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Metal-Free C(sp^3)−H Allylation via Aryl Carboxyl Radicals Enabled by Donor−Acceptor Complex

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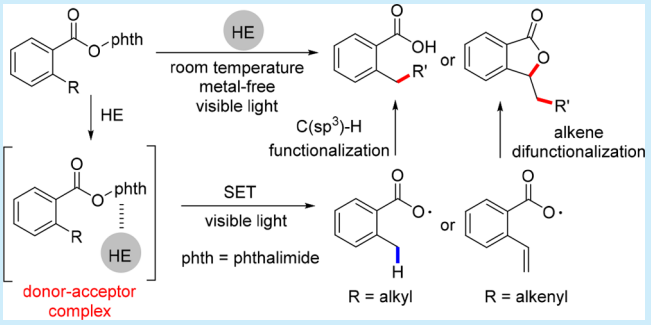
Supporting Information

ABSTRACT: The first aryl carboxyl radical generation by the donor−acceptor complex with *N*-acyloxyphthalimides and Hantzsch esters is reported. Regio- and chemoselective C(sp^3)−H bond allylation is enabled by aryl carboxyl radicals with visible light irradiation under mild and metal-free conditions.

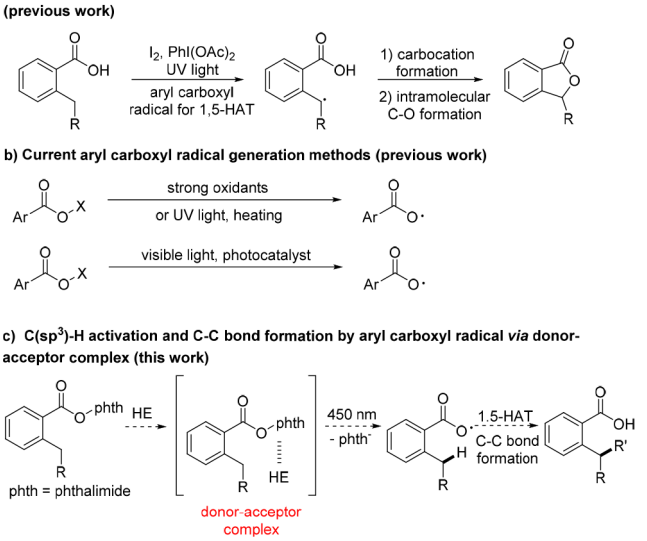


The engagement of unactivated C(sp^3)−H bonds for new C−C bond formation is fundamental in organic synthesis, in which excellent regio- and chemoselectivity are challenging to achieve.[1] The oxygen-centered radical provides a valuable entry to activate C(sp^3)−H bonds via the 1,5-hydrogen atom transfer (1,5-HAT) reaction; however, such reactivity is only demonstrated by the alkoxyl radicals,[2] and the use of aryl carboxyl radicals for 1,5-HAT reaction is less studied.[3] Currently, the use of aryl carboxyl radicals for C(sp^3)−H bond functionalization is limited to lactone formation under oxidative conditions via the carbocation intermediate (Scheme 1a).[3a,4] The use of aryl carboxyl radicals for C(sp^3)−H bond functionalization with new C−C bond formation is unknown.[3a,5,6]

Traditionally, the generation of aryl carboxyl radicals requires harsh reaction conditions such as strong oxidants, heating, or UV light irradiation (Scheme 1b).[7] Recently, the resurgence of photoredox catalysis has enabled aryl carboxyl radical generation under mild and visible-light-induced radical initiation conditions. However, heavy metal photocatalysts are typically required.[5] We expect that a new metal-free aryl carboxyl radical generation method will be very valuable, especially for material and biological applications.[8] We and others recently discovered that the donor−acceptor complex demonstrated unique visible-light-induced reactivity, and we envision the donor−acceptor complex approach may enable the aryl carboxyl radical generation.[9] In this letter, we report the first visible-light-induced aryl carboxyl radical generation via the donor−acceptor complex, with which the regio- and chemoselective C(sp^3)−H bond allylation is achieved (Scheme 1c).

