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Article

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Conjugate Addition of Carbon acids to *β,γ*-Unsaturated α-Keto Esters: Product Tautomerism and Application for Asymmetric Synthesis of Benzo[*a*]phenazin-5-ol Derivatives

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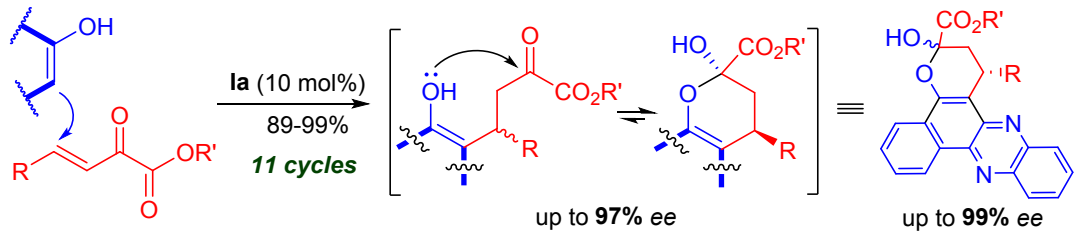


ABSTRACT: A correlation between the equilibrium ratio of tautomeric products generated by the asymmetric Michael reactions of cyclic carbon acids with *β,γ*-unsaturated *α*-keto esters and the chemical shift of the α-proton in starting nucleophilic substrates was revealed which makes equilibration predictable. New tetrahydropyran-fused benzo[*a*]phenazins were enantioselectively (up to 99% *ee*) synthesized from *β,γ*-unsaturated *α*-keto esters and benzo[*a*]phenazin-5-ol, a powerful anti-cancer agent sAJM589. Facile recyclability of catalyst **Ia** in the catalytic reactions was demonstrated.

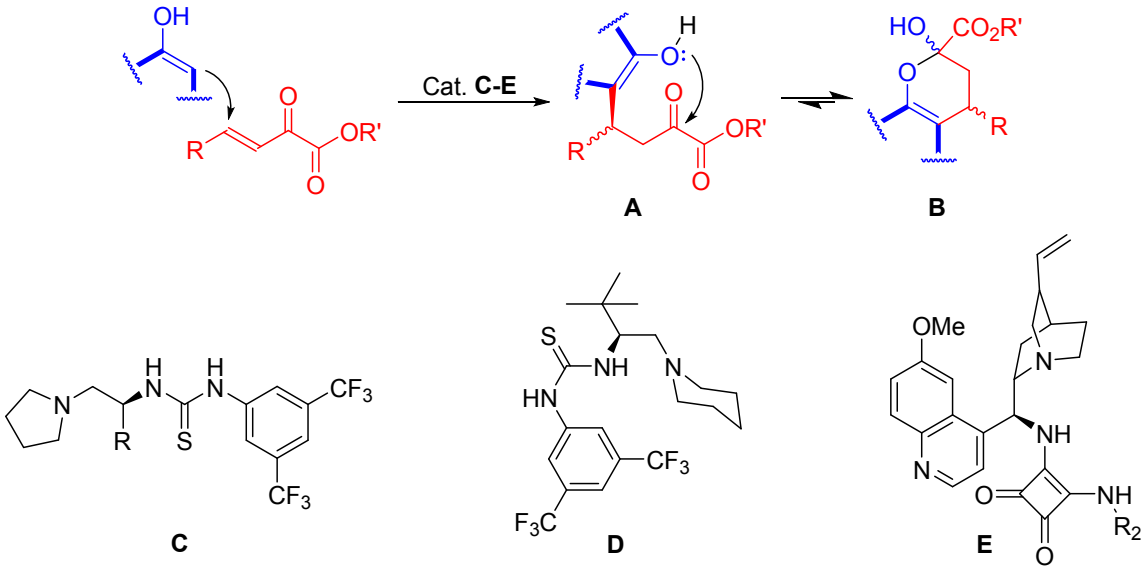
Introduction

The ring-chain tautomerism of organic compounds is of great significance in Nature and organic chemistry.[1] A classic example of this phenomena is the gradual interconversion of linear carbohydrates into their cyclic forms, which results in the change in the optical rotation (mutarotation).[2] The capability of linear γ– and δ–hydroxycarbonyl compounds to transform reversibly into cyclic hemiacetals or hemiketals enables a large scale production of useful heterocyclic compounds, such as furaldehyde,[3] chromanes, chromenes,[4] β-nicotinamide riboside and its analogues[5] etc.

The ring-chain tautomerism also occurs in some recently developed asymmetric reactions,[6] particularly, in bifunctional tertiary amine-catalyzed[7] asymmetric addition of 4-hydroxycoumarin to β,γ-unsaturated α-keto esters.[8] Regardless of the catalyst used (**C**, **D** or **E**), the reaction produces a mixture of linear Michael adducts **A** and fused tetrahydropyran derivatives **B**, bearing a quaternary stereogenic center (Scheme 1). The tetrahydropyran unit is found in numerous natural compounds and pharmaceuticals.[9] In some cases, heterocycles **B** were isolated and their structure was confirmed by the single-crystal X-ray analysis.[8a,c,10] However, the rate and stereoselectivity of the **A**/**B** equilibrium have not been examined to date that restricts application of the cascade process in the asymmetric synthesis of valuable heterocyclic products (for applications of asymmetric Michael reactions to enantioselective synthesis of pharmacology-relevant compounds see ref.[11]).

Herein we first investigated the correlation between the α-C-H bond polarization in nucleophilic substrates (^{1}H NMR data) and the **A** ↔ **B** equilibrium ratio in the corresponding reaction products and applied it for designing configurationally stable 2-hydroxytetrahydropyrans fused with benzo[*a*]phenazine, the key structural unit of powerful anti-cancer agent sAJM589.[12]

Scheme 1. The ring-chain tautomerism between compounds **A** and **B**

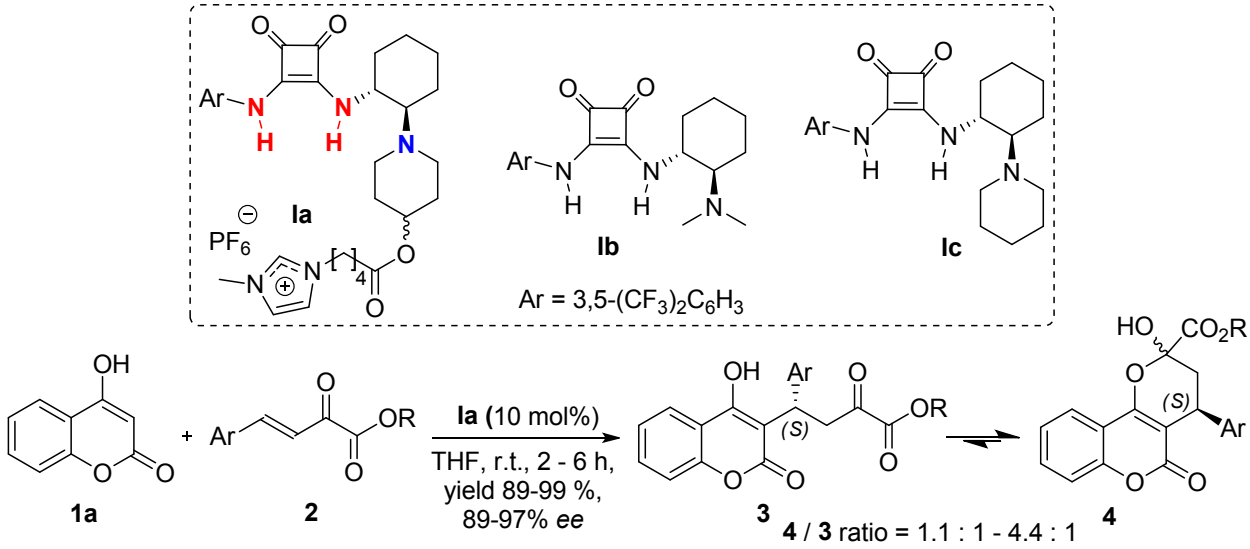


Results and Discussion

To evaluate the role of the acceptor component, we examined the reaction of 4-pydroxycoumarin **1a** with 2-oxo-4-arylbut-3-enoates **2** in the presence of bifunctional tertiary

amine – squaramide catalyst **Ia** modified with ionic group (THF, r.t.) (Scheme 2). This catalyst, recently developed by our research group,[13] exhibited better stereoinduction in the model reaction than similar catalysts[14] **Ib** and **Ic** without ionic groups and allowed asymmetric synthesis of the corresponding tautomeric products **3** and **4** in nearly quantitative yield with up to 97% *ee* (for experimental details, see Supporting Information). The equilibrium ratio between cyclic and linear components **4** / **3** in the raw adducts ranged from ~1.1 : 1 to ~3.2 : 1 being the highest for compounds **4h** / **3h** bearing 4-cyano group in the aromatic ring (^{1}H NMR data). Crystallization of an oily **4b** / **3b** mixture resulted in a crystalline cyclic tautomer **4b**. According to X-ray diffraction data, the key stereocenter in thus obtained crystals has the (*S*)-absolute configuration (Fig. 1). Similar (*S*)- configuration was assigned to the other products **4** / **3** by analogy.

