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Crown ether derived from D-glucose as an efficient phase-transfer catalyst for the enantioselective Michael addition of malonates to enones

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Abstract

A monoaza-15-crown-5 lariat ether derived from D-glucose (**1**) has been applied as chiral phase-transfer catalyst in the Michael addition of diethyl, dimethyl, diisopropyl and dibenzyl malonates to enones under mild conditions to afford the adducts in good to excellent enantioselectivities. In the reaction of diethyl malonate with substituted *trans*-chalcone, the adducts formed in enantioselectivities up to 89% ee. Among the reactions of substituted diethyl malonates, that of diethyl acetoxymalonate gave the best results (96% ee). The effect of the substituents of the chalcone was also investigated in reaction with diethyl acetoxymalonate. Among the chalcones substituted on the β side, the *para*-substituted compounds resulted in the highest enantioselectivities (88-97% ee). The substituents on the α-side of chalcone caused a decrease in the enantioselectivity, as compared to the unsubstituted case. The adducts having furyl or thiophenyl substituents were formed with >99% ee. The glucose-based catalyst also proved to be effective in the cases of diisopropyl and dibenzyl acetoxymalonates (including ee-s up to 99% ee). The reactions of diethyl acetoxymalonate with cyclic enones gave the corresponding Michael adducts in enantioselectivities up to 83%.

The absolute configuration of one of the new Michael adducts was determined by CD spectroscopy.

Keywords: asymmetric Michael reactions, enantioselectivity, phase-transfer catalysis, sugar-based crown ethers

1. Introduction

The formation of carbon-carbon bonds by the Michael addition of the appropriate carboanionic reagents to α,β-unsaturated carbonyl compounds is one of the most useful methods of remote functionalization in organic synthesis. The conjugate addition of malonates to enones, for example to chalcones, is particularly well-studied. Compounds with the chalcone backbone were reported to possess a wide range of biological activity, such as nematicide, antifungal, antiallergenic, antimicrobial, anticancer, antimalarial, and antifeedant properties. Malonates are traditionally regarded as important materials for the synthesis of the key intermediates of numerous active substances, but rarely found as pharmacophores belonging to the target compounds.[1,2] Experiments are under way for the preparation of novel drugs for the treatment of type 2 diabetes.[3,4] Therefore, the catalytic asymmetric version of the Michael addition of dialkyl malonates to chalcones has been studied extensively in the presence of different catalysts in recent years. For example, La-BINOL complexes,[5] L-proline derivatives,[6] chiral aminoalcohol-Al complexes,[7] pyrrolidylalkyl ammonium hydroxides,[8] chiral ammonium salts,[9] chiral ionic liquids,[10] chiral *N*,*N*'-dioxide-Sc complexes,[11] chiral bis-sulfonamide-Sr complexes,[12] chiral bisphosphazide-Li complexes,[13] chiral SIPAD-Co complexes,[14] DPEN/NAP-MgO,[15] were investigated as catalysts and organocatalysts.[16] A few asymmetric syntheses were described using cinchona alkaloid-type quaternary ammonium salts as chiral phase-transfer catalysts.[17]

Many phase-transfer catalytic methods have been developed that are simple and environmentally friendly.[18] The phase-transfer catalytic asymmetric syntheses represent an attractive approach, in which the enantioselectivity is generated by a chiral crown catalyst. Optically active crown ethers belonging to this group may incorporate a carbohydrate scaffold as the source of chirality. The attachment of a side arm with potential cation coordination sites to the crown ethers results in complexing agents called lariat ethers. Previously, chiral monoaza-15-crown-5 type lariat ethers incorporating an α-D-glucopyranoside unit and a side-arm containing a heteroatom at the end were synthesized in our laboratory. These

macrocycles possess a special complexing ability due to the flexible *N*-substituent. The overall complexing ability is influenced by the steric and electronic properties of the side arm.[19] The crown ether derived from D-glucose (**1**) proved to be an efficient catalyst in a few asymmetric reactions.[20] In this paper, the addition of diethyl, diisopropyl, dibenzyl malonates and their α-substituted variants to various α,β-unsaturated ketones under simple phase-transfer catalytic conditions in the presence of lariat ether **1** is described. The effect of the substituents of the Michael acceptors and nucleophiles on the asymmetric induction was investigated.

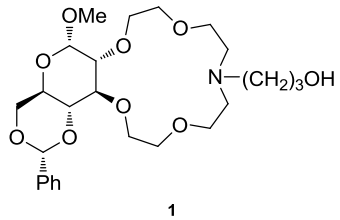

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Figure 1. Lariat ether **1** incorporating a methyl-α-D-glucopyranoside unit used as a catalyst in the Michael reactions

2. Results and discussion

The methyl-α-D-glucopyranoside-based lariat ether **1** synthetized by us earlier[19] was found to be an efficient enantioselective catalyst in the addition of diethyl malonate and α-substituted diethyl malonates to *trans*-chalcones and cyclic enones.

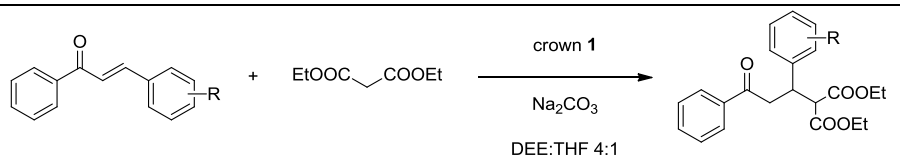
In our experiments, the conjugate addition of diethyl malonates to *trans*-chalcones **2a-m** was carried out in a solid-liquid two phase system employing the starting materials in a 1:4 mixture of THF and diethyl ether as the solvent, and using 15 mol% of crown ether **1**, and 2 equiv. of dry Na_2CO_3 as the solid phase at ambient temperature. The Michael adducts were obtained by preparative TLC, and the enantiomeric purity was measured by chiral HPLC.

First, the reaction of diethyl malonate with substituted chalcones (**2a-g**) was studied. The experimental results are shown in Table 1.

As it can be seen in Table 1, the reactions resulted in the corresponding Michael adducts (**4a-g**) after a reaction time of 10-14 days in variable yields of 50-81%. Catalyst **1** induced only a modest enantiomeric excess (36%) in the reaction of chalcone (**2a)** with diethyl malonate (Table 1, entry 1). Interestingly, the enantioselectivity decreased or increased depending on the position of the substituent of chalcone. The lowest ee values were observed in the reaction of 2-OMe and 2-Cl substituted chalcones (Table 1, entries 2 and 5).

The 3-OMe and 3-Cl adducts were formed with 25% and 36% ee (Table 1, entries 3 and 6), while the highest optical purities (89% and 85% ee) were measured in the case of the *para*-substituted compounds (Table 1, entries 4 and 7). It seems that independently of the electronic properties of the substituents, mainly steric effects influence the asymmetric induction.

Table 1. Asymmetric addition of diethyl malonate (**3a**) to *trans*-chalcones (**4a-g**) in the presence of lariat ether **1**



2a-g **3a** **4a-g**

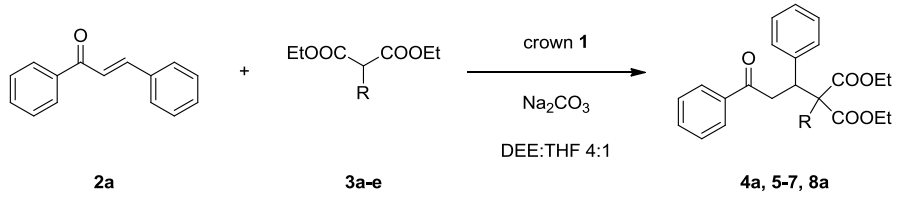
Entry	Chalcone	R	Time (day)	Product and yield (%) [a]	ee (%)
1	**2a**	H	10	**4a**: 63	36 (*S*)[b]
2	**2b**	2-OMe	12	**4b**: 50	24
3	**2c**	3-OMe	11	**4c**: 81	25
4	**2d**	4-OMe	14	**4d**: 56	89
5	**2e**	2-Cl	12	**4e**: 66	27
6	**2f**	3-Cl	12	**4f**: 53	36
7	**2g**	4-Cl	14	**4g**: 65	85

[a] Based on isolation by preparative TLC; [b] The absolute configuration was determined by comparison of the optical rotation value in the literature [5f]

Thereafter, we wished to investigate the effect of the substituents of diethyl malonate. A few α-substituted (R = NHAc, Me, allyl, OAc) diethyl malonates were reacted with chalcone (**2a**). In case of substituents R = Et, Bu, Bn, Ph and NO_2, chalcone **2a** did not enter into reaction with the corresponding diethyl malonates. The results are shown in Table 2.

As it can be seen from Table 2, the keto-diester products (**4a**, **5, 6, 7**, **8a**) could be obtained in moderate to good yields (55-72%). Product **7** was obtained in a modest yield of 27%. Catalyst **1** induced only a modest enantiomeric excess in the reaction of chalcone **2a** with diethyl malonate (**3a**), diethyl acetamidomalonate (**3b**), diethyl methylmalonate (**3c)**, and diethyl allylmalonate (**3d)**, when the ee values were 36%, 46%, 31% and 63%, respectively. Surprisingly, the ee was increased to 96%, when diethyl acetoxymalonate (**3e**) was used as the nucleophile (Table 2, entry 5).

Table 2. Asymmetric addition of α-substituted diethyl malonates (**3a-e**) to *trans*-chalcone (**2a**) in the presence of lariat ether **1**

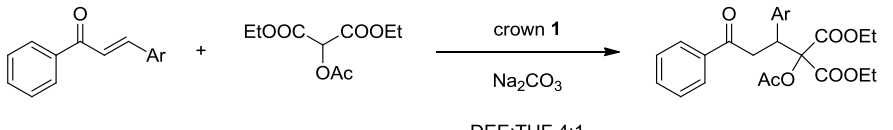


2a **3a-e** **4a, 5-7, 8a**

Entry	Malonate	R	Time (day)	Product and yield (%) [a]	ee (%)
1	**3a**	H	10	**4a**: 63	36
2	**3b**	NHAc	9	**5**: 55	46
3	**3c**	Me	7	**6**: 65	31
4	**3d**	CH-CH=CH_2	9	**7**: 27	63
5	**3e**	OAc	7	**8a**: 72	96

[a] Based on isolation by preparative TLC

Table 3. Asymmetric addition of diethyl acetoxymalonate (**3e**) to *trans*-chalcones (**8a-k**) in the presence of lariat ether **1**



2a-k **3e** **8a-k**

Entry	Chalcone	Ar	Time (day)	Product and yield (%) [a]	ee (%)
1	**2a**	C_6H_5	7	**8a**: 72	96 (*S*)
2	**2b**	2-MeO-C_6H_4	9	**8b**: 40	39
3	**2c**	3-MeO-C_6H_4	3	**8c**: 57	72
4	**2d**	4-MeO-C_6H_4	3	**8d**: 73	97
5	**2e**	2-Cl-C_6H_4	6	**8e**: 45	15
6	**2f**	3-Cl-C_6H_4	3	**8f**: 61	81
7	**2g**	4-Cl-C_6H_4	1.5	**8g**: 76	88
8	**2h**	2-NO_2-C_6H_4	3	**8h**: 60	72
9	**2i**	3-NO_2-C_6H_4	1.5	**8i**: 78	81
10	**2j**	4-NO_2-C_6H_4	1	**8j**: 73	89
11	**2k**	naphthalene-2-yl	3	**8k**: 42	52

12	**2l**	thiophen-2-yl	2	**8l**: 72	33
13	**2m**	pyridin-3-yl	3	**8m**: 23	36

[a] Based on isolation by preparative TLC

In the following part of our work, the effect of the nature and position of the substituents of the chalcone (**2b-j**) on the enantioselectivity has been studied in reaction with diethyl acetoxymalonate (**3e**)**.** A few preliminary results have already been published.[21] Besides that, we used enones containing naphthalene, thiophene and pyridine rings as the aryl substituents (Table 3).

