

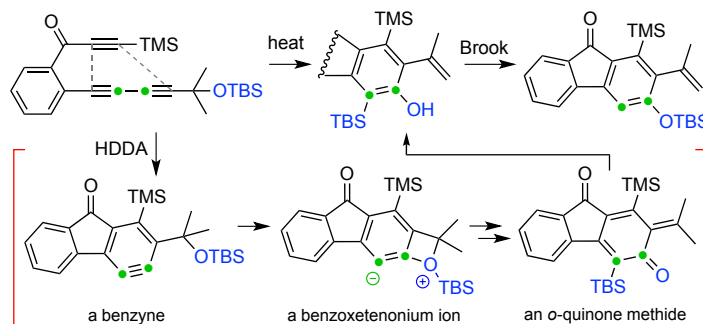
Benzynes Cascade Reactions via Benzoxetenonium Ions and their Rearrangements to *o*-Quinone Methides

Hang Shen,[†] Xiao Xiao, Thomas R. Hoye*

Department of Chemistry, University of Minnesota, 207 Pleasant Street SE, Minneapolis, Minnesota 55455, United States.

Supporting Information Placeholder

ABSTRACT: A new thermal isomerization of polyynes is described. Benzyne intermediates substituted by a C(RR')OR" substituent adjacent to one of the benzyne sp-hybridized carbons give rise to products in which the OR" moiety has migrated to the proximal benzyne carbon. This process likely proceeds via sequential formation of multiple reactive intermediates: an initial thermally generated benzyne, a strained benzoxetenonium ion, and an *o*-quinone methide. As some examples demonstrate, the overall transformation can be quite efficient. The mechanism of this novel reaction is further supported by experiments and DFT calculations.

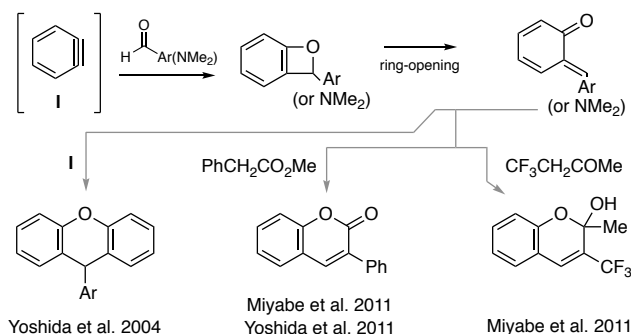


Quinone methides (QMs) are reactive intermediates of interest from the perspectives of preparative, mechanistic, and structural organic chemistry as well as their roles in chemical biology (e.g., biosynthetic pathways, prodrug cleavage, and electrophilic capture of biological nucleophiles).¹ QMs are often generated by eliminative processes of phenol derivatives or by photochemical reactions (including reversible generation in photochromic molecules). Besides these two methods, benzyne, itself a versatile reactive intermediate, can also generate *o*-QMs by reaction with the C=O π -bond in carbonyl-containing functional groups (Figure 1a).² For example, Yoshida and co-workers demonstrated a coupling reaction of two arynes with aldehydes to give 9-arylxanthene derivatives through QM intermediates. They, as well as Miyabe's group, have also reported insertion reactions of arynes into formamide to afford coumarin derivatives following in situ trapping of the *o*-QM by esters, nitriles, and ketones.

We now report a reaction (Figure 1b) that represents an alternative mechanistic paradigm for producing *o*-QMs in which a thermally generated benzyne derivative bearing a benzylic ether group can produce a four-membered benzoxetenonium 1,3-zwitterion (middle structure in the brackets in Figure 1b) by an intramolecular nucleophilic attack to the strained aryne bond. Electrocyclic ring-opening of the oxetene ring³ affords an *O*-substituted *o*-QM intermediate, and a subsequent hydrogen atom migration gives a formal C–O bond insertion product. In this process, the steric bulk of the R¹ group is crucial, possibly facilitating passage through the strained four-membered ring transition state geometry that leads to the strained four-membered zwitterion.⁴ Indeed, when R¹ is a hydrogen, the reaction proceeds through other pathways.⁵ The highly substituted benzyne

intermediate is accessed conveniently from a triyne precursor via a cycloisomerization event, namely, the hexadehydro-Diels–Alder (HDDA) reaction,⁶ and therefore, the overall cascade is essentially a net thermal isomerization of the triyne.

