Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2023, **14**, 11850

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 5th July 2023
Accepted 22nd September 2023

DOI: 10.1039/d3sc03452f

rsc.li/chemical-science

Construction of 4-hydroxycoumarin derivatives with adjacent quaternary and tertiary stereocenters *via* ternary catalysis†

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4-Hydroxycoumarin derivatives represent one of the most important scaffolds in biologically active substances, pharmaceuticals and functional materials. Herein, we describe an efficient Pd/amine/Brønsted acid ternary-catalytic multicomponent reaction for the rapid construction of substituted 4-hydroxycoumarin derivatives with adjacent quaternary and tertiary stereocenters *via* convergent assembly of two *in situ* generated active intermediates. Furthermore, the late-stage transformations of coumarin derivatives and their *in vitro* trial of antitumor activity successfully demonstrated the potential utilities of the products as platform molecules.

Introduction

4-Hydroxycoumarin derivatives are privileged drug skeletons that are frequently encountered in pharmaceutical molecules,[1] such as warfarin,[2] dicoumarol,[3] bothrioclinin,[4] cyclocoumarol,[5] pyranocoumarin,[6] *etc.* (Scheme 1a). Owing to their diverse biological activities, it is continuingly attractive to develop highly effective synthetic methods for the practical construction of coumarin scaffolds with structural diversity and complexity for drug discovery.

In the past few decades, a variety of important advances have made for the construction of dihydropyran-fused coumarin derivatives with commercially available 4-hydroxycoumarin[7–13] (Scheme 1b). For example, the Shivashankar group developed a Mitsunobu etherification to provide fused pyranobiscoumarin analogues from 1,2-diols at 80 °C.[14] Bezuidenhoudt *et al.*[15] and Abedi-Madiseh *et al.*[16] also synthesized pyrano[3,2-*c*]coumarins with substituted chalcones at 100 °C, independently. Jeong and coworkers also reported a microwave-promoted reaction with 4-hydroxycoumarins, aldehydes, and acetophenones to afford diverse pyranocoumarins.[17] Moreover, formal Friedel–Crafts alkylation between 4-hydroxycoumarins and propargylic alcohols has been reported as an efficient way to furnish multi-substituted pyranocoumarins by different research groups.[18–21] However, approaches toward these scaffolds were limited to using bench-stable reagents and usually under harsh conditions, such as high temperature and microware-mediated conditions.[22] Considering these inherent drawbacks, highly effective synthetic methods with operational simplicity and mild conditions to construct functionalized coumarin derivatives are still highly desired.

Multicomponent reactions have emerged as a powerful strategy for efficient synthesis of complex heterocycles.[23–30] In past decades, an astounding number of binary-catalytic multicomponent reactions *via* interception of active ylide intermediates or zwitterionic intermediates derived from different carbene precursors have been developed by Gong,[31,32] Schneider,[33] Wang,[34] us[35–42] and others,[43,44] providing an efficient access to structurally diverse and functionalized heterocyclic scaffolds with one-pot operation under mild conditions (Scheme 1c). However, the development of ternary catalysis systems among higher-order multicomponent reactions is sluggish. The challenges of ternary catalysis are (1) the construction of a compatible reaction system to form two *in situ* intermediates; (2) the matching issue between two different active intermediates; and (3) the selectivity issue for the convergent assembly of abovementioned two intermediates. In our latest studies,[45,46] we reported a novel ternary-catalytic higher-order multicomponent reaction *via* assembly of *in situ* generated α,β-unsaturated iminium ions with zwitterionic or ylide intermediates under operationally simple conditions. Inspired by these advances[47–50] and as a continuation of our interest in ternary-catalytic higher-order multicomponent reactions, we envisioned that 4-hydrocoumarin might be used as a coupling partner in ternary-catalytic multicomponent reactions to furnish substituted coumarin derivatives *via* carbene *gem*-difunctionalization process. Notably, we found that 4-

