DOI: 10.1002/adsc.201200456

The Synthesis of *trans*-Perhydroindolic Acids and their Application in Asymmetric Domino Reactions of Aldehyde Esters with β,γ-Unsaturated α-Keto Esters

Jiefeng Shen,[a] Delong Liu,[b] Qianjin An,[b] Yangang Liu,[b] and Wanbin Zhang[a,b,*]

[a] School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, People's Republic of China
Fax: (+86)-21-5474-3265; phone: (+86)-21-5474-3265; e-mail: wanbin@sjtu.edu.cn
[b] School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, People's Republic of China

Received: May 24, 2012; Revised: July 13, 2012; Published online: November 13, 2012

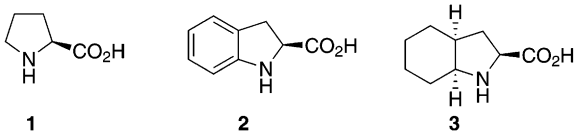
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200456.

Abstract: (2*S*,3*aR*,7*aS*)-Perhydroindolic acid, the key intermediate in the synthesis of trandolapril, and its *trans*-isomers, were readily prepared. These proline-like molecules are unique in that they contain a rigid bicyclic structure, with two hydrogen atoms *trans* to each other at the bridgehead carbon atoms. These molecules were used successfully as chiral organocatalysts in asymmetric domino Michael addition/cyclization reactions of aldehyde esters with β,γ-unsaturated α-keto esters. They proved to have excellent catalytic behavior, allowing for the synthesis of multi-substituted, enantiomerically enriched hemiacetal esters. Under optimal conditions (using 10 mol% catalyst loading), a series of β,γ-unsaturated α-keto esters was examined with up to 99% *de*, *ee* and yield, respectively. Additionally, the enantiomerically enriched hemiacetal esters could be readily transformed into their corresponding bioactive pyrano[2,3-*b*]pyrans (possessing a multi-substituted bicyclic backbone).

Keywords: asymmetric Michael addition; chiral organocatalysts; key intermediates; trandolapril; β,γ-unsaturated α-keto esters

Introduction

During the past decade there has been an explosive growth in the area of organocatalysis and asymmetric synthesis. Many organocatalysts are not only relatively non-toxic and inexpensive, but also stable to both air and moisture.[1] L-Proline (**1**, Figure 1) and its derivatives represent some of the most extensively studied organocatalysts that have been used successfully in a number of asymmetric catalytic reactions.[2] However, proline possesses several shortcomings for its use in some asymmetric catalyses such as a low reaction activity, high catalytic loading requirements, and poor yields.[3] These shortcomings were improved by the preparation of proline-like molecules with highly rigid structures and increased steric hindrance (such as **2** and **3**, Figure 1).[4] In addition to the aforementioned structural features, these types of molecules are distinctive for possessing both acidic and basic functional groups. The synthesis of such catalysts with a rigid structure thus remains a worthwhile endeavour.



1 2 3

Figure 1. Proline and some proline-like molecules.

(2*S*,3*aR*,7*aS*)-Perhydroindolic acid **4a**, a proline-like molecule, is a key intermediate in the synthesis of the cardiovascular drug trandolapril, a highly efficient angiotensin-converting enzyme inhibitor (Figure 2). Trandolapril consists of three important structural motifs, these being the ethyl 4-phenylbutyrate, L-alanine, and (2*S*,3*aR*,7*aS*)-perhydroindolic acid moieties. Ethyl 4-phenylbutyrate and L-alanine can be obtained from large-scale industrial production and natural sources, respectively. *trans*-Perhydroindolic acid **4a** remains the most troublesome intermediate to synthesise, with current methodologies requiring long synthetic sequences producing poor yields, and resulting in the production of large quantities of the undesired *cis*-perhydroindolic acid by-product.[5] These factors make trandolapril expensive to prepare and thus un-

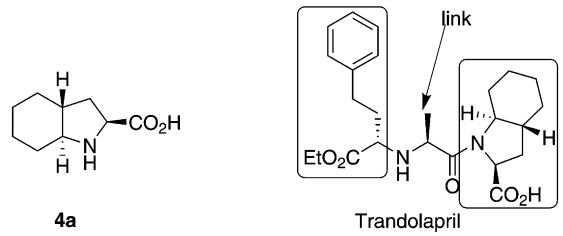


Figure 2. Trandolapril and its key intermediate **4a**

popular for use medicinally. We have therefore developed an efficient and convenient route for the synthesis of intermediate **4a**.

In addition, **4a** and its isomers **4b**, **4c** and **4d**, are unique in that they contain a rigid bicyclic structure with two H atoms *trans* to each other at the bridgehead C atoms (**4a/4b** being a pair of enantiomers, and **4c**/**4d** their corresponding diastereoisomers). Therefore they should make excellent chiral organocatalysts for use in asymmetric catalytic reactions.[6] Thus, the efficient synthesis of **4a–d** not only makes the synthesis of trandolapril more accessible, it also allows for the synthesis of a novel proline-like organocatalyst (Figure 3).

Results and Discussion

We developed a convenient synthetic route for the preparation of **4a–d** as shown in Scheme 1. *trans*-2-Allyl-*N*-*p*-toluenesulfonylcyclohexanamine (**6**) was first prepared by treating aziridine (**5**) with allylmagnesium bromide in a yield of 95%.[7] Subsequent oxidation of **6** with *m*-CPBA, followed by treatment with solid K_2CO_3 gave the cyclic *trans*-*N*-tosyl-1*H*-indole-2-methanol (**7**) in 91% yield. Intermediate **7** was further oxidized with Jone's reagent at 0 °C to give *trans*-*N*-tosyl-1*H*-indole-2-carboxylic acid (**8**) in 68% yield. *trans*-Perhydroindolic acid (**4**) was then prepared in 92% yield as a mixture by the deprotection of **8** with Na/naphthalene at room temperature and purification *via* an ion-exchange resin (Dowex 50×2, 100–200 mesh). In order to isolate (2*S*,3a*R*,7a*S*)-perhydroin-

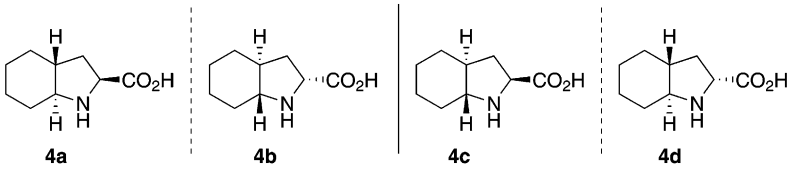
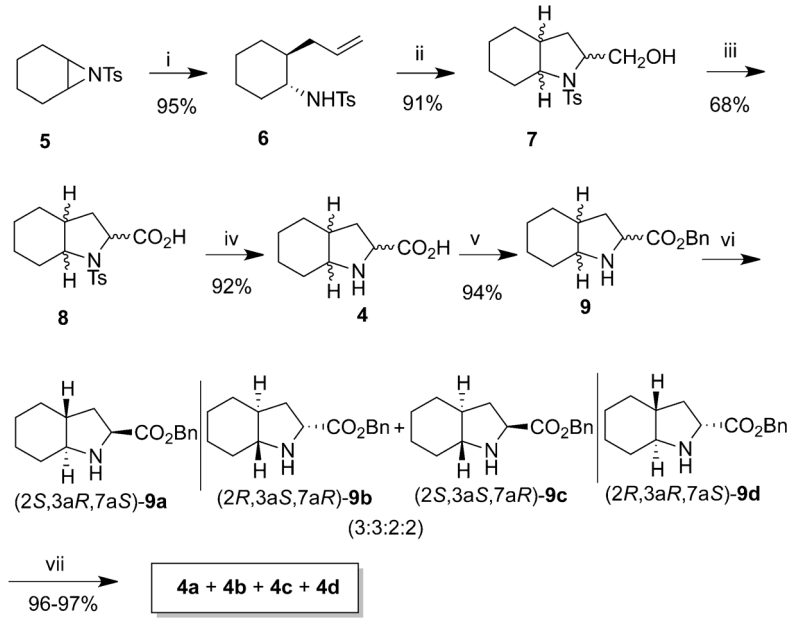
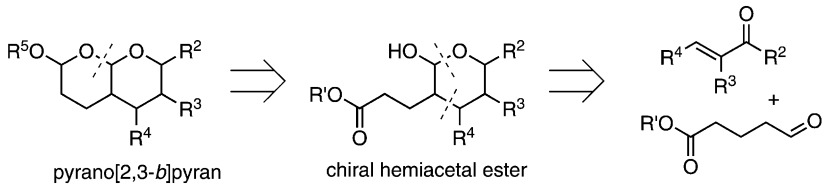


Figure 3. *trans*-Perhydroindolic acids **4a–d**.



(i) a) 3-Bromopropene, Mg, I_2, Et_2O; b) CuBr•DMS, Et_2O. (ii) a) *m*-CPBA, DCM, 0 °C; b) K_2CO_3, DCM, r.t. (iii) Jone's regeant, acetone/H_2O, 0 ° C. (iv) a) Na, naphthene, DME, r.t.; b) −70 °C to r.t. c) Amberlite IR-120, Dowex-50. (v) PTSA, benzyl alcohol, reflux. (vi) Chiral resolution. (vii) H_2 (10 atm), Pd/C, MeOH.

Scheme 1. The synthetic route for the synthesis of *trans*-perhydroindolic acids **4a–d**.



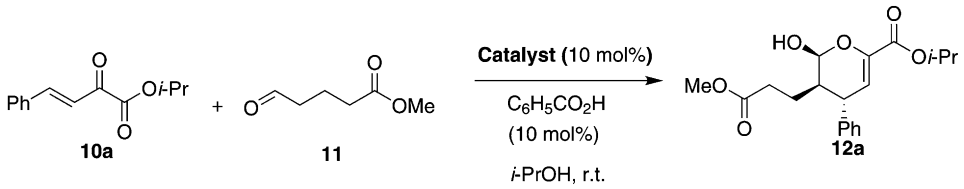
Scheme 2. The *retro*-synthesis of pyrano[2,3-*b*]pyran compounds.

dolic acid **4a**, **4** was first converted to benzyl octahydro-1*H*-indole-2-carboxylate (**9**) *via* an esterification procedure in 94% yield. Ester **9** could be separated into two pairs of enantiomers *via* recrystallization from a suitable solvent. In this small scale synthesis, **9** was separated into four optically pure isomers **9a–d** by using preparative chiral HPLC with a chiral OD-H column (**9a**/**9b**/**9c**/**9d** = 3:3:2:2). Finally, enantiomerically pure **4a** was obtained *via* hydrogenation with Pd/C in 96% yield. The procedure provided **4a** in an overall yield of 14.8%. Subsequently, **4b–d** were obtained using the same method. No *cis*-perhydroindolic acid was found throughout any of the syntheses.

The chiral multi-substituted pyrano[2,3-*b*]pyran moiety exhibits interesting biological activities and is a prevalent structural subunit in numerous natural products.[8] Much effort has been made to try and synthesise this promising structural motif;[9,10] the most commonly used method utilizing a hetero-Diels–Alder (HDA) reaction.[10] Unfortunately this method requires harsh reaction conditions (very low or high temperatures), the use of metal-containing reagents, and often only allows for the synthesis of less substituted products. Thus far few asymmetric catalytic methodologies have been reported,[11] therefore a convenient and enantioselective approach to pyrano[2,3-*b*]pyrans is desirable. We found that the most feasible approach was to first construct the hemiacetal ester. This could be achieved from readily available starting materials *via* an asymmetric domino Michael addition/cyclization reaction (Scheme 2). We report herein the asymmetric domino reaction of aldehyde esters to β,γ-unsaturated α-keto esters with the organocatalysts **4a–d**, which showed excellent asymmetric behaviour. Chiral hemiacetal esters were prepared, which could subsequently be converted into their corresponding pyrano[2,3-*b*]pyran compounds.

