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Metal-free, intermolecular carbopyridylation of alkenes *via* visible-light-induced reductive radical coupling†

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An efficient, metal-free strategy for the intermolecular three-component carbopyridylation of styrenes, enabled by Hantzsch ester and visible light, has been described. This versatile protocol gives access to important β -CF₃ pyridines, through the regioselective, sequential formation of two C–C bonds without the use of exogenous catalysts. The value of this benign protocol has been demonstrated through functionalizations of natural-product- and drug-based complex molecules.

Pyridines are important heterocycles widely found in bioactive natural products, pharmaceuticals, agrochemicals and functional materials.¹ Top selling pharmaceuticals such as antihistamine drug loratadine and anti-depressant drug mirtazapina contain the pyridine core. Moreover, pyridines are also versatile ligand scaffolds widely employed in the areas of transition-metal catalysis.² As a result, the development of novel and mild methodologies for the regioselective construction of complex pyridines employing simple starting materials is highly desired.

Alkene–pyridine cross-coupling represents an efficient and powerful strategy to access alkylpyridines with chemo- and regio-selectivity due to the fact that alkenes are simple and abundant building blocks in organic synthesis.³ Significant achievement has been made *via* transition metal catalysis, enabling the efficient intermolecular hydroxyridylation of alkenes with pyridines and their derivatives (*e.g.* *N*-oxides and *N*-methoxy pyridinium salts).⁴ Recently, several elegant examples, through visible light-induced photoredox catalysis,⁵ of hydroxyridylation of alkenes with simple pyridyl halides under mild conditions have been developed.⁶ Nevertheless, carbopyridylation of alkenes, which simultaneously forge two consecutive C–C bonds across double bonds and would enable rapid buildup of complex pyridines, is highly desired yet remains a challenge. To date, only a few examples of alkene carbopyridylations have been reported. The Zhu group described the visible-light-mediated fluoroalkyl-heteroarylation of alkenes *via* an intramolecular heteroaryl *ipso*-migration, mainly focusing on five-membered heteroaromatic substrates with very few

examples of simple pyridines.⁷ Liu and co-worker also developed a Cu-catalyzed trifluoromethylarylation of alkenes, with one pyridine substrate.⁸ Very recently, Su and coworkers reported a visible-light induced carbo-2-pyridylation of electron-deficient alkenes with pyridinium salts *via* an electron donor–acceptor complex.⁹ Nevertheless, these elegant protocols are restricted to two-component mode.^{7–9} A general protocol for the intermolecular, three-component carbopyridylation of alkenes has yet to be developed.

In our continuing efforts to pursue radical functionalization of alkenes,¹⁰ we envisioned that a light-induced, sequential radical-addition/radical-coupling protocol between alkenes and pyridines could provide a generic solution to this challenging carbopyridylation of alkenes. Given the importance of trifluoromethyl groups in pharmaceuticals and agrochemicals¹¹ as well as elegant progress in radical trifluoromethylation of alkenes,¹² we focused on the development of pyridyl functionalization of alkenes with concomitant construction of C(sp³)-CF₃ bonds. Herein, we reported the intermolecular, three-component carbopyridylation of olefins through visible light-induced reductive radical coupling under transition metal-free conditions (Fig. 1). Particularly, this protocol utilizes the potent redox ability of photoexcited Hantzsch ester (HE)^{13,14} to generate open-shell radical intermediates, thus facilitating the construction of two consecutive C–C bonds in one pot without the need for exogenous photocatalysts. Although two elegant examples of intermolecular trifluoromethylarylation of styrenes with arylboronic acids have been described recently, this Cu-catalyzed platform is inapplicable to heteroarenes.¹⁵ We expected that our new photo-chemical protocol would complement the known transition-metal protocols.

