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PAPER

Chiral indane skeleton based thiourea catalyzed highly stereoselective cascade Michael–enolation–cyclization reaction†

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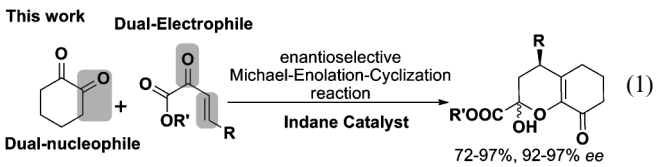
An efficient asymmetric cascade reaction catalyzed by a chiral bifunctional indane amine–thiourea catalyst has been developed. From a broad substrate scope, chiral dihydro-2*H*-pyran complexes that contained two stereogenic centers were obtained in a one-pot manner in good to excellent yields (72–97%) and high to excellent stereoselectivities (92–97% ee).

Introduction

The scope of metal-free organocatalysts to promote asymmetric cascade reactions has expanded in the last few years.[1] Recently, a number of useful cascade reactions have been reported.[2] Undoubtedly, the utilization of cascade reactions provides a useful synthetic tool for organic synthesis. It offers a possibility to form multiple chemical bonds in a one-pot process without isolating intermediates, changing reaction conditions, or adding reagents. Finally, this strategy reduces the synthetic costs and simplifies synthetic steps and processes. Inspired by the advantages and significances of this cascade strategy, we have become interested in exploring a new enantioselective cascade reaction.

In contrast, the utilization of 1,2-diones is still rare.[3] However, their functionality offers a good starting point for additional transformations. Therefore, we wish to use them as a group of interesting synthetic blocks for further asymmetric transformations. Herein, we report a new enantioselective organocatalytic cascade reaction with the formation of functionalized 3,4-dihydro-2*H*-pyran complexes [eqn (1)]. Notably, the features of the strategy include: (1) a novel indane amine–thiourea catalyst; (2) good to excellent yields (72–97%) and high to excellent enantioselectivities (92–97% ee); (3) a first trial of addition of 1,2-diones to β,γ-unsaturated α-keto esters.



(1)

Rueping *et al.* have reported a stereoselective Lewis base catalyzed domino Michael–aldol reaction which results in the formation of chiral bicycle[3.2.1]octane-6-carbaldehydes [eqn (2)].[4]

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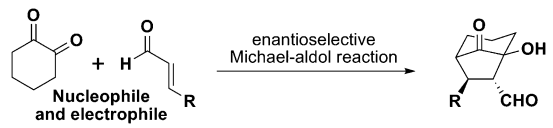
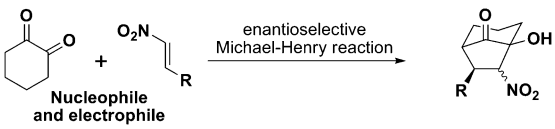
Several α,β-unsaturated aldehydes have been applied to this system to access the target compounds. Furthermore, nitroolefins have also been utilized as a replacement for α,β-unsaturated aldehydes to afford a similar bicycle[3.2.1]octane structure discovered by the Rueping and Zhao groups independently [eqn (3)].[5] As a significant complement, we document an interesting reaction which tolerated 1,2-diones as a dual-nucleophile to react with β,γ-unsaturated α-keto esters which were firstly utilized as dual electrophile. An amazing 4-dihydro-2*H*-pyran structure (eqn (1)) was finally constructed.



(2)

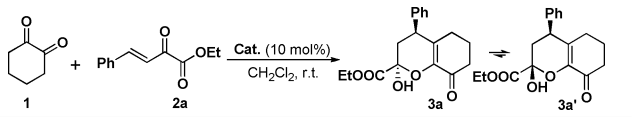


(3)

Results and discussion

To probe the feasibility of the proposed cascade reaction, (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate (**2a**) was treated with 1,2-cyclohexadione **1** in the presence of catalyst **I**, developed by the Soós,[6] Dixon[7a] and Connon[7b] groups respectively, in CH_2Cl_2 at room temperature (Table 1). As shown in Table 1, unfortunately, catalyst **I** exhibited a poor catalytic activity so that a very trace amount of desired product was generated after 96 h (Table 1, entry 1). Therefore, we wished to discover an active chiral catalyst that could promote the reaction and result in high efficiency and excellent stereo-control. In planning our catalyst investigation, we were inspired by our group's reported indane bifuncational amine–thiourea catalysts. This type of catalyst demonstrated some interesting aspects, such as high activity, good stereo-control, and flexible chiral structure.[8] On the basis of these experiences we decided to examine the catalytic activity and stereoselectivity

