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Efficient Asymmetric Synthesis of 4*H*-Chromene Derivatives through a Tandem Michael Addition–Cyclization Reaction Catalyzed by a Salen–Cobalt(II) Complex

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The asymmetric synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene derivatives was achieved through a tandem Michael addition–cyclization reaction of easily available cyclohexane-1,3-dione and ethyl 2-cyano-3-phenylacrylates. Moderate to good yields (up to 81 %) and high enantioselectivities (up to 89 % *ee*) were obtained with a chiral salen–cobalt(II) complex. This process was air tolerant and easily performed, which provides an efficient method for the synthesis of chiral 4*H*-chromene derivatives.

Introduction

The chromene skeleton, including that of 2*H*-chromene and 4*H*-chromene, is probably one of the most familiar structural units in naturally occurring compounds.[1–3] Due to various pharmacological properties such as anticoagulant, anticancer, antianaphylactic, and fungicidal activities, 2-amino-4*H*-chromenes are rather unusual among the chromene family members.[4] Some representative examples are gathered in Figure 1. HA14-1 (**A**) can effectively induce apoptosis of human acute myeloid leukemia cells.[4a] Pyrazole derivative **B** is an inhibitor of human Chk 1 kinase.[4b] 2-Amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene (**C**) has an important antibacterial activity.[4c] Owing to the importance of the 2-amino-4*H*-chromene framework, its synthesis has attracted considerable attention.[5] The conventional method for the racemic synthesis of 2-amino-4*H*-chromenes is the Brønsted base catalyzed tandem conjugate addition–cyclization reaction; there are only a few examples of an asymmetric synthesis of this class of compounds. Recently, the Zhao group used cupreine and cinchona alkaloid derived thioureas as organocatalysts for the asymmetric synthesis of pyranopyrazole derivatives and 2-amino-8-oxo-4*H*-chromene analogues by the Michael addition–cyclization reaction of α-carbonyl compounds and α,α-dicyanoolefins.[6a,6b] The enantioselective synthesis of naphthopyran derivatives was performed with a bifunctional thiourea catalyzed tandem asymmetric addition–cyclization reaction of 2-naphthol with α,α-dicyanoolefins.[6c] Moderate yields and enantioselectivities were obtained. Xie disclosed an efficient synthesis of 2-amino-2-chromene through a different tandem reaction of hydroxy substituted α,β-unsaturated ketones and malononitrile.[6d]

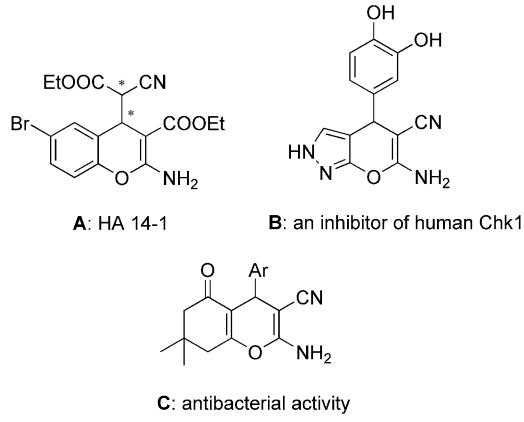

Figure 1. Selected examples of 4*H*-chromenes embodied with biological and pharmacological activity.

To the best of our knowledge, there is no report on a direct catalytic asymmetric method for the synthesis of optically active 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene derivatives using readily available reagents. Thus, the development of an effective asymmetric method for their preparation attracted our interest.[7] In addition, chiral salen ligands are among the most widely useful ligands in asymmetric synthesis. Salen–cobalt complexes have been shown to be highly efficient in many asymmetric procedures.[8,9] Herein, we wish to present the first asymmetric synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-

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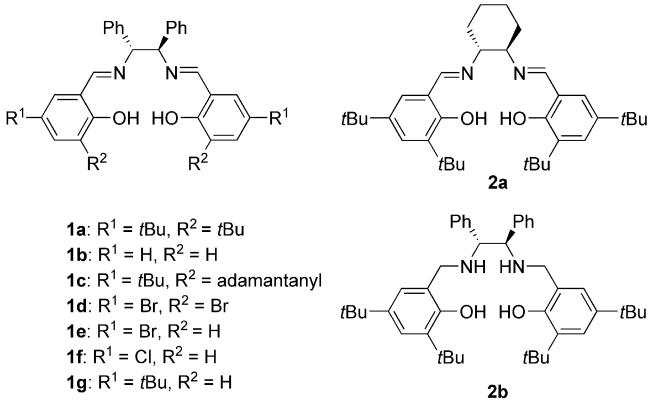
chromene derivatives based on a tandem strategy of Michael addition and cyclization between cyclohexane-1,3-dione and ethyl 2-cyano-3-phenylacrylates catalyzed by salen–cobalt(II) complexes.

