# Highly enantioselective Michael addition of malononitrile to α,β-unsaturated ketones†

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The highly enantioselective Michael addition of malononitrile to acyclic and cyclic α,β-unsaturated ketones has been developed. The Michael reaction catalyzed by a primary amine derived from quinidine proceeded smoothly and provided the desired adducts with excellent enantioselectivities (83–97% ee).

## Introduction

The Michael addition of carbon-base nucleophiles to α,β-unsaturated systems represents one of the classical carbon–carbon bond-forming reaction. The process often provides synthetically useful adducts possessing various functional groups such as nitro,[1] ester,[2] ketone[3] and other moieties[4] for further elaboration. Accordingly, the development of enantioselective catalysis protocols for this reaction has been the subject of intensive research. In addition to the substantial progress realized with metallic complexes,[5] a number of asymmetric Michael additions catalyzed by organocatalysts have received renewed attention.[6] Although a variety of structurally diverse organocatalysts have been developed to catalyze the asymmetric Michael reaction and impressive results have been achieved, the reactions were mostly narrow in substrate scope and restricted to a particular combination of nucleophile and electrophile type. Malononitrile is an equivalent of a 1,3-dicarbonyl compound and the nitrile group is a versatile functional group that can be converted to carboxylic acids,[7] esters,[8] and amines.[9e] However, examples using malononitrile as a nucleophile[9] have been relatively less explored and most of them didn't achieve high enantioselectivity in the presence of organocatalysts, except that reported by Takemoto *et al*.[9a]

Recently we have reported the Michael addition of α,β-unsaturated ketones catalyzed by a newly developed primary amine derived from quinine; excellent enantioselectivities and high efficiency were observed for almost all the adducts.[10a] However, the substrates were generally limited to cyclic and alkyl enones. Herein we report a highly enantioselective and efficient Michael addition of malononitrile to acyclic and cyclic α,β-unsaturated ketones catalyzed by primary amine **1a**.[10,11] The derivatives of 9-*epi*-amino cinchona alkaloids are selected as primary amine organocatalysts on the basis of two reasons: (i) the *in situ* generation of a ketimine cation from a primary amine salt and the ketone carbonyl should be much more feasible than from a secondary amine;[10a,f,g] (ii) a possible bifunctional activation[4b,c,9a,b,10e,f] would facilitate the Michael-type coupling reaction (Fig. 1).

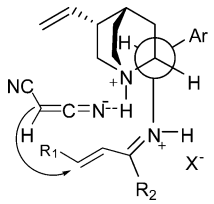


**Fig. 1** A possible model for bifunctional activation.

## Results and discussion

To our delight, 9-amino-9-deoxy-*epi*-quinidine **1a** (Fig. 2) in combination with TFA exhibited high catalytic activity for the asymmetric addition of malononitrile **2** to benzylideneacetone **3a** in THF at 22 °C. The reaction gave the Michael adduct **4a** in 87% yield with a promising 93% ee after 12 h (Table 1, entry 1). Use of 9-amino-9-deoxy-*epi*-cinchonine **1b**[10c,d,h] resulted in a decrease in both chemical yield and enantioselectivity (entry 2). 9-Amino-9-deoxy-*epi*-quinine **1c**,[10a,b] the pseudoenantiomer of **1a**, afforded the adduct in 94% ee with opposite configuration and lower yield (entry 3). This also implied that both enantiomers of **4a** can be obtained in high selectivities. Encouraged by the excellent results obtained with **1a**, we subsequently investigated the effects of the solvents and acid additives. In comparison with THF, better reactivity and enantioselectivity were obtained in DCM (entry 4). Excepting 1,4-dioxane, the reactions resulted in lower enantioselectivities in other solvents (entries 5–9).

