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Introduction

The enamide is a privileged subunit in pharmaceuticals and biomolecules featuring excellent biological and physiological properties,¹ as well as being a useful and versatile synthetic platform for further elaboration in organic synthesis.² Several approaches for the preparation of enamides have been reported,³ including condensation of amides with carbonyls,^{3a} carbofunctionalization of ynamides,^{3b,c} transition-metal catalyzed *N*-alkenylation of amides,^{3d-f} isomerization of allylamides,^{3g,h} hydroamidation of alkynes,^{3i-l} dehydrogenation of the corresponding amides,^{3m-p} and others.^{3q-w} However, one of the most straightforward approaches to access enamides is arguably the vicinal difunctional carboamidation of alkynes.

The intermolecular radical 1,2-difunctionalization reaction of alkyne is a straightforward route for expeditiously increasing the complexity of the common feedstock alkyne starting materials for target molecule synthesis.⁴ This reaction typically proceeds through the addition of the radical species to the alkyne, followed by recombination of the formation vinyl radical intermediate with a metal catalyst or other radical species. Although it has been studied extensively in the past several decades, the intermolecular radical carboamination of alkyne remains a long-standing challenge (Fig. 1a). The difficulty in this transformation originates perhaps from either the strong Lewis basicity of the amines⁵ or the weak coordinating

ability of the amides,⁶ interfering with the generation of the vinyl-metal–nitrogen intermediate. In 2015, the groups of Liu^{7a} and Liang^{7b} independently established an elegant synthetic route involving a copper-catalyzed trifluoromethylazidation of alkynes, while seminal work by Bao⁸ in 2019 identified

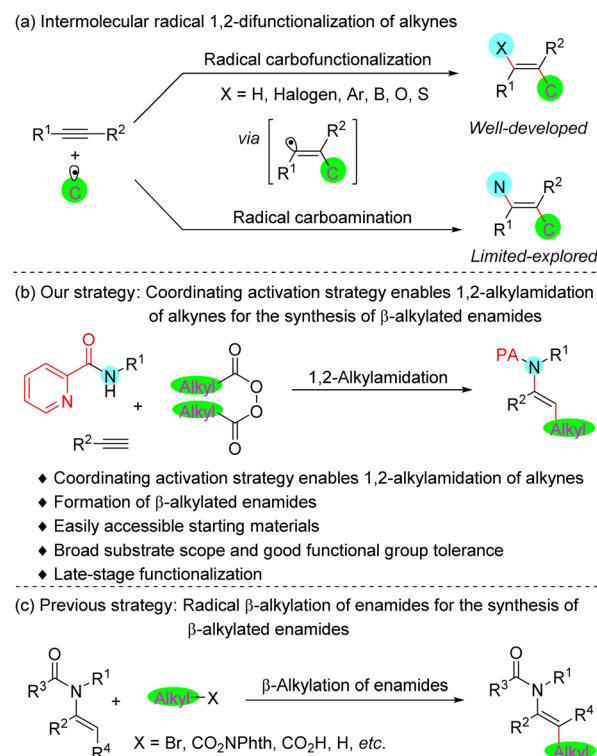


Fig. 1 Background and project synopsis.

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carboazidated alkynes as attractive candidates for the synthesis of fluoroalkylated azirines. Very recently, Liu and co-workers reported another pioneering work on the efficient synthesis of vinylarene atropisomers through copper-catalyzed enantioselective trifluoromethylazidation of alkynes.^{7c} These exceptions mainly rely on employing azide that serves as a reagent with good coordinating ability, and where coordination of the metal catalyst enables capture of the vinyl radical to form a vinyl-metal-N₃ intermediate. Notwithstanding these significant breakthroughs, a general strategy that enables the intermolecular radical carboamination of alkynes utilizing common amine derivatives as the nitrogen source with general alkyl groups remains an unsolved problem.

In order to achieve this challenging catalytic process, we considered installing a 2-pyridylacyl group⁹ on the amine to serve as the coordinating group. We surmised that the metal-lacycle species, a coordination product formed from the reaction of the metal catalyst with a substrate bearing a bidentate auxiliary, could efficiently catch the vinyl radical intermediate, thus providing a straightforward strategy for the realization of difunctionalization carboamidation of alkynes. Herein, we report the general 1,2-difunctional alkylamidation of alkynes by utilizing this coordinating activation strategy for the synthesis of β -alkylated enamides (Fig. 1b). Recently, tremendous progress on radical β -alkylation of enamides has been demonstrated for the construction of such compounds (Fig. 1c).¹⁰ However, the representative known synthetic strategies typically start from prefunctionalized enamide substrates. Our current protocol is the first universal strategy that could straightforwardly build β -alkylated enamides from commercially available alkynes and readily accessible amides and diacyl peroxides. In addition, a variety of reactants derived from pharmaceuticals and natural products bearing proven biological activities can be adopted in this protocol and lead to the late-stage modifications of bioactive compounds.

