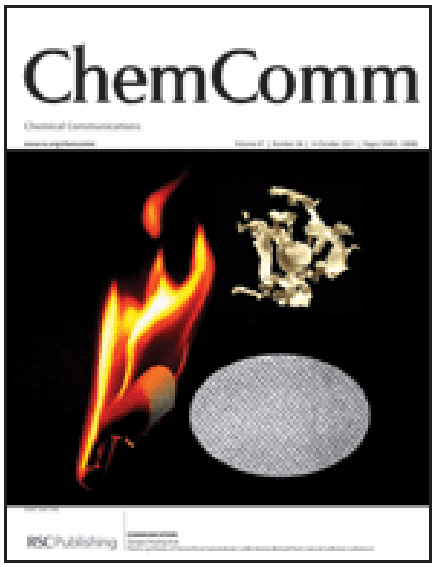

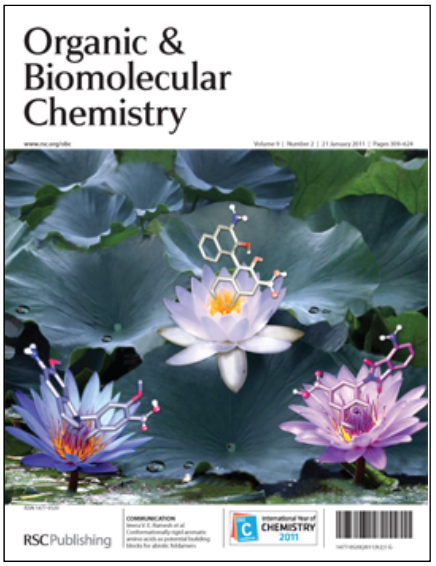

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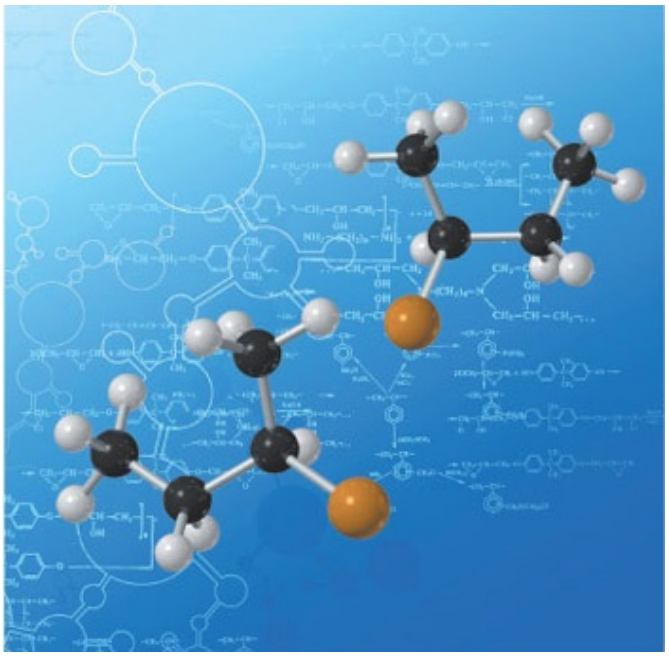

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PAPER

Simple chiral sulfonamide primary amine catalysed highly enantioselective Michael addition of malonates to enones†‡

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A chiral sulfonamide primary amine-organocatalysed, highly enantioselective Michael addition of malonates to enones has been developed. This reaction afforded the corresponding products in excellent yields (up to 99%) and excellent enantioselectivity (up to 99% ee).

Introduction

The catalytic asymmetric Michael reaction is one of the most powerful carbon–carbon bond-forming reactions, which provides access to various optically active compounds or synthons.[1] Among the various stabilized carbanion nucleophiles, the versatile nucleophilic enol and related species, such as malonate esters,[2] β-ketoesters,[3] 1,3-diketones,[4] α-nitro or α-cyano esters,[5] α-nitroketone[6] and malononitrile,[7] are very important nucleophiles for the asymmetric Michael addition to α,β-unsaturated systems. The catalytic asymmetric Michael additions of nucleophilic enol species to α,β-enones would produce synthetically useful building blocks in organic synthesis owing to them possessing various functional groups, such as nitro, ester, carbonyl, and cyano, for further transformation. As a result, considerable efforts have been directed towards the development of catalytic asymmetric Michael addition of malonates to enones in recent years and many improvements to this reaction have been made. Many types of chiral catalysts such as chiral metal complexes,[8] phase-transfer catalysts,[9] metal salts of carboxylic acids,[10] organocatalysts,[11] and chiral ionic liquids[12] have been developed for this important carbon–carbon bond forming reaction. Jørgensen reported the first highly enantioselective organocatalytic Michael addition of malonates to enones using an imidazoline catalyst in 2003.[11a] Subsequently, other organocatalysts such as thioureas,[11b,c,h] proline tetrazole[11i] and primary–secondary diamine[11f,g] were explored to catalyze this reaction. Despite excellent enantioselectivities having been achieved in a few cases, nevertheless some of the reported methods suffer, to a greater or lesser extent, from several drawbacks such as reaction times up to weeks in some cases, the need for a large excess of malonate, a narrow substrate scope, and restriction to a limited combination of nucleophile and electrophile type. Therefore, the successful design of a simple and more efficient organocatalyst remains a challenging task in order to enable a wide range of nucleophilic enol species to engage in this reaction.

On the other hand, during the past several years the inspiring successful applications of sulfonamide derivatives as organocatalysts have been reported in catalytic asymmetric Michael addition.[13] To the best of our knowledge, chiral sulfonamide primary amine-catalysed asymmetric Michael addition of malonates to enones has been rarely reported. We report herein a highly efficient enantioselective Michael addition of malonates to enones catalysed by a simple chiral sulfonamide primary amine; the desired products were obtained with excellent yields and enantioselectivities (up to 99% ee).

Results and discussion

A series of chiral sulfonamide primary amine organocatalysts **1a–f** (Fig. 1) were readily synthesized from chiral primary amino alcohol or 1,2-diamine in a few steps according to our previous report.[14] These primary amine organocatalysts were evaluated in the Michael addition of malonates to α,β-unsaturated ketones. Initially, the Michael reaction of dibenzyl malonate **2a** to

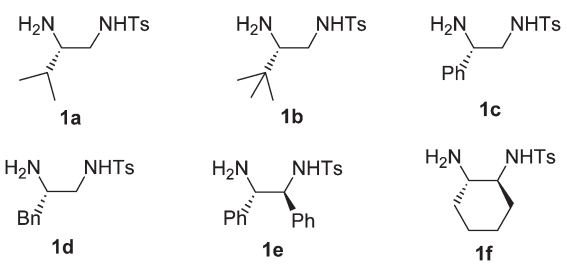

Fig. 1 Structures of sulfonamide primary amine organocatalysts (**1a–f**).

