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https://doi.org/10.1038/s42004-024-01364-3

Feedstock chemical dichloromethane as the C1 source for the chemoselective multicomponent synthesis of valuable 1,4,2-dioxazoles

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The development of mild and practical strategies to produce value-added fine chemicals directly from inexpensive and readily available commodity chemicals is actively pursued by chemists. However, the application of feedstock chemical dichloromethane (DCM) as the C1 source in organic synthesis is still in its infancy. Herein, we describe a multicomponent strategy for the chemoselective synthesis of valuable 1,4,2-dioxazoles by using DCM as a C1 source. Critical to the success of this process is tuning of the type of nucleophiles to inhibit the easily-occurring side reactions. This approach features mild and simple conditions, excellent chemoselectivity, metal free, and broad substrate scope covering different types of nucleophiles. Furthermore, its synthetic utility is further demonstrated by the preparation of deuterated 1,4,2-dioxazoles, the late-stage functionalization of complex molecules and large-scale synthesis. Preliminary mechanistic studies indicate the dual roles of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as both a proton scavenger and a nucleophilic catalyst. This work provides not only a platform for DCM application, but also an excellent complementary strategy to the established 1,4,2-dioxazoles synthesis.

The development of mild and practical strategies to produce high-value pharmaceuticals and fine chemicals from inexpensive and readily available commodity chemicals is a central goal in organic synthesis[1,2]. DCM, a fundamental chemical in the chemical industry and laboratory organic synthesis, is commonly used as an organic solvent to mediate organic reactions, purification processes, or sample analysis, however, is rarely applied as a C1 building block in organic reactions in the past decades (Scheme 1a)[3–8]. This is because that compared with alkyl bromides [C(sp^3)-Br = 285 kJmol^{-1}] and alkyl iodides [C(sp^3)-I = 213 kJmol^{-1}], the activation of C(sp^3)-Cl bond requires high energy (327 kJmol^{-1})[9,10]. Hence, the development of novel organic transformations to synthesize value-added chemicals from stable and abundant feedstock chemical DCM is highly desired. Indeed, such transformations would potentially open up new vistas in organic synthesis.

1,4,2-Dioxazoles widely existed in bioactive molecules such as **I** (antiamoebic activity)[11] and **II** (modest central nervous system depressant activity)[12] (Scheme 1b). Furthermore, 1,4,2-dioxazoles were also important building blocks which could be utilized as nitrene transfer reagents[13], nitrene precursors[14], amidating reagents[15], and protecting agents[16]. Recently, some methods to access 1,4,2-dioxazoles have been reported (Scheme 1c). Velo and Polat-Cakir achieved the synthesis of 1,4,2-dioxazoles via the 1,3-dipolar cycloaddition reaction of nitrile oxides with acyl derivatives[17–19]. 1,4,2-Dioxazoles were also prepared by the reaction of acyl azides with ketones reported by Abraham[20]. Besides, 1,4,2-dioxazoles synthesis could be accomplished via the addition of benzhydroxamic acids to alkynes, diethylketals or vinyl aryl ethers[12,21–25]. Despite these advances, these developed methods suffered from inconveniently available starting materials, limited substrate scope and harsh reaction conditions such as high temperatures or noble metal catalysts. Furthermore, some of them involved multistep reactions and required tedious operation and complex purification processes. The aforementioned aspects would significantly thwart their wide practical application. Given the impressive pharmacological and synthetic characters of 1,4,2-dioxazoles, and in continuation of our efforts in developing novel organic transformations[26,27], we wondered if 1,4,2-dioxazoles

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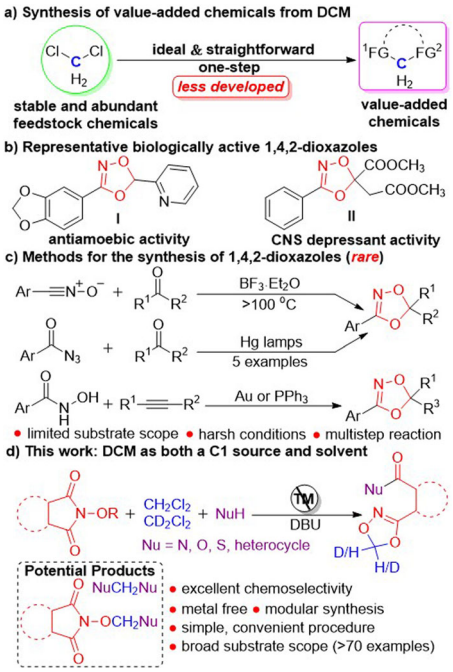


