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L-Proline Derived Bifunctional Organocatalysts: Enantioselective Michael Addition of Dithiomalonates to *trans*-β-Nitroolefins

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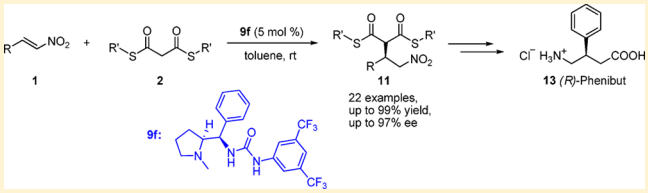
Supporting Information

ABSTRACT: A series of novel L-proline derived tertiary amine bifunctional organocatalysts **9** are reported, which were applied to the asymmetric Michael addition of dithiomalonates **2** to *trans*-β-nitroolefins **1**. The reaction proceeded in high yields (up to 99%) with high enantioselectivities (up to 97% ee). The synthetic utility of this methodology was demonstrated in the short synthesis of (*R*)-phenibut in high yield.



INTRODUCTION

The organocatalytic asymmetric Michael addition of various nucleophiles with nitroolefins represents a convenient route to highly functionalized synthetic building blocks in organic synthesis.[1] The nitro group can serve as a masked functionality for transformation into an amine,[2a] ketone,[2b] oxime,[2c] nitrile oxide,[2d] etc. after the addition has taken place. Among these reactions, the asymmetric organic catalyst-promoted Michael addition of malonates and their equivalents to nitroolefins were shown to be an efficient approach to a wide range of synthetically interesting compounds and valuable bioactive chiral compounds.[3]

After the first report of an enantioselective Michael addition of malonates to nitroolefins catalyzed by the Takemoto tertiary amino-thiourea catalyst,[4a] many kinds of tertiary amine bifunctional organocatalysts were exploited to promote this type of reaction, including the most widely used cinchona alkaloid,[5] saccharide,[4b] and amino acid[4c] derived bifunctional organocatalysts. However, most reported organocatalytic Michael reactions of malonates to nitroolefins require a long reaction time and high catalyst loadings due to the low reactivity of malonates, except for the very recent report from the Song group in which the reaction was performed "on water" in a short time.[5c]

Since thioesters are less conjugated than ordinary esters, dithiomalonates[6] are expected to be more reactive than malonates in Michael additions with nitroolefins. Furthermore, although thioesters possess similar reactivity to esters, they can more easily be transformed into an aldehyde or ketone.[7] Wennemers and co-workers reported the use of mono thiomalonates as a Michael donor.[8] To the best of our knowledge, the use of dithiomalonates for the Michael addition with nitroolefins is without precedent. Herein, we disclose the first enantioselective Michael addition of dithiomalonates **2** to *trans*-β-nitroolefins **1** in excellent yields and enantioselectivities catalyzed by a novel L-proline derived urea organocatalyst **9f**.

RESULTS AND DISCUSSION

Initially, the asymmetric Michael addition between *S*,*S*′-diphenyl dithiomalonate **2a** and *trans*-nitrostyrene **1a** was examined in the presence of 10 mol % of the widely used quinine derived tertiary amino thiourea catalyst **3** (Table 1, entry 1). When the reaction was carried out at 25 °C in methyl *t*-butyl ether (MTBE), the desired product **11aa** was obtained in 83% yield and 60% ee in 2.5 h. Due to the moderate enantioselectivity with **3**, we turned our attention to a new class of chiral bifunctional organocatalyst based on L-proline. Catalysts **9a**−**9f** were synthesized from commercially available *N*-Boc-L-proline methyl ester **4** in 7 steps (Scheme 1).[9] *N*-Boc-L-proline methyl ester **4** was treated with DIBAL-H, followed by the addition of the corresponding arylmagnesium bromide to afford the prolinols **5** diastereoselectively.[10] Then the prolinols **5** were transformed to azides **6** under Mitsunobu condition with chiral center inverted. Azides **6** were then converted into **7** by *N*-Boc deprotection using TFA followed by a *N*-methylation or *N*-benzylation. Finally, azides **7** were reduced with $LiAlH_4$ to amines which were reacted in situ with 3,5-bis(trifluoromethyl)phenyl isothiocyanate, 3,5-bis-(trifluoromethyl)phenyl isocyanate or **8** to provide **9a**−**9f**. The absolute configuration of **9a**−**9f** was confirmed by comparison of the ^{1}H, ^{13}C NMR and optical rotation data of **7d** with the reported product, of which the stereochemistry was confirmed by X-ray diffraction analysis.[11]

In order to reveal the effect of the chiral center that bears the urea/thiourea/squaramide moiety in **9a**−**9f**, the catalyst **9g** was synthesized (Scheme 2). Amino azide **10**[12] was *N*-methylated, followed by the azide reduction to amine, which was treated with 3,5-bis(trifluoromethyl)phenyl isocyanate to afford the desired organocatalyst **9g**.

With several newly synthesized catalysts in hand, catalyst screening was carried out and the results are outlined in Table

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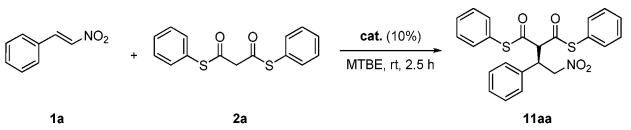
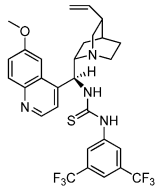
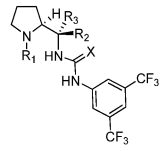
Table 1. Screening of Organocatalysts for the Enantioselective Michael Addition of 2a to 1a[a]

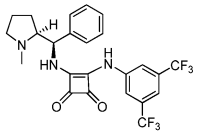


1a 2a 11aa



3





9e

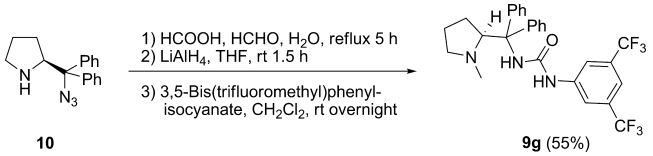
9a X = S, R_1 = Me, R_2 = Phenyl, R_3 = H
9b X = S, R_1 = Me, R_2 = 3,5-Dimethylphenyl, R_3 = H
9c X = S, R_1 = Me, R_2 = 2-Naphthyl, R_3 = H
9d X = S, R_1 = Benzyl, R_2 = Phenyl, R_3 = H
9f X = O, R_1 = Me, R_2 = Phenyl, R_3 = H
9g X = O, R_1 = Me, R_2 = Phenyl, R_3 = Phenyl

entry	cat.	yield (%)[b]	ee (%)[c]
1	**3**	83	60 (+)[d]
2	**9a**	94	81 (−)
3	**9b**	92	81 (−)
4	**9c**	82	80 (−)
5	**9d**	68	64 (−)
6	**9e**	67	10 (−)
7	**9f**	96	90 (−)
8	**9g**	53	49 (−)

[a]The reaction of **2a** (0.17 mmol) and **1a** (0.15 mmol) was performed in the presence of cat. (10 mol %) in 1.5 mL of MTBE at 25 °C for 2.5 h. [b]Isolated yield of **11aa**. [c]The ee of **11aa** was determined by chiral HPLC analysis. [d]Optical rotation.

1. Fortunately, compared with quinine derived thiourea **3**, L-proline derived thiourea **9a** yielded the product with an improved enantioselectivity of 81% ee under identical conditions (Table 1, entry 2). When the phenyl group of **9a** on the carbon bearing the thiourea moiety was changed to larger 3,5-dimethylphenyl (**9b**) or 2-naphthyl (**9c**) groups, little change in enantioselectivity was observed (Table 1, entries 3 and 4). The efficiency with **9d** decreased significantly compared to **9a** (Table 1, entry 5), which indicated a small substituent on the pyrrolidine nitrogen is better. Comparing different hydrogen bond donor moieties in the catalyst, we found the urea structure (**9f**) to be more suitable for this reaction than thiourea (**9a**) or squaramide (**9e**), yielding the product in 96% yield and 90% ee (Table 1, entries 2, 6, and 7). Diphenyl substituted catalyst **9g** with the urea moiety linked to an achiral carbon showed much lower efficiency than **9f**, which determined the requirement of the chiral center in **9f** (Table 1, entry 8). In summary, **9f** was identified as the most suitable catalyst for the present reaction.

Scheme 2. Synthesis of Organocatalyst 9g

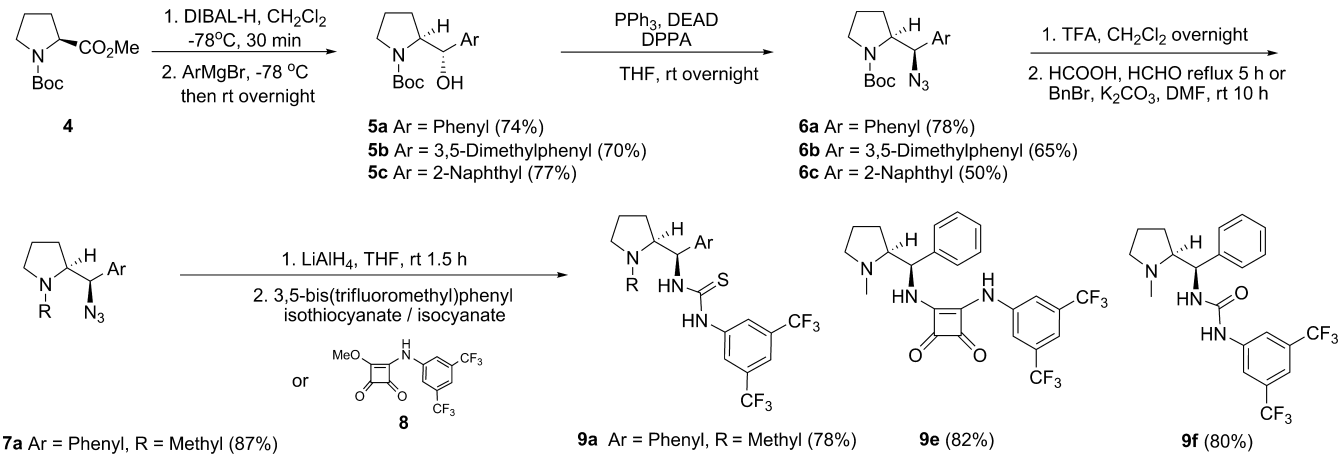


10 **9g** (55%)

Further optimization of the reaction conditions was carried out, after which other dithiomalonates were investigated (Table 2). Screening the solvents MTBE, CH_2Cl_2, and toluene, determined toluene to be the best solvent (Table 2, entries 1 and 2). Lowering the catalyst loading to 5 mol % did not affect either the yield or the enantioselectivity. When the reaction was carried out with 5 mol % of **9f** at 25 °C, **11aa** was obtained in 94% yield and 90% ee, which were identified as the optimized conditions (Table 2, entry 3). We then applied these catalytic conditions to other dithiomalonates (Table 2, entries 4−6).[13] Both aromatic and aliphatic dithiomalonates provided Michael adducts **11** in high yield and good enantioselectivity, with aromatic dithiomalonates displaying higher reactivity than aliphatic dithiomalonates.

With optimized reaction conditions in hand, a variety of aromatic and heteroaromatic *trans*-β-nitroolefins were investigated (Table 3). Regardless of the electronic properties of substituents on the aromatic *trans*-β-nitroolefin, the products **11** were obtained with high enantioselectivities and in excellent yields, and *ortho*-substituted aromatic nitroolefins furnished the desired products with better enantioselectivities (Table 3, entries 3, 5, and 9).

