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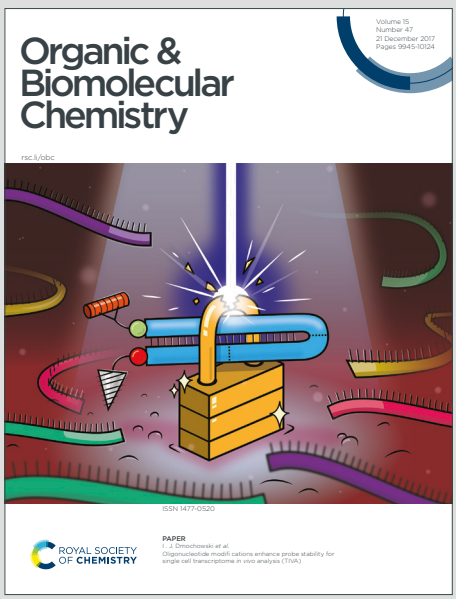

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Tf_2O-activated modular assembly of tetrasubstituted alkenes

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A novel, efficient multicomponent strategy for constructing tetrasubstituted alkenes bearing both C(sp^2)-S and C(sp^2)-N bonds has been developed, utilizing Tf_2O-mediated activation of 1,3-diketones and featuring high stereoselectivity and broad substrate compatibility.

Tetrasubstituted alkenes constitute a privileged structural motif prevalent in natural products, pharmaceuticals, and functional materials due to their versatile reactivity and stereochemical complexity.[1-6] Particularly, α-sulfenylated enaminones—a subclass tetrasubstituted alkenes featuring both C(sp^2)-S and C(sp^2)-N bonds—have emerged as pivotal scaffolds in medicinal chemistry.[7-9] Exemplifying their significance, cyclic thioenamine-containing peptides[7] exhibit enhanced binding affinity through the α-thioenamine motif, and small-molecule therapeutics such as Cdc25B phosphatase inhibitors[8] and U0126[9], a clinically relevant MEK inhibitor (Fig 1a).

Despite the well-established sulfenylation of β-ketoesters,[10-12] conventional synthesis strategies for α-sulfenylated enaminones predominantly employ prefunctionalized enaminones as precursors.[13-17] In addition, Monfared and Khalili recently achieved direct sulfenylation of enaminoesters using dialkyl acetylenedicarboxylates,[18] while Müller and coworkers developed an alternative approach via alkyne functionalization, albeit requiring a three-step cascade[19] (Fig 1b). Despite these improvements, the synthesis of α-sulfenylated enaminones remains a significant challenge in synthetic organic chemistry.

The emergence of triflic anhydride (Tf_2O)-mediated carbonyl activation has revolutionized modern synthetic methodology.[20-26] This approach enables the generation of highly reactive sulfonate ester intermediates from carbonyl compounds, facilitating subsequent diverse transformations. Representative work includes the study by Xie, Zhu, and Xue,[27] which demonstrated a photoredox/Ni dual-catalyzed synthesis of all-carbon tetrasubstituted alkenes using carboxylic acids and vinyl triflates as substrates. Another seminal contribution came from Zhang and Gosselin,[28] who developed a stereoselective synthesis of all-carbon tetrasubstituted alkenes via enol sulfonate formation followed by Pd-catalyzed Suzuki-Miyaura coupling (Fig 1c).

Recently, our group has reported Tf_2O-activated transformations of imides[29] and 1,3-cyclohexanedione compounds[30]. Building on these results, we now report a novel multicomponent reaction strategy that enables the direct assembly of tetrasubstituted alkenes bearing both C(sp^2)-S and C(sp^2)-N bonds (Fig 1d). Our approach leverages Tf_2O activation of 1,3-diketones in conjunction with electrophilic sulfur sources and sulfonamides. This strategy not only circumvents the need for prefunctionalized substrates but also achieves exceptional stereocontrol, delivering products with defined configurations.

