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Enantioselective Asymmetric Michael Addition of Cyclic Diketones to β,γ-Unsaturated α-Keto Esters

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An efficient, organocatalytic enantioselective addition of cyclic diketones with β,γ-unsaturated α-keto esters has been developed that affords products in high yields (up to 95 %) and excellent enantioselectivity (up to >99 % *ee*) under mild conditions with a low catalyst loading (2.5 mol-%). The unsaturated α-keto esters are effectively coordinated and activated through hydrogen bonds with the squaramides and proved to be excellent hydrogen-bond acceptors in this asymmetric organocatalytic reaction. This reaction provides valuable and easy access to chiral Michael adducts, which are important moieties in the skeletons of biological and pharmaceutical molecules.

Introduction

The organocatalytic Michael reaction is often regarded as one of the most efficient and broadly applicable carbon–carbon bond-forming reactions, because a wide variety of acceptors and donors can be employed and high stereoselectivity has been realized.[1] The organocatalytic Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds[2] has aroused great interest because of it offers an extremely effective way to synthesize a variety of useful chiral functionalized organic molecules that may have biological and pharmaceutical activities.[3] In particular, Jørgensen et al., Feng et al., Calter et al., and Yan et al. have reported high enantioselectivities for reactions of β,γ-unsaturated α-keto esters as Michael acceptors by using either chiral copper(II) complex catalysts[4] or organocatalysts,[5] but nevertheless, the development of new efficient catalytic systems are still in demand.

Recently, we described for the first time the development of a general and practical organocatalytic enantioselective Michael addition of 4-hydroxycoumarins and 4-hydroxypyrone with β,γ-unsaturated α-keto esters.[6] This reaction catalyzed by easily prepared tertiary amine-squaramides[7] provided chiral coumarins and pyrones in good yields with excellent enantioselectivities. Additionally, we were able to extend this procedure to the catalytic enantioselective reaction of 1,3-cyclohexanedione and dimedone with β,γ-unsaturated α-keto esters, whose corresponding adducts can be modified readily to hexahydroquinolines, which have wide applications in medicinal chemistry,[8] including prospective antihyperglycemic activity, calcium channel activity, bronchodilators, antiatherosclerotics, antidiabetic, and so on.

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Results and Discussion

On the basis of our previous strategy and our interest in the development of organocatalytic reactions, the reaction of 1,3-cyclohexanedione (**1**) with β,γ-unsaturated α-keto ester **2a** was chosen as a model reaction to screen the catalysts (Table 1). We found that squaramide catalysts **I** (Figure 1), which were used in our previous work, also showed good efficiency in this reaction (Table 1, Entries 1–4). Similarly, the reaction exhibited moderate performance with thiourea catalysts **II** because of the lack of the characteristic H-bonding activation and the orientation of the α-keto esters (Table 1, Entries 5–9). Catalyst **III**, which was highly effective in the reported dynamic kinetic resolution of racemic azlactones,[7d] did not function well for the present transformation (Table 1, Entries 10 and 11). With further studies of other chiral moieties, including (*R*,*R*)-1,2-diaminocyclohexane and (*R*,*R*)-1,2-diphenylethylenediamine (Table 1, Entries 12–17), we were delighted to find that excellent yields and enantioselectivities were obtained in shorter times when catalysts possessing the (*R*,*R*)-1,2-diphenylethylenediamine unit were employed. Evaluation of the effects of other parts of the squaramide catalyst showed that catalyst **Vc** containing a bis(trifluoromethyl)phenyl group was most effective (Table 1, Entry 17). Further exploration of the potential of **Vc** revealed that no noticeable impact on the efficiency could be observed when lowering the catalyst loading to 2.5 mol-% (Table 1, Entries 18 and 19), whereas a slightly decreased yield and enantioselectivity were obtained when 1 mol-% of **Vc** was used (Table 1, Entry 20).

