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The Coupling of Alkylboronic Acids and Esters with Baylis−Hillman Derivatives by Lewis Base/Photoredox Dual Catalysis

Hongqiang Ye,[a] He Zhao,[a] Shujian Ren,[a] Hongfeng Ye,[a] Dongping Cheng,*[b] Xiaonian Li,*[a] and Xiaoliang Xu*[a]

[a]*College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310014, P. R. China*
[b]*College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, P. R. China*

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ABSTRACT

Utilizing Lewis base/photoredox dual catalysis, carbon radicals generated from either alkylboronic acids or esters were coupled with Baylis−Hillman derivatives under visible light irradiation. This protocol provides a mild and operationally simple method for the synthesis of a variety of α,β-unsaturated carbonyl compounds in a broad scope of the substrates. The mechanism of Lewis base activation and reductive quenching cycle was probably involved.

∗ Corresponding author. Tel.: +86-571-88320920; e-mail: chengdp@zjut.edu.cn; xnli@zjut.edu.cn; xuxiaoliang@zjut.edu.cn

Introduction

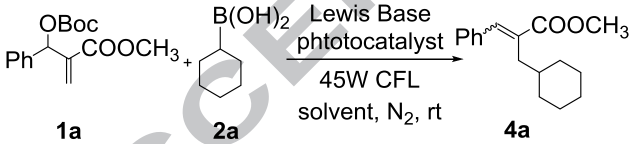
Recently the visible light photoredox catalysis has seeded several types of novel chemical transformations.[1] Visible light photoredox catalysis has exhibited tremendous prospects and wide applications in organic synthesis owing to the rich and renewable resource of visible light, high reaction efficiency, and mild conditions. Moreover, it showed obvious advantages over traditional methods in sustainability for using visible light.

The trisubstituted alkene moieties have been found in a variety of bioactive molecules.[2] Especially, they are also key intermediates in organic synthesis. As a result, it's very important to develop the methods for the preparation of trisubstituted alkenes.[3] The Baylis-Hillman adducts[4] such as 3-hydroxy-2-methylene-alkanoates (derived from acrylate esters) have become one of the important and attractive intermediates for stereoselective synthesis of different multifunctional trisubstituted alkene molecules. Several traditional methods[5] such as nucleophilic addition of Grignard reagent, Friedel-Crafts reaction and Pd-catalyzed cross-coupling reaction have been developed for the synthesis of similar trisubstituted acrylate derivatives from Baylis-Hillman adducts. While these methods have emerged as reliable tools in generating diverse trisubstituted alkenes, they have several drawbacks such as harsh reaction condition and poor tolerance of functional groups. Carbon-centered radicals[6] are currently available to generate in the context of a photocatalytic cycle[1] and some of them could be coupled with Baylis-Hillman adducts. Recently we[7] reported the coupling of potassium organotrifluoroborates with Baylis-Hillman derivatives via visible-light photoredox catalysis.[8] However, due to the unfavorable redox potential, primary alkyltrifluoroborates and phenyltrifluoroborate are not suitable substrates.[9] Recently, it was demonstrated that Lewis base catalysis could be introduced to enhance the reactivity of electrophilic p orbitals.[10] Based on this concept, we investigated the combination of Lewis base and photoredox catalysis could promote the alkylboronic acid derivatives[11] to generate carbon radicals. Herein, we report the synthesis of α,β-unsaturated carbonyl compounds through a dual catalysis approach from a broad scope of alkylboronic acids and esters under mild conditions.

