


 Cite this: *RSC Adv.*, 2026, 16, 7702

Thiophenol-mediated metal-free chemoselective conjugate reduction strategy for 3-alkylidene oxindoles

 Baliram R. Patil,^{ab} Chandrakant B. Nichinde,^{ab} Amardipsing S. Girase,^{ab} Suryakant S. Chaudhari^{ab} and Anil K. Kinage^{ab*}

A mild and metal-free thiophenol-mediated chemoselective conjugate reduction of 3-alkylidene oxindoles via a thiol-ene-type Michael addition was effectively carried out. Thiophenol as an efficient reductant is used in DMSO, and the transformation proceeds without the need for metal catalyst, external hydrogen source, or harsh reagents. The reaction displays a broad substrate scope, accommodating both electron-donating and electron-withdrawing substituents, and delivers 3-alkyloxindoles in high yields with excellent β -selectivity. This sustainable and operationally simple method unveils a distinct thiol-mediated reduction mechanism, providing a green and versatile approach for accessing reduced oxindole derivatives and related Michael acceptors.

 Received 27th November 2025
 Accepted 30th January 2026

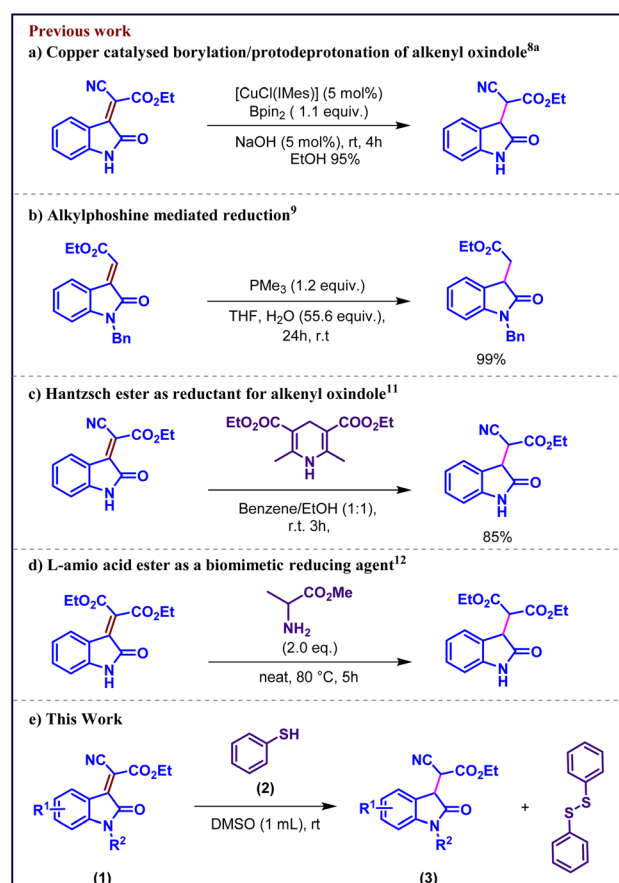
DOI: 10.1039/d5ra09175f

rsc.li/rsc-advances

Introduction

The oxindole framework represents a privileged structural motif that frequently occurs in a wide range of natural products and pharmacologically active molecules.¹ Considerable attention has been directed toward oxindole derivatives owing to their diverse biological profiles, including antioxidant,² neuroprotective,³ anticancer,⁴ and anti-HIV activities.⁵ Among these, 3-substituted oxindoles have emerged as key synthetic intermediates in the construction of spirocyclic and polycyclic heterocyclic architectures,⁶ which are prevalent in numerous bioactive natural products and therapeutic agents.⁷

Despite their importance, conventional methods for accessing 3-substituted oxindoles often rely on transition-metal-catalyzed hydrogenation or stoichiometric reductants, which limit regioselectivity, functional-group tolerance, and sustainability. The predominant approach involves selective reduction of the conjugated C=C bond in 3-alkylidene oxindoles. Classical strategies include metal-catalyzed hydrogenation (Scheme 1a),⁸ alkylphosphane-mediated reductions (Scheme 1b)⁹ and biocatalytic processes utilizing baker's yeast or *Pseudomonas* strains.¹⁰ In recent years, biomimetic and photoredox systems have emerged as alternative methods, employing Hantzsch esters (Scheme 1c),¹¹ L-amino acid esters (Scheme 1d),¹² and visible-light-driven photoredox catalysis using formate donors or Eosin Y.¹³ However, these transformations often suffer from inherent limitations such as harsh reaction conditions, use of



Scheme 1 Background and synopsis of the present work.

