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Calixarene-derived chiral tertiary amine–thiourea organocatalyzed asymmetric Michael additions of acetyl acetone and dimethyl malonate to nitroolefins

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ABSTRACT

Novel bifunctional chiral thiourea-tertiary amines bearing a calix[4]arene scaffold were synthesized and applied in catalytic asymmetric Michael addition of acetyl acetone and dimethyl malonate to nitroolefins. The corresponding adducts were obtained in excellent yields (up to 99%) and with high enantioselectivities (up to 94% ee).

1. Introduction

Asymmetric organocatalysis through hydrogen bond activation has become an efficient activation mode in many enantioselective syntheses.[1] Among the different hydrogen bonding moieties, bifunctional organocatalysts, which incorporate both H-bond donor and Lewis base functionalities into a single asymmetric molecular scaffold, have emerged as efficacious catalysts and have been successfully applied to various types of asymmetric reactions[2,3] since the pioneering work of Jacobsen,[4] Schreiner[5] and Takemoto.[6] The key to the high activity as well as selectivity of these catalysts was assigned to their ability to activate both electrophilic and nucleophilic centers of the reacting partners independently and simultaneously in a controlled chiral environment.

The Michael reaction, the nucleophilic addition of appropriate carboanionic reagents to α,β-unsaturated carbonyl compounds, represents a direct and attractive approach for the construction of versatile intermediates by remote functionalization in organic synthesis.[7] Therefore, their catalytic asymmetric versions have been studied extensively.[8] In particular, the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes is one of the most important methods for the preparation of optically active nitro carbonyl compounds, which play an important role as precursors of biologically active compounds or chiral building blocks in synthetic and medicinal chemistry. Although significant progress has been achieved in this area, there is still need for new strategies to design efficient, recyclable chiral catalysts for asymmetric Michael addition reactions.

Calixarenes, cyclic oligomers of phenolic units linked through the *ortho*-positions, represent an important class of macrocyclic compounds due to their potential to form host–guest complexes with numerous classes of compounds in supramolecular chemistry.[9] Chiral derivatives of these macrocycles, which can be synthesized by attaching chiral substituents at one of the rims (lower or upper) may have potential applications, such as being organocatalysts,[10] ionophores in catalysis, carriers in liquid membrane technology, extractants for anions and cations, and chemical sensors.[11]

As part of our ongoing studies to develop novel types of organocatalysts for asymmetric transformations, we have recently reported that calix[4]arene-based chiral primary amine–thioureas can function as multiple H-bond donor organocatalysts and have shown excellent performances in the catalytic asymmetric Michael additions of aldehydes to nitroalkenes and maleimides.[12] Herein we report the synthesis of calixarene-based chiral bifunctional tertiary amine–thiourea organocatalysts and their application in the catalytic conjugate addition of 1,3-dicarbonyl compounds to a variety of nitroolefins under mild conditions.

2. Results and discussion

At first, calixarene-based primary amine–thioureas **1a–b** were readily prepared in two steps from *p-tert*-butylcalix[4]arene diamine and chiral isothiocyanates according to our previous method.[12a] The introduction of the methyl groups using HCHO/$NaBH_3CN$ in AcOH/CH_3CN solvent mixture afforded **2a–b** in 87% and 86% yields respectively (Scheme 1).

In the literature, conjugate additions were found to be suitable reactions for evaluating the catalytic activities of these new chiral

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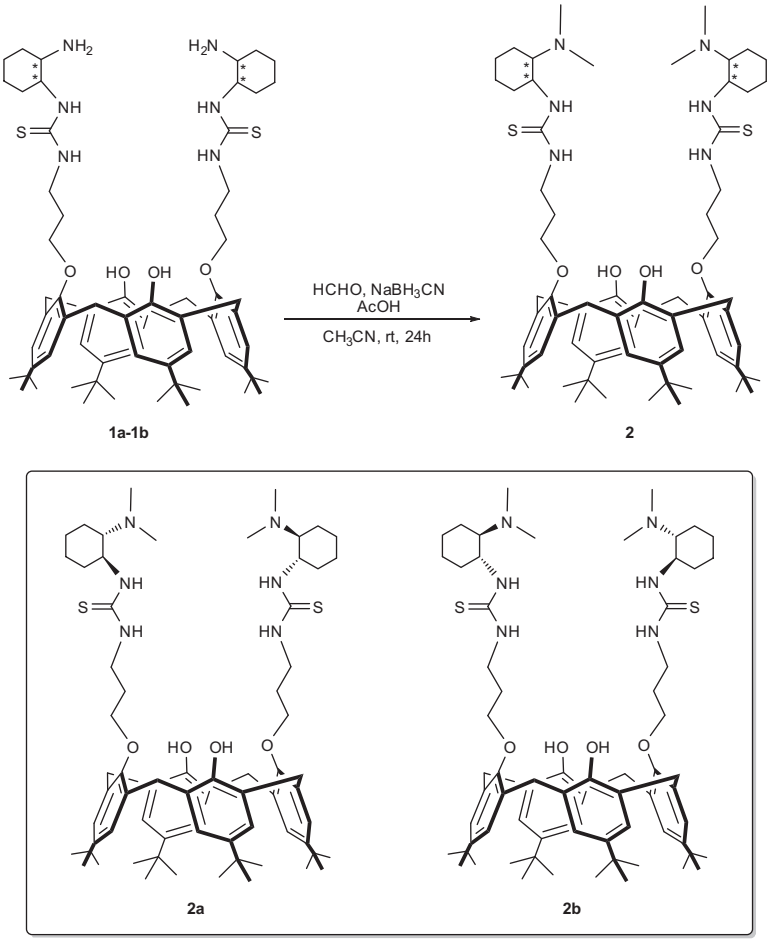


Scheme 1. Synthesis of calix[4]arene-based tertiary amine–thiourea organocatalysts **2a**, **2b**.

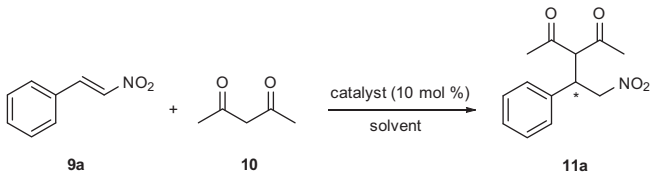
tertiary amine–thioureas.[13] Hence, the conjugate addition reaction of 2,4-pentanedione to *trans*-β-nitrostyrene was chosen as the model reaction to examine the efficacy of **2a**–**b** as organocatalysts. In the presence of 10 mol % of **2a**, the reaction of *trans*-β-nitrostyrene **9a** with 2,4-pentanedione in CH_2Cl_2, afforded the Michael adduct (*S*)-**11a** in 95% yield and with 76% ee in 24 h (Table 1, entry 1). From the results of recent studies[14] we expected reversed senses of asymmetric induction with catalyst **2b**. However, thiourea **2b** catalyzed the Michael addition with great efficiency to yield the product in 93% yield but with a poor enantioselectivity of 15% (Table 1, entry 2). Similar results were obtained when the solvent was changed to toluene (Table 1, entries 3 and 4). In further experiments, other influencing factors, such as solvent, reaction temperature and catalyst loading were thoroughly investigated, employing **2a** as the catalyst (Table 1, entries 5–15). Solvent evaluation revealed that the enantioselectivity was highly dependent on the solvent, with acetonitrile being found as the best solvent. We expected that the resulting ee would be higher at a lower temperature. However, reducing the reaction temperature from room temperature to 0 °C did not improve the enantioselectivity (Table 1, entry 14). When the catalyst loading was reduced to 5 mol %, the yield and enantioselectivity were not significantly affected, but the reaction time was prolonged (Table 1, entry 15). Thus, the optimized catalyst loading was chosen as 10 mol %.

