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A General Method for the Catalytic Nazarov Cyclization of Heteroaromatic Compounds

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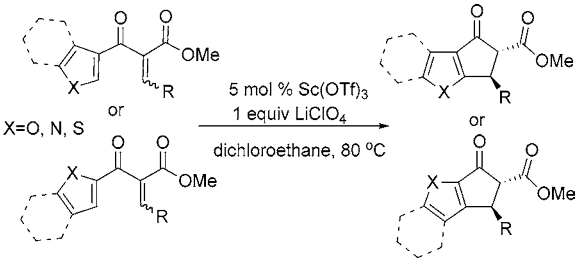
ABSTRACT



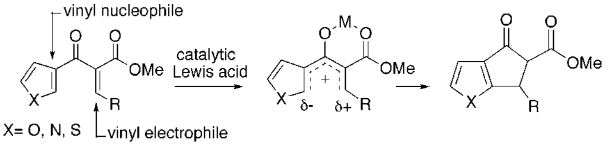
A general, catalytic method for efficient Nazarov cyclization of systems containing heteroaromatic components has been developed. Scandium triflate was identified as the most reactive promoter, and it was found that addition of lithium perchlorate was necessary for synthetically useful catalytic cyclizations. The method was used to synthesize a range of cyclopentanone-fused heteroaromatic systems in 36–97% yield, and the reactivity trends observed demonstrate the impact of polarization on cyclization efficiency.

The synthetic utility of the Nazarov cyclization[1] has been developing steadily since the groundbreaking silicon-directed cyclizations of Denmark and Jones were reported over 20 years ago.[2] Interrupted cyclization methods developed by West allow stereospecific installation of multiple racemic chiral centers,[3] and Tius has demonstrated that axial-to-tetrahedral chirality transfer is possible in the cyclization of allenylvinyl ketones.[4]

Efforts from our laboratory have focused on the study of substrates that are favorably polarized, so that the divinyl ketone is electronically primed for cyclization.[5] With appropriate substrate design, the 4π electrocyclization begins to take on characteristics of the reaction of an electron-rich π-system with an electron-poor one, which should lower the activation barrier for cyclization. The validity of this approach is demonstrated by a number of studies from several laboratories that have reported the efficient, catalytic cyclization of various polarized divinyl ketones.[6]

This communication describes the development of a cyclization procedure for aromatic heterocycle-containing precursors, a synthetically significant but relatively unreactive class of substrates. It was hoped that the electron-rich aromatic system could be cast in the role of the vinyl nucleophile, allowing catalytic Nazarov cyclization to occur under mild Lewis acidic conditions (Scheme 1).

Scheme 1. Heteroaromatics as Polarized Nazarov Substrates



A number of isolated examples of heteroaromatic Nazarov cyclizations can be found in the chemical literature,[7−10] but

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[1] For reviews, see: (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N.Y.)* **1994**, *45*, 1. (b) Frontier, A.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (d) Tius, M. *Eur. J. Org. Chem.* **2005**, *11*, 2193.

[2] (a) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. (b) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377. (c) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2397.

10.1021/ol062403v CCC: $33.50

in each case stoichometric (and often *super*stoichometric) amounts of Brønsted acids (H_3PO_4, HCl, TFA) or Lewis acids ($FeCl_3$, $BF_3{\cdot}Et_2O$, $AlCl_3$) were needed to furnish the annulated product. The most recent account of a pyrrole cyclization, reported by Knight et al.,[11] prompted us to disclose the protocol we have developed for the catalytic Nazarov cyclization of heteroaromatic compounds.

The mild conditions identified will be compatible with a range of sensitive functionality and should be effective for a wide variety of heteroaromatic substrates. The study also constitutes a survey of the reactivity of a series of heteroaromatic compounds in the Nazarov cyclization, with results consistent with the idea that reaction rates correlate with the extent of polarization in the substrate.

