



Cite this: *RSC Adv.*, 2025, 15, 25965

Facile access to quinazolin-4(3*H*)-ones by tandem Cu-catalyzed annulation of 2-nitrobenzonitrile and alcohols under air†

Xuan Lam Vu,^a Ban Van Phuc,^b Minh Hoang Nguyen,^a Thuy Anh T. Nguyen,^a Thuy Linh Nguyen,^a Hien Nguyen,^c Quoc Anh Ngo,^{bd} Nguyen Quang An,^b Tran Quang Hung^{ib}*^{bd} and Tuan Thanh Dang^{ib}*^a

Received 4th March 2025
 Accepted 9th July 2025

DOI: 10.1039/d5ra01550b

rsc.li/rsc-advances

A convenient Cu-catalyzed synthesis of 2-arylquinazolin-4(3*H*)-one derivatives has been developed from simple starting materials such as 2-nitrobenzonitriles and alcohols under mild conditions. This procedure showed a broad substrate scope and tolerance of functional groups, high yields, and no need to use oxidants or reductants, making synthesis simple, convenient, and sustainable. Our methodology may be utilized for the one-pot synthesis of glycosminine alkaloid.

Fused N-heterocyclic compounds have been recognized as critical targets in designing of new bioactive molecules, agrochemicals, medicines, and advanced materials.^{1,2} Among these, 2-arylquinazolin-4(3*H*)-ones have been studied and found to have interesting bioactivities, for example, anti-allergy, antidepressant, antihypertensive, anti-malarial, antimicrobial, anti-convulsant, anti-inflammatory, anti-cancer, and others.³ Notably, 2-arylquinazolin-4(3*H*)-ones have been found in the structures of several alkaloids.⁴ In fact, over 75 quinazolinone-based natural products with intriguing biological activities have been identified (Fig. 1).^{3,4} Interestingly, a number of major quinazolinone-based pharmaceuticals have been utilized clinically to treat a variety of disorders, including albaconazole, afloqualone, balaglitazone, halofuginone, cloroqualone, metolazone, febrifugine, quinethazone A, luotonin, raltitrexed, and others.^{3,4}

Numerous synthetic methods to prepare quinazolinone structures have been described because 2-arylquinazolin-4(3*H*)-ones are crucial to the advancement of pharmaceutical studies and drug discovery.^{3,4} Quinazolinones can generally be made using the following methods (Scheme 1): (i) the classical cyclocondensations of 2-aminobenzamides with aldehydes and carboxylic acids,⁵ (ii) the annulation reactions of 2-nitrobenzonitriles, aminobenzonitriles with carbonyl compounds

including aldehydes, ketones as well as carboxylic acids,⁶ (iii) the cyclization reactions of 2-halobenzamide derivatives with aldehydes, benzylamines, α -amino acids, nitriles, amidines and other related transformations with 2-halobenzoic acids,⁷ (iv) the autohydrogen-transfer and/or dehydrogenation tandem annulations of 2-aminobenzonitriles, 2-nitrobenzamides or 2-aminobenzamides with alcohols.⁸

These previous methods have some advantages; however, they frequently have several drawbacks such as narrow substrate scope, hard conditions, and require the employment of an excessive number of nonrenewable oxidants. In recent years, the advancement of more convenient and greener synthetic approaches based on cost-effective and non-hazardous starting materials has tremendously benefited sustainable operations in future.⁹ In comparison to classical

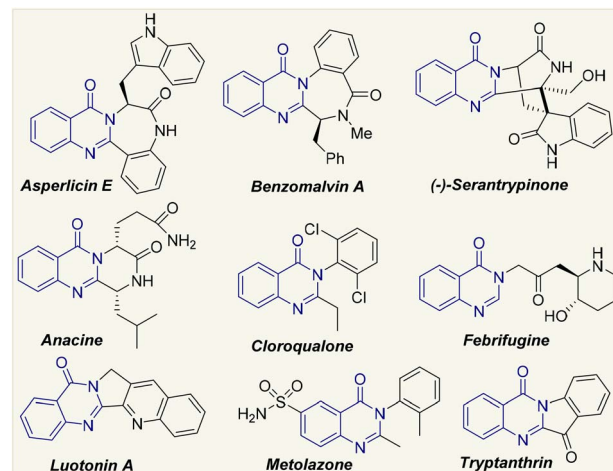


Fig. 1 Quinazolinone derivatives as bioactive alkaloids and drugs.

