


 Cite this: *RSC Adv.*, 2025, 15, 16183

Received 9th April 2025

Accepted 7th May 2025

DOI: 10.1039/d5ra02454d

[rsc.li/rsc-advances](https://rsc.li/rsc-advances)

# Access to quaternary-carbon-containing $\beta$ -alkyl amides *via* persulfate-promoted domino alkylation/smiles rearrangement of alkenes†

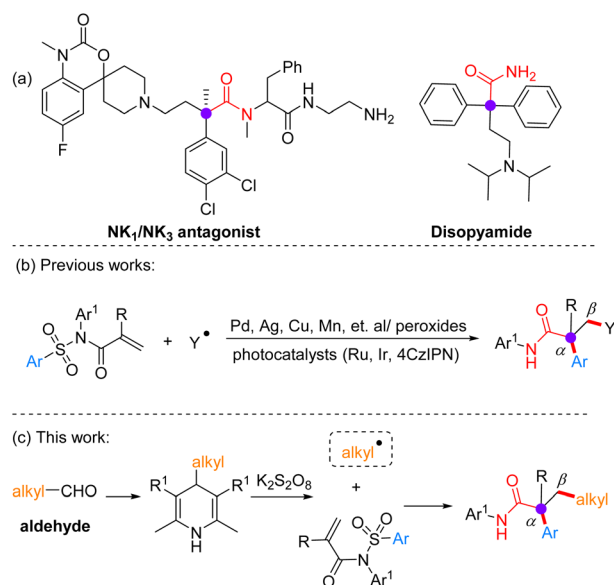
 Xiaohu Yang,<sup>a</sup> Xiaoqing Wan,<sup>a</sup> Wen-Chao Yang<sup>b</sup> and Hegui Fang<sup>\*a</sup>

In this study, we present an efficient approach for synthesizing all-carbon quaternary-centered  $\beta$ -alkyl amides. This method entails a persulfate-promoted cascade alkylative annulation/arylation of *N*-(arylsulfonyl)acrylamide with 4-alkyl-1,4-dihydropyridines (DHP). The reaction mechanism comprises four consecutive steps: (1) *in situ* generation of alkyl radical intermediates, (2) radical addition to the alkene moiety, (3) 1,4-aryl migration, and (4) finally desulfonation.

All-carbon substituted tetrahedral stereocenters with an amide backbone exhibit biological activity and are common structural motifs in drug molecules (Scheme 1a).<sup>1</sup> Consequently, substantial efforts have been directed towards synthesizing or modifying this motif. The direct difunctionalization of unsaturated hydrocarbons is acknowledged as a valuable strategy for accessing complex molecules, including all-carbon quaternary-centered scaffolds.<sup>2,3</sup> Recently, radical cascade difunctionalization of acrylamides has emerged as a powerful strategy for constructing all-carbon quaternary-centered amides (Scheme 1b).<sup>4</sup> This method generates radical intermediates through various reaction systems, including metal catalysis, oxidant promotion, photocatalysis, electrocatalysis, among others. For example, a photochemical smiles rearrangement reaction of *N*-sulfinyl acrylamides with bromodifluoroacetamides was established by Huang's group, resulting in the synthesis of aryl difluoroglutaramides.<sup>5</sup> In 2024, Chen and Zhang innovated a copper-catalyzed cascade reaction utilizing *N*-(arylsulfonyl) acrylamides, and silanes to produce  $\beta$ -silyl amide derivatives.<sup>6</sup> Very recently, Xu and co-workers reported a photo-induced deboronative generation of alkyl radicals from alkylboronic acids and guided to arylalkylation of *N*-sulfonylacrylamides, preparing amides containing a quaternary carbon center.<sup>7</sup> Given the important role of alkyl skeletons in human health and biological processes, there is an urgent need to develop efficient synthetic methods for constructing all-carbon-substituted tetrahedral stereocenters with an amide backbone.

