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Synthesis of 4-aryl-3,4-dihydrocoumarins and 4-aryl-4H-chromenes *via* Er(OTf)₃-catalyzed cascade reactions of *p*-quinone methides with 1,3-dicarbonyl compounds†

Xiaobo Bao,‡[a] Wei Yu,‡[b] Lilin Wang,[c] Xu Dong,[b] Guoli Wang,[b] Weilin Chen,*[b] Fei Li*[b] and Dongyin Chen [ID] *[b]

The Er(OTf)₃-catalyzed cascade cyclization reaction of *para*-quinone methides (*p*-QMs) with various 1,3-dicarbonyl compounds has been developed, which efficiently constructed a series of versatile 4-aryl-3,4-dihydrocoumarins and 4-aryl-4H-chromenes. Herein, we not only propose a novel cyclization strategy of *p*-QMs, but also provide an easy access to structurally diverse coumarins and chromenes.

Introduction

4-Aryl-3,4-dihydrocoumarin and 4-aryl-4H-chromene are important structural motifs that broadly occur in many natural products and biologically active compounds.[1] Molecules containing the 4-aryl-3,4-dihydrocoumarin or 4-aryl-4H-chromene scaffold exhibit noteworthy pharmacological effects. For example, compound **1** isolated from *Aloe vera* displays remarkable antioxidative and immunomodulatory properties.[2] Compound **2** is a synthetic analog of podophyllotoxin and exhibits interesting antimitotic activity.[3] Compound **3**, a specific inhibitor of insulin-regulated aminopeptidase, has potential ability in the enhancement of cognitive functions.[4] Compound **4**, also called crolibulin, is a tubulin polymerization inhibitor with potent apoptosis induction and cell growth inhibition, which has progressed to phase I/II clinical trial for anaplastic thyroid cancer.[5] Due to their wide biological applications, significant efforts have been devoted to the synthesis of 4-aryl-3,4-dihydrocoumarin and 4-aryl-4H-chromene derivatives. The conventional synthetic methods for 4-aryl-3,4-dihydrocoumarins involve (i) catalytic hydrogenation of 4-aryl-coumarins,[6] (ii) hydroarylation of cinnamic acids with phenols,[7] (iii) annulation reaction of phenols with Meldrum's acid derivatives,[8] (iv) lactonization of 3-aryl-3-(2-hydroxyphenyl) propanoates,[9] (v) asymmetric formal [4 + 2] cyclization of *o*-

quinone methides (*o*-QMs) with various two-carbon reaction partners,[10] and (vi) multicomponent reaction between phenols, malonates and aryl aldehydes.[11] Meanwhile, several facile methodologies have been developed for the synthesis of 4-aryl-4H-chromenes including the electrophilic substitution of aromatic compounds with 4-methylsulfanyl-4H-chromenes,[12] dehydration of the 1,4-adducts between arylboronic acids and β-(2-hydroxyaryl)-enones,[13] tandem benzylation–cyclization of 2-(hydroxymethyl)phenols with 1,3-dicarbonyl compounds,[14] domino Michael addition–cyclization of 2-hydroxychalcone with indoles,[15] and multicomponent reaction between phenols, aryl aldehydes and malononitrile.[16] To our knowledge, however, all of these approaches are hardly realized the simultaneous synthesis of 4-aryl-3,4-dihydrocoumarins and 4-aryl-4H-chromenes under current conditions (Fig. 1).

In recent years, the application of *p*-QMs in the construction of oxygen/nitrogen-containing heterocyclic frameworks has attracted much attention in the synthetic community. Especially, Fan and coworkers described an efficient synthesis of 4-aryl-3,4-dihydrocoumarins through an intramolecular vinylogous Rauhut–Currier reaction of *ortho*-acryloyloxyphenyl-substituted *p*-QMs (Scheme 1, eqn (1)).[17] Shi[18a] and Hu[18b] reported a [4 + 2] cyclization of *o*-hydroxyphenyl-substituted *p*-QMs with alkynes, which provided an efficient method for the
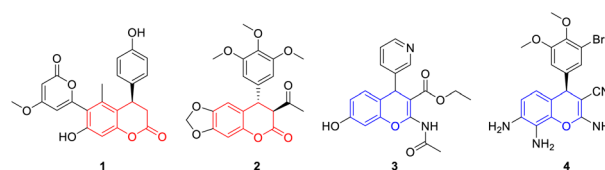
[a]College of Pharmacy, Jiangsu Vocational College of Medicine, Yancheng, 224005, China
[b]School of Pharmacy, Nanjing Medical University, Nanjing, 211166, China. E-mail: chendongyin@njmu.edu.cn; kldlf@njmu.edu.cn; chenweilin@njmu.edu.cn
[c]Sir Run Run Hospital, Nanjing Medical University, Nanjing 211166, China
† Electronic supplementary information (ESI) available. CCDC 2246898 and 2248199. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ra02267f
‡ These authors contributed equally to this work.