Scheme 2. **Ia**-Catalyzed asymmetric reactions of **1a** with β,γ-unsaturated α-keto esters **2**



2-4: R = Me, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-F_3CC_6H_4 (**c**), 4-NCC_6H_4 (**d**), 2-Furyl (**e**), 2-Thienyl (**f**);
R = Et, Ar = 2-ClC_6H_4 (**g**), 2-NCC_6H_4 (**h**);
R = *i*-Pr, Ar = 4-MeC_6H_4 (**i**), 4-F_3CC_6H_4 (**j**), 4-NCC_6H_4 (**k**);
R = *t*-Bu, Ar = Ph (**l**)

Tautomeric equilibration between **4** and **3** proved to be a dynamic process. The ^{1}H NMR spectra of the crystalline compound **4b** recorded 5 min after dissolution in $CDCl_3$ exhibited only characteristic signals of the methyl protons of semi-ketal **4b** at 2.35 and 3.90 ppm (Fig. 1, line 1, red picks). However, in the ^{1}H NMR spectra of the same solution recorded 2 h after, the corresponding proton signals of linear adduct **3b** appeared at 2.34 and 3.94 ppm (line 2, blue picks) and their intensity gradually increased with the solution ageing time (lines 3 and 4, blue picks). The equilibrium ratio **4b** / **3b** ~2 : 1 was attained 16 h after dissolution of **4b** (line 5) and showed no further changes (line 6). Catalyst **Ia** exerted no influence on the tautomerization

process: similar ^{1}H NMR experiment with solution of **4b** in $CDCl_3$ in the presence of **Ia** (10 mol %) showed that **4b** / **3b** ratio was ~6 : 1 after 5 h and ~2.1 : 1 after 24 h. On the other hand, in more polar solvent (DMSO) the equilibrium ratio **4b** / **3b** ~2 : 1 was attained already 5 h after dissolution of **4b** (see SI). Crystalline product **4e** (was obtained by crystallization of the raw product **4e** / **3e**) in the $CDCl_3$ solution also gave equilibrium mixture of the two tautomers (~1 : 1) (see Experimental Section and in SI).

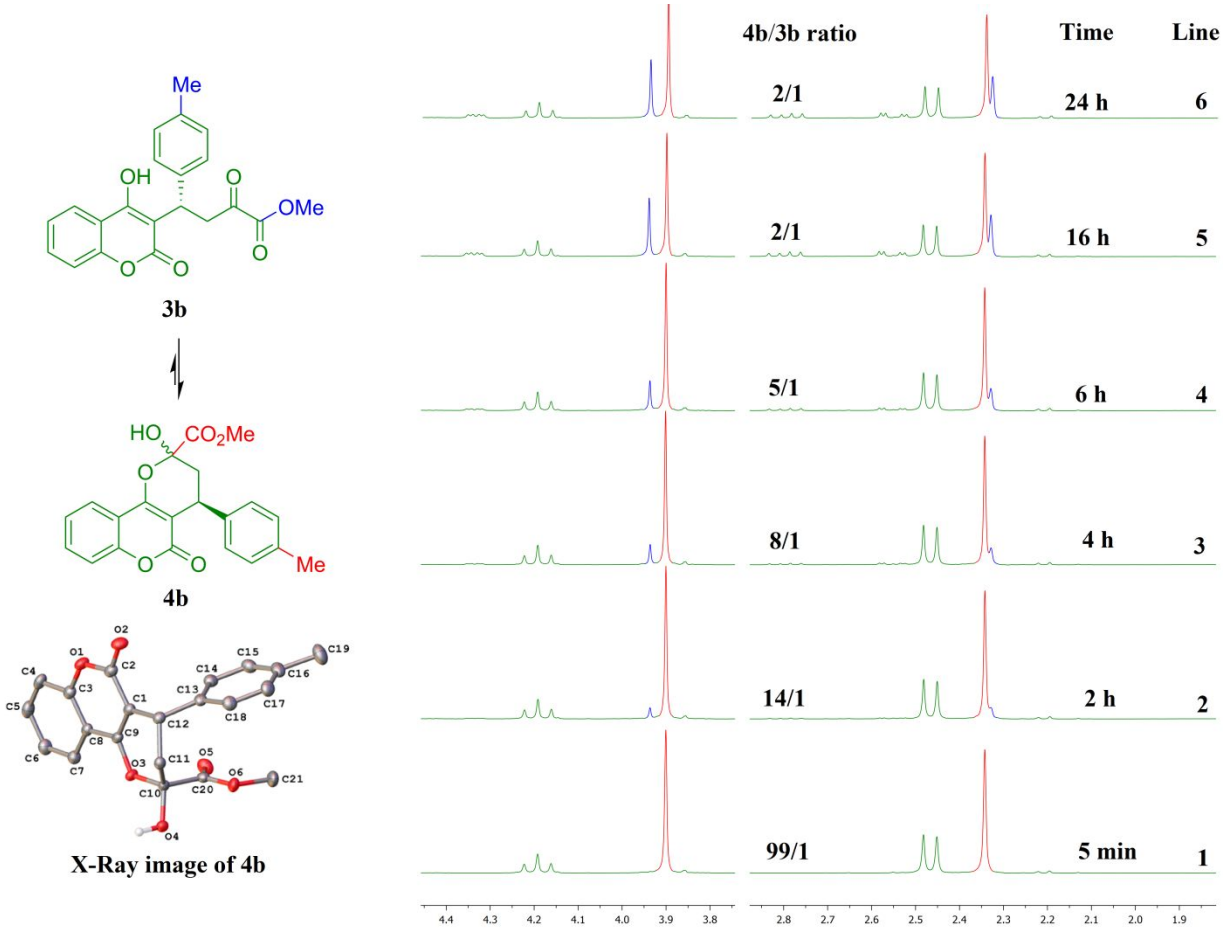
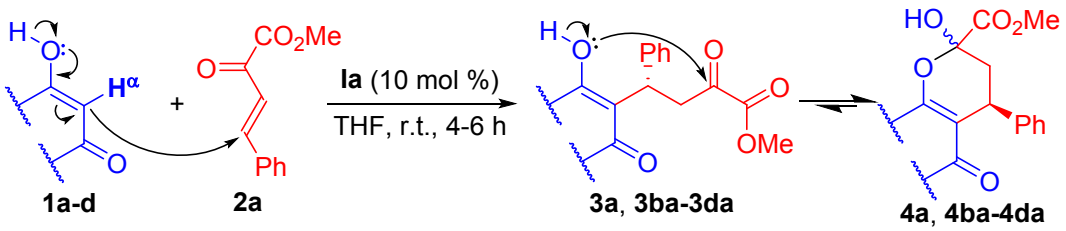


Figure 1. X-ray image of crystalline product **4b** and fragments of the ^{1}H NMR spectra of the $CDCl_3$ solution of **4b** recorded after specified times (characteristic signals of C*H*$_3$ protons in **4b** and **3b** are shown by red and blue lines, respectively).