Results and discussion

Optimization of the reaction conditions

Based on our hypothesis, the bench-stable, commercially available chemical feedstock dilauroyl peroxide¹¹ (LPO, 3a) was first used to serve as the alkylating and oxidizing agent simultaneously to illustrate the feasibility of the difunctional alkylamidation reaction. We initiated our studies by screening metal catalysts in the alkylamidation reaction of ethyl picolinoylglycinate (1a) with ethynylbenzene (2a) in the presence of LPO (3a). To our delight, Cu(acac)₂ could lead to the desired alkylamidation product 4a in 36% yield in benzene at 120 °C (Table 1, entry 1). When the reaction temperature was increased to 130 °C, the yield of 4a was improved to 45% (entry 2). The copper catalyst examination suggested Cu(tfacac)₂ was the better choice (entries 2–5). However, other copper salts, for instance CuCl, CuBr, CuI, Cu(OAc)₂ and CuBr₂, gave only trace amount of product (entry 6). A control experiment demonstrated copper anions played

Table 1 Reaction conditions screening^a

Entry	Cat. (equiv.)	Solvent	t (h)	Yield ^b (%)
1 ^c	Cu(acac) ₂ (0.2)	Benzene	20	36
2	Cu(acac) ₂ (0.2)	Benzene	20	45
3	Cu(hmacac) ₂ (0.2)	Benzene	20	51
4	Cu(tfacac) ₂ (0.2)	Benzene	20	65
5	Cu(hfacac) ₂ (0.2)	Benzene	20	53
6 ^d	Copper salt (0.2)	Benzene	20	Trace
7 ^e	Cu(OAc) ₂ (0.2)	Benzene	20	44
8 ^f	M(acac) ₂ (0.2)	Benzene	20	n.d.
9	Cu(tfacac) ₂ (0.1)	Benzene	24	74
10 ^g	Cu(tfacac) ₂ (0.1)	Benzene	24	72
11	Cu(tfacac) ₂ (0.1)	Benzene	28	81
12	Cu(tfacac) ₂ (0.1)	Benzene	32	72
13	Cu(tfacac) ₂ (0.1)	Cyclohexane	28	43
14	Cu(tfacac) ₂ (0.1)	Toluene	28	67
15	Cu(tfacac) ₂ (0.1)	PhCF ₃	28	75
16	Cu(tfacac) ₂ (0.1)	PhCl	28	73
17	Cu(tfacac) ₂ (0.1)	MeOH	28	48
18	Cu(tfacac) ₂ (0.1)	HOAc	28	n.d.
19	—	Benzene	28	n.d.

^a Reaction conditions: 1a (0.10 mmol, 1.0 equiv.), 2a (0.20 mmol, 2.0 equiv.), LPO (3a, 0.30 mmol, 3.0 equiv.), cat. and solvent (1.0 mL) at 130 °C under N₂ atmosphere. ^b Isolated yield after chromatographic purification. ^c The reaction at 120 °C. ^d CuCl, CuBr, CuI, Cu(OAc)₂ or CuBr₂ was used as the metal catalyst. ^e 2,2,6,6-Tetramethylheptane-3,5-dione (20 mol%) was added. ^f Fe(acac)₂, Co(acac)₂, Ni(acac)₂ or Mn(acac)₂ was used as the metal catalyst. ^g The reaction at 140 °C. Cu(hmacac)₂ = copper(II) bis(2,2,6,6-tetramethyl-3,5-heptanedionate). Cu(tfacac)₂ = copper(II) trifluoroacetylacetone. Cu(hfacac)₂ = copper(II) hexafluor-2,4-pentanedionate. n.d. = no product detected. PA = 2-pyridylacyl.

an important role in the catalytic activity (entry 7). Besides, some other metal catalysts, such as Fe(acac)₂, Co(acac)₂, Ni(acac)₂, and Mn(acac)₂, were proven to be inert for this reaction (entry 8). Gratifyingly, the yield could be improved by appropriately increasing the reaction time. In terms of the solvent effect, several solvents were assessed, and benzene turned out to be the best (entries 13–18). No reaction occurred in the absence of a metal catalyst (entry 19). Finally, further optimization of the reaction conditions revealed that the best yield was obtained with the help of 10 mol% Cu(tfacac)₂ in benzene at 130 °C under a nitrogen atmosphere for 28 h (entry 11, for detailed optimization, see Table S1†).

Investigation of reaction scope

After having established the optimal reaction conditions, the substrate scope of the terminal alkynes was firstly examined and the results are summarized in Table 2. In general, the current protocol was applicable to terminal aryl alkynes



Table 2 Scope of alkynes and 2-picolinamide derivatives^a

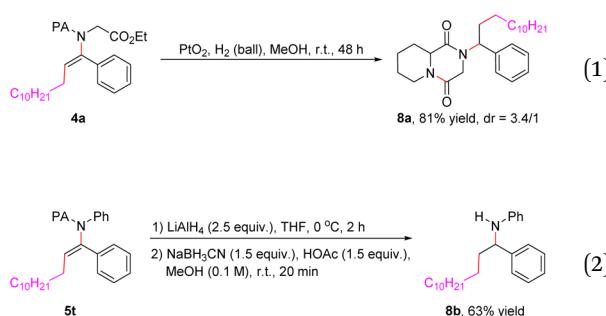
^a Reaction conditions: 1 (0.1 mmol, 1.0 equiv.), 2 (0.2 mmol, 2.0 equiv.), 3 (0.30 mmol, 3.0 equiv.), and Cu(tfacac)₂ (0.01 mmol, 0.1 equiv.) in benzene (1.0 mL) under N₂ atmosphere at 130 °C for 28 h; isolated yield is given. ^b The reaction was conducted on a 5.0 mmol scale. ^c 3a (0.40 mmol, 4.0 equiv.) was used. ^d Ethynylbenzene (2a) was used instead of methyl 4-ethynylbenzoate (2q) for 32 h. ^e *tert*-Butyl 2,2-dimethylpropaneperoxoate 3k (0.30 mmol, 3.0 equiv.) was used.