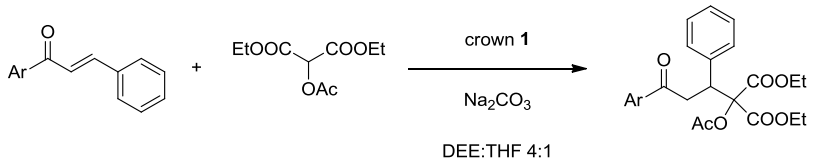
In the presence of lariat ether **1** derived from D-glucose, adducts **8a-j** were obtained in moderate to good yields (40-78%) and in varying enantioselectivities (15-97% ee). The outcome was highly dependent on the nature of the substituents, and on their position in the phenyl ring. It can be seen that in the cases investigated, the substituents on the β side, with one exception, decreased the extent of the asymmetric induction as compared to the unsubstituted instance (**8a**). The methoxy-substituted adducts **8b**, **8c** and **8d** were obtained in ee values of 39%, 72% and 97%, respectively (Table 3, entries 2-4). In the reaction of 2-Cl, 3-Cl and 4-Cl-chalcones (**2e-g**) with malonate **3e**, ee-s of 15%, 81% and 88%, respectively, were detected (Table 3, entries 5-7), while with the 2-, 3- and 4-nitro-chalcones (**2h-j**), ee values of 72%, 81% and 89%, respectively, were measured (Table 3, entries 8-10). It can be seen that the *meta*- and especially the *ortho*-substituents, that are closer to the reaction center, cause a significant decrease in the ee values (Table 3, entries 2-3, 5-6 and 8-9), while, within the above series, the maximum ee values were obtained with the *para*-substituted chalcones (Table 3, entries 4, 7 and 10). This tendency seems to be almost independent of the nature of the substituent, as electron-withdrawing and electron-donating groups have had a rather similar effect. The above phenomenon refers to the negative effect of steric hindrance if catalyst **1** is applied. Among the substituted chalcones, the 4-methoxy adduct (**8d**) was formed with the highest (97%) enantioselectivity. Adduct **8k** containing a naphthalene unit and products **8l** and **8m** with heteroaromatic ring were formed with 52%, 33% and 36% ee, respectively. All Michael adducts obtained in the above experiments have a positive optical rotation.

Subsequently, we studied the effect of the substituents on the α-side of the chalcones (**9a-i**) on the enantioselectivity using diethyl acetoxymalonate (**3e**) as the reaction partner (Table 4, entries 1-10).

One can see from Table 4 that the yield of the Michael adducts **11** decreased in the following order of the substituents: NO_2 (73-84%), Cl (50-67%) and MeO (35-50%). At the

same time, with one exception (**11h**), the adducts **11** were obtained in low to medium ee values. The 3-MeO-substituted compound **11h** was formed in an ee of 96%. No regularity on the effect of the position of the ring substituents could be found. Using the nitro-chalcones, the 4-NO_2 derivative **11c** was obtained in the best ee (58%). The chloro-substituted adducts (**11d-f**) were formed in ee values of 26-33%, while the products with MeO-groups (**11g-i**) were prepared in ee values of 27%, 96%, and 59%. It can be seen that regarding the reaction of the chalcones substituted on the α-side, catalyst **1** generated the highest asymmetric induction (96%) in the addition to the 3-MeO-chalcone (**9h**).

Table 4. Asymmetric addition of diethyl acetoxymalonate (**3e**) to *trans*-chalcones (**2a**, **9a-i**, **10a-d**) in the presence of lariat ether **1**



2a, 9a-i, 10a-b **3e** **8a, 11a-i, 12a-b**

Entry	Chalcone	Ar	Time (day)	Product and yield (%) [a]	ee (%)
1	**2a**	Ph	7	**8a**: 72	96
2	**9a**	2-NO_2-C_6H_4	5	**11a**: 73	2
3	**9b**	3-NO_2-C_6H_4	4	**11b**: 84	7
4	**9c**	4-NO_2-C_6H_4	4	**11c**: 77	58
5	**9d**	2-Cl-C_6H_4	4	**11d**: 67	33
6	**9e**	3-Cl-C_6H_4	3	**11e**: 59	31
7	**9f**	4-Cl-C_6H_4	3	**11f**: 50	26
8	**9g**	2-MeO-C_6H_4	9	**11g**: 35	27
9	**9h**	3-MeO-C_6H_4	9	**11h**: 50	96
10	**9i**	4-MeO-C_6H_4	8	**11i**: 42	59
11	**10a**	naphthalen-1-yl	3	**12a**: 78	28[b]
12	**10b**	naphthalen-2-yl	72	**12b**: 52	45[c]
13	**10c**	furan-2-yl	2	**12c**: 75	>99
14	**10d**	thiophen-2-yl	2	**12d**: 76	>99

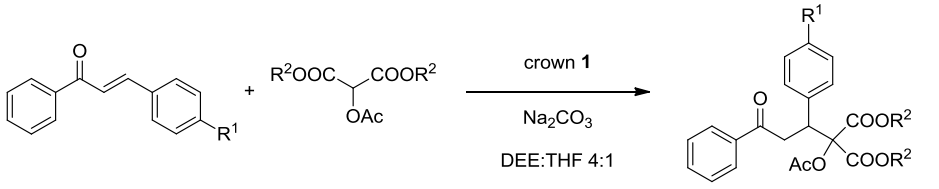
[a] Based on isolation by preparative TLC; [b] $[\alpha]_D^{22}$ -7.6; [c] $[\alpha]_D^{22}$ +41.7, in $CHCl_3$, *c* 1;

The asymmetric induction was modest (28% and 45% ee) for the 1-naphthyl and 2-naphthyl compounds. All substituted Michael adducts displayed a positive optical rotation.

The Michael reaction of the two naphthyl-enones (**10a** and **10b**) with malonate **3e** is of interest (Table 4, entries 11-12), as the adduct (**12a**) derived from 1-naphthyl enone **10a** revealed a negative optical rotation, and hence the opposite enantiomer may have predominated in the mixture, than in the reaction of the 2-naphthyl enone (**10b**). Substitution of the naphthyl group by a heteroaryl moiety led to a drastic increase of the ee values. The 2-furyl and 2-thiophenyl derivatives (**12c** and **12d**) were obtained with >99% ee (Table 4, entries 13 and 14).

Next, we synthesized the acetoxy derivatives of the dimethyl, diisopropyl and dibenzyl malonates (**3f-h**). These acetoxymalonates were reacted with chalcone and 4-methoxychalcone. Results can be seen in Table 5. The reactions required relatively long times, and gave the adducts (**13a-f**) in variable yields (23-75%). The reaction of the dimethyl, diisopropyl and dibenzyl malonates (**3f-h**) with chalcone (**2a**) gave the Michael adduct **13a-f** with 61%, 92% and 34% ee, respectively (Table 5, entries 1-3).

Table 5. Asymmetric addition of acetoxymalonates (**3f-h**) to chalcones (**2a**, **2d**) in the presence of catalyst **1**



2a, 2d **3f-h** **13a-f**

Entry	R^1	R^2	Time (day)	Product and yield (%)[a]	ee (%)
1	H	Me	12	**13a**: 53	61
2	H	*i*Pr	12	**13b**: 51	92
3	H	Bn	6	**13c**: 75	34
4	OMe	Me	9	**13d**: 46	17
5	OMe	*i*Pr	12	**13e**: 23	35
6	OMe	Bn	8	**13f**: 59	>99

[a] Based on isolation by preparative TLC

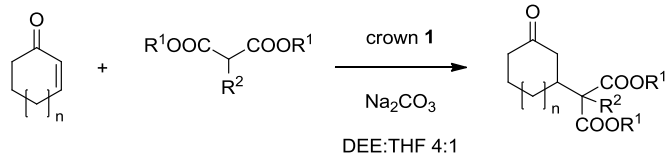
Another tendency was found for the reactions with the 4-methoxychalcone (**2d**) (where an ee of 97% was measured with the diethyl acetoxymalonate (Table 3, entry 4)). The reactions with dimethyl acetoxymalonate (**3f**) and diisopropyl malonate (**3g**) led to moderate 17% and

35% ee, but, surprisingly, in the case of dibenzyl acetoxymalonate (**3h**), adduct **13f** was formed in an ee of >99% (Table 5, entry 6). It is noteworthy that the best combinations were the chalcone (**2a**) and diisopropyl malonate (**3g**), and the 4-methoxychalcone (**2d**) and dibenzyl malonate (**3h**) giving the adducts in ee-s of 92% and 99%, respectively.

The glucose-based catalyst **1** was also tested in the reaction of dialkyl and dibenzyl acetoxymalonates (**3e-h**) with cyclic enones. Earlier, different catalysts have been developed for the asymmetric conjugate addition of dialkyl malonates to cyclic enones. [5e, 5c, 22] To the best of our knowledge, α-substituted malonates were not the subject of this type of study. In our experiments, the addition of acetoxymalonates (**3e-h**) to cyclic enones was carried out under solid-liquid phase-transfer conditions as described above (Table 6).

It can be seen that applying the catalysts **1** in the case of diethyl acetoxymalonate, using 2-cyclopenten-1-one (**14a**) or 2-cyclohexen-1-one (**14b**), the Michael adducts (**15a** and **15b**) were obtained in 67% and 41% yields, respectively, and in ee values of 46% and 80%, respectively (Table 6, entries 1 and 2). Interestingly in the case of dimethyl and diisopropyl acetoxymalonates (**13f** and **13g**) no addition could be observed even after a longer reaction time.

Table 6. Asymmetric addition of substituted malonates (**3e-j**) to cyclic enones (**14a-b**) in the presence of lariat ether **1**



14a-b **3e-j** **15a-c**

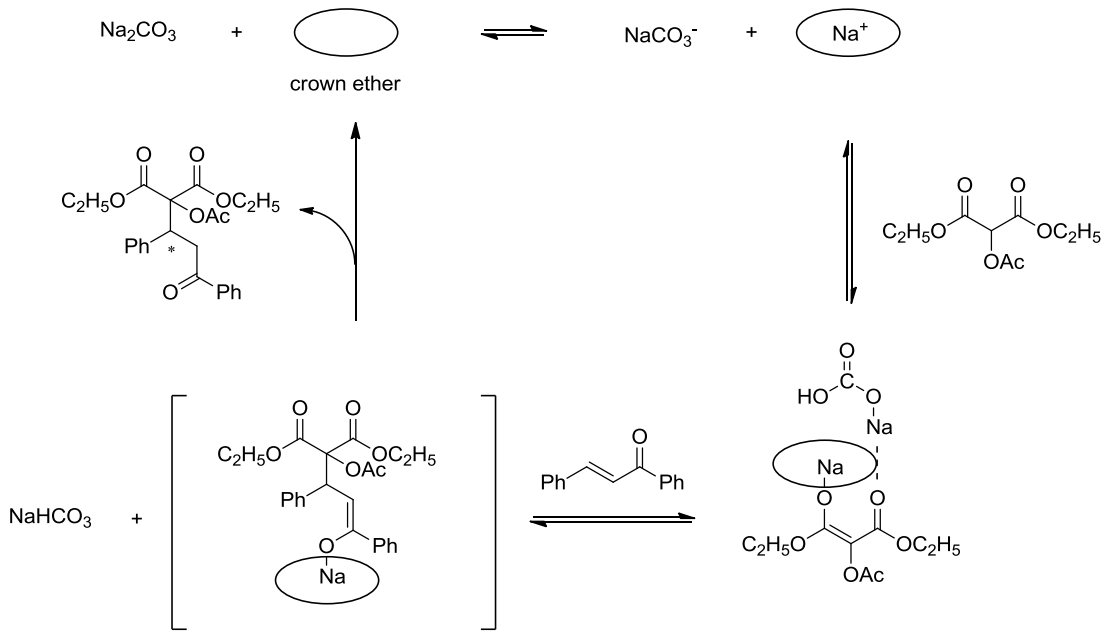
Entry	Enone	R^1	R^2	Time (day)	Product and yield (%) [a]	ee (%)
1	**14a**: n=0	Et	OAc	7	**15a**: 67	46
2	**14b**: n=1	Et	OAc	6	**15b**: 41	80
3	**14b**: n=1	Me	OAc	12	no product	-
4	**14b**: n=1	*i*Pr	OAc	11	no product	-
5	**14b**: n=1	Bn	H	12	**15c**: 58	83
6	**14b**: n=1	*i*Pr	H	10	no product	-

[a] Based on isolation by preparative TLC

From among the unsubstituted malonates, crown **1** generated asymmetric induction only in the addition of dibenzyl malonate (**3i**), adduct **15c** was formed in an ee of 83% (Table 6, entry 5). Applying diisopropyl malonate (**3j**), there was no reaction at all (Table 6, entry 6).