Optimization studies were conducted with the model reaction between *p*-toluenesulfonamide (**1a**), acetylacetone (**2a**), and sulfur sources (**3**) in a one-pot system. Selected conditions are shown in the table 1, and more optimization details are provided in the Supporting Information. Initially, we screened various sulfur sources. As shown in Table 1, nucleophilic *p*-bromothiophenol (**3c**) and diphenyl disulfide (**3d**) failed to produce the desired product. Among electrophilic sulfur sources, *N*-thiosuccinimide (**3a**) afforded the product in 69% yield, while other electrophilic sulfur sources (**3b**) showed significantly lower reactivity (10% yield).

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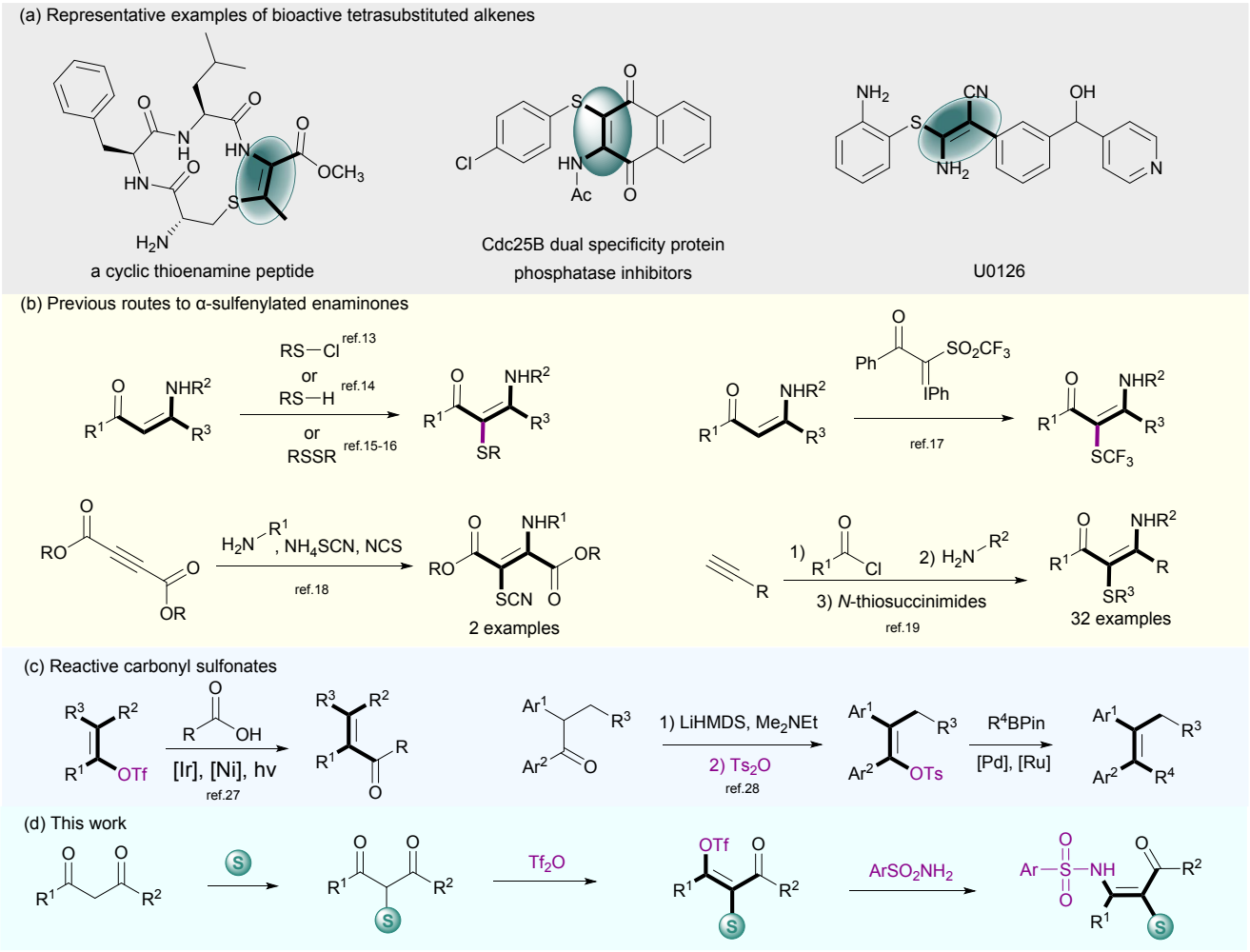