^aChemical Engineering and Process Development Division, CSIR-National Chemical Laboratory, Pune, 410008, India. E-mail: ak.kinage.ncl@csir.res.in

^bAcademy of Scientific and Innovative Research (AcSIR), Ghaziabad-201 002, India


aggressive or expensive reagents, limited substrate scope, and challenging purification due to the generation of byproducts.

Within this domain, the selective reduction of conjugated alkenes continues to be of substantial research interest. Despite notable advances in chemoselective reduction methodologies, the thiol-mediated reduction of conjugated alkenes in oxindole systems remains unexplored, presenting an opportunity to develop a mild, sustainable, and metal-free reductive strategy.

As we are working on the functionalization of oxindole moiety¹⁴ extending that, herein we disclose a mild and chemoselective thiophenol mediated reduction of oxindole-derived conjugated alkenes, providing straightforward access to 3-substituted oxindoles under metal-free conditions. This approach circumvents the disadvantages of metal-based systems and harsh reductants by taking advantage of the Michael addition of thiols to electron-deficient double bonds, providing a sustainable substitute for the production of medicinally significant oxindole derivatives.

Results and discussion

We initiate our study by examining the reaction of thiophenol with isatylidene cyanoester **1A** in ethanol, anticipating the formation of a thia-Michael addition product. Remarkably, instead of the expected adduct, the reaction predominantly afforded the reduced product **3Aa** via a selective conjugate C=C bond reduction pathway, corresponding product **3Aa** is isolated as a mixture of diastereomers. The formation of 1,2-diphenyldisulfane **4** as a byproduct was also observed and confirmed by NMR analysis (Table 1, entry 1). Encouraged by this unexpected reactivity, we subsequently investigated the generality of the transformation using a series of isatin derived Michael acceptors.

To verify the essential role of thiophenol, the reaction was performed in absence thiophenol no conversion of the starting material **1A** was observed, and the substrate remained intact throughout the reaction course, indicating that thiophenol is crucial for initiating the reduction process (Table 1, entry 2). Subsequently, the influence of different solvents on the efficiency of the transformation was investigated. Among the solvents examined, DMSO provided the best yield of the desired reduced product with 1 : 1 *dr* ratio (Table 1, entries 3–10). The study on the effect of thiophenol loading revealed that the reaction exhibited equal efficiency with increase loading of thiophenol up to 3 equiv. and time of reaction also decrease effectively while reducing loading of thiophenol to 1 equiv. reduced yielding up to 30% and also increase reaction time (Table 1, entry 11 and 12). To assess the effect of substituents on thiophenol, a series of derivatives (**2a–2i**) were evaluated under the optimized conditions. Halogen-substituted thiophenols demonstrated enhanced reactivity, with 4-bromothiophenol (**2b**) providing the reduced product in excellent yield within 1 h. While thiophenols bearing electron-donating groups such as amino, methoxy, or methyl substituents exhibited significantly lower reactivity, affording the corresponding products in poor to moderate yields. No reaction occurred with thioanisole (**2i**), confirming that the S–H proton of thiophenol is essential for

