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Regioselective and divergent opening of vinyl epoxides with ethoxyacetylene†

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A divergent protocol for nucleophilic opening of vinyl epoxides with ethoxyacetylide has been developed and demonstrated to give complete regioselectivity depending on reaction conditions.

The opening of epoxides by various nucleophiles provides a powerful tool in organic synthesis for stereoselective C–C bond formation.[1] One limitation to this methodology is that unsymmetrical oxiranes often give rise to regioisomeric products, thus restricting the number of useful substrates.

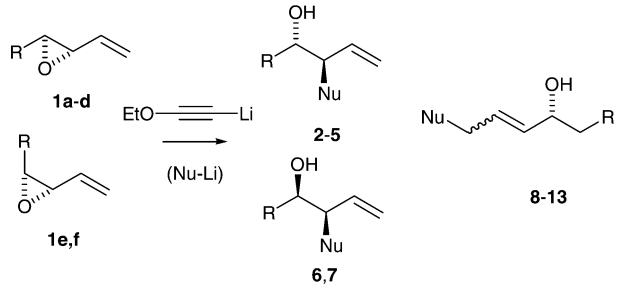
Vinyl epoxides can, for electronic reasons, often be regioselectively ring-opened in the allylic position by hard nucleophiles (attack at A, Scheme 1).[2] Soft nucleophiles often prefer S_N2' addition (attack at B), albeit the chemoselectivity is sometimes moderate. Recently, an efficient protocol using lithiated dithiane anions for the regioselective ring opening of vinyl epoxides was described.[3] In this case the selectivity was controlled by fine-tuning the steric properties of the nucleophile. Sterically unencumbered dithiane anions preferentially afforded the S_N2 product, while sterically hindered ones provided the S_N2' adducts. In an ongoing project we became interested in the regioselective opening of vinyl epoxides using alkynyl anions. Due to the unencumbered nature of these nucleophiles, this process would require an electronic differentiation between the S_N2 and S_N2' reaction manifolds. Herein, we report the realization of this strategy using ethoxyacetylide as the preferred nucleophile, affording the S_N2 or S_N2' adducts with complete regiocontrol depending on reaction conditions. This approach provides a novel entry to β,γ-disubstituted γ-butyrolactones, a class of synthetically useful compounds.[4]

Chemoselective S_N2 alkylations of vinyl epoxides have been studied previously. For example, it has been shown that titanium acetylides[5] and the combination of alkyllithiums and $BF_3{\cdot}OEt_2$[6] promote the S_N2 addition to vinyl epoxides. The latter observation prompted us to investigate the S_N2 alkynylation of vinyl epoxides **1a** using the same combination of reagents (R–Li/ $BF_3{\cdot}OEt_2$ in Et_2O), assuming that the allylic position would be the preferred reaction site under charge control. Disappointingly, the lithium acetylides derived from 1-hexyne, (trimethylsilyl)acetylene and phenylacetylene added to **1a** with poor regioselectivity. A substantial improvement was observed when employing lithium ethoxyacetylide which gave complete S_N2 regioselectivity (Table 1, entry 1). Encouraged by this result, our attention was directed towards the nature of the vinyl epoxide and substrates **1b–f**[7] were selected for further investigation. Ring opening with ethoxyacetylide gave exclusively the homoallylic alcohols **3–7** in good yields and complete regioselectivity. Furthermore, the reaction proceeded with comparable yields irrespective of the electronic and steric properties of the R-group (entries 1–4) or epoxide configuration (entries 5 and 6), thus broadening the scope of the transformation.

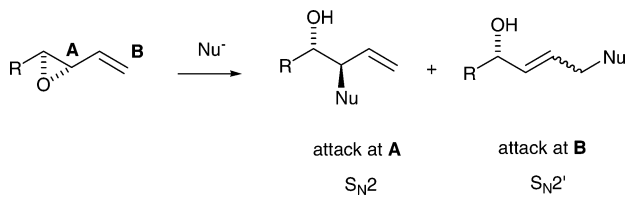
Table 1 Regioselective and divergent opening of vinyl epoxides **1a–f**[a,b]

Entry	1	Yield (%)[c]	S_N2 : S_N2'[d]	Product
1[a]	**1a**	64	>98(*anti*) : <2	**2**
2[a]	**1b**	61	>98(*anti*) : <2	**3**
3[a]	**1c**	62	>98(*anti*) : <2	**4**
4[a]	**1d**	61	>98(*anti*) : <2	**5**
5[a]	**1e**	63	>98(*syn*) : <2	**6**
6[a]	**1f**	65	>98(*syn*) : <2	**7**
7[b]	**1a**	65	<2 : >98 (*E*:*Z* 22:78)	**8**
8[b]	**1b**	59	<2 : >98[e] (*E*:*Z* 70:30)	**9**
9[b]	**1c**	55	<2 : >98 (*E*:*Z* 70:30)	**10**
10[b]	**1d**	65	<2 : >98 (*E*:*Z* 32:68)	**11**
11[b]	**1e**	55	34 : 66 (*E*:*Z* 100:0)	**12**, **6**
12[b]	**1f**	65	62 : 38 (*E*:*Z* 100:0)	**13,7**

[a] Conditions: 2.5 equiv. of lithium ethoxyacetylide and $BF_3{\cdot}OEt_2$ in Et_2O. [b] Conditions: 2 equiv. of lithium ethoxyacetylide and $AlClEt_2$ in PhMe. [c] Isolated yield. [d] Determined by ^1H NMR on the crude product. [e] Compound **14** formed as by-product, see text. Ratio **9**:**14**, 4.6:1.