Fig. 1 Selected bioactive 4-aryl-3,4-dihydrocoumarins and 4-aryl-4H-chromenes.
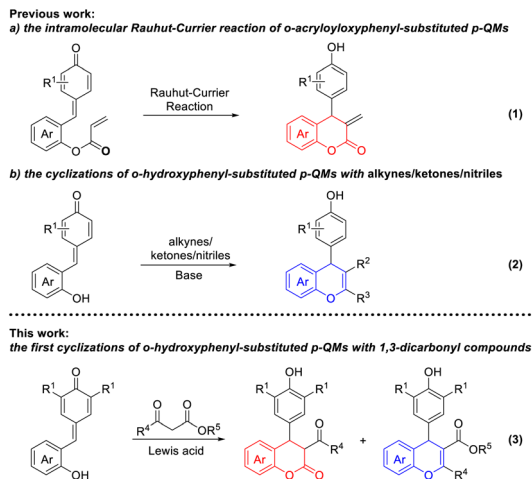
**Scheme 1** Cyclization strategies for the synthesis of 4-aryl-3,4-dihydrocoumarins and 4-aryl-4H-chromenes from p-QMs.

construction of 4-aryl-4H-chromene scaffold (Scheme 1, eqn (2)). In addition, two reports involving an organocatalytic domino reaction of o-hydroxyphenyl-substituted p-QMs with β-functionalized ketones/nitriles have been presented for the synthesis of chiral 4-aryl-4H-chromenes.[18c,d] Very recently, our group developed an efficient synthetic approach to 7-amino-coumarins via Er(OTf)$_3$-catalyzed Pechmann condensation of 3-aminophenols with β-ketoesters.[19] As we know, Er(OTf)$_3$ as a very gentle Lewis acid catalyst can effectively activate carbonyl,

epoxide and alkene compounds even in the presence of trace amount of water.[20] 1,3-Dicarbonyl compounds have been widely used as versatile and highly active building blocks in organic synthesis because of their intrinsic reactivities.[21] Based on these discoveries, we envisioned that the simultaneous synthesis of 4-aryl-3,4-dihydrocoumarin and 4-aryl-4H-chromene could be realized through the union of p-QMs and different 1,3-dicarbonyl compounds via a Er(OTf)$_3$-catalyzed cascade reaction (Scheme 1, eqn (3)).

Results and discussion

To verify our hypothesis, o-hydroxyphenyl-substituted p-QM **5a** and β-ketoester **6a** were employed as model substrates for the optimization of the cascade reaction conditions; the results are presented in Table 1. The screening of solvent was carried out first because the use of a suitable solvent is crucial for Lewis acid-catalyzed reaction. Notably, when toluene was used at reflux temperature for 8 h, the expected 4-aryl-3,4-dihydrocoumarin **7a** and 4-aryl-4H-chromene **8a** could be obtained in 62% and 22% yields, respectively (entry 4). However, DCE, ACN and dioxane with low boiling point were inefficient for the generation of **8a**, only affording the desired product **7a** in low yields (10–38%) even with extended reaction times (entries 1–3). The polar solvent with high boiling point, like DMSO and DMF, directly prevented this transformation due to the coordination of these solvents with the Lewis acid catalysts (entries 5 and 6). Next, our attention turned to investigate the effect of reaction time and temperature on the formation of **7a** and **8a**

