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A General Organocatalytic Enantioselective Malonate Addition to α,β-Unsaturated Enones

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Abstract: A general enantioselective organocatalytic conjugate addition procedure of a variety of malonates to α,β-unsaturated enone systems is presented. The reaction is efficiently catalysed by the pyrrolidinyl tetrazole catalyst **1**. Cyclic, acyclic and aromatic enones can be used and the reaction with ethyl malonates **3b** provides the Michael addition products in high yields with good to excellent enantioselectivities. Since only 1.5 equivalents of malonate are used as a reagent, the reaction is readily scaled and practical to operate. Furthermore, the malonate addition products can be easily mono decarboxylated without loss in enantiomeric excess by enzymatic or sodium hydroxide mediated methods.

Keywords: asymmetric catalysis · chirality · enantioselectivity · Michael addition · organocatalysis

Introduction

Catalytic asymmetric conjugate additions play a prominent role in carbon–carbon bond-forming reactions in modern synthetic chemistry and natural product assembly especially during the synthesis of polyketides.[1] The 1,4-addition has in recent years been the subject of numerous advances aimed at the discovery of efficient chiral catalysts. As a result, many methods have been developed for the stereoselective 1,4-addition,[2] and malonates most notably have been proved to be easily accessible nucleophilic donors,[3] as the two electron-withdrawing esters enable enolate formation under mild conditions.

Since the start of this decade, great progress has been made in the field of asymmetric organocatalysis.[4] The increasing interest is mainly due to the possibility of easy and environmentally acceptable access to important chiral building blocks for life science and agriculture applications. Furthermore, organocatalysts can be used in a range of reactions with a multitude of advantages over metal-mediated reactions: for example, they are usually robust, inexpensive and readily available, non-toxic and inert toward moisture and oxygen.[4c]

Proline rubidium salts have been used for the 1,4-addition of malonates to α,β-unsaturated enones,[5] but the first highly enantioselective truly organocatalytic reaction was developed in the presence of an imidazoline catalyst.[6] Other organocatalysts,[7] for example, thioureas,[8] chinchona alkaloids,[9] diaryl-2-pyrrolidine-methanols[10] or chiral ionic liquids[11] have also been introduced to catalyse this important carbon–carbon forming reaction. Unfortunately, these methods often have drawbacks such as tedious procedures, reaction times up to weeks in some cases and the enantioselectivities can be variable depending on the nature of the α,β-unsaturated enones and malonates employed. Furthermore, the malonates were often employed in excess or as the reaction solvent and since these malonates are not volatile, their removal is problematic.

Since the introduction of the pyrrolidinyl tetrazole derivative **1** in enantioselective organocatalysed reactions by ourselves,[12] Yamamoto[13] and Arvidsson,[14] its use is now widely accepted.

In recent studies in this area, we described an enantioselective conjugate addition of different malonates to mainly aromatic enones in the presence of piperidine (**4**) and the pyrrolidinyl tetrazole catalyst **1**, after an extensive screening of different organocatalysts (Scheme 1).[12j]

Here, we report the evolution of these studies and the resulting development of a more general and practical enantioselective organocatalytic conjugate addition of malonates

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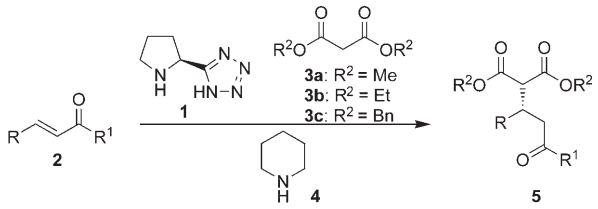


Scheme 1. Enantioselective organocatalytic malonate addition to different enones **2**.

to α,β-unsaturated enones with excellent yields and enantioselectivities, where cyclic, acyclic and aromatic enones are also be applied.

Results and Discussion

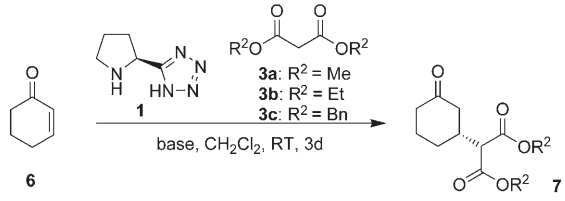
We have shown that the tetrazole derivative **1** is an improved catalyst for the conjugate addition of nitroalkanes to both cyclic and acyclic enones,[12g] using the *meso* base 2,5-dimethylpiperazine **8** as an additive under conditions adapted from those previously developed by Hanessian and Pham for the addition of nitroalkanes to cyclic enones catalysed by proline.[15]

Using these reaction conditions, we were able to obtain the benzyl malonate-addition product **7c** in 65% conversion and 77% *ee* (Table 1, entry 4). Due to the fact that malonates (diethyl malonate pK_a 13) are less acidic than nitroalkanes ($MeNO_2$ pK_a 10), the use of stronger bases was next investigated. Indeed, piperidine (**4**) increased the enantioselection of the reaction of 2-cyclohexenone **6** with methyl, ethyl and benzyl malonates (Table 1).[12j]

On closer examination of the reaction solvent chloroform proved to be the optimal solvent in terms of both yield and enantioselection (Table 2, entries 2, 4 and 6). The use of non-chlorinated solvents, for example, acetonitrile (Table 2, entry 7) led to a decrease in both yield and enantioselectivity.

To obtain the best result in the conjugate malonate addition methyl, ethyl and benzyl malonates **3a–c** were added to 2-cyclohexenone **6** and to *trans* 4-phenyl-3-butene-2-one **9** as a less reactive Michael acceptor (Table 3). In contrast to other publications, under these optimised conditions with the use of the pyrrolidinyl tetrazole catalyst **1** ethyl malonate **3b** gave the best results in enantioselection and was chosen for use in the next investigations. It is interesting to note that usually benzyl malonate **3c** has been selected as the malonate of choice in these Michael addition to α,β-unsaturated enones[6] and α,β-unsaturated aromatic aldehydes.[10a] Indeed, only one other publication uses ethyl malonates in the conjugate addition to various chalcones catalysed by an amine thiourea.[8a]

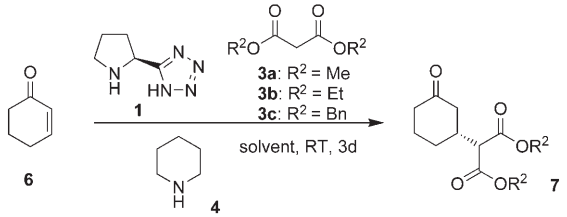
Table 1. Optimisation of the malonate addition: base screen.[12j]



Entry	Malonate	Base[b]	Product	Conversion [%][c]	*ee* [%][d]
1	**3a**	**4**	**7a**	85	83
2	**3b**	**8**	**7b**	65	79
3	**3b**	**4**	**7b**	89	92
4	**3c**	**8**	**7c**	65	77
5	**3c**	**4**	**7c**	63	82
6	**3c**	Et_2NH	**7c**	49	81

[a] Conditions: 2-cyclohexenone **6** (0.5 mmol), malonate **3** (0.75 mmol), base (0.5 mmol), (*S*)-pyrrolidinyl tetrazole **1** (15 mol%), CH_2Cl_2 (2 mL), 3 d, RT. [b] Piperidine (**4**); *meso*-2,5-dimethylpiperazine (**8**). [c] Determined by ^{1}H NMR. [d] Determined by chiral GC.

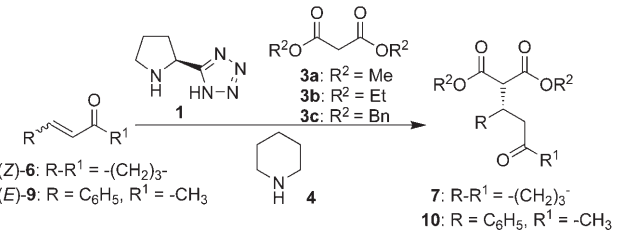
Table 2. Optimisation of the malonate addition: solvent screen.[12j]



Entry	Malonate	Solvent	Product	Conversion [%][b]	*ee* [%][c]
1	**3a**	CH_2Cl_2	**7a**	85	83
2	**3a**	$CHCl_3$	**7a**	87	85
3	**3b**	CH_2Cl_2	**7b**	89	92
4	**3b**	$CHCl_3$	**7b**	69	93
5	**3c**	CH_2Cl_2	**7c**	63	82
6	**3c**	$CHCl_3$	**7c**	87	81
7	**3c**	CH_3CN	**7c**	80	70

[a] Conditions: 2-cyclohexenone **6** (0.5 mmol), malonate **3** (0.75 mmol), **4** (0.5 mmol), (*S*)-**1** (15 mol%), solvent (2 mL), 3 d, RT. [b] Determined by ^{1}H NMR. [c] Determined by chiral GC.

Table 3. Malonate addition to cyclic and aromatic enones.



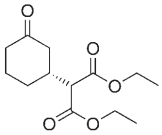
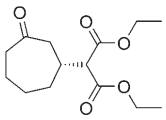
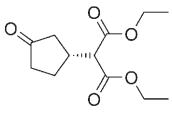
Entry	Malonate	Enone	Product [%]	Yield [%][b]	*ee* [%][c]
1	**3a**	**6**	**7a**	87	83
2	**3a**	**9**	**10a**	89	86
3	**3b**	**6**	**7b**	94	93
4	**3b**	**9**	**10b**	89	87
5	**3c**	**6**	**7c**	86	81
6	**3c**	**9**	**10c**	85	83

[a] Conditions: Enone **6** or **9** (0.5 mmol), malonate **3** (0.75 mmol), **4** (0.5 mmol), (*S*)-**1** (15 mol%), $CHCl_3$ (2 mL), 3 d, RT. [b] Isolated yield. [c] Determined by chiral HPLC or GC.