N-Acyloxyphthalimides are readily accessible and stable aryl carboxyl radical precursors.[5e,10] We started our investigation with

Scheme 1. Generation and Reactivity of Aryl Carboxyl Radicals



N-acyloxyl derivatives **1**−**4**, which could be prepared in one step from 4-toluic acids (Scheme 2a). When *N*-acyloxyphthalimide **1**, tetrachloro-substituted *N*-acyloxyphthalimide **2**, or *N*-acyloxynaphthalimide **3** was mixed with Hantzsch ester (HE) **5**, the UV/vis absorption spectrometry of HE **5** showed clear red shifts. In particular, a strong red shift together with a charge-transfer

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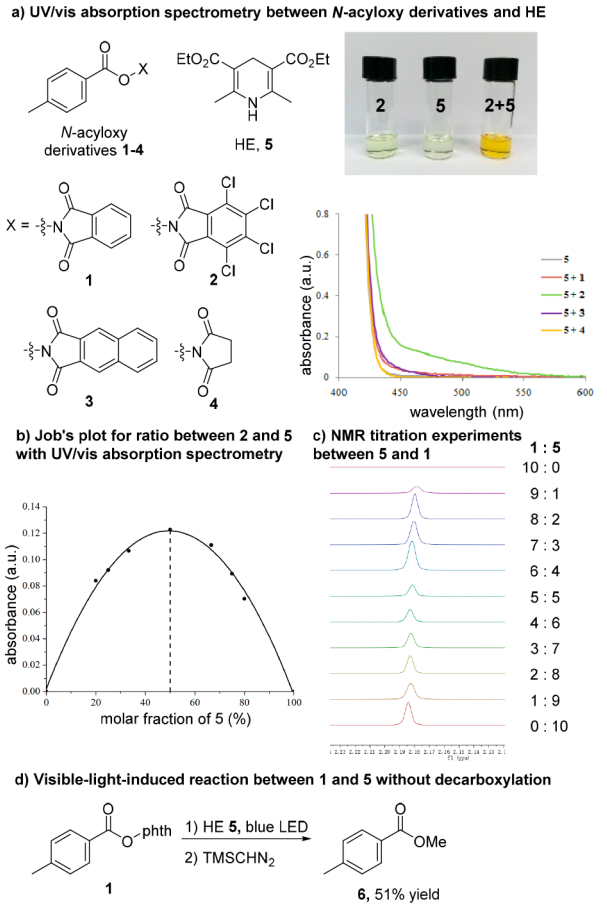
Scheme 2. Interaction between *N*-Acyloxy Derivatives and Hantzsch Esters

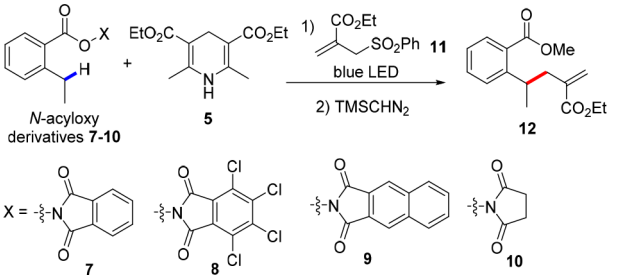


orange-yellowish color appeared when HE **5** was mixed with the electron-deficient **2**, which was consistent with the *N*-acyloxyphthalimides as electron acceptors (Scheme 2a). In contrast, no signal change was observed between *N*-acyloxysuccinimide **4** and HE **5**.[9j]

The Job's plot was next performed with UV/vis absorption spectrometry and indicated the 1:1 ratio of complexation between **2** and **5** (Scheme 2b).[11] The dissociation constant K_{EDA} between **2** and **5** was calculated to be 3.7 M^{-1} in dichloromethane.[12] The ^{1}H NMR signal of HE **5** shifted with the addition of *N*-acyloxyphthalimide **1** by NMR titration experiments (Scheme 2c). When the *N*-acyloxyphthalimide **1** and HE **5** were subjected to blue LED light irradiation, the phthalimides and methyl 4-tolylate **6** were yielded after (trimethylsilyl)diazomethane treatment, which suggested the aryl carboxyl radical generation (Scheme 2d).

