

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/8952641>

Efficient Nazarov Cyclizations of 2-Alkoxy-1,4-pentadien-3-ones

ARTICLE *in* ORGANIC LETTERS · JANUARY 2004

Impact Factor: 6.36 · DOI: 10.1021/ol036019z · Source: PubMed

CITATIONS

108

READS

54

3 AUTHORS, INCLUDING:



Dirk Trauner

Ludwig-Maximilians-University of Munich

233 PUBLICATIONS 5,855 CITATIONS

SEE PROFILE

Efficient Nazarov Cyclizations of
2-Alkoxy-1,4-pentadien-3-ones

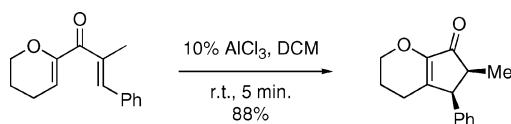
Guangxin Liang, Stefan N. Gradl, and Dirk Trauner*

Center for New Directions in Organic Synthesis, Department of Chemistry,
University of California–Berkeley, Berkeley, California 94720

trauner@cchem.berkeley.edu

Received October 15, 2003

ABSTRACT



Expeditious and high-yielding Nazarov cyclizations of 2-alkoxy-1,4-pentadien-3-ones are described. An example of a catalytic asymmetric Nazarov cyclization is presented.

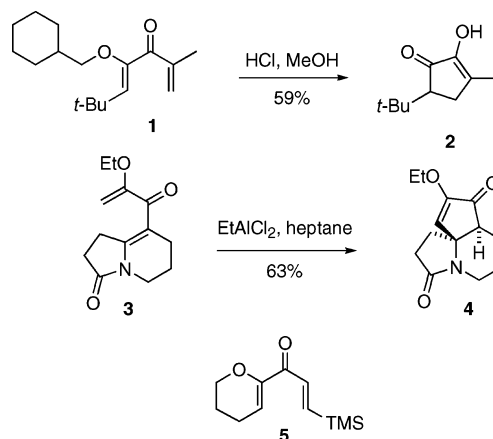
The Nazarov cyclization is one of the most versatile methods for the synthesis of five-membered carbocycles. It has been used in the construction of numerous complex target molecules, including polyquinane natural products and prostanoids.¹ Modern variants are based on the interception of cationic intermediates² or the use of highly reactive allene substrates,³ and even include examples of the reverse reaction.⁴

Since the mechanism of the Nazarov cyclization involves a conrotatory 4π electrocyclic cyclization of a pentadienyl cation, it has been placed among pericyclic reactions. In fact, the Nazarov cyclization is a rare example of an electrocyclic reaction subject to Lewis acid catalysis. Somewhat surprisingly, catalytic asymmetric versions of the reaction have not yet surfaced in the literature.

In the context of our studies on the total synthesis of guanacastepene antibiotics,⁵ we became interested in Nazarov

cyclizations of 2-alkoxy-1,4-pentadien-3-ones. Few reactions involving these substrates have been studied before (Scheme 1). In 1994, Kocienski described the acid-catalyzed cycliza-

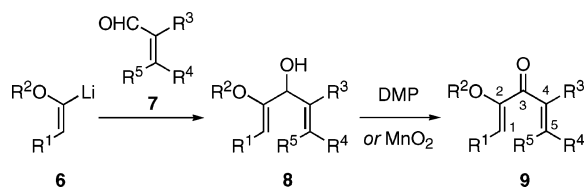
Scheme 1



tion of **1** to afford cyclopentenone **2**.⁶ A related reaction (**3** \rightarrow **4**) was used by Cha in a synthetic approach toward the cephalotaxine class of alkaloids.⁷ Previously, Denmark reported the attempted cyclization of silyl alkoxydienone **5**.⁸ Systematic studies involving substrates of this type, however, have apparently not been disclosed.

