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Visible-light-promoted selenylation/cyclization of *o*-(1-alkynyl) benzoates to access seleno-substituted isocoumarins†

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A simple and efficient method to access 4-selenyl-isocoumarin derivatives through visible-light-promoted selenylation/cyclization of *o*-(1-alkynyl) benzoates has been developed. This transformation is performed under mild conditions and has the advantages of functional group tolerance and broad substrate scope.

Organoselenium compounds have attracted considerable attention, owing to their applications in synthetic intermediates,[1] catalysis,[2] drugs,[3] agriculture chemistry,[4] and materials.[5] In particular, the installation of an organoselenium group into organic molecules can significantly improve their physical and chemical features as well as enhance their biological activities, which has been widely used in medicinal chemistry.[6]

Isocoumarins represent an important class of naturally occurring compounds that display a range of biological activities.[7] Capillarin shows a potent antifungal activity.[8] Cytogenin shows a potent anticancer activity.[9] (+)-Epoxyartemidin shows a potent antimalarial activity (Figure 1).[10]

The fascinating biological profiles of organoselenium and isocoumarins have motivated researchers to develop many methods for preparing selenated isocoumarins. It is a simple and convenient approach to prepare selenated isocoumarin derivatives by using *o*-(1-alkynyl) benzoates as materials. One of the most commonly used strategies for the preparation of selenated isocoumarins is the intramolecular electrophilic addition of PhSeCl/R_FCl to *o*-(1-alkynyl) benzoates (Scheme 1a).[11] However, selenenyl chlorides used as selenium reagents are usually unstable, costly and not easily available, eroding their overall appeal. Zeni's group[12] reported an $FeCl_3$-mediated cyclization of *o*-(1-alkynyl) benzoates with diselenides to afford 4-selenyl-isocoumarins, in which 1.5 equiv. $FeCl_3$ is required (Scheme 1b). Du's group[13] reported an efficient approach to *in situ* generate ArSeCl from diselenides and $PhICl_2$, which enabled electrophilic intramolecular of *o*-(1-alkynyl) benzoates to afford 4-selenyl-isocoumarins

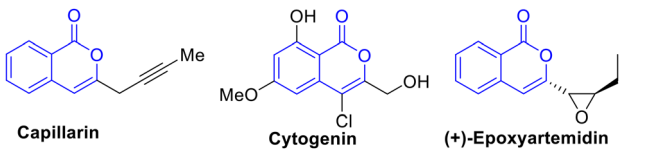
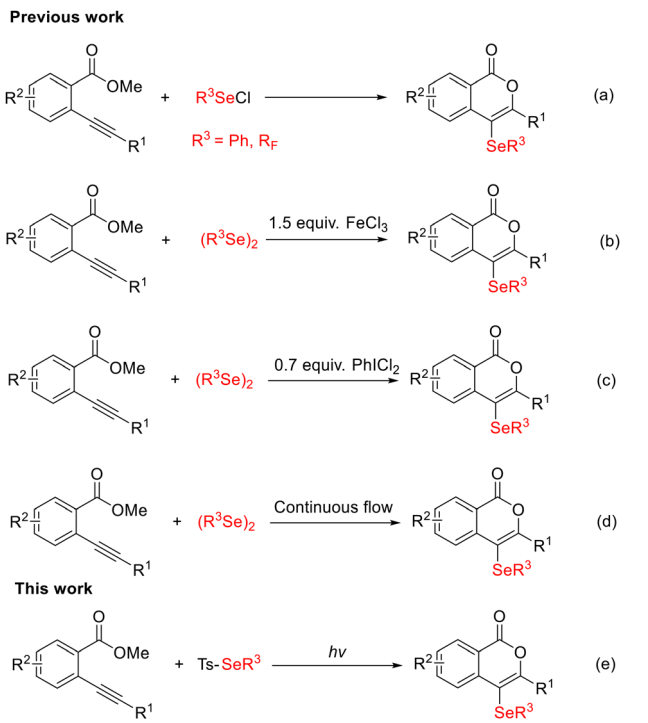


Fig. 1 Biologically active molecules including an isocoumarin scaffold.



Scheme 1 Synthesis of 4-selenyl-isocoumarins from alkynes.

