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Regio- and diastereoselective synthesis of *trans*-3,4-diaryldihydrocoumarins *via* metal-free [4+2] annulation of ynamides with *o*-hydroxybenzyl alcohols†

Wen-Feng Luo,[a] Long-Wu Ye,[b] Long Li *[a] and Peng-Cheng Qian*[a]

An efficient regio- and diastereoselective method for the construction of valuable *trans*-3,4-diaryldihydrocoumarins *via* metal-free [4+2] annulation of ynamides with *o*-hydroxybenzyl alcohols has been developed. Ynamides are first treated as 2–π partners to react with *o*-hydroxybenzyl alcohols *via* traceless sulfonamide directing groups, affording *trans*-3,4-diaryldihydrocoumarins in good yields with high regio- and diastereoselectivities. This metal-free methodology is also characterized by a wide substrate scope, good functional group tolerance, and efficiency on a gram scale.

Heterocyclic structural skeletons containing coumarins and their derivatives widely exist in a series of natural products and pharmaceuticals.[1] In particular, *trans*-3,4-diaryldihydrocoumarin derivatives have received much attention because of their promising anti-breast cancer and anti-osteogen biological activities (Fig. 1).[2] However, successful examples of straightforward synthesis of these valuable O-heterocycles remain scarce.[2g,h] Thus, it is highly desirable to develop novel synthetic strategies to construct *trans*-3,4-diaryldihydrocoumarin skeletons in a flexible, efficient, and good diastereoselective fashion.

Ortho-quinone methides (*o*-QMs), which are generated *in situ* from the corresponding *o*-hydroxybenzyl alcohols by organocatalysts or transition-metal catalysts, have been proven as powerful intermediates for the efficient synthesis of various valuable functionalized heterocycles, especially O-heterocycles through a diverse range of formal [4+2] annulations in the past few decades.[3,4] Among them, catalytic [4+2] annulations of *ortho*-quinone methides (*o*-QMs) with carbonyl compounds have shown unique advantages for constructing diarylcoumarin motifs (Scheme 1a).[5] These significant processes have been achieved; however, most of the intermolecular formal [4+2] annulations have so far been limited to *cis*-3,4-diaryldihydrocoumarin frameworks, and important *trans*-products were rarely reported.[5b,c] In addition, alkynes employed as two-carbon synthons with *o*-QMs for the preparation of 3,4-diaryldihydrocoumarins have not been explored.[6]

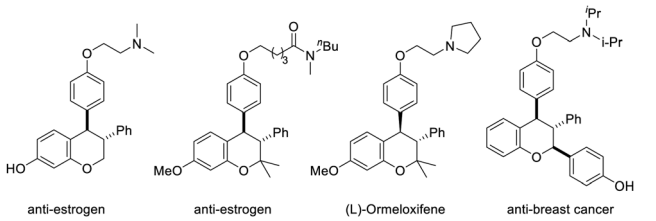
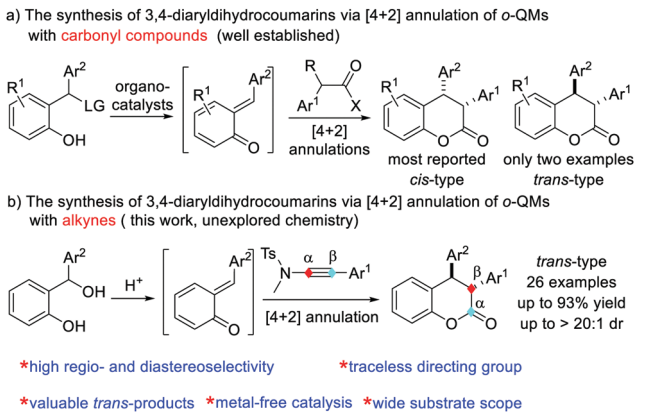


Fig. 1 Selected *trans*-3,4-diaryldihydrocoumarin derivatives in bioactive and natural products.

Owing to their unique reactivity and regioselectivity, ynamides, which are special alkynes directly connected with N-atoms, have attracted much attention in the past decade.[7,8] Ynamides have been regarded as versatile building blocks to react with diverse bifunctional starting materials containing both nucleophilic and



Scheme 1 Catalytic [4+2] annulations for the synthesis of 3,4-diaryldihydrocoumarins involving *o*-QMs.

