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Indium-Catalyzed Homo-Nazarov Cyclizations of Alkenyl Cyclopropyl Ketones

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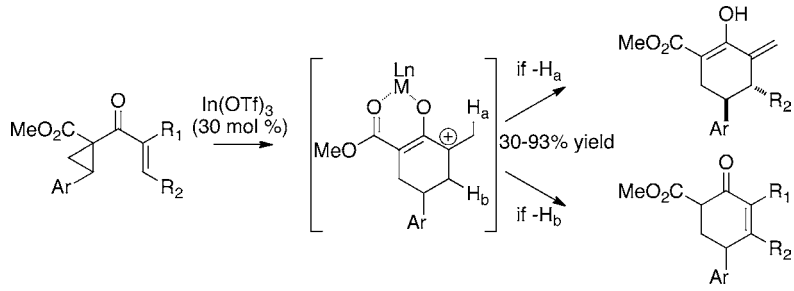
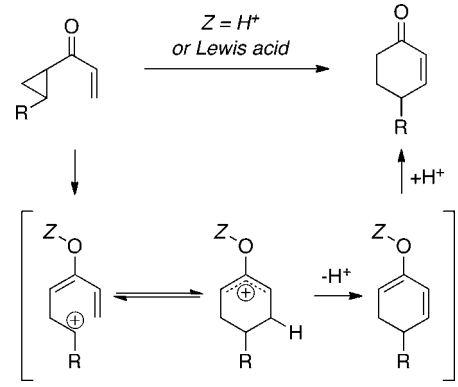
ABSTRACT



Herein, an efficient Lewis acid catalyzed protocol for the homo-Nazarov cyclizations of alkenyl cyclopropyl ketones is reported. Alkenes bearing β-hydrogens (or silyl groups) provide 1.5:1 mixtures of methylene cyclohexenols and cyclohexenones. When no β-hydrogens (or silyl groups) are present, only cyclohexenones are observed. Products are rapidly formed in good to high yields (up to 93%) under mild conditions and could be readily derivatized.

Cyclopropanes play a unique role in organic synthesis due to their inherent ring strain. Consequently, they can participate in a variety of reactions that are not accessible to linear or larger cyclic molecules.[1] Moreover, the appropriate choice of substituents about the cyclopropane ring has a direct effect on the observed reactivity. For instance, one of the C−C bonds of a cyclopropyl ring can be polarized when an electron-accepting group is located on one carbon and an electron-donating substituent is located on another. These vicinal donor−acceptor (D−A) cyclopropanes have generated a tremendous amount of interest from organic chemists for their predictable reactivity and can often be considered as "masked" 1,3-dipoles and homologues of Michael acceptors.[2] Furthermore, their application in [3 + 2] and [3 + 3] cycloadditions has been fully recognized.[3] Along these lines, a viable but underexplored approach to six-membered carbo- and heterocycles has been exemplified by the homo-Nazarov cyclization (Scheme 1). In this reaction, cyclopropyl vinyl ketones are converted into α,β-unsaturated cyclohexenones. Although mechanistically distinct, this reaction is homolo-

Scheme 1. Homo-Nazarov Cyclization



(1) (a) Reissig, H.-U. In *Small Ring Compounds in Organic Synthesis III*; Meijere, A. de, Ed.; Topics in Current Chemistry; Springer-Verlag: Berlin, Heidelberg, Germany, 1988; *Vol. 144*, p 1. (b) Hudlicky, T. Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991; *Vol. 5*, p 899.

(2) (a) Rubin, M.; Rubia, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.

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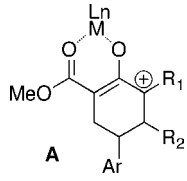
gous to the well-established Nazarov cyclization,[4] which involves the cyclization of divinyl ketones to make cyclopentenones via a similar cyclic oxyallyl cation.

Several groups have reported examples of this reaction where either aryl or heteroaryl groups replace the vinyl group, known as the (hetero)aromatic homo-Nazarov cyclization.[5] Unfortunately, in each of these earlier reports, stoichiometric amounts of acids (Bronsted and Lewis) or high temperatures are required for cyclization.

