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Diastereodivergent Synthesis of 2-Ene-1,4-hydroxy Sulfides from 2-Sulfinyl Dienes via Tandem Sulfa-Michael/Sulfoxide-Sulfenate Rearrangement

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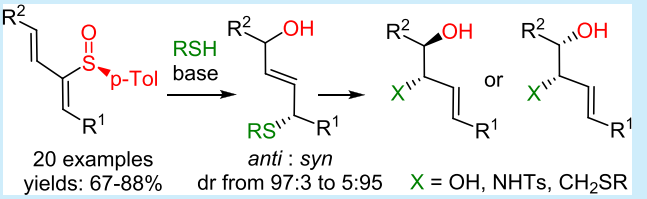
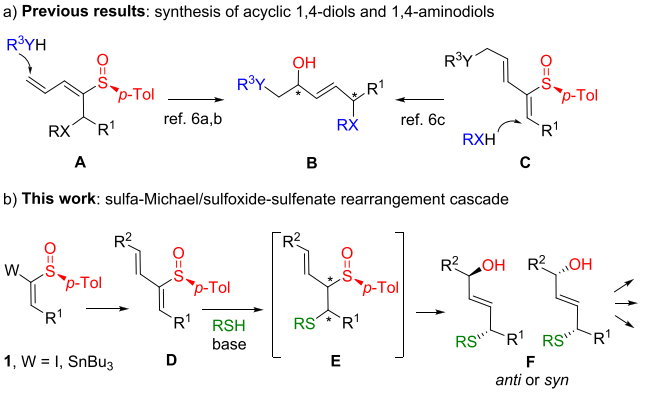
ABSTRACT: The highly diastereoselective sulfa-Michael addition of thiolates to enantiopure 2-sulfinyl dienes leads to *anti* or *syn* 2-ene-1,4-hydroxy sulfides in good yields and selectivities dependent on the reaction conditions in a diastereodivergent process. Synthetic applications of these enantiopure hydroxy sulfides by subsequent sigmatropic rearrangements have been outlined.



The asymmetric sulfa-Michael addition is a particularly useful, general, and versatile method to prepare carbon−sulfur bonds, of considerable importance in biological processes, material science, medicinal chemistry, and synthetic methodologies.[1] Within this field, thiol or thiolate additions to substituted alkenyl sulfoxides are relatively rare and unselective in some cases.[2] In recent years we have been involved in the application of readily available 1-sulfinyl dienes **A**[3] and 2-sulfinyl dienes **C**[4] (X = O, NTs, NR′; Y = O, NR′; Scheme 1)

Scheme 1. Cascade Processes for Syntheses of 2-Ene-1,4-difunctionalized Products



in stereoselective synthesis, including the conjugate addition of amines and alkoxides (R^3YH, RXH) to produce allylic sulfoxide intermediates that underwent a [2,3]-sigmatropic rearrangement,[5] ultimately leading to 1,4-diol or 1,4-amino-alcohol derivatives **B** in a cascade process, with good yields and stereoselectivities.[6] These results prompted us to examine the conjugate addition of thiolates to 2-sulfinyl dienes **D**, readily available from iodides or stannanes **1** (Scheme 1),[7] that could afford allylic sulfoxides **E**, and ultimately lead to allylic sulfides **F**.[8] The possibility of benefiting from the useful reactivity of enantiopure allylic sulfides **F** in highly stereocontrolled processes entailing sigmatropic rearrangements was an additional point of interest to embark on this study.[5,9−11]

In this report, we summarize our preliminary results on the stereocontrolled addition of thiolates to enantiopure 2-sulfinyl dienes followed by [2,3]-sigmatropic rearrangement and sulfenate cleavage to produce *anti* or *syn* hydroxy allylic sulfides **F** at will, in good yields and selectivities. In addition, further synthetic applications of allylic sulfides **F** in subsequent sigmatropic processes via allylic sulfoxides, sulfilimines, and sulfur ylides have been explored.

