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Spirodiepoxide-Based Cascades: Direct Access to Diverse Motifs

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Abstract



Allene epoxide formation/opening reaction sequences enabled direct access to diverse products. Described here are a single flask procedure for allene preparation and allene oxidation/ derivatization reactions that give, among others, diendiol, diyndiol, α' -hydroxy- γ -enone, dihydrofuranone, butenolide, δ -lactone products.

Here we report a simplified procedure for allene synthesis and several unprecedented spirodiepoxide-based transformations with hetero and carbon nucleophiles as well as ambiphilic reagents. Our aim is to develop a framework for spirodiepoxide reactivity, to demonstrate the strategic advantages that allene oxidation offers in complex molecule synthesis, and to identify reactions that give access to diverse structural motifs.¹ This disclosure is focused on simple procedures, novel cascade sequences, and diversity oriented transformations.

There are many methods for allene synthesis.² Cuprate addition to activated propargyl alcohol derivatives is mild and probably the most general, convergent, and reliable method available.³ A three step sequence is usually employed: (1) a propargyl alcohol is assembled, (2) the hydroxyl of the substrate is converted to suitable leaving group, and then (3) copper mediated S_N2' substitution is then applied to give the allene.⁴ We use an abbreviated variant that does not require purification, or even isolation, of the intermediates (Table 1). The combination of an alkyne with base, sequential addition of an aldehyde or ketone, methanesulfonyl chloride, triethylamine, and then exposure of the reaction mixture to a cuprate reagent gives the desired allene directly. The use of triethylamine for propargyl activation is not strictly necessary. However, this additive was found to improve reproducibility. Upon addition of the propargyl mesylate mixture to the cuprate reagent, low temperature conditions were found to suppress the S_N2 product and favor S_N2' product formation. In total, this sequential component coupling procedure⁵ produces minimal waste,

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Supporting Information Available: Synthetic methods and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

requires ~5 hours of reaction time, and is efficient for a range of substituents, including aryl (Table 1, entries 1, 2, 10, 14–16, and 20), silyl (Table 1, entries 7, 9, 11, and 16), halo (Table 1, entries 12–20), and α -branched alkyl (Table 1, entries 4, 6, 17 and 19).⁶

Reactions of allene-derived spirodiepoxides that deviate from what would be expected based on earlier reports and/or simple epoxides are summarized in Tables 2–4. Dimethyldioxirane (DMDO) rapidly converts allenes to spirodiepoxides via sequential oxygen delivery (I \rightarrow III, eq 1). The first epoxidation is reliably selective for 1,3-disubstituted allenes and for trisubstituted allenes. This oxidation simultaneously sets the absolute configuration and alkene geometry of the allene oxide, II, with high fidelity (dr >20:1), and although the selectivity of the second oxidation (\rightarrow III) may be near 1:1, for suitable substrates the stereoselectivity is excellent (>20:1). For all experiments described here, the allene was oxidized in DMDO/chloroform solutions⁷ and then exposed to the conditions indicated without isolation and purification of the intermediate spirodiepoxide.



(eq 1)

Table 2 lists data for heteronucleophile addition to spirodiepoxides that suggest this electrophile, though highly reactive, is probably best thought of as relatively soft. Table 2, entry 1 shows that the spirodiepoxide reacts with sodium benzenesulfinate to give the sulfone.⁸ No*O*-alkylation was observed in this case. Approximately stoichiometric sodium trifluoroethoxide adds efficiently (Table 2, entry 2), however, trifluoroethanol does not add to the spriodiepoxide under neutral conditions even in large excess, in contrast to water and other alcohols.^{9–11} Base is also required to effect spirodiepoxide opening with indole. This takes place in the absence of added Lewis acid and occurs exclusively on the indole nitrogen (Table 2, entry 3).¹² The highly versatile haloketone functionality⁹ can be derived from spirodiepoxides as well. These reactions proceed in servicable but capricious yield when tetraalkylammonium salts are used (e.g. Table 2, entries 4–6).¹¹ In contrast, lithium halide salts react rapidly and reliably to give the haloketones in excellent yield (Table 2, entries 7–9). The benefit of the lithium gegenion is especially noteworthy, since there are no reported examples of Lewis acid promoted spirodiepoxide opening.

