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Catalytic asymmetric cycloetherification via intramolecular oxy-Michael addition of enols

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ABSTRACT

Carbonyl compounds employed as carbon nucleophiles have played a dominant role in synthetic organic chemistry; however, there is very limited use of these compounds as oxygen nucleophiles. In particular, there are only a few reports on the oxy-Michael addition of the enol forms of carbonyl nucleophiles. In this study, we present the asymmetric cycloetherification of enols, which are generated *in situ* from enone-bearing ketones, using chiral bifunctional organocatalysts bearing amino and squaramide groups. This transformation chemo- and enantioselectively afforded dihydropyran derivatives, which are the core structures of building blocks for synthesizing glycans.

1. Introduction

Carbonyl compounds as carbon nucleophiles have played a dominant role in synthetic organic chemistry [1], but have not been widely employed as oxygen nucleophiles [2]. In particular, the oxy-Michael addition of the enol forms of carbonyl nucleophiles is challenging, as strongly basic conditions should be avoided due to the potential oligomerization of Michael acceptors and the intrinsic reversibility of the reaction [3]. The sole enantioselective precedent employs highly enolizable α-aryl aldehydes [2a]; however, for promoting the formation of enol forms of ketones under nearly neutral conditions, it is useful to introduce electron-withdrawing groups for increasing the acidity at the α-position (Scheme 1a, **A**). However, this also accelerates competing nucleophilic additions to the carbonyl group, providing transient saturated alcohols, which serve as more nucleophilic oxygen nucleophiles to afford side products (Scheme 1a, **B**). We have reported the organocatalytic asymmetric cycloetherification reactions of such intermediary saturated alcohols to synthesize optically active tetrahydropyran derivatives [4]. In the course of the most recent study on the cycloetherification of *gem*-diols, which are generated *in situ* from electron-deficient ketones and water, intramolecular oxy-Michael addition of the enol forms of the ketone substrates proceeded as a side reaction [4f]. Inspired by these results, we then decided to identify catalysts for selectively promoting the intramolecular oxy-Michael addition via enol formation. In this study, we present the asymmetric cycloetherification of enols, which are generated *in situ* from enone-bearing ketones under mild conditions, using chiral bifunctional organocatalysts bearing amino and squaramide groups (Scheme 1b). This transformation chemo- and enantioselectively afforded dihydropyran derivatives, which are the core structures of building blocks for glycan synthesis [5].

2. Results and discussions

2.1. Optimization of catalysts and reaction conditions

We began our investigations using ethyl (*E*)-8-(4-methoxyphenyl)-2,8-dioxooct-6-enoate (**1a**) with 10 mol % of a bifunctional organocatalyst (**4a**–**4k**, Fig. 1) [6] in CH_2Cl_2 at 25 °C (Table 1, entries 1–11). First, hydrogen bond donors in quinine-derived bifunctional catalysts were screened (Table 1, entries 1–4). Thiourea catalyst **4a** provided the desired product **2a** in 72 % yield with 86 % *ee*, along with 11 % yield of a side product **3a**, which was formed through cycloetherification of a *gem*-diol generated *in situ* from **1a** and trace amounts of water present even in dehydrated solvents (Table 1, entry 1). The formation of **3a** could not be

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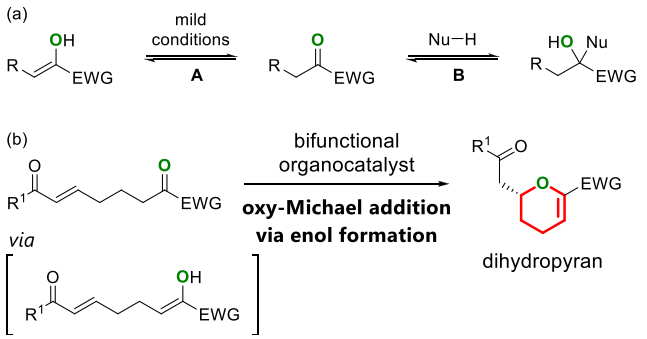


Scheme 1. Asymmetric intramolecular oxy-Michael addition via formation of enol forms of ketones.