Table 1 Optimization of reaction conditions^a

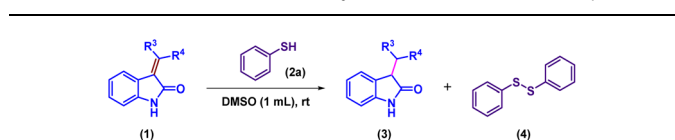
Entry	2 (equiv.)	Solvent (1 mL)	Time (h)	Yield ^b (%)
1	2a (2.0)	EtOH	5	35
2	—	DMSO	24	n.d.
3	2a (2.0)	DMF	5	45
4	2a (2.0)	DCE	3	62
5	2a (2.0)	ACN	6	Trace
6	2a (2.0)	THF	6	Trace
7	2a (2.0)	DCM	3	60
8	2a (2.0)	DMSO	1	92
9	2a (2.0)	H ₂ O	8	n.d.
10	2a (2.0)	Toluene	3	55
11 ^c	2a (3)	DMSO	0.5	92
12 ^d	2a (1.0)	DMSO	3	30
13	2b (2.0)	DMSO	1	92
14	2c (2.0)	DMSO	1.5	88
15	2d (2.0)	DMSO	1.5	85
16	2e (2.0)	DMSO	2.5	63
17	2f (2.0)	DMSO	2.5	72
18	2g (2.0)	DMSO	5	<20
19	2h (2.0)	DMSO	5	<20
20	2i (2.0)	DMSO	12	n.d.
21	2j (2.0)	DMSO	12	n.d. ^e

^a Unless otherwise noted, a mixture of **1** (0.3 mmol, 1 equiv.) **2** (0.6 mmol, 2 equiv.) in DMSO (1 mL) stirred continuously till get formation of **3**. ^b Isolated yield of two diastereomers. ^c **2a** (0.9 mmol, 3 equiv.). ^d **2a** (0.3 mmol, 1 equiv.); n. d. = not detected. ^e Only thio-Michael addition product was observed.

the conjugate reduction (Table 1, entry 13–20). We further evaluated the feasibility of the reaction with an aliphatic thiol; however, only the thio-Michael adduct was observed instead of the desired reduction (Table 1, entry 21).

With initial results in hand, we check efficiency of reaction with different alkylidene oxindole with substituents at the *R*³ and *R*⁴ positions summarizes in Table 2. Substrates **1A** and **1B**, containing strongly electron-withdrawing groups at these positions, displayed the highest reactivity, affording the corresponding products in comparable yields within 1 h (Table 2, entries 1–2). In contrast, substrate **1C**, bearing a weak electron-withdrawing substituent, required a longer reaction time 3 h and furnished product **3C** in lower yield compared to **3A** and **3B**. Replacement of the electron-withdrawing group at *R*³ with hydrogen (**1D**) led to a significant decrease in reaction rate 6 h and yield. Moreover, substrates bearing electron-donating substituents at *R*³ and *R*⁴ showed negligible conversion, and the reduced product **3E** was not formed.



Table 2 Reduction of different alkylidene oxindole with thiophenol^a

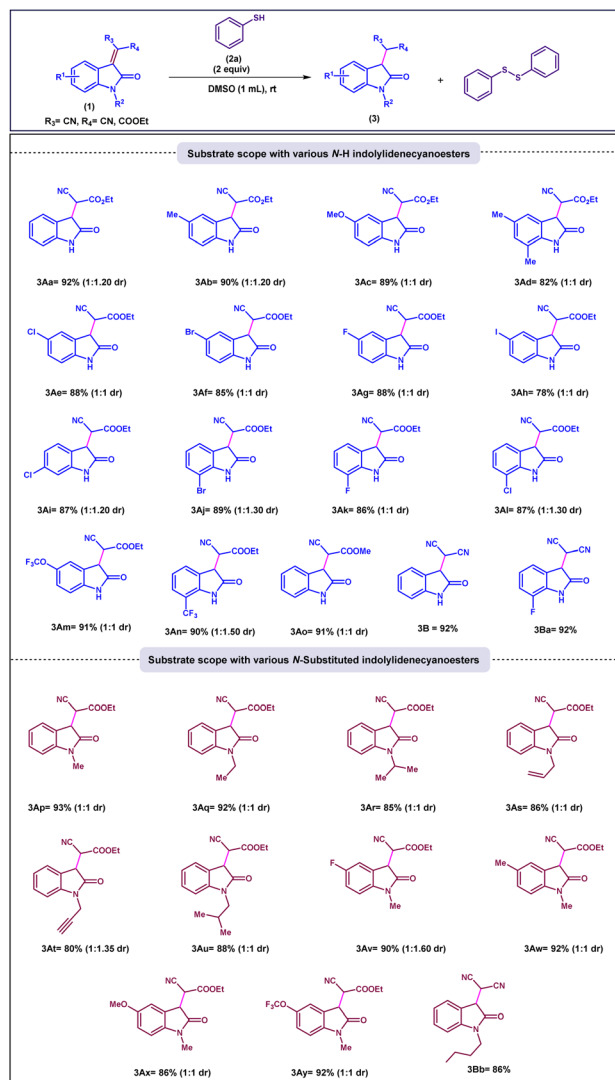
Entry	Substrate	Product	R ³	R ⁴	Yield ^b (%)
1	1A	3Aa	CN	COOEt	90 ^c
2	1B	3B	CN	CN	92
3	1C	3C	COOEt	COOEt	74
4	1D	3D	H	COOEt	56
5	1E	3E	Me	Me	N. R

