

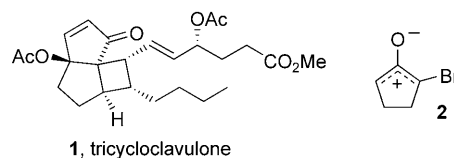
An Interrupted [4+3] Cycloaddition Reaction: A Hydride Shift (Ene Reaction) Intervenes**

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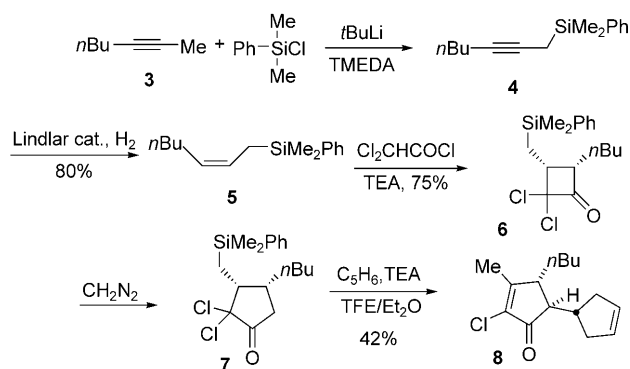
Cyclopentenyl cations are synthetically very useful in organic synthesis. They are intermediates in both the Nazarov electrocyclization^[1] and in [4+3] cycloaddition reactions.^[2] The West group has in fact coupled both procedures to produce polycyclic compounds with great efficiency.^[3] The same group has also introduced protocols for trapping the cyclopentenyl oxyallylic cations produced as intermediates in the Nazarov cyclization. These include [3+2] cycloadditions,^[4] addition reactions with alkenes,^[5] polyolefin cyclizations,^[6] ionic hydrogenation,^[7] halide addition,^[8] rearrangement,^[9] electrophilic aromatic substitution,^[10] and Schmidt reactions.^[11] Tius and co-workers have shown that related intermediates can be trapped with amines.^[12] Furthermore, these observations have led to the development of a new approach to the generation of pentadienylic cations that electrocyclize to produce cyclopentenyl cations closely related to those produced in a Nazarov cyclization of dienones.^[13]

Oxyallylic cations are enolonium ion equivalents, formally enabling nucleophilic addition in the α -position relative to a ketone. This umpolung of reactivity^[14] plays a key role in the chemistry of such species as dienophiles in the [4+3] cycloaddition reaction, but the scope of the chemistry is incredibly broad, as illustrated by the West and Tius groups' recent work.

Our interest in this chemistry stems from our work with cyclopentenyl cations in the context of [4+3] cycloaddition reactions and their application to total synthesis and the [4+3] cycloaddition/quasi-Favorskii process on which our lab is presently focusing.^[15] For example, we recently reported the synthesis of the carbocyclic skeleton of tricyclocavulone (**1**) using this approach.^[16] The oxyallylic cation **2** served as the dienophile in the key [4+3] cycloaddition with cyclopentadiene.



In attempting a total synthesis of **1**, we required a more substituted oxyallylic cation and consequently a more substituted precursor. A very appealing synthesis of an appropriate species was developed on the basis of the addition of dichloroketene to an allylic silane. Thus, **3** was deprotonated and quenched with dimethylphenylsilyl chloride to afford **4**.^[17] Lindlar reduction and reaction with dichloroketene afforded the cyclobutanone **6**.^[18] Ring expansion with diazomethane afforded **7**, which could be used directly to generate a halogenated allylic cation (Scheme 1).



Scheme 1. Synthesis of pro-(di)enophile **7** and its reaction product with cyclopentadiene. TMEDA = *N,N,N',N'*-tetramethylethylenediamine, TEA = triethylamine, TFE = 2,2,2-trifluoroethanol.

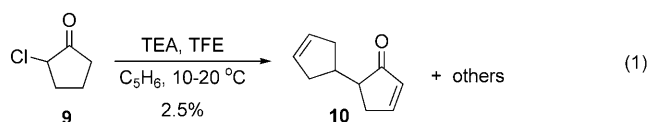
We thus combined **7** with ten equivalents of cyclopentadiene in a solution of trifluoroethanol and diethyl ether (1:1), typical for many cycloaddition reactions we have performed. The major product (**8**) was clearly not a [4+3] cycloadduct.