Meanwhile, prearomatics such as dihydroquinazolinone, derived from ketones, have been employed as alkylating, tri/difluoromethylating, and acylating reagents.<sup>8</sup> This

methodology provides efficient conversion pathway for diverse ketone derivatives. For example, Chen and Shang collaborated on a blue-light-mediated trifluoromethylation, alkylation, and acylation of alkynyl bromides with unstrained ketones.<sup>8b</sup> More recently, He & Pan and co-workers established a dual catalytic strategy that employs dihydroquinazolinones, derived from ketone analogs, as versatile intermediates for acylation.<sup>9</sup> On the other hand, aldehydes, akin to ketones, are also abundant chemical entities possessing versatile functional groups. Hence, there is a strong impetus to explore novel transformations utilizing aldehydes as readily available functionalization reagents. DHPs (4-alkyl-1,4-dihydropyridines) derived from aldehydes have proved to be an important radical precursor in radical cascade reactions.<sup>10</sup> Inspired by these elegant studies



Scheme 1 Summary of the previous works and our new current.

<sup>a</sup>Department of Pharmacy, Zhejiang Hospital, Hangzhou, Zhejiang 310013, P. R. China. E-mail: zjyfhg@163.com

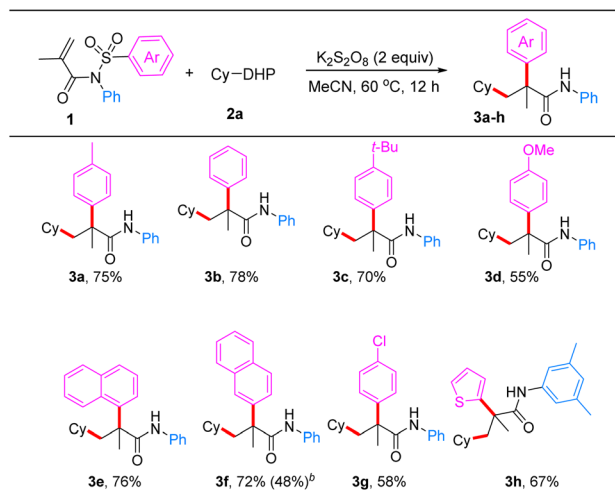
<sup>b</sup>School of Plant Protection, Yangzhou University, Yangzhou 225009, P. R. China

 † Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d5ra02454d>


and our ongoing interest in radical cascade reactions,<sup>11</sup> we present a simple method for the synthesis of all-carbon quaternary-center  $\beta$ -functionalized amides, using persulfates as promoters and aldehydes-derived DHPs as the alkyl source. Our methodology is distinguished by its mild reaction conditions, high yields, and facile operation.

To initiate our investigation, we selected *N*-(arylsulfonyl)acrylamide (**1a**) and 4-cyclohexyl-DHP (**2a**) as model substrates for evaluating the cascade reaction. We were pleased to find that the target product **3a** was obtained in a satisfactory yield of 62% when the reaction was carried out using  $K_2S_2O_8$  as the oxidant and THF as the solvent at 60 °C for 12 h (Table 1, entry 1). The systematic investigation of different persulfate variants revealed negligible effects on the experimental results, as clearly shown in Table 1 (entries 2 and 3). However, the use of other organic peroxide oxidants, including di-*tert*-butyl peroxide (DTBP), *tert*-butyl hydroperoxide (TBHP),  $H_2O_2$ , and dicumyl peroxide (DCP), led to significantly lower yields (Table 1, entries 4–7). Similarly, the employment of polar solvents such as DMF, DMSO, or DMA resulted in only marginal yields of the desired product (Table 1, entries 8–10). The influence of other polar solvent was also examined (Table 1, entry 11), to our delight, the yield of product **3a** was increased to 75% when MeCN was used as solvent. The variation of the reaction conditions, such as no oxidant involved resulted in no reaction proceeding (Table 1, entry 12). After exploring various parameters, the best reaction conditions were determined to be **1a** (0.2 mmol), **2a** (0.4 mmol), and  $K_2S_2O_8$  (2 equiv.) in MeCN (2 mL) at 60 °C for 12 h.