Table 1 Investigation of conditions for lanthanide triflate-catalyzed synthesis of 4-aryl-3,4-dihydrocoumarin **7a** and 4-aryl-4H-chromene **8a**[a]
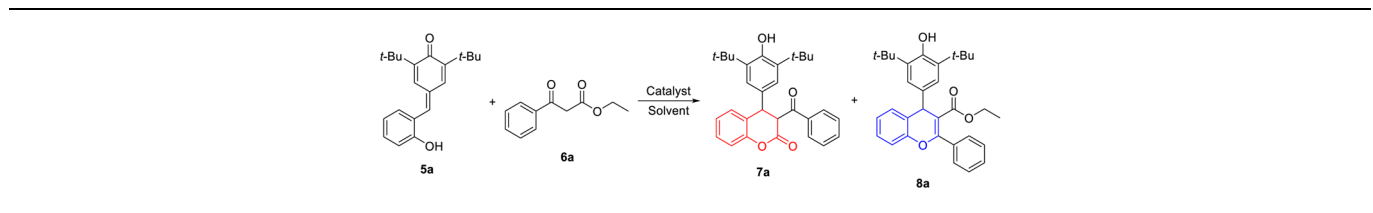
Entry	Catalyst	Solvent	Temp. (°C)	T (h)	Yield of **7a**[b] (%)	Yield of **8a**[b] (%)
1	Er(OTf)$_3$	DCE	84	24	38	0
2	Er(OTf)$_3$	ACN	82	24	33	0
3	Er(OTf)$_3$	Dioxane	100	24	10	0
4	Er(OTf)$_3$	Toluene	110	8	62	22
5	Er(OTf)$_3$	DMF	120	12	0	0
6	Er(OTf)$_3$	DMSO	140	12	0	0
7	Er(OTf)$_3$	Toluene	110	12	68	22
8	Er(OTf)$_3$	Toluene	110	24	64	23
9	Er(OTf)$_3$	Toluene	110	48	61	24
10	Er(OTf)$_3$	Toluene	70	24	52	0
11	Er(OTf)$_3$	Toluene	90	24	71	11
12	Sc(OTf)$_3$	Toluene	110	12	28	37
13	Y(OTf)$_3$	Toluene	110	12	21	34
14	La(OTf)$_3$	Toluene	110	12	25	44
15	Ce(OTf)$_3$	Toluene	110	12	35	10
16	Yb(OTf)$_3$	Toluene	110	12	24	23

[a] Reaction conditions: **5a** (1.0 mmol), **6a** (1.1 mmol), salt (20 mol%), solvent (3 mL). [b] Isolated yield.

(entries 7–11). After several attempts, we found that prolonging the reaction time was beneficial to improve the yield and 12 h was the appropriate reaction time. The reaction temperature was the key factor for the formation of **8a**. When the reaction proceeded at 70 °C, the expected **7a** was produced in 52% yield without the generation of **8a** (entry 10). At 90 °C, we obtained **7a** in 71% yield and **8a** in 11% yield (entry 11). In addition, a set of lanthanide triflates were investigated for this reaction under the same reaction conditions. Compared with $Er(OTf)_3$, other lanthanide salts such as $Sc(OTf)_3$, $Y(OTf)_3$, $La(OTf)_3$, $Ce(OTf)_3$ and $Yb(OTf)_3$ provided lower total yields of **7a** and **8a** (entries 12–16). However, these explorations are difficult to achieve product specificity. Finally, the optimal reaction conditions for the simultaneous synthesis of **7a** and **8a** are selected as those shown in entry 7 (1.0 equiv. of p-QM **5a**, 1.1 equiv. of β-ketoester **6a**, 0.2 equiv. of $Er(OTf)_3$ as catalyst in toluene at 110 °C for 12 h).

