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Dithiane Additions to Vinyl Epoxides: Steric Control over the S_N2 and S_N2' Manifolds

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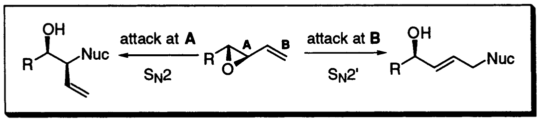
Lithiated dithiane anions, important umpolung linchpins in organic chemistry,[1] are frequently exploited for both the stereocontrolled generation of a wide variety of protected aldol linkages[2] and for the union of advanced fragments in complex molecule synthesis.[3] Recently, we became interested in the addition of lithiated dithianes to vinyl epoxides, electrophiles that contain more than one nucleofugal site. Herein, we report that high chemoselectivity *vis-à-vis* the S_N2 and S_N2' manifolds can be achieved by varying the steric properties of the dithiane anions (Scheme 1). In addition, we demonstrate that the S_N2' process proceeds via *syn* addition to the epoxide.

Scheme 1

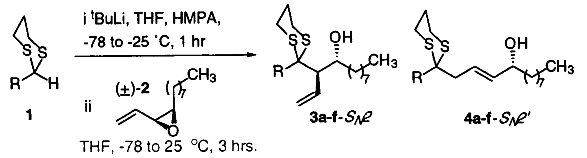


Although nucleophilic additions to alkenes possessing a leaving group at the allylic position (e.g., S_N2 versus S_N2') have been studied extensively during the past 40 years,[4] there are relatively few reports on the addition of carbon nucleophiles to vinyl epoxides,[5] in contrast to the data available for heteroatom additions.[4e,g] Notable exceptions are Lewis acid-promoted S_N2 additions of alkyllithiums,[6] transition metal-catalyzed reactions with vinyl epoxides,[7] and selective S_N2' additions of organocuprates,[8] We were particularly interested in reactions proceeding via the S_N2' manifold (position **B**, Scheme 1) for complex natural product construction.

At the outset, we speculated that tuning the steric properties of lithiated 2-substituted-1,3-dithianes might lead to chemoselectivity during the addition step. A small nucleophile was reasoned to attack preferentially at the activated allylic position[9] via S_N2 addition, whereas a more sterically demanding nucleophile would add to the more accessible alkene terminus in an S_N2' fashion. The ultimate goal was selective production of either the S_N2 or S_N2' adduct. To test this thesis, vinyl epoxide **2**[10] was treated with 2-lithio-1,3-dithiane (**1a**) in THF containing 2−3 equiv of hexamethylphosphoramide (HMPA); only the S_N2 adduct **3a** was observed (83% yield, Table 1). Similarly, 2-lithio-2-phenyl-1,3-dithiane (**1b**) produced only the S_N2 adduct **3b** in good yield. Our development of the multicomponent linchpin coupling protocol of 2-trialkylsilyl-1,3-dithianes with simple epoxides[3b] led us to test the trimethylsilyl derivative **1c**; again only S_N2 addition occurred, albeit furnishing a 1:1 mixture of the homoallylic alcohol (**3c**) and the TMS−ether resulting from 1,4-Brook rearrangement. These results suggested that the allylic position in vinyl epoxide **2** is indeed activated, thereby promoting nucleophilic attack exclusively at position **A** (Scheme 1).[9]

Importantly, the lithium anions derived from alkyl-substituted dithianes (**1d** and **1e**) and the sterically more demanding 2-triisopropylsilyl-1,3-dithiane (**1f**) led to a complete reversal of selectivity. With epoxide **2**, the S_N2' adducts (**4d**−**f**) were observed exclusively in good yield (Table 1); only the *E*-alkene was generated. To rationalize these results we postulated that in the presence of HMPA, the 2-lithio-1,3-dithiane derivatives are monomeric,[11] hence permitting an accurate correlation of the steric environment of the dithiane anion.[12]

Table 1. Addition of Substituted Dithiane Anions to Vinyl Epoxides



dithiane	R	yield (%)	ratio 3:4[a]
1a	H	83	100:0
1b	Ph	85	100:0
1c	$SiMe_3$	83	100:0[b]
1d	Et	81	0:100
1e	iPr	81	0:100
1f	$Si\text{-}iPr_3$	85	0:100

[a] Ratio of isolated compounds. [b] Underwent 1,4-Brook rearrangement to a 1:1 mixture of non Brook:Brook products.

Encouraged by these results, attention was directed toward the nature of the vinyl epoxide. With the lithium anions derived from dithianes **1a**−**c** (Table 2), vinyl epoxides **5**, **6**, **7**, and **8** afforded only the S_N2 adducts in good yield (entries 1−12). Not surprisingly, in the presence of HMPA, adducts obtained with TMS-dithiane **1c** underwent 1,4-Brook rearrangement to give the TMS−ethers (entries 9−12).[13] Importantly, *cis* vinyl epoxides **5** and **6** provided exclusively the *anti* S_N2 adduct, whereas the *trans* epoxides **7** and **8** afforded only the *syn* S_N2 adduct.[14] In both cases yields were good. Likewise, the lithium anions derived from dithianes **1d** and **1e** added to epoxide **5** to give the S_N2' products **9d′** and **9e′**, respectively (entries 13 and 17); although chemoselectivity was compromised with epoxides **6**, **7**, and **8**, the S_N2' adducts did predominate (ca. 3−5:1; entries 14−16 and 18−20).[15] Importantly, addition of the highly encumbered lithium anion derived from TIPS−dithiane **1f** proceeded in good yield exclusively via S_N2' attack with all vinyl epoxides (entries 21−24). Thus, at the two extremes of dithiane anion substitution (R = H or R = TIPS), either the S_N2 or the S_N2' manifold can be accessed with excellent selectivity.

