Oxyanion-Accelerated C^2-C^6 Cyclization of Benzannulated Enyne-allenes

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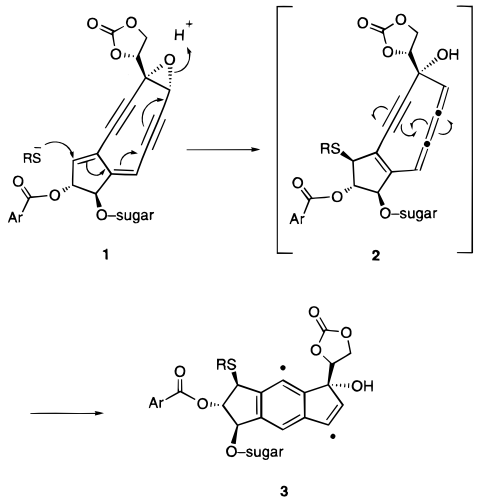
The cyclization of oxyanion-substituted, benzannulated enyne-allenes was found to proceed rapidly and efficiently at room temperature, producing substituted indanones and fluorenones through a C^2-C^6 cyclization pathway. These reactions bear close resemblance to thermal C^2-C^6 cyclizations of enyne-allenes previously reported by Schmittel and others, though the oxyanion-substituted cases cyclize far more rapidly, and stand in noteworthy contrast to the C^2-C^7 (Myers) cyclization of (*Z*)-1,2,4-heptatrien-6-yne, the parent enyne-allene. The rate of reaction was found to be sensitive to the size of the alkyne and allene substituents, though the electronic effects of substitution are not known. The acceleration imparted by the oxyanion substituent is consistent with the electronic stabilization of a proposed diradicaloid transition state for the C^2-C^6 cyclization, but the available evidence does not permit the distinction between concerted and stepwise mechanisms. Studies are ongoing to further elucidate the mechanism and expand the scope of these transformations.

Introduction

The remarkable cyclization of the highly unsaturated chromophore of the antitumor antibiotic neocarzinostatin A (**1**) to an aromatic diradical (**3**) (Scheme 1)[1] has inspired numerous synthetic and mechanistic studies.[2] The proposed mechanism[1d] of this unprecedented cyclization was given further support by the studies of Myers and Saito, who reported the thermal cyclization of the (*Z*)-1,2,4-heptatrien-6-yne skeleton to α,3-tolyl diradicals.[3] These initial reports stimulated further investigation of related enyne-allene systems that, upon thermal cyclization, afford aromatic diradicals.[4] Among those studies are the work of Schmittel[5] and others[6] in which an alternate cyclization pathway was observed (Scheme 2), leading not to the expected naphthyl products (**5** and **7**) but rather to indenyl (**4**) and fluorenyl (**6**) products. Such reactions were characterized by their apparent lack of diradical character and formation of a five-membered, rather than a six-membered, ring; these two alternative modes of cyclization have been termed C^2-C^7 (Myers) and C^2-C^6.

Scheme 1



Both the precise mechanism of the C^2-C^6 cyclization and the factors responsible for toggling between the two cyclizations continue to be investigated. Schmittel has proposed that the C^2-C^6 cyclization, like the Myers cyclization, produces a diradical intermediate,[5] and recently reported trapping such a diradical with 1,4-cyclohexadiene.[5g] Recent theoretical work by Engels and

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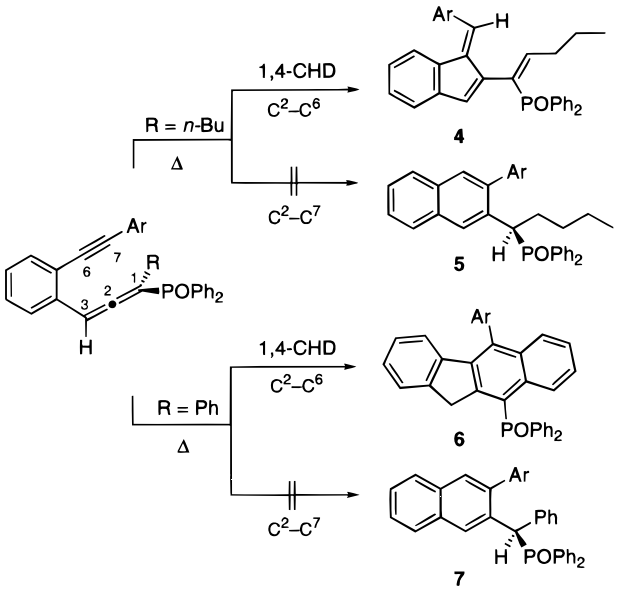
Scheme 2



