EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: Diboron-Mediated Rhodium-Catalysed Transfer Hydrogenation of Alkenes and Carbonyls

Authors: Xiao Lin, Yuhan Wang, Yan Hu, Wanjiang Zhu, and Xiaowei Dou

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000049

Link to VoR: http://dx.doi.org/10.1002/ejoc.202000049

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

Diboron-Mediated Rhodium-Catalysed Transfer Hydrogenation of Alkenes and Carbonyls

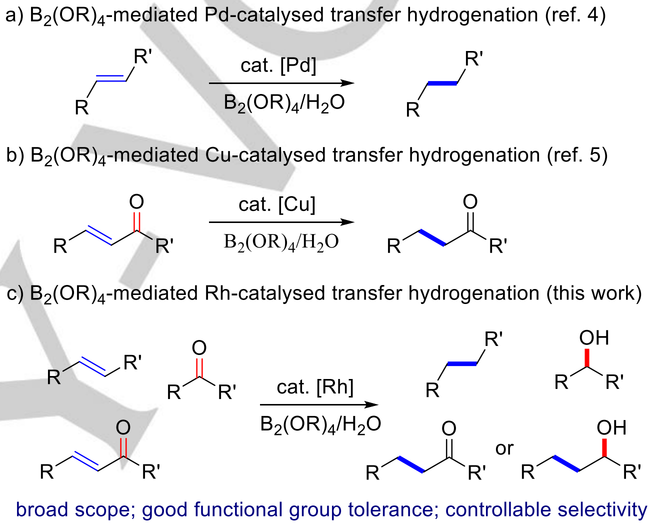
Xiao Lin, Yuhan Wang, Yan Hu, Wanjiang Zhu and Prof. Dr. Xiaowei Dou*

Department of Chemistry, School of Science
China Pharmaceutical University
Longmian Avenue 639, Nanjing 211198, China
E-mail: dxw@cpu.edu.cn
Web: https://www.x-mol.com/groups/dou_xiaowei

Abstract: A diboron-mediated rhodium-catalysed transfer hydrogenation system using water as the hydrogen donor is developed. In addition to a series of alkenes with good functional group tolerance, this rhodium-based catalytic system also effectively reduces aldehydes and ketones. A plausible mechanism involving the Rh(I)-catalysed hydrogen generation and Rh(0)-catalysed hydrogenation is proposed for the reaction.

Transition-metal-catalysed hydrogenation is arguably one of the most useful transformations in organic synthesis and catalysis. In this type of reaction, hydrogen gas is usually employed as the H donor, but its flammable nature and the operational issues associated with its use can be troublesome, especially for bench chemist. In this context, transfer hydrogenation,[1] which uses alternative H donors other than hydrogen gas, has been developed as an attractive approach. Among various H donors in transfer hydrogenation, water is undoubtly the most inexpensive and easy to handle one. Moreover, transfer deuteration can be easily achieved by using deuterium oxide to prepare valuable deuterated molecules. Therefore, development of practical and versatile methods for transfer hydrogenation with water is highly desirable.[2]

The diboron reagents (e.g., $B_2(OH)_4$) are bench-stable, nontoxic, and easy to handle, and they proved to be useful reducing reagents in organic synthesis.[3] In recent years, there has been a great interest in studying the diboron-mediated transfer hydrogenation with water. Different metals including palladium,[4] copper,[5] and ruthenium[6] have been explored to catalyse this transformation, and it is found that the reactivity and selectivity of the reaction are highly metal-dependent. For example, the diboron/water system in concert with palladium catalyst effective reduces unactivated alkenes,[4a] while the copper catalyst promotes the formal reduction of the activated alkenyl moiety of enones via a hydroboration-protodeboronation pathway.[5a] Herein, we report our serendipitous finding that rhodium is also able to effectively catalyse the diboron-mediated transfer hydrogenation with water (Scheme 1). The current rhodium catalytic system features the following advantages compared with the established methods: 1) broad substrate scope: it works well for both activated and unactivated alkenes, as well as aldehydes and ketones; 2) better functional group tolerance: for example, aryl bromide is sensitive to palladium catalyst, but it is tolerated under the current system; 3) controllable chemoselectivity: the selective reduction of enones can be easily controlled via adjusting the amount of diboron reagent. Thus, this rhodium-based catalytic system provides a new tool for transfer hydrogenation with water.



