Reaction Mechanisms

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Spirodiepoxides: Heterocycle Synthesis and Mechanistic Insight**

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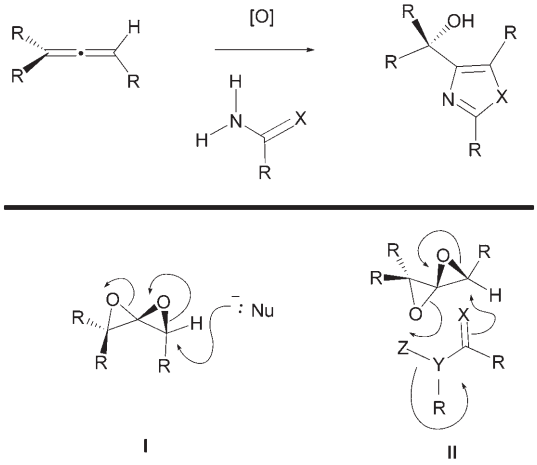
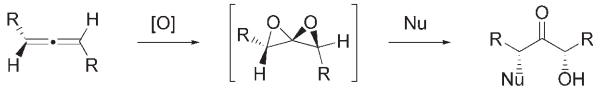
The spirodiepoxide (SDE) functional group has emerged as an electrophile with potential applications in synthesis.[1–10] Sequential allene oxidation gives SDEs. Nucleophilic SDE opening effectively translates the three-carbon axis of chirality of the allene into a densely functionalized motif: two differentially functionalized stereogenic centers separated by a ketone. To be applied generally, nucleophiles that effect SDE opening must continue to be identified, a general method for the stereoselective formation of SDEs must be developed, and a mechanistic understanding of nucleophilic opening must be established. This report is focused on new mechanistic insight gained through investigations on the formation of heterocycles from SDEs. We relate herein the formation of azoles from SDEs, the first crystal structure of an SDE, and a new mechanistic model for nucleophilic SDE opening supported by computational analysis.

Despite the mechanistic rationales suggested by others,[5–9] the structure of the SDE, along with certain other observations,[11] led us to hypothesize that SDE opening proceeds such that both epoxides open in a concerted fashion (**I**, Scheme 1). This hypothesis is consistent with the mild reaction conditions under which SDEs react and is reasonable in terms of stereoelectronics. To test this hypothesis, we examined a series of related nucleophiles, a key subset of which is shown in Table 1. Anionic and neutral nucleophiles have been shown to add to SDEs efficiently under non-acidic conditions, including deprotonated benzenesulfonamide, lithium benzimidate, azide,[1] certain aliphatic alkoxides, phenyl thiolate, chloride, fluoride,[5] organocuprates,[2] along with ammonia and a limited number of secondary amines.[5] Cyanide, an anionic carbon nucleophile, as well as the anionic oxygen nucleophiles acetate[12] and phenoxide, added to give the corresponding products in good yield (Table 1, entries 1–3). Stoichiometric quantities of water, aliphatic alcohols, and phenol do not add at useful rates to SDEs under neutral conditions (for example, entry 4 in Table 1). When used as a solvent or cosolvent, however, water,[5] methanol, and ethanol, but not *tert*-butanol, were found to add efficiently to SDEs (data not shown). Surprisingly, one equivalent of 2-hydroxypyridine added smoothly under neutral conditions to give the O-alkylated product (Table 1, entry 5).



Scheme 1. Proposed mechanistic models for SDE opening.