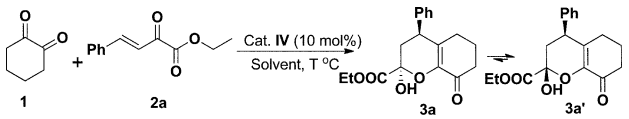
Table 1 Evaluation of bifunctional chiral organocatalysts[a]



Entry	Cat.	t (h)	Yield (%)[b]
1	**I**	96	<5
2	**II-a**	96	<5
3	**II-b**	96	<5
4	**II-c**	96	<5
5	**III**	96	<5
6	**IV**	**48**	**53**
7	**V**	96	<5

[a] Reaction was conducted on 0.1 mmol scale in CH_2Cl_2 (0.5 mL) at r.t. for 48–96 h, and the ratio of **1**:**2a** is 1.5:1. [b] Yield of isolated product after column chromatography.

Table 2 Optimization of the reaction conditions[a]



Entry	Solvent	T/°C	t (h)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	23	48	53	96
2	CH_2Cl_2	40	16	66	92
3	Et_2O	40	16	88	94
4	$Cl(CH_2)_2Cl$	50	14	73	96
5	Anisole	50	12	75	94
6	**Toluene**	**50**	**8**	**94**	**95**
7	Xylenes	50	8	84	95
8	$PhCF_3$	50	8	78	93
9	*i*-PrOH	50	12	44	85
10	DMSO	50	24	50	37

[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (ee) was determined by HPLC.

of our indane catalysts in this type of reaction. Unfortunately, catalyst **II** showed a similar performance as catalyst **I** (Table 1, entries 2–4). With regard to catalyst **II**'s structure (Fig. 1), we found that two functional groups, amine and thiourea, are in the anti-position. We then wondered if the relative position of the two functional groups would affect the catalyst's activity. However, the results showed that our inference was wrong (Table 1, entry 5, <5%). A switch of these important functional groups would not enhance the catalytic performance. Then the next exploration was the change of the chiral center's orientation. As demonstrated in Fig. 1, catalyst **V** was synthesized and investigated. It is noteworthy that catalyst **V** was firstly discovered by our research group and already verified as an active catalyst in some catalytic transformations.[8] Surprisingly, it still could not efficiently promote this reaction (Table 1, entry 7). It appeared that indane amine–thiourea catalysts have not enough power to complete such a task. However, we did not cease our exploration before we reached our target. By chance, we finally disclosed a novel indane bifunctional catalyst **IV** which demonstrated a superior performance in both activity and stereoselectivity (Table 1, entry 6, 53%, 96% ee). It was obvious that catalyst **IV** was derived from catalyst **V** *via* a switch of the two functional groups. These results again emphasized the uniqueness of our indane C-1 symmetric catalytic system. Based on NMR data, we found compound **3a** coexisted with its anomer **3a′** (Scheme 1). In this reaction, the compound **3a** was kinetically

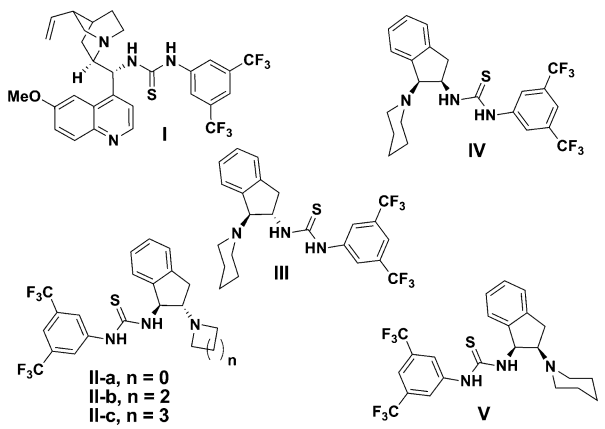


Fig. 1 Evaluated bifunctional amine–thiourea organocatalysts.

