RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2025, **15**, 8913

Brønsted acid-catalyzed two-component tandem condensation and cycloisomerization to 6(2*H*)-isoquinolinones†

Fang Yang,‡ Lin-Lin Wang,‡ Yu-Hua Liu, Ke-Xin Wu, Zi-Sheng Chen * and Kegong Ji *

Received 21st February 2025
Accepted 12th March 2025

DOI: 10.1039/d5ra01267h

rsc.li/rsc-advances

An attractive Brønsted acid-catalyzed two-component reaction of 2-alkynyl-4-hydroxybenzaldehydes **1** and primary amines **2** to various 6(2*H*)-isoquinolinones **3** has been developed. This catalytic system realized an efficient tandem condensation and cycloisomerization reaction to 6(2*H*)-isoquinolinones **3** in good to excellent yields *via* a one-pot synthesis, in which two different kinds of C–N bonds were constructed in a straightforward manner. Remarkably, the reaction tolerated various aliphatic, aryl-substituted amines, including chiral amino alcohols and amino acids. The practicality of this approach rendered it a viable alternative for the construction of various 6(2*H*)-isoquinolinones.

Introduction

Isoquinolinones and their derivatives,[1] like 6(2*H*)-isoquinolinones and natural nitrogenated azaphilone products, bearing a highly nitrogenated pyridinoquinone bicyclic core, have continuously aroused considerable attention owing to their structural diversity and significant biological activities (Fig. 1).[2,3] As a class of alkaloids, isoquinolinone derivatives have antiplasmodial, anticancer, anti-MRSA, antimicrobial, antiviral, and cytotoxicity activities and other functional properties.[2a,b,4–8]

As a privileged core structure, the traditional strategies for the synthesis of 6(2*H*)-isoquinolinones are achieved through the following two pathways, as shown in Scheme 1. (a) The conversion strategies based on 6-hydroxyisochromenylium **A** as the precursor. Normally, the transformation of 6-hydroxyisochromenylium is initiated by the addition of primary amines under basic conditions and followed by isomerizations to 6(2*H*)-isoquinolinones. This strategy was applied by the Thamyongkit group in the synthesis of alkaloid Cassiarin **B** from barakol in four steps with a 16.6% total yield (Scheme 1a).[2c] Alternatively, Cassiarin **B** could also be synthesized from 8-chromenone **B**. In 2008, Yao and co-workers reported a silver-catalyzed 6-*exo*-*dig* cycloisomerization to 8-chromenone B in 75% yield under acidic and harsh conditions, which was directly converted to Cassiarin B in a moderate yield, as shown in Scheme 1b.[2a] (b) The other conversion strategy was based on 6-isoquinolinol as the nucleophilic reagent. The transformation of 6-isoquinolinol was accessed *via* the selective activation of a nitrogen atom by highly active electrophilic reagents to realize the C–N bond formation and isomerization to 6(2*H*)-isoquinolinone, as shown in Scheme 1c. You and co-workers have reported an Ir-catalyzed enantiodivergent synthesis of chiral 6(2*H*)-isoquinolinones **3aa** from 6-isoquinolinol.[2d] However, these strategies also need more steps, harsh conditions or noble metals, which demands more efforts in exploring more efficient strategies in the synthesis of 6(2*H*)-isoquinolinones.

2-Alkynylbenzaldehyde, as a useful precursor, was successfully applied in the synthesis of many nature products *via* the isochromenylium salt intermediate.[3a,9] For a more useful application of 2-alkynylbenzaldehyde and the development of an efficient approach to 6(2*H*)-isoquinolinones, as shown in