Table 1: Allene oxidation and reaction with various nucleophiles.[a]



Entry	Nucleophile	Solvent	*t* [h]	Yield [%][e]
1[b]	$nBu_4N^+CN^-$	$CHCl_3$	1	77
2[b]	$nBu_4N^+OAc^-$	$CHCl_3$	1	70
3[c]	PhO^-	$CHCl_3$	4	65[f,g]
4[c]	PhOH	$CHCl_3$	12	0
5[c]	2-hydroxypyridine	$CHCl_3$	12	98[g]
6[d]	*N*,*N*-dimethylacetamide	$CHCl_3$	45 min	0[h]
7[d]	*N*-ethylacetamide	$CHCl_3$	45 min	trace[h]
8[d]	2-pyrrolidinone	$CHCl_3$	45 min	75[i]

[a] Conditions: 3.0 equiv DMDO (1:1 d.r.). [b] 1.1 equiv nucleophile. [c] 1 equiv nucleophile. [d] 5 equiv nucleophile. [e] Yield after chromatography based on SDE except where noted. [f] 1 equiv PhOH, 1.1 equiv K_2CO_3, 10 mol% [18]crown-6 in THF. [g] Yield after chromatography based on nucleophile. [h] Determined by ^1H NMR of crude reactions. [i] Product unstable (see the Supporting Information). DMDO = 2,2-dimethyldioxirane.

One explanation for the facile addition of 2-hydroxypyridine invokes the amide tautomer. Consequently, the reactivity of a series of amides was examined under identical conditions. Although virtually no reaction took place between SDEs and *N*,*N*-dimethyl acetamide or *N*-ethyl acetamide, the *cis* amide 2-pyrrolidinone added rapidly to give the O-alkylated imidate in good yield (see entries 6–8 in Table 1).

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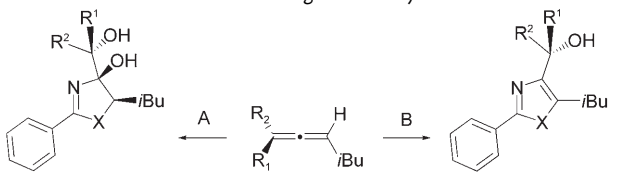
Table 2 illustrates that benzamide, thiobenzamide, and benzamidine also add to SDEs. This result constitutes a novel entry to heterocycles from allenes that complements other methods (for example, the Hantzsch method), as the synthesis is highly modular and gives carbinol-functionalized azolines and azoles.[13] Benzamide added very slowly (Table 2, entries 1 and 3). Nevertheless, even in the presence of five equivalents of water, a potentially competitive nucleophile, only the oxazoline product was obtained. Thiobenzamide (Table 2, entries 2 and 4) and benzamidine (Table 2, entries 7 and 10) added more rapidly to SDEs than benzamide, consistent with the expected increased nucleophilicity of these reagents. SDE stereochemistry was assigned based on analogy to earlier models: The first oxidation is highly selective, the second oxidation is less selective, and the product ratios matched the SDE ratios.[1–5] Although spontaneous formation of imidazoles from the imidazolines complicated imidazoline isolation, thiazolines and oxazolines were readily obtained in pure form. NOE analysis allowed *trans* assignment of the carbinol and the alkyl substutuents of the azolines (**2a** and **2b**), as expected based on thermodynamic considerations. In a separate step, dehydration to the corresponding imidazoles, thiazoles, and oxazoles was readily achieved. Moreover, oxazoles, imidazoles, and thiazoles were conveniently prepared in a single flask from the allene without isolation of intermediates (Table 2, entries 5–10).

The structural dependence and generality of these findings are difficult to reconcile with earlier models of SDE opening. Previous models suggest that each epoxide of the SDE opens sequentially (**III**→**IV**,[5] **V**→**VI**,[6] **VII**→**VIII**; Scheme 2).[7] A mechanism wherein both epoxides open in concert could account for the new findings and is consistent with the earlier data as well (Scheme 1, compare **I** with **II**, X = O, N, S; Y = N; Z = H).

