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Organocatalytic asymmetric addition of aliphatic thiols to nitro olefins and nitrodienes

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ABSTRACT

The *N*-3,5-bis(trifluoromethyl)phenyl thiourea derivative of readily available chiral 1-benzyl-3-aminopyrrolidine was an effective organocatalyst for the asymmetric sulfa-Michael reaction. The adducts of aliphatic thiols to nitro olefins and nitrodienes were formed in good yields and with up to 87% ee in the presence of 2.5 mol % of the organocatalyst.

1. Introduction

The direct addition of sulfur-centered nucleophiles onto Michael acceptors is a straightforward approach to C–S bond formation.[1] The discovery of *Cinchona* alkaloid catalyzed sulfa-Michael reactions is a milestone of organocatalysis.[2] Reactions using both metal- and organocatalysts gave access to the asymmetric sulfa-Michael adducts of thiols to unsaturated amides,[3] aldehydes,[4] cyclic,[5] linear[6] and branched α,β-unsaturated ketones.[7] Moreover, asymmetric additions of thiols to highly active Michael acceptors, such as nitro olefins, give useful intermediates for the synthesis of 1,2-aminothiols. This synthetic approach exploits the reaction of thioacetic acid with aromatic or aliphatic nitro olefins.[8] As an alternative to this addition, we were interested in the development of a new organocatalytic protocol for the sulfa-Michael reaction of thioalkyl nucleophiles.

The successful enantioselective additions of aromatic thiols to Michael acceptors have already been accomplished in the presence of thiourea-type catalysts.[3f,g,9] Aliphatic thiols[10] are characterized by reduced acidity in comparison to their aromatic counterparts (e.g., thiophenol's pK_a is 6.52, for benzyl mercaptan, pK_a = 9.43).[11] While thiophenols react with nitro olefins without a catalyst,[12] analogous reactions of mercaptans require prolonged reaction times or an additional basic catalyst. Therefore, the activation of a nucleophile by a basic function together with the binding of an acceptor by a bifunctional catalyst should facilitate the reaction. However, organization of the transition state resulting from the binding of the aliphatic thiol by an amino group in the typically tested *Cinchona* derivatives has been suggested to be poor.[13] In fact, relatively weaker interactions between the basic moiety of the catalyst and the aliphatic thiol, in addition to the conformational lability of the C(sp^3)–S bond seems to be responsible for the failure of the previously developed catalytic systems. Consequently, only a few isolated examples of such sulfa-Michael reactions have been reported[14] and the direct enantioselective addition of aliphatic thiols to nitro alkenes remains a difficult task.[15] Recently, a derivative of a *Cinchona* alkaloid has been designed and successfully applied to the enantioselective addition of benzyl type thiols to nitro alkenes.[13] All of these facts encouraged us to report our new results on the catalyzed enantioselective sulfa-Michael reaction of demanding aliphatic thiols and nitro alkenes.

2. Results and discussion

First, quinine **1** (Fig. 1) was examined in the test reaction of benzyl thiol with *trans*-β-nitrostyrene and, similar to the reported result,[14] practically no enantioselectivity was observed. The introduction of an extra donor of a hydrogen bond in cupreine **2** or in the *epi*-quinine based thiourea **3** also led to a nearly racemic product. These results were in agreement with the observations of Connon.[13] Changing the chiral core from the *Cinchona* alkaloid to *trans*-1,2-diaminocyclohexane (Takemoto catalyst **4** and bis-thiourea **5**), gave no satisfactory results. Thus, we decided to devise a new catalyst that activated both the thiol and nitro alkene with a chiral unit that was structurally different from the classical (privileged) one. We noted that the simple, commercially available (*R*)-(−)-1-benzyl-3-aminopyrrolidine[16] offers a useful scaffold for the bifunctional thioureas **6** and **7**. The opposite enantiomer of *N*-3,5-bis(trifluoromethyl)phenyl thiourea derivative **7** has already been tested in the organocatalytic asymmetric hetero-Diels–Alder reaction but it was found to be ineffective.[17] However, Bolm et al. have recently described the successful use of bifunctional catalysts of similar structures in stereoselective quaternary carbon–carbon bond formations.[18] Both compounds **6** and **7** were easily prepared from (*R*)-1-benzyl-3-aminopyrrolidine and the corresponding isothiocyanates in a simple, one-step procedure. The

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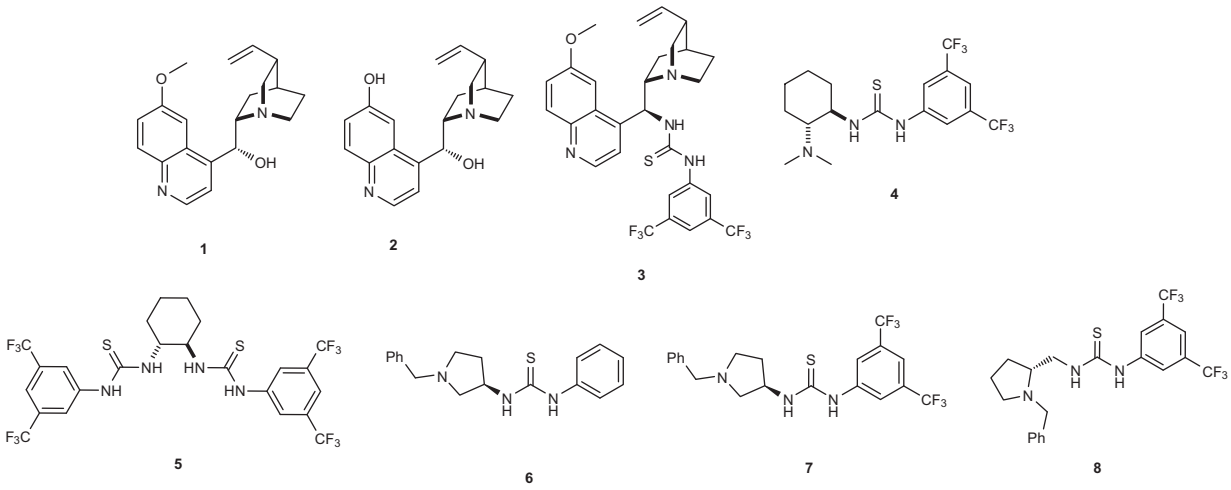
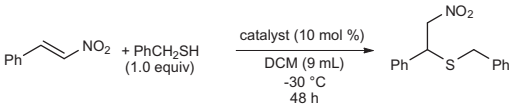


Figure 1. Structures of catalysts tested.

application of 10 mol % of thiourea **7** in dichloromethane at −30 °C gave the desired sulfa-Michael adduct in 81% yield and 70% ee. In contrast, the closely related catalyst **8**, based on another five-membered nitrogen heterocycle with a proline core, leading to the product with only 4% ee (Table 1).

Table 1
Screening of catalysts in the reaction of benzyl mercaptan and β-nitrostyrene[a]



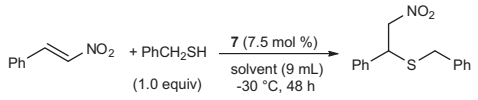
Catalyst[b]	Yield[c] (%)	ee[d] (%)
1	84	7
2	82	2
3	71	14
4	97	17
5	84	0
6	78	41
7	81	70
8	79	4

[a] Reactions were performed on a 0.33 mmol scale in 9.0 mL of dichloromethane at −30 °C for 48 h, applying 10 mol % of catalyst.
[b] Structures of the catalysts are shown in Figure 1.
[c] Isolated yield after flash chromatography.
[d] Determined by chiral HPLC.

Similarity in the results between thiourea **7** and Takemoto catalyst **4** suggests that effective hydrogen bonding[19] also occurs in our case. This effect can be fine-tuned by the proper choice of solvent and concentration. Thus, the reactions in different solvents were tested and the results obtained clearly indicate the superiority of halogenated alkanes over ethers and acetonitrile (Table 2).

When the reaction was performed in trifluorotoluene, it was more effective than in dichloromethane. However, due to the high melting point of $PhCF_3$ (−30 °C) the system turned out to be partially non-homogenous and thus precluded potential optimization by lowering the temperature. For practical reasons, dichloromethane was chosen for further examination. Generally, the test reactions were run with equimolar amounts of both β-nitrostyrene and benzyl mercaptan, using 7.5 mol % of **7** at −30 °C. In order to examine the influence of possible self-association of the catalyst, we diluted the reaction mixture with different volumes of solvent, running it at 2.75 and 16.5 mM of **7**. The product was obtained in 86% yield, 67% ee and 82% yield, 69% ee, respectively. Accordingly,

Table 2
Influence of the solvent in reaction of benzyl mercaptan and β-nitrostyrene[a]



Entry	Solvent	Yield [b] (%)	ee[c] (%)
1	$ClCH_2CH_2Cl$	76	61
2	CH_2Cl_2	86	67
3	$CHCl_3$	83	64
4[d]	CCl_4	86	68
5	$PhCF_3$	84	75
6	$CH_2Cl_2/PhCF_3$ (1:1, v/v)	84	67
7	$PhCH_3$	81	60
8	Et_2O	71	38
9	*t*-BuOMe	82	27
10	DME	63	24
11	CH_3CN	90	16

[a] Unless otherwise stated, reactions were performed on a 0.33 mmol scale in 9.0 mL of solvent at −30 °C for 48 h, applying 7.5 mol % of catalyst **7** (2.75 mM).
[b] Isolated yield after flash chromatography.
[c] Determined by chiral HPLC.
[d] Reaction was performed at −20 °C.