Leitch and Heise reported that treatment of a trifluoroethanol solution of 2-chlorocyclopentanone (**9**) with triethylamine in the presence of excess cyclopentadiene afforded **10** in 2.5% yield, in addition to the expected [4+3] cycloaddition product, which was obtained in excellent overall yield [Eq. (1)].^[19] Other products related to **10** were produced when various alkenes and dienes were used in the reaction, but none were obtained in good yield. Isolated reports of similar chemistry have appeared, but none with yields that were synthetically useful.^[20–22]

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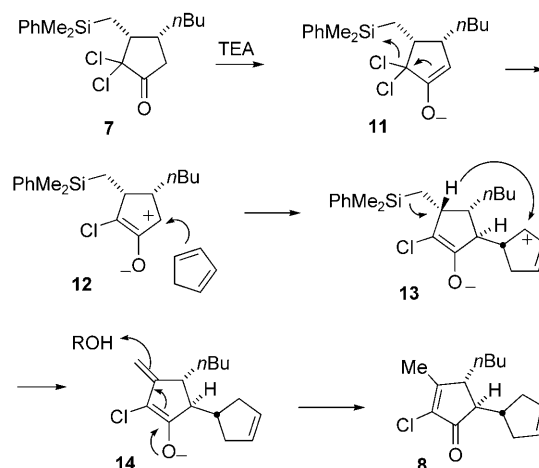
[**] This work was supported by a grant from the National Science Foundation to which we are grateful. We acknowledge an informative exchange with Dr. Benjamin Miller (Rochester).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200803487>.

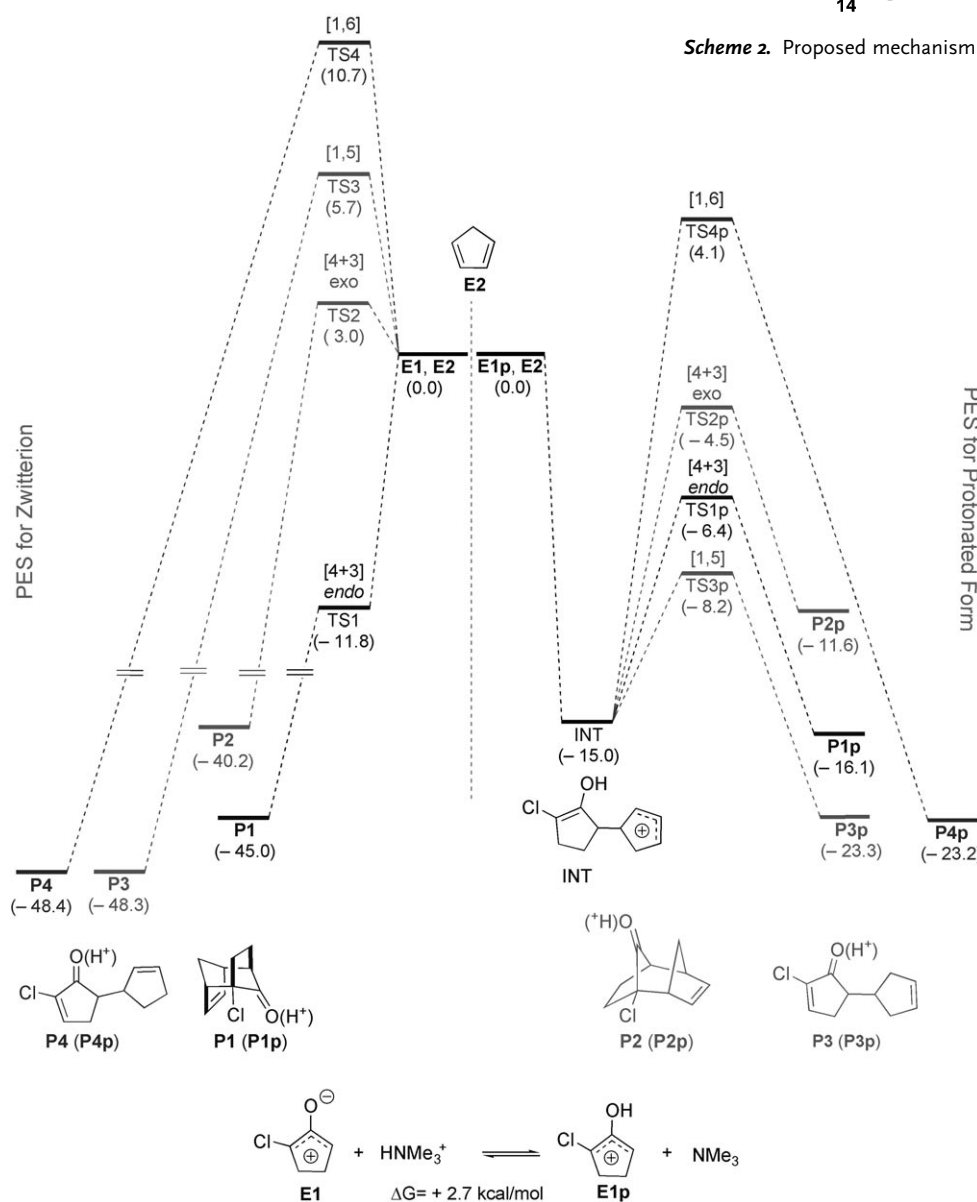


Under our initial set of reaction conditions, it appeared that a small amount of the desired [4+3] cycloadduct was formed. However, efforts to improve the yield of this compound were fruitless.

