JOC The Journal of Organic Chemistry

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Rerouting Radical Cascades: Intercepting the Homoallyl Ring Expansion in Enyne Cyclizations via C−S Scission

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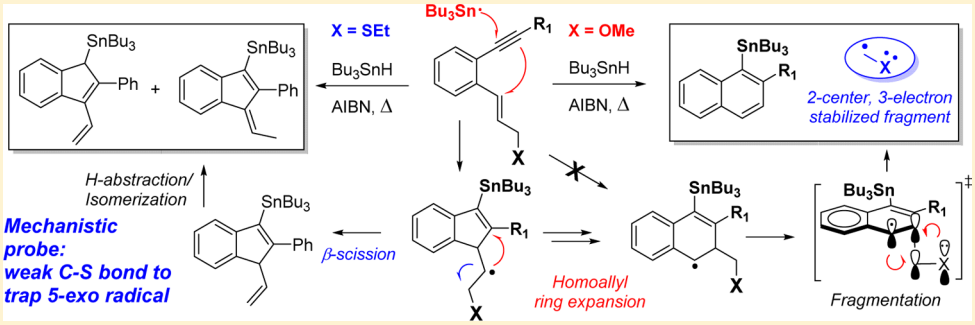
Supporting Information



ABSTRACT: The switch from 5-exo- to 6-endo-trig selectivity in the radical cyclization of aromatic enynes was probed via the combination of experimental and computational methods. This transformation occurs by kinetic self-sorting of the mixture of four equilibrating radicals via 5-exo-trig cyclization, followed by homoallyl (3-exo-trig/fragmentation) ring expansion to afford the benzylic radical necessary for the final aromatizing C−C bond fragmentation. The interception of the intermediate 5-exo-trig product via β-scission of a properly positioned weak C−S bond provides direct mechanistic evidence for the 5-exo cyclization/ring expansion sequence. The overall cascade uses alkenes as synthetic equivalents of alkynes for the convenient and mild synthesis of Bu_3Sn-functionalized naphthalenes.

INTRODUCTION

The alkyne functional group is a high-energy moiety whose versatile reactivity[1] can be harnessed for useful transformations.[2] In particular, radical cascade cyclizations[3] of alkynes[4] provide a convenient route to structures desirable in conjugated functional materials[5] such as polycyclic aromatics.[6]

We recently reported that the Bu_3Sn-mediated radical cyclization of aromatic enynes provides a facile route to Sn-substituted indenes[7] and naphthalenes.[8] The selectivity of this transformation is controlled by substitution at the alkene end (Scheme 1). Reactants with radical stabilizing groups (CO_2R/Ph) afford indenes, while $-CH_2X$ (X = H, alkyl, OR, NR_2, Ph) substitution gives six-membered products. In the cases of X = OR, NR_2, Ph, the cyclizations afford aromatic products by the *concomitant loss of the* $-CH_2X$ *group* via β-scission of a C−C bond.[9] The energetic penalty for breaking a strong σ-bond is compensated by the aromaticity gained in the product and by the rational design of radical leaving groups stabilized by two-center, three-electron bonding between the radical and the lone pair of an adjacent heteroatom (or benzylic stabilization). In the latter "self-terminating" radical cyclization, alkenes serve as synthetic equivalents of alkynes, providing fully aromatized products without external oxidants.

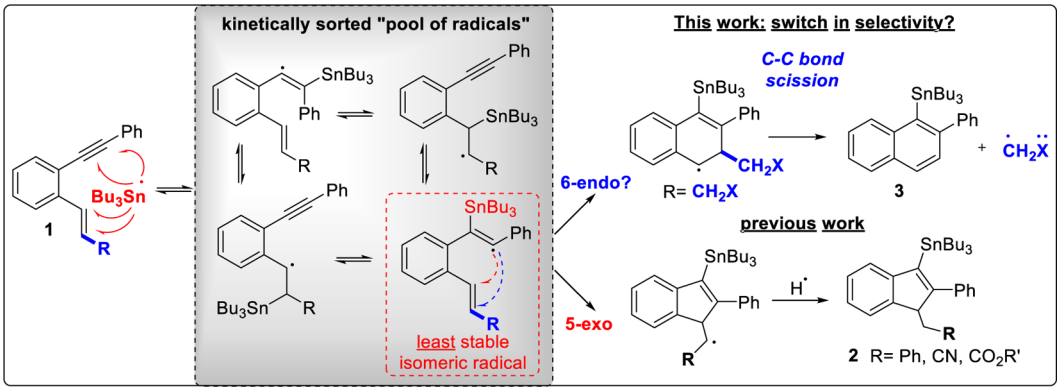
On the basis of the stereoelectronic preferences in alkyne and alkene cyclizations,[10] we were intrigued by the formation of formal 6-endo products. Radical attack at π-bonds intrinsically favors the exo path,[10] unless special factors such as steric or polar effects are used in the reaction design.[11−13] Considering the unexpected regioselectivity of the overall transformation, we set out to investigate how the nature of the substituent at the alkene controls the competition between 5-exo-trig and 6-endo-trig pathways without affecting the high chemo- and regioselectivity of the initial radical attack at the enyne. We had previously shown that the reaction selectivity stems from kinetic sorting[14] of the equilibrating "pool" of radicals via the lowest activation barrier escape route. However, the role of alkene substitution in changing the nature of the final cyclization step has so far remained unclear. In particular, we were interested in understanding whether it involves selective stabilization of the 6-endo transition state (TS) or relative destabilization of the 5-exo TS or whether the situation is even more complex.

In particular, the observed change in selectivity could rather originate from ring expansion of the initially formed 5-exo intermediate into the six-membered product and not from direct 6-endo trig cyclization, as shown in Scheme 2. Such expansion, rendered possible by the presence of an adjacent π-bond and the intrinsically low barriers of radical 3-exo cyclizations,[10d] has been implicated in a variety of radical rearrangements such as Dowd−Beckwith,[15] neophyl,[27] O-neophyl,[16,17] and homoallyl[18,19] rearrangements (Scheme 2).

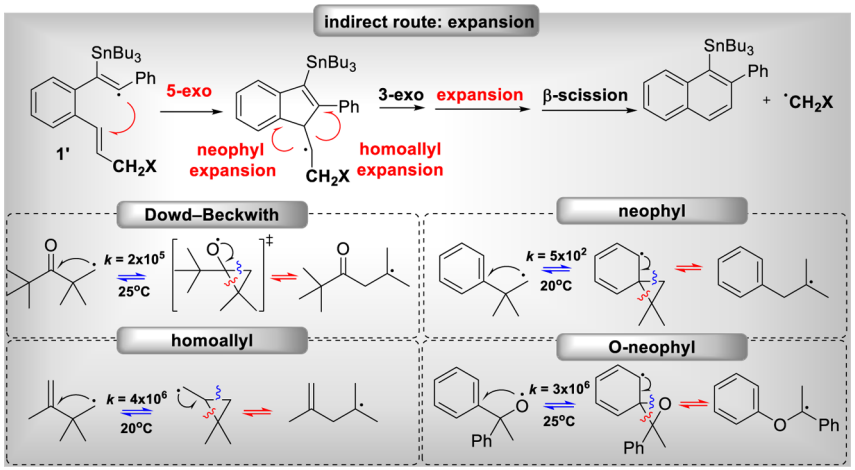
Received: May 29, 2014
Published: July 10, 2014

   dx.doi.org/10.1021/jo5012043 | J. Org. Chem. 2014, 79, 7491−7501

Scheme 1. Kinetic Self-Sorting and Alkene Substituent Effects on Reactivity of Enynes: (Bottom) Radical-Stabilizing Groups Favoring Hydrogen Atom Abstraction To Form Indenes; (Top) Radical Leaving Groups Fragmenting To Form Naphthalenes



Scheme 2. Top: Indirect (Rearrangement) Routes for the Formation of "6-endo" Products (Top) and Family of Radical Rearrangements Proceeding via a Three-Membered-Ring Intermediate (Bottom)[a]



[a]The rate constants are from refs 20 and 21.

If such rearrangement is involved prior to the terminating fragmentation step, the overall reaction cascade's selectivity is guided through a sequence of two radical cyclizations and two radical fragmentations by utilizing a single radical from an equilibrating radical mixture. The combination of experimental and computational results, provided herein, elucidate the mechanism of this transformation.

RESULTS AND DISCUSSION

To understand the switch in reactivity, a variety of enynes were synthesized with different alkene substituents. Depending on the availability of the starting materials, we used strategies based on sequential Wittig reaction and Sonogashira coupling, as shown in Scheme 3 (see the Experimental Section for details).

In the presence of Bu_3Sn radical in refluxing toluene, enynes **1a–c** cyclized to the substituted naphthalenes selectively in good yields (Figure 1). To avoid complications associated with the partial hydrolysis of tin-containing compounds on silica, the Bu_3Sn moiety was removed by protodestannylation prior to purification. In the case of **1b,c**, the starting enyne was obtained as a mixture of *cis* and *trans* isomers (see the Supporting Information for details); however, upon cyclization, each substrate still gave a high yield of a single naphthalene product.

