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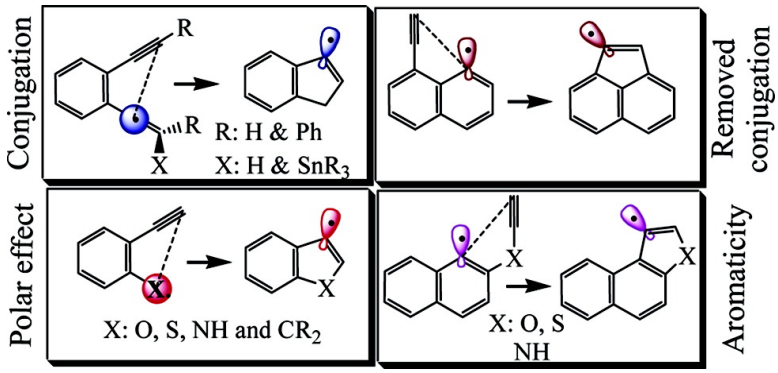

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5-Endo-Dig Radical Cyclizations: "The Poor Cousins" of the Radical Cyclizations Family

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Abstract: Kinetics and thermodynamics of 5-endo-dig radical cyclizations were studied using a combination of DFT computations and Marcus theory. When the reactant is stabilized by conjugation of the radical center with the bridge π-system, the cyclization starts with reorientation of the radical orbital needed to reach the in-plane acetylene π-orbital in the bond-forming step. This reorientation leads to loss of the above conjugative stabilization, increases the activation energy, and renders such cyclizations less exothermic. As a result, even when the radical needed for the 5-endo cyclization is formed efficiently, it undergoes either H-abstraction or equilibration with an isomeric radical. Only when the bridging moiety is saturated or when intramolecular constraints prevent the overlap of the bridge π-orbital and the radical center, 5-endo cyclizations may be able to proceed with moderate efficiency under conditions when H-abstraction is slow. The main remaining caveat in designing such geometrically constrained 5-endo-dig cyclizations is their sensitivity to strain effects, especially when polycyclic systems are formed. The strain effects can be counterbalanced by increasing the stabilization of the product (e.g., by introducing heteroatoms into the bridging moiety). Electronic effects of such substitutions can be manifested in various ways, ranging from aromatic stabilization to a hyperconjugative β-Si effect. The 4-exo-dig cyclization is kinetically competitive with the 5-endo-dig process but less favorable thermodynamically. As a result, by proper design of reaction conditions, 5-endo-dig radical cyclizations should be experimentally feasible.

1. Introduction

Radical cyclizations are commonly utilized in synthesis of carbo- and heterocyclic compounds.[1] Stereoelectronic requirements for radical cyclizations that involve triple bonds[2] (commonly referred to as *dig*, or digonal, cyclizations according to the Baldwin classification[3]) are significantly different from such requirements in the case of *trig*, or trigonal, cyclizations involving additions to double bonds. The trig cyclizations commonly follow a "Bürgi−Dunitz"-like[4] trajectory which provides the best overlap of the incoming reactive center with the π-system.[5] This trajectory imposes significant limitations on the feasibility of some trigonal radical cyclizations, such as the 5-endo-trig pathway, which are unfavorable due to geometric restrictions on the Bürgi-Dunitz trajectory within a five-membered TS. These restrictions are of lesser importance in those dig cyclizations where the reacting orbital may attack the in-plane π-system of an acetylene moiety. This approach alleviates geometric demands and, along with the relatively low energy penalty for bending of the acetylene moeity,[6] renders many digonal cyclization modes possible. A particularly interesting case is provided by 5-endo-dig cyclizations (Scheme 1), which, in contrast to 5-endo-trig cyclizations,[7] are favorable according to the Baldwin rules. There are examples of 5-endo-dig processes involving nucleophilic and electrophilic additions to the triple bond.[8]

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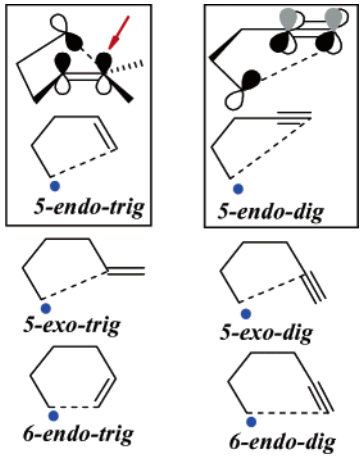
Scheme 1. Representative Radical Cyclizations[a]



[a] The Bürgi−Dunitz trajectory is shown with an arrow.

Nevertheless, in sharp contrast to the commonly encountered 5-exo-dig[9,10] and 6-endo-dig[11] radical cyclizations, their 5-endo-dig counterparts are scarce. The first examples of radical 5-endo-dig cyclizations of O- and S-centered radicals formed during flash vacuum pyrolysis (FVP) of 2-methoxyphenyl- and 2-methylthiophenyl-substituted phosphorus ylides were reported by Aitken and co-workers.[12] Their report received little attention, and thus discovery of the first 5-endo-dig radical cyclization (involving addition of a Si-centered radical in a relatively flexible nonconjugated system) was claimed again in 2002 (vide infra, Scheme 11).[13]

5-Endo-dig radical cyclizations involving C-centered radicals entered in the spotlight only in 2003 when Matzger and co-workers proposed that the radical polymerization of enediynes may involve 5-endo radical cyclizations in addition to 5-exo and 6-endo pathways.[14] In 2004, the same group suggested the possibility of other 5-endo cyclizations in related systems, albeit in very low yields.[15] To make the situation even more intriguing, Anthony and co-workers[16] reported a surprisingly efficient 73% yield transformation of a constrained enediyne system and suggested that it involves a 5-endo-dig cyclization as a part of the unprecedented 6-endo-dig and 5-endo-dig cascade (vide infra).

These experimental results suggest that it may be possible to include 5-endo-dig radical cyclizations in the arsenal of synthetically useful transformations but the necessary understanding of general factors that control the efficiency of these processes is lacking. The present theoretical study aims to fill this existing gap by determining the structural and electronic requirements for these processes. To achieve this goal, we adopt the following strategy. First, we determine the activation energies for the 5-endo-dig pathway of the several archetypal systems and compare them with the barriers for competing processes. When appropriate, we separate the thermodynamic contributions to the reaction barrier by using Marcus theory.[17] After analyzing electronic effects in the parent systems, we discuss the role of structural restraints in changing reaction energies and intrinsic barriers of 5-endo-dig cyclizations.

2. Computational Details and Method

All reactant, product, and transition state geometries involved in radical cyclizations were optimized at the UB3LYP/6-31G** level[18] using Gaussian 98 and 03 programs.[19] The B3LYP gas-phase reaction barriers of a number of radical reactions were shown to agree well with the experimental values.[20] Hence, this level of theory has been used throughout the article, except in tin-substituted systems. In the latter case, B3LYP computations with the LANL2DZ[21] basis set that provides acceptable accuracy[22] were performed instead. In all cases, the nature of transition structures were confirmed by a single negative eigenvalue in the force constant matrix. The NBO computations were carried out to analyze the electronic properties of radical systems using the NBO 4.0[23] that is implemented in Gaussian software.

Marcus theory[17] was applied to understand how the reaction exothermicity alters cyclization barriers. In this description, the energy of activation ($\Delta E^{\ddagger}$) of a nondegenerate reaction is the sum of the intrinsic barrier and the thermodynamic contribution (reaction energy). The intrinsic barrier ($\Delta E_o^{\ddagger}$) in eq 1 represents the barrier of a thermoneutral process (e.g., a degenerate transformation) in the absence of thermodynamic bias. Intrinsic barriers can be used to compare

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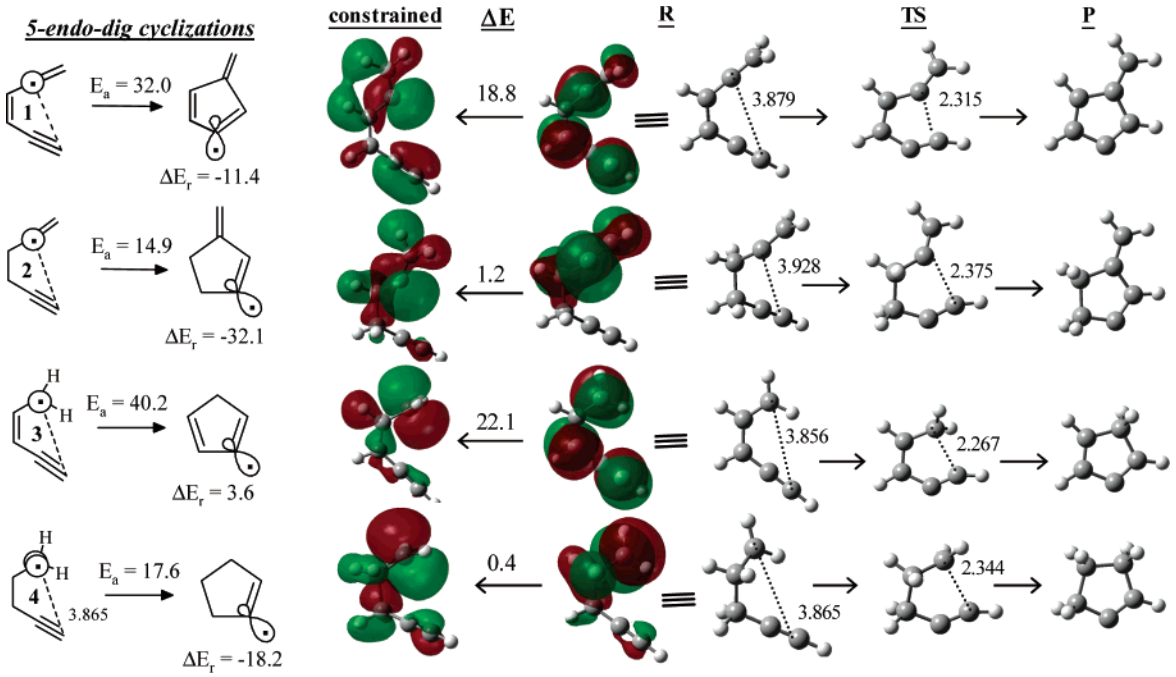