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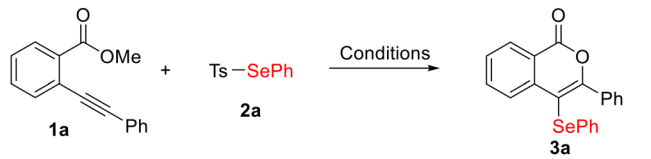
(Scheme 1c). Guo's group[14] reported a method for the synthesis of 4-selenyl-isocoumarins by using a continuous electrochemical microreactor to initiate an oxidative cyclization reaction of *o*-(1-alkynyl) benzoates and radicals (Scheme 1d). Although various methods for the preparation of selenated isocoumarins are available, the development of an efficient approach for the construction of 4-selenyl-isocoumarins is still in high demand.

Visible-light photocatalysis has recently drawn considerable attention from the scientific community owing to its mild, economical, and environmentally benign nature.[15] Recently, our group reported an efficient visible-light-promoted selenylation/cyclization of *o*-alkynyl benzylazides/*o*-propargyl arylazides with sulfonoselenoates for the synthesis of seleno-substituted isoquinolines and quinolines.[16] In continuation of our interest in the formation of a C–Se bond,[17] herein, we describe a metal-free synthesis of 4-selenyl-isocoumarins *via* visible-light-promoted selenylation/cyclization of *o*-(1-alkynyl) benzoates (Scheme 1e), in which a C–Se bond and C–O bond were constructed simultaneously under air conditions.

Initially, the reaction of methyl 2-(phenylethynyl)benzoate (**1a**) with Se-phenyl 4-methylbenzenesulfonoselenoate (**2a**) was chosen as a model system for optimization studies and the results are summarized in Table 1. The reaction of **1a** and **2a** in CH_3CN under irradiation of 50 W white LEDs in an air atmosphere gave the product 3-phenyl-4-(phenylselanyl)-1*H*-isochromen-1-one (**3a**) in 45% yield, in which the material **1a** and the byproduct $(PhSe)_2$ were detected by LC-MS (Table 1, entry 1). Screening of other solvents, such as DMF, 1,4-dioxane, DCE, toluene, HOAc, and DMSO, indicated that HOAc was the most suitable solvent for this transformation and the desired product **3a** was obtained in 70% yield (Table 1, entries 6 *vs.* 2–7). When the reaction was performed under dark conditions, no product (**3a**) was detected and most of the materials **1a** and **2a** were recovered, which indicated that light is essential for this transformation (Table 1, entry 8). The reaction of **1a** and **2a** performed in an atmosphere of N_2 and O_2 gave **3a** in 42% and 70% yields, respectively (Table 1, entries 9 and 10). When 30 W white LEDs were applied, this reaction produced **3a** in 50% yield (Table 1, entry 11). The reaction of **1a** and **2a** performed under 50 W blue LEDs gave **3a** in 40% yield (Table 1, entry 12). The reaction of **1a** and **2a** performed under 50 W green LEDs gave **3a** in 5% yield (Table 1, entry 13). These results suggest that 50 W white LEDs provided the optimal light for this transformation (Table 1, entries 6 *vs.* 11–13). When the reaction of **1a** and **2a** was performed in different molar ratios such as 1 : 1 and 1 : 1.2, product **3a** was obtained in 55% and 70% yields, respectively (Table 1, entries 14 and 15). The desired product **3a** was afforded in 62% yield when the reaction was performed on a 1.0 mmol scale of **1a** (Table 1, entry 16). Therefore, the best conditions for the synthesis of **3a** were a molar ratio of **1a** and **2a** of 1 : 1.1, with HOAc as the solvent under the irradiation of 50 W white LEDs in an air atmosphere.

