

Cite this: *Chem. Sci.*, 2019, **10**, 8792

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 21st June 2019

Accepted 4th August 2019

DOI: 10.1039/c9sc03070k

rsc.li/chemical-science

Introduction

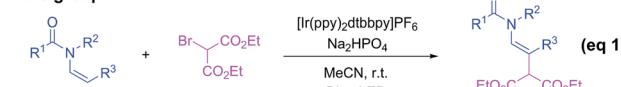
As a crucial subclass of enamines endowed with a delicate balance of reactivity and stability, enamides have attracted increasing attention among the chemical community as pivotal and versatile building blocks which are of recognized synthetic value in the construction of biologically and pharmaceutically active molecules,¹ especially small but complex nitrogen-containing compounds.² In the past few decades, we have witnessed a booming development in new synthetic strategies for the regio- and stereo-selective functionalization of enamides, especially at their β -C(sp²)-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 sulfonylation⁹ and other useful transformations.¹⁰ Nevertheless, the coupling of alkyl moieties to enamides has been considered 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 through visible-light photoredox-catalysis (Scheme 1a, eqn (1))^{11a} and by our group through a palladium-catalyzed strategy (Scheme 1a, eqn (2))^{11b}. Recently, another elegant methodology for the branch-selective alkylation of enamides with terminal olefins was demonstrated by Dong and co-workers (Scheme 1b).^{11c} However, the success to

date has been 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 a remaining challenge.

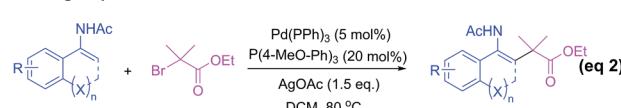
The redox-active alkyl *N*-hydroxyphthalimide esters (NHP) derived from alkanoic acids, as demonstrated for the first time by Okada¹² and Overman,¹³ have entered into an era of “Renaissance” in the past few years in a myriad of cross-electrophile coupling reactions as C(sp³) radical equivalents

a) Alkylation of enamides with electron-deficient bromides:

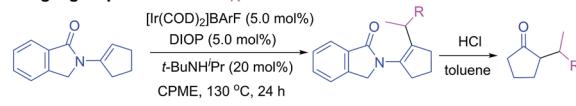
Yu's group



Loh's group

**b) Branched-selective alkylation of enamides with terminal olefins:**

Dong's group

**c) This Work: Stereoselective photoredox-catalyzed alkylation of enamides:**

● Excellent functional group tolerance
● General availability to all types of alkyl groups

● Excellent stereoselectivity

Scheme 1 Alkylation of enamides.

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[†] Electronic supplementary information (ESI) available. CCDC 1874601. For ESI and crystallographic data in CIF or other electronic format see DOI: [10.1039/c9sc03070k](https://doi.org/10.1039/c9sc03070k)



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(sp³)-C or C(sp³)-X (X = Si, B, Se, etc.) bonds *via* transition-metal^{14,15} and photoredox catalysis,^{16,17} as elegantly established by the groups of Baran,^{14a-g,o,15b} Weix,^{14h,i} Fu,^{16c-g,17a,b} Oestreich,¹⁵ Phipps,^{16a} Xiao,^{16l} and many others.¹⁸ Very recently, Fu and co-workers demonstrated a brand new catalytic combination of sodium iodide and triphenylphosphine for the cross-coupling of redox-active esters with silyl enol ethers or heteroarenes without resorting to the use of dye or transition-metal based photocatalysts.¹⁹ Enlightened by these seminal breakthroughs, we herein demonstrate a robust and practical protocol for 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 into enamides, which represents a significant advance and a crucial complement to existing methods^{11a,b} which only enable the incorporation of electron-deficient secondary alkyl groups.

