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One-Pot, Four-Step Organocatalytic Asymmetric Synthesis of Functionalized Nitrocyclopropanes

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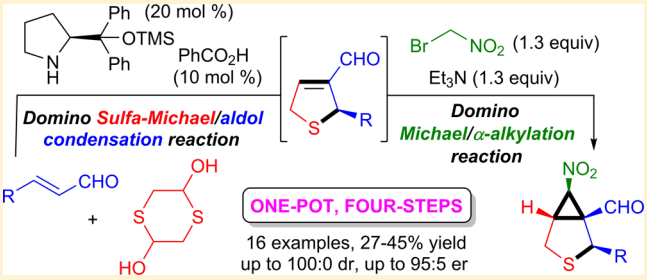
Supporting Information

ABSTRACT: The asymmetric synthesis of functionalized nitrocyclopropanes has been achieved by a one-pot, four-step method catalyzed by (*S*)-diphenylprolinol TMS ether, which joins two sequential domino reactions, namely a domino sulfa-Michael/aldol condensation of α,β-unsaturated aldehydes with 1,4-dithiane-2,5-diol, and a domino Michael/α-alkylation reaction of the derived chiral dihydrothiophenes with bromonitromethane. The title compounds were obtained in 27−45% yields, with high levels of diastereoselectivity (93:7 to 100:0 dr) and generally good enantioselectivities (up to 95:5 er).



INTRODUCTION

About 130 years after the first synthesis of a cyclopropane derivative by William Henry Perkin, the strained three-membered carbocyclic ring motif still attracts attention from synthetic organic chemists.

Cyclopropane compounds are widely distributed among natural products and biologically active agents,[1] such as the *N*-methyl-D-aspartate (NMDA) receptor partial agonist 1-amino-cyclopropane-1-carboxylic acid (ACC, **1**),[2] the antibiotic and antitumor duocarmycin A **2**,[3] the phytotoxin coronatine **3**,[4] and the cholesteryl ester transfer protein inhibitor U-106305 **4**[5] (Figure 1).

Due to their distinguishing structural features, cyclopropanes can also serve as convenient synthons in several types of reactions.[6]

Nitrocyclopropanes represent a special family of cyclopropane compounds, which are found in natural products, such as the peptide lactone hormaomycin **5**[7] (Figure 2), and used in many synthetic transformations,[8] including the preparation of the broad-spectrum antibiotic Trovafloxacin.[9]

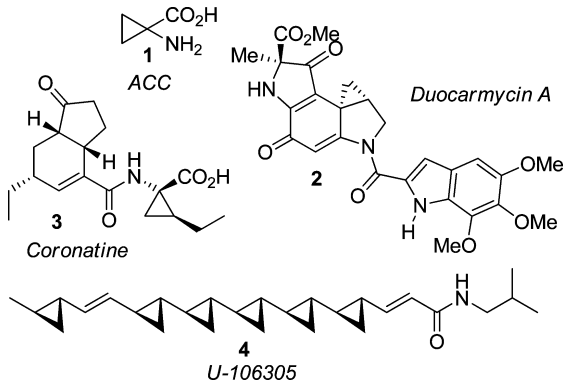


Figure 1. Structures of the cyclopropane-based bioactive compounds **1**−**4**.

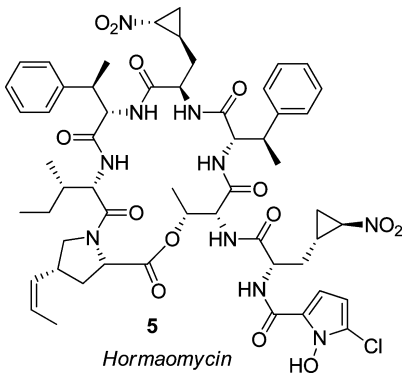


Figure 2. Structure of hormaomycin **5**.

In the past few decades, there has been a growing interest in developing stereoselective approaches to cyclopropanes.[10,11]

In this context, the Michael-initiated ring-closure (MIRC) reaction strategy[12] has been largely used to obtain nitrocyclopropane derivatives.[10b] In this approach, the target compounds are formed through a domino Michael/α-alkylation reaction, wherein the conjugate addition of a nucleophile to an electron-poor alkene generates a stabilized carbanion intermediate that then undergoes intramolecular ring-closure.

We have recently demonstrated that racemic 2,5-dihydrothiophene-3-carbaldehydes **8**, obtained by secondary amine-catalyzed domino sulfa-Michael/aldol condensations between

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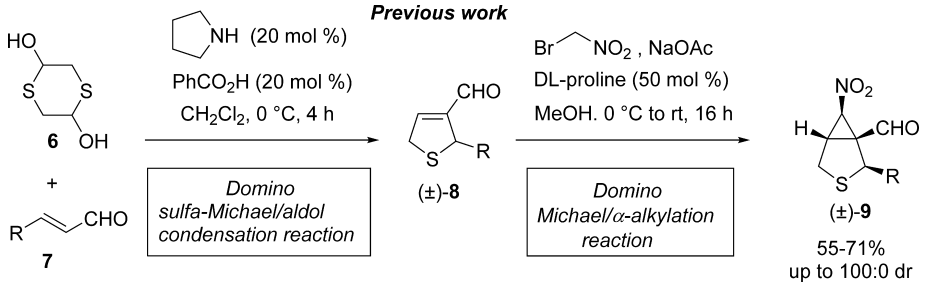
Scheme 1. Diastereoselective Nitrocyclopropanation of Racemic Dihydrothiophenes 8 Derived from Sulfa-Michael/Aldol Condensation Reaction



1,4-dithiane-2,5-diol **6** and α,β-unsaturated aldehydes **7**, were suitable substrates for cyclopropanations with bromonitromethane catalyzed by DL-proline (Scheme 1).[13] These reactions provided unprecedented bicyclic nitrocyclopropanes, namely 6-nitro-3-thiabicyclo[3.1.0]hexane-1-carbaldehydes **9**, in fair to good yields (55−71%) and good to excellent diastereoselectivities (up to 100:0 dr).

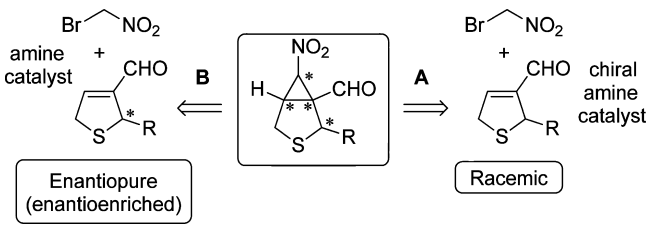
The compounds obtained are highly interesting bicyclic systems, due to the fusion of the nitrocyclopropane moiety to a tetrahydrothiophene nucleus, which is comprised in a number of pharmacologically important systems too. To date, structurally related derivatives have been already proved to be effective as agonists of metabotropic glutamate receptors.[14]

As a logical extension of our previous work, we embarked on the development of an asymmetric variant using chiral proline surrogates as catalysts, with a view to join the two catalytic domino sequences in a challenging four-step reaction, one-pot tandem process. Herein, we report the details of our studies which led us to disclose a one-pot, four-step asymmetric organocatalytic method, promoted by a single proline-based catalyst, giving the functionalized nitrocyclopropanes **9** with good to high diastereo- and enantioselectivies.