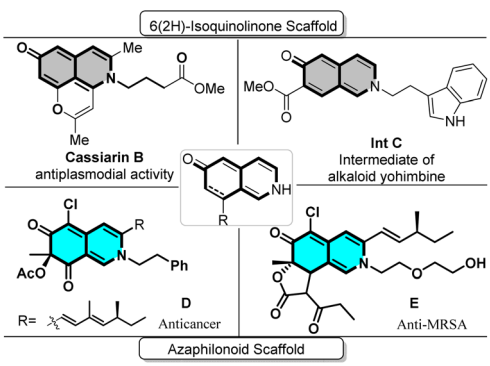
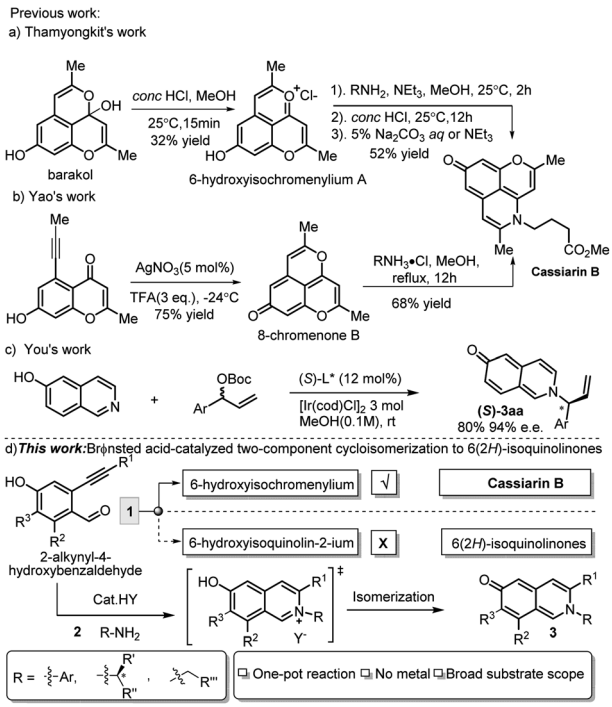


Fig. 1 Representative bioactive molecules containing isoquinolinone skeleton.

College of Chemistry and Pharmacy, Northwest A&F University, Shaanxi Key Laboratory of Natural Products & Chemical Biology, 3 Taicheng Road, Yangling, 712100, Shaanxi, P. R. China. E-mail: jikegong@nwsuaf.edu.cn

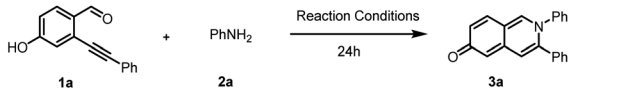
† Electronic supplementary information (ESI) available. CCDC 2081746. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5ra01267h

‡ These authors contributed equally to this work.



Scheme 1 Strategies for the synthesis of 6(2*H*)-isoquinolinone derivatives.

Table 1 Screening conditions[a]



Entry	**2a** (equiv.)	Catalyst (mol%)	Solvent	Yield[b] (%)
1	1.0	CF_3COOH (20)	DCE	76
2	1.0	CF_3COOH (20)	1,4-Dioxane	65
3	1.0	CF_3COOH (20)	DMSO	66
4	1.0	CF_3COOH (20)	DMF	73
5	1.0	CF_3COOH (20)	Toluene	82
6	1.0	CF_3COOH (20)	PhCl	79
7	1.0	CH_3SO_3H (20)	Toluene	78
8	1.0	$HCl\cdot Et_2O$ (20)	Toluene	71
9	1.0	HOTf (20)	Toluene	64
10	1.0	CH_3COOH (20)	Toluene	72
11	1.0	CF_3COOH (10)	Toluene	83
12	1.0	CF_3COOH (5)	Toluene	79
13	**1.1**	**CF_3COOH (10)**	**Toluene**	**92**
14	1.3	CF_3COOH (10)	Toluene	90
15[c]	1.1	CF_3COOH (10)	Toluene	55

[a] Reaction conditions: The reaction was carried out in a tube in the presence of **1a** (0.2 mmol) and **2a** with 3.4 equivalent of $MgSO_4$ at 80 °C for 24 h; [**1a**] = 0.1 M. [b] Isolated yields. [c] Instead of $MgSO_4$, 5 Å molecular sieve (100 mg) as additive was added.

Scheme 1d, our design anticipated that with 2-alkynyl-4-hydroxybenzaldehydes **1** and primary amines **2** as substrates, a novel 6-hydroxyisoquinolin-2-ium salt intermediate could be selectively generated under acidic conditions,[10] which was subsequently isomerized to 6(2*H*)-isoquinolinones **3**. As part of our ongoing work in the field of alkyne chemistry,[11] we reported herein a Brønsted acid-catalyzed two-component tandem condensation and cycloisomerization to 6(2*H*)-isoquinolinones in one-pot.

