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Polarizing the Nazarov Cyclization: Efficient Catalysis under Mild Conditions

Wei He, Xiufeng Sun, and Alison J. Frontier*

Department of Chemistry, University of Rochester, Rochester, New York 14627

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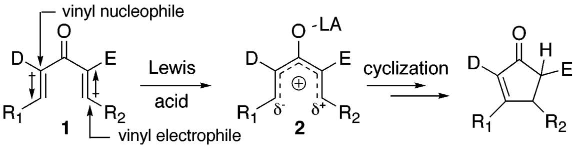
The Nazarov cyclization is a 4π-electrocyclization that converts divinyl ketones to cyclopentenones by activation with a Lewis acid.[1] The potential synthetic utility of the reaction is considerable,[2,3] given the stereospecific nature of the cyclization[4] and the ability of existing stereocenters to effect diastereoselective ring closure (torquoselectivity).[1a,5] However, these advantages have been overshadowed by the following shortcomings: in general, either protic acid or strong Lewis acid (e.g., BF_3, $SnCl_4$, $TiCl_4$, $AlCl_3$) is required to promote the reaction, one or more molar equivalents of Lewis acid is necessary for best results,[6] and the regioselectivity of the elimination step can be poor, giving a mixture of cyclopentenone isomers.[7]

In contrast, Diels–Alder, aldol, Michael, and ene-like reactions can be effected using mild Lewis acids as catalysts.[8] These reaction types involve addition of an electron-rich π-system to an electron-poor π-system, a bond-forming process similar to the 4π Nazarov cyclization. With this in mind, we designed divinyl ketones with a "vinyl nucleophile" and a "vinyl electrophile"(see **1**, Scheme 1). We reasoned that activation of **1** might occur with a mild Lewis acid to give **2**, and that polarized pentadienyl cation **2** should cyclize more readily than a symmetric, unpolarized π-system.[9–12]

Scheme 1. A Polarized Nazarov Reaction



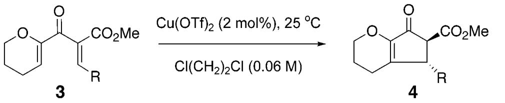
(D=electron-donating group; E=electron-withdrawing group)

Initial experiments were conducted on divinyl ketones **3**[13] bearing an oxygen at the α-position of the vinyl nucleophile and an ester at the α-position of the vinyl electrophile. The potential for coordination of both carbonyl groups to a chiral promoter to induce asymmetry during the cyclization was an important motivation for the study of these substrates. Copper triflate (2 mol %) catalyzed the Nazarov cyclization of β-aryl-substituted enoates **3a**–**e** in chlorinated solvent at room temperature in air to give excellent yields of cyclopentenones **4** (Table 1).[14] Electron-rich aromatic substituents increased reaction rates, especially when the electron-donating group was a resonance contributor to the enone system (compare entries 1–5). Even the nonaromatic cyclohexyl substrate **3f** (entries 6 and 7) could be induced to cyclize efficiently if the reaction was run at higher concentration and elevated temperature.

Each β-keto ester **4** was isolated as a single regio- and stereoisomer with a trans relationship of the α and β substituents on the former vinyl electrophile. Stereochemical assignments were made based on the assumption that thermodynamic cyclopentenone products **4** are formed under the reaction conditions.[15]

Substrates equipped with a range of vinyl nucleophiles were examined under optimized cyclization conditions (Table 2). Cyclic, acylic, and aromatic vinyl nucleophiles (entries 1, 2, and 3) cyclized smoothly, but more slowly than the dihydropyran vinyl nucleophile (Table 1, entry 1). Quaternary center formation was also possible; cyclization of divinyl ketone **11a** gave cyclopentenone **12a** as a single regio- and stereoisomer (entry 4).[16] However, cyclization of α-unsubstituted **13a** (entry 5) was slower and low-yielding, and elimination was less regioselective.