^aFaculty of Chemistry, VNU-Hanoi University of Science, 19 Le Thanh Tong, Hanoi, Vietnam. E-mail: dangthanhtuan@hus.edu.vn

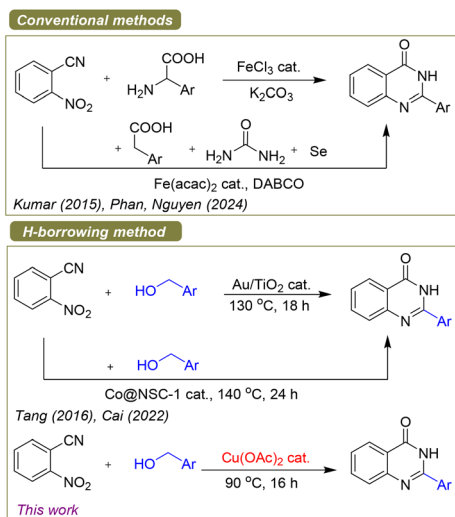
^bInstitute of Chemistry, Vietnamese Academy of Science and Technology (VAST), 18 Hoang Quoc Viet, Hanoi, Vietnam. E-mail: tqhung@ich.vast.vn

^cFaculty of Chemistry, Hanoi National University of Education (HNUE), Vietnam

^dGraduate University of Science and Technology, Vietnam Academy of Science and Technology, Vietnam

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d5ra01550b>



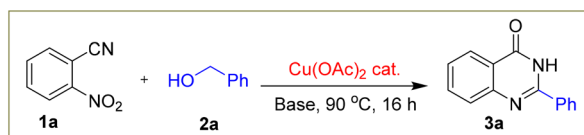


Scheme 1 Several synthetic methods to prepare quinazolinone derivatives along with this study.

condensation methods, acceptorless dehydrogenation and hydrogen-auto transfer pathways in the employment of less toxic and low-cost chemicals such as amines, alcohols, nitro compounds and nitriles, which produce only hydrogen gas and/or water as byproducts, could be a more sustainable solution to preparing *N*-heterocyclic compounds.¹⁰ Interestingly, 2-arylquinazolin-4(3*H*)-ones could be prepared using readily low-cost

starting materials, for example, 2-nitrobenzonitriles and alcohols. Up to now, two catalytic methods have been developed so far for generating the 2-arylquinazolin-4(3*H*)-ones from 2-nitrobenzonitrile derivatives.¹¹ In 2016, Tang *et al.* disclosed the first preparation of 2-arylquinazolin-4(3*H*)-ones by hydrogen-transfer process employing Au nanoparticles/TiO₂ as heterogeneous catalyst.^{11a} Cai and coworkers recently reported a unique Co nanoparticles/N,S co-doped carbon as a cheap and active heterogeneous catalyst for the production of 2-arylquinazolin-4(3*H*)-one derivatives from 2-nitrobenzonitriles and benzyl alcohols.^{11b} In fact, these approaches using heterogeneous catalysts demonstrated advantages, their catalysts needed huge effort to synthesize and characterize the nanostructure catalysts, which may limit potential uses in organic synthesis and medicinal chemistry research. Additionally, their processes had to be carried out at high temperatures (over 130 °C) in an inert gas atmosphere. To address these limitations, in early 2025, we reported an efficient method for the 2-arylquinazolin-4(3*H*)-ones synthesis from 2-nitrobenzonitriles and alcohols using [Ru(COD)Cl₂]_n catalyst.^{11c} However, Ru metal has been known as a precious and quite toxic transition metal which limits its possible application in pharmaceutical and fine chemical industries. In continuous progress, herein, we present the first homogeneous copper catalyst for producing high yields of various quinazolin-4(3*H*)-ones, therefore aiding in the advancement of hydrogen-transfer methods using cheap transition metal catalysts. This tandem procedure involved the first reduction of the nitro group by copper hydride to generate an

