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Communication

Asymmetric Michael addition reactions catalyzed by a novel upper-rim functionalized calix[4]squaramide organocatalyst

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Available online-A novel upper-rim functionalized calix[4]squaramide organocatalyst bearing bis-squaramide and cyclohexanediamine scaffolds was designed and prepared to catalyse a serial of asymmetric Michael addition of 1,3-dicarbonyl compounds to *α,β*-unsaturated carbonyl compounds in high yields (up to 99%) and good to excellent enantiomeric excesses (up to 99% *ee*). The comparative experiments indicated that the cooperative effect between calixarenes cavitives and chiral catalytic centers on this calix[4]squaramide catalyst could promote these reactions. Moreover, this strategy also provides valuable and easy access to chiral chromene, naphthoquinone and acetylacetone derivatives, which are important skeletons in biological and pharmaceutical compounds.

Keywords:*Calix[4]squaramide;; Supramolecular catalyst; Asymmetric catalysis; Michael addition; Organic synthesis*-

In recent years, asymmetric Michael reactions have become a powerful strategy to construct C-C bonds in organic chemistry [1-8]. Among them, the organocatalytic Michael addition of 1,3-dicarbonyl compounds to *α,β*-unsaturated carbonyl compounds has attracted much attention due to it offers a facile, green and effective way to synthesize various important chiral biological and pharmaceutical skeletons [9-13]. Meanwhile, squaramide is also a very important scaffold in this process due to its rigid four-membered ring, higher acidity and the appropriate distance between two donor hydrogens [14-18]. Although the significant progress has been made in this research field, the development of a novel and efficient chiral organic squaramide catalyst for asymmetric Michael addition is a challenging issue.

Calixarenes, as the ideal supramolecular catalysts, have been widely used in asymmetric Michael reactions because of their tunable three-dimensional molecular platforms with the relatively easy modification at the lower and upper rims [19-25]. In 2016, Durmaz group demonstrated the synthesis of a lower-rim functionalized calix[4]squaramide organocatalyst (Fig. 1a) and its catalytic performance in the asymmetric Michael addition of acetylacetone to nitroolefins [26]. In the past decade, our group also prepared a series of lower- and upper-rim functionalized calix[4]arene organocatalysts to achieve the different asymmetric organic reactions in good yields and enantioselectivities [27-31]. It is worth noting that preparing the cavity of upper-rim functionalized calixarene is much more valuable and difficult than the lower-rim in the cone conformation of calixarene, because the synergistic effect between calixarene cavitive and chiral catalytic center could lead the better catalytic performance. In our continuing efforts for

developing novel types of chiral organocatalysts, herein the novel upper-rim functionalized calix[4]squaramide cyclohexanediamine catalyst (Fig. 1b) has been synthesized to catalyze a serial of asymmetric Michael addition of 1,3-dicarbonyl compounds to *α,β*-unsaturated carbonyl compounds.

The chemical structures and synthetic pathways for catalysts **1** and **2** are shown in Scheme 1. The upper rim-functionalized calix[4]arene-based cyclohexanediamine catalyst **1** has been prepared by the following methods. First of all, calix[4]arene derivative **I** with amino group on upper rim was obtained according to literature report [32]. Then the amino group was converted to squaramide group to obtain compound **II**. Subsequently, chiral cyclohexanediamine derivatives were reacted with calix[4]arene-based compound **II** to form squaramide groups, producing the corresponding calix[4]squaramide cyclohexanediamine catalyst **1**. Moreover, in order to investigate the role of the cavity of calix[4]arene, a model catalyst **2** was also obtained through the similar synthetic methods. Catalysts **1** and **2** were well characterized by NMR and HRMS analyses, more details are deposited in Supporting information.

