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Cu-Catalyzed highly selective reductive functionalization of 1,3-diene using H₂O 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, B₂Pin₂, 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.

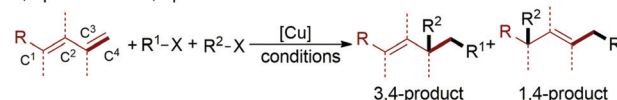
Developing new organic transformation strategies to preserve an active functional group is important for the synthesis of drugs, natural products and functional material molecules.¹ Among a lot of versatile starting compounds, 1,3-diene has caught more and more attention, because the difunctionalization 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 B₂Pin₂ 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

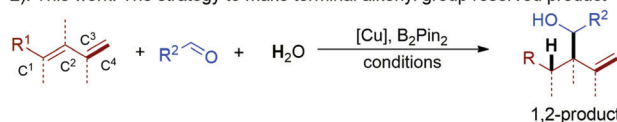
conditions, so the preparation of this kind of compound has been studied intensely.⁵ Among these methods, the hydroboration of dienes affords important boron reagents, which are powerful intermediates in many transformations.⁶ However, some air or moisture sensitive reagents and catalysts, such as Ni(cod)₂ 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/H₂O/B₂Pin₂ system, which makes this method more practical. Importantly, examples of the catalytic transfer hydrogenation of simple alkenes using H₂O 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 H₂O 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**), B₂Pin₂ and H₂O. 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).

1). Previous work: Cu-catalyzed functionalization of terminal 1,3-diene to make 3,4-product and 1,4-product



2). This work: The strategy to make terminal alkenyl group reserved product



Scheme 1 Functionalization of terminal 1,3-diene.

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Table 3 Cu-Catalyzed B₂Pin₂ mediated reductive reaction of **1a** with different aldehydes (**2**)^a

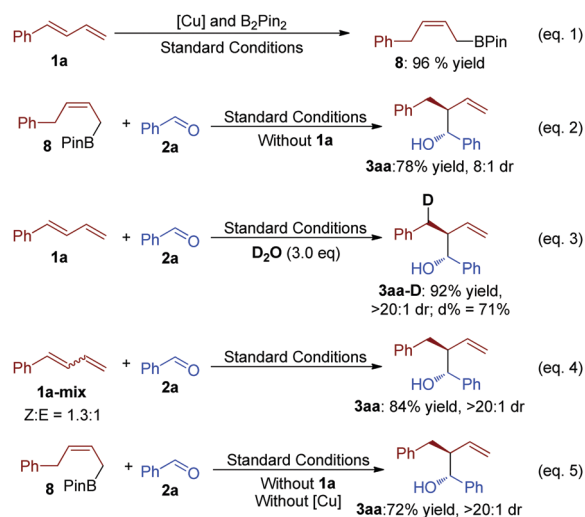


^a Standard reaction conditions: **1a** (0.25 mmol), **2** (0.5 mmol), B₂Pin₂ (0.5 mmol), LiO^t-Bu (0.5 mmol), Cu(OTf)₂ (10 mol%), PPh₃ (11 mol%), H₂O (3.0 equiv.), DCE (1.5 ml), 70 °C, under N₂ condition. ^b Isolated yield, diastereomers are inseparable, dr was determined by ¹H-NMR.

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 D₂O, and the D-labeled product could be detected (eqn (3), Scheme 3). This result proved that H₂O is the stoichiometric H atom donor of the Cu-catalyzed B₂Pin₂ 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



Scheme 2 Gram-scale reaction and further transformation of the product. **1a** (11.5 mmol), **2a** (23 mmol), B₂Pin₂ (23 mmol), LiO^t-Bu (23 mmol), PPh₃ (11 mol%), Cu(OTf)₂ (10 mol%), DCE (69 ml), isolated yield. **3aa** (0.25 mmol), *m*-CPBA (0.375 mmol), DCM (1.3 ml), isolated yield. **3aa** (0.185 mmol), Ph-I (0.37 mmol), Pd(OAc)₂ (10 mol%), Et₃N (1.85 mmol), CH₃CN (1.8 ml), isolated yield. **3aa** (0.2 mmol), BH₃-SMe₂ (0.6 mmol), NaOH (0.9 mmol), H₂O₂ (1.2 mmol), THF (2.0 ml), isolated yield. **3aa** (0.2 mmol), BrCF₂CO₂Et (0.3 mmol), CuI (10 mol%), PMDETA (0.3 mmol), CH₃CN (1.0 ml), isolated yield.



Scheme 3 Control experiments.

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 B₂Pin₂ mediated highly selective reductive functionalization of 1,3-diene using H₂O 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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