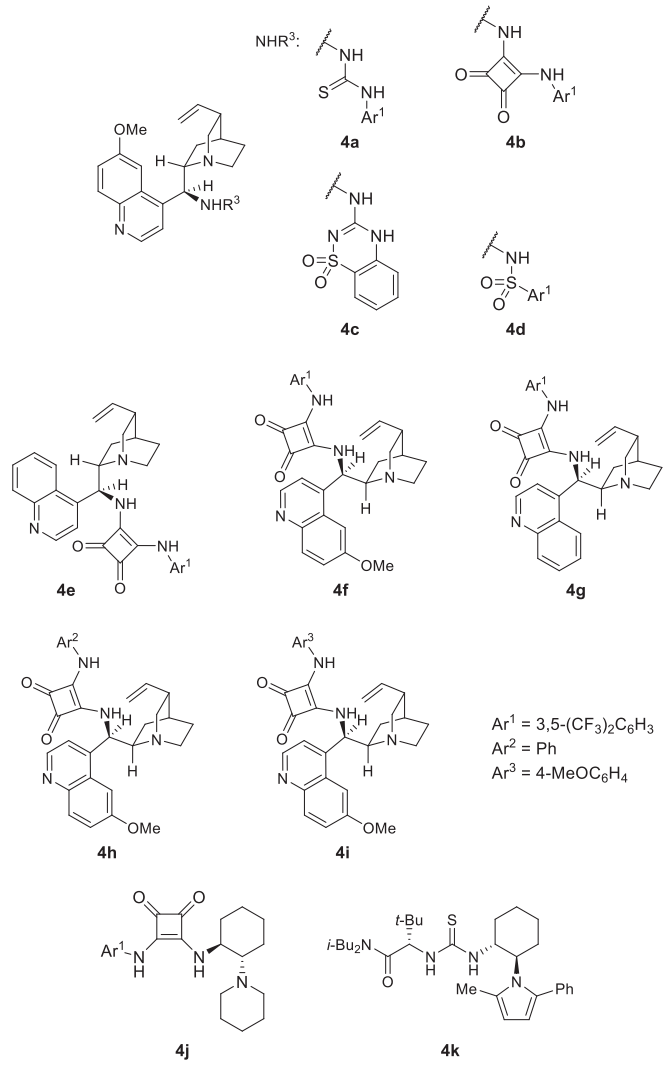
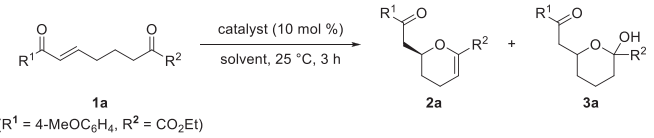


Fig. 1. Organocatalysts.

inhibited even after the addition of various dehydrating agents (see Table S1 in the SI for details). To solve this problem, the catalyst was then modified. The use of squaramide [7] catalyst **4b** selectively afforded **2a** in 93 % yield without the formation of **3a** (Table 1, entry 2). Benzothiadiazine [8] **4c** and sulfonamide [9] **4d** were much less effective (Table 1, entries 3 and 4). Next, squaramide catalysts bearing various chiral structures were investigated (Table 1, entries

Table 1
Optimization of conditions.[a]



entry	catalyst	solvent	yield of **2a** (%)[b]	ee of **2a** (%)	yield of **3a** (%)[b]
1	**4a**	CH_2Cl_2	72	86	11
2	**4b**	CH_2Cl_2	93	85	<1
3	**4c**	CH_2Cl_2	18	74	16
4	**4d**	CH_2Cl_2	6	14	19
5	**4e**	CH_2Cl_2	91	86	2
6	**4f**	CH_2Cl_2	92	−90	2
7	**4g**	CH_2Cl_2	95	−85	2
8	**4h**	CH_2Cl_2	89	−92	1
9	**4i**	CH_2Cl_2	91 (92[c])	−93	1 (1[c])
10	**4j**	CH_2Cl_2	65	−57	8
11	**4k**	CH_2Cl_2	<1	–	<1
12	**4i**	$CHCl_3$	81	−91	1
13	**4i**	toluene	45	−89	2
14	**4i**	hexane	26	−85	7
15	**4i**	THF	62	−92	1
16	**4i**	Et_2O	33	−90	2
17	**4i**	EtOAc	51	−92	1
18	**4i**	MeCN	53	−90	<1

[a] Reactions were run using **1a** (0.15 mmol) and the catalyst (0.015 mmol) in the solvent (0.30 mL).
[b] NMR yields.
[c] Isolated yields.

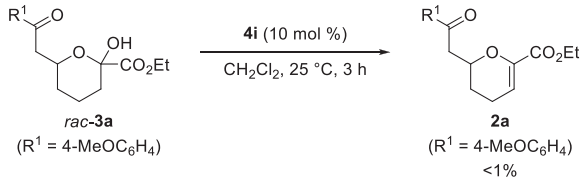
5–10). Other cinchona alkaloid derivatives **4e**–**4g** resulted in similarly efficient reactions (Table 1, entries 5–7), and quinidine- and cinchonine-derived catalysts **4f** and **4g** afforded the opposite enantiomer of **2a** with high enantioselectivities. The electronic properties of the squaramide groups of quinidine-derived catalysts were also altered, and more electron-rich catalysts proved to be more enantioselective while maintaining high yields of **2a** (Table 1, entries 6, 8, and 9). In contrast, catalyst **4j**, which has a cyclohexanediamine framework, afforded **2a** in a lower yield and enantioselectivity along with a higher amount of **3a** (Table 1, entry 10). Thus, the efficiency of the current catalytic system is attributed not only to the functionality of the squaramide group but also to the chiral scaffolds of the catalysts [10]. In addition, catalyst **4k**, which has a significantly less basic nitrogen atom, did not provide **2a** (Table 1, entry 11), thus demonstrating the significance of the bifunctionality of the catalyst containing hydrogen bond donor and acceptor moieties. Various solvents were next investigated using **4i** as the catalyst (Table 1, entries 12–18); the use of CH_2Cl_2 led to better results (Table 1, entry 9).