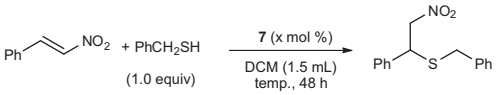
catalyst association effects can be excluded. When the transformation was performed at 0 °C, the adduct was formed in 97% yield and 56% ee after 24 h. Lowering the temperature increased the stereoselectivity and at −30 °C we obtained 72% ee while at −80 °C, 76% ee was obtained (Table 3).

Next, we examined the influence of the catalyst loading. The test reaction in the presence of 2.5 and 20 mol % of **7** gave 76 and 77% ee, respectively. The effectiveness of the developed catalyst was rather invariable for a broad range of loadings (Table 3).

In the final step of the optimization process, the influence of the thiol/β-nitrostyrene ratio was examined (Table 4). Even when 2 or 5 equiv of benzyl thiol was used, the enantioselectivity remained unchanged (Table 4, entries 2 and 4). The reaction worked well when the total volume of solvent was decreased six times (entries 2 and 3). Therefore, the efficiency of the catalytic system remained unaffected by an increase in the thiol concentration.

Bearing in mind that lowering the temperature from −30 to −80 °C did not improve the enantioselectivity by much (76 vs 72% ee), for practical reasons we performed further experiments at −30 °C, applying 2.5 mol % of catalyst **7**.

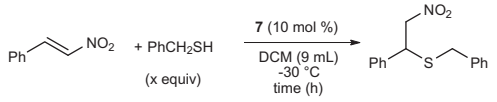
Table 3
Influence of catalyst loading for the yield and ee in the test reaction[a]



Entry	**7** (mol %)	Temp (°C)	Yield[b] (%)	ee[c,d] (%)
1	1.0	−30	83	70
2	2.5	−30	82	72
3	2.5	−80	84	76
4	7.5	−80	79	77
5	10	−80	93	78
6	20	−80	90	77

[a] Reactions were performed on a 0.33 mmol scale in 1.5 mL of dichloromethane for 48 h.
[b] Isolated yield after flash chromatography.
[c] Determined by chiral HPLC.
[d] Configuration (*S*) of the main product was ascribed by analogy to the product of a known Michael adduct of this type.[13]

Table 4
Influence of the thiol/β-nitrostyrene ratio for yield and ee[a]



Entry	Thiol/nitrostyrene ratio	Time (h)	Yield[b] (%)	ee [c] (%)
1	1.2	48	99	69
2	2.0	48	99	73
3[d]	2.0	24	79	71
4	5.0	48	96	73

[a] Unless otherwise stated, reactions were performed on a 0.33 mmol scale in 9 mL of dichloromethane at −30 °C applying 10 mol % of **7**.
[b] Isolated yield after flash chromatography.
[c] Determined by chiral HPLC.
[d] Reaction performed in 1.5 mL of dichloromethane.

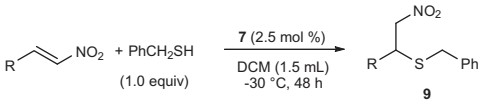
The absolute configuration of the sulfa-Michael adducts obtained in the presence of (*R*)-**7** was determined to be (*S*) by comparison the sign of the specific rotation with that for the known compounds [e.g., (*S*)-**10a**].[13] Moreover, the order of elution of the enantiomers from the identical chiral stationary phases was the same as previously described by Connon.[13] For further details, see Section 4.

With the optimized protocol in hand, we studied the scope of the addition of the benzyl mercaptan to different nitro olefins (Table 5). The amount of solvent used depended on the solubilities of the reactants and the products.

Reactions of various aromatic nitro olefins with benzyl mercaptan led to the products with enantiomeric excesses ranging from 50% (entry 8) to 75% (entry 4) in good to excellent yields. These results showed that the character of the atom or group located at the *para* position of the aromatic ring had only a little influence on the enantioselectivity. Indeed, the application of unsubstituted (entry 1), 4-methoxy- (entry 9), and 4-fluoro- (entry 2) derivatives gave 72, 69, and 69% ee, respectively. Moreover, 2-chloro and 2,6-dichloro derivatives did not give very different results (entries 5 and 7), although a diminished enantioselectivity was seen for the 4-nitro derivative (entry 8). Heteroaromatic (entry 11) and alkyl (entry 12) nitro olefins gave products with good yields and moderate ee values.

In order to gain a better understanding of the activation mode exerted by catalyst **7**, substrates with hydrogen bond donor/acceptor groups, such as phenolic OH and indolyl NH were tested (entries 13 and 14). The observed ee values were much less than those obtained with the other nitro olefins (entries 1–12). It seems

Table 5
Scope of the nitro olefins in the reaction with benzyl mercaptan catalyzed by **7**[a]



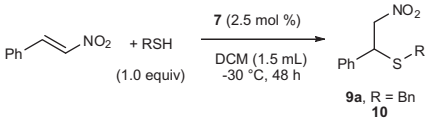
Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	Ph	**9a**	82	72
2	4-F-C_6H_4	**9b**	95	69
3[d]	4-Br-C_6H_4	**9c**	78	70
4	4-Cl-C_6H_4	**9d**	81	75
5	2,6-Cl_2-C_6H_3	**9e**	92	66
6[e]	2,4-Cl_2-C_6H_3	**9f**	88	68
7	2-Cl-C_6H_4	**9g**	85	67
8[f]	4-NO_2-C_6H_4	**9h**	83	50
9	4-MeO-C_6H_4	**9i**	83	69
10[e]	2-Naphthyl	**9j**	92	70
11	2-Thienyl	**9k**	92	68
12	Cyclohexyl	**9l**	87	63
13[g]	2-OH-C_6H_4	**9m**	74	26
14[f]	3-Indolyl	**9n**	50	0

[a] Unless otherwise noted, reactions were performed on a 0.33 mmol scale in 1.5 mL of dichloromethane at −30 °C for 48 h applying 2.5 mol % of catalyst **7**.
[b] Isolated yield after flash chromatography.
[c] Determined by chiral HPLC.
[d] 5 mL of dichloromethane was used.
[e] 2 mL of dichloromethane was used.
[f] 9 mL of dichloromethane was used.
[g] 7 mL of dichloromethane was used.

that NH and OH can specifically interact with the thiourea functionality of **7** and such competitive withdrawal of the catalyst is responsible for a decrease in the ee.[19a]

Further studies were focused on the effects caused by the structurally different alkyl thiols in the catalyzed reaction of β-nitrostyrene. Hence, benzyl-type, thioglycolic acid methyl ester and cyclohexyl thiols were screened (Table 6).

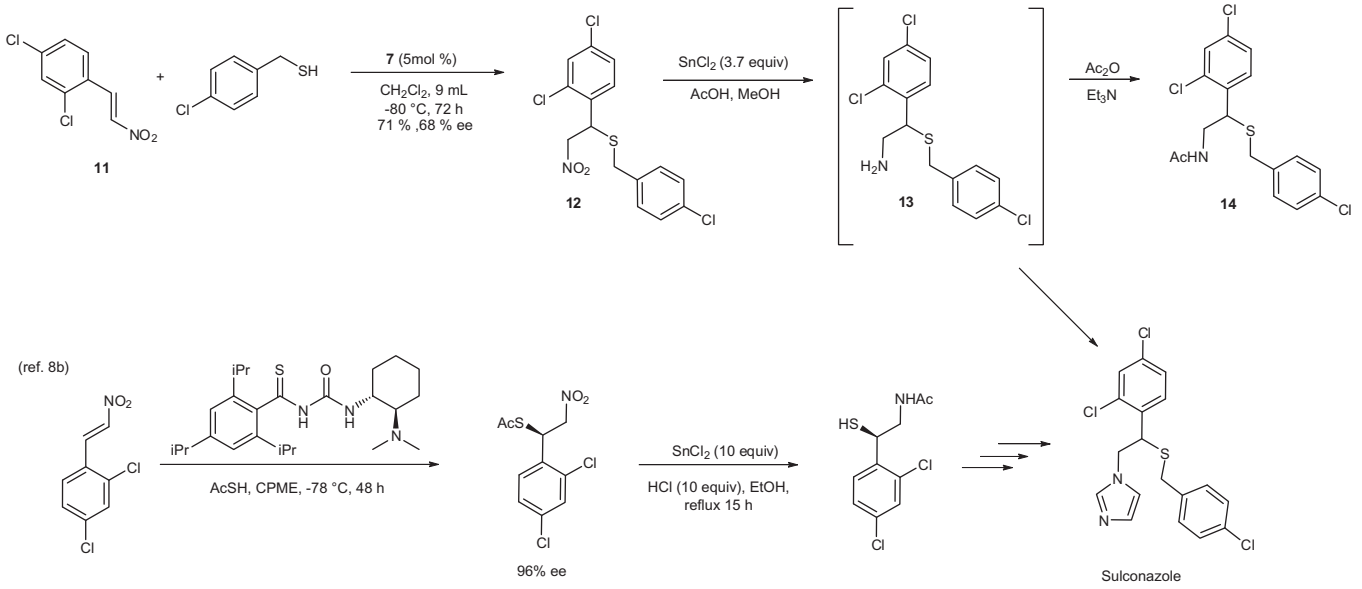
Table 6
Scope of the thiols in the reaction of β-nitrostyrene catalyzed by **7**[a]



Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	Bn	**9a**	82	72
2	4-MeO-$C_6H_4CH_2$	**10a**	79	72
3	4-*t*-Bu-$C_6H_4CH_2$	**10b**	85 (76)[d]	76 (87)[d]
4	4-Cl-$C_6H_4CH_2$	**10c**	73	60
5[e]	MeOC(O)CH_2	**10d**	84 (76)[d]	43 (35)[d]
6	Cyclohexyl	**10e**	30	36
7[e]	$HOCH_2CH_2$	**10f**	55	22

[a] Unless otherwise noted, reactions were performed on a 0.33 mmol scale in 1.5 mL of dichloromethane at −30 °C for 48 h applying 2.5 mol % of catalyst **7**.
[b] Isolated yield after flash chromatography.
[c] Determined by chiral HPLC.
[d] Reaction was performed at −80 °C.
[e] Reaction was performed on a 0.5 mmol scale in 2.5 mL of dichloromethane.

The *para*-substituted benzyl mercaptans showed similar activities in the test reaction and gave products with small variations in ee compared to the unsubstituted nucleophile. Better stereoselectivity was achieved for 4-*tert*-butylbenzyl mercaptan (Table 6, entry 3), especially when the reaction was performed at −80 °C with 2.5 mol % of catalyst. It is worth mentioning that a similar result (88% ee) was observed in the same reaction in the presence of 5 mol % of the alkaloid catalyst.[13] Moderate ee values were obtained in the case of methyl thioglycolate, and only 22% ee for



Scheme 1. Synthetic approaches to *Sulconazole*.

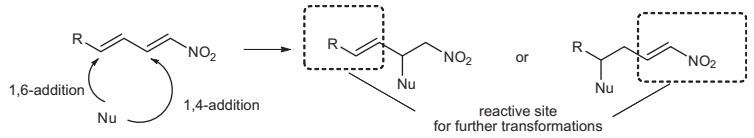


Figure 2. 1,4- and 1,6-addition to nitrodienes.

2-mercaptoethanol. Such observation can again be rationalized by the ability of the nucleophile to compete with the nitro group for the hydrogen bond to the catalyst. If the lower stereocontrol was caused by the higher reactivity of the thiol, the reaction of methyl thioglycolate performed at −80 °C should have assured better chirality transfer. However, at this temperature the product was obtained in only 35% ee.

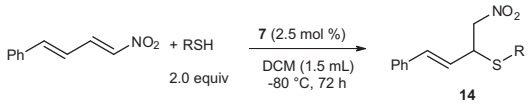
The more sterically congested, and thus more demanding, nucleophiles such as cyclohexanethiol turned out to be non-compatible with the catalytic system, generating the product with 36% ee and 30% yield.

For an extension of the reaction scope, we carried out the addition of *p*-chlorobenzyl mercaptan to the acceptor **11** (Scheme 1, upper part). The oily sulfa-Michael adduct **12** was obtained in 71% yield and 68% ee. The subsequent reduction of **12** with the $SnCl_2$ dihydrate[20] followed by acylation led to **14** in 41% yield over two steps. However, the crude amine **13** can be directly transformed into the respective imidazole antifungal drug, *Sulconazole*. The reported synthesis of *Sulconazole* (Scheme 1, lower part) required additional steps (thiol deprotection, alkylation of the sulfur atom with *p*-chlorobenzyl bromide and finally hydrolytic removal of the acyl function) to give the free amine necessary for the formation of the imidazole ring.[8b] The proposed direct methodology offers an alternative and shorter approach to the synthesis of *Sulconazole* and its derivatives.

Finally, we tested the catalytic reaction of aliphatic thiols with nitrodienes. Although one can speculate as to whether the nucleophile adds at the β- or δ-position of the nitrodiene,[21] the resulting adduct would be amenable for further transformations at the remaining double bond (either in the reactions of α,β-conjugated system or cycloadditions, Fig. 2).[22]

In order to establish the regio- and stereoselectivity of the addition of the sulfur centered nucleophiles to nitrodienes in the presence of **7**, these dienes were reacted with various aliphatic thiols (Table 7). The reaction was performed under the usual conditions (−30 °C) and gave the product **14a** with 57% ee. Hence, with the aim of obtaining better enantioselectivity in the next set of experiments, we lowered the temperature to −80 °C. Due to the reduced activity of the nitrodienes in comparison to the nitro olefins, 2 equiv of the respective mercaptan was used. Excess thiol was

Table 7
Addition of thiols to nitrodienes catalyzed by **7**[a]



Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	Bn	**14a**	93	67
2[d]	Bn	**14b**	—	70
3	4-MeO-$C_6H_4CH_2$	**14c**	68	70
4	4-*t*Bu-$C_6H_4CH_2$	**14d**	85	82
5	2-furylmethyl	**14e**	64	78
6	4-Cl-$C_6H_4CH_2$	**14f**	75	58
7	$MeOC(O)CH_2$	**14g**	92	5

[a] Reactions were performed on a 0.33 mmol scale in 1.5 mL of dichloromethane at −80 °C for 72 h applying 2.5 mol % of catalyst **7**.
[b] Isolated yield after flash chromatography.
[c] Determined by chiral HPLC.
[d] Nitrodiene: 4-MeO–C_6H_4CH=CH–CH=CH–NO_2 was used. An attempt to isolate pure product by chromatography failed. Ee was determined by HLPC after column chromatography.

also used in order to force the reaction to completion and to avoid the problematic separation of the unreacted nitrodiene from the desired product with nearly identical R_f values. The results are presented in Table 7.

Both benzyl-type compounds and 2-furylmethanethiol reacted well, leading exclusively to the respective 1,4-adducts[21c,23] in good yields and enantiomeric excesses ranging from 67% to 82%. The regioselectivity of the addition was determined by ^{1}H NMR, and analyzing the chemical shifts of the vinyl protons. Additional structural evidence for the 1,4-addition was obtained from HMBC correlations of carbon–proton couplings in the adduct of methyl thioglycolate to the nitrodiene (Fig. 3).

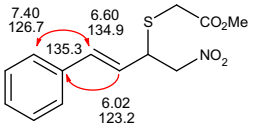


Figure 3. Selected HMBC correlations for adduct **14g**. Numbers correspond to ^{1}H and ^{13}C chemical shifts (ppm).

Application of 4-chlorobenzenemethanethiol gave the product with only 58% ee while the use of methyl thioglycolate furnished a product with negligible enantioselectivity.

3. Conclusion

In conclusion, we have reported a simple organocatalytic system for the sulfa-Michael reaction of aliphatic thiols and nitro olefins, leading to the respective adducts in good to excellent yields and with up to 87% ee. Application of the more demanding nitrodienes led exclusively to 1,4-adducts with up to 82% ee. Catalyst **7** was obtained from a commercially available enantiomeric amine and isothiocyanate in a one step-procedure as a crystalline, air-stable product. The catalytic system developed is effective using as little as 2.5 mol % of **7** and works well in a broad range of catalyst concentrations as well as in an excess of the thiols.

4. Experimental

4.1. General

Commercially available starting materials were used without further purification. Carbon tetrachloride and α,α,α-triflurotoluene were used as received. Chloroform and 1,2-dichloroethane were distilled over P_2O_5 under argon. Dichloromethane, *tert*-butylmethyl ether, dimethoxyethane, and acetonitrile were distilled with CaH_2 under argon and further stored over 3 Å molecular sieves. Diethyl ether was distilled over sodium/benzophenone and stored over 4 Å molecular sieves. Toluene was dried over sodium wires.

Nitro olefins were prepared by following literature precedents and yields were not optimized.[24] Nitrodienes were prepared according to the literature.[25] Catalysts **2**,[26] **3**[27] and **5**[28] were prepared according to the literature. Catalyst **4** was purchased from a commercial supplier.

