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# Highly Efficient Trapping of the Nazarov Intermediate with Substituted Arenes

**Cindy C. Browder, Fredrik P. Marmsäter, and F. G. West***

*Department of Chemistry, University of Utah, 315 South 1400 East, Rm 2020, Salt Lake City, Utah 84112-0850*

*west@chemistry.chem.utah.edu*

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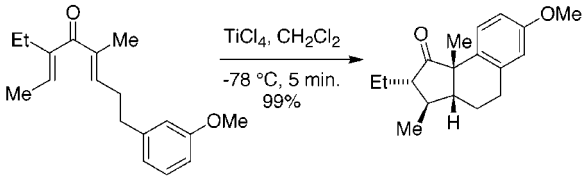
## ABSTRACT




**1,4-Dien-3-ones bearing pendant arylethyl side chains were readily prepared from substituted dihydrocinnamaldehydes. When treated with $TiCl_4$ at low temperature, these compounds underwent domino cyclization to give benzohydrindenones in near-quantitative yield and with complete diastereoselectivity.**

Benzohydrindan ring skeletons are useful intermediates in the construction of steroidal targets[1] and alkaloids[2] and also can be found in other biologically important substances.[3] We have previously reported that hydrindan skeletons can be assembled by domino Nazarov cyclization/6-endo cation-olefin cyclization.[4] This process typically consumed the starting trienone with high efficiency but furnished a mixture of products via several termination pathways. In a related study, we also described the cascade cyclization of aryl trienones, in which 6-endo cyclization of a trisubstituted olefin and the Nazarov oxyallyl intermediate was followed by clean termination via addition of the resulting carbocation to a pendant phenyl group.[5] In light of these results, we sought to learn whether the direct trapping of the Nazarov intermediate by pendant aryl moieties was possible. Following is a preliminary report of this work, which describes the high-yield and stereoselective conversion of aryl dienones to benzohydrindenones.

The necessary substrates to test the feasibility of this process could be prepared from readily available hydrocinnamaldehydes **1a**−**c** (Scheme 1).[6] Horner−Emmons olefination under the Roush−Masamune conditions,[7] followed by a reduction/oxidation sequence, yielded the key enals **2a**−**c**. Treatment with either 2-propenylmagnesium bromide, 3-lithiohexene, or 1-lithiocyclohexene gave the corresponding dienols, which were then oxidized to dienones **3a**−**g** using $BaMnO_4$.[8]

Initial experiments employed the simple, phenyl-substituted substrate **3a** (Scheme 2). The Lewis acids $BF_3{\cdot}OEt_2$ and $TiCl_4$ were chosen, as they have been found to be the most generally effective mediators of other Nazarov-based domino processes.[4,5,9] Unfortunately, treatment of **3a** with $TiCl_4$ led to complex mixtures containing no apparent domino