[a] *Institute of New Materials & Industry Technology, College of Chemistry & Materials Engineering, Wenzhou University, Wenzhou 325035, China. E-mail: qpc@wzu.edu.cn, longwzu1990@wzu.edu.cn*

[b] *State Key Laboratory of Physical Chemistry of Solid Surfaces and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China*

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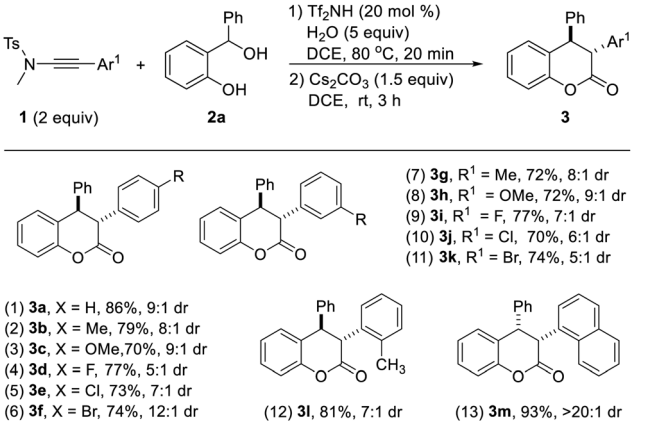
electrophilic moieties, providing a concise and flexible approach to construct various valuable functionalized heterocycles, which contained core scaffolds in many natural products and drugs.[9] Inspired by the above-mentioned results, for the synthesis of heterocycles, we envisioned that ynamides might be treated as bifunctional 2–π partners to undergo catalytic tandem intermolecular formal [4+2] annulation/hydration with *o*-hydroxybenzyl alcohols *via* traceless directing groups, rendering the formation of 3,4-diaryldihydrocoumarins. Interestingly, after the treatment with Cs_2CO_3, the annulation products were smoothly isomerized into important *trans*-3,4-diaryldihydrocoumarins, which have been found in an array of bioactive molecules and natural products (Scheme 1b). Herein, we reported a novel Brønsted acid-catalyzed formal [4+2] annulation of ynamides with *o*-hydroxybenzyl alcohols, which allows a highly regioselective and diastereoselective synthesis of *trans*-3,4-diaryldihydrocoumarins. Notably, ynamides were first treated as bifunctional 2–π partners with *ortho*-quinone methides (*o*-QMs) to prepare useful *trans*-3,4-diaryldihydrocoumarins, compared with well-established various carbonyl compounds. Importantly, sulfonamide groups acted as traceless directing groups resulting in different regioselectivities of ynamides in this metal-free [4+2] annulation, compared with $AlCl_3$-catalyzed annulation by Chang.[6e] In addition, this metal-free methodology was also characterized by a wide substrate scope, good functional group tolerance and efficiency on a gram scale.

In order to test our initial design, ynamide **1a** and *o*-hydroxybenzyl alcohol **2a** were employed as the model substrates and some screening results are summarized in Table S1 (ESI†).[11] Various non-noble metal catalysts were first examined including $AlCl_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$ and $Fe(OTf)_3$ in the presence of DCE as the solvent and 5 equiv. H_2O as the additive (Table S1, ESI†, entries 1–5). Although the diastereoselectivities were poor, most of the Lewis acid catalysts showed good catalytic reactivity for this formal [4+2] annulation, giving the regioselective annulation product in 40–72% yields without the formation of Chang's product.[6e] Meanwhile, various typical Brønsted acid catalysts were investigated for this cascade reaction covering TsOH, MsOH, HOTf, and $HNTf_2$ (Table S1, ESI†, entries 6–9). Surprisingly, the expected annulation product could be obtained in 90% yield using the strong Brønsted acid $HNTf_2$ as the catalyst.[6b,10] In addition, the solvent, temperature and amount of catalyst were screened, but the yield and diastereoselectivity could not be improved (Table S1, ESI†, entries 10–13). Furthermore, an array of different bases were evaluated to increase the diastereoselectivity of the annulation product (see the ESI† for details).[11] Gratifyingly, after the treatment with Cs_2CO_3, the thermodynamically stable *trans*-3,4-diaryldihydrocoumarin **3a** was achieved in 86% isolated yield with 9 : 1 diastereoselectivity (Table S1, ESI†, entry 14).[12] It needs to be emphasized again that the $AlCl_3$-catalyzed regioselective annulation product was not observed in this metal-free tandem reaction.[6e]

With the optimal reaction conditions in hand, we then explored the scope of this metal-free [4+2] annulation of ynamides **1** with *o*-hydroxybenzyl alcohols **2a**. First of all, a series of diverse ynamides **1** were investigated, and this tandem reaction showed excellent functional group tolerance, leading to the desired

Table 1 Brønsted acid-catalyzed formal [4+2] annulation of different ynamides **1** with *o*-hydroxybenzyl alcohols **2a**[a]



