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Catalytic Enantioselective Domino Oxa-Michael/Aldol Condensations: Asymmetric Synthesis of Benzopyran Derivatives

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Abstract: The first direct organocatalytic asymmetric domino oxa-Michael/aldol condensation reaction is presented. The unprecedentedly simple, chiral, pyrrolidine-catalyzed asymmetric domino reactions between salicylic aldehyde derivatives and α,β-unsaturated aldehydes proceed with high chemo- and enantioselectivities to give the corresponding chromene-3-carbaldehyde derivatives in high yields and with *ee* values of 83–98%.

Keywords: asymmetric catalysis · diphenylprolinol · domino reactions · heterocycles · oxa-Michael reaction

Introduction

Hetereocycles play a fundamental role in the design and discovery of new physiologically active compounds.[1] In this context, groups of compounds based on the principle of "privileged structures", a term originally introduced by Evans et al. to describe structural motifs (originally benzodiazepines and benzazepines) that bind as high-affinity ligands to multiple unrelated classes of protein receptors, are important.[2] The benzopyrans also belong among these privileged structures, as described and shown by Nicolaou et al.[2b,c,3]

Condensations between Michael acceptors and 2-hydroxybenzaldehydes have proven to be a versatile route to benzopyrans.[4] The reaction is base-promoted and represents a simple pathway to racemic carbonyl compounds containing a benzopyran moiety. DABCO-mediated reactions (DABCO = 1,4-diazabicyclo[2.2.2]octane) between salicylic aldehyde derivatives and α,β-unsaturated ketones and aldehydes, for instance, are a direct route to tetrahydroxanthones and chromene-3-carbaldehyde derivatives, respectively.[4c,d] To the best of our knowledge, however, there is no report of a catalytic asymmetric version.

The development of asymmetric reactions with metal-free organic molecules as catalysts has attracted intense attention in recent years.[5] Moreover, organocatalytic enantioselective domino and tandem reactions have been developed,[6,7] with chiral amines and amino acid derivatives having been successfully used as catalysts in this context. Inspired by work on the synthesis of racemic chromene derivatives,[4,8] and by our research interest in organocatalysis,[9] we envisioned that possible chiral, amine-catalyzed direct asymmetric domino reactions between 2-hydroxyaldehydes and α,β-unsaturated aldehydes would be an excellent enantioselective route to benzopyrans (Scheme 1).

Iminium activation of α,β-unsaturated aldehydes **2** by a chiral amine or amino acid should thus lead to enantioselective oxa-Michael addition by, say, 2-hydroxybenzaldehyde (**1a**) and generate enamine intermediates that should undergo subsequent intramolecular 6-*exo-trig* aldol condensations to give the corresponding chromene-3-carbaldehyde derivatives **3**. Here we report the direct organocatalytic asymmetric domino oxa-Michael/aldol condensation reaction, which gives chromene-3-carbaldehyde derivatives in high yields and with *ee* values of 83–98%.

Results and Discussion

Reactions: In an initial screening, we investigated several catalysts for their ability to catalyze the direct asymmetric domino oxa-Michael/aldol reaction between salicylic aldehyde (**1a**) and cinnamaldehyde (**2a**). To our delight, we

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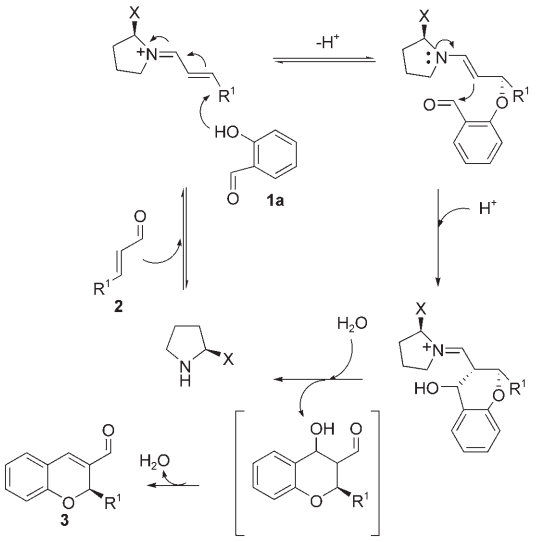
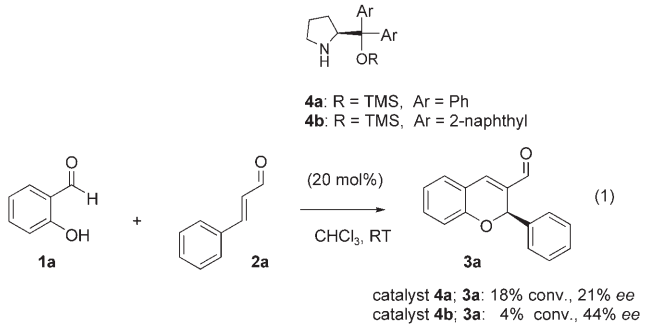


Scheme 1. A plausible reaction pathway for an asymmetric tandem oxy-Michael/aldol condensation reaction catalyzed by a chiral amine.