Schreiner on the parent (*Z*)-1,2,4-heptatrien-6-yne system[7] supports a diradical C^2-C^6 cyclization pathway and estimates a 10 kcal mol^{-1} preference for the C^2-C^7 transition state (25 vs 35 kcal mol^{-1}). Schmittel has identified several factors that may switch a C^2-C^6 to a C^2-C^7 cyclization: bulky alkyne substituents that preferentially destabilize the C^2-C^7 transition state by steric congestion, aromatic allene substituents that stabilize an incipient radical at C^7, and ring strain.

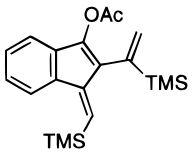
Herein we report the preparation and cyclization of oxyanion-substituted, benzannulated enyne-allenes at cryogenic temperatures. These substrates were chosen to study the electronic role of substituents on enyne-allene cyclizations, with the goal of providing additional mechanistic information and investigating the factors responsible for preferential C^2-C^6 cyclization.

Results and Discussion

The synthesis of oxygen-substituted allenes was envisaged to arise from the trapping of enolates resulting from conjugate addition to an acetylenic ketone. To this end, several acetylenic ketones were prepared from 2-iodobenzoic acid (**8**, Scheme 3) in a three-step sequence involving Weinreb amide formation,[8] Sonogashira coupling,[9] and lithium acetylide addition. Employing different alkynes in the Sonogashira coupling resulted in the formation of substituted acetylenic ketones **11a**−**d** in generally high yields.

Preparation of the oxygen-substituted allenes was accomplished by treating the acetylenic ketones **11a**−**d** with several cuprates and trapping the resultant enolates with acetic anhydride to afford the enol acetates **12a**−**h** (Scheme 3). Although this strategy proved largely successful, the *n*-butyl-substituted ketone **11d** failed to afford any enol acetate when subjected to the reaction conditions; instead, reaction with cuprates resulted in the rapid formation of unidentifiable side-products. The methyl-substituted allene **12a** was chosen for our initial studies. Regeneration of the enolate using methyllithium at −20 °C (Scheme 4) led to the rapid formation of a new, highly UV-active species that proved upon investigation to be the indanone **14a**, the product of a C^2-C^6 cyclization of the enyne-allene core. Although similar, formal Alder ene reactions had been previously observed by Schmittel,[5] in general these transformations required elevated temperatures. The remarkably facile cyclization of the oxyanion-substituted allene **13a** led us to examine the reaction in more detail.

The deuterated analogue **12b** was used to trace the source of the hydrogen substituent on the exocyclic olefin; ^1H NMR analysis of **14b** indicated that the deuterium had been quantitatively and stereoselectively transferred to the alkene. The stereochemistry of **14a** was established through ^1H NMR (NOESY) analysis of the stable enol acetate **15,** the result of acetic anhydride trapping of the cyclized product prior to workup, as the exocyclic olefin in **14a** was found to slowly isomerize. The observed geometry is consistent with an intramolecular transfer of the hydrogen or deuterium substituent; however, efforts to trap a putative diradical intermediate with 1,4-cyclohexadiene proved unsuccessful. Allene **12e**, bearing a *tert*-butyl alkyne substituent, behaved similarly to **12a**, but cyclized more slowly, presumably a result of the increased steric bulk of the *tert*-butyl substituent.



