Highly diastereo- and enantioselective organocatalytic addition of acetone to β-substituted α-ketoesters *via* dynamic kinetic resolution†

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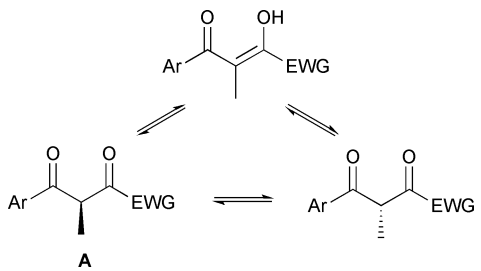
L-Proline catalyzes the aldol addition reaction of acetone to β-substituted α-ketoesters with dynamic kinetic resolution, providing the desired adduct in good yield with excellent diastereoselectivity (up to >99:1 dr) and enantioselectivity (up to 98% ee). The absolute configuration of the chiral adduct was assigned by single-crystal X-ray diffraction analysis. A tentative explanation of the stereochemical outcome is proposed.

Introduction

Among the numerous synthetic methods that are capable of producing chiral substances with high enantiomeric excess, catalytic resolution of racemates is still the most important industrial approach.[1,2] Dynamic kinetic resolution (DKR)[3] which overcomes the drawbacks of kinetic resolution,[4] has become a powerful tool to obtain products with high enantioselectivity from racemic starting materials. In DKR the kinetic resolution of a racemic mixture is combined with *in situ* racemization of the substrate, so that the complete conversion of a racemate to a single diastereomer is theoretically possible.[5] However, the theoretical limit is seldom reached, and so it is highly desirable to develop more efficient asymmetric reaction with good diastereo- and enantioselectivity.

There are several ways to obtain compounds of high ee through a DKR process. The use of enzymes for the DKR of racemic substrates has always been an important strategy in synthesis.[6] In addition to biocatalysts, the use of metal complexes bearing chiral ligands or chiral auxiliaries for DKR also gained popularity at the end of the last century. In recent years, the rapidly developing field of asymmetric organocatalysis has attracted an increasing number of research groups. Although there has been an explosive growth of research activities in organocatalysis, examples of organocatalysed DKR processes are rare.[3]

As one of the basic reactions to create C–C bond, the organocatalytic[7] intermolecular aldol reaction has received much attention since the pioneering work of Barbas, List, and co-workers in 2000.[8] DKR processes using an intermolecular aldol reaction between aldehydes and ketones have also been reported.[9] However, in most cases, the acceptors in organocatalytic aldol reactions are aldehydes. Recent work has shown that some activated ketones, which have an electron-withdrawing group adjacent to the carbonyl carbon, undergo the asymmetric aldol reaction as acceptors under mild reaction conditions.[10] If the activated carbonyl is next to a configurationally labile stereogenic centre (Scheme 1, structure **A**), DKR could be achieved during the asymmetric aldol reaction; indeed, our group reported the first organocatalytic aldol reaction of an activated ketone *via* DKR.[11] However, the diastereoselectivity of this reaction was not very satisfactory (4:1 dr). As a logical extension of our studies on aldolization with functionalized ketones as acceptors, dicarbonyl substrates of type **A** (Scheme 1) were investigated. Here we describe the results of the aldol process of activated ketones catalyzed by proline and its derivatives.

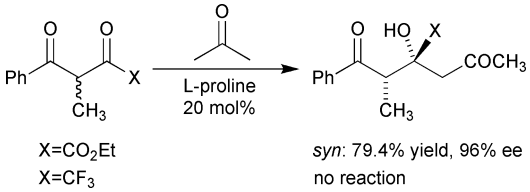


Scheme 1 Racemization of activated ketone **A** through keto–enol transformation (EWG = CO_2Et or CF_3).

Results and discussion

As there is a fast keto–enol equilibration of the activated ketone **A**, it is possible that when the stereoselective aldolization creates a new chiral center in the activated carbonyl carbon, one enantiomer of the racemate pair might be preferred, and thus DKR would be achieved, providing just one diastereoisomer of the four possible products.

In our initial studies, acetone was used to react with two different activated ketones in the presence of L-proline as shown in Scheme 2. The ketone activated by CF_3 failed to react with acetone,



Scheme 2 Direct aldol reaction of acetone and activated ketones.