With the optimized conditions in hand, we subsequently explored the substrate scope of the *N*-(arylsulfonyl)acrylamides **1** for the synthesis of all-carbon quaternary-centered  $\beta$ -alkyl amides, as illustrated in Scheme 2. The influence of the aryl ring



Scheme 2 Substrates scop. <sup>a</sup>Reaction conditions: *N*-(arylsulfonyl)acrylamide (**1**, 0.20 mmol), **2** (0.40 mmol),  $K_2S_2O_8$  (2.0 equiv.),  $CH_3CN$  (2 mL), 60 °C, 12 h. Yields are given for isolated products; <sup>b</sup>2 mmol scale.

in *N*-(arylsulfonyl)acrylamides **1** was systematically investigated as a primary focus of this study. This synthetic strategy exhibits exceptional functional group tolerance, accommodating a diverse array of substituents on the aromatic ring, including both electron-donating and electron-withdrawing groups, in the target products. In general, the target products are typically obtained in good yields when the aryl ring is substituted with electron-donating groups, including methyl (**3a**), *tert*-butyl (**3c**), and methoxy (**3d**) groups. In addition, investigations into the naphthalene-substituted *N*-(arylsulfonyl)acrylamides **1e** and **1f** successfully produced the corresponding compounds **3e** and **3f** in satisfactory yields of 76% and 72%, respectively. Furthermore, halogen-substituted *N*-(arylsulfonyl)acrylamide was successfully transformed into the desired product **3g** with an isolated yield of 58%. Moreover, heterocyclic-substituted *N*-(arylsulfonyl)acrylamide proved to be suitable substrate for this radical cascade reaction, affording product **3h** in 67% yield.

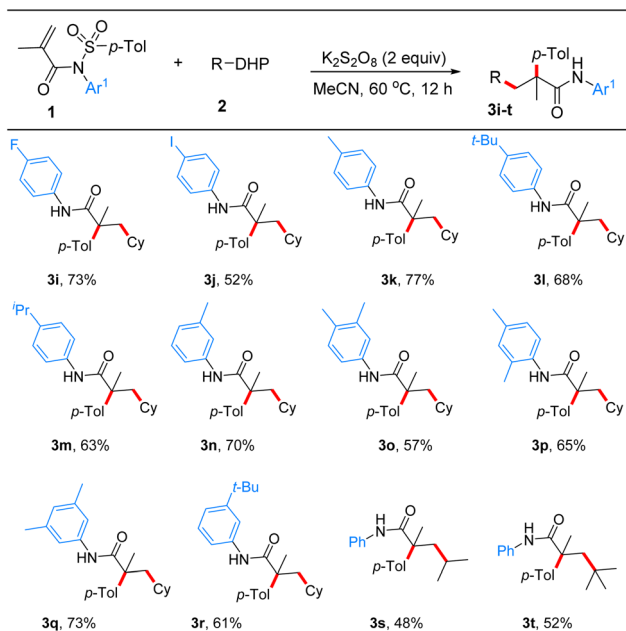
After a comprehensive evaluation of various substituents on the aromatic ring (Ar) in compound **1**, our investigation was subsequently directed towards exploring the scope and limitations associated with the Ar<sup>1</sup> aromatic ring in the same structure. As shown in Scheme 3, both electron-donating ( $-CH_3$ ,  $-tBu$  and  $-iPr$ ) and electron-withdrawing group ( $-F$ ) on the Ar<sup>1</sup> ring of *N*-(arylsulfonyl)acrylamides were all well compatible. Furthermore, the substrate featuring a methyl group at the *meta*-position of the Ar<sup>1</sup> ring in *N*-(arylsulfonyl)acrylamide also successfully underwent the reaction with **2a**, yielding the target  $\beta$ -phenyl amine **3n** with a 79% yield. Notably, when double-substituted *N*-(arylsulfonyl)acrylamides (**1o–1q**) were employed as substrates in this transformation, the corresponding  $\beta$ -functionalized amides were obtained in satisfactory yields (**3o**: 57%; **3p**: 65%; **3q**: 73%). Moreover, the optimized conditions were also suitable for the transformation of *N*-(3-(*tert*-butyl)phenyl)-*N*-tosylmethacrylamide **1r** with **2a**, and the target product **3r** was isolated in 61% yield. Finally, we showed the

Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Oxidant	Solvent	Yield <sup>b</sup> (%)
1	$K_2S_2O_8$	THF	62
2	$Na_2S_2O_8$	THF	47
3	$(NH_4)_2S_2O_8$	THF	54
4	DTBP	THF	Trace
5	TBHP	THF	Trace
6	$H_2O_2$	THF	Trace
7	DCP	THF	8
8	$K_2S_2O_8$	DMF	26
9	$K_2S_2O_8$	DMSO	30
10	$K_2S_2O_8$	DMA	35
11	$K_2S_2O_8$	MeCN	75
12	—	MeCN	n.r.

