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Anion Relay Chemistry: An Effective Tactic for Diversity Oriented Synthesis

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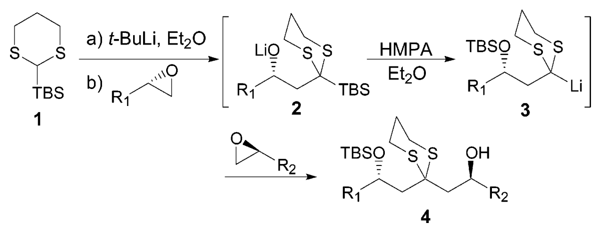
For nearly 40 years, dithiane anions, introduced by Corey and Seebach, have served as effective acyl anion equivalents (umpolung) for construction of carbon−carbon bonds.[1,2] Particularly attractive is the efficient elaboration of aldol linkages with precise stereocontrol employing epoxides as the electrophile; this reaction sequence serves as a viable alternative to the aldol reaction without advent of the retro-aldol process. In 1997, based on the precedent by Tietze,[3] we reported that lithiation of silyl dithiane **1** with *t*-BuLi in diethyl ether (Scheme 1), followed by alkylation with an epoxide, results in an intermediate oxyanion (**2**), which upon treatment with HMPA triggers a solvent-controlled 1,4-Brook rearrangement,[4] thereby generating a new reactive dithiane anion (**3**), available to react with a second, *different* epoxide to furnish a differentially protected monosilyl 1,5-diol **4**.[5] From the strategic sense, location of the silyl protecting group can be orchestrated simply by the order of the epoxide additions. The success of this linchpin process, now a central theme in several completed and ongoing synthetic ventures in our laboratory,[6] led us to recognize the considerable utility, and thereby the need, for additional synthetic tactics which would permit similar rapid access to high levels of molecular diversity. In this communication, we disclose a new multicomponent linchpin protocol involving the concept of anion relay chemistry (ARC), which holds great promise in the area of diversity oriented synthesis.

Scheme 1



The ARC concept, outlined in general form in Figure 1, calls for addition of an anion (**5**) to an epoxide (**6**), bearing on a distal carbon a trialkyl silyl group and an anion stabilizing group (ASG), to furnish upon epoxide ring opening oxyanion **7**. Addition of HMPA or other polar solvents to trigger a solvent-controlled 1,4-Brook rearrangement then leads to a *new distal* anion (**8**), which in turn is available to react with a variety of second electrophiles. Critical to the success of this tactic is the precise timing of the Brook rearrangement. To avoid formation of complex reaction mixtures, completion of the first alkylation must be achieved prior to triggering the Brook rearrangement.

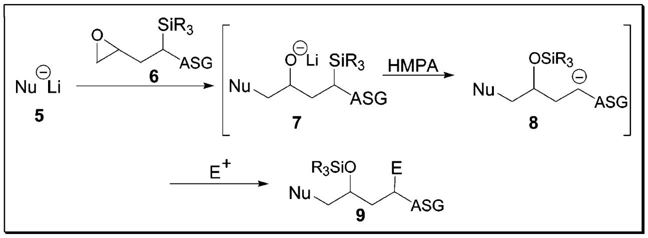
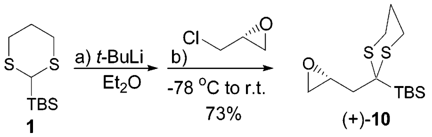


Figure 1. Anion Relay Chemistry (ARC).

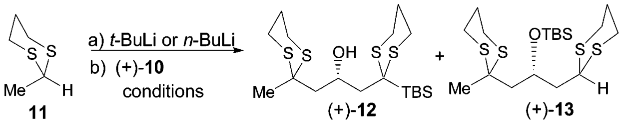
We began this study with designed anion relay linchpin (+)-**10**, readily prepared on multigram scale by treatment of the lithium anion of dithiane **1** with (−)-epichlorohydrin in diethyl ether (Scheme 2).[7] The results are summarized in Table 1.

Scheme 2



In the tri-component linchpin coupling process (Scheme 1),[5] Et_2O proved to be the solvent of choice for *initial* alkylation to suppress premature silyl migration. However the dithiane anion derived from **11** (Table 1) was observed to form aggregates in Et_2O at low temperature (−78 to −20 °C), thereby precluding effective reaction with (+)-**10** (entry 1). Pleasingly, upon warming to room temperature, the aggregates appear to disappear and the anion reacts with (+)-**10** to furnish the desired product (+)-**12** in 71% yield, along with a small amount of the silyl migrated product (+)-**13** (<5% yield, entry 2). This reaction, however, requires ca. 3 h to achieve good yields and thus was deemed unsuitable for the prospective one-flask multicomponent coupling protocol (vide infra). On the other hand, when THF was employed, the reaction was complete in 20 min at −30 °C, but a significant amount of Brook rearrangement product (+)-**13** was observed (entry 3). This result was not unexpected since it is known that THF can trigger Brook rearrangements at low temperature.[4,5] However, when a solvent system composed of THF/Et_2O (1:3, v/v) was employed, clean alkylation was observed in 20 min at −30 °C to provide (+)-**12** in 87% yield, accompanied only by a small amount of (+)-**13** (entry 4). These optimized conditions proved equally successful with 2-substituted dithianes **14**, **15**, and **16** (Scheme 3). In general, best results were obtained with *n*-BuLi; however, *t*-BuLi can be employed in many cases.