bearing a series of substituents on the aromatic ring, including electron-withdrawing and electron-donating groups. In addition, various synthetically useful functional substituents, including halogen, ester, cyano, nitro, and amide groups, were tolerated with the reaction conditions, thus suggesting the suitability of the alkylamidation products for further structural elaboration. It is notable that an amide or sulfamide group is present at the 2-picolinamide moiety, C–N cross-coupling selectively took place at the 2-picolinamide–nitrogen, delivering the related products (**4u–4w**) in acceptable yields. This result not only establishes the importance of chelation for this transformation but also highlights the exquisite chemoselectivity of our strategy. Gratifyingly,

heteroaryl substituted alkynes, such as 3-ethynylthiophene, 3-ethynylpyridine and 2-ethynylpyridine, could also proceed smoothly to furnish corresponding products in satisfactory yields. It is notable that the conjugated alkenyl acetylene 1-ethynylcyclohex-1-ene could also furnish the desired product **4ac** with moderate yield. Unfortunately, no desired products were detected when internal and alkyl-substituted alkynes were utilized (see details in the ESI†). Notably, the reaction also proved to be scalable, with only a modest reduction in the yield of **4a** from 81% to 77% observed when the reaction was performed on a 5.0 mmol scale in the presence of a lower catalyst loading (for details, see the ESI†).



The scope with respect to 2-picolinamide derivatives was next evaluated, and the results are also summarized in Table 2. We were pleased to observe that a diverse range of 2-picolinamides were suitable for this difunctional alkylamidation reaction. The 2-picolinamides having (hetero)benzyl (5a–5e), aryl (5s–5v) and tethered aliphatic amines (5f–5q) exhibited good compatibility and produced the corresponding products in satisfactory yields. To our delight, the widespread natural and non-proteinogenic amino acids also proceeded smoothly to afford the desired products (5w–5ab). Notably, α,α -disubstituted 2-picolinamides did not turn out to be well-suited coupling partners for this transformation, possibly due to steric hindrance (5r, 5w, and 5x). The scope of the diacyl peroxides, which are readily prepared from carboxylic acids, as alkylating reagents was then studied under the optimized reaction conditions. The results showed that various primary alkyl radicals could be generated from the corresponding alkyl peroxides and afforded the alkylamidation products 6a–6e in good yields. A chlorine-substituted diacyl peroxide is compatible with the reaction conditions, providing the related product (6d) in 53% yield. In addition, products containing secondary and tertiary alkyl groups also could be obtained in relatively low yields from alkyl diacyl peroxides or alkyl peresters under the present reaction conditions (6f–6i). More importantly, the 2-pyridylacyl auxiliary group could be transformed (eqn (1)) or removed (eqn (2)) efficiently after achievement of the desired reactivity.



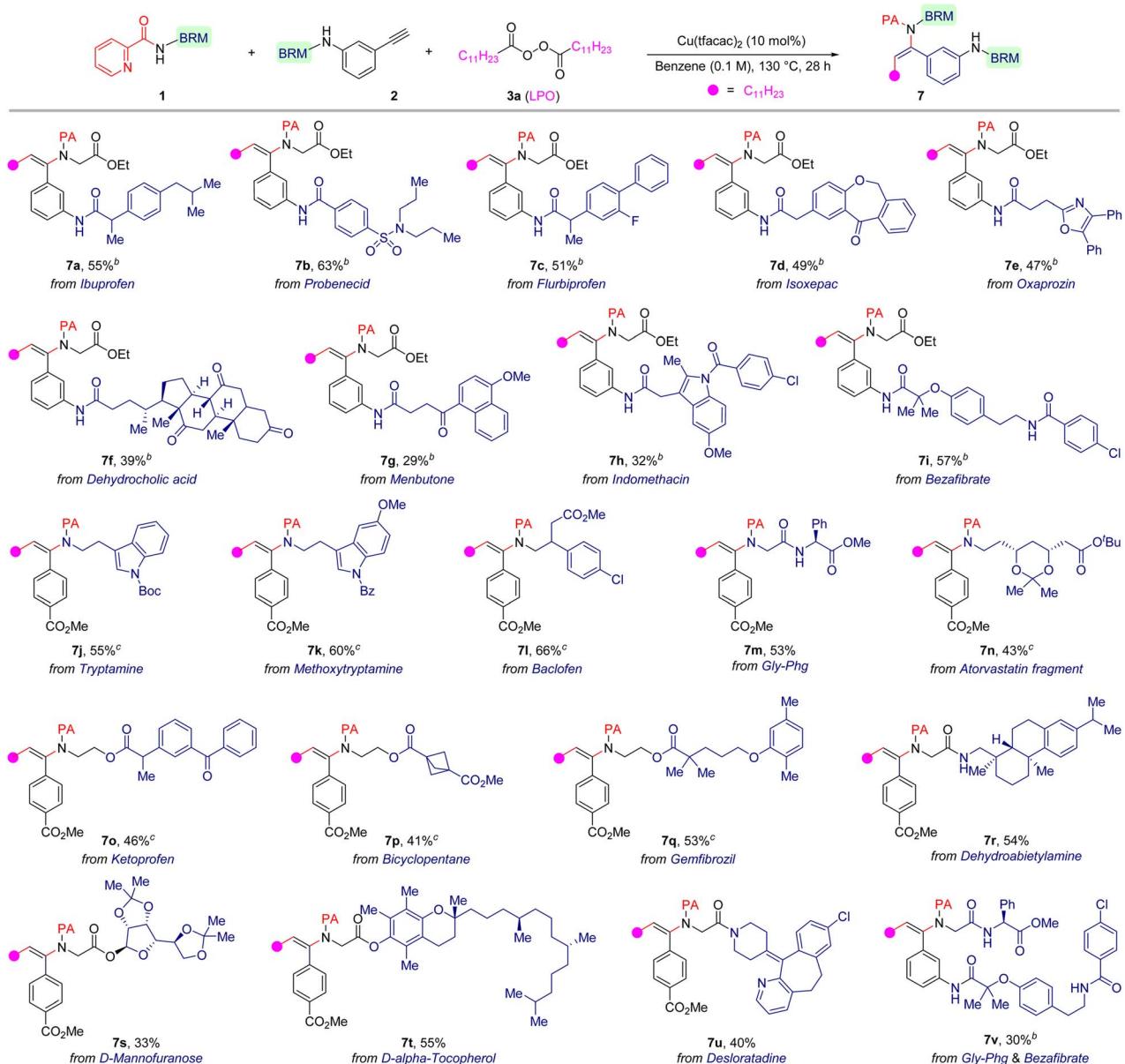
Because of the good functional group compatibility in this reaction, we evaluated its practicality for late-stage functionalization of multifunctionalized medicinally relevant molecules to show the generality of this method (Table 3). Pleasingly, the title reaction proved to be a reliable and robust methodology. We found that terminal alkynes derived from ibuprofen (7a), probenecid (7b), flurbiprofen (7c), isoxepac (7d), oxaprozin (7e), dehydrocholic acid (7f), menbutone (7g), indomethacin (7h) and bezafibrate (7i) could be used as substrates to deliver the corresponding β -alkylated enamides in acceptable yields (29–63%) with *trans*-selectivity. The current method was also applicable for sophisticated 2-picolinamides derived from bioactive compounds or drugs, such as tryptamine (7j), baclofen (7l), atorvastatin fragment (7n), ketoprofen (7o), gemfibrozil (7q), dehydroabietylamine (7r), D-mannofuranose (7s), D- α -tocopherol (7t) and desloratadine (7u), which deliver the corresponding products in moderate yields (33–66%). Significantly, a dipeptide could also serve as