2.2. Mechanistic insights

To gain insights into the chemoselectivity, racemic **3a** (*rac*-**3a**) was exposed to the reaction conditions, and no dehydrated product **2a** was obtained (Scheme 2). This result suggested that the formation of **2a** was kinetically controlled by **4i** through the oxy-Michael addition of the enol, and not through dehydration after the formation of **3a** [11].

2.3. Substrate scope and gram-scale synthesis

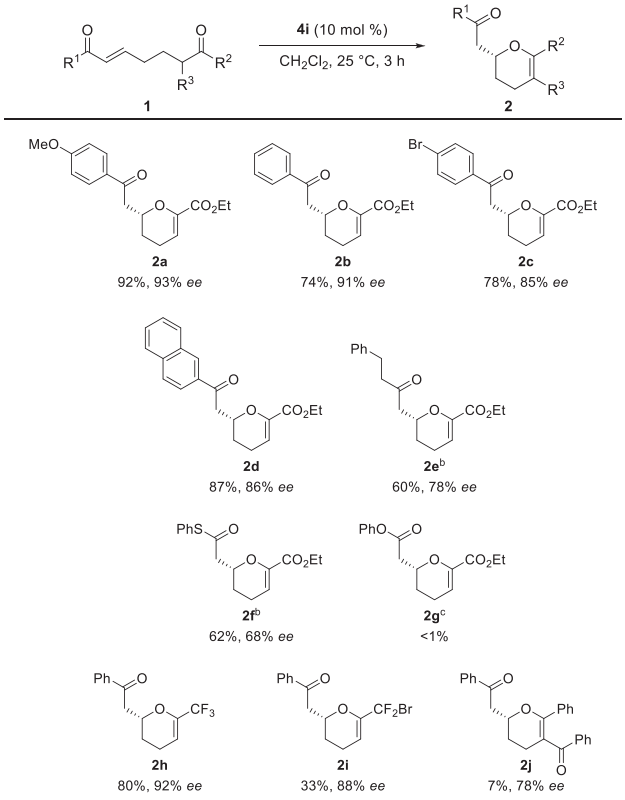
With the optimized conditions in hand, we next explored the substrate scope (Table 2). Not only electron-rich but also less



Scheme 2. Reaction of **3a**.

fluorinated dihydropyran derivative in high yield and enantioselectivity (Table 2, **2h**), even though the ketone of **1h** was likely to be hydrated [4f]. A bromodifluoromethyl ketone also provided the desired product in moderate yield with high enantioselectivity (Table 2, **2i**). Such halodifluoromethyl groups give access to a wide variety of difluoroalkylated compounds [14], which impart unique pharmacological properties associated with fluorinated functional groups. As another type of substrate, a 1,3-diketone yielded the

Table 2
Substrate scope.[a]

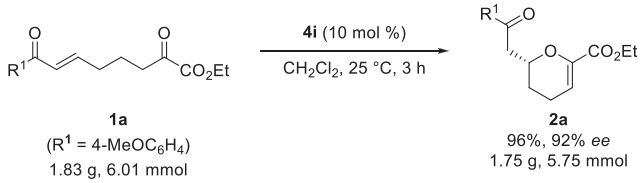


[a] Reactions were run using **1** (0.15 mmol) and **4i** (0.015 mmol) in CH_2Cl_2 (0.30 mL). Yields represent material isolated after silica gel column chromatography.

[b] Reaction was run for 24 h.

[c] Reaction was run at 50 °C for 24 h.

electron-rich enones were tolerated under the reaction conditions, affording the corresponding products in good yields with high enantioselectivities (Table 2, **2a**–**2c**). The halogen group is useful as it can be converted to other functional groups (Table 2, **2c**). An enone bearing a 2-naphthyl group also provided the product in high yield with good enantioselectivity (Table 2, **2d**). An aliphatic enone also yielded the product in moderate yield with good enantioselectivity after 24 h (Table 2, **2e**). In addition, an α,β-unsaturated thioester, which is useful for further transformations because of its higher oxidation state [12,13], afforded the desired product in moderate yield and enantioselectivity after 24 h (Table 2, **2f**), while an α,β-unsaturated ester failed to furnish the product even at higher temperatures and after longer reaction times (Table 2, **2g**). We also investigated the effect of substituents (R^2) on the ketones. A trifluoromethyl group-bearing ketone formed a corresponding product with moderate enantioselectivity, albeit in a low yield (Table 2, **2j**). Furthermore, the gram-scale synthesis of **2a** was carried out (Scheme 3). The reaction proceeded smoothly when using 1.83 g (6.01 mmol) of **1a** under the optimized conditions, and 1.75 g (5.75 mmol, 96%) of **2a** was obtained with 92 % *ee*.



