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Chemoselective Catalytic Reduction of Conjugated α, β-Unsaturated Ketones to Saturated Ketones via Hydroboration/Protodeboronation Strategy
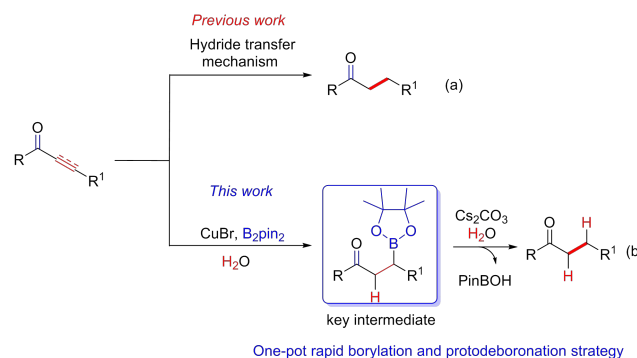
Wen Ding[a] and Qiuling Song[a, b]*

A novel copper-catalyzed chemoselective reduction of carbon-carbon double or triple bond to carbon-carbon single bond in α,β-unsaturated ketones is developed. This reaction proceeds under hydrogen gas or stoichiometric metal hydride free conditions. Saturated ketones were obtained in good to excellent yields with a broad substrate scope. Mechanistic studies reveal that the two hydrogen atoms come from H_2O in the system. Thus this reaction represents a highly efficient, and remarkably chemoselective strategy.

Arylboronic acids or arylboronic esters are widely employed as a coupling partner in cross-coupling reactions for the formation of C-C bond due to their ready accessibility.[1] In contrast, the cross-coupling reaction of alkylboronic ester with alkyl electrophiles, and the protodeboronation of organoboronic ester have rarely been investigated. Among them, the cross-coupling reaction between alkylboronic ester and alkyl electrophiles has attracted more attention compared to protodeboronation. For instance, Fu *et al.* reported a pioneering work on Pd-catalyzed[2] coupling reaction of alkyl 9-BBN reagents with inert alkyl electrophiles and Ni-catalyzed[3] coupling reaction of alkyl 9-BBN reagent with secondary alkyl halides. Very recently, Shibata[4] and Morken[5] successfully developed novel alkylboron compounds, respectively, to employ them in the cross-coupling reaction. Moreover, Cu-catalyzed cross coupling reaction of alkylboronic ester with primary alkyl electrophiles was also achieved.[6]

However, progress on protodeboronation of alkylboronic ester moves slowly. There are only few known reports of protodeboronation of alkylboronic ester, yet all made excellent contributions to modern organic chemistry. For example, Aggarwal[7] has well described his "F-B bond strategy" for protodeboronation of tertiary alkylboronic esters, which was successfully applied to the synthesis of 1,1-diarylalkanes[7a] and hydroxyphthioceranic acid;[7b] Renaud [8] reported his classical TBC (4-tert-Butylcatechol) system for protodeboronation of alkylboronic esters, which has been applied to reduce olefins. Apart from the above-mentioned seminal works,

there are no more precedents on this topic, although protodeboronation of alkylboronic ester becomes a fascinating area for the synthetic community.

Chemoselective reduction of α, β-unsaturated ketones leading to saturated ones is one of the most prevalent reactions in organic synthesis yet crucial due to its wide applications in the synthesis of industrial chemicals and pharmaceutical.[9,10,11] 1,2-Reduction and full reduction usually occur as the side reactions in the course of conjugated reduction of α,β-unsaturated carbonyl compounds, so it is always highly desirable to increase the chemoselectivity on such reduction. Great advances have been made in this field. Several expensive transition-metal catalysts system, such as rhodium,[12] ruthenium,[13] palladium,[14] iridium[15] and other metal complexes,[16] have been developed and applied to the reduction of α , β -unsaturated carbonyl compounds. In 1988, Stryker *et al.*[17] developed an inexpensive copper catalyst (CuH), known as Stryker's Reagent, which has been widely used as an effective reagent in the highly regioselective conjugated reductions of various carbonyl derivatives. Usually a hydride transfer mechanism are involved in majority of the reported reduction methods, leading to formidable requirement on sheltering from air (O_2).[18] Meanwhile, utilizing H_2O as hydrogen source is scarcely reported owing to the difficulty of the formation of a negative hydrogen from H_2O in a reductive reaction. Very recently, we discovered that the C-B bond of alkylboronic esters can be easily transformed into C-H bond in the present of K_2CO_3 or Cs_2CO_3 at 90 ℃ (see supporting information), which stands in contrast to previous work.