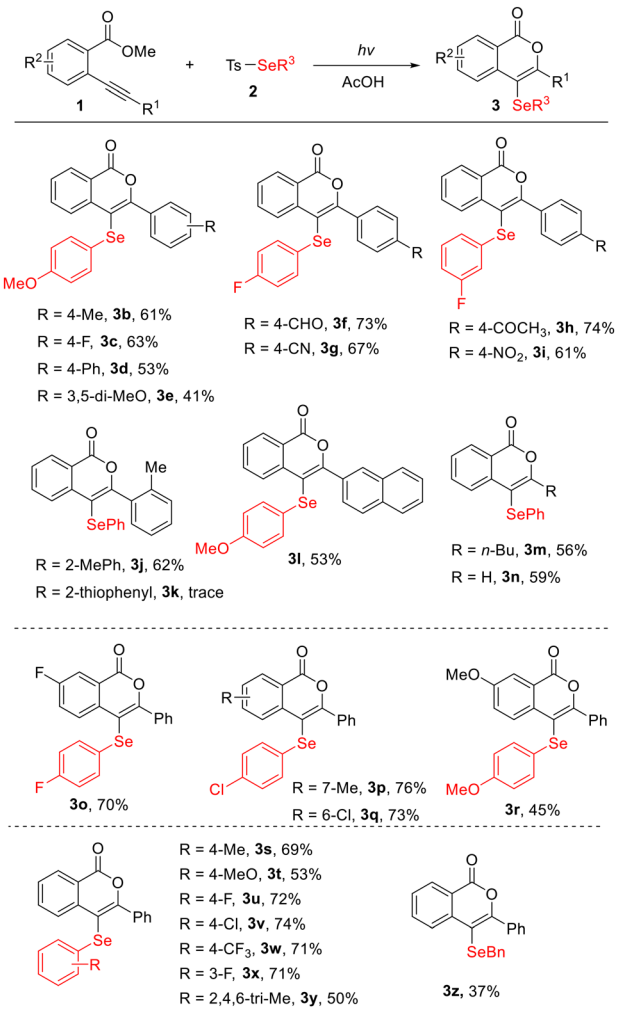
Table 1 Optimization of reaction conditions[a]



Entry	Solvent	Yield (%)
1	CH_3CN	45
2	DMF	40
3	1,4-Dioxane	20
4	DCE	50
5	Toluene	35
6	HOAc	70
7	DMSO	0
8[b]	HOAc	0
9[c]	HOAc	42
10[d]	HOAc	70
11[e]	HOAc	50
12[f]	HOAc	40
13[g]	HOAc	5
14[h]	HOAc	55
15[i]	HOAc	70
16[j]	HOAc	62

[a] Reaction conditions: **1a** (0.10 mmol) and **2a** (0.11 mmol) in solvent (1 mL), 50 W white LEDs, air, at room temperature for 3 h. Isolated yield based on **1a**. [b] Thereaction was performed in the dark. [c] The reaction was performed in an N_2 atmosphere. [d] The reaction was performed in an O_2 atmosphere. [e] The reaction was performed under 30 W white LEDs. [f] The reaction was performed under 50 W blue LEDs. [g] The reaction was performed under 50 W green LEDs. [h] 0.10 mmol **2a** was used. [i] 0.12 mmol **2a** was used. [j] The reaction was performed on a 1.0 mmol scale of **1a**.

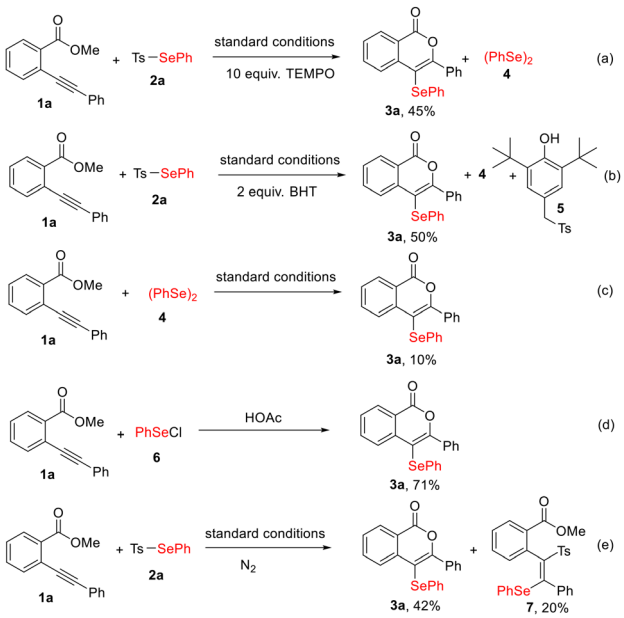
With the optimal reaction conditions identified, we next examined the scope of this new protocol (Scheme 2). A series of substrates with either an electron-donating group (Me and MeO) or an electron-withdrawing group (CHO, CN, $COCH_3$, and NO_2) substituted on the aromatic ring of *o*-alkynylbenzoate **1** all reacted smoothly, giving the corresponding products **3b–3j** in 41%–74% yields. Disappointingly, the reaction provided **3k** in trace yield (detected by LC-MS) as R^1 was a thiophene ring, in which the materials were decomposed and no major product was observed. To our delight, when R^1 was a naphthalene ring, the corresponding product **3l** was obtained in 53% yield. We found an alkyl substituted R^1 group was well tolerated and gave the desired product **3m** in 56% yield. The reaction produced the desired product **3n** in 59% yield when the reaction was performed using the terminal alkyne substrate. Furthermore, *o*-alkynylbenzoate substrates bearing different R^2 groups, such as F, Cl, Me and MeO, were well tolerated, providing the desired products **3o–3r** in 45%–76% yields. In addition, selenesulfonate substrates bearing different R^3 groups, including electron-donating (Me and OMe) and electron-withdrawing (F, Cl, and CF_3) substituents on the benzene ring, reacted smoothly to afford the desired products **3s–3y** in 50%–73% yields. The results suggested that the $TsSeR^3$ substrate with an electron-donating group on the benzene ring gave the corresponding products in lower yields than those with an electron-withdrawing group on the benzene ring. And the substrate Se-benzyl 4-methylbenzenesulfonoselenoate