In the literature, it has been reported that the presence of additives, bases, or acids has a significant influence on asymmetric reactions.[15] We were thus inspired to carry out the enantioselective conjugate addition in the presence of additives to determine the optimal reaction conditions. As depicted in Table 2, various typical acids, bases, and water were employed. Among the screened additives, reduced reaction times and good yields were obtained with H_2O and Et_3N (Table 2, entries 1 and 5), but the enantioselectivity was poor. In the presence of AcOH and $PhCO_2H$, prolonged reaction times, lower yields, and enantioselectivities were observed (Table 2, entries 2 and 3).

In order to confirm the role of the achiral calixarene backbone of **2a**, the monomeric analogue **8** was also prepared in order to carry out key control reactions since simple tertiary amine–thioureas are known to be good catalysts for the asymmetric Michael additions of 1,3-dicarbonyl compounds to nitroalkenes. The chiral tertiary amine–thiourea **8** was synthesised starting from *p*-*tert*-butyl phenol in five steps and 50% overall yield by the procedure shown in Scheme 2. In the first control experiment, catalyst **8** afforded the Michael adduct in lower yield and enantioselectivity (Table 1, entry 16) than the calixarene-based chiral tertiary amine–thiourea derivatives. In another experiment to mimic the effect of calixarene-thiourea **2a**, 20 mol % of catalyst **8** was used (Table 1, entry 17). Only a slight increase in the enantioselectivity and chemical yield was observed. In order to explain the role of the bulky calixarene moiety of thiourea and the phenolic hydroxy groups on the calixarene scaffold, we performed a conjugate addition using **8** as the catalyst and *p*-*tert*-butyl phenol as an acidic additive (Table 2, entry 6). Even in this case, the employment of **8**-*p*-*tert*-butyl phenol system did not provide a better enantioselectivity than that achieved with chiral calix[4]arene thiourea **2a**.

With the optimized reaction conditions in hand, we next evaluated the scope of the Michael addition reaction with a number of nitroolefins **9** with 2,4-pentanedione **10** in the presence of

Table 1
Optimization of the reaction conditions for the asymmetric Michael addition of acetylacetone to *trans*-β-nitrostyrene catalyzed by **2a**–**b** and **8**[a]

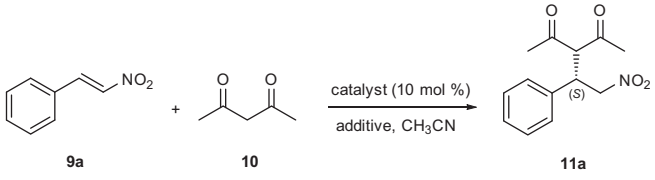


9a **10** **11a**

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a**	CH_2Cl_2	24	95	76 (*S*)
2	**2b**	CH_2Cl_2	24	93	15 (*R*)
3	**2a**	Toluene	24	93	81 (*S*)
4	**2b**	Toluene	24	95	10 (*R*)
5	**2a**	$CHCl_3$	24	91	72 (*S*)
6	**2a**	$ClCH_2CH_2Cl$	24	97	79 (*S*)
7	**2a**	EtOAc	24	98	82 (*S*)
8	**2a**	CCl_4	24	97	71 (*S*)
9	**2a**	CH_3CN	24	99	**94** (*S*)
10	**2a**	THF	24	98	77 (*S*)
11	**2a**	MTBE	24	95	75 (*S*)
12	**2a**	MeOH	4	82	12 (*S*)
13	**2a**	DMF	4	64	55 (*S*)
14[d]	**2a**	CH_3CN	36	94	85 (*S*)
15[e]	**2a**	CH_3CN	40	98	93 (*S*)
16	**8**	CH_3CN	30	87	38 (*S*)
17[f]	**8**	CH_3CN	24	91	44 (*S*)

[a] The reactions were performed with 0.05 mmol **9a**, and 0.1 mmol of **10** in 0.125 mL of solvent in the presence of 10 mol % of catalyst.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H), and the configuration was assigned by comparison of the retention time and specific rotation with literature data.
[d] Reaction performed at 0 °C.
[e] 5 mol % catalyst was used.
[f] 20 mol % catalyst was used.

Table 2
Screening of conditions for the asymmetric Michael addition of acetylacetone **10** and *trans*-β-nitrostyrene **9a**[a]



9a **10** **11a**

Entry	Catalyst	Additive	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a**	H_2O	4	96	59
2	**2a**	AcOH	96	88	61
3	**2a**	$PhCO_2H$	48	75	73
4	**2a**	Pyridine	24	98	83
5	**2a**	Et_3N	4	93	31
6	**8**	*p*-*t*-Butylphenol	24	98	59

[a] The reactions were performed with 0.05 mmol **9a** 0.1 mmol **10** in 0.125 mL of solvent in the presence of 10 mol % of catalyst and 15 mol % additive at room temperature.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H), and the configuration was assigned by comparison of the retention time and specific rotation with literature data.

10 mol % catalyst **2a** at room temperature. The results are summarized in Table 3. It appears that the position and the electronic properties of the substituents for aromatic rings of nitroolefins are well tolerated by the conjugate addition reactions. A wide range of nitroolefins bearing either electron donating or electron withdrawing groups reacted well with acetylacetone to give the desired Michael adducts **11b**–**11l** in generally high yields (59–98%) and with moderate to good enantioselectivities (48–89%).

To further extend the application of our new organocatalyst, we examined the catalytic properties of **2a** in the conjugate addition of dimethylmalonate to nitroalkenes. Parameters such as solvent (Table 4, entries 1–11), temperature (Table 4, entry 12) and catalyst loading (Table 4, entry 13) were also examined.

Table 5 shows the generality and scope of the Michael addition reaction with a variety of nitroolefins and dimethyl malonate. As demonstrated in Table 5 using 10 mol % of **2a**, the reactions of all nitrostyrenes, bearing *ortho*-, *meta*- or *para*-electron-donating or electron-withdrawing substituents, with dimethylmalonate **12** proceeded smoothly and gave the corresponding products **13b**–**m** in high yields (up to 98%) and with good enantioselectivities (up to 88%).

Although the real catalytic mechanism still needs further study to explain the observed enantioselectivity in Michael additions catalyzed by calix[4]arene-based chiral tertiary amine–thiourea derivatives, we propose a plausible synergistic dual activation model for the reaction. First, the scaffold of the calixarene catalyst was assumed to create reaction sites surrounded by two thioureas, which interact through hydrogen bonding with the nitro group of the nitrostyrene and enhance their electrophilicity, while the tertiary amine deprotonates an acidic proton of 1,3-dicarbonyl compound, to generate a ternary complex. From the observed (*S*)-absolute configuration of the conjugate adduct **11a**, the new C–C bond was formed by the nuclephilic attack on the *re*-face of nitrostyrene **9a**.