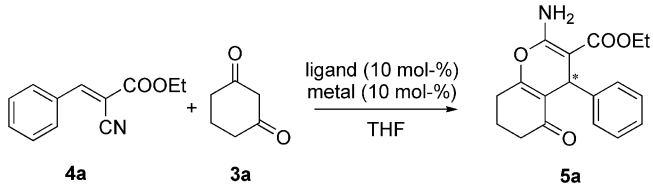
Results and Discussion

Initially, cyclohexane-1,3-dione (**3a**) and ethyl 2-cyano-3-phenylacrylate (**4a**) were chosen as the model compounds. Salen **1a** (Scheme 1) derived from (*R*,*R*)-1,2-diphenylethane-1,2-diamine and 3,5-di-*tert*-butylsalicylaldehyde reacted in situ with various metal reagents to form complexes to catalyze the asymmetric tandem addition–cyclization reaction. As shown in Table 1, $Co(OAc)_2{\cdot}4H_2O$ was more efficient than other metals, giving the desired products in 52% yield with 53%*ee* (Table 1, Entry 1). Other metals including Ni, Fe, Cu, and even Co with different counterions either did not catalyze reaction or gave a product in a very low yield and enantioselectivity (Table 1, Entries 2–8). The results indicated that the central metal and negative ions were both important for the reaction. To further improve the reactivity and enantioselectivity of the reaction, the steric and electronic effects of the salen ligand were then examined (Table 1, Entries 9–16). As shown in Table 1, it was found that the *tert*-butyl groups in the *para* and *ortho* positions to the OH group in the ligands were both crucial for the enantioselectivity. Other substituents on the salen ligand did not provide satisfactory results. In particular, ligand **1d** bearing Br groups in the *para* and *ortho* positions to the OH group showed no activity in this reaction (Table 1, Entry 11). Further optimization showed that the yield and enantioselectivity of product **5a** were greatly affected by the chiral backbone of the salen ligands. Salen **2a** derived from (*R*,*R*)-cyclohexane-1,2-diamine catalyzed the reaction in near-quantitative yield but gave a racemic product (Table 1, Entry 15). Although the backbone of ligands **1a** and **2b** have the same absolute configuration, [H_4]salen ligand **2b** afforded the desired product in only 19% yield and 11%*ee* (Table 1, Entry 16). Thus, salen **1a**-$Co(OAc)_2{\cdot}4H_2O$ was chosen as the catalyst for further research. Moreover, the reaction was air tolerant and easily performed with readily available reagents.



Scheme 1. Chiral ligands used in the study.

Table 1. Survey of ligand and central metal on the asymmetric tandem reaction.[a]



4a 3a 5a

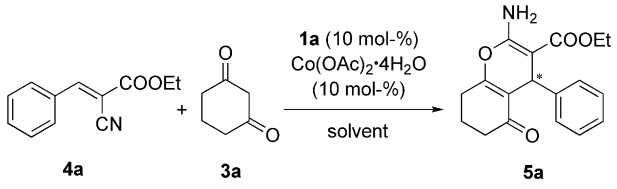
Entry	Salen	Metal	Yield [%][b]	*ee* [%][c]
1	**1a**	$Co(OAc)_2{\cdot}4H_2O$	52	53
2	**1a**	$Co(acac)_2$	4	27
3	**1a**	$Co(acac)_3$	nr[d]	–
4	**1a**	$CoCl_2{\cdot}6H_2O$	nr	–
5	**1a**	$Ni(acac)_2$	17	–7
6	**1a**	$NiCl_2$	nr[d]	–
7	**1a**	$Fe(OAc)_2$	nr[d]	–
8	**1a**	$Cu(OAc)_2$	nr[d]	–
9	**1b**	$Co(OAc)_2{\cdot}4H_2O$	70	7
10	**1c**	$Co(OAc)_2{\cdot}4H_2O$	28	13
11	**1d**	$Co(OAc)_2{\cdot}4H_2O$	nr[d]	–
12	**1e**	$Co(OAc)_2{\cdot}4H_2O$	70	8
13	**1f**	$Co(OAc)_2{\cdot}4H_2O$	45	0
14	**1g**	$Co(OAc)_2{\cdot}4H_2O$	41	5
15	**2a**	$Co(OAc)_2{\cdot}4H_2O$	94	0
16	**2b**	$Co(OAc)_2{\cdot}4H_2O$	19	11

[a] Unless otherwise noted, all reactions were carried out with **3a** (0.1 mmol) and **4a** (0.12 mmol) in THF (1.0 mL) with the catalyst (10 mol-%, metal/ligand = 1:1) at room temperature for 24 h. [b] Yield of the isolated product. [c] Determined by chiral HPLC analysis. [d] nr = no reaction.

