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Highly Enantioselective Michael Addition of Dithiomalonates to Nitroolefins Catalyzed by New Bifunctional Chiral Thioureas

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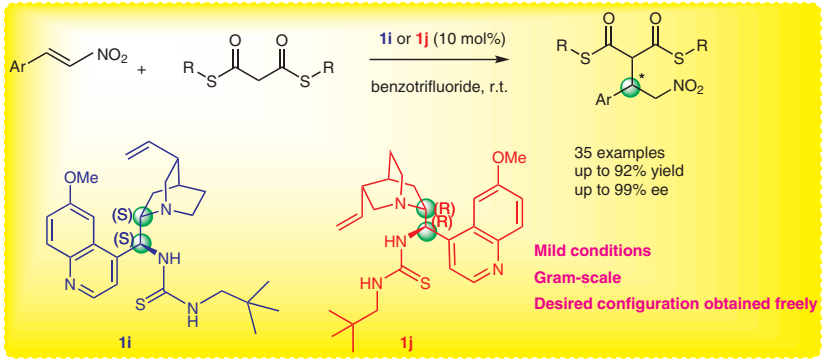

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Abstract We report a highly efficient asymmetric Michael addition of dithiomalonates to *trans*-β-nitroolefins catalyzed by versatile cinchona-based bifunctional thioureas, which provides the corresponding adducts in high yields (up to 92%) and with excellent enantioselectivities (up to 99% ee) under mild conditions. Replacement of the catalyst with its pseudo-enantiomer gives the Michael adducts with opposite configuration in similar yields and enantioselectivities.

Key words Michael addition, cinchona alkaloids, chirality, hydrogen bonds, γ-aminobutyric acids

With the requirement of chirality in the pharmaceutical industry, the growing demands for enantiomerically pure, biologically active compounds have stimulated the rapid development of enantioselective synthetic methods to provide exceptional stereocontrol. As a result, organocatalysis has emerged as one of the most rapidly growing and promising areas in synthetic organic chemistry. Organocatalytic procedures are advantageous because they are metal-free, environmentally friendly, operationally simple, and readily available when compared with transition-metal or enzyme catalysis.[1]

During the last two decades, many chiral organocatalysts have been developed and successfully applied in a variety of transformations, resulting in the identification of several 'privileged' scaffolds, such as proline,[1e] cinchona alkaloids,[2] phosphoric acid derivatives,[3] etc. As part of our ongoing program to develop facile and effective chiral catalysts for asymmetric transformations, we have rationally combined two different 'privileged' structural motifs, i.e., cinchona alkaloids and β-amino alcohols, into one molecule through a urea or thiourea linker to provide a new class of bifunctional organocatalyst possessing multiple hydrogen bonds (Figure 1).

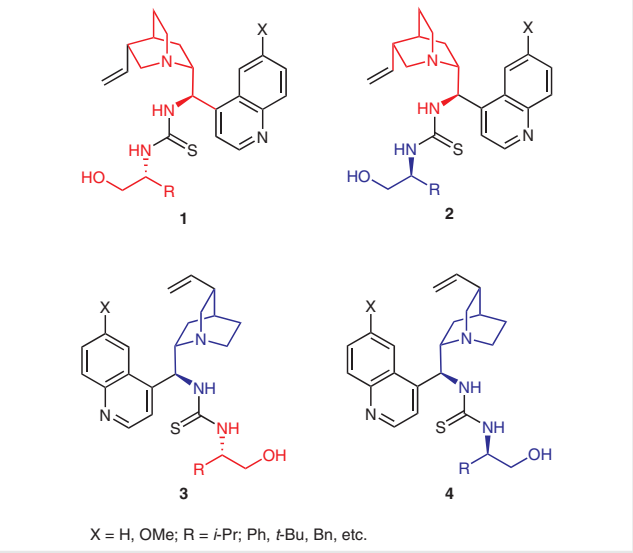


Figure 1 Chiral bifunctional organocatalysts developed by our group and used for Michael additions

These versatile organocatalysts have the potential to produce an unexpected synergistic effect in a number of asymmetric transformations. For example, they have been applied successfully in several transformations, such as the Michael addition of acetylacetone[2a] or acetone[2b] to nitroolefins, the aza-Henry reaction,[2b] the addition of diethyl malonate to chalcones,[2c] and the epoxidation of aldimines.[2d]

The asymmetric Michael addition reaction of different carbon-centered nucleophiles to electron-deficient nitroolefins represents one of the most practical and direct

approaches to a wide range of synthetically valuable chiral nitroalkanes, in which the nitro group can easily be transformed into a nitrile oxide, a ketone, an amine, or a carboxylic acid, among others. In 2003, Takemoto[4] firstly reported the asymmetric Michael addition of malonates to nitroolefins catalyzed by the Takemoto tertiary amino-thiourea catalyst, which involves an electron-withdrawing aryl substituent and a chiral tertiary amine-thiourea group. Following this strategy, several bifunctional thiourea organocatalysts were developed to promote this type of reaction, and the ability to activate reactants through both hydrogen bond interactions and acid–base effects to produce a well-defined orientation for the transition state of the process is essential to their success.[5] In comparison with the asymmetric Michael addition of malonates with nitroolefins, the use of less conjugated dithiomalonates[6] to form a trisubstituted carbon center is well appreciated,[7] because they can be transformed into an aldehyde or a ketone more easily.[8] Initially, Ryu and co-workers[9] worked on the Michael addition of dithiomalonates to *trans*-β-nitroolefins in the presence of L-proline-derived urea as the organocatalyst. Very recently, Sim and Song[10] described an 'on water' protocol for the addition of dithiomalonates to β,β-disubstituted nitroalkenes, affording the Michael adducts with all-carbon quaternary stereogenic centers at the β-position by using a catalytic amount of a chiral cinchona-based squaramide catalyst. All these adducts could be easily transformed into optically active γ-aminobutyric acid (GABA),[11] the most common inhibitory neurotransmitter in the mammalian central nervous system (CNS).

Herein we report our recent efforts on the Michael addition of dithiomalonates to *trans*-β-nitroolefins using new modular bifunctional organocatalysts **1a–k** (Figure 2), which were prepared in high yields using natural cinchona alkaloids as the starting materials and employing simple procedures.