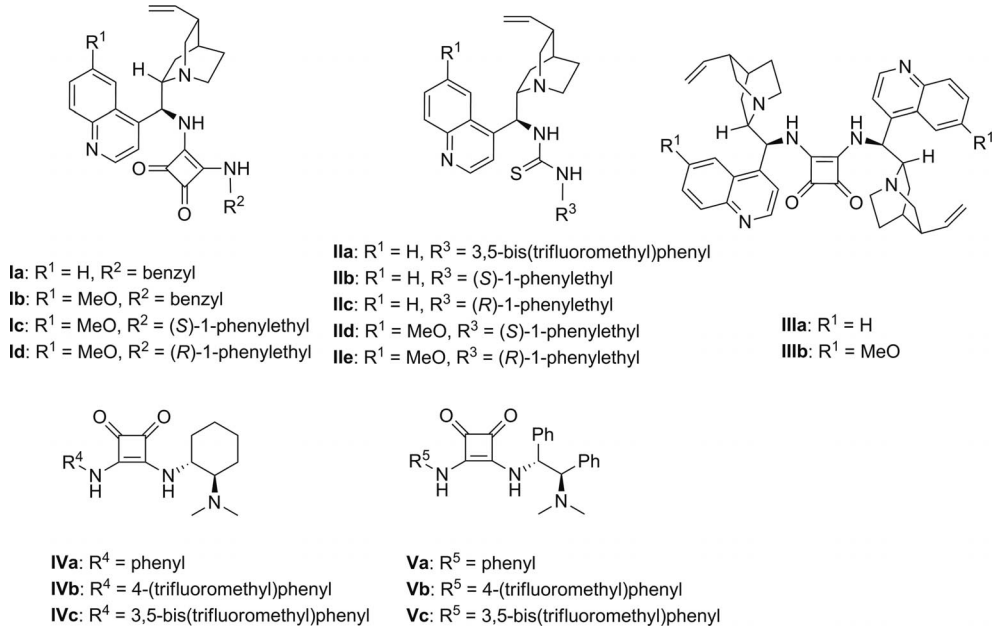
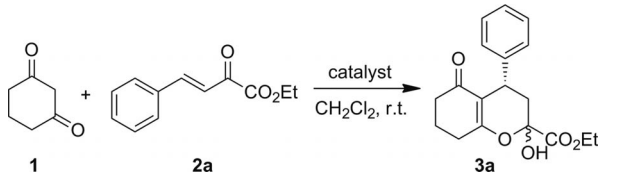


Figure 1. Organocatalysts tested in this study.

Table 1. Evaluation of catalysts with the model reaction.[a]



Entry	Catalyst	Catalyst loading [mol-%]	*T* [h]	Yield [%][b]	*ee*[c] [%]
1	**Ia**	10	1	87	–89
2	**Ib**	10	1	86	–93
3	**Ic**	10	1	89	–95
4	**Id**	10	1	90	–95
5	**IIa**	10	1	85	–86
6	**IIb**	10	1	82	–79
7	**IIc**	10	1	81	–78
8	**IId**	10	1	82	–80
9	**IIe**	10	1	84	–81
10	**IIIa**	10	1	83	–75
11	**IIIb**	10	1	84	–61
12	**IVa**	10	0.5	91	86
13	**IVb**	10	0.5	93	88
14	**IVc**	10	0.5	92	90
15	**Va**	10	0.5	93	92
16	**Vb**	10	0.5	92	94
17	**Vc**	10	0.5	93	96
18	**Vc**	5	1	93	96
19	**Vc**	2.5	3	92	95
20	**Vc**	1	12	90	92

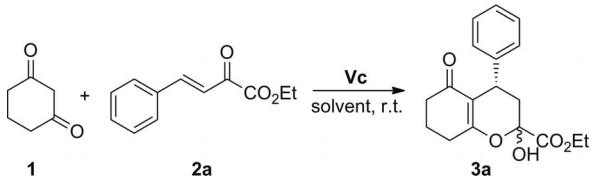
[a] Unless otherwise specified, all reactions were carried out with 1,3-cyclohexanedione (**1**, 0.125 mmol), β,γ-unsaturated α-keto ester **2a** (0.125 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiralcel AD-H, hexane/*i*PrOH = 70:30, 0.7 mL/min). A minus sign before the *ee* value signifies the opposite enantiomer.

