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# Bifunctional squaramide-catalyzed synthesis of chiral dihydrocoumarins *via ortho*-quinone methides generated from 2-(1-tosylalkyl)phenols†

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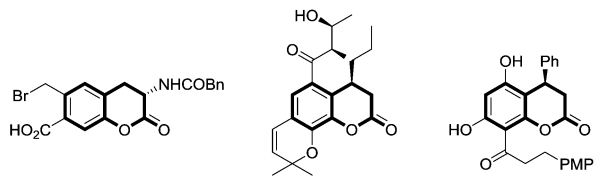
**A bifunctional squaramide-catalyzed reaction of azlactones with *o*-quinone methides *in situ* generated from 2-(1-tosylalkyl)-phenols has been successfully developed under basic conditions, providing an efficient and mild access to chiral dihydrocoumarins bearing adjacent tertiary and quaternary stereogenic centers in high yields with excellent diastereo- and enantioselectivities.**

As an important and central structural motif, the chiral dihydrocoumarin skeleton is not only found in a broad range of natural and pharmaceutical molecules which exhibit diverse biological activities such as anti-cancer,[1] anti-oxidation,[2] and anti-inflammatory activities[3] and anti-microbial properties[4] (Scheme 1), but is also applied in numerous synthetic processes.[5] Not surprisingly, considerable attention has been paid to the development of asymmetric synthesis of dihydrocoumarin derivatives and many methods have been reported in recent years.[6] However, only a few examples have been concerned about the access to chiral dihydrocoumarins bearing a quaternary amino acid moiety,[6k–n] a unique skeleton possessing pharmacological activities.[7] Among these methods, the reaction of readily available *ortho*-quinone methides (*o*-QMs) with enolates was considered to be an efficient way. As to the *o*-QMs, it is fairly well known that they are a crucial class of key intermediates in various biological processes[8] and have been regarded as highly reactive chemical motifs.[9,10] In view of enolates, the azlactones,[11] being endowed with both nucleophilic[12] and electrophilic[13] properties due to their interconvertible keto and enol forms, would naturally be the best option as enolates to react with *o*-QMs and acquire chiral dihydrocoumarin derivatives bearing a quaternary amino acid moiety. In 2015, Feng's group developed the first asymmetric synthesis of dihydrocoumarins from readily prepared *o*-QMs and azlactones catalyzed by a chiral *N*,*N*′-dioxide–Sc(III) complex (Scheme 2).[6k] Subsequently, Xiao's group reported the construction of the same scaffold by the triple Brønsted acid catalyzed formal [4+2] cycloaddition of the azlactones and *in situ* generated *o*-QMs from *o*-hydroxy benzhydryl alcohols.[6n] Although the above protocols have achieved satisfying results, the limited substrate scope and relatively low yields suppress their further application. Hence, development of unified catalytic asymmetric strategies remains highly desirable.

As part of our ongoing interest in the utilization of *o*-QMs,[14] we focused on bifunctional organocatalytic reactions of *in situ* generated *o*-QMs. Based on this consideration, we envisioned that the combination of 2-(1-tosylalkyl)phenols and azlactones would enable the synthesis of chiral dihydrocoumarin derivatives in the presence of inorganic bases and bifunctional organocatalysts[15] (Scheme 2). The bifunctional organocatalysts could be used for deprotonation of azlactones to form nucleophilic species in the chiral environment. Moreover, the inorganic base should not promote the subsequent Michael addition to guarantee effective control of enantioselectivity by the chiral organocatalyst. Thus, the key point of this tandem reaction is to find a suitable match of bifunctional organocatalysts and inorganic bases. Herein, we present a facile bifunctional squaramide-catalyzed enantioselective synthesis of dihydrocoumarin derivatives *via* the *in situ* generated *o*-QMs and azlactones under basic conditions in excellent diastereo- and enantioselectivities with a broad substrate scope.

At the outset, 2-(1-tosylalkyl)naphthol **1a** and azlactone **2a** were chosen as model substrates. The experiment was conducted




**TEM β-lactamase inhibitor** **Soulamarin** **Calomelanol A**

Scheme 1 Bioactive chiral dihydrocoumarin derivatives.