The absolute configuration of the compounds was confirmed by a comparison of the sign of optical rotation with literature values,[8a,16] and the compounds proved to be (*R*)-configured in the case of cyclic enones and (*S*)-configured in the case of linear and aromatic enones. Thus, the pyrrolidinyl tetrazole catalyst **1** gave products with the same sense of stereoinduction as observed in the addition to nitroalkanes.[12g]

The enantioselective organocatalytic conjugate addition was first applied to cyclic enones (Table 4). It was pleasing to find that as well as the known compound **7b**, the seven-membered congener (Table 4, entry 2) was also formed in a similarly high yield (91%) and enantioselectivity (93%). In fact, only the five-membered 2-cyclopentenone (Table 4, entry 3) gave a moderate enantioselectivity (30%), but retained the high yield (88%).

Table 4. 1,4-Addition of ethyl malonate to cyclic α,β-unsaturated enones.[a]

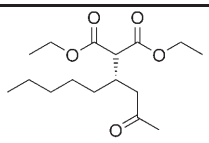
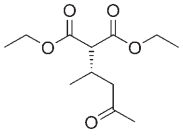
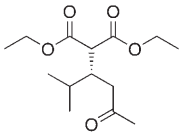
Entry	Product	Yield [%][b]	*ee* [%][c]
1	 **7b**	94	93
2	 **11**	91	89
3	 **12**	88	30

[a] Conditions: enone (0.5 mmol), diethyl malonate **3b** (0.75 mmol), **4** (0.5 mmol), (*S*)-**1** (15 mol%), $CHCl_3$ (2 mL), 3 d, RT. [b] Isolated yield. [c] Determined by chiral HPLC or GC.

The ethyl malonates **3b** were next applied in the addition to linear (*E*)-enones (Table 5). Again, it was most encouraging to see that they did indeed react with generally comparable high yields and enantioselectivities as the 2-cyclohexenone system **6**. 3-Nonen-2-one (Table 5, entry 1) worked just as well as the truncated linear enone 3-penten-2-one (Table 5, entry 2) with very good yields and enantioselectivities. Furthermore, the branched example **15** (Table 5, entry 3) also worked well and was obtained in good yields (82%), retaining the good enantioselectivity (77%).

To further explore the scope of the reaction, a series of aromatic (*E*)-α,β-unsaturated enones were used as substrates in the 1,4-addition of ethyl malonate **3b** (Table 6). It was pleasing to find that these also worked very well and the Michael adducts were all formed in high yields and generally excellent enantioselectivities. Both electron-withdrawing

Table 5. The 1,4-addition of ethyl malonate to linear α,β-unsaturated enones.[a]

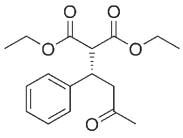
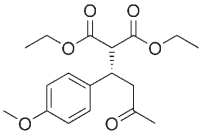
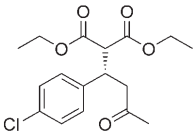
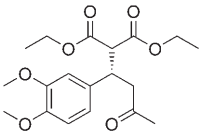
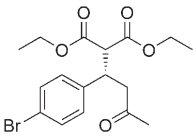
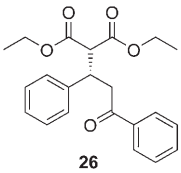
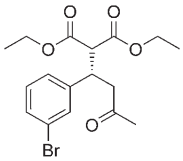
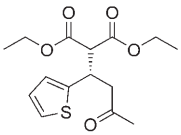
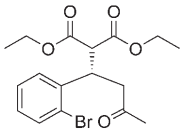
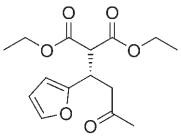
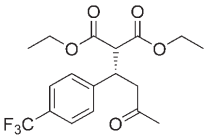
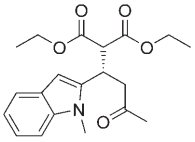
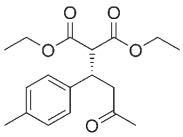
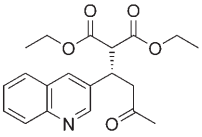
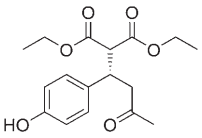
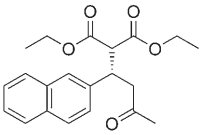
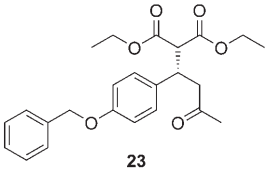
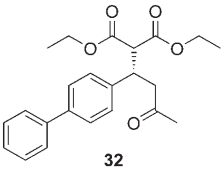
Entry	Product	Yield [%][b]	*ee* [%][c]
1	 **13**	86	87
2	 **14**	82	64
3	 **15**	82	77

[a] Conditions: α,β-unsaturated enone (0.5 mmol), diethyl malonate **3b** (0.75 mmol), piperidine **4** (0.5 mmol), (*S*)-pyrrolidinyl tetrazole **1** (15 mol%), $CHCl_3$ (2 mL), 3 d, RT. [b] Isolated yield. [c] Determined by chiral HPLC or GC.

(Cl, Br, CF_3, Table 6, entries 2–6) and electron-donating (OH, OR, Table 6, entries 7–11) substituents can be introduced on the aromatic ring without loss in yield or enantioselection. Furthermore, the position of the substituent on the aromatic ring, for example, bromine seems to have no influence, apart from the *ortho*-position (Table 6, entry 5). It is thought that in this case an unfavourable interaction with the methyl carbonyl function takes place, but regardless, the Michael addition product **19** was isolated in a similar high yield (81%) with a slightly reduced enantioselectivity (60%).

In the case of the *para*-hydroxy substituted aromatic enone (Table 6, entry 8) the reaction was run with two equivalents of base **4** required to increase yield and enantioselectivity, since the pK_a of the phenol proton is comparable to that of the malonate.[12j] This afforded the product **22** in a moderate yield (68%) and enantioselectivity (51%). After protection of the *para*-hydroxy substituent as a benzyl ether the product **23** was obtained again with the use of one equivalent of **4** in very good yield (82%) and enantioselectivity (85%) (Table 6, entry 9). Afterwards, the protective group may be removed under standard hydrogenation conditions without affecting the ethyl esters. The only exception to the generally high enantioselectivities with aromatic enones was the Michael addition to a chalcone, where the α-methyl group is replaced with an α-phenyl group. Here the product **26** was only obtained in a moderate enantioselectivity (44% *ee*) (Table 6, entry 12) and it is thought that an unfavourable interaction with the other aromatic ring takes place. Furthermore, the reaction was quite slow and further trials to optimise this reaction have so far been unsuccessful. However, the product **26** was obtained in a very

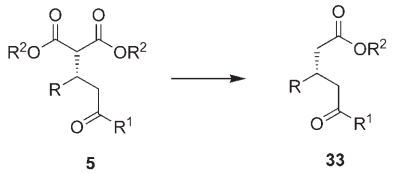
Table 6. 1,4-Addition of ethyl malonate to aromatic α,β-unsaturated enones.[a]

Entry	Product	Yield [%] [b]	*ee* [%][c]	Entry	Product	Yield [%] [b]	*ee* [%][c]
1		89	87	10		88	84
	10b				**24**		
2		94	83	11		87	84
	16				**25**		
3		88	85	12		86[e]	44
	17				**26**		
4		87	86	13		81	88
	18				**27**		
5		81	60	14		84	85
	19				**28**		
6		82	79	15		91	84
	20				**29**		
7		93	88	16		83	79
	21				**30**		
8		68[d]	51	17		89	88
	22				**31**		
9		82	85	18		88	85
	23				**32**		

[a] Conditions: α,β-unsaturated enone (0.5 mmol), diethyl malonate **3b** (0.75 mmol), **4** (0.5 mmol), (*S*)-**1** (15 mol%), $CHCl_3$ (2 mL), 3 d, RT. [b] Isolated yield. [c] Determined by chiral HPLC or GC. [d] Two equivalents of piperidine was used. [e] 5 d reaction time.

high yield (86%) without formation of by-products and it was only the enantiomeric excess that was moderate. Consequently, it was pleasing to find that both heteroaromatic enones and biaryl compounds were also good substrates for this malonate addition, retaining the very high yield and enantioselection formed in the more standard aromatic examples (Table 6, entries 13–18). It should be noted that no by-products were observed in any of these reactions with cyclic, acyclic and aromatic enones.

As the general nature of the reaction protocol has been proven, obtaining the products in good to excellent yields and enantioselectivities, the Michael adducts **5** could be further decarboxylated to give the corresponding optically active δ-ketoesters **33** (Scheme 2). Usually, for this reaction benzyl esters are used, which are first deprotected via hydrogenolysis to yield the free acids, then mono-decarboxylated and finally re-esterified. Although this reaction can be performed in a one-pot decarboxylation–transesterification procedure, the reaction protocol is tedious and the yields are poor.[6]



5 **33**

Scheme 2. Decarboxylation of Michael addition product **5** to the δ-ketoesters **33**.

The Krapcho reaction[17] is another well-known one-pot decarboxylation procedure which yields the corresponding monoester **33** directly and was investigated using the cyclic six-membered Michael addition products **7a** and **7b**. A variety of methods were employed, where the kind of salt and the equivalents of water were changed (Table 7). Furthermore, a microwave procedure[18] was investigated (Table 7, entry 3). However, unexpectedly, in all cases, there was a loss in enantiomeric excess with both methyl and ethyl diesters, which could have been due to the use of inorganic salts, because during a simple heating with water no reaction takes place and all starting material could be recovered (Table 7, entry 1). It is postulated that this loss of enantiomeric excess arises from a retro-Michael addition reaction and indeed with 1,5-dicarbonyl compounds a facile retro-Michael addition[19] can take place instead of formation of the expected products **34a**,**b**.

