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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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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.



indicating a radical sequence involved in this novel transformation. Furthermore, light on/off experiments (Fig. 2C), as well as light control experiments (Table 1, entries 3–4), indicated that constant photoirradiation is essential for this transformation. In addition, direct illumination of the reaction mixture with a commercial laser (532 nm, in which HE has no absorption) led to no product formation (see the ESI† for details), suggesting the unique role of the photoexcited HE. Importantly, Stern–Volmer fluorescence quenching analysis indicated that photoexcited HE* ($E_{\text{red}}^* \approx -2.2$ V vs. SCE)^{13c} was quenched by Togni II **4** ($E_{\text{red}} = -1.11$ V vs. SCE in CH₃CN)¹⁷ as well as 4-cyanopyridine **3** ($E_{\text{red}} = -1.87$ V vs. SCE in CH₃CN),¹⁸ respectively (Fig. 2D).

On the basis of these experimental results, a proposed mechanism has been exemplified in Fig. 2E. A thermodynamically feasible single-electron reduction between photoexcited HE* and 4-cyanopyridine **3** would produce the persistent radical anion species **I**. At the same time, the CF₃ radical **II** could be generated through the SET reduction of photoexcited HE* and Togni reagent **4**. Subsequent facile addition of CF₃ radical **II** to styrene led to the formation of the nucleophilic benzylic radical **III**, which would undergo a selective radical–radical coupling with **I** to deliver the desired alkylpyridine product *via* the extrusion of cyanide (pathway I). At this stage, we cannot rule out the possibility that alternative pathways might be involved in this transformation. First, the generation of the CF₃ radical could proceed through multiple pathways: (i) triggered by photoexcited HE, which is supported by the Stern–Volmer fluorescence quenching study; (ii) through an electron donor–acceptor (EDA) complex between the Togni reagent and DABCO, which is suggested by a bathochromic shift in UV–Vis absorption spectrometry (see Fig. S7 in the ESI† for details);^{19,20} (iii) triggered by visible light. Control experiments showed that the major side reactions were dimerization and hydrogen abstraction of benzyl radicals (generated *via* CF₃ radical additions) in the absence of HE and/or DABCO, while no dimers were observed under the dark conditions (see Table S1 in the ESI† for more details). These phenomena indicated that visible light could solely promote the generation of the CF₃ radical from the Togni reagent.²¹ Second, an alternative pathway might be involved for the coupling step between the benzylic radical and cyanopyridine: nucleophilic addition of benzylic radical **III** to pyridine **3** at the C2 position to give rise to aryl radical species **IV**;²² radical **IV** could be reduced by HE* or DABCO to afford aryl anion **V**, which undergoes elimination of cyanide to form the C2-substituted product **VI** (pathway II). Nevertheless, the available experimental results with no observation of **VI** might not support this hypothesis.

Conclusions

In conclusion, we have developed an efficient, transition metal-free strategy for the intermolecular, three-component carbopyridylation of styrenes enabled by photoexcited Hantzsch ester. This visible light-induced protocol enables a facile access to β-CF₃ alkylpyridines, through the regioselective, sequential formation of two C–C bonds in one step without the need for

