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Bifunctional cinchona alkaloids-catalyzed asymmetric [4+2] cycloaddition reaction of β,γ-unsaturated α-keto esters with oxazolones

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ABSTRACT

A highly enantioselective [4+2] cycloaddition reaction of β,γ-unsaturated α-keto esters with oxazolones was realized with readily available cinchona alkaloids as the catalysts. Using this reaction, a series of highly functionalized δ-lactones with adjacent α-quaternary-β-tertiary stereocenters were obtained in high yields (up to 97%) and with good-to-excellent enantioselectivities (up to 97% ee).

1. Introduction

Chiral six-membered oxygenated heterocycles are one of the most common structural motifs present in numerous biologically active compounds. Consequently, a myriad of methods have been developed for their stereoselective construction.[1] Recently, our group has engaged in the chemistry of β,γ-unsaturated α-keto esters as a versatile reaction partner in a series of organocatalyzed reactions.[2–7] Compared to simple α,β-unsaturated ketones, these keto esters not only usually demonstrated better reactivities due to their enhanced electrophilicity, but also allowed facile conversions of the corresponding products to many other useful structure mainly based on the ready convertibility of the ester group. Some previous works from our group and others[2b,d,f,g,3a,c–j,l–n,4c,5a,i] have demonstrated the utility of β,γ-unsaturated α-keto esters to prepare chiral six-membered oxygenated heterocycles with certain nucleophiles. In most of these works, both the alkene and carbonyl groups in the keto esters served as electrophilic sites. We recently discovered a cinchona alkaloids-catalyzed unexpected Michael addition/oxa-nucleophilic rearrangement reaction of β,γ-unsaturated α-keto esters with substituted malonates.[2a] In this reaction, the carbonyl oxygen atom of the keto esters was found to act as a nucleophile after the initial Michael addition. Thus, we assumed that the use of a reaction partner with rightly positioned nucleophilic and electrophilic sites would allow the formation chiral six-membered oxygenated heterocycles.

With orthogonal nucleophilic and electrophilic reactive sites, the oxazolone then came to our sight as a suitable candidate for the above purpose. Oxazolones, also known as azlactones, have been utilized as versatile partners in a range of different reactions.[8] Gong and co-workers reported a three-component cyclization reaction between enals, aryl amines, and oxazolones to give chiral 3-amino-δ-lactones.[9] As our work is in progress, Feng and co-workers reported an asymmetric bisguanidine-catalyzed inverse-electron-demand hetero-Diels–Alder reaction of oxazolones with chalcones.[10] We now report here the cycloaddition of β,γ-unsaturated α-keto esters with oxazolones.[11] With readily available cinchona alkaloid catalysts, the reaction could be completed within several hours at room temperature to provide highly functionalized δ-lactones with adjacent α-quaternary-β-tertiary stereocenters in high yields and enantioselectivities.

2. Results and discussion

The reaction of 4-methyl-2-phenyloxazol-5(4*H*)-one **1a** with (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **2a** was selected as model reaction for the optimization of reaction parameters. With our experience in the reactions of β,γ-unsaturated α-keto esters,[2] we began the initial catalyst evaluation with several cinchona alkaloids (Table 1). The commercially available quinine **4a** catalyst gave the desired product **3a** in a highly encouraging 82% yield and 70% ee

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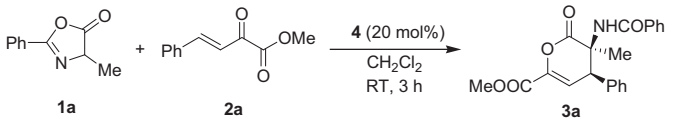
Table 1
Screening of different catalysts[a]



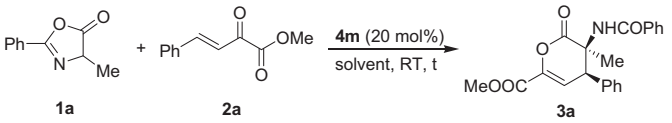
Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	**4a**	82	−70
2	**4b**	86	−91
3	**4c**	85	−85
4	**4d**	52	−3
5	**4e**	62	−5
6	**4f**	58	−60
7	**4g**	62	12
8	**4h**	82	90
9	**4i**	80	90
10	**4j**	94	91
11	**4k**	67	87
12	**4l**	92	92
13	**4m**	92	94
14[d]	**4m**	85	92
15[e]	**4m**	79	79
16[f]	**4m**	75	50

[a] Unless otherwise noted, the reaction was conducted with 0.11 mmol of **1a**, 0.1 mmol of **2a**, and 20 mol % of **4** in 1.0 mL of CH_2Cl_2.
[b] Isolated yields after column chromatography on silica gel.
[c] Determined by chiral HPLC analysis on a chiral column OD column. Only a single diastereoisomer was observed by ^1H and ^{13}C NMR.
[d] Compound **4m** of 15 mol % was used.
[e] Compound **4m** of 10 mol % was used.
[f] Compound **4m** of 5 mol % was used.

with exclusive diastereoselectivity (entry 1). While catalysts **4b** and **4c** with a free phenolic hydroxyl group and a protected alcohol moiety improved the results further, catalysts with both hydroxyl groups protected (**4d**) or exposed (**4e**) gave extremely poor results (entries 2–5). Such a phenomenon highlights the importance of the bifunctionality of the catalyst in this reaction. Two bifunctional thiourea catalysts **4f** and **4g**, which we have previously used to catalyze other reactions of β,γ-unsaturated α-keto esters,[2b,d,f,g] provided much inferior results here (entries 6 and 7). Changing the skeleton from quinine to quinidine in general led to similar results to their quinine counterparts, except that products of the opposite absolute configuration (entries 8–13). The optimal catalyst **4m** gave the desired product in 92% yield and 94% ee (entry 13). Unfortunately, decreasing the loading amount of the catalyst was found to be detrimental to both the yield and enantioselectivity (entries 14–16) (Fig. 1).