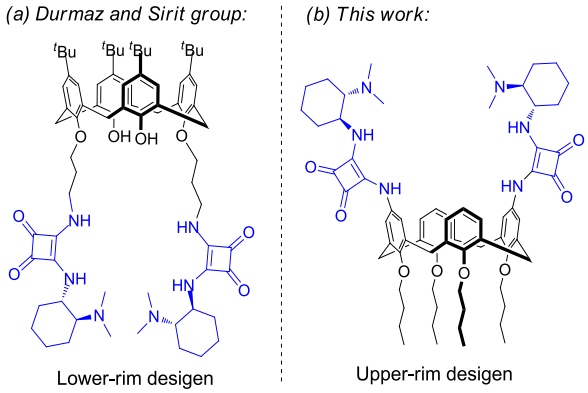
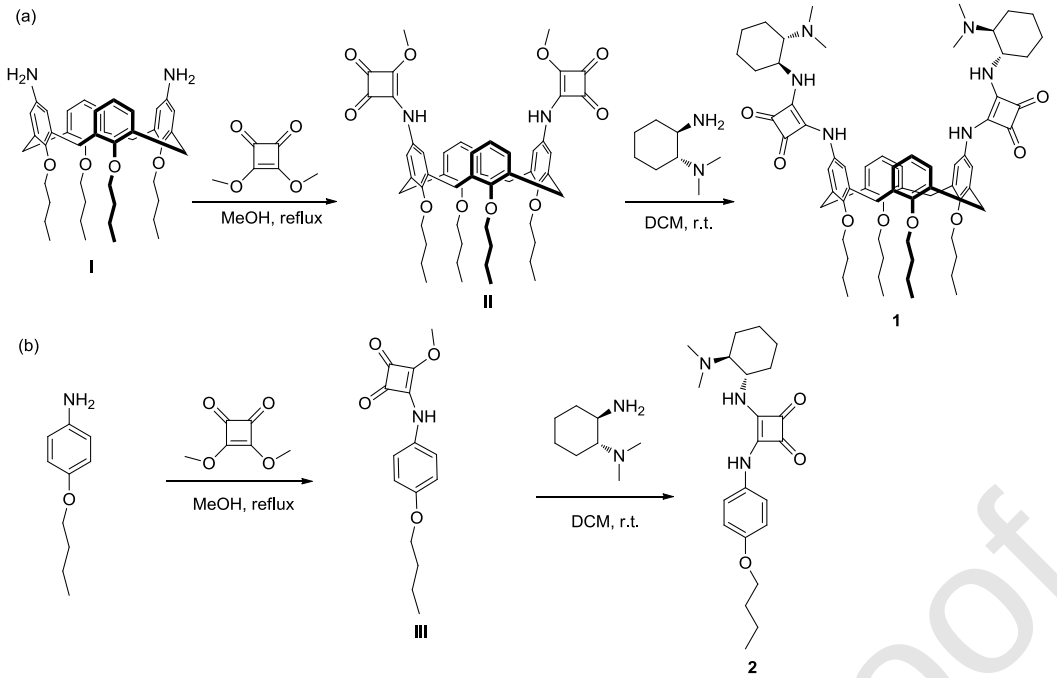


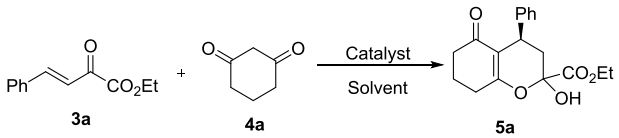
Fig. 1. The lower-rim and upper-rim functionalized calix[4]squaramide organocatalyst.

Our investigation began with the Michael addition reaction of ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **3a** to cyclohexane-1,3-dione **4a** in the presence of catalytic calix[4]squaramide cyclohexanediamine **1** (2.5 mol%) in the water at 25 °C. The desired product **5a** was detected in 79% yield and 74% *ee* (Table 1, entry 1). The subsequent examination of different solvents revealed that this process could be obtained in an improved yield (98% yield) and enantioselectivity (90% *ee*) in the solvent of DCM (entries 2-10). Next, decreasing the amount of calix[4]squaramide cyclohexanediamine to 1.0 mol% gave the desired product in 90% yield and 82% *ee*. However, further optimization showed that the amount of catalyst was increased to 5.0% without an apparent effect on the reaction. Additionally, decreasing the reaction temperature to 0 °C or -10 °C also showed no apparent effect on this process. Finally, the comparative experiment demonstrated that the low yield and poor enantioselectivity of desired product **5a** was obtained in the presence of catalyst **2**, and these results further confirm the cooperative effect between calixarenes cavitives and chiral catalytic centers in this catalytic process (entry 15).



Scheme 1. The chemical structures and synthetic pathways for catalysts **1** and **2**.