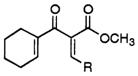
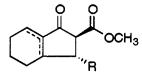
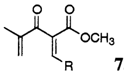
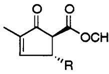
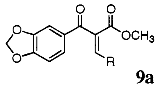
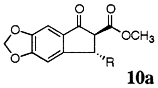
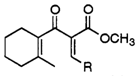
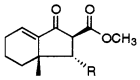
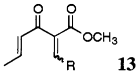
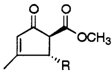
Table 1. Effect of Vinyl Electrophile β-Substitution on Reactivity



entry	ketone	*R*	time	yield
1	**3a**	2,4,6-trimethoxyphenyl	5 min	>99%
2	**3b**	4-methoxyphenyl	3.5 h	99%
3	**3c**	3-methoxyphenyl	48 h	96%
4	**3d**	phenyl	108 h	99%
5	**3e**	2-furyl	12 h	99%
6	**3f**	cyclohexyl	240 h	<50%
7[a]	**3f**	cyclohexyl	2 h	>99%

[a] Optimized conditions: $Cu(OTf)_2$ (2 mol %), $Cl(CH_2)_2Cl$ (0.5 M), 55 °C.

Table 2. Effect of Vinyl Nucleophile α-Substitution on Reactivity[a]

entry	divinyl ketone	product	temp	time	%y
1	 **5a**	 **6a**	40	0.25 h	86[b]
2	 **7a**	 **8a**	55	8 h	75
3	 **9a**	 **10a**	53	20 h	92
4	 **11a**	 **12a**	25	4 h	95
5	 **13a**	 **14a**	50	44 h	58[c]

[a] *R* = 2,4,6-trimethoxyphenyl. Reaction conditions: 2 mol % $Cu(OTf)_2$, CH_2Cl_2, or $Cl(CH_2)_2Cl$ (0.06 M). [b] 1.2/1 ratio of cyclohexene regioisomers. [c] Isolated yield of the major component of a regioisomeric mixture.

Substrates with α-unsubstituted vinyl electrophiles were also submitted to the optimized cyclization conditions. In every case, substrates with carbomethoxy substitution cyclized more efficiently (compare entry 1 to 2, 3 to 4, etc; Table 3). In general, the more polarizing groups on the divinyl ketone, the more efficient the reaction. Some substrates missing key substituents still cyclized well (entries 2, 4, 5, and 7), but as polar substitution on the divinyl ketone was reduced to a minimum, reaction behavior became complex and decomposition began to compete with cyclization (entries 4, 6, and 8).[17]

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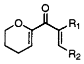
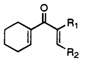
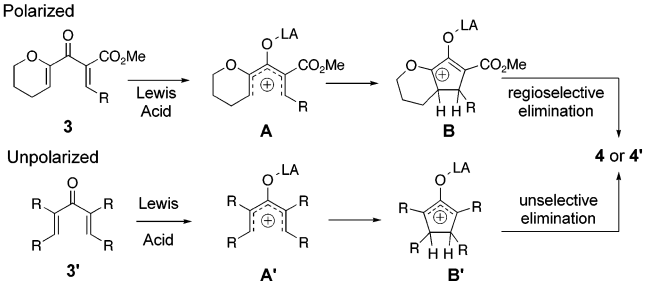
Table 3. Effect of Vinyl Electrophile α-Substitution on Reactivity[d]

entry	ketone	prod	R_1	R_2	temp	time[a]	%y
							
1	**3a**	**4a**	CO_2Me	TMP	25	<0.1 h	>99
2	**15a**	**16a**	H	TMP	25	0.33 h	86
3	**3f**	**4f**	CO_2Me	Chx	55	2 h	>99
4	**15f**	**16f**	H	Chx	55	0.5 h	60
							
5	**5a**	**6a**[b]	CO_2Me	TMP	40	0.25 h	86
6	**17a**	**18a**[c]	H	TMP	40	5 h	30-40
7	**5f**	**6f**[b]	CO_2Me	Chx	65	14 h	70
8	**17f**	**18f**[c]	H	Chx	65	4 h	37-42

[a] Reaction was stopped when all divinyl ketone was consumed. [b] Mixture of cyclohexene regioisomers. [c] Multicomponent product mixture; see Supporting Information. [d] TMP = 2,4,6-trimethoxyphenyl; Chx = cyclohexyl. Reaction conditions: $Cu(OTf)_2$ (2 mol %), $Cl(CH_2)_2Cl$ (0.2 M).

