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Through-Bond/Through-Space Anion Relay Chemistry Exploiting Vinylepoxides as Bifunctional Linchpins**

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Abstract: *The development of new bifunctional linchpins that permit the union of diverse building blocks is essential for the synthetic utility of anion relay chemistry (ARC). The design, synthesis, and validation of three vinylepoxide linchpins for through-bond/through-space ARC are now reported. For negative charge migration, this class of bifunctional linchpins employs initial through-bond ARC by an S_N2' reaction, followed by through-space ARC exploiting a 1,4-Brook rearrangement. The trans-disubstituted vinylepoxide linchpin yields a mixture of E/Z isomers, whereas the cis-disubstituted and the trans-trisubstituted vinylepoxide linchpins proceed to deliver three-component adducts with excellent E selectivity.*

Multi-component anion relay chemistry (ARC) holds great promise for the construction of architecturally complex natural and unnatural products of biological significance.[1] This strategy permits the rapid and efficient assembly of molecular complexity in a “single flask” with precise stereocontrol. The ARC tactic can be broadly divided into two classes based on the mode of negative charge migration, that occurs either “through-bond” or “through-space” (Figure 1).[1b] Through-bond ARC is defined as the transfer of negative charge through the bonding system of a molecule (e.g., conjugate addition reactions), whereas in through-space ARC, a carrier species is employed to facilitate negative charge migration (e.g., Brook rearrangement). Over the past decade, we have reported extensive studies in the area of through-space ARC employing Brook rearrangements, which led to the discovery of Type I and Type II ARC.[2] The synthetic utility of both Type I and Type II ARC tactics has been demonstrated in a number of completed or ongoing synthetic ventures, including those on (+)-spongistatins 1 and 2,[3] (+)-rimocidin,[4] (+)-spirastrellolide A and B,[5] the indolizidine alkaloids (−)-223AB and (−)-205B,[6] and the Cryptocarya family of polyhydroxylated pyrone natural products.[7] For the future, the development of new bifunctional linchpins that permit the reaction of diverse building blocks is essential for the synthetic utility of the ARC method.

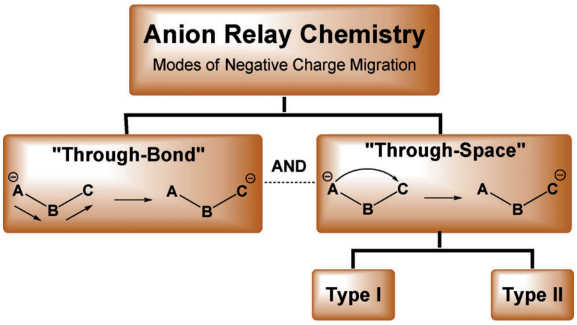

Figure 1. Classification of anion relay chemistry.

With this goal in mind, we now present for the first time the combination of through-bond and through-space ARC with a new class of bifunctional linchpins, namely vinylepoxides **1**, for the propagation of negative charge to deliver structural motifs that were previously not readily accessible (Figure 2). Specifically, addition of an external nucleophile to vinylepoxide linchpin **1** in an S_N2' fashion first generates an alkoxide anion upon negative charge migration through the bonding system (“through-bond”). Subsequent 1,4-Brook rearrangement, triggered by the addition of a polar additive [e.g., hexamethylphosphoramide (HMPA)], relays the negative charge to a new carbon center (“through-space”). Trapping of the resultant dithiane anion with an electrophile would furnish multi-component adduct **4**.

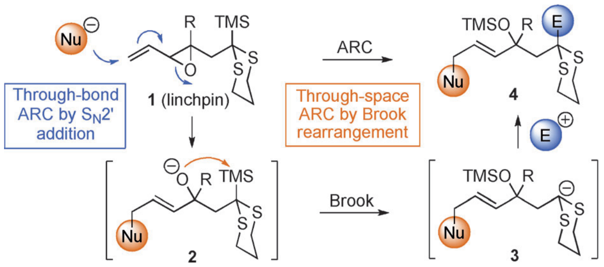

Figure 2. Through-bond/through-space ARC exploiting vinylepoxides as bifunctional linchpins. TMS = trimethylsilyl.