(1) Nemoto, H.; Miyata, J.; Yoshida, M.; Raku, N.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 7850.
(2) Kopach, M. E.; Fray, A. H.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 9876.
(3) Zeng, C.; Han, M.; Covey, D. F. *J. Org. Chem.* **2000**, *65*, 2264.
(4) Browder, C. C.; West, F. G. *Synlett* **1999**, 1363.
(5) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443.
(6) Hydrocinnamaldehydes **1b**,**c** were prepared from the commercially available (Aldrich) cinnamic acids via exhaustive reduction ($LiAlH_4$/THF) followed by oxidation with TPAP/NMO.
(7) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(8) Barium manganate is a mild and effective oxidant for the conversion of dienols to dienones: (a) Denmark, S. E.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 195. (b) Firouzabadi, H.; Ghaderi, E. *Tetrahedron Lett.* **1978**, 839. (c) See also ref 9a.
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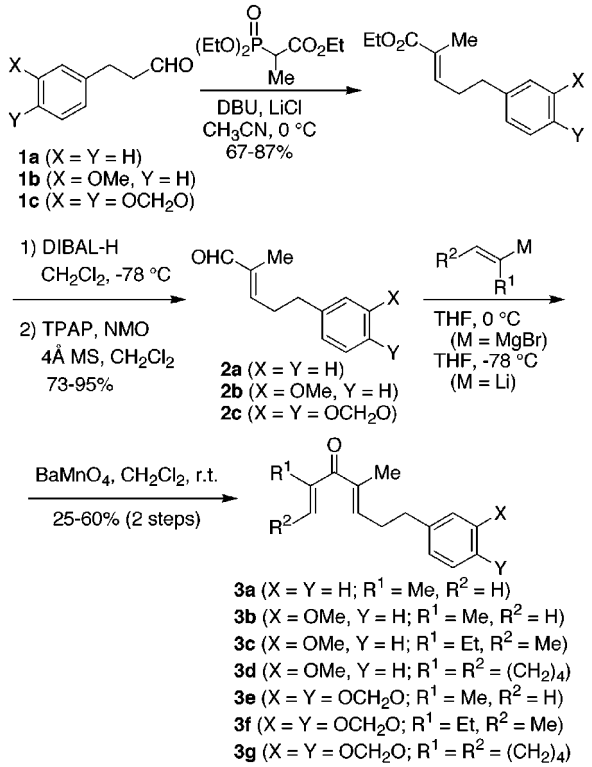
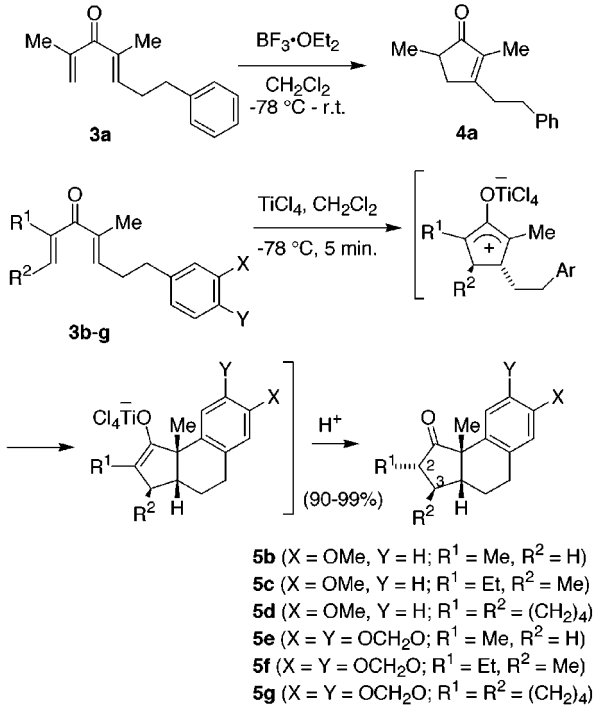
**Scheme 1**




**Scheme 2**



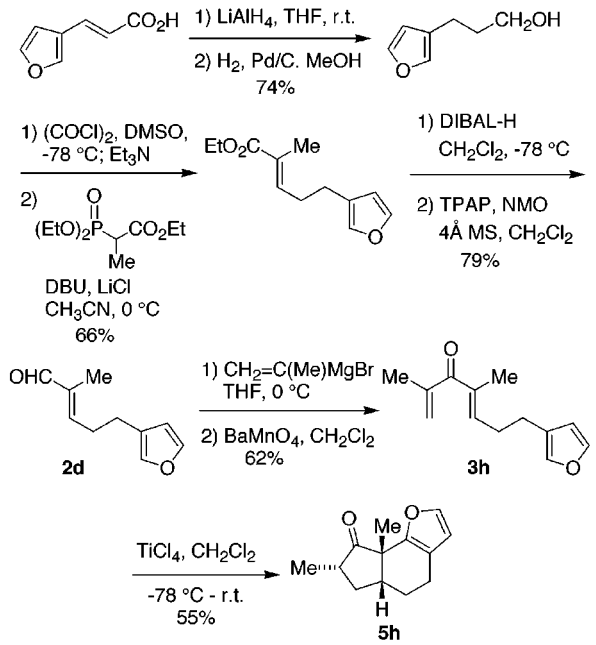

cyclization products, while $BF_3$·$OEt_2$ effected clean conversion to cyclopentenone **4a** resulting from Nazarov cyclization followed by the standard eliminative termination pathway. Failure to observe the desired domino process in this case was likely due to inadequate nucleophilicity of the phenyl trap, in analogy to earlier related photochemical studies.[10] We therefore directed our attention to the more electron-rich substrates **3b**−**g**.

Again, $BF_3$·$OEt_2$ proved unsuitable as the Lewis acid initiator, giving mixtures of simple Nazarov cyclization and domino cyclization products. In contrast, $TiCl_4$ rapidly and cleanly effected the desired transformation of **3b**−**g** to **5b**−**g** in 90−99% yield.[11] As expected, the arene substitution reaction occurred at the sterically less demanding position in all cases (*para* to the methoxy substituent for **5b**−**d** and *meta*/*para* to the methylenedioxy group for **5e**−**g**). This was readily apparent from the coupling pattern of the aromatic protons. In analogy to other Nazarov-based domino processes, the ring-fusion stereochemistry was assigned as *cis*, while the neighboring $R^2$ group at C-3 (e.g., **5c**,**d**,**f**,**g**) must be *cis* to the bridgehead proton after conrotatory closure per the demands of orbital symmetry.[12] The configuration at C-2 was assigned as shown on the basis of prior observation of selective enolate protonation from the convex face of the *cis*-hydrindan system.[13] This stereochemical assignment was confirmed by X-ray crystallography in the case of **5f**, and those of the other products were assigned by analogy.

