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Spirodiepoxide-Based Cascades: Direct Access to Diverse Motifs

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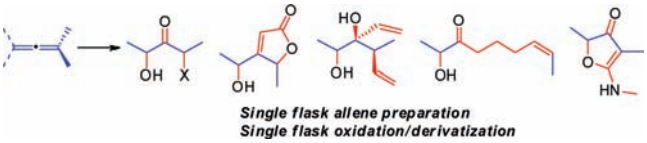
ABSTRACT



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, and δ-lactone products.

Here we report a simplified procedure for allene synthesis and several unprecedented spirodiepoxide-based transformations with heteronucleophiles 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 a suitable leaving group, and (3) copper mediated S_N2' substitution is then

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(1) (a) Joyasawal, S.; Lotesta, S. D.; Akhmedov, N. G.; Williams, L. J. *Org. Lett.* **2010**, *12*, 988. (b) Zhang, Y.; Cusick, J. R.; Shangguan, N.; Katukojvala, S.; Inghrim, J.; Emge, T. J.; Williams, L. J. *J. Org. Chem.* **2009**, *74*, 7707. (c) Ghosh, P.; Zhang, Y.; Emge, T. J.; Williams, L. J. *Org. Lett.* **2009**, *11*, 4402. (d) Ghosh, P.; Cusick, J. R.; Inghrim, J.; Williams, L. J. *Org. Lett.* **2009**, *11*, 4672. (e) Wang, Z. H.; Shangguan, N.; Cusick, J. R.; Williams, L. J. *Synlett* **2008**, *2*, 213. (f) Kolakowski, R. V.; Williams, L. J. *Tetrahedron Lett.* **2007**, *48*, 4761. (g) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129*, 2438. (h) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093. (i) Lotesta, S. D.; Kiren, S. K.; Sauers, R. R.; Williams, L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 15. (j) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348. (k) D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869.

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(3) (a) Hoffmann-Röder, A.; Krause, N. Metal-Mediated Synthesis of Allenes. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vol. 1, pp 52−70 and references therein. (b) Ogasawara, M.; Hayashi, T. Transition Metal-Catalyzed Synthesis of Allenes. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vol. 1, pp 107−110 and references therein. (c) Ohno, H.; Nagaoka, Y.; Tomioka, K. Enantioselective Synthesis of Allenes. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vol. 1, pp 141−151 and references therein.

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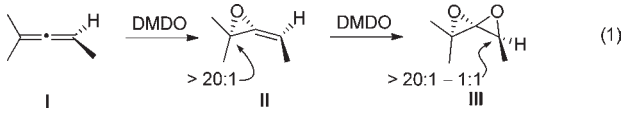
applied to give the allene.[4] We use an abbreviated variant that does not require purification, or even isolation, of the intermediates (Table 1). The combination of an alkyne with a base; sequential addition of an aldehyde or ketone, methanesulfonyl chloride, and triethylamine; and then exposure of 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 procedure[5] produces minimal waste, requires ~5 h 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) groups.[6]

Table 1. Single Flask Allene Synthesis[a]

entry	R^1	R^2	R^3	R^4	yield %
1	*n*-Bu	$PhCH_2CH_2$	H	CH_3	93
2	$TBSOCH_2$	$PhCH_2CH_2$	H	CH_3	82
3	$TBSOCH_2$	*i*-Bu	H	CH_3	93
4	$CH_3CH_2CH(OTBS)$	*i*-Pr	H	CH_3	79
5	*n*-Bu	*i*-Bu	H	*n*-Bu	91
6	*t*-Bu	*i*-Bu	H	*n*-Bu	84
7	TMS	*i*-Bu	H	*n*-Bu	78
8	$BnOCH_2$	*i*-Bu	H	*n*-Bu	92
9	TMS	*n*-Bu	H	*n*-Bu	80
10	*n*-Bu	$PhCH_2CH_2$	H		81
11	*n*-Bu	*i*-Bu	H	$PhMe_2Si$	74
12[b]	*n*-Bu	*i*-Bu	H	Cl	68
13[b]	*n*-Bu	*n*-Bu	H	Cl	62
14[b]	*n*-Bu	$PhCH_2CH_2$	H	Cl	65
15[b]	*n*-Bu	Ph	H	Cl	61
16[b]	TMS	$PhCH_2CH_2$	H	Cl	60
17[b]	$TBSOCH_2$	*t*-Bu	H	Cl	64
18[b,c]	$TBSOCH_2$	Et	Et	Cl	58
19[b,c]	*t*-Bu	*t*-Bu	H	Br	50
20[b,c]	*n*-Bu	$PhCH_2CH_2$	H	I	63