RESULTS AND DISCUSSION

At the outset, we conceived that the asymmetric synthesis of compounds **9** could be achieved by carrying out the two catalytic domino reactions separately, as we have done in racemic series. With this in mind, we explored two different MIRC strategies to install the nitrocyclopropane moiety onto a preformed 2,5-dihydrothiophene-3-carbaldehyde scaffold (Scheme 2): the reaction of bromonitromethane with a racemic

Scheme 2. Potential Strategies for the Asymmetric Synthesis of Functionalized Nitrocyclopropanes

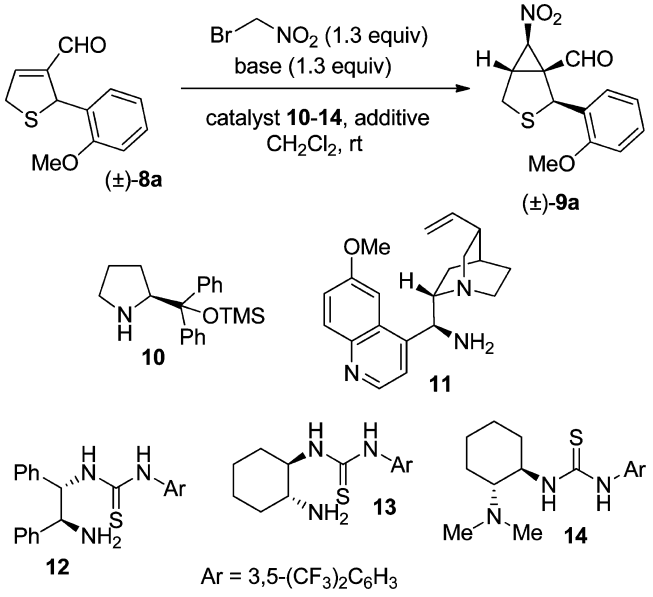


substrate catalyzed by a chiral amine organocatalyst (route A) or the reaction between bromonitromethane and an enantiopure (or enantioenriched) substance (route B).

In the first case, we hoped to obtain enantioenriched nitrocyclopropane adducts through kinetic resolution of the racemic dihydrothiophene substrate by means of the chiral organocatalyst, while in the second case we counted on the stereochemical bias of the preexisting stereogenic center upon nitrocyclopropanation.

To test the feasibility of our hypotheses, we performed a series of experiments using the model compound **8a** as reaction partner of bromonitromethane. As shown in Scheme 3,

Scheme 3. Investigation of Route A



investigation of route A was undertaken on racemic **8a**, conveniently prepared as reported.[13] We used catalysts **10**,[15] **11**,[16] and **12**,[17] which have been selected among the ones most efficiently used in asymmetric nitrocyclopropanation reactions of α,β-unsaturated carbonyl compounds.[18−20] Catalysts **13**[21] and **14**[22] were also included in our study.

With particular regards to catalyst **14**, we believed that it could promote the nitrocyclopropanation process through simultaneous activation of the Michael donor and the electrophilic aldehyde group by the tertiary amine and thiourea moieties, respectively.

Successful reactions were observed when (±)-**8a** was reacted with bromonitromethane (1.3 equiv) and triethylamine (1.3 equiv) in CH_2Cl_2 at room temperature, using primary and secondary amine catalysts **10**−**13** (20−40 mol %) in the presence of benzoic acid (10−40 mol %) as an additive. The expected nitrocyclopropane **9a** was obtained in yields ranging from 43 to 65% (Table S1, Supporting Information). In terms of enantioselectivity, the results were totally disappointing. In all cases, compound **9a** was obtained as a racemate, albeit

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Scheme 4. Re-examined Synthesis of Diidrothiophene (+)-8a

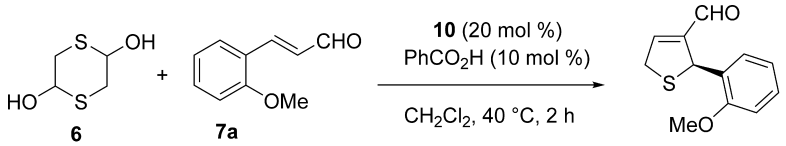
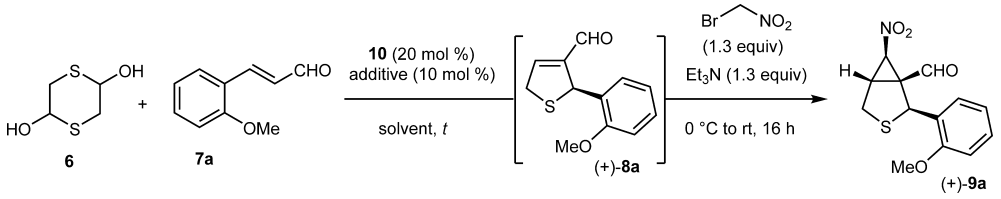


Table 1. One-Pot, Four-Step Organocatalytic Asymmetric Synthesis of Nitrocyclopropane (+)-9a[a]



entry	additive	solvent	t (°C)[b]	t (h)[c]	yield (%)[d]	er (%)[e]
1	**$PhCO_2H$**	**CH_2Cl_2**	**40**	**2**	**45**	**95:5**
2	$PhCO_2H$	EtOH	rt	2	–[f]	–
3	$PhCO_2H$	MeOH	rt	2	–[f]	–
4	$PhCO_2H$	PhMe	rt	5	26	90:10
5	$PhCO_2H$	CH_2Cl_2	rt	4	20	92:8
6	4-$NO_2C_6H_4CO_2H$	CH_2Cl_2	rt	4	18	92:8
7	4-$NO_2C_6H_4CO_2H$	PhMe	rt	16	18	99:1
8	4-$NO_2C_6H_4CO_2H$	PhMe	40	2	32	89:11

[a]Reaction conditions: **6** (0.372 mmol), **7a** (0.62 mmol), catalyst **10** (20 mol %), and additive (10 mol %) were stirred in solvent (2.0 mL) at the given temperature for the indicated time. Upon completion, the reaction mixture was cooled down to 0 °C, bromonitromethane (0.8 mmol) and triethylamine (0.8 mmol) were sequentially added, and the reaction mixture was kept at room temperature overnight. [b]Temperature at which the dihydrothiophene-forming step took place. [c]Duration of the dihydrothiophene-forming step. [d]Yield of isolated product. [e]Determined by HPLC analysis on a chiral stationary phase. [f]The thiophene product was obtained exclusively.

diastereomerically pure. On the basis of these results, we turned our attention to route B. Hence, an enantiopure (or enantioenriched) 2,5-dihydrothiophene-3-carbaldehyde substance was needed.

The recent work on the enantioselective synthesis of functionalized dihydrothiophenes through organocatalytic domino sulfa-Michael/aldol condensation reaction was selected for this purpose.[23] Accordingly, we attempted to prepare the known chiral dihydrothiophene (+)-**8a** under the reported experimental conditions. Thus, cinnamaldehyde **7a** and 1,4-dithiane-2,5-diol **6** (0.6 equiv) were reacted in toluene at room temperature for 12 h in the presence of (*S*)-diphenylprolinol TMS ether **10** (20 mol %) and 4-nitrobenzoic acid (10 mol %) as additive. Disappointingly, we were unable to reproduce the authors' findings. As a matter of fact, compound (+)-**8a** has been isolated in only 25% yield, with >99.5:0.5 er. Therefore, the reaction was re-examined (Table S2, Supporting Information) and slightly improved conditions were determined by carrying out the domino sulfa-Michael/aldol condensation reaction in CH_2Cl_2 at 40 °C for 2 h using benzoic acid (10 mol %) as additive (Scheme 4).

Although we ran the reaction under very carefully controlled conditions, we could not completely avoid the formation of various uncharacterized byproducts together with a certain amount of the aromatic thiophene derivative arising from oxidation of (+)-**8a**. Therefore, a very time-consuming and wasteful chromatographic purification of the crude reaction mixture was needed in order to isolate the target compound. At best, (+)-**8a** was obtained in 52% yield and 98:2 er.

We doubted that these difficulties might depend on the selected model compound, so we attempted the synthesis of some other chiral dihydrothiophenes among those reported,[23] but we experienced the same hurdles in any case. On the strength of this, we reasoned that a "one-pot" process, wherein the intermediate dihydrothiophene was not isolated but treated *in situ* with bromonitromethane anion, could circumvent the observed problems. In doing so, we envisioned to use the single organocatalyst **10** to promote both the dihydrothiophene-forming step and the following Michael/α-alkylation reaction rather than exploiting different amine organocatalysts for each domino process.

