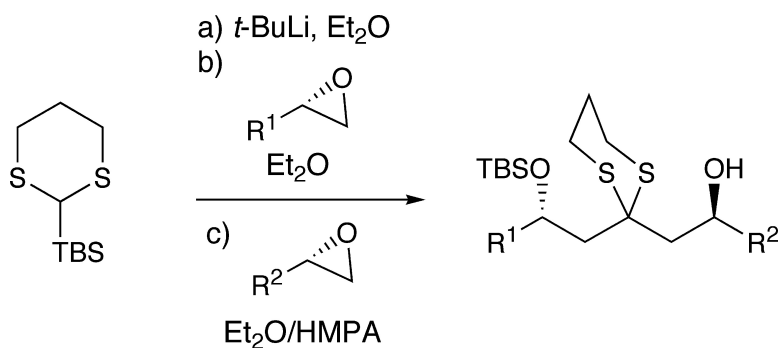**Article**

Multicomponent Linchpin Couplings. Reaction of Dithiane Anions with Terminal Epoxides, Epichlorohydrin, and Vinyl Epoxides: Efficient, Rapid, and Stereocontrolled Assembly of Advanced Fragments for Complex Molecule Synthesis

Amos B. Smith, Suresh M. Pitram, Armen M. Boldi, Matthew J. Gaunt, Chris Sfouggatakis, and William H. Moser

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Multicomponent Linchpin Couplings. Reaction of Dithiane Anions with Terminal Epoxides, Epichlorohydrin, and Vinyl Epoxides: Efficient, Rapid, and Stereocontrolled Assembly of Advanced Fragments for Complex Molecule Synthesis

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Contribution from the Department of Chemistry, Monell Chemical Senses Center and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104

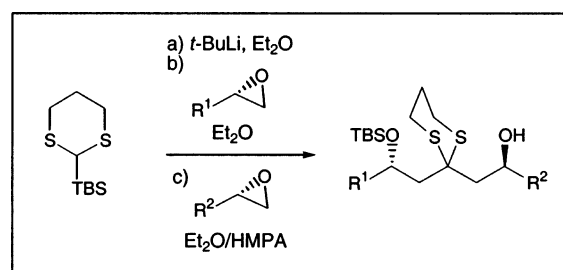Received July 29, 2003; E-mail: smithab@sas.upenn.edu

Abstract: The development, application, and advantages of a one-flask multicomponent dithiane linchpin coupling protocol, over the more conventional stepwise addition of dithiane anions to electrophiles leading to the rapid, efficient, and stereocontrolled assembly of highly functionalized intermediates for complex molecule synthesis, are described. Competent electrophiles include terminal epoxides, epichlorohydrin, and vinyl epoxides. High chemoselectivity can be achieved with epichlorohydrin and vinyl epoxides. For vinyl epoxides, the steric nature of the dithiane anion is critical; sterically unencumbered dithiane anions afford S_N2 adducts, whereas encumbered anions lead primarily to S_N2' adducts. Mechanistic studies demonstrate that the S_N2' process occurs via syn addition to the vinyl epoxide. Integration of the multicomponent tactic with epichlorohydrin and vinyl epoxides permits the higher-order union of four and five components.

Dithianes have evolved as invaluable tools in organic synthesis, serving primarily as acyl anion equivalents for constructing carbon-carbon bonds.[1,2] The efficient, convergent construction of partially or fully protected aldol linkages in a stereocontrolled manner employing epoxides as the electrophile is a particularly attractive feature of dithiane chemistry and, as such, serves as an effective alternative to the classical aldol reaction. Indeed, an early prominent aspect of several synthetic ventures undertaken in this laboratory comprised the assembly of subtargets of varying structural complexity exploiting dithianes as linchpins.[3] In these early examples, two building blocks were joined, one a substituted lithiated 1,3-dithiane, the other an electrophile such as an iodide, epoxide, aldehyde, or ketone.

In 1997, we disclosed a three-component, one-flask linchpin tactic employing 2-*tert*-(butyldimethylsilyl)-1,3-dithiane with two different epoxide electrophiles to construct unsymmetrical

adducts, exploiting a solvent-controlled Brook rearrangement (Scheme 1).[4] The tactic proved efficient and was subsequently

Scheme 1

employed with considerable success in the construction of the spiroketal segments of the potent antitumor spongistatins.[5] Extension of this tactic to a five-component process achieved in a single flask enabled the rapid assembly of the extended 1,3-polyol segment of the polyene macrolides, mycoticins A and B.[6]

More recently, we developed the chemoselective addition of lithiated dithianes to various vinyl epoxides. Selectivity between the S_N2 and S_N2' addition manifolds could be easily controlled

(1) (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075. (b) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

(2) Reviews: (a) Seebach, D. *Synthesis* **1977**, 357. (c) Page, P. C. B.; Van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643. (d) Kolb, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 5, pp 2983. (e) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147.

(3) (a) Smith, A. B., III; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35 and references therein. (b) Smith, A. B., III; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249. (c) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191. (d) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196. (e) Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350.

(4) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925.

(5) (a) Smith, A. B., III; Zhuang, L.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667. (b) Smith, A. B., III; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. M. *Tetrahedron Lett.* **1997**, *38*, 8671. (c) Smith, A. B., III; Lin, Q.; Nakayama, K.; Boldi, A. M.; Brook, C. S.; McBriar, M. D.; Moser, W. H.; Sobukawa, M.; Zhuang, L. *Tetrahedron Lett.* **1997**, *38*, 8675.

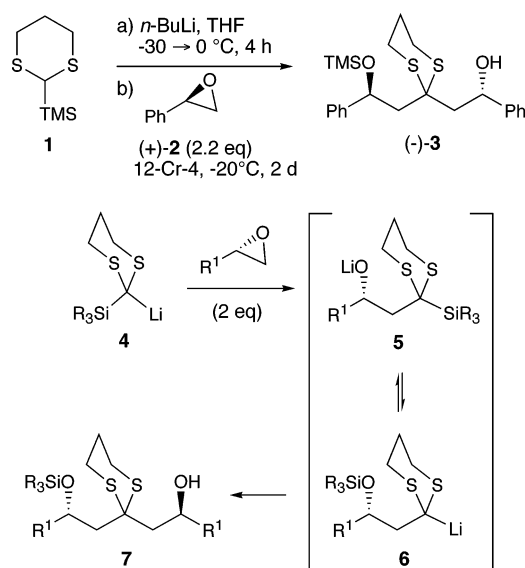(6) Smith, A. B., III; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001.

by appropriately tuning the steric properties of the dithiane anion.[7] Integration of the latter protocol with the earlier multicomponent tactic has now led to the rapid generation of a series of complex targets.

In this, a full account, we present in turn the development, application, and advantages of the one-flask multicomponent dithiane linchpin coupling protocol over the more conventional stepwise dithiane additions. The study comprises the reactions of dithiane anions with terminal epoxides, epichlorohydrin, and vinyl epoxides. Integration of these reactions led to new, higher-order multicomponent unions capable of coupling four and five components in a single flask. The overall goal of this program was, and continues to be, the rapid, efficient, and stereocontrolled assembly of highly functionalized intermediates for complex molecule synthesis.

Results and Discussion.