With the distinctive proline-like molecules **4a–d** in hand, we developed an organocatalyzed asymmetric domino reaction to synthesise chiral hemiacetal esters. Thus, the reaction of (*E*)-isopropyl 2-oxo-4-phenylbut-3-enoate (**10a**) and methyl 5-oxopentanoate (**11**) was carried out in the presence of 10 mol% **4a–d** at room temperature in *i*-PrOH (Table 1). All the organocatalysts produced moderate to good asymmetric catalytic results (entries 1–4). The by-products of trandolapril, **4c** and **4d**, provided the highest enantioselectivities for this reaction (entries 3 and 4). L-Proline and (*S*)-indoline-2-carboxylic acid were also used for comparison; however these reagents showed poor results. We therefore decided to use organocatalyst **4d** in subsequent reactions.

Table 1. Asymmetric domino reaction with different catalyst.



Entry[a]	Catalyst	Time [d]	Yield [%][b]	*de* [%][c]	*ee* [%][d]
1	**4a**	7	58	99	−48
2	**4b**	7	57	99	49
3	**4c**	3	89	99	−89
4	**4d**	3	90	99	88
5	**1**	2	98	99	22
6	**2**	3	–	–	–

[a] Reactions were conducted with 0.1 mmol enone **10a** and 0.3 mmol aldehyde **11** at room temperature in the presence of 10 mol% catalyst and $C_6H_5CO_2H$ with *i*-PrOH as a solvent.
[b] Isolated yield.
[c] Determined by HPLC.
[d] Determined by HPLC.

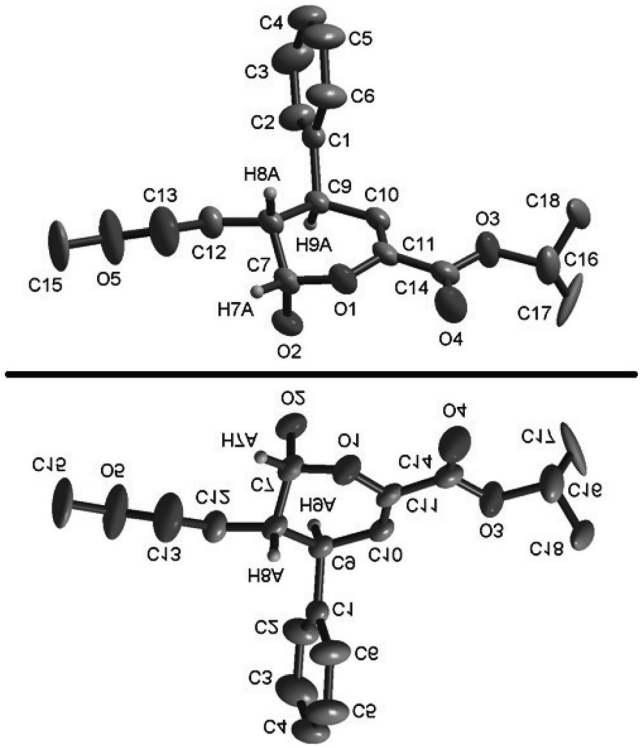


Figure 4. Single crystal of racemic hemiacetal **12a**.

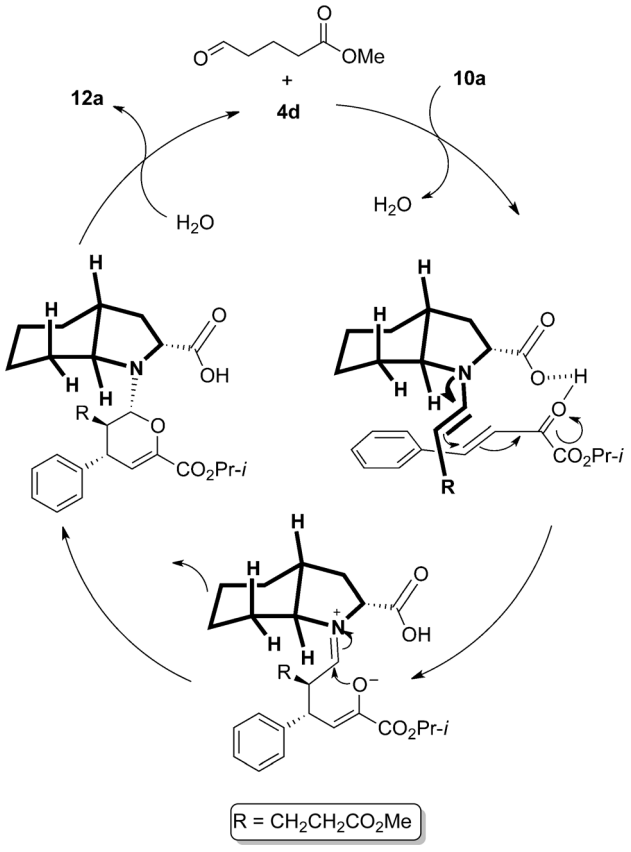


Figure 5. Proposed transition state for the stereochemical outcome.

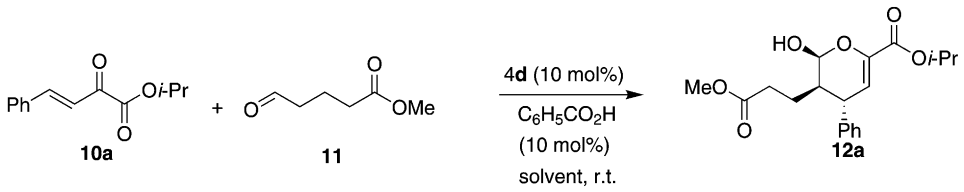
To determine the absolute configuration of the domino reaction product, X-ray crystallography studies were performed on chiral hemiacetal **12a**. A single, enantiomerically pure crystal of **12a** could not be obtained. Alternatively, a single crystal of the corresponding racemic hemiacetal **12a** could be obtained *via* recrystallization from dichloromethane and petroleum ether. X-Ray crystal analysis shows that the hemiacetal hydroxy group and the adjacent ester group lie on the opposite side of the phenyl ring (Figure 4).[12]

A transition state model was proposed to account for the stereochemical outcome when using **4d** as a catalyst (Figure 5). The aldehyde ester **11** reacts with **4d** to give a nucleophilic enamine intermediate whilst the (*E*)-isopropyl 2-oxo-4-phenylbut-3-enoate (**10a**) is directed toward the carboxylic acid group by a hydrogen bond (with the molecule lying behind the enamine) enhancing the electrophilic character of **10a**. The resulting enamine attacks the double C–C bond of **10a** (from above the plane of the alkene) to give the imine-enol intermediate with the adjacent ester group lying on the opposite side of the phenyl ring. Following cyclization, front-side attack by H_2O gives the desired product and catalyst **4d**.

The influence of solvent on the reaction outcome was investigated using 10 mol% **4d** at room temperature in a number of solvents (Table 2). No reaction occurred in the least polar solvent toluene, even after stirring the reaction mixture at room temperature for 14 days (entry 1). When solvent polarity was increased (Et_2O and $CHCl_3$), the reaction proceeded with good to excellent enantioselectivity, however low yields were obtained (entries 2 and 3). Increased solvent polarity appeared to benefit the reaction. This was further confirmed by use of DMF as a solvent (entry 4), which improved the reaction yield, and diastereo- and enantioselectivities. We therefore envisaged that polar alcohol solvents would be most suitable for this asymmetric domino reaction. The reaction was performed in EtOH and an excellent asymmetric catalytic result was obtained with higher reaction activity (entry 5). Subsequently, other commonly used alcohols, *i*-PrOH, *n*-PrOH and isopentanol, were examined, giving rise to excellent asymmetric catalytic behaviour (entries 6–8). *i*-PrOH was found to be the best solvent for this catalytic system and was used for subsequent reactions.

It was mentioned in our previous work that basic additives are favourable in the asymmetric Michael addition with this proline-like organocatalyst.[6] As shown in Table 3, many basic additives (entries 1–6) dramatically shortened the the reaction time, providing excellent diastereoselectivity and yields (up to 92% yield within 24 h). However they did not appear to affect the enantioselectivity. Brønsted acids could promote the formation of enamine in the proline-cat-

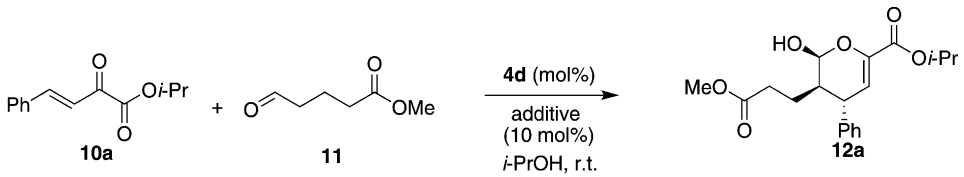
Table 2. The influence of solvent on the asymmetric domino reaction.



Entry[a]	Solvent	Time [d]	Yield [%][b]	*de* [%][c]	*ee* [%][d]
1	toluene	14	–	–	–
2	Et_2O	14	32	99	88
3	$CHCl_3$	14	33	99	69
4	DMF	12	87	99	87
5	EtOH	7	82	99	85
6	*n*-PrOH	7	80	99	90
7	*i*-PrOH	3	90	99	88
8	isopentanol	7	69	99	91

[a] Reactions were conducted with 0.1 mmol enone **10a** and 0.3 mmol aldehyde **11** at room temperature in the presence of 10 mol% **4d** and $C_6H_5CO_2H$ in a suitable solvent.
[b] Isolated yield.
[c] Determined by HPLC.
[d] Determined by HPLC.

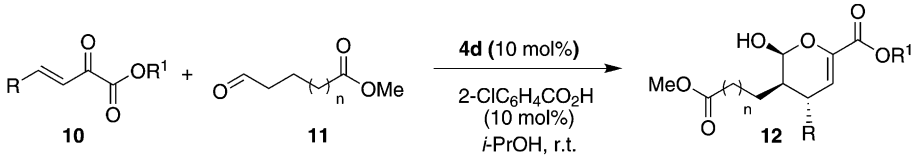
Table 3. The influence of additives, catalyst loading and temperature on the asymmetric domino reaction.



Entry[a]	Additive	Time [d]	Yield [%][b]	*de* [%][c]	*ee* [%][d]
1	–	3	75	99	86
2	NaOAc	1	86	99	76
3	quinine	1	84	99	80
4	DMAP	1	92	99	82
5	Et_3N	1	91	99	86
6	DIPEA	1	88	99	82
7	(+)-10-camphorsulfonic acid	14	36	99	92
8	CH_3CO_2H	7	90	99	87
9	$C_6H_5CO_2H$	3	90	99	88
10	4-$CH_3C_6H_4CO_2H$	7	81	99	87
11	4-$FC_6H_4CO_2H$	7	88	99	87
12	2-$ClC_6H_4CO_2H$	3	95	99	91
13[e]	2-$ClC_6H_4CO_2H$	3	94	99	90
14[f]	2-$ClC_6H_4CO_2H$	7	92	99	90
15[g]	2-$ClC_6H_4CO_2H$	14	43	99	90
16[h]	2-$ClC_6H_4CO_2H$	2	84	99	88

[a] Reactions were conducted with 0.1 mmol enone **10a** and 0.3 mmol aldehyde **11** at room temperature in the presence of 10 mol% **4d** and additive with *i*-PrOH as the solvent.
[b] Isolated yield.
[c] Determined by HPLC.
[d] Determined by HPLC.
[e] 20 mol% catalyst.
[f] 5 mol% catalyst.
[g] Temperature 0 °C.
[h] Temperature 50 °C.

Table 4. Asymmetric domino reactions for a series of aromatic β,γ-unsaturated α-keto esters with **4d** as a catalyst.