Fig. 1 Introduction.

Subsequently, various Lewis acids were investigated (entries 2-6). The results indicated that no product was observed, except for TMSOTf which afforded the product in low yield (17%). Further optimization of Tf_2O loading demonstrated that the reaction proceeded with only trace amounts of product in the absence of Tf_2O (entries 7). After systematic optimization, the optimal reaction conditions were established as acetonitrile solvent at 80 °C for 5 hours with 1.5 equivalents of Tf_2O, affording the product in 69% isolated yield (entry 1).

To gain further insight into the mechanism of this multicomponent reaction, a series of experiments were conducted (Fig. 2). Initial observations revealed the formation of 3-arylthio-2,4-dione **5** during the reaction process. When independently synthesized **5** was subjected to standard conditions, target product **4a** was obtained in yields consistent with the model reaction (Fig. 2a), suggesting its potential role as a reaction intermediate. Notably, control experiments demonstrated that omission of Tf_2O drastically reduced the yield to merely 8%, underscoring its critical role in facilitating the transformation. Building upon literature precedents[14,16], we explored the possibility of *N*-vinylsulfonamide **6** as an alternative intermediate. However, when pre-synthesized **6** was subjected to reaction conditions, no conversion to **4a** was observed (Fig. 2b), effectively ruling out this pathway. Furthermore, the reaction in the presence of TEMPO (2.0 equiv.) or BHT (2.0 equiv.) gave a yield of **4a** similar to that of the reaction under standard conditions, excluding the possibility of a radical pathway[14-16] in the reaction.

Based on these experimental results and supported by literature reports[22,23], we propose the following mechanistic pathway (Fig. 2): The reaction initiates with tautomerization of acetylacetone **2a** to form enol **INT1**, which undergoes

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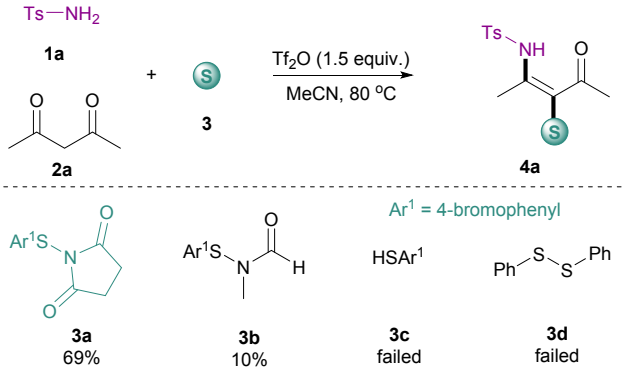
Table 1 Selected optimization of reaction conditions.[a]



Entry	Changes from standard conditions	Yield[b]
1	**None**	**69%**
2	$BF_3{\cdot}Et_2O$	N. D.
3	$CoCl_2$	N. D.
4	I_2	N. D.
5	TMSOTf	17%
6	$ZnCl_2$	N. D.
7	absence of Tf_2O	Trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.3 mmol), Tf_2O (0.3 mmol), MeCN (3.0 mL), 80 °C, 5 h, air atmosphere. [b] isolated yield. N. D. = not detected.

nucleophilic attack on the sulfur atom of *N*-thiosuccinimide **3**, concomitant with succinimide elimination to yield 3-arylthio-2,4-dione intermediate **INT2**. Then, **INT2** is activated by Tf_2O, resulting in the formation of thioenyl triflate **INT3** with concomitant elimination of TfOH. Subsequently, **INT3** reacts with the sulfonamide to form adduct **INT4**, which undergoes proton migration followed by elimination to ultimately yield (*E*)-α-sulfenylated enaminones products.

