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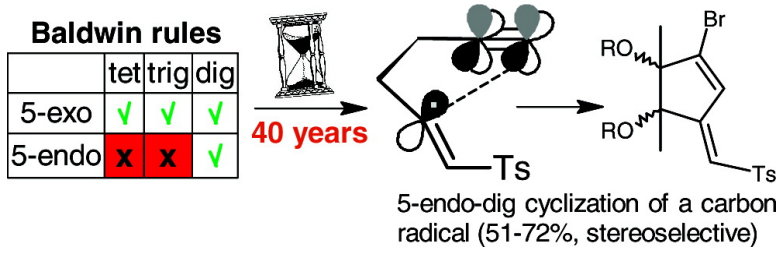

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In Search of Efficient 5-Endo-dig Cyclization of a Carbon-Centered Radical: 40 Years from a Prediction to Another Success for the Baldwin Rules

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Abstract: Despite being predicted to be stereoelectronically favorable by the Baldwin rules, efficient formation of a C−C bond through a 5-endo-dig radical cyclization remained unknown for more than 40 years. This work reports a remarkable increase in the efficiency of this process upon β-Ts substitution, which led to the development of an expedient approach to densely functionalized cyclic 1,3-dienes. Good qualitative agreement between the increased efficiency and stereoselectivity for the 5-endo-dig cyclization of Ts-substituted vinyl radicals and the results of density functional theory analysis further confirms the utility of computational methods in the design of new radical processes. Although reactions of Br atoms generated through photochemical Ts−Br bond homolysis lead to the formation of cyclic dibromide side products, the yields of target bromosulfones in the photochemically induced reactions can be increased by recycling the dibromide byproduct into the target bromosulfones through a sequence of addition/elimination reactions at the exocyclic double bond. Discovery of a relatively efficient radical 5-endo-dig closure, accompanied by a C−C bond formation, provides further support to stereoelectronic considerations at the heart of the Baldwin rules and fills one of the last remaining gaps in the arsenal of radical cyclizations.

Introduction

More than 40 years ago, a paper which eventually became the most cited in the history of *Chemical Communications*[1] outlined the "Baldwin rules"[2]—a set of general stereoelectronic guidelines to predict which cyclization patterns are favorable. In particular, Baldwin suggested that the 5-endo-trig cyclization of alkenes[3] should be unfavorable from the stereoelectronic perspective because the attack of a reactive center at the π-bond cannot easily follow the ideal Bürgi−Dunitz trajectory.[4] In contrast, a similar reaction in alkynes (the 5-endo-dig cyclization) was predicted to be easily achievable. The second *in-plane* π-bond presents a much better target for the incoming reactive center, thus avoiding the stereoelectronic restrictions inherent to the 5-endo-trig process (Figure 1a).

However, despite being favorable according to the Baldwin rules and known in its electrophilic, nucleophilic, and metal-catalyzed versions, the radical 5-endo-dig cyclization[5] remains a surprisingly scarcely documented process. Although a few isolated reports of 5-endo-dig cyclizations of either O- and S-centered radicals[6] or a Si-centered radical[7] exist, efficient formation of a C−C bond in a 5-endo-dig radical cyclization step remained, until now, an unachieved goal (in contrast with the "forbidden" 5-endo-trig process[8]). Only two recently reported radical cascade transformations involve such process as a possible but unlikely mechanistic alternative.[9,10]

Since our recent research has concentrated on both stereoelectronic effects[11] and chemistry of alkynes,[12] we found the apparent discrepancy between the Baldwin rules and the lack of efficient 5-endo-dig cyclizations intriguing. Analysis of general factors controlling the efficiency of this process using coupled cluster and density functional theory (DFT) methods[13] reveals that, although 5-endo-dig cyclizations are feasible, they are likely to be sufficiently slow, allowing a number of side reactions to become kinetically competitive. In particular, alternative cyclization paths, such as the even more exotic 4-exo-

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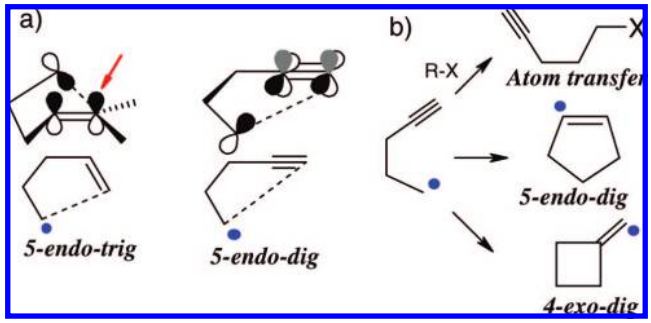


Figure 1. (a) Comparison of stereoelectronic requirements in 5-endo-trig and 5-endo-dig radical cyclizations. The "unachievable" 5-endo-trig Bürgi−Dunitz trajectory is shown with an arrow. (b) Three competing reactions of 4-pentyn-1-yl radical.

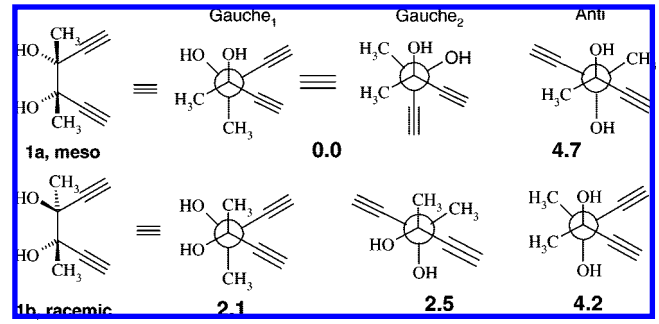
dig cyclization[14,15] and atom transfer (Figure 1b) before the cyclization, should be considered carefully. Herein, we report an experimental validation of these predictions along with the discovery of a substitution pattern that allowed, for the first time, the achievement of a relatively efficient 5-endo-dig cyclization of carbon-centered radicals.

The choice of cyclization substrates in this experimental study was based on the prediction that cyclization of vinyl radicals should proceed faster than cyclization of alkyl and allyl radicals (Scheme 1). We expected that the closely matched 4-exo/5-endo selectivity could be controlled through appropriate substitution and careful introduction of strain effects.[13,16]

Scheme 1. UB3LYP/6-31G** Activation (E_a) and Reaction (E_r) Energies (kcal/mol) for the 5-Endo-dig and 4-Exo-dig Cyclizations of (a) Nonconjugated sp^3 Radical, (b) sp^2 Radical, and (c) Conjugated Radical[13]

Pattern	a	b	c
E_a (4-exo):	17.6	**14.1**	40.2
E_a (5-endo):	17.6	**14.9**	40.2
ΔE_r (4-exo):	-0.8	-12.0	26.4
ΔE_r (5-endo):	-18.2	-32.1	3.6

Scheme 2. Control of the Conformational Equilibrium in Diastereomeric 3,4-Dimethylhexa-1,5-diyne-3,4-diols through the Gauche Effect[a]



[a] Relative energies are in kcal/mol at the B3LYP/6-31G** level. "Gauche" and "anti" refer to the relative positions of the vicinal OH groups.

Bis-alkynes without terminal substituents were chosen to take advantage of regioselective radical attack at the terminal carbon, which is favored sterically and electronically over attack at the internal carbon. To achieve efficient and "strain-free" conformational control in acyclic precursors, we utilized a stereoelectronic preference for two acceptor groups to be in a gauche rather than an antiperiplanar arrangement (the gauche effect).[17] This strategy relies on the well-defined conformational profile of the two-carbon bridge in the diols readily available from the reaction of metal acetylides with α,β-dicarbonyl compounds.[18] Such control is especially efficient in *meso*-diol **1a**, where the unfavorable anti conformer is ca. 4 kcal/mol higher in energy than the two identical gauche forms preorganized for the cyclization (Scheme 2).