2-Sulfinyl dienes **2a−h** were selected for this study to address the influence of aryl and alkyl substitution, need for hydroxyl protection, and geometry of the dienes. These substrates have been synthesized from enantiopure 1-iodo vinyl sulfoxides, originally prepared from (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate, by Stille coupling[7] or coupling with vinyl boronic acids.[6c]

Table 1 summarizes our efforts directed to examine the viability and selectivity of the proposed tandem conjugate addition/[2,3]-sigmatropic rearrangement (for full details, see Supporting Information (SI)). We selected diene (*E*,*Z*)-**2a**, octanethiol, and benzyl thiol in the presence of NaH and *n*-BuLi in toluene, in analogy with previous results on alkoxide additions.[6c] After some experimentation, we found that sodium and lithium octyl thiolates afforded the desired 2-ene-1,4-hydroxy sulfide *anti*-**3a** in good yield and excellent diaster-

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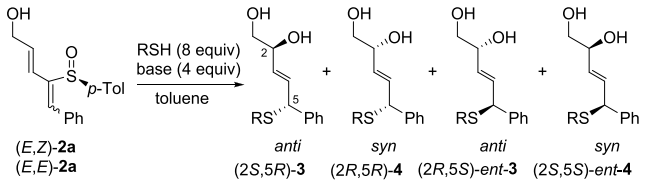
Table 1. Optimization of the Tandem Thiolate Conjugate Addition/[2,3]-Sigmatropic Rearrangement



entry	compd	RSH	base/temp/time	*anti*/*syn*[a,b]	yield[c]
1	(*E*,*Z*)-**2a**	octylSH	NaH/0 °C−rt/1 h	**3a**:**4a** 97:3	88%
2	(*E*,*Z*)-**2a**	octylSH	BuLi/0 °C−rt/3 h	**3a**:**4a** 97:3	86%
3	(*E*,*Z*)-**2a**	octylSH	20%DBU/rt/20 h	**3a**:**4a** 95:5	50%
4	(*E*,*Z*)-**2a**	BnSH	NaH/0 °C−rt/2 h	**3b**:**4b** 67:33	99%
5	(*E*,*Z*)-**2a**	BnSH	BuLi/0 °C−rt/3 h	**3b**:**4b** 75:25	80%
6	(*E*,*Z*)-**2a**	BnSH	BuLi/45 °C/2 h	**3b**:**4b** 90:10	87%
7	(*E*,*Z*)-**2a**	PhSH	NaH/0 °C−rt/3 h	**3c**:**4c** 9:91	71%
8	(*E*,*Z*)-**2a**	$MeOC_6H_4SH$	NaH/0 °C−rt/3 h	**3d**:**4d** 9:91	90%
9	(*E*,*Z*)-**2a**	$MeOC_6H_4SH$	BuLi/0 °C−rt/2 h	**3d**:**4d** 67:33	53%[d]
10	(*E*,*E*)-**2a**	octylSH	BuLi/0 °C−rt/24 h	**3a**:(*ent*-**4a**:**4a**) 0:(88:12)	76%
11	(*E*,*E*)-**2a**	BnSH	BuLi/0 °C−rt/20 h	**3b**:(*ent*-**4b**:**4b**) 10:(81:9)	78%

