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The Reductive Nazarov Cyclization

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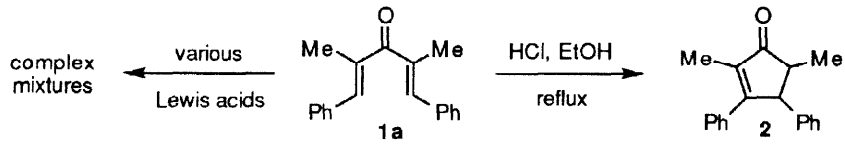
Abstract: Tri- and tetrasubstituted 1,4-dien-3-ones **1** were treated with Lewis acid in the presence of triethylsilane, furnishing either silyl enol ethers **4** or cyclopentanones **5** in good yields, depending upon work-up conditions. This reaction is presumed to occur through oxyallyl intermediate **3**, which undergoes intermolecular hydride transfer and O-silylation to give **4**. In most cases, only 2 equiv. of silane was required, and catalytic amounts of Lewis acid could be used. Trienone substrate **7** was found to undergo clean conversion to tricyclic ether **8**, indicating fast capture of the oxyallyl intermediate by the pendant olefin.

Keywords: annulation, cyclization, dienones, electrocyclic reactions, Nazarov reactions

The Nazarov cyclization has enjoyed widespread use in synthetic organic chemistry as a vehicle for the selective introduction of cyclopentene rings.[1] The initial observation of the protic acid-mediated cyclization of cross-conjugated dienones and related systems[2] was followed by several important innovations, such as the use of Lewis acids under aprotic conditions,[3] and various forms of "directed Nazarov cyclizations" employing silyl- or stannyl-substituted dienones.[4] In fact, these two improvements are interconnected, as the use of Lewis acid to initiate the electrocyclization demands the availability of a facile termination event. While loss of R_3Si^+ or R_3Sn^+ satisfies this requirement, the more common deprotonation pathway can be inefficient and unselective. For example, 2,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-one **1a** underwent clean conversion to cyclopentenone **2** upon reflux in ethanolic HCl (eq 1).[5] However, we found that attempted cyclization with Lewis acids under a variety of conditions led to low yields and complex mixtures.



(1)

We have recently shown that the oxyallyl intermediate formed upon electrocyclization of dienones can be efficiently intercepted by pendant alkenes, a process termed the interrupted Nazarov reaction.[6] This suggested that the intervention of an effective trapping process might render substrates such as **1a** more tractable. In particular, intermolecular trapping of the oxyallyl intermediate **3** with a Lewis acid-tolerant hydride source could provide a general method for the direct conversion of dienones to cyclopentanones (Scheme 1). An important advantage of such a "reductive Nazarov cyclization" would be the preservation of both newly formed stereocenters at carbons 3 and 4 of the cyclopentanone. In contrast, eliminative termination usually leads to the loss of some of this stereochemical information (e.g., **1a** → **2**).[7]

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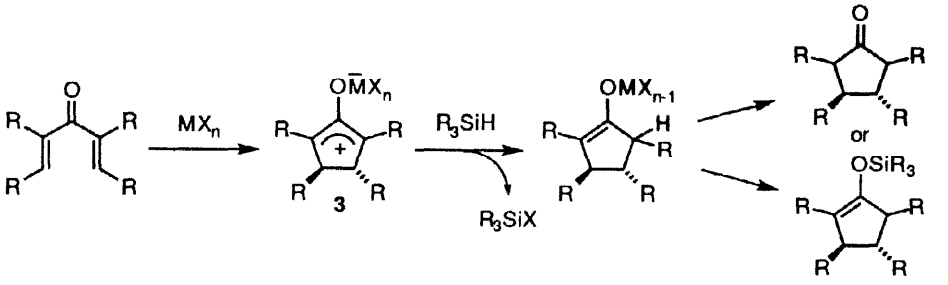
Scheme 1



