

Hypervalent Reagents

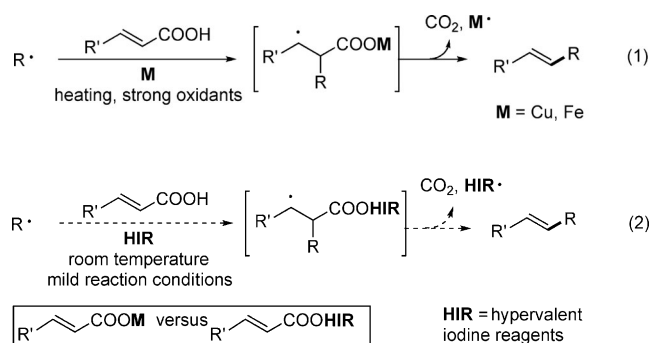
Hypervalent Iodine Reagents Enable Chemoselective Deboronative/Decarboxylative Alkenylation by Photoredox Catalysis**

Hanchu Huang, Kunfang Jia, and Yiyun Chen*

Abstract: Chemoselective $C(sp^3)$ – $C(sp^2)$ coupling reactions under mild reaction conditions are useful for synthesizing alkyl-substituted alkenes having sensitive functional groups. Reported here is a visible-light-induced chemoselective alkenylation through a deboronation/decarboxylation sequence under neutral aqueous reaction conditions at room temperature. This reaction represents the first hypervalent-iodine-enabled radical decarboxylative alkenylation reaction, and a novel benziodoxole-vinyl carboxylic acid reaction intermediate was isolated. This $C(sp^3)$ – $C(sp^2)$ coupling reaction leads to aryl- and acyl-substituted alkenes containing various sensitive functional groups. The excellent chemoselectivity, stable reactants, and neutral aqueous reaction conditions of the reaction suggest future biomolecule applications.

The chemoselective $C(sp^3)$ – $C(sp^2)$ coupling reaction under mild reaction conditions is a useful synthetic transformation for building alkyl-substituted alkenes.^[1] With a latent and removable carboxylate group to direct reactivity, vinyl carboxylic acids are readily available, stable, and selective alkene equivalents to build alkyl-substituted alkenes.^[2] However, the reported alkyl radical addition to vinyl carboxylic acids require transition-metal coordination to the carboxylate, followed by strong heating or strong oxidants to facilitate the CO_2 extrusion, reaction conditions which limit their functional-group compatibility [Eq. (1)].^[3] Hypervalent iodine reagents (HIR) are known to demonstrate similar reactivity to that of transition metals under mild reaction conditions.^[4] We hypothesized that a hypervalent-iodine-bound vinyl carboxylic acid^[5] might enable alkyl radical addition and decarboxylation of vinyl carboxylic acids [Eq. (2)].

Organoboronates are readily available and stable alkyl radical building blocks,^[6] but the chemoselectivity and functional-group compatibility are limited by the radical reaction



conditions, such as heating or use of strong oxidants.^[7] Recently, alkyl boronates were shown to undergo Michael additions or couple with aryl bromides under mild photoredox conditions, but the iridium photocatalyst only applied to benzyl or alkoxyalkyl boronates.^[8] Our group recently reported a photoredox system for general deboronative alkynylation.^[9] From the hypothesis that hypervalent iodine enables alkyl radical addition and decarboxylation of vinyl carboxylic acids, we envision a photoredox system with hypervalent iodine will facilitate both deboronative radical formation and decarboxylative radical alkenylation, thus an unprecedented $C(sp^3)$ – $C(sp^2)$ alkenylation reaction will be achieved.

