SCIENCE CHINA
Chemistry

•ARTICLES•

October 2021 Vol.64 No.10: 1743–1749
https://doi.org/10.1007/s11426-021-1049-9

Diboron-mediated palladium-catalyzed asymmetric transfer hydrogenation using the proton of alcohols as hydrogen source

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Received April 1, 2021; accepted June 16, 2021; published online August 31, 2021

The developments of hydrogen sources stand at the forefront of asymmetric reduction. In contrast to the well-studied alcohols as hydrogen sources *via* β-hydride elimination, the direct utilization of the proton of alcohols as a hydrogen source for activator-mediated asymmetric reduction is rarely explored. Herein we report the proton of alcohols as a hydrogen source in diboron-mediated palladium-catalyzed asymmetric transfer hydrogenation of 1,3-diketones and indoles, providing a series of chiral β-hydroxy ketones and indolines with excellent yields and enantioselectivities. This strategy would be useful for the synthesis of chiral deuterium-labelled compounds due to the ready availability of deuterium-labelled alcohols. Mechanistic investigations and DFT calculations revealed that active chiral Pd-H species was generated from the proton of alcohols by activating of tetrahydroxydiboron, hydrogen transfer was the rate-determining step, and the reaction preferred Pd(0)-catalyzed mechanism.

proton of alcohols, hydrogen source, asymmetric reduction

Citation: Wu B, Yang J, Hu SB, Yu CB, Zhao ZB, Luo Y, Zhou YG. Diboron-mediated palladium-catalyzed asymmetric transfer hydrogenation using the proton of alcohols as hydrogen source. *Sci China Chem*, 2021, 64: 1743–1749, https://doi.org/10.1007/s11426-021-1049-9

1 Introduction

Asymmetric reduction is one of the most powerful and straightforward methods to produce chiral pharmaceuticals, agrochemicals, fragrances and fine chemicals in industrial processes and has impressive importance in synthetic chemistry [1–4]. Great progress has been made in asymmetric reduction based on the developments of chiral catalysts and hydrogen sources owing to the significance of asymmetric reduction [5–9]. Among the numerous hydrogen sources, alcohols, such as isopropanol, are efficient and common hydrogen sources in asymmetric transfer hydrogenation [10–14]. Generally, C–H and O–H of isopropanol serve as hydrogen sources. Isopropanol undergoes β-hydride elimination in the presence of chiral metal catalysts to form chiral metal hydride species along with releasing acetone. These chiral metal hydride species have been widely applied in the asymmetric transfer hydrogenation of ketones and imines [10–14] (Scheme 1a). In contrast, the proton as a hydrogen source to directly form metal hydride species *via* activator activation and their applications in reduction has been less explored. There are only a few examples of racemic activator-mediated reduction reactions using the proton of water as a hydrogen source [15–24]. In 2007, Oltra's group [15] disclosed hydrogen transfer from water to alkenes and alkynes mediated by titanocene chloride with late transition metals and presumed that the O–H bond of water might be

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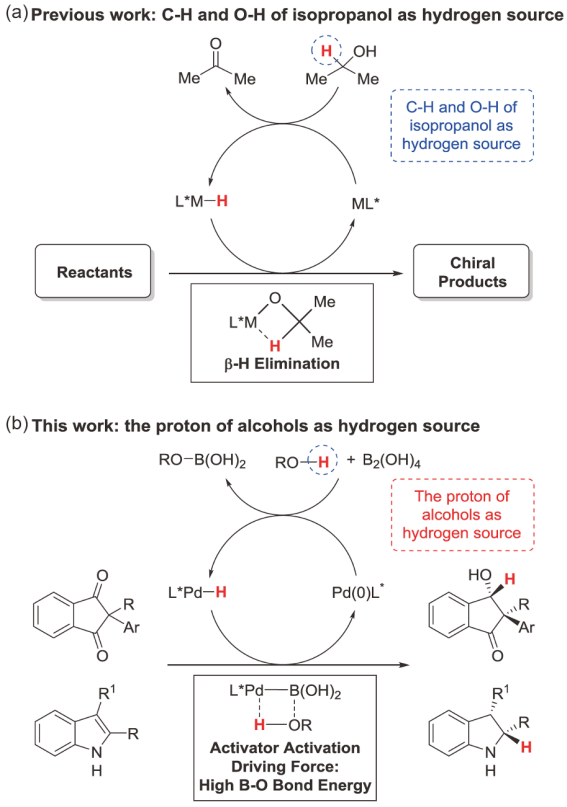
activated by titanocene chloride to generate metal hydride species. In 2016, Stokes and co-workers [16] developed palladium-catalyzed transfer hydrogenation of alkenes and alkynes with the proton of water as the hydrogen source and tetrahydroxydiboron as an activator. Subsequently, diboron-assisted transfer hydrogenation of the *N*-heteroaromatics, nitroarenes and alkenes was reported with the proton of water as a hydrogen source catalyzed by palladium catalyst [17–19]. Additionally, diboron-mediated reduction with the proton of water as a hydrogen source also has been successfully realized under metal-free conditions [22–24]. To the best of our knowledge, the direct utilization of the proton as a hydrogen source for activator-mediated transition-metal-catalyzed asymmetric reduction is still unknown. Therefore, the development of the proton as a hydrogen source in activator-mediated asymmetric reduction would provide a new strategy for the synthesis of chiral compounds, especially chiral deuterium-labeled compounds, which are important in pharmaceuticals [25,26], since deuterium-labeled alcohols and deuterium oxide are usually commercially available.

