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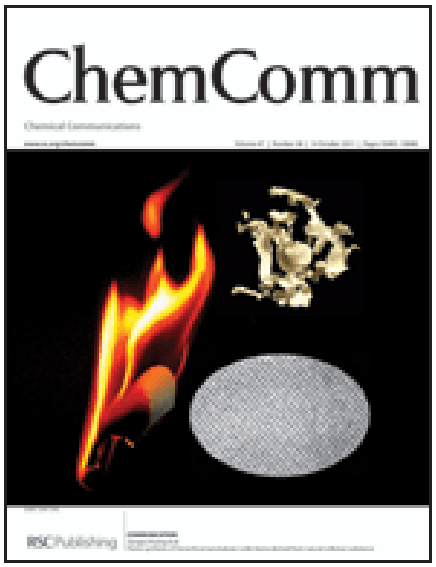

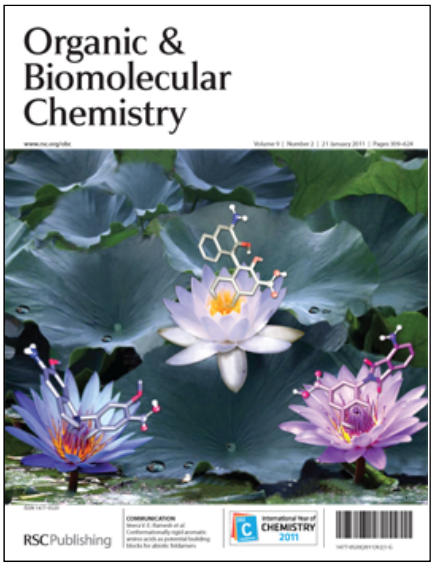

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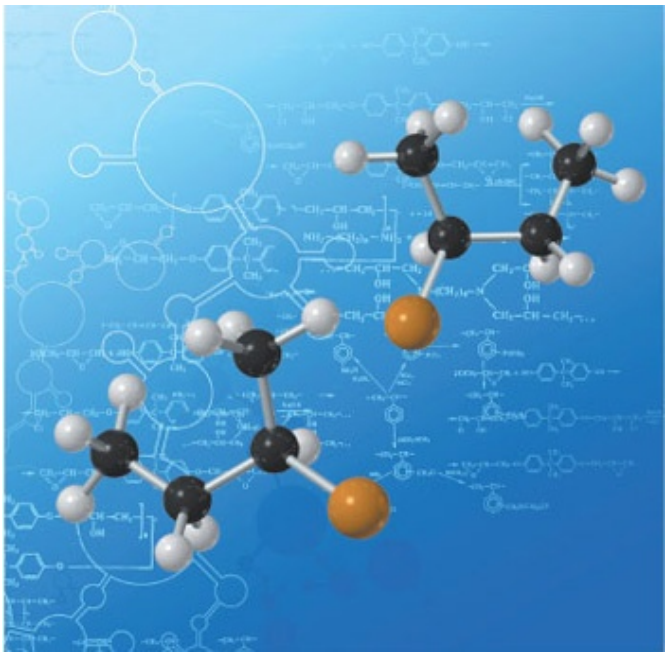

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Squaramide-catalyzed enantioselective Michael addition of malononitrile to chalcones†

Wen Yang, Yang Jia and Da-Ming Du*

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A highly enantioselective Michael addition of malononitrile to chalcones catalyzed by a chiral quinine-derived squaramide catalyst has been developed. This organocatalytic reaction at a very low catalyst loading (0.5 mol%) led to chiral γ-cyano carbonyl compounds in good yields with high enantioselectivities (up to 96% ee) under mild reaction conditions.

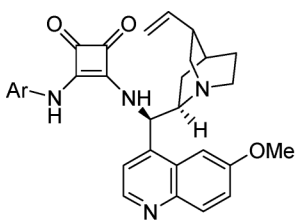
Introduction

The conjugate addition of carboanion nucleophiles to electron-deficient olefins is one of the fundamental carbon–carbon bond forming reactions in organic synthesis, and it is also a powerful tool for the construction of highly functionalized carbon skeletons.[1,2] Malononitrile is a valuable source of stabilized carboanion due to the strong electron-withdrawing property of the nitrile group and its facile transformations to other useful functional groups.[3] However, studies on the asymmetric Michael addition employing malononitrile are currently limited.[4,5] In this context, we were intrigued to develop an organocatalytic asymmetric Michael addition of malononitrile to chalcones. To date, only a few efficient catalytic enantioselective methods to perform this reaction are reported.[5] Wang first reported the asymmetric Michael addition of malononitrile to *trans*-chalcone catalyzed by cinchona-derived thiourea to give the product in 77% yield with 88% ee.[5a] Recently, Feng and co-workers developed an efficient quinine-Al(O^{i}Pr)$_3$ complex catalytic system to promote this reaction with high yields and good enantioselectivities.[5b] Lattanzi and co-workers employed quinine as an efficient catalyst to achieve good results.[5c] More recently, Lattanzi reported α,α-L-diaryl prolinols as promoters, even though the enantioselectivities obtained were not ideal.[5d] Despite these successes, the development of efficient catalytic systems in pursuit of excellent enantioselectivity, low catalyst loading, and mild reaction conditions is still challenging and in great demand.

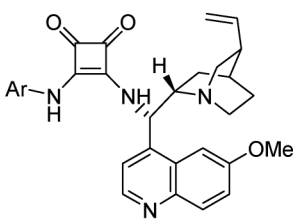
Chiral squaramide is a novel type of good hydrogen bond donor.[6,7] In 2008, Rawal first developed a chiral squaramide derivative to promote the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes.[7a] After the pioneering report, a series of chiral squaramide organocatalysts were developed and successfully applied in various asymmetric reactions,[7] including asymmetric Michael addition,[7a–h] Friedel–Crafts reaction,[7i] α-amination of 1,3-dicarbonyl compounds,[7j] Morita–Baylis–Hillman reaction,[7k] and Aldol reaction.[7l] Recently, our group also reported chiral squaramide-catalyzed asymmetric reactions.[7e,g] Herein, we would like to describe the highly enantioselective Michael addition of malononitrile to chalcones catalyzed by chiral squaramide organocatalysts.

