JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

The Asymmetric Piers Hydrosilylation

Lars Süsse, Julia Hermeke, and Martin Oestreich*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 115, 10623 Berlin, Germany

Supporting Information

ABSTRACT: An axially chiral, cyclic borane decorated with just one C_6F_5 group at the boron atom promotes the highly enantioselective hydrosilylation of acetophenone derivatives without assistance of an additional Lewis base (up to 99% ee). The reaction is an unprecedented asymmetric variant of Piers' $B(C_6F_5)_3$-catalyzed carbonyl hydrosilylation. The steric congestion imparted by the 3,3′-disubstituted binaphthyl backbone of the borane catalyst as well as the use of reactive trihydrosilanes as reducing agents are keys to success.

Piers' discovery that $B(C_6F_5)_3$ catalyzes carbonyl hydrosilylation[1] opened a new chapter in reduction methodology that still continues to grow.[2] Part of the fascination with this reaction came from its, at the time, peculiar mechanism. Early insight had already suggested that it proceeds through activation of the hydrosilane reagent by $B(C_6F_5)_3$ rather than conventional Lewis pair formation with the carbonyl substrate.[3] Over recent years, the full mechanistic picture evolved,[4] and η^1 coordination of the Si−H bond to $B(C_6F_5)_3$ followed by S_N2-Si displacement of hydride at the silicon atom with the carbonyl group as the nucleophile is now well accepted. The borohydride emerging from that step is the actual reducing agent.

An asymmetric variant of the Piers hydrosilylation would therefore require a chiral $B(C_6F_5)_3$ congener that is sufficiently electron deficient to promote the Si−H bond activation and meets the challenge of inducing enantioselectivity as its borohydride. For this, we introduced axially chiral (*S*)-**1**·THF with one C_6F_5 group at the boron atom a few years ago (Figure 1, left),[5] but enantioinduction was low (≤15% ee).[6] Substantially better levels of enantioselection were obtained with (*S*)-**1**·THF in the related catalytic hydrosilylation of imines[7] (≤62% ee).[8] Even higher enantiomeric excesses (≤87% ee) were achieved by borrowing from the concept of frustrated Lewis pairs (FLPs[9]):[10] Klankermayer and co-workers employed an FLP·H_2 adduct composed of a terpene-derived borane and a bulky phosphine in the imine hydrosilylation; the hydrosilylation of acetophenone was again inferior (37% ee).[11] The FLP strategy was also successful in the hydrosilylation of α-keto carbonyl and carboxyl compounds (>99% ee), using one of Du's in situ-generated catalysts (*S*)-**2** (Figure 1, right).[12,13] The same catalytic setup afforded 42% ee in the reduction of acetophenone. To date, the asymmetric Piers hydrosilylation catalyzed by an electron-deficient borane alone[14] is elusive, and we disclose here a solution to this long-standing problem.

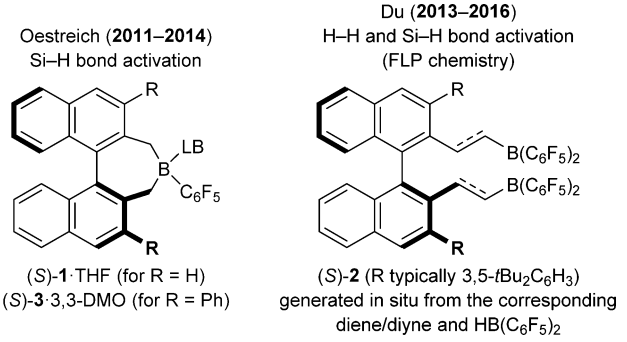


Figure 1. Axially chiral congeners of $B(C_6F_5)_3$ for Si−H bond activation (LB = Lewis base).