Chiral palladium-based catalytic systems have achieved great success in the asymmetric hydrogenation of various unsaturated compounds [27–36]. As our continuous efforts on transition-metal-catalyzed asymmetric reduction, we previously reported the homogeneous palladium-catalyzed enantioselective hydrogenation of imines, ketones, heteroaromatic compounds and olefins [30–36]. Considering that the O–H bond of alcohols might be activated by reductive tetrahydroxydiboron in the presence of chiral palladium catalysts to form chiral palladium hydride species due to the high B–O bond energy, we envisioned the application of this chiral palladium hydride species in asymmetric reduction of 1,3-diketones and indoles. Herein, we report the proton of alcohols as a hydrogen source in diboron-mediated palladium-catalyzed asymmetric reduction of 1,3-diketones and indoles, affording a series of chiral β-hydroxy ketones and indolines with high enantioselectivities (Scheme 1b). Mechanistic studies based on isotopic labeling experiments and capture of the active species, as well as DFT calculations, provided important insight into the diboron-mediated asymmetric reduction using the proton of alcohols as the hydrogen source.



Scheme 1 Transition-metal-catalyzed asymmetric reduction using alcohols (color online).

2 Experimental

General procedure for palladium-catalyzed asymmetric reduction of 1,3-diketones. $Pd(OCOCF_3)_2$ (6.6 mg, 0.02 mmol) and ligand (*S*)-SynPhos (16.6 mg, 0.026 mmol) were placed in a dried sealed tube under nitrogen atmosphere, and degassed anhydrous acetone was added. The mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum to give the catalyst. 1,3-Diketones (0.20 mmol), tetrahydroxydiboron (53.8 mg, 0.60 mmol) were added to the sealed tube. The sealed tube was taken into a glove box filled with nitrogen and the hexafluoroisopropanol (3.0 mL) was added. The mixture was stirred at 80 °C for 24 h. After cooling to room temperature, methanol (5.0 mL) was added and the reaction mixture was stirred at room temperature for 2 h. The mixture was evaporated. Then, ethyl acetate (5.0 mL) and saturated ammonia chloride (5.0 mL) were added. The reaction mixture was extracted with ethyl acetate (20 mL×3). The combined organic layer was dried by anhydrous sodium sulfate, concentrated *in vacuo*. Then, the crude product was purified by silica gel column chromatography using heanes/dichloromethane as eluent to give the reductive products. The optical purity was determined by chiral high performance liquid chromatography (HPLC) analysis.

3 Results and discussion

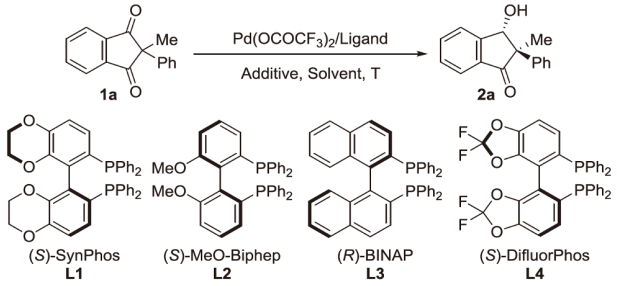
3.1 Reaction optimization

Chiral hydroxy ketones are prominent scaffolds in natural products and pharmaceuticals [37,38]. Asymmetric hydrogenation of 1,3-diketones is one of the most straightforward access to obtain chiral β-hydroxy ketones. Recerntly, tansition metal-catalyzed asymmetric reduction of 1,3-diketones

has been exploited and the hydrogen sources are focused on hydrogen gas and azeotrope of formic acid and triethylamine [36,39–43]. Considering alcohols and deuterium-labeled alcohols are usually commercially available, using the proton of alcohols in asymmetric reduction of 1,3-diketones would be an efficient approach for the preparation of chiral β-hydroxy ketones, especially chiral deuterium-labeled β-hydroxy ketones.