Under the optimized reaction conditions, we first examined the substrate scope of 1,3-diketones (Fig. 3). The screening revealed that the reaction proceeded smoothly with a diverse range of R^1 and R^2 substituents, including alkyl and alkoxy groups (**4a–4e**). Notably, alkene functional group (**4b**) exhibited excellent compatibility with this transformation. However, simple ketones such as acetone, 2-butanone, 3-pentanone, and 3-oxobutyronitrile failed to afford the desired products. We hypothesize that the enhanced nucleophilicity of the active methylene group in 1,3-diketones is crucial for the successful progression of the reaction.

Subsequently, we investigated the scope of sulfonamide substrates. As shown in Fig. 3, a wide array of sulfonamides incorporating both electron-donating and electron-withdrawing groups exhibited significant reactivity (**4f–4z**). The exact structure of **4g** was determined by X-ray analysis. Additionally, ortho-, meta-, and para-substituted sulfonamides all participated effectively in the reaction, affording the desired products in moderate to excellent yields, indicating minimal positional influence on reactivity (**4f–4v**).

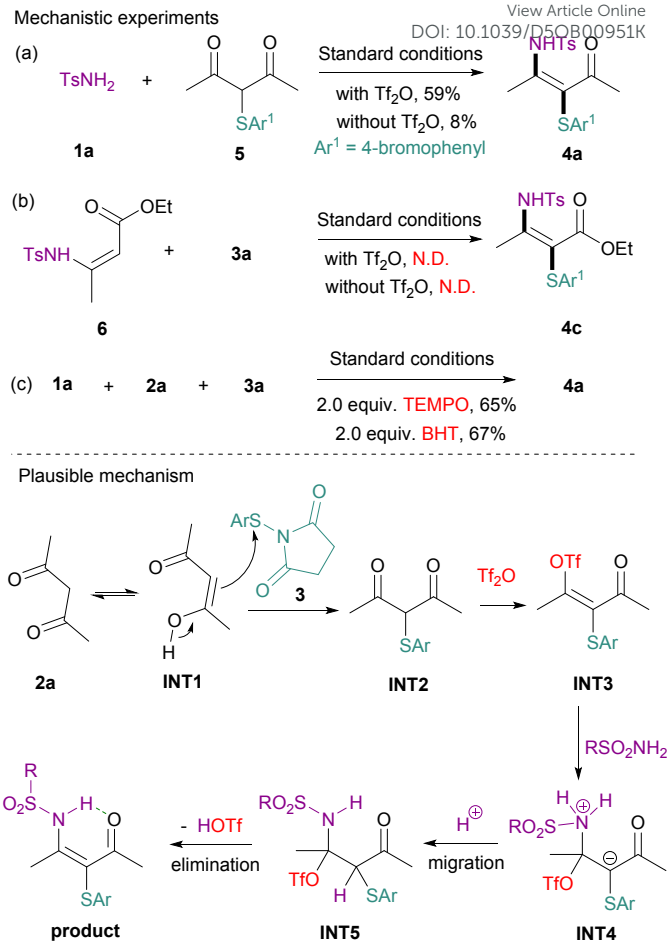


Fig. 2 Mechanistic experiments and plausible mechanism

A broad range of functional groups were well tolerated, including ethers (**4u**), nitro groups (**4q** and **4t**), bromides (**4o**), chlorides (**4j**, **4x**), fluorides (**4i**, **4n**, **4p**, and **4q**), aliphatic halides (**4k**, **4l**, and **4u**), esters (**4k**, **4l**), trifluoromethyl groups (**4h**, **4s**, and **4z**), and trifluoromethoxy groups (**4r**). Polysubstituted sulfonamides also reacted efficiently (**4p**, **4q**), as did various aromatic systems, including naphthalene and bioactive thiophene derivatives (**4m**, **4w**, **4x**).