Initially, we chose the Michael reaction of dithiomalonate **2a** to *trans*-β-nitroolefin **3a** as the model reaction with benzotrifluoride as the solvent at room temperature. Firstly, a series of cinchona alkaloid derived thioureas was prepared and examined as catalysts for the reaction. The results showed that the catalysts **1a–d** derived from cinchona alkaloids and phenyl amino alcohol gave good chiral induction (Table 1, entries 1–4). Moreover, the diastereomers **1a** (from quinine and D-phenylglycinol) and **1d** (from quinidine and L-phenylglycinol) gave similar enantioselectivities of **4aa** but with opposite asymmetric induction. Interestingly, **1b** (from quinine and L-phenylglycinol) and **1c** (from quinidine and D-phenylglycinol) gave almost the same results as **1a** and **1d**, respectively (Table 1, entries 2 and 3 vs entries 1 and 4). These results demonstrate that the configurations of the products are decided by the cinchona alkaloids and not the phenylglycinol in this reaction, which is different from the results of our previous study of the Michael reaction of

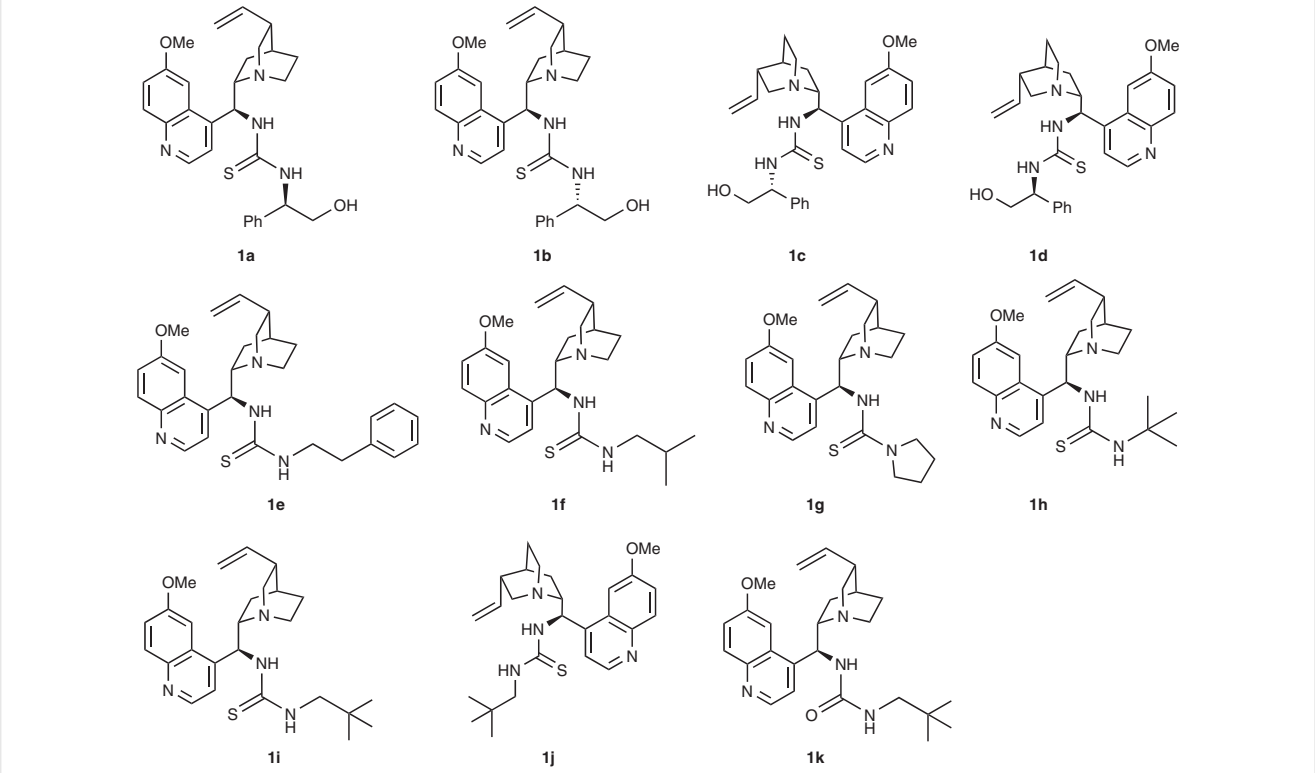
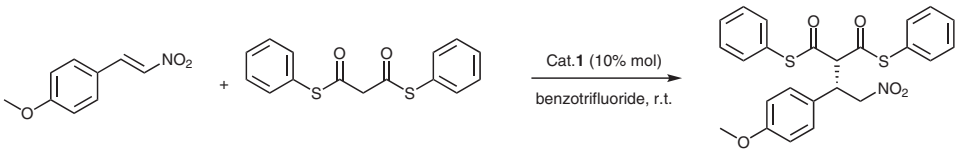


Figure 2 Chiral organocatalysts **1a–k** screened in the Michael addition of dithiomalonates to *trans*-β-nitroolefins[2c,d]

Table 1 Screening of the Thiourea Catalysts **1a–k** in the Asymmetric Michael Addition of Dithiomalonate **3a** to *trans*-β-Nitroolefin **2a**



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

Entry[a]	Cat.	Yield (%)[b]	ee (%)[c]	Config.[d]
1	**1a**	87	85	*S*
2	**1b**	86	83	*S*
3	**1c**	81	84	*R*
4	**1d**	86	83	*R*
5	**1e**	80	83	*S*
6	**1f**	85	81	*S*
7	**1g**	87	trace	–
8	**1h**	85	81	*S*
9	**1i**	93	88	*S*
10	**1j**	90	85	*R*
11	**1k**	85	86	*S*

[a] Reaction conditions: **2a** (0.1 mmol), **3a** (0.1 mmol), catalyst **1** (0.01 mmol), benzotrifluoride (1 mL), r.t., 12 h.
[b] Yield of isolated product; conversion was >99% in each case.
[c] The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H).[11]
[d] Determined by comparison with available literature HPLC data.[9]

diethyl malonate with chalcones.[2c] Similarly, catalysts **1e**,**f**,**h–j** also gave quite good chiral induction results (Table 1, entries 5, 6 and 8–10). However, the catalyst **1g**, bearing only one NH moiety, showed poor chiral induction, which indicated that both NHs of the thiourea moiety were crucial. It is worth mentioning that **1g** was previously used in the highly enantioselective oxaziridination of aldimines by our group and in catalytic asymmetric oxaziridination, with catalysts possessing multi-hydrogen bonds giving lower enantioselectivities.[2d] Besides, the urea **1k** also demonstrated good catalytic effects (Table 1, entry 11). Finally, taking into account the simplicity of the catalyst structure, we chose **1i**, derived from quinine and neopentylamine, as the optimum catalyst for further screening of the reaction conditions (Table 1, entry 9).