At the outset of the investigation, 1,3-diketone **1a** was chosen as a model substrate to explore diboron-mediated asymmetric reduction using the proton as a hydrogen source. Solvent played an important role in reactivity and stereoselectivity. Trace product was obtained with water as hydrogen source and solvent, probably due to the poor solubility of substrate and catalyst in water (Table 1, entry 6).

Table 1 Optimization of reaction conditions



Entry[a)]	Solvent	L	Additive	Yield (%)[b)]	ee (%)[c)]	dr[d)]
1 [e)]	CH_2Cl_2	**L1**	$B_2(OH)_4$	trace	–	–
2 [e)]	THF	**L1**	$B_2(OH)_4$	6	41	1:1
3 [e)]	^{i}PrOH	**L1**	$B_2(OH)_4$	trace	–	–
4 [e)]	TFE	**L1**	$B_2(OH)_4$	58	86	8:1
5 [e)]	HFIP	**L1**	$B_2(OH)_4$	90	98	21:1
6	H_2O	**L1**	$B_2(OH)_4$	trace	–	–
7	HFIP	**L1**	$B_2(OH)_4$	93	99	20:1
8 [f)]	HFIP	**L1**	$B_2(OH)_4$	78	92	9:1
9	HFIP	**L2**	$B_2(OH)_4$	94	97	15:1
10	HFIP	**L3**	$B_2(OH)_4$	95	81	12:1
11	HFIP	**L4**	$B_2(OH)_4$	56	91	8:1
12	HFIP	**L1**	$B_2(pin)_2$	37	88	5:1
13	HFIP	**L1**	$B_2(cat)_2$	complex	–	–
14 [g)]	HFIP	**L1**	$B_2(OH)_4$	82	98	14:1
15	HFIP	**L1**	–	trace	–	–
16 [h)]	HFIP	**L1**	$B_2(OH)_4$	93	97	15:1
17 [i)]	HFIP	**L1**	$B_2(OH)_4$	88	98	17:1
18 [j)]	HFIP	**L1**	$B_2(OH)_4$	89	97	13:1

a) Reaction conditions: **1a** (0.20 mmol), $Pd(OCOCF_3)_2$ (10 mol%), **L** (13 mol%), additive (0.60 mmol), solvent (3.0 mL), 80 °C, 24 h. b) Yield of the isolated mixture of the two diastereoisomers. c) Determined by HPLC. d) Determined by ^{1}H NMR spectroscopy. e) With H_2O (2.0 equiv.). f) $Pd(dba)_2$ (10 mol%) was used instead of $Pd(OCOCF_3)_2$ (10 mol%). g) $B_2(OH)_4$ (0.40 mmol) was used. h) $Pd(OCOCF_3)_2$ (5.0 mol%) and **L** (6.5 mol%) were used. i) 60 °C. j) 100 °C.

