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PAPER

Synthesis of optically active dihydropyrans from asymmetric [4 + 2] cycloaddition of β,γ-unsaturated α-ketoesters with allenic esters†

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β-Isocupreidine (**β-ICD**) catalyzed asymmetric [4 + 2] cycloaddition of β,γ-unsaturated α-ketoesters with allenic esters afforded ester-substituted functionalized dihydropyran derivatives in high yields along with high enantioselectivities under mild conditions.

Introduction

Ester-substituted pyran rings are an important class of oxygenated heterocycles, which have attracted much synthetic interest because of the biological activity of naturally occurring representatives.[1] Given their high importance, many excellent methods have been developed to synthesize functional group substituted pyrans.[2] For example, the cyclization of β,γ-unsaturated α-ketoesters has been proved as a powerful and convenient tool to afford these compounds.[3] Recently, allenoates, which served as an attractive substrate class for Lewis base-catalyzed reactions, have attracted much synthetic interest.[4] In contrast to the well-developed phosphine catalysis of allenoates,[5–7] the corresponding amine analogues are relatively rare and only a few examples, as far as we know, have been reported.[8] The success of our previous study on the racemic cycloaddition of β,γ-unsaturated α-ketoesters with allenic esters[8f] allowed us to develop the asymmetric variants of the allenoate-cycloaddition reactions. Herein, we wish to report a β-isocupreidine (**β-ICD**) catalyzed asymmetric [4 + 2] cycloaddition of β,γ-unsaturated α-ketoesters with allenic esters to afford ester-substituted dihydropyran derivatives in high yields along with high enantioselectivities, which are structural motifs in many natural products and biologically active substances.

Results and discussion

We initially utilized (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate **1a** (0.10 mmol, 1.0 equiv) and ethyl 2,3-butadienoate **2a** (0.12 mmol, 1.2 equiv) as the substrates and **β-ICD** (Fig. 1) (20 mol%) as the catalyst in toluene at room temperature to examine the reaction outcome and the result is shown in Table 1. It was found that the corresponding cyclic product **3aa** was obtained in 90% yield and 76% ee (Table 1, entry 1). In order to improve the ee value of product **3aa**, we screened various cinchona alkaloid derived catalysts (Fig. 1) for this reaction, and the results are summarized in Table 1 (Table 1, entries 2–12). As can be seen from Table 1, **cat. 1–cat. 6**, which are very useful catalysts in our previous report on the asymmetric [4 + 2] cycloaddition reaction of salicyl *N*-tosylimine with allenic esters,[8j] did not perform efficiently in this reaction (Table 1, entries 2–7). **Cat. 9**, which is effectively used in asymmetric cycloaddition between allenoates and imines,[8g] was not a suitable catalyst for the reaction (Table 1, entry 10). **Cat. 10** and **cat. 11**, which are effective catalysts for asymmetric cycloaddition of allenoates and α,β-unsaturated ketone,[8h,i] could not make the reaction outcome become better (Table 1, entries 11 and 12). Therefore, the

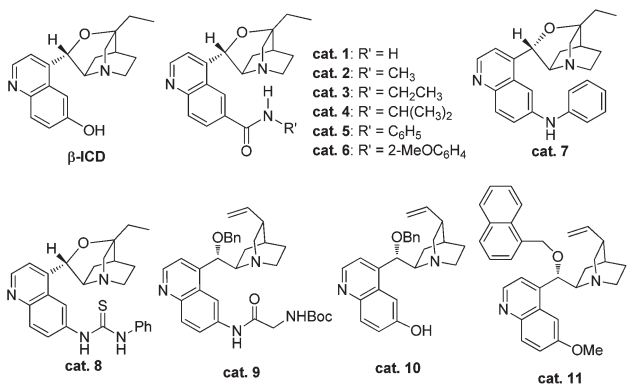

Fig. 1 Multifunctional cinchona alkaloid derivatives.

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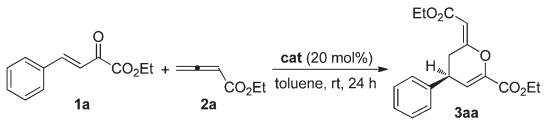
optimal chiral organocatalyst was identified as **β-ICD** (20 mol%) in this asymmetric [4 + 2] cycloaddition reaction to give the corresponding product in high yield (90% yield) along with a good ee value (76% ee).

Table 1 Screening of catalysts for asymmetric [4 + 2] cyclization[a]



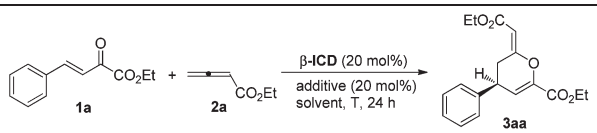
Entry	Cat	Yield[b] (%)	ee[c] (%)
1	**β-ICD**	90	76
2	**cat. 1**	64	40
3	**cat. 2**	75	31
4	**cat. 3**	68	27
5	**cat. 4**	73	43
6	**cat. 5**	Trace	—
7	**cat. 6**	Trace	—
8	**cat. 7**	68	34
9	**cat. 8**	76	50
10	**cat. 9**	70	42
11	**cat. 10**	Trace	—
12	**cat. 11**	20	78

[a] All reactions were carried out using **1a** (0.10 mmol) and **2a** (0.12 mmol) in toluene (3.00 mL) for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis.