Table 1 Optimization for the synthesis of 2-phenylquinazolin-4(3*H*)-one^a



Entry	Catalyst	Ligand	Base	Temp. (°C)	Yield ^b (%)
1	CuI	BINAP	LiOtBu	120	67
2	Cu(OAc) ₂	BINAP	LiOtBu	120	75
3	Cu(OAc) ₂	dppe	LiOtBu	120	50
4	Cu(OAc) ₂	1,10-Phenanthroline	LiOtBu	120	70
5	Cu(OAc) ₂	<i>L</i> -Proline	LiOtBu	120	60
6	Cu(OAc) ₂	—	LiOtBu	120	77
7	Cu(OAc) ₂	—	LiOtBu	120	63
8	Cu(OAc) ₂	—	KOtBu	120	80
9	Cu(OAc) ₂	—	NaOEt	120	78
10	Cu(OAc) ₂	—	KOH	120	84
11	Cu(OAc) ₂	—	NaOH	120	80
12	Cu(OAc) ₂	—	K ₂ CO ₃	120	20
13	Cu(OAc) ₂	—	KOH	100	85
14	Cu(OAc) ₂	—	KOH	80	84
15	Cu(OAc) ₂	—	KOH	80	86 ^c
16	Cu(OAc) ₂	—	KOH	70	60
17	—	—	KOH	80	n.d.
18	Cu(OAc) ₂	—	—	80	n.d.

^a Condition: **1a** (0.34 mmol), **2a** (5 equiv.), base (2.0 equiv.), Cu(OAc)₂ catalyst (10 mol%), ligand (5 mol%), 16 h. ^b Yield of isolated products are reported. ^c Reaction was conducted under air.



amine group, followed by the second cyclization step of this amine intermediate with *in situ*-formed aldehyde under mild conditions.

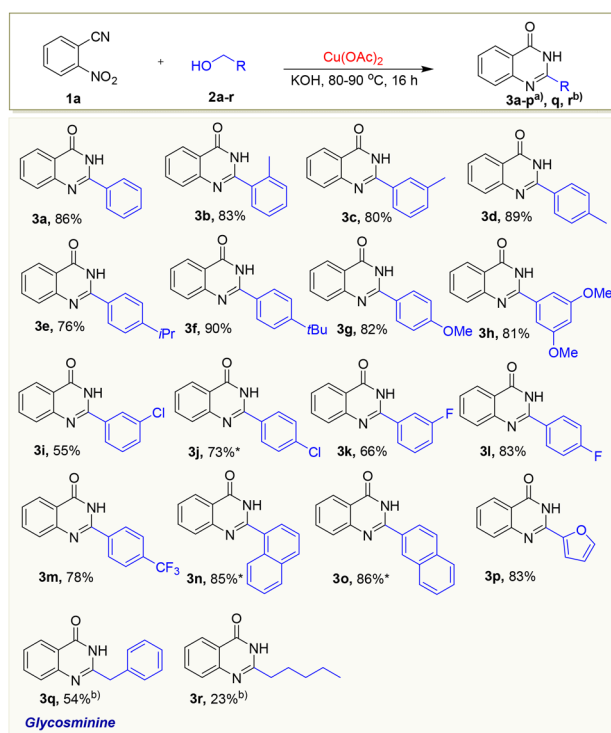
To develop a straightforward approach for synthesizing 2-phenylquinazolin-4(3*H*)-one product **3a**, we choose the reaction of 2-nitrobenzonitrile **1a** with benzyl alcohol **2a** in the employment of LiOtBu base to optimize copper catalysts. Table 1 lists the key factors that may influence the reaction, such as ligands, Cu precursors, and bases, at 120 °C. First, we used bidentate phosphines as ligands when combined with Cu(OAc)₂ precursor using well-established methods. Under these conditions, the BINAP ligand in conjunction with Cu(OAc)₂ appears to be the best choice for this transformation, resulting in 75% yield of the product **3a** (Table 1, entry 2). Especially, when we carried out this reaction using only Cu(OAc)₂ catalyst in the absence of any ligands, product **3a** was received with 77% yield (Table 1, entry 6). After that, a number of common bases were also looked into. Notably, using KOH as the base and solvent, respectively, allowed us to achieve a yield of up to 84% of the target product **3a** (entry 10). Product **3a**'s synthesis at 80 °C produced a comparable yield when the reaction temperature was lowered (entries 14). Notably, when this transformation was carried out in an air atmosphere, the Cu(OAc)₂ catalyst was discovered to be stable and extremely active, allowing for the preparation of product **3a** in an 86% yield (Entry 15). It means that oxygen (in air) did not play a critical role in this transformation. Then, two control reactions were conducted in which either the base or the