Figure 1. Activation barriers, reaction energies, intrinsic barriers, energy cost of the reorientation of radical orbitals (all in kcal/mol at UB3LYP/6-31G** level)[32] for model 5-endo-dig radical cyclizations involving different radicals (**1**−**4**). The SOMO contours and distance between the reacting carbons (Å) at the selected points of the cyclization PES.

intrinsic stereoelectronic requirements of different reactions. In the classic Marcus analysis, $\Delta E^{\ddagger}$ is given by eq 1.

$$\Delta E^{\ddagger} = \Delta E_o^{\ddagger} + {}^1/_2\Delta E_R + (\Delta E_R)^2/16(\Delta E_o^{\ddagger}) \quad (1)$$

Simple rearrangement of eq 1 and solution of the resulting quadratic equation for $\Delta E_o^{\ddagger}$ gives eq 2, which provides the intrinsic activation energy when reaction barrier and reaction energy are known.

$$\Delta E_o^{\ddagger} = \frac{\Delta E^{\ddagger} - ({}^1/_2)\Delta E_R + \sqrt{\Delta E^{\ddagger 2} - \Delta E^{\ddagger}\Delta E_R}}{2} \quad (2)$$

Marcus theory was originally developed for electron-transfer reactions but was subsequently successfully applied to a wide variety of organic reactions,[24−26] including reactions with cyclic transition states.[27] Since the *absolute* accuracy of eqs 1 and 2 in describing radical cyclizations should depend on how well the parabolic approximation describes potential energy surfaces and the details of their interaction at the crossing point, we will use these equations only to compare the *relative* trends in related reactions. The curve-crossing model of Shaik and Pross,[28] which is similar in spirit to the Marcus analysis, has been successfully applied to radical addition reactions.[29]

3. Results and Discussion

Model Reactions. Since this is the first computational study of radical 5-endo-dig cyclizations, we will start with an analysis of the kinetic and thermodynamic profiles of several model 5-exo-dig radical cyclizations shown in Figure 1. The substrates were chosen to investigate the differences in reactivity between sp^3- and sp^2-hybridized radicals and the role of moiety bridging the radical center with the acetylene π-system.

The first surprise is that the activation energy for the "stereoelectronically allowed" 5-endo-dig cyclization of 4-pentyne-1-yl (**4**) is 1.6 kcal/mol *greater* than that for the "disallowed" 5-endo-trig cyclization of 4-pentene-1-yl[30] (16.0 kcal/mol)! Second, the barrier for the formation of the highly strained product resulting from 4-exo-dig cyclization of **4** is *the same* as that for a 5-endo-dig reaction (17.6 kcal/mol) even though the former reaction is only 0.8 kcal/mol exothermic. Similarly, the 4-exo pathway is predicted to be kinetically competitive with other three 5-endo processes (see Figure 1) although the 4-exo products are 17−25 kcal/mol less stable.[31]

Several other observations are interesting. Since a σ-bond is formed at the expense of a π-bond, these processes are expected to be exothermic. However, the relative exothermicities of the four 5-endo-dig cyclizations were found to depend strongly on the structure of reacting radicals and, in the case of the radical **3**, the cyclization was found to be 3.6 kcal/mol *endo*thermic. In general, both the activation and reaction energies for the cyclization of radical with the vinyl bridge (**1** and **3**) are ca. 20 kcal/mol greater than that for their nonconjugated counterparts

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(30) See ref 7b for a detailed discussion of the 5-endo-trig cyclizations in which the UB3LYP/6-31G* method also provides a comparable barrier ca. 16.3 kcal/mol.
(31) The 4-exo-dig cyclizations of **1**−**4** in Figure 1 exhibit the corresponding activation barriers (31.0, 14.1, 40.2, and 17.6 kcal/mol) and reaction energies (13.5, −12.0, 26.4, and −0.8 kcal/mol).

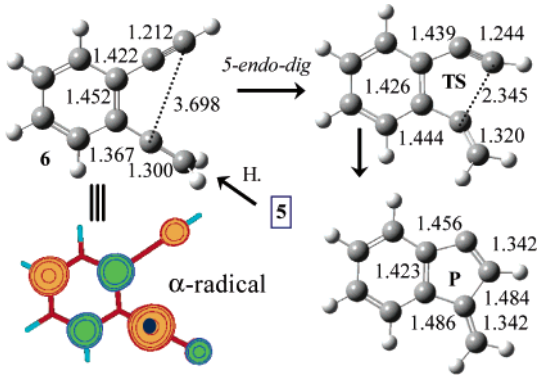
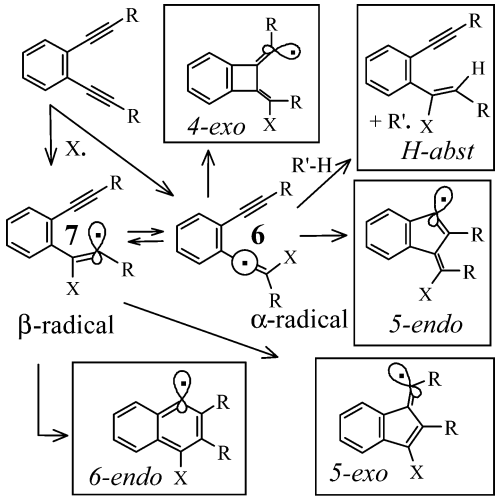


Figure 2. Structural parameters of 5-endo cyclization involving 1,2-diethynyl benzene (**5**).

(**2** and **4**) despite the shorter incipient C−C distances in respective reactants. The second observation is that the higher reactivity of vinyl radicals leads to lower barriers and higher exothermicity of the respective cyclizations, especially when the cyclizations are assisted by new conjugation between double bonds in the product.

In all of the acyclic reactants, the radical orbital is nearly orthogonal to the in-plane π-orbital of the acetylene moiety, which it needs to reach to close the cycle. As a result, the cyclizations involve two "elementary" steps: (a) reorientation of the radical orbital and (b) the new σ-bond formation. In the case of radicals **1** and **3** with vinyl bridges (Figure 1), the reorientation of the radical leads to loss of conjugation between the radical and the π-system. Loss of this strongly stabilizing interaction explains the unfavorable cyclization energies for these radicals. On the other hand, in the case of a CH_2-CH_2 bridge (**2** and **4**), the conformational change results not only in a loss of hyperconjugative interactions between the radical orbital and C−H bonds but also in simultaneous gain of a similar interaction with the bridge σ(C−C) bond. Since the difference in these hyperconjugative interactions is relatively small,[33] no significant energy penalty is associated with the reorientation of these radicals. Thus, to increase the efficiency of the 5-endo cyclizations it is beneficial to use saturated bridging moieties or to utilize structural restraints that keep the radical centers orthogonal to the bridge π-system. Another way to decrease the deactivating effect of the conjugating bridge is to trade a double bond for an aromatic moiety (Figure 2). This modification significantly lowers the 5-endo activation barrier (Figure 3). Part of this decrease stems from a lesser stabilization of the radical center by conjugation with a benzene ring in comparison with the allylic stabilization discussed earlier. In the case of benzyl radical **6**, the barrier is sufficiently lowered to become readily accessible under the usual conditions for thermally induced cyclizations.

Scheme 2. Competition between Cyclizations of α- and β-Radicals and H-Abstraction by the α-Radical



Nevertheless, despite the relatively low 5-endo cyclization barrier, a recent experimental study[10] found that derivatives of enediyne **5** with terminal aryl substituents undergo 5-exo cyclization from an isomeric radical instead of 5-endo cyclization. This discrepancy is a consequence of another problem that complicates the experimental design of 5-endo radical cyclizations. To illustrate this difficulty, below we compare energy profiles of the 5-endo cyclization and the most important competing processes utilizing 1,2-diethynyl benzene **5** as a model reactant.

Reactions Competing with 5-Endo Cyclization. Even when the activation energies for 5-endo-dig cyclizations are in the range that should be accessible at ambient temperatures, these processes can only be successful when competing processes are relatively slow. The most important competing processes are 4-exo-dig cyclization, hydrogen abstraction leading to the respective cyclic-reduced acyclic products, and isomerization of the radical to a different species capable of a more efficient cyclization through a lower barrier.