Scheme 2. Effect of Polarization on the Electrocyclic Process



We have found that Nazarov cyclization is facilitated by the presence of polar substituents on the divinyl ketone. One possible factor is the greater Lewis basicity of **3**: formation of carbocation **A** from **3** is expected to be more favorable than formation of carbocation **A′** from **3′** (Scheme 2).[18] The electron-donating and withdrawing groups should polarize the π-system of cation **A**, which would be expected to cyclize more readily than the symmetric π-system of cation **A′**. Finally, regioselectivity of the elimination of **B** is likely controlled by the position of the positive charge, localized adjacent to the stabilizing oxygen atom. In oxyallyl cation **B′**, the positive charge is fully delocalized and elimination is not expected to be regioselective.

In summary, we report a mild, Lewis acid-catalyzed procedure for Nazarov cyclization of polarized divinyl ketones. Further research will focus upon improving our understanding of polarization in the cyclization, utilizing Lewis acids with chiral ligands to promote enantioselective cyclization, and synthetic applications of the methodology.

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Supporting Information Available: Representative experimental procedure, spectral data for **3**−**18** (PDF), X-ray structure data for **3a** and **12a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Germany, 1970; pp 38−64.

(5) Houk, K. N. In *Strain and Its Implications in Organic Chemistry*; deMeijere, A., Blechert, S., Eds.; Kluwer Academic Publishers: Dodrecht, The Netherlands,1989; pp 25−37.

(6) Isolated examples of Nazarov cyclization with catalytic Lewis acid have been reported: (a) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377 (40 mol % $FeCl_3$ for β-silyl divinyl ketones). (b) Reference 2d (10 mol % $SnCl_4$, 200 mol % Et_3SiH). (c) Reference 2e (10 mol % $BF_3 \cdot OEt_2$).

(7) Denmark's β-silyl alkenes, which suffer elimination with excellent regioselectivity, are an exception. Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. Also see ref 1a and references therein.

(8) For leading references for all four reaction types, see: (a) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 8. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

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(11) α-Heteroatom-substituted divinyl ketones have been found to be particularly reactive substrates in Nazarov cyclizations: Tius, M. A.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871.

(12) For a study of the influence of divinyl ketone substituents on the silicon-directed Nazarov cyclization, see Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim.* Acta **1988**, *71*, 168.

(13) Synthesis of all α-carboalkoxy divinyl ketones was achieved by Knoevenagel condensation of a β-keto ester and an aldehyde, catalyzed by a secondary amine. Desimoni, G.; Faita, G.; Ricci, M.; Righetti, P. *Tetrahedron* **1998**, *54*, 9581. Most divinyl ketones were isolated as a single trisubstituted olefin and are drawn as the *Z*-isomer, but we have been unable to confidently assign the olefin geometry at this time.

(14) When the catalyst was stirred with 2.5 mol % potassium carbonate before addition of substrate, the rate of cyclization was unchanged, ruling out adventitious catalysis by triflic acid. Reactions run under argon gave comparable results.

(15) Support for the stereochemical assignments: The stereochemistry of representative β-ketoester **4b** is stable under equilibrating conditions (NaOH/MeOH/THF/55 °C, 2h), trans stereochemistry was found to be thermodynamically favored for similar compounds reported in the literature (refs 7 and 10c), and trans stereochemistry of **3a** was confirmed by an X-ray diffraction study.

(16) The structure of **12a** was determined by an X-ray diffraction study.

(17) After submission, it was found that cyclization of **17f** improved significantly when conducted in an inert atmosphere. This anomalous result will be examined carefully in due course.

(18) Copper triflate probably coordinates to both carbonyl groups: (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. (b) Evans, D. A.; Scheidt, K. A.; Johnson, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

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