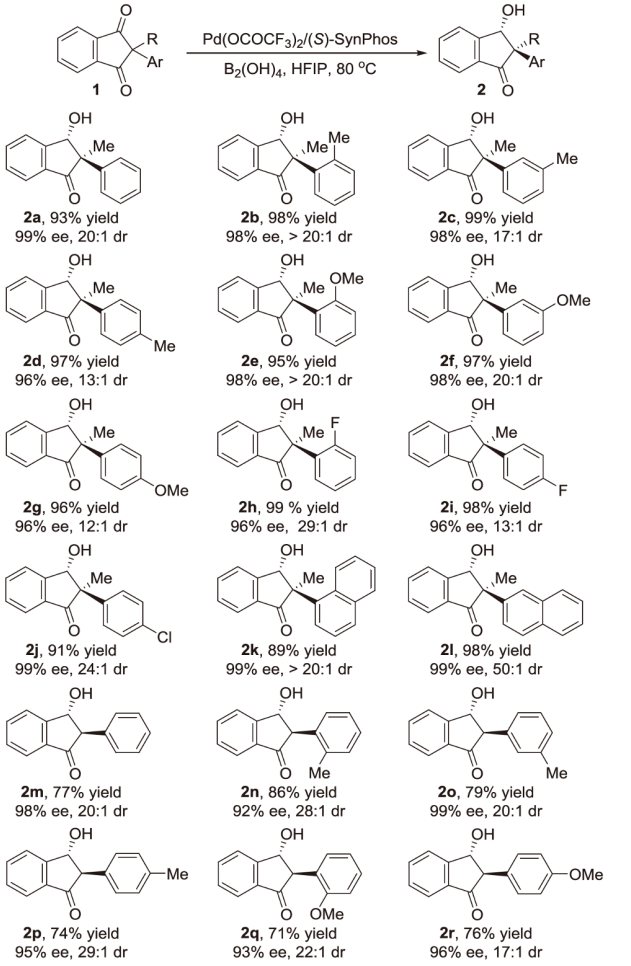
Hexafluoroisopropanol (HFIP) proved to be the most favorable solvent in view of enantioselectivity and diastereoselectivity (entries 1–6). When the asymmetric reduction was performed in HFIP without water, the desired product **2a** was obtained without the loss of reactivity and stereoselectivity (entry 7), suggesting that the addition of water was not necessary for alcoholic solvent. When metal precursor $Pd(dba)_2$ was used instead of $Pd(OCOCF_3)_2$, product **2a** was obtained in 78% yield, 92% ee (entry 8). Subsequently, commercially available chiral bisphosphine ligands were evaluated. It turned out that electron-donating ligand (*S*)-SynPhos **L1** was the best in overall terms (entries 7 and 9–11). The effect of the diboron reagents was explored. The moderate yield was obtained with bis(pinacolato)diboron ($B_2(pin)_2$) (entry 12). The yield decreased to 82% with 2.0 equiv. of $B_2(OH)_4$ (entry 14). This asymmetric transfer hydrogenation needed 3.0 equiv. of $B_2(OH)_4$, probably because $B_2(OH)_4$ could competitively be alcoholized by HFIP [44]. No reaction took place in the absence of diboron (entry 15). Finally, the influence of temperature was examined. Regardless of whether reaction temperature decreased or increased, the yield and diastereoselectivity could not be improved (entries 17 and 18).

3.2 Substrate scope

With the optimal reaction conditions, we explored the scope and generality of this transformation. As summarized in Scheme 2, in all cases, the asymmetric reduction performed successfully, delivering the corresponding β-hydroxy ketones containing two adjacent stereocenters in good yields with excellent enantioselectivities and diastereoselectivities.

For 1,3-cyclopentanediones **1a**–**1l** containing one α-quarternary stereocenter, the electronic and steric properties had no obvious influence on the enantioselective and diastereoselectivities of the reaction. For example, the asymmetric reduction furnished the desired products **2h** and **2k** in 96% and 99% ee, respectively. When using the non-benzofused 1,3-diketone as substrate, the desired product was achieved in excellent enantioselectivity albeit with low diastereoselectivity (see the Supporting Information for details). Moreover, 1,3-cyclopentandiones **1m**–**1r** containing one α-tertiary stereocenter were also suitable reduction substrates, providing the desired β-hydroxy ketones with good yields and up to 99% ee.

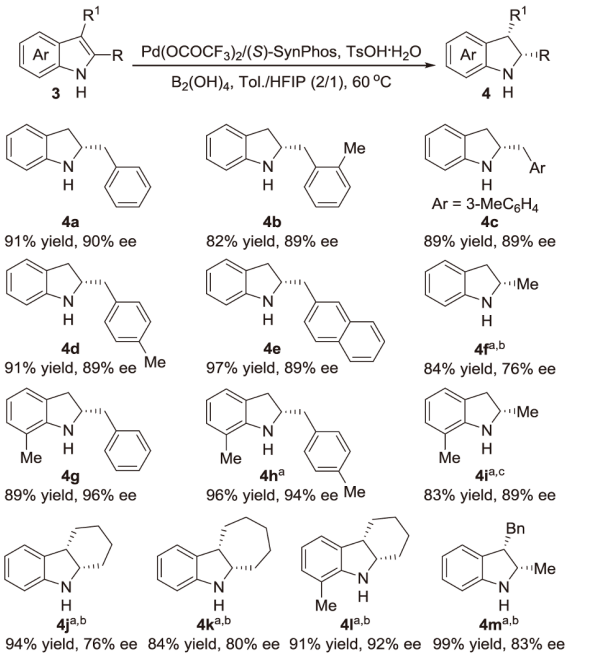
The initial success of the proton of alcohols as a hydrogen source in the enantioselective reduction of 1,3-diketones encouraged us to estimate their practical utility further. Chiral indolines are a significant class of alkaloids in a myriad of bioactive molecules [45–48]. Transition metal-catalyzed asymmetric reduction of unprotected indoles is an efficient and convenient method for the synthesis of chiral indolines [27,33,49–53]. We sought to evaluate this strategy