Symmetrical Bisalkylation of 2-Silyl-1,3-dithianes. In 1994, Tietze and co-workers reported a tandem bisalkylation of 2-trimethylsilyl-1,3-dithiane (**1**) with enantiomerically pure epoxides.[8] The procedure called for the addition of lithiated **1** (Scheme 2) to 2.2 equiv of epoxide (+)-**2** in the presence of a
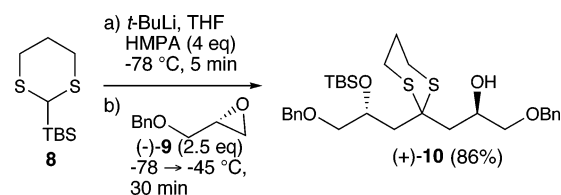
Scheme 2

crown ether to yield the pseudo-C_2-symmetrical 1,5-diol (**3**) in 65% yield. The reaction was presumed to involve a 1,4-Brook rearrangement[9] after the initial alkylation process, wherein the silyl group is transferred to the intermediate alkoxide (**5**), generating a new dithiane anion (**6**) for a second alkylation (Scheme 2). An appealing feature of this transformation was the differentiation between the two resulting hydroxy groups permitting subsequent selective manipulation. Long reaction times (2 days) and use of a single epoxide, however, limited the general synthetic utility of this reaction sequence. We reasoned that if two different electrophiles could be employed,

this reaction would have a wider impact. Critical to this proposition would be control of the Brook rearrangement (*vide infra*).
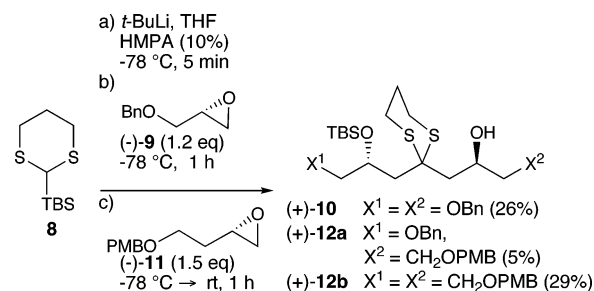
Initial Studies. Our point of departure was 2-*tert*-(butyldi-methylsilyl)-1,3-dithiane (**8**), a substrate also successfully employed by Tietze.[8] The more robust TBS protecting group was anticipated to hold a significant synthetic advantage over the TMS group. We also enlisted the lithiation conditions of Williams and co-workers [e.g., *t*-BuLi in 10% hexamethylphos-phoramide (HMPA)/THF at −78 °C],[10] a protocol used extensively in our laboratory for the effective deprotonation of simple dithianes. The initial experiment called for generation of the lithium anion of **8**, *à la* Williams, followed by the addition of 2.5 equiv of epoxide (−)-**9**; bis-adduct (+)-**10** was obtained in 86% yield (Scheme 3). The dramatic improvement in reaction time was quite pleasing.

Scheme 3

Early studies to expand the scope of this reaction, employing two different epoxides to furnish unsymmetrical adducts, however, were not promising; when epoxides (−)-**9** and (−)-**11** were added sequentially to lithiated **8** in THF (Scheme 4),

Scheme 4

the two symmetrical adducts (+)-**10** and (+)-**12b** predominated over the unsymmetrical adduct (+)-1**2a**. Presumably, the initial alkylation of **8** was rate-limiting, with the subsequent Brook rearrangement occurring more rapidly, such that competitive alkylation could occur with the newly generated dithiane anion **6**, thereby leading to a mixture of adducts. Taken together, these results suggested that the linchpin union of different electrophiles would *only* be feasible if the Brook rearrangement could be suppressed until the first alkylation was complete.

Solvent Effects on Brook Rearrangements. Utimoto and co-workers, in an elegant study, revealed a dramatic solvent effect on the Brook rearrangement with adducts derived from the lithiation of dihalo(trialkylsilyl)methanes (Scheme 5).[11] Addition of benzaldehyde to **13** provided a critical observation

(7) Smith, A. B., III; Pitram, S. M.; Gaunt, M. J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 14516.
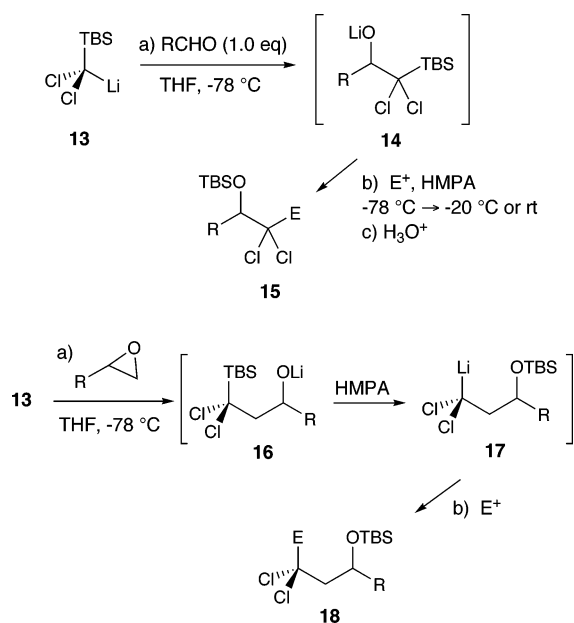
(8) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511.

(9) (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77. (b) Brook, A. G.; Bassindale, A. R. In *Rearrangements Ground Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 2, pp 149. (c) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065 and references therein.

(10) (a) Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949. See also: (b) Merrifield, E.; Steel, P. G.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1826. (c) Toshima, H.; Suzuki, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6725.

(11) (a) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1993**, *34*, 1951. (b) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1996**, *52*, 503.

Scheme 5

vis-à-vis our interest in controlling the timing of silyl migration. With **13**, the 1,3-Brook rearrangement did not occur at −78 °C following initial alkylation in THF but did proceed readily upon addition of HMPA. Complete consumption of the initial anion could thus be achieved prior to silyl migration, permitting alkylation with a second electrophile. Similar effects on the corresponding 1,4-Brook rearrangement were observed when **13** was reacted with an epoxide. In Et$_2$O and THF, silyl group migration was completely suppressed at −78 °C, although, in THF, warming to −40 °C led to rearrangement. Again, HMPA triggered silyl transfer; addition of a second electrophile to anion **17** derived via Brook rearrangement then furnished the unsymmetrical adduct **18**.[12]

With these observations as a guide, metalation and alkylation of the lithium anion derived from **8** with epoxide (−)-**9** in Et$_2$O furnished primarily the unrearranged carbinol (+)-**22**, whereas alkylation in THF resulted in a mixture of compounds (Table 1, entries 1 and 2). Thus, Et$_2$O rather than THF appeared to be the solvent of choice to achieve the *initial* alkylation and, most importantly, to suppress premature silyl migration. Addition of HMPA or DMPU[13] after an appropriate reaction time (ca. 1 h; entries 3 and 4) then triggered the 1,4-Brook rearrangement to afford predominantly silyl ether (+)-**23**. Rigorous degassing of

(12) Matsuda and co-workers previously reported an analogous unsymmetrical bisalkylation of trimethylsilylacetonitrile (**19**) with two different epoxides in DME (see scheme below). In this example, how the timing of the Brook rearrangement was controlled is unclear. One could speculate that the first alkylation occurs more rapidly than silyl migration. Alternatively, lithiated **19** could be more reactive than the intermediate formed after Brook rearrangement (**21**) reducing competitive alkylation. See: Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 26.

(13) DMPU is an abbreviation for *N,N′*-dimethyl- *N,N′*-propylene urea. For substituting DMPU in place of HMPA, see: Mukhopadhyay, H.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.

Table 1. Solvent Effects on the Brook Rearrangement

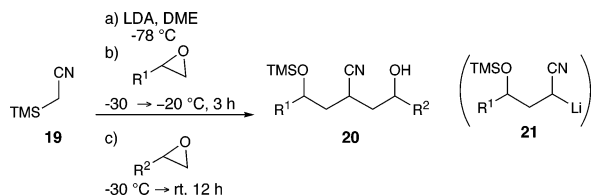| entry	solvent	additive	yield (%) (+)-**22**	yield (%) (+)-**23**	yield (%) (+)-**10**
1	Et$_2$O	−	88	−	−
2	THF	−	6	33	14
3	Et$_2$O	HMPA	−	83	−
4	Et$_2$O	DMPU	−	91	−

the solvents was critical to achieve optimal yields, presumably due to the instability of the lithiated 2-silyl-1,3-dithianes.