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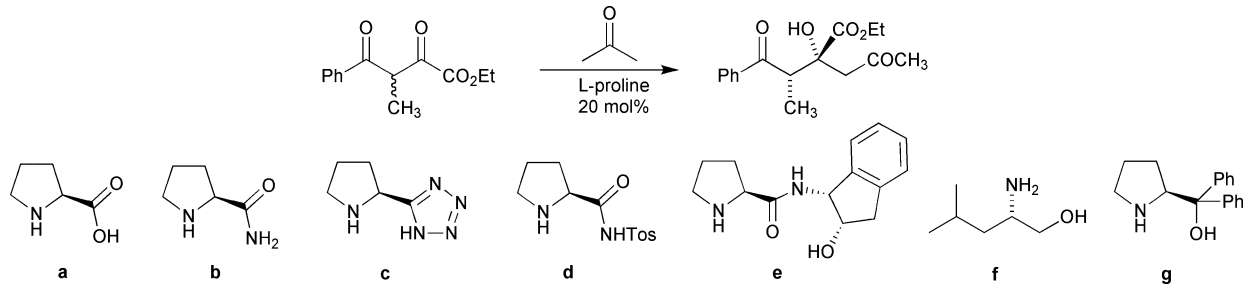
Table 1 Direct asymmetric aldol reactions catalyzed by various organocatalysts[a]



Entry	Catalyst	Catalyst loading/mol%	Time/d	Yield/%[b]	dr[c]	ee/% (major)[c]
1	**a**	5	3	48	66:1	97
2	**a**	10	3	75	32:1	96
3	**a**	20	3	81	43:1	96
4	**a**	30	3	92	11:1	90
5	**b**	20	6	46	25:1	96
6	**c**	20	0.5	67	29:1	95
7	**d**	20	6	74	85:1	70
8	**e**	20	6	36	40:1	84
9	**f**	20	3	67	22:1	84
10	**g**	20	3	37	>99:1	72

[a] All reactions ware carried out using 0.5 mmol of substrate and 3 ml of acetone at rt. [b] Isolated yields. [c] The ee and the dr of the products were determined by HPLC analysis using a Chiralpak AD-H column.

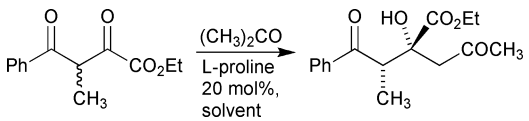
probably because of the stability of the emamine formed between L-proline and the substrate. However, to our delight, when an α-ketoester (EWG = CO_2Et) was used as the aldol acceptor, excellent diastereoselectivity (43:1 dr) and enantioselectivity (96% ee) were achieved.

We then undertook a detailed examination of this reaction. We first screened some readily available proline derivatives as the catalysts in a model reaction – the addition of acetone to ethyl 3-methyl-2,4-dioxo-4-phenylbutanoate. As shown in Table 1, this cross-aldol reaction proceeded smoothly at room temperature in acetone with most of these catalysts, and excellent ee values were obtained with L-proline (entry 3), L-prolinamide (entry 5), or an L-proline-derived tetrazole (entry 6). L-Prolinamide and an L-proline-derived tetrazole gave a moderate dr and yield, while *N*-tosyl-L-prrolinamide showed good distereoselectivity, but poor enantioselectivity (entry 7). The L-proline-derived amino alcohol **g** displayed the best diastereoselectivity, but lower enantioselectivity (entry 10). Moderate yield and ee were obtained with leucinol, but the dr was poor (entry 9). Overall therefore, the results using L-proline were the most promising.

Using L-proline as the organocatalyst, we next studied the influence of catalyst loading on the DKR reactions. As shown in Table 1, even when the catalyst loading was as low as 5 mol%, good dr and excellent ee were observed (Entry 1). However, the reaction was quite slow, and higher catalyst loading resulted in decreased dr (Entry 4). Therefore, 20 mol% L-proline was employed subsequently.

We then explored the solvent effects on the DKR reaction. As shown in Table 2, the reaction yield and diastereoselectivity were highly solvent-dependent. High diastereomeric ratio and ee were observed when polar aprotic solvents were used (Table 2, entries 7–10), but the yield was relatively low. The protic solvent CH_3OH seemed to have an adverse influence on enantio- and diastereoselectivity, as well as the reaction yield (entry 5). Tetrahydrofuran,

Table 2 Results of solvents screening for the model reaction



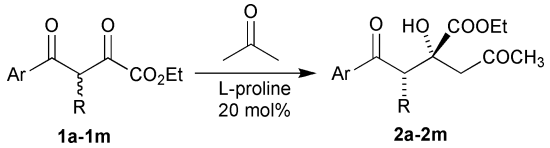
Entry	Solvent	Time/d	Yield/%[a]	dr[b]	ee/% (major)[b]
1	Acetone	3	81	43:1	96
2	THF	6	50	70:1	97
3	CH_2Cl_2	6	57	51:1	97
4	Toluene	6	22	18:1	97
5	CH_3OH	6	40	1.3:1	29
6	$CHCl_3$	6	30	18:1	96
7	CH_3CN	6	48	64:1	96
8	DMF	6	37	>99:1	96
9	DMSO	6	20	90:1	96
10	NMP	6	62	>99:1	96

[a] Isolated yields. [b] The ee value and the diastereomeric ratio (dr) of the products were determined by HPLC analysis using a Chiralpak AD-H column.

dichloromethane and toluene gave high ee and moderate dr values, but low yields, as did chloroform. In contrast, in acetone, the product was obtained in high yield with excellent ee, and the dr was satisfactory.