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The cyclopropyl-bearing allenes **12d** and **12g** failed to cyclize altogether when deprotected with methyllithium, affording only monocyclic enones after prolonged reaction time (Scheme 4). Successful cyclization of a cyclopropyl-substituted allene was finally realized when phenyl-substituted enol acetate **12h** was treated with methyllithium at −20 °C. This led to rapid consumption of starting material and formation of a modest amount of a cyclized product **14d**, retaining an intact cyclopropyl substituent. Although this result argues against the existence of a long-lived diradical intermediate, a transient diradical or diradicaloid transition state cannot be discounted. Furthermore, the enhanced stability of enyne-allenes bearing TMS or *tert*-butyl substitution relative to the phenyl-substituted example clearly illustrates the relationship between steric bulk at both the allenic and acetylenic termini and the inherent propensity for cyclization.

Phenyl-substituted enol acetate **12c** (Scheme 5) was synthesized to investigate the effect of preventing an intramolecular hydrogen transfer by removal of all allylic hydrogen atoms. In this case, liberation of the enolate using methyllithium at −20 °C resulted in the rapid formation of benzofluorenone **17a**. An analogous reaction of **12f** resulted in formation of **17b**, although the cyclization was slower than that of **12c** and is again believed to be derived from the increased steric bulk of *tert*-butyl versus TMS. Several features of these cyclizations are noteworthy. First, these cyclizations are formally [4+2]

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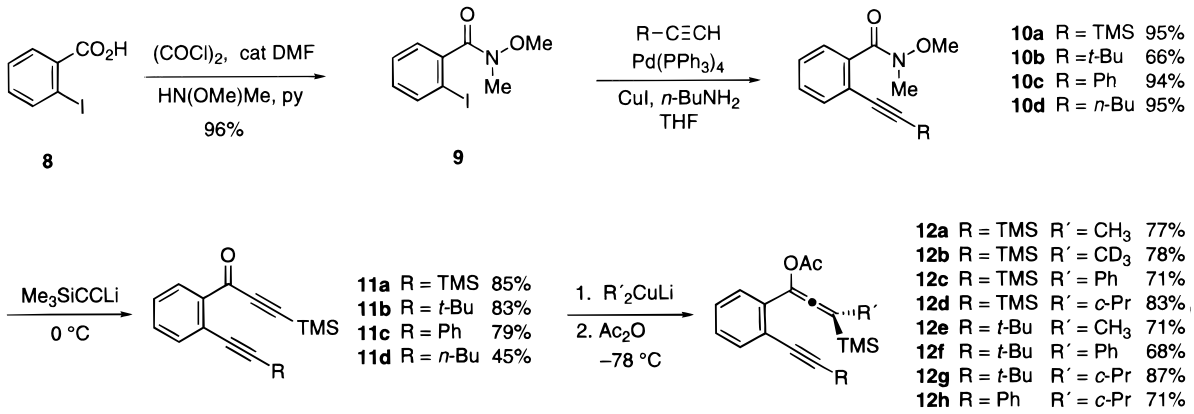
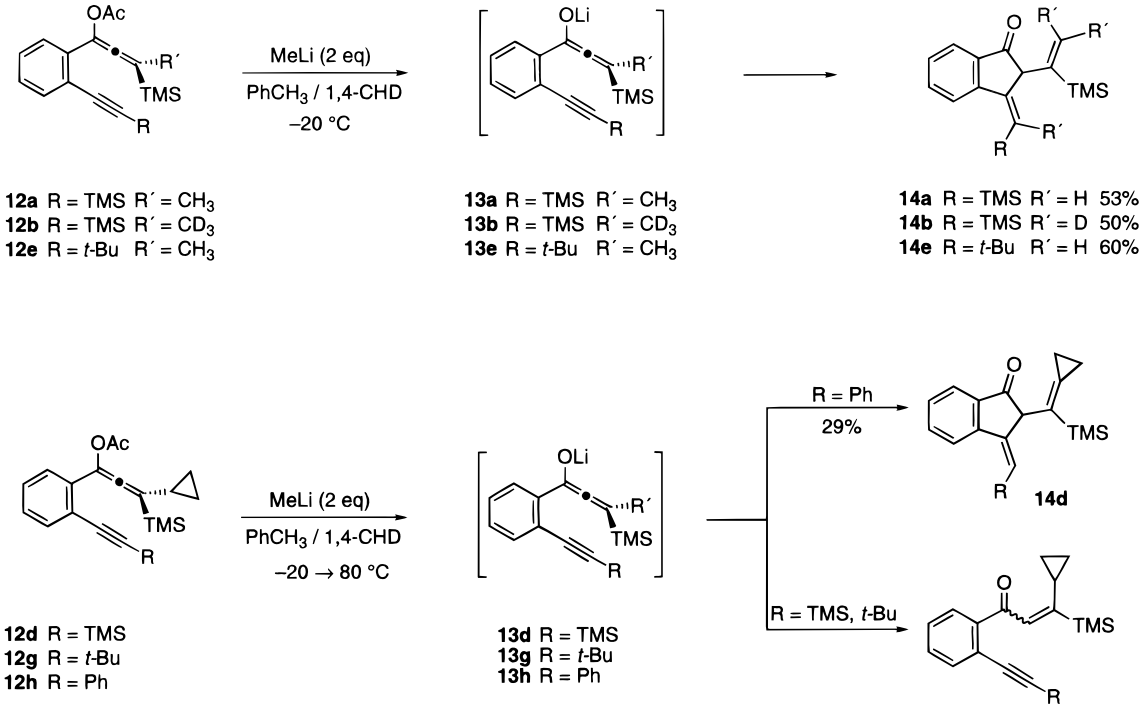
Scheme 3