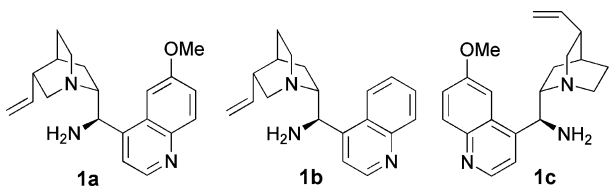


**Fig. 2** Structure of primary amine catalysts **1a**, **1b** and **1c** derived from quinidine, cinchonine and quinine, respectively.

The acid additives had an obvious effect on the reactivity of the Michael addition and less than 30% yield was obtained after

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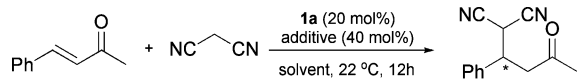
**Table 1** Screening studies of organocatalytic Michael addition of malononitrile **2** to benzylideneacetone **3a**[a]




**3a** **2** **4a**

| Entry | Solvent | Additive | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | THF | TFA | 87 | 93 |
| 2[d] | THF | TFA | 46 | 86 |
| 3[e] | THF | TFA | 59 | −94 |
| 4 | DCM | TFA | 93 | 95 |
| 5 | $Et_2O$ | TFA | 68 | 82 |
| 6 | Dioxane | TFA | 74 | 94 |
| 7 | Toluene | TFA | 87 | 59 |
| 8 | MeOH | TFA | 41 | 19 |
| 9 | DMF | TFA | 77 | 28 |
| 10 | DCM | HOAc | 5 | −56 |
| 11 | DCM | TsOH | 90 | 90 |
| 12 | DCM | $CF_3SO_3H$ | 26 | 90 |
| 13 | THF | **5a** | 69 | 85 |
| 14 | THF | **5b** | 49 | 86 |
| 15[f] | DCM | TFA | 91 | 96 |
| 16[f] | $CHCl_3$ | TFA | 95 | 94 |
| 17[f] | THF | TFA | 63 | 87 |
| 18[g] | DCM | TFA | 67 | 93 |
| 19[h] | DCM | TFA | 49 | 87 |
| 20[i] | THF | TFA | 72 | 89 |

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **3a**, 0.2 mmol of **2**, in the presence of 20 mol% of **1a** and 40 mol% of TFA in 1 mL of solvent at 22 °C for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Using 20 mol% of **1b**. [e] Using 20 mol% of **1c**. [f] At 0 °C for 96 h. [g] Using 20 mol% of TFA. [h] Using 10 mol% of **1a**. [i] Using 0.1 mmol of **2**.

12 h in the presence of HOAc and $CF_3SO_3H$ (entries 10 and 12). The Michael addition proceeded smoothly in the presence of TsOH and provided the desired adduct in a somewhat lower enantioselectivity in comparison with TFA (entry 4 *vs.* entry 11). Notably, the coupling reaction afforded the adducts with opposite configuration in the presence of the weaker acid HOAc (entry 10). Considering that asymmetric counterion-directed catalysis (ACDC)[12] has recently been recognized as an efficient strategy for enantioselective transformation, we combined (*R*) and (*S*)-phosphoric acids derived from binol (Fig. 3, **5a** and **5b**) with **1a** and obtained the adducts with the same configuration and in similar enantioselectivities (entries 13 and 14).

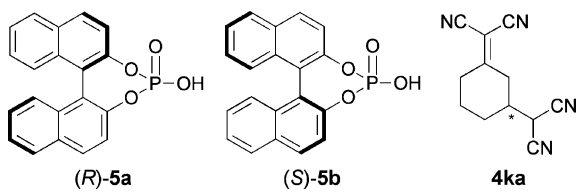



**Fig. 3** Structure of additives **5a** and **5b**, and the adduct **4ka**.

In the hope of enhancing the enantioselectivity, we carried out the reaction at 0 °C. Unfortunately, no beneficial effect was observed (entries 15–17). At the same time, the Michael addition proceeded somewhat faster in chloroform than DCM, however, it resulted in lower enantioselectivity (entry 15 *vs.* entry 16). To our surprise, the enantioselectivity in THF sharply decreased at 0 °C (entry 17). Moreover, the composition of the catalyst system and the ratio of malononitrile **2** to benzylideneacetone **3a** also affected both reaction rate and enantioselectivity (entries 18–20).

