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Organocatalytic Asymmetric Mannich Reactions with *N*-Boc and *N*-Cbz Protected α-Amido Sulfones (Boc: *tert*-Butoxycarbonyl, Cbz: Benzyloxycarbonyl)

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Abstract: Different malonates and β-ketoesters can react with *N*-*tert*-butoxycarbonyl- (*N*-Boc) and *N*-benzyloxycarbonyl- (*N*-Cbz) protected α-amido sulfones in an organocatalytic asymmetric Mannich-type reaction. The reaction makes use of a simple and easily obtained phase-transfer catalyst and proceeds under very mild and user-friendly conditions. The optimised protocol avoids the preparation and the isolation of the relatively unstable *N*-Boc and *N*-Cbz imines that are generated in situ from the bench-stable α-amido sulfones. The corresponding Mannich bases are generally obtained in good yields and enantioselectivities, and can be readily transformed into key compounds, such as optically active β^3-amino acids in one easy step. Enantioenriched *N*-Boc and *N*-Cbz protected β-amino acids that are suitable for peptide synthesis are also available from the Mannich adducts through simple manipulations. Control experiments showed the dual role of the enolate–catalyst ion pair in this reaction, as well as the crucial role of the presence of water to achieve high enantioselectivities.

Keywords: amido sulfones · amino acids · asymmetric catalysis · Mannich bases · organocatalysis

Introduction

The Mannich reaction, which involves the nucleophilic addition of enolates to the C=N double bond of imines and related compounds, is arguably one of the most direct methods to prepare β-amino carbonyl derivatives.[1] Owing to the strategic importance of these derivatives in an enantioenriched form, tremendous efforts have been made over the past few years towards the development of enantioselective protocols for this transformation, with a special focus on catalytic asymmetric methodologies.[2] Several conceptually different approaches have been devised, each based on a different strategy for the formation/activation of nucleophile and electrophile. The first and simplest approach involves the use of pre-formed enolates, in particular silylenol ethers or silylketene acetals, in combination with chiral Lewis or Brønsted acids for the activation of the imine moiety (indirect Mannich reaction).[3] However, unmodified carbonyl compounds can also be used directly, which avoid prior functionalisation of the nucleophile (direct Mannich reaction).[4] In this context, coordinating appropriate chiral Lewis acid complexes to carbonyl compounds can considerably increase their acidity, thus triggering the enolisation process to form a reactive chiral metal enolate.[5] Another possibility is given by the use of chiral secondary amine catalysts, which are able to combine with aldehydes or ketones to form reactive nucleophilic enamine species that add to the imine in an enantioselective fashion.[6] Also β-dicarbonyl and related compounds (malonates, β-ketoesters, β-diketones etc.) can be conveniently employed as donors in direct Mannich reactions, not only with chiral Lewis or Brønsted acids,[7] but also under very mild basic conditions.[8,9] Even weakly basic chiral tertiary amines or mild inorganic bases in combination with a chiral phase-transfer catalyst[10] are able to promote the enolisation of these relatively acidic compounds, which gives chiral ion pairs that can eventually react enantioselectively with an electrophilic imine.

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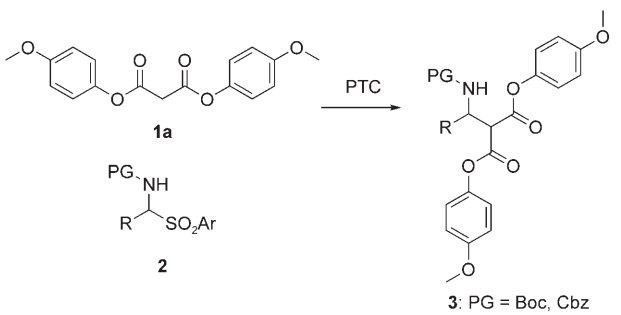
The direct asymmetric Mannich reaction of β-dicarbonyl compounds has been recently intensively investigated, especially with chiral bifunctional catalysts derived from cinchona alkaloids,[8a–h] to give the first examples of asymmetric Mannich reactions of malonates with simple imines, which may be considered one of the simplest approaches to prepare highly valuable β^3-amino acid derivatives.[11] However, the synthetic utility of this transformation depends on the protecting group (PG) on the nitrogen atom of the resulting amine, which should be, in principle, either easily removed after the catalytic reaction or inserted without difficulty into a broader synthetic sequence. *tert*-Butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) protecting groups certainly fulfil these requirements, but the corresponding parent *N*-Boc and Cbz imines are relatively unstable, especially if they are derived from aliphatic enolisable aldehydes.[12] However, by using the corresponding α-amido sulfones (**2**) it is possible to prepare these imines in situ in some cases to avoid their synthesis and isolation, thus circumventing their instability.[13] On these grounds, we[8i] and others[8h] have recently employed α-amido sulfones **2** in catalytic asymmetric Mannich reactions of malonates **1** with *N*-Boc and Cbz imines, thus broadening the scope and the synthetic utility of this asymmetric transformation.[14,15] Our approach involved the use of a phase-transfer catalyst that was easily obtained from quinine in combination with a mild inorganic base, which was able to promote both the formation of the *N*-carbamoyl imine in situ and the asymmetric addition of the enolate derived from tailor-made malonate **1a** that has *p*-methoxyphenyl ester groups (Scheme 1).[8i]

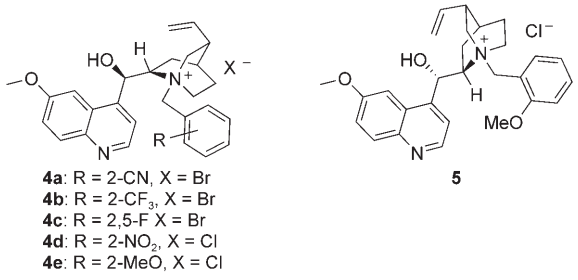


Scheme 1. Catalytic asymmetric Mannich reaction with malonate **1a**. PTC: phase-transfer catalysis.

Although excellent results could be achieved, even with low catalyst loadings, the use of that specific malonate for targeting optically active β^3-amino acid derivatives posed some concerns owing to the requirement for two additional synthetic steps, that is, the preparation of **1a** and a transesterification prior to decarboxylation. Therefore, we thought it would be of interest to continue our investigations into the development of new catalytic systems and/or reaction conditions that are able to accommodate simpler malonates, and possibly different β-dicarbonyl derivatives. Herein we present our efforts towards this goal, uncovering a structurally related catalyst that allows the reaction with commercially available malonates, and more importantly, which gives the opportunity of using β-ketoesters in an asymmetric, catalytic Mannich reaction with α-amido sulfones for the first time. The high synthetic versatility of β-ketoesters, as well as the broad scope connected with the use of α-amido sulfones as imine surrogates, render this reaction a useful platform for the asymmetric synthesis of nitrogen-containing compounds.

Results and Discussion

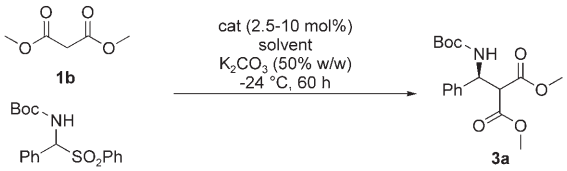
Asymmetric Mannich reactions of malonates: During the development of the asymmetric Mannich reaction of **1a** by using cinchona alkaloid-derived phase-transfer catalysts, we became aware of the requirement of some specific features of the catalyst structure for obtaining satisfactory enantioselectivities in the reaction. In particular, catalysts derived from quinine with a free hydroxy group at the 9-position and an *ortho*-substituted aromatic at the benzylic moiety of the quinuclidinic nitrogen,[16] such as **4a**, afforded consistently better results in terms of activity and enantioselectivity. Based on the assumption that a fine tuning of this structure might also render the catalyst suitable for the reaction with different malonates, we prepared other different quaternary ammonium salts (**4b–e**) that are derived from quinine and have these common structural features.



These catalysts were then tested in the reaction between dimethyl malonate (**1b**) and *N*-Boc α-amido sulfone **2a** as representative substrates, under similar conditions to those that proved to be successful with malonate **1a**, that is, by using a mild, aqueous inorganic base, such as K_2CO_3 (50% w/w), with toluene as the organic phase at −24 °C. Some representative results are collected in Table 1.

An initial experiment with catalyst **4a** strongly indicated the possibility of developing an asymmetric Mannich reaction with **1b** (Table 1, entry 1) because product **3a** was obtained with a moderate conversion and a promising enantioselectivity. Following our working hypothesis, other quaternary ammonium salts **4b–e** were screened in the reaction. Whereas catalysts **4b–d**, which contain electron-withdrawing groups at the *ortho* position of the *N*-benzylic substituent, gave slightly worse or similar results to those obtained with **4a** (Table 1, entries 2–4), catalyst **4e** with a methoxy substituent[17] on the aromatic ring proved to be superior and

Table 1. Representative results from screening different catalysts and reaction conditions for the catalytic asymmetric Mannich reaction between **1b** and **2a**.[a]



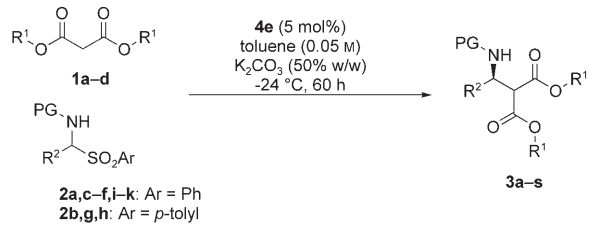
Entry	Catalyst ([mol %])	Solvent	Conversion[b] [%]	*ee*[c] [%]
1	**4a** (10)	toluene	80	81
2	**4b** (10)	toluene	90	79
3	**4c** (10)	toluene	78	70
4	**4d** (10)	toluene	>95	82
5	**4e** (10)	toluene	>95	91
6	**4e** (10)	toluene/CH_2Cl_2 7:1	>95[d]	81
7	**4e** (10)	*o*-xylene	75	85
8	**4e** (10)	mesitylene	65	73
9[e]	**4e** (5)	toluene	>95	90
10	**4e** (2.5)	toluene	>95	83
11	**5** (10)	toluene	>95	45[f]

[a] Reactions carried out with **2a** (0.10 mmol), **1b** (0.12 mmol), catalyst **4**–**5** (2.5–10 mol %) and K_2CO_3 (50 % w/w, 27 μL, 0.15 mmol) in the stated solvent (2 mL) at −24 °C for 60 h. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral stationary phase HPLC. [d] 22 h reaction time. [e] K_2CO_3 (50 % w/w, 6 equiv) were used. [f] *ent*-**3a** was obtained.

resulted in the formation of product **3a** with full conversion and a satisfactory enantioselectivity (Table 1, entry 5). By using this catalyst, different solvents were then tested in an attempt to increase the reaction rate (Table 1, entries 6–8). Only the reaction performed in a mixture of toluene/CH_2Cl_2 gave **3a** with full conversion in a shorter time (Table 1, entry 6), however, the enantioselectivity was considerably lower compared with the reaction in toluene. By using toluene as the organic phase, the catalyst loading could be reduced to 5 mol % without affecting the enantioselectivity, although a further decrease to 2.5 mol % had a negative effect on the enantiomeric excess (*ee*) of the product (Table 1, entries 9 and 10). It was also found that performing the reaction with a larger excess of base (6 equiv) improved the reproducibility of the reaction in terms of conversion without affecting the enantioinduction in the product (Table 1, entry 9). Unfortunately, the use of quasienantiomeric catalyst **5** derived from quinidine gave the corresponding enantiomeric product *ent*-**3a** with reduced enantiopurity (Table 1, entry 11).

