Chemical Science

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Guo, Z. Zhang, T. Guan, L. Mao, Q. Ban, K. ZHAO and T. Loh, *Chem. Sci.*, 2019, DOI: 10.1039/C9SC03070K.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemical-science

View Article Online
DOI: 10.1039/C9SC03070K

ARTICLE

Photoredox-Catalyzed Stereoselective Alkylation of Enamides with *N*-Hydroxyphthalimide Esters *via* Decarboxylative Cross-Coupling Reactions†

Received 00th January 20xx,
Accepted 00th January 20xx

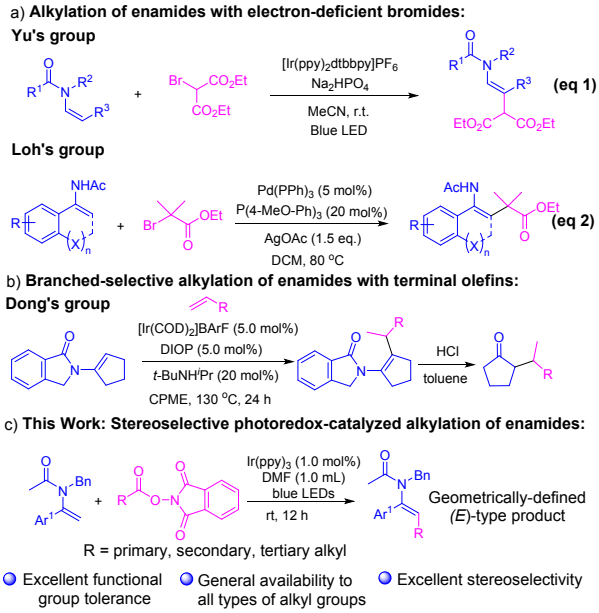
DOI: 10.1039/x0xx00000x

Jing-Yu Guo,[a] Ze-Yu Zhang,[a] Ting Guan,[a] Lei-Wen Mao,[a] Qian Ban,[a] Kai Zhao*[a] and Teck-Peng Loh*[b]

A stereoselective β-C(sp^2)–H alkylation of enamides with redox-active *N*-hydroxyphthalimide esters *via* photoredox-catalyzed decarboxylative cross-coupling reaction is demonstrated. This methodology features operational simplicity, broad substrate scopes, excellent stereoselectivities and functional group tolerence , affording a diverse array of geometrically-defined and synthetically valuable enamides bearing primary, secondary or tertiary alkyl groups in satisifying yields.

Introduction

As a crucial subclass of enamines being endowed with a delicate balance of reactivity and stability, enamides have attracted increasing attention among the chemical community as pivotal and versatile building blocks which are of recognized synthetic value in the construction of biologically and pharmaceutically active molecules,[1] especially small but complex nitrogen-containing compounds.[2] In the past few decades, we have witnessed a blooming development on new synthetic strategies for the regio- and stereoselective functionalization of enamides, especially on their β-C(sp^2)–H bond, which are capable of producing enamides bearing a diverse array of functional groups through arylation,[3] alkenylation,[4] trifluoromethylation,[5] difluoroacetylation,[6] alkynylation,[7] acylation,[8] sulfonylation[9] and other useful transformations.[10] Nevertheless, the deployment of alkyl moieties to enamides has been considering as a more challenging task with scarce advances demonstrated.[11] One of the existing scenarios for the direct C-H alkylation of enamides was achieved by using electron-deficient bromides as alkylating agents as established by Yu and co-workers by using visible-light photoredox-catalysis (Scheme 1a, eq 1) [11a] and our group through a palladium-catalyzed strategy (Scheme 1a, eq 2),[11b] respectively. Recently, another elegant methodology on the branched-selective alkylation of enamides with terminal olefins was demonstrated by Dong and coworkers (Scheme 1b).[11c] However, success to date was somewhat restricted with respect to the limited scope of both enamides and alkylating reagents and the relatively strict reaction conditions. Thus, the development of a robust and generally applicable method for the preparation of enamides bearing a diverse range of alkyl groups with versatile functionalities has been considered as a remaining challenge.



Scheme 1 Alkylation of enamides

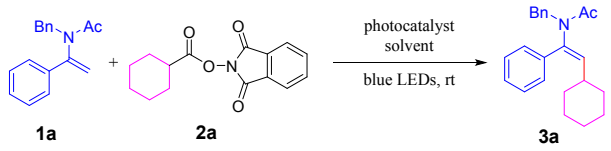
The redox-active alkyl *N*-hydroxyphthalimide esters (NHP) derived from alkanoic acids, as pioneeringly demonstrated by Okada[12] and Overman,[13] have entered into an era of "Renaissance" in the past few years in a myriad of cross-electrophile coupling reactions as C(sp^3) radical equivalents through single-electron-transfer reduction and decarboxylation. Recent advances in this arena have witnessed a rapid development in a broad range of decarboxylative cross-coupling reactions to forge C(sp^3)-C or C(sp^3)-X (X = Si, B, Se *etc.*) bond *via*