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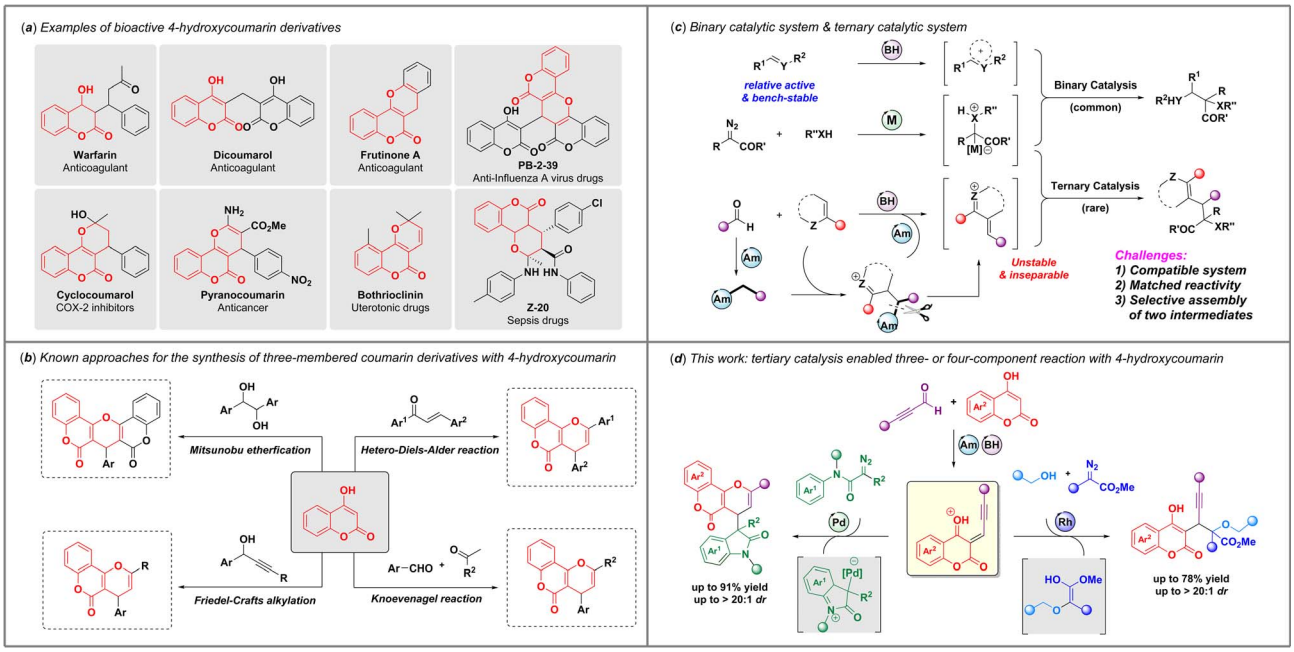
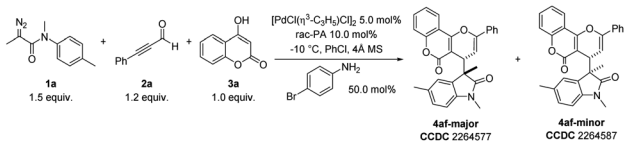
† Electronic supplementary information (ESI) available. CCDC 2264577, 2264587, 2264580, 2269933. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3sc03452f



Scheme 1 (a) Representative examples of bioactive 4-hydroxycoumarin derivatives. (b) Methods for synthesizing pyranocoumarin derivatives. (c) Binary catalysis and ternary catalysis. (d) This work.