A plausible mechanism for the formation of **8** is presented in Scheme 2. Formation of the oxyallylic cation **12** is followed by trapping with cyclopentadiene to give the zwitterion **13**.



Scheme 2. Proposed mechanism for the formation of **8**.



Scheme 3. Computed potential energy hypersurface at B3PW91/cc-pVDZ using SCIPCM to approximate aqueous solution. ZPVE corrections are taken from gas phase optimizations at B3PW91/cc-pVDZ. Relative energies [$\Delta H_{0(\text{soln})}$] are given in kcal mol⁻¹. Note that the reactions starting from the zwitterion **E1** and the protonated form **E1p** have different stoichiometries (the energies of the starting materials **E1**, **E2** as well as **E1p** and **E2** are arbitrarily set to zero).

Hydride transfer and concomitant desilylation via a six-membered-ring transition state affords **14**. Protonation and conjugation of the resulting double bond then gives **8**. Leitich and Heise^[19] pointed out that this process could be a concerted ene reaction. It is possible that such a mechanism applies here, though further studies would be necessary to support this idea. A different [1,6]-H-shift is possible, as of course is the desired [4+3] cycloaddition process.

To probe the [1,5]- and [1,6]-H-shifts implied by the experiments, we examined these two and alternative [4+3] cycloaddition pathways computationally (Scheme 3). We modeled these reaction paths with the simplified reactants **E1**, **E1p** (**p** stands for protonated), and cyclopentadiene (**E2**). We considered an equilibrium between oxyallyl zwitterion **E1** and its protonated form, the hydroxyallyl cation **E1p**, taking trimethylammonium as the Brønsted acid ($\Delta G = 2.7$ kcal mol⁻¹). Thus, we examined the reaction of **E1** or **E1p** with **E2** to give products **P1–P4** and **P1p–**

P4p, respectively. As the theoretical approach for a system of this size, we chose density functional theory (DFT) utilizing the B3PW91^[23] combination of functionals in conjunction with a correlation-consistent double- ζ basis set^[24] (cc-pVDZ), because this level has been shown to be qualitatively reliable for hydrocarbon structures.^[25,26]

Along the unprotonated pathway, oxyallyl zwitterion **E1** reacts with cyclopentadiene (**E2**) at the diffusion limit to give the *endo* [4+3] cycloadduct **P1**, which is favored over the analogous *exo* product **P2** kinetically as well as thermodynamically. We also examined alternative H-shift pathways and found that these reactions lead through transition states TS3 for a [1,5]-H-shift to **P3** ($\Delta H_0^\ddagger = 5.7$ kcal mol⁻¹) and via TS4 for a [1,6]-H-shift to **P4** ($\Delta H_0^\ddagger = 10.7$ kcal mol⁻¹). The computed potential energy hypersurface favors **P1** kinetically as the main product, which is typical for oxyallyl zwitterions.

Hydroxyallyl cation **E1p** shows an entirely different reactivity pattern. The highly electrophilic **E1p** attacks **E2** to give the intermediate adduct **INT**, which undergoes either a [1,5]-H-shift to the product **P3p** through the lowest-lying TS3p ($\Delta H_0^\ddagger = 6.8$ kcal mol⁻¹), or a formal [4+3] *endo* closure through TS1p ($\Delta H_0^\ddagger = 8.6$ kcal mol⁻¹). An alternative [1,6]-H-shift cannot compete owing to a much higher barrier (TS4p, $\Delta H_0^\ddagger = 19.1$ kcal mol⁻¹).

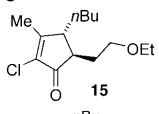
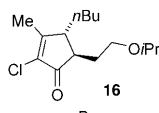
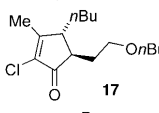
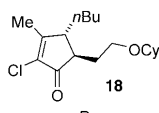
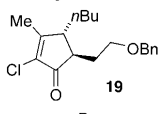
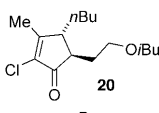
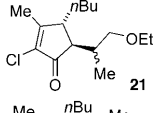
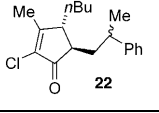
In fact, experimentally, **E1** reacts with cyclopentadiene to produce **P1** in 75% yield as a 9:1 mixture of *endo* and *exo* diastereomers. It would appear that with **12**, structural features may result in conformational changes that favor the [1,5]-H-shift. Alternatively, it may be the case that larger amounts of a hydroxyallyl cation are produced with this oxyallyl cation, changing the “normal” reactivity pattern to favor the [1,5]-H-shift. In any case, the computational work supports the idea that the [1,5]-H-shift could be important in the reactions of cyclopentenyl oxyallylic cations and suggests that some control over the reaction might be exerted by appropriate changes in reaction conditions.