Results and discussion

At the outset of our investigation, *N*-benzyl-*N*-(1-phenylvinyl)acetamide (**1a**) and 1,3-dioxoisindolin-2-yl cyclohexanecarboxylate (**2a**) were selected as model substrates for the screening of optimal reaction conditions (Table 1). Initial screening of common photocatalysts showed that *fac*-Ir(ppy)₃ was superior to Ru(bpy)₃Cl₂ and Eosin Y (Table 1, entry 1 *vs.*

Table 1 Optimization of the reaction conditions^a

Entry	Photocatalyst (mol%)	Solvent	Time (h)	Yield ^b
1	<i>fac</i> -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	<i>fac</i> -Ir(ppy) ₃ (0.1)	DMF	24	58
5	<i>fac</i> -Ir(ppy) ₃ (0.2)	DMF	24	58
6	<i>fac</i> -Ir(ppy) ₃ (2.0)	DMF	12	49
7	<i>fac</i> -Ir(ppy) ₃ (1.0)	DMAc	12	57
8	<i>fac</i> -Ir(ppy) ₃ (1.0)	CH ₃ CN	12	24
9	<i>fac</i> -Ir(ppy) ₃ (1.0)	DCM	12	Trace
10 ^c	<i>fac</i> -Ir(ppy) ₃ (1.0)	DMF	12	63
11 ^d	<i>fac</i> -Ir(ppy) ₃ (1.0)	DMF	12	68
12 ^{d,e}	<i>fac</i> -Ir(ppy) ₃ (1.0)	DMF	12	76
13	None	DMF	12	0
14 ^f	<i>fac</i> -Ir(ppy) ₃ (1.0)	DMF	12	0

^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), and 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.

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 revealed that the photoredox catalyst and light were both of crucial importance for this transformation, and no desired product was formed in the absence of the photocatalyst or without irradiation (Table 1, entries 13 and 14).

With the optimal reaction conditions in hand, we next examined the substrate scope with regard to different enamides or enecarbamates **1a–1s** with NHP esters **2a** or **2s**; the results are 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

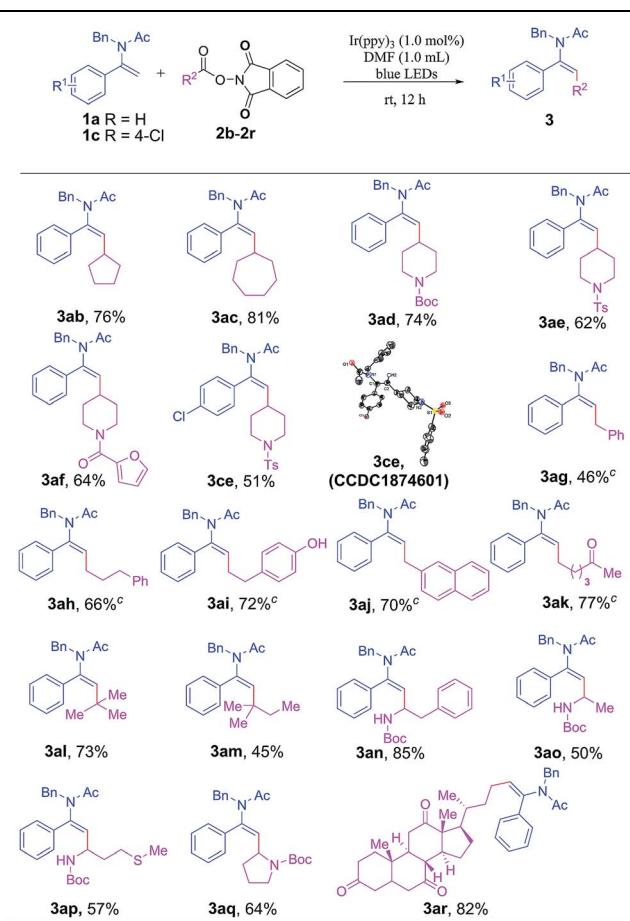
Table 2 Scope of enamides^{a,b}

1a–1s	2a: R ³ = Cy	3
1 : R ¹ = Bn, Boc etc. R ² = Ac, Boc, Cbz etc.	2s: R ³ = Ph(CH ₂) ₂	

^a Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), Ir(ppy)₃ (1.0 mol%), DMF (1.0 mL) in N₂. ^b Isolated yields.