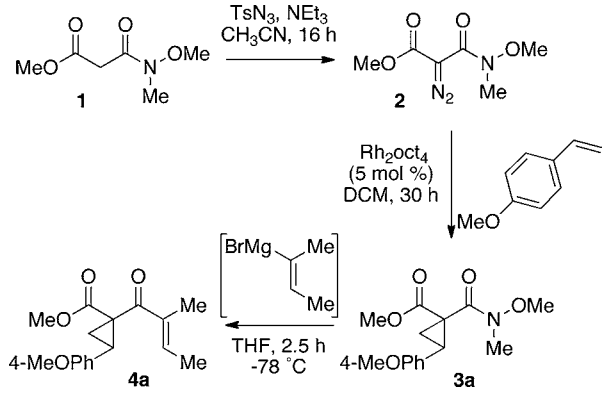
In contrast, the reactions of alkenyl cyclopropyl ketones have been less studied. In a seminal report, Tsuge reported the treatment of various alkenyl cyclopropyl ketones with polyphosphoric acid in hopes of obtaining cyclohexenone products.[6] However, the reaction had three major drawbacks: (1) lack of generality—only 5 out of 16 substrates provided the desired cyclohexenones; (2) poor product yields (15−63%); and (3) harsh reaction conditions—excess PPA in refluxing benzene for >24 h. All of these limitations have resulted in sparse application of the alkenyl homo-Nazarov protocol. More recently, Waser reported a Bronsted acid catalyzed homo-Nazarov cyclization.[7] This study has provided invaluable insight into the potential of the alkenyl reaction with one limitation: simple alkenes did not work (an α-heteroatom was required to activate the alkenyl group). In this communication, we describe an efficient Lewis acid catalyzed homo-Nazarov cyclization of donor−acceptor cyclopropyl ketones bearing substituted alkenes.



In an attempt to facilitate cyclization and, ultimately, expand the scope and applicability of the reaction, we envisioned using donor−acceptor cyclopropyl vinyl ketones bearing a secondary electron acceptor (such as an ester) in the α′-position that would coordinate with Lewis acids, as in **A**. The secondary acceptor group would serve to further "polarize" the resulting cyclic oxyallyl cation by localizing the charge density. This polarization allows for a predictable reaction outcome for the oxyallyl cation. Frontier has similarly demonstrated the benefit of using esters as acceptor groups to polarize the classic Nazarov cyclization.[8] Finally, for these donor−acceptor−acceptor (D−A−A) cyclopropanes, the C−C bond is weaker as compared to the parent donor−acceptor cyclopropanes, allowing for milder conditions for bond cleavage, more variety of functionality about the cyclopropanes, and greater stabilization of the resulting dipole.[9]

To test the rationale of using D−A−A cyclopropanes to promote catalysis, we set out to probe the reactivity of alkenyl substrates. Concerned about ensuring the stability of the resulting oxyallyl cation as compared to that of the benzylic cation, we chose to synthesize a substrate bearing an α-alkyl substituent to offer further stabilization (Scheme 2).[10] Thus, alkenyl substrate **4a** was synthesized from the malonate derived Weinreb amide **1** via sequential diazo transfer, cyclopropanation[11] (with 4-methoxystyrene), and ketone formation.

Scheme 2. Synthesis of a Model D−A−A Homo-Nazarov Substrate **4a**



In hopes of finding the best catalyst for the reaction, we screened substoichiometric amounts (30 mol %) of various metal catalysts, primarily focusing on readily available triflate salts. The initial reaction with **4a** was conducted in dichloromethane at room temperature in the presence of 30 mol % catalyst (Scheme 3). While we anticipated that cyclization would afford cyclohexenone **6a** based on a standard Nazarov-type eliminative pathway, we were intrigued to find that while we did form **6a**, another putative homo-Nazarov product **5a**, a cross-conjugated enol system with an exocyclic alkene, was observed. Beyond these two products, dihydrofuran **7a**, which presumably arises from the enolate attack upon the acyclic benzylic cation, was observed, as well as unreacted **4a** (Scheme 4).

(3) For recent representative examples, see: (a) Carson, C. A.; Young, I. S.; Kerr, M. A. *Synthesis* **2008**, 485. (b) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem.* **2008**, *120*, 1123. (c) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (d) Sugita, Y.; Yamadoi, S.; Hosoya, H.; Yokoe, I. *Chem. Pharm. Bull.* **2001**, *49*, 657.

(4) For reviews, see: (a) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 732. (b) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (c) Frontier, A. J.; Collison, C *Tetrahedron* **2005**, *61*, 7577. (d) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479.