Results

Choice of Radical Reagents. Although the choice of cyclization topology described above was guided by computational

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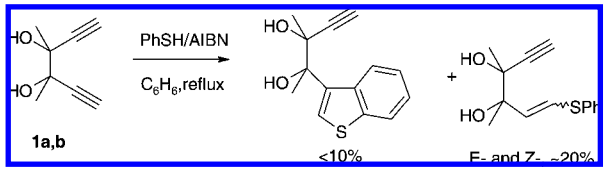
Scheme 3. Formation of Substituted Benzothiophenes from Alkynes and PhSH



analysis, its practical implementation depended on the choice of available radical agents capable of attack at the triple bond. Initially, we explored the PhSH/AIBN[19] and Bu_3SnH/AIBN systems, the latter of which we had successfully utilized for 5-exo cyclizations of enediynes.[20]

Unfortunately, Bu_3SnH-mediated reactions of acyclic diols initiated either with AIBN in refluxing benzene or with Et_3B/air at lower temperatures[21] led to complicated mixtures of products, none of which possessed the characteristic NMR signature of the 5-endo product. In a similar way, the only cyclic product that we isolated from the reactions with PhS radicals was a product of cyclization of the intermediate vinyl radical at the phenyl group of PhS moiety (Scheme 3).

Only when the two oxygen atoms in the diol **1a** were tethered through a two-atom bridge did we observe a small amount of compound **2**, which can be formed through a 5-endo-dig cyclization of a C-centered radical (Scheme 4). We also isolated a small amount of the 5-exo-dig product, apparently formed from an isomeric radical created via the alternative direction of the Bu_3Sn-radical attack at the triple bond. Even though the 5-exo product comes from a less stable primary radical, the difference in the activation barriers for the 5-exo and 5-endo cyclizations is large enough for the 5-exo path to become competitive, as long as the two vinyl radicals equilibrate under the conditions where the Curtin−Hammett principle applies. The 5-endo and 5-exo products can be either separated or hydrolyzed to converge to the same product **4**. Polymer byproducts, presumably derived from thermal decomposition/polymerization of the products of the competing 4-exo cyclization, constitute the rest of the reaction mixture.

Although the above results suggested that the 5-endo-dig cyclization may be possible, low yields and numerous byproducts complicated mechanistic studies and prompted us to search for more efficient and cleaner reactions. In this search, our attention turned to the tosyl (Ts) radical. This electrophilic species,[22] which can be generated either thermally or photochemically, is known to add regioselectively to the terminal carbon of monosubstituted alkynes with the formation of reactive vinyl radicals.[23,24] TsBr was chosen as a convenient Ts radical precursor which often provides better yields of cyclized products than TsSePh.[25] Generation of the Ts radical under the two sets of conditions is also interesting from a mechanistic perspective. While the AIBN-initiated thermal processes were expected to generate Ts radical as the major radical species, photochemical homolysis of the Ts−Br bond should generate Ts and Br radicals in equimolar amounts. Thus, the photochemical initiation should be useful for gauging the relative efficiency of the two types of radical species in promoting the cyclization. Note, however, that independent of which of the radicals initiates the cyclization, Br atom transfer to the cyclic radical formed in the cyclization step should establish a radical propagation sequence which continuously regenerates the Ts radical and, thus, should eventually take over as the main source of radical species (Scheme 5).

In marked contrast to the Bu_3SnH and PhSH-mediated reactions, the TsBr-mediated radical cyclizations of 1,5-diynes give five-membered products in acceptable yields and provide an expedient synthetic approach to substituted 1-sulfonyl-1,3-dienes. The synthetic utility of this versatile class of densely functionalized molecules is based on the presence of the sulfonyl group, which imparts electrophilic character to the diene moiety and can be readily transformed into different functionalities.[26]

Formation of small amounts of cyclic dibromides **6** along with the stereoisomeric bromosulfones **5** (Scheme 6) under photochemical conditions suggests that both Br and Ts radicals produced in the Ts−Br bond homolysis can initiate the cyclization. In this context, the formation of the same bromosulfones **5** under both thermal and photochemical conditions is important because it eliminates the possibility that cyclic bromosulfones are generated through an initial attack of Br atom at the *internal* alkyne carbon and subsequent 5-exo cyclization. Unlike photochemical activation, where both Br and Ts radicals are formed due to the Ts−Br bond homolysis, thermal activation involves the usual radical chain propagation process, where the Ts radical should be the major species reacting with the bis-alkynes (Scheme 5). From a practical point of view, however, thermally activated reactions were sluggish and led to considerably lower conversions and yields of bromosulfones **5** than their photochemical counterparts. In order to avoid possible complications caused by these factors, we concentrated on the photoinitiated reactions.

Representative results are summarized in Table 1. The regiochemistry of addition and stereochemistry of the products were determined through a combination of GHMBC and NOESY 2D NMR techniques. Complete ^1H and ^{13}C NMR assignments for the two isomers of the bromosulfone **5d** are given in Figure 2. For example, in the GHMBC spectrum of bromosulfone (*Z*)-**5d**, the proton at 6.29 ppm couples with both carbons at 93.4 and 87.8 ppm, as well as with carbons 144.6 and 159.1 ppm; therefore, its carbon at 129.8 ppm is linked to these latter two carbons, which provides the proof for the five-membered ring. On the other hand, the proton at 6.21 ppm couples with carbons at 87.8, 129.8, and 159.1 ppm; therefore, its carbon at 123.9 ppm is linked to the carbon at 159.1 ppm. Cross-peaks in the NOESY spectrum between the signals at 7.88 and 6.21 ppm and between those at 7.88 and 1.85 ppm place the Ts group on the exocyclic double bond and syn to

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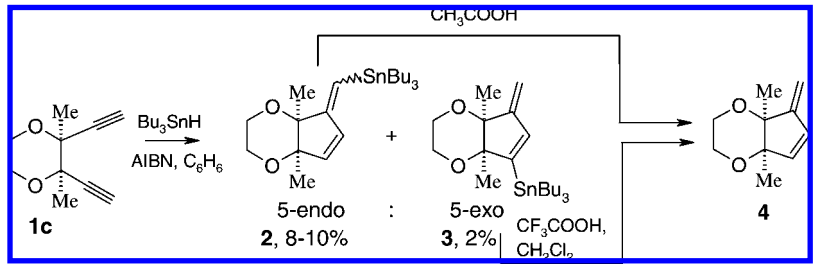
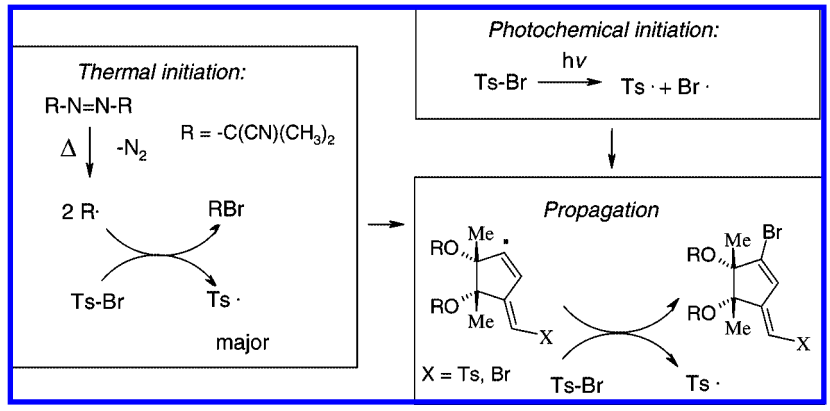
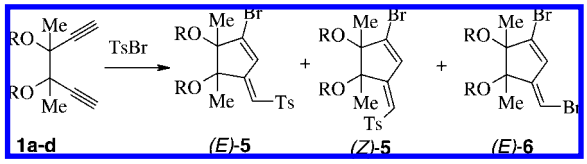
Scheme 4. Bu_3SnH-Promoted Cyclization of **1c**



Scheme 5. Comparison of Thermal and Photochemical Activation of TsBr



Scheme 6. TsBr-Mediated 5-Endo-dig Cyclization of 1,5-Diynes



the proton at 1.85 ppm, which is confirmed by a strong nuclear Overhauser effect (NOE) between 6.21 and 6.29 ppm. Of the methyl protons at 0.89 and 1.41 ppm, only the former display NOEs with 6.21 and 6.29 ppm; therefore, the 0.89 ppm proton is trans to methyl protons at 1.36 and 1.85 ppm. The presence of the ~1 Hz long-range coupling constant between the two vinyl hydrogens in the (*E*)-isomer is useful for rapid assignment of stereochemistry in the isomeric cyclic products.