[a] *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Jiangsu National Synergetic Innovation Center for Advanced Materials, Nanjing Tech University, Nanjing 211816, China.*
[b] *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore. E-mails: ias_kzhao@njtech.edu.cn; teckpeng@ntu.edu.sg.*
†Electronic Supplementary Information (ESI) available. CCDC 1874601. For ESI and crystallographic data in CIF or other electronic format. See DOI: 10.1039/x0xx00000x

transition-metal[14,15] and photoredox catalysis,[16,17] as elegantly established by the groups of Baran,[14a-g,14o,15b] Weix,[14h,i] Fu,[16c-g,17a,b] Oestreich,[15] Phipps,[16a] Xiao,[16l] and many others.[18] Very recently, Fu and coworkers demonstrated a brand new catalytic combination of sodium iodide and triphenylphosphine for the cross-coupling of redox-active ester with silyl enol ethers or heteroarenes without resorting to dye or transition-metal based photocatalyst.[19] Enlightened by those seminal breakthroughs, we herein demonstrated a robust and practical protocol for a stereoselective decarboxylative cross-coupling of NHP esters with enamides, forging a diverse array of geometrically-defined alkylated enamides bearing various functional groups under mild conditions (Scheme 1c). Notably, this approach allows the incorporation of various primary, secondary and tertiary alkyl groups to enamides, which represents a significant advance and a crucial complement to existing methods[11a,b] that only enables the deployment of electron-deficient secondary alkyl groups.

Results and discussion

Table 1 Optimization of the reaction conditions[a]

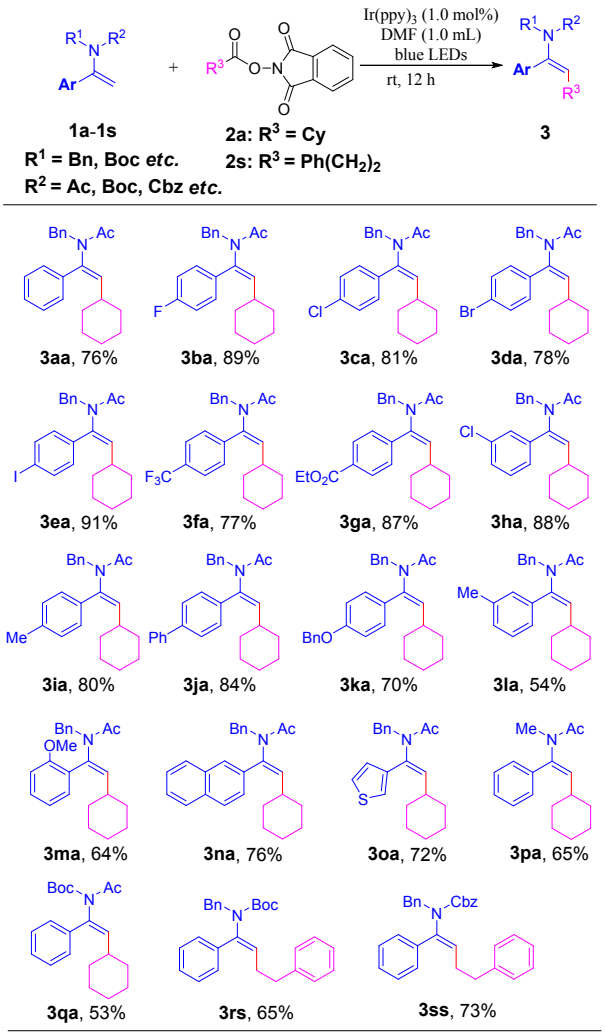


Entry	photocatalyst	solvent	Time (h)	yield[b]
1	*fac*-Ir(ppy)$_3$ (1.0)	DMF	12	63
2	Eosin Y (10)	DMF	12	36
3	Ru(bpy)$_3$Cl$_2$ (1.0)	DMF	12	52
4	*fac*-Ir(ppy)$_3$ (0.1)	DMF	24	58
5	*fac*-Ir(ppy)$_3$ (0.2)	DMF	24	58
6	*fac*-Ir(ppy)$_3$ (2.0)	DMF	12	49
7	*fac*-Ir(ppy)$_3$ (1.0)	DMAc	12	57
8	*fac*-Ir(ppy)$_3$ (1.0)	CH_3CN	12	24
9	*fac*-Ir(ppy)$_3$ (1.0)	DCM	12	trace
10[c]	*fac*-Ir(ppy)$_3$ (1.0)	DMF	12	63
11[d]	*fac*-Ir(ppy)$_3$ (1.0)	DMF	12	68
12[d,e]	*fac*-Ir(ppy)$_3$ (1.0)	DMF	12	76
13	none	DMF	12	0
14[f]	*fac*-Ir(ppy)$_3$ (1.0)	DMF	12	0

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), solvent (3.0 mL). [b]Isolated yields. [c]2.0 mL DMF. [d]1.0 mL DMF. [e]0.36 mmol **2a** was used. [f]The reaction was carried out in darkness.

At the outset of our investigation, *N*-benzyl-*N*-(1-phenylvinyl)acetamide (**1a**) and 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate (**2a**) were selected as model substrates for the screening of optimal reaction conditions (Table 1). Initial screening of the common photocatalysts showed that *fac*-Ir(ppy)$_3$ was superior to Ru(bpy)$_3$Cl$_2$ and Eosin Y (Table 1, entry 1 *vs* entries 2 and 3). Further investigation of solvents revealed that DMF was the optimal choice for the transformation (Table 1, entry 1 *vs* entries 7-9) and the most appropriate concentration of the enamides was 0.3 M (Table 1, entries 11 and 12 *vs* entries 1 and 10). The optimal loading of the photocatalyst proved to be 1.0 mol% with respect to reaction time and efficiency (Table 1, entries 4-6 *vs* entry 1). The employment of 1.2 eq. of NHP esters instead of 1.5 eq. led to an increase of the product yield. (Table 1, entry 12 *vs* entry 11). Control experiments found that photoredox catalyst and light were both of crucial importance for this transformation, no desired product was formed in the absence of photocatalyst or without irradiation (Table 1, entries 13 and 14).