- (1) (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N. Y.)* **1994**, 45, 1–158. (b) Krohn, K. *Org. Synth. Highlights* **1991**, 137–44. (c) Santellirouvier, C.; Santelli, M. *Synthesis (Stuttgart)* **1983**, 429–442. (2) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 1970. (3) Tius, M. A. *Acc. Chem. Res.* **2003**, 36, 284–290. (4) Harmata, M.; Lee, D. R. *J. Am. Chem. Soc.* **2002**, 124, 14328–14329. (5) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, ASAP. (6) Casson, S.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1187–91. (7) Kim, S.-H.; Cha, J. K. *Synthesis* **2000**, 2113–2116. (8) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, 71, 168–94. For an alternative synthesis of **9r**, see: Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, 55, 3114–3118.

Scheme 2



We now report the further development of 2-alkoxy-1,4-pentadiene-3-ones as a class of highly reactive substrates for Nazarov cyclizations, which appear to be well suited for studies in asymmetric synthesis.⁹ Under optimized conditions, these substrates react at room temperature, some within minutes, to afford 2-alkoxy-2-cyclopentenones in high yields and with excellent regioselectivities.

The 2-alkoxy substituents render the substrates not only highly reactive but also allow for regioselective bidentate binding of a Lewis acid, preorganizing one side of the molecule in the reactive *s*-trans conformation. The second enone moiety can be biased toward the *s*-trans conformation by substitution in the 4-position, further increasing the reactivity.

The alkoxydienone substrates **9a–t** can be easily assembled by addition of a lithiated enol ether **6** such as 2-lithio-dihydropyran to an unsaturated aldehyde **7** followed

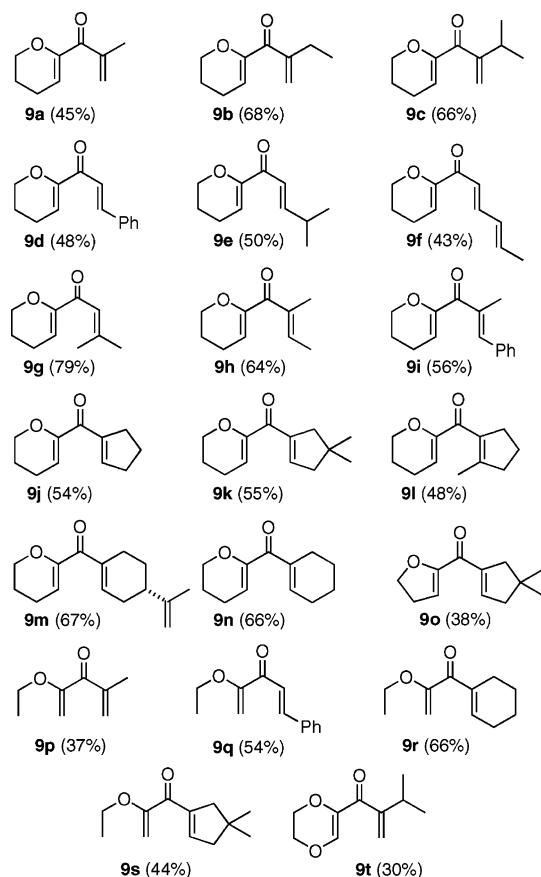
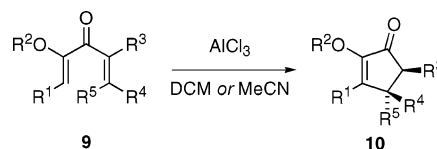


Figure 1.

by oxidation of the resulting divinylcarbinol **8** (Scheme 2, Figure 1).⁸ Subsequent oxidation using either Dess–Martin periodinane (DMP) or manganese dioxide gave alkoxydienones **9** (see Supporting Information). Combined yields for both the addition and oxidation step are shown in Figure 1.

After an extensive survey of various Lewis acids and solvents, we determined that aluminum chloride (10 mol %) in dichloromethane (DCM) or acetonitrile (MeCN) was most effective in promoting the cyclization (Scheme 3, Figure 2).

