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Drawing from a Pool of Radicals for the Design of Selective Enyne Cyclizations

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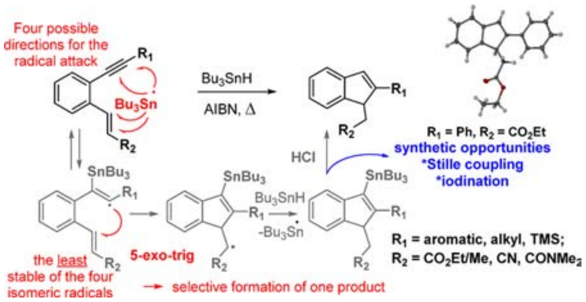
ABSTRACT



Despite the possibility of intermolecular attack at four different locations, the Bu_3Sn-mediated radical cyclization of aromatic enynes is surprisingly selective. The observed reaction path originates from the *least* stable of the equilibrating pool of isomeric radicals produced by intermolecular Bu_3Sn attack at the π-bonds of substrates. The radical pool components are kinetically self-sorted via 5-exo-trig closure, the fastest of the four possible cyclizations. The resulting Sn-substituted indenes are capable of further transformations in reactions with electrophiles.

Alkenes and alkynes are close chemical cousins. Both have reactivity determined by the presence of the relatively weak π-bonds capable of undergoing addition reactions. Both functionalities commonly participate in reaction cascades where the π-bonds are sacrificed for the formation of multiple C–C bonds in the construction of polycyclic moieties. As the complexity of synthetic targets continues to increase, the subtle differences between alkenes and alkynes become increasingly important for the chemo-, regio-, and stereoselectivity of such cascades.[1]

Although alkyne π-bonds are stronger and less reactive[2] than π-bonds of alkenes, the present work will show how the less reactive functionality (alkyne) is activated in the presence of a more reactive functionality (alkene). In order to achieve this "inversion of reactivity," the combination of reversible addition to the two π-targets (alkene vs alkyne) is coupled with stereoelectronic guidelines in order to "funnel" the potentially multichannel reactivity of a "pool" of intermediate radicals toward the formation of one major product. Conceptually, this is dynamic covalent chemistry with kinetic self-sorting.[3]

Although selective radical attacks at a *terminal* alkyne in enynes are known (Scheme 1),[4] a chemoselective attack at a disubstituted alkyne in the presence of an electronically and sterically similar alkene is a greater challenge.

In this work, we report a *chemo*- and *regioselective* radical transformation of enynes which is mediated by intermolecular radical addition to the triple bond, followed by intramolecular 5-exo-trig closure of the vinyl radical onto the tethered alkene. This reaction provides a convenient approach to Bu_3Sn-functionalized indenes,

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(1) (a) Wille, U. *Chem. Rev.* **2013**, *113*, 813. Selected examples: (b) Alabugin, I. V.; Gilmore, K.; Patil, S.; Manoharan, M.; Kovalenko, S. V.; Clark, R. J.; Ghiviriga, I. *J. Am. Chem. Soc.* **2008**, *130*, 11535. (c) Byers, P.; Alabugin, I. V. *J. Am. Chem. Soc.* **2012**, *134*, 9609.

(2) Alabugin, I. V.; Gold, B. *J. Org. Chem.* **2013**, *78*, 7777.

(3) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem.* **2002**, *114*, 938.

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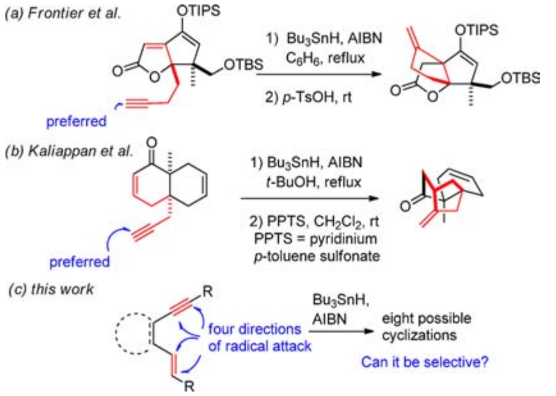
10.1021/ol4028072

Scheme 1. Chemo- and Regioselective Addition of Sn Radical to Terminal Alkyne Moiety of Enynes in the Preparation of Complex Polycyclic Frameworks



with potential applications as metallocene complex precursors, NHC ligands, and functional materials.[5]

Reported methods for indene preparation have included the cyclization of phenyl-vinyl or phenyl-substituted allylic alcohols,[6] metal-mediated (Pd, Ni, Pt, Co, Au, Fe) carboannulations of alkynes,[7] reductive photocyclizations of enediynes,[8] and Brønsted acid catalyzed cyclizations of aryl-1,3-dienes.[9] Despite the variety of reported synthetic approaches, the intramolecular radical cyclization of enynes to yield functionalized indenes has, to the best of our knowledge, remained undiscovered until the present report.