Table 2 Scope of enamides[a,b]



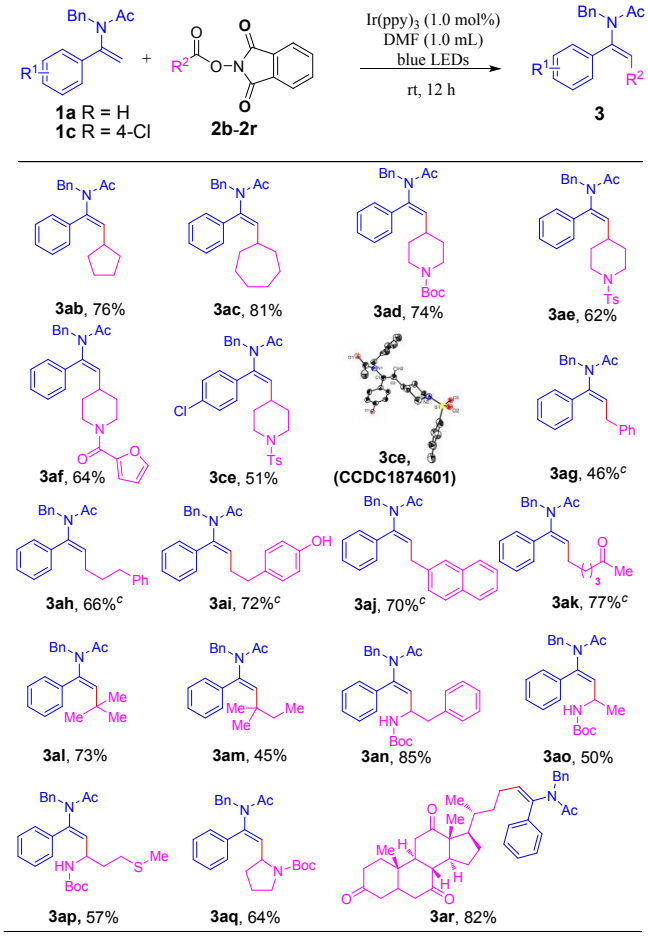
[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), Ir(ppy)$_3$ (1.0 mol%), DMF (1.0 mL) under N_2. [b]Isolated yields.

With the optimal reaction conditions in hand, we next examined the substrate scope with regard to different enamides or enecarbamates **1a-1s** with NHP ester **2a**, the results were summarized in Table 2. It was found that substrates bearing either electron-withdrawing (**1b-1h**) or electron-donating groups (**1i-1n**) were viable in this transformation to furnish the desired products **3ba-3na** in considerable yields. The substrates with *ortho*- or *meta*- substituents were also well tolerated to give **3ma**, **3ha** and **3la** in synthetically applicable yields, respectively. Substrates bearing halogen atoms (-Cl, –Br, -I) also afford **3ca**-

View Article Online DOI: 10.1039/C9SC02070K

3ea in excellent yields, enabling them to be amenable for further functionalizations through cross-coupling reactions. A range of useful functional groups such as CF_3 and CO_2Et were also applicable to this reaction to give **3fa** and **3ga** in 77% and 78% yield, respectively. Notably, heterocyclic skeleton such as 3-thienyl moiety was also well tolerated to give the target product **3oa** in 72% yield. Replacing the *N*-protecting benzyl group with methyl and Boc did not attenuate the reaction efficiency, affording **3pa** and **3qa** in synthetically useful yields. Gratifyingly, a handful of enecarbamates with *N*-Boc (**1r**) or *N*-Cbz (**1s**) substituents could smoothly react with redox-active ester **2s**, giving rise to alkylated enamides **3rs** and **3ss** in 65% and 73% yields, respectively. Notably, in all cases, this transformation proceeded smoothly in a stereoselective manner to afford the geometrically defined *E*-type alkylated enamides (See ESI† for details), the stereochemistry has been unambiguously confirmed through X-ray crystallography of **3ce** as shown in Table 3.[20]

Table 3 Scope of *N*-(Acyloxy)pthalimides[a,b]