(A) 5-Exo and 6-Endo Cyclizations of Isomeric Radicals. To understand the nature of these complications, let us first analyze reactions triggered by addition of a radical initiator to 1,2-diethynylbenzene. The three most likely cyclization pathways involve 5-endo cyclization of α-radical **6** and the more common 5-exo and 6-endo-dig cyclizations of a regioisomeric β-radical **7** (Scheme 2). In the parent system, the α-radical that undergoes 5-endo cyclization (Scheme 2) is not only formed selectively[34] but also is more stable and thus represents the major component in the equilibrating mixture of α- and β-radicals[35] produced by addition of radical X to a triple bond. Nevertheless,

(32) The trans/anti form of the reactant radical is only slightly more stable than the cis/syn isomer (∼0.1−0.8 kcal/mol). Only Z-pent-3-en-1-yne (**3**) derivative has another conformer (less stable by 22.1 kcal/mol) with in-plane π-radical as an energy minimum. The energy of "in-plane" conformers for other systems (**1**, **2**, and **4**) was obtained by using geometry constraints on the respective dihedral angles.

(33) For recent discussions of the relative donor and acceptor abilities of C−C and C−H bonds in hyperconjugative interactions, see: (a) Spiniello, M.; White, J. M. *Org. Biomol. Chem.* **2003**, *1*, 3094. (b) Alabugin, I. V.; Manoharan, M. *J. Org. Chem.* **2004**, *69*, 9011. (c) Rablen, P. R.; Hoffmann, R. W.; Hrovat, D. A.; Borden, W. T. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1719. (d) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265. See also: (e) Alabugin, I. V.; Zeidan, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 3175. (f) Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910.

(34) Both steric and electronic effects are important in controlling regioselectivity of radical attack at a triple bond. Steric effects direct the attack at the least substituted atom of acetylene moiety. In the case of monosubstituted arylacetylenes, electronic effects direct radical attack at the same carbon because of the formation of a more stable conjugated radical (the α-radical). Thus, such systems are strongly biased toward the α-radical formation, both kinetically and thermodynamically. On the other hand, when both termini of acetylene moiety have phenyl substituents, there are no significant steric differences between the two modes of addition whereas the differences in the relative stability of the two radicals decrease to ∼2 kcal/mol.

(35) Electronic structures of the α- and β-radicals are significantly different. Spin density is delocalized in the aromatic ring and the acetylene moiety in the α-radical as expected for a nonbonding MO in the corresponding Hückel approximation. Spin delocalization in the β-radical is more interesting. It involves the radical center, adjacent C−H bond (direct hyperconjugation), and the in-plane π-bond at the opposite acetylene terminus.

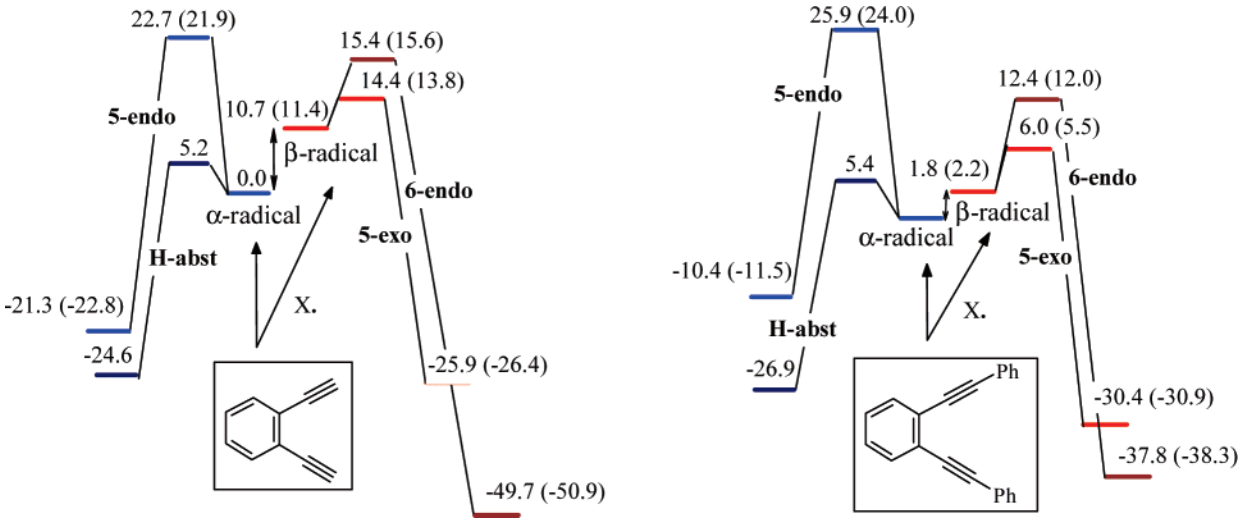


Figure 3. Curtin−Hammett analysis of competition between cyclizations of α- and *β*-radicals (**6** and **7** in Scheme 2) and H-abstraction by the α-radical. The structures of reactants and products are given in Scheme 2 (X = H, R′ = Me_3Sn). The energies are given relative to α-radical at the B3LYP/LANL2DZ level (UB3LYP/6-31G** data are given in the parentheses). See also Table S1a in SI.

because the stabilizing benzylic conjugation with the α-radical is lost in the TS and in the product of 5-endo cyclization, the 5-endo barrier is significantly higher than that for the 5-exo and 6-endo processes (>20 kcal/mol versus 1−5 kcal/mol), and thus this pathway is the least exothermic among the three processes.

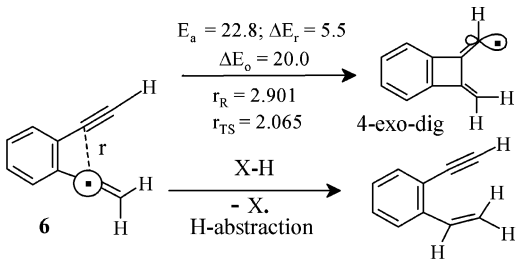
Two scenarios are possible in the kinetic competition between the highly exothermic and essentially irreversible cyclizations. In the first of them, equilibration of the α- and *β*-radicals is slower than the cyclizations (e.g., essentially irreversible addition of a carbon-centered radical to the first triple bond). In this case, the regioselectivity of the intermolecular addition of the initiator to the triple bond determines whether the 5-endo/4-exo or the 5-exo/6-endo products are formed. In the second scenario, the vinyl radical generation step is reversible (e.g., addition of Sn- or S-centered radical initiators to a triple bond).[36] The Curtin-Hammett principle applies to this situation, and the ratio of 5-endo/(5-exo + 6-endo) products equals the product of the equilibrium constant *K* for the α- and *β*-radical interconversion times the ratio of the reaction rate constants $k_{5-endo}/(k_{5-exo} + k_{6-endo})$.[37] In other words, for the rapidly equilibrating system to enter the TS for the 5-exo cyclization instead of 5-endo process, the energy difference between the two radicals ($\Delta E_{\alpha\beta}$) must be paid in addition to the TS energy relative to the *β*-radical. When the $\Delta E_{\alpha\beta}$ value is small (e.g., in enediynes with terminal aryl substitution, Figure 3b), the 5-endo cyclization has little chance of competing with the much faster 5-exo- and 6-endo alternatives as recently reported by Kovalenko et al.[10]

Only when the α-radical → *β*-radical isomerization is significantly uphill and $\Delta E_{5-exo/6-endo}^{\ddagger} + \Delta E_{\alpha\beta} > \Delta E_{5-endo}^{\ddagger} >$ ~20 kcal/mol for the situation illustrated in Figure 3, the 5-endo cyclization becomes possible in such equilibrating systems. However, even in such cases where the barrier for the interconversion of two radicals is relatively large,[38] direct H-abstraction by the α-radical from an appropriate hydrogen atom donor may compete with the 5-endo and 4-exo cyclizations. The H-abstraction from *β*-radical **7** is not important in the presence of the low barrier unimolecular reactions (the 5-exo and 6-endo cyclizations).

(B) H-Atom Abstraction and 4-Exo-Dig Cyclization. First, clearly the 4-exo cyclization of radical **6** is kinetically competitive with the 5-endo process since the latter has only a ca. 0.9 kcal/mol lower barrier. On the other hand, the 4-exo pathway is moderately endothermic and, thus, should be reversible. From a practical point of view, this means that to achieve acceptable yields of 5-endo products, the cyclizations should be carried out under thermodynamic control conditions when H-abstraction is slower than the cyclizations and the ring opening of the 4-exo product.

To gain further insight into the competition between the two cyclizations and H-abstraction, we determined the barrier for H-atom abstraction from Me_3SnH by α-radicals **6** computationally (Scheme 3, Figure 4). Not surprisingly, hydrogen abstraction from the weaker C−H bonds (e.g., R_3SnH and 1,4-cyclohexadiene) is predicted to be faster than that from the stronger C−H bond of methanol.

Scheme 3. Activation and Reaction Energies (All in kcal/mol) for the 4-Exo Cyclization of α-Radical **6** (UB3LYP/6-31G**) and for H-Atom Abstraction by the Same Radical from R_3SnH, 1,4-CHD, and Methanol Calculated at the UB3LYP/LANL2DZ and UB3LYP/6-31G** (in Italics) Levels[43]



	E_a	ΔE_r		E_a	ΔE_r
X=SnH_3:	4.6	-26.0	X=C_6H_{11}:	7.9	-27.7
				8.0	*-25.8*
X=$SnMe_3$:	5.2	-24.6	X=CH_2OH	12.9	-4.1
				10.6	*-2.7*

(36) (a) Stork G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829. (b) Russell, G.; Ngoviwatchai, P.; Tashtoush, H. I. *Organometallics* **1988**, *7*, 696. (c) Chatgilialoglu, C.; Altieri, A.; Fischer, H. *J. Am. Chem. Soc.* **2002**, *124*, 12816. (d) Melandri, D.; Montevecchi, P. C.; Navacchia, M. L. *Tetrahedron* **1999**, *55*, 12227.