Scheme 2 Substrate scope: 1,3-diketones. Reaction conditions: **1** (0.20 mmol), $Pd(OCOCF_3)_2$ (10 mol%), (*S*)-SynPhos (13 mol%), $B_2(OH)_4$ (0.60 mmol), HFIP (3.0 mL), 80 °C, 24 h.

for asymmetric reduction of unprotected indoles. Firstly, the optimal reaction conditions were established by a variety of screening experiments. When the reduction was conducted with [(*S*)-SynPhos] $Pd(OCOCF_3)_2$ as a catalyst, tetrahydroxydiboron as an activator and *p*-toluenesulfonic acid monohydrate as the acid in toluene/HFIP (2/1) at 60 °C, the target product was delivered in 91% yield and 90% ee (see Table S1 in the Supporting Information for details).

With the optimal reaction conditions in hand, we tested the substrate scope of this reduction (Scheme 3). A series of 2-benzyl-substituted indoles **3a**–**3e** were reduced smoothly with excellent yields and enantioselectivities, regardless of the steric properties of the substituent on the aromatic ring. For 2-methylindole, when the reaction was carried out in HFIP at 80 °C, the desirable indoline **4f** was obtained in good yield, albeit with moderate enantioselectivity. Delightedly, 2-substituted indoles with a methyl group at the 7-position exhibited higher enantioselectivities (up to 96% ee). Moreover, six or seven fused ring indoles were employed in the reduction, delivering the desired products **4j**–**4l** with 76%–



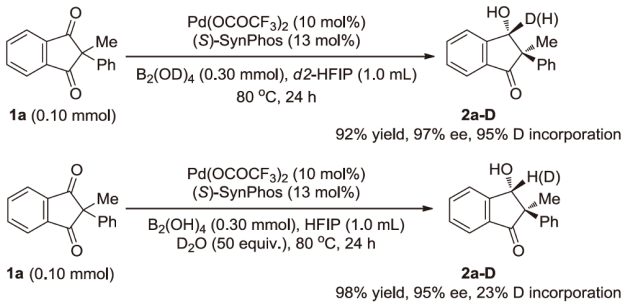
Scheme 3 Substrate scope: indoles. Reaction conditions: **3** (0.30 mmol), $Pd(OCOCF_3)_2$ (2.0 mol%), (*S*)-SynPhos (2.6 mol%), $B_2(OH)_4$ (0.90 mmol), Tol./HFIP (2.0 mL/1.0 mL), 60 °C, 24 h. a) 80 °C. b) HFIP (3.0 mL). c) Tol./HFIP (1.0 mL/2.0 mL).

92% ee. 3-Benzyl-2-methylindole was compatible, giving the target product **4m** in 83% ee.

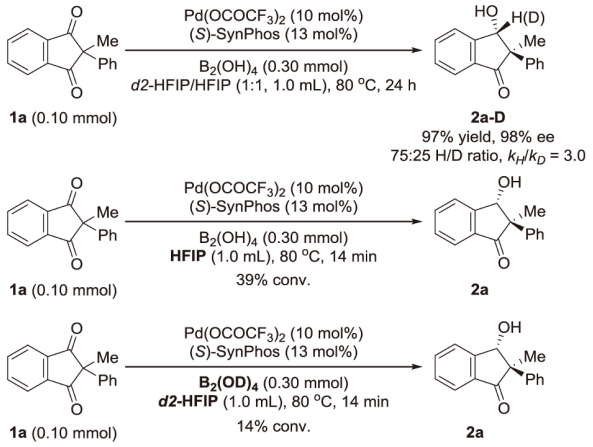
3.3 Mechanistic investigations

To well understand the origin of hydrogen source in the transformations, deuterium labeling experiments with 1,3-diketone **1a** were conducted. Subjection of **1a** to the standard conditions using prepared tetradeuteroxydiboron as activator and *d2*-HFIP (99% D, Acros Organics) as solvent with careful operation in dry atmosphere, 95% deuterium incorporation product **2a-D** was achieve (Scheme 4a). This result demonstrated that the hydrogen source for this asymmetric reduction was from the proton of alcohols. To further confirm it, another isotopic labeling experiment was performed. When the asymmetric reduction was run in HFIP (1.0 mL) with 50 equiv. of deuterium oxide, 23% deuterium incorporation was observed due to rapid proton/deuterium exchange between HFIP and deuterium oxide (Scheme 4b). This result could exclude that the hydrogen source for the reduction was from the β-hydride elimination of alcohols.