To our delight, this approach successfully enabled late-stage derivatizations of pharmaceutical sulfonamides (**4y**, **4z**), as demonstrated by modifications of Zonisamide (an antiepileptic drug), and Celecoxib (NSAIDs).

Finally, we examined the scope of *N*-thiosuccinimides. The reaction proceeded smoothly with substituents at different ortho-, meta-, and para-positions (**4a**, **4aa–4ac**), and the structure of **4aa** was further confirmed by X-ray analysis. Moreover, *N*-Thiosuccinimides bearing moderately electron-withdrawing halogen groups demonstrated moderate to good reactivity (**4a**, **4aa–4ac**). However, substrates with electron-donating substituents failed to undergo the reaction (**3h–3j**). These results further support the role of *N*-thiosuccinimides as electrophiles in this reaction system.

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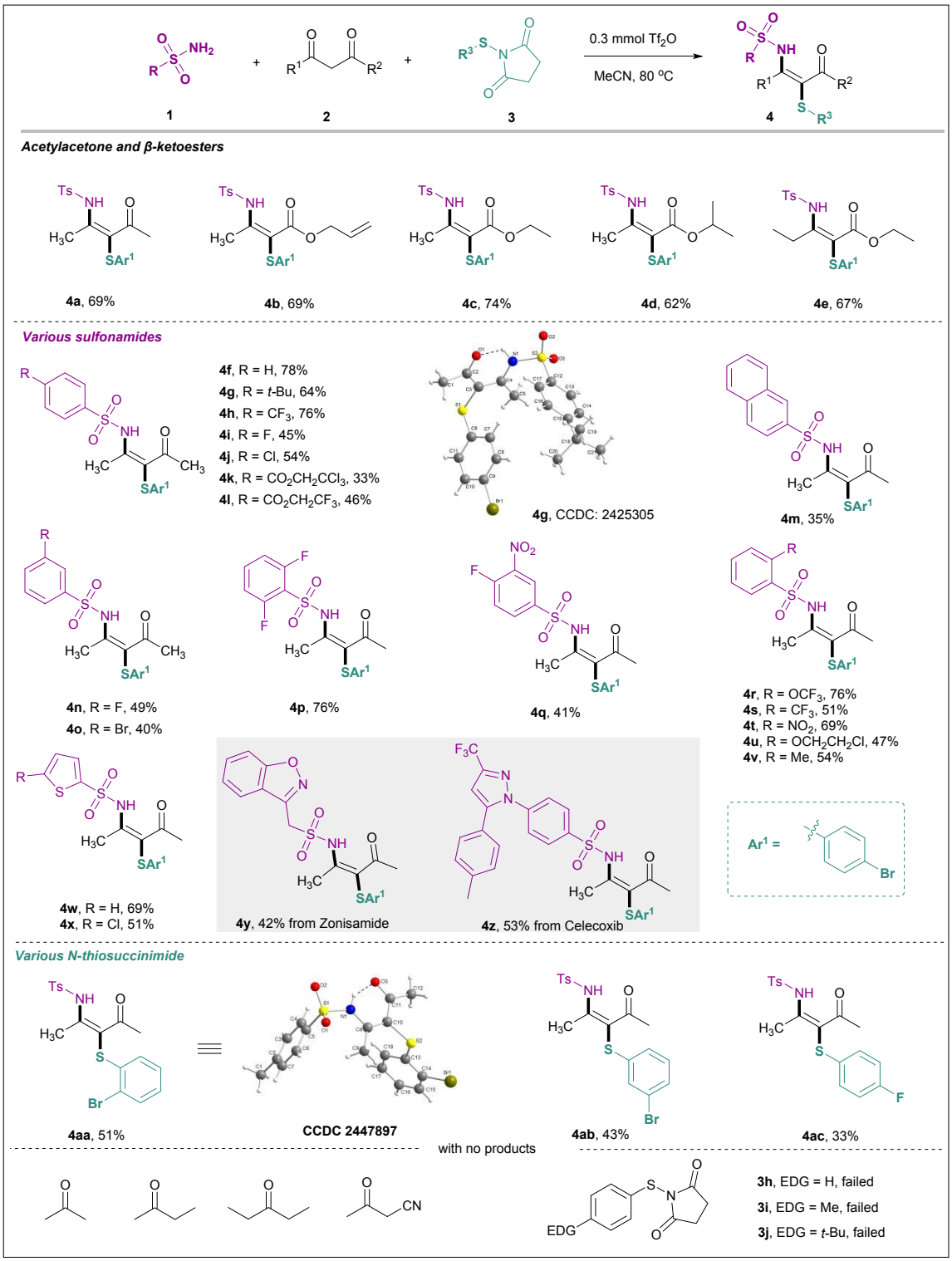