With the best catalyst **4m**, a variety of solvents were examined for the model reaction (Table 2). This reaction showed an excellent tolerance of solvents of different types: most solvents examined gave comparable good yields and enantioselectivities, and invariably exclusive diastereoselectivity. The only significantly lower yields obtained in the case of *n*-hexane may be ascribed to the poor solubility of the catalyst in this solvent (entry 5). In view of both the yield and enantioselectivity, the present reaction was best performed with 20 mol % of **4m** in Et_2O at room temperature (entry 4).

Table 2
Effect of the solvent on the reaction[a]



Entry	Solvent	*t* (h)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	3	92	94
2	Toluene	3	87	95
3	$CHCl_3$	3.5	89	95
4	Et_2O	3	92	95
5	*n*-Hexane	8	42	69
6	$PhCF_3$	4	82	93
7	Xylene	4	84	92
8	THF	5	95	92
9	$ClCH_2CH_2Cl$	5	85	93
10	MTBE	6	82	93

[a] Unless otherwise noted, the reaction was conducted with 0.11 mmol of **1a** and 0.10 mmol of **2a** in the presence of 20 mol % of **4m** in 1.0 mL of solvent.
[b] Isolated yields after column chromatography on silica gel.
[c] Determined by chiral HPLC analysis on an OD chiral column. Only a single diastereoisomer was observed by ^1H and ^{13}C NMR.

Having established the optimum reaction conditions, various β,γ-unsaturated α-keto esters were first tested to explore the reaction scope and the results were presented in Table 3. A broad substrate scope was observed here with the desired products obtained in high yields, excellent ee values and exclusive diastereoselectivity. Substrates **2a**–**g** with various differently substituted phenyl groups (R^1) on the alkene moiety, all worked well for the reaction, irrespective of the electronic nature or position of the substituents on the benzene ring (entries 1–7). Substrates bearing electron-donating substituents seemed to exhibit a higher ee value than those with electron-withdrawing ones (entries 6 and 7). Heterocyclic substrate **2h** (R^1=furan-2-yl) was also well tolerated (entry 8). In addition, variation in the substituents on the ester

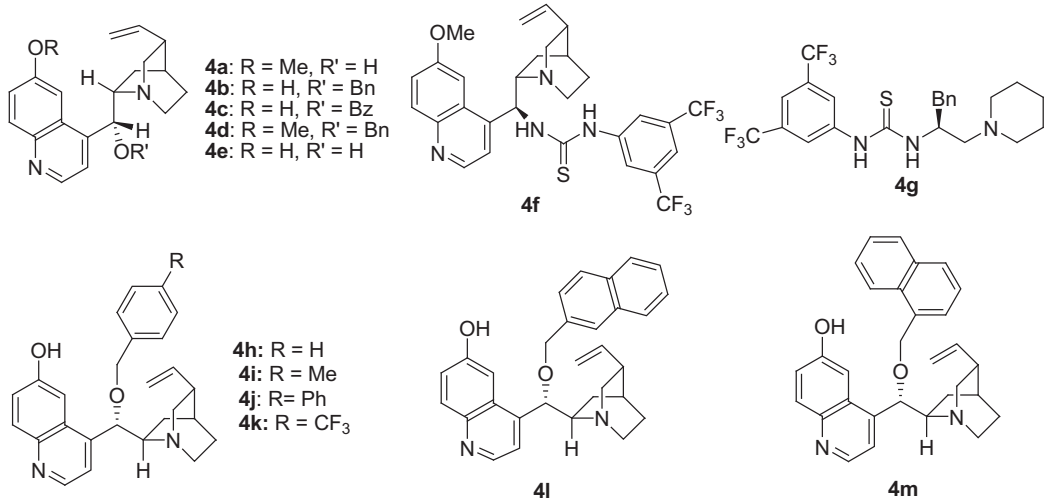
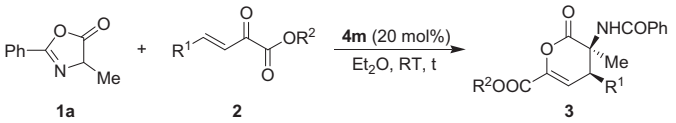


Fig. 1. Structures of chiral catalysts used in this reaction.

Table 3
Scope study with different β,γ-unsaturated α-keto esters[a]



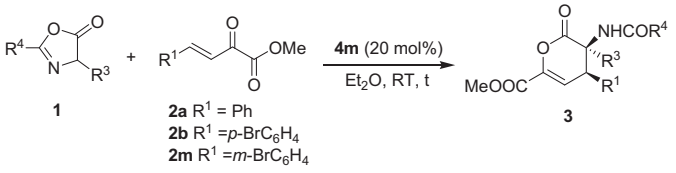
Entry	R^1, R^2, **2**	*t* (h)	**3**	Yield[b] (%)	Ee[c] (%)
1	C_6H_5, Me, **2a**	3	**3a**	91	95
2	*p*-BrC_6H_4, Me, **2b**	3	**3b**	95	94
3	*p*-MeC_6H_4, Me, **2c**	3.5	**3c**	85	93
4	*m*-FC_6H_4, Me, **2d**	4	**3d**	88	87
5	*o*-FC_6H_4, Me, **2e**	4	**3e**	91	88
6	*p*-$EtOC_6H_4$, Me, **2f**	2.5	**3f**	95	97
7	*p*-$NO_2C_6H_4$, Me, **2g**	5	**3g**	88	90
8	Furan-2-yl, Me, **2h**	3.5	**3h**	90	95
9	C_6H_5, *p*-Br-Bn, **2i**	3	**3i**	96	94
10	C_6H_5, Et, **2j**	4	**3j**	90	90
11	C_6H_5, *i*-Pr, **2k**	4	**3k**	92	91
12	$C_6H_5CH_2CH_2$, Et, **2l**	4	—[d]	—	—