Scheme 2 The scope of alkynylaryl esters and selenesulfonates. Reaction conditions: **1** (0.30 mmol) and **2** (0.33 mmol) in HOAc (3 mL), 50 W white LEDs, air, at room temperature for 3 h. Isolated yield.

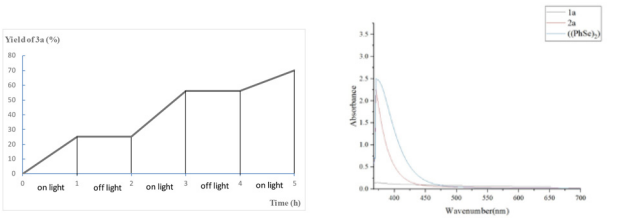
reacted smoothly, and the desired product **3z** was obtained in 37% yield.

To explore the possible pathway, several control experiments were conducted, as depicted in Scheme 3. Firstly, the reaction of **1a** and **2a** with 10 equiv. of TEMPO under standard conditions gave **3a** in 45% yield, in which the substrate **1a** was recovered and the byproduct $(PhSe)_2$ (**4**) was isolated (Scheme 3a). The reaction of **1a** and **2a** with 2.0 equiv. of BHT under standard conditions provided **3a** in 50% yield with $(PhSe)_2$ (**4**) and **5** (detected by LC-MS) (Scheme 3b). The reaction of **1a** and $(PhSe)_2$ under standard conditions gave **3a** in 10% yield by prolonging the reaction time to 24 h and most of the materials were recovered. The result suggests that $PhSe^{\bullet}$ may be formed by the photoinduced homolysis of the byproduct $(PhSe)_2$ (Scheme 3c). The reaction of **1a** and PhSeCl (**6**) in HOAc at room temperature afforded **3a** in 71% yield (Scheme 3d), which suggested that $PhSe^{+}$ is a possible intermediate for the formation of **3a.** The reaction of **1a** and **2a** performed in an N_2 atmosphere gave **3a** in 42% yield and byproduct **7** in 20% yield (detected by LC-MS) (Scheme 3e). Furthermore, the light on–off experiment suggests that continuous light is essential for the formation of **3a** (Fig. 2a). The UV-vis analysis of **1a**, **2a** and $(PhSe)_2$ showed that TsSePh (**2a**) and the byproduct $(PhSe)_2$ (**4**) could absorb visible light (Fig. 2b), indicating that **2a** and/or **4** served as photoactive substrates absorbing in the visible region and undergoing homolysis.



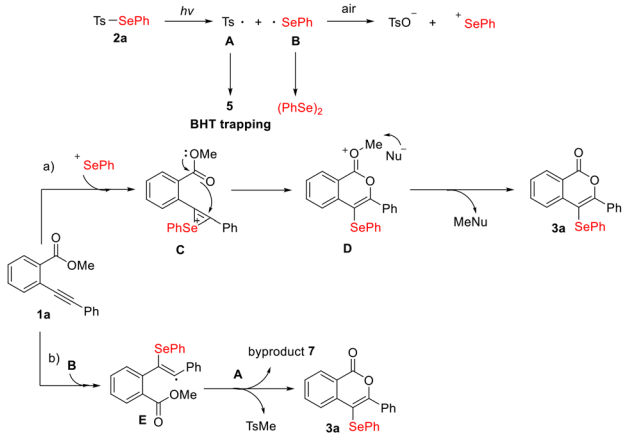
Scheme 3 Control experiments.