Table 2: Allene conversion to nitrogen heterocycles via SDEs.[a]



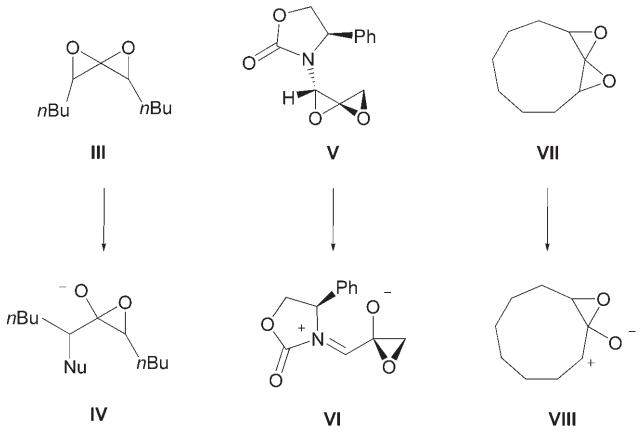
2a: R^1 = H, R^2 = *i*Bu
2b: R^1 = CH_3, R^2 = CH_2OTIPS

1a: R^1 = H, R^2 = *i*Bu
1b: R^1 = CH_3, R^2 = CH_2OTIPS

3a: R^1 = H, R^2 = *i*Bu
3b: R^1 = CH_3, R^2 = CH_2OTIPS

Entry	Allene	Amide/ amidine	Conditions	*t* [h]	Product[b]	Yield [%][b]
1	**1a**	$C_6H_5CONH_2$	A[c]	24	**2a** (X = O)	74
2	**1a**	$C_6H_5CSNH_2$	A	12	**2a** (X = S)	80
3	**1b**	$C_6H_5CONH_2$	A	84	**2b** (X = O)	81
4	**1b**	$C_6H_5CSNH_2$	A	17	**2b** (X = S)	76
5	**1a**	$C_6H_5CONH_2$	B	48	**3a** (X = O)	66
6	**1a**	$C_6H_5CSNH_2$	B	24	**3a** (X = S)	83
7	**1a**	$C_6H_5CNHNH_2$	A	60	**3a** (X = NH)	83
8	**1b**	$C_6H_5CONH_2$	B	72	**3b** (X = O)	47
9	**1b**	$C_6H_5CSNH_2$	B	35	**3b** (X = S)	60
10	**1b**	$C_6H_5CNHNH_2$	B	21	**3b** (X = NH)	78

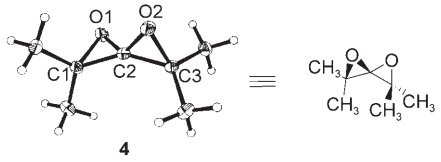
[a] Conditions A: DMDO, −40 °C, 1 h (**1a** 1:1 d.r., **1b** 3:2 d.r.), 5 equiv nucleophile, $CHCl_3$, RT; conditions B: DMDO, −40 °C, 1 h; 5 equiv amide, $CHCl_3$, RT, then 10 mol% *p*-TsOH, reflux. [b] Yield after chromatography based on SDE. [c] Reaction run in 1:1 $CHCl_3$/THF. TIPS = triisopropylsilyl.



Scheme 2. Earlier proposed intermediates for SDE opening.

To further evaluate this proposal, we gathered additional structural and computational data. Table 3 presents the first crystal structure of an SDE (**4**). Key bond lengths are tabulated and compared with computation. Importantly, molecular-mechanics-based methods (for example, MM2, MM3, MM4) do not provide accurate optimization of SDEs. PM3- or higher-level computations, which incorporate quantum effects, appear necessary for accurate SDE modeling (for example, DFT, HF, MP2). The C2–O1/O2 bond lengths of **4** are shorter than those of simple acetals **5**. The C2–C1/C3 and

Table 3: Key bond lengths [Å] for SDE and proposed transition states.