One-Flask Three-Component Couplings with 2-TBS-1,3-dithianes. We next conducted a series of linchpin couplings with the lithium anion of dithiane **8**, exploiting the solvent controlled Brook rearrangement to generate a diverse array of unsymmetrical bis-adducts; in general, yields were good to excellent (Table 2). The optimized protocol calls for deprotonation of **8** with *t*-BuLi in Et$_2$O at −78 °C, warming the reaction mixture to −45 °C over a 1 h period, followed by cooling to −78 °C and addition of the first epoxide in Et$_2$O. Completion of the first alkylation is achieved in ca. 1 h at −25 °C. The Brook rearrangement is then triggered by the addition of HMPA or DMPU (0.3−0.4 equiv) in Et$_2$O. Addition of the second electrophile (2 equiv) in Et$_2$O completes the reaction sequence.

Terminal scalemic epoxides comprise excellent electrophiles for the three-component process, since the stereogenicity of the resulting carbinol stereocenter is predetermined, thereby circumventing formation and separation of diastereomers. The substitution pattern *vis-à-vis* the silyl ether and free hydroxyl can be readily achieved simply by the order of epoxide addition. Thus, access to all possible diastereomers of the 1,3,5-polyol structural motif is possible by alternating the order of addition and stereochemistry of the epoxides, followed by stereocontrolled reduction of the ketone derived by unmasking the dithiane. A wide variety of other electrophiles should also prove viable in the second addition (*vide infra*) based upon related studies, both in our laboratory[4,6] and in others.[14] Importantly, the highly functionalized 1,3,5-polyol adducts are poised for further elaboration.

Epichlorohydrin as the Second Electrophile. The use of epichlorohydrin as the second electrophile presents the interesting issue of dithiane anion attack at either the carbon bearing the chloride or the terminal epoxide carbon, followed by alkoxide displacement of the chloride to generate a new terminal epoxide. In either case, the coupling process, if successful, would lead to a new epoxide permitting further elaboration. The stereochemistry of the resultant epoxide however would differ.

(14) (a) Le Merrer, Y.; Gravier-Pelletier, C.; Maton, W.; Numa, M.; Depezay, J.-C. *Synlett* **1999**, 1322. (b) Brauer, N.; Dreeben, S.; Schaumann, E. *Tetrahedron Lett.* **1999**, *40*, 2921. (c) Hale, K. J.; Hummersome, H. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189. (d) Gravier-Pelletier, C.; Maton, W.; Le Merrer, Y. *Tetrahedron Lett.* **2002**, *43*, 8285. (e) Petri, A. F.; Kuhnert, S. M.; Scheufler, F.; Maier, M. E. *Synthesis* **2003**, *6*, 940.
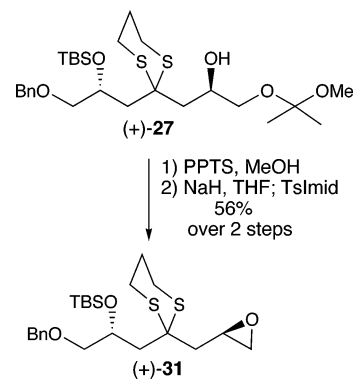
Table 2. Three-Component Couplings with 2-TBS-1,3-dithiane in One Flask

a) *t*-BuLi, Et₂O,
   -78 → -45 °C, 1 h
b) E₁⁺ (1 eq), Et₂O,
   -78 → -25 °C, 1 h
c) E₂⁺ (2 eq), Et₂O,
   HMPA (0.3-0.4 eq)
   -78 → 0 °C, 1 h → rt, 1 h

→ Product

8

Entry	E₁⁺	E₂⁺	Product	Yield (%)
1	(-)-**9**	(-)-**24**	(+)-**25**	56
2	(-)-**9**	(-)-**26**	(+)-**27**	74
3	(-)-**9**	**28**	(+)-**29**	62
4	(-)-**9**	(-)-**30**	(+)-**31**	60[a]
5	(-)-**9**	(+)-**30**	(+)-**32**	71[a]
6	(+)-**33**	(-)-**34**	(+)-**35**	59
7	(+)-**33**	(-)-**36**	(-)-**37**	65
8	(-)-**38**	(-)-**39**	(-)-**40**	72

[a] Only 1 equiv of E₂⁺ was used.

Literature precedent suggests that carbon nucleophiles attack preferentially at C(1) of the epoxide versus C(3) bearing the halide.[15] In the event, execution of the three-component protocol with the two enantiomers of epichlorohydrin (−)-**30** and (+)-**30** furnished (+)-**31** and (+)-**32**, respectively, as the sole product (Table 2, entries 4 and 5). The stereochemistry of epoxides (+)-**31** and (+)-**32** were readily established by the conversion of mixed ketal (+)-**27**, of known stereochemistry, to epoxide (+)-**31**, which proved identical in all respects to (+)-**31** derived from (−)-**30** (Scheme 6). Thus attack occurred selectively at the terminal epoxide carbon followed by displacement of the chloride.
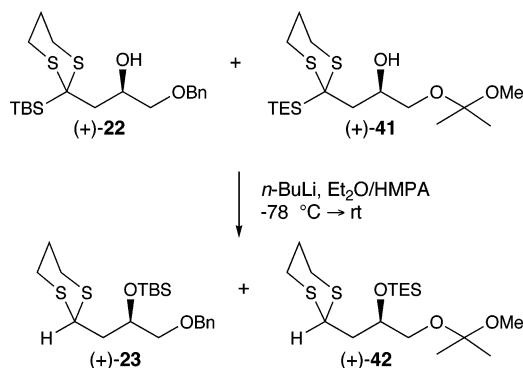
(15) (a) Kasai, N.; Suzuki, T.; Furukawa, Y. *J. Mol. Cat. B.* **1998**, *4*, 237. (b) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.

Scheme 6

(+)-**27**

1) PPTS, MeOH
2) NaH, THF; TsImid
   56%
   over 2 steps

(+)-**31**

Intra- versus Intermolecular Silyl Migration. To establish the mode of silyl migration in the multicomponent linchpin tactic (i.e., intra- or intermolecularity), we carried out a crossover experiment, wherein an equimolar mixture of the lithium anions derived from dithianes (+)-**22** and (+)-**41** was generated in the presence of HMPA at −78 °C, followed by warming the mixture to room temperature (Scheme 7). No crossover products were observed. Thus, as expected silyl migration occurs intramolecularly.
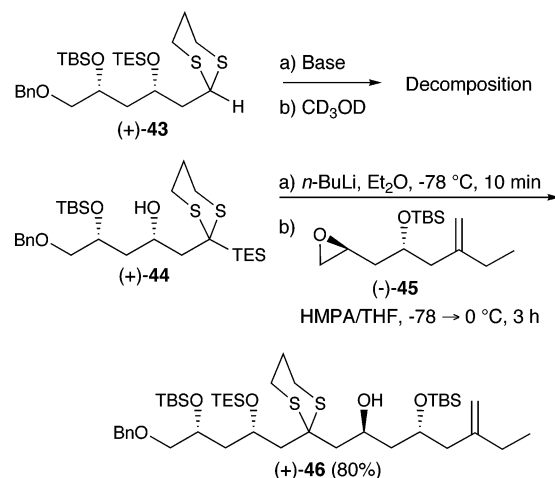
Scheme 7

Reversible Nature of Silyl Migration. To determine the potential reversibility of the silyl migration process, dithiane (+)-**23** was deprotonated with *t*-BuLi in THF at −78 °C followed by warming to 0 °C; a mixture of (+)-**22** and (+)-**23** (1.0:1.3) was observed after 3 h. Repeating the same reaction in Et₂O also yielded (+)-**22** and (+)-**23** (1.0:1.5). Alternatively, deprotonation of alcohol (+)-**22** in Et₂O, employing the identical conditions, provided (+)-**22** and (+)-**23** (1.4:1.0). Taken together, these results demonstrate that the Brook rearrangement is indeed reversible under these conditions; however, the equilibrium state could not be achieved due to the instability of the dithiane anions over the time and/or temperature required to achieve complete equilibration.