Subsequently, a survey of solvents showed that protic solvents such as CH_3OH and *i*PrOH are not suitable for this H-bonding catalytic process (Table 2, Entries 1 and 2). Generally, better results in terms of enantioselectivity were obtained with similarly high yields in non-polar solvents (Table 2, Entries 3–10). Specifically, when the process was carried out in $CHCl_3$, the reaction afforded the most encouraging results (93% yield, 98%*ee*; Table 2, Entry 5). However, relatively poor results were observed with the polar solvent CH_3CN (Table 2, Entry 11). This is expected because non-polar, aprotic solvents can minimize the disruption of hydrogen-bonding interactions between the catalyst and the substrates; thus, high catalytic activity and stereoselectivity towards the reaction are generally observed.

With the optimal reaction conditions in hand (Table 2, Entry 5), subsequently we explored the generality of this reaction with a spectrum of β,γ-unsaturated α-keto esters (Table 3). It was discovered that all the reactions with β,γ-unsaturated α-keto esters bearing an γ-aryl substituent were complete within 12 h with good to high yields (75–93%) and excellent enantioselectivities (93–98%*ee*), irrespective of the electronic nature or position of the substituents on the phenyl ring. Besides, the reaction also took place with a naphthalen-2-yl or heteroaromatic substituents with excellent yields and enantioselectivities (Table 3, Entries 11 and 12).

To explore further the potential of this addition process, the reaction of dimedone (**4**) with various β,γ-unsaturated α-keto esters **2** was also investigated (Table 4). The yields and enantioselectivities of these reactions are even higher compared with those obtained for the reaction between 1,3-cyclohexanedione and β,γ-unsaturated α-keto esters. It is noteworthy that substrates with an alkyl group also provided the desired products in good yields with good to high enantioselectivities (Table 4, Entries 9–11). As shown in Schemes 1 and 2, this catalytic system is also suitable for other cyclic 1,3-diketones, such as 4-hydroxycoumarin, 4-

Table 2. Screening of the solvents for the organocatalytic enantioselective Michael reaction by using catalyst **Vc**.[a]

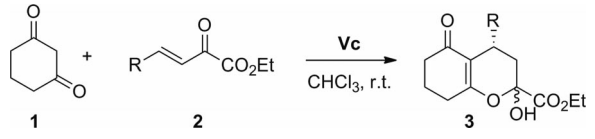


1 2a 3a

Entry	Solvent	Yield[b] [%]	*ee*[c] [%]
1	CH_3OH	45	18
2	*i*PrOH	55	58
3	CH_2Cl_2	92	95
4	CH_2Cl/CH_2Cl	88	95
5	$CHCl_3$	93	98
6	Et_2O	84	95
7	iPr_2O	82	94
8	THF	80	78
9	dioxane	77	89
10	toluene	85	93
11	CH_3CN	67	85

[a] Unless otherwise specified, all reactions were carried out with 1,3-cyclohexanedione (**1**, 0.125 mmol), β,γ-unsaturated α-keto ester **2a** (0.125 mmol), catalyst **Vc** (3.125×10^{-3} mmol, 2.5 mol-%) in solvent (1.0 mL) at room temperature for 3 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiralcel AD-H, hexane/*i*PrOH = 70:30, 0.7 mL/min).

Table 3. Substrate scope of the enantioselective Michael addition of 1,3-cyclohexanedione with β,γ-unsaturated α-keto esters.[a]