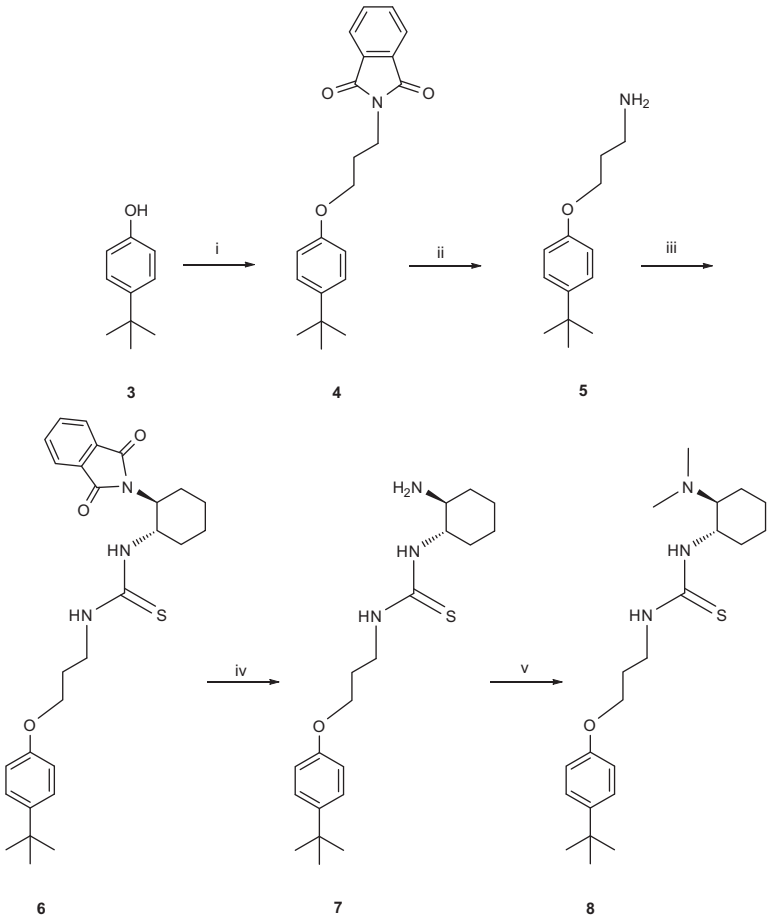
3. Conclusion

In conclusion, we have developed novel calix[4]arene-based chiral bifunctional tertiary amine–thiourea catalysts as multiple H-bond donor–acceptor organocatalysts for the asymmetric Michael additions of nitroolefins to 1,3-dicarbonyl compounds. The reaction was efficient in terms of productivity (up to 99% yield) and enantioselectivity (up to 94% ee). These results might pave the way for immobilizing these calixarene derivatives either onto polymers or magnetic nanoparticles for batch and continuous flow applications.

4. Experimental

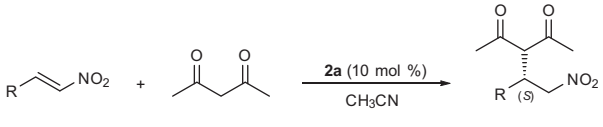
4.1. General

Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature on Varian 400 instrument. Chemical shifts are reported in ppm. Data were reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constants (Hz). Infrared (IR) spectra were recorded on a Termo Scientific Nicolet iS5 spectrometer equipped with an ATR unit and are reported in wavenumbers (cm^{-1}). The HPLC measurements were carried out on Agilent 1100 equipment connected with Chiralpak Daicel AD-H, OD-H and AS-H columns. Optical rotations were measured on an Atago AP-100 digital polarimeter using a 1 dm cell. Elemental analyses were performed using a Leco CHNS-932 analyzer. Analytical TLC was performed using Merck prepared plates (silica gel 60 F254 on aluminum). Flash chromatography separations were performed on a Merck Silica Gel 60 (230–400 Mesh). All starting materials and reagents used were of standard analytical grade from Fluka, Merck, Aldrich, Acros or TCI and used without further purification. Dichloromethane was dried ($CaCl_2$), distilled from CaH_2 and



Scheme 2. Synthesis of chiral *p*-*tert*-butylphenol analogue **8**. Reagents and conditions: (i) K_2CO_3, *N*-(3-bromopropyl)phthalimide, dry DMF, rt; (ii) $N_2H_4{\cdot}H_2O$, EtOH, reflux; (iii) chiral isothiocyanate, CH_2Cl_2, rt, 24 h; (iv) $N_2H_4{\cdot}H_2O$, EtOH, reflux; (v) HCHO, $NaBH_3CN$, AcOH, CH_3CN, rt, 4 h.

Table 3
Asymmetric Michael addition of acetylacetone with different nitrostyrenes catalyzed by organocatalyst **2a**[a]



9 10 11

Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	2-Br-C_6H_4 **9b**	**11b**	61	89
2	3-Br-C_6H_4 **9c**	**11c**	86	77
3	4-Br-C_6H_4 **9d**	**11d**	78	78
4	2-MeO-C_6H_4 **9e**	**11e**	97	72
5	3-MeO-C_6H_4 **9f**	**11f**	98	84
6	4-MeO-C_6H_4 **9g**	**11g**	97	81
7	2-F-C_6H_4 **9h**	**11h**	59	48
8	4-F-C_6H_4 **9i**	**11i**	87	89
9	4-Me-C_6H_4 **9j**	**11j**	90	70
10	4-Cl-C_6H_4 **9k**	**11k**	75	70
11	2,4-Cl-C_6H_3 **9l**	**11l**	62	80

[a] The reactions were performed with 2 equiv of acetylacetone and 1 equiv of **9** in 0.125 mL of CH_3CN in the presence of 10 mol % **2a** at room temperature for 4–24 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis, and the configuration was assigned by comparison of the retention time and specific rotation with literature data.

stored over molecular sieves. Other commercial grade solvents were distilled, and then stored over molecular sieves. The drying agent employed was anhydrous $MgSO_4$.

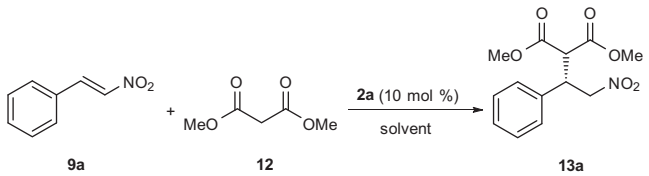
4.2. Synthesis of catalysts

4.2.1. General procedure for the synthesis of chiral calix[4]arene-based tertiary amine thioureas 2a and 2b

To a solution of **1a**/**1b** (1.48 g, 1.38 mmol) in 20 mL of acetonitrile, formaldehyde (0.48 g, 16.13 mmol) was added and the resulting mixture was stirred at room temperature for 15 min. Next, $NaBH_3CN$ (0.60 g, 9.49 mmol) was added, followed 15 min later by AcOH (1.79 mL, 18.32 mmol). After for stirring 24 h at room temperature, the reaction mixture was diluted with 2% CH_3OH–$CHCl_3$ (100 mL) and washed with 1 M NaOH (4 × 50 mL). The aqueous layer was re-extracted with $CHCl_3$ (3 × 30 mL), the combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with $CHCl_3$–MeOH mixtures.