Having established the optimized conditions for the model reaction, we next probed the generality of this DKR reaction in acetone at room temperature in the presence of 20 mol% of L-proline. The results are summarized in Table 3. The data showed that for most of the 3-methyl-2,4-dioxo-4-aryl-butanoates with R = CH_3, good yield, excellent dr (up to > 99:1) and ee (up to 97%) could be achieved. Bulkier R groups such as ethyl and isopropyl groups decreased the reaction rate and dr of the product, although the ee was not affected. It was found that neither *para*-alkyl nor *para*-halogen substitution of the

Table 3 Dynamic kinetic resolution of 2,4-dioxo-3-methyl-4-aryl-butanoates [a]



Entry	Ar	R	Time/d	Product	Yield/%[b]	dr[c]	ee (major)[c]
1	Ph	CH_3	3	**2a**	81	98:2	96
2	Ph	C_2H_5	6	**2b**	61	87:13	96
3	Ph	C_3H_7	6	**2c**	51	80:20	96
4	*p*-Cl-C_6H_4	CH_3	3	**2d**	72	>99:1	92
5	*p*-Br-C_6H_4	CH_3	3	**2e**	76	>99:1	98
6	*p*-MeO-C_6H_4	CH_3	3	**2f**	70	>99:1	85
7	*p*-*i*Pr-C_6H_4	CH_3	3	**2g**	72	>99:1	94
8	2,5-$Me_2C_6H_3$	CH_3	3	**2h**	75	94:6	96
9	2,4,6-$Me_3C_6H_2$	CH_3	3	**2i**	<5	—	—
10	2-Naphthyl	CH_3	3	**2j**	74	>99:1	94
11	Furan-2-yl	CH_3	6	**2k**	77	97:3	97
12	Thiophen-2-yl	CH_3	6	**2l**	81	95:5	97
13	Pyridin-4-yl	CH_3	3	**2m**	—	—	—

[a] All reactions ware carried out using 0.5 mmol of substrate, 3 ml of acetone and 20 mol% L-proline at rt. [b] Isolated yield. [c] The ee values and the diastereomeric ratios of the products were determined by HPLC analysis using a Chiralpak AD-H or OD-H (for **2h** and **2l**) column.

benzene ring significantly influenced the selectivity (entries 4, 5 and 7). However, the strongly electron-donating *para*-methoxyl group lowered the stereoselectivity to some extent (entry 6). The 4-(2,5-dimethylphenyl) substrate gave a slight decrease in dr (entry 8). Aryl groups other than phenyl groups, such as 2-naphthyl (entry 10), furan-2-yl (entry 11) and thiophen-2-yl (entry 12), all gave satisfactory results. However, when Ar was 2,4,6-trimethylphenyl or pyridin-4-yl, the reactions were unsuccessful, probably because the substrates exist almost entirely as the enol form.[12] Attempts using butanone, cyclohexanone, or propanal as the donor for the above reaction were unsuccessful, and no desired products were formed. For the determination of the absolute configuration of the products, a single crystal of **2e** was prepared and X-ray-analyzed (Fig. 1).[13]

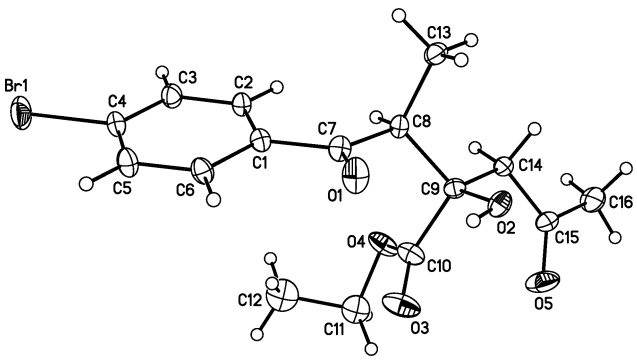


Fig. 1 ORTEP plot of the major diastereomer of **2e** (ORTEP drawing at 10% probability level).

The L-proline-catalysed addition of acetone to the substrate should occur through the enamine formation process.[14] The faster consumption of the substrate in the *R* configuration than the *S* and their fast equilibration through keto–enol transformation resulted in dynamic kinetic resolution taking place. The stereochemical outcome could be explained by examination of the four plausible transition states (Fig. 2).