(37) (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562. (c) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83. (d) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 2719.

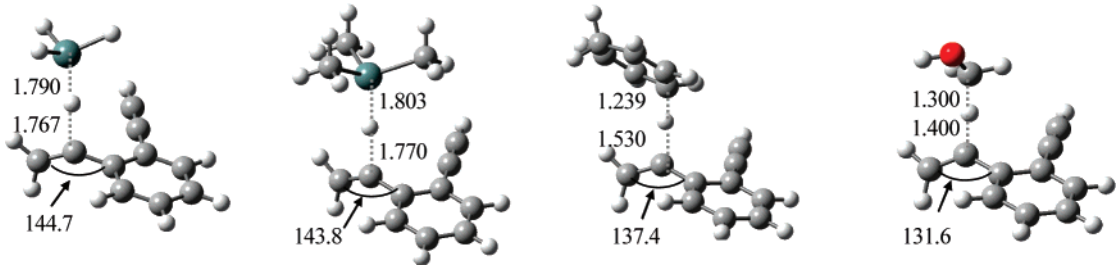
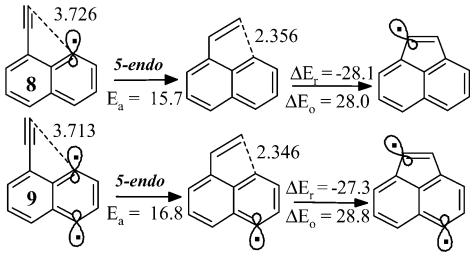


Figure 4. Computed TS geometries for H-abstraction reactions of α-radical **6** by R_3SnH, 1,4-CHD, and methanol (UB3LYP/LANL2DZ).

Although the absolute values of the barriers for R_3SnH should be taken with caution given that the theoretical methods are not well-calibrated in the case of Sn-containing substrates, comparison of the reaction energies for H-abstraction from Me_3SnH and 1,4-CHD provides an estimate of the computational accuracy. Since the bond dissociation energies (BDE) of these two H-donors are within 1 kcal/mol,[39] the exothermicity of H-atom abstractions should be very close as well. Taking this into consideration, the data in Scheme 3 suggest that B3LYP/LANL2DZ slightly underestimates reaction exothermicity of H-abstraction from Me_3SnH reaction by ca. 3 kcal/mol and, thus, may also slightly overestimate the reaction barrier. The calculated barrier heights are similar to the experimental data for H-abstraction from Bu_3SnH by alkyl radicals (~3 kcal/mol for Me and t-Bu).[40] However, even with a generous margin for error, the activation barrier in the case of Sn−H donors (~5 kcal/mol) remains significantly below that for the 5-endo cyclizations discussed above. On the other hand, H-atom abstraction from C−H donors should proceed slower[41,42] for C−H bonds of comparable strength and be further controlled by the strength of C−H bonds. In addition, the noticeably shorter incipient C···H distances in the respective transition states (Figure 4) may make H-abstraction from C−H donors more sensitive to steric effects.

Thus, in contrast to the respective nucleophilic and electrophilic 5-endo cyclizations,[8] the competition with 4-exo-dig cyclization and H-abstraction should be taken seriously in the design of experimentally feasible radical 5-endo cyclizations. Changing X−H bond strengths in the donor molecule as well as other experimental strategies that slow the unproductive H-atom abstraction (e.g., a judicial use of concentration control techniques such as slow addition via a syringe pump or radical polarity reversal methods) may alleviate the problem to some extent.[44] However, these techniques may work only up to a certain point after which one has to find ways to increase the rate of cyclization by decreasing the 5-endo cyclization barrier. The next section discusses possible approaches to solve this problem by an analysis of conjugation, aromaticity, strain, and polar effects on the rate of 5-endo-dig cyclization.[45]

Scheme 4. Geometric Parameters and Activation and Reaction and Intrinsic Activation Energies for 5-Endo Cyclization in Constrained Naphthyl Monoradical (**8**) and Diradicals (**9**, Bergman Reaction of Triyne)



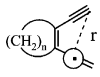
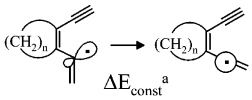
Efficiency of 5-Endo Cyclization. (A) Conjugation. As discussed above, a loss of the stabilizing interaction of α-radicals with the π-system of the bridge moiety (vinyl, aryl) results in the additional energy penalty that is incorporated in both the reaction barrier and the enthalpy of 5-endo cyclizations. The magnitude of the above conjugative effect can be estimated either as $\Delta E(\alpha - \beta)$, the difference in stabilities between the two isomeric radicals **6** and **7** (Figure 3), or as the energy increase when a radical is constrained to remove this conjugation (e.g., **1** and **3** in Figure 1). The two estimates suggest that the stabilizing effect is in the order of ~11−15 kcal/mol in the benzannelated system (Figure 3) and ca. ~19 kcal/mol in the parent system derived from hex-3-ene-1,5-diyne (Figure 1). The different stabilization energies are translated into the ca. 9 kcal/mol difference in the 5-endo activation energies between the parent and benzannelated systems.

This observation leads to the first practical rule for designing efficient 5-endo-dig cyclizations: *the radical center in the reactant should not be deactivated by conjugation*. When the conjugative stabilization is completely removed by structural restraints (e.g., **8** and **9**), the barrier decreases further as illustrated by an example given in Scheme 4.

This rule is not limited to conjugation with the bridge orbitals but also applies to other stabilizing interactions that decrease

(38) The magnitude of such barriers is unknown. They are likely to be large for the highly exothermic addition of carbon-centered radicals but much smaller for addition of Bu_3Sn radical (Alabugin, I. V.; Manoharan, M., submitted for publication).
(39) 7 kcal/mol for Bu_3SnH and 73 kcal/mol for 1,4-CHD. Burkey, T. J.; Majewski, M.; Griller, D. *J. Am. Chem. Soc.* **1986**, *108*, 2218.
(40) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.
(41) The differences in the barrier height between R_3SnH and 1,4-CHD can be explained by polar effects on the avoided crossing between the reactant and product states: (a) Donahue, N. M.; Clarke, J. S.; Anderson, J. G. *J. Phys. Chem. A* **1998**, *102*, 3923. (b) Clarke, J. S.; Kroll, J. H.; Donahue, N. M.; Anderson, J. G. *J. Phys. Chem. A* **1998**, *102*, 9847. For a recent thorough study, see: (c) Tichy, S. E.; Thoen, K. K.; Price, J. M.; Ferra, J. J., Jr.; Petucci, C. J.; Kenttämaa, H. I. *J. Org. Chem.* **2001**, *66*, 2726. Note, however, that although H-atom abstraction by excited azoalkanes indeed proceeds faster from Bu_3SnH than from 1,4-CHD, the difference is not dramatic: (d) Adam, W.; Moorthy, J. N.; Nau, W. M.; Scaiano, J. C. *J. Org. Chem.* **1997**, *62*, 8082.
(42) The barriers for H-abstraction by p-benzyne and phenyl radicals from methanol were calculated to be 9.5 and 8.0 kcal/mol at the CASPT2N/6-31G**//CAS/3-21G level. Logan, C. F.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 2113.
(43) The reaction energies for H-abstraction from 1,4-CHD and MeOH calculated with the LANL2DZ and 6-31G** basis sets are similar (see Supporting Information).
(44) (a) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25. For a creative application of the polarity reversal catalysis for *increasing* the rate of H-abstraction, see: (b) Crich, D.; Hao, X.; Lucas, M. A. *Org. Lett.* **1999**, *1*, 269. (c) Crich, D.; Yao, Q. *J. Org. Chem.* **1995**, *60*, 84. (d) Crich, D.; Jiao, X.-Y.; Yao, Q.; Harwood, J. S. *J. Org. Chem.* **1996**, *61*, 2368. (e) Crich, D.; Mo, X.-S. *J. Am. Chem. Soc.* **1998**, *120*, 8298. (f) Crich, D.; Hwang, J.-T.; Gastaldi, S.; Recupero, F.; Wink, D. J. *J. Org. Chem.* **1999**, *64*, 2788.
(45) Although steric effects may also play a significant role, their analysis goes beyond the scope of this article, which mostly concentrates on the ways to *accelerate* the cyclization.

Table 1. UB3LYP/6-31G** C−C Distances (Å) between the Two Reacting Carbons in 5-Endo Cyclizations of Ring-Fused Systems along with the Activation and Reaction Energies, Intrinsic Barriers, Relative Energies of α- and *β*-Radicals (**10a**−**13a** and **10b**−**13b**), and Relative Energies of Constrained α-Radicals (**10c**−**13c**), ΔE_{const} (All in kcal/mol)

	r, (R)	r(TS)	$\Delta E^{\neq}$	ΔE_r	$\Delta E_{\alpha-\beta}$	 ΔE_{const} [a]	$\Delta E^{\neq b}$	ΔE_r [b]	ΔE_o [b]
n = 0 (**1**)	3.879	2.315	32.0	-11.4	-19.9	-18.8	13.2	-30.2	26.1
n = 1 (**10**)	4.825	2.256	61.3	22.3	-23.0	-20.0	41.3	2.3	40.1
n = 2 (**11**)	4.301	2.334	42.6	7.4	-20.4	-19.0	23.6	-11.6	29.1
n = 3 (**12**)	3.935	2.349	33.9	-5.4	-19.7	-19.2	14.7	-24.6	25.5
n = 4 (**13**)	3.707	2.330	28.0	-14.8	-18.4	-18.5	9.5	-33.3	23.2

[a] The energy difference between the α-radical and the constrained system with the radical orbital in-plane of the molecule. [b] Herein, the energies were computed using the constrained system as the reactant to separate the energy costs for orbital reorientation and cyclization.