Having established an efficient protocol for the enantioselective Mannich reaction of **1b** with **2a**, we investigated the generality of the reaction, first focusing on possible variations on the α-amido sulfone partner (Table 2, entries 1–11). Aside from the reaction with **2a**, which could also be performed with identical results on a preparative scale (Table 2, entry 1), its Cbz-protected counterpart **2b** was found to be a competent substrate for this transformation to give the corresponding product **3b** in a very good yield (97 %) and enantioselectivity (94 % *ee*) (Table 2, entry 2). The tolerance

Table 2. Scope of the catalytic asymmetric Mannich reaction of malonates **1a–d** with α-amido sulfones **2a–k**.[a]



Entry	**1**	R^1	**2**	R^2	PG	Product	Yield[b] [%]	*ee*[c] [%]
1	**1b**	Me	**2a**	Ph	Boc	**3a**	85[d]	90[e]
2	**1b**	Me	**2b**	Ph	Cbz	**3b**	97	94[e]
3	**1b**	Me	**2c**	*o*-BrC_6H_4	Boc	**3c**	98	90
4	**1b**	Me	**2d**	*p*-ClC_6H_4	Boc	**3d**	97	83
5	**1b**	Me	**2e**	*p*-MeO-C_6H_4	Cbz	**3e**	99	94
6	**1b**	Me	**2f**	1-naphthyl	Cbz	**3f**	97	91
7	**1b**	Me	**2g**	$PhCH_2CH_2$	Boc	**3g**	80	78
8	**1b**	Me	**2h**	*i*Bu	Boc	**3h**	78	83
9	**1b**	Me	**2i**	Me	Cbz	**3i**	99	81
10	**1b**	Me	**2j**	*i*Pr	Cbz	**3j**	88	85[f]
11	**1b**	Me	**2k**	cyclohexyl	Cbz	**3k**	90	97
12	**1c**	allyl	**2a**	Ph	Boc	**3l**	97	90
13	**1c**	allyl	**2b**	Ph	Cbz	**3m**	95	92
14	**1c**	allyl	**2k**	cyclohexyl	Cbz	**3n**	84	94
15	**1d**	Bn	**2a**	Ph	Boc	**3o**	96	92[e]
16	**1d**	Bn	**2b**	Ph	Cbz	**3p**	92	93
17	**1d**	Bn	**2h**	*i*Bu	Boc	**3q**	77	91
18[g]	**1a**	*p*-MeO-C_6H_4	**2a**	Ph	Boc	**3r**	90	98[e]
19[g]	**1a**	*p*-MeO-C_6H_4	**2b**	Ph	Cbz	**3s**	96	99[e]

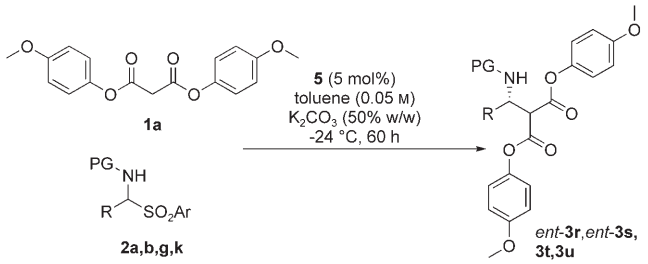
[a] Reactions carried out with **2** (0.10 mmol), **1** (0.12 mmol), catalyst **4e** (5 mol %) and K_2CO_3 (50 % w/w, 108 μL, 0.60 mmol) in toluene (2 mL) at −24 °C for 60 h. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] Reaction performed on a 1.0 mmol scale. [e] Absolute configuration was determined to be *S* (see the Experimental Section). [f] Absolute configuration was found to be *R* (see Experimental Section). [g] K_2CO_3 (1.5 equiv, 50 % w/w) were used.

of the catalytic reaction to these two different protecting groups on the nitrogen atom of the α-amido sulfones is of considerable interest when considering the possibility of obtaining the corresponding *N*-protected β^3-amino acid derivatives (see below). The catalytic asymmetric reaction of **1b** with α-amido sulfones **2c–f**, which were derived from aromatic aldehydes (Table 2, entries 3–6), further demonstrated the possibility of using different substrates and/or protecting groups with the present system. The corresponding products **3c–f** were in fact obtained in very good yields (97–99 %) and enantioselectivities (83–94 % *ee*), irrespective of the electronic and/or steric properties of the substituents at the aromatic ring and the protecting group on the nitrogen atom. Sulfones **2g–k**, which were derived from aliphatic, enolisable aldehydes, were then tested in the catalytic reaction (Table 2, entries 7–11) because a major advantage of the present method is the avoidance of the isolation of the corresponding, somewhat unstable, imines. By using catalyst **4e** under standard reaction conditions, the corresponding products **3g–k** were obtained in good yields (78–99 %) and

enantioselectivities (78–97% *ee*), although in most cases the optical purity of **3g–k** was not as high as for their aromatic counterparts **3a–f**. Exploring the possibility of using other malonates in the catalytic reaction, we focused our attention on diallyl malonate **1c** and dibenzyl malonate **1d** because the Mannich adducts that result from these compounds can be transformed into the corresponding *N*-Boc protected β^3-amino acids without the use of acidic or basic hydrolytic conditions.[8f] Good yields (77–97%) and enantioselectivities (90–94% *ee*) for products **3l–q** were obtained (Table 2, entries 12–17), with results that were comparable to that obtained for **1b**. For the sake of comparison, we also tested **1a** in the catalytic reaction with the newly developed catalyst **4e** (Table 2, entries 18–19). Catalyst **4e** was also found to be superior to our previously employed catalyst **4a**,[8i] to give the corresponding products **3r** and **3s** in very high yields (90 and 96%, respectively) and outstanding enantioselectivities (98 and 99% *ee*, respectively).

As anticipated from the results in Table 1 (entry 11), the present system does not allow the preparation of the opposite enantiomer of the products derived from **1b** with satisfactory levels of enantioselectivity because **5** was found to be a much less efficient catalyst. However, access to the antipodal Mannich adducts can be achieved by using **1a** (Table 3). Exploiting the superior affinity of this malonate

Table 3. Catalytic asymmetric Mannich reaction of **1a** by using catalyst **5** to give enantiomeric products **3**.[a]

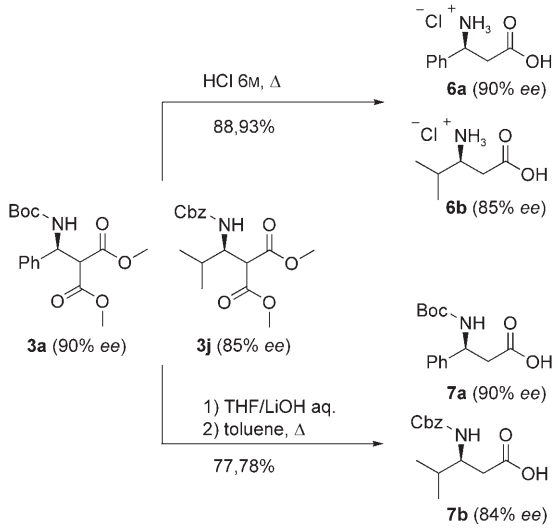


Entry	2	R	PG	Product	Yield[b] [%]	*ee*[c] [%]
1	**2a**	Ph	Boc	*ent*-**3r**	98	93
2	**2b**	Ph	Cbz	*ent*-**3s**	95	99
3	**2g**	$PhCH_2CH_2$	Boc	**3t**	88	77
4	**2k**	Cyclohexyl	Cbz	**3u**	89	93

[a] Reactions carried out using **2** (0.10 mmol), **1a** (0.12 mmol), catalyst **5** (5 mol%) and K_2CO_3 (50% w/w, 27 μL, 0.15 mmol) in toluene (2 mL) at −24 °C for 60 h. [b] Yield of isolated product. [c] Determined by chiral stationary phase HPLC.

for this class of catalysts, it was indeed possible to prepare some representative products with the opposite absolute configuration with good results, in terms of both yields (88–98%, Table 3) and enantioselectivities (77–99% *ee*). As we have previously demonstrated the possibility of transforming these types of adducts into the corresponding dimethyl ester derivatives,[8i] also the opposite enantiomer of the Mannich adducts derived from **1b** are available by using the present method, although an additional transesterification step is required.

β-Amino acids and their derivatives are key compounds in organic and pharmaceutical chemistry. Aside from being present in a variety of natural products, they are finding increasing use as pharmaceutically active agents, often incorporated into peptides and β-peptides, because of the promise shown by β-peptides as biostable peptidomimetics.[11] The asymmetric Mannich reaction of malonates is conceivably a very direct route to prepare optically active β^3-amino acids. In particular, our approach, which involves the use of simple malonates and easily removed protecting groups on the nitrogen atom, allows the straightforward transformation of either *N*-Boc or *N*-Cbz protected Mannich adducts into the corresponding β^3-amino acid hydrochlorides (Scheme 2,



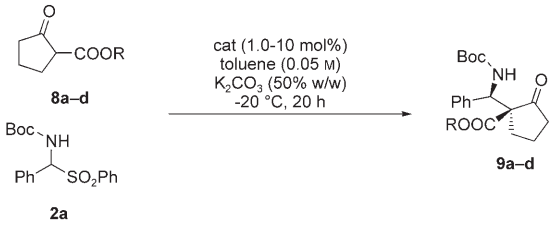
Scheme 2. Preparation of unprotected and protected β^3-amino acids **6** and **7** from Mannich adducts **3a** and **3j**.

top). For example, treatment of **3a** and **3j** with 6 M aqueous HCl for several hours resulted in malonate hydrolysis, decarboxylation and nitrogen deprotection in a single step, which cleanly gave the corresponding β^3-amino acid hydrochlorides **6a** and **6b** (Scheme 2, top) irrespective of the nature of the side chain and the nitrogen protecting group.[18] Mild basic hydrolysis followed by thermal decarboxylation instead afforded the analogous *N*-protected β^3-amino acids **7a** and **7b** (Scheme 2, bottom), thus showing the possibility of obtaining both β-aryl and β-alkyl amino acids with orthogonal carbamate protecting groups that are suitable for peptide synthesis.[8e]

Asymmetric Mannich reactions of β-ketoesters: We then proceeded to evaluate the possibility of extending the catalytic asymmetric Mannich reaction of **2** to a different class of β-dicarbonyl compounds, namely, β-ketoesters **8**. The catalytic asymmetric Mannich reaction of these compounds has received a great deal of attention in recent times owing to their obvious synthetic utility as masked ketone donors.[7a,-c,8a–f] However, to the best of our knowledge catalytic asymmetric versions of the Mannich reaction of β-ketoesters by

using α-amido sulfones are still unexplored. We therefore thought to develop an efficient protocol for this transformation based on our approach. In the search for suitable parameters to enable an enantioselective transformation, we began our investigations by performing the catalytic reaction of β-ketoesters **8a–d** derived from cyclopentanone with **2a** by using catalysts **4**. In the first instance, we attempted the reaction by using conditions similar to the corresponding transformation with malonates **1**. As shown in Table 4, initial experiments with **8a** indicated that an enantioselective

Table 4. Representative results from screening different catalysts and reaction conditions for the catalytic asymmetric Mannich reaction between β-ketoesters **8a–d** and α-amido sulfone **2a**.[a]



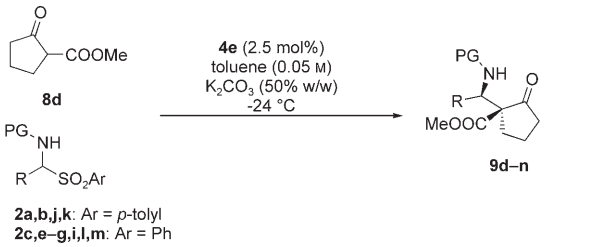
Entry	8	R	Catalyst ([mol%])	Product	Conversion[b] [%]	d.r.[c]	*ee* [%][d]
1	**8a**	Et	**4a** (10)	**9a**	>90	98:2	80
2	**8a**	Et	**4b** (10)	**9a**	>90	98:2	83
3	**8a**	Et	**4d** (10)	**9a**	>90	98:2	84
4	**8a**	Et	**4e** (10)	**9a**	>90	98:2	88
5	**8b**	Bn	**4e** (10)	**9b**	>90	87:13	87
6	**8c**	*t*Bu	**4e** (10)	**9c**	77	95:5[e]	71[e]
7	**8d**	Me	**4e** (10)	**9d**	>90	>98:2	93
8	**8d**	Me	**4e** (2.5)	**9d**	>90	>98:2	91
9	**8d**	Me	**4e** (1.0)	**9d**	>90	97:3	88
10	**8d**	Me	**5** (2.5)	*ent*-**9d**	>90	98:2	54