With the optimal reaction conditions in hand, the generality of $Er(OTf)_3$-catalyzed cyclization between p-QMs **5** and β-ketoesters **6** was investigated. As shown in Table 2, a wide range of β-ketoesters **6** could readily react with p-QM **5a** (R^4 = H), which simultaneously afforded the corresponding 4-aryl-3,4-dihydrocoumarins **7b–7m** and 4-aryl-4H-chromenes **8b–8m** in good overall yields. In detail, β-ketoesters **6** bearing alkane groups (R^4 = Me, Et, i-Pr, cyclopropyl, cyclobutyl and cyclopentyl) mainly provided **8b–8g** in moderate to good yields (41–75%), with **7b–7g** in low yields (14–37%). By contrast, when R^4 was cyclohexyl group, the corresponding 4-aryl-3,4-dihydrocoumarin **7h** was obtained in good yield (63%), together with 4-aryl-4H-chromenes **8h** in low yield (25%). Encouraged by the above results, we further explored the effects of (heter)aryl groups on the product yields. Interestingly, β-ketoester **6** with a strong electron-donating group on the benzene ring gave the corresponding product **8j** (R^4 = 4-methoxyphenyl) in good yield (60%); however, **8a** (R^4 = phenyl), **8i** (R^4 = 4-methylphenyl) and **8k** (R^4 = 4-chlorophenyl) were produced in low yields (19–29%) under the same reaction conditions. When R^4 were heteraryl groups, the corresponding 4-aryl-3,4-dihydrocoumarins **7l** (R^4 = 2-furanyl) and **7m** (R^4 = 2-thiophenyl) were the main products in 59–62% yields. However, the substituents on the benzene ring of p-QMs **5** could affect the proportion of products, and the corresponding products **7n–7o** and **8n–8o** were obtained in 52–55% and 26–39% yields, compared to **7j** and **8j**. Moreover, NMR data displayed **7b**, **7c**, **7e**, **7f** with enol form, and **7d**, **7g–7o** with keto form. The structure of **8h** was determined by single-crystal X-ray diffraction analyses.[22]

Subsequently, to realize the exclusive synthesis of 4-aryl-3,4-dihydrocoumarins, we extended this protocol to various malonates **9** under the standard conditions (Table 3). To our delight, a series of malonates could be employed to the reaction with p-QMs **5**, which delivered functionalized 4-aryl-3,4-dihydrocoumarins **10a–10j** in generally acceptable to good yields (up to 90%). It was found that the stability of malonate esters could affect the reaction efficiency in this intramolecular transesterification–cyclization process, and the corresponding products **10c** (R^5 = i-Pr) and **10d** (R^5 = benzyl) were formed in

**Table 2** $Er(OTf)_3$-catalyzed simultaneous synthesis of 4-aryl-3,4-dihydrocoumarin **7** and 4-aryl-4H-chromene **8**[a,b]

X-ray of **8h**
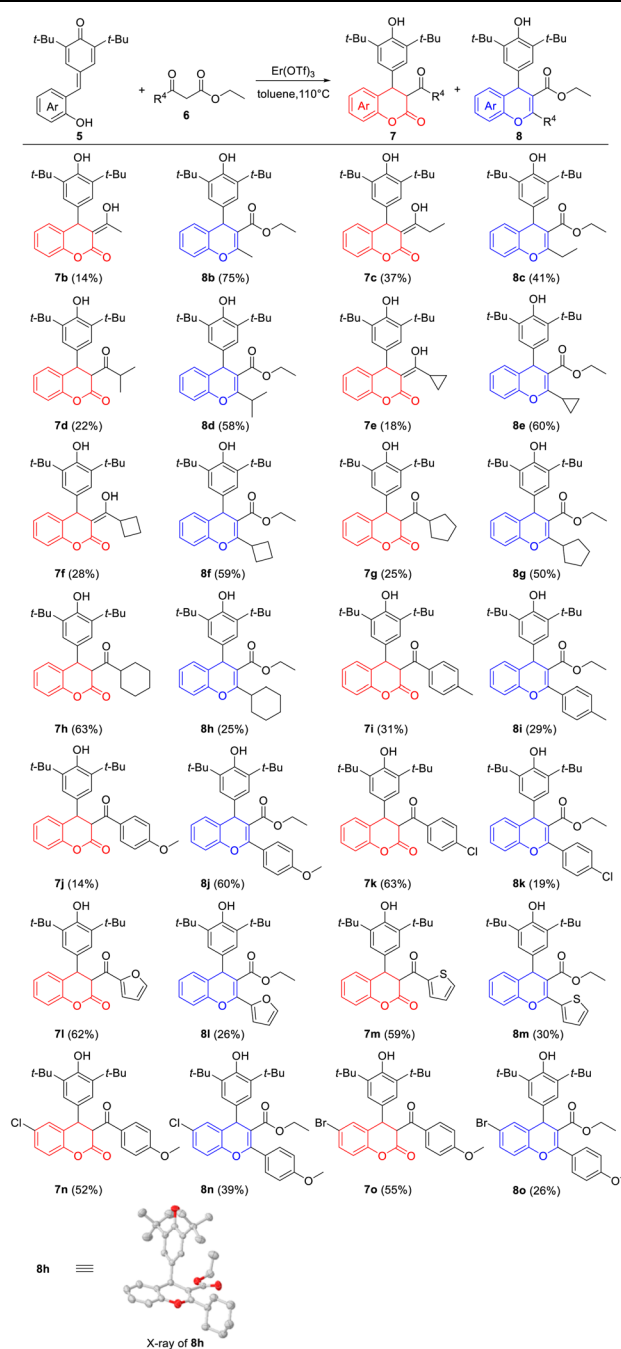
[a] Reaction conditions: **5** (1.0 mmol), **6** (1.1 mmol) and $Er(OTf)_3$ (20 mol%) in toluene (3 mL) at 110 °C for 12 h. [b] Isolated yield.