[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), $HNTf_2$ (0.04 mmol), DCE (4 mL), 80 °C, 20 min, in vials; then, Cs_2CO_3 (1.5 equiv.), r.t., 3 h; isolated yields and diastereoselectivities are reported.

trans-3,4-diaryldihydrocoumarins **3** in mostly good to excellent yields with high regio- and diastereoselectivities, as shown in Table 1. Diverse substituted groups, for example, electron-donating groups such as Me and MeO (Table 1, entries 2, 3, 7 and 8) or electron-withdrawing groups such as F, Cl, and Br (Table 1, entries 4–6 and 9–11) on the *para*- or *meta*-position of the aromatic ring, were suitable for this metal-free system to smoothly deliver the corresponding *trans*-3,4-diaryldihydrocoumarins **3a–3k** in 70–86% yields with 5 : 1–12 : 1 dr values. Interestingly, the ynamide **1l** bearing a steric *o*-position methyl group also proceeded well in this [4+2] annulation, affording the expected products **3l** in 81% yield with 7 : 1 diastereoselectivity (Table 1, entry 12). In addition, the effects of π–π conjugation of the benzene and naphthalene rings might result in *cis*-3,4-diaryldihydrocoumarin **3m** in 93% yield with excellent diastereoselectivity after the treatment with Cs_2CO_3 (Table 1, entry 13). Notably, ynamides were first employed as 2–π partners in the formation of 3,4-diaryldihydrocoumarins with *ortho*-quinone methides (*o*-QMs) *via* traceless directing sulfonamide groups. More importantly, no $AlCl_3$-catalyzed annulation product was obtained in all examples.[6e]

Then, an array of different *o*-hydroxybenzyl alcohols **2** were also evaluated, as outlined in Table 2. A variety of *o*-hydroxybenzyl alcohols **2** containing both electron-withdrawing and electron-donating groups on the Ar_2 at the *para*, *meta*, or steric *o*-position successfully underwent tandem intermolecular [4+2] annulation/hydration under mild conditions, delivering the desired *trans*-3,4-diaryldihydrocoumarins **3n–3t** in 60–74% yields with 7 : 1–12 : 1 dr values (Table 2, entries 1–7). Finally, the expected regio- and diastereoselective *trans*-3,4-diaryldihydrocoumarins **3u–3w** substituted with different groups such as Br, Me, and OMe were achieved in 63–78% yields with 6 : 1–7 : 1 dr values, revealing that the electronic nature of substituents on the phenyl ring had little effect on the yields and diastereoselectivities (Table 2, entries 8–10). The *cis*-product **3x** was also observed in 45% yield with >20 : 1 dr, probably because of the effect of π–π

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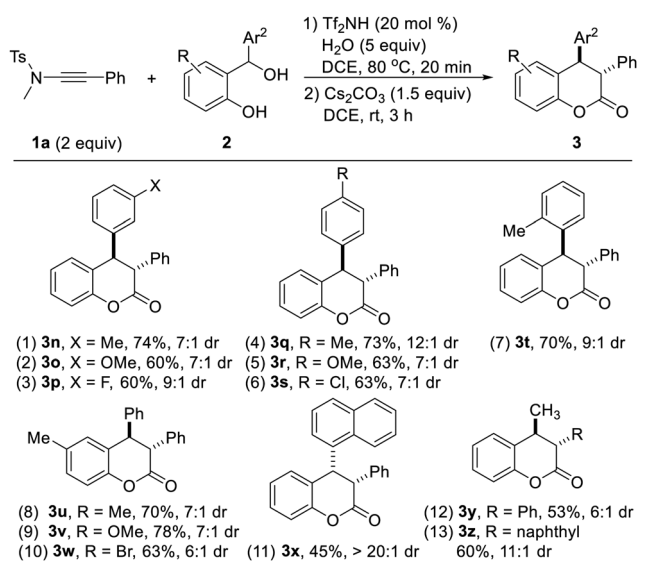
Table 2 Brønsted acid-catalyzed formal [4+2] annulation of ynamides **1a** with different *o*-hydroxybenzyl alcohols **2**[a]

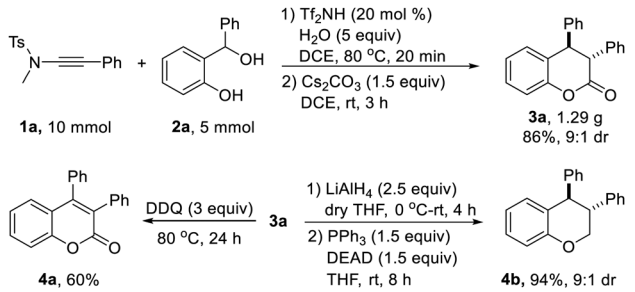


[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), $HNTf_2$ (0.04 mmol), DCE (4 mL), 80 °C, 20 min, in vials; then, Cs_2CO_3 (1.5 equiv.), r.t., 3 h; isolated yields and diastereoselectivies are reported.