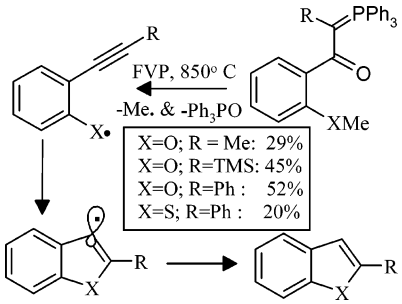
radical reactivity. For example, the activation energy for a topologically similar case involved in the Bergman[46]/5-endo cyclization cascade of 1,2,3-triethynyl benzene (Scheme 4) is further increased by the loss of through-bond (TB) stabilizing interaction between the two radical centers of **9**.[47]

However, even in the case of monoradical **8**, the observed decrease in the reaction barrier constitutes only half of the ca. 10 kcal/mol that one would expect from the radical stabilization energy in α-radical **6** (Scheme 2). To understand this observation, one has to analyze the effect of strain on the formation of polycyclic moieties.

(B) Strain. When a *poly*cyclic system is formed, the effects of strain in the product and TS may differ significantly from those in the parent system. To illustrate this point, we have estimated the role of strain by incorporating the bridge double bond into cyclic moieties. The 5-endo cyclizations in these systems are very sensitive to the ring size (Table 1): as ring size increases from three to six carbons, both the C1−C5 distance in the reactant and the activation energy for the cyclizations decrease, whereas both reaction exothermicity and difference in stability between α- and *β*-radicals increase. The effect on $\Delta E(\alpha - \beta)$ is interesting from a fundamental perspective and indicates that more strained π-bonds benefit more from delocalization.

Not surprisingly, the presence of a cyclopropene ring ($n = 1$) introduces the most strain (∼34 kcal/mol) in the cyclization product, whereas annealing to a cyclopentene ring (**10**) costs only about 6 kcal/mol. The other cyclizations for systems (**10**−**13**) with $n < 4$ are also disfavored by strain, albeit to a smaller extent. Only in a six-membered ring (**13**), the 5-endo cyclization is more favored than that in the acyclic analogue. *Thus, the second general rule states that strain effects should be carefully considered in the design of compounds capable of 5-endo cyclizations.* Interestingly, 5-exo-dig cyclizations show similar sensitivity to strain effects but analogous 6-endo cyclizations do not.[48]

Scheme 5. 5-Endo-Dig Radical Cyclizations Involved in FVP of Substituted Phosphorus Ylides

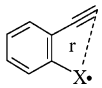


(C) Polar Effects. Polar effects[49] are known to be important in radical additions. Two established approaches toward rationalizing these effects are FMO analysis and incorporation of charge-transfer configurations in the VB state correlation diagram.[28,29] The FMO theory concentrates on the dominant SOMO−LUMO and SOMO−HOMO interactions, both of which are capable of stabilizing the TS.[50,51] To analyze possible polar effects, we chose 5-endo cyclizations of radicals (**14**−**20**) closely related to the systems studied by Aitken and coworkers (Scheme 5).[12] We focus on the effect of "SOMO−LUMO interactions",[52] whose role in 5-endo-dig radical cyclizations is unexplored.

In all cases, the magnitudes of the activation energies suggest that the cyclizations are indeed possible under FVP conditions. The trends in calculated reaction energies are controlled by the interplay of *gain* of aromatic stabilization and *loss* of conjugative radical stabilization when the starting materials are transformed into the products. The differences in reaction exothermicities are partially translated into the activation barriers complicating

(46) (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (b) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660.
(47) (a) Squires, R. R.; Cramer, C. J. *J. Phys. Chem. A* **1998**, *102*, 9072. (b) Davico, G. E.; Bierbaum, V. M.; DePuy, C. H.; Ellison, G. B.; Squires, R. R. *J. Am. Chem. Soc.* **1995**, *117*, 2590. (c) Logan, C. F.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 2113. (d) Schottelius, M. J.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896. (e) Hoffner, J.; Schottelius, J.; Feichtinger, D.; Chen, P. *J. Am. Chem. Soc.* **1998**, *120*, 376. (f) Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **2000**, *122*, 8245. (g) Kraka, E.; Cremer, D. *J. Comput. Chem.* **2001**, *22*, 216. (h) Stahl, F.; Moran, D.; Schleyer, P. v. R.; Prall, M.; Schreiner, P. R. *J. Org. Chem.* **2002**, *67*, 1453. (i) Alabugin, I. V.; Manoharan M. *J. Am. Chem. Soc.* **2003**, *125*, 4495. (j) de Visser, S P.; Filatov, M.; Schreiner, P. R.; Shaik, S. *Eur. J. Org. Chem.* **2003**, 4199. (k) Winkler, M. *J. Phys. Chem. A* **2005**, *109*, 1240.
(48) Alabugin, I. V.; Manoharan, M. Submitted for publication.
(49) For the most recent work, see: (a) Lalevée, J.; Allonas, X.; Fouassier, J.-P. *J. Org. Chem.* **2005**, *70*, 814 and references therein. Also: (b) Weber, M.; Fischer, H. H. *Helv. Chim. Acta* **1998**, *81*, 770. (c) Beckwith, A. L. J.; Poole, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 9489. (d) Zytowski, T.; Knuehl, B.; Fischer, H. *Helv. Chim. Acta* **2000**, *83*, 658. (e) Heberger, K.; Lopata, A. *J. Org. Chem.* **1998**, *63*, 8646. (f) Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* **1996**, *118*, 437. (g) Batchelor, S. N.; Fischer, H. *J. Phys. Chem.* **1996**, *100*, 9794. (h) Walbiner, M.; Fischer, H. *J. Phys. Chem.* **1993**, *97*, 4880. (i) Martschke, R.; Farley, R. D.; Fischer, H. *Helv. Chim. Acta* **1997**, *80*, 1363. (j) Lalevée, J.; Allonas, X.; Fouassier, J.-P. *J. Phys. Chem. A* **2004**, *108*, 4326.
(50) The SOMO−LUMO interaction has a much larger effect than the SOMO−HOMO interaction in 5-exo-trig cyclizations: Park, S. U.; Chung, S. K.; Newcomb, M. *J. Am. Chem. Soc.* **1986**, *108*, 240.
(51) SOMO−HOMO interaction dominates in addition of strongly electrophilic radicals to alkenes: (a) Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Dolbier, W. R.; Pan, H. Q. *J. Am. Chem. Soc.* **1993**, *115*, 1577. (b) Hartung, J.; Kneuer, R.; Rummey, C.; Bringmann, G. *J. Am. Chem. Soc.* **2004**, *126*, 12121.
(52) The overall trends in reactivity of acetynes and alkenes suggest that this interaction should be particularly important for acetylenes: Nicolaides, A.; Borden, W. T. *J. Am. Chem. Soc.* **1991**, *113*, 6750.

Table 2. Calculated Activation Barriers, Reaction Energies, and Intrinsic Barriers (kcal/mol) for the 5-Endo-Dig Cyclization of O−X-Substituted (X = S, N, O, CR_2, and SiR_2) Ethynyl Benzenes along with the Incipient C···X Distances (Å) at the UB3LYP/6-31G** Level



	r (R)	*r* (TS)	$\Delta E^{\ddagger}$	ΔE_r	ΔE_0
X = S (**14**)	3.882	2.491	14.6	−6.3	17.6
X = NH (**15**)	3.631	2.060	29.9	−13.0	36.1
X = O (**16**)	3.640	1.922	31.7	−0.5	32.0
X = CH_2 (**17**)[a]	3.706	2.316	31.1	−5.5	33.8
X = CHCN (**18**)[b]	3.668	2.216	31.9	6.0	28.2
X = $CHNMe_2$ (**19**)[c]	3.951	2.325	21.3	5.0	18.7
X = $SiMe_2$ (**20**)[c]	3.895	2.690	10.3	−20.4	19.1

[a] The out-of-plane π-radical is more stable than the in-plane σ-radical by 15.2 kcal/mol. [b] It shows only one isomer with the out-of-plane π-radical. [c] Only one isomer is found with the out-of-plane π-radical slightly twisted due to a bulky group (NMe_2 and $SiMe_2$).

analysis of electronic effects. Note, however, that the cyclizations of CN (**18**)- and NMe_2 (**19**)-substituted radicals have almost identical reaction energies, but the barrier is >10 kcal/mol lower in the case of the donor substituent. The data strongly suggest that both the activation energy ($\Delta E^{\ddagger}$) and the intrinsic reaction barrier (ΔE_0) decrease dramatically when electron density increases at the radical center (Table 2). As a result, the cyclizations of radicals **14** and **20** should proceed readily even at ambient conditions despite the loss of benzylic stabilization.