Scheme 1. Synthesis of Organocatalysts 9a−9f



4

5a Ar = Phenyl (74%)
5b Ar = 3,5-Dimethylphenyl (70%)
5c Ar = 2-Naphthyl (77%)

6a Ar = Phenyl (78%)
6b Ar = 3,5-Dimethylphenyl (65%)
6c Ar = 2-Naphthyl (50%)

8

7a Ar = Phenyl, R = Methyl (87%)
7b Ar = 3,5-Dimethylphenyl
R = Methyl (88%)
7c Ar = 2-Naphthyl, R = Methyl (91%)
7d Ar = Pheny, R = Benzyl (95%)

9a Ar = Phenyl, R = Methyl (78%)
9b Ar = 3,5-Dimethylphenyl
R = Methyl (80%)
9c Ar = 2-Naphthyl, R = Methyl (75%)
9d Ar = Pheny, R = Benzyl (83%)

9e (82%)

9f (80%)

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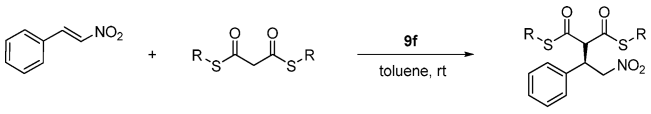
Table 2. Reaction Condition Optimization for the Enantioselective Michael Addition of 2 to 1a Using 9f as a Catalyst[a]



1a 2 11

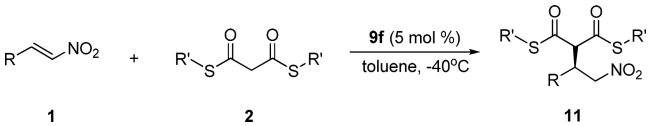
entry	2	R	11	9f (mol %)	t (h)	yield (%)[b]	ee (%)[c]
1	2a	Ph	11aa	10	1.5	98	90
2[d]	2a	Ph	11aa	10	1.5	80	87
3	2a	Ph	11aa	5	1.5	94	90
4	2b	4-MeOPh	11ab	5	1.5	92	92
5	2c	*n*-propyl	11ac	5	12	95	73
6	2d	ethyl	11ad	5	12	93	89

[a]Unless otherwise noted, all reactions were carried out between **2** (0.15 mmol) with **1a** (0.30 mmol) in 1.5 mL of toluene at 25 °C. [b]Isolated yield of **11**. [c]The ee of **11** was determined by chiral HPLC analysis. [d]CH_2Cl_2 was used instead of toluene.

Encouraged by the results exhibited in Table 3, we applied these catalytic conditions to reactions between dithiomalonates **2** and a range of aliphatic *trans*-*β*-nitroolefins **1**. However, when the optimized conditions were applied to the reaction between (*E*)-1-nitropent-1-ene **1m** and **2a**, the desired product **11ma** was obtained in 78% ee (Table 4, entry 1). Lowering the temperature to −40 °C significantly improved the enantioselectivity to 90% ee (Table 4, entry 2). When R substituents of **1** were primary alkyl groups such as *n*-propyl, isobutyl, 2-phenylethyl, and the long-chain *n*-hexyl group, the reactions proceeded well in high yields and enantioselectivities (Table 4, entries 2−6), By contrast, this protocol with secondary substituents, such as a cyclohexyl group, provided the corresponding products **11qa** and **11qb** in lower yields and enantioselectivities at 25 °C (Table 4, entries 7 and 8).

To demonstrate the synthetic utility of our methodology, further chemical transformations of adduct **11aa** were carried out as illustrated in Scheme 3. (*R*)-Phenibut is a therapeutically useful agonist of *γ*-aminobutyric acid (GABA) type-B receptors and is used as a neuropsychotropic drug.[14] Reduction of the nitro group of **11aa** to the amine using zinc/acetic acid and $TiCl_3$, followed by intramolecular cyclization to form the lactam **12**,[8c] and acidic hydrolysis generated the antidepressant (*R*)-phenibut **13**. Additionally, adduct **11aa** was desymmetrized through a tandem hydrolysis-decarboxylation reaction to form **14** under mildly basic conditions in 94% yield. Monothioester **14** was converted to **15** by Fukuyama reduction in the presence of activated 4 Å molecular sieves,[7c] and **14** was also transformed to the known lactam **16**[15] in 82% yield through the reduction-cyclization reaction sequence described above. Comparison of the optical rotation data and chiral HPLC spectrum of **16** with reported data[16] confirmed the absolute stereochemistry of **11aa** as the *R* enantiomer.

Table 4. Enantioselective Michael Addition of 2 to Aliphatic *trans*-*β*-Nitroolefins Catalyzed by 9f[a]

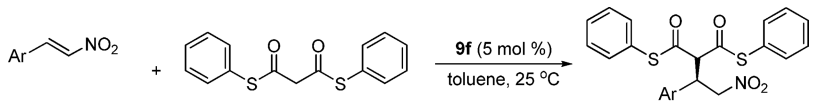


1 2 11

entry	1	R	2	11	t (h)	yield (%)[b]	ee (%)[c]
1[d]	1m	*n*-propyl	2a	11ma	1	96	78
2	1m	*n*-propyl	2a	11ma	16	93	90
3	1n	isobutyl	2a	11na	16	96	86
4	1o	2-phenylethyl	2a	11oa	14	95	90
5	1p	*n*-hexyl	2a	11pa	12	97	86
6	1p	*n*-hexyl	2b	11pb	48	95	85
7[d,e]	1q	cyclohexyl	2a	11qa	72	65	81
8[d,e]	1q	cyclohexyl	2b	11qb	120	82	82

[a]Unless otherwise noted, all of the reactions were carried out between **2** (0.15 mmol) and **1** (0.30 mmol) in the presence of **9f** (5 mol %) in 1.5 mL of toluene at −40 °C. [b]Isolated yield. [c]The ee was determined by chiral HPLC analysis. [d]The reaction was conducted at 25 °C. [e]10 mol % **9f** was used.

Table 3. Enantioselective Michael Addition of 2a to Aromatic *trans*-*β*-Nitroolefins Catalyzed by 9f[a]



1 2a 11

entry	1	Ar	11	t (h)	yield (%)[b]	ee (%)[c]	ee (%)[d]
1	1a	phenyl	11aa	1.5	94	90	98
2	1b	4-F-C_6H_4	11ba	1.0	92	87	>99
3	1c	2-F-C_6H_4	11ca	0.5	99	91	–[e]
4	1d	4-Br-C_6H_4	11da	1.0	98	90	>99
5	1e	2-Br-C_6H_4	11ea	0.5	98	97	–[e]
6	1f	4-CF_3-C_6H_4	11fa	1.5	88	92	>99
7	1g	4-Me-C_6H_4	11ga	1.0	94	90	93
8	1h	4-MeO-C_6H_4	11ha	2.0	98	87	94
9	1i	2-MeO-C_6H_4	11ia	1.0	98	94	–[e]
10	1j	2-thienyl	11ja	0.5	99	90	–[e]
11	1k	2-furyl	11ka	0.5	98	93	–[e]
12	1l	2-naphthyl	11la	0.5	92	86	>99

[a]All of the reactions were carried out between **2a** (0.15 mmol) and **1** (0.30 mmol) in the presence of **9f** (5 mol %) in 1.5 mL of toluene at 25 °C. [b]Isolated yield of **11**. [c]The ee was determined by chiral HPLC analysis. [d]The ee was determined after recrystallization from ethanol. [e]Not determined.

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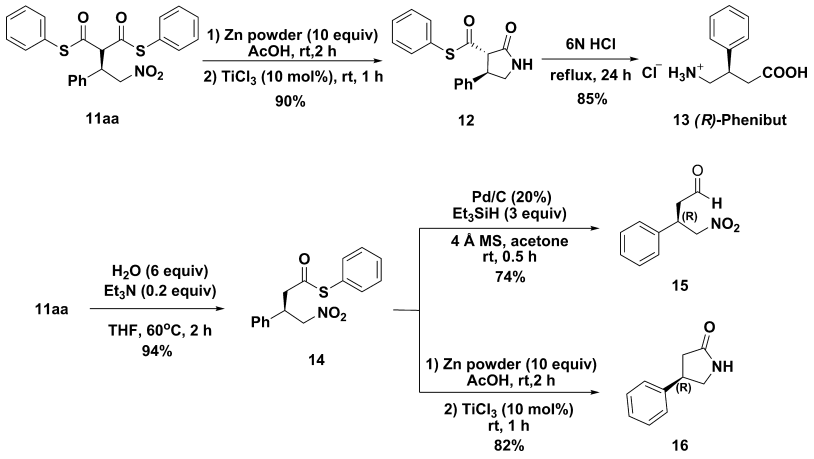
Scheme 3. Transformations of Adduct 11aa



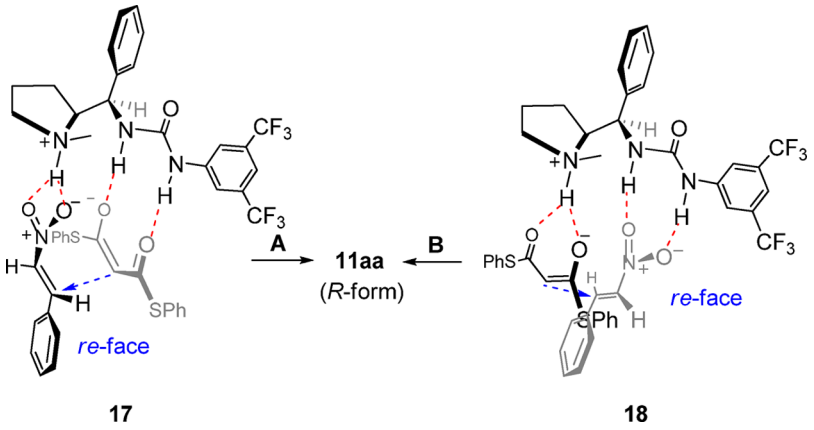


Figure 1. Transition-state model for the asymmetric Michael addition between **2a** and **1a** catalyzed by **9f**.

The observed stereochemistry for the asymmetric Michael addition of dithiomalonates **2** to *trans*-β-nitroolefins **1** using **9f** as catalyst can be rationalized by the transition-state model shown in Figure 1. There are two generally accepted mechanisms for adduct formation in relevant catalytic Michael addition reactions.[17] Deprotonation of the acidic proton from dithiomalonate **2a** by the tertiary amino group of *N*-methylpyrrolidine leads to formation of an ammonium ion. In route A, nitroolefin **1a** is activated through interaction with the protonated amino group of **9f**, while simultaneously the enolate of **2a** interacts with the urea moiety of **9f** through hydrogen bonding to form the ternary complex **17**.[17a,b] By contrast, in route B, **1a** is activated by the urea moiety of **9f** while the enolate of **2a** coordinates to the protonated amino group of **9f** to form the ternary complex **18**.[17c] With either complex **17** or **18**, nucleophilic addition of the enolate of **2a** from the *re* face of **1a** leads to the same adduct, *R*-**11aa**, as the major enantiomer.

In conclusion, we have prepared seven novel L-proline derived bifunctional organocatalysts, among which **9f** was successfully applied to the asymmetric Michael reaction of dithiomalonates **2** to *trans*-β-nitroolefins **1** in high yields and enantioselectivities. To the best of our knowledge, this is the first example of the Michael addition to nitroolefins using dithiomalonates as Michael donors. This methodology was successfully applied to an efficient synthesis of the neuropsychotropic drug, (*R*)-phenibut. The absolute configuration of **11** was the same as that predicted by the transition-state model in Figure 1. Further investigations of the application of these novel catalysts are in progress.

EXPERIMENTAL SECTION

General Information. Unless stated otherwise, reagents were used directly as obtained commercially. Reactions were monitored by thin layer chromatography. Flash column chromatography was performed using silica gel (40−60 μm particle size). ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured and chemical shifts are reported in ppm using TMS or the residual solvent peak as a reference. Infrared spectra were recorded on FT-IR. HRMS were recorded on an EI/FAB-Magnetic Sector mass spectrometer and MS were obtained using an ESI-QTOF mass spectrometer. Analytical high performance liquid chromatography (HPLC) was performed using the indicated chiral column (4.6 mm × 25 cm). Optical rotations were determined on a polarimeter at 589 nm. Melting points were determined using a melting point apparatus and are uncorrected.