To further improve the reactivity and enantioselectivity, other parameters of the reaction conditions were optimized. Various solvents were screened under the model reaction conditions, and the results are summarized in Table 2 (Entries 1–7). Solvents such as MeOH, CH_2Cl_2, Et_2O, PhMe, as well as THF were all not suitable for this reaction, as moderate yields and low enantioselectivities were obtained. Fortunately, ethyl acetate and MeCN gave better results and higher enantioselectivities (Table 2, Entries 6 and 7). Ethyl acetate as the solvent produced a higher enantioselectivity at room temperature. However, MeCN gave a better result with 78% yield and 69%*ee* when the temperature was decreased to 0 °C (Table 2, Entries 8 and 9). So, we carried out further screening at 0 °C in MeCN. The effect of additive was also investigated to further improve the enantioselectivity. A series of additives including acid, base, alcohol, and phenol were tested, and we noted that the *ee* could be improved to 73% with a lower yield when 10 mol-% of 3,5-dinitrosalicylic acid was used (Table 2, Entry 10). Adjusting the ratio of ligand, metal, and additive to 1:2:1.5 slightly increased the enantioselectivity (Table 2, Entry 11). Increasing the catalyst loading to 15 mol-% [15 mol-% salen, 30 mol-% $Co(OAc)_2{\cdot}4H_2O$, 22.5 mol-% 3,5-dinitrosalicylic acid] increased the enantioselectivity to 76%*ee* (Table 2, Entry 12). In the hope of enhancing the yield, the reaction time was extended to 48 h and the ratio of reactants **4a** and **3a** was altered to 1.1:1, which increased the yield to 77% with a better enantioselectivity up to 78%*ee*

(Table 2, Entry 13). Therefore, the optimal reaction conditions were 15 mol-% salen **1a**, 30 mol-% $Co(OAc)_2·4H_2O$, and 22.5 mol-% 3,5-dinitrosalicylic acid as additive, 0.11 mmol **4a**, and 0.10 mmol **3a** in 1 mL MeCN at 0 °C for 48 h.

Table 2. Optimization of reaction conditions.[a]



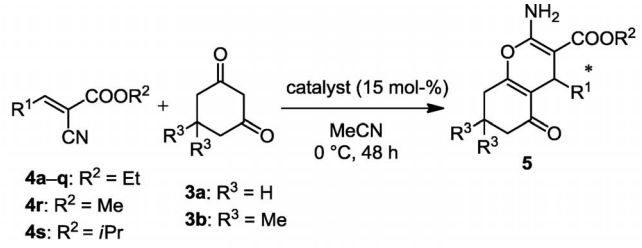
4a 3a 5a

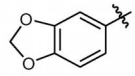
Entry	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	THF	r.t.	52	53
2	MeOH	r.t.	65	17
3	CH_2Cl_2	r.t.	12	11
4	Et_2O	r.t.	23	45
5	PhMe	r.t.	56	39
6	MeCN	r.t.	99	54
7	EtOAc	r.t.	82	61
8	MeCN	0	78	69
9	EtOAc	0	70	65
10[d]	MeCN	0	54	73
11[d,e]	MeCN	0	57	75
12[d–f]	MeCN	0	56	76
13[d–g]	MeCN	0	77	78

[a] Unless otherwise noted, all reactions were carried out with **3a** (0.1 mmol) and **4a** (0.12 mmol) in solvent (1.0 mL) with the catalyst (10 mol-%, metal/ligand = 1:1) for 24 h. [b] Yield of the isolated product. [c] Determined by chiral HPLC analysis. [d] 10 mol-% of 3,5-dinitrosalicylic acid was added. [e] 10 mol-% of **1a**, 20 mol-% of $Co(OAc)_2·4H_2O$, and 15 mol-% of 3,5-dinitrosalicylic acid was used. [f] 15 mol-% catalyst loading [15 mol-% **1a**, 30 mol-% $Co(OAc)_2·4H_2O$, and 22.5 mol-% 3,5-dinitrosalicylic acid]. [g] 48 h, **4a** (0.11 mmol) and **3** (0.10 mmol).