Comparison of cyclization efficiencies for the *rac*- and *meso*-diols **1a** and **1b** illustrates that, in the case of photoactivation at room temperature, the gauche effect indeed leads to a noticeable increase in the cyclization efficiency in the *meso*-compound **1a** (e.g., 68% vs 51%, Table 1). The difference becomes even larger when the reaction is carried out without excess TsBr (1.0 equiv) in CH_3CN (35% vs 7%). The presence of a six-membered ring in **1c** does not have an adverse effect on the cyclization, whereas the more strained five-membered ring in **1d** disfavors formation of a second five-membered cycle in the cyclization step, especially in the thermal reaction. Trans-junction in the analogous acetonide derived from **1b** completely stopped the cyclization.

Reaction parameters were optimized using bis-alkyne **1c** (Table 2). We found that both efficiency and selectivity can be further enhanced by a proper choice of solvent. The cyclization proceeds more efficiently in benzene, where the combined yields for all cyclized products exceed 80% and exclusive (*E*)-selectivity is observed (entries 4, 6, and 7 in Table 2). If necessary, formation of the dibromide byproduct can be minimized without significant loss of efficiency (entries 8−10) by switching to such solvents as CH_3CN, CH_2Cl_2, and acetone. Formation of small amounts of the (*Z*)-isomer of sulfone **5** is observed at the higher conversion in several solvents. The higher (*E*):(*Z*) ratio at lower irradiation times suggests that most of the (*Z*)-isomer is formed from the (*E*)-isomer through photoequilibration (Figure 3).

The amount of TsBr is particularly important, as the yields substantially increase when a 3−5-fold excess of TsBr is utilized. This observation suggests the presence of unproductive pathways that intercept Ts radicals. One possibility that we will discuss later is that the rate of 5-endo-dig cyclization of the intermediate vinyl radical is slower than the rate of its fragmentation to Ts radical and diyne **1**, especially at the elevated temperatures.

Another indication of the relatively slow rate of the 5-endo-dig process is given by the lower cyclization efficiency when TsI is used as a source of Ts radicals. Under these conditions, formation of acyclic iodosulfones **7** becomes a major pathway (Scheme 7). Evidently, in this case, iodine transfer to the vinyl radical proceeds faster than the 5-endo closure—a notion that is fully consistent with the increased reactivity of TsI vs TsBr in reactions involving halogen transfer to sp^2 radicals.[27]

Another interesting feature of the TsI-mediated reactions is the formation of stereoisomeric four-membered bis-sulfones **8** and **9** (Scheme 7). Control experiments with acyclic iodosulfone **7** as the starting material confirmed that it serves as the precursor for the cyclic bis-sulfones **8** and **9**. The conversion is relatively inefficient, since the maximum yields of the bis-sulfones **8** and **9** reach 28 and 18%, respectively, after 30 min of irradiation in the presence of 2 equiv of TsI (~50% of unreacted **7**) and start to decrease slowly at longer irradiation times.

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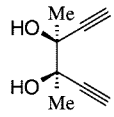
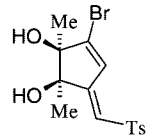
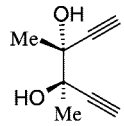
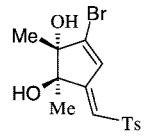
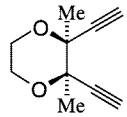
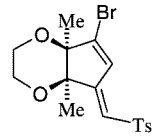
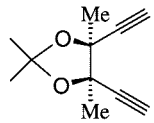
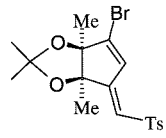
Table 1. TsBr-Mediated Cyclization of 1,5-Diynes **1a**−**d** under Thermal and Photochemical Conditions[a]

	1	*Yield (E)-5, %*	*Yield (E)-6, %*
a		 68[b] 15[c]	- -
b		 51[b] 23[c]	- -
c		 72[d] 16[e]	16 3
d		 51[f] 2[c]	24 3

[a] All photochemical experiments were carried out at room temperature. Yields are determined by ^{1}H NMR with Ph_3CH internal standard, based on initial 1,5-diyne. [b] *hν*/TsBr (3.3 equiv)/C_6H_6/2 h. [c] TsBr (2.2 equiv)/AIBN/refluxing C_6H_6/6 h. [d] *hν*/TsBr (4.7 equiv)/C_6H_6/2 h. [e] TsBr (3.0 equiv)/AIBN/refluxing C_6H_6/25 h. [f] *hν*/TsBr (4.0 equiv)/C_6H_6/4 h.

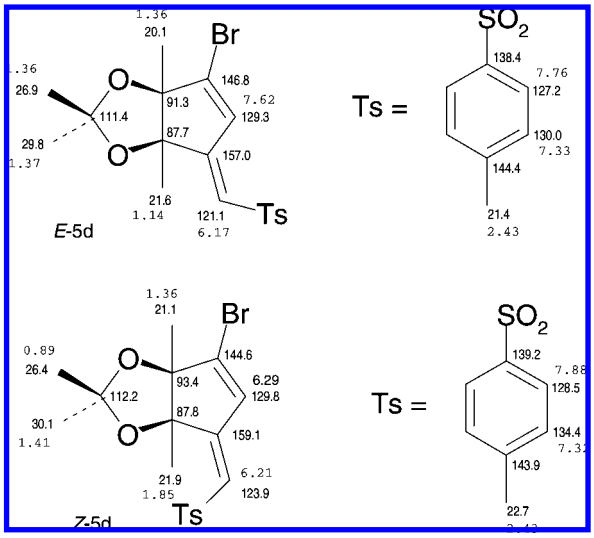


Figure 2. Complete ^{1}H and ^{13}C NMR assignments for the two isomers of the bromosulfone **5d**.