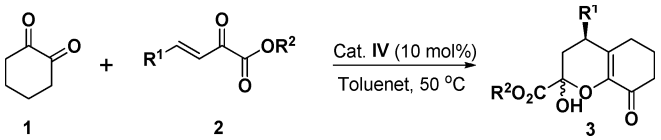
favored based on the ratio (>10:1) between **3a** and its anomer (see ESI†).

For further optimization, solvent, as well as reaction temperature, was varied (Table 2). These experiments revealed that the best results with regard to reactivity and stereoselectivity were obtained with toluene at 50 °C (Table 2, entry 5). The process was completed within 8 h and afforded 3,4-dihydro-2*H*-pyran complex **3a** in 94% yield and with an excellent enantioselectivity (95% ee). In varying the reaction temperature, the catalytic activity can be dramatically enhanced by a slight increase in temperature. Most importantly, stereoselectivity was not reduced significantly in the process (Table 2, entries 1 and 2, 48 to 16 h, 53% to 66% yield, 96% to 92% ee). Furthermore, less polar solvents are fundamental for obtaining high enantioselectivities (Table 2, entries 1–8, 92–95% ee). For high polarity solvents, relatively lower enantioselectivities were aroused by potential destruction of H-bonding interactions (Table 2, entries 9 and 10, 85% and 37% ee).

Under the optimized reaction conditions, the generality of our cascade process was examined by using various β,γ-unsaturated α-keto esters **3** (Table 3). Aromatic β,γ-unsaturated α-keto esters having both electron-withdrawing (Table 3, entries 2–7) and electron-donating substituents (Table 3, entries 8–13) can effectively be applied to this transformation; the substitution pattern of the arene had limited influence on the enantioselectivity of the reaction (Table 3, entries 2–13). In addition, it was possible to use both heteroaromatic (Table 3, entry 14) and aliphatic β,γ-unsaturated α-keto esters (Table 3, entry 16) in this reaction. Meanwhile, modification of the ester also had no obvious effect on the enantioselectivity (Table 3, entry 17). The ability to control the formation of two new stereogenic centers permitted the assembly of a diverse set of functionalized 3,4-dihydro-2*H*-pyran complexes **3** in good to high yields (72–97%) and with high to excellent enantioselectivities (92–97% ee). The absolute configuration of the products was determined by single-crystal X-ray analysis† of **3i** (Fig. 2).[9]

With regard to the reaction mechanism, an enantioselective cascade Michael–enolation–cyclization process is proposed for the formation of the highly stereo-controlled products **3** (Scheme 1). Catalyst **IV** activates 1,2-cyclohexadione and β,γ-unsaturated

Table 3 Substrate scope[a]



1 2 3

Entry	R^1	R^2	t (h)	Yield (%)[b]	ee (%)[c]
1	Ph (**3a**)	Et	8	94	95
2	2-ClC_6H_4 (**3b**)	Et	6	92	96
3	3-ClC_6H_4 (**3c**)	Et	6	95	92
4	4-ClC_6H_4 (**3d**)	Et	6	90	96
5	4-FC_6H_4 (**3e**)	Et	6	91	95
6	2-BrC_6H_4 (**3f**)	Et	6	95	97
7	4-$NO_2C_6H_4$ (**3g**)	Et	4	84	93
8	4-$MeOC_6H_4$ (**3h**)	Et	24	82	95
9	4-$MeSC_6H_4$ (**3i**)	Et	24	82	95
10	4-allyloxyC_6H_4 (**3j**)	Et	24	87	94
11	3-$PhOC_6H_4$ (**3k**)	Et	12	94	96
12	4-$BnOC_6H_4$ (**3l**)	Et	24	86	93
13	4-*i*PrC_6H_4 (**3m**)	Et	12	91	95
14	2-thiophenyl (**3n**)	Et	24	84	93
15	1-naphthyl (**3o**)	Et	24	91	95
16	Et (**3p**)	Et	24	72	96
17	Ph (**3q**)	Me	6	97	96

[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (ee) was determined by HPLC.