4.2.1.1. Catalyst 2a. White solid; 87% yield; mp 145–147 °C, $[\alpha]_D^{25} = -14.5$ (*c* 1.0, $CHCl_3$); *Catalyst* ***2b****:* White solid; 86% yield; mp 144–146 °C; $[\alpha]_D^{25} = +15.4$ (*c* 1.0, $CHCl_3$); IR (cm^{-1}): 3328, 2931, 2861, 1772, 1734, 1717, 1653, 1636, 1540, 1484, 1361, 1299, 1194, 1123, 1094; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (br s, 2H), 6.97 (s, 4H), 6.88 (s, 4H), 4.32–3.81 (m, 12H), 3.29 (t, $J = 11.9$ Hz, 4H), 2.56–1.91 (m, 20H), 1.83–1.63 (m, 4H), 1.62–1.45 (m, 4H), 1.17 (s, 22H), 1.04–1.13 (m, 4H), 1.01 (s, 18H) ppm; NH-signals could not be detected; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.3$, 147.5, 132.8, 132.6, 127.6, 127.5, 125.9, 125.8, 125.7, 125.4, 40.1, 34.1, 33.8, 33.2, 32.9, 32.5, 32.3, 32.0, 31.6, 31.4,

Table 4
Asymmetric Michael addition of dimethyl malonate to *trans*-β-nitrostyrene catalyzed by **2a**[a]

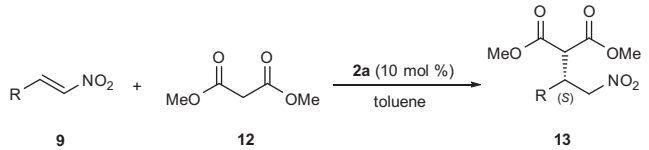


9a **12** **13a**

Entry	Solvent	Time (d)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	6	95	71
2	Toluene	4	99	79
3	$CHCl_3$	6	94	64
4	CCl_4	4	91	72
5	$ClCH_2CH_2Cl$	6	92	74
6	EtOAc	6	98	74
7	CH_3CN	4	97	65
8	THF	4	98	68
9	MTBE	4	89	75
10	MeOH	2	93	16
11	DMF	2	96	7
12[d]	Toluene	10	98	74
13[e]	Toluene	5	95	73

[a] The reactions were performed with 0.05 mmol of **9a**, 0.15 mmol of **12** in 0.2 mL of solvent in the presence of 10 mol % of catalyst.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralpak AD-H), and the configuration was assigned by comparison of the retention time and specific rotation with literature data.
[d] Reaction performed at 0 °C.
[e] 5 mol % catalyst was used.

Table 5
Asymmetric Michael addition of dimethylmalonate with different nitrostyrenes catalyzed by organocatalyst **2a**[a]



9 **12** **13**

Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	2-Br-C_6H_4 **9b**	**13b**	86	86
2	3-Br-C_6H_4 **9c**	**13c**	92	75
3	4-Br-C_6H_4 **9d**	**13d**	95	84
4	2-MeO-C_6H_4 **9e**	**13e**	96	81
5	3-MeO-C_6H_4 **9f**	**13f**	97	50
6	4-MeO-C_6H_4 **9g**	**13g**	98	67
7	2-F-C_6H_4 **9h**	**13h**	91	81
8	4-F-C_6H_4 **9i**	**13i**	97	80
9	4-Me-C_6H_4 **9j**	**13j**	91	84
10	4-Cl-C_6H_4 **9k**	**13k**	84	79
11	2,4-Cl-C_6H_3 **9l**	**13l**	91	88
12	2-NO_2-C_6H_4	**13m**	96	79

[a] The reactions were performed with 3 equiv of dimethylmalonate and 1 equiv of **9** in 0.2 mL of toluene in the presence of 10 mol % **2a** at room temperature.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis, and the configuration was assigned by comparison of the retention time and specific rotation with literature data.

31.1, 29.7, 29.4, 25.0, 24.9, 24.7, 24.6 ppm. Anal. Calcd for: $C_{68}H_{102}N_6O_4S_2$ (1131.71): C, 72.17, H, 9.08, N, 7.43. Found: C, 72.15, H, 9.09, N, 7.44.

4.2.2. 2-(3-(4-(*tert*-Butyl)phenoxy)propyl)isoindoline-1,3-dione 4

To a stirred suspension of *p*-*tert*-butylphenol (0.90 g, 6.0 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) in dry DMF (10 mL), *N*-(3-bromopropyl)phthalimide (1.34 g, 5.0 mmol) was added. After stirring for 12 h at room temperature, the reaction was quenched with water (10 mL) and extracted with EtOAc (5 mL) three times. The combined organic phase was dried over $MgSO_4$ and concentrated to give the crude product, which was purified by flash chromatography on silica gel eluting with hexane–ethyl acetate mixtures. Yellow oil; 91% yield; IR (cm^{-1}): 2960, 2868, 2253, 1772, 1708, 1610, 1513, 1393, 1245, 1038, 907; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.82 (m, 2H, Ar*H*), 7.71–7.69 (m, 2H, Ar*H*), 7.26–7.24 (m, 2H, Ar*H*), 6.77–6.75 (m, 2H, Ar*H*), 4.01 (t, 2H, *J* = 6.0 Hz, $-OCH_2CH_2$), 3.90 (t, 2H, *J* = 6.9, $-NCH_2CH_2$), 2.21–2.14 (m, 2H, $CH_2CH_2CH_2$), 1.28 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 157.2, 144.1, 134.8, 134.6, 132.9, 126.9, 124.1, 123.9, 114.7, 66.3, 36.3, 34.8, 32.3, 29.2 ppm. Anal. Calcd for: $C_{21}H_{23}NO_3$ (337.41): C, 74.75, H, 6.87, N, 4.15. Found: C, 74.71; H, 7.01; N, 4.12.

4.2.3. 3-(4-(*tert*-Butyl)phenoxy)propan-1-amine 5

Compound **4** (7.5 g, 22.23 mmol) and hydrazine hydrate (7.5 mL, 85% in H_2O) were dissolved in EtOH (40 mL) and refluxed for 4 h. The mixture was cooled to room temperature and filtered. The solvent was then removed under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL), washed with water (50 mL), dried over $MgSO_4$ and purified by flash chromatography on silica gel eluting with hexane–ethyl acetate mixtures. Green oil; 88% yield; IR (cm^{-1}): 3307, 2958, 2867, 1608, 1513, 1473, 1246, 1184, 588. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 2H, Ar*H*), 6.84 (d, *J* = 8.8 Hz, 2H, Ar*H*), 4.03 (t, *J* = 6.0 Hz, 2H, $-OCH_2CH_2$), 2.91 (t, *J* = 6.7 Hz, 2H, $NH_2CH_2CH_2$), 1.96–1.89 (m, 2H, $CH_2CH_2CH_2$), 1.62 (s, 2H, NH_2), 1.30 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.3, 126.2, 113.9, 65.8, 39.3, 34.0, 34.9, 31.5, 31.3, 29.7 ppm. Anal. Calcd for: $C_{13}H_{21}NO$ (207.31): C, 75.32, H, 10.21, N, 6.76. Found: C, 75.26, H, 10.40, N, 6.70.

4.2.4. 1-(3-(4-(*tert*-Butyl)phenoxy)propyl)-3-((1*S*,2*S*)-2-(1,3-dioxoisoindolin-2-yl)-cyclohexyl)thiourea 6

To a solution of chiral isothiocyanate[16] (0.143 g, 0.5 mmol) in dry CH_2Cl_2 (15 mL) was added 3-(4-(*tert*-butyl)phenoxy)propan-1-amine **5** (0.104 g, 0.5 mmol). The reaction mixture was stirred for 24 h at rt. After removal of the solvent, the crude product was purified by flash chromatography (hexane–EtOAc) to afford **6**. Yellow oil; 87% yield; $[\alpha]_D^{25} = -2.1$ (*c* 1.0, $CHCl_3$); IR (cm^{-1}): 3354, 2938, 2864, 1767, 1704, 1390, 1241, 1046, 639. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.72 (m, 2H), 7.63–7.61 (m, 2H), 7.31–7.28 (m, 2H), 6.87–6.85 (m, 2H), 6.34–6.22 (m, 1H), 6.00–5.97 (m, 1H), 4.70 (br s, 2H), 3.98–3.89 (m, 2H), 3.48–3.29 (m, 2H), 2.46–2.13 (m, 2H), 2.02–1.65 (m, 6H), 1.44–1.34 (m, 2H), 1.28 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.5, 168.8, 156.0, 143.8, 134.0, 131.7, 126.3, 123.2, 114.0, 54.7, 34.1, 32.9, 31.5, 28.9, 28.7, 25.2, 24.4 ppm. Anal. Calcd for: $C_{28}H_{35}N_3O_3S$ (493.66): C, 68.12, H, 7.15, N, 8.51. Found: C, 68.18, H, 7.83, N, 8.44.