The structure of the four-membered disulfones was established by 2D NMR studies, as illustrated for the major isomer **8** in Scheme 7. In particular, coupling of protons at 7.83 and 6.47 ppm with the carbons at both 150.8 and 152.8 ppm provides proof for the four-membered ring. The nonequivalence of groups with similar connectivity indicates that the stereochemistry of the two double bonds is different. A strong NOE between protons at 6.47 and 1.34 ppm identifies the E double bond and allows for the assignment of these groups. The long-range couplings of the alkene protons agree with these assignments; i.e., the coupling 6.47−150.8 (11 Hz) is larger than the coupling 7.83−152.8 (7 Hz), and the coupling 7.83−88.9 (7 Hz) is larger than the coupling 6.47−88.8 (4 Hz).[28]

Table 2. Optimization of Reaction Conditions for Photoinitiated TsBr-Mediated Cyclization of 1,5-Diyne **1c**[a]

				yield (%)		
entry	TsBr (equiv)	solvent	time (h)	(*E*)-**5c**	(*Z*)-**5c**	(*E*)-**6c**
1	1.1	MeCN	4	24	9	11
2	1.1	C_6H_6	2	27	0	14
3	2.2	C_6H_6	2	53	0	23
4	3.3	C_6H_6	2	64	0	22
5	4.6	C_6H_6	0.5	50	0	24
6	4.6	C_6H_6	1	60	0	24
7	4.6	C_6H_6	2	72	0	16
8	4.5	MeCN	16.5	60	9	1
9	4.6	CH_2Cl_2	15	48	4	2
10	4.7	acetone	15	55	11	trace
11	4.5	CCl_4	15	29	0	10

[a] All photochemical experiments were carried out at room temperature. Yields are determined by ^{1}H NMR with Ph_3CH internal standard, based on initial 1,5-diyne **1c**. Additional data are given in the Supporting Information, Table S2.

Computational Analysis of Substituent Effects at the Cyclizations. In order to gain further insight into the reaction cascades described in the previous section, we performed computational studies of the key reaction steps. For Sn-substituted systems, UB3LYP computations with the LANL2DZ[29] basis set were used.[30] All other reactant, product, and transition-state geometries involved in radical cyclizations were optimized at the UB3LYP/6-31G** level[31] using Gaussian

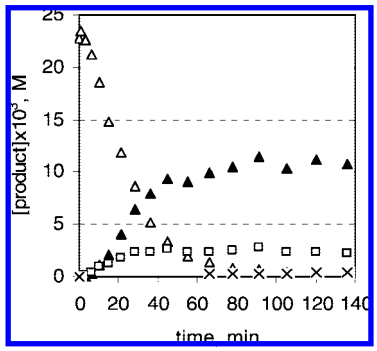
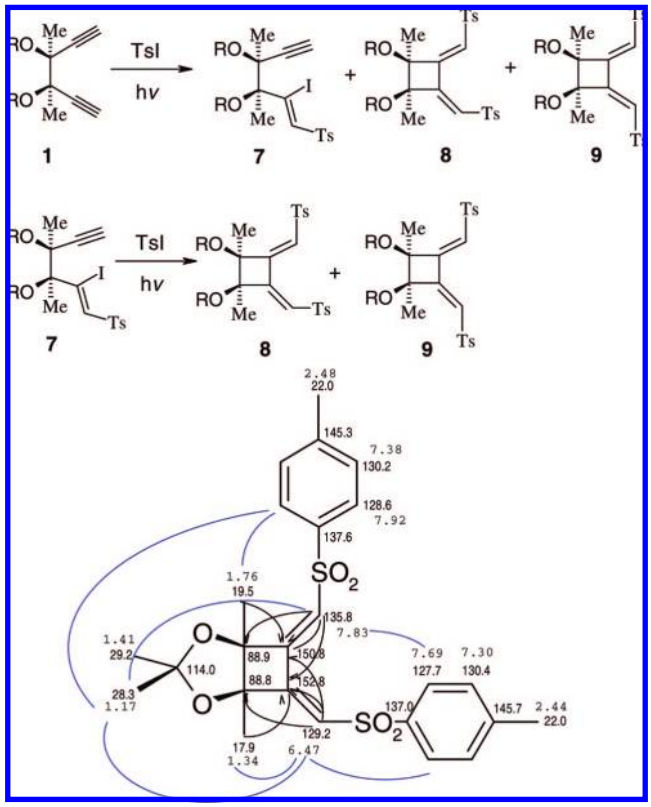


Figure 3. Kinetic data for the photoinitiated TsBr-mediated cyclization of **1c**. Reaction conditions: [**1c**] = 0.023 M, [TsBr] = 0.069 M, CD_3CN, 25 °C. △, **1c**; ▲, (*E*)-**5c**; ×, (*Z*)-**5c**; □, (*E*)-**6c**.

Scheme 7. Formation of Four-Membered Products **8** and **9** in the TsI-Mediated Reactions and NMR Assignments in the Product **8**[a]



[a] Dotted lines represent NOEs between protons, and arrows represent H1−C13 long-range couplings, from H1 to C13.

98 and 03 programs.[32] This level of theory has been shown to provide reaction barriers that agree well with the experimental values for a number of radical reactions.[33] We have found previously that computational results for the related radical cyclizations of alkynes[16] at this level are similar to those obtained with the higher level BD(T)/cc-pVDZ calculations (BD(T) = Brueckner doubles calculation with a triples contribution).[34] We further investigated the basis set effects through single-point UB3LYP/6-311+G**//UB3LYP/6-31G** and UB3LYP/cc-pVTZ calculations at the UB3LYP/6-31G** geometries. We focused on the role of substituents on the rate of 5-endo cyclization, its competition with the 4-exo path, and the origin of the high (*E*)-stereoselectivity observed in the 5-endo process.[35]

First, the computations show that, in the absence of the Ts substituent, the kinetic competition between 4-exo- and 5-endo-dig cyclizations should favor the 4-exo products (Table 3). For X = $SnMe_3$, H, Br, and SPh, the 4-exo cyclization is predicted to have a lower barrier for both syn- and anti-isomers[36] of the reacting radical. This result is fully consistent with the absence of 5-endo products and with the formation of complex reaction mixtures observed in these systems experimentally, as described earlier.

In contrast, the computational analysis of the Ts-mediated cyclization (Table 3) revealed that, although the barriers for the 5-endo and 4-exo cyclizations of the anti-isomer of the Ts-substituted vinyl radical are very close to those in the parent and other substituted systems in Table 3, *the reactivity of the syn-isomer is significantly different*. Even though both 4-exo and 5-endo barriers for the anti-isomer are decreased relative to the other examples in Table 3, the 5-endo cyclization is affected *much more* by the introduction of a syn-Ts group, which decreases the activation barrier by ∼2−3 kcal/mol relative to the parent system. In contrast, only ∼1 kcal/mol decrease is found for the respective 4-exo cyclization, and even smaller effects are observed for both 5-endo and 4-exo cyclizations of the anti-isomer. As a result, the 5-endo-dig cyclization of the syn-isomer has the lowest activation energy among the possible cyclization choices of Ts-substituted radicals. All of these computational results agree exceedingly well with the experimentally observed (*E*)-stereoselectivity (Table 2) and with the marked increase in the 5-endo cyclization efficiency for the TsBr-mediated cyclizations.[37]

(28) The tosyl group bound to 129.2 was identified from an NOE between 6.47 and 7.69. The ortho protons in the other tosyl group, at 7.92, display an NOE with the methyl protons at 1.76. The quaternary sp^2 carbons at 152.8 and 150.8 are assigned on the basis of their coupling with the protons at 1.34 and 1.76, correspondingly. In the minor component, the two tosyl groups are equivalent. An NOE between the signals at 7.84 (ortho protons at Ts) and 1.78 ppm demonstrates that the double bonds have the *Z* configuration. The couplings of proton at 6.44 ppm with carbons at 154.1 ppm (5 Hz) and with 89.8 ppm (8 Hz) further support this configurational assignment.