To refine catalyst (*S*)-**1**·THF, we created steric congestion in the proximity of the boron atom by installation of phenyl groups in the 3 and 3′ positions. These substituents had a dramatic effect on both catalyst preparation and purification. Introduction of the $B(C_6F_5)$ unit by conventional tin−boron exchange failed,[5] and we had to develop a dummy-ligand strategy to overcome chemoselectivity issues [(*S*)-**4** → (*S*)-**3**, Scheme 1].[15] Moreover, Lewis pair formation between (*S*)-**3** and various Lewis bases to precipitate or crystallize adducts of type (*S*)-**3**·LB was hampered by the steric situation around the boron atom in (*S*)-**3**. We eventually succeeded using 3,3-dimethyloxetane (3,3-DMO) and were able to crystallographically characterize (*S*)-**3**·3,3-DMO.[15] However, considerable experimentation was required to reliably remove stoichiometrically formed **5** by precipitation and several washing cycles [(*S*)-**3** → (*S*)-**3**·3,3-DMO, Scheme 1]. Alternatively, dimethyl sulfide (DMS) worked equally well, and (*S*)-**3**·DMS was isolated with <1% tin contamination [(*S*)-**3** → (*S*)-**3**·DMS, Scheme 1; see the Supporting Information (SI) for the molecular structure of (*S*)-**3**·DMS]. Although both complexes of (*S*)-**3** as well as the free borane (*S*)-**3** (burdened with **5**) induced similar levels of enantioselection (*vide infra*), we decided to continue with (*S*)-**3**·DMS.

With catalyst (*S*)-**3**·DMS, we tested representative hydrosilanes as reductants in the hydrosilylation of acetophenone [**6** → (*S*)-**7**, Table 1, entries 1−8]. Not surprisingly, monohydrosilanes including $EtMe_2SiH$ were too sterically hindered. This was also true for Ph_2SiH_2, but with $MePhSiH_2$ carbonyl compound **6** was fully converted within 2 days, affording (*S*)-**7** with 28% ee. Trihydrosilanes such as $PhSiH_3$ and $MesSiH_3$ performed even better, reaching enantioselectivities of 81 and 87% ee, respectively; *t*-$BuSiH_3$ did not react. The use of an equimolar amount of the trihydrosilane is likely to be

Received: April 4, 2016
Published: May 23, 2016

DOI: 10.1021/jacs.6b03443
J. Am. Chem. Soc. 2016, 138, 6940−6943

Scheme 1. Catalyst Preparation

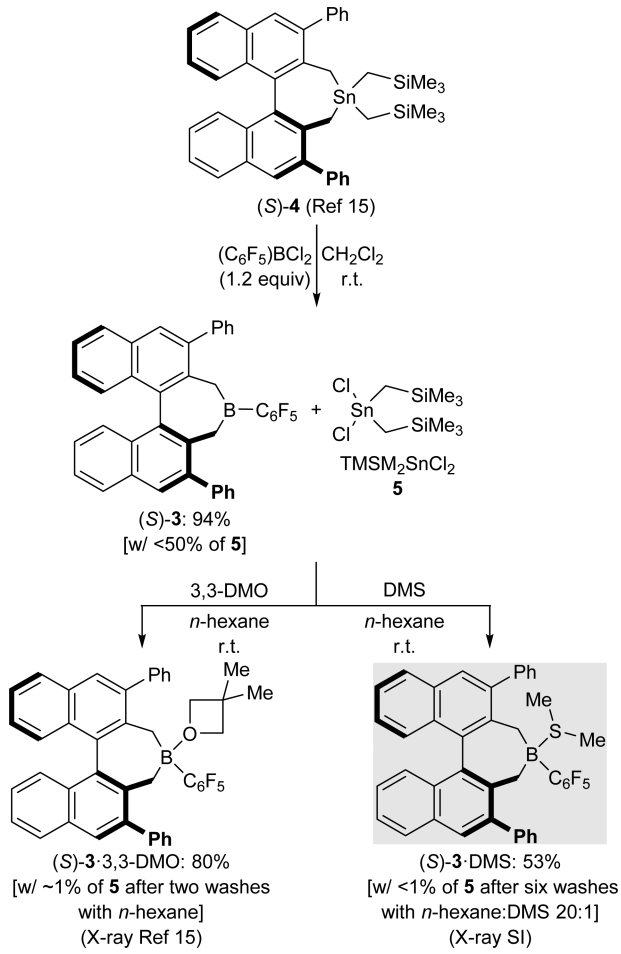
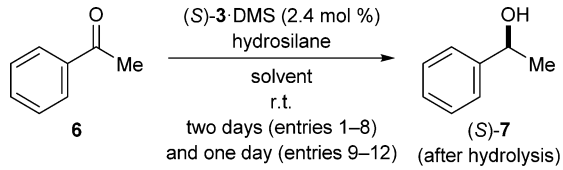