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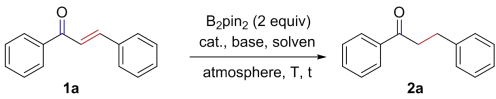*Fax:86-592-6162990; email:qsong@hqu.edu.cn.*
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Scheme 1. Strategies on Conjugated Reduction of α,β-Unsaturated Ketones

Based on the understanding of our novel protodeboronation pathway, we would like herein to report the first domino reaction

of highly chemoselective conjugated reduction of α,β-unsaturated ketones by utilizing costless but quite efficient H_2O as hydrogen source *via* a protodeboronation strategy without special requirement on reaction atmosphere. Thus, a novel, simple and efficient borylation/protodeboronation reaction was developed to lead to the highly chemoselective reduction of C-C unsaturated bond. More importantly, this reaction shows great chemoselectivity over other unconjugated C-C multiple bonds and can be readily scaled up without loss of its efficiency.

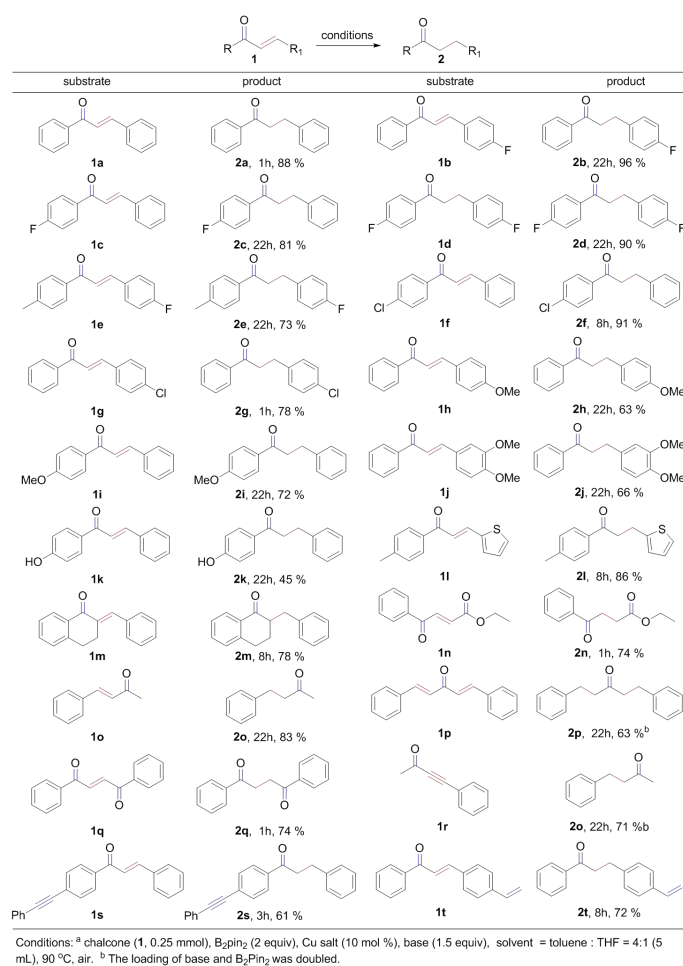**Table 1.** Selected Results for the Optimization of the Reaction Conditions.[a]