General Procedure for the Synthesis of Dithiomalonates 2.[18] To a stirred solution of malonyl chloride (0.19 mL, 2 mmol, 1 equiv) in dry Et_2O (5 mL), thiol (4.4 mmol, 2.2 equiv) was added and the resulting mixture was stirred for 16 h at room temperature. The mixture was quenched with H_2O (10 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel.

*S,S′-Diphenyl dithiomalonate (**2a**).* Following the general procedure with thiophenol (0.45 mL, 4.4 mmol, 2.2 equiv), **2a** was obtained as a white solid (536 mg, 93% yield). Analytical data are consistent with reported values.[18] R_f 0.43 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.41 (m, 10H), 3.96 (s, 2H)

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ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.8, 134.5, 129.9, 129.4, 126.7, 56.5 ppm; IR (neat) 2955, 2916, 1715, 1691, 1477, 1440, 1396, 1307, 1030, 975, 707, 689 cm^{-1}; MS (ESI-QTOF) m/z [M + Na]$^+$ Calcd for $C_{15}H_{12}NaO_2S_2$ 311.018, found 311.011; mp 95−96 °C.

*S,S′-Bis(4-methoxyphenyl) dithiomalonate (**2b**).* Following the general procedure with 4-methoxythiophenol (0.54 mL, 4.4 mmol, 2.2 equiv), **2b** was obtained as a white solid (488 mg, 70% yield). R_f 0.23 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.33 (m, 4H), 6.96−6.93 (m, 4H), 3.91 (s, 2H), 3.83 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 161.0, 136.2, 117.4, 115.1, 56.1, 55.4 ppm; IR (neat) 2941, 2840, 1713, 1689, 1593, 1495, 1291, 1250, 1174, 1028, 976, 827 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{17}H_{16}O_4S_2$ 348.0490, found 348.0489; mp 67−70 °C.

*S,S′-Dipropyl dithiomalonate (**2c**).* Following the general procedure with 1-propanethiol (0.40 mL, 4.4 mmol, 2.2 equiv), **2c** was obtained as a colorless oil (278 mg, 63% yield). R_f 0.63 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 2H), 2.91 (t, J = 7.2 Hz, 4H), 1.67−1.59 (m, 4H), 0.97 (t, J = 7.4 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 57.8, 31.5, 22.6, 13.3 ppm; IR (neat) 2965, 2932, 2875, 1701, 1676, 1458, 1408, 1379, 1290, 1242, 1195, 1060, 1041, 990, 910, 785 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_9H_{16}O_2S_2$ 220.0592, found 220.0593.

*S,S′-Diethyl dithiomalonate (**2d**).* Following the general procedure with ethanethiol (0.32 mL, 4.4 mmol, 2.2 equiv), 2d was obtained as a light yellow oil (250 mg, 65% yield). Analytical data are consistent with reported values.[19] R_f 0.60 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 2H), 2.94 (q, J = 7.4 Hz, 4H), 1.28 (t, J = 7.4 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 57.7, 24.1, 14.4 ppm; IR (neat) 2977, 2865, 1700, 1675, 1454, 1265, 1054, 1033, 1014 cm^{-1}; MS (ESI-QTOF) m/z [M + Na]$^+$ Calcd for $C_7H_{12}NaO_2S_2$ 215.018, found 215.013.

General Procedure for Synthesis of 5a, 5b, 5c.[10] DIBAL-H (1.0 M in hexane, 2.61 mL, 2.61 mmol, 1.2 equiv) was added to a solution of *N*-boc proline methyl ester **4** (500 mg, 2.17 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at −78 °C. The resulting solution was stirred at −78 °C for 30 min, followed by the addition of ArMgBr (1.0 M in THF, 6.52 mL, 6.52 mmol, 3.0 equiv) dropwise at −78 °C. The solution was then allowed to slowly warm to r.t. overnight. Sat. aq NH_4Cl (10 mL) was added to quench the reaction. Sat. sodium tartrate solution (10 mL) was added to the resulting gel. The mixture was stirred at r.t. for 30 min, and then the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel to provide the product **5**.

*(S)-tert-Butyl 2-((S)-hydroxy(phenyl)methyl)pyrrolidine-1-carboxylate (**5a**).* Following the general procedure with phenyl magnesium bromide (1.0 M in THF, 6.52 mL, 6.52 mmol), **5a** was obtained as a colorless oil (445 mg, 74% yield). Analytical data are consistent with reported values.[20] R_f 0.23 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 5.89 (br s, 1H), 4.52 (br d, J = 7.2 Hz, 1H), 4.09 (td, J = 8.4, 3.8 Hz, 1H), 3.48−3.43 (m, 1H), 3.38−3.34 (m, 1H), 1.80−1.69 (m, 2H), 1.64−1.39 (m, 2H), 1.52 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 142.7, 128.4, 127.8, 127.3, 80.8, 79.3, 64.3, 47.8, 28.7, 28.6, 23.9 ppm; IR (neat) 3406 (br signal), 2989, 1692, 1669, 1405, 1254, 1164, 1117, 1054, 1033, 703 cm^{-1}; MS (ESI-QTOF) m/z [M + Na]$^+$ Calcd for $C_{16}H_{23}NNaO_3$ 300.158, found 300.151; $[\alpha]^{20}_D$ = −2.4 (c = 1.0, $CHCl_3$).

*(S)-tert-Butyl 2-((S)-(3,5-dimethylphenyl)(hydroxy)methyl)-pyrrolidine-1-carboxylate (**5b**).* Following the general procedure with 3,5-dimethylphenyl magnesium bromide (1.0 M in THF, 6.52 mL, 6.52 mmol), **5b** was obtained as a colorless oil (464 mg, 70% yield). R_f 0.29 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96−6.88 (m, 3H), 5.76 (br s, 1H), 4.42 (br d, J = 6.9 Hz, 1H), 4.08 (td, J = 8.6, 3.5 Hz, 1H), 3.48−3.42 (m, 1H), 3.39−3.34 (m, 1H), 2.30 (s, 6H), 1.85−1.69 (m, 2H), 1.64−1.38 (m, 2H), 1.51 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 142.6, 137.8, 129.4, 125.1, 80.7, 79.3, 64.1, 47.6, 28.6, 28.5, 23.8, 21.3 ppm; IR (neat) 3401 (br signal), 2974, 1664, 1402, 1366, 1265, 1166, 1120, 849 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{18}H_{28}NO_3$ 306.2069, found 306.2071; $[\alpha]^{20}_D$ = +6.0 (c = 1.0, $CHCl_3$).

*(S)-tert-Butyl 2-((S)-hydroxy(naphthalen-2-yl)methyl)pyrrolidine-1-carboxylate (**5c**).* Following the general procedure with naphthyl magnesium bromide (1.0 M in THF, 6.52 mL, 6.52 mmol), **5c** was obtained as a light yellow oil (547 mg, 77% yield). R_f 0.25 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ) 7.83−7.77 (m, 4H), 7.54−7.43 (m, 3H), 6.00 (br s, 1H), 4.69 (br d, J = 7.5 Hz, 1H), 4.19 (td, J = 8.4, 4.3 Hz, 1H), 3.49−3.44 (m, 1H), 3.39−3.31 (m, 1H), 1.76−1.66 (m, 2H), 1.62−1.40 (m, 2H), 1.53 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 140.1, 133.22, 133.19, 128.2, 128.0, 127.7, 126.4, 126.0, 125.8, 125.1, 80.9, 79.5, 64.2, 47.8, 28.8, 28.5, 23.9 ppm; IR (neat) 3400 (br signal), 3057, 2975, 2881, 1690, 1665, 1402, 1367, 1256, 1169, 1124, 1062, 901, 858, 821, 775, 750 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{20}H_{25}NO_3$ 327.1834, found 327.1837; $[\alpha]^{20}_D$ = −6.8 (c = 1.0, $CHCl_3$).

General Procedure for Synthesis of 6a, 6b, 6c. A 25 mL flame-dried flask was charged with compound **5** (1.5 mmol, 1 equiv) and PPh_3 (0.787 g, 3.0 mmol, 2 equiv). The reaction vessel was evacuated and backfilled with argon and this process repeated three times. Anhydrous THF (7 mL) was added and the mixture was cooled to 0 °C whereupon diethyl azodicarboxylate (0.47 mL, 3.0 mmol, 2 equiv) was added dropwise. Then diphenyl phosphoryl azide (0.39 mL, 1.8 mmol, 1.2 equiv) was added by a similar way. The reaction vessel was slowly warmed to 25 °C and stirred overnight. The reaction mixture was concentrated in vacuo, after which water (10 mL) was added. The mixture was extracted with EtOAc three times (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel to afford the product **6**.

*(S)-tert-Butyl 2-((R)-azido(phenyl)methyl)pyrrolidine-1-carboxylate (**6a**).* Following the general procedure with compound **5a** (416 mg, 1.5 mmol), the desired product was obtained as a colorless oil (354 mg, 78% yield). R_f 0.55 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.35−7.26 (m, 5H), 5.54 (br s, 0.57H), 5.20 (br s, 0.39H), 4.06 (br s, 0.61H), 3.98 (br s, 0.40H), 3.63−3.59 (m, 0.42H), 3.53−3.48 (m, 0.61H), 3.45−3.40 (m, 1H), 2.04−1.96 (m, 1H), 1.91−1.80 (m, 1H), 1.73−1.68 (m, 1H), 1.62−1.57 (m, 1H), 1.54 (s, 3.62H), 1.51 (s, 5.43H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (mixture of rotamers) δ 154.8, 154.2, 137.8, 128.7, 128.5, 127.8, 127.5, 126.5, 126.4, 80.1, 79.8, 67.4, 65.6, 62.9, 62.8, 47.7, 47.2, 28.6, 26.0, 25.1, 24.3, 23.6 ppm; IR (neat) 2979, 2103, 1691, 1393, 1259, 1172, 1120, 700 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{16}H_{23}N_4O_2$ 303.1821, found 303.1818; $[\alpha]^{20}_D$ = −93.5 (c = 1.0, $CHCl_3$).

*(S)-tert-Butyl 2-((R)-azido(3,5-dimethylphenyl)methyl)-pyrrolidine-1-carboxylate (**6b**).* Following the general procedure with compound **5b** (458 mg, 1.5 mmol), the desired product was obtained as a colorless oil (322 mg, 65% yield). R_f 0.60 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 6.97−6.90 (m, 3H), 5.47 (br s, 0.59H), 5.12 (br s, 0.36H), 4.04 (br s, 0.60H), 3.96 (br s, 0.40H), 3.65−3.57 (m, 0.40H), 3.52−3.47 (m, 0.60H), 3.45−3.41 (m, 1H), 2.30 (s, 6H), 2.05−1.97 (m, 1H), 1.94−1.83 (m, 1H), 1.73−1.69 (m, 1H), 1.68−1.58 (m, 1H), 1.54 (s, 3.61H), 1.51 (s, 5.43H) ppm; ^{13}C NMR (125 MHz) (mixture of rotamers) δ 154.9, 154.2, 138.2, 138.1, 137.7, 129.4, 129.2, 124.23, 124.16, 80.1, 79.7, 67.5, 65.8, 62.9, 62.7, 47.7, 47.2, 28.6, 26.1, 25.0, 24.3, 23.6, 21.3 ppm; IR (neat) 2978, 2882, 2101, 1689, 1603, 1391, 1366, 1273, 1257, 1165, 1118, 852, 775, 700 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{18}H_{27}N_4O_2$ 331.2134, found 331.2137; $[\alpha]^{20}_D$ = −97.0 (c = 1.0, $CHCl_3$).