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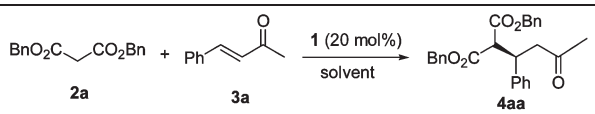
‡ Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of new compounds and HPLC chromatograms of the Michael addition products. See DOI: 10.1039/c2ob07191f

benzylideneacetone **3a** was selected as a model reaction. The model reaction was performed in $CHCl_3$ in the presence of 20 mol% catalyst loading at room temperature. The catalytic effects of the various primary amine catalysts were examined and the results are summarized in Table 1. To our delight, amino alcohol-derived sulfonamide primary amines **1a** and **1d** gave the desired products in good yields with high enantioselectivities (91% ee and 90% ee, respectively) in 72 h (Table 1, entries 1 and 4). Especially, up to 91% yield and 94% ee were obtained with catalyst **1b** (Table 1, entry 2). However, poor results were obtained when catalyst **1e** and **1f** derived from 1,2-diamine were employed (Table 1, entries 5 and 6).

With the best catalyst in hand, optimization of the reaction conditions was performed. It was found that the reaction medium had an obvious impact on the catalytic process (Table 1, entries 7–20). Without solvent, the product was formed in 91% yield with 91% ee (Table 1, entry 7). As expected, *i*-PrOH (Table 1, entry 13, 25% yield and 62% ee), H_2O (Table 1, entry 14, 65% yield and 75% ee), MeOH (Table 1, entry 15, 27% yield and 57% ee) and DMSO (Table 1, entry 16, 62% yield and 68% ee) provided the corresponding product in poor yield with low enantioselectivity. The low enantioselectivities in protic solvents may be ascribed to the competitive hydrogen bonding interactions of these protic solvents with the substrates or catalysts. Common solvents such as $CHCl_3$, Et_2O, hexane, CH_2Cl_2 and CH_2ClCH_2Cl gave excellent yields and enantioselectivities (90–94% ee) (Table 1, entries 2, 9, 12, 17, and 18), and the best results were obtained with toluene (Table 1, entry 20, 99% yield and 94% ee). When using 10 mol% catalyst loading, the corresponding product was obtained in lower yield with maintenance of enantioselectivity (Table 1, entry 21). For most catalytic systems, moderate conversion could be achieved at lower reaction temperature within a longer time, but was generally accompanied by increased enantioselectivity. However, when this reaction was carried out at 0 °C, a good yield (85%) and low enantioselectivity (57% ee) were observed after a prolonged time (Table 1, entry 22). The decrease in enantioselectivity of the product at low temperature may be ascribed to a deficiency in forming the iminium intermediate.

We further evaluated the effect of several acid and base additives, because acid additives were beneficial for the Michael addition of malonates to enones in Zhao and Yang's report,[11f] whereas base additives were used by Ley *et al.*[11i] It was noted that the acid and base additives had an obvious effect on the reactivity of the Michael addition in our catalytic system, and the results are summarized in Table 2. Among the acids screened, the reaction rate, yield, and enantiomeric excess were decreased when a carboxylic acid additive was added, such as 2-nitrobenzoic acid (Table 2, entry 3; 41% yield, 81% ee), *p*-toluenesulfonic acid (Table 2, entry 6; 25% yield, 87% ee), *p*-hydroxybenzoic acid (Table 2, entry 10; 49% yield, 88% ee). In the presence of CF_3CO_2H (20 mol%) and CF_3SO_3H, no product was obtained (Table 2, entries 7 and 9). Furthermore, base additives such as Et_3N, DMAP and pyridine were also evaluated, and no significant improvements were obtained (Table 2, entries

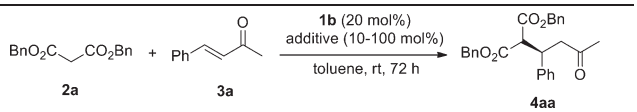
Table 1 Catalyst and reaction solvent screen for the asymmetric Michael addition of dibenzyl malonate **2a** to benzylideneacetone **3a**[a]



Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	**1a**	$CHCl_3$	81	91
2	**1b**	$CHCl_3$	94	94
3	**1c**	$CHCl_3$	91	75
4	**1d**	$CHCl_3$	87	90
5	**1e**	$CHCl_3$	33	57
6	**1f**	$CHCl_3$	31	39
7	**1b**	Neat	91	91
8	**1b**	CH_3CN	51	88
9	**1b**	Et_2O	73	91
10	**1b**	EtOAc	58	90
11	**1b**	DMF	50	91
12	**1b**	Hexane	95	91
13	**1b**	*i*-PrOH	25	62
14	**1b**	H_2O	65	75
15	**1b**	MeOH	27	57
16	**1b**	DMSO	62	68
17	**1b**	CH_2Cl_2	92	94
18	**1b**	$ClCH_2CH_2Cl$	86	94
19	**1b**	THF	51	83
20	**1b**	Toluene	99	94
21[d]	**1b**	Toluene	79	94
22[e]	**1b**	Toluene	85	57

[a] Unless otherwise specified, all reactions were carried out with benzylideneacetone **3a** (36.5 mg, 0.25 mmol), dibenzyl malonate **2a** (142 mg, 0.50 mmol), and catalyst **1** (0.05 mmol, 20 mol%) in the solvent (1 mL) at room temperature for 72 h. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by HPLC using Daicel Chiralpak AS-H column, the configuration was assigned according to literature.[11a] [d] The catalyst was loaded at 10 mol%. [e] The reaction was run for 96 h at 0 °C.

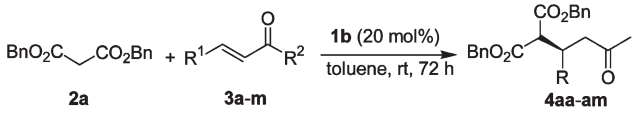
Table 2 The effect of additives[a]



Entry	Additive	Loading (mol%)	Yield[b] (%)	ee[c] (%)
1	—	—	99	94
2	$C_6H_5CO_2H$	20	89	91
3	2-$O_2NC_6H_4CO_2H$	20	41	81
4	CH_3CO_2H	20	77	89
5	4-$CH_3C_6H_4CO_2H$	20	72	83
6	TsOH	20	25	87
7	CF_3SO_3H	20	—	—
8	CF_3CO_2H	10	41	79
9	CF_3CO_2H	20	—	—
10	4-$HOC_6H_4CO_2H$	20	49	88
11	4-$HO_2CC_6H_4CO_2H$	20	65	94
12	4-$O_2NC_6H_4OH$	20	39	83
13	Et_3N	100	41	86
14	DMAP	100	—	—
15	Pyridine	100	45	89