Dienones **1a-e**[8] were treated with Lewis acid in the presence of 2-10 equiv. of triethylsilane (Table 1).[9] Initial studies with **1a** and either Et_2AlCl or $BF_3{\cdot}OEt_2$ led to mixtures of silyl enol ether **4a** and cyclopentanones **5a** in excellent combined yield (entries 1 and 2). To simplify the reaction mixture, the aqueous quench was replaced by treatment with 1N HCl (entry 3), which provided **5a** in 98% yield (ca. 9:1 ratio).[10] It is also notable that this process could be effected with catalytic amounts of Lewis acid (entry 4), albeit in somewhat lower overall yield.[11] Dicyclopentenyl ketone **1b** could be converted to the triquinane **5b** in good yield, along with a small amount of the simple conjugate reduction product **6b** (entry 5). Catalytic amounts of $BF_3{\cdot}OEt_2$ in this case led to incomplete consumption of the starting dienone, while $SnCl_4$ gave reduction product **6b** only (entry 6).

In analogy to **1a**, dienone **1c** gave a mixture of silyl enol ether **4c** and cyclopentanones **5c** with a simple aqueous work-up, and **5c** only with a 1N HCl quench (entries 7 and 8). Trisubstituted dienone **1d** led to a 3.3:1 mixture of **5d** in good yield (entry 9). Notably, when its (*Z*)-isomer, **1e**, was subjected to the same conditions, an identical ratio of products was obtained in comparable yield (entry 10). Orbital symmetry considerations require that an (*E,Z*)-dienone such as **1e** should lead to a cis relationship between the phenyl and methyl groups at C-3 and C-4. The isolation of the same trans-disubstituted products obtained with **1d** suggests a prior isomerization of the (*Z*)-alkene.[12] This was confirmed by analysis of unreacted starting material in an

Table 1. Reductive Nazarov Cyclization of Dienones 1a-e.

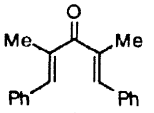
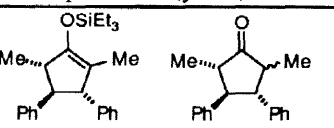
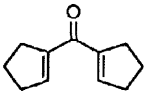
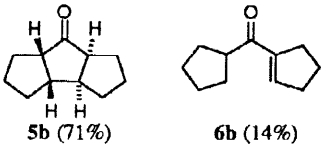
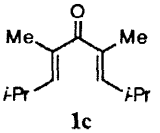
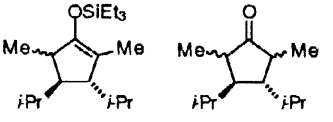
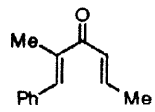
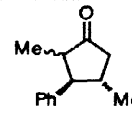
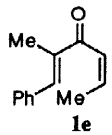
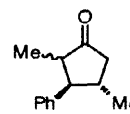
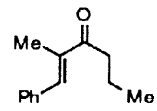
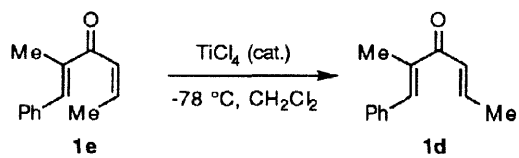
entry	substrate	conditions[a]	products (yield)[b]
1	 **1a**	1.1 equiv. Et_2AlCl, 10 equiv. Et_3SiH; H_2O	 **4a** (49%) **5a** (44%; 4.5:1 β-Me/α-Me)
2	**1a**	1.1 equiv. $BF_3{\cdot}OEt_2$, 10 equiv. Et_3SiH; H_2O	**4a** (44%), **5a** (54%; 3.5:1 β-Me/α-Me)
3	**1a**	1.1 equiv. $BF_3{\cdot}OEt_2$, 2 equiv. Et_3SiH; 1N HCl	**5a** (98%; 8.8:1 β-Me/α-Me)
4	**1a**	0.1 equiv. $BF_3{\cdot}OEt_2$, 2 equiv. Et_3SiH; 1N HCl	**5a** (80%; 7.0:1 β-Me/α-Me)
5	 **1b**	1.1 equiv. $BF_3{\cdot}OEt_2$, 2 equiv. Et_3SiH; 1N HCl	 **5b** (71%) **6b** (14%)
6	**1b**	0.1 equiv. $SnCl_4$, 2 equiv. Et_3SiH; 1N HCl	**6b** (61%)
7	 **1c**	1.1 equiv. $BF_3{\cdot}OEt_2$, 10 equiv. Et_3SiH; H_2O	 **4c** (24%; 5.7:1 Me epimers) **5c** (69%; 2.6:1 Me epimers)
8	**1c**	1.1 equiv. $BF_3{\cdot}OEt_2$, 2 equiv. Et_3SiH; 1N HCl	**5c** (84%; 1.2:2.8:1 ratio of 3 diast.)

