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5-Exo-dig Radical Cyclization of Enediynes: The First Synthesis of Tin-Substituted Benzofulvenes

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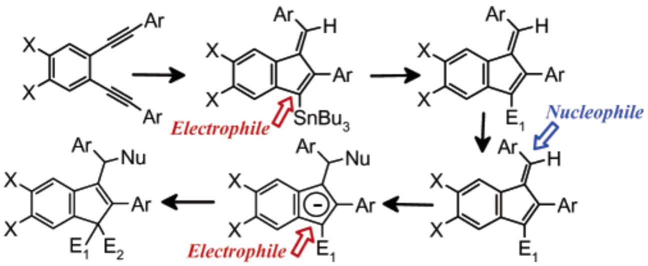
ABSTRACT



Bu_3Sn-mediated 5-exo-dig radical cyclization of diaryl enediynes provides a mild and efficient approach to tin-substituted fulvenes. Further synthetic opportunities opened by this process and general factors responsible for the observed regio- and stereoselectivity are outlined.

The astounding biological activity of natural enediyne antibiotics[1] is based on the transformation of (*Z*)-3-ene-1,5-diyne moiety into reactive *p*-benzyne diradicals (the Bergman cyclization).[2] It has been suggested that these diradical species can also be used as radical initiators in polymerization of enediynes[3] and other substrates.[4] However, a clear understanding of how the enediyne moiety itself reacts with radical reagents is still lacking. In a recent study, Matzger and co-workers provided evidence that, in the case of radical polymerization of enediynes, the picture is rather complex and involves formation of fulvenes through either 5-exo or 5-endo radical cyclizations.[5] König et al. reported an example of a 5-exo-dig cyclization in reaction of an enediyne with stable TEMPO (tetramethylpiperidyl oxide) radical,[6a] while Anthony et al. showed that intramolecular radical cyclizations are highly sensitive to substitution.[6b]

In this paper, we report that Bu_3SnH-promoted radical cyclizations of diaryl enediynes follow the 5-exo-dig pathway and can be efficient and selective. Moreover, such cyclizations lead to the preparation of versatile organometallic benzofulvene reagents capable of numerous synthetic transformations.

This reaction was discovered in a search for a mild method for the synthesis of fulvenes such as **15**,[7] which cannot be prepared through interaction of enediynes with electro-

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[1] *Enediyne Antibiotics as Antitumor Agents*; Borders, D. B., Doyle, T. W., Eds.; Marcel Dekker: New York, 1995.

[2] Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660.

[3] It was suggested that Bergman polymerization of neat enediynes leads to formation of polymeric polynaphthalene networks with increased thermal increased stability. Chen, X.; Tolbert, L. M.; Hess, D. W.; Henderson, C. *Macromolecules* **2001**, *34*, 4104. Shah, H. V.; Babb, D. A.; Smith, D. W., Jr. *Polymer* **2000**, *41*, 4415. John, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 5011. Lewis, K. D.; Rowe, M. P.; Matzger, A. J. *Tetrahedron* **2004**, in press.

[4] Rule, J. D.; Wilson, S. R.; Moore, J. S. *J. Am. Chem. Soc.* **2003**, *125*, 12992.

[5] Johnson, J. P.; Bringley, D. A.; Wilson, E. E.; Lewis, K. D.; Beck, L. W.; Matzger, A. *J. Am. Chem. Soc.* **2003**, *125*, 14708.

[6] (a) König, B.; Pitsch, W.; Klein, M.; Vasold, R.; Prall, M. Schreiner, P. R. *J. Org. Chem.* **2001**, *66*, 1742. (b) Scott, J. L.; Parkin, S. R.; Anthony, J. E. *Synlett* **2004**, 161.

[7] This molecule is a proposed intermediate in the transformation of enediynes to indenes under photoreductive conditions, the process which is different in mechanism from reactions reported in this paper: Alabugin, I. V.; Kovalenko, S. V. *J. Am. Chem. Soc.* **2002**, *124*, 9052. Acyclic addition products constitute the rest of the reaction mixture.