Vinylepoxides comprise an interesting class of electrophiles, as they possess more than one nucleofugal site; therefore, nucleophilic addition can proceed either in an S_N2 or S_N2' fashion.[8] In the case at hand, selective S_N2' addition is necessary for the subsequent 1,4-Brook rearrangement. Furthermore, as a new double bond is generated upon

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Supporting information for this article, including a general procedure for the through-bond/through-space ARC reaction and characterization of all new compounds, is available on the WWW under http://dx.doi.org/10.1002/anie.201309270.

S_N2' addition, issues concerning the *E*/*Z* selectivity must also be addressed and resolved.

To explore the proposed through-bond/through-space ARC, we first constructed *trans*-disubstituted vinylepoxide **7** (Figure 3) as a bifunctional linchpin. Condensation of acrolein with malonic acid, followed by reduction with $LiAlH_4$, furnished 2,4-pentadiene-1-ol (**5**).[9] Tungstic acid catalyzed chemoselective epoxidation of the internal alkene,[10] followed by an Appel reaction[11] with CBr_4, led to bromovinylepoxide **6**,[2b] which upon treatment with lithiated TMS-dithiane underwent a highly chemoselective substitution reaction to furnish vinylepoxide **7**. The structure of **7** was confirmed by X-ray crystallography.

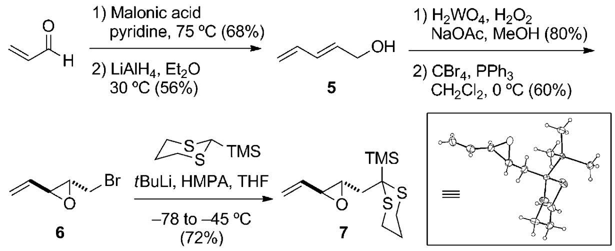


Figure 3. Synthesis of *trans*-disubstituted vinylepoxide linchpin **7**.

With linchpin **7** in hand, the initial through-bond ARC by S_N2' addition was explored. We previously demonstrated that the reaction of vinylepoxides with sterically hindered 2-substituted 1,3-dithiane anions proceeds predominantly in an S_N2' fashion.[12] Organocuprates are also known to undergo selective S_N2' addition with vinylepoxides.[13] Therefore, lithiated dithianes and organocuprates were chosen as the initiating nucleophiles (Figure 4a). With lithiated TBS-dithiane, the optimal reaction conditions include Et_2O as the solvent, ambient reaction temperature, and a reaction time of two hours. Premature Brook rearrangement was observed when the reaction was carried out in THF or for an extended time in Et_2O. Performing the reaction at 0 °C led to low conversion. Exploiting the optimized conditions, lithiation of TBS-dithiane (**8**) with *n*BuLi in Et_2O followed by addition to **7** furnished exclusively the S_N2' addition product **9** in 80 % yield, albeit with a modest level of *E*/*Z* selectivity [*E*/*Z*=2.5:1; Figure 4a, Eq. (1)]. Lithium dibutyl cuprate (**10**; generated in situ from *n*BuLi and CuI) proved to be a better nucleophile, as the S_N2' addition proceeded readily at 0 °C with equally high efficiency and chemoselectivity to furnish adduct **11** in 93 % yield, again as a 2.5:1 mixture of the *E*/*Z* isomers [Figure 4a, Eq. (2)].

Having achieved a highly selective S_N2' addition to vinylepoxide **7**, we next examined the combination of through-bond and through-space ARC in a single flask (Figure 4b). After addition of an external nucleophile to **7** under the aforementioned reaction conditions, HMPA was added to the resulting alkoxide at −40 °C to trigger a 1,4-Brook rearrangement to generate a new dithiane anion, which was trapped with allyl bromide. Subsequent removal of the TMS group using HCl (1.0 N) furnished the three-component adduct. Both lithiated TBS-dithiane and lithium dibutyl cuprate readily participated in through-bond/through-space ARC to yield the three-component adducts **12** and **13**, each as a 2.5:1 mixture of the *E*/*Z* isomers in 55 % and 70 % yield, respectively [Figure 4b, Eqs. (3) and (4)]. It is noteworthy that the *E* and *Z* isomers undergo Brook rearrangement and subsequent alkylation with equal efficiency.