[a] Unless otherwise specified, all reactions were carried out with benzylideneacetone **3a** (36.5 mg, 0.25 mmol), dibenzyl malonate **2a** (142 mg, 0.50 mmol), catalyst **1b** (13.5 mg, 0.05 mmol, 20 mol%), and the additive in toluene (1 mL) at room temperature for 72 h. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral HPLC analysis, the configuration was assigned according to literature.[11a]

Table 3 Substrate scope of the catalytic asymmetric Michael addition of dibenzyl malonate **2a** to enones **3**[a]



2a **3a-m** **4aa-am**

Entry	R^1	R^2	Product	Yield[b] (%)	ee[c] (%)
1	Ph	CH_3	**4aa**	99	94
2	4-BrC_6H_4	CH_3	**4ab**	99	97
3	4-ClC_6H_4	CH_3	**4ac**	99	98
4	4-$CH_3C_6H_4$	CH_3	**4ad**	98	94
5	4-$MeOC_6H_4$	CH_3	**4ae**	94	94
6	4-$NO_2C_6H_4$	CH_3	**4af**	99	94
7	4-$N(CH_3)_2C_6H_4$	CH_3	**4ag**	62	87
8	3-$NO_2C_6H_4$	CH_3	**4ah**	99	94
9	2-$MeOC_6H_4$	CH_3	**4ai**	84	80
10	2-BrC_6H_4	CH_3	**4aj**	99	83
11	3,4-$(MeO)_2C_6H_3$	CH_3	**4ak**	75	94
12	1-Naphthyl	CH_3	**4al**	90	91
13	*i*-Pr	CH_3	**4am**	70	95
14	2-Cyclohexenone (**3n**)		**4an**	61	18
15	Ph	Cyclohexyl	**4ao**	—	—
16	*t*-Bu	Ph	**4ap**	—	—
17	Ph	Ph	**4aq**	—	—
18	2-Benzylidene-3,4-dihydronaphthalen-1(2*H*)-one (**3r**)		**4ar**	—	—

[a] Unless otherwise specified, all reactions were carried out with enones **3** (0.25 mmol), dibenzyl malonate **2a** (142 mg, 0.50 mmol), and catalyst **1b** (13.5 mg, 0.05 mmol, 20 mol%) in toluene (1 mL) at room temperature for 72 h. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by HPLC using Daicel Chiralpak AS-H column, the configuration was assigned according to literature.[11a,f]

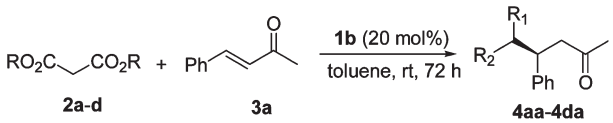
13–15). Thus, the reaction was best performed using catalyst **1b** in toluene with no any additive.

With the optimized reaction conditions in hand, the substrate scope of this catalytic asymmetric Michael reaction was explored. As shown in Table 3, a series of α,β-unsaturated enones **3a–n** were reacted with dibenzyl malonate **2a** in the presence of 20 mol% of catalyst **1b**. This catalytic system was well applicable to various β-aryl-substituted butenones, and the conjugate addition products were obtained with very high yields and enantioselectivities; 3- or 4-substituted aryl enones with electron-withdrawing or electron-donating groups all gave excellent yields and enantioselectivities. These results demonstrate that the substitution position and the electronic properties of the substituents on the aromatic rings have limited effects on the enantioselectivities. The exceptions to the generally high enantioselectivities with aromatic enones were the sterically more hindered 2-OMe substituted substrate **3i** (Table 3, entry 9; 80% ee) and 2-Br substituted substrate **3j** (Table 3, entry 10; 83% ee). Low reactivity was observed for the alkyl-substituted enone **3m**, with which only moderate yields were obtained, although excellent enantioselectivity was obtained (Table 3, entry 13; 70% yield, 95% ee). Cyclic enone was also evaluated, but poor results were obtained when cyclohex-2-enone (**3n**) was employed (Table 3, entry 14; 61% yield, 18% ee). If the R^2 substituent is a group other than methyl, such as cyclohexyl or phenyl, no reaction take place at all (Table 3, entries 15 and 16). Meanwhile, other enones such as *trans*-chalcone (Table 3, entry 17), rigid enone 2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one (Table 3, entry 18) were also evaluated, but also no reactions were observed. These results may be ascribed to the lower reactivity for iminium formation of the carboxyl group in chalcone, rigid or sterically hindered enones than in methyl enones.

It is known that the ester group has a large effect on the asymmetric induction of the reaction. To our great delight, the reactions of the symmetrical malonates **2a–d** all proceeded with excellent yields and enantioselectivities. Especially, a high yield was observed for the diisopropyl malonate **2d**, with up to 99% ee (Table 4, entry 4). Using diisopropyl malonate **2d** as the reagent, investigation of substrates **3g**, **3i**, **3j** and **3n**, which gave only moderate to good ee when using **2a** as reagent, were further investigated. Diisopropyl malonate **2d** reacted with enone **3g** for eight days at room temperature to afford the corresponding product **4dg** in 53% yield and 95% ee. The corresponding reaction of the other three enones **3i**, **3j** and **3n** did not take place at all.[15]

On the basis of the experimental results described above, we suggest a possible catalytic activation mode for the asymmetric induction in this catalytic system. This catalytic activation mode has no significant difference with those previously reported.[11a,f] The two substrates involved in the reaction are activated simultaneously by catalyst **1b**, as shown in Fig. 2. The carbonyl group

Table 4 Catalytic asymmetric Michael addition of malonates **2a–d** to benzylideneacetone **3a**[a]



2a-d **3a** **4aa-4da**

Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	Bn	**4aa**	99	94
2	Me	**4ba**	98	94
3	Et	**4ca**	94	92
4	*i*Pr	**4da**	99	99

[a] Unless otherwise specified, all reactions were carried out with benzylideneacetone **3a** (36.5 mg, 0.25 mmol), malonates **2** (0.50 mmol), and catalyst **1b** (13.5 mg, 0.05 mmol, 20 mol%) in toluene (1 mL) at room temperature for 72 h. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral HPLC analysis, the configuration was assigned according to literature.[11a,f]

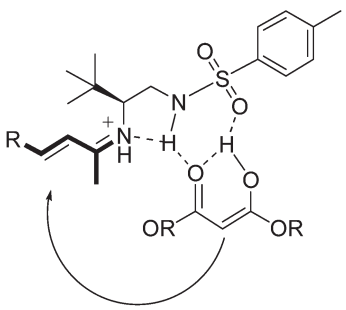


Fig. 2 Proposed catalytic activation mode for the observed enantioselectivity of the catalysis of **1b**.

of the enones is assumed to be activated by the primary amine moiety of catalyst **1b** *via* an iminium ion formation, while the sulfonamide activates the nucleophile malonate **2** through hydrogen bond.[13c] The *Re* face of the enone is shielded by the bulky *tert*-butyl group of the chiral catalyst, and the malonate approaches the open *Si* face of the enone to afford the desired *R* product.