Naphthalene formation has to involve initial attack at the triple bond (Figure 2). As discussed above, the mode of cyclization can either be 5-exo-trig or 6-endo-trig; however, fragmentation can only occur from the six-membered radical. If 5-exo cyclization is preferred, this radical must undergo further rearrangement/ring expansion[18] to give the formal 6-endo radical. This can be initiated by 3-exo attack at the vicinal benzene ring as a neophyl expansion (blue pathway, Figure 2) or the "isolated" double bond as a homoallyl expansion (red pathway, Figure 2).

In lieu of labor-intensive isotope labeling, we utilized enynes **1b,c** to differentiate between the two possible ring expansion pathways: neophyl vs homoallyl. By this simple strategy, the alkyl substituents at the two alkene carbons were used to track the position of the reacting carbon atoms (Figure 3). The lack of carbon transposition in each respective cyclization product for enynes **1b,c** eliminated the neophyl expansion path (blue) in Figure 2, which would require transient loss of aromaticity. While this observation does not rule out the 6-endo cyclization, it suggests that the ring expansion proceeds via the homoallyl rearrangement, initiated by cyclization onto the "isolated" double bond (red pathway).

In agreement with the experimental data, the computed activation barriers suggest that neophyl rearrangement should be significantly slower than the homoallyl path (Figure 4, 18.8 vs 13.6 kcal/mol, respectively). The barrier for the 3-exo closure onto the "isolated" alkene is much lower than the barrier for cyclization which disrupts aromaticity; however, the former is

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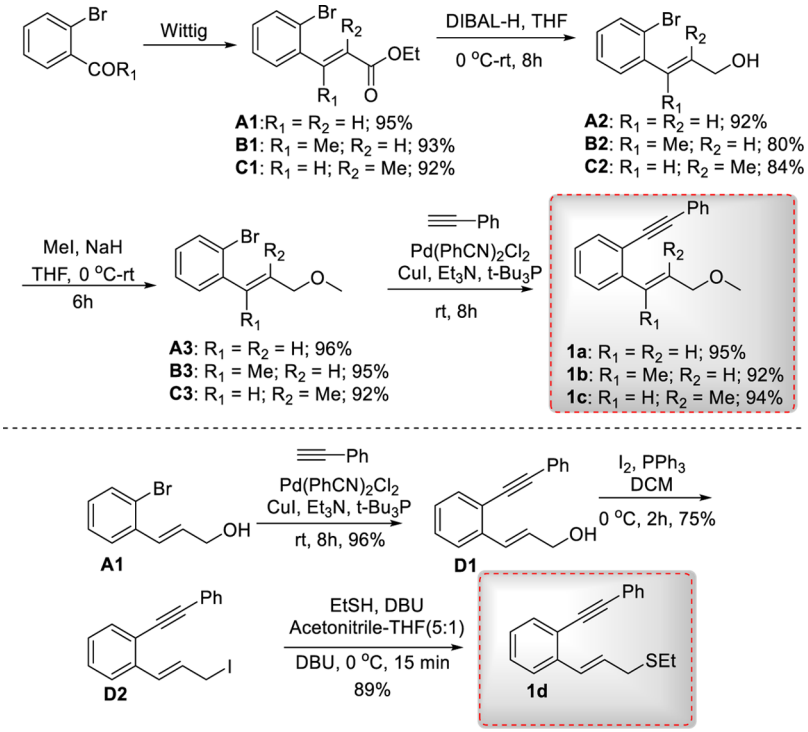
Scheme 3. Synthetic Approaches to the Synthesized Library of Enynes



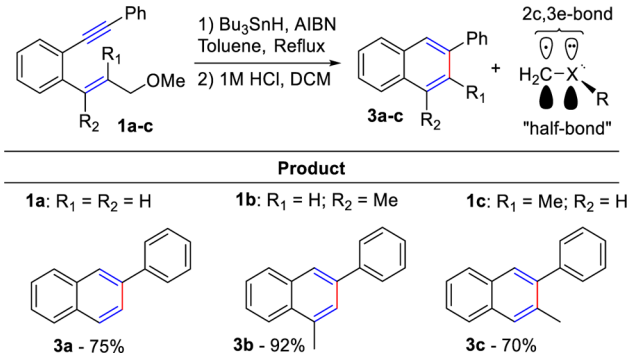


Figure 1. Tin-mediated enyne cyclization/fragmentation to naphthalene.

still quite significant due to accumulation of strain in the tricyclic moiety.

Both the neophyl and homoallyl ring openings are exergonic (~16 and ~12 kcal/mol relative to the 5-exo radical) because the less strained six-membered radicals enjoy significant stabilization by additional electronic effects: allylic vs benzylic resonances and the through-bond (TB) interaction between the radical center and the lone pair of the exocyclic oxygen atom.[8] The six-membered radical resulting from the neophyl rearrangement is more stable due to the greater stabilization provided by the allylic resonance relative to the benzylic resonance in addition to α-Sn stabilization.[22]

We had found earlier that such TB stabilizing interactions increase even further in the TS for the subsequent C−C bond fragmentation.[8] Due to this selective TS stabilization effect and assistance by the developing aromatic character of the final product, the barrier for the fragmentation of the relatively strong (C−C) bond is relatively small (~20 vs ~24 kcal/mol relative to the respective 6-endo radical for the red and blue pathways, respectively).

Our further computational studies focused on the competition between homoallyl and direct 6-endo pathways given in Figure 2.

From the calculated energy profile for enyne **1a**, it is apparent that 5-exo-trig cyclization is more facile than 6-endo cyclization ($\Delta G^{\ddagger}$(398 K) = 7.3 vs 9.9 kcal/mol; Figure 5). At the relatively high reaction temperatures where addition processes are disfavored by the negative entropy, the free energy for β-scission of the initially formed radical back to the starting enyne is lower than the barrier for 5-exo-trig cyclization (6.3 vs 7.3 kcal/mol), suggesting a precascade equilibration between enyne reactant and acyclic vinyl radical intermediate.

The 5-exo-trig cyclization is ~20 kcal/mol exergonic and can be considered irreversible from a practical point of view. From this point, two 3-exo-trig cyclizations are possible to initiate either the homoallyl or neophyl rearrangement. As discussed above, the homoallyl rearrangement has a lower activation barrier and provides a product which, albeit considerably strained, is still only slightly uphill from the 5-exo product (~2 kcal/mol). The relatively low thermodynamic penalty for the 3-exo step likely stems from the combination of benzylic stabilization and α-Sn effect at the radical center.[22]

Trapping the 5-exo Radical. An interesting consequence from the above computational study is that the relatively high (13.6 kcal/mol) barrier for the 3-exo-trig step presented an opportunity for trapping the 5-exo radical and intercepting the ring expansion pathways. A literature search for the possible ways for outcompeting the 3-exo-trig cyclization presented several choices.

For example, the elegant work of Crich and co-workers reported that relatively stable radicals can be trapped prior to intramolecular reactions by accelerating intermolecular H abstraction via polarity reversal catalysis.[20,23] Successful utilization of this strategy using catalytic amounts of PhSeH allowed trapping of the 5-exo radical prior to the ring expansion rearrangement. This intermolecular trapping was possible because the initially formed vinyl (or aryl) radical was highly reactive and underwent rapid 5-exo-trig cyclization,[24] generating a relatively

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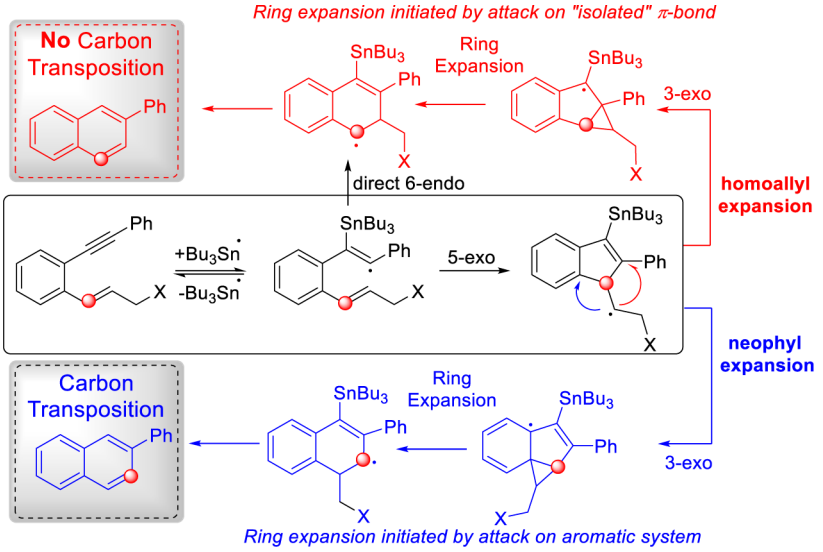

Figure 2. Plausible mechanisms for the formation of the observed naphthalene products. Direct 6-endo cyclization and the 5-exo/3-exo cascade with the participation of an alkene do not lead to carbon transposition in the product. In contrast, the 5-exo/3-exo cascade with the involvement of an aromatic system would lead to alkene carbon transposition.