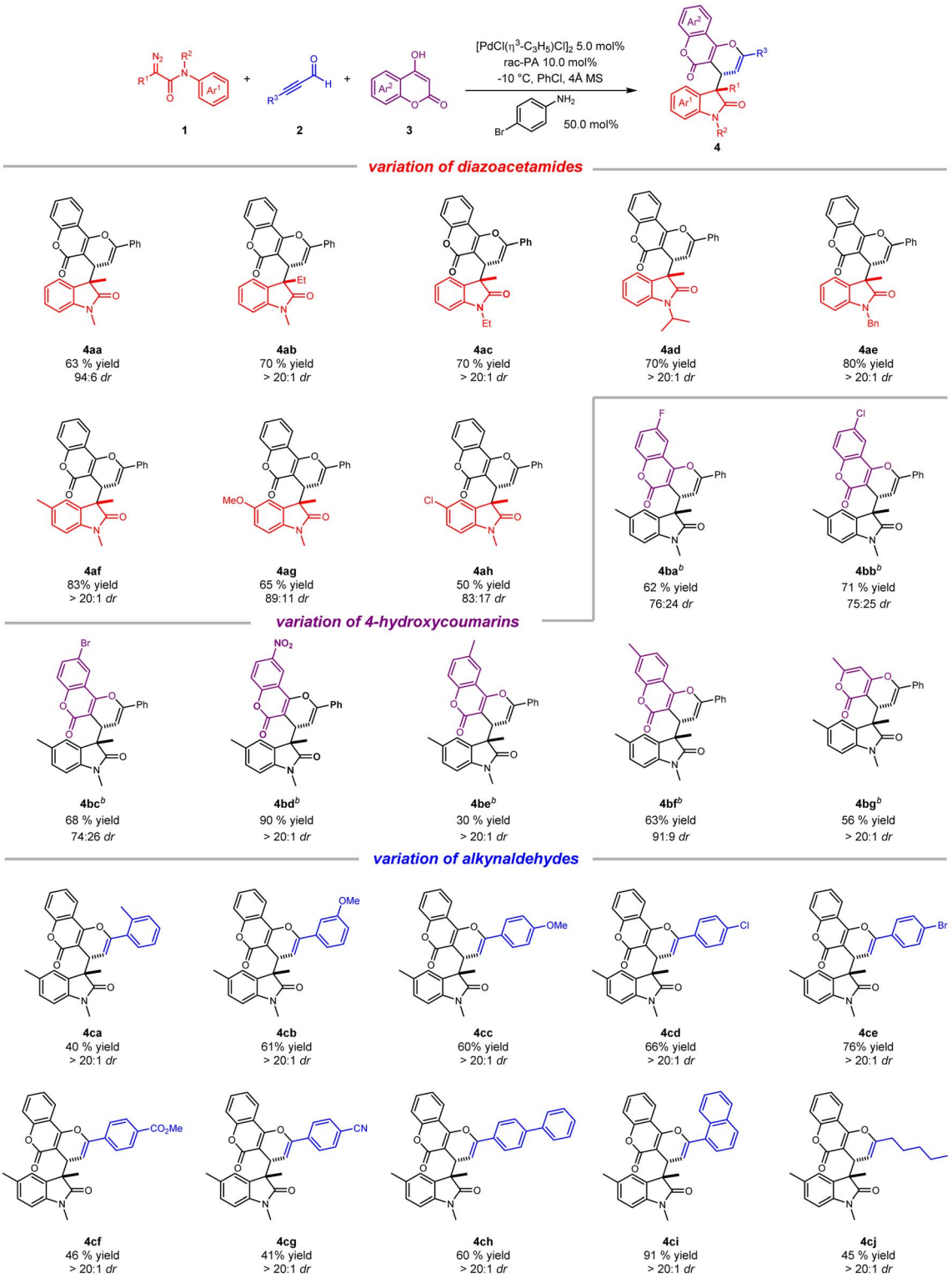
hydroxycoumarins and alkynaldehydes could generate active electrophilic intermediates under catalysis of phosphoric acid and amine catalyst, which provided a fundamental basis to develop an effective and mild protocol for the synthesis of functionalized coumarin derivatives through electrophilic interception of ylide or zwitterionic intermediates. Herein, we report a ternary-catalytic multicomponent reaction through interception of zwitterionic intermediates with active electrophilic intermediates, *in situ* generated from 4-hydroxycoumarins and alkynaldehydes, enabling convenient access to pyranocoumarins with good yields and diastereoselectivities. More importantly, such coumarin intermediates could also be

Table 1 Optimization of the reaction conditions[a]



Entry	Deviation from the "standard conditions"	Yield[b] (%)	dr[c]
1	None	85 (83)[d]	>20 : 1
2	Without 4-$BrC_6H_4NH_2$	<5	—
3	Without $[PdCl(\eta^3\text{-}C_3H_5)]_2$	<5	—
4	Without *rac*-PA	48	>20 : 1
5	Without 4 Å MS	10	>20 : 1
6	$Rh_2(OAc)_4$, $Cu(MeCN)_4PF_6$, AgOTf, or FeTPPCl instead of $[PdCl(\eta^3\text{-}C_3H_5)]_2$	<5	—
7	$[PdCl(\pi\text{-cinnyl})]_2$ instead of $[PdCl(\eta^3\text{-}C_3H_5)]_2$	67	93 : 7
8	THF instead of PhCl	53	76 : 24
9	DCM instead of PhCl	67	>20 : 1
10	Toluene instead of PhCl	86	85 : 15
11	Reaction performed at 0 °C	63	92 : 8
12	Reaction performed at −20 °C	71	>20 : 1

