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Cu-Catalyzed highly selective reductive functionalization of 1,3-diene using H_2O as a stoichiometric hydrogen atom donor†

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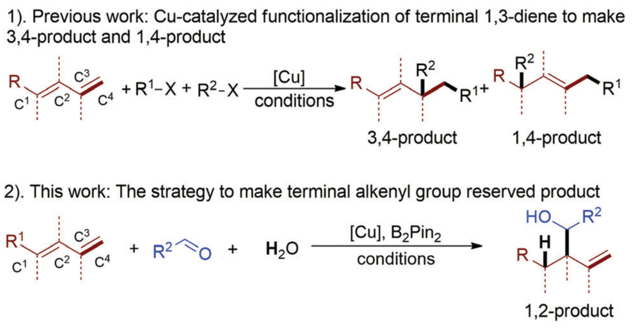
A copper-catalyzed highly regio- and diastereo-selective reductive reaction of terminal 1,3-diene with water and aldehyde has been developed. This chemistry afforded a product containing a terminal alkenyl group, which is a versatile kind of precursor for organic synthesis, with the scope for various substrates. The present reaction system could realize the catalytic transfer of hydrogen to diene using water as a stoichiometric H atom donor. In this transformation, B_2Pin_2, a mild and practical kind of reductant was used as the mediator. The reaction pathway of this practical strategy was illustrated by a control experiment.

Developing new organic transformation strategies to preserve an active functional group is important for the synthesis of drugs, natural products and functional material molecules.[1] Among a lot of versatile starting compounds, 1,3-diene has caught more and more attention, because the difunctionalization of a conjugated diene with high regio- and diastereo-selectivity is an important type of transformation, which allows the controlled formation of multiple complex isomeric products from a simple precursor.[2,3] In recent years, copper-catalyzed reaction systems have been extensively applied in such reactions, owing to the low price of copper-catalysts, ambient reaction conditions or practical reaction protocols.[4] With such a powerful strategy, the terminal diene can be converted into a 1,4- or 3,4-functionalized product with good selectivity (1, Scheme 1). Compared with the above synthetic strategy, we have developed a novel copper-catalyzed B_2Pin_2 mediated highly regio- and diastereo-selective functionalization of terminal 1,3-diene to afford a 1,2-functionalized product (2, Scheme 1).

In contrast to other metal reagents, the organic boron-reagent is much more stable, and practical as it reacts under ambient conditions, so the preparation of this kind of compound has been studied intensely.[5] Among these methods, the hydroboration of dienes affords important boron reagents, which are powerful intermediates in many transformations.[6] However, some air or moisture sensitive reagents and catalysts, such as $Ni(cod)_2$ or HBPin, are usually used for these reactions. The present transformation results in the formation of an allyl boron intermediate with good regioselectivity using a copper-salt/H_2O/B_2Pin_2 system, which makes this method more practical. Importantly, examples of the catalytic transfer hydrogenation of simple alkenes using H_2O as the stoichiometric H atom donor show that it is a sustainable strategy for organic synthesis.[7] Our work exploits a new way of using H_2O as a safe and cost-efficient hydrogen atom source for a highly selective catalytic reductive transformation process.

Our study commenced with the copper-catalyzed reaction of (*E*)-buta-1,3-dien-1-ylbenzene (**1a**), benzaldehyde (**2a**), B_2Pin_2 and H_2O. Interestingly, this practical one-pot reaction afforded 2-benzyl-1-phenylbut-3-en-1-ol (**3aa**) with 76% yield and 5 : 1 diastereoselectivity (entry 1, Table 1 and ESI†). The efficiency of this reaction decreased when other kinds of bases were used, such as NaO^t-Bu, KO^t-Bu, or LiOMe (entries 1–4, Table 1 and ESI†). We then surveyed the effect of different solvents. Compared with THF, 1,4-dioxane induced low yield and selectivity, but toluene and DCE afforded much better results (entries 5 to 7, Table 1).



Scheme 1 Functionalization of terminal 1,3-diene.