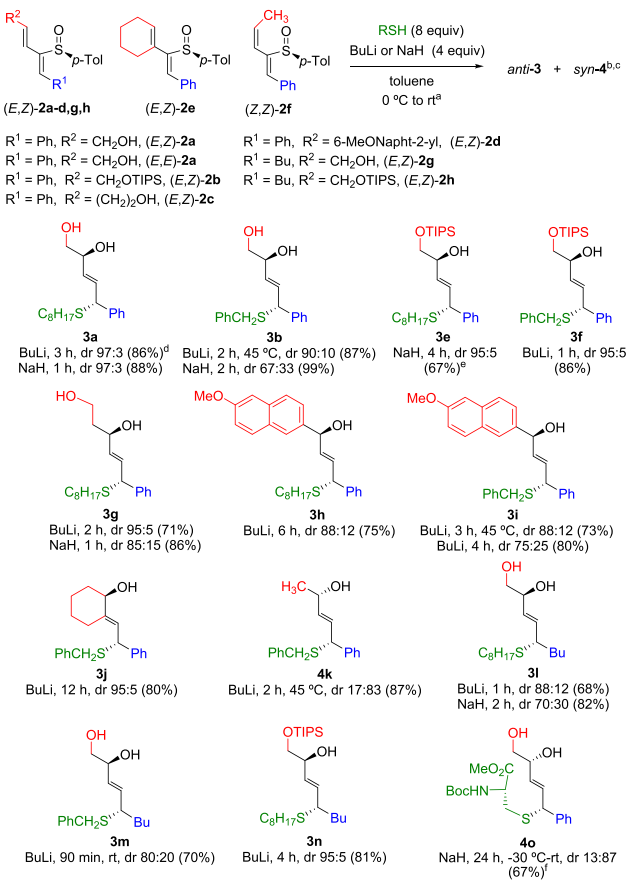
[a]Measured from the ^{1}H NMR of the reaction mixture. [b]Absolute configuration at C-2 was determined as (*S*)-MPA esters **5** and **6** (see SI). [c]Combined yield of **3** and **4**. [d]Minor amounts (5%) of (*E*,*E*)-**2a** were detected in the ^{1}H NMR of the reaction crude.

eoselectivity (*anti*/*syn*, 97:3). Other reaction conditions such as the addition of octanethiol in the absence of a base did not produce any addition product and DBU, frequently used as an initiator in sulfa-Michael reactions,[12] gave *anti*-**3a** in lower yield (Table 1, entries 1−3). In contrast to octanethiol, benzyl thiol using NaH or *n*-BuLi as bases led to a decrease in *anti*/*syn* selectivity that interestingly was improved by raising the reaction temperature to 45 °C (entries 4−6) to produce *anti*-**3b** in good yield and diastereoselectivity (87%, 90:10).

In sharp contrast, the use of aromatic thiols and NaH led to good yields and selectivities of *syn* 1,4-hydroxy sulfides **4c** and **4d** (9:91) with opposite configuration at C-2 determined by analysis of their (*S*)-MPA derivatives (see SI) (Table 1, entries 7 and 8). This stereochemical outcome was reversed with the lithium thiolate albeit in moderate selectivity to produce predominantly *anti*-**3d** (Table 1, entry 9). Finally, treatment of less reactive diene (*E*,*E*)-**2a** with LiSoctyl and LiSBn was examined in slower reactions (20−24 h) to produce predominantly *syn* products with lower enantiomeric ratios (Table 1, entries 10 and 11). Also, lower conversions and selectivities were observed for diene (*E*,*E*)-**2a** using sodium aryl thiolates (see, SI).[13]

Encouraged by these preliminary results we continued this study by focusing on octyl and benzyl thiolates and a variety of sulfinyl dienes with *Z* geometry at the sulfoxide bearing double bond, and the results obtained are summarized in Scheme 2. In addition, to **3a** and **3b**, discussed in Table 1, installing a TIPS silyl ether at the allylic alcohol produced excellent diastereoselectivities affording **3e** and **3f**. The addition is compatible with a homoallylic hydroxyl group in **2c** to afford **3g** in good yield and more demanding sterically or electronically sulfinyl dienes **2d**, **2e**, and **2f** are also viable substrates for this chemistry by using lithium thiolates (**3h**−**3j**, **4k**). In contrast with the addition of oxygen nucleophiles,[6c] 2-sulfinyl dienes **2g** and **2h** with an alkyl substituent at the position that undergoes the thiolate conjugate addition (R^1 = Bu) produced good yields of the *anti* products **3l**, **3m**, and **3n** with good to excellent diastereoselectivities. Interestingly, the use of sodium thiolates in some cases decreases the amount of *anti*-**3** in the mixture. Finally, we examined briefly the use of *N*-Boc cysteine

Scheme 2. Scope for the Reaction of Alkyl and Benzyl Thiolates[a]



[a]Conditions: The reaction was performed from 0 °C to rt unless otherwise stated. [b]The absolute configuration of **3** and **4** was determined from the MPA esters **5** and **6** (see SI). [c]Dr expressed as *anti*/*syn* ratio. [d]Combined yield. [e]Minor byproducts were also isolated (20%) and characterized (see SI). [f]A 5% of (*E*,*E*)-**2a** was also detected in the crude reaction mixture.