[a] Unless otherwise noted, the reaction was conducted with 0.11 mmol of **1a** and 0.10 mmol of **2** in the presence of 20 mol % of **4m** in 1.0 mL of Et_2O for appropriate time.
[b] Isolated yields after column chromatography on silica gel.
[c] Determined by chiral HPLC analysis on a chiral column. Only a single diastereoisomer was observed by ^1H and ^{13}C NMR.
[d] No product was observed.

moiety (R^2) of the substrate did not bring in significant changes in the yield and ee value (entries 9–11). Unfortunately, no product was observed when substrate with aliphatic substituent (R^1=$C_6H_5CH_2CH_2$, R^2=Et) was screened (entry 12).

Next, several oxazolones bearing different substituents were also examined to explore the reaction scope further (Table 4). Compared to the model substrate **1a** (R^3=Me, R^4=Ph), the substrate with bulkier R^3 substituent, which was directly linked to reactive site, demonstrated both poorer yield and ee value, together with a longer reaction time (entries 1 and 2). Varying the substituents on the benzene ring of R^4 may also lead to some changes to the result to certain extent (entries 3–5). However, the diastereoselectivity remained exclusive in all these cases examined. The absolute configuration of the product **3p** was determined to be 4*R*,5*S* by X-ray crystallographic analysis, and the others were assigned by analogy (Fig. 2).[12]

Table 4
Scope study with different oxazolones [a]



2a R^1 = Ph
2b R^1 = *p*-BrC_6H_4
2m R^1 = *m*-BrC_6H_4

Entry	R^3, R^4, **1**	**2**	*t* (h)	**3**	Yield[b] (%)	ee[c] (%)
1	Bn, Ph, **1b**	**2a**	5	**3l**	80	87
2	*i*-Bu, Ph, **1c**	**2a**	8	**3m**	44	20
3	Bn, Ph, **1b**	**2b**	3	**3n**	94	93
4	Bn, *m*-BrC_6H_4, **1d**	**2m**	5	**3o**	92	90
5	Bn, *m*-ClC_6H_4, **1e**	**2m**	6	**3p**	82	83 (>99[d])

[a] Unless otherwise noted, the reaction was conducted with 0.11 mmol of **1** and 0.10 mmol of **2** in the presence of 20 mol % of **4m** in 1.0 mL of Et_2O.
[b] Isolated yields after column chromatography on silica gel.
[c] Determined by chiral HPLC analysis on a chiral column. Only a single diastereoisomer was observed by ^1H and ^{13}C NMR.
[d] The enantioselectivity was determined after a single recrystallization.

Currently, two mechanisms may be proposed for this reaction as shown in Scheme 1. As we originally intended, route I involves a catalyzed Michael addition as the stereocontrol step, followed by intramolecular O-acylation of the new born enolate and opening of

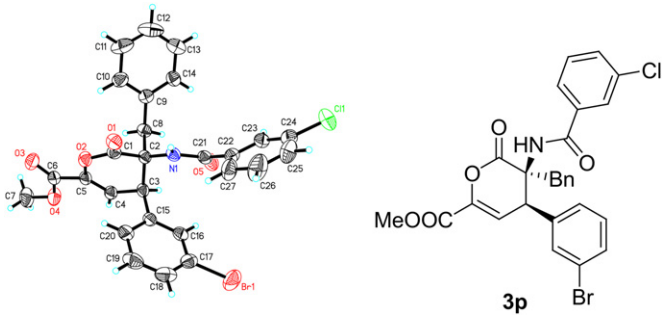


Fig. 2. ORTEP structure of compound **3p**.

the oxazolone ring;[11] route II is the inverse-electron-demand hetero-Diels–Alder (IEDDA) mechanism as proposed by Feng and coworkers[10] for the related reaction with chalcones. In route II, the reaction may proceed in an *endo* way under the catalysis of the bifunctional catalyst. Considering the exclusive diastereoselectivity observed in the present reaction (consistent with the Feng's observation), route II should be the preferred one in our case.[13]

3. Conclusion

In summary, we have developed a highly enantioselective and diastereoselective cyclization reaction of oxazolones with β,γ-unsaturated α-keto esters by using readily available cinchona alkaloids as the catalysts. This reaction provides an easy access to highly functionalized chiral δ-lactones with adjacent α-quaternary-β-tertiary stereocenters.