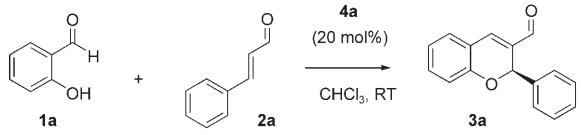
found that protected α,α-diphenyl-2-pyrrolidinemethanol (diphenylprolinol, **4a**)[9] and α,α-bis(naphthalen-2-yl)-2-pyrrolidinemethanol (**4b**)[10] were indeed able to catalyze the formation of 2-phenyl-2*H*-chromene-3-carbaldehyde (**3a**), but only with low conversions and with 21 and 44% *ee*, respectively [Eq. (1)].



Nevertheless, we decided to investigate the simple diphenylprolinol (**4a**) as the catalyst and to optimize the reaction conditions. Several different sets of reaction conditions were tested and a few are shown in Table 1.

We found that the addition of a substoichiometric amount of an organic acid (20 mol%) increased the enantioselectivity and efficiency of the reaction: addition of 2-nitrobenzoic acid (20 mol%), for instance, increased the enantioselectivity of the reaction in toluene from 9% to 88% *ee* (entries 2 and 10, respectively). Notably, the reaction is highly chemoselective and the chromene **3a** was the only product formed. The highest levels of conversion to **3a** were achieved when benzoic acid (20 mol%) was used as the additive and toluene or isopropanol as the solvent (entries 8 and 9). Moreover, decreasing the reaction temperature to −20°C increased the stereoselectivity of the catalytic domino reaction

Table 1. Direct catalytic asymmetric domino oxa-Michael/aldol condensation reactions between **1a** and **2a**.[a]



Entry	Additive (20 mol%)	Solvent	*T* [°C]	*t* [h]	Conv.[b] (%)	*ee*[c] [%]
1	none	$CHCl_3$	RT	16	18	21
2	none	toluene	RT	16	10	9
3	$C_6H_5CO_2H$	$CHCl_3$	RT	12	17	76
4	2-$NO_2C_6HCO_2H$	$CHCl_3$	RT	12	4	83
5	4-$NO_2C_6HCO_2H$	$CHCl_3$	RT	12	5	78
6	2-$NO_2C_6HCO_2H$	$CHCl_3$	4	96	2	88
7	$C_6H_5CO_2H$	$CHCl_3$	−20	48	4	91
8	$C_6H_5CO_2H$	*i*PrOH	RT	16	50	57
9	$C_6H_5CO_2H$	toluene	RT	16	50	66
10	2-$NO_2C_6HCO_2H$	toluene	RT	16	37	88

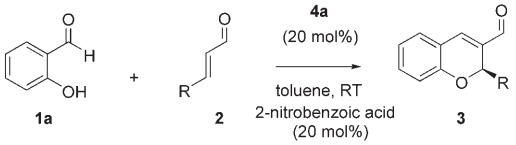
[a] Experimental conditions: a mixture of **1a** (0.25 mmol), cinnamaldehyde (**2a**, 0.3 mmol), and catalyst (20 mol%) in solvent (0.5 mL) was stirred at the temperature and under the conditions displayed in the table. [b] The degree of conversion was determined by ^{1}H NMR and GC analyses. [c] Determined by chiral-phase GC analyses.

and gave **3a** with 91% *ee* but with only 4% conversion. From these results we decided that the best trade-off between reactivity and enantioselectivity for the chiral pyrrolidine-catalyzed asymmetric domino reaction would be to use 2-nitrobenzoic acid as the additive and toluene as the solvent (entry 10), and so we investigated asymmetric oxa-Michael/aldol additions between 2-hydroxybenzaldehyde (**1a**) and a set of different α,β-unsaturated aldehydes **2** catalyzed by protected diphenylprolinol (**4a**) in toluene (Table 2).

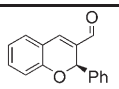
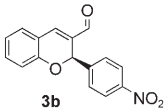
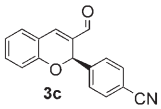
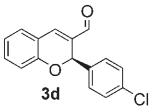
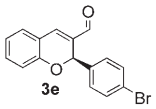
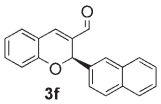
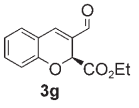
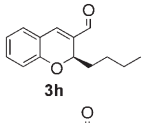
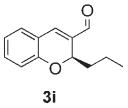
The reactions proceeded with high chemo- and enantioselectivities and gave the corresponding chromene-3-carbaldehyde derivatives **3** in moderate to high yields and with 83–96% *ee*; the reactions with aldehydes **2b** and **2c** as acceptors, for instance, furnished the corresponding chromene-3-carbaldehydes **3b** and **3c** in 52 and 71% yields and with 90 and 94% *ee*, respectively. In addition, the α,β-unsaturated aldehyde **2g** was an excellent substrate and gave the corresponding benzopyran **3g** in 70% yield and with 96% *ee*. The protected diphenylprolinol-catalyzed asymmetric domino oxa-Michael/aldol dehydration reactions with aliphatic aldehydes **2h** and **2i** produced the chromene-3-carbaldehydes **3h** and **3i**, respectively, with high enantioselectivity (entries 8 and 9). Notably, the aliphatic α,β-unsaturated aldehydes **2** had to be added by syringe pump in order to achieve high chemoselectivities in the asymmetric domino reactions.