The library of enynes was synthesized by varying substituents at both the alkynyl and alkenyl ends. Depending on the availability of starting materials, we used strategies based on the combination of either Wittig or Heck reactions with Sonogashira coupling, as shown in Scheme 2 (see Supporting Information (SI) for the details).

Scheme 2. Synthetic Strategies for the Enyne Synthesis

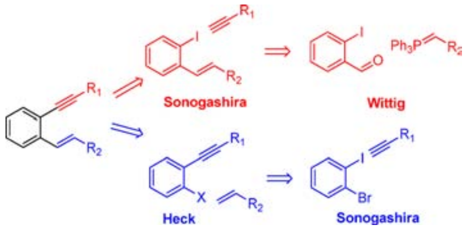
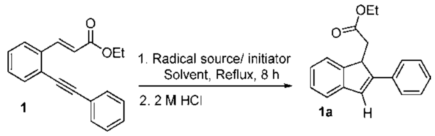


Table 1. Optimizing Conditions for the 5-exo-trig Radical Cyclization of Enynes



entry	reagent (1.2 equiv)/ initiator (0.4 equiv)	solvent	yield (%)
1	Bu_3SnH/AIBN	benzene	40
2	Bu_3SnH/AIBN	acetonitrile	24
3	Bu_3SnH/AIBN	toluene	87
4	$(Me_3Si)_3SiH$/AIBN	toluene	complex mixture
5	Et_3SiH/AIBN	toluene	NR
6	Ph_3SnH/AIBN	toluene	20
7	Bu_3SnH/DTBPB	toluene	52
8	Bu_3SnH/TOOT	toluene	18
9	Bu_3SnH/ABCN	toluene	60

The cyclization of enyne **1** was screened with a variety of initiators and radical reagents, as shown in Table 1. The combination of Bu_3SnH and AIBN in refluxing toluene was the most efficient, producing indene **1a** in 87% yield. The Bu_3SnH/AIBN ratios and reaction times were separately optimized for each substrate, as detailed in the SI. It was essential to maintain a relatively low concentration of reacting radicals using syringe pump addition.

The scope of this reaction is demonstrated by the successful cyclization of enynes shown in Table 2. The variations of substituents at the alkyne terminus illustrates that the reaction is particularly efficient when the vinyl radical, formed via the intermolecular attack, enjoys delocalization with an electron rich π-system. Alkyl and TMS-substituted alkynes also give acceptable yields (Table 2, entries 6, 7), but the reaction proceeds considerably slower. The reaction retains its efficiency when the alkene substitution was changed from ester to amide, cyano, and aryl groups (Table 2, entries 8, 9, 10).

The highly selective cyclization of enyne **10** having the identical substituents at the ene and yne termini is particularly interesting. In the latter case, it is evident that it is the differences between the close chemical cousins, alkene and alkyne, rather than the substituent effects that are responsible for the observed selectivity.

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Table 2. Library of Indenes Obtained from the 5-exo-trig Cyclization of Enynes

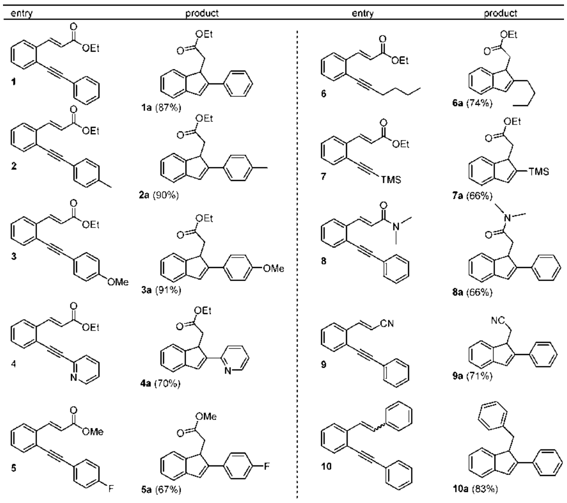
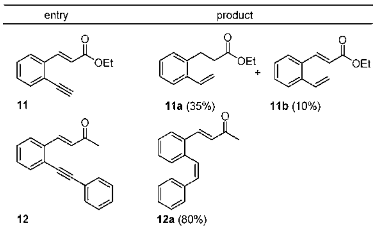
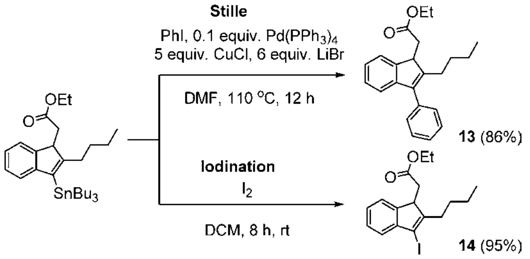