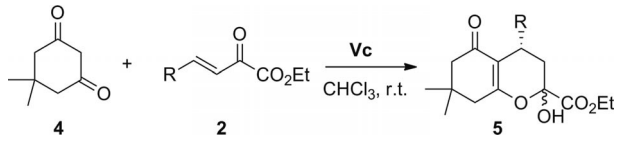
1 2 3

Entry	R	*T* [h]	Adduct **3**	Yield[b] [%]	*ee*[c] [%]
1	Ph	3	**3a**	93	98
2	4-MeC_6H_4	12	**3b**	75	95
3	4-$MeOC_6H_4$	12	**3c**	82	98
4	4-ClC_6H_4	6	**3d**	91	97
5	4-BrC_6H_4	6	**3e**	87	96
6	4-$CF_3C_6H_4$	6	**3f**	92	96
7	4-$NO_2C_6H_4$	9	**3g**	79	93
8	2-ClC_6H_4	9	**3h**	82	95
9	3-BrC_6H_4	9	**3i**	81	96
10	2,4-$Cl_2C_6H_3$	9	**3j**	86	96
11	naphthalen-2-yl	12	**3k**	84	93
12	thiophen-2-yl	12	**3l**	87	98

[a] Unless otherwise specified, all reactions were carried out with 1,3-cyclohexanedione (**1**, 0.125 mmol), β,γ-unsaturated α-keto ester **2** (0.125 mmol), catalyst **Vc** (3.125×10^{-3} mmol, 2.5 mol-%) in $CHCl_3$ (1.0 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiralcel AD-H, hexane/*i*PrOH = 70:30).

hydroxypyrone, and 2-hydroxy-1,4-naphthoquinone, which afforded the Michael adducts in high yields and enantioselectivities. We also tried acyclic 1,3-diketones as Michael donors, such as acetylacetone and diethyl malonate; however, we did not observe a significant conversion even by prolonging the reaction time. Besides, the highly enantiomerically enriched Michael adducts obtained by this method can be easily converted into hexahydroquinoline **9** without any loss in optical activity[5a] (Scheme 3).

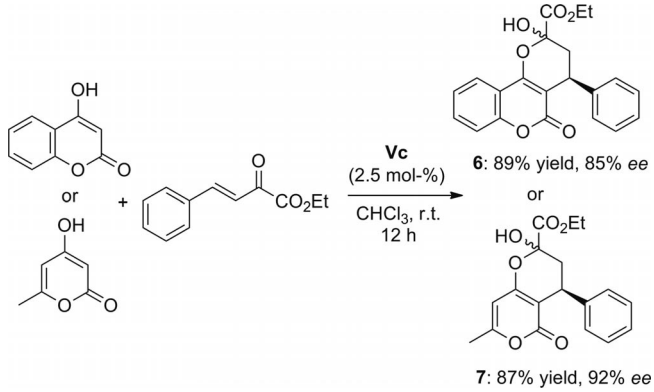
Table 4. Substrate scope of the enantioselective Michael addition of dimedone with β,γ-unsaturated α-keto esters.[a]



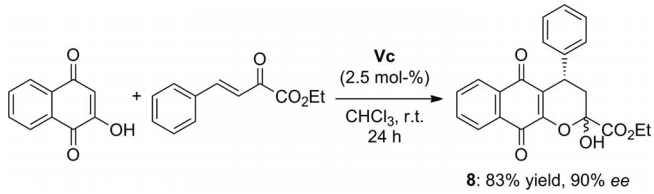
4 2 5

Entry	R	*T* [h]	Adduct **5**	Yield[b] [%]	*ee*[c] [%]
1	Ph	2	**5a**	95	99
2	4-$MeOC_6H_4$	12	**5b**	86	95
3	4-ClC_6H_4	3	**5c**	92	99
4	4-$CF_3C_6H_4$	4	**5d**	94	99
5	3-BrC_6H_4	6	**5e**	83	98
6	2,4-$Cl_2C_6H_3$	6	**5f**	89	98
7	naphthalen-2-yl	12	**5g**	85	95
8	thiophen-2-yl	6	**5h**	88	97
9	ethyl	12	**5i**	78	98[d]
10	propyl	12	**5j**	82	97[d]
11	butyl	12	**5k**	75	79[d]

[a] Unless otherwise specified, all reactions were carried out with dimedone (**4**, 0.125 mmol), β,γ-unsaturated α-keto ester **2** (0.125 mmol), catalyst **Vc** (3.125×10^{-3} mmol, 2.5 mol-%) in CH_3Cl (1.0 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiralcel AD-H, hexane/*i*PrOH = 70:30). [d] Determined by HPLC analysis of the derived hexahydroquinoline (Daicel Chiralcel OD-H, hexane/*i*PrOH = 95:5).