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Table 3. Calculated Activation and Reaction Energies for 5-Endo-dig and 4-Exo-dig Cyclizations at the UB3LYP/LANL2DZ and UB3LYP/6-31G** Levels

	5-endo		4-exo			5-endo		4-exo	
	E_a	ΔE_r	E_a	ΔE_r		E_a	ΔE_r	E_a	ΔE_r
X = H[a]	16.3	-30.7	14.0	-11.6	X = H[a]	16.3	-30.7	14.0	-11.6
X = $SnMe_3$[a,b]	17.6	-26.6	14.7	-8.0	X= $SnMe_3$[a,b]	16.6	-26.0	14.2	-8.1
X = H[c]	14.9	-32.1	14.1	-12.0	X = H[c]	14.9	-32.1	14.1	-12.0
X = Br[c,d]	13.5	-33.1	13.3	-13.1	X = Br[c,d]	14.6	-30.3	14.1	-9.6
X = Ts[c,e]	11.8	-34.0	12.8	-12.9	X = Ts[c,e]	14.6	-30.9	14.0	-10.0
X = SPh[c]	14.2	-33.1	13.8	-14.0	X = SPh[c]	14.5	-32.1	13.7	-12.1

[a] UB3LYP/LANL2DZ. [b] $\Delta E_{anti\rightarrow syn}$(reactant) = 0.4 kcal/mol; $\Delta E_{anti\rightarrow syn}$(product) = 0.2 kcal/mol. [c] UB3LYP/6-31G**. [d] $\Delta E_{anti\rightarrow syn}$(reactant) = 3.9 kcal/mol; $\Delta E_{anti\rightarrow syn}$(product) = 1.1 kcal/mol. [e] $\Delta E_{anti\rightarrow syn}$(reactant) = 3.4 kcal/mol; $\Delta E_{anti\rightarrow syn}$(product) = 0.4 kcal/mol. "Syn" and "anti" refer to the relative positions of substituent X toward the radical center in the reactant or the endocyclic double bond in the product.

Table 4. Activation and Reaction Energies (kcal/mol) for 5-Endo-dig and 4-Exo-dig Cyclizations Calculated at the UB3LYP/6-311+G**//UB3LYP/6-31G** (**I**) and UB3LYP/cc-pVTZ//UB3LYP/6-31G** (**II**) Levels

	Method	5-endo		4-exo			5-endo		4-exo	
		E_a	ΔE_r	E_a	ΔE_r		E_a	ΔE_r	E_a	ΔE_r
X = H	**I**	16.4	-27.3	16.0	-7.1	X = H	16.4	-27.3	16.0	-7.1
	II	16.3	-27.5	16.0	-7.3		16.3	-27.5	16.0	-7.3
X = Br	**I**	15.6	-27.6	15.8	-8.1	X = Br	16.3	-24.9	16.1	-6.3
	II	15.6	-27.8	15.6	-8.2		16.2	-25.2	15.8	-6.4
X = Ts	**I**	14.1	-29.0	15.0	-7.9	X = Ts	16.2	-25.9	16.1	-5.0
	II	14.2	-29.1	15.1	-7.7		16.2	-26.0	15.9	-5.2

The noticeable difference between UB3LYP/LANL2DZ and UB3LYP/6-31G** activation energies for X = H in Table 3 prompted us to investigate the basis sets effect more carefully by single-point calculations with extended basis sets of both Pople and Dunning types for the three most interesting substituents (X = H, Br, and Ts, Table 4). Gratifyingly, all of the relative trends, most importantly the predicted preference for the 5-endo cyclization of the correct stereoisomer of the Ts-substituted radical) remain the same. Interestingly, results with the larger basis sets are closer to the UB3LYP/LANL2DZ values for the parent radical. We also tested the effect of ZPVE correction (given in the Supporting Information) and found that it does not change general trends in the calculated substituent effects. In addition, one has to bear in mind that comparison of *relative* trends in reactivity, especially for the (*E*)- and (*Z*)-stereoisomers, for the same substituent X benefits from the cancelation of errors and should be even more accurate. This notion is further confirmed by the final test of the theoretical method, shown in Table 5, which provides computational analysis with a different DFT functional (BLYP). Since B3LYP and BLYP have different contributions from the HF exchange (20% vs 0%, respectively), they should be affected to a different extent by the self-interaction error (SIE), which, in a number of cases, is important for odd-electron systems. Encouragingly, the difference in the activation energies for the observed 5-endo-dig cyclization of the Ts-substituted radical and the respective 4-exo-dig path remains essentially the same when different basis

(35) In order to simplify the analysis and reduce the number of conformers in the computational studies, we omitted the hydroxyl substituents at the bridge carbons.

(36) "Syn" and "anti" refer to the relative positions of substituent X toward the radical center in the reactant or the endocyclic double bond in the product.

(37) The computations suggest that Br substitution also has an accelerating effect on the cyclization. In this case, however, one should not correlate directly the calculated differences in the barriers for the cyclizations of Ts- and Br-substituted vinyl radicals with the observed experimental bromosulfone/dibromide ratios. Although both Ts and Br radicals are generated simultaneously and in equal amounts as the result of the initial photochemical Ts−Br bond homolysis, the experimental ratios will depend not only on the cyclization rates but also on the rate of Ts and Br radical attack of the triple bond of bis-alkynes **1** and on the extent of reversibility of this reaction for Ts vs Br. In addition, reaction of the cyclized sp^2 radical with TsBr establishes a separate chain process, which keeps regenerating Ts radicals through Br atom transfer to the carbon-centered radical. Finally, as we will show below, a certain part of dibromides is transformed into bromosufones under the experimental conditions.

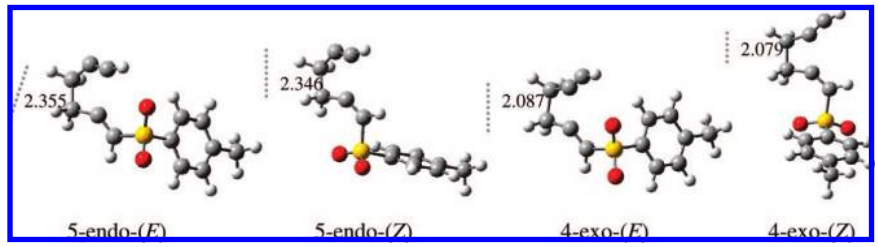
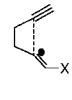
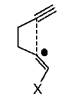


Figure 4. Computed transition-state geometries for 5-endo and 4-exo-dig cyclizations of Ts-substituted radicals along with the respective incipient C···C bond length (Å) at the UB3LYP/6-31G** level.

Table 5. Activation and Reaction Energies (kcal/mol) for 5-Endo-dig and 4-Exo-dig Cyclizations Calculated at the UBLYP/6-311+G**//UBLYP/6-31G** Level

	*5-endo*		*4-exo*			*5-endo*		*4-exo*	
	E_a	ΔE_r	E_a	ΔE_r		E_a	ΔE_r	E_a	ΔE_r
X = H	14.1	-24.8	13.8	-6.0	X = H	14.1	-24.8	13.8	-6.0
X = Br	13.7	-24.4	13.9	-6.4	X = Br	14.2	-21.4	14.1	-2.4
X = Ts	11.8	-25.7	13.4	-6.0	X = Ts	14.2	-22.1	14.4	-2.7

Table 6. Intrinsic, $\Delta E_o^{\ddagger}$, and Thermodynamic, $\Delta E_{thermo}^{\ddagger}$, Contributions to Reaction Barrier, ΔE_a (in kcal/mol), for 5-Endo-dig and 4-Exo-dig Cyclizations of the Ts-Substituted Radicals at the UB3LYP/6-311+G**//UB3LYP/6-31G** Level