Results and discussion

At the outset, we employed 2-alkynyl-4-hydroxybenzaldehyde (**1a**) and aniline (**2a**) as the template substrates for condition optimization as shown in Table 1. Initially, CF_3COOH (20 mol%) was chosen as the catalyst, the reaction was carried out in 1,2-dichloroethane (DCE) with $MgSO_4$ (3.4 equiv.) as an additive at 80 °C for 24 h. To our delight, the desired product **3a** was indeed formed in 76% isolated yield (Table 1, entry 1). The structure of product **3a** was unambiguously assigned by X-ray crystallography (Fig. 2. CCDC 2081746). An attempt to optimize this reaction in the absence of the catalyst was fruitless (see the ESI†). Solvent effect was also considered, toluene was found to be the most effective solvent and afford **3a** in 82% yield (entries 2–6). Other catalysts such as CH_3SO_3H, $HCl\cdot Et_2O$, HOTf and CH_3COOH were also investigated, but no superior results were obtained even after a longer time (entries 7–10, respectively). The catalyst loading was also studied, it was found that 10 mol% of CF_3COOH gave a better yield of **3a** (entry 11). Furthermore, the equivalent of aniline **2a** was also investigated, it was found that aniline **2a** (1.1 equivalent) gave the optimal yield of **3a** in 92% (entry 13). Other additive, like 5 Å molecular sieve, was also considered, but no better yields were observed (entry 15, for more details, see the ESI†).

With the optimal reaction conditions in hand (Table 1, entry 13), the reaction scope was investigated. As shown in Table 2, a broad range of primary amines **2b–2s** could be utilized in this tandem condensation and cycloisomerization to 6(2*H*)-isoquinolinones **3b–3s** with 2-alkynyl-4-hydroxybenzaldehyde **1a**. Aryl-substituted primary amines, like **2b–2h**, upon installation both electron-withdrawing groups (**2b–2d**) and electron-donating groups (**2e–2h**) on aryl ring, worked as expected to give **3b–3h** in good to excellent yields. The aryl amines with more steric hindrance, like 2, 6-dimethylaniline **2g**, proceeded smoothly to provide corresponding product **3g** in 94% yield. Furthermore, the reaction was also tolerated different aliphatic-substituted primary amines. Substrates **2i–2o** possessing different aliphatic substituted R groups, such as benzyl, β-

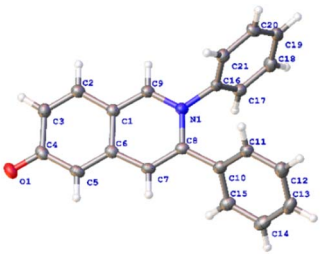
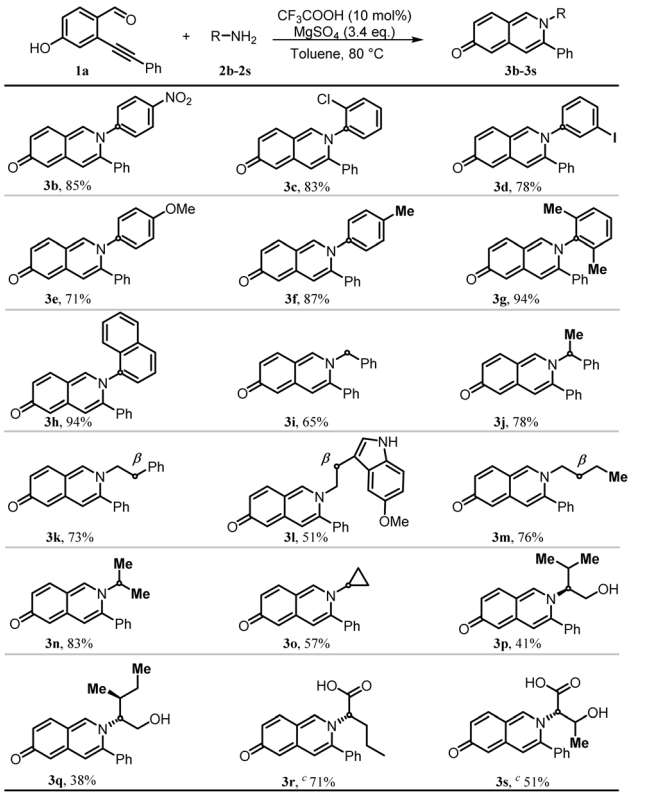