(5) (a) Murphy, W. S.; Wattansin, S. *Tetrahedron Lett.* **1980**, *21*, 1887. (b) Murphy, W. S.; Wattansin, S. *J. Chem. Soc., Perkins Trans. 1* **1981**, 2920. (c) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1029. (d) Yadav, V. K.; Kumar, N. V. *Chem. Commun.* **2008**, 3774.

(6) Tsuge, O.; Kanemasa, S.; Otsuka, T.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2897.

(7) De Simone, F.; Andres, J.; Torosantucci, R.; Waser, J. *Org. Lett.* **2009**, *11*, 1023.

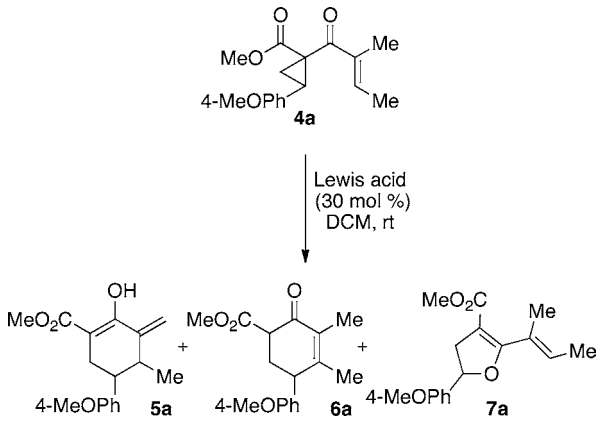
(8) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003.

(9) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

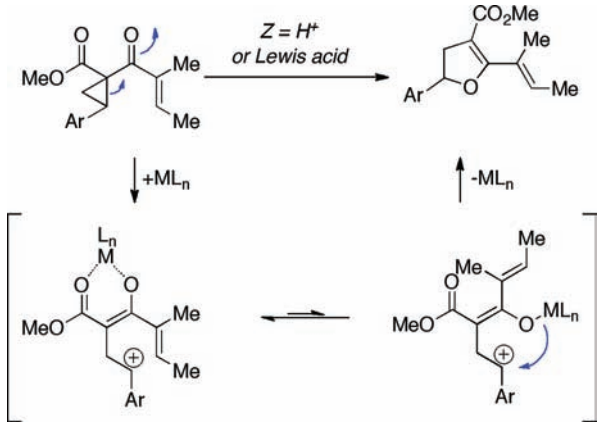
(10) This hypothesis was confirmed later when no desired cyclizations were observed with substrates bearing an α-hydrogen.

(11) Marcoux, D.; Charette, A. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 10155.

Scheme 3. Initial Lewis Acid Screening



Scheme 4. Formation of Dihydrofuran **7a**



Based on the crude ^{1}H NMR spectra of the individual screening reactions, the ratios of homo-Nazarov products **5a** and **6a** were compared directly against those of **4a** and **7a** and plotted the data in Figure 1. To our satisfaction, In(OTf)$_3$ emerged as the most efficient promoter (full conversion of **4a** to **5a** and **6a** within 3 h), while Zn(OTf)$_2$ and Cu(OTf)$_2$ were the next best Lewis acids, although neither gave full conversion of **4a** even after 105 h. Pd(0) and Pd(II) complexes did not give any homo-Nazarov products. Lastly, no conversion of **4a** was observed for Ir(acac)$_3$, which was chosen based on Frontier's successes with Ir(III) complexes for polarized Nazarov substrates.

We next turned our attention to probing for any noticeable solvent effects. When a variety of solvents (i.e., tetrahydrofuran, benzene, dichloroethane, acetonitrile, nitromethane, etc.) were screened, dichloromethane remained the best choice and no observable changes in product distributions were observed with any of the other solvents.