	5-endo-dig				4-exo-dig			
								
	$\Delta E_o^{\ddagger}$	$\Delta E_{(thermo)}^{\ddagger}$	$\Delta E_o^{\ddagger}$	$\Delta E_{(thermo)}^{\ddagger}$	$\Delta E_o^{\ddagger}$	$\Delta E_{(thermo)}^{\ddagger}$	$\Delta E_o^{\ddagger}$	$\Delta E_{(thermo)}^{\ddagger}$
X=H	28.4	12.0	28.4	12.0	19.4	-3.4	19.4	-3.4
X=Br	27.7	-12.1	27.3	-11.0	19.6	-3.8	19.1	3.0
X=Ts	26.6	-12.5	27.7	-11.5	18.7	-2.7	18.4	-2.5

sets and functionals are compared (1.7 kcal/mol for UB3LYP/6-311+G**//6-31G** level, 1.4 kcal/mol for UB3LYP/cc-pVTZ//6-31G** level, and 1.6 kcal/mol for UBLYP/6-311+G**//6-31G** level).[38]

In order to gain further insight into the origin of the Ts substitution effect, we separated intrinsic and thermodynamic contributions to the reaction barrier using Marcus theory,[39] which, although originally developed for electron-transfer reactions, has been successfully applied to a wide variety of organic reactions.[40–42]This treatment provides an estimate for a barrier for a hypothetical thermoneutral reaction (intrinsic barrier) in the absence of thermodynamic bias. The difference between intrinsic and real barriers gives the thermodynamic contribution to the observed reaction barrier. The results of the Marcus analysis are summarized in Table 6. Importantly, both the intrinsic barrier and the thermodynamic contribution are favorable for the experimentally observed 5-endo-dig pathway. This result suggests that the reason for the higher efficiency in the case of the Ts-substituted vinyl radical is not only the higher exothermicity of reactions where the radical center and sub-

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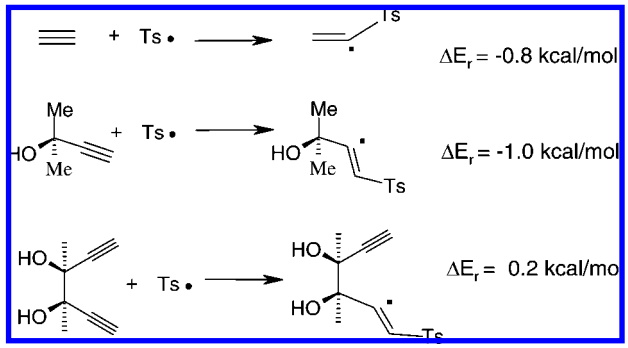
(40) (a) Shaik, S. S.; Schlegel, H. B.; Wolfe, S. *Theoretical Aspects of Physical Organic Chemistry*; John Wiley and Sons: New York, NY, 1992; pp 33−44. (b) Pross, A. *Theoretical and Physical Principles of Organic Reactivity*; Wiley: New York, 1995.

Scheme 8. B3LYP/6-31G** Reaction Energies for Addition of the Ts Radical to Model Alkynes



stituent X are syn-periplanar, but also a specific electronic effect that selectively stabilizes the respective transition state.[43]

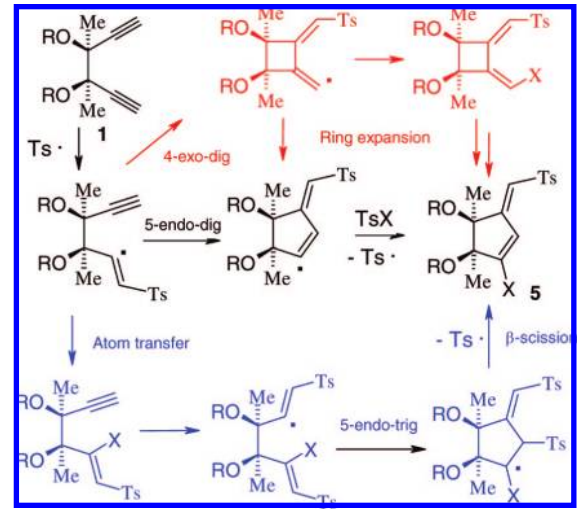
Structures of the calculated 4-exo and 5-endo transitions states are given in Figure 4. Earlier transition states are observed for more exothermic reactions, as expected from the Hammond−Leffler postulate.[44] Comparison of relative energies for the vinyl radical stereoisomers suggests that the higher reactivity of the (*E*)-isomer is due to its selective destabilization relative to the (*Z*)-isomer. Although the Curtin−Hammett analysis of the relative energies of the (*Z*)- and (*E*)-isomers of Ts-substituted radicals suggests that the (*E*)-isomer may be too high in energy to contribute to the observed cyclization in *the parent system,* the presence of propargylic Me substituents in the bis-alkynes **1** should decrease the energy difference through selective steric destabilization of the (*Z*)-isomer.

Overall, comparison of the experimental stereochemistry/reactivity and competition between the possible cyclization pathways with the above computational values validates the choice of theoretical methods. Excellent agreement between experiments and computations should provide further impetus for combining theory and experiment in the design of new radical processes.

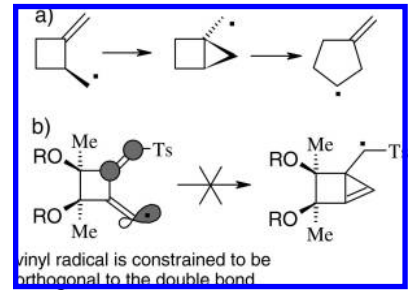
Mechanistic Questions

On the Relative Efficiency of Radical Addition and Fragmentations in Ts-Promoted Reactions. In order to understand the reasons for the lower efficiency of thermally activated TsBr-mediated reactions, we also carried out computational analysis of addition of the Ts radical to several alkynes. Although the absolute values for the calculated reaction energies should be regarded with caution because of the lack of quantitative experimental data for calibration of the computational methods, the results suggest that the reversibility of Ts radical addition to the triple bond should be taken into account because all three isodesmic reactions given in Scheme 8 are essentially thermoneutral. Since entropy for addition reactions is negative, an increase in the reaction temperature should shift the equilibrium away from the vinyl radicals and disfavor the cyclization. In fact, β-elimination of sulfonyl radicals turns out to be sufficiently efficient for applications in a number of interesting radical cascades.[45] Competition between the fragmentation and cyclization of the vinyl Ts-substituted radicals may also explain why an excess of TsBr is needed to achieve high conversions.

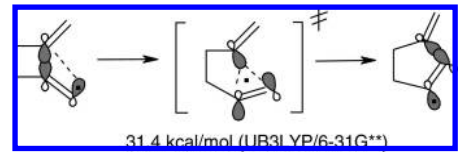
Scheme 9. Alternative Pathways for the Formation of Cyclic Sulfones **5**



Scheme 10. (a) Ring Expansion of the Homoallylic Radical Product of 4-Exo-trig Cyclization into the Formal 5-Endo-trig Product, and (b) Stereoelectronic Objections to the Analogous Ring Expansion of the 4-Exo-dig Products



Scheme 11. Hypothetical Ring Expansion through Direct 1,2-Carbon Shift



Alternative Cyclization Mechanisms. Although the 5-endo-dig cyclization provides the most direct explanation to the observed experimental results, and although the DFT analysis of the 5-endo-dig potential energy surface agrees very well with both the increased efficiency and the (*E*)-stereoselectivity