[a] Reactions carried out with **2a** (0.10 mmol), **8** (0.12 mmol), catalyst **4** (1.0–10 mol%) and K_2CO_3 (50% w/w, 27 μL, 0.15 mmol) in toluene (2 mL) at −20°C for 20 to 29 h. [b] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c] Diastereomeric ratio, determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [d] Major isomer, *ee* value determined by chiral stationary phase HPLC. [e] Relative and absolute configuration determined by comparison of the ^{1}H NMR spectrum and HPLC retention times with literature values. See ref.[7c]

reaction with β-ketoesters **8** could be developed under these conditions because the corresponding product **9a** was obtained with excellent diastereoselectivity and with promising levels of enantioselectivity (Table 4, entries 1–4). Also in this case, catalyst **4e**, which has an *ortho*-methoxy substituent at the benzyl moiety of the quinuclidinic nitrogen, was found to be more effective (Table 4, entry 4) than the other *ortho*-substituted catalysts tested (**4a–d**, Table 4, entries 1–3). A brief inspection of the influence of the steric hindrance of the ester group revealed that an increase in the bulkiness of this moiety by using benzyl (**8b**) or *tert*-butyl β-ketoesters (**8c**) was detrimental to the enantioselectivity of the products (Table 4, entries 5–6), whereas the least bulky methyl β-ketoester (**8d**) gave the best results (Table 4, entry 7). By using **8d** under these conditions, the catalyst loading could be decreased to 2.5 mol% with only marginal effects on the optical purity of the product **9d** (Table 4, entry 8), although a further reduction to 1 mol% gave a more significant decrease in the enantioselectivity observed (Table 4, entry 9). Unfortunately, catalyst **5** was found to be much less efficient also for this reaction in terms of enantioinduction (Table 4, entry 10).

We then explored the possibility of using different α-amido sulfones with **8d** under the optimised reaction conditions. As shown in Table 5, sulfone **2b**, which is the *N*-Cbz

Table 5. Scope of the catalytic asymmetric Mannich reaction of β-ketoesters **8** with α-amido sulfones **2** determined by varying of the α-amido sulfone partner.[a]



Entry	2	R	PG	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**2a**	Ph	Boc	**9d**	98	>98:2	95
2	**2b**	Ph	Cbz	**9e**	90	>98:2	92
3	**2c**	*o*-BrC_6H_4	Boc	**9f**	60	94:6	69
4	**2l**	*o*-BrC_6H_4	Cbz	**9g**	85	96:4	77
5	**2m**	*p*-ClC_6H_4	Cbz	**9h**	98	96:4	73
6	**2e**	*p*-$MeOC_6H_4$	Cbz	**9i**	70	95:5	77
7	**2f**	1-naphthyl	Cbz	**9j**	50	90:10	85
8	**2g**	$PhCH_2CH_2$	Boc	**9k**	55	97:3	90
9	**2i**	Me	Cbz	**9l**	70	97:3	75
10	**2j**	*i*Pr	Cbz	**9m**	74	96:4	74
11	**2k**	Cyclohexyl	Cbz	**9n**	77	>98:2	99

[a] Reactions carried out with **2** (0.12 mmol), **8d** (0.10 mmol), catalyst **4e** (2.5 mol%), in toluene (2 mL) with K_2CO_3 (50% w/w, 27 μL, 0.15 mmol) at −24°C for 21 to 84 h. [b] Isolated yield of the diastereomeric mixture. [c] Diastereomeric ratio, determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [d] Major isomer, *ee* value determined by chiral stationary phase HPLC.

analogoue of **2a**, also gave the corresponding product **9e** with an excellent yield and excellent diastereo- and enantioselectivities (Table 5, entries 1 and 2, 98 and 90% yield, and 95 and 92% *ee*, respectively). Having shown the tolerance of the reaction to both Boc and Cbz protecting groups, other aromatic and aliphatic α-amido sulfones **2** were subsequently tested in the catalytic reaction with β-ketoester **8d** (Table 5, entries 3–11). Mannich adducts **9f–n** were obtained in moderate to good yields (50–98%), generally good diastereomeric ratios, but variable enantiopurities (69–99% *ee*). Compared to the model reaction with **2a** and **2b** the enantioselectivities observed for these products were generally lower; however, the possibility of reaching excellent levels of enantiopurity in some cases (Table 5, entries 8 and 11) must be recognised.

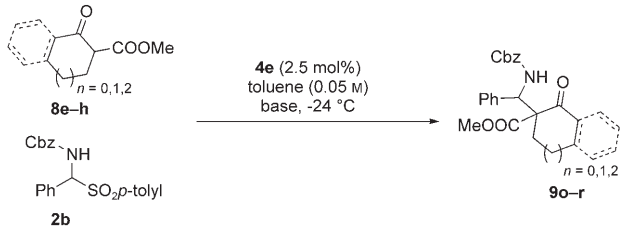
Finally, we investigated the behaviour of some other different cyclic β-ketoesters in the reaction with **2b**. A practical

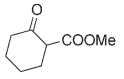
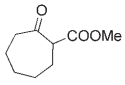
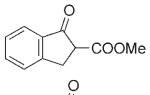
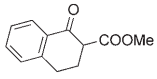
asset of the present method is the use of methyl β-ketoesters as donors. The synthesis of these compounds is straightforward, especially those that are cyclic and ring fused, if compared with other β-ketoesters that have more bulky ester groups, such as *tert*-butyl, which are often used in catalytic asymmetric transformations.[19] Accordingly, cyclic β-ketoesters **8e–h** with different ring sizes and/or ring fused were readily synthesised and tested in the reaction (Table 6). In accordance with previous reports,[17a,19,20] the different reactivity of these compounds reflected in the necessity for tuning the strength of the inorganic base and/or reaction temperature employed in the catalytic reaction. For example, cyclohexanone- and cycloheptanone-derived β-ketoesters **8e** and **8f** did not give the expected Mannich adducts under the conditions used with the more reactive cyclopentanone derivative **8d** (K_2CO_3 50% w/w, −24°C). However, by using a stronger base (K_3PO_4 50% w/w) it was possible to obtain the corresponding products **9o** and **9p** in satisfactory yields (77 and 96%, respectively) and enantioselectivities (91 and 95% *ee*, respectively) (Table 6, entries 1 and 2). Instead ring-fused β-ketoesters **8g** and **8h** proved to be more reactive since the reactions performed with aqueous K_2CO_3 as the base gave Mannich products **9q** and **9r** with good results (Table 6, entries 3 and 4, 95 and 96% yield, and 87 and 92% *ee*, respectively). In the former case, a less concentrated K_2CO_3 solution (30% w/w instead of 50% w/w) resulted in a slight improvement of the enantioselectivity of product **9q**, presumably owing to a background reaction, although the low diastereomeric ratio was unchanged. Non-cyclic β-ketoesters were also tested in the reaction, but unsurprisingly,[17a,19,20] gave the corresponding products with low enantioselectivity with the present catalytic system.

Mechanistic considerations: A few ancillary experiments were then carried out with **1b** to get some insights into the possible reaction pathways. These can be summarised as follows: 1) under the standard reaction conditions, but in the absence of either malonate **1b** or catalyst **4e**, formation of the imine from **2a** proceeded only sluggishly (<60% after 84 h); 2) a reaction with the pre-formed *N*-Boc imine derived from **2a** gave very similar results, both in terms of yield and enantioselectivity, to the reaction performed with **2a**; 3) a sterically demanding α-amido sulfone derived from pivalaldehyde did not produce the expected Mannich product in the reaction, presumably for steric reasons, although it did provide substantial amounts of the corresponding imine. On these grounds we propose the following catalytic cycle (Scheme 3), wherein the malonate, which is deprotonated by the inorganic base at the interface, combines with the quaternary ammonium salt to give an organic soluble anion that acts first as a base to promote the formation of the imine from the α-amido sulfone. The sulfinate formed can be dissolved in the aqueous phase, whereas the malonate can be deprotonated again to give a chiral ion pair with the catalyst, which adds in an enantioselective fashion to the formed imine. An anionic carbamate adduct is then formed with the catalyst as the counterion. This highly basic species presumably deprotonates the most acidic compound in the reaction mixture, that is, another molecule of malonate, thus restoring the catalytic cycle.[21]

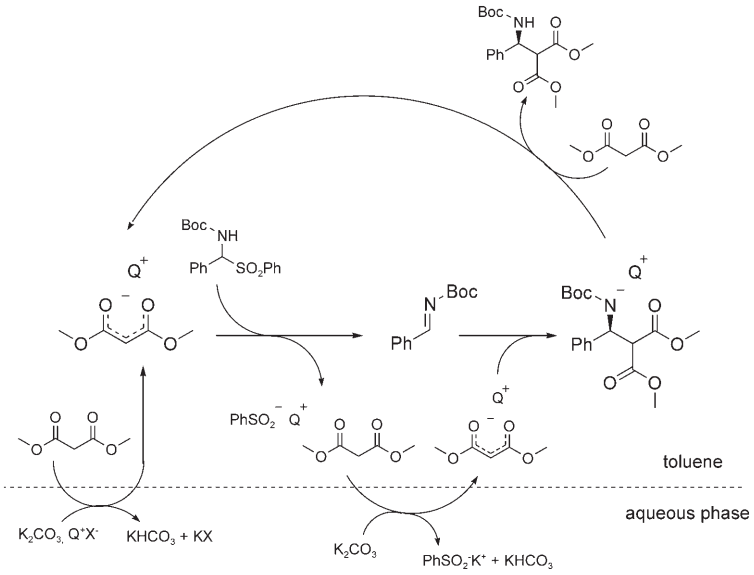
The absolute configuration of adducts **3** and **9** has been determined for some derivatives by comparison of their optical and/or HPLC properties with literature values (see Tables 2 and 4). The simple diastereoselectivity observed in the asymmetric Mannich reaction of β-ketoesters **8** can be explained by an open transition state,[7c] whereas the absolute configuration of the adducts results from attack of the ion pair catalyst–enolate on the *Re* face of the intermediate imine in all cases when quinine-derived catalysts **4** were used. Previous reports based on X-ray structures of this class of catalysts showed the importance of the presence of a molecule of water in rigidifying the structure of these am-

Table 6. Scope of the catalytic asymmetric Mannich reaction of β-ketoesters **8** with α-amido sulfones **2**: variation of the β-ketoester partner.[a]



Entry	β-Ketoester	8	Base	Product	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1[e]		**8e**	K_3PO_4[f]	**9o**	77[g]	85:15	91
2		**8f**	K_3PO_4[f]	**9p**	96[g]	96:4	95
3		**8g**	K_2CO_3[h]	**9q**	95	58:42	87[i]
4		**8h**	K_2CO_3[f]	**9r**	96	80:20	92

[a] Reactions carried out with **2b** (0.12 mmol), **8** (0.10 mmol), catalyst **4e** (2.5 mol%) and the stated base (1.5–5 equiv) in toluene (2 mL) at −24°C for 24 to 71 h. [b] Isolated yield of the diastereomeric mixture. [c] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [d] Major isomer, *ee* value determined by chiral stationary phase HPLC. [e] Reaction performed at 0°C with catalyst **4e** (10 mol%). [f] 50% w/w. [g] Isolated yield of the enriched major diastereoisomer. [h] 30% w/w. [i] Minor diastereoisomer 85% *ee*, determined by chiral stationary phase HPLC.