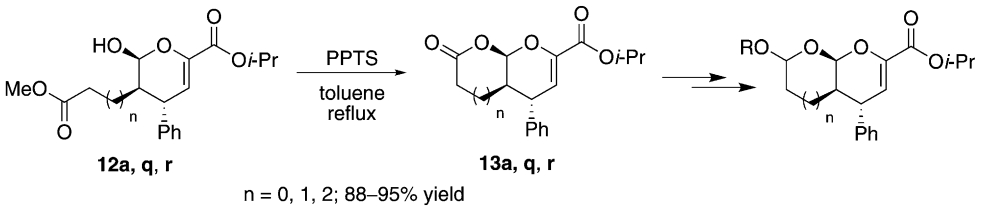
Entry[a]	12	n	R	R^1	Time [d]	Yield [%][b]	*de* [%][c]	*ee* [%][d]
1	**12a**	1	C_6H_5	*i*-Pr	3	95	99	91
2	**12b**	1	2-BrC_6H_5	*i*-Pr	3	82	99	93
3	**12c**	1	3-BrC_6H_4	*i*-Pr	3	94	99	91
4	**12d**	1	4-BrC_6H_4	*i*-Pr	3	94	99	90
5	**12e**	1	2-ClC_6H_4	*i*-Pr	3	92	99	93
6	**12f**	1	4-ClC_6H_4	*i*-Pr	3	99	99	93
7	**12g**	1	2-FC_6H_4	*i*-Pr	3	99	99	91
8	**12h**	1	4-FC_6H_4	*i*-Pr	3	93	99	91
9	**12i**	1	4-$CF_3C_6H_4$	*i*-Pr	3	95	99	92
10	**12j**	1	2,6-$Cl_2C_6H_3$	*i*-Pr	3	89	99	93
11	**12k**	1	4-MeC_6H_4	*i*-Pr	5	74	99	91
12	**12l**	1	2-$CH_3OC_6H_4$	*i*-Pr	5	72	99	98
13	**12m**	1	3-$CH_3OC_6H_4$	*i*-Pr	3	90	99	93
14	**12n**	1	4-$CH_3OC_6H_4$	*i*-Pr	7	66	99	90
15	**12o**	1	2-naphthyl	*i*-Pr	3	93	99	92
16	**12p**	1	2-furyl	*i*-Pr	3	92	99	91
17	**12q**	0	C_6H_5	*i*-Pr	3	96	99	90
18	**12r**	2	C_6H_5	*i*-Pr	3	95	99	90
19	**12s**	1	C_6H_5	Et	3	90	99	91
20	**12t**	1	C_6H_5	Bn	3	98	99	95
21	**12u**	1	2-ClC_6H_4	Bn	3	92	99	97
22	**12v**	1	2-$CH_3OC_6H_4$	Bn	4	87	99	99
23	**12w**	1	4-$CH_3OC_6H_4$	Bn	6	76	99	96
24[e]	**12x**		2-$CH_3OC_6H_4$	Bn	1	93	99	97
25[f]	**12y**		2-$CH_3OC_6H_4$	Bn	1	92	99	97
26[g]	**12z**		2-$CH_3OC_6H_4$	Bn	10	42	99	98
27	**12aa**	1	Et	Et	5	87	99	95
28	**12ab**	1	*n*-pentyl	Et	5	73	99	92

[a] Reactions were conducted with 0.1 mmol enone **10** and 0.3 mmol aldehyde **11** in the presence of 10 mol% **4d** with 2-$ClC_6H_4CO_2H$ as an additive in *i*-PrOH at room temperature
[b] Isolated yield.
[c] Determined by HPLC.
[d] Determined by HPLC.
[e] Propaldehyde was used.
[f] *n*-Butyraldehyde was used.
[g] Isopentyl aldehyde was used.

alyzed reaction, thereby improving chemical yields and increasing stereoselectivity.[13] Therefore several kinds of Brønsted acids were used as additives in this reaction. It was shown that acidic additives prolonged reaction times (entries 7–12) but some did increase enantioselectivity such as 2-$ClC_6H_4CO_2H$. In fact, 2-$ClC_6H_4CO_2H$ was found to be the best acidic additive and was used in the following reactions.

Investigations on catalyst loading were also performed in order to reduce the quantity of chiral catalyst needed for the reaction. No effect on diastereo- and enantioselectivity was observed when using 5 and 20 mol% of catalyst **4d**, however using 5 mol% of **4d** did reduce reaction activity (entries 13 and 14). Temperature was also found to alter reactivity with reaction activity being reduced at 0 °C. Increasing the reaction temperature to 50 °C resulted in a decrease in enantioselectivity and yield. The best reaction conditions were therefore found to be using *i*-PrOH as a solvent at room temperature in the presence of 10 mol% **4d** and 2-$ClC_6H_4CO_2H$.

With the optimal reaction conditions in hand, the asymmetric domino reaction was extrapolated to a series of aromatic β,γ-unsaturated α-keto esters (Table 4). At first the substituents on the aromatic ring were modified. Excellent diastereo- and enantio-



Scheme 3. The synthesis of pyrano[2,3-*b*]pyran compounds.

selectivities and high yields were observed for electron-withdrawing aromatic β,γ-unsaturated α-keto esters (entries 1–10). Similarly, electron-donating groups also provided excellent asymmetric catalytic results, albeit with moderate yields for certain substrates (entries 11–14). The enantioselectivity of the reaction was affected by steric hindrance, with aromatic β,γ-unsaturated α-keto esters with a 2-methoxy group giving *ee*s of 98% (entries 12–14). When the phenyl ring was replaced with a naphthalene or furan ring, excellent *de*/*ee* values and high yields were obtained (entries 15 and 16). In addition, altering the chain length of the aldehyde ester did not appear to have an adverse effect on the reaction (entries 17 and 18).

Finally the influence of the ester group of **10** was examined (entries 1, 19–23). No obvious difference in *ee* was observed for the ethyl and isopropyl esters but an increase in *ee* was observed when using a benzyl ester (entry 20). Benzyl esters **10u–w** were also examined in the reaction and all gave excellent de and *ee* values (up to 99% *de* and *ee*, entries 21–23). We were also curious as to whether the ester functional group in the aldehydes was really necessary. Several simple aldehydes lacking the ester functionality were examined (Table 4, entries 24–26). Almost all of them showed high reaction activity and excellent catalytic behavior while isopentyl aldehyde provided low reaction activity because of its large steric hindrance. Alkyl-substituted β,γ-unsaturated α-keto esters **11x** and **11y** were also examined and all gave excellent *de* and *ee* values (Table 4, entries 27 and 28).

Following the synthesis of chiral hemiacetal esters *via* asymmetric domino reactions, we converted some of them to their corresponding pyrano[2,3-*b*]pyrans. Thus, **12a** was dissolved in toluene in the presence of a catalytic amount of PPTS and heated under reflux conditions for 2 h. The corresponding bicyclic lactone **13a** was obtained in 95% yield. Compounds **13q** and **13r** containing different sized lactone rings could be obtained easily with the same method. Lactons **13a**, **q**, and **r** could then be converted to multi-substituted pyrano[2,3-*b*]pyran compounds by modifying their carbonyl groups *via* reported procedures (Scheme 3).[14] These results show that this method allows for the efficient and mild synthesis of pyrano-[2,3-*b*]pyran compounds with multi-substituent groups.

Conclusions

In summary, we have developed an efficient synthetic route towards *trans*-perhydroindolic acids, providing a convenient and efficient route towards the synthesis of trandolapril. The acids were used as organocatalysts in asymmetric domino reactions of aldehyde esters to β,γ-unsaturated α-keto esters. These proline-like *trans*-perhydroindolic acids are unique in that they contain a bicyclic structure with the two H atoms *trans* to each other at the bridgehead C atoms. They were used as efficient chiral organocatalysts in asymmetric domino reactions of aldehyde esters to β,γ-unsaturated α-keto esters to give multi-substituted enantiomerically enriched hemiacetal esters. Under optimal conditions, excellent diastereo- and enantioselectivities (up to 99% *de* and *ee*) were obtained with high yields (up to 99% yield) for a series of β,γ-unsaturated α-keto esters using 10 mol% **4d**. The resulting enantiomerically enriched hemiacetal esters could be transformed into their corresponding multi-substituted pyrano[2,3-*b*]pyrans. The method provides an efficient and environmentally green route for the preparation of multi-substituted enantiomerically enriched hemiacetal esters and pyrano[2,3-*b*]pyran moieties.

Experimental Section

General Remarks

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian MERCURY plus-400 spectrometer with TMS as an internal standard. HR-MS was performed at the Analysis Center of Shanghai Jiao Tong University. Enantioselectivity was measured by high-performance liquid chromatography (HPLC) using Daicel Chiralcel OD-H, OJ-H and OA3100-H columns with hexane/*i*-PrOH as a eluent. Column chromatography was performed using 100–200 mesh silica gel. Melting points were measured with the SGW X-4 micro melting point apparatus. Optical rotations were measured on a Rudolph Research Analytical Autopol VI automatic polarimeter using a 50 mm path-length cell at 589 nm.

Synthesis of *trans*-2-Allyl-*N*-*p*-toluenesulfonyl-cyclohexanamine (6)

A solution of 3-bromopropene (43 g, 0.30 mol) in ether (200 mL) was added dropwise to a mixture of Mg (2.4 g,

0.10 mol) and I_2 (0.10 g) in ether (20 mL) at 0 °C under an N_2 atmosphere. After the addition was completed, the reaction mixture was heated at reflux for another 2 h to ensure completion of the reaction. A solution of CuBr·DMS (2.05 g, 0.010 mol) was added to the above Grignard solution (200 mL) at −78 °C and stirred for 1 h. A solution of compound **5** (25.1 g, 0.10 mol) in ether (100 mL) was added. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (200 mL × 3), and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (using a continuous gradient from petroleum ether and ending with 5:1 petroleum ether/ethyl acetate) to give **6** as a white solid **6**; yield: 27.8 g (95%).[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 5.74–5.51 (m, 1H), 5.02–4.91 (m, 2H), 4.79 (d, J = 8.8 Hz, 1H), 2.89–2.81 (m, 1H), 2.39 (s, 3H), 1.86–1.56 (m, 5H), 1.27–0.79 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 138.9, 136.8, 129.8, 127.1, 116.4, 57.3, 42.9, 37.1, 34.5, 30.9, 25.4, 25.2, 21.7.

Synthesis of *trans*-*N*-Tosyl-1*H*-indole-2-methanol (7)

A solution of *m*-CPBA (17.2 g, 0.10 mol) in CH_2Cl_2 (200 mL) was added to a solution of compound **6** (29.3 g, 0.10 mol) in CH_2Cl_2 (100 mL) at 0 °C. After the addition was completed, the reaction mixture was allowed to warm to room temperature and stirred overnight. The resulting white solid was filtered and K_2CO_3 (6.9 g, 0.050 mol) was added to the filtrate. The resulting mixture was stirred for another 2 h and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (using a continuous gradient from petroleum ether and ending with 4:1 petroleum ether/ethyl acetate) to give **7** as a pale yellow oil as a mixture of four isomers; yield: 28.1 g (91%).[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 3.96–3.78 (m, 1H), 3.69–3.51 (m, 1H), 3.61–3.58 (m, 2H), 2.49–2.45 (m, 1H), 2.39 (s, 3H), 2.30–3.24 (m, 1H), 1.81–1.62 (m, 5H), 1.38-1.33 (m, 1H), 1.10–1.02 (m, 2H), 0.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 133.1, 129.9, 128.1, 67.4, 66.6, 62.3, 43.7, 32.9, 32.7, 29.9, 25.4, 24.8, 21.8.

Synthesis of *trans*-*N*-Tosyl-1*H*-indole-2-carboxylic Acid (8)

To a solution of **7** (15.5 g, 0.05 mol) in acetone (100 mL) was added Jone's reagent (80 mL) at 0 °C. After the addition was completed, the solution was left stirring overnight at 0 °C. The reaction mixture was filtered *via* celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (using a continuous gradient from petroleum ether and ending with 1:1 petroleum ether/ethyl acetate) to give **8** as a white solid as a mixture of four isomers; yield: 21.9 g (68%).[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.71 (m, 2H), 7.33–7.24 (m, 2H), 4.52 (t, J = 8.0 Hz, 1H), 3.08–2.95 (m, 1H), 2.65–2.42 (m, 1H), 2.41 (s, 3H), 2.29–2.24 (m, 1H), 1.87–1.41 (m, 5H), 1.27–0.99 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.0, 143.4, 139.5, 129.9, 129.7, 127.4, 127.1, 65.6, 58.0, 46.1, 40.4, 35.3, 32.6, 29.9, 25.3, 24.7, 21.8.