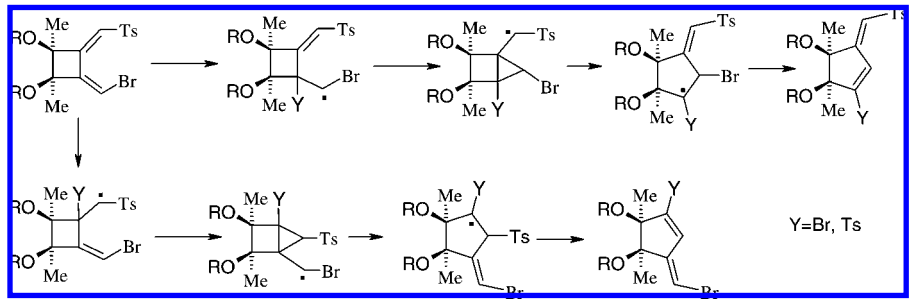
(41) For the extension of Marcus theory to describe processes that have no identity reactions such as internal rotation and conformational rearrangements, see: (a) Chen, M. Y.; Murdoch, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 4735. For other selected examples: (b) Gas-phase proton-transfer: Magnoli, D. E.; Murdoch, J. R. *J. Am. Chem. Soc.* **1981**, *103*, 7465. (c) Group transfer reactions involving radicals: Newcomb, M.; Makek, M. B.; Glenn, A. G. *J. Am. Chem. Soc.* **1991**, *113*, 949. (d) Reactions of carbonyl compounds: Guthrie, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 5529. (e) Electron transfer dynamics in synthetic DNA hairpins: Lewis, F. D.; Kalgutkar, R. S.; Wu, Y.; Liu, X.; Liu, J.; Hayes, R. T.; Miller, S. E.; Wasielewksi, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 12346. (f) Pericyclic reactions: Aviyente, V.; Houk, K. N. *J. Phys. Chem. A* **2001**, *105*, 383. (g) Alabugin, I. V.; Manoharan Breiner, B.; Lewis, F. *J. Am. Chem. Soc.* **2003**, *125*, 9329.

(42) For the first applications of Marcus theory to radical cyclizations, see refs 13 and 16. See also: (a) Wu, C. W.; Ho, J. J. *J. Org. Chem.* **2006**, *71*, 9595. (b) Yu, Y.-Y.;; Fu, Y.; Xie, M.; Liu, L.; Guo, Q.-X. *Org. Chem.* **2007**, *72*, 8025.

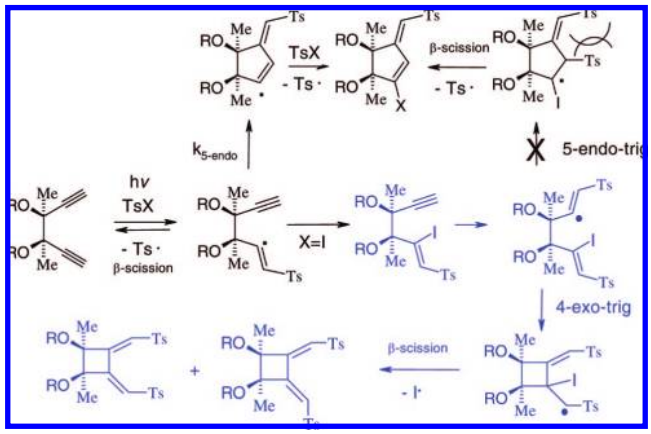
(43) Further analysis of electronic effects responsible for this remarkable change in reactivity goes beyond the scope of this paper and will be reported in due course.

(44) (a) Leffler, J. E. *Science* **1953**, *117*, 340. (b) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

Scheme 12. Hypothetical Intramolecular Pathway for the 4-Exo/5-Endo Ring Expansion



Scheme 13. Transformation of Acyclic Halosulfones into Cyclic Products Promoted by Ts Radicals



of Ts-mediated cyclizations, other mechanistic possibilities for the formation of 5-endo-dig products can be suggested *a priori*. Such possibilities can be broadly divided into two groups: (a) ring expansion of the 4-exo-dig products (the top part of Scheme 9) and (b) a sequence of reactions that involve (i) formation of acyclic products due to formal addition of TsX (or Bu_3SnH) to one of the triple bonds (vide infra), (ii) attack of Ts radical at the second triple bond, (iii) 5-endo-trig radical cyclization, and (iv) termination through β-scission and loss of Ts radical (the bottom part of Scheme 9). We will briefly discuss these alternative mechanistic scenarios in the context of available experimental and computational data.

Ring-Expansion of 4-Exo Products. Although the relatively low barriers for the formation of 4-exo-dig cyclizations suggest that their involvement should be considered, three observations argue against this pathway for the formation of the Ts-substituted 5-endo products **5**.

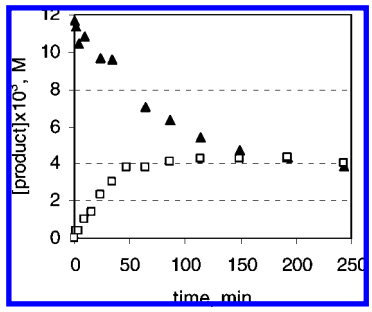


Figure 5. Kinetic data for the TsBr-mediated photoinduced transformation of cyclic dibromide (*E*)-**6c** into the bromosulfone (*E*)-**5c**. Reaction conditions: [(*E*)-**6c**] = 0.012 M, [TsBr] = 0.048 M, C_6D_6, 25 °C. ▲, (*E*)-**6c**; □, (*E*)-**5c**.

First, although the Dowd−Beck with 4-exo/5-endo expansion sequence, which involves intramolecular radical addition to the exocyclic double bond of the 4-exo product with formation of a bicyclo[4.1.0] intermediate that is converted to the 5-endo product through cyclopropyl ring opening, is common for trigonal cyclizations,[46] the first step of such a sequence is forbidden for the digonal cyclization product shown in Scheme 10, due to stereoelectronic considerations. Not only is the vinyl radical in the 4-exo-dig product constrained to be orthogonal to the target π-system, but their reaction would also yield a very strained product.

Due to the above stereoelectronic restrictions, a direct 1,2-carbon shift remains the only reasonable alternative. However, computational analysis suggests that the activation energy for the 1,2-shift should be prohibitively large for a reaction proceeding at room temperature. The 31.4 kcal/mol UB3LYP/6-31G** barrier calculated for the simple vinyl radical is unlikely to decrease sufficiently with the Ts substitution to allow such ring expansion under the reaction conditions (Scheme 11).[47] The larger barrier for 1,2-migrations in radicals relative to that in cations is not surprising because the 3e transition state for the radical 1,2-shift is destabilized relative to its 2e counterpart for the cationic 1,2-shift.

The final possible path for the 4-exo/5-endo ring expansion is an intermolecular process that involves reaction of the 4-exo product with another molecule of TsX (Scheme 12). However, in order to account for the experimentally observed products, such a sequence has to include radical attack at the *internal* carbon of the exocyclic double bond, rather than attack at the *external* carbon, which produces an allylic radical. Moreover, since the attacking radical species Y can be either Ts or Br, this should lead to the formation of bis-Ts substituted cyclopentenes as well isomeric bromosulfones with Br at the exocyclic double bond.[48] Neither of these two types of products was observed.