Therefore, a mono-hydrolysis decarboxylation strategy was investigated as an alternative way to obtain the monoester **33** directly (Scheme 2). Indeed, the six-membered mono-acids **35a**,**b** could be produced from the corresponding starting material **7a**,**b** by sodium hydroxide-mediated hydrolysis[23] or alternatively by the use of the enzyme porcine liver esterase[24] (PLE) (Table 8). The use of an alternative enzyme mixture, for example, liver acetone powder[25] gave the product without a loss in enantiomeric excess, but

Table 7. Krapcho decarboxylation of **7a**, and **7b**.

34a: R = Me
34b: R = Et

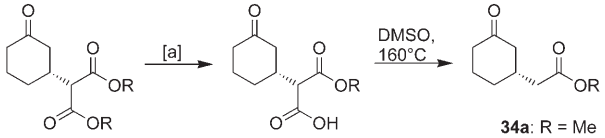
7a: R = Me (83% *ee*)
7b: R = Et (93% *ee*)

Entry	R	Conditions	Yield [%][a]	*ee* [%][b]
1	Et	DMSO, 2 equiv H_2O, 3 h, 175 °C	0[c]	–
2	Et	2 equiv LiBr, 1 equiv H_2O, 0.2 equiv Bu_4NBr, 3 h, 175 °C[18]	53	47
3	Et	2 equiv LiBr, 2 equiv H_2O, 0.2 equiv Bu_4NBr, microwave[d]	84[e]	76
4	Et	2 equiv LiBr, 2 equiv H_2O, 0.1 equiv Bu_4NBr, 5 h, 175 °C[18]	46	44
5	Me	2 equiv LiBr, 2 equiv H_2O, 0.1 equiv Bu_4NBr, 5 h, 175 °C[18]	0[f]	–
6	Me	4 equiv $(CH_3)_4NOAc$, 6 equiv H_2O, 100 °C, 5 h[17a]	16	10
7	Me	1 equiv LiI, 6 equiv H_2O, 170 °C, 1 h[20]	34	79
8	Et	1 equiv LiCl, 1 equiv H_2O, 3 h, 170 °C[21]	42	37
9	Et	1 equiv NaCl, 1 equiv H_2O, 3 h, 175 °C[22]	33[g]	73
10	Et	1 equiv NaCl, 0.1 equiv H_2O, 3 h, 175 °C[22]	36[g]	86

[a] Isolated yield. [b] Determined by chiral HPLC or GC. [c] Full recovery of starting material. [d] Lit.:[18] 30 W for 10 min. [e] Many by-products are formed. [f] Decomposition of starting material. [g] Mixture of product/starting material 1:1.

the yield decreased dramatically (Table 8, entry 3). Furthermore, the buffer used for the enzymatic reaction must be carefully chosen, with PLE in a Tris/HCl buffer[26] (pH 7.4) the product was obtained in a yield of 90–96% whereas a potassium phosphate buffer[27] (pH 7.0) decreased the yield slightly (Table 8, entry 4). By heating to 160 °C, the mono acids **35a**,**b** decarboxylate to the corresponding mono ester **34a**,**b** without a loss in enantiomeric excess (Table 8).

Table 8. Decarboxylation of cyclic malonate adducts **7a**,**b**.



7a: R = Me (83% *ee*)
7b: R = Et (93% *ee*)

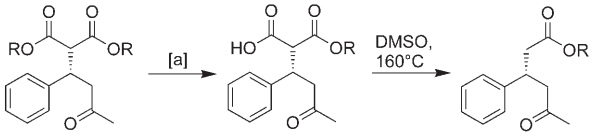
35a: R = Me
35b: R = Et

34a: R = Me
34b: R = Et

Entry	R	Conditions[a]	Yield[b]	*ee*[c]
1	Me	A	92	86
2	Et	A	92	92
3	Et	B[d]	64	92
4	Et	B[e]	87	93
5	Et	B	90	93
6	Me	B	96	85

[a] Conditions A: diester (0.5 mmol), THF/H_2O (12 mL, 1:11), NaOH (0.25 M; 0.6 mmol for Me, 3.5 mmol for Et), RT; then DMSO (2 mL), H_2O (drops), 160 °C, 1–3 h. Conditions B: diester (0.5 mmol), Tris/HCl buffer (2 mL, 0.375 M, pH 7.5), DMSO (25% v/v), pig liver esterase (1–2 mg), 25 °C, pH 7.5; then DMSO (2 mL), H_2O (10 μL), 160 °C, 1–3 h. [b] Isolated yield. [c] Determined by chiral GC. [d] Liver acetone powder (Sigma) was used instead of PLE. [e] 50 mM potassium phosphate buffer was used instead of the Tris/HCl buffer.

Table 9. Decarboxylation of aromatic malonate adducts **10a**,**b**.



10a: R = Me (86% *ee*)
10b: R = Et (87% *ee*)
36a: R = Me
36b: R = Et
37a: R = Me
37b: R = Et

Entry	R	Conditions[a]	Yield[b]	*ee*[c]
1	Me	A	94	84
2	Et	A	99	89
3	Me	B	97	84
4	Et	B	97	90

[a] Conditions A: diester (0.5 mmol), THF/H_2O (12 mL, 1:11), NaOH (0.25 M; 0.6 mmol for R = Me, 3.5 mmol for R = Et), RT; then DMSO (2 mL), H_2O (10 μL), 160 °C, 1–3 h. Conditions B: diester (0.5 mmol), Tris/HCl buffer (2 mL, 0.375 M, pH 7.5), DMSO (25 % v/v), pig liver esterase (1–2 mg), 25 °C, pH 7.5; then DMSO (2 mL), H_2O (drops), 160 °C, 1–3 h. [b] Isolated yield. [c] Determined by chiral HPLC.

Correspondingly, it was pleasing to find that the aromatic Michael addition products **10a**,**b** could also be successfully mono-decarboxylated under the developed conditions by both sodium hydroxide or enzymatic methods without loss in enantiomeric excess (Table 9).

Conclusion

In summary, a general enantioselective organocatalytic conjugate addition procedure of a variety of malonates to α,β-unsaturated enone sytems has been developed. The reaction is efficiently catalysed by the pyrrolidinyl tetrazole catalyst **1**. Cyclic, acyclic and aromatic enones can be used and the reaction with ethyl malonates **3b** provides the Michael addition products in high yields with good to excellent enantioselectivities. Because only 1.5 equivalents of malonate are used as a reagent, the reaction is readily scaled and practical to operate. Furthermore, the malonate addition products can be easily mono decarboxylated without loss in enantiomeric excess by enzymatic or sodium hydroxide mediated methods.

Experimental Section

General: Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh). ^{1}H NMR were recorded on a Bruker DRX-400 and Bruker DRX-600 spectrometer. The residual protic solvent $CHCl_3$ ($\delta_H = 7.26$ ppm) in $CDCl_3$ was used as an internal standard. ^{13}C NMR spectra were recorded on the same spectrometer at 100 and 150 MHz, using central resonance of $CDCl_3$ ($\delta_C = 77.0$ ppm). Accurate mass data were obtained on Micromass Q-TOF by electrospray ionisation (ESI). Optical rotations were measured on a Perkin Elmer 343 polarimeter at 25 °C; concentrations (*c*) are reported in g per 100 mL. Melting points were measured on a Reichert hot stage apparatus, and are uncorrected. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase GC or SFC.

Materials: All reactions were carried out under an atmosphere of argon. Petroleum ether (PE) used refers to the 40–60 °C boiling point fraction of petroleum. Anhydrous chloroform was bought from Sigma-Aldrich. Enones were bought or synthesised according to reference.[28] All other reagents and solvents were used as supplied

General procedure for the conjugate addition of malonate to α,β-unsaturated aldehydes: To a stirred suspension of the enone starting material (0.5 mmol) and pyrrolidinyl tetrazole **1** (15 mol %) in $CHCl_3$ (2 mL) was added diethylmalonate (0.75 mmol) and piperidine (0.5 mmol) at RT for 3 d. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed one time with saturated ammonium chloride solution (10 mL). The aqueous phase was then extracted three times with CH_2Cl_2 (10 mL). The combined organic phase was dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by flash chromatography.

General procedure for the enzyme-mediated decarboxylation of the malonate aducts: The diester (0.5 mmol) was dissolved in tris(hydroxymethyl)aminomethane (2 mL, Tris/HCl, 0.375 M, pH 7.5) buffered batches containing DMSO (25 % v/v). To this solution pig liver esterase (1–2 mg) was added. The reaction temperature was kept at 25 °C and the reaction pH value was carefully monitored (pH 7 to 8) until the consumption of the starting diester was detected (TLC control). Then the reaction mixture was acidified with 1 N HCl at 0 °C, saturated with NaCl, extracted three times with ethyl acetate (10 mL), and dried with magnesium sulphate. The solvent was evaporated and the residue solved in DMSO (2 mL) and water (10 μL). The reaction mixture was heated to 160 °C for 1 to 3 h. After cooling to ambient temperature, the solution was diluted with water (10 mL) and extracted three times with diethyl ether. The combined organic phase was dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by flash chromatography.

