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Formal Intermolecular 4 + 4 Approach to Cyclooctanoids: 4 + 3 Capture of the Nazarov Oxyallyl Intermediate with Simple 1,3-Dienes

Yong Wang, Brenden D. Schill,[†] Atta M. Arif, and F. G. West*[,†]

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

frederick.west@ualberta.ca

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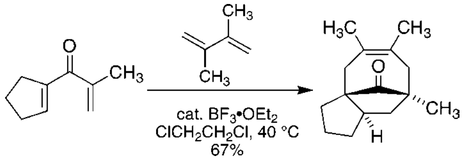
ABSTRACT



Simple 1,4-dien-3-ones and 1,3-dienes react in the presence of $BF_3{\cdot}OEt_2$ via a domino Nazarov electrocyclization/intermolecular [4 + 3]-cycloaddition sequence to furnish keto-bridged cyclooctenes in good yield. Most cases showed high diastereofacial selectivity and/or endo/exo selectivity, and surprising levels of regioselectivity were observed when isoprene was used as the diene partner.

The unique challenges associated with synthesis of the cyclooctanoid system have prompted the development of many clever synthetic approaches.[1] Among these, methods that construct the eight-membered ring through a 4 + 4 cycloaddition process are especially attractive, since they often involve the combination of two relatively simple and comparably sized fragments.[2] Recent examples include the Ni-mediated coupling of 1,3-dienes,[3] photochemical [4 + 4]-dimerization of 2-pyridones[4] or crossed [4 + 4]-cycloaddition of 2-pyrones,[5] and [4 + 3]-cycloaddition of cyclopentenyl cations with 1,3-dienes.[6] For the most part, these strategies have been limited to intramolecular cases, due to the need for rapid capture of short-lived reactive intermediates or excited states.[7,8] Our observation of efficient domino processes involving *intermolecular* trapping of the Nazarov oxyallyl intermediate by silyl hydride and allylsilanes[9] prompted an examination of the bimolecular version of the [4 + 3]-cycloaddition process, which has enjoyed considerable attention. Described here are the preliminary

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[†] Current address: Department of Chemistry, University of Alberta, W5-67 Chemistry Centre, Edmonton, Alberta T6G 2G2, Canada.

(1) Review: Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930.

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(7) For an important exception describing intermolecular crossed [4 + 4]-photocycloadditions of 2-pyridones, see: Sieburth, S. McN.; McGee, K. F., Jr.; Zhang, F.; Chen, Y. *J. Org. Chem.* **2000**, *65*, 1972−1977.

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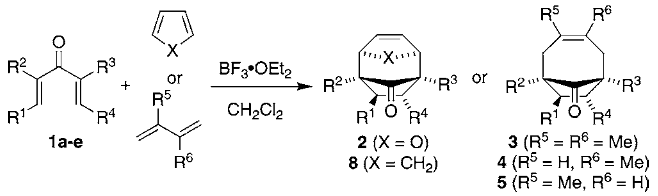
Table 1. Domino Nazarov/Intermolecular [4 + 3]-Cycloaddition Reactions of Dienones with Simple Dienes[a]