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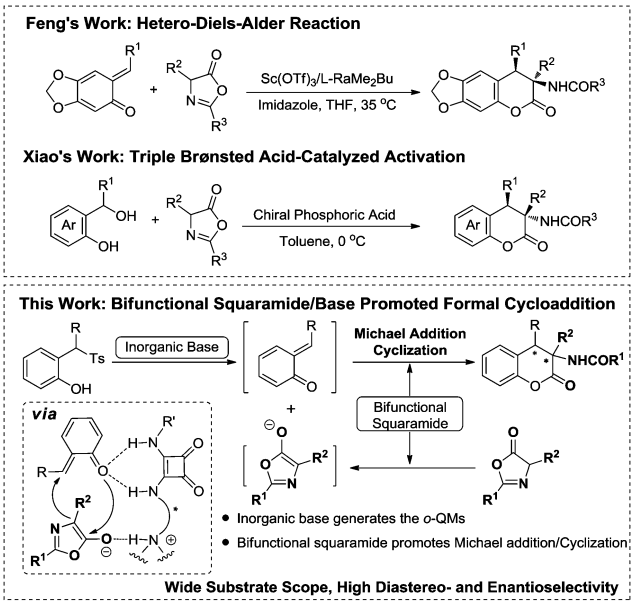
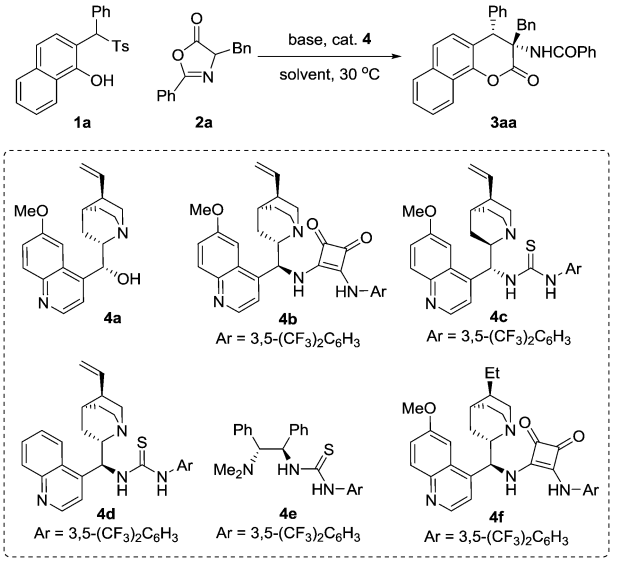



Scheme 2 Strategies for the synthesis of chiral dihydrocoumarins based on *ortho*-quinone methides (*o*-QMs).

Table 1 Optimization of reaction parameters[a]




| Entry | Base | Solvent | Cat. | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | $Na_2CO_3$ | $CH_2Cl_2$ | **4a** | 83 | 32 |
| 2 | $Na_2CO_3$ | THF | **4a** | 81 | 4 |
| 3 | $Na_2CO_3$ | DMF | **4a** | 95 | 0 |
| 4 | $Na_2CO_3$ | DCE | **4a** | 93 | 33 |
| 5 | $Na_2CO_3$ | $CHCl_3$ | **4a** | 91 | 36 |
| 6 | $Na_2CO_3$ | $CHCl_3$ | **4b** | 89 | 96 |
| 7 | $Na_2CO_3$ | $CHCl_3$ | **4c** | 83 | 66 |
| 8 | $Na_2CO_3$ | $CHCl_3$ | **4d** | 74 | 66 |
| 9 | $Na_2CO_3$ | $CHCl_3$ | **4e** | 83 | 61 |
| 10 | $Na_2CO_3$ | $CHCl_3$ | **4f** | 66 | 96 |
| 11[d] | $Na_2CO_3$ | $CHCl_3$ | **4b** | 91 | 93 |
| 12[e] | $Na_2CO_3$ | $CHCl_3$ | **4b** | 95 | 96 |
| 13[f] | $Na_2CO_3$ | $CH_2Cl_2/H_2O$ | **4b** | 93 | 91 |

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), cat. **4** (0.01 mmol), base (0.12 mmol), solvent (1.5 mL), 30 °C, 48 h. The dr were all over 20 : 1 detected using $^1$H NMR spectra. [b] Isolated yields. [c] Determined by chiral HPLC. [d] 50 °C. [e] 72 h. [f] $CH_2Cl_2/H_2O$ (100 μL/2.0 mL).