Scheme 3. Gram-scale synthesis of **2a**.

The absolute configuration of **2h** was determined by comparing the optical rotation with the literature value [4f], and the configurations of all other products **2** were assigned analogously.

2.4. Transformations of the product

The utility of the dihydropyran derivatives was demonstrated by the transformation of the products. In the presence of *N*-bromosuccinimide in an aqueous medium, difunctionalization of the unsaturated bond of **2a** occurred efficiently to furnish bromohydrin **5** bearing a structure analogous to that of sialic acids, without erosion of the enantiomeric purity (Scheme 4).

3. Conclusions

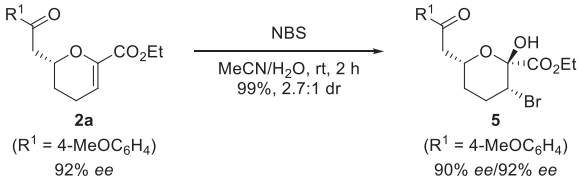
In conclusion, asymmetric cycloetherification via intramolecular oxy-Michael addition of enols, which are generated *in situ* from enone-bearing ketones, was developed using chiral bifunctional organocatalysts bearing amino and squaramide groups. This transformation afforded dihydropyran derivatives, that is artificial glycals, with high chemo- and enantioselectivities. The product was also transformed through difunctionalization by taking advantage of the presence of an unsaturated bond moiety. Further studies to expand the scope of this methodology and its application to the asymmetric synthesis of bioactive glycans are underway in our laboratory.

4. Experimental section

4.1. Instrumentation and chemicals

^{1}H and ^{13}C Nuclear magnetic resonance spectra were taken on a Varian UNITY INOVA 500 (^{1}H, 500 MHz; ^{13}C, 125.7 MHz) spectrometer using tetramethylsilane as an internal standard for ^{1}H NMR (δ = 0 ppm) and $CDCl_3$ as an internal standard for ^{13}C NMR (δ = 77.0 ppm). When a ^{13}C NMR spectrum was measured using DMSO-d_6 as a solvent, DMSO-d_6 was used as an internal standard (δ = 39.52 ppm). When a ^{13}C NMR spectrum was measured using C_6D_6 as a solvent, C_6D_6 was used as an internal standard (δ = 128.06 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{19}F NMR spectra were measured on a Varian Mercury 200 (^{19}F, 188 MHz) spectrometer with hexafluorobenzene as an internal standard (δ = 0 ppm). Mass spectra were recorded on a SHIMADZU GCMS-QP2010 Plus (EI) and a Thermo Scientific Exactive (ESI, APCI) spectrometers. High performance liquid chromatography (HPLC) was performed with a SHIMADZU Prominence. Infrared (IR) spectra were determined on a SHIMADZU IR Affinity-1 spectrometer. Melting points were determined using a YANAKO MP-500D. Optical rotations were measured on a HORIBA SEPA-200. X-ray data were taken on a Rigaku XtaLAB mini diffractometer equipped with a CCD detector. TLC analyses were performed by means of Merck Kieselgel 60 F_{254} (0.25 mm) Plates. Visualization was accomplished with UV light (254 nm) and/or such as an aqueous alkaline $KMnO_4$ solution followed by heating.

Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 μm). Preparative recycling gel permeation chromatography (GPC) was performed with LC-9160II NEXT equipped with JAIGEL-1H column. Unless otherwise noted, commercially available reagents were used without purification.



Scheme 4. Bromohydroxylation of **2a**.

4.2. Experimental procedure

General procedure for asymmetric synthesis of dihydropyrans 2. Substrate **1** (0.15 mmol), CH_2Cl_2 (0.30 mL), and catalyst **4i** (7.9 mg, 0.015 mmol) were sequentially added to a 10-mL vial with a screw cap. The mixture was stirred in an oil bath maintained at 25 °C for 3 h. The reaction mixture was subsequently diluted with EtOAc, passed through a short silica gel pad to remove **4i**, and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1–3:1) as an eluent afforded the corresponding dihydropyran **2**.

Racemic dihydropyrans **2** were prepared using 1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-(dimethylamino)ethyl)thiourea (**4l**) as a catalyst. The synthesis was carried out in an oil bath maintained at 50 °C for 24 h (10–60 % yields).

Procedure for bromohydroxylation of 2a. [15] A solution of **2a** (0.030 g, 0.10 mmol, 92 % *ee*) and NBS (20 mg, 0.11 mmol) in MeCN/H_2O (v/v = 5:2, 0.66 mL) was stirred at ambient temperature for 2 h. The mixture was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 5:1) as an eluent gave bromohydrin **5**.