Although the reactions with α,β-unsaturated aldehydes containing aryl moieties were useful, we wanted to improve the yields of some of the compounds further, and we believed that removal of water by addition of molecular sieves (200 mg, 4 Å) should increase the yields of the products derived from these reactions. Notably, this strategy improved the yield of chromene-3-carbaldehyde (**3a**) from 42 to 81% without affecting the enantioselectivity. As a result of this

Table 2. Direct organocatalytic asymmetric domino oxa-Michael/aldol condensations between **1a** and α,β-unsaturated aldehydes **2**.[a]



1a 2 3

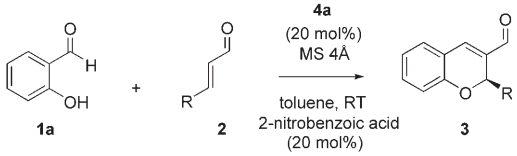
Entry	R	Product	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	Ph	 **3a**	20	42	88
2	4-$NO_2C_6H_4$	 **3b**	16	52	94
3	4-CNC_6H_4	 **3c**	16	72	90
4	4-ClC_6H_4	 **3d**	21	43	83
5	4-BrC_6H_4	 **3e**	20	51	84
6	naphthalen-2-yl	 **3f**	20	40	84
7	CO_2Et	 **3g**	21	70	96
8	*n*-butyl	 **3h**	16[d]	67	87
9	*n*-propyl	 **3i**	16[d]	57	87

[a] Experimental conditions: a mixture of **1a** (0.25 mmol), aldehyde **2** (0.3 mmol), 2-nitrobenzoic acid (20 mol%), and catalyst (20 mol%) in toluene (0.5 mL) was stirred at room temperature. The crude product **3** obtained after aqueous workup was purified by column chromatography. [b] Isolated yield of pure product **3** after silica gel column chromatography. [c] Determined by chiral-phase GC or HPLC analyses. [d] The α,β-unsaturated aldehydes **1h** and **1i** were added by syringe pump.

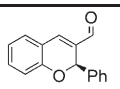
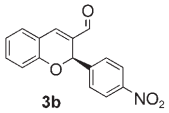
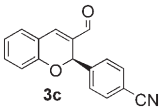
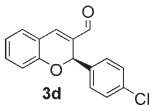
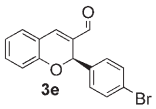
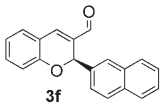
experiment, we decided also to perform the reactions with α,β-unsaturated aldehydes **2a–f** under these reaction conditions (Table 3).

We found that the high chemo- and enantioselectivities of the reactions were not affected, and the corresponding chromene-3-carbaldehyde derivatives **3a–f** were isolated in 81–95% yields and with 83–90% *ee*, so the removal of water by the molecular sieves had significantly improved the yields of the reactions.

Table 3. Direct organocatalytic asymmetric domino oxa-Michael/aldol condensations between **1a** and α,β-unsaturated aldehydes **2** in the presence of molecular sieves.[a]



1a 2 3

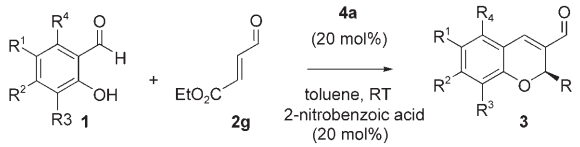
Entry	R	Product	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	Ph	 **3a**	16	81	88
2	4-$NO_2C_6H_4$	 **3b**	24	95	90
3	4-CNC_6H_4	 **3c**	26	81	90
4	4-ClC_6H_4	 **3d**	31	89	83
5	4-BrC_6H_4	 **3e**	20	80	86
6	naphthalen-2-yl	 **3f**	22	87	84

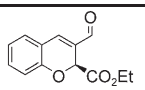
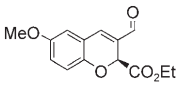
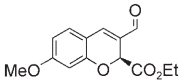
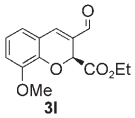
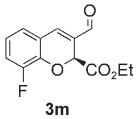
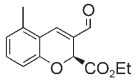
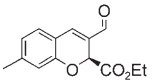
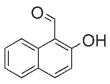
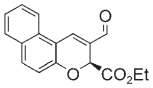
[a] Experimental conditions: a mixture of **1a** (0.25 mmol), aldehyde **2** (0.3 mmol), 2-nitrobenzoic acid (20 mol%), molecular sieves (4 Å, 0.2 g), and catalyst (20 mol%) in toluene (0.5 mL) was stirred at room temperature. The crude product **3** obtained after aqueous workup was purified by column chromatography. [b] Isolated yield of pure product **3** after silica gel column chromatography. [c] Determined by chiral-phase GC or HPLC analyses.

We next investigated diphenylprolinol (**4a**) catalysis of asymmetric domino oxa-Michael/aldol dehydration reactions between different substituted 2-hydroxybenzaldehydes **1** and aldehyde **2g** (Table 4).