Having established the optimum reaction conditions for the enantioselective Michael addition of benzylideneacetone **3a**, we next screened a series of analogues which bear various substituents on the terminal double bond and the carbonyl group. The Michael reaction was generally conducted with 20 mol% of **1a** and 40 mol% TFA at 22 °C (Table 2). As illustrated in Table 2, enones **3a–k** cleanly underwent conjugate addition and excellent enantioselectivities were achieved regardless of the electronic properties (entries 1–11). The coupling reaction with aryl substituents **3a–e** proceeded with 93–96% ee to afford the adducts **4a–e** in high yields (entries 1–5). Similarly, the substrate **3h** with a 2-furanyl group as the β-substituent underwent smooth reaction as well and furnished the desired adduct **4h** in 99% yield with 95% ee (entry 8). Moreover, **3i**, bearing an aliphatic group on the β-position, was tolerated to exhibit 93% ee with 35% yield after 72 h (entry 9). On the other hand, bulkier alkyl enone **3j** was also tolerated to give the highest enantioselectivity (97% ee, entry 10). Furthermore, reaction of the cyclic acceptor **3k** occurred smoothly to furnish the desired adduct **4k** with excellent enantioselectivity (95% ee), but a by-product, α,α-dicyanoalkene **4ka** (Fig. 3), was obtained in 30% yield with 90% ee (entry 11), which may be derived from the desired adduct **4k** and malononitrile.[13] Gratifyingly, reaction of chalcone **3l**, which was inert with vinylogous donors,[10a] proceeded smoothly to give the desired adduct **4l** with 88% ee despite the longer time required (entry 12). As aromatic ketones ($R_1 = R_2 =$ Ar) might be unfavorable for the formation of iminium ions with amine catalysts, the Michael addition of chalcone analogues with amine as catalyst has rarely been reported.[10g] It turned out that the substituents on the phenyl group of chalcone had a large influence on the yields and **3m**, **3n** and **3o** gave ≤40% yield with ≥83% ee (entries 13–15). It is notable that higher yields were achieved at elevated temperature, yet the enantioselectivities only slightly decreased. These observations indicated that the temperature markedly affected the reaction rate while it only slightly affected the enantioselectivity (Table 1, entry 4 *vs.* 15, and Table 2, entries 13–15).

## Conclusions

In summary, we have developed the first general and highly enantioselective organocatalytic Michael addition of malononitrile[14,15] with various α,β-unsaturated ketones in the presence of 9-amino-9-deoxy-*epi*-quinidine **1a**. Noticeably, this novel primary amine organocatalyst can effectively activate chalcone and its analogues, which were inert in the case of secondary amine organocatalysts. Moreover, to the best our knowledge, no Michael additions of malononitrile catalyzed by amine organocatalysts[6,9] have been reported. Further investigation into the synthetic application is underway.

## Experimental

### General Methods

$^1$H NMR spectra were recorded at 300 MHz and $^{13}$C NMR spectra were recorded at 75 MHz. Chemical shifts ($\delta$) are reported in ppm relative to $CHCl_3$ ($\delta = 7.27$ ppm) for $^1$H NMR and relative

