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PAPER

I₂-DMSO mediated multi-component cascade cyclization to construct pyrazolo[3,4-b]pyrrolo[3,4-d]pyridine-6-one skeleton

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A one-pot synthesis of the pyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-6-one skeleton has been developed using aryl methyl ketones, 3-aminopyrazoles, and enaminamides as substrates. This method features metal-free catalysis and broad substrate compatibility (36 examples). The reaction involves the formation of two C–C and two C–N bonds, while constructing a tetrasubstituted carbon stereocenter bearing a reactive hydroxyl group.

Pyrazolo[3,4-b]pyridines, as an important class of fused heterocyclic systems,[1] have attracted substantial interest due to their unique biological activities and luminescent properties.[2] Particularly, pyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-6-one derivatives exhibit remarkable neuromodulatory activity because of their unique tricyclic fused-ring system[3] and have been widely used in the design of drug molecules, including sedative agents (I, II),[4] antitumor candidates (III),[5] and fluorescent materials

(IV) (Fig. 1).[6] Therefore, it is desirable to develop efficient synthetic strategies for constructing pyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-6-one derivatives.

According to the literature, the current synthetic approaches for pyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-6-one scaffolds can be categorized into two types based on the different imination reagents. The first approach involves the initial imination reaction of 5-aminopyrazole with dimethylformamide dimethylacetal (DMF-DMA) to form a formimidamide that then undergoes the Aza-Diels–Alder cycloaddition with maleimide as the dienophile, to construct the target scaffold (Scheme 1a).[4,7] The second approach uses trimethyl orthoformate (TMOF) as the imination reagent to generate a formimidate, followed by the Aza-Diels–Alder reaction to afford the pyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-6-one framework (Scheme 1b).[7a] However, unlike the 3H-pyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-6-one skeleton framework, synthetic routes to the 2H-pyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-6-one skeleton remain unreported. The structural

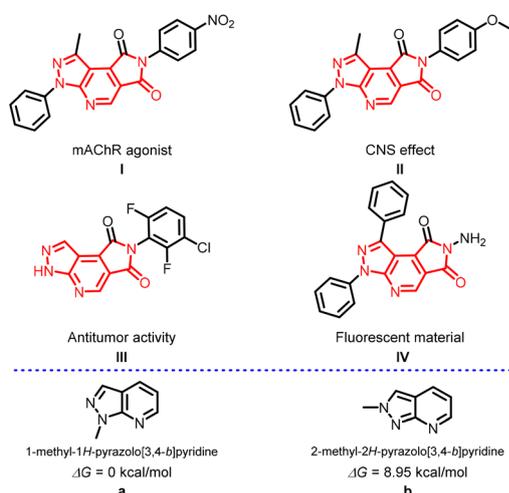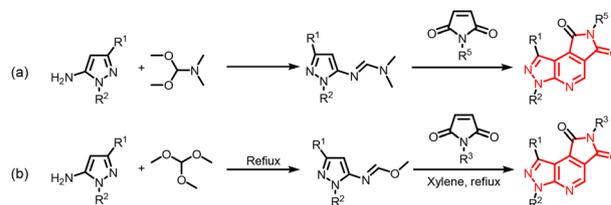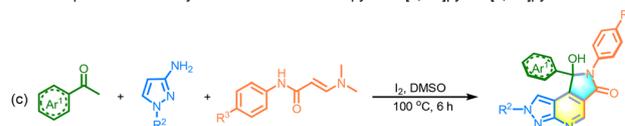Fig. 1 Bioactive molecules of pyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-6-one derivatives and two pyrazolo[3,4-b]pyridine skeletons.

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Scheme 1 Background (a and b) and synopsis of the current work (c).

distinction between these two skeletons arises from differing π-electron conjugation patterns. Moreover, density functional theory (DFT) calculations demonstrate that the energy of 2H-pyrazolo[3,4-b]pyridine (b) is 8.95 kcal mol⁻¹ higher than that of 1H-pyrazolo[3,4-b]pyridine (a). The higher energy of 2H-pyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-6-one makes its synthesis thermodynamically unfavorable, posing a major challenge.