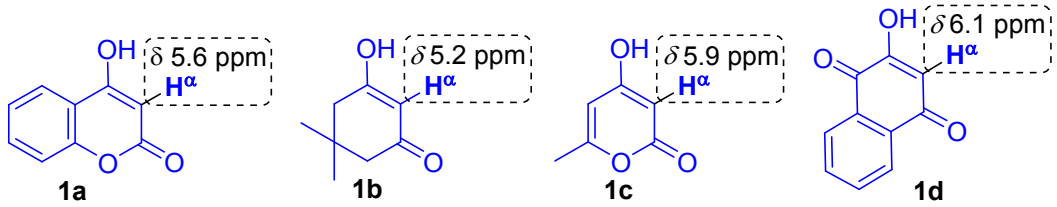
Then, to evaluate the impact of the donor counterpart, we studied the corresponding reactions of cyclic 1,3-dicarbonyl compounds **1b-d** with *β*,*γ*-unsaturated *α*-keto ester **2a** in the presence of catalyst **Ia**. The reactions afforded mixtures of cyclic (**4ba-4da**) and linear products (**3ba-3da**) in nearly quantitative yield and 90-97% *ee* (Scheme 3). We noticed that the larger the α-protone chemical shift (δH^{α}, ^{1}H NMR) in the corresponding substrates **1**, the higher the **4** / **3** ratio in the synthesized mixtures [1.7 : 1 for **4ba** / **3ba** ($\delta H^{\alpha}_{\mathbf{1b}}$ 5.2 ppm), 2.1 : 1 for **4a** / **3a** ($\delta H^{\alpha}_{\mathbf{1a}}$ 5.6 ppm), 3.4 : 1 for **4ca** / **3ca** ($\delta H^{\alpha}_{\mathbf{1c}}$ 5.9 ppm) and 4.4 : 1 for **4da** / **3da** ($\delta H^{\alpha}_{\mathbf{1d}}$ 6.1 ppm)]. Most likely, this range correlates with the polarity order of substrates **1** and Michael adducts **3**.

Apparently, the enhanced α-proton chemical shift reflects a higher electron-withdrawing ability of cyclic moiety in β-dicarbonyl compound **1a-d**. The latter leads in turn to increasing both nucleophilicity of the hydroxyl group and electrophilicyty of the carbonyl group in corresponding linear Michael adducts **3** which makes the ketalization step energetically more favorable (Scheme 3). Pure adduct **4da** was isolated from the equilibrium **4da** / **3da** mixture by crystallization (see Experimental Section and in SI).

Scheme 3. Asymmetric reactions of cyclic carbon acids **1a-d** with *β*,*γ*-unsaturated *α*-keto ester **2a** catalyzed by **Ia**



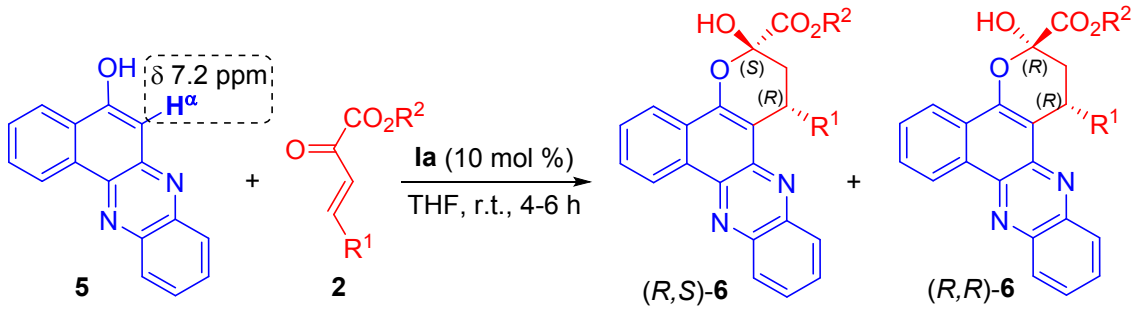
4a / **3a** (2.1 : 1): Yield: 98%, 90% *ee*;
4ba / **3ba** (1.7 : 1): Yield: 99%, 93% *ee* (Lit. 91% *ee*,[8a] 45% *ee*[10a]);
4ca / **3ca** (3.4 : 1): Yield: 98%, 90% *ee*;
4da / **3da** (4.4 : 1): Yield: 97%, 93% *ee* (Lit. 77% *ee*,[8a] 50% *ee*[10a])



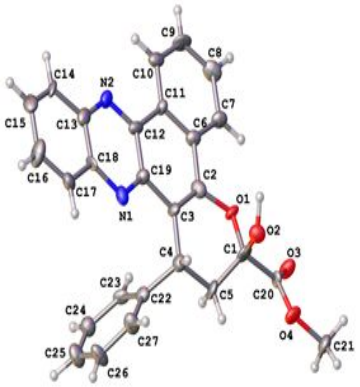
We expected that the usage of stronger carbon acids would further enhance chemoselectivity of their reactions with *β*,*γ*-unsaturated *α*-keto esters **2**. To verify this hypothesis, we studied the reactions of compounds **2** with benzo[*a*]phenazin-5-ol **5** (δH^{α} 7.2 ppm) in the presence of catalyst **Ia**. Indeed, these reactions afforded exclusively novel cyclic hemiketals **6a-e** in 85-95% yields regardless the substituents R^1 and R^2 in keto esters **2** (Scheme 4). According to ^{1}H NMR and chiral HPLC analysis data, heterocycles **6** are the mixtures of two diastereomers in a 1 : 1–1.5 : 1 ratio. We succeeded to isolate the major diastereomer of **6a** by crystallization of a raw reaction product from *n*-hexane-EtOAc (5 : 1) and determine its absolute (*R*,*S*) configuration (X-ray diffraction analysis). The same (*R*,*S*) configuration was assigned to the major diastereomers of products **6c-e** by analogy. To our delight, cyclic hemiketals **6a-e** did not undergo reversible opening of the tetrahydropyran ring to give the corresponding linear Michael adducts. ^{1}H NMR spectra of fresh solution and a one-week aged solution of **6a** in $CDCl_3$ or d_6-DMSO were identical. To the best of our knowledge, compounds **6a-e** are the first stable chiral cyclic hemi-ketals.[10a]

The phenazine scaffold is an important pharmacophoric motif and is present in various natural compounds and medications.[15] For instance, benzo[*a*]phenazin-5-ol **5** used as the starting substrate in this research is a powerful anti-cancer agent sAJM589.[12] The developed approach may be useful for enantioselective synthesis of biologically active compounds in this series of pharmacology-relevant heterocyclic system. The practicality of the proposed catalytic approach was clearly demonstrated by recyclability of ionic liquid supported catalyst **Ia**, which could be readily separated from the reaction mixture and 11 times reused in the catalytic reaction between compounds **1a** and **2a** without a significant decrease in the yield or *ee* values of products **3a** / **4a** (for details, see Experimental Section and SI).

Scheme 4. Asymmetric reactions of benzo[*a*]phenazin-5-ol **5** with *β*,*γ*-unsaturated *α*-keto esters **2** catalyzed by **Ia**



6a (R^1 = Ph, R^2 = Me): Yield: 85%, *R,S*/*R,R* 1.3 : 1, *ee* 97% (*R,S*), 97% (*R,R*);
6b (R^1 = 2-ClC_6H_4, R^2 = Et): Yield: 91%, *S,S*/*R,S* 1 : 1, *ee* 97% (*S,S*), 96% (*S,R*);
6c (R^1 = 4-NCC_6H_4, R^2 = Et): Yield: 90%, *R,S*/*R,R* 1.3 : 1, *ee* 98% (*R,S*), 96% (*R,R*);
6d (R^1 = 4-$F_3CC_6H_4$, R^2 = ^{i}Pr): Yield: 93%, *R,S*/*R,R* 1.5 : 1, *ee* 95% (*R,S*), 99% (*R,R*);
6e (R^1 = 2-Thienyl, R^2 = ^{i}Pr): Yield: 95%, *R,S*/*R,R* 1.4 : 1, *ee* 92% (*S,S*), 94% (*S,R*).



X-Ray image of (*R,S*)-**6a**

Conclusions

In summary, in the present work we revealed the correlation between the equilibrium ratio of tautomeric products **3** / **4** generated upon the asymmetric Michael reactions of carbon acids **1** with *β*,*γ*-unsaturated *α*-keto esters **2** and the chemical shift of the α-proton of the starting carbon acids **1**. Previously unknown benzo[*a*]phenazine derivatives fused with tetrahydropyran moieties were enantioselectively (up to 99% *ee*) synthesized from *β*,*γ*-unsaturated *α*-keto esters **2** and

benzo[*a*]phenazin-5-ol **5**. The developed enantioselective approach is applicable for synthesizing potentially bioactive compounds which contain this pharmacology-relevant heterocyclic motif.

Experimental Section

General information. High-resolution electrospray ionization mass spectrometry (HRMS (ESI)) was performed on a Fluka time-of-flight (TOF) instrument. The measurements were taken in the positive ion mode (interface capillary voltage 4500 V) in the mass range from m/z = 50 Da tom/z = 3000 Da; external or internal calibration was done with an electrospray calibrant solution. NMR spectra were recorded on a 300 MHz spectrometer. The ^{1}H and ^{13}C chemical shifts were measured relative to Me_4Si, $CDCl_3$, respectively. Optical rotations were measured on a polarimeter calibrated with pure solvent as a blank. Atoms in the X-ray image of compound **4b** and **6a** are represented by thermal ellipsoids at the 50% probability level. CCDC 1870961 (**4b**) and 1878178 (**6a**) contains the supplementary crystallographic data for this paper. The HPLC analyses were performed on chiral stationary phase columns Chiralpak AD-H and Chiralpak AS-H, detection at 254 nm. Silica gel (0.060−0.200 mm) was used for column chromatography. All reagents and solvents were purified according to standard methods. Centrifugation was performed at 3500 rpm. All *β*,*γ*-unsaturated *α*-keto-esters **2** were prepared according to the reported procedures.[16] Racemic compounds **3/4** and **6** were prepared from **1** or **5** and **2** using TEA (10 mol %) as a catalyst.

*Methyl 4-(4-cyanophenyl)-2-oxobut-3-enoate (**2d**).* Yellow powder, m.p. 149-151 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 16.2 Hz, 1H), 7.74 (s, 4H), 7.47 (d, *J* = 16.2 Hz, 1H), 3.97 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 181.8, 161.9, 145.5, 138.1, 132.7, 129.2, 123.3, 118.1, 114.5, 53.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{12}H_{10}NO_3$ 216.0655, found 216.0658.

*Ethyl 4-(2-chlorophenyl)-2-oxobut-3-enoate (**2g**).* Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 16.2 Hz, 1H), 7.73 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.46 – 7.27 (m, 4H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 182.8, 162.1, 143.9, 136.1, 132.3, 130.4, 127.9, 127.3, 122.8, 62.6, 14.1, 13.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{12}H_{12}ClO_3$ 239.0470 and 241.0440, found 239.0471 and 241.0446.

*Ethyl 4-(4-cyanophenyl)-2-oxobut-3-enoate (**2h**).* Yellow powder, m.p. 139-141 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 16.2 Hz, 1H), 7.71 (s, 4H), 7.43 (d, *J* = 16.1 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 177.0, 156.4, 140.1,

132.9, 127.5, 123.9, 118.1, 112.9, 109.1, 57.5, 8.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{13}H_{12}NO_3$ 230.0812, found 230.0825.

*Isopropyl 4-(4-cyanophenyl)-2-oxobut-3-enoate (**2k**).* Yellow powder, m.p. 93-95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 16.2 Hz, 1H), 7.71 (s, 4H), 7.43 (d, *J* = 16.1 Hz, 1H), 5.22 (sept, *J* = 6.3 Hz, 1H), 1.39 (d, *J* = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 182.6, 161.3, 145.1, 138.2, 132.4, 129.1, 123.5, 118.1, 114.3, 71.1, 21.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{14}H_{14}NO_3$ 244.0968, found 244.0976.

General Procedure for Asymmetric Michael Reaction:

A mixture of carbon acid **1a-d** or **5** (0.2 mmol), *β*,*γ*-unsaturated *α*-keto esters **2a-n** (0.21 mmol), organocatalyst **Ia** (16.3 mg, 0.02 mmol) in THF (0.3 mL) was stirred at ambient temperature for specified time (TLC–monitoring). The solvent was evaporated under reduced pressure (50 °C, 50 Torr), diethyl ether (6 mL) was added to the residue and the resulting suspension was subjected to centrifugation. Clear organic solution was decanted from solid catalyst **Ia**. The combined organic extracts were evaporated under reduced pressure (20 Torr) and the residue was purified by silica gel column chromatography (*n*-hexane/ EtOAc 1:1) to afford the corresponding Michael adduct **4/3** or **6**. The ^{1}H NMR data for all compounds are given in Supporting Information. Physicochemical properties of all compounds are given bellow.

*(S)-Methyl 2-hydroxy-5-oxo-4-phenyl-2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate (**4a**) / Methyl (S)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-4-phenylbutanoate (**3a**).*[8d] Yield 73 mg (99%). Colorless solid, m.p. 161-163 °C (lit.[8a] 88-89 °C). ^{1}H NMR (300 MHz,): *δ* 7.87 – 7.74 (m, 1.28H), 7.61 – 7.48 (m, 1.44H), 7.40 – 7.28 (m, 5.26H), 7.24 – 7.19 (m, 1.41H), 4.40 – 4.31 (m, 0.34H), 4.28 – 4.14 (m, 0.91H), 3.92 (s, 0.96H), 3.88 (s, 2H), 2.80 (dd, *J* = 14.3, 7.4 Hz, 0.34H), 2.58 (dd, *J* = 13.8, 10.4 Hz, 0.40H), 2.46 (d, *J* = 9.4 Hz, 1.50H) ppm. HPLC data: 91% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 70 : 30; 254 nm, flow rate: 0.8 mL/min, t_{minor}= 6.5 min, t_{major} = 10.1 min).

*(S)-Methyl 2-hydroxy-5-oxo-4-(p-tolyl)- 2,3,4,5-tetrahydropyrano [3,2-c]chromene-2-carbo xylate **(4b)**/ Methyl (S)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-4-(p-tolyl)butanoate (**3b**).*[8d] Yield 70 mg (91%). Colorless solid, m.p. 165-167 °C (lit.[8a] 164-166 °C). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.83 (ddd, *J* = 16.8, 7.9, 1.4 Hz, 1.05H), 7.64 – 7.50 (m, 1.09H), 7.42 – 7.24 (m, 2H), 7.20 – 7.08 (m, 4.16H), 4.34 (dd, *J* = 7.3, 3.1 Hz, 0.37H), 4.19 (t, *J* = 9.2 Hz, 0.75H), 3.94 (s, 0.96H, **3ab**), 3.90 (s, 2.04H, **4ab**) , 2.80 (dd, *J* = 14.3, 7.4 Hz, 0.37H), 2.55 (dd, *J* = 14.3, 3.2 Hz, 0.43H), 2.47 (d, *J* = 9.2 Hz, 1.40H), 2.34 (s, 2.11H), 2.33 (s, 0.88H) ppm. ^{13}C{^{1}H} NMR (75

MHz, $CDCl_3$): δ 169.0, 160.7, 157.9, 152.8, 139.2, 136.2, 131.8, 129.4, 126.9, 123.7, 122.7, 116.5, 115.3, 105.0, 95.6, 53.8, 38.2, 34.1, 21.1 ppm. HPLC data: 90% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 0.8 mL/min, t_{minor}= 11.0 min, t_{major} = 19.7 min).