Reactions were performed in reaction tubes with the gas inlet. Tubes were heated to 550 °C for 3–5 min under high vacuum, cooled down and then flushed with argon.

Flash chromatography (FC) was performed using silica gel 35–70 μm. Thin layer chromatography was performed using silica gel on aluminium foil plates with an indicator. Chromatograms were visualized using UV-lamp and $KMnO_4$ dip.

^{1}H and ^{13}C NMR (300 and 75 MHz or 600 and 151 MHz, respectively) spectra were recorded in $CDCl_3$ and DMSO-d_6 on Bruker Avance DRX 300 and NMR Bruker Avance™ 600 MHz. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS, δ 0.00 ppm) and $CHCl_3$ (δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) and $CDCl_3$ (δ 77.0 ppm) or DMSO-d_6 (39.52 ppm). FT-IR spectra were recorded on System 2000 FT-IR Perkin–Elmer spectrometer. ESI HRMS spectra were recorded on WATERS LCT Premier XE apparatus. HPLC analysis was performed on Thermo Scientific System (SCM 1000, Spectra System P4000 pump and Spectra System UV 2000 detector) using Chiralpak AD-H, Chiralcel OD-H and Chiralpak AS-H columns (4.6 mm × 25 cm). No guard column was used. Each HPLC analysis was controlled by comparison with the pure sample and the racemate. Optical rotations were measured on an automatic polarimeter at λ = 589 nm (*c* g/100 mL).

The absolute configuration of the sulfa-Michael adduct was ascribed as (*S*) by analogy to known compounds for example, **10a, 10b**[13] and by comparison of the sign of the specific rotation measured in the same solvent as described for analogues. Moreover, the order of elution of enantiomers from the chiral stationary phases was the same as that described for known, analogue compounds for example, **10a**.

4.2. General procedure 1 for the synthesis of thioureas 6, 7, and 8

Amine (1.0 equiv) and isothiocyanate (1.3 equiv) were mixed in dichloromethane and stirred at rt for 24 h. Then, the solvent was evaporated and the residue was subjected to column chromatography on silica gel (hexanes/EtOAc, 1:1, v/v) that afforded the desired thiourea.

4.2.1. Thiourea 6

The reaction was carried out with (*R*)-(−)-1-benzyl-3-aminopyrrolidine (0.39 mL, 2.3 mmol, and 1.0 equiv) and phenyl isothiocyanate (0.7 mL, 3.0 mmol, 1.3 equiv) in 6 mL of CH_2Cl_2 to give the desired thiourea as a solid, yield 85%; mp: 63–64 °C (hexanes/diethyl ether), R_f = 0.18 (hexanes/EtOAc, 1/1, v/v), $[\alpha]_D^{20} = -39.3$ (*c* 0.89, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.74 (br s, 1H), 2.17–2.37 (m, 2H), 2.46 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.72 (br s, 1H), 2.91 (br s, 1H), 3.53 (d, *J* = 12.9 Hz, 1H), 3.62 (d, *J* = 12.9 Hz, 1H), 4.91 (br s, 1H), 6.66 (br s, 1H), 7.16–7.32 (m, 8H), 7.40–7.45 (m, 2H), 8.09 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.9, 52.2, 54.5, 59.4, 59.7, 124.8, 126.5, 127.0, 128.2, 128.5, 129.7, 136.4, 138.2, 179.2; IR (KBr) *ν*: 3249, 3193, 3173, 3028, 2978, 2808, 1531, 1496, 1452, 1397, 1344, 1313, 1244, 1194, 1181, 1136, 1119, 1072, 746 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{22}N_3S$ ([M+H]$^+$): 312.1529, found 312.1534.

4.2.2. Thiourea 7

The enantiomer of **7** is a known[17] compound, however, no spectra are available. Reaction applying (*R*)-(−)-1-benzyl-3-aminopyrrolidine (0.49 mL, 2.8 mmol, 1.0 equiv) and 3,5-bis(trifluoromethyl) phenyl isothiocyanate (0.44 mL, 3.7 mmol, 1.3 equiv) in 8 mL of CH_2Cl_2 gave the desired thiourea as colorless crystals, yield 95%; mp: 127–128 °C, lit.[17] 129.0–132.0 °C, R_f = 0.15 (hexanes/EtOAc, 1/1, v/v); $[\alpha]_D^{20} = -56.5$ (*c* 0.46, CH_2Cl_2); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.69 (br s, 1H), 2.21–2.27 (m, 1H), 2.36 (br s, 1H), 2.57 (d, *J* = 7.2 Hz, 1H), 2.64–2.81 (m, 2H), 3.61 (br s, 2H), 4.69 (br s, 1H), 7.24–7.27 (m, 1H), 7.32–7.33 (m, 4H), 7.71 (br s, 1H), 8.25 (s, 2H), 8.39 (br s, 1H), 9.97 (br s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 31.0, 52.2, 53.1, 59.2, 59.6, 115.9, 121.7, 123.2 (q, J_{CF} = 273 Hz), 126.9, 128.2, 128.6, 130.0 (q, J_{CF} = 33 Hz), 138.7, 141.9, 179.9; IR (KBr) *ν*: 3228, 3121, 3064, 3028, 2986, 2958, 2815, 1613, 1542, 1474, 1457, 1387, 1340, 1282, 1182, 1124, 885, 726, 700,

682 cm^{-1}. HRMS (ESI): calcd for $C_{20}H_{20}F_6N_3S$ ($[M+H]^+$): 448.1277, found 448.1282.

4.2.3. Thiourea 8

An application of compound **8** was reported,[29] no spectroscopic data were provided. Reaction applying (*R*)-2-aminomethyl-l-benzyl-pyrrolidine[30] (170 mg, 0.9 mmol, and 1.0 equiv) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.26 mL, 1.1 mmol, 1.2 equiv) in 5 mL of CH_2Cl_2 gave the desired thiourea as a colorless liquid, yield 30%; R_f = 0.36 (hexanes/EtOAc, 1/1, v/v); $[\alpha]_D^{20} = +7.8$ (*c* 0.32, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45–1.69 (m, 3H), 2.07–2.26 (m, 2H), 2.62 (d, *J* = 11.1 Hz, 1H), 2.79 (d, *J* = 7.7 Hz, 1H), 2.77–2.80 (m, 1H), 3.33 (d, *J* = 13.1 Hz, 1H), 3.46 (d, *J* = 13.1 Hz, 1H), 4.54 (br s, 1H), 6.90 (br s, 2H), 7.10–7.21 (m, 4H), 7.78–7.79 (m, 3H), 8.73 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 27.5, 50.6, 53.7, 56.9, 62.7, 119.3, 122.9 (q, J_{CF} = 272 Hz), 123.9, 127.3, 128.2, 128.7, 133.3 (J_{CF} = 35 Hz), 137.5, 138.8, 178.4; HRMS (ESI): calcd for $C_{21}H_{22}F_6N_3S$ ($[M+H]^+$) 462.1433, found 462.1432.

4.3. General procedure 2 for the reaction of nitro olefins and aliphatic thiols leading to racemates

At first, DABCO (0.10 mmol, 10 mol %, 11 mg) was added to a solution of thiol (1.5 equiv, 1.5 mmol) in dichloromethane (2.5 mL) at 20 °C, stirred for 15 min followed by the addition of nitro olefin or nitrodiene (1.0 mmol, 1.0 equiv). The resulting solution was stirred from 3 to 20 h at 20 °C and filtered through a plug of silica gel (10 g). The filtrate was concentrated in vacuo and dried under high vacuum to afford the crude sulfa-Michael adduct. Purification, if needed, was performed using flash chromatography on silica-gel (40 g) eluting by hexanes/EtOAc, 25:1, v/v.

4.4. General procedure for the catalytic reaction of nitro olefins and aliphatic thiols

A reaction tube was charged with catalyst **7** (3.7 mg, 0.008 mmol, 2.5 mol %), nitro olefin (1.0 equiv, 0.33 mmol) and dichloromethane (1.0 mL) under argon at 20 °C. The resulting solution was stirred at 20 °C for 20 min, and cooled to −30 °C for 10 min Then, a solution of thiol (1.0 equiv, 0.33 mmol) in dichloromethane (0.5 mL) was added slowly over 10 min via syringe. The resulting solution was stirred for 3 h at −30 °C, flushed with argon, sealed and put into a freezer (−30 °C). After 48 h, the cold reaction mixture was filtered through a plug of silica (4 × 4 cm) eluting with dichloromethane (100 mL). The resulting filtrate was concentrated in vacuo and the residue was subjected to flash chromatography (silica gel, 20 g, hexanes/EtOAc, 25:1, v/v) to afford the desired product.

In the case of the limited solubility of a nitro olefin, an increased amount of solvent was used. Such information is provided below in each case, where relevant.