*(S)-tert-Butyl 2-((R)-azido(naphthalen-2-yl)methyl)pyrrolidine-1-carboxylate (**6c**).* Following the general procedure with compound **5c** (491 mg, 1.5 mmol), the desired product **6c** was obtained as a colorless oil (264 mg, 50% yield). R_f 0.40 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.83−7.78 (m, 4H), 7.49−7.37 (m, 3H), 5.71 (br s, 0.61H), 5.36 (br s, 0.37H), 4.18 (br s, 0.60H), 4.09 (br s, 0.40H), 3.65−3.61 (m, 0.40H), 3.55−3.50 (m, 0.62H), 3.49−3.44 (m, 1H), 2.07−2.00 (m, 1H), 1.99−1.90 (m, 1H), 1.74−1.69 (m, 1H), 1.67−1.58 (m, 1H), 1.55 (s,

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3.64H), 1.52 (s, 5.47H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (mixture of rotamers) δ 154.9, 154.2, 135.3, 133.2, 132.8, 128.5, 128.2, 128.0, 127.7, 126.5, 126.3, 126.0, 125.3, 124.5, 124.3, 80.2, 79.8, 67.6, 65.8, 62.8, 62.6, 47.7, 47.3, 28.6, 26.1, 25.1, 24.3, 23.6 ppm; IR (neat) 3060, 2974, 2102, 1688, 1392, 1367, 1258, 1168, 1120, 928, 900, 861, 815, 775, 744 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{20}H_{25}N_4O_2$ 353.1978, found 353.1976; $[\alpha]^{20}_D$ = −122 (c = 1.0, $CHCl_3$).

General Procedure for Synthesis of 7a, 7b, 7c. TFA (3 mL) was added to a stirred solution of **6** (1 mmol, 1 equiv) in CH_2Cl_2 (3 mL) at 0 °C under an argon atmosphere. The resulting solution was warmed to 25 °C and stirred overnight. The reaction mixture was concentrated in vacuo, the residue was dissolved in 5 mL of CH_2Cl_2 and then treated with saturated aqueous $NaHCO_3$ solution for 1 h at 25 °C. The resulting mixture was extracted with $CHCl_3$ three times (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. Then H_2O (1 mL), HCOOH (98%, 0.5 mL) and HCHO (37% aqueous solution, 0.75 mL) were added to the residue. The resulting mixture was refluxed for 5 h. The reaction mixture was then cooled to room temperature, basified with saturated aqueous NaOH solution, and extracted with CH_2Cl_2 (3 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the product **7**.

*(S)-2-((R)-Azido(phenyl)methyl)-1-methylpyrrolidine (**7a**).* Following the general procedure with compound **6a** (302 mg, 1 mmol), the desired product was obtained as a yellow oil (188 mg, 87% yield). R_f 0.33 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.35 (m, 2H), 7.32−7.28 (m, 3H), 4.70 (d, J = 3.9 Hz, 1H), 3.14−3.11 (m, 1H), 2.51−2.47 (m, 1H), 2.34 (s, 3H), 2.26−2.20 (m, 1H), 1.94−1.88 (m, 1H), 1.83−1.74 (m, 1H), 1.68−1.63 (m, 1H), 1.62−1.54 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.6, 127.8, 127.0, 71.0, 66.6, 57.5, 41.0, 25.9, 22.8 ppm; IR (neat) 2791, 2101, 1451, 1353, 1288, 1253, 700 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{12}H_{17}N_4$ 217.1453, found 217.1455; $[\alpha]^{20}_D$ = −161.5 (c = 1.0, $CHCl_3$).

*(S)-2-((R)-Azido(3,5-dimethylphenyl)methyl)-1-methylpyrrolidine (**7b**).* Following the general procedure with compound **6b** (330 mg, 1 mmol), the desired product was obtained as a yellow solid (215 mg, 88% yield). R_f 0.33 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92−6.90 (m, 3H), 4.63 (d, J = 3.8 Hz, 1H), 3.14−3.11 (m, 1H), 2.48−2.44 (m, 1H), 2.35 (s, 3H), 2.32 (s, 6H), 2.24−2.17 (m, 1H), 1.94−1.88 (m, 1H), 1.84−1.74 (m, 1H), 1.67−1.62 (m, 1H), 1.61−1.55 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.1, 129.5, 124.7, 71.0, 66.6, 57.5, 40.9, 25.8, 22.8, 21.4 ppm; IR (neat) 2959, 2786, 2100, 1604, 1457, 1352, 1275, 848, 701 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{14}H_{21}N_4$ 245.1766, found 245.1768; $[\alpha]^{20}_D$ = −187.3 (c = 1.0, $CHCl_3$); mp 50−55 °C.

*(S)-2-((R)-Azido(naphthalen-2-yl)methyl)-1-methylpyrrolidine (**7c**).* Following the general procedure with compound **6c** (352 mg, 1 mmol), the desired product was obtained as a yellow oil (242 mg, 91% yield). R_f 0.23 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.79 (m, 4H), 7.51−7.41 (m, 3H), 4.86 (d, J = 4.0 Hz, 1H), 3.15−3.12 (m, 1H), 2.61−2.57 (m, 1H), 2.35 (s, 3H), 2.26−2.21 (m, 1H), 2.00−1.93 (m, 1H), 1.85−1.76 (m, 1H), 1.67−1.62 (m, 1H), 1.61−1.54 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 133.2, 132.9, 128.4, 128.0, 127.7, 126.4, 126.2, 126.1, 124.8, 70.9, 66.8, 57.6, 41.1, 26.1, 22.9 ppm; IR (neat) 3058, 2966, 2844, 2783, 2100, 1602, 1509, 1454, 1364, 1271, 1046, 897, 857, 818, 746 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{16}H_{19}N_4$ 267.1610, found 267.1611; $[\alpha]^{20}_D$ = −215.7 (c = 1.0, $CHCl_3$).

*(S)-2-((R)-Azido(phenyl)methyl)-1-benzylpyrrolidine (**7d**).* TFA (3 mL) was added to a stirred solution of **6a** (302 mg, 1 mmol, 1 equiv) in CH_2Cl_2 (3 mL) at 0 °C under an argon atmosphere. The resulting solution was warmed to 25 °C and stirred overnight. The reaction mixture was concentrated in vacuo, the residue was dissolved in 5 mL of CH_2Cl_2 and then treated with a saturated aqueous $NaHCO_3$ solution for 1 h at 25 °C. The aqueous layer was extracted with $CHCl_3$ three times (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. Without purification, the residue was dissolved in dry DMF (2.4 mL), whereupon K_2CO_3 (166 mg, 1.2 mmol, 1.2 equiv) was added and stirred for 10 min. Then benzyl bromide (0.14 mL, 1.2 mmol, 1.2 equiv) was added and the resulting mixture was stirred for additional 10 h at room temperature. The reaction mixture was diluted with water (8 mL) and extracted with CH_2Cl_2 (5 mL × 3). The extract was washed three times with water (10 mL × 3), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the product **7d** as a light yellow oil (278 mg, 95%). Analytical data are consistent with reported values.[11] R_f 0.70 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.29 (m, 6H), 7.26−7.20 (m, 4H), 4.57 (d, J = 3.7 Hz, 1H), 3.92 (d, J = 12.9 Hz, 1H), 3.47 (d, J = 12.9 Hz, 1H), 3.04−3.00 (m, 1H), 2.94−2.90 (m, 1H), 2.27−2.22 (m, 1H), 1.94−1.88 (m, 1H), 1.82−1.74 (m, 1H), 1.68−1.58 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 138.6, 128.9, 128.5, 128.4, 127.7, 127.1, 127.0, 69.8, 67.4, 59.8, 55.0, 26.1, 23.7 ppm; IR (neat) 3068, 2970, 2794, 2100, 1495, 1452, 1351, 1293, 698 cm^{-1}; MS (ESI-QTOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{21}N_4$ 293.177, found 293.171; $[\alpha]^{20}_D$ = −100.4 (c = 1.0, $CHCl_3$), [lit.[11] $[\alpha]^{20}_D$ = −97 (c = 1.0, $CHCl_3$)].

General Procedure for Synthesis of 9a, 9b, 9c, 9d. To a stirred suspension of $LiAlH_4$ (30 mg, 0.8 mmol, 1 equiv) in 0.8 mL of dry THF, a solution of compound **7** (0.8 mmol, 1 equiv) in 1.6 mL of dry THF was added dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 1.5 h and then quenched by a 5% aqueous sodium potassium tartarate solution. The resulting mixture was filtered through a pad of Celite, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2 (2.4 mL), then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.18 mL, 0.96 mmol, 1.2 equiv) was added and stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel to afford the desired product.

*1-(3,5-Bis(trifluoromethyl)phenyl)-3-((R)-((S)-1-methylpyrrolidin-2-yl)(phenyl)methyl)thiourea (**9a**).* Following the general procedure with compound **7a** (173 mg, 0.8 mmol), the desired product was obtained as a white solid (288 mg, 78% yield). R_f 0.69 (methylene chloride:methanol = 10:1); ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 (s, 2H), 7.59 (s, 1H), 7.33−7.27 (m, 4H), 7.24−7.19 (m, 1H), 5.78 (br s, 1H), 3.07 (t, J = 7.2 Hz, 1H), 2.66 (br s, 1H), 2.37 (s, 3H), 2.26 (br s, 1H), 1.72−1.46 (m, 4H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 183.0, 143.4, 141.7, 132.6 (q, J = 33.2 Hz), 129.5, 128.2, 127.8, 124.7 (q, J = 271.3 Hz), 123.2, 117.6, 71.6, 58.6, 58.1, 41.1, 26.9, 22.8 ppm; IR (neat) 1612, 1473, 1384, 1276, 1176, 1131, 883, 699, 682 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{21}H_{22}F_6N_3S$ 462.1439, found 462.1437; $[\alpha]^{20}_D$ = −52.4 (c = 1.0, $CHCl_3$); mp 49−51 °C.

*1-(3,5-Bis(trifluoromethyl)phenyl)-3-((R)-(3,5-dimethylphenyl)-((S)-1-methylpyrrolidin-2-yl)methyl)thiourea (**9b**).* Following the general procedure with compound **7b** (195 mg, 0.8 mmol), the desired product was obtained as a light yellow foam (313 mg, 80% yield). R_f 0.48 (methylene chloride:methanol = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.80 (br s, 1H), 8.09 (s, 2H), 7.59 (s, 1H), 6.98 (s, 1H), 6.90 (s, 2H), 6.45 (s, 1H), 4.92 (s, 1H), 3.19 (br s, 1H), 2.84 (br s, 1H), 2.61 (s, 3H), 2.52−2.43 (m, 1H), 2.32 (s, 6H), 2.29−2.25 (m, 1H), 2.09−2.04 (m, 1H), 1.93−1.85 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 142.3, 139.2, 138.8, 131.8 (q, J = 33.4 Hz), 130.3, 124.6, 123.3 (q, J = 272.7 Hz), 122.5, 117.6, 71.5, 62.1, 56.1, 40.8, 25.6, 24.4, 21.4 ppm; IR (neat) 1610, 1474, 1385, 1276, 1178, 1132, 883, 699, 685 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{23}H_{25}F_6N_3S$ 489.1673, found 489.1675; $[\alpha]^{20}_D$ = −61.9 (c = 1.0, $CHCl_3$); mp 55−59 °C.

