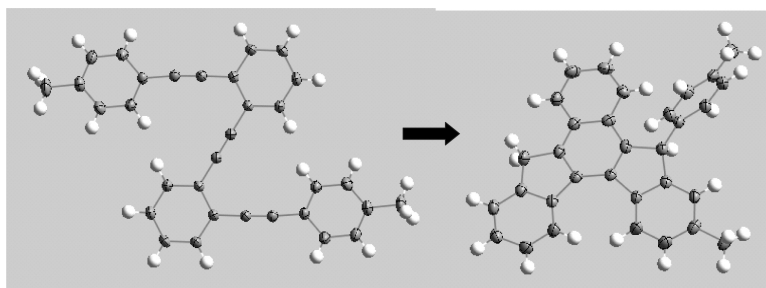


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Radical Cascade Transformations of Tris(*o*-aryleneethynyls) into Substituted Benzo[*a*]indeno[2,1-*c*]fluorenes

Igor V. Alabugin,^{*,†} Kerry Gilmore,[†] Satish Patil,[†] Mariappan Manoharan,[†] Serguei V. Kovalenko,[†] Ronald J. Clark,[†] and Ion Ghiviriga[‡]

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390 and Department of Chemistry, University of Florida, Gainesville, Florida, 32611-7200

Received May 21, 2008; E-mail: alabugin@chem.fsu.edu

Abstract: Oligomeric *o*-aryleneethynyls with three triple bonds undergo cascade radical transformations in reaction with a Bu₃SnH/AIBN system. These cascades involve three consecutive cycle closures with the formation of substituted benzo[*a*]indeno[2,1-*c*]fluorene or benzo[1,2]fluoreno[4,3-*b*]silole derivatives. The success of this sequence depends on regioselectivity of the initial attack of the Bu₃Sn radical at the central triple bond of the *o*-aryleneethynylene moiety. The cascade is propagated through the sequence of 5-exo-dig and 6-exo-dig cyclizations which is followed by either a radical attack at the terminal Ar substituent or radical transposition which involves H-abstraction from the terminal TMS group and 5-endo-trig cyclization. Overall, the transformation has potential to be developed into an approach to a new type of graphite ribbons.

1. Introduction

The rich potential of alkyne functionality is manifested particularly well in cascade cyclizations. Such transformations allow for the efficient and atom-economical preparation of polycyclic frameworks¹ found in natural products,² carbon nanostructures, and other useful molecules.³ Since each alkyne carbon has the ability to form more than one new bond without the involvement of heteroatom containing functional groups, alkynes lend themselves particularly well to the preparation of carbon-rich materials.⁴

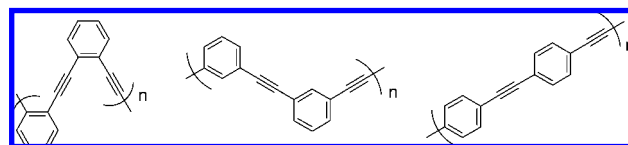


Figure 1. *o*-, *m*-, and *p*-Phenyleneethynyls

Oligomeric and polymeric aryleneethynyls (Figure 1) represent a particularly interesting class of alkyne-containing compounds which have found applications in the design of many other electronic and photonic devices⁵ including TNT chemosensory materials,⁶ molecular nanowires bridging gold nanoelectrodes,⁷ and jacketed blue-emitting rods.⁸ Although *para*-aryleneethynyls are used most often, recent work of Moore⁹ and Schanze¹⁰ on *meta*-aryleneethynyls clearly demonstrated new opportunities presented by the different substitution patterns. In this context, it is interesting that *ortho*-aryleneethynyls, the final member of the family, remain scarcely studied¹¹ even though the chemistry and structures of the simplest members of this family which are benzannelated analogues¹² of enediyne natural antibiotics¹³ continue to be of great interest. An understanding of reactivity of *ortho*-arylene-

[†] Florida State University.

[‡] University of Florida.

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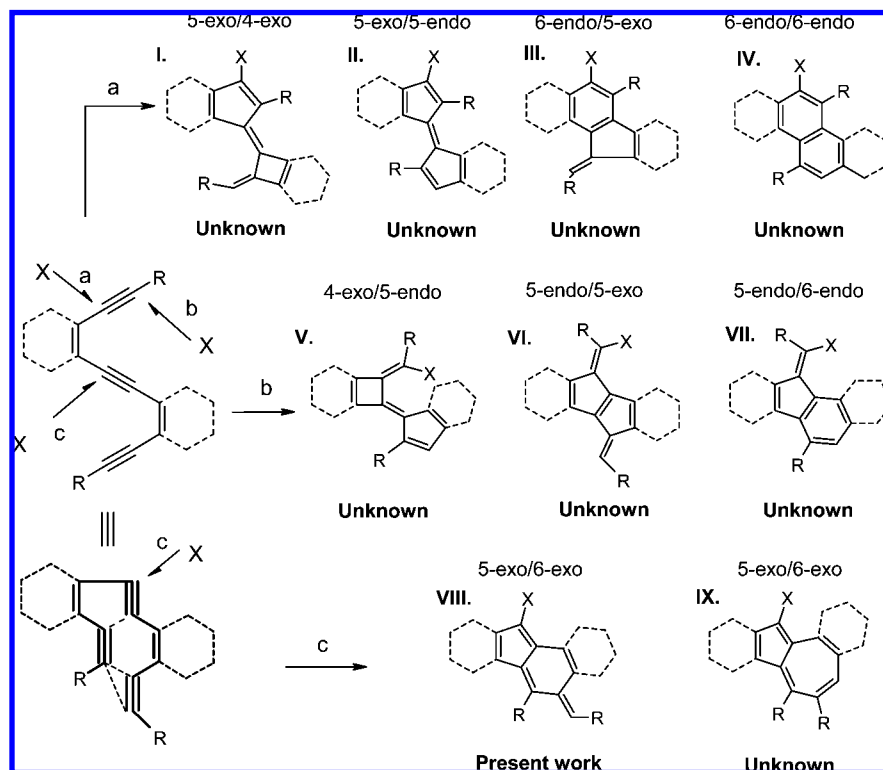


Figure 2. Selected possible radical cyclization cascades triggered by the addition of a radical to a substituted (*Z,Z*)-deca-3,7-diene-1,5,9-triynes. “Unknown” refers to the processes triggered by the addition of an external radical species. For specific examples of related radical cascades developed by Bergman, Vollhard, and Wu, see Figure 3.

ethynylenes is important not only for the development of new polymers incorporating this structural unit but also for the understanding of structure and properties of conjugated materials prepared through radical polymerization of enediyne.^{14,15}

The inherent diversity of radical cascade transformations of oligo-*o*-aryleneethynylenes with just three triple bonds and the

types of polycyclic systems potentially available through this chemistry are illustrated in Figure 2.