The reactions were highly chemo- and enantioselective and provided the corresponding chromene-3-carbaldehyde derivatives **3j–3p** with 92–98% *ee*. Use of 2-hydroxybenzaldehyde **1b**, with a methoxy group in the position *para* to the phenol moiety, for instance, gave chromene derivative **3j** in 92% yield and with 93% *ee* (entry 2). Chromene derivatives that are generated by reactions with 5-alkoxy-2-hydroxybenzaldehydes are potent 5-lipoxygenase inhibitors.[4d] Moreover, the asymmetric domino reaction with 2-hydroxy-4-methoxybenzaldehyde (**1c**) was slow but highly enantioselective (entry 3), so the presence of an electron-donating methoxy substituent in the position *para* to (rather than *meta* to) the phenol moiety in aldehydes **1** increased the degree of conversion of the organocatalytic asymmetric domino oxa-Michael/aldol condensation reaction. This was further

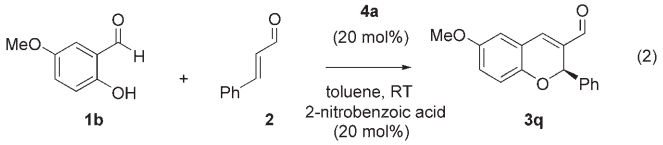
Table 4. Direct organocatalytic asymmetric domino oxa-Michael/aldol condensations between 2-hydroxyaldehydes **1** and α,β-unsaturated aldehyde **2g**.[a]



Entry	Aldehyde **1**	R^1	R^2	R^3	R^4	Product	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	**1a**	H	H	H	H	 **3g**	21	70	96
2	**1b**	OMe	H	H	H	 **3j**	64	92	93
3	**1c**	H	OMe	H	H	 **3k**	64	20	92
4	**1d**	H	H	OMe	H	 **3l**	24	68	95
5	**1e**	H	H	F	H	 **3m**	23	72	98
6	**1f**	H	H	H	Me	 **3n**	24	65	97
7	**1g**	H	Me	H	H	 **3o**	36[d]	70	98
6	**1h**					 **3p**	29	28	92

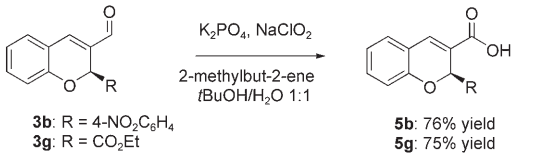
[a] Experimental conditions: A mixture of **1** (0.5 mmol), aldehyde **2g** (0.6 mmol), 2-nitrobenzoic acid (20 mol%), and catalyst (20 mol%) in toluene (1 mL) was stirred at room temperature. The crude product **3** obtained after aqueous workup was purified by column chromatography. [b] Isolated yield of pure product **3** after silica gel column chromatography. [c] Determined by chiral-phase HPLC analyses. [d] Molecular sieves (4 Å, 200 mg) were added.

confirmed by the **4a**-catalyzed asymmetric domino reaction between aldehyde **1b** and cinnamaldehyde (**2a**), which gave the corresponding chromene derivative **3q** in 68% yield and with 74% *ee* [Eq. (2)].



(2)

In comparison, the asymmetric domino reaction with 2-hydroxybenzaldehyde (**1a**) is slightly slower and more enantioselective. Notably, the presence of a methyl group *meta* to the phenol moiety in aldehydes **1** did not affect the reactivity, and the chromene-3-carbaldehyde **3o** was isolated in high yield and with 98% *ee* (entry 7). The chromene-3-carbaldehyde **3** derivatives were also readily oxidized to the corresponding chromenecarboxylic acids **5** [Eq. (3)]. X-ray analysis of the enantiopure chromene-3-carboxylic acid **5b**



(3)

established that the absolute configuration at C2 was *R* (Figure 1).[11]

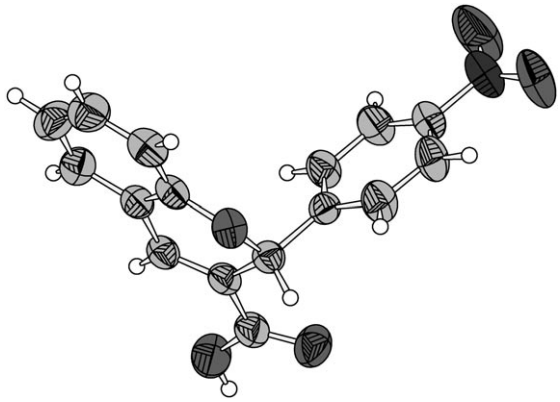


Figure 1. Ortep picture of chromene-3-carboxylic acid **5b**.

Mechanism: From the X-ray analysis and from previous **4a**-catalyzed reactions,[10c–h] we propose that the following mechanism is responsible for the stereochemical outcome of the reaction. The direct organocatalytic asymmetric domino oxa-Michael/aldol condensation reaction starts with iminium activation of the α,β-unsaturated aldehyde by the chiral pyrrolidine derivative **4a**. The efficient shielding of the *Si*-face of the chiral iminium intermediate by the bulky aryl groups results in a stereoselective *Re*-facial nucleophilic conjugate attack on the β-carbon by the phenol **1**, resulting in a chiral enamine intermediate (Scheme 1; if R^1 is equal to aryl *Si*-facial attack occurs). Next, the chiral enamine undergoes an intramolecular 6-*exo-trig* nucleophilic attack on the benzaldehyde moiety, followed by hydrolysis of the resulting iminium intermediate and elimination of water. In fact, the aldol product can be observed as an intermediate by NMR analysis. The addition of a substoichiometric amount of an organic acid plausibly accelerates the catalytic domino reaction by providing a Brønsted acid, which activates the benzaldehyde moiety towards the intramolecular 6-*exo-trig* aldol condensation. In addition, the organic acid will stabilize the iminium intermediate and consequently push the equilibrium towards the oxa-Michael addition. The addition of molecular sieves removes water from the reaction medium, which increases the rate of aldol condensation and pushes the equilibrium towards product formation.

