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N-heterocyclic carbene-catalyzed [4 + 2] cycloaddition of ketenes and 3-aroylcoumarins: highly enantioselective synthesis of dihydrocoumarin-fused dihydropyranones†

Teng-Yue Jian, Xiang-Yu Chen, Li-Hui Sun and Song Ye*

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The *N*-heterocyclic carbene-catalyzed [4 + 2] cyclization of ketenes and 3-aroylcoumarins has been developed to give the corresponding dihydrocoumarin-fused multisubstituted dihydropyranones in high yield with good diastereoselectivity and high enantioselectivity.

Introduction

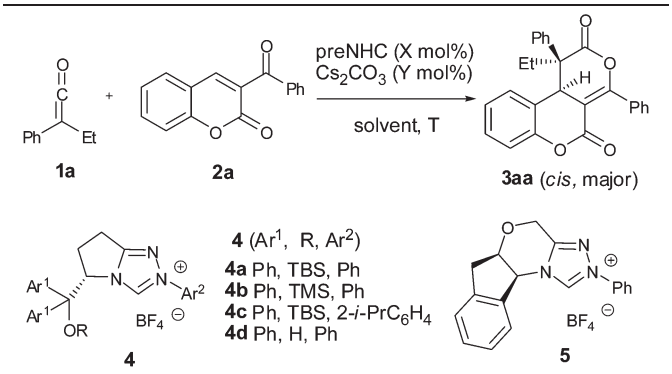
Compounds with two or more heterocycles fused play a vital role in natural and unnatural bioactive compounds.[1] Coumarins are present in large quantities in human diets and, more importantly, they are the active molecules in many traditional herbal medicines.[2] Thus the synthesis of coumarin and its derivatives attracts intensive attention.[3] In this paper, we wish to report an *N*-heterocyclic carbene-catalyzed cycloaddition reaction of ketenes with aroylcoumarins for the construction of dihydrocoumarin-fused dihydropyranones.

Since Staudinger's discovery of ketenes in the early 1900s,[4] their cycloaddition reactions have become a powerful methodology for the construction of cyclic compounds.[5,6] Over the past decades, *N*-heterocyclic carbene (NHC) catalysis has been very successful for a variety of reactions.[7] We,[8] independently with Smith *et al.*,[9] demonstrated that *N*-heterocyclic carbenes (NHCs) were efficient catalysts for the formal cycloaddition reactions of ketenes. In 2008 and later, we reported the NHC-catalyzed enantioselective [4 + 2] cycloaddition of ketenes with activated enones, giving the corresponding dihydropyranones in good yield with high enantioselectivity.[10] We envisaged that 3-aroylcoumarin may act as the oxodiene for the NHC-catalyzed [4 + 2] cycloaddition of ketenes, and thus provide a facile enantioselective access to coumarin-fused dihydropyranones.

Results and discussion

Initially, the reaction of phenyl(ethyl)ketene (**1a**) and 3-benzoyl-2*H*-chromen-2-one (**2a**) was investigated under NHC catalysis (Table 1). We were encouraged to find that the

Table 1 Screening of NHC catalysts and optimization of reaction conditions



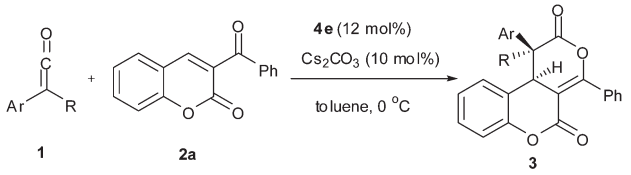
Entry	**4–5** (X)[a]	Cs_2CO_3 (Y)	Solvent	*T* (°C)	Yield[b] (%)	ee[c] (%)	dr[e]
1	**4a** (10)	20	DCM	rt	49	29[d]	8 : 1
2	**4b** (10)	20	DCM	rt	77	6[d]	6 : 1
3	**4c** (10)	20	DCM	rt	82	18[d]	7 : 1
4	**4d** (10)	20	DCM	rt	81	80	10 : 1
5	**5** (10)	20	DCM	rt	88	67	8 : 1
6	**4d** (10)	20	THF	rt	67	10	8 : 1
7	**4d** (10)	20	Toluene	rt	89	87	8 : 1
8	**4d** (10)	20	Toluene	0 °C	91	83	10 : 1
9	**4d** (12)	10	Toluene	0 °C	87	91	12 : 1

[a] NHC **4′–5′** was generated from its precursor **4–5** (10–12 mol%) in the presence of Cs_2CO_3 (10–20 mol%) in the noted solvent at room temperature for 30 min. [b] Isolated yield of pure *cis*-**3aa**. [c] Determined by HPLC. [d] *ent*-**3aa** was isolated as the major enantiomer for entries 1–3. [e] Determined by ^{1}H NMR (300 MHz) of the reaction mixture.