<sup>a</sup> Reaction conditions: *N*-(arylsulfonyl)acrylamide (**1a**, 0.20 mmol), **2a** (0.40 mmol),  $K_2S_2O_8$  (2.0 equiv.),  $CH_3CN$  (2 mL), 60 °C, 12 h. <sup>b</sup> Yields are given for isolated products, n.r. = no reaction.





**Scheme 3** Substrate scope. <sup>a</sup>Reaction conditions: *N*-(arylsulfonyl)acrylamide (**1**, 0.20 mmol), **2** (0.40 mmol),  $K_2S_2O_8$  (2.0 equiv.),  $CH_3CN$  (2 mL), 60 °C, 12 h. Yields are given for isolated products, n.r. = no reaction.

possible synthesis of isopropyl- and *t*-butyl-substituted  $\beta$ -functionalization amide starting from 4-isopropyl-DHP and 4-butyl-DHP. The products **3s** and **3t** were obtained in moderate yields (48% and 52%, respectively).

To gain deeper insights into the reaction mechanism, control experiments were performed. As depicted in Scheme 4, a critical observation was made: the addition of the radical scavenger 2,2,6,6-tetramethyl-1-oxylpiperidine (TEMPO) under standard reaction conditions completely inhibited the formation of the  $\beta$ -alkyl amide product (Scheme 4a). This compelling evidence strongly suggests that the cascade reaction proceeds

through a radical-mediated pathway. Moreover, the coupling product, **Int-I**, resulting from the coupling of TEMPO with the cyclohexyl radical intermediate, was identified by ESI-HRMS spectrometry (Scheme 4a).

On the basis of the mechanistic investigations and previously related literature reports,<sup>10</sup> a possible mechanism for the formation of  $\beta$ -functionalization amide is proposed in Scheme 4. Initially, a cyclohexyl radical intermediate **A** was generated after the oxidation of the DHP **2a** by  $K_2S_2O_8$  to afford pyridine **I**. Then, the Cy radical is intercepted by the alkene skeleton of *N*-(arylsulfonyl)acrylamide **1a** to deliver radical intermediate **B**, which subsequently adds to the aromatic ring near sulfone group to give sulfonyl radical intermediate **C**. Then a desulfonylation will occur to furnish amide radical intermediate **D**, which may abstract hydrogen atom from solvent to afford final product **3a**.

In summary, we have developed a mild and convenient method for constructing all-carbon quaternary-centered  $\beta$ -alkyl amides from 4-alkyl-1,4-dihydropyridines and *N*-(arylsulfonyl)acrylamides. Detailed mechanistic investigation has revealed that the reaction mechanism comprises four consecutive steps: (1) *in situ* generation of alkyl radical intermediates, (2) radical addition to the alkene moiety, (3) 1,4-aryl migration, and (4) final desulfonylation. This process is characterized by its mild reaction conditions and excellent functional group compatibility. Our methodology provides a novel and efficient strategy for the alkylation of  $\beta$ -functionalized amides, which may facilitate the synthesis of high-value-added fine chemicals.

## Data availability

The data underlying this study are available in the published article and its ESI.†

## Conflicts of interest

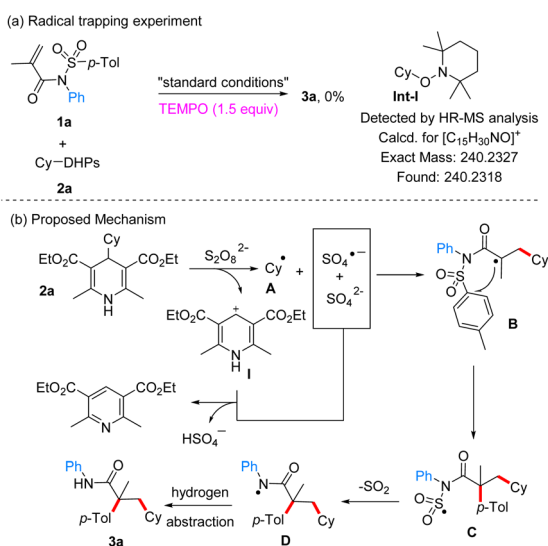
There are no conflicts to declare.