a suitable precursor and smoothly take part in this alkylamidation reaction, and the reaction only occurred at the 2-picolinamide-nitrogen with the other amide group intact (7m). Excitingly, 2-picolinamide derived from a peptide and alkyne derived from a drug scaffold could likewise be employed to couple together, resulting in an unprecedented peptide/drug conjugate (7v).

Mechanistic study

To shed light on the mechanism, a series of mechanistic experiments were carried out (Fig. 2). First, a series of N-protecting groups on phenylmethanamine were examined under the optimized conditions (Fig. 2a). It was found that N-protecting groups with non-chelating properties, such as 3-pyridinecarbonyl, 4-pyridinecarbonyl, benzoyl, and *p*-toluenesulfonyl, were incapable of promoting the reaction. This further underlines the unique character of this coordinating activation strategy. Next, the reaction of 1a with deuterated alkyne [D]-2m proceeded smoothly to give the product with deuterium being partly incorporated into the product (81% deuterium content). Meanwhile, in the presence of deuterium oxide (D_2O), the reaction of 1a with 2m afforded a deuterated product with 55% deuterium incorporation. This is possibly caused by the reversible H/D atom exchange of the terminal alkyne under the copper/heating conditions (Fig. 2b).¹² Furthermore, intermolecular competition experiments with differently substituted aryl alkynes were carried out (Fig. 2c). The results showed that electron-withdrawing groups in the aryl alkyne gave a higher reactivity. In addition, competition experiments between differently *N*-substituted 2-picolinamides were examined as well, and the order of reactivity is $CH_2COOEt > Bn > Et$. This trend presumably is due to the decreased acidity of the N-H bond of 2-picolinamide substrates.¹³ Notably, the rate of the reaction is sensitive to the amino group steric hindrance as shown by a similar competition experiment with *N*-benzyl-picolinamide 1b and *N*-(1-phenylethyl)-picolinamide 1s, which predominantly forms 5a (5a/5r > 20/1). Moreover, bis(*N*-phenylpicolinamido)copper(II) IM1a, which was prepared according to the literature¹⁴ and characterized using X-ray crystallographic analysis,¹⁵ along with an acetylacetone type ligand could be used to achieve this alkylamidation process (Fig. 2d). This result suggested that a ligand exchange of 2-picolinamide with $Cu(tfacac)_2$ might occur initially in the mechanistic pathway. Additionally, when stoichiometric radical scavengers, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1,1-diphenylethene (DPE), were added to the reaction of 1a and 2b under standard conditions, the formation of β -alkylated enamide 4a was suppressed (Fig. 2e). Instead, alkyl and alkylated vinyl radical intermediates were confirmed by the formation of radical scavengers trapped adducts that were detected using HRMS (High Resolution Mass Spectrometry), demonstrating the radical property of this process and the possible involvement of alkyl and alkylated vinyl radicals (for details, see the ESI[†]).