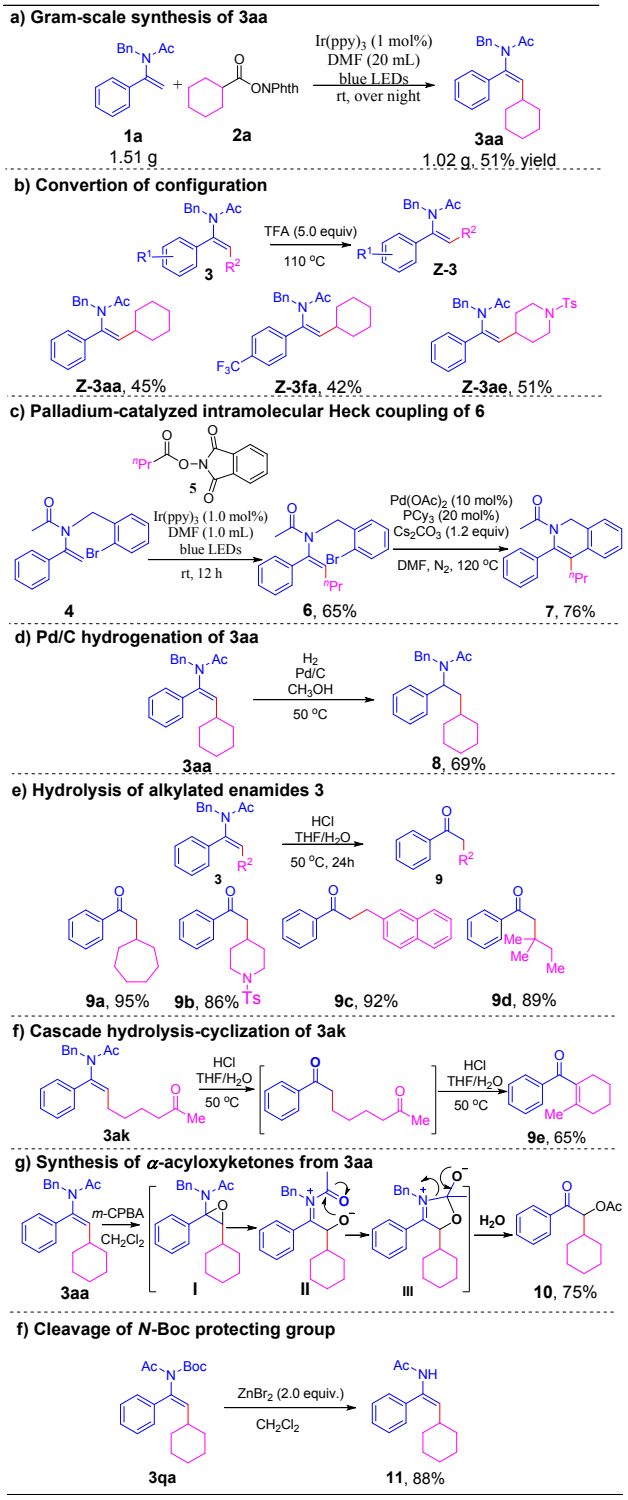


[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), $Ir(ppy)_3$ (1.0 mol%), DMF (1.0 mL) under N_2. [b]Isolated yields after purification. [c]2.0 eq. of NHP ester **2** (0.6 mmol) was used.

Next, we investigated the generality of this reaction with respect to the scope of various NHP esters (Table 3). A broad range of NHP esters with different cyclic moieties were amenable to this transformation to give **3ab**-**3af** and **3ce** in moderate to good yields. It is worth noting that the protecting groups on piperidine such as *tert*-butyloxycarbonyl (Boc), *p*-toluenesulfonyl (Ts) or even heterocyclic 2-furancarbonyl were well tolerated. A plethora of NHP esters with primary alkyl groups were also readily applicable to this reaction to forge **3ag**-**3ak** smoothly. Several useful functional groups such as phenol and ketone were also compatible with this transformation to give **3ai** and **3ak** in good yields, respectively. Especially noteworthy were the excellent compatibility of tertiary alkyl groups for this transformation, enabling the formation of enamides **3al** and **3am** bearing a quaternary carbon centre which were relatively difficult to be produces through other synthetic methods. In addition, various natural amino acid-derived NHP esters were viable substrates, affording synthetically valuable products **3an**-**3aq** in moderate to good yields. Gratifyingly, NHP ester bearing naturally occurring dehydrocholic acid fragment containing three base-sensitive ketone groups was readily amenable to the transformation to afford **3ar** in 82% yield.

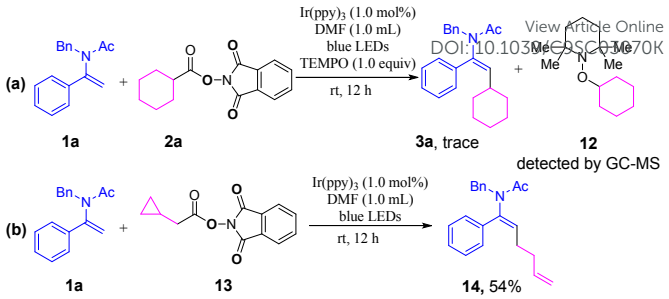
To showcase the synthetic utility and practicality of this transformation. We have conducted a range of further transformations of the alkylated enamides. A gram-scale reaction of **1a** with **2a** proceeded smoothly, affording **3aa** in good yield and stereoselectivity (Scheme 2a). Notably, upon treatment with trifluoroacetic acid at 110 °C, the *E*-configured enamides **3aa**, **3fa** and **3ae** could be converted to their *Z*-isomers in moderate yields (which might be attributed to decomposition), allowing us to easily control the stereochemistry of the alkylated enamides (Scheme 2b).[21] The alkylation of enamides **4** with NHP esters **5** proceeded smoothly under standard reaction conditions to give the desired product **6** in 65% yields, which underwent an ensuing palladium-catalyzed intramolecular Heck coupling to furnish a synthetically and pharmaceutically crucial isoquinoline derivative **7** in 76% yields (Scheme 2c). Next, a Pd/C-catalyzed hydrogenation of enamide **3aa** was successfully conducted under mild conditions to give benzylamine **8** in 69% yield (Scheme 2d). To our delight, the hydrolysis of alkylated enamides in the presence of concentrated HCl (aq) afforded a broad range of α-alkylated ketones in excellent yields (Scheme 2e). Interestingly, when **3ak** was applied to the hydrolysis condition, a cascade hydrolysis-intramolecular cyclization reaction occurred to give **9e** in 65% yield (Scheme 2f). Gratifyingly, when alkylated enamides **3aa** was treated with *m*-chloroperoxybenzoic acid (*m*-CPBA), α-acyloxyketone **10** was obtained in 75% yield after a tandem epoxidation-intramolecular nucleophilic addition-elimination-hydrolysis process (Scheme 2g). It was worth noting that the *N*-Boc protecting group of **3qa** could be removed efficiently by treatment of zinc bromide to give the desired product **11** under mild reaction conditions (Scheme 2f).