Result and discussion

In order to achieve the optimal conditions for the above transformation, a series of experiments were carried out (Table 1). The initial reaction of methyl 3-phenyl-2-methylene-3-(tert-butoxycarbonyl)oxypropanoate **1a** and cyclohexylboronic acid **2a** was performed in the presence of 0.2 equiv of 4-dimethylaminopyridine (DMAP) and 1 mol% photocatalyst **PC(1)** in *N*-methyl pyrrolidone (NMP). Irradiation of the mixture with 45W CFL at ambient temperature for 20 h led to the coupling product **4a** in 71% yield (entry 1). Among other photocatalysts tested, none of them gave better yields (entries 2-4). A range of solvents such as DMSO, DMF, acetone, MeCN, Et_2O, EtOAc, DCE and DCM was tried but gave disappointing results (entries 5-12). Then we decided to investigate the catalytic activity of other Lewis bases (entries 13-16). DABCO (triethylenediamine) was identified as an excellent base, leading to the yield of **4a** up to 82%. Based on above conditions, neither extending the reaction time nor switching to blue LEDs could improve product yield (entries 17-18). However, increasing the amount of DABCO to 50 mol% provided **4a** in a lower yield (entry 19). It was finally revealed that the combination of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as a photocatalyst, DABCO as a Lewis base, NMP as a solvent and 20hrs was most effective and the desired product was obtained in 82% yield (entry 13). Notably, the control experiments showed that there was no desired coupling product observed in the absence of photocatalyst, base or light (entries 20-22).

Table 1: Optimization of the reaction conditions[a]



1a **2a** **4a**

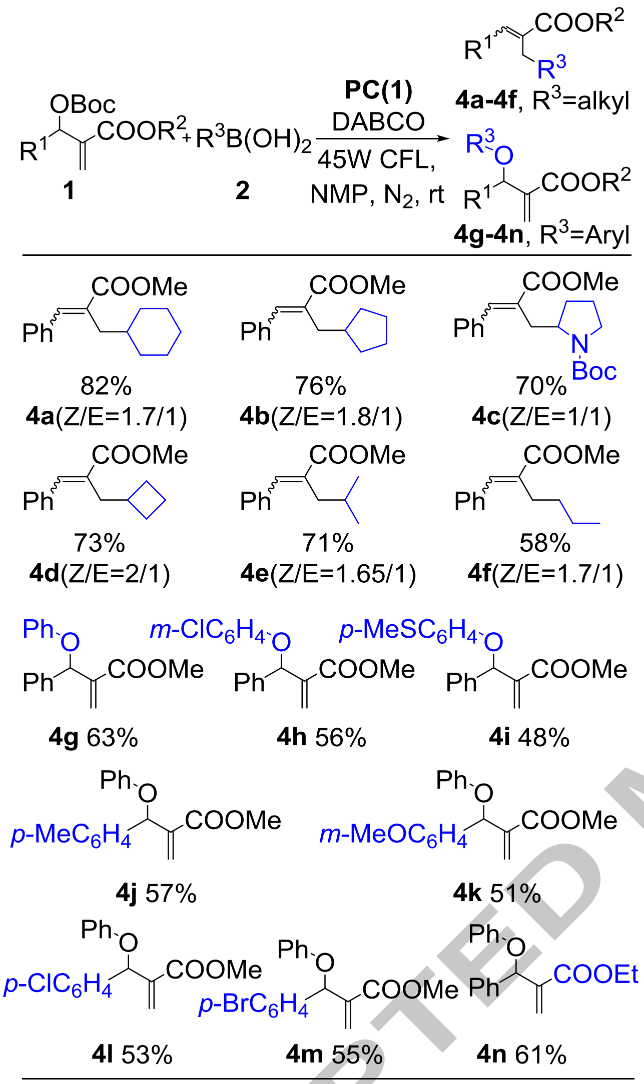
Entry	Photocatalyst	Solvent	Base	yield (%) [b]
1	**PC(1)**	NMP	DMAP	71
2	**PC(2)**	NMP	DMAP	13
3	**PC(3)**	NMP	DMAP	0
4	**PC(4)**	NMP	DMAP	51
5	**PC(1)**	DMSO	DMAP	31
6	**PC(1)**	DMF	DMAP	28
7	**PC(1)**	Acetone	DMAP	17
8	**PC(1)**	MeCN	DMAP	36
9	**PC(1)**	Et_2O	DMAP	33
10	**PC(1)**	EtOAc	DMAP	50

