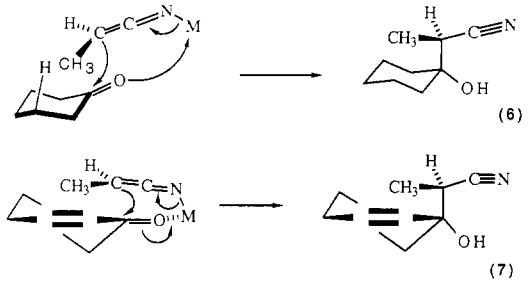


(6)

(7)

portance relative to torsional strain. Since equatorial attack does not lead to as large an increase in nonbonded interactions, enhanced addition from the equatorial direction occurs.

As eq 7 reveals, enones offer a relief of this increased steric strain in the axial attack mode by allowing the methyl group to find an empty pocket by placing itself over the double bond—an orientation we may refer to as a syn mode. Indeed, X-ray analysis confirms precisely this stereochemistry in two cases. By analogy, the axial syn stereochemistry is assigned to the major diastereomer for all the cases.

The results suggest that the preference for axial attack in enones is surprisingly insensitive to an increased steric bulk of the approaching nucleophile. It may derive, in part, from the planar nature of the attacking nucleophile. However, most importantly, the reacting system finds a way to steer the nucleophile to minimize steric strain, even at a cost of increased entropy of activation. From a synthetic viewpoint, this approach appears to be an excellent strategy to introduce side chains onto ring systems with excellent double diastereoselectivity.

Acknowledgment. We thank the National Institutes of Health for their generous support of our programs. J.F. was a Spanish Ministry of Education and Science Postdoctoral Fellow.

Supplementary Material Available: X-ray crystallographic analysis of adducts **10** and **14** (14 pages). Ordering information is given on any current masthead page.

Barry M. Trost,* Josefa Florez, Kenneth J. Haller

Departments of Chemistry
University of Wisconsin
Madison, Wisconsin 53706, and
Stanford University
Stanford, California 94305
Received December 30, 1987

Deuterium Isotope Effects and the Mechanism of Kinetic Enolate Formation. A Correction[1]

Sir: Contrary to a previous report from this laboratory that the deuterium isotope effect in the reaction of 2-methyl-3-pentanone at the 4-position with LDA in THF is negligibly small (k_H/k_D = 0.9 ± 0.1 at 0 °C),[2] independent rechecks by three of the undersigned (H.P.B., L.X., and D.J.M.) have convinced us that there are substantial isotope effects at *both* the 4-position (k_H/k_D = 3.3) and the 2-position (k_H/k_D = 3.8), and this pattern holds for a variety of solvent–base combinations. Details will follow in a full paper.

(1) This work was supported by the National Science Foundation.
(2) Miller, D. J.; Saunders, W. H., Jr. *J. Org. Chem.* **1982**, *47*, 5039–5041.
(3) Sherman Clarke Fellow.

Hans P. Beutelman,† Linfeng Xie†,3
David J. Miller,‡ William H. Saunders, Jr.*,†

Department of Chemistry
University of Rochester
Rochester, New York 14627, and
Research and Development Department
Union Carbide Corporation
P.O. Box 8361
South Charleston, West Virginia 25303
Received February 16, 1988

Tandem Cycloaddition/Radical Cyclization, a Widely Applicable Strategy for the Rapid Assembly of Polycyclic Systems

Summary: By treating a diene (or 1,3-dipole) that contains an appropriately located potential radical site successively with a dienophile (or dipolarophile) and a radical source one can construct a variety of polycyclic systems in two steps.

Sir: The construction of polycyclic systems using a minimum number of synthetic manipulations remains a challenging problem. Cycloaddition[1] and radical cyclization[2] are two frequently used reactions for ring construction. Here we report a versatile synthetic strategy that uses these reaction types in a tandem mode, thus permitting the rapid construction of a variety of polycyclic systems, often with considerable regio- and stereocontrol. The double bond generated in the cycloaddition step serves as the trap for the radical generated in the cyclization step.