Results and discussion

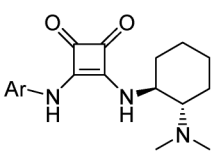
Initially, the reaction of *trans*-chalcone **1a** with malononitrile **2** was carried out in the presence of squaramide catalyst **I** (10% mol) at room temperature, and the desired product **3a** was obtained in 75% yield with 33% ee. In order to identify a more efficient catalyst, we prepared a series of chiral squaramide organocatalysts **I–VIII** (Fig. 1) and performed a systematic catalyst screening. When



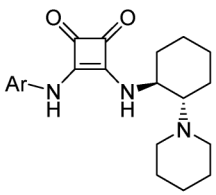
I: Ar = 3,5-$(CF_3)_2C_6H_3$
II: Ar = 4-$CF_3C_6H_4$



III: Ar = 3,5-$(CF_3)_2C_6H_3$
IV: Ar = 4-$CF_3C_6H_4$



V: Ar = 3,5-$(CF_3)_2C_6H_3$
VI: Ar = 4-$CF_3C_6H_4$



VII: Ar = 3,5-$(CF_3)_2C_6H_3$
VIII: Ar = 4-$CF_3C_6H_4$

Fig. 1 Screened squaramide catalysts.

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of Michael addition compounds, and HPLC chromatographs. See DOI: 10.1039/c1ob06302b

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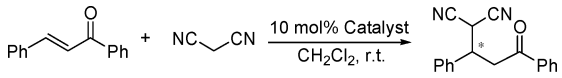
Table 1 Screening of organocatalysts for the asymmetric Michael addition of malononitrile to *trans*-chalcone[a]



1a 2 3a

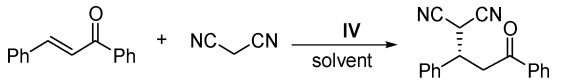
Entry	Catalyst	Yield[b] (%)	ee[c] (%)	Config.
1	**I**	75	33	*R*
2	**II**	83	59	*R*
3	**III**	73	82	*S*
4	**IV**	78	86	*S*
5	**V**	82	81	*S*
6	**VI**	80	79	*S*
7	**VII**	68	81	*S*
8	**VIII**	74	79	*S*

[a] Unless noted otherwise, reactions were carried out with *trans*-chalcone **1a** (0.20 mmol) and malononitrile (0.24 mmol) in CH_2Cl_2 (0.5 mL) at room temperature for 24 h. [b] Isolated yields after column chromatography purification. [c] Determined by chiral HPLC.

quinidine-derived squaramide catalyst **II** with *para*-CF_3 group was used, an obvious increase in the enantioselectivity (59% ee) was observed. To our delight, quinine-derived squaramides **III** and **IV** afforded the corresponding products with the opposite configuration in good yields with significantly higher enantioselectivities (82 and 86% ee, respectively). Squaramide catalysts **V–VIII** derived from chiral cyclohexane-1,2-diamine were also tested, but no better results were obtained (Table 1, entries 5–8). Therefore, squaramide **IV** was selected as the best catalyst for further optimization.

With squaramide **IV** as the optimal catalyst, a simple solvent screening was first carried out. The screening results were shown in Table 2. Variation of the solvents had a pronounced effect on the yields and enantioselectivities. The use of THF and toluene led to an obvious decrease in the yields and enantioselectivities (entries 2 and 3), while the polar solvent MeOH gave almost racemic product in excellent yield (entry 4). Other chlorinated solvents were also screened, and the best result (76% yield, 88% ee) was obtained in $CHCl_3$ (entries 5 and 6). Subsequently, the effects of temperature and substrate concentration were investigated. Neither heating nor cooling the reaction gave a better result (entries 7 and 8). Variation of substrate concentration affected the enantioselectivity slightly (entries 9 and 10). Finally, the effect of catalyst loading was investigated. Interestingly, the yield and enantioselectivity were slightly improved with a reduced catalyst loading from 10 to 0.5 mol% (entries 1 and 11–13). When the catalyst loading was reduced to 0.2 mol%, the adduct was obtained with high enantioselectivity but in low yield (entry 14). The phenomena of increased enantioselectivity with decreased catalyst loading may be ascribed to the decreased self-association of this type of catalyst, as it is known that urea and thiourea based organocatalysts can form hydrogen-bonded dimmers or aggregates, resulting in the dependency of enantioselectivity on the concentration.[8] For comparison, a simple catalyst, quinine, was investigated under identical or similar conditions, with toluene as the best solvent, and inferior results were obtained (entries 15 and 16). The results show the superiority of the squaramide-modified quinine catalyst in a low catalyst loading.

Table 2 Optimization of reaction conditions for the asymmetric Michael addition of malononitrile to *trans*-chalcone[a]



1a 2 3a

Entry	Solvent	Loading (mol%)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	10	78	86
2	THF	10	44	61
3	Toluene	10	37	61
4	MeOH	10	95	2
5	CH_2ClCH_2Cl	10	68	74
6	$CHCl_3$	10	76	88
7[d]	$CHCl_3$	10	87	76
8[e]	$CHCl_3$	10	50	86
9[f]	$CHCl_3$	10	79	85
10[g]	$CHCl_3$	10	58	89
11	$CHCl_3$	5	79	89
12	$CHCl_3$	1	82	89
13	$CHCl_3$	0.5	82	90
14	$CHCl_3$	0.2	39	91
15[h]	$CHCl_3$	0.5	67	73
16[h]	Toluene	0.5	74	80

[a] Unless noted otherwise, reactions were carried out with *trans*-chalcone **1a** (0.20 mmol) and malononitrile **2** (0.24 mmol) in the solvent (0.5 mL) at room temperature for 24 h. [b] Isolated yields after column chromatography purification. [c] Determined by chiral HPLC. [d] Reaction was performed at 60 °C for 12 h. [e] Reaction was performed at 0 °C for 96 h. [f] 0.25 mL of $CHCl_3$ was used. [g] 1.0 mL of $CHCl_3$ was used. [h] Quinine was used as the catalyst.