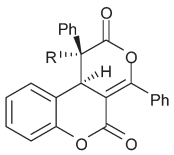
Beijing National Laboratory for Molecular Sciences, Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China. E-mail: songye@iccas.ac.cn; Fax: (+86) 10 6255 4449; Tel: (+86) 10 6264 1156

†Electronic supplementary information (ESI) available. CCDC 901312. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26804c

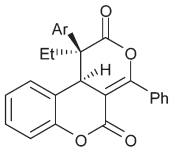
Table 2 Variation of ketenes



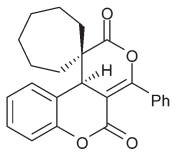
Isolated yield and ee of pure major diastereomer, followed by dr of the reaction mixture



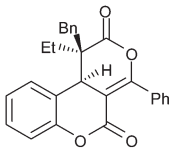
3aa (R = Et): 87% yield, 91% ee, 12:1 dr
3ba (R = Me): 85% yield, 87% ee, 8:1 dr
3ca (R = n-Pr): 87% yield, 91% ee, 9:1 dr
3da (R = i-Bu): 78% yield, 70% ee, 11:1 dr



3ea (Ar = 4-BrC_6H_4): 87% yield, 91% ee, 10:1 dr
3fa (Ar = 4-ClC_6H_4): 87% yield, 90% ee, 10:1 dr
3ga (Ar = 4-MeC_6H_4): 77% yield, 66% ee, 10:1 dr
3ha (Ar = 2-ClC_6H_4), trace

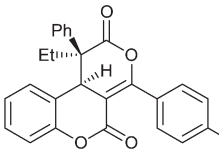


3ia: 83% yield, 98% ee

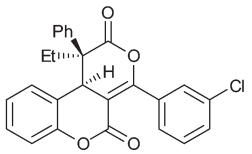


3ja: 76% yield, 50% ee, 2:1 dr

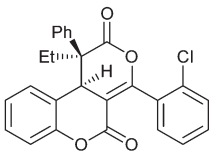
Table 3 Variation of 3-aroylcoumarins[a]



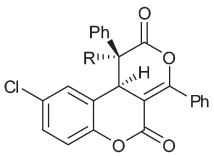
3ab (Y = Me): 87% yield, 87% ee, 10:1 dr
3ac (Y = Br): 87% yield, 80% ee, 13:1 dr
3ad (Y = Cl): 89% yield, 87% ee, 11:1 dr



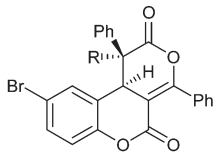
3ae: 86% yield, 66% ee, 10:1 dr



3af: 81% yield, 42% ee, > 20:1 dr



3ag: 87% yield, 91% ee, 11:1 dr



3ah: 85% yield, 82% ee, 12:1 dr

[a] Reaction conditions as Table 2.

desired [4 + 2] cycloadduct **3aa** was isolated in 49% yield with 29% ee and 8 : 1 dr in the presence of 10 mol% NHC **4a′**,[8a,11] generated from L-pyroglutamic acid derived triazolium salt **4a** and 20 mol% of Cs_2CO_3 (entry 1). NHC **4b′** with a less bulky TMS group and NHC **4c′** with a bulky *N*-(2-isopropyl)phenyl group resulted in better yields but decreased enantioselectivity (entries 2 and 3). NHC **4d′** with a free hydroxyl group[12] led to a reversed but high enantioselectivity (80% ee) for this reaction (entry 4). Tetracyclic NHC **5′**, derived from aminoindanol, also worked well in the reaction, giving the cycloadduct **3aa** in 88% yield with 67% ee and 8 : 1 dr (entry 5).

Solvent screening revealed that the reaction performed better in toluene than in DCM or THF in terms of enantioselectivity (87% ee *vs.* 80% ee or 10% ee, entries 4, 6–7). Lowering the reaction temperature to 0 °C benefits the yield but with decreased enantioselectivity (entry 8). Careful examination revealed that excess Cs_2CO_3 could also promote the reaction, giving the cycloadduct as a racemate. Thus the reaction employing 10 mol% of Cs_2CO_3 and 12 mol% triazolium NHC precursor **4d** resulted in an improved enantioselectivity (91% ee) and diastereoselectivity (12 : 1 dr) (entry 9).