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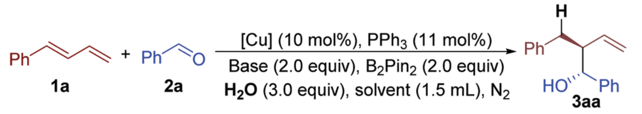
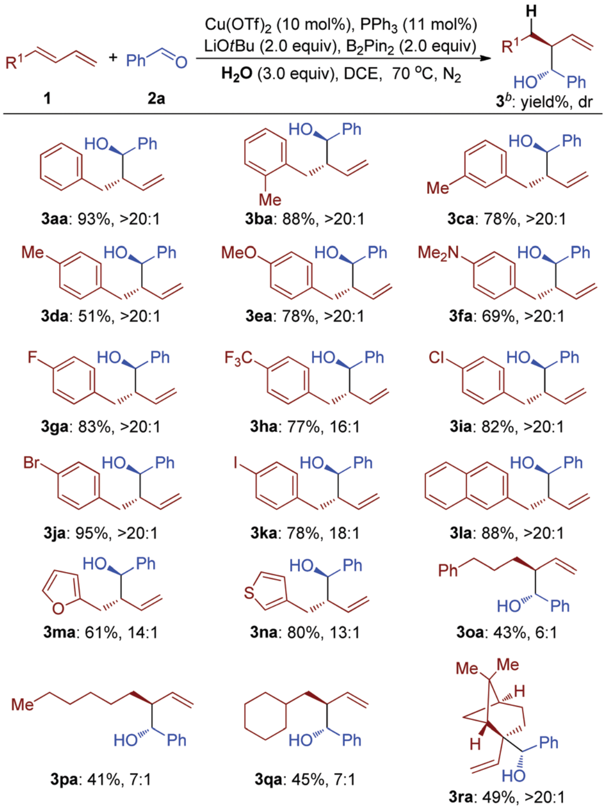
Table 1 The effect of different reaction conditions[a]



Entry	Solvent	Base	[Cu]	Yield[b] (%)	dr
1	THF	LiO^t-Bu	Cu(OTf)$_2$	76	5 : 1
2	THF	NaO^t-Bu	Cu(OTf)$_2$	52	4 : 1
3	THF	KO^t-Bu	Cu(OTf)$_2$	69	5 : 1
4	THF	LiOMe	Cu(OTf)$_2$	66	2 : 1
5	1,4-Dioxane	LiO^t-Bu	Cu(OTf)$_2$	64	4 : 1
6	Toluene	LiO^t-Bu	Cu(OTf)$_2$	80	9 : 1
7	DCE	LiO^t-Bu	Cu(OTf)$_2$	93	> 20 : 1
8	DCE	LiO^t-Bu	Cu(acac)$_2$	76	> 20 : 1
9	DCE	LiO^t-Bu	CuCl	78	> 20 : 1
10	DCE	LiO^t-Bu	CuOAc	23	13 : 1
11[c]	DCE	LiO^t-Bu	Cu(OTf)$_2$	0	—
12	DCE	LiO^t-Bu	None	0	—

[a] **1a** (0.25 mmol), **2a** (0.5 mmol), B_2Pin_2 (0.5 mmol), base (0.5 mmol), cat (10 mol%), PPh_3 (11 mol%), H_2O (3.0 equiv.), solvent (1.5 ml). [b] Isolated yield, diastereomers are inseparable, dr was determined by ^{1}H-NMR. [c] Without B_2Pin_2.

Table 2 Cu-Catalyzed B_2Pin_2 mediated reductive reaction of **2a** with different terminal 1,3-dienes (**1**)[a]



[a] Standard reaction conditions: **1** (0.25 mmol), **2a** (0.5 mmol), B_2Pin_2 (0.5 mmol), LiO^t-Bu (0.5 mmol), Cu(OTf)$_2$ (10 mol%), PPh_3 (11 mol%), H_2O (3.0 equiv.), DCE (1.5 ml), 70 °C, under N_2 condition. [b] Isolated yield, diastereomers are inseparable, dr was determined by ^{1}H-NMR.