To prove the feasibility of this tactic, we ran an optimization study based on the findings obtained thus far. As shown in Table 1, the one-pot process could be run in CH_2Cl_2 (Table 1, entries 1, 5, and 6) or toluene (Table 1, entries 4, 7, and 8), with yields and enantioselectivities being influenced by both the acid additive and the temperature at which the dihydrothiophene-forming step took place.

Optimal conditions (Table 1, entry 1) were established by reacting dithiane **6**, cinnamaldehyde **7a**, amine catalyst **10** (20 mol %), and benzoic acid (10 mol %) in CH_2Cl_2 at 40 °C for 2 h, under inert atmosphere. Upon completion (TLC analysis), the reaction mixture was cooled down to 0 °C, treated with a bromonitromethane/triethylamine (1.3 equiv each) system, and kept at room temperature overnight. Gratifyingly, nitrocyclopropane (+)-**9a** was obtained as a single diastereomer in 45% isolated yield and 95:5 er (Table 1, entry 1).

Having established the best conditions for the one-pot, four-step organocatalytic process, we proceeded to investigate its scope using a variety of α,β-unsaturated aldehydes as partners of 1,4-dithiane-2,5-diol **6**. The results of these studies are summarized in Table 2.

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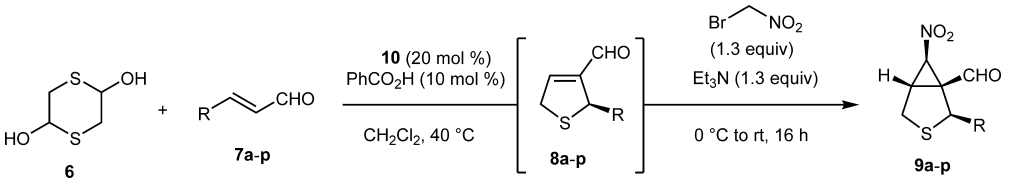
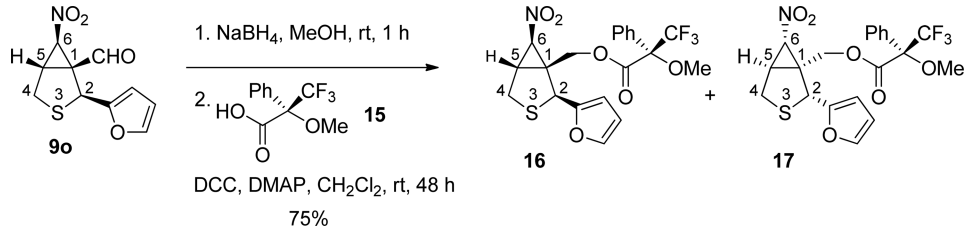
Table 2. One-Pot, Four-Step Organocatalytic Asymmetric Synthesis of Functionalized Nitrocyclopropanes 9a–p[a]



entry	aldehyde	R	product	t (h)	yield (%)[b]	dr (%)[c]	er (%)[d]
1	**7a**	2-MeOC$_6$H$_4$	**9a**	2	45	100:0	95:5
2	**7b**	3-MeOC$_6$H$_4$	**9b**	2	40	94:6	nd[e]
3	**7c**	4-MeOC$_6$H$_4$	**9c**	2	28	100:0	86:14
4	**7d**	2-MeC$_6$H$_4$	**9d**	1	40	100:0	93:7
5	**7e**	3-MeC$_6$H$_4$	**9e**	2	40	94:6	82:18[f]
6	**7f**	4-MeC$_6$H$_4$[g]	**9f**	2	35	94:6	85:15[f]
7	**7g**	2-NO$_2$C$_6$H$_4$	**9g**	1	42	100:0	90:10
8	**7h**	2-Me-5-NO$_2$C$_6$H$_4$	**9h**	1	30	100:0	92:8
9	**7i**	2-BrC$_6$H$_4$	**9i**	1	31	100:0	91:9
10	**7j**	3-BrC$_6$H$_4$	**9j**	1	27	96:4	87:13[f]
11	**7k**	4-BrC$_6$H$_4$	**9k**	1	27	100:0	93:7
12	**7l**	4-ClC$_6$H$_4$	**9l**	1	30	100:0	92:8
13	**7m**	2-CF$_3$C$_6$H$_4$	**9m**	1	35	100:0	94:6
14	**7n**	3-CF$_3$C$_6$H$_4$	**9n**	1	27	100:0	93:7
15	**7o**	2-furanyl[h]	**9o**	1	27	94:6	80:20[f]
16	**7p**	Ph	**9p**	1	31[i]	93:7	nd[e]

[a]Reaction conditions: **6** (0.372 mmol), **7** (0.62 mmol), catalyst **10** (20 mol %), and PhCO$_2$H (10 mol %) were stirred in CH$_2$Cl$_2$ (2.0 mL) at 40 °C for the indicated time. Upon completion, the reaction mixture was cooled down to 0 °C, bromonitromethane (0.8 mmol) and triethylamine (0.8 mmol) were sequentially added, and the reaction mixture was kept at room temperature overnight. [b]Yield of isolated product. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC analysis on a chiral stationary phase. [e]Not determined. [f]The er value of the major isomer. [g]Additional 10 mol % of catalyst **10** and 5 mol % of PhCO$_2$H were used in the cyclopropanation step. [h]40 mol % of catalyst **10** and 20 mol % of PhCO$_2$H were used. [i]Compound **9p** was slightly contaminated by uncharacterized byproducts.

Scheme 5. Derivatization of Nitrocyclopropane 9o to the Mosher Esters 16 and 17



β-Phenyl (Table 2, entry 16) and substituted β-phenyl (Table 2, entries 1–14) α,β-unsaturated aldehydes were suitable substrates for the organocatalytic process, providing the target nitrocyclopropanes in 27–45% yields. The position and nature of substituents on the β-phenyl ring had slight effect on stereocontrol. Good to very good enantioselectivities were observed (85:15 to 95:5 er), except for compound **9e** (82:18 er, Table 2, entry 5). The one-pot, four-step method was also applicable to the β-heteroaryl α,β-unsaturated aldehyde **7o**, providing compound **9o** in 27% yield and 80:20 er (Table 2, entry 15).

On the contrary, the reactions of 1,4-dithiane-2,5-diol **6** with alkyl α,β-unsaturated aldehydes were completely unsuccessful, leading to complex product mixtures.

It should be pointed out that the organocatalytic reactions gave moderate yields mainly due to the low efficiency of the dihydrothiophene-forming step. Similarly to what we have observed in the optimization studies of the sulfa-Michael/aldol condensation reaction, the chiral dihydrothiophenes were generally formed together with the corresponding thiophene derivatives and various uncharacterized byproducts, as confirmed by TLC and ^{1}H NMR monitoring. Every attempt to improve these outcomes failed, regardless of the reaction conditions and the α,β-unsaturated aldehyde used. Even so, it is worth noting that the observed yields are in regard with a process that takes place through four sequential reaction steps involving the formation of one C–S and three C–C bonds as well as one dehydration step, all of them occurring in a single operation.

Notably, the organocatalytic process displayed high diastereoselectivity. The nitrocyclopropane derivatives have been obtained as single diastereomers (100:0 dr, Table 2, entries 1, 3, 4, 7–9, and 11–14) or as mixtures of two diastereomers (93:7 to 96:4 dr, Table 2, entries 2, 5, 6, 10, 15, and 16). The latter were inseparable except for **9o** (94:6 dr, Table 2, entry 15). In this case, the major diastereomer was partially isolated by flash chromatography.