Table 3. Enynes Which Did Not Follow the 5-exo-trig Pathway and Products Obtained from Their Reaction with Bu_3SnH/AIBN



Scheme 3. Further Transformations of the Sn-Containing Indene



Structures of the indene products were confirmed by heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond correlation (HMBC), and X-ray crystallography (Figure 1; see SI for the details).

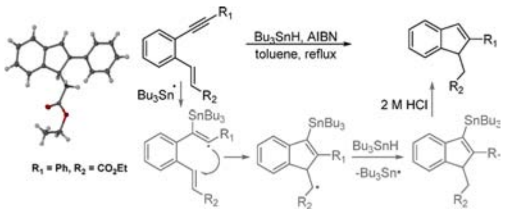


Figure 1. ORTEP diagram of indene **1a** and the proposed mechanism.

As expected, terminal alkynes such as enyne **11** (Table 3, entry 1) failed to cyclize due to the instability of primary vinyl radicals. The more stable vinyl radical formed by addition to the terminal alkyne carbon did not provide 5-endo-trig products.[10] Instead, the reaction produced the over-reduced product **11a** and diene **11b**. More interestingly, the cyclization did not work with vinyl ketones; i.e., the reaction of ketone **12** led to selective partial reduction of the triple bond.[11] Subjecting the respective aldehyde to the optimized conditions produced a mixture without the characteristic aldehyde NMR signals.

As shown in Scheme 3, synthetic utility of the new enyne–indene transformation is extended by subsequent cross-coupling reactions. Alternatively, the product can be converted into an electrophilic indene building block via iodination.

The nature of the products **1a**–**10a** suggests chemoselective intermolecular addition of the tin radical to the alkyne. This step generates a reactive vinyl radical for rapid intramolecular trapping by the tethered alkene (Figure 1). It has been suggested that electronic effects disfavor radical additions to alkynes relative to alkenes.[12] These literature data are fully consistent with the notion that alkyne π-bonds are stronger and less reactive than alkene π-bonds.[3,13]

Computational analysis compared the four possible pathways for the formation of five-membered rings in this system (5-exo-dig, 5-endo-dig, 5-exo-trig, and 5-endo-trig). As expected, all reactions of alkynes have higher barriers and are less exothermic[14] relative to the analogous reactions of alkenes (Figure 2). This trend has two reasons: stronger π-bonds in alkynes and greater reactivity of vinyl radicals. Due to the combination of these effects, the 5-exo-trig attack of a vinyl radical at a double bond has a barrier ~11 kcal/mol lower than that of the "mismatched" 5-exo-dig[15] attack of an alkyl radical at the triple bond. This result fully agrees with the experimentally observed 5-exo-trig selectivity.

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(10) 5-endo-trig: Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10765.

(11) The reasons for this unusual behavior will be analyzed in future work. However, the lack of reactivity in the absence of AIBN does rule out direct carbonyl reduction of enones via a nonradical mechanism: Krafft, M. E.; Vidhani, D. V.; Cran, J. W. *Synlett* **2011**, *16*, 2355.

(12) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340.

(13) Nicolaides, A.; Borden, W. T. *J. Am. Chem. Soc.* **1991**, *113*, 6750.

(14) Unlike the other 5-membered radicals, the 5-endo-dig product is not stabilized by benzylic conjugation. Furthermore, such cyclizations are slow: (a) Alabugin, I. V.; Timokhin, V. I.; Abrams, J. N.; Manoharan, M.; Ghiviriga, I.; Abrams, R. *J. Am. Chem. Soc.* **2008**, *130*, 10984. (b) Alabugin, I. V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, *127*, 9534.

(15) Note that similar 5-exo-dig cyclizations of vinyl radical are much faster: (a) Kovalenko, S. V.; Peabody, S.; Manoharan, M.; Clark, R. J.; Alabugin, I. V. *Org. Lett.* **2004**, *6*, 2457. (b) Alabugin, I. V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, *127*, 12583.