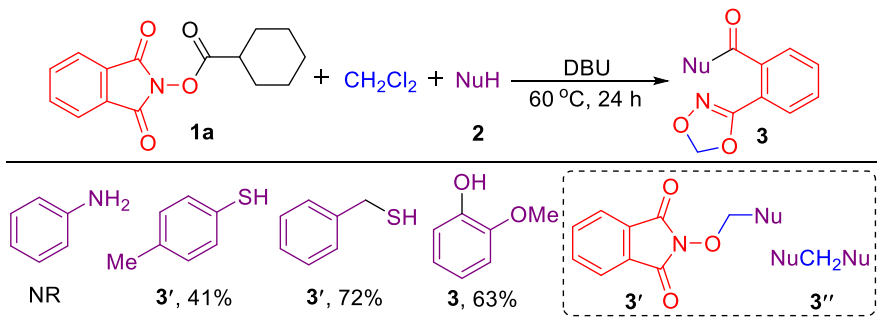
Scheme 1 | Chemoselective multicomponent synthesis of 1,4,2-dioxazoles from DCM. [a]Synthesis of value-added chemicals from DCM. [b]Representative biologically active 1,4,2-dioxazoles. [c]Methods for the synthesis of 1,4,2-dioxazoles. [d]This work: DCM as both a C1 source and solvent.

could be synthesized from readily available feedstock chemical DCM as the C1 source in a simple, economical and metal-free fashion with a broader substrate scope (Scheme 1d). One of the key challenges in this multicomponent reaction is chemoselective control since several side reactions can occur to produce undesired products, such as those from the direct nucleophilic attack on DCM by different nucleophiles[28,29]. The success of this approach would provide not only a new platform for DCM application, but also an excellent complementary strategy to the established 1,4,2-dioxazoles synthesis.