We started our investigation with the alkyl trifluoroborate **1** and vinyl carboxylic acid **2** using the hypervalent iodine photoredox system under blue LED ($\lambda_{max} = 468 \pm 25$ nm) irradiation. Gratifyingly, we observed the desired alkenylation product **3** in 82% yield with $[Ru(bpy)_3](PF_6)_2$ /hydroxybenziodoxole (BI-OH; entry 1, Table 1). The use of other radical acceptors^[10] including vinyl boronates, terminal alkenes, vinyl bromides, or vinyl sulfones was not effective (see Table S1 in the Supporting Information). The widely used noncyclic iodine(III) reagents^[4a,c,d] $PhIO$, $PhI(OAc)_2$, and $PhI(OCOCF_3)_2$ gave no product (entries 2–4), although they were previously shown to facilitate electrophilic halogenation,^[5a] selenization,^[5b] and azidation^[11] of vinyl carboxylic acids. In contrast, the milder oxidants, that is, cyclic iodine(III) reagents^[4b] methoxybenziodoxole (BI-OMe) and acetoxybenziodoxole (BI-OAc) gave efficient results, while the reactivity with vinyl carboxylic acids was unknown (entries 5 and 6). The use of BI-OAc with DCE/ H_2O as solvents gave an optimal 95% yield at room temperature (87% yield upon isolation; entry 7). Photocatalyst, light irradiation, and oxidant were all critical for the reaction (entries 8–10).

We next explored the reaction mechanism by adding the radical quencher TEMPO^[12] to the optimized reaction con-

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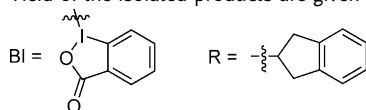
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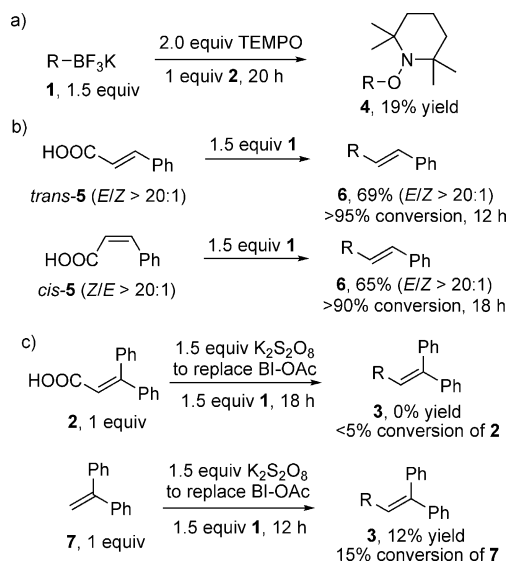
Table 1: Optimization of the alkenylation reaction.

Entry	Conditions	Conversion [%] ^[b]	Yield [%] ^[b]
1	BI-OH, CH ₂ Cl ₂ /H ₂ O	> 95	82 (79)
2	PhIO, CH ₂ Cl ₂ /H ₂ O	< 5	0
3	PhI(OAc) ₂ , CH ₂ Cl ₂ /H ₂ O	12	0
4	PhI(OCOCF ₃) ₂ , CH ₂ Cl ₂ /H ₂ O	39	0
5	BI-OMe, CH ₂ Cl ₂ /H ₂ O	> 95	76
6	BI-OAc, CH ₂ Cl ₂ /H ₂ O	> 95	93
7	BI-OAc, DCE/H ₂ O	> 95	95 (87)
8	entry 7, no [Ru(bpy) ₃](PF ₆) ₂	< 5	0
9	entry 7, no blue LED	< 5	0
10	entry 7, no BI-OAc	< 5	0

[a] Reaction conditions: **1** (0.15 mmol, 1.5 equiv), **2** (0.10 mmol, 1 equiv), [Ru(bpy)₃](PF₆)₂ (0.002 mmol, 0.02 equiv), and oxidants (0.15 mmol, 1.5 equiv) in 2.0 mL (1:1) organic solvent/H₂O under nitrogen with 4 W blue LED irradiation at 25 °C for 15 h, unless otherwise noted. [b] Conversions and yields were determined by ¹H NMR analysis. Yield of the isolated products are given within parentheses.