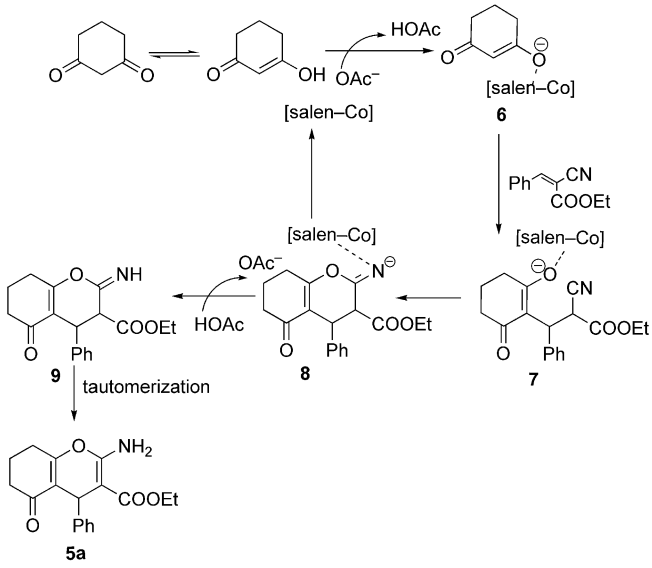
Under the optimized conditions, a wide range of ethyl 2-cyano-3-phenylacrylates were explored. The corresponding products **5a**–**t** were obtained in moderate to good yields with high enantioselectivities, as summarized in Table 3. The results show that the electronic nature of the substituent in the aromatic ring has an obvious effect on the yield and enantioselectivity. In general, except for 3-methoxy derivative **5g**, which gave a better yield (up to 75%; Table 3, Entry 7), electron-withdrawing substituents gave the product in higher yields (Table 3, 71–81%) than substrates with electron-donating substituents (Table 3, Entries 2–6 vs. 8–14). Additionally, most of the substrates with substituents in the *para* position gave products with better enantioselectivities (81–83% *ee*; Table 3, Entries 4, 6, 9, and 13), especially for *para*-phenyl derivative **5o** (89% *ee*; Table 3, Entry 15). Moreover, the 2-naphthyl substrate also produced the product in good yield and enantioselectivity (Table 3, Entry 16). Heteroaromatic substrate **4q** was also tested with a moderate enantioselectivity (Table 3, Entry 17). Substrates **4r** and **4s** with different substituents on the ester moiety (R^2) also gave good yields and *ee* values (Table 3, Entries 18 and 19). In addition, dimedone (**3b**) was also a good nucleophile for the reaction with 70% yield and 77% *ee* (Table 3, Entry 20).

Table 3. Scope of the tandem reaction.[a]



Entry	R^1	Product	Yield [%][b]	*ee* [%][c]
1	Ph (**4a**)	**5a**	77	78
2	2-MeC_6H_4 (**4b**)	**5b**	51	77
3	3-MeC_6H_4 (**4c**)	**5c**	52	71
4	4-MeC_6H_4 (**4d**)	**5d**	46	83
5	 (**4e**)	**5e**	57	72
6	4-$MeOC_6H_4$ (**4f**)	**5f**	55	81
7	3-$MeOC_6H_4$ (**4g**)	**5g**	75	74
8	3-ClC_6H_4 (**4h**)	**5h**	71	73
9	4-ClC_6H_4 (**4i**)	**5i**	79	81
10	4-$NO_2C_6H_4$ (**4j**)	**5j**	80	77
11	4-FC_6H_4 (**4k**)	**5k**	81	77
12	3-BrC_6H_4 (**4l**)	**5l**	76	74
13	4-BrC_6H_4 (**4m**)	**5m**	76	83
14	4-$CF_3C_6H_4$ (**4n**)	**5n**	72	79
15	4-PhC_6H_4 (**4o**)	**5o**	73	89
16	2-naphthyl (**4p**)	**5p**	64	81
17	2-thienyl (**4q**)	**5q**	75	69
18	Ph (**4r**)	**5r**	71	73
19	Ph (**4s**)	**5s**	72	69
20	Ph (**4a**)[d]	**5t**	70	77

[a] Unless otherwise noted, all reactions were carried out with **3a** (0.10 mmol) and **4** (0.11 mmol) in MeCN (1.0 mL) with **1a** (15 mol-%), $Co(OAc)_2·4H_2O$ (30 mol-%), and 3,5-dinitrosalicylic acid (22.5 mol-%) for 48 h at 0 °C. [b] Yield of the isolated product. [c] Determined by chiral HPLC analysis. [d] Dimedone (**3b**) instead of **3a**.