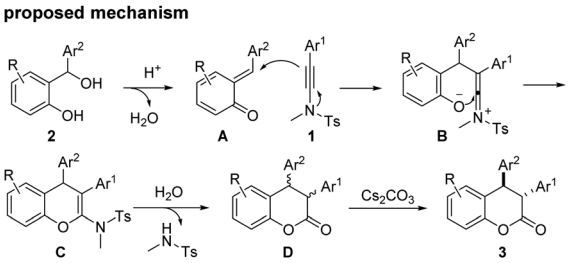
conjugation (Table 2, entry 11). The *o*-hydroxymethyl alcohol **2l** could successfully react with **1a** and **1m**, giving the corresponding *trans*-products **3y** and **3z** in moderate yields with good diastereoselectivities (Table 2, entries 12 and 13).

To further examine the applicability of this metal-free [4+2] annulation, a gram-scale reaction of ynamide **1a** with *o*-hydroxybenzyl alcohol **2a** was carried out under standard reaction conditions, and 1.29 g of the desired *trans*-3,4-diaryldihydrocoumarin **3a** was readily obtained in 86% yield with 9 : 1 diastereoselectivity, as illustrated in Scheme 2. With **3a** in hand, the subsequent chemical transformations were explored. First, **4a** containing the core skeleton of coumarins could be successfully achieved in 60% yield *via* oxidation using DDQ.[1] In addition, the **3a** could be smoothly converted into the valuable O-heterocycle **4b** in 94% yield with good diastereoselectivity by reduction/intramolecular Mitsunobu reaction, which was found in a series of natural products and pharmaceuticals.[2]

To understand the reaction mechanism, several control experiments were carried out (Scheme S1, ESI†). We first performed this metal-free [4+2] annulation in dry DEC under



Scheme 2 Gram-scale synthesis and further transformations of **3a**.



Scheme 3 Mechanism studies.

a N_2 atmosphere without water, and isolated the annulation product **3aa** in 75% yield. Importantly, further hydration and isomerization of **3aa** could afford the expected product **3a** by treating with water and base, strongly supporting the notion that **3aa** was the key intermediate of this cascade reaction (Scheme S1, ESI†, eqn (a)).[9d,e] In addition, **3ab**, which was the hydration product of ynamide **1a**, was employed to react with **2a** under standard conditions, and no desired **3a** was observed, thus ruling out the enolate-type pathway (Scheme S1, ESI†, eqn (b)).[10] On the basis of the above-mentioned experimental observations, a plausible mechanism to rationalize this metal-free annulation in the formation of *trans*-3,4-diarylcoumarins **3** is proposed (Scheme 3). Initially, the Brønsted acid could smoothly activate the *o*-hydroxybenzyl alcohols **2** to generate *o*-QM intermediates **A**, releasing one molecular water. Then, intermolecular ynamides **1**, serving as nucleophiles, rapidly attacked the *o*-QM intermediates **A** to deliver **B** *via* the intermolecular Michael addition, which underwent another addition to keteniminiums, affording the [4+2] annulation products **C**. Subsequently, the hydration of **C** afforded the benzolactone frameworks **D**,[9d,e] along with the generation of sulfonamide groups. Finally, the thermodynamically stable *trans*-3,4-diarylcoumarins **3** could be achieved *via* enolization isomerization in the presence of Cs_2CO_3.[12]

In summary, we have developed a novel Brønsted acid-catalyzed formal [4+2] annulation reaction of ynamides with *o*-hydroxybenzyl alcohols. This metal-free method provides a facile and practical avenue to efficiently construct valuable *trans*-3,4-diaryldihydrocoumarins in good to excellent yields with good regio- and diastereoselectivities under mild reaction conditions. This tandem reaction also shows a wide substrate scope, and excellent functional group tolerance and efficiency on a gram scale. Notably, ynamides are first treated as 2–π partners for direct formal [4+2] annulation with *o*-hydroxybenzyl alcohols *via* traceless directing groups to the best of authors' knowledge, which not only significantly enriches the chemistry of *o*-QMs, but also promotes further development of ynamides chemistry. Further explorations into the synthetic applications of this metal-free protocol are in progress in our lab.

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Conflicts of interest

There are no conflicts to declare.

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