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Chiral Squaramides as Highly Enantioselective Catalysts for Michael Addition Reactions of 4-Hydroxycoumarins and 4-Hydroxypyrone to β,γ-Unsaturated α-Keto Esters

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Coumarin derivatives are an important class of compounds found in a variety of natural products and bioactive molecules and are used as versatile intermediates in organic and natural-product synthesis.[1] Consequently, several approaches have been taken to develop catalytic, enantioselective modifications of coumarins, which are reported to have various biological activities, such as antimalarial, antibacterial, anticoagulant, and anti-HIV activities.[2] Recently, the organocatalytic, asymmetric Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones and aldehydes through iminum ion catalysis by chiral amines to afford a highly atom-economic procedure for the formation of optically active coumarins was reported.[3]

Squaramide derivatives have been intensively investigated within the area of molecular recognition because of their strong hydrogen-bonding activity.[4] However, applications of squaramide derivatives for electrophilic activation by hydrogen bonding in enantioselective reactions appear scarce compared with their corresponding thioureas, which were recognized as a "privileged" platform for dual hydrogen-bonding catalysis over the past decade.[5,6] Very recently, the utility of chiral squaramides as organocatalysts was disclosed by Rawal's group for the conjugate-addition reaction of 1,3-dicarbonyl compounds to nitroolefins, which benefit from squaramide's characteristic dual hydrogen-bonding catalysis, in which the two hydrogen atoms are further apart than those in thioureas.[7]

Herein, we describe the development of a squaramide-promoted, asymmetric Michael addition of 4-hydroxycoumarins and a 4-hydroxypyrone to β,γ-unsaturated α-keto esters.[8] The corresponding adducts of these chiral coumarin derivatives are of particular interest, since they not only exhibit highly reactive carbonyl functionalities, but also can be readily modified to form various functional groups. We postulated that β,γ-unsaturated α-keto esters, which are electrophiles with two adjacent carbonyl groups connected by a two-carbon link, could be suitably activated and orientated by squaramide, as its two acidic hydrogen atoms are also separated by a two-carbon link. Satisfactorily, the organocatalytic process is effective for both 4-hydroxycoumarins and the analogous 4-hydroxypyrone to afford highly optically enriched compounds (up to 99% *ee*) in good yields by using easy-to-prepare chiral squaramides as catalysts with low catalyst loadings.

The addition of 4-hydroxycoumarin **1a** to the α-keto ester **2a** was used as a test reaction to explore the feasibility of the enantioselective Michael addition reaction catalyzed by chiral, tertiary-aminosquaramide-based derivatives **I** and **IIa–d** (Scheme 1). As shown in Table 1, the preliminary results revealed that, in the presence of the diaminocyclohexane-derived squaramide catalyst **I** (Table 1, entry 1), the reaction proceeded smoothly to yield the desired Michael adduct **3aa** in good yield (77%) with moderate *ee* (75%) within a short reaction time (3 h). Changing an amine moiety to a cinchona alkaloid framework to form the epiquinine-derived squaramide catalysts **IIa** and **b** increased the enantioselectivities to 90 and 86% *ee*, respectively (Table 1, entries 2 and 3). Catalysts also containing chiral substituents on the other end of the squaramide (**IIc** and **d**) resulted in even higher yields and enantioselectivities (Table 1, entries 4 and 5). In contrast, the reaction per-

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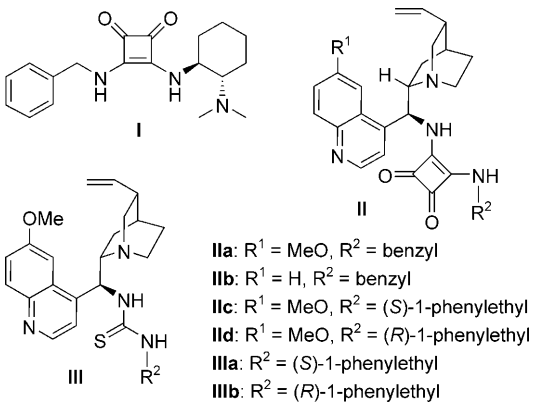
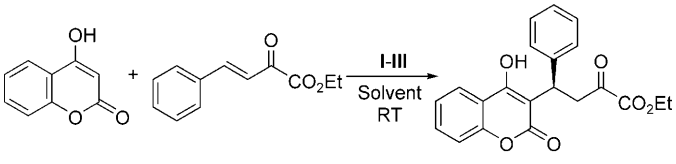


Scheme 1. Applied squaramide and thiourea organocatalysts.