Conclusion

In summary, we report the first direct organocatalytic, asymmetric, domino oxa-Michael/aldol condensation reaction. The catalytic domino reactions between salicylic aldehyde derivatives and α,β-unsaturated aldehydes proceed with high chemo- and enantioselectivities and furnish chromene-3-carbaldehydes in good to high yields and with 83–98 % *ee*. The reaction constitutes a direct catalytic asymmetric route to benzopyran derivatives. Further elaboration of this transformation and of similar asymmetric reactions, together with its synthetic application, is currently in progress in our laboratory.

Experimental Section

General: Chemicals and solvents were either purchased puriss p.A. from commercial suppliers or purified by standard techniques. Silica gel plates (Merck 60 F254) were used for thin-layer chromatography (TLC), and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (10 g), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating, or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed on silica gel (Merck 60, particle size 0.040–0.063 mm), while ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian AS 400 instrument. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants (J) are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature, TMS served as internal standard ($\delta = 0$ ppm) for ^{1}H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR. HPLC was carried out on a Waters 2690 Millennium fitted with a photodiode array detector. GC was carried out by using a Varian 3800 GC instrument. Chiral GC-column used: CP-Chirasil-Dex CB 25 m × 0.32 mm. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter ($\lambda = 589$ nm, 1 dm cell). Mass data (ESI) were obtained with a Bruker MicrOTOF spectrometer.

Typical experimental procedure for the catalyst screening: α,β-Unsaturated aldehyde **2a** (1.2 equiv, 0.6 mmol) and 2-hydroxybenzaldehyde (**1a**, 1 equiv, 0.5 mmol) were added to a stirred solution of catalyst (20 mol %) in $CHCl_3$ (1.0 mL). The reaction mixture was vigorously stirred and the degree of conversion was determined by NMR. The *ee* of the pure chromene-3-carbaldehyde (**3a**) product was determined by chiral-phase HPLC analysis (Daicel AD column, $\lambda = 244$ nm, $v = 0.5$ mL min^{-1}, *i*Hex/*i*PrOH) after silica gel column chromatography.

Typical experimental procedure for the optimization of reaction conditions: α,β-Unsaturated aldehyde **2a** (1.2 equiv, 0.6 mmol) and 2-hydroxybenzaldehyde (**1a**, 1 equiv, 0.5 mmol) were added to a stirred solution of catalyst (20 mol %) and organic acid in solvent (1.0 mL). The reaction mixture was vigorously stirred for the time shown in Table 2 and the degree of conversion was determined by NMR. The *ee* of the pure chromene-3-carbaldehyde (**3a**) product was determined by chiral-phase HPLC analysis (Daicel AD column, $\lambda = 244$ nm, $v = 0.5$ mL min^{-1}, *i*Hex/*i*PrOH) after silica gel column chromatography.

Typical experimental procedure for the direct catalytic enantioselective domino oxa-Michael/aldol condensation reactions: An α,β-unsaturated aldehyde **2** (1.2 equiv, 0.6 mmol) and a 2-hydroxybenzaldehyde **1** (1 equiv, 0.5 mmol) were added to a stirred solution of catalyst (20 mol %) and 2-nitrobenzoic acid (20 mol %) in toluene (1.0 mL). The reaction mixture was vigorously stirred for the time shown in Tables 2 or 4. Next, the crude product was purified by silica gel chromatography (pentane/EtOAc mixtures) to give the corresponding chromene-3-carbaldehyde **3**. The *ee* of the oxa-Michael/aldol condensation product **3** was determined by chiral-phase HPLC or GC analysis.

Typical experimental procedure for the direct catalytic enantioselective domino oxa-Michael/aldol condensation reactions in the presence of molecular sieves: An α,β-unsaturated aldehyde **2** (1.2 equiv, 0.6 mmol) and a 2-hydroxybenzaldehyde **1** (1 equiv, 0.5 mmol) were added to a stirred solution of molecular sieves (4 Å, 0.2 g), catalyst (20 mol %), and 2-nitrobenzoic acid (20 mol %) in toluene (1.0 mL). The reaction mixture was vigorously stirred for the time shown in Table 3 or 4, and the crude product was purified by silica gel chromatography (pentane/EtOAc mixture) to give the corresponding chromene-3-carbaldehyde **3**. The *ee* of the oxa-

Michael/aldol condensation product **3** was determined by chiral-phase HPLC or GC analysis.

Compound 3a: HPLC (Daicel Chiralpak AD, isohexanes/*i*PrOH 96:4, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R major isomer = 18.21 min; t_R minor isomer = 20.51 min; $[\alpha]_D^{25}$ = −65.1 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (s, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.95 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.28 (m, 3H), 7.34 (m, 2H), 7.41 (s, 1H), 7.46 (m, 2H), 9.65 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 74.6, 117.4, 120.2, 122.0, 127.0, 128.0, 128.8, 128.9, 129.4, 129.6, 133.9, 141.0 153.0, 190.2 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{13}O_2$: 237.0910; found: 237.0913 $[M+H]^+$.