With the optimized reaction condition in hand, the reaction scope was then briefly investigated (Table 2). It was found that aryl(alkyl)ketenes with ethyl, methyl and *n*-propyl all worked well to give the corresponding cycloadduct (**3aa**, **3ba** and **3ca**) in high yield with high enantioselectivity and diastereoselectivity. However, ketenes with a bulky isobutyl group resulted in decreased yield and enantioselectivity (**3da**). Electron-withdrawing substituents (4-Br, 4-ClC_6H_4) are well tolerated, giving cycloadducts (**3ea** and **3fa**) in high yield with high enantioselectivity, while an electron-donating group (4-MeC_6H_4) led to some loss of yield and enantioselectivity (**3ga**). It should be noted that reaction of ketene containing an *o*-chlorophenyl group gave only a trace of cycloaddduct (**3ha**). Interestingly, ketene **1i** derived from cycloheptanecarbonyl chloride worked very well, giving the desired cycloadduct **3ia** in 83% yield with 98% ee, while benzyl(ethyl)ketene (**1j**) resulted in decreased yield and low diastereo- and enantioselectivity (**3ja**).

Several 3-aroylcoumarins were also tested for the reaction (Table 3). Both an electron-donating group (4-MeC_6H_4) and electron-withdrawing groups (4-BrC_6H_4, 4-ClC_6H_4) on the aroyl are tolerated, giving the desired cycloadduct in high yield with good diastereo- and enantioselectivity (**3ab**, **3ac** and **3ad**). However, aroyl groups with *meta*- or *ortho*-substituents (3-ClC_6H_4, 2-ClC_6H_4) led to decreased enantioselectivity albeit in high yield and good to high diastereoselectivity (**3ae** and **3af**). 6-Halocoumarin derivatives (X = Cl, Br) also worked as well as the parent one (**3ag** and **3ah**).

The absolute stereochemistry of cycloadduct (+)-**3fa** was unambiguous established by the X-ray analysis† of its crystal (Fig. 1),[13] and that of all other cycloadducts is proposed by analogy. The crystal of (+)-**3fa** was prepared from a solution in DCM–ether (90 : 10) with a trace of petroleum ether.

Based on the dramatic effect of the free hydroxyl group of the NHC catalyst, and the diastereo- and enantioselectivity observed,[14] a likely transition state is proposed as in Fig. 2. The enolate generated by addition of the NHC to ketene favors its *Z*-isomer, which minimizes the steric repulsion. The hydrogen-bonding between the hydroxy group of the NHC–ketene adduct and aroyl group of the coumarin derivative directs the

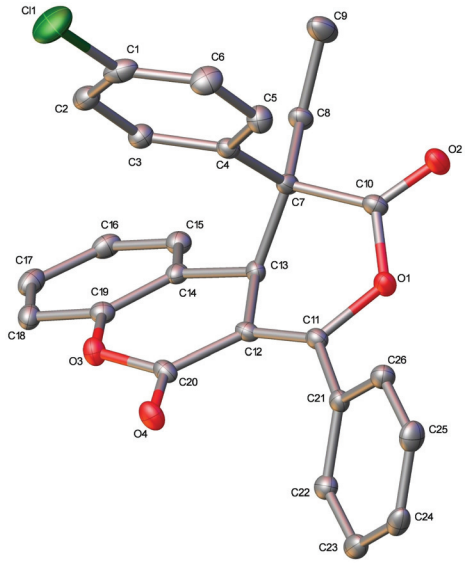


Fig. 1 X-ray structure of cycloadduct (+)-**3fa**.

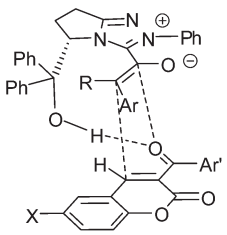


Fig. 2 Proposed model for stereochemical outcome.

facial selectivity. The *endo* transition state of the Diels–Alder reaction is favored and results in the *cis*-cycloadduct observed.

Conclusions

In summary, *N*-heterocyclic carbenes were found to be efficient catalysts for the [4 + 2] cycloaddition of ketenes and 3-aroylcoumarins. When the NHC derived from L-pyroglutamic acid and featuring a free hydroxyl group was used as the catalyst, the desired dihydrocoumarin-fused dihydropyranones were obtained in high yield with good to high diastereo- and enantioselectivity.

Experimental

Typical procedure for NHC-catalyzed [4 + 2] cycloaddition of ketenes with 3-aroylcoumarins

An oven-dried 50 mL Schlenk tube equipped with a stir bar was charged with triazolium salt **4d** (27.3 mg, 0.06 mmol) and anhydrous Cs_2CO_3 (17 mg, 0.05 mmol). This tube was closed with a septum, evacuated, and back-filled with argon. To this mixture was added freshly distilled toluene (5 mL) and stirred for 30 min at room temperature. After stirring for 10 min at 0 °C, ketene **1a** (146 mg, 1 mmol) and 3-aroylcoumarin **2a** (125 mg, 0.5 mmol) were added. After stirring for 24 h, the reaction mixture was diluted with diethyl ether and passed through a short silica pad. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (ethyl acetate–petroleum ether, typically 1 : 100) to give the desired product.