11	**PC(1)**	DCE	DMAP	65
12	**PC(1)**	DCM	DMAP	46
13	**PC(1)**	NMP	DABCO	82
14	**PC(1)**	NMP	DBU	66
15	**PC(1)**	NMP	DBN	22
16	**PC(1)**	NMP	PPh_3	67
17[c]	**PC(1)**	NMP	DABCO	82
18[d]	**PC(1)**	NMP	DABCO	81
19[e]	**PC(1)**	NMP	DABCO	69
20[f]	**PC(1)**	NMP	DABCO	0
21	-	NMP	DABCO	0
22	**PC(1)**	NMP	-	0

[a] Reaction conditions：**1a** (0.5 mmol), **2a** (0.75 mmol), photocatalyst (0.005 mmol, 1 mol%), Lewis base (0.1 mmol), solvent (3 mL), 45 W CFL (compact fluorescent lamp) irradiation under N_2 atmosphere at ambient temperature for 20 h, unless otherwise noted. **PC(1)** Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6: 4,4'-di- tert-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-(5-trifluoromethyl-2-pyridinyl-kN)phenyl-kC]iridium(III) hexafluorophosphate. **PC(2)** Ir(ppy)$_2$(dtbbpy)PF_6: (4,4'-di-tert-butyl-2,2'-bipyridine)bis(2-phenylpyridine)iridium(III) hexafluorophosphate. **PC(3)** Ir(ppy)$_3$: tris(2-phenylpyridine)iridium(III). **PC(4)** Ru(bpz)$_3$(PF_6)$_2$: tris(2,2'-bipyrazine)ruthenium(II) hexafluorophosphate. [b] Isolated yield after silica gel flash column chromatography. [c] Extending the reaction time to 25 h. [d] Irradiation with blue LEDs. [e] 0.25 mmol of DABCO. [f] No light.

With the optimal reaction conditions in hand, several structurally diverse organoboronic acids were examined. As demonstrated in Table 2, the secondary alkylboronic acids possessing four-, five- and six-membered ring were coupled in good yields (**4a**-**4d**) and the aliphatic, heterocyclic boronic acid containing protected nitrogen atom afforded product in 70% isolated yield (**4c**). Specifically, Z/E isomers of **4c** could be isolated by silica gel flash column chromatography. Moreover, isopropylboronic acid was efficiently applied in this transformation (**4e**). Finally, primary alkylboronic acid could also be used under this protocol and the coupling product was obtained, albeit in a slightly lower yield (**4f**). To our disappointment, arylboronic acids were not suitable for the reaction but afforded different products (**4g**-**4n**). On the observed results and literatures, the reason may be that the arylboronic acids could be oxidized to give substituted phenols easily under this condition.[12] Subsequently, a catalytic successive S_N2'–S_N2' reaction happened due to the very suitable nucleophilicity of DABCO and phenol[13].