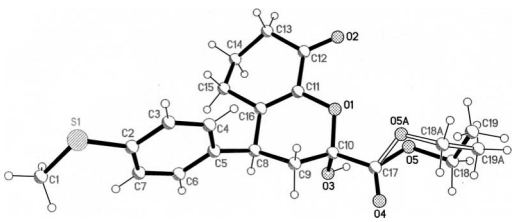
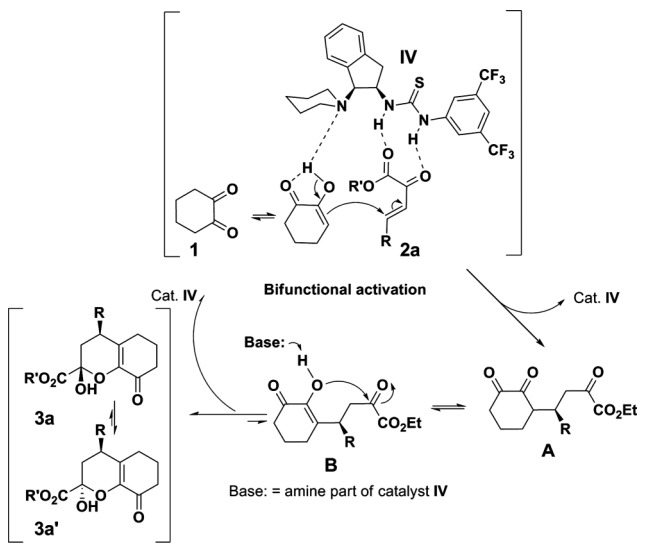


Fig. 2 X-ray crystal structure of **3i**.



Scheme 1 Bifunctional activation mode: a proposed catalytic cycle for the asymmetric cascade reaction.

α-keto ester *via* its amine and thiourea functional groups (Scheme 1). After formation of Michael adduct **A**, an enolation automatically occurs to generate a tautomeric structure, intermediate **B**, an active enol which subsequently undergoes an *oxa*-nucleophilic attack to trigger the completion of the cyclization step. Finally, complex **3**, involving two possible anomers, was in equilibrium with the Michael product **A**.

Conclusions

In conclusion, we have presented a novel and highly stereoselective Michael–enolation–cyclization cascade catalyzed by an indane amine–thiourea catalyst. Our investigation, with a new reaction mode, expands the scope of asymmetric organocatalytic reactions. Further applications of this activation mode, with respect to other organic transformations, will be reported shortly together with detailed mechanistic aspects.

Experimental

General methods

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 (300 MHz) or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), bs (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in EI mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T mass spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with $KMnO_4$ solution, or ninhydrin followed by heating using a heat gun. Flash chromatography separations were performed on Merck 60 (0.040–0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral phase HPLC analysis. Optical rotations were recorded on Jasco DIP-1000 polarimeter.

General procedure

To a solution of (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate **2a** (20.4 mg, 0.1 mmol) and cyclohexane-1,2-dione **1** (16.8 mg, 0.15 mmol) in 0.2 ml toluene, catalyst **IV** (4.9 mg, 0.01 mmol) was added. The reaction mixture was stirred at 50 °C for 8h. The crude product was purified by column chromatography on silica gel, eluted by hexane : EtOAc = 5 : 1 then 3 : 1 to afford 30.0 mg (94% yield) of the desired product **3a** as colorless oil.

(2*R*,4*S*)-Ethyl 2-hydroxy-8-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3a). (Table 3, entry 1). 94% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 7.24 (d, J = 7.2 Hz, 2H), 4.50 (br, 1H), 4.38–4.23 (m, 2H), 3.81 (dd, J = 12.5, 6.5 Hz, 1H), 2.55–2.41 (m, 2H), 2.34 (t, J = 13.1 Hz, 1H), 2.23 (dd, J = 13.6, 6.5 Hz, 1H), 2.09–2.01 (m, 2H), 1.96–1.84 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ = 192.83, 169.13, 142.88, 140.83, 134.12, 128.94, 128.53, 127.31, 93.67, 63.01, 40.09, 38.29, 36.86, 27.81, 22.11, 13.93; HRMS (EI) calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1307; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 9.6 min, t_R (minor) = 11.9 min, *ee* = 95%; $[\alpha]_D^{25}$ = +113.0 (*c* = 1.11 in $CHCl_3$).