We then investigated the aryl carboxyl radical reactivity and synthesized 2-ethylbenzoic phthalimide **7** for either 1,5-HAT or 1,6-HAT reaction. Under blue LED irradiation with allyl sulfone **11** as the radical acceptor, we observed the methyl ester **12** in 74% yield after (trimethylsilyl)diazomethane treatment, which indicated the sequential reaction of aryl carboxyl radical generation, 1,5-HAT reaction, and radical allylation (entry 1 in Table 1).[13] The solvent screening indicated DMF was optimal to give **12** in 80% yield (70% isolated yield in two steps, entries 1–3). The use of tetrachloro-substituted *N*-acyloxyphthalimide **8** and *N*-acyloxynaphthalimide **9** gave similar 79–83% yields, while the *N*-acyloxysuccinimide **10** did not lead to any conversion due to

Table 1. Reaction between *N*-Acyloxy Derivatives and Hantzsch Ester for Selective C(sp^3)–H Allylation



entry	conditions[a]	conversion (%)[b]	yield (%)[b]
1	**7** + HE, dioxane	>95	74
2	**7** + HE, DCM	38	12
3	**7** + HE, DMF	95	80(70)
4	**8** + HE, DMF	95	79
5	**9** + HE, DMF	95	83
6	**10** + HE, DMF	0	0
7	entry 3, iPr_2NEt	95	70
8	entry 3, HCO_2H	95	84(67)
9	entry 3, band-pass 450 nm	93	82
10	entry 3, band-pass 475 nm	82	65

[a]Reaction conditions: *N*-acyloxy derivatives (0.10 mmol, 1.0 equiv), **11** (0.30 mmol, 3.0 equiv), and Hantzsch ester **5** (0.15 mmol, 1.5 equiv) in 1.0 mL of solvent under nitrogen with 8 W blue LED irradiation at ambient temperature for 15 h, unless otherwise noted. [b]Conversion and yields were determined by ^{1}H NMR analysis, and isolated yields are in parentheses.

the lack of donor–acceptor complex formation (entries 4–6). We also tested the addition of acids or bases to the reaction and found the reaction was not significantly affected (entries 7–8).

The possible reaction initiation with shorter wavelength irradiation for the direct photoexcitation of *N*-acyloxyphthalimides or HE was next tested.[5e,14] Using irradiation with a band-pass at 450 nm, in which *N*-acyloxyphthalimides or HE has minimal absorption, the reaction went uncompromised with 82% yield (entry 9). Using a 475 nm band-pass without emission below 460 nm (see Figures S9–S10), the 65% yield of **12** could be obtained (entry 10). Taken together, the donor–acceptor complex formation is essential for the reaction with visible light at longer wavelengths. The light irradiation and HE are both found to be critical for the reaction (see Table S2).

Subsequently, the substrate scope of the C(sp^3)–H allylation was tested (Scheme 3). The electron-rich methyl or electron-deficient chloride and fluoride groups as the aryl substituents did not affect the reaction to give methyl esters **13**–**15** in 58–64% yields. For substrates **16a** and **17a** with secondary C(sp^3)–H bonds at both the 5- and 6-position, only 1,5-HAT adducts were obtained exclusively in 62–65% yields. We tested benzyl, phenolic, and silyl ether derivatives **18a**–**20a** and observed the allylation adducts **18**–**20** in 58–65% yields. For substrates **21a** with a fused ring or **22a** with a tertiary C(sp^3)–H bond, the decreased 45% yields of **21** and **22** were obtained. It is worth noting that there is no lactone product formation in the aryl carboxyl radical HAT reactions via the carbocation intermediate.[6]