Surprisingly, *all* such cascades starting with an addition of an *external radical* to one of the triple bonds are still

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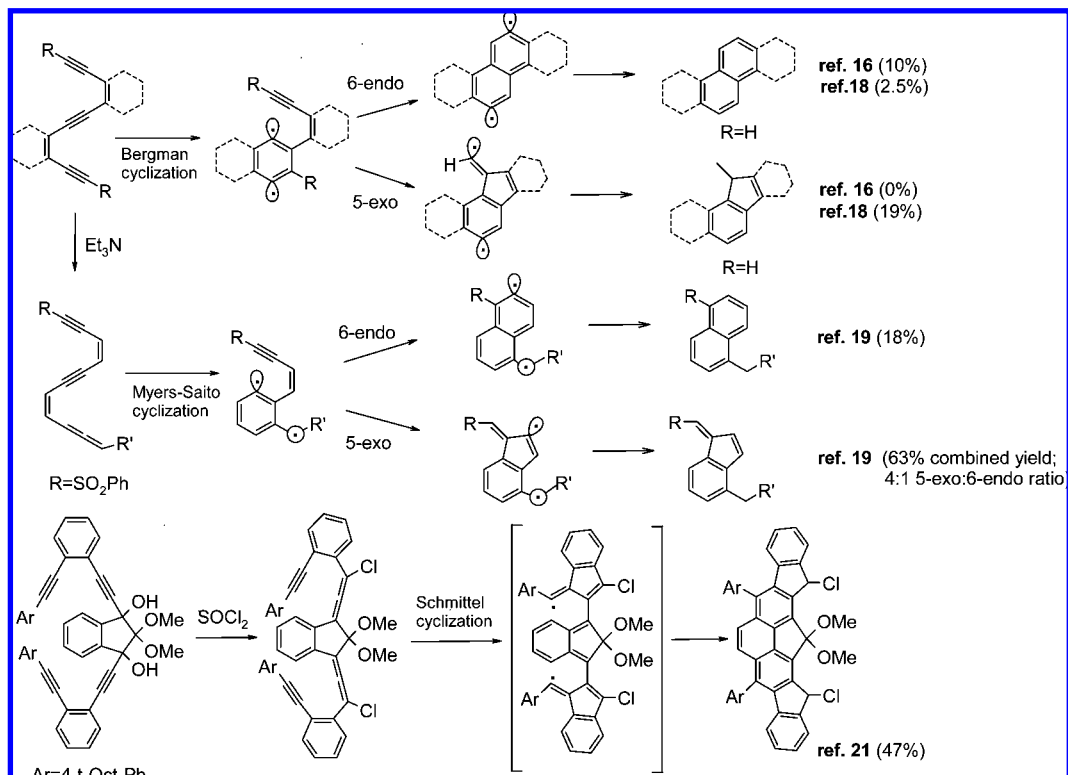


Figure 3. Thermal cascade cyclizations of triynes and tetraynes.

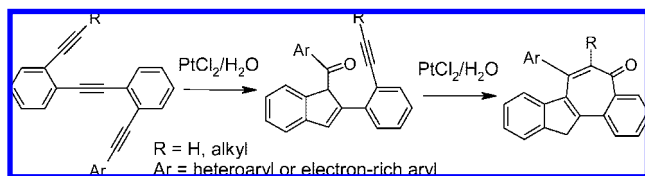


Figure 4. $\text{PtCl}_2/n\text{-H}_2\text{O}$ catalyzed cyclization of unsymmetrical 2,2'-(bis(ethynyl)diphenyl)acetylene.

undocumented. In a few known examples, which have provided structures analogous to those resulting from cascades **III** and **IV** in Figure 2, formation of the reactive radical was achieved through a different approach (either the Bergman or the Myers-Saito cyclization). In particular, Bergman himself was the first to explore initiation of a radical cascade transformation in (*Z*-*Z*)-deca-3,7-diene-1,5,9-triyn¹⁶ with the thermal Bergman cyclization of enediynes¹⁷ and discovered that the intermediate *p*-benzyne diradical can be trapped through a 6-endo-dig cyclization to give naphthalene (Figure 3, cyclic system **IV** in

Figure 2). Vollhardt and Matzger found that the Bergman cyclization of benzannelated enediynes can also be followed by the 5-*exo*-dig cyclization¹⁸ and that, in some cases, the 5-*exo* path predominates (Figure 3, cyclic system **III** in Figure 2). Wu et al.¹⁹ triggered analogous cyclization cascades utilizing the σ -radical from the σ,π -diradical generated through a Myers-Saito cyclization (Figure 3). Competition between 5-*exo*- and 6-*endo* cyclizations in these systems has been analyzed computationally by Alabugin and Manoharan who dissected the contributions of stereoelectronic, strain, and thermodynamic effects to the selectivity and explained the observed experimental differences in the above systems.²⁰ Finally, Wang described an interesting example where a cyclization cascade²¹ (bottom of Figure 3) is initiated by the Schmittel cyclization.²²

Transition metal catalyzed cascade transformations of such systems have started to attract attention as well. Apart from numerous examples of ruthenium, rhodium, palladium, and cobalt catalyzed [2 + 2 + 2] cyclizations of unconjugated

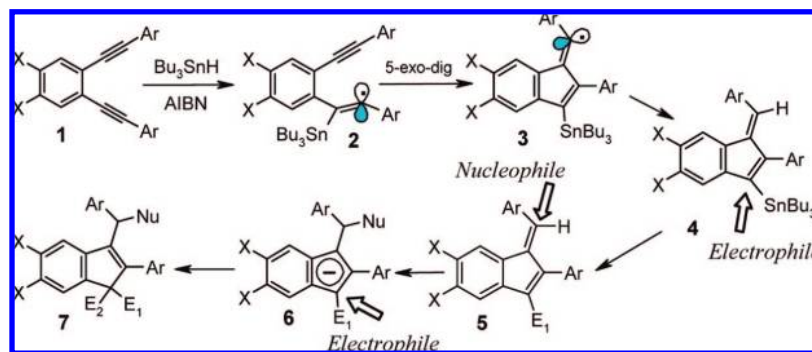


Figure 5. Bu_3SnH -promoted 5-*exo*-dig radical cyclization of enediynes.