Based on the experimental results and literature precedence, a plausible reaction mechanism is proposed in Fig. 2f. Initially,

Table 3 Late-stage functionalization of natural compounds and biologically active molecules^a

^a Reaction conditions: **1** (0.1 mmol, 1.0 equiv.), **2** (0.2 mmol, 2.0 equiv.), LPO (0.30 mmol, 3.0 equiv.), and Cu(tfacac)₂ (0.01 mmol, 0.1 equiv.) in benzene (1.0 mL) under N₂ atmosphere at 130 °C for 28 h; isolated yield is given. ^b **2** (0.15 mmol, 1.5 equiv.) was used. ^c **3a** (0.4 mmol, 4.0 equiv.) was used. BRM = biologically relevant motif.

an alkyl radical is generated from the diacyl peroxide with the aid of the copper catalyst and/or thermal decomposition,¹¹ which subsequently undergoes regioselective addition to the alkyne to furnish the alkylated vinyl radical. Meanwhile, the 2-picolinamide acts as a ligand to coordinate with copper(II) to yield the intermediate **IM1**, and then the alkylated vinyl radical is trapped by this coordinated species to form a copper(III) intermediate **IM2**, followed by reductive elimination to furnish the difunctionalization product. The intermediates **IM1** and **IM2** could be detected based on HRMS analysis of the reaction

mixture. Finally, the released low-valent metal catalyst Cu(I) is reoxidized by diacyl peroxides to fulfill a catalytic cycle. Diacyl peroxide serves simultaneously as the alkylating and oxidizing agent. The role of the 2-picolinamide group is assumed to involve the following aspects. First, the coordination of catalyst copper toward the 2-picolinamide group enables the N–H bond activation.^{9c–j} Secondly, the 2-picolinamide group serving as a bidentate ligand gives access to the stabilization of the Cu(II) and Cu(III) intermediates, **IM1** and **IM2**, and from the latter to the desired C–N bond formation.



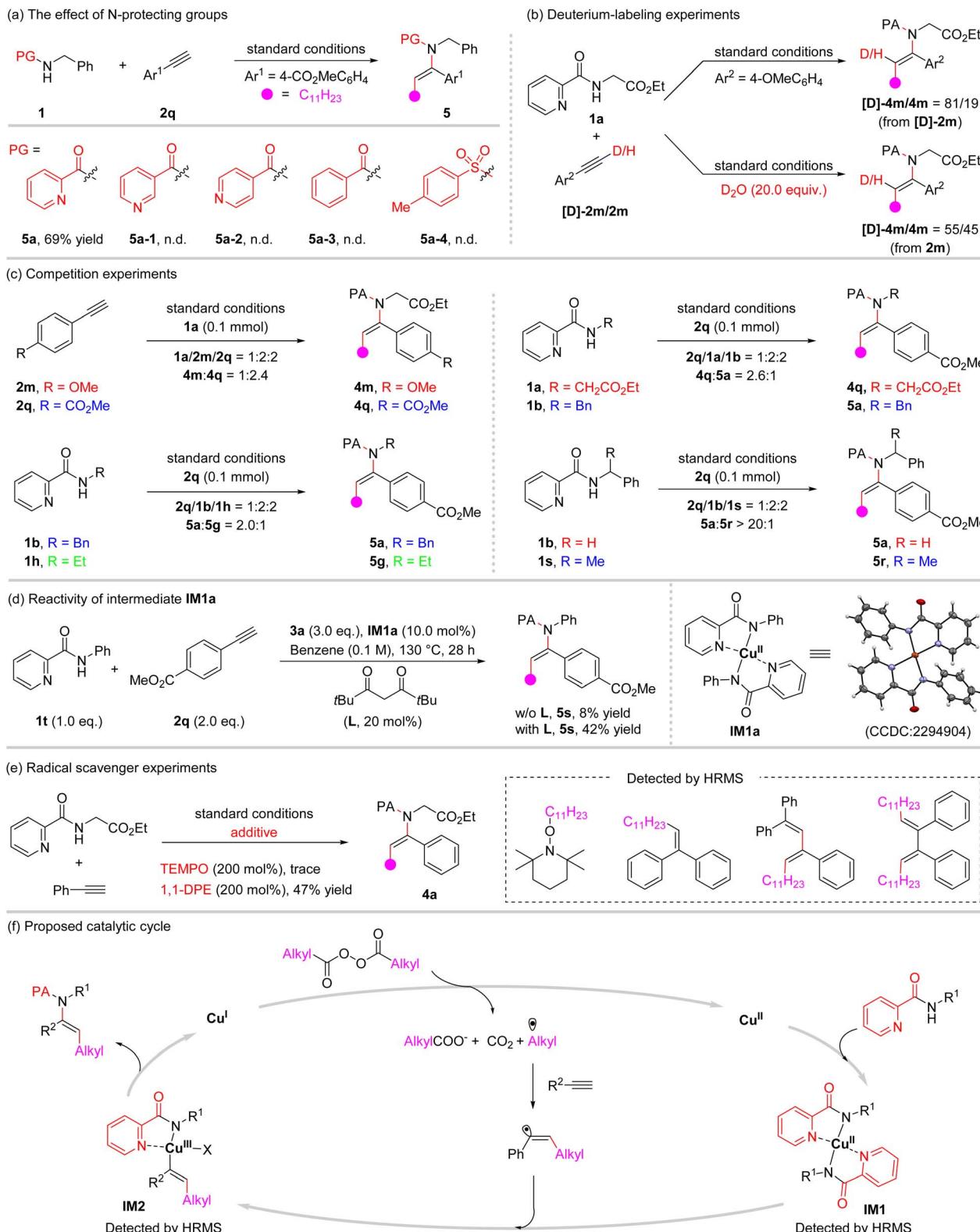


Fig. 2 Mechanistic investigations. (a) The effect of N-protecting groups. (b) Deuterium-labeling experiments. (c) Competition experiments. (d) Reactivity of intermediate IM1a. (e) Radical scavenger experiments. (f) Proposed catalytic cycle. TEMPO = 2,2,6,6-tetramethylpiperidinyloxy. 1,1-DPE = 1,1-diphenylethylene.