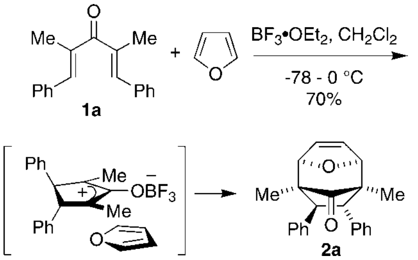
entry	dienone	R1	R2	R3	R4	1,3-diene[b]	X	R5	R6	temperature/time	products (% yield)[c]
1	**1a**	Ph	Me	Me	Ph	furan	O			−78 °C/0.5 h	**2a** (70)
2	**1a**	Ph	Me	Me	Ph	DMB		Me	Me	−78 °C/3 h[d]	**3a** (50)
3	**1a**	Ph	Me	Me	Ph	isoprene		Me	H	−25 °C/2.5 h[d]	**4a** (20)
4	**1b**	Ph	Me	Me	H	furan	O			−50 °C/2 h	**2b** (71)
5	**1b**	Ph	Me	Me	H	C_5H_6	CH_2			−20 °C/2 h	**8b** (62)
6	**1b**	Ph	Me	Me	H	DMB		Me	Me	−20 °C/2 h	**3b** (91)
7	**1b**	Ph	Me	Me	H	isoprene		Me	H	−20 °C/2 h	**4b** + **5b** (84; 5:1)[e]
8	**1c**	Et	Me	Me	H	furan	O			−50 °C/3 h	**2c** (72)[f]
9	**1c**	Et	Me	Me	H	C_5H_6	CH_2			−20 °C/2 h	**8c** (64)
10	**1c**	Et	Me	Me	H	DMB		Me	Me	−20 °C/2 h	**3c** (93)
11	**1c**	Et	Me	Me	H	isoprene		Me	H	−20 °C/2 h	**4c** + **5c** (84; 4.2:1)[e]
12	**1d**	$(CH_2)_4$		Me	H	DMB		Me	Me	−20 °C/1.5 h	**3d** (92)
13	**1e**	$(CH_2)_3$		Me	H	DMB		Me	Me	40 °C/1 h[g]	**3e** (67)
14	**1e**	$(CH_2)_3$		Me	H	isoprene		Me	H	40 °C/1 h[g]	**4e** + **5e** (55; 1.4:3)[e]

[a] Standard Procedure. To a solution of dienone **1** and 1,3-diene (2.0 equiv) in CH_2Cl_2 at −20 °C was added BF_3•OEt_2 (1.0 equiv), and the reaction was maintained at that temperature for 2 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was allowed to warm to room temperature. Following extraction of the aqueous phase with CH_2Cl_2, the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated, and the resulting crude product was purified by flash chromatography. [b] Abbreviations: DMB = 2,3-dimethylbutadiene; C_5H_6 = cyclopentadiene. [c] Isolated yields after chromatography. [d] In entries 2 and 3, 10 equiv of diene was used. [e] Regioisomers **4** and **5** were isolated as an inseparable mixture and the ratios determined by integration of ^1H NMR signals. [f] Cycloadduct **2c** was isolated as a 1.3:1 ratio of diastereomers epimeric at R^1. [g] Reactions carried out in $ClCH_2CH_2Cl$ using 0.1 equiv of BF_3•OEt_2.

results of that study, a remarkably general and efficient method for the convergent assembly of functionalized, keto-bridged cyclooctenes from simple 1,3-diene and 1,4-dien-3-one building blocks.

Initial efforts focused on dibenzylidenepentanone **1a** and furan due to the exceptional reactivity of **1a** toward electrocyclic closure even at low temperature[9] and the well precedented efficiency of furan in the capture of oxyallyls.[6,8] In the event, treatment of **1a** with 1.25 equiv of BF_3•OEt_2 at −78 °C in the presence of 2 equiv of furan, followed by warming to 0 °C, furnished a single cycloadduct **2a** in 70% yield (Scheme 1). The efficiency of the bimolecular trapping process is surprising, given the availability of the typical eliminative pathway of the Nazarov reaction; however, none of the simple cyclopentenone resulting from elimination was observed. The product was assigned as the endo isomer (cycloaddition via the compact transition state) based upon literature precedent and spectral data,[10] and none of the corresponding exo product (via the extended transition state) was isolated.[11]

Scheme 1



Given the initial success with **1a** and furan, a range of reaction partners was then surveyed (Table 1). Dienone **1a** also underwent domino electrocyclization/[4 + 3]-cycloaddition with 2,3-dimethylbutadiene and isoprene to give **3a** and **4a**, albeit in moderate yields (entries 2 and 3). The isolation of only isomer **4a** upon reaction with isoprene (structure unambiguously established by X-ray crystallography) deserves comment. The presumed oxyallyl intermediate possesses C_2 symmetry, so that approach of the diene