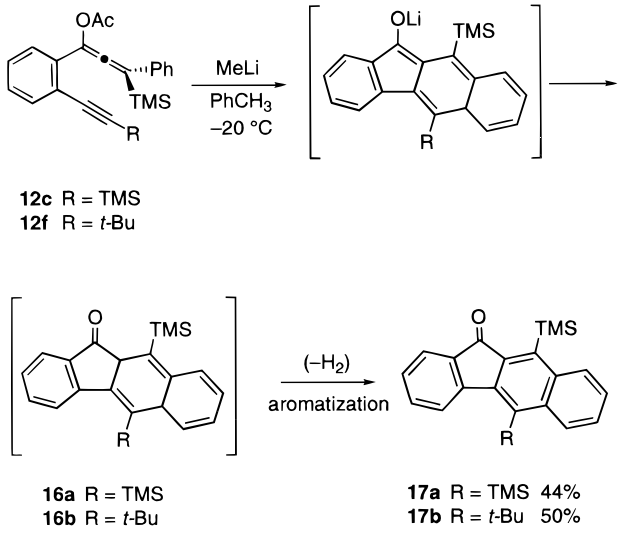


Scheme 4



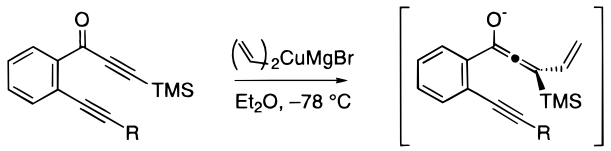
cycloadditions, but the geometric constraints of a pericyclic transition state would appear to disfavor a concerted transition state. Second, transformation of **12c** and **12f** to the products **17a** and **17b** involves dehydrogenation, and likely results from a rapid atmospheric oxidation of the presumed initial products **16a** and **16b**. The structures of **16a** and **16b** indicate that the aromaticity of a benzene ring is lost during reaction; thus, the cyclization of **12c** appears to be exothermic enough to result in the dearomatization of benzene at cryogenic temperature. This notion was corroborated by the results obtained through treatment of acetylenic ketones **11a** and **11b** (Scheme 6) with vinyl cuprate reagents, in which cyclization of the initially formed enolate at −78 °C led to the rapid formation of fluorenones **18a** and **18b**. Thus, when the cyclization is unencumbered by the dearomatization of benzene, it proceeds rapidly even at −78 °C. That the presumed intermediate fluorenyl acetates could not be isolated suggests that aromatization by autoxidation is extremely facile.