A number of preliminary mechanistic studies were conducted to shed more light on the reaction pathway. Initially, a radical-trapping experiment in the presence of a radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was performed. A complete inhibition of the reaction was observed and the alkyl radical could be intercepted by TEMPO to generate intermediate **12** as detected by GC-MS, which suggested that the reaction



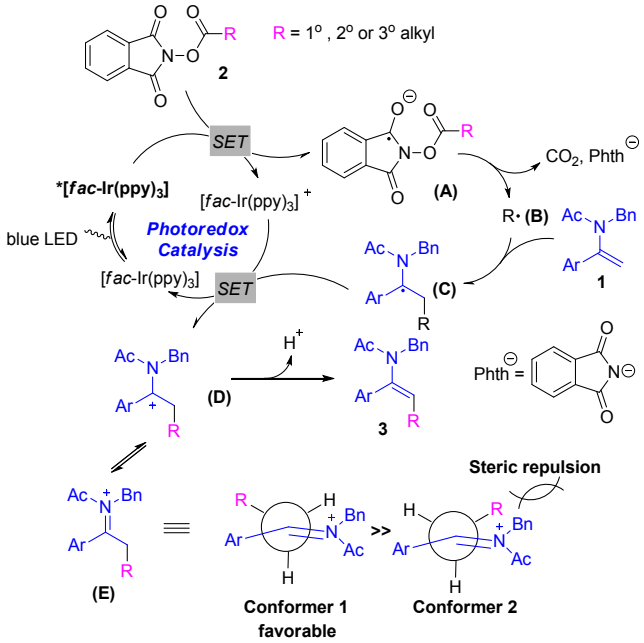
Scheme 2 Synthetic Applications of Alkylated Enamides

went through a plausible radical mechanism (Scheme 3a). Secondly, the coupling of a radical-clock-containing NHP ester **13** with enamides **1a** afforded the ring-opening product **14**, which strongly supported the participation of radical intermediates (Scheme 3b). In addition, we have determined a quantum yield of $\Phi = 0.71$ for the model reaction of **1a** with **2a** (See ESI† for details),[22] implying that the reaction is highly possible to proceed through a photoredox catalytic pathway rather than a radical-chain mechanism.



Scheme 3 Preliminary Mechanistic Studies

Based on the above observations, we have proposed a plausible mechanism for the photoredox-catalyzed decarboxylative alkylation of enamides with NHP esters. Initially, the iridium photocatalyst [*fac*-Ir(ppy)$_3$] is excited into [*fac*-Ir(ppy)$_3$]* *via* the absorption of a photon under blue LEDs irradiation. Secondly, the single electron transfer (SET) between [*fac*-Ir(ppy)$_3$]* and NHP ester **2** generates a radical anion **A** which is readily available to produce a alkyl radical species **B** *via* decarboxylation. Thirdly, the alkyl radical is intercepted by enamides to furnish a radical intermediate **C** which is subsequently oxidized by oxidative photocatalyst [*fac*-Ir(ppy)$_3$]$^+$ through SET to forge a cationic intermediate **D**, which is equilibrium with iminium ion **E**, along with the regeneration of [*fac*-Ir(ppy)$_3$]. Finally, the deprotonation of **D** or **E** gives the alkylated enamides. The stereoselectivity for this transformation could be rationalized through the conformational analysis of iminium ion **E**,[23] **conformer 1** is sterically favorable in contrast to **conformer 2** in view of minimized allylic strain between the benzyl group and alkyl group, leading to the formation of the *E*-configured alkylated enamides.



Scheme 4. Plausible Mechanism

Conclusions

We have developed a novel, efficient and generally-applicable approach for the chemo- and stereoselective alkylation of enamides with NHP esters. A wide array of enamides and NHP esters bearing various functional groups were viable to this protocol to afford synthetically important and geometrically-defined enamides bearing primary secondary or tertiary alkyl groups in moderate to good yields and excellent stereoselectivities. A plethora of further transformations were applied to showcase the synthetical value of this transformation. A radical reaction pathway was proposed through mechanistic investigation. The simple operation and the easy availability of the starting materials also allowed this method to pave a new route for the preparation of synthetically crucial alkylated enamides.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

We gratefully acknowledge the financial support from Nanjing Tech University (Start-up Grant No. 39837137, 39837101 and 3827401739), National Natural Science Foundation of China (21372210, 21672198, 21801129), the State Key Program of National Natural Science Foundation of China (21432009), and Natural science research projects in Jiangsu higher education institutions (18KJB150018) for financial support.

References

1 (a) R. Matsubara and S. Kobayashi, *Acc. Chem. Res.,* **2008**, *41*, 292; (b) C. Curti, M. Laget, A. O. Carle, A. Gellis and P. Vanelle, *Eur. J. Med. Chem.,* **2007**, *42*, 880; (c) H. Yang, R. G. Carter and L. N. Zakharov, *J. Am. Chem. Soc.,* **2008**, *130*, 9238; (d) J.-H. Xie, S.-F. Zhu and Q.-L. Zhou, *Chem. Rev.,* **2011**, *111*, 1713; (e) K. Gopalaiah and H. B. Kagan, *Chem. Rev.,* **2011**, *111*, 4599.

2 (a) S. Tong, D.-X. Wang, L. Zhao, J. Zhu and M.-X. Wang, *Angew. Chem., Int. Ed.,* **2012**, *51*, 4417; (b) M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Chem. Commun.,* **2012**, *48*, 8105; (c) G. Liu, X. Liu, Z. Cai, G. Jiao, G. Xu and W. Tang, *Angew. Chem., Int. Ed.,* **2013**, *52*, 4235; (d) C.-H. Lei, D.-X. Wang, L. Zhao, J. Zhu and M.-X. Wang, *J. Am. Chem. Soc.,* **2013**, *135*, 4708; (e) M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Org. Lett.,* **2014**, *16*, 608; (f) C.-H. Lei, L. Zhao, D.-X. Wang, J. Zhu and M.-X. Wang, *Org. Chem. Front.,* **2014**, 1, 909; (g) N. Hu, G. Zhao, Y. Zhang, X. Liu, G. Li and W. Tang, *J. Am. Chem. Soc.,* **2015**, *137*, 6746; (h) P. Song, P. Yu, J.-S. Lin, Y. Li, N.-Y. Yang and X.-Y. Liu, *Org. Lett.* **2017**, *19*, 1330.