Table 1. The enantioselective Michael addition of 4-hydroxycoumarin (**1a**) with 4-phenyl-2-oxo-3-butenoate ethyl ester (**2a**) using squaramide and thiourea organocatalysts.[a]



1a **2a** **3aa**

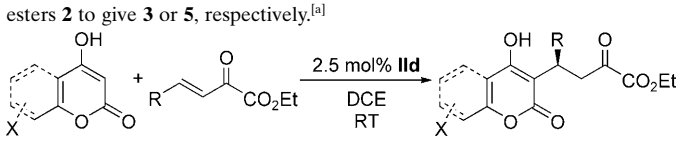
	Catalyst	[mol%]	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**I**	20.0	DCM[d]	3	77	75
2	**IIa**	20.0	DCM	3	87	90
3	**IIb**	20.0	DCM	3	85	86
4	**IIc**	20.0	DCM	3	90	92
5	**IId**	20.0	DCM	3	91	93
6	**IIIa**	20.0	DCM	12	75	64
7	**IIIb**	20.0	DCM	12	69	55
8	**IId**	10.0	DCM	5	92	94
9	**IId**	5.0	DCM	8	91	93
10	**IId**	2.5	DCM	12	92	93
11	**IId**	2.5	DCE[e]	12	93	96
12	**IId**	2.5	$CHCl_3$	12	88	87
13	**IId**	2.5	Et_2O	12	76	83
14	**IId**	2.5	PhMe	12	70	81

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), solvent (1 mL), RT. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a Chiralcel AD-H column. [d] DCM = dichloromethane. [e] DCE = 1,2-dichloroethane.

formed poorly on using the equivalent thioureas **IIIa** and **b** (Table 1, entries 6 and 7), probably due to the lack of effective activation and orientation of the α-keto esters. Furthermore, the squaramide-based catalyst **IId** maintained the high yields and enantioselectivities with a reduced catalyst loading from 20 to 2.5 mol% with only an extension of the reaction time (Table 1, entries 5 and 8–10). Of the investigated nonpolar solvents, which are all generally suitable for hydrogen bonding catalysis, 1,2-dichloroethane (DCE) was found to be the most effective and the reaction was completed within 12 h with 93% yield and 96% *ee* (Table 1, entries 10–14).

The investigation of the Michael addition was then extended to a variety of β,γ-unsaturated α-keto esters with catalyst **IId** (2.5 mol%) in DCE (Table 2). It was discovered

Table 2. Catalyst **IId**-promoted enantioselective Michael addition of 4-hydroxycoumarins **1** or 4-hydroxy-6-methyl-2-pyrone (**4**) with α-keto esters **2** to give **3** or **5**, respectively.[a]