In particular, when DCE was chosen as a solvent, the product could be obtained with 93% yield and better than 20 : 1 diastereoselectivity (entry 7, Table 1). Further studies indicated that different kinds of copper-salts affected the result of this reaction (entries 8 to 10, Table 1). Among them, Cu(OTf)$_2$ was the best choice. The data for entries 11 and 12 proved that this reaction did not proceed without a copper catalyst or B_2Pin_2 (Table 1).

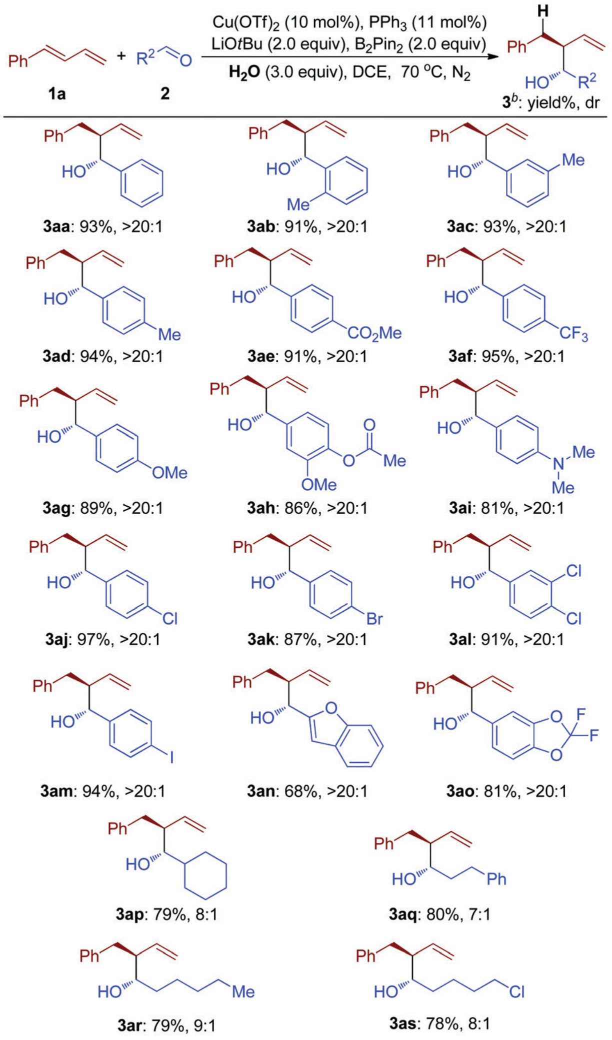
Using H_2O as a hydrogen atom donor and B_2Pin_2 as a mediator for this reductive transformation, the substrate scope of terminal 1,3-diene was investigated (Table 2). In general, modest to good yields and diastereoselectivity using either electron-rich (MeO– and Me$_2$N–), or electron-deficient (F–, CF$_3$– and Cl–) aryl substituted 1,3-diene were observed (**3aa** to **3ka**, Table 2). And, substituents at the *ortho*-position of the arene group did not affect the efficiency (**3ba**, Table 2). Notably, when bromo-substituted aromatic 1,3-diene was employed as a substrate, the corresponding product was afforded in 95% yield with great selectivity, which could be used for further transformation (**3ja**, Table 2). The iodo-substituted aromatic 1,3-diene still worked, but with lower efficiency (**3ka**, Table 2). To our delight, the naphthyl, furyl and thienyl groups survived under these reductive reaction conditions (**3la** to **3na**, Table 2). Importantly, alkyl 1,3-diene was smoothly transformed into the corresponding products (**3oa** to **3ra**, Table 2). The 1,2-disubstituted 1,3-diene still worked well, giving a product containing a quaternary carbon atom (**3ra**, Table 2).