Lithiation of 2-Substituted Dithianes: A More Effective Tactic. In contrast to the parent 1,3-dithiane, which is easily metalated with *n*-BuLi, a myriad of strong bases, solvent additives, and time/temperature regimens have been employed to generate the lithium anion of 2-substituted derivatives, sometimes to no avail.[16] Indeed, dithianes possessing a high level of oxygenation and unsaturation are often difficult to deprotonate and, in some cases, result in capricious behavior.[17]
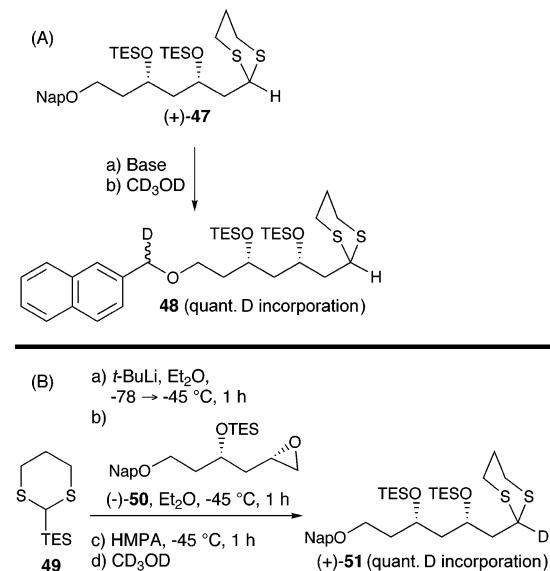
We have not been spared from such difficulties. In our second generation synthesis of the CD-spiroketal fragment of the potent antitumor agents, the spongistatins,[18] attempts to generate the lithium anion of (+)-**43** (Scheme 8) employing a variety of

(16) (a) Lipshutz, B. H.; Garcia, E. *Tetrahedron Lett.* **1990**, *31*, 7261. (b) Ide, M.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491 and references therein.
(17) (a) Hanessian, S.; Pougny, J.-R.; Boessenkool, I. K. *Tetrahedron* **1984**, *40*, 1289. (b) Oppong, I.; Pauls, H. W.; Liang, D.; Fraser-Reed, B. *J. Chem. Soc., Chem. Commun.* **1986**, 1241. (c) Kinoshita, M.; Taniguchi, M.; Morioka, M.; Takami, H.; Mizusawa, Y. *Bull. Chem. Soc. Jpn.* **1986**, *61*, 2147. (d) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998. (e) Okamura, H.; Kuroda, S.; Ikegami, S.; Tomita, K.; Sugimoto, Y.; Sakaguchi, S.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron* **1993**, *49*, 10531. (f) De Brabander, J.; Vandewalle, M. *Synthesis* **1994**, 855. (g) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J.* **1996**, *2*, 847. (h) Smith, A. B., III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J. W. *J. Am. Chem. Soc.* **1999**, *121*, 10468. (i) Armstrong, A.; Barsanti, P. A.; Jones, L. H.; Ahmed, G. *J. Org. Chem.* **2000**, *65*, 7020 and references therein.

Scheme 8

metalation conditions led only to decomposition. The successful generation and reaction of the corresponding lithium anion of (+)-**44**, however, could be achieved via the lithium alkoxide. That is, addition of epoxide (−)-**45** in a mixture of HMPA/THF to the anion of (+)-**44** furnished (+)-**46** in 80% yield by way of a Brook rearrangement. In another case, all attempts to effect lithiation of (+)-**47**, as demonstrated by deuterium incorporation, did not lead to the desired dithiane (+)-**51** (Scheme 9). Instead, quantitative deuterium incorporation oc-

Scheme 9

curred at the benzylic position of the naphthyl protecting group (**48**).[19] The requisite dithiane anion could however be generated, as illustrated by formation of the 2-*d*-dithiane (+)-**51**, by the reaction of epoxide (−)-**50** with the lithium anion obtained from 2-TES-1,3-dithiane (**49**), followed by a Brook rearrangement triggered by HMPA.

To understand the steric and stereoelectronic issues associated with the metalation of 2-substituted-1,3-dithianes, we turned to
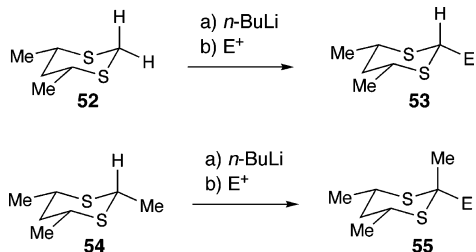
(18) Smith, A. B., III; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783.
(19) This observation was not surprising since the pKₐ's of both the dithiane and benzylic protons are quite similar. See: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

the elegant work of Eliel and co-workers.[20] Their pioneering studies established (a) that deprotonation of conformationally constrained 4,6-disubstituted-1,3-dithianes, such as **52** and **54**, occurs with high stereoselectivity at the equatorial position, (b) that the equatorial anion is thermodynamically more stable, and (c) that, upon exposure to an electrophile, the new group is introduced in the equatorial position (Scheme 10). In addition,
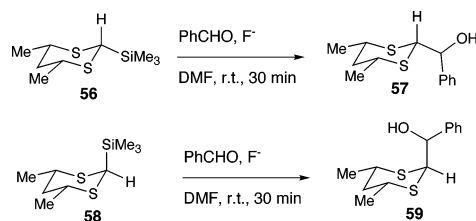
Scheme 10

abstraction of an axial methine hydrogen (e.g., **54**) was found to be quite sluggish, requiring long reaction times and higher temperatures, compared to the equatorial isomer. Thus, the difficulties experienced with direct metalation of structurally complex dithianes can, in some cases, be attributed to the preference for removal of equatorial hydrogens. This analysis, however, does not completely explain why some 2-substituted dithianes are readily deprotonated and others are not. From a pragmatic point of view, however, it is often possible to circumvent such difficulties by taking advantage of the solvent controlled Brook rearrangement as illustrated in Schemes 8 and 9. These observations suggest that migration of the 2-silyl group may not suffer the same conformational limitations as direct metalation. Support here comes from the recent study by Degl'Innocenti and Pollicino,[21] demonstrating that both axial and equatorial silyl groups on conformationally constrained 1,3-dithianes couple to benzaldehyde with essentially the same rate upon treatment with fluoride ion.