a) $B_2(OR)_4$-mediated Pd-catalysed transfer hydrogenation (ref. 4)

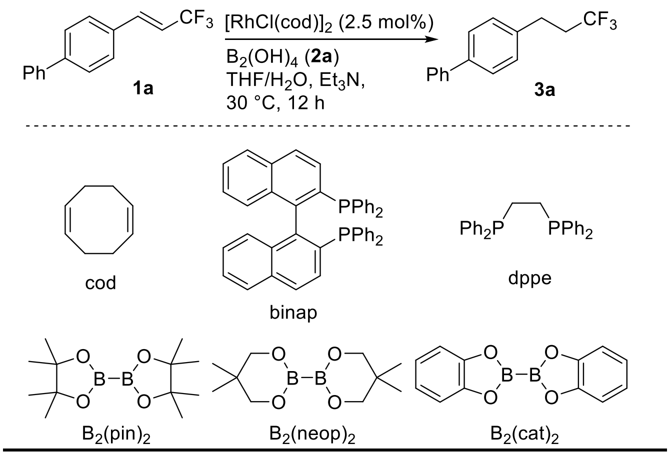
b) $B_2(OR)_4$-mediated Cu-catalysed transfer hydrogenation (ref. 5)

c) $B_2(OR)_4$-mediated Rh-catalysed transfer hydrogenation (this work)

Scheme 1. Diboron-mediated transition-metal-catalysed transfer hydrogenation of alkenes and carbonyls with water.

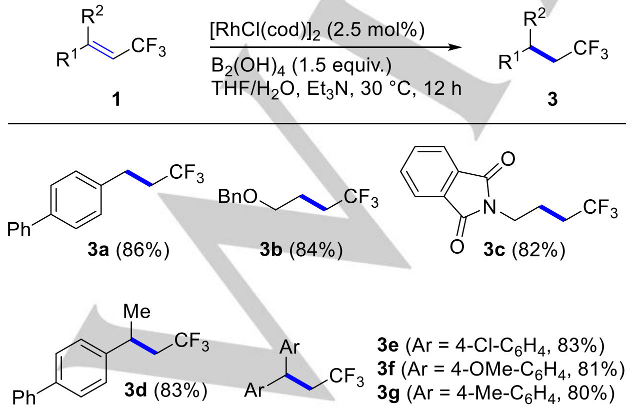
As part of our ongoing efforts on the Rh(I)-catalysed conjugate addition of organoborons to alkenes,[7] we investigated the Rh(I)-catalysed addition of diborons to CF_3-activated alkene **1a**, aiming to achieve the conjugate borylation of this β-aryl substituted substrate, which remains a formidable task in borylation of trifluoromethyl alkenes.[8] To our surprise, no conjugate borylation product was detected during our investigation, but reduction of **1a** was observed. As shown in Table 1, the reaction between trifluoromethyl alkene **1a** and tetrahydroxydiboron **2a** proceeded smoothly in the presence of rhodium catalyst under mild reaction conditions in aqueous THF, giving the reduced product **3a** in high yield (86%, entry 1). Other diboron reagents including bis(neopentylglycolate) diboron $B_2(neop)_2$ and bis(catecholate) diboron $B_2(cat)_2$ also worked well, but bis(pinacolate) diboron $B_2(pin)_2$ was found to be ineffective (entries 2–4). The coordinating ligand on rhodium was crucial for the catalytic activity, and bis(phosphine) ligands were found to be not suitable for this catalytic system (entries 5–6). Control experiments revealed that the rhodium catalyst was essential, as no conversion of **1a** was observed without catalyst (entry 7). The use of triethylamine as the base was also necessary for the high yield of the reaction (entries 8–10). The reaction did not proceed under anhydrous conditions, validating the important role of water as the H donor (entry 11, $B_2(cat)_2$ was used to avoid the introduction of water from $B_2(OH)_4$). It is noteworthy that the defluorination product, which can be generated via β-F elimination from the alkyl-rhodium species,[9] was not observed.