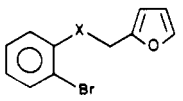
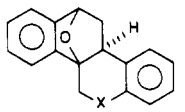
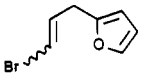
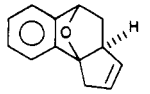
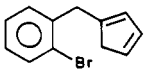
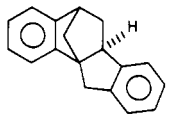
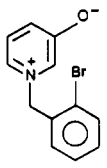
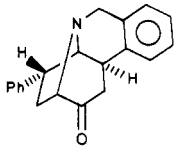
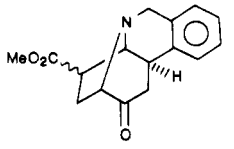
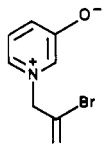
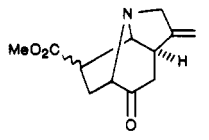
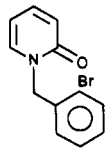
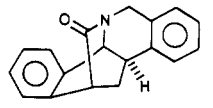
The primary building block is a diene (or 1,3-dipole) which contains the functionality needed for generating a radical at an appropriate site. A simple example is diene **1**, which has the advantage of being cisoid and in which the bromine is located on a carbon atom appropriately situated from C2 of the diene moiety. Diene **1** was readily prepared from 2-lithiofuran (**2**) and 2-bromobenzyl bromide (**3**) (Scheme I). Treatment of **1** with benzyne (generated from benzenediazonium carboxylate) gave cycloadduct **4** (50%) which, on heating with 1 equiv of Bu_3SnH (AIBN, benzene, reflux) gave a single cyclized product (**5**), mp 104–108 °C (67%). The carbon framework of **5** was established by dehydration to the known[3] benzo[*a*]fluorene (**6**). Although the ^1H NMR spectrum showed **5** to be a single stereoisomer, the stereochemistry could not be definitively assigned. An X-ray structure[4] of the naphtho analogue **7** (prepared analogously, using 2,3-naphthyne in place of benzyne) established the exo geometry of the new C–C bond formed in the radical cyclization step.[5] The

† University of Rochester.
‡ Union Carbide Corporation.

(1) For a list of reviews, see: *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol 6, p 880. For more recent reviews, see: *Index of Reviews in Organic Chemistry*, Royal Society of Chemistry.
(2) Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–carbon Bonds*; Pergamon: Oxford, 1986. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.
(3) Cook, J. W.; Hewett, C. L. *J. Chem. Soc.* **1934**, 365. Datta, B. B.; Bardhan, J. C. *J. Chem. Soc.* **1962**, 3974.
(4) Carried out by Dr. Donald L. Ward and to be published elsewhere.

0022-3263/88/1953-2396$01.50/0

Table I. Examples of Tandem Cycloaddition/Radical Cyclization

entry	diene (1,3-dipole)	dienophile (dipolarophile)	product[a] (two steps)	yield,[b] %
1				
	8, X = O		11	75, 70
	9, X = NCH_3		12	65, 54
	10, X = SO		13	72, 70
2				50, 67
	14		15	
3				60, 70
	16		17	
4		$PhCH{=}CH_2$		34, 45
	18		19	
5	18	$CH_2{=}CHCO_2Me$		65, 55
			20	
6		$CH_2{=}CHCO_2Me$		50, 63
	21		22	
7				25, 70
	23		24	

[a] All products gave satisfactory high resolution mass spectra and NMR spectra consistent with the assigned structures. [b] The first yield is for the cycloaddition, the second for the radical cyclization. Yields are of isolated, pure products and are not optimized.

nonaromatic portions of the ^1H NMR spectra of **5** and **7** were virtually identical. Thus the pentacyclic **5** is synthesized in a stereoselective manner from monocyclic precursors in just a few steps.

The generality of this strategy is illustrated by the additional examples listed in Table I.

The starting dienes or 1,3-dipoles listed in Table I were prepared in one or two steps from readily available precursors.[6-8]

All of the products listed in Table I are new, and the structures were assigned on the basis of spectral data. Almost all the ring systems are new.[9] Cleavage of the

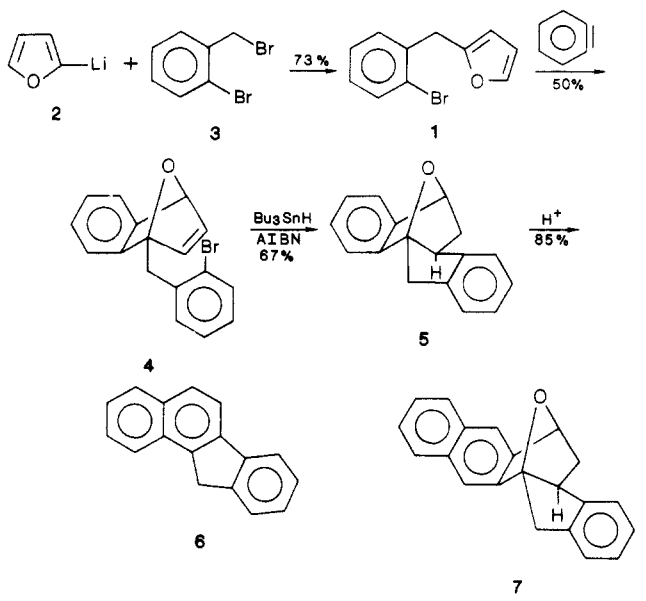
(5) Although we are unaware of really good analogous cyclizations onto double bonds in a bicyclic system, the stereochemical outcome is not surprising because (a) it results from exo addition to a norbornene-type double bond and (b) the new five-membered ring is cis-fused to a 5-ring and trans-fused to a 6-ring, which should be a considerably more stable arrangement than the alternative.