(2*R*,4*R*)-Ethyl 4-(2-chlorophenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3b). (Table 3, entry 2). 92% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 11.8, 4.7 Hz, 1H), 7.32–7.17 (m, 3H), 4.54 (br, 1H), 4.38–4.23 (m, 2H), 2.59–2.43 (m, 2H), 2.35–2.03 (m, 4H), 2.00–1.93 (m, 2H), 1.32 (td, *J* = 7.1, 3.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.77, 168.96, 144.26, 138.11, 134.14, 133.59, 131.86, 129.83, 129.72, 128.50, 128.35, 127.49, 126.86, 94.51, 93.66, 63.04, 62.79, 38.41, 38.26, 35.55, 34.09, 34.04, 28.06, 27.59, 22.25, 22.10, 13.96, 13.92; HRMS (EI) calcd for $C_{18}H_{19}O_5Cl$ 350.0921, found 350.0916; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 9.8 min, t_R (minor) = 11.9 min, *ee* = 96%; $[\alpha]_D^{25}$ = +75.3 (*c* = 0.98 in $CHCl_3$).

(2*R*,4*S*)-Ethyl 4-(3-chlorophenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3c). (Table 3, entry 3). 95% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 3H), 7.13 (dt, *J* = 7.0, 1.5 Hz, 1H), 4.71 (br, 1H), 4.38–4.24 (m, 2H), 3.81 (dd, *J* = 12.3, 6.7 Hz, 1H), 2.57–2.41 (m, 2H), 2.34–2.26 (m, 1H), 2.23 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.14–1.99 (m, 2H), 1.94–1.89 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.80, 168.93, 142.95, 142.90, 134.75, 132.98, 130.21, 128.59, 127.57, 126.72, 93.57, 63.04, 39.86, 38.18, 36.66, 27.69, 22.05, 13.90; HRMS (EI) calcd for $C_{18}H_{19}O_5Cl$ 350.0921, found 350.0918; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 9.0 min, t_R (minor) = 11.4 min, *ee* = 92%; $[\alpha]_D^{25}$ = +104.2 (*c* = 0.96 in $CHCl_3$).

(2*R*,4*S*)-Ethyl 4-(4-chlorophenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3d). (Table 3, entry 4). 90% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 4.54 (br, 1H), 4.38–4.21 (m, 2H), 3.80 (dd, *J* = 12.4, 6.6 Hz, 1H), 2.56–2.41 (m, 2H), 2.29 (t, *J* = 13.0 Hz, 1H), 2.21 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.09–1.98 (m, 2H), 1.96–1.85 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.70, 168.96, 153.86, 142.97, 139.32, 133.19, 129.85, 129.16, 93.58, 63.08, 39.53, 38.24, 36.77, 27.75, 22.08, 13.92; HRMS (EI) calcd for $C_{18}H_{19}O_5Cl$ 350.0921, found 350.0910; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 11.1 min, t_R (minor) = 14.0 min, *ee* = 96%; $[\alpha]_D^{25}$ = +120.9 (*c* = 1.09 in $CHCl_3$).

(2*R*,4*S*)-Ethyl 4-(4-fluorophenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3e). (Table 3, entry 5). 91% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.05 (t, *J* = 8.6 Hz, 2H), 4.50 (br, 1H), 4.36–4.27 (m, 2H), 3.81 (dd, *J* = 12.5, 6.6 Hz, 1H), 2.54–2.46 (m, 2H), 2.30 (t, *J* = 13.1 Hz, 1H), 2.21 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.08–2.02 (m, 2H), 1.93–1.88 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.83, 169.01, 162.96, 161.00, 142.88, 136.45, 136.42, 133.68, 130.03, 129.96, 115.94, 115.78, 93.62, 63.10, 39.34, 38.24, 36.88, 27.77, 22.08, 13.93; HRMS (EI) calcd for $C_{18}H_{19}O_5F$ 334.1217, found 334.1216; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 10.7 min, t_R (minor) = 13.5 min, *ee* = 95%; $[\alpha]_D^{25}$ = +102.4 (*c* = 1.15 in $CHCl_3$).