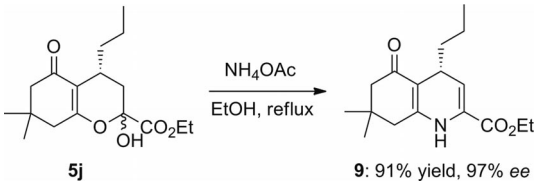


Scheme 1. 4-Hydroxycoumarin or 4-hydroxy-6-methyl-2-pyrone as Michael donors.



Scheme 2. 2-Hydroxy-1,4-naphthoquinone as Michael donor.

On the basis of previous mechanistic proposals and the experimental results described above, a possible transition-state model was hypothesized (Figure 2). The β,γ-unsatu-



Scheme 3. Conversion of **5j** into hexahydroquinoline **9**.

rated α-keto ester is fixed and activated by the squaramide moiety through the formation of two characteristic hydrogen bonds between the NH groups and the α-keto ester group. Direct approach of the deprotonated cyclic diketones from the *Si* face to the β,γ-unsaturated α-keto esters would justify the observed stereochemistry of the products.

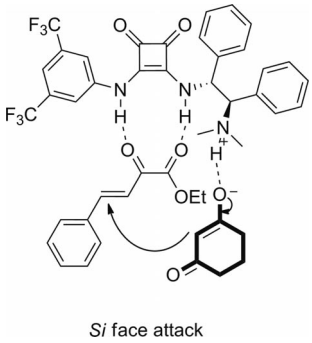


Figure 2. Proposed transition-state model.

Conclusions

In summary, tertiary amine–squaramide organocatalysts were found to promote the highly enantioselective Michael addition of cyclic diketones to β,γ-unsaturated α-keto esters. With this procedure, the desired Michael products could be obtained in good to high yields (75–95%) with excellent enantioselectivities (up to >99%*ee*) under mild conditions with a low catalyst loading (2.5 mol-%). Compared with Calter's procedure,[5a] even higher yields and enantioselectivities can be achieved with a reduced catalyst loading (2.5 vs. 10 mol-%) in a shorter reaction time. Studies aimed at investigating the application of the products and expanding the scope and applications of chiral squaramides in organocatalysis are underway in our laboratory.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ with a Bruker Avance III (500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR). TMS served as an internal standard (δ = 0 ppm) for ^{1}H NMR and $CDCl_3$ was used as internal standard (δ = 77.0 ppm) for ^{13}C NMR. HPLC experiments were carried out with a JASCO LC-2000 Plus system with MD-2010 HPLC diode array detector. Flash chromatography (FC) was carried out with silica gel (200–300 mesh). Monitoring of reactions was performed by TLC on silica gel precoated on glass plates, and spots were visualized with UV light at 254 nm. Catalyst **II**;[9] catalysts **I**, **III**, **IV**, and **V**;[7a,7h] and γ-aryl[10] and alkyl[11] β,γ-unsaturated α-keto esters **2** were synthesized according to reported procedures. Commercially available cyclic diketones and solvents were used without further purification or drying. All reactions were carried out in oven-dried glassware.