[a] The reactions were conducted on a 0.1 mmol scale: **1a** : **2a** : **3a** = 1.5 : 1.2 : 1.0, $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0 mol%), racemic phosphoric acid (*rac*-PA) catalyst (10 mol%), 4-$BrC_6H_4NH_2$ (50 mol%), 4 Å MS (100 mg). **1a**, **2a** in 1.0 mL solvent were added into a solution of **3a**, $[PdCl(\eta^3\text{-}C_3H_5)]_2$, *rac*-PA, 4-$BrC_6H_4NH_2$, and 100 mg 4 Å MS in 1.0 mL solvent *via* a syringe pump for 1 h, and the resulting mixture was stirred overnight. [b] Determined by ^{1}H NMR spectroscopy analyses using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by ^{1}H NMR spectroscopy analyses. [d] Isolated yields.



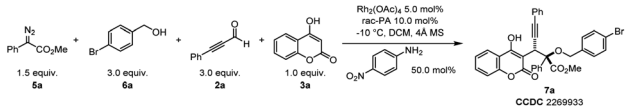
Scheme 2 Substrate scope for the synthesis of 4-hydroxycoumarin derivatives[a]. [a] Reaction conditions: **1** (0.15 mmol), **2** (0.12 mol), **3** (0.10 mol), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0 mol%), *rac*-PA (10 mol%), 4-$BrC_6H_4NH_2$ (50 mol%), 4 Å MS (100 mg), PhCl (2 mL), −10 °C, 12 h. Isolated yields. The dr was determined by ^{1}H NMR spectroscopy analyses of the crude reaction mixture. [b] Mixed solvent (PhCl : THF = 1 : 1, 2 mL) was used.

trapped by oxonium ylide intermediates derived from diazoacetates and alcohols, leading to a valuable and efficient four-component reaction to build diverse coumarin skeletons with adjacent quaternary and tertiary stereocenters.

Results and discussion

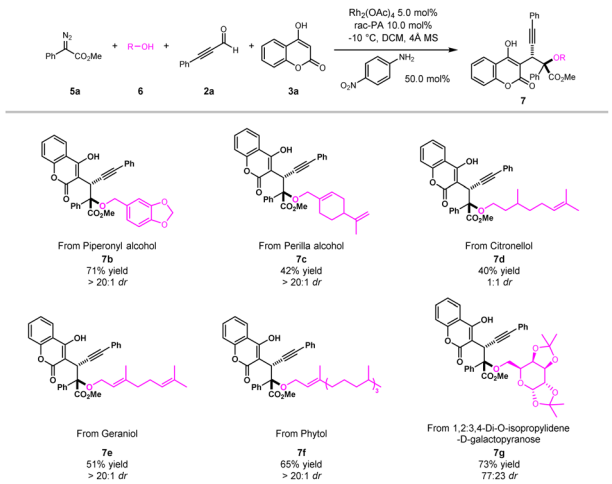
To validate our speculation, we chose commercially available 3-phenylpropiolaldehyde (**2a**), 4-hydroxy-2*H*-chromen-2-one (**3a**),

Table 2 Optimization of the four-component reaction conditions[a]



Entry	Deviation from the "standard conditions"	Yield[b] (%)	dr[c]
1	None	80 (78)[d]	>20 : 1
2	Without 4-$NO_2C_6H_4NH_2$	<5	—
3	Without $Rh_2(OAc)_4$	<5	—
4	Without *rac*-PA	<5	—
5	Without 4 Å MS	49	>20 : 1
6	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ in place of $Rh_2(OAc)_4$	36	>20 : 1

[a] The reactions were conducted on a 0.1 mmol scale: **5a** : **6a** : **2a** : **3a** = 1.5 : 3.0 : 3.0 : 1.0, $Rh_2(OAc)_4$ (5.0 mol%), *rac*-PA (10 mol%), 4-$NO_2C_6H_4NH_2$ (50 mol%) and 4 Å MS (100 mg). **5a**, **2a** in 1.0 mL DCM were added into a solution of **6a**, **3a**, $Rh_2(OAc)_4$, *rac*-PA, 4-$NO_2C_6H_4NH_2$, and 100 mg 4 Å MS in 1.0 mL DCM *via* a syringe pump for 1 hour, and the resulting mixture was stirred for another 2 hours. [b] Determined by ^{1}H NMR spectroscopy analyses using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by ^{1}H NMR spectroscopy analyses. [d] Isolated yield.