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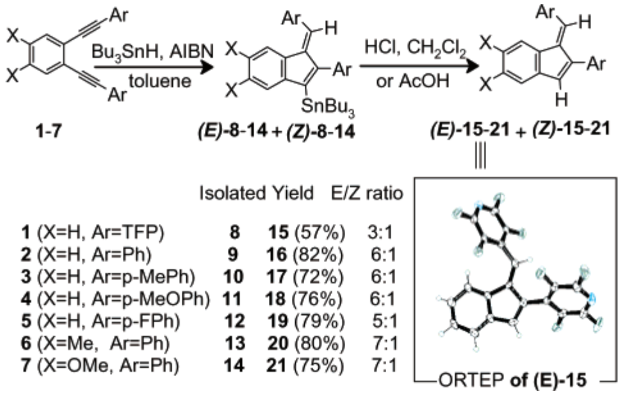
philes,[8,9] nucleophiles,[8] or Li naphthalenide[8] because of the sensitivity of the tetrafluropyridynyl (TFP) moiety to reductive conditions. In contrast, the Bu_3SnH-induced radical cyclization[10] is fully compatible with the highly reactive TFP group and leads to a 57% yield of 3/1 mixture of two stereoisomeric fulvenes **8**, which can be hydrolyzed to the requisite protodestannylated fulvenes **15** in almost quantitative yield (Scheme 1).

Scheme 1. Radical Cyclizations of 1,2-Bis(arylethynyl)benzenes



		Isolated Yield	E/Z ratio
1 (X=H, Ar=TFP)	**8**	**15** (57%)	3:1
2 (X=H, Ar=Ph)	**9**	**16** (82%)	6:1
3 (X=H, Ar=p-MePh)	**10**	**17** (72%)	6:1
4 (X=H, Ar=p-MeOPh)	**11**	**18** (76%)	6:1
5 (X=H, Ar=p-FPh)	**12**	**19** (79%)	5:1
6 (X=Me, Ar=Ph)	**13**	**20** (80%)	7:1
7 (X=OMe, Ar=Ph)	**14**	**21** (75%)	7:1

Intrigued by the mild conditions, we expanded the study to include a larger number of benzannelated enediynes with terminal aromatic substituents. In contrast to the cyclization of the parent 1,2-diethynyl benzene and its bis-TMS derivative, the cyclization of diaryl enediynes proceeds in good yields leading in every case to predominant formation of only one fulvene isomer (Scheme 1) through a pathway that involves regioselective Bu_3Sn radical attack at the internal acetylene carbon of the enediyne moiety followed by 5-exo-dig cyclization of the intermediate vinyl radical (Scheme 2).

The observed selectivity is interesting, taking into account that addition of Bu_3Sn radical to the weakly polarized triple bonds is unlikely to be regioselective per se and should produce both "α-type" and "β-type" radicals as illustrated in Scheme 2. Although the β-radical produced from 1,2-diethynyl benzene is considerably less stable than the respective α-radical, this difference decreases dramatically in enediynes **1**−**7** due to the stabilizing effect of terminal aryl substituents (Table 1). Taking into account the reversibility of Bu_3Sn addition,[11,12] both α- and β-radicals are likely to thermally equilibrate with starting material and, thus, the observed reaction selectivity indicates that 5-exo-dig cyclization has a lower activation barrier than the competing 6-endo-dig and 5-endo-dig cyclizations (Scheme 2).