General procedure for the NaOH-mediated decarboxylation of the malonate adducts: The diester (0.5 mmol) was dissolved in THF/H_2O (12 mL, 1:11) and cooled to 0 °C. To this solution 0.25 N NaOH (0.6 mmol for Me and 3.5 mmol for Et esters) was added in small portions with stirring until the consumption of the starting diester was detected (TLC control). Then the reaction mixture was acidified with 1 N HCl at 0 °C, saturated with NaCl, extracted three times with ethyl acetate (10 mL), and dried with magnesium sulphate. The solvent was evaporated and the residue solved in DMSO (2 mL) and water (10 μL). The reaction mixture was heated to 160 °C for 1 to 3 h. After cooling to ambient temperature, the solution was diluted with water (10 mL) and extracted three times with diethyl ether. The combined organic phase was dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by flash chromatography.

Dimethyl 2-((*R*)-3-oxocyclohexyl)malonate (7a): The title compound was obtained according to the general procedure. White solid; Yield: 87 %; $R_f = 0.14$ (PE/Et_2O 2:1); m.p. 35 °C; $[\alpha]_D^{20} = +2.4$ (*c* = 1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.39$–1.49 (m, 1H, CH_{2a}), 1.56–1.68 (m, 1H, CH_{2b}), 1.86–1.90 (m, 1H, CH_{2c}), 1.98–2.05 (m, 1H, CH_{2d}), 2.16–2.24 (m, 2H, CH_2), 2.32–2.38 (m, 2H, CH_2), 2.42–2.51 (m, 1H, C*H*CH_2), 3.29 ppm (d, ^3J(H,H) = 8.0 Hz, 1H, C*H*$(COOMe)_2$), 3.68 (s, 3H, $COOCH_3$), 3.69 ppm (s, 3H, $COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.88$, 29.13 (2×CH_2), 38.47 (*C*H), 41.33, 45.42 (2×CH_2), 52.95 (2×$COOCH_3$), 56.94 ($CH(COOMe)_2$), 168.54, 168.63 (2×CO, ester), 209.88 ppm (CO); HRMS-ESI: *m*/*z*: calcd for $C_{11}H_{16}O_5Na$: 251.0895; found: 251.0898 $[M+Na]^+$; the *ee* was determined by GC analysis by using a Chirasil DEx-CB column (83 % *ee*).

Diethyl 2-((*R*)-3-oxocyclohexyl)malonate (7b): The title compound was obtained according to the general procedure. Colourless oil; Yield: 94 %; $R_f = 0.27$ (PE/Et_2O 2:1); $[\alpha]_D^{20} = +3.3$ (*c* = 1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.18$–1.22 (m, 6H, 2×$COOCH_2CH_3$), 1.45–1.73 (m, 2H, CH_2), 1.93–2.10 (m, 2H, CH_2), 2.21–2.30 (m, 2H, CH_2), 2.63–2.57 (m, 3H, CH_2, C*H*CH_2), 3.28 (d, ^3J(H,H) = 8.1 Hz, 1H, C*H*-$(COOEt)_2$), 4.17–4.23 ppm (m, 4H, 2×$COOCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.01$, 14.03 (2×$COOCH_2CH_3$), 24.49, 28.71 (2×CH_2), 37.97 (*C*H), 40.95, 45.02 (2×CH_2), 56.81 (*C*H$(COOEt)_2$), 61.47 (2×$COOCH_2CH_3$), 167.73, 167.82 (2×CO, ester), 209.60 ppm (CO); HRMS-ESI: *m*/*z*: calcd for $C_{13}H_{20}O_5Na$: 279.1208; found: 279.1208 $[M+Na]^+$; the *ee* was determined by GC analysis by using a Chirasil DEx-CB column (93 % *ee*).

Dibenzyl 2-((*R*)-3-oxocyclohexyl)malonate (7c): The title compound was obtained according to the general procedure. White solid; Yield: 86 %;

R_f=0.22 (PE/Et_2O 2:1); m.p. 46 °C; $[\alpha]_D^{20}$ = −1.1 (c=1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.41–1.51 (m, 1H, CH_{2a}), 1.56–1.68 (m, 1H, CH_{2b}), 1.84–1.92 (m, 1H, CH_{2c}), 1.97–2.04 (m, 1H, CH_{2d}), 2.15–2.27 (m, 2H, CH_2), 2.34–2.38 (m, 1H, CH_{2e}), 2.42–2.47 (m, 1H, CH_{2e}), 2.51–2.61 (m, 1H, C*H*CH_2), 3.42 (d, ^3J(H,H)=7.7 Hz, 1H, C*H*$(COOMe)_2$), 5.14 (s, 2H, CH_2Ph), 5.15 (s, 2H, CH_2Ph), 7.26–7.34 ppm (m, 10H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.48, 28.64 (2×CH_2), 38.10 (*C*H), 40.94, 45.04 (2×CH_2), 56.75 (*C*H$(COOMe)_2$), 67.22, 67.25 (2×CH_2Ph), 128.25, 128.45, 128.47, 128.59 (10×$CH_{arom.}$), 167.46, 167.52 (2×CO, ester), 209.26 ppm (CO); HRMS-ESI: m/z: calcd for $C_{23}H_{24}O_5Na$: 403.1521; found: 403.1511 $[M+Na]^+$; the *ee* was determined by GC analysis by using a Chirasil DEx-CB column (81% *ee*).

Dimethyl 2-((*S*)-3-oxo-1-phenylbutyl)malonate (10a): The title compound was obtained according to the general procedure. White solid; Yield: 89%; R_f=0.17 (PE/Et_2O 2:1); m.p. 42 °C; $[\alpha]_D^{20}$ = +11.4 (c=1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.99 (s, 3H, $COCH_3$), 2.86–2.98 (m, 2H, CH*C*H_2), 3.46 (s, 3H, $COOCH_3$), 3.69–3.72 (m, 4H, $COOCH_3$, C*H*$COOCH_3$), 3.92–3.98 (m, 1H, C*H*CH_2), 7.14–7.26 ppm (m, 5H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.28 (CO*C*H_3), 40.39 (*C*HCH_2), 47.10 (CH_2), 52.36, 52.63 (2×$COOCH_3$), 57.10 (*C*H$(COOMe)_2$), 127.26, 127.96, 128.53 (5×$CH_{arom.}$), 140.77 (C_q), 168.44, 168.97 (2×CO, ester), 206.41 ppm (CO); HRMS-ESI: m/z: calcd for $C_{15}H_{18}O_5Na$: 301.1052; found: 301.1049 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate=1.0 mL min^{-1}; τ_{major}=8.3, τ_{minor}=7.4 min (89% *ee*).

Diethyl 2-((*S*)-3-oxo-1-phenylbutyl)malonate (10b): The title compound was obtained according to the general procedure. White solid; Yield: 89%; R_f=0.30 (PE/Et_2O 2:1); m.p. 38 °C; $[\alpha]_D^{20}$ =+15.8 (c=1.1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.98 (d, ^3J(H,H)=7.1 Hz, 3H, $COOCH_2CH_3$), 1.22 (d, ^3J(H,H)=7.2 Hz, 3H, $COOCH_2CH_3$), 1.98 (s, 3H, $COCH_3$), 2.85–2.96 (m, 2H, CH*C*H_2), 3.67 (d, ^3J(H,H)=9.7 Hz, 1H, C*H*$(COOEt)_2$), 3.81–4.03 (m, 3H, $COOCH_2CH_3$, C*H*CH_2), 4.13–4.18 (m, 2H, $COOCH_2CH_3$), 7.14–7.26 ppm (m, 5H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.14, 14.41 (2×$COOCH_2CH_3$), 30.70 (CO*C*H_3), 40.86 (*C*HCH_2), 47.82 (CH_2), 57.81 (*C*H$(COOEt)_2$), 61.72, 62.05 (2×$COOCH_2CH_3$), 127.61, 128.54, 128.87 (5×$CH_{arom.}$), 140.79 (C_q), 168.053, 168.60 (2×CO, ester), 206.51 ppm (CO); HRMS-ESI: m/z: calcd for $C_{17}H_{22}O_5Na$: 329.1365; found: 329.1354 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate=1.0 mL min^{-1}; τ_{major}=9.9, τ_{minor}=7.5 min (87% *ee*).

Dibenzyl 2-((*S*)-3-oxo-1-phenylbutyl)malonate (10c): The title compound was obtained according to the general procedure. White solid; Yield: 85%; R_f=0.37 (PE/Et_2O 2:1); m.p. 59 °C; $[\alpha]_D^{20}$ = +5.1 (c=1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.96 (s, 3H, $COCH_3$), 2.91 (d, ^3J(H,H)=6.9 Hz, 2H, CH*C*H_2), 3.87 (d, ^3J(H,H)=9.9 Hz, 1H, C*H*COO), 4.02–4.08 (m, 1H, C*H*CH_2), 4.91 (s, 2H, CH_2Ph), 5.12–5.17 (m, 2H, CH_2Ph), 7.07–7.09 (m, 2H, $CH_{arom.}$), 7.18–7.37 ppm (m, 13H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.20 (CO*C*H_3), 40.51 (*C*HCH_2), 47.12 (CH_2), 57.37 (*C*H$(COOMe)_2$), 67.10, 67.29 (2×CH_2Ph), 127.26, 128.14, 128.17, 128.25, 128.29, 128.42, 128.46, 128.57, 128.59 (15×$CH_{arom.}$), 135.11, 135.24, 140.37 (3×C_q), 167.39, 167.87 (2×CO, ester), 205.79 ppm (CO); HRMS-ESI: m/z: calcd for $C_{27}H_{27}O_5$: 431.1858; found: 431.1855 $[M+Na]^+$; the *ee* was determined by HPLC analysis by using a Chiralpak AD-H column (hexane/*i*PrOH 90:10); flow rate=1.0 mL min^{-1}; τ_{major}=37.1, τ_{minor}=25.8 min (83% *ee*).