Cu(OAc)₂ catalyst was absent in order to obtain useful insights of the catalyst's actual function. Product **3a** was only observed in trace amounts (entries 17 and 18).

Using optimized conditions, we began to study the possibility of the cyclization reaction of compound **1a** with several alcohols **2a-r**, as shown in Table 2. The intended quinazolinone compounds were successfully produced, with isolated yields reaching up to 90%. Typically, the cyclization of compound **1a** using benzylic alcohol derivatives produced the desired products **3a-p** in high yield, with the tolerance of several functional groups reaching up to 90%. Interestingly, furan-2-ylmethanol may be efficiently used as an alcohol substrate in this reaction, yielding the matching quinazolinone **3p** in 83% isolated yield. Notably, the cyclization of starting material **1a** with challenging aliphatic alcohols could be achieved when these reactions were conducted under harsh conditions (160 °C, 48 h). Especially, product **3q** which was known as a bioactive alkaloid (glycosminine) isolated from Indian medicinal plant (*Glycosmis arborea*).¹²

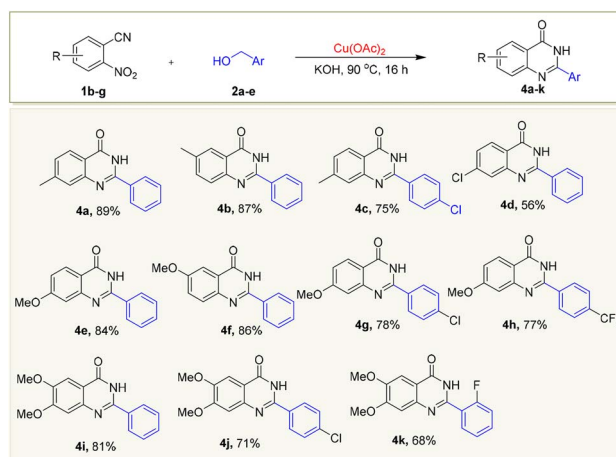
Finally, we intended to investigate the scope of this reaction by using 2-nitrobenzonitrile derivatives **1b-g** as starting materials in a one-pot annulation process with benzyl alcohols **2a-e** and Cu(OAc)₂ catalyst under our optimal conditions. Notably, the 2-arylquinazolin-4(3*H*)-one products **4a-k** were achieved in up to 89% isolated yield (Table 3). The preparation of quinazolinones utilizing earlier heterogeneous catalysts necessitated well-designed catalysts operating at high temperatures (over

Table 2 Cu(OAc)₂-catalyzed synthesis of quinazolin-4(3*H*)-ones **3a-r**^{a,b,c}



^a Condition: **1a** (0.34 mmol), **2a-r** (5 equiv.), KOH (2.0 equiv.), Cu(OAc)₂ catalyst (10 mol%). ^b Yields of isolated products are given. Reactions were performed under air atmosphere at 90 °C. ^c Reaction were conducted under air atmosphere at 160 °C, 48 h.