Scheme 3



Alkoxydienones **9** reacted smoothly to afford alkoxy cyclopentenones **10** in good to excellent yields. Only dihydrofuran derivative **9o**, whose product would contain a severely strained tetrasubstituted double bond, failed to give a clean product.

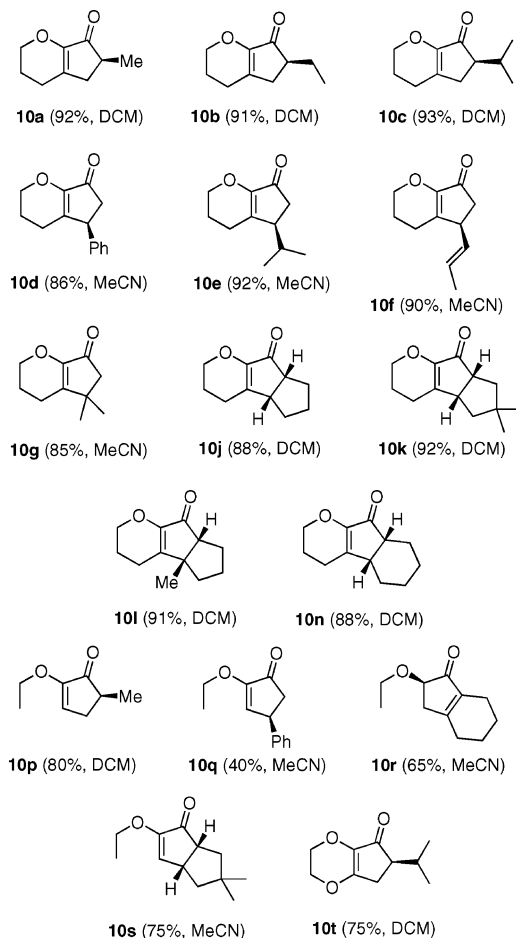


Figure 2.

All substrates underwent the Nazarov cyclization with complete regioselectivity, usually placing the double bond on the side of the alkoxy substituents. In the case of **9r**, however, the cyclization afforded **10r** wherein the double bond resides in the more substituted position.

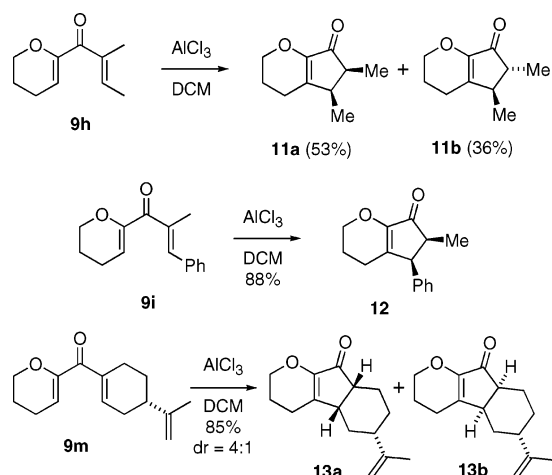
Note that trienone **9f** and terminally disubstituted substrates **9g,l** reacted cleanly to afford vinyl cyclopentenone **10f** and products featuring quaternary stereocenters **10g,l**, respectively. Dihydrodioxine **9t** gave compound **10t** in good yield.

While many substrates underwent the reaction with reasonable rates in dichloromethane, we found that acetonitrile was a better choice for less reactive, sterically more hindered substrates. This polar, coordinating solvent, which is rarely used in combination with aluminum chloride, may facilitate proton-transfer steps or catalyst turnover.

Remarkably, 2-ethoxypentadienones **9p–s** underwent the reaction at a considerably slower rate than their dihydropyranyl counterparts under otherwise identical conditions.¹⁰ The nature of the solvent was found to be less important in these cases.