The sign of the optical rotation for all compounds was positive, and the absolute configurations of a few products will be proved in the future.

The mechanism of this reaction is well-known for the homogeneous variation. The mechanism is expanded with one step in the phase-transfer reaction (Scheme 1). In the first step, the lariat ether transfers the sodium cation accompanied by the anion into the organic phase, where the CH acid compound is deprotonated by a naked carbonate anion, and a (crown-Na^+)-activated nucleophile-anion complex is formed that is an optically active supramolecular associate. This chiral associate is the attacking agent; its structure determines the chiral environment, and consequently the degree of the asymmetric induction in the reaction with chalcone. This step involves the nucleophilic addition of the conjugated base on the double bond of the chalcone. Finally, the keto-diester derivative is formed by proton abstraction from the protonated carbonate anion. The nucleophilic attack to the chalcone is governed by electronic and steric factors determined by the substituents of the chalcone. This situation is supported by the above results.

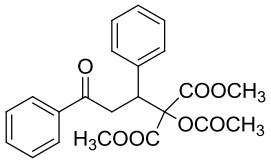


Scheme 1

Stereostructure of ***8a***

The absolute configuration of the title compound (**8a**) was determined by combined spectroscopic and theoretical investigations. The experimental UV absorption and circular

dichroism (CD) spectra, together with the theoretically calculated spectra are displayed in Figure 2.



8x

The theoretical calculations were carried out on model molecule **8x**, in which the two ethyl groups of **8a** were replaced by methyl units. Although, **8x** has the same structure that **13a**, however, **8x** is a theoretical pure enantiomer of **13a** which could not been obtained experimentally (see Table 5, entry 1). This way, the very large number of the possible conformers **8a** had been reduced. It could, however, be presumed that the shortening of the alkyl chains affected the spectra only to a small extent.

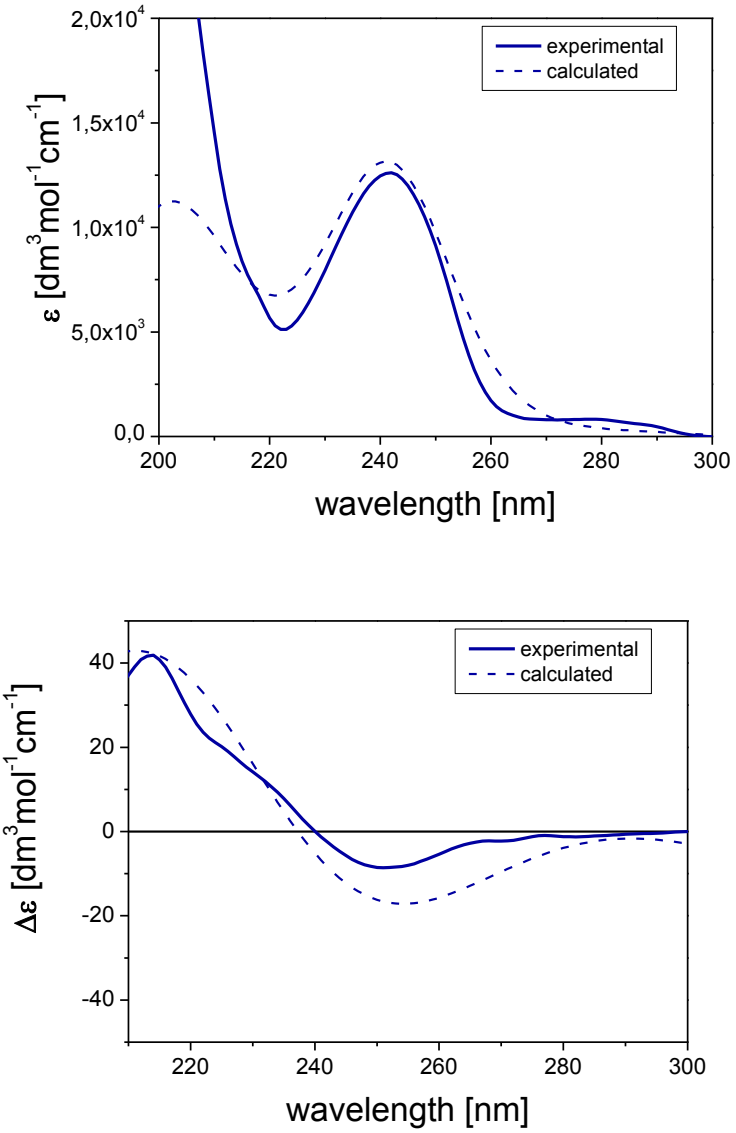


Figure 2. Experimental UV absorption (top) and CD (below) spectra of **8a** and the theoretically calculated spectra of the model molecule **8x**.

First, a molecular mechanics conformational analysis was performed. 18 stable conformers were identified, the energies of which were at most 10 kJ/mol above the energy of the most stable conformer. The geometries of these conformers were further optimized by DFT calculations, and their accurate conformational energies were computed applying the direct random phase approximation (dRPA) approach.

The DFT optimization of the 18 initial structures resulted only in two low-energy conformers. The reason behind this may be that presumably strong repulsion forces act among the bulky substituents on the adjacent chiral and quaternary carbon atoms, which restrict the

conformational flexibility. The structures of the two low energy conformers are shown in Figure 3. The relative energy of **8x-B** is higher by 1.1 kJ/mol, corresponding to molar fractions 0.61 for **8x-A** and 0.39 for **8x-B** at room temperature.

These two conformers were selected for the calculation of the spectra. Their excitation energies, the oscillator strengths and rotator strengths were computed at the time-dependent DFT (TD-DFT) level. The theoretical UV absorption and CD curves for the individual conformers were obtained as the superposition of Gaussian functions, with centers at the wavelengths of the computed transitions, and with heights proportional to the corresponding calculated oscillator (rotator) strengths. The theoretical UV absorption / CD spectra were obtained as the Boltzmann-weighted average of the spectra of the two conformers, shifted and normalized so that the wavelength and the intensity of the strongest UV/CD band were identical in the calculated and experimental spectra.

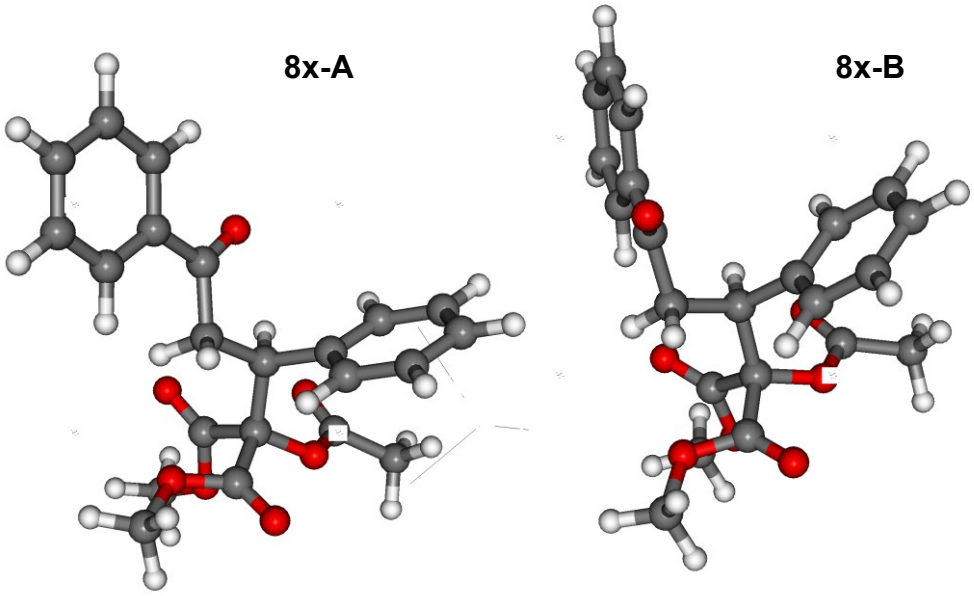


Figure 3. DFT-optimized geometry for the stable conformers of **8x** with the randomly selected (*S*) configuration**.**

The similarity of the calculated UV absorption spectrum of **8x** to the experimental spectrum of **8a** proves that the theoretical method applied was adequate. The structures of the calculated CD spectrum of **8x** and the measured spectrum of **8a** are rather similar. The signs of the dominant bands in the two spectra are identical, and their positions are close to each other. Therefore, the theoretical calculations suggest that the absolute configuration of the enantiomer obtained in the asymmetric reaction is (*S*), like the configuration of the

enantiomer considered in the calculations. It has to be noted, however, that a fully reliable result can not be expected for this molecule, since the CD spectra of the two low-lying conformers are completely different, and very accurate Boltzmann weights would be required to model the experimental spectra. Though the applied computational protocol is relatively accurate, an error of a few kJ/mol in the calculated conformational energies is possible, which may considerably influence the averaged spectrum.

3. Conclusions

The chiral monoaza-15-crown-5 type lariat ether incorporating an α-D-glucopyranoside unit (**1**) was tested as an enantioselective catalyst in the Michael addition of diethyl, dimethyl, diisopropyl and dibenzyl malonates to enones, carried out under mild solid-liquid phase-transfer conditions. We found that in the presence of this catalyst the substituents of the malonate and the chalcone had a significant impact on the yield and enantioselectivity. Among the reactions of substituted diethyl malonates, that of diethyl acetoxymalonate gave the best results (97% ee). The effect of the substituents of the chalcone was also investigated in reaction with diethyl acetoxymalonate. We found a correlation between the enantioselectivity and the position of the substituents of the chalcone. Among the chalcones substituted on the β side, the *para*-substituted compounds resulted in the corresponding Michael adducts with the highest enantioselectivity (88-97% ee). This phenomenon may refer to the role of steric effect on the asymmetric induction. The substituents on the α-side of chalcone caused a decrease in the enantioselectivity, as compared to the unsubstituted chalcone. The best enantioselectivities (>99%) were obtained in the case of the ketone derivatives containing heteroaromatic moiety. The addition of malonates and acetoxymalonates was also investigated with cyclic enones. The best result was achieved in the reaction of diethyl acetoxymalonate (80% ee) and dibenzyl malonate with 2-cyclohexen-1-one (83% ee). We proposed a mechanism for the reaction of diethyl acetoxymalonate with chalcone under phase-transfer conditions. Absolute configuration of the new Michael adduct formed from diethyl acetoxymalonate with chalcone (**8a)** having positive optical rotation proved to be *S* on the basis of a joint CD spectral and theoretical study.

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5. Experimental

5.1. General

Melting points were determined using a Büchi 510 apparatus and are uncorrected. The specific rotation was measured on a Perkin-Elmer 241 polarimeter at 22 °C. NMR spectra were obtained on a Bruker DRX-500 or Bruker-300 instrument in $CDC1_3$ with Me_4Si as an internal standard. The exact mass measurements were performed using Q-TOF Premier mass spectrometer (Waters Corporation, 34 Maple St, Milford, MA, USA) in positive electrospray ionization mode. The UV absorption and CD spectra were measured in acetonitrile. The UV absorption spectra were recorded on an Agilent 8453 diode array spectrometer, the CD spectra on a JASCO-810 spectropolarimeter Analytical and preparative thin layer chromatography was performed on silica gel plates (60 GF-254, Merck), while column chromatography was carried out using 70-230 mesh silica gel (Merck). Chemicals were purchased from Aldrich Chem. Co.

5.2. General procedure for preparation dialkyl acetoximalonates

Dialkyl acetoxymalonates were synthesized by the method of Gortatowski and Armstrong.[23] Dialkyl malonate (10 mmol) was dissolved in glacial acetic acid (5 mL) and the solution was heated to 100 °C. Lead tetraacetate (4.43 g, 10 mmol) was added to the solution in small portions and the resulting mixture was stirred for 3 hours at 100 °C. After completion of the reaction the mixture was concentrated in vacuum. The resulting slurry was diluted with ether (20 mL) and filtered. The solid part was washed with ether (3 x 20 mL) then the combined organic phase was washed with saturated Na_2CO_3 solution (20 mL), dried and concentrated. Further purification was not necessary in case of dimethyl acetoxymalonate (**3f**) and diisopropyl acetoxymalonate (**3g**), while dibenzyl acetoxymalonate (**3h**) was purified by column chromatography (silica gel, $CHCl_3$ as eluent).