The relative and absolute configurations of the major diastereomers have been unambiguously assigned by X-ray crystallography. Since we were unable to obtain good quality single crystals of any diastereomerically pure nitrocyclopropane, we carried out a series of chemical transformations to prepare

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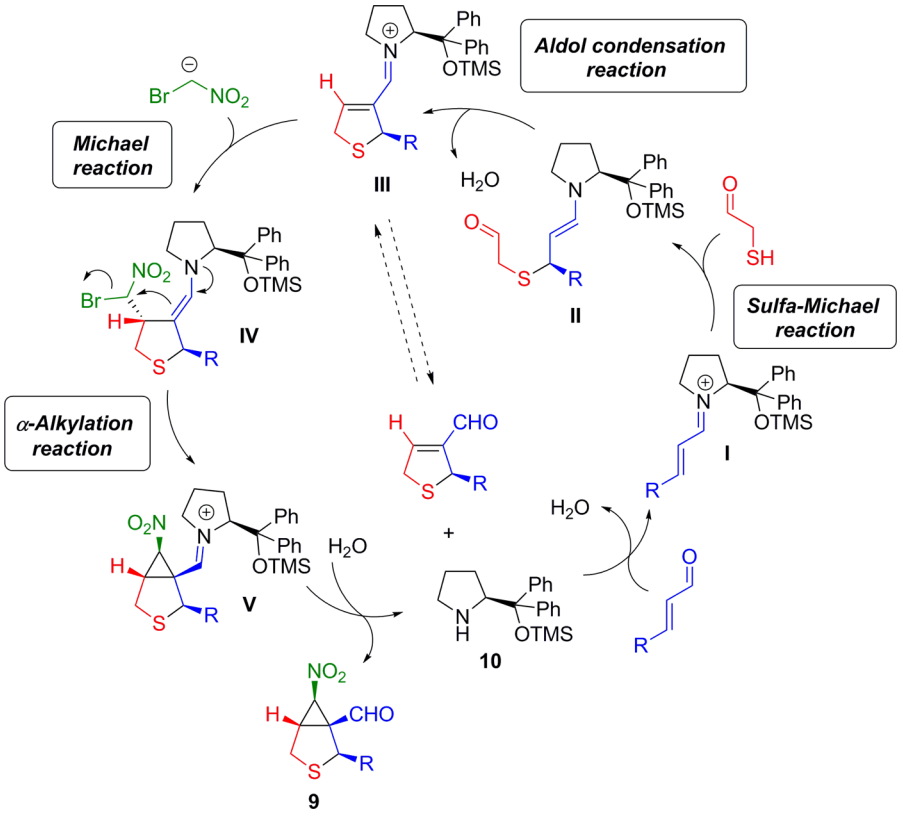
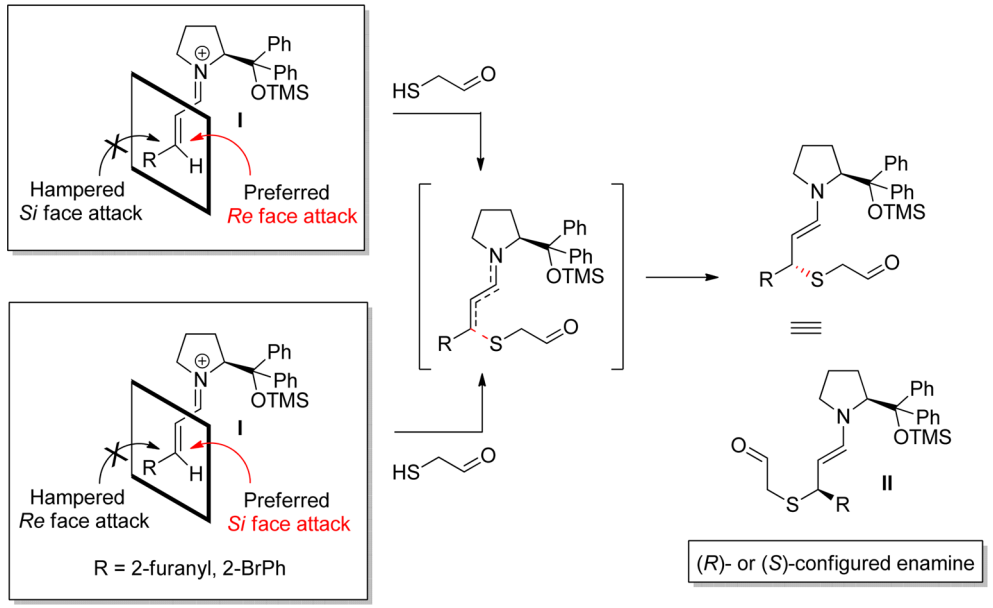
Scheme 6. Plausible Mechanism for the One-Pot, Four-Step Organocatalytic Process



Scheme 7. Enantiofacial Discrimination of Activated Olefin I



compounds suitable for X-ray structure determination. To our delight, reduction of the pure diastereomer **9o** (80:20 er) to the corresponding primary alcohol under standard conditions ($NaBH_4$, MeOH, rt), followed by DMAP-catalyzed esterification with (*S*)-Mosher acid **15**, gave diastereomeric esters **16** and **17** (80:20 dr) in 75% combined yield (Scheme 5). Purification by flash chromatography provided analytical samples of both products, and a single crystal of the minor ester **17** was produced by slow evaporation of an EtOAc solution at room temperature.

X-ray diffraction analysis of **17** allowed us to determine the (1*S*,2*R*,5*R*,6*S*) absolute configuration of its bicyclic core (Figure S3, Supporting Information).[24] This result revealed a *cis*-relationship between the nitro functional group, the hydroxymethyl ester moiety and the substituent at C2. Accordingly, we assigned the structure to compound **16**, and the configurations of all the major nitrocyclopropanes **9a**–**p** were

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established by analogy. Importantly, NMR analysis further supported this assignment. Indeed, ^{1}H NMR spectra of **9a−p** showed a diagnostic doublet signal for hydrogen H6 with $J_{H5,H6}$ = 3.3−3.6 Hz, which reflects its *trans* configuration with hydrogen H5.[25]

On the other hand, the structures of the minor nitrocyclopropane isomers have not been definitively identified. However, we may tentatively assume that the nitro and formyl groups have a *cis*-relationship, due to the H5−H6 coupling constants observed in the ^{1}H NMR spectra of these compounds.

Based on previous literature results,[23,26] a plausible mechanism for the one-pot, four-step organocatalytic process has been postulated (Scheme 6). Thus, activation of the α,β-unsaturated aldehyde by the organocatalyst **10** generates the iminium-ion **I**, which is attacked by *in situ* generated mercaptoacetaldehyde (sulfa-Michael reaction) to give the stereodefined enamine **II**. Next, intramolecular aldol reaction and dehydration (aldol condensation reaction) form intermediate **III** that undergoes reaction with bromonitromethane anion (Michael reaction) providing adduct **IV**. It is likely that the *Re* face of the carbon−carbon double bond in the iminium-ion **III** is effectively shielded by the bulky substituent on the organocatalyst framework, leaving the *Si* face exposed for carbon−carbon bond formation. Intramolecular nucleophilic substitution (α-alkylation reaction) of **IV** and hydrolysis of the resulting iminium-ion intermediate **V** provide the major nitrocyclopropane isomer **9**.

It may be assumed that benzoic acid promotes both the formation of **I** and the aldol condensation step as well as the hydrolysis of intermediate **V**. Moreover, we cannot exclude that intermediate **III** could be hydrolyzed to the corresponding aldehyde, but a plausible re-equilibration to **III** might take place under the reaction conditions.

In terms of enantiocontrol during the dihydrothiophene-forming step, we anticipated that the sterically demanding group at the organocatalyst residue efficiently shielded one face of the olefin in intermediate **I**. Hence, the incoming *S*-nucleophile preferentially attacked at the opposite, less hindered face (Scheme 7). Thus, shielding of the *Si* face forced the nucleophile to attack on the *Re* face to provide the (*R*)-configured enamine **II**. Notable exceptions would be the 2-furanyl- and 2-bromophenyl-substituted activated olefins, which gave the (*S*)-configured product via conjugate addition of mercaptoacetaldehyde from the deshielded *Si* face.