Conclusions

In summary, we have developed a novel strategy to allow the radical difunctional alkylamidation of alkynes. With the employment of the diacyl peroxides as both alkylating reagents and internal oxidants, various β -alkylated enamides are constructed in a three-component manner from readily accessible amides and alkynes. This methodology exhibits broad substrate scope with good functional group compatibility and is amenable for late-stage functionalization of natural molecules and biologically relevant motifs. Additionally, various mechanistic experiments have been carried out to obtain a better understanding of the reaction process, such as competition experiments, H/D isotopic exchange experiments and radical trap experiments. We anticipate that this protocol will simplify the synthesis of a series of β -alkylated enamides, helping to fuel the design and discovery of novel biologically molecules. Though further improvements of the reaction are certainly needed, such as lowering the reaction temperature, reducing equivalents of diacyl peroxides, improving the yields of secondary and tertiary alkyl products, and replacement of benzene by eco-friendly solvents, and this will be explored in due course.

Data availability

All experimental procedures, characterisation data, control experiments and NMR spectra for all compounds can be found in the ESI.[†]

Author contributions

J. R. and J. X. contributed equally to this work. K. L. conceived the concept and prepared the manuscript. J. R. and J. X. performed and analyzed the data. X. K. and J. L. conducted preparation of starting materials. K. L. directed the project. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- For selected references of pharmaceutical and natural molecules containing enamides and their derivatives, see: (a) R. Shen, C. T. Lin, E. J. Bowman, B. J. Bowman and J. A. Porco, *J. Am. Chem. Soc.*, 2003, **125**, 7889–7901; (b) S. Lin, Z.-Q. Yang, B. H. B. Kwok, M. Koldobskiy, C. M. Crews and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2004, **126**, 6347–6355; (c) M. J. Martín, L. Coello, R. Fernández, F. Reyes, A. Rodríguez, C. Murcia, M. Garranzo, C. Mateo, F. Sánchez-Sancho, S. Bueno, C. de Eguilior, A. Francesch, S. Munt and C. Cuevas, *J. Am. Chem. Soc.*, 2013, **135**, 10164–10171; (d) T. Kuranaga, Y. Sesoko and M. Inoue, *Nat. Prod. Rep.*, 2014, **31**, 514–532.
- For selected reviews on application of enamides, see: (a) R. Matsubara and S. Kobayashi, *Acc. Chem. Res.*, 2008, **41**, 292–301; (b) D. R. Carbery, *Org. Biomol. Chem.*, 2008, **6**, 3455–3460; (c) J.-H. Xie, S.-F. Zhu and Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713–1760; (d) K. Gopalaiah and H. B. Kagan, *Chem. Rev.*, 2011, **111**, 4599–4657; (e) N. Gigant, L. Chausset-Boissarie and I. Gillaizeau, *Chem.-Eur. J.*, 2014, **20**, 7548–7564; (f) G. Bernadat and G. Masson, *Synlett*, 2014, **25**, 2842–2867; (g) T. Courant, G. Dagousset and G. Masson, *Synthesis*, 2015, **47**, 1799–1826; (h) M.-X. Wang, *Chem. Commun.*, 2015, **51**, 6039–6049; (i) T. Zhu, S. Xie, P. Rojsitthisak and J. Wu, *Org. Biomol. Chem.*, 2020, **18**, 1504–1521; (j) F. Beltrana and L. Miesch, *Synthesis*, 2020, **52**, 2497–2511.
- For selected references for enamide synthesis, see: (a) J. Genovino, B. Lagu, Y. Wang and B. B. Touré, *Chem. Commun.*, 2012, **48**, 6735–6737; (b) B. Gourdet and H. W. Lam, *J. Am. Chem. Soc.*, 2009, **131**, 3802–3803; (c) L. L. Baldassari, A. de la Torre, J. Li, D. S. Lüdtke and N. Maulide, *Angew. Chem., Int. Ed.*, 2017, **56**, 15723–15727; (d) T. Kuranaga, Y. Sesoko and M. Inoue, *Nat. Prod. Rep.*, 2014, **31**, 514–532; (e) Y. Bolshan and R. Batey, *Angew. Chem., Int. Ed.*, 2008, **47**, 2109–2112; (f) T. Kuranaga, Y. Sesoko, K. Sakata, N. Maeda, A. Hayata and M. Inoue, *J. Am. Chem. Soc.*, 2013, **135**, 5467–5474; (g) B. M. Trost, J. J. Cregg and N. Quach, *J. Am. Chem. Soc.*, 2017, **139**, 5133–5139; (h) L. Wang, C. Liu, R. Bai, Y. Pan and A. Lei, *Chem. Commun.*, 2013, **49**, 7923–7925; (i) S. S. Yudha, Y. Kuninobu and K. Takai, *Org. Lett.*, 2007, **9**, 5609–5611; (j) N. Panda and R. Mothkuri, *J. Org. Chem.*, 2012, **77**, 9407–9412; (k) C. Kuai, L. Wang, H. Cui, J. Shen, Y. Feng and X. Cui, *ACS Catal.*, 2016, **6**, 186–190; (l) C. Yamamoto, K. Hirano and M. Miura, *Chem. Lett.*, 2017, **46**, 1048–1050; (m) P. Chuentragool, M. Parasram, Y. Shi and V. Gevorgyan, *J. Am. Chem. Soc.*, 2018, **140**, 2465–2468; (n) G. Li, P. A. Kates, A. K. Dilger, P. T. Cheng, W. R. Ewing and J. T. Groves, *ACS Catal.*, 2019, **9**, 9513–9517; (o) N. Holmberg-Douglas, Y. Choi, B. Aquila, H. Huynh and D. A. Nicewicz, *ACS Catal.*, 2021, **11**, 3153–3158; (p) P. Spieß, M. Berger, D. Kaiser and N. Maulide, *J. Am. Chem. Soc.*, 2021, **143**, 10524–10529; (q) X. Wang and J. A. Porco Jr, *J. Org. Chem.*, 2001, **66**, 8215–8221; (r) M. J. V. Villa,



