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Catalytic Formal Homo-Nazarov Cyclization

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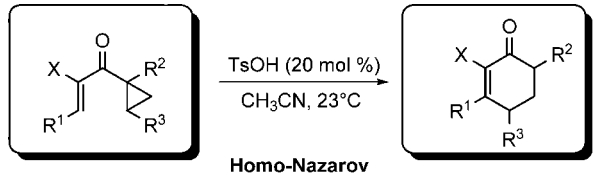
ABSTRACT

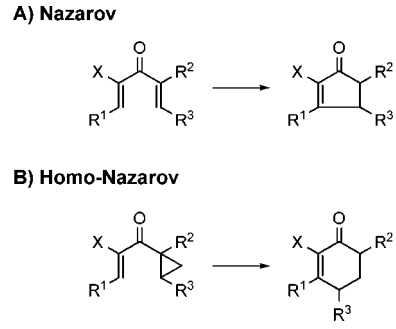


The first catalytic method for the cyclization of vinyl-cyclopropyl ketones (formal homo-Nazarov reaction) is reported. Starting from activated cyclopropanes, heterocyclic, and carbocyclic compounds were obtained under mild conditions using Brønsted acid catalysts. Preliminary investigation of the reaction mechanism indicated a stepwise process.

Carbocyclic and heterocyclic scaffolds occupy a privileged position in both natural products and pharmaceuticals.[1] Consequently, the development of cyclization and cycloaddition reactions for the efficient formation of cyclic structures is a very important goal in organic chemistry. In this respect, the development of new, highly stereoselective catalytic methods is crucial to allow a more efficient and environmentally friendly access to polycyclic molecules.[2]

One classical approach toward the construction of cyclopentenone rings is the Nazarov reaction, which is the electrocyclic ring closure of a pentadienyl cation, followed by proton transfer (**A**, Scheme 1).[3] The potential of the

Scheme 1. Nazarov and Homo-Nazarov Cyclizations



Nazarov cyclization was recognized at an early stage in organic synthesis. Solutions to control the termination of the reaction were devised several decades ago,[3b] but the necessity of using a stoichiometric amount of strong Lewis or Brønsted acids has limited the use of this reaction. However, in the last five years, the first examples of catalytic Nazarov

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(2) (a) Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736. (b) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323.
(3) (a) Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk. SSSR. Ser. Khim.* **1941**, 211. (b) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N. Y.)* **1994**, *45*, 1–158. (c) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221. (d) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747. (e) Aggarwal, V. K.; Beffield, A. J. *Org. Lett.* **2003**, *5*, 5075. (f) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927. (g) He, W.; Sun, X. F.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278. (h) Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2004**, *126*, 6864. (i) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661. (j) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003. (k) Liang, G. X.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931. (l) Liang, G. X.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544. (m) Walz, I.; Bertogg, A.; Togni, A. *Eur. J. Org. Chem.* **2007**, 2650. (n) Walz, I.; Togni, A. *Chem. Commun.* **2008**, 4315. (o) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097. (p) Amere, M.; Blanchet, J.; Lasne, M. C.; Rouden, J. *Tetrahedron Lett.* **2008**, *49*, 2541. For reviews, see: (q) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (r) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (s) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479.

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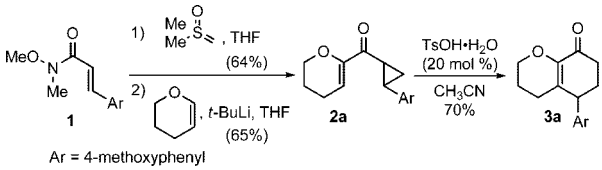
reactions using milder Lewis[3c−n] or Brønsted[3o,p] acids were reported, together with the first examples of asymmetric induction.[3e,k,l,n,o]

When considering these recent successes in the Nazarov reaction, we wondered if similar concepts could be successful in other cyclization reactions to access larger ring systems. A viable approach to access homologous rings via electrocyclic reactions is the substitution of a double bond by a cyclopropyl group, as exemplified by the divinylcyclopropyl rearrangement.[4] Intra- and intermolecular ring-opening of cyclopropyl ketones and diesters have been examined extensively.[5] The reaction of vinyl-cyclopropyl ketones has been less studied (**B**, Scheme 1).[6] Tsuge has reported the cyclization of vinyl-cyclopropyl ketones using an excess of polyphosphoric acid at 80 °C, but this reaction was not general and several other products were obtained beside the desired cyclohexenones.[6a] More work has been done on the related aryl-cyclopropyl ketones, first by Murphy for the synthesis of tetralones using an excess of $SnCl_4$ as reagent.[6b−d] During completion of our work, Yadav also demonstrated that diverse polycyclic heterocycles could be accessed using 3 equivalents $SnCl_4$ at 80 °C, but no vinyl-cyclopropyl ketones were reported.[6e] Up to now, the harsh conditions needed have limited the use of the homo-Nazarov reaction in organic synthesis. Herein, we report the first example of a catalytic formal homo-Nazarov process for non aromatic substrates which lead to the formation of valuable polycyclic cyclohexenones at room temperature as well as preliminary experiments to probe the reaction mechanism.