The addition of carbon nucleophiles to spirodiepoxides is particularly appealing and diverse C-C bond forming reactions are given in Table 3. As noted previously, cyanide adds smoothly to spirodiepoxides to give the corresponding nitrile derivative.¹ⁱ The anion derived from acetonitrile and LDA gave the homologous ketonitrile (Table 3, entry 1). Although such anions are known to add to ketones, in this case the reaction cleanly gives monoaddition and the ketone is isolated. In contrast, ambiphilic isonitriles follow a different course. The combination *n*-butylisonitrile in *t*-BuOH and the epoxidized allene led to the slow but efficient formation of dihydrofuranone (Table 3, entry 2). The outcome is consistent with formation of nitrilium ion intermediate **IV** (eq 2), cyclization to **V**, and then isomerization of the olefin. This mild transformation is remarkable, especially since spontaneous opening of conventional epoxides with isonitriles is unknown.¹³

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(eq 2)

Conceptually similar to the isonitrile reaction, and as shown in Table 3, entry 3, the use of diethyl malonate and sodium hydride established new C-C, C-O, and new ring connectivity – and a new stereocenter (dr 6:1).¹⁴ Table 3, entry 4 demonstrates a different reaction cascade. Exposure of the spirodiepoxide to 2-(diethoxyphosphoryl)acetic acid in the presence of K₂CO₃ and crown ether gave the butenolide. In this case, the nascent tertiary alkoxide is parlayed into a new C-C bond: upon addition of the carboxylate to the spirodiepoxide resultant alkoxide **VI** (eq 3) acts as base and generates the ylide, which then effects ring-closure to give butenolide **VII**.¹⁵



(eq 3)

In previous work, organocuprates were necessary to promote nucleophilic opening over eliminative opening.^{1d,1g} However, we have found that vinyl and alkynyl lithium reagents add directly and efficiently to spirodiepoxides in the absence of copper (I) salts (Table 3, entries 5–7). This result appears traceable to the reduced basicity of these organolithium reagents in comparison to alkyl lithium reagents. Unlike less reactive nucleophiles, these reagents add twice (c.f. Table 3, entry 1) - initially to the spirodiepoxide and then to the carbonyl produced upon spirodiepoxide opening. In each instance, a single diastereomer was obtained, indicative of stereoselective carbonyl addition. This outcome appears readily understood in terms of steric congestion. It is likely that upon spirodiepoxide opening, the lithium alkoxide is involved in chelation with carbonyl VIII (eq 4). The combination of steric congestion and the comparatively small alkynyl and alkenyl substituents favor π -facial addition, as drawn, to give IX.¹⁶ Exposure of the divinyl addition reaction mixture of Table 3, entry 5 to HMPA, instead of the work-up conditions that gave the diendiol product, effected the formation of the cis-olefin shown in Table 3, entry 8. The facility of this Evans-Cope rearrangement¹⁷ is consistent with solvent destabilization of the vicinal tertiary lithium alkoxides. Reaction by way of conformers that avoid syn-pentane interactions accounts for the cis olefin geometry as shown for \mathbf{X} (eq 5).¹⁸



(eq 4)



(eq 5)

Taken together, Tables 2 and 3 demonstrate the conversion of a single allene to a diverse range of products via oxidation/derivatization reactions. In order to further demonstrate diversity-focused methodology, we evaluated three other allenes in four of the reactions described in Tables 2 and 3. The allenes were taken from Table 1, entries 2, 3, and 8, and include those with aromatic and common heterofunctionality. The transformations examined were the oxidation/bromide and oxidation/iodide additions (Table 4, entries 1 and 2), and the oxidation/dihydrofuranone and oxidation/butenolide cascades (Table 4, entries 3 and 4) under the same conditions as before. The yields for these substrates are excellent and parallel the yields of the simpler allene.

