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Selective Syntheses of *Z*-Alkenes via Photocatalyzed Decarboxylative Coupling of *N*-Hydroxyphthalimide Esters with Terminal Arylalkynes

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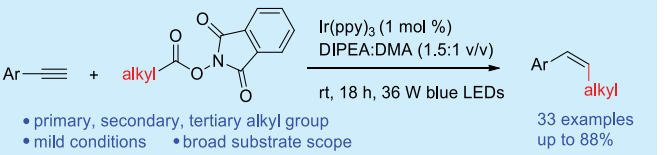
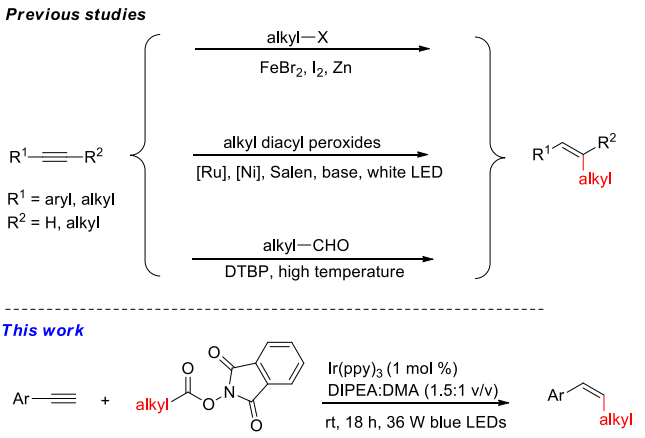
Supporting Information

ABSTRACT: A novel, efficient *Z*-alkene synthesis via photocatalyzed decarboxylative couplings between terminal aryl alkynes and alkyl *N*-hydroxyphthalimide (NHPI) esters, which are derived from aliphatic carboxylic acids, is described. A wide range of primary, secondary, and tertiary carboxylates as well as α-amino acid and α-oxyacid-derived esters were employed as suitable substrates. The mild reaction conditions, broad substrate scope, functional group tolerance, and operational simplicity make this decarboxylative coupling reaction a valuable method in organic syntheses.



Alkenes are among the most important structural motifs that frequently appear in chemical, material, natural product, and pharmaceutical fields.[1] While compared with the synthesis of more stable *E*-alkene, there were few reports on the preparation of *Z*-alkene. The most general method of *Z*-alkene synthesis is the Wittig-type reaction, which is noncatalytic and generates a stoichiometric amount of phosphine oxide waste.[2] As nontoxic, abundant, stable, and inexpensive substrates, carboxylic acids are highly useful starting materials in coupling reactions. Macmillan and co-workers reported the selective intermolecular addition of nucleophilic radicals to alkynes via Ir- and Ni-catalyzed decarboxylative hydroalkylation of alkynes.[3] As aliphatic carboxylic acids derivatives, *N*-hydroxyphthalimide (NHPI) esters have attracted considerable attention and were usually used as efficient alkyl electrophiles in alkyl coupling reactions, such as with organometallic reagents,[4] aryl iodides,[5] α,β-unsaturated acids,[6] alkynes,[7] alkenes,[8] boron reagents,[9] and other substrates.[10] In recent years, several methods were reported to access *Z*-alkenes by coupling of terminal alkynes with alkyl electrophiles (Scheme 1). For example, in 2015, Hu and co-workers developed the first *Z*-selective olefin synthesis via iron-catalyzed reductive coupling of terminal alkynes with alkyl iodides and alkyl tosylates as electrophiles.[11] Bao and co-workers have reported the *Z*-preferred olefin syntheses via Ru- and Ni-catalyzed hydroalkylation of terminal aryl alkynes with alkyl diacyl peroxides as electrophiles.[12] Li and co-workers disclosed a radical-mediated oxidative decarbonylative hydroalkylation of alkynes with alkyl aldehydes using di-*tert*-butyl peroxide (DTBP) as oxidant.[13] In organic chemistry, visible light as a safe, renewable, and inexpensive source of chemical energy to facilitate the construction of complex organic molecules has always been harnessed. With those advantages, we wondered if NHPI esters could be also used to react with terminal aryl alkynes to access *Z*-alkene via a photocatalyzed decarboxylative coupling strategy, and herein we report our results.