Inspired by recent progress in the catalytic Nazarov reaction,[3j] we decided to examine dihydropyran-derived substrate **2a** (Scheme 2). Substrate **2a** was synthesized from

Scheme 2. Synthesis and Cyclization of Model Substrate **2a**



Weinreb amide **1** via Corey−Chaykovsky cyclopropanation[7] followed by addition of a lithiated nucleophile to afford **2a** in good yield (Scheme 2).

With our model substrate in hand, we began our studies by examining the most frequently used procedure for homo-Nazarov cyclization: stoichiometric $SnCl_4$.[6b−e] Using these conditions, complete polymerization of the sensitive substrate was observed.[8]

As most Lewis acid led to extensive polymerization, we then turned toward Brønsted acid catalysts. The pK_a value of the catalyst had a strong influence on the outcome of the reaction: sulfuric and toluenesulfonic acids were optimal. Stronger acids led to decomposition of the starting material and no full conversion could be achieved with weaker acids. Examination of solvent effects showed that the reaction was faster in noncoordinating solvents, like dichloromethane, but polymerization was also difficult to suppress. Acetonitrile finally offered the best compromise, with sufficient reactivity but less pronounced polymerization. The cyclization of **2a** in acetonitrile with 20 mol % toluenesulfonic acid at room temperature led to the formation of the desired cyclohexenone **3a** in 70% isolated yield (Scheme 2).

The scope of the reaction was examined next (Table 1). Variation of the aromatic substituent on the cyclopropane confirmed the importance of its electron-donating ability; whereas no reaction was observed with a simple phenyl group (entry 2), a quantitative yield was observed with a 3,4- or 2,4- dimethoxyphenyl group (entries 3 and 4). This result is noteworthy, as electron-rich aromatic substituents are well represented in bioactive natural products[9] and are easily oxidized to the corresponding carboxylic acids.[10] A furan group was also tolerated at this position, although the yield was moderate due to partial polymerization (entry 5).

Finally, the influence of a methyl group α to the ketone was examined. Interestingly, a strong accelerating effect was observed and cyclohexenone **3f** was obtained in quantitative yield after only 15 min (entry 6). A plausible explanation would be a faster ring-opening of the cyclopropane ring due to sterical strain release and the higher stability of the formed enol intermediate.[11] Importantly, this accelerating effect on the formal homo-Nazarov cyclization has never been reported before.

We then examined variation of the electron-rich side of the ketone. A dihydrofuran group proved to be more prone to polymerization and the desired product was isolated only in low yield with a 4-methoxyphenyl group on the cyclopropane (entry 7). The stronger stabilizing effect of the 2,4-dimethoxyphenyl substituent allowed the isolation of the desired 5−6 ring system in quantitative yield (entry 8). Replacing the dihydropyran group with an electron-rich *N*-methylindole heterocycle lead to an efficient cyclization in quantitative yield (entry 9), but only polymerization was observed with a benzofuran ring (entry 10). Interestingly, similar results were obtained in the related Nazarov cyclization.[3i]

(4) Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 5, pp 971−998.

(5) For a few selected examples, see: (a) Stork, G.; Marx, M. *J. Am. Chem. Soc.* **1969**, *91*, 2371. (b) Grieco, P. A.; Finkelhor, R. S. *Tetrahedron Lett.* **1974**, 527. (c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

(6) (a) Tsuge, O.; Kanemasa, S.; Otsuka, T.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2897. (b) Murphy, W. S.; Wattanasin, S. *Tetrahedron Lett.* **1980**, *21*, 1887. (c) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc. Perkin Trans. 1* **1981**, 2920. (d) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1029. (e) Yadav, V. K.; Kumar, N. V. *Chem. Commun.* **2008**, 3774.

(7) Rodriques, K. E. *Tetrahedron Lett.* **1991**, *32*, 1275.