5.3.1. Dimethyl acetoxymalonate (3f)

Yield: 52% (0.99 g), colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 5.57 (s, 1H, C*H*), 3.84 (s, 6H, 2 x OCH_3), 2.23 (s, 3H, COCH_3).

5.3.2. Diisopropyl acetoxymalonate (3g)

Yield: 86% (2.12 g), colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 5.45 (s, 1H, C*H*), 5.13 (sep, *J* = 6.3 Hz, 2H, 2 x OC*H*$(CH_3)_2$), 2.22 (s, 3H, COCH_3), 1.29 (t, *J* = 6.3 Hz, 12H, 4 x CH_3).

5.3.3. Dibenzyl acetoxymalonate (3h)

Yield: 34% (1.15 g), colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.76 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.55-7.47 (m, 1H, Ar*H*), 7.41-7.34 (m, 2H, Ar*H*), 7.20-7.08 (m, 5H, Ar*H*), 5.15 (dd, *J* = 26.4 Hz, *J* = 12.3 Hz, 2H, PhCH_2), 4.89 (s, 2H, PhCH_2), 4.36 (s, 1H, C*H*), 2.17 (s, 3H, COCH_3).

5.4. General procedure for Michael additions

Unsaturated compound (1.0 mmol), substituted malonate (1.5 mmol) and the crown ether (0.15 mmol) were dissolved in a mixture of anhydrous THF (0.6 mL) and Et_2O (2.4 mL) and dry Na_2CO_3 (2.0 mmol) was added. The reaction mixture was stirred at room temperature. After completion of the reaction, the organic phase was concentrated in vacuo and the residue was taken up in CH_2Cl_2 (10 mL), and washed with cold 10% HCl (3 x 10 mL) and then with water (10 mL), dried (Na_2CO_3 and Na_2SO_4) and concentrated. The crude product was purified by preparative TLC using silica gel and hexane-EtOAc (5:1) as the eluent. The enantioselectivities were determined by chiral HPLC analysis in comparison with authentic racemic materials.

5.5.1. Diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate (4a)

Yield: 63% (0.23 g), off-white solid; M.p 64-65 °C. $[\alpha]_D^{22}$= +17.0 (*c*=1, $CHCl_3$); 36% ee; major enantiomer t_r = 16.2 min, minor enantiomer t_r = 8.4 min (Chiralpack AD-H column,

80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.89 (dd, *J* = 8.5 Hz, 1.5 Hz, 2H, Ar*H*), 7.52 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, Ar*H*), 7.42 (t, *J* = 8.5 Hz, 2H, Ar*H*), 7.29-7.21 (m, 4H, Ar*H*), 7.19-7.14 (m, 1H, Ar*H*), 4.25-4.14 (m, 2H, OCH_2), 4.19 (d, *J* = 10 Hz, 1H, OCC*H*CO) 3.95 (q, *J* = 6 Hz, 2H, OCH_2), 3.82 (d, *J* = 10 Hz, 1H, PhC*H*) 3.54 (dd, *J* = 16.5 Hz, 4.5 Hz, 1H, COCH_2), 3.46 (dd, *J* = 16.5 Hz, 9.5 Hz, 1H, COCH_2), 1.24 (t, *J* = 6 Hz, 3H, CH_2CH_3), 1.01 (t, *J* = 6 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 197.58, 168.31, 167.74, 140.42, 136.80, 133.07, 128.52, 128.44, 128.23, 128.11, 127.16, 61.38, 61.66, 57.64, 42.60, 40.87, 14.05, 13.77. HRMS calcd for $C_{22}H_{24}O_5$ 368.1624. Found 368.1629.

5.5.2. Diethyl 2-(1-(2-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (4b)

Yield: 50% (0.20 g), light yellow oil; $[\alpha]_D^{22}$ = +13 (*c*=1, $CHCl_3$); 24% ee; major enantiomer t_r = 7.6 min, minor enantiomer t_r = 6.1 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.90 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.51 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.41 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.17-7.12 (m, 2H, Ar*H*), 6.82-6.77 (m, 2H, Ar*H*), 4.33 (dt, *J* = 9.5 Hz, 4Hz, 1H, ArC*H*), 4.24-4.13 (m, 3H, OCC*H*CO, OCH_2), 3.92 (q, *J* = 7 Hz, 2H, OCH_2), 3.81 (s, 3H, OCH_3), 3.63 (dd, *J* = 16.5 Hz, 9.5 Hz, 1H, COCH_2), 3.46 (dd, *J* = 16.5 Hz, 4 Hz, 1H, COCH_2), 1.23 (t, *J* = 7 Hz, 3H, CH_2CH_3), 0.98 (t, *J* = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{23}H_{26}O_6$ 398.1729. Found 398.1731.

5.5.3. Diethyl 2-(1-(3-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (4c)

Yield: 81% (0.32 g), white solid; M.p 64-66 °C; $[\alpha]_D^{22}$ = +18.6 (*c*=1, $CHCl_3$); 25% ee; major enantiomer t_r = 12.2 min, minor enantiomer t_r = 9.9 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.90 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.53 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.42 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.15 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.85 (d, *J* = 7.8 Hz, 1H, Ar*H*), 6.80 (s, 1H, Ar*H*), 6.71 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H, Ar*H*), 4.25-4.11 (m, 3H, ArC*H*, OCH_2), 3.97 (q, *J* = 7.2 Hz, 2H, OCH_2), 3.82 (d, *J* = 9.5 Hz, 1H, OCC*H*CO), 3.74 (s, 3H, OCH_3), 3.52 (dd, *J* = 16.8 Hz, 5.1 Hz, 1H, COCH_2), 3.45 (dd, *J* = 16.8 Hz, 9 Hz, 1H, COCH_2), 1.24 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.04 (t, *J* = 7.2 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{23}H_{26}O_6$ 398.1729. Found 398.1728.

5.5.4. Diethyl 2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (4d)

Yield: 56% (0.22 g), white solid; M.p 65-67 °C; $[\alpha]_D^{22}$= +17.1 (*c*=1, $CHCl_3$); 89% ee; major enantiomer t_r = 13.4 min, minor enantiomer t_r = 20.7 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.89 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.53 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.42 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.17 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.77 (d, *J* = 8.7 Hz, 2H, Ar*H*), 4.26-4.08 (m, 3H, ArC*H*, OCH_2), 3.96 (q, *J* = 7.2 Hz, 2H, OCH_2), 3.78 (d, *J* = 9.6 Hz, 1H, OCC*H*CO), 3.74 (s, 3H, OCH_3), 3.51 (dd, *J* = 16.5 Hz, 4.5 Hz, 1H, COCH_2), 3.40 (dd, *J* = 16.5 Hz, 9.3 Hz, 1H, COCH_2), 1.23 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 0.98 (t, *J* = 7.2 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{23}H_{26}O_6$ 398.1729. Found 398.1732.

5.5.5. Diethyl 2-(1-(2-chlorophenyl)-3-oxo-3-phenylpropyl)malonate (4e)

Yield: 66% (0.27 g), yellow oil; $[\alpha]_D^{22}$= + 14.1 (*c*=1, $CHCl_3$); 27% ee;, major enantiomer t_r = 13.8 min, minor enantiomer t_r = 6.7 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.95 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.55 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.44 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.38-7.30 (m, 2H, Ar*H*), 7.21-7.09 (m, 2H, Ar*H*), 4.72-4.62 (m, 1H, ArC*H*), 4.27-4.09 (m, 2H, OCH_2), 4.10 (d, *J* = 8.7 Hz, 1H, OCC*H*CO), 4.05 (q, *J* = 6.9 Hz, 2H, OCH_2), 3.72 (dd, *J* = 16.8 Hz, 8.7 Hz, 1H, COCH_2), 3.46 (dd, *J* = 16.8 Hz, 5.1 Hz, 1H, COCH_2), 1.22 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.10 (t, *J* = 6.9 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{22}H_{23}ClO_5$ 402.1234. Found 402.1237.

5.5.6. Diethyl 2-(1-(3-chlorophenyl)-3-oxo-3-phenylpropyl)malonate (4f)

Yield: 53% (0.21 g), yellow oil; $[\alpha]_D^{22}$= +15.2 (*c*=1, $CHCl_3$); 36% ee; major enantiomer t_r = 10.3 min, minor enantiomer t_r = 8.5 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.90 (dd, *J* = 7.5 Hz, 1.5 Hz, 2H, Ar*H*), 7.54 (tt, *J* = 7.5 Hz, 1.5 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.27 (s, 1H, Ar*H*), 7.20-4.14 (m, 3H, Ar*H*), 4.25-4.13 (m, 3H, ArC*H*, OCH_2), 4.00 (q, *J* = 7 Hz, 2H, OCH_2), 3.79 (d, *J* = 9.5 Hz, 1H, OCC*H*CO), 3.54 (dd, *J* = 17 Hz, 4.5 Hz, 1H, COCH_2), 3.45 (dd, *J* = 17 Hz, 9.5 Hz, 1H, COCH_2), 1.24 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.05 (t, *J* = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{22}H_{23}ClO_5$ 402.1234. Found 402.1233.

5.5.7. Diethyl 2-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)malonate (4g)

Yield: 65% (0.26 g), yellow oil; $[\alpha]_D^{22}$= +11.9 (*c*=1, $CHCl_3$); 85% ee;, major enantiomer t_r = 9.6 min, minor enantiomer t_r = 5.0 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C).^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.89 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.54 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.22 (d, *J* = 7.2 Hz, 4H, Ar*H*), 4.26-4.10 (m, 3H, ArC*H*, OCH_2), 3.98 (q, *J* = 6.9 Hz, 2H, OCH_2), 3.78 (d, *J* = 9.6 Hz, 1H, OCC*H*CO), 3.53 (dd, *J* = 16.8 Hz, 4.5 Hz, 1H, COCH_2), 3.43 (dd, *J* = 16.8 Hz, 9.3 Hz, 1H, COCH_2), 1.25 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.05 (t, *J* = 6.9 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{22}H_{23}ClO_5$ 402.1234. Found 402.1240.

5.5.8. Diethyl 2-acetamido-2-(3-oxo-1,3-diphenylpropyl)malonate (5)

Yield: 55% (0.23 g), light yellow powder; M.p. 84-86 °C; $[\alpha]_D^{22}$= + 6.7 (*c*=1, $CHCl_3$); 46% ee; major enantiomer t_r = 11.8 min, minor enantiomer t_r = 15.3 min (Chiralpack AS-H column, 90/10 hexane/*i*PrOH, 0.8 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.92 (d, *J* = 7.8 Hz, 2H, Ar*H*), 7.52-7.46 (m, 1H, Ar*H*), 7.40 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.25-7.15 (m, 5H, Ar*H*), 6.66 (br s, 1H, N*H*), 4.52 (dd, *J* = 10.8 Hz, 1.8 Hz, 1H, PhC*H*), 4.34-4.00 (m, 5H, 2 x OCH_2, COCH_2), 3.39 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H, COCH_2), 2.16 (s, 3H, COCH_3), 1.26 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.23 (t, *J* = 6.9 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 197.97, 169.58, 167.70, 166.58, 138.23, 136.97, 132.76, 128.83, 128.42, 128.33, 128.18, 127.67, 68.86, 63.06, 62.29, 46.30, 40.96, 23.40, 14.02, 13.87. HRMS calcd for $C_{24}H_{27}NO_6$ 425.1838. Found 425.1840.

5.5.9. Diethyl 2-methyl-2-(3-oxo-1,3-diphenylpropyl)malonate (6)

Yield: 65% (0.25 g), white powder; M.p. 88-91 °C; $[\alpha]_D^{22}$= + 19.9 (*c*=1, $CHCl_3$); 31% ee; major enantiomer t_r = 19.0 min, minor enantiomer t_r = 15.4 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 0.8 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.91 (d, *J* = 7.8 Hz, 2H, Ar*H*), 7.54-7.45 (m, 1H, Ar*H*), 7.41 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.24-7.12 (m, 5H, Ar*H*), 4.19-4.02 (m, 5H, 2 x OCH_2, PhC*H*), 3.81-3.68 (m, 1H, COCH_2), 3.64-3.51 (m, 1H, COCH_2), 1.41 (s, 3H, CCH_3), 1.28 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.19 (t, *J* = 6.9 Hz, 3H,

CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 197.80, 171.60, 171.37, 139.12, 137.05, 132.83, 129.38, 128.46, 128.11, 128.06, 127.22, 61.45, 61.38, 57.92, 45.47, 41.31, 19.48, 14.04, 13.95. HRMS calcd for $C_{23}H_{26}NO_5$ 382.1780. Found 382.1777.