*1-(3,5-Bis(trifluoromethyl)phenyl)-3-((R)-((S)-1-methylpyrrolidin-2-yl)(naphthalen-2-yl)methyl)thiourea (**9c**).* Following the general procedure with compound **7c** (213 mg, 0.8 mmol), the desired product was obtained as a light yellow foam (307 mg, 75% yield). R_f 0.53 (methylene chloride:methanol = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.85 (br s, 1H), 8.09 (s, 2H), 7.87−7.81 (m, 3H), 7.75 (s,

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1H), 7.61 (s, 1H), 7.53−7.52 (m, 2H), 7.38 (dd, J = 8.5, 1.7 Hz, 1H), 6.58 (br s, 1H), 5.18 (br s, 1H), 3.23−3.20 (m, 1H), 2.95−2.89 (m, 1H), 2.63 (s, 3H), 2.51−2.46 (m, 1H), 2.39−2.30 (m, 1H), 2.15−2.04 (m, 1H), 1.98−1.85 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 142.1, 136.1, 133.3, 133.0, 131.9 (q, J = 32.5 Hz), 129.5, 128.0, 127.8, 127.0, 126.8, 125.7, 124.4, 123.2 (q, J = 272.8 Hz), 122.5, 117.6, 71.4, 62.0, 56.1, 40.7, 25.6, 24.4 ppm; IR (neat) 1610, 1473, 1385, 1277, 1177, 1132, 1038, 1002, 964, 883, 819, 700, 681 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{25}H_{23}F_6N_3S$ 511.1517, found 511.1514; $[\alpha]^{20}_D$ = −83.6 (c = 1.0, $CHCl_3$); mp 56−59 °C.

*1-((R)-((S)-1-Benzylpyrrolidin-2-yl)(phenyl)methyl)-3-(3,5-bis-(trifluoromethyl)phenyl)thiourea (**9d**).* Following the general procedure with compound **7d** (234 mg, 0.8 mmol), the desired product was obtained as a light yellow foam (357 mg, 83% yield). R_f 0.83 (methylene chloride:methanol = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.16 (br s, 1H), 7.72 (s, 2H), 7.60 (s, 1H), 7.39−7.34 (m, 3H), 7.25−7.18 (m, 3H), 7.15 (s, 4H), 6.51 (br s, 1H), 4.88 (br s, 1H), 4.01 (d, J = 12.4 Hz, 1H), 3.66 (d, J = 12.1 Hz, 1H), 3.19−3.14 (m, 2H), 2.59−2.54 (m, 1H), 2.30 (br s, 1H), 2.03−1.84 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.1, 141.4, 138.9, 136.2, 131.7 (q, J = 32.5 Hz), 129.7, 129.5, 128.8 (x2), 128.3, 126.9, 124.4, 123.1 (q, J = 272.8 Hz), 118.4, 69.7, 63.2, 60.7, 54.1, 25.7, 24.5 ppm; IR (neat) 1608, 1473, 1383, 1276, 1175, 1133, 886, 699, 681 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{27}H_{25}F_6N_3S$ 537.1673, found 537.1670; $[\alpha]^{20}_D$ = −117.0 (c = 1.0, $CHCl_3$); mp 47−49 °C.

*3-(3,5-Bis(trifluoromethyl)phenylamino)-4-((R)-((S)-1-methylpyrrolidin-2-yl)(phenyl)methylamino)cyclobut-3-ene-1,2-dione (**9e**).* To a stirred suspension of $LiAlH_4$ (30 mg, 0.8 mmol, 1 equiv) in 0.8 mL of dry THF, a solution of compound **7a** (173 mg, 0.8 mmol, 1 equiv) in 1.6 mL of dry THF was added dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 1.5 h and then quenched by a 5% aqueous sodium potassium tartarate solution. The resulting mixture was filtered through a pad of Celite, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2 (2.4 mL), then **8** (273 mg, 0.8 mmol, 1 equiv) was added and stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel to obtain the desired product as a yellow solid (326 mg, 82% yield). R_f 0.57 (methylene chloride:methanol = 10:1); ^{1}H NMR (500 MHz, CD_3OD) δ 8.10 (br s, 2H), 7.55 (s, 1H), 7.39−7.35 (m, 4H), 7.30−7.26 (m, 1H), 5.59 (br s, 1H), 3.12−3.10 (m, 1H), 2.75 (br s, 1H), 2.41 (s, 3H), 2.38−2.31 (m, 1H), 1.81−1.70 (m, 4H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 185.6, 182.4, 171.5, 164.4, 142.5, 141.1, 133.9 (q, J = 33.5 Hz), 129.9, 128.8, 127.5, 124.6 (q, J = 272.1 Hz), 119.2, 116.5, 71.5, 59.2, 58.3, 41.0, 26.1, 23.1 ppm; IR (neat) 1792, 1680, 1594, 1558, 1448, 1380, 1278, 1182, 1133, 751, 699 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{24}H_{22}F_6N_3O_2$ 498.1616, found 498.1619; $[\alpha]^{20}_D$ = −60.4 (c = 0.5, $CHCl_3$); mp 150−160 °C decomposed.

*1-(3,5-Bis(trifluoromethyl)phenyl)-3-((R)-((S)-1-methylpyrrolidin-2-yl)(phenyl)methyl)urea (**9f**).* To a stirred suspension of $LiAlH_4$ (30 mg, 0.8 mmol, 1 equiv) in 0.8 mL of dry THF, a solution of compound **7a** (173 mg, 0.8 mmol, 1 equiv) in 1.6 mL of dry THF was added dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 1.5 h and then quenched by 5% aqueous sodium potassium tartarate solution. The resulting mixture was filtered through a short Celite pad, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2 (2.4 mL), then 3,5-bis(trifluoromethyl)phenyl isocyanate (0.14 mL, 0.8 mmol, 1 equiv) was added and stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel to obtain the desired product as a white solid (285 mg, 80% yield). R_f 0.52 (methylene chloride:methanol = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 2H), 7.35 (s, 1H), 7.26−7.23 (m, 2H), 7.19−7.18 (m, 3H), 5.70 (br s, 1H), 4.81 (s, 1H), 3.07−3.04 (m, 1H), 2.66−2.64 (m, 1H), 2.43 (s, 3H), 2.32−2.27 (m, 1H), 2.00−1.97 (m, 1H), 1.68 (br s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 141.6, 140.1, 132.1 (q, J = 33.1 Hz), 129.0, 127.9, 126.4, 123.3 (q, J = 272.7 Hz), 118.1, 115.2, 71.0, 56.6 (×2), 40.3, 25.1, 23.2 ppm; IR (neat) 1660, 1574, 1507, 1476, 1390, 1277, 1193, 1131, 701, 649 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{21}H_{22}F_6N_3O$ 446.1667, found 446.1669; $[\alpha]^{20}_D$ = −43.6 (c = 1.0, $CHCl_3$); mp 188−190 °C.

*(S)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1-methylpyrrolidin-2-yl)diphenylmethyl)urea (**9g**).* A 10 mL round-bottom flask was charged with amino azide **10**[12] (415 mg, 1.49 mmol, 1 equiv), then H_2O (1.7 mL), HCOOH (98%, 0.85 mL) and HCHO (37% aqueous solution, 1.25 mL) were added. The resulting mixture was refluxed for 5 h. The reaction mixture was then cooled to room temperature, basified with saturated aqueous NaOH solution, and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was dissolved in 2 mL of dry THF and was slowly added to a suspension of $LiAlH_4$ (57 mg, 1.49 mmol, 1 equiv) in 1 mL of dry THF at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 1.5 h, and then quenched using a 5% aqueous sodium potassium tartarate solution. The resulting mixture was filtered through a pad of Celite, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2 (4 mL), then 3,5-bis(trifluoromethyl)phenyl isocyanate (0.26 mL, 1.49 mmol, 1 equiv) was added and stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel to obtain the desired product **9g** as a white solid (427 mg, 55% yield). R_f 0.32 (methylene chloride:methanol = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.34 (br s, 1H), 7.70 (s, 2H), 7.44−7.36 (m, 5H), 7.29−7.24 (m, 4H), 7.21−7.16 (m, 2H), 5.59 (br s, 1H), 4.17 (dd, J = 9.6, 3.4 Hz, 1H), 3.06−3.02 (m, 1H), 2.57−2.52 (m, 1H), 2.31−2.22 (m, 1H), 2.26 (s, 3H), 2.08−2.04 (m, 1H), 1.76−1.75 (m, 1H), 1.63 (br s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 146.0, 142.8, 141.6, 132.0 (q, J = 33.1 Hz), 128.8, 128.3, 127.7, 127.4, 127.1, 126.7, 123.3 (q, J = 272.6 Hz), 118.1, 115.1, 71.8, 69.8, 58.5, 44.3, 30.7, 24.4 ppm; IR (neat) 1658, 1564, 1389, 1278, 1169, 1136, 885, 668 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{27}H_{25}F_6N_3O$ 521.1902, found 521.1898; $[\alpha]^{20}_D$ = +193.6 (c = 1.0, $CHCl_3$); mp 158−159 °C.

General Procedure for Asymmetric Michael Addition Reaction. To a stirred solution of catalyst **9f** (3.3 mg, 0.0075 mmol, 5%) and β-nitroolefin **1** (0.3 mmol), dithiomalonate **2** (0.15 mmol) was added under an argon atmosphere. The reaction mixture was stirred at room temperature or −40 °C. After the reaction was completed (monitored by TLC), the reaction mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel.

*(R)-2-(2-Nitro-1-phenylethyl)-malonic acid diphenyl dithioester (**11aa**).* Following the general procedure with nitroolefin **1a** (45 mg, 0.30 mmol), S,S'-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (62 mg, 94% yield, 90% ee). R_f 0.33 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.33 (m, 11H), 7.30−7.27 (m, 2H), 7.17−7.15 (m, 2H), 4.90−4.82 (m, 2H), 4.49 (d, J = 9.6 Hz, 1H), 4.40 (ddd, J = 9.6, 8.8, 4.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 189.6, 135.2, 134.3, 134.2, 130.3, 130.1, 129.6, 129.4, 129.1, 128.6, 128.4, 126.11, 126.08, 77.1, 69.4, 44.4 ppm; IR (neat) 1703, 1550, 1478, 1442, 1380, 1268, 944, 748 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$ Calcd for $C_{23}H_{20}NO_4S_2$ 438.0834, found 438.0837; HPLC Chiracel OD-H column, i-PrOH/n-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 16.92 min (minor), t_R = 22.90 min (major); $[\alpha]^{20}_D$ = −102.0 (c = 1.0, $CHCl_3$; 98% ee); mp 160−162 °C.

*(R)-2-(2-Nitro-1-phenylethyl)-malonic acid bis-4-methoxyphenyl dithioester (**11ab**).* Following the general procedure with nitroolefin **1a** (45 mg, 0.30 mmol), S,S'-bis(4-methoxyphenyl) dithiomalonate **2b** (52 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the reaction was completed in 1.5 h at r.t.. After column chromatography, the desired product was obtained as a white solid (69 mg, 92% yield, 92% ee). R_f 0.30 (ethyl acetate:hexane = 1:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.31 (m, 5H), 7.27−7.26 (m, 2H), 7.06−7.03 (m, 2H), 6.99−6.96 (m, 2H), 6.89−6.86 (m, 2H), 4.89−4.81 (m, 2H), 4.44 (d, J = 9.5 Hz, 1H), 4.40−4.35 (m, 1H), 3.84 (s, 3H), 3.80 (s,

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3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 190.7, 161.2, 161.1, 136.0, 135.9, 135.3, 129.1, 128.6, 128.4 (x2), 116.7, 115.2, 115.0, 68.8, 55.5, 55.4, 44.3 ppm; IR (neat) 1700, 1593, 1550, 1496, 1457, 1378, 1292, 1254, 1174, 971, 824, 654 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{25}H_{23}NO_6S_2$ 497.0967, found 497.0968; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 30/70, 40 °C, 1.0 mL/min, λ = 254 nm, t_R = 21.92 min (minor), t_R = 23.91 min (major); $[\alpha]^{20}_D$ = −100.5 (c = 1.0, $CHCl_3$; 92% ee); mp 110−135 °C decomposed.