Scheme 3. Proposed reaction pathway. ($Q^+X^- = \mathbf{4e}$).

monium salts.[16] This conformational control, which occurs through hydrogen-bond interactions between the oxygen atom at the 9-position of the cinchona scaffold, a molecule of water and the *ortho* group of the quinuclidinic benzyl substituent, was found to be essential in attaining optimal enantioselectivities in the alkylation of the benzophenone imine derived from *tert*-butyl glycine ester. Accordingly, we tested the catalytic reaction between **1b** and **2a** with catalyst **4e** under anhydrous conditions with dry K_2CO_3 as the base. Aside from lowering the conversion, presumably owing to a less efficient interfacial exchange of the enolate anion, we also observed a dramatic decrease in the enantioselectivity of product **3a**, which was obtained with an *ee* value of 27%, instead of 90% when aqueous K_2CO_3 was employed. This result suggests that the presence of water is also a requirement, in our case, for obtaining high enantioselectivities by using this class of catalysts. The higher efficiency of catalyst **4e**, which has a methoxy moiety at the *ortho* position, with respect to the other catalysts **4** may, therefore, be attributed to a more efficient contribution to this hydrogen-bond interaction, thus giving a better conformational control that results in a better recognition of the *Re* face of the imine by the chiral ion pair.

Conclusion

We have developed a new catalytic system that allows the asymmetric Mannich reaction of different malonates and β-ketoesters with *N*-Boc and *N*-Cbz protected α-amido sulfones. The reaction makes use of a simple phase-transfer catalyst that is easily obtained from quinine in a single step. The Mannich adducts are generally obtained in good yields and diastereo- and enantioselectivities. The synthetic relevance of the present asymmetric transformation is shown by the straightforward conversion of the catalytic adducts into *N*-Boc and *N*-Cbz β^3-amino acids that are suitable for peptide synthesis. Unprotected β^3-amino acids can also be readily obtained in a single step by acidic hydrolysis. Mild, user-friendly reaction conditions and avoiding the need for isolating the *N*-Boc and *N*-Cbz imines are good assets for this organocatalytic asymmetric Mannich reaction. As demonstrated by control experiments, the catalyst–enolate ion pair first acts as a base to promote the elimination of sulfinic acid and then it adds to the imine that is formed in an enantioselective fashion. The presence of water in the reaction was also found to be essential for obtaining high enantioselectivities, presumably by influencing the conformational rigidity of the catalyst through hydrogen-bond interactions.

Experimental Section

General methods: ^{1}H and ^{13}C NMR spectra were recorded by using a Varian AS 400 spectrometer running at 400 and 100 MHz, respectively. Chemical shifts are reported relative to residual solvent peaks (^{1}H NMR: 7.26 ppm for $CDCl_3$, 3.31 ppm for CD_3OD, 4.79 ppm for D_2O; ^{13}C NMR: 77.0 ppm for $CDCl_3$, 48.0 ppm for CD_3OD, sodium 3-(trimethylsilyl)-propionate external reference, 0.0 ppm for D_2O). ^{13}C NMR were recorded by using a broad band decoupled mode. Mass spectra were recorded by using a Micromass LCT spectrometer with electrospray (ES) ionisation techniques. Optical rotations were measured by using a Perkin–Elmer 241 polarimeter. The *ee* value of the products was determined by chiral stationary phase HPLC equipped with a UV detector operating at $\lambda =$ 215 or 254 nm. Melting points were measured on a Büchi smp-20 apparatus and are uncorrected. Chromatographic purifications were performed by using 70–230 mesh silica.

Materials: All commercially available solvents and reagents were used as received. Malonate **1a**,[8i] α-amido sulfones **2a**–**m**,[22] and β-ketoesters **8b**, **8c**, **8g**, and **8h**[23] were obtained by following literature procedures. Racemic samples were obtained at room temperature by using tetrabutylammonium bromide as the catalyst.

Preparation of *N*-(2-methoxybenzyl)-quininium chloride (4e): Quinine (648 mg, 2.0 mmol) was added to a solution of *o*-methoxybenzyl chloride (360 μL, 2.6 mmol) in toluene (6 mL). The resulting mixture was heated to 80 °C with stirring. After 5 h the reaction mixture was allowed to cool to room temperature and evaporated in vacuo. The residue was purified by column chromatography (CH_2Cl_2/MeOH mixtures) to give **4e** as a pale red solid (63%). M.p. >120 °C (dec); $[\alpha]_D^{20} = -166$ ($c = 0.31$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.76$ (d, $J = 4.7$ Hz, 1H), 8.07–7.99 (m, 2H), 7.79 (d, $J = 4.5$ Hz, 1H), 7.51–7.44 (m, 2H), 7.37 (dd, $J =$ 9.5, 2.8 Hz, 1H), 7.16 (d, $J = 2.8$ Hz, 1H), 7.09 (dt, $J = 7.3$, $J = 1.2$ Hz, 1H), 6.98 (d, $J = 7.7$ Hz, 1H), 6.70 (br s, 1H), 6.23 (d, $J = 11.7$ Hz, 1H), 5.63–5.49 (m, 1H), 5.25–5.12 (m, 1H), 5.08–4.93 (m, 2H), 4.67 (d, $J =$ 11.9 Hz, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.64 (dd, $J = 10.2$–6.3 Hz, 1H), 3.31–3.12 (m, 2H), 3.04 (ddd, $J = 13.1$, 6.5, 3.0 Hz, 1H), 2.60–2.48 (m, 1H), 2.48–2.25 (m, 2H), 2.05–1.98 (m, 1H), 1.82–1.69 (m, 1H), 1.52–

1.38 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 158.0, 147.8, 144.2, 143.6, 136.7, 136.1, 132.6, 132.3, 125.6, 121.9, 121.6, 120.4, 117.7, 115.3, 111.1, 100.4, 71.1, 63.3, 60.6, 58.7, 55.7, 55.6, 50.8, 38.1, 26.4, 24.8, 21.2 ppm; ESIMS: *m/z*: 445 [M^+].

General procedure for the catalytic reaction of 1 with α-amido sulfone 2: Malonate **1** (0.12 mmol) was added to a test tube that contained a mixture of α-amido sulfone **2** (0.10 mmol) and catalyst **4e** (2.3 mg, 0.005 mmol) in toluene (2 mL). After the resulting mixture had been cooled to −24 °C, a pre-cooled aqueous K_2CO_3 solution (50 % w/w, 108 μL, 0.60 mmol) was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After 60 h, the reaction product was directly isolated by column chromatography on silica gel.

*2-(*S-tert-*Butoxycarbonylaminophenylmethyl)malonic acid dimethyl ester (**3a**)*: Following the general procedure and by performing the reaction on a 1.0 mmol scale, **3a** was obtained as a white solid in a yield of 85 % after column chromatography on silica gel (petroleum ether/Et_2O mixtures). The *ee* value of the product was determined by HPLC by using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 15.9 min; t_{minor} = 20.2 min; 90 % *ee*). M.p. 102–103 °C; $[\alpha]_D^{20}$ = +15 (*c* = 1.10 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5H), 6.14 (brs, 1H), 5.49 (brs, 1H), 3.92 (brs, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 1.42 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 167.5, 155.1, 139.4, 128.6, 127.6, 126.2, 79.8, 56.7, 53.4, 52.8, 52.5, 28.3 ppm; ESIMS: *m/z*: 360 [M^++Na]. The absolute configuration of **3a** was assigned as the *S* isomer by comparison of its optical rotation with a literature value (lit.:[8e] $[\alpha]_D^{25}$ = +17 (*c* = 1.14 in $CHCl_3$), for the *S* isomer 89 % *ee*).

*2-(*S-*Benzyloxycarbonylaminophenylmethyl)malonic acid dimethyl ester (**3b**)*: Following the general procedure, compound **3b** was obtained as a white waxy solid in a yield of 97 % after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 50.7 min; t_{minor} = 73.5 min; 94 % *ee*). $[\alpha]_D^{20}$ = +11 (*c* = 0.97 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.24 (m, 10H), 6.46 (brd, *J* = 8.5 Hz, 1H), 5.56 (dd, *J* = 9.1, 4.4 Hz, 1H), 5.10 (d, *J* = 12.6 Hz, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 3.95 (brd, *J* = 3.4 Hz, 1H), 3.70 (s, 3H), 3.63 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 167.3, 155.7, 139.0, 136.4, 128.7, 128.4, 128.1, 127.8, 126.2, 66.9, 56.5, 53.9, 52.9, 52.6 ppm; ESIMS: *m/z*: 394 [M^++Na]. The absolute configuration of **3b** was assigned as the *S* isomer by comparison of its optical rotation with a literature value (lit.:[8e] $[\alpha]_D^{25}$ = +9 (*c* = 1.0 in $CHCl_3$), for the *S* isomer, 92 % *ee*).

*2-[*S-*(2-Bromo-phenyl)-*tert-*butoxycarbonylaminomethyl]malonic acid dimethyl ester (**3c**)*: Following the general procedure, compound **3c** was obtained as a colourless thick oil in a yield of 98 % after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 8.9 min; t_{minor} = 10.9 min; 90 % *ee*). $[\alpha]_D^{20}$ = +37 (*c* = 0.80 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.37 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.28 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.13 (dt, *J* = 7.8, 1.7 Hz, 1H), 6.52 (brd, *J* = 9.2 Hz, 1H), 5.76 (brdd, *J* = 8.8, 2.8 Hz, 1H), 4.16 (brd, *J* = 3.0 Hz, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 1.41 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 167.5, 154.9, 138.1, 133.1, 129.3, 128.2, 127.5, 122.6, 79.9, 53.7, 53.3, 52.9, 52.4, 28.2 ppm; ESIMS: *m/z*: 438 [M^++Na].

*2-[*S-tert-*Butoxycarbonylamino(4-chloro-phenyl)methyl]malonic acid dimethyl ester (**3d**)*: Following the general procedure, compound **3d** was obtained as a white solid in a yield of 97 % after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 21.8 min; t_{minor} = 18.0 min; 83 % *ee*). M.p. 94–96 °C; $[\alpha]_D^{20}$ = +10 (*c* = 0.97 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.22 (m, 4H), 6.13 (brs, 1H), 5.44 (brs, 1H), 3.87 (brd, *J* = 3.4 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 1.40 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 167.3, 154.9, 138.0, 133.5, 128.7, 127.6, 80.0, 56.4, 52.9, 52.6, 28.2 ppm; ESIMS: *m/z*: 394 [M^++Na].

*2-[*S-*Benzyloxyamino(4-methoxyphenyl)methyl]malonic acid dimethyl ester (**3e**)*: Following the general procedure, compound **3e** was obtained as white solid in a yield of 99 % after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 76.5 min; t_{minor} = 63.9 min; 94 % *ee*). M.p. 108–110 °C; $[\alpha]_D^{20}$ = +1 (*c* = 0.95 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5H), 7.24–7.19 (m, 2H), 6.87–6.83 (m, 2H), 6.38 (brd, *J* = 8.3 Hz, 1H), 5.49 (brdd, *J* = 9.4, 4.9 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 5.08 (d, *J* = 12.5 Hz, 1H), 3.90 (brd, *J* = 4.1 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.65 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 167.3, 159.0, 155.6, 136.4, 131.1, 128.4, 128.0, 127.4, 114.0, 66.8, 56.6, 55.2, 53.5, 52.7, 52.5 ppm; ESIMS: *m/z*: 424 [M^++Na].

*2-(*S-*Benzyloxycarbonylaminonaphthalen-1-ylmethyl)malonic acid dimethyl ester (**3f**)*: Following the general procedure, compound **3f** was obtained as a waxy white solid in a yield of 97 % after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 30.2 min; t_{minor} = 38.3 min; 91 % *ee*). $[\alpha]_D^{20}$ = +38 (*c* = 0.80 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 6.4 Hz, 1H), 7.56–7.46 (m, 2H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.39–7.27 (m, 5H), 6.88 (brd, *J* = 10.0 Hz, 1H), 6.38 (brdd, *J* = 9.4, 3.9 Hz, 1H), 5.15 (brd, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 4.13 (brd, *J* = 3.3 Hz, 1H), 3.78 (s, 3H), 3.55 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 167.6, 155.6, 136.4, 134.4, 133.8, 129.9, 129.2, 128.7, 128.5, 128.0, 126.9, 125.8, 125.2, 123.6, 122.1, 66.9, 55.2, 53.1, 52.4, 50.7 ppm; ESIMS: *m/z*: 444 [M^++Na].