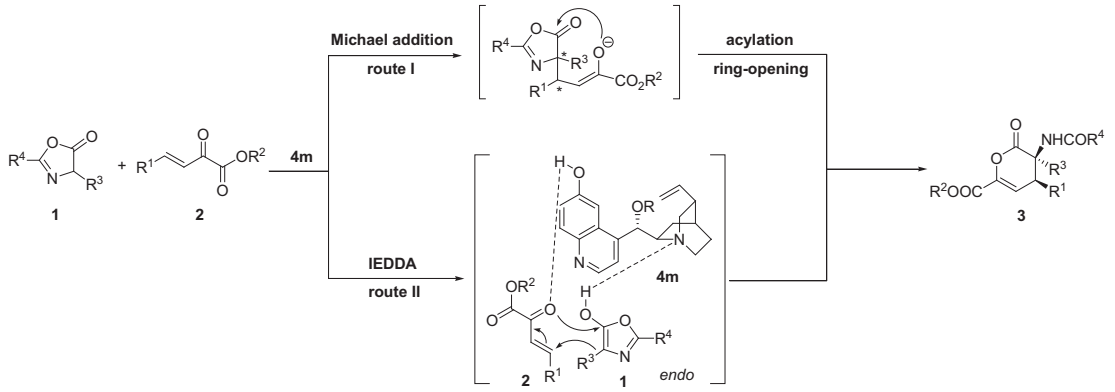
4. Experimental section

4.1. General

Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers and purified by standard techniques. Flash column chromatography was performed using silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. The ^1H NMR and ^{13}C NMR spectra were recorded on a DPX-400 (100 MHz) with TMS as the internal standard. ^{19}F NMR spectra were recorded at 282 MHz with $CFCl_3$ as the external standard. All chemical shifts (δ) are given in parts per million. Data are reported as follows: chemical shift, multiplicity (s=single, d=doublet, t=triplet, q=quartet, br=broad, and m=multiplet) and coupling constants (Hz), integration. Analytical high-performance liquid chromatography (HPLC) was carried out on WATERS equipment using a chiral column. Melting points were determined on a SGW X-4 apparatus, and are uncorrected. Optical rotations were measured on a JASCO P-1030 Polarimeter at λ=589 nm. IR spectra were recorded on a Perkin–Elmer 983G instrument. Elementary analysis was taken on a Vario EL III elementary analysis instrument. Mass spectra analysis was performed on API 200 LC/MS system (Applied Biosystems Co. Ltd).

4.2. Typical procedure for synthesis of product 3

A mixture of 4-methyl-2-phenyloxazol-5(4*H*)-one (0.11 mmol) (**1a**), (*E*)-methyl-2-oxo-4-phenylbut-3-enoate (**2a**), and catalyst **4m** (9 mg, 0.02 mmol) in 1.0 mL of ethyl ether was stirred at room temperature for 3 h until the disappearance of **2a** (monitored by TLC). The reaction mixture was then concentrated, and the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether=1/10) to give the desired product **3a**.



Scheme 1. Proposed possible catalytic mechanism for the formation of product **3**.

*4.2.1. (4R,5S)-Methyl 5-benzamido-5-methyl-6-oxo-4-phenyl-5,6-dihydro-4H-pyran-2-carboxylate (**3a**).* White solid (32.6 mg, 91% isolated yield, 95% ee). $[\alpha]_{D^{24}}$ −189.0 (*c* 1.00, $CHCl_3$). Mp: 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H), 3.93 (s, 3H), 4.85 (d, *J*=6.8 Hz, 1H), 6.82 (d, *J*=6.8 Hz, 1H), 6.99 (s, 1H), 7.13–7.24 (m, 5H), 7.29–7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 167.2, 160.1, 140.8, 135.3, 134.6, 131.6, 128.9, 128.5, 128.4, 127.9, 126.6, 118.0, 59.4, 52.8, 46.9, 22.4; MS (ESI): 366.3 ($[M+1]^+$); HRMS (EI) calcd for $C_{21}H_{19}NO_5$ ($[M^+]$): 365.1263, found 365.1261; IR (KBr) ν 3421, 1772, 1663, 1706, 1486, 1283, 1107, 721 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel OD column, hexane/2-propanol: 19/1, flow rate: 0.70 mL/min, t_R (minor)=19.33 min, t_R (major)=24.50 min.

*4.2.2. (4R,5S)-Methyl 5-benzamido-4-(4-bromophenyl)-5-methyl-6-oxo-5,6-dihydro-4H-pyran-2-carboxylate (**3b**).* White solid (44.2 mg, 95% isolated yield, 94% ee). $[\alpha]_{D^{24}}$ 148.6 (*c* 1.00, $CHCl_3$). Mp: 133–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (s, 3H), 3.91 (s, 3H), 4.83 (d, *J*=6.8 Hz, 1H), 6.75 (d, *J*=7.2 Hz, 1H), 6.99–7.02 (m, 3H), 7.32–7.37 (m, 4H), 7.46–7.48 (m, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 169.1, 167.1, 160.0, 141.0, 134.4, 132.1, 131.9, 129.6, 128.7, 128.6, 126.7, 122.5, 117.5, 59.2, 52.9, 46.2, 22.3; MS (ESI): 446.0 ($[M+1]^+$); HRMS (EI) calcd for $C_{21}H_{18}BrNO_5$ ($[M^+]$): 443.0368, found 443.0373; IR (KBr) ν 3411, 1742, 1650, 1489, 1281, 1185, 1010, 731 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 19/1, flow rate: 0.70 mL/min, t_R (minor)=57.76 min, t_R (major)=80.86 min.