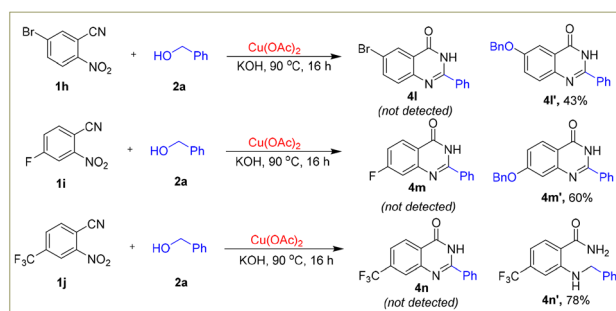
Table 3 Cu-catalyzed synthesis of 2-phenylquinazolin-4(3H)-ones **4a–k**^a

^a Condition: **1b–g** (0.34 mmol), **2a–e** (5 equiv.), KOH (2.0 equiv.), Cu(OAc)₂ catalyst (10 mol%). Yields of isolated products are given. Reaction were performed under air atmosphere.

130 °C), which may be cumbersome for convenient applications in medicinal chemistry and organic synthesis. Our method significantly improved the preparation of 2-arylquinazolin-4(3H)-one derivatives under milder conditions, utilizing a low-cost and air-stable Cu(OAc)₂ catalyst.

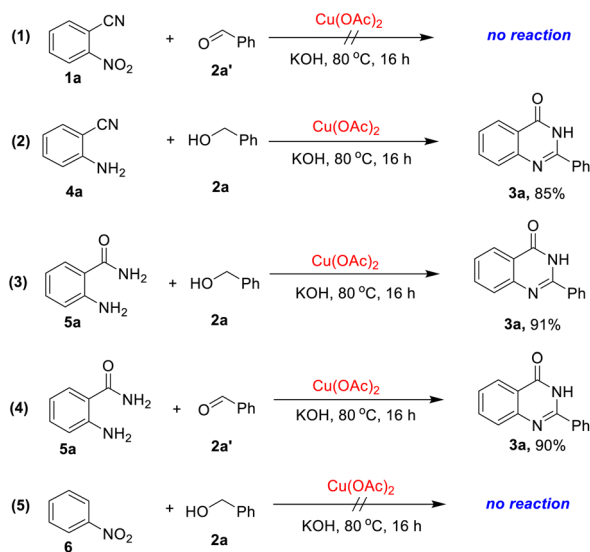
Specifically, the Cu-catalyzed annulation reactions of starting materials containing bromine and fluorine substituents (**1h,i**) with benzyl alcohol **2a** did not produce the predicted products (**4l,m**). Instead of obtaining desired products (**4l,m**), 2-phenylquinazolin-4(3H)-one products (**4l',m'**) were isolated in 43% and 60%, respectively (Table 4). In fact, S_NAr (Nucleophilic Aromatic Substitution) reaction of substrates (**1h,i**) with the *in situ*-formed benzylic alkoxide occurred faster than the hydrogen-transfer and annulation reactions. Finally, the coupling reaction of 2-nitro-4-(trifluoromethyl)benzonitrile substrate **1j** with benzyl alcohol **1a** resulted in the formation of uncyclized amide **4n'** as a side product in 78% isolated yield. It means that the *in situ*-formed amide should be the key intermediate in this transformation.

To better understand the reaction process and the true role of the Cu(OAc)₂ catalyst in this reaction, we conducted some control experiments, as shown in Scheme 2. First, to investigate the hydrogen-transfer reaction in the presence of Cu(OAc)₂ catalyst, the reaction of 2-nitrobenzonitrile **1a** with benzaldehyde **2a'** was conducted under optimum conditions (Scheme 2, reaction (1)). In fact, we did not observe even a trace amount of quinazolinone **3a**. In this Cu-catalyzed reaction, we hypothesize that 2-aminobenzonitrile **4a** and 2-aminobenzamide **5a** would be *in situ*-formed intermediates. Then, 2-aminobenzonitrile **4a** and 2-aminobenzamide **5a** were used in the annulation processes with benzyl alcohol **1a**. Indeed, quinazolinone **3a** was obtained in 85% and 91% of cases (Scheme 2, reaction (2) and (3)). Finally, Cu-catalyzed annulation of 2-aminobenzamide **5a** with benzaldehyde **2a'** produced the dehydrogenative product **3a** in 90% isolated yield (Scheme 2, reaction (4)). Based on these achievements, we can realize that benzyl alcohol **2a** and nitro group in the compound **1a** contributed as hydrogen donors and acceptors in the Cu(OAc)₂-catalyzed preparation of

Table 4 Cu-catalyzed synthesis of 2-phenylquinazolin-4(3H)-ones **4l',m'**^a

^a Condition: **1h–j** (0.34 mmol), **2a** (5 equiv.), KOH (2.0 equiv.), Cu(OAc)₂ catalyst (10 mol%). Yields of isolated products are given. Reactions were performed under air atmosphere.