Synthesis of Perhydroindolic Acids (4)

Na particles (11.5 g, 0.50 mol) were added to a solution of naphthalene (64.0 g, 0.50 mol) in dry DME (100 mL) and the reaction mixture was stirred at room temperature for 4 h under an N_2 atmosphere to give a green solution. To the green solution was slowly added a solution of **8** (16.2 g, 0.050 mol) in dry DME (50 mL) at −78 °C. After being stirred for 30 min at −78 °C, the mixture was allowed to warm to room temperature and stirred overnight. Isopropyl alcohol was added to this reaction mixture carefully until the green colour of solution turned colourless. After neutralization with dilute HCl (5%) to pH 7, the separated aqueous solution was loaded on to an acidic ion-exchange resin (Dowex 50 × 2, 100–200 mesh), and the column was eluted with water followed by 5% NH_4OH solution. The resulting ammonia solution was concentrated to give a white solid **4** as a mixture of four isomers; yield: 7.8 g (92%).[15]

Synthesis of Benzyl Octahydro-1*H*-indole-2-carboxylates (9)

A solution of compound **4** (8.45 g, 0.050 mol), BnOH (10.2 mL, 0.10 mol) and PTSA (9.5 g, 0.050 mol) in toluene (200 mL) was heated under Dean–Stark conditions. After 2 h, another portion of toluene (100 mL) was added and the reaction mixture heated under reflux for 6 h. The solution was cooled to room temperature and ether (300 mL) was added. The resulting mixture was placed in refrigerator at 0 °C overnight. The resulting solid was filtered and dissolved in CH_2Cl_2 (200 mL) at 0 °C. The aqueous solution of $NaHCO_3$ saturated (300 mL) was added to this solution and the mixture was stirred for 1 h at 0 °C. After extraction with CH_2Cl_2 (100 mL × 3), the combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (using a continuous gradient from petroleum ether and ending with 1:1 petroleum ether/ethyl acetate) to give **9** as a yellow oil as a mixture of four isomers; yield: 12.4 g (94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 5H), 5.15 (m, 2H), 4.0–3.89 (m, 1H), 2.49–2.38 (m, 1H), 2.37–2.31 (m, 1H), 2.00–1.97 (m, 1H), 1.87–1.85 (m, 1H), 1.79–1.62 (m, 2H), 1.47–0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 136.0, 128.8, 128.5, 128.3, 66.8, 63.7, 57.6, 45.7, 36.2, 32.3, 29.8, 26.0, 24.4; HR-MS (ESI): m/z = 260.1658, calcd. for $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1645.

Synthesis of Compounds 4a–4d

First, the optically pure compound **9a–d** was obtained (**9a**/**9b**/**9c**/**9d** = 3:3:2:2) by using preparative chiral HPLC with a chiral OD-H column (20 mmΦ × 250 mm, particle size: 5 μm. hexane/*i*-PrOH = 97.5:2.5, UV = 230 nm, flow rate = 9 mL min^{-1}). Then, the optically pure **9a–d** (0.50 g, 1.9 mmol) and Pd/C (10%, *w*/*w*) were placed in an autoclave equipped with a magnetic stirrer bar. MeOH (4.0 mL) was added to the mixture. The autoclave was then closed, purged three times with hydrogen (less than the pressure needed), and finally pressurized to 20 bar. The reaction mixture was stirred at room temperature for 48 h. Hydrogen gas was slowly released and the solvent was evaporated. The crude product was purified by chromatography using a CH_2Cl_2/MeOH mixture (10:1) as eluent.

Compound 4a: white solid; yield: 0.314 g (96%); mp 211–212 °C; $[\alpha]_D^{25}$: −92 (c 0.50, MeOH).

Compound 4b: white solid; yield: 0.316 g (97%); mp 210–211 °C; $[\alpha]_D^{25}$: +91 (c 0.30, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.98 (t, J = 8.8 Hz, 1H), 3.30 (dt, J = 3.2, 1.6 Hz, 1H), 2.81–2.75 (m, 1H), 2.54–2.49 (m, 1H), 2.29–2.16 (m, 1H), 2.07–1.97 (m, 1H), 1.91–1.89 (m, 1H), 1.809–1.77 (m, 1H), 1.66–1.52 (m, 2H), 1.52–1.06 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 173.3, 64.2, 59.7, 42.1, 34.5, 29.0, 28.7, 24.7, 24.3.

Compound 4c: white solid; yield: 0.316 g (97%); mp 200–201 °C; $[\alpha]_D^{25}$: −35 (*c* 0.30, MeOH).

Compound 4d: white solid; yield: 0.314 g (96%); mp 201–202 °C; $[\alpha]_D^{25}$: +35 (*c* 0.20, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 4.02 (dd, J = 10.4, 2.0 Hz, 1H), 3.31 (dt, J = 3.2, 1.6 Hz, 1H), 2.83–2.76 (m, 1H), 2.30–2.25 (m, 1H), 2.23–2.14 (m, 1H), 2.08–1.85 (m, 3H), 1.83–1.68 (m, 1H), 1.65–1.45 (m, 2H), 1.40–1.04 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 173.2, 64.2, 59.7, 42.1, 34.5, 29.0, 28.7, 24.7, 24.3.

General Procedure for Asymmetric Catalysis

The catalyst **4d** (1.69 mg, 0.01 mmol), *o*-chlorobenzoic (1.58 mg, 0.01 mmol), enone **10** (0.1 mmol) and aldehyde **11** (0.3 mmol) were added to a screw-capped vial containing *i*-PrOH (1 mL) at room temperature. The reaction mixture was stirred at room temperature until the complete consumption of enone **12** (monitored by TLC). The solvent was then evaporated and the residue was purified by flash column silica-gel chromatography (PE/EA = 8/1) to provide the corresponding domino reaction products. Diastereoselectivity (*de*) and the enantiomeric excess (*ee*) of optically pure products were determined by HPLC analysis.

Isopropyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (12a): pale yellow oil; yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.16 (m, 5H), 6.09 (d, J = 2.4 Hz, 1H), 5.61–5.58 (m, 1H), 5.14–5.11 (m, 1H), 3.58 (s, 3H), 3.46 (dd, J = 4.0, 2.4 Hz, 1H), 2.27–2.17 (m, 2H), 1.96–1.90 (m, 1H), 1.15–1.10 (m, 2H), 1.27 (dd, J = 6.2, 4.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 163.0, 142.1, 140.0, 129.0, 128.7, 127.4, 115.6, 93.2, 69.3, 51.8, 42.0, 40.4, 31.5, 24.3, 21.9; HR-MS (ESI): m/z = 371.1461, calcd for $C_{19}H_{24}O_6Na$ $[M+Na]^+$: 371.1465; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 95:5, UV = 254 nm, flow rate = 0.7 mL min^{-1}): t_{R1} = 14.16 min (major) and t_{R2} = 27.69 min (minor); *ee* = 93%; *de* > 99%; $[\alpha]_D^{25}$: +75 (*c* 0.40, MeOH).

Isopropyl 4-(2-bromophenyl)-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12b): pale yellow oil; yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 8.0 Hz, 1H), 7.34–7.27 (m, 2H), 7.20–7.18 (m, 1H), 7.16–7.09 (m, 1H), 5.99 (d, J = 2.8 Hz, 1H), 5.58 (d, J = 1.8 Hz, 1H), 5.13–5.10 (m, 1H), 4.19–4.11 (m, 1H), 3.59 (s, 3H), 2.35–3.20 (m, 3H), 1.90–1.84 (m, 1H), 1.69–1.65 (m, 1H), 1.26 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 163.0, 141.3, 140.6, 133.4, 130.0, 128.8, 128.1, 125.4, 114.3, 93.4, 69.5, 51.8, 41.9, 39.6, 31.6, 23.9, 21.9; HR-MS (ESI): m/z = 449.0585, calcd. for $C_{19}H_{23}BrO_6Na$ $[M+Na]^+$: 449.0570, found; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OJ-H, hexane/*i*-PrOH = 88:12, UV = 254 nm, flow rate = 0.4 mL min^{-1}): t_{R1} = 24.68 min (major) and t_{R2} = 19.16 min (minor); *ee* = 93%; *de* > 99%; $[\alpha]_D^{25}$: +100 (*c* 0.40, MeOH).

Isopropyl 4-(3-bromophenyl)-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12c): white solid; yield: 94%; mp 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.28 (m, 2H), 7.23–7.07 (m, 2H), 6.01 (d, J = 2.4 Hz, 1H), 5.63 (s, 1H), 5.17–5.10 (m, 1H), 3.61–3.53 (m, 2H), 3.45 (dd, J = 4.0, 2.4 Hz, 1H), 2.312-2.27 (m, 3H), 1.91–1.87 (m, 1H), 1.81–1.76 (m, 1H), 1.64–1.62 (m, 1H), 1.25 (dd, J = 9.0, 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 163.3, 144.7, 140.2, 131.6, 130.5, 127.6, 123.1, 114.8, 93.1, 69.6, 51.8, 41.9, 40.3, 31.4, 24.4, 21.9; HR-MS (ESI): m/z = 449.0576, calcd. for $C_{19}H_{23}BrO_6Na$ $[M+Na]^+$: 449.0570; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 91.5:8.5, UV = 254 nm, flow rate = 0.6 mL min^{-1}): t_{R1} = 23.82 min (major) and t_{R2} = 16.23 min (minor); *ee* = 91%; *de* > 99%; $[\alpha]_D^{25}$: +111 (*c* 0.50, MeOH).

Isopropyl 4-(4-bromophenyl)-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12d): pale yellow oil; yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.01 (d, J = 2.4 Hz, 1H), 5.63 (s, 1H), 5.14–5.01 (m, 1H), 3.59 (s, 3H), 3.45 (d, J = 2.4 Hz, 1H), 2.44–2.11 (m, 3H), 1.78–1.73 (m, 2H), 1.26 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 163.2, 141.2, 140.2, 132.1, 130.5, 130.2, 121.2, 115.0, 93.2, 69.6, 51.8, 41.9, 39.9, 31.4, 24.3, 21.9; HR-MS (ESI): m/z = 449.0572, calcd. for $C_{19}H_{23}BrO_6Na$ $[M+Na]^+$: 449.0570; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 92:8, UV = 254 nm, flow rate = 0.55 mL min^{-1}): t_{R1} = 14.70 min (major) and t_{R2} = 27.24 min (minor); *ee* = 90%; *de* > 99%; $[\alpha]_D^{25}$: +84 (*c* 0.20, MeOH).

Isopropyl 4-(2-chlorophenyl)-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12e): white solid; yield: 92%; mp 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.38 (m, 1H), 7.26–7.19 (m, 3H), 6.00 (d, J = 2.8 Hz, 1H), 5.59 (s, 1H), 5.17–5.09 (m, 1H), 4.15–4.10 (m, 1H), 3.59 (s, 3H), 2.33–2.30 (m, 2H), 2.05–2.01 (m, 1H), 1.86 (m, 1H), 1.64 (m, 1H), 1.25 (dd, J = 6.2, 4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 163.2, 140.7, 139.7, 130.0, 128.5, 127.5, 114.5, 93.4, 69.5, 51.8, 41.7, 36.9, 31.5, 23.9, 21.9; HR-MS (ESI): m/z = 405.1084, calcd. for $C_{19}H_{23}ClO_6Na$ $[M+Na]^+$: 405.1075; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 92:8, UV = 254 nm, flow rate = 0.55 mL min^{-1}): t_{R1} = 13.62 min (major) and t_{R2} = 43.77 min (minor); *ee* = 93%; *de* > 99%; $[\alpha]_D^{25}$: +129 (*c* 0.50, MeOH).