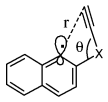
The above results not only illustrate rule #3 (i.e., *polar effects can be successfully used to increase efficiency of 5-endo-dig radical cyclizations*), but also show that the reaction energies are dramatically different and depend strongly on the nature of radical center and aromaticity of the product. The following section discusses in more detail how product stabilization controls efficiency of these processes.

(D) Aromatic and Hyperconjugative Stabilization of the Products. Finally, cyclization energy barriers can be influenced by reaction exothermicity. Many effects can stabilize the radical product (e.g., aromaticity of the newly formed ring when the bridge system includes a heteroatom X (e.g., X = O, N, S) or anomeric type $n(X) \rightarrow n(C)$ interactions of newly formed radical orbitals with lone pairs). Both of these effects contribute to the calculated trends in the energies of the 5-endo-dig cyclizations of various radicals (**21**−**28**) in Table 3. Formation of aromatic products leads to a ∼20 kcal/mol increase in reaction exothermicites compared to a CH_2-substituted case.[53] The relative trends do not directly follow the order of aromatic stabilization energies (furan (**20**) < thiophene (**22**) < pyrrole (**26**), all in kcal/mol) because of the contribution from the anomeric interactions. This interaction is significant for oxygen, less important for sulfur,[54] and absent in the case of nitrogen where the only lone pair is already involved in the aromatic π-system and, thus, is orthogonal to the radical orbital.

The trends in intrinsic activation barriers provide an interesting insight into the differences between X = NH, O, and CH_2.

Table 3. Calculated Activation Barriers, Reaction Energies, and Intrinsic Barriers (kcal/mol) for 5-Endo-Dig Cyclizations Yielding Aromatic Rings along with the Incipient C···C Distances (Å) and C−X−C Bond Angles (deg) at the UB3LYP/6-31G** Level

	r (R)	*θ* (R)	*r* (TS)	*θ* (TS)	$\Delta E^{\ddagger}$	ΔE_r	ΔE_0
X = S (**21**)	3.758	103.0	2.466	93.7	8.2	−53.0	28.6
X = NH (**22**)	3.777	124.2	2.468	111.6	11.2	−53.1	32.3
X = O (**23**)	3.569	117.4	2.474	108.0	8.9	−56.3	30.6
X = CH_2 (**24**)	3.698	115.1	2.377	104.6	13.1	−33.8	27.4



	r (R)	*θ* (R)	*r* (TS)	*θ* (TS)	$\Delta E^{\ddagger}$	ΔE_r	ΔE_0
X = S (**25**)	3.712	102.5	2.459	93.6	8.2	−50.1	27.6
X = NH (**26**)	3.731	124.2	2.447	112.0	11.5	−48.7	31.1
X = O (**27**)	3.565	117.5	2.456	108.2	9.4	−52.5	29.9
X = CH_2 (**28**)	3.657	114.7	2.376	104.4	12.2	−35.2	26.9

The observed decrease in the CXC valence angle (NH > O > CH_2) parallels a decrease in the intrinsic barriers. The relative trends in valence angles are readily explained by Bent's rule,[55,56] which states that atoms tend to maximize the amount of p-character in hybrid orbitals aimed toward electronegative substituents while directing hybrid orbitals with the larger amount of s-character toward more electropositive substituents.[57] Increase in the p-character of C−X bond-forming hybrid orbitals of atom X decreases both the CXC angle and the intrinsic barrier.[58]

Literature Examples: A Critical Overview. The above discussion suggests that although one should not suggest occurrence of 5-endo-dig radical cyclizations casually, such processes may be possible under certain circumstances. With this idea in mind, let us apply computational scrutiny to four proposed 5-endo-dig radical cyclizations from the literature.

(A) Radical Cyclizations of Enediynes. It was suggested recently that 5-endo-dig cyclizations along with their 5-exo-dig and 6-endo-dig counterparts may be one of the three alternative radical processes occurring during thermal polymerizations of enediynes. Importantly, intermolecular addition of the carbon-centered p-benzyne radical to a triple bond should be irreversible, unlike the recent example of Bu_3Sn-triggered 5-exo-dig cyclizations.[10] As a result, the competition between 5-endo cyclization and combined 5-exo- and 6-endo cyclizations should be controlled by regioselectivity of initial radical addition to the enediyne triple bonds. For the situation in Scheme 6,

(53) The aromatic stabilization energies are 19.8 kcal/mol for furan, 22.4 kcal/mol for thiophene, and 25.5 kcal/mol for pyrrole: (a) Schleyer, P. v. R.; Freeman, P. K.; Jiao, H.; Goldfuss, B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 337. (b) Schleyer, P. v. R.; Puhlhofer, F. *Org. Lett.* **2002**, *4*, 2873. (c) Schleyer, P. v. R.; Jiao, H. *Pure Appl. Chem.* **1996**, *28*, 209. See also: (d) Alabugin, I. V.; Manoharan, M.; Breiner, B.; Lewis, F. J. *Am. Chem. Soc.* **2003**, *125*, 9329. Earlier discussions: (e) Bernardi, F.; Bottoni, A.; Venturini, A. *J. Mol. Struct. (THEOCHEM)* **1988**, *163*, 173 and references therein.

(54) In this case, anomeric stabilization between the radical center and S lone pair is less important. According to NBO analysis, $n(S) \rightarrow n(C^{\bullet})$ interaction is only 0.4 kcal/mol in the product. This observation is not surprising and can be explained by unfavorable hybridization of the in-plane S lone pair having little p-character (ca. 35%) in contrast to the respective O-lone pair (ca. >60%). Alabugin, I. V.; Manoharan, M.; Zeidan, T. A. *J. Am. Chem. Soc.* **2003**, *125*, 14014.

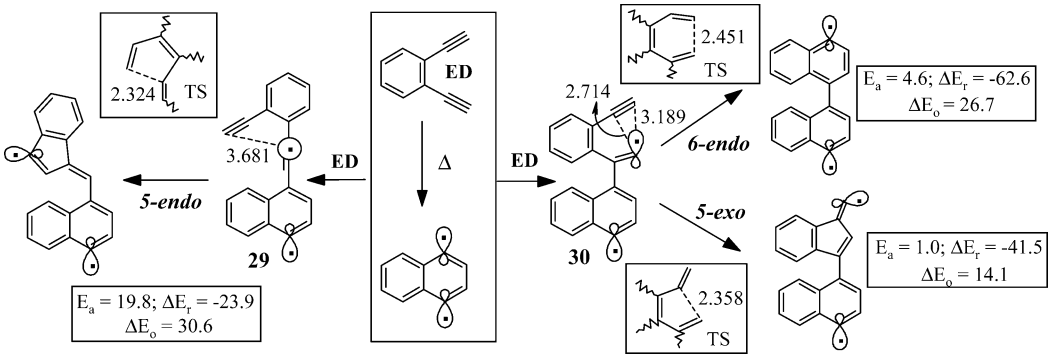
(55) Bent, H. A. *Chem. Rev.* **1961**, *61*, 275.

(56) For selected applications of Bent's rule, see: (a) Baldridge, K. K.; Siegel, J. S. *Chem. Rev.* **2002**, *124*, 5514. (b) Kaupp, M.; Malkina, O. L. *J. Chem. Phys.* **1999,** *108*, 3648. (c) Palmer, M. H. *J. Mol. Struct.* **1997**, *405*, 193. (d) Jonas, V.; Boehme, C.; Frenking G. *Inorg. Chem.* **1996**, *35*, 2097. (e) Root, D. M.; Landis, C. R.; Cleveland, T. *J. Am. Chem. Soc.* **1993**, *115*, 4201. (f) Kaupp, M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1993**, *115*, 1061. For consequences of Bent's rule for the "improper" or "blue-shifted" hydrogen bonding, see: (g) Alabugin, I. V.; Manoharan, M.; Peabody S.; Weinhold, F. *J. Am. Chem. Soc.* **2003**, *125*, 5973. (h) Alabugin, I. V.; Manoharan, M.; Weinhold, F. *J. Phys. Chem. A* **2004**, *108*, 4720.

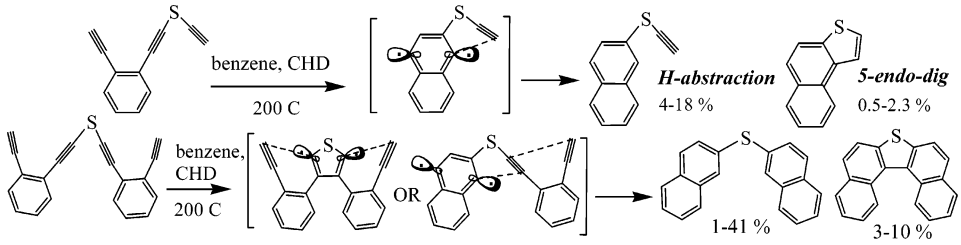
(57) The NBO hybridization analysis is given in the SI ,Tables S2 and S3.

(58) A slight increase in the intrinsic barrier for X = S can be explained by the perturbation of the TS geometry by the longer C−S bonds.