The 5-exo alkene addition of aryl carboxyl radicals was further investigated. While it is a typical reactivity of oxygen-centered radicals, such reports of aryl carboxyl radicals are limited,[4b] and the new C–C bond formation following 5-exo alkene addition is unknown.[15] Under our standard reaction conditions (entry 3 in Table 1), we observed the alkene difunctionalization adduct **24** in

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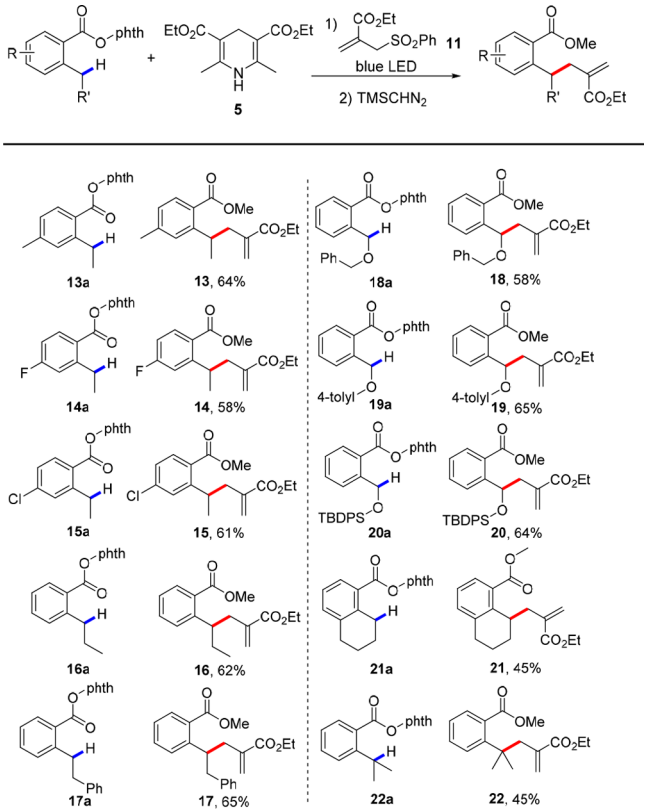
Scheme 3. Substrate Scope of C(sp^3)–H Allylation[a]

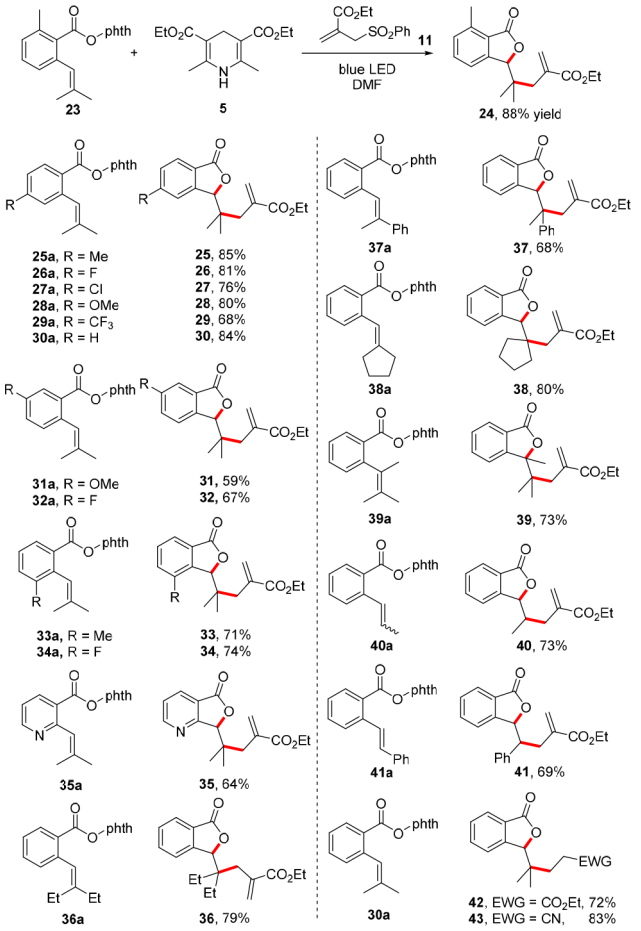


[a]Reaction conditions are the same as those in entry 3 of Table 1, and isolated yields are reported.