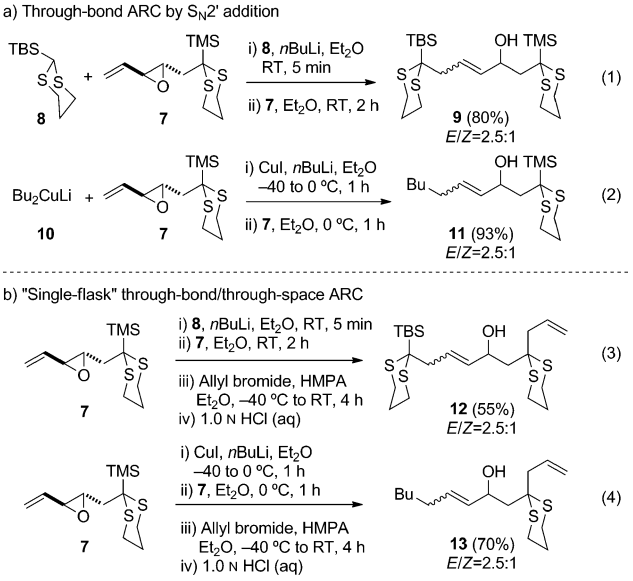


Figure 4. Through-bond/through-space ARC with linchpin **7**. TBS = *tert*-butyldimethylsilyl.

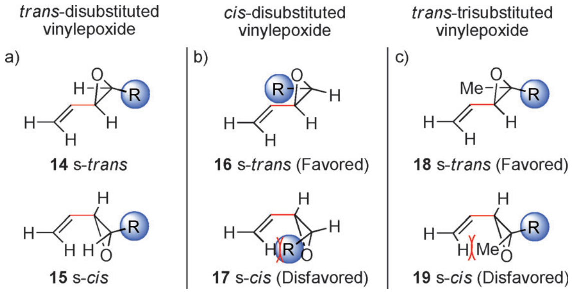


Figure 5. Transition-state models to rationalize *E*/*Z* selectivity.

To define the origin of the modest *E*/*Z* selectivity of the S_N2' addition to **7**, transition-state models were proposed based on the stereoelectronic requirement[8] that necessitates a nearly coplanar arrangement of the alkene and the epoxide to permit effective interaction between the π orbital and the breaking C−O bond (Figure 5a). Because of the lack of significant steric interactions between the s-*trans* (**14**) and s-*cis* (**15**) conformers, S_N2' addition results in a mixture of *E*/*Z* isomers. However, the possibility of greatly improved *E*/*Z* selectivity in the case of *cis*-disubstituted and *trans*-trisubstituted vinylepoxides can be seen in Figure 5b and c. The presence of a destabilizing steric interaction in the s-*cis* conformers (**17** and **19**) would be expected to strongly disfavor these conformers, thus favoring the formation of the *E* alkene by S_N2' addition to the s-*trans* conformers (**16** and **18**). To explore this scenario, we turned to *cis*-disubstituted and *trans*-trisubstituted vinylepoxide linchpins.

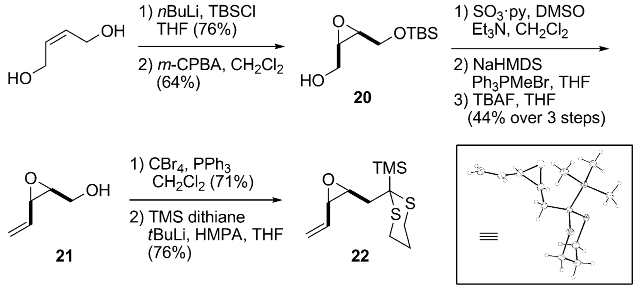


Figure 6. Synthesis of *cis*-disubstituted vinylepoxide linchpin **22**.