4.4.1. (*S*)-Benzyl (2-nitro-1-phenylethyl) sulfide 9a

Pale yellow liquid, yield 90%, 77% ee; $[\alpha]_D^{20} = +185.5$ (*c* 1.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.56 (d, *J* = 13.5 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 4.38 (dd, *J* = 8.9, 6.8 Hz, 1H), 4.57–4.67 (m, 2H), 7.19–7.7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.0, 45.9, 79.0, 127.5, 127.7, 128.5, 128.7, 128.9, 129.0, 136.9, 137.0. Spectra are in agreement with the reported ones for a racemic sample.[31] HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 11.89 min (minor); t_r = 12.95 (major); 77% ee.

4.4.2. (*S*)-Benzyl (1-(4-fluorophenyl)-2-nitroethyl) sulfide 9b

Colorless oil, yield 95%, 69% ee; $[\alpha]_D^{20} = +172.0$ (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.50 (d, *J* = 13.5 Hz, 1H), 3.60 (d, *J* = 13.5 Hz, 1H), 4.30 (dd, *J* = 8.6, 7.1 Hz, 1H), 4.53 (s, 1H), 4.56 (d, *J* = 1.3 Hz, 1H), 6.96–7.04 (m, 2H), 7.18–7.28 (m, 6H), 7.30–7.33 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.0, 45.1, 79.0, 116.0 (J_{CF} = 21.6 Hz), 127.6, 128.7, 128.8, 129.5 (d, J_{CF} = 8.3 Hz), 132.8 (d, J_{CF} = 3.3 Hz), 136.7, 162.5 (d, J_{CF} = 248 Hz); IR (neat) ν: 3063, 3030, 2918, 1603, 1555, 1509, 1454, 1428, 1375, 1227, 1160, 1100, 839, 798, 768, 704 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{14}FNO_2S$-Na $[M+Na]^+$: 314.0627, found: 314.0615; HPLC: AD-H, *n*-hexane/IPA 97:3; 0.7 mL/min; λ = 254 nm; t_r = 13.59 min (minor); t_r = 14.79 (major); 69% ee.

4.4.3. (*S*)-Benzyl (1-(4-bromophenyl)-2-nitroethyl) sulfide 9c

Reaction was performed in 5 mL of CH_2Cl_2; colorless oil, yield 78%, 70% ee; $[\alpha]_D^{20} = +170.0$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.49 (d, *J* = 13.7 Hz, 1H), 3.60 (d, *J* = 13.5 Hz, 1H), 4.26 (dd, *J* = 8.4, 7.2 Hz, 1H), 4.53 (s, 1H), 4.54 (d, *J* = 1.3 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.13–7.17 (m, 2H), 7.19–7.27 (m, 3H), 7.38 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.0, 45.2, 78.7, 122.4, 127.6, 128.7, 128.8, 129.4, 132.1, 136.1, 136.6; IR (neat) ν: 3029, 2918, 1555, 1489, 1375, 1074, 1011, 705 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{14}Br^{79}NO_2SNa$ $[M+Na]^+$: 373.9826, found: 373.9818; HPLC: AD-H, *n*-hexane/IPA 97:3; 0.7 mL/min; λ = 254 nm; t_r = 15.36 min (minor); t_r = 17.82 (major); 70% ee.

4.4.4. (*S*)-Benzyl (1-(4-chlorophenyl)-2-nitroethyl) sulfide 9d

Colorless oil, yield 81%, 75% ee; $[\alpha]_D^{20} = +185.7$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.55 (d, *J* = 13.5 Hz, 1H), 3.65 (d, *J* = 13.7 Hz, 1H), 4.33 (dd, *J* = 8.5, 7.2 Hz, 1H), 4.58 (s, 1H), 4.60 (d, *J* = 1.1 Hz, 1H), 7.14–7.23 (m, 4H), 7.24–7.33 (m, 3H), 7.24–7.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.0, 45.1, 78.8, 127.6, 128.7, 128.8, 129.1, 129.2, 134.3, 135.6, 136.6. Spectra are in agreement with the reported ones for a racemic sample;[31] IR (neat) ν: 3063, 3030, 1555, 1493, 1454, 1427, 1411, 1375, 1092, 1015, 843, 831, 705 cm^{-1}; HPLC: AD-H, *n*-hexane/IPA 97:3; 0.7 mL/min; λ = 254 nm; t_r = 14.59 min (minor); t_r = 16.51 (major); 75% ee.

4.4.5. (*S*)-Benzyl (1-(2,6-dichlorophenyl)-2-nitroethyl) sulfide 9e

Colorless oil, yield 92%, 66% ee; $[\alpha]_D^{20} = +138.0$ (*c* 0.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (d, *J* = 13.4 Hz, 1H), 3.87 (d, *J* = 13.4 Hz, 1H), 4.68 (dd, *J* = 13.2, 7.1 Hz, 1H), 5.02 (dd, *J* = 13.4, 8.4 Hz, 1H), 5.33 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.05 (dd, *J* = 8.6, 7.3 Hz, 1H), 7.16–7.30 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.6, 42.5, 77.1, 127.6, 128.65, 128.7, 129.0, 129.5, 129.9, 133.8, 135.06, 135.1, 136.9; IR (neat) ν: 3063, 3030, 2967, 1553, 1495, 1454, 1436, 1374, 1179, 1089, 778, 702 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{13}Cl_2{}^{35}NO_2SNa$ $[M+Na]^+$: 363.9942; found: 363.9953; HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 14.54 min (minor); t_r = 16.25 (major); 66% ee

4.4.6. (*S*)-Benzyl (1-(2,4-dichlorophenyl)-2-nitroethyl) sulfide 9f

Reaction was performed in 2 mL of CH_2Cl_2; colorless oil, yield 88%, 68% ee; $[\alpha]_D^{20} = +100.6$ (*c* 0.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 2H), 4.51 (dd, *J* = 13.2, 7.2 Hz, 1H), 4.67 (dd, *J* = 13.2, 8.0 Hz, 1H), 4.85 (t, *J* = 7.5 Hz, 1H), 7.18–7.28 (m, 6H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.8, 42.2, 77.6, 127.6, 127.7, 128.7, 128.9, 129.5, 129.9, 133.3, 134.4, 134.6, 136.4; IR (neat) ν: 3090, 2919, 1588, 1555, 1490, 1472, 1427, 1375, 1095, 10523, 1016, 871, 826, 778, 722, 674, 652 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{13}Cl_2{}^{35}NO_2SNa$ $[M+Na]^+$: 363.9942, found: 363.9951; HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 19.11 min (minor); t_r = 21.25 (major); 68% ee.

4.4.7. (*S*)-Benzyl (1-(2-chlorophenyl)-2-nitroethyl) sulfide 9g

Colorless oil, yield 85%, 67% ee; $[\alpha]_D^{20} = +83.2$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 2H), 4.59 (dd, *J* = 13.1, 7.4 Hz, 1H), 4.77 (dd, *J* = 13.1, 7.9 Hz, 1H), 5.00 (t, *J* = 7.7 Hz, 1H), 7.21–

7.36 (m, 7H), 7.38–7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.0, 42.9, 78.0, 127.5, 127.6, 128.7, 128.8, 129.0, 129.5, 130.3, 133.8, 134.7, 136.8; IR (neat) ν: 3063, 3030, 2918, 1555, 1495, 1475, 1454, 1431, 1375, 1053, 1071, 1036, 755, 702 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{14}Cl^{35}NO_2SNa$ [M+Na]$^+$: 330.0331, found: 330.0338; HPLC: OD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 53.32 min (minor); t_r = 60.53 (major); 67% ee.

4.4.8. (*S*)-Benzyl (1-(4-nitrophenyl)-2-nitroethyl) sulfide 9h

Racemic product is known,[32] however no spectra were available. Reaction was performed in 9 mL of CH_2Cl_2; light yellow solidifying oil, yield 83%, 50% ee; $[\alpha]_D^{20} = +134.7$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.66 (d, *J* = 13.6 Hz, 1H), 3.77 (d, *J* = 13.9 Hz, 1H), 4.49 (t, *J* = 7.9 Hz, 1H), 4.72 (dd, *J* = 7.5, 0.8 Hz, 2H), 7.26–7.27 (m, 2H), 7.31–7.34 (m, 1H), 7.35–7.38 (m, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 8.22 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 36.3, 45.0, 78.3, 124.2, 127.9, 128.8, 128.85, 128.9, 136.2, 144.6, 147.7; IR (neat) ν: 3082, 3029, 2928, 1605, 1552, 1516, 1346, 1180. 1110, 859, 697 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{14}N_2O_4SNa$ [M+Na]$^+$: 341.0572, found: 341.0562; HPLC: OD-H, *n*-hexane/IPA 80:20; 1 mL/min; λ = 225 nm; t_r = 27.19 min (minor); t_r = 29.04 (major); 50% ee.