To expand the scope of this method we explored the effect of substitution on the alkene of the vinyl epoxide. Success would offer insight into the mechanism of the S_N2' reaction.[16] Toward this end,

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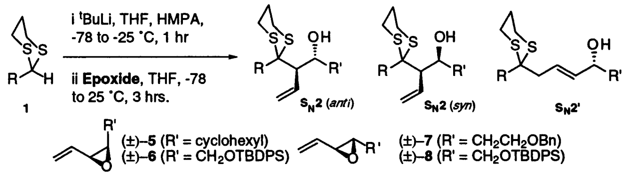
Table 2. Reaction Scope

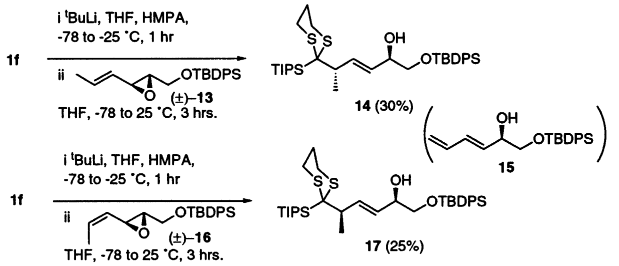


entry	dithiane[a]	epoxide	yield (%)	S_N2:S_N2'[b]	product
1	**1a** (R=H)	5	74	100 (*anti*):0	**9a**
2	**1a**	6	85	100 (*anti*):0	**10a**
3	**1a**	7	89	100 (*syn*):0	**11a**
4	**1a**	8	69	100 (*syn*):0	**12a**
5	**1b**(R=Ph)	5	82	100 (*anti*):0	**9b**
6	**1b**	6	88	100 (*anti*):0	**10b**
7	**1b**	7	86	100 (*syn*):0	**11b**
8	**1b**	8	74	100 (*syn*):0	**12b**
9	**1c**(R=TMS)	5	85	100 (*anti*):0	**9c**[c]
10	**1c**	6	88	100 (*anti*):0	**10c**[c]
11	**1c**	7	76	100 (*syn*):0	**11c**[c]
12	**1c**	8	78	100 (*syn*):0	**12c**[c]
13	**1d**(R=Et)	5	78	0:100	**9d′**
14	**1d**	6	84	1 (*anti*):3.5	**10d/10d′**
15	**1d**	7	82	1 (*syn*):3	**11d/11d′**
16	**1d**	8	73	1 (*syn*):5	**12d/12d′**
17	**1e**(R=iPr)	5	84	0:100	**9e′**
18	**1e**	6	74	1 (*anti*):5	**10e/10e′**
19	**1e**	7	63	1 (*syn*):4	**11e/11e′**
20	**1e**	8	74	1 (*syn*):3	**12e/12e′**
21	**1f**(R=TIPS)	5	86	0:100	**9f ′**
22	**1f**	6	81	0:100	**10f ′**
23	**1f**	7	84	0:100	**11f ′**
24	**1f**	8	80	0:100	**12f ′**

[a] Reagent and conditions: tBuLi, THF, HMPA, −78 to −25 °C, 1 h then epoxide in THF, −78 to 25 °C, 3 h. [b] Ratio of isolated compounds. [c] **9c**, **10c**, **11c**, and **12c** underwent 1,4-Brook rearrangement to a 1:1 mixture of non-Brook:Brook products.

vinyl epoxides **13** and **16** were subjected to lithiated dithiane **1f**; adducts **14** and **17**, resulting from S_N2' addition were isolated, albeit in modest yield (Scheme 2); the corresponding diene elimination product **15** was also produced. Importantly, only one S_N2' product was observed in each case. The relative stereochemistry of **14** and **17**, established via chemical correlation with compounds of known stereochemistry,[17] revealed that the dithiane addition takes place in a *syn* fashion with respect to the epoxide.

Scheme 2



In summary, high chemoselectivity can be achieved in the addition of lithium dithiane anions to vinyl epoxides by exploiting the steric nature of the dithiane. Unencumbered dithiane anions afford S_N2 adducts, whereas sterically encumbered anions lead primarily to S_N2' additions. Furthermore, the S_N2' additions occur *syn* to the vinyl epoxide. The utility of the observed S_N2 versus S_N2' selectivities both in multicomponent- and target-oriented syntheses will be presented in due course.

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Note Added after ASAP: The initial ASAP version of this paper published 11/13/2002 on the Web did not include ref 11c. The final Web version published 11/18/2002 and the print version are correct.

Supporting Information Available: Spectroscopic data for **1**−**17** as well as representative experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See Supporting Information for determinination of the *anti/syn* configurations of the S_N2 adducts.

(15) A remote stereoelectronic effect may be responsible for this loss in selectivity in view of the fact that the TBDPS ethers in **6** and **8** do not significantly affect the outcome of the reaction, thus ruling out the possibility of lithium-chelated activation of the vinyl epoxide.

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(17) See Supporting Information for the details of the chemical correlation.

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