Entry	Catalyst (10 mol %)	base (1.5 equiv)	atmosphere	temp (oC)	solvent (mL)	Time (22 h)	yield (%)[b]
1	CuBr	Cs_2CO_3	O_2	90	Toluene (4)/ THF (1)		65
2	CuBr	Cs_2CO_3	air	90	Toluene (4)/ THF (1)		86[c]
3	CuBr	Cs_2CO_3	N_2	90	Toluene (4)/ THF (1)		88
4	$CuBr_2$	Cs_2CO_3	air	90	Toluene (4)/ THF (1)		71
5	CuI	Cs_2CO_3	air	90	Toluene (4)/ THF (1)		85
6	CuCl	Cs_2CO_3	air	90	Toluene (4)/ THF (1)		75
7	$Cu(OAc)_2$	Cs_2CO_3	air	90	Toluene (4)/ THF (1)		79
8	CuO	Cs_2CO_3	air	90	Toluene (4)/ THF (1)		trace
9	$Cu(OTf)_2$	Cs_2CO_3	air	90	Toluene (4)/ THF (1)		83
10	$CuCl_2$	Cs_2CO_3	air	90	Toluene (4)/ THF (1)		68
11	CuBr	Cs_2CO_3	air	90	Toluene (5)		38
12	CuBr	Cs_2CO_3	air	90	THF (5)		trace
13	CuBr	Cs_2CO_3	air	90	DMF (5)		0
14	CuBr	Cs_2CO_3	air	90	Dioxane (5)		41
15	CuBr	Cs_2CO_3	air	90	H_2O (5)		24
16	**CuBr**	**Cs_2CO_3**	**air**	**90**	**Toluene (4)/ THF (1)**	**1 h**	**88**
17	-	Cs_2CO_3	air	90	Toluene (4)/ THF (1)	1 h	0
18	CuBr	-	air	90	Toluene (4)/ THF (1)	1 h	0
19[d]	CuBr	Cs_2CO_3	air	90	Toluene (4)/ THF (1)	1 h	0
20	CuBr	Cs_2CO_3	air	70	Toluene (4)/ THF (1)	1 h	70

Reaction Conditions: [a] chalcone (**1a**, 0.25 mmol), B_2pin_2 (2 equiv), Cu salt (10 mol%), base (1.5 equiv), solvent (5 mL), 22 h, temp., corresponding atmosphere. [b] GC yield. [c] Isolated yield.

Our initial investigation commenced with chalcone (**1**) as the model substrates to investigate the copper salt-catalyzed chemoselective reduction (Table 1 and Table S1 in the Supporting Information). Gratifyingly, both Cu^I and Cu^{II} salts demonstrated good activities on this novel transformation (Table 1, entries 1-7, 9-10) except CuO (Table 1, entry 8) and 86% or 88% of desired product was obtained respectively by using 10 mol% of CuBr with B_2pin_2 (2 equiv) and Cs_2CO_3 (1.5 equiv) at 90 °C in toluene:THF = 4:1 (5 mL) under air or N_2 in a sealed tube (Table 1, entry 2, 3). Further screening of solvents and base revealed that Cs_2CO_3 (1.5 equiv) and toluene:THF = 4:1 (5 mL) are the optimal choices. When the reaction was conducted in one single solvent, inferior results were obtained. Temperature affected this reaction dramatically and when temperature was decreased to 70 °C, the yield of desired product **3** was dropped to 70% (Table 1, entry 20). Without CuBr, no reaction occured; in the absence of base, B_2pin_2 or Cs_2CO_3, no reaction happened either. Interestingly, solvent greatly affect the reaction. Reduction can even be directly performed in H_2O although it is slower than organic solvents. Moreover, to our suprise, we later

found that this reduction reaction gave as good result in only 1 hour as in 22 hours (Table 1, entry 16).