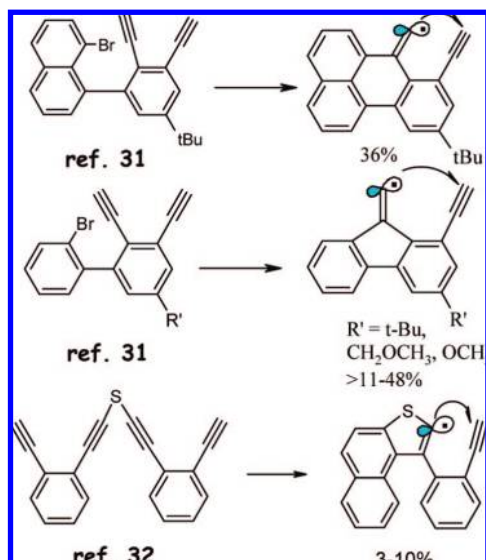
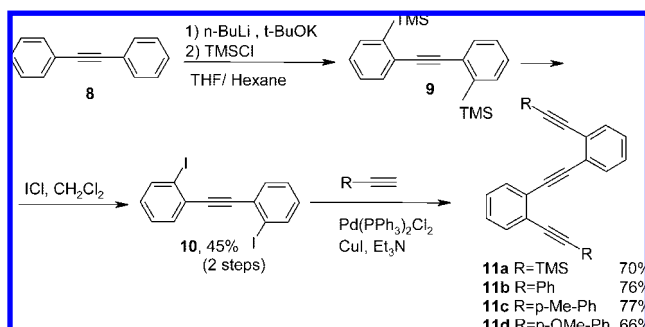


Figure 6. Radical cascade cyclizations of alkynes in constrained systems.

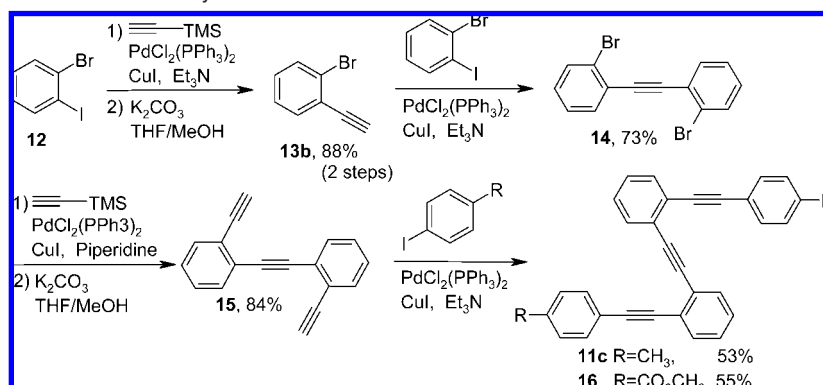
Scheme 1. Synthetic Route A to Substituted Triynes from the Kowalik–Tolbert Intermediate **10**



trienes,²³ a particularly interesting cascade reaction promoted by $\text{PtCl}_2/n\text{-H}_2\text{O}$ was recently reported by Liu et al. (Figure 4).^{24,25} This mechanistically different transformation proceeds through hydration of a triple bond and sequential cyclizations of ketone intermediates, leading to the formation of a type **IX** polycyclic system from Figure 2.

In this work, we have chosen a different strategy for initiating the cyclization cascades. This strategy is based on Bu_3SnH -mediated radical 5-exo-dig cyclization of the enediyne moiety - a process that we developed recently²⁶ for mechanistic studies of photochemical C1C5 cyclization of enedynes.²⁷ The utility of this radical cyclization for the preparation of polysubstituted fulvenes and indenes is illustrated in Figure 5.²⁸

Scheme 2. Synthetic Route B to Substituted Triynes



This transformation is initiated by the attack of a Bu_3Sn radical at the internal carbon of one of the triple bonds, resulting in the formation of an intermediate vinyl radical **2**. This radical undergoes a 5-exo-dig radical cyclization resulting in the fulvene radical **3**, which is subsequently quenched by H-abstraction from Bu_3SnH . The present study aimed to determine whether a 5-exo-cyclization can be followed by another C–C bond forming step through an intramolecular reaction of radical **3** with an appropriately positioned alkyne π -system in a radical cyclization cascade.

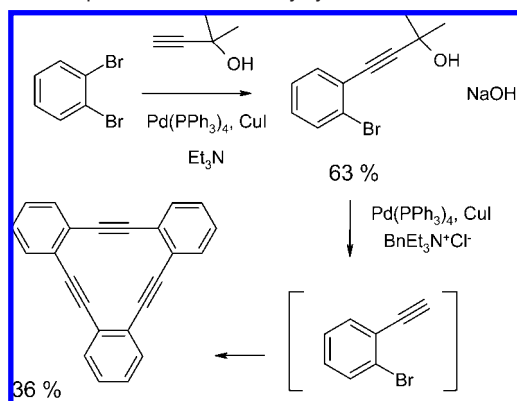
The requisite substrates were first prepared and investigated by Grubbs and Kratz,^{11,29} who studied the thermolysis of oligomeric *o*-aryleneethynyls and reported evidence of an exothermic reaction, yet isolated no structurally defined products. Other interesting and potentially relevant examples of cascade radical transformations of alkynes include selective 6-endo-dig cyclizations in constrained systems by Anthony and co-workers^{30,31} and Matzger et al. (Figure 6).³²

Although the literature data suggest a significant diversity of radical cascade cyclizations involving several triple bonds, none of the above examples affords the same type of polycyclic skeleton as structures potentially available through a cascade initiated by the 5-exo-dig cyclizations of the central “enediyne” moiety. Research described below was undertaken to fill this gap and to test the feasibility of this chemistry for the rapid construction of polycyclic systems.

2. Results

2.1. Synthesis of Starting Materials. The target oligomeric *o*-aryleneethynyls were synthesized by two methods. In the first approach, the key intermediate is prepared from diphenyl acetylene (tolane) through a sequence outlined earlier by Kowalik and Tolbert.³³ This sequence involves directed metalation with the LICKOR superbase, quenching of the resulting dianionic species with TMSCl , and exchange of TMS for iodine (Scheme 1). Although this method requires both anhydrous and oxygen-free conditions, it provides a very convenient diiodide precursor **10** which yields the requisite triynes through Sonogashira coupling with 2 mol of an appropriate terminal acetylene. In the second approach, four sequential Sonogashira reactions transform *ortho*-bromoiodobenzene into the key bis(2-ethynylphenyl)acetylene intermediate (Scheme 2).³⁴ These Sonogashira reactions are more amenable to scaleup than reactions of toluene dianion, but overall the two methods are complementary. Although the second sequence is one step longer, the average overall yield for the triynes produced through the two sequences are comparable ($\sim 30\%$). The first method is par-

Scheme 3. Preparation of Tribenzocyclyne



ticularly convenient when appropriate terminal alkynes are readily available. The second method takes better advantage of the potentially larger pool of iodo/bromo substituted aromatics.