Table 1. Rhodium-catalysed reduction of trifluoromethyl alkene **1a** with diboron/water.[a]



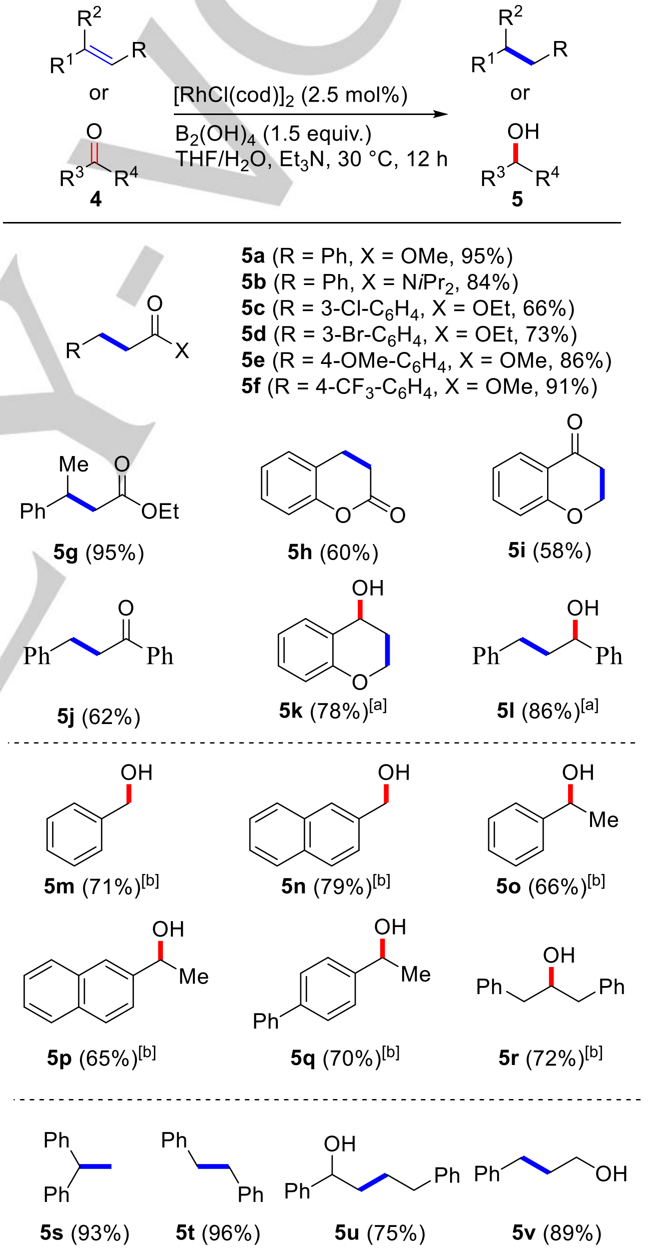
Entry	Variation from standard conditions	Yield [%][b]
1	none	86
2	$B_2(pin)_2$ instead of $B_2(OH)_4$	<5
3	$B_2(neop)_2$ instead of $B_2(OH)_4$	71
4	$B_2(cat)_2$ instead of $B_2(OH)_4$	81
5	binap instead of cod	<5
6	dppe instead of cod	<5
7	w/o $[RhCl(cod)]_2$	<5
8	w/o Et_3N	35
9	Cs_2CO_3 instead of Et_3N	78
10	pyridine instead of Et_3N	<5
11	w/o H_2O[c]	<5

[a] Standard conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), $[RhCl(cod)]_2$ (5 μmol, 2.5 mol%), and Et_3N (0.60 mmol) in THF/H_2O (2.0 mL/0.05 mL) at 30 °C for 12 h. [b] Isolated yield of **3a**. [c] $B_2(cat)_2$ was used for anhydrous conditions.