CONCLUSION

In summary, we have developed the asymmetric synthesis of functionalized nitrocyclopropanes via a one-pot, four-step organocatalytic process, catalyzed by (*S*)-diphenylprolinol TMS ether, which evolves through domino sulfa-Michael/aldol condensation of α,β-unsaturated aldehydes and 1,4-dithiane-2,5-diol followed by domino Michael/α-alkylation reaction of the derived chiral dihydrothiophene adducts with bromonitromethane. In spite of quite moderate yields (up to 45%), the products were obtained in good to high diastereoselectivities (up to 100:0 dr) and enantioselectivities (up to 95:5 er).

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were run under argon atmosphere, using freshly distilled solvents under anhydrous conditions. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 precoated plates, and all compounds were visualized by UV light and $KMnO_4$ (2% aqueous) spray test. Flash column chromatography was performed on silica gel 60 (230−400 mesh), using reagent grade solvents. Melting points (mp) were recorded with a melting point apparatus and are uncorrected.

^{1}H (300 MHz), ^{13}C (101 MHz), and ^{19}F (376 MHz) NMR spectra were recorded on 300 and 400 MHz spectrometers in $CDCl_3$, at room temperature unless otherwise stated. Chemical shifts are reported in δ (ppm), and coupling constants (*J*) are given in Hertz (Hz).

Optical rotations (α) were measured on a polarimeter with a sodium lamp in the given solvent at the indicated concentration (c, g/100 mL) and temperature (°C).

High resolution mass spectra (HRMS) data were obtained using a QTOF LC/MS mass spectrometer with a dual-electrospray ionization (ESI) source. Samples were dissolved in 10 mM solution of formic acid (0.1%) in 60:40 MeCN/H_2O, and the compounds were detected in positive ion mode by HPLC-Chip Q/TOF-MS (nanospray) analysis using a quadrupole and a time-of-flight unit to produce spectra.

Enantiomeric ratios (er) were determined by chiral HPLC analysis using 250 × 4.6 mm Lux 5 μm Cellulose-1 and 250 × 4.6 mm 5 μm ChiralPak ID columns. The mobile phase was a binary mixture *n*-hexane/*i*-PrOH.

Catalysts **10**[15] and **14**[22] were commercially available and were used without purification. Catalysts **11**,[16] **12**,[17] and **13**[21] were known compounds. They were synthesized according to the literature procedures, starting from quinine,[16] (1*S*,2*S*)-diphenylethylenediamine,[17] and (1*R*,2*R*)-1,2-diamino cyclohexane,[21] respectively.

Aldehydes **7a**, **7g**, **7o**, and **7p** were commercial products and were used as received. Aldehydes **7b−f**,[27] **7j**,[28] **7l**,[27] **7m**,[29] and **7n**[27] were known compounds, and aldehyde **7h** was a new compound. All of them were prepared from the appropriate aryl halide and acrolein diethyl acetal according to the literature procedure.[27] Aldehydes **7i** and **7k** were known compounds[28] and were prepared from a suitable benzaldehyde precursor and triphenylphosphoranilidene acetaldehyde following known directions.[30]

General Procedure for the Nitrocyclopropanation of Dihydrothiophene (±)-8a. The amine catalyst and the additive were added to a solution of (±)-**8a** (55 mg, 0.25 mmol) in CH_2Cl_2 (0.5 mL). After cooling to 0 °C, bromonitromethane (0.023 mL, 0.325 mmol) and the base (0.325 mmol) were sequentially added, and stirring was continued at room temperature for the indicated time (Table S1, Supporting Information). Upon completion (TLC analysis), the reaction mixture was evaporated to dryness, and the crude residue was purified by flash chromatography (7:1 cyclohexane/EtOAc) to afford compound (±)-**9a**. The physical and spectral data obtained are in accordance with those reported in the literature.[13]

*(+)-(R)-2-(2-Methoxyphenyl)-2,5-dihydrothiophene-3-carbaldehyde (**8a**).* To a solution of catalyst **10** (40 mg, 0.124 mmol) and $PhCO_2H$ (8 mg, 0.062 mmol) in CH_2Cl_2 (2 mL), cinnamaldehyde **7a** (100 mg, 0.62 mmol) and 1,4-dithiane-2,5-diol **6** (57 mg, 0.372 mmol) were sequentially added, and the reaction mixture was heated at 40 °C for 2 h. After cooling down, the reaction mixture was loaded onto a silica-gel column for purification (7:1 cyclohexane/EtOAc) to afford the product (+)-**8a**[23] (71 mg, 52%) as an amorphous yellow solid. $[\alpha]_D^{20}$ + 194 (c 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.24−7.16 (m, 1H), 7.15−7.10 (m, 1H), 7.00−6.94 (m, 1H), 6.90−6.82 (m, 2H), 5.88 (dt, *J* = 5.5, 1.7 Hz, 1H), 4.13 (ddd, *J* = 18.1, 5.5, 2.5 Hz, 1H), 4.02−3.91 (m, 1H), 3.87 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 187.5, 156.5, 150.7, 147.9, 130.6, 128.6, 126.9, 120.8, 111.0, 55.8, 47.9, 38.3 ppm; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{12}H_{13}O_2S$ 221.0631, Found 221.0637; HPLC conditions: Chiralpak ID, *n*-hexane/*i*-PrOH = 95:5, flow rate = 0.5 mL min^{-1}, λ = 220 nm, 25 °C, t_R = 31.69 (major), 33.46 (minor), 98:2 er.

*(E)-3-(2-Methyl-5-nitrophenyl)acrylaldehyde (**7h**).* Compound **7h** was obtained as an amorphous yellow solid (67 mg, 70%) from 2-methyl-5-nitrobenzaldehyde (96 mg, 0.5 mmol) according to the literature procedure.[27] The compound was purified by column chromatography (10:1 cyclohexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (d, *J* = 7.4 Hz, 1H), 8.43 (d, *J* = 2.4 Hz, 1H), 8.17 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.73 (d, *J* = 15.9 Hz, 1H), 7.43 (d, *J* = 8.4 Hz,

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1H), 6.77 (dd, J = 15.9, 7.4 Hz, 1H), 2.58 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 192.8, 146.9, 144.7, 134.2, 132.0, 131.8, 124.9, 121.8, 121.7, 20.1 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{10}NO_3$ 192.0655, Found 192.0658.

General Procedure for the One-Pot, Four-Step Organocatalytic Asymmetric Synthesis of Nitrocyclopropanes 9. To a solution of catalyst **10** (0.124 mmol) and $PhCO_2H$ (0.062 mmol) in CH_2Cl_2 (2 mL), cinnamaldehyde **7** (0.62 mmol) and 1,4-dithiane-2,5-diol **6** (0.372 mmol) were sequentially added, and the reaction mixture was heated at 40 °C for the indicated time (Table 2). Upon completion (TLC analysis), the reaction mixture was cooled down to 0 °C, bromonitromethane (0.8 mmol) and triethylamine (0.8 mmol) were sequentially added, and stirring was continued at room temperature overnight. The crude reaction mixture was loaded onto a silica-gel column for purification (cyclohexane/EtOAc) to afford the nitrocyclopropanation products **9**.