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*, or *-I*) also afford **3ca**–**3ea** in excellent yields, enabling them to be amenable for further functionalization 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 87% yields, respectively. Notably, a heterocyclic skeleton such as a 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 geometrically defined *E*-type alkylated enamides (see the 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)phthalimides^{a,b}



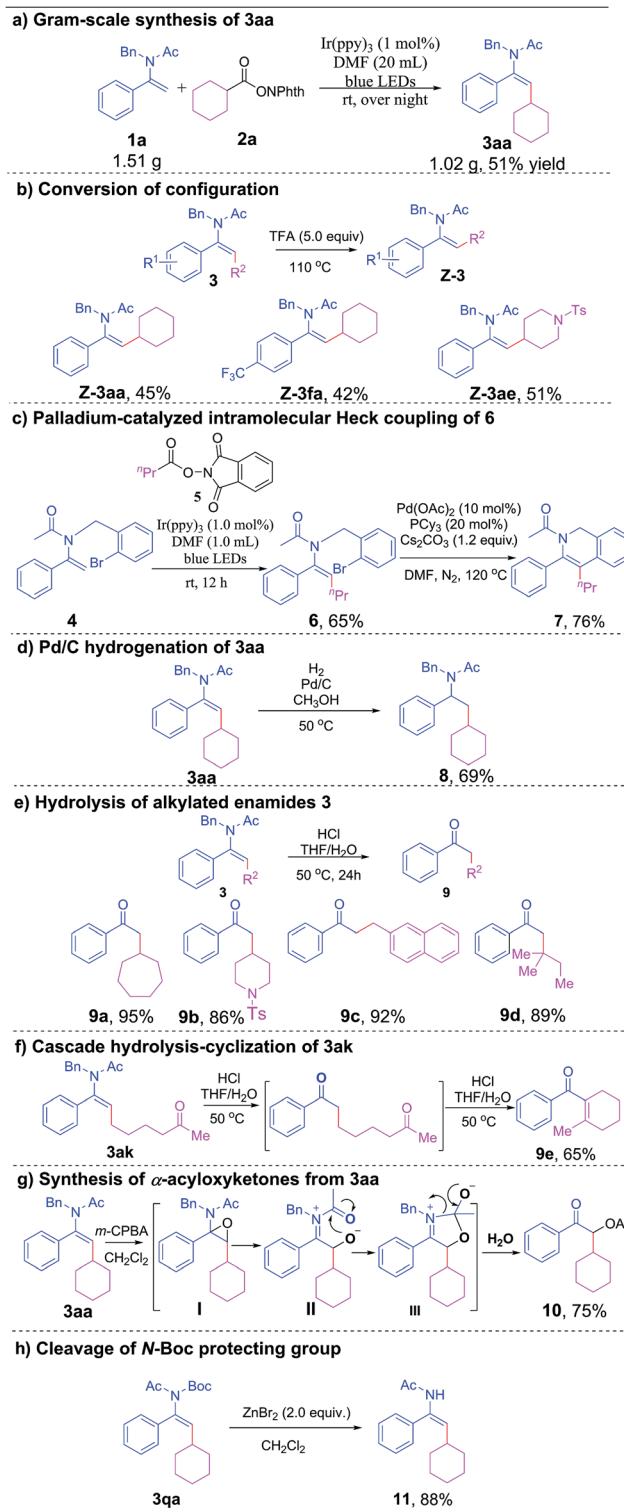
^a Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), Ir(ppy)₃ (1.0 mol%), DMF (1.0 mL) in N_2 . ^b Isolated yields after purification. ^c 2.0 eq. of NHP ester **2** (0.6 mmol) was used.

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 was 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 produced 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, an NHP ester bearing a 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 enamide **4** with NHP ester **5** proceeded smoothly under standard reaction conditions to give the desired product **6** in 65% yield, which underwent a subsequent palladium-catalyzed intramolecular Heck coupling to furnish a synthetically and pharmaceutically crucial isoquinoline derivative **7** in 76% yield (Scheme 2c). Next, 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 under the hydrolysis condition, a cascade hydrolysis-intramolecular cyclization reaction occurred to give **9e** in 65% yield (Scheme 2f). Gratifyingly, when alkylated enamide **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 is worth noting that the *N*-Boc protecting group of **3qa** could be removed efficiently by treatment with zinc bromide to give the desired product **11** under mild reaction conditions (Scheme 2h).