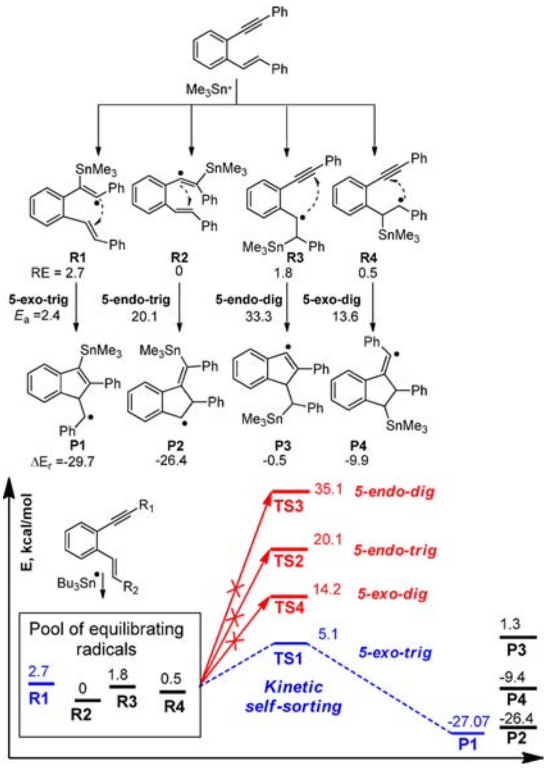


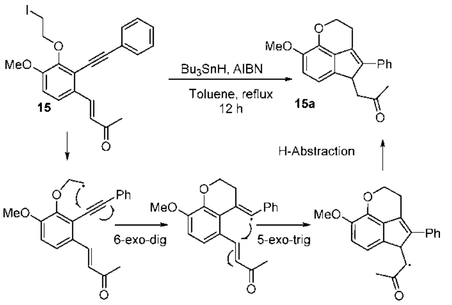
Figure 2. Computational analysis of the four competing reaction pathways at the M06-2X/Lanl2dZ level.

The counterintuitive feature of this selective process is that the productive cyclization path originates from the *least stable* of the four equilibrating radicals. Nevertheless, according to the Curtin–Hammett principle, as long as equilibration of such radicals through β- Bu_3Sn-group scission[16] proceeds faster than any of their subsequent reactions, the reaction outcome is determined by the lowest energy transition state (Figure 2). The relative energies of the rapidly interconverting reactants are unimportant. Conceptually, this formation of a single product from a complex mixture can be considered as an example of dynamic covalent chemistry (DCC) in a radical process[17] where a fast cyclization provides a mechanism for kinetic self-sorting.

Intrigued by the lack of cyclic product formation from ketone **12**, we investigated whether introduction of a more reactive functionality (CH_2I group) will initiate the cyclization (Scheme 4). The structure of the major tricyclic compound **15a** indicates that the initial intermolecular attack of a tin radical proceeds exclusively at the C–I bond and that the intermediate vinyl radical can attack the C=C moiety of the vinyl ketone. From a mechanistic perspective, this finding suggests that the absence of cyclization products in the case of **12** is not due to the inefficiency of the 5-exo-trig step but probably lies at earlier stages of the cascade. We will investigate this question in our future work.

The subsequent sequence of two radical exo-cyclizations is fully consistent with the stereoelectronic preferences of radical cyclizations.[18] The chemoselective radical attack at the alkyl halide in the presence of an alkyne and alkene establishes a useful hierarchy of substituent reactivity in Bu_3Sn-radical mediated reactions: $CH_2I > \pi$-bonds.

Scheme 4. Selective Attack of Bu_3Sn-Radical on Alkyl Iodide in Presence of an Alkyne and an Alkene



In conclusion, we have shown that the intermolecular addition of a tin radical to enynes proceeds selectively at alkynes, despite the presence of the more reactive pendant alkene functionality. This selectivity is a consequence of the Curtin–Hammett principle since the observed 5-exo-trig radical ring closure derives from the reaction of the least stable from the pool of equilibrating radical species but proceeds through the lowest absolute activation barrier. This example illustrates the potential of dynamic covalent chemistry with kinetic self-sorting in the design of selective radical reactions. Aromatic enynes are readily converted into Sn-containing indenes which can be used as convenient building blocks for the preparation of functionalized indenes.

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Supporting Information Available. Full synthetic procedures, ^1H NMR, ^{13}C NMR, and 2D NMR spectra, X-ray structure of **1a**, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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[17] For DCC with the much longer lived persistent radicals, see: Otsuka, H.; Aotani, K.; Higaki, Y.; Amamoto, Y.; Takahara, A. *Macromolecules* **2007**, *40*, 1429.

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