The cyclic version of tris(*o*-aryleneethynylene)s (tribenzo-hexadehydro[12]annulene or tribenzocyclyne)³⁵ involves cyclooligomerization of an appropriate *o*-haloethynylbenzene

and tetrakis(triphenylphosphine)palladium copper(I) iodide catalyst under phase-transfer conditions in 36% yield (Scheme 3).³⁶

2.2. Cyclizations. Radical reactions of the triynes were initiated by slow addition of Bu_3SnH and AIBN using a syringe pump. The products are shown in Figure 7, whereas the reaction yields are summarized in Table 1. X-ray structure of the cyclic product **17c** along with that for the starting tris-alkyne **11c** is given in Figure 8. Comparison of the two structures illustrates the remarkable change in the molecular structure as the result of this one-pot transformation where all three triple bonds are involved and three new cycles are formed in the cascade process.

The efficiency of radical cascades of triynes **11a–c** exceeds those of thermal reactions initiated by cycloaromatizations¹⁶ and approaches that of transition metal catalyzed cyclizations.²³ Greater efficiency compared to the Bergman cyclization is not surprising because the formation of the Bergman six-membered diradical (*p*-benzyne) is reversible.³⁷ The diradical can open back up to the enediyne (retro-Bergman ring opening) or abstract a hydrogen atom before it attacks

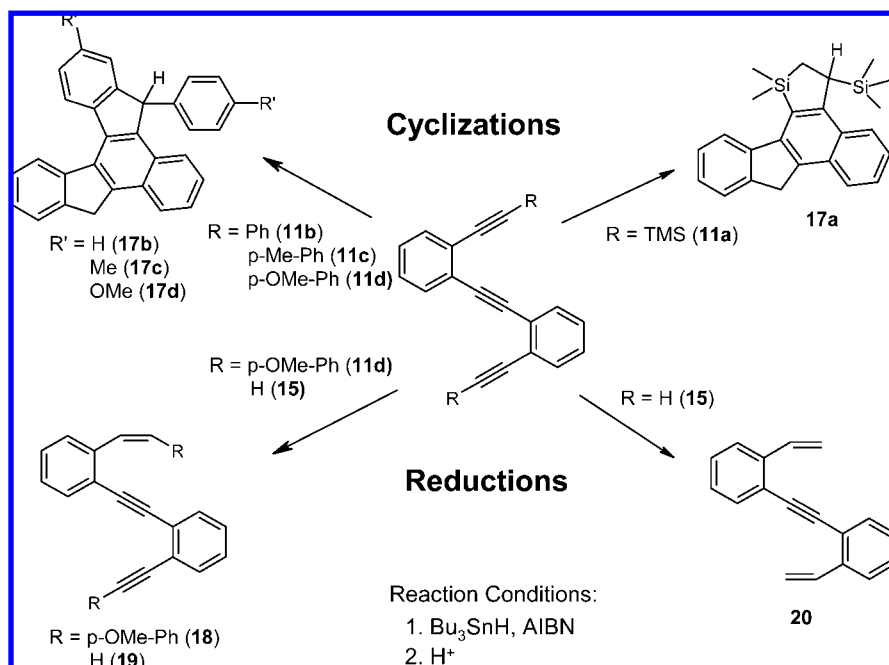


Figure 7. Products of reaction of substituted triynes **11**, **15** with Bu_3SnH and AIBN.

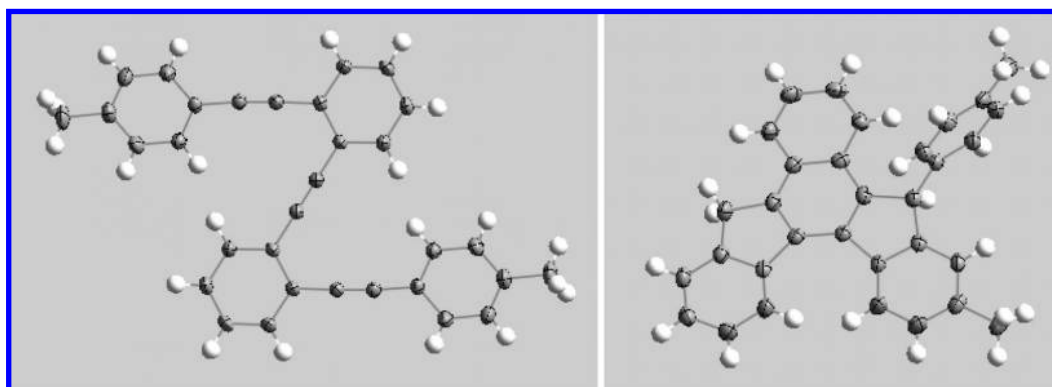


Figure 8. X-ray geometries of tris-alkyne **11c** (on the left) and cyclized product **17c**.