3 (a) S. Pankajakshan, Y.-H. Xu, J. K. Cheng, M. T. Low and T.-P. Loh, *Angew. Chem., Int. Ed.,* **2012**, *51*, 5701; (b) H.-L. Wang, R.-B. Hu, H. Zhang, A.-X. Zhou and S.-D. Yang, *Org. Lett.,* **2013**, *15*, 5302; (c) F. Bartoccini, D. M. Cannas, F. Fini and G. Piersanti, *Org. Lett.,* **2016**, *18*, 2762; (d) N. Gigant, L. Chausset-Boissarie, M. Belhomme, T. Poisson, X. Pannecoucke, I. Gillaizeau, *Org. Lett.*, **2013**, *15*, 278.

4 (a) T. Besset, N. Kuhl, F. W. Patureau and F. Glorius, *Chem. Eur. J.,* **2011**, *17*, 7167; (b) Y.-H. Xu, Y. K. Chok and T.-P. Loh, *Chem. Sci.,* **2011**, *2*, 1822; (c) N. Gigant and I. Gillaizeau, *Org. Lett.,* **2012**, *14*, 3304; (d) W. Zhu, L. Zhao and M.-X. Wang, *J. Org. Chem.,* **2015**, *80*, 12047.

5 (a) C. Feng and T.-P. Loh, *Chem. Sci.,* **2012**, *3*, 3458; (b) R. Rey-Rodriguez, P. Retailleau, P. Bonnet, I. Gillaizeau, *Chem. Eur. J.,* **2015**, *21*, 3572; (c) H. Wang, Y. Cheng and S. Yu, *Sci. China Chem.,* **2016**, *59*, 195.

6 G. Caillot, J. Dufour, M.-C. Belhomme, T. Poisson, L. Grimaud, X. Pannecoucke and I. Gillaizeau, *Chem. Commun.,* **2014**, *50*, 5887.

7 C. Feng, D. Feng and T.-P. Loh, *Chem. Commun.,* **2014**, *50*, 9865.

8 (a) K. D. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.,* **2011**, *133*, 11430; (b) H. Wang, L.-N. Guo and X.-H. Duan, *Org. Lett.,* **2012**, *14*, 4358; (c) R. Ding, Q.-C. Zhang, Y.-H. Xu and T.-P. Loh, *Chem. Commun.,* **2014**, *50*, 11661; (d) Z. Xiong, D. Liang and S. Luo, *Org. Chem. Front.,* **2017**, *4*, 1103.

9 (a) Y. Li, K. Cheng, X. Lu and J. Sun, *Adv. Synth. Catal.,* **2010**, *352*, 1876; (b) D. Sun and R. Zhang, *Org. Chem. Front.,* **2018**, *5*, 92; (c) T.-H. Zhu, X.-C. Zhang, K. Zhao, T.-P. Loh, *Org. Chem. Front.,* **2019**, *6*, 94. (d) T.-H. Zhu, X.-C. Zhang, X.-L. Cui, Z.-Y. Zhang, H. Jiang, S.-S. Sun, L.-L. Zhao, K. Zhao, T.-P. Loh, *Adv. Synth. & Catal.* **2019**, DOI: 10.1002/adsc.201900257.

10 W. Yu, J. Chen, K. Gao, Z. Liu, Y. Zhang, *Org. Lett.,* **2014**, *16*, 4870.

11 (a) H. Jiang, C. Huang, J. Guo, C. Zeng, Y. Zhang and S. Yu, *Chem. Eur. J.,* **2012**, *18*, 15158; (b) R. Ding, Z.-D. Huang, Z.-L. Liu, T.-X. Wang, Y.-H. Xu and T.-P. Loh, *Chem. Commun.*, **2016**, *52*, 5617; (c) D. Xing and G. Dong, *J. Am. Chem. Soc.,* **2017**, *139*, 13664; (d) C. Baudequin, A. Zamfir and S. B. Tsogoeva, *Chem. Commun.,* **2008**, *0*, 4637; (e) B. Maji, S. Lakhdar and H. Mayr, *Chem. Eur. J.,* **2012**, *18*, 5732; (f) M.-N. Zhao, W. Du, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Eur. J. Org. Chem.,* **2013**, 7989; (g) P. Li, J. Zhao, C. Xia and F. Li, *Org. Lett.,* **2014**, *16*, 5992; (h) M. Giedyk, K. Goliszewska, K. ó. Proinsias and D. Gryko, *Chem. Commun.,* **2016**, *52*, 1389.

12 (a) K. Okada, K. Okamoto and M. Oda, *J. Am. Chem. Soc.,* **1988**, *110*, 8736; (b) K. Okada, K. Okamoto and M. Oda, *J. Chem. Soc. Chem. Commun.,* **1989**, 1636; (c) K. Okada, K. Okamoto, N. Morita, K. Okubo and M. Oda, *J. Am. Chem. Soc.,* **1991**, *113*, 9401; (d) K. Okada, K. Okubo, N. Morita and M. Oda, *Tetrahedron Lett.,* **1992**, *33*, 7377; (e) K. Okada, K. Okubo, N. Morita and M. Oda, *Chem. Lett.,* **1993**, *22*, 2021.