Results and discussion

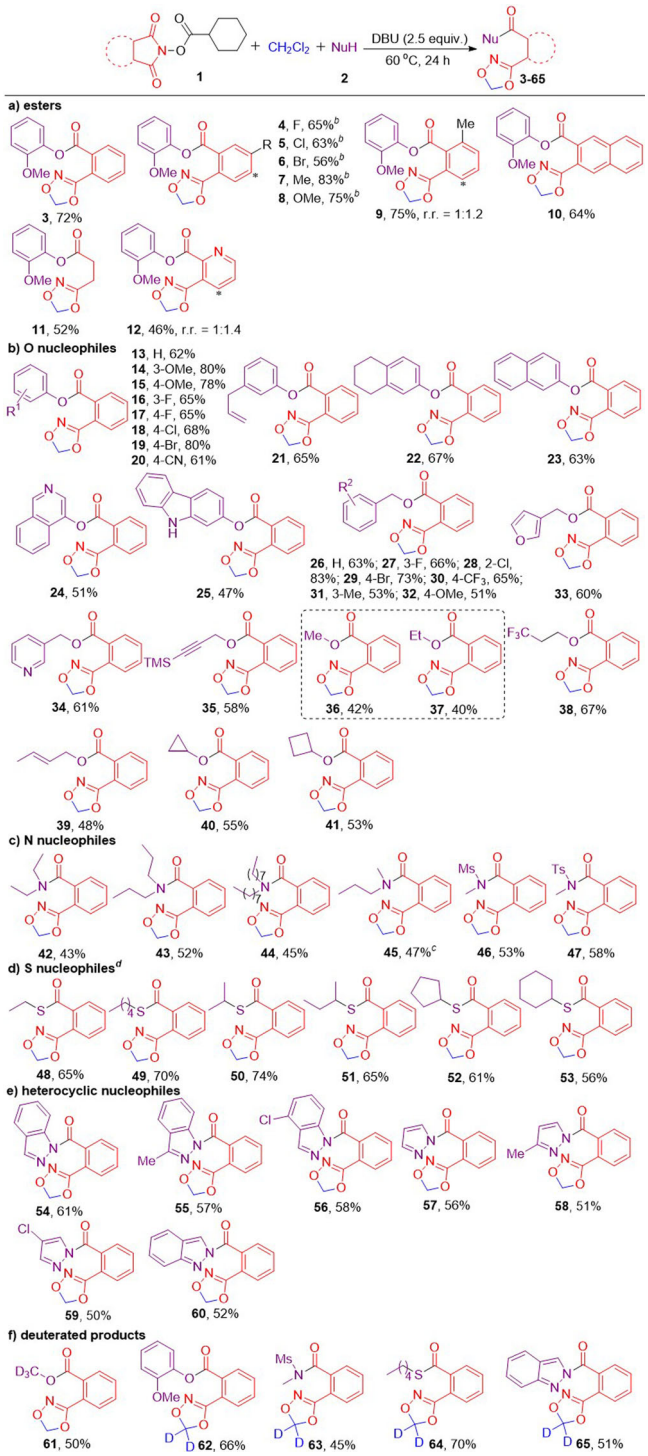
To realize this transformation, we initially chose 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate **1a**, DCM, and various nucleophiles as starting materials (Table 1). Unfortunately, the multicomponent reaction did not occur when using aniline as the nucleophile in the presence of DBU. In addition, the sole side product **3′** was obtained in 41 and 72% yields employing 4-methylbenzenethiol and phenylmethanethiol, respectively. Excitingly, 2-methoxyphenol as the nucleophile exclusively led to the formation of the desired product 1,4,2-dioxazole **3** in 63% yield (Table 1, entry 1). The possible side product **3″** was not observed in the process. Inspired by the above results, we further screened various additives and found that DBU was superior. Surprisingly, neither organic bases (entries 3–7) nor inorganic bases (entries 9 and 10) could yield 1,4,2-dioxazole **3**. The reaction using Et_3N or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as the additive gave **3** in poor yield (entries 2 and 8). It was worth noting that the yield of **3** was improved to 72% when 2.5 equivalents of **2** and DBU was used (entry 11). Control experiments indicated that DBU played a vital role in this reaction (entry 12, for more optimization details, see Supplementary Tables S1–S5).

Table 1 | Optimization of reaction conditions[a]



Entry	Additive	Isolated yield (%)
1	DBU	63
2	Et_3N	13
3	DIPEA	ND
4	DABCO	NR
5	Pyridine	NR
6	2,4,6-Collidine	ND
7	DMAP	ND
8	TBD	58
9	Cs_2CO_3	ND
10	KO^{t}Bu	ND
11[b]	DBU	72
12	-	NR

ND not detected, *NR* no reaction.
[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), DBU (0.2 mmol) in DCM (1 mL) at 60 °C for 24 h under argon.
[b]**2** (0.25 mmol), DBU (0.25 mmol).