## Acknowledgements

We acknowledge financial support from the Zhejiang Pharmaceutical Association Joint Funds of Zhejiang Provincial Natural Science Foundation of China under Grant No. LYY22H280003, traditional Chinese Medicine Science and technology Project of Zhejiang Province of China under Grant No. 2020ZB008.

## Notes and references

- (a) T. Ling and F. Rivas, *Tetrahedron*, 2016, **72**, 6729–6777; (b) D. M. Black, D. Bentley, S. Chapel, J. Lee, E. Briggs and T. Heinonen, *Clin. Pharmacokinet.*, 2018, **57**, 1359–1367; (c) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756; (d) Y.-X. Zhu, Y.-Y. Zhang, X.-Y. Wang, Y. Yin and Y. Z. Du, *Environ. Microbiol. Rep.*, 2024, **16**, e70013; (e) G. Xu, L. Fu, L. Wu, J. Lu, M. Xu, R. Qian, C. Shao, M. Qian, Y. Zhang and G. Yang, *Pestic. Biochem. Physiol.*, 2025, **209**, 106335; (f) G. Xu, C. Li, W. Guo, M. Xu,



**Scheme 4** Control experiments and proposed mechanism.



- J. Lu, M. Qian, Y. Zhang and G. Yang, *Pest Manage. Sci.*, 2024, **80**, 4386.
- 2 (a) W. Yang, M. Zhang, W. Chen, X. Yang and J. Feng, *Chin. J. Org. Chem.*, 2020, **40**, 4060; (b) M.-M. Zhang, Y. Sun, W.-W. Wang, K.-K. Chen, W. Yang and L. Wang, *Org. Biomol. Chem.*, 2021, **19**, 3844–3849; (c) W. Yang, J.-G. Feng, L. Wu and Y. Zhang, *Adv. Synth. Catal.*, 2019, **361**, 1700–1709; (d) J. Shen, X. Yue, J. Xu and W. Li, *Org. Lett.*, 2023, **25**, 1994–1998; (e) S. Gupta, A. Kundu, S. Ghosh, A. Chakraborty and A. Hajra, *Green Chem.*, 2023, **25**, 8459–8493; (f) K. Wang, H. Ji, L. Ou and W.-M. He, *Eur. J. Org. Chem.*, 2023, **26**, e202300752; (g) D. Yang, Q. Yan, E. Zhu, J. Lv and W.-M. He, *Chin. Chem. Lett.*, 2022, **33**, 1798; (h) Z. Wang, Y. Sun, L.-Y. Shen, W.-C. Yang, F. Meng and P. Li, *Org. Chem. Front.*, 2022, **9**, 853–873; (i) X. Yang, C. Yang, X. Wan, W. Yang and H. Fang, *Asian J. Org. Chem.*, 2024, **13**, e202400354; (j) J. Wu, S. Li, S. Han, Y. Wang, W. Zhang, Z. Wang and Y. Zeng, *Org. Biomol. Chem.*, 2023, **21**, 5356–5360; (k) Y.-X. Duan, Y.-H. Zhuang, Y.-X. Wu, T.-W. Huang, Z.-R. Song, Y.-Z. Du and Y.-X. Zhu, *Microorganisms*, 2025, **13**, 302.
- 3 (a) W. Yang, B. Li, M. Zhang, S. Wang, Y. Ji, S. Dong, J. Feng and S. Yuan, *Chin. Chem. Lett.*, 2020, **31**, 1313–1316; (b) F. Wang, J. Jiang, T. Xu, W. Yang, S. Zhang, M. Wang and P. Li, *Tetrahedron Org. Chem. Ser.*, 2025, **13**, 100119; (c) W.-C. Yang, M.-M. Zhang and J.-G. Feng, *Adv. Synth. Catal.*, 2020, **362**, 4446–4461; (d) T. Tasnim, M. J. Ayodele and S. P. Pitre, *J. Org. Chem.