exogenous photocatalysts. Given the importance of both pyridine and CF₃ moieties in medicinal agents, we expect that the generality of this methodology and ready availability of the starting materials will allow it to enjoy extensive application in the area of organic chemistry.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257; (b) J. J. Li, *Heterocyclic Chemistry in Drug Discovery*, John Wiley & Sons, Hoboken, NJ, 2013.
- M. N. Zafar, A. H. Atif, M. F. Nazar, S. H. Sumrra, E. S. Gul and R. Paracha, *Russ. J. Coord. Chem.*, 2016, **42**, 1.
- Y. Nakao, *Synthesis*, 2011, **2011**, 3209.
- (a) G. Song, W. N. O. Wylie and Z. Hou, *J. Am. Chem. Soc.*, 2014, **136**, 12209; (b) J. Diesel, A. M. Finogenova and N. Cramer, *J. Am. Chem. Soc.*, 2018, **140**, 4489; (c) S. D. Friis, M. T. Pirnot and S. L. Buchwald, *J. Am. Chem. Soc.*, 2016, **138**, 8372; (d) S. Yu, L. Sang Hui and S. Ge, *Angew. Chem., Int. Ed.*, 2017, **56**, 15896; (e) M. W. Gribble Jr., S. Guo and S. L. Buchwald, *J. Am. Chem. Soc.*, 2018, **140**, 5057; (f) J. C. Lewis, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2007, **129**, 5332.
- (a) C. R. J. Stephenson, T. P. Yoon and D. W. C. MacMillan, *Visible Light Photocatalysis in Organic Chemistry*, Wiley-VCH, 2018; (b) L. Marzo, S. K. Pagire, O. Reiser and B. König, *Angew. Chem., Int. Ed.*, 2018, **57**, 10034; (c) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans and D. W. C. MacMillan, *Nat. Rev. Chem.*, 2017, **1**, 0052; (d) J. K. Matsui, S. B. Lang, D. R. Heitz and G. A. Molander, *ACS Catal.*, 2017, **7**, 2563; (e) M. N. Hopkinson, A. Tlahuext-Aca and F. Glorius, *Acc. Chem. Res.*, 2016, **49**, 2261; (f) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075; (g) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322.
- (a) R. A. Aycocock, D. B. Vogt and N. T. Jui, *Chem. Sci.*, 2017, **8**, 7998; (b) A. J. Boyington, M.-L. Y. Riu and N. T. Jui, *J. Am. Chem. Soc.*, 2017, **139**, 6582; (c) R. A. Aycocock, H. Wang and N. T. Jui, *Chem. Sci.*, 2017, **8**, 3121; (d) I. Ghosh, L. Marzo, A. Das, R. Shaikh and B. König, *Acc. Chem. Res.*, 2016, **49**, 1566; (e) A. Arora and J. D. Weaver, *Acc. Chem. Res.*, 2016, **49**, 2273.
- (a) Z. Wu, D. Wang, Y. Liu, L. Huan and C. Zhu, *J. Am. Chem. Soc.*, 2017, **139**, 1388; (b) J. Yu, D. Wang, Y. Xu, Z. Wu and C. Zhu, *Adv. Synth. Catal.*, 2018, **360**, 744.
- L. Li, Q.-S. Gu, N. Wang, P. Song, Z.-L. Li, X.-H. Li, F.-L. Wang and X.-Y. Liu, *Chem. Commun.*, 2017, **53**, 4038.