5.5.10. Diethyl 2-allyl-2-(3-oxo-1,3-diphenylpropyl)malonate (7)

Yield: 27% (0.12 g), yellow oil; $[\alpha]_D^{22}$ = +18.5 (*c*=1, $CHCl_3$); 63% ee; major enantiomer t_r = 6.6 min, minor enantiomer t_r = 11.1 min (Chiralpack AS-H column, 80/20 hexane/*i*PrOH, 0.8 mL/min, 20 °C). ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.90 (d, *J* = 7.8 Hz, 2H, Ar*H*), 7.51 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.40 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.25-7.15 (m, 5H, Ar*H*), 5.90-5.72 (m, 1H, C*H*=CH_2), 5.12-5.05 (m, 2H, CH=CH_2), 4.36-4.24 (m, 2H, OCH_2), 4.22-4.12 (m, 3H, OCH_2, PhC*H*), 3.79 (dd, *J* = 17.4 Hz, 10.5 Hz, 1H, COCH_2), 3.64 (dd, *J* = 17.4 Hz, 2.4 Hz, 1H, COCH_2), 2.56 (dd, *J* = 14.1 Hz, 6.6 Hz, 1H, CH_2CH=CH_2), 2.35 (dd, *J* = 14.1 Hz, 7.8 Hz, 1H, CH_2CH=CH_2), 1.33 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.24 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 197.78, 168.62, 168.47, 138.71, 137.08, 134.02, 132.80, 129.16, 128.56, 128.19, 128.11, 127.34, 117.36, 61.67, 61.48, 55.93, 45.56, 41.27, 32.48, 14.01, 13.92. HRMS calcd for $C_{25}H_{28}O_5$ 408.1937. Found 408.1932.

5.5.11. Diethyl 2-acetoxy-2-(3-oxo-1,3-diphenylpropyl)malonate (8a)

Yield: 72% (0.31 g), yellow oil; $[\alpha]_D^{22}$ = + 15.6 (*c*=1, $CHCl_3$); 96% ee; major enantiomer t_r = 9.9 min, minor enantiomer t_r = 13.2 min (Chiralpack AS-H column, 90/10 hexane/*i*PrOH, 0.8 mL/min, 20 °C). ^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.90 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.53 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.35 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.26-7.20 (m, 3H, Ar*H*), 4.37 (dd, *J* = 8.5 Hz, 4 Hz, 1H, PhC*H*), 4.24-4.16 (m, 2H, OCH_2), 4.02-3.89 (m, 2H, OCH_2), 3.67 (dd, *J* = 16 Hz, 4 Hz, 1H, COCH_2), 3.59 (dd, *J* = 17.5 Hz, 8.5 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.23 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.06 (t, *J* = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 196.75, 169.50, 165.95, 165.34, 138.35, 136.76, 133.13, 129.47, 128.56, 128.10, 128.01, 127.65, 84.38, 62.45, 62.03, 45.49, 39.87, 20.76, 13.82, 13.68. HRMS calcd for $C_{24}H_{26}O_7$ 426.1679. Found 426.1680.

5.5.12. Diethyl 2-acetoxy-2-(1-(2-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (8b)

Yield: 40% (0.18 g), yellow oil; $[\alpha]_D^{22}$ = + 22.1 (*c*=1, $CHCl_3$); 39% ee; major enantiomer t_r = 11.6 min, minor enantiomer t_r = 9.1 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.88 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.52 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.41 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.35 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H, Ar*H*), 7.17 (td, *J* = 7.5 Hz, 1 Hz, 1H, Ar*H*), 6.86 (t, *J* = 7.5 Hz, 1H, Ar*H*), 6.78 (d, *J* = 8.5 Hz, 1H, Ar*H*), 4.97 (dd, *J* = 9 Hz, *J* = 4.5 Hz, 1H, ArC*H*), 4.27-4.20 (m, 2H, OCH_2), 4.03-3.91 (m, 2H, OCH_2), 3.74 (s, 3H, PhOCH_3), 3.71 (dd, *J* = 17 Hz, 4.5 Hz, 1H, COCH_2), 3.52 (dd, *J* = 17 Hz, *J* = 9 Hz, 1H, COCH_2), 2.19 (s, 3H, COCH_3), 1.25 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.03 (t, *J* = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{25}H_{28}O_8$ 456.1784. Found 456.1790.

5.5.13. Diethyl 2-acetoxy-2-(1-(3-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (8c)

Yield: 57% (0.26 g), yellow oil; $[\alpha]_D^{22}$ = +15.9 (*c*=1, $CHCl_3$); 72% ee; major enantiomer t_r = 23.1 min, minor enantiomer t_r = 17.5 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.90 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.54 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.14 (t, *J* = 8 Hz, 1H, Ar*H*), 6.96-6.90 (m, 2H, Ar*H*), 6.75 (dd, *J* = 8 Hz, 2.5 Hz, 1H, Ar*H*), 4.35 (dd, *J* = 9 Hz, 4 Hz, 1H, ArC*H*), 4.25-4.15 (m, 2H, OCH_2), 4.05-3.94 (m, 2H, OCH_2), 3.76 (s, 3H, ArOCH_3), 3.71 (dd, *J* = 18 Hz, 4 Hz, 1H, COCH_2), 3.56 (dd, *J* = 18 Hz, 9 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.23 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.09 (t, *J* = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{25}H_{28}O_8$ 456.1784. Found 456.1788.

5.5.14. Diethyl 2-acetoxy-2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (8d)

Yield: 73% (0.33 g), light yellow oil; $[\alpha]_D^{22}$ = + 17.9 (*c*=1, $CHCl_3$); 97% ee; major enantiomer t_r = 24.9 min, minor enantiomer t_r = 22.8 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.89 (dd, *J* = 7.5 Hz, 1 Hz, 2H, Ar*H*), 7.53 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.26 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.77 (d, *J* = 8.5 Hz, 2H, Ar*H*), 4.31 (dd, *J* = 8.5 Hz, *J* = 4 Hz, 1H, ArC*H*), 4.24-4.15 (m, 2H, OCH_2), 4.06-3.92 (m, 2H, OCH_2), 3.75 (s, 3H, ArOCH_3), 3.71 (dd, *J* = 18 Hz, 4 Hz, 1H, COCH_2), 3.56 (dd, *J* = 18 Hz, *J* = 9 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.23 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.10 (t, *J* = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{25}H_{28}O_8$ 456.1784. Found 456.1785.

5.5.15. Diethyl 2-acetoxy-2-(1-(2-chlorophenyl)-3-oxo-3-phenylpropyl)malonate (8e)

Yield: 45% (0.21 g), yellow oil; $[\alpha]_D^{22}$ = +14.6 (*c*=1, $CHCl_3$); 15% ee; major enantiomer t_r = 6.2 min, minor enantiomer t_r = 7.7 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.90 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.54 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.47 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.34 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H, Ar*H*), 7.20-7.12 (m, 2H, Ar*H*), 5.05 (dd, *J* = 9 Hz, 4 Hz, 1H, ArC*H*), 4.29-4.21 (m, 2H, OCH_2), 4.10-3.94 (m, 2H, OCH_2), 3.69 (dd, *J* = 17.5 Hz, 4 Hz, 1H, COCH_2), 3.59 (dd, *J* = 17.5 Hz, 9 Hz, 1H, COCH_2), 2.24 (s, 3H, COCH_3), 1.26 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.09 (t, *J* = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{24}H_{25}ClO_7$ 460.1289. Found 460.1295.

5.5.16. Diethyl 2-acetoxy-2-(1-(3-chlorophenyl)-3-oxo-3-phenylpropyl)malonate (8f)

Yield: 61% (0.28 g), yellow oil; $[\alpha]_D^{22}$ = +14.9 (*c*=1, $CHCl_3$); 81% ee; major enantiomer t_r = 4.16 min, minor enantiomer t_r = 11.30 min (Chiralpack AS-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.91 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.55 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.44 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.37-7.35 (m, 1H, Ar*H*), 7.26-7.24 (m, 1H, Ar*H*), 7.21-7.17 (m, 2H, Ar*H*), 4.35 (dd, *J* = 8.5 Hz, 4 Hz, 1H, ArC*H*), 4.24-4.16 (m, 2H, OCH_2), 4.07-3.94 (m, 2H, OCH_2), 3.76 (dd, *J* = 18 Hz, 4 Hz, 1H, COCH_2), 3.56 (dd, *J* = 18 Hz, 8.5 Hz, 1H, COCH_2), 2.24 (s, 3H, COCH_3), 1.23 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.11 (t, *J* = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{24}H_{25}ClO_7$ 460.1289. Found 460.1293.

5.5.17. Diethyl 2-acetoxy-2-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)malonate (8g)

Yield: 76% (0.35 g), yellow oil; $[\alpha]_D^{22}$ = + 13.6 (*c*=1, $CHCl_3$); 88% ee; major enantiomer t_r = 13.7 min, minor enantiomer t_r = 11.9 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.89 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.55 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.44 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.29 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.22 (d, *J* = 8.5 Hz, 2H, Ar*H*), 4.34 (dd, *J* = 9 Hz, *J* = 4 Hz, 1H, ArC*H*), 4.24-4.17 (m, 2H, OCH_2), 4.06-3.92 (m, 2H, OCH_2), 3.73 (dd, *J* = 17.7 Hz, 4.5 Hz, 1H, COCH_2), 3.56 (dd, *J* = 18 Hz, 9 Hz,

1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.24 (t, J = 7 Hz, 3H, CH_2CH_3), 1.10 (t, J = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{24}H_{25}ClO_7$ 460.1289. Found 460.1294.

5.5.18. Diethyl 2-acetoxy-2-(1-(2-nitrophenyl)-3-oxo-3-phenylpropyl)malonate (8h)

Yield 60% (0.28 g), brown powder; M.p. 124-126 °C; $[\alpha]_D^{22}$ +14.7 (c=1, $CHCl_3$); 72% ee; major enantiomer t_r = 13.8 min, minor enantiomer t_r = 15.7 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.90 (d, J = 12.5 Hz, 2H, ArH), 7.79 (d, J = 8 Hz, 1H, ArH), 7.60-7.54 (m, 2H, ArH), 7.49 (t, J = 8 Hz, 1H, ArH), 7.44 (t, J = 8 Hz, 2H, ArH), 7.37 (t, J = 8 Hz, 1H, ArH), 5.18 (dd, J = 9.5 Hz, 4 Hz, 1H, ArCH) 4.19 (q, J = 7 Hz, 2H, OCH_2), 4.15-4.01 (m, 2H, OCH_2), 3.78 (dd, J = 18 Hz, 9.5 Hz, 1H, COCH_2), 3.61 (dd, J = 18 Hz, 4 Hz, 1H, COCH_2), 2.21 (s, 3H, COCH_3), 1.21 (t, J = 7 Hz, 3H, CH_2CH_3), 1.15 (t, J = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{24}H_{25}NO_9$ 471.1529. Found 471.1533.

5.5.19. Diethyl 2-acetoxy-2-(1-(3-nitrophenyl)-3-oxo-3-phenylpropyl)malonate (8i)

Yield: 78% (0.37 g), orange oil; $[\alpha]_D^{22}$ = + 20.1 (c=1, $CHCl_3$); 81% ee; major enantiomer t_r = 25.0 min, minor enantiomer t_r = 21.1 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.30 (s, 1H, ArH), 8.10 (d, J = 8 Hz, 1H, ArH), 7.91 (d, J = 7 Hz, 2H, ArH), 7.71 (d, J = 7.5 Hz, 1H, ArH), 7.57 (t, J = 7.5 Hz, 1H, ArH), 7.45 (td, J = 8 Hz, 2 Hz, 3H, ArH), 4.49 (dd, J = 9.2 Hz, 4 Hz, 1H, ArCH), 4.27-4.20 (m, 2H, OCH_2), 4.08-3.95 (m, 2H, OCH_2), 3.81 (dd, J = 18.2 Hz, 4 Hz, 1H, COCH_2), 3.64 (dd, J = 18.2 Hz, 9 Hz, 1H, COCH_2), 2.25 (s, 3H, COCH_3), 1.26 (t, J = 7 Hz, 3H, CH_2CH_3), 1.12 (t, J = 7 Hz, 3H CH_2CH_3). HRMS calcd for $C_{24}H_{25}NO_9$ 471.1529. Found 471.1531.