In TS1 and TS2, the α-carbonyl oxygen atom is hydrogen-bonded so that an *S*-stereogenic centre would be created by the addition of an acetone molecule, where the large $CH(CH_3)Bz$ group is close to the enamine moiety, and hence energetically less favoured. In TS3 and TS4, the substrate molecule directs itself in the way to create an *R*-stereogenic centre, where the small COOEt group is close to the enamine. In TS3, the configurationally labile *R*-configured substrate molecule is hydrogen-bonded by the proline OH. As the carbonyl group is crowded, the large group on the β-carbon, COPh, lies *anti* to the oxygen atom, and thus the attacking CH_2 experiences less hindrance compared to that in TS4, where the CH_3 group in the (*S*)-form must be considered. This arrangement results in preferential reaction *via* TS3, giving (*R*)-ethyl 2-hydroxy-4-oxo-2-((*S*)-1-oxo-1-phenylpropan-2-yl)pentanoate as the major isomer. Although the transformation of CO to CHOH leaves the adjacent carbon geometrically fastened and unchanged, the configuration at this carbon has changed from (*R*) to (*S*) because the ordering of substituents has changed.

Conclusions

In summary, a DKR process employing an asymmetric aldol addition of acetone to 2,4-dioxo-3-methyl-4-aryl-butanoates that generates two adjacent stereogenic centers in a single transformation was developed by using configurationally labile β-substituted α-ketoesters as aldol acceptors. This proline-catalyzed aldol reaction offers an elegant way to create two adjacent stereogenic centers simultaneously in a single chemical operation with excellent diastereoselectivity (up to >99:1 dr) and enantioselectivity (ee up to 98% ee), providing a truly useful tool for preparing important chiral compounds. This DKR reaction afforded essentially only one diastereomeric product in most cases, its configuration was determined by X-ray analysis of **2e**. The stereochemical outcome has been explained with the help of transition state models.

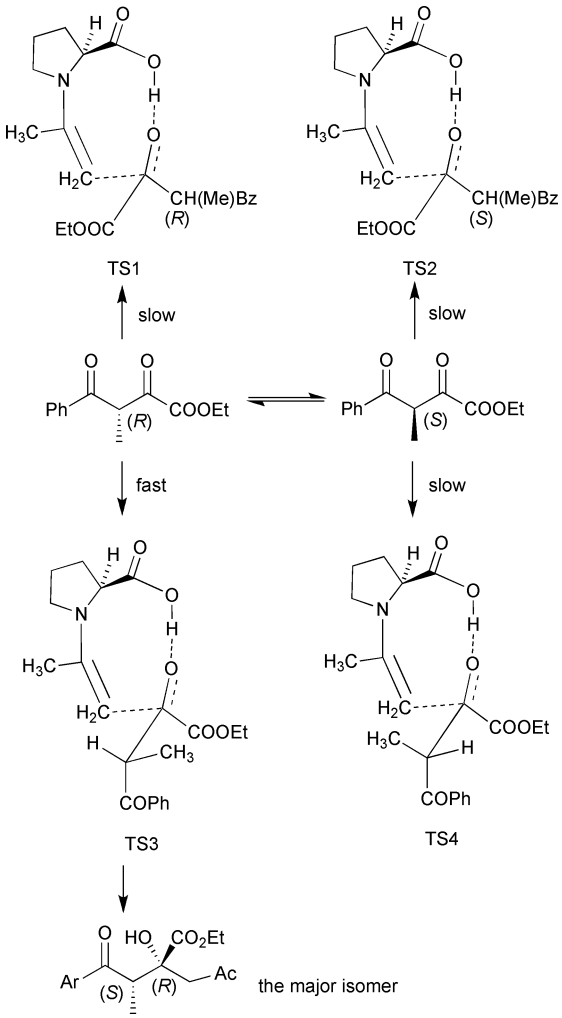


Fig. 2 Proposed transition states for the DKR.

Experimental

General methods and materials

General methods. $^{1}H/^{13}C$ NMR spectra were recorded on a Varian-Inova-400 instrument at 400/100 MHz, with TMS/$CDCl_3$ as internal standard, respectively. Infrared spectra were obtained on a Nicolet-Avatar-360 FT-IR spectrometer. Mass spectra were recorded on a MicroMass TOF-MS spectrometer (EI). Optical rotations were measured at 589 nm (Na D line) on a Autopol IV automatic polarimeter. The enantiomeric excesses of the products were determined by HPLC analysis on a Chiralpak AD-H/or OD-H column using 2-propanol/hexane as the eluent.