ditions (entry 7 in Table 1). After 20 hours, we observed neither the desired alkenylation adduct **3** nor the alkene-TEMPO adduct; only the alkyl-TEMPO adduct **4** was isolated in 19% yield (Scheme 1 a). The TEMPO experiments with the vinyl carboxylic acid **2** alone or other combinations did not yield the alkene-TEMPO adduct either (see Scheme S5). These results excluded alkenyl radical formation and confirmed the presence of alkyl R radical. We also found this reaction was stereoconvergent as both *trans*-cinnamate and *cis*-cinnamate exclusively yielded the *trans*-alkene product **6**, which additionally confirmed the radical mechanism

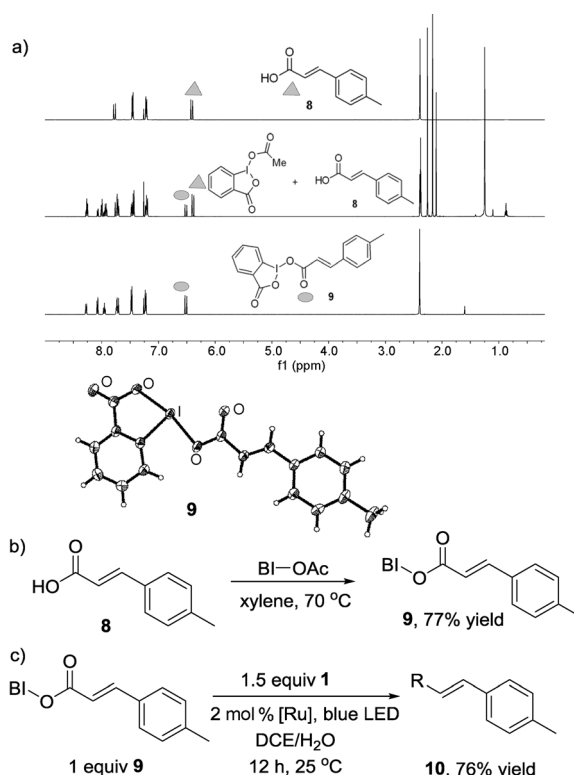


Scheme 1. Mechanistic investigations of the alkenylation. Reaction conditions are those specified in entry 7 of Table 1.

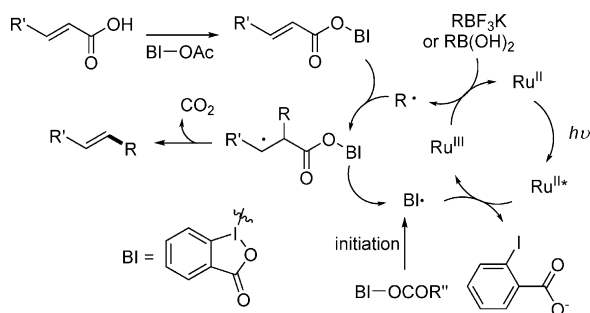
(Scheme 1 b). To test if the alkyl R radical added directly to the free vinyl carboxylic acid, we used K₂S₂O₈ to replace BI-OAc and observed no alkenylation product (Scheme 1 c).^[13] In a parallel experiment with the same reaction conditions, K₂S₂O₈ generated alkyl R radical and added to diphenylethylene (**7**) to yield **3**.^[7b,d] These results suggested BI-OAc was not simply an oxidant for alkyl R radical formation, but might contribute to an unknown reaction intermediate.

We then monitored the vinyl carboxylic acid **8** in the reaction mixture by NMR spectrometry and observed the formation of a new vinyl carboxylic acid complex **9** (Scheme 2 a; see Scheme S8 for details). This unprecedented complex **9** was stable and characterized by X-ray crystallography. An oxygen-iodine bond (2.12 Å) was shown between the vinyl carboxylic acid and the benziodoxole moiety, which was similar to the oxygen-iodine bond (2.12 Å) in the benziodoxole moiety. We also discovered that **9** could be prepared in higher yield by refluxing under vacuum (Scheme 2 b). Additionally, this stable complex **9** could replace BI-OAc/vinyl carboxylic acid **8** as the alkenylation reagent for obtaining the alkene **10** in 76% yield (Scheme 2 c).