Table 1. (continued)

entry	substrate	conditions[a]	products (yield)[b]
9	 **1d**	1.1 equiv. BF_3•OEt_2, 10 equiv. Et_3SiH; H_2O	 **5d** (77%; 3.3:1 β-Me/α-Me)
10	 **1e**	1.1 equiv. BF_3•OEt_2, 10 equiv. Et_3SiH; H_2O	**5d** (81%; 3.3:1 β-Me/α-Me)
11	**1e**	0.1 equiv. $SnCl_4$, 2 equiv. Et_3SiH; H_2O	 **5d** (63%; 5.6:1 β-Me/α-Me)  **6d** (12%)

[a]All reactions were carried out at -78 °C in CH_2Cl_2. See reference 9 for a representative experimental procedure. [b]Isolated yields after chromatography. All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR and combustion analysis or HRMS.

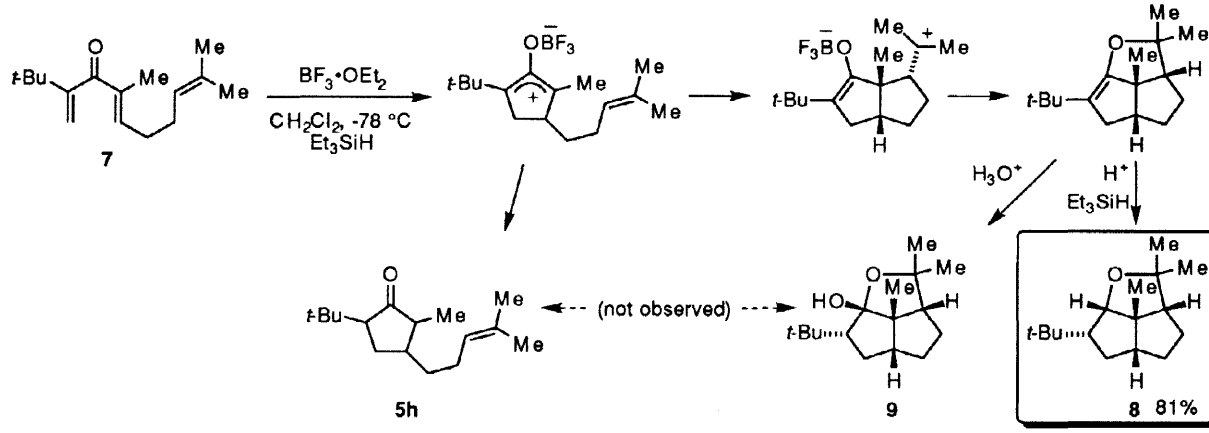
incomplete reaction, which indicated that significant isomerization had occurred prior to Nazarov cyclization. Careful treatment of **1e** with a catalytic amount of $TiCl_4$ at low temperature furnished **1d** in high yield (eq 2). As in the case of **1b** (entry 6) treatment of **1e** with $SnCl_4$ resulted in the formation of some conjugate reduction product **6d** along with **5d** (entry 11). Silyl enol ethers were not isolated with **1d-e**, even with bicarbonate work-up. This presumably results from their greater lability due to lighter substitution.[13]



1e **1d** (2)

Finally, trienone **7** was subjected to the reductive Nazarov conditions (Scheme 2). This substrate had previously been shown to undergo efficient conversion to the tricyclic hemiketal **9**,[6] but the efficiency of the hydride trapping seen with **1a-e** suggested that reductive cyclization to give **5h** might compete effectively with the interrupted Nazarov pathway. In the event, tricyclic ether **8** was obtained in high yield, suggesting rapid capture of the oxyallyl intermediate by the alkene, and a short lifetime for the resulting tertiary carbocation. Ionic hydrogenation[14] of the intermediate enol ether would then lead to **8**.