4.3. Characterization data of products

Ethyl 2-(2-(4-methoxyphenyl)-2-oxoethyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (2a). Yield: 92 % (42 mg), 93 % *ee*, yellow oil, yield of **3a**: 1 %. $[\alpha]_D^{18}$ +14.8 (*c* 1.15, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.10 (dd, *J* = 4.0, 4.0 Hz, 1H), 4.51 (m, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 3.55 (dd, *J* = 16.5, 4.5 Hz, 1H), 3.17 (dd, *J* = 16.5, 8.0 Hz, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.61 (m, 1H), 1.29 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 195.9, 163.7, 162.9, 144.2, 130.5, 130.0, 113.8, 111.2, 73.0, 61.0, 55.5, 43.3, 26.5, 20.5, 14.2. TLC: R_f 0.20 (hexane/EtOAc = 3:1). IR (neat): 2935, 1736, 1679, 1654, 1601, 1576, 1521, 1267, 1173, 1105, 1029, 830, 748 cm^{-1}. HRMS Calcd for $C_{17}H_{20}O_5Na$: $[M+Na]^+$, 327.1203. Found *m/z* 327.1204. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 96/4, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 13.1 min, t_{major} = 15.7 min.

Ethyl 2-hydroxy-6-(2-(4-methoxyphenyl)-2-oxoethyl)tetrahydro-2*H*-pyran-2-carboxylate (3a). The diastereomers and unidentified products could not be separated. **Diastereomer mixture**: yield: 1 % (4.8 mg), ca. 1:1 dr, orange oil. ^{1}H NMR ($CDCl_3$) δ 7.92–7.88 (m, 4H), 6.95–6.90 (m, 4H), 4.64–4.59 (m, 2H), 4.28–4.18 (m, 4H), 3.83 (s, 3H), 3.83 (s, 3H), 3.58–3.52 (m, 2H), 3.18–3.10 (m, 2H), 2.46–2.23 (m, 8H), 1.87–1.79 (m, 2H), 1.72–1.59 (m, 2H), 1.58–1.46 (m, 2H), 1.28–1.23 (m, 6H). ^{13}C NMR ($CDCl_3$) δ194.7 (2C), 167.9 (2C), 163.3 (2C), 130.7, 130. 5, 130.4, 130.3, 113.8, 113.7, 86.2, 86.1, 75.1, 75.0, 62.3 (2C), 55.4, 55.3, 42.6, 42.4, 31.9 (2C), 26.2, 26.1, 21.7, 21.6, 14.0 (2C). TLC: R_f 0.20 (hexane/EtOAc = 1:1). IR (neat): 3540, 2936, 2842, 1788, 1671, 1599, 1508, 1466, 1432, 908, 856, 729 cm^{-1}. HRMS Calcd for $C_{17}H_{22}O_6Na$: $[M+Na]^+$, 345.1309. Found *m/z* 345.1310.

Ethyl 2-(2-oxo-2-phenylethyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (2b). Yield: 74 % (31 mg), 91 % *ee*, colorless oil, yield of **3b**: <1 %. $[\alpha]_D^{18}$ − 1.81 (*c* 1.16, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.98 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.0 Hz, 1H), 7.48 (dd, *J* = 7.5, 7.0 Hz, 2H), 6.11 (dd, *J* = 4.0, 4.0 Hz, 1H), 4.54 (m, 1H), 4.23 (q, *J* = 7.0 Hz, 2H),

3.61 (dd, J = 17.0, 4.5 Hz, 1H), 3.23 (dd, J = 17.0, 8.0 Hz, 1H), 2.34 (m, 1H), 2.20 (m, 1H), 2.12 (m, 1H), 1.62 (m, 1H), 1.29 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 197.4, 162.9, 144.2, 136.9, 133.3, 128.7, 128.2, 111.2, 73.0, 61.0, 43.6, 26.5, 20.5, 14.2. TLC: R_f 0.25 (hexane/EtOAc = 3:1). IR (neat): 2981, 2928, 1733, 1692, 1649, 1597, 1449, 1270, 1222, 1105, 1002, 756, 692 cm^{-1}. HRMS Calcd for $C_{16}H_{18}O_4Na$: $[M+Na]^+$, 297.1097. Found m/z 297.1092. HPLC (Daicel Chiralpak IA, hexane/i-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 230 nm, 30 °C): t_{minor} = 4.1 min, t_{major} = 4.9 min.