Scheme 3 Late-stage functionalization of complex and biorelevant molecules[a]. [a] Reaction conditions: **5a** (0.30 mmol), **6** (0.60 mol), **2a** (0.60 mol), **3a** (0.20 mol), $Rh_2(OAc)_4$ (5.0 mol%), *rac*-PA (10 mol%), 4-$NO_2C_6H_4NH_2$ (50 mol%), 4 Å MS (100 mg), DCM (4 mL), −10 °C, 3 h. Isolated yields. The dr was determined by ^{1}H NMR spectroscopy analyses.

and 2-diazo-*N*-methyl-*N*-(*p*-tolyl)propanamide (**1a**) as benchmark substrates for the optimization (Table 1). The desired three-component product **4af** could be obtained in 85% yield with diastereomeric ratio (dr) > 20 : 1 when **1a** and **2a** were added slowly to $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0 mol%), racemic phosphoric acid (*rac*-PA) (10.0 mol%), and 4-bromoaniline (50.0 mol%) at −10 °C with 4 Å molecular sieves (MS) as an additive in PhCl for one hour (entry 1). Control experiments revealed that 4-bromoaniline and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ catalyst proved critical to the overall success of the transformation (entries 2 and 3). The absence of *rac*-PA led the yield of **4af** decreasing to 48% (entry 4) and only trace amounts of desired product were observed without 4 Å MS (entry 5). Replacing $[PdCl(\eta^3\text{-}C_3H_5)]_2$ with other metal catalysts such as Rh(II), Cu(I), Ag(I) and Fe(III) provided either lower yields or decreased diastereoselectivities (entries 6 and 7). Solvent-screening (entries 8–10) revealed that PhCl was the best choice, leading to a satisfactory outcome. Moreover, increasing or reducing the reaction temperature was proved to be ineffective and could be detrimental to yield and dr (entries 11 and 12). Importantly, the relative stereochemistry of **4af-major** and **4af-minor** was unambiguously confirmed by X-ray analysis.

With the optimal reaction conditions in hand, we sought to explore the generality of this ternary-catalytic multicomponent reaction. As shown in Scheme 2, a variety of substituted coumarin derivatives was easily obtained with moderate to good yield and up to dr > 20 : 1. We firstly investigated the scope of diazoacetamides **1** by employing commercially available **2a** and **3a** as reaction partners. With regard to various R^1 groups of diazoacetamides, methyl and ethyl substituents were well tolerated, furnishing corresponding products **4aa** and **4ab** in 63% and 70% yields, respectively. *N*-Substituted diazoacetamides tethered with ethyl, isopropyl and benzyl substituents also reacted smoothly to afford **4ac–4ae** in high yields (70–80%) with dr > 20 : 1. Moreover, due to the electronic effect, diazoacetamides with an electron-donating substituent on the aryl group worked better than electron-withdrawing substituents, delivering the desired products with better yields and diastereoselectivities (**4af–4ah**). We then turned our attention to exploring the scope of substituted coumarins **2**. Owing to poor solubility of substituted coumarins in PhCl, the reaction was performed in mixed solvent (PhCl : THF = 1 : 1). Generally, a wide range of 4-hydroxycoumarins possessing different functional groups, such as 6-F, 6-Cl, 6-Br, 6-NO_2, 6-methyl and 7-methyl, were all amenable to the transformation, yielding the desired products (**4ba–4bf**) with moderate to good yields and diastereoselectivities. Of note, six-membered ring-containing 4-hydroxy-6-methyl-2-pyrone also worked well and gave corresponding product **4bg** in 56% yield and dr > 20 : 1. Lastly, a broad array of alkynaldehydes were checked for their substrate scope. As expected, this catalytic process was well compatible with different alkynaldehydes bearing electron-donating and electron-withdrawing substituents at the *para*-, *ortho*-, and *meta*-positions on the aromatic ring, leading to three-component products (**4ca–4cg**) with good yields (40–76%) and excellent diastereoselectivities. Importantly, alkynaldehydes bearing electron-donating substituents seemed to be much superior to those bearing electron-withdrawing substituents for the yields of products on account of electronic effect. It is worth mentioning that alkynaldehydes bearing an extended aromatic ring such as biphenyl and 1-naphthyl were readily converted to desired products (**4ch** and **4ci**) in high yields and dr > 20 : 1. Apart from aromatic alkynaldehydes, a long-chain alkyl with alkynaldehyde substrate was also tolerant to this reaction, producing **4cj** in moderate yield and excellent diastereoselectivity.