*(R)-2-(2-Nitro-1-phenylethyl)-malonic acid dipropyl dithioester (**11ac**).* Following the general procedure with nitroolefin **1a** (45 mg, 0.30 mmol), *S*,*S*′-dipropyl dithiomalonate **2c** (33 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (53 mg, 95% yield, 73% ee). R_f 0.48 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.24 (m, 3H), 7.22−7.19 (m, 2H), 4.78−4.71 (m, 2H), 4.39−4.34 (m, 1H), 4.27 (d, J = 10.1 Hz, 1H), 2.95 (t, J = 7.2 Hz, 2H), 2.79−2.74 (m, 1H), 2.71−2.66 (m, 1H), 1.67−1.60 (m, 2H), 1.43−1.31 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H), 0.77 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 191.3, 135.5, 129.1, 128.5, 128.3, 77.6, 70.6, 44.3, 32.0, 31.8, 22.7, 22.5, 13.4, 13.1 ppm; IR (neat) 1697, 1559, 1381, 977, 663 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{17}H_{23}NO_4S_2$ 369.1069, found 369.1071; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 6.93 min (major), t_R = 7.76 min (minor); $[\alpha]^{20}_D$ = −27.4 (c = 1.0, $CHCl_3$; 73% ee); mp 66−69 °C.

*(R)-2-(2-Nitro-1-phenylethyl)-malonic acid diethyl dithioester (**11ad**).* Following the general procedure with nitroolefin **1a** (45 mg, 0.30 mmol), *S*,*S*′-diethyl dithiomalonate **2d** (29 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (48 mg, 93% yield, 89% ee). R_f 0.41 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.25 (m, 3H), 7.22−7.20 (m, 2H), 4.79−4.72 (m, 2H), 4.40−4.35 (m, 1H), 4.25 (d, J = 10.1 Hz, 1H), 2.98 (qd, J = 7.4, 1.1 Hz, 2H), 2.81−2.74 (m, 1H), 2.74−2.67 (m, 1H), 1.29 (t, J = 7.4 Hz, 3H), 1.02 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 191.1, 135.3, 128.9, 128.4, 128.2, 77.4, 70.3, 44.2, 24.5, 24.3, 14.2, 14.1 ppm; IR (neat) 2929, 1692, 1560, 1457, 1379, 1261, 1090, 967, 701, 640 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{15}H_{19}NO_4S_2$ 341.0756, found 341.0756; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 5/95, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 13.85 min (major), t_R = 15.02 min (minor); $[\alpha]^{20}_D$ = −34.3 (c = 1.0, $CHCl_3$; 89% ee); mp 72−75 °C.

*(R)-2-(1-(4-Fluoro-phenyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11ba**).* Following the general procedure with nitroolefin **1b** (50 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (63 mg, 92% yield, 87% ee). R_f 0.33 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.36 (m, 8H), 7.27−7.25 (m, 2H), 7.18−7.16 (m, 2H), 7.09−7.04 (m, 2H), 4.81 (d, J = 6.7 Hz, 2H), 4.45 (d, J = 9.7 Hz, 1H), 4.42−4.37 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 189.5, 162.7 (d, J = 248.2 Hz), 134.3, 134.2, 131.0 (d, J = 3.3 Hz), 130.3, 130.2, 130.1, 129.6, 129.5, 125.9 (d, J = 6.6 Hz), 116.2, 116.1, 77.1, 69.3, 43.6 ppm; IR (neat) 1709, 1558, 1512, 1478, 1442, 1375, 1231, 1163, 968, 838, 668 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{23}H_{18}FNO_4S_2$ 455.0661, found 455.0664; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 16.83 min (minor), t_R = 24.81 min (major); $[\alpha]^{20}_D$ = −92.8 (c = 1.0, $CHCl_3$; > 99% ee); mp 141−145 °C.

*(R)-2-(1-(2-Fluoro-phenyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11ca**).* Following the general procedure with nitroolefin **1c** (50 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (68 mg, 99% yield, 91% ee). R_f 0.40 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.42 (m, 5H), 7.38−7.33 (m, 4H), 7.25−7.22 (m, 1H), 7.14−7.10 (m, 4H), 4.94 (dd, J = 13.2, 9.7 Hz, 1H), 4.80 (dd, J = 13.2, 4.0 Hz, 1H), 4.65 (d, J = 10.1 Hz, 1H), 4.59 (ddd, J = 10.1, 9.7, 4.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 189.4, 161.3 (d, J = 246.6 Hz), 134.3, 134.2, 131.6 (d, J = 4.2 Hz), 130.6 (d, J = 8.8 Hz), 130.3, 130.1, 129.6, 129.4, 126.0 (d, J = 2.6 Hz), 124.8 (d, J = 3.3 Hz), 122.1 (d, J = 12.7 Hz), 116.4, 116.2, 75.7 (d, J = 2.9 Hz), 67.2 (d, J = 2.2 Hz), 40.5 ppm; IR (neat) 2974, 2927, 1708, 1556, 1494, 1441, 1377, 1052, 1033, 1006, 969, 650 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{23}H_{18}FNO_4S_2$ 455.0661, found 455.0664; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 11.00 min (minor), t_R = 18.32 min (major); $[\alpha]^{20}_D$ = −85.5 (c = 1.0, $CHCl_3$; 91% ee); mp 88−92 °C.

*(R)-2-(1-(4-Bromo-phenyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11da**).* Following the general procedure with nitroolefin **1d** (68 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (76 mg, 98% yield, 90% ee). R_f 0.43 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.45 (m, 5H), 7.44−7.36 (m, 5H), 7.20−7.14 (m, 4H), 4.85−4.79 (m, 2H), 4.44 (d, J = 9.6 Hz, 1H), 4.39−4.34 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 189.4, 134.34, 134.26, 134.2, 132.3, 130.3, 130.2, 130.0, 129.6, 129.5, 125.93, 125.86, 122.8, 76.8, 69.0, 43.7 ppm; IR (neat) 2923, 2850, 1701, 1555, 1478, 1441, 1377, 1059, 1033, 1012, 967, 752, 655 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{23}H_{18}BrNO_4S_2$ 514.9861, found 514.9863; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 19.86 min (minor), t_R = 31.74 min (major); $[\alpha]^{20}_D$ = −100.2 (c = 1.0, $CHCl_3$; > 99% ee); mp 147−149 °C.

*(R)-2-(1-(2-Bromo-phenyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11ea**).* Following the general procedure with nitroolefin **1e** (68 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a light yellow oil (76 mg, 98% yield, 97% ee). R_f 0.42 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, J = 8.0, 1.0 Hz, 1H), 7.47−7.35 (m, 8H), 7.33−7.27 (m, 3H), 7.26−7.18 (m, 2H), 5.13−5.08 (m, 1H), 4.97−4.78 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 189.8, 134.4, 134.32, 134.29, 134.1, 130.3, 130.2, 130.1, 129.6, 129.5, 128.0 (x2), 126.2, 126.0, 124.9, 75.1, 67.0, 43.0 ppm; IR (neat) 2919, 1706, 1558, 1478, 1442, 1377, 1058, 1033, 747, 668 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{23}H_{18}BrNO_4S_2$ 514.9861, found 514.9857; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 11.31 min (minor), t_R = 21.30 min (major); $[\alpha]^{20}_D$ = −21.5 (c = 1.0, $CHCl_3$; 97% ee).

*(R)-2-(1-(4-Trifluoromethyl-phenyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11fa**).* Following the general procedure with nitroolefin **1f** (65 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (67 mg, 88% yield, 92% ee). R_f 0.45 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 2H), 7.50−7.35 (m, 10H), 7.15−7.12 (m, 2H), 4.90−4.82 (m, 2H), 4.50−4.45 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 189.4, 139.4, 134.3, 134.2, 130.9 (q, J = 33.0 Hz), 130.4, 130.3, 129.6, 129.5, 129.0, 126.1 (q, J = 3.7 Hz), 125.8, 125.7, 123.8 (q, J = 272.3 Hz), 76.7, 68.8, 43.9 ppm; IR (neat) 2919, 1738, 1696, 1558, 1479, 1442, 1377, 1327, 1167, 1124, 1070, 966, 852, 747, 658 cm^{-1}; HRMS (EI-Magnetic Sector) m/z [M]$^+$ Calcd for $C_{24}H_{18}F_3NO_4S_2$ 505.0629, found 505.0632; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 15.00 min (minor), t_R = 28.76 min (major); $[\alpha]^{20}_D$ = −95.0 (c = 1.0, $CHCl_3$; > 99% ee); mp 110−120 °C.

*(R)-2-(1-(4-Methyl-phenyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11ga**).* Following the general procedure with nitroolefin **1g** (49 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (64 mg, 94% yield, 90% ee). R_f 0.36 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.40 (m, 5H), 7.40−7.34 (m, 3H), 7.19−7.13 (m, 6H), 4.87−4.79 (m, 2H), 4.46 (d, J = 9.5 Hz, 1H), 4.36 (ddd, J = 9.5, 8.7, 5.0 Hz, 1H), 2.34(s,1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 189.6, 138.4, 134.3, 134.2, 132.1, 130.2, 130.0, 129.8, 129.5, 129.4, 128.2, 126.18, 126.16 77.2, 69.5, 44.1, 21.2 ppm; IR (neat) 1708, 1555, 1478, 1441, 1376, 1257, 954 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z [M + H]$^+$

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Calcd for $C_{24}H_{22}NO_4S_2$ 452.0990, found 452.0993; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 14.31 min (minor), t_R = 20.09 min (major); $[\alpha]^{20}_D$ = −88.5 (*c* = 1.0, $CHCl_3$; 93% ee); mp 150−155 °C.

*(R)-2-(1-(4-Methoxy-phenyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11ha**).* Following the general procedure with nitroolefin **1h** (54 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (69 mg, 98% yield, 87% ee). R_f 0.32 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.42 (m, 5H), 7.39−7.34 (m, 3H), 7.20−7.17 (m, 4H), 6.90−6.86 (m, 2H), 4.84−4.77 (m, 2H), 4.45 (d, *J* = 9.7 Hz, 1H), 4.37−4.33 (m, 1H), 3.80 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 189.6, 159.7, 134.3, 134.2, 130.2, 130.1, 129.6, 129.5, 129.4, 127.0, 126.17, 126.16, 114.5, 77.3, 69.6, 55.3, 43.8 ppm; IR (neat) 2984, 1703, 1559, 1515, 1442, 1376, 1255, 1181, 1057, 1033, 968, 831, 751, 646 cm^{-1}; HRMS (EI-Magnetic Sector) *m*/*z* [M]$^+$ Calcd for $C_{24}H_{21}NO_5S_2$ 467.0861, found 467.0864; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 30/70, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 14.62 min (minor), t_R = 19.86 min (major); $[\alpha]^{20}_D$ = −105.6 (*c* = 1.0, $CHCl_3$; 94% ee); mp 130−135 °C.

*(R)-2-(1-(2-Methoxy-phenyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11ia**).* Following the general procedure with nitroolefin **1i** (54 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (69 mg, 98% yield, 94% ee). R_f 0.37 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.41 (m, 5H), 7.37−7.29 (m, 4H), 7.15−7.13 (m, 1H), 7.06−7.04 (m, 2H), 6.93−6.89 (m, 2H), 5.08 (dd, *J* = 12.9, 9.8 Hz, 1H), 4.86 (d, *J* = 10.2 Hz, 1H), 4.73 (dd, *J* = 12.9, 4.2 Hz, 1H), 4.53 (ddd, *J* = 10.2, 9.8, 4.2 Hz, 1H), 3.94 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 189.8, 157.7, 134.34, 134.25, 131.9, 130.1, 130.0, 129.9, 129.5, 129.3, 126.3 (x2), 122.5, 121.0, 111.2, 75.6, 66.6, 55.5, 42.6 ppm; IR (neat) 3059, 1711, 1555, 1495, 1441, 1378, 1247, 973, 745, 652 cm^{-1}; HRMS (EI-Magnetic Sector) *m*/*z* [M]$^+$ Calcd for $C_{24}H_{21}NO_5S_2$ 467.0861, found 467.0858; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 30/70, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 8.11 min (minor), t_R = 10.29 min (major); $[\alpha]^{20}_D$ = −128.8 (*c* = 1.0, $CHCl_3$; 94% ee); mp 110−113 °C.