(6) **8**: from 2-bromophenoxide and 2-furfuryl bromide (2-FB). **9**: from 2-bromo-*N*-methylaniline, by treatment first with sodium hydride, then with 2-FB. **10**: from 2-bromothiophenoxide and 2-FB followed by *m*-CPBA oxidation. **14**: from 1,3-dibromopropene and **2**. **16**: from lithium cyclopentadienide and **3** at room temperature in ether, 3 h (longer times or reflux gives alkylation at both C-1 and C-2 of cyclopentadiene).

(7) Precursors for entries 4–6 were prepared by N-alkylation of 3-hydroxypyridine with either **3** or 2,3-dibrompropene (THF, reflux); the resulting quaternary salt was converted to the betaine in situ with triethylamine, followed by addition of the dipolarophile. For analogous methodology, see: Katritzky, A. R.; Takeuchi, Y. *J. Am. Chem. Soc.* **1970**, *92*, 4134. Dennis, N.; Ibrahim, B.; Katritzky, A. R.; Taulov, I. G.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1883. Banerji, J.; Dennis, N.; Frank, J.; Katritzky, A. R.; Matsuo, T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2334. Katritzky, A. R.; Banerji, J.; Boonyarakvanich, A.; Cutler, A. T.; Dennis, N.; Rizvi Abbas, S. Q.; Sobongi, G. J.; Wilde, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 399. Katritzky, A. R.; Dennis, N.; Sabongi, G.; Turker, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1525. Katritzky, A. R.; Banerji, J.; Dennis, N.; Ellison, J.; Sabongi, G.; Wurthwein, E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2528. Katritzky, A. R.; Abdallah, M.; Bayyuk, S.; Bolouri, A. A.; Dennis, N.; Sabongi, J. *Pol. J. Chem.* **1979**, *53*, 57.

(8) For **23**, 2-hydroxypyridine was treated with **3** (K_2CO_3, dimethoxyethane, reflux, 1 h).

Scheme I



endoxide or nitrogen bridges by standard methods can, however, lead to variously functionalized known ring systems present in natural products.

Whereas the conversion of **4** to **5** and entries 2, 3, and 6 in Table I involve construction of a five-membered ring in the radical cyclization step, entries 1, 4, 5, and 7 show that six-membered rings are formed with equal effectiveness. The stereochemistry created in this step is assigned for **11–13**, **15**, and **17** by similarity of their proton NMR spectra to that of **7** and for **19**, **20**, **22**, and **24** by the structure of the precursor. Entry 1 illustrates application of the methodology to heterocycles, by including a heteroatom in the tether between the diene moiety and radical site in the starting diene.[10] Entries 2 and 6 demonstrate the use of vinyl halides in place of aryl halides at the radical-generating site. Entry 3 is an application using a carbocyclic diene.

Entries 4–6 illustrate some results with unsymmetric 1,3-dipoles. The regioisomer shown predominated by a large factor,[11] and in the case of styrene (entry 4) only the endo adduct **19** was obtained; with **20** and **22**, however, exo/endo mixtures were obtained.

We are extending the scope of these studies to include acyclic dienes, radical cyclizations that are not terminated by hydride, tandem sequences in which both steps are intramolecular, and to examples where the radical site is attached to the dienophile instead of the diene.

Acknowledgment. We are indebted to the National Institutes of Health (GM 15997) for financial support.

(9) Structures related to **11** and **12** were recently synthesized by using intramolecular Diels–Alder methodology: Tsuge, O.; Ueno, K.; Kanemasa, S. *Heterocycles* **1986**, *24*, 629.

(10) The sulfide could be obtained from **13** by lithium aluminum hydride reduction; it coult *not* be obtained directly from **10** (X = S) due to competing reactions of the sulfur with benzyne. Details will appear in a full account.