**Table 2** Asymmetric Michael addition of malononitrile **2** to α,β-unsaturated ketones **3**[a]


| Entry | $R_1$ | $R_2$ (**3**) | **4** | Time/h | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | Ph | Me (**3a**) | **4a** | 12 | 93 | 95 |
| 2 | *p*-$MeC_6H_4$ | Me (**3b**) | **4b** | 22 | 87 | 93 |
| 3 | *p*-$MeOC_6H_4$ | Me (**3c**) | **4c** | 12 | 94 | 94 |
| 4 | *p*-$ClC_6H_4$ | Me (**3d**) | **4d** | 18 | 85 | 96 |
| 5 | *p*-$BrC_6H_4$ | Me (**3e**) | **4e** | 48 | 84 | 93 |
| 6 | *p*-$NO_2C_6H_4$ | Me (**3f**) | **4f** | 48 | 70 | 87 |
| 7 | 2-Naphthyl | Me (**3g**) | **4g** | 22 | 87 | 88 |
| 8 | 2-Furanyl | Me (**3h**) | **4h** | 12 | 99 | 95 |
| 9 | *n*-Pr | Me (**3i**) | **4i** | 72 | 35 (95)[d] | 93[e] |
| | | | | | 39[f] (94)[d] | 92[e,f] |
| 10 | Ph | Et (**3j**) | **4j** | 12 | 85 | 97 |
| 11 | -$C_4H_8$- (**3k**) | | **4k** | 12 | 60 | 95[e] |
| | | | **4ka** | | 30 | 90 |
| 12 | Ph | Ph (**3l**) | **4l** | 72 | 60 | 88[g] |
| 13 | *p*-$MeOC_6H_4$ | Ph (**3m**) | **4m** | 72 | 20 | 87 |
| | | | | | 80[f] | 85[f] |
| 14 | *p*-$FC_6H_4$ | Ph (**3n**) | **4n** | 72 | 40 | 83 |
| | | | | | 78[f] | 80[f] |
| 15 | Ph | *p*-$MeOC_6H_4$ (**3o**) | **4o** | 72 | 36 | 87 |
| | | | | | 79[f] | 87[f] |

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **3a**, 0.2 mmol of **2**, in the presence of 20 mol% of **1a** and 40 mol% of TFA in 1 mL of DCM at 22 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Yield in parentheses is based on recovered **3i**. [e] Determined by GC analysis. [f] Performed at 40 °C. [g] The absolute configuration of **4l** was the (*S*)-form determined by comparison of the specific optical rotation with that reported in the literature,[8] and the other adducts were assigned accordingly.

to the central $CDCl_3$ resonance ($\delta$ = 77.0 ppm) for $^{13}C$ NMR spectroscopy. Coupling constants ($J$) are given in Hz. ESI-HRMS spectra were measured with a Finnigan LCQ$^{DECA}$ ion trap mass spectrometer. Optical rotation data were recorded on Perkin-Elmer Polarimeter-341. Enantiomeric excess was determined by HPLC analysis on chiral columns and GC analysis on a chiral CP-Chirasil-DEX CB column in comparison with the authentic racemates. TLC was performed on glass-backed silica plates. Column chromatography was performed using silica gel (200–300 mesh) eluting with ethyl acetate and petroleum ether. Commercial grade solvents were dried and purified by standard literature procedures.[16] Primary aminocatalysts **1a–1c** were prepared according to literature procedures.[11]

### General procedure for asymmetric Michael addition of malononitrile to α,β-unsaturated ketones

Benzylideneacetone **3a** (14.6 mg, 0.1 mmol), malononitrile **2** (13.2 mg, 0.2 mmol), 9-amino-9-deoxy-*epi*-quinidine **1a** (6.4 mg, 0.02 mmol) and TFA (3.0 μL, 0.04 mmol) were stirred in DCM (1 mL) at 22 °C for 12 h. Then the reaction was quenched by adding 1 mol $L^{-1}$ HCl (1.0 mL). The mixture was extracted with EtOAc (10 mL) and dried with anhydrous sodium sulfate. The solvent was removed and flash chromatography on silica gel (20% ethyl acetate–petroleum ether) gave **4a** as a white solid (19.7 mg, 93% yield).