With the optimal reaction conditions established, we explored the scope of this asymmetric Michael addition. The results are shown in Table 3. The position and the electronic property of substituent on the aromatic ring have a very limited effect on the enantioselectivity. A wide array of chalcones bearing electron-withdrawing or electron-donating substitutions reacted smoothly with malononitrile **2** to afford the corresponding adducts with good to high enantioselectivities (entries 2–16). The electronic property of substituent has a certain effect on the yield. Generally, those substrates with electron-withdrawing groups gave high yields, and moderate to good yields were achieved for electron-rich substrates. Other chalcone analogues were also tested in the reaction. When substrate **1q** derived from 1-naphthlaldehyde was used as an acceptor, good yield and high enantioselectivity (74% yield, 89% ee) were obtained (entry 17). Substrate **1r** with a furan ring gave moderate yield and good enantioselectivity (54% yield, 83% ee) after a prolonged time (entry 18). Aliphatic enones **1s** and **1t** were proved to be viable substrates to give the corresponding products with good enantioselectivities, even though they exhibited low reactivity (entries 19 and 20).

Further substrate scope was investigated as shown in Scheme 1. (2*E*,4*E*)-1,5-Diphenylpenta-2,4-dien-1-one **4** reacted with malononitrile **2** to afford the 1,4-addition product **5** in moderate yield with high enantioselectivity. 1-Phenyl-2-buten-1-one as a substrate was also investigated, but no reaction occurred. Inspired by Wang's recent report,[9] the reaction of (*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one **6** and malononitrile **2** was carried out with 1 mol% **IV**, and the cascade Michael–oxa-Michael–tautomerization process occurred to give the corresponding product **7** in moderate yield with high enantioselectivity. To further

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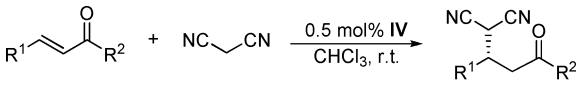
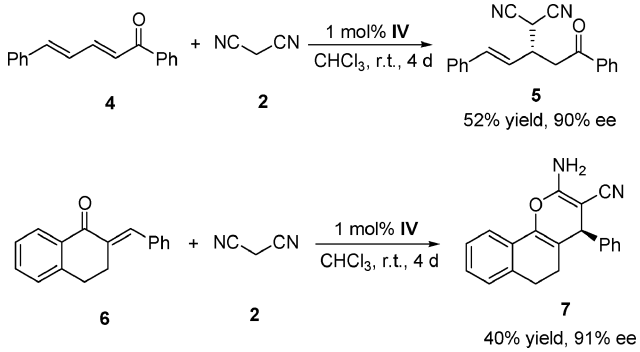
Table 3 Scope of the asymmetric Michael addition of malononitrile to *trans*-chalcones and other enones[a]



1a-t 2 3a-t

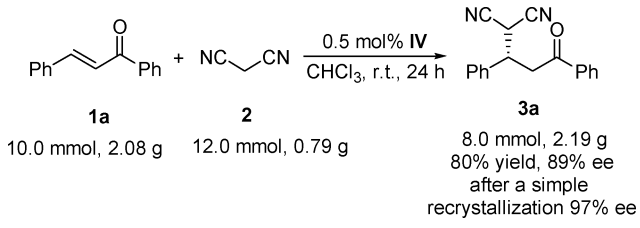
Entry	R^1	R^2	Product	Yield[b] (%)	ee[c] (%)
1	C_6H_5	C_6H_5	**3a**	82	90 (*S*)[d]
2	4-FC_6H_4	C_6H_5	**3b**	77	96
3	4-ClC_6H_4	C_6H_5	**3c**	83	91
4	2-ClC_6H_4	C_6H_5	**3d**	91	80
5	2,4-$Cl_2C_6H_3$	C_6H_5	**3e**	96	86
6	4-BrC_6H_4	C_6H_5	**3f**	91	91
7	3-BrC_6H_4	C_6H_5	**3g**	94	88
8	4-MeC_6H_4	C_6H_5	**3h**	79	90
9	4-$OMeC_6H_4$	C_6H_5	**3i**	50	90
10	2-$OMeC_6H_4$	C_6H_5	**3j**	70	89
11	C_6H_5	4-FC_6H_4	**3k**	79	89
12	C_6H_5	4-ClC_6H_4	**3l**	90	89
13	C_6H_5	4-BrC_6H_4	**3m**	88	90
14	C_6H_5	4-$OMeC_6H_4$	**3n**	60	91
15	4-MeC_6H_4	4-MeC_6H_4	**3o**	71	92
16	4-ClC_6H_4	4-ClC_6H_4	**3p**	92	88
17	1-Naphthyl	C_6H_5	**3q**	74	89
18[e]	2-Furyl	C_6H_5	**3r**	54	83
19[e]	Cyclohexyl	C_6H_5	**3s**	23	86
20[e]	^{t}Bu	C_6H_5	**3t**	35	88

[a] Unless noted otherwise, reactions were carried out with *trans*-chalcones **1** (0.20 mmol) and malononitrile **2** (0.24 mmol) in $CHCl_3$ (0.5 mL) at room temperature for 24 h. [b] Isolated yields after column chromatography purification. [c] Determined by chiral HPLC. [d] Absolute configuration was determined by comparison of the optical rotation with literature data.[5b,c,10] [e] Reaction was performed for 48 h.



Scheme 1 Further investigation of substrate scope.

evaluate the synthetic potential of the catalytic system, the gram-scale preparation of **3a** was performed. As shown in Scheme 2, the catalytic reaction was readily gram-scaled without significant



Scheme 2 The gram-scale preparation of **3a**.

changes in yield or enantioselectivity, and the adduct **3a** with 97% ee was obtained after a simple recrystallization.