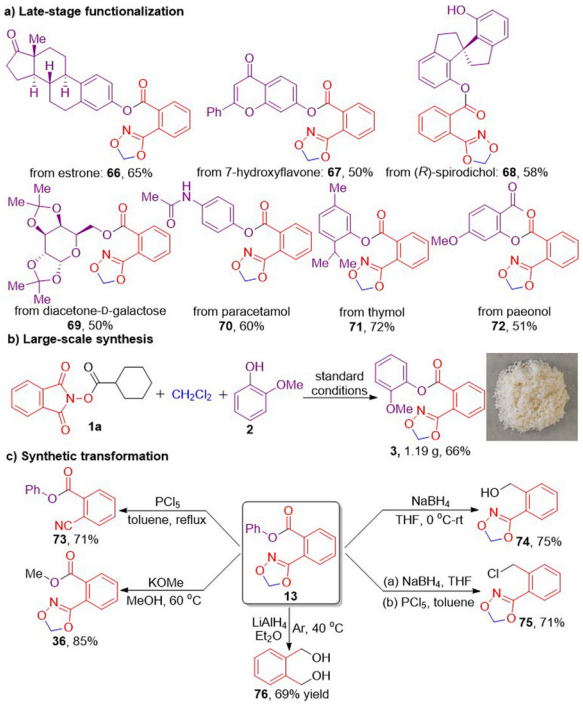


Scheme 2 | Substrate scope. [a]Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol) and DBU (0.5 mmol) in DCM (2 mL) at 60 °C for 24 h under argon. Isolated yields are reported. [b]**4, 5**: r.r. = 1:1.3; **6**: r.r. = 1:1; **7, 8**: r.r. = 1:1.1; [c]At 80 °C in DCM (1 mL) and CH_3CN (3 mL). [d]At 80 °C in DCM (1 mL) and dioxane (3 mL).

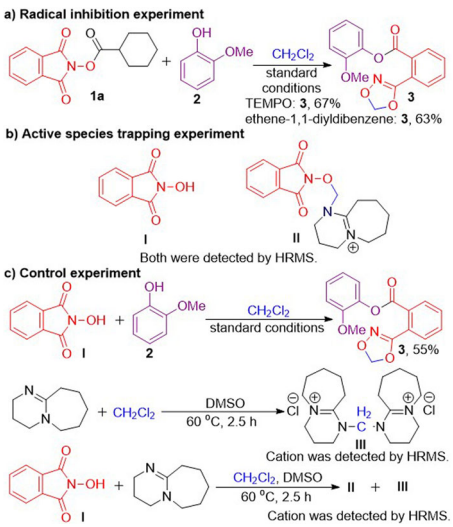
With the optimal reaction conditions established, the generality of this method was then explored (Scheme 2). As shown in Scheme 2a, a range of esters, including those bearing halides (**4**-**6**), methyl (**7** and **9**), or methoxyl (**8**) groups at different positions (*ortho* or *meta*) of phenyl rings and a naphthalene ring (**10**), reacted smoothly to yield the desired 1,4,2-dioxazoles in moderate to good yields with excellent chemoselectivity. The structure of **3** was further confirmed by X-ray crystallography (Supplementary Data 1). Notably, the aliphatic (**11**) and heterocyclic (**12**) succinimide derivatives were also compatible with the optimized conditions to afford 1,4,2-dioxazoles in moderate yields. Next, we investigated various nucleophiles. Phenols with diverse functional groups including methoxyl (**14** and **15**), halides (**16**-**19**), and some potentially reactive groups such as nitrile (**20**) and terminal alkene (**21**) worked well to exclusively furnish the desired products in 61-80% yields. Moreover, 1,4,2-dioxazoles **22** and **23** could be successfully obtained with 5,6,7,8-tetrahydronaphthalen-2-ol and naphthol. The reactions using heterocyclic phenols also gave the corresponding products **24** and **25**. In addition, acyclic and cyclic alcohols with different functional groups as the nucleophiles were well tolerated to exclusively afford 1,4,2-dioxazoles **26**-**41** in 48-83% yields. More importantly, the multicomponent reaction could smoothly proceed with two types of simple commodity chemicals DCM and methanol or ethanol to synthesize value-added 1,4,2-dioxazoles **36** and **37**. Subsequently, we turned our attention to assess amines as nucleophiles and found that secondary aliphatic amines, including sulfamides, exclusively led to the formation of 1,4,2-dioxazoles **42**-**47**. When a series of thiols were subjected to the standard conditions, the desired 1,4,2-dioxazoles **48**-**53** were obtained in good to high yields. Noteworthy is that this transformation has excellent chemoselectivity and the potential side products **3′** was not observed. Pharmaceutically important motifs, including 1*H*-indazoles (**54**-**56**), 1*H*-pyrazoles (**57**-**59**) and 2*H*-indazole (**60**), were also successfully incorporated into the 1,4,2-dioxazole skeleton. The structure of **54** was also confirmed by X-ray crystallography (Supplementary Data 2). Unfortunately, the reaction of **1a** with other chloralkanes, including 1,2-dichloroethane, 1,1-dichloroethane, chloroform and tetrachloromethane, did not produce the desired product. The pharmacokinetic properties of small-molecule drugs can be positively influenced by deuterium incorporation, resulting in improved safety, tolerability or efficacy[30]. As such, a variety of deuterated 1,4,2-dioxazoles **61**-**65** were smoothly synthesized by using readily available CD_3OD and CD_2Cl_2. This newly developed approach using DCM as a C1 source could offer a facile and inexpensive means for late-stage deuterium incorporation into pharmaceutically active compounds.

