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Remote Stereocontrol in the Synthesis of Acyclic 1,4-Diols and 1,4-Aminoalcohols from 2-Sulfinyl Dienes

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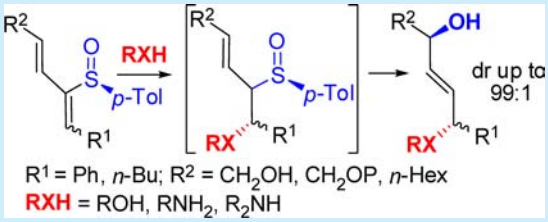
Supporting Information

ABSTRACT: The highly diastereoselective conjugate addition of alcohols and amines (RXH) to enantiopure 2-sulfinyl dienes renders transient allylic sulfoxides which undergo sulfoxide−sulfenate rearrangement and sulfenate cleavage providing 2-ene-1,4-diols and 2-ene-1,4-aminoalcohols with up to 99:1 dr. The method allows for the generation of two stereocenters in a single synthetic operation with remote chirality transfer of one center into the other.

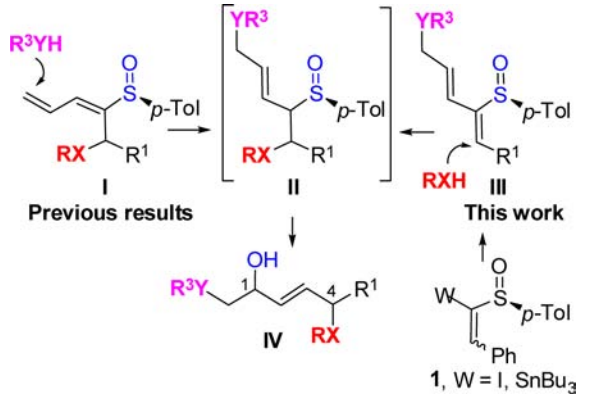


The enantioselective synthesis of molecules containing two nonadjacent stereocenters such as 1,4-diols and 1,4-aminoalcohols is an appealing task for synthetic chemists due to the inherent difficulties of the synthesis,[1] and their presence in biologically significant products.[2] Some of the existing approaches for the synthesis of acyclic stereodefined unsaturated 1,4-diols entail the addition of organometallic reagents to carbonyl derivatives,[3] olefin metathesis of chiral allylic alcohols,[4] and stereoselective reduction of functionalized ketones.[5] Alternative methods involve 1,4-hydroxycarbonyl compounds, epoxides, or 1,3-dienes as starting materials.[6] In contrast, reports on the preparation of substituted 2-ene-1,4-aminoalcohols are less frequent with routes mainly focused on Pd-catalyzed allylic substitution, enantioselective alkylation of 4-aminoaldehydes, or reduction of 1,2-oxazines derived from asymmetric [4 + 2] cycloaddition.[7]

The diastereoselective sulfoxide−sulfenate rearrangement of acyclic allylic sulfoxides has been scarcely documented in the literature.[8] Recently, a sequence comprising olefination of α-thio β-amino and β-hydroxy aldehydes followed by sulfoxide−sulfenate rearrangement has been employed for the synthesis of 1,4-diols and 1,4-aminoalcohols.[8c]

In recent years, we have applied readily available α-heterosubstituted 1-sulfinyl dienes **I** (RX = OH, NHTs; Scheme 1) to the stereoselective synthesis of densely functionalized products.[9] In particular, Michael addition of a suitable amine (R^3YH)[9a] to **I** followed by base-induced isomerization produces *E*-allylic sulfoxide **II**. The ensuing [2,3]-sigmatropic rearrangement leads, after sulfenate cleavage, to valuable 1,4-diol or 1,4-aminoalcohol derivatives **IV** with high diastereoselectivity in many cases. However, when alcohols are used as nucleophiles (R^3YH = alcohols) lower dr's of 1,4-diols were found. Besides, the low diastereoselectivity of the synthesis of the starting materials **I** (RX = OH)[9c] undermines the efficiency of the route and requires additional steps to transform the undesired diastereomer by a Mitsunobu protocol.

Scheme 1. Strategies for the Synthesis of 1,4-Diols and 1,4-Aminoalcohols



This prompted us to explore the diastereocontrolled conjugate addition of nucleophiles (RXH) to enantiopure 2-sulfinyl dienes **III**, readily available from **1**, that could also render allylic sulfoxides **II** and provide 1,4-diols or 1,4-aminoalcohols through subsequent diastereoselective [2,3]-sigmatropic rearrangement.