Application of the Multicomponent Tactic in Natural Product Synthesis. We, along with other research groups,[14] have demonstrated the considerable utility of the one-step, multicomponent coupling protocol as strategic reactions in several ongoing synthetic programs.[3b,c,18] Importantly, these three-component coupling reactions can be conducted routinely on a multigram scale.[18]
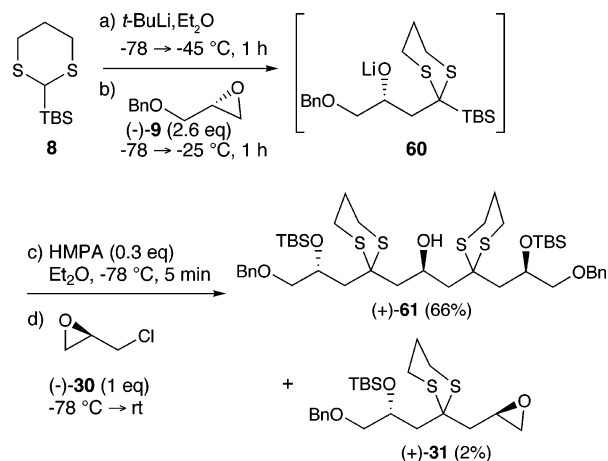
Higher-Order Multicomponent Couplings: Union of Five Components. We reasoned that, by careful choice of the second

electrophile, higher-order multicomponent couplings might be possible. Such a tactic would provide exceptionally concise routes to advanced subtargets required for the 1,3-polyol backbone segments of the polyene macrolides.[22] The first example, leading to the formation of four carbon−carbon σ-bonds in one-flask, involved alkylation of the anion derived from dithiane **8** with epoxide (−)-**9** to generate ca. 2 equiv of the lithium alkoxide **60** (Scheme 11). Sequential addition of

Scheme 11

HMPA and epichlorohydrin (−)-**30** (1 equiv) furnished the bis-(silyloxy dithiane) carbinol (+)-**61** in 66% yield, accompanied by a minor amount (ca. 2%) of epoxide (+)-**31**.[4]

A second example[6] of a five-component coupling tactic was designed to permit ready access to the pseudo-C_2-symmetric trisacetonide (+)-**64** employed by Schreiber et al. in a synthesis of (+)-mycoticin A.[23] Lithiation of dithiane **8** (2.5 equiv) followed in turn by alkylation with (−)-**9** (Scheme 12), addition

Scheme 12

of HMPA to trigger the 1,4-Brook rearrangement, and diep-oxypentane (+)-**62**[24] (1.0 eq) furnished diol (+)-**63** in 59% yield,

(20) (a) Hartmann, A. A.; Eliel, E. L. *J. Am. Chem. Soc.* **1971**, *93*, 2572. (b) Eliel, E. L.; Abatjoglou, A.; Hartmann, A. A. *J. Am. Chem. Soc.* **1972**, *94*, 4786. (c) Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. *J. Am. Chem. Soc.* **1974**, *96*, 1807. (d) Eliel, E. L. *Tetrahedron* **1974**, *30*, 1503. (e) Abatjoglou, A.; Eliel, E. L.; Kuyper, L. F. *J. Am. Chem. Soc.* **1977**, *99*, 8262.
(21) The following scheme illustrates that the conformationally constrained 2-silyl-1,3-dithianes **56** and **58** furnish **57** and **59** upon treatment with benzaldehyde and a fluoride source. See: Capperucci, A.; Cere, V.; Degl'Innocenti, A.; Nocentini, T.; Pollicino, S. *Synlett* **2002**, *9*, 1447.

accompanied again by a minor amount (ca. 13%) of the epoxide, arising from an incomplete second alkylation. Notably, use of THF as the cosolvent with HMPA in the *second* alkylation resulted in higher yields as compared to Et$_2$O (ca. 33%). Alternatively, when DMPU was employed to trigger the Brook rearrangement, diol (+)-**63** was obtained in a somewhat lower yield (55%) compared with HMPA. Enhanced efficiency with HMPA versus DMPU is a general observation in our laboratory. Due *caution* with HMPA must, of course, be observed. In both examples, four new carbon-carbon σ-bonds were generated efficiently in one flask.

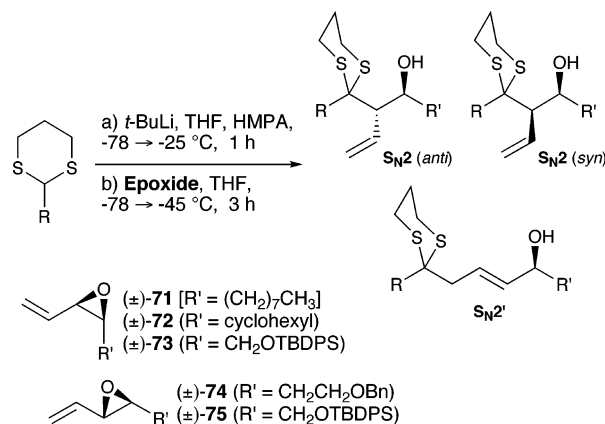**Vinyl Epoxides as Electrophiles: The S$_N$2 versus the S$_N$2′ Manifold.** As with epichlorohydrin, the use of vinyl epoxides as electrophiles holds the interesting promise of reactivity at two electrophilic sites. Surprisingly, relatively few reports exist on the addition of carbon nucleophiles, particularly dithiane anions, to vinyl epoxides (e.g., S$_N$2 versus S$_N$2′),[25] although nucleophilic additions to alkenes possessing a leaving group at the allylic position have been examined extensively over the past 40 years.[26] Controlled access to the S$_N$2 and S$_N$2′ reaction manifolds would significantly augment the utility of dithiane linchpins and would permit expansion of the multicomponent tactic (Scheme 13).

Scheme 13

From the outset of this strategy, we speculated that selectivity over the S$_N$2 and S$_N$2′ reaction manifolds might be achievable by varying the steric properties of the lithiated 2-substituted-1,3-dithianes. That is, a small nucleophile would be expected to attack preferentially at the allylic position via an S$_N$2 process, whereas a more sterically demanding nucleophile would add to the more accessible alkene terminus in an S$_N$2′ fashion. Toward this end, a series of dithianes (**65**−**70**) were metalated (*t*-BuLi in 10% HMPA/THF) and reacted with a series of vinyl epoxides (**71**−**75**)[27] in THF (Table 3). Lithium anions derived from dithianes with small substituents (R = H, Ph, and TMS) afforded solely the S$_N$2 adduct in good yield (entries 1−15), suggesting that the allylic position of the vinyl epoxide is indeed

(22) For reviews on polyol syntheses, see: (a) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375. (b) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635. (c) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021.

(23) Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360.

(24) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161.

(25) For examples, see: (a) Semeniuk, F.; Jenkins, G. L. *J. Am. Pharm. Assoc., Sci. Ed.* **1948**, *37*, 118. (b) Herr, R. W.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 4979. For Lewis acid promoted S$_N$2 additions of alkyllithiums, see: (c) Alexakis, A.; Vrancken, E.; Mangeney, P.; Chemla, F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3352. For transition metal catalyzed reactions with vinyl epoxides, see: (d) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319. (e) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968 and references therein. For a review on S$_N$2′ additions of organocuprates to vinyl epoxides, see: Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.

(26) (a) Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1953**, *75*, 4119. (b) Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1956**, *78*, 4609. (c) Magid, R. M. *J. Org. Chem.* **1971**, *36*, 2105. (d) Stork, G.; Kreft, A. F., III. *J. Am. Chem. Soc.* **1977**, *75*, 3850. (e) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (f) Bordwell, F. G.; Clemens, A. H.; Cheng, J.-P. *J. Am. Chem. Soc.* **1987**, *109*, 1773. (g) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383.