a previous examples of benzynes leading to *o*-quinonemethides



b a new route from benzynes to *o*-quinonemethides

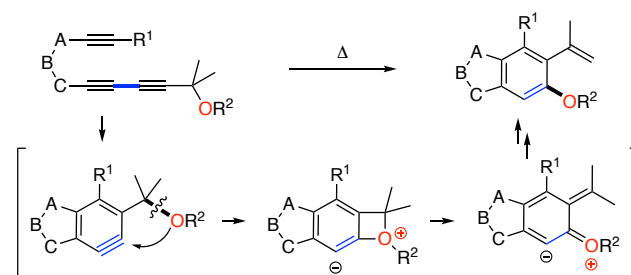
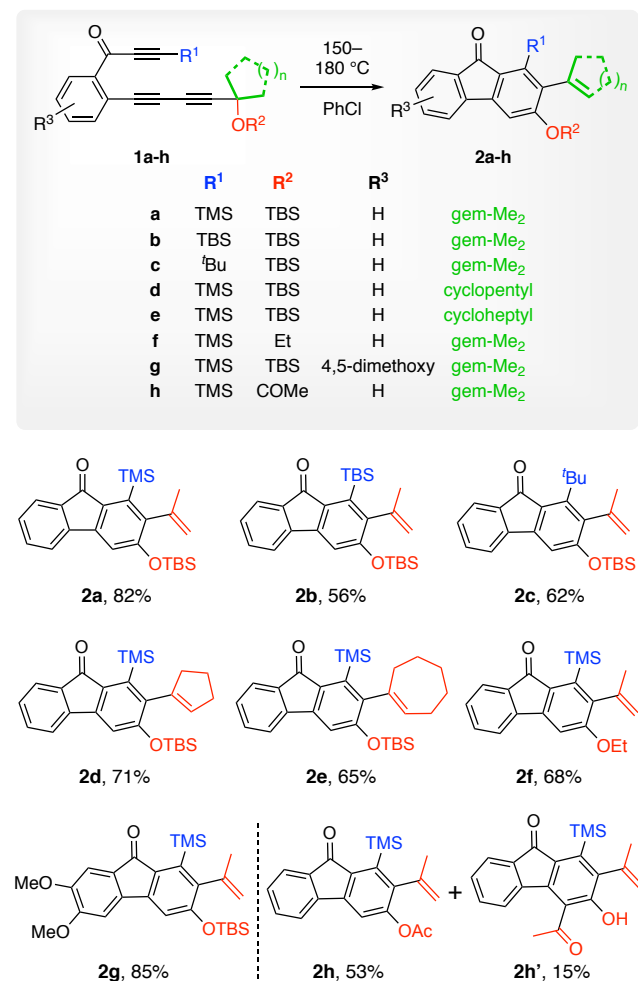


Figure 1. Generation of *o*-quinone methides via benzynes.

Chart 1. The major products (2a-h) isolated from reactions of triyne precursors 1a-h.^a



^aYields are for isolated, purified (SiO₂) material.

The first time we encountered this unusual transformation was upon heating the ynone substrate **1a**. The fluorenone derivative **2a** was produced in excellent yield (Chart 1). We proposed a mechanism to account for this outcome, which is shown in Figure 2. Initially, triyne **1a** undergoes a HDDA reaction to generate benzyne **3**, which is trapped by the pendant benzylic silyl ether to give the benzoxetenonium species **4**. Silyl migration to the anionic carbon in this zwitterion (a retro-Brook-like rearrangement) could occur at this stage, although the stereoelectronic features for that process appear to be much more favorable following ring-opening to the *O*-silylated *o*-QM **5**. Moreover, that electrocyclic opening itself might be expected to be quite rapid because it is accompanied by delocalization of the cationic portion of the zwitterion (cf. the computed **TS2** in Figure 3, which suggests that this process is barrierless). A [1,5]-hydrogen atom shift in the neutral QM **6** yields the *o*-silylated phenol **7**. We presumed that under the reaction conditions for this experiment (150 °C, 14 h), this species had rearranged (see later discussion) to the observed product **2a**. Similar thermal Brook rearrangements of *o*-silylated phenols have been reported.⁸ Due to the size of each of the two substituents at

the termini of triyne **1** (blue and red colors), the ease of these HDDA cycloisomerizations—necessarily the rate-limiting step in each case—required more elevated temperatures to form the benzyne compared to analogous ynone-triynes substrates.⁹ The transformation was shown to be general, as evidenced by the examples of substrates **1b-h** leading to **2b-h**. Propargylic substitution other than geminal dimethyl in **1** is tolerated (cf. **2d-e**). The R² group can be alkyl in addition to a silyl substituent (**2f**). When it is acetyl (cf. **1h**), two products, **2h** and **2h'**, were observed. The latter could arise by either an intermolecular transfer or an intramolecular, Fries-like process.