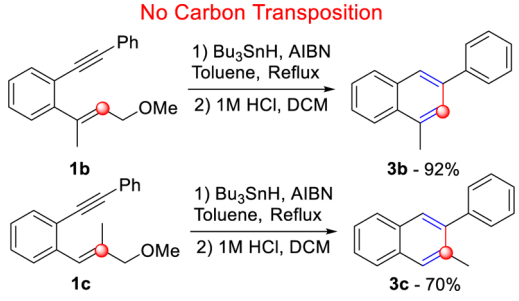

Figure 3. Cyclizations of substituted alkenes do not display carbon transposition, ruling out the neophyl pathway in Figure 2.

stable alkyl radical (Figure 6). Trapping of this longer-lived alkyl radical gave the 5-exo product as the major product.[23] This method was successful for both the neophyl and homoallyl rearrangements.

In our case, the situation is less favorable because our reaction pathway is initiated from the least stable equilibrating radical, which is formed reversibly and is present in a relatively small amount. As a consequence, the increase in intermolecular H-abstraction rate did not allow us to obtain the 5-exo product. Instead, addition of a catalytic amount of thiol gave an inseparable mixture of reduced alkyne products,[8] presumably because the radical pool is depleted when the more stable radicals

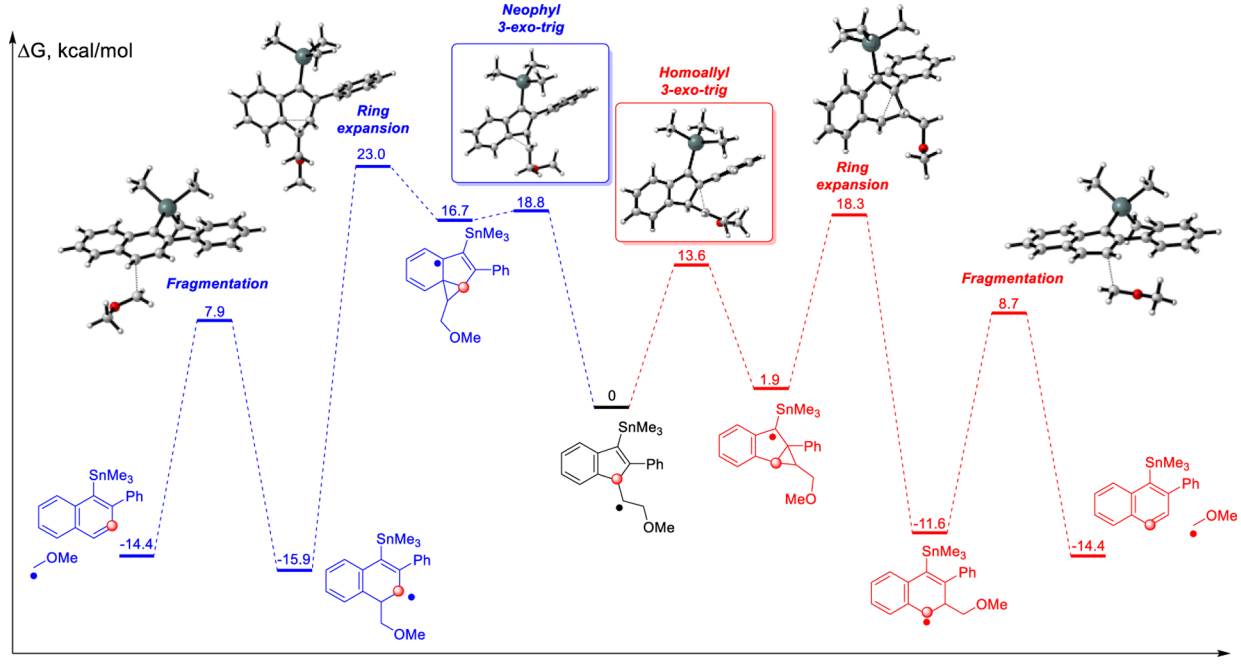

Figure 4. Calculated free energy profile for the two possible ring expansions (neophyl (blue) and homoallyl (red)) at the UM062X/LanL2DZ level of theory. ΔG values (in kcal/mol) are calculated at 384 K.

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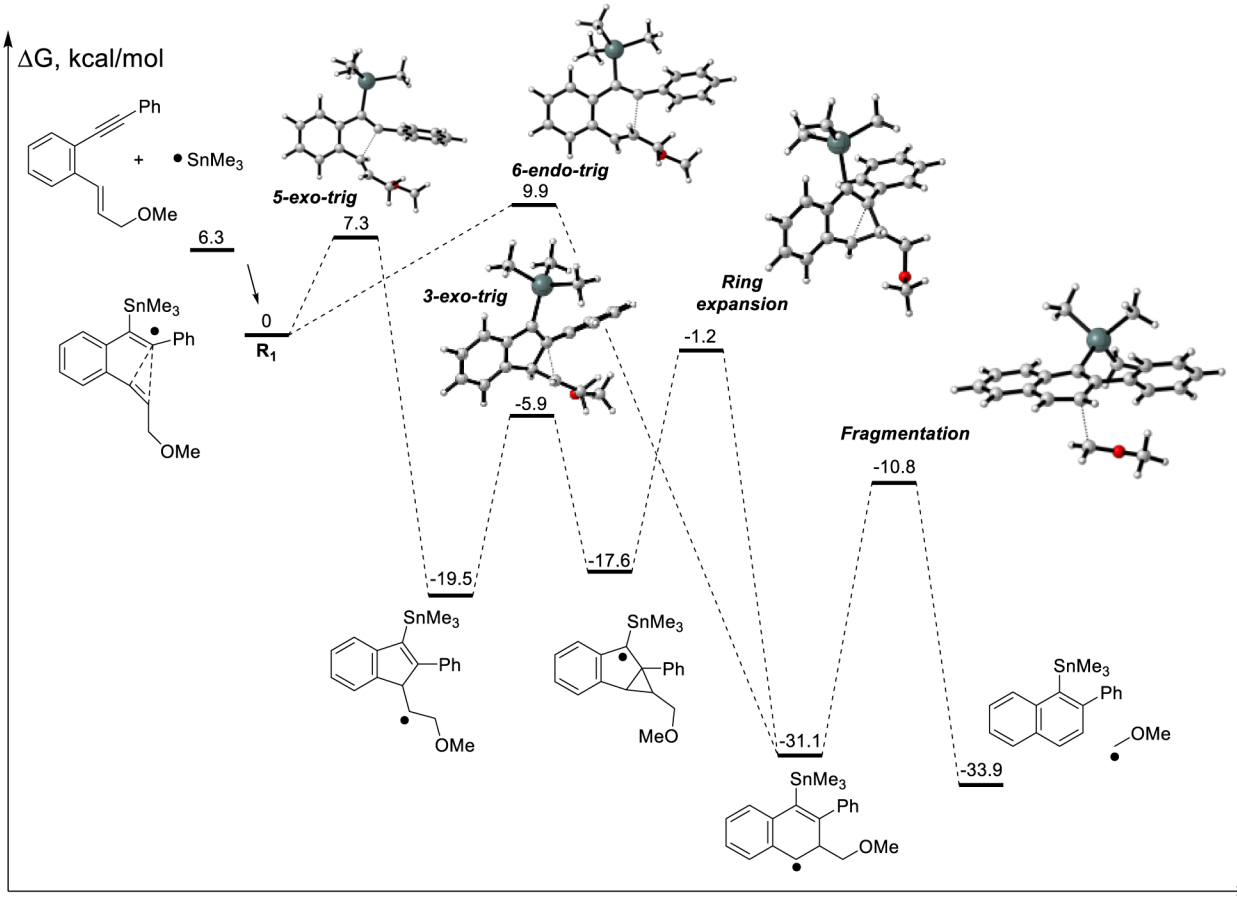

Figure 5. Calculated free energy profile for the Sn-mediated cyclization/fragmentation at the UM062X/LanL2DZ level of theory. ΔG values (in kcal/mol) are calculated at 384 K.

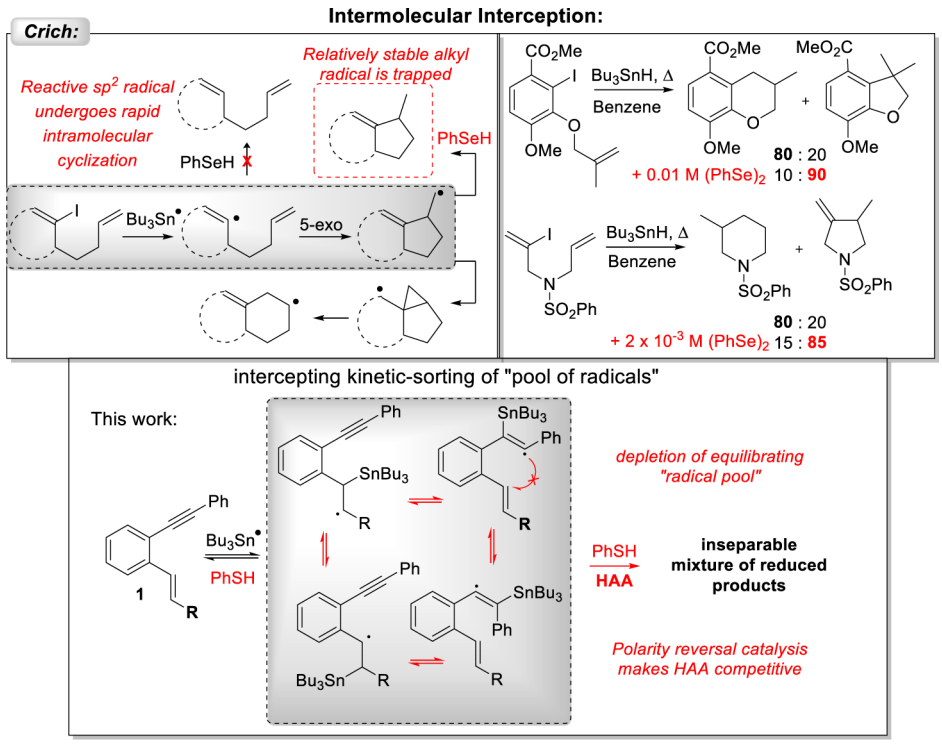

Figure 6. Intermolecular trapping of 5-exo radical prior to ring expansion using H atom abstraction (HAA) and polarity reversal catalysis.