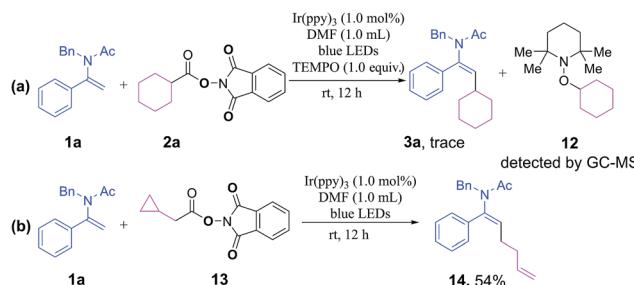
A number of preliminary mechanistic studies were conducted to shed more light on the reaction pathway. Initially, a radical-trapping experiment in the presence of a radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was performed. A complete inhibition of the reaction was observed





Scheme 2 Synthetic applications of alkylated enamides.

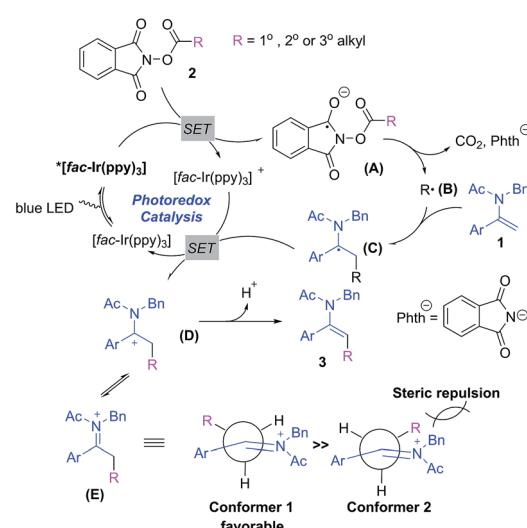
and the alkyl radical could be intercepted by TEMPO to generate intermediate **12** as detected by GC-MS, which suggested that the reaction went through a plausible radical mechanism (Scheme 3a). Secondly, the coupling of a radical-clock-containing NHP ester **13** with enamide **1a** afforded the ring-opening product **14**,



Scheme 3 Preliminary mechanistic studies.

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 the ESI† for details),²² implying that it is highly possible for the reaction to proceed through a photoredox catalytic pathway rather than a radical-chain mechanism.

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 to [*fac*-Ir(ppy)₃]^{*} *via* the absorption of a photon under blue LED irradiation. Secondly, the single electron transfer (SET) between [*fac*-Ir(ppy)₃]^{*} and NHP ester **2** generates a radical anion **A** which is readily able to produce an 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 the oxidative photocatalyst [*fac*-Ir(ppy)₃]⁺ through SET to forge a cationic intermediate **D**, which is in equilibrium with iminium ion **E**, along with the regeneration of [*fac*-Ir(ppy)₃]. Finally, the deprotonation of **D** or **E** gives alkylated enamides. The stereo-selectivity 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,



Scheme 4 Plausible mechanism.

leading to the formation of the *E*-configured alkylated enamides (Scheme 4).

Conclusions

We have developed a novel, efficient and generally applicable approach for the chemo- and stereo-selective alkylation of enamides with NHP esters. A wide array of enamides and NHP esters bearing various functional groups were viable for this protocol to afford synthetically important and geometrically defined enamides bearing primary secondary or tertiary alkyl groups in moderate to good yields and excellent stereo-selectivities. A plethora of further transformations were applied to showcase the synthetic 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 way 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), the National Natural Science Foundation of China (21372210, 21672198, and 21801129), the State Key Program of National Natural Science Foundation of China (21432009), and the Natural Science Research Projects in Jiangsu Higher Education Institutions (18KJB150018).

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hydrogens in ^1H NMR. In addition, NOESY experiments for ***E*-3aa** and ***Z*-3aa** have been performed to further verify the assignment of stereochemistry.

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

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