Scheme 1. Hydroalkylation of Alkynes with Alkyl Electrophiles



Our studies were commenced with the model reaction between *N*-acyloxyphthalimide (**1b**) and phenylacetylene (**1a**) (Table 1). Previous reports indicated that *fac*-Ir(ppy)$_3$ and diisopropylethylamine (DIPEA) played important roles in styrene's (*E*)- to (*Z*)-isomerization.[14] Inspired by this result, we discovered that simply mixing **1a** (0.2 mmol), **1b** (0.5 mmol, 2.5 equiv), DIPEA (3 equiv), and *fac*-Ir(ppy)$_3$ (1 mol %) in DMA for 18 h afforded 29% (*Z*/*E* = 67:33) of product **1** after irradiation by 36 W blue LED lamps under Ar. This initial

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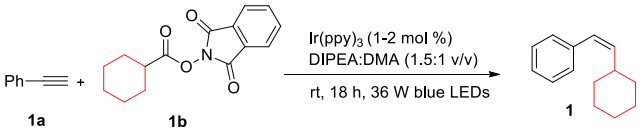
Table 1. Optimization of Reaction Conditions[a]



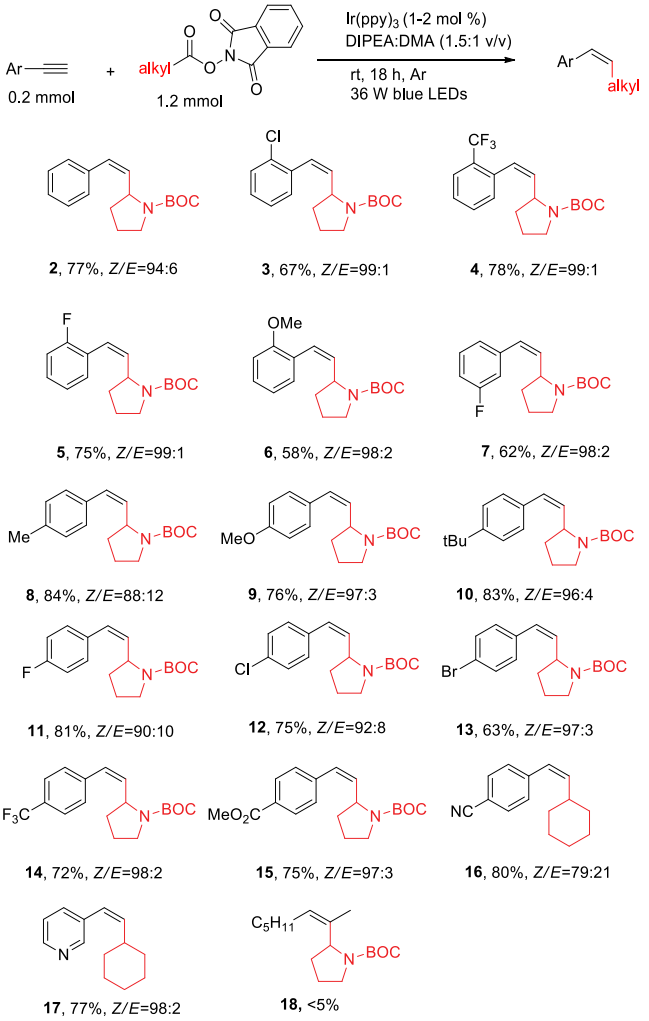
entry	change from standard condition	yield % (*Z*/*E*)
1	no change	77 (79:21)
2[b]	no $Ir(ppy)_3$	0
3[b]	no blue LEDs	0
4[b]	no DIPEA	0
5[b]	DABCO instead of DIPEA	18 (50:50)
6[b]	TMEDA instead of DIPEA	20 (57:43)
7[b]	Et_3N instead of DIPEA	17 (57:43)
8[b]	DMAP instead of DIPEA	13 (56:44)
9[b]	DBU instead of DIPEA	15 (58:42)
10[b]	CH_3COOLi instead of DIPEA	0
11[b]	K_2CO_3 instead of DIPEA	0
12[c]	20 equiv of DIPEA	34 (74:26)
13[c]	70 equiv of DIPEA	56 (89:11)
14[d]	DMSO instead of DMA	31 (86:14)
15[d]	THF instead of DMA	37 (73:27)
16[d]	MeCN instead of DMA	40 (86:14)
17[d]	Cy-COOH instead of **1b**	0