*(S)-2-(1-(2-Thiophenyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11ja**).* Following the general procedure with nitroolefin **1j** (47 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (66 mg, 99% yield, 90% ee). R_f 0.40 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.36 (m, 8H), 7.29−7.24 (m, 3H), 6.99−6.96 (m, 2H), 4.88−4.81 (m, 2H), 4.69 (ddd, *J* = 7.8, 8.9, 5.1 Hz, 1H), 4.55 (d, *J* = 8.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 189.6, 137.7, 134.3, 130.3, 130.2, 129.6, 129.5, 127.6, 127.2, 126.09, 126.06, 125.9, 77.7, 69.8, 39.8 ppm; IR (neat) 1700, 1556, 1478, 1441, 1378, 1264, 1059, 963, 747, 673 cm^{-1}; HRMS (EI-Magnetic Sector) *m*/*z* [M]$^+$ Calcd for $C_{21}H_{17}NO_4S_3$ 443.0320, found 443.0322; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 15.72 min (minor), t_R = 23.07 min (major); $[\alpha]^{20}_D$ = −45.6 (*c* = 1.0, $CHCl_3$; 90% ee); mp 133−137 °C.

*(S)-2-(1-(2-Furyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11ka**).* Following the general procedure with nitroolefin **1k** (42 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (63 mg, 98% yield, 93% ee). R_f 0.40 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.39 (m, 9H), 7.32−7.31 (m, 2H), 6.35 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.27 (d, *J* = 3.3 Hz, 1H), 4.88−4.79 (m, 2H), 4.62 (d, *J* = 8.9 Hz, 1H), 4.51 (ddd, *J* = 8.9, 8.6, 4.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 189.7, 148.5, 143.2, 134.32, 134.29, 130.3, 130.2, 129.6, 129.5, 126.08, 126.06, 110.7, 109.5, 75.1, 66.9, 38.1 ppm; IR (neat) 2930, 1708, 1555, 1478, 1442, 1376, 1257, 982 cm^{-1}; HRMS (FAB-Magnetic Sector) *m*/*z* [M + H]$^+$ Calcd for $C_{21}H_{18}NO_5S_2$ 428.0626, found 428.0624; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 30/70, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 10.81 min (minor), t_R = 17.04 min (major); $[\alpha]^{20}_D$ = −64.9 (*c* = 1.0, $CHCl_3$; 93% ee); mp 114−122 °C decomposed.

*(R)-2-(1-(2-Naphthyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11la**).* Following the general procedure with nitroolefin **1l** (60 mg, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (67 mg, 92% yield, 86% ee). R_f 0.37 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88−7.81 (m, 3H), 7.74−7.71 (m, 1H), 7.53−7.49 (m, 2H), 7.48−7.33 (m, 7H), 7.30−7.25 (m, 2H), 7.07−7.05 (m, 2H), 5.02−4.91 (m, 2H), 4.60−4.55 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 189.6, 134.3, 134.2, 133.3, 133.1, 132.6, 130.3, 130.0, 129.6, 129.4, 129.1, 128.04, 127.96, 127.8, 126.7, 126.1, 126.0, 125.3, 77.0, 69.3, 44.5 ppm; IR (neat) 3064, 2926, 1710, 1684, 1561, 1478, 1441, 1425, 1379, 1251, 1069, 1023, 962, 911, 859, 828, 746, 668 cm^{-1}; HRMS (EI-Magnetic Sector) *m*/*z* [M]$^+$ Calcd for $C_{27}H_{21}NO_4S_2$ 487.0912, found 487.0910; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 30/70, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 26.03 min (major), t_R = 33.66 min (minor); $[\alpha]^{20}_D$ = −81.5 (*c* = 1.0, $CHCl_3$; > 99% ee); mp 165−175 °C decomposed.

*(S)-2-(1-(n-Propyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11ma**).* Following the general procedure with nitroolefin **1m** (35 μL, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a yellow solid (56 mg, 93% yield, 90% ee). R_f 0.45 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 5H), 7.44 (s, 5H), 4.73 (dd, *J* = 13.6, 4.090 Hz, 1H), 4.49 (dd, *J* = 13.6, 6.4 Hz, 1H), 4.34 (d, *J* = 7.2 Hz, 1H), 3.07−3.01 (m, 1H), 1.57−1.40 (m, 4H), 0.95 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.98, 190.96, 134.37, 134.32, 130.19, 130.16, 129.55, 129.52, 126.37, 126.32, 76.0, 67.6, 38.4, 32.0, 19.9, 13.8 ppm; IR (neat) 2960, 2930, 1707, 1552, 1478, 1441, 1381, 1266, 997, 971, 688 cm^{-1}; HRMS (FAB-Magnetic Sector) *m*/*z* [M + H]$^+$ Calcd for $C_{20}H_{22}NO_4S_2$ 404.0990, found 404.0988; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 6.57 min (minor), t_R = 9.44 min (major); $[\alpha]^{20}_D$ = −46.6 (*c* = 1.0, $CHCl_3$; 90% ee); mp 63−67 °C.

*(S)-2-(1-Isobutyl-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11na**).* Following the general procedure with nitroolefin **1n** (40 μL, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a colorless oil (60 mg, 96% yield, 86% ee). R_f 0.48 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 5H), 7.44 (s, 5H), 4.74 (dd, *J* = 13.7, 4.1 Hz, 1H), 4.49 (dd, *J* = 13.7, 6.1 Hz, 1H), 4.34 (d, *J* = 6.8 Hz, 1H), 3.11−3.05 (m, 1H), 1.78−1.70 (m, 1H), 1.40 (t, *J* = 7.1 Hz, 2H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.05, 191.02, 134.4, 134.3, 130.18, 130.15, 129.55, 129.51, 126.4, 126.3, 76.3, 67.5, 38.8, 36.6, 25.2, 22.6, 22.0 ppm; IR (neat) 2962, 2918, 1708, 1552, 1478, 1441, 1382, 1270, 1208, 979, 744, 669, 640 cm^{-1}; HRMS (EI-Magnetic Sector) *m*/*z* [M]$^+$ Calcd for $C_{21}H_{23}NO_4S_2$ 417.1069, found 417.1066; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 5.64 min (minor), t_R = 8.25 min (major); $[\alpha]^{20}_D$ = −48.6 (*c* = 1.0, $CHCl_3$; 86% ee).

*(S)-2-(1-(2-Phenylethyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11oa**).* Following the general procedure with nitroolefin **1o** (48 μL, 0.30 mmol), *S*,*S*′-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (66 mg, 95% yield, 90% ee). R_f 0.47 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.43 (m, 10H), 7.32−7.29 (m, 2H), 7.24−7.17 (m, 3H), 4.76 (dd, *J* = 13.7, 4.1 Hz, 1H), 4.52 (dd, *J* = 13.7, 6.4 Hz, 1H), 4.37 (d, *J* = 7.2 Hz, 1H), 3.10−3.04 (m, 1H), 2.81−2.69 (m, 2H), 1.94−1.80 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.93, 190.86, 140.1, 134.4, 134.3, 130.22, 130.21, 129.56, 129.55, 128.8, 128.3, 126.5, 126.3, 126.2, 75.9, 67.4, 38.2, 33.0, 31.6 ppm; IR (neat) 2919, 1704, 1551, 1478, 1442, 1382, 1271, 970, 746, 688 cm^{-1}; HRMS (FAB-Magnetic Sector) *m*/*z* [M + H]$^+$ Calcd for $C_{25}H_{24}NO_4S_2$ 466.1147, found 466.1146; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/

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min, λ = 254 nm, t_R = 13.27 min (minor), t_R = 17.46 min (major); $[\alpha]^{20}_D$ = −40.9 (c = 1.0, $CHCl_3$; 90% ee); mp 94−98 °C.

*(S)-2-(1-(n-Hexyl)-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11pa**).* Following the general procedure with nitroolefin **1p** (47 μL, 0.30 mmol), *S,S′*-diphenyl dithiomalonate **2a** (43 mg, 0.15 mmol) and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a white solid (65 mg, 97% yield, 86% ee). R_f 0.60 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.43 (m, 10H), 4.74 (dd, J = 13.6, 4.0 Hz, 1H), 4.50 (dd, J = 13.6, 6.5 Hz, 1H), 4.35 (d, J = 7.3 Hz, 1H), 3.05−2.99 (m, 1H), 1.59−1.48 (m, 2H), 1.47−1.37 (m, 2H), 1.35−1.25 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.00, 190.98, 134.4, 134.3, 130.20, 130.17, 129.55, 129.52, 126.34, 126.28, 76.0, 67.5, 38.6, 31.5, 29.8, 29.0, 26.5, 22.5, 14.1 ppm; IR (neat) 2957, 2932, 2856, 1707, 1551, 1478, 1441, 1380, 967, 746, 688, 668 cm^{-1}; HRMS (EI-Magnetic Sector) m/z $[M]^+$ Calcd for $C_{23}H_{27}NO_4S_2$ 445.1382, found 445.1383; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 5.79 min (minor), t_R = 7.90 min (major); $[\alpha]^{20}_D$ = −41.5 (c = 1.0, $CHCl_3$; 86% ee); mp 68−73 °C.

*(S)-2-(1-(n-Hexyl)-2-nitro-ethyl)-malonic acid bis(4-methoxyphenyl) dithioester (**11pb**).* Following the general procedure with nitroolefin **1p** (47 μL, 0.30 mmol), *S,S′*-bis-4-methoxyphenyl dithiomalonate **2b** (52 mg, 0.15 mmol), and catalyst **9f** (3.3 mg, 5 mol %), the desired product was obtained as a colorless oil (72 mg, 95% yield, 85% ee). R_f 0.34 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.33 (m, 4H), 6.99−6.95 (m, 4H), 4.73 (dd, J = 13.6, 4.0 Hz, 1H), 4.48 (dd, J = 13.6, 6.6 Hz, 1H), 4.32 (d, J = 7.1 Hz, 1H), 3.835 (s, 3H), 3.832 (s, 3H), 3.03−2.97 (m, 1H), 1.58−1.48 (m, 2H), 1.44−1.36 (m, 2H), 1.33−1.26 (m, 6H), 0.90 (t, J = 6.9 Hz, 3H). ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.10, 192.06, 161.19, 161.16, 136.06, 136.00, 116.96, 116.90, 115.17, 115.14, 76.1, 66.9, 55.4, 38.6, 31.5, 29.9, 29.0, 26.5, 22.5, 14.1 ppm; IR (neat) 2932, 2857, 1707, 1593, 1552, 1496, 1440, 1380, 1291, 1251, 1174, 1029, 968, 826, 668 cm^{-1}; HRMS (EI-Magnetic Sector) m/z $[M]^+$ Calcd for $C_{25}H_{31}NO_6S_2$ 505.1593, found 505.1597; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 30/70, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 10.10 min (minor), t_R = 12.56 min (major); $[\alpha]^{20}_D$ = −43.2 (c = 1.0, $CHCl_3$; 85% ee).