(S)-Methyl 2-hydroxy-5-oxo-4-(p-tolyl)-2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate ***(4b)***. Colorless crystals, m.p. 164-166 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (dd, J = 7.8, 0.8 Hz, 1H), 7.59–7.51 (m, 1H), 7.35 – 7.27 (m, 2H), 7.19 – 7.11 (m, 4H), 4.77 (br s, 1H), 4.19 (t, J = 9.2 Hz, 1H), 3.90 (s, 3H), 2.47 (d, J = 9.2 Hz, 2H), 2.34 (s, 3H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.9, 160.8, 158.0, 152.8, 139.2, 136.2, 131.8, 129.4, 126.9, 123.7, 122.7, 116.5, 115.3, 104.9, 95.6, 53.8, 38.2, 34.1, 21.1 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{19}O_6$ 367.1176, found 367.1182.

(S)-Methyl 2-hydroxy-5-oxo-4-(4-(trifluoromethyl)phenyl) -2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate ***(4c)*** */ Methyl (S)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-4-(4-(trifluoromethyl)phenyl)butanoate* ***(3c)***. Yellow wax. Yield 86 mg (98%). $[\alpha]^{20}_D$: +3.0 (c 0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 – 7.75 (m, 1H), 7.64 – 7.48 (m, 3H), 7.43 – 7.24 (m, 4.29H), 4.99 (br s, 0.41H), 4.73 (br s, 0.31H), 4.39 (d, J = 5.1 Hz, 0.35H), 4.29 (dd, J = 11.2, 7.3 Hz, 0.64H), 3.92 (s, 0.90H, **3c**), 3.89 (s, 1.70H, **4c**), 2.83 (dd, J = 14.0, 7.6 Hz, 0.36H), 2.58 – 2.36 (m, 1.53H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.6, 160.6, 158.7, 158.4, 152.8, 146.6, 145.9, 132.3, 132.1, 127.9, 127.5, 125.6, 125.2, 124.1, 123.9, 122.9, 122.8, 116.7, 116.6, 115.1, 104.0, 102.1, 95.9, 95.3, 54.1, 53.9, 37.8, 35.1, 34.5, 33.6 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{16}F_3O_6$ 421.0893, found 421.0906. HPLC data: 89% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 0.8 mL/min, t_{minor} = 8.2 min, t_{major} = 18.6 min).

(S)-Methyl 4-(4-cyanophenyl)-2-hydroxy-5-oxo-2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate ***(4d)*** */ Methyl (S)-4-(4-cyanophenyl)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxobutanoate* ***(3d)***. Yellow wax. Yield 74 mg (94%). $[\alpha]^{20}_D$: +153.1 (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (m, 1H), 7.66 – 7.51 (m, 2.44H), 7.43 – 7.25 (m, 3.82H), 4.39 – 4.33 (m, 0.27H), 4.28 (dd, J = 11.5, 6.8 Hz, 0.46H), 3.94 (s, 0.63H, **3d**), 3.91 (s, 1.22H, **4d**), 2.84 (dd, J = 14.3, 7.7 Hz, 0.27H), 2.56 – 2.34 (m, 1.21H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.6, 168.4, 166.5, 162.0, 161.2, 159.3, 159.1, 153.6, 152.7, 148.2, 147.7, 132.5, 132.4, 132.1, 128.5, 128.1, 124.4, 124.2, 123.5, 122.9, 118.8, 116.5, 115.0, 114.8, 110.4, 110.1, 103.3, 101.6, 96.1, 95.6, 91.9, 54.1, 53.9, 37.6, 35.1, 34.8, 33.9 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{16}NO_6$ 378.0972, found 378.0964. HPLC data: 89% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 70 : 30; 254 nm, flow rate: 0.8 mL/min, t_{minor}= 10.9 min, t_{major} = 20.5 min).

*(R)-Methyl 4-(furan-2-yl)-2-hydroxy-5-oxo-2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate (**4e**) / Methyl (R)-4-(furan-2-yl)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxobutanoate (**3e**).*[8a] Yield 69 mg (97%). Yellow solid, m.p. 140-142 °C (lit.[8a] 136-138 °C).[1]H NMR (300 MHz, $CDCl_3$): δ 7.85 – 7.77 (m, 0.98H), 7.61 – 7.49 (m, 1.03H), 7.37 – 7.23 (m, 3.12H), 6.34 – 6.29 (m, 0.97H), 6.16 (d, J = 3.2 Hz, 0.63H), 6.10 (d, J = 3.2 Hz, 0.34H), 5.10 (br s, 0.57H), 4.90 (br s, 0.3H), 4.45 – 4.31 (m, 1.01H), 3.95 (s, 1.05H, **3ae**), 3.82 (s, 1.9H, **4ae**), 2.84 – 2.70 (m, 1H), 2.62 (dd, J = 14.4, 6.9 Hz, 0.36H), 2.44 – 2.34 (m, 0.64H) ppm. HPLC data (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 70 : 30; 254 nm, flow rate: 0.8 mL/min, t_{minor}= 6.7 min, t_{major} = 8.3 min).

*(R)-Methyl 4-(furan-2-yl)-2-hydroxy-5-oxo-2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate (**4e**)*. Yellow crystals, m.p. 159-161 °C. [1]H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.38 – 7.24 (m, 3H), 6.38 – 6.32 (m, 1H), 6.20 (d, J = 3.1 Hz, 1H), 4.81 (br s, 1H), 4.37 (dd, J = 10.2, 6.5 Hz, 1H), 3.87 (s, 3H), 2.76 (dd, J = 13.8, 10.4 Hz, 1H), 2.41 (dd, J = 13.9, 6.5 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.6, 160.9, 158.1, 153.2, 152.7, 141.3, 132.1, 123.8, 122.9, 116.5, 115.1, 110.4, 106.6, 102.1, 95.7, 53.8, 34.3, 28.4 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{18}H_{15}O_7$343.0812, found 343.0815.

*(R)-Methyl 2-hydroxy-5-oxo-4-(thiophen-2-yl)-2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate (**4f**) / Methyl (R)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-4-(thiophen-2-yl)butanoate (**3f**).*[17] Yield 53 mg (99%). Yellow solid, m.p. 95-97 °C (lit. no data). [1]H NMR (300 MHz, $CDCl_3$): δ 7.88 – 7.76 (m, 0.96H), 7.63 – 7.51 (m, 1.12H), 7.41 – 7.29 (m, 1.96H), 7.23 – 7.15 (m, 1.04H), 7.00 – 6.90 (m, 1.86H), 4.87 (br s, 0.49H), 4.71 – 4.52 (m, 1.35H), 3.95 (s, 1.44H, **3af**), 3.88 (s, 1.71H, **4af**), 2.86 – 2.52 (m, 2.05H) ppm. HPLC data: 90% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 70 : 30; 254 nm, flow rate: 0.8 mL/min, t_{minor}= 7.2 min, t_{major} = 10.5 min).

*(R)-Ethyl 4-(2-chlorophenyl)-2-hydroxy-5-oxo-2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate (**4g**) / Ethyl (R)-4-(2-chlorophenyl)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxobutanoate (**3g**)*. Colorless wax. Yield 79 mg (95%). $[\alpha]^{20}_D$: -24.6 (c 0.7, CH_2Cl_2). [1]H NMR (300 MHz, $CDCl_3$): δ 7.91 – 7.78 (m, 1.H), 7.65 – 7.52 (m, 1.20H), 7.46 – 7.28 (m, 2.98H), 7.24 – 7.08 (m, 2.69H), 5.46 (dd, J = 8.2, 4.7 Hz, 0.10H), 5.01 (dd, J = 11.2, 6.5 Hz, 0.27H), 4.81 – 4.65 (m, 1H), 4.47 – 4.28 (m, 1.97H), 2.80 (dd, J = 14.5, 7.6 Hz, 0.40H, **3g**), 2.65 – 2.50 (m, 0.81H, **4g**), 1.44 – 1.32 (m, 3.58H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.6, 168.3, 161.3, 160.5, 158.9, 152.8, 138.4, 133.3, 132.1, 131.9, 129.6, 129.2, 128.0, 127.9, 127.1, 126.3, 124.0, 123.8, 122.8, 122.7, 116.7, 116.5, 104.2, 102.4, 96.0, 95.5, 63.6, 63.5, 32.5, 31.5, 31.2, 14.0, 13.9 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{18}ClO_6$ 401.0786 and 403.0759,

found 401.0780 and 403.0760. HPLC data: 91% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 1.0 mL/min, t_{minor} = 7.7 min, t_{major} = 9.7 min).