Having identified the best organocatalyst for this reaction, we next carried out the reaction of **1a** with **2a** catalyzed by **β-ICD** (20 mol%) in various solvents to examine the solvent effects and the results are outlined in Table 2. We found that fluorobenzene was the solvent of choice in comparison with those reactions carried out in other organic solvents, affording **3aa** in 95% yield with 81% ee value (Table 2, entries 1–14). Lowering the reaction temperature to 0 °C or −15 °C could improve the ee value of **3aa** from 81% to 85% (Table 2, entries 15 and 16). Further reducing the reaction temperature brought down the yield of **3aa** without improvement of the ee value (Table 2, entries 16 and 17). Moreover, we also attempted to add some additives such as 4-nitrophenol, benzoic acid, H_2O, *tert*-amyl alcohol, diisopropylethylamine (DIEA) and hexafluoropropanol to improve the enantiomeric excess of **3aa** in fluorobenzene at −15 °C. However, no improvement was observed under the standard conditions (Table 2, entries 19–24).

Having established the optimal reaction conditions, we next surveyed the substrate scope of the reaction by varying the structures of β,γ-unsaturated α-ketoesters **1** and allenoates **2**. The results are summarized in Table 3. As shown in Table 3, changing the ester moiety of allenic esters **2** from OEt to O^{i}Pr, O^{t}Bu and OBn did not improve the reaction outcome, affording the desired products **3ab–3ad** in 76–80% yield along with 77–83% ee values (Table 3, entries 2–4). The substituent on the ester moiety of β,γ-unsaturated α-ketoesters **1** significantly affected the reaction outcome, as the sterically bulky R^2 group such as

Table 2 Optimization of the reaction conditions catalyzed by **β-ICD**[a]



Entry	Solvent	*T* (°C)	Additive	Yield[b] (%)	ee[c] (%)
1	Toluene	rt	—	90	76
2	Et_2O	rt	—	82	73
3	CH_3CN	rt	—	38	57
4	DCM	rt	—	87	73
5	DCE	rt	—	85	73
6	$CHCl_3$	rt	—	83	74
7	Dioxane	rt	—	85	69
8	Benzene	rt	—	80	77
9	1,2-Dichlorobenzene	rt	—	87	81
10	*o*-Xylene	rt	—	88	77
11	Fluorobenzene	rt	—	95	81
12	1,4-Difluorobenzene	rt	—	90	78
13	(Trifluoromethyl)benzene	rt	—	85	60
14	Chlorobenzene	rt	—	90	76
15	Fluorobenzene	0	—	90	82
16	Fluorobenzene	−15	—	87	85
17	Fluorobenzene	−30	—	80	84
18	Fluorobenzene	−40	—	75	83
19	Fluorobenzene	−15	4-Nitrophenol	75	79
20	Fluorobenzene	−15	PhCOOH	NR	—
21	Fluorobenzene	−15	H_2O	80	84
22	Fluorobenzene	−15	*t*-Amyl-OH	70	81
23	Fluorobenzene	−15	DIEA	80	83
24	Fluorobenzene	−15	Hexafluoropropanol	60	77

[a] All reactions were carried out using **1a** (0.10 mmol) and **2a** (0.12 mmol) in solvent (3.00 mL) for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis.

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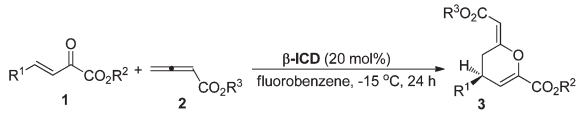
Table 3 Substrate scope of the reactions of **β-ICD**-catalyzed asymmetric cyclization of β,γ-unsaturated α-ketoesters **1** with **2**[a]



Entry	No	R^1	R^2	R^3	No	Yield[b] (%)	ee[c] (%)
1	**1a**	C_6H_5	Et	Et (**2a**)	**3aa**	90	85
2	**1a**	C_6H_5	Et	^{i}Pr (**2b**)	**3ab**	80	77
3	**1a**	C_6H_5	Et	^{t}Bu (**2c**)	**3ac**	78	83
4	**1a**	C_6H_5	Et	Bn (**2d**)	**3ad**	76	83
5	**1b**	C_6H_5	^{i}Pr	Et (**2a**)	**3ba**	90	86
6	**1c**	C_6H_5	Bn	Et (**2a**)	**3ca**	90	83
7	**1d**	C_6H_5	^{t}Bu	Et (**2a**)	**3da**	85	90
8	**1e**	4-MeC_6H_4	^{t}Bu	Et (**2a**)	**3ea**	90	90
9	**1f**	4-MeOC_6H_4	^{t}Bu	Et (**2a**)	**3fa**	89	87
10	**1g**	4-ClC_6H_4	^{t}Bu	Et (**2a**)	**3ga**	92	90
11	**1h**	4-BrC_6H_4	^{t}Bu	Et (**2a**)	**3ha**	92	90
12	**1i**	4-FC_6H_4	^{t}Bu	Et (**2a**)	**3ia**	89	90
13	**1j**	3-BrC_6H_4	^{t}Bu	Et (**2a**)	**3ja**	85	88
14	**1k**	2-BrC_6H_4	^{t}Bu	Et (**2a**)	**3ka**	91	80
15	**1l**	2-Naphthyl	^{t}Bu	Et (**2a**)	**3la**	90	91
16	**1m**	2-Furyl	^{t}Bu	Et (**2a**)	**3ma**	72	90
17	**1n**	2-Thiophene	^{t}Bu	Et (**2a**)	**3na**	75	90
18	**1o**	Cyclopropyl	^{t}Bu	Et (**2a**)	**3oa**	83	86

[a] All reactions were carried out using **1** (0.10 mmol) and **2** (0.12 mmol) in fluorobenzene (3.00 mL) for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis.

