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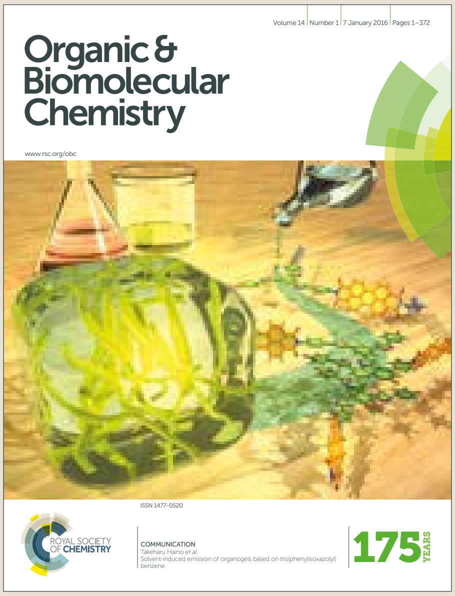

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ARTICLE

Umpolung of Proton from H_2O: A Metal-free Chemoselective Reduction of Carbonyl Compounds via B_2pin_2/H_2O Systems

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Qingqing Xuan,[a] Cong Zhao[a] and Qiuling Song[b]

H_2O is routinely described as proton donor, however, in the presence of diboron compounds, the successful umpolung reaction of H_2O under metal-free conditions was developed, which could afford hydride species, leading to a highly efficient and chemoselective reduction of C=O bonds. This strategy exhibits excellent chemoselectivities toward carbonyl group in the presence of ester, olefin, halogen, thioether, sulfonyl, cyano as well as heteroaromatic groups.

Introduction

Diboron compounds have been extensively explored in the past few decades, and these compounds now feature prominently in both metal-catalyzed and metal-free methodologies for the formation of B–C bonds.[1] However, as good deoxygenating reagents, the "reductive" property of diboron compounds has been far underdeveloped and underestimated.[2] Very recently, Stokes reported that $B_2(OH)_4$ could efficiently mediate the transfer of H or D atoms from water directly onto unsaturated C–C bonds using a palladium catalyst with CH_2Cl_2 as solvent.[3] Almost at the same time, we found that diboron compounds could chemoselectively promote the reductions of N-heteroaromatics under ambient temperature via transfer hydrogenation with water as both solvent and H donor.[4] Soon after, Prabhu and coworkers disclosed that H_2 was generated from H_2O in the presence of B_2pin_2 in toluene and C=C bonds, C≡C bonds were reduced smoothly.[5] These reports suggest that in the system of B_2pin_2/H_2O, H_2O may act as hydrogen source in transfer hydrogenations (TH). Although alcohols, formic acid, Hantzsch esters, hydrazine had been widely employed in TH,[6] H_2O was scarely used. With our ongoing pursuit of the new reactivities of diboron compounds, we, herein, would like report a highly chemoselective reduction of C=O bonds based on the umpolung reaction of proton from H_2O in B_2pin_2/H_2O systems.

H_2O, which is one of the most abundant molecules in the world, contains incredible capabilities and is the most important matter for living animals and plants. However, due to the intrinsic electronic difference between H and O atoms, H_2O is usually considered as a proton donor (Figure 1A). Presumably, if the polarity of proton from H_2O could be inverted (Figure 1B), just like umpolung reactions of carbonyls[7] and imines,[8] it would afford hydride species and create new opportunities for the efficient hydrogenation reactions from the most abundant and greenest H source on the earth.

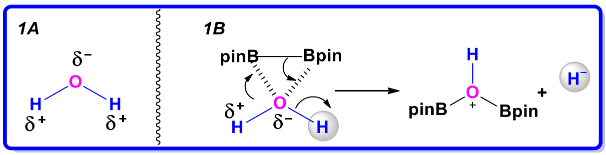
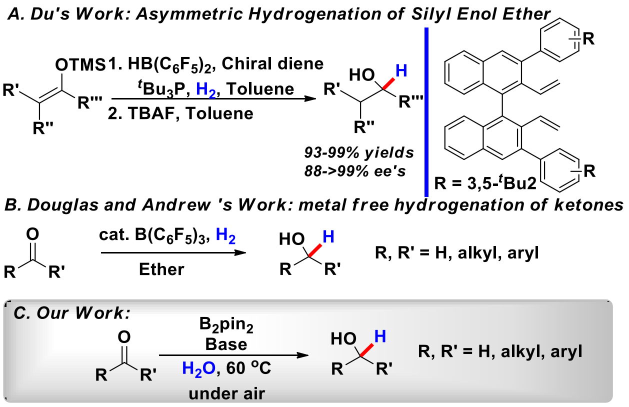


Figure 1. Natural and Inverted Polarity of H-atom of H_2O

The reduction of carbonyl compounds to alcohols is one of important processes for the synthesis of chemicals that are vital to our daily life. However, the catalysts that facilitate these reactions are predominantly based on rare, expensive, and often toxic transition metals.[9] Consequently there exists a strong incentive for chemists to develop new systems based on transition metal-free conditions.[10] In 2014, Du and coworkers reported a highly enantioselective H_2 involved synthesis of alcohols via FLPs (frustrated Lewis pairs) strategy from silyl enol ethers rather than ketones, as C=O bonds are more thermodynamically inert (Scheme 1A).[11] However, soon after, Douglas and Andrew independently reported the direct hydrogenation of C=O bonds still based on the concept of FLPs,



Scheme 1. Metal-free Hydrogenation of C=O Bonds

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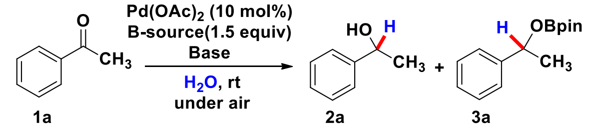
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x under totally metal-free conditions under H_2 atmosphere in ether (Scheme 1B).[12] Herein, we'd like to report our progress on the non-metal catalyzed hydrogenation of carbonyl compounds mediated by diboron reagents with water as hydride source as well as solvent (Scheme 1C).

Results and discussion

Our initial studies were carried out by examining the reduction of acetophenone (**1a**) under the standard conditions reported by our previous work (Table 1, entry 1).[4] Acetophenone (**1a**) was converted completely, affording the desired alcohol **2a** as well as unexpected **3a** in quantitative yield. After purification through silica gel chromatography, the B-O bond of **3a** was protonated and completely converted to **2a**.[13] The ratio of **2a** and **3a** was also determined by GC-MS. However, when more active diboron compound, $B_2(Cat)_2$, was employed, it gave messy results (Table 1, entry 2). Comparingly, when more inert $B_2(OH)_2$ was used, only trace amount of product was detected (Table 1, entry 3). The necessity of metal and base was also examined (Table 1, entry 4-5). Surprisingly, $Pd(OAc)_2$ was unnecessary; on the contrary, base was indispensible in our systems and it was found that the desired product was obtained in 51% yield in the presence of Cs_2CO_3 (0.5 equiv) alone. Thus, the metal-free mechanism might be quite different from the aforementioned [Pd-H] intermediate, which is sensitive to air. In order to prove our hypothesis, this metal-free reaction was conducted under air, to our delight, the desired product was obtained in 52% yield (Table 1, entry 6), which clearly demonstrated that this reaction undertakes a totally different pathway from our previous report. Next, the amount of base and temperature were furtherly investigated (Table 1, entry 7-8). It suggested that chemical equivelent of base was necessary and excellent yield was obtained at 60 °C.

Table 1. Reaction Optimization[a]

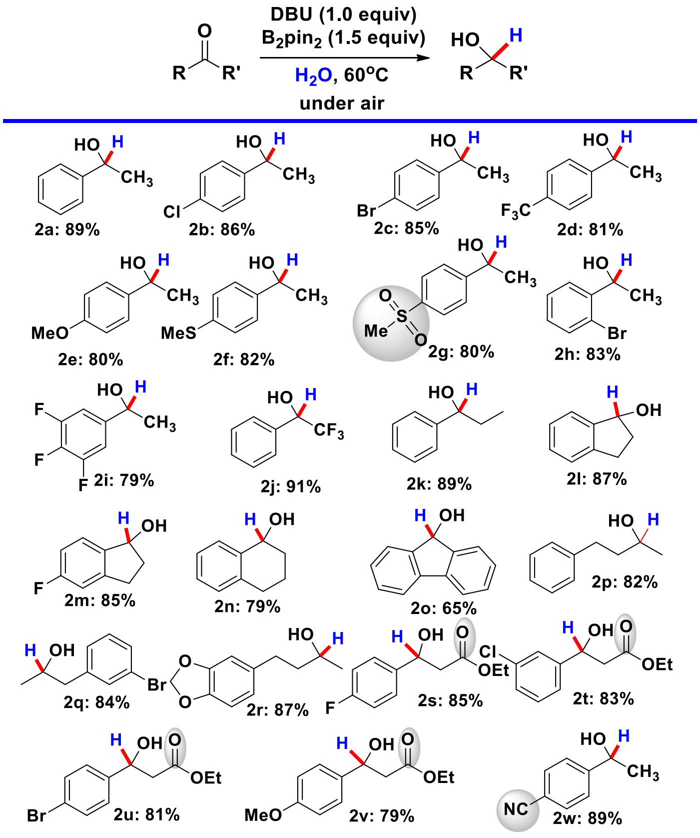


Entry	Metal	Base (equiv)	B-source	Yield (2a+3a)(%)[b]	Ratio (2a/3a)(%)[b]
1[c]	$Pd(OAc)_2$	Cs_2CO_3 (0.5)	B_2pin_2	quantitative	63/37
2[c]	$Pd(OAc)_2$	Cs_2CO_3 (0.5)	$B_2(Cat)_2$	complex	-
3[c]	$Pd(OAc)_2$	Cs_2CO_3 (0.5)	$B_2(OH)_4$	trace	-
4[c]	$Pd(OAc)_2$		B_2pin_2	trace	-
5[c]	-	Cs_2CO_3 (0.5)	B_2pin_2	51%	78/22
6	-	Cs_2CO_3 (0.5)	B_2pin_2	52%	81/19
7	-	Cs_2CO_3 (1.0)	B_2pin_2	78%	80/20
8[d]	-	Cs_2CO_3 (1.0)	B_2pin_2	95%	85/15
9[d]		DBU (1.0)	B_2pin_2	98%	86/14
10[d]		DBU (0.5)	B_2pin_2	71%	ND[e]
11[d]		DBU (0.2)	B_2pin_2	25%	ND[e]

[a] General procedure: **1a** (0.2 mmol), B-source (0.24 mmol), H_2O (2 ml), under air. [b] Determined by GC-MS. [c] The reaction was carried out under N_2. [d] The reaction was carried out at 60 °C. [e] Not detected.

In addition, organic base, such as DBU was tested in our reaction systems as well, and it showed superior reactivity over Cs_2CO_3 (Table 1, entry 9 vs entry 8), therefore DBU was chosen as the optimal base under our conditions. And with no surprise, the yield was decreased dramatically with catalytic amount of DBU (Table 1, entry 10-11).

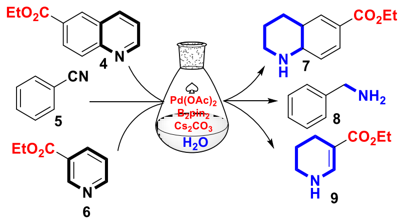
Gratifyingly, this metal-free catalytic systems were demonstrated to be highly effective and chemoselective toward the reduction of ketones (Scheme 2). Aryl ketones with either electron-donating or electron-withdrawing substituents on the benzene ring were all well tolerated under this reaction (**2a-2i**). When more electron deficient ketone, such as trifluoroacetophenone **1j** was used, the desired product was obtained in higher yield (**2j**). 1-Indanones (**1l-1m**), 1-tetralone (**1n**) and 9-fluorenone (**1o**) were also effective substrates to give the desired product in 65-87% yields (**2l-2o**). In addition, alkyl ketones underwent the reductive process smoothly, and afforded the corresponding alcohols in high yields (**2p-2r**). This catalytic system exhibited excellent chemoselectivity toward C=O bonds in the presence of ester and cyano groups as well as sulphone group (**2g**, **2s-2w**). Ester groups were very inert functional group, and they could be retained even in the presence of $Pd(OAc)_2$.



[a] All reactions were carried out with 1 (0.2 mmol), and isolated yields are reported.

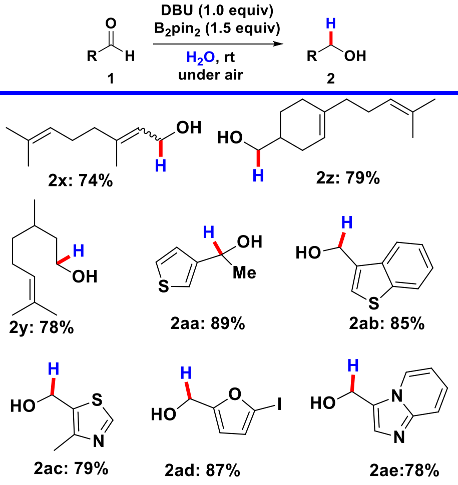
Scheme 2. Metal-free Chemoselective Hydrogenaton of Ketones

In fact, the reduction ability of B_2pin_2/H_2O systems can be fine controlled through the addition of $Pd(OAc)_2$ or not (Scheme 3). For instance, ethyl quinoline-6-carboxylate (**4**) and ethyl nicotinate (**6**) could be selectively hydrogenated on N-heterocycles in the presence of $Pd(OAc)_2$ under B_2pin_2/H_2O systems(under our previous condition B)[4], while ester groups were kept untouched.[1] In addition, benzonitrile (**5**) could also underwent the hydrogenation process smoothly, delivering benzylamine (**8**) under the above conditions.[14] Thus, compared with our current standard conditions, obviously, the reductive ability was increased when $Pd(OAc)_2$ was presented since cyano group was intact under our current standard condition yet it was reduced with $Pd(OAc)_2$ as catalyst. So, it's deemed that there would be great potential of B_2pin_2/H_2O systems to be developed.



Scheme 3. Chemoselective Hydrogenation on Various Functional Groups under $Pd(OAc)_2$, B_2pin_2, Cs_2CO_3 in Water.

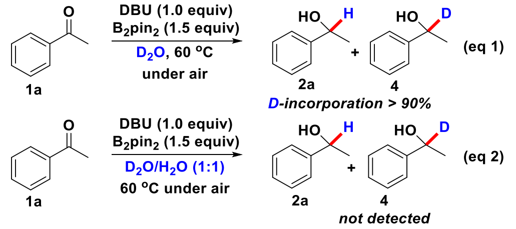
Chemoselective hydrogenation of unsaturated carbonyl compounds while maintaining the C=C bonds is an important class of reactions, because the corresponding unsaturated alcohols often serve as valuable intermediates in fragrances as well as pharmaceuticals.[15] However, these transformations are challenging, since the hydrogenation of C=O bond is thermodynamically and kinetically unfavored.[16] Several heterogeneous catalysts (metal nanoparticles supported on metal oxides) have been reported effectively to realize this transformation, as the metal oxides can serve as Lewis acid centre which might activate C=O bonds.[17] In our reaction systems, B_2pin_2 not only acted as deoxygenating reagent, but also served as Lewis acid. Thus, geraniol (**2x**), myrac alcohol (**2y**) and citronellol (**2z**) could be successfully afforded from the corresponding aldehydes (Scheme 4). In addition, heteroaromatic aldehydes could undergo hydrogenation smoothly on the C=O bonds under the standard conditions, while the hetero-aromaticity was well kept (**2aa**-**2ae**). It's worth to mention that N-heterocycles constructed pyridine-rings in our previous report; however, under this metal-free condition, the heteroaromatic rings was retained, while C=O bond was smoothly hydrogenated to afford product **2ae**.



[a]All reactions were carried out with 1 (0.2 mmol), and isolated yields are reported.

Scheme 4. Metal-free Chemoselective Hydrogenaton of Aldehydes with Various Unsaturated Systems.

In order to understand the origin of hydrogen, deuterium-labeled experiments were carried out with **1a** under standard conditions (Scheme 5). Deuterated product **4** was obtained with high deuterium incorporation (>90%) when the reaction was performed in absolute D_2O (eq 1). When the reaction was conducted with the mixture of H_2O/D_2O (1:1), interestingly, only product **2a** was obtained, and no deuterium was incorporated into the final product at all (eq 2). This reaction suggested that H atom transfer from polymer A to C=O bounds might be the rate-determing step (rds) in the entire process (Scheme 6), and it could not be a hydrogen gas involved reaction, which is consistent with our previous report as well as precedent literature.



Scheme **5**. Deuterium-Labeled Experiments

To figure out the B species which were existed during our transformation, the reaction was monitored by ^{11}B NMR spectroscopy (Figure 2). As we can see, the peak of starting material B_2pin_2, which showed at about 31.2 ppm, gradually diminished in our reaction process and a new peak showed at about 22.7 ppm, which was identical with the pinBOBpin, and became stronger along with the reaction going.

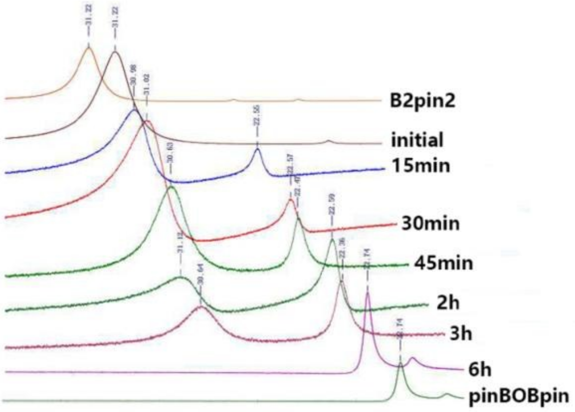


Figure 2 ^{11}B NMR Spectra of reaction process

Diborylation (type **I**) and monoborylation (type **II**) of C=O bonds had been achieved under the catalyst of copper (I) and base, which were deemed processing via copper(I) boryl complex.[18] Noteworthily, the two types of boronates were reported to be stable in water system[18a], and deboronation could not be easily occured even under basic conditions (heating is usually required to achieve the proton deboronation process whilst our reactions were proceeded under ambient temperature).[2c, 19] Under our systems, first of all , type **I** and type **II** products were not deteced by GC-MS in