On the basis of the above experimental results, two possible pathways are proposed and depicted in Scheme 4. Firstly, the irradiation of Se-phenyl 4-methylbenzenesulfonoselenoate (**2a**) produces $Ts^{\bullet}$ (**A**) and $PhSe^{\bullet}$ (**B**) free radicals, which are oxidized to TsO^{-} and $PhSe^{+}$ under an air atmosphere,[18] respectively. In path (a), an electrophilic addition of $PhSe^{+}$ to the triple bond of **1a** gave selenonium ion **C**. Then an intramolecular attack by the double bond of the carbonyl group afforded the intermediate **D**, followed by a displacement of the methyl group with a nucleophile (OAc^{-} and TsO^{-}), which gave the desired product **3a**.[11b] In path (b), $PhSe^{\bullet}$ added to the alkynyl group of **1a** to give intermediate **E** that underwent the subsequent 6-endo-dig



(a) On/off experiments (b) UV/Vis Absorption experiments

Fig. 2 Mechanistic studies: (a) on/off experiments and (b) UV/Vis absorption experiment.



Scheme 4 The possible pathways.

cyclization process to give product **3a**, in which a byproduct of 7 was also detected by LC-MS.[19]

Conclusions

In summary, we have developed a simple and efficient method to access 4-selenyl-isocoumarin derivatives through visible-light-promoted selenylation/cyclization of *o*-(1-alkynyl) benzoates. This transformation is performed under mild conditions, without a transition metal catalyst and photocatalyst, providing a rapid method to synthesize 4-selenyl-isocoumarin derivatives. Further studies on the applications of 4-selenyl-isocoumarins in drug design are currently underway in our laboratory.

Data availability

The data that support the findings of this study are available in the ESI of this article.†

Conflicts of interest

There are no conflicts to declare.

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References

1 (*a*) A. D. Sonawane, R. A. Sonawane, M. Ninomiya and M. Koketsu, *Dalton Trans.*, 2021, **50**, 12764; (*b*) M. D. Kostic and V. M. Divac, *Curr. Org. Synth.*, 2022, **19**, 317.
2 For selected examples, see. (*a*) L. Liao and X. Zhao, *Synlett*, 2021, 1262; (*b*) P. Oswal, A. Arora, S. Gairola, A. Datta and A. Kumar, *New J. Chem.*, 2021, **45**, 21449; (*c*) A. Arora, P. Oswal, R. G. Kumar, S. Kumar and A. Kumar, *Dalton Trans.*, 2021, **50**, 8628; (*d*) D. Sharma, A. Arora, P. Oswal, A. Bahuguna, A. Datta and A. Kumar, *Dalton Trans.*, 2022, **51**, 8103.
3 For selected examples, see. (*a*) C. Moran-Serradilla, D. Plano, C. Sanmartin and A. K. Sharma, *J. Med. Chem.*, 2024, **67**, 7759; (*b*) W. Hou and H. Xu, *J. Med. Chem.*, 2022, **65**, 4436; (*c*) H. Chuai, S. Zhang, H. Bai, J. Li, Y. Wang, J. Sun, E. Wen, J. Zhang and M. Xin, *Eur. J. Med. Chem.*, 2021, **223**, 113621; (*d*) J. M. Sonego, S. I. de Diego, S. H. Szajnman, C. Gallo-Rodriguez and J. B. Rodriguez, *Chem. – Eur. J.*, 2023, **29**, e202300030; (*e*) B. G. Singh and A. Kunwar, *Free Radic. Res.*, 2021, **55**, 641.
4 T. Shah, T. A. Alahmadi, M. J. Ansari, Z. Khan and H. S. Khan, *Afr. J. Bot.*, 2024, **168**, 253.
5 (*a*) H. Liu, L. Chen, Y. Shen, L. Fan, J. Zhang, H. Zhu and S. Yan, *Nanotechnology*, 2024, **35**, 242003; (*b*) B. Liang, S. Lu, J. Hu, J. Liu and Y. Liu, *ACS Appl. Mater. Interfaces*, 2024, **16**, 15931; (*c*) K. Obata, T. Higashi, M. Hasegawa, M. Katayama and K. Takanabe, *Chem. – Eur. J.*, 2022, **28**, e202201951; (*d*) D. Yadav, A. K. Dixit, S. Raghothama and S. A. Kumar, *Dalton Trans.*, 2020, **49**, 12266; (*e*) L. McAlary, V. K. Shephard, G. S. A. Wright and J. J. Yerbury, *J. Biol. Chem.*, 2022, **298**, 101612; (*f*) Y. Huang, E. Su, J. Ren and X. Qu, *Nano Today*, 2021, **38**, 101205.
6 (*a*) W. Hou, H. Dong, X. Zhang, Y. Wang, L. Su and H. Xu, *Drug Discovery Today*, 2022, **27**, 2268; (*b*) M. Gao, M. Vuagnat, M. Chen, X. Pannecoucke, P. Jubault and T. Besset, *Chem. – Eur. J.*, 2021, **27**, 6145; (*c*) A. D. Sonawane, R. A. Sonawane, M. Ninomiya and M. Koketsu, *Dalton Trans.*, 2021, **50**, 12764.
7 (*a*) Y. Zhang, G. Yan, C. Sun, L. Nan, X. Wang, W. Xu and K. Chu, *Inflammation*, 2019, **42**, 506; (*b*) S. G. Nerella, P. Singh, M. Arifuddin and C. T. Supuran, *Expert Opin. Ther. Pat.*, 2022, **32**, 833; (*c*) N. A. Akwu, M. Lekhooa, D. Deqiang and A. O. Aremu, *Eur. J. Pharmacol.*, 2023, **956**, 175958.
8 K. M. Meepagala, G. Sturtz and D. E. J. Wedge, *J. Agric. Food Chem.*, 2002, **50**, 6989.
9 A. Saeed, *Eur. J. Med. Chem.*, 2016, **116**, 290.
10 D. Engelmeier, F. Hadacek, O. Hofer, G. Lutz-Kutschera, M. Nagl, G. Wurz and H. J. Greger, *Nat. Prod.*, 2004, **67**, 19.
11 (*a*) Q. Glenadel, E. Ismalaj and T. Billard, *Org. Lett.*, 2018, **20**, 56; (*b*) T. Yao and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 5936.
12 A. Speranca, B. Godoi, S. Pinton, D. F. Back, P. H. Menezes and G. Zeni, *J. Org. Chem.*, 2011, **76**, 6789.
13 L. Xing, Y. Zhang, B. Li and Y. Du, *Org. Lett.*, 2019, **21**, 3620.