(±)-**1a** R=$CH_2OTBDPS$ (±)-**1d** R=cyclohexyl
(±)-**1b** R=CH_2CH_2Ph (±)-**1e** R=cyclohexyl
(±)-**1c** R=$CH_2CH_2OTBDPS$ (±)-**1f** R=$CH_2OTBDPS$



Scheme 1

The conjugated alkylations of vinyl epoxides, most frequently employing organocopper reagents, have been extensively studied during the last decades.[8] However, alkynyl groups are not transferred from copper, making this approach impracticable. In contrast, alkynylalanes have been used for ring opening of oxiranes[9] and the soft character of these reagents has successfully been utilized in Michael additions to enones.[10] Somewhat surprisingly, these reagents have not been exploited to S_N2' opening of vinyl epoxides.[11] In our efforts to develop a divergent protocol for regioselective alkynylations of vinyl epoxides we became interested in examining the feasibility of alkynylalanes for the S_N2' reaction. To our delight, the alkynylalanes derived from ethoxyacetylide gave a complete reversal in regioselectivity in favour of the S_N2'

† Electronic supplementary information (ESI) available: ^1H NMR and ^{13}C spectra of compounds **2–13** and **15**. See http://www.rsc.org/suppdata/cc/b4/b408610d/

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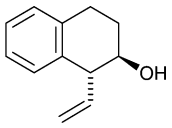


14

Fig. 1 Compound **14**.

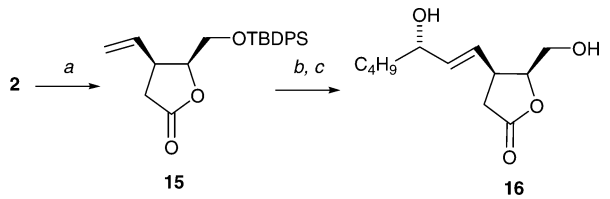
products, in the additions to *trans*-vinyl epoxides **1a–d** (entries 7–10). Unfortunately, no general trends could be observed in *E*:*Z* selectivities in the conjugated additions to *trans*-vinyl epoxides **1a–d**. In contrast, *cis*-vinyl epoxides **1e** and **1f** gave a complete *E* selectivity (entries 11 and 12). For steric reasons, the *cis*-vinyl epoxides **1e** and **1f** probably react through the s-*trans* conformation to exclusively produce the *E*-isomers whereas no such restrictions occur in the *trans*-vinyl epoxides, hence the low *E*:*Z* selectivity. Other protocols for conjugated additions to vinyl epoxides have resulted in various *E:Z* selectivities: In the S_N2' additions of dithianes to vinyl epoxides the corresponding (*E*)-alkenes are formed exclusively,[3] whereas the *E:Z* ratio obtained in conjugated additions of organocopper reagents has been shown to be highly substrate dependent.[8]

The conjugated alkynylation of *trans*-vinyl epoxides **1a–d** (entries 7–10) gave the S_N2' adducts as the only detectable products with one exception (entry 8). The S_N2' addition to **1b** afforded alcohol **14** along with the expected allylic alcohol **9** (Fig. 1). Compound **14** is most probably the result of a Friedel–Crafts type of intramolecular ring-opening and similar transformations have been described before.[12]

The S_N2' additions to *cis*-vinyl epoxides **1e** and **1f** proceeded with low regioselectivity (entries 11 and 12). Previous studies have shown that conjugated additions to enones can only proceed when the substrate–alane complex can adopt a conformation in which the reacting moieties are in close proximity in space.[10] Alane complexation to *cis*-vinyl epoxides **1e** and **1f** is likely to occur *trans* to the vinyl moiety, thus retarding the S_N2' manifold and making the S_N2 pathway more preferred.

To probe the stereochemical outcome of the S_N2 alkynylation, alcohol **2** was transformed into the γ-butyrolactone **15**, by a retro-ene reaction followed by intramolecular trapping of the ketene (Scheme 2).[13,14] The relative stereochemistry of lactone **15** was established *via* chemical correlation[15] and revealed that the addition takes place with an S_N2 mechanism. Consequently, the relative stereochemistry of the formed homoallylic alcohols **2–7** is directly related to the *cis*- or *trans*-stereochemistry of the starting vinylic epoxides.

γ-Butyrolactones have frequently been used as intermediates in natural product synthesis.[4] One interesting example concerns the synthesis of prostaglandin $PGF_{2\alpha}$ from D-glucose by Stork and



Scheme 2 Reagents and conditions: a, refluxing xylenes, 98%; b, TBAF, 97%; c, (*S*)-oct-1-en-3-ol, Grubbs 2nd cat., 57%.

coworkers.[16] In this approach lactone **16** was used as a key intermediate. By exploiting the potential of the regioselective S_N2 opening of vinyl epoxides (*vide supra*), compound **16** could be prepared in two steps from γ-butyrolactone (*S*,*S*)-**15**[17] by a cross-metathesis approach (Scheme 2).[18] Attempts to couple enantiomerically pure lactone (*S*,*S*)-**15** with (*S*)-oct-1-en-3-ol[19] using a cross-metathesis reaction suffered from low conversions, probably due to steric hindrance. Gratifyingly, desilylation of (*S*,*S*)-**15** to afford the corresponding alcohol, followed by cross-metathesis gave lactone **16** in 57% yield. This approach provides a facile convergent synthesis of compound **16**.

In conclusion, we have developed a divergent protocol for regioselective alkynylations of vinyl epoxides. The combination of lithium ethoxyacetylides and $BF_3{\cdot}OEt_2$ gave S_N2 displacement, whereas alkynylalanes derived from ethoxyacetylide afforded the S_N2' adduct. This approach provides an efficient entry to β,γ-disubstituted γ-butyrolactones. The utility of the observed S_N2 *versus* S_N2' selectivities is under further investigation and will be presented in due course.

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