4.2.5. 1-((1*S*,2*S*)-2-Aminocyclohexyl)-3-(3-(4-(*tert*-butyl)phenoxy)propyl)thiourea 7

The protected thiourea–amine **6** (1.35 g, 2.73 mmol) and hydrazine hydrate (1.35 mL mL, 85% in H_2O) were dissolved in EtOH (35 mL) and refluxed for 6 h. The solvent was evaporated under vacuum and the residue was dissolved in $CHCl_3$ (20 mL), washed with water (3 × 15 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated to yield a greenish oil (0.834 g, 84%), which was used in the next step without further purification.

4.2.6. 1-(3-(4-(*tert*-Butyl)phenoxy)propyl)-3-((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)-thiourea 8

To a solution of **7** (40.0 mg, 0.11 mmol) in 10 mL of acetonitrile, formaldehyde (0.107 mL, 3.9 mmol) was added and the resulting mixture was stirred at room temperature for 15 minute. Next,

$NaBH_3CN$ (49.0 mg, 0.78 mmol) was added, followed 15 min later by AcOH (0.144 mL, 2.52 mmol). After stirring for 4 h at room temperature, the reaction mixture was diluted with 2% $CHCl_3$–CH_3OH (30 mL), and washed with 1 M NaOH (4 × 25 mL). The aqueous layer was re-extracted with $CHCl_3$ (3 × 20 mL), the combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with $CHCl_3$–MeOH mixtures. Pale yellow oil; 85% yield; $[\alpha]_D^{25} = -3.2$ (*c* 1.2, $CHCl_3$); IR (cm^{-1}): 3218, 2933, 2862, 1608, 1512, 1362, 1240, 1060, 734. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.24 (m, 2H), 6.80–6.78 (m, 2H), 6.60 (br s, 2H), 4.09–3.97 (m, 3H), 3.69–3.48 (m, 3H), 2.41–2.28 (m, 2H), 2.18 (s, 6H), 2.00–1.58 (m, 5H), 1.25 (s, 9H), 1.16–0.98 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.1, 156.2, 143.6, 126.2, 113.9, 66.8, 65.4, 55.7, 40.2, 34.0, 33.0, 31.5, 29.0, 25.0, 24.6, 21.6 ppm. Anal. Calcd for: $C_{22}H_{37}N_3OS$ (391.61): C, 67.47, H, 9.52, N, 10.73. Found: C, 67.24, H, 9.88, N, 10.71.

4.3. Representative procedure for the asymmetric addition of 2,4–pentanedione to nitroalkenes

To a stirred solution of nitroalkene (0.05 mmol) and chiral catalyst (0.005 mmol, 10 mol %) in 0.125 mL of solvent was added 2,4-pentanedione (0.1 mmol). After the reaction was complete (monitored by TLC), the resulting mixture was concentrated and the residue was purified through column chromatography on silica gel (eluent, ethyl acetate/hexane 1:4 to 1:1) to afford product **11a–11l**. The enantiomeric purity of the product was determined by using chiral HPLC analysis. Racemic samples of the Michael adducts were prepared using a racemic catalyst.

4.3.1. (*S*)-3-(2-Nitro-1-phenylethyl)-pentane-2,4-dione 11a[17a]

White solid; yield 99%; 94% ee; mp 112–113 °C; IR (cm^{-1}): 1732, 1703, 1550, 1496, 1433, 1361, 1272, 1140, 702. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 3H), 7.12–7.10 (m, 2H), 4.58–4.55 (m, 2H), 4.30 (d, *J* = 10.5 Hz, 1H), 4.21–4.17 (m, 1H), 2.23 (s, 3H), 1.87 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 201.0, 135.9, 129.3, 128.6, 127.9, 78.2, 70.7, 42.7, 30.5, 29.6 ppm. HPLC analysis [Chiralpak AS-H column, hexane–2-propanol = 85:15, flow rate: 1.0 mL/min, wavelength = 210 nm: t_R (major) = 15.1 min, t_R (minor) = 24.1 min]. $[\alpha]_D^{25}$ = +196.2 (*c* 1.0, $CHCl_3$).

4.3.2. (*S*)-3-[1-(2-Bromophenyl)-2-nitroethyl]-pentane-2,4-dione 11b[17b]

Orange solid; yield 61%, 89% ee; mp 87 °C; IR (cm^{-1}): 1727, 1702, 1553, 1472, 1433, 1359, 1259, 1154, 762. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.9 Hz, 1H), 7.30–7.26 (m, 1H), 7.19–7.12 (m, 2H), 4.85–4.71 (m, 2H), 4.68–4.64 (m, 1H), 4.59 (d, *J* = 9.4 Hz, 1H), 2.29 (s, 3H), 2.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 200.8, 135.0, 134.0, 129.9, 128.3, 76.2, 69.1, 41.0, 30.9, 28.3 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 97:3, flow rate: 0.5 mL/min, wavelength = 210 nm: t_R (major) = 21.8 min, t_R (minor) = 27.3 min]. $[\alpha]_D^{25}$ = +209.3 (*c* 1.0, $CHCl_3$).

4.3.3. (*S*)-3-[1-(3-Bromophenyl)-2-nitroethyl]-pentane-2,4-dione 11c[17b]

White solid; yield 86%; 77% ee; mp 102–103 °C; IR (cm^{-1}): 1727, 1703, 1550, 1477, 1433, 1383, 1367, 1252, 1141, 790, 699. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.9 Hz, 1H), 7.35 (s, 1H), 7.26–7.11 (m, 2H), 4.63–4.61 (m, 2H), 4.33 (d, *J* = 10.6 Hz, 1H), 4.23–4.18 (m, 1H), 2.29 (s, 3H), 2.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.3, 200.4, 138.5, 131.8, 131.0, 130.8, 126.6, 123.3, 77.7, 70.3, 42.3, 30.5, 29.8 ppm. HPLC analysis [Chiralpak AS-H column, hexane–2-propanol = 85:15, flow rate: 1.0 mL/min, wavelength = 210 nm: t_R (major) = 18.4 min, t_R (minor) = 37.3 min]. $[\alpha]_D^{25}$ = +132.6 (*c* 1.0, $CHCl_3$).