Conclusions

In summary, we have developed a highly enantioselective organocatalysed Michael addition of malonates to enones by using simple chiral sulfonamide primary amine. A series of simple chiral sulfonamide primary amine organocatalysts is readily available from chiral primary amino alcohol or 1,2-diamine, making this methodology cheap and facile in practice. These organocatalysts have been successfully applied to promoting the asymmetric Michael addition of malonates to enones and the corresponding products were obtained in excellent yields (up to 99%) with excellent enantioselectivities (up to 99% ee). Further investigation of the application of this catalyst in other asymmetric catalytic reactions is in progress.

Experimental

General methods

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was carried out using silica gel (200–300 mesh). Melting points were measured with a XT-4 melting point apparatus. The ^{1}H NMR spectra were recorded with Varian Mercury-plus 400 MHz spectrometers, while the ^{13}C NMR spectra were recorded at 100 MHz. Infrared spectra were obtained with a Perkin Elmer Spectrum One spectrometer. The EI mass spectra were obtained with VG-ZAB-HS mass spectrometer. The ESI-HRMS spectra were obtained with Bruker APEX IV mass spectrometer. Optical rotations were measured with a WZZ-3 polarimeter. The enantiomeric excesses (ee values) of the products were determined by chiral HPLC analysis using an Agilent HP 1200 instrument (*n*-hexane–2-propanol as eluent).

Materials

Dimethyl malonate, diethyl malonate, dibenzyl malonate were commercially available and used as received. 2-Cyclohexanone were purchased from Acros and other α,β-unsaturated enones were prepared according to literature.[16] The chiral sulfonamide primary amine catalysts **1a–1e** were prepared following the previously reported procedure.[14]

General procedure for the enantioselective Michael addition reaction

To a solution of toluene (1.0 mL) was added α,β-unsaturated ketone **3** (0.25 mmol), malonate **2** (0.50 mmol), catalyst **1b** (13.5 mg, 0.05 mmol, 20 mol%). The reaction mixture was stirred at given temperature for 72 h and then the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel to yield the desired addition product **4**.

(*R*)-Dibenzyl 2-(3-oxo-1-phenylbutyl)malonate (4aa)

Compound **4aa** was obtained according to the general procedure as a white solid; yield: 99%; mp 85–87 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 15.6 min, major enantiomer t_R = 17.2 min, 94% ee; $[\alpha]_D^{25}$: −5.64 (*c* 2.06, CH_2Cl_2), Lit.[11a] $[\alpha]_D^{rt}$ = −7.1 (*c* 1.0, $CHCl_3$, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (s, 3H, CH_3), 2.88 (d, *J* = 6.4 Hz, 2H, CH_2), 3.82 (d, *J* = 9.6 Hz, 1H, CH), 3.97–4.03 (m, 1H, CH), 4.89 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 7.04–7.07 (m, 2H, ArH), 7.19–7.32 (m 13H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 430 (M^+, 1), 339 (4), 261 (9), 91 (100).

(*R*)-Dibenzyl 2-(1-(4-bromophenyl)-3-oxobutyl)malonate (4ab)

Compound **4ab** was obtained according to the general procedure as a white solid; yield: 99%; mp 79–81 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 16.6 min, major enantiomer t_R = 17.8 min, 96% ee; $[\alpha]_D^{25}$: −2.83 (*c* 1.84, CH_2Cl_2), Lit.[11f] $[\alpha]_D^{24}$ = −6.9 (*c* 1.0, $CHCl_3$, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (s, 3H, CH_3), 2.84 (d, *J* = 6.0 Hz, 2H, CH_2), 3.77 (d, *J* = 9.6 Hz, 1H, CH), 3.91–3.97 (m, 1H, CH), 4.92 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 7.03–7.07 (m, 4H, ArH), 7.28–7.33 (m, 10H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 510 (M^+, 1.2, ^{81}Br), 508 (M^+, 1.2, ^{79}Br), 419 (4), 357 (6), 91 (100).

(*R*)-Dibenzyl 2-(1-(4-chlorophenyl)-3-oxobutyl)malonate (4ac)

Compound **4ac** was obtained according to the general procedure as a white solid; yield: 99%; mp 83–85 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 16.2 min, major enantiomer t_R = 17.5 min, 98% ee; $[\alpha]_D^{25}$: −9.14 (*c* 1.75 mL, CH_2Cl_2), Lit.[11a] $[\alpha]_D^{rt}$ = −8.1 (*c* 1.0, $CHCl_3$, 98% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (s, 3H, CH_3), 2.84 (d, *J* = 6.0 Hz, 2H, CH_2), 3.78 (d, *J* = 9.6 Hz, 1H, CH), 3.93–3.99 (m, 1H, CH), 4.92 (s, 2H, CH_2), 5.14 (s, 2H, CH_2), 7.05–7.16 (m, 6H, ArH), 7.27–7.33 (m, 8H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 464 (M^+, 0.6), 313 (4), 295 (4), 91 (100).

(*R*)-Dibenzyl 2-(1-(4-methylphenyl)-3-oxobutyl)malonate (4ad)

Compound **4ad** was obtained according to the general procedure as a white solid; yield: 98%; mp 87–89 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 14.2 min,

major enantiomer t_R = 15.5 min, 94% ee; $[\alpha]_D^{25}$: −5.20 (*c* 2.04, CH_2Cl_2), Lit.[11f] $[\alpha]_D^{25}$ = −8.1 (*c* 1.0, $CHCl_3$, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 2.85 (d, *J* = 6.8 Hz, 2H, CH_2), 3.79 (d, *J* = 9.6 Hz, 1H, CH), 3.92–3.99 (m, 1H, CH), 4.90 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 7.00–7.06 (m, 6H, ArH), 7.26–7.32 (m, 8H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 444 (M^+, 1.8), 353 (4), 293 (5), 275 (20), 227 (5), 91 (100).

(*R*)-Dibenzyl 2-(1-(4-methoxyphenyl)-3-oxobutyl)malonate (4ae)

Compound **4ae** was obtained according to the general procedure as a white solid; yield: 94%; mp 55–57 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 20.5 min, major enantiomer t_R = 21.8 min, 94% ee; $[\alpha]_D^{25}$: −6.41 (*c* 1.37, CH_2Cl_2), Lit.[11f] $[\alpha]_D^{25}$ = −10.2 (*c* = 1.0, $CHCl_3$, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3H, CH_3), 2.83 (d, *J* = 6.8 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.77 (d, *J* = 9.6 Hz, 1H, CH), 3.91–3.97 (m, 1H, CH), 4.90 (s, 2H, CH_2), 5.14 (s, 2H, CH_2), 6.74 (d, *J* = 4.4 Hz, 2H, ArH), 7.06–7.11 (m, 4H, ArH), 7.26–7.32 (m, 8H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 460 (M^+, 2.4), 369 (4), 291 (10), 265 (6), 243 (6), 91 (100).