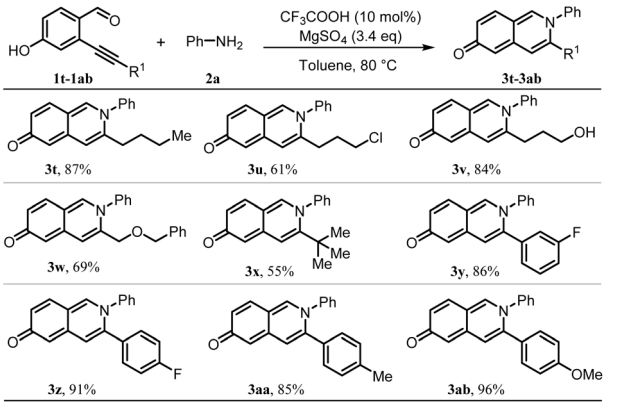
Fig. 2 Solid-state molecular structure of **3a**.

Table 2 Reaction scope of primary amines 2[a,b]

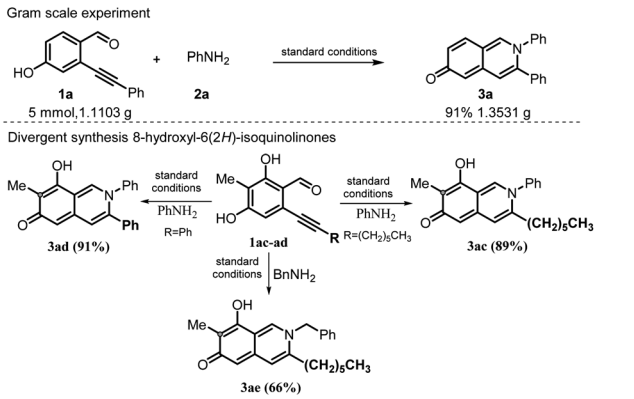


[a] Conditions: **1a** (0.3 mmol), **2** (0.33 mmol), CF_3COOH (0.03 mmol) and $MgSO_4$ (120 mg) in 2 mL toluene at 80 °C. [b] Isolated yields. [c] CH_3COOH was used as solvent.

Table 3 Reaction scope of 2-alkynyl-4-hydroxybenzaldehydes 1[a,b]



[a] Conditions: **1** (0.3 mmol), **2a** (0.33 mmol), CF_3COOH (0.03 mmol) and $MgSO_4$ (120 mg) in 2 mL toluene at 80 °C. [b] Isolated yields.



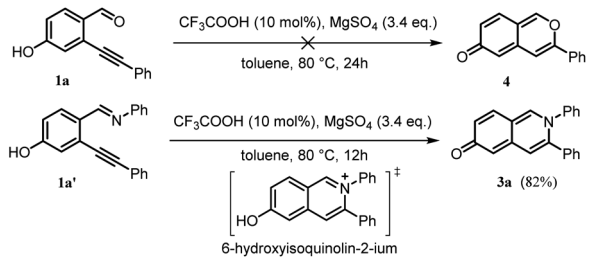
Scheme 2 Applications.

substituted ethyl, isopropyl and cyclopropyl groups, proceeded smoothly to give **3i–3o** in 57–83% yields. Interestingly, primary amines, like chiral amino alcohols **2p–2q** with two nucleophilic sites, also worked as expected to give the desired products **3p–3q** in 38% and 41% yields, respectively. However, chiral amino acids, like **2s–2r**, almost gave no desired products under the standard conditions, which implied that the relative low solubility of substrates in toluene and multi-nucleophilic sites of amino acids may affect the overall yields of the transformation. To our delight, chiral amino acids, like **2s–2r**, proceeded smoothly to give desired products **3s–3r** in 71% and 51% yields, respectively, by employing acetic acid as the solvent.