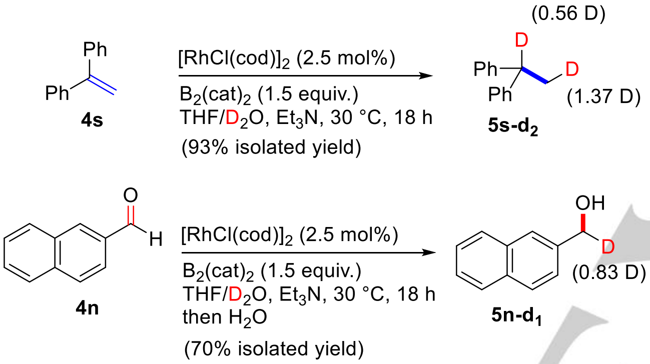
Scheme 2. Substrate scope of trifluoromethyl alkenes.

With the established reaction conditions for transfer hydrogenation of trifluoromethyl alkenes, the scope of this catalytic transformation was studied, and the results are summarized in Scheme 2 (isolated yields of products were shown). In addition to the β-aryl substituted trifluoromethyl alkenes, the current catalytic system also efficiently reduced the β-alkyl substituted substrates (**3b** and **3c**). Moreover, the β,β-disubstituted trifluoromethyl alkenes were also suitable in this system, producing the corresponding β,β-disubstituted trifluoromethyl alkanes in high yields (**3d**–**3g**). Considering the easy preparation of trifluoromethyl alkenes, the current method provides a useful approach to accessing functionalized trifluoromethyl alkanes.[10]



Scheme 3. Scope of alkenes and carbonyls. [a] 2.5 equiv. $B_2(OH)_4$ was used. [b] EtOH was used as the solvent.

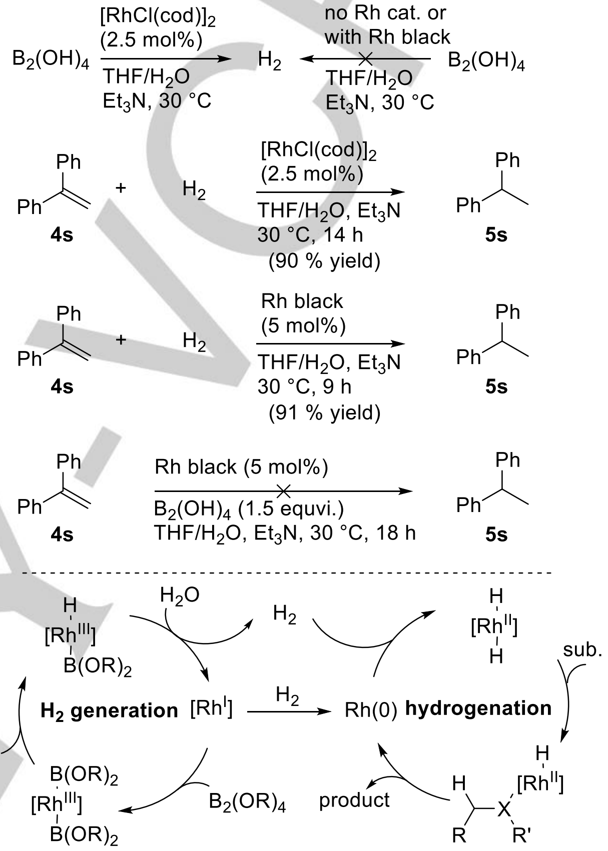
With the success achieved on transfer hydrogenation of trifluoromethyl alkenes, we further explored the generality of the rhodium-based catalytic system for other types of substrates. As shown in Scheme 3 (isolated yields of products were shown), the ester or amide-activated alkenyl substrates, including those bearing aryl chloride or aryl bromide moieties, worked well under the standard conditions (**5a**–**5f**). The catalytic system was also suitable for the reduction of β,β-disubstituted substrate (**5g**) and cyclic substrate (**5h**). Both cyclic and acyclic α,β-unsaturated ketones can be reduced to saturated ketones under the standard conditions (**5i**–**5j**). Furthermore, we were delighted to achieve the reduction of the keto moiety with an excess amount of diboron reagent (**5k**–**5l**).[11] The utility of the current catalytic system for transfer hydrogenation of carbonyls was then next explored, and both aldehydes and ketones were found to be suitable substrates (**5m**–**5r**). Finally, the unactivated alkenes were investigated, and the transfer hydrogenation reaction worked very well (**5s**–**5v**). The wide scope and good functional group tolerance distinguish the current method from other known.