(*R*)-Dibenzyl 2-(1-(4-nitrophenyl)-3-oxobutyl)malonate (4af)

Compound **4af** was obtained according to the general procedure as a yellow solid; yield: 99%; mp 68–69 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 29.0 min, major enantiomer t_R = 33.1 min, 94% ee; $[\alpha]_D^{25}$: −7.33 (*c* 1.83, CH_2Cl_2), Lit.[11a] $[\alpha]_D^{rt}$ = −9.3 (*c* 1.0, $CHCl_3$, 89% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, 3H, CH_3), 2.89 (d, *J* = 8.8 Hz, 2H, CH_2), 3.82 (d, *J* = 9.6 Hz, 1H, CH), 4.04–4.10 (m, 1H, CH), 4.93 (s, 2H, CH_2), 5.15 (s, 2H, CH_2), 6.74 (d, *J* = 4.4 Hz, 2H, ArH), 7.07 (d, *J* = 6.4 Hz, 2H, ArH), 7.21–7.34 (m, 10H, ArH), 7.96 (d, *J* = 4.4 Hz, 2H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 445 (M^+, 0.3), 260 (5), 220 (4), 107 (24), 91 (100).

(*R*)-Dibenzyl 2-(1-(4-dimethylaminophenyl)-3-oxobutyl)-malonate (4ag)

Compound **4ag** was obtained according to the general procedure as yellow oil; yield: 62%. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.75 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 19.1 min, major enantiomer t_R = 13.0 min, 87% ee; $[\alpha]_D^{25}$: −9.03 (*c* 1.15, CH_2Cl_2), Lit.[11a] $[\alpha]_D^{rt}$ = −2.9 (*c* 1.0, $CHCl_3$, 77% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3H, CH_3), 2.82 (d, *J* = 7.2 Hz, 2H, CH_2), 2.89 (s, 6H, NCH_3), 3.77 (d, *J* = 10.0 Hz, 1H, CH), 3.87–3.94 (m, 1H, CH), 4.90 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 6.57 (d, *J* = 8.4 Hz, 2H, ArH), 7.03–7.07 (m, 4H, ArH), 7.24–7.31 (m, 8H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 473 (M^+, 22), 190 (55), 148 (36), 107 (100), 91 (100).

(*R*)-Dibenzyl 2-(1-(3-nitrophenyl)-3-oxobutyl)malonate (4ah)

Compound **4ah** was obtained according to the general procedure as a white solid; yield: 99%; mp 123–125 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.75 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 19.4 min, major enantiomer t_R = 15.7 min, 94% ee; $[\alpha]_D^{25}$: −8.58 (*c* 2.12, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 (s, 3H, CH_3), 2.92 (d, *J* = 6.4 Hz, 2H, CH_2), 3.85 (dd, *J* = 2.0, 9.4 Hz, 1H, CH), 4.06–4.12 (m, 1H, CH), 4.93 (AB, *J* = 12.6 Hz, 2H, CH_2), 5.15 (AB, *J* = 12.8Hz, 2H, CH_2), 7.08 (d, *J* = 6.8 Hz, 2H, ArH), 7.22–7.34 (m, 9H, ArH), 7.55 (d, *J* = 7.6 Hz, 1H, ArH), 7.96–7.99 (m, 1H, ArH), 8.04 (d, *J* = 1.6 Hz, 1H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.9, 167.3, 166.9, 148.0, 142.4, 135.0, 134.8, 134.6, 129.2, 128.52, 128.47, 128.38, 128.27, 122.7, 122.2, 67.4, 67.2, 56.4, 46.5, 39.6, 30.0 ppm. IR (KBr): *ν* 3067, 3034, 2958, 2922, 1739, 1727, 1702, 1529, 1458, 1354, 1266, 1182, 749, 701 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{26}NO_7$ $[M + H]^+$ 476.17038, found 476.17082.

(*R*)-Dibenzyl 2-(1-(2-methoxyphenyl)-3-oxobutyl)malonate (4ai)

Compound **4ai** was obtained according to the general procedure as a colorless oil; yield: 84%. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 13.1 min, major enantiomer t_R = 15.1 min, 80% ee; $[\alpha]_D^{25}$: −3.83 (*c* 1.62, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, 3H, CH_3), 2.85 (dd, *J* = 3.4, 16.6 Hz, 1H, CH), 3.00–3.07 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 4.15–4.23 (m, 2H, CH_2), 4.86 (s, 2H, CH_2), 5.12 (AB, *J* = 12.4 Hz, 2H, CH_2), 6.76–6.82 (m, 2H, ArH), 7.05–7.19 (m, 4H, ArH), 7.23–7.33 (m, 8H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.6, 168.2, 167.7, 157.1, 135.2, 135.1, 130.2, 128.4, 128.34, 128.28, 128.20, 128.1, 128.0, 127.5, 120.4, 110.8, 67.0, 66.8, 55.1, 54.8, 45.3, 37.1, 29.8 ppm. IR (KBr): *ν* 3066, 3033, 2951, 1733, 1716, 1602, 1542, 1496, 1456, 1356, 1244, 1145, 1023, 903, 752, 697 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{28}H_{29}O_6$ $[M + H]^+$ 461.19587, found 461.19635.

(*R*)-Dibenzyl 2-(1-(2-bromophenyl)-3-oxobutyl)malonate (4aj)

Compound **4aj** was obtained according to the general procedure as a colorless oil; yield: 84%. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.75 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 11.9 min, major enantiomer t_R = 10.0 min, 83% ee; $[\alpha]_D^{25}$: +6.38 (*c* 1.97 mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, 3H, CH_3), 2.94–3.07 (m, 2H, CH_2), 4.09 (d, *J* = 7.6 Hz, 1H, CH), 4.45–4.52 (m, 1H , CH), 4.99 (s, 2H, CH_2), 5.08 (s, 2H, CH_2), 6.69–7.03 (m, 1H, ArH), 7.10–7.28 (m, 12H, ArH), 7.49 (d, *J* = 7.6 Hz, 1H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 167.8, 167.5, 139.3, 135.2, 133.5, 128.9, 128.7, 128.6, 128.55, 128.47, 128.35, 128.2, 127.6, 124.8, 67.3, 55.0, 45.2, 39.3, 30.1 ppm. IR (KBr): *ν* 3065, 3034, 2956, 2924, 1732, 1606, 1587, 1567, 1498, 1455, 1147, 1022, 908, 751, 697 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{26}BrO_5$ $[M + H]^+$ 509.50981, found 509.09617.