Materials. Commercially available starting materials and solvents were used without further purification. Catalysts **a** and **b** are commercially available and **c**,[15] **d**,[16] **e**,[17], **f**[18] and **g**[19] were prepared according to the literature. Substrate α-ketoesters were synthesized according to literature methods.[20,21]

General procedure for the aldol reactions

Catalyst (20 mol%) was added to a mixture of acetone (1 mL) in the desired solvent (3 mL). The β-substituted α-ketoester (0.5 mmol) was added and the mixture stirred at room temperature for the time given in the text. The mixture was filtered, concentrated, and purified by column chromatography over silica gel (ethyl acetate/petroleum ether) to obtain the desired diastereomer. When a high-boiling solvent (such as NMP, DMF, or DMSO) was used, the reaction mixture was dissolved in 20 mL water and extracted with ethyl acetate (3 × 20 mL), the combined extracts washed with brine (10 mL), and dried over anhydrous sodium sulfate. After removal of the solvent, the crude products were purified by column chromatography. The aldol products were characterized by HRMS, IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

(*R*)-Ethyl 2-hydroxy-4-oxo-2-((*S*)-1-oxo-1-phenylpropan-2-yl)pentanoate (2a). White solid. 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.99 (d, $J = 7.5$, 2H, ArH), 7.60 (t, $J = 7.4$, 1H, ArH), 7.49 (t, $J = 7.8$, 2H, ArH), 4.68 (s, 1H, OH), 4.13 (q, $J = 7.1$, 2H, OCH_2CH_3), 4.05 (q, $J = 7.2$, 1H, CH_3CH), 3.17 (d, $J = 16.8$, 1H, $COCHH$), 3.03 (d, $J = 16.8$, 1H, $COCHH$), 2.23 (s, 3H, $COCH_3$), 1.27 (d, $J = 7.2$, 3H, $CHCH_3$), 1.18 (t, $J = 7.1$, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.74, 204.64, 174.25, 137.00, 133.99, 129.09, 77.87, 62.25, 48.15, 44.90, 31.59, 14.37, 12.97; IR (KBr) ν_{max}: 3542.2, 3070.0, 2985.2, 1719.9, 1668.9, 1590.4, 1441.7, 1364.6, 1227.6, 966.7, 747.9, 687.4 cm^{-1}. HRMS calculated for $C_{16}H_{20}O_5$: 292.1311; found: 292.1322. HPLC: Chiralpak AD-H (*i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): $t_{major} = 14.3$ min, $t_{minor} = 17.7$ min; $[\alpha]^{21}_D = +31.8$ (*c* 1.01, acetone), ee = 96%.

(2*R*,3*S*)-Ethyl 3-benzoyl-2-hydroxy-2-(2-oxopropyl)pentanoate (2b). White solid, 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.01 (d, $J = 7.5$, 2H, ArH), 7.59 (t, $J = 7.3$, 1H, ArH), 7.48 (t, $J = 7.6$, 2H, ArH), 4.54 (s, 1H, OH), 4.17–4.05 (m, 2H, OCH_2CH_3), 3.92 (dd, $J = 3.2$, 11.2, 1H, $CHCH_2$), 3.15 (s, 2H, $COCH_2$), 2.20 (s, 3H, $COCH_3$), 1.98–1.84 (m, 1H, $CHCHHCH_3$), 1.70–1.58 (m, 1H, $CHCHHCH_3$), 1.20 (t, $J = 7.1$, 3H, OCH_2CH_3), 0.81 (t, $J = 7.4$, 3H, $CHCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.87, 204.27, 174.23, 139.30, 133.84, 129.10, 129.03, 78.21, 62.33, 52.32, 47.28, 31.42, 21.84, 14.41, 12.89; IR (KBr) ν_{max}: 3503.6, 3070.5, 2976.5, 1725.7, 1658.5, 1593.9, 1447.7, 1368.3, 1221.1, 1127.4, 990.2, 849.8, 693.1 cm^{-1}. HRMS calculated for $C_{17}H_{22}O_5$: 306.1467; found: 306.1466; HPLC: Chiralpak AD-H (*i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): $t_{major} = 11.9$ min, $t_{minor} = 14.3$ min; $[\alpha]^{21}_D = +44.6$ (*c* 1.04, acetone); ee = 96%.

(2*R*,3*S*)-Ethyl 3-benzoyl-2-hydroxy-2-(2-oxopropyl)hexanoate (2c). White solid, 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.04–7.97 (m, 2H, ArH), 7.58 (t, $J = 7.4$, 1H, ArH), 7.48 (t, $J = 7.6$, 2H, ArH), 4.55 (s, 1H, OH), 4.17–4.05 (m, 2H, OCH_2), 3.99 (dd, $J = 3.0$, 11.3, 1H, CH), 3.15 (s, 2H, $COCH_2$), 2.21 (s, 3H, $COCH_3$), 1.97–1.84 (m, 1H), 1.56–1.46 (m, 1H), 1.28–1.06 (m, 5H, $CH_2CH_2CH_3$ and OCH_2CH_3), 0.84 (t, $J = 7.3$, 3H, $CH_2CH_2CH_3$). ^{13}C NMR (100 MHz) δ: 208.98, 204.20, 174.17, 139.11, 133.81, 129.07, 129.00, 78.25, 62.29, 50.58, 47.14, 31.41, 30.82, 21.58, 14.67, 14.39; IR (KBr) ν_{max}: 3489.5, 3062.5, 2962.4, 2871.8, 1725.6, 1677.8, 1594.3, 1448.7, 1364.8, 1217.0, 1097.9, 760.4, 693.6 cm^{-1}. HRMS calculated for $C_{18}H_{24}O_5$: 320.1624; found: 320.1625; HPLC: Chiralpak AD-H (*i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): $t_{major} = 11.4$ min, $t_{minor} = 13.1$ min; $[\alpha]^{21}_D = +44.5$ (*c* 1.1, acetone); ee = 96%.