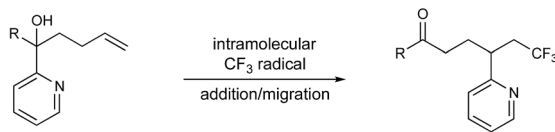
Inspired by elegant examples of radical coupling with cyanopyridines,^{13a,16} we chose cyanopyridines as the coupling partners and Hantzsch ester (HE) as the stoichiometric photo-reductant. Irradiating a solution of styrene 2, 4-cyanopyridine 3,

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A) Intramolecular heteroaryl ipso-migration of alkenes



B) This work: Transition-metal-free, intermolecular carbopyridylation of olefins

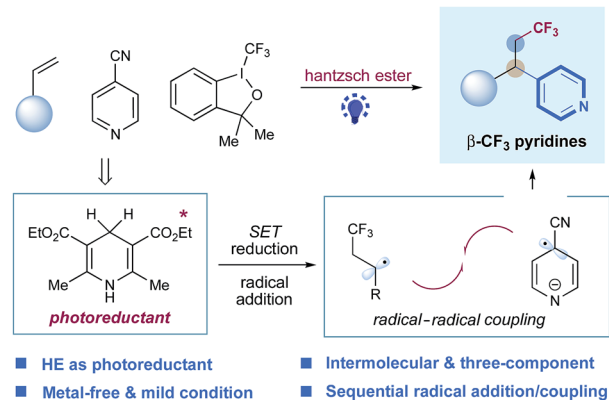


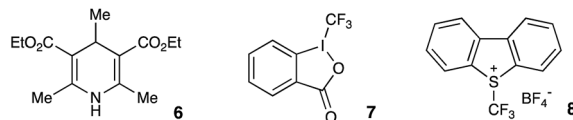
Fig. 1 Design of intermolecular carbopyridylation of alkenes via photoexcited Hantzsch ester-enabled reductive radical coupling.

and 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole **4** (Togni II reagent) in the presence of HE **1** and 1,4-diazabicyclo[2.2.2]octane (DABCO) with a 90 W blue LED gave the desired trifluoromethylpyridylation product **5** in 83% yield (Table 1, entry 1). Control experiments indicated that HE and visible light are required for the reductive coupling, as no products were observed in the absence of HE or under dark conditions (entries 2–4). Notably, DABCO had a dramatic influence on the reaction efficiency. Only 22% yield of product **5** was observed in the absence of DABCO (entry 5). Employing other organic or inorganic bases instead of DABCO resulted in a dramatic decrease in the reaction efficiency (entries 6–10). Additionally, replacing HE with 4-methyl Hantzsch ester **6**, an analog of HE, led to the formation of product **5** with a significantly low efficiency (entry 11). Moreover, the choice of the electrophilic trifluoromethylating reagents was also found to have a dramatic effect on the reaction efficiency, with Togni reagent **4** proving to be optimal (entries 12–13).

Having identified the optimal reaction conditions for the visible light-induced reductive pyridylation of alkenes, we investigated the olefin partner using 4-cyanopyridine. As shown in Scheme 1, a variety of styrenes bearing electron-donating- and electron-withdrawing substituents are viable partners for this transformation, affording the corresponding β -CF₃ pyridines in moderate to excellent yields (products **5** and **9–32**, 42–86% yields). Styrenes containing reactive functional groups, including esters, amides, tosylates, alkynes, and even free amines, underwent the desired coupling with high efficiency (products **5**, **16**, **18–19**, **22**, and **29**, 58–86% yields). Notably, the reaction of varied halides, from fluorides to iodides, gave the desired coupling product with halo atoms untouched (products **13–14**, **21**, **23–25**, and **27–28**, 65–85% yields). Halides are important synthetic manipulation handles *via* transition-metal-

Table 1 Optimization of reaction conditions^a

| Entry | Variations from the standard conditions | Yield ^b |
|-------|--|--------------------|
| 1 | None | 83% |
| 2 | w/o HE | 0% ^c |
| 3 | Dark | 0% |
| 4 | Dark, 80 °C | 0% ^c |
| 5 | w/o DABCO | 22% ^c |
| 6 | TMEDA, instead of DABCO | 43% |
| 7 | DBU, instead of DABCO | 19% |
| 8 | Et ₃ N, instead of DABCO | 26% |
| 9 | Pyridine, instead of DABCO | 19% |
| 10 | Cs ₂ CO ₃ , instead of DABCO | 21% |
| 11 | 6 , instead of HE | 25% |
| 12 | 7 , instead of 4 | 19% |
| 13 | 8 , instead of 4 | 25% |