Scheme 2 Control experiments.

quinazolinone products. In order to explain the negative effect of any ligands in this transformation (Table 1), the reaction of nitrobenzene with benzyl alcohol **1a** was performed under optimized conditions (reaction (5)). As we predicted, this

reaction did not work due to the lack of any directing group as the primary amide in the intermediate **B** which is proposed in Scheme 3. Indeed, ligands may well hinder the formation of Cu–H complex as well as the hydrogen transfer process in the intermediate **B**.

Based on the achieved results in control experiments, a plausible mechanism for the $\text{Cu}(\text{OAc})_2$ -catalyzed preparation of quinazolinones is described (Scheme 3). Firstly, benzyl alcohol **2a** was transformed into benzaldehyde **2a'** in the employment of $\text{Cu}(\text{OAc})_2$ catalyst and KOH base. This step produced the catalytic active species $(\text{AcO})\text{Cu}-\text{H}$ (intermediate **A**) reducing the intro group of **1a'** to give an amino group of the benzamide intermediate **4** via Cu–H complex intermediate **B**. Indeed, the *in situ*-formed amide group played a key role as the directing group for the success of this transformation. In the next step, the benzamide intermediate **4** reacted with benzaldehyde **2a'** to form the dihydroquinazolinone intermediate **5**, which was further transformed into the quinazolinone product **3a** in the presence of $\text{Cu}(\text{OAc})_2$ catalyst, and catalytic $(\text{AcO})\text{Cu}-\text{H}$ species **A** could be again *in situ*-generated, which are required for the reduction of the nitro group in the structure of starting material **1a** in order to attend the next catalytic cycle.

Conclusions

In conclusion, we disclosed a feasible and practical approach for synthesizing a series of 2-arylquinazolin-4(3*H*)-one products in high yields from readily available compounds such as 2-nitrobenzonitriles and alcohols under mild conditions. Relying on the results of the control reactions, a viable mechanism for this transformation involving a $\text{Cu}(\text{OAc})_2$ catalyst and a hydrogen-borrowing route was proposed. Our approach, which employed a practical, air-stable, and inexpensive $\text{Cu}(\text{OAc})_2$ catalyst, outperformed earlier methods that used heterogeneous catalysts and required multiple steps to prepare. The findings given herein may be useful to explore promising applications in organic synthesis and medicinal chemistry.

Data availability

The data supporting this research are available in the ESI.†

Conflicts of interest

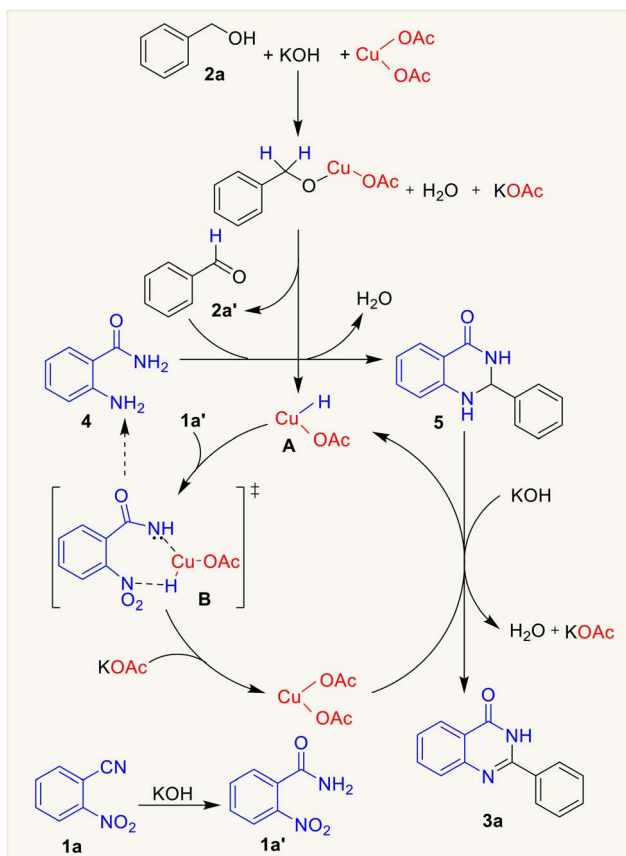
There are no conflicts to declare.