Scheme 2. Competing Reaction Cascades Following Addition of a Radical to the Enediyne Moiety

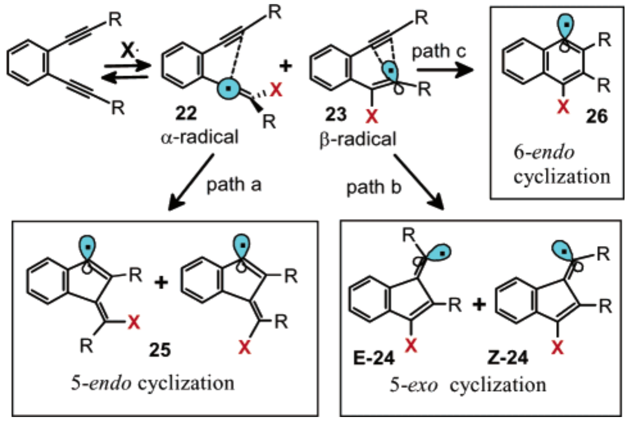
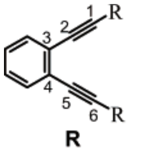
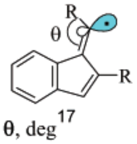


Table 1. Relative Energies of α- and β-Radicals Formed from 1,2-Diethynylbenzene and Its Diaryl Derivatives, Difference in Energies between the (*E*)- and (*Z*)-Isomers of Fulvene Products, and Geometries of Respective Fulvene Radicals at the UB3LYP/3-21G* Level[a]

 **R**	$\Delta E_{\alpha\beta}$ kcal mol^{-1}	ΔE_r (5-*exo*) kcal mol^{-1}	ΔE_{EZ}, kcal mol^{-1}	 **θ, deg**
H, **25**	-10.9	-37.8	NA	137.6
TFP, **1**	-3.6	-32.5	0.2	177.8
Ph. **2**	-0.8	-33.1	1.8	156.9
p-OMe-Ph, **4**	-0.5	-33.1	1.9	152.7
p-F-Ph, **5**	-0.9	-33.0	1.6	154.7

[a] See Supporting Information for more details.

Although none of the three cyclization pathways is forbidden by the Baldwin rules,[12] the relative unimportance of the 5-endo pathway is readily explained by stereoelectronic factors involved in the cyclization processes. The α-radical[13] has to lose its conjugation with the central aromatic ring in order to reach the in-plane π-bond in the bond-forming step. By contrast, in 5-exo- and 6-endo cyclizations of the β-radical, the radical center is predisposed for the cyclization by being coplanar and spatially close to the in-plane π-orbital.

On the other hand, the competition between 5-exo and 6-endo cyclizations of the β-radical is more subtle: the potential energy barrier for the 5-exo-dig cyclization of the parent 1,3-hexadiene-5-yn-1-yl radical was calculated to be only 0.9 kcal/mol less at the CASSCF/6-31(d) level than that for its 6-endo-dig cyclization,[14] and both of these pathways

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(8) Whitlock, H. W.; Sandvick, P. E.; Overman, L. E.; Reichard, P. B. *J. Org. Chem.* **1969**, *34*, 879.

(9) Schreiner, P. R.; Prall, M.; Lutz, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5757.

(10) For the transformation of enediynes to fulvenes under radical-cationic conditions, see: Ramkumar, D.; Kalpana, M.; Varghese, B.; Sankararaman, S.; Jagadeesh, M. N.; Chandrasekhar, J. *J. Org. Chem.* **1996**, *61*, 2247.

(11) Kuivila, H. G.; Sommer, R. *J. Am. Chem. Soc.* **1967**, *89*, 5616. Stork, G.; Mook, R. *Tetrahedron Lett.* **1986**, *27*, 4529.

(12) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(13) For analysis of electronic structure of α-radical produced in the radical hydrostannation of phenylacetylene, see: Petraco, N. D. K.; Modarelli, D. A.; Cochran, J. C. *Synth. React. Inorg. Met.-Org. Chem.* **2001**, *31*, 757.