Scheme 4. Transfer deuteration with D_2O.

One important advantage of the transfer hydrogenation with water is that the transfer deuteration can be easily achieved by using cheap deuterium oxide. In the current rhodium catalytic system, the transfer deuteration was also feasible. As shown in Scheme 4, both alkenyl and carbonyl substrates were reduced with high levels of deuterium incorporation. The scrambling of deuterium in **5s-d_2** indicates the involvement of a rhodium hydride species during the catalytic process, which can lead to the observed scrambling via a migratory insertion/ -H elimination/regio-reversed reinsertion process.

There are two important experimental phenomena observed during the study. The first one is the fast formation of hydrogen gas bubbles at the initial stage of the reaction; and the second one is the fast formation of rhodium black during the reaction process. To gain insight into the possible reaction mechanism, several control experiments were conducted in Scheme 5 based on the aforementioned observations. Control experiments showed that the rhodium(I) catalyst was essential for the production of hydrogen gas. Both rhodium(I) catalyst and rhodium black were found to catalyse the hydrogenation of **4s** with hydrogen gas, however, rhodium black was not able to catalyse the transfer hydrogenation with diboron as the reducing reagent. Based on the experimental results and literature precedents, a plausible mechanism for the current catalytic system is proposed (Scheme 5). The first cycle accounts for the formation of hydrogen gas: oxidation of rhodium(I) to diboron generates the rhodium(III) intermediate,[12] which reacts with water and produces hydrogen gas upon reductive elimination. The second cycle is the rhodium black-catalysed hydrogenation: in the presence of hydrogen gas, the cyclooctadiene-ligated rhodium(I) catalyst is reduced to rhodium black, which then catalyses the hydrogenation of alkenes and carbonyls.[13]



Scheme 5. Mechanistic studies and proposed mechanism.

In summary, we have developed a rhodium catalytic system that catalyses the diboron-mediated transfer hydrogenation with water. The new system features broad substrate scope, good functional group tolerance, and controllable chemoselectivity. This rhodium-based catalytic system provides a new tool for transfer hydrogenation.

Acknowledgements

We are grateful for the generous financial support from the "Double First-Class" University project (CPU2018GY35) of China Pharmaceutical University and the "Six Talent Peaks Plan" of Jiangsu Province.

Keywords: Rhodium • Transfer Hydrogenation • Diboron • Alkenes • Carbonyls

[1] For a comprehensive review, see: D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621–6686.