Representative Procedure for the Asymmetric Michael Addition of Cyclic Diketones to β,γ-Unsaturated α-Keto Esters: To a solution of catalyst **Vc** (0.003125 mmol, 2.5 mol-%) in $CHCl_3$ (1.0 mL) was added 1,3-cyclohexanedione (**1**, 0.125 mmol) and β,γ-unsaturated α-keto ester **2a** (0.125 mmol). The reaction mixture was then stirred at room temperature for 3 h (monitored by TLC). The crude mixture was purified by column chromatography (silica gel; petroleum ether/EtOAc, 5:1 to 2:1) to give desired product **3a** in 93% yield, 98%*ee*, which was found to exist in equilibrium between the cyclic and linear anomers. This equilibration proceeded slowly enough that they showed up as separate compounds by ^{1}H and ^{13}C NMR spectroscopy, but quickly enough that they did not resolve by chromatography. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.29 (t, J = 7.13 Hz, 2.00 H), 1.33 (t, J = 7.13 Hz, 1.00 H), 1.98–2.11 (m, 2.00 H), 2.22–2.64 (m, 6.00 H), 3.90 (t, J = 9.15 Hz, 0.66 H), 4.11 (d, J = 6.92 Hz, 0.36 H), 4.17–4.32 (m, 2.26 H), 4.56 (s, 0.59 H), 7.15–7.19 (m, 3.00 H), 7.24–7.29 (m, 2.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.85, 13.94, 20.12, 20.62, 28.73, 28.85, 31.82, 33.27, 35.86, 36.87, 36.92, 38.25, 62.98, 63.09, 94.69, 95.64, 113.16, 115.31, 126.05, 126.16, 126.89, 127.16, 128.19, 128.34, 142.83, 144.06, 168.81, 168.89, 168.95, 169.49, 196.44, 196.97 ppm. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 70:30, flow rate = 0.7 mL/min): t_R = 10.1 (major), 8.1 (minor) min.

(*S*)-Ethyl 2-Hydroxy-5-oxo-4-*p*-tolyl-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3b): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.28 (t, J = 7.12 Hz, 1.90 H), 1.32 (t, J = 7.13 Hz, 1.09 H), 1.95–2.26 (m, 4.00 H), 2.28 (s, 1.10 H), 2.29 (s, 1.88 H), 2.33–2.62 (m, 4.00 H), 3.86 (t, J = 9.24 Hz, 0.64 H), 4.07 (d, J = 7.07 Hz, 0.36 H), 4.19–4.46 (m, 3.00 H), 7.06–7.08 (m, 4.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.83, 13.93, 20.10, 20.61, 20.97, 28.73, 28.86, 31.42, 32.84, 35.92, 36.87, 36.89, 38.34, 62.95, 63.07, 94.73, 95.72, 113.32, 115.53, 126.76, 127.00, 129.01, 129.07, 135.44, 135.63, 139.70, 141.02, 168.81, 168.85, 169.02, 169.48, 196.65, 197.14 ppm. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 85:15, flow rate = 0.7 mL/min): t_R = 18.4 (major), 15.4 (minor) min.

(*S*)-Ethyl 2-Hydroxy-4-(4-methoxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3c): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.29 (t, J = 7.17 Hz, 1.90 H), 1.33 (t, J = 7.13 Hz, 1.09 H), 1.97–2.11 (m, 2.00 H), 2.20–2.62 (m, 6.00 H), 3.75 (s, 1.11 H), 3.77 (s, 1.87 H), 3.86 (t, J = 9.13 Hz, 0.64 H), 4.07 (d, J = 6.92 Hz, 0.37 H), 4.18–4.32 (m, 2.38 H), 4.50 (s, 0.61 H), 6.79–6.82 (m, 2.00 H), 7.08–7.11 (m, 2.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.87, 13.94, 20.14, 20.65, 28.74, 28.87, 30.93, 32.46, 35.83, 36.96, 36.99, 38.35, 55.12, 55.16, 62.95, 63.08, 94.73, 95.67, 113.40, 113.74, 113.83, 115.61, 127.85, 128.15, 134.75, 136.09, 157.83, 157.93, 168.56, 168.81, 168.99, 169.20, 196.36, 196.87 ppm. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 70:30, flow rate = 0.7 mL/min): t_R = 15.2 (major), 10.8 (minor) min.

(*S*)-Ethyl 4-(4-Chlorophenyl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3d): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.29–1.35 (m, 3.00 H), 1.97–2.61 (m, 8.00 H), 3.85–3.88 (m, 0.66 H), 4.05 (d, J = 7.24 Hz, 0.35 H), 4.22–4.34 (m, 2.00 H), 4.34 (s, 0.29 H), 4.57 (s, 0.62 H), 7.09–7.13 (m, 2.00 H), 7.19–7.25 (m, 2.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.88, 13.94, 20.06, 20.61, 28.72, 28.85, 31.32, 32.83, 35.39, 36.85, 36.91, 38.05, 63.18, 63.26, 94.54, 95.35, 112.85,

115.05, 128.15, 128.26, 128.51, 128.73, 131.62, 141.62, 142.74, 168.80, 168.84, 169.09, 169.58, 196.33, 196.90 ppm. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 70:30, flow rate = 0.7 mL/min): t_R = 12.5 (major), 9.4 (minor) min.