[a] Conditions: (1) *n*-BuLi (1.05 equiv), THF, −78 to 0 °C, 35 min; (2) aldehyde/ketone (1.0 equiv), −78 to 0 °C, 0.5–2 h; (3) MsCl (1.05 equiv), Et_3N (1.05 equiv), 0 °C, 1–2 h; (4) $R^4CuCNLi$, THF, −78 °C to rt, 1–3 h. [b] $(R^4)_2CuLi$ was used instead of $R^4CuCNLi$. [c] Ms_2O was used instead of MsCl.

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**→**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 (→**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 solutions[7] and then exposed to the conditions indicated without isolation and purification of the intermediate spirodiepoxide.



(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 an added Lewis acid and occurs exclusively on the indole nitrogen (Table 2, entry 3).[12] The highly versatile haloketone functionality[9] 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 yields (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

(5) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. The authors make the distinction between multicomponent reactions (MCRs) and sequential component reactions (SCRs). The transformations described in the present work are properly characterized as SCRs.

(6) Enantioenriched allenes are readily prepared from enantioenriched propargyl alcohols with this procedure, beginning at step 3, Table 1.

(7) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) For photo of the experimental setup for this procedure, see ref 1i. (c) Gilbert, M.; Ferrer, M.; Sanchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1997**, *53*, 8643.

(8) Meek, J. S.; Fowler, J. S. *J. Org. Chem.* **1968**, *33*, 3422.

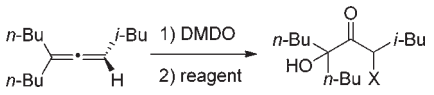
(9) For example, see: Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240.

(10) Exceptions are known, see ref 1b, 1d, 1h, and 1i.

(11) Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Ling, F. *J. Org. Chem.* **1991**, *56*, 1153. The history of the tetraalkyl ammonium reagent appears to strongly influence reproducibility.

(12) *Cf.* Westermaier, M.; Mayr, H. *Chem.—Eur. J.* **2008**, *14*, 1638.

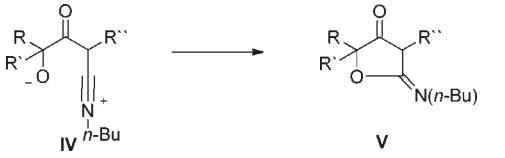
Table 2. Simple Nucleophile Addition[a]



entry	reagent	X	yield %
1[b]	$PhSO_2Na$	$-SO_2Ph$	50
2[c]	CF_3CH_2ONa	OCH_2CF_3	75
3[d]	Indole/LDA		50
4[e]	$(n\text{-Bu})_4NF$	F	51
5[f]	$PhCH_2(CH_3)_3NCl$	Cl	60
6[g]	$(n\text{-Bu})_4NBr$	Br	50
7[h]	LiBr	Br	88
8[h]	LiCl	Cl	85
9[i]	LiI	I	85

