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

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Abstract

The development of new bifunctional linchpins that permits the union of diverse building blocks is essential for the synthetic utility of Anion Relay Chemistry (ARC). Herein, we report the design, synthesis and validation of three vinylepoxide linchpins for through-bond/through-space ARC. For negative charge migration, this class of bifunctional linchpins employs initial through-bond ARC via an S_N2' reaction, followed by through-space ARC exploiting a 1,4-Brook rearrangement. Trans-Disubstituted vinylepoxide linchpin yields a mixture of E/Z-isomers, while cis-disubstituted and trans-trisubstituted vinylepoxide linchpins proceed to deliver three-component adducts with excellent E-selectivity.

Keywords

through-bond/through-space; anion relay chemistry; vinylepoxides; S_N2' addition; Brook rearrangement

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 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 is either “through-bond” or “through-space” (Figure 1).^[1b] Through-bond ARC is defined as the transfer of negative charge via the bonding system of a molecule (*i.e.*, conjugate addition reactions), while in through-space ARC, a carrier species is employed to facilitate negative charge migration (*i.e.*, Brook rearrangement). Over the past decade we have reported extensive studies in the area of through-space ARC employing Brook rearrangements leading 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 (+)-spongistatins 1 and 2,^[3] (+)-rimocidin,^[4] (+)-spirastrellodlide A and B,^[5] the indolizidine alkaloids (–)-223AB and (–)-205B,^[6] and the *Cryptocarya* family of polyhydroxylated pyrone natural products.^[7] For the future, development of new bifunctional linchpins that permit the union of diverse building blocks is essential for the synthetic utility of the ARC protocol.

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

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 vinyl epoxides **1**, for the propagation of negative charge to deliver structural motifs not previously readily accessible (Figure 2). Specifically, addition of an external nucleophile to vinyl epoxide linchpin **1** in an S_N2' fashion first generates an alkoxide anion upon negative charge migration through the bonding system (*i.e.*, through-bond). Subsequent 1,4-Brook rearrangement, triggered by the addition of a polar additive (*i.e.*, HMPA), relays the negative charge to a new carbon center (*i.e.*, through-space). Trapping of the resultant dithiane anion with an electrophile would furnish multi-component adduct **4**.

Vinyl epoxides comprise an interesting class of electrophiles, as they possess more than one nucleofugal site, thus nucleophilic addition can proceed either through the S_N2 or S_N2' manifold.^[8] In the case at hand, selective S_N2' addition is necessary for the subsequent 1,4-Brook rearrangement. In addition, since a new double bond is generated upon the S_N2' addition, issues concerning *E/Z*-selectivity must also be addressed and resolved.

To explore the proposed through-bond/through-space ARC, we first constructed *trans*-disubstituted vinyl epoxide **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 Appel reaction^[11] with CBr_4 , led to bromovinyl epoxide **6**,^[2b] which upon treatment with lithiated TMS-dithiane, underwent a highly chemoselective substitution reaction to furnish vinyl epoxide **7**. The structure of **7** was confirmed by X-ray crystallography.

With linchpin **7** in hand, the initial through-bond ARC via S_N2' addition was explored. We previously demonstrated that reaction of vinyl epoxides with sterically hindered 2-substituted 1,3-dithiane anions proceeds predominantly in S_N2' fashion.^[12] Organocuprates are also known to undergo selective S_N2' addition with vinyl epoxides.^[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 solvent, ambient reaction temperature, and a two hour reaction time. 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 optimal 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 modest level of *E/Z*-selectivity (*E/Z* = 2.5:1) (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 *E/Z*-isomers (Eq. 2).

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

To define the modest *E/Z*-selectivity of the S_N2' addition to **7**, transition state models are 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). Due to 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. The possibility, however, of greatly improved *E/Z*-selectivity in the case of *cis*-disubstituted and *trans*-trisubstituted vinyloxyepoxides can be seen in Figure 5B and 5C. The presence of destabilizing steric interaction in *S-cis* conformers (**17** and **19**) would be expected to strongly disfavor these conformers, thus favoring the formation of *E*-alkene via S_N2' addition to the *S-trans* conformers (**16** and **18**). To explore this scenario, we turned to *cis*-disubstituted and *trans*-trisubstituted vinyloxyepoxide linchpins.