4.3.4. (*S*)-3-[1-(4-Bromophenyl)-2-nitroethyl)]-pentane-2,4-dione 11d[17c]

White solid; yield 78%; 78% ee; mp 71 °C; IR (cm^{-1}): 1729, 1699, 1547, 1490, 1431, 1362, 1264, 1140, 818. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 4.61–4.59 (m, 2H), 4.33 (d, *J* = 10.8 Hz, 1H), 4.24–4.18 (m, 1H), 2.30 (s, 3H), 1.98 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 200.6, 135.0, 132.5, 129.6, 122.7, 77.8, 70.4, 42.2, 30.5, 29.7 ppm. HPLC analysis [Chiralpak AS-H column, hexane–2-propanol = 85:15, flow rate: 1.0 mL/min, wavelength = 210 nm: t_R (major) = 17.7 min, t_R (minor) = 32.5 min]. $[\alpha]_D^{25}$ = +137.1 (*c* 1.0, $CHCl_3$).

4.3.5. (*S*)-3-[1-(2-Methoxyphenyl)-2-nitroethyl]-pentane-2,4-dione 11e[17c]

Colorless oil; yield 97%; 72% ee; IR (cm^{-1}): 1727, 1702, 1596, 1552, 1494, 1359, 1247, 1159, 1024, 758. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 1H), 7.09–7.07 (m, 1H), 6.91–6.87 (m, 2H), 4.86–4.75 (m, 1H), 4.61–4.56 (m, 2H), 4.51–4.45 (m, 1H), 3.88 (s, 3H), 2.28 (s, 3H), 1.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.3, 201.5, 130.2, 129.7, 123.5, 121.2, 111.2, 69.1, 55.4, 38.9, 30.4, 29.7, 28.7 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 97:3, flow rate: 0.5 mL/min, wavelength = 210 nm: t_R (major) = 38.4 min, t_R (minor) = 40.6 min]. $[\alpha]_D^{25}$ = +186.1 (*c* 0.5, $CHCl_3$).

4.3.6. (*S*)-3-[1-(3-Methoxyphenyl)-2-nitroethyl]-pentane-2,4-dione 11f[17c]

White solid; yield 98%; 84% ee; mp 95 °C; IR (cm^{-1}): 1732, 1703, 1600, 1554, 1543, 1495, 1437, 1361, 1262, 1141, 1040, 793, 704. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (s, 1H), 6.82–6.70 (m, 3H), 4.64–4.57 (m, 2H), 4.36 (d, *J* = 10.8 Hz, 1H), 4.23–4.18 (m, 1H), 3.77 (s, 3H), 2.29 (s, 3H), 1.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.8, 201.0, 160.0, 137.5, 130.4, 119.9, 114.1, 113.6, 78.1, 70.6, 55.2, 42.7, 30.4, 29.6 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 85:15, flow rate: 1.0 mL/min, wavelength = 210 nm: t_R (major) = 9.7 min, t_R (minor) = 12.4 min]. $[\alpha]_D^{25}$ = +207.3 (*c* 0.25, $CHCl_3$).

4.3.7. (*S*)-3-[1-(4-Methoxyphenyl)-2-nitroethyl]-pentane-2,4-dione 11g[17a]

White solid; yield 97%; 81% ee; mp 116–118 °C; IR (cm^{-1}): 1733, 1705, 1614, 1549, 1515, 1438, 1363, 1261, 1171, 1141, 812. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.09 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.58–4.55 (m, 2H), 4.32 (d, *J* = 10.9 Hz, 1H), 4.21–4.15 (m,1H), 3.76 (s, 3H), 2.28 (s, 3H), 1.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 201.2, 159.4, 129.0, 127.6, 114.6, 78.4, 70.8, 55.2, 42.1, 30.4, 29.5 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 90:10, flow rate: 1.0 mL/min, wavelength = 210 nm: t_R (major) = 15.4 min, t_R (minor) = 24.0 min]. $[\alpha]_D^{25}$ = +119.7 (*c* 2.5, $CHCl_3$).

4.3.8. (*S*)-3-[1-(2-Fluorophenyl)-2-nitroethyl]-pentane-2,4-dione 11h[17b]

White solid; yield 59%; 48% ee; mp 57–58 °C; IR (cm^{-1}): 1730, 1704, 1554, 1494, 1426, 1361, 1267, 1234, 1178, 1144, 767. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 1H), 7.20–7.03 (m, 3H), 4.75–4.60 (m, 2H), 4.49–4.47 (m, 2H), 2.29 (s, 3H), 2.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.3, 200.7, 130.5, 124.9, 116.4, 76.6, 69.0, 37.9, 30.4, 29.2 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 90:10, flow rate: 1.0 mL/min, wavelength = 210 nm: t_R (major) = 10.4 min, t_R (minor) = 11.8 min]. $[\alpha]_D^{25}$ = +186.8 (*c* 0.4, $CHCl_3$).

4.3.9. (*S*)-3-[1-(4-Fluorophenyl)-2-nitroethyl]-pentane-2,4-dione 11i[17c]

Colorless oil; yield 87%; 89% ee; IR (cm^{-1}): 1733, 1704, 1550, 1513, 1437, 1363, 1267, 1141, 827. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.15 (m, 2H), 7.04–6.99 (m, 2H), 4.61–4.59 (m, 2H), 4.33 (d, J = 10.8 Hz, 1H), 4.26–4.21 (m, 1H), 2.29 (s, 3H), 1.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.5, 200.8, 163.7, 161.2, 131.7, 131.7, 129.7, 129.6, 116.5, 116.3, 78.1, 70.6, 42.0, 30.5, 29.6 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 90:10, flow rate: 1.0 mL/min, wavelength = 210 nm: t_R (major) = 13.0 min, t_R (minor) = 26.4 min]. $[\alpha]_D^{25}$ = +12.9 (c 1.0, $CHCl_3$).

4.3.10. (*S*)-3-[1-(4-Methylphenyl)-2-nitroethyl]-pentane-2,4-dione 11j[17a]

White solid; yield 90%; 70% ee; mp 88–90 °C; IR (cm^{-1}): 1731, 1702, 1548, 1430, 1362, 1267, 1140, 813. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.07 (m, 4H), 4.61–4.58 (m, 2H), 4.33 (d, J = 10.8 Hz, 1H), 4.23–4.17 (m, 1H), 2.29 (s, 6H), 1.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 201.1, 138.3, 132.8, 130.0, 127.8, 78.3, 70.8, 42.4, 30.4, 29.4, 21.0 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 90:10, flow rate: 1.0 mL/min, wavelength = 210 nm: t_R (major) = 10.2 min, t_R (minor) = 16.5 min]. $[\alpha]_D^{25}$ = +78.2 (c 2.8, $CHCl_3$).

4.3.11. (*S*)-3-[1-(4-Chlorophenyl)-2-nitroethyl]-pentane-2,4-dione 11k[17a]

White solid; yield 75%; 70% ee; mp 110–111 °C; IR (cm^{-1}): 1732, 1701, 1549, 1482, 1361, 1332, 1270, 1141, 821. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.23 (m, 2H), 7.08–7.06 (m, 2H), 4.55–4.53 (m, 2H), 4.27 (d, J = 10.5 Hz, 1H), 4.19–4.13 (m, 1H), 2.23 (s, 3H), 1.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 200.6, 134.5, 134.5, 129.6, 129.3, 77.9, 70.5, 42.1, 30.5, 29.7 ppm. HPLC analysis [Chiralpak AS-H column, hexane–2-propanol = 85:15, flow rate: 1.0 mL/min, wavelength = 210 nm: t_R (major) = 16.4 min, t_R (minor) = 34.0 min]. $[\alpha]_D^{25}$ = +19.2 (c 0.5, $CHCl_3$).

