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 activities3 and anti-microbial properties4 (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.6–8n 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 processes8 and have been regarded as highly reactive chemical motifs.9,10 In view of enolates, the azlactones,11 being endowed with both nucleophilic12 and electrophilic13 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).6c Subsequently, Xiao’s group reported the construction of the same scaffold by the triple Bronsted 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 organocatalysts15 (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...
in CH₂Cl₂ 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 catalyst, 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 (entry 12, Table 1). Notably, the diastereoselectivity of the reaction was over 20:1 in all cases. Finally, we also tried the reaction with methoxyl 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 biphasic conditions, which were previously reported by us and Liu’s group. Then we shifted our focus to the water–oil diphasic conditions, which were previously reported by us and Liu’s group14g 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.), CHCl₃, 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 R¹ 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 R² substituent for both benzylic and alkyl groups was also examined. Chlorine on the benzylic 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. 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...
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 1i ran smoothly in the water–oil biphasic system, which indicated that the water–oil biphasic 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-2H-benzo[1]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 (3S,4S) based on single crystal X-ray diffraction analysis.\(^{16}\) (For details, please see the ESL.)

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.

Financial support from the National Natural Science Foundation of China (20102348, 51578224) is acknowledged.

### Notes and references


11 For the asymmetric reactions of α-QMs, see: (a) Y. Luan and S. E. Schaus, *J. Am. Chem. Soc.*, 2012, 134, 19965; (b) J. Izquierdo, A. Orue and K. A. Scheidt, *J. Am. Chem. Soc.*, 2013, 135, 10634;


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16 CCDC 1516157.