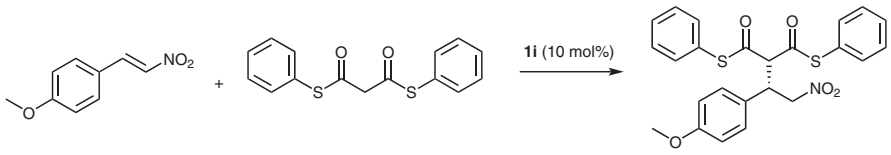
In many of these important asymmetric reactions, solvents have been shown to have an interesting influence. Therefore, screening different solvents is an important part of methodology development. Thus the influence of various solvents in the asymmetric Michael addition reaction were investigated.

Fifteen solvents were examined with **1i** as the catalyst at room temperature (Table 2). We found that the solvent had a very significant effect on the experimental results. Generally speaking, substituted benzenes were suitable solvents for this transformation (Table 2, entries 1–6), although *o*-xylene and chlorobenzene gave poor enantioselectivities (Table 2, entries 8 and 9). When methanol was used as the solvent, the enantioselectivity was good, but a low yield of product was obtained (Table 2, entry 10). Both the enantioselectivities and yields were lower in other aprotic solvents (Table 2, entries 11–15). Benzotrifluoride was found to be the optimum solvent with regard to the enantioselectivity and yield (Table 2, entry 1).

Further investigation of the reaction temperature showed that the yield was very low at 40 °C and that the racemic product was obtained (Table 2, entry 16). The enantioselectivity was improved at reduced temperatures. When the temperature decreased to 30 °C, the enantioselectivity increased to 70% and further increased to 88% between 0–20 °C (Table 2, entries 17–20). However, when the temperature was below 0 °C, the enantioselectivity began to decrease again (Table 2, entries 21 and 22). Thus, we chose room temperature for further investigations.

With the optimum conditions for this process having been established, a broad range of nitroolefins were tested (Table 3). Overall, nearly all the tested substrates gave good yields and excellent enantioselectivities. We found that a wide range of aryl-substituted nitroolefins bearing either electron-withdrawing or electron-donating groups on the phenyl ring afforded the Michael products in high yields and enantioselectivities (Table 3, entries 1 and 3 vs entries

Table 2 Screening of the Reaction Conditions in the Asymmetric Michael Addition of Dithiomalonate **3a** to *trans*-β-Nitroolefin **2a**



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

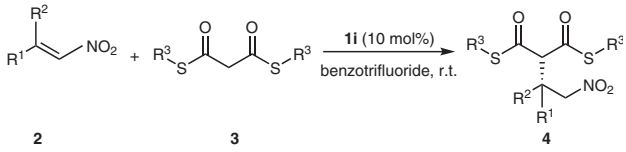
Entry[a]	Solvent	Temp (°C)	Yield (%)[b]	ee (%)[c]	Conv. (%)
1	benzotrifluoride	r.t.	93	88	>99
2	toluene	r.t.	95	57	>99
3	xylene	r.t.	93	71	>99
4	*m*-xylene	r.t.	93	69	>99
5	*p*-xylene	r.t.	92	75	>99
6	mesitylene	r.t.	82	77	>99
7	Et_2O	r.t.	82	81	>99
8	*o*-xylene	r.t.	88	15	95
9	chlorobenzene	r.t.	80	33	>99
10	MeOH	r.t.	50	79	>95
11	EtOAc	r.t.	75	51	>99
12	CH_2Cl_2	r.t.	88	23	>99
13	1,4-dioxane	r.t.	87	3	93
14	*n*-hexane	r.t.	40	17	50
15	cyclopentyl methyl ether	r.t.	85	81	>99
16	benzotrifluoride	40	50	trace	>99
17	benzotrifluoride	30	70	70	>99
18	benzotrifluoride	20	90	88	>99
19	benzotrifluoride	10	90	88	>99
20	benzotrifluoride	0	91	88	>99
21	benzotrifluoride	–10	95	73	>99
22	benzotrifluoride	–20	99	71	>99

[a] Reaction conditions: **2a** (0.1 mmol), **3a** (0.1 mmol), **1i** (0.01 mmol), solvent (1 mL), r.t., 12 h.
[b] Yield of isolated product.
[c] The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H).

6–8). Additionally, heteroaryl-substituted β-nitroolefins **2m** and **2n** afforded the corresponding Michael adducts in yields of 80% (98% ee) and 78% (81% ee), respectively (Table 3, entries 12 and 13). The substrate **2o** bearing a naphthyl group also gave the expected product in a good yield and with a high ee value (Table 3, entry 14). In addition, a β,β-disubstituted nitroolefin gave the desired product with a high ee value (Table 3, entry 15). However, when the R^1 substituent of **2** was a primary alkyl group such as ethyl or isopropyl, the reactions afforded moderate yields and enantioselectivities (Table 3, entries 16 and 17).

The good results obtained with these substrates have laid a solid foundation for the synthesis of chiral GABA drugs and analogues. However, when the phenyl group of the dithiomalonate was changed to an aliphatic group, the yield was maintained but the ee value decreased dramatically and the configuration was reversed (Table 3, entry 18). Interestingly, when **1j**, derived from quinidine and neopentylamine, was used as the catalyst, addition products with opposite configurations were obtained (Table 4). To our delight, the yields and good enantioselectivities for most of the substrates were maintained. These experimental results confirmed that the chiral induction in this catalytic system is decided by the configuration of the cinchona alkaloid skeleton rather than the configuration of the amine. The catalysts were easy to prepare and their structures are relatively simple, which enhances the applicability of this methodology.