To explore the existence of kinetic isotope effect, the reaction was conducted with an equimolar mixture of *d2*-HFIP and HFIP, and the deuterium isotope effect of 3.0 was observed (Scheme 5a), indicating that hydrogen transfer might be the rate-determining step in the entire reduction process. To further probe the rate-determining step, we compared the reaction rate of a separate experiment. When asymmetric reduction of 1,3-diketone **1a** was carried out in HFIP for



Scheme 4 Isotopic labeling experiments.



Scheme 5 Experiments for the rate-determining step.

14 min, the conversion was 39% (Scheme 5b). The 14% conversion of **1a** was observed in *d2*-HFIP using prepared tetradeuteroxydiboron for 14 min (Scheme 5c). The reaction rate ratio was 2.8 and consistent with the deuterium isotope effect of 3.0.

To identify whether the diboron-mediated Pd-catalyzed asymmetric transfer hydrogenation was Pd(0)-catalyzed mechanism or Pd(II)-catalyzed mechanism and understand the origin of enantioselectivity, density functional theory (DFT) calculations were conducted. The possible pathways were calculated (see the Supporting Information for details). The full computed Gibbs energy profile of the most favorable pathway for diboron-mediated asymmetric transfer hydrogenation of 1,3-diketone **1a** using chiral catalyst [(*S*)-SynPhos]Pd(OCOCF$_3$)$_2$ **5** was shown in Figure 1. Initial transmetalation between catalyst **5** and tetrahydroxydiboron afforded Pd-B intermediate **A** *via* stepwise B–B bond cleavage and B–O bond formation with energy barriers of 28.4 and 28.6 kcal/mol, respectively. Subsequently, the reductive elimination of Pd(II) species **A** could occur to give Pd(0) species **B** by release of $CF_3COOB(OH)_2$, followed by the oxidative addition of $B_2(OH)_4$ to Pd(0) species **B**, giving Pd-B intermediate **C**. Then, σ-bond metathesis between **C** and alcohol could furnish the Pd-H species **D**, which was the rate-determining step with free energy barrier of 33.8 kcal/mol. However, the formation of Pd-H species from **5** by