The synthesis of *cis*-disubstituted vinylepoxide **22** is depicted in Figure 6. Mono-protection of (*Z*)-2-butene-1,4-diol with TBSCl, followed by epoxidation with *meta*-chloroperoxybenzoic acid (*m*-CPBA) furnished epoxy alcohol **20**. Parikh–Doering oxidation[14] of the alcohol, followed by Wittig reaction with Ph_3PMeBr[15] and removal of the TBS group then led to vinylepoxy alcohol **21**. Appel halogenation[11] with CBr_4 and chemoselective substitution with lithiated TMS-dithiane completed the synthesis of **22**, the structure of which was confirmed by X-ray crystallography.

With linchpin **22** in hand, we first explored the through-bond ARC by S_N2' addition (Figure 7). As expected, addition of lithiated TBS-dithiane to **22** at ambient temperature proceeded with excellent chemo- and stereoselectivity to furnish adduct (*E*)-**9** exclusively in 67 % yield [Figure 7, Eq. (1)]. Likewise, S_N2' addition of Bu_2CuLi to **22** afforded adduct (*E*)-**11** in 90 % yield with an *E*/*Z* ratio of ≥20:1 [Figure 7, Eq. (2)].

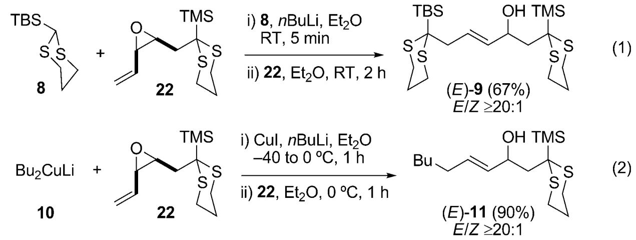
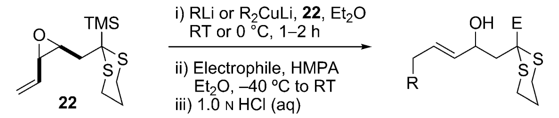
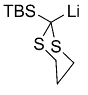
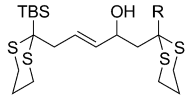
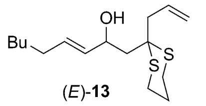
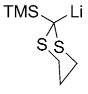
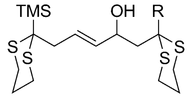
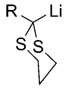
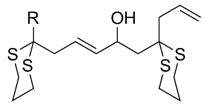


Figure 7. Through-bond ARC by S_N2' addition to linchpin **22**.

We next examined the combined through-bond and through-space ARC with linchpin **22**. Both lithiated TBS-dithiane and Bu_2CuLi underwent sequential S_N2' addition to **22**, 1,4-Brook rearrangement, and alkylation with high efficiency and excellent selectivity (Table 1, entries 1–3). Lithiated TMS-dithiane, which has previously been shown to undergo exclusive S_N2 addition with vinylepoxides in THF/HMPA,[12] reacted with **22** in a strictly S_N2' fashion in Et_2O to deliver adducts **24** and **25** in 85 % and 56 % yield, respectively (entries 4 and 5), demonstrating that a subtle change in solvent and additive can completely reverse the chemoselectivity of the nucleophilic addition to vinylepoxides. Lithiated alkyl dithianes also proved to be competent nucleophiles (entries 6 and 7). Both ethyl and isopropyl dithianes participated in the through-bond/through-space ARC with **22** to deliver three-component adducts **26** and **27** in 57 % and 47 % yield, respectively. In all cases, excellent chemoselectivity and *E*/*Z* selectivity (*E*/*Z* ≥ 20:1) were observed.

Table 1: Through-bond/through-space ARC with linchpin **22**.[a]



Entry	NuLi	Yield [%]	*E*/*Z*[b]	Product
				
1		80	≥20:1	(*E*)-**12**, R = allyl
2		67	≥20:1	**23**, R = prenyl
3	Bu_2CuLi	71	≥20:1	 (*E*)-**13**
				
4		85	≥20:1	**24**, R = allyl
5		56	≥20:1	**25**, R = Bn
				
6		57	≥20:1	**26**, R = Et
7		47	≥20:1	**27**, R = *i*Pr

[a] Reaction conditions: i) **22**, RLi, Et_2O, RT, 2 h or **22**, R_2CuLi, 0 °C, 1 h; ii) electrophile, HMPA, Et_2O, −40 °C to RT, 1 h; then RT, 3 h; iii) 1.0 N HCl (aq). [b] The *E*/*Z* ratio was determined by ^1H NMR analysis of the crude product mixture. Bn = benzyl.