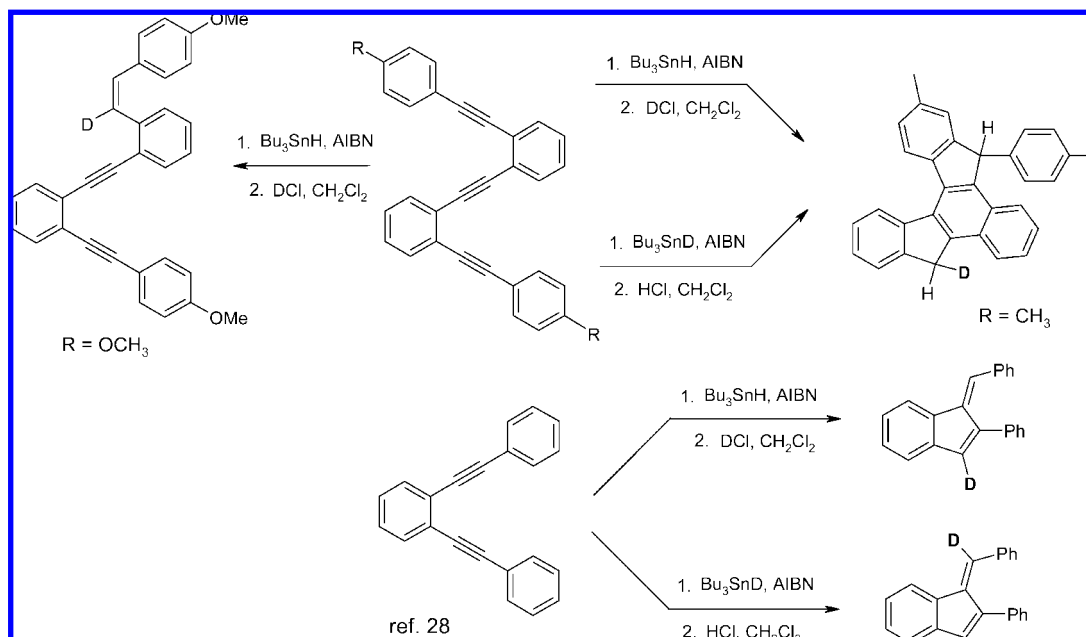


Figure 9. Regioselective deuterium incorporation in the acyclic product (left, R = OCH₃) and convergent incorporation of deuterium in the cyclization cascade through two alternative pathways (right, R = CH₃). Contrasting regioselectivity for D-incorporation in the analogous cyclization of enediynes from ref 28 is shown for comparison below.

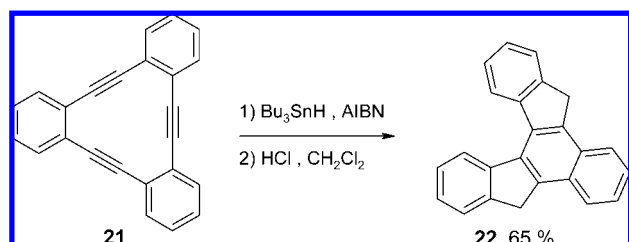


Figure 10. Bu₃SnH-promoted cascade cyclization of tribenzocyclane.

the remaining triple bond. Even though Myers–Saito cyclization is exothermic and its reversibility is less important, the cyclized products are still formed in relatively low (<20%) yields (Figure 3). Increased efficiency of cascades initiated by the 5-*exo*-dig radical cyclization suggests that the side processes are less important for the transformations discussed in this paper.

As destannylation can be achieved with a source of either protons or deuterons (HCl/DCl), the position of the tributyltin moiety in the products can be shown unequivocally, thus revealing the chemo- and regioselectivity of the first step and confirming addition of the tributyltin radical to the internal triple bond. The termination point of the radical cascade can also be determined through an alternative deuteration process with Bu₃SnD as the reactant (Figure 9). Interestingly, the location of the deuterium shows that the initiation and termination of the radical cascade cyclization occur at the same carbon!³⁸ This observation contrasts the observation of the different location for the deuterium in the respective cyclizations of enediynes (bottom part of Figure 9).²⁸

Radical cyclization of symmetric molecule tribenzocyclane **21** proceeded without complications to yield 65% of 1,6-dihydrobenzo[*a*]indeno[2,1-*c*]fluorene **22** (Figure 10). Spectroscopic data for this product are identical to the data reported earlier by Youngs and co-workers who achieved the same transformation through a lithium-induced cyclization.^{35b}

Table 1. Yields in the Bu₃SnH/AIBN-Promoted Cyclizations and Reductions of Substituted Triynes

triyne	R	cyclized	monoreduced	direduced
11a	trimethylsilyl	17a 73% ^a		
11b	phenyl	17b 65%		
11c	<i>p</i> -Me-phenyl	17c 70%		
11d	<i>p</i> -OMe-phenyl	17d 10%	18 9% ^b	0%
15	H		19 50%	20 42%
16b	<i>p</i> -(CO ₂ Me)-phenyl		complex mixture	

^a The structure was elucidated from the ¹H and ¹³C NMR one-bond and long-range couplings revealed by the GHMQC and GHMBC spectra discussed in detail in the Supporting Information. ^b Presence of byproduct with similar R_f values complicated separation, which is reflected in the low yield of the pure isolated product. NMR analysis of the crude reaction mixture suggests the yield of ~35%.

Most interestingly, the products of Bu₃SnH-mediated cyclizations **17a–d** differ from the products of thermal and transition metal catalyzed reactions (Figures 3–6). The cyclization proceeds through a sequence of the 5-*exo*-dig and 6-*exo*-dig cyclizations which is terminated by a reaction of a vinyl radical with a substituent (an Ar or TMS group) at the terminal triple bond (Figures 11, 12). Aromatization through a H-atom shift completes the transformation (*vide infra*). Note that unless the starting material is symmetric tribenzocyclane **21**, directing the initial Sn radical attack at the *central* triple bond is essential for the success of this cascade process. As a result, the cyclization success depends on the nature of terminal substituents: only reduction of the terminal alkynes is observed for R = H, while mixture of reduction and cyclization products is formed for R = *p*-OMePh. The presence of an ester group (R = CO₂Me) leads to a complex mixture of unidentified products (Table 1). NMR analysis of this mixture suggests that the ester functionality is reactive under these conditions.

3. Discussion

Initial attack of the tris-aryleneethynylene system by the tributyltin radical is sensitive to substitution at the terminal triple