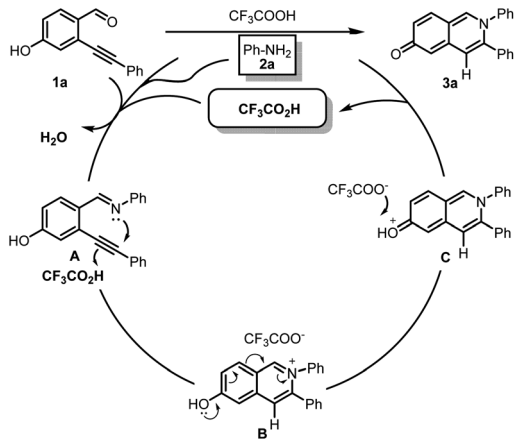
Moreover, for more synthetically useful transformations, various 2-alkynyl-4-hydroxybenzaldehydes, like **1t–1ab**, possessing different R^1 substitutions were also investigated under the standard conditions and gave the desired **3t–3ab**, respectively, in good to excellent yields, as shown in Table 3. The reaction was tolerant of various aliphatic and aromatic R^1 groups. Substrates **1u–1w**, by installing different substituents at the end of the alkyl chain, such as Cl, OH and OBn group, were readily tolerated and afforded the corresponding products **3u–3w** in moderate to good yields (61–87%). Substrate **1x**, with more steric hindrance R^1 group, proceeded smoothly to afford the desired product **3x** in a moderate yield. Moreover, 2-alkynyl-4-hydroxybenzaldehydes **1y–1ab**, by installing different electron-withdrawing and electron-donating aryl R^1 groups, worked smoothly to provide corresponding products **3y–3ab** in excellent yields (up to 96% yield).

To demonstrate the synthetic utility of this method, 2-alkynyl-4-hydroxybenzaldehyde **1a** was reacted at a gram scale to afford the desired product **3a** in 91% yield (Scheme 2). Furthermore, this approach was also successfully applied in the synthesis more useful 8-hydroxyl-6(2*H*)-isoquinolinones **3ac–3ae** in good to excellent yields, which can be easily modified to construct natural azaphilone scaffolds[12] (Scheme 2).

In order to gather additional experimental evidence for the mechanism, the control experiments were conducted, as shown in Scheme 3. 2-Alkynyl-4-hydroxybenzaldehyde **1a** was carried out under the standard conditions without primary amines **2**, no desired 3-phenyl-6*H*-isochromen-6-one **4** was observed. However, when the substrate 3-(phenylethynyl)-4-((phenylimino)methyl)phenol **1a′** was investigated under the standard conditions, the desired 6(2*H*)-isoquinolinone **3a** was obtained in 80% yield, which indicated that the 6-



Scheme 3 Control experiments.



Scheme 4 Proposed mechanisms.

hydroxyisoquinolin-2-ium might be the real intermediate of this transformations.

On the basis of the above observations and literature reported,[1c] we proposed the following plausible mechanism for this transformation (Scheme 4). Firstly, the substrates 2-alkynyl-4-hydroxybenzaldehyde **1a** and aniline **2a** are condensed and dehydrated to form imine **A** in acidic condition. Secondly, the proton (H^+) generated from CF_3COOH selectively coordinates with the C–C triple bonds of imine **A**. Subsequently, the nitrogen of imine attacks the activated C–C triple bonds *via* a 6-*endo-dig* cyclization[1c] to afford 6-hydroxyisoquinolinium intermediate **B**, which is isomerized to (2,3-diphenylisoquinolin-6(2*H*)-ylidene)oxonium **C**. Finally, the proton on oxonium intermediate **C** is trapped by trifluoroacetate to give final product **3a** and releases CF_3COOH for next catalytic cycle.

Conclusions

In summary, we have developed a novel one-pot strategy to construct 6(2*H*)-isoquinolinones **3** from 2-alkynyl-4-hydroxybenzaldehydes **1** and primary amines **2** *via* a Brønsted acid-catalyzed tandem condensation and cycloisomerization reaction. This approach provides a facile access to various 6(2*H*)-isoquinolinones **3** in good to excellent yields, including chiral 6(2*H*)-isoquinolinones. This protocol tolerates various commercially available materials, such as aliphatic, aryl-substituted amines, including chiral amino alcohols and amino acids. The mild metal-free conditions, atom economy and gram scale application of the reaction render the present method attractive for future applications.