Table 1. Optimization of the Carbonyl Hydrosilylation



entry	hydrosilane	equiv	solvent	conv. (%)[a]	ee (%)[b]
1	Ph_3SiH	1.0	1,2-$F_2C_6H_4$	–	–
2	Me_2PhSiH	1.0	1,2-$F_2C_6H_4$	–	–
3	$EtMe_2SiH$	1.0	1,2-$F_2C_6H_4$	–	–
4	Ph_2SiH_2	1.0	1,2-$F_2C_6H_4$	–	–
5	$MePhSiH_2$	1.0	1,2-$F_2C_6H_4$	quant.	28
6	$PhSiH_3$	1.0	1,2-$F_2C_6H_4$	quant.	81
7	$MesSiH_3$	1.0	1,2-$F_2C_6H_4$	quant.	87
8	t-$BuSiH_3$	1.0	1,2-$F_2C_6H_4$	traces	–
9	$PhSiH_3$	2.0	1,2-$F_2C_6H_4$	quant.	93
10	$PhSiH_3$	3.0	1,2-$F_2C_6H_4$	quant.	93
11	$PhSiH_3$	3.0	neat	quant.	93
12	$PhSiH_3$	5.0	neat	quant.	93

[a]Determined by GLC analysis using tetracosane as internal standard. [b]Determined by HPLC analysis using a chiral stationary phase.

detrimental to enantioinduction as intermediate chiral alkoxy-substituted hydrosilanes will potentially act as reductants (Table 1, entry 6 vs entries 9–12). With 2.0 instead of 1.0 equiv of $PhSiH_3$, the level of enantiocontrol was improved to 93% ee. No further increase of the enantiomeric excess was seen with more hydrosilane. It made no difference whether the catalysis was run in 1,2-$F_2C_6H_4$ as solvent or neat. The catalayst loading also had an effect on conversion and enantioinduction (for a discussion of this observation, see below):[7c] 1.0 mol % resulted in 80% ee at 42% conversion and 5.0 mol % yielded 94% ee at full conversion (both within 1 day; see the SI for details).

Application of the optimized procedure (Table 1, entry 11) to ether-coordinated (*S*)-**3**·3,3-DMO required double the reaction time; the enantiomeric excess (90% ee) was in the same range. Importantly, the free borane (*S*)-**3** in an almost equimolar mixture with tin byproduct **5** catalyzed the hydrosilylation as efficiently as (*S*)-**3**·DMS with 92% ee. Hence, we believe that neither Lewis base interferes in the reaction as is the case with phosphine additives.[11,12]