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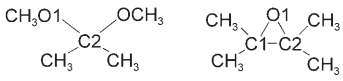

5 **6**

	Structure	C1-O1	C2-O1	C2-O2	C3-O2	C2-C1	C2-C3
crystal	**4**	1.517	1.393	1.393	1.517	1.446	1.446
calculated	**4**	1.495	1.398	–	–	1.454	–
	5	–	1.429	–	–	–	–
	6	–	1.446	–	–	1.489	–
	7	1.490	1.390	–	–	–	–
	8	2.010	1.270	1.750	–	–	–
	10	2.079	1.280	1.607	–	–	–
	12	1.489	1.384	1.397	–	–	–
	13	1.910	1.260	1.960	–	–	–
	15	1.929	1.331	1.439	–	–	–

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C2–O1/O2 bond lengths of **4** are shorter than those of epoxides **6**; however, the C1–O1 and C3–O2 bonds are longer than the average length of C–O bonds of epoxides.

Reaction pathways consistent with models **I** and **II** have been identified by DFT[14] calculations as highly exothermic transformations wherein both epoxides open in concert. As shown in Figure 1 and Scheme 3, the reaction paths and transition-state geometries for nucleophilic addition by water, amide, and chloride are very similar. Key interatomic distances of reactants and transition structures are included for comparison in Table 3. As judged by intrinsic reaction-coordinate calculations, singly opened SDEs (for example, **IV**; Scheme 2) do not represent stable intermediates.

We focused our computational analysis on the addition of water and related nucleophiles to SDEs (Figure 1 and Scheme 3). A single transition barrier **8** connects water and the SDE **7** with the substituted ketone **9**. Stable hydrogen-bonded complexes of weak acids, such as methanol, to O2 of SDE **7** (to give **12**) were also identified. Addition of water to C1 of **12** (to give **14**) was found to proceed by way of a lower enthalpy of activation (19.3 kcal mol^{-1}) than addition to **7** (22.3 kcal mol^{-1}). The alternative pathway, in which water attacks C3 of **12** (not shown), represents a higher enthalpic barrier (ca. 1 kcal mol^{-1}).

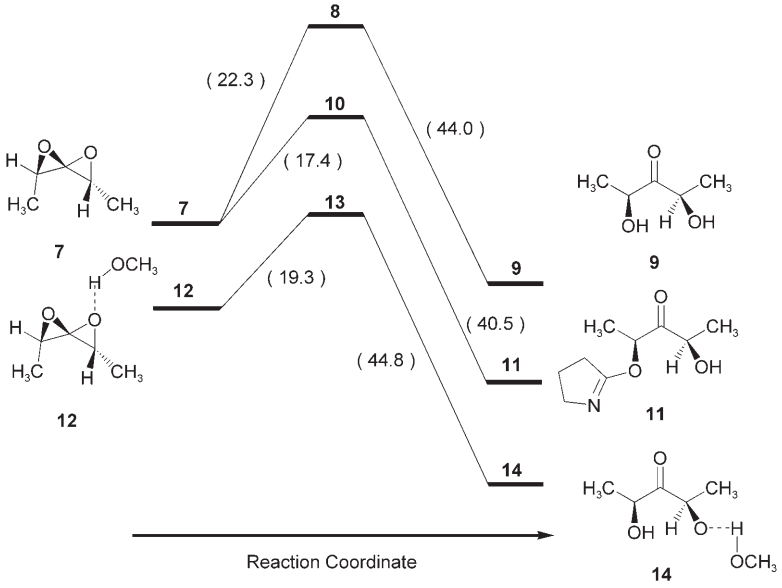
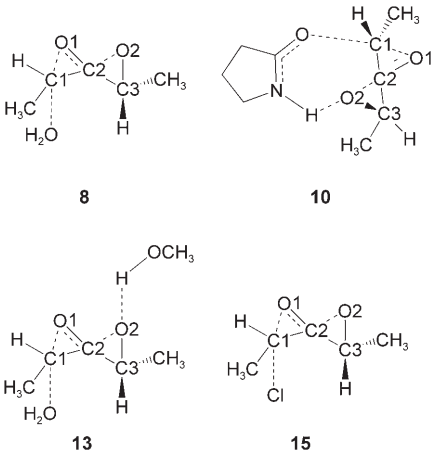


Figure 1. Calculations of relative enthalpies of activation (in kcal mol^{-1}).[14]



Scheme 3. Transition-state structures for SDE opening.