To realize the synthesis of this skeleton and based on previous works on heterocyclic synthesis,[8] we developed a three-component cyclization reaction using an I₂-DMSO combination reagent system, with readily available aryl methyl ketones, 3-aminopyrazoles, and enaminamides as substrates (Scheme 1c). This strategy established a streamlined one-pot protocol for constructing the 2H-pyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-6-one skeleton, offering a new pathway for the skeleton.

In the initial investigation, we used acetophenone (1a), 1-methyl-1H-pyrazol-3-amine (2a), and 3-(dimethylamino)-N-phenylacrylamide (3a) as model substrates (Table 1). Fortunately, the target product 4a was obtained in 48% yield (entry 1). Encouraged by this result, we tested different reaction conditions to improve the yield. Initially, a series of Brønsted acids and Lewis acids were employed as additives to investigate their effects on the reaction yield, we found that the addition of TsOH led to a significant improvement, boosting the yield to 68% (entries 2–11). A study of the equivalents of TsOH and I₂ was then carried out. It was found that using 1.5 equiv. of TsOH and

1.6 equiv. of I₂ in the reaction was the optimum choice (entries 12–17). Finally, through a comparison of different reaction temperatures, we confirmed that 100 °C remained the optimal temperature, affording a yield of 75% (entries 18–19).

Under the optimal reaction conditions, we investigated the effects of different substituents on acetophenones, 3-aminopyrazoles and enaminamides (Scheme 2).

Various acetophenones with alkyl and electron-donating group substituents performed smoothly in the reaction, yielding the target products at a yield of 55–76% (4a–p), and the structure of product 4a was confirmed by X-ray single crystal diffraction (CCDC: 2423210). Substitution at the para-position of acetophenone with halogens also provided products in good yields (4q–t, 66–73%). Electron-withdrawing groups on the acetophenone gave the corresponding products, but a decrease in reaction yield was observed (4u–w, 47–68%). Simultaneously,

Table 1 Optimization of the reaction conditions[a]
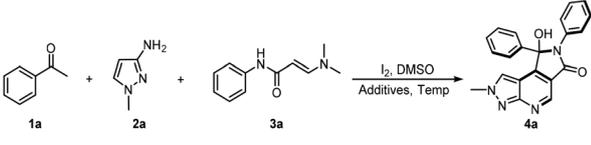
Entry	I₂ (x eq.)	Additives (x eq.)	Temp (°C)	Yield[b] (%)
1	1.6	—	100	48
2	1.6	50% HI (1.0)	100	55
3	1.6	CH₃CO₂H (1.0)	100	53
4	1.6	CF₃CO₂H (1.0)	100	32
5	1.6	CF₃SO₃H (1.0)	100	51
6	1.6	TsOH (1.0)	100	68
7	1.6	ZnCl₂ (1.0)	100	61
8	1.6	CuBr₂ (1.0)	100	57
9	1.6	Cu(OTf)₂ (1.0)	100	44
10	1.6	FeCl₃ (1.0)	100	59
11	1.6	Fe(OTf)₃ (1.0)	100	52
12	1.6	TsOH (0.5)	100	60
13	1.6	TsOH (1.5)	100	75
14	1.6	TsOH (2.0)	100	69
15	0.8	TsOH (1.5)	100	51
16	1.2	TsOH (1.5)	100	62
17	2.0	TsOH (1.5)	100	67
18	1.6	TsOH (1.5)	80	47
19	1.6	TsOH (1.5)	120	70