4.3.12. (*S*)-3-[1-(2,4-Dichlorophenyl)-2-nitroethyl]-pentane-2,4-dione 11l[17b]

Colorless oil; yield 62%; 80% ee; IR (cm^{-1}): 1730, 1704, 1550, 1475, 1378, 1360. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 2.1 Hz, 1H), 7.24–7.21 (m, 1H), 7.10 (d, J = 8.4 Hz, 1H), 4.84–4.80 (m, 1H), 4.71–4.61 (m, 2H), 4.54 (d, J = 9.7 Hz, 1H), 2.29 (s, 3H), 2.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 200.5, 135.1, 134.5, 132.1, 130.5, 128.0, 76.0, 68.8, 38.4, 30.9, 28.6 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 90:10, flow rate: 1.0 mL/min, wavelength = 210 nm: t_R (minor) = 10.0 min, t_R (major) = 13.8 min]. $[\alpha]_D^{25}$ = +59.1 (c 2.25, $CHCl_3$).

4.4. Representative procedure for the asymmetric addition of dimethyl malonate to nitroalkenes

A solution of nitroalkene (0.05 mmol), dimethylmalonate (19.82 mg, 0.15 mmol) and chiral catalyst (0.005 mmol, 10 mol %) in 0.2 mL of the desired solvent was stirred at a certain temperature and for the appropriate time (monitored by TLC). The resulting mixture was concentrated and the residue was purified via column chromatography on silica gel (eluent, ethyl acetate/hexane 1:10 to 1:2) to afford product **13a–13m**. The enantiomeric purity of the product was determined by using chiral HPLC analysis. Racemic samples of the Michael adducts were prepared using racemic catalyst.

4.4.1. Dimethyl (*S*)-2-(2-nitro-1-phenylethyl)malonate 13a[18a]

White solid; yield 99%; 79% ee; mp 59–61 °C; IR (cm^{-1}): 2985, 1727, 1557, 1498, 1456, 1435, 1380, 1266, 1082, 985, 756, 699. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 5H), 4.95–4.84 (m, 2H), 4.26–4.22 (m, 1H), 3.86 (d, J = 9.1 Hz, 1H), 3.75 (s, 3H), 3.55 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 167.2, 136.1, 129.0, 128.4, 127.8, 77.4, 54.7, 53.0, 52.8, 42.9 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 90:10, flow rate: 1.0 mL/min, wavelength = 220 nm: t_R (minor) = 17.0 min, t_R (major) = 28.1 min]. $[\alpha]_D^{25}$ = −3.7 (c 1.0, CH_2Cl_2).

4.4.2. Dimethyl (*S*)-2-(1-(2-bromophenyl)-2-nitroethyl)malonate 13b[18b]

Colorless oil; yield 86%; 86% ee; IR (cm^{-1}): 2958, 1740, 1558, 1435, 1379, 1159, 1025, 756. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.59 (m, 1H), 7.32–7.20 (m, 2H), 7.19–7.11 (m, 1H), 5.15–5.10 (m, 1H), 4.98–4.94 (m, 1H), 4.79–4.74 (m, 1H), 4.10 (d, J = 7.9 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 167.2, 135.2, 133.9, 129.8, 127.9, 124.7, 75.5, 53.0, 52.9 (2C), 41.4 ppm. HPLC analysis [Chiralcel OD-H column, hexane–2-propanol = 80:20, flow rate: 0.9 mL/min, wavelength = 220 nm: t_R (major) = 11.7 min, t_R (minor) = 19.1 min]. $[\alpha]_D^{25}$ = +5.1 (c 1.0, $CHCl_3$).

4.4.3. Dimethyl (*S*)-2-(1-(3-bromophenyl)-2-nitroethyl)malonate 13c[18c]

Colorless oil; yield 92%; 75% ee; IR (cm^{-1}): 2956, 1736, 1556, 1437, 1379, 1237, 1042. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 2H), 7.22–7.16 (m, 2H), 4.94–4.83 (m, 2H), 4.24–4.18 (m, 1H), 3.82 (d, J = 8.8 Hz, 1H), 3.75 (s, 3H), 3.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 167.0, 138.5, 131.6, 131.1, 130.5, 126.5, 122.9, 76.9, 54.5, 53.1, 53.0, 42.4 ppm. HPLC analysis [Chiralcel OD-H column, hexane–2-propanol = 90:10, flow rate: 1.0 mL/min, wavelength = 220 nm: t_R (minor) = 21.1 min, t_R (major) = 23.5 min]. $[\alpha]_D^{25}$ = +3.1 (c 1.0, $CHCl_3$).

4.4.4. Dimethyl (*S*)-2-(1-(4-bromophenyl)-2-nitroethyl)malonate 13d[18c]

White solid; yield 95%; 84% ee; mp 92–94 °C; IR (cm^{-1}): 2956, 2922, 1751, 1732, 1554, 1489, 1435, 1344, 1257, 1157, 1013, 829. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.44 (m, 2H), 7.13–7.11 (m, 2H), 4.93–4.81 (m, 2H), 4.24–4.18 (m, 1H), 3.82 (d, J = 9.0 Hz, 1H), 3.76 (s, 3H), 3.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 167.0, 135.1, 132.2, 129.6, 122.5, 77.1, 54.4, 53.1, 53.0, 42.3 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 75:25, flow rate: 1.5 mL/min, wavelength = 220 nm: t_R (minor) = 7.3 min, t_R (major) = 10.7 min]. $[\alpha]_D^{25}$ = +4.9 (c 1.0, $CHCl_3$).

4.4.5. Dimethyl (*S*)-2-(1-(2-methoxyphenyl)-2-nitroethyl)malonate 13e[18c]

Colorless oil; yield 96%; 81% ee; IR (cm^{-1}): 2923, 2254, 1793, 1700, 1554, 1493, 1381, 1247, 1158, 1095, 908, 734, 651. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.22 (m, 1H), 7.13 (dd, J = 1.6 Hz, 7.8 Hz, 1H), 6.88–6.85 (m, 2H), 5.05–4.99 (m, 1H), 4.90–4.85 (m, 1H) 4.42–4.36 (m, 1H), 4.17 (d, J = 9.9 Hz, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 3.50 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 167.6, 157.3, 130.5, 129.7, 123.6, 120.8, 111.1, 76.0, 55.4, 52.8, 52.6, 52.5, 40.3 ppm. HPLC analysis [Chiralcel OD-H column, hexane–2-propanol = 70:30, flow rate: 0.5 mL/min, wavelength = 220 nm: t_R (major) = 14.1 min, t_R (minor) = 18.3 min]. $[\alpha]_D^{25}$ = +4.4 (c 1.0, $CHCl_3$).

4.4.6. Dimethyl (*S*)-2-(1-(3-methoxyphenyl)-2-nitroethyl)malonate 13f[18c]

White solid; yield 97%; 50% ee; mp 53–55 °C; IR (cm^{-1}): 2922, 2852, 1737, 1602, 1552, 1460, 1258, 1040. ^1H NMR (400 MHz,

$CDCl_3$): δ = 7.24–7.20 (m, 1H), 6.81–6.76 (m, 3H), 4.93–4.83 (m, 2H), 4.24–4.18 (m, 1H), 3.85 (d, J = 8.9 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.58 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 167.2, 159.8, 137.7, 130.0, 119.8, 113.9, 113.6, 77.3, 55.2, 54.7, 53.0, 52.8, 42.9 ppm. HPLC analysis [Chiralcel OD-H column, hexane–2-propanol = 70:30, flow rate: 0.5 mL/min, wavelength = 220 nm: t_R (minor) = 23.7 min, t_R (major) = 27.3 min]. $[\alpha]_D^{25}$ = +1.4 (*c* 1.0, $CHCl_3$).