^a Reaction conditions: styrene **2** (0.1 mmol), 4-cyanopyridine **3** (2.0 equiv.), Togni reagent **4** (1.5 equiv.), Hantzsch ester (HE, 1.5 equiv.), DABCO (1.5 equiv.), MTBE [0.05 M], 90 W blue LED, and rt. ^b Yields were determined by ¹⁹F NMR using an internal standard. ^c Major byproducts determined were dimers of benzylic radicals; see the ESI for details. DABCO: 1,4-diazabicyclo[2.2.2]octane; MTBE: methyl *tert*-butyl ether.

catalyzed cross-coupling, further indicating the complementary ability of this visible-light-induced metal-free technique. *ortho*-Substituents on the aryl rings have little effect on the reaction efficiency (products **23–26**, 64–70% yields). Alkenes attached to electron-deficient arenes, exemplified as 1,2,3,4,5-pentafluoro-6-vinylbenzene, were found to be suitable substrates with moderate efficiency (product **31**, 42% yield). Heteroarenes, in the form of indoles, were well tolerated, albeit with lower yields (product **33**, 55% yield). Furthermore, 1,1-disubstituted alkenes, such as α -methyl styrene, can be successfully employed, furnishing the expected adducts with moderate efficiency (product **34**, 65% yield). Notably, this three-component reductive coupling protocol can be applicable to other types of olefins. Reactions of electron-rich olefins (products **35–36**) as well as un-activated alkenes (product **37**) furnished the desired trifluoromethylpyridine products with moderate efficiency in the presence of 1 mol% of Ir(ppy)₃ (40–52% yields). We assume that the addition of Ir(ppy)₃ could facilitate the single-electron reduction of 4-cyanopyridine, thereby improving the reaction efficiency.

Next, we evaluated the scope of the pyridine component in this metal-free protocol. As illustrated in Scheme 1, substituted





Scheme 1 Substrate scope. Reaction conditions: alkene (0.2 mmol), cyanopyridine (2.0 equiv.), Togni II **4** (1.5 equiv.), HE **1** (1.5 equiv.), DABCO (1.5 equiv.), MTBE [0.05 M], 90W blue LED, and rt. All cited yields are isolated yields. ^aWith 1 mol% Ir(ppy)₃. ^bDetermined by ¹⁹F NMR of the reaction mixture. R₂ = *n*-C₄H₉; Ar = *tert*-Bu-phenyl.



cyanopyridines reacted well under the mild conditions, furnishing the β -CF₃ alkylpyridines with moderate to high efficiency. A number of substituents on the 2- or 3-position were tolerated, including alkyl, chloro, bromo, aryl, and cyano (products **38–48**, 49–82% yields). Both 2,4- and 3,4-dicyanopyridines underwent selective coupling at the 4-position, affording corresponding 4-alkylated pyridines in synthetically useful yields (products **41** and **47**, 65% and 49% yields, respectively). Notably, azaindole nitrile was found to readily undergo the desired three-component coupling to afford the alkylated azaindole **48** in satisfactory yield (56% yield).

To further highlight the potential application of this metal-free protocol, we have employed several natural-product- and drug-derived complex molecules in this system. As depicted

in Scheme 1, derivatives of estrone, indomethacin (anti-inflammatory drug), ezetimibe (lipid-lowering drug), and non-ivamide all functioned as competent coupling partners, furnishing each of the desired adducts with moderate efficiency (products **49–51**, 56–60% yields; S3 in the ESI†, 55% yield, see the ESI† for details).

To probe the mechanism of this alkene carbopyridylation reaction, we have conducted some preliminary mechanistic experiments (Fig. 2). Radical trap and radical clock experiments have been conducted. The addition of TEMPO completely shut down the desired reaction, with the observation of CF₃-TEMPO adduct **52** (48% yield) (Fig. 2A). Vinyl cyclopropane **53** underwent radical addition/ring opening, affording **54** as the major isolated product (40% yield, *E/Z* = 3.5 : 1) (Fig. 2B), further



Fig. 2 Mechanistic studies. (A) Radical inhibition reaction. (B) Radical clock reaction. (C) Light on/off experiments; (D) Stern–Volmer quenching studies. (E) Proposed mechanism.