42–54% yield. The electronic properties of substituents on the benzene ring of p-QMs **5** almost had no influence on the efficiency of this reaction; **10e–10i** were obtained in 82–88% yield. Interestingly, however, the presence of strong electron-withdrawing nitro group promoted the hydrolysis and decarboxylation at the 3-position under the standard conditions, giving **10j** in 90% yield. Moreover, the structure of **10c**, which

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Table 3 Er(OTf)$_3$-catalyzed exclusive synthesis of 4-aryl-3,4-dihydrocoumarin 10[a,b]

Table 4 Er(OTf)$_3$-catalyzed exclusive synthesis of 4-aryl-4H-chromene 12[a,b]
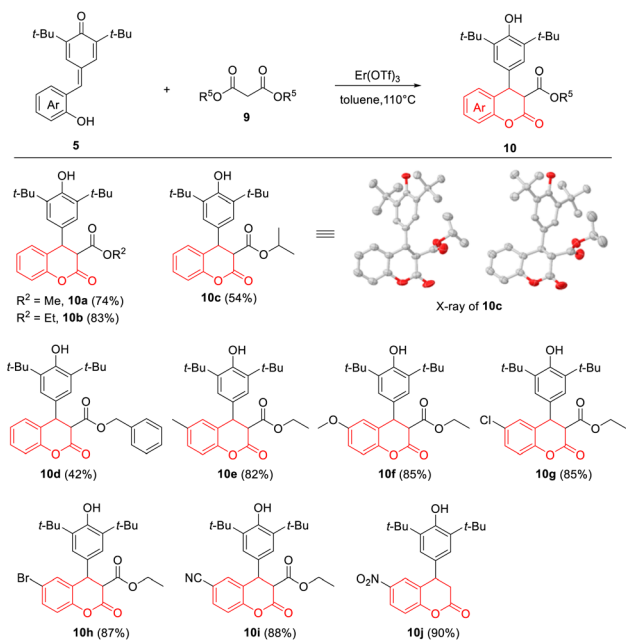
[a] Reaction conditions: **5** (1.0 mmol), **9** (1.1 mmol) and Er(OTf)$_3$ (20 mol%) in toluene (3 mL) at 110 °C for 12 h. [b] Isolated yield.

[a] Reaction conditions: **5** (1.0 mmol), **11** (1.1 mmol) and Er(OTf)$_3$ (20 mol%) in toluene (3 mL) at 110 °C for 12 h. [b] Isolated yield.

was a pair of enantiomers, was further assigned by X-ray crystallographic analysis.[22]

Furthermore, to verify whether it is suitable for the exclusive synthesis of 4-aryl-4H-chromenes, this protocol was extended to various β-diketones **11** under similar conditions (Table 4). We were pleased to find that the reaction of p-QM **5a** with 2,4-pentanedione occurred readily to afford the desired 4-aryl-4H-chromene **12a** in 39% yield. Significantly, a variety of 1-(hetero) aryl-1,3-butanediones reacted with p-QMs **5** smoothly to give the corresponding 2-(hetero)aryl-3-acetyl-4-aryl-4H-chromenes **12b–12j** in 38–60% yields, without the generation of 2-acetyl-3-(hetero)aryl-4-aryl-4H-chromenes. This result was attributed to intramolecular π-conjugated effects and steric hindrance effects. To further check the substrate scope of this reaction, cyclic 1,3-diketones were taken under consideration, which provided products **12k** and **12l** in good yields (77–82%).