Table 3. Reactions of Dithiane Lithium Anions with Vinyl Epoxides

entry	R	epoxide	yield(%)	S$_N$2:S$_N$2′[a]	product
1	**65** (R = H)	**71**	83	100 (anti):0	**76**
2	**65**	**72**	74	100 (anti):0	**77**
3	**65**	**73**	85	100 (anti):0	**78**
4	**65**	**74**	89	100 (syn):0	**79**
5	**65**	**75**	69	100 (syn):0	**80**
6	**66** (R = Ph)	**71**	85	100 (anti):0	**81**
7	**66**	**72**	82	100 (anti):0	**82**
8	**66**	**73**	88	100 (anti):0	**83**
9	**66**	**74**	86	100 (syn):0	**84**
10	**66**	**75**	74	100 (syn):0	**85**
11	**67** (R = TMS)[b]	**71**	83	100 (anti):0	**86**
12	**67**	**72**	85	100 (anti):0	**87**
13	**67**	**73**	88	100 (anti):0	**88**
14	**67**	**74**	76	100 (syn):0	**89**
15	**67**	**75**	78	100 (syn):0	**90**
16	**68** (R = Et)	**71**	81	0:100	**91**
17	**68**	**72**	78	0:100	**92**
18	**68**	**73**	84	1 (anti):3.5	**93a/b**
19	**68**	**74**	82	1 (syn):3	**94a/b**
20	**68**	**75**	73	1 (syn):5	**95a/93b**
21	**69** (R = *i*-Pr)	**71**	81	0:100	**96**
22	**69**	**72**	84	0:100	**97**
23	**69**	**73**	74	1 (anti):5	**98a/b**
24	**69**	**74**	63	1 (syn):4	**99a/b**
25	**69**	**75**	74	1 (syn):3	**100a/98b**
26	**70** (R = TIPS)	**71**	85	0:100	**101**
27	**70**	**72**	86	0:100	**102**
28	**70**	**73**	81	0:100	**103**
29	**70**	**74**	84	0:100	**104**
30	**70**	**75**	80	0:100	**103**

[a] Ratio of isolated compounds. [b] Products from entries 11−15 underwent 1,4-Brook rearrangement to a 1:1 mixture of non-Brook:Brook products.

activated.[28] Not surprisingly, in the presence of HMPA, reactions with 2-TMS-1,3-dithiane (**67**) led to a mixture of homoallylic alcohols and the corresponding TMS-ethers resulting from 1,4-Brook rearrangement. The stereochemical outcome of the S$_N$2 reaction with cis vinyl epoxides **71**, **72** and **73** provided, as anticipated, exclusively the anti vicinal adducts, whereas the trans epoxides **74** and **75** afforded only the syn vicinal adducts.[29] The yields were good in both series.

A complete reversal of selectivity to the S$_N$2′ manifold was achieved with the lithium anions derived from alkyl-substituted dithianes (R = Et and *i*-Pr, entries 16−25); again yields were good. The chemoselectivity was however compromised with

(27) For syntheses of vinyl epoxides **71**−**73**, see: (a) Hu, S.; Jayaraman, S.; Oehleschlager, A. C. *J. Org. Chem.* **1996**, *61*, 7513. For synthesis of vinyl epoxides **74**−**75**, see: (b) Diez-Martin, D.; Kotecha, N. R.; Ley, S. V.; Mantegani, S.; Menedez, J. C.; Osbourn, H. M.; White, A. D.; Banks, J. B. *Tetrahedron* **1992**, *48*, 7899.

(28) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

epoxides **73**, **74**, and **75**. Addition of the more sterically demanding 2-triisopropylsilyl-1,3-dithiane (**70**) (entries 26−30) also proceeded exclusively via S_N2' attack in good yield with all vinyl epoxides. Thus, at the two extremes of dithiane anion steric encumberance (R = H or R = TIPS), access to either the S_N2 or the S_N2' manifold can be achieved with excellent selectivity.[30]

Effect of Lewis Acids on the S_N2 and S_N2' Reaction Manifolds. In an attempt to provide additional control over the S_N2 and S_N2' reaction manifolds, we explored the effect of Lewis acids.[25c] We selected the reactions of 2-Et- and 2-*i*-Pr-1,3-dithianes (**68** and **69**) with vinyl epoxide **71** (Table 3, entries 16 and 21); the reaction proceeds exclusively via the S_N2' manifold. No reaction was observed in the presence of 1.0 equiv of either zinc chloride or magnesium bromide (Table 4, entries

Table 4. Effect of Additives on the Addition of Dithiane Anions to Vinyl Epoxides

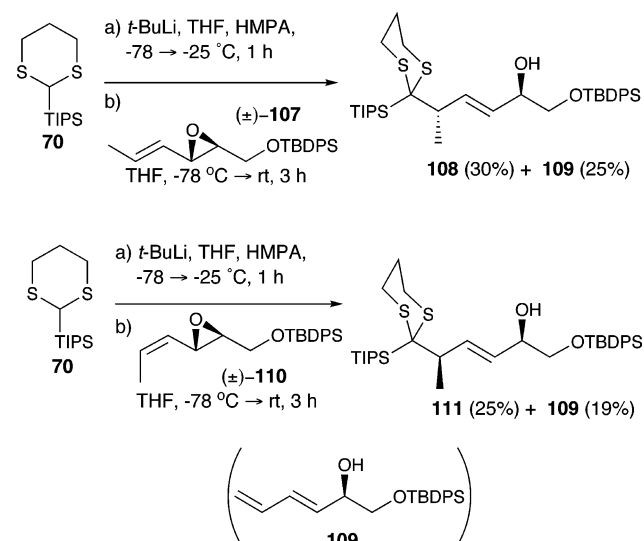| entry	R	additive	yield	S_N2:S_N2'
1	Et	ZnCl$_2$	−	−
2	*i*-Pr	ZnCl$_2$	−	−
3	Et	MgBr$_2$	−	−
4	*i*-Pr	MgBr$_2$	−	−
5	Et	LiCl	65	4 (**105**):1 (**91**)
6	*i*-Pr	LiCl	63	3 (**106**):1 (**96**)
7[a]	Et	BF$_3$·OEt$_2$	35	3 (**105**):1 (**91**)
8[a]	*i*-Pr	BF$_3$·OEt$_2$	40	2 (**106**):1 (**96**)

[a] Entries 7 and 8 were conducted in Et$_2$O.

1−4). However, dithiane addition did occur in the presence of 1.0 equiv of lithium chloride or boron trifluoride etherate (entries 5−8), with reversal of selectivity to favor the S_N2 product. With boron trifluoride etherate, addition of the dithiane anions to THF was solely observed; thus Et$_2$O was the solvent of choice in these examples.[31] Yields, while not optimized, were modest to good.

Stereochemistry of the S_N2' Addition Process. To define the stereochemical outcome of the S_N2' addition process, we explored the effect of substitution at the terminal position of the alkene in the vinyl epoxide.[32] Toward this end, vinyl epoxides **107**[33] and **110**[33] were subjected to the lithium anion of 2-triisopropylsilyl-1,3-dithiane (**70**). Adducts **108** and **111**, resulting from S_N2' addition, were isolated, albeit in modest

(29) The relative configurations of the S_N2 adducts derived from the cis and trans vinyl epoxides were determined by chemical correlation (see Supporting Information).
(30) We recently employed this tactic toward the synthesis of rimocidin: Smith, A. B.; Pitram, S. M.; Fuertes, M. J. *Org. Lett.* **2003**, *5*, 2751.
(31) Fang, J.-M.; Chen, M.-Y. *Tetrahedron Lett.* **1988**, *29*, 5939.
(32) For references on the mechanism of the S_N2' reaction, see: (a) Magid, R. M.; Fruchey, O. S. *J. Am. Chem. Soc.* **1970**, *92*, 2107. (b) Denmark, S. E. PhD. Thesis, Swiss Federal Institute of Technology, Zurich, 1982. (c) Stohrer, W.-D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 613. (d) Park, Y. S.; Kim, C. K.; Lee, B.-S.; Lee, I. *J. Phys. Chem.* **1995**, *99*, 13103.