Acknowledgements

This work is supported by the Vietnam Academy of Science and Technology under Grant Number: NCXS 01.02/24-26.

Notes and references

- (a) R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845; (b) J. A. Joule and K. Mills,

Scheme 3 Proposed mechanism for the $\text{Cu}(\text{OAc})_2$ -catalyzed preparation of quinazolin-4(3*H*)-ones.

- Heterocyclic Chemistry*, Wiley, Chichester, UK, 5th edn, 2010; (c) R. Vardanyan and V. Hruby, *Synthesis of Best-Seller Drugs*, Elsevier Science, 2016.
- 2 (a) M. L. Fascio, M. I. Errea and N. B. D'Accorso, *Eur. J. Med. Chem.*, 2015, **90**, 666; (b) L. Kielesinski, M. Tasior and D. T. Gryko, *Org. Chem. Front.*, 2015, **2**, 21; (c) T. N. Ngo, P. Ehlers, T. T. Dang and P. Langer, *Org. Biomol. Chem.*, 2015, **13**, 3321; (d) T. N. Ngoc, O. A. Akrawi, T. T. Dang, A. Villinger and P. Langer, *Tetrahedron Lett.*, 2015, **56**, 86; (e) B. V. Phuc, N. T. Nguyen, N. T. H. Van, T. L. Nguyen, V. H. Nguyen, C. M. Tran, H. Nguyen, M. T. Nguyen, T. Q. Hung and T. T. Dang, *Chem. Commun.*, 2023, **59**, 1947; (f) T. Q. Hung, N. N. Thang, D. H. Hoang, T. T. Dang, A. Villinger and P. Langer, *Org. Biomol. Chem.*, 2014, **12**, 2596; (g) T. Q. Hung, N. N. Thang, D. H. Hoang, T. T. Dang, A. Villinger, K. Ayub, S. Lochbrunner, G. Flechsig and P. Langer, *Eur. J. Org. Chem.*, 2015, **5**, 1007; (h) T. T. Dang, U. Albrecht, K. Gerwien, M. Siebert and P. Langer, *J. Org. Chem.*, 2006, **71**, 2293; (i) N.-K. Nguyen, M.-T. Ha, H. Y. Bui, Q. T. Trinh, B. N. Tran, T. Q. Hung, T. T. Dang and X. H. Vu, *Catal. Commun.*, 2021, **149**, 106240; (j) N.-K. Nguyen, D. H. Nam, B. V. Phuc, V. H. Nguyen, Q. T. Trinh, T. Q. Hung and T. T. Dang, *Mol. Catal.*, 2021, **505**, 111462.
- 3 P. S. Auti, G. George and A. T. Paul, *RSC Adv.*, 2020, **10**, 41353.
- 4 S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787.
- 5 (a) N. Y. Kim and C. H. Cheon, *Tetrahedron Lett.*, 2014, **55**, 2340; (b) Z. Bie, G. Li, L. Wang, Y. Lv, J. Niu and S. Gao, *Tetrahedron Lett.*, 2016, **57**, 4935; (c) R. Cheng, L. L. Tang, T. J. Guo, D. Zhang-Negrerie, Y. F. Du and K. Zhao, *RSC Adv.*, 2014, **4**, 26434; (d) X. Chen, T. Chen, F. Ji, Y. Zhou and S.-F. Yin, *Catal. Sci. Technol.*, 2015, **5**, 2197.
- 6 (a) M. Kumar, Richa, S. Sharma, V. Bhatt and N. Kumar, *Adv. Synth. Catal.*, 2015, **357**, 2862; (b) T. B. Nguyen, J. L. Bescont, L. Ermolenko and A. Al-Mourabit, *Org. Lett.*, 2013, **15**, 6218; (c) T. T. Nguyen, D. T. M. Chung, K. X. Nguyen, V. P. T. Nguyen, N. T. S. Phan and T. T. Nguyen, *ChemistrySelect*, 2024, **9**, e202303762.