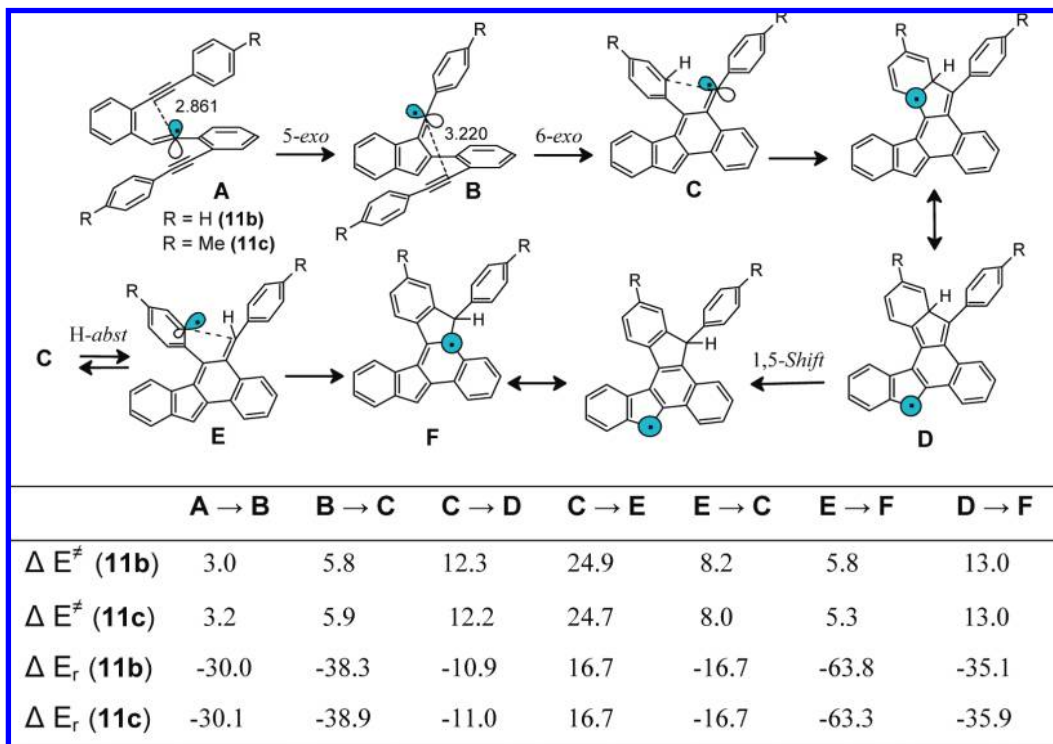


Figure 11. Competing pathways with calculated activation barriers and reaction energies (kcal mol^{-1}) of the radical cascade cyclization at the UB3LYP/6-31G**/UB3LYP/3-21G* level.

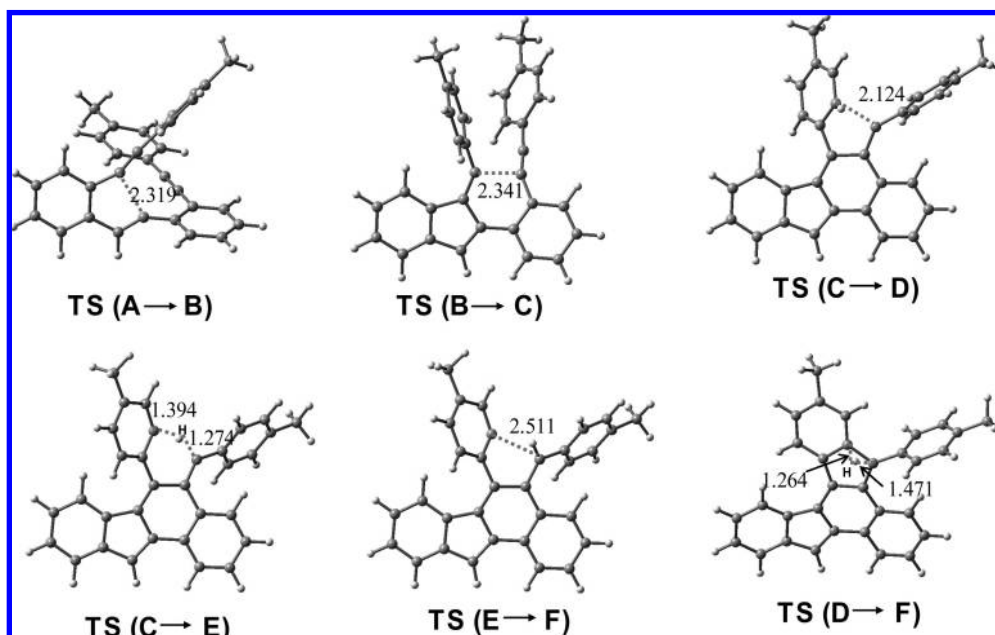


Figure 12. Transition state structures involved in the cascade reactions shown in Figure 11 calculated at the UB3LYP/3-21G* level along with the incipient distances for the forming bonds.

bond and can occur at only three positions: the internal triple bond and either the internal or external carbon of the terminal alkyne moieties. Only attack at the internal triple bond will lead to the 5-exo, 6-endo cascade reported in this paper. In alkyne **15**, the attack proceeds at the terminal carbon where the approaching radical species encounter no steric hindrance. Attack at the *internal* carbon of the external triple bond of **15** would produce a radical which is not stabilized by the benzylic resonance. The directing effect of TMS group in **11a** is not surprising since this moiety kinetically deactivates the terminal

alkyne. As a result, the Bu_3Sn radical attack proceeds at the internal triple bond. Much more interesting is the selectivity in

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the aryl-substituted triynes where all triple bonds have similar properties and, thus, attack at the terminal alkyne moiety should be possible as well. Here the balance is quite subtle, since phenyl and *p*-tolyl groups favor Bu₃Sn radical attack at the center alkyne moiety (Figure 7), whereas the *p*-OMe-Ph substituted tris-alkyne **11d** shows a lack of selectivity.

Although formation of significant amounts of acyclic products for R = OMe is surprising especially in contrast with the efficient cyclization for R = Me, the regioselectivity of Bu₃Sn addition to the tris-alkyne **11d** offers some insight into the possible origin of this difference. A possible explanation (consistent with the results of DFT computations) is that the *p*-OMe group provides additional stabilization to the radical at the benzylic position.³⁹ In agreement with such stabilization, the attack proceeds at the *internal* carbon of the triple bond. It is not clear why we do not observe any cyclization products from the radical in the above step because both 5-*exo*-dig and 6-*endo*-dig closure are usually favorable.²⁶ Since the geometry of aryl substituted vinyl radicals is not far from linear,^{26a} it is conceivable that destabilizing steric interactions may occur in the cyclization transition state due to the presence of an aryl group at the terminal carbon (Scheme 4). It is also possible that