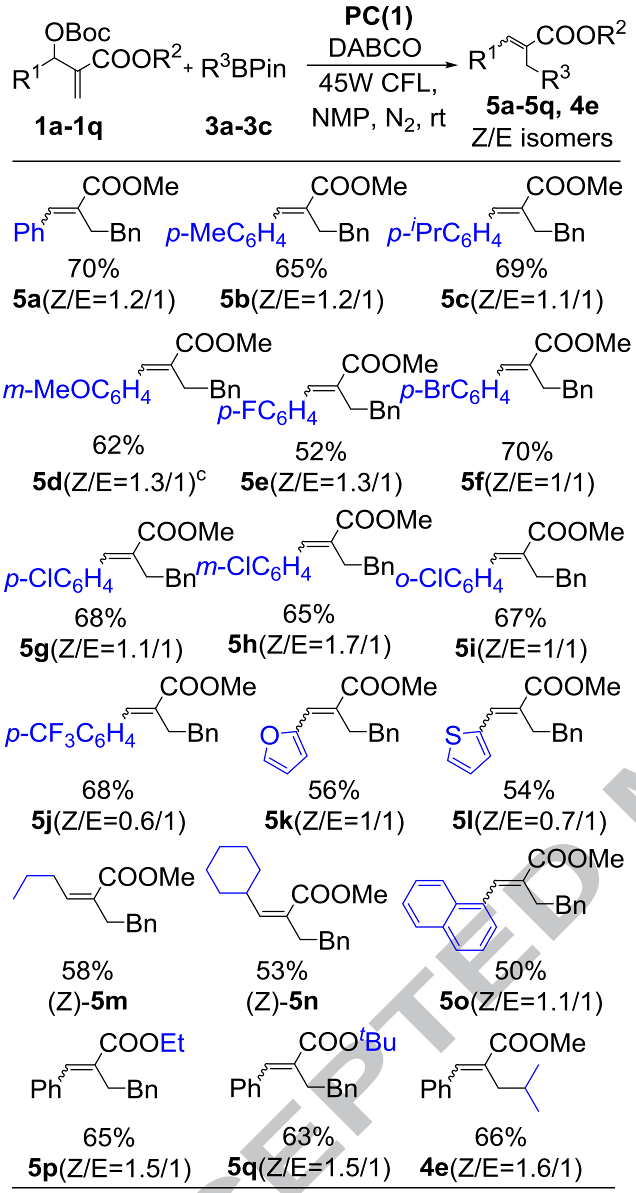
Table 2: Scope of organoboronic acids



[a]Reaction conditions：**1** (0.5 mmol), **2** (0.75 mmol), Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (0.005 mmol), DABCO (0.1 mmol), NMP (3 mL), 20 h, 45W compact fluorescent lamp irradiation under N$_2$ atmosphere at rt. [b]Isolated yield based on **4a-4n**.

In order to further explore the generality of this method, we assessed the scope of Baylis−Hillman *tert*-butyl carbonates and boronic pinacol esters (Table 3). The Baylis−Hillman *tert*-butyl carbonates containing substituents such as methyl, isopropyl and methoxyl on the aryl rings underwent the reaction smoothly (**5b-5d**). For substrates with halogenated aryl ring, the desired products were also isolated in good yields (**5e-5g**). However, the fluoro substituted reactant gave the corresponding product in slightly lower yield (**5e**). There was no obvious steric effect (**5g-5i**). Pleasingly, the strong electron withdrawing group trifluoromethyl had no influence on the reaction and **5j** was provided in good yield. Heterocyclic substituted Baylis–Hillman *tert*-butyl carbonates were also suitable for the reaction (**5k-5l**). While aliphatic substituted Baylis–Hillman *tert*-butyl carbonates were introduced, the reactions were successfully performed and E-isomers of desired products were not detected (**5m-5n**). Then, naphthyl substituted starting material was examined and the corresponding product **5o** was obtained in moderate yield. The reaction of ethyl 3-phenyl-2-methylene-3-(tert-butoxycarbonyl)oxypropanoate and *t*-butyl 3-phenyl-2-methylene-3-(tert-butoxycarbonyl)oxypropanoate with benzyl boronic ester **3a** proceeded smoothly to give **5p** and **5q** in 65% and 63% yields, respectively. The coupling reaction of isopropyl boronic ester **3b** with **1a** proceeded well. In contrast to primary and secondary alkylboronic ester, tertiary butyl boronic ester **3c** was not a suitable substrate. It is important to note that Z/E isomers of **5d** could be isolated by silica gel flash column chromatography and the Z/E isomers were confirmed by NOE spectra (See Supporting Information).