^a Unless otherwise noted, a mixture of **1** (0.3 mmol, 1 equiv.), thiophenol (0.6 mmol, 2.0 equiv.) in DMSO (1 mL) was stirred at rt up to the formation of products **3**. ^b Isolated yield of products **3**. ^c 1:1 Diastereomeric mixture of product. N. R = No Result.

Among all tested substrates (**1A–1D**), **1A** proved to be the most reactive isomer under the optimized conditions, though without notable enhancement in yield or diastereomeric ratio (Table 2, entries 1–5).

With the optimized reaction condition established, the substrate scope of indolydene cyanoesters bearing various substituents was systematically investigated to assess the generality of the transformation. Initially, substrates featuring electron-donating groups such as 5-Me, 5-OMe, and 5,7-DiMe were examined. These substrates underwent smooth conversion to afford the corresponding reduced products (**3Ab–3Ad**) in good to excellent yields, although the reactions provided diastereoselectivity with an approximate *dr* of 1:1. Encouraged by these results, the influence of halogen substituents at different positions of the indole ring (5-, 6-, and 7-) was explored. Substrates bearing halogens such as 5-Cl, 5-Br, and 5-F demonstrated enhanced reactivity, delivering products (**3Ai–3Ak**) in good to excellent yields. In contrast, the 5-I derivative (**3Ah**) displayed sluggish reactivity, affording a comparatively lower yield (78%), likely due to steric and electronic effects associated with the larger iodine atom. Further evaluation of the 6- and 7-halogen-substituted derivatives revealed excellent reactivity and yields (86–89%), with diastereomeric ratios reaching up to 1:1.3 (**3Ai–3Al**). Interestingly, indolydene cyanoesters substituted with electron-withdrawing groups such as 5-OCF₃ and 7-CF₃ exhibited markedly enhanced reactivity, providing the desired products (**3Am, 3An**) in higher yields (90–91%) compared to their electron-donating counterparts (Scheme 2).

Under the optimised reaction condition, the substrate scope was expanded to various *N*-substituted indolydene cyanoester derivatives, such as *N*-methyl, *N*-ethyl, *N*-isopropyl, *N*-propargyl, *N*-isobutyl and all these tolerated well and afforded the corresponding products with high to excellent yield and *dr* up to 1:1.4 (**3Ap–3Au**). Additionally, the optimised reaction condition also work well for derivatives from **3Av** to **3Ay** which are substituted on both aromatic ring as well as *N*-substitution and also provided desired product in excellent yields (86–92%) and