Isopropyl 4-(4-chlorophenyl)-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12f): pale yellow oil; yield: 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 5.99 (d, J = 2.4 Hz, 1H), 5.61 (s, 1H), 5.13–5.10 (m, 1H), 3.55 (s, 3H), 3.45 (dd, J = 4.0, 2.4 Hz, 1H), 2.35–2.28 (m, 1H), 2.19–2.14 (m, 1H), 1.88–1.85 (m, 1H), 1.77–1.72 (m, 1H), 1.18–1.57 (m, 1H), 1.23 (d, J = 6.4, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 163.5, 140.9, 140.3, 130.3, 129.2, 115.3, 93.3, 69.7, 51.9, 42.2, 40.1, 31.5, 24.5, 22.1; HR-MS (ESI): m/z = 405.1082, calcd. for $C_{19}H_{23}ClO_6Na$ $[M+Na]^+$: 405.1075; the enantiomeric excess and and diastereoselective excess were

determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 94:6, UV = 254 nm, flow rate = 0.8 mL min^{-1}): t_{R1} = 12.18 min (major) and t_{R2} = 25.19 min (minor); *ee* = 93%; *de* > 99%; $[\alpha]_D^{25}$: +118 (*c* 0.50, MeOH).

Isopropyl 4-(2-fluorophenyl)-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12g): white solid; yield: 99%; mp 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–6.97 (m, 4H), 6.03 (d, *J* = 4.2, 2.6 Hz, 1H), 5.61 (d, *J* = 2.4 Hz, 1H), 5.13–5.10 (m, 1H), 3.90 (dd, *J* = 2.4 Hz, 1H), 3.59 (s, 3H), 2.34–2.30 (m, 2H), 2.04–2.01 (m, 1H), 1.84–1.81 (m, 1H), 1.67–1.62 (m, 1H), 1.26 (dd, *J* = 6.2, 4.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 163.2, 140.6, 130.1, 128.9 128.8, 124.7, 116.0, 115.8, 114.5, 93.3, 69.5, 51.8, 41.2, 33.5, 31.4, 24.2, 21.9; HR-MS (ESI): *m/z* = 389.1378, calcd. for $C_{19}H_{23}FO_6Na$ $[M+Na]^+$: 389.1371; The enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 92:8, UV = 254 nm, flow rate = 0.85 mL min^{-1}): t_{R1} = 17.46 min (major) and t_{R2} = 10.70 min (minor); *ee* = 91%; *de* > 99%; $[\alpha]_D^{25}$: +84 (*c* 0.50, MeOH).

Isopropyl 4-(4-fluorophenyl)-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12h): white solid; yield: 93%; mp 111–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.15 (m, 2H), 7.05–7.01 (m, 2H), 6.03 (d, *J* = 2.4 Hz, 1H), 5.61 (s, 1H), 5.14–5.10 (m, 1H), 3.59 (s, 3H), 3.46 (d, *J* = 2.8 Hz, 1H), 2.29–2.25 (m, 2H), 1.89–1.82 (m, 1H), 1.78–1.73 (m, 1H), 1.66–1.62 (m, 1H), 1.26 (t, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 163.3, 160.9, 140.1, 137.9, 130.2, 130.1, 115.9, 115.7, 115.5, 115.4, 93.2, 69.5, 51.8, 42.2, 39.2, 31.4, 24.3, 21.9; HR-MS (ESI): *m/z* = 389.1378, calcd. for $C_{19}H_{23}FO_6Na$ $[M+Na]^+$: 389.1371; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 94:6, UV = 254 nm, flow rate = 0.6 mL min^{-1}): t_{R1} = 15.54 min (major) and t_{R2} = 34.48 min (minor); *ee* = 91%; *de* > 99%; $[\alpha]_D^{25}$: +118 (*c* 0.40, MeOH).

Isopropyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-[4-(trifluoromethyl)phenyl]-3,4-dihydro-2*H*-pyran-6-carboxylate (12i): white solid; yield: 95%; mp 98–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.6 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.02 (d, *J* = 2.4 Hz, 1H), 5.65 (s, 1H), 5.13–5.10 (m, 1H), 3.58 (s, 3H), 3.57–3.54 (m, 1H), 2.34–2.30 (m, 1H), 2.23–2.19 (m, 1H), 1.95–1.91 (m, 1H), 1.79–1.77 (m, 1H), 1.65–1.61 (m, 1H), 1.25 (d, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 163.2, 146.4, 140.3, 129.2, 125.9, 114.5, 93.1, 69.6, 51.8, 41.9, 40.4, 31.2, 24.3, 21.9; HR-MS (ESI): *m/z* = 439.1342, calcd. for $C_{20}H_{23}F_3O_6Na$ $[M+Na]^+$: 439.1339; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 95:5, UV = 254 nm, flow rate = 0.8 mL min^{-1}): t_{R1} = 12.98 min (major) and t_{R2} = 27.76 min (minor); *ee* = 92%; *de* > 99%; $[\alpha]_D^{25}$: +124 (*c* 0.40, MeOH).

Isopropyl 4-(2,6-dichlorophenyl)-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12j): pale yellow oil; yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.73 (m, 1H), 7.67–7.60 (m, 1H), 7.55–7.51 (m, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.06 (s, 1H), 5.53–5.49 (m, 1H), 5.22 (br, 1H), 5.04 (dd, *J* = 4.8, 2.2 Hz, 1H), 3.96 (s, 3H), 3.07–3.03 (m, 1H), 2.75–2.49 (m, 2H), 2.27–2.24 (m, 1H), 1.98–1.95 (m, 1H), 1.60 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 163.1, 140.0, 137.3, 136.1, 136.0, 130.4, 129.0, 128.7, 114.7, 93.3, 69.2, 51.8, 37.2, 36.5, 31.5, 24.6, 21.9; HR-MS (ESI): *m/z* = 439.0686, calcd. for $C_{19}H_{22}Cl_2O_6Na$ $[M+Na]^+$: 439.0686; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 90:10, UV = 254 nm, flow rate = 0.7 mL min^{-1}): t_{R1} = 9.18 min (major) and t_{R2} = 12.20 min (minor); *ee* = 93%; *de* > 99%; $[\alpha]_D^{25}$: +69 (*c* 0.20, MeOH).

Isopropyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-*p*-tolyl-3,4-dihydro-2*H*-pyran-6-carboxylate (12k): pale yellow oil; yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.04 (m, 4H), 6.07 (d, *J* = 2.5 Hz, 1H), 5.63 (s, 1H), 5.12–5.09 (m, 1H), 5.07–5.04 (m, 1H), 3.58 (s, 3H), 3.44 (dd, *J* = 4.0, 2.4 Hz, 1H), 2.34 (s, 3H), 2.26 (m, 1H), 1.90 (m, 1H), 1.83–1.57 (m, 2H), 1.26 (dd, *J* = 8.0, 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 163.4, 139.8, 139.2, 137.1, 129.8, 128.7, 128.4, 116.2, 93.4, 69.5, 51.8, 42.2, 40.1, 31.6, 24.6, 22.0, 21.4; HR-MS (ESI): *m/z* = 385.1624, calcd. for $C_{20}H_{26}O_6Na$ $[M+Na]^+$: 385.1622; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OJ-H, hexane/*i*-PrOH = 90:10, UV = 254 nm, flow rate = 0.8 mL min^{-1}): t_{R1} = 14.99 min (major) and t_{R2} = 8.56 min (minor); *ee* = 91%; *de* > 99%; $[\alpha]_D^{25}$: +92 (*c* 0.40, MeOH).

Isopropyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-(2-methoxyphenyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12l): pale yellow oil; yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.22 (m, 1H), 7.13–7.11 (m, 1H), 6.98–6.96 (m, 2H), 6.04 (d, *J* = 3.2, 1.6 Hz, 1H), 5.50 (dd, *J* = 4.0, 2.2 Hz, 1H), 5.14–5.11 (m, 1H), 4.00 (dd, *J* = 3.2 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 2.36–2.31 (m, 2H), 2.02–1.98 (m, 1H), 1.88–1.81 (m, 1H), 1.62–1.58 (m, 1H), 1.27 (dd, *J* = 6.4, 3.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 162.8, 157.5, 140.8, 130.5, 129.3, 129.0, 128.3, 120.9, 115.2, 110.8, 93.7, 69.2, 55.5, 51.8, 41.3, 33.7, 33.6, 31.6, 23.6, 22.0; HR-MS (ESI): *m/z* = 401.1574, calcd. for $C_{20}H_{26}O_7Na$ $[M+Na]^+$: 401.1571; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 90:10, UV = 254 nm, flow rate = 0.5 mL min^{-1}): t_{R1} = 14.24 min (major) and t_{R2} = 34.38 min (minor); *ee* = 98%; *de* > 99%; $[\alpha]_D^{25}$: +79 (*c* 0.20, MeOH).

Isopropyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-(3-methoxyphenyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12m): pale yellow oil; yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.22 (m, 1H), 6.81–6.78 (m, 2H), 6.76–6.73 (m, 1H), 6.06 (d, *J* = 2.4 Hz, 1H), 5.63 (s, 1H), 5.10–5.07 (m, 1H), 3.78 (s, 3H), 3.56 (s, 3H), 3.46 (dd, *J* = 4.0, 2.0 Hz, 1H), 2.29–2.23 (m, 1H), 2.18–2.15 (m, 1H), 1.92 (s, 1H), 1.78–1.74 (m, 1H), 1.67–1.64 (m, 1H), 1.25–1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 163.4, 160.1, 143.8, 139.8, 129.9, 121.1, 115.7, 114.5, 112.4, 93.3, 69.4, 55.4, 51.7, 41.9, 40.5, 31.5, 24.5, 21.9; HR-MS (ESI): *m/z* = 401.1570, calcd. for $C_{20}H_{26}O_7Na$ $[M+Na]^+$: 401.1571; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 90:10, UV = 254 nm, flow rate = 0.5 mL min^{-1}): t_{R1} = 14.53 min (major) and t_{R2} = 29.26 min (minor); *ee* = 93%; *de* > 99%; $[\alpha]_D^{25}$: +70 (*c* 0.50, MeOH).

Isopropyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12n): pale yellow oil; yield: 66%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.06 (d, *J* = 2.4 Hz, 1H), 5.60 (d, *J* = 2.0 Hz, 1H), 5.12–5.09 (m, 1H),

3.80 (s, 3H), 3.59 (s, 3H), 3.43–3.39 (m, 1H), 2.33–2.10 (m, 2H), 1.90–1.80 (m, 1H), 1.72–1.57 (m, 2H), 1.27–1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 163.4, 158.8, 139.8, 134.1, 129.6, 116.2, 114.3, 93.4, 69.3, 55.4, 51.7, 42.2, 39.6, 31.5, 29.9, 24.5, 21.9; HR-MS (ESI): *m/z* = 401.1578, calcd. for $C_{20}H_{26}O_7Na$ $[M+Na]^+$: 401.1571; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 92:8, UV = 254 nm, flow rate = 0.55 mL min^{-1}): t_{R1} = 16.04 min (major) and t_{R2} = 27.33 min (minor); *ee* = 90%; *de* > 99%; $[\alpha]_D^{25}$: +104 (*c* 0.40, MeOH).

Isopropyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-(naphthalen-2-yl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12o): white solid; yield: 93%; mp 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.81 (m, 3H), 7.68 (s, 1H), 7.50–7.47 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 6.15 (d, *J* = 2.4 Hz, 1H), 5.69 (s, 1H), 5.13 (m, 1H), 3.66 (d, *J* = 2.4 Hz, 1H), 3.54 (s, 3H), 2.37–2.26 (m, 1H), 2.25–2.14 (m, 1H), 2.09–2.06 (m, 1H), 1.82–1.65 (m, 2H), 1.26 (dd, *J* = 7.0, 4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 163.3, 140.1, 139.5, 133.7, 132.8, 128.8, 127.9, 127.6, 126.4, 126.0, 115.6, 93.3, 69.4, 51.7, 41.9, 40.7, 31.5, 24.5, 21.9; HR-MS (ESI): *m/z* = 421.1632, calcd. for $C_{23}H_{26}O_6Na$ $[M+Na]^+$: 421.1622; the enantiomeric and diastereoselective excess were was determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 94:6, UV = 254 nm, flow rate = 0.7 mL min^{-1}): t_{R1} = 17.88 min (major) and t_{R2} = 33.65 min (minor); *ee* = 92%; *de* > 99%; $[\alpha]_D^{25}$: +64 (*c* 0.40, MeOH).