Construction of *cis*-disubstituted vinyloxyepoxide **22** is depicted in Figure 6. Mono-protection of (*Z*)-2-butene-1,4-diol with TBSCl, followed by epoxidation with *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 vinyloxy 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 via 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 (Eq. 1). Likewise, S_N2' addition of Bu_2CuLi to **22** afforded adduct **E-11** in 90% yield with *E:Z* = 20:1 (Eq. 2).

We next examined the combined through-bond and through-space ARC with linchpin **22**. As shown in Table 1, 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 (entry 1–3). Lithiated TMS-dithiane, which has previously been shown to undergo exclusive S_N2 addition with vinyloxyepoxides 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% yields, respectively (entry 4–5), demonstrating that a subtle change in solvent and additive, as illustrated here, can completely reverse the chemoselectivity in the nucleophilic addition to vinyloxyepoxides.

Lithiated alkyl dithianes also proved to be competent nucleophiles (entry 6–7). 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% yields, respectively. In all cases, excellent chemoselectivity and *E/Z*-selectivity was observed (*E:Z* = 20:1).

We next constructed *trans*-trisubstituted vinyloxyepoxide **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 requiring catalytic TBAI due to steric encumbrance, completed the synthesis of vinyloxyepoxide **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, the initial S_N2' addition of lithiated TBS-dithiane to **30** proceeded with excellent *E*-selectivity. However, due to premature Brook rearrangement, a 1:1 mixture of pre-Brook (**31**) and post-Brook (**32**) products was isolated in a combined yield of 83% (Eq. 1). Multiple attempts to minimize the premature Brook rearrangement in this case were

unsuccessful. Pleasingly, “single-flask” through-bond/through-space ARC with **30** did proceed to deliver the desired product **33**, albeit in only 35% yield (Eq. 2).^[17]

In summary, we have achieved the design, synthesis and validation of three vinyl epoxide linchpins (**7**, **22** and **30**) for through-bond/through-space ARC.^[18] These vinyl epoxides 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 three-component union.

Experimental Section

General procedure for the through-bond/through-space ARC reaction and characterization of all new compounds are provided in the Supporting Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 with the quenched Brook intermediate.
18. Transition state energy calculations using B3LYP density functional theory were performed for the three vinylepoxides (**7**, **22** and **30**). See supporting information for full computational details.

Figure 1.
Classification of Anion Relay Chemistry.

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

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

A. Through-bond ARC via S_N2' addition

B. "Single-flask" through-bond/through-space ARC

Figure 4.
Through-bond/through-space ARC with linchpin 7.

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

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

Figure 9.

Through-bond/through-space ARC with linchpin **30**. Reaction conditions: (a) i. **8**, *n*-BuLi, Et₂O, rt, 5 min; ii. **30**, Et₂O, rt, 2 h; (b) i. **8**, *n*-BuLi, Et₂O, rt, 5 min; ii. **30**, Et₂O, rt, 2 h; iii. Allyl bromide, HMPA, TBAI (2.5 mol%), rt, 5 h; iv. 2.0 N HCl, 36 h.

Table 1

Through-bond/through-space ARC with linchpin **22**.^a

Entry	NuLi	Yield	E:Z ^b	Products
1)		80%	20:1
2)		67%	20:1	E-12 R = Allyl 23 R = Prenyl
3)	Bu ₂ CuLi	71%	20:1	E-13
4)		85%	20:1
5)		56%	20:1	24 R = Allyl 25 R = Bn
6)		57%	20:1
7)		47%	20:1	26 R = Et 27 R = <i>i</i> -Pr

[^a] Reaction conditions: i. **22**, RLi, Et₂O, rt, 2 h, or **22**, R₂CuLi, 0 °C, 1 h; ii. Electrophile, HMPA, Et₂O, -40 °C to rt, 1 h, then, rt, 3 h; iii. 1.0 N HCl (aq).

[^b] E/Z ratio was determined by ¹H NMR of the crude.