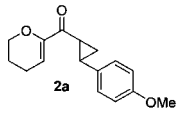
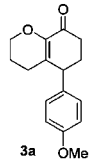
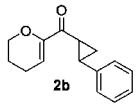
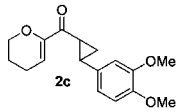
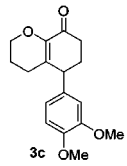
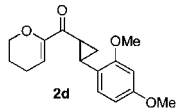
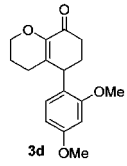
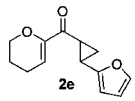
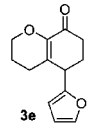
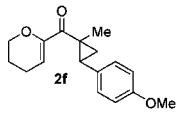
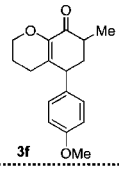
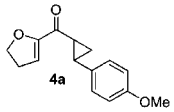
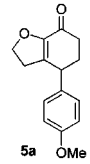
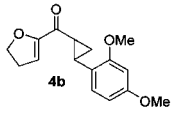
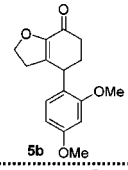
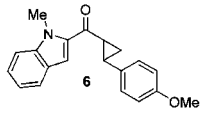
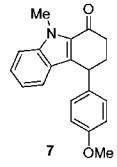
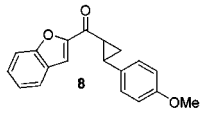
(8) Oligomerization, then polymerization was apparent in ^{1}H NMR via formation of broad signals in several regions of the spectra, see Supporting Information (Figure S5).

(9) For example in Podophyllotoxin natural products and their derivatives: Bohlin, L.; Rosen, B. *Drug Discov. Today* **1996**, *1*, 343.

(10) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Voight, E. A.; Rein, C.; Burke, S. D. *J. Org. Chem.* **2002**, *67*, 8489.

(11) As an alternative explanation, a higher fraction of the more stable enol tautomer could be envisaged to favor cyclization.

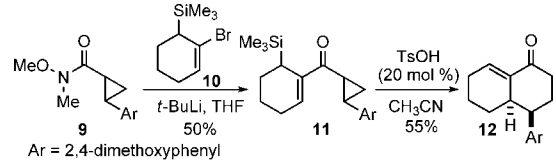
Table 1. Scope of the Formal Homo-Nazarov Cyclization

entry	substrate	product	isolated yield[a] reaction time
1	 2a	 3a	70% 18 h
2	 2b	-	No Reaction
3	 2c	 3c	quant 5 h
4	 2d	 3d	quant 15 min
5	 2e	 3e	50% 3h
6	 2f	 3f	quant (dr = 5:1) 2 h
7	 4a	 5a	15% 36 h
8	 4b	 5b	quant 1 h
9	 6	 7	quant 5 h
10	 8	-	Polymerization

[a] Reaction conditions: 0.4 mmol substrate in 8 mL CH_3CN with 20 mol % TsOH at 23 °C.

To further increase the versatility of the formal homo-Nazarov process, it would be important to diminish the strong electronic constraints which limit the number of structures that can be synthesized. The use of substrates lacking an electron-donating heteroatom on the double-bond is highly desirable. Based on the seminal work of Denmark on silyl group-directed Nazarov reactions,[3b,12] we decided to use an allyl silane group to enhance the nucleophilicity of the double bond and favorize cyclization (Scheme 3).

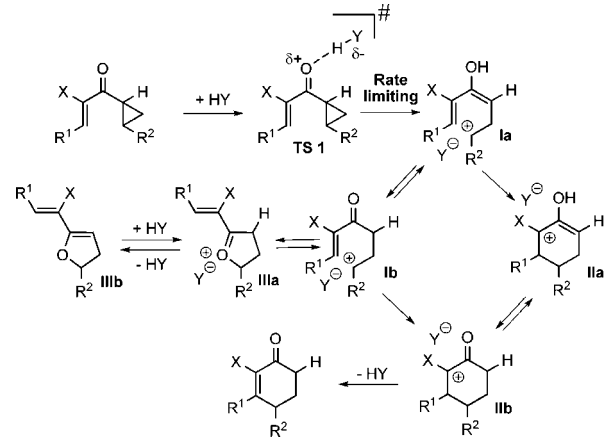
Scheme 3. Cyclization for Carbocycles Synthesis



Gratifyingly, submitting vinyl-cyclopropyl ketone **11** to the optimized reaction conditions led to the formation of bicyclic ketone **12** in 30 min and 55% yield. The regioselectivity of the double bond formation was completely controlled by the elimination of the silyl group. Interestingly, only one diastereoisomer of **12** was isolated. The structure of **12** was tentatively assigned by NMR experiments (COSY, HSQC, NOESY).[13] This preliminary result held promises for the application of the method in the synthesis of carbocyclic compounds.

The strong influence of electron-donating groups and acid strength on the reaction rate led us to propose a tentative stepwise mechanism for the reaction with cyclopropane opening as rate-limiting (Scheme 4).