Diethyl 2-((*R*)-3-oxocycloheptyl)malonate (11): The title compound was obtained according to the general procedure. Colourless oil; Yield: 91%; R_f=0.20 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +23.4 (c=0.1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.25–1.28 (m, 6H, 2×$COOCH_2CH_3$), 1.36–1.62 (m, 3H, CH_2, CH_{2a}), 1.84–1.97 (m, 3H, CH_2, CH_{2b}), 2.45–2.60 (m, 5H, 2×CH_2, CH), 3.29 (d, ^3J(H,H)=7.5 Hz, 1H, C*H*$(COOEt)_2$), 4.17–4.23 ppm (m, 4H, 2×$COOCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.49 (2×$COOCH_2CH_3$), 24.86, 29.20, 34.56 (3×CH_2), 36.05 (*C*H), 44.01, 47.68 (2×CH_2), 57.88 (*C*H$(COOEt)_2$), 61.95 (2×$COOCH_2CH_3$), 168.56, 168.63 (2×CO, ester), 213.10 ppm (CO); HRMS-ESI: m/z: calcd for $C_{14}H_{23}O_5$: 271.1545; found: 271.1551 $[M+H]^+$; the *ee* was determined by GC analysis by using a Chirasil DEx-CB column (89% *ee*).

Diethyl 2-((*R*)-3-oxocyclopentyl)malonate (12): The title compound was obtained according to the general procedure. Colourless oil; Yield: 88%; R_f=0.19 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +22.2 (c=0.9 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24–1.30 (m, 6H, 2×$COOCH_2CH_3$), 1.52–1.76 (m, 1H, CH_{2a}), 1.98–2.05 (m, 1H, CH_{2b}), 2.14–2.36 (m, 3H, CH_2, CH_{2c}), 2.47–2.53 (m, 1H, CH_{2d}), 2.81–2.88 (m, 1H, C*H*CH_2), 3.32 (d, ^3J(H,H)=9.0 Hz, 1H, C*H*$(COOEt)_2$), 4.17–4.25 ppm (m, 4H, 2×$COOCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.45, 14.48 (2×$COOCH_2CH_3$), 27.88 (CH_2), 36.71 (*C*H), 38.56, 43.28 (2×CH_2), 56.94 (*C*H$(COOEt)_2$), 61.96, 61.99 (2×$COOCH_2CH_3$), 168.43, 168.52 (2×CO, ester), 217.42 ppm (CO); HRMS-ESI: m/z: calcd for $C_{12}H_{18}O_5Na$: 265.1052; found: 265.1042 $[M+Na]^+$; the *ee* was determined by GC analysis by using a Chirasil DEx-CB column (30% *ee*).

Diethyl 2-((*S*)-2-oxononan-4-yl)malonate (13): The title compound was obtained according to the general procedure. Colourless oil; Yield: 86%; R_f=0.56 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +8.5 (c=1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.84 (t, ^3J(H,H)=6.8 Hz, 3H, ωCH_3), 1.21–1.40 (m, 14H, 2×$COOCH_2CH_3$, 4×CH_2), 2.19 (s, 3H, $COCH_3$), 2.45–2.51 (m, 1H, C*H*CH_2), 2.60–2.74 (m, 2H, CH_2CO), 3.50 (d, ^3J(H,H)=5.6 Hz, 1H, C*H*$(COOEt)_2$), 4.12–4.18 ppm (m, 4H, 2×$COOCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.32, 14.43 (2×$COOCH_2CH_3$), 14.44 (ωCH_3), 22.83, 26.96 (CH_2), 30.61 (CH_3), 32.07, 32.55 (2×CH_2), 33.93 (*C*H), 45.68 (CH_2), 54.43 (*C*H$(COOEt)_2$), 61.51, 61.61 (2×$COOCH_2CH_3$), 169.08, 169.34 (2×CO, ester), 207.82 ppm (CO); HRMS-ESI: m/z: calcd for $C_{16}H_{28}O_5Na$: 323.1834; found: 323.1834 $[M+Na]^+$; the *ee* was determined by GC analysis by using a Chirasil DEx-CB column (87% *ee*).

Diethyl 2-((*S*)-2-oxopentan-4-yl)malonate (14): The title compound was obtained according to the general procedure. Colourless oil; Yield: 82%; R_f=0.41 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +9.0 (c=0.75 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.01 (t, ^3J(H,H)=7.0 Hz, 3H, ωCH_3), 1.25 (t, ^3J(H,H)=7.2 Hz, 6H, 2×$COOCH_2CH_3$), 2.11 (s, 3H, $COCH_3$), 2.36–2.43 (m, 1H, C*H*CH_2), 2.65–2.86 (m, 2H, CH_2CO), 3.33 (d, ^3J(H,H)=6.9 Hz, 1H, C*H*$(COOEt)_2$), 4.14–4.20 ppm (m, 4H, 2×$COOCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.03, 14.04 (2×$COOCH_2CH_3$), 17.68 (ωCH_3), 28.88 (CH_3), 30.22 (*C*H), 47.59 (CH_2), 56.22 (*C*H$(COOEt)_2$), 61.20 (2×$COOCH_2CH_3$), 168.51, 168.55 ppm (2×CO, ester), 207.08 (CO); HRMS-ESI: m/z: calcd for $C_{12}H_{21}O_5$: 245.1389; found: 245.1391 $[M+H]^+$; the *ee* was determined by GC analysis by using a Chirasil DEx-CB column (64% *ee*).

Diethyl 2-((*R*)-2-methyl-5-oxohexan-3-yl)malonate (15): The title compound was obtained according to the general procedure. Colourless oil; Yield: 82%; R_f=0.41 (PE/Et_2O 2:1); m.p. 20 °C; $[\alpha]_D^{20}$ = +14.1 (c=1.1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.81 (d, ^3J(H,H)=6.5 Hz, 3H, CH_3), 0.89 (d, ^3J(H,H)=7.0 Hz, 3H, CH_3), 1.21–1.28 (m, 6H, 2×$COOCH_2CH_3$), 1.66–1.74 (m, 1H, CH), 2.13 (s, 3H, $COCH_3$), 2.45–2.52 (m, 1H, C*H*CH_2), 2.64–2.71 (m, 2H, CH_2CO), 3.48 (d, ^3J(H,H)=5.8 Hz, 1H, C*H*$(COOEt)_2$), 4.10–4.19 ppm (m, 4H, 2×$COOCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.36, 14.37 (2×$COOCH_2CH_3$), 19.21, 20.95 (CH_3), 30.23 (CH), 30.59 (CH_3), 39.29 (CH), 43.07 (CH_2), 54.05 (*C*H$(COOEt)_2$), 61.58, 61.73 (2×$COOCH_2CH_3$), 169.29, 169.59 (2×CO, ester), 207.6 ppm (CO); HRMS-ESI: m/z: calcd for $C_{14}H_{24}O_5Na$: 295.1521; found: 295.1517 $[M+Na]^+$; the *ee* was determined by GC analysis by using a Chirasil DEx-CB column (77% *ee*).

Diethyl 2-((*S*)-1-(4-chlorophenyl)-3-oxobutyl)malonate (16): The title compound was obtained according to the general procedure. Pale-yellow solid; Yield: 94%; R_f=0.28 (PE/Et_2O 2:1); m.p. 39 °C; $[\alpha]_D^{20}$ =+13.9 (c=1.2 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.90–1.03 (m, 3H, $COOCH_2CH_3$), 1.19–1.23 (m, 3H, $COOCH_2CH_3$), 1.99 (s, 3H, $COCH_3$), 2.82–2.95 (m, 2H, CH*C*H_2), 3.63 (d, ^3J(H,H)=10.0 Hz, 1H, C*H*$(COOEt)_2$), 3.88–3.97 (m, 3H, $COOCH_2CH_3$, C*H*CH_2), 4.12–4.17 (m, 2H, $COOCH_2CH_3$), 7.15–7.21 ppm (m, 4H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.76, 13.98 (2×$COOCH_2CH_3$), 30.28 (CO*C*H_3), 39.64 (*C*HCH_2), 47.14 (CH_2), 57.05 (*C*H$(COOEt)_2$), 61.42, 61.71 (2×$COOCH_2CH_3$), 128.56, 129.60 (4×$CH_{arom.}$), 132.88 (C_qCl), 139.05 (C_q), 167.45, 167.95 ppm (2×CO, ester), 205.67 (CO); HRMS-ESI: m/z: calcd for $C_{17}H_{21}Cl_1O_5Na$: 363.0975; found: 363.0972 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate=1.0 mL min^{-1}; τ_{major}=14.1, τ_{minor}=9.6 min (83% *ee*).

Diethyl 2-((*S*)-1-(4-bromophenyl)-3-oxobutyl)malonate (17): The title compound was obtained according to the general procedure. White solid; Yield: 88%; R_f = 0.27 (PE/Et_2O 2:1); m.p. 42 °C; $[\alpha]_D^{20}$ = +12.3 (c = 1.1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99–1.05 (m, 3H, $COOCH_2CH_3$), 1.19–1.25 (m, 3H, $COOCH_2CH_3$), 2.08 (s, 3H, $COCH_3$), 2.80–2.97 (m, 2H, $CHCH_2$), 3.63 (d, ^3J(H,H) = 9.9 Hz, 1H, $CH(COOEt)_2$), 3.86–3.99 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 4.10–4.20 (m, 2H, $COOCH_2CH_3$), 7.08–7.14 (m, 2H, $CH_{arom.}$), 7.33–7.40 ppm (m, 2H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.76, 14.28 (2× $COOCH_2CH_3$), 30.26 ($COCH_3$), 39.70 ($CHCH_2$), 47.07 (CH_2), 56.98 ($CH(COOEt)_2$), 61.42, 61.69 (2× $COOCH_2CH_3$), 121.06 (C_qBr), 129.96, 131.51 (4× $CH_{arom.}$), 139.63 (C_q), 167.43, 167.92 (2× CO, ester), 205.56 ppm (CO); HRMS-ESI: m/z: calcd for $C_{17}H_{22}Br_1O_5$: 385.0651; found: 385.0648 $[M+H]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 17.4, τ_{minor} = 11.9 min (85% *ee*).