Racemic samples for the standard of chiral HPLC spectra were prepared using 2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*]-[1,2,4]triazolium chloride as the catalyst.

(*1S,10bS*)-1-Ethyl-1,4-diphenyl-1,10*b*-dihydropyrano[3,4-*c*]chromene-2,5-dione (**3aa**). Yield: 172.4 mg (87%), white solid, mp 130–132 °C, R_f = 0.67 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +158.4 (*c* 1.2, $CHCl_3$), HPLC analysis: 91% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 90 : 10, 1.0 mL min^{-1}, 254 nm, 16.3 min (major), 25.9 min (minor)]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.42 (*m*, 3H), 7.40–7.37 (*m*, 4H), 7.25–7.24 (*m*, 1H), 7.19–7.02 (*m*, 3H), 7.04 (*d*, *J* = 8.1 Hz, 1H), 6.73 (*dd*, *J* = 6.6 Hz, *J* = 1.8 Hz, 2H), 4.67 (*s*, 1H), 2.40–2.32 (*m*, 2H), 1.20 (*t*, *J* = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.0, 164.0, 158.1, 151.7, 136.5, 131.6, 131.4, 130.0, 129.9, 129.4, 128.9, 128.3, 127.9, 126.0, 124.1, 117.1, 116.8, 104.1, 56.5, 40.2, 29.6, 10.2. IR (KBr) ν 3044, 1951, 1774, 1612, 1321, 785, 515, 468. HRMS (EI) *m*/*z*: M^+ Calc. for $C_{26}H_{20}O_4$, 396.1362, Found 396.1366.

(*1S,10bS*)-1-Methyl-1,4-diphenyl-1,10*b*-dihydropyrano[3,4-*c*]chromene-2,5-dione (**3ba**). Yield: 161.4 mg (85%), white solid, mp 90–92 °C, R_f = 0.56 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +167.3 (*c* 1.0, $CHCl_3$), HPLC analysis: 87% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 90 : 10, 1.0 mL min^{-1}, 254 nm, 12.3 min (major), 19.4 min (minor)]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.45 (*m*, 1H), 7.42–7.27 (*m*, 6H), 7.25–7.21 (*m*, 1H), 7.20–7.17 (*m*, 3H), 7.0–7.06 (*m*, 1H), 6.81–6.77 (*m*, 2H), 4.53 (*s*, 1H), 1.94 (*s*, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.8, 164.2, 157.9, 151.5, 137.4, 131.5, 131.3, 130.1, 129.8, 129.4, 129.0, 128.3, 127.9, 125.5, 124.1, 117.7, 116.7, 104.5, 52.0, 42.6, 25.0. IR (KBr) ν 3024, 1855, 1774, 1642, 1221, 775, 550, 468. HRMS (EI) *m*/*z*: M^+ Calc. for $C_{25}H_{18}O_4$, 382.1205, Found 382.1212.

(*1S,10bS*)-1,4-Diphenyl-1-propyl-1,10*b*-dihydropyrano[3,4-*c*]chromene-2,5-dione (**3ca**). Yield: 178.1 mg (87%), white solid, mp 122–124 °C, R_f = 0.70 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +241 (*c* 1.5, $CHCl_3$), HPLC analysis: 91% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 85 : 15, 1.0 mL min^{-1}, 254 nm, 11.5 min (major), 15.9 min (minor)]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.40 (*m*, 7H), 7.38–7.15 (*m*, 4H), 7.05 (*d*, *J* = 8.1 Hz, 1H), 6.74 (*d*, *J* = 6.0 Hz, 2H), 4.66 (*s*, 1H), 2.35 (*t*, *J* = 8.7 Hz, 2H), 1.96–1.86 (*m*, 1H), 1.36–1.23 (*m*, 1H), 1.02 (*t*, *J* = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.1, 164.0, 158.1, 151.6, 136.6, 131.6, 131.4, 130.0, 129.8, 129.3, 128.8, 128.2, 127.9, 125.9, 124.1, 117.7, 116.8, 104.1, 56.1, 40.5, 38.9, 18.7, 14.4. IR (KBr) ν 3030, 1961, 1834, 1644, 1331, 765, 545, 455. HRMS (EI) *m*/*z*: M^+ Calc. for $C_{27}H_{22}O_4$, 410.1518, Found 410.1523.