Scheme 4. Postulated Mechanism

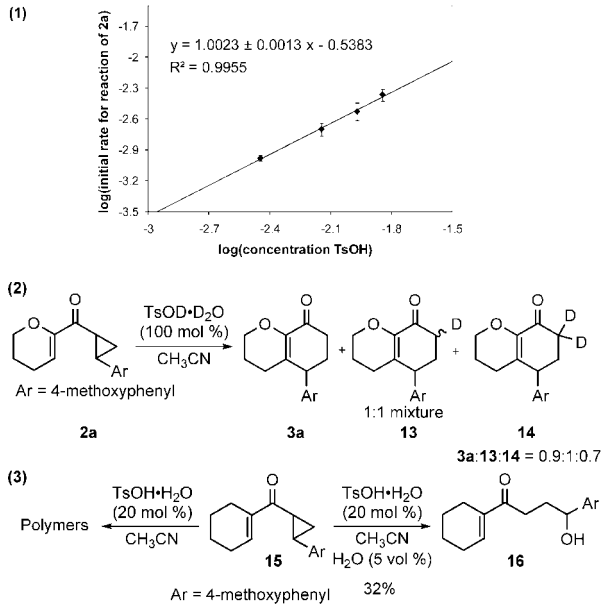


In order to further support this mechanism, the following experiments were performed (Scheme 5): (1) The reaction

(12) Denmark, S. E.; Klix, R. C. *Tetrahedron* **1988**, *44*, 4043.

(13) The obtained 2D NMR data strongly support the proposed structure assignment for **12**. Further confirmation of the structure will be attempted by X-rays analysis of the corresponding thiosemicarbazone, a procedure developed by Denmark.[12]

Scheme 5. Mechanism Investigation: (1) Van't Hoff Plot and Reaction Order, (2) Deuterium, and (3) Trapping Experiments



kinetic was followed via ^{1}H NMR spectroscopy, and the reaction was found to be first order in tosic acid for substrate **2a**. (2) The use of stoichiometric deuterated tosic acid resulted in a mixture of nondeuterated, mono and bis-deuterated products at the α position to the ketone. A control experiment showed that no deuterium exchange was observed for the isolated cyclization product in the presence of deuterated tosic acid. A possible explanation for this surprising results would be the intramolecular attack of the oxygen atom of intermediates **Ia** or **Ib** to form an oxonium intermediate **IIIa**. From **IIIa**, proton-deuterium exchange should be easy via dihydrofuran **IIIb**. Dihydrofuran products have indeed been isolated in the related stoichiometric reaction of aryl vinyl ketones.[6c] Alternatively, proton exchange could be more rapid on cyclized intermediate **IIb** and **IIa**. Proton lost form **IIb**, or proton lost followed by tautomerization from **IIa** would then lead to the cyclohexenone product. Additionally, a weak kinetic isotope effect (1.15) was observed using 40 mol % deuterated tosic acid, but this result is difficult to interpret due to fast proton exchange between substrate and catalyst. (3) Attempts were made to trap the proposed intermediates (enol and carbocation) of the catalytic cycle.[14] With substrate **2a**, all nucleophilic (water, allyl silane, butyl vinyl ether) and electrophilic (benzaldehyde, ethyl glyoxalate, acetic anhydride, ethyl acrylate) trapping agents tested so far were not successful. With cyclohexene derivative **15**, however, alcohol **16** was obtained in 31% yield when the reaction was conducted in the presence of water.

All the data collected so far are in agreement with a rate-determining cyclopropane opening, followed by a fast cyclization. In the case were the cyclization is too slow (as with **15**), polymerization can occur instead of the desired process. We speculate that key for catalysis is the fast tautomerization of the enol intermediates, which contrasts with the strong binding of stoichiometric reagents like $SnCl_4$, which prevent catalytic turnover.

In summary, we have reported the first catalytic formal homo-Nazarov process. We have demonstrated that principles successful in the corresponding Nazarov reaction could also be applied to vinyl-cyclopropyl ketones, which allow the first high-yielding cyclization reaction for this class of substrates under mild conditions. First investigations of the reaction mechanism seem to indicate a stepwise mechanism with a rate-limiting cyclopropane ring opening: consequently, the reaction is mechanistically different from the classical Nazarov cyclization. Our future work will focus on the development of asymmetric variations as well as on applications in the synthesis of natural products and their analogs.

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Supporting Information Available: Experimental procedures, spectroscopic information for new compounds and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) To gain stronger evidence for the cationic mechanism, we will study the influence of the cyclopropane stereochemistry on the reaction outcome, for example using **11** with a *cis*-substituted cyclopropane.