Diethyl 2-((*S*)-1-(3-bromophenyl)-3-oxobutyl)malonate (18): The title compound was obtained according to the general procedure. Colourless oil; Yield: 87%; R_f = 0.54 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +12.0 (c = 0.5 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.19 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.99 (s, 3H, $COCH_3$), 2.82–2.96 (m, 2H, $CHCH_2$), 3.62 (d, ^3J(H,H) = 9.4 Hz, 1H, $CH(COOEt)_2$), 3.86–3.95 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 4.10–4.16 (m, 2H, $COOCH_2CH_3$), 7.06–7.35 ppm (m, 4H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.73, 13.95 (2× $COOCH_2CH_3$), 30.20 ($COCH_3$), 39.84 ($CHCH_2$), 46.93 (CH_2), 56.95 ($CH(COOEt)_2$), 61.38, 61.65 (2× $COOCH_2CH_3$), 122.32 (C_qBr), 127.01, 129.96, 130.24, 131.20 (4× $CH_{arom.}$), 143.05 (C_q), 167.36, 167.85 (2× CO, ester), 205.35 ppm (CO); HRMS-ESI: m/z: calcd for $C_{17}H_{22}Br_1O_5$: 385.0651; found: 385.0648 $[M+H]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 11.4, τ_{minor} = 9.6 min (86% *ee*).

Diethyl 2-((*S*)-1-(2-bromophenyl)-3-oxobutyl)malonate (19): The title compound was obtained according to the general procedure. Colourless oil; Yield: 81%; R_f = 0.46 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +1.6 (c = 0.5 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.19 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 2.06 (s, 3H, $COCH_3$), 3.04 (d, ^3J(H,H) = 6.6 Hz, 2H, $CHCH_2$), 3.93 (d, ^3J(H,H) = 8.3 Hz, 1H, $CH(COOEt)_2$), 3.99–4.05 (m, 2H, $COOCH_2CH_3$), 4.09–4.18 (m, 2H, $COOCH_2CH_3$), 4.40–4.46 (m, 1H, $CHCH_2$), 7.02–7.06 (m, 1H, $CH_{arom.}$), 7.19–7.26 (m, 2H, $CH_{arom.}$), 7.51–7.53 ppm (m, 1H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.78, 13.93 (2× $COOCH_2CH_3$), 30.01 ($COCH_3$), 39.15 ($CHCH_2$), 45.59 (CH_2), 55.18 ($CH(COOEt)_2$), 61.46, 61.51 (2× $COOCH_2CH_3$), 124.76 (C_qBr), 127.46, 128.56, 133.41 (4× $CH_{arom.}$), 139.54 (C_q), 167.64, 168.01 (2× CO, ester), 205.86 ppm (CO); HRMS-ESI: m/z: calcd for $C_{17}H_{22}Br_1O_5$: 385.0651; found: 385.0638 $[M+H]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 16.3, τ_{minor} = 9.9 min (60% *ee*).

Diethyl 2-((*S*)-1-(4-(trifluoromethyl)phenyl)-3-oxobutyl)malonate (20): The title compound was obtained according to the general procedure. White solid; Yield: 82%; R_f = 0.37 (PE/Et_2O 2:1); m.p. 49 °C; $[\alpha]_D^{20}$ = +12.2 (c = 1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.21 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 2.01 (s, 3H, $COCH_3$), 2.88–3.01 (m, 2H, $CHCH_2$), 3.68 (d, ^3J(H,H) = 9.5 Hz, 1H, $CH(COOEt)_2$), 3.90–3.95 (m, 2H, $COOCH_2CH_3$), 3.98–4.04 (m, 1H, $CHCH_2$), 4.10–4.22 (m, 1H, $COOCH_2CH_3$), 7.50 (d, ^3J(H,H) = 8.0 Hz, 2H, $CH_{arom.}$), 7.36 ppm (d, ^3J(H,H) = 8.4 Hz, 2H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.64, 13.93 (2× $COOCH_2CH_3$), 30.21 ($COCH_3$), 39.90 ($CHCH_2$), 46.91 (CH_2), 56.80 ($CH(COOEt)_2$), 61.47, 61.78 (2× $COOCH_2CH_3$), 122.64 (C_q), 125.34, 128.67 (4× $CH_{arom.}$), 129.49 (CF_3), 144.81 (C_q), 167.38, 167.86 (2× CO, ester), 205.39 ppm (CO); HRMS-ESI: m/z: calcd for $C_{18}H_{21}F_3O_5Na$: 397.1239; found: 397.1236 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 6.5, τ_{minor} = 5.2 min (79% *ee*).

Diethyl 2-((*S*)-3-oxo-1-*p*-tolylbutyl)malonate (21): The title compound was obtained according to the general procedure. Colourless oil; Yield: 93%; R_f = 0.11 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +14.0 (c = 1.1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.22 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.98 (s, 3H, $COCH_3$), 2.25 (s, 3H, CH_3), 2.82–2.94 (m, 2H, $CHCH_2$), 3.64 (d, ^3J(H,H) = 9.9 Hz, 1H, $CH(COOEt)_2$), 3.87–3.95 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 4.13–4.18 (m, 1H, $COOCH_2CH_3$), 7.03 (d, ^3J(H,H) = 8.1 Hz, 2H, $CH_{arom.}$), 7.09 ppm (d, ^3J(H,H) = 8.0 Hz, 2H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.16, 14.41 (2× $COOCH_2CH_3$), 21.41 (CH_3), 30.68 ($COCH_3$), 40.51 ($CHCH_2$), 47.88 (CH_2), 57.91 ($CH(COOEt)_2$), 61.67, 61.98 (2× $COOCH_2CH_3$), 128.36, 128.53 (4× $CH_{arom.}$), 137.11, 137.68 (2× C_q), 168.07, 168.64 (2× CO, ester), 206.61 ppm (CO); HRMS-ESI: m/z: calcd for $C_{18}H_{24}O_5Na$: 343.1521; found: 343.1514 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 10.9, τ_{minor} = 8.2 min (88% *ee*).

Diethyl 2-((*S*)-1-(4-hydroxyphenyl)-3-oxobutyl)malonate (22): The title compound was obtained according to the general procedure. White solid; Yield: 68%; R_f = 0.50 (PE/Et_2O 1:3); m.p. 49 °C; $[\alpha]_D^{20}$ = +13.0 (c = 0.6 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.24 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 2.02 (s, 3H, $COCH_3$), 2.81–2.95 (m, 2H, $CHCH_2$), 3.62 (d, ^3J(H,H) = 10.0 Hz, 1H, $CH(COOEt)_2$), 3.83–3.97 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 4.08–4.22 (m, 2H, $COOCH_2CH_3$), 6.58 (d, ^3J(H,H) = 8.4 Hz, 2H, $CH_{arom.}$), 6.76 (br, 1H, OH), 7.02 ppm (d, ^3J(H,H) = 8.6 Hz, 2H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.19, 14.42 (2× $COOCH_2CH_3$), 30.61 ($COCH_3$), 40.42 ($CHCH_2$), 48.19 (CH_2), 58.18 ($CH(COOEt)_2$), 61.97, 62.17 (2× $COOCH_2CH_3$), 115.88, 129.57 (4× $CH_{arom.}$), 131.48, 155.75 (2× C_q), 168.41, 168.70 (2× CO, ester), 208.38 ppm (CO); HRMS-ESI: m/z: calcd for $C_{17}H_{23}O_6Na$: 323.1495; found: 323.1494 $[M+H]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 45.0, τ_{minor} = 28.3 min (51% *ee*).

Diethyl 2-((*S*)-1-(4-(benzyloxy)phenyl)-3-oxobutyl)malonate (23): The title compound was obtained according to the general procedure. Colourless oil; Yield: 82%; R_f = 0.37 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +11.6 (c = 0.5 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.24 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.99 (s, 3H, $COCH_3$), 2.82–2.95 (m, 2H, $CHCH_2$), 3.65 (d, ^3J(H,H) = 9.8 Hz, 1H, $CH(COOEt)_2$), 3.89–3.96 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 4.13–4.21 (m, 2H, $COOCH_2CH_3$), 4.99 (s, 2H, CH_2OBn), 6.81–6.88 (m, 2H, $CH_{arom.}$), 7.09–7.17 (m, 2H, $CH_{arom.}$), 7.26–7.40 ppm (m, 5H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.21, 14.42 (2× $COOCH_2CH_3$), 30.66 ($COCH_3$), 40.24 ($CHCH_2$), 47.97 (CH_2), 58.00 ($CH(COOEt)_2$), 61.65, 61.95 (2× $COOCH_2CH_3$), 70.34 (CH_2OBn), 115.20, 127.85, 128.31, 128.93, 129.64 (9× $CH_{arom.}$), 133.10, 137.42, 158.26 (3× C_q), 168.09, 168.61 (2× CO, ester), 206.52 ppm (CO); HRMS-ESI: m/z: calcd for $C_{24}H_{28}O_6Na$: 435.1784; found: 435.1788 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 62.4, τ_{minor} = 35.1 min (85% *ee*).