O^{i}Pr, OBn or O^{t}Bu group could improve the enantioselectivities of the products (up to 90% ee) (Table 3, entries 5–7). When R^1 are aromatic groups, irrespective of whether there are electron-donating or electron-withdrawing groups at *meta*- or *para*-positions of their benzene rings in **1**, the reactions proceeded smoothly, giving the corresponding products **3** in good yields with high ee values (Table 2, entries 8–14). The substrate **1l**, in which R^1 is 2-naphthyl group, was also tolerable in this reaction to give the corresponding product **3la** in 90% yield along with 91% ee value (Table 3, entry 15). Heterocyclic substrates **1m** and **1n** were also suitable in this reaction to give the desired products **3ma** and **3na** in 72% yield along with 90% ee value and 75% yield along with 90% ee value, respectively (Table 3, entries 16 and 17). As for the substrate **1o**, in which R^1 is a cyclopropyl group and R^2 is an ethyl group, the reaction proceeded smoothly to give the desired product **3oa** in 83% yield along with 86% ee value (Table 3, entry 18). The absolute configuration of products **3** was unequivocally assigned the (*S*) configuration by X-ray diffraction of **3na**. The CIF data are presented in the ESI† and its ORTEP drawing is shown in Fig. 2.

Based on the above Experimental results and the previous mechanistic investigations,[8g–j] a plausible transition-state model has been proposed as shown in Fig. 3. In the transition-state, we hypothesize that the carbonyl groups of substrate **1** and the ester moiety of allenoate can both bond with the phenolic OH of **β-ICD** through hydrogen bonding and therefore, the substrate **1** and the allenoate **2** can be fixed as depicted in Fig. 3. To avoid steric interactions between the R^1 group (R^1 = Ar) of substrate **1**

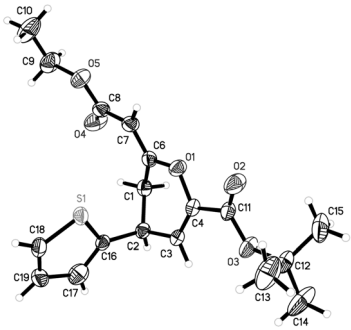


Fig. 2 ORTEP drawing of **3na**.

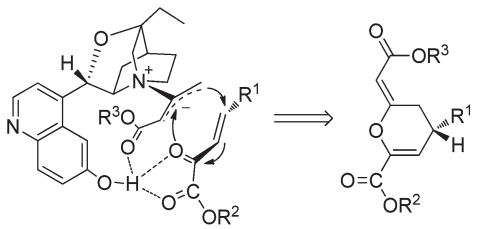


Fig. 3 A plausible transition-state model.

and the *in situ* generated enolate, the attack to the *Re* face of substrate **1** is favored, consequently providing product **3** as the *S*-configuration predominantly.

In conclusion, we have reported an efficient asymmetric [4 + 2] cycloaddition of β,γ-unsaturated α-ketoesters with allenic esters catalyzed by **β-ICD** to afford highly functionalized dihydropyran derivatives in high yields along with high enantioselectivities. The obtained multiple functionalized dihydropyran derivatives are useful building blocks in organic synthesis of biologically useful compounds.[1] Current efforts are in progress to use the cinchona alkaloid derived catalysts in other asymmetric reactions and apply this new methodology to synthesize biologically active products.

Experimental section

General remarks

^{1}H NMR spectra were recorded on a Bruker AM-300 or AM-400 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J*-values are in Hz. Mass spectra were recorded with a HP-5989 instrument. All of the compounds reported in this paper gave satisfactory HRMS analytic data. Melting points were determined on a digital melting point apparatus and temperatures were uncorrected. Infrared spectra were recorded on a Perkin-Elmer PE-983 spectrometer with absorption in cm^{-1}. Optical rotations were determined at 589 nm (sodium D line) by using a Perkin-Elmer-341 MC digital polarimeter; $[\alpha]_D$-values are given in unit of 10^{-1} deg cm^2 g^{-1}. Chiral HPLC was performed on a SHIMADZU SPD-10A vp series with chiral columns (Chiralpak AD-H, IC-H columns 4.6 × 250 mm, (Daicel Chemical Ind., Ltd)). THF, toluene and Et_2O were distilled from sodium (Na) under argon (Ar) atmosphere. CH_3CN, 1,2-dichloroethane and

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dichloromethane were distilled from CaH_2 under argon (Ar) atmosphere. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. All β,γ-unsaturated α-ketoesters were prepared according to the literature.[9] The cinchona alkaloid derivatives catalysts were prepared according to the literature.[10]

General procedure for the preparation of 3 from the reaction of 1 with 2 in the presence of β-ICD

Under argon atmosphere, allenoates **2** (0.12 mmol) were added to a solution of β,γ-unsaturated α-ketoesters **1** (0.10 mmol) and **β-ICD** (0.02 mmol) in fluorobenzene (3.0 mL) and stirred at −15 °C or room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified *via* column chromatography on silica gel (eluting with petroleum ether–ethyl acetate = 8 : 1–4 : 1) to provide compounds **3**.