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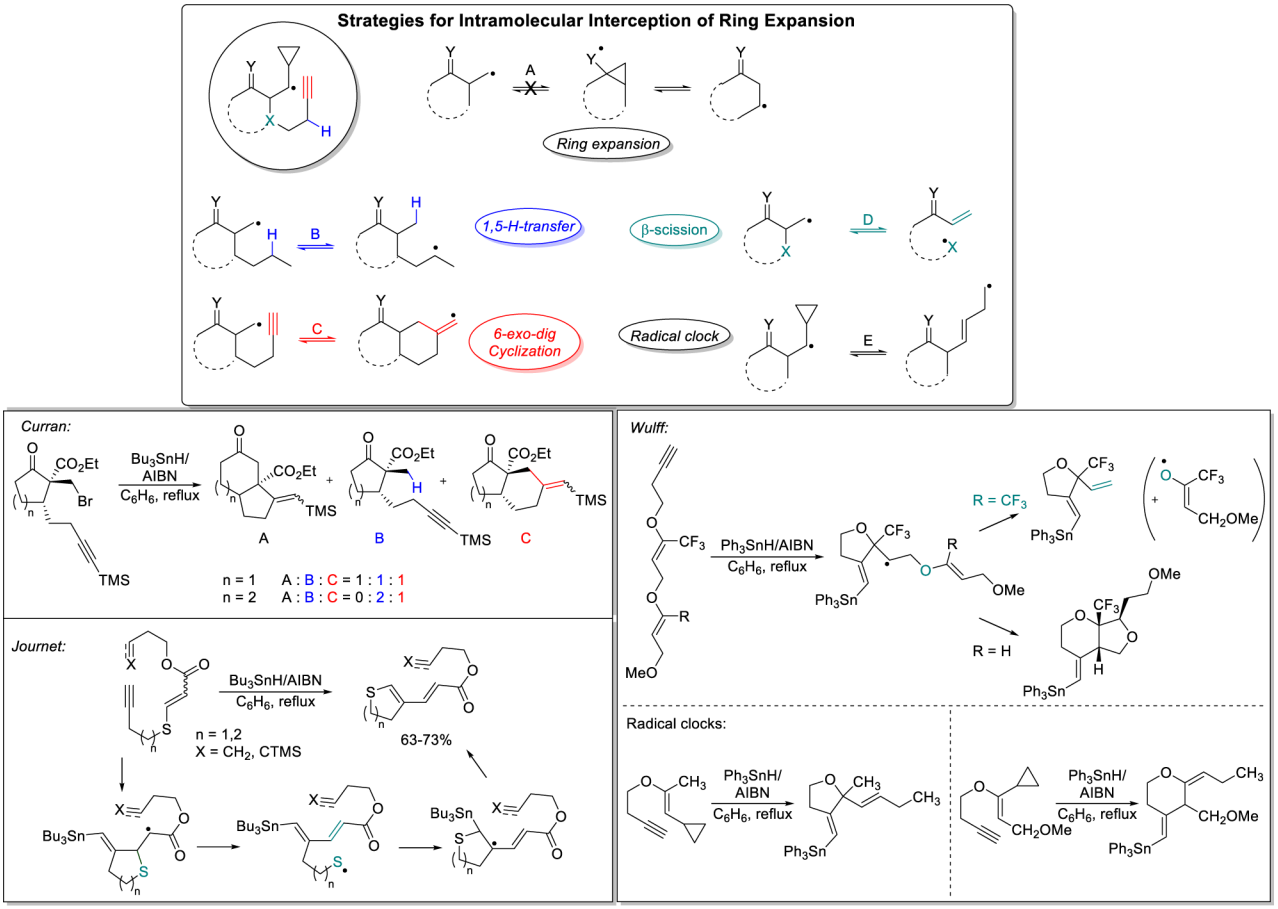

Figure 7. Intramolecular diversions of reactivity away from the ring expansion pathway involve H-abstraction, alternative faster cyclizations, or β-scission of a weak bond.

(incapable of cyclization) find a suitable intermolecular reaction path.

Since trapping via H-abstraction was not a viable option for the 5-exo radical in our systems, we turned to intramolecular alternatives (Figure 7). Curran had introduced a tethered alkyne to show that facile 6-exo-dig cyclization or intramolecular H-abstraction can compete against the 3-exo-trig cyclization (Figure 7).[25]

Alternatively, Wulff and co-workers[26] used "radical clock" strategies based on cyclopropane ring opening[24] to investigate whether cascading radical cyclizations of bis-vinyl ethers involved a sequence of 5-exo-trig addition followed by ring expansion instead of direct 6-endo-trig cyclization. Interestingly, one of the key observations pointing to the more complex mechanism was the fragmentation of a C−O bond observed upon altering one of the vinyl substituents (Figure 7, right).

We were attracted to the possibility of using β-scission of a C−S bond as a way to intercept the ring expansion pathway. An early report of Parker and co-workers disclosed that C−S scission successfully intercepted the neophyl rearrangement.[27] However, our system is more challenging because the homoallyl rearrangement is a faster process that is harder to intercept.

An indication that such an approach can be successful was given by a more recent work of Journet et al., who provided evidence suggesting that C−S bond scission can intercept the more rapid homoallyl rearrangement in the radical cascades of acyclic vinyl sulfides (Figure 7, bottom).[28] In this case, the radical generated after the first cyclization could potentially participate in three reactions in addition to the ring expansion: further cyclization, H-abstraction, or fragmentation via β-scission of a weak C−S bond. The only observed products stemmed from the β-scission, followed by subsequent cyclization. Although the authors did not allude to the potential use of the fragmentation as a mechanistic probe for the rearrangement, they did note that this process was able to efficiently outcompete other reactions.[23]

Considering the above and the relative ease of incorporating an allylic sulfide in the reactant, we decided to test whether β-scission of a weak C−S vicinal bond[28,29] can be utilized for the interception of the 5-exo radical prior to ring expansion (Figure 8).

Indeed, the reaction of allylic sulfide gave mostly five-membered products. The absence of the alkylthio moiety in the products indicated that the 5-exo radical is successfully intercepted via β-C−S scission (Figure 9). A very small amount (~4%) of the naphthalene product **3a** may originate directly via the 6-endo path, presumably due to the smaller $\Delta G^{\ddagger}$ difference between the 5-exo and 6-endo pathways for this substrate (0.6 kcal/mol, Figure 10) relative to X = OMe (2.6 kcal/mol). The smaller 5-exo/6-endo difference for the alkylthio-substituted enyne allows direct 6-endo-trig cyclization to compete with the initial 5-exo-trig cyclization.

Computational analysis confirms that the successful diversion of the homoallyl ring expansion results from outcompeting the usually facile 3-exo-trig cyclization (Figure 10). Rapid β-scission of the C−S bond has a calculated barrier of only 4.3 kcal/mol, in comparison to 13.8 kcal/mol for the 3-exo path. The fragmented thiyl radical is relatively reactive and may assist in isomerization

dx.doi.org/10.1021/jo5012043 | J. Org. Chem. 2014, 79, 7491−7501

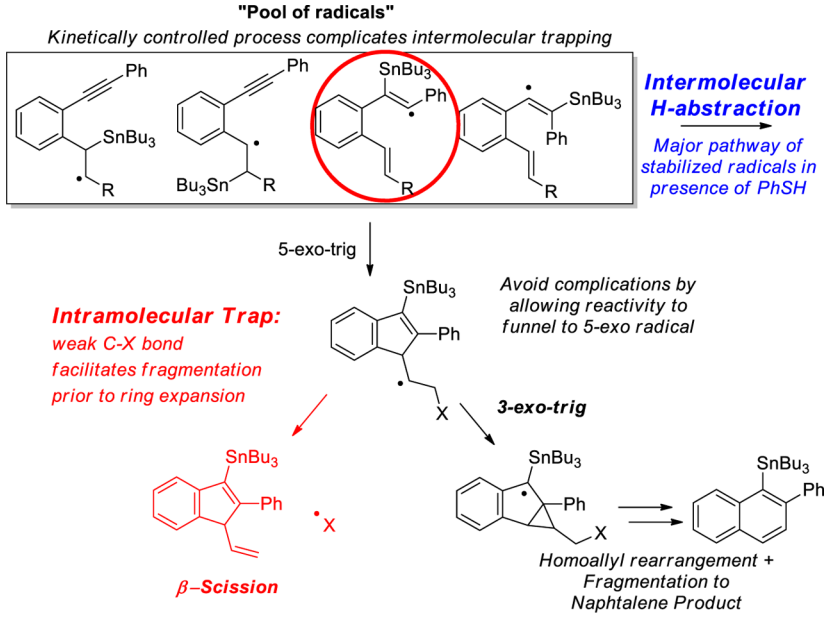

Figure 8. Planned trapping of 5-exo radical via β-scission of a weakened C–X bond.