[2] a) E. Shirakawa, H. Otsuka, T. Hayashi, *Chem. Commun.* **2005**, 5885–5886; b) T. Sato, S. Watanabe, H. Kiuchi, S. Oi, Y. Inoue, *Tetrahedron Lett.* **2006**, *47*, 7703–7705; c) A. G. Campaña, R. E. Estévez, N. Fuentes, R. Robles, J. M. Cuerva, E. Buñuel, D. Cárdenas, J. E. Oltra, *Org. Lett.* **2007**, *9*, 2195–2198; d) O. Muhammad, S. U. Sonavane, Y. Sasson, M. Chidambaram, *Catal. Lett.* **2008**, *125*, 46–51; e) K. Li, R. Khan, X. Zhang, Y. Gao, Y. Zhou, H. Tan, J. Chen, B. Fan, *Chem. Commun.* **2019**, *55*, 5663–5666; f) X. Hu, G. Wang, C. Qin, X. Xie, C. Zhang, W. Xu, Y. Liu, *Org. Chem. Front.* **2019**, *6*, 2619–2623; g) G. Shen, J. Chen, D. Xu, X. Zhang, Y. Zhou, B. Fan, *Org. Lett.* **2019**, *21*, 1364–1367; h) C.-Q. Zhao, Y.-G. Chen, H. Qiu, L. Wei, P. Fang, T.-S. Mei, *Org. Lett.* **2019**, *21*, 1412–1416.

[3] For a review, see: a) E. C. Neeve, S. J. Geier, I. A. I. Mkhalid, S. A. Westcott, T. B. Marder, *Chem. Rev.* **2016**, *116*, 9091–9161. For selected examples, see: b) Y.-T. Xia, X.-T. Sun, L. Zhang, K. Luo, L. Wu, *Chem. Eur. J.* **2016**, *22*, 17151–17155; c) K. Yang, Q. Song, *Green Chem.* **2016**, *18*, 932–936. d) G. Gao, J. Yan, K. Yang, F. Chen, Q. Song, *Green Chem.* **2017**, *19*, 3997–4001. e) D. Chen, G. Xu, Q. Zhou, L. W. Chung, W. Tang, *J. Am. Chem. Soc.* **2017**, *139*, 9767–9770; f) H.-C. Du, N. Simmons, J. C. Faver, Z. Yu, M. Palaniappan, K. Riehle, M. M. Matzuk, *Org. Lett.* **2019**, *21*, 2194–2199; g) F. Takahashi, K. Nogi, T. Sasamori, H. Yorimitsu, *Org. Lett.* **2019**, *21*, 4739–4744.

[4] a) S. P. Cummings, T.-N. Le, G. E. Fernandez, L. G. Quiambao, B. J. Stokes, *J. Am. Chem. Soc.* **2016**, *138*, 6107–6110; b) Q. Xuan, Q. Song, *Org. Lett.* **2016**, *18*, 4250–4253; c) D. P. Ojha, K. Gadde, K. R. Prabhu, *Org. Lett.* **2016**, *18*, 5062–5065; d) Y. Zhou, H. Zhou, S. Liu, D. Pi, G. Shen, *Tetrahedron* **2017**, *73*, 3898–3904; e) K. A. Korvinson, H. K. Akula, C. T. Malinchak, D. Sebastian, W. Wei, T. A. Khandaker, M. R. Andrzejewska, B. Zajc, M. K. Lakshman, *Adv. Synth. Catal.* **2019**, doi: 10.1002/adsc.201901099.

[5] a) W. Ding, Q. Song, *Org. Chem. Front.* **2016**, *3*, 14–18; b) D. Pi, H. Zhou, Y. Zhou, Q. Liu, R. He, G. Shen, Y. Uozumi, *Tetrahedron* **2018**, *74*, 2121–2129; c) H. Bao, B. Zhou, H. Jin, Y. Liu, *J. Org. Chem.* **2019**, *84*, 3579–3589; d) X. Han, J. Hu, C. Chen, Y. Yuan, Z. Shi, *Chem. Commun.* **2019**, *55*, 6922–6925.

[6] Y. Wei, C. Zhao, Q. Xuan, Q. Song, *Org. Chem. Front.* **2017**, *4*, 2291–2295.