Given that the formation of **8** proceeded in reasonable yield, we examined the scope of the process, using Mayr et al.’s classification of alkene nucleophilicity as a guide to choose appropriate alkene or diene partners for the process.^[29] The results are summarized in Table 1.

In exploring solvents for this reaction, we found that the yield of **8** could be improved to 68% when a 1:1 mixture of hexafluoroisopropyl alcohol (HFIP) and diethyl ether was used as solvent (Table 1, entry 2). Most of the reactions studied employed the TFE/ether solvent system, and solvent optimization may be required for certain difficult substrates.

We found that terminal enol ethers in particular were quite suitable for this reaction (Table 1, entries 3–8). A disubstituted enol ether also afforded product in good yield but with low diastereoselectivity (Table 1, entry 9), possibly owing to the fact that the enol ether itself was a mixture of isomers.^[30] Dihydrofuran, dihydropyran, α -trimethylsilyloxy-styrene, α -methoxystyrene, and 2-methoxypropene led to complicated reaction mixtures that were not studied further. Styrene itself gave a low yield of product, but α -methylstyrene afforded product in 67% yield, and the diastereoselectivity was high, though further studies of diastereoselectivity in this process are needed to establish reliable trends.

Table 1: Reaction of **11** with various alkenes.

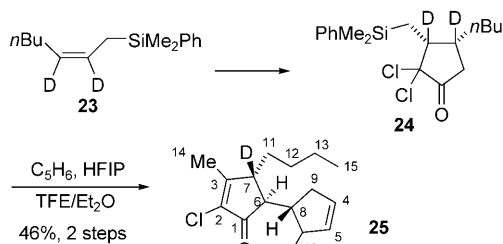
Entry	Alkene	Product	Yield [%]
1	cyclopentadiene	8	42
2	cyclopentadiene	8	68 ^[a]
3			57
4			73
5			69
6			53 ^[b]
7			63
8			69
9			69 ^[c]
10			67 ^[a,d]

[a] Reaction run in HFIP/diethyl ether 1:1. [b] Cy=cyclohexyl. [c] Two diastereomers formed in a ratio of 2.5:1. [d] Two diastereomers formed in a ratio of 10:1; diastereomer ratio determined by ¹H NMR spectroscopy of purified product, as the crude product was not amenable to such analysis.

Though allylsilanes have been used to trap oxyallylic cations,^[4b] allyltrimethylsilane reacted with **11** in the presence of base to give a complex mixture of products. Other allylsilanes have not yet been investigated.

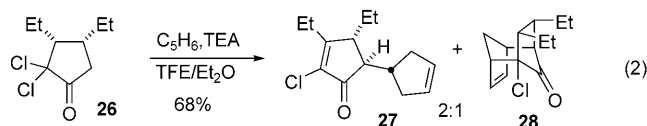
To examine the mechanism of the process further, dideuterated alkene **23** was prepared and carried through the reaction sequence (Scheme 4). NMR spectroscopic examination of the product indicated the presence of two D atoms at positions expected on the basis of the mechanism presented in Scheme 3. Thus, the signals assigned to carbons 7 and 10 appeared as triplets ($J_{CD} = 20.1$ Hz) in the proton-decoupled ¹³C NMR spectrum. The data also supported the assignments previously made in that signals appearing at 2.32 and 2.57 ppm in the ¹H NMR spectrum of **8** were not observed in the ¹H NMR spectrum of **25**.

We wondered if the presence of the Me₂PhSi group had a major impact on the course of the reaction. However, when **26** was treated with triethylamine in the presence of cyclopentadiene, an inseparable 2:1 mixture of the cyclopentenone **27** and the [4+3] cycloadduct **28** was isolated in 68% yield



Scheme 4. Mechanistic study using dideuterated analogues of **11** and ketone **24**.

[Eq. (2)]. Thus, while the silyl group in **7** may influence the course of the reactions, it is not the sole factor in favoring the hydride shift observed.



In conclusion, we have shown that an ene-like reaction involving a hydride shift can take place between oxyallylic cations and alkenes in synthetically useful yields. This reaction further expands the growing number of bond-forming processes of cyclopentenyl cations that can be used in a synthetic context. The structural limitations of this process with respect to the oxyallylic cation remain to be completely established. Diastereoselectivity and the potential for an intramolecular process are also being explored. The computational studies suggest that the base used in the reaction could affect its course. Allylic cations generated in other ways could also reflect the fundamentally different reactivity of oxyallylic and 2-hydroxyallylic cations.

Received: July 18, 2008

Published online: September 18, 2008

Keywords: carbocations · cycloaddition · ene reaction · hydrogen shift · oxyallylic cations

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