With the optimized condition in hand, we explored the scope and limitations of the chemoselective reaction. Firstly, we surveyed different substituted chalcones. To our delight, all substituted chalcones were competent candidates in this transformation (Scheme 2) and corresponding desired products were obtained in good to excellent yields. Special attentions should be paid to halogen substituted chalcones (Scheme 2, **1b**, **1d**, **1f**), since in each case, corresponding products were afforded in >90% yield. Remarkably, α,β-unsaturated ketones with an additional substituent at the α-position (**1m**) was performed good. α,β-Unsaturated ketones which contain heterocycle (**1l**) and ester group (**1n**) are also tolerable with good yields in this strategy. The compound (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one (dba) (**1p**), which is usually used as an excellent ligand in palladium-catalyzed reactions, is compatible with this system as well and can be reduced to saturated product in a good yield. Moreover, yneone (**1r**) was reduced to saturated ketone when the loading of base and B_2pin_2 was doubled.

Conditions: [a] chalcone (**1**, 0.25 mmol), B_2pin_2 (2 equiv), Cu salt (10 mol %), base (1.5 equiv), solvent = toluene : THF = 4:1 (5 mL), 90 °C, air. [b] The loading of base and B_2Pin_2 was doubled.

Scheme 2. Substrate Scope of the Chemoselective Reduction.[a]

Notably, this reaction showed very good chemoselectivity when various unsaturated C-C bonds are on the molecules: for example, the C≡C bond of **1s** and the C=C bond of **1t** were both untouched under the standard conditions, no corresponding LCu-Bpin adduct over the unconjugated C-C multiple bonds were ever

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detected, suggesting the α , β -unsaturated carbonyl system is essential for the success of the reduction.

The chemoselective reduction of α , β -unsaturated ketones could be easily scaled up without decreasing on its efficiency (Scheme 3), which clearly indicated the potential practical applications of this strategy.
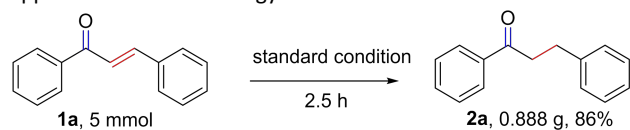

Scheme 3. Scale-up Reaction

To gain insight on the originality of the hydrogen source of the reduced product in this reaction system, chalcone (**1a**) was subjected in anhydrous solvent with D_2O (4 equiv) under the standard conditions (Scheme 4a). The result revealed that deuterated ratio of β -position is 82% and deuterated ratio of α - position is 155 % (because of keto-enol tautomerism) (determined by ^{1}HNMR and GC-MS, see details in Supporting Information), while almost no reaction occurred when the experiment was performed in anhydrous solvent under the standard conditions (Scheme 4b), which clearly indicated that water should be hydrogen source for this reduction reaction. Interestingly, when the radical scavenger (BHT or TEMPO) was added into the reaction, the reaction gave > 99% yields of **3a** (Scheme 4c and 4d), which reveal that a radical pathway may be involved in the protodeboronation process, although no free radical intermediates **7** (Scheme 6) was captured thus far.
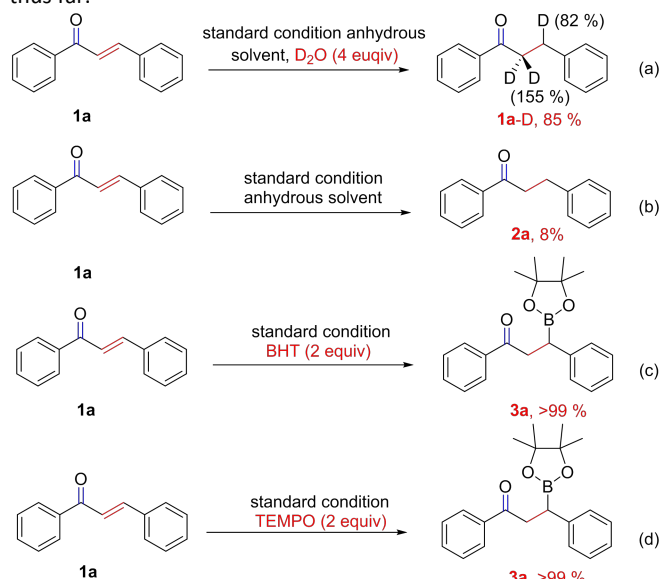