(*S*)-Ethyl 4-(4-Bromophenyl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3e): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.29–1.34 (m, 3.00 H), 1.97–2.61 (m, 8.00 H), 3.83–3.87 (m, 0.66 H), 4.03 (d, J = 6.97 Hz, 0.34 H), 4.21–4.32 (m, 2.00 H), 4.37 (s, 0.37 H), 4.60 (s, 0.62 H), 7.03–7.08 (m, 2.00 H), 7.34–7.39 (m, 2.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.86, 13.93, 20.06, 20.58, 28.71, 28.84, 31.50, 32.90, 35.45, 36.82, 36.88, 38.01, 63.13, 63.20, 94.57, 95.40, 112.83, 114.93, 119.65, 119.71, 128.68, 129.15, 131.05, 131.42, 142.22, 143.26, 168.76, 168.80, 169.18, 169.66, 196.35, 196.90 ppm. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 70:30, flow rate = 0.7 mL/min): t_R = 13.2 (major), 9.8 (minor) min.

(*S*)-Ethyl 2-Hydroxy-7,7-dimethyl-5-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (5a): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.09 (s, 1.94 H), 1.11 (s, 1.06 H), 1.17 (s, 1.95 H), 1.20 (s, 1.05 H), 1.28 (t, J = 7.13 Hz,1.96 H), 1.33 (t, J = 7.12 Hz, 1.04 H), 2.21–2.59 (m, 6.00 H), 3.89 (t, J = 9.02 Hz, 0.65 H), 4.09 (d, J = 6.81 Hz, 0.37 H), 4.15–4.32 (m, 2.38 H), 4.53 (s, 0.57 H), 7.15–7.18 (m, 2.00 H), 7.24–7.29 (m, 2.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.86, 13.94, 27.61, 28.22, 28.74, 29.25, 31.67, 32.01, 32.06, 33.46, 35.33, 37.91, 42.40, 42.45, 50.73, 63.25, 63.30, 94.64, 95.39, 111.47, 113.41, 124.97, 125.00, 125.39, 127.33, 127.82, 128.19, 128.45, 147.52, 148.56, 167.54, 168.00, 168.70, 168.77, 196.17, 196.71 ppm. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 70:30, flow rate = 0.7 mL/min): t_R = 10.2 (major), 7.5 (minor) min.

(*S*)-Ethyl 2-Hydroxy-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (5b): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.08 (s, 1.85 H), 1.11 (s, 1.15 H), 1.16 (s, 1.85 H), 1.19 (s, 1.15 H), 1.28 (t, J = 7.13 Hz, 1.85 H), 1.32 (t, J = 7.12 Hz,1.15 H), 2.20–2.56 (m, 6.00 H), 3.75 (s, 1.14 H), 3.76 (s, 1.85 H), 3.83–3.87 (m, 0.62 H), 4.05 (d, J = 6.73 Hz, 0.39 H), 4.16–4.32 (m, 2.39 H), 4.50 (s, 0.57 H), 6.79–6.82 (m, 2.00 H), 7.08–7.10 (m, 2.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.85, 13.94, 27.67, 28.29, 28.70, 29.22, 31.20, 31.61, 31.98, 32.52, 36.00, 38.30, 42.40, 42.45, 50.84, 55.11, 55.14, 62.94, 63.02, 94.91, 95.80, 112.27, 113.72, 113.81, 114.12, 127.98, 128.24, 134.96, 136.06, 157.79, 157.90, 166.88, 167.48, 168.80, 168.92, 196.37, 196.78 ppm. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 70:30, flow rate = 0.7 mL/min): t_R = 15.4 (major), 9.3 (minor) min.