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(8) Efficient intermolecular [4 + 3]-cycloadditions of cyclic oxyallyls with reactive cyclic dienes are precedented: (a) Harmata, M.; Bohnert, G. J. *Org. Lett.* **2003**, *5*, 59−61. (b) Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2001**, *3*, 2533−2525. (c) Leitch, J.; Heise, I. *Eur. J. Org. Chem.* **2001**, 2707−2718. (d) Harmata, M.; Shao, L.; Kürti, L.; Abeywardane, A. *Tetrahedron Lett.* **1999**, *40*, 1075−1078. (e) Cha, J. K.; Oh, J. *Curr. Org. Chem.* **1998**, *2*, 217−232. (f) Föhlisch, B.; Joachimi, R. *Chem. Ber.* **1987**, *120*, 1951−1960.

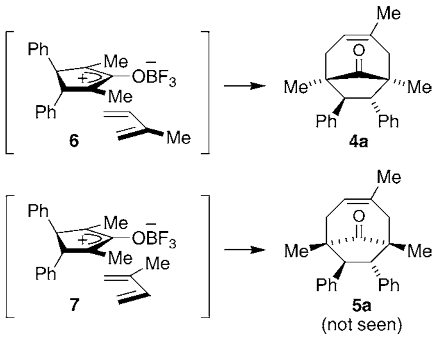
(9) (a) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221−10228. (b) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem.* **2000**, 1970−1973.

(10) There is ample precedent for preferred compact approach of furan to oxyallyl partners.[6] See Supporting Information for a discussion of the structural assignments.

(11) For a recent discussion of the theoretical basis of endo/exo preferences in [4 + 3]-cycloadditions, see: Cramer, C. J.; Harmata, M.; Rashatasakhon, P. *J. Org. Chem.* **2001**, *66*, 5641−5644.

from either face is energetically comparable. While **4a** and the unseen isomer **5a** are diastereomers, the origin of the selectivity also can be viewed from a regiochemical perspective (Scheme 2). Transition state **6** entails bonding between C-1 of isoprene and the oxyallyl terminus in which the adjacent phenyl is syn to the approaching diene, while transition state **7** involves the other possible orientation. The origins of the high selectivity seen in this case are obscure.[12]

Scheme 2



Unsymmetrically substituted dienones **1b**−**e** were examined with several 1,3-dienes, giving good to excellent yields of the [4 + 3]-adducts. Optimal general conditions employed 1.0 equiv of $BF_3\cdot OEt_2$ and 2 equiv of diene at −20 °C. As in the case with **1a** and furan, cyclic dienes furan and cyclopentadiene (entries 4, 5, 8, and 9) reacted via a compact transition state to provide the endo isomers.[10] In most cases, the diene approached selectively from the less hindered face of the cyclic oxyallyl (anti to R^1), although in one instance low facial selectivity was observed (entry 8).[13] This is consistent with the excellent facial selectivity previously reported in the intramolecular version of this process.[6b] The generally high yields obtained from dimethylbutadiene and isoprene (entries 6, 7, and 10−14) are gratifying in light of the paucity of examples of efficient intermolecular [4 + 3]-cycloadditions involving acyclic 1,3-dienes,[6f] especially with cyclic oxyallyls.[8] Moreover, complete diastereofacial selectivity was obtained in all of the cases employing acyclic dienes.