S. M. Targett, J. C. Barnes, W. G. Whittingham and R. Marquez, *Org. Lett.*, 2007, **9**, 1631–1633; (s) J. E. Mathieson, J. J. Crawford, M. Schmidtmann and R. Marquez, *Org. Biomol. Chem.*, 2009, **7**, 2170–2175; (t) H. Liu, Y. Zhou, X. Yan, C. Chen, Q. Liu and C. Xi, *Org. Lett.*, 2013, **15**, 5174–5177; (u) M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Org. Lett.*, 2014, **16**, 608–611; (v) X.-T. Min, D.-W. Ji, H. Zheng, B.-Z. Chen, Y.-C. Hu, B. Wan and Q.-A. Chen, *Org. Lett.*, 2020, **22**, 3386–3391; (w) L. Kong, X. Han, P. Hu, F. Wang and X. Li, *Chem. Commun.*, 2023, **59**, 6690–6693.

4 For selected reviews on radical difunctionalization of alkynes, see: (a) U. Wille, *Chem. Rev.*, 2013, **113**, 813–853; (b) S. R. Chemler and M. T. Bovino, *ACS Catal.*, 2013, **3**, 1076–1091; (c) Y. Shimizu and M. Kanai, *Tetrahedron Lett.*, 2014, **55**, 3727–3737; (d) P. Gao, X.-R. Song, X.-Y. Liu and Y.-M. Liang, *Chem.-Eur. J.*, 2015, **21**, 7648–7661; (e) V. P. Boyarskiy, D. S. Ryabukhin, N. A. Bokach and A. V. Vasilyev, *Chem. Rev.*, 2016, **116**, 5894–5986; (f) H. Mei, Z. Yin, J. Liu, H. Sun and J. Han, *Chin. J. Chem.*, 2019, **37**, 292–301; (g) C. Lin and L. Shen, *ChemCatChem*, 2019, **11**, 961–968; (h) X. Ren and Z. Lu, *Chin. J. Catal.*, 2019, **40**, 1003–1019; (i) W. Liu and W. Kong, *Org. Chem. Front.*, 2020, **7**, 3941–3955; (j) D. Bag, S. Mahajan and S. D. Sawant, *Adv. Synth. Catal.*, 2020, **362**, 3948–3970; (k) K. Keerthika, S. Nath and K. Geetharani, *Catal. Sci. Technol.*, 2020, **10**, 7142–7159; (l) D. Bag, H. Kour and S. D. Sawant, *Org. Biomol. Chem.*, 2020, **18**, 8278–8293; (m) H. Yao, W. Hu and W. Zhang, *Molecules*, 2021, **26**, 105–136; (n) S. Ghosh, R. Chakrabortty and V. Ganesh, *ChemCatChem*, 2021, **13**, 4262–4298; (o) J. Corpas, P. Mauleón, R. G. Arrayás and J. C. Carretero, *ACS Catal.*, 2021, **11**, 7513–7551; (p) N. Chalotra, J. Kumar, T. Naqvi and B. A. Shah, *Chem. Commun.*, 2021, **57**, 11285–11300; (q) J.-B. Tang, J.-Q. Bian, Y.-S. Zhang, Y.-F. Cheng, H.-T. Wen, Z.-L. Yu, Z.-L. Li, Q.-S. Gu, G.-Q. Chen and X.-Y. Liu, *Org. Lett.*, 2022, **24**, 2536–2540.

5 (a) A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, *Nature*, 2014, **510**, 129–133; (b) M.-L. Li, J.-H. Yu, Y.-H. Li, S.-F. Zhu and Q.-L. Zhou, *Science*, 2019, **366**, 990–994.

6 H. Sigel and R. B. Martin, *Chem. Rev.*, 1982, **82**, 385–462.

7 (a) F. Wang, N. Zhu, P. Chen, J. Ye and G. Liu, *Angew. Chem., Int. Ed.*, 2015, **54**, 9356–9360; (b) Y.-T. He, Q. Wang, J. Zhao, X.-Y. Liu, P.-F. Xu and Y.-M. Liang, *Chem. Commun.*, 2015, **51**, 13209–13212; (c) L. Fu, X. Chen, W. Fan, P. Chen and G. Liu, *J. Am. Chem. Soc.*, 2023, **145**, 13476–13483.

8 H. Xiong, N. Ramkumar, M.-F. Chiou, W. Jian, Y. Li, J.-H. Su, X. Zhang and H. Bao, *Nat. Commun.*, 2019, **10**, 122–128.

