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The coupling of potassium organotrifluoroborates with Baylis–Hillman derivatives via visible-light photoredox catalysis

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ABSTRACT

Catalyzed by Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$, the coupling of potassium organotrifluoroborates with Baylis–Hillman derivatives under visible light irradiation has been developed. Based on the mechanism of reductive quenching cycle, it provides an easy, mild, efficient method for the synthesis of a variety of α,β-unsaturated carboxylic esters derivatives in a broad scope of the substrates.

Introduction

Visible light photoredox catalysis showed tremendous advantages over conventional synthetic methods in several aspects because of the rich and renewable resource of visible light, mild reaction conditions and high efficiency.[1] Although the concept of visible light catalysis has been put forward by Ciamician for more than 100 years,[2] it was not until recently since MacMillan reported the α-alkylation of aldehydes and ketones by photocatalysis that it has aroused great interest.[3] After several years of rapid growth, visible light catalysis has been evolved as a significant bond formation protocol in organic synthesis.

Recently Molander reported the dual catalytic cross-coupling reactions of potassium organotrifluoroborates with organohalides via visible light catalysis.[4] The scope of substrates applied in these coupling reactions was more broad than the published Pd-catalyzed reaction systems.[4g] A variety of substituted benzylic trifluoroborates and heteroaryl halides could be tolerated. Secondary alkyltrifluoroborates were also suitable partners in the cross-coupling reactions.[5] Baylis-Hillman adducts are important intermediates and widely used as electrophilic partners in organic synthesis.[6] With the interest in the visible light catalysis,[7] herein we wish to report the coupling reaction of potassium organotrifluoroborates with Baylis–Hillman adducts via visible light photoredox catalysis, which provides a new method for the synthesis of 2-alkylsubstituted acrylate derivatives. Several methods such as Pd-catalyzed cross-coupling reaction,[8] nucleophilic addition of Grignard reagent[9] and Friedel-Crafts reaction[10] have been reported for the synthesis of similar acrylate derivatives from Baylis-Hillman adducts. Although these methods were very useful, the problems were narrow scope of substrates and poor tolerance of functional groups.

Result and discussion

Initial studies were conducted on the starting materials between potassium benzyltrifluoroborate **1a** and 2-(acetoxy(phenyl)methyl)-acrylate **2** (Scheme 1). Firstly, catalyzed by 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), it revealed that the desired product **6a** was isolated in 3% yield and compound **7** was the main product after checked by ^{1}H NMR. When CH$_3$COONa was added into the reaction, no desired product was detected and in contrast **7** was isolated in 77% yield. It showed obviously that the nucleophilicity of acetate anion is better than benzylic radical in this reaction condition. Next three Baylis–Hillman adduct analogs **3a**, **4**, **5** were synthesized. Unfortunately compound **4** was not stable and **5** was difficult to be purified. After several tries, it was found that replacing of the acetate of Baylis–Hillman adduct with Boc group was a better choice and the product **6a** was isolated in 28% yield.

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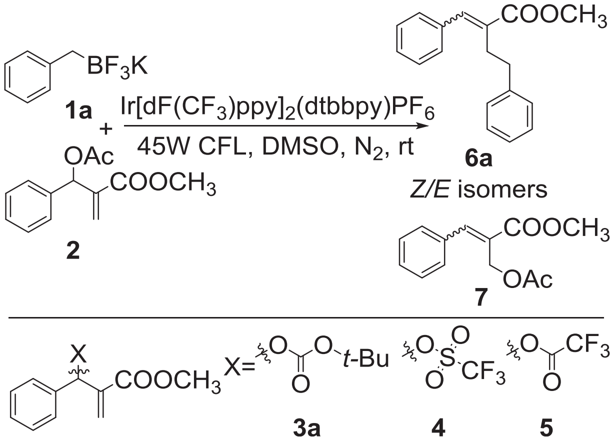
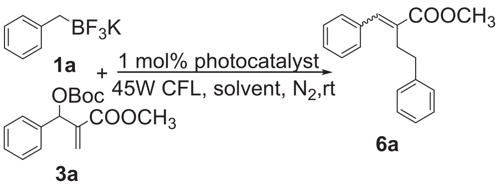


Scheme 1. Reactions between potassium benzyltrifluoroborates and Baylis–Hillman adduct derivatives under visible light irradiation.