Ethyl 2-(2-(4-bromophenyl)-2-oxoethyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (2c). Yield: 78 % (41 mg), 85 % *ee*, white solid, yield of **3c**: <1 %. $[\alpha]_D^{18}$ +5.29 (c 1.21, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 9.0 Hz, 2H), 6.11 (m, 1H), 4.51 (m, 1H), 4.22 (q, J = 7.0 Hz, 2H), 3.55 (dd, J = 17.0, 5.0 Hz, 1H), 3.16 (dd, J = 17.0, 8.0 Hz, 1H), 2.32 (m, 1H), 2.20 (m, 1H), 2.09 (m, 1H), 1.60 (m, 1H), 1.29 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 196.5, 162.8, 144.4, 135.6, 132.0, 129.7, 128.6, 111.2, 72.8, 61.0, 43.6, 26.5, 20.5, 14.2. Mp. 59.5–60.5 °C. TLC: R_f 0.25 (hexane/EtOAc = 3:1). IR (KBr): 1722, 1689, 1641, 1585, 1459, 1398, 1264, 1220, 1125, 1093, 1071, 996, 962 cm^{-1}. HRMS Calcd for $C_{16}H_{17}BrO_4Na$: $[M+Na]^+$, 375.0202. Found m/z 375.0202. HPLC (Daicel Chiralpak IA, hexane/i-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 230 nm, 30 °C): t_{minor} = 15.4 min, t_{major} = 23.2 min.

Ethyl 2-(2-(naphthalen-2-yl)-2-oxoethyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (2d). Yield: 87 % (42 mg), 86 % *ee*, colorless oil, yield of **3d**: <1 %. $[\alpha]_D^{18}$ +29.1 (c 1.19, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.52 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.91–7.87 (m, 2H), 7.63–7.55 (m, 2H), 6.13 (m, 1H), 4.60 (m, 1H), 4.22 (q, J = 7.0 Hz, 2H), 3.75 (dd, J = 17.0, 4.5 Hz, 1H), 3.35 (dd, J = 17.0, 8.5 Hz, 1H), 2.33 (m, 1H), 2.24–2.14 (m, 2H), 1.67 (m, 1H), 1.27 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 197.3, 162.9, 144.2, 135.7, 134.2, 132.5, 130.2, 129.7, 128.6, 128.5, 127.8, 126.8, 123.7, 111.2, 73.0, 61.0, 43.7, 26.5, 20.5, 14.2. TLC: R_f 0.25 (hexane/EtOAc = 3:1). IR (neat): 2927, 1735, 1682, 1648, 1270, 1218, 1106, 748 cm^{-1}. HRMS Calcd for $C_{20}H_{20}O_4Na$: $[M+Na]^+$, 347.1254. Found m/z 347.1253. HPLC (Daicel Chiralpak IA, hexane/i-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 230 nm, 30 °C): t_{minor} = 17.2 min, t_{major} = 23.7 min.

Ethyl 2-(2-oxo-4-phenylbutyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (2e). Yield: 60 % (27 mg), 78 % *ee*, colorless oil, yield of **3e**: <1 %. $[\alpha]_D^{18}$ − 21.9 (c 0.913, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 2H), 7.19–7.17 (m, 3H), 6.06 (dd, J = 4.0, 4.0 Hz, 1H), 4.31 (m, 1H), 4.22 (q, J = 7.0 Hz, 2H), 2.98–2.77 (m, 5H), 2.60 (dd, J = 16.0, 7.0 Hz, 1H), 2.27 (m, 1H), 2.14 (m, 1H), 1.92 (m, 1H), 1.53 (m, 1H), 1.28 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 207.5, 162.8, 144.0, 140.9, 128.5, 128.3, 126.1, 110.9, 72.5, 61.0, 47.8, 45.2, 29.5, 26.4, 20.4, 14.2. TLC: R_f 0.25 (hexane/EtOAc = 3:1). IR (neat): 2928, 1722, 1648, 1372, 1300, 1270, 1220, 1105, 751, 700 cm^{-1}. HRMS Calcd for $C_{18}H_{22}O_4Na$: $[M+Na]^+$, 325.1410. Found m/z 325.1407. HPLC (Daicel Chiralpak IB, hexane/i-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 18.1 min, t_{minor} = 21.8 min.

Ethyl 2-(2-oxo-2-(phenylthio)ethyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (2f). Yield: 62 % (31 mg), 68 % *ee*, yellow oil, yield of **3e**: 9 %. $[\alpha]_D^{18}$ +81.5 (c 0.130, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.42 (m, 5H), 6.10 (dd, J = 5.0, 5.0 Hz, 1H), 4.41 (m, 1H), 4.25 (q, J = 7.0 Hz, 2H), 3.21 (dd, J = 16.0, 6.0 Hz, 1H), 2.89 (dd, J = 16.0, 7.5 Hz, 1H), 2.30–2.18 (m, 2H), 2.04 (m, 1H), 1.67 (m, 1H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 194.5, 162.7, 143.9, 134.7, 129.6, 129.2, 127.4, 111.0, 72.6, 61.1, 48.0, 26.0, 20.1, 14.2. TLC: R_f 0.40 (hexane/EtOAc = 3:1). IR (neat): 2985, 2928, 1728, 1649, 1481, 1442, 1300, 1270, 1226, 1103, 987, 751 cm^{-1}. HRMS Calcd for $C_{16}H_{18}O_4SNa$: $[M+Na]^+$, 329.0818. Found m/z 329.0821. HPLC (Daicel Chiralpak IC, hexane/i-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 225 nm, 30 °C): t_{minor} = 9.8 min, t_{major} = 10.7 min.