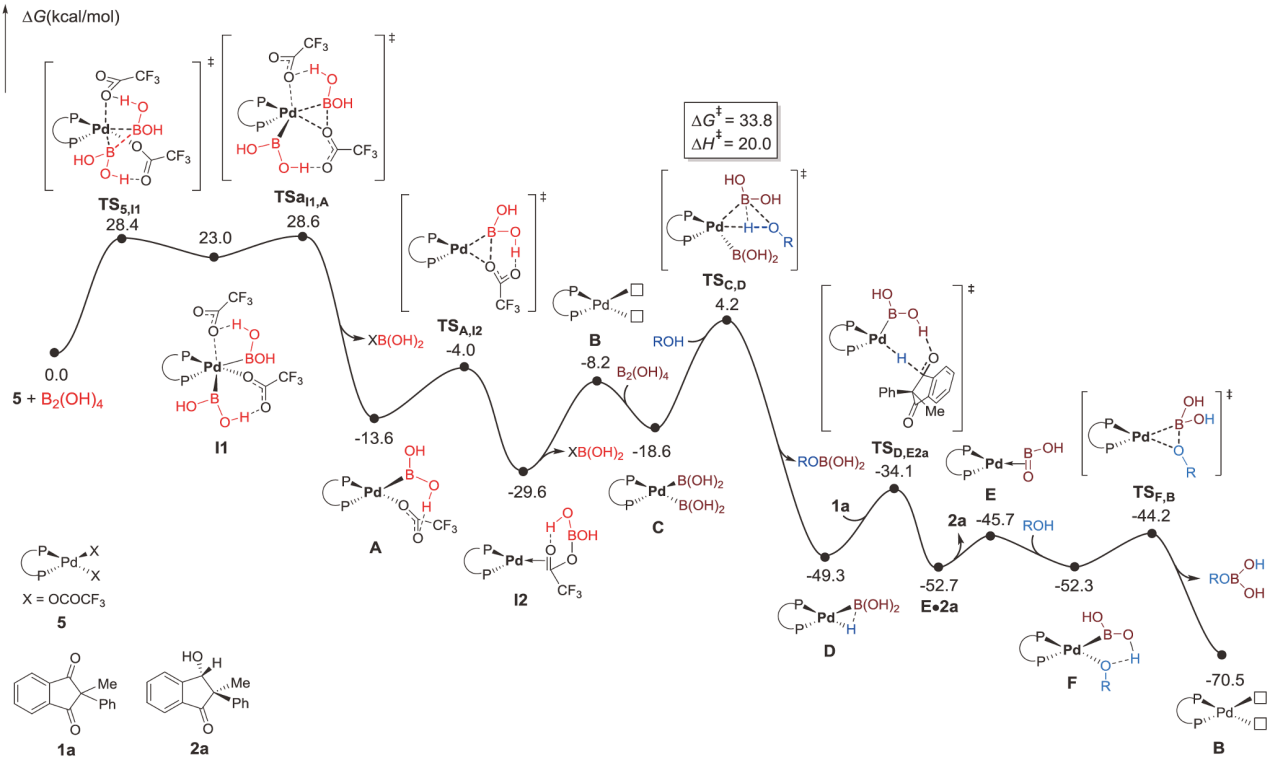
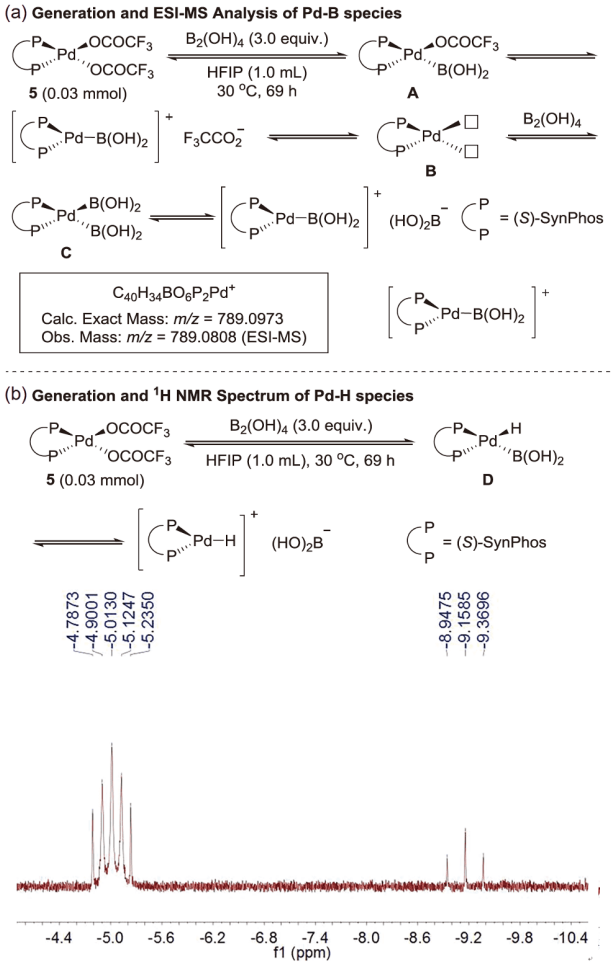


Figure 1 DFT computed free energy profile of favorable pathway for diboron-mediated Pd-catalyzed asymmetric transfer hydrogenation of 1,3-diketone (color online).

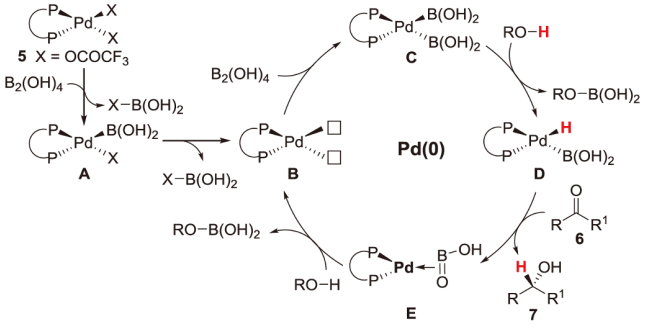
HFIP and $B_2(OH)_4$ was highly exergonic by 49.3 kcal/mol. Then, the asymmetric addition of Pd-H species **D** to ketone **1a** affords (2*R*,3*S*)-product **2a** and intermediate **E** with energy barrier of 15.2 kcal/mol and relative energy of −52.7 kcal/mol of **E•2a**, which was most kinetically and thermodynamically favorable (see Figure S17 for details). The calculated enantioselectivity was consistent with experimental observations. Finally, regeneration of Pd(0) species **B** from intermediate **E** could feasibly occur in the presence of HFIP.