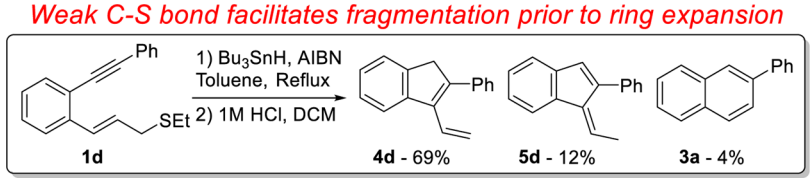

Figure 9. Alternate reactivity observed for thio-substituted enynes.

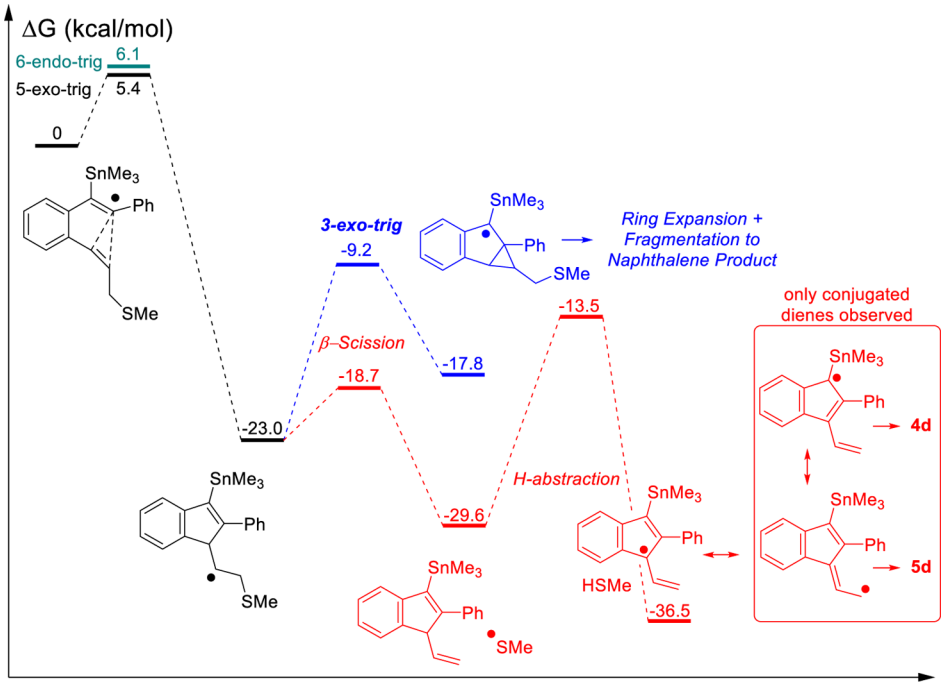

Figure 10. Calculated free energy profile (UM062X/LanL2DZ) for thio-substituted enynes. Energies are given in kcal/mol. ΔG values are calculated at 384 K.

of the initially formed nonconjugated dienes into two conjugated diene products, the major of which is derived from the benzylic radical stabilized by the adjacent C–Sn bonds.[22]

The structure of the major indene isomer was confirmed via single-crystal X-ray analysis of the Diels–Alder product with *N*-phenylmaleimide (Figure 11).

dx.doi.org/10.1021/jo5012043 | J. Org. Chem. 2014, 79, 7491–7501

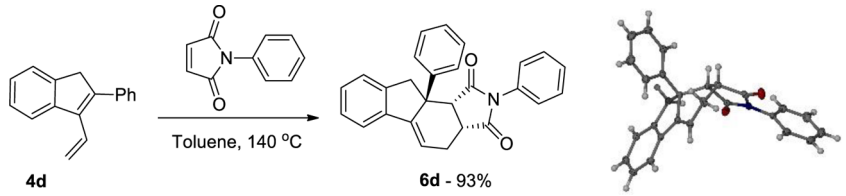

Figure 11. Diels–Alder trapping of diene product (left) and single-crystal X-ray structure (right).

While removal of tin was generally conducted prior to characterization, the direction of tin attack can be confirmed via Stille coupling or iodination. Such reactivity illustrates a synthetic advantage of the "tin handle" for facile functionalization of the naphthalene core. Not only is the Bu_3Sn radical a synthetic equivalent of the H radical for the preparation of pristine hydrocarbons via radical cyclizations but it also offers other synthetic opportunities via reactions with suitable electrophilic reagents. Through either direct cross-coupling or iodination followed by coupling, one can generate highly substituted naphthalene derivatives that are difficult to prepare from the parent aromatic core (Figure 12).

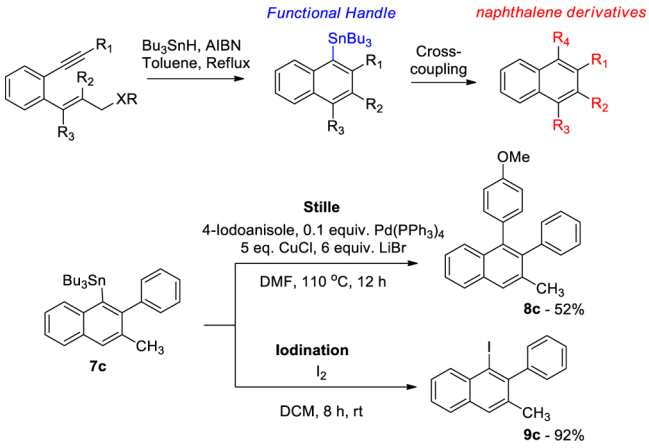

Figure 12. Initial substitution along with tin as a functional handle provides naphthalene building blocks.

Oxidative closure of aromatic substituents can afford larger polycyclic aromatic hydrocarbon structures. Investigation of such reactivity is underway and will be reported in due course, as well as expansion of this reaction toward larger systems.

CONCLUSIONS

We have found a new and efficient radical method for the synthesis of substituted naphthalene building blocks by using radical-stabilizing substitution at the allylic position in the enyne system. The experimental and computational evidence converges on the mechanism proposed in Figure 13. All substrates undergo kinetic self-sorting via 5-exo-trig cyclization of the least stable of the rapidly equilibrating radicals as the major pathway. This transformation illustrates the versatility of radical reactivity, as small electronic perturbations lead to large changes in observed reactivity. While alkene substitution does not alter the cyclization mode, decreased stabilization of the cyclized radicals can allow for further reactivity: i.e., ring expansion/fragmentation.

When X = OMe, the 5-exo radical undergoes homoallyl[18] ring expansion (3-exo-trig followed by cyclopropyl opening), affording the formal 6-endo radical. This radical is stabilized via

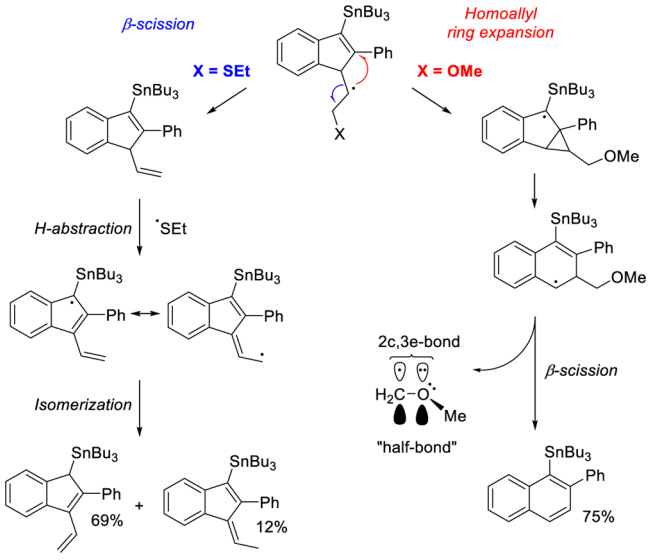

Figure 13. Proposed mechanistic diversion from the homoallyl ring expansion path.

TB interactions, which become even stronger in the fragmentation TS.[8] The self-terminating fragmentation[8] affords substituted naphthalene products and stabilized radicals which do not seem to provide efficient propagation.

Diversion away from the ring expansion pathway is possible in the respective allyl sulfides, where the weak C–S bond readily undergoes β-scission after the initial 5-exo-trig cyclization. Isomerization provides indene and fulvene products. While other mechanistic probes for diverting reactivity away from ring expansion exist, this method benefits from simple incorporation of the fragmenting group into starting materials.