(*1S,10bS*)-1-Isobutyl-1,4-diphenyl-1,10*b*-dihydropyrano[3,4-*c*]chromene-2,5-dione (**3da**). Yield: 166.7 mg (78%), white solid, mp

121–123 °C, R_f = 0.40 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +241.3 (*c* 1.0, $CHCl_3$), HPLC analysis: 70% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 85 : 15, 1.0 mL min^{-1}, 254 nm, 10.2 min (major), 15.5 min (minor)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.35 (*m*, 7H), 7.26–7.20 (*m*, 4H), 7.10 (*d*, *J* = 8.7 Hz, 1H), 6.94–6.91 (*m*, 2H), 4.58 (*s*, 1H), 2.30–2.17 (*m*, 2H), 2.04–1.95 (*m*, 1H), 1.09 (*d*, *J* = 7.5 Hz, 3H), 0.33 (*d*, *J* = 6.6 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.4, 164.0, 158.5, 151.5, 136.1, 131.5, 131.3, 130.1, 130.0, 129.7, 128.9, 128.4, 127.9, 126.6, 124.0, 117.7, 117.2, 104.1, 54.8, 45.7, 42.3, 25.9, 25.5, 23.6. IR (KBr) ν 3030, 1871, 1674, 1512, 1221, 780, 535. HRMS (EI) *m*/*z*: M^+ Calc. for $C_{28}H_{24}O_4$, 424.1675, Found 424.1682.

(*1S,10bS*)-1-(4-Bromophenyl)-1-ethyl-4-phenyl-1,10*b*-dihydropyrano-[3,4-*c*]chromene-2,5-dione (**3ea**). Yield: 206.4 mg (87%), white solid, mp 140–141 °C, R_f = 0.65 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +231.4 (*c* 1.5, $CHCl_3$), HPLC analysis: 91% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 90 : 10, 1.0 mL min^{-1}, 254 nm, 15.6 min (major), 18.9 min (minor)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.38 (*m*, 7H), 7.32–7.20 (*m*, 3H), 7.05 (*d*, *J* = 7.8 Hz, 1H), 6.61 (*d*, *J* = 5.7 Hz, 2H), 4.67 (*s*, 1H), 2.37–2.29 (*m*, 2H), 1.19 (*t*, *J* = 6.9 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.5, 164.0, 158.0, 151.65, 135.6, 132.0, 131.6, 131.3, 130.2, 129.9, 129.3, 128.0, 127.7, 124.3, 122.5, 117.8, 116.4, 103.9, 56.2, 39.9, 29.6, 10.1. IR (KBr) ν 2980, 1836, 1658, 1556, 1262, 755. HRMS (EI) *m*/*z*: M^+ Calc. for $C_{26}H_{19}Br^{79}O_4$, 474.0467, Found 474.0475, M^+ Calc. for $C_{26}H_{19}Br^{81}O_4$, 476.0446, Found 474.0443.

(*1S,10bS*)-1-(4-Chlorophenyl)-1-ethyl-4-phenyl-1,10*b*-dihydropyrano-[3,4-*c*]chromene-2,5-dione (**3fa**). Yield: 187.2 mg (87%), white solid, mp 119–122 °C, R_f = 0.70 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +211.3 (*c* 1.4, $CHCl_3$), HPLC analysis: 90% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 90 : 10, 1.0 mL min^{-1}, 254 nm, 8.6 min (major), 10.7 min (minor)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.51 (*m*, 2H), 7.50–7.48 (*m*, 2H), 7.44–7.39 (*m*, 3H), 7.27–7.22 (*m*, 1H), 7.16 (*d*, *J* = 8.7 Hz, 2H), 7.06 (*d*, *J* = 8.1 Hz, 1H), 6.68 (*d*, *J* = 8.7 Hz, 2H), 4.67 (*s*, 1H), 2.38–2.29 (*m*, 2H), 1.20 (*t*, *J* = 6.9 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.6, 164.0, 158.1, 151.6, 135.1, 134.3, 131.6, 131.4, 130.2, 129.9, 129.4, 129.1, 128.0, 127.4, 124.3, 117.8, 116.4, 103.9, 56.1, 40.0, 29.7, 10.1. IR (KBr) ν 3010, 1856, 1648, 1556, 1262, 775. HRMS (EI) *m*/*z*: M^+ Calc. for $C_{26}H_{19}ClO_4$, 430.0972, Found 430.0979.