(2*R*,4*S*)-Ethyl 2-hydroxy-4-(4-nitrophenyl)-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3g). (Table 3, entry 7). 84% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 4.50 (br, 1H), 4.37–4.28 (m, 2H), 3.97 (dd, *J* = 12.4, 6.6 Hz, 1H), 2.61–2.43 (m, 2H), 2.31 (dd, *J* = 20.1, 7.7 Hz, 1H), 2.24 (dd, *J* = 13.5, 6.6 Hz, 1H), 2.07–1.87 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.48, 168.68, 148.57, 147.38, 143.28, 131.47, 129.46, 124.29, 93.40, 63.29, 40.09, 38.25, 36.63, 27.80, 22.11, 13.94; HRMS (EI) calcd for $C_{18}H_{19}O_7N$ 361.1162, found 361.1160; HPLC (Chiralcel OD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 17.8 min, t_R (minor) = 29.3 min, *ee* = 93%; $[\alpha]_D^{25}$ = +127.2 (*c* = 1.00 in $CHCl_3$).

(2*R*,4*S*)-Ethyl 2-hydroxy-4-(4-methoxyphenyl)-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3h). (Table 3, entry 8). 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.52 (br, 1H), 4.39–4.22 (m, 2H), 3.81 (s, 3H), 3.77 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.55–2.41 (m, 2H), 2.31 (t, *J* = 13.1 Hz, 1H), 2.20 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.12–2.01 (m, 2H), 1.95–1.83 (m, 2H), 1.32 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 192.76, 169.16, 158.88, 142.77, 134.53, 132.69, 129.48, 114.39, 93.74, 62.94, 55.28, 39.22, 38.28, 36.90, 27.80, 22.11, 13.91; HRMS (EI) calcd for $C_{19}H_{22}O_6$ 346.1416, found 346.1413; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 12.8 min, t_R (minor) = 16.9 min, *ee* = 95%; $[\alpha]_D^{25}$ = +142.6 (*c* = 0.95 in $CHCl_3$).

(2*R*,4*S*)-Ethyl 2-hydroxy-4-(4-(methylthio)phenyl)-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3i). (Table 3, entry 9). 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 4.50 (br, 1H), 4.39–4.22 (m, 2H), 3.77 (dd, *J* = 12.5, 6.5 Hz, 1H), 2.56–2.41 (m, 5H), 2.31 (t, *J* = 13.0 Hz, 1H), 2.20 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.13–2.01 (m, 2H), 1.97–1.83 (m, 2H), 1.32 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.85, 169.07, 142.86, 137.57, 137.51, 133.98, 128.98, 127.07, 93.62, 63.05, 39.53, 38.26, 36.74, 27.79, 22.08, 15.80, 13.92; HRMS (EI) calcd for $C_{19}H_{22}O_5S$ 362.1188, found 362.1180; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 12.6 min, t_R (minor) = 17.2 min, *ee* = 95%; $[\alpha]_D^{25}$ = +140.8 (*c* = 0.97 in $CHCl_3$).

(2*R*,4*S*)-Ethyl 4-(4-(allyloxy)phenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3j). (Table 3, entry 10). 87% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16–7.11(m, 2H), 6.93–6.88 (m, 2H), 6.12–5.98 (m, 1H), 5.42 (ddd, *J* = 17.3, 3.1, 1.6 Hz, 1H), 5.30 (ddd, *J* = 10.5, 2.7, 1.3 Hz, 1H), 4.55–4.53 (m, 3H), 4.39–4.22 (m, 2H), 3.76 (dd, *J* = 12.5, 6.6 Hz, 1H), 2.56–2.41 (m, 2H), 2.36–2.27 (m, 1H), 2.20 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.13–1.98 (m, 2H), 1.97–1.83 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.02, 169.19, 157.85, 142.71, 134.73, 133.18, 132.77, 129.48, 117.71, 115.14, 93.71, 68.87, 63.01, 39.20, 38.25, 36.84, 27.80, 22.08, 13.93; HRMS (EI) calcd for $C_{21}H_{24}O_6$ 372.1573, found 372.1561; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 11.7 min, t_R (minor) = 15.0 min, *ee* = 94%; $[\alpha]_D^{25}$ = +144.6 (*c* = 0.83 in $CHCl_3$).