We next constructed *trans*-trisubstituted vinylepoxide **30** for through-bond/through-space ARC (Figure 8). Wittig reaction of (carbethoxyethylidene)triphenylphosphorane with acrolein,[16] followed by reduction with $LiAlH_4$ and chemoselective epoxidation catalyzed by tungstic acid,[10] furnished dienol **28**. Appel reaction[11] with CBr_4 and chemoselective substitution with lithiated TMS-dithiane, in this case

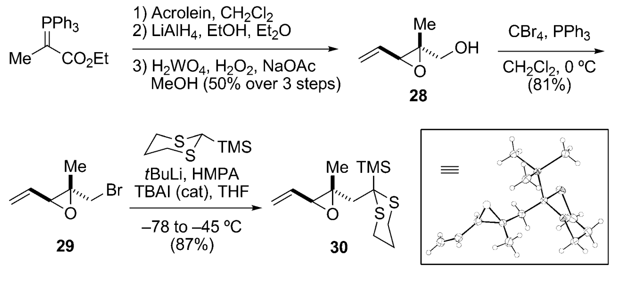


Figure 8. Synthesis of *trans*-trisubstituted vinylepoxide linchpin **30**.

requiring catalytic amounts of tetrabutylammonium iodide (TBAI) because of steric encumbrance, completed the synthesis of vinylepoxide **30**, the structure of which was confirmed by X-ray crystallography.

The results for through-bond/through-space ARC with linchpin **30** are illustrated in Figure 9. As expected, initial S_N2' addition of lithiated TBS-dithiane to **30** proceeded with excellent *E* selectivity. However, owing to a premature Brook rearrangement, a 1:1 mixture of the pre-Brook (**31**) and post-Brook (**32**) products was isolated in a combined yield of 83% [Figure 9, Eq. (1)]. Multiple attempts to suppress the premature Brook rearrangement were unsuccessful in this case. Pleasingly, single-flask through-bond/through-space ARC with **30** did proceed to deliver the desired product **33**, albeit in only 35% yield [Figure 9, Eq. (2)].[17]

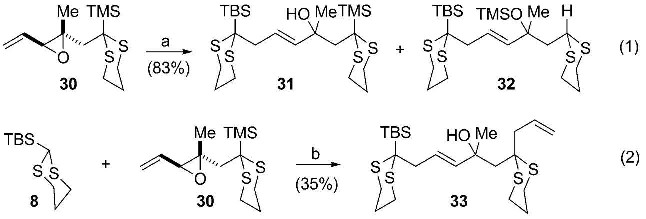


Figure 9. Through-bond/through-space ARC with linchpin **30**. Reaction conditions: a) i) **8**, *n*BuLi, Et_2O, RT, 5 min; ii) **30**, Et_2O, RT, 2 h. b) i) **8**, *n*BuLi, Et_2O, RT, 5 min; ii) **30**, Et_2O, RT, 2 h; iii) allyl bromide, HMPA, TBAI (2.5 mol%), RT, 5 h; iv) HCl (2.0 N), 36 h.

In summary, we have achieved the design, synthesis, and validation of three vinylepoxide linchpins (**7**, **22**, and **30**) for through-bond/through-space ARC.[18] These vinylepoxides represent the first examples of a new class of bifunctional linchpins that employ both through-bond and through-space modes of negative charge migration to facilitate the synthesis of three-component adducts.

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Keywords: anion relay chemistry · Brook rearrangement · nucleophilic addition · through-bond interactions · through-space interactions

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[17] This reaction proceeded to deliver the TMS-protected three-component adduct in ca. 52% yield. However, the desired product was inseparable from the quenched Brook intermediate.

[18] Transition-state energy calculations using B3LYP density functional theory were performed for three vinylepoxides (**7**, **22**, and **30**). See the Supporting Information for full computational details.