Synthesis of nearly all Nazarov substrates was carried out as outlined in Scheme 2. Addition of methyl acetate to the appropriate 2- or 3-substituted heteroaromatic acid chloride **A** or aldehyde **B** (followed by MnO_2 oxidation in the cases where aldehydes were used) provided β-ketoesters **C**. The olefin was installed via Knovenagel condensation to provide the Nazarov substrates **D** as a mixture of *E*/*Z* isomers, which were subjected to cyclization conditions.[12]

Scheme 2. Substrate Synthesis

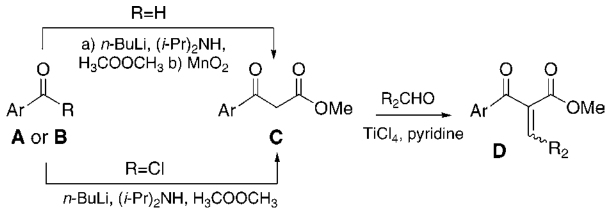
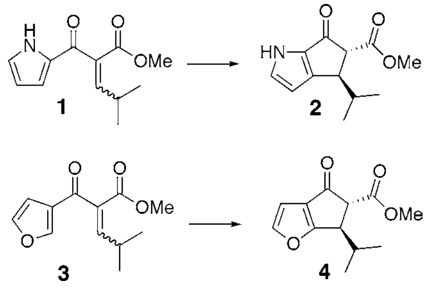


Table 1. Catalyst Screening



entry	sm	mol % catalyst	conditions[a]	time (h)	% yield (**2** or **4**)
1	**1**	200% $Cu(OTf)_2$	DCE; 60 °C	72[b]	<20
2	**1**	10% $Sc(OTf)_3$	toluene; 60 °C	72[b]	50
3	**1**	10% $In(OTf)_3$	toluene; 60 °C	72[b]	52
4	**1**	5% $FeCl_3$	DCE; 80 °C	72[b]	26
5	**1**	5% Ir(III)[c]	DCE; 80 °C	72[b]	<20
6	**1**	10% $Sc(OTf)_3$	DCE; 50 °C	24	47
7	**1**	30% $In(OTf)_3$	DCE; 50 °C	12	54
8	**3**	10% $Cu(OTf)_2$	DCE; 60 °C	72	[d]
9	**3**	10% $Sc(OTf)_3$	DCE; 60 °C	23	47
10	**3**	10% $In(OTf)_3$	DCE; 80 °C	4	32

[a] DCE = dichloroethane. [b] Incomplete conversion of starting material. [c] $[IrMe(CO)(dppf)diiodobenzene][BARF]_2$. [d] No reaction.

Catalyst screening was carried out with pyrrole **1** and furan **3**. The results are shown in Table 1. It was surprising to find that $Cu(OTf)_2$, a catalyst that effectively cyclizes more reactive (nonaromatic) substrates,[5] showed little reactivity even when 2 equiv was present. $Sc(OTf)_3$ and $In(OTf)_3$ were more effective, and cyclization did occur in the presence of catalytic amounts of these complexes, but the reaction would stall before the starting material was completely consumed (entries 2, 3, 6, and 7). The dicationic iridium species (entry 7), though found to be particularly competent with divinyl ketone substrates, gave poor results in this screen. With catalytic $FeCl_3$ (entry 4), a number of undesired byproducts were observed in the reaction mixture. No reaction was observed after 72 h with 10 mol % of $Mg(OTf)_2$, $AlCl_3$, or $Zn(OTf)_2$. Catalytic amounts of $Sc(OTf)_3$ and $In(OTf)_3$ also promoted cyclization of furan derivative **3**, again with incomplete conversion (entries 9 and 10). A number of solvents were screened during the optimization process, and it was found that cyclization efficiency was comparable for reactions run in toluene, chlorinated hydrocarbons, and nitromethane. The reactions worked best when the temperature was between 60 and 80 °C, but no adjustment of solvent or temperature led to complete conversion in the cyclization.