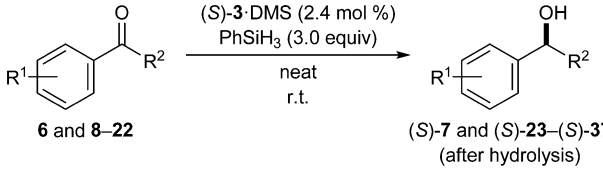
We then examined various electronically modified acetophenone derivatives **8**–**14**, and the effects were substantial (Scheme 2). Compared to parent **6** (full conversion in 1 day), CF_3- and NO_2-substituted **8** and **9** were less reactive (4 and 2 days, respectively). Conversely, MeO-substituted **14** showed full conversion in 1 day. The difference in enantioselectivity between these extremes was even more pronounced with 80% ee for **9** and 28% ee for **14**. Remarkably, the carboxyl group in **10** was tolerated, and an impressive 98% ee in 87% isolated yield were reached. The results for Cl- and Me-substituted **11** and **12** were also satisfactory, but the enantiomeric excess collapsed for the corresponding Ph-substituted acetophenone **13**. Steric hindrance was also detrimental to both reactivity and enantioinduction; mesityl-substituted **15** afforded 24% conversion after 4 days and no better than 17% ee. A similar result was obtained from the systematic investigation of the three regioisomeric monobrominated acetophenones **16**–**18**. The para- and meta-substituted compounds **16** and **17** reacted as good as acetophenone itself, and the level of enantioselection was excellent (95% ee and 99% ee, respectively). However, ortho-substitution as in **18** again slowed down the hydrosilylation, and enantioinduction dropped to 73% ee. Replacing the methyl by a benzyl or cyclohexyl group at the carbonyl carbon atom led to far less reactive **19** and **20**, and asymmetric induction gradually decreased with increasing steric bulk. Good enantiomeric excess was seen with β-naphthyl derivative **21**. Likewise, the enantiomeric excess measured for benzophenone **22** as substrate was even lower. These are the current limitations of the method. The discrepancy between conversion and isolated yield is mainly due to competing deoxygenation known to occur with $B(C_6F_5)_3$/hydrosilane combinations.[16]

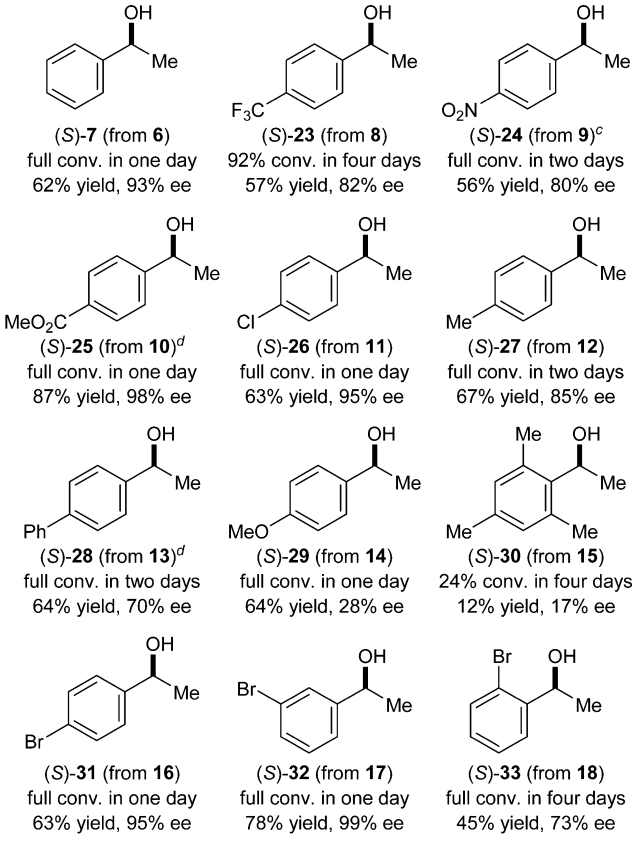
Both α-diketones and α-keto esters were the privileged substrates for Du's catalytic system (*S*)-**2** in the presence of Cy_3P (91% yield, >99% ee and 96% yield, 98% ee, respectively).[12] Remarkably, benzil was completely inert against our catalyst (*S*)-**3**·DMS, and ethyl phenylglyoxylate was reduced within 4 days yet without any enantioselectivity (not shown). These results emphasize that Du's and our catalyst system are complementary.