Based on the absolute configuration of the adduct **3a**, a possible transition-state model for the catalytic reaction of chalcone **1a** and malononitrile **2** is hypothesized and shown in Fig. 2. The chiral squaramide **IV** may act as a bifunctional catalyst. Malononitrile **2** is deprotonated by the basic nitrogen atom of the tertiary amine. Meanwhile, the squaramide moiety as a Brønsted acid activates chalcone **1a** through double hydrogen bonding. The deprotonated malononitrile attacks the activated chalcone from the *Re*-face to afford the *S*-configured product, which is consistent with the observed result.

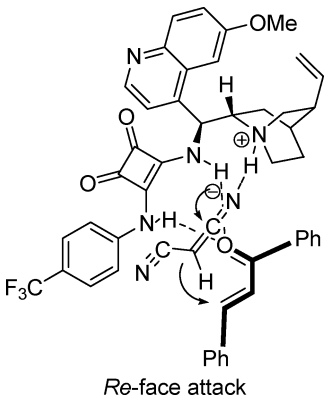


Fig. 2 Proposed transition state model.

Conclusions

In summary, we have developed a squaramide-catalyzed highly enantioselective Michael addition of malononitrile to chalcones. This catalytic reaction at a very low catalyst loading (0.5 mol%) was effective to give the Michael adducts with high yields and good enantioselectivities (up to 96% ee) under mild reaction conditions. Moreover, this catalytic reaction was readily gram-scaled without significant changes in yield or enantioselectivity. Further studies on asymmetric reactions catalyzed by squaramides are underway in our laboratory.

Experimental

Geneal methods

Commercially available compounds were used without further purification, unless otherwise stated. Column chromatography was carried out with silica gel (200–300 mesh). Melting points were measured with a XT-4 melting point apparatus without correction. ^{1}H NMR spectra were recorded with a Varian Mercury-plus 400 MHz spectrometer. Chemical shifts were reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br s = broad singlet), coupling constant(s) in Hz, integration assignment. ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Infrared spectra were obtained with a Perkin Elmer Spectrum One spectrometer. The ESI-MS

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spectra were obtained with a Bruker APEX IV mass spectrometer or a Varian MS-500 mass spectrometer. Optical rotations were measured with Krüss P8000 or WZZ-3 polarimeter at the indicated concentration with units g/100 mL. The enantiomeric excesses of the products were determined by chiral HPLC using an Agilent 1200 LC instrument with a Daicel Chiralpak IA or AS-H column. The absolute configurations of the known adducts were assigned by HPLC and optical rotation comparisons with the reported data,[5b,c,10] and those of other adducts were assigned by analogy.

Preparation of squaramide organocatalysts I–VIII

The squaramide organocatalysts **I–VIII** were prepared following the reported procedures.[7e,g]

General procedure for the enantioselective Michael addition reaction

Organocatalyst **IV** (11.3 mg, 0.02 mmol) was added to chloroform to afford the solution of catalyst **IV** (10.0 mL, 2.0 mmol L^{-1}). To a solution of *trans*-chalcones **1** (0.20 mmol) in the above catalyst **IV** solution (0.5 mL, 0.001 mmol, 0.5 mol% catalyst) was added malononitrile **2** (15.9 mg, 0.24 mmol). The reaction mixture was stirred at room temperature for 24 h. Then the mixture was directly purified by silica gel column chromatography (ethyl acetate–petroleum ether 1 : 15) to give the corresponding adducts **3**.

(*S*)-2-(3-Oxo-1,3-diphenylpropyl)malononitrile (3a). Compound **3a** was obtained according to the general procedure as a white solid (44.7 mg, 82% yield); mp 109–111 °C. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 14.3 min, major enantiomer t_R = 18.5 min, 90% ee; $[\alpha]_D^{20}$ −11.6 (*c* 0.50, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.6 Hz, 2H, ArH), 7.63 (t, *J* = 7.2 Hz, 1H, ArH), 7.52–7.39 (m, 7H, ArH), 4.66 (d, *J* = 5.2 Hz, 1H, CN-CH), 3.98–3.94 (m, 1H, Ar-CH), 3.76–3.62 (m, 2H, CH_2) ppm; MS (ESI): *m*/*z* (% rel. intensity) 272.9 $[M - H]^+$ (100). Lit.[5b] $[\alpha]_D^{20}$ −12.59 (*c* 0.27, CH_2Cl_2), 89% ee.

(*S*)-2-[1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl]malononitrile (3b). Compound **3b** was obtained according to the general procedure as a white solid (45.1 mg, 77% yield); mp 103–104 °C. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 15.4 min, major enantiomer t_R = 22.2 min, 96% ee; $[\alpha]_D^{20}$ −6.0 (*c* 1.44, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 2H, ArH), 7.64 (t, *J* = 7.2 Hz, 1H, ArH), 7.51 (t, *J* = 7.6 Hz, 2H, ArH), 7.46–7.43 (m, 2H, ArH), 3.99–3.94 (m, 1H, Ar-CH), 3.73–3.59 (m, 2H, CH_2) ppm; MS (ESI): *m*/*z* (% rel. intensity) 290.9 $[M - H]^+$ (100). Lit.[5b] $[\alpha]_D^{20}$ −5.56 (*c* 0.288, CH_2Cl_2), 89% ee.

(*S*)-2-[1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl]malononitrile (3c). Compound **3c** was obtained according to the general procedure as a white solid (51.0 mg, 83% yield); mp 132–133 °C. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 16.9 min, major enantiomer t_R = 25.1 min, 91% ee; $[\alpha]_D^{20}$ −2.4 (*c* 1.08, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.2 Hz, 2H, ArH), 7.64 (t, *J* = 7.2 Hz, 1H, ArH), 7.51 (t, *J* = 8.0 Hz, 2H, ArH), 7.44–7.39 (m, 4H, ArH), 4.64 (d, *J* = 4.8 Hz, 1H, CN-CH), 3.98–3.93 (m, 1H, Ar-CH), 3.73–3.59 (m, 2H, CH_2) ppm; MS (ESI): *m*/*z* (% rel. intensity) 308.7 $[M - H]^+$ (28, ^{37}Cl), 306.9 $[M - H]^+$ (100, ^{35}Cl). Lit.[5b] $[\alpha]_D^{20}$ −5.15 (*c* 0.194, CH_2Cl_2), 89% ee.