(*E*)-Ethyl 2-(2-ethoxy-2-oxoethylidene)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate 3aa. A slightly yellow liquid (28.4 mg, 90%); This is a known compound;[8f] ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.23 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 3.11 (dd, J = 8.0 Hz, 4.8 Hz, 1H), 3.68–3.72 (m, 2H), 4.07–4.14 (m, 2H), 4.28–4.34 (m, 2H), 5.75 (s, 1H), 6.45 (d, J = 4.8 Hz, 1H), 7.20–7.22 (m, 2H), 7.26–7.28 (m, 1H), 7.31–7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.1, 14.2, 29.7, 35.8, 59.8, 61.6, 101.0, 116.5, 127.2, 128.8, 141.3, 141.7, 161.1, 164.6, 166.9; $[\alpha]_D^{20}$ = −76.5 (*c* 1.00, CH_2Cl_2) (85% ee); Chiralcel AD-H, hexane/^{i}PrOH = 80/20, 0.6 mL min^{-1}, 254 nm, t_{major} = 7.97 min, t_{minor} = 7.35 min.

(*E*)-Ethyl 2-(2-isopropoxy-2-oxoethylidene)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate 3ab. A slightly yellow liquid (26.4 mg, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.19 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 3.09 (dd, J = 14.4 Hz, 7.2 Hz, 1H), 3.64–3.74 (m, 2H), 4.28–4.35 (m, 2H), 4.97 (sept, J = 6.4 Hz, 1H), 5.72 (s, 1H), 6.46 (d, J = 4.4 Hz, 1H), 7.20–7.22 (m, 2H), 7.26–7.28 (m, 1H), 7.31–7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.1, 21.8, 29.7, 35.9, 61.6, 67.1, 101.5, 116.4, 127.2, 127.3, 128.8, 141.4, 141.8, 161.2, 164.3, 166.4; IR (CH_2Cl_2) ν 3063, 3029, 2984, 2937, 1727, 1694, 1667, 1607, 1576, 1496, 1450, 1376, 1261, 1078, 982, 917, 848, 820, 742, 688, 636, 570 cm^{-1}; MS (ESI) m/z 353.0 (M + Na$^+$); HRMS (ESI) Calcd for $C_{19}H_{22}O_5Na$ requires (M + Na$^+$): 353.1359, Found: 353.1360; $[\alpha]_D^{20}$ = −57 (*c* 0.30, CH_2Cl_2) (77% ee); Chiralcel AD-H, hexane/^{i}PrOH = 90/10, 0.6 mL min^{-1}, 254 nm, t_{major} = 10.06 min, t_{minor} = 8.98 min.

(*E*)-Ethyl 2-(2-(*tert*-butoxy)-2-oxoethylidene)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate 3ac. A slightly yellow liquid (26.8 mg, 78%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.34 (t, J = 7.2 Hz, 3H), 1.42 (s, 9H), 3.01 (dd, J = 17.6 Hz, 11.2 Hz, 1H), 3.65–3.73 (m, 2H), 4.25–4.33 (m, 2H), 5.68 (s, 1H), 6.42 (d, J = 3.6 Hz, 1H), 7.20–7.23 (m, 2H), 7.26–7.27 (m, 1H), 7.31–7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.1, 28.2, 29.6, 36.0, 61.6, 80.0, 102.8, 116.3, 127.2, 127.3, 128.8, 141.5, 141.8, 161.3, 163.5, 166.3; IR (CH_2Cl_2) ν 2979, 2932, 2359, 2342, 1736, 1702, 1655, 1455, 1393, 1370, 1255, 1159, 1114, 862, 759, 700 cm^{-1}; MS (ESI) m/z 367.1 (M + Na$^+$); HRMS (ESI) Calcd for $C_{20}H_{24}O_5Na$ requires (M + Na$^+$): 367.1516, Found: 367.1516; $[\alpha]_D^{20}$ = −114.5 (*c* 0.90, CH_2Cl_2) (83% ee); Chiralcel AD-H, hexane/^{i}PrOH = 90/10, 0.6 mL min^{-1}, 254 nm, t_{major} = 12.96 min, t_{minor} = 11.77 min.

(*E*)-Ethyl 2-(2-(benzyloxy)-2-oxoethylidene)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate 3ad. A slightly yellow liquid (28.7 mg, 76%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.34 (t, J = 7.2 Hz, 3H), 3.13 (dd, J = 14.8 Hz, 7.6 Hz, 1H), 3.64–3.73 (m, 2H), 4.28–4.34 (m, 2H), 5.09 (d, J = 12.8 Hz, 1H), 5.13 (d, J = 12.8 Hz, 1H), 5.82 (s, 1H), 6.46 (d, J = 4.8 Hz, 1H), 7.19–7.21 (m, 2H), 7.26–7.28 (m, 1H), 7.30–7.35 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.1, 29.8, 35.8, 61.7, 65.6, 100.6, 116.6, 127.2, 127.3, 127.9, 128.0, 128.5, 128.8, 136.2, 141.2, 141.7, 161.1, 165.2, 166.7; IR (CH_2Cl_2) ν 3060, 3035, 1732, 1694, 1612, 1575, 1450, 1320, 1307, 1261, 1205, 1089, 996, 904, 746, 697 cm^{-1}; MS (ESI) m/z 401.0 (M + Na$^+$); HRMS (ESI) Calcd for $C_{23}H_{22}O_5Na$ requires (M + Na$^+$): 401.1359, Found: 401.1353; $[\alpha]_D^{20}$ = −131.0 (*c* 1.70, CH_2Cl_2) (83% ee); Chiralcel AD-H, hexane/^{i}PrOH = 98/2, 0.6 mL min^{-1}, 254 nm, t_{major} = 21.53 min, t_{minor} = 17.49 min.