Fig. 3 Substrate scope. Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.3 mmol), Tf_2O (0.3 mmol), MeCN (3.0 mL), under air at 80 °C for 5 h, isolated yield.

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Conclusions

This work introduces a novel multicomponent reaction strategy for synthesizing tetrasubstituted alkenes with C(sp^2)-S and C(sp^2)-N bonds via Tf_2O activation of 1,3-diketones in the presence of electrophilic sulfur sources and sulfonamides. The method eliminates the need for prefunctionalized substrates while demonstrating excellent stereocontrol and compatibility with diverse functional groups, including pharmaceutical motifs. The practicality and scalability of this approach make it a promising tool for accessing structurally complex alkenes with potential applications in drug development and materials innovation.

Author contributions

X. W. conceived and supervised the project. W. Y., Y. C., X. L., Y. H. and Y. Z. performed the experiments and developed the reactions. X. W. wrote the manuscript with feedback from all authors. All authors analyzed the results and commented on the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

The data that support the findings of this study are available in the Supporting Information of this article.

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Notes and references

1 R. K. Vander Meer, F. D. Williams and C. S. Lofgren, *Tetrahedron Lett.*, 1981, **22**, 1651–1654.
2 A. Takahashi, Y. Kirio, M. Sodeoka, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1989, **111**, 643–647.
3 M. R. Becker, R. B. Watson and C. S. Schindler, *Chem. Soc. Rev.*, 2018, **47**, 7867–7881.
4 M. L. Beer, J. Lemon and J. F. Valliant, *J. Med. Chem.*, 2010, **53**, 8012–8020.
5 A. Schreivogel, J. Maurer, R. Winter, A. Baro and S. Laschat, *Eur. J. Org. Chem.*, 2006, **2006**, 3395–3404.
6 A. Schultz, S. Laschat, S. Diele and M. Nimtz, *Eur. J. Org. Chem.*, 2003, **2003**, 2829–2839.
7 D. Pappo and Y. Kashman, *Org. Lett.*, 2006, **8**, 1177–1179.
8 J. S. Lazo, K. Nemoto, K. E. Pestell, K. Cooley, E. C. Southwick, D. A. Mitchell, W. Furey, R. Gussio, D. W. Zaharevitz, B. Joo and P. Wipf, *Mol. Pharmacol.*, 2002, **61**, 720–728.
9 J. Wityak, F. W. Hobbs, D. S. Gardner, J. B. Santella, 3rd, J. J. Petraitis, J. H. Sun, M. F. Favata, A. J. Daulerio, K. Y. Horiuchi, R. A. Copeland, P. A. Scherle, B. D. Jaffe, J. M. Trzaskos, R. L. Magolda, G. L. Trainor and J. V. Duncia, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1483–1486.
10 Y. Wang, H. Zhou, K. Yang, C. You, L. Zhang and S. Luo, *Org. Lett.*, 2019, **21**, 407-411.