Compound 3b: HPLC (Daicel Chiralpak AS, isohexanes/*i*PrOH 80:20, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R major isomer = 46.97 min; t_R minor isomer = 74.27 min; $[\alpha]_D$ = −70.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.33 (s, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.96 (dt, *J* = 7.4, 1.0 Hz, 1H), 7.23 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.28 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.82 (s, 1H), 8.14 ppm (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 74.0, 117.2, 119.9, 122.5, 122.6, 124.1, 128.2, 129.8, 133.8, 136.9, 146.2, 148.3 153.7, 170.0 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{12}NO_4$: 282.0761; found: 282.0753 $[M+H]^+$.

Compound 3c: HPLC (Daicel Chiralpak AS, isohexanes/*i*PrOH 80:20, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R major isomer = 46.11 min; t_R minor isomer = 59.1 min; $[\alpha]_D$ = −44.4 (*c* = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (s, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 7.28 (m, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.97, (d, *J* = 8.3 Hz, 2H), 9.66 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 73.5, 117.3, 118.7, 119.8, 122.6, 127.5, 129.3, 130.0, 132.6, 133.0, 134.0, 141.6, 144.5, 154.7, 190.1 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{17}H_{12}NO_2$: 262.0863; found: 262.0859 $[M+H]^+$.

Compound 3d: HPLC (Daicel Chiralpak OD-H, isohexanes/*i*PrOH 95:5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R major isomer = 26.32 min; t_R minor isomer = 29.52 min; $[\alpha]_D$ = −60.6 (*c* = 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.30 (s, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.97 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.22–7.34 (m, 6H), 7.43 (s, 1H), 9.65 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 73.6, 117.3, 120.0, 122.1, 128.3, 128.9, 129.6, 133.5, 134.0, 134.7, 137.7, 141.1, 154.7, 190.0 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{12}ClO_2$: *m*/*z*: 271.0520; found: 271.0518 $[M+H]^+$.

Compound 3e: HPLC (Daicel Chiralpak OD-H, isohexanes/*i*PrOH 95:5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R major isomer = 28.41 min; t_R minor isomer = 38.74 min; $[\alpha]_D$ = −27.6 (*c* = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (s, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.24 (m, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.42, (s, 1H), 9.64 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 73.8, 117.4, 119.7, 122.3, 123.0, 128.8, 129.8, 132.0, 133.6, 134.2, 138.3, 141.2, 154.7, 190.1 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{12}BrO_2$: 315.0015; found: 315.0009 $[M+H]^+$.

Compound 3f: HPLC (Daicel Chiralpak OD-H, isohexanes/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R major isomer = 22.62 min; t_R minor isomer = 38.41 min; $[\alpha]_D$ = −40.5 (*c* = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50 (s, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.95 (t, *J* = 7.8 Hz, 1H), 7.24 (s, 1H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.43 (m, 2H), 7.45 (s, 1H), 7.50 (m, 2H), 7.80 (m, 2H), 9.71 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 74.5, 117.5, 120.5, 122.1, 125.0, 126.3, 126.4, 126.6, 127.8, 128.6, 128.8, 129.7, 131.1, 134.0, 141.3, 153.0, 190.2 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{15}O_2$: 287.1067; found: 286.1067 $[M+H]^+$.

Compound 3g: The enantiomeric excess was determined by HPLC on Daicel Chiralpak ODH with isohexanes/*i*PrOH 90:10) as the eluent: t_R minor isomer = 24.53 min; t_R major isomer = 26.54 min; $[\alpha]_D^{25}$ = −158.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 6.9 Hz, 3H), 4.12 (dq, *J* = 6.9, 2.1 Hz, 2H), 5.81 (s, 1H), 6.96–7.04 (m, 2H), 7.24 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.32–7.37 (m, 2H), 9.63 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 61.9, 70.5, 117.1, 119.7, 122.6, 129.8, 130.0, 133.9, 140.8, 155.0, 168.7, 188.9 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{13}O_4$: 233.0808; found: 233.0808 $[M+H]^+$; MALDI-TOF MS: *m*/*z*: calcd fo $C_{13}H_{12}O_4$: 255.0633; found: 255.0634 $[M+Na]^+$.

Compound 3h: *trans*-Hept-2-enal (4 equiv, 0.325 mmol, in 0.875 mL toluene) was added by syringe pump overnight at room temperature to a stirred solution of catalyst (20 mol%, 0.05 mmol), 2-nitrobenzoic acid (20 mol%, 0.05 mmol), and salicylaldehyde (0.25 mmol) in toluene (0.5 mL). The product was purified by silica gel chromatography (pure toluene) to give chromene-3-carbaldehyde **3h** in 67% yield and with 87% *ee* as a clear oil. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak ODH column (*n*-hexane/*i*PrOH 99.2:0.8, λ = 254 nm), 0.5 mL min^{-1}; t_R minor enantiomer = 16.7 min; t_R major enantiomer = 17.0 min; $[\alpha]_D$ = +31.9 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3H), 1.25–1.56 (m, 7H), 1.70–1.80 (m, 1H), 5.27 (dd, *J* = 9.3, 3.1 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.97 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.19–7.21 (m, 2H), 7.30 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H), 9.55 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 22.4, 27.3, 33.6, 73.5, 117.4, 120.5, 121.8, 129.3, 133.5, 135.8, 140.7, 154.8, 190.3 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{17}O_2$: 217.1223; found: 217.1222 $[M+H]^+$.