Table 3 Scope of the Asymmetric Michael Addition of Dithiomalonates **3** to *trans*-β-Nitroolefins **2** Using Chiral Thiourea **1i** as the Catalyst

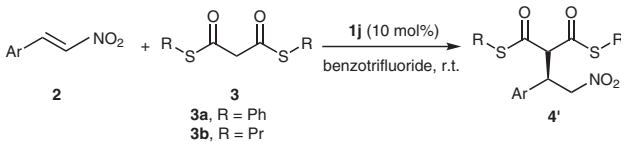


2 3 4

Entry[a]	R^1	R^2	R^3	Product	Yield (%)[b]	ee (%)[c]
1	2-$MeOC_6H_4$ (**2b**)	H	Ph	**4ba**	91	84
2	Ph (**2c**)	H	Ph	**4ca**	92	96
3	3-$MeOC_6H_4$ (**2d**)	H	Ph	**4da**	80	88
4[d]	4-MeC_6H_4 (**2e**)	H	Ph	**4ea**	78	73
5	4-FC_6H_4 (**2f**)	H	Ph	**4fa**	90	77
6	2-FC_6H_4 (**2g**)	H	Ph	**4ga**	90	99
7	4-BrC_6H_4 (**2h**)	H	Ph	**4ha**	80	95
8	2-BrC_6H_4 (**2i**)	H	Ph	**4ia**	85	94
9	2-ClC_6H_4 (**2j**)	H	Ph	**4ja**	90	89
10[e]	3-ClC_6H_4 (**2k**)	H	Ph	**4ka**	90	89
11	4-$F_3CC_6H_4$ (**2l**)	H	Ph	**4la**	85	88
12[f]	2-thienyl (**2m**)	H	Ph	**4ma**	80	98
13	2-furyl (**2n**)	H	Ph	**4na**	78	81
14	2-naphthyl-C_6H_4 (**2o**)	H	Ph	**4oa**	83	88
15	Ph (**2c**)	Me	Ph	**4pa**	83	85
16	Et (**2q**)	H	Ph	**4qa**	67	61
17	*i*-Pr (**2r**)	H	Ph	**4ra**	65	55
18[g]	Ph (**2c**)	H	*n*-Pr	**4cb**	88	31

[a] Reaction conditions: **2** (0.1 mmol), **3** (0.1 mmol), **1i** (0.01 mmol), benzotrifluoride (1 mL), r.t., 12 h.
[b] Yield of isolated product.
[c] The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H).[11]
[d] *p*-Xylene, 18 h.
[e] Xylene.
[f] Reaction time: 5 h.
[g] For this substrate, the opposite enantiomer (compared with the others in this table) was formed as the major product.

Table 4 Scope of the Asymmetric Michael Addition of Dithiomalonates **3a**,**b** to *trans*-β-Nitroolefins **2** Using Chiral Thiourea **1j** as the Catalyst



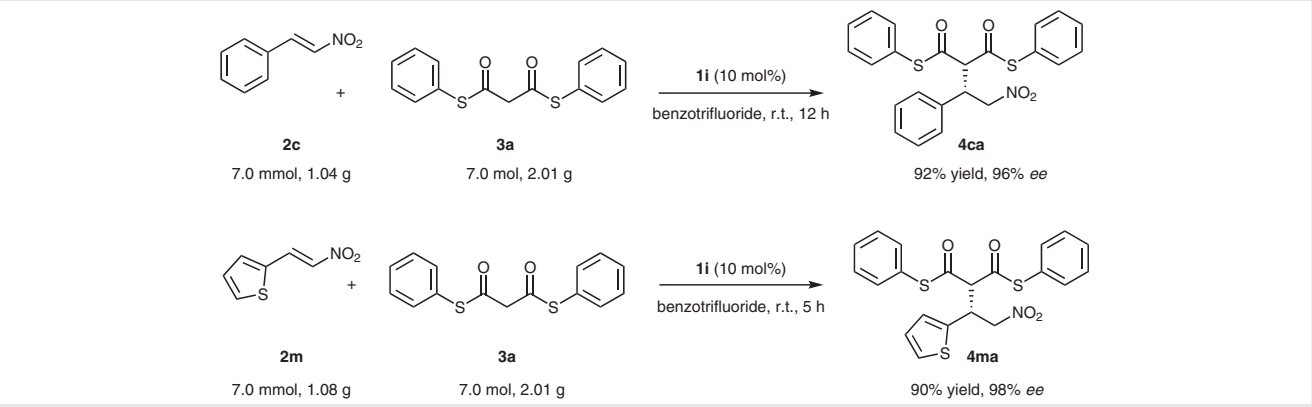
2 3 4'
3a, R = Ph
3b, R = Pr

Entry[a]	Ar	R	Product	Yield (%)[b]	ee (%)[c]
1	2-$MeOC_6H_4$ (**2b**)	**3a**	**4′ba**	85	90
2	Ph (**2c**)	**3a**	**4′ca**	80	96
3	3-$MeOC_6H_4$ (**2d**)	**3a**	**4′da**	81	72
4[d]	4-MeC_6H_4 (**2e**)	**3a**	**4′ea**	89	72
5	4-FC_6H_4 (**2f**)	**3a**	**4′fa**	89	80
6	2-FC_6H_4 (**2g**)	**3a**	**4′ga**	88	85
7	4-BrC_6H_4 (**2h**)	**3a**	**4′ha**	83	91
8	2-BrC_6H_4 (**2i**)	**3a**	**4′ia**	84	98
9	2-ClC_6H_4 (**2j**)	**3a**	**4′ja**	90	97
10[e]	3-ClC_6H_4 (**2k**)	**3a**	**4′ka**	91	49
11	4-$F_3CC_6H_4$ (**2l**)	**3a**	**4′la**	90	98
12[f]	2-thienyl (**2m**)	**3a**	**4′ma**	83	61
13	2-furyl (**2n**)	**3a**	**4′na**	80	91
14	2-naphthyl-C_6H_4 (**2o**)	**3a**	**4′oa**	87	90
15[g]	Ph (**2c**)	**3b**	**4′cb**	87	34

[a] Reaction conditions: **2** (0.1 mmol), **3** (0.1 mmol), **1j** (0.01 mmol), benzotrifluoride (1 mL), r.t., 12 h.
[b] Yield of isolated product.
[c] The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H).[11]
[d] *p*-Xylene, 18 h.
[e] Xylene.
[f] Reaction time: 5 h.
[g] For this substrate, the opposite enantiomer (compared with the others in this table) was formed as the major product.

To investigate the practicality of this new methodology, we conducted gram-scale asymmetric Michael reactions under the optimized conditions using **2c** and **2m** as substrates. Pleasingly, the gram-scale synthesis of **4ca** was achieved maintaining a similar yield (93%) and enantioselectivity (96%) (see Table 3, entry 2), while **4ma** was obtained in a higher 90% yield and identical 98% (see Table 3, entry 12) ee (Scheme 1).