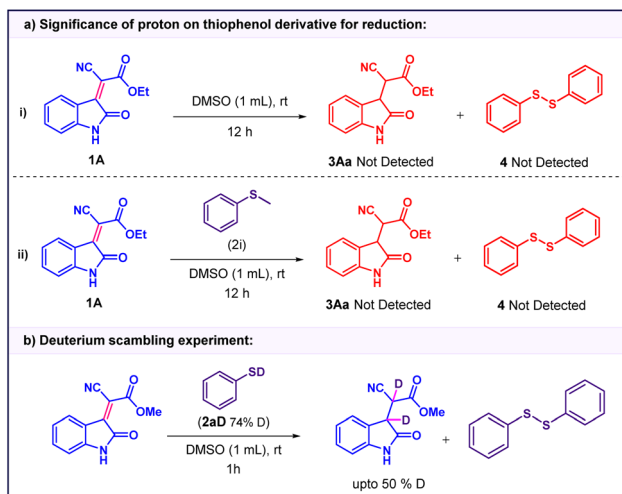


Scheme 2 Substrate scope. Reaction condition: mixture of **1** (0.3 mmol, 1 equiv.) and **2a** (0.6 mmol, 2 equiv.) are stirred continuously till get formation of **3** checked by TLC. Isolated yield of two diastereomers, *dr* of product calculated by ¹H NMR of product.

dr up to 1:1.6 (**3Av–3Ay**). Further, isatylidene malonitrile derivatives were employed under the optimised conditions the corresponding products were obtained with good yield (**3B, 3Ba, 3Bb**).

To identify the hydrogen source responsible for the reduction, a series of control experiments were performed. As indicated in the optimization studies, thiophenol is essential for the reaction, as no product formation was observed in its absence. To probe the role of the thiol proton, thioanisole (**2i**) in which the S–H proton of thiophenol is replaced by a methyl group (S–Me) was employed under identical conditions. In this case, the starting material remained unreacted, and no formation of the reduced product or 1,2-diphenyldisulfane was detected (Scheme 3a), confirming that the S–H bond of thiophenol is crucial for the reduction process. To gain deeper mechanistic insight, an isotopic scrambling experiment was subsequently conducted

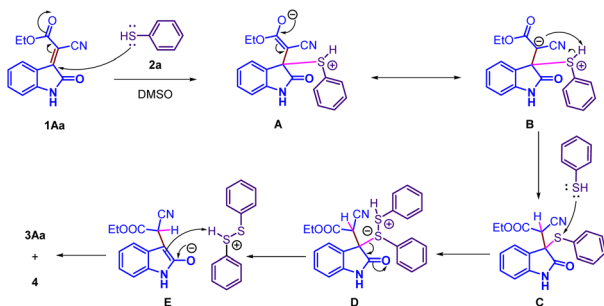




Scheme 3 Control experiments.

using deuterated thiophenol (**2aD**) (<75% D), enabling direct verification of the thiol proton's participation as the hydrogen donor in the transformation. Under the standard reaction conditions to afford the crude product **3Aa** up to 91% yield with up to 50% D contents by ^1H NMR (Scheme 3b). This isotope labelling experiments clearly indicate that the source of proton is only thiophenol (S–H) in reduction reaction.

Based on previous literature precedents on thia-Michael reactions¹⁵ and our control experiments, we propose a plausible mechanism for the thiophenol-mediated, metal-free conjugate reduction of 3-alkylidene oxindoles. The transformation proceeds *via* a thiol-ene-type Michael addition-elimination sequence. Under the reaction conditions, thiophenol undergoes chemoselective nucleophilic attack at the C3-position of the 3-alkylidene oxindole, affording the thio-Michael adduct **C** *via* intermediate **B**. The pronounced polarization of the α , β -unsaturated system adjacent to the electron-withdrawing carbonyl group ensures high chemoselectivity in this conjugate addition step. Subsequent proton transfer furnishes the β -thiolated intermediate, which, in the presence of excess thiophenol, undergoes β -elimination or hydride transfer to expel the diphenyl disulfide (**4**) moiety and generate the reduced C–H bond (**3Aa**). Throughout the process, thiophenol (PhSH) serves a dual role as both the nucleophile and



Scheme 4 Plausible reaction mechanism.

the hydrogen donor, thus enabling an efficient metal-free conjugate reduction pathway (Scheme 4).