Scheme 6. Three Possible Radical Cyclizations Potentially Involved in Polymerization of Benzannelated Enediynes along with Activation and Reaction Energies (kcal/mol) at the UB3LYP/6-31G** Level



Scheme 7. Cycloaromatization/Radical Cyclization Cascades of Polyacetylenic Sulfides[15,60]



formation of radical **29** is favored by both steric and electronic points of view, and since there is no kinetic competition between reactions proceeding from α- and *β*-radicals (**29** and **30**), the ratio of reaction products is controlled by competition between 5-endo and 4-exo cyclizations and H-abstraction.

Since the reactant α-radical (**29**) is stabilized by conjugation, the activation barrier for the 5-endo pathway is rather high. Only because good H-atom donors are absent under these reaction conditions (the cycloaromatization is carried out with neat enediynes), the 5-endo pathway is possible. However, the efficiency of this process seems to be low because the authors reported a considerable amount of unreacted triple bonds in the polymeric products.

(B) Cascade Cyclizations of Triynes. The 5-endo cyclizations become more favorable (both kinetically and thermodynamically) when the moiety that bridges the vinyl radical and the triple bond is saturated or when the radical orbital is forced to coplanarity with the in-plane *π*-orbital of acetylene moiety by intramolecular restraints. An example is provided by the recent literature 5-endo product formation in a radical cascade initiated by Bergman cycloaromatization (Scheme 7). Although formation of acyclic-reduced products is still the dominant reaction (the amount of 5-endo product is as low as <2.3%),[59] this important result shows that 5-endo-dig cyclizations *are capable of* competing (albeit not very efficiently) with H-abstraction even in the presence of a good H-atom donor (1,4-cyclohexadiene).

The experimental observations agree very well with the computed activation barriers for 5-endo cyclization in the case of diradical analogues (**31**−**34**) of monoradicals **25**−**28**. The full computational details are given in the SI (Scheme S1), but interestingly, both activation and intrinsic barriers for the cyclization of biradicals **31**−**34** are 0.5−1 kcal/mol higher than those for the respective monoradicals. This difference is physically meaningful and consistent with the magnitude of the stabilizing TB interaction[47] deactivating the diradicals. This result also supports the use of eq 2 for analyzing the *relative* magnitudes of intrinsic barriers in radical cyclizations.

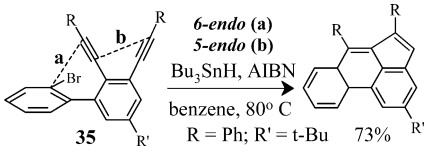
From a practical point of view, the barriers are dramatically decreased to the extent where the cyclization should be able to compete with H-atom abstraction from C−H donors. Most of the decrease comes from the thermodynamic component: the reaction is 26−30 kcal/mol more exothermic than the parent reactions in Table 1 due to both reactant destabilization and product stabilization. Since the radical orbital in the reactant is kept out of conjugation by intramolecular restraints, the system does not need to lose this stabilizing interaction to reach the transition state. Thus, reactant destabilization relative to the parent case contributes ∼11−15 kcal/mol to the increased exothermicity of the cyclization compared with the analogous reactions of conjugated α-radicals. Aromaticity of benzothiophene moiety is only partially offset by strain effects and contributes to the 12−16 kcal/mol of increased stability of the product. *Thus, this example provides the first demonstration of aromatic stabilization as a driving force for 5-endo-dig radical cyclizations as well as the only unambiguous experimental example of a 5-endo-dig cyclization involving a carbon-centered radical.*

Note that direct H-atom abstraction leading to the formation of acyclic-reduced products dominates under the reaction conditions because of the relatively high cyclization barrier for the 5-endo cyclization. Using lower concentrations of H-atom donor or less-active H-donors should improve the ratio of cyclic to acyclic products. However, the problem of polymeric products arising from other competing radical processes (e.g., 4-exo-dig cyclization) is still likely to persist and needs to be addressed separately for this process to become of practical value.

(C) Bu_3Sn-Triggered Cyclizations of Bromoaryl-Substituted Enediynes. Considering the above, the fact that radical-induced cyclizations of bromoaryl-substituted enediynes **35** (Scheme 6) proceed in a very respectable 73% yield constitutes a surprising finding. The authors of ref 16 suggested that the

(59) Lewis, K. D.; Rowe, M. P.; Matzger, A. J. *Tetrahedron* **2004**, *60*, 7191.

Scheme 8. Proposed 6-Endo-Dig/5-Endo-Dig[16] Radical Cyclization Cascade in Brominated Biphenyl Diacetylenes



reaction mechanism involves initial formation of an aryl radical by reaction of a Bu_3Sn radical with the C−Br bond. In this mechanism, the first step is followed by either 5-exo/6-endo (R═H) or 6-endo/5-endo (R═Ph) cyclization cascades leading, respectively, to acenaphthene and phenanthrene derivatives (Scheme 8). Parts of this mechanism such as the preference for 6-endo over 5-exo mode and especially the observation of an efficient 5-endo process are very intriguing and, if correct, would constitute very important results of general significance for radical chemistry.[61]

At first glance, the suggested 5-endo-dig cyclization step is perfectly reasonable because the geometry of the reactant is constrained in a way that prevents conjugation of the vinyl radical with the bridge π-system (rule #1 above). Indeed, this structural feature is favorably reflected in a ∼7 kcal/mol decrease in the activation energy and a ∼8 kcal/mol increase (Scheme 9) in the reaction exothermicity compared with that of the parent case (Figure 2). Nevertheless, both of these effects are *less* than what might be expected from the ca. 11−14 kcal/mol of benzylic stabilization, which suggests that an unfavorable factor (e.g., increased strain in the five-membered TS annealed at the polycyclic skeleton) destabilizes the product.

As a result, the activation energy remains relatively high (∼6 kcal/mol, higher than in the case discussed in the previous section), rendering this cyclization pathway unlikely to compete with H-abstraction from Bu_3SnH, which has a ca. 10 kcal/mol lower barrier. In addition, the introduction of two Ph substituents, which leads to the experimentally observed switch from the "5-exo/6-endo" cascade to the "6-endo/5-endo" path, is predicted to result in a further *increase* in the activation barrier for the 5-endo step (Scheme 9). Moreover, the presence of a terminal aryl group should further decrease the barrier for the 5-exo cyclization of the initially formed aryl radical **36** and simultaneously *increase* the 6-endo barrier by 1.8 kcal/mol. Thus, even the *first* step in the proposed "6-endo/5-endo" cascade needed to form the starting material for the 5-endo step is also unlikely!

Taken together, the data suggest that the actual reaction mechanism may be different from the one suggested in Scheme 8. An interesting alternative explanation for a switch in the observed cyclization cascade is a change in *chemo*selectivity of the Bu_3SnH reaction with the substrate. It is likely that this reaction is initiated by the addition of a radical to the triple bond instead of an attack on the C−Br bond. Unlike homolytic cleavage of C−X (X = halogens) bonds, Bu_3Sn radical additions to the triple bonds are likely to be reversible[36] and, thus, may be invisible unless a suitable cyclization pathway is available.

We have investigated this possibility computationally and found that it indeed provides a viable alternative to the mechanism proposed earlier. When Ph substituents are present, the β-radical is stabilized by conjugation with the *terminal* π-system and, thus, can be formed efficiently and be present in sufficiently high concentration to undergo 5-exo cyclization through a low (2.1−2.6 kcal/mol) energy TS (Scheme 10). This step is followed by cyclization at the bromosubstituted aromatic ring through either a five- or a six-membered TS. Formation of the six-membered ring is favored both kinetically and thermodynamically and leads to the observed products after loss of Br atom and rearomatization. Interestingly, the final radical addition to an aromatic ring has a relatively high intrinsic barrier and is made possible (E_a = 9.8 kcal/mol) by the extremely large thermodynamic contribution. The fate of the R_3Sn substituent remains uncertain, but it is possible that it is lost during the workup. Another possibility is that it is removed by reaction with a bromine atom lost from **44** in the aromatization step.

Experiments with deuterated substrates (e.g., comparison of deuterium label distributions in the products of 1.Bu_3SnD/2.HCl and 1.Bu_3SnH/2.DCl sequences) may differentiate between the possible mechanisms but, in any case, it seems unlikely that formation of compound **35** involved the 6-endo/5-endo pathway suggested in the original report. Although the above example illustrates how difficult it may be to engineer efficient 5-endo-dig radical cyclizations, it also highlights the fascinating complexity of radical chemistry where stereo-, regio-, and chemoselectivities should be considered under kinetic and thermodynamic controls. To incorporate and rationally utilize new radical cyclizations in synthetic designs constitutes a major challenge that requires dissection of this complexity by a combination of experimental and theoretical studies.