The simultaneous coordination of 2-pyrrolidinone to a proximal SDE oxygen atom (O1) and attack at the proximal carbon atom (C1) is not geometrically feasible. Nonetheless, a transition structure for 2-pyrrolidinone-induced SDE opening was found (**7**→**10**→**11**) and proved closely related to the other addition reactions of this study. This transition-state structure features attack by the carbonyl lone pair at the proximal carbon atom (C1) and *cis* amide hydrogen coordination to the distal oxygen atom (O2).

Three classes of nucleophiles that add to SDEs are discernable. First, SDE opening is readily achieved by anionic carbon, nitrogen, oxygen, sulfur, and halide nucleophiles. As with other nucleophilic openings, SDE opening takes place with inversion at the least-substituted site.[1,2,5] Second, weakly acidic reagents, for example, water, methanol, and phenol, open SDEs very slowly under neutral conditions. Consequently, a large excess of reagent is required for reasonable reaction times. This observation may be reflective of the influence of mass action, higher-order transition states, hydrogen-bond activation, or a combination of these effects. Third, there is a structural requirement for certain nucleophiles to add to SDEs under neutral conditions. Amides, amidines, and thioamides add to SDEs to give oxazoles and oxazolines, imidazoles and imidazolines, and thiazoles and thiazolines, respectively (Table 2). Evidently, alkylation of these nucleophiles is followed by addition of the nitrogen atom to the carbonyl. The structural requirement appears to be an NH group *cis* to the amide carbonyl group, or its analogue (compare entries 6–8, Table 1).

Computational studies reveal strikingly similar transistion states for the three classes of nucleophile. The angle of nucleophilic attack (Nu-C1-O1: 158° (**8**), 168° (**10**), 161° (**13**), 170° (**15**); Scheme 3) reflects a degree of cationic character at C1.[15] For all nucleophiles in this study, the C1–O1 bond lengthens, the O1–C2 bond shortens, and the C2–O2 bond lengthens upon nucleophilic attack of the SDE, although the epoxide opening occurs at different rates (compare **8**, **10**, **13**, and **15**, Table 3). Hydrogen bonding to the SDE oxygen atom that is destined to become the hydroxy group, by solvent or by the attacking nucleophile, facilitates SDE opening by stabilizing the transition state. It is noteworthy that this analysis does not preclude sequential epoxide opening; one may observe (see above) these pathways computationally and would expect that these pathways could become relevant in instances in which the solvent or reagent interacts strongly with alkoxide. Still, taken together, the analysis supports a

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mechanistic framework wherein nucleophilic addition to SDEs involves concerted, asynchronous opening of both epoxides.

Anionic reagents are excellent nucleophiles for SDE opening, although side reactions can be problematic. Although many neutral reagents are not good nucleophiles, SDEs can be activated in the presence of hydroxylic reagents.[3,4] Coordination to the distal SDE oxygen atom (O2 in **13**) lowers the barrier for attack at the proximal SDE carbon atom (C1 in **13**). In this way, hydrogen-bond activation, and presumably Lewis or Brønsted acid activation in general, acts cooperatively to relieve ring strain in both epoxides through SDE opening. The remarkable finding that amides, amidines, and thioamides give heterocycles upon addition to SDEs is readily understood: Certain nucleophiles are able to act simultaneously as hydrogen-bonding activators and as nucleophiles.

The new mechanistic model presented here is consistent with all the available data. Nucleophilic SDE opening is rationalized in terms of a reactivity continuum that involves the concerted, asynchronous opening of both epoxides. This process is facilitated by coordination to the oxygen atom destined to become the hydroxy group.

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