Importantly, the reactions described in Tables 1–4 have been run on scales ranging from ~20 mg to >1 g. As noted above in eq 1, despite the sometimes low selectivity in the second oxidation, the first oxidation stereoselectivity is excellent. As such, the first oxidation for the entries in Table 4 was >20:1, and where relevant, the second oxidation was modest (dr ~ 3:2). Nevertheless, the overall structural complexity achieved for these reactions is remarkable.¹⁹

The motifs accessed and tabulated in this report were obtained in one or two flask procedures. The combination of alkynes, aldehydes, and cuprates gives allenes directly and in good yield. In a second maneuver, allene epoxidation and subsequent reaction gives diverse product motifs of considerable use in complex molecule synthesis and the search for bioactive compounds. These data underscore the distinct reactivity and consequences of allene oxidation/derivatization for chemical synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- 18. The cis olefin product is also consistent with the stereochemical assignments of the products of entries 5–7 (Table 3).
- 19. Reagent-controlled diastereoselective allene oxidation will be described separately (G. Hu and L. J. Williams, manuscript in preparation).

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Single Flask Allene Synthesis

| | ۍ ۲ | yield % | 93 | 82 | 93 | 79 | 91 | 84 | 78 | 92 | 80 | 81 | 74 | 68 | 62 | 65 | 61 | 09 | 64 | 58 | 50 | 63 |
|--------------|-------------------------------------------------|----------------|-----------------------------------|-----------------------------------|--------------|----------------|--------------|--------------|--------------|--------------|------|-----------------------------------|----------------------|--------------|--------------|-----------------------------------|--------------|-----------------------------------|--------------|------------|--------------|-----------------------------------|
| | | \mathbb{R}^4 | CH ₃ | CH_3 | CH_3 | CH_3 | <i>n</i> -Bu | n-Bu | n-Bu | n-Bu | n-Bu | | PhMe ₂ Si | CI | CI | CI | CI | CI | CI | CI | Br | I |
| | 4) R ⁴ C | \mathbb{R}^3 | Н | Η | Η | Н | Н | Н | Н | Н | Η | Н | Η | Н | Η | Н | Н | Η | Н | 茁 | Η | н |
| | | \mathbb{R}^2 | PhCH ₂ CH ₂ | PhCH ₂ CH ₂ | <i>i</i> -Bu | <i>i</i> -Pr | <i>i</i> -Bu | <i>i</i> -Bu | <i>i</i> -Bu | <i>i</i> -Bu | n-Bu | PhCH ₂ CH ₂ | <i>i</i> -Bu | <i>i</i> -Bu | <i>n</i> -Bu | PhCH ₂ CH ₂ | Ph | PhCH ₂ CH ₂ | <i>t</i> -Bu | Et | <i>t</i> -Bu | PhCH ₂ CH ₂ |
| 1) BuLi O | $-R^{1}\frac{2}{R^{2}}\frac{R^{3}}{R^{3}}R^{3}$ | \mathbb{R}^1 | n-Bu | $TBSOCH_2$ | $TBSOCH_2$ | CH3CH2CH(OTBS) | <i>n</i> -Bu | t-Bu | TMS | $BnOCH_2$ | TMS | nB-n | n-Bu | <i>n</i> -Bu | n-Bu | <i>n</i> -Bu | <i>n</i> -Bu | TMS | $TBSOCH_2$ | $TBSOCH_2$ | <i>t</i> -Bu | <i>n</i> -Bu |
| | ll. | entry | - | 2 | 3 | 4 | 5 | 9 | Ζ | 8 | 6 | 10 | 11 | 12^{a} | 13^{d} | 14^{a} | 15^{a} | 16^{a} | 17a | $18^{a,b}$ | $19^{a,b}$ | $20^{a,b}$ |

Conditions: 1) n-BuLi (1.05 equiv), THF, -78 °C to 0 °C, 35 min; 2) aldehyde/ketone (1.0 equiv), -78 °C to 0 °C, 0.5–2 h; 3) MsCl (1.05 equiv), Et3N (1.05 equiv), 0 °C, 1–2 h; 4) R⁴CuCNLi, THF, -78 $^\circ\mathrm{C}$ to rt, 1–3 h.

 $^{a}(\mathrm{R}^{4})$ 2CuLi was used instead of R^{4} CuCNLi.

 $^b{
m Ms2O}$ was used instead of MsCl.