*(+)-(1R,2R,5S,6R)-2-(2-Methoxyphenyl)-6-nitro-3-thiabicyclo-[3.1.0]hexane-1-carbaldehyde (**9a**).* Column chromatography with 7:1 cyclohexane/EtOAc afforded the title compound **9a** (78 mg, 45%) as an amorphous yellow solid. $[\alpha]_D^{20}$ + 70.3 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.51 (s, 1H), 7.30−7.20 (m, 1H), 7.11−7.03 (m, 1H), 6.96−6.83 (m, 2H), 5.22 (s, 1H), 5.10 (d, J = 3.6 Hz, 1H), 3.86 (s, 3H), 3.67 (t, J = 3.8 Hz, 1H), 3.56 (dd, J = 11.5, 3.8 Hz, 1H), 3.26 (d, J = 11.5 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 192.2, 155.9, 129.6, 128.5, 128.3, 121.3, 111.2, 77.2, 67.0, 55.6, 52.2, 38.1, 33.0 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_4S$ 280.0638, Found 280.0647; HPLC conditions: Lux Cellulose-1, n-hexane/i-PrOH = 70:30, flow rate = 1 mL min^{-1}, λ = 280 nm, 25 °C, t_R = 36.85 (minor), 21.27 (major), 95:5 er.

*(1R,2R,5S,6R)-2-(3-Methoxyphenyl)-6-nitro-3-thiabicyclo[3.1.0]-hexane-1-carbaldehyde (**9b**).* Column chromatography with 6:1 cyclohexane/EtOAc afforded the yellow oil **9b** (69 mg, 40%) as a diastereomeric mixture (94:6 dr); ^1H NMR (300 MHz, $CDCl_3$) (as major isomer): δ 9.53 (s, 1H), 7.31−7.19 (m, 1H), 6.83−6.76 (m, 1H), 6.76−6.69 (m, 1H), 6.68−6.65 (m, 1H), 5.11 (d, J = 3.5 Hz, 1H), 4.82 (s, 1H), 3.79 (s, 3H), 3.73 (t, J = 3.5 Hz, 1H), 3.58 (dd, J = 12.1, 3.9 Hz, 1H), 3.33 (d, J = 12.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) (as major isomer): δ 192.0, 160.2, 142.7, 130.6, 118.7, 113.0, 112.9, 66.4, 55.2, 53.3, 52.6, 36.3, 32.5 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_4S$ 280.0644, Found 280.0650.

*(+)-(1R,2R,5S,6R)-2-(4-Methoxyphenyl)-6-nitro-3-thiabicyclo-[3.1.0]hexane-1-carbaldehyde (**9c**).* Column chromatography with 6:1 cyclohexane/EtOAc afforded **9c** (49 mg, 28%) as a yellow oil. $[\alpha]_D^{20}$ + 60.3 (c 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.50 (s, 1H), 7.10−7.04 (m, 2H), 6.88−6.81 (m, 2H), 5.09 (d, J = 3.5 Hz, 1H), 4.85 (s, 1H), 3.78 (s, 3H), 3.71 (t, J = 3.7 Hz, 1H), 3.58 (dd, J = 12.0, 3.9 Hz, 1H), 3.32 (d, J = 12.0 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 192.1, 159.4, 133.1, 127.9, 114.7, 66.5, 55.3, 53.0, 52.8, 36.3, 32.5 ppm; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{13}NNaO_4S$ 302.0457, Found 302.0469; HPLC conditions: Lux Cellulose-1, n-hexane/i-PrOH = 70:30, flow rate = 1 mL min^{-1}, λ = 280 nm, 25 °C, t_R = 22.38 (minor), 20.40 (major), 86:14 er.

*(+)-(1R,2R,5S,6R)-6-Nitro-2-(2-methylphenyl)-3-thiabicyclo-[3.1.0]hexane-1-carbaldehyde (**9d**).* Column chromatography with 10:1 cyclohexane/EtOAc afforded **9d** (65 mg, 40%) as an amorphous yellow solid. $[\alpha]_D^{20}$ + 120 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.57 (s, 1H), 7.20−7.12 (m, 3H), 6.99−6.91 (m, 1H), 5.19 (d, J = 3.4 Hz, 1H), 5.12 (s, 1H), 3.78 (t, J = 3.6 Hz, 1H), 3.52 (dd, J = 12.1, 3.7 Hz, 1H), 3.33 (d, J = 12.1 Hz, 1H), 2.39 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 192.4, 139.4, 135.2, 131.3, 128.0, 127.1, 125.2, 66.4, 52.4, 48.7, 36.5, 32.1, 20.1 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_3S$ 264.0694, Found 264.0696; HPLC conditions: Lux Cellulose-1, n-hexane/i-PrOH = 70:30, flow rate = 1 mL min^{-1}, λ = 210 nm, 25 °C, t_R = 26.32 (minor), 18.28 (major), 93:7 er.

*(1R,2R,5S,6R)-6-Nitro-2-(3-methylphenyl)-3-thiabicyclo[3.1.0]-hexane-1-carbaldehyde (**9e**).* Column chromatography with 8:1 cyclohexane/EtOAc afforded the yellow oil **9e** (65 mg, 40%) as a diastereomeric mixture (94:6 dr); ^1H NMR (300 MHz, $CDCl_3$) (as major isomer): δ 9.51 (s, 1H), 7.26−7.15 (m, 1H), 7.11−7.02 (m, 1H), 6.97−6.89 (m, 2H), 5.11 (d, J = 3.6 Hz, 1H), 4.83 (s, 1H), 3.74 (t, J = 3.7 Hz, 1H), 3.58 (dd, J = 12.0, 3.9 Hz, 1H), 3.32 (d, J = 12.0 Hz, 1H), 2.33 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) (as major isomer): δ 192.3, 141.2, 139.3, 129.4, 129.1, 127.4, 123.7, 66.6, 53.5, 52.7, 36.5, 32.6, 21.6 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_3S$ 264.0689, Found 264.0688; HPLC conditions: Lux Cellulose-1, n-hexane/i-PrOH = 70:30, flow rate = 1 mL min^{-1}, λ = 210 nm, 25 °C, t_R = 20.20 (minor), 17.08 (major), 82:18 er (for major isomer).

*(1R,2R,5S,6R)-6-Nitro-2-(4-methylphenyl)-3-thiabicyclo[3.1.0]-hexane-1-carbaldehyde (**9f**).* Column chromatography with 11:1 cyclohexane/EtOAc afforded the orange oil **9f** (57 mg, 35%) as a diastereomeric mixture (94:6 dr); ^1H NMR (300 MHz, $CDCl_3$) (as major isomer): δ 9.51 (s, 1H), 7.16−7.09 (m, 2H), 7.06−7.00 (m, 2H), 5.11 (d, J = 3.5 Hz, 1H), 4.84 (s, 1H), 3.75−3.70 (m, 1H), 3.62−3.54 (m, 1H), 3.32 (d, J = 12.0 Hz, 1H), 2.31 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) (as major isomer): δ 192.1, 138.1, 130.1, 126.5, 66.4, 53.2, 52.7, 36.3, 32.5, 26.9, 21.1 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_3S$ 264.0694, Found 264.0690; HPLC conditions: Lux Cellulose-1, n-hexane/i-PrOH = 70:30, flow rate = 1 mL min^{-1}, λ = 210 nm, 25 °C, t_R = 19.33 (minor), 16.00 (major), 85:15 er (for major isomer).

*(+)-(1R,2R,5S,6R)-6-Nitro-2-(2-nitrophenyl)-3-thiabicyclo[3.1.0]-hexane-1-carbaldehyde (**9g**).* Column chromatography with 3:1 cyclohexane/EtOAc afforded **9g** (77 mg, 42%) as an amorphous orange solid. $[\alpha]_D^{20}$ + 19 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 55 °C): δ 9.56 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.26−7.19 (m, 1H), 5.51 (s, 1H), 5.21 (d, J = 3.3 Hz, 1H), 3.82 (t, J = 3.6 Hz, 1H), 3.53 (dd, J = 12.1, 3.8 Hz, 1H), 3.35 (d, J = 12.2 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, 55 °C): δ 191.3, 148.1, 136.2, 133.6, 128.7, 128.2, 125.4, 66.2, 52.5, 48.4, 37.2, 32.4 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{11}N_2O_5S$ 295.0383, Found 295.0374; HPLC conditions: Chiralpak ID, n-hexane/i-PrOH = 40:60, flow rate = 0.5 mL min^{-1}, λ = 254 nm, 25 °C, t_R = 18.20 (minor), 19.20 (major), 90:10 er.