The substrate scope of the Cu-catalyzed B_2Pin_2 mediated highly selective reductive transformation was further expanded to a variety of substituted aldehydes (**2**) (Table 3). These results indicated that aryl aldehyde with both electron-donating and electron-withdrawing groups proceeded well with good yields and great diastereoselectivity (**3aa** to **3ap**, Table 3). Substrate groups at the *para*-, *meta*-, and *ortho*-positions of the arene ring did not affect the efficiency (**3ab** to **3ad**, Table 3). Notably, even when bromo-substituted or iodo-substituted arylaldehyde was employed as a starting material, good results were afforded (**3ak** and **3am**, Table 3). These products could be used for a further coupling reaction to make complicated molecules. Moreover, under these ambient reaction conditions, the substrates with hetero-cycle groups could be converted into the desired products with good efficiency, which demonstrated the good substrate tolerance of this method (**3an** and **3ao**, Table 3). Furthermore, the substrate scope was expanded to alkyl aldehydes, affording good yields and moderate diastereoselectivity (**3ap** to **3as**, Table 3).

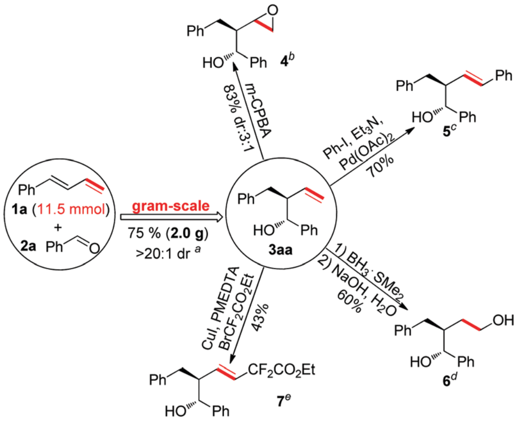
To test the feasibility of a large-scale reaction, the reaction of (*E*)-buta-1,3-dien-1-ylbenzene (**1a**) (11.5 mmol) and benzaldehyde (**2a**) (23 mmol) was investigated. The reaction afforded 2.0 g of **3aa** (75% yield) with great diastereoselectivity (a, Scheme 2). The product of this chemistry, which installed a terminal alkenyl group, is a kind of versatile intermediate for chemical synthesis. As shown in Scheme 2, the product **3aa** went through an epoxidation reaction,[8] a Heck reaction,[9] a hydroboration–oxidation reaction[10] and a radical coupling reaction[11] to afford the desired complex products smoothly (b, c, d and e, Scheme 2).

To investigate the mechanism of this transformation, control experiments were designed. Firstly, without benzaldehyde (**2a**), compound **8** was separated with 96% yield (eqn (1), Scheme 3).

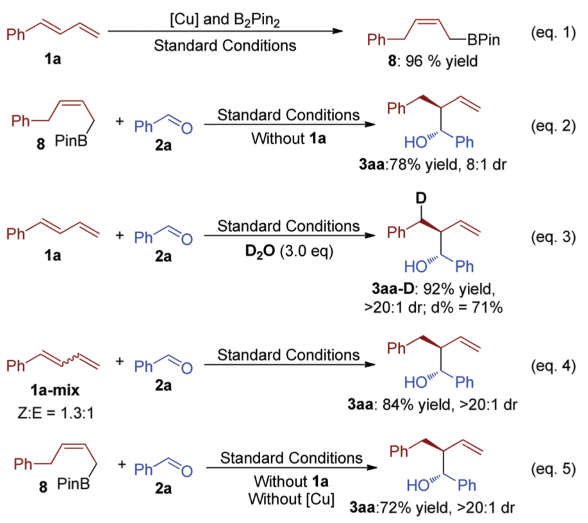
Table 3 Cu-Catalyzed B_2Pin_2 mediated reductive reaction of **1a** with different aldehydes (**2**)[a]



[a] Standard reaction conditions: **1a** (0.25 mmol), **2** (0.5 mmol), B_2Pin_2 (0.5 mmol), LiO^t-Bu (0.5 mmol), $Cu(OTf)_2$ (10 mol%), PPh_3 (11 mol%), H_2O (3.0 equiv.), DCE (1.5 ml), 70 °C, under N_2 condition. [b] Isolated yield, diastereomers are inseparable, dr was determined by ^1H-NMR.