(*E*)-Isopropyl 2-(2-ethoxy-2-oxoethylidene)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate 3ba. A slightly yellow liquid (37.0 mg, 90%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.23 (t, J = 7.2 Hz, 3H), 1.32 (d, J = 6.0 Hz, 6H), 3.11 (dd, J = 13.6 Hz, 6.8 Hz, 1H), 3.64–3.71 (m, 2H), 4.08–4.14 (m, 2H), 5.16 (sept, J = 6.0 Hz, 1H), 5.75 (s, 1H), 6.41 (d, J = 4.0 Hz, 1H), 7.20–7.22 (m, 2H), 7.26–7.28 (m, 1H), 7.31–7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 21.7, 29.7, 35.9, 59.8, 69.4, 100.9, 116.2, 127.25, 127.29, 128.8, 141.4, 142.0, 160.7, 164.7, 167.0; IR (CH_2Cl_2) ν 2984, 2937, 1727, 1694, 1667, 1607, 1576, 1496, 1450, 1376, 1261, 1078, 982, 917, 848, 820, 742, 688, 636, 570 cm^{-1}; MS (ESI) m/z 331.0 (M + H$^+$); HRMS (MALDI) Calcd for $C_{19}H_{22}O_5Na$ requires (M + Na$^+$): 353.1360, Found: 353.1371; $[\alpha]_D^{20}$ = −205.1 (*c* 1.35, CH_2Cl_2) (86% ee); Chiralcel AD-H, hexane/^{i}PrOH = 95/5, 0.6 mL min^{-1}, 254 nm, t_{major} = 12.14 min, t_{minor} = 11.38 min.

(*E*)-Benzyl 2-(2-ethoxy-2-oxoethylidene)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate 3ca. A slightly yellow liquid (34.0 mg, 90%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.23 (t, J = 7.2 Hz, 3H), 3.11 (dd, J = 13.6 Hz, 6.8 Hz, 1H), 3.63–3.71 (m, 2H), 4.07–4.13 (m, 2H), 5.25 (d, J = 12.4 Hz, 1H), 5.31 (d, J = 12.4 Hz, 1H), 5.74 (s, 1H), 6.48 (d, J = 3.2 Hz, 1H), 7.18–7.20 (m, 2H), 7.23–7.27 (m, 1H), 7.30–7.39 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 29.7, 35.9, 59.8, 67.2, 101.0, 117.0, 127.2, 128.4, 128.5, 128.6, 128.8, 135.2, 141.2, 141.6, 161.0, 164.5, 166.9; IR (CH_2Cl_2) ν 2359, 2342, 1734, 1716, 1654, 1276, 1260, 1168, 1116, 750, 668 cm^{-1}; MS (ESI) m/z 401.0 (M + Na$^+$); HRMS (ESI) Calcd for $C_{23}H_{22}O_5Na$ requires (M + Na$^+$): 401.1359, Found: 401.1353; $[\alpha]_D^{20}$ = −112.3 (*c* 0.40, CH_2Cl_2) (84% ee); Chiralcel AD-H, hexane/^{i}PrOH = 90/10, 0.7 mL min^{-1}, 254 nm, t_{major} = 14.58 min, t_{minor} = 13.68 min.

(*E*)-*tert*-Butyl 2-(2-ethoxy-2-oxoethylidene)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate 3da. A slightly yellow liquid (29.2 mg, 85%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.23

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(t, J = 7.2 Hz, 3H), 1.53 (s, 9H), 3.11 (dd, J = 13.2 Hz, 6.4 Hz, 1H), 3.62–3.71 (m, 2H), 4.07–4.13 (m, 2H), 5.73 (s, 1H), 6.34 (d, J = 3.2 Hz, 1H), 7.10–7.22 (m, 2H), 7.26–7.28 (m, 1H), 7.32–7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 28.0, 29.7, 35.8, 59.8, 82.4, 100.7, 115.5, 127.2, 127.3, 128.8, 141.5, 142.4, 161.2, 164.9, 167.0; IR (CH_2Cl_2) ν 2928, 2360, 2342, 1792, 1772, 1733, 1716, 1647, 1541, 1473, 1373, 1339, 1259, 1164, 1116, 750, 669 cm^{-1}; MS (ESI) m/z 345.1 (M + H^+); HRMS (MALDI) Calcd for $C_{20}H_{24}O_5Na$ requires (M + Na^+): 367.1516, Found: 367.1515; $[\alpha]_D^{20}$ = −214.4 (c 1.50, CH_2Cl_2) (90% ee); Chiralcel IC, hexane/^{i}PrOH = 95/5, 0.6 mL min^{-1}, 254 nm, t_{major} = 18.45 min, t_{minor} = 18.42 min.

(*E*)-*tert*-Butyl 2-(2-ethoxy-2-oxoethylidene)-4-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-6-carboxylate 3ea. A slightly yellow liquid (32.4 mg, 90%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.23 (t, J = 7.2 Hz, 3H), 1.53 (s, 9H), 2.33 (s, 3H), 3.08 (dd, J = 13.2 Hz, 6.4 Hz, 1H), 3.59–3.67 (m, 2H), 4.06–4.14 (m, 2H), 5.72 (s, 1H), 6.32 (d, J = 3.2 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 21.0, 28.0, 29.7, 35.4, 59.8, 82.4, 100.6, 115.9, 127.1, 129.4, 136.8, 138.5, 142.2, 160.2, 165.0, 167.0; IR (CH_2Cl_2) ν 2980, 2932, 2359, 1732, 1716, 1659, 1515, 1394, 1371, 1259, 1165, 1117, 1046, 848, 758, 750 cm^{-1}; MS (ESI) m/z 359.1 (M + H^+); HRMS (MALDI) Calcd for $C_{21}H_{26}O_5Na$ requires (M + Na^+): 381.1673, Found: 381.1671; $[\alpha]_D^{20}$ = −228.0 (c 1.65, CH_2Cl_2) (90% ee); Chiralcel IC, hexane/^{i}PrOH = 95/5, 0.6 mL min^{-1}, 254 nm, t_{major} = 15.77 min, t_{minor} = 14.80 min.