*(+)-(1R,2R,5S,6R)-2-(2-Methyl-5-nitrophenyl)-6-nitro-3-thiabicyclo[3.1.0]hexane-1-carbaldehyde (**9h**).* Column chromatography with 5:1 cyclohexane/EtOAc afforded **9h** (57 mg, 30%) as an amorphous yellow solid. $[\alpha]_D^{20}$ + 54.7 (c 1.62, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.62 (s, 1H), 8.00 (dd, J = 8.4, 2.3 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 5.27 (d, J = 3.3 Hz, 1H), 5.07 (s, 1H), 4.00 (t, J = 3.4 Hz, 1H), 3.64 (dd, J = 12.4, 3.7 Hz, 1H), 3.44 (d, J = 12.4 Hz, 1H), 2.50 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 192.4, 147.0, 143.0, 141.9, 132.0, 122.6, 119.9, 66.0, 52.7, 48.2, 36.4, 32.5, 20.4 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{13}N_2O_5S$ 309.0540, Found 309.0554; HPLC conditions: Lux Cellulose-1, n-hexane/i-PrOH = 50:50, flow rate = 1 mL min^{-1}, λ = 210 nm, 50 °C, t_R = 13.52 (minor), 9.91 (major), 92:8 er.

*(+)-(1R,2S,5S,6R)-2-(2-Bromophenyl)-6-nitro-3-thiabicyclo[3.1.0]-hexane-1-carbaldehyde (**9i**).* Column chromatography with 4.5:1 cyclohexane/EtOAc afforded **9i** (63 mg, 31%) as an amorphous yellow solid. $[\alpha]_D^{20}$ + 82.8 (c 1.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.32−7.25 (m, 1H), 7.13 (td, J = 7.8, 1.5 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 5.44 (s, 1H), 5.22 (d, J = 3.3 Hz, 1H), 3.80 (t, J = 3.5 Hz, 1H), 3.46 (dd, J = 12.2, 3.5 Hz, 1H), 3.32 (d, J = 12.2 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 191.9, 140.1, 133.7, 129.4, 128.5, 126.9, 123.8, 66.1, 52.1, 51.9, 36.3, 31.7 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{11}BrNO_3S$ 327.9617, Found 327.9622; HPLC conditions: Lux Cellulose-1, n-hexane/i-PrOH = 70:30, flow rate = 1 mL min^{-1}, λ = 210 nm, 25 °C, t_R = 33.16 (minor), 40.21 (major), 91:9 er.

*(1R,2R,5S,6R)-2-(3-Bromophenyl)-6-nitro-3-thiabicyclo[3.1.0]-hexane-1-carbaldehyde (**9j**).* Column chromatography with 5:1 cyclohexane/EtOAc afforded the yellow solid **9j** (45 mg, 27%) as a diastereomeric mixture (96:4 dr); ^1H NMR (300 MHz, $CDCl_3$) (as major isomer): δ 9.53 (s, 1H), 7.43−7.36 (m, 1H), 7.28 (t, J = 1.8 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.09−7.03 (m, 1H), 5.13 (d, J = 3.5 Hz, 1H), 4.79 (s, 1H), 3.78 (t, J = 3.6 Hz, 1H), 3.59 (dd, J = 12.2, 3.9 Hz, 1H), 3.35 (d, J = 12.2 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz,

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$CDCl_3$) (as major isomer): δ 192.0, 143.6, 131.4, 131.0, 129.7, 125.4, 123.4, 66.4, 52.9, 52.7, 36.4, 32.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{11}BrNO_3S$ 327.9643, Found: 327.9650; HPLC conditions: Chiralpak ID, *n*-hexane/*i*-PrOH = 40:60, flow rate = 0.5 mL min^{-1}, λ = 230 nm, 25 °C, t_R = 13.53 (minor), 14.78 (major), 87:13 er (for major isomer).

*(+)-(1R,2R,5S,6R)-2-(4-Bromophenyl)-6-nitro-3-thiabicyclo[3.1.0]-hexane-1-carbaldehyde (**9k**).* Column chromatography with 7:1 cyclohexane/EtOAc afforded **9k** (45 mg, 27%) as a yellow oil. $[\alpha]_D^{20}$ + 50.9 (c 0.67, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.51 (s, 1H), 7.48−7.42 (m, 2H), 7.05−6.98 (m, 2H), 5.13 (d, *J* = 3.5 Hz, 1H), 4.82 (s, 1H), 3.76 (t, *J* = 3.6 Hz, 1H), 3.57 (dd, *J* = 12.2, 3.9 Hz, 1H), 3.36 (d, *J* = 12.2 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 191.8, 140.3, 132.5, 128.3, 122.1, 66.2, 52.8, 52.6, 36.2, 32.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{11}BrNO_3S$ 327.9637, Found 327.9626; HPLC conditions: Lux Cellulose-1, *n*-hexane/*i*-PrOH = 50:50, flow rate = 1 mL min^{-1}, λ = 210 nm, 40 °C, t_R = 11.11 (minor), 9.15 (major), 93:7 er.

*(+)-(1R,2R,5S,6R)-2-(4-Chlorophenyl)-6-nitro-3-thiabicyclo[3.1.0]-hexane-1-carbaldehyde (**9l**).* Column chromatography with 4:1 cyclohexane/EtOAc afforded **9l** (53 mg, 30%) as an orange oil. $[\alpha]_D^{20}$ + 54.9 (c 2.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.51 (s, 1H), 7.33−7.26 (m, 2H), 7.11−7.04 (m, 2H), 5.13 (d, *J* = 3.5 Hz, 1H), 4.83 (s, 1H), 3.76 (t, *J* = 3.7 Hz, 1H), 3.58 (dd, *J* = 12.1, 3.9 Hz, 1H), 3.36 (d, *J* = 12.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 192.0, 139.9, 134.1, 129.6, 128.1, 66.4, 52.8, 52.5, 36.3, 32.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{11}ClNO_3S$ 284.0143, Found 284.0149; HPLC conditions: Lux Cellulose-1, *n*-hexane/*i*-PrOH = 50:50, flow rate = 1 mL min^{-1}, λ = 240 nm, 40 °C, t_R = 10.54 (minor), 8.90 (major), 92:8 er.

*(+)-(1R,2R,5S,6R)-6-Nitro-2-[2-(trifluoromethyl)phenyl]-3-thiabicyclo[3.1.0]hexane-1-carbaldehyde (**9m**).* Column chromatography with 4.5:1 cyclohexane/EtOAc afforded **9m** (69 mg, 35%) as an amorphous orange solid. $[\alpha]_D^{20}$ + 78.8 (c 3.54, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 5.26 (s, 1H), 5.21 (d, *J* = 3.6 Hz, 1H), 3.85 (t, *J* = 3.6 Hz, 1H), 3.54 (dd, *J* = 12.3, 3.8 Hz, 1H), 3.35 (d, *J* = 12.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 191.6, 140.6, 133.0, 128.0, 127.3 (q, $^2J_{C-F}$ = 30 Hz), 127.0, 126.7 (q, $^3J_{C-F}$ = 5.6 Hz), 124.2 (q, $^1J_{C-F}$ = 274 Hz), 66.2, 52.6, 47.9, 36.7, 32.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ − 58.1 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{11}F_3NO_3S$ 318.0406, Found 318.0403; HPLC conditions: Lux Cellulose-1, *n*-hexane/*i*-PrOH = 70:30, flow rate = 1 mL min^{-1}, λ = 210 nm, 25 °C, t_R = 14.21 (minor), 22.14 (major), 94:6 er.