Scheme 4. Hydrogen Isotope Labeling and Radical Trapping Experiments

To determine the possible intermediate of this process, two control experiments were conducted (Scheme 5). 1,3-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (**3a**) was subjected under various conditions: the standard conditions or in the absence of copper salt can both lead desired product **2a** in ca. 75% yield (Scheme 5a and 5c), yet no reaction happened in the absence of base (Scheme 5b), these results obviously demonstrate that 1,3-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (**3**) is the key intermediate in this chemoselective conjugated reduction of α,β-unsaturated carbonyl compounds.
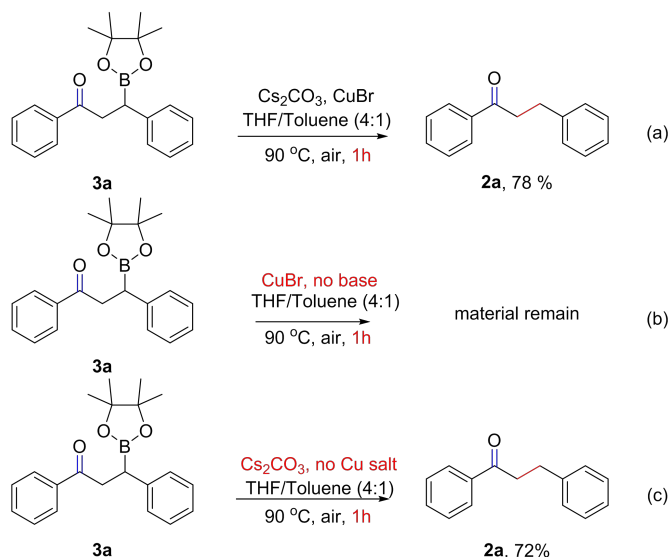
Scheme 5. Control Experiments

Based on the above control and isotope labeled experiments and related literature report,[19] we propose the mechanism (Scheme 6): in the presence of copper salt, base, and B_2pin_2, α,β-unsaturated carbonyl compounds (**1**) was firstly transformed into a borylated copper enolate (**4**), which was rapidly converted into boronic ester substituted ketones (**3**) by H_2O. Then saturated compound **2** was obtained after protodeboration of the key intermediate (**3**) in the presence of base and H_2O. The protodeboronation process was supposed to be relevant to an alkylboronic ester /water complex (**5**), which might furnish a species activated for O-H bond homolysis.[20] This hypothesis was also supported by the work of Wood et al,[20] in which a related trimethyl-borane/water complex was formed.[20]
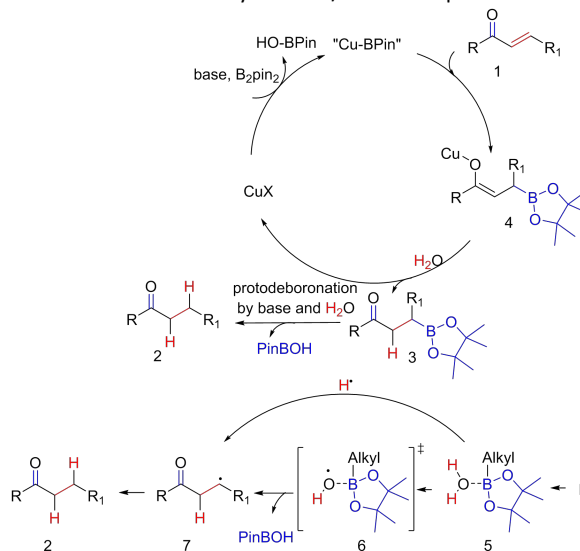
Scheme 6. Proposed Mechanism

Conclusions

In summary, we have developed the first copper-catalyzed conjugated reduction of α, β-unsaturated ketones making use of bis(pinacolato)diboron and H_2O as a hydrogen source via a protodeboronation strategy under simple and mild conditions. This strategy is efficient, and highly

chemoselective. It requires low catalyst loadings and tolerates various functional groups and can be easily scaled up without loss of its efficiency. Ongoing studies are directed at further reactivity, synthetic utility and mechanism of this catalytic system in our laboratory.

Acknowledgement

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