We had observed before that conversion and enantiomeric excess are dependent on the amount of catalyst employed (*vide supra*). Moreover, several of the hydrosilylations displayed slightly deviating values for the enantiomeric excess with 2.4 mol % fixed catalyst loading when conversions were lower or higher than those reported in Scheme 2. We interpret these findings on the basis of our recent mechanistic investigation of

DOI: 10.1021/jacs.6b03443
J. Am. Chem. Soc. 2016, 138, 6940–6943

Scheme 2. Scope and Limitations of the Enantioselective Carbonyl Hydrosilylation[a,b]

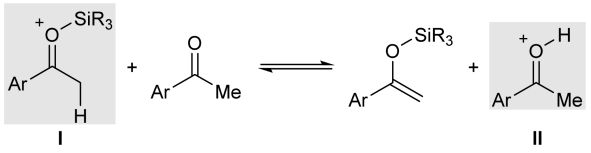




[a]Determined by GLC analysis using mesitylene as internal standard. [b]Determined by HPLC analysis using chiral stationary phases. [c]For better solubility, double the amount of $PhSiH_3$ used. [d]Addition of 1,2-$F_2C_6H_4$ as solvent to secure homogeneous solution.

the cognate ketimine hydrosilylation.[7c] In that work, we demonstrated that deprotonation of the intermediate α-C–H acidic silyliminium ion by the unreacted imine substrate forms the corresponding iminium ion. Both iminium ions engage in the enantioselectivity-determining borohydride reduction, resulting in two competing reaction pathways with potentially different stereochemical outcomes. The same scenario likely applies to the present ketone hydrosilylation where the catalytic cycle proceeds through either a silylcarboxonium ion **I** or a "hidden" protonated carboxonium ion **II** (Scheme 3).

Scheme 3. Generation of Another Activated Carbonyl Group by α-Deprotonation (Borohydride Counteranion Omitted for Clarity)



To summarize, we developed an enantioselective variant of Piers' $B(C_6F_5)_3$-catalyzed carbonyl hydrosilylation.[1] A combination of a binaphthyl-based boron catalyst with just one C_6F_5 group at the boron atom and reactive trihydrosilanes as the stoichiometric reductant was crucial for achieving acceptable conversion (1 day) and high enantioselection (up to 99% ee). The new method distinguishes itself from previous FLP-type approaches,[11−13] as no additional Lewis base is needed. As in the original protocol by Piers,[1] the borane catalyst alone promotes the hydrosilylation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03443.

Experimental details and data (PDF)
Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*martin.oestreich@tu-berlin.de

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

M.O. is indebted to the Einstein Foundation (Berlin) for an endowed professorship. We thank Dr. Elisabeth Irran (TU Berlin) for the X-ray analysis.

■ REFERENCES

(1) Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, *118*, 9440−9441.
(2) For reviews, see: (a) Oestreich, M.; Hermeke, J.; Mohr, J. *Chem. Soc. Rev.* **2015**, *44*, 2202−2220. (b) Piers, W. E.; Marwitz, A. J. V.; Mercier, L. G. *Inorg. Chem.* **2011**, *50*, 12252−12262.
(3) Parks, D. J.; Blackwell, J. M.; Piers, W. E. *J. Org. Chem.* **2000**, *65*, 3090−3098.
(4) (a) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5997−6000. (b) Sakata, K.; Fujimoto, H. *J. Org. Chem.* **2013**, *78*, 12505−12512. (c) Houghton, A. Y.; Hurmalainen, J.; Mansikkamäki, A.; Piers, W. E.; Tuononen, H. M. *Nat. Chem.* **2014**, *6*, 983−988.
(5) Mewald, M.; Fröhlich, R.; Oestreich, M. *Chem. - Eur. J.* **2011**, *17*, 9406−9414.
(6) Mewald, M. Ph.D. Thesis, Westfälische Wilhelms-Universität Münster, Germany, 2012.
(7) (a) Blackwell, J. M.; Sonmor, E. R.; Scoccitti, T.; Piers, W. E. *Org. Lett.* **2000**, *2*, 3921−3923. (b) Hog, D. T.; Oestreich, M. *Eur. J. Org.*