On the basis of the experimental results described above and Ryu's report,[9] a plausible catalytic model for the Michael addition of the dithiomalonates to *trans*-β-nitroolefins in the presence of **1i** as the catalyst is shown in Figure 3.



Scheme 1 Gram-scale reactions

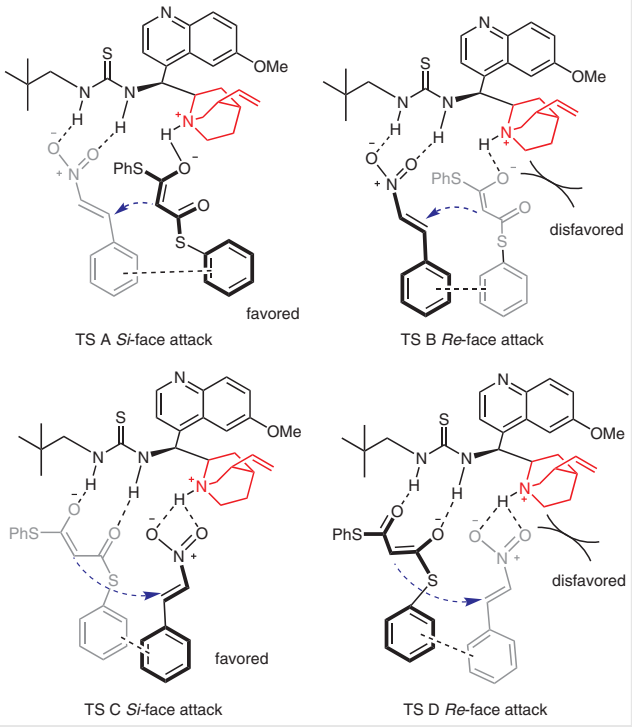


Figure 3 Proposed transition states

There are two possible mechanisms for adduct formation in relevant catalytic Michael addition reactions. In TS A, nitroolefin **2c** forms hydrogen bonds with the thiourea moiety of **1i**, while simultaneously the enolate of **3** is activated by the bridgehead nitrogen atom of the quinine unit. On the other hand, in TS C, the enolate of **3** is activated by the thiourea moiety of **1i** through hydrogen bonding, while nitroolefin **2c** is activated by the bridgehead nitrogen atom of the quinine unit. With either TS A or TS C, nucleophilic addition of the enolate of **3** from the *Si*-face of **2c** leads to the same adduct, the *S* product, as the major enantiomer. By contrast, in TS B and TS D, due to the existence of steric hindrance, the process is not conducive to *Re*-face attack. In all cases, π-π stacking between the phenyl ester and nitroaromatic olefins may exist, which may also provide an explanation for the fact that when the phenyl ester was substituted by an aliphatic group (e.g., in **3b**) the ee value decreased dramatically and the configuration was not maintained.

In summary, an efficient catalytic system for the asymmetric addition of dithiomalonates to *trans*-β-nitroolefins has been developed. Under the optimized conditions, organocatalyst **1i** showed high efficiency (up to 92% yield) and delivered excellent enantioselectivities (up to 99%). Notably, catalyst **1j** showed similar catalytic activity and enantioselectivity, albeit giving the opposite enantiomers. Transition-state models and gram-scale experiments add weight to the practicality of this new methodology. Further detailed catalytic mechanistic studies and investigations of the catalytic performance in other asymmetric reactions using this type of bifunctional tertiary amine–thiourea are currently underway in our laboratory.

All the starting materials and reagents were purchased from commercial suppliers and were used without further purification. Solvents were purified by standard procedures. CH_2Cl_2, toluene and xylene were freshly distilled prior to use. The reactions were monitored by thin-layer chromatography (TLC) on 25 mm silica gel plates; spots were examined under UV light (230 nm) or developed using phosphomolybdic acid (PMA). The yields are of materials isolated by column chromatography over silica gel (particle size 200-300 mesh). Melting points were obtained using a standard melting point apparatus. Optical rotations were recorded using a PERKIN-ELMER 343 polarimeter. IR spectra were obtained using a FTIR-8400S/CE) spectrophotometer. NMR spectra were recorded using a Varian INOVA-400 MHz spectrometer on samples prepared as solutions in $CDCl_3$. The ^1H NMR chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) (δ = 0.00)/$CHCl_3$ (δ = 7.26) as the internal standard. HRMS was performed using a Bruker micrOTOF-QII spectrometer. Determination of the enantiomeric excess (ee) was carried out on an Agilent 1260 interfaced to a HP 71 series computer workstation with a Chiralcel OD-H column.

Chiral Thiourea Catalysts 1; General Procedure

The catalysts **1a–j** were synthesized according to our previous report.[2] Compounds **1a–i** are known, whilst **1j** and **1k** are novel.

Catalyst 1j

Yield: 660 mg (60 %); white solid; mp 153–155 °C; $[\alpha]_D^{25}$ +283 (*c* 0.5, $CHCl_3$).

IR (KBr): 3247, 2939, 2868, 1708, 1620, 1535, 1508, 1473, 1434, 1361, 1296, 1226, 1083, 1029, 918, 825 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.76 (d, *J* = 3.6 Hz, 1 H), 8.05 (d, *J* = 9.2 Hz, 1 H), 7.76 (s, 1 H), 7.62–7.57 (m, 1 H), 7.49–7.40 (m, 2 H), 5.94–5.85 (m, 1 H), 5.14 (d, *J* = 8.0 Hz, 1 H), 3.97 (s, 3 H), 3.34 (br s, 1 H), 3.07–2.87 (m, 6 H), 2.33 (d, *J* = 6.4 Hz, 1 H), 1.69 (s, 1 H), 1.59–1.50 (m, 3 H), 1.38–1.25 (m, 2 H), 0.98–0.84 (m, 2 H), 0.54 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.04, 158.70, 148.14, 145.38, 140.61, 132.56, 122.92, 115.41, 57.36, 56.11, 49.58, 49.48, 47.39, 39.27, 37.55, 31.85, 27.77, 27.50, 27.44, 26.86, 26.36, 26.11, 25.44, 12.40.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{37}N_4OS$: 453.2683; found: 453.2683.