Because Nazarov cyclizations of aryl vinyl ketones can also be termed *intramolecular vinylogous Friedel−Crafts acylations*,[13] it seemed prudent to investigate the observation that $LiClO_4$ can play an important role as an additive in Friedel−Crafts acylations using catalytic $Sc(OTf)_3$,[14] $In(OTf)_3$,[15] or $Hf(OTf)_4$.[16]

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(3) (a) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430. (b) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443. (c) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876. (d) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1970.

(4) Hu, H. P.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 9895.

(5) Frontier, A. J.; He, W.; Sun, X. *J. Am. Chem. Soc.* **2003**, *125*, 14278.

(6) (a) Aggarwal, V.; Belfield, A. *Org. Lett.* **2003**, *5*, 5075. (b) Occhiato, E.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728. (c) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927. (d) Trauner, D.; Gradl, S.; Liang, G. *Org. Lett.* **2003**, *5*, 4913.

(7) For cyclizations of indole substrates, see: (a) Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6067. (b) Ishikura, M.; Imaizumi, K.; Katagiri, N. *Heterocycles* **2000**, *53*, 2201. (c) Cheng, K.; Chan, K.; Lai, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2461.

(8) For cyclizations of thiophene substrates, see: (a) Kang, K.; Kim, S.; Lee, J.; U, J. *Tetrahedron Lett.* **1992**, *33*, 3495. (b) Maffrand, J. P.; Boigegrain, R.; Courregelongue, J.; Ferrand, G.; Frehel, D. *J. Heterocycl. Chem.* **1981**, *18*, 727. (c) Blanchard, P.; Brisset, H.; Illien, B.; Riou, A.; Roncali, J. *J. Org. Chem.* **1997**, *62*, 2401.

(9) For cyclizations of pyrrole substrates, see: (a) Song, C.; Knight, D.; Whatton, M. *Org. Lett.* **2005**, *8*, 163. (b) Kang, K.; Kim, S.; Lee, J.; U. J. *Tetrahedron Lett.* **1992**, *33*, 3495.

(10) For cyclizations of a benzofuran substrate, see: Grant, H. *J. Heterocycl. Chem.* **1978**, *15*, 1235.

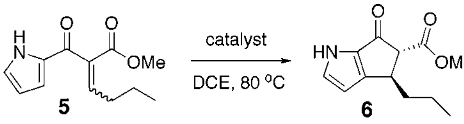
(11) Song, C.; Knight, D.; Whatton, M. *Org. Lett.* **2006**, *8*, 163.

(12) *E*/*Z* isomerization takes place under the reaction conditions.

(13) Upon Lewis acid activation of heteroaryl vinyl ketones, a pentadienyl cation is created. This extended π-system includes two p-orbitals of an aromatic ring, and although it will adopt conformations in which the aromatic system is decoupled from the companion allyl cation, overlap of all five p-orbitals must occur when the system cyclizes, so orbital symmetry should be conserved.

We were pleased to discover that although reactions did not go to completion after 24 h with catalytic scandium triflate alone (Table 2, entry 1), the reaction was complete in 8.5 h in the presence of 1 equiv of $LiClO_4$ as additive (entry 2). When less than 1 equiv of $LiClO_4$ was used, the reaction did go to completion but was not as efficient (entry 3). This is consistent with the findings of Frost et al., who noted that the best results were obtained when 1 equiv of $LiClO_4$ was employed as an additive in Friedel−Crafts acylations.[15]