Conclusions

In summary, we have developed an efficient thiophenol-mediated, metal-free, chemoselective conjugate reduction strategy for the transformation of 3-alkylidene oxindoles into their corresponding 3-alkyl oxindoles. This protocol operates under mild, transition-metal-free conditions and exhibits excellent chemoselectivity and functional group tolerance. Mechanistic investigations, supported by control experiments and literature precedents, suggest that the transformation proceeds *via* a thiol-ene-type Michael addition-elimination pathway, wherein thiophenol serves a dual role as both the nucleophile and the hydrogen donor. The pronounced polarization of the α , β -unsaturated oxindole framework ensures high chemoselectivity during the conjugate addition step, while the subsequent β -elimination or hydride transfer delivers the reduced product in a redox-neutral manner. Overall, this methodology provides a practical, sustainable, and mechanistically insightful approach to the selective reduction of C=C bond in electron-deficient isatylidene systems, enriching the synthetic utility of thiol-mediated transformations in modern organic synthesis.

Author contributions

B. R. P. and A. S. G. perform the experiment and developed the method. B. R. P. expanded the substrate scope. S. S. C. and C. B. N. finalized the data, A. K. K. directed the project. B. R. P. and C. B. N. wrote main manuscript with the help of A. K. K. and feedback from other authors.

Conflicts of interest

No conflicts of interest to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5ra09175f>.

Acknowledgements

B. R. P. and S. S. C. thank UGC for a fellowship. C. B. N. thanks CSIR-New Delhi, India, for the fellowship. We sincerely acknowledge the support from the central NMR, HRMS facility, and CSIR-NCL.

Notes and references

- (a) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**(46), 8748–8875; (b) S. Peddibhotla, *Curr. Bioact. Compd.*, 2009, **5**, 20–38; (c) J. J. Badillo, N. V. Hanhan and A. K. Franz, *Curr. Opin. Drug Discovery Dev.*, 2010, **13**, 758;