Scheme 5

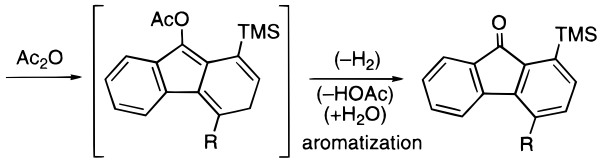


Although the observed C^2-C^6 cyclization regiochemistry has been reported for analogous enyne-allenes, the rate at which the oxyanion-bearing systems cyclize is markedly faster than nearly all known examples.[5d] To

Scheme 6

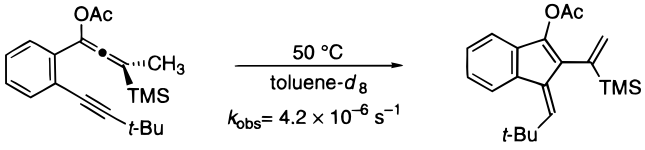


11a R = TMS
11b R = *t*-Bu



18a R = TMS 35%
18b R = *t*-Bu 6%

Scheme 7



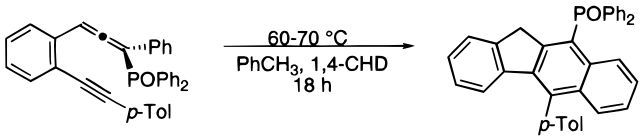
12e **19**

distinguish between the steric and electronic roles of the oxyanion substituent on cyclization, the neutral enol acetate **12e** was heated to 50 °C and monitored by ^{1}H NMR spectroscopy (Scheme 7). Integration of the acetate methyl signal of **12e** was monitored using the residual methyl signal of toluene-d_8 as an internal standard. It was found that **12e** slowly cyclized to the corresponding indenol acetate **19**, with an estimated unimolecular rate constant of 4.2×10^6 sec^{-1}, a value that places the half-life of **12e** at 50 °C more than 45 times longer than that of the corresponding oxyanion **13e**.

The mechanism of these transformations remains open to question. Although indanone products arise from a formal Alder ene reaction, and benzofluorenone products arise from a formal Diels–Alder reaction, there is no compelling evidence for a concerted mechanism at this point. In addition, the requisite geometry of a cyclic transition state appears quite unfavorable in these highly constrained, unsaturated systems. Alternatively, one can envisage a stepwise process involving either diradical or anionic intermediates. While the lack of ring opening of the cyclopropyl substituent in **14d** is inconsistent with a long-lived cyclopropylmethyl radical intermediate, a transient diradical intermediate cannot be ruled out. A similar, cyclopropyl-substituted enyne-allene is reported to proceed through a C^2-C^6 reaction pathway to yield a cyclized product bearing an intact cyclopropyl ring.[5b]

The computational studies of Engels and Schreiner suggest that the favorability of the C^2-C^6 cyclization may arise from the stabilization afforded through orbital overlap of a developing radical center with the existing conjugated π system. Within the context of this interpretation, the role of the oxyanion substituent at this center would be one of additional stabilization and consistent with the observed rate enhancement of the oxyanion-bearing systems over that of nonionic analogues. Importantly, along with lacking any bulky terminal substitution, the theoretical system investigated by Engels differs from most systems known to undergo C^2-C^6 cyclization by its lack of benzannulation. The consequence of this difference, in the event of a C^2-C^7 cyclization, would be to form the second ring of naphthalene rather than an isolated phenyl ring. In this case, given the difference in resonance energy gained by the system upon cyclization, benzannulation of the enyne-allene system is expected to reduce the energetic preference of a C^2-C^7 event over that of a C^2-C^6 event by roughly 10 kcal mole^{-1}.[10]

Scheme 8



20 **21**

Evidence for the role of benzannulation in the C^2-C^6 cyclization event is provided by Wang, whose examples of acyclic enyne-allene systems bearing terminal aryl substitution were expected to result in C^2-C^6 cyclization, but instead cyclize with C^2-C^7 regiochemistry.[4d] At the very least, these examples suggest that benzannulation of the enyne-allene system is not an innocuous modification to the parent system and have led us to begin the investigation of oxyanion-bearing enyne-allene systems without a central benzene ring, the results of which will be disclosed in due course.