(10) West, F. G.; Willoughby, D. W. *J. Org. Chem.* **1993**, *58*, 3796.

Finally, use of a furan terminator[14] was examined to further probe the scope of this process. Furan-containing dienone **3h** was prepared from (*E*)-3-furanacrylic acid in analogy to the route employed above (Scheme 3). Notably, enal

**Scheme 3**




intermediate **2d** (perillenal) is a naturally occurring pheromone of the pine saw fly.[15] The route described here offers a convenient method for preparing this substance in quan-

tity.[16] Upon treatment with $TiCl_4$, **3h** was converted to furohydrindenone **5h** in 55% yield. In contrast to the other examples, warming to room temperature was required for complete consumption of the starting dienone. Although it was not possible to characterize the remaining material, it is likely that the lower yield in this case may be due to competing oligomerization or other decomposition processes that can occur at higher temperatures.

The efficiency with which **3b**−**h** underwent electrophilic aromatic substitution in competition with other termination pathways is striking. Acyclic oxyallyl cations can react with simple arenes in intermolecular processes to give a mixture of simple substitution products and [4 + 3] adducts.[17] The geometric constraints of the intramolecular substrates militate against the formation of similar bridged structures in the present study. However, it is possible that formation of products **5b**−**h** may occur through an abortive cycloaddition pathway.[18]

In summary, 1,4-dien-3-ones with pendant electron-rich aryl groups undergo domino cyclization to give arene-fused hydrindenones stereoselectively and in high yield. Further mechanistic studies and application of this facile process to other structural classes will be reported elsewhere in due course.

**Acknowledgment.** We thank NIH (GM 44720) for support of this work and Dr. Atta Arif for assistance in obtaining the X-ray crystal structure of **5f**.

**Supporting Information Available:** Representative procedures for the synthesis of substrates **3a**−**h**; characterization data for **3a**−**h**, **4a** and **5b**−**h**; $^1$H NMR spectra of **2a**−**d**, **3a**,**c**−**e**,**g**, **4a**, and **5b**−**h**, and X-ray data for **5f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **Representative procedure** for domino Nazarov cyclization/arene trapping. Dienone **3f** (51 mg, 0.18 mmol) was dissolved in $CH_2Cl_2$ (18 mL) and cooled to −78 °C. A solution of $TiCl_4$ in $CH_2Cl_2$ (0.050 mL of a 3.51 M solution, 0.18 mmol) was added dropwise, and after 5 min TLC showed complete consumption of starting material. The reaction was quenched with water (5 mL) and allowed to warm to room temperature, the layers were then separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were dried (MgSO4) and concentrated to give 51 mg (99%) of **5f** as colorless crystals, deemed pure by TLC and NMR analysis: mp 71−72 °C; $R_f$ 0.48 (1:4 EtOAc/hexanes); IR (thin film) 2959, 2923, 2867, 1731 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 6.97 (s, 1H), 6.49 (s, 1H), 5.86 (s, 2H), 2.76 (ddd, $J$ = 17.2, 13.0, 6.0 Hz, 1H), 2.63 (ddd, $J$ = 17.1, 6.2, 1.6 Hz, 1H), 2.02 (dddd, $J$ = 13.9, 5.2, 3.3, 1.8 Hz, 1H), 1.87 (dddd, $J$ = 13.5, 13.5, 6.1, 3.7 Hz, 1H), 1.82−1.75 (m, 2H), 1.71-1.66 (m, 1H), 1.54−1.45 (m, 2H), 1.34 (s, 3H), 1.12 (d, $J$ = 6.1 Hz, 3H), 0.65 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 221.6, 146.3, 146.3, 129.1, 128.4, 108.8, 108.4, 100.9, 56.6, 51.9, 48.8, 33.3, 27.2, 25.1, 21.9, 18.4, 17.7, 11.2.

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(13) For other examples of selective protonation from the convex face of the enolate intermediate, see refs 4, 5, and 9a.

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(18) We thank an anonymous reviewer for the suggestion of this intriguing possibility.