4.4.9. (*S*)-Benzyl (1-(4-methoxyphenyl)-2-nitroethyl) sulfide 9i

Light yellow oil, yield 83%, 69% ee; $[\alpha]_D^{20} = +175.5$ (*c* 0.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.60 (d, *J* = 13.7 Hz, 1H), 3.69 (d, *J* = 13.5 Hz, 1H), 3.81 (s, 3H), 4.40 (dd, *J* = 8.9, 6.9 Hz, 1H), 4.59–4.71 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.24–7.33 (m, 4H), 7.34–7.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.9, 45.4, 55.2, 79.2, 114.3, 127.4, 128.6, 128.7, 128.85, 129.0, 137.0, 159.5. Spectra are in agreement with the reported ones for racemic sample.[12] HPLC: AD-H, *n*-hexane/IPA 95:5; 1 mL/min; λ = 254 nm; t_r = 10.31 min (minor); t_r = 11.27 (major); 69% ee.

4.4.10. (*S*)-Benzyl (1-(naphthlen-2-yl)-2-nitroethyl) sulfide 9j

Reaction was performed in 2 mL of CH_2Cl_2; yellow solid, yield 92%, 70% ee; $[\alpha]_D^{20} = +191.0$ (*c* 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.55 (d, *J* = 13.5 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 4.55 (dd. *J* = 9.0, 6.6 Hz, 1H), 4.69 (dd, *J* = 12.9, 6.6 Hz, 1H), 4.77 (dd, *J* = 12.9, 9.0 Hz, 1H), 7.20–7.32 (m, 5H), 7.40 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.44–7.49 (m, 2H), 7.62 (br s, 1H), 7.75–7.84 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 35.9, 46.1, 78.9, 124.9, 126.57, 126.6, 127.2, 127.5, 127.7, 127.9, 128.7, 128.9, 129.2, 133.1, 133.2, 134.1, 136.9; IR (KBr) ν: 3054, 3028, 2910, 1548, 1494, 1375, 810, 801, 745, 724 cm^{-1}; HRMS (ESI): calcd for $C_{19}H_{17}NO_2SNa$ [M+Na]$^+$: 346.0878, found: 346.0888; HPLC: AD-H, *n*-hexane/IPA 95:5; 1 mL/min; λ = 254 nm; t_r = 10.73 min (minor); t_r = 12.32 (major); 70% ee. Crystallization from $CHCl_3$/hexanes afforded colorless crystals, yield 53%, mp: 71.6–72.2 °C, 68% ee; $[\alpha]_D^{20} = +199.2$ (c 0.60, $CHCl_3$).

4.4.11. (*R*)-2-(1-(Benzylthio)-2-nitroethyl)thiophene 9k

Light brown oil, yield 92%, 68% ee; $[\alpha]_D^{20} = +175.3$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (d, *J* = 13.5 Hz, 1H), 3.78 (d, *J* = 13.5 Hz, 1H), 4.62–4.77 (m, 3H), 6.96 (d, *J* = 3.7 Hz, 2H), 7.25–7.30 (m, 3H), 7.31–7.34 (m, 2H), 7.35–7.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.1, 41.2, 79.5, 126.1, 126.6, 126.9, 127.6, 128.7, 128.9, 136.6, 140.9; IR (neat) ν: 3030, 2927, 2854, 1551, 1495, 1452, 1428, 1377, 768, 703 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{13}NO_2S_2Na$ [M+Na]$^+$: 302.0285, found: 302.0304; HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 13.84 min (minor); t_r = 15.11 (major); 68% ee.

4.4.12. Benzyl (1-cyclohexyl-2-nitroethyl) sulfide 9l

Colorless oil, yield 87%, 63% ee; $[\alpha]_D^{20} = 0.0$ (*c* 0.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95–1.34 (m, 5H), 1.43–1.54 (m, 2H), 1.62–1.77 (m, 4H), 3.15 (td, *J* = 7.5, 3.8 Hz, 1H), 3.72 (d, *J* = 13.4 Hz, 1H), 3.77 (d, *J* = 13.4 Hz, 1H), 4.36 (dd, *J* = 12.6, 7.3 Hz, 1H), 4.56 (dd, *J* = 12.6, 7.6 Hz, 1H), 7.24–7.30 (m, 1H), 7.31–7.37 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 26.03, 28.4, 30.2, 37.2, 40.1, 48.7, 78.0, 127.4, 128.6, 129.0, 137.5. Spectra are in agreement with the reported ones for a racemic sample.[31] IR (neat) ν: 3029, 2928, 2854, 2552, 1494, 1451, 1428, 1377, 767, 702 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{21}NO_2SNa$ [M+Na]$^+$: 302.1191, found: 302.1191; HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 8.59 min (major); t_r = 9.58 (minor); 63% ee.

4.4.13. (*S*)-2-(1-(Benzylthio)-2-nitroethyl)phenol 9m

Reaction was performed in 7 mL of CH_2Cl_2; reddish oil, yield 74%, 26% ee; $[\alpha]_D^{20} = +72.4$ (*c* 0.38, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.70 (d, *J* = 13.2 Hz, 1H), 3.76 (d, *J* = 13.2 Hz, 1H), 4.70–4.74 (m, 2H), 4.86 (dd, *J* = 15.4, 10.5 Hz, 1H), 5.96 (br s, 1H), 6.87 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.95 (dt, *J* = 7.5, 0.8 Hz, 1H), 7.13 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.25 (td, *J* = 7.9, 1.5 Hz, 1H), 7.27–7.32 (m, 3H), 7.34–7.37 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 36.1, 42.5, 77.4, 117.4, 121.3, 122.3, 127.6, 128.7, 128.9, 129.3, 129.9, 136.6, 154.0; IR (neat) ν: 3480, 3063, 3031, 1596, 1557, 1495, 1455, 1427, 1377, 1335, 1237, 1103, 841, 756, 704 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{15}NO_3SNa$ [M+Na]$^+$: 312.0670, found: 312.0658. HPLC: AD-H, *n*-hexane/IPA 90:10; 1 mL/min; λ = 254 nm; t_r = 13.84 min (minor); t_r = 15.11 (major); 26% ee.

4.4.14. 3-(1-(Benzylthio)-2-nitroethyl)-1*H*-indole 9n

Reaction was performed in 9 mL of CH_2Cl_2; light brown oil, yield 50%, 0% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (d, *J* = 13.7 Hz, 1H), 3.72 (d, *J* = 13.7 Hz, 1H), 4.74 (dd, *J* = 9.3, 4.0 Hz, 1H), 4.80–4.92 (m, 2H), 7.09 (d, *J* = 2.6 Hz, 1H), 7.16 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.23–7.39 (m, 7H), 7.61 (dd, *J* = 8.1, 0.6 Hz, 1H), 8.11 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.1, 38.9, 78.8, 111.4, 111.6, 119.3, 120.2, 122.9, 123.0, 125.4, 127.5, 128.7, 129.0, 136.6, 137.5; IR (neat) ν: 3420, 3060. 3029, 2917, 1554, 1494, 1456, 1421, 1378, 1340, 1249, 1102, 746, 704 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{16}N_2O_2SNa$ [M+Na]$^+$: 335.0830, found: 335.0831. HPLC: AD-H, *n*-hexane/IPA 90:10; 1 mL/min; λ = 254 nm; t_r = 20.59 min; t_r = 24.20; 0% ee.

4.4.15. (*S*)-(4-Methoxybenzyl) (2-nitro-1-phenylethyl) sulfide 10a[13]

Light yellow oil, yield 79%, 72% ee; $[\alpha]_D^{20} = +175.0$ (*c* 1.0, $CHCl_3$), lit.[13] +55 (*c* 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.57 (d, *J* = 13.6 Hz, 1H), 3.65 (d, *J* = 13.6 Hz, 1H), 3.82 (s, 3H), 4.42 (dd, *J* = 9.0, 6.8 Hz, 1H), 4.66 (dd, *J* = 13.2, 6.8 Hz, 1H), 4.70 (dd, *J* = 12.8, 9.0 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.27–7.29 (m, 2H), 7.31–7.33 (m, 1H), 7.35–7.38 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 35.4, 45.8, 55.3, 79.1, 114.1, 127.7, 128.4, 128.7, 129.0, 130.0, 137.1, 158.9; HRMS (ESI): calcd for $C_{16}H_{17}NO_3SNa$ [M+Na]$^+$: 326.0827, found: 326.0836; HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 26.33 min (minor); t_r = 28.85 (major); 72% ee, lit.[13] AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 220 nm; t_r = 26.65 min (minor); t_r = 31.50 (major).