Conclusion

Direct comparison of our data to the examples of Schmittel is complicated by the use of different synthetic routes to obtain the respective enyne-allenes. The most relevant comparison that can be drawn is between the cyclization of **12c** in this work and Schmittel's observed cyclization of the related enyne-allene **20** (Scheme 8).[5e] Whereas the cyclization of **12c** is complete within 20 min at −20 to 0 °C, the complete cyclization of **20** required heating it at 60–70 °C for 18 h. This suggests a minimum rate acceleration of approximately 3000-fold. When one additionally considers the steric difference between the alkyne subsituents in **20** and **12c**, the rate difference quoted above is almost certainly underestimated.

Direct comparison of the cyclization of enol acetate **12e** with that of its corresponding enolate **13e** shows roughly a 45-fold rate enhancement that accompanies ionization. This further suggests that placing a negative charge on the oxygen substituent results in a stabilization of the C^2-C^6 cyclization. This argues for an electronic stabilization of the C^2-C^6 transition state, in addition to any steric role of the oxygen substituent. The relatively small rate difference between the neutral and anionic cyclizations stands in stark contrast to our comparison with Schmittel's data and implies that the acetoxy substituent imparts much of the stabilization to the C^2-C^6 transition state that the oxyanion substituent also provides.

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The acceleration afforded C^2-C^6 cyclization by oxyanion substituents may have the same origin as the well-known acceleration of sigmatropic rearrangements.[11] In those cases, it has been proposed that the oxyanion substituent stabilizes a diradicaloid transition state through electronic interaction with an α radical.[11a,b] A similar interaction can be proposed in the present study by invoking a diradicaloid transition state for C^2-C^6 cyclizations, leading either to a diradical intermediate, as Schmittel has suggested,[5] or directly to product through an asynchronous, concerted transition state.[12]

The C^2-C^6 regiochemistry of cyclization can be traced to both the bulky acetylenic substituents and the benzannulation of the substrates. Engels and Schreiner have estimated that the C^2-C^6 transition state is destabilized by 10 kcal mol^{-1} relative to that of the C^2-C^7 path for (*Z*)-1,2,4-heptatrien-6-yne.[7] When one adjusts this value for the difference in resonance energy gained from formation of benzene and naphthalene, the energy of the C^2-C^6 transition state appears to be roughly comparable to that of the Myers (C^2-C^7) transition state. Thus, substituent effects, both steric and electronic, are likely to play the major role in the discrimination between the two competing reaction pathways. Recent studies by Schmittel[5f] and Wang[4f] have shown that the introduction of ring strain can also be used to disfavor C^2-C^6 cyclization and promote C^2-C^7 instead. In the present instance, the trimethylsilyl, *tert*-butyl, and phenyl substituents are sufficiently bulky to favor the C^2-C^6 pathway to the exclusion of C^2-C^7 cyclization.

The ability of an oxyanion substituent to accelerate the C^2-C^6 cyclization should facilitate the use of these reactions in organic synthesis. Likewise, the carbonyl functionality of the products permits the introduction of a wide variety of functional groups. Studies are currently underway in our laboratory to further examine the nature of the C^2-C^6 transition state and to determine whether the same acceleration applies to the Myers cyclization.

Experimental Section

General. All reactions requiring an anhydrous or oxygen-free environment were performed in flame- or oven-dried glassware under positive N_2 pressure. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Toluene ($PhCH_3$) and acetonitrile (CH_3CN) were distilled from calcium hydride. Acetic anhydride was redistilled from quinoline and stored over 4 Å molecular sieves. CuI was purchased 99.999% pure and azeotropically dried from toluene. Grignard and alkyl/aryllithium reagents were titrated prior to use. All other reagents were used as commercially provided without further purification. Thin-layer chromatography (TLC) was performed using silica gel 60 F-254 (EM reagents, 0.25 mm) filmed-glass plates. Flash chromatography was performed using 230−400-mesh silica gel 60. Melting points of all solids are reported uncorrected. Combustion analysis was performed in the microanalysis laboratory at Purdue University.