Scheme 2. Proposed catalytic cycle.

A possible catalytic cycle for the tandem reaction is proposed, as shown in Scheme 2. The key step for the process involves deprotonation–reprotonation. The chiral salen–cobalt complex first abstracts a proton from the enol to form intermediate **6**. Intermediate **6** then reacts with ethyl 2-cyano-3-phenylacrylate (**4a**) through a Michael addition process. Cyclization then occurs quickly so that no Michael reaction intermediate is detected. Reprotonation of **8** affords imine intermediate **9**, which liberated the chiral salen–cobalt complex. Finally, product **5a** is formed after tautomerization.

Conclusions

In summary, the chiral compound ethyl 2-amino-5-oxo-4-aryl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate was synthesized through a tandem Michael addition–cyclization process catalyzed by a salen–cobalt(II) complex. The corresponding products, which have extensive biological and pharmacological activities, can be obtained in moderate to good yields (up to 81%) with high enantioselectivities (up to 89%*ee*). This pathway is air tolerant, and the catalyst is prepared easily with readily available reagents. A possible catalytic cycle was proposed to explain the formation of the products. Further efforts will be devoted to improve the reactivity and enantioselectivity of the reaction as well as to synthesize 4*H*-chromene analogues.

Experimental Section

General Procedures: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a 400 MHz spectrometer. TMS served as an internal standard (δ = 0 ppm) for ^{1}H NMR and $CDCl_3$ was used as the internal standard (δ = 77.0 ppm) for ^{13}C NMR. Chemical shifts are reported in ppm with the solvent reference as the internal standard ($CHCl_3$: δ = 7.26 ppm). Purification of reaction products was carried out by flash chromatography. Enantiomeric excess (*ee*) values were determined by chiral HPLC by using a Chiralcel AD column. Optical rotations were measured with a polarimeter. HRMS were recorded with a commercial apparatus (ESI or ES source).

Typical Procedure for the Enantioselective Tandem Reaction: Chiral salen ligand **1a** (9.7 mg, 0.015 mmol), $Co(OAc)_2{\cdot}4H_2O$ (7.5 mg, 0.03 mmol), and 3,5-dinitrosalicylic acid (5.1 mg, 0.0225 mmol) were added into a test tube and then MeCN (0.5 mL) was added. After stirring for 1 h at room temperature, the mixture was cooled to 0 °C. A solution of **4a** (22.1 mg, 0.11 mmol) and **3a** (11.2 mg, 0.10 mmol) in MeCN (0.5 mL) was then added. The reaction mixture was stirred at 0 °C for 48 h. Then, the reaction was diluted with ethyl acetate (40 mL). After extraction with 1 N NaOH (4 × 30 mL), the organic layer was combined and dried with sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/petroleum ether, 1:2) to afford product **5a**. White solid (24.2 mg, 77%, 78%*ee*). $[a]^{21.4}$ = 13.9 (*c* = 0.101, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.2 Hz, 3 H), 1.90–2.03 (m, 2 H), 2.28–2.36 (m, 2 H), 2.51–2.59 (m, 2 H), 3.97–4.03 (m, 2 H), 4.70 (s, 1 H), 6.14 (s, 2 H), 7.07–7.10 (t, *J* = 7.6 Hz, 1 H), 7.16–7.19 (t, *J* = 7.2 Hz, 2 H), 7.23–7.25 (d, *J* = 6.8 Hz, 2 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 6.42 (major), 8.38 (minor) min.

5b: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (16.7 mg, 51%, 77%*ee*). $[a]^{22.3}$ = 15.1 (*c* = 0.106, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.2 Hz, 3 H), 1.97–2.02 (m, 2 H), 2.28–2.32 (m, 2 H), 2.53–2.59 (m, 2 H), 2.69 (s, 3 H), 3.97–4.09 (m, 2 H), 4.86 (s, 1 H), 6.18 (s, 2 H), 6.98–7.04 (m, 4 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 11.90 (major), 14.72 (minor) min.