4.4.16. (*S*)-(4-*tert*-Butylbenzyl) (2-nitro-1-phenylethyl) sulfide 10b[13]

Pale yellow oil, yield 76%, 87% ee; $[\alpha]_D^{20} = +243.2$ (*c* 0.27, $CHCl_3$), lit.[13] +135 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 3.59 (d, *J* = 13.4 Hz, 1H), 3.68 (d, *J* = 13.4 Hz, 1H), 4.45 (dd, *J* = 9.0, 6.7 Hz, 1H), 4.63–4.76 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.27–7.39 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 31.3, 34.5, 35.6, 45.9, 79.1, 125.6, 127.7, 128.4, 128.5, 128.9, 133.7, 137.1, 150.5; HRMS (ESI): calcd for $C_{19}H_{23}NO_2SNa$ [M+Na]$^+$: 352.1347, found: 352.1339; HPLC: AD-H, *n*-hexane/IPA 99:1; 0.7 mL/min; λ = 254 nm; t_r = 12.30 min (minor); t_r = 14.12 (major); 87% ee.

4.4.17. (*S*)-(4-Chlorobenzyl) (2-nitro-1-phenylethyl) sulfide 10c

Colorless oil, yield 73%, 60% ee; $[\alpha]_D^{20} = +157.5$ (*c* 0.8, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 3.55 (d, *J* = 13.6 Hz, 1H), 3.64 (d, *J* = 13.6 Hz, 1H), 4.41 (m, 1H), 4.66–4.73 (m, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.27–7.31 (m, 4H), 7.32–7.34 (m, 1H), 7.36–7.39 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 35.2, 46.0, 79.0, 127.8, 128.6, 128.8, 129.1, 130.2, 133.3, 135.4, 136.8; IR (neat) *ν*: 3064, 3031, 2920, 1555, 1491, 1427, 1376, 1093, 1015, 830, 747, 700 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{14}Cl^{35}NO_2SNa$ $[M+Na]^+$: 330.0331, found: 330.0342; HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 21.03 min (minor); t_r = 22.87 (major); 60% ee.

4.4.18. Methyl 2-((2-nitro-1-phenylethyl)thio)acetate 10d

Reaction was performed in 0.5 mmol scale in 2.5 mL of CH_2Cl_2; colorless oil, yield 84%, 43% ee; $[\alpha]_D^{20} = +90.0$ (*c* 0.49, $CHCl_3$), lit.[15b] $[\alpha]_D$ = +20.4 (*c* 1.031, $CHCl_3$,); ^1H NMR (600 MHz, $CDCl_3$): δ 3.08 (d, *J* = 15.4 Hz, 1H), 3.17 (d, *J* = 15.4 Hz, 1H), 3.71 (s, 3H), 4.80–4.89 (m, 3H), 7.31–7.36 (m, 4H), 7.37–7.39 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 32.5, 46.5, 52.6, 78.5, 127.8, 128.7, 129.1, 136.0, 170.2; IR (neat) *ν*: 3032, 2955, 1736, 1555, 1435, 1377, 1285, 1197, 1136, 1006, 701 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_{13}NO_4SNa$ $[M+Na]^+$: 278.0463, found: 278.0475; HPLC: AS-H, *n*-hexane/IPA 90:10; 1 mL/min; λ = 254 nm; t_r = 19.11 min (major); t_r = 20.61 (minor); 43% ee.

4.4.19. Cyclohexyl (2-nitro-1-phenylethyl) sulfide 10e

Colorless oil, yield 30%, 36% ee; ^1H NMR (600 MHz, $CDCl_3$): δ 1.20–1.28 (m, 3H), 1.30–1.39 (m, 2H), 1.57–1.60 (m, 1H), 1.69–1.77 (m, 2H), 1.86 (d, *J* = 13.2 Hz, 1H), 1.95 (bd, *J* = 12.8 Hz, 1H), 2.59 (tt, *J* = 10.5, 3.7 Hz, 1H), 4.62 (dd, *J* = 8.7, 6.8 Hz, 1H), 4.70–4.76 (m, 2H), 7.29–7.32 (m, 1H), 7.34–7.37 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.6, 25.7, 25.8, 33.4, 33.5, 44.0, 45.1, 79.9, 127.6, 128.3, 129,0, 138.1. Spectra are in agreement with the reported ones for racemic sample.[12] HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 225 nm; t_r = 7.27 min (minor); t_r = 8.58 (major); 36% ee.

4.4.20. 2-((2-Nitro-1-phenylethyl)thio)ethanol 10f

Compound **10f** is known, however, no spectra were provided.[33] Reaction was performed on a 0.5 mmol scale in 2.5 mL of CH_2Cl_2. Compound **10f** was purified using flash chromatography using gradient CH_2Cl_2–hexanes (1:1, v/v) to CH_2Cl_2 (100%); colorless oil, yield 55%, 22% ee; $[\alpha]_D^{20} = +14.2$ (*c* 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.03 (br s, 1H), 2.58–2.73 (m, 2H), 3.70 (br s, 2H), 4.62–4.70 (m, 1H), 4.74–4.84 (m, 2H), 7.32–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.5, 46.4, 60.9, 79.2, 127.6, 128.6, 129.1, 137.1; IR (neat) *ν*: 3392, 3031, 2927, 2879, 1555, 1377, 1048, 701 cm^{-1}; HRMS (ESI): calcd for $C_{10}H_{13}NO_3SNa$ $[M+Na]^+$: 250.0514, found: 250.0530; HPLC: AD-H, *n*-hexane/IPA 90:10; 1 mL/min; λ = 254 nm; t_r = 14.01 min (major); t_r = 14.79 (minor); 22% ee.

4.4.21. (*S*)-(4-Chlorobenzyl) (1-(2,4-dichlorophenyl)-2-nitroethyl) sulfide 12

Reaction was performed using 5 mol % of catalyst **7** in 9 mL of CH_2Cl_2 at −80 °C; yellow oil, yield 71%, 68% ee; $[\alpha]_D^{20} = +99.5$ (*c* 0.27, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.65 (d, *J* = 13.6 Hz, 1H), 3.72 (d, *J* = 13.6 Hz, 1H), 4.60 (dd, *J* = 13.2, 7.8 Hz, 1H), 4.71 (dd, *J* = 13.2, 7.5 Hz, 1H), 4.89 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.24–7.30 (m, 3H), 7.36–7.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.0, 42.2, 77.6, 127.8, 128.8, 129.6, 130.0, 130.2, 133.1, 133.4, 134.4, 134.8, 135.0; IR (neat) *ν*: 3090, 3028, 2919, 1588, 1555, 1490, 1472, 1427, 1375, 1095, 1016, 871, 826, 778, 750, 674, 652 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{12}Cl_3{}^{35}NO_2SNa$ $[M+Na]^+$: 397.9552, found: 397.9571; HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 20.40 min (minor); t_r = 25.41 (major); 68% ee.

4.5. General procedure for the catalytic reaction of nitrodienes and aliphatic thiols

A reaction tube was charged with catalyst **7** (3.7 mg, 0.008 mmol, 2.5 mol %), nitrodiene (1.0 equiv, 0.33 mmol) and dichloromethane (1.0 mL) under argon at 20 °C. The resulting solution was stirred at 20 °C for 20 min, and cooled to −78 °C for 10 min. Then, a solution of thiol (2.0 equiv, 0.66 mmol) in dichloromethane (0.5 mL) was slowly added over 10 min via syringe. The resulting solution was stirred for 3 h at −78 °C, flushed with argon, sealed and maintained at −80 °C. After 72 h, the cold reaction mixture was filtered through a plug of silica gel (4 × 4 cm) eluting with dichloromethane (100 mL). The resulting filtrate was concentrated in vacuo and the residue was subjected to flash chromatography (silica gel, 25 g, hexanes/EtOAc, 30:1, v/v) to afford the desired product.

4.5.1. (*S*)-(*E*)-Benzyl(1-nitro-4-phenylbut-3-en-2-yl) sulfide 14a

Light brown oil, yield 93%, 67% ee; $[\alpha]_D^{20} = +154.8$ (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.78 (d, *J* = 13.7 Hz, 1H), 3.84 (d, *J* = 13.7 Hz, 1H), 4.04 (m, 1H), 4.49–4.57 (m, 2H), 6.06 (dd, *J* = 15.9, 9.0 Hz, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 7.32–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.3, 44.4, 77.9, 124.4, 126.6, 127.5, 128.3, 128.6, 128.7, 128.9, 134.0, 135.5, 137.0; IR (neat) *ν*: 3061, 3029, 2918, 1555, 1494, 1375, 966, 746, 695 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{17}NO_2SNa$ $[M+Na]^+$: 322.0878, found: 322.0860; HPLC: AD-H, *n*-hexane/IPA 97:3; 0.7 mL/min; λ = 225 nm; t_r = 15.86 min (minor); t_r = 18.64 (major); 67% ee.