*2-(*R-*1-*tert-*Butoxycarbonylamino-3-phenylpropyl)malonic acid dimethyl ester (**3g**)*: Following the general procedure, compound **3g** was obtained as a colourless oil in a yield of 80 % after column chromatography on silica gel (petroleum ether/Et_2O mixtures). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AS column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 29.3 min; t_{minor} = 35.3 min; 78 % *ee*). $[\alpha]_D^{20}$ = +31 (*c* = 0.70 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.24 (m, 2H), 7.21–7.15 (m, 3H), 5.39 (brd, *J* = 10.4 Hz, 1H), 4.34–4.24 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.62 (brd, *J* = 4.2 Hz, 1H), 2.80–2.70 (m, 1H), 2.68–2.58 (m, 1H), 1.98–1.85 (m, 1H), 1.85–1.74 (m, 1H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 168.2, 155.4, 141.2, 128.4, 128.3, 126.0, 79.4, 55.1, 52.6, 52.4, 50.1, 35.5, 32.7, 28.3 ppm; ESIMS: *m/z*: 388 [M^++Na].

*2-(*R-*1-*tert-*Butoxycarbonylamino-3-methylbutyl)malonic acid dimethyl ester (**3h**)*: Following the general procedure, compound **3h** was obtained as a colourless oil in a yield of 78 % after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 98:2, flow rate 0.75 mL min^{-1}, t_{major} = 26.3 min; t_{minor} = 30.7 min; 83 % *ee*). $[\alpha]_D^{20}$ = +44 (*c* = 0.80 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.26 (brd, *J* = 10.2 Hz, 1H), 4.37–4.24 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.59 (brd, *J* = 4.4 Hz, 1H), 1.64–1.44 (m, 1H), 1.41 (s, 9H), 1.32–1.18 (m, 2H), 0.91 (d, *J* = 4.2 Hz, 3H), 0.89 ppm (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 168.4, 155.3, 79.3, 55.2, 52.6, 52.4, 48.5, 42.7, 28.3, 25.0, 23.0, 21.9 ppm; ESIMS: *m/z*: 340 [M^++Na].

*2-(*R-*1-Benzyloxycarbonylaminoethyl)malonic acid dimethyl ester (**3i**)*: Following the general procedure, compound **3i** was obtained as a colourless oil in a yield of 99 % after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 18.2 min; t_{minor} = 15.9 min; 81 % *ee*). $[\alpha]_D^{20}$ = +29 (*c* = 0.97 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5H), 5.61 (brd, *J* = 8.7 Hz, 1H), 5.08 (brs, 2H), 4.49–4.37 (m, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.62 (brd, *J* = 4.1 Hz, 1H), 1.28 ppm (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 167.9, 155.5, 136.4, 128.4, 128.0, 127.9, 66.6, 55.6, 52.6, 52.5, 46.5, 19.0 ppm; ESIMS: *m/z*: 332 [M^++Na].

*2-(*R-*1-Benzyloxycarbonylamino-2-methylpropyl)malonic acid dimethyl ester (**3j**)*: Following the general procedure, compound **3j** was obtained as a colourless oil in a yield of 88 % after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by

HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 22.7 min; t_{minor} = 10.6 min; 85% *ee*). $[\alpha]_D^{20}$ = +56 (c = 0.97 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5H), 5.75 (br d, J = 9.8 Hz, 1H), 5.11 (d, J = 12.3 Hz, 1H), 5.06 (d, J = 12.3 Hz, 1H), 4.09–4.01 (m, 1H), 3.74 (s, 3H), 3.72 (br d, J = 4.1 Hz, 1H), 3.63 (s, 3H), 1.83–1.68 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.91 ppm (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 168.4, 156.2, 136.7, 128.4, 127.9, 66.6, 56.6, 52.8, 52.5, 52.4, 31.9, 19.8, 19.2 ppm; ESIMS: m/z: 360 [M^++Na]. The absolute configuration of **3j** was assigned as (*R*) after the transformation in the corresponding *N*-Cbz protected acid **7b** (see below).

*2-(*R*-1-Benzyloxycarbonylaminocyclohexylmethyl)malonic acid dimethyl ester (**3k**)*: Following the general procedure, compound **3k** was obtained as a colourless oil in a yield of 90% after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 20.6 min; t_{minor} = 16.3 min; 97% *ee*). $[\alpha]_D^{20}$ = +50 (c = 1.03 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5H), 5.76 (br d, J = 10.7 Hz, 1H), 5.10 (d, J = 12.1 Hz, 1H), 5.04 (d, J = 12.1 Hz, 1H), 4.08 (dt, J = 9.8, 4.0 Hz, 1H), 3.76 (d, J = 4.1 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 1.88–1.56 (m, 5H), 1.47–1.35 (m, 1H), 1.22–0.95 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 168.6, 156.2, 136.7, 128.3, 127.9, 66.6, 55.7, 52.6, 52.5, 52.3, 40.9, 30.1, 29.5, 26.0, 25.8, 25.7 ppm; ESIMS: m/z: 400 [M^++Na].

*2-(*S-tert-*Butoxycarbonylaminophenylmethyl)malonic acid diallyl ester (**3l**)*: Following the general procedure, compound **3l** was obtained as a white solid in a yield of 97% after column chromatography on silica gel (petroleum ether/Et_2O mixtures). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 19.0 min; t_{minor} = 14.8 min; 90% *ee*). M.p. 77–79 °C; $[\alpha]_D^{20}$ = +10 (c = 1.17 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 5H), 6.17 (br s, 1H), 5.94–5.82 (m, 1H), 5.79–5.68 (m, 1H), 5.52 (br s, 1H), 5.31 (dq, J = 17.1, 1.3 Hz, 1H), 5.24 (dq, J = 10.4, 1.1 Hz, 1H), 5.20–5.11 (m, 2H), 4.69–4.59 (m, 2H), 4.58–4.47 (m, 2H), 3.97 (br s, 1H), 1.41 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 166.7, 155.0, 139.4, 131.2, 131.1, 128.5, 127.6, 126.2, 118.9, 118.7, 79.7, 66.4, 66.1, 56.8, 53.4, 28.2 ppm; ESIMS: m/z: 412 [M^++Na].

*2-(*S-*Benzyloxycarbonylaminophenylmethyl)malonic acid diallyl ester (**3m**)*: Following the general procedure, compound **3m** was obtained as a white solid in a yield of 95% after column chromatography on silica gel (petroleum ether/Et_2O mixtures). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 70:30, flow rate 0.50 mL min^{-1}, t_{major} = 41.9 min; t_{minor} = 40.0 min; 92% *ee*). M.p. 88–89 °C; $[\alpha]_D^{20}$ = +8 (c = 0.92 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 10H), 6.47 (br d, J = 9.5 Hz, 1H), 5.89–5.79 (m, 1H), 5.78–5.67 (m, 1H), 5.59 (br dd, J = 9.0, 5.0 Hz, 1H), 5.29 (dq, J = 17.2, 1.4 Hz, 1H), 5.21 (dq, J = 10.4, 1.3 Hz, 1H), 5.18–5.15 (m, 1H), 5.15–5.12 (m, 1H), 5.12–5.05 (m, 2H), 4.62–4.58 (m, 2H), 4.58–4.48 (m, 2H), 3.99 ppm (br d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 166.5, 155.6, 138.9, 136.4, 131.2, 131.0, 128.6, 128.4, 128.1, 127.8, 126.2, 119.1, 118.8, 66.9, 66.5, 66.2, 56.7, 53.9 ppm; ESIMS: m/z: 446 [M^++Na].

*2-(*R*-Benzyloxycarbonylaminocyclohexylmethyl)malonic acid diallyl ester (**3n**)*: Following the general procedure, compound **3n** was obtained as colourless oil in a yield of 84% after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 15.4 min; t_{minor} = 10.4 min; 94% *ee*). $[\alpha]_D^{20}$ = +37 (c = 0.83 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5H), 5.95–5.75 (m, 3H), 5.34 (dq, J = 17.1, 1.2 Hz, 1H), 5.28 (dq, J = 9.2, 1.2 Hz, 1H), 5.26–5.24 (m, 1H), 5.19 (dq, J = 10.4, 1.0 Hz, 1H), 5.09 (d, J = 12.6 Hz, 1H), 5.05 (d, J = 12.6 Hz, 1H), 4.68–4.63 (m, 2H), 4.57–4.47 (m, 2H), 4.12 (dt, J = 9.7, 3.7 Hz, 1H), 3.80 (d, J = 3.7 Hz, 1H), 1.89–1.54 (m, 5H), 1.48–1.36 (m, 1H), 1.22–0.92 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 167.7, 156.1, 136.7, 131.4, 131.3, 128.4, 127.9, 119.0, 118.9, 66.6, 66.4, 66.0, 55.7, 52.5, 41.1, 30.1, 29.5, 25.9, 25.8, 25.7 ppm; ESIMS: m/z: 452 [M^++Na].

*2-(*S-tert-*Butoxycarbonylaminophenylmethyl)malonic acid dibenzyl ester (**3o**)*: Following the general procedure, compound **3o** was obtained as a white solid in a yield of 96% after column chromatography on silica gel (petroleum ether/Et_2O mixtures). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AS column (hexane/*i*PrOH = 98:2, flow rate 1.5 mL min^{-1}, t_{major} = 12.6 min; t_{minor} = 10.8 min; 92% *ee*). M.p. 56–57 °C; $[\alpha]_D^{20}$ = +23 (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 13H), 7.13–7.08 (m, 2H), 6.20 (br s, 1H), 5.56 (br s, 1H), 5.18 (d, J = 12.6 Hz, 1H), 5.13 (d, J = 12.6 Hz, 1H), 5.06 (s, 2H), 4.02 (br s, 1H), 1.41 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 166.8, 155.0, 139.3, 135.0, 134.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.6, 126.2, 79.7, 67.6, 67.3, 56.9, 53.5, 28.3 ppm; ESIMS: m/z: 512 [M^++Na]. The absolute configuration of **3n** was assigned as the *S* isomer by comparison of its optical rotation with a literature value (lit.:[8f] $[\alpha]_D^{25}$ = +14 (c = 0.98 in $CHCl_3$), for the *S* isomer, 96% *ee*).

*2-(*S-*Benzyloxycarbonylaminophenylmethyl)malonic acid dibenzyl ester (**3p**)*: Following the general procedure, compound **3p** was obtained as a white solid in a yield of 92% after column chromatography on silica gel (petroleum ether/Et_2O mixtures). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 89.5 min; t_{minor} = 68.2 min; 93% *ee*). M.p. 85–87 °C; $[\alpha]_D^{20}$ = +13 (c = 1.12 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.23 (m, 18H), 7.13–7.08 (m, 2H), 6.48 (br d, J = 8.3 Hz, 1H), 5.63 (br dd, J = 9.1, 4.3 Hz, 1H), 5.13 (d, J = 12.1 Hz, 1H), 5.10 (d, J = 12.1 Hz, 1H), 5.08 (br s, 2H), 5.05 (br s, 2H), 4.04 ppm (br d, J = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 166.6, 155.9, 138.9, 136.4, 134.9, 134.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 126.2, 67.7, 67.4, 66.9, 56.8, 53.7 ppm; ESIMS: m/z: 546 [M^++Na].

*2-(*R*-1-*tert*-Butoxycarbonylamino-3-methylbutyl)malonic acid dibenzyl ester (**3q**)*: Following the general procedure, compound **3q** was obtained as a colourless oil in a yield of 77% after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 95:5, flow rate 0.75 mL min^{-1}, t_{major} = 27.9 min; t_{minor} = 30.8 min; 91% *ee*). $[\alpha]_D^{20}$ = +40 (c = 0.75 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 10H), 5.26 (br d, J = 9.6 Hz, 1H), 5.21 (d, J = 11.4 Hz, 1H), 5.18 (d, J = 12.8 Hz, 1H), 5.16 (d, J = 11.4 Hz, 1H), 5.10 (d, J = 12.8 Hz, 1H), 4.41–4.31 (m, 1H), 3.70 (d, J = 4.4 Hz, 1H), 1.65–1.44 (m, 2H), 1.41 (s, 9H), 1.29–1.18 (m, 1H), 0.87 ppm (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 167.7, 155.2, 135.1, 128.5, 128.4, 128.3, 128.2, 79.2, 67.3, 67.2, 55.3, 48.6, 42.2, 28.3, 25.0, 22.9, 21.8 ppm; ESIMS: m/z: 492 [M^++Na].