**2-(3-Oxo-1-phenylbutyl)malononitrile (4a).** White solid. Mp 72–74 °C. $[\alpha]_D^{25} = -38.1$ ($c$ = 0.40, $CHCl_3$). $^1H$-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.45–7.34 (m, 5H), 4.48 (d, $J$ = 5.5 Hz, 1H), 3.77–3.70 (m, 1H), 3.24–3.04 (m, 2H), 2.21 (s, 3H) ppm. $^{13}C$-NMR ($CDCl_3$, 75 MHz) $\delta$ 205.3, 136.2, 129.3, 129.1, 127.8, 111.7, 111.5, 44.7, 40.8, 30.3, 28.5 ppm. ESI-HRMS calcd for $C_{13}H_{12}N_2O$ − H 211.0866, found 211.0859. 96% ee determined by HPLC on AS-H column, hexane–i-propanol (70 : 30), 1.0 mL $min^{-1}$, UV 254 nm, $t_{major}$ = 13.886 min, $t_{minor}$ = 16.383 min.

**2-(3-Oxo-1-*p*-tolylbutyl)malononitrile (4b).** Light yellow oil. Yield 87%. $[\alpha]_D^{25} = -33.0$ ($c$ = 0.13, $CHCl_3$). $^1H$-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25–7.19 (m, 4H), 4.45 (d, $J$ = 5.3 Hz, 1H), 3.73–3.67 (m, 1H), 3.21–3.02 (m, 2H), 2.36 (s, 3H), 2.20 (s, 3H) ppm. $^{13}C$-NMR ($CDCl_3$, 75 MHz) $\delta$ 205.4, 139.1, 133.2, 129.9, 127.6, 111.8, 111.6, 44.8, 40.5, 30.3, 28.7, 21.1 ppm. ESI-HRMS calcd for $C_{14}H_{14}N_2O$ − H 225.1022, found 225.1032. 93% ee determined by HPLC on OD-H column, hexane–i-propanol (70 : 30), 1.0 mL $min^{-1}$, UV 254 nm, $t_{minor}$ = 11.208 min, $t_{major}$ = 13.161 min.

**2-(1-(4-Methoxyphenyl)-3-oxobutyl)malononitrile (4c).** Light yellow solid. Yield 94%, mp 84–87 °C. $[\alpha]_D^{25} = -35.5$ ($c$ = 0.47, $CHCl_3$). $^1H$-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.28 (d, $J$ = 8.7 Hz, 2H), 6.92 (d, $J$ = 8.7 Hz, 2H), 4.44 (d, $J$ = 5.3 Hz, 1H), 3.81 (s, 3H), 3.72–3.68 (m, 1H), 3.21–3.00 (m, 2H), 2.21 (s, 3H) ppm. $^{13}C$-NMR ($CDCl_3$, 75 MHz) $\delta$ 205.4, 160.2, 129.0, 128.1, 114.6, 111.8, 111.6, 55.3, 44.9, 40.2, 30.3, 28.8 ppm. ESI-HRMS calcd for $C_{14}H_{14}N_2O_2$ − H 241.0972, found 241.0978. 94% ee determined by HPLC on OJ-H column, hexane–i-propanol (70 : 30), 1.0 mL $min^{-1}$, UV 254 nm, $t_{minor}$ = 29.937 min, $t_{major}$ = 36.018 min.

**2-(1-(4-Chlorophenyl)-3-oxobutyl)malononitrile (4d).** Colorless oil. Yield 85%. $[\alpha]_D^{25} = -45.0$ ($c = 0.20$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.42–7.38 (m, 2H), 7.33–7.28 (m, 2H), 4.47 (d, $J = 5.3$ Hz, 1H), 3.76–3.69 (m, 1H), 3.21–3.01 (m, 2H), 2.23 (s, 3H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 204.9, 135.3, 134.6, 129.5, 129.3, 111.5, 111.3, 44.6, 40.3, 30.3, 28.4 ppm. ESI-HRMS calcd for $C_{13}H_{11}ClN_2O$ − H 245.0476, found 245.0477. 96% ee determined by HPLC on AS-H column, hexane–i-propanol (70 : 30), 1.0 mL min$^{-1}$, UV 254 nm, $t_{major} = 13.307$ min, $t_{minor} = 16.906$ min.