Chiral Thiourea Catalyst 1k (Scheme 2)[12]

The quinine was transformed into (8*S*,9*S*)-9-amino-(9-deoxy)-epiquinine according to the literature.[2] Next, *N*,*N*-carbonyldiimidazole (CDI) (356 mg, 2.2 mmol) was added to a flask and (8*S*,9*S*)-9-amino-(9-deoxy)-epiquinine (648 mg, 2 mmol) dissolved in THF (15 mL) was added dropwise with a constant pressure dropping funnel. Et_3N (33 mL, 2.2 mmol) and neopentylamine (0.25 mL, 2.2 mmol) were then added to the reaction mixture. After stirring overnight, the mixture was diluted with CH_2Cl_2. The organic phase was dried over anhydrous sodium sulfate, filtered and then evaporated. The residue was purified by column chromatography using silica gel (200–300 mesh) to give chiral thiourea catalyst 1k.

Yield: 632 mg (70%); white solid; mp 100–102 °C; $[\alpha]_D^{25}$ = –40 (*c* 0.5, $CHCl_3$).

IR (KBr): 3025, 3078, 2964, 2931, 2862, 1643, 1558, 1550, 1508, 1473, 1365, 1230, 1029, 910, 829 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 4.8 Hz, 1 H), 8.01 (d, *J* = 9.2 Hz, 1 H), 7.71 (d, *J* = 2.4 Hz, 1 H), 7.41 (d, *J* = 4.8 Hz, 1 H), 7.36 (dd, *J* = 9.2, 2.4 Hz, 1 H), 5.90 (br s, 1 H), 5.73–5.65 (m, 1 H), 5.15 (br s, 1 H), 4.98–4.93 (m, 2 H), 4.54 (t, *J* = 6.0 Hz, 1 H), 3.96 (s, 3 H), 3.26–3.20 (m, 1 H), 3.07 (br s, 1 H), 2.86 (d, *J* = 6.0 Hz, 1 H), 2.77–2.66 (m, 2 H), 2.29 (s, 1 H), 2.19 (s, 1 H), 1.67–1.62 (m, 3 H), 1.41–1.36 (m, 1 H), 0.98–0.93 (m, 1 H), 0.70 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.38, 157.89, 147.50, 144.79, 141.07, 131.65, 121.78, 114.70, 101.88, 65.10, 55.83, 55.67, 51.65, 42.00, 39.35, 31.74, 30.15, 29.13, 27.73, 27.33, 26.99, 26.12, 23.35, 23.10, 14.11, 11.10.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{37}N_4O_2$: 437.2911; found: 437.2912.

Asymmetric Michael Addition; General Procedure

To a stirred solution of catalyst **1i** (4.52 mg, 0.01 mmol, 10 mol%) and *trans*-β-nitroolefin **2** (0.1 mmol) in benzotrifluoride (1 mL) was added dithiomalonate **3** (0.1 mmol) at room temperature. After the reaction was complete (monitored by TLC), the resulting mixture was purified by column chromatography using silica gel (200-300 mesh) to afford the desired product.

(*S*)-2-[1-(4-Methoxyphenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4aa)[9]

Yield: 43.4 mg (93%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 18.4 min, t_R (minor) = 26.7 min; 88% ee.

IR (KBr): 1701, 1558, 1550, 1515, 1477, 1438, 1377, 1253, 1180, 1026, 964, 833, 748, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.35 (m, 8 H), 7.19–7.16 (m, 4 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 4.81–4.79 (m, 2 H), 4.45 (d, *J* = 9.6 Hz, 1 H), 4.38–4.32 (m, 1 H), 3.79 (s, 3 H).

(*S*)-2-[1-(2-Methoxyphenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4ba)[9]

Yield: 42.5 mg (91%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 9.3 min, t_R (minor) = 11.7 min; 84% ee.

IR (KBr): 1708, 1685, 1550, 1496, 1477, 1377, 1245, 1122, 1022, 968, 883, 783, 748, 705, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.42 (m, 5 H), 7.37–7.30 (m, 4 H), 7.15 (d, *J* = 7.6 Hz, 1 H), 7.06 (d, *J* = 6.8 Hz, 2 H), 6.92 (t, *J* = 7.4 Hz, 2 H), 5.09 (dd, *J* = 12.8, 10.0 Hz, 1 H), 4.87 (d, *J* = 10.4 Hz, 1 H), 4.74 (dd, *J* = 12.8, 4.0 Hz, 1 H), 4.56–4.50 (m, 1 H), 3.96 (s, 3 H).

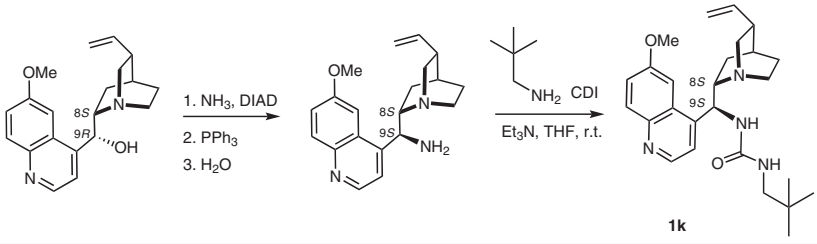
(*S*)-2-(2-Nitro-1-phenylethyl)-malonic Acid Diphenyldithioester (4ca)[9]

Yield: 40.2 mg (92%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 15.6 min, t_R (minor) = 19.7 min; 96% ee.

IR (KBr): 1697, 1670, 1558, 1473, 1438, 1377, 1261, 1022, 964, 798, 748, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.41 (m, 5 H), 7.39–7.33 (m, 6 H), 7.28–7.26 (m, 2 H), 7.14 (dd, *J* = 7.60 Hz, *J* = 1.60 Hz, 2 H), 4.88–4.82 (m, 2 H), 4.48 (d, *J* = 8.80 Hz, 1 H), 4.42–4.36 (m, 1 H) ppm.



Scheme 2 Synthetic route to chiral thiourea catalyst **1k**

(*S*)-2-[1-(3-Methoxyphenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4da)

Yield: 37.0 mg (80%); white solid; mp 127–130 °C; $[\alpha]_D^{25}$ +72.4 (*c* 0.25, $CHCl_3$).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 18.4 min, t_R (minor) = 20.8 min; 88% ee.