Diethyl 2-((*S*)-1-(4-methoxyphenyl)-3-oxobutyl)malonate (24): The title compound was obtained according to the general procedure. Colourless oil; Yield: 88%; R_f = 0.21 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = + 16.4 (c = 1.1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.20 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.96 (s, 3H, $COCH_3$), 2.79–2.91 (m, 2H, $CHCH_2$), 3.61 (d, ^3J(H,H) = 9.8 Hz, 1H, $CH(COOEt)_2$), 3.70 (s, 3H, OCH_3), 3.84–3.93 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 4.11–4.17 (m, 2H, $COOCH_2CH_3$), 6.73–6.77 (m, 2H, $CH_{arom.}$), 7.09–7.13 ppm (m, 2H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.75, 13.97 (2× $COOCH_2CH_3$), 30.22 ($COCH_3$), 39.77 ($CHCH_2$), 47.54 (CH_2), 55.09 (OCH_3), 57.57 ($CH(COOEt)_2$), 61.20, 61.51 (2× $COOCH_2CH_3$), 113.77, 129.14 (4× $CH_{arom.}$), 132.27, 158.56 (2× C_q), 167.63, 168.18 (2× CO, ester), 206.15 ppm (CO); HRMS-ESI: m/z: calcd for $C_{18}H_{24}O_6Na$: 359.1417; found: 359.1463 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 15.7, τ_{minor} = 10.2 min (84% *ee*).

Diethyl 2-((*S*)-1-(3,4-dimethoxyphenyl)-3-oxobutyl)malonate (25): The title compound was obtained according to the general procedure. Pale-yellow oil; Yield: 87%; R_f = 0.46 (PE/Et_2O 1:3); $[\alpha]_D^{20}$ = + 8.7 (c = 1.2 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, ^3J(H,H) = 7.1 Hz,

3H, $COOCH_2CH_3$), 1.17 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.94 (s, 3H, $COCH_3$), 2.77–2.86 (m, 2H, $CHCH_2$), 3.60 (d, ^3J(H,H) = 9.9 Hz, 1H, $CH(COOEt)_2$), 3.74 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.80–3.90 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 4.03–4.16 (m, 2H, $COOCH_2CH_3$), 6.66–6.70 ppm (m, 3H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.78, 13.95 ($2\times COOCH_2CH_3$), 30.28 ($COCH_3$), 40.09 ($CHCH_2$), 47.47 (CH_2), 55.69, 55.76 ($2\times OCH_3$), 57.45 ($CH(COOEt)_2$), 61.22, 61.53 ($2\times COOCH_2CH_3$), 110.92, 111.55, 119.92 ($3\times CH_{arom.}$), 132.86, 147.90, 148.56 ($3\times C_q$), 167.61, 168.13 ($2\times$CO, ester), 206.17 (CO); HRMS-ESI: *m/z*: calcd for $C_{19}H_{26}O_7Na$: 389.1576; found: 389.1572 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 14.3, τ_{minor} = 10.1 min (84% *ee*).

Diethyl 2-((*S*)-3-oxo-1,3-diphenylpropyl)malonate (26): The title compound was obtained according to the general procedure (reaction time 5 days). White solid; Yield: 86%; R_f = 0.42 (PE/Et_2O 2:1); m.p. 54 °C; $[\alpha]_D^{20}$ = + 10.0 (*c* = 0.25 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.24 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 3.42–3.57 (m, 2H, $CHCH_2$), 3.82 (d, ^3J(H,H) = 9.6 Hz, 1H, $CH(COOEt)_2$), 3.92–3.97 (m, 2H, $COOCH_2CH_3$), 4.13–4.25 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 7.14–7.18 (m, 1H, $CH_{arom.}$), 7.21–7.27 (m, 4H, $CH_{arom.}$), 7.39–7.43 (m, 2H, $CH_{arom.}$), 7.50–7.54 (m, 1H, $CH_{arom.}$), 7.88–7.91 ppm (m, 1H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.17, 14.43 ($2\times COOCH_2CH_3$), 41.21 ($CHCH_2$), 43.04 (CH_2), 57.99 ($CH(COOEt)_2$), 61.77, 62.08 ($2\times COOCH_2CH_3$), 127.55, 128.50, 128.64, 128.80, 128.96, 133.45 ($10\times CH_{arom.}$), 137.18, 140.84 ($2\times C_q$), 168.16, 168.77 ($2\times$CO, ester), 197.95 ppm (CO); HRMS-ESI: *m/z*: calcd for $C_{22}H_{24}O_5Na$: 391.1521; found: 391.1519 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 45.1, τ_{minor} = 31.0 min (44% *ee*).

Diethyl 2-((*S*)-3-oxo-1-(thiophen-2-yl)butyl)malonate (27): The title compound was obtained according to the general procedure. Colourless oil; Yield: 81%; R_f = 0.29 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +14.3 (*c* = 1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.20 (t, ^3J(H,H) = 7.0 Hz, 3H, $COOCH_2CH_3$), 2.04 (s, 3H, $COCH_3$), 2.97 (d, ^3J(H,H) = 6.7 Hz, 2H, $CHCH_2$), 3.69 (d, ^3J(H,H) = 9.5 Hz, 1H, $CH(COOEt)_2$), 3.98–4.03 (m, 2H, $COOCH_2CH_3$), 4.12–4.15 (m, 2H, $COOCH_2CH_3$), 4.23–4.29 (m, 1H, $CHCH_2$), 6.82–6.86 (m, 2H, $CH_{arom.}$), 7.09–7.11 ppm (m, 1H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.82, 13.97 ($2\times COOCH_2CH_3$), 30.27 ($COCH_3$), 35.61 ($CHCH_2$), 47.90 (CH_2), 57.03 ($CH(COOEt)_2$), 61.48, 61.63 ($2\times COOCH_2CH_3$), 124.18, 125.72, 126.56 ($3\times CH_{arom.}$), 143.51 (C_q), 167.51, 167.84 ($2\times$CO, ester), 205.66 ppm (CO); HRMS-ESI: *m/z*: calcd for $C_{15}H_{20}S_1O_5Na$: 335.0929; found: 335.0924 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 9.2, τ_{minor} = 7.8 min (88% *ee*).

Diethyl 2-((*S*)-1-(furan-2-yl)-3-oxobutyl)malonate (28): The title compound was obtained according to the general procedure. Pale-yellow oil; Yield: 84%; R_f = 0.29 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +10.1 (*c* = 1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.20 (t, ^3J(H,H) = 7.0 Hz, 3H, $COOCH_2CH_3$), 2.06 (s, 3H, $COCH_3$), 2.85–3.00 (m, 2H, $CHCH_2$), 3.73 (d, ^3J(H,H) = 9.1 Hz, 1H, $CH(COOEt)_2$), 4.02–4.09 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 4.11–4.16 (m, 2H, $COOCH_2CH_3$), 6.05–6.07 (m, 1H, $CH_{arom.}$), 6.20–6.22 (m, 1H, $CH_{arom.}$), 7.22–7.26 ppm (m, 1H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.30, 14.37 ($2\times COOCH_2CH_3$), 30.45 ($COCH_3$), 34.25 ($CHCH_2$), 44.89 (CH_2), 55.35 ($CH(COOEt)_2$), 61.91, 61.95 ($2\times COOCH_2CH_3$), 107.31, 110.64, 141.97 ($3\times CH_{arom.}$), 153.85 (C_q), 168.08, 168.24 ($2\times$CO, ester), 206.17 ppm (CO); HRMS-ESI: *m/z*: calcd for $C_{15}H_{20}O_6Na$: 319.1158; found: 319.1156 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 6.0, τ_{minor} = 5.6 min (85% *ee*).

Diethyl 2-((*S*)-1-(1-methyl-1*H*-indol-2-yl)-3-oxobutyl)malonate (29): The title compound was obtained according to the general procedure. Yellow oil; Yield: 91%; R_f = 0.44 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = −4.0 (*c* = 1.1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.28 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 2.02 (s, 3H, $COCH_3$), 2.97–3.01 (m, 2H, $CHCH_2$), 3.79 (d, ^3J(H,H) = 9.9 Hz, 1H, $CH(COOEt)_2$), 3.88 (s, 3H, NCH_3), 3.92–4.05 (m, 2H, $COOCH_2CH_3$), 4.17–4.30 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 6.29 (s, 1H, CH=), 7.05–7.08 (m, 1H, $CH_{arom.}$), 7.16–7.20 (m, 1H, $CH_{arom.}$), 7.29–7.31 (m, 1H, $CH_{arom.}$), 7.51–7.53 ppm (m, 1H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.76, 14.03 ($2\times COOCH_2CH_3$), 29.70 ($COCH_3$), 30.44 ($CHCH_2$), 31.25 (NCH_3), 47.79 (CH_2), 57.23 ($CH(COOEt)_2$), 61.50, 61.76 ($2\times COOCH_2CH_3$), 98.35 (CH=), 109.38, 119.31, 120.02, 121,12 ($4\times CH_{arom.}$), 127.67, 136.98, 141.10 ($3\times C_q$), 167.57, 167.96 ($2\times$CO, ester), 205.64 ppm (CO); HRMS-ESI: *m/z*: calcd for $C_{20}H_{25}N_1O_5Na$: 382.1630; found: 382.1645 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 14.3, τ_{minor} = 13.4 min (84% *ee*).