*(+)-(1R,2R,5S,6R)-6-Nitro-2-[3-(trifluoromethyl)phenyl]-3-thiabicyclo[3.1.0]hexane-1-carbaldehyde (**9n**).* Column chromatography with 4.5:1 cyclohexane/EtOAc afforded **9n** (53 mg, 27%) as a yellow oil. $[\alpha]_D^{20}$ + 44.1 (c 1.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.38 (s, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 5.18 (d, *J* = 3.4 Hz, 1H), 4.90 (s, 1H), 3.83 (t, *J* = 3.6 Hz, 1H), 3.61 (dd, *J* = 12.2, 3.8 Hz, 1H), 3.39 (d, *J* = 12.2 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 191.8, 142.5, 131.8 (q, $^2J_{C-F}$ = 32 Hz), 130.1, 130.0, 125.1 (q, $^3J_{C-F}$ = 3.7 Hz), 123.8 (q, $^1J_{C-F}$ = 271 Hz), 123.5 (q, $^3J_{C-F}$ = 3.7 Hz), 66.3, 53.0, 52.8, 36.3, 32.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ − 63.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{11}F_3NO_3S$ 318.0406, Found 318.0403; HPLC conditions: Lux Cellulose-1, *n*-hexane/*i*-PrOH = 70:30, flow rate = 1 mL min^{-1}, λ = 210 nm, 25 °C, t_R = 18.92 (minor), 14.13 (major), 93:7 er.

*(+)-(1R,2S,5S,6R)-2-(Furan-2-yl)-6-nitro-3-thiabicyclo[3.1.0]-hexane-1-carbaldehyde (**9o**).* Column chromatography with 9:1 cyclohexane/EtOAc afforded the pure red brick oil **9o** and an unseparable mixture of **9o** and its diastereomer (40 mg, 27% combined yield). $[\alpha]_D^{20}$ + 74.4 (c 0.76, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.57 (s, 1H), 7.31 (d, *J* = 1.4 Hz, 1H), 6.31 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.22−6.18 (m, 1H), 5.14 (d, *J* = 3.5 Hz, 1H), 4.93 (s, 1H), 3.68 (t, *J* = 3.7 Hz, 1H), 3.61 (dd, *J* = 11.7, 3.8 Hz, 1H), 3.26 (d, *J* = 11.7 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 191.7, 152.3, 142.6, 110.8, 107.2, 65.7, 50.4, 45.8, 36.0, 32.2 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{10}NO_4S$ 240.0325, Found 240.0330; HPLC conditions: Lux Cellulose-1, *n*-hexane/*i*-PrOH = 70:30, flow rate = 1 mL min^{-1}, λ = 210 nm, 25 °C, t_R = 20.36 (minor), 22.54 (major), 80:20 er.

*(1R,2R,5S,6R)-6-Nitro-2-phenyl-3-thiabicyclo[3.1.0]hexane-1-carbaldehyde (**9p**).* Column chromatography with 5:1 cyclohexane/EtOAc afforded the orange oil **9p** as a diastereomeric mixture (93:7 dr) slightly contaminated by uncharacterized byproducts (48 mg, 31%); ^1H NMR (300 MHz, $CDCl_3$) (as major isomer): δ 9.51 (s, 1H), 7.38−7.21 (m, 3H), 7.18−7.10 (m, 2H), 5.13 (d, *J* = 3.5 Hz, 1H), 4.86 (s, 1H), 3.74 (t, *J* = 3.4 Hz, 1H), 3.59 (dd, *J* = 12.1, 3.9 Hz, 1H), 3.34 (d, *J* = 12.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) (as major isomer): δ 192.1, 141.3, 129.5, 128.3, 126.8, 66.5, 53.5, 52.8, 36.5, 32.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{12}NO_3S$ 250.0538, Found 250.0544.

Synthetic Procedure for the Preparation of Mosher Esters 16 and 17. To a cooled (0 °C) solution of **9o** (30 mg, 0.12 mmol) in MeOH (0.7 mL), $NaBH_4$ (6 mg, 0.16 mmol) was added, and the reaction mixture was vigorously stirred for 1 h at room temperature. The solvent was then removed *in vacuo*, and the crude product dissolved in CH_2Cl_2 (3 mL). (*S*)-Mosher acid **15** (35 mg, 0.15 mmol), DCC (37 mg, 0.18 mmol), and a catalytic amount of DMAP were sequentially added. The reaction mixture was left to stand at room temperature for 48 h, then filtered and evaporated. Purification of the crude residue by flash-chromatography (6:1 petroleum ether/EtOAc) gave esters **16** and **17** (41 mg, 75% overall yield).

*(+)-(S)-{(1R,2S,5S,6R)-2-(Furan-2-yl)-6-nitro-3-thiabicyclo[3.1.0]-hexan-1-yl}methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**16**).* White amorphous solid; $[\alpha]_D^{20}$ + 80.5 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45−7.34 (m, 6H), 6.32 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.13−6.04 (m, 1H), 5.00 (d, *J* = 3.1 Hz, 1H), 4.70 (d, *J* = 12.7 Hz, 1H), 4.61 (s, 1H), 4.19−4.11 (m, 1H), 3.59 (dt, *J* = 16.6, 8.3 Hz, 1H), 3.44 (d, *J* = 1.1 Hz, 3H), 3.23−3.09 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.7, 152.5, 143.1, 131.8, 129.7, 128.5, 127.3, 123.6 (q, $^1J_{C-F}$ = 287 Hz), 110.5, 108.0, 84.7 (q, $^2J_{C-F}$ = 28 Hz), 62.7, 61.4, 55.4, 47.9, 43.6, 35.9, 33.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ − 71.9 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}F_3NO_6S$ 458.0879, Found 458.0886.

*(−)-(S)-{(1S,2R,5R,6S)-2-(Furan-2-yl)-6-nitro-3-thiabicyclo[3.1.0]-hexan-1-yl}methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**17**).* White solid, mp 128−129 °C (EtOAc); $[\alpha]_D^{20}$ − 109.8 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.46−7.33 (m, 6H), 6.24 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.78 (d, *J* = 3.2 Hz, 1H), 5.03 (d, *J* = 3.0 Hz, 1H), 4.54 (d, *J* = 2.5 Hz, 2H), 4.12 (d, *J* = 12.7 Hz, 1H), 3.60 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.44 (d, *J* = 1.0 Hz, 3H), 3.16 (dd, *J* = 8.7, 5.7 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.8, 152.2, 143.0, 131.9, 129.7, 128.5, 127.1, 123.2 (q, $^1J_{C-F}$ = 287 Hz), 110.5, 108.1, 84.5 (q, $^2J_{C-F}$ = 28 Hz), 62.7, 61.6, 55.5, 47.7, 43.5, 35.8, 33.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ − 71.5 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}F_3NO_6S$ 458.0879, Found 458.0882.

Crystal Structure Determinations. X-ray diffraction suitable single crystals of **17** were obtained by slow evaporation of an EtOAc solution at room temperature. The crystal data of compound **17** were collected at room temperature using a diffractometer with graphite monochromated Mo−Kα radiation.

The data sets were integrated with the Denzo-SMN package[31] and corrected for Lorentz and polarization effects. The structure was solved by direct methods using SIR97[32] system of programs and refined using full-matrix least-squares with all non-hydrogen atoms anisotropically and hydrogens included on calculated positions, riding on their carrier atoms. All calculations were performed using SHELXL-97[33] implemented in WINGX[34] system of programs.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01607.

Table S1 (screening of route A), Table S2 (re-examination and optimization of the organocatalytic

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domino sulfa-Michael/aldol condensation reaction), Figure S3 (ORTEP/X-ray view of compound 17), copies of ^{1}H, ^{13}C, ^{19}F NMR spectra, and HPLC chromatograms (PDF)
X-ray crystallographic data (CIF)
(PDF)

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Notes

The authors declare no competing financial interest.

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