The diastereoselectivity of the cyclization was further investigated using substrates **9h**, **9i**, and **9m** (Scheme 4). The

Scheme 4



4,5-disubstituted dienone **9h** underwent fast cyclization with the anticipated low diastereoselectivity to afford a 1.5:1 mixture of the cis and trans products **11a,b**. By contrast, substrate **9i** gave exclusively cis diastereomer **12**. The X-ray crystal structure of **12** is shown in Figure 3.

Induced diastereoselection was investigated using compound **9m**, which could be obtained in two straightforward steps from perillaldehyde and dihydropyran (see Supporting Information). In the presence of 10 mol % aluminum

(9) Concomitant to our work, the Tius group has studied Nazarov cyclizations of 2-alkoxy-1,4-penten-3-ones and catalytic asymmetric variants thereof. Tius, M. A.; Bee, C.; Leclerc, E. *Org. Lett.* **2003**, *5*, 4927–4930. For a related system, see: He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278–14279.

(10) Compound **10p** has been previously described: Katritzky, A. R.; Zhang, G. F.; Jiang, J. L. *J. Org. Chem.* **1995**, *60*, 7605–7611.

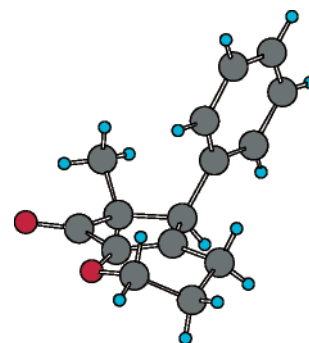
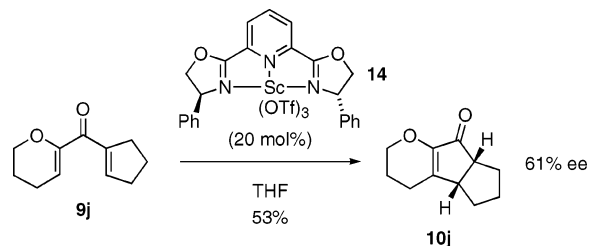


Figure 3. X-ray structure of compound **12**.

chloride, **9m** cyclized to afford a 1:4 mixture of pyrano-indenones **13a,b** in good overall yield.

Due to their ability to engage in bidendate binding and their high reactivity, substrates **9** should lend themselves well toward catalytic asymmetric synthesis. So far, attempts to develop a catalytic asymmetric version of the Nazarov cyclization have only been moderately successful. For instance, alkoxydienone **9j** underwent Nazarov cyclization in the presence of 20 mol % chiral scandium triflate pybox complex **14** to afford enantiomerically enriched tricycle **10j** in 53% yield and 61% ee (Scheme 5).¹¹ The enantiomeric

Scheme 5



excess was found to be very dependent on the solvent, with THF providing the highest value. No attempts were made to elucidate the absolute configuration of the major enantiomer. Note that **10j** cannot easily undergo racemization, which was found to be a persistent problem with other substrates.

Although the enantiomeric excess is modest, this reaction represents, to the best of our knowledge, the first catalytic asymmetric Nazarov cyclization reported in the literature.⁹

In summary, the development of an efficient Nazarov cyclization involving a highly reactive class of substrates has been described. Its products include highly functionalized heterobicyclic and -tricyclic compounds that could serve as valuable synthetic building blocks.

(11) For the use of scandium pybox complexes in asymmetric synthesis, see: (a) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162–10163. (b) Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375–3378.

Proof of principle has been given that the Nazarov cyclization can be rendered asymmetric. The development of highly enantioselective versions of the Nazarov cyclization is well underway in our laboratories and will be disclosed in due course.

Acknowledgment. We thank Aaron Lee for assistance in the preparation of compounds **9** and thank Dr. Frederick J. Hollander as well as Dr. Allen G. Oliver for the crystal structure determination of compound **12**.

Financial support by Merck & Co. is also gratefully acknowledged.

Supporting Information Available: Spectroscopic and analytical data for compounds **8–13**, as well as X-ray structural data of compound **12** (the crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 219932)). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL036019Z