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), I₂ (x equiv), additive (x equiv), 6 h, DMSO (6.0 mL), indicated temperature, unless otherwise noted. [b] Isolated yields.
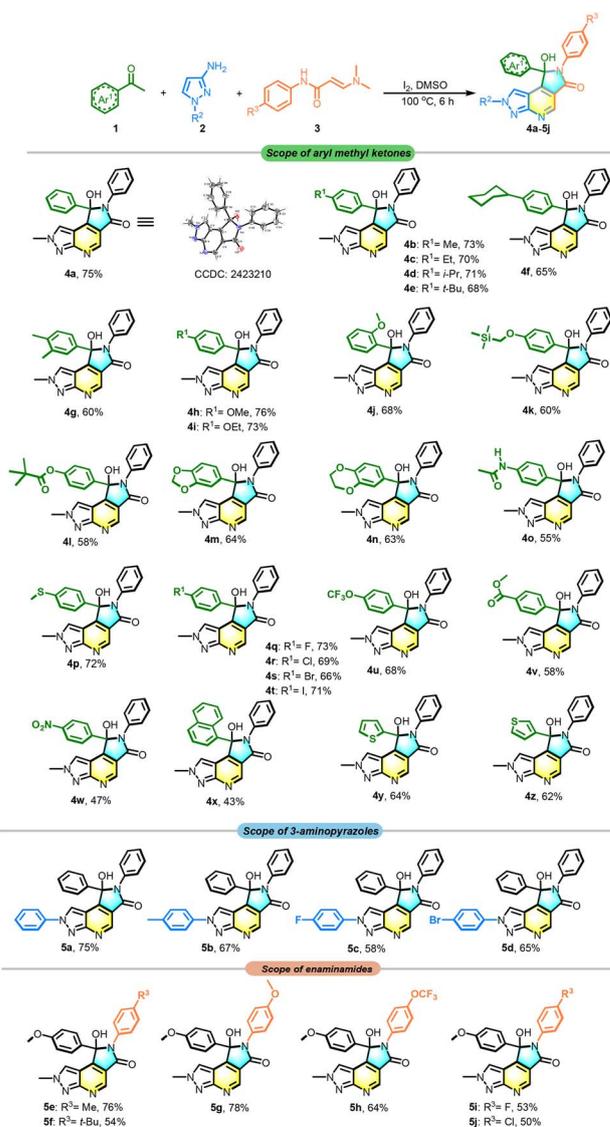

Scheme 2 Substrate scope of acetophenones, 3-aminopyrazoles, and enaminamides. Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), I₂ (1.6 mmol), TsOH (1.5 mmol) in DMSO (6.0 mL) at 100 °C for 6 h.

naphthalene ring and thiophenes also underwent the reaction, furnishing the products in moderate yields (**4x–z**, 43–64%). Furthermore, we investigated the compatibility of 3-amino-pyrazoles. Fortunately, the *N*-aryl-substituted 3-aminopyrazole gave target product **5a** in 75% yield. Substitution at the *para*-position of the benzene ring with methyl, fluorine, or bromine groups gave the aim products in moderate yields (**5b–d**, 58–67%). Finally, *para*-substituted enaminamides bearing diverse electron-donating (CH₃, C(CH₃)₃, OCH₃) and electron-withdrawing groups (OCF₃, F, Cl) were compatible with the reaction conditions, and gave the corresponding products in 50–78% isolated yields (**5e–j**). This broad functional group tolerance highlights the synthetic versatility of the protocol.

To validate the applicability of this method, we performed the reaction on a gram scale firstly, the reaction scaled up to 5.0 mmol and the target product **4a** was obtained in 60% yield (Scheme 3a). In addition, the derivatization of product **4a** was carried out. Fortunately, product **4a** could react with 4-([1,1′-biphenyl]-4-yl)-4-oxobutanoic acid to give product **7** in 62% yield (Scheme 3b). Besides, the hydroxy of **4a** could coupled with benzyl bromide to give product **9** in 65% yield (Scheme 3c).