(11) With **20** and **22**, in the cycloaddition step the corresponding regioisomer was formed (less than 15% of the total yield of cycloadducts).

Tirthankar Ghosh, Harold Hart*

Department of Chemistry
Michigan State University
East Lansing, Michigan 48824

Received February 19, 1988

2-Phenylsulfonyl 1,3-Dienes as Versatile Synthons in Organic Transformations. Functionalizations via Epoxidation Reactions

Summary: 2-Phenylsulfonyl 1,3-dienes were regioselectively epoxidized at either of the double bonds in high selectivity. These epoxides are useful synthons and react with nucleophiles with complete regio- and stereospecificity. By changing the order of epoxidation and nucleophilic addition a complementary stereocontrol was obtained.

Sir: Conjugated dienes with electron-donating or electron-withdrawing substituents within the diene unit have attracted considerable attention during recent years.[1-4] Such dienes are useful reagents in cycloadditions as well as other reactions. We have recently shown that 2-phenylsulfonyl 1,3-dienes are versatile synthons that can be used as multicoupling reagents and Diels–Alder dienes with a dual electron demand.[4] We have now studied selective epoxidation reactions of these sulfonyl dienes and their derivatives.

2-Phenylsulfonyl 1,3-dienes have two double bonds of very different reactivity. One of the double bonds is fairly electron rich whereas the other is electron deficient. Regioselective epoxidation to give either epoxide therefore seemed possible (Scheme I). Such epoxides are important classes of synthetic intermediates.[5]

Reaction of 2-(phenylsulfonyl)-1,3-cyclohexadiene (**1**) with *m*-chloroperbenzoic acid (*m*-CPBA) in methylene chloride resulted in a selective epoxidation to give the expected epoxide **5** (Table I, entry 1). The selectivity for epoxidation at the electron-rich double bond was ~95% as determined on the crude product. The epoxide **5** was isolated after workup[6] in 80% yield completely free from the isomeric epoxide. When the epoxidation procedure was carried out by using alkaline hydrogen peroxide,[7,8] epoxide **6** was formed exclusively (Table I, entry 2). In this case analysis of the crude product indicated a 100% selectivity for epoxidation at the electron-deficient double bond.

The selective epoxidations also worked fine for acyclic 2-phenylsulfonyl 1,3-dienes (entries 3–8, Table I). Thus, **2** was transformed to **7** by the use of *m*-CPBA and to **8** by the use of H_2O_2/OH^-. Analogously, sulfonyl dienes **3** and **4** were transformed to either epoxide in high selectivity. For the acyclic dienes it was necessary to run the alkaline hydrogen peroxide epoxidation in acetone[8] since the use

(1) (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. (b) Grayson, J. I.; Petrzilka, M. *Synthesis* **1981**, 753. (c) Hickmott, P. W. *Tetrahedron* **1984**, *40*, 2989.

(2) (a) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891. (b) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554. (c) Cohen, T.; Kosarych, Z. *J. Org. Chem.* **1982**, *47*, 4005.

(3) (a) Halazy, S.; Magnus, P. *Tetrahedron Lett.* **1984**, *25*, 1421. (b) Åkermark, B.; Nyström, J. E.; Rein, T.; Bäckvall, J. E.; Helquist, P.; Aslanian, R. *Ibid.* **1984**, *25*, 5719. (c) Bloom, A. J.; Mellor, J. M. *Ibid.* **1986**, *27*, 873. (d) Posner, G. H.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7373. (e) Posner, G. H.; Harrison, W. *J. Chem. Soc., Chem. Commun.* **1985**, 1786.

(4) Bäckvall, J. E.; Juntunen, S. K. *J. Am. Chem. Soc.* **1987**, *109*, 6396.

(5) (a) Saddler, J. C.; Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2110. (b) Saddler, J. C.; Fuchs, P. L. *Ibid.* **1981**, *103*, 2112. (c) Hardinger, S. A.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 2739.

(6) The precipitate formed was filtered off and the organic phase was washed with aqueous solutions of Na_2SO_3, Na_2CO_3, and brine. The crude product was purified by flash chromatography (silica, EtOAc/hexane = 10/90 and 20/80).

(7) Wasson, R. L.; House, H. O. *Org. Synth.* **1957**, *37*, 58. Wasson, R. L.; House, H. O. *Organic Syntheses*; Wiley: New York, 1963; *Collect. Vol. IV*, p 552.

(8) Zwanenburg, B.; ter Weil, J. *Tetrahedron Lett.* **1970**, 935.

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