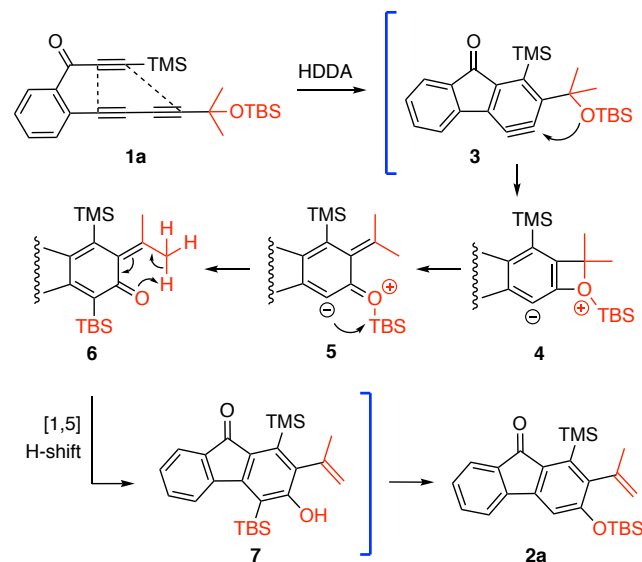


Figure 2. A proposed mechanism for the conversion of **1a** to **2a**.

DFT calculations [SMD(PhCl)/B3LYP-D3BJ/6-311+G**//B3LYP/6-31G*, Figure 3] were used to further explore the mechanistic thinking laid out in Figure 2. A slightly simplified and symmetrized [e.g., TMS instead of TBS and an ester linker (cf. **8a**, later)] set of structures was used. The HDDA-produced benzyne **A** is seen to cyclize to the benzoxetenonium ion **B** with a very low barrier (**TS1**, 3.5 kcal·mol⁻¹), although this strained species is 1.7 kcal·mol⁻¹ higher in free energy than the benzyne. This proceeds by way of an extremely facile, indeed, barrierless, electrocyclic ring-opening to afford the more stable zwitterion **C**. Subsequent retro-Brook reaction within the zwitterion **C** results in formation of the *o*-QM **D** via another low-barrier process (**TS3**, ΔG[‡] = 4.0 kcal·mol⁻¹). A 1,5-hydrogen atom shift in *o*-QM **D** gives the phenol **E** via **TS4** (ΔG[‡] = 10.2 kcal·mol⁻¹). The keto tautomer **F** is seen to be less stable than the phenol by only 12.3 kcal·mol⁻¹, although we do not know the specifics of the mediator that is promoting this symmetry-forbidden 1,3-hydrogen atom migration. By contrast, processes like the 1,3-silyl migration of **F** to the silyl ether product **G** are known to be symmetry allowed and concerted (cf. **TS5**, ΔG[‡] = 21.2 kcal·mol⁻¹).¹⁰ Finally, note that when the R group attached to the oxonium ion is not a silyl substituent (e.g., Et in **2f**), Et migration is not observed. Instead, a protonation/deprotonation sequence via the benzylic carbenium ion **H** is presumed to lead to products like **I** (i.e., **2f**).