A series of control experiments were strategically conducted to reveal the reaction mechanism. Under the I₂-DMSO combination reagent, acetophenone (**1a**) was converted to phenyl-glyoxal (**1ab**) or phenylglyoxal monohydrate (**1ac**) in an almost quantitative manner (Scheme 4a). When acetophenone (**1a**) was replaced with α-iodo acetophenone (**1aa**) or phenylglyoxal monohydrate (**1ac**), product **4a** was obtained in 50% and 58% yields. These control experiments indicated that α-iodo acetophenone (**1aa**) and phenylglyoxal monohydrate (**1ac**) were likely intermediates in this reaction (Scheme 4b and c). When phenylglyoxal monohydrate (**1ac**) was used as the substrate instead of acetophenone (**1a**) while without I₂, the result showed that product **4a** was not detected. This result suggested that I₂ played an important role in this reaction (Scheme 4d). Finally, when *N*-methyl-substituted compound **3h** was employed, product **10** was obtained with a yield of 76%. This clearly indicated that the reaction initially undergoes [4 + 2] cyclo-dition and subsequently follows the nucleophilic reaction pathway (Scheme 3e).
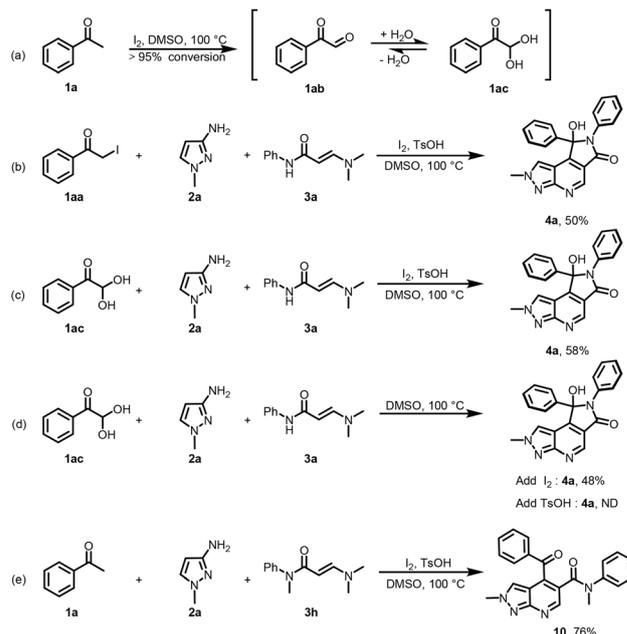

Scheme 4 Control experiments (a–d) and uncyclic products (e).