*4.2.3. (4R,5S)-Methyl 5-benzamido-5-methyl-6-oxo-4-p-tolyl-5,6-dihydro-2H-pyran-2-carboxylate (**3c**).* White solid (32.0 mg, 85% isolated yield, 93% ee). $[\alpha]_{D^{24}}$ 186.3 (*c* 1.20, $CHCl_3$). Mp: 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.16 (s, 3H), 3.83 (s, 3H), 4.72 (d, *J*=6.8 Hz, 1H), 6.71 (d, *J*=6.8 Hz, 1H), 6.90 (s, 1H), 6.93 (s, 4H), 7.18–7.28 (m, 2H), 7.35–7.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.2, 160.2, 140.7, 136.2, 134.8, 132.2, 131.4, 129.6, 128.5, 127.8, 126.7, 118.3, 59.3, 52.6, 46.4, 22.3, 20.8; MS (ESI): 402.1 ($[M+Na]^+$); HRMS (EI) calcd for $C_{22}H_{21}NO_5$ ($[M^+]$): 379.1420, found 379.1422; IR (KBr) ν 3421, 2954, 1770, 1670, 1607, 1514, 1249, 1145, 803 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel OD column, hexane/2-propanol: 19/1, flow rate: 0.70 mL/min, t_R (minor)=21.86 min, t_R (major)=25.13 min.

*4.2.4. (4R,5S)-Methyl 5-benzamido-4-(3-fluorophenyl)-5-methyl-6-oxo-5,6-dihydro-4H-pyran-2-carboxylate (**3d**).* White solid (32.5 mg, 88% isolated yield, 87% ee). $[\alpha]_{D^{24}}$ 136.5 (*c* 1.00, $CHCl_3$). Mp: 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H), 3.95 (s, 3H), 4.89 (d, *J*=7.2 Hz, 1H), 6.80 (d, *J*=6.8 Hz, 1H), 6.88–6.96 (m, 3H), 7.04 (s, 1H), 7.18–7.23 (m, 1H), 7.36–7.42 (m, 2H), 7.48–7.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 167.4, 162.8 (d, *J*=246 Hz), 160.0, 141.1, 137.8 (d, *J*=6.3 Hz), 134.4, 131.7, 130.5 (d, *J*=8.0 Hz), 128.6, 126.6, 123.6 (d, *J*=2.5 Hz), 117.3, 115.4 (d, *J*=20 Hz), 115.2 (d, *J*=22 Hz), 59.2, 52.9, 46.4, 22.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −112.7 (s, 1F); MS (ESI): 384.1 ($[M+1]^+$); HRMS (EI) calcd for $C_{21}H_{18}FNO_5$ ($[M^+]$): 383.1169, found 383.1163; IR (KBr) ν 3417, 1775, 1742, 1666, 1607, 1518, 1150, 779 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel PC-2 column, hexane/2-propanol: 9/1, flow rate: 0.70 mL/min, t_R (minor)=23.28 min, t_R (major)=25.28 min.

*4.2.5. (4R,5S)-Methyl 5-benzamido-4-(2-fluorophenyl)-5-methyl-6-oxo-5,6-dihydro-4H-pyran-2-carboxylate (**3e**).* White solid (34.5 mg, 91% isolated yield, 88% ee). $[\alpha]_{D^{24}}$ 137.7 (*c* 1.00, $CHCl_3$). Mp: 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H), 3.95 (s, 3H), 4.89 (d, *J*=6.4 Hz, 1H), 6.80 (d, *J*=6.8 Hz, 1H), 6.90–6.96 (m, 3H), 7.04 (s, 1H), 7.18–7.23 (m, 1H), 7.36–7.46 (m, 2H), 7.46–7.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 167.3, 162.8 (d, *J*=246.0 Hz), 160.0, 141.1, 137.8 (d, *J*=7.0 Hz), 134.4, 131.7, 130.5 (d, *J*=8.0 Hz), 128.6, 126.6, 123.7 (d, *J*=2.5 Hz), 117.3, 115.4 (d, *J*=22.0 Hz), 115.0 (d, *J*=22.0 Hz, 1C), 59.2, 52.9, 46.5, 22.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −112.7 (s, 1F); MS (ESI): 384.1 ($[M+1]^+$); HRMS (EI) calcd for $C_{21}H_{18}FNO_5$ ($[M^+]$): 383.1169, found 383.1165; IR (KBr) ν 3417, 1775, 1742, 1666, 1607, 1488, 1440, 1185, 717 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel PC-2 column, hexane/2-propanol: 9/1, flow rate: 0.70 mL/min, t_R (minor)=22.93 min, t_R (major)=24.93 min.

*4.2.6. (4R,5S)-Methyl 5-benzamido-4-(4-ethoxyphenyl)-5-methyl-6-oxo-5,6-dihydro-4H-pyran-2-carboxylate (**3f**).* White solid (39.0 mg, 95% isolated yield, 97% ee). $[\alpha]_{D^{25}}$ 201.9 (*c* 1.00, $CHCl_3$). Mp: 77–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.2 Hz, 3H), 1.99 (s, 3H), 3.90–3.95 (m, 5H), 4.78 (d, *J*=6.8 Hz, 1H), 6.70–6.72 (m, 2H), 6.78 (d, *J*=7.5 Hz, 1H), 6.98 (s, 1H), 7.01–7.03 (m, 2H), 7.33–7.35 (m, 2H), 7.44–7.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.2, 160.2, 158.9, 140.5, 134.6, 131.6, 129.0, 128.5, 126.8, 118.4, 114.8, 114.8, 63.4, 59.6, 52.8, 46.1, 22.3, 14.7; MS (ESI): 432.1 ($[M+Na]^+$); HRMS (EI) calcd for $C_{23}H_{23}NO_6$ ($[M^+]$): 409.1525, found 409.1531; IR (KBr) ν 3406, 1783, 1740, 1669, 1284, 1173, 764, 708 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 80/20, flow rate: 0.70 mL/min, t_R (minor)=15.96 min, t_R (major)=20.16 min.