This alternative approach would install both stereocenters in a single synthetic operation with overall remote stereocontrol of one center into the other. Our previous reports on the synthesis of dihydropyrans and tetrahydropyridines through an intramolecular conjugate addition to (*Z*,*Z*)-2-sulfinyl dienes supported the viability of the approach.[10] Some years ago we reported an efficient Stille coupling protocol to prepare 2-sulfinyl dienes (**III**) from iodo vinyl sulfoxides **1** and vinyl stannanes as a general methodology.[11] Nevertheless, to expand

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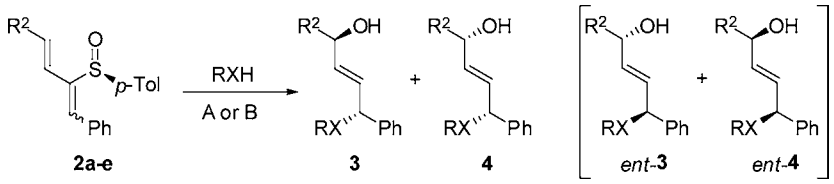
Table 1. Synthesis of 1,4-Diol and 1,4-Aminoalcohol Derivatives from Dienyl Sulfoxides



entry	method[a]	2, diene (R^2)	RXH	*anti*/*syn*	ratio[b]	yield[c]
1	**A**	(*E*,*Z*)-**2a** (CH_2OH)	BnOH	**3a**:**4a**	85:15	63
2	**A**	(*E*,*E*)-**2b** (CH_2OH)	BnOH	*ent*-**3a**:*ent*-**4a**	16:84	63[d]
3	**A**	(*E*,*Z*)-**2a** (CH_2OH)	*p*-$MeOC_6H_4CH_2OH$	**3b**:**4b**	70:30	82
4	**A**	(*E*,*E*)-**2b** (CH_2OH)	*p*-$MeOC_6H_4CH_2OH$	*ent*-**3b**:*ent*-**4b**	10:90	57[d]
5	**A**	(*E*,*Z*)-**2a** (CH_2OH)	(*S*)-PhCH(Me)OH	**3c**:**4c**	99:1	70
6	**A**	(*E*,*Z*)-**2a** (CH_2OH)	(*R*)-PhCH(Me)OH	**3d**:**4d**	95:5	64[e]
7	**A**	(*E*,*Z*)-**2c** ($CH_2OTBDPS$)	BnOH	**3e**:**4e**	95:5	77[f]
8	**A**	(*E*,*Z*)-**2d** (CH_2OTIPS)	BnOH	**3f**:**4f**	95:5	60
9	**A**	(*E*,*Z*)-**2d** (CH_2OTIPS)	*p*-$MeOC_6H_4CH_2OH$	**3g**:**4g**	92:8	87
10	**A**	(*E*,*Z*)-**2d** (CH_2OTIPS)	*o*-$IC_6H_4CH_2OH$	**3h**:**4h**	92:8	70
11	**A**	(*E*,*Z*)-**2e** (*n*-Hex)	(*S*)-PhCH(Me)OH	**3i**:**4i**	99:1	65
12	**A**[g]	(*E*,*Z*)-**2d** (CH_2OTIPS)	$BnNH_2$	**3j**:**4j**	90:10	30
13	**B**	(*E*,*Z*)-**2a** (CH_2OH)	$BnNH_2$	**3k**:**4k**	90:10	75
14	**B**	(*E*,*Z*)-**2a** (CH_2OH)	allylamine	**3l**:**4l**	95:5	85
15	**B**	(*E*,*Z*)-**2a** (CH_2OH)	piperidine	**3m**:**4m**	92:8	68

[a]**A**: ROH, NaH, toluene, rt. **B**: Neat RR′NH, 70−90 °C. [b]Diastereomeric *anti*/*syn* ratio measured in the crude mixture of **3** and **4** or α-methoxyphenyl acetate derivatives; the ee's for **3** and **4** are higher than 95:5 unless otherwise noted. [c]Combined yield of pure compounds. [d]*ent*-**3** (dr = 90:10) and *ent*-**4** (dr = 90:10) from the ^{1}H NMR of the α-methoxyphenyl acetates. [e]5% of dimer **SI-1** was also obtained. [f]15% of silyl migration product was also obtained. [g]$BnNH_2$, *n*-BuLi or NaH, toluene, rt.

the scope of the method, we have also examined alternative routes to 2-sulfinyl dienes, such as the coupling of vinyl boronic acids and iodo alkenes (R^2 = *n*-Hex) with iodides and stannanes **1** respectively (Scheme 1).[12] These procedures provide good yields of 2-dienyl sulfoxide (*E*,*Z*)-**2e** (Table 1) increasing the versatility of the overall sequence.