(*S*)-2-[1-(2-Chlorophenyl)-3-oxo-3-phenylpropyl]malononitrile (3d). Compound **3d** was obtained according to the general procedure as a white solid (56.0 mg, 91% yield); mp 119–121 °C. Enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 90 : 10, flow rate 0.8 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 38.9 min, major enantiomer t_R = 42.4 min, 80% ee; $[\alpha]_D^{20}$ = +3.6 (*c* 1.10, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.6 Hz, 2H, ArH), 7.63 (t, *J* = 7.2 Hz, 1H, ArH), 7.53–7.47 (m, 4H, ArH), 7.36–7.30 (m, 2H, ArH), 4.68–4.64 (m, 2H, 2CH), 3.81–3.64 (m, 2H, CH_2) ppm; MS (ESI): *m*/*z* (% rel. intensity) 308.6 $[M - H]^+$ (30, ^{37}Cl), 306.9 (100, ^{35}Cl) $[M - H]^+$. Lit.[5c] $[\alpha]_D^{22}$ = +4.0 (*c* 0.44, $CHCl_3$), 94% ee.

(*S*)-2-[1-(2,4-Dichlorophenyl)-3-oxo-3-phenylpropyl]malononitrile (3e). Compound **3e** was obtained according to the general procedure as a white solid (65.7 mg, 96% yield); mp 123–125 °C. Enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 90 : 10, flow rate 0.8 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 29.5 min, major enantiomer t_R = 31.6 min, 86% ee; $[\alpha]_D^{20}$ = +13.2 (*c* 1.09, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.0 Hz, 2H, ArH), 7.64 (t, *J* = 7.2 Hz, 1H, ArH), 7.53–7.44 (m, 4H, ArH), 7.33 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 4.65–4.59 (m, 2H), 3.78–3.63 (m, 2H, CH_2) ppm; MS (ESI): *m*/*z* (% rel. intensity) 342.7 $[M - H]^+$ (58, $^{37}Cl^{35}Cl$), 340.9 $[M - H]^+$ ($^{35}Cl^{35}Cl$, 100). Lit.[5b] $[\alpha]_D^{20}$ = +10.34 (*c* 0.232, CH_2Cl_2), 89% ee.

(*S*)-2-[1-(4-Bromophenyl)-3-oxo-3-phenylpropyl]malononitrile (3f)[5d,11]. Compound **3f** was obtained according to the general procedure as a white solid (60.8 mg, 91% yield); mp 127–129 °C. Lit.[11] mp 126–127 °C (racemate). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 18.0 min, major enantiomer t_R = 27.3 min, 91% ee; $[\alpha]_D^{20}$ −23.4 (*c* 0.35, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.0 Hz, 2H, ArH), 7.64 (t, *J* = 7.2 Hz, 1H, ArH), 7.57 (d, *J* = 8.4 Hz, 2H, ArH), 7.51 (t, *J* = 7.6 Hz, 1H, ArH), 7.34 (d, *J* = 8.4 Hz, 2H, ArH), 4.63 (d, *J* = 5.2 Hz, 1H, CN-CH), 3.96–3.91 (m, 1H, Ar-CH), 3.72–3.58 (m, 2H, CH_2) ppm; MS (ESI): *m*/*z* (% rel. intensity) 352.7 $[M - H]^+$ (100, ^{81}Br), 350.9 $[M - H]^+$ (98, ^{79}Br).

(*S*)-2-[1-(3-Bromophenyl)-3-oxo-3-phenylpropyl]malononitrile (3g). Compound **3g** was obtained according to the general procedure as a white semi-solid (66.6 mg, 94% yield). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 14.6 min, major enantiomer t_R = 18.0 min, 88% ee; $[\alpha]_D^{20}$ −6.0 (*c* 1.47, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.2 Hz, 2H, ArH), 7.63–7.28 (m, 7H, ArH), 4.63 (d, *J* = 4.8 Hz, 1H, CN-CH), 3.94–3.92 (m, 1H, Ar-CH), 3.72–3.58 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 138.6, 135.4, 134.2, 132.3, 131.0, 130.8, 128.9, 128.0, 126.7, 123.2, 111.5, 111.4, 40.6, 39.8, 28.5 ppm. IR (KBr): ν 3031, 2921,

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2255, 1721, 1679, 1608, 1573, 1516, 1450, 1410, 1368, 1291, 1276, 1223, 1207, 1183, 1121, 1001, 811, 728, 577 cm^{-1}. HRMS (ESI): *m/z* calc. for $C_{18}H_{14}BrN_2O$ $[M + H]^+$ 353.02840, found 353.02826.

(*S*)-2-[1-(4-Methylphenyl)-3-oxo-3-phenylpropyl]malononitrile (3h). Compound **3h** was obtained according to the general procedure as a colorless oil (45.5 mg, 79% yield). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 13.8 min, major enantiomer t_R = 19.2 min, 90% ee; $[\alpha]_D^{20}$ −7.3 (*c* 1.10, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.6 Hz, 2H, ArH), 7.62 (t, *J* = 7.2 Hz, 1H, ArH), 7.49 (t, *J* = 8.0 Hz, 2H, ArH), 7.33 (d, *J* = 8.0 Hz, 2H, ArH), 7.23 (d, *J* = 8.0 Hz, 2H, ArH), 4.61 (d, *J* = 5.2 Hz, 1H, CN-CH), 3.94–3.90 (m, 1H, Ar-CH), 3.72–3.59 (m, 2H, CH_2), 2.36 (s, 3H, CH_3) ppm; MS (ESI): *m/z* (% rel. intensity) 286.9 $[M - H]^+$ (100). Lit.[5b] $[\alpha]_D^{20}$ −2.41 (*c* 0.166, CH_2Cl_2), 87% ee.