*, 2022, **87**, 10555–10563; (e) L.-Y. Shen, Y. Sun, Y. Wang, B. Li, W.-C. Yang and P. Dai, *Tetrahedron*, 2022, **106**, 132649; (f) Z. Wang, J. Li, S. Zhang and W. Yang, *Mol. Catal.*, 2023, **535**, 113469; (g) W.-C. Yang, L.-Y. Shen, J.-N. Li, J.-G. Feng and P. Li, *Adv. Synth. Catal.*, 2022, **364**, 3651–3656; (h) Y. Lu, C. Wu, J. Hou, Z. Wu, M. Zhou, X. Huang and W.-M. He, *ACS Catal.*, 2023, **13**, 13071–13076; (i) C. Sun, Q. Zhou, C. Li, Z.-W. Hou and L. Wang, *Org. Lett.*, 2024, **26**, 883–888; (j) C. S. Nishad, P. Suman, H. Saha and B. Banerjee, *J. Org. Chem.*, 2023, **88**, 11010–11022; (k) S. Zhao, P. Zhu, B. Xu, S. Ling, L. Zhang and F. Sun, *J. Org. Chem.*, 2023, **88**, 9283–9292; (l) Y. Zhao, Y. Gu, D. Zhang, M. Ruan and G.-K. Liu, *J. Org. Chem.*, 2023, **88**, 10711–10720; (m) G. Zhang, Y. Zhang, P. Li, C. Zhou, M. Wang and L. Wang, *J. Org. Chem.*, 2023, **88**, 12341–12356; (n) H. Song, M. Liu, J. Huang, D. Wang, J. Jiang, J.-Y. Chen, T.-B. Yang and W.-M. He, *J. Org. Chem.*, 2023, **88**, 2288–2295; (o) S. K. Hota, S. P. Panda, S. Das, S. K. Mahapatra, L. Roy, S. D. Sarkar and S. Murarka, *J. Org. Chem.*, 2023, **88**, 2543–2549.
- 4 For selected examples, please see: (a) W. Kong, E. Merino and C. Nevado, *Angew. Chem., Int. Ed.*, 2014, **53**, 5078–5082; (b) W. Kong, M. Casimiro, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2013, **135**, 14480–14483; (c) X. Wu, X. Zhang, X. Ji, G.-J. Deng and H. Huang, *Org. Lett.*, 2023, **25**, 5162–5167; (d) J.-N. Li, Z.-J. Li, L.-Y. Shen, P. Li, Y. Zhang and W.-C. Yang, *Org. Biomol. Chem.*, 2022, **20**, 6659–6666; (e) J.-H. Fan, J. Yang, R.-J. Song and J.-H. Li, *Org. Lett.*, 2015, **17**, 836–839; (f) H. Zhang, C. Pan, N. Jin, Z. Gu, H. Hua and C. Zhu, *Chem. Commun.*, 2015, **51**, 1320–1322; (g) Z.-W. Zhao, Y.-S. Ran, Y.-J. Hou, X. Chen, X.-L. Ding, C. Zhang and Y.-M. Li, *J. Org. Chem.*, 2022, **87**, 4183–4194; (h) M. Li, C.-T. Wang, Q.-F. Bao, Y.-F. Qiu, W.-X. Wei, X.-S. Li, Y.-Z. Wang, Z. Zhang, J.-L. Wang and Y.-M. Liang, *Org. Lett.*, 2021, **23**, 751–756; (i) Y. Dai, W. Niu, J. Huang, J. Sun and X. Xu, *Org. Biomol. Chem.*, 2025, **23**, 1330–1337; (j) J. Zhang, H. Miao, H. Xin, G. Wang, X. Yang, X. Wang, P. Gao, X.-H. Duan and L.-N. Guo, *Chem. Commun.*, 2024, **60**, 5334–5337; (k) J.-T. Yu, R. Chen, J. Zhu and J. Cheng, *Org. Biomol. Chem.*, 2017, **15**, 5476–5479.
- 5 L. Tian, P. Chen, X. Ji, G.-J. Deng and H. Huang, *Org. Lett.*, 2024, **26**, 455–461.