(14) Olivella, S.; Solé, A. *J. Am. Chem. Soc.* **2000**, *122*, 11416.

were observed experimentally in related substituted systems. For example, Anthony et al. found an example of predominant 6-endo cyclization of a more constrained enediyne,[6b] whereas Rainier and Kennedy[15] reported formation of mixtures resulted from 5-exo- and 6-endo-dig cyclizations of vinyl radicals produced by radical addition of Bu_3SnH to arylisonitriles with pendant alkynes. On the other hand, Schmittel et al. found that triplet diradicals formed photochemically from enyne-carbodiimides and enyne-ketenimines undergo selective 5-exo-dig cyclization.[16] A similar observation was made by König et al. who provided the only literature example of a radical 5-exo cyclization of an enediyne[6a] reported before our work was started. The combination of the above computational data and literature precedents suggests that the 5-exo-dig cyclization is intrinsically favorable. Moreover, the presence of bulky aryl substituents in the diaryl enediynes studied in this paper should further disfavor their 6-endo-dig cyclization and contribute to the observed selectivity.

Assuming that α- and β-radicals thermally equilibrate with starting material, the nature of reaction products is likely to be determined by competition between H-abstraction by the more thermodynamically stable and, thus, more abundant, α-radicals and 5-exo-cyclization of β-radicals. The balance can be rather subtle as illustrated by the results for the TFP and Ph enediynes **1** and **2**, where lesser stabilization of the β-radical correlates with the decreased yield of the cyclized product (Scheme 1, Table 1).

The modest *E*/*Z* stereoselectivity is consistent with the less hindered approach by the H-atom donor, which, in turn, is determined by hybridization and geometry of the fulvene radical. Conjugation with terminal aryl groups leads to rehybridization and linearization at the radical center relative to the unsubstituted vinyl radical. This effect is more pronounced in the TFP-substituted radical approaching the perfectly linear geometry of vinyl cations.[18] As a result, the stereoselectivity of H-abstraction by the TFP radical is slightly lower than by the phenyl- and *p*-anisyl-substituted radicals, which are slightly bent in a way that favors formation of (*E*)-fulvene (Figure 1, Table 1).

From a practical perspective, tin-promoted 5-exo-dig radical cyclization of enediynes provides a facile approach to versatile organometallic reagents, which can be used in the synthetic routes illustrated in Scheme 3. For example, the high reactivity of the Bu_3Sn moiety in fulvene **26** can be utilized in reactions with electrophiles such as iodine and in Stille coupling with aryl iodides under Corey's conditions.[19] X-ray analysis of the Stille coupling and iodination products further confirmed the 5-exo-cyclization mode and the regio- and stereoselectivity of the reaction (Scheme 3).

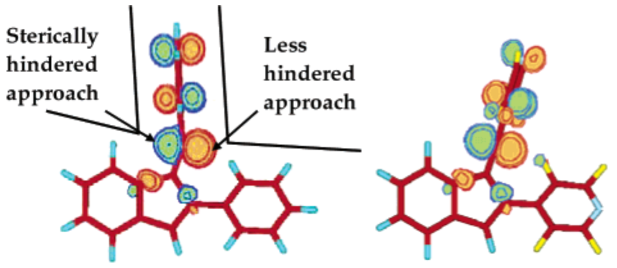
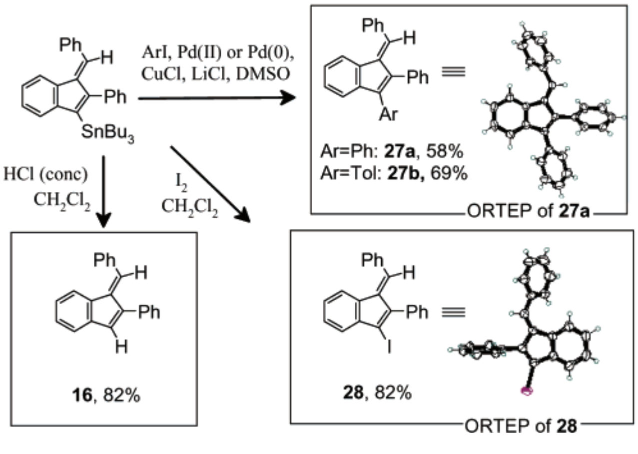


Figure 1. Calculated spin density and geometry of fulvene radicals (*Z*)-**24** (R = Ph, on the left; R = TFP, on the right) at the B3LYP/3-21G* level.