**2-(1-(4-Bromophenyl)-3-oxobutyl)malononitrile (4e).** Colorless oil. Yield 84%. $[\alpha]_D^{25} = -31.2$ ($c = 0.50$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.55 (d, $J = 8.2$ Hz, 2H), 7.24 (d, $J = 8.5$ Hz, 2H), 4.47 (d, $J = 5.2$ Hz, 1H), 3.74–3.68 (m, 1H), 3.21–3.00 (m, 2H), 2.22 (s, 3H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 204.9, 135.1, 132.5, 129.5, 123.4, 111.5, 111.3, 44.5, 40.4, 30.3, 28.3 ppm. ESI-HRMS calcd for $C_{13}H_{11}BrN_2O$ − H 288.9971, found 288.9968. 93% ee determined by HPLC on OD-H column, hexane–i-propanol (85 : 15), 1.0 mL min$^{-1}$, UV 254 nm, $t_{minor} = 22.636$ min, $t_{major} = 24.013$ min.

**2-(1-(4-Nitrophenyl)-3-oxobutyl)malononitrile (4f).** Brown solid. Yield 70%, mp 136.3–138.5 °C. $[\alpha]_D^{25} = -32.0$ ($c = 0.33$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 8.31–8.27 (m, 2H), 7.60–7.56 (m, 2H), 4.55 (d, $J = 5.4$ Hz, 1H), 3.91–3.84 (m, 1H), 3.29–3.07 (m, 2H), 2.25 (s, 3H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 204.4, 148.4, 143.0, 129.1, 124.5, 111.2, 110.9, 44.4, 40.6, 30.2, 27.9 ppm. ESI-HRMS calcd for $C_{13}H_{11}N_3O_3$ − H 256.0717, found 256.0716. 87% ee determined by HPLC on AS-H column, hexane–i-propanol (70 : 30), 1.0 mL min$^{-1}$, UV 254 nm, $t_{minor} = 24.079$ min, $t_{major} = 33.490$ min.

**2-(1-(Naphthalen-2-yl)-3-oxobutyl)malononitrile (4g).** White solid. Yield 87%, mp 132–133 °C. $[\alpha]_D^{25} = -50.4$ ($c = 0.43$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.91–7.83 (m, 4H), 7.56–7.50 (m, 2H), 7.47–7.44 (m, 1H), 4.55 (d, $J = 5.5$ Hz, 1H), 3.96–3.89 (m, 1H), 3.34–3.14 (m, 2H), 2.23 (s, 3H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 205.2, 133.6, 133.3, 133.2, 129.3, 128.1, 127.7, 127.4, 126.8, 126.7, 124.9, 111.7, 111.6, 44.9, 41.0, 30.3, 28.5 ppm. ESI-HRMS calcd for $C_{17}H_{14}N_2O$ − H 261.1022, found 261.1009. 88% ee determined by HPLC on AS-H column, hexane–i-propanol (70 : 30), 1.0 mL min$^{-1}$, UV 254 nm, $t_{minor} = 13.128$ min, $t_{major} = 15.598$ min.

**2-(1-(Furan-2-yl)-3-oxobutyl)malononitrile (4h).** Brown oil. Yield 99%. $[\alpha]_D^{25} = -12.0$ ($c = 0.23$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.43 (br, 1H), 6.38 (br, 2H), 4.45 (d, $J = 5.3$ Hz, 1H), 3.96–3.89 (m, 1H), 3.13–3.10 (m, 2H), 2.24 (s, 3H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 204.6, 149.2, 143.4, 111.4, 111.1, 110.8, 109.2, 43.1, 35.3, 30.1, 26.9 ppm. ESI-HRMS calcd for $C_{11}H_{10}N_2O_2$ − H 201.0659, found 201.0673. 95% ee determined by HPLC on AS-H column, hexane–i-propanol (70 : 30), 1.0 mL min$^{-1}$, UV 230 nm, $t_{major} = 16.057$ min, $t_{minor} = 25.791$ min.