- 7 (a) W. Xu, Y. Jin, H. Liu, Y. Jiang and H. Fu, *Org. Lett.*, 2011, **13**, 1274; (b) T. Kotipalli, V. Kavala, D. Janreddy, V. Bandi, C. W. Kuo and C. F. Yao, *Eur. J. Org. Chem.*, 2016, 1182; (c) W. Xu and H. Fu, *J. Org. Chem.*, 2011, **76**, 3846; (d) X. Yu, L. Gao, L. Jia, Y. Yamamoto and M. Bao, *J. Org. Chem.*, 2018, **83**, 10352; (e) T. Songsichan, J. Promsuk, V. Rukachaisirikul and J. Kaeobamrung, *Org. Biomol. Chem.*, 2014, **12**, 4571; (f) L. Xu, Y. Jiang and D. Ma, *Org. Lett.*, 2012, **14**, 1150; (g) W. Xu and H. Fu, *J. Org. Chem.*, 2011, **76**, 3846.
- 8 (a) H. Wang, X. Cao, F. Xiao, S. Liu and G. J. Deng, *Org. Lett.*, 2013, **15**, 4900; (b) S. Mondal, S. Chakraborty, S. Khanra, S. Chakraborty, S. Pal, P. Brandao and N. D. Paul, *J. Org. Chem.*, 2024, **89**, 5250; (c) J. Zhou and J. Fang, *J. Org. Chem.*, 2011, **76**, 7730; (d) A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *Org. Biomol. Chem.*, 2012, **10**, 240; (e) Z. Bie, G. Li, L. Wang, Y. Lv, J. Niu and S. Gao, *Tetrahedron Lett.*, 2016, **57**, 4935; (f) S. Parua, S. Das, R. Sikari, S. Sinha and N. D. Paul, *J. Org. Chem.*, 2017, **82**, 7165; (g) W. Zhang, C. Meng, Y. Liu, Y. Tang and F. Li, *Adv. Synth. Catal.*, 2018, **360**, 3751; (h) Y. Hu, S. Li, H. Li, Y. Li, J. Li, C. Duanmu and B. Li, *Org. Chem. Front.*, 2019, **6**, 2744; (i) Sk. A. Samim, B. C. Roy, S. Nayak and S. Kundu, *J. Org. Chem.*, 2020, **85**(17), 11359; (j) S. M. A. H. Siddiki, K. Kon, A. S. Touchy and K. I. Shimizu, *Catal. Sci. Technol.*, 2014, **4**, 1716; (k) J. Qiao, H. Jiang, X. Liu, C. Xu, Z. Sun and W. Chu, *Eur. J. Org. Chem.*, 2019, **13**, 2428; (l) M. Vageesh, P. Omkar, P. Hima and D. Raju, *Synlett*, 2024, **35**, 2496–2502.
- 9 C.-J. Li and B. Trost, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 13197.
- 10 (a) N. Hofmann and K. C. Hultsch, *Eur. J. Org. Chem.*, 2021, **46**, 6206; (b) B. Paul, M. Maji, K. Chakrabarti and S. Kundu, *Org. Biomol. Chem.*, 2020, **18**, 2193.
- 11 (a) L. Tang, X. Zhao, G. Zou, Y. Zhou and X. Yang, *Asian J. Org. Chem.*, 2016, **5**, 335; (b) T. Su, K. Sun, G. Lu and C. Cai, *ACS Sustain. Chem. Eng.*, 2022, **10**, 3872; (c) B. V. Phuc, T. D. Nguyen, N. T. M. Tuan, P. A. Dao, P. T. T. Vy, N. T. Nguyen, Q. A. Ngo, T. Q. Hung and T. T. Dang, *Org. Biomol. Chem.*, 2025, **23**, 603.
- 12 S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson and H. Budzikiewicz, *Tetrahedron*, 1963, **19**, 1011.