(*S*)-2-[1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl]malononitrile (3i). Compound **3i** was obtained according to the general procedure as a colorless oil (30.7 mg, 50% yield). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 20.1 min, major enantiomer t_R = 31.0 min, 90% ee; $[\alpha]_D^{20}$ −5.6 (*c* 1.15, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 2H, ArH), 7.63 (t, *J* = 7.2 Hz, 1H, ArH), 7.50 (t, *J* = 7.6 Hz, 2H, ArH), 7.38 (d, *J* = 8.8 Hz, 2H, ArH), 6.94 (d, *J* = 8.8 Hz, 2H, ArH), 4.62 (d, *J* = 5.2 Hz, 1H, CN-CH), 3.94–3.90 (m, 2H, Ar-CH), 3.82 (s, 3H, CH_3), 3.74–3.58 (m, 2H, CH_2) ppm; MS (ESI): *m/z* (% rel. intensity) 302.9 $[M - H]^+$ (100). Lit.[4g] $[\alpha]_D^{25}$ −11.0 (*c* 0.21, $CHCl_3$), 87% ee.

(*S*)-2-[1-(2-Methoxyphenyl)-3-oxo-3-phenylpropyl]malononitrile (3j). Compound **3j** was obtained according to the general procedure as a white solid (42.5 mg, 70% yield); mp 116–118 °C. Enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 32.5 min, major enantiomer t_R = 45.2 min, 89% ee; $[\alpha]_D^{20}$ −5.8 (*c* 1.06, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 6.8 Hz, 2H, ArH), 7.61 (t, *J* = 7.2 Hz, 1H, ArH), 7.49 (t, *J* = 7.6 Hz, 2H, ArH), 7.36–7.31 (m, 2H, ArH), 7.00–6.93 (m, 2H, ArH), 4.68 (d, *J* = 6.4 Hz, 1H, CN-CH), 4.46 (q, *J* = 6.8 Hz, 1H, Ar-CH), 3.90 (s, 3H, CH_3), 3.80–3.61 (m, 2H, CH_2) ppm; MS (ESI): *m/z* (% rel. intensity) 302.9 $[M - H]^+$ (100). Lit.[5b] $[\alpha]_D^{20}$ = +24.22 (*c* 0.194 in CH_2Cl_2), 87% ee.

(*S*)-2-[3-(4-Fluorophenyl)-3-oxo-1-phenylpropyl]malononitrile (3k)[12]. Compound **3k** was obtained according to the general procedure as a colorless oil (46.4 mg, 79% yield). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 15.7 min, major enantiomer t_R = 18.4 min, 89% ee; $[\alpha]_D^{20}$ −6.3 (*c* 0.76, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 8.02–7.98 (m, 2H, ArH), 7.44–7.40 (m, 5H, ArH), 7.16 (t, *J* = 8.4 Hz, 2H, ArH), 4.63 (d, *J* = 5.2 Hz, 1H, CN-CH), 3.98–3.93 (m, 1H, Ar-CH), 3.71–3.58 (m, 2H, CH_2) ppm; MS (ESI): *m/z* (% rel. intensity) 290.9 $[M - H]^+$ (100). Lit.[12] $[\alpha]_D^{20}$ = +10.5 (*c* 0.48, ethyl acetate), 75% ee.

(*S*)-2-[3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl]malononitrile (3l). Compound **3l** was obtained according to the general procedure as a white solid (55.2 mg, 90% yield); mp 124–126 °C. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 18.6 min, major enantiomer t_R = 22.5 min, 89% ee; $[\alpha]_D^{20}$ = +11.5 (*c* 1.08, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.4 Hz, 2H, ArH), 7.48–7.41 (m, 7H, ArH), 4.62 (d, *J* = 5.2 Hz, 1H, CN-CH), 3.97–3.93 (m, 1H, Ar-CH), 3.71–3.58 (m, 2H, CH_2) ppm; MS (ESI): *m/z* (% rel. intensity) 308.8 $[M - H]^+$ (40, ^{37}Cl), 306.8 $[M - H]^+$ (100, ^{35}Cl). Lit.[5b] $[\alpha]_D^{20}$ = +7.87 (*c* 0.254, CH_2Cl_2), 80% ee.

(*S*)-2-[3-(4-Bromophenyl)-3-oxo-1-phenylpropyl]malononitrile (3m). Compound **3m** was obtained according to the general procedure as a white solid (62.1 mg, 88% yield); mp 146–147 °C. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–isopropanol 90 : 10 v/v, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 20.9 min, major enantiomer t_R = 25.0 min, 90% ee; $[\alpha]_D^{20}$ = +12.6 (*c* 1.38, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.4 Hz, 2H, ArH), 7.63 (d, *J* = 8.4 Hz, 2H, ArH), 7.44–7.40 (m, 5H, ArH), 4.61 (d, *J* = 5.2 Hz, 1H, CN-CH), 3.97–3.92 (m, 1H, Ar-CH), 3.70–3.57 (m, 2H, CH_2) ppm; MS (ESI): *m/z* (% rel. intensity) = 352.7 $[M - H]^+$ (100, ^{81}Br), 350.7 $[M - H]^+$ (99, ^{79}Br). Lit.[12] $[\alpha]_D^{20}$ = +30.1 (*c* 0.19, ethyl acetate), 81% ee.

(*S*)-2-[3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl]malononitrile (3n). Compound **3n** was obtained according to the general procedure as a white semi-solid (36.5 mg, 60% yield). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10 v/v, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 30.6 min, major enantiomer t_R = 41.9 min, 91% ee; $[\alpha]_D^{20}$ = +12.2 (*c* 1.21, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.8 Hz, 2H, ArH), 7.45–7.37 (m, 5H, ArH), 6.93 (d, *J* = 8.8 Hz, 2H, ArH), 4.66 (d, *J* = 4.8 Hz, 1H, CN-CH), 3.95–3.90 (m, 1H, Ar-CH), 3.85 (s, 3H, CH_3), 3.67–3.53 (m, 2H, CH_2) ppm; MS (ESI): *m/z* (% rel. intensity) 302.8 $[M - H]^+$ (100). Lit.[4g] $[\alpha]_D^{25}$ = +11.0 (*c* 0.1, $CHCl_3$), 87% ee.