**2-(2-Oxoheptan-4-yl)malononitrile (4i).** Colorless oil. Yield 39%. $[\alpha]_D^{25} = +41.7$ ($c = 0.40$, $CHCl_3$), lit.[9e] ee = 94%, $[\alpha]_D^{25} = +45$ ($c = 0.98$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 4.29 (d, $J = 4.5$ Hz, 1H), 2.79–2.73 (m, 1H), 2.66–2.64 (m, 1H), 2.57–2.51 (m, 1H), 2.20 (s, 3H), 1.64–1.37 (m, 4H), 0.96 (t, $J = 7.2$ Hz, 3H) ppm. 92% ee determined by GC and derivation to the corresponding 1,3-dioxolane on CP-Chirasil-DEX CB column, 135 °C isothermal, $t_{major} = 21.863$ min, $t_{minor} = 22.678$ min.

**2-(3-Oxo-1-phenylpentyl)malononitrile (4j).** Colorless oil. Yield 85%. $[\alpha]_D^{25} = -34.0$ ($c = 0.45$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.42–7.34 (m, 5H), 4.50 (d, $J = 5.4$ Hz, 1H), 3.78–3.72 (m, 1H), 3.21–3.02 (m, 2H), 2.54–2.42 (m, 2H), 1.07 (t, $J = 7.3$ Hz, 3H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 208.2, 136.3, 129.3, 129.1, 127.8, 111.7, 111.6, 43.5, 40.9, 36.4, 28.6, 7.5 ppm. ESI-HRMS calcd for $C_{14}H_{14}N_2O$ − H 225.1022, found 225.1019. 97% ee determined by HPLC on OJ-H column, hexane–i-propanol (70 : 30), 1.0 mL min$^{-1}$, UV 254 nm, $t_{minor} = 12.339$ min, $t_{major} = 15.397$ min.

**2-(3-Oxocyclohexyl)malononitrile (4k).** [13] Light yellow oil. Yield 60%. $[\alpha]_D^{25} = +16.0$ ($c = 0.12$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 3.75 (d, $J = 4.9$ Hz, 1H), 2.67–2.64 (m, 1H), 2.48–2.19 (m, 6H), 1.77–1.73 (m, 2H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 206.1, 111.0, 110.8, 44.2, 40.2, 39.4, 28.7, 28.1, 23.6 ppm. ESI-HRMS calcd for $C_9H_{10}N_2O$ − H 161.0709, found 161.0726. 95% ee determined by GC on CP-Chirasil-DEX CB column, 150 °C isothermal, $t_{major} = 30.681$ min, $t_{minor} = 32.768$ min.

**2,2′-(Cyclohexan-1-yl-3-ylidene)dimalononitrile (4ka).** [13] Light yellow solid. Yield 30%, mp 98–100 °C. $[\alpha]_D^{25} = -76.0$ ($c = 0.18$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 3.92 (d, $J = 3.6$ Hz, 1H), 3.18 (d, $J = 10.6$ Hz, 1H), 3.07 (d, $J = 13.8$ Hz, 1H), 2.41–2.13 (m, 5H), 1.66–1.56 (m, 2H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 178.8, 111.0, 110.9, 110.8, 85.2, 39.5, 36.5, 33.2, 28.4, 27.7, 24.8 ppm. ESI-HRMS calcd for $C_{12}H_{10}N_4$ − H 209.0822, found 209.0823. 90% ee determined by HPLC on AD-H column, hexane–i-propanol (80 : 20), 1.0 mL min$^{-1}$, UV 254 nm, $t_{minor} = 9.411$ min, $t_{major} = 11.315$ min.