14 X. Lin, Z. Fang, C. Zeng, C. Zhu, X. Pang, C. Liu, W. He, J. Duan, N. Qin and K. Guo, *Chem. – Eur. J.*, 2020, **26**, 13738.
15 (*a*) W. F. Zhu, C. Empel, S. Pelliccia, R. M. Koenigs, E. Proschak and V. Hernandez-Olmos, *J. Med. Chem.*, 2024, **67**, 4322; (*b*) L. Di Terlizzi, L. Nicchio, S. Protti and M. Fagnoni, *Chem. Soc. Rev.*, 2024, **53**, 4926; (*c*) Y. Zhang, J. Tan and Y. Chen, *Chem. Commun.*, 2023, **59**, 2413.
16 X. Gong, S. Sun, M. Ren, Q. Wu, Y. Chen and Y. Xu, *J. Org. Chem.*, 2024, **89**, 4176.
17 (*a*) S. Sun, Zu. Mo, Y. Chen and Y. Xu, *J. Org. Chem.*, 2022, **87**, 12447; (*b*) H. Liu, J. Zhang, G. Huang, Y. Zhou, Y. Chen and Y. Xu, *Adv. Synth. Catal.*, 2021, **363**, 1656; (*c*) J. Zhang, H. Liu, T. Fan, Y. Chen and Y. Xu, *Adv. Synth. Catal.*, 2021, **363**, 497; (*d*) X. Ma, Q. Wang, X. Feng, Z. Mo, Y. Pan, Y. Chen, M. Xin and Y. Xu, *Green Chem.*, 2019, **21**, 3547; (*e*) F. Cui, J. Chen, Z. Mo, S. Su, Y. Chen, X. Ma, H. Tang, H. Wang, Y. Pan and Y. Xu, *Org. Lett.*, 2018, **20**, 925; (*f*) X. Gong, Y. Zhou, M. Ren, Y. Chen and Y. Xu, *Synthesis*, 2024, 2529.
18 Z. Zhang, P. Tan, S. Wang, H. Wang, L. Xie, Y. Chen, L. Han, S. Yang and K. Sun, *Org. Lett.*, 2023, **25**, 4208.
19 G. Jin, W. Gao, Y. Zhou, M. Liu and H. Wu, *RSC Adv.*, 2020, **10**, 30439.