yield (Scheme 14); the corresponding diene elimination product **109** was also observed (25% and 19%, respectively). Importantly, of the two reaction manifolds, only the S_N2' product was observed in each case.
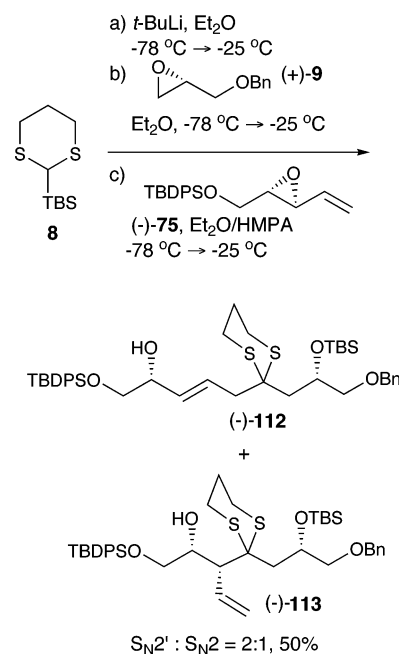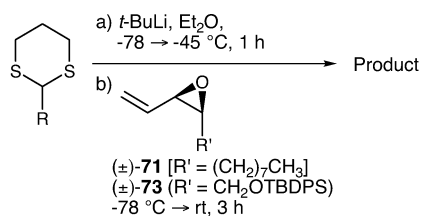
Scheme 14

Attempts to determine the relative stereochemistry of **108** and **111** via X-ray crystallography proved unsuccessful; a chemical correlation with compounds of known stereochemistry was therefore established, demonstrating that this S_N2' addition of lithiated dithiane anions occurs via a syn process.[34]

Multicomponent Tactic Employing Vinyl Epoxides as Electrophiles. Recognizing the potential of the S_N2 versus S_N2' addition manifolds of vinyl epoxides, we explored the possibility of higher-order multicomponent couplings, first utilizing vinyl epoxide (−)-**75** as the second electrophile (Scheme 15). Toward

Scheme 15

this end, deprotonation of dithiane **8**, followed in turn by addition of (+)-**9** and vinyl epoxide (−)-**75** in Et$_2$O/HMPA,

furnished a mixture (2:1) of **112** and **113** in a modest yield (50%), favoring the expected S_N2' pathway in the second alkylation.
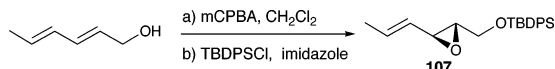
We next examined vinyl epoxides as the first electrophile. In this case, if the addition of a 2-silyl-1,3-dithiane anion were to occur via the S_N2 manifold, 1,4-Brook rearrangement would lead to a new dithiane anion available for a second alkylation. Alternatively, if the S_N2' manifold were to pertain, an analogous 1,6-silyl migration across the *E*-alkene would not be possible. However, since our initial studies on the reactions of dithiane anions with vinyl epoxides had been performed in THF with HMPA, control of the Brook rearrangement under these conditions would not be feasible. We therefore examined the addition of lithiated 2-silyl-1,3-dithianes to vinyl epoxides in Et$_2$O, in the absence of HMPA (Table 5). The addition occurred smoothly to furnish exclusively the S_N2' congeners. Thus, vinyl epoxides are not viable first electrophiles in a three-component process. Nonetheless, we were pleased with the high selectivity observed.

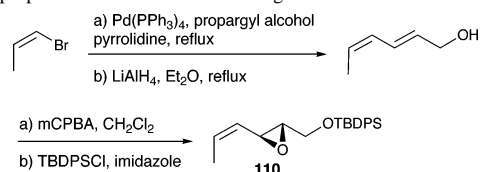**Table 5.** Addition of Dithiane Anions to Vinyl Epoxides in the Absence of HMPA

a) *t*-BuLi, Et$_2$O, -78 → -45 °C, 1 h
b)
(±)-**71** [R' = (CH$_2$)$_7$CH$_3$]
(±)-**73** (R' = CH$_2$OTBDPS)
-78 °C → rt, 3 h

Entry	R	Epoxide	Product	Yield (%)
1	TBS	**73**	**114**	68
2	TMS	**73**	**115**	65
3	Et	**73**	**93b**	56
4	TMS	**71**	**116**	53

(33) Vinyl epoxide (±)-**107** was prepared from commercially available *trans*, *trans*-2,4-hexadien-1-ol as shown in the following scheme:

a) mCPBA, CH$_2$Cl$_2$
b) TBDPSCl, imidazole
107

Vinyl epoxide (±)-**110** was prepared from propargyl alcohol and *Z*-1-bromopropene as shown in the following scheme:

a) Pd(PPh$_3$)$_4$, propargyl alcohol pyrrolidine, reflux
b) LiAlH$_4$, Et$_2$O, reflux

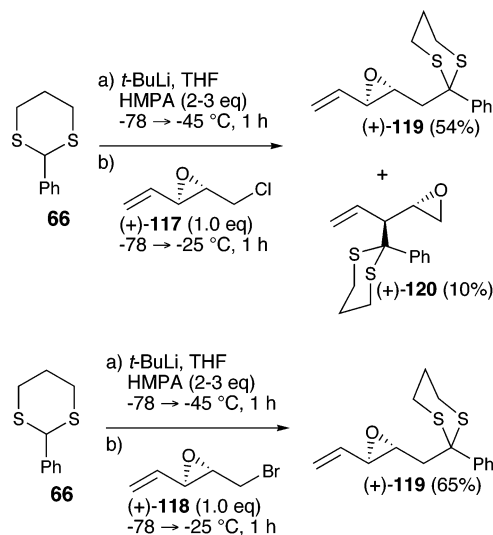a) mCPBA, CH$_2$Cl$_2$
b) TBDPSCl, imidazole
110

(34) See Supporting Information.

That a change in the solvent system (THF/HMPA to Et$_2$O) affects the observed selectivity between the S_N2 and S_N2' manifolds did not come as a complete surprise. Studies by Reich and co-workers[35] demonstrated that in THF/HMPA dithiane anions are monomeric entities; therefore selectivity between the S_N2 and S_N2' manifolds can be attributed to the steric nature of the 2-substituent of the dithiane. However, in Et$_2$O at low temperature (−78 to −25 °C) the dithiane anions form aggregates.[36] In this case, we would expect the aggregate to favor S_N2' addition. Indeed, in THF/HMPA, the lithium anion derived from 2-TMS-1,3-dithiane (**67**) afforded exclusively the S_N2 adduct with epoxides **71** and **73** (Table 3, entries 11 and 13), whereas in Et$_2$O the S_N2' adduct was the sole product observed with both epoxides (Table 5, entries 2 and 4). Similarly, 2-Et-1,3-dithiane (**68**) resulted in a 3.5:1 mixture of $S_N2':S_N2$ adducts in THF/HMPA (Table 3, entry 18), versus exclusive S_N2' addition in Et$_2$O, albeit in modest yield (Table 5, entry 3).
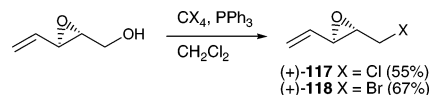
One-Flask, Three- and Four-Component Coupling Reactions with a Halomethyl Vinyl Epoxide Hybrid. Having demonstrated the utility of both epichlorohydrin and vinyl epoxides in multicomponent couplings, we turned next to halomethyl vinyl epoxides (**117** and **118**; Scheme 16), hybrids of the two electrophiles readily available from the corresponding alcohol. Addition of lithiated 2-Ph-1,3-dithiane (**66**, 1.2 equiv) to the chloro congener (+)-**117**[37] furnished a mixture of (+)-**119** and (+)-**120** (Scheme 16), the outcome, respectively, of

Scheme 16

a) *t*-BuLi, THF HMPA (2-3 eq) -78 → -45 °C, 1 h
b)
(+)-**117** (1.0 eq) -78 → -25 °C, 1 h
66
(+)-**119** (54%)
+
(+)-**120** (10%)

a) *t*-BuLi, THF HMPA (2-3 eq) -78 → -45 °C, 1 h
b)
(+)-**118** (1.0 eq) -78 → -25 °C, 1 h
66
(+)-**119** (65%)

direct chloride displacement and epoxide opening at the allylic position, followed in the latter case by ring closure to furnish a

(35) (a) Reich, H. J.; Borst, J. P.; Dykstra, R. R. *Tetrahedron* **1994**, *50*, 5869. (b) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527. (c) Reich, H. J.; Sanders, A. W.; Fiedler, A. T.; Bevan, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 13386.