(*R*)-Dibenzyl 2-(1-(3,4-dimethoxyphenyl)-3-oxobutyl)malonate (4ak)

Compound **4ak** was obtained according to the general procedure as a white solid; yield: 75%; mp 78–80 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 18.8 min, major enantiomer t_R = 21.8 min, 94% ee; $[\alpha]_D^{25}$: −7.68 (*c* 1.46, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3H, CH_3), 2.84 (d, *J* = 6.8 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.83 (br s, 1H, CH), 3.91–3.97 (m, 1H, CH), 4.91 (AB q, *J* = 12.2 Hz, 2H, CH_2), 5.14 (AB q, *J* = 12.2 Hz, 2H, CH_2), 6.67–6.73 (m, 3H, ArH), 7.03–7.06 (m, 2H, ArH), 7.23–7.33 (m, 8H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 167.8, 167.3, 148.6, 147.9, 135.1, 134.9, 132.6, 128.5, 128.3, 128.1, 128.0, 119.8, 111.5, 110.9, 67.2, 67.0, 57.4, 55.7, 55.6, 47.3, 40.2, 30.2 ppm. IR (KBr): *ν* 3034, 3008, 2957, 2940, 2836, 1745, 1714, 1591, 1516, 1469, 1457, 1448, 1374, 1358, 1263, 1195, 1148, 1025, 900, 817, 762, 750, 698 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{29}H_{31}O_7$ $[M + H]^+$ 491.20643, found 491.20709.

(*R*)-Dibenzyl 2-(1-(naphthalen-1-yl)-3-oxobutyl)malonate (4al)

Compound **4al** was obtained according to the general procedure as a colorless oil; yield: 90%. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 15.3 min, major enantiomer t_R = 17.0 min, 91% ee; $[\alpha]_D^{25}$: +19.0 (*c* 1.12, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3H, CH_3), 3.09 (d, *J* = 4.8 Hz, 2H, CH_2), 4.09 (d, *J* = 7.6 Hz, 1H, CH), 4.82 (s, 2H, CH_2), 4.97 (br s, 1H , CH), 5.10 (s, 2H, CH_2), 6.88–6.97 (m, 2H, ArH), 7.17–7.30 (m, 10H, ArH), 7.45–7.51 (m, 2H, ArH), 7.69 (d, *J* = 3.2 Hz, 1H, ArH), 7.81 (d, *J* = 7.2 Hz, 1H, ArH), 8.25 (d, *J* = 7.6 Hz, 1H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 168.0, 167.5, 136.9, 135.1, 134.9, 134.0, 131.2, 128.8, 128.5, 128.3, 128.22, 128.16, 128.08, 127.98, 127.8, 126.4, 125.7, 125.1, 123.1, 109.6, 67.2, 67.1, 56.6, 46.7, 30.1 ppm. IR (KBr): *ν* 3060, 3035, 2956, 2923, 1759, 1722, 1598, 1509, 1498, 1454, 1149, 1003, 905, 796, 780, 751, 696 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{31}H_{29}O_5$ $[M + H]^+$ 481.20095, found 481.20146.

(*R*)-Dibenzyl 2-(1-isopropyl-3-oxobutyl)malonate (4am)

Compound **4am** was obtained according to the general procedure as a colorless oil; yield: 70%. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol 95 : 5 v/v, flow rate 1.0 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 11.1 min, major enantiomer t_R = 9.9 min, 95% ee; $[\alpha]_D^{25}$: −4.3 (*c* 3.10, CH_2Cl_2), Lit.[11a] $[\alpha]_D^{rt}$ = −9.7 (*c* 1.0, $CHCl_3$, 84% ee). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.8 Hz, 3H, CH_3), 0.87 (d, *J* = 6.8 Hz, 3H, CH_3), 1.72–1.64 (m, 1H, CH), 2.06 (s, 3H, $COCH_3$), 2.48 (dd, *J* = 5.6, 18 Hz, 1H, $COCH_2$), 2.66 (dd, *J* = 4.2, 18 Hz, 1H, $COCH_2$), 2.77–2.71 (m, 1H, CH), 3.63 (d, *J* = 6.8 Hz, 1H, CO_2CHCO_2), 5.10 (s, 2H, OCH_2), 5.11 (s, 2H, OCH_2), 7.34–7.27 (m, 10H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.1, 168.8, 168.5, 135.2, 128.5, 128.3, 128.2, 67.1, 67.0, 53.5, 42.7, 38.9, 30.1, 29.8, 20.5, 18.8 ppm.

(*R*)-Dibenzyl 2-(3-oxocyclohexyl)malonate (4an)

Compound **4an** was obtained according to the general procedure as a white solid; yield: 61%; mp 54–56 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 25.8 min, major enantiomer t_R = 29.8 min, 18% ee; $[\alpha]_D^{25}$: −2.15 (*c* 1.02, CH_2Cl_2), Lit.[11a] $[\alpha]_D^{rt}$ = −1.4 (*c* 1.0, $CHCl_3$, 83% ee). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.51 (m, 1H, CH_2), 1.58–1.68 (m, 1H, CH_2), 1.91 (d, *J* = 12.4 Hz, 1H, CH_2), 2.00–2.04 (m, 1H, CH_2), 2.15–2.27 (m, 2H, CH_2), 2.35–2.46 (m, 2H, CH_2), 2.51–2.58 (m, 1H, CH), 3.14 (d, *J* = 7.6 Hz, 1H, CH), 5.15 (s, 4H, CH_2), 7.26–7.34 (m, 10H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 289 (M^+, 4), 183 (12), 139 (5), 107 (22), 91 (100).

(*R*)-Dimethyl 2-(3-oxo-1-phenylbutyl)malonate (4ba)

Compound **4ba** was obtained according to the general procedure as a white solid; yield: 98%; mp 44–45 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 14.6 min, major enantiomer t_R = 18.3 min, 94% ee; $[\alpha]_D^{25}$: −13.33 (*c* 1.20, CH_2Cl_2), Lit.[11a] $[\alpha]_D^{rt}$ = −9.7 (*c* 1.0, $CHCl_3$, 73% ee). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.03 (s, 3H, CH_3), 2.88–3.03 (m, 2H, CH_2), 3.50 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 3.74 (d, *J* = 7.6 Hz, 1H, CH), 3.94–4.01 (m, 1H, CH), 7.20–7.27 (m, 5H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 278 (M^+, 10), 215 (16), 187 (28), 176 (34), 147 (58), 132 (13), 115 (14), 91 (6), 43 (100).

(*R*)-Diethyl 2-(3-oxo-1-phenylbutyl)malonate (4ca)

Compound **4ca** was obtained according to the general procedure as a white solid; yield: 94%; mp 41–42 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 11.8 min, major enantiomer t_R = 13.2 min, 92% ee; $[\alpha]_D^{25}$: −17.61 (*c* 1.42, CH_2Cl_2), Lit.[11a] $[\alpha]_D^{rt}$ = −12.1 (*c* 1.0, $CHCl_3$, 91% ee). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.2 Hz, 3H, CH_3), 1.25 (t, *J* = 7.2 Hz, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.87–2.99 (m, 2H, CH_2), 3.69 (d, *J* = 9.6 Hz, 1H, CH), 3.91–3.99 (m, 3H, CH + CH_2), 4.16–4.20 (m, 2H, CH_2), 7.20–7.26 (m, 5H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 306 (M^+, 15), 215 (26), 187 (56), 160 (22), 147 (45), 145 (22), 91 (8), 43 (100).