*2-(*S-tert-*Butoxycarbonylaminophenylmethyl)malonic acid bis(4-methoxyphenyl) ester (**3r**)*: Following the general procedure and by adding aqueous K_2CO_3 solution (1.5 equiv, 50% w/w, 27 μL, 0.15 mmol), compound **3r** was obtained as a white solid in a yield of 90% after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 47.5 min; t_{minor} = 77.0 min; 98% *ee*). M.p. 144–146 °C; $[\alpha]_D^{20}$ = +3 (c = 0.700 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.31 (m, 5H), 7.06–7.03 (m, 2H), 6.90–6.87 (m, 2H), 6.83 (br s, 4H), 6.18 (br s, 1H), 5.82 (br s, 1H), 4.40 (br s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 166.0, 157.6, 155.1, 143.8, 143.5, 139.0, 128.8, 127.9, 126.4, 122.1, 122.0, 114.4, 80.0, 57.1, 55.6, 53.4, 28.3 ppm; ESIMS: m/z: 544 [M^++Na]. The absolute configuration of **3p** has been assigned as the *S* isomer in our previous work.[8i]

*2-(*S-*Benzyloxycarbonylaminophenylmethyl)malonic acid bis(4-methoxyphenyl) ester (**3s**)*: Following the general procedure and by adding aqueous K_2CO_3 solution (1.5 equiv, 50% w/w, 27 μL, 0.15 mmol), compound **3s** was obtained as a white solid in a yield of 96% after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralcel OD column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL min^{-1}, t_{major} = 30.9 min; t_{minor} = 26.5 min; 99% *ee*). M.p. 161–163 °C; $[\alpha]_D^{20}$ = +3 (c = 0.70 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.34 (m, 10H), 6.97–6.95 (m, 4H), 6.86–6.84 (m, 4H), 6.48 (d, J = 10.1 Hz, 1H), 5.88 (br s, 1H), 5.20 (d, J = 12.4 Hz, 1H), 5.10

(d, $J=12.4$ Hz, 1H), 4.43 (d, $J=4.1$ Hz, 1H), 3.80 (s, 3H), 3.77 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.7$, 165.8, 157.6, 155.3, 143.7, 143.4, 138.6, 128.8, 128.5, 128.1, 126.4, 122.0, 121.9, 114.5, 67.0, 56.9, 55.6, 55.5, 54.0 ppm; ESIMS: m/z: 578 [M^++Na]. The absolute configuration of **3q** has been assigned as the *S* isomer in our previous work.[8i]

*2-(*R-tert-*Butoxycarbonylaminophenylmethyl)malonic acid bis(4-methoxyphenyl) ester (*ent-***3r***)*: Following the general procedure and by adding catalyst **5** and aqueous K_2CO_3 solution (1.5 equiv, 50% w/w, 27 μL, 0.15 mmol), compound *ent*-**3r** was obtained as a white solid in a yield of 98% after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, $t_{major}=77.0$ min; $t_{minor}=47.5$ min; 93% *ee*). M.p. 147–149 °C; $[\alpha]_D^{20}=-4$ ($c=1.10$ in $CHCl_3$); spectral data were identical to compound **3p**.

*2-(*S-*Benzyloxycarbonylaminophenylmethyl)malonic acid bis(4-methoxyphenyl) ester (*ent-***3s***)*: Following the general procedure and by adding catalyst **5** and aqueous K_2CO_3 solution (1.5 equiv, 50% w/w, 27 μL, 0.15 mmol), compound *ent*-**3s** was obtained as a white solid in a yield of 95% after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralcel OD column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL min^{-1}, $t_{major}=26.5$ min; $t_{minor}=30.9$ min; 99% *ee*). M.p. 166–168 °C; $[\alpha]_D^{20}=-2$ ($c=0.96$ in $CHCl_3$); spectral data were identical to compound **3q**.

*2-(*S-tert-*Butoxycarbonylamino-3-phenylpropyl)malonic acid bis(4-methoxy-phenyl) ester (***3t***)*: Following the general procedure and by adding catalyst **5** and aqueous K_2CO_3 solution (1.5 equiv, 50% w/w, 27 μL, 0.15 mmol), compound **3t** was obtained as a white solid in a yield of 88% after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralcel OD column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL min^{-1}, $t_{major}=10.6$ min; $t_{minor}=8.9$ min; 77% *ee*). M.p. 114–116 °C; $[\alpha]_D^{20}=-32$ ($c=0.76$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.33$–7.27 (m, 2H), 7.25–7.19 (m, 3H), 7.09 (br d, $J=9.6$ Hz, 2H), 7.05 (br d, $J=8.6$ Hz, 2H), 6.88 (br d, $J=8.2$ Hz, 4H), 5.50 (d, $J=10.2$ Hz, 1H), 4.66–4.56 (m, 1H), 4.08 (d, $J=3.9$ Hz, 1H), 3.80 (s, 6H), 2.89–2.79 (m, 1H), 2.79–2.67 (m, 1H), 2.17–1.96 (m, 2H), 1.46 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=167.1$, 166.6, 157.6, 157.5, 155.5, 143.8, 143.6, 141.1, 128.5, 128.4, 126.1, 122.2, 122.1, 114.5, 114.4, 79.7, 55.6, 55.4, 50.2, 35.8, 32.7, 28.3 ppm; ESIMS: m/z: 572 [M^++Na].

*2-(*S-*1-Benzyloxycarbonylaminocyclohexylmethyl)malonic acid bis(4-methoxyphenyl) ester (***3u***)*: Following the general procedure and by adding catalyst **5** and aqueous K_2CO_3 solution (1.5 equiv, 50% w/w, 27 μL, 0.15 mmol), compound **3u** was obtained as a white solid in a yield of 89% after column chromatography on silica gel (CH_2Cl_2). The *ee* value of the product was determined by HPLC with a Daicel Chiralcel OD column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL min^{-1}, $t_{major}=11.1$ min; $t_{minor}=13.9$ min; 93% *ee*). M.p. 101–102 °C; $[\alpha]_D^{20}=-54$ ($c=0.64$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.34$–7.30 (m, 5H), 7.07–6.80 (m, 8H), 5.85 (d, $J=10.4$ Hz, 1H), 5.16 (d, $J=12.4$ Hz, 1H), 5.08 (d, $J=12.4$ Hz, 1H), 4.40 (dt, $J=9.6$, 3.9 Hz, 1H), 4.22 (d, $J=3.9$ Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 1.95–1.60 (m, 6H), 1.29–1.09 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=167.5$, 167.1, 157.7, 157.5, 156.3, 143.8, 143.6, 136.5, 128.4, 128.0, 127.9, 122.1, 114.5, 114.4, 66.7, 55.8, 55.6, 55.5, 52.8, 41.3, 30.3, 29.6, 26.0, 25.9, 25.7 ppm;. ESIMS: m/z: 550 [M^++Na].

Preparation of the β^3-amino acid hydrochlorides:[18] Malonic acid dimethyl ester **3a** or **3j** (0.20 mmol) was suspended in 6 M aqueous HCl (0.80 mL), and the mixture was then heated at 100 °C for 1 h 30 min for **3a** and 5 h for **3j**. After cooling to room temperature, the solution was evaporated to dryness under reduced pressure. Crude β^3-amino acid hydrochlorides were then purified by trituration with Et_2O.

S-*3-Amino-3-phenylpropionic acid hydrochloride (***6a***)*: Following the general procedure, compound **6a** was obtained as a white solid in a yield of 93%. The *ee* value of the product was determined on the corresponding *N*-Boc ethyl ester, (prepared by esterification ($SOCl_2$, EtOH)[18] followed by Boc protection (Boc_2O, EtOAc/Na_2CO_3 aq)) with by using a Daicel Chiralcel OD column (hexane/*i*PrOH = 98:2, flow rate 1.5 mL min^{-1}, $t_{major}=8.6$ min; $t_{minor}=7.5$ min; 90% *ee*), and was found to be consistent with the *ee* value of **3a** (90% *ee*). M.p. 204–205 °C; $[\alpha]_D^{20}=+3$ ($c=0.47$ in H_2O); ^{1}H NMR (400 MHz, D_2O):$\delta=7.54$–7.48 (m, 5H), 3.19 (dd, $J=17.2$, 7.9 Hz, 1H), 3.11 ppm (dd, $J=17.2$, 6.9 Hz, 1H), [C*H*N signal below the residual solvent peak]; ^{13}C NMR (100 MHz, D_2O): $\delta=177.0$, 138.4, 132.8, 132.6, 130.2, 54.8, 41.1 ppm; ESIMS: m/z: 166 [M^+].

S-*3-Amino-4-methylpentanoic acid hydrochloride (***6b***)*: Following the general procedure, compound **6b** was obtained as a white solid in a yield of 88%. The *ee* value of the product was determined on the corresponding *N*-Cbz methyl ester (prepared by Cbz protection (CbzCl, 1 M aqueous NaOH) followed by esterification with trimethylsilyldiazomethane)[24] with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL min^{-1}, $t_{major}=21.4$ min; $t_{minor}=17.3$ min; 85% *ee*), and was found to be consistent with the *ee* value of **3j** (85% *ee*). M.p. 180–181 °C; $[\alpha]_D^{20}=-24$ ($c=0.55$ in H_2O); ^{1}H NMR (400 MHz, D_2O):$\delta=3.55$–3.49 (m, 1H), 2.86 (dd, $J=17.8$, 4.1 Hz, 1H), 2.69 (dd, $J=17.4$, 9.0 Hz, 1H), 2.08–1.99 (m, 1H), 1.03 (d, $J=6.6$ Hz, 3H), 1.01 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (100 MHz, D_2O): $\delta=177.9$, 56.6, 36.5, 32.9, 20.3, 19.9 ppm; ESIMS: m/z: 132 [M^+].

Preparation of the *N*-protected β^3-amino acids: A 1 M solution of LiOH in H_2O (0.4 mL) was added to a cooled (0 °C) solution of **3a** or **3j** (0.10 mmol) in THF (0.4 mL). The solution was stirred at 0 °C for 2 h, then at room temperature for an additional 4 h. H_2O was then added and the mixture acidified to pH ≈ 2 by using a 0.5 M aqueous $KHSO_4$ solution. The malonic acid was then extracted with EtOAc (3 × 3 mL), the organic phases dried over Na_2SO_4, filtered and the solvent evaporated. The malonic acid obtained was then suspended in toluene (4 mL) and then heated to reflux for 2 h 30 min. After cooling to room temperature, the solvent was evaporated and the residue purified by chromatography on silica gel.

S-*3-tert-Butoxycarbonylamino-3-phenylpropionic acid (***7a***)*: Following the general procedure, compound **7a** was obtained as a white solid in a yield of 77% after column chromatography on silica gel (hexane/EtOAc/AcOH 80:20:1). The *ee* value of the product was determined on the corresponding methyl ester (prepared by esterification with trimethylsilyldiazomethane)[24] with a Daicel Chiralcel OD column (hexane/*i*PrOH = 95:5, flow rate 1.5 mL min^{-1}, $t_{major}=7.4$ min; $t_{minor}=6.1$ min; 90% *ee*), and was found to be consistent with the *ee* value of the starting **3a** (90% *ee*). M.p. 127–129 °C; $[\alpha]_D^{20}=-26$ ($c=0.50$ in CH_3OH); ^{1}H NMR (400 MHz, CD_3OD):$\delta=7.35$–7.20 (m, 6H), 5.02 (br s, 1H), 2.75 (dd, $J=15.4$, 8.3 Hz, 1H), 2.66 (dd, $J=15.9$, 13.4 Hz, 1H), 1.41 ppm (s, 9H); ^{13}C NMR (100 MHz, CD_3OD): $\delta=174.4$, 157.5, 134.6, 129.5, 128.3, 127.4, 80.3, 52.9, 42.3, 28.7 ppm; ESIMS: m/z: 288 [M^++Na].