Table 2. Counterion Effects

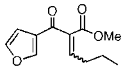
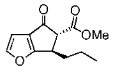
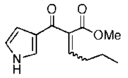
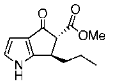
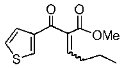
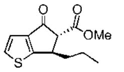
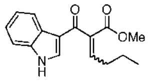
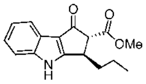
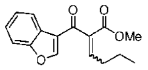
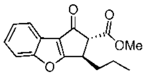
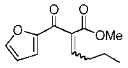
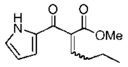
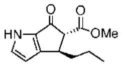
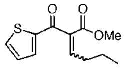
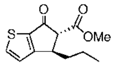
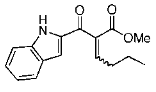
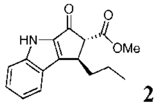
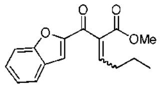


entry	catalyst	mol %	additive	time (h)	% yield **6**
1	$Sc(OTf)_3$	5	none	24	23
2	$Sc(OTf)_3$	5	1 equiv of $LiClO_4$	8.5	97
3	$Sc(OTf)_3$	5	0.25 equiv of $LiClO_4$	22	77
4	none		1 equiv of $LiClO_4$	12	5
5	$Sc(ClO_4)_3$	5	none	9	71
6	$Sc(ClO_4)_3$	5	1 equiv of $LiClO_4$	7	79
7	$Cu(ClO_4)_2$	5	none	24	49

$LiClO_4$ alone did catalyze cyclization,[17] but not nearly as efficiently as the $Sc(OTf)_3/LiClO_4$ combination (entry 4). This suggested that the active catalyst under these conditions might be $Sc(ClO_4)_3$.[18] Experiments were then conducted to test the efficiency of the scandium(III) and copper(II) metal centers with both triflate and perchlorate counterions. $Sc(ClO_4)_3$ was indeed a better catalyst than $Sc(OTf)_3$, (entry 5 vs entry 1). Additional lithium perchlorate had no significant effect on the scandium perchlorate cyclization (entry 6). Furthermore, copper(II) catalysis became possible using perchlorate as counterion (cf. Table 1, entry 1 vs Table 2, entry 7), although the scandium catalysts were clearly superior. Overall, the scandium triflate/lithium perchlorate system gave the best results and was the most convenient and cost-efficient procedure.

With an optimized set of conditions in hand we completed our survey of heteroaromatic Nazarov cyclizations (Table 3). Reaction rates and yields are consistent with the expected reactivity of heteroaromatic systems,[19] which here represent the electron-donating component of the polarized reactant in the Nazarov cyclization. For furan, pyrrole, thiophene, and benzofuran,[20] reaction rates for ring closure at the 2-position (entries 1, 2, 3, and 5) are faster than their 2-substituted analogs (entries 6, 8, 9, and 10). As expected, ring closure of the indole occurs faster at the 3-position than at the 2-position (entries 4 vs 9). Finally, the 2-substituted

Table 3. Heteroaromatic Nazarov Cyclizations[a]

entry	substrate	time (h)	product	yield (%)
1	 **7**	4.75	 **8**	75
2	 **9**	1.25	 **10**	68
3	 **11**	1.5	 **12**	75
4	 **13**	5	 **14**	80
5	 **15**	3.5	 **16**	66
6	 **17**	>24	no reaction	--
7	 **5**	8.5	 **6**	97
8	 **18**	96	 **19**	36
9	 **20**	0.75	 **21**	68
10	 **22**	>24	no reaction	--

[a] Reaction conditions: 5 mol % $Sc(OTf)_3$, 1 equiv of $LiClO_4$, DCE, 80 °C.

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(15) Chapman, C.; Frost, C.; Hartley, J.; Whittle, A. *Tetrahedron Lett.* **2001**, *42*, 773.

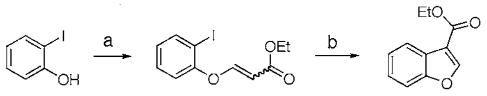
(16) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* **1995**, *36*, 409.

(17) For reactions in which lithium perchlorate acts as a Lewis acidic catalyst, