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Organocatalytic Reductive Coupling of Aldehydes with 1,1-Diarylethylenes Using the *in situ* Generated Pyridine-Boryl Radical

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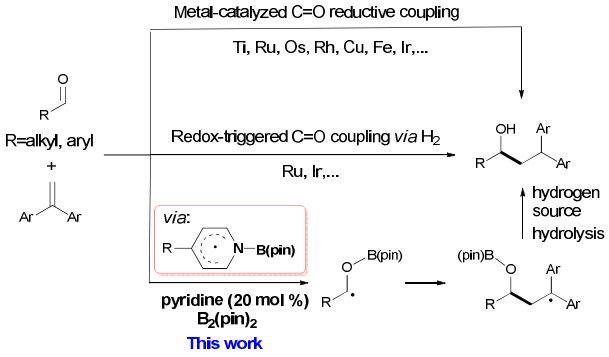
A pyridine-boryl radical promoted reductive coupling reaction of aldehydes with 1,1-diarylethylenes has been established *via* a combination of computational and experimental studies. Density functional theory calculations and control experiments suggest that the ketyl radical from the addition of the pyridine-boryl radical to aldehyde is the key intermediate for this C-C bond formation reaction. This metal-free reductive coupling reaction features a broad substrate scope and good functional compatibility.

Introduction

Carbon-carbon bond formation is the most important transformation in organic synthesis.[1] The catalytic reductive coupling of olefins with carbonyl compounds is one of the most economical C-C bond constructing method, due to the abundant source of olefins and carbonyl compounds.[2] Traditionally, transition metal catalysts have played privileged roles in these transformations, including the metal-catalyzed C=O reductive coupling (Scheme 1, top),[3-5] and redox-triggered C=O coupling via H_2 transfer (Scheme 1, middle).[4] However, sensitive organometallic reagents or transition-metal catalysts are usually required in these reactions. In contrast, organocatalytic reductive coupling of olefins with carbonyl derivatives for C-C bond formation in the presence of sensitive functional groups or congested structural environments is still rare.[5d]

Boron containing radicals are important reactive intermediates in organic synthesis.[6-13] In this context, our group recently revealed that the pyridine-ligated boryl radical (Py-Bpin·) could be readily generated from (pinacolato)diboron (B_2pin_2) through a cooperative catalysis involving two 4-cyanopyridine molecules.[11] This kind of the pyridine-boryl radical was used for the catalytic reduction of azo-compounds,[11] or as a carbon-centered radical for the synthesis of 4-substituted pyridines.[12] Moreover, the pyridine-boryl radical can act as a persistent radical[13] for the synthesis of organoboronate derivatives.[14] Because the precursors (pyridines and B_2pin_2) of these pyridine-boryl radicals are inexpensive and stable,[15] the development of new chemical transformations with these pyridine-boryl radicals is attractive. In this work, we further explored pyridine-boryl radical chemistry in the organocatalytic reductive coupling of aldehydes with 1,1-diarylalkenes (Scheme 1, bottom), which, to the best of our knowledge, has not been reported previously.



Scheme 1. Reductive coupling of carbonyl compounds with olefins.

Results and discussion

It will be shown that the reductive coupling of aldehydes and olefins can be promoted by the *in situ* generated pyridine-boryl radical, following the proposed pathway as shown in Scheme 2. The proposed catalytic cycle consists of the following four steps: (1) activation of the B–B bond of B_2pin_2 by pyridines to form a pyridine-boryl radical (**Int1**); (2) the addition of the pyridine-boryl radical to aldehyde **1a** to generate a new ketyl radical (**Int3**), and the pyrdine catalyst is

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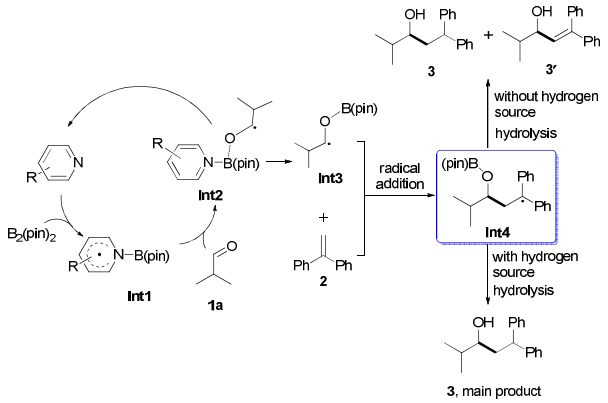
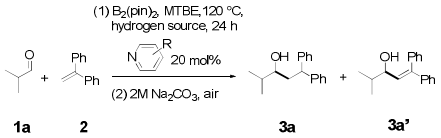
regenerated; (3) the addition of the new ketyl radical to 1,1-diphenylethylene to yield a diaryl-stabilized radical species (**Int4**); and (4) the hydrogen abstraction of **Int4** from an appropriate H-source to yield the final reductive coupling product. In addition, one molecule of I**nt4** may also abstract a hydrogen atom from another molecule of I**nt4** to give the reductive coupling product and another disproportionation product. To make this catalytic cycle happen, it is necessary to inhibit the possible radical-radical C-C coupling reaction between the pyridine-boryl radical and the ketyl radical, as observed between α,β-unsaturated ketones and 4-cyanopyridine in the presence of B_2pin_2.[12] Thus, other pyridines with different substituents may be better catalysts than 4-cyanopyridine for the proposed reaction. With a pyridine-boryl radical bearing a suitable substituent, its reactivity might be tuned so that the newly generated ketyl radical could react with 1,1-diphenylethylene to yield a diaryl-stabilized radical species, which then undergoes a hydrogen atom abstraction from an appropriate hydrogen source to produce the reductive coupling product.



Scheme 2. Proposed mechanism for the reductive coupling of isobutyraldehyde and 1,1-diphenylethylene.

To find out suitable pyridines which can react with B_2pin_2 to form the corresponding pyridine-boryl radical under mild conditions, we first performed density functional theory (DFT) calculations with the M06-2X[16] functional to screen a series of pyridines. A careful analysis of stationary points revealed that the formation of the pyridine-boryl radical proceed through a [3,3]-sigmatropic rearrangement/homolytic C-C bond cleavage pathway [17] rather than *via* the direct homolytic cleavage of the B-B bond [11,18] (see Figures S1 and S2 in supporting information for details). As shown in Figures S1-S12, the [3,3]-sigmatropic rearrangement is the rate-determining step for the formation of the corresponding pyridine-boryl radical. The activation barrier of this step with different pyridines is highly dependent on the substituent in the pyridine ring. Pyridines with an electron-withdrawing group at the C4 position, such as CN (**A**), 4-cyano phenyl (**B**), Ph (**C**), CF_3 (**D**), have lower barriers than the unsubstituted pyridine, and pyridines with an electron-donating group (CH_3, CH_3O, $N(CH_3)_2$). The pyridine with a CF_3 group at the C3 position has a slightly higher activation barrier than that with the same group at the C4 position (**D**>**E**). These results indicate that the activation barrier of pyridines correlates closely with the resonance effect and the inductive effect of the substituents. According to the calculated activation barriers, five pyridines (**A**, **B**, **C**, **D**, **E**) with barriers of no more than 28.5 kcal/mol are possible candidates for cleaving the B-B bond of B_2pin_2.

Table 1. Optimization of the reaction conditions.[a]



Entry	Hydrogen source	Pyridines with different R substituents	ratio [**3a**/**3a'**][b]
1	TMe-1,4-CHD	4-CN (**A**)	28%: 0%
2	TMe-1,4-CHD	4-(4-cyanophenyl) (**B**)	**78%: 6% (70%)**[c]
3	TMe-1,4-CHD	4-Ph (**C**)	16%: 2%
4	TMe-1,4-CHD	4-CF_3 (**D**)	21%: 1%
5	TMe-1,4-CHD	3-CF_3 (**E**)	0%
6	Et_3SiH	4-(4-cyanophenyl) (**B**)	62%:16%
7	--	4-(4-cyanophenyl) (**B**)	52%:16%

[a] Reaction conditions: isobutyraldehyde (0.2 mmol), $B_2(pin)_2$ (0.2 mmol), catalyst (0.04 mmol), 1,1-diphenylethylene (0.4 mmol), H-donor (0.2 mmol), 24 hours, 120 °C, MTBE (1 mL). [b] Yields were determined by ^{1}H-NMR analysis of the crude mixture using CH_2Br_2 as the internal standard. [c] isolated yield of **3a**. TMe-1,4-CHD=1,3,5-trimethyl-1,4-cyclohexadiene.

In order to determine a suitable combination of a pyridine catalyst and a hydrogen source, we conducted an initial investigation on the reaction between isobutyraldehyde **1a** and 1,1-diphenylethylene **2** (see Table S1 to S3 for details). As shown in Table 1, heating a mixture of isobutyraldehyde **1a** (1.0 equiv.), 1,1-diphenylethylene (2.0 equiv.), B_2pin_2 (1.0 equiv.) in the presence of 1,3,5-trimethyl-1,4-cyclohexadiene (a hydrogen source, 1.0 equiv.) and 4-cyanopyridine **A** (0.2 equiv.) in *tert*-butyl methyl ether (MTBE) at 120 °C, the desired reductive coupling product **3a** was observed in 28% yield (entry 1), together with a small amount of pyrdine-aldehyde adducts (12% yield, see supporting information for details). When 4-(4-pyridinyl)benzonitrile **B** was used as the catalyst (entry 2), the NMR yield of **3a** improved to 78%, and the yield of a byproduct **3a'** from the disproportionation of the diaryl radical intermediate (**Int4**) was 6%. However, when other pyridines (for example **C**, **D**, or **E**, entry 3-5) were adopted, the yield of **3a** decreased significantly. If Et_3SiH was chosen as the hydrogen source, the yield of **3a** is somewhat lower than that with 1,3,5-trimethyl-1,4-cyclohexadiene as a hydrogen source (entry 6). In the absence

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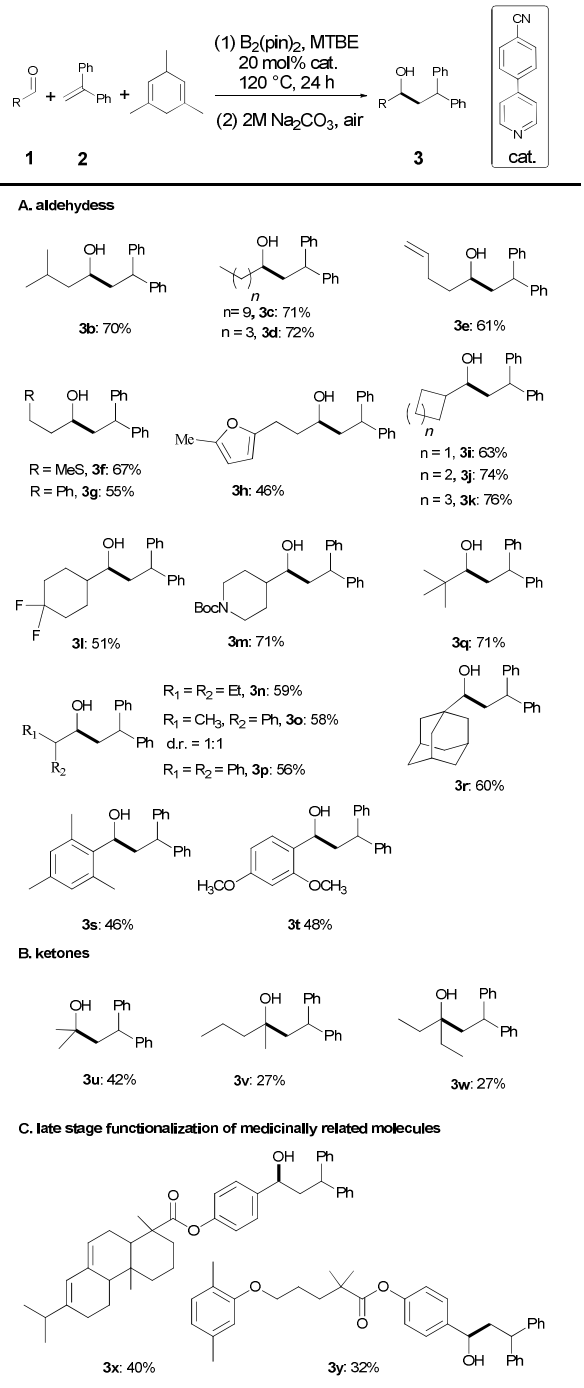
of a hydrogen source (entry 7), the ratio of **3a/3a'** was 52%: 16%, suggesting that the addition of a hydrogen source is important for improving the yield of **3a** (see Table S2).

Table 2. Substrate scope for the reductive coupling of aldehydes or ketones with 1,1-diphenylethylene.[a]



[a] Reaction conditions: aldehyde (0.2 mmol), $B_2(pin)_2$ (0.2 mmol), 4-(4-pyridinyl)benzonitrile (0.04 mmol), 1,1-diphenylethylene (0.4 mmol), 1,3,5-trimethyl-1,4-cyclohexadiene (0.2 mmol), MTBE (1.0 mL), 24 h, 120 °C. Isolated yield. The diastereoselectivities (d. r.) was determined by ^{1}H NMR analysis of the crude mixture. Boc=*tert*-butoxycarbonyl.

With the optimum conditions (Table 1, entry 2), we explored the generality of this transformation with a series of alkyl and aryl aldehydes. As shown in Table 2, the reductive coupling reactions of several fully aliphatic aldehydes proceeded with good efficiency (**1a**-**1d**). It was noteworthy that aldehydes with C=C double bonds (**1e**), methylthio (**1f**), or furyl (**1h**) functionalities on the alkyl chain were tolerated, giving the reductive coupling products in moderate to good yields. The α-branched aldehyde (**1i**-**1r**), in particular, pivaldehyde (**1q**) and 1-adamantylcarboxaldehyde (**1r**), also reacted well to afford the desired products in good yields. It should be mentioned that the substrates with congested structure environment show less reactivity in transtion-metal catalyzed reductive coupling of olefins and aldehydes, possibly because the coordination between metal centre and the corresponding substrates is difficult to occur.[4c] However, our method is also suitable for the bukyl aldehydes (**1q** and **1r**). Beside alkyl aldehydes, aryl aldehydes (**1s**, **1t**) bearing electron-donating groups (CH_3, CH_3O) could also serve as the coupling partners, furnishing corresponding products in moderate yields. In addition to aldehydes, alkyl ketones (**1u**-**1w**) also reacted smoothly to provide the desired alcohols in 27-42% yield.

Diarylalkanes are an important pharmacophore in drugs.[19] It would be attractive to apply this metal-free method in the late stage functionalization of medicinally related molecules. As shown in Table 2C, an abietic acid derivative (**1x**) and gemfibrozil derivative (**1y**) reacted smoothly with 1,1-diphenylethylene to form **3x** and **3y** in acceptable yields, respectively.

Next, the scope of 1,1-diarylalkenes (**4**) was examined (Table 3**a**). Both the symmetric (**4a**-**d**) and unsymmetric (**4e**-**o**) 1,1-diarylalkenes were converted into the corresponding products **5** in moderate to good yields with modest diastereoselectivities. The reaction tolerated substrates bearing various functional groups on the benzene ring, such as halogen functionalities (**4c**, **4d**), CF_3 (**4e**), CN (**4f**, **4g**), MeO (**4h**), CH_3S (**4i**), CO_2Me (**4j**), *t*Bu (**4k**). More importantly, 1,1-diarylalkenes containing heterocyclic structures (**4m**-**o**), such as benzofuran (**4o**) and thioxanthene (**4p**), also reacted smoothly to give the expected products in reasonable yields. Additionally, we also tested the reactivity of other alkenes with pivaldehyde **1q** (Table 3**b**). However, our results show that other alkenes, including ethyl 2-phenylacrylate (**4q**), styrenes (**4r**, **4s**) or aliphatic olefin (**4t**), generally gave little or no desired product. The reason why 1,1-diarylalkenes are suitable coupling partners of ketyl radicals may be due to (1) the radical stabilization effect of two aryl groups, and (2) the less nucleophilicity of present boron-ketyl radicals (compared with typical ketyl radicals).[5b] Thus, this protocol provides a metal-free reductive coupling method of 1,1-diarylalkenes with aldehydes (via the radical addition mechanism), which traditionally requires transition metal catalysts, or organometallic reagents.[12-16]

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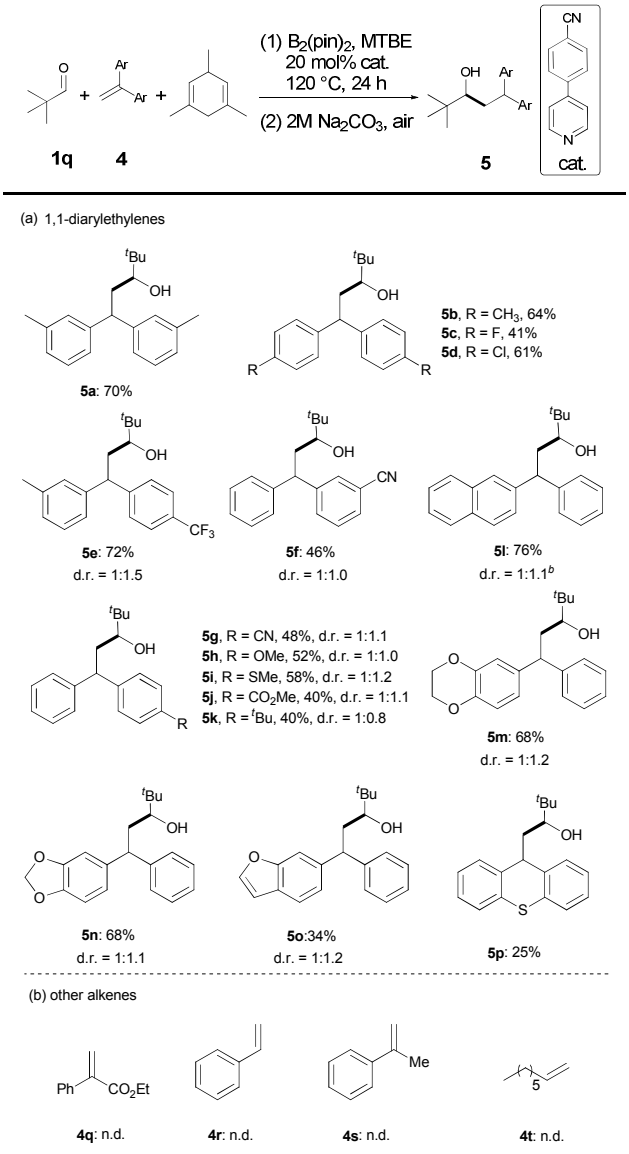
Table 3. Substrate scope for the reductive coupling of pivaldehyde with 1,1-diarylethylenes.[a]



[a] Reaction conditions: pivaldehyde (0.2 mmol), $B_2(pin)_2$ (0.2 mmol), 4-(4-pyridinyl)benzonitrile (0.04 mmol), 1,1-diarylethylene (0.4 mmol), 1,3,5-trimethyl-1,4-cyclohexadiene (0.2 mmol), MTBE (1.0 mL), 24 h, 120 °C. Isolated yield. The diastereoselectivities (d. r.) were determined by ^{1}H NMR analysis of the crude mixture. [b] The diastereoselectivities (d. r.) was determined by GC-MS analysis of the crude mixture. ^{t}Bu = *tert*-butyl.

To understand the mechanism of the reductive coupling of 1,1-diarylalkenes with aldehydes, we have performed DFT calculations with the M06-2X functional to explore the free energy profile of the proposed mechanism for the reaction between isobutyraldehyde (**1a**) and 1,1-diphenylethylene (**2**) in the presence of **Int1** as an reactive intermediate. Our theoretical studies have shown that the generation of **Int1** from B_2pin_2 and 4-(4-pyridinyl)benzonitrile is exergonic by 13.4 kcal/mol (see Figure S4). The calculated free energy profile and transition state structures are displayed in Figure 1 (the optimized structures of all minimum species are shown in Figure S12). First, the coordination of the oxygen atom of isobutyraldehyde to the boron atom of the pyridine-boryl radical **Int1** generates a boron-containing intermediate (**Int2**) via **TS1**, with a barrier of 13.3 kcal/mol. Then, the breaking of the B-N bond in **Int2** yields a ketyl radical (**Int3**) and regenerates the 4-(4-pyridinyl)benzonitrile catalyst. This process is exothermic by 4.5 kcal/mol, with a barrier of 3.2 kcal/mol (relative to **Int2**), suggesting that the formation of the ketyl radical (**Int3**) from **Int2** is possible. Next, the addition of **Int3** to the *β*-position of 1,1-diphenylethylene to form a diaryl-stabilized radical (**Int4**) via **TS3** is exothermic by 15.6 kcal/mol, with a barrier of 15.5 kcal/mol (with respect to the radical **Int3**). Finally, the final product is obtained with a hydrogen atom abstraction from 1,3,5-trimethyl-1,4-cyclohexadiene via **TS4** with a barrier of 26.3 kcal/mol (relative to the radical **Int4)**. The whole reductive coupling reaction is exergonic by 11.7 kcal/mol (with respect to the reactants **1a** and **Int1**). These results suggest that the studied reaction is thermodynamically and kinetically feasible under the experimental conditions. In addition, our calculations suggest that the direct single electron transfer (SET) process between pyridine-boryl radical and isobutyraldehyde is highly endergonic (see details in Figure S13 and Figure S14). Thus, the SET mechanism for the present reaction can be excluded.

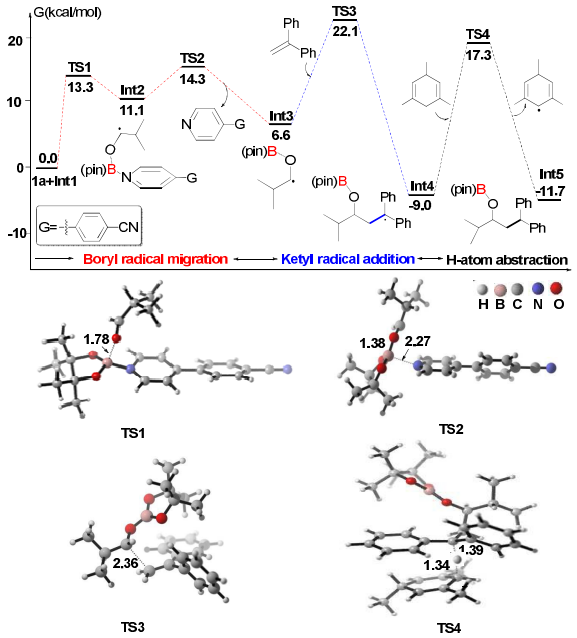


Figure 1. Computed Gibbs free energy profile of the reductive coupling reaction between isobutyraldehyde (**1a**) and 1,1-diphenylethylene (**2**) promoted by 4-(4-pyridinyl)benzonitrile-boryl radical (**Int1**). The optimized structures of transition states in the reaction path are also displayed. Interatomic distances are in Å.

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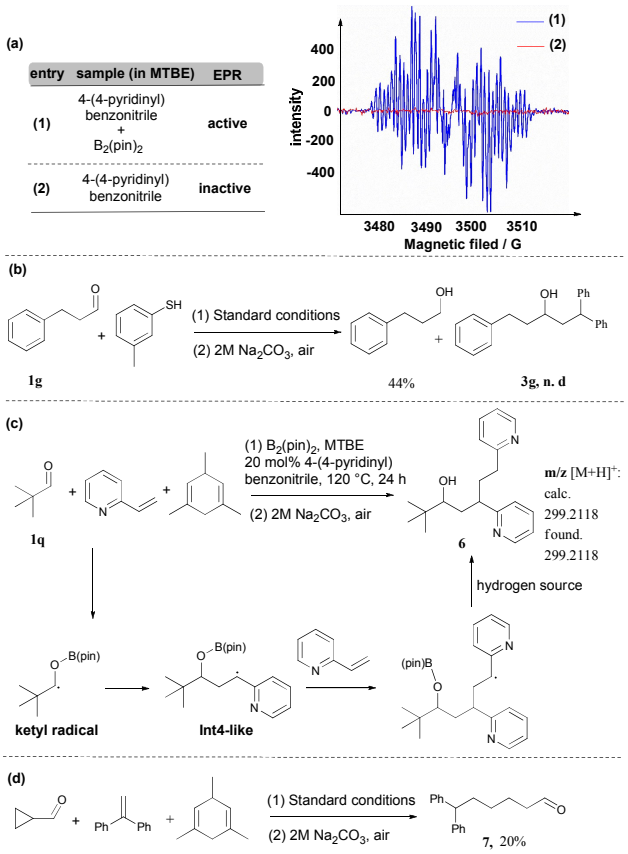

Scheme 3. Controlled experiments.

In addition to DFT calculations described above, we also conducted several experiments to verify the proposed pathway. First, EPR signal was observed for the reaction of 4-(4-pyridinyl)benzonitrile and $B_2(pin)_2$, which supports the formation of the proposed pyridine-boryl radical, as shown in Scheme 3a. Second, the involvement of the ketyl radical was confirmed by a competition experiment (Scheme 3b). It has been reported that thiols are quick hydrogen atom donors that can interfere the radical reaction.[20] When the hydrogen source 1,3,5-trimethyl-1,4-cyclohexadiene was replaced by 3-methylbenzenethiol, the ketyl radical quickly abstracted a hydrogen atom from 3-methylbenzenethiol to yield the reductive product, 3-phenyl-1-propanol, so that its addition to 1,1-diphenylethylene (to form the reductive coupling product) was inhibited (see page S20). This result clearly indicated the involvement of the ketyl radical. Third, the generation of the radical species **Int4** (or its analogues) *via* the addition of the ketyl radical to the β-position of arylethene was confirmed by an intermolecular trapping experiment (Scheme 3c). When 2-vinylpyridine and trimethylacetaldehyde was subjected to the standard reaction condition, the species **6** could be detected by HRMS analysis for the crude reaction mixture (see page S21). This result suggests that in this reaction, the radical species **Int4-like** was further trapped by another 2-vinylpyridine molecule. However, in the presence of 2-vinylpyridine as a substrate, the yield of **6** is quite low and its isolation from the reaction mixture was not successful. Besides, we further conducted analysis of ^{11}B NMR spectrum and HRMS to detect the formation of the proposed O-boron intermediate (**Int6,** Figure S17). The ^{11}B NMR of the crude reaction mixture displays resonances at ~21 ppm, which is consistent with the signal of a boron atom bound to three oxygen atoms.[21] In addition, our HRMS analysis (with 4-vinylpyridine as the substrate) also indicates the formation of the O-boron intermediate (**Int7**), as shown in Figure S18. Moreover, we have performed a radical-clock study using cyclopropanecarboxaldehyde as the substrate. The experimental results indicate that some ketyl radicals first convert into the corresponding carbon radicals (via a ring-opening process) and then add to the alkene to form the ring-opening product (Scheme 3d). The experiments described above provide a strong evidence on the involvement of a radical addition step betw0een the ketyl radical and 1,1-diarylethylene in this reaction.

Conclusions

In summary, we have established the organocatalytic reductive coupling of aldehydes with 1,1-diarylalkenes *via* a combination of computational and experimental studies. This study showed that 4-(4-pyridinyl)benzonitrile is a suitable catalyst for cleaving the B–B bond of B_2pin_2, and the ketyl radical from the addition of the *in situ* generated pyridine-boryl radical to aldehyde is a key intermediate for the C-C bond formation. The reaction is practical, and applicable to a broad range of aldehydes and 1,1-diarylalkenes with good functional group tolerance. DFT calculations and control experiments were conducted to verify the proposed mechanism. This pyridine-boryl radical promoted radical addition mechanism represents a metal-free reductive coupling reaction of aldehydes with 1,1-diarylalkenes. Further studies will be directed toward the development of new transformations involving the readily formed pyridine-boryl radicals with the aid of combined theoretical and experimental studies.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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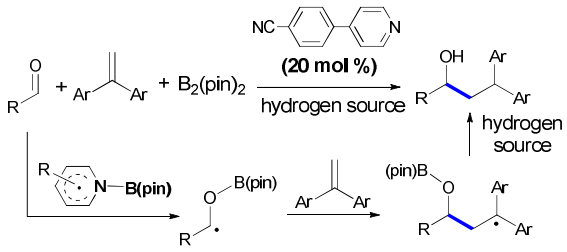
Organocatalytic Reductive Coupling of Aldehydes with 1,1-Diarylethylenes Using the *in situ* Generated Pyridine-Boryl Radical

*Jia Cao,+ Guoqiang Wang,+ Liuzhou Gao, Xu Cheng, and Shuhua Li**



A pyridine-boryl radical promoted reductive coupling reaction of aldehydes with 1,1-diarylethylenes has been established.