[a] Step 1: DMDO, $CHCl_3$, −40 °C, 30 min. [b] Step 2: $PhSO_2Na$ (1.5 equiv), 15-crown-5 (1.5 equiv), THF 0 °C to rt, 5 h. [c] Step 2: NaH (1.5 equiv), CF_3CH_2OH, 0 °C to rt, 1 h. [d] Step 2: *n*-BuLi (3.0 equiv), indole (3.0 equiv), THF, −78 to 0 °C, 4 h. [e] Step 2: TBAF (2.0 equiv), THF, 0 °C to rt, 4 h. [f] Step 2: Benzyltrimethylammonium chloride (2.0 equiv), THF, 0 °C to rt, 4 h. [g] Step 2: TBAB (2.0 equiv), THF, 0 °C to rt, 4 h. [h] Step 2: LiX (X = Cl, Br; 3.0 equiv), THF, 0 °C to rt, 4 h, [i] Step 2: LiI (10.0 equiv), $CHCl_3$, 0 °C to rt, 4 h.

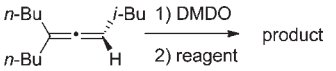
ketone is isolated. In contrast, ambiphilic isonitriles follow a different course. The combination of *n*-butylisonitrile in *t*-BuOH and the epoxidized allene led to the slow but efficient formation of dihydrofuranone (Table 3, entry 2). The outcome is consistent with formation of nitrilium ion intermediate **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]

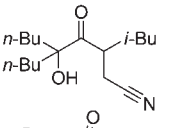
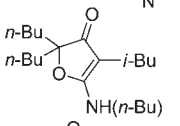
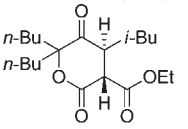
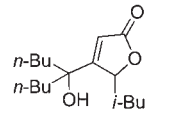
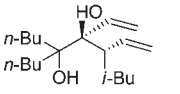
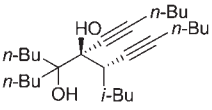
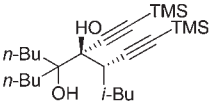
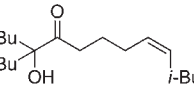


(2)

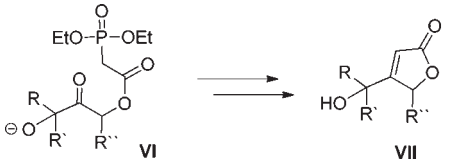
Conceptually similar to the isonitrile reaction, and as shown in Table 3, entry 3, the use of diethyl malonate and sodium hydride established new C−C, C−O, and new ring connectivity—and a new stereocenter (dr 6:1).[14] Table 3, entry 4 demonstrates a different reaction cascade. Exposure of the spirodiepoxide to 2-(diethoxyphosphoryl)acetic acid in the presence of K_2CO_3 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]

Table 3. Complex Nucleophile Addition[a]



entry	reagent	product	yield %
1[b]	CH_3CN, LDA		65
2[c]	*n*-BuNC, t-BuOH		81
3[d]	Diethyl malonate, NaH		45
4[e]	$(EtO)_2OPCH_2CO_2H$ K_2CO_3, 18-C-6		71
5[f]			81
6[g]			65
7[g]			65
8[h]	 , THF then HMPA (20 equiv.)		61

[a] Step 1: DMDO, $CHCl_3$, −40 °C, 30 min. [b] Step 2: LDA (3.0 equiv), CH_3CN (3.0 equiv), −78 to 0 °C, 4 h. [c] Step 2: *n*-BuNC (10 equiv), *t*-BuOH, rt, 2 d. [d] Step 2: Diethyl malonate (1.5 equiv), NaH (1.5 equiv), 0 °C to rt, 4 h. [e] Step 2: $(EtO)_2OPCH_2CO_2H$ (2.0 equiv), K_2CO_3 (6.0 equiv), 18-C-6 (2 equiv), rt, 4 h. [f] Step 2: $LiCHCH_2$ (4.0 equiv), 0 °C to rt, 2 h. [g] Step 2: *n*-BuLi (4.0 equiv), HCCR (R = Bu, TMS; 4.0 equiv), −78 to 0 °C, 2 h. [h] Step 2: $LiCHCH_2$ (4.0 equiv), 0 °C to rt, 1 h; HMPA (20 equiv), 0 °C to rt, 1 h.