Compound 3i: This compound was prepared by the procedure used for **3h**. The enantiomeric excess was determined by HPLC with an Daicel Chiralpak ODH column (*n*-hexane/*i*PrOH 99.1:0.9, λ = 254 nm), 0.5 mL min^{-1}; t_R minor enantiomer = 15.3 min, t_R major enantiomer = 16.9 min; $[\alpha]_D$ = +32.8 (*c* = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3H), 1.34–1.60 (m, 3H), 1.69–1.81 (m, 1H), 5.28 (dd, *J* = 9.6, 3.1 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.94 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.19–7.21 (m, 2H), 7.30 (ddd, *J* = 8.1, 7.5, 1.7 Hz, 1H), 9.55 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.5, 35.9, 73.3, 117.4, 120.5, 121.7, 129.3, 133.5, 135.7, 140.7, 154.8, 190.3 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{15}O_2$: 203.1067; found: 203.1076 $[M+H]^+$.

Compound 3j: The enantiomeric excess was determined by HPLC on Daicel Chiralpak ODH with isohexanes/*i*PrOH 85:15 as the eluent: t_R major isomer = 22.980 min; t_R minor isomer = 26.878 min; $[\alpha]_D^{25}$ = −113.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.2 Hz, 3H), 3.75 (s, 3H), 4.11 (dq, *J* = 7.2, 4.4 Hz, 2H), 5.75 (s, 1H), 6.75 (d, *J* = 2.8 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 7.29 (s, 1H), 9.62 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 55.7, 61.8, 70.3, 113.2, 117.8, 119.99, 120.02, 130.5, 140.7, 148.9, 154.7, 168.8, 188.8 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{15}O_5$: 262.0914; found: 263.0905 $[M+H]^+$.

Compound 3k: The enantiomeric excess was determined by HPLC on Daicel Chiralpak As with isohexanes/*i*PrOH 90:10 as the eluent: t_R major isomer = 40.857 min; t_R minor isomer = 51.317 min; $[\alpha]_D^{25}$ = −109.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 6.8 Hz, 3H), 3.82 (s, 3H), 4.13 (dq, *J* = 6.8, 3.2 Hz, 2H), 5.81 (s, 1H), 6.54–6.58 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.30 (s, 1H), 9.57 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 55.7, 61.9, 70.8, 101.9, 109.9, 113.0, 127.0, 131.0, 141.2, 157.0, 164.7, 169.0, 188.6 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{15}O_5$: 263.0914; found: 263.0904 $[M+H]^+$.

Compound 3l: The enantiomeric excess was determined by HPLC on Daicel Chiralpak ODH with isohexanes/*i*PrOH 85:15 as the eluent: t_R minor isomer = 35.808 min; t_R major isomer = 44.380 min; $[\alpha]_D^{25}$ = −225.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.2 Hz, 3H), 3.87 (s, 3H), 4.03–4.12 (m, 2H), 5.85 (s, 1H), 6.82–6.84 (m, 1H), 6.88–6.96 (m, 2H), 7.30 (s, 1H), 9.59 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 56.4, 61.8, 70.4, 116.5, 120.4, 121.4, 122.3, 129.9, 140.8, 144.2, 148.3, 168.5, 188.7 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{15}O_5$: 263.0914; found: 263.0920 $[M+H]^+$.

Compound 3m: The enantiomeric excess was determined by HPLC with an ODH column (*n*-hexane/*i*PrOH 95:5, λ = 254 nm), 1 mL min^{-1}; t_R minor enantiomer = 22.1 min, t_R major enantiomer = 23.9 min; $[\alpha]_D$ = −144.3 (*c* = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 5.4 Hz, 3H), 4.54 (m, 2H), 5.89 (s, 1H), 6.94 (m, 1H), 7.05 (m, 1H), 7.16 (ddd, *J* = 12.0, 8.3, 1.6 Hz, 1H), 7.36 (d, 1H), 9.66 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 13.9, 62.0, 70.5, 120.4 (d, *J* = 17.6 Hz), 121.8 (d, *J* = 1.9 Hz), 122.3 (d, *J* = 6.6 Hz), 124.7 (d, *J* = 3.6 Hz), 130.8, 139.6 (d, *J* = 4.0 Hz), 142.7 (d, *J* = 11.6 Hz), 151.1 (d, *J* = 247.4 Hz), 168.1, 188.5 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{12}FO_4$: 251.0714; found: 251.0723 $[M+H]^+$.

Compound 3n: The enantiomeric excess was determined by HPLC with an AD column (*n*-hexane/*i*PrOH 95:5, $\lambda = 254$ nm), 1 mL min^{-1}; t_R minor enantiomer = 15.2 min; t_R major enantiomer = 17.9 min; $[\alpha]_D = -111.2$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.19$ (t, $J = 7.2$ Hz, 3H), 2.29 (s, 3H), 4.13 (m, 2H), 5.79 (s, 1H), 6.94 (d, $J = 8.5$ Hz, 1H), 7.04 (d, $J = 2.1$ Hz, 1H), 7.16 (dd, $J = 8.5$, 2.1 Hz, 1H), 7.30 (s, 1H), 9.63 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 13.9, 20.4, 61.7, 70.3, 116.7, 119.4, 129.7, 129.9, 131.9, 134.6, 141.0, 152.8, 168.8, 188.8 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{12}H_{15}O_4$: 247.0965; found: 247.0962 $[M+H]^+$.