(*E*)-*tert*-Butyl 2-(2-ethoxy-2-oxoethylidene)-4-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyran-6-carboxylate 3fa. A slightly yellow liquid (33.1 mg, 89%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.23 (t, J = 7.2 Hz, 3H), 1.53 (s, 9H), 3.13 (dd, J = 14.8 Hz, 8.0 Hz, 1H), 3.57 (dd, J = 14.8 Hz, 6.4 Hz, 1H), 3.62–3.66 (m, 1H), 3.79 (s, 3H), 4.07–4.13 (m, 2H), 5.72 (s, 1H), 6.32 (d, J = 4.0 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 28.0, 29.8, 35.0, 55.2, 59.8, 82.4, 100.6, 114.1, 115.9, 128.3, 133.5, 142.2, 158.7, 160.3, 165.0, 167.0; IR (CH_2Cl_2) ν 2978, 2359, 2342, 1733, 1716, 1654, 1647, 1509, 1457, 1370, 1258, 1164, 1114, 1039, 750, 669 cm^{-1}; MS (ESI) m/z 375.1 (M + H^+); HRMS (MALDI) Calcd for $C_{21}H_{26}O_6Na$ requires (M + Na^+): 397.1622, Found: 397.1627; $[\alpha]_D^{20}$ = −184.4 (c 1.45, CH_2Cl_2) (87% ee); Chiralcel AS-H, hexane/^{i}PrOH = 95/5, 0.6 mL min^{-1}, 254 nm, t_{major} = 10.79 min, t_{minor} = 9.49 min.

(*E*)-*tert*-Butyl 4-(4-chlorophenyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydro-2*H*-pyran-6-carboxylate 3ga. A slightly yellow liquid (44.8 mg, 92%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.23 (t, J = 7.2 Hz, 3H), 1.54 (s, 9H), 3.18 (dd, J = 15.6 Hz, 8.0 Hz, 1H), 3.54 (dd, J = 15.6 Hz, 6.0 Hz, 1H), 3.65–3.68 (m, 1H), 4.07–4.13 (m, 2H), 5.73 (s, 1H), 6.29 (d, J = 4.4 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 27.9, 29.5, 35.2, 59.8, 82.6, 101.0, 114.6, 128.7, 128.9, 133.0, 139.9, 142.6, 160.1, 164.3, 166.9; IR (CH_2Cl_2) ν 2980, 2359, 2341, 1716, 1655, 1492, 1371, 1347, 1258, 1164, 1117, 1015, 848, 764 cm^{-1}; MS (ESI) m/z 379.0 (M + H^+); HRMS (ESI) Calcd for $C_{20}H_{24}ClO_5$ requires (M + H^+): 379.1307, Found: 379.1322; $[\alpha]_D^{20}$ = −162.4 (c 1.95, CH_2Cl_2) (90% ee); Chiralcel IC, hexane/^{i}PrOH = 95/5, 0.6 mL min^{-1}, 254 nm, t_{major} = 24.55 min, t_{minor} = 23.06 min.

(*E*)-*tert*-Butyl 4-(4-bromophenyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydro-2*H*-pyran-6-carboxylate 3ha. A slightly yellow liquid (36.8 mg, 92%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.24 (t, J = 7.2 Hz, 3H), 1.53 (s, 9H), 3.18 (dd, J = 15.2 Hz, 7.6 Hz, 1H), 3.53 (dd, J = 15.2 Hz, 6.4 Hz, 1H), 3.64–3.68 (m, 1H), 4.07–4.13 (m, 2H), 5.73 (s, 1H), 6.28 (d, J = 4.0 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 28.0, 29.4, 35.3, 59.9, 82.6, 101.1, 114.5, 121.1, 129.0, 131.9, 140.5, 142.7, 160.1, 164.3, 166.9; IR (CH_2Cl_2) ν 2359, 2342, 1734, 1716, 1370, 1275, 1260, 1114, 750, 640, 605, 576 cm^{-1}; MS (ESI) m/z 423.0 (M + H^+); HRMS (ESI) Calcd for $C_{20}H_{24}BrO_5$ requires (M + H^+): 423.0802, Found: 423.0814; $[\alpha]_D^{20}$ = −186.8 (c 0.45, CH_2Cl_2) (90% ee); Chiralcel IC, hexane/^{i}PrOH = 98/2, 0.6 mL min^{-1}, 254 nm, t_{major} = 15.08 min, t_{minor} = 14.21 min.