(*1S,10bS*)-1-Ethyl-4-phenyl-1-*p*-tolyl-1,10*b*-dihydropyrano[3,4-*c*]-chromene-2,5-dione (**3ga**). Yield: 157.2 mg (77%), white solid, mp 121–123 °C, R_f = 0.60 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +153.3 (*c* 1.1, $CHCl_3$), HPLC analysis: 66% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 85 : 15, 1.0 mL min^{-1}, 254 nm, 14.9 min (major), 18.5 min (minor)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.37 (*m*, 8H), 7.25–7.23 (*m*, 1H), 7.05–6.95 (*m*, 2H), 6.61 (*d*, *J* = 7.5 Hz, 2H), 4.64 (*s*, 1H), 2.35–2.30 (*m*, 2H), 2.22 (*s*, 3H), 1.19 (*t*, *J* = 6.9 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.3, 164.1, 158.4, 151.8, 138.1, 133.5, 131.8, 131.5, 130.0, 129.7, 129.5, 128.0, 126.0, 124.2, 117.8, 117.0, 104.2, 56.3, 40.3, 29.8, 21.1, 10.3. IR (KBr) ν 3026, 1851, 1674, 1512, 1221, 765, 565, 480. HRMS (EI) *m*/*z*: M^+ Calc. for $C_{27}H_{22}O_4$, 410.1518, Found 410.1523.

(*S*)4′-Phenyl-2′*H*-spiro[cycloheptane-1,1′-pyrano[3,4-*c*]chromene]-2′,5′(10*b*′*H*)-dione (**3ia**). Yield: 155.4 mg (83%), white solid, mp 95–97 °C, R_f = 0.50 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +142.1 (*c* 1.0, $CHCl_3$), HPLC analysis: 98% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 90 : 10, 1.0 mL min^{-1}, 254 nm, 16.9 min (major), 28.5 min (minor)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (*d*, *J* = 7.2 Hz, 2H), 7.50–7.32 (*m*, 5H), 7.16–7.09 (*m*, 2H), 4.27 (*s*, 1H), 2.32–2.24 (*m*, 1H), 2.04–2.02 (*m*, 1H), 2.02–2.00 (*m*, 1H), 1.80–1.08 (*m*, 8H), 0.87–0.85 (*m*, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.0, 160.0, 151.8, 131.7, 131.4, 130.2, 129.7, 129.5, 128.3, 127.9, 124.0, 117.7, 103.0, 49.2, 43.4, 34.8, 30.6, 30.5, 28.8, 24.8, 23.1. IR (KBr) ν 3030, 1816, 1658, 1356, 1262, 760. HRMS (EI) *m*/*z*: M^+ Calc. for $C_{24}H_{22}O_4$, 374.1518, Found 374.1526.

(*1R,10bS*)-1-Benzyl-1-ethyl-4-phenyl-1,10*b*-dihydropyrano[3,4-*c*]-chromene-2,5-dione (**3ja**). Yield: 155.1 mg (76%), white solid, mp 89–91 °C, R_f = 0.60 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +173.1 (*c* 1.0, $CHCl_3$), HPLC analysis: 48% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 85 : 15, 1.0 mL min^{-1}, 254 nm, 12.9 min (major), 15.4 min (minor)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (*d*, *J* = 7.2 Hz, 1H), 7.39 (*d*, *J* = 6.9 Hz, 2H), 7.40–7.09 (*m*, 10H), 7.02 (*d*, *J* = 7.8 Hz, 1H), 4.33 (*s*, 1H), 4.04 (*d*, *J* = 15.0 Hz, 1H), 3.11 (*d*, *J* = 15.3 Hz, 1H), 2.01–1.91 (*m*, 1H), 1.88–1.75 (*m*, 1H), 0.90 (*t*, *J* = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.3, 161.1, 160.9, 151.3, 135.9, 132.1, 131.1, 129.8, 129.3, 129.1, 128.8, 128.1, 127.9, 127.3, 124.1, 118.9, 118.1, 101.4, 49.6, 39.2, 37.0, 26.0, 8.7. IR (KBr) ν 2990, 1766, 1556, 1455, 1262, 779. HRMS (EI) *m*/*z*: M^+ Calc. for $C_{27}H_{22}O_4$, 410.1518, Found 410.1523.