(*R*)-Ethyl 2-((*S*)-1-(4-chlorophenyl)-1-oxopropan-2-yl)-2-hydroxy-4-oxopentanoate (2d). White solid, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.92 (d, J = 8.5, 2H, ArH), 7.45 (d, J = 8.4, 2H, ArH), 4.63 (s, 1H, OH), 4.14 (q, J = 7.1, 2H, OCH_2), 3.98 (q, J = 7.2, 1H, $CHCH_3$), 3.13 (d, J = 17.0, 1H, $COCHH$), 3.03 (d, J = 17.0, 1H, $COCHH$), 2.22 (s, 3H, $COCH_3$), 1.23–1.18 (m, 6H, $CHCH_3$ and CH_2CH_3); ^{13}C NMR (100 MHz), δ: 12.88, 14.38, 31.51, 44.82, 47.72, 62.30, 77.92, 129.34, 130.55, 135.45, 140.42, 174.07, 203.27, 207.95; IR (KBr) $\nu_{max:}$ 3507.9, 2994.9, 1745.2, 1661.4, 1585.4, 1403.4, 1221.9, 972.7, 851.1, 771.4 cm^{-1}. HRMS calculated for $C_{16}H_{17}ClO_4$: (M^+–H_2O) 308.0815; found: 308.0818; HPLC: Chiralpak AD-H (*i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 17.9 min, t_{minor} = 26.0 min; $[\alpha]^{21}{}_D$ = +37.8 (*c* 1.1, acetone); ee = 92%.

(*R*)-Ethyl 2-((*S*)-1-(4-bromophenyl)-1-oxopropan-2-yl)-2-hydroxy-4-oxopentanoate (2e). White solid, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.85 (d, J = 8.6, 2H, ArH), 7.62 (d, J = 8.6, 2H, ArH), 4.63 (s, 1H, 0H), 4.14 (qd, J = 1.1, 7.1, 2H, OCH_2CH_3), 3.98 (q, J = 7.2, 1H, $CHCH_3$), 3.12 (d, J = 17.0, 1H, $COCHH$), 3.03 (d, J = 17.0, 1H, $COCHH$), 2.22 (s, 3H, $COCH_3$), 1.23-1.18 (m, 6H, $CHCH_3$ and OCH_2CH_3).; ^{13}C NMR (100 MHz) δ: 207.99, 203.49, 174.06, 135.83, 132.34, 130.64, 129.23, 77.88, 62.32, 47.69, 44.78, 31.52 14.39, 12.89; IR (KBr) $\nu_{max:}$ 3505.7, 3095.6, 2993.7, 1744.6, 1720.7, 1661.9, 1580.8, 1399.8, 1219.5, 1135.2, 971.8, 849.1, 767.7 cm^{-1}, HRMS calculated for $C_{16}H_{19}BrO_5$: 372.0395; found: 372.0408; HPLC: Chiralpak AD-H (*i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 19.5 min, t_{minor} = 28.3 min; $[\alpha]^{21}{}_D$ = +31.4 (*c* 1.01, acetone); ee = 98%.

(*R*)-Ethyl 2-hydroxy-2-((*S*)-1-(4-methoxyphenyl)-1-oxopropan-2-yl)-4-oxopentanoate (2f). White solid, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.97 (d, J = 8.9, 2H, ArH), 6.95 (d, J = 8.9, 2H, ArH), 4.78 (s, 1H, OH), 4.11 (qd, J = 1.8, 7.1, 2H, OCH_2CH_3), 3.98 (q, J = 7.2, 1H, $CHCH_3$), 3.88 (s, 3H, OCH_3), 3.14 (d, J = 16.7, 1H, $COCHH$), 2.99 (d, J = 16.7, 1H, $COCHH$), 2.22 (s, 3H, $COCH_3$), 1.25 (d, J = 7.2, 3H, $CHCH_3$), 1.17 (t, J = 7.1, 3H, OCH_2CH_3).; ^{13}C NMR (100 MHz), δ: 207.30, 202.76, 174.04, 164.08, 131.18, 129.46, 113.95, 77.50, 61.79, 55.64, 48.02, 44.14, 31.27 14.04, 12.74; IR (KBr) $\nu_{max:}$ 3525.5, 2968.2, 1746.0, 1715.6, 1657.4, 1600.1, 1368.9, 1223.5, 1178.1, 1133.9, 1024.6, 973.5, 854.7 cm^{-1}. HRMS calculated for $C_{17}H_{22}O_6$: 322.1416; found: 322.1408; HPLC: Chiralpak OD-H (*i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 11.2 min, t_{minor} = 12.5 min; $[\alpha]^{21}{}_D$ = +13.3 (*c* 1.03, acetone); ee = 85%.