1 or **4** **2** **3** or **5**

	X	R	**3**(**5**)	*t* [h][b]	Yield [%][b,c]	*ee* [%][b,d]
1	H(**1a**)	Ph(**2a**)	**3(5)aa**	12(12)	93(85)	96(94)
2	H(**1a**)	4-MeC_6H_4(**2b**)	**3(5)ab**	12(12)	88(86)	93(95)
3	H(**1a**)	4-$MeOC_6H_4$(**2c**)	**3(5)ac**	12(12)	65(80)	92(96)
4	H(**1a**)	4-ClC_6H_4(**2d**)	**3(5)ad**	1(1)	92(89)	>99(96)
5	H(**1a**)	4-BrC_6H_4(**2e**)	**3(5)ae**	1(1)	94(90)	95(96)
6	H(**1a**)	4-$CF_3C_6H_4$(**2f**)	**3(5)af**	1(1)	95(88)	>99(96)
7	H(**1a**)	4-$NO_2C_6H_4$(**2g**)	**3(5)ag**	10(24)	73(68)	91(94)
8	H(**1a**)	3-BrC_6H_4(**2h**)	**3(5)ah**	10(8)	81(82)	92(95)
9	H(**1a**)	2, 4-$Cl_2C_6H_3$(**2i**)	**3(5)ai**	10(8)	86(82)	92(92)
10	H(**1a**)	naphthalen-2-yl(**2j**)	**3(5)aj**	10(8)	89(83)	92(93)
11	H(**1a**)	furan-2-yl(**2k**)	**3(5)ak**	10(12)	86(79)	92(91)
12	H(**1a**)	thien-2-yl(**2l**)	**3(5)al**	10(12)	87(75)	91(92)
13	H(**1a**)	Me(**2m**)	**3(5)am**	10(12)	76(67)	86(90)
14	H(**1a**)	Pr(**2n**)	**3(5)an**	10(12)	71(71)	89(93)
15	6-Me(**1b**)	Ph(**2a**)	**3ba**	12	87	98
16	6-Me(**1b**)	4-$CF_3C_6H_4$(**2f**)	**3bf**	12	82	97
17	6-Cl(**1c**)	Ph(**2a**)	**3ca**	12	82	95
18	6-Cl(**1c**)	4-BrC_6H_4(**2e**)	**3ce**	12	80	94

[a] Reaction conditions: **1** or **4** (0.1 mmol), **2** (0.1 mmol), **IId** (2.5 mol%), DCE (1.0 mL), RT. [b] Results of adducts **5** in parentheses. [c] Yield of the isolated product. [d] Determined by HPLC analysis using a chiral stationary phase.

that most reactions with α-keto esters containing γ-aryl or -heteroaryl substituents were completed within 12 h in good-to-excellent yields (73–95%) and excellent enantioselectivities (91–>99% *ee*;Table 2, entries 1–12). It appears that the position and electronic properties of substituents on aromatic rings have a limited effect on the efficiency of this process. Notably, γ-alkyl-substituted α-keto esters also gave good yields and high enantioselectivities (Table 2, entries 13 and 14). 4-Hydroxycoumarins **1b** and **c,** containing electron-donating or -withdrawing groups, also afforded excellent results (Table 2, entries 15–18). Moreover, the scope of the reaction can be successfully extended utilizing to 4-hydroxy-6-methyl-2-pyrone (**4**), a 4-hydroxycoumarin analogue, as the Michael donor, which leads to differently substituted α-keto esters **5** with 90–96% *ee* (Table 2, entries 1–14 in parentheses). The lower reactivity of compound **2g** compared with **2d–f** may be attributed to the interference of the nitro group with the hydrogen-bonding catalysis (Table 2, entry 7).

To confirm the reasons for the observed differences in the catalytic activity of squaramide and thiourea, ab initio calculations at the HF/6-31+G (d,p) level were performed, utilizing the geometry of initial optimizations by means of the

Gaussian 03W program.[9] On the basis of the QST3 procedure, two optimized transition-state structures **IV** and **V** that link the α-keto ester **2a** and the simplified catalysts were located with only a single imaginary frequency of −1450i and −1624i cm^{-1}, respectively (Figure 1). Two hydrogen bonds (lengths: H35···O31 = 2.341 Å, H34···O29 = 2.045 Å for **IV**, and H39···O35 = 2.451 Å, H38···O33 = 2.059 Å for **V**) could be observed for each transition state. Natural bond orbital (NBO) analyses[10] were carried out to understand the nature of the activation of the γ-carbon of **2a**; this showed that the NBO value at C29 in **V** (q(C29) = −0.073 e) was less negative than that of C25 in **IV** (q(C25) = −0.082 e), implying that the C29 site of **V** is more electrophilic than that of **IV**, which is consistent with the reaction performance and results.[11]