To demonstrate the robustness of this novel method, the late-stage functionalization of biologically active molecules, such as estrone (**66**), 7-hydroxyflavone (**67**), (*R*)-spirodichol (**68**), diacetone-D-galactose (**69**), paracetamol (**70**), thymol (**71**), and paeonol (**72**), was evaluated under the optimized conditions and the desired products were obtained in 50-72% yields with excellent chemoselectivity (Scheme 3a). Furthermore, a large-scale reaction was conducted to yield **3** in 66% yield (Scheme 3b). 1,4,2-Dioxazoles were also versatile synthetic blocks, and their synthetic transformation was explored (Scheme 3c). A new ring-opening reaction of **13** by PCl_5 smoothly occurs to form phenyl 2-cyanobenzoate **73** in 71% yield. **13** could also be reduced by $NaBH_4$ to afford **74** in 75% yield. In addition, the yield of **36** was significantly improved by the transesterification of **13** with KOMe. Upon treatment of **13** with $NaBH_4$ and PCl_5, **75** was generated in a 71% yield, and more importantly, the Cl atom in **75** could serve as a handle for the construction of more complex molecules. Excitingly, 1,2-phenylenedimethanol (**76**), serving as the versatile synthetic blocks and ligand was obtained in 69% yield through the reduction of **13**[31,32].

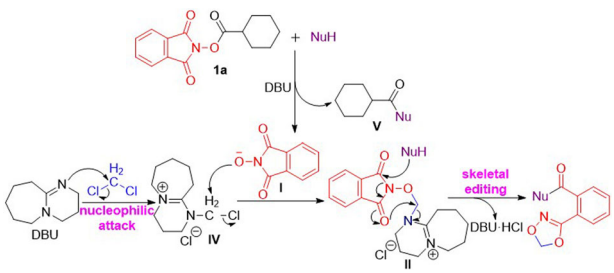
To better elucidate the reaction mechanism, we carried out a series of control experiments. The yield of **3** was not significantly influenced when the radical scavenger TEMPO or ethene-1,1-diyldibenzene was added to the model reaction (Scheme 4a), indicating that a radical process might not be involved in this reaction. The model reaction after 2.5 h was analysed by HRMS, and the possible intermediate **I** was detected (Scheme 4b). When **I** was subjected to the standard conditions, **3** was obtained in 55% yield, which further verified the intermediacy of **I** (Scheme 4c). Intriguingly, **II**, a DBU-containing intermediate, was also detected by HRMS in the model reaction (Scheme 4b). DBU has been demonstrated to serve as a superior nucleophilic catalyst in Baylis-Hillman reactions[33] and for the synthesis of methyl esters[34] and amides[35,36]. In order to further verify the role of DBU in the multicomponent reaction, the reaction of DBU with DCM was performed and the cationic part of **III** was detected by HRMS. Furthermore, when **I** was added to the reaction mixture of DBU and DCM, we observed the cationic



Scheme 3 | Late-stage functionalization and synthetic applications. [a]Late-stage functionalization of biologically active molecules. [b]Large-scale synthesis of **3**. [c]Synthetic transformation of **13**.



Scheme 4 | Mechanistic studies. [a]Radical inhibition experiment. [b]Active species trapping experiment. [c]Control experiment.



Scheme 5 | Proposed reaction mechanism. DBU functioned as not only a proton scavenger, but also a nucleophilic catalyst.

part of **II** and **III** by HRMS (Scheme 4c). The aforementioned experimental results showed that DBU might serve as a nucleophilic catalyst in 1,4,2-dioxazoles synthesis using DCM as a C1 source.