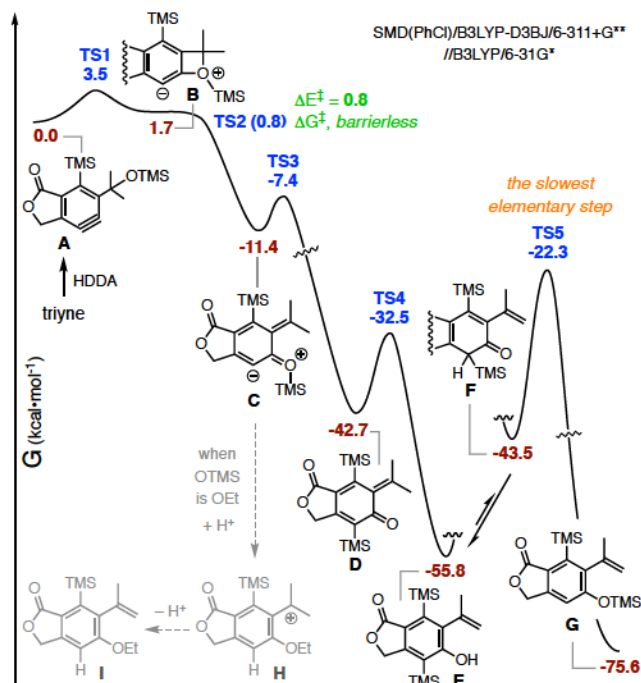
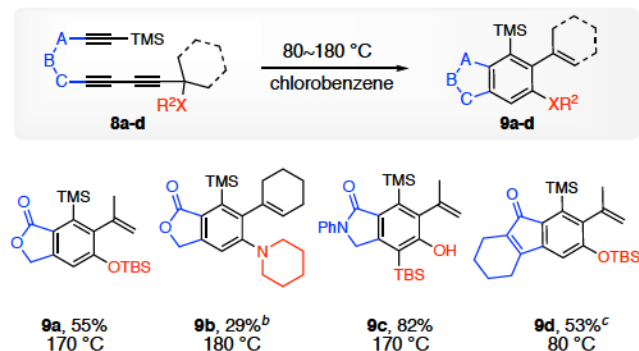


Figure 3. Computed energy profile (See Figure S1 in Supporting Information for more details).

To address the question of whether the transformation of **1** to **2** is tolerant of triyne precursors containing other types of linkers, we examined the HDDA substrates **8a–d** (Chart 2). Once again we observed that the benzyne formation step in these substrates is slower than expected based on analogous triynes that we have previously studied having the same linker but a less bulky substituent (CH_2R) on the terminal diyne.⁹ The trapping nucleophile is not limited to oxygen. The tertiary amino group in substrate **8b** migrated to give **9b** in an analogous fashion to the reaction of the ethoxylated analog (cf. **1f** to **2f**), now by accessing a four-membered benzazetene species. In the case of **8c**, the silylated phenol product **9c** was formed cleanly (cf. **2h'**). We do not have a good explanation for the reluctance of this compound to undergo the Brook rearrangement (it remained intact even following recording of the melting point ($= 235\text{--}237^\circ\text{C}$)).

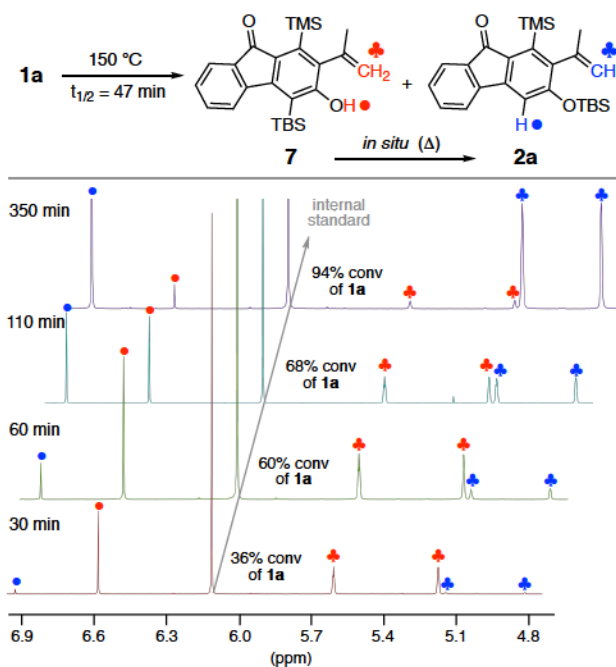
Chart 2. The major products (**9a–d**) isolated from triyne precursors **7a–d**.^a



^aYields are for isolated, purified (SiO_2) material. ^bDCB was the reaction solvent; **9b** was the major compound seen in the crude product mixture (^1H NMR analysis). ^cChloroform was the reaction solvent.