Isopropyl 4-(furan-2-yl)-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12p): pale yellow oil; yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.35 (m, 1H), 6.33–6.31 (m, 1H), 6.16 (d, *J* = 3.2 Hz, 1H), 6.06 (d, *J* = 2.6 Hz , H), 5.60–5.59 (m, 1H), 5.11–5.08 (m, 1H), 3.63 (s, 3H), 2.33–2.19 (m, 2H), 2.07–2.03 (m, 1H), 1.82–1.17 (m, 3H), 1.26 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 163.1, 154.7, 142.1, 141.9, 140.4, 112.7, 112.6, 110.5, 107.1, 93.4, 69.5, 51.8, 39.6, 34.3, 31.4, 24.6, 21.9; HR-MS (ESI): *m/z* = 361.1259, calcd. for $C_{17}H_{22}O_7Na$ $[M+Na]^+$: 361.1258; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 88:12, UV = 254 nm, flow rate = 0.5 mL min^{-1}): t_{R1} = 11.44 min (major) and t_{R2} = 28.28 min (minor); *ee* = 91%; *de* > 99%; $[\alpha]_D^{25}$: +66 (*c* 0.50, MeOH).

Isopropyl 2-hydroxy-3-(2-methoxy-2-oxoethyl)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (12q): white solid; yield: 96%; mp 122–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.21 (m, 5H), 6.10 (d, *J* = 1.4 Hz, 1H), 5.72 (s, 1H), 5.13–5.10 (m, 1H), 3.68 (d, *J* = 4.4 Hz, 1H), 3.52 (s, 3H), 2.56–2.52 (m, 1H), 2.44-2.42 (m, 1H), 2.31–2.27 (m, 1H), 1.25 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 163.4, 141.6, 140.3, 129.0, 128.9, 127.5, 115.1, 93.3, 69.5, 51.8, 39.8, 33.6 21.9; HR-MS (ESI): *m/z* = 357.1307, calcd. for $C_{18}H_{22}O_6Na$ $[M+Na]^+$: 357.1309; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OA3100-H, hexane/*i*-PrOH = 92:8, UV = 254 nm, flow rate = 0.6 mL min^{-1}): t_{R1} = 16.25 min (major) and t_{R2} = 19.15 min (minor); *ee* = 91%; *de* > 99%; $[\alpha]_D^{25}$: +132 (*c* 0.50, MeOH).

Isopropyl 2-hydroxy-3-(4-methoxy-4-oxobutyl)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (12r): white solid; yield: 95%; mp 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.18 (m, 5H), 6.08 (d, *J* = 2.4 Hz, 1H), 5.68 (s, 1H), 5.12–5.08 (m, 1H), 3.55 (s, 3H), 3.47–3.43 (m, 1H), 2.17–2.15 (m, 2H), 1.91–1.83 (m, 1H), 1.81–1.61 (m, 2H), 1.59–1.34 (m, 2H), 1.23 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 163.5, 142.6, 139.9, 128.9, 128.8, 127.2, 115.9, 93.4, 69.4, 51.7, 42.2, 40.5, 34.2, 28.6, 22.4, 21.9; HR-MS (ESI): *m/z* = 385.1639, calcd. for $C_{20}H_{26}O_6Na$ $[M+Na]^+$: 385.1627; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OA3100-H, hexane/*i*-PrOH = 92:8 UV = 254 nm, flow rate = 0.6 mL min^{-1}): t_{R1} = 17.77 min (major) and t_{R2} = 21.16 min (minor); *ee* = 90%; *de* > 99%; $[\alpha]_D^{25}$: +109 (*c* 0.50, MeOH).

Ethyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (12s): white solid; yield: 90%; mp 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.34–7.32 (m, 2H), 7.27–7.26 (m, 1H), 7.23–7.16 (m, 2H), 6.12 (d, *J* = 2.4 Hz, 1H), 5.61 (s, 1H), 4.27–4.23 (m, 2H), 3.58 (s, 3H), 3.47 (dd, *J* = 4.0, 2.4 Hz, 1H), 2.26 (m, 2H), 1.85–1.58 (m, 3H), 1.29–1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 163.8, 142.3, 139.9, 129.1, 128.8, 127.5, 116.2, 93.4, 61.8, 42.3, 40.6, 31.6, 24.5, 14.4; HR-MS (ESI): *m/z* = 357.1308, calcd. for $C_{18}H_{22}O_6Na$ $[M+Na]^+$: 357.1309; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 94:6, UV = 254 nm, flow rate = 0.6 mL min^{-1}): t_{R1} = 19.41 min (major) and t_{R2} = 28.85 min (minor); *ee* = 94%; *de* > 99%; $[\alpha]_D^{25}$: +52 (*c* 0.50, MeOH).

Benzyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (12t): white solid; yield: 98%; mp 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.13 (m, 10H), 6.16 (d, *J* = 2.4 Hz, 1H), 5.61 (d, *J* = 7.6 Hz, 1H), 5.29–5.16 (m, 2H), 3.57 (s, 3H), 3.48 (dd, *J* = 2.4 Hz, 1H), 2.28–2.20 (m, 2H), 1.82–1.59 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.9, 163.5, 142.1, 139.8, 135.6, 129.1, 128.8, 128.7, 127.5, 116.6, 93.4, 67.4, 51.9, 42.2, 40.6, 31.6, 24.5; HR-MS (ESI): *m/z* = 419.1462, calcd. for $C_{23}H_{24}O_6Na$ $[M+Na]^+$: 419.1465; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OJ-H, hexane/*i*-PrOH = 85:15, UV = 254 nm, flow rate = 0.8 mL min^{-1}): t_{R1} = 33.29 min (major) and t_{R2} = 22.15 min (minor); *ee* = 95%; *de* > 99%; $[\alpha]_D^{25}$: +65 (*c* 0.50, MeOH).

Benzyl 4-(2-chlorophenyl)-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12u): white solid; yield: 92%; mp 122–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.05 (m, 9H), 6.07 (d, *J* = 2.8 Hz, 1H), 5.59–5.56 (m, 1H), 5.28–5.16 (m, 2H), 4.55–4.51 (m, 1H), 3.59 (s, 3H), 2.39–2.20 (m, 2H), 1.95–1.77 (m, 2H), 1.68–1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 163.1, 140.5, 139.4, 135.5, 134.6, 130.1, 130.0, 128.7, 128.6, 127.5, 115.1, 93.4, 67.3, 51.8, 41.7, 37.1, 31.5, 23.8; HR-MS (ESI): *m/z* = 453.1071, calcd. for $C_{23}H_{23}ClNaO_6$ $[M+Na]^+$: 453.1075; the enantiomeric excess and and diastereoselective excess were determined by HPLC (Chiralcel OJ-H, hexane/*i*-PrOH = 80:20, UV = 254 nm, flow rate = 0.6 mL min^{-1}): t_{R1} = 21.99 min (minor) and t_{R2} = 24.98 min (major); *ee* = 97%; *de* > 99%; $[\alpha]_D^{25}$: +134 (*c* 0.30, MeOH).

Benzyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-(2-methoxyphenyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12v): pale yellow oil; yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.27 (m, 4H), 7.27–7.17 (m, 2H), 7.09 (dd, *J* = 4.0, 1.6 Hz, 1H), 6.96–6.93 (m, 2H), 6.11 (d, *J* = 3.2 Hz, 1H),

5.50–5.49 (m, 1H), 5.34–5.08 (m, 2H), 4.01 (dd, $J=3.2$, 1.6 Hz, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 2.39–2.25 (m, 2H), 2.05–1.98 (m, 1H) 1.88–1.83 (m, 1H), 1.68–1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.1$, 163.2, 157.5, 140.5, 130.3, 129.4, 128.7, 128.5, 128.3, 120.9, 116.1, 110.9, 93.7, 67.1, 55.5, 51.7, 41.3, 33.9, 31.6, 23.6; HR-MS (ESI): $m/z=$ 449.1573, calcd. for $C_{24}H_{26}NaO_7$ $[M+Na]^+$: 449.1571; the enantiomeric excess and and diastereoselective excess were determined by HPLC (Chiralcel OD-H, hexane/*i*-PrOH= 80:20, UV=254 nm, flow rate=0.7 mL min^{-1}): $t_{R1}=$ 13.26 min (major) and $t_{R2}=32.49$ min (minor); *ee*=99%; *de* >99%; $[\alpha]_D^{25}$: +124 (*c* 0.30, MeOH).

Benzyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12w): pale yellow oil; yield: 76%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.45$–7.28 (m, 5H), 7.11–7.08 (m, 2H), 6.87–6.84 (m, 2H), 6.13 (d, $J=2.6$ Hz, 1H), 5.59 (s, 1H), 5.22 (dd, $J=12.0$, 9.6 Hz, 2H), 3.79 (s, 3H), 3.59 (s, 3H), 3.43–3.39 (m, 1H), 2.39–2.04 (m, 3H), 1.76–1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=173.7$, 163.3, 158.9, 139.5, 135.8, 129.8, 129.6, 129.3, 128.7, 128.6, 116.8, 114.4, 93.4, 67.2, 55.4, 51.7, 42.2, 39.6, 31.5, 24.4; HR-MS (ESI): $m/z=449.1564$, calcd. for $C_{24}H_{26}NaO_7$ $[M+Na]^+$: 449.1571; the enantiomeric excess and and diastereoselective excess were determined by HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=80:20, UV= 254 nm, flow rate=0.8 mL min^{-1}): $t_{R1}=25.88$ min (minor) and $t_{R2}=38.07$ min (major); *ee*=96%; *de* >99%; $[\alpha]_D^{25}$: +78 (*c* 0.20, MeOH).

Benzyl 2-hydroxy-4-(2-methoxyphenyl)-3-methyl-3,4-dihydro-2*H*-pyran-6-carboxylate (12x): pale yellow oil; yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.44$–7.28 (m, 5H), 7.23 (d, $J=1.6$ Hz, 1H), 7.11 (dd, $J=2.0$, 1.6 Hz, 1H), 6.93-6.88 (m, 2H), 6.16 (d, $J=2.8$ Hz, 1H), 5.48 (d, $J=2.4$ Hz, 1H), 5.23 (d, $J=9.6$ Hz, 2H), 3.97 (dd, $J=4.8$, 2.8 Hz, 1H), 3.81 (s, 3H), 2.15–2.11 (m, 1H), 0.94 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=163.7$, 157.8, 140.0, 135.7, 130.7, 129.2, 128.5, 128.5, 120.9, 117.1, 110.9, 95.7, 67.1, 55.6, 37.4, 34.4, 14.3; HR-MS (ESI): $m/z=377.1349$, calcd. for $C_{21}H_{22}NaO_5$ $[M+Na]^+$: 377.1359; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OZ-H, hexane/*i*-PrOH=90:10, UV=254 nm, flow rate=0.5 mL min^{-1}): $t_{R1}=14.67$ min (major) and $t_{R2}=$ 36.55 min (minor); *ee*=97%; *de* >99%; $[\alpha]_D^{25}$: +101 (*c* 0.40, MeOH).

Benzyl 3-ethyl-2-hydroxy-4-(2-methoxyphenyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12y): pale yellow oil; yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.42$–7.28 (m, 5H), 7.25–7.20 (m, 1H), 7.11 (dd, $J=4.0$, 1.6 Hz, 1H), 6.99- 6.81 (m, 2H), 6.12 (d, $J=2.8$ Hz, 1H), 5.61 (d, $J=2.0$ Hz, 1H), 5.22 (dd, $J=12.4$, 9.6 Hz, 2H), 4.02 (dd, $J=4.0$, 2.4 Hz, 1H), 3.80 (s, 3H), 1.93–1.82 (m, 1H), 1.59–1.45 (m, 1H), 1.36–1.21 (m, 1H), 0.86 (t, $J=7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 157.7, 140.0, 135.7, 130.8, 130.2, 129.3, 129.0, 128.7, 128.6, 128.5, 128.1, 120.9, 117.0, 110.8, 93.7, 67.1, 55.5, 43.6, 33.4, 21.4, 11.6; HR-MS (ESI): $m/z=$ 391.1508, calcd. for $C_{22}H_{24}NaO_5$ $[M+Na]^+$: 391.1516; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OZ-H, hexane/*i*-PrOH= 90:10, UV=254 nm, flow rate=0.5 mL min^{-1}): $t_{R1}=$ 12.72 min (major) and $t_{R2}=43.81$ min (minor); *ee*=97%; *de* >99%; $[\alpha]_D^{25}$: +87 (*c* 0.20, MeOH).