On the basis of experimental results and previous reports[33–36], we proposed a plausible reaction mechanism in which DBU functioned as not only a proton scavenger, but also a nucleophilic catalyst (Scheme 5). First, the reaction of **1a** with the nucleophile gave the intermediate **I** and the acyl derivative **V** in the presence of DBU. **V** has been isolated in >95% yield when using **2** as the nucleophile. The nucleophilic attack on DCM by DBU generated DBU adduct **IV**. With a quaternary ammonium ion and a chlorine atom attached, **IV** is extremely electrophilic, making the intermediate much more reactive than DCM[37]. Then, the disubstituted intermediate **II** was formed via the reaction of **IV** with **I**. Finally, the nucleophilic attack-induced skeletal editing of **II** was achieved to yield the target product 1,4,2-dioxazoles.

In conclusion, we have developed a novel multicomponent strategy for the chemoselective synthesis of valuable 1,4,2-dioxazoles by using stable and abundant feedstock chemical DCM as a C1 source. Notably, the easily-occurring side reactions are successfully inhibited by tuning the type of nucleophiles. The reaction operates under mild and simple conditions, exhibiting excellent chemoselectivity, metal free, and broad substrate scope covering different types of nucleophiles. Furthermore, the potential of this method is further demonstrated by the preparation of deuterated 1,4,2-dioxazoles, the late-stage functionalization of biologically active molecules, and large-scale synthesis. Preliminary mechanistic studies suggest the dual roles of DBU as both a proton scavenger and a nucleophilic catalyst. Further endeavors toward the development of novel strategies for expanding the application of DCM as a C1 source in organic synthesis are ongoing in our laboratory.

Methods

Reagents were used as received from commercial suppliers without further purification, unless otherwise stated. TLC was carried out on SiO_2 (silica gel 60 F254, Merck). Flash chromatography was carried out on SiO_2 (type: specifications 3, 300– mesh). NMR spectra were recorded for ^1H NMR (400 and 600 MHz), ^{13}C NMR (100 and 150 MHz) and ^{19}F NMR (565 MHz) using TMS as an internal standard and Bruker AV 400 and 600 as an instrument. The following abbreviations were used to describe peak patterns where appropriate: singlet (s), doublet (d), triplet (t), and multiplet (m). High-resolution mass spectroscopy (HRMS) were obtained using Bruker Apex IV RTMS. The X-ray diffraction data were collected on an XtaLab PRO MM007HF-DW diffractometer.

Procedure for the synthesis of 1,4,2-dioxazoles

To a 10 mL Schlenk tube equipped with a stir bar, starting material **1** (0.2 mmol, 1.0 equiv.) was added. The Schlenk tube was purged with argon, and then CH_2Cl_2 (2.0 mL), **2** (55.0 μL, 0.5 mmol, 2.5 equiv.) and DBU (74.7 μL, 0.5 mmol, 2.5 equiv.) were added. The reaction mixture was stirred at 60 °C for 24 h. Subsequently, the mixture was evaporated under reduced pressure and the crude residue was purified by column chromatography on silica gel to afford the desired 1,4,2-dioxazoles.

Data availability

Experimental procedures and characterization data are available in the Supplementary Information file. The X-ray crystallographic coordinates for structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 2352220 (**3**, Supplementary Data 1) and 2352221 (**54**, Supplementary Data 2). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The NMR spectra are available in Supplementary Data 3.

Received: 7 July 2024; Accepted: 12 November 2024;
Published online: 21 November 2024

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Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (22301094), Guangdong Basic and Applied Basic Research Foundation (2023A1515010728, 2022A1515110829, and 2023A1515010873), STU Scientific Research Initiation Grant (NTF24002T), the Special Fund for the Sci-Tech Innovation Strategy of Guangdong Province (STKJ202209066 and 210730166882026) and Chemistry and Chemical Engineering Guangdong Laboratory (2111008, 2011006, 2132013, and 2211003).

Author contributions

M.-J.X., X.L., X.-X.L., L.-H.W., S.-L.X., K.-W.Z., and Y.Z. performed experiments. Y.-N.D., D.L., and H.-D.X. wrote and revised the paper. All authors discussed the results and commented on the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s42004-024-01364-3.

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Peer review information *Communications Chemistry* thanks Yunfei Du and the other, anonymous, reviewers for their contribution to the peer review of this work. Peer review reports are available.