[a]Conditions: **1a** (0.2 mmol), **1b** (1.2 mmol), and $Ir(ppy)_3$ (1−2 mol %) in a mixture of DIPEA/DMA (2.4 mL/1.6 mL) were irradiated by 36 W blue LEDs for 18 h under Ar. Isolated yields. The *Z*/*E* ratio was determined by ^{1}H NMR. [b]**1b** (2.5 equiv), $Ir(ppy)_3$ (1−2 mol %), and DIPEA (3 equiv) in DMA (2 mL). [c]**1b** (2.5 equiv). [d]**1b** (2.5 equiv) and DIPEA (70 equiv) in DMA (2 mL).

result promoted us to improve both yield and *Z*/*E* ratio of this reaction. The control experiments indicated that photocatalyst, blue LED, and DIPEA were essential for the transformation to occur (entries 2−4). When DIPEA was replaced by other organic bases such as DABCO, TMEDA, Et_3N, DMAP, and DBU, both yields and *Z*/*E* ratios decreased significantly (entries 5−9). There was no product formed when replacing DIPEA with inorganic bases(CH_3COOLi, K_2CO_3) (entries 10 and 11). Increasing the amount of DIPEA significantly improved both yield and selectivity. Different ratios (see the Supporting Information for details) of DIPEA were tested for this condition. The best selectivity was observed when 70 equiv of DIPEA was added (entries 12 and 13). Next, different solvents (DMSO, THF, MeCN, DCM, dioxane, DCE, acetone, ethyl acetate) were screened. DMA was established as the best solvent (entries 14−16). It should be noted that no product was formed when cyclohexanecarboxylic acid was employed instead of its NHPI ester **1b**, probably because of the lower oxidation capacity of the photocatalyst (entry 17).[15] Finally, lowering concentration to 0.05 mmol/mL and increasing the amount of **1b** to 6 equiv (see the Supporting Information for details) produced coupling product **1** with 77% yield and *Z*/*E* selectivity of 79:21. Overall, optimal choice of solvent and equivalents of base were the keys for this transformation.

With the optimized reaction conditions in hand, we explored the substrate scope with various aryl alkynes (Scheme 2). A wide range of alkynyl arenes with either electron-withdrawing or electron-donating functional groups at the *para*-, *meta*-, and *ortho*-positions were converted to *Z*-alkenes with good yields and *Z*/*E* selectivities. The tolerance to the reactive functional groups like halogen (**3**, **5**, **7**, **11**, **12**, and **13**), ester (**15**), and cyano (**16**) groups further broadens the application of this

Scheme 2. Substrate Scope with Respect to Terminal (Hetero)arylalkynes[a]



[a]Conditions: Terminal (hetero)arylalkynes (0.2 mmol), NHPI esters (1.2 mmol), and $Ir(ppy)_3$ (1−2 mol %) in a mixture of DIPEA/DMA (2.4 mL/1.6 mL) were irradiated by 36 W blue LEDs for 18 h under Ar. Isolated yields of *Z*/*E* mixtures and the *Z*/*E* ratio were determined by ^{1}H NMR.