(2*R*,4*S*)-ethyl 2-hydroxy-8-oxo-4-(3-phenoxyphenyl)-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3k). (Table 3, entry 11). 94% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 3H), 7.13 (t, J = 7.4 Hz, 1H), 7.05–6.99 (m, 2H), 6.97 (d, J = 7.7 Hz, 1H), 6.94–6.88 (m, 2H), 4.52 (br, 1H), 4.38–4.23 (m, 2H), 3.78 (dd, J = 12.4, 6.6 Hz, 1H), 2.56–2.40 (m, 2H), 2.31 (t, J = 13.0 Hz, 1H), 2.23 (dd, J = 13.6, 6.6 Hz, 1H), 2.18–2.02 (m, 2H), 1.98–1.85 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.82, 169.02, 157.82, 156.82, 142.85, 142.83, 133.60, 130.19, 129.80, 123.56, 123.21, 118.95, 118.85, 117.44, 93.58, 63.04, 39.94, 38.24, 36.64, 27.71, 22.08, 13.92; HRMS (EI) calcd for $C_{24}H_{24}O_6$ 408.1573, found 408.1559; HPLC (Chiralpak IA, *i*-propanol/hexane = 5/95, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 17.5 min, t_R (minor) = 21.9 min, *ee* = 96%; $[\alpha]_D^{25}$ = +95.0 (c = 1.05 in $CHCl_3$).

(2*R*,4*S*)-Ethyl 4-(4-(benzyloxy)phenyl)-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3l). (Table 3, entry 12). 86% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.30 (m, 5H), 7.17–7.12 (m, 2H), 6.99–6.94 (m, 2H), 5.06 (s, 2H), 4.51 (br, 1H), 4.37–4.23 (m, 2H), 3.76 (dd, J = 12.5, 6.5 Hz, 1H), 2.56–2.40 (m, 2H), 2.35–2.27 (m, 1H), 2.20 (dd, J = 13.6, 6.5 Hz, 1H), 2.12–1.97 (m, 2H), 1.96–1.83 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.91, 169.17, 158.08, 142.75, 136.89, 134.60, 132.94, 129.53, 128.59, 128.00, 127.43, 115.28, 93.71, 70.12, 63.00, 39.22, 38.26, 36.87, 27.82, 22.09, 13.92; HRMS (EI) calcd for $C_{25}H_{26}O_6$ 422.1729, found 422.1709; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 17.5 min, t_R (minor) = 22.4 min, *ee* = 93%; $[\alpha]_D^{25}$ = +104.5 (c = 1.11 in $CHCl_3$).

(2*R*,4*S*)-Ethyl 2-hydroxy-4-(4-isopropylphenyl)-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3m). (Table 3, entry 13). 91% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.1 Hz, 2H), 7.16–7.12 (m, 2H), 4.53 (br, 1H), 4.38–4.22 (m, 2H), 3.78 (dd, J = 12.5, 6.5 Hz, 1H), 2.91 (dt, J = 13.9, 6.9 Hz, 1H), 2.56–2.41 (m, 2H), 2.33 (t, J = 13.1 Hz, 1H), 2.21 (dd, J = 13.6, 6.6 Hz, 1H), 2.15–1.99 (m, 2H), 1.96–1.83 (m, 2H), 1.31 (t, J = 7.3 Hz, 3H), 1.26 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.01, 169.21, 147.95, 142.76, 137.97, 134.69, 128.41, 126.93, 93.69, 62.99, 39.65, 38.27, 36.89, 33.70, 27.85, 23.92, 22.07, 13.92; HRMS (EI) calcd for $C_{21}H_{26}O_5$ 358.1780, found 358.1764; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 7.0 min, t_R (minor) = 9.8 min, *ee* = 95%; $[\alpha]_D^{25}$ = +121.1 (c = 0.95 in $CHCl_3$).