(*S*)-2-[1,3-Bis(4-methylphenyl)-3-oxopropyl]malononitrile (3o). Compound **3o** was obtained according to the general procedure as a colorless oil (43.0 mg, 71% yield). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 16.9 min, major enantiomer t_R = 25.9 min, 92% ee; $[\alpha]_D^{20}$ = +8.4 (*c* 1.10, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 2H, ArH), 7.35–7.22 (m, 6H, ArH), 4.65 (d, *J* = 4.8 Hz, 1H, CN-CH), 3.93–3.88 (m, 1H, Ar-CH), 3.70–3.55 (m, 2H, CH_2), 2.43 (s, 3H, CH_3), 2.37 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 145.2, 139.0, 133.5, 133.3, 129.9, 129.5, 128.2, 127.8, 112.0, 111.7, 40.8, 39.9, 28.9, 21.7, 21.1 ppm. IR (KBr): ν 3063, 2910, 2256, 1683, 1597, 1570, 1477, 1449, 1432, 1368, 1307, 1212, 1076, 998, 756, 689 cm^{-1}. HRMS (ESI): *m/z* calc. for $C_{20}H_{18}N_2NaO$ $[M + Na]^+$ 325.13113, found 325.13097.

(*S*) - 2 - [1,3 - Bis(4 - chlorophenyl) - 3 - oxopropyl]malononitrile (3p)[13]. Compound **3p** was obtained according to the general procedure as a white solid (63.0 mg, 92% yield); mp 90–91 °C. Lit.[13] mp 81–82 °C (racemate). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10,

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flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 21.8 min, major enantiomer t_R = 30.9 min, 88% ee; $[\alpha]_D^{20}$ = +13.4 (*c* 1.03, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.4 Hz, 2H, ArH), 7.47 (d, *J* = 8.4 Hz, 2H, ArH), 7.42–7.37 (m, 4H, ArH), 4.60 (d, *J* = 5.2 Hz, 1H, CN-CH), 3.96–3.92 (m, 1H, Ar-CH), 3.68–3.55 (m, 2H, CH_2) ppm; MS (ESI): *m*/*z* (% rel. intensity) = 344.6 $[M - H]^+$ (14, $^{37}Cl^{37}Cl$), 342.6 $[M - H]^+$ (51, $^{35}Cl^{37}Cl$), 340.9 $[M - H]^+$) (100, $^{35}Cl^{35}Cl$).

(*S*)-2-[1-(Naphthalen-1-yl)-3-oxo-3-phenylpropyl]malononitrile (3q). Compound **3q** was obtained according to the general procedure as a white solid (48.2 mg, 74% yield); mp 167–169 °C. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 16.1 min, major enantiomer t_R = 18.4 min, 89% ee; $[\alpha]_D^{20}$ = +13.0 (*c* 1.34, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.4 Hz, 1H, ArH), 7.98–7.86 (m, 4H, ArH), 7.68 (d, *J* = 7.2 Hz, 1H, ArH), 7.65–7.46 (m, 6H, ArH), 5.02 (q, *J* = 6.0 Hz, 1H, Ar-CH), 4.70 (d, *J* = 4.8 Hz, 1H, CN-CH), 3.90–3.77 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 135.7, 134.1, 132.5, 130.9, 130.7, 129.5, 128.9, 128.1, 127.3, 126.3, 125.3, 124.3, 121.7, 112.1, 111.6, 40.5, 28.0 ppm. IR (KBr): ν 3049, 2906, 2256, 1679, 1596, 1514, 1449, 1356, 1230, 1002, 796, 775, 763, 689 cm^{-1}. HRMS (ESI): *m*/*z* calc. for $C_{22}H_{16}N_2NaO$ $[M + Na]^+$ 347.11548, found 347.11548.

(*S*)-2-[1-(Furan-2-yl)-3-oxo-3-phenylpropyl]malononitrile (3r). Compound **3r** was obtained according to the general procedure as a pale yellow oil (28.3 mg, 54% yield). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 18.0 min, major enantiomer t_R = 20.5 min, 83% ee; $[\alpha]_D^{20}$ = +13.5 (*c* 1.45, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.0 Hz, 2H, ArH), 7.63 (t, *J* = 7.2 Hz, 1H, ArH), 7.50 (t, *J* = 7.6 Hz, 2H, ArH), 7.45 (s, 1H, CH), 6.44 (d, *J* = 3.2 Hz, 1H, CH), 6.39 (s, 1H, CH), 4.60 (d, *J* = 4.8 Hz, 1H, CN-CH), 4.18–4.13 (m, 1H, Ar-CH), 3.72–3.59 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 149.4, 143.4, 135.5, 134.2, 128.9, 128.1, 111.5, 111.2, 110.8, 109.1, 38.5, 35.6, 27.1 ppm. IR (KBr): ν 3124, 3063, 2917, 2257, 1683, 1597, 1581, 1504, 1450, 1414, 1364, 1216, 1183, 1015, 1002, 908, 760, 689, 598 cm^{-1}. HRMS (ESI): *m*/*z* calc. for $C_{16}H_{22}N_2NaO_2$ $[M + Na]^+$ 287.07910, found 287.07923.