The cyclopentenyl substrate **1e** was unreactive under the standard conditions. We attribute this to a higher barrier to Nazarov electrocyclization in this case due to the strain associated with the resulting bicyclo[3.3.0]octenyl cation. A similar result was seen in a series of fused bicyclic pyran-4-ones, in which those fused to a six-membered or larger ring underwent photochemical ring contraction via a Nazarov-like process, while the cyclopenteno-fused example was inert to extended irradiation.[14] In the case of **1e**, higher temperature was found to effect the Nazarov electrocyclization, but Lewis acid-catalyzed polymerization of the diene was a serious complication. Eventually, use of catalytic amounts (0.1 equiv) of $BF_3\cdot OEt_2$ at 40 °C in 1,2-dichloroethane was found to be optimal. To our knowledge, this is one of only two examples of Nazarov processes successfully employing catalytic quantities of Lewis acid.[9a]

Use of **1b**,**c**,**e** together with isoprene explicitly introduced the issue of regiochemistry in the cycloaddition process (entries 7, 11, and 14). Significant regiocontrol was not expected a priori, given the similar substitution pattern at the oxyallyl termini and the low regioselectivity usually observed for [4 + 3]-cycloadditions employing isoprene and related monosubstituted dienes.[15] However, in the event, regioisomeric mixtures of 4.2:1→5:1 were obtained in all three cases. Provisional regiochemical assignment of the major isomers was possible in two cases (Figure 1). The major isomer from the reaction of **1b** with isoprene was assigned as **4b** on the basis of the observation of a NOE interaction between the benzylic methine and one of the allylic protons and a strong vicinal coupling of the same allylic proton to the adjacent alkene proton. In the case of **1e** + isoprene, a NOE interaction between the protons of the angular methyl and the allylic methylene adjacent to the alkene proton supported the assignment of the major isomer as **5e**. Although a similar analysis was not possible for the cycloadducts derived from **1c** and isoprene, the major isomer was tentatively assigned as **4c** due to its analogy to **4b**. In all cases, the minor isomer was presumed to be a regioisomer rather than a stereoisomer, since the analogous reactions with dimethylbutadiene gave a single product. Formation of **4e** in preference to **5e** is especially significant, as this adduct possesses most of the carbon skeleton of the cyclooctanoid natural products dactylol and poitediol.

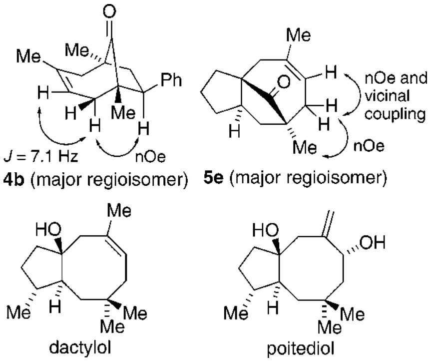


Figure 1. Regiochemical assignments of **4b** and **5e**.

This methodology provides access to keto-bridged cyclooctenes in a single step from simple dienone and diene

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(12) Intervention of a competing stepwise cycloaddition mechanism in unsymmetrical cases cannot be ruled out as a possible contributor to the regioselectivity. We thank one of the reviewers for this suggestion.

(13) See Supporting Information for a discussion of the stereochemical assignments of **2c**.

(14) Fleming, M.; Fisher, P. V.; Gunawardena, G. U.; Jin, Y.; Zhang, C.; Zhang, W.; Arif, A. M.; West, F. G. *Synthesis* **2001**, 1268−1274.

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reactants. The conditions are relatively mild, and the yields are generally good to excellent. Efficient intermolecular trapping with acyclic dienes such as dimethylbutadiene and isoprene is especially notable. In general, high diastereofacial selectivity is seen with approach of the diene away from the larger substituent on the cyclopentenyl cation, and complete selectivity for the compact transition state was observed with cyclic dienes. Oxyallyl cations with comparable α substituents but differential β substitution display a surprising degree of regioselectivity with isoprene. The origins of the regioselectivity, the scope of this process with more elaborate diene and dienone partners, and its potential application to natural product targets are under current study, and the results will be described in due course.

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Supporting Information Available: Experimental procedures and physical data for dienones **1b**−**e** and all [4 + 3]-cycloadducts, ^{1}H NMR spectra for **1c**−**e**, **2a**, **4a**, **3b**, **8b**, and **5c**, and X-ray data for **4a** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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