Compound 3o: The enantiomeric excess was determined by HPLC with an ODH column (*n*-hexane/*i*PrOH 99:1, $\lambda = 254$ nm), 0.5 mL min^{-1}; t_R minor enantiomer = 54.8 min; t_R major enantiomer = 59.6 min; $[\alpha]_D = -190.0$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.19$ (t, $J = 7.1$ Hz, 3H), 2.31 (s, 3H), 4.12 (m, 2H), 5.86 (s, 1H), 6.91 (t, $J = 7.7$ Hz, 1H), 7.09 (d, $J = 7.7$ Hz, 1H), 7.22 (d, $J = 7.7$, Hz, 1H), 7.34 (s, 1H), 9.65 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 15.5, 61.7, 70.3, 119.3, 122.0, 126.8, 127.2, 129.9, 135.0, 141.2, 153.0, 168.8, 188.8 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{12}H_{15}O_4$: 247.0965; found: 247.0959 $[M+H]^+$.

Compound 3p: The enantiomeric excess was determined by HPLC with an ODH column (*n*-hexane/*i*PrOH 99:1, $\lambda = 254$ nm), 1 mL min^{-1}; t_R minor enantiomer = 52.4 min; t_R major enantiomer = 59.8 min; $[\alpha]_D = 25.7$ (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$ (t, $J = 1.9$ Hz, 3H), 4.12 (m, 2H), 5.97 (s, 1H), 7.28 (d, $J = 9.3$ Hz, 1H), 7.44 (ddd, $J = 9.2$, 7.0, 1.1 Hz, 1H), 7.60 (ddd, $J = 9.8$, 7.0, 1.3 Hz, 1H), 7.80 (d, $J = 8.2$ Hz, 1H), 7.89 (d, $J = 8.8$ Hz, 1H), 8.02 (d, $J = 7.39$ Hz, 1H), 7.03 (s, 1H), 9.77 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 13.9, 61.9, 70.2, 113.2, 117.8, 121.1, 124.9, 127.9, 128.2, 129.0, 129.6, 130.6, 134.8, 136.8, 154.8, 168.8, 188.6 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{17}H_{15}O_4$: 283.0965; found: 283.0975 $[M+H]^+$.

Compound 3q: The enantiomeric excess was determined by HPLC with a Kromasil KR100–5CHI-DMB column (hexane/*i*PrOH 95:5, $\lambda =$ 250 nm), 0.25 mL min^{-1}; t_R minor enantiomer = 36.3 min; t_R major enantiomer = 38.4 min; $[\alpha]_D = +7.1$ ($c = 1.7$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.77$ (s, 3H), 6.30 (s, 1H), 6.77 (d, $J = 2.8$ Hz, 1H), 6.82 (d, $J = 8.8$ Hz, 1H), 6.87 (dd, $J = 9.3$, 3.1 Hz, 1H), 7.25–7.27 (m, 3H), 7.33–7.36 (m, 3H), 9.65 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 55.9, 74.0, 113.1, 118.1, 120.0, 120.5, 126.9, 128.6, 128.7, 134.5, 139.0, 141.0, 148.9, 154.4, 190.1 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{17}H_{15}O_3$: 267.1021; found: 267.1022 $[M+H]^+$.

Typical experimental procedure for the conversion of chromene-3-carbaldehydes 3 into the corresponding carboxylic acids 5: NaH_2PO_4 (1.5 mmol), 2-methylbut-2-ene (6 mmol), and $NaClO_2$ (3 mmol) were added successively to a stirred solution of the chromene-3-carbaldehyde (1.0 mmol) in *t*BuOH/H_2O 5:1 (10 mL). The resulting mixture was stirred for 16 h, the solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate, washed with water and brine, and dried with Na_2SO_4. Subsequent filtration, concentration, and purification by silica gel column chromatography (EtOAc/pentane mixtures) gave the pure carboxylic acids **5**.

Compound 5b: $[\alpha]_D = -70.6$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.33$ (s, 1H), 6.86 (d, $J = 8.3$ Hz, 1H), 6.96 (dt, $J = 7.4$, 1.0 Hz, 1H), 7.23 (dd, $J = 7.7$, 1.6 Hz, 1H), 7.28 (dt, $J = 7.9$, 1.6 Hz, 1H), 7.56 (d, $J = 8.8$ Hz, 2H), 7.82 (s, 1H), 8.14 ppm (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 74.0, 117.2, 119.9, 122.5, 122.6, 124.1, 128.2, 129.8, 133.8, 136.9, 146.2, 148.3 153.7, 170.0 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{12}NO_5$: 298.0715; found: 298.0720 $[M+H]^+$.

Compound 5g: $[\alpha]_D = -121.1$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.21$ (t, $J = 7.1$ Hz, 3H), 1.13–1.21 (m, 2H), 5.78 (s, 1H), 6.98 (dt, $J = 7.5$, 1.1 Hz, 1H), 7.03 (d, $J = 8.3$ Hz, 1H), 7.22 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.32 (t, $J = 8.9$ Hz, 1H), 7.67 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 62.1, 71.6, 116.9, 119.8, 120.4, 122.7, 129.8, 133.4, 136.3, 154.4, 169.3 170.0 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{13}O_5$: 249.0763; found: 249.0765 $[M+H]^+$.

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[11] CCDC-602109 contains the supplementary crystallographic data for this paper. 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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