On the basis of the experimental results, a plausible mechanism was suggested (Scheme 2). As exemplified by the formation of products **7a** and **8a**, in the presence of Er(OTf)$_3$, the whole cascade reaction was initiated by the 1,6-addition reaction of p-QM **5a** and 1,3-dicarbonyl compound **6a**, which produced the key intermediate 1,6-adduct **I** possessing two reactive sites. Then, intermediate **I** underwent an intramolecular transesterification between phenolic hydroxyl group and carboxylate group to accomplish the cyclization, which afforded 4-aryl-3,4-dihydrocoumarin **7a** (Scheme 2, path a). Meanwhile, the intramolecular nucleophilic attack of phenolic hydroxyl group at the keto carbonyl group completed the cyclization of intermediate **I** to form 4-aryl-4H-chromene **8a** with elimination of a water molecule (Scheme 2, path b).
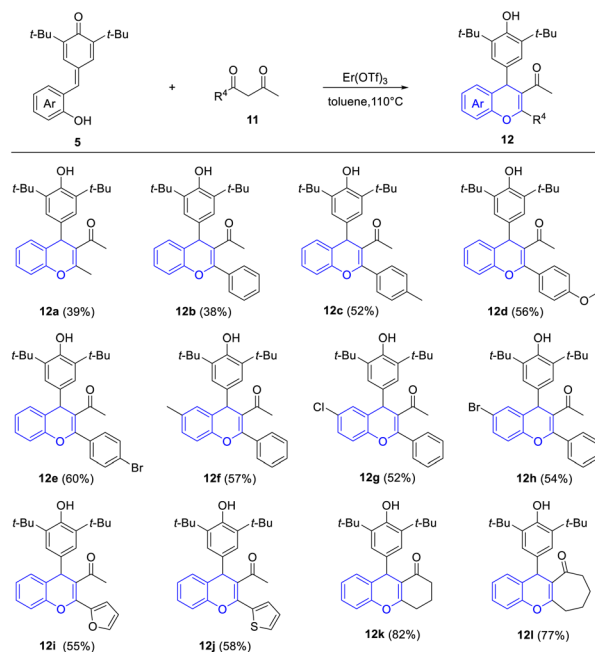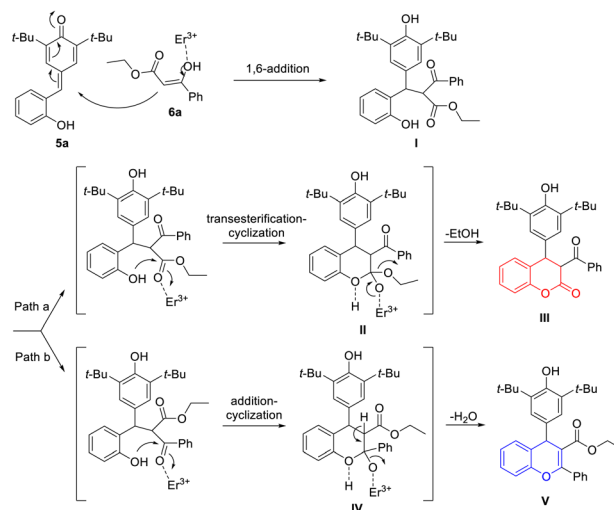
Scheme 2 Plausible reaction path for the formation of 4-aryl-3,4-dihydrocoumarin and 4-aryl-4H-chromene.

Conclusions

In summary, we have established the first cyclization of para-quinone methide derivatives with 1,3-dicarbonyl compounds by utilizing Er(OTf)$_3$-catalyzed cascade reaction, which efficiently constructed the scaffolds of 4-aryl-3,4-dihydrocoumarin and 4-aryl-4H-chromene. This protocol could not only fulfill the task of developing new cyclization strategies of p-QMs, but also

provide an easy access to structurally diverse coumarins and chromenes. The further applications of Er(OTf)$_3$-catalyzed cascade transformations of *p*-QMs are ongoing in our laboratory.

Author contributions

DC, XB, and WY conceived the idea and designed the research. XB and WY performed the research. LW, XD, and GW analyzed the data. DC, XB, and WY wrote the original manuscript. WC and FL reviewed the manuscript and suggested improvements. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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22 CCDC 2248199 (**8h**) and 2246898 (**10c**) contain the supplementary crystallographic data (ESI†).