Scheme 2 Gram-scale reaction and further transformation of the product. [a] **1a** (11.5 mmol), **2a** (23 mmol), B_2Pin_2 (23 mmol), LiO^t-Bu (23 mmol), PPh_3 (11 mol%), $Cu(OTf)_2$ (10 mol%), DCE (69 ml), isolated yield. [b] **3aa** (0.25 mmol), *m*-CPBA (0.375 mmol), DCM (1.3 ml), isolated yield. [c] **3aa** (0.185 mmol), Ph-I (0.37 mmol), $Pd(OAc)_2$ (10 mol%), Et_3N (1.85 mmol), CH_3CN (1.8 ml), isolated yield. [d] **3aa** (0.2 mmol), $BH_3{\cdot}SMe_2$ (0.6 mmol), NaOH (0.9 mmol), H_2O_2 (1.2 mmol), THF (2.0 ml), isolated yield. [e] **3aa** (0.2 mmol), $BrCF_2CO_2Et$ (0.3 mmol), CuI (10 mol%), PMDETA (0.3 mmol), CH_3CN (1.0 ml), isolated yield.

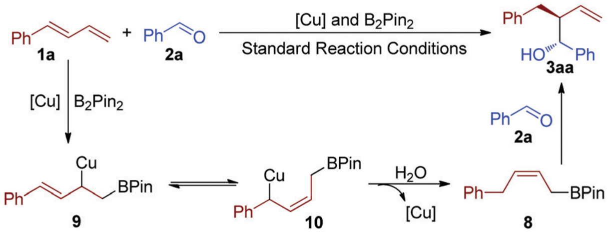


Scheme 3 Control experiments.

This result suggested that **8** should be the key intermediate of the present transformation. Furthermore, when it was put under similar standard conditions, the desired product **3aa** was afforded with good yield (eqn (2), Scheme 3). A slight difference in the reaction system might affect the diastereoselectivity and yield, which exhibited the advantage of this one pot-reaction strategy. The reaction of **1a** and **2a** was tested in the presence of D_2O, and the D-labeled product could be detected (eqn (3), Scheme 3). This result proved that H_2O is the stoichiometric H atom donor of the Cu-catalyzed B_2Pin_2 mediated highly selective reductive transformation. Importantly, when a mixed *Z* and *E* version of buta-1,3-dien-1-ylbenzene was selected as the starting material, this chemistry afforded a similar result to the example of **3aa** from Table 1 (eqn (4), Scheme 3). This data suggests that the isomerization process of the allyl copper intermediate might be involved in this transformation. Furthermore, without a copper-catalyst, **8** reacted with **2a** afforded **3aa** with good yield and diastereoselectivity (eqn (5), Scheme 3). This result suggests that copper did not participate in this step of the reaction.

On the basis of the above control experiments, a proposed mechanism for the highly selective reductive reaction is illustrated in Scheme 4. The first step of this reaction is the formation of the tautomeric copper complexes **9** and **10**.[4c,f,12] The intermediate **10** reacted with water to give intermediate **8**, which was proved by the control experiment.[4f] Further reaction of **8** with benzaldehyde (**2a**) afforded product **3aa**.[13]

In summary, we have demonstrated a novel Cu-catalyzed B_2Pin_2 mediated highly selective reductive functionalization of 1,3-diene using H_2O as the hydrogen donor. This practical chemistry afforded the terminal alkenyl group containing



Scheme 4 The proposed reaction mechanism.

product with various substrate scopes, a useful building block for use in organic synthesis. Furthermore, this method supported gram-scale preparation without diminished diastereoselectivity. Further studies into synthetic applications are ongoing in our laboratory.

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Conflicts of interest

The authors declare no competing financial interest.

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