*(S)-2-(1-Cyclohexyl-2-nitro-ethyl)-malonic acid diphenyl dithioester (**11qa**).* Following the general procedure with nitroolefin **1q** (21 μL, 0.15 mmol), *S,S′*-diphenyl dithiomalonate **2a** (22 mg, 0.075 mmol) and catalyst **9f** (3.3 mg, 10 mol %), the desired product was obtained as a white solid (22 mg, 65% yield, 81% ee). R_f 0.47 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.41 (m, 10H), 4.82 (dd, J = 14.8, 3.2 Hz, 1H), 4.60 (dd, J = 14.8, 7.1 Hz, 1H), 4.42 (d, J = 5.4 Hz, 1H), 3.04−3.00 (m, 1H), 1.83−1.69 (m, 5H), 1.57−1.50 (m, 1H), 1.31−1.26 (m, 1H), 1.23−1.03 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 191.1, 134.5, 134.3, 130.2, 130.1, 129.6, 129.5, 126.4, 126.3, 74.9, 65.7, 44.3, 40.0, 30.6, 29.8, 26.32, 26.25, 26.0 ppm; IR (neat) 2930, 2853, 1706, 1553, 1442, 1375, 1264, 745, 619 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z $[M + H]^+$ Calcd for $C_{23}H_{26}NO_4S_2$ 444.1303, found 444.1301; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 20/80, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 5.45 min (minor), t_R = 7.68 min (major); $[\alpha]^{20}_D$ = −80.6 (c = 1.0, $CHCl_3$; 81% ee); mp 80−85 °C.

*(S)-2-(1-Cyclohexyl-2-nitro-ethyl)-malonic acid bis(4-methoxyphenyl) dithioester (**11qb**).* Following the general procedure with nitroolefin **1q** (21 μL, 0.15 mmol), *S,S′*-bis-4-methoxyphenyl dithiomalonate **2b** (26 mg, 0.075 mmol) and catalyst **9f** (3.3 mg, 10 mol %), the desired product was obtained as a light yellow oil (31 mg, 82% yield, 82% ee). R_f 0.27 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.35 (m, 2H), 7.34−7.31 (m, 2H), 6.99−6.94 (m, 4H), 4.81 (dd, J = 14.8, 3.1 Hz, 1H), 4.59 (dd, J = 14.8, 7.2 Hz, 1H), 4.40 (d, J = 5.3 Hz, 1H), 3.835 (s, 3H), 3.828 (s, 3H), 3.01−2.97 (m, 1H), 1.82−1.77 (m, 3H), 1.73−1.68 (m, 2H), 1.54−1.48 (m, 1H), 1.24−1.19 (m, 2H), 1.17−1.01 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 192.3, 161.21, 161.15, 136.2, 136.0, 117.0, 116.9, 115.2, 115.1, 75.1, 65.1, 55.4, 44.3, 40.0, 30.6, 29.8, 26.32, 26.26, 26.0 ppm; IR (neat) 2924, 1706, 1593, 1559, 1496, 1464, 1378, 1295, 1252, 1174, 1097, 827, 668, 649 cm^{-1}; HRMS (EI-Magnetic Sector) m/z $[M]^+$ Calcd for $C_{25}H_{29}NO_6S_2$ 503.1436, found 503.1439; HPLC Chiracel OD-H column, *i*-PrOH/*n*-hexane = 30/70, 25 °C, 1.0 mL/min, λ = 254 nm, t_R = 8.95 min (minor), t_R = 10.30 min (major); $[\alpha]^{20}_D$ = −83.9 (c = 1.0, $CHCl_3$; 82% ee).

*(3S,4R)-S-Phenyl 2-oxo-4-phenylpyrrolidine-3-carbothioate (**12**).*[8c] Adduct **11aa** (118 mg, 0.27 mmol, 1.0 equiv) was dissolved in 5.0 mL of AcOH. A freshly activated zinc powder (178 mg, 2.72 mmol, 10 equiv) was added and the mixture was stirred at 25 °C under an argon atmosphere for 2 h. After this period, $TiCl_3$ (30 μL, 0.027 mmol, 0.1 equiv; 12% solution in 5% HCl) was added and the resulting mixture was stirred for additional 1 h. The mixture was filtered through a pad of Celite, the filter cake was washed with EtOAc and the obtained solution was concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel to obtain the product **12** as a white solid (72 mg, 90% yield). R_f 0.24 (ethyl ether:hexane = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.28 (m, 7H), 7.25−7.18 (m, 4H), 4.06 (dd, J = 15.6, 8.0 Hz, 1H), 3.79−3.75 (m, 2H), 3.38 (dd, J = 9.8, 7.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 172.2, 140.3, 134.5, 129.8, 129.3, 129.1, 127.7, 127.05, 127.01, 62.7, 48.0, 44.1 ppm; IR (neat) 3237 (br signal), 3095, 2917, 2106, 1692, 1478, 1419, 1265, 1017, 701 cm^{-1}; HRMS (FAB-Magnetic Sector) m/z $[M + H]^+$ Calcd for $C_{17}H_{16}NO_2S$ 298.0902, found 298.0901; $[\alpha]^{20}_D$ = −218.5 (c = 1.0, $CHCl_3$); mp 128−129 °C.

*(3R)-4-Amino-3-phenylbutanoic acid hydrochloride (**13**).* The lactam **12** (48 mg, 0.16 mmol) was refluxed in 6 N HCl (0.5 mL) for 24 h. After cooling, the reaction mixture was washed with EtOAc. The volatile components were removed under reduced pressure to give (*R*)-Phenibut (**13**) in HCl salt form as a white solid (29 mg, 85% yield). Analytical data are consistent with reported values.[14c] ^{1}H NMR (500 MHz, D_2O) δ 7.48−7.45 (m, 2H), 7.41−7.38 (m, 3H), 3.48−3.39 (m, 2H), 3.30−3.25 (m, 1H), 2.91−2.86 (m, 1H), 2.81−2.76 (m, 1H) ppm; ^{13}C NMR (125 MHz, D_2O) δ 175.4, 138.3, 129.4, 128.3, 127.9, 43.8, 39.9, 38.2 ppm; MS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{14}NO_2$ 180.102, found 180.098; $[\alpha]^{20}_D$ = +3.1 (c = 2.0, 1 M HCl).

*(3R)-Phenyl 4-nitro-3-phenylbutanethioate (**14**).* To a solution of **11aa** (57 mg, 0.13 mmol, 1 equiv) and H_2O (14 μL, 0.78 mmol, 6 equiv) in THF (1.3 mL), Et_3N (5 μL, 0.03 mmol, 0.2 equiv) was added. The reaction mixture was stirred at 60 °C for 2 h. The resulting mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel to obtain the product **14** as a white solid (37 mg, 94% yield). Analytical data are consistent with reported values.[21] R_f 0.45 (ethyl acetate:hexane = 1:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.34 (m, 5H), 7.33−7.27 (m, 3H), 7.24−7.22 (m, 2H), 4.76 (dd, J = 12.7, 6.8 Hz, 1H), 4.67 (dd, J = 12.7, 8.1 Hz, 1H), 4.09−4.03 (m, 1H), 3.11 (d, J = 7.1 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 137.8, 134.4, 129.8, 129.3, 129.2, 128.2, 127.4, 126.8, 79.1, 46.2, 40.5 ppm; IR (neat) 1700, 1552, 1441, 1381, 981, 751, 657, 639 cm^{-1}; MS (ESI-QTOF) m/z $[M + Na]^+$ Calcd for $C_{16}H_{15}NNaO_3S$ 324.067, found 324.060; $[\alpha]^{20}_D$ = −67.2 (c = 0.5, $CHCl_3$); mp 60−63 °C.

*(R)-4-Nitro-3-phenylbutanal (**15**).*[7c] Compound **14** (37 mg, 0.12 mmol, 1 equiv) was dissolved in 1 mL of dry acetone under an argon atmosphere. To the solution, fresh activated 4 Å molecular sieve (15 mg) and Pd/C (10% Pd, 26 mg, 20 mol %) were added. Triethylsilane (0.36 mmol, 58 μL, 3 equiv) was added dropwise over 5 min, then stirred at room temperature for 0.5 h. The reaction mixture was filtered through a pad of Celite and the solvent was removed at reduced pressure. The crude material was purified by flash column chromatography on silica gel to obtain the product **15** as a colorless oil (17 mg, 74% yield). Analytical data are consistent with reported values.[14d] R_f 0.27 (ethyl acetate:hexane = 1:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (t, J = 1.0 Hz, 1H), 7.37−7.33 (m, 2H), 7.31−7.28 (m, 1H), 7.25−7.22 (m, 2H), 4.69 (dd, J = 12.5, 7.2 Hz, 1H), 4.62 (dd, J = 12.5, 7.6 Hz, 1H), 4.09 (p, J = 7.3 Hz, 1H), 2.96 (ddd, J = 6.9, 3.0, 1.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 138.1, 129.3, 128.2, 127.4, 79.4, 46.4, 38.0 ppm; IR (neat) 2925, 2852, 1731, 1556, 1460, 1381, 1093, 668, 635 cm^{-1}; MS (ESI-QTOF) m/z $[M + MeOH + Na]^+$ Calcd for $C_{11}H_{15}NNaO_4$ 248.090, found 248.084; $[\alpha]^{20}_D$ =

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+7.1 (c = 1.0, $CHCl_3$). [lit.[14d] $[\alpha]^{20}_D$ = +8.0 (c = 1.0, $CHCl_3$; 93.8% ee) for *R* enantiomer].

(R)-4-Phenyl-2-pyrrolidinone (16).[8c] Compound **14** (18 mg, 0.06 mmol, 1.0 equiv) was dissolved in 1.2 mL of AcOH. A freshly activated zinc powder (39 mg, 0.60 mmol, 10 equiv) was added and the mixture was stirred at 25 °C under an argon atmosphere for 2 h. After this period, $TiCl_3$ (7 μL, 0.006 mmol, 0.1 equiv; 12% solution in 5% HCl) was added and the resulting mixture was stirred for additional 1 h. The mixture was filtered through a pad of Celite, the filter cake was washed with EtOAc and the obtained solution was concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel to obtain the product **16** as a white solid (8 mg, 82% yield, 91% ee). Analytical data are consistent with reported values.[16] R_f 0.33 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.34 (m, 2H), 7.29−7.26 (m, 3H), 6.42 (br s, 1H), 3.81−3.78 (m, 1H), 3.74−3.67 (m, 1H), 3.43 (dd, J = 9.3, 7.4 Hz, 1H), 2.75 (dd, J = 16.9, 8.9 Hz, 1H), 2.52 (dd, J = 16.9, 8.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 142.1, 128.9, 127.2, 126.8, 49.5, 40.4, 37.9 ppm; IR (neat) 3310 (br signal), 3064, 2924, 1646, 1488, 1453, 1372, 1293, 1265, 1044, 757, 700 cm^{-1}; MS (ESI-QTOF) m/z $[M + Na]^+$ Calcd for $C_{10}H_{11}NNaO$ 184.074, found 184.069; HPLC Chiralpak IA column, *i*-PrOH/*n*-hexane = 10/90, 25 °C, 1.0 mL/min, λ = 210 nm, t_R = 10.46 min (major), t_R = 11.64 min (minor); $[\alpha]^{20}_D$ = −30.0 (c = 0.3, MeOH; 91% ee); The absolute configuration was determined to be *R* by the comparison of the optical rotation and HPLC spectra with reported data [lit.[16] $[\alpha]^{20}_D$ = −31.7 (c = 0.29, MeOH; 93% ee); HPLC Chiralpak IA column, *i*-PrOH/*n*-hexane = 10/90, 25 °C, 1.0 mL/min, λ = 210 nm, t_R = 10.6 min (major), t_R = 12.2 min (minor)].

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00218.

^{1}H NMR, ^{13}C NMR spectra for all products and HPLC traces for ee determination. (PDF)

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Notes

The authors declare no competing financial interest.

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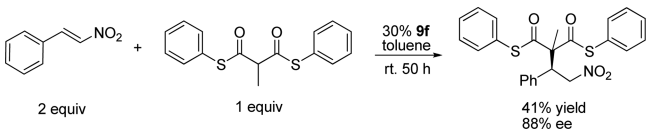

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