(*R*)-Diisopropyl 2-(3-oxo-1-phenylbutyl)malonate (4da)

Compound **4da** was obtained according to the general procedure as a colorless oil; yield: 99%. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 80 : 20 v/v, flow rate 0.5 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 10.1 min, major

enantiomer t_R = 11.4 min, 99% ee; $[\alpha]_D^{25}$: −20.02 (*c* 1.76, CH_2Cl_2), Lit.[11a] $[\alpha]_D^{rt}$ = −13.6 (*c* 1.0, $CHCl_3$, 71% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.0 Hz, 3H, CH_3), 1.04 (d, *J* = 6.0 Hz, 3H, CH_3), 1.22–1.24 (m, 6H, CH_3), 2.01 (s, 3H, CH_3), 2.84–2.97 (m, 2H, CH_2), 3.64 (d, *J* = 10.0 Hz, 1H, CH), 3.91–3.97 (m, 1H, CH), 4.74–4.81 (m, 1H, CH), 5.01–5.08 (m, 1H, CH), 7.20–7.25 (m, 5H, ArH) ppm. MS (EI): *m*/*z* (% rel. intensity) 334 (M^+, 15), 233 (18), 214 (36), 187 (32), 162 (17), 147 (76), 104 (18), 43 (100).

(*R*)-Diisopropyl 2-[1-(4-dimethylaminophenyl)-3-oxobutyl]-malonate (4dg)

Compound **4dg** was obtained according to the general procedure as a colorless oil; yield: 53% (at room temperature for 8 days). The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 70 : 30 v/v, flow rate 0.75 mL min^{-1}, detection at 254 nm): minor enantiomer t_R = 11.4 min, major enantiomer t_R = 7.0 min, 95% ee; $[\alpha]_D^{15}$: −19.8 (*c* 2.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.4 Hz, 3H, CH_3), 1.07 (d, *J* = 6.0 Hz, 3H, CH_3), 1.22 (d, *J* = 3.2 Hz, 3H, CH_3), 1.24 (d, *J* = 3.2 Hz, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.79–2.93 (m, 8H, CH_2 + $2CH_3$), 3.59 (d, *J* = 10.0 Hz, 1H, CH), 3.81–3.87 (m, 1H, CH), 4.74–4.84 (m, 1H, CH), 5.00–5.09 (m, 1H, CH), 6.63 (d, *J* = 8.4 Hz, 2H, ArH), 7.09 (d, *J* = 8.8 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 168.1, 167.4, 149.7, 128.9, 112.7, 69.1, 68.7, 58.2, 48.1, 40.7, 39.9, 30.4, 21.8, 21.6, 21.51, 21.45 ppm. IR (KBr): ν 2980, 1725, 1614, 1522, 1467, 1353, 1255, 1157, 1103, 821 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{32}NO_5$ $[M + H]^+$ 378.22750, found 378.222710.

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Notes and references

1 P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, 1992. For selected reviews of asymmetric Michael additions, see: (*a*) O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, 1877; (*b*) D.-M. Du and W.-T. Hua, *Chin. J. Org. Chem.*, 2002, **22**, 164; (*c*) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 1701; (*d*) J. Christoffers, G. Koripelly, A. Rosiak and M. Rössle, *Synthesis*, 2007, 1279; (*e*) S. Sulzer-Mossé and A. Alexakis, *Chem. Commun.*, 2007, 3123; (*f*) J. L. Vicario, D. Badía and L. Carrillo, *Synthesis*, 2007, 2065; (*g*) D. Almaşi, D. A. Alonso and C. Nájera, *Tetrahedron: Asymmetry*, 2007, **18**, 299; (*h*) D. Enders, C. Wang and J. X. Liebich, *Chem.–Eur. J.*, 2009, **15**, 11058; (*i*) C. Hawner and A. Alexakis, *Chem. Commun.*, 2010, **46**, 7295; (*j*) M. Thirumalaikumar, *Org. Prep. Proced. Int.*, 2011, **43**, 67; (*k*) J. L. Vicario, D. Badía, L. Carrillo and E. Reyes, *Organocatalytic Enantioselective Conjugate Additions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, RSC Publishing, Cambridge, 2010.

2 For selected examples of asymmetric Michael additions of malonates, see: (*a*) G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazznti, P. Ricci, L. Sambri and P. Melchiorre, *Angew. Chem.*, 2006, **118**, 5088; G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazznti, P. Ricci, L. Sambri and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2006, **45**, 4966; (*b*) A. Lattanzi, *Tetrahedron: Asymmetry*, 2006, **17**, 837; (*c*) J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun.*, 2005, 4481; (*d*) H. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906; (*e*) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119; (*f*) S. H. McCooey and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367; (*g*) S. Brandau, A. Landa, J. Franzén, M. Marigo and K. A. Jørgensen, *Angew. Chem.*, 2006, **118**, 4415; S. Brandau, A. Landa, J. Franzén, M. Marigo and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2006, **45**, 4305; (*h*) D. A. Evans and D. Seidel, *J. Am. Chem. Soc.*, 2005, **127**, 9958; (*i*) A. Ma, S. Zhu and D. Ma, *Tetrahedron Lett.*, 2008, **49**, 3075; (*j*) L. Zhou, L. Lin, W. Wang, J. Ji, X. Liu and X. Feng, *Chem. Commun.*, 2010, **46**, 3601; (*k*) Z. Wang, D. Chen, Z. Yang, S. Bai, X. Liu, L. Lin and X. Feng, *Chem.–Eur. J.*, 2010, **16**, 10130.

3 For selected examples of asymmetric Michael additions of keto esters, see: (*a*) Y. Hoashi, T. Yabuta and Y. Takemoto, *Tetrahedron Lett.*, 2004, **45**, 9185; (*b*) K. Majima, R. Takita, A. Okada, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 15837; (*c*) F. Wu, H. Li, R. Hong and L. Deng, *Angew. Chem., Int. Ed.*, 2006, **45**, 947; (*d*) M. Watanabe, A. Ikagawa, H. Wang, K. Murata and T. Ikariya, *J. Am. Chem. Soc.*, 2004, **126**, 11148; (*e*) H.-P. Cui, P. Li, X.-W. Wang, Z. Chai, Y.-Q. Yang, Y.-P. Cai, S.-Z. Zhu and G. Zhao, *Tetrahedron*, 2011, **67**, 312; (*f*) Z. Yu, X. Liu, L. Zhou, L. Lin and X. Feng, *Angew. Chem., Int. Ed.*, 2009, **48**, 5195.