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the crude reaction mixtures, secondly, ^{11}B NMR experiment for the entire reaction process (see Figure 2) also supported our observation in which only B_2pin_2 and pinBOBpin peaks showed up in the spectra and no other type of ^{11}B NMR was detected; presumably, if type **I** or type **II** products were generated in the reaction, they are stale in the reaction and could be either detected by GC-MS or observed by ^{11}B NMR. Based on the observations and analysis, we have reasons to believe that the Domino-Borylation-Protodeboronation (DBP) process did not occur in our system and thus it could be excluded.

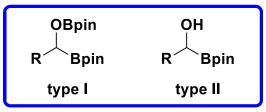
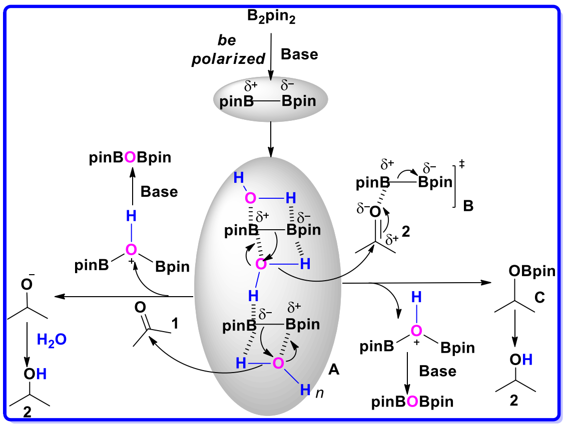


Figure 3 Diborylation and Monoborylation Products C=O bonds

Based on all the results of our experiments, we proposed the following mechanism (Scheme 6). B-B bond, which was polarized in the presence of base, could chelate with H_2O, forming species **A** under the electronic field effect, which was somewhat similar to solvation effect. In thes pecies **A**, the *O*-atom of H_2O was inserted into the polarized B-B bond, forcing *H*-atom to leave as a hydride species. Then, C=O bond was attacked by the hydride, followed by hydrolysis, affording the corresponding alcohols **2**. In our reaction system, compound **C** was also detected by GC-MS. It's deemed that, C=O bond would chelate with the polarized B-B bond to form species **B**, when attacked by the newly generated hydride, it gave compounds **C**. In this process, diboron compounds acted as Lewis acid, which could activate C=O bonds. This result might be the explanation for the selective hydrogenation of C=O bonds, even in the presence of conjugated C=C bonds. However, species **C** was unstable, it would be hydrolyzed to the corresponding alcohol when purified through silica gel column.



Scheme 6. Proposed Mechanism

Experimental

To a reaction tube equipped with a stir bar, 76.2 mg of B_2pin_2 (0.3 mmol) and base (0.02 mmol) were added. Next, 24.0mg (0.2 mmol) of acetophenone (**1a**) and H_2O (2ml) was added via syringe, then sealed the reaction tube. The mixture was stired at 60°C for about 10h. After the reaction was finished, the mixture was extracted with ethyl acetate, repeat three times. The combined organic layer was evaporated under reduced pressure, and the product was purified by column chromatography.

Conclusions

In conclusion, a novel and highly chemoselective hydrogenation of C=O bonds mediated by B_2pin_2 via umpolung of H_2O was disclosed. It is the first report that H_2O could serve as hydride donor activated by diboron reagent under metal-free conditions. This strategy exhibits excellent chemoselectivity on carbonyl group in the existence of halogen, ester, olefin, sulfonyl, thioether, cyano and heteroaromatic groups. The proposed mechanism suggested that diboron reagent might act as both activator of water as well as Lewis acid for activation of C=O group, which might explain the high chemoselectivity of this method. Enantioselective version of this transformation as well as further synthetic utility and detailed mechanism study is under the way in our laboratory.

Acknowledgements

The acknowledgements come at the end of an article after the conclusions and before the notes and references.

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