(*E*)-*tert*-Butyl 2-(2-ethoxy-2-oxoethylidene)-4-(4-fluorophenyl)-3,4-dihydro-2*H*-pyran-6-carboxylate 3ia. A slightly yellow liquid (32.1 mg, 89%); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.23 (t, J = 7.2 Hz, 3H), 1.54 (s, 9H), 3.16 (dd, J = 15.0 Hz, 7.8 Hz, 1H), 3.55 (dd, J = 15.0 Hz, 6.3 Hz, 1H), 3.65–3.71 (m, 1H), 4.10 (dq, J = 7.2 Hz, 0.9 Hz, 2H), 5.73 (s, 1H), 6.30 (d, J = 3.9 Hz, 1H), 7.01 (t, J = 8.4 Hz, 2H), 7.17 (dd, J = 8.4 Hz, 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 14.2, 28.0, 29.7, 35.1, 59.8, 82.6, 100.0, 115.0, 115.6 (d, J_{C-F} = 21.5 Hz), 128.8 (d, J_{C-F} = 8.0 Hz), 137.2 (d, J_{C-F} = 2.9 Hz), 142.5, 160.1, 161.9 (d, J_{C-F} = 244.0 Hz), 164.5, 166.9; ^{19}F NMR ($CDCl_3$, 282 MHz, $CFCl_3$): δ −115.822 ∼ −115.724 (m, 1F); IR (CH_2Cl_2) ν 2359, 2342, 1734, 1716, 1653, 1558, 1541, 1507, 1276, 1108, 750, 669 cm^{-1}; MS (ESI) m/z 385.1 (M + Na^+); HRMS (ESI) Calcd for $C_{20}H_{23}FO_5Na$ requires (M + Na^+): 385.1422, Found: 385.1421; $[\alpha]_D^{20}$ = −183.1 (c 1.40, CH_2Cl_2) (90% ee); Chiralcel AS-H, hexane/^{i}PrOH = 98/2, 0.6 mL min^{-1}, 254 nm, t_{major} = 12.00 min, t_{minor} = 11.22 min.

(*E*)-*tert*-Butyl 4-(3-bromophenyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydro-2*H*-pyran-6-carboxylate 3ja. A slightly yellow liquid (35.8 mg, 85%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.24 (t, J = 7.2 Hz, 3H), 1.54 (s, 9H), 3.12 (dd, J = 14.8 Hz, 7.2 Hz, 1H), 3.58–3.67 (m, 2H), 4.11 (dq, J = 7.2 Hz, 1.6 Hz, 2H), 5.74 (s, 1H), 6.28 (d, J = 3.6 Hz, 1H), 7.13–7.16 (m, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.38–7.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 28.0, 29.4, 35.5, 59.8, 82.7, 101.1, 114.3, 122.8, 126.0, 130.4, 142.8, 143.8, 160.0, 164.2, 166.9; IR (CH_2Cl_2) ν 2979, 2932, 2360, 2342, 1733, 1716, 1655, 1593, 1568, 1475, 1394, 1371, 1347, 1257, 1164, 1115, 1045, 848, 764 cm^{-1}; MS (ESI) m/z 445.0 (M + Na^+); HRMS (ESI) Calcd for $C_{20}H_{23}BrO_5Na$ requires (M + Na^+): 445.0621, Found: 445.0619; $[\alpha]_D^{20}$ = −195.7 (c 1.65, $CHCl_3$) (88% ee); Chiralcel IC, hexane/^{i}PrOH = 98/2, 0.6 mL min^{-1}, 254 nm, t_{major} = 26.85 min, t_{minor} = 23.17 min.

(*E*)-*tert*-Butyl 4-(2-bromophenyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydro-2*H*-pyran-6-carboxylate 3ka. A slightly yellow liquid (36.4 mg, 91%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.22 (t, J = 7.2 Hz, 3H), 1.54 (s, 9H), 3.23 (dd, J = 15.2 Hz, 7.2 Hz, 1H), 3.55 (dd, J = 15.2 Hz, 6.4 Hz, 1H), 4.06–4.14

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(m, 2H), 4.16–4.21 (m, 1H), 5.73 (s, 1H), 6.31 (d, J = 4.4 Hz, 1H), 7.10–7.14 (m, 1H), 7.16 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.26–7.30 (m, 1H), 7.57 (dd, J = 7.6 Hz, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 28.0, 28.2, 35.2, 59.8, 82.6, 101.3, 114.1, 124.0, 127.9, 128.4, 128.8, 133.1, 140.2, 143.1, 160.1, 164.1, 166.7; IR (CH_2Cl_2) ν 2980, 2360, 2342, 1734, 1717, 1654, 1472, 1372, 1275, 1260, 1165, 1113, 848, 750, 669 cm^{-1}; MS (ESI) m/z 423.0 (M + H$^+$); HRMS (ESI) Calcd for $C_{20}H_{24}BrO_5$ requires (M + H$^+$): 423.0802, Found: 423.0810; $[\alpha]_D^{20}$ = −52.9 (c 2.00, CH_2Cl_2) (80% ee); Chiralcel IC, hexane/^{i}PrOH = 98/2, 0.6 mL min^{-1}, 254 nm, t_{major} = 29.29 min, t_{minor} = 25.58 min.