4.5.2. (*S*)-(*E*)-Benzyl(4-(4-methoxyphenyl)-1-nitrobut-3-en-2-yl) sulfide 14b

An attempt to isolate the pure compound failed; HPLC: AD-H, *n*-hexane/IPA 90:10; 1 mL/min; λ = 254 nm; t_r = 10.89 min (minor); t_r = 13.60 (major); 70% ee.

4.5.3. (*S*)-(*E*)-(4-Methoxybenzyl)(1-nitro-4-phenylbut-3-en-2-yl) sulfide 14c

Yellow oil, yield 68%, 70% ee; $[\alpha]_D^{20} = +166.5$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (d, *J* = 2.6 Hz, 2H), 3.82 (s, 3H), 3.99–4.07 (m, 1H), 4.48–4.57 (m, 2H), 6.04 (dd, *J* = 15.7, 9.0 Hz, 1H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.86–6.91 (m, 2H), 7.23–7.28 (m, 2H), 7.29–7.33 (m, 1H), 7.34–7.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.8, 44.3, 55.2, 77.9, 114.1, 124.5, 126.6, 128.3, 128.6, 128.9, 130.0, 133.9, 135.6, 158.9; IR (neat) *ν*: 3029, 3004, 2957, 2935, 2914, 2837, 1610, 1558, 1512, 1463, 1449, 1427, 1375, 1302, 1250, 1176, 1033, 966, 833, 748, 694 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{19}NO_3SNa$ $[M+Na]^+$: 352.0983, found: 352.0994; HPLC: AD-H, *n*-hexane/IPA 90:10; 1 mL/min; λ = 254 nm; t_r = 10.34 min (minor); t_r = 11.93 (major); 70% ee.

4.5.4. (*S*)-(*E*)-(4-(*tert*-Butyl)benzyl)(1-nitro-4-phenylbut-3-en-2-yl) sulfide 14d

Pale yellow oil, yield 85%, 82% ee; $[\alpha]_D^{20} = +213.6$ (*c* 0.66, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9H), 3.78 (s, 2H), 4.03–4.11 (m, 1H), 4.49–4.61 (m, 2H), 6.04 (dd, *J* = 15.7, 9.0 Hz, 1H), 6.49 (d, *J* = 15.7 Hz, 1H), 7.26–7.39 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.3, 34.5, 34.9, 44.4, 77.9, 124.5, 125.6, 126.6, 127.7 (C_{IV°), 128.3, 128.5, 128.6, 133.9, 135.6, 150.4; IR (neat) *ν*: 3028, 2963, 1624, 1556, 1495, 1375, 1332, 1269, 965, 837, 745, 694 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{25}NO_2SNa$ $[M+Na]^+$: 378.1504, found: 378.1497; HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 12.83 min (minor); t_r = 16.26 (major); 82% ee.

4.5.5. (*S*)-(*E*)-2-(((1-Nitro-4-phenylbut-3-en-2-yl)thio)methyl) furan 14e

Sandy amorphous solid that turned brown during storage, yield 64%, 78% ee; $[\alpha]_D^{20} = +261.0$ (*c* 0.40, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 2H), 4.13–4.22 (m, 1H), 4.51–4.60 (m, 2H), 6.04 (dd, *J* = 15.6, 9.0 Hz, 1H), 6.24 (dd, *J* = 3.2, 0.7 Hz, 1H), 6.36 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.56 (d, *J* = 15.6 Hz, 1H), 7.29–7.42 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.3, 44.6, 77.8, 108.1, 110.6, 124.0, 126.7, 128.4, 128.7, 134.4, 135.5, 142.5, 150.6; IR (neat) *v*: 3028, 1556, 1376, 1150, 1012, 967, 744, 694 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{15}NO_3SNa$ $[M+Na]^+$: 312.0670, found: 312.0664; HPLC: AD-H, *n*-hexane/IPA 99:1; 1 mL/min; λ = 254 nm; t_r = 28.04 min (minor); t_r = 32.03 (major); 78% ee.

4.5.6. (*S*)-(*E*)-(4-Chlorobenzyl)(1-nitro-4-phenylbut-3-en-2-yl) sulfide 14f

Pale yellow oil, yield 75%, 58% ee; $[\alpha]_D^{20} = +169.9$ (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (d, *J* = 1.5 Hz, 2H), 4.02 (dd, *J* = 16.4, 7.8 Hz, 1H), 4.55 (d, *J* = 7.7 Hz, 2H), 6.01 (dd, *J* = 15.7, 9.0 Hz, 1H), 6.45 (d, *J* = 15.7 Hz, 1H), 7.25–7.29 (m, 2H), 7.30–7.37 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.6, 44.5, 77.9, 124.2, 126.6, 128.4, 128.7, 128.9, 130.2, 133.3, 134.2, 135.4, 135.6; IR (neat) *v*: 3028, 2919, 1555, 1490, 1375, 1093, 1015, 966, 834, 747, 693 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{16}Cl^{35}NO_2SNa$ $[M+Na]^+$: 356.0488, found 356.0483; HPLC: AD-H, *n*-hexane/IPA 90:10; 1 mL/min; λ = 254 nm; t_r = 8.81 min (minor); t_r = 10.46 (major); 58% ee.

4.5.7. (*S*)-(*E*)-Methyl-2-((1-nitro-4-phenylbut-3-en-2-yl)thio)acetate 14g

Compound **13f** was purified using flash chromatography using gradient CH_2Cl_2–hexanes (1:1, v/v) to CH_2Cl_2 (100%); light yellow oil, yield 92%, 5% ee; $[\alpha]_D^{20} = +12.2$ (*c* 0.59, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 3.29 (d, *J* = 1.9 Hz, 2H), 3.72 (s, 3H), 4.37 (td, *J* = 8.7, 6.4 Hz, 1H), 4.63 (dd, *J* = 12.8, 8.7 Hz, 1H), 4.71 (dd, *J* = 12.8, 6.4 Hz, 1H), 6.02 (dd, *J* = 15.8, 9.0 Hz, 1H), 6.60 (d, *J* = 15.8 Hz, 1H), 7.27–7.30 (m, 1H), 7.33–7.35 (m, 2H), 7.38–7.40 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 31.9, 45.2, 52.6, 77.6, 123.2, 126.7, 128.5, 128.6, 134.9, 135.3, 170.3; IR (neat) *v*: 3028, 2954, 1734, 1555, 1436, 1376, 1295, 1154, 1006, 968, 749, 695 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{15}NO_4SNa$ $[M+Na]^+$: 304.062, found 304.0628; HPLC: AD-H, *n*-hexane/IPA 90:10; 1 mL/min; λ = 254 nm; t_r = 12.02 min (minor); t_r = 13.31 (major); 5% ee.

4.6. Reduction of the nitro group in 12 followed by acylation

The reduction was performed by adopting a literature procedure.[19] Tin(II) chloride dihydrate (790 mg, 3.52 mmol 3.66 equiv) was added to a solution of racemic **12** (360 mg, 0.96 mmol, 1.0 equiv) in methanol (2.0 mL) and acetic acid (1.0 mL). The resulting solution was stirred at reflux for 3 h and then cooled. Volatiles were removed in vacuo. The oily residue was treated with a mixture of diethyl ether/chloroform (20 mL/5 mL) and K_2CO_3 (satd, aq, 20 mL). The phases were separated and the aqueous layer was washed twice with a mixture of diethyl ether/chloroform (8 mL/2 mL). The combined organic extracts were dried ($MgSO_4$) and the solvents were removed in vacuo. The resulting yellow oil (268 mg) was dried under vacuum for 1 h. TLC revealed the consumption of the starting material.

Crude amine **13** was directly subjected to reaction with acetic anhydride: acetic anhydride (360 μL, 5.0 equiv. to nitro compound) was added dropwise via syringe to a solution of crude amine **13** (268 mg) and Et_3N (1.0 mL, 10 equiv) in dry CH_2Cl_2 (2 mL) at 0 °C (ice-water bath). The temperature was allowed to reach 20 °C and the mixture was stirred overnight. Next, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and treated with water (10 mL). The phases were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with $NaHCO_3$ (satd aq 10 mL) and dried ($MgSO_4$). After evaporation of the solvent, the oily residue was subjected to flash chromatography (silica gel, 30 g, $CHCl_3$) to afford 154 mg (41% yield after two steps) of the desired racemic amide **14**: light brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 1.88 (s, 3H), 3.47–3.64 (m, 2H), 3.53 (d, *J* = 13.4 Hz, 1H), 3.68 (d, *J* = 13.4 Hz, 1H), 4.36 (t, *J* = 7.3 Hz, 1H), 5.64–5.68 (m, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.21–7.26 (m, 3H), 7.35 (d, *J* = 2.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 35.3, 43.4, 44.7, 121.8, 128.7, 129.5, 130.0, 130.3, 133.1, 133.9, 134.7, 136.03, 136.04, 170.0. Spectra are in agreement with the reported ones.[8b]

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