(*S*)-Ethyl 4-(4-Chlorophenyl)-2-hydroxy-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (5c): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.09 (s, 1.89 H), 1.11 (s, 1.10 H), 1.16 (s, 1.89 H), 1.18 (s, 1.11 H), 1.29–1.35 (m, 3 H), 2.15–2.58 (m, 6.00 H), 3.84–3.88 (m, 0.66 H), 4.04 (d, J = 6.21 Hz, 0.36 H), 4.20–4.33 (m, 2.00 H), 4.35 (s, 0.33 H), 4.55 (s, 0.59 H), 7.09–7.12 (m, 2.00 H), 7.20–7.24 (m, 2.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.88. 13.96, 27.68, 28.25, 28.74, 29.20, 31.67, 31.69, 32.02, 32.98, 35.68, 38.08, 42.45, 42.51, 50.85, 63.13, 63.19, 94.77, 95.55, 111.88, 113.73, 128.20, 128.43, 128.53, 128.86, 131.68, 131.70, 141.85, 142.80, 167.21, 167.72, 168.78, 168.84, 196.14, 196.60 ppm. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 70:30, flow rate = 0.7 mL/min): t_R = 14.1 (major), 7.7 (minor) min.

(*S*)-Ethyl 2-Hydroxy-7,7-dimethyl-5-oxo-4-[4-(trifluoromethyl)-phenyl]-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (5d): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.10 (s, 1.90 H), 1.12 (s, 1.10 H), 1.17 (s, 1.90 H), 1.20 (s, 1.10 H), 1.30 (t, J = 7.18 Hz,1.90 H), 1.34 (t, J = 7.16 Hz, 1.10 H), 2.16–2.62 (m, 6.00 H), 3.92–3.96 (m, 0.63 H), 4.12 (d, J = 6.96 Hz, 0.37 H), 4.21–4.33 (m, 2.00 H), 4.35 (s, 0.40 H), 4.56 (s, 0.60 H), 7.27–7.29 (m, 2.00 H), 7.48–7.54 (m, 2.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.87, 13.95, 27.62, 28.23, 28.75, 29.25, 31.68, 32.02, 32.07, 33.46, 35.34, 37.92, 42.41, 42.46, 50.74, 50.76, 63.25, 63.30, 94.64, 95.39, 111.48, 113.41, 124.97, 125.00, 125.39, 125.42, 127.34, 127.83, 128.19, 128.45, 147.52, 148.56, 167.54, 168.00, 168.70, 168.78, 196.17, 196.71 ppm. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 70:30, flow rate = 0.7 mL/min): t_R = 11.4 (major), 6.9 (minor) min.

(*S*)-Ethyl 4-(3-Bromophenyl)-2-hydroxy-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (5e): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.09 (s, 1.89 H), 1.11 (s, 1.09 H), 1.17 (s, 1.91 H), 1.20 (s, 1.09 H), 1.29–1.35 (m, 3 H), 2.16–2.58 (m, 6.00 H), 3.85 (t, J = 9.07 Hz, 0.64 H), 4.04 (d, J = 7.28 Hz, 0.37 H), 4.20–4.33 (m, 2.00 H), 4.37 (s, 0.34 H), 4.58 (s, 0.57 H), 7.10–7.16 (m, 2.00 H), 7.27–7.30 (m, 2.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.90, 13.96, 27.66, 28.22, 28.75, 29.20, 31.70, 31.84, 32.05, 33.23, 35.51, 37.98, 42.38, 42.44, 50.75, 63.16, 63.23, 94.72, 95.49, 111.51, 113.39, 122.14, 122.40, 125.91, 126.14, 129.13, 129.18, 129.54, 129.92, 130.00, 130.68, 145.72, 146.67, 167.43, 167.91, 168.74, 168.77, 196.17, 196.66 ppm. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 70:30, flow rate = 0.7 mL/min): t_R = 11.1 (major), 7.8 (minor) min.

Supporting Information (see footnote on the first page of this article): Additional characterization data and copies of the NMR spectra of the Michael adducts.

Acknowledgments

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