5.5.20. Diethyl 2-acetoxy-2-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)malonate (8j)

Yield: 73% (0.35 g), yellowish-brown powder; M.p. 93-96 °C; $[\alpha]_D^{22}$ = + 13.8 (c=1, $CHCl_3$); 89% ee; major enantiomer t_r = 54.1 min, minor enantiomer t_r = 40.5 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 0.8 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.27 (d, J = 9 Hz, 2H, ArH), 8.04 (d, J = 9 Hz, 2H, ArH), 7.35-7.21 (m, 5H, ArH), 4.36 (dd, J = 8.2 Hz, 5 Hz, 1H, ArCH), 4.25-4.18 (m, 2H, OCH_2), 4.02-3.87 (m, 3H, COCH_2, OCH_2),

3.55 (dd, *J* = 18 Hz, 8.5 Hz, 1H, COCH_2), 2.24 (s, 3H, COCH_3), 1.25 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.07 (t, *J* = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{24}H_{25}NO_9$ 471.1529. Found 471.1527.

5.5.21. Diethyl 2-acetoxy-2-(1-(naphthalen-2-yl)-3-oxo-3-phenylpropyl)malonate (8k)

Yield: 42% (0.20 g), yellow oil; $[\alpha]_D^{22}$ = + 32.4 (*c*=1, $CHCl_3$); 52% ee; major enantiomer t_r = 24.9 min, minor enantiomer t_r = 22.8 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.90 (dd, *J* = 8.5 Hz, 1.5 Hz, 2H, Ar*H*), 7.89-7.73 (m, 4H, Ar*H*), 7.55-7.50 (m, 2H, Ar*H*), 7.45-7.39 (m, 4H, Ar*H*), 4.56 (dd, *J* = 8.5 Hz, 4.5 Hz, 1H, ArC*H*), 4.26-4.16 (m, 2H, OCH_2), 3.96-3.87 (m, 2H, OCH_2), 3.84 (dd, *J* = 18 Hz, 4 Hz, 1H, COCH_2), 3.71 (dd, *J* = 18 Hz, 8.5 Hz, 1H, COCH_2), 2.25 (s, 3H, COCH_3), 1.22 (t, *J* = 7 Hz, 3H, CH_2CH_3), 0.98 (t, *J* = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 196.70, 169.56, 165.99, 165.30, 146.20, 137.22, 133.69, 132.14, 133.14, 128.61, 128.19, 127.86, 127.61, 127.55, 125.80, 125.67, 125.04, 124.08, 84.36, 62.44, 62.08, 45.53, 40.17, 20.76, 13.85, 13.62. HRMS calcd for $C_{28}H_{28}O_7$ 476.1835. Found 476.1840.

5.5.22. Diethyl 2-acetoxy-2-(3-oxo-3-phenyl-1-(thiophen-2-yl)propyl)malonate (8l)

Yield: 72% (0.31 g), yellow oil; $[\alpha]_D^{22}$ = + 13.7 (*c*=1, $CHCl_3$); 33% ee; major enantiomer t_r = 6.6 min, minor enantiomer t_r = 8.0 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.91 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.54 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.15 (d, *J* = 5 Hz, 1H, Ar*H*), 6.96 (d, *J* = 3.5 Hz, 1H, Ar*H*), 6.85 (dd, *J* = 5 Hz, 3.5 Hz, 1H, Ar*H*), 4.76 (dd, *J* = 8.5 Hz, 4.5 Hz, 1H, ArC*H*), 4.25-4.00 (m, 4H, 2 x OCH_2), 3.69 (dd, *J* = 18 Hz, 4.5 Hz, 1H, COCH_2), 3.56 (dd, *J* = 18 Hz, 8.5 Hz, 1H, COCH_2), 2.24 (s, 3H, COCH_3), 1.22 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.15 (t, *J* = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 196.30, 169.34, 165.28, 165.26, 140.39, 136.59, 133.23, 128.60, 128.05, 127.40, 126.06, 125.35, 84.07, 62.53, 62.27, 41.35, 41.12, 20.77, 13.79, 13.78. HRMS calcd for $C_{22}H_{24}O_7S$ 432.1243. Found 432.1248.

5.5.23. Diethyl 2-acetoxy-2-(3-oxo-3-phenyl-1-(pyridin-3-yl)propyl)malonate (8m)

Yield: 23% (0.10 g), dark orange oil; $[\alpha]_D^{22}$ = + 16.1 (*c* = 1, $CHCl_3$); ee 36%; major enantiomer t_r = 13.6 min, minor enantiomer t_r = 9.8 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.62 (d, *J* = 1.2 Hz, 1H, Ar*H*), 8.46 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H, Ar*H*), 7.89 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.70 (dt, *J* = 7.5 Hz, 1.2 Hz, 1H, Ar*H*), 7.56 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.44 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.20 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H, Ar*H*), 4.39 (dd, *J* = 8.7 Hz, 4.2 Hz, 1H, ArC*H*), 4.28-4.16 (m, 2H, OCH_2), 4.08-3.92 (m, 2H, OCH_2), 3.79 (dd, *J* = 18 Hz, 4.2 Hz, 1H, COCH_2), 3.59 (dd, *J* = 18 Hz, 8.7 Hz, 1H, COCH_2), 2.24 (s, 3H, COCH_3), 1.24 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.09 (t, *J* = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 196.16, 169.26, 165.62, 165.13, 150.80, 148.88, 136.86, 136.42, 134.13, 133.41, 128.67, 127.99, 123.07, 83.98, 62.69, 62.33, 43.34, 39.43, 20.71, 13.82, 13.74. HRMS calcd for $C_{23}H_{25}NO_7$ 427.1631. Found 427.1637.

5.5.24. Diethyl 2-acetoxy-2-(3-(2-nitrophenyl)-3-oxo-1-phenylpropyl)malonate (11a)

Yield: 73% (0.32 g), light orange oil; $[\alpha]_D^{22}$ = +0.1 (*c*=1, $CHCl_3$); ee 2% ee; major enantiomer t_r = 25.7 min, minor enantiomer t_r = 11.9 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 8.05 (dd, *J* = 8.5 Hz, 1Hz, 1H, Ar*H*), 7.59 (td, *J* = 7.5 Hz, 1Hz, 1H, Ar*H*), 7.54 (td, *J* = 7.5 Hz, 1.5 Hz, 1H, Ar*H*), 7.34-7.30 (m, 2H, Ar*H*), 7.28-7.24 (m, 3H, Ar*H*), 7.02 (dd, *J* = 7.5 Hz, 1Hz, 1H, Ar*H*), 4.30-4.24 (m, 3H, OCH_2, COCH_2), 4.01-3.89 (m, 2H, OCH_2), 3.69 (dd, *J* = 18 Hz, 4 Hz, 1H, COCH_2), 3.41 (dd, *J* = 18 Hz, 8.5 Hz, 1H, COCH_2), 2.19 (s, 3H, COCH_3), 1.31 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 1.06 (t, *J* = 7.5 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{24}H_{25}NO_9$ 471.1529. Found 471.1528.

5.5.25. Diethyl 2-acetoxy-2-(3-(3-nitrophenyl)-3-oxo-1-phenylpropyl)malonate (11b)

Yield: 84% (0.38 g), orange oil; $[\alpha]_D^{22}$ = +2.8 (*c*=1, $CHCl_3$); 7% ee; major enantiomer t_r = 19.5 min, minor enantiomer t_r = 17.6 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.71 (t, *J* = 2 Hz, 1H, Ar*H*), 8.39 (d, *J* = 8 Hz, 1H, Ar*H*), 8.23 (dt, *J* = 8 Hz, 1 Hz, 1H, Ar*H*), 7.65 (t, *J* = 8 Hz, 1H, Ar*H*), 7.38-7.34 (m, 2H, Ar*H*), 7.28-7.19 (m, 3H, Ar*H*), 4.38 (dd, *J* = 8 Hz, 4.5 Hz, 1H, ArC*H*), 4.26-4.17 (m, 2H, OCH_2), 4.04-3.89 (m, 2H, OCH_2), 3.90 (dd, *J* = 18 Hz, 4.5 Hz, 1H, COCH_2), 3.56 (dd, *J*

= 18 Hz, 8 Hz, 1H, COCH_2), 2.26 (s, 3H, COCH_3), 1.26 (t, J = 6.5 Hz, 3H, CH_2CH_3), 1.06 (t, J = 6.5 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{24}H_{25}NO_9$ 471.1529. Found 471.1531.

5.5.26. Diethyl 2-acetoxy-2-(3-(4-nitrophenyl)-3-oxo-1-phenylpropyl)malonate (11c)

Yield: 77% (0.35 g), yellow solid. M.p 97-99 °C. $[\alpha]_D^{22}$ = +1.3 (*c*=1, $CHCl_3$); 58% ee; major enantiomer t_r = 21.4 min, minor enantiomer t_r = 19.3 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.27 (d, J = 9 Hz, 2H, Ar*H*), 8.04 (d, J = 9 Hz, 2H, Ar*H*), 7.36-7.32 (m, 2H, Ar*H*), 7.28-7.21 (m, 3H, Ar*H*), 4.35 (dd, J = 8 Hz, 4.5 Hz, 1H, ArC*H*), 4.25-4.17 (m, 2H, OCH_2), 4.03-3.90 (m, 2H, OCH_2), 3.90 (dd, J = 18 Hz, 4.5 Hz, 1H, COCH_2), 3.55 (dd, J = 18 Hz, 8.5 Hz, 1H, COCH_2), 2.24 (s, 3H, COCH_3), 1.25 (t, J = 6 Hz, 3H, CH_2CH_3), 1.07 (t, J = 6 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{24}H_{25}NO_9$ 471.1529. Found 471.1534.

5.5.27. Diethyl 2-acetoxy-2-(3-(2-chlorophenyl)-3-oxo-1-phenylpropyl)malonate (11d)

Yield: 67% (0.31 g), yellow oil; $[\alpha]_D^{22}$ = +12 (*c*=1, $CHCl_3$); ee 33% ee; major enantiomer t_r = 15.9 min, minor enantiomer t_r = 7.7 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.37-7.32 (m, 2H, Ar*H*), 7.30-7.27 (m, 2H, Ar*H*), 7.25-7.20 (m, 4H, Ar*H*), 7.16 (dd, J = 8.5 Hz, 1.5 Hz, 2H, Ar*H*), 4.28-4.22 (m, 3H, OCH_2, ArC*H*), 4.00-3.89 (m, 2H, OCH_2), 3.72 (dd, J = 18 Hz, 4.5 Hz, 1H, COCH_2), 3.56 (dd, J = 18 Hz, 9 Hz, 1H, COCH_2), 2.20 (s, 3H, COCH_3), 1.29 (t, J = 7 Hz, 3H, CH_2CH_3), 1.05 (t, J = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{24}H_{25}ClO_7$ 460.1289. Found 460.1285.

5.5.28. Diethyl 2-acetoxy-2-(3-(3-chlorophenyl)-3-oxo-1-phenylpropyl)malonate (11e)

Yield: 59% (0.27 g), yellow oil. $[\alpha]_D^{22}$ = +13 (*c*=1, $CHCl_3$); ee 31%, major enantiomer t_r = 8.3 min, minor enantiomer t_r = 11.0 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 7.85 (t, J = 2 Hz, 1H, Ar*H*), 7.78 (dt, J = 7.5 Hz, 1 Hz, 1H, Ar*H*), 7.51 (d, J = 8 Hz, 1H, Ar*H*), 7.38 (d, J = 8 Hz, 1H, Ar*H*), 7.36-7.33 (m, 2H, Ar*H*), 7.25-7.19 (m, 3H, Ar*H*), 4.34 (dd, J = 8 Hz, 4.5 Hz, 1H, ArC*H*), 4.24-4.16 (m, 2H, OCH_2), 3.98-3.89 (m, 2H, OCH_2), 3.77 (dd, J = 18 Hz, 4.5 Hz, 1H, COCH_2), 3.53

(dd, *J* = 18 Hz, 8 Hz, 1H, COC*H*$_2$), 2.24 (s, 3H, COC*H*$_3$), 1.24 (t, *J* = 7 Hz, 3H, CH$_2$C*H*$_3$), 1.06 (t, *J* = 7 Hz, 3H, CH$_2$C*H*$_3$). HRMS calcd for $C_{24}H_{25}ClO_7$ 460.1289. Found 460.1293.