^1H NMR spectroscopy was used to monitor the progress of the reaction of **1a** (Figure 4a). The consumption of **1a** proceeded with a half-life that is estimated to be 47 min at 150°C in chlorobenzene. As a comparison, the cyclization half-life of another ynone substrate with the same linker structure is ca. 5 h at 80°C .⁹ Intriguingly, at an early stage (30 min) of conversion, we observed quite clean the formation of phenol **7**. As the reaction proceeded (60 and 110 min), the signal of silyl ether **2a** started to appear and increase. Eventually (350 min), most of **7** was isomerized to the thermodynamically more stable constitutional isomer **2a**. This NMR study clearly suggests that phenol **7** indeed is a metastable intermediate, the initially formed product arising from rearomatization of the *o*-QM **6**, which then undergoes rearrangement to **2a**.⁸

a NMR monitoring^a



b crossover experiment

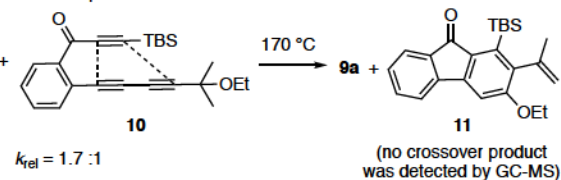


Figure 4. ^1H NMR monitoring and crossover experiment. ^a1,3,5-Trimethoxybenzene was used as an internal standard (IS) to monitor the conversion of **1a**; the indicated %conversions were measured by integration of a unique aromatic resonance for **1a** vs. the IS.

Finally, to rule out the possibility of a bimolecular silyl or alkyl group transfer, we carried out a crossover experiment using triynes **8a** and **10**, whose cyclization half-lives are comparable. No evidence of either of the two possible crossover products was

observed after full consumption of both **8a** and **10** (Figure 4b). This supports the mechanism in which an intramolecular retro-Brook rearrangement of **5** produces o-QM **6** (Figure 2).

In conclusion, we have shown that certain polyyne substrates can efficiently undergo a tandem thermal isomerization via an o-QM intermediate. This represents a new pathway of formation of this class of intermediate. The scope of the reaction was briefly demonstrated (Charts 1–2), and a plausible mechanistic pathway was proposed (Figure 2). Furthermore, DFT calculations and mechanistic studies provided additional support of the proposed mechanism (Figure 3–4). This represents another example of the HDDA reaction serving as a platform to support fundamentally new types of reactivity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures for all new reactions; spectroscopic characterization data for all new compounds; results of DFT computations (3D structures, geometries, and energies of all minima and maxima); copies of ¹H and ¹³C NMR spectra (PDF).

AUTHOR INFORMATION

Corresponding Author

hoye@umn.edu

Present Addresses

†H.S.: Department of Chemistry, University of Wisconsin–Madison, 1101 University Ave, Madison, WI 53706.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the Institute of General Medical Sciences of the U.S. Department of Health and Human Services (R35 GM127097) and the National Science Foundation (CHE-1665389). Most of the NMR data were obtained with an instrument acquired through the NIH Shared Instrumentation Grant program (S10OD011952).

REFERENCES

- (1) (a) Van De Water, R. W.; Pettus, T. R. R. o-Quinone Methides: Intermediates Underdeveloped and Underutilized in Organic Synthesis. *Tetrahedron* **2002**, *58*, 5367–5405. (b) Ferreira, S. B.; Silva, F. D. C. D.; Pinto, A. C.; Gonzaga, D. T. G.; Ferreira, V. F. Syntheses of Chromenes and Chromanes via o-Quinone Methide Intermediates. *J. Heterocycl. Chem.* **2009**, *46*, 1080–1097. (c) Singh, M. S.; Nagaraju A.; Anand, N.; Chowdhury, S. ortho-Quinone Methide (o-QM): A Highly Reactive, Ephemeral and Versatile Intermediate in Organic Synthesis. *RSC Adv.* **2014**, *4*, 55924–55959.
- (2) (a) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. A 2:1 Coupling Reaction of Arynes with Aldehydes via o-Quinone Methides: Straightforward Synthesis of 9-Arylxanthenes. *Org. Lett.* **2004**, *6*, 4049–40051. (b) Yoshida, H.; Ito, Y.; Ohshita, J. Three-component Coupling Using Arynes and DMF: Straightforward Access to Coumarins via ortho-Quinone Methides. *Chem. Commun.* **2011**, *47*, 8512–8514. (c)

Yoshioka, E.; Kohtani, S.; Miyabe, H. A Multicomponent Coupling Reaction Induced by Insertion of Arynes into the C=O Bond of Formamide. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638–6642.

(3) (a) Adam, W.; Hadjarapoglou, L.; Peters, K.; Sauter, M. Dimethyldioxirane Epoxidation of Benzofurans: Reversible Thermal and Photochemical Valence Isomerization between Benzofuran Epoxides, Quinone Methides, and Benzoxetenes. *J. Am. Chem. Soc.* **1993**, *115*, 8603–8608. (b) Tomioka, H.; Matsushita, T. Benzoxetene. Direct Observation and Theoretical Studies. *Chem. Lett.* **1997**, 399–400.