9 For selected reviews, see: (a) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726–11743; (b) S. Rej, Y. Ano and N. Chatani, *Chem. Rev.*, 2020, **120**, 1788–1887. For selected examples on application of bidentate directing groups in N–H bond functionalization, see: (c) X. Li, B. Li, J. You and J. Lan, *Org. Biomol. Chem.*, 2013, **11**, 1925–1928; (d) N. Xu, J. Liu, D. Lia and L. Wang, *Org. Biomol. Chem.*, 2016, **14**, 4749–4757; (e) H. Sahoo, S. Mukherjee, G. S. Grandhi, J. Selvakumar and M. Baidya, *J. Org. Chem.*, 2017, **82**, 2764–2771; (f) Q. Yue, Z. Xiao, Z. Kuang, Z. Su, Q. Zhang and D. Li, *Adv. Synth. Catal.*, 2018, **360**, 1193–1198; (g) Z. Xiao, S. Shu, Y. Lin, Q. Zhang, P. Ren and D. Li, *Asian J. Org. Chem.*, 2018, **7**, 2053–2056; (h) S. Bera, S. Roy, S. C. Pal, A. Anoop and R. Samanta, *ACS Catal.*, 2021, **11**, 10847–10854; (i) H. Ji, H. Zhan, S. Chen, Z. Fang, Q. Zhang and D. Li, *Asian J. Org. Chem.*, 2022, **11**, e202200454; (j) J. Ren, K. Liu, N. Wang, X. Kong, J. Li and K. Li, *ACS Catal.*, 2023, **13**, 11001–11011.

10 For selected references on radical β -alkylation of enamides, see: (a) H. Jiang, C. Huang, J. Guo, C. Zeng, Y. Zhang and S. Yu, *Chem.-Eur. J.*, 2012, **18**, 15158–15166; (b) P. Li, J. Zhao, C. Xia and F. Li, *Org. Lett.*, 2014, **16**, 5992–5995; (c) R. Ding, Z.-D. Huang, Z.-L. Liu, T.-X. Wang, Y.-H. Xu and T.-P. Loh, *Chem. Commun.*, 2016, **52**, 5617–5620; (d) R. Ding, W.-G. Lu, H. Ci, Y.-Y. Mao and L. Liu, *ChemistrySelect*, 2019, **4**, 6954–6957; (e) J.-Y. Guo, T. Guan, J.-Y. Tao, K. Zhao and T.-P. Loh, *Org. Lett.*, 2019, **21**, 8395–8399; (f) J.-Y. Guo, Z.-Y. Zhang, T. Guan, L.-W. Mao, Q. Ban, K. Zhao and T.-P. Loh, *Chem. Sci.*, 2019, **10**, 8792–8798; (g) S. Bertho, I. Dondasse, P. Retailleau, C. Nicolas and I. Gillaizeau, *New J. Chem.*, 2020, **44**, 7129–7141; (h) S. Bertho, R. Maazaoui, D. Torun, I. Dondasse, R. Abderrahim, C. Nicolas and I. Gillaizeau, *New J. Chem.*, 2021, **45**, 17475–17482; (i) J.-X. Wang, Y.-T. Wang, H. Zhang and M.-C. Fu, *Org. Chem. Front.*, 2021, **8**, 4466–4472; (j) X.-D. Su, B.-B. Zhang, Q. Liu, J.-T. Cheng, Z.-X. Wang and X.-Y. Chen, *Org. Lett.*, 2021, **23**, 8262–8266; (k) X. Zhang, T.-M. Yang, L.-M. Hu and X.-H. Hu, *Org. Lett.*, 2022, **24**, 8677–8682; (l) T. Guan, J.-Y. Guo, Q.-H. Xu, X.-W. Zhang, X.-Y. Yu, Y. Zhang and K. Zhao, *Green Chem.*, 2022, **24**, 6524–6530; (m) J.-Y. Tao, Y.-X. Wang, Q.-H. Zhang, K. Ni, T.-H. Zhu and K. Zhao, *Green Chem.*, 2022, **24**, 4004–4011; (n) K. Minami, K. Ohmatsu and T. Ooi, *ACS Catal.*, 2022, **12**, 1971–1976; (o) X.-Y. Lu, J.-C. Wang, X.-M. Sun, M.-T. Gao, W.-J. Ying, M.-Y. Ge, Z.-H. Wei, Z. Liu and X.-K. Chen, *J. Org. Chem.*, 2023, **88**, 513–524; (p) H. Liu, Y. Wu, L. Liu, J.-T. Yu and C. Pan, *Chem. Commun.*, 2023, **59**, 8556–8559.

11 (a) H. Liu, J.-T. Yu and C. Pan, *Chem. Commun.*, 2021, **57**, 6707–6724; (b) S. Kawamura, S. Mukherjee and M. Sodeoka, *Org. Biomol. Chem.*, 2021, **19**, 2096–2109.

12 A. Adeleke, A. P. N. Brown, L.-J. Cheng, K. A. M. Mosleh and C. J. Cordier, *Synthesis*, 2017, **49**, 790–801.

13 The pK_a values of the N–H bond of the substrates (**1a**, **1b**, and **1h**) were calculated using theoretical calculations, and the values are 44.4, 45.3, and 45.8, respectively (see the ESI† for computational details).

14 C. Sambiagio, R. H. Munday, S. P. Marsden, A. J. Blacker and P. C. McGowan, *Chem.-Eur. J.*, 2014, **20**, 17606–17615.

15 The crystal data of **IM1a** has been deposited in the Cambridge Crystallographic Data Centre as CCDC 2294904†.