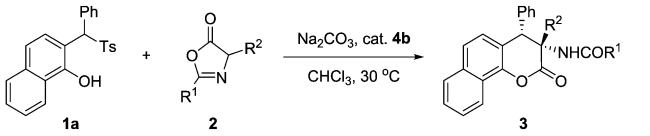
in $CH_2Cl_2$ by using quinine **4a** as catalyst and sodium carbonate as base, respectively. The reaction proceeded smoothly to give the desired product **3a** in 83% yield with 32% ee (entry 1, Table 1). Then, the solvent effect was tested (entries 2–5, Table 1). Among the different kinds of solvents, chloroform was proved to be the most favorable solvent in terms of enantioselectivity and yield. Subsequently, a series of bifunctional organocatalysts were investigated (entries 6–10, Table 1). In contrast to quinine **4a**, bifunctional thiourea or squaramide catalysts gave higher enantioselectivities. Obviously, quinine-based squaramide catalyst **4b** was the best catalyst with 96% ee. In order to improve the activity of the reaction, the temperature was also evaluated (entry 11, Table 1). Upon increasing the reaction temperature, the rate of the reaction was accelerated slightly but the enantioselectivity decreased. So we prolonged the reaction time to 72 h and obtained satisfying results with 95% yield and 96% ee (entry 12, Table 1). Notably, the diastereoselectivity of the reaction was over 20 : 1 in all cases. Finally, we also tried the water–oil diphasic system developed by us and Liu's group[14g] for comparison, which delivered relatively worse results with 93% yield and 91% ee (entry 13, Table 1). Thus, the optimized conditions were established as: quinine-based squaramide catalyst **4b** (10 mol%), sodium carbonate (1.2 equiv.), $CHCl_3$, 30 °C, 72 h.

Having established the optimal reaction conditions, we then investigated a wide range of azlactones, and the results are shown in Table 2. Gratifyingly, azlactones with either electron-withdrawing or electron-donating substituents on the phenyl ring in the $R^1$ group could be smoothly converted to the corresponding products in high yields, good enantioselectivities as well as excellent diastereoselectivities (up to 95% yield, 97% ee, >20 : 1 dr) (**3aa–3ai**). Next, the $R^2$ substituent for both benzyl and alkyl groups was also examined. Chlorine on the benzyl group apparently increased the yield to 98% (**3ai**). For simple alkyl substituted azlactones **2k** and **2l**, low activities and enantioselectivities were obtained under the above standard conditions (no activity for **2k**, 82% yield and 69% ee for **2l**). Then we shifted our focus to the water–oil diphasic conditions, which were previously reported by us and Liu's group,[14g] and excellent yields and enantioselectivities could also be obtained (entries 11 and 12).

Encouraged by the abovementioned results, we continued to investigate into the variation of the 2-(1-tosylalkyl)phenols. As shown in Scheme 3, in most cases, the transformations proceeded successfully, delivering the corresponding chiral dihydrocoumarins in excellent enantioselectivities and high yields. For 2-(1-tosylalkyl)-naphthols **1a–1h**, electronic and steric properties had a slight influence on the enantioselectivities and yields. In addition, the alkyl substituted substrate **1i** was also a suitable reaction partner and the reaction performed well with 91% yield and 85% ee. Furthermore, the reaction proceeded smoothly with methoxyl substituent substrate **1k** and the sesamol-based substrate **1l**. It is worth mentioning that the water–oil diphasic system worked well

Table 2 Substrate scope of azlactones[a]




| Entry | $R^1$ | $R^2$ | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | Ph | Bn | 91 (**3aa**) | 96 |
| 2 | 4-$ClC_6H_4$ | Bn | 85 (**3ab**) | 94 |
| 3 | 4-$FC_6H_4$ | Bn | 90 (**3ac**) | 95 |
| 4 | 4-$BrC_6H_4$ | Bn | 91 (**3ad**) | 92 |
| 5 | 4-$F_3CC_6H_4$ | Bn | 91 (**3ae**) | 92 |
| 6[d] | 3,5-$Me_2C_6H_3$ | Bn | 95 (**3af**) (89) | 97 (96) |
| 7 | 4-$MeC_6H_4$ | Bn | 95 (**3ag**) | 88 |
| 8[e] | 3-$MeC_6H_4$ | Bn | 95 (**3ah**) | 82 |
| 9 | 4-$MeOC_6H_4$ | Bn | 94 (**3ai**) | 95 |
| 10 | Ph | 4-$ClC_6H_4CH_2$ | 98 (**3aj**) | 93 |
| 11[f] | Ph | Cy | 89 (**3ak**) | 90 |
| 12[f] | Ph | Et | 95 (**3al**) | 90 |

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.20 mmol), $Na_2CO_3$ (0.24 mmol), cat. **4** (0.02 mmol), $CHCl_3$ (3.0 mL), 72–96 h. The dr were all over 20 : 1 in all cases. [b] Isolated yields. [c] Determined by chiral HPLC. [d] The reaction at the gram scale was presented in parentheses. [e] 50 °C. [f] $CH_2Cl_2/H_2O$ (100 μL/2.0 mL).

for substrate **1j** and simple 2-(1-tosylalkyl)phenol **1m**, which had low activity under the standard conditions, delivering the corresponding products **3ja** and **3ma** with satisfying results. In addition, the reaction of alkyl substituted azlactones **2k** and **2l** with 2-(1-tosylalkyl)phenols **1d** and **1l** ran smoothly in the water–oil diphasic system, which indicated that the water–oil diphasic system and the chloroform monophasic system are complementary to some extent.