*4.2.7. (4R,5S)-Methyl 5-benzamido-5-methyl-4-(4-nitrophenyl)-6-oxo-5,6-dihydro-4H-pyran-2-carboxylate (**3g**).* Yellow solid (36.2 mg, 88% isolated yield, 90% ee). $[\alpha]_{D^{25}}$ 286.9 (*c* 1.45, $CHCl_3$). Mp: 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.93 (s, 3H), 5.02 (d, *J*=6.8 Hz, 1H), 6.76 (d, *J*=6.8 Hz, 1H), 7.08 (s, 1H), 7.31–7.38 (m, 4H), 7.47–7.49 (m, 3H), 8.06–8.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 167.1, 159.8, 147.8, 142.9, 141.6, 133.7, 132.1, 129.0, 128.8, 126.6, 124.0, 116.0, 58.9, 53.1, 46.6, 22.5; MS (ESI): 411.1 ($[M+1]^+$); HRMS (EI) calcd for $C_{21}H_{18}N_2O_7$ ($[M^+]$): 410.1114, found

410.1118; IR (KBr) ν 3412, 1743, 1521, 1347, 1292, 1185, 852, 700 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 80/20, flow rate: 0.70 mL/min, t_R (minor)=25.46 min, t_R (major)=55.06 min.

*4.2.8. (4R,5S)-Methyl 5-benzamido-4-(furan-2-yl)-5-methyl-6-oxo-5,6-dihydro-4H-pyran-2-carboxylate (**3h**).* Yellow solid (32.0 mg, 90% isolated yield, 95% ee). $[\alpha]_{D^{25}}$ 282.2 (*c* 0.90, $CHCl_3$). Mp: 155–157 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3H), 3.89 (s, 3H), 5.03 (d, *J*=6.8 Hz, 1H), 6.66 (d, *J*=6.8 Hz, 1H), 6.81–6.20 (m, 2H), 7.10 (s, 1H), 7.37–7.38 (m, 2H), 7.43–7.47 (m, 1H), 7.52–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 167.4, 160.3, 148.5, 143.2, 141.5, 134.5, 131.6, 128.7, 126.7, 114.6, 110.5, 109.5, 58.2, 53.4, 40.1, 21.6; MS (ESI): 378.1 ($[M+Na]^+$); HRMS (EI) calcd for $C_{19}H_{17}NO_6$ ($[M^+]$): 355.1056, found 355.1054; IR (KBr) ν 3400, 1782, 1743, 1663, 1519, 1170, 764, 708 cm^{-1}.The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 9/1, flow rate: 0.70 mL/min, t_R (minor)=31.86 min, t_R (major)=35.66 min.

*4.2.9. (4R,5S)-4-Bromobenzyl-5-benzamido-5-methyl-6-oxo-4-phenyl-5,6-dihydro-4H-pyran-2-carbpxylate (**3i**).* White oil (50.2 mg, 96% isolated yield, 94% ee). $[\alpha]_{D^{24}}$ 89.7 (*c* 1.20, $CHCl_3$). Mp: 66–68 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H), 4.85 (d, *J*=6.8 Hz, 1H), 5.30 (s, 2H), 6.83 (d, *J*=6.8 Hz, 1H), 6.99 (s, 1H), 7.13 (s, 1H), 7.14–7.16 (m, 2H), 7.23–7.25 (m, 3H), 7.33–7.37 (t, *J*=8.4 Hz, 4H), 7.43–7.46 (m, 2H), 7.55 (d, *J*=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 167.3, 159.5, 140.7, 135.3, 134.6, 133.7, 131.9, 131.6, 130.3, 129.0, 128.5, 128.4, 127.9, 126.6, 122.9, 118.5, 67.0, 59.4, 47.0, 29.6, 22.4; MS (ESI): 520.0 ($[M+1]^+$); HRMS (EI) calcd for $C_{20}H_{16}NO_5$ ($[M-p\text{-Br-Bn}]^+$): 350.1028, found 350.1031; IR (KBr) ν 3418, 1738, 1667, 1514, 1151, 699 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 19/1, flow rate: 0.70 mL/min, t_R (minor)=47.28 min, t_R (major)=55.72 min.

*4.2.10. (4R,5S)-Ethyl 5-benzamido-5-methyl-6-oxo-4-phenyl-5,6-dihydro-4H-pyran-2-carboxylate (**3j**).* White solid (34.0 mg, 90% isolated yield, 90% ee). $[\alpha]_{D^{22}}$ 322.0 (*c* 0.85, $CHCl_3$). Mp: 160–162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J*=7.2 Hz, 3H), 2.05 (s, 3H), 4.36–4.42 (q, *J*=7.2 Hz, 2H), 4.85 (d, *J*=7.2 Hz, 1H), 6.81 (d, *J*=6.8 Hz, 1H), 7.00 (s, 1H), 7.14–7.17 (m, 2H), 7.23–7.25 (m, 3H), 7.33–7.36 (m, 2H), 7.43–7.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.2, 159.7, 140.9, 135.4, 134.6, 131.6, 128.9, 128.5, 128.4, 127.9, 126.6, 117.7, 62.3, 59.4, 46.9, 22.4, 14.1; MS (ESI): 402.1 ($[M+Na]^+$); HRMS (EI) calcd for $C_{22}H_{21}NO_5$ ($[M^+]$): 379.1420, found 379.1418; IR (KBr) ν 3420, 1770, 1738, 1669, 1514, 1279, 1109, 759 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 80/20, flow rate: 1.0 mL/min, t_R (minor)=9.57 min, t_R (major)=10.90 min.