- 9 R. B. Hu, S. Sun and Y. Su, *Angew. Chem., Int. Ed.*, 2017, **56**, 10877.
- 10 J. Sun, P. Li, L. Guo, F. Yu, Y.-P. He and L. Chu, *Chem. Commun.*, 2018, **54**, 3162.
- 11 (a) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (c) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881.
- 12 (a) C. Alonso, E. Martínez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847; (b) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650; (c) L. L. Chu and F. L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513; (d) T. Besset, T. Poisson and X. Pannecoucke, *Chem.-Eur. J.*, 2014, **20**, 16830; (e) H. Egami and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294; (f) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598; (g) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214; (h) A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950.
- 13 (a) L. Buzzetti, A. Prieto, S. R. Roy and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2017, **56**, 15039; (b) M. A. Emmanuel, N. R. Greenberg, D. G. Oblinsky and T. K. Hyster, *Nature*, 2016, **540**, 414; (c) J. Jung, J. Kim, G. Park, Y. You and E. J. Cho, *Adv. Synth. Catal.*, 2016, **358**, 74; (d) W. Chen, H. Tao, W. Huang, G. Wang, S. Li, X. Cheng and G. Li, *Chem.-Eur. J.*, 2016, **22**, 9546; (e) L. I. Panferova, A. V. Tsymbal, V. V. Levin, M. I. Struchkova and A. D. Dilman, *Org. Lett.*, 2016, **18**, 996; (f) W. Huang, W. Chen, G. Wang, J. Li, X. Cheng and G. Li, *ACS Catal.*, 2016, **6**, 7471; (g) J. Zhang, M.-Z. Jin, W. Zhang, L. Yang and Z.-L. Liu, *Tetrahedron Lett.*, 2002, **43**, 9687; (h) M.-Z. Jin, L. Yang, L.-M. Wu, Y.-C. Liu and Z.-L. Liu, *Chem. Commun.*, 1998, 2451; (i) S. Fukuzumi, K. Hironaka and T. Tanaka, *J. Am. Chem. Soc.*, 1983, **105**, 4722.
- 14 (a) V. Balzani, P. Ceroni and A. Juris, *Photochemistry and Photophysics: Concepts, Research, Applications*, Wiley-VCH, 2014; (b) N. J. Turro, V. Ramamurthy and J. C. Scaiano, *Modern Molecular Photochemistry of Organic Molecules*, University Science Books, 2010.
- 15 (a) L. Wu, F. Wang, X. Wan, D. Wang, P. Chen and G. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 2904; (b) F. Wang, D. Wang, X. Mu, P. Chen and G. Liu, *J. Am. Chem. Soc.*, 2014, **136**, 10202.
- 16 (a) G. Wang, J. Cao, L. Gao, W. Chen, W. Huang, X. Cheng and S. Li, *J. Am. Chem. Soc.*, 2017, **139**, 3904; (b) F. Lima, M. A. Kabeshov, D. N. Tran, C. Battilocchio, J. Sedelmeier, G. Sedelmeier, B. Schenkel and S. V. Ley, *Angew. Chem., Int. Ed.*, 2016, **55**, 14085; (c) J. D. Cuthbertson and D. W. C. MacMillan, *Nature*, 2015, **519**, 74; (d) Z. Zuo and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2014, **136**, 5257; (e) K. Qvortrup, D. A. Rankic and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2014, **136**, 626; (f) A. McNally, C. K. Prier and D. W. C. MacMillan, *Science*, 2011, **334**, 1114; (g) D. Mangion and D. R. Arnold, *Acc. Chem. Res.*, 2002, **35**, 297; (h) R. Bernardi, T. Caronna, S. Morrocchi and M. Ursini, *J. Heterocycl. Chem.*, 1996, **33**, 1137; (i) X. Zeng, J. Cai and Y. Gu, *Tetrahedron Lett.*, 1995, **36**, 7275.
- 17 Y. Yasu, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2012, **51**, 9567.
- 18 P. McDevitt and M. Vittimberga Bruno, *J. Heterocycl. Chem.*, 2009, **27**, 1903.
- 19 For a recent review on EDA complex, see: C. G. S. Lima, T. de M. Lima, M. Duarte, I. D. Jurberg and M. W. Paixão, *ACS Catal.*, 2016, **6**, 1389.
- 20 For recent examples on EDA-enabled radical trifluoromethylation, see: (a) H. Jiang, Y. He, Y. Cheng and S. Yu, *Org. Lett.*, 2017, **19**, 1240; (b) Y. Cheng and S. Yu, *Org. Lett.*, 2016, **18**, 2962; (c) Q. Guo, M. Wang, H. Liu, R. Wang and Z. Xu, *Angew. Chem., Int. Ed.*, 2018, **57**, 4747; (d) M. Zhu, K. Zhou, X. Zhang and S.-L. You, *Org. Lett.*, 2018, **20**, 4379.
- 21 H. Wang, Q. Xu and S. Yu, *Org. Chem. Front.*, 2018, **5**, 2224.
- 22 J. G. Traynham, *Chem. Rev.*, 1979, **79**, 323.