(*1S,10bS*)-1-Ethyl-1-phenyl-4-*p*-tolyl-1,10*b*-dihydropyrano[3,4-*c*]-chromene-2,5-dione (**3ab**). Yield: 178.5 mg (87%), white solid, mp 95–97 °C, R_f = 0.61 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +256.4 (*c* 1.5, $CHCl_3$), HPLC analysis: 87% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 85 : 15, 1.0 mL min^{-1}, 254 nm, 12.3 min (major), 16.2 min (minor)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.46(*m*, 3H), 7.42–7.36 (*m*, 1H), 7.25–7.15 (*m*, 6H), 7.03 (*d*, *J* = 8.1 Hz, 1H), 6.71 (*d*, *J* = 6.6 Hz, 2H), 4.64 (*s*, 1H), 2.39–2.31 (*m*, 3H), 1.18 (*t*, *J* = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.2, 164.2, 158.3, 151.6, 142.2, 136.4, 130.0, 129.9, 129.4, 128.8, 128.6, 128.5, 128.2, 126.0, 124.0, 117.6, 116.8, 103.2, 56.8, 40.2, 29.5, 21.7, 10.1. IR (KBr) ν 3030, 1851, 1674, 1512, 1322, 775, 525, 458. HRMS (EI) *m*/*z*: M^+ Calc. for $C_{27}H_{22}O_4$, 410.1518, Found 410.1522.

(*1S,10bS*)-4-(4-Bromophenyl)-1-ethyl-1-phenyl-1,10*b*-dihydropyrano-[3,4-*c*]chromene-2,5-dione (**3ac**). Yield: 205.5 mg (87%), white solid, mp 127–129 °C, R_f = 0.61 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +163 (*c* 1.0, $CHCl_3$), HPLC analysis: 80% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 90 : 10, 1.0 mL min^{-1}, 254 nm, 15.2 min (major), 21.7 min (minor)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.48 (*m*, 3H), 7.43–7.37 (*m*, 3H), 7.27–7.16 (*m*, 4H), 7.04 (*d*, *J* = 8.1 Hz, 1H), 6.71 (*d*, *J* = 6.6 Hz, 2H), 4.64 (*s*, 1H), 2.39–2.31 (*m*, 3H), 1.18 (*t*, *J* = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.7, 162.7,

158.0, 151.5, 136.3, 131.4, 131.2, 130.3, 130.0, 129.4, 128.9, 128.3, 126.1, 125.9, 124.2, 117.7, 116.5, 104.6, 56.4, 40.2, 29.5, 10.1. IR (KBr) ν 3030, 1851, 1774, 1542, 1221, 785, 468. HRMS (EI) m/z: $C_{26}H_{19}Br^{79}O_4$, 474.0467, Found 474.0475, M^+ Calc. for $C_{26}H_{19}Br^{81}O_4$, 476.0446, Found 474.0443.

(*1S,10bS*)-4-(4-Chlorophenyl)-1-ethyl-1-phenyl-1,10*b*-dihydropyrano-[3,4-*c*]chromene-2,5-dione (**3ad**). Yield: 191.5 mg (89%), white solid, mp 127–129 °C, R_f = 0.62 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +189.7 (*c* 1.3, $CHCl_3$), HPLC analysis: 87% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 90 : 10, 1.0 mL min^{-1}, 254 nm, 16.2 min (major), 25.8 min (minor)]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.41 (*m*, 3H), 7.40–7.36 (*m*, 3H), 7.28–7.14 (*m*, 4H), 7.05 (*d*, *J* = 7.5 Hz, 1H), 6.71 (*d*, *J* = 6.6 Hz, 2H), 4.66 (*s*, 1H), 2.40–2.32 (*m*, 3H), 1.19 (*t*, *J* = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.8, 162.7, 158.1, 151.5, 137.7, 136.3, 131.3, 130.1, 130.2, 129.4, 128.9, 128.4, 128.3, 125.9, 124.3, 117.7, 116.6, 104.6, 56.5, 40.2, 29.6, 10.2. IR (KBr) ν 3040, 1851, 1674, 1512, 1221, 760, 545, 480. HRMS (EI) m/z: M^+ Calc. for $C_{26}H_{19}ClO_4$, 430.0972, Found 430.0979.

(*1S,10bS*)-4-(3-Chlorophenyl)-1-ethyl-1-phenyl-1,10*b*-dihydropyrano[3,4-*c*]chromene-2,5-dione (**3ae**). Yield: 184.5 mg (86%), white solid, mp 99–101 °C, R_f = 0.61 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +241.2 (*c* 1.5, $CHCl_3$), HPLC analysis: 66% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 85 : 15, 1.0 mL min^{-1}, 254 nm, 9.4 min (major), 13.4 min (minor)]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.46 (*m*, 3H), 7.44–7.36 (*m*, 3H), 7.28–7.14 (*m*, 4H), 7.05 (*d*, *J* = 8.7 Hz, 1H), 6.71 (*d*, *J* = 6.6 Hz, 2H), 4.65 (*s*, 1H), 2.40–2.31 (*m*, 2H), 1.19 (*t*, *J* = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.9, 162.8, 158.2, 151.6, 140.3, 137.8, 136.4, 131.5, 131.4, 130.2, 130.0, 129.5, 129.0, 128.5, 128.4, 126.0, 124.4, 117.8, 116.7, 104.7, 56.6, 40.3, 29.7, 10.3. IR (KBr) ν 3034, 1851, 1774, 1512, 1221, 790, 515, 468. HRMS (EI) m/z: M^+ Calc. for $C_{26}H_{19}ClO_4$, 430.0972, Found 430.0979.