Data availability

Data available within the article or its ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from Natural Science Foundation of Shaanxi province (2023-JC-QN-0139) and the National Natural Science Foundation of China (NSF-22171228).

Notes and references

1 (*a*) P. Pigeon and B. Decroix, A New Access to Isoindolo[2,1-b][2,4]benzodiazepines through an N-Acyliminium Ion-Amide Cyclization, *Tetrahedron Lett.*, 1997, **38**, 2985–2988; (*b*) S. Dhanasekaran, A. Suneja, V. Bisai and V. K. Singh, Approach to Isoindolinones, Isoquinolinones, and THIQs via Lewis Acid-Catalyzed Domino Strecker-Lactamization/Alkylations, *Org. Lett.*, 2016, **18**, 634–637; (*c*) P. Fernández, F. J. Fañanás and F. Rodríguez, Nitrogenated Azaphilone Derivatives through a Silver-Catalysed Reaction of Imines from *ortho*-Alkynylbenzaldehydes, *Chem.–Eur. J.*, 2017, **23**, 3002–3006; (*d*) W. Chen, R. Chen, Q. Liu, Y. He, K. He, X. Ding, L. Kang, X. Guo, N. Xie, Y. Zhou, Y. Lu, R.-J. Cox, I. Molnár, M. Li, Y. Shao and F. Chen, Orange, red, yellow: biosynthesis of azaphilone pigments in Monascus fungi, *Chem. Sci.*, 2017, **8**, 4917–4925.

2 (*a*) Y.-S. Yao and Z.-J. Yao, Biomimetic Total Syntheses of Cassiarins A and B, *J. Org. Chem.*, 2008, **73**, 5221–5225; (*b*) E. Wenkert, J. S. Pyrek, S. Uesato and Y. D. Vankar, A Synthesis of (±)-Yohimbine, *J. Am. Chem. Soc.*, 1982, **104**, 2244–2246; (*c*) S. Kanputhorn, A. Petsom and P. Thamyongkit, Transformation of barakol into cassiarins A, B, and their derivatives, *Tetrahedron*, 2010, **66**, 7539–7543; (*d*) H.-F. Tu, P. Yang, Z.-H. Lin, C. Zheng and S.-L. You, Time-dependent enantio divergent synthesis via sequential kinetic resolution, *Nat. Chem.*, 2020, **12**, 838–844.

3 (*a*) J. M. Gao, S. X. Yang and J. C. Qin, Azaphilones: Chemistry and Biology, *Chem. Rev.*, 2013, **113**, 4755–4811; (*b*) C. Chen, H. Tao, W. Chen, B. Yang, X. Zhou, X. Luo and Y. Liu, Recent advances in the chemistry and biology of structurally diverse azaphilones from 2012 to 2019, *RSC Adv.*, 2020, **10**, 10197–10220; (*c*) C. Pavesi, V. Flon, S. Mann, S. Leleu, S. Prado and X. Franck, Biosynthesis of azaphilones: a review, *Nat. Prod. Rep.*, 2021, **38**, 1058–1071; (*d*) N. Osmanova, W. Schultze and N. Ayoub, Azaphilones: a class of fungal metabolites with diverse biological activities, *Phytochem. Rev.*, 2010, **9**, 315–342.

4 (*a*) Y. Zheng, Y. Xin, X. Shi and Y. Guo, Cytotoxicity of Monascus Pigments and Their Derivatives to Human

Cancer Cells, *J. Agric. Food Chem.*, 2010, **58**, 9523–9528; (*b*) W. Wang, J. Yang, Y.-Y. Liao, G. Cheng, J. Chen, X.-D. Cheng, J.-J. Qin and Z. Shao, Cytotoxic Nitrogenated Azaphilones from the Deep-Sea-Derived Fungus *Chaetomium globosum* MP4-S01-7, *J. Nat. Prod.*, 2020, **83**, 1157–1166.

5 M. Chen, N. X. Shen, Z. Q. Chen, F. M. Zhang and Y. Chen, Penicilones A–D, Anti-MRSA Azaphilones from the Marine-Derived Fungus Penicillium janthinellum HK1-6, *J. Nat. Prod.*, 2017, **80**, 1081–1086.