Based on the mechanistic investigations above, we propose that vinyl carboxylic acid and BI-OAc generated a benziodoxole vinyl carboxylic acid complex (BI-OOCCH=CHR') in situ, which then oxidized the photoexcited [Ru(bpy)₃]^{2+*} to [Ru(bpy)₃]³⁺ for reaction initiation (Scheme 3).^[14] The alkyl trifluoroborate (or boronic acid) was deboronated by [Ru(bpy)₃]³⁺ to an alkyl R radical and regenerated [Ru(bpy)₃]²⁺. The alkyl R radical adds to the



Scheme 2. Characterization and reactivity of the benziodoxole vinyl carboxylic acid complex **9**. Reaction conditions are those specified in entry 7 of Table 1. Thermal ellipsoids are shown at 30% probability.^[23]



Scheme 3. Mechanistic proposal of the alkenylation reaction.

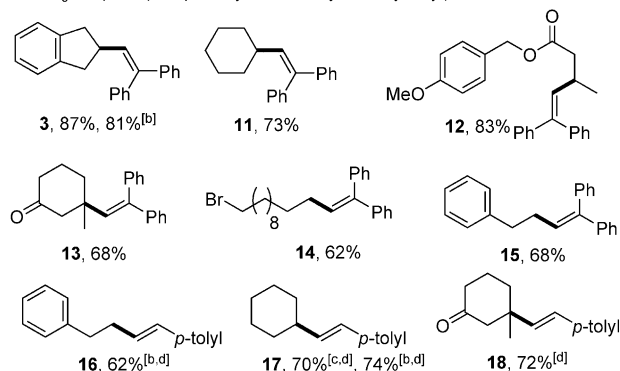
α carbon atom^[15] of BI-OOCCH=CHR', the adduct of which undergoes benziodoxole-facilitated decarboxylation to release the benziodoxole radical^[16] and yields the alkene product.^[17] It is unclear at this point if a charge-separated intermediate is formed by an internal single-electron transfer, however the exclusive *trans*-alkene product formation may suggest the formation of the carbocation intermediate.^[18]

With the optimized reaction conditions, the deboronative/decarboxylative alkenylation was tested on various substrates. Primary, secondary, and tertiary alkyl trifluoroborates (or boronic acids) bearing esters, ketones, or alkyl bromides all deboronated smoothly to give good to excellent alkenylation results (**3**, **11–18** in Scheme 4; for reaction conditions see entry 7, in Table 1). Notably, the unactivated tertiary-alkyl-substituted alkenes **13** and **18** are difficult to synthesize by transition-metal-catalyzed alkyl Heck-type reactions.^[19] When the benziodoxole vinyl carboxylic acid complex was pre-formed and used as the alkenylation reagent, similar alkenylation yields were obtained (**10**, **16–18**, **20–22**).