(36) Visual evidence for aggregation was observed where upon treatment of 2-Et-1,3-dithiane with *t*-BuLi in Et$_2$O (ca. 0.2 M) at −78 °C, a cloudy suspension formed and gradually dissipated upon warming.

(37) Vinyl epoxides (+)-**117** and (+)-**118** were prepared from the preceding alcohol as shown in the following scheme:

CX$_4$, PPh$_3$
CH$_2$Cl$_2$
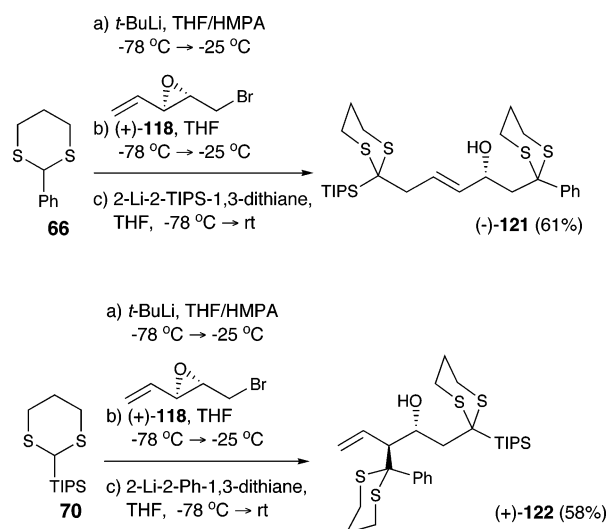(+)-**117** X = Cl (55%)
(+)-**118** X = Br (67%)

For preparation of epoxy alcohol, see: Romero, A.; Wong, C. H. *J. Org. Chem.* **2000**, *65*, 8264.

new epoxide. Interestingly, the bromo congener (+)-**118**[37] furnished only (+)-**119**. These results are in complete agreement with the reactions observed with epichloro- and epibromohydrin, although chloride displacement is only rarely observed.[15] A similar lack of selectivity with the chloro congener (**117**) was observed with other dithiane anions. We therefore employed the bromo congener (+)-**118** in all future studies to limit side products arising via attack at the epoxide.

A three-component coupling employing vinyl epoxide (+)-**118** as the initial electrophile appeared quite feasible given our earlier results with epichlorohydrin. Toward this end, addition of the anion derived from 2-Ph-1,3-dithiane (**66**) to (+)-**118**, followed by addition of a second sterically encumbered dithiane anion (**70**) furnished adduct (−)-**121** in 61% yield (Scheme 17).

Scheme 17

Importantly, the second addition occurred exclusively via the S_N2' manifold, a result anticipated from our earlier studies. In a similar fashion, reversing the order of additions resulted in the adduct (+)-**122**. Again, as expected we observed exclusive S_N2 addition of the second dithiane anion. Additional examples of this class of three-component couplings, providing advanced intermediates suitable for further elaboration are illustrated in Table 6.

To expand the scope of the latter synthetic tactic with the intention to incorporate a Brook rearrangement, we again took
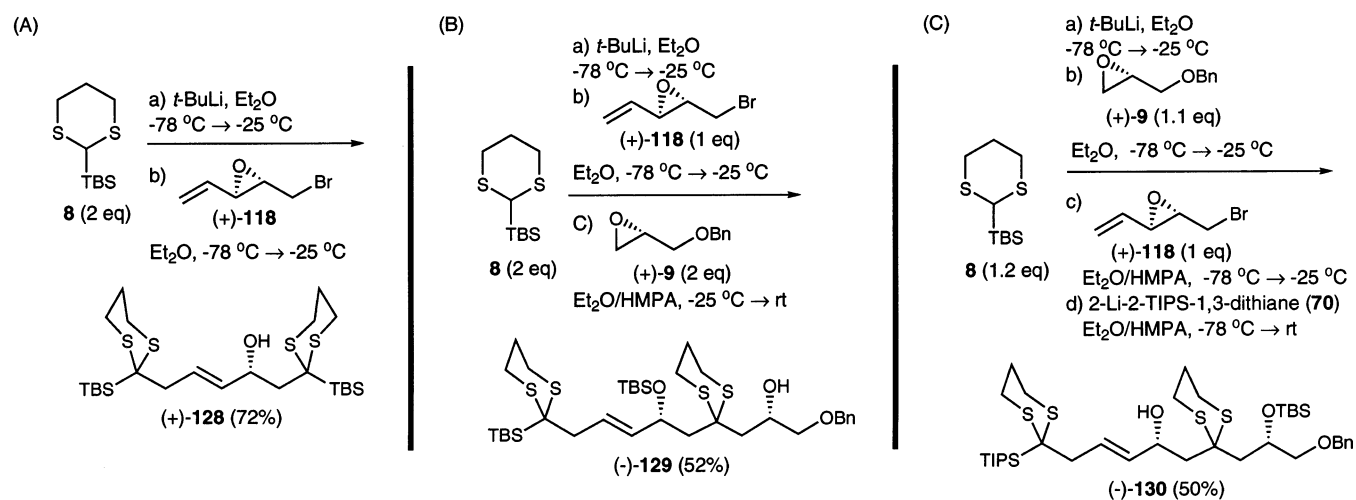
Table 6. Multicomponent Addition of Dithiane Anions to Bromomethyl Vinyl Epoxide (+)-**118**

Entry	R₁	R₂	Product	Yield (%)
1	Et	Ph	**123**	70
2	Et	TIPS	**124**	65
3	Ph	H	**125**	56
4	TIPS	H	**126**	53
5	(acetonide chain)	Ph	**127**	63

advantage of solvent effects. Since THF/HMPA would not permit control of the Brook rearrangement, we employed Et₂O in the absence of HMPA. Under these conditions, treatment of (+)-**118** with 2 equiv of the lithium anion of **8** delivered the bis-adduct (+)-**128** in 72% yield (Scheme 18). We could also induce a Brook rearrangement in this reaction after addition of (+)-**118** by introducing HMPA. Alkylation with epoxide

Scheme 18

(+)-**9**, as the second electrophile, furnished the four-component adduct (−)-**129** in 52% yield (Scheme 18). Importantly, no S_N2 adducts were observed, again highlighting the preference for the S_N2' manifold with sterically encumbered anions. An expanded version of this example leading to the union of four different building blocks employs vinyl epoxide (+)-**118** as the second electrophile, followed by addition of the lithium anion derived from 2-TIPS-1,3-dithiane (**70**); the resultant adduct (−)-**130** was produced in 50% yield (Scheme 18).

Summary

The development of a one-flask multicomponent dithiane linchpin coupling protocol exploiting a solvent controlled Brook rearrangement has been achieved. Competent electrophiles include terminal epoxides, epichlorohydrin, and vinyl epoxides. High chemoselectivity can be achieved with epichlorohydrin and vinyl epoxides. For vinyl epoxides, the steric nature of the dithiane anion is critical; sterically unencumbered dithiane anions afford S_N2 adducts, whereas encumbered anions lead primarily to S_N2' adducts. Mechanistic studies demonstrate that the S_N2' process occurs via syn addition to the vinyl epoxide. Finally, integration of the multicomponent tactic with epichlorohydrin and vinyl epoxides permits the ready higher-order union of four and five components in a single flask.

Supporting Information Available: Spectroscopic and analytical data and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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