(R)-ethyl 2-hydroxy-2-((S)-1-(4-isopropylphenyl)-1-oxopropan-2-yl)-4-oxopentanoate (2g). White solid, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.91 (d, J = 8.3, 2H, ArH), 7.32 (d, J = 8.3, 2H, ArH), 4.72 (s, 1H, OH), 4.12 (q, J = 7.1, 2H, OCH_2CH_3), 4.01 (q, J = 7.2, 1H, $CHCH_3$), 3.15 (d, J = 16.7, 1H, $COCHH$), 3.04–2.92 (m, 2H, $COCHH$ and $CH(CH_3)_2$), 2.22 (s, 3H, $COCH_3$), 1.28-1.24 (m, 9H, $CH(CH_3)_2$ and $CHCH_3$), 1.17 (t, J = 7.1, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz) δ: 207.30, 203.89, 173.98, 155.26, 134.40, 129.03, 126.85, 77.50, 61.81, 47.94, 44.45, 34.33, 31.23, 23.69, 13.99, 12.64; IR (KBr) $\nu_{max:}$ 3508.0, 2966.2, 2877.8, 1721.1, 1657.3, 1600.9, 1566.4, 1404.5, 1225.0, 972.8, 858.5, 779.7 cm^{-1}. HRMS calculated for $C_{19}H_{26}O_5$: 334.1780; find: 334.1779; HPLC: Chiralpak AD-H (*i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 10.9 min, t_{minor} = 14.0 min; $[\alpha]^{21}{}_D$ = +22.3 (*c* 1.09, acetone); ee = 94%.

(*R*)-Ethyl 2-((*S*)-1-(2,5-dimethylphenyl)-1-oxopropan-2-yl)-2-hydroxy-4-oxopentanoate (2h). White solid, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.45 (s, 1H, ArH), 7.19 (d, J = 7.8, 1H, ArH), 7.12 (d, J = 7.8, 1H, ArH), 4.54 (s, 1H, OH), 4.12 (q, J = 7.1, 2H, OCH_2CH_3), 3.83 (q, J = 7.2, 1H, $CHCH_3$), 3.19 (d, J = 16.5, 1H, $COCHH$), 2.95 (d, J = 16.6, 1H, $COCHH$), 2.38 (s, 3H, $ArCH_3$), 2.36 (s, 3H, $ArCH_3$), 2.22 (s, 3H, $COCH_3$), 1.23–1.20 (m, 6H, OCH_2CH_3 and $CHCH_3$); ^{13}C NMR (100 MHz), δ: 208.08, 207.32, 174.42, 138.08, 135.55, 135.47, 132.62, 132.01, 129.34, 77.50, 62.13, 48.53, 48.40, 31.54, 21.28, 20.69, 14.28, 12.32; IR (KBr) $\nu_{max:}$ 3510.0, 2979.4, 2933.5, 1721.9, 1569.1, 1365.7, 1177.5, 1022.7, 971.9, 873.1, 821.1 cm^{-1}. HRMS calculated for $C_{18}H_{24}O_5$: 320.1624; found: 320.1620; HPLC: Chiralpak AD-H (*i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 8.4 min, t_{minor} = 11.6 min; $[\alpha]^{21}{}_D$ = +7.8 (*c* 1.06, acetone); ee = 96%.

(*R*)-Ethyl 2-hydroxy-2-((*S*)-1-(naphthalen-2-yl)-1-oxopropan-2-yl)-4-oxopentanoate (2j). White solid, 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.51 (s, 1H, ArH), 8.01 (t, J = 9.1, 2H, ArH), 7.96–7.84 (m, 2H, ArH), 7.62 (t, J = 7.0, 1H, ArH), 7.57 (t, J = 7.1, 1H, ArH), 4.73 (s, 1H, OH), 4.20 (q, J = 7.2, 1H, $CHCH_3$), 4.11 (q, J = 7.1, 2H, OCH_2CH_3), 3.21 (d, J = 16.8, 1H, $COCHH$), 3.06 (d, J = 16.8, 1H, $COCHH$), 2.24 (s, 3H, $COCH_3$), 1.32 (d, J = 7.2, 3H, $CHCH_3$), 1.16 (t, J = 7.1, 3H, OCH_2CH_3).; ^{13}C NMR (100 MHz), δ: 207.73, 204.58, 174.35, 136.22, 134.28, 132.88, 131.08, 130.23, 129.24, 129.03, 128.20, 127.32, 124.55, 77.95, 62.30, 48.31, 45.00, 31.64, 14.41, 13.18; IR (KBr) $\nu_{max:}$ 3539.5, 3055.9, 2983.7, 2899.4, 1722.7, 1668.7, 1629.2, 1595.8, 1465.6, 1402.3, 1367.6, 1250.6, 1221.0, 1129.4, 979.9, 833.4, 793.1, 741.4 cm^{-1}. HRMS calculated for $C_{20}H_{22}O_5$: 342.1467; found: 342.1482; HPLC: Chiralpak AD-H (*i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 38.5 min, t_{minor} = 45.7 min; $[\alpha]^{21}{}_D$ = –4.4 (*c* 1.04, acetone); ee = 94%.