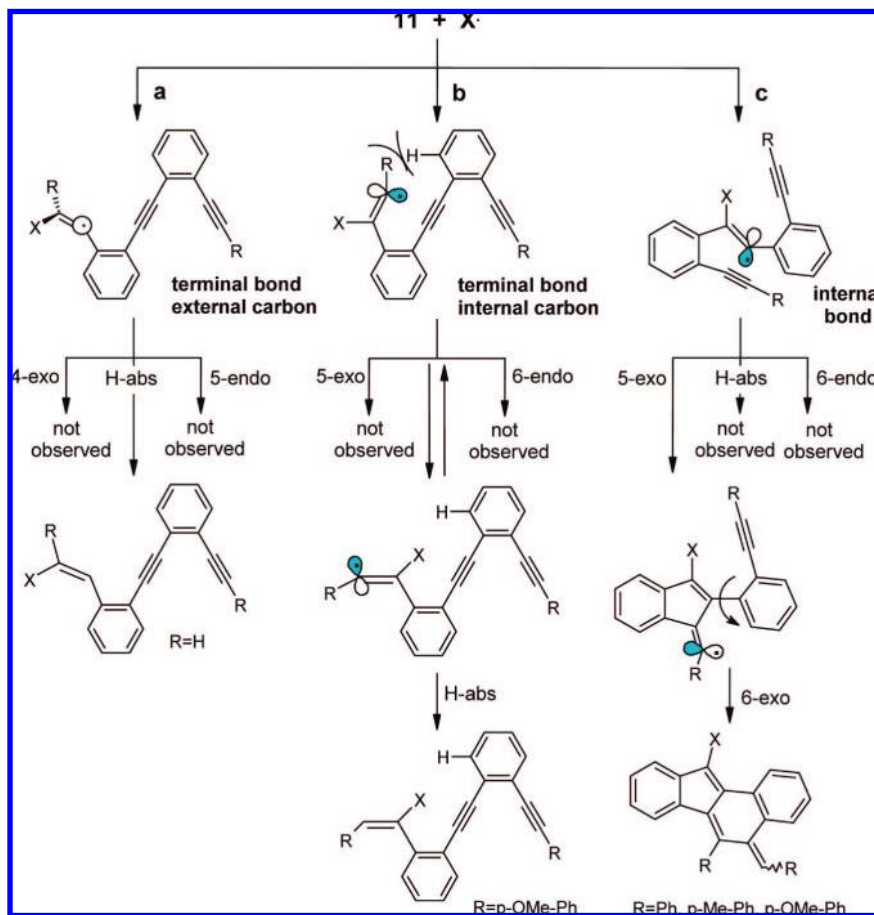
similar steric interactions depopulate the near-attack conformation of the reactant.

The experimentally observed “internal” preference (path c of Scheme 4) for the radical attack in tris-alkynes **11b,c** may be explained by reversibility of the Bu₃Sn radical addition to the triple bond and lack of cyclization pathways with comparable activation energies for the cyclization of vinyl radicals formed from the two alternative addition paths a and b (Scheme 4). Note also that cyclizations of a nonconjugated vinyl radical to an unsaturated system where breaking of a π -bond leads to the formation of a carbon–carbon σ -bond are exothermic by 20–30 kcal/mol unless the reacting vinyl radical is deactivated by benzylic or allylic conjugation.²⁰ Thus, the alternative cyclization steps should be essentially irreversible under the reaction conditions, and competition between the alternative cyclization pathways of each of the isomeric vinyl radicals should be under kinetic control. In this scenario, the effect of the different stabilities of isomeric radicals on the selectivity should be described by the Curtin–Hammett principle. The 5-*endo* and 4-*exo*-dig cyclizations of the vinyl radical formed through path b were shown to have a high barrier because the radical orbital has to rotate out of conjugation with the aromatic system in order to attack the in-plane π -bond of the alkyne moiety. Such loss of benzylic conjugation strongly increases the cyclization barriers as shown in the earlier computational work and illustrated by the lack of such cyclizations in the literature.^{20,40}

Computational analysis was carried out (at the UB3LYP/6-31G**//UB3LYP/3-21G* level of theory^{41,42}) in order to gain better insight into the nature of the potential energy surface for the proposed radical cascade mechanism and to distinguish between mechanistic alternatives (Scheme 4, Figures 11, 13). The first two 5-*exo* and 6-*exo* (Figure 11: **A** \rightarrow **B**, **B** \rightarrow **C**) cyclizations are predicted to be both fast and essentially irreversible with the respective activation barriers of \sim 3 and 6 kcal/mol and exothermicity of \sim 30 kcal/mol. The only mecha-

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Scheme 4. Possible and Observed Cascade Cyclization Pathways Resulting from the Three Directions of the Radical Attack at the Three Triple Bonds



nistic ambiguity arises after the 6-exo cyclization step. At this point, the vinyl radical can react through one of two alternative pathways: (a) 1,5 hydrogen abstraction followed by a 5-endo cyclization ($C \rightarrow E \rightarrow F$) or b) cyclization at a terminal aryl ring followed by a 1,5 hydrogen shift which rearomatizes the ring ($C \rightarrow D \rightarrow F$). The former process is endothermic by ~ 16 kcal/mol and proceeds via an unconjugated radical, **E**, through a relatively high activation barrier (~ 25 kcal/mol). In contrast, the latter ($A \rightarrow B \rightarrow C \rightarrow D \rightarrow F$) pathway is much more favorable energetically. Even taking into account the quantitative uncertainty of the computational method, the ~ 12 kcal/mol barrier for the formation of **D** is certainly lower than that for the formation of **E**. The 1,5-hydrogen shift producing **F** is highly exothermic and has a relatively low barrier because it is assisted by aromatization.⁴³

Trimethylsilyl substituted tris-alkynes follow the same 5-exo, 6-exo sequence of steps at the initial stage of the radical cascade. The differences are minor: the cyclizations have slightly higher activation barriers and are not quite as exothermic because the α -effect of Si in **H** and **I** is less effective in radical stabilization than benzylic conjugation in **B** and **C** (Figure 13). Since, unlike the intermediate **C** in Figure 11, the resulting vinyl radical **I** has no available cyclization choices, it abstracts a hydrogen from the TMS group. 5-Endo-trig cyclization of the resulting radical **J** has a remarkably low barrier and is highly exothermic because it is accompanied by aromatization. The last two steps represent the classic 1,5-radical translocation/cyclization sequence of Curran.⁴⁴

3.1. Relation to the Preparation of New Graphite Ribbons. The efficiency of cascade transformations of tris-alkynes described in this paper suggests that similar cascades

may prove to be useful for the preparation of interesting conjugated carbon-rich materials such as, in particular, graphite ribbons. Graphite ribbons are predicted to have very interesting electronic properties which combine the relatively small band gap with high switching speeds and carrier mobility.⁴⁵ Not surprisingly, a number of synthetic approaches to such ribbons illustrated in Figure 14 have been developed in recent years.⁴⁶ However, not all possible types of the ribbons have been prepared so far, and thus, it is interesting to envision “zipping up” the sequence of alkyne bonds into a new system shown at the bottom right corner of Figure 14. Cascades described in this paper represent the first steps in the proposed approach. In the present paper, these cascades are terminated through addition to the terminal aryl group or by H-abstraction only because of the absence of another triple bond which would provide a much more favorable 6-exo-cyclization pathway. Comparison of activation barriers for the 6-exo-dig cyclization and cyclization at the aromatic ring (5.8 vs 12.3 kcal/mol for steps $B \rightarrow C$ and $C \rightarrow D$ respectively in Figure 11) strongly supports that 6-exo-