88% isolated yield, which indicated the sequential reaction of aryl carboxyl radical generation, 5-exo cyclization, and radical allylation (Scheme 4).[13] As substrate **23** has both possible 1,5-HAT and 5-exo reaction pathways, the exclusive formation of the lactone **24** suggested the preferred 5-exo cyclization.[16] The aryl substitution of electron-rich or -deficient methoxyl, methyl, fluoro, chloro, and trifluoromethyl groups did not significantly affect the reaction to give **25**–**34** in 59–85% yields. The pyridine heterocycle was well tolerated to give **35** in 64% yield, and the alkyl or aryl substituents at the alkene were both tolerated to give **36**–**38** in 68–80% yields. The di-, tri-, and tetra-substituted alkenes all reacted uneventfully to give **39**–**41** in 69–73% yields. The ethyl acrylate and acrylonitrile were also used as radical acceptors to give **42**–**43** in 72–83% yields.

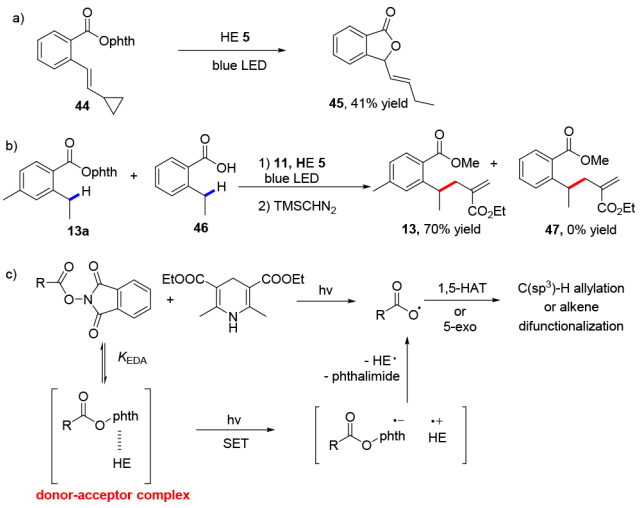
To gain mechanistic insight, we prepared vinylcyclopropane-substituted *N*-acyloxyphthalimide **44** and subjected it to the standard reaction conditions. The ring-opening adduct **45** was obtained in 41% yield and suggested the radical reaction pathway (Scheme 5a). We also performed the crossover experiment with *N*-acyloxyphthalimide **13a** and 2-ethylbenzoic acid **46** (Scheme 5b). The exclusive formation of product **13** suggested the intermolecular hydrogen abstraction reaction was unlikely. Based on the mechanistic investigations above, we propose that the reaction is initiated by the donor–acceptor complex formation between *N*-acyloxyphthalimides and Hantzsch esters (Scheme 5c). After the visible-light-induced electron transfer, the *N*-acyloxyphthalimide radical anion is formed and eliminates phthalimides to generate the aryl carboxyl radical. Afterward, the aryl carboxyl radical engages in either 1,5-HAT reaction or 5-exo alkene addition to yield the alkyl radical for C(sp^3)–H

Scheme 4. Substrate Scope of Alkene Difunctionalization[a]



[a]Reaction conditions are the same as those in entry 3 of Table 1, and isolated yields are reported.

Scheme 5. Mechanistic Investigations and Proposals



allylation or alkene difunctionalization, while the eliminated sulfone radical is reduced by the Hantzsch ester radical.

In conclusion, we have developed the first donor–acceptor complex approach to generate aryl carboxyl radicals under metal-free conditions with visible light irradiation. C(sp^3)–H allylation and alkene difunctionalization of *N*-acyloxyphthalimides were realized via aryl carboxyl radicals. We envision this metal-free

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donor−acceptor complex approach will enable the visible-light-induced reactions for further pharmaceutical, material, and biological applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01172.

Complete mechanistic experiments, optimization tables, experimental methods, and additional experimental data (PDF)

NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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