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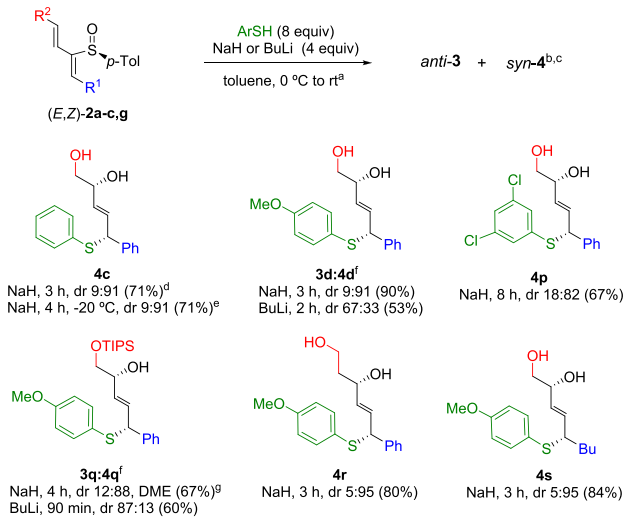
methyl ester as a representative example of a more functionalized thiol, and after some experimentation, adduct **4o** was obtained in acceptable yield and fair selectivity, along with minor amounts (5%) of (*E*,*E*)-**2a** detected in the ^{1}H NMR of the crude reaction mixture. It should be pointed out that unexpectedly **4o** has a *syn* relationship of chiral centers as determined from the MPA ester.

The scope of the cascade reaction for aromatic thiolates was examined next (Scheme 3). A remarkable inversion of

Scheme 3. Scope for the Reaction of Aryl Thiolates[a]

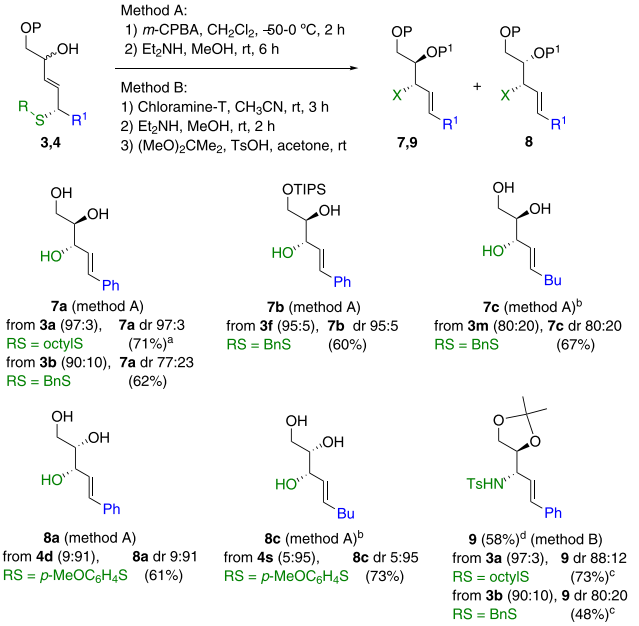


[a]Conditions: The reaction was performed in toluene from 0 °C to rt unless otherwise stated. [b]The absolute configuration was determined from the MPA esters **5** and **6** (see SI). [c]Dr expressed as *anti*/*syn* ratio. [d]Combined yield. [e]20% of (*E*,*E*)- and (*E*,*Z*)-**2a** was detected as a 50:50 mixture. [f]Monosilylation of **4d** provides **4q** in good yield (see SI). [g]10% of (*E*,*E*)-**2b** was also observed in the ^{1}H NMR of the crude mixture.