Benzyl 2-hydroxy-3-isopropyl-4-(2-methoxyphenyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12z): pale yellow oil; yield: 42%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.43$–7.29 (m, 5H), 7.25–7.18 (m, 1H), 7.13 (dd, $J=1.6$, 1.2 Hz, 1H), 6.97–6.85 (m, 2H), 6.10 (d, $J=2.8$ Hz, 1H), 5.68 (d, $J=2.0$ Hz, 1H), 5.26 (d, $J=12.4$ Hz, 2H), 4.24 (dd, $J=2.8$, 2.4 Hz, 1H), 3.81 (s, 3H), 2.09–2.01 (m, 1H), 1.73–1.58 (m, 1H), 0.95 (d, $J=$ 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=163.5$, 157.6, 139.3, 135.8, 130.7, 129.4, 129.3, 128.7, 128.5, 128.4,128.1, 128.0, 120.9, 118.3, 111.0, 93.8, 67.0, 55.5, 46.7, 33.5, 27.3, 21.3, 19.2; HR-MS (ESI): $m/z=405.1669$, calcd. for $C_{23}H_{26}NaO_5$ $[M+Na]^+$: 405.1672; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OZ-H, hexane/*i*-PrOH=90:10, UV=254 nm, flow rate=0.5 mL min^{-1}): $t_{R1}=11.28$ min (major) and $t_{R2}=$ 23.29 min (minor); *ee*=98%; *de* >99%; $[\alpha]_D^{25}$: +78 (*c* 0.40, MeOH).

Ethyl 4-ethyl-2-hydroxy-3-(3-methoxy-3-oxopropyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (12aa): pale oil; yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.07$ (d, $J=3.2$ Hz, 1H), 5.43 (d, $J=2.0$ Hz, 1H), 4.23–4.20 (m, 2H), 3.64 (s, 3H), 2.44–2.39 (m, 2H), 2.23–2.19 (m, 1H), 1.84–1.50 (m, 5H), 1.28 (t, $J=7.2$ Hz, 3H), 0.92 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.1$, 163.5, 140.1, 115.8, 93.1, 61.5, 51.8, 38.9, 34.7, 31.5, 25.1, 23.6, 14.4, 10.6; HR-MS (ESI): $m/z=309.1299$, calcd. for $C_{14}H_{22}NaO_6$ $[M+Na]^+$: 309.1309; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OZ-H, hexane/*i*-PrOH=91:9, UV=254 nm, flow rate=0.7 mL min^{-1}): $t_{R1}=15.46$ min (major) and $t_{R2}=39.90$ min (minor); *ee*=95%; *de* >99%; $[\alpha]_D^{25}$: +117 (*c* 0.40, MeOH).

Ethyl 2-hydroxy-3-(3-methoxy-3-oxopropyl)-4-pentyl-3,4-dihydro-2*H*-pyran-6-carboxylate (12ab): pale yellow oil; yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.07$ (d, $J=$ 3.2 Hz, 1H), 5.42 (d, $J=2.0$ Hz, 1H), 4.23–4.20 (m, 2H), 3.64 (s, 3H), 2.47–2.34 (m, 2H), 2.20–2.18 (m, 1H), 1.80–1.76 (m, 1H), 1.62–1.47 (m, 2H), 1.28–1.26 (m, 11H), 0.86 (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.1$, 163.5, 139.9, 116.1, 93.1, 61.5, 51.8, 39.6, 33.5, 32.5, 32.1,31.5, 25.9, 23.7, 22.8, 14.4, 14.3; HR-MS (ESI): $m/z=351.1769$, calcd. for $C_{17}H_{28}NaO_6$ $[M+Na]^+$: 351.1778; the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel OZ-H, hexane/*i*-PrOH=92:8, UV= 254 nm, flow rate=0.6 mL min^{-1}): $t_{R1}=17.35$ min (major) and $t_{R2}=48.10$ min (minor); *ee*=93%; *de* >99%; $[\alpha]_D^{25}$: +113 (*c* 0.40, MeOH).

General Procedure for Cyclization

The hemiacetal ester (5 mmol) was dissolved in toluene (20 mL) and was treated with pyridinium *para*-toluenesulfonate (PPTS, 0.1 equiv.). The solution was refluxed for 4 h. The solvent was then evaporated and the residue was purified by flash column silica-gel chromatography (PE/EA=8/1) to provide the corresponding adducts of cyclization.

Isopropyl 7-oxo-4-phenyl-4,4a,5,6,7,8a-hexahydropyrano-[2,3-*b*]pyran-2-carboxylate (13a): pale yellow oil; yield: 1.45 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.53$–6.98 (m, 5H), 6.19 (d, $J=3.6$ Hz, 1H), 5.74 (d, $J=2.2$ Hz, 1H), 5.17–5.13 (m, 1H), 3.40 (dd, $J=6.4$, 3.8 Hz, 1H), 2.83–2.46 (m, 2H), 2.32–2.29 (m, 1H), 1.91–1.88 (m, 2H), 1.31 (d, $J=$ 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=168.9$, 161.3,

141.7, 141.3, 129.3, 128.2, 127.9, 112.4, 96.7, 69.7, 40.2, 36.7, 27.5, 22.0, 19.9; HR-MS (ESI): $m/z = 339.1206$, calcd. for $C_{18}H_{20}O_6Na$ $[M+Na]^+$: 339.1203.

Isopropyl 2-oxo-4-phenyl-3,3a,4,7a-tetrahydro-2*H*-furo-[2,3-*b*]pyran-6-carboxylate (13q): pale yellow oil; yield: 1.41 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$–7.35 (m, 2H), 7.32–7.30 (m, 1H), 7.22–7.14 (m, 2H), 6.23 (d, $J = 4.6$ Hz, 1H), 5.93 (d, $J = 4.4$ Hz, 1H), 5.16–5.13 (m, 1H), 3.47 (m, 1H), 2.82–2.64 (m, 2H), 2.55–2.40 (m, 1H), 1.31 (dd, $J = 6.4$, 2.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 173.7, 161.1, 142.3, 141.1, 129.5, 128.0, 127.8, 110.3, 97.6, 69.8, 40.7, 39.1, 33.1, 22.0; HR-MS (ESI): $m/z = 325.1036$, calcd. for $C_{17}H_{18}O_5Na$ $[M+Na]^+$: 325.1046.

Isopropyl 8-oxo-4-phenyl-4a,5,6,7,8,9a-hexahydro-4*H*-pyrano [2,3-*b*]oxepine-2-carboxylate (13r): pale yellow oil; yield: 1.50 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$–7.11 (m, 5H), 6.44 (s, 1H), 5.99 (d, $J = 4.4$ Hz, 1H), 5.17–5.00 (m, 1H), 4.07 (d, $J = 4.4$ Hz, 1H), 3.60 (s, 1H), 2.24–2.17 (m, 2H), 1.72–1.68 (m, 3H), 1.61–1.57 (m, 1H), 1.24 (dd, $J = 8.4$, 3.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 173.9, 161.5, 143.3, 140.3, 136.5, 128.9, 128.7, 114.0, 113.0, 69.3, 51.7, 40.3, 33.3, 29.4, 21.9 21.5; HR-MS (ESI-TOF): $m/z = 353.1371$, calcd. for $C_{19}H_{22}O_5Na$ $[M+Na]^+$: 353.1359.

Acknowledgements

This work was partly supported by the National Nature Science Foundation of China (No. 20972095, 21172143 and 21172145), Science and Technology Commission of Shanghai Municipality (No. 10dz1910105), Nippon Chemical Industrial Co., Ltd. and the Instrumental Analysis Center of Shanghai Jiao Tong University. We thank Prof. Tsuneo Imamoto and Dr. Masashi Sugiya for helpful discussions.

References

[1] For recent reviews on asymmetric organocatalysis, see: a) A. Berkessel, H. Groger, *Asymmetric Organocatalysis: From Biomemetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; b) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; c) B. List, J. W. Yang, *Science* **2006**, *313*, 1584; d) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; e) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655; f) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; g) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; h) A. Erkkila, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; i) T. Hashimoto, K. J. Maruoka, *Chem. Rev.* **2007**, *107*, 5656–5682; j) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655; k) T. Alkiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; l) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; m) G. Michelangelo, G. Francesco, N. Renato, *Chem. Soc. Rev.* **2008**, *37*, 1666–1688; n) O. A. Wong, Y. A. Shi, *Chem. Rev.* **2008**, *108*, 3958–3987; o) C. Plomo, M. Oiarbide, R. Lopez, *Chem. Soc. Rev.* **2009**, *38*, 632–653; p) S. L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190–2201; q) Z. H. Shao, H. B. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745–2755; r) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395–456; s) W.-J. Liu, N. Li, L.-Z. Gong, *Top. Organomet. Chem.* **2011**, *36*, 153–206; t) G. Francesco, G. Michelangelo, A. Paola, N. Renato, *Chem. Soc. Rev.* **2012**, *41*, 2406–2447.

[2] For selected reviews, see: a) B. List, *Synlett* **2001**, 1675–1686; b) E. R. Jarvo, S. J. Miller, *Tetrahedron* ***2002***, *58*, 2481–2495; c) B, List, *Acc. Chem. Res.* **2004**, *37*, 548–557; d) S. J. Miller, *Acc. Chem. Res.* **2004**, *37*, 601–610; e) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; f) C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Soc. Rev.* **2004**, *33*, 65–75; g) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591; h) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; i) U. Kazmaier, *Angew. Chem.* **2005**, *117*, 2224–2226; *Angew. Chem. Int. Ed.* **2005**, *44*, 2186–2188; j) Y. Hayashi, *Yuki Gosei Kagaku Kyokaishi* **2005**, *63*, 464–477; k) F. Tanaka, C. F. Barbas III, *Yuki Gosei Kagaku Kyokaishi* **2005**, *63*, 709–717; l) M. M. B. Marques, *Angew. Chem.* **2006**, *118*, 356–360; *Angew. Chem. Int. Ed.* **2006**, *45*, 348–352; m) B. List, *Chem. Commun.* **2006**, 819–824; n) R. M. Kellogg, *Angew. Chem.* **2007**, *119*, 498–502; *Angew. Chem. Int. Ed.* **2007**, *46*, 494–497; o) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; p) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 493–529; q) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 757–797; for selected recent papers: r) B. Hahn, F. Roland, H. Klause, G. Frank, *Angew. Chem.* **2008**, *120*, 10134–10137; *Angew. Chem. Int. Ed.* **2008**, *47*, 9985–9988; s) C. Chandler, G. Patrizia, M. Anna, B. List, *Angew. Chem.* **2009**, *121*, 2012–2014; *Angew. Chem. Int. Ed.* **2009**, *48*, 1978–1980; t) B. Donna, M. Antonio, H. Matthew, A. Alan, *J. Am. Chem. Soc.* **2010**, *132*, 7598–7599; u) K. Ananta, M. Tapan, W. Sebastian, R. Oliver, *Chem. Eur. J.* **2011**, *17*, 11024–11029; v) M. Castaneda, B. Poladura, H. R. Solla, V. Amo, *Org. Lett.* **2011**, *13*, 3032–3035.