2-Iodo-*N*-methoxy-*N*-methylbenzamide (9). To a suspension of 2-iodobenzoic acid (5.00 g, 20.2 mmol) in CH_2Cl_2 (50 mL) was added oxalyl chloride (3.53 mL, 40.4 mmol), followed by catalytic DMF (50 μL). The reaction was stirred at 25 °C for 2 h, at which time the clear, colorless solution was concentrated in vacuo. The crude acid chloride was resuspended in CH_2Cl_2 (50 mL) and cooled to 0 °C. To this solution was added $ClH_2N(OMe)Me$ (2.17 g, 22.2 mmol), followed by pyridine (3.95 mL, 48.8 mmol). The reaction was allowed to warm to 25 °C and continued for 12 h. The reaction product was diluted with EtOAc and poured into saturated, aqueous $CuSO_4$. The aqueous phase was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The resultant oil was purified via flash chromatography with EtOAc/petroleum ether (50:50) to afford **9** as a white solid (5.64 g, 96%). Mp = 55−57 °C. ^1H NMR (500 MHz, C_6D_6, 50 °C): δ 7.49 (d, J = 7.8, 1H), 6.95 (m, 1H), 6.81 (m, 1H), 6.47 (m, 1H), 2.95 (b, 6H). IR (KBr): ν_{max} 1636 cm^{-1}. Anal. Calcd for $C_9H_{10}INO_2$: C, 37.14; H, 3.46; N, 4.81. Found: C, 37.24; H, 3.20; N, 4.70. EIMS *m*/*z*: 291 (M^+).

Sonogashira Coupling of Terminal Alkynes with Aryl Iodide 9, General Procedure. A 0.149-g portion of $Pd[PPh_3]_4$ (0.129 mmol) was dissolved in THF (20 mL) and the reaction vessel was thoroughly flushed with N_2. To this solution was added **9** (1.49 g, 5.14 mmol), alkyne (10.3 mmol), CuI (0.196 g, 1.03 mmol), and *n*-$BuNH_2$ (1.02 mL, 10.3 mmol). The solution was stirred for 2 h at 25 °C, diluted with EtOAc, and poured into saturated, aqueous NH_4Cl. The aqueous phase was separated and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The resultant residue was purified via flash chromatography with EtOAc/petroleum ether (25:75).

Acetylide Addition to Amides 10a−d, General Procedure. Trimethylsilylacetylene (0.952 g, 6.75 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. To this solution was added *n*-BuLi as a 2.6 M solution in hexanes (2.1 mL, 5.46 mmol), dropwise. After 20 min, Weinreb amide **10** (4.50 mmol) in THF (3 mL) was added dropwise via syringe, and the reaction was allowed to slowly warm to 25 °C over 2 h. The reaction was diluted with Et_2O, the mixture was poured into saturated aqueous NH_4Cl solution, and the aqueous phase was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The resultant residue was purified by flash chromatography with Et_2O/pentane (5:95).

Preparation of Cuprate Reagents, General Procedure. The cuprate reagents Me_2CuLi, CD_3CuLi, and Ph_2CuLi, were prepared by reacting MeLi, $CD_3Li{\cdot}LiI$, and PhLi (2.05 equiv), as commercially provided solutions, with CuI (1.0 equiv) suspended in Et_2O at 0 °C then cooled to −78 °C for immediate use. The *c*-Pr_2CuLi was prepared as follows. Cyclopropyl bromide (0.106 mL, 1.32 mmol) in Et_2O (2.0 mL) was cooled to −78 °C. To this solution was added *t*-BuLi as a 1.99 M solution in hexanes (0.663 mL, 1.32 mmol), dropwise, and the resultant mixture was allowed to warm to 0 °C over 20 min. This solution was transferred to a suspension of CuI (0.126 g, 0.662 mmol) in Et_2O (1.0 mL) by syringe and, after complete addition, the mixture was cooled to −78 °C for immediate use.

Cuprate Addition to Ketones 11a−d and Subsequent Acetic Anhydride Trap of Resultant Enolate, General Procedure. To a solution of the cuprate reagent (0.71 mmol) in Et_2O (3.5 mL) at −78 °C was added the acetylenic ketone **11** (0.47 mmol), dropwise, as a solution in Et_2O (0.5 mL). Acetic anhydride (0.226 mL, 2.4 mmol) in Et_2O (0.5 mL) was then added dropwise to the reaction. The reaction was allowed to slowly warm to 25 °C over 2 h and diluted with Et_2O. The reaction mixture was poured into saturated aqueous NH_4Cl, and the aqueous phase was separated and extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The resultant residue was purified by flash chromatography with Et_2O/pentane (5:95).