In order to find optimal conditions, the reaction of potassium benzyltrifluoroborate **1a** and methyl 2-(((*tert*-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **3a** was performed in the presence of 1 mol% photocatalyst under 45 W CFL irradiation at ambient temperature (Table 1). Of the catalyst that has been tried, only Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 photocatalyst took effect and **6a** was isolated in 28% yield (entries 1–3). Besides DMSO, other solvents such as DMF, NMP (*N*-methyl pyrrolidone), DCE, DCM, EtOAc, Et_2O and THF were tried. Except NMP, most solvents gave disappointing results (entries 3–10). Use of NMP as a solvent, the yield could increase to 60% (entry 5). Based on these, extending the reaction time to more than 24 h could not improve the yield (entries 11–12). Best results were obtained in the 1.5:1 ratio of **1a** and **3a** (entries 5, 13–14). It was finally found that the combination of Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 as a photocatalyst, NMP as a solvent and 24 h was most effective and the desired product can be obtained in 71% yield (entry 13). Notably, the control experiment showed that there was no desired coupling product in the absence of a photocatalyst or light.

With the optimal reaction conditions in hand, the scope of Baylis–Hillman *tert*-butyl carbonate derivatives was examined (Table 2). The substrates containing substituents such as methyl, methoxy and isopropyl on the aryl ring underwent the reaction smoothly (**6b**–**6d**). For substrates with halogenated aryl ring, the desired products were also isolated in good yields (**6e**–**6g**). However, the fluoro substituted reactant gave a slightly lower yield. There was no obvious steric effect (**6g**–**6i**). Heterocyclic substituted Baylis–Hillman *tert*-butyl carbonates were also suitable for the reaction (6**j**–**6l**). While aliphatic substituted Baylis–Hillman *tert*-butyl carbonates were introduced, the reactions were successfully performed (**6m**–**6n**) and *E*-isomers of desired products were not detected. Then, naphthyl substituted starting material was examined and the corresponding product **6o** was obtained in moderate yield. The reaction of ethyl 2-(((*tert*-butoxycarbonyl)oxy)(phenyl)methyl)acrylate and 2-(((*tert*-butoxycarbonyl)oxy)(phenyl)methyl)-acrylonitrile proceeded smoothly to give **6p** and **6q**. It is important to note that *Z*/*E* isomers of most products can't be isolated by silica gel flash column chromatography except **6c** and **6l**. For product **6c**, the *Z*/*E* isomers were confirmed by NOE spectra (See Supporting Information).

Table 1
Optimization of the reaction conditions.[a]



Entry	Solvent	Photocatalyst	Time/h	Yield (%)[b]
1	DMSO	Ru(bpz)$_3$(PF_6)$_2$	24	0
2	DMSO	Ir(ppy)$_2$(dtbbpy)PF_6	24	0
3	DMSO	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	28
4	DMF	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	27
5	NMP	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	60
6	DCE	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	44
7	DCM	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	34
8	EtOAc	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	29
9	Et_2O	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	27
10	THF	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	27
11	NMP	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	12	40
12	NMP	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	36	59
13[c]	NMP	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	71
14[d]	NMP	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	71
15[c,e]	NMP	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	24	0
16[c]	NMP	–	24	0

[a] Reaction conditions: **1a** (0.6 mmol), **3a** (0.5 mmol), photocatalyst (0.005 mmol, 1 mol%), solvent (2 mL), 45 W CFL (compact fluorescent lamp) irradiation under N_2 atmosphere at ambient temperature, unless otherwise noted. Ir(ppy)$_2$(dtbbpy)PF_6: (4,4′-Di-*tert*-butyl-2,2′-bipyridine)bis[(2-*pyridinyl*)*phenyl*]iridium(III) Hexafluorophosphate. Ru(bpz)$_3$(PF_6)$_2$: Tris(2,2′-bipyrazine)ruthenium(II) hexafluorophosphate.

[b] Isolated yield after silica gel flash column chromatography.

[c] 0.75 mmol of **1a**.

[d] 1.0 mmol of **1a**.

[e] No light.