EXPERIMENTAL SECTION

General Procedures. Toluene and THF were obtained from a Glass Contour Solvent Purification System. Hexanes for column chromatography and preparatory thin-layer chromatography was distilled prior to use. All other solvents were used as purchased. Column chromatography was performed using silica gel (60 Å), and preparatory thin-layer chromatography was performed using a 1000 μm glass-backed plate containing UV dye. Unless otherwise noted, ^{1}H NMR spectra were run on 400 and 600 MHz spectrometers in $CDCl_3$ and ^{13}C NMR spectra were run on 100 and 150 MHz spectrometers in $CDCl_3$. Proton chemical shifts are given relative to the residual proton signal of $CDCl_3$ (7.26 ppm). Carbon chemical shifts were internally referenced to the $CDCl_3$ (77.23 ppm) signal. All J coupling values are reported in hertz (Hz).

Preparation of Wittig Salt: Ethyl (Triphenylphosphoranylidene)-acetate. Ethyl bromoacetate (2.9 mL, 26.7 mmol) was added dropwise into a solution of triphenylphosphine (7 g, 26.7 mmol) in benzene at room temperature. It was stirred for 4–5 h. The separated solid was filtered using a Buchner funnel and the residue washed with hexane. The resulting white solid was taken up in benzene (200 mL) and a solution of 15 g of NaOH in 100 mL of water was added to it. The mixture was

dx.doi.org/10.1021/jo5012043 | J. Org. Chem. 2014, 79, 7491–7501

stirred until both layers became clear. The benzene layer was dried over sodium sulfate and concentrated. The salt was recrystallized from distilled petroleum ether (60−80 °C) to provide 8.9 g (96% yield) of white solid.

Synthesis of Compound A1 by Wittig Reaction. Ethyl (triphenylphosphoranylidene)acetate (2.80 g, 8.17 mmol) was added to a solution of bromobenzaldehyde (1.0 g, 5.4 mmol) in dry DCM (dichloromethane) at 0 °C and stirred for 6 h at room temperature. The solvent was then evaporated under vacuum. The colorless oil was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. It was then filtered and evaporated to give an oil from which the title compound **C1** was isolated by column chromatography (Si-gel, PE/EA 15/1). Yield: 1.3 g (95%); State: colorless oil.

DIBAL-H Reduction of α,β-Unsaturated Ester A1 (A2). A THF solution of compound **A1** (2.0 g, 7.8 mmol) was cooled to 0 °C. Diisobutylaluminum hydride (DIBAL-H; 1.0 M in hexane, 15 mL, 15 mmol) was slowly added to this solution under nitrogen. The reaction mixture was stirred for 6 h, quenched with aqueous NH_4Cl solution (20 mL), and extracted with ethyl acetate (100 mL). The extract was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was eluted with 10% ethyl acetate in hexane through a silica column to afford **A2** as a colorless oil (92%).

(*E*)-1-Bromo-2-(3-methoxyprop-1-en-1-yl)benzene (A3). To a suspension of NaH (60% dispersion in mineral oil) in THF (20 mL) was added 2-bromocinnamyl alcohol **A2** (1.0 g, 4.7 mmol) at room temperature. The mixture was stirred for 100 min at room temperature, after which MeI (0.9 mL, 14 mmol, 3 equiv) was added in one portion. The mixture was stirred for 1 h at room temperature and then filtered through a pad of silica gel. The solid was washed using hexane/ethyl acetate (1/1) as the eluent, and the filtrate was concentrated and purified by silica gel column chromatography, using 5% ethyl acetate in hexane as the eluent, to afford the title compound **A3** (96% yield) as a colorless oil: R_f = 0.5 (3% ethyl acetate in hexane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.54 (2H, dt, J =7.9, 1.1 Hz), 7.26 (1H, t, J = 7.6 Hz), 7.09 (1H, dt, J = 7.7, 1.5 Hz), 6.80 (1H, d, J = 15.8 Hz), 6.22 (1H, td, J = 15.8, 5.6 Hz), 4.12 (2H, dd, J = 5.9, 1.4 Hz), 3.41 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 136.8, 133.1, 131.3, 129.2, 129.1, 127.7, 127.3, 123.8, 73.1, 58.3; HRMS (EI, TOF) calcd for $C_{10}H_{11}BrO$ $[M]^+$ 225.9993, found 225.9984; IR (neat, cm^{-1}) 3055, 1440, 1113.

(*E*)-1-(3-Methoxyprop-1-en-1-yl)-2-(phenylethynyl)benzene (1a). A suspension of aryl bromide (4.5 mmol), $PdCl_2(PhCN)_2$ (0.23 mmol), and Cu(I) iodide (0.23 mmol) in 20 mL of triethylamine was degassed three times with the freeze/pump/thaw technique in a flame-dried round-bottom flask. Once the reaction mixture was completely thawed and the atmosphere replaced with argon, tri-*tert*-butylphosphine (0.45 mmol in a 10% solution of toluene) was added, immediately followed by 1.2 equiv of phenylacetylene (5.4 mmol) using a syringe. The mixture was allowed to react for 8 h and monitored by TLC. After total consumption of the aryl bromide, the reaction mixture was filtered through Celite and extracted with DCM (3 × 30 mL). The organic layer was washed with a saturated solution of ammonium chloride and water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Chromatographic purification (5% ethyl acetate in hexane) afforded compound **1a** (95% yield) as a brown oil: R_f = 0.6 (5% ethyl acetate in hexane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.61−7.54 (4H, m), 7.41−7.36 (3H, m), 7.31 (1H, t, J = 7.6 Hz), 7.26−7.20 (2H, m), 6.41 (1H, td, J = 16.0, 6.0 Hz), 4.18 (2H, dd, J = 6.0, 1.1 Hz), 3.43 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 138.3, 132.7, 131.7 (2C), 130.7, 128.7, 128.6, 128.5 (2C), 128.1, 127.5, 125.4, 123.5, 122.1, 94.2, 88.0, 73.4, 58.2; HRMS (EI, TOF) calcd for $C_{18}H_{16}O$ $[M]^+$ 248.1201, found 248.1195; IR (neat, cm^{-1}) 3055, 2214, 1489, 965.

Synthesis of Compound B1 by Wittig Reaction. To a suspension of sodium hydride (60% dispersion in mineral oil, 8 mmol) in dry THF (200 mL) was added dropwise triethyl phosphonoacetate (4 mmol) at 0 °C under an argon atmosphere. After 30 min, 2′-bromoacetophenone (5.4 mmol) was added to the reaction mixture, which was then warmed to room temperature and stirred for 8 h. A saturated aqueous ammonium chloride solution (20 mL) was then added dropwise to the mixture. The aqueous phase was extracted with diethyl ether (4 × 50 mL), and the combined organic phase was washed with brine (3 × 50 mL), dried over sodium sulfate, and concentrated in vacuo. Flash chromatography (5% ethyl acetate in hexanes) yielded ester **B1** as a clear oil in 93% yield.

DIBAL-H Reduction of α,β-Unsaturated Ester B1 to B2. **B2** was synthesized using the same procedure described for the synthesis of compound **A2**.

(*E*)-1-Bromo-2-(4-methoxybut-2-en-2-yl)benzene (B3). **B3** was synthesized using the procedure described for the synthesis of compound **A3**. Chromatographic purification (5% ethyl acetate in hexane) afforded compound **B3** (95% yield) as a colorless oil: R_f = 0.6 (10% ethyl acetate in hexane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.53 (1H, d, J = 8.0 Hz), 7.26−7.22 (1H, m), 7.19−7.17 (1H, m), 7.12−7.09 (1H, m), 5.55 (1H, tm), 4.12 (2H, d, J = 6.6 Hz), 3.40 (3H, d, J = 0.7 Hz), 2.02 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 145.6, 140.1, 132.7, 129.9, 128.4, 127.3, 127.2, 121.9, 68.8, 56.0, 18.0; HRMS (EI, TOF) calcd for $C_{11}H_{13}BrO$ $[M]^+$ 240.0150, found 240.0141; IR (neat, cm^{-1}) 3052, 2198, 1479.

(*E*)-1-(4-Methoxybut-2-en-2-yl)-2-(phenylethynyl)benzene (1b). This compound was obtained using the procedure described for the synthesis of **1a**. Chromatographic purification (5% ethyl acetate in hexane) afforded compound **1b** (92% yield) as a brown oil: R_f = 0.6 (10% ethyl acetate in hexane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.56 (1H, d, J = 7.6 Hz), 7.53−7.49 (2H, m), 7.37−7.33 (3H, m), 7.29−7.25 (3H, m), 5.80 (1H, m), 4.19 (2H, d, J = 6.6 Hz), 3.42 (3H, s), 2.19 (3H, s).^{13}C NMR (100 MHz; $CDCl_3$) δ 147.3, 139.6, 132.8, 131.6 (2C), 128.5 (2C), 128.4, 128.3, 128.2, 127.1, 126.9, 123.7, 121.1, 92.8, 89.2, 69.3, 58.0, 18.0; HRMS (EI, TOF) calcd for $C_{19}H_{18}O$ $[M]^+$ 262.1358, found 262.1351; IR (neat, cm^{-1}) 3065, 2240, 1498, 966.