- 6 F. Chen, S.-Y. Liu, X. Li, J.-L. Jia, Y. Li, X.-L. Lu, L. Jia, Y. Zheng, Z. Yan, G. Li, Y. Lv and H. Rong, *Adv. Synth. Catal.*, 2024, **366**, 1325–1330.
- 7 During the preparation of the manuscript, a similar work was published, please see: J. Wu, Y. Tian, X. Zhao, S. Liu, L. Xu and H. Song, *Org. Chem. Front.*, 2025, **12**, DOI: [10.1039/D5QO00323G](https://doi.org/10.1039/D5QO00323G).
- 8 (a) G. S. Yedase, M. Arif, R. Kuniyil and V. R. Yatham, *Org. Lett.*, 2023, **25**, 6200–6205; (b) H. Wu, S. Chen, D. Xiao, F. Li, K. Zhou, X. Yin, C. Liu, X. He and Y. Shang, *Org. Lett.*, 2023, **25**, 1166–1171; (c) H. Wu, S. Chen, C. Liu, Q. Zhao, Z. Wang, Q. Jin, S. Sun, J. Guo, X. He, P. J. Walsh and Y. Shang, *Angew. Chem., Int. Ed.*, 2024, **63**, e202314790; (d) S.-C. Lee, L.-Y. Li, Z.-N. Tsai, Y.-H. Lee, Y.-T. Tsao, P.-G. Huang, C.-K. Cheng, H.-B. Lin, T.-W. Chen, C.-H. Yang, C.-C. Chiu and H.-H. Liao, *Org. Lett.*, 2022, **24**, 85–89; (e) P. P. Mondal, S. Das, S. Venugopalan, M. Krishnan and B. Sahoo, *Org. Lett.*, 2023, **25**, 1441–1446; (f) H. Miao, J. Zhang, W. Li, W. Yang, H. Xin, P. Gao, X.-H. Duan and L.-N. Guo, *Chem. Sci.*, 2024, **15**, 8993–8999.
- 9 K. He, N. Jin, J. Chen, Y.-F. Zheng and F. Pan, *Org. Lett.*, 2024, **26**, 9503.
- 10 (a) Á. Gutiérrez-Bonet, C. Remeur, J. K. Matsui and G. A. Molander, *J. Am. Chem. Soc.*, 2017, **139**, 12251–12258; (b) X. He, J. Lu, A. Zhang, Q. Zhang, G. Xu and J. Xuan, *Org. Lett.*, 2020, **22**, 5984–5989; (c) H. Zhang, Z. Cui, J. Wang, L. Zhu and C. Li, *Org. Chem. Front.*, 2024, **11**, 4502–4507; (d) J. Wang, Z. Zhang, C. Li, M. Wang, J. Tan, H. Du and N. Chen, *Org. Chem. Front.*, 2024, **11**, 6213–6222; (e) W.-C. Yang, Y. Sun, L.-Y. Shen, X. Xie and B. Yu, *Mol. Catal.*, 2023, **535**, 112819; (f) Á. Gutiérrez-Bonet, J. C. Tellis, J. K. Matsui, B. A. Vara and G. A. Molander, *ACS Catal.*, 2016, **6**, 8004–8008.
- 11 (a) S.-P. Zhang, J.-X. Lan, M.-L. Yang, J.-Y. Cao and W.-C. Yang, *Org. Lett.*, 2024, **26**, 9990–9995; (b) S.-P. Zhang, D.-W. Guo, M.-L. Yang and W.-C. Yang, *J. Org. Chem.*, 2024, **89**, 10614–10623; (c) Y.-G. Ji, Z.-H. Li, Y.-Q. Yang, X. Yang and W.-C. Yang, *Chem.–Eur. J.*, 2024, **30**, e202402891; (d) W. Yang, Y. Sun, X.-B. Bao, S.-P. Zhang and L.-Y. Shen, *Green Chem.*, 2023, **25**, 3111–3116; (e) W.-C. Yang, M.-M. Zhang, Y. Sun, C.-Y. Chen and L. Wang, *Org. Lett.*, 2021, **23**, 6691–6696; (f) Y. Sun, S.-P. Zhang and W.-C. Yang, *J. Org. Chem.*, 2023, **88**, 13279–13290; (g) M.-M. Zhang, L.-Y. Shen, S. Dong, B. Li, F. Meng, W.-J. Si and W.-C. Yang, *Eur. J. Org. Chem.*, 2021, **31**, 4465–4468.