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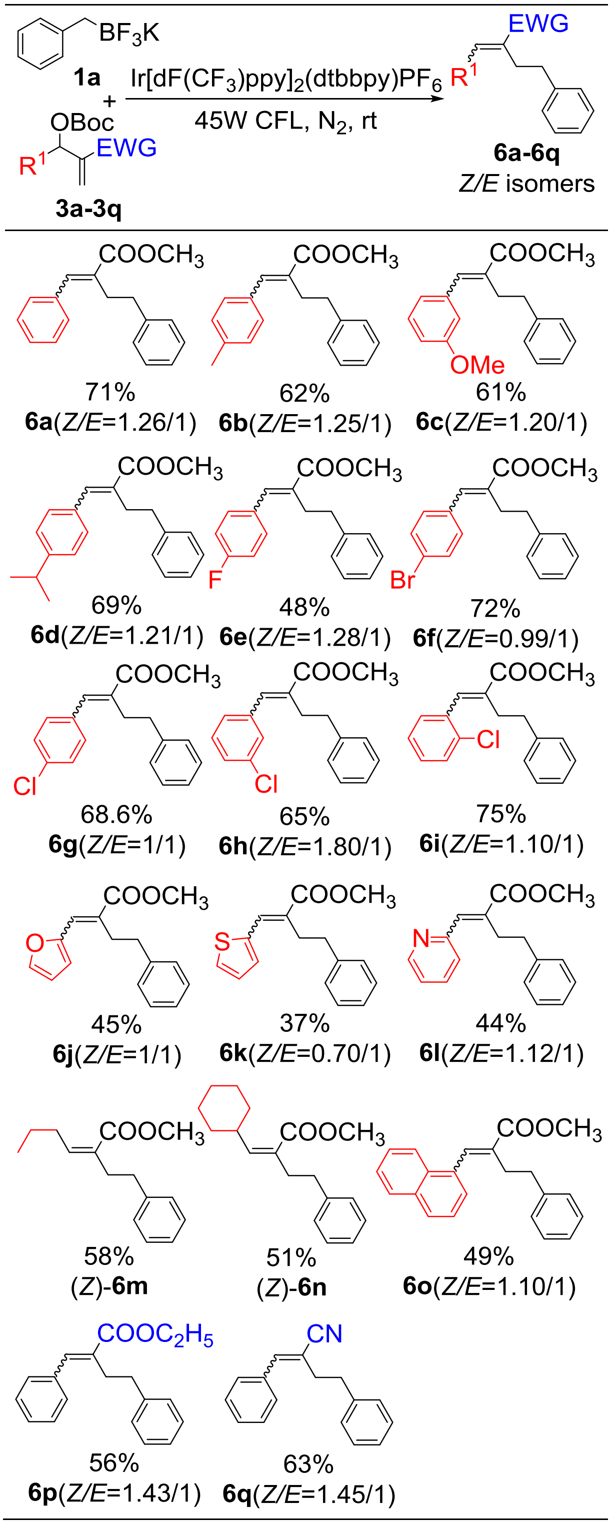
Table 2
Scope of Baylis–Hillman *Tert*-butyl Carbonates in Coupling with Potassium Benzyltrifluoroborate **1a**.



[a] Reaction conditions: **1a** (1.5 mmol), **3a**–**3q** (1 mmol), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.01 mmol), NMP (4 mL), 24 h, 45 W compact fluorescent lamp irradiation under N_2 atmosphere at rt.

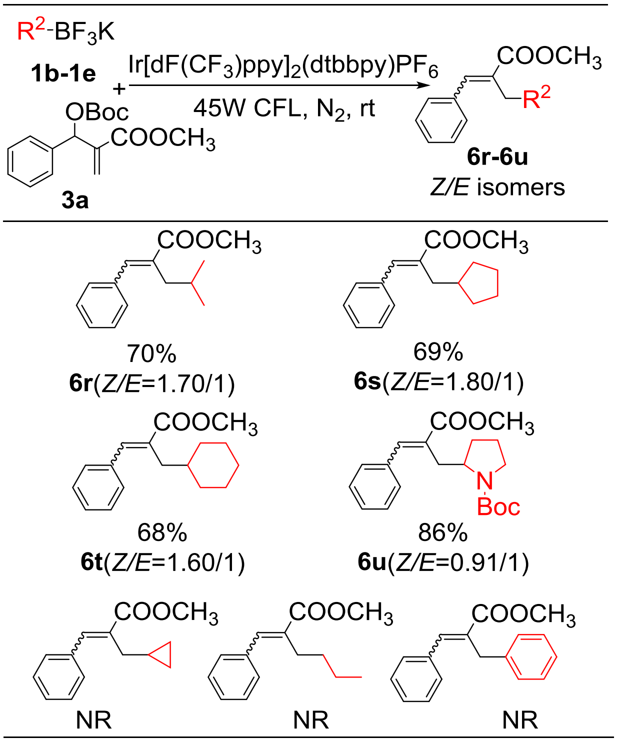
[b] Isolated yield based on **3a**–**3q**.