5c: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (16.8 mg, 52%, 71%*ee*). $[a]^{22.4}$ = 34.6 (*c* = 0.104, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14–1.17 (t, *J* = 7.2 Hz, 3 H), 1.95–2.05 (m, 2 H), 2.31–2.36 (m, 5 H), 2.53–2.59 (m, 2 H), 4.00–4.05 (q, *J* = 7.2, 14.4 Hz, 2 H), 4.69 (s, 1 H), 6.14 (s, 2 H), 6.92 (d, *J* = 7.2 Hz, 1 H), 7.04–7.11 (m, 3 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 11.39 (major), 15.20 (minor) min.

5d: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (15.1 mg, 46%, 83%*ee*). $[a]^{22.4}$ = 25.9 (*c* = 0.108, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.18 (t, *J* = 7.2 Hz, 3 H), 1.99 (m, 2 H), 2.27 (s, 3 H), 2.33 (t, *J* = 4.4 Hz, 2 H), 2.56 (m, 2 H), 4.00–4.05 (m, 2 H), 4.70 (s, 1 H), 6.13 (s, 2 H), 7.00–7.02 (d, *J* = 8.0 Hz, 2 H), 7.14–7.16 (d, *J* = 8.0 Hz, 2 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 6.11 (major), 9.14 (minor) min.

5e: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (20.4 mg, 57%, 72%*ee*). $[a]^{22.9}$ = 26.7 (*c* = 0.120, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.21 (t, *J* = 7.2 Hz, 3 H), 1.95–2.07 (m, 2 H), 2.30–2.41 (m, 2 H), 2.54–2.62 (m, 2 H), 4.04–4.11 (m, 2 H), 4.67 (s, 1 H), 5.89 (d, *J* = 2.8 Hz, 2 H), 6.19 (s, 2 H), 6.67 (d, *J* = 8.8 Hz, 1 H), 6.77 (d, *J* = 6.0 Hz, 2 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 10.30 (major), 12.74 (minor) min.

5f: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (18.9 mg, 55%, 81%*ee*). $[a]^{22.9}$ = 50.5 (*c* = 0.103, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16–1.19 (t, *J* = 7.2 Hz, 3 H), 1.93–2.06 (m, 2 H), 2.32–2.39 (m, 2 H), 2.53–2.61 (m, 2 H), 3.76 (s, 3 H), 4.01–4.09 (m, 2 H), 4.69 (s, 1 H), 6.20 (s, 1 H), 6.75–6.77 (d, *J* = 8.8 Hz, 2 H), 7.19 (d, *J* = 8.8 Hz, 2 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 7.92 (major), 12.74 (minor) min.

5g: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (25.7 mg, 75%, 74%*ee*). $[a]^{20.4}$ = 4 (*c* = 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.18 (t, *J* = 7.2 Hz, 3 H), 1.94–2.02 (m, 2 H), 2.31–2.37 (m, 2 H), 2.52–2.58 (m, 2 H), 3.78 (s, 3 H), 3.95–4.10 (m, 2 H), 4.72 (s, 1 H), 6.18 (s, 2 H), 6.65–6.68 (dd, *J* = 2.4, 8.0 Hz, 1 H), 6.84–6.88 (t, *J* = 8.4 Hz, 2 H), 7.11–7.15 (t, *J* = 8.0 Hz, 1 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 7.63 (major), 9.90 (minor) min.

5h: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (24.6 mg, 71%, 73%*ee*). $[a]^{22.5}$ = 37.3 (*c* = 0.118, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14–1.17 (t, *J* = 6.8 Hz, 3 H), 2.02 (m, 2 H), 2.32–2.36 (m, 2 H), 2.59 (m, 2 H), 4.01–4.06 (q, *J* = 6.8, 14.0 Hz, 2 H), 4.70 (s, 1 H), 6.13 (s, 2 H), 7.10–7.22 (m, 4 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/

n-hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 12.57 (major), 15.68 (minor) min.

5i: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (27.4 mg, 79%, 81%*ee*). $[\alpha]^{22.6}$ = 51.5 (*c* = 0.132, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14–1.18 (t, *J* = 6.8 Hz, 3 H), 1.93–2.08 (m, 2 H), 2.30–2.40 (m, 2 H), 2.55–2.63 (m, 2 H), 4.00–4.09 (m, 2 H), 4.71 (s, 1 H), 6.22 (s, 2 H), 6.18–7.24 (m, 4 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 6.45 (major), 9.36 (minor) min.