Having established that In(OTf)$_3$ in dichloromethane was the best overall catalyst system to promote the reaction,[12] this method was applied to a diverse set of alkenyl cyclopropyl ketone substrates to determine the reaction scope and applicability (Table 1). When α-alkyl substrates are subjected

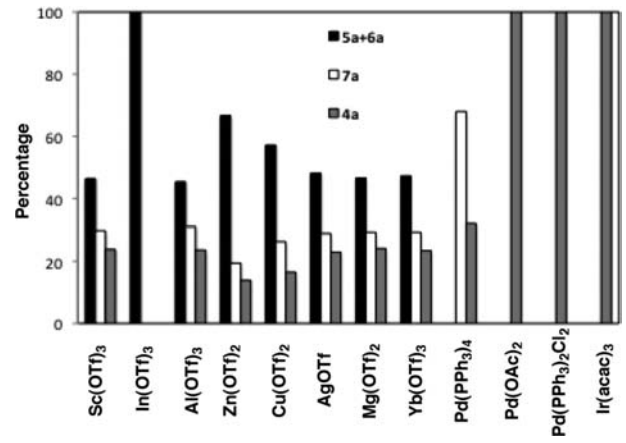


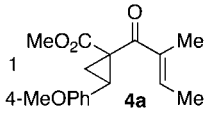
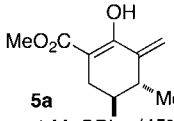
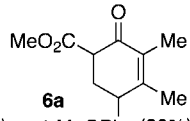
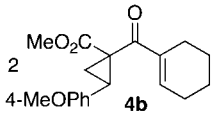
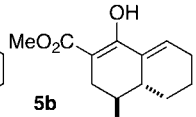
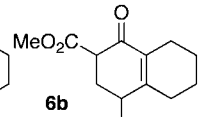
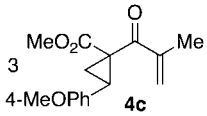
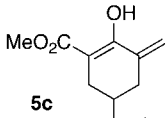
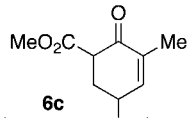
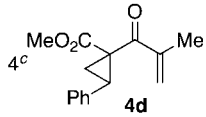
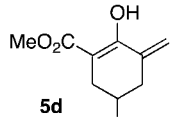
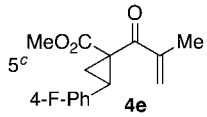
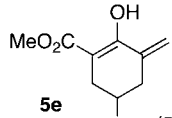
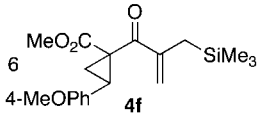
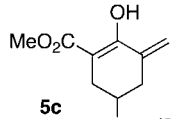
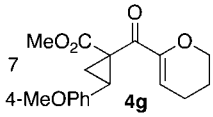
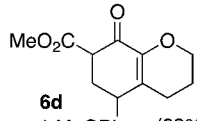
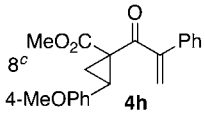
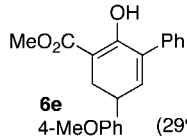
Figure 1. Lewis acid catalyst screen for alkenyl cyclopropyl ketone cyclization. Reactions were conducted in dichloromethane at room temperature in the presence of 30 mol % catalyst. Percentages are based on product ratios calculated from crude ^{1}H NMR spectra for each individual reaction.

to the reaction conditions, mixtures of **5** and **6** are observed. Model substrate **4a** provided alkenes **5a** and **6a** in 75% yield as a 1.5:1 mixture (entry 1). For **5a**, the methyl group and phenyl were oriented in a trans relationship (5:1 trans/cis *dr*) as confirmed by NMR.[13] Similarly, cyclohexenyl ketone **4b** also proved to be a good substrate, affording the 1.5:1 alkene mixture in 75% yield (entry 2). Using **4c**, products **5c** and **6c** were formed in 77% yield as a 1.5:1 mixture (entry 3). Interestingly, when the aryl substituent was changed to phenyl or 4-fluorophenyl (entries 4 and 5), **5d** and **5e** were the only cyclized products observed in 46% (80% BRSM) and 56% yields (77% BRSM), respectively. The reactions did not go to completion after 24 h, only offering starting material **4**. These observations can be rationalized based on the decreased cation stabilizing ability of the phenyl and 4-fluorophenyl groups in comparison to the donating 4-methoxyphenyl. With hopes of influencing the product ratio, we installed a silyl group on the α-substituent in **4f** to further stabilize the resulting oxyallyl cation. The reaction proceeded rapidly to **5c** in 92% yield within 0.5 h (entry 6). The formation of this product agrees with the mechanistic hypothesis of carbocation formation due to the β-silyl effect. When the α-substituent was a heteroatom, efficient cyclization of **4g** was observed to give product **6d** in 93% yield (entry 7). Finally, we looked at a substrate bearing an α-phenyl group (entry 8). We anticipated that the phenyl group would serve to stabilize the resulting cyclic oxyallyl cation, if formed, allowing for increased reaction rates. However, when **4h** (bearing a α-phenyl substituent) was subjected to the reaction conditions, only a 30% yield (50% BRSM) of the expected cyclized product **6e** was observed after 35 h. Along with unreacted starting material, the major component was the dihydrofuran byproduct. This marks the