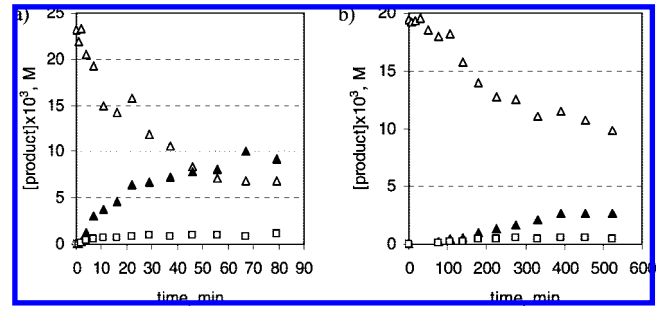
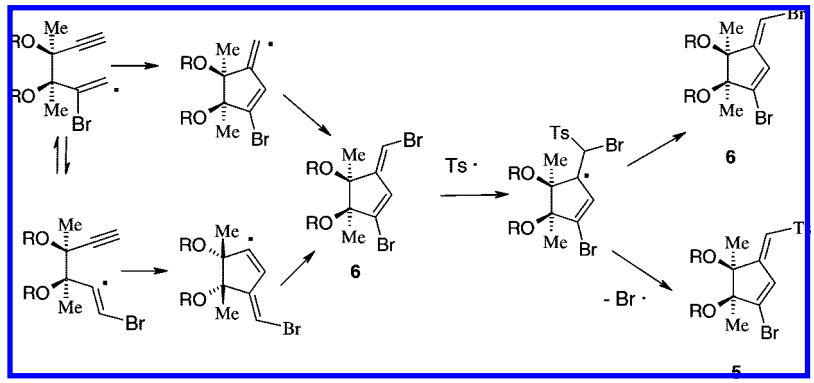


Figure 6. (a) Kinetic data for the photoinduced reaction of **1b** with TsBr. Reaction conditions: [**1b**] = 0.023 M, [TsBr] = 0.069 M, C_6D_6, 25 °C. △, **1b**; ▲, (*E*)-**5b**; □, (*E*)-**6b**. (b) Kinetic data for the thermal reaction of **1c** with TsBr. Reaction conditions: [**1c**] = 0.019 M, [TsBr] = 0.057 M, [AIBN] = 0.0068 M, C_6D_6, 75 °C. △, **1c**; ▲, (*E*)-**5c**; □, (*E*)-**6c**.

Scheme 14. Possible Mechanisms for the Formation of Dibromides **6** and Their Transformation to Bromosulfones **5**



Addition/5-Endo-trig/β-Scission Cascade. Since we observed formation of acyclic addition products in reactions with PhSH, Bu_3SnH, and TsI, we also considered the possibility that 5-endo products in TsBr-mediated reactions were formed through reaction of the remaining triple bond of the addition products with Ts radical, followed by 5-endo-trig cyclization and β-scission (Scheme 13). Even though we do not find such intermediates in reactions with TsBr, one can make an argument that they react too fast to be accumulated.

Fortunately, the formation of acyclic β-halosulfone intermediates **7** in the TsI-mediated reactions of bis-alkynes provided an opportunity to probe this scenario directly by allowing us to test the viability of such an addition/5-endo-trig/β-scission cascade experimentally. We observed that, even though the acyclic products are formed efficiently in the TsI-mediated process, their accumulation does not lead to the formation of five-membered cyclic products **5**. This outcome is contrary to the expectations based on the mechanism in Scheme 13, where the cyclic products are derived from the acyclic addition products.

Even more definitive evidence against the multistep addition/5-endo-trig/β-scission and in favor of direct 5-endo-dig closure is provided by the formation and structure of the four-membered products observed only in the case of TsI-mediated reactions (but not for their TsBr-mediated counterparts).

Not only formation of a cyclobutane ring but also the fact that *two Ts groups were introduced under these conditions* provide significant insight into the mechanistic picture. Additional experiments verified that such compounds were indeed produced from the acyclic products through an addition/cyclization/β-scission cascade but that the selectivity of this cascade is different, since this reaction follows the 4-exo-dig direction instead of the 5-endo-trig closure. Different selectivity of the cyclization step results in a different β-scission direction, which eliminates iodine instead of Ts radical (Scheme 13).

The final plausible alternative for the formation of bromosulfones **5** involves transformation of cyclic dibromides **6** through addition of Ts radical to the exocyclic double bond, followed by β-scission of a Br atom (Scheme 14). Although analysis of the experimental data at low conversions and computational barriers argues against this pathway as the *major* route to the cyclic bromosulfones, it is possible that this path occurs to some extent under the photochemical conditions, where both Br and Ts radicals are generated simultaneously through the Ts−Br bond homolysis. Indeed, our independent experiments on the transformation of the cyclic dibromides to the respective bromosulfones found that this reaction does occur on the time scale of our experiments. Although yields of bromosulfones in this reaction are lower than for the reaction of the acyclic bis-diynes **1**, and although the transformation of dibromides **6** is slower than direct formation of bromosulfones through the 5-endo-dig path, the secondary chemistry of dibromides should provide an additional pathway to the bromosulfone products.

A more thorough analysis of the evolution of product yields with increasing irradiation time confirms that bromosulfones and dibromides are formed in parallel (Figure 6). Experiments illustrated in Figure 5 also gave an estimate for the contribution (<30% for **1c**) of the dibromide−bromosulfone transformation to the yield of the bromosulfones. This value should be considered as an upper limit, because the above experiments start with pure dibromides at concentrations much higher than those occurring transiently in the reaction of bis-alkynes.

Conclusion

Although 5-endo-dig radical cyclizations require careful experimental design, it is now clear that this stereoelectronically favorable but, until now, overlooked process is experimentally feasible and can be utilized in synthetically useful transformations.[49]

(45) Selected examples: (a) Xiang, J.; Evarts, J.; Rivkin, A.; Curran, D. P.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 4163. (b) Van Dort, P. C.; Fuchs, P. L. *J. Org. Chem.* **1997**, *62*, 7142. (c) Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486. (d) Xiang, J.; Jiang, W.; Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1997**, *119*, 4123. (e) Ouvry, G.; Zard, S. Z. *Chem. Commun.* **2003**, 778. (f) Ouvry, G.; Zard, S. Z. *Synlett* **2003**, 1627. (g) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 1209. (h) Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1998**, *37*, 2864. (i) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H.; Hershberger, J. *Organometallics* **1987**, *6*, 1414. (j) Russell, G. A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622. (k) Russell, G. A.; Ngoviwatchai, P.; Wu, Y. W. *J. Am. Chem. Soc.* **1989**, *111*, 4921. (l) Wang, C.; Russell, G. A. *J. Org. Chem.* **1999**, *64*, 2346.

(46) (a) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565. (b) Dowd, P.; Choi, S. C. *Tetrahedron* **1989**, *45*, 77. (c) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091. For the computational analysis, see: (d) Ardura, D.; Sordo, T. L. *Tetrahedron Lett.* **2004**, *45*, 8691.

(47) For a similar observation of significant increase in the activation energies of such 1,2-carbon shifts in sp^2-hybridized systems, see: Lewis, K. D.; Matzger, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 9968.

(48) Also, from a more general perspective, it is hard to reconcile the increased efficiency that is observed only for the Ts radical-mediated reactions with a scenario where the above paths provide a major road to the 5-endo products.

(49) Our initial experiments suggest that cyclic bromosulfones formed in this reaction have diverse reactivity.

The presence of 5-endo-dig products under thermal conditions unambiguously established that 5-endo-dig cyclization of Ts-substituted vinyl radicals is experimentally feasible. The cyclization becomes much more efficient under photochemical conditions due to the combination of two factors: a decrease in the importance of β-scission at the lower temperatures and partial "recycling" of dibromides to bromosulfones. Reactions of TsI lead to the formation of acyclic iodosulfones as the major primary products. Under photochemical conditions, these compounds undergo a secondary radical process that transforms them into four-membered cyclic bis-sulfones.

Further studies of the reasons for the apparent increase in the 5-endo vs 4-exo selectivity in the TsBr-mediated reactions as well as the scope and generality of this process are in progress. More work is needed to solve the problems that originate from the reversibility of the Ts radical addition to the alkyne moiety. However, there is no doubt that the 5-endo-dig cyclizations of carbon-centered radicals are possible, and the stereoelectronic considerations at the heart of the Baldwin rules remain untarnished!

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Supporting Information Available: Yields and kinetic data for a larger selection of experimental conditions for the cyclizations, general experimental procedures, synthesis of starting materials, ^{1}H and ^{13}C NMR spectra, Cartesian coordinates and energies of conformers of bis-alkynes **1a** and **b**, as well transition states and products of 4-exo- and 5-endo cyclizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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