Synthesis of Compound C1 by Wittig Reaction. This compound was obtained using the procedure described for **B1.**

DIBAL-H Reduction of α,β-Unsaturated Ester C1 to C2. **C2** was synthesized using the procedure described for the synthesis of compound **A2**.

(*E*)-1-Bromo-2-(3-methoxy-2-methylprop-1-en-1-yl)benzene (C3). **C3** was synthesized using the procedure described for the synthesis of compound **A3**. Chromatographic purification (5% ethyl acetate in hexane) afforded compound **C3** (92% yield) as a colorless oil: R_f = 0.5 (5% ethyl acetate in hexane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.57 (1H, d, J = 7.8 Hz), 7.28−7.24 (2H, m), 7.12−7.06 (1H, m), 6.52 (1H, s), 4.01 (2H, s), 3.40 (3H, s), 1.76 (3H, d, J = 1.3 Hz).); ^{13}C NMR (100 MHz; $CDCl_3$) δ 137.8, 136.6, 132.6, 130.9, 128.3, 126.9, 126.5, 124.3, 78.0, 57.9, 15.2; HRMS (EI, TOF) calcd for $C_{11}H_{13}BrO$ $[M]^+$ 240.0150, found 240.0147; IR (neat, cm^{-1}) 3066, 2222, 1491.

(*E*)-1-(3-Methoxy-2-methylprop-1-en-1-yl)-2-(phenylethynyl)-benzene (1c). This compound was obtained by following the procedure described for the synthesis of **1a**. Chromatographic purification (5% ethyl acetate in hexane) afforded compound **1c** (94% yield) as a brown oil: R_f = 0.6 (5% ethyl acetate in hexane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.60 (1H, dd, J = 7.5, 0.9 Hz), 7.57−7.54 (2H, m), 7.40−7.32 (5H, m), 7.26 (1H, dt, J = 7.4, 1.4 Hz), 6.90 (1H, s), 4.09 (2H, d, J = 0.8 Hz), 3.44 (3H, s), 1.91 (3H, d, J = 1.2 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 139.6, 136.3, 132.2, 131.6 (2C), 129.1, 128.5 (2C), 128.3, 128.0, 126.6, 126.0, 123.6, 123.0, 93.9, 88.6, 78.6, 57.7, 15.6; HRMS (EI, TOF) calcd for $C_{19}H_{18}O$ $[M]^+$ 262.1358, found 262.1344; IR (neat, cm^{-1}) 3071, 2220, 1469, 981.

(*E*)-3-(2-(Phenylethynyl)phenyl)prop-2-en-1-ol (D1). This compound was obtained by following the procedure described for the synthesis of **1a**. Chromatographic purification (5% ethyl acetate in hexane) afforded compound **1C** (96% yield) as a brown solid: mp 59 °C; R_f = 0.6 (5% ethyl acetate in hexane); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.58−7.53 (4H, m), 7.38−7.34 (3H, m), 7.30 (1H, t, J = 7.4 Hz), 7.25−7.22 (1H, m), 7.20 (1H, d, J = 15.9 Hz), 6.48 (1H, td, J = 15.9, 5.7 Hz), 4.38 (2H, dd, J = 5.7, 1.3 Hz), 1.73 (1H, bs); ^{13}C NMR (150 MHz; $CDCl_3$) δ 138.2, 132.6, 131.6 (2C), 130.8, 128.8, 128.6, 128.5 (2C), 128.4, 127.3, 125.2, 123.3, 121.9, 94.1, 87.9, 63.7; HRMS (EI, TOF) calcd for $C_{17}H_{14}O$ $[M]^+$234.1045, found 234.1039; IR (neat, cm^{-1}) 3325 (b), 3056, 2856, 1491.

dx.doi.org/10.1021/jo5012043 | J. Org. Chem. 2014, 79, 7491−7501

(*E*)-1-(3-Iodoprop-1-en-1-yl)-2-(phenylethynyl)benzene (D2). A DCM solution of compound **D1** (0.5 g, 2.13 mmol) was cooled to 0 °C. Triphenylphosphine (0.61 g, 2.35 mmol), iodine (0.59 g, 2.35 mmol), and imidazole (0.29 g, 4.26 mmol) were slowly added to this solution. After it was stirred at 0 °C for 2 h, the reaction mixture was quenched with water and extracted with ethyl acetate (50 mL). The extract was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was eluted through a silica column to afford compound **D2** (75%) as a dark brown solid: mp 63 °C; R_f = 0.3 (hexane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.60−7.52 (4H, m), 7.42−7.37 (3H, m), 7.31 (1H, dt, J = 7.6, 1.5 Hz), 7.24 (1H, dt, J = 7.5, 1.4 Hz), 7.18 (1H, d, J = 15.6 Hz), 6.57 (1H, td, J = 15.6, 8.2 Hz), 4.18 (2H, dd, J = 8.2, 1.0 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 137.4, 132.9, 131.8 (2C), 131.2, 128.9, 128.7 (2C), 128.6 (2C), 128.0, 125.5, 123.4, 122.3, 94.6, 87.7, 7.0; HRMS (EI, TOF) calcd for $C_{17}H_{13}I$ $[M]^+$ 344.0062, found 344.0054; IR (neat, cm^{-1}) 3015, 2923, 1490, 1135, 958.

(*E*)-Ethyl(3-(2-(phenylethynyl)phenyl)allyl)sulfane (1d). A solution of compound **D2** (2.13 mmol) in acetonitrile/THF (5/1 mixture) was cooled to 0 °C. DBU (2.35 mmol) was added to this solution. Then ethanethiol (2.35 mmol) was added slowly to the reaction mixture. The reaction mixture was stirred at 0 °C for 15 min. The reaction mixture was then quenched with water and extracted with ethyl acetate (50 mL). The extract was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatographic purification (5% ethyl acetate in hexane) afforded compound **3d** (89% yield) as a yellow oil: R_f = 0.7 (5% ethyl acetate in hexane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.58−7.52 (4H, m), 7.40−7.36 (3H, m), 7.31 (1H, t, J = 7.5 Hz), 7.23 (1H, t, J = 7.3 Hz), 7.02 (1H, d, J = 15.7 Hz), 6.34−6.26 (1H, m), 3.38 (2H, d, J = 7.4 Hz), 2.56 (2H, q, J = 7.2 Hz), 1.27 (3H, t, J = 7.2 Hz).^{13}C NMR (100 MHz; $CDCl_3$) δ 138.5, 132.7, 131.7 (2C), 130.2, 127.7, 128.6 (3C), 128.2, 127.3, 125.3, 123.5, 94.2, 88.1, 34.2, 24.7, 14.7; HRMS (EI, TOF) calcd for $C_{19}H_{18}S$ $[M]^+$ 278.1129, found 278.1123; IR (neat, cm^{-1}) 3022, 2885, 14780, 1002, 848.

General Procedure for AIBN/Bu_3SnH-Mediated Cyclizations. The starting enyne (0.34 mmol) was degassed in 4 mL of toluene and heated to reflux. Two separate solutions of AIBN (0.5 equiv) and Bu_3SnH (1.2 equiv) each in 3 mL of toluene were added using a syringe pump through the top of a condenser over the course of 4 h into the refluxing solution. The reaction mixture was stirred at reflux for 12 h. After completion, as confirmed by TLC, the solvent was evaporated and the product was dissolved in 20 mL of DCM and washed with a 2 M HCl solution to accomplish protodestannylation. The products were purified on silica gel using a gradient of hexanes followed by ethyl acetate/hexane eluent.

*2-Phenylnaphthalene (**3a**).* Chromatographic purification (hexane) afforded compound **3a** (75% yield) as a white solid: mp 105−106 °C; R_f = 0.5 (hexane); ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.06 (1H, s), 7.94−7.88 (3H, m), 7.78−7.74 (3H, m), 7.54−7.50 (4H, m), 7.40 (1H, t, J = 7.3 Hz); ^{13}C NMR (150 MHz; $CDCl_3$) δ 141.3, 38.8, 133.8, 132.8, 129.1 (2C), 128.6, 128.4, 127.8, 127.6 (2C), 127.5, 126.5, 126.1, 126.0, 125.8; HRMS (EI, TOF) calcd for $C_{16}H_{12}$ $[M]^+$ 204.0939, found 204.0938; IR (neat, cm^{-1}) 3056, 2921, 1947, 1453.

*1-Methyl-3-phenylnaphthalene (**3b**).* Chromatographic purification (hexane) afforded compound **3b** (92% yield) as a white solid: mp 44−45 °C; R_f = 0.6 (in hexane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.10−8.06 (1H, m), 7.98−7.95 (2H, m), 7.81−7.78 (2H, m), 7.68 (1H, s), 7.61−7.53 (4H, m), 7.46−7.42(1H, m), 2.82 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 141.4, 138.4, 135.0, 134.1, 132.0, 129.0 (3C), 127.6 (2C), 127.5, 126.5, 126.2, 126.0, 124.5, 124.2, 19.7; HRMS (EI, TOF) calcd for $C_{17}H_{14}$ $[M]^+$ 218.1096, found 218.1095.