5j: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (28.6 mg, 80%, 77%*ee*). $[\alpha]^{23.1}$ = 61.8 (*c* = 0.110, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.14 (t, *J* = 6.8 Hz, 3 H), 1.92–2.08 (m, 2 H), 2.33–2.36 (m, 2 H), 2.57–2.65 (m, 2 H), 3.98–4.06 (m, 2 H), 4.82 (s, 1 H), 6.28 (s, 2 H), 7.44–7.46 (d, *J* = 8.8 Hz, 2 H), 8.07–8.09 (d, *J* = 8.4 Hz, 2 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 8.71 (major), 13.66 (minor) min.

5k: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (26.8 mg, 81%, 77%*ee*). $[\alpha]^{23.1}$ = 68.1 (*c* = 0.091, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.15 (t, *J* = 7.2 Hz, 3 H), 1.92–2.06 (m, 2 H), 2.27–2.38 (m, 2 H), 2.53–2.62 (m, 2 H), 4.00–4.06 (q, *J* = 7.2 Hz, 2 H), 4.70 (s, 1 H), 6.18 (s, 2 H), 6.86–6.91 (t, *J* = 8.8 Hz, 2 H), 7.21–7.25 (dd, *J* = 5.6, 8.4 Hz, 2 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 6.24 (major), 7.99 (minor) min.

5l: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (29.7 mg, 76%, 74%*ee*). $[\alpha]^{19.7}$ = 13.5 (*c* = 0.104, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14–1.17 (t, *J* = 7.2 Hz, 3 H), 1.94–2.07 (m, 2 H), 2.28–2.40 (m, 2 H), 2.50–2.65 (m, 2 H), 4.01–4.06 (q, *J* = 7.2 Hz, 2 H), 4.68 (s, 1 H), 6.20 (s, 2 H), 7.06–7.09 (t, *J* = 8.0 Hz, 1 H), 7.21–7.25 (t, *J* = 7.6 Hz, 2 H), 7.38 (s, 1 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 6.24 (major), 7.99 (minor) min.

5m: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (29.7 mg, 76%, 83%*ee*). $[\alpha]^{20.5}$ = –8 (*c* = 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.16 (t, *J* = 7.2 Hz, 3 H), 1.92–2.06 (m, 2 H), 2.27–2.38 (m, 2 H), 2.50–2.61 (m, 2 H), 3.98–4.07 (m, 2 H), 4.68 (s, 1 H), 6.20 (s, 2 H), 7.14–7.16 (d, *J* = 8.4 Hz, 2 H), 7.31–7.33 (d, *J* = 8.0 Hz, 2 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 6.51 (major), 9.77 (minor) min.

5n: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (27.4 mg, 72%, 79%*ee*). $[\alpha]^{20.7}$ = –16 (*c* = 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.15 (t, *J* = 7.2 Hz, 3 H), 1.92–2.07 (m, 2 H), 2.32–2.36 (m, 2 H), 2.55–2.60 (m, 2 H), 3.98–4.06 (m, 2 H), 4.78 (s, 1 H), 6.24 (s, 2 H), 7.38–7.40 (d, *J* = 8.0 Hz, 2 H), 7.45–7.47 (d, *J* = 8.4 Hz, 2 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 5.22 (major), 6.63 (minor) min.

5o: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (28.4 mg, 73%, 89%*ee*). $[\alpha]^{20.9}$ = –3.8 (*c* = 0.106, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.18 (t, *J* = 7.2 Hz, 3 H), 1.98–2.01 (m, 2 H), 2.31–2.36 (m, 2 H), 2.53–2.57 (m, 2 H), 4.02–4.12 (m, 2 H), 4.77 (s, 1 H), 6.22 (s, 2 H), 7.25–7.45 (m, 7 H), 7.53–7.55 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.26, 20.24, 26.99, 33.51, 36.91, 59.73, 80.62, 118.03, 126.61, 126.92, 127.00, 128.64, 128.67, 138.87, 1414.18, 145.20, 158.40, 163.17, 169.12, 196.67 ppm. HRMS: calcd. for $C_{24}H_{23}NO_4$ $[M]^+$ 390.1661; found 390.1704. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 8.74 (major), 12.17 (minor) min.

