-catalyzed asymmetric hydrogenation of enol esters, see: (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518−8519. (b) Boaz, N. W. *Tetrahedron Lett.* **1998**, *39*, 5505−5508. (c) Jiang, Q.; Xiao, D.; Zhao, Z.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *36*, 516−518. (d) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. *Org. Lett.* **2002**, *4*, 4495−4497. (e) Liu, Y.; Wang, Z.; Ding, K. *Tetrahedron* **2012**, *68*, 7581−7585. (f) Konrad, T. M.; Schmitz, P.; Leitner, W.; Franciò, G. *Chem.—Eur. J.* **2013**, *19*, 13299−13303.

(15) (a) Chen, D.; Klankermayer, J. *Chem. Commun.* **2008**, 2130−2131. (b) Chen, D.; Wang, Y.; Klankermayer, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 9475−9478. (c) Ghattas, G.; Chen, D.; Pan, F.; Klankermayer, J. *Dalton Trans.* **2012**, *41*, 9026−9028.

(16) Sumerin, V.; Chernichenko, K.; Nieger, M.; Leskelä, M.; Rieger, B.; Repo, T. *Adv. Synth. Catal.* **2011**, *353*, 2093−2110.

(17) (a) Parks, D. J.; Spence, R. E.; von, H.; Piers, W. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 809−811. (b) Parks, D. J.; Piers, W. E.; Yap, G. P. A. *Organometallics* **1998**, *17*, 5492−5503.

(18) Liu, Y.; Du, H. *J. Am. Chem. Soc.* **2013**, *135*, 6810−6813.

(19) Heiden, Z. M.; Stephan, D. W. *Chem. Commun.* **2011**, *47*, 5729−5731.

(20) For FLP-catalyzed asymmetric hydrosilylation, see: (a) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5997−6000. (b) Chen, D.; Leich, V.; Pan, F.; Klankermayer, J. *Chem.—Eur. J.* **2012**, *18*, 5184−5187. (c) Mewald, M.; Oestreich, M. *Chem.—Eur. J.* **2012**, *18*, 14079−14084. (d) Hermeke, J.; Mewald, M.; Oestreich, M. *J. Am. Chem. Soc.* **2013**, *135*, 17537−17546.

(21) Cao, Z.; Du, H. *Org. Lett.* **2010**, *12*, 2602−2605.