(*R*)-2-(1-Cyclohexyl-3-oxo-3-phenylpropyl)malononitrile (3s). Compound **3s** was obtained according to the general procedure as a colorless oil (13.0 mg, 23% yield). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 95 : 5, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 12.2 min, major enantiomer t_R = 13.4 min, 86% ee; $[\alpha]_D^{20}$ = +44.0 (*c* 0.65, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.4 Hz, 2H, ArH), 7.63–7.59 (m, 1H, ArH), 7.49 (t, *J* = 7.6 Hz, 2H, ArH), 4.36 (d, *J* = 4.8 Hz, 1H, CN-CH), 3.35 (dd, J_1 = 18.4 Hz, J_2 = 4.8 Hz, 1H, CH_2), 3.16 (dd, J_1 = 18.4 Hz, J_2 = 8.0 Hz, 1H, CH_2), 2.76–2.70 (m, 1H, cyclohexyl-CH), 1.86–1.69 (m, 6H, cyclohexyl), 1.37–1.05 (m, 5H, cyclohexyl) ppm. MS (ESI): *m*/*z* (% rel. intensity) 278.9 $[M - H]^+$ (100). Lit.[5c] $[\alpha]_D^{26}$ = +34.7 (*c* 0.33, $CHCl_3$), 95% ee.

(*S*)-2-(2, 2-Methyl-5-oxo-5-phenylpentyl)malononitrile (3t). Compound **3t** was obtained according to the general procedure as a colorless oil (17.8 mg, 35% yield). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane/2-propanol 95 : 5, flow rate 1.0 mL min^{-1}, detection at 254 nm), major enantiomer t_R = 12.0 min, minor enantiomer t_R = 14.4 min, 88% ee; $[\alpha]_D^{25}$ = +25.6 (*c* 0.50, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.6 Hz, 2H, ArH), 7.63 (t, *J* = 7.2 Hz, 1H, ArH), 7.51 (t, *J* = 8.0 Hz, 2H, ArH), 4.10 (d, *J* = 2.8 Hz, 1H, CN-CH), 3.41 (dd, J_1 = 18.4 Hz, J_2 = 4.4 Hz, 1H, CH_2), 3.19 (dd, J_1 = 18.4 Hz, J_2 = 7.2 Hz, 1H, CH_2), 2.95–2.92 (m, 1H, ^{t}Bu-CH), 1.10 (s, 9H, CH_3) ppm; MS (ESI): *m*/*z* (% rel. intensity) 252.9 $[M - H]^+$ (100). Lit.[5b] $[\alpha]_D^{20}$ = +38.10 (*c* 0.042, CH_2Cl_2), 93% ee.

(*R*,*E*)-2-(5-Oxo-1,5-diphenylpent-1-en-3-yl)malononitrile (5). To a solution of catalyst **IV** (2.3 mg, 0.004 mmol) in chloroform (0.5 mL) was added ((1*E*,3*E*)-4-nitrobuta-1,3-dienyl)benzene **4** (93.7 mg, 0.40 mmol) and malononitrile **2** (31.7 mg, 0.48 mmol). The reaction mixture was stirred for 4 days at room temperature. Then the mixture was concentrated and purified by silica gel column chromatography (ethyl acetate–petroleum ether 1 : 30) to afford the product **5** as a colorless oil (62.4 mg, 52% yield). Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 14.3 min, major enantiomer t_R = 19.5 min, 90% ee; $[\alpha]_D^{20}$ −25.0 (*c* 2.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.6 Hz, 2H, ArH), 7.63 (t, *J* = 7.2 Hz, 1H, ArH), 7.50 (t, *J* = 8.0 Hz, 2H, ArH), 7.42 (d, *J* = 7.2 Hz, 2H, ArH), 7.36–7.30 (m, 3H, ArH), 6.79 (d, *J* = 8.0 Hz, 1H, CH═), 6.23 (dd, J_1 = 8.8 Hz, J_2 = 16.0 Hz, 1H, CH═), 4.57 (d, *J* = 4.8 Hz, 1H, CN-CH), 3.59–3.52 (m, 1H, CH), 3.51–3.39 (m, 2H, CH_2) ppm; MS (ESI): *m*/*z* (% rel. intensity) = 298.9 $[M - H]^+$ (100). Lit.[5c] $[\alpha]_D^{21}$ −14.4 (*c* 0.3, $CHCl_3$), 89% ee.

(*S*)-2-Amino-4-phenyl-5,6-dihydro-4*H*-benzo[*h*]chromene-3-carbonitrile (7)[9]. To a solution of catalyst **IV** (2.3 mg, 0.004 mmol) in chloroform (0.5 mL) was added (*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one **6** (93.7 mg, 0.40 mmol) and malononitrile **2** (31.7 mg, 0.48 mmol). The reaction mixture was stirred for 4 days at room temperature. Then the mixture was concentrated and purified by silica gel column chromatography (ethyl acetate–petroleum ether 1 : 20) to afford the product **7** as a yellow solid (48.1 mg, 40% yield); mp 206–208 °C. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-hexane–2-propanol 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm), minor enantiomer t_R = 9.6 min, major enantiomer t_R = 13.2 min, 91% ee; $[\alpha]_D^{30}$ −55.2 (*c* 0.33, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.2 Hz, 1H, ArH), 7.35–7.20 (m, 7H, ArH), 7.12 (d, *J* = 6.8 Hz, 1H, ArH), 4.56 (s, 2H, NH_2), 4.08 (s, 1H, CH), 2.83–2.66 (m, 2H, CH_2), 2.22–2.14 (m, 1H, CH_2), 2.10–2.02 (m, 1H, CH_2) ppm; MS (ESI): *m*/*z* (%) = 322.9 $[M + Na]^+$ (100), 301.0 $[M + H]^+$ (25). Lit.[9] $[\alpha]_D^{20}$ −39.5 (*c* 0.45, $CHCl_3$), 80% ee.

The gram-scale preparation of 3a

To a solution of *trans*-chalcone **1a** (10.0 mmol, 2.08 g) and catalyst **IV** (0.05 mmol, 28.2 mg) was added malononitrile **2** (12.0 mmol, 0.79 g). The reaction mixture was stirred at room temperature for 24 h. Then the mixture was directly purified by silica gel column chromatography (ethyl acetate–petroleum

ether 1 : 15) to give the corresponding adduct **3a** as a white solid (2.19 g, 80% yield). Enantiomeric excess (89% ee, 97% ee after a simple recrystallization with ethyl acetate–petroleum ether) was determined by HPLC with a Chiralpak IA column.

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