5p: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (23.2 mg, 64%, 81%*ee*). $[\alpha]^{23.0}$ = 46.7 (*c* = 0.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.14 (t, *J* = 7.2 Hz, 3 H), 1.92–2.04 (m, 2 H), 2.30–2.32 (m, 2 H), 2.52–2.59 (m, 2 H), 3.93–4.05 (m, 2 H), 4.90 (s, 1 H), 6.25 (s, 2 H), 7.36–7.44 (m, 3 H), 7.68–7.73 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.21, 20.22, 26.99, 34.01, 36.86, 59.67, 80.65, 118.03, 125.15, 125.57, 126.73, 127.00, 127.37, 127.46, 127.82, 132.26, 133.33, 143.49, 158.42, 163.04, 169.11, 196.48 ppm. HRMS: calcd. for $C_{22}H_{21}NO_4$ $[M]^+$ 364.1504; found 364.1542. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 30:70, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 5.23 (major), 9.65 (minor) min.

5q: Purified by flash chromatography (petroleum/EtOAc, 2:1) to afford a white solid (23.9 mg, 75%, 69%*ee*). $[\alpha]^{23.0}$ = 52.5 (*c* = 0.099, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.22 (t, *J* = 7.2 Hz, 3 H), 1.98–2.04 (m, 2 H), 2.33–2.58 (m, 4 H), 4.09–4.15 (m, 2 H), 5.10 (s, 1 H), 6.23 (s, 2 H), 6.82–6.86 (m, 2 H), 7.03–7.04 (d, *J* = 4.8 Hz, 1 H) ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 7.46 (major), 10.35 (minor) min.

5r: Purified by flash chromatography (petroleum/EtOAc, 3:1) to afford a white solid (21.2 mg, 71%, 73%*ee*). $[\alpha]^{29.1}$ = 14.1 (*c* = 0.075, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.90–2.04 (m, 2 H), 2.16–2.43 (m, 2 H), 2.44–2.59 (m, 2 H), 3.58 (s, 3 H), 4.73 (s, 1 H), 6.18 (br. s, 2 H), 7.10–7.13 (t, *J* = 7.2 Hz, 1 H), 7.19–7.22 (t, *J* = 7.2 Hz, 2 H), 7.26–7.27 (d, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.18, 26.95, 33.54, 36.85, 50.97, 80.57, 118.27, 126.11, 127.93, 128.04, 145.87, 158.56, 163.04, 169.49, 196.48 ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 14.60 (major), 21.08 (minor) min.

5s: Purified by flash chromatography (petroleum/EtOAc, 3:1) to afford a white solid (23.5 mg, 72%, 69%*ee*). $[\alpha]^{22.3}$ = 52.3 (*c* = 0.153, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.2 Hz, 3 H), 1.21 (d, *J* = 6.2 Hz, 3 H), 1.91–2.04 (m, 2 H), 2.28–2.36 (m, 2 H), 2.49–2.61 (m, 2 H), 4.70 (s, 1 H), 4.85–4.89 (m, 1 H), 6.16 (br. s, 1 H), 7.08–7.11 (t, *J* = 7.3 Hz, 1 H), 7.18–7.21 (t, *J* = 7.4 Hz, 2 H), 7.26 (d, *J* = 7.1 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.22, 21.58, 22.17, 26.97, 33.89, 36.88, 66.89, 81.12, 118.03, 125.98, 127.68, 128.39, 146.08, 158.13, 162.93, 168.67, 196.60 ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 10.11 (major), 13.81 (minor) min.

5t: Purified by flash chromatography (petroleum/EtOAc, 3:1) to afford a white solid (23.9 mg, 70%, 77%*ee*). $[\alpha]^{29.1}$ = 16.1 (*c* = 0.114, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 (s, 3 H), 1.09 (s, 3 H), 1.14–1.17 (t, *J* = 7.1 Hz, 3 H), 2.14–2.24 (dd, *J* = 16.2 Hz, 2 H), 2.42 (s, 2 H), 3.99–4.06 (m, 2 H), 4.69 (s, 1 H), 6.17 (br. s, 2 H), 7.10 (s, 1 H), 7.18–7.21 (t, *J* = 7.4 Hz, 2 H), 7.25–7.26 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.20, 27.41, 29.09, 32.24, 33.83, 40.66, 50.72, 59.67, 80.84, 116.82, 126.03, 127.77, 128.24, 145.79, 158.32, 161.35, 169.14, 196.41 ppm. HPLC (Daicel Chiralcel AD, 2-propanol/*n*-hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 10.11 (major), 13.81 (minor) min.

Supporting Information (see footnote on the first page of this article): HPLC traces, ^{1}H and ^{13}C NMR spectra, mass spectra.

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