4.4.7. Dimethyl (*S*)-2-(1-(4-methoxyphenyl)-2-nitroethyl)malonate 13g[18c]

Colorless oil; yield 98%; 67% ee; IR (cm^{-1}): 3011, 2957, 2841, 1733, 1557, 1516, 1436, 1258, 1032. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.12 (m, 2H), 6.84–6.81 (m, 2H), 4.90–4.78 (m, 2H), 4.21–4.15 (m, 1H), 3.82 (d, J = 9.2 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.55 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 168.0, 160.2, 129.8, 128.6, 115.1, 78.4, 55.9, 55.6, 53.8, 53.6, 43.0 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 70:30, flow rate: 1.0 mL/min, wavelength = 220 nm: t_R (minor) = 10.3 min, t_R (major) = 18.2 min]. $[\alpha]_D^{25}$ = +1.9 (*c* 1.0, $CHCl_3$).

4.4.8. Dimethyl (*S*)-2-(1-(2-fluorophenyl)-2-nitroethyl)malonate 13h[18d]

Colorless oil; yield 91%; 81% ee; IR (cm^{-1}): 2958, 2848, 1733, 1557, 1495, 1436, 1259. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.21 (m, 2H), 7.13–7.04 (m, 2H), 4.93 (d, J = 6.9 Hz, 2H), 4.48–4.42 (m, 1H), 4.00 (d, J = 9.7 Hz, 1H), 3.77 (s, 3H), 3.55 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 167.1, 162.1, 159.7, 130.49, 130.45, 130.34, 130.3, 124.62, 124.58, 123.0, 122.9, 116.2, 116.0, 76.00, 75.98, 53.10, 53.07, 52.99, 52.97, 52.86, 52.84, 38.6 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 70:30, flow rate: 1.0 mL/min, wavelength = 220 nm: t_R (minor) = 7.4 min, t_R (major) = 9.8 min]. $[\alpha]_D^{25}$ = −4.2 (*c* 1.0, $CHCl_3$).

4.4.9. Dimethyl (*S*)-2-(1-(4-fluorophenyl)-2-nitroethyl)malonate 13i[18a]

Colorless oil; yield 97%; 80% ee; IR (cm^{-1}): 3015, 2956, 2915, 1735, 1702, 1555, 1473, 1381, 1096, 908, 734, 650. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.20 (m, 2H), 7.03–6.99 (m, 2H), 4.93–4.80 (m, 2H), 4.26–4.20 (m, 1H), 3.82 (d, J = 9.1 Hz, 1H), 3.75 (s, 3H), 3.56 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 167.1, 163.7, 161.2, 131.9, 131.8, 129.7, 129.6, 116.1, 115.9, 77.4, 54.6, 53.0, 52.9, 42.2 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 70:30, flow rate: 1.0 mL/min, wavelength = 220 nm: t_R (minor) = 8.1 min, t_R (major) = 14.6 min]. $[\alpha]_D^{25}$ = −4.1 (*c* 1.0, $CHCl_3$).

4.4.10. Dimethyl (*S*)-2-(1-(4-methylphenyl)-2-nitroethyl)malonate 13j[18c]

White solid; yield 91%; 84% ee; mp 92–94 °C; IR (cm^{-1}): 3019, 2958, 2254, 1794, 1736, 1702, 1556, 1469, 1380, 1248, 1156, 1095, 908, 734, 650. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.08 (m, 4H), 4.92–4.82 (m, 2H), 4.21 (dt, J = 5.3 Hz, 9.0 Hz, 1H), 3.84 (d, J = 9.1 Hz, 1H), 3.76 (s, 3H), 3.57 (s, 3H), 2.30 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 167.3, 138.2, 133.0, 129.7, 127.7, 77.5, 54.8, 53.0, 52.8, 42.6, 21.1 ppm. HPLC analysis [Chiralpak AD-H column, hexane–2-propanol = 75:25, flow rate: 1.0 mL/min, wavelength = 220 nm: t_R (minor) = 8.6 min, t_R (major) = 12.8 min]. $[\alpha]_D^{25}$ = −4.9 (*c* 1.0, $CHCl_3$).

4.4.11. Dimethyl (*S*)-2(1-(4-chlorophenyl)-2-nitroethyl)malonate 13k[18c]

White solid; yield 84%; 79% ee; mp 88–90 °C; IR (cm^{-1}): 3155, 2923, 2254, 1794, 1703, 1556, 1469, 1380, 1095, 908, 734, 650. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.29 (m, 2H), 7.19–7.17 (m, 2H), 4.93–4.82 (m, 2H), 4.25–4.20 (m, 1H), 3.82 (d, J = 9.0 Hz, 1H), 3.76 (s, 3H), 3.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 167.0, 134.6, 134.4, 129.3, 129.2, 77.2, 54.5, 53.1, 53.0, 42.3 ppm. HPLC analysis [Chiralcel OD-H column, hexane–2-propanol = 85:15, flow rate: 0.5 mL/min, wavelength = 220 nm: t_R (major) = 34.7 min, t_R (minor) = 39.2 min]. $[\alpha]_D^{25}$ = +3.7 (*c* 1.0, $CHCl_3$).

4.4.12. Dimethyl (*S*)-2-(1-(2,4-dichlorophenyl)-2-nitroethyl)malonate 13l

Yellowish oil; yield 91%; 88% ee; IR (cm^{-1}): 2955, 2917, 2848, 1733, 1598, 1377, 1232, 1052. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 1.8 Hz, 1H), 7.24–7.18 (m, 2H), 5.12–5.07 (m, 1H), 4.96–4.91 (m, 1H), 4.73–4.67 (m, 1H), 4.07 (d, J = 8.3 Hz, 1H), 3.74 (s, 3H), 3.66 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 167.1, 134.9, 134.8, 132.2, 130.4, 129.4, 127.7, 75.2, 53.11, 53.08, 52.6, 38.9 ppm. HPLC analysis [Chiralcel OD-H column, hexane–2-propanol = 70:30, flow rate: 0.8 mL/min, wavelength = 220 nm: t_R (major) = 10.1 min, t_R (minor) = 21.5 min]. $[\alpha]_D^{25}$ = +5.6 (*c* 1.0, $CHCl_3$).

4.4.13. Dimethyl (*S*)-2-(2-nitro-1-(2-nitrophenyl)ethyl)malonate 13m[18d]

Yellowish oil; yield 96%; 79% ee; IR (cm^{-1}): 3018, 2958, 1733, 1558, 1436, 1361. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, J = 1.2 Hz, 8.1 Hz, 1H), 7.61–7.57 (m, 1H), 7.50–7.46 (m, 1H), 7.42–7.40 (m, 1H), 5.17 (dd, J = 8.2 Hz, 13.9 Hz, 1H), 5.05 (dd, J = 4.3 Hz, 14.0 Hz, 1H), 4.77 (td, J = 4.5 Hz, 8.1 Hz, 1H), 4.24 (d, J = 7.9 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 167.1, 149.9, 133.3, 131.1, 129.3, 128.8, 125.5, 75.9, 53.4, 53.2, 53.1, 37.5 ppm. HPLC analysis [Chiralcel OD-H column, hexane–2-propanol = 70:30, flow rate: 0.9 mL/min, wavelength = 220 nm: t_R (major) = 12.8 min, t_R (minor) = 19.4 min]. $[\alpha]_D^{25}$ = +3.4 (*c* 1.0, $CHCl_3$).

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