5.5.29. Diethyl 2-acetoxy-2-(3-(4-chlorophenyl)-3-oxo-1-phenylpropyl)malonate (11f)

Yield: 50% (0.23 g), yellow solid; M.p. 70-72 °C; $[\alpha]_D^{22}$ = +3.9 (*c*=1, $CHCl_3$); 26% ee; major enantiomer t_r = 15.8 min, minor enantiomer t_r = 9.2 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C).^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.84 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.40 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.36-7.30 (m, 2H, Ar*H*), 7.28-7.19 (m, 3H, Ar*H*), 4.34 (dd, *J* = 8.1 Hz, 4.2 Hz, 1H, ArC*H*), 4.25-4.14 (m, 2H, OC*H*$_2$), 4.04-3.88 (m, 2H, OC*H*$_2$), 3.76 (dd, *J* = 17.7 Hz, 4.2 Hz, 1H, COC*H*$_2$), 3.52 (dd, *J* = 17.7 Hz, 8.1 Hz, 1H, COC*H*$_2$), 2.23 (s, 3H, COC*H*$_3$), 1.23 (t, *J* = 6.9 Hz, 3H, CH$_2$C*H*$_3$), 1.06 (t, *J* = 6.9 Hz, 3H, CH$_2$C*H*$_3$). HRMS calcd for $C_{24}H_{25}ClO_7$ 460.1289. Found 460.1291.

5.5.30. Diethyl 2-acetoxy-2-(3-(2-methoxyphenyl)-3-oxo-1-phenylpropyl)malonate (11g)

Yield: 35% (0.26 g), light yellow oil; $[\alpha]_D^{22}$ = +11.9 (*c*=1, $CHCl_3$); 27% ee;, major enantiomer t_r = 19.2 min, minor enantiomer t_r = 22.0 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 0.8 mL/min, 10 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.44-7.35 (m, 2H, Ar*H*), 7.31-7.25 (m, 2H, Ar*H*), 7.24-7.17 (m, 3H, Ar*H*), 6.95-6.86 (m, 2H, Ar*H*), 4.27 (dd, *J* = 9 Hz, 6 Hz, 1H, ArC*H*), 4.22 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$), 4.01-3.98 (m, 2H, OC*H*$_2$), 3.87 (s, 3H, OC*H*$_3$), 3.70-3.64 (m, 2H, COC*H*$_2$), 2.20 (s, 3H, COC*H*$_3$), 1.26 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$), 1.05 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$). HRMS calcd for $C_{25}H_{28}O_8$ 456.1787. Found 456.1792.

5.5.31. Diethyl 2-acetoxy-2-(3-(3-methoxyphenyl)-3-oxo-1-phenylpropyl)malonate (11h)

Yield: 50% (0.23 g), light yellow oil; $[\alpha]_D^{22}$ = +7.0 (*c*=1, $CHCl_3$); 96% ee; major enantiomer t_r = 7.3 min, minor enantiomer t_r = 6.0 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.50 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.39 (m, 1H, Ar*H*), 7.36 (m, 1H, Ar*H*), 7.35-7.31 (m, 2H, Ar*H*), 7.26-7.19 (m, 3H, Ar*H*), 7.08 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H, Ar*H*), 4.35 (dd, *J* = 8.4 Hz, 4.2 Hz, 1H, ArC*H*), 4.26-4.14 (m, 2H, OC*H*$_2$), 4.05-3.89 (m, 2H, OC*H*$_2$), 3.82 (s, 3H, OC*H*$_3$), 3.73 (dd, *J* = 18 Hz, 4.2 Hz, 1H,

COCH_2), 3.58 (dd, J = 18 Hz, 8.4 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.23 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.06 (t, J = 7.2 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{25}H_{28}O_8$ 456.1787. Found 456.1790.

5.5.32. Diethyl 2-acetoxy-2-(3-(4-methoxyphenyl)-3-oxo-1-phenylpropyl)malonate (11i)

Yield: 42% (0.19 g), light yellow oil; $[\alpha]_D^{22}$ = +16.8 (c=1, $CHCl_3$); 59% ee, major enantiomer t_r = 18.3 min, minor enantiomer t_r = 9.6 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.89 (d, J = 8.5 Hz, 2H, ArH), 7.35 (d, J = 7.5 Hz, 2H, ArH), 7.24 (t, J = 7.5 Hz, 2H, ArH), 7.19 (t, J = 7.5 Hz, 1H, ArH), 6.89 (d, J = 8.5 Hz, 2H, ArH), 4.35 (dd, J = 8.5 Hz, 4 Hz, 1H, ArCH), 4.24-4.14 (m, 2H, OCH_2), 4.01-3.89 (m, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.67 (dd, J = 17.5 Hz, 4 Hz, 1H, COCH_2), 3.58 (dd, J = 17.5 Hz, J = 8.5 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.22 (t, J = 7 Hz, 3H, CH_2CH_3), 1.06 (t, J = 7 Hz, 3H, CH_2CH_3). HRMS calcd for $C_{25}H_{28}O_8$ 456.1787. Found 456.1790.

5.5.33. Diethyl 2-acetoxy-2-(3-(naphthalen-1-yl)-3-oxo-1-phenylpropyl)malonate (12a)

Yield: 78% (0.36 g), orange oil; $[\alpha]_D^{22}$ = -7.6 (c=1, $CHCl_3$); 28% ee; major enantiomer t_r = 14.0 min, minor enantiomer t_r = 9.9 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.07 (d, J = 8.5 Hz, 1H, ArH), 7.94 (d, J = 8.5 Hz, 1H, ArH), 7.82 (dd, J = 8.5 Hz, 1 Hz, 1H, ArH), 7.77 (d, J = 7.5 Hz, 1 Hz, 1H, ArH), 7.49-7.40 (m, 3H, ArH), 7.33 (d, J = 7.5 Hz, 2 Hz, 2H, ArH), 7.25-7.20 (m, 3H, ArH), 4.38 (dd, J = 9 Hz, 4.5 Hz, 1H, ArCH), 4.30-4.21 (m, 2H, OCH_2), 4.01-3.89 (m, 2H, OCH_2), 3.85 (dd, J = 17.5 Hz, 4.5 Hz, 1H, COCH_2), 3.63 (dd, J = 17.5 Hz, 9 Hz, 1H, COCH_2), 2.22 (s, 3H, COCH_3), 1.28 (t, J = 7 Hz, 3H, CH_2CH_3), 1.05 (t, J = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 201.28, 169.49, 166.03, 165.32, 138.02, 136.11, 133.82, 132.41, 129.90, 129.59, 128.24, 128.16, 127.73, 127.64, 126.94, 126.38, 125.50, 124.28, 84.31, 62.52, 62.02, 46.00, 43.50, 20.74, 13.90, 13.67. HRMS calcd for $C_{28}H_{28}O_7$ 476.1835. Found 476.1833.

5.5.34. Diethyl 2-acetoxy-2-(3-(naphthalen-2-yl)-3-oxo-1-phenylpropyl)malonate (12b)

Yield: 52% (0.24 g), yellow oil; $[\alpha]_D^{22}$ = +41.7 (*c*=1, $CHCl_3$); 45% ee; major enantiomer t_r = 21.8 min, minor enantiomer t_r = 13.4 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.44 (s, 1H, Ar*H*), 7.96 (d, *J* = 8 Hz, 1H, Ar*H*), 7.94 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H, Ar*H*), 7.85 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.59 (td, *J* = 8 Hz, 1 Hz, 1H, Ar*H*), 7.55 (td, *J* = 8 Hz, 1 Hz, 1H, Ar*H*), 7.41-7.37 (m, 2H), 7.26-7.23 (m, 2H, Ar*H*), 7.22-7.20 (m, 1H, Ar*H*), 4.43 (dd, *J* = 8.5 Hz, 4 Hz, 1H, ArC*H*), 4.26-4.15 (m, 2H, OCH_2), 4.03-3.91 (m, 2H, OCH_2), 3.88 (dd, *J* = 18 Hz, 4 Hz, 1H, COCH_2), 3.74 (dd, *J* = 18 Hz, 8.5 Hz, 1H, COCH_2), 2.26 (s, 3H, COCH_3), 1.24 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.07 (t, *J* = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 196.68, 169.52, 165.99, 165.38, 138.35, 135.59, 134.08, 132.45, 129.64, 129.56, 129.50, 128.48, 128.42, 128.12, 127.75, 127.67, 126.78, 123.79, 84.43, 62.46, 62.05, 45.65, 39.90, 20.79, 13.84, 13.69. HRMS calcd for $C_{28}H_{28}O_7$ 476.1835. Found 476.1841.

5.5.35. Diethyl 2-acetoxy-2-(3-(furan-2-yl)-3-oxo-1-phenylpropyl)malonate (12c)

Yield: 75% (0.31 g), light yellow oil; $[\alpha]_D^{22}$ = +10.5 (*c*=1, $CHCl_3$); >99% ee; major enantiomer t_r = 8.0 min, minor enantiomer t_r = 6.1 min (Chiralpack AS-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.53 (d, *J* = 1 Hz, 1H, Ar*H*), 7.33 (d, *J* = 7 Hz, 2H, Ar*H*), 7.25-7.19 (m, 3H, Ar*H*), 7.13 (dd, *J* = 3.5 Hz, 1 Hz, 1H, Ar*H*), 6.48 (dd, *J* = 3.5 Hz, 2 Hz, 1H, Ar*H*), 4.30 (dd, *J* = 8.5 Hz, 5 Hz, 1H, ArC*H*), 4.27-4.16 (m, 2H, OCH_2), 4.01-3.87 (m, 2H, OCH_2), 3.55 (dd, *J* = 17.5 Hz, 5 Hz, 1H, COCH_2), 3.51 (dd, *J* = 17.5 Hz, 8.5 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.25 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.05 (t, *J* = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 185.92, 169.45, 165.85, 165.25, 152.52, 146.24, 137.97, 129.47, 128.09, 127.70, 117.02, 112.23, 84.33, 62.46, 62.01, 45.24, 39.62, 20.73, 13.82, 13.65. HRMS calcd for $C_{22}H_{24}O_6$ 416.1471. Found 416.1472.

5.5.36. Diethyl 2-acetoxy-2-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)malonate (12d)

Yield: 76% (0.33 g), light yellow oil; $[\alpha]_D^{22}$ = +13.1 (*c*=1, $CHCl_3$); >99% ee; major enantiomer t_r = 8.9 min, minor enantiomer t_r = 7.6 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.73 (d, *J* = 3.5 Hz, 1H, Ar*H*), 7.59 (d, *J* = 5 Hz, 1H, Ar*H*), 7.34 (d, *J* = 6 Hz, 2H, Ar*H*), 7.26-7.19 (m, 3H, Ar*H*), 7.10 (dd, *J* = 5 Hz, 3.5 Hz, 1H, Ar*H*), 4.32 (dd, *J* = 8.5 Hz, 4 Hz, 1H, ArC*H*), 4.26-4.15 (m, 2H, OCH_2),

4.02-3.88 (m, 2H, OCH_2), 3.66 (dd, J = 17.5 Hz, 4 Hz, 1H, COCH_2), 3.54 (dd, J = 17.5 Hz, 8.5 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.24 (t, J = 7 Hz, 3H, CH_2CH_3), 1.06 (t, J = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 189.59, 169.44, 165.86, 165.26, 143.90, 138.00, 133.65, 131.89, 129.43, 128.13, 128.03, 127.72, 84.32, 62.48, 62.04, 45.65, 40.50, 20.73, 13.81, 13.66. HRMS calcd for $C_{22}H_{24}O_7S$ 432.1243. Found 432.1244.