13 (a) C. R. Jamison and L. E. Overman, *Acc. Chem. Res.,* **2016**, *49*, 1578; (b) D. J. Tao, Y. Slutskyy, M. Muuronen, A. Le, P. Kohler and L. E. Overman, *J. Am. Chem. Soc.,* **2018**, *140*, 3091; (c) M. R. Garnsey, Y. Slutskyy, C. R. Jamison, P. Zhao, J. Lee, Y. H. Rhee and L. E. Overman *J. Org. Chem.,* **2018**, *83*, 6958.

14 For selected examples on transition metal-catalyzed C(sp^3)-C formation, see: (a) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.,* **2016**, *138*, 2174; (b) T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate and P. S. Baran, *Science,* **2016**, *352*, 801; (c) F. Toriyama, J. Cornella, L. Wimmer, T.-G. Chen, D. D. Dixon, G. Creech and P. S. Baran, *J. Am. Chem. Soc.,* **2016**, *138*, 11132; (d) T. Qin, L. R. Malins, J. T. Edwards, R. R. Merchant, A. J. E. Novak, J. Z. Zhong, R. B. Mills, M. Yan, C. Yuan, M. D. Eastgate and P. S. Baran, *Angew. Chem., Int. Ed.,* **2017**, *56*, 260; (e) J. M. Smith, T. Qin, R. R. Merchant, J. T. Edwards, L. R. Malins, Z. Liu, G. Che, Z. Shen, S. A. Shaw, M. D. Eastgate and P. S. Baran, *Angew. Chem., Int. Ed.,* **2017**, *56*, 11906; (f) J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D.-H. Bao, F.-L. Wei, T. Zhou, M. D. Eastgate and P. S. Baran, *Nature,* **2017**, *545*, 213; (g) S. Ni, A. F. Garrido-Castro, R. R. Merchant, J. N. de Gruyter, D. C. Schmitt, J. J. Mousseau, G. M. Gallego, S. Yang, M. R. Collins, J. X. Qiao, K.-S. Yeung, D. R. Langley, M. A. Poss, P. M. Scola, T. Qin and P. S. Baran, *Angew. Chem., Int. Ed.,* **2018**, *57*, 14560; (h) K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackerman and D. J. Weix, *J. Am. Chem. Soc.,*

2016, *138*, 5016; (i) L. Huang, A. M. Olivares and D. J. Weix, *Angew. Chem., Int. Ed.,* **2017**, *56*, 11901; (j) X. Lu, B. Xiao, L. Liu and Y. Fu, *Chem. Eur. J.,* **2016**, *22*, 11161; (k) N. Suzuki, J. L. Hofstra, K. E. Poremba and S. E. Reisman, *Org. Lett.,* **2017**, *19*, 2150; (l) S. S. R. Bernhard, G. M. Locke, S. Plunkett, A. Meindl, K. J. Flanagan and M. O. Senge, *Chem. Eur. J.,* **2018**, *24*, 1026; (m) X. Lu, X.-X. Wang, T.-J. Gong, J.-J. Pi, S,-J, He and Y. Fu, *Chem. Sci.,* **2019**, *10*, 809; (n) T. Koyanagi, A. Herath, A. Chong, M. Ratnikov, A. Valiere, J. Chang, V. Molteni and J. Loren, *Org. Lett.,* **2019**, *21*, 816; (o) T.-G. Chen, H. Zhang, P. K. Mykhailiuk, R. R. Merchant, C. A. Smith, T. Qin and Phil S. Baran, *Angew. Chem. Int. Ed.*, **2019**, *58*, 2454; (p) M. Montesinos-Magraner, M. Costantini, R. Ramírez-Contreras, M. E. Muratore, M. J. Johansson and A. Mendoza, *Angew. Chem. Int. Ed.,* **2019**, *58*, 5930.

15 For selected examples on transition metal-catalyzed C(sp^3)-X formation, see (a) W. Xue and M. Oestreich, *Angew. Chem., Int. Ed.,* **2017**, *56*, 11649; (b) J. Wang, M. Shang, H. Lundberg, K. S. Feu, S. J. Hecker, T. Qin, D. G. Blackmond and P. S. Baran, *ACS Catal.,* **2018**, *8*, 9537.