IR (KBr): 1701, 1558, 1550, 1488, 1477, 1438, 1377, 1261, 1041, 960, 748, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.44 (m, 3 H), 7.43–7.41 (m, 2 H), 7.40–7.35 (m, 3 H), 7.29 (t, *J* = 16.0 Hz, 1 H), 7.19 (dd, *J* = 7.6, 1.2 Hz, 2 H), 6.88–6.85 (m, 2 H), 6.79 (t, *J* = 1.8 Hz, 1 H), 4.85 (t, *J* = 4.8 Hz, 2 H), 4.47 (d, *J* = 9.2 Hz, 1 H), 4.39–4.33 (m, 1 H), 3.80 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.52, 189.66, 160.06, 136.84, 134.38, 134.34, 130.33, 130.25, 130.16, 129.63, 129.48, 126.18, 120.41, 114.30, 114.13, 69.33, 55.41, 44.41.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{21}NNaO_5S_2$: 490.0755; found: 490.0753.

(*S*)-2-[1-(4-Methylphenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4ea)[9]

Yield: 21.7 mg (78%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 13.9 min, t_R (minor) = 18.3 min; 73% ee.

IR (KBr): 1701, 1685, 1620, 1550, 1477, 1431, 1377, 1261, 1022, 960, 910, 817, 748, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.41 (m, 5 H), 7.40–7.34 (m, 3 H), 7.18–7.14 (m, 6 H), 4.85–4.80 (m, 2 H), 4.46 (d, *J* = 9.2 Hz, 1 H), 4.38–4.32 (m, 1 H), 2.34 (s, 3 H).

(*S*)-2-[1-(4-Fluorophenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4fa)[9]

Yield: 41.0 mg (90%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 15.9 min, t_R (minor) = 22.0 min; 77% ee.

IR (KBr): 1701, 1620, 1550, 1508, 1442, 1377, 1234, 1161, 964, 879, 837, 748, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.45 (m, 3 H), 7.44–7.40 (m, 2 H), 7.39–7.35 (m, 3 H), 7.28–7.24 (m, 2 H), 7.17 (dd, *J* = 7.6, 1.2 Hz, 2 H), 7.07 (t, *J* = 8.6 Hz, 2 H), 4.81 (d, *J* = 6.4 Hz, 2 H), 4.45 (d, *J* = 9.6 Hz, 1 H), 4.46–4.36 (m, 1 H).

(*S*)-2-[1-(2-Fluorophenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4ga)[9]

Yield: 40.8 mg (90%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 10.0 min, t_R (minor) = 14.6 min; 99% ee.

IR (KBr): 1701, 1620, 1550, 1477, 1438, 1377, 1261, 1157, 1022, 964, 794, 748, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.43 (m, 5 H), 7.39–7.32 (m, 4 H), 7.24–7.21 (m, 1 H), 7.15–7.10 (m, 4 H), 4.94 (dd, *J* = 13.6, 10.0 Hz, 1 H), 4.80 (dd, *J* = 13.6, 4.4 Hz, 1 H), 4.65 (d, *J* = 10.0 Hz, 1 H), 4.61–4.55 (m, 1 H).

(*S*)-2-[1-(4-Bromophenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4ha)[9]

Yield: 41.2 mg (80%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 18.4 min, t_R (minor) = 33.6 min; 95% ee.

IR (KBr): 1701, 1685, 1568, 1550, 1488, 1477, 1261, 1072, 1010, 964, 825, 748, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.45 (m, 5 H), 7.44 –7.37 (m, 5 H), 7.19 (d, *J* = 1.6 Hz, 1 H), 7.17 (t, *J* = 2.2 Hz, 2 H), 7.15 (s, 1 H), 4.81 (d, *J* = 7.2 Hz, 2 H), 4.44 (d, *J* = 9.6 Hz, 1 H), 4.39–4.34 (m, 1 H).

(*S*)-2-[1-(2-Bromophenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4ia)[9]

Yield: 43.8 mg (85%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 10.9 min, t_R (minor) = 16.9 min; 94% ee.

IR (KBr): 1716, 1558, 1550, 1473, 1438, 1377, 1261, 1095, 1022, 968, 798, 748, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.47–7.35 (m, 8 H), 7.33–7.27 (m, 3 H), 7.25–7.19 (m, 2 H), 5.14–5.09 (m, 1 H), 4.96 (d, *J* = 13.2 Hz, 1 H), 4.88–4.79 (m, 2 H).

(*S*)-2-[1-(2-Chlorophenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4ja)

Yield: 42.4 mg (90%); white solid; 89–90 °C; $[\alpha]_D^{25}$ +85.6 (*c* 0.5, $CHCl_3$).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 10.4 min, t_R (minor) = 16.5 min; 89% ee.

IR (KBr): 2923, 2854, 1701, 1558, 1477, 1438, 1377, 1261, 964, 748, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.36 (m, 9 H), 7.31–7.22 (m, 5 H), 5.13–5.07 (m, 1 H), 4.94–4.85 (m, 2 H), 4.79 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.11, 189.31, 137.21, 134.84, 134.14, 134.11, 130.27, 130.21, 130.07, 129.45, 129.33, 128.78, 128.38, 126.37, 125.71, 125.66, 68.74, 43.68.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{18}ClNNaO_4S_2$: 494.0251; found: 494.0258.

(*S*)-2-[1-(3-Chlorophenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4ka)

Yield: 42.0 mg (90%); white solid; mp 99–103 °C; $[\alpha]_D^{25}$ +70.2 (*c* 0.25, $CHCl_3$).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 16.8 min, t_R (minor) = 20.8 min; 89% ee.

IR (KBr): 1701, 1558, 1550, 1477, 1438, 1377, 1276, 1261, 964, 748, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.45 (m, 3 H), 7.44–7.42 (m, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.33–7.31 (m, 2 H), 7.28–7.26 (m, 2 H), 7.22–7.16 (m, 3 H), 4.85 (d, *J* = 6.8 Hz, 2 H), 4.43 (d, *J* = 9.2 Hz, 1 H), 4.40–4.34 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.23, 188.44, 136.34, 133.96, 133.27, 133.23, 129.39, 129.33, 129.19, 128.58, 128.46, 127.90, 127.51, 125.50, 124.84, 124.79, 67.86, 42.81.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{18}ClNNaO_4S_2$: 494.0247; found: 494.0247.

(*S*)-2-[1-(4-Trifluoromethylphenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4la)[9]

Yield: 42.9 mg (85%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 14.1 min, t_R (minor) = 29.1 min; 88% ee.