S-*3-Benzyloxycarbonylamino-4-methylpentanoic acid (***7b***)*: Following the general procedure, compound **7b** was obtained as a white solid in a yield of 78% after column chromatography on silica gel (CH_2Cl_2/CH_3OH 95:5). The *ee* value of the product was determined on the corresponding methyl ester, (prepared by esterification with trimethylsilyldiazomethane)[24] with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL min^{-1}, $t_{major}=21.4$ min; $t_{minor}=17.3$ min; 84% *ee*), and was found to be consistent with the *ee* value obtained for **3j** (85% *ee*). M.p. 82–84 °C; $[\alpha]_D^{20}=+24$ ($c=0.20$ in $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD):$\delta=7.38$–7.23 (m, 5H), 6.97 (br d, $J=8.0$ Hz, 1H), 5.07 (s, 2H), 3.91–3.82 (m, 1H), 2.51 (dd, $J=15.4$, 5.8 Hz, 1H), 2.39 (dd, $J=15.4$, 8.9 Hz, 1H), 1.79 (oct, $J=6.5$ Hz, 1H), 0.93 (d, $J=6.6$ Hz, 3H), 0.91 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): $\delta=175.4$, 158.6, 138.5, 129.4, 128.9, 128.6, 67.3, 55.0, 38.0, 33.5, 19.5, 18.4 ppm; ESIMS: m/z: 288 [M^++Na]. The absolute configuration of **7b** was assigned as the *S* isomer by comparison of its optical rotation with a literature value (lit.:[25] $[\alpha]_D^{25}=-33$ ($c=0.2$ in $CHCl_3$), for the (*R*)-isomer).

General procedure for the catalytic reaction of β-ketoesters 8 with α-amido sulfones 2: β-Ketoester **8** (0.10 mmol) was added to a test tube that contained a mixture of α-amido sulfone **2** (0.12 mmol) and catalyst **4e** (1.2 mg, 0.025 mmol) in toluene (2 mL). After the resulting mixture had been cooled to −24 °C, a pre-cooled aqueous solution of K_2CO_3 (50% w/w, 27 μL, 0.15 mmol) was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After the time stated, the reaction product was filtered through a short plug of silica, the plug was washed with CH_2Cl_2 (4 mL) and Et_2O (4 mL) and the solvent was evaporated.

The crude product was analysed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio before it was purified by chromatography on silica gel.

S-*1-(*R-tert-*Butoxycarbonylaminophenylmethyl)-2-oxocyclopentanecarboxylic acid methyl ester (**9d**)*: Following the general procedure (21 h reaction time), compound **9d** was obtained as a colourless oil in a yield of 98% after column chromatography on silica gel (hexane/Et_2O 1:1) and as a single diastereoisomer, as determined by measurements on the crude mixture. The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 98:2, flow rate 0.75 mL min^{-1}, t_{major} = 118.0 min; t_{minor} = 36.2 min, 95% *ee*). $[\alpha]_D^{20}$ = +25 (*c* = 0.85 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.21 (m, 5H), 5.95 (brs, 1H), 5.20 (d, *J* = 9.7 Hz, 1H), 3.67 (s, 3H), 2.57–2.25 (m, 1H), 2.37–2.25 (m, 2H), 2.05–1.82 (m, 3H), 1.38 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.9, 170.0, 155.2, 138.3, 128.4, 128.1, 127.8, 79.8, 64.9, 55.7, 52.7, 37.5, 30.6, 28.2, 18.8 ppm; ESIMS: *m*/*z*: 370 [M^++Na].

S-*1-(*R-*Benzyloxycarbonylaminophenylmethyl)-2-oxocyclopentanecarboxylic acid methyl ester (**9e**)*: Following the general procedure (28 h reaction time), compound **9e** was obtained as a colourless oil in a yield of 90% after column chromatography on silica gel (hexane/Et_2O 6:4) and as a single diastereoisomer, as determined by measurements on the crude mixture. The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 49.3 min; t_{minor} = 19.4 min, 92% *ee*). $[\alpha]_D^{20}$ = +30 (*c* = 0.88 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 10H), 6.23 (brd, *J* = 8.3 Hz ,1H), 5.23 (brd, *J* = 8.3 Hz, 1H), 5.05 (s, 2H), 3.65 (s, 3H), 2.57–2.46 (m, 1H), 2.42–2.22 (m, 2H), 2.07–1.80 ppm (m, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ?210.5, 169.7, 155.8, 138.2, 136.5, 128.5, 128.4, 128.1, 127.9, 66.9, 64.6, 56.8, 52.6, 37.6, 30.4, 18.9 ppm; ESIMS: *m*/*z*: 404 [M^++Na].

*1-[(2-Bromophenyl)-*tert-*butoxycarbonylaminomethyl]-2-oxocyclopentanecarboxylic acid methyl ester (**9f**)*: Following the general procedure (73 h reaction time), compound **9f** was obtained as a colourless oil in a yield of 60% after column chromatography on silica gel (CH_2Cl_2) and as a mixture of diastereoisomers (94:6 diastereomeric ratio, as determined on the crude mixture). The *ee* value of the products was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL min^{-1}, major diastereoisomer: t_{major} = 16.1 min; t_{minor} = 18.3 min, 69% *ee*, enantiomers of the minor diastereoisomer not separated). ^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer): δ = 7.59–7.50 (t, *J* = 8.3 Hz, 2H), 7.30–7.22 (t, *J* = 7.3 Hz, 1H), 7.14–7.08 (t, *J* = 7.3 Hz, 1H), 6.22 (brs, 1H), 5.62 (brd, *J* = 7.8 Hz, 1H), 3.66 (s, 3H), 2.65–2.50 (m, 1H), 2.49–2.33 (m, 2H), 2.33–2.18 (m, 1H), 2.15–2.05 (m, 1H), 2.05–1.91 (m, 1H), 1.39 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ = 210.7, 170.3, 155.4, 138.6, 133.2, 129.4, 129.3, 127.9, 125.1, 79.8, 64.3, 54.0, 52.6, 37.5, 31.3, 28.3, 19.1 ppm; ESIMS: *m*/*z*: 448 [M^++Na].

*1-[1-Benzyloxycarbonylamino(2-bromophenyl)methyl]-2-oxocyclopentanecarboxylic acid methyl ester (**9g**)*: Following the general procedure (73 h reaction time), compound **9g** was obtained as a colourless oil in a yield of 85% after column chromatography on silica gel (hexane/EtOAc 8:2) and as a mixture of diastereoisomers (96:4 diastereomeric ratio, as determined on the crude mixture). The *ee* value of the products was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL min^{-1}, major diastereoisomer: t_{major} = 33.2 min; t_{minor} = 26.0 min, 77% *ee*, minor diastereoisomer: t_{major} = 27.0 min; t_{minor} = 30.1 min, 47% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer): δ = 7.60–7.51 (m, 2H), 7.38–7.22 (m, 5H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.55 (brd, *J* = 8.7 Hz, 1H), 5.65 (d, *J* = 8.7 Hz, 1H), 5.05 (s, 2H), 3.66 (s, 3H), 2.69–2.50 (m, 1H), 2.50–2.34 (m, 2H), 2.14–1.89 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ = 210.7, 170.1, 155.7, 138.3, 136.3, 133.2, 129.4, 129.3, 128.4, 128.0, 125.1, 67.0, 64.0, 54.6, 52.7, 37.6, 31.4, 19.2 ppm; ESIMS: *m*/*z*: 482 [M^++Na].

*1-[1-Benzyloxycarbonylamino(4-chlorophenyl)methyl]-2-oxocyclopentanecarboxylic acid methyl ester (**9h**)*: Following the general procedure (21 h reaction time), compound **9h** was obtained as a colourless oil in a yield of 98% after column chromatography on silica gel (hexane/EtOAc 85:15) and as a mixture of diastereoisomers (96:4 diastereomeric ratio, as determined on the crude mixture). The *ee* value of the products was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, major diastereoisomer: t_{major} = 51.0 min; t_{minor} = 16.2 min, 73% *ee*, minor diastereoisomer: t_{major} = 99.6 min; t_{minor} = 25.6 min, 61% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer, 50°C): δ = 7.40–7.21 (m, 9H), 6.08 (brs, 1H), 5.20 (d, *J* = 8.8 Hz, 1H), 5.08 (d, *J* = 11.8 Hz, 2H), 5.03 (d, *J* = 11.8 Hz, 1H), 3.81 (s, 3H), 2.56–2.47 (m, 1H), 2.43–2.32 (m, 2H), 2.04–1.84 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ = 210.8, 169.7, 155.8, 136.6, 136.1, 133.9, 129.7, 128.7, 128.6, 128.5, 128.1, 67.0, 64.5, 55.9, 52.9, 37.6, 30.9, 19.0 ppm; ESIMS: *m*/*z*: 438 [M^++Na].

*1-[1-Benzyloxycarbonylamino(4-methoxyphenyl)methyl]-2-oxocyclopentanecarboxylic acid methyl ester (**9i**)*: Following the general procedure (65 h reaction time), compound **9i** was obtained as a colourless oil in a yield of 70% after column chromatography on silica gel (hexane/EtOAc 80:20) and as a mixture of diastereoisomers (95:5 diastereomeric ratio, as determined on the crude mixture). The *ee* value of the products was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 95:5, flow rate 0.75 mL min^{-1}, major diastereoisomer: t_{major} = 50.3 min; t_{minor} = 20.7 min, 77% *ee*, minor diastereoisomer: t_{major} = 87.1 min; t_{minor} = 32.9 min, 53% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer): δ = 7.41–7.19 (m, 7H), 6.85–6.80 (m, 2H), 6.18 (brs, 1H), 5.18 (brd, *J* = 9.2 Hz, 1H), 5.05 (s, 2H), 3.78 (s, 3H), 3.65 (s, 3H), 2.51 (dt, *J* = 13.6, 6.6 Hz, 1H), 2.40–2.23 (m, 2H), 2.05–1.86 ppm (m, 3H);.^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ = 211.0, 169.8, 159.2, 155.8, 136.3, 130.1, 129.3, 128.4, 128.0, 113.8, 66.9, 64.8, 55.9, 55.2, 52.7, 37.5, 29.2, 18.9 ppm, ESIMS: *m*/*z*: 434 [M^++Na].

*1-(1-Benzyloxycarbonylaminonaphthalen-1-ylmethyl)-2-oxocyclopentanecarboxylic acid methyl ester (**9j**)*: Following the general procedure (40 h reaction time), compound **9j** was obtained as a colourless oil in a yield of 50% after column chromatography on silica gel (hexane/Et_2O 80:20) and as a mixture of diastereoisomers (90:10 diastereomeric ratio, as determined on the crude mixture). The *ee* value of the products was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 95:5, flow rate 0.75 mL min^{-1}, major diastereoisomer: t_{major} = 55 min; t_{minor} = 57 min, 85% *ee*, enantiomers of the minor diastereoisomer not separated). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.7 Hz, $1H_{major}$, $1H_{minor}$), 7.85 (d, *J* = 8.0 Hz, $1H_{major}$, $1H_{minor}$), 7.79 (d, *J* = 8.0 Hz, $1H_{major}$, $1H_{minor}$), 7.68–7.45 (m, $3H_{major}$, $3H_{minor}$), 7.41 (t, *J* = 8.2 Hz, $1H_{major}$, $1H_{minor}$), 7.36–7.21 (m, $5H_{major}$, $5H_{minor}$), 6.42 (d, *J* = 9.7 Hz, $1H_{minor}$), 6.20 (brd, *J* = 9.4 Hz, $1H_{major}$), 6.08 (d, *J* = 9.4 Hz, $1H_{major}$, $1H_{minor}$), 5.12 (d, *J* = 12.4 Hz, $1H_{major}$), 5.06 (d, *J* = 12.4 Hz, $1H_{major}$, $1H_{minor}$), 4.96 (d, *J* = 12.4 Hz, $1H_{minor}$), 3.76 (s, $3H_{minor}$), 3.63 (s, $3H_{major}$), 2.69–2.26 (m, $3H_{major}$, $3H_{minor}$), 2.22–1.87 ppm (m, $3H_{major}$, $3H_{minor}$); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ = 211.4, 171.2, 156.2, 136.5, 134.5, 133.9, 131.9, 128.8, 128.4, 128.0, 127.9, 126.8, 125.8, 125.3, 125.0, 123.3, 67.0, 64.4, 52.7, 50.9, 37.7, 32.8, 19.2 ppm; ESIMS: *m*/*z*: 454 [M^++Na].