[c] The *Z*-isomer of **6l** was difficult to purify.

In order to further explore the generality of this method to other potassium organotrifluoroborates, several structurally diverse potassium organotrifluoroborates were examined. As demonstrated in Table 3, most secondary alkyltrifluoroborates were efficiently applied in this transformation. Isopropyltrifluoroborate was employed in 70% isolated yield (**6r**) and the secondary alkyltrifluoroborates possessing five- and six-ring sizes were coupled to give the corresponding products in good yields respectively (**6s** and **6t**). Moreover, the aliphatic five membered nitrogenous heterocyclic trifluoroborate successfully gave the coupling product under this protocol (**6u**). However, potassium cyclopropyltrifluoroborate did not work under the standard conditions. In contrast to secondary alkyltrifluoroborates, primary alkyltrifluoroborates and phenyltrifluoroborate are not suitable substrates probably owing to the unfavorable redox potential (oxidation potential of Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 = +1.21 V vs SCE; reduction potentials of potassium organotrifluoroborates: aryl counterparts [+1.81 V vs SCE]; primary counterparts [+1.83 V vs SCE]; secondary counterparts [+1.50 V vs SCE]; benzylic counterparts [+1.10 V vs SCE]).[11]

To explore the mechanism, radical scavenger TEMPO was added. The product **6a** was obtained in only 5% yield after 48 h and most of reactant **3a** was left. On the other hand the reductive coupling reaction via visible light photoredox catalysis of organotrifluoroborates reported by Molander was applied in several reactions and the dual catalytic cycle mechanism was involved.[4] On the basis of literatures and the above experimental results, a plausible reaction mechanism is proposed in Scheme 2. Firstly, the ground state of Ir^{3+} is excited to provide Ir^{*3+} under the irradiation of visible light, which is then reduced by organotrifluoroborate **1** to produce Ir^{2+}. And simultaneously **1** is oxidized to generate the alkyl radical **A**, which can react with Baylis–Hillman *tert*-butyl carbonate **3** to produce the alkyl radical **B**. The key intermediate alkyl anion **C** was generated from the reduction of **B** by the photocatalyst Ir^{2+}, which itself was

Table 3
Scope of Potassium Organotrifluoroborates.



[a] Reaction conditions: **1b**–**1e** (1.5 mmol), **3a** (1 mmol), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.01 mmol), NMP (4 mL), 24 h, 45 W compact fluorescent lamp irradiation under N_2 atmosphere at rt.

[b] Isolated yield based on **1b**–**1e**.

[c] NR: No reaction.

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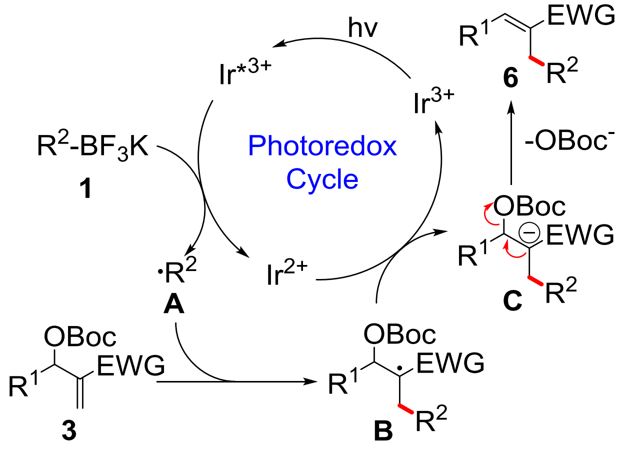

Scheme 2. A Plausible Reaction Mechanism.

oxidized to the initial photocatalyst Ir^{3+}. Subsequently, elimination of $BocO^{-}$ from the alkyl anion **C** formed the target product **6**.