Scheme 2



These results demonstrate that the intermediate oxyallyl cation formed from the electrocyclization step of the Nazarov reaction can be efficiently intercepted by an intermolecular hydride source with no competing elimination to cyclopentenone. This reductive Nazarov cyclization complements existing methodology for directed cyclopentenone formation, and may expand the potential of the previously reported olefin trapping reactions. Further examples of synthetically useful intermolecular trapping of Nazarov intermediates will be reported elsewhere.

Acknowledgments. We thank NIH (GM-44720) for their generous support of this research, and Fonds der Chemischen Industrie for a Kekulé Fellowship (SG).

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5. Nazarov, I. N.; Kotlyarevsky, I. L. *J. Gen. Chem. USSR* **1950**, *20*, 1509.
6. Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430.
7. Preservation of the β and β' stereocenters has also been accomplished using the Si-directed Nazarov cyclization: Denmark, S. E.; Klix, R. C. *Tetrahedron* **1988**, *44*, 4043.
8. (a) Substrates **1a** and **1c** have been previously described. **1a**: Yates, P.; Yoda, N.; Brown, W.; Mann, B. *J. Am. Chem. Soc.* **1958**, *80*, 202. **1c**: Eaton, P. E.; Giordano, C.; Schloemer, G.; Vogel, U. *J. Org. Chem.* **1976**, *41*, 2238. (b) Substrate **1b** was prepared in analogy to **1a** from 3 pentanone and isobutyraldehyde. (c) Substrates **1d,e** were prepared by addition of an *E/Z* mixture of 1-propenylmagnesium bromide to 2-methylcinnamaldehyde, followed by oxidation of the resulting dienol with $BaMnO_4$.
9. (a) Representative procedure: A solution of **1a** (50 mg, 0.19 mmol) and Et_3SiH (44 mg, 0.38 mmol) in CH_2Cl_2 (20 mL) was stirred at -78 °C under N_2. $BF_3{\cdot}OEt_2$ (27 μL, 0.21 mmol) was added dropwise via syringe, and the resulting yellow solution was allowed to warm slowly to 0 °C. Aq. 1 N HCl (9 mL) was added and the mixture was stirred overnight at rt. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the crude product was purified by radial chromatography (silica gel, 2 mm plate, hexanes/EtOAc 30:1→25:1→20:1) to give 44 mg (88%) of the major diastereomer (β-Me) of **5a** and 5 mg (10%) of its minor α-Me epimer. Spectral data for the major (β) isomer were in agreement with those previously reported.[10] Selected data for the minor (α) isomer: solid, mp 82 °C; R_f 0.21 (hexanes/EtOAc 7:1); IR (thin film) 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.12 (m, 10H), 3.89 (dd, J = 11.9, 8.5 Hz, 1H), 3.28 (dd, J = 11.9, 11.9 Hz, 1H), 2.85 (dqd, J = 8.4, 8.1, 1.3 Hz, 1H), 2.45 (dqd, J = 11.9, 6.9, 1.6 Hz, 1H), 1.12 (d, J = 7.0 Hz, 3H), 0.78 (d, J = 7.9 Hz, 3H). (b) These reactions have been carried out on up to a 2 mmol scale with little diminution in yield (e.g., **1a** → **5a**, 87% comb. yield).
10. The formation of **5a** under reductive conditions (HI and red phosphorus) has been previously described: Shoppee, C. W.; Cooke, B. J. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1026.
11. We are not aware of any literature precedent for the use of less than a stoichiometric amount of Lewis acid to effect the Nazarov cyclization. Catalysis by various Et_3Si-X species generated *in situ* may contribute to this process.
12. (a) We have previously observed $TiCl_4$ mediated *Z-E* isomerization of a dienone: White, T. W. *Torquoselectivity and Chloride Trapping in the Nazarov Cyclization of Facially Biased Dienones*, University of Utah, 1998. (b) For a somewhat related example of Lewis acid-mediated alkene isomerization, see: Faita, G.; Mella, M.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1994**, *50*, 10955.
13. We assume delivery of hydride to the more substituted terminus of the intermediate oxyallyl cation due to greater charge localization at that carbon.
14. (a) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633. (b) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: New York, 1983; pp 273-287.