Based on the aforementioned experimental results and in conjunction with relevant literature,[9] a possible mechanism of this reaction was proposed (Scheme 5). First, acetophenone (**1a**) undergoes iodination and Kornblum oxidation mediated by I₂-DMSO combination reagent, yielding phenylglyoxal (**1ab**). Subsequently, phenylglyoxal (**1ab**) undergoes a condensation reaction with 3-aminopyrazole (**2a**) to afford intermediate **A**. Under acidic catalysis, intermediate **A** loses a molecule of water, generating cationic intermediate **B**, which participates in a [4 + 2] cycloaddition reaction with substrate **3a**, deprotonation
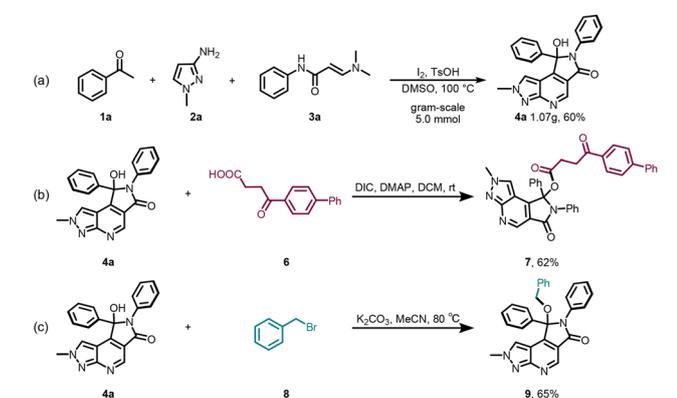
Scheme 3 Gram-scale experiments (a) and late-modification (b and c).
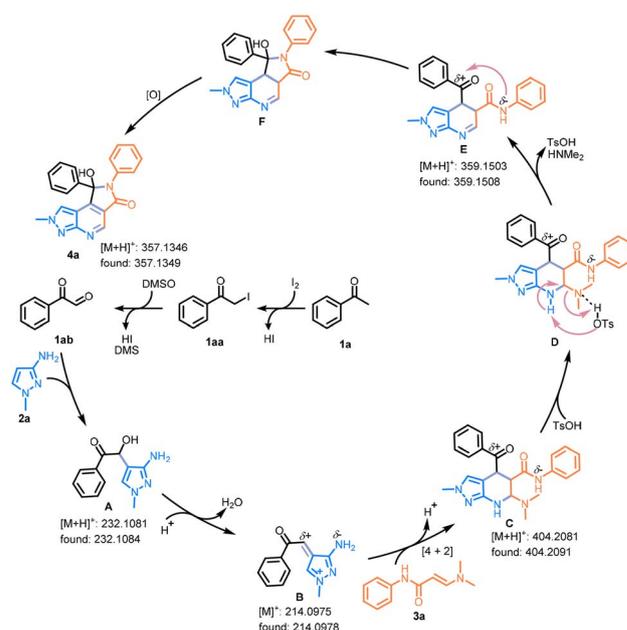
Scheme 5 Proposed mechanism.

leading to the formation of the intermediate **C**. Next, in the presence of TsOH, **C** undergoes the removal of dimethylamine, affording **E**. Intramolecular nucleophilic cyclization of intermediate **E** generates **F**. Oxidative aromatization of intermediate **F** yields final product **4a**.

Conclusions

In summary, we developed a three-component cyclization reaction based on I$_2$-DMSO combination reagent system, which realizes the efficient construction of 2*H*-pyrazolo[3,4-*b*]pyrrolo[3,4-*d*]pyridin-6-one skeleton for the first time. It is worth noting that the skeleton contains a high-energy 2*H*-pyrazolo[3,4-*b*]pyridine moiety. This method features metal-free catalysis and broad substrate compatibility. In addition, two C–C bonds, two C–N bonds, and a tetrasubstituted carbon stereocenter with a reactive hydroxyl group were constructed. Further research on the synthesis of nitrogen-containing condensed heterocycles using enaminamides based on domino cascade reactions is ongoing in our laboratory.

Author contributions

Y.-M. Song, Y.-D. Wu and A.-X. Wu conceived and designed the experiments. Y.-M. Song carried out the experiments. All the authors interpreted the results and cowrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI.

CCDC 2423210 contains the supplementary crystallographic data for this paper.[10]

General procedure for the synthesis of **2**, **3**, **4**, **7**, **9**, detailed mechanistic studies, 1H and 13C NMR data for **4**, **5**, **7**, **9** and **10** and copies of the spectra. See DOI: https://doi.org/10.1039/d5ra04871k.