Scheme 3. Reactions of Sn-Substituted Fulvenes with Electrophiles



Furthermore, one can expand the synthetic utility of these processes by utilizing the intrinsic propensity of the fulvene moiety toward facile addition of nucleophilic reagents to the polarized exocyclic double bond (Scheme 4).[20] The intermediate cyclopentadienyl anion **29** can be quenched by aqueous workup or trapped by a different electrophile (e.g., TMSCl). The combination of synthetic sequences outlined in Schemes 3 and 4 should allow for a sequential electrophile/

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(15) Rainier, J. D.; Kennedy, A. R. *J. Org. Chem.* **2000**, *65*, 6213.

(16) Schmittel, M.; Rodriguez, D.; Steffen, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2152.

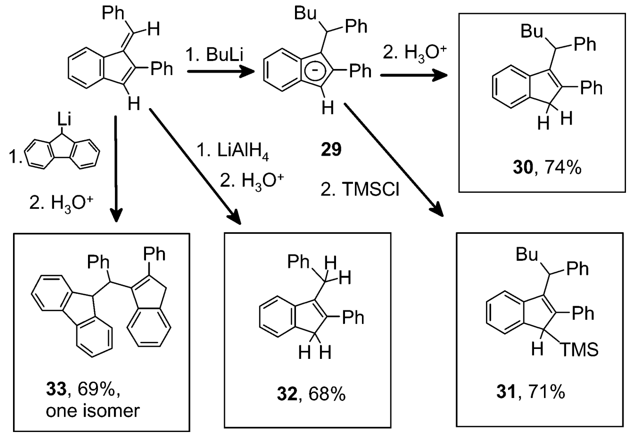
(17) Only (*E*)-isomers of aryl-substituted radicals **24** are minima at the B3LYP/3-21G* potential energy surface. The calculations were performed using the Gaussian 98 suite of programs: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

(18) A similar correlation of hybridization of radical center with acceptor ability of substituents has been observed earlier. Galli, C.; Guarnieri, A.; Koch, H.; Mencarelli, P.; Rappoport, Z. *J. Org. Chem.* **1997**, *62*, 4072. Galli, C.; Rappoport, Z. *Acc. Chem. Res.* **2003**, *36*, 580.

(19) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

(20) Recent applications of similar reactions in organometallic chemistry: Shapiro, P. J.; Kane, K. M.; Vij, A., Stelck, D.; Matare, G. J.; Hubbard, R. L.; Caron, B. *Organometallics* **1999**, *18*, 3468. Rogers, J. S.; Lachicotte, R. J.; Bazan, G. C. *Organometallics* **1999**, *18*, 3976. Wang, S.; Yang, Q.; Mak, T. C. W.; Xie, Z. *Organometallics* **2000**, *19*, 334.

Scheme 4. Reactions of Fulvenes with Nucleophiles



nucleophile/electrophile introduction into an indene moiety, and, thus provides unique opportunities for the rational design of catalysts for the homogeneous polymerization of olefins (e.g., the fluorenyl adduct **33**). It is known that indenyl complexes often perform better than their cyclopentadienyl analogues and that the introduction of substituents at the indenyl moiety has a dramatic influence on catalytic properties.[21]

In summary, we have developed a mild regio- and stereoselective approach to a variety of substituted benzofulvenes and indenes and have outlined general factors responsible for the efficiency and regio- and stereoselectivity of radical cyclizations of enediynes. Further research will involve more detailed studies of substituent effects and further exploration of the synthetic potential of this reaction for synthesis of new metallocene catalysts[21] and new types of conjugated polymers.[3,9] Synthetically useful reactions with other radical agents are under investigation as well.

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Supporting Information Available: Experimental procedures, ^{1}H, ^{13}C, and ^{19}F NMR spectra for all compounds, details of B3LYP computations, and X-ray analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Alt, H. G.; Köppl, A. *Chem. Rev.* **2000**, *100*, 1205. Lin, S.; Waymouth, R. M. *Acc. Chem. Res.* **2002**, *35*, 765.