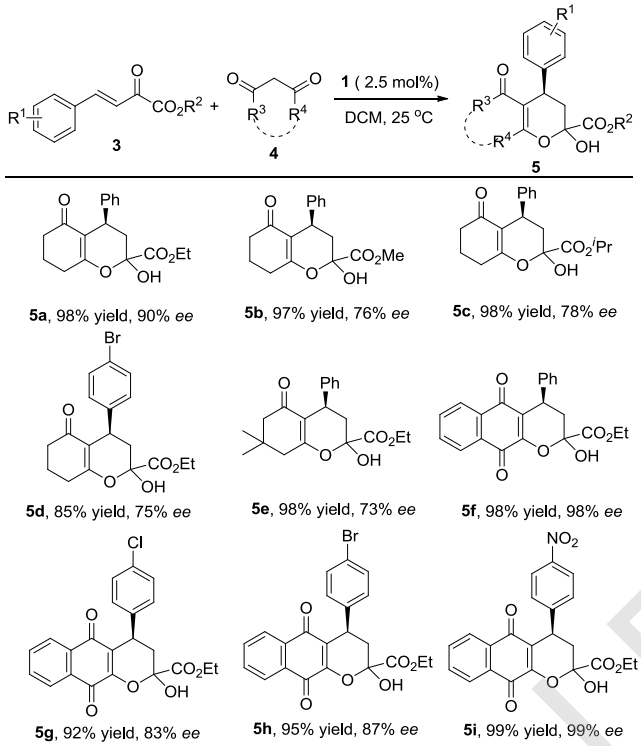
Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst (mol%)	Solvent	Yield (%)[b]	*ee* (%)[c]
1	**1** (2.5)	H_2O	79	74
2	**1** (2.5)	DMSO	98	52
3	**1** (2.5)	CH_3OH	92	62
4	**1** (2.5)	CH_3CN	91	65
5	**1** (2.5)	THF	98	82
6	**1** (2.5)	Et_2O	98	75
7	**1** (2.5)	1,4-Dioxane	90	79
8	**1** (2.5)	PhMe	95	83
9	**1** (2.5)	DCM	98	90
10	**1** (2.5)	$CHCl_3$	98	85
11	**1** (1.0)	DCM	90	82
12	**1** (5.0)	DCM	98	90
13[d]	**1** (2.5)	DCM	95	90
14[e]	**1** (2.5)	DCM	92	90
15	**2** (2.5)	DCM	70	80

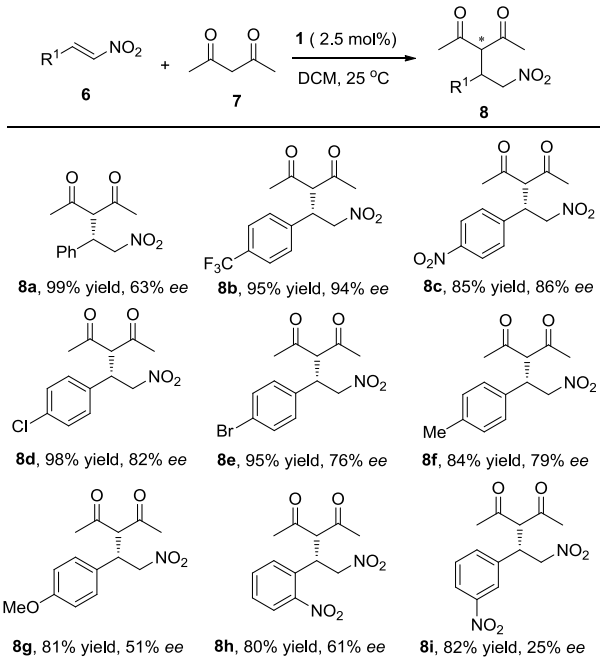
[a] Reagents and conditions: **3a** (0.5 mmol), **4a** (0.55 mmol), catalyst, solvent (4.0 mL), 25 °C and 6 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 0 °C.
[e] -10 °C.

With the optimized reaction conditions in hand, we investigated the scope of asymmetric Michael addition reactions of *β*–unsaturated *α*–keto esters and 1,3-dicarbonyl compounds. As shown in Scheme 2, different *β*–unsaturated *α*–keto esters reacted smoothly with cyclohexane-1,3-dione **4a** to afford the corresponding products (**5a-d**) in excellent isolated yield (85%-98%) and good enantioselectivities (75%-90% *ee*). Furthermore, various other cyclic 1,3-dicarbonyl compounds, including dimedone and 2-hydroxy-1,4-naphthoquinone, have also been used to construct the corresponding products. Using dimedone as the starting material, the corresponding product **5e** was obtained in 98% yield and 73% *ee*. To our delight, using 2-hydroxy-1,4-naphthoquinone as the reaction partner, excellent enantioselectivity and especially high efficiency was achieved. Then, several aromatic *β*–unsaturated *α*–keto esters reacted smoothly with 2-hydroxy-1,4-naphthoquinone to afford the desired products in excellent yields (92%-99%) and enantioselectivities (83%-99% *ee*). Moreover, using chalcone as the substrate to react with different 1,3-dicarbonyl compounds such as cyclohexane-1,3-dione, dimedone, 2-hydroxy-1,4-naphthoquinone or acetylacetone, however, no desired products could be isolated in current conditions.