*(S)-Ethyl 4-(4-cyanophenyl)-2-hydroxy-5-oxo-2,3,4,5-tetrahydropyrano[3,2-c] chromene -2-carboxylate (**4h**) / Ethyl (S)-4-(4-cyanophenyl)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxobutanoate (**3h**)*. Yellow wax. Yield 78 mg (95%). $[\alpha]^{20}_D$: +100.8 (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 – 7.77 (m, 1.07H), 7.66 – 7.53 (m, 2.95H), 7.43 – 7.29 (m, 4H), 4.39 (dd, *J* = 14.1, 7.0 Hz, 2.42H, **4h**), 4.27 (dd, *J* = 11.7, 6.8 Hz, 0.81H, **3h**), 2.86 (dd, *J* = 14.3, 7.5 Hz, 0.38H), 2.54 – 2.31 (m, 1.68H), 1.49 – 1.33 (m, 3.24H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.2, 168.1, 161.6, 160.6, 158.9, 158.6, 152.8, 148.3, 147.5, 132.6, 132.5, 132.3, 132.0, 128.5, 128.0, 124.2, 124.0, 122.9, 122.8, 118.8, 116.8, 116.6, 115.1, 110.6, 110.3, 103.6, 101.6, 95.7, 95.2, 63.7, 37.5, 34.9, 34.7, 33.8, 14.0 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$: calcd. for $C_{22}H_{18}NO_6$ 392.1129, found 392.1122. HPLC data: 93% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 7 : 3; 254 nm, flow rate: 0.8 mL/min, t_{minor}= 8.4 min, t_{major} = 9.5 min).

*(S)-Isopropyl 2-hydroxy-5-oxo-4-(p-tolyl)-2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate (**4i**) / Isopropyl (S)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-4-(p-tolyl)butanoate (**3i**)*. Colorless wax. Yield 80 mg (97%). $[\alpha]^{20}_D$: +35.3 (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 – 7.75 (m, 0.95H), 7.64 – 7.50 (m, 1.06H), 7.41 – 7.26 (m, 2.37H), 7.23 – 7.09 (m, 3.73H), 5.29 – 5.15 (m, 1H), 4.33 (d, *J* = 4.5 Hz, 0.35H), 4.27 – 4.10 (m, 3H), 2.80 (dd, *J* = 14.1, 7.3 Hz, 0.33H), 2.52 (dd, *J* = 14.3, 2.5 Hz, 0.32H), 2.46 – 2.39 (m, 1.21H, **3i**). 2.35 (s, 2.9H, **4i**), 1.43 – 1.32 (m, 7.66H) ppm. ^{13}C NMR{^{1}H} (75 MHz,) δ 168.2, 158.0, 152.9, 139.6, 138.5, 136.3, 136.2, 132.0, 131.8, 129.5, 129.2, 127.3, 127.0, 124.0, 123.7, 122.7, 116.7, 116.6, 116.4, 115.4, 115.2, 105.1, 102.9, 96.1, 95.3, 71.9, 71.8, 38.1, 35.4, 34.3, 33.3, 21.7, 21.5, 21.1 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{23}H_{23}O_6$ 395.1489, found 395.1458. HPLC data: 91% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 0.8 mL/min, t_{minor} = 8.8 min, t_{major} = 17.1 min).

*(S)-Isopropyl 2-hydroxy-5-oxo-4-(4-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydropyrano [3,2-c]chromene-2-carboxylate (**4j**) / Isopropyl (S)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-4-(4-(trifluoromethyl)phenyl)butanoate (**3j**)*. Yellow wax. Yield 92 mg (98%). $[\alpha]^{20}_D$: +10.1 (c 0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 – 7.76 (m, 1H), 7.68 – 7.50 (m, 2.94H), 7.46 – 7.31 (m, 3.35H), 5.29 – 5.16 (m, 1.02H), 4.43 – 4.36 (m, 0.39H, **3j**), 4.29 (dd, *J* = 11.5, 7.0 Hz, 0.66H, **4j**), 2.86 (dd, *J* = 14.2, 7.4 Hz, 0.37H), 2.55 – 2.32 (m, 1.60H), 1.46 – 1.32 (m, 6.62H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.8, 160.6, 158.4, 152.9, 146.8, 132.3, 132.1, 127.9, 127.5, 125.7, 125.7, 125.1, 124.1, 123.9, 122.7, 116.7, 116.6, 115.2, 104.1, 95.7, 95.2, 72.2, 72.1, 37.7, 34.8, 34.6, 33.6, 21.5 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{23}H_{20}F_3O_6$

449.1206, found 449.1201. HPLC data: 93% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 1.0 mL/min, t_{minor} + 8.9 min, t_{major} = 12.8 min).

*(S)-Isopropyl 4-(4-cyanophenyl)-2-hydroxy-5-oxo-2,3,4,5-tetrahydropyrano[3,2-c] chromene -2-carboxylate (**4k**) / Isopropyl (S)-4-(4-cyanophenyl)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxobutanoate (**3k**)*. Yellow wax. Yield 83 mg (98%). $[\alpha]^{20}_D$: +85.8 (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 – 7.74 (m, 1.05H), 7.66 – 7.51 (m, 3.28H), 7.44 – 7.29 (m, 3.77H), 5.28 – 5.15 (m, 1.40H), 4.89 (br s, 0.33H), 4.36 (d, *J* = 6.4 Hz, 0.40H, **3k**), 4.27 (dd, *J* = 11.8, 6.6 Hz, 0.70H, **4k**), 2.84 (dd, *J* = 14.2, 7.5 Hz, 0.39H), 2.53 – 2.26 (m, 1.81H), 1.43 – 1.31 (m, 6.53H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.7, 167.6, 161.6, 160.7, 159.1, 158.7, 152.8, 148.4, 147.6, 132.6, 132.5, 132.3, 132.0, 128.5, 128.1, 124.2, 124.0, 122.8, 118.9, 118.8, 116.7, 116.6, 115.1, 114.9, 110.5, 110.2, 103.6, 101.6, 95.8, 95.2, 72.1, 37.5, 34.9, 34.7, 33.8, 21.5 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{23}H_{20}NO_6$ 406.1285, found 406.1280. HPLC data: 90% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 70 : 30; 254 nm, flow rate: 1.0 mL/min, t_{minor} = 7.3 min, t_{major} = 15.0 min).

*(S)-Tert-butyl 2-hydroxy-5-oxo-4-phenyl-2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate (**4l**) / Tert-butyl (S)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-4-phenylbutanoate (**3l**)*. Yellow wax. Yield 73 mg (89%). $[\alpha]^{20}_D$: +13.8 (c 0.5, CH_2Cl_2, 80% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 17.9, 7.7 Hz, 1.18H), 7.67 – 7.47 (m, 1.38H), 7.44 – 7.20 (m, 9.40H), 4.95 (br s, 0.58H), 4.40 – 4.30 (m, 0.49H), 4.21 (dd, *J* = 11.5, 7.2 Hz, 0.95H), 2.79 (dd, *J* = 14.3, 7.4 Hz, 0.51H), 2.57 – 2.28 (m, 2.13H), 1.58 (s, 5.33H, **4l**), 1.55 (s, 3.39H, **3l**) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.6, 160.6, 158.2, 152.8, 142.7, 141.8, 131.9, 131.7, 128.7, 128.3, 127.4, 127.1, 126.7, 126.6, 123.9, 123.7, 122.7, 122.7, 116.6, 116.5, 115.5, 105.0, 103.0, 96.2, 95.4, 85.1, 85.0, 38.1, 35.5, 34.8, 34.1, 29.7, 27.7 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{23}H_{23}O_6$ 395.1489, found 395.1484. HPLC data: 89% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 1.0 mL/min, t_{minor} = 10.6 min, t_{major} = 15.6 min).