(*E*)-*tert*-Butyl 2-(2-ethoxy-2-oxoethylidene)-4-(naphthalen-2-yl)-3,4-dihydro-2*H*-pyran-6-carboxylate 3la. A slightly yellow liquid (46.2 mg, 90%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.21 (t, J = 7.2 Hz, 3H), 1.55 (s, 9H), 3.27 (dd, J = 15.6 Hz, 8.0 Hz, 1H), 3.69 (dd, J = 15.6 Hz, 6.0 Hz, 1H), 3.83–3.87 (m, 1H), 4.04–4.12 (m, 2H), 5.75 (s, 1H), 6.42 (d, J = 4.0 Hz, 1H), 7.34 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.43–7.50 (m, 2H), 7.64 (s, 1H), 7.78–7.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 28.0, 29.5, 35.9, 59.8, 82.5, 100.8, 115.3, 125.5, 125.80, 125.84, 126.2, 127.6, 127.7, 128.6, 132.5, 133.4, 138.8, 142.5, 160.2, 164.8, 167.0; IR (CH_2Cl_2) ν 2979, 2931, 2359, 2341, 1733, 1717, 1654, 1508, 1457, 1394, 1373, 1260, 1163, 1113, 847, 749 cm^{-1}; MS (ESI) m/z 395.1 (M + H$^+$); HRMS (ESI) Calcd for $C_{24}H_{27}O_5$ requires (M + H$^+$): 395.1853, Found: 395.1865; $[\alpha]_D^{20}$ = −301.6 (c 1.50, CH_2Cl_2) (91% ee); Chiralcel IC, hexane/^{i}PrOH = 98/2, 0.6 mL min^{-1}, 254 nm, t_{major} = 34.00 min, t_{minor} = 30.70 min.

(*E*)-*tert*-Butyl 2-(2-ethoxy-2-oxoethylidene)-4-(furan-2-yl)-3,4-dihydro-2*H*-pyran-6-carboxylate 3ma. A slightly yellow liquid (24.0 mg, 72%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.27 (t, J = 7.2 Hz, 3H), 1.52 (s, 9H), 3.35 (dd, J = 15.6 Hz, 7.6 Hz, 1H), 3.52 (dd, J = 15.6 Hz, 6.0 Hz, 1H), 3.76–3.80 (m, 1H), 4.15 (dq, J = 7.2 Hz, 1.6 Hz, 2H), 5.73 (s, 1H), 6.12 (d, J = 3.2 Hz, 1H), 6.30 (dd, J = 3.2 Hz, 1.6 Hz, 1H), 6.34 (d, J = 4.4 Hz, 1H), 7.35 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.3, 26.4, 28.0, 29.7, 59.9, 82.6, 101.1, 105.6, 110.3, 112.5, 142.0, 142.5, 153.7, 160.1, 164.4, 167.0; IR (CH_2Cl_2) ν 2360, 2342, 1733, 1716, 1275, 1260, 1116, 846, 750, 669, cm^{-1}; MS (ESI) m/z 357.1 (M + Na$^+$); HRMS (ESI) Calcd for $C_{18}H_{22}O_6Na$ requires (M + Na$^+$): 357.1309, Found: 357.1322; $[\alpha]_D^{20}$ = −42.0 (c 0.30, CH_2Cl_2) (90% ee); Chiralcel IC, hexane/^{i}PrOH = 98/2, 0.6 mL min^{-1}, 254 nm, t_{major} = 23.11 min, t_{minor} = 26.68 min.

(*E*)-*tert*-Butyl 2-(2-ethoxy-2-oxoethylidene)-4-(thiophen-2-yl)-3,4-dihydro-2*H*-pyran-6-carboxylate 3na. A slightly yellow liquid (26.3 mg, 75%); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.25 (t, J = 7.2 Hz, 3H), 1.53 (s, 9H), 3.40 (dd, J = 15.6 Hz, 7.2 Hz, 1H), 3.54 (dd, J = 15.6 Hz, 6.0 Hz, 1H), 3.96–4.00 (m, 1H), 4.13 (dq, J = 7.2 Hz, 2.4 Hz, 2H), 5.75 (s, 1H), 6.37 (d, J = 4.4 Hz, 1H), 6.90 (d, J = 3.2 Hz, 1H), 6.95 (dd, J = 5.2 Hz, 3.2 Hz, 1H), 7.20 (d, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.2, 28.0, 29.7, 31.2, 59.9, 82.6, 101.4, 114.8, 124.3, 124.4, 126.9, 142.1, 144.4, 160.1, 164.2, 166.9; IR (CH_2Cl_2) ν 2983, 2360, 2342, 1733, 1715, 1659, 1507, 1372, 1276, 1260, 1115, 848, 750, 668 cm^{-1}; MS (ESI) m/z 351.1 (M + H$^+$); HRMS (ESI) Calcd for $C_{18}H_{23}SO_5$ requires (M + H$^+$): 351.1261, Found: 351.1275; $[\alpha]_D^{20}$ = −178.8 (c 0.50, CH_2Cl_2) (91% ee); Chiralcel IC, hexane/^{i}PrOH = 98/2, 0.6 mL min^{-1}, 254 nm, t_{major} = 26.81 min, t_{minor} = 30.47 min.

(*E*)-Ethyl 4-cyclopropyl-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydro-2*H*-pyran-6-carboxylate 3oa. A slightly yellow liquid (26.0 mg, 83%); This is a known compound;[8f] ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 0.23–0.26 (m, 2H), 0.52–0.56 (m, 2H), 0.70–0.76 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.72–1.79 (m, 1H), 2.92 (dd, J = 15.2 Hz, 8.4 Hz, 1H), 3.48 (dd, J = 15.2 Hz, 5.6 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 4.27–4.32 (m, 2H), 5.70 (s, 1H), 6.32 (d, J = 4.0 Hz, 1H); $[\alpha]_D^{20}$ = −69.1 (c 1.00, CH_2Cl_2) (86% ee); Chiralcel OJ-H, hexane/^{i}PrOH = 98/2, 0.6 mL min^{-1}, 254 nm, t_{major} = 17.47 min, t_{minor} = 22.76 min.

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