Conclusions

In summary, we have developed the coupling reaction of potassium organotrifluoroborates with Baylis–Hillman derivatives via visible light photoredox catalysis. The potassium organotrifluoroborates can serve as a useful synthon in this C–C bond-forming reaction. The advantages of this reaction are mild conditions and a broad scope of substrates.

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A. Supplementary data

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 https://doi.org/10.1016/j.tetlet.2018.04.035.

References

1. (a) Zeitler K. *Angew Chem Int Ed*. 2009;48:9785;
   (b) Yoon TP, Ischay MA, Du J. *Nat Chem*. 2010;2:527;
   (c) Narayanam JMR, Stephenson CRJ. *Chem Soc Rev*. 2011;40:102;
   (d) Teply F. *Collect Czech Chem Commun*. 2011;76:859;
   (e) Shi L, Xia WJ. *Chem Soc Rev*. 2012;41:7687;
   (f) You Y, Nam W. *Chem Soc Rev*. 2012;41:7061;
   (g) Xuan J, Xiao WJ. *Angew Chem Int Ed*. 2012;51:6828;
   (h) Xi YM, Yi H, Lei AW. *Org Biomol Chem*. 2013;11:2387;
   (i) Twilton J, Le C, Zhang P, Shaw MH, Evans RW, MacMillan DWC. *Nat Rev Chem*. 2017;1:0052.
2. Ciamician G. *Science*. 1912;36:385.
3. Nicewicz DA, MacMillan DWC. *Science*. 2008;322:77.
4. (a) Molander GA, Colombel V, Braz VA. *Org Lett*. 1852;2011:13;
   (b) Molander GA. *J Org Chem*. 2015;80:7837;
   (c) Alam R, Molander GA. *J Org Chem*. 2017;82:13728;
   (d) Primer DN, Molander GA. *J Am Chem Soc*. 2017;139:9847;
   (e) Amani J, Molander GA. *Org Lett*. 2017;19:3612;
   (f) Amani J, Alam R, Badir S, Molander GA. *Org Lett*. 2017;19:2426;
   (g) Tellis JC, Primer DN, Molander GA. *Science*. 2014;345:433.
5. (a) Primer DN, Karakaya I, Tellis JC, Molander GA. *J Am Chem Soc*. 2015;137:2195;
   (b) Matsui EK, Molander GA. *Org Lett*. 2017;19:436;
   (c) Amani J, Molander GA. *J Org Chem*. 1856;2017:82.
6. (a) Basavaiah D, Rao AJ, Satyanarayana T. *Chem Rev*. 2003;103:811;
   (b) Price KE, Broadwater SJ, Walker BJ, McQuade DT. *J Org Chem*. 2005;70:3980;
   (c) Singh V, Batra S. *Tetrahedron*. 2008;64:4511;
   (d) Basavaiah D, Reddy BS, Badsara SS. *Chem Rev*. 2010;110:5447.
7. (a) Dai X, Cheng D, Guan B, Mao W, Xu X, Li X. *J Org Chem*. 2014;79:7212;
   (b) Dai X, Mao R, Guan B, Xu X, Li X. *RSC Adv*. 2015;5:55290;
   (c) Chen J, Cen J, Xu X, Li X. Catal. *Sci. Technol.*. 2016;6:349;
   (d) Guan B, Xu X, Wang H, Li X. *Chin J Org Chem*. 2016;36:1564;
   (e) Ye Q, Xu X, Cheng D, Guan B, Ye H, Li X. *Arkivoc*. 2017;314.
8. Kabalka GW, Dong G, Venkataiah B, Chen C. *J Org Chem*. 2005;70:9207.
9. Basavaiah D, Sarma PKS, Bhavani AKD. *J Chem Soc, Chem Commun*. 1994;1091.
10. Basavaiah D, Krishnamacharyulu M, Hyma RS, Pandiaraju S. *Tetrahedron Lett*. 1997;38:2141.
11. Yasu Y, Koike T, Akita M. *Adv Synth Catal*. 2012;354:3414.

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