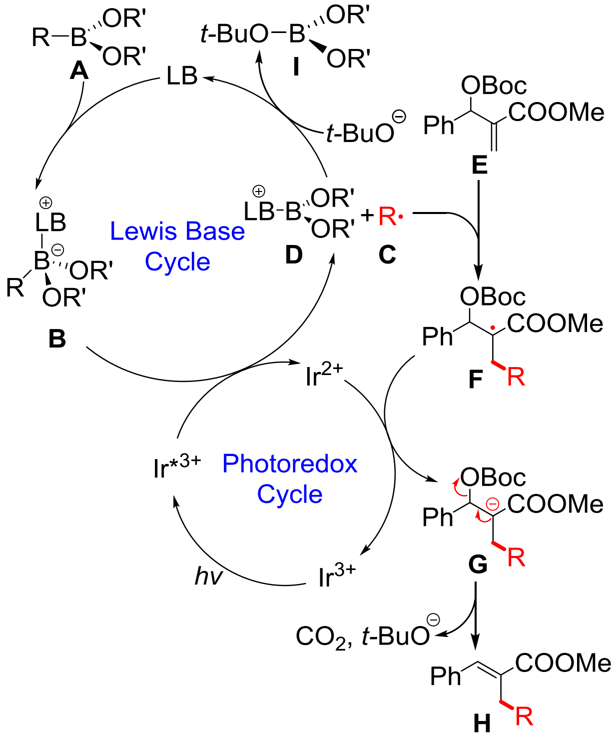
Table 3: Scope of Baylis–Hillman *tert*-butyl carbonates and boronic pinacol esters.



[a]Reaction conditions: **1a-1q** (0.5 mmol), **3a-3c** (0.75 mmol), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.005 mmol), DABCO (0.1 mmol), NMP (3 mL), 20 h, 45W compact fluorescent lamp irradiation under N_2 atmosphere at rt. [b]Isolated yield based on **5a-5q, 4e**. [c]Z/E isomers of **5d** were confirmed by NOE spectra.

To explore the mechanism, radical scavenger TEMPO was added. The product **4a** was obtained in only 5% yield after 30 h with most of reactant **1a** left. Moreover, a dynamic equilibrium between the boronic acid or boronic ester and the Lewis base catalyst (LB) was confirmed by Steven V. Ley.[11] On the basis of literatures[14] and above experimental results, a plausible reaction mechanism is proposed in Scheme 1. Firstly, boronic acid or boronic ester **A** can be activated by Lewis base to form intermediate **B**. The ground state of Ir^{3+} is excited to provide Ir^{*3+} under the irradiation of visible light, which is reduced by intermediate **B** to produce Ir^{2+}. Simultaneously, **B** is oxidized to generate **D** and the alkyl radical **C**, which can react with Baylis-Hillman *tert*-butyl carbonate **E** to produce radical **F**. The key intermediate alkyl anion **G** was generated from the reduction of **F** by the photocatalyst Ir^{2+}, which itself was oxidized to the initial photocatalyst Ir^{3+}. Subsequently, the target product **H** was formed after the elimination of CO_2 and $^tBuO^-$ from anion **G**. Finally, Lewis base is regenerated from **D** and $^tBuO^-$.

Scheme 1: A plausible reaction mechanism.



Conclusions

In conclusion, we have developed a new coupling reaction of alkylboronic acids and esters with Baylis−Hillman adducts via visible light photoredox catalysis. The alkylboronic acids and esters can serve as a useful synthon in the C-C bond-forming reaction utilizing Lewis base/photoredox dual catalysis. The reaction can proceed with a broad scope of substrates under mild conditions.

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Supplementary Material

Supplementary data (copies of ^{1}H NMR, ^{13}C NMR spectra of all products) associated with this article can be found in the online version at http://.

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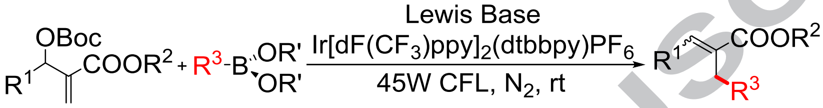

Highlights

The coupling of alkylboronic acids or esters with B-H adducts via dual catalysis

New method for the synthesis of 2-alkyl substituted acrylate derivatives

Broad scope of the substrates, moderate to excellent yields, simple operations