To further gain insight into the reaction mechanism, possible active Pd-B and Pd-H species were captured. As shown in Scheme 6a, the chiral catalyst [(*S*)-SynPhos]Pd-$(OCOCF_3)_2$ was treated in HFIP with tetrahydroxydiboron at 30 °C for 69 h. Fortunately, electrospray ionization (ESI) mass spectroscopic analysis of the mixture showed a peak at m/z^+ 789.0808, matching the proposed structure of [(*S*)-SynPhos]Pd-$B(OH)_2$ cation (calc. mass: 789.0973) which could be generated from [(*S*)-SynPhos]Pd$(OCOCF_3)_2$ catalyst **5** and tetrahydroxydiboron. The active metal hydride species have been regarded as the key intermediate in the reduction reaction. Generally, the metal hydride species are formed in very low concentrations and are unstable in many conditions, and their determination is challenging [54–57]. To our delight, some proofs of Pd-H species were achieved in strictly controlled conditions and careful operation. A diagnostic virtual triplet was observed at −9.16 ppm (J = 84.4 Hz) in ^{1}H NMR spectrum (Scheme 6b). The chemical shift and coupling constants of hydrogen with phosphorus were consistent with the previous report of Pd-H species [33]. Additionally, we also found a diagnostic virtual quintet at −5.01 ppm (J = 111.9 Hz). This might be Pd-H species **D**, the hydrogen atom in which is possibly coupled with phosphorus and boron. These results revealed that the O–H bond of alcohols could be activated by diboron reagent for the generation of active Pd-H species.

Based on the aforementioned experimental results, DFT calculations and precedent reports [16,17,19], we proposed a plausible Pd(0) mechanism for proton as a hydrogen source in asymmetric reduction using the ketone **6** as a representative unsaturated compound (Scheme 7). Firstly, Pd(II) catalyst **5** was reduced by tetrahydroxydiboron to afford Pd(0) species **B** *via* transmetalation and reductive elimination [58]. The oxidative addition of tetrahydroxydiboron to Pd(0) species **B** could deliver Pd-B intermediate **C** [59]. Subsequently, alcohols coordinated to boron atom of intermediate **C** and hydrogen transferred from alcohols to palladium *via* σ-bond metathesis, generating chiral Pd-H active species **D**. Finally, the asymmetric migratory insertion of intermediate **D** into ketone **6** delivered the desired chiral reduced product **7** and intermediate **E**, which could conveniently regenerate Pd(0) species **B** and complete the catalytic cycle.



Scheme 6 (a) Generation and ESI-Mass analysis of Pd-B species, and (b) generation and ^{1}H NMR spectrum of Pd-H species (color online).



Scheme 7 Proposed Pd(0) mechanism (color online).

4 Conclusions

In conclusion, we have developed the first proton as a hydrogen source in diboron-mediated palladium-catalyzed asymmetric reduction. A series of chiral β-hydroxy ketones with two adjacent stereocenters including one α-tertiary or quaternary stereocenter and indolines are obtained with excellent yields and enantioselectivities. The experimental

mechanistic investigations revealed that the active chiral Pd-H species is generated from the proton of alcohols by the activation of tetrahydroxydiboron. Theoretical studies *via* DFT calculations suggested that hydrogen transfer was the rate-determining step and this asymmetric transfer hydrogenation preferred Pd(0)-catalyzed mechanism. This strategy using the proton of alcohol as hydride source will be useful for the development of activator-mediated asymmetric reduction and the facile synthesis of chiral deuterium-labelled compounds. Further studies are currently underway toward the expanding of this strategy to other unsaturated compounds and the application of the proton of water as hydrogen source in activator-mediated asymmetric reduction.

Acknowledgements This work was supported by the National Natural Science Foundation of China (21901239, 21532006) and the Strategic Priority Program of Chinese Academy of Sciences (XDB17020300, QYZDJ-SSW-SLH035).

Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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