Diethyl 2-((*S*)-3-oxo-1-(quinolin-3-yl)butyl)malonate (30): The title compound was obtained according to the general procedure. Colourless oil; Yield: 83%; R_f = 0.46 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +25.0 (*c* = 0.25 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.19 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.99 (s, 3H, $COCH_3$), 2.99–3.11 (m, 2H, $CHCH_2$), 3.82 (d, ^3J(H,H) = 9.5 Hz, 1H, $CH(COOEt)_2$), 3.85–3.92 (m, 2H, $COOCH_2CH_3$), 4.07–4.27 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 7.44–7.48 (m, 1H, $CH_{arom.}$), 7.59–7.63 (m, 1H, $CH_{arom.}$), 7.70–7.72 (m, 1H, $CH_{arom.}$), 7.99–8.01 (m, 2H, $CH_{arom.}$), 8.82–8.84 ppm (m, 1H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.68, 13.94 ($2\times COOCH_2CH_3$), 30.19 ($COCH_3$), 37.76 ($CHCH_2$), 46.83 (CH_2), 56.69 ($CH(COOEt)_2$), 61.49, 61.76 ($2\times COOCH_2CH_3$), 126.72, 127.64, 129.11, 129.26 ($4\times CH_{arom.}$), 133.59 (C_q), 134.84 ($CH_{arom.}$), 147.31, 147.32 ($2\times C_q$), 151.22 ($CH_{arom.}$), 167.35, 167.83 ($2\times$CO, ester), 205.14 ppm (CO); HRMS-ESI: *m/z*: calcd for $C_{20}H_{24}O_5N_1$: 358.1654; found: 358.1653 $[M+H]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (40% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 6.4, τ_{minor} = 5.0 min (79% *ee*).

Diethyl 2-((*S*)-1-(naphthalen-3-yl)-3-oxobutyl)malonate (31): The title compound was obtained according to the general procedure. White solid; Yield: 89%; R_f = 0.31 (PE/Et_2O 2:1); m.p. 46 °C; $[\alpha]_D^{20}$ = +15.3 (*c* = 1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.24 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 2.00 (s, 3H, $COCH_3$), 3.03 (d, ^3J(H,H) = 6.7 Hz, 2H, $CHCH_2$), 3.82 (d, ^3J(H,H) = 9.5 Hz, 1H, $CH(COOEt)_2$), 3.85–3.93 (m, 2H, $COOCH_2CH_3$), 4.13–4.23 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 7.38–7.45 (m, 3H, $CH_{arom.}$), 7.70–7.71 (m, 1H, $CH_{arom.}$), 7.75–7.77 ppm (m, 3H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.69, 14.00 ($2\times COOCH_2CH_3$), 30.28 ($COCH_3$), 40.54 ($CHCH_2$), 47.37 (CH_2), 57.40 ($CH(COOEt)_2$), 61.29, 61.62 ($2\times COOCH_2CH_3$), 125.79, 126.06, 126.16, 127.08, 127.55, 127.79, 128.18 ($7\times CH_{arom.}$), 132.59, 133.29, 138.05 ($3\times C_q$), 167.62, 168.19 ($2\times$CO, ester), 205.89 ppm (CO); HRMS-ESI: *m/z*: calcd for $C_{21}H_{25}O_5$: 357.1702; found: 357.1700 $[M+H]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 27.1, τ_{minor} = 19.7 min (88% *ee*).

Diethyl 2-((*S*)-1-(4-phenyl-phenyl)-3-oxobutyl)malonate (32): The title compound was obtained according to the general procedure. White solid; Yield: 88%; R_f = 0.36 (PE/Et_2O 2:1); m.p. 64 °C; $[\alpha]_D^{20}$ = + 14.3 (*c* = 1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.25 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 2.03 (s, 3H, $COCH_3$), 2.91–3.03 (m, 2H, $CHCH_2$), 3.73 (d, ^3J(H,H) = 9.7 Hz, 1H, $CH(COOEt)_2$), 3.93–4.05 (m, 3H, $COOCH_2CH_3$, $CHCH_2$), 4.17–4.22 (m, 2H, $COOCH_2CH_3$), 7.28–7.33 (m, 3H, $CH_{arom.}$), 7.38–7.41 (m, 2H, $CH_{arom.}$), 7.48–7.57 ppm (m, 4H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.75, 14.01 ($2\times COOCH_2CH_3$), 30.27 ($COCH_3$), 40.12 ($CHCH_2$), 47.35 (CH_2), 57.36 ($CH(COOEt)_2$), 61.32, 61.62 ($2\times COOCH_2CH_3$), 126.93, 127.09, 127.24, 128.61, 128.73 ($9\times CH_{arom.}$), 139.61, 139.97, 140.64 ($3\times C_q$), 167.67, 168.17 ($2\times$CO, ester), 205.94 ppm (CO); HRMS-ESI: *m/z*: calcd for $C_{23}H_{26}O_5Na$: 405.1678; found: 405.1666 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (10% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 46.9, τ_{minor} = 25.9 min (85% *ee*).

Methyl 2-((*R*)-3-oxocyclohexyl)acetate (34a): The title compound was obtained according to the general procedure. Pale-yellow oil; Yield: 92%; R_f = 0.27 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = +4.3 (*c* = 1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.43 (m, 1H, CH_{2a}), 1.59–1.71 (m, 1H, CH_{2b}), 1.86–1.93 (m, 1H, CH_{2c}), 1.97–2.10 (m, 2H, CH_2), 2.17–2.43

(m, 6H, CH_{2d}, $2\times CH_2$, CH), 3.63 ppm (s, 3H, $COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.15, 31.25 ($2\times CH_2$), 35.91 (*C*H), 41.07, 41.42, 47.79 ($3\times CH_2$), 51.97 ($COOCH_3$), 172.52 (CO, ester), 210.62 ppm (CO); HRMS-ESI: *m*/*z*: calcd for $C_9H_{14}O_3Na$: 193.0841; found: 193.0846 $[M+Na]^+$; the *ee* was determined by GC analysis by using a Chirasil DEx-CB column (86% *ee*).

Ethyl 2-((*R*)-3-oxocyclohexyl)acetate (34b): The title compound was obtained according to the general procedure. Pale-yellow oil; Yield: 90%; R_f = 0.31 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = + 8.0 (*c* = 1 in chloroform); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, ^3J(H,H) = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.36–1.44 (m, 1H, CH_{2a}), 1.62–1.72 (m, 1H, CH_{2b}), 1.88–1.96 (m, 1H, CH_{2c}), 1.99–2.10 (m, 2H, CH_2), 2.19–2.45 (m, 6H, CH_{2d}, $2\times CH_2$, CH), 4.11 ppm (q, ^3J(H,H) = 7.1 Hz, 2H, $COOCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.19 ($COOCH_2CH_3$), 24.76, 30.86 ($2\times CH_2$), 35.55 (*C*H), 40.96, 41.05, 47.42 ($3\times CH_2$), 60.42 ($COOCH_2CH_3$), 171.69 (CO, ester), 210.29 ppm (CO); HRMS-ESI: *m*/*z*: calcd for $C_{10}H_{17}O_3$: 185.1178; found: 185.1183 $[M+H]^+$; the *ee* was determined by GC analysis by using a Chirasil DEx-CB column (93% *ee*).

Methyl 5-oxo-(3*S*)-phenylhexanoate (37a): The title compound was obtained according to the general procedure. Pale-yellow solid; Yield: 97%; R_f = 0.31 (PE/Et_2O 2:1); m.p. 39 °C; $[\alpha]_D^{20}$ = −4.6 (*c* = 1 in chloroform); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.03 (s, 3H, $COCH_3$), 2.56–2.70 (m, 2H, CH_2), 2.75–2.87 (m, 2H, CH_2), 3.56 (s, 3H, $COOCH_3$), 3.63–3.70 (m, 1H, *C*HCH$_2$), 7.16–7.20 (m, 3H, $CH_{arom.}$), 7.25–7.29 ppm (m, 2H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.74 ($COCH_3$), 37.68 (*C*HCH$_2$), 40.98, 49.74 ($2\times CH_2$), 51.91 ($COOCH_3$), 127.24, 127.61, 129.03 ($5\times CH_{arom.}$), 143.48 (C_q), 172.56 (CO, ester), 207.09 ppm (CO); HRMS-ESI: *m*/*z*: calcd for $C_{13}H_{16}O_3Na$: 243.0997; found: 243.1009 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (7% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 11.4, τ_{minor} = 12.4 min (84% *ee*).

Ethyl 5-oxo-(3*S*)-phenylhexanoate (37b): The title compound was obtained according to the general procedure. Pale-yellow oil; Yield: 99%; R_f = 0.35 (PE/Et_2O 2:1); $[\alpha]_D^{20}$ = −6.6 (*c* = 1 in chloroform); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, ^3J(H,H) = 7.2 Hz, 3H, $COOCH_2CH_3$), 2.04 (s, 3H, $COCH_3$), 2.55–2.68 (m, 2H, CH_2), 2.75–2.86 (m, 2H, CH_2), 3.62–3.70 (m, 1H, *C*HCH$_2$), 4.02 (d, ^3J(H,H) = 7.2 Hz, 2H, $COOCH_2CH_3$), 7.16–7.21 (m, 3H, $CH_{arom.}$), 7.25–7.29 ppm (m, 5H, $CH_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.45 ($COOCH_2CH_3$), 30.74 ($COCH_3$), 37.76 (*C*HCH$_2$), 41.22, 49.81, 60.73 ($3\times CH_2$), 127.18, 127.66, 128.96 ($5\times CH_{arom.}$), 143.45 (C_q), 172.08 (CO, ester), 207.09 ppm (CO); HRMS-ESI: *m*/*z*: calcd for $C_{14}H_{18}O_3Na$: 257.1154; found: 257.1152 $[M+Na]^+$; the *ee* was determined by SFC analysis by using a Chiralpak AD-H column (7% *i*PrOH); flow rate = 1.0 mL min^{-1}; τ_{major} = 7.7, τ_{minor} = 7.1 min (90% *ee*).

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