transformation, as various structural motifs can be accessed by those functionalities by well-established methods such as cross-coupling or simple reduction. Alkynyl heteroarene like pyridine (**17**) was also a suitable substrate for this transformation. At last, the alkyl alkyne (**18**) and aryl internal alkyne were also tested for this coupling, and no desired products were observed. A nickel-catalyzed decarboxylative coupling of NHPI esters with internal alkynes was previously reported by the other research group.[10s]

Subsequently, substrate scopes with different NHPI esters were investigated (Scheme 3). A wide range of redox-active esters derived from aliphatic carboxylic acids including primary, secondary, and tertiary alkyl NHPI esters were subjected to the optimized conditions and afforded the desired products. Moderate yields were observed for the reactions of primary alkyl NHPI esters (**19**, **20**, and **21**), probably due to their low efficiencies of decarboxylation and relative instability of primary alkyl radicals.[14c] NHPI esters with sensitive functional groups such as halogen (**21**), ether (**29**), and N-

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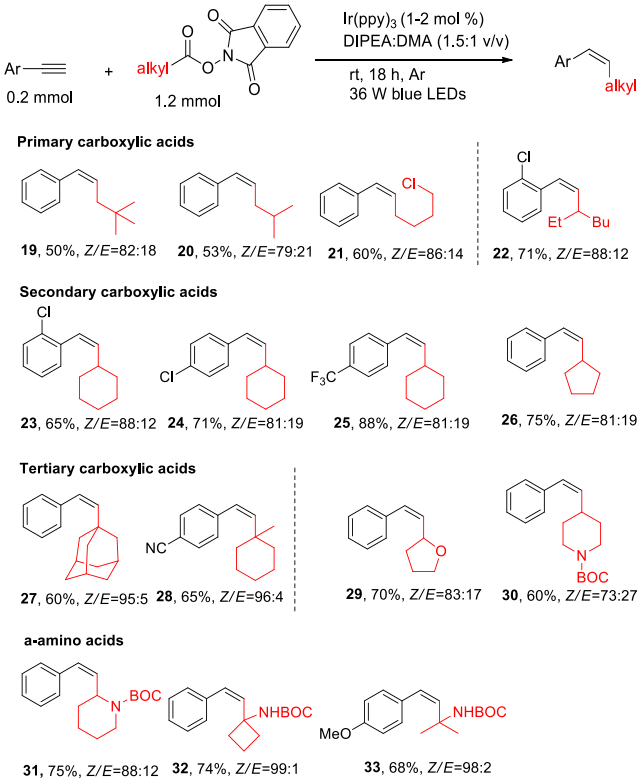
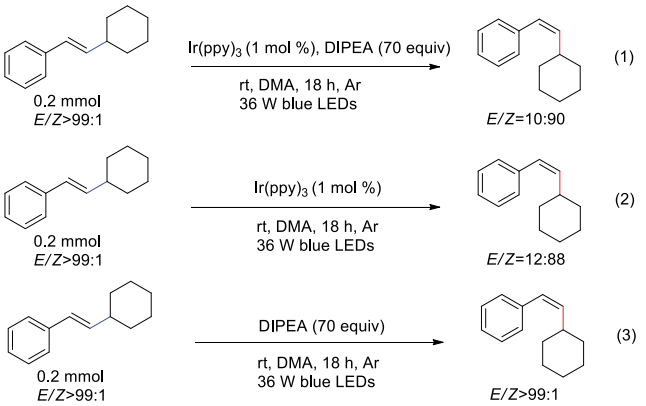
Scheme 3. Substrate Scope with Respect to Aliphatic Carboxylates[a]