16 For selected examples on photoredox-catalyzed C(sp^3)-C formation, see: (a) R. S. J. Proctor, H. J. Davis and R. J. Phipps, *Science,* **2018**, *360*, 419; (b) J. Schwarz and B. König, *Green Chem*., **2016**, *18*, 4743; (c) Y. Jin, H. Yang and H. Fu *Org. Lett.,* **2016**, *18*, 6400; (d) Y. Jin, M. Jiang, H. Wang and H. Fu, *Sci. Rep.,* **2016**, *6*, 20068; (e) J. Li, H. Tian, M. Jiang, H. Yang, Y. Zhao and H. Fu, *Chem. Commun.,* **2016**, *52*, 8862; (f) C. Gao, J. Li, J. Yu, H. Yang and H. Fu, *Chem. Commun.,* **2016**, *52*, 7292; (g) H. Zhang, P. Zhang, M. Jiang, H. Yang and H. Fu, *Org. Lett.,* **2017**, *19*, 1016; (h) A. Tlahuext-Aca, R. A. Garza-Sanchez and F. Glorius *Angew. Chem., Int. Ed.,* **2017**, *56*, 3708; (i) A. F. Garrido-Castro, H. Choubane, M. Daaou, M. C. Maestro and J. Alemán, *Chem. Commun.,* **2017**, *53*, 7764; (j) W. Sha, S. Ni, J. Han and Y. Pan, *Org. Lett.,* **2017**, *19*, 5900; (k) J.-C. Yang, J.-Y. Zhang, J.-J. Zhang, X.-H. Duan and L.-N. Guo, *J. Org. Chem.,* **2018**, *83*, 1598; (l) Y. Zhao, J.-R. Chen and W.-J. Xiao, *Org. Lett.,* **2018**, *20*, 224; (m) W. Kong, C. Yu, H. An and Q. Song, *Org. Lett.,* **2018**, *20*, 349; (n) A. Tlahuext-Aca, R. A. Garza-Sanchez, M. Schäfer and F. Glorius, *Org. Lett.,* **2018**, *20*, 1546; (o) L. Ren and H. Cong, *Org. Lett.,* **2018**, *20*, 3225; (p) X.-H. Ouyang, Y. Li, R.-J. Song and J.-H. Li, *Org. Lett.,* **2018**, *20*, 6659; (q) W.-M. Cheng, R. Shang and Fu, Y. *ACS Catal.,* **2017**, *7*, 907; (r) W.-M. Cheng, R. Shang, M.-C. Fu and Y. Fu, *Chem. Eur. J.,* **2017**, *23*, 2537; (s) J.-J. Zhang, J.-C. Yang, L.-N. Guo and X.-H. Duan, *Chem. Eur. J.,* **2017**, *23*, 10259; (t) K. Xu, Z. Tan, H. Zhang, J. Liu, S. Zhang and Z. Wang, *Chem. Commun.,* **2017**, *53*, 10719; (u) Z.-H. Xia, C.-L. Zhang, Z.-H. Gao and S. Ye, *Org. Lett.,* **2018**, *20*, 3496; (v) Q. Tang, X. Liu, S. Liu, H. Xie, W. Liu, J. Zeng and P. Cheng, *RSC Adv*., **2015**, *5*, 89009; (w) J. Yang, J. Zhang, L. Qi, C. Hu and Y. Chen, *Chem. Commun.,* **2015**, *51*, 5275; (x) C. Jin, Z. Yan, B. Sun and J. Yang, *Org. Lett.,* **2019**, *21*, 2064; (y) G.-L. Dai, S.-Z. Lai, Z. Luo and Z.-Y. Tang, *Org. Lett.*, **2019**, *21*, 2269; (z) L. Liu, J. Dong, Y. Yan, S.-F. Yin, L.-B. Han and Y. Zhou, *Chem. Commun.*, **2019**, *55*, 233.

17 For selected examples on photoredox-catalyzed C(sp^3)-X formation, see: (a) M. Jiang, H. Yang and H. Fu, *Org. Lett.,* **2016**, *18*, 1968; (b) Y. Jin, H. Yang and H. Fu, *Chem. Commun.,* **2016**, *52*, 12909; (c) L. Candish, M. Teders and F. Glorius, *J. Am. Chem. Soc.,* **2017**, *139*, 7440; (d) A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers and V. K. Aggarwal, *Science,* **2017**, *357*, 283; (e) D. Hu, L. Wang, P. Li, *Org. Lett.,* **2017**, *19*, 2770; (f) R. Mao, J. Balon, X. Hu, *Angew. Chem., Int. Ed.,* **2018**, *57*, 9501; (g) C. Zheng, Y. Wang, Y. Xu, Z. Chen, G. Chen and S. H. Liang, *Org. Lett.,* **2018**, *20*, 4824.

18 (a) D. Wang, N. Zhu, P. Chen, Z. Lin and G. Liu, *J. Am. Chem. Soc.,* **2017**, *139*, 15632; (b) G.-Z. Wang, R. Shang and Y. Fu, *Org. Lett.,* **2018**, *20*, 888; (c) L. Yu, M.-L. Tang, C.-M. Si, Z. Meng, Y. Liang, J. Han, X. Sun, *Org. Lett.,* **2018**, *20*, 4579; (d) L. Gao, G. Wang, J. Cao, D. Yuan, C. Xu, X. Guo and S. Li, *Chem. Commun.,* **2018**, *54*, 11534.

19 M.-C. Fu, R. Shang, B. Zhao, B. Wang and Y. Fu, *Science*, **2019**, *363*, 1429.

20 Product **3ce** in Table 3 CCDC 1874601 contains the crystallographic data for this paper. All other *E*-adducts **3aa-3ss** (Table 2), **3ab-3ar** (Table 3) exhibit similar signals to **3ce** for their alkene and benzylic hydrogens in ^{1}H NMR. In addition, the NOESY experiments of ***E*-3aa** and ***Z*-3aa** have been performed to further testify the assignment of stereochemistry.

21 ***Z*-3aa**, ***Z*-3fa** and ***Z*-3ae** show ^{1}H NMR signals similar to each other, which are different from their *E*-isomers, especially for the chemical shift of olefinic hydrogens and the spin splitting of benzylic hydrogens.

22 M. A. Cismesiaa and T. P. Yoon, *Chem. Sci*., **2015**, *6*, 5426.

23 In iminium ion **E**, the acetyl group is posed *cis* to Ar group for simplify, the plausible conformer with benzyl group *cis* to Ar group would also give rise to *E*-alkylated enamides in order to minimize the allylic strain between the acetyl group on nitrogen and the alkyl group.

View Article Online
DOI: 10.1039/C9SC03070K

Table of Content (TOC) Entry

A stereoselective β-C(sp^2)–H alkylation of enamides with *N*-hydroxyphthalimide esters is demonstrated, affording geometrically-defined alkylated enamides bearing various functional groups.