DOI: 10.1021/jacs.6b03443
J. Am. Chem. Soc. 2016, 138, 6940−6943

Chem. **2009**, 5047−5056. (c) Hermeke, J.; Mewald, M.; Oestreich, M. *J. Am. Chem. Soc.* **2013**, *135*, 17537−17546.
(8) (a) Mewald, M.; Oestreich, M. *Chem. - Eur. J.* **2012**, *18*, 14079−14084. For the enantioselective hydrosilylation catalyzed by (*S*)-**2** (R = 3,5-(3,5-tBu$_2$C$_6$H$_3$)$_2$; ≤82% ee), see: (b) Zhu, X.; Du, H. *Org. Biomol. Chem.* **2015**, *13*, 1013−1016.
(9) For authoritative reviews, see: (a) Stephan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 10018−10032. (b) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 6400−6441.
(10) Asymmetric FLP-type hydrogenation is closely connected to the present hydrosilylation, and Klankermayer's and Du's chiral boranes have been applied in both transformations. For reviews, see: (a) Feng, X.; Du, H. *Tetrahedron Lett.* **2014**, *55*, 6959−6964. (b) Chen, D.; Klankermayer, J. In *Frustrated Lewis Pairs II, Expanding the Scope*; Erker, G., Stephan, D. W., Eds.; Springer: Heidelberg, Germany, 2013; Topics in Current Chemistry, Vol. *334*, pp 1−26. For asymmetric imine hydrogenation, see: (c) Chen, D.; Wang, Y.; Klankermayer, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 9475−9478. (d) Sumerin, V.; Chernichenko, K.; Nieger, M.; Leskelä, M.; Rieger, B.; Repo, T. *Adv. Synth. Catal.* **2011**, *353*, 2093−2110. (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) Ghattas, G.; Chen, D.; Pan, F.; Klankermayer, J. *Dalton Trans.* **2012**, *41*, 9026−9028. (g) Wang, X.; Kehr, G.; Daniliuc, C. G.; Erker, G. *J. Am. Chem. Soc.* **2014**, *136*, 3293−3303.
(11) Chen, D.; Leich, V.; Pan, F.; Klankermayer, J. *Chem. - Eur. J.* **2012**, *18*, 5184−5187.
(12) Ren, X.; Du, H. *J. Am. Chem. Soc.* **2016**, *138*, 810−813.
(13) The net outcome of the FLP-type hydrogenation of silyl enol ethers is that of the carbonyl hydrosilylation: (a) Wei, S.; Du, H. *J. Am. Chem. Soc.* **2014**, *136*, 12261−12264. (b) Ren, X.; Li, G.; Wei, S.; Du, H. *Org. Lett.* **2015**, *17*, 990−993.
(14) For enantioselective imine hydrogenation catalyzed by electron-deficient boranes without the need for a bulky phosphine as an additive, see: (a) Chen, D.; Klankermayer, J. *Chem. Commun.* **2008**, 2130−2131. (b) Liu, Y.; Du, H. *J. Am. Chem. Soc.* **2013**, *135*, 6810−6813.
(15) Hermeke, J.; Mewald, M.; Irran, E.; Oestreich, M. *Organometallics* **2014**, *33*, 5097−5100.
(16) (a) Gevorgyan, V.; Rubin, M.; Benson, S.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 6179−6186. (b) Nimmagadda, R. D.; McRae, C. *Tetrahedron Lett.* **2006**, *47*, 5755−5758.

DOI: 10.1021/jacs.6b03443
J. Am. Chem. Soc. 2016, 138, 6940−6943