Efficient 5-Endo-Dig Radical Cyclizations. Thus far, the literature examples observed above have painted a rather pessimistic picture of inefficient or questionable 5-endo-dig cyclizations and raised the question of whether this reaction has the potential of ever becoming an efficient tool for the construction of polycyclic systems or will remain an esoteric process of little practical value. To illustrate how most factors outlined above can be combined to increase the efficiency of these processes, let us analyze a recent literature report of a surprisingly efficient 5-endo-dig radical cyclization (Scheme 11), which was involved as a key step in the reaction sequence proceeding in overall 55% yield.[13]

The increased efficiency of this 5-endo cyclization is in excellent agreement with the cyclization barrier of only ∼6 kcal/mol, which is the lowest of all of the examples (Scheme 12).[62] Since the reaction is only mildly exothermic (28 kcal/mol), the thermodynamic contribution to the observed barrier is significant but not extremely large and suggests a low intrinsic barrier for the cyclization step.[63]

Several structural features of the reactant account for the low cyclization barrier. First, the radical in the reactant is connected to the triple bond through a saturated C−O bridge and, thus, is not deactivated by conjugation (rule #1, vide supra). Second, there are no strain complications due to formation of a polycyclic skeleton (rule #2). Third, the σ(C−Si) → n(C) interaction involving a β-C−Si σ-bond with good donor ability provides significant hyperconjugative stabilization to the radical center in the product (Scheme 12). This is a manifestation of the β-Si

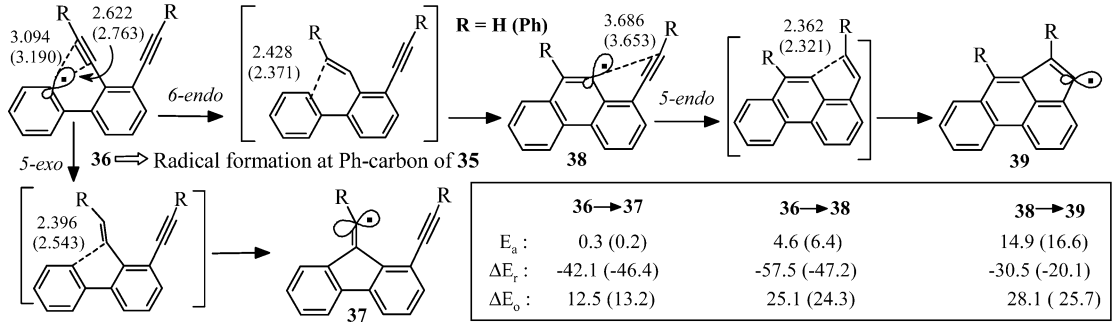
(60) For the mechanism of rearrangements of 1,4-pentadiynes, see: (a) Kawatkar, S. P.; Schreiner, P. R. *Org. Lett.* **2002**, *4*, 3643. (b) Bui, B. H.; Schreiner, P. R. *Org. Lett.* **2003**, *5*, 4871.

(61) We will discuss only the 5-endo cyclizations below. The other details of the mechanism will be discussed elsewhere.

(62) The transoid conformer of the radical **88** is only 0.1 kcal/mol lower in energy than the cisoid radical.

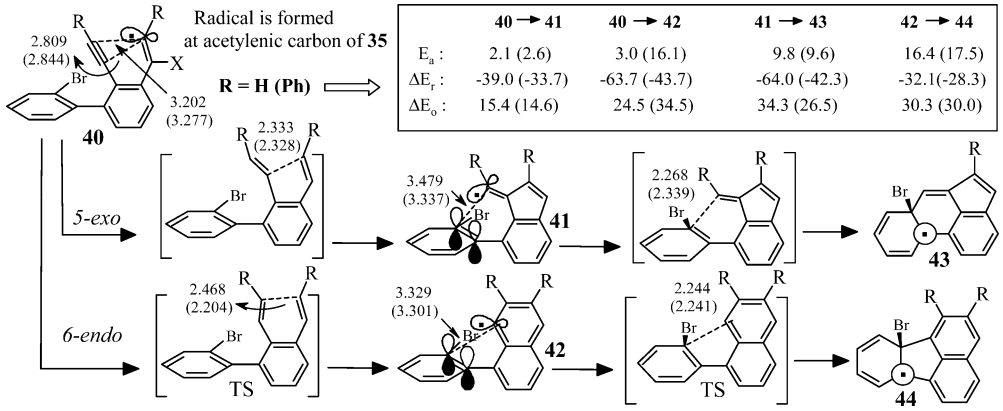
(63) Additionally, the reactivity of Si-centered radicals and C-centered radicals toward H-abstraction should be different.

Scheme 9. Reaction Barriers and Energies (kcal/mol) at the UB3LYP/6-31G** Level for 5-Endo Cyclization Proposed in Ref 16



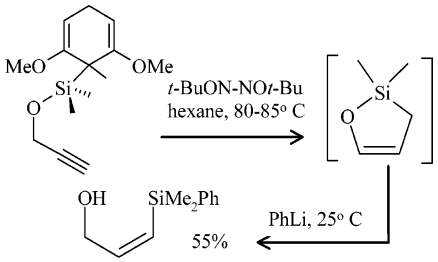
	36→37	36→38	38→39
E_a :	0.3 (0.2)	4.6 (6.4)	14.9 (16.6)
ΔE_r :	-42.1 (-46.4)	-57.5 (-47.2)	-30.5 (-20.1)
ΔE_o :	12.5 (13.2)	25.1 (24.3)	28.1 (25.7)

Scheme 10. Alternative Radical Cyclization Cascades of Bromoaryl Enediynes with the Reaction Barriers and Energies (kcal/mol) at the UB3LYP/6-31G** Level, X = H

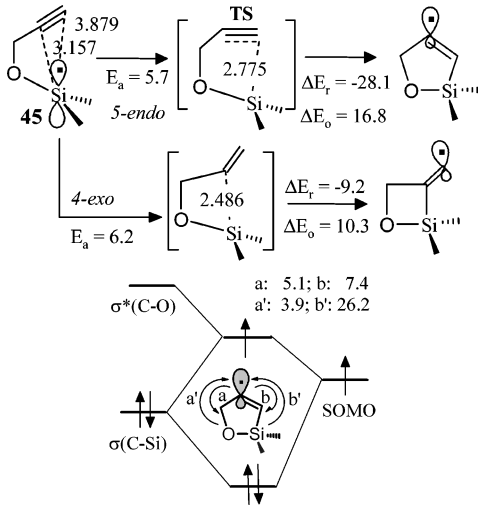


	40→41	40→42	41→43	42→44
E_a :	2.1 (2.6)	3.0 (16.1)	9.8 (9.6)	16.4 (17.5)
ΔE_r :	-39.0 (-33.7)	-63.7 (-43.7)	-64.0 (-42.3)	-32.1(-28.3)
ΔE_o :	15.4 (14.6)	24.5 (34.5)	34.3 (26.5)	30.3 (30.0)

Scheme 11. 5-Endo-Dig Radical Cyclization of Si-Centered Radical



Scheme 12. B3LYP PES Data and Second-Order Perturbation NBO Energies (in kcal/mol) of Vicinal Hyperconjugative Interactions in the Si-Substituted Radical **45**[a]



[a] The two dominant interactions are shown with arrows.

effect, a phenomenon that is well-known in the chemistry of cations[33b] but not in radical chemistry. As a result, the cyclization is 10 kcal/mol more exothermic than that in the parent case (**3** in Figure 1), thus providing a favorable thermodynamic contribution to the reaction barrier (rule #4).[64] Finally, the polar factors in the reactant are organized in a way that maximizes the SOMO−LUMO interaction in the TS of the cyclization (rule #3). The nucleophilic Si radical is a good electron donor, whereas the acceptor ability of the in-plane π-orbital of the triple bond is increased by hyperconjugative interaction with the vicinal σ^*(CO) acceptor (Scheme 12).

The relative magnitudes of stereoelectronic effects in the product were obtained from NBO analysis (Scheme 12). As expected, the donor/acceptor hyperconjugative interaction with the C−Si moiety is dominated by strong donation from the σ-(C−Si) bond. The interaction with the C−O moiety is more evenly balanced, but the n(C) → σ^*(C−O) interaction is almost twice as great as the σ(C−O) → n(C) interaction. As a result, the radical center serves simultaneously as a donor and as an acceptor, providing an electronic relay between C−O and C−Si bonds as discussed above.

In summary, all four general rules outlined in the previous sections combine in this example to provide a highly efficient 5-endo-dig cyclization. Overall, this result clearly illustrates that with proper design such processes should become a part of a synthetic arsenal of useful transformations.

4. Conclusions

We have analyzed the interplay of stereoelectronic, polar, and thermodynamic contributions to the activation barriers for

(64) This is an interesting observation because cyclizations of Si-centered radicals should be in general less exothermic than those of C-centered radicals because C−Si bonds are weaker than C−C bonds.

5-endo-dig radical cyclizations using DFT computations. A critical overview and analysis of the literature shows that one has to exercise caution in designing these processes and suggesting them as mechanistic steps in radical cascades. Unsaturation in the bridge connecting the vinyl radical and the triple bond imposes an additional penalty on 5-endo cyclizations unless the radical centers in the reactant are constrained to prevent their conjugation with the bridging π-system. Increased rigidity of these systems leads to a high sensitivity of 5-endo cyclizations to the strain effects. From a practical perspective, the success of 5-endo cyclizations depends on the competition with the 4-exo-dig process and with radical H-atom abstraction. Only when structural and energetic factors decrease the cyclization barrier, when H-atom abstraction is slow, and when competition with 4-exo-dig pathway is thermodynamically controlled, are efficient 5-endo-dig radical cyclizations possible. Lack of conjugation of the radical center in the reactant with the bridge orbital accompanied by stabilization of the 5-endo product through aromaticity and/or hyperconjugative effects involving donor σ-orbitals and the radical center are especially promising ways to accelerate 5-endo-dig radical cyclizations.

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Supporting Information Available: Optimized geometries of cyclizations involving tin-substituted radicals with the incipient C···C distances of radical cyclizations at difference levels of theory. NBO analysis of hybridization effects. Complete citation for refs 19 and 25. Cartesian coordinates of all stationary point geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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