5.5.37. Dimethyl 2-acetoxy-2-(3-oxo-1,3-diphenylpropyl)malonate (13a)

Yield: 53% (0.20 g), yellowish-brown oil; $[\alpha]_D^{22}$= + 16.2 (c=1, $CHCl_3$); 61% ee; major enantiomer t_r = 25.0 min, minor enantiomer t_r = 22.4 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 10 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.90 (d, J = 7.2 Hz, 2H, ArH), 7.54 (t, J = 7.2 Hz, 1H, ArH), 7.43 (t, J = 7.2 Hz, 2H, ArH), 7.36-7.30 (m, 2H, ArH), 7.29-7.20 (m, 3H, ArH), 4.37 (dd, J = 7.8 Hz, 4.8 Hz, 1H, PhCH), 3.77 (dd, J = 18 Hz, 3.9 Hz, 1H, COCH_2), 3.72 (s, 3H, COOCH_3), 3.56 (dd, J = 18 Hz, 8.1 Hz, 1H, COCH_2), 3.52 (s, 3H, COOCH_3), 2.23 (s, 3H, COCH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 196.64, 169.60, 166.38, 165.85, 138.16, 136.71, 133.16, 129.32, 128.57, 128.20, 128.02, 127.77, 84.36, 53.16, 52.77, 45.58, 39.66, 20.74. HRMS calcd for $C_{22}H_{22}O_7$ 398.1366. Found 398.1372.

5.5.38. Diisopropyl 2-acetoxy-2-(3-oxo-1,3-diphenylpropyl)malonate (13b)

Yield: 51% (0.23 g), yellowish-brown oil; $[\alpha]_D^{22}$= + 15.7 (c=1, $CHCl_3$); 92% ee; major enantiomer t_r = 2.6 min, minor enantiomer t_r = 4.9 min (Chiralpack AS-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.88 (d, J = 7.2 Hz, 2H, ArH), 7.52 (t, J = 7.2 Hz, 1H, ArH), 7.41 (t, J = 7.2 Hz, 2H, ArH), 7.37 (d, J = 7.8 Hz, 2H, ArH), 7.25-7.15 (m, 3H, ArH), 5.05 (sep, J = 6.3 Hz, 1H, CHCH$_3$), 4.82 (sep, J = 6.3 Hz, 1H, CHCH$_3$), 4.34 (dd, J = 9 Hz, 3.9 Hz, 1H, PhCH), 3.75 (dd, J = 18 Hz, 3.9 Hz, 1H, COCH_2), 3.60 (dd, J = 18 Hz, 9 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.26 (d, J = 6.3 Hz, 3H, CHCH_3), 1.23 (d, J = 6.3 Hz, 3H, CHCH_3), 1.04 (d, J = 6.3 Hz, 6H, 2 x CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 196.93, 169.40, 165.60, 164.88, 138.56, 136.89, 133.10, 129.68, 128.57, 128.10, 128.04, 127.57, 84.50, 70.52, 70.12, 45.38, 40.28, 21.61, 21.51, 21.38, 21.24, 20.83. HRMS calcd for $C_{26}H_{30}O_7$ 454.1992. Found 454.1999.

5.5.39. Dibenzyl 2-acetoxy-2-(3-oxo-1,3-diphenylpropyl)malonate (13c)

Yield: 75% (0.33 g), yellowish-brown oil; $[\alpha]_D^{22}$= + 16.9 (*c*=1, $CHCl_3$); 34% ee; major enantiomer t_r = 11.5 min, minor enantiomer t_r = 14.4 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.76 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.51 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.37 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.30-7.21 (m, 10H, Ar*H*), 7.20-7.08 (m, 5H, Ar*H*), 5.15 (q, *J* = 12.6 Hz, 2H, OCH_2Ph), 4.89 (s, 2H, OCH_2Ph), 4.36 (t, *J* = 6.3 Hz, 1H, PhC*H*), 3.55 (d, *J* = 6.3 Hz, 2H, COCH_2), 2.17 (s, 3H, COCH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 196.50, 169.63, 165.69, 165.28, 137.91, 136.70, 134.83, 134.76, 133.12, 129.48, 128.57, 128.52, 128.48, 128.43, 128.33, 128.21, 128.03, 127.76, 84.52, 77.50, 77.08, 76.66, 68.24, 67.98, 45.71, 39.57, 20.74. HRMS calcd for $C_{34}H_{30}O_7$ 550.1992. Found 550.1997.

5.5.40. Dimethyl 2-acetoxy-2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (13d)

Yield: 46% (0.19 g), yellow gum; $[\alpha]_D^{22}$= + 20.1 (*c* = 1, $CHCl_3$); 17% ee; major enantiomer t_r = 10.7 min, minor enantiomer t_r = 8.6 min (Chiralpack AD-H column, 90/10 hexane/*i*PrOH, 2 mL/min, 10 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.90 (dd, *J* = 7.2 Hz, 2H, Ar*H*), 7.54 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.25 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.78 (d, *J* = 8.5 Hz, 2H, Ar*H*), 4.31 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H, PhC*H*), 3.73 (dd, *J* = 18 Hz, 4.5 Hz, 1H, COCH_2), 3.75 (s, 3H, COOCH_3), 3.72 (s, 3H, ArOCH_3), 3.51 (dd, *J* = 18 Hz, 8.1 Hz, 1H, COCH_2), 3.55 (s, 3H, COOCH_3), 2.23 (s, 3H, COCH_3). HRMS calcd for $C_{23}H_{24}O_8$ 428.1471. Found 428.1476.

5.5.41. Diisopropyl 2-acetoxy-2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (13e)

Yield: 23% (0.11 g), yellow oil; $[\alpha]_D^{22}$= + 18.6 (*c*=1, $CHCl_3$); 35% ee; major enantiomer t_r = 9.6 min, minor enantiomer t_r = 13.4 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 10 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm):7.88 (dd, *J* = 7.2 Hz, 2H, Ar*H*), 7.53 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.42 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.28 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.75 (d,

J = 8.7 Hz, 2H, Ar*H*), 5.08 (sep, *J* = 6.3 Hz, 1H, C*H*CH$_3$), 4.84 (sep, *J* = 6.3 Hz, 1H, C*H*CH$_3$), 4.29 (dd, *J* = 9 Hz, 3.9 Hz, 1H, PhC*H*), 3.73 (s, 3H, ArOC*H$_3$*), 3.71 (dd, *J* = 18 Hz, 3.9 Hz, 1H, COC*H$_2$*), 3.57 (dd, *J* = 18 Hz, 9 Hz, 1H, COC*H$_2$*), 2.23 (s, 3H, COC*H$_3$*), 1.27 (d, *J* = 6.3 Hz, 3H, CHC*H$_3$*), 1.24 (d, *J* = 6.3 Hz, 3H, CHC*H$_3$*), 1.08 (d, *J* = 6.3 Hz, 3H, CHC*H$_3$*), 1.06 (d, *J* = 6.3 Hz, 3H, CHC*H$_3$*). HRMS calcd for $C_{27}H_{32}O_8$ 484.2097. Found 484.2104.

5.5.42. Dibenzyl 2-acetoxy-2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (13f)

Yield: 59% (0.24 g), yellow oil; $[\alpha]_D^{22}$ = + 18.1 (*c*=1, $CHCl_3$); > 99% ee; major enantiomer t_r = 27.1 min, minor enantiomer could not been detected (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.75 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.51 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.37 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.31-7.22 (m, 8H, Ar*H*), 7.18-7.10 (m, 4H, Ar*H*), 6.68 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.15 (q, *J* = 12 Hz, 2H, OC*H$_2$*Ph), 4.92 (dd, *J* = 15.6 Hz, 12 Hz, 2H, OC*H$_2$*Ph), 4.30 (t, *J* = 6.6 Hz, 1H, PhC*H*), 3.72 (s, 3H, ArOC*H$_3$*), 3.50 (d, *J* = 6.6 Hz, 2H, COC*H$_2$*), 2.17 (s, 3H, COC*H$_3$*). HRMS calcd for $C_{35}H_{32}O_8$ 580.2097. Found 580.2100.

5.5.43. Diethyl 2-acetoxy-2-(3-oxocyclopentyl)malonate (15a)

Yield: 67% (0.20 g), light yellow oil; $[\alpha]_D^{22}$ = + 0.5 (*c*=1, $CHCl_3$); 46% ee; major enantiomer t_r = 9.2 min, minor enantiomer t_r = 8.2 min (Chiralpack AS-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 4.35-4.20 (m, 4H, 2 x OC*H$_2$*), 3.12-2.98 (m, 1H, CC*H*), 2.47-1.90 (m, 6H, C*H$_2$*C*H$_2$*COC*H$_2$*), 2.18 (s, 3H, COC*H$_3$*), 1.31 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.29 (t, *J* = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 217.66, 208.98, 169.45, 165.45, 83.70, 62.35, 62.33, 43.75, 42.32, 40.95, 25.82, 24.24, 20.52, 14.01. HRMS calcd for $C_{14}H_{20}O_7$ 300.1209. Found 300.1212.

5.5.44. Diethyl 2-acetoxy-2-(3-oxocyclohexyl)malonate (15b)

Yield: 41% (0.14 g), light yellow oil; $[\alpha]_D^{22}$ = + 3.9 (*c*=1, $CHCl_3$); 80% ee; major enantiomer t_r = 4.1 min, minor enantiomer t_r = 3.6 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 2 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 4.27 (q, *J* = 7.2 Hz, 2H, OC*H$_2$*), 4.26

(q, *J* = 7.2 Hz, 2H, OC*H*$_2$), 2.65-2.50 (m, 1H, CC*H*), 2.45-2.35 (m, 3H, C*H*$_2$COCH$_2$CH, CH$_2$COC*H*$_2$CH,), 2.32-2.20 (m, 1H, CH$_2$COC*H*$_2$CH), 2.18 (s, 3H, COC*H*$_3$), 2.15-2.05 (m, 1H, CHC*H*$_2$CH$_2$CH$_2$CO), 2.00-1.89 (m, 1H, CHCH$_2$C*H*$_2$CH$_2$CO), 1.66-1.55 (m, 2H, CHC*H*$_2$C*H*$_2$CH$_2$CO), 1.30 (t, *J* = 7.2 Hz, 6H, 2 x CH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 217.66, 208.98, 169.45, 165.45, 83.71, 62.35, 62.33, 43.75, 42.32, 40.95, 25.82, 24.24, 20.52, 14.01. HRMS calcd for $C_{15}H_{22}O_7$ 314.1366. Found 314.1364.

5.5.45. Dibenzyl 2-(3-oxocyclohexyl)malonate (15c)

Yield: 58% (0.22 g), white solid; Mp.67-68 °C; $[\alpha]_D^{22}$= + 8.1 (*c* = 1, $CHCl_3$); 83% ee; major enantiomer t_r = 16.6 min, minor enantiomer t_r = 13.3 min (Chiralpack AD-H column, 80/20 hexane/*i*PrOH, 1 mL/min, 20 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.37-7.23 (m, 10H, Ar*H*), 5.15 (s, 2H, PhC*H*$_2$), 5.14 (s, 2H, PhC*H*$_2$), 2.65-2.50 (m, 1H, CC*H*), 3.41 (d, *J* = 6.9 Hz, 1H, OOCC*H*CH), 2.64-2.49 (m, 1H, OOCCHC*H*), 2.48-2.32 (m, 2H, C*H*$_2$COCH$_2$CH), 2.30-2.13 (m, 2H, CH$_2$COC*H*$_2$CH), 2.08-1.96 (m, 1H, CHC*H*$_2$CH$_2$CH$_2$CO), 1.95-1.85 (m, 1H, CHCH$_2$C*H*$_2$CH$_2$CO), 1.73-1.38 (m, 2H, CHC*H*$_2$C*H*$_2$CH$_2$CO). HRMS calcd for $C_{23}H_{24}O_5$ 314.1366. Found 314.1364.

5.6. Quantum chemical calculations

The molecular mechanical conformation analysis was carried out using the MMFF[24] force field and the Marvin[25] program. The DFT and TD-DFT[26,27] calculations were performed using the PBE0[28] functional and the 6-311++G** basis set with the Gaussian 09 package[29]. The DFT calculations were performed using the polarized continuum model[30] with acetonitrile as the solvent. Rotator strengths were calculated in the velocity gauge. Accurate conformational energies were obtained invoking the direct random phase approximation (dRPA)[31] and the aug-cc-pVTZ basis set using the MRCC suite of quantum chemistry programs.[32] The dRPA calculations used PBE0 orbitals.

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