diastereoselectivity was observed upon treatment of diene (*E*,*Z*)-**2a** with sodium thiolates from thiophenol, thioanisole, and 3,5-dichlorobenzenethiol leading mainly to *syn*-2-ene-1,4-hydroxy sulfides **4c**, **4d**, and **4p**. Lowering the reaction temperature to −20 °C did not improve the diastereoselectivity for **4c** but led to lower conversion with partial double bond isomerization to the less reactive (*E*,*E*)-**2a**. A similar trend has been found for (*E*,*Z*)-dienes **2c** and **2g** to produce *syn* 1,4-hydroxy sulfides (**4r** and **4s**) in excellent yields and selectivities. Sulfinyl dienes lacking a hydroxyl group (**2d**, **2e**, **2f**) gave sluggish reactions with aryl thiolates except for **2b** which selectively yielded **4q** using the more polar solvent DME. Interestingly, the addition of aromatic lithium thiolates increases significantly the amount of *anti* 1,4-hydroxy sulfides (**3d** and **3q**), particularly for silyloxy diene **2b** that produces *anti*-**3q** with a complete reversal of diastereoselectivity compared with sodium thiolate.

The diastereodivergent preparation of allylic sulfides **3** and **4** from sulfinyl dienes **2** allowed us to take advantage of the rich reactivity of this moiety by stereocontrolled [2,3]-sigmatropic rearrangements (Scheme 4). Initially, we examined the tandem sulfide oxidation/sulfoxide-sulfenate reaction with *m*-CPBA and Et_2NH as a thiophile (method A) for *anti* hydroxy sulfides **3** that consistently led to triol derivatives **7a**−**7c** maintaining the *anti*/*syn* ratio of the starting materials (**3a**, **3f**, and **3m**). Interestingly, a decrease in selectivity was observed for **7a**

Scheme 4. Synthesis of Triol and Hydroxy Sulfonamido Derivatives[a]



[a]Combined yield unless otherwise stated. [b]Et_2NH, toluene, 85 °C, 6 h (**7c**); Et_2NH, MeOH, 40 °C, 2 h (**8c**). [c]Combined yield for diols (not shown). [d]Overall isolated yield for *anti*-**9** from **3a**.

when benzyl sulfide **3b** was submitted to the reaction conditions compared with octyl sulfide **3a** (from 90:10 to 77:23). Similarly to the *anti* diastereoisomers, *syn* aromatic sulfides **4d** and **4s** (R = 4-MeO-C_6H_4) gave triols **8a** and **8c** in good yields and with no loss of diastereoselectivity. Notably, substrates **3m** and **4s** with an alkyl group at the double bond (R^1 = Bu) needed higher temperatures to undergo the [2,3]-sigmatropic rearrangement. It should be pointed out that diastereomeric triols *anti*-**7** and *syn*-**8** can be prepared at will from the same sulfinyl diene by choosing the suitable thiolate. The structure of the known triols **7a** and **8a** was further confirmed by transformation to the isopropylidene ketals and comparison of the NMR data[14] allowing establishment of the absolute configuration for the carbon−sulfide center in the precursors (**3a** and **4d**) which evolved through a suprafacial sulfoxide-sulfenate rearrangement, transferring the chirality from the C_5−S bond to the new C_3−O bond.[1j,5a] On the other hand, imination of *anti* allylic sulfides **3a** and **3b** with chloramine-T and subsequent [2,3]-sigmatropic rearrangement of the transient sulfilimines (method B) gave a bis-hydroxy sulfonamide derivative that was isolated as isopropylidene ketal **9** in moderate yield and with a small decrease in diastereoselectivity from the starting materials.