Table 1. Solvent and Temperature Effects on the Coupling of Dithiane **11** with Epoxide (+)-**10**



Entry	Solvent	Reaction temperature/time	Yield **12** (%)	Yield **13** (%)
1	Et_2O	−78 to −20 °C	0	0
2	Et_2O	r.t./3 h	71	<5
3	THF	−30 °C/20 min	47	24
4	THF/Et_2O (1:3)	−30 °C/20 min	87	<5

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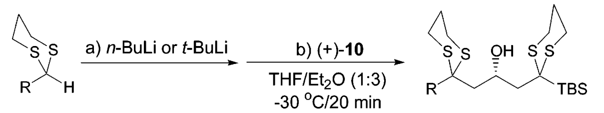
Scheme 3

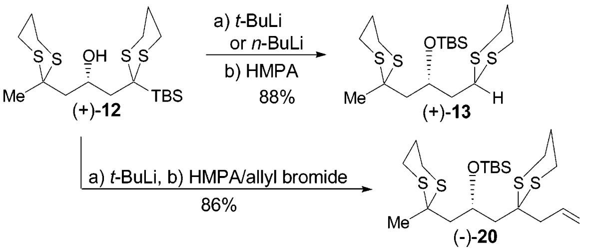


14 R = Isopropyl
15 R = *n*-Hexyl
16 R = Ph

(+)-**17** R = Isopropyl (85%)
(+)-**18** R = *n*-Hexyl (79%)
(+)-**19** R = Ph (89%)

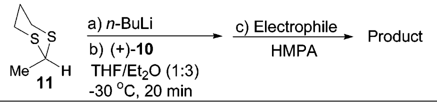
With alcohol (+)-**12** in hand, we next explored the Brook rearrangement (Scheme 4). Deprotonation of the hydroxyl of (+)-**12** with *t*- or *n*-BuLi in THF followed by addition of HMPA furnished silyl ether (+)-**13** in good yield. Furthermore, when allyl bromide was added with the HMPA, coupling product (−)-**20** was obtained in 86% yield.

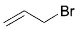
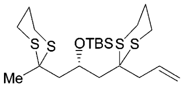
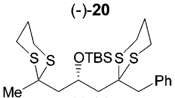
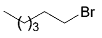
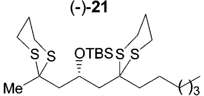
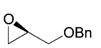
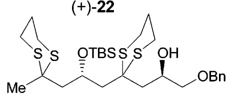
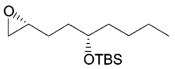
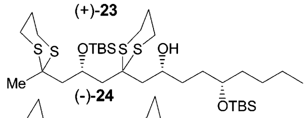
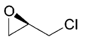
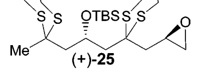
Scheme 4



Encouraged by these results, we turned to the development of a one-flask three-component coupling protocol, employing anion relay linchpin (+)-**10**, 2-methyl dithiane **11**, and a series of second electrophiles (Table 2). Optimal conditions entail deprotonation of **11** in THF at room temperature for 5 min,[8] followed by cannula addition of the resulting anion to a solution of the linchpin (+)-**10** in Et$_2$O, such that the resultant solvent system becomes 1:3 (v/v) in THF and Et$_2$O, respectively. Completion of the first alkylation is achieved in ca. 20 min at −30 °C (TLC).

Table 2. Three-Component Linchpin Couplings of Dithiane **11**

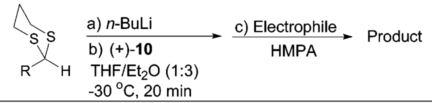


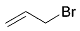
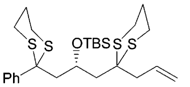
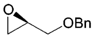
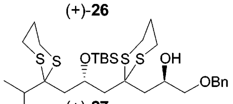
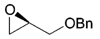
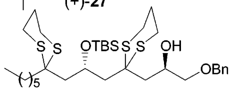
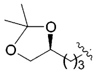
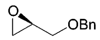
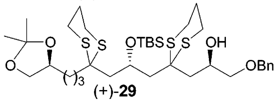
Entry	Electrophile	Product	Yield (%)
1		 (-)-**20**	73
2		 (-)-**21**	65
3		 (+)-**22**	72
4		 (+)-**23**	75
5		 (-)-**24**	65
6		 (+)-**25**	69

Addition of the second electrophile, premixed with HMPA (10% v/v in Et$_2$O), completes the reaction sequence. In general, the yields of anion relay products (**20**−**25**) are good. Terminal epoxides and alkyl halides serve as excellent electrophiles in this reaction sequence. Particularly interesting is the example illustrated in entry 6, which leads to (+)-**25**, possessing a new electrophilic epoxide site for further diversity.

The anion relay protocol was next applied to a series of 2-substituted dithiane substrates (Table 3). Again, the desired products were obtained in good yield. Importantly, the dithiane moieties can be removed without loss of the silyl moiety,[9] thereby providing a diverse series of 1,3,5-oxygenated systems.

Table 3. Three-Component Couplings of Different Dithianes



Entry	R	Electrophile	Product	Yield (%)
1	Ph		 (+)-**26**	81
2	*i*-Propyl		 (+)-**27**	77
3	*n*-Hexyl		 (+)-**28**	60
4			 (+)-**29**	52

In summary, an effective one-flask multicomponent linchpin coupling protocol employing the concept of anion relay chemistry (ARC) has been developed (Figure 1). Given the potential to extend the anion relay tactic *both* to non-dithiane nucleophiles and linchpin electrophiles, this method holds considerable promise in diversity oriented synthesis to access complex molecular architecture in a concise fashion.

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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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(7) If the reaction of the lithium anion of dithiane **1** with epichlorohydrin was stopped at −25 °C, the corresponding 1-chloro-2-hydroxy derivative was obtained exclusively (>95% yield).
(8) Ide, M.; Nakata, M. *Bull. Chem. Soc. Jpn*. **1999**, *72*, 2491.
(9) See Supporting Information.

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