(4) Gupta, S.; Lin, Y.; Xia, Y.; Wink, D.; Lee, D. Alder-Ene Reactions Driven by High Steric Strain and Bond Angle Distortion to Form Benzocyclobutenes. *Chem. Sci.* **2019**, DOI: 10.1039/c8sc04277b.

(5) Xiao, X.; Woods, B. P.; Xiu, W.; Hoyer, T. R. Benzocyclobutadienes: An Unusual Mode of Access Reveals Unusual Modes of Reactivity. *Angew. Chem., Int. Ed.* **2018**, *57*, 9901–9905.

(6) (a) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. Cycloaromatization of a Non-Conjugated Polyyne System. *Tetrahedron Lett.* **1997**, *38*, 3943–3946. (b) Bradley, A. Z.; Johnson, R. P. Thermolysis of 1,3,8-Nonatriyne: Evidence for Intramolecular [2 + 4] Cycloaromatization to a Benzynes Intermediate. *J. Am. Chem. Soc.* **1997**, *119*, 9917–9918. (c) Tsui, J. A.; Sterenberg, B. T. A Metal Templated 4 + 2 Cycloaddition Reaction of an Alkyne and a Diyne To Form a 1,2-Aryne. *Organometallics* **2009**, *28*, 4906–4908. (d) Yun, S. Y.; Wang, K.-P.; Lee, N.-K.; Mamidipalli, P.; Lee, D. Alkane C–H Insertion by Aryne Intermediates with a Silver Catalyst. *J. Am. Chem. Soc.* **2013**, *135*, 4668–4671. (e) Hoyer, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. The hexahydro-Diels–Alder reaction. *Nature*, **2012**, *490*, 208–212. For a review: (f) Diamond, O. J.; Marder, T. B. Methodology and applications of the hexahydro-Diels–Alder (HDDA) reaction. *Org. Chem. Front.* **2017**, *4*, 891–910.

(7) Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.-L.; Pettus, T. R. R. The Domestication of ortho-Quinone Methides. *Acc. Chem. Res.* **2014**, *47*, 3655–3664.

(8) (a) Copper, G. D. Preparation and Thermal Rearrangement of Poly(trimethylsilyl)phenols. *J. Org. Chem.* **1961**, *26*, 925–929. (b) Eastham, S. A.; Ingham, S. P.; Hallett, M. R.; Herbert, J.; Quayle, P.; Raftery, J. A Formal Synthesis of Aflatoxin B₂: a Dötz Benzannulation Approach. *Tetrahedron Lett.* **2006**, *47*, 2299–2304. (c) Austin, W. F.; Zhang, Y.; Danheiser, R. L. A Benzannulation Strategy for the Synthesis of Phenols and Heteroaromatic Compounds Based on the Reaction of (Trialkylsilyl)vinylketenes with Lithium Ynolates. *Tetrahedron* **2008**, *64*, 915–925. (d) Schön, W.; Messinger, J.; Solodenko, W.; Kirschning, A. Synthetic Approaches towards 4-Functionalized Estrone Derivatives. *Synthesis* **2012**, *44*, 3822–3828.

(9) Woods, B. P.; Baire, B.; Hoyer, T. R. Rates of Hexahydro-Diels–Alder (HDDA) Cyclizations: Impact of the Linker Structure. *Org. Lett.* **2014**, *16*, 4578–4581.

(10) (a) Brook, A. G.; MacRae, D. M.; Limburg, W. W. Stereochemistry of the Formation and Thermal Rearrangement of β -Ketosilanes. *J. Am. Chem. Soc.* **1967**, *89*, 5493–5495. (b) Slutsky, J.; Kwart, H. The Kinetics, Stereochemistry, and Mechanisms of the Silaallylic and Silapropynylic Rearrangements. *J. Am. Chem. Soc.* **1972**, *95*, 8678–8685. (c) Yamabe, T.; Nakamura, K.; Shiota, Y.; Yoshizawa, K.; Kawauchi, S.; Ishikawa, M. Novel Aspects of the [1,3] Sigmatropic Silyl Shift in Allylsilane. *J. Am. Chem. Soc.* **1997**, *119*, 807–815. (d) Takahashi, M.; Kira, M. *J. Am. Chem. Soc.* **1999**, *121*, 8597–8603.