4 For selected examples of asymmetric Michael additions of diketones, see: (*a*) J. Pulkkinen, P. S. Aburel, N. Halland and K. A. Jøgensen, *Adv. Synth. Catal.*, 2004, **346**, 1077; (*b*) J. Wang, H. Li, W.-H. Duan, L. Zu and W. Wang, *Org. Lett.*, 2005, **7**, 4713; (*c*) M. Terada, H. Ube and Y. Yaguchi, *J. Am. Chem. Soc.*, 2006, **128**, 1454; (*d*) Z. Dong, J. Feng, W. Cao, X. Liu, L. Lin and X. Feng, *Tetrahedron Lett.*, 2011, **52**, 3433.

5 For review of catalytic asymmetric Michael addition of α-cyanoacetates, see: (*a*) S. Jautze and R. Peters, *Synthesis*, 2010, 365. For selected examples of asymmetric Michael additions of α-nitro or α-cyanoesters, see: (*b*) M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2003, **125**, 11204; (*c*) I. T. Raheem, S. N. Goodman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 706; (*d*) T. Ikariya, H. Wang, M. Watanabe and K. Murata, *J. Organomet. Chem.*, 2004, **689**, 1377; (*e*) A. Prieto, N. Halland and K. A. Jørgensen, *Org. Lett.*, 2005, **7**, 3897; (*f*) C. Liu and Y. Lu, *Org. Lett.*, 2010, **10**, 2278.

6 Y. Gao, Q. Ren, W.-Y. Siau and J. Wang, *Chem. Commun.*, 2011, **47**, 5819.

7 For selected examples of asymmetric Michael additions of nitriles, see: (*a*) Y. Hoashi, T. Okino and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2005, **44**, 4032; (*b*) J. Wang, H. Li, L. Zu, W. Jiang, H. Xie, W. Duan and W. Wang, *J. Am. Chem. Soc.*, 2006, **128**, 12652; (*c*) X. Li, L. Cun, C. Lian, L. Zhong, Y. Chen, J. Liao, J. Zhu and J. Deng, *Org. Biomol. Chem.*, 2008, **6**, 349; (*d*) J. Shi, M. Wang, L. He, K. Zheng, X. H. Liu, L. L. Lin and X. M. Feng, *Chem. Commun.*, 2009, 4711; (*e*) A. Russo, A. Perfetto and A. Lattanzi, *Adv. Synth. Catal.*, 2009, **351**, 3067; (*f*) A. Russo, A. Capobianco, A. Perfetto, A. Lattanzi and A. Peluso, *Eur. J. Org. Chem.*, 2011, **1922**.

8 For selected examples, see: (*a*) N. End, L. Macko, M. Zehnder and A. Pfaltz, *Chem.–Eur. J.*, 1998, **4**, 818; (*b*) Y. S. Kim, S. Matsunaga, J. Das, A. Sekine, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2000, **122**, 6506; (*c*) H. Sasai, T. Arai, Y. Satow, K. N. Houk and M. Shibasaki, *J. Am. Chem. Soc.*, 1995, **117**, 6194; (*d*) M. Agostinho and S. Kobayashi, *J. Am. Chem. Soc.*, 2008, **130**, 2430; (*e*) D. Chen, Z. Chen, X. Xiao, Z. Yang, L. Lin, X. Liu and X. Feng, *Chem.–Eur. J.*, 2009, **15**, 6807.

9 (*a*) D. Y. Kim, S. C. Huh and S. M. Kim, *Tetrahedron Lett.*, 2001, **42**, 6299; (*b*) R. T. Dere, R. R. Pal, P. S. Patil and M. M. Salunkhe, *Tetrahedron Lett.*, 2003, **44**, 5351; (*c*) T. Ooi, D. Ohara, K. Fukumoto and K. Maruoka, *Org. Lett.*, 2005, **7**, 3195.

10 (*a*) M. Yamaguchi, T. Shiraishi and M. Hirama, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1176; (*b*) M. Yamaguchi, T. Shiraishi and M. Hirama, *J. Org. Chem.*, 1996, **61**, 3520.

11 (*a*) N. Halland, P. S. Aburel and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 661; (*b*) T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2003, **125**, 12672; (*c*) J. Wang, H. Li, L. Zu, W. Jiang, H. Xie, W. Duan and W. Wang, *J. Am. Chem. Soc.*, 2006, **128**, 12652; (*d*) V. Wascholowski, K. R. Knudsen, C. E. T. Mitchell and S. V. Ley, *Chem.–Eur. J.*, 2008, **14**, 6155; (*e*) Z. Jiang, W. Ye, Y. Yang and C.-H. Tan, *Adv. Synth. Catal.*, 2008, **350**, 2345; (*f*) Y.-Q. Yang and

G. Zhao, *Chem.–Eur. J.*, 2008, **14**, 10888; (*g*) Z. Mao, Y. Jia, W. Li and R. Wang, *J. Org. Chem.*, 2010, **75**, 7428; (*h*) P. Li, S. Wen, F. Yu, Q. Liu, W. Li, Y. Wang, X. Liang and J. Ye, *Org. Lett.*, 2009, **11**, 753; (*i*) K. R. Knudsen, C. E. T. Mitchell and S. V. Ley, *Chem. Commun.*, 2006, 66.

12 Z. Wang, Q. Wang, Y. Zhang and W. Bao, *Tetrahedron Lett.*, 2005, **46**, 4657.

13 (*a*) B. K. Ni, Q. Y. Zhang, K. Dhungana and A. D. Headley, *Org. Lett.*, 2009, **11**, 1037; (*b*) L. Zu, J. Wang, H. Li and W. Wang, *Org. Lett.*, 2006, **8**, 3077; (*c*) J. Wang, H. Li, B. Lou, L. Zu, H. Guo and W. Wang, *Chem.–Eur. J.*, 2006, **12**, 4321; (*d*) W. Wang, J. Wang and H. Li, *Angew. Chem., Int. Ed.*, 2005, **44**, 1369; (*e*) S. R. Ban, D.-M. Du, H. Liu and W. Yang, *Eur. J. Org. Chem.*, 2010, 5160; (*f*) C. Luo and D.-M. Du, *Synthesis*, 2011, 1968.

14 (*a*) H. Liu and D.-M. Du, *Adv. Synth. Catal.*, 2010, **352**, 1113; (*b*) X. Du, H. Liu and D.-M. Du, *Eur. J. Org. Chem.*, 2011, 786.

15 These results were obtained at room temperature (about 15 °C in March) during the revision period; the data in Table 3 were obtained at room temperature in June last year.

16 (*a*) S. Paul and M. Gupta, *Synth. Commun.*, 2005, **35**, 213; (*b*) G.-F. Han, J.-J. Wang and G.-J. Jiang, *Chin. J. Org. Chem.*, 2003, **23**, 1004; (*c*) M. Wang, L. Lin, J. Shi, X. Liu, Y. Kuang and X. Feng, *Chem.–Eur. J.*, 2011, **17**, 2365.