(*1S,10bS*)-4-(2-Chlorophenyl)-1-ethyl-1-phenyl-1,10*b*-dihydropyrano[3,4-*c*]chromene-2,5-dione (**3af**). Yield: 174.1 mg (81%), white solid, mp 107–109 °C, R_f = 0.71 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +106.8 (*c* 1.0, $CHCl_3$), HPLC analysis: 42% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 85 : 15, 1.0 mL min^{-1}, 254 nm, 19.0 min (major), 22.4 min (minor)]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (*d*, *J* = 7.8 Hz, 1H), 7.43–7.28 (*m*, 3H), 7.27–7.23 (*m*, 5H), 7.08 (*d*, *J* = 5.1 Hz, 1H), 6.92–6.82 (*br*, 2H), 4.80 (*s*, 1H), 2.41–2.35 (*t*, *J* = 6.0 Hz, 3H), 1.25–1.23 (*br*, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.2, 159.9, 157.4, 151.6, 136.8, 133.7, 132.2, 131.2, 130.0, 129.7, 129.3, 128.9, 128.3, 127.9, 126.7, 126.2, 124.3, 116.7, 55.8, 38.8, 30.2, 10.3. IR (KBr) ν 3030, 1871, 1772, 1642, 1221, 780, 548, 468. HRMS (EI) m/z: M^+ Calc. for $C_{26}H_{19}ClO_4$, 430.0972, Found 430.0979.

(*1S,10bS*)-9-Chloro-1-ethyl-1,4-diphenyl-1,10*b*-dihydropyrano[3,4-*c*]chromene-2,5-dione (**3ag**). Yield: 187.5 mg (87%), white solid, mp 120–122 °C, R_f = 0.61 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +251.4 (*c* 1.5, $CHCl_3$), HPLC analysis: 91% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 90 : 10, 1.0 mL min^{-1}, 254 nm, 14.8 min (major), 19.0 min (minor)]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.48 (*m*, 4H), 7.47–7.31 (*m*, 3H), 7.25–7.18 (*m*, 3H), 6.99 (*d*, *J* = 8.7 Hz, 1H), 6.76–6.73 (*m*, 2H), 4.62 (*s*, 3H), 2.36 (*q*, *J* = 7.2 Hz, 2H), 1.20 (*t*, *J* = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.5, 164.5, 157.6, 150.2, 136.1, 131.6, 131.3, 130.1, 129.9, 129.2, 129.0, 128.95, 128.4, 127.9, 125.9, 119.0, 118.5, 103.1, 56.5, 40.2, 29.4, 10.1. IR (KBr) ν 3040, 1972, 1774, 1610, 1221, 780, 468. HRMS (EI) m/z: M^+ Calc. for $C_{26}H_{19}ClO_4$, 430.0972, Found 430.0979.

(*1S,10bS*)-9-Bromo-1-ethyl-1,4-diphenyl-1,10*b*-dihydropyrano[3,4-*c*]chromene-2,5-dione (**3ah**). Yield: 201.4 mg (85%), white solid, mp 131–133 °C, R_f = 0.60 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{25}$ +213.3 (*c* 1.0, $CHCl_3$), HPLC analysis: 82% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane–*i*-PrOH = 90 : 10, 1.0 mL min^{-1}, 254 nm, 16.1 min (major), 25.8 min (minor)]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (*s*, 1H), 7.61–7.34 (*m*, 6H), 7.25–7.17 (*m*, 3H), 6.93 (*d*, *J* = 8.7 Hz, 1H), 6.75 (*d*, *J* = 6.0 Hz, 2H), 4.61 (*s*, 1H), 2.35 (*q*, *J* = 6.9 Hz, 2H), 1.19 (*t*, *J* = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.5, 164.5, 157.5, 150.7, 136.0, 133.0, 132.0, 131.6, 131.3, 129.9, 128.9, 128.4, 127.9, 125.9, 119.4, 118.9, 116.5, 103.0, 56.4, 40.1, 29.4, 10.1. IR (KBr) ν 3030, 1816, 1658, 1556, 1462, 775. HRMS (EI) m/z: $C_{26}H_{19}Br^{79}O_4$, 474.0467, Found 474.0475, M^+ Calc. for $C_{26}H_{19}Br^{81}O_4$, 476.0466, Found 474.0460.

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