(12) For recent reviews of In(III) catalysis, see: (a) Ghosh, R.; Maiti, S. *J. Mol. Catal. A: Chem.* **2007**, *264*, 1. (b) Frost, C. G.; Hartley, J. P. *Mini-Rev. Org. Chem.* **2004**, *1*, 1–7.

(13) See Supporting Information.

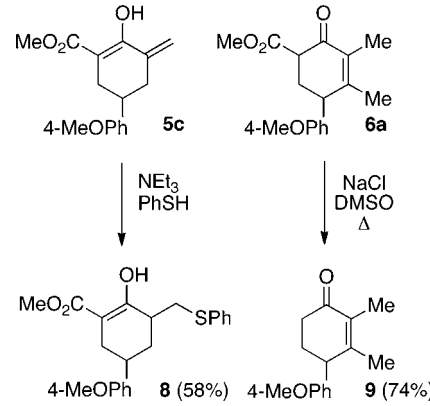
Table 1. In(OTf)$_3$-Catalyzed Homo-Nazarov Cyclization of Alkenyl Cyclopropyl Ketones[a]

entry	substrate	product(s) (% yield)[b]	
1	 **4a**	 **5a** (45%)	 **6a** (30%)
2	 **4b**	 **5b** (45%)	 **6b** (30%)
3	 **4c**	 **5c** (46%)	 **6c** (31%)
4[c]	 **4d**	 **5d** (46%)[d]	
5[c]	 **4e**	 **5e** (55%)[d]	
6	 **4f**	 **5c** (92%)	
7	 **4g**	 **6d** (93%)	
8[c]	 **4h**	 **6e** (29%)[d]	

[a] Reactions run with 1 equiv of substrate **4** and 30 mol % In(OTf)$_3$ in CH_2Cl_2 at 25 °C and complete within 1 h. [b] Isolated yields after column chromatography. [c] Reaction did not go to completion over 24 h. [d] Yields based on recovered starting material are as follows: **5d** (80%); **5e** (77%); and **6e** (50%).

only instance in which this byproduct is observed when In(OTf)$_3$ is used as the catalyst. This can be rationalized if **4h** exists in the less reactive *s-cis* enone conformation. MMFF calculations revealed that the *s-cis* conformation is more stable than the *s-trans* conformation by more than 6 kcal/mol due to the presence of stabilizing π-interactions between the α-phenyl substituent and the oxygen lone pairs of the adjacent ester group.[14] Consequently, upon cyclopropane ring opening, enolate trapping of the acyclic cation directly outpaces the homo-Nazarov cyclization pathway due to the difficulty in rotating into the more reactive *s-trans* enone conformer.

Scheme 5. Examples of Facile Product Derivatization



As a further illustration of the utility of our reaction, we sought to use our alkenyl products as synthetic building blocks by converting them into other useful compounds (Scheme 5). For instance, when **5c** was treated with thiophenol,[15] thioether **8** was obtained in 58% yield as a 1:1 mixture of diastereomers. Similarly, **6a** was subjected to Krapcho[16] decarbalkoxylation conditions to generate **9** in 74% yield.

In conclusion, an efficient protocol for the homo-Nazarov cyclization of alkenyl cyclopropyl ketones has been reported. Further studies are underway to apply this protocol to the heteroaromatic homo-Nazarov cyclization. Other activities include the determination of the reaction kinetics as well as full elucidation of the effects of substituents on the reaction mechanism. Lastly, reactions employing chiral catalyst complexes are being explored. The results of each of these studies will be reported in due course.

Acknowledgment. S.F. thanks the NSF FACES Program for a Career Initiation Grant and ORAU for the Ralph E. Powe Junior Faculty Enhancement Award.

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

OL102497W

(14) MMFF calculations were run using Trident software available from Wavefunction, Inc.

(15) Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 121–125.

(16) Krapcho, A. P.; Jahngen, E. G. E.; Lovey, A. J.; Short, F. W. *Tetrahedron Lett.* **1974**, *15*, 1091.