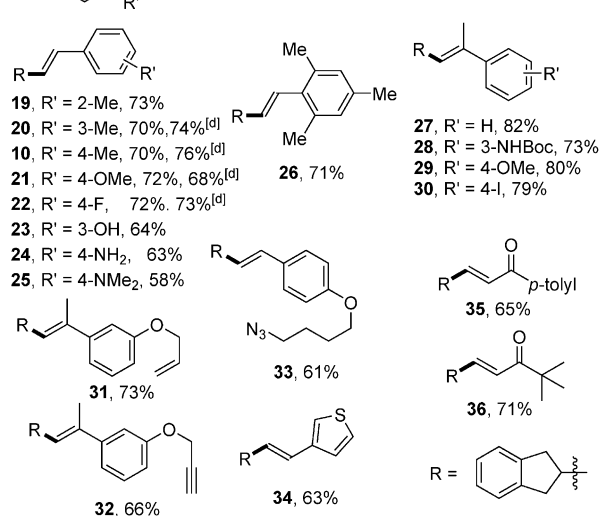
The *trans*-alkene products (*E/Z* > 20:1) were exclusively obtained from cinnamic acids having either electron-rich or electron-deficient groups at the *ortho*-, *meta*-, and *para*-positions (**19–25**). The oxidation-sensitive phenols, anilines, or dimethylanilines were all compatible and gave alkene products which are difficult to access using other alkyl Heck-type reactions^[10,19] (**23–25**). The sterically crowded 2,4,6-trisubstituted cinnamic acid gave **26** in 71% yield. Cinnamic acids with β substitution reacted smoothly to yield the *trans*-alkene products, where functional groups such as Boc, methoxy, aryl iodides, terminal alkenes, terminal alkynes, alkyl azides, and heterocycles were all tolerated (**27–34**). The compatibility of these transition-metal-sensitive functional groups highlighted the excellent chemoselectivity compared to other commonly-used alkyl Heck-type reactions.^[19] This alkenylation reaction was applicable to vinyl carboxylic acids other than cinnamic acid analogues. We found that acyl-substituted vinyl carboxylic acids yielded the *trans*-alkenes **35** and **36** smoothly, thus significantly expanding the synthetic scope of the reaction.^[3,19]

With the excellent chemoselectivity and mild reaction conditions, this visible-light-induced alkenylation reaction has potential for applications for biomolecules if neutral aqueous reaction conditions can be achieved.^[20] To our delight, the water-soluble vinyl carboxylic acid **38** reacted smoothly at pH 7.4 in a phosphate saline buffer to deliver the alkene **39** in 73% yield [Eq. (3)]. It has been shown that the photoredox

RBF₃ scope^[c] (R = primary, secondary, tertiary alkyl)

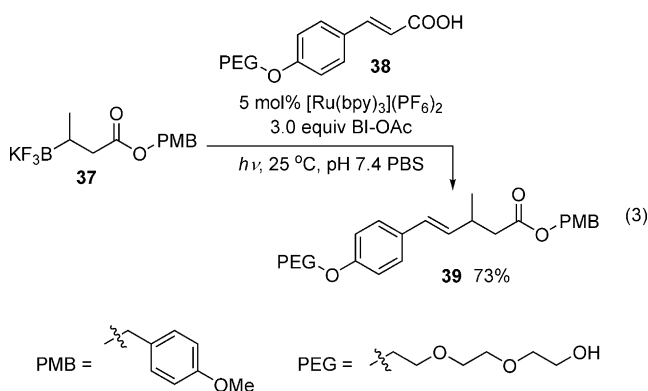


HOOC-CH=CHR' scope^[c] (R' = aryl, acyl)



Scheme 4. Substrates scope and functional-group compatibility of the alkenylation.^[a] [a] Reaction conditions are those specified in entry 7 of Table 1. Trifluoroborates were used, unless otherwise noted. [b] Boronic acids were used and DCE as the solvent. [c] *E/Z* > 20:1 for all alkene products. [d] For reaction conditions see Scheme 2c. The benziodoxole vinyl carboxylic acid complex was used as the alkenylation reagent.

system with hypervalent iodine is compatible with various biomolecules, including cell lysates, and we envision that the use of boronates and carboxylic acids as stable reactants will further improve its biocompatibility.^[9]



In conclusion, we have developed a visible-light-induced deboronative/decarboxylative alkenylation, which represented the first hypervalent-iodine-enabled alkyl-alkene coupling using aryl- or acyl-substituted^[21] vinyl carboxylic acids.^[22] Compared to other commonly used alkyl Heck-type reactions, this C(sp³)-C(sp²) coupling reaction demonstrated excellent chemoselectivity under mild reaction conditions, and is useful for constructing aryl- and acyl-substituted alkyl alkenes containing sensitive functional groups. The additional reactivity and biomolecule applications of this novel photo-redox/hypervalent iodine reagent system are under investigation in our laboratory.

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