*4.2.11. (4R,5S)-Isopropyl 5-benzamido-5-methyl-6-oxo-4-phenyl-5,6-dihydro-4H-pyran-2-carboxylate (**3k**).* White solid (35.5 mg, 92% isolated yield, 91% ee). $[\alpha]_{D^{23}}$ 114.6 (*c* 0.76, $CHCl_3$). Mp: 174–176 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, *J*=6.4 Hz, 3H), 1.40 (d, *J*=6.4 Hz, 3H), 2.05 (s, 3H), 4.84 (d, *J*=6.4 Hz, 1H), 5.20–5.27 (m, 1H), 6.78 (d, *J*=6.4 Hz, 1H), 7.00 (s, 1H), 7.15–7.17 (m, 2H), 7.23–7.25 (m, 3H), 7.33–7.37 (m, 2H), 7.43–7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 167.2, 159.2, 141.2, 135.5, 134.6, 131.6, 128.9, 128.5, 128.3, 127.9, 126.6, 117.4, 70.3, 59.4, 46.9, 22.4, 21.8; MS (ESI): 416.1 ($[M+Na]^+$); HRMS (EI) calcd for $C_{22}H_{20}NO_5$ ($[M-Me]^+$): 378.1341, found 378.1337; IR (KBr) ν 3432, 1764, 1720, 1671, 1520, 1309, 1097, 917, 707 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 80/20, flow rate: 1.0 mL/min, t_R (minor)=8.03 min, t_R (major)=10.05 min.

*4.2.12. (4R,5S)-Methyl 5-benzamido-5-benzyl-6-oxo-4-phenyl-5,6-dihydro-4H-pyran-2-carboxylate (**3l**).* White solid (35.0 mg, 80% isolated yield, 87% ee). $[\alpha]_{D^{23}}$ −145.2 (*c* 0.25, $CHCl_3$). Mp: 191–193 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.33 (d, *J*=13.6 Hz, 1H), 3.95 (s, 3H), 4.21 (d, *J*=14.4 Hz, 1H), 5.00 (d, *J*=6.4 Hz, 1H), 6.59 (s, 1H), 6.86 (d, *J*=6.4 Hz, 1H), 7.09–7.11 (m, 2H), 7.16–7.27 (m, 7H), 7.27–7.31 (m, 4H), 7.39–7.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 167.4, 160.2, 140.7, 135.5, 134.8, 134.4, 131.6, 130.7, 128.9, 128.6, 128.5, 128.4, 128.2, 127.6, 126.6, 117.9, 64.8, 53.0, 47.3, 38.9; MS (ESI): 442.1 ($[M+1]^+$); IR (KBr) ν 3419, 1768, 1739, 1510, 1280, 1108, 981, 737 cm^{-1}. Anal. Calcd for $C_{24}H_{23}NO_5$: C, 73.46; H, 5.25; N, 3.17. Found: C, 73.65; H, 5.51; N, 3.06. The ee was determined by HPLC analysis using a chiralcel AD-H column, hexane/2-propanol: 80/20, flow rate: 0.70 mL/min, t_R (minor)=24.50 min, t_R (major)=65.83 min.

*4.2.13. (4R,5S)-Methyl 5-benzamido-5-isobutyl-6-oxo-4-phenyl-5,6-dihydro-4H-pyran-2-carboxylate (**3m**).* White solid (22.0 mg, 44% isolated yield, 20% ee). $[\alpha]_{D^{24}}$ 144.5 (*c* 0.95, $CHCl_3$). Mp: 116–118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J*=6.8 Hz, 3H), 0.93 (d, *J*=6.8 Hz, 3H), 1.68–1.78 (m, 1H), 1.94 (dd, J_1=6.8 Hz, J_2=8.4 Hz, 1H), 2.92 (dd, J_1=6.8 Hz, J_2=8.4 Hz, 1H), 3.91 (s, 3H), 4.78 (d, *J*=6.4 Hz, 1H), 6.74 (d, *J*=6.4 Hz, 1H), 6.89 (s, 1H), 7.10–7.12 (m, 2H), 7.19–7.21 (m, 3H), 7.31–7.33 (m, 2H), 7.38–7.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 167.0, 160.2, 140.9, 135.2, 134.9, 131.5, 128.9, 128.6, 128.3, 128.2, 126.5, 118.0, 63.1, 52.8, 48.1, 41.7, 25.0, 23.8, 23.4; MS (ESI): 408.3 ($[M+1]^+$); HRMS (EI) calcd for $C_{24}H_{25}NO_5$ ($[M^+]$): 407.1733, found 407.1732; IR (KBr) ν 3413, 1762, 1741, 1656, 1514, 1277, 1140, 1112, 710 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AS-H column, hexane/2-propanol: 80/20, flow rate: 0.70 mL/min, t_R (minor)=8.47 min, t_R (major)=9.47 min.