- (d) S. Hibino and T. Choshi, *Nat. Prod. Rep.*, 2002, **18**, 66; (e) N. Ye, H. Chen, E. A. Wold, P. Y. Shi and J. Zhou, *ACS Infect. Dis.*, 2016, **2**, 382.
- 2 B. Volk, J. Barkóczy, E. Hegedus, S. Udvari, I. Gacsályi, T. Mezei, K. Pallagi, H. Kompagne, G. Lévy, A. Egyed, L. G. J. Hársing, M. Spedding and G. Simig, *J. Med. Chem.*, 2008, **51**, 2522–2532.
- 3 B. Volk, I. Gacsályi, K. Pallagi, L. Posszvacz, I. Gynos and E. Szabo, *J. Med. Chem.*, 2011, **54**, 6657.
- 4 B. Yu, D. Q. Yu and H. M. Liu, *Eur. J. Med. Chem.*, 2015, **97**, 673–698.
- 5 (a) T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Y.-H. Wu and Y. He, *Bioorg. Med. Chem. Lett.*, 2006, **16**(8), 2105–2108; (b) M. Eissenstat, T. Guerassina, S. Gulnik, E. Afonina, A. M. Silva, D. Ludtke, H. Yokoe, B. Yu and J. Erickson, *Bioorg. Med. Chem. Lett.*, 2012, **22**(15), 5078–5083.
- 6 (a) J.-Q. Zhao, Z.-J. Wu, M.-Q. Zhou, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *Org. Lett.*, 2015, **17**, 5020–5023; (b) L. Chen, Y. You, M.-L. Zhang, J.-Q. Zhao, J. Zuo, X.-M. Zhang, W.-C. Yuan and X.-Y. Xu, *Org. Biomol. Chem.*, 2015, **13**, 4413–4417; (c) A. Millemaggi and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2010, **2010**, 4527; (d) F. Zhou, Y. L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381; (e) S. Pramanik, R. Karmakar and C. Mukhopadhyay, *Tetrahedron*, 2025, **184**, 134757.
- 7 (a) C. Jaghta and M. Singh, *Chemistry Select*, 2025, **10**, e00743; (b) Y. M. Khetmalis, M. Shivani, S. Murugesan and K. V. G. Chandra Sekhar, *Biomed. Pharmacother.*, 2021, **141**, 111842; (c) M. Kaur, M. Singh, N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2016, **123**, 858–894.
- 8 (a) M. E. Contreira, D. S. Lüdtke and A. V. Moro, *Tetrahedron Lett.*, 2018, **59**, 2784–2787; (b) Y. Liu, Y. Mao, Y. Hu, J. Gui, L. Wang, W. Wang and S. Zhang, *Adv. Synth. Catal.*, 2019, **361**, 1554–1558.
- 9 S.-H. Cao, X.-C. Zhang, Y. Wei and M. Shi, *Eur. J. Org. Chem.*, 2011, **2011**(14), 2668–2672.
- 10 (a) A. Rossetti, A. Sacchetti, M. Bonfanti, G. Roda, G. Rainoldi and A. Silvani, *Tetrahedron*, 2017, **73**, 4584–4590; (b) J. Zhao, S. Guan, X. Zhou, W. Han, B. Cui and Y. Chen, *Tetrahedron*, 2016, **72**, 3098–3104.
- 11 S. J. Garden, C. R. W. Guimarães, M. B. Corrêa, C. A. F. Oliveira, A. C. Pinto and R. Bicca de Alencastro, *J. Org. Chem.*, 2003, **68**, 8815–8822.
- 12 J.-W. Ren, Q.-H. Zhang, C.-S. Han, H.-X. Zhang, Y.-B. Wang, H.-R. Shi, J.-H. Suna and Y.-F. Han, *Org. Biomol. Chem.*, 2025, **23**, 654–659.
- 13 (a) C. U. Brzezinski, A. R. LeBlanc, M. G. Clerici and W. M. Wuest, *Org. Lett.*, 2024, **26**, 5534–5538; (b) A. Bhowmick, P. K. Warghude and R. G. Bhat, *Asian J. Org. Chem.*, 2022, **11**, e202200205.
- 14 (a) C. B. Nichinde, B. R. Patil, S. S. Chaudhari, B. P. Mali, R. G. Gonnade and A. K. Kinage, *RSC Adv.*, 2023, **13**, 13206–13212; (b) B. R. Patil, C. B. Nichinde, S. S. Chaudhari, R. K. Gamidi and A. K. Kinage, *RSC Adv.*, 2024, **14**, 2873–2877; (c) C. B. Nichinde, M. Bhati, A. S. Girase, B. R. Patil, S. S. Chaudhari, R. Krishna Gamidi, K. Joshi and A. K. Kinage, *Eur. J. Org. Chem.*, 2025, **28**, e202401121; (d) B. R. Patil, C. B. Nichinde, S. S. Chaudhari and A. K. Kinage, *Org. Biomol. Chem.*, 2025, **23**, 6214–6219; (e) S. S. Chaudhari, C. B. Nichinde, B. R. Patil, R. K. Gamidi and A. K. Kinage, *Org. Biomol. Chem.*, 2024, **22**, 1727–1732; (f) S. S. Chaudhari, C. B. Nichinde, B. R. Patil, A. S. Girase and A. K. Kinage, *Select*, 2025, **10**, e202405996; (g) S. S. Chaudhari, C. B. Nichinde, B. R. Patil, A. S. Girase, S. H. Kaulage and A. K. Kinage, *Org. Biomol. Chem.*, 2025, **23**, 8687–8694.
- 15 (a) X. Huang, E. David, P. Jubault, T. Besset and S. Couve-Bonnaire, *J. Org. Chem.*, 2020, **85**, 14055–14067; (b) X. Ding, C. Tian, Y. Hu, L. Gong and E. Meggers, *Eur. J. Org. Chem.*, 2016, **2016**, 887–890; (c) S. Shaw and J. D. White, *Org. Lett.*, 2015, **17**, 4564–4567; (d) P. Wadhwa, A. Kharbanda and A. Sharma, *Asian J. Org. Chem.*, 2018, **7**, 634–661; (e) P. B. Momo, E. F. Mizobuchi, R. Echemendía, I. Baddeley, M. N. Grayson and A. C. B. Burtoloso, *J. Org. Chem.*, 2022, **87**, 3482–3490.