*2-Methyl-3-phenylnaphthalene (**3c**).* Chromatographic purification (hexane) afforded compound **3c** (70% yield) as a colorless oil: R_f = 0.6 (in hexane); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.81 (2H, t, J = 7.0 Hz), 7.73 (1H, s), 7.71 (1H, s), 7.48−7.44 (5H, m), 7.43−7.38 (3H, m), 2.42 (3H, s); ^{13}C NMR (150 MHz; $CDCl_3$) δ 142.1, 141.2, 134.1, 133.1, 132.2, 129.5 (2C), 128.6, 128.4, 128.3 (2C), 127.8, 127 1 (2C), 126.1, 125.6, 21.3; HRMS (EI, TOF) calcd for $C_{17}H_{14}$ $[M]^+$ 218.1096, found 218.1092.

*2-Phenyl-3-vinyl-1H-indene (**4d**).* Chromatographic purification (hexane) afforded compound **4d** (69% yield) as a yellow solid: mp 94−95 °C; R_f = 0.6 (in hexane); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.73 (1H, d, J = 7.6 Hz), 7.53−7.50 (3H, m), 7.42 (2H, t, J = 7.6 Hz), 7.35 (1H, t, J = 7.5 Hz), 7.32 (1H, t, J = 7.4 Hz), 7.26 (1H, dt, J = 7.3, 0.8 Hz), 6.87 (1H, dd, J = 18.1, 11.7 Hz), 5.89 (1H, dd, J = 18.1, 0.5 Hz), 5.54 (1H, d, J = 11.7 Hz), 3.82 (2H, s); ^{13}C NMR (150 MHz; $CDCl_3$) δ 144.8, 143.7, 143.0, 137.3, 136.3, 131.3, 129.0 (2C), 128.5 (2C), 127.5, 126.6, 125.2, 123.9, 121.0, 118.1, 41.3; HRMS (EI, TOF) calcd for $C_{17}H_{14}$ $[M]^+$ 218.1096, found 218.1090; IR (neat, cm^{-1}) 3021, 2922, 1702, 1598, 1384.

Procedure for Diels−Alder Reaction of 4d with *N*-Phenylmaleimide. *2,10a-Diphenyl-4,10,10a,10b-tetrahydroindeno[2,1-e]-isoindole-1,3(2H,3aH)-dione (**6d**).* A solution of **1d** (0.34 mmol) in toluene was brought to reflux. A solution of tributyltin hydride (1.2 equiv) and AIBN (0.5 equiv) in toluene was added dropwise to the reaction mixture. The resulting mixture was refluxed for 12 h. Toluene was evaporated in vacuo, and the reaction mixture was dissolved in 20 mL of DCM and washed with a 2 M HCl solution to accomplish protodestannylation. DCM was then evaporated, and the residue was dissolved in 2 mL of toluene. The reaction mixture was transferred to a pressure tube, and *N*-phenylmaleimide (1 equiv) was added to it. The mixture was heated to 140 °C for 12 h. Toluene was removed in vacuo, and the residue was purified by column chromatography (25% ethyl acetate in hexanes) to afford **6d** (93%) as a white solid: mp 220−221 °C; R_f = 0.6 (5% ethyl acetate in hexane); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.57−7.55 (1H m), 7.40 (2H, t, J = 7.4 Hz), 7.35−7.30 (5H, m), 7.25−7.20 (4H, m), 7.16−7.14 (2H, m), 6.46 (1H, dd, J = 7.5, 3.4 Hz), 4.85 (1H, d, H = 17.2 Hz), 4.15 (1H, d, J = 8.5 Hz), 3.23 (1H, t, J = 8.13 Hz), 3.051 (1H, d, J = 17.2 Hz), 2.75−2.71 (1H, m), 2.14 (1H, dq, J = 8.6, 3.4 Hz); ^{13}C NMR (150 MHz; $CDCl_3$) δ 179.0, 176.9, 149.9, 145.3, 144.3, 138.6, 13.0, 129.3, 129.1 (4C), 128.7, 16.9, 126.8, 126.6 (2C), 125.8, 125.6 (2C), 120.2, 114.6, 52.3, 47.5, 45.2, 40.2, 25.8; HRMS (EI, TOF) calcd for $C_{27}H_{21}NO_2$[M]$^+$ 391.1572, found 391.1565; IR (neat, cm^{-1}) 3020, 1772, 1700, 1493, 1348.

Procedure for Stille Coupling. *1-(4-Methoxyphenyl)-3-methyl-2-phenylnaphthalene (**8c**).* A solution of **1c** (0.34 mmol) in toluene was brought to reflux. A solution of tributyltin hydride (1.2 equiv) and AIBN (0.5 equiv) in toluene was added dropwise to the refluxing solution of **1c**. The reaction mixture was allowed to reflux for 12 h. Toluene was evaporated under vacuum. A two-necked flask was charged with lithium bromide (2.04 mmol) and flame-dried under high vacuum. Upon cooling, tetrakis(triphenylphosphine)palladium(0) (0.034 mmol) and CuCl (1.7 mmol) were added, and the mixture was degassed (4×) under high vacuum with an argon purge. Dry DMF (4.0 mL) was introduced with concomitant stirring, followed by the addition of 4-iodoanisole (0.35 mmol) and the tributyltin reaction mixture. The resulting mixture was rigorously degassed (4×) by the freeze−pump−thaw method using liquid nitrogen under an argon atmosphere. The reaction mixture was stirred at room temperature for 1 h and then heated to 110 °C for 12 h. Following completion of the coupling as monitored by TLC, the reaction mixture was cooled, diluted with Et_2O, and washed with brine. The aqueous layer was further extracted with Et_2O (3×), and the combined organic layers were washed with water (2 × 40 mL) and brine (2 × 40 mL) and dried over Na_2SO_4. Concentration under vacuum afforded a residue that was purified by column chromatography (Si-gel/10% ethyl acetate in hexane) to afford **8c** (52%) as a yellow solid: mp 161−162 °C; R_f = 0.6 (in hexane); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.84 (1H, d, J = 8.2 Hz), 7.76 (1H, s), 7.52 (1H, d, J = 8.5 Hz), 7.47−7.44 (1H, m), 7.34−7.31 (1H, m), 7.22−7.19 (2H, m), 7.15−7.14 (1H, m), 7.05−7.01 (4H, m), 6.77−6.75 (2H, m), 3.77 (3H, s), 2.26 (3H, s); ^{13}C NMR (150 MHz; $CDCl_3$) δ 158.1, 141.0, 140.3, 138.5,134.7, 133.2, 132.2 (2C), 131.9, 131.8, 130.3 (2C), 127.8 (2C), 127.5, 127.3, 127.1, 126.3, 125.9, 125.4, 113.1 (2C), 55.3, 22.1; HRMS (APCI, TOF) calcd for $C_{24}H_{20}O$[M]$^+$ 324.1514, found 324.1509; IR (neat, cm^{-1}) 3031, 2855, 1150, 972.

*1-Iodo-3-methyl-2-phenylnaphthalene (**9c**).* A solution of **1c** (0.34 mmol) in toluene was brought to reflux. A solution of tributyltin hydride (1.2 equiv) and AIBN (0.5 equiv) in toluene was added dropwise to the refluxing solution of **1c**. The reaction mixture was refluxed for 12 h. Toluene was evaporated under vacuum, and the reaction mixture was dissolved in 2 mL of dichloromethane. Iodine

dx.doi.org/10.1021/jo5012043 | J. Org. Chem. 2014, 79, 7491−7501

(0.51 mmol) was added and the reaction mixture stirred at room temperature for 8 h. The reaction mixture was quenched with a saturated aqueous solution of sodium bisulfite. The aqueous layer was extracted with dichloromethane (4×), and the combined organic layer was dried over sodium sulfate and concentrated. Chromatographic purification (hexane) afforded compound **9c** (92% yield) as a white solid: mp 95−96 °C; R_f = 0.4 (in hexane); ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.23 (1H, dd, J = 8.3, 0.7 Hz), 7.75−7.73 (1H, m). 7.69 (1H, s), 7.55−7.49 (4H, m), 7.46−7.43 (1H, m), 7.19−77.18 (2H, m), 2.22 (3H, d, J = 0.6 Hz); ^{13}C NMR (150 MHz; $CDCl_3$) δ 147.3, 146.1, 135.3, 133.9 (2C), 133.5, 129.3 (2C), 128.9, 128.6 (2C), 127.7 (2C), 127.3, 126.8, 106.2, 23.1; HRMS (EI, TOF) calcd for $C_{19}H_{13}I[M]^+$ 344.0062, found 344.0055; IR (neat, cm^{-1}) 3021, 2861, 1141, 958.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, tables, and a CIF file giving ^{1}H NMR, ^{13}C NMR, and 2D NMR spectra for all of the compounds prepared, X-ray crystallographic data for **6d**, and computational details and Cartesian coordinates for all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

I.V.A. is grateful to the National Science Foundation (CHE-1213578 and CHE-1152491) for support of the fundamental and applied components of this research project.

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