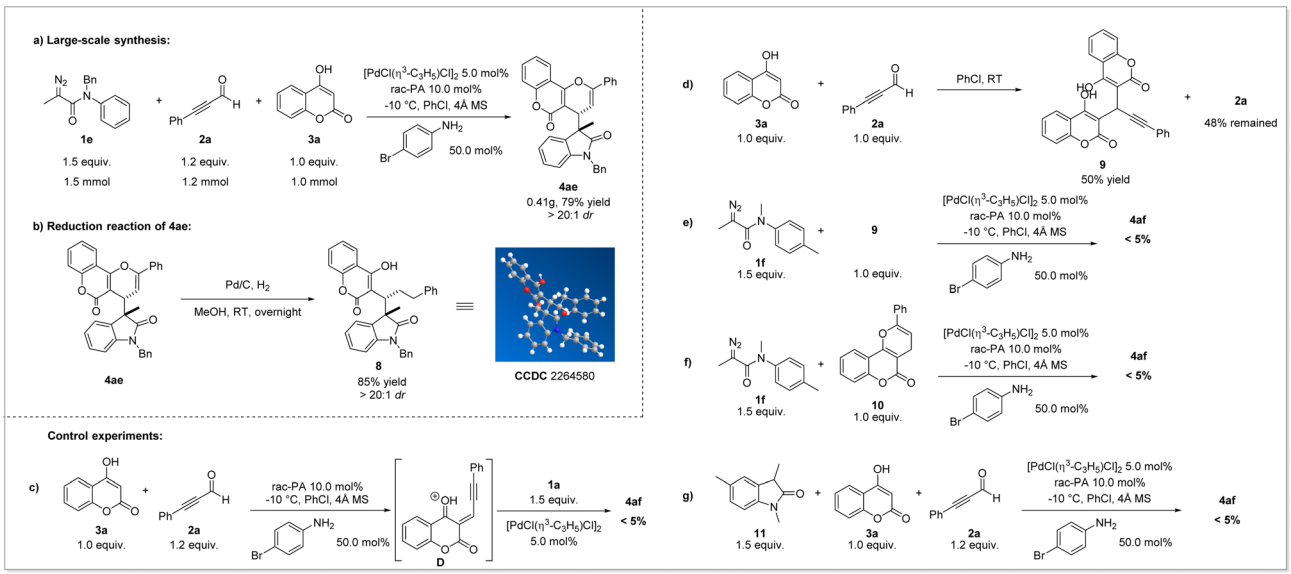
In an effort to exploit the generality of this ternary-catalytic higher-order multicomponent reaction to synthesize 4-hydrocoumarin derivatives, we next pursued the development of an

efficient four-component reaction to directly trap oxonium ylides *in situ* generated from diazoacetates and alcohols by coumarin intermediates (Table 2). Encouragingly, a desirable four-component reaction with diazoacetate **5a**, 4-bromobenzyl alcohol **6a**, phenylpropiolaldehyde **2a** and 4-hydroxycoumarin **3a** was accomplished by skillfully altering the metal catalyst and amine catalyst as well as modifying the loading of reaction substrates, leading to functionalized 4-hydroxycoumarin derivatives with newly formed quaternary and tertiary stereocenters (Table 2). The best result was obtained under the catalysis of $Rh_2(OAc)_4$, 4-nitroaniline, and *rac*-PA, leading to the corresponding product **7a** with 78% isolated yield and dr > 20 : 1 (entry 1). The structure of **7a** was unambiguously confirmed by a later X-ray diffraction study. Control experiments showed that 4-nitroaniline, $Rh_2(OAc)_4$, *rac*-PA and 4 Å MS were indispensable for the higher-order multicomponent reaction (entries 2–5). In particular, replacing $Rh_2(OAc)_4$ with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ gave lower yield (entry 6). This protocol enabled operationally facile access to valuable coumarin derivatives with adjacent quaternary and tertiary stereocenters using common, bench-stable, and readily accessible starting materials.