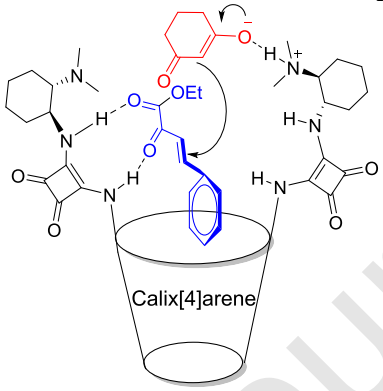
Scheme 2. The asymmetric Michael addition reaction of *β*–unsaturated *α*–keto esters and 1,3-dicarbonyl compounds. Reagents and conditions: **3** (0.5 mmol), **4** (0.55 mmol), **1** (2.5 mol%), DCM (4.0 mL) and 25 ^{o}C. Isolated yield. The *ee* value was determined by chiral HPLC analysis.

Besides, the asymmetric Michael additions of aryl nitroolefins (**6a-6i**) with acetylacetone **7** were also employed to explore the generality of this protocol. The results are summarized in Scheme 3. Although product **8a** obtained from nitrostyrolene only gave the moderate enantioselectivity (63% *ee*), electronic effects of the substituents on the phenyl ring exhibited a significant influence on this process. Both electron-donating (Me and MeO) and electron-withdrawing groups (Cl, Br, NO_2 and CF_3) at the *para*-position on the phenyl ring of nitroolefins were all compatible in the current reaction system, affording the corresponding products (**8b-g**) in high yields (81%-98%) and moderate to good enantioselectivities (51%-94% *ee*). It was also noticed that the strong electron-withdrawing groups (NO_2 and CF_3) afforded obviously better enantioselective products than others. Furthermore, (*E*)-1-nitro-2-(2-nitrovinyl)benzene was also tolerated under the current catalytic system to afford the desired product **8h** in 80% yield and 61% *ee*. However, *meta*-nitro-substituted nitrostyrolene only gave the desired product **8i** in 82% yield and 25% *ee*.



Scheme 3. The asymmetric Michael addition of aryl nitroolefins with acetylacetone. Reagents and conditions: **6** (0.5 mmol), **7** (0.55 mmol), **1** (2.5 mol%), DCM (4.0 mL) and 25 °C. Isolated yield. The *ee* value was determined by chiral HPLC analysis.

On the basis of the above results and the previous asymmetric Michael reactions [33-35], a possibly synergistic catalytic transition-state model was proposed in Scheme 4. The *α*-keto ester group of the substrate **3a** is activated *via* double hydrogen bonding with the one squaramide moiety, while its benzene group is held by *π*···*π* stacking supramolecular host-guest interaction with the calixarene cavities. Meanwhile, the deprotonated form of the substrate **4a** is assumed to interact with the protonated tertiary amine group of the other squaramide moiety, leading the corresponding transition-state. The cooperative effect between calixarene cavity and squaramide moieties facilitates the substrate **4a** to stereoselectively attack **3a** to form the desired product **5a** in good yield and enantioselectivity.



Scheme 4. The possible transition-state model.

In summary, a novel upper rim-functionalized calix[4]arene-based chiral cyclohexanediamine squaramide catalyst **1** as multiple H-bond donor–acceptor organocatalyst for the enantioselective Michael reactions of 1,3-dicarbonyl compounds and *α,β*-unsaturated carbonyl compounds. These Michael reactions were performed smoothly in DCM at room temperature by using 2.5 mol% of chiral catalyst **1**, leading to the Michael adducts in good yields (up to 99%) and enantioselectivities (up to 99% *ee*). Moreover, the scaffold of calixarene, especially its hydrophobic cavity of catalyst **1** played important roles in controlling reaction activities and enantioselectivities by comparing with model catalyst **2**. Further study on this reaction mechanism in detail is ongoing in our laboratory.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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