IR (KBr): 1701, 1542, 1473, 1438, 1377, 1261, 1207, 964, 748, 690, 636 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.0 Hz, 2 H), 7.49–7.35 (m, 10 H), 7.13 (d, *J* = 6.8 Hz, 2 H), 4.87–4.85 (m, 2 H), 4.89–4.85 (m, 2 H).

(*R*)-2-[1-(2-Thiophenyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4ma)[9]

Yield: 35.4 mg (80%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 14.8 min, t_R (minor) = 20.6 min; 98% ee.

IR (KBr): 1697, 1620, 1550, 1473, 1438, 1338, 1253, 964, 879, 786, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.38 (m, 8 H), 7.30–7.26 (m, 3 H), 6.98 (d, *J* = 3.2 Hz, 2 H), 4.85 (t, *J* = 3.8 Hz, 2 H), 4.72–4.66 (m, 1 H), 4.55 (d, *J* = 8.8 Hz, 1 H).

(*R*)-2-[1-(2-Furyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4na)[9]

Yield: 33.3 mg (78%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 13.7 min, t_R (minor) = 20.2 min; 81% ee.

IR (KBr): 1701, 1685, 1620, 1550, 1438, 1373, 1338, 1261, 1145, 1060, 972, 744, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 9 H), 7.32–7.31 (m, 2 H), 6.35–6.28 (m, 2 H), 4.89–4.80 (m, 2 H), 4.62 (d, *J* = 8.40 Hz, 1 H), 4.53–4.49 (m, 1 H).

(*S*)-2-[1-(2-Naphthyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4oa)[9]

Yield: 40.4 mg (83%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (major) = 17.5 min, t_R (minor) = 26.4 min; 88% ee.

IR (KBr): 2954, 2923, 1716, 1701, 1685, 1558, 1550, 1508, 1473, 1438, 1377, 775, 743, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.4 Hz, 1 H), 7.90–7.83 (dd, *J* = 20.4, 8.0 Hz, 2 H), 7.62–7.59 (m, 1 H), 7.55–7.51 (m, 1 H), 7.49–7.39 (m, 6 H) 7.37–7.20 (m, 4 H), 7.03 (d, *J* = 7.2 Hz, 2 H), 5.36 (s, 1 H), 5.15–5.02 (m, 2 H), 4.70 (d, *J* = 7.6 Hz, 1 H).

(*S*)-2-[1-(Phenylethyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4pa)

Yield: 37.4 mg (83%); yellow solid; mp 46.4–48.6 °C; $[\alpha]_D^{25}$ +57.5 (*c* 0.25, $CHCl_3$).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (80:20), 1.0 mL/min, t_R (major) = 11.7 min, t_R (minor) = 15.3 min; 85% ee.

IR (KBr): 2360, 2322, 1701, 1685, 1550, 1438, 1373, 1315, 1261, 1157, 1022, 914, 789, 744, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 10 H), 7.26–7.19 (m, 5 H), 5.50 (d, *J* = 13.2 Hz, 1 H), 5.09 (d, *J* = 13.2 Hz, 1 H), 4.20 (s, 1 H), 1.86 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.46, 189.68, 139.38, 134.42, 134.38, 130.33, 129.60, 129.57, 129.51, 129.04, 128.24, 126.59, 80.50, 75.57, 46.19, 22.52.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{21}NNaO_4S_2$: 474.0804; found: 474.0804.

(*S*)-2-[(1-Ethyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4qa)

Yield: 26.1 mg (67%); yellow solid; mp 52.9–53.5 °C, $[\alpha]_D^{25}$ +69.2 (*c* 0.25, $CHCl_3$).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (80:20), 1.0 mL/min, t_R (major) = 9.1min, t_R (minor) = 12.9 min; 61% ee.

IR (KBr): 1701, 1685, 1550, 1438, 1380, 968, 914, 744, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.45 (m, 10 H), 4.75 (dd, *J* = 4.0, 3.6 Hz, 1 H), 4.51 (dd, *J* = 6.4, 6.4 Hz, 1 H), 4.35 (d, *J* = 7.2 Hz, 1 H), 3.01–2.93 (m, 1 H), 1.67–1.52 (m, 2 H), 1.05 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.06, 191.02, 134.48, 134.44, 130.30, 130.27, 129.65, 126.46, 126.42, 75.70, 67.52, 40.20, 23.07, 11.31.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{20}NO_4S_2$: 390.0828; found: 390.0827.

(*S*)-2-[(1-Isopropyl)-2-nitroethyl]-malonic Acid Diphenyldithioester (4ra)[9]

Yield: 26.2 mg (65%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (80:20), 1.0 mL/min, t_R (minor) = 6.8 min, t_R (major) = 11.6min; 55% ee.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–9.43 (m, 10 H), 4.85–4.80 (dd, *J* = 14.8, 3.2 Hz, 1 H), 4.60–4.55 (m, 1 H), 4.38 (d, *J* = 5.6 Hz, 1 H), 3.04–3.02 (m, 1 H), 1.93–1.89 (m, 1 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H).

(*R*)-2-(2-Nitro-1-phenylethyl)-malonic Acid Dipropyldithioester (4cb)[9]

Yield: 32.5 mg (88%).

HPLC: Chiralcel OD column, hexane/*i*-PrOH (70:30), 1.0 mL/min, t_R (minor) = 9.4 min, t_R (major) = 10.4 min; 31% ee.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.21 (m, 5 H), 4.76–4.74 (m, 2 H), 4.42–4.36 (m, 1 H), 4.28 (d, *J* = 10.0 Hz, 1 H), 2.96 (t, *J* = 7.2 Hz, 2 H), 2.81–2.65 (m, 2 H), 1.69–1.60 (m, 2 H), 1.40–1.30 (m, 2 H), 0.98 (t, *J* = 7.4 Hz, 3 H), 0.77 (t, *J* = 7.4 Hz, 3 H).

Gram-Scale Michael Reaction

To a stirred solution of *trans*-β-nitroolefin **2c** or **2m** (**2c**: 1.04 g, 7 mmol or **2m**: 1.08 g, 7 mmol) and dithiomalonate **3a** (2.01 g, 7 mmol) was added catalyst **1i** (31.6 mg, 0.7 mmol, 10 mol%) at room temperature. The resulting mixture was purified by column chromatography using silica gel (200-300 mesh) to afford **4ca** (92% yield, 96% ee) or **4ma** (90% yield, 98% ee) as white products.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591987.

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