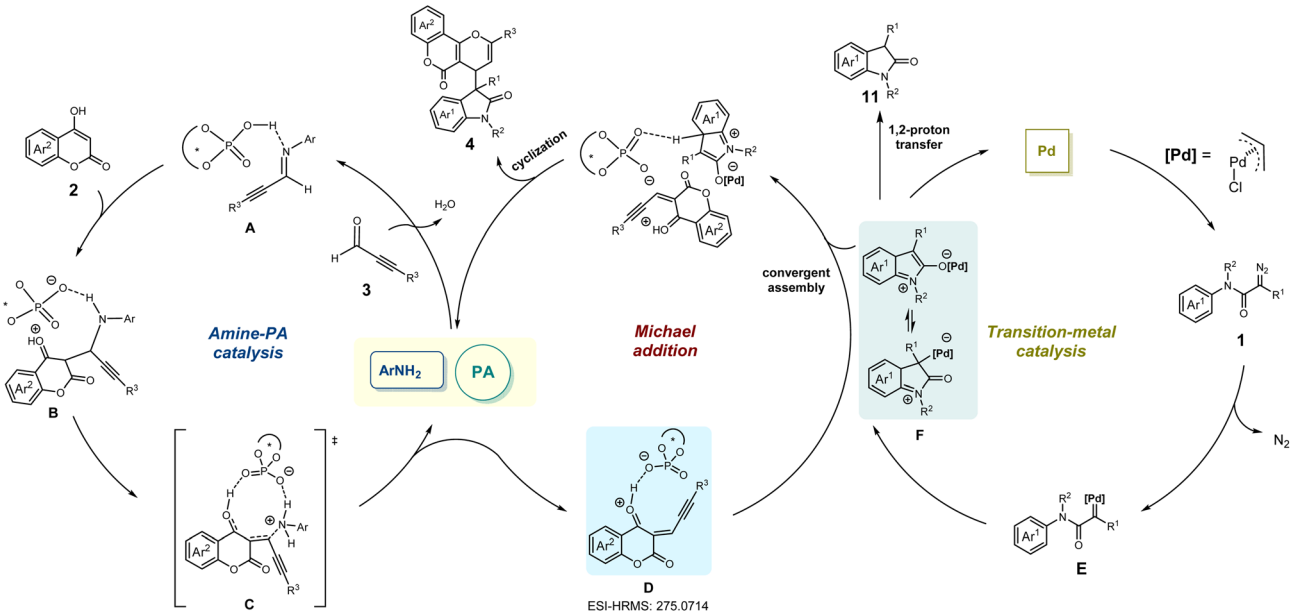
Late-stage modifications of bioactive molecules have become an efficient tool for rapid access to new drug candidates. To showcase the practicability of the novel multicomponent method for late-stage synthesis, a series of drugs and their derivatives were evaluated (Scheme 3). For example, natural alcohols, such as piperonyl alcohol, perilla alcohol, citronellol, geraniol and phytol, could be easily transformed into desired products (**7b–7f**) with satisfactory yields and good diastereoselectivities. Furthermore, drug derived substrate like 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose was compatible with this protocol to furnish the corresponding product **7g** with good yield and moderate diastereoselectivity. These results highlighted the excellent scalability of our newly developed ternary-catalytic method.

To demonstrate the practicability of this reaction, we carried out a large-scale synthesis (Scheme 4a). The desired product **4ae** was obtained in 79% yield (0.41 g) with dr > 20 : 1. Under the catalysis of Pd/C and H_2, the reduction of **4ae** could be realized, providing unexpected product **8** in 85% yield with maintained stereoselectivity (Scheme 4b). The relative configuration of **8** was determined by X-ray diffraction analysis.