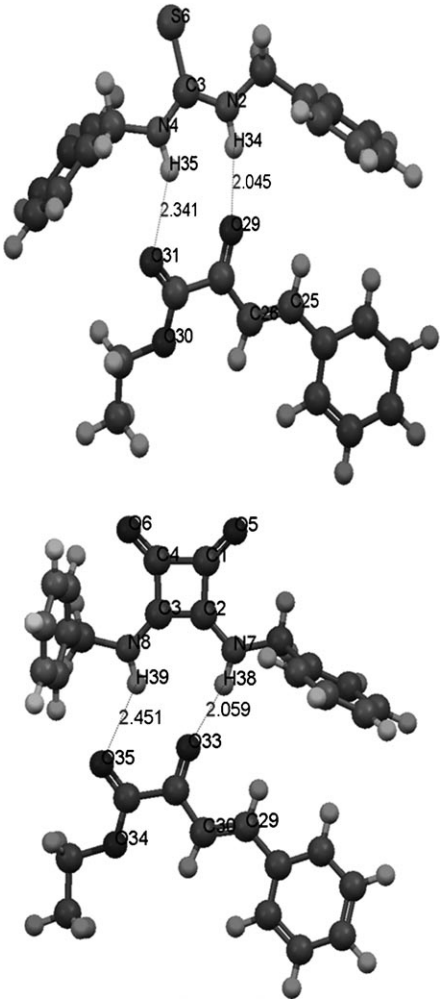
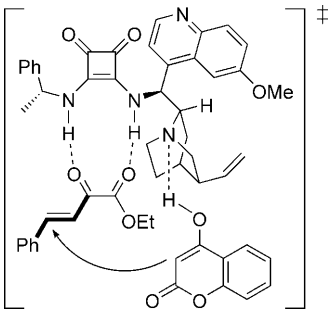


Figure 1. Molecular geometry of the hydrogen-bonding interactions in **IV** (top) and **V** (bottom).

To account for the observed stereochemical outcome of the reaction, a transition state model was proposed and is depicted in Scheme 2. The NH groups of the squaramide moiety in the catalyst are believed to form hydrogen-bonding interactions with the two adjacent carbonyl groups and increase the electrophilicity of the γ-position of the α-keto ester. Furthermore, the *Re* face approach of 4-hydroxycoumarin is induced by the tertiary amine of the catalyst and leads to the formation of the major stereoisomer, which was assigned as the *R* configuration on the basis of the X-ray structure.[12]



Scheme 2. Proposed transition-state model for the Michael addition.

In conclusion, we have disclosed the first highly enantioselective organocatalytic Michael addition of 4-hydroxycoumarins and the analogous 4-hydroxy-6-methyl-2-pyrone to β,γ-unsaturated α-keto esters by using squaramide **IId** as an organocatalyst. In this efficient catalytic asymmetric reaction only 2.5 mol% of the catalyst is sufficient to afford chiral 3-functionalized 4-hydroxycoumarin and 4-hydroxypyrone derivatives in good yields with excellent enantioselectivities (up to >99% *ee*). Given that this is the first example of the activation of carbonyl esters by a chiral squaramide, this discovery is likely to find immediate synthetic applications. Considering the high efficiency of the potent transformations further investigation of the applications of this catalysis system is underway in our group.

Experimental Section

General procedure: A mixture of 4-hydroxycoumarin **1** (0.1 mmol), β,γ-unsaturated α-keto ester **2** (0.1 mmol) and the catalyst **IId** (0.0025 mmol) in DCE (1.0 mL) was stirred at room temperature for 1–12 h (monitored by TLC). The mixture was purified by column chromatography on silica gel, eluted by petroleum ether/EtOAc (10:1 to 3:1) to give the desired Michael adduct **3** (e.g. the adduct **3aa** in 93% yield and 96% *ee*; HPLC on a Chiralcel AD-H column, hexane:*i*PrOH (70:30) containing 0.15% TFA at 1.0 mL min^{-1}; t_{major} = 5.8 min, t_{minor} = 9.1 min).

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Keywords: asymmetric catalysis · hydrogen bonds · Michael addition · organocatalysis · squaramides

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[11] Please see the Supporting Information for more details.

[12] CCDC-756209 (**3ad**), 756208 (**5ad**) contains the supplementary crystallographic data for this manuscript. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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