(*R*)-1-Phenyl-2-(6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-yl)ethan-1-one (2h). Yield: 80 % (33 mg), 92 % *ee*, white solid, yield of **3g**: 17 %. $[\alpha]_D^{18}$ − 24.3 (c 0.803, CH_2Cl_2). ^{1}H NMR (C_6D_6) δ 7.69 (m, 2H), 7.11 (tt, J = 7.0, 1.5 Hz, 1H), 7.02 (m, 2H), 5.15 (m, 1H), 4.34 (m, 1H), 3.02 (dd, J = 17.0, 4.5 Hz, 1H), 2.42 (dd, J = 17.0, 8.0 Hz, 1H), 1.66–1.56 (m, 2H), 1.47 (m, 1H), 1.11 (m, 1H). ^{13}C NMR (C_6D_6) δ 195.6, 142.6 (q, J = 34.6 Hz), 136.8, 132.8, 128.3, 127.9, 120.3 (q, J = 272.3 Hz), 102.7 (q, J = 3.9 Hz), 73.1, 42.9, 26.1, 18.9. ^{19}F NMR (C_6D_6) δ 90.4 (s, 3F). Mp. 51.0–52.0 °C. TLC: R_f 0.40 (hexane/EtOAc = 3:1). IR (KBr): 2925, 1701, 1690, 1680, 1653, 1560, 1508, 1457, 1437, 1420, 1318, 1183, 1120, 1090, 947 cm^{-1}. HRMS Calcd for $C_{14}H_{13}F_3O_2Na$: $[M+Na]^+$, 293.0760. Found: m/z 293.0759. HPLC (Daicel Chiralpak IA, hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, λ = 225 nm, 30 °C): t_{minor} = 6.7 min, t_{major} = 8.7 min.

2-(6-(Bromodifluoromethyl)-3,4-dihydro-2*H*-pyran-2-yl)-1-phenylethan-1-one (2i). Yield: 33 % (16 mg), 88 % *ee*, white solid, yield of **3h**: 22 %. $[\alpha]_D^{18}$ − 5.46 (c 0.513, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 8.5 Hz, 2H), 7.59 (tt, J = 7.0, 1.5 Hz, 1H), 7.48 (dd, J = 8.5, 7.0 Hz, 2H), 5.43 (m, 1H), 4.64 (m, 1H), 3.57 (dd, J = 17.0, 5.5 Hz, 1H), 3.19 (dd, J = 17.0, 7.5 Hz, 1H), 2.26 (m, 1H), 2.20–2.09 (m, 2H), 1.69 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.1, 147.5 (t, J = 38.7 Hz), 136.8, 133.4, 128.7, 128.2, 114.1 (t, J = 452 Hz), 100.4 (t, J = 7.1 Hz), 73.4, 43.2, 26.6, 19.3. ^{19}F NMR ($CDCl_3$) δ 107.5 (s, 1F), 107.4 (s, 1F). Mp. 64.0–65.0 °C. TLC: R_f 0.50 (hexane/EtOAc = 3:1). IR (KBr): 1689, 1680, 1451, 1272, 1215, 1153, 1085, 880, 788 cm^{-1}. HRMS Calcd for $C_{14}H_{13}BrF_2O_2Na$: $[M+Na]^+$, 352.9959. Found: m/z 352.9959. HPLC (Daicel Chiralpak IA, hexane/i-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 230 nm, 30 °C): t_{minor} = 3.2 min, t_{major} = 3.8 min.