Finally, diastereomerically enriched 1,4-hydroxy sulfides *anti*-**3q** (87:13) and *syn*-**4q** (9:91) were protected as MOM acetals (**10** and **11**) and treated with CH_2I_2/$ZnEt_2$ in oxygenated toluene to afford sulfide *anti*-**12** or *syn*-**13**, respectively, resulting from a [2,3]-sigmatropic rearrangement of a sulfur ylide intermediate with excellent diastereoselectivity and good isolated yields. It should be pointed out that both sulfides are ultimately derived from a single starting diene (*E*,*Z*)-**2a** (Scheme 5). The absolute configuration of **12** and **13** was further confirmed through selective removal of the MOM protecting group ($ZnBr_2$/$C_8H_{17}SH$/CH_2Cl_2/rt) to give

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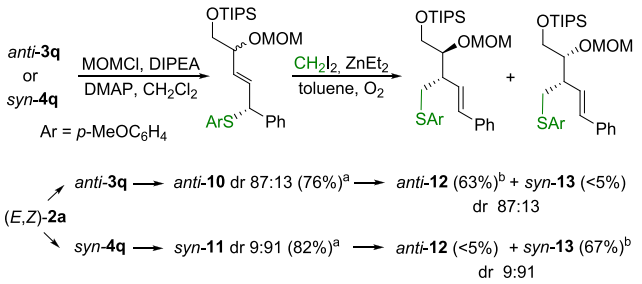
Scheme 5. Sulfur Ylide Rearrangement[a]

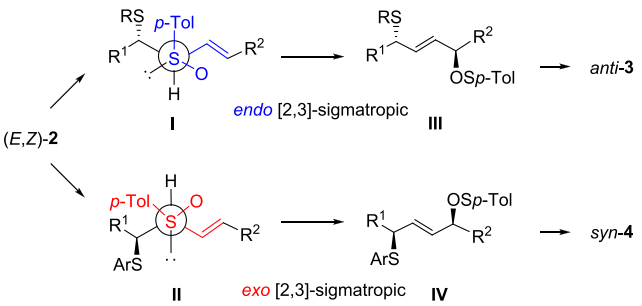


[a]Combined yield. [b]Isolated yield.

hydroxy sulfides *anti*-**14** and *syn*-**15** (not shown) and preparation of the MPA esters (see SI).

The simplified rationalization of the stereochemical outcome of this tandem process shown in Scheme 6 results from a

Scheme 6. Stereochemical Outcome for the Synthesis of 3 and 4



delicate interplay of factors such as starting material, thiol, counterion, solvent, and temperature. We believe that initial fast conjugate addition of alkyl thiolates onto the *si*-face of the dienyl sulfoxide and stereoselective α protonation gives transient allylic sulfoxide **I** that undergoes a favorable *endo* [2,3]-sigmatropic rearrangement to sulfenate **III**, rapidly cleaved by excess thiolate to produce *anti*-**3**. In contrast, the use of aryl thiolates results in an enhanced *syn* selectivity that may be attributed to β protonation of the intermediate sulfinyl carbanion to produce allylic sulfoxide **II**, probably due to stabilizing interactions between aromatic rings (*p*-Tol and ArS) at the carbanion stage that bring about a conformational change prior to protonation; this trend is particularly important for sodium aryl thiolates. Subsequent *exo* [2,3]-sigmatropic rearrangement produces sulfenate **IV** and ultimately 2-ene-1,4-hydroxy sulfide *syn*-**4** as the main product. Interestingly, benzyl thiolates stand at an intermediate stage consistently producing *anti*-**3** with lower diastereoselectivities than alkyl thiolates.

In summary, a diastereodivergent synthesis of *anti* and *syn* 2-ene-1,4-hydroxy sulfides from enantiopure 2-sulfinyl dienes has been described. The transformation entails a cascade reaction triggered by a conjugate addition of thiolates to give a transient allylic sulfoxide that undergoes sulfoxide-sulfenate rearrangement followed by in situ sulfenate cleavage. The overall diastereoselectivity is strongly influenced by the nature of thiolate and counterion as well as by the structure of the starting diene. We have also outlined that subsequent [2,3]-sigmatropic rearrangements of these highly useful enantiopure 1,4-hydroxy sulfides provide an efficient and diastereoselective access to *anti* or *syn* acyclic triol and hydroxy sulfide derivatives that can be obtained at will from a single 2-sulfinyl diene by the proper choice of thiolate and counterion.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03929.

Experimental details and chemical compound information; copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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