*(S)-Methyl 2-hydroxy-7,7-dimethyl-5-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**4ba**) / Methyl (S)-4-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-2-oxo-4-phenylbutanoate (**3ba**)*.[8d] Yield 69 mg (99%). Colorless solid, m.p. 154-156 °C (lit. no data). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.24 (m, 2.23H), 7.22 – 7.12 (m, 2.87H), 4.15 – 4.07 (m, 0.37H), 3.97 – 3.90 (m, 0.49H), 3.87 (s, 1.06H), 3.75 (s, 1.86H), 2.66 – 2.18 (m, 6H), 1.21 (d, *J* = 7.1 Hz, 2.79H), 1.12 (d, *J* = 6.7 Hz, 2.92H) ppm. HPLC data: 93% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 1.0 mL/min, t_{minor}= 6.0 min, t_{major} = 9.4 min).

*(S)-Methyl 2-hydroxy-7-methyl-5-oxo-4-phenyl-2,3,4,5-tetrahydropyrano[4,3-b]pyran-2-carboxylate (**4ca**) / Methyl (S)-4-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-2-oxo-4-phenylbutanoate (**3ca**).*[8d] Yield 65 mg (98%). White solid, m.p. 115-117 °C (lit. no data). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 7.27 (m, 2H), 7.22 – 7.16 (m, 3H), 5.87 (s, 1H), 4.23 – 3.98 (m, 1.13H), 3.89 (s, 0.79H), 3.81 (s, 2.29H), 2.69 (dd, J = 14.3, 7.4 Hz, 0.27H), 2.45 (dd, J = 14.2, 3.4 Hz, 0.21H), 2.35 (d, J = 9.0 Hz, 1.36H), 2.27 (s, 0.65H), 2.23 (s, 2.20H) ppm. HPLC data: 90% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 8 : 2; 254 nm, flow rate: 1.0 mL/min, t_{minor}= 8.0 min, t_{major} = 11.9 min).

*(S)-Methyl 2-hydroxy-5,10-dioxo-4-phenyl-3,4,5,10-tetrahydro-2H-benzo[g]chromene-2-carboxylate (**4da**) / Methyl (S)-4-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2-oxo-4-phenylbutanoate (**3da**).*[10a] Yield 74 mg (97%). Yellow solid, m.p. 115-117 °C (lit. no data). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 – 7.88 (m, 2.12H), 7.78 – 7.62 (m, 2.40H), 7.49 (d, J = 7.4 Hz, 0.66H), 7.37 – 7.18 (m, 4H), 5.08 – 4.96 (m, 0.40H), 4.49 – 4.09 (m, 1.30H), 3.90 (s, 0.53H, **3da**), 3.87 (s, 2.33H, **4da**), 3.79 – 3.64 (m, 0.50H), 3.37 – 3.08 (m, 0.41H), 2.80 – 2.65 (m, 0.29H), 2.55 – 2.36 (m, 1.35H), 2.15 – 2.04 (m, 0.24H) ppm. HPLC data: 93% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 1.0 mL/min, t_{minor}= 12.0 min, t_{major} = 16.9 min).

*(S)-Methyl 2-hydroxy-5,10-dioxo-4-phenyl-3,4,5,10-tetrahydro-2H-benzo[g]chromene-2-carboxylate (**4da**)*. Yellow crystals, m.p. 118-120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 – 8.11 (m, 1H), 7.96 – 7.91 (m, 1H), 7.72 – 7.66 (m, 2H), 7.34 – 7.23 (m, 5H), 4.79 (br s, 1H), 4.33 – 4.27 (m, 1H), 3.90 (s, 3H), 2.47 – 2.41 (m, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 183.1, 179.3, 168.6, 152.9, 142.7, 135.1, 134.2, 133.2, 132.1, 130.8, 128.8, 128.6, 128.4, 128.2, 127.6, 127.2, 126.7, 126.4, 126.3, 125.1, 95.3, 53.9, 37.9, 34.7 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{17}O_6$ 365.1020, found 365.1019.

*(1R,3S)-Methyl 3-hydroxy-1-phenyl-2,3-dihydro-1H-benzo[a]pyrano[2,3-c]phenazine-3-carboxylate (**6a**, R,S/R,R = 1.3 : 1)*. Yellow solid (59 mg, 85%), m.p. 196-197 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.48 – 9.29 (m, 0.99H), 8.42 – 8.15 (m, 2.01H), 7.96 (d, J = 8.0 Hz, 0.46H), 7.89 – 7.57 (m, 4.6H), 7.31 – 7.05 (m, 5.17H), 5.47 – 5.37 (m, 0.43H), 5.10 (t, J = 9.0 Hz, 0.57H), 4.78 (br s, 0.44H), 4.35 (s, 1H), 3.94 (s, 1.27H), 3.89 (s, 1.6H), 3.03 (dd, J = 14.1, 7.2 Hz, 0.44H), 2.87 – 2.68 (m, 1.56H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.9, 150.4, 150.3, 145.9, 143.9, 142.8, 142.4, 141.7, 140.4, 140.1, 139.9, 131.1, 129.8, 129.6, 129.4, 129.3, 129.3, 129.1, 128.8, 128.7, 128.4, 128.2, 128.1, 127.8, 125.9, 125.6, 125.2, 125.1, 122.6, 122.3, 114.2, 112.2, 95.9, 95.1, 53.6, 53.5, 38.9, 35.8, 35.6, 33.5 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{27}H_{21}N_2O_4$ 437.1496, found 437.1487. HPLC data: (*R*,*S*) 97%/(*R*,*R*) 97% *ee*, (Chiralpak

AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 0.8 mL/min, Diastereomer (*R*,*S*): t_{major} = 6.39 min, t_{minor} = 7.05 min. Diastereomer (*R*,*R*): t_{minor} = 8.51 min, t_{major} = 9.39 min).

*(1S,3S)-Ethyl 1-(2-chlorophenyl)-3-hydroxy-2,3-dihydro-1H-benzo[a]pyrano[2,3-c]phenazine-3-carboxylate (**6b**, S,S/S,R = 1 : 1)*. Yellow solid (70 mg, 91%), m.p. 196-198 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.48 – 9.40 (m, 0.45H), 9.39 – 9.32 (m, 0.46H), 8.40 – 8.21 (m, 1.85H), 7.92 (d, *J* = 8.2 Hz, 0.46H), 7.88 – 7.61 (m, 4.15H), 7.48 (d, *J* = 7.8 Hz, 1.09H), 7.32 (br s, 0.4H), 7.12 – 7.01 (m, 0.95H), 6.97 – 6.78 (m, 1.75H), 6.34 – 6.27 (m, 0.23H), 5.71 – 5.62 (m, 0.44H), 5.60 – 5.49 (m, 0.46H), 4.76 (br s, 0.36H), 4.55 (s, 0.42H), 4.49 – 4.37 (m, 1.88H), 3.02 (dd, *J* = 14.3, 7.7 Hz, 0.44H), 2.87 – 2.76 (m, 0.89H), 2.75 – 2.62 (m, 0.5H), 1.48 – 1.36 (m, 3.1H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.6, 169.4, 150.7, 150.5, 143.7, 142.6, 142.4, 142.0, 141.3, 140.3, 140.0, 139.9, 133.9, 133.4, 131.0, 130.9, 130.4, 129.8, 129.7, 129.4, 129.3, 129.1, 129.0, 128.8, 128.4, 128.2, 128.0, 127.2, 126.8, 126.7, 125.8, 125.2, 122.5, 122.3, 117.9, 115.9, 114.3, 112.1, 95.6, 95.1, 67.1, 63.2, 36.3, 32.6, 31.4, 14.1 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{28}H_{22}ClN_2O_4$ 485.1263 and 487.1236, found 485.1254 and 487.1236. HPLC data: (*S*,*S*) 97%/(*S*,*R*) 96% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 0.8 mL/min, Diastereomer (*R*,*S*): t_{major} = 10.04 min, t_{minor} = 11.57 min. Diastereomer (*R*,*R*): t_{minor} = 15.09 min, t_{major} = 16.44 min).