Table 2

Simple Nucleophile Addition

| n-Bu ∕∕− | i-Bu 1) DMI | DO n-Bu gent HO n-B | <i>i-</i> Bu | | | |
|----------------|-------------------------------------------------------|----------------------------------|--------------|--|--|--|
| entry | reagent | X | yield % | | | |
| 1^a | PhSO ₂ Na | -{- SO₂Ph | 50 | | | |
| 2^b | CF ₃ CH ₂ ONa | OCH ₂ CF ₃ | 75 | | | |
| 3 ^c | Indole/LDA | And N | 50 | | | |
| 4^d | (n-Bu) ₄ NF | F | 51 | | | |
| 5 ^e | PhCH ₂ (CH ₃) ₃ NCl | Cl | 60 | | | |
| 6 ^f | (n-Bu) ₄ NBr | Br | 50 | | | |
| 7 <i>8</i> | LiBr | Br | 88 | | | |
| 8^g | LiCl | Cl | 85 | | | |
| 9^h | Lil | Ι | 85 | | | |

Conditions: 1) DMDO, CHCl₃, -40 °C, 30 min; 2)

 a PhSO₂Na (1.5 equiv), 15-crown-5 (1.5 equiv), THF 0 °C to rt, 5 h.

^bNaH (1.5 equiv), CF3CH2OH, 0 °C to rt, 1 h.

 c n-BuLi (3.0 equiv), indole (3.0 equiv), THF, $-78\ ^{\circ}\mathrm{C}$ to 0 $^{\circ}\mathrm{C},$ 4 h.

 $^{d}{\rm TBAF}$ (2.0 equiv), THF, 0 °C to rt, 4 h.

 $^{e}\mathrm{Benzyltrimethylammonium}$ chloride (2.0 equiv), THF, 0 °C to rt, 4 h.

 f_{TBAB} (2.0 equiv), THF, 0 °C to rt, 4 h.

^gLiX (X= Cl, Br, I; 3.0 equiv), THF, 0 °C to rt, 4 h,

 h LiX (X= Br, I; 10.0 equiv), CHCl₃, 0 °C to rt, 4 h.

n-Bu

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product reagent n-Bu н reagent product yield % entry 1^a CH₃CN, LDA 65 0 *n*-Bu *i-*Bu *n*-Bu′ óн ₽N 2^b n-BuNC, t-BuOH 81 n-Bu n-Bu -Bu . NH(*n*-Bu) 3^c Diethyl malonate, NaH 45 н *n-*Bu -Bu n-Bu (EtO)₂OPCH₂CO₂H K₂CO₃, 18-C-6 71 4^d n-Bu n-Bu ĊН Bu 81 5^e n-Bu *n*-Bu -Bu 65 6^f -*п*-Ви n-Bu i-Bu *n*-Bu n-Bu . Bu 65 7f -TMS Li *n-*Bu n-Bu 'nн i-Bu 8*8* 61 Li′ \sim *n-*Bu , THF then HMPA (20 equiv.) *n-*Bu′ όн i-Bu

-Bu 1) DMDO

Conditions: 1) DMDO, CHCl3, -40 °C, 30 min; 2)

^aLDA (3.0 equiv), CH₃CN (3.0 equiv), -78 °C to 0 °C, 4 h.

^b *n*-BuNC (10 equiv), *t*-BuOH, rt, 2 d.

 $^{\it C}$ Diethyl malonate (1.5 equiv), NaH (1.5 equiv), 0 °C to rt, 4 h.

^d(EtO)₂OPCH₂CO₂H (2.0 equiv), K₂CO₃ (6.0 equiv), 18-C-6 (2 equiv), rt, 4 h.

^eLiCHCH₂ (4.0 equiv), 0 °C to rt, 2 h.

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 f_{n} -BuLi (4.0 equiv), HCCR (R= Bu, TMS; 4.0 equiv), -78 °C to 0 °C, 2 h.

^gLiCHCH₂ (4.0 equiv), 0 °C to rt, 1 h; HMPA (20 equiv), 0 °C to rt, 1 h.

Table 4

Nucleophile Addition



Conditions: 1) DMDO, CHCl3, -40 °C, 30-120 min; 2)

 $^{a}\mathrm{LiX}$ (X= Br, I; 10.0 equiv), CHCl3, 0 °C to rt, 2 h.

^b *n*-BuNC (30 equiv), *t*-BuOH, rt, 5 d.

^с(ЕtO)20PCH2CO2H (2.0 equiv), K2CO3 (6.0 equiv), 18-С-6 (6.0 equiv), rt, 4 h.