Initial treatment of diene (*E*,*Z*)-**2a** with NaOMe or K_2CO_3 in MeOH promoted the conjugate addition followed by the [2,3]-sigmatropic rearrangement in reasonable yield, but the desired 1,4-diol derivatives were obtained with poor *syn*/*anti* diastereoselectivity. After considerable experimentation, we found that using NaH and benzyl alcohol in toluene provided an 85:15 *anti*/*syn* mixture of **3a** and **4a**. The conversion is readily improved when 4 equiv of NaH are used along with an excess (10−15 equiv) of alcohol reaching 63% yield. A parallel result (**3b**/**4b**, 70:30) was obtained for *p*-methoxybenzyl alcohol (Table 1, entries 1 and 3). In contrast, when (*E*,*E*)-**2b** was treated under similar conditions, the *anti*/*syn* ratio was reversed with *ent*-**4a** and *ent*-**4b** as the major products (Table 1, entries 2 and 4). Despite the slight increase in diastereomeric ratio, a lower enantiomeric ratio (er: 90:10) for each diastereomer was observed after conversion into the α-methoxyphenyl acetates.

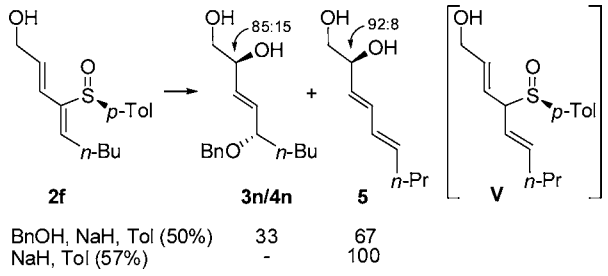
The diastereoselectivity significantly improved using chiral nucleophiles. Thus, the addition of (*S*)- and (*R*)-1-phenyl ethanol afforded *anti*-1,4-diols **3c** and **3d** practically as single products; however, occasionally long reaction times allowed for the formation of minor amounts (8%) of a dimer **SI-1** resulting from nucleophilic addition of the primary hydroxyl group in **3d** (R^2 = CH_2OH) to unreacted diene **2a**.[13]

Installing a silyl ether group in the 2-sulfinyl diene (**2c**, R^2 = CH_2OSiPh_2t-Bu) significantly improved the diastereoselectivity (**3e**/**4e**, 95:5); however using a TIPS group (**2d**) is more convenient to prevent silyl migration products in the reaction mixtures (Table 1, entries 8−10). Subsequent desilylation of **3f** smoothly led to 1,4-diol **3a** in higher purity. Substitution of R^2 by a simple alkyl group [*n*-Hex, (*E*,*Z*)-**2e**] does not alter the good diastereoselectivity of the process (Table 1, entry 11).

Subsequently, we explored the addition of nitrogen nucleophiles to (*E*,*Z*)-**2a**. We initially examined different reaction conditions (amine/NaH or *n*-BuLi/toluene; amine/EtOH) that led to crude mixtures with high diastereoselectivities but low conversion and reproducibility. Alternatively, good yields and *anti* stereoselectivities for **3k**−**m** (Table 1, entries 13−15) were obtained by heating (70−90 °C) the diene in the neat amine for primary ($BnNH_2$, $allylNH_2$) or secondary (piperidine) amines.

Finally, we examined the behavior of diene **2f** (R^1 = *n*-Bu, Scheme 2). The use of methanol as a nucleophile led to a high yield of a modestly selective mixture (80:20) of *anti* and *syn* diols. In contrast, treatment of **2f** with BnOH/NaH/toluene gave a 33:67 mixture of conjugate addition products and dienyl diol [**3n**,**4n**/**5**; dr (**3n**/**4n**): 85:15]. Diene **5** was presumably formed by allylic deprotonation of the alkyl chain followed by regioselective sigmatropic rearrangement. Treating 2-sulfinyl

Scheme 2. Conjugate Addition to Butyl Sulfinyl Dienes



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diene **2f** with NaH in toluene gave a fair yield of dienyl diol **5**, formed as a 92:8 mixture of enantiomers; this remarkable finding provides a measure for regio- and stereocontrol in the sulfoxide−sulfenate rearrangement of a bis allylic sulfoxide **V**.