Deprotection and Cyclization of Enol Acetates 12a−h, General Procedure. To a solution of the enol acetate **12** (0.24 mmol) in $PhCH_3$/1,4-cyclohexadiene (1:1, 3.0 mL), cooled to −20 °C, was added MeLi as a 1.4 M solution in Et_2O (0.35

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mL, 0.49 mmol). The reaction was slowly allowed to warm to 25 °C over 30 min and monitored via TLC for reactivity. Results were identical to those obtained in the absence of 1,4-cyclohexadiene. For TMS analogues **(12a−d)**, cyclization was complete in 20 min, but *tert*-butyl analogues **(12e−g)** required an additional 2 h at 50 °C. When complete, the reaction was diluted with Et_2O and poured into saturated aqueous NH_4Cl. The aqueous phase was extracted twice with Et_2O and the combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The resultant residue was purified by flash chromatography.

Acetic Acid 3-Trimethylsilanylmethylene-2-(1-trimethylsilanyl-vinyl)-3*H*-inden-1-yl Ester (15). A 0.192 g portion of CuI (1.01 mmol) was suspended in Et_2O (3 mL) and cooled to 0 °C. MeLi as a 0.58 M solution in Et_2O (3.5 mL) was added dropwise. The suspension was stirred for 5 min and transferred via cannula to acetylenic ketone **11a** (0.200 g, 0.671 mmol) in Et_2O (2 mL), whereupon the solution immediately turned deep red. After 5 min, acetic anhydride (0.127 mL, 1.34 mmol) in Et_2O (0.5 mL) was added slowly. The solution was allowed to warm slowly to 25 °C, changing from red to yellow-orange as it warmed. The reaction was diluted with Et_2O, the mixture was poured into saturated aqueous NH_4Cl, and the aqueous phase was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The resultant residue was purified by flash chromatography with Et_2O/pentane (5:95) to give **15** as a dark yellow oil (0.170 g, 71%). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.71 (m, 1H), 7.25 (m, 2H), 7.09 (m, 1H), 6.30 (s, 1H), 5.91 (d, J = 3.4, 1H), 5.71 (d, J = 3.6, 1H), 2.29 (s, 3H), 0.36 (s, 9H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, acetone-d_6): δ 177.2, 161.4, 155.9, 154.6, 147.9, 144.3, 143.3, 142.3, 140.8, 137.3, 134.7, 132.3, 126.9, 30.1, 8.4, 7.8. IR (film): ν_{max} 1772, 773, 755 cm^{-1}. Anal. Calcd for $C_{20}H_{28}O_2Si_2$: C, 67.36; H, 7.91; Si, 15.75. Found: C, 67.56; H, 8.00; Si, 15.52.

Vinyl Cuprate Addition and In Situ Cyclization of Acetylenic Ketones 11a−b, General Procedure. A 0.135-g portion of CuI (0.710 mmol) was suspended in Et_2O (2 mL) and cooled to 0 °C. To this suspension was added vinylmagnesium bromide as a 0.93 M solution in THF (1.5 mL, 1.40 mmol). The mixture was stirred for 5 min and then cooled to −78 °C. Acetylenic ketone **11** (0.355 mmol) in Et_2O (0.5 mL) was added to the cuprate reagent, dropwise. After 5 min, acetic anhydride (0.168 mL, 1.78 mmol) in Et_2O (0.25 mL) was added dropwise, and the reaction was allowed to warm to 25 °C over 2 h. The reaction was worked up analogously to the lithium cuprate additions to **11a−d**. The resultant residue was purified by flash chromatography with Et_2O/pentane (2:98).

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Supporting Information Available: Compound characterization data for **10a−d**, **11a−d**, **12a−h**, **14a−d**, **17a−b**, and **18a−b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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