2-(5-Benzoyl-6-phenyl-3,4-dihydro-2*H*-pyran-2-yl)-1-phenylethan-1-one (2j). Yield: 7 % (4.0 mg), 78 % *ee*, white solid. $[\alpha]_D^{18}$ +40.5 (c 0.153, CH_2Cl_2, −36 % *ee*). ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 7.0 Hz, 2H), 7.60 (t, J = 7.0 Hz, 1H), 7.55 (d, J = 7.5 Hz, 2H), 7.50 (dd, J = 7.0, 7.0 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.0 Hz, 2H), 7.08 (dd, J = 7.5, 7.5 Hz, 2H), 7.03 (t, J = 7.0 Hz, 1H), 6.98 (dd, J = 7.0, 7.0 Hz, 2H), 4.85 (m, 1H), 3.67 (dd, J = 17.0, 7.5 Hz, 1H), 3.23 (dd, J = 17.0, 5.5 Hz, 1H), 2.99 (ddd, J = 17.5, 6.0, 2.5 Hz, 1H), 2.51 (ddd, J = 17.5, 11.0, 7.0 Hz, 1H), 2.27 (dddd, J = 13.5, 7.0, 2.5, 2.0 Hz, 1H), 1.84 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 198.7, 197.3, 160.9, 139.0, 136.9, 135.2, 133.4, 131.4, 129.5, 129.4, 129.3, 128.7, 128.2, 127.6 (2C), 112.1, 73.6, 43.5, 27.3, 23.8. Mp. 71.0–72.0 °C. TLC: R_f 0.30 (hexane/EtOAc = 3:1). IR (KBr): 1685, 1645, 1623, 1597, 1448, 1351, 1288, 1163, 693 cm^{-1}. HRMS Calcd for $C_{26}H_{22}O_3Na$: $[M+Na]^+$, 405.1461. Found m/z 405.1452. HPLC (Daicel Chiralpak IA, hexane/i-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 16.9 min, t_{major} = 18.8 min.

Ethyl 3-bromo-2-hydroxy-6-(2-(4-methoxyphenyl)-2-oxoethyl)tetrahydro-2*H*-pyran-2-carboxylate. Yield: 99 % (40 mg), 2.7:1 dr. **Major diastereomer (5)**: 90 % *ee*, yellow oil. $[\alpha]_D^{18}$ +19.1 (c 1.10, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 4.75 (dddd, J = 12.0, 6.0, 6.0, 2.5 Hz, 1H), 4.37 (dd, J = 3.0, 3.0 Hz, 1H), 4.31–4.21 (m, 2H), 3.87 (s, 3H), 3.48 (dd, J = 17.5, 6.0 Hz, 1H), 3.06 (dd, J = 17.5, 6.0 Hz, 1H), 2.65 (m, 1H), 2.06 (m, 1H), 1.93 (m, 1H), 1.68 (m, 1H), 1.30 (dd, J = 7.0, 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 196.4, 168.8, 163.7, 130.6, 130.5, 113.7, 95.3, 68.1, 62.2, 55.5, 49.1, 44.0, 27.2, 25.0, 14.0. TLC: R_f 0.40 (hexane/EtOAc = 1:1). IR (neat): 3403, 2966, 1740, 1672, 1601, 1576, 1507, 1262, 1174, 844, 749 cm^{-1}. HRMS Calcd for $C_{17}H_{21}BrO_6Na$: $[M+Na]^+$, 423.0414. Found m/z 423.0418. HPLC (Daicel Chiralpak IC, hexane/i-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 7.0 min, t_{minor} = 21.9 min. **Minor diastereomer (5′)**: 92 % *ee*, colorless oil. $[\alpha]_D^{18}$ +3.46 (c 0.693, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 4.72 (dddd, J = 12.0, 7.0, 7.0, 2.5 Hz, 1H), 4.41–4.36 (m, 2H), 4.27 (br s, 1H), 4.25 (dq, J = 18.0, 7.0 Hz, 1H), 3.87 (s, 3H), 3.23 (dd, J = 15.5, 7.0 Hz, 1H), 2.82 (dd, J = 15.5, 7.0 Hz, 1H), 2.43 (m, 1H), 2.21 (m, 1H), 1.97 (m, 1H), 1.63 (m, 1H), 1.33 (dd, J = 7.0, 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 195.7, 168.7, 163.6, 130.5, 130.1, 113.7, 95.0, 67.4, 63.2, 55.5, 48.6, 43.7, 33.1, 29.4,

14.0. TLC: R_f 0.55 (hexane/EtOAc = 1:1). IR (neat): 3457, 2952, 1753, 1676, 1600, 1264, 1213, 1173, 1054, 916, 839, 731 cm^{-1}. HRMS Calcd for $C_{17}H_{21}BrO_6Na$: $[M+Na]^+$, 423.0414. Found *m/z* 423.0415. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 9.3 min, t_{major} = 18.3 min.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132381.

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[10] Even in the presence of 3.0 equiv of water, **3a** was formed only in 2%, and **2a** was obtained in 73% yield with 91% ee (see Scheme S1 in the SI for details).
[11] The enantioselectivity gradually decreased as the reaction time increased (see Scheme S2 in the SI for details). The reaction time of 3 h was the optimal from the viewpoints of both yield and enantioselectivity. When racemic **2a** was exposed to the reaction conditions, the hydrated product **3a** was obtained, and **2a** recovered in an optically active form (see Scheme S3 in the SI for details). These results indicate the reversibility of the oxy-Michael addition of the enol, even under such near-neutral conditions, implying the intrinsic difficulty of the reaction. In addition, **4i** selectively catalyzed the retro-Michael addition from one enantiomer of **2a**, which is the major enantiomer of the product mentioned in Table 2, leading to a gradual change in the optical purity of **2a**.
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