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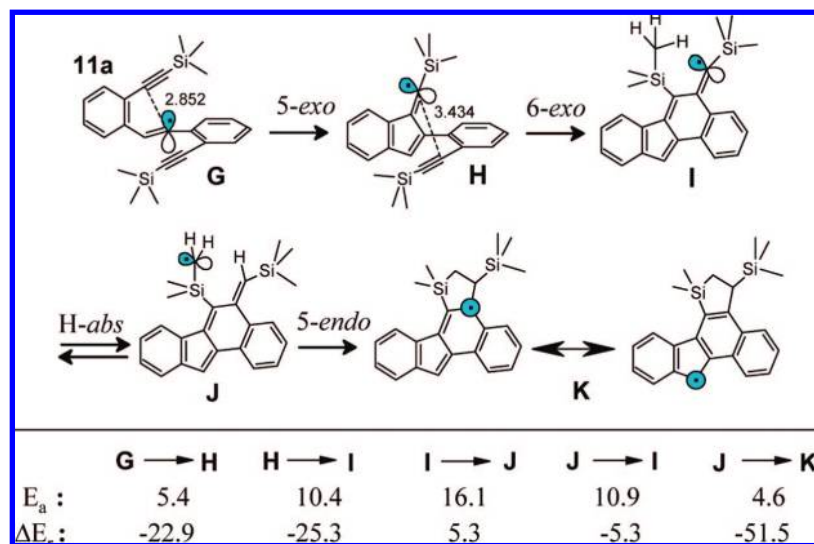


Figure 13. Proposed mechanism for the radical cyclization of 2,2'-bis(trimethylsilyl)ethynyl diphenylacetylene along with the calculated activation barriers and reaction energies (kcal mol^{-1}) at the UB3LYP/6-31G**//UB3LYP/3-21G* level.

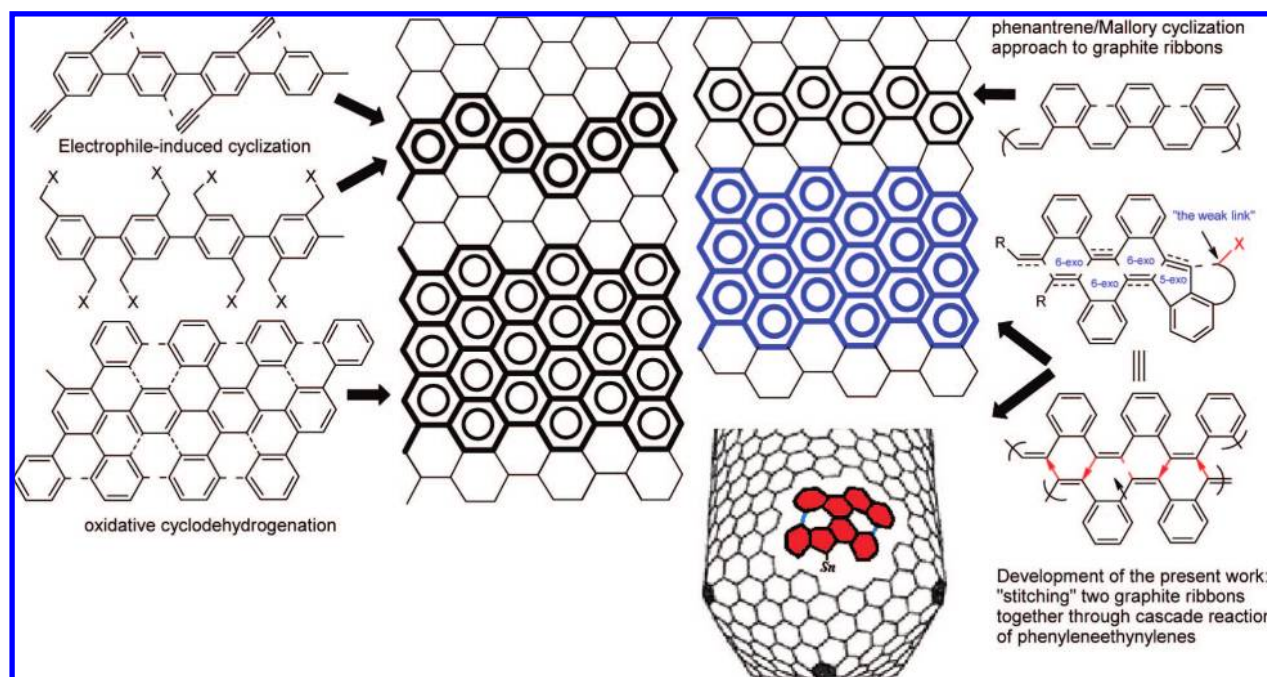


Figure 14. Comparison of known approaches to graphite ribbons with cascade cyclizations of phenyleneethynylenes.

dig cyclization should be much faster than the alternatives and, thus, the growth of the polycyclic system should continue as long as the triple bonds at the appropriate position are available. It is possible that the presence of the additional triple bonds will require careful control of the chemoselectivity of the initial radical attack which must occur at the central triple bond in order for the cascade to involve all alkyne moieties of the reactant. If necessary, such control can be achieved if a “weak link”, a chemically orthogonal functional group for selective radical formation, is introduced near the central alkyne moiety of the reactant (Figure 14). Formation of a radical center at the “weak link” will transform the initial cascade initiation step from an intermolecular to an intramolecular process, thus, solving the problem of chemoselective initiation of this cascade. The final bonds between the “outside” phenyl rings can be formed

through the Mallory reaction.⁴⁷ One can speculate that the length of the linker should provide us with control of the shape of the molecule. For example, a five-membered ring in the product can be used to introduce additional curvature⁴⁸ reminiscent of that at the tip of carbon nanotubes (Figure 14). Our research in identifying and synthesizing such systems is under way.

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4. Conclusions

In summary, we have developed a new mild, chemo- and regioselective transformation of conjugated acyclic triynes to polycyclic systems via a radical cascade process which involves formation of four new σ -bonds. The products can be either destannylated with the relatively mild conditions described above or, potentially, utilized in further reactions such as Stille cross-coupling.

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Supporting Information Available: Detailed comparison of computational data for 5-exo-dig and 6-endo-dig radical cyclizations of vinyl and aryl radicals at the UB3LYP/6-31G** and UB3LYP/6-31G**//3-21G* levels. Full experimental procedures, spectral data including ^1H and ^{13}C NMR, MS, and X-ray crystallography data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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