6 (*a*) S. A. S. Mapari, U. Thrane and A. S. Meyer, *Trends Biotechnol.*, 2010, **28**, 300–307; (*b*) N. Osmanova, W. Schultze and N. Ayoub, *Phytochem. Rev.*, 2010, **9**, 315–342; (*c*) H. Hussain, A. M. Al-Sadi, B. Schulz, M. Steinert, A. Khan, I. R. Green and I. Ahmed, *Future Med. Chem.*, 2017, **9**, 1631–1648.

7 (*a*) J.-L. Tang, Z.-Y. Zhou, T. Yang, C. Yao, L.-W. Wu and G.-Y. Li, Azaphilone Alkaloids with Anti-inflammatory Activity from Fungus Penicillium sclerotiorum cib-411, *J. Agric. Food Chem.*, 2019, **67**, 2175–2182; (*b*) K. Becker, S. Pfütze, E. Kuhnert, R. J. Cox, M. Stadler and F. Surup, Hybridorubrins A–D: Azaphilone Heterodimers from Stromata of Hypoxylon fragiforme and Insights into the Biosynthetic Machinery for Azaphilone Diversification, *Chem.–Eur. J.*, 2021, **27**, 1438–1450.

8 S. A. S. Mapari, U. Thrane and A. S. Meyer, Fungal polyketide azaphilone pigments as future natural food colorants?, *Trends Biotechnol.*, 2010, **28**, 300–307.

9 For selected references on isochromenylium chemistry: (*a*) B. Yu, Gold(I)-Catalyzed Glycosylation with Glycosyl o-Alkynylbenzoates as Donors, *Acc. Chem. Res.*, 2018, **51**, 507–516; (*b*) Z.-L. Hu, W.-J. Qian, S. Wang, S. Wang and Z.-J. Yao, Construction of Multiring Frameworks by Metal-Free Cascade Reactions of Stable Isochromenylium Tetrafluoroborate, *J. Org. Chem.*, 2009, **74**, 8787–8793; (*c*) T. Miao, Z.-Y. Tian, Y.-M. He, F. Chen, Y. Chen, Z.-X. Yu and Q.-H. Fan, Asymmetric Hydrogenation of In Situ Generated Isochromenylium Intermediates by Copper/Ruthenium Tandem Catalysis, *Angew. Chem., Int. Ed.*, 2017, **56**, 4135–4139; (*d*) J. Zhu, A. R. Germain and J. A. Porco, Synthesis of Azaphilones and Related Molecules by Employing Cycloisomerization of o-Alkynylbenzaldehydes, *Angew. Chem., Int. Ed.*, 2004, **43**, 1239–1243.

10 T. Wang, Y. Wang, D. Feng, M. Wang, X. Yang and Z.-J. Yao, Isochromenylium/Isoquinolinium-Mediated One-Pot Annulation to Hexahydropyrazinoisoquinolines. Synthesis of Quinocarcinol, *Org. Lett.*, 2023, **25**, 8803–8808.

11 For selected work: (*a*) W.-S. Chen, F. Yang, T. Wang, G.-Q. Zhang, Y. Wei, M.-H. Wang, Z.-S. Chen and K. Ji, Chemoselective Transformations of Amides: An Approach to Quinolones from β-Amido Ynones, *Org. Lett.*, 2023, **25**, 5762–5767; (*b*) G.-Q. Zhang, F. Yang, W.-S. Chen, X. Zhao, T. Wang, Z.-S. Chen and K. Ji, A practical and economic route for regioselective cyclization of β-phenoxyl ynones to flavonoid derivatives, *Green Chem.*, 2024, **26**, 8711–8717.

12 (*a*) R. C. Clark, S. Y. Lee and D. L. Boger, Total Synthesis of Chlorofusin, Its Seven Chromophore Diastereomers, and Key Partial Structures, *J. Am. Chem. Soc.*, 2008, **130**, 12355–12369; (*b*) J. Zhu, N. P. Grigoriadis, J. P. Lee and J. A. Porco, Synthesis of the Azaphilones Using Copper-Mediated Enantioselective Oxidative Dearomatization, *J. Am. Chem. Soc.*, 2005, **127**, 9342–9343.