*4.2.14. (4R,5S)-Methyl 5-benzamido-5-benzyl-4-(4-bromophenyl)-6-oxo-5,6-dihydro-4H-pyran-2-carboxylate (**3n**).* White solid (47.0 mg, 94% isolated yield, 93% ee). $[\alpha]_{D^{23}}$ −145.2 (*c* 0.25, $CHCl_3$). Mp: 108—110 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.36 (d, *J*=13.6 Hz, 1H), 3.99 (s, 3H), 4.20 (d, *J*=14.0 Hz, 1H), 5.03 (d, *J*=6.4 Hz, 1H), 6.68 (s, 1H), 6.86 (d, *J*=6.8 Hz, 1H), 7.08–7.12 (m, 4H), 7.25–7.26 (m, 3H), 7.36–7.41 (m, 6H), 7.45–7.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.1, 160.1, 141.0, 134.5, 134.2, 134.0, 132.1, 131.7, 130.0, 129.9, 128.7, 128.5, 127.7, 126.6, 122.5, 117.2, 64.6, 53.0, 46.7, 38.9; MS (ESI): 520.1 ($[M+1]^+$); HRMS (EI) calcd for $C_{27}H_{22}BrNO_5$ ($[M^+]$): 519.0681, found 519.0679; IR (KBr) ν 3413, 1742, 1668, 1509, 1282, 1112, 1096, 901 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel PC-2 column, hexane/2-propanol: 7/3, flow rate: 0.70 mL/min, t_R (minor)=9.48 min, t_R (major)=20.23 min.

*4.2.15. (4R,5S)-Methyl 5-benzyl-5-(3-bromobenzamido)-4-(3-bromophenyl)-6-oxo-5,6-dihydro-4H-pyran-2-carboxylate (**3o**).* White solid (40.0 mg, 92% isolated yield, 90% ee). $[\alpha]_{D^{23}}$ 29.5 (*c* 0.45, $CHCl_3$). Mp: 155–157 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.32 (d, *J*=14.0 Hz, 1H), 3.97 (s, 3H), 4.13 (d, *J*=14.0 Hz, 1H), 4.95 (d, *J*=6.4 Hz, 1H), 6.57 (s, 1H), 6.81 (d, *J*=6.4 Hz, 1H), 7.08–7.17 (m, 5H), 7.22–7.23 (m, 4H), 7.34–7.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.9, 160.0, 140.7, 136.0, 134.3, 134.1, 133.8, 132.3, 130.3, 130.2, 129.4, 128.6, 127.4, 122.6, 119.7, 117.2, 64.7, 53.0, 46.9, 39.2; MS (ESI): 598.0 ($[M+1]^+$); HRMS (ESI) calcd for $C_{25}H_{18}Br_2NO_3$ ($[M-COOMe]^+$): 537.9653, found 537.9652; IR (KBr) ν 3392, 1769, 1738, 1669, 1497, 1579, 1265, 827 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel PC-2 column, hexane/2-propanol: 5/1, flow rate: 0.70 mL/min, t_R (minor)=12.32 min, t_R (major)=18.98 min.

*4.2.16. (4R,5S)-Methyl 5-benzyl-4-(3-bromophenyl)-5-(3-chlorobenzamido)-6-oxo-5,6-dihydro-4H-pyran-2-carboxylate (**3p**).* White solid (40.0 mg, 82% isolated yield, 83% ee). $[\alpha]_{D^{23}}$ 218.0 (*c* 2.26, $CHCl_3$). Mp: 146–148 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.32 (d, *J*=14.0 Hz, 1H), 3.97 (s, 3H), 4.13 (d, *J*=14.0 Hz, 1H), 4.95 (d,

J=6.4 Hz, 1H), 6.57 (s, 1H), 6.81 (d, J=6.4 Hz, 1H), 7.08–7.17 (m, 5H), 7.22–7.23 (m, 4H), 7.34–7.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.6, 159.9, 141.2, 136.3, 134.9, 133.9, 131.8, 131.4, 130.4, 129.9, 128.6, 127.8, 127.0, 126.5, 124.5, 123.0, 116.7, 64.7, 53.0, 46.8, 39.0; MS (ESI): 554.2 ($[M+1]^+$); IR (KBr) ν 3391, 1768, 1738, 1497, 1265, 1009, 821,701 cm^{-1}. Anal. Calcd for $C_{27}H_{21}BrClNO_5$: C, 58.45; H, 3.82; N, 2.52. Found: C, 58.81; H, 3.82; N, 2.38. The ee was determined by HPLC analysis using a chiralcel OD-H column, hexane/2-propanol: 80/20, flow rate: 0.70 mL/min, t_R (minor)=11.46 min, t_R (major)=14.99 min.

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Supplementary data

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11. During the preparation of this paper, Terada also reported the reaction between β,γ-unsaturated α-keto esters and for oxazolones using axially chiral guanidine catalysts. Their system requires a low reaction temperature (−60 °C) and enantioselectivities for most substrates do not exceed 90% ee: *Chem.—Eur. J.* **2011**, *17*, 1760.
12. Crystal data: MW=554.81, Monoclinic, space group $P2(1)$, final R indices [$I>2\sigma(I)$], R_1=0.0458, wR_2=0.1055, a=14.930(5) Å, b=10.005(4) Å, c=17.163(6) Å, α=90°, β=90.923(7)°, γ=90°, V=2525.5(15) Å^3, crystal size 0.360×0.320×0.235 mm^3, T=293(2) K, Z=4, D=1.459 Mg/m^3, Reflections collected/unique 14,733/10,149 (R_{int}=0.0247), 10,149 data, 3 restraints, 641 parameters, absolute structure parameter 0.016(7). Largest diffraction peak and hole: 0.574 and −0.359 e Å^{-3}. CCDC 806009 contains the supplementary crystallographic data for **3p**. These data can be obtained free of charge from the Cambridge Crystallographic Data center via www.ccdc.cam.ac.uk/data_request/cif.
13. Our results and Feng's implies that the use of bifunctional catalysts might favor the IEDDA mechanism. In Ref. 11, where guanidine was used as the catalyst, good-to-excellent diastereoselectivities were observed and the authors preferred route I based on some experimental studies.