[7] a) L. Yin, J. Xing, Y. Wang, Y. Shen, T. Lu, T. Hayashi, X. Dou, *Angew. Chem. Int. Ed.* **2019**, *58*, 2474–2478; b) J. Yao, N. Liu, L. Yin, J. Xing, T. Lu, X. Dou, *Green Chem.* **2019**, *21*, 4946–4950; c) J. Yao, L. Yin, Y. Shen, T. Lu, T. Hayashi, X. Dou, *Org. Lett.* **2018**, *20*, 6882–6885; d) J. Huang, N. Liu, T. Lu, X. Dou, *Adv. Synth. Catal.* **2018**, *360*, 3466–3470.

[8] a) P. Gao, C. Yuan, Y. Zhao, Z. Shi, *Chem* **2018**, 4, 2201–2211; b) R. Kojima, S. Akiyama, H. Ito, *Angew. Chem. Int. Ed.* **2018**, *57*, 7196–7199.

[9] a) T. Miura, Y. Ito, M. Murakami, *Chem. Lett.* **2008**, *37*, 1006–1007; b) Y. Huang, T. Hayashi, *J. Am. Chem. Soc.* **2016**, *138*, 12340–12343; c) Y. J. Jang, D. Rose, B. Mirabi, M. Lautens, *Angew. Chem. Int. Ed.* **2018**, *57*, 16147–16151.

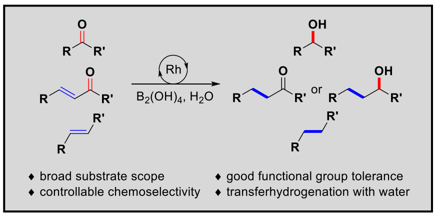
[10] a) N. J. W. Straathof, S. E. Cramer, V. Hessel, T. Noël, *Angew. Chem. Int. Ed.* **2016**, *55*, 15549–15553; b) S. Choi, Y. J. Kim, S. M. Kim, J. W. Yang, S. W. Kim, E. J. Cho, *Nat. Commun.* **2014**, *5*, 4881–4887.

[11] Reduction of carbonyls was achieved with other diboron reagents in the absence of a metal catalyst, but tetrahydroxydiboron did not work in those systems, see: a) M. Flinker, H. Yin, R. W. Juhl, E. Z. Eikeland, J. Overgaard, D. U. Nielsen, T. Skrydstrup, *Angew. Chem. Int. Ed.* **2017**, *56*, 15910–15915; b) Q. Xuan, C. Zhao, Q. Song, *Org. Biomol. Chem.* **2017**, *15*, 5140–5144.

[12] For examples involving oxidative addition of $B_2(OR)_4$ to rhodium, see: a) P. Nguyen, G. Lesley, N. J. Taylor, T. B. Marder, *Inorg. Chem.* **1994**, *33*, 4623–4624; b) S. Trudeau, J. B. Morgan, M. Shrestha, J. P. Morken, *J. Org. Chem.* **2005**, *70*, 9538–9544; c) J. Ramírez, A. M. Segarra, E. Fernández, *Tetrahedron: Asymmetry* **2005**, *16*, 1289–1294; d) N. Hu, G. Zhao, Y. Zhang, X. Liu, G. Li, W. Tang, *J. Am. Chem. Soc.* **2015**, *137*, 6746–6749.

[13] H. Miyamura, A. Suzuki, T. Yasukawa, S. Kobayshi, *J. Am. Chem. Soc.* **2018**, *140*, 11325–11334.

Entry for the Table of Contents



Transfer Hydrogenation: A diboron-mediated rhodium-catalysed transfer hydrogenation system using water as the hydrogen donor is developed. The new system features broad substrate scope, good functional group tolerance, and controllable chemoselectivity. This rhodium-based catalytic system provides a new tool for transfer hydrogenation.