(R)-Ethyl 2-((S)-1-(furan-2-yl)-1-oxopropan-2-yl)-2-hydroxy-4-oxopentanoate (2k). White solid, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.64 (dd, J = 0.6, 1.5, 1H, ArH), 7.29 (dd, J = 0.6, 3.6, 1H, ArH), 6.57 (dd, J = 1.7, 3.6, 1H, ArH), 4.46 (s, 1H, OH), 4.16 (q, J = 7.1, 2H, OCH_2CH_3), 3.76 (q, J = 7.2, 1H, $CHCH_3$), 3.15 (d, J = 17.1, 1H, $COCHH$), 3.04 (d, J = 17.1, 1H, $COCHH$), 2.21 (s, 3H, $COCH_3$), 1.25 (d, J = 7.2, 3H, $CHCH_3$), 1.21 (t, J = 7.1, 3H, CH_2CH_3).; ^{13}C NMR (100 MHz) δ: 207.77, 191.51, 173.90, 152.56, 147.50, 119.15, 112.81, 77.50, 62.09, 47.42, 46.02, 31.25, 14.16, 12.49; IR (KBr) $\nu_{max:}$ 3454.8, 3128.9, 2990.1, 1723.4, 1649.7, 1564.5, 1465.1, 1397.4, 1255.6, 1214.1, 1139.4, 1028.6, 979.4, 901.5, 784.5 cm^{-1}. HRMS calculated for $C_{14}H_{18}O_6$: 282.1103; found: 282.1098; HPLC: Chiralpak AD-H (*i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 27.6 min, t_{minor} = 35.7 min; $[\alpha]^{21}{}_D$ = +47.6 (c 1.05, acetone); ee = 97%.

(*R*)-Ethyl 2-hydroxy-4-oxo-2-((*S*)-1-oxo-1-(thiophen-2-yl)propan-2-yl)pentanoate (2l). White solid, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$),δ 7.83–7.77 (m, 1H, ArH), 7.69 (dd, J = 0.9, 4.9, 1H, ArH), 7.15 (dd, J = 3.9, 4.8, 1H, ArH), 4.55 (s, 1H, OH), 4.14 (qd, J = 1.7, 7.1, 2H, OCH_2CH_3), 3.79 (q, J = 7.2, 1H, $CHCH_3$), 3.13 (d, J = 17.1, 1H, $COCHH$), 3.04 (d, J = 17.0,

1H, COCH*H*), 2.21 (s, 3H, COCH_3), 1.29 (d, J = 7.2, 3H, CHCH_3), 1.20 (t, J = 7.1, 3H, OCH$_2$CH_3).; ^{13}C NMR (100 MHz) δ: 207.69, 196.18, 173.99, 144.39, 135.40, 133.69, 128.70, 77.61, 62.17, 47.69, 47.12, 31.38, 14.25, 13.11; IR (KBr) $\nu_{max.}$ 3506.9, 3091.6, 2981.0, 1727.4, 1637.6, 1518.5, 1411.1, 1223.7, 1137.0, 1021.3, 982.4, 915.0, 859.9, 829.3, 743.2 cm^{-1}. HRMS calculated for $C_{14}H_{18}O_5S$: 298.0875; found: 298.0875; HPLC: Chiralpak OD-H (*i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 13.8 min, t_{minor} = 22.1 min; $[\alpha]^{21}{}_D$ = +70.2 (*c* 1.16, acetone); ee = 97%.

Ethyl 2-hydroxy-4-mesityl-3-methyl-4-oxobut-2-enoate (1i) (ref. 12). White solid. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.42 (t, J = 7.1 Hz, OCH$_2$CH_3), 1.72 (s, 3H, CCH_3), 2.20 (s, 6H, ArCH_3 ×2), 2.31 (s, 3H, ArH_3), 4.40 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 6.90 (s, 1H, ArH), 15.55 (s, 1H, OH).

Ethyl 2-hydroxy-3-methyl-4-oxo-4-(pyridin-4-yl)but-2-enoate (1m) (ref. 12). Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.32 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 1.71 (s, CCH_3), 3.66-3.45 (m, 2H, OCH_2CH$_3$), 7.49 (dd, J = 1.5, 4.8 Hz, 2H, ArH), 8.71 (dd, 1.5, 4.8 Hz, 2H, ArH).

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