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Notes and references

1 (*a*) S. P. Rekowski, B. K. Kroener, D. Kathuria, A. A. Wani, S. S. Chourasiya, J. Conrad, P. V. Bharatam, W. Frey and U. Beifuss, *Tetrahedron*, 2021, **91**, 132192; (*b*) S. Diab, P. Li, S. K. Basnet, J. Lu, M. Yu, H. Albrecht, R. W. Milne and S. Wang, *Future Med. Chem.*, 2016, **8**, 271–285; (*c*) Q. Ye, Y. Shen, Y. Zhou, D. Lv, J. Gao, J. Li and Y. Hu, *Eur. J. Med. Chem.*, 2013, **68**, 361–371; (*d*) P. M. Lukasik, S. Elabar, F. Lam, H. Shao, X. Liu, A. Y. Abbas and S. Wang, *Eur. J. Med. Chem.*, 2012, **57**, 311–322; (*e*) B. M. Lynch, M. A. Khan, H. C. Teo and F. Pedrotti, *Can. J. Chem.*, 1988, **66**, 420–428; (*f*) S. L. Wang, Y. P. Liu, B. H. Xu, X. H. Wang, B. Jiang and S. J. Tu, *Tetrahedron*, 2011, **67**, 9417–9425.

2 (*a*) M. El-borai, H. Rizk, M. Abd-Aal and I. El-Deeb, *Eur. J. Med. Chem.*, 2012, **48**, 92–96; (*b*) D. B. Kendre, R. B. Toche and M. N. Jachak, *Tetrahedron*, 2007, **63**, 11000–11004; (*c*) Y. T. Tao, C. H. Chuen, C. W. Ko and J. W. Peng, *Chem. Mater.*, 2002, **14**, 4256–4261.

3 (*a*) T. C. Mendes, J. M. Raimundo, N. M. Nascimento-Junior, C. A. Fraga, E. J. Barreiro, R. T. Sudo and G. Zapata-Sudo, *Pharmacol., Biochem. Behav.*, 2009, **94**, 70–74; (*b*) H. Möhler, F. Crestani and U. Rudolph, *Curr. Opin. Pharmacol.*, 2001, **1**, 22–25.

4 (*a*) R. Menegatti, G. M. Silva, G. Zapata-Sudo, J. M. Raimundo, R. T. Sudo, E. J. Barreiro and C. A. Fraga, *Bioorg. Med. Chem.*, 2006, **14**, 632–640; (*b*) N. M. Nascimento-Júnior, T. C. Mendes, D. M. Leal, C. M. N. Corrêa, R. T. Sudo, G. Zapata-Sudo, E. J. Barreiro and C. A. Fraga, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 74–77.

5 J. Hill, M. Tandon, N. Namdev, R. Palma, N. Westlund and A. Filikov, US 20100249120, 2010.

6 C. C. Tseng, C. Y. Chung, S. E. Tsai, H. Takayama, N. Uramaru, C. Y. Lin and F. F. Wong, *Molecules*, 2020, **25**, 2409.

7 (*a*) J. Quiroga, A. Valencia, A. Perez, J. Galvez, R. Abonia and B. Insuasty, *Lett. Org. Chem.*, 2013, **10**, 337–341; (*b*) L. Y. Wang, N. Uramaru and F. F. Wong, *Tetrahedron*, 2014, **70**, 7439–7444; (*c*) W. P. Yen, P. L. Liu, N. Uramaru, H. Y. Lin and F. F. Wong, *Tetrahedron*, 2015, **71**, 8798–8803; (*d*) A. Díaz-Ortiz, A. de la Hoz and F. Langa, *Green Chem.*, 2000, **2**, 165–172.

8 For selected examples, see: (*a*) Y. Han, L. Zhou, C. Wang, S. Feng, R. Ma and J. P. Wan, *Chin. Chem. Lett.*, 2024, **35**, 108977; (*b*) Y. Guo, Y. Xiang, L. Wei and J. P. Wan, *Org. Lett.*, 2018, **20**, 3971–3974; (*c*) J. P. Wan, Y. Zhou, Y. Liu and S. Sheng, *Green Chem.*, 2016, **18**, 402–405; (*d*) X. Li, Z. Chen, W. Chen, X. Xie, H. Zhou, Y. Liao, F. Yu and J. Huang, *Org. Lett.*, 2022, **24**, 7372–7377; (*e*) J. Zeng, J. P. Wan and Y. Liu, *J. Org. Chem.*, 2025, **90**, 7540–7545; (*f*) C. Wang, Y. Liu and J. P. Wan, *Org. Lett.*, 2025, **27**, 3983–3987; (*g*) Z. Zhong, Y. Liu, L. Liao and J. P. Wan, *Org. Lett.*, 2025, **27**, 2537–2541; (*h*) Z. Zhang, Y. Xu, M. Peng, S. Song, Y. Wei, H. Hu, X. Wang and F. Yu, *Chem. Commun.*, 2024, **60**, 14968–14971; (*i*) Y. Xie, Z. Zhang, B. Zhang, N. He, M. Peng, S. Song, B. Wang and F. Yu, *J. Org. Chem.*, 2024, **89**, 8521–8530.