Later, representative compounds (**4ab**, **4ae**, **4af**, **4bc**, **4be**, **4cc**, **4cd**, and **4cf**) were subjected to an anticancer activity test using cell viability *via* the CCK8 assay for HCT116 (colon cancer), MCF-7 (breast cancer) and SJSA-1 (osteosarcoma) human cancer cell lines (see the ESI† for details). The results showed that these pyrano[3,2-*c*]coumarin scaffolds exhibited significant and broad anticancer potency, especially compound **4ab** (HCT116, IC_{50} < 10 μM).[51–53] Furthermore, to shed light on the reaction mechanism, a series of mechanistic exploration experiments were performed. At first, when alkynaldehyde **2a** was treated with 4-hydroxycoumarin **3a** for 1 h, the subsequent addition of diazoacetamides **1a** was unable to afford the Michael-type addition product **4af** which cast doubt on the existence of intermediate **D** (Scheme 4c). This confusing result prompted us to identify the intermediate derived from alkynaldehyde **2a** and 4-hydroxycoumarin **3a**. Interestingly, the reaction of 4-hydroxycoumarin **3a** with the same equivalent of alkynaldehyde **2a** without any other additive could rapidly afford the adduct **9** with 50% yield, which showed the strong nucleophilicity of **3a** and proved the occurrence of intermediate **D** (Scheme 4d). Furthermore, the reaction of diazoacetamides **1a** with the adduct **9** failed to afford the desired product **4af** (Scheme 4e), indicating that the adduct **9** was not the intermediate during the whole reaction time. We then deliberately prepared other envisioned intermediates: 2-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (**10**) and 1,3,5-trimethylindolin-2-one (**11**). The reaction of **1a** with **10** under standard conditions did not give targeted product **4af** (Scheme 4f). Moreover, the



Scheme 4 Synthetic transformations and preliminary mechanistic investigation.



Scheme 5 Proposed mechanism.

reaction of **11** in the presence of alkynaldehyde **2a** and 4-hydroxycoumarin **3a** was monitored and no formation of **4af** was observed (Scheme 4g). These results implied that neither **10** nor **11** was the intermediate of this multicomponent reaction and proved that a synergetic process involving convergent assembly of two *in situ* generated active intermediates might be more plausible.

On the basis of the aforementioned results and previous reports,[45,46] a plausible reaction pathway was proposed as shown in Scheme 5. Initially, the imine intermediate **A** *in situ* generated from alkynaldehydes **3** in the presence of *rac*-PA and amine catalysts could easily react with 4-hydroxycoumarins **2** to deliver intermediate **B**. Under amine-PA catalysis, the phosphate anion-coordinated species **D** was derived from the intermediate **C** after releasing the amine catalyst. Additionally, the existence of intermediate **D** (calculated *m*/*z* 275.0703) was confirmed through ESI-HRMS analyses of the MCR mixture (observed *m*/*z* 275.0714) (for more details see ESI†).

Meanwhile, a palladium carbene intermediate **E** was obtained by extraction of nitrogen from diazoacetamides **1** under the catalysis of palladium(II) complex, which could convert into zwitterionic intermediate or enolate form **F** *via* an intramolecular interception process. Finally, such zwitterionic intermediate or enolate form **F** reacted with active electrophilic intermediate **D**, followed by intramolecular cyclization to furnish the multi-component product **4**.

Conclusions

In conclusion, we have developed a straightforward protocol for building 4-hydroxycoumarin scaffolds *via* coupling of two *in situ* generated active intermediates, leading to an array of coumarin derivatives bearing adjacent quaternary and tertiary stereocenters with moderate to good yields and diastereoselectivities. The method features ternary catalysis, broad substrate scope, and mild reaction conditions. This strategy could inspire more efforts to exploit the *in situ* generated active intermediate for the synthesis of polyfunctionalized skeletons for drug discovery.

Data availability

Further experimental details, synthetic procedures, characterization data, copies of NMR spectra and X-ray crystallographic data are available in the ESI.†

Author contributions

M. Z., S. Y., H. Q., Y. Q. and W. H. conceived and designed the project; M. Z. conducted most of the experiments; T. Z. performed the anticancer activity test on cell viability with most compounds; M. Z., A. Y. and X. X. analysed the data and contributed to the preparation of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Support for this research from the National Natural Science Foundation of China (92056201, 22171294, 81973176, 22001268), the Natural Science Foundation of Guangdong Province, China (2021A1515010401), Key-Area Research and Development Program of Guangdong Province (2022B1111050003), Guangdong Provincial Key Laboratory of Construction Foundation (2023B1212060022), Guangdong Natural Science Fund (2023A1515011486) and the Key

Laboratory Open Project of Xinjiang Uygur Autonomous Region (2021D04018) is gratefully acknowledged.

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