*(1R,3S)-Ethyl 1-(4-cyanophenyl)-3-hydroxy-2,3-dihydro-1H-benzo[a]pyrano[2,3-c]phenazine-3-carboxylate (**6c**, R,S/R,R = 1.3 : 1)*. Yellow solid (68 mg, 90%), m.p. = 189-191 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.46 – 9.39 (m, 0.43H), 9.37 – 9.29 (m, 0.5H), 8.36 – 8.28 (m, 0.86H), 8.27 – 8.19 (m, 1.01H), 7.94 – 7.62 (m, 5.02H), 7.49 (t, *J* = 8.7 Hz, 1.86H), 7.42 – 7.31 (m, 1.97H), 5.41 – 5.34 (m, 0.41H), 5.09 (dd, *J* = 11.5, 7.3 Hz, 0.54H), 4.88 (br s, 0.4H), 4.55 (s, 0.4H), 4.50 – 4.36 (m, 1.95H), 3.07 (dd, *J* = 14.0, 7.7 Hz, 0.47H), 2.77 – 2.55 (m, 1.5H), 1.48 – 1.34 (m, 3H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.3, 169.1, 152.3, 150.7, 150.6, 150.4, 142.4, 142.2, 141.5, 140.5, 140.2, 140.1, 132.1, 131.6, 131.1, 129.9, 129.8, 129.7, 129.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.5, 128.1, 127.8, 125.3, 125.2, 122.5, 122.3, 119.2, 119.1, 112.9, 110.9, 109.4, 109.3, 95.3, 94.7, 63.3, 38.3, 36.4, 34.7, 34.0, 14.1 ppm. HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{29}H_{22}N_3O_4$: 476.1605, found 476.1615. HPLC data: (*R*,*S*) 98%/(*R*,*R*) 96% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 0.8 mL/min, Diastereomer (*R*,*S*): t_{minor} = 11.53 min, t_{major} = 12.65 min. Diastereomer (*R*,*R*): t_{minor} = 14.62 min, t_{major} = 21.06 min).

*(1R,3S)-Isopropyl 3-hydroxy-1-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-benzo[a]pyrano[2,3-c]phenazine-3-carboxylate (**6d**, R,S/R,R = 1.5 : 1)*. Yellow solid (79 mg, 93%), m.p. 246-248 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.50 – 9.42 (m, 0.41H), 9.41 – 9.34 (m, 0.45H), 8.40 – 8.19 (m,

1.79H), 7.96 (d, *J* = 8.4 Hz, 0.43H), 7.90 – 7.79 (m, 1.86H), 7.78 – 7.62 (m, 2.45H), 7.58 – 7.34 (m, 4.31H), 5.44 (d, *J* = 6.2 Hz, 0.45H), 5.34 – 5.19 (m, 1.02H), 5.16 – 5.05 (m, 0.7H), 4.75 (br s, 0.47H), 4.52 (s, 0.57H), 3.07 (dd, *J* = 13.9, 7.6 Hz, 0.48H), 2.79 – 2.57 (m, 1.43H), 1.54 – 1.11 (m, 6H) ppm. $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 168.8, 150.8, 148.6, 142.5, 142.2, 141.6, 140.4, 140.2, 139.9, 131.1, 129.9, 129.8, 129.7, 129.6, 129.3, 129.1, 128.9, 128.5, 128.4, 128.1, 125.3, 125.2, 125.1, 125.0, 124.7, 124.6, 122.5, 122.3, 113.4, 111.5, 95.4, 94.7, 84.1, 71.6, 71.4, 38.5, 36.1, 34.8, 33.7, 21.6 ppm. HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{30}H_{24}F_3N_2O_4$ 533.1683, found 533.1674. HPLC data: (*R*,*S*) 95%/(*R*,*R*) 99% *ee* (Chiralpak AS-H, *n*-hexane : *i*-PrOH = 90 : 10; 254 nm, flow rate: 0.8 mL/min, Diastereomer (*R*,*R*): t_{major} = 17.74 min, t_{minor} = 23.86 min. Diastereomer (*R*,*S*): t_{major} = 21.0 min, t_{minor} = 29.87 min).

*(1S,3S)-Isopropyl 3-hydroxy-1-(thiophen-2-yl)-2,3-dihydro-1H-benzo[a]pyrano[2,3-c]phenazine-3-carboxylate (**6e**, S,S/S,R = 1.4 : 1)*. Yellow solid (71 mg, 95%), m.p. = 167-169 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 – 9.40 (m, 0.56H), 9.37 – 9.31 (m, 0.36H), 8.37 – 8.30 (m, 1.17H), 8.28 – 8.20 (m, 0.77H), 8.15 – 8.09 (m, 0.55H), 7.98 – 7.93 (m, 0.4H), 7.89 – 7.68 (m, 4H), 7.13 (d, *J* = 4.6 Hz, 0.59H), 7.06 (d, *J* = 4.8 Hz, 0.35H), 6.91 – 6.80 (m, 1.4H), 6.76 (d, *J* = 3.3 Hz, 0.56H), 5.70 (d, *J* = 5.4 Hz, 0.58H), 5.44 (dd, *J* = 9.9, 7.9 Hz, 0.4H), 5.33 – 5.17 (m, 1.06H), 4.84 (br s, 0.25H), 4.58 (s, 0.61H), 3.03 (dd, *J* = 14.1, 6.6 Hz, 0.62H), 2.96 – 2.74 (m, 1.46H), 1.45 – 1.35 (m, 6H) ppm. $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 168.7, 168.6, 150.1, 149.5, 147.9, 142.7, 142.6, 142.3, 141.6, 140.5, 140.0, 139.9, 131.1, 131.0, 129.8, 129.7, 129.6, 129.5, 129.3, 129.1, 128.9, 128.8, 128.5, 128.4, 128.3, 128.0, 126.3, 126.2, 125.2, 125.1, 124.9, 124.4, 123.4, 122.6, 122.5, 122.4, 113.9, 112.3, 95.6, 95.0, 71.4, 71.1, 39.3, 35.4, 31.1, 28.9, 21.6, 21.6 ppm. HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{27}H_{23}N_2O_4S$ 471.1373, found 471.1362. HPLC data: (*S*,*S*) 92%/(*S*,*R*) 94% *ee* (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 80 : 20; 254 nm, flow rate: 0.8 mL/min, Diastereomer (*R*,*S*): t_{minor} = 13.06 min, t_{major} = 14.25 min. Diastereomer (*R*,*R*): t_{minor} = 16.02 min, t_{major} = 23.61 min).

Synthesis of 6a. **Scaling procedure**.

The reaction with **5** (1.00 g, 4.08 mmol), **2a** (0.85 g, 4.48 mmol), **Ia** (0.33 g, 0.40 mmol), and THF (4.0 mL) was performed as described above to afford 1.44 g (81%) of **6a** with 97% *ee* (***6a*** *R,S/R,R = 1.3 : 1*).

^{1}H NMR monitoring of the 4b/3b ratio in the $CDCl_3$ solution: Compound **4b** (20 mg, 0.054 mmol) was placed in a NMR-tube and dissolved in $CDCl_3$ (0.4 mL). ^{1}H NMR spectra of the resulting solution were recorded in 5 min, 2 h, 4 h, 6 h, 16 h and 24 h after dissolution of **4b** (see Fig. 1).

Recycling procedure: Catalyst **Ia** recovered by centrifugation was dried under reduced pressure (60 °C, 50 Torr, 30 min). Then the fresh portions of the starting substrates **1a** (37.2 mg, 0.20 mmol) and **2a** (38.0 mg, 0.20 mmol) and THF (0.3 mL) were added to the catalyst and the reaction was re-performed as described above.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: http://pubs.acs.org.

Copies of ^{1}H, ^{13}C, and HPLC spectra (PDF)

X-ray of **4b** (CIF)

X-ray of **6a** (CIF)

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Notes

The authors declare no competing financial interest

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