One of the main difficulties of this research was the analysis of the inseparable diastereomeric mixtures (**3**/**4**). Measuring the *anti*/*syn* ratios in the ^{1}H NMR spectra of the reaction crudes was often very difficult since the diastereomers are practically identical. Conversion of the mixtures into the separable diastereomeric α-methoxyphenyl acetates was necessary to clearly observe splitting of signals providing the ratio of diastereomers and also, through differences in chemical shifts, a reliable description for the absolute configuration of the allylic hydroxyl.[14] After many attempts to prepare a suitable crystalline derivative of **3**,[15] a complete structural description was possible by X-ray analysis of bis-dinitrobenzoate **6** (Figure 1).

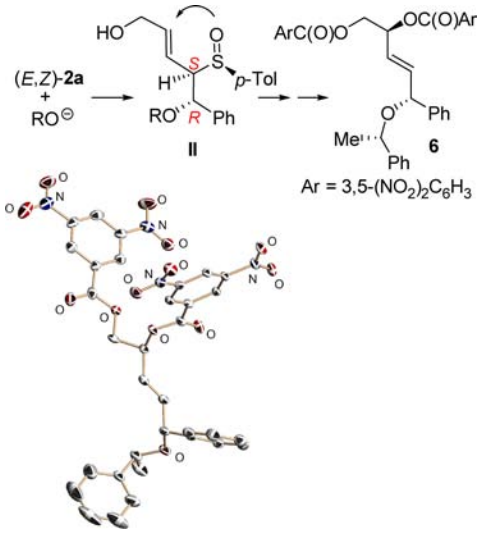
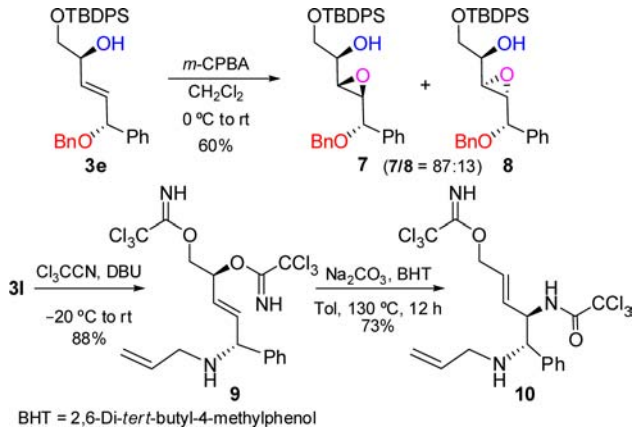


Figure 1. Stereochemical outcome and crystal structure of bis-3,5-dinitrobenzoate from *anti*-**3c**.

Our proposal to account for the stereochemical outcome of the process entails sulfoxide directed conjugate addition of the nucleophile (RONa or RNH_2) onto the *si* face of (*E*,*Z*)-dienes **2a** similarly to our previous results for diastereoselective nucleophilic epoxidation of vinyl and dienyl sulfoxides (ROONa).[16] This addition generates a transient (1*R*,2*S*)-allylic sulfoxide **II** that undergoes [2,3]-sigmatropic rearrangement affording predominantly (*E*)-2-ene *anti*-1,4-diols and 1,4-aminoalcohols **3**. The excess of nucleophile (ROH, 10−15 equiv) probably participates as a source of protons to quench the α-sulfinyl carbanion as well as a thiophile for sulfenate cleavage. Alternatively from (*E*,*E*)-dienes **2b**, with a mixture of reactive sulfinyl conformers, the *re* attack provides a *syn* major product *ent*-**4** albeit with lower stereocontrol in the conjugate addition leading to an overall less enantioselective result.

To explore upcoming synthetic applications of the 1,4-diols we have briefly examined the epoxidation of **3e** and the Overman rearrangement of **3l** (Scheme 3). Thus, treatment of **3e** with *m*-CPBA in CH_2Cl_2 produced an 87:13 mixture of diastereomeric epoxides with generation of four contiguous oxygenated stereocenters in just two steps from a 2-sulfinyl diene. Alternatively, the thermal rearrangement of bis-trichoroacetimidate **9** led smoothly to trichloroacetamide **10** in good yield.

Scheme 3. Diastereoselective Epoxidation of 3e and Rearrangement of 9



In summary, we have outlined a novel method for the diastereoselective synthesis of enantiopure acyclic unsymmetrical 2-ene-1,4-diols and 2-ene-1,4-aminoalcohols from 2-sulfinyl dienes with construction of both stereocenters in a single synthetic operation. This protocol entails conjugate addition of alcohols and amines to produce a transient allylic sulfoxide that undergoes sigmatropic rearrangement and sulfenate cleavage in high overall selectivity. The scope and applications of the methodology are being examined in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of new compounds, crystal data and cif file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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