9 For selected examples, see: (*a*) L. S. Wang, J. C. Xiang and A. X. Wu, *Chem. Commun.*, 2024, **60**, 12803–12815; (*b*) Y. X. Tang and A. X. Wu, *Tetrahedron*, 2024, **166**, 134210; (*c*) D. S. Yang, X. L. Chen and A. X. Wu, *Org. Chem. Front.*, 2024, **11**, 2665–2692; (*d*) X. Shen, Z. Yu, Y. Zhou, Y. Wu and A. Wu, *Adv. Synth. Catal.*, 2024, **366**, 4399–4403; (*e*)

Y. Zhou, S. G. Lei, B. Abudureheman, L. S. Wang, Z. C. Yu, J. C. Xiang and A. X. Wu, *Nat. Commun.*, 2024, **15**, 10907; (*f*) X. Guo, M. Miao, P. Zhao and Y. Ma, *Chin. J. Chem.*, 2025, **43**, 1009–1014; (*g*) L. S. Wang, Y. M. Song, Y. Zhou, Y. X. Tang, C. Y. Wu, Z. C. Yu, H. Zhou, K. L. Zheng and A. X. Wu, *Org. Lett.*, 2024, **27**, 91–96; (*h*) Y. Zhou, L. S. Wang, S. G. Lei, B. C. Tang, Z. C. Yu, X. Li, Y. D. Wu, K. L. Zheng and A. X. Wu, *Chin. Chem. Lett.*, 2025, **36**, 109799; (*i*) Y. Zhou, L. S. Wang, S. G. Lei, Y. X. Gao, J. T. Ma, Z. C. Yu, Y. D. Wu and A. X. Wu, *Org. Chem. Front.*, 2022, **9**, 4416–4420; (*j*) W. Zuo, Y. Cheng, Z. Zhu, L. Zuo, X. Geng, Z. Li and L. Wang, *Chin. J. Chem.*, 2024, **42**, 2346–2350; (*k*) S. G. Lei, Y. Zhou, L. S. Wang, Z. C. Yu, T. Chen, Y. D. Wu, M. Gao and A. X. Wu, *J. Org. Chem.*, 2023, **88**, 11150–11160; (*l*) S. G. Lei, Y. Zhou, L. S. Wang, Z. C. Yu, T. Chen, Y. D. Wu, M. Gao and A. X. Wu, *Org. Chem. Front.*, 2023, **10**, 4843–4847; (*m*) Y. X. Tang, S. Y. Zhuang, J. Y. Liu, Y. Zhou, L. S. Wang, Y. D. Wu and A. X. Wu, *Org. Chem. Front.*, 2023, **10**, 4080–4085; (*n*) Q. Gao, S. He, X. Wu, J. Zhang, S. Bai, Y. Wu and A. Wu, *Org. Chem. Front.*, 2018, **5**, 765–768.

10 Y. M. Song, L. S. Wang, Y. Zhou, Y. X. Tang, C. Y. Wu, Y. D. Wu and A. X. Wu, CDDC 2423210: Experimental Crystal Structure Determination, 2024, DOI: **10.5517/ccdc.csd.cc2mbk2m**.