S-*1-(*R-*1-*tert-*Butoxycarbonylamino-3-phenylpropyl)-2-oxocyclopentanecarboxylic acid methyl ester (**9k**)*: Following the general procedure (45 h reaction time), compound **9k** was obtained as a colourless oil in a yield of 55% after column chromatography on silica gel (CH_2Cl_2) and as a mixture of diastereoisomers (97:3 diastereomeric ratio, as determined on the crude mixture). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, major diastereoisomer: t_{major} = 8.1 min; t_{minor} = 7.4 min, 90% *ee*, enantiomers of the minor diastereoisomer not separated). ^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer): δ = 7.28 (t, *J* = 7.8 Hz, 2H), 7.22–7.14 (m, 3H), 5.12 (d, *J* = 10.3 Hz, 1H), 3.96 (t, *J* = 11.0 Hz, 1H), 3.69 (s, 3H), 2.99–2.73 (m, 1H), 2.63–2.23 (m, 4H), 1.99–1.83 (m, 4H), 1.76–1.65 (m, 1H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ = 211.9, 170.6, 156.2, 141.4, 128.5, 128.4, 126.0, 79.5, 64.5, 52.5, 52.1, 37.7, 33.7, 33.0, 31.8, 28.3, 18.9 ppm; ESIMS: *m*/*z*: 398 [M^++Na].

*1-(1-Benzyloxycarbonylaminoethyl)-2-oxocyclopentanecarboxylic acid methyl ester (**9l**)*: Following the general procedure (47 h reaction time), compound **9l** was obtained as a colourless oil in a yield of 70% after column chromatography on silica gel (CH_2Cl_2) and as a mixture of diaste-

reoisomers (97:3 diastereomeric ratio, as determined on the crude mixture). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL min^{-1}, major diasteroisomer: t_{major} = 13.1 min; t_{minor} = 18.4 min, 75% *ee*, enantiomers of the minor diasteroisomer not separated). ^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer): δ = 7.38–7.27 (m, 5H), 5.38 (br d, J = 8.5 Hz ,1H), 5.16–4.97 (m, 2H), 4.24–4.12 (m, 1H), 3.71 (s, 3H), 2.61–2.47 (m, 1H), 2.43–2.30 (m, 2H), 2.10–1.84 (m, 3H), 1.25 ppm (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ = 212.1, 170.4, 156.0, 136.4 ,128.4, 128.03, 128.00, 66.7, 64.1, 52.6, 48.8, 37.8, 31.7, 19.1, 17.4 ppm, ESIMS: m/z: 342 [M^++Na].

*1-(1-Benzyloxycarbonylamino-2-methylpropyl)-2-oxocyclopentanecarboxylic acid methyl ester (**9m**)*: Following the general procedure (64 h reaction time), compound **9m** was obtained as a colourless oil in a yield of 74% after column chromatography on silica gel (hexane/Et_2O 70:30) and as a mixture of diastereoisomers (96:4 diastereomeric ratio, as determined on the crude mixture). The *ee* value of the products was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, major diastereoisomer: t_{major} = 10.3 min; t_{minor} = 9.5 min, 74% *ee*; minor diastereoisomer: t_{major} = 13.3 min; t_{minor} = 15.6 min, 67% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer): δ = 7.43–7.24 (m, 5H), 5.59 (d, J = 10.7 Hz, 1H), 5.12 (d, J = 12.2 Hz, 1H), 5.06 (d, J = 12.2 Hz, 1H), 3.92 (dd, J = 10.5, 4.7 Hz, 1H), 3.69 (s, 3H), 2.62 (dt, J = 14.3, 6.5 Hz, 1H), 2.51–2.23 (m, 2H), 2.13–1.84 (m, 4H), 0.95 (d, J = 6.5 Hz, 3H), 0.85 ppm (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ = 210.9, 170.2, 156.9, 136.6, 128.4, 128.0, 127.9, 66.8, 63.5, 57.7, 52.6, 37.5, 31.9, 30.5, 21.8, 19.1, 18.1 ppm; ESIMS: m/z: 370 [M^++Na].

S-*1-(*R-*1-Benzyloxycarbonylaminocyclohexylmethyl)-2-oxocyclopentanecarboxylic acid methyl ester (**9n**)*: Following the general procedure (84 h reaction time), compound **9n** was obtained as a colourless oil in a yield of 77% after column chromatography on silica gel (hexane/Et_2O 80:20) and as a single diastereoisomer, as determined on the crude mixture. The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, t_{major} = 14.4 min; t_{minor} = 17.1 min, 99% *ee*). $[\alpha]_D^{20}$ = +43 (c = 0.0.87 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5H), 5.57 (br d, J = 10.8 Hz, 1H), 5.13–5.03 (m, 2H), 3.94–3.82 (m, 1H), 3.68 (s, 3H), 2.66–2.54 (m, 1H), 2.49–2.37 (m, 1H), 2.37–2.25 (m, 1H), 2.13–1.84 (m, 3H), 1.81–1.67 (m, 2H), 1.66–1.49 (m, 3H), 1.32–0.97 ppm (m, 6H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.1, 170.4, 156.8, 136.6 ,128.4, 128.0, 66.8, 66.7, 64.1, 57.3, 40.7, 37.5, 32.1, 31.7, 28.7, 26.4, 25.9, 25.3, 19.1 ppm; ESIMS: m/z: 410 [M^++Na].

*1-(1-Benzyloxycarbonylaminophenylmethyl)-2-oxocyclohexanecarboxylic acid methyl ester (**9o**)*: Following the general procedure (24 h reaction time) with K_3PO_4 (5 equiv, 50% w/w) as the base and performing the reaction at 0°C, compound **9o** was obtained as a colourless oil in a yield of 77% after column chromatography on silica gel (hexane/Et_2O 70:30) and as a mixture of diastereoisomers (97:3 diastereomeric ratio after column chromatography, 85:15 diastereomeric ratio determined on the crude mixture). The *ee* value of the products was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 95:5, flow rate 0.75 mL min^{-1}, major diastereoisomer: t_{major} = 74.4 min; t_{minor} = 39.7 min, 91% *ee*, minor diastereoisomer: t_{major} = 48.2 min; t_{minor} = 42.0 min, 9% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer): δ = 7.40–7.22 (m, 10H), 6.52 (br d, J = 9.9 Hz ,1H), 5.25 (d, J = 9.9 Hz, 1H), 5.10–4.99 (m, 2H), 3.52 (s, 3H), 2.66–2.55 (m, 1H), 2.55–2.39 (m, 2H), 2.05–1.79 (m, 4H), 1.74–1.60 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ = 208.4, 170.9, 155.9, 138.1, 136.2, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 66.9, 66.8, 58.4, 52.2, 40.8, 34.8, 27.7, 27.8 ppm; ESIMS: m/z: 418 [M^++Na].

*1-(1-Benzyloxycarbonylaminophenylmethyl)-2-oxocycloheptanecarboxylic acid methyl ester (**9p**)*: Following the general procedure (71 h reaction time), compound **9p** was obtained as a white solid in a yield of 96% after column chromatography on silica gel (hexane/Et_2O 80:20) and as a single diastereoisomer (96:4 diastereomeric ratio determined on the crude mixture). The *ee* value of the product was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL min^{-1}, t_{major} = 62.3 min; t_{minor} = 35.1 min, 95% *ee*). M.p. 113–115°C; $[\alpha]_D^{20}$ = +22 (c = 0.95 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 10H), 6.73 (d, J = 10.2 Hz, 1H), 5.23 (d, J = 10.2 Hz, 1H), 5.02 (d, J = 12.1 Hz, 1H), 4.98 (d, J = 12.2 Hz, 1H), 3.66 (s, 3H), 2.82 (t, J = 13.3 Hz, 1H), 2.52–2.42 (m, 1H), 2.13–2.03 (m, 1H), 1.93–1.72 (m, 3H), 1.73–1.60 (m, 1H), 1.56–1.32 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.6, 171.8, 155.6, 137.8, 136.2, 128.7, 128.4, 128.3, 127.98, 127.94, 66.8, 60.4, 53.4, 52.1, 40.6, 33.5, 30.2, 26.4, 25.5 ppm; ESIMS: m/z: 432 [M^++Na].

*2-(1-Benzyloxycarbonylaminophenylmethyl)-1-oxoindan-2-carboxylic acid methyl ester (**9q**)*: Following the general procedure (39 h reaction time) by adding K_2CO_3 (1.5 equiv, 30% w/w) as the base, compound **9q** was obtained after column chromatography on silica gel (hexane/Et_2O 80:20) as a colourless oil in a yield of 95% and as a mixture of diastereoisomers (58:42 diastereomeric ratio, as determined on the crude mixture). The *ee* value of the products was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 85:15, flow rate 0.6 mL min^{-1}, major diastereoisomer: t_{major} = 205.6 min; t_{minor} = 58.3 min, 87% *ee*; minor diastereoisomer: t_{major} = 221.9 min; t_{minor} = 90.3 min, 85% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$, both diastereoisomers): δ = 7.76–7.69 (m, 1H), 7.57 (t, J = 7.0 Hz, 1H), 7.49 (t, J = 7.0 Hz, 1H), 7.41–7.20 (m, 12H), 7.19–7.10 (m, 1H), 7.04 (br d, J = 8.8 Hz, 1H), 6.38 (br s, 1H), 5.52 (d, J = 9.2 Hz, 1H), 5.31 (br s, 1H), 5.14–4.98 (m, 1H), 3.78 (d, J = 17.4 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.47 (d, J = 17.4 Hz, 1H), 3.26–3.17 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, both diastereoisomers): δ = 198.4, 171.1, 155.7, 151.9, 138.4, 137.2, 136.4, 136.3, 135.7, 135.5, 134.3, 128.5, 128.4, 128.3, 128.2, 128.03, 128.00, 127.9, 126.1, 126.0, 125.1, 124.4, 66.9, 66.8, 58.8, 58.3, 53.0, 36.1, 34.7 ppm; ESIMS: m/z: 452 [M^++Na].

*2-(Benzyloxycarbonylaminophenylmethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid methyl ester (**9r**)*: Following the general procedure (63 h reaction time), compound **9r** was obtained as a colourless oil in a yield of 96% after column chromatography on silica gel (hexane/EtOAc 80:20) and as a mixture of diastereoisomers (93:7 diastereomeric ratio, as determined on the crude mixture). The *ee* value of the products was determined by HPLC with a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL min^{-1}, major diastereoisomer: t_{major} = 70.6 min; t_{minor} = 76.5 min, 92% *ee*, enantiomers of the minor diastereoisomer not separated); ^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer): δ = 8.01 (dd, J = 7.9, 1.1 Hz, 1H), 7.56–7.18 (m, 13H), 6.30 (br d, J = 10.5 Hz, 1H), 5.38 (d, J = 10.5 Hz, 1H), 5.04 (d, J = 12.4 Hz, 1H), 5.00 (d, J = 12.4 Hz, 1H), 3.47 (s, 3H), 3.11–3.02 (m, 2H), 2.78–2.66 (m, 1H), 2.36–2.26 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ = 194.5, 170.3, 155.8, 142.3, 138.5, 136.2, 133.8, 132.2, 128.76, 128.70, 128.4, 128.25, 128.20, 128.0, 127.8, 126.9, 125.7, 66.9, 63.0, 58.7, 52.5, 30.7, 25.9 ppm; ESIMS: m/z: 466 [M^++Na].

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