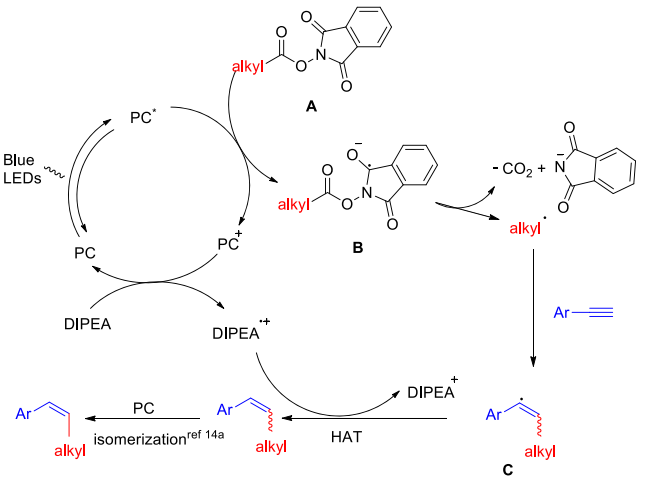


[a]Conditions: terminal (hetero)arylalkynes (0.2 mmol), NHPI esters (1.2 mmol), and $Ir(ppy)_3$ (1−2 mol %) in a mixture of DIPEA/DMA (2.4 mL/1.6 mL) were irradiated by 36 W blue LEDs for 18 h under Ar. Isolated yields of *Z*/*E* mixtures and the *Z*/*E* ratio were determined by ^{1}H NMR.

Scheme 4. Control Experiments



Scheme 5. Proposed Mechanism



Boc (**30**−**33**) groups successfully coupled with aryl alkynes to afford the *Z*-alkenes with good yields and *Z*/*E* selectivities. The position of the heteroatoms to the NHPI ester functional group played important roles on this transformation. For example, N-Boc-piperidine-2-carboxylic acid ester (**31**) resulted in better yield than N-Boc-piperidine-4-carboxylic acid ester (**30**). This is probably due to the nitrogen atom's stabilization ability to the neighboring radicals. Similar results were observed for the *ortho*-, chloro-substituted substrate (**23**), which produced better *Z*/*E* selectivity than the *para*-substituted one (**24**). Finally, a series of amino-acid-derived NHPI esters (**32** and **33**) underwent the decarboxylative coupling with the aryl alkyne to afford highly selective *Z*-alkenes.

To investigate the mechanism, a series of control experiments were conducted (Scheme 4). In the presence of iridium photoredox catalyst and DIPEA, a synthetic pure *E* isomer of **1** was converted to the *Z* isomer in 18 h under standard conditions. Further experiment established the iridium catalyst as the only essential one for this *Z*/*E* conversion. This result further proved Prof. Weaver's report and extended this transformation's substrate scope.[14a]

Based on the above mechanistic studies, a possible mechanism is proposed in Scheme 5. With the redox potential of the Ir-photoredox catalyst *fac*-$Ir(ppy)_3$ ($E_{1/2}{}^{*IV/III}$ = −1.73 V vs SCE, $E_{1/2}{}^{IV/III}$ = +0.77 V vs SCE), redox active ester ($E_{1/2}$ = −1.26 to −1.37 V vs SCE), and DIPEA (+0.72 V vs SCE in CH_3CN),[6a,8i] an Ir ^{IV}/Ir ^{III} redox mechanism is proposed. The photocatalyst (PC) is excited to a strongly reducing excited state (PC*) by visible-light irradiation. Radical anion **B** was formed by single electron transfer (SET) from PC*. Further, CO_2 and phthalimide anion extrusion produced an alkyl radical. The coupling of an alkyl radical with alkyne resulted in the radical intermediate **C**. Hydrogen atom transfer (HAT) from DIPEA to intermediate **C** finished the final product. Isotope experiments have excluded the hydrogen transfer from solvent and trace water content in solvents (see the Supporting Information for details).[6a,8i] The *Z* selectivity of the formed alkene resulted from the isomerization effect of the iridium catalyst.[14a]

In conclusion, we successfully developed an efficient strategy to synthesize *Z*-selective alkenes with good yields and *Z*/*E* selectivities via visible-light photoredox catalysis. This method tolerates a wide range of functional groups and demonstrates a broad scope with regard to both the carboxylic acid and arylalkyne components. In addition, the reactions can be carried out under mild conditions without the requirement for organometallic activation.

■ ASSOCIATED CONTENT

Supporting Information

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General information, experimental section, general procedure and compound characterization, control experiment and mechanistic studies, and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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