

Carbolithiation for the Generation of Cyclooctadienyl Anions and Tandem Electrocyclization/Alkylation to Functionalized *cis*-Bicyclo[3.3.0]octenes

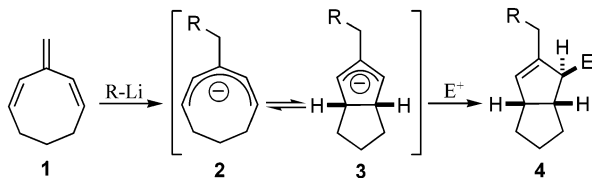
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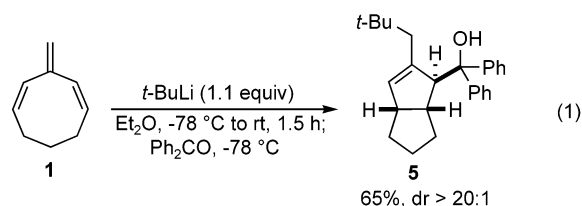
Thermally induced “valence tautomerism” of 1,3,5-cyclooctatriene to *cis*-bicyclo[4.2.0]octa-2,4-diene was first reported by A. C. Cope¹ in 1950 and was later studied in detail by Winstein.² The stereospecific nature of the electrocyclization, and indeed all pericyclic reactions, was subsequently rationalized in terms of conservation of orbital symmetry by Woodward and Hoffmann.³ Their conclusions regarding electrocyclic reactions predicted that a charged species should behave in the same way as the corresponding isoelectronic neutral system.^{3a} This prediction was confirmed for the anionic equivalent of the cyclooctatriene system with the first example of electrocyclization of a pentadienyl anion as shown by the disrotatory conversion of cyclooctadienyllithium to *cis*-bicyclo[3.3.0]octenyllithium reported by Bates in 1969.⁴ Subsequently, electrocyclization of 1,5-diphenylpentadienyl anion to isomeric diphenylcyclopentenes was disclosed.⁵ Additional reports have described unsuccessful attempts for cyclization of cyclic⁶ and acyclic⁷ pentadienyl anions. To utilize the facile nature of the cyclooctadienyl electrocyclization, we proposed generation of the requisite pentadienyl anion through carbolithiation⁸ of triene **1** (Scheme 1). Disrotatory ring closure of the resultant pentadienyl anion **2** to bicyclic allyl anion **3** and subsequent electrophilic capture would provide the functionalized *cis*-bicyclo[3.3.0]octene **4**. This reaction cascade would allow formation of three C–C bonds and three stereocenters in a single operation from simple starting materials. We report herein the successful realization of this process, its scope, and its application to the preparation of a linear triquinane.

Scheme 1. Cascade Carbolithiation/Electrocyclization/Alkylation



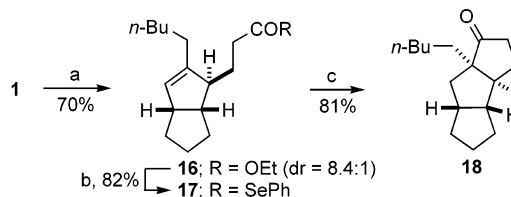
Wittig methylenation⁹ of readily available 2,7-cyclooctadiene¹⁰ provided 3-methylene-1,4-cyclooctadiene (**1**). Preliminary studies employing *tert*-butyllithium for carbolithiation revealed Et₂O as the optimal solvent (eq 1). Thus, dropwise addition of 1.1 equiv of *t*-BuLi to an Et₂O solution of **1** at –78 °C, stirring at room temperature for 1.5 h, and quenching with benzophenone at –78 °C provided a 65% yield of bicycle **5** as a single diastereomer.¹¹ Generation of the pentadienyl carbanion **2** permits the concerted, disrotatory ring closure to the *cis*-fused allyl anion **3**. Introduction of the electrophile proceeds via stereocontrolled alkylation of the more accessible convex face of the *cis*-bicyclo[3.3.0]octenyl anion. While factors such as the additional conjugation in **2**, the introduction of ring strain in **3**, and the formation of a new C–C bond might suggest an equilibrium state of **2** and **3**, the absence of

alkylated or protonated **2** in the product mixture implies electrocyclization is highly favored.¹²