(2*R*,4*R*)-Ethyl 2-hydroxy-8-oxo-4-(thiophen-2-yl)-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3n). (Table 3, entry 14). 84% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (dd, J = 5.0, 0.6 Hz, 1H), 7.00–6.94 (m, 2H), 4.60 (br, 1H), 4.41–4.24 (m, 2H), 4.19 (dd, J = 12.5, 6.3 Hz, 1H), 2.51–2.40 (m, 3H), 2.33 (dd, J = 13.5, 6.4 Hz, 1H), 2.21–2.11 (m, 2H), 1.91 (dd, J = 10.2, 4.2 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.04, 168.90, 143.29, 142.01, 133.44, 126.84, 126.43, 124.65, 93.60, 63.10, 38.12, 37.04, 35.00, 27.24, 21.98, 13.91; HRMS (EI) calcd for $C_{16}H_{18}O_5S$ 322.0875, found 322.0870; HPLC (Chiralpak IA, δ-propanol/hexane = 5/95, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 17.4 min, t_R (minor) = 20.8 min, *ee* = 93%; $[\alpha]_D^{25}$ = +82.9 (c = 1.02 in $CHCl_3$).

(2*R*,4*S*)-Ethyl 2-hydroxy-4-(naphthalen-1-yl)-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3o). (Table 3, entry 15). 91% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24–7.98 (m, 1H), 7.94–7.87 (m, 1H), 7.86–7.75 (m, 1H), 7.61–7.32 (m, 4H), 4.86–4.63 (m, 1H), 4.38–4.21 (m, 2H), 2.89 (t, J = 13.3 Hz, 0.4H), 2.65–2.45 (m, 2H), 2.39 (d, J = 8.5, 1H), 2.29 (dd, J = 14.9, 7.9 Hz, 0.8H), 2.20 (dd, J = 13.8, 6.5 Hz, 1H), 2.05–1.79 (m, 4H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.93, 169.13, 143.80, 141.98, 137.31, 136.05, 135.50, 134.95, 134.50, 133.95, 132.03, 131.04, 129.45, 129.33, 129.13, 128.70, 127.61, 126.60, 126.42, 125.91, 125.75, 125.66, 125.60, 125.48, 125.42, 123.57, 122.32, 93.93, 93.83, 63.02, 41.71, 38.38, 38.21, 37.12, 34.30, 34.08, 29.65, 27.74, 27.25, 22.23, 22.05, 14.01, 13.90; HRMS (EI) calcd for $C_{22}H_{22}O_5$ 366.1467, found 366.1481; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 9.2 min, t_R (minor) = 11.1 min, *ee* = 95%; $[\alpha]_D^{25}$ = +84.8 (c = 1.01 in $CHCl_3$).

(2*R*,4*R*)-Ethyl 4-ethyl-2-hydroxy-8-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3p). (Table 3, entry 16). 72% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.40–4.19 (m, 2H), 2.63–2.22 (m, 4H), 2.11–1.78 (m, 4H), 1.45–1.16 (m, 6H), 0.96 (t, J = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.96, 169.51, 142.24, 135.43, 93.72, 62.97, 37.98, 33.10, 32.36, 29.69, 26.78, 23.74, 22.02, 13.96, 10.71; HRMS (EI) calcd for $C_{14}H_{20}O_5$ 268.1311, found 268.1310; HPLC (Chiralpak AD-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 34.5 min, t_R (minor) = 37.3 min, *ee* = 96%; $[\alpha]_D^{25}$ = +13.3 (c = 0.15 in $CHCl_3$).

(2*R*,4*S*)-Methyl 2-hydroxy-8-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromene-2-carboxylate (3q). (Table 3, entry 17). 97% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (t, J = 7.4 Hz, 2H), 7.31–7.27 (m, 1H), 7.23 (dd, J = 5.2, 3.1 Hz, 2H), 4.48 (br, 1H), 3.85 (s, 3H), 3.81 (dd, J = 12.6, 6.6 Hz, 1H), 2.56–2.41 (m, 2H), 2.39–2.30 (m, 1H), 2.24 (dd, J = 13.6, 6.6 Hz, 1H), 2.13–2.00 (m, 2H), 1.96–1.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 192.90, 169.56, 142.74, 140.67, 134.26, 128.94, 128.49, 127.33, 93.74, 53.54, 39.97, 38.22, 36.82, 27.78, 22.06; HRMS (EI) calcd for $C_{17}H_{18}O_5$ 302.1154, found 302.1151; HPLC (Chiralpak IA, *i*-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 10.4 min, t_R (minor) = 13.1 min, *ee* = 96%; $[\alpha]_D^{25}$ = +124.0 (c = 1.05 in $CHCl_3$).

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