**2-(3-Oxo-1,3-diphenylpropyl)malononitrile (4l).** White solid. Yield 60%. $[\alpha]_D^{25} = -12.5$ ($c = 0.20$, $CHCl_3$), lit.[8] ee = 11%, $[\alpha]_D^{25} = -1.6$ ($c = 1.0$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.98–7.96 (m, 2H), 7.63–7.61 (m, 1H), 7.53–7.40 (m, 7H), 4.64 (d, $J = 5.1$ Hz, 1H), 3.99–3.93 (m, 1H), 3.77–3.62 (m, 2H) ppm. 88% ee determined by HPLC on OD-H column, hexane–i-propanol (70 : 30), 1.0 mL min$^{-1}$, UV 254 nm, $t_{minor} = 12.312$ min, $t_{major} = 19.071$ min.

**2-(1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl)malononitrile (4m).** Colorless oil. Yield 20%. $[\alpha]_D^{25} = -11.0$ ($c = 0.21$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.98–7.95 (m, 2H), 7.62–7.59 (m, 1H), 7.52–7.47 (m, 2H), 7.39–7.36 (m, 2H), 6.96–6.93 (m, 2H), 4.60 (d, $J = 5.1$ Hz, 1H), 3.95–3.89 (m, 1H), 3.81 (s, 3H), 3.73–3.58 (m, 2H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 196.7, 159.9, 135.7, 134.1, 129.1, 128.8, 128.4, 128.0, 114.5, 111.9, 111.8, 55.2, 40.4, 40.1, 29.0 ppm. ESI-HRMS calcd for $C_{19}H_{16}N_2O_2$ + Na 327.1104, found 327.1118. 87% ee determined by HPLC on AS-H column, hexane–i-propanol (70 : 30), 1.0 mL min$^{-1}$, UV 254 nm, $t_{minor} = 13.304$ min, $t_{major} = 23.322$ min.

**2-(1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)malononitrile (4n).** White solid. Yield 40%, mp 99–101 °C. $[\alpha]_D^{25} = -18.0$ ($c = 0.14$, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.99–7.96 (m, 2H), 7.64–7.61 (m, 1H), 7.53–7.43 (m, 4H), 7.16–7.10 (m, 2H), 4.63 (d, $J = 5.0$ Hz, 1H), 3.99–3.93 (m, 1H), 3.75–3.57 (m, 2H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 196.4, 162.9 (d, $J^1_{CF} = 248.9$ Hz),

135.6, 134.2, 132.2, 129.8 (d, $J^3_{CF}$ = 8.3 Hz), 128.9, 128.1, 116.3 (d, $J^2_{CF}$ = 21.7 Hz), 111.7, 111.5, 40.5, 40.7, 28.8 ppm. ESI-HRMS calcd for $C_{18}H_{13}FN_2O$ + Na, 315.0904, found 315.0909. 83% ee determined by HPLC on AS-H column, hexane–i-propanol (90 : 10), 1.0 mL min$^{-1}$, UV 254 nm, $t_{minor}$ = 9.562 min, $t_{major}$ = 11.143 min.

**2-(3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl)malononitrile (4o).** Colorless oil. Yield 79%. $[\alpha]^{25}_D$ = +11.0 ($c$ = 0.10, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.97–7.94 (m, 2H), 7.47–7.39 (m, 5H), 6.97–6.94 (m, 2H), 4.70 (d, $J$ = 5.1 Hz, 1H), 3.97–3.90 (m, 1H), 3.88 (s, 3H), 3.71–3.55 (m, 2H) ppm. $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 195.0, 164.3, 136.6, 130.5, 129.7, 129.1, 128.8, 127.9, 114.0, 111.9, 111.7, 55.6, 41.2, 39.6, 28.7 ppm. ESI-HRMS calcd for $C_{19}H_{16}N_2O_2$ + Na 327.1104, found 327.1099. 87% ee determined by HPLC on AS-H column, hexane–i-propanol (70 : 30), 0.8 mL min$^{-1}$, UV 254 nm, $t_{major}$ = 22.195 min, $t_{minor}$ = 25.903 min.

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