The reaction scope with respect to alkyllithium and electrophile was examined (Table 1). Reactions with secondary and tertiary alkyllithiums (entries 1–5, 8–10) proceeded in Et₂O, while primary alkyllithium reagents (entries 6–7) required hexanes and 1 equiv of a diamine additive such as TMEDA or preferably (–)-sparteine to effect carbolithiation.¹³ Modest asymmetric induction was observed using *n*-BuLi·(–)-sparteine (entry 6).¹⁴ Alkyllithium reagents generated in situ from the corresponding iodides by lithium/halogen exchange with *t*-BuLi reacted smoothly (entries 5 and 7), demonstrating the potential for incorporation of base-stable functionality. Quenching with heteroatom electrophiles provided access to useful allylic sulfide, alcohol, and silane moieties (entries 1–3). Alkylation with ketones, aldehydes, and CO₂ efficiently led to formation of a new C–C bond (entries 4–7). Transmetalation of the intermediate allyllithium species to copper was possible using CuCN/LiCl.¹⁵ This permitted conjugate additions to unsaturated ketones and esters (entry 8 and Scheme 2, *vide infra*) in the presence of TMSCl, and alkylations with alkyl iodide (entry 9) and epoxide (entry 10) electrophiles also proved feasible.

Scheme 2^a



^a Conditions: (a) *n*-BuLi, (–)-sparteine, hexanes, –78 °C to room temperature, 1 h; CuCN·2 LiCl, THF, –78 °C; ethyl acrylate, TMSCl, –78 °C to room temperature. (b) i. LiOH, THF/H₂O; ii. *N*-(phenylselenenyl)phthalimide, *n*-Bu₃P, THF. (c) *n*-Bu₃SnH, AIBN, PhH, reflux.

The rapid preparation of a linear triquinane using the carbolithiation/electrocyclization/conjugate addition cascade is detailed in Scheme 2. Carbolithiation/electrocyclization of **1** using *n*-BuLi·(–)-sparteine followed by transmetalation to copper and 1,4-addition to ethyl acrylate provided the adduct **16** in 70% yield (dr = 8.4:1). Conversion to phenylselenenyl ester¹⁶ **17** and acyl radical cyclization¹⁷ provided triquinane **18** in 81% yield as a single diastereomer.¹⁸

Table 1. Scope of Cascade Carbolithiation/Electrocyclization/Alkylation Reaction^a

Entry	RLi / Electrophile	Product	Yield (%) ^b	dr ^c	Entry	RLi / Electrophile	Product	Yield (%) ^b	dr ^c
1	<i>t</i> -BuLi / PhSSPh		71	10:1	6	<i>n</i> -BuLi / PhCHO		72	1:1 ^e
2	<i>t</i> -BuLi /		49	>20:1	7	TIPSO(CH ₂) ₅ Li ^d / Et ₂ CO		77	>20:1
3	<i>i</i> -PrLi / PhMe ₂ SiCl		70	>20:1	8 ^f	<i>t</i> -BuLi /		63	2.5:1
4	<i>i</i> -PrLi / CO ₂		71	6.8:1	9 ^f	<i>t</i> -BuLi /		46	4.7:1
5	<i>c</i> -HexLi ^d / CH ₂ O		48	11.4:1	10 ^f	<i>i</i> -PrLi /		61	9.7:1

^a Reaction conducted with **1** in Et₂O (entries 1–5, 8–10) or hexanes/1 equiv (–)-sparteine (entries 6–7). ^b Isolated yields after purification. ^c Diastereomeric ratios determined by ¹H NMR of crude product mixtures. ^d Generated from the corresponding iodides by treatment with *t*-BuLi (2.2 equiv) and cannulation away from precipitated LiI. ^e Enantiomeric excesses of **9** and **16** determined by Mosher's ester analysis of each diastereomer. ^f A solution of CuCN (1 equiv) and LiCl (2 equiv) in THF added prior to electrophile.

In conclusion, a powerful cascade reaction process for the rapid construction of functionalized *cis*-bicyclo[3.3.0]octenes has been developed. The reaction is compatible with 1°, 2°, and 3° organolithium reagents, and a diverse array of electrophiles may be employed. Transmetalation from lithium to copper prior to electrophilic quench allows access to the cuprate manifold of reactivity. The expedient preparation of a linear triquinane using this methodology should prove useful for natural products synthesis. This process represents the first synthetic application of the electrocyclization of a pentadienyl anion, and the generation of a reaction-competent carbanion by a C–C bond-forming carbolithiation event. Excellent atom economy, as well as the potential for variation of three different reaction components, adds to the overall value of the process. Full details of this work, including extension to other ring sizes, will be reported in due course.

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Supporting Information Available: Full experimental details, ¹H NMR spectra of all compounds, and COSY and NOESY spectra of representative compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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