(3)

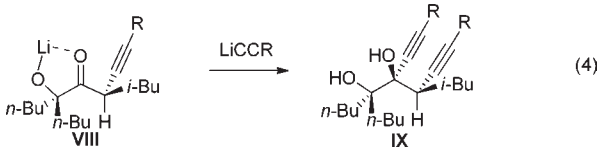
In previous work, organocuprates were necessary to promote nucleophilic opening over eliminative opening.[1d,g] However, we have found that vinyl and alkynyl lithium

(13) (a) Imi, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 1013. (b) Kern, O. T.; Motherwell, W. B. *Chem. Commun.* **2003**, *24*, 2988. (c) The analogous reaction where neat DMF was used, instead of 30 equiv of *n*-butyl isonitrile, gave the formate addition product in 83% yield; see Supporting Information for details.

(14) *Cf.* the reaction of malonates with epoxides: Van Zyl, G.; Van Tamelen, E. E. *J. Am. Chem. Soc.* **1950**, *72*, 1357.

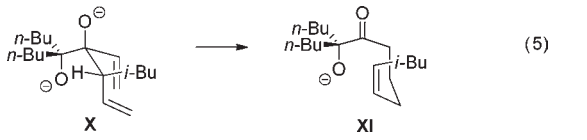
(15) The formation of a highly basic species by the release of ring strain is well known, as in the Favorskii rearrangement. See: Guijarro, D.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 1713.

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 (cf. 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 the carbonyl of **VIII** (eq 4). The



(4)

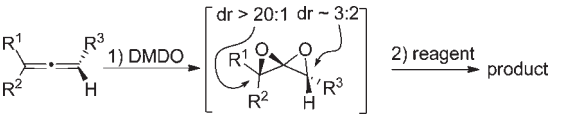
combination of steric congestion and the comparatively small alkynyl and alkenyl substituents favor π-facial addition, as drawn, to give **IX**.[16] Exposure of the divinyl addition reaction mixture of Table 3, entry 5 to HMPA, instead of the workup conditions that gave the diendiol product, effected the formation of the *cis*-olefin shown in Table 3, entry 8. The facility of this Evans−Cope rearrangement[17] 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 **X** (eq 5).[18]

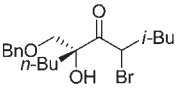
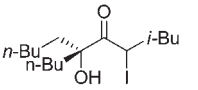
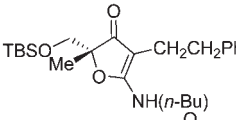
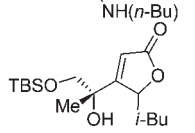


(5)

Taken together, Tables 2 and 3 demonstrate the conversion of a single allene to a diverse range of products via oxidation/derivatization reactions. To further demonstrate a 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

Table 4. Nucleophile Addition[a]



entry	reagent	product	yield %
1[b]	LiBr		95
2[b]	LiI		90
3[c]	*n*-BuNC, *t*-BuOH		77
4[d]	$(EtO)_2OPCH_2CO_2H$ K_2CO_3, 18-C-6		71

[a] Step 1: DMDO, $CHCl_3$, −40 °C, 30−120 min. [b] Step 2: LiX (X = Br, I; 10.0 equiv), $CHCl_3$, 0 °C to rt, 2 h. [c] Step 2: *n*-BuNC (30 equiv), *t*-BuOH, rt, 5 d. [d] Step 2: $(EtO)_2OPCH_2CO_2H$ (2.0 equiv), K_2CO_3 (6.0 equiv), 18-C-6 (6.0 equiv), rt, 4 h.

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 give 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.

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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.

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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 (Hu, G.; Williams, L. J. Manuscript in preparation).