[3] a) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737–3740; b) P. Kotrusz, I. Kmentova, B. Gotov, *Chem. Commun.* **2002**, 2510–2512; c) V. Chan, J. G. Kim, C. Jimeno, P. J. Carroll, P. J. Walsh, *Org. Lett.* **2004**, *6*, 2051–2053; d) R. Thayumanavan, F. Tanka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 3541–3544; e) S. Chandrasekhar, N. R. Reddy, S. S. Sultana, C. Narsihmulu, K. V. Reddy, *Tetrahedron* **2006**, *62*, 338–345; f) T. Kano, H. Sugimoto, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 18130–18133; g) M. R. Monaco, P. Renzi, D. M. Scarpino Schietroma, M. Bella, *Org. Lett.* **2011**, *13*, 4546–4549.

[4] a) R. K. Kunz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3240–3241; b) S. Chandrasekhar, N. R. Reddy, S. S. Sultana, C. Narsihmulu, K. V. Reddy, *Tetrahedron* **2006**, *62*, 338–345; c) X.-P. Tang, B. Liégault, J. L. Renaud C. Bruneau, *Tetrahedron: Asymmetry* **2006**, *17*, 2187–2190; d) J.-W. Xie, L. Yue, D. Xue, X.-L. Ma, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Chem. Commun.* **2006**, 1563–1565; e) A. Hartikka, P. I. Arvidsson, *J. Org. Chem.* **2007**, *72*, 5874–5877; f) J. Vesely, G.-L. Zhao, A. Bartoszewicz, A. Córdova, *Tetrahedron Lett.* **2008**, *49*, 4209–4212; g) T. Kano, H. Sugimoto, K.

Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 18130–18133; h) D. Roca-Lopez, P. Merino, F. J. Sayago, C. Cativiela, R. P. Herrera, *Synlett* **2011**, 249–253; i) J. Xiao, F.-X. Xu, Y.-P. Lu, Y.-L. Liu, T. P. Loh, *Synthesis* **2011**, 1912–1917.

[5] a) R. Henning, H. Urbach, *Tetrahedron Lett.* **1983**, *24*, 5343–5346; b) F. Brion, C. Marie, P. Mackiewicz, J. M. Roul, J. Buendia, *Tetrahedron Lett.* **1992**, *33*, 4889–4892; c) R. Henning, H. Urbach, U.S. Patent 4,691,022, **1985**; d) F. Brion, J. Buendia, C. Marie, European Patent 267098, **1988**; e) P. Cid, S. L. Polabo, WO Patent 05054194, **2005**; f) E. Kalaus, O. Frank, U.S. Patent 6,599,318, **2003**; g) J.-H. Li, J.-F. Zhong, H.-L. Shi, *Chin. J. Pharm.* **2007**, *38*, 465–467.

[6] This type of compounds has shown excellent catalytic behaviour in asymmetric Michael addition. The result has been communicated: L. Zhao, J. Shen, D. Liu, Y. Liu, W. Zhang, *Org. Biomol. Chem.* **2012**, *10*, 2840–2846.

[7] P. Müller, P. Nury, *Org. Lett.* **1999**, *1*, 439–441.

[8] a) T. Fukai, Y. Hano, K. Hirakura, T. Nornura, J. Uzawa, K. Fukushima, *Heterocycles* **1984**, *22*, 1007–1011; b) T. Fukai, Y. Hano, K. Hirakura, T. Nornura, J. Uzawa, K. Fukushima, *Chem. Pharm. Bull.* **1985**, *33*, 3195; c) A. J. Castellino, H. Rapoport, *J. Org. Chem.* **1986**, *51*, 1006–1011; d) Y. Hano, J. Yamanaka, Y. Momose, T. Nomura, *Heterocycles* **1995**, *41*, 2811–2282; e) F. Alonso, *Tetrahedron Lett.* **2005**, *46*, 6519–6524; f) Q.-J. Zhang, Y.-B. Tang, R.-Y. Chen, D.-Q. Yu, *Chem. Biodiversity* **2007**, *4*, 1533–1540; g) S. B. Ferroira, *Eur. J. Med. Chem.* **2011**, *46*, 3071–3077.

[9] a) T. Miyazaki, S. Yokoshima, S. Simizu, H. Osada, H. Tokuyama, T. Fukuyama, *Org. Lett.* **200**7, 9, 4737–4474; b) D. Ergunes, V. Kumbaraci, B. Karliga, N. Talinli, *J. Heterocycl. Chem.* **2007**, *44*, 1493–1495; c) M. Rueping, M.-Y. Lin, *Chem. Eur. J.* **2010**, *16*, 4169–4172; d) M. M. A. R. Moustafa, A. C. Stevens, B. P. Machin, B. L. Pagenkopf, *Org. Lett.* **2010**, *12*, 4736–4738.

[10] For selected papers on the hetero-Diels–Alder (HDA) reaction, see: a) E. Wada, S. Kanemasa, O. Tsuge, *Chem. Lett.* **1989**, 675–678; b) K. B. Szwed, A. Palasz, *Monatsh. Chem.* **1997**, *128*, 1157–1172; c) D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649; d) W. Li, K. T. Mead, L. T. Smith, *Tetrahedron Lett.* **2003**, *44*, 6351–6353; e) K. Juhl, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1536–1539; *Angew. Chem. Int. Ed.* **2003**, *42*, 1498–1501; f) R. S. Kumar, R. Nagarajan, K. Vijay, P. T. Perumal, *Lett. Org. Chem.* **2005**, *2*, 458–460; g) K. Tchabanenko, M. G. O. Taylor, R. M. Adlington, J. E. Baldwin, *Tetrahedron Lett.* **2006**, *47*, 39–41; h) G. S. Ramanjaneyulu, S. Prabhakar, G. Bhaskar, A. Venkatesham, K. Nagaiah, R. N. Rao, Y. Soujanya, G. N. Sastry, *Rapid Commun. Mass Spectrom.* **2007**, *21*, 3511–3519; i) S. Samanta, J. Krause, T. Mandal, C.-G. Zhao, *Org. Lett.* **2007**, *9*, 2745–2748; j) C. D. Bray, *Org. Biomol. Chem.* **2008**, *6*, 2815–2819; k) J. Wang, F.-X. Xu, X.-F. Lin, Y.-G. Wang, *Tetrahedron Lett.* **2008**, *49*, 5208–5210; l) J. Wang, F. Yu, X.-J. Zhang, D.-W. Ma, *Org. Lett.* **2008**, *10*, 2561–2564; m) V. Kumbaraci, D. Ergunes, M. Midilli, S. Begen, N. Talinli, *J. Heterocycl. Chem.* **2009**, *46*, 226–230; n) S. Kobayashi, T. Kinoshita, H. Uehara, T. Sudo, I. Ryu, *Org. Lett.* **2009**, *11*, 3934–3937; o) J.-J. Wang, J.-H. Lao, Z.-P. Hu, R.-J. Lu; S.-Z. Nie, Q.-S. Du, M. Yan, *Arkivoc* **2010**, *ix*, 229–243; p) A. Kumar, S. Srivastava, G. Gupta, V. Chaturvedi, S. Sinha, R. Srivastava, *Comb. Sci.* **2011**, *13*, 65–71; q) Y. Luan, H. Sun, S. E. Schaus, *Org. Lett.* **2011**, *13*, 6480–6483; r) T. Liu, Y.-M. Wang, G.-P. Wu, H.-B. Song, Z.-H. Zhou, C.-C. Tang, *J. Org. Chem.* **2011**, *76*, 4119–4124.

[11] a) J. Thorhauge, M. Johannsen, K. A. Jørgensen, *Angew. Chem.* **1998**, *110*, 2543–2546; *Angew. Chem. Int. Ed.* **1998**, *37*, 2404–2406; b) D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649; c) Y. Zhu, M.-S. Xie, S.-X. Dong, X.-H. Zhao, L.-L. Lin, X.-H. Liu, X.-M. Feng, *Chem. Eur. J.* **2011**, *17*, 8202–8208.

[12] CCDC 881386 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[13] For selected examples, see: a) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; b) N. Mase, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2003**, *5*, 4369–4372; c) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2004**, *116*, 2474–2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420–2423; d) P. Dinér, M. Nielsen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 2029–2033; *Angew. Chem. Int. Ed.* **2007**, *46*, 1983–1987; e) Z.-L. Zheng, B. L. Perkins, B. Ni, *J. Am. Chem. Soc.* **2010**, *132*, 50–51.

[14] For selected paprers, see: a) S. Corsano, G. Piancatelli, *J. Chem. Soc. (D)* **1971**, 1106; b) A. J. Lin, D. L. Klayman, J. M. Hoch, *J. Org. Chem.* **1985**, *50*, 4504–4508; c) M. Jung, X. Li, D. A. Bustos, H. N. ElSohly, J. D. McChesney, W. K. Milhous, *J. Med. Chem.* **1990**, *33*, 1516–1518; d) R. A. Vishwakarma, R. Mehrotra, *J. Nat. Prod.* **1992**, *55*, 1142–1144; e) Y.-H. Yang, Y. Li, Y.-L. Shi, J.-D. Yang, B.-A. Wu, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1791–1794; f) M. A. Avery, S. Mehrotra, T. L. Johnson, J. D. Bonk, J. A. Vroman, R. Miller, *J. Med. Chem.* **1996**, *39*, 4149–4155; g) N. A. Powell, S. D. Rychnovsky, *J. Org. Chem.* **1999**, *64*, 2026–2037; h) J. Ma, E. Katz, D. E. Kyle, H. Ziffer, *J. Med. Chem.* **2000**, *43*, 4228 4232; i) Y.-D. Zhang, T. Rovis, *Org. Lett.* **2004**, *6*, 1877–1879; j) Y.-G. Liu, V. K. W. Wong, B. C. B. Ko, M.-K. Wong, C.-M. Che, *Org. Lett.* **2005**, *7*, 1561–1564; k) I. H. Paik, S.-J. Xie, T. A. Shapiro, T. Labonte, A. A. N. Sarjeant, A. C. Baege, G. H. Posner, *J. Med. Chem.* **2006**, *49*, 2731–2734; l) G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, S. L. Maslen, S. V. Ley, *Angew. Chem.* **2007**, *119*, 7773–7776; *Angew. Chem. Int. Ed.* **2007**, *46*, 7629–7632; m) M. Boehm, P. C. Fuenfschilling, M. Krieger, E. Kuesters, F. Struber, *Org. Process Res. Dev.* **2007**, *11*, 336–340; n) S. V. Ley, M. N. Tackett, M. L. Maddess, J. C. Anderson, P. E. Brennan, M. W. Cappi, J. P. Heer, C. Helgen, M. Kori, C. Kouklovsky, S. P. Marsden, J. Norman, D. P. Osborn, M. Á. Palomero, J. B. J. Pavey, C. Pinel, L. A. Robinson, J. Schnaubelt, J. S. Scott, C. D. Spilling, H. Watanabe, K. E. Wesson, M. C. Willis, *Chem. Eur. J.* **2009**, *15*, 2874–2914; o) G.-F. Wei, X.-J. Liao, G.-Y. Pan, Z.-L. Huang, J.-S. Cheng, Y.-C. He, *J. Nat. Prod.* **2010**, *3*, 161–164; p) J. P. Marino, K. A. Kieler, M. W. Kimb, *Tet-*

rahedron **2011**, *67*, 837–841; q) Y. Liu, K.-Q. Cui, W.-Q. Lu, W. Luo, J. Wang, J. Huang, C. Guo, *Molecules* **2011**, *16*, 4527–4538; r) M. J. Miller, A. J. Walz, H. Zhu, C.-R. Wu, G. Moraski, U. Mollmann, E. M. Tristani, A. L. Crumbliss, M. T. Ferdig, L. Checkley, R. L. Edwards, H. I. Boshoff, *J. Am. Chem. Soc.* **2011**, *133*, 2076–2079; s) R. D. Slack, B. T. Mott, L. E. Woodard, A. Tripathi, D. Sullivan, E. Nenortas, S. C. T. Girdwood, T. A. Shapiro, G. H. Posner, *J. Med. Chem.* **2012**, *55*, 291–296.

[15] A. Nuhrich, J. Moulines, *Tetrahedron* **1991**, *47*, 3075–3088.