11 Y. Jiang, J.-X. Zou, L.-T. Huang, X. Peng, J.-D. Deng, L.-Q. Zhu, Y.-H. Yang, Y.-Y. Feng, X.-Y. Zhang and Z. Wang, *Org. Biomol. Chem.*, 2018, **16**, 1641-1645.
12 L. Fang, A. Lin, H. Hu and C. Zhu, *Chem. Eur. J.*, 2009, **15**, 7039-7043.
13 E. Korkmaz and M. Zora, *J. Org. Chem.*, 2020, **85**, 4937–4950.
14 J. P. Wan, S. Zhong, L. Xie, X. Cao, Y. Liu and L. Wei, *Org. Lett.*, 2016, **18**, 584–587.
15 J. Sun, D. Zhang-Negrerie and Y. Du, *Adv. Synth. Catal.*, 2016, **358**, 2035–2040.
16 B. Hu, P. Zhou, K. Rao, J. Yang, L. Li, S. Yan and F. Yu, *Tetrahedron Lett.*, 2018, **59**, 1438–1442.
17 Y. D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro and N. Shibata, *J. Am. Chem. Soc.*, 2013, **135**, 8782–8785.
18 A. Monfared, G. Khalili, *Monatsh. Chem.*, 2022, **153**, 1235–1241.
19 G. Hendrik Schmitz, W. Kramer, L. Karl, C. Ganter and T. J. J. Müller, *Eur. J. Org. Chem.*, 2025, **28**, e202401308.
20 W. Zawodny, C. J. Teskey, M. Mishevska, M. Völkl, B. Maryasin, L. González and N. Maulide, *Angew. Chem. Int. Ed.*, 2020, **59**, 20935-20939.
21 A. Tavakoli and G. B. Dudley, *J. Org. Chem.*, 2022, **87**, 5773-5784.
22 A. Cutler, L.-N. Chen, Z.-K. Jin, J.-L. Ye and P.-Q. Huang, *Arkivoc*, 2024, **2024**, 202412191.
23 L. Shan, Y. Weng, H. Li, L. Min, X. Wang and Y. Hu, *J. Org. Chem.*, 2022, **87**, 4124–4133.
24 Y. Lin, S. F. He, H. Geng, Y. C. Xiao, K. L. Ji, J. F. Zheng and P. Q. Huang, *J. Org. Chem.*, 2021, **86**, 5345-5353.
25 C. Bhujanga Rao, N. Zhang, J. Hu, Y. Wang, Y. Liang, R. Zhang, J. Yuan and D. Dong, *J. Org. Chem.*, 2020, **85**, 4695–4705.
26 Z. Xu, X.-G. Wang, Y.-H. Wei, K.-L. Ji, J.-F. Zheng, J.-L. Ye and P.-Q. Huang, *Org. Lett.*, 2019, **21**, 7587-7591.
27 Y. Li, Q. Shao, H. He, C. Zhu, X. S. Xue and J. Xie, *Nat. Commun.*, 2022, **13**, 10.
28 B. X. Li, D. N. Le, K. A. Mack, A. McClory, N. K. Lim, T. Cravillion, S. Savage, C. Han, D. B. Collum, H. Zhang and F. Gosselin, *J. Am. Chem. Soc.*, 2017, **139**, 10777–10783.
29 W. Ye, A. Lu, Z. Zhang, G. Lu, X. Du, Y. Wang and X. Wan, 2025, **14**, e202400600.
30 W. Ye, Y. Huang, Y. Chen, X. Liu, G. Lu and X. Wan, 2025, **367**, e202500154.

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Data Availability Statement

All data, including experimental procedures, compound characterizations and mechanistic studies are available in the main text or the Supplementary Information. Crystallographic data for compounds **4g** and **4aa** are available from the Cambridge Crystallographic Data Centre under references CCDC 2425305 and CCDC 2447897, respectively. Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/