Considering the potential biological activities of the chiral dihydrocoumarins and in order to show the synthetic utility of this methodology, the scale-up synthesis of **3af** was performed. 2.0 mmol **1a** and 2.0 mmol azlactone **2f** reacted well under the standard reaction conditions, affording the desired product **3af** in 89% yield (0.907 g) with 96% ee and >20 : 1 dr without any loss of reactivity and enantioselectivity.

To determine the absolute configuration of products, optically pure (+)-*N*-(3-benzyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-benzo[*h*]-chromen-3-yl)-3,5-dimethyl-benzamide (+)-**3af** was obtained as a colorless crystal after single recrystallization from dichloromethane/*n*-hexane/toluene, and the absolute configuration was determined to be (3*S*,4*S*) based on single crystal X-ray diffraction analysis.[16] (For details, please see the ESI.†)

In summary, we have successfully realized the bifunctional squaramide-catalyzed Michael addition/cyclization of *o*-QMs generated from 2-(1-tosylalkyl)phenols with azlactones, giving a facile access to chiral dihydrocoumarin derivatives bearing a quaternary amino acid moiety with high yields, excellent diastereo- and enantioselectivities. Highlights of this method involve the mild reaction conditions and a wide substrate scope. Further explorations on the extension of this strategy to synthesize other compounds are ongoing in our laboratory.

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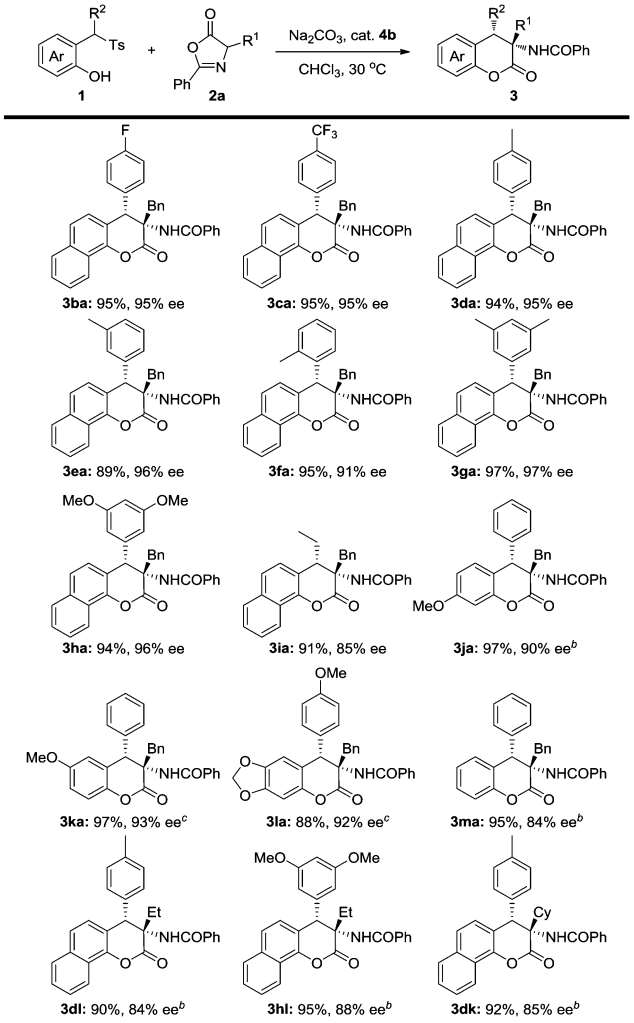


Scheme 3 Substrate scope of 2-(1-tosylalkyl)phenols. [a] Reaction conditions: **1** (0.20 mmol), **2a** (0.20 mmol), $Na_2CO_3$ (0.24 mmol), cat. **4** (0.02 mmol), $CHCl_3$ (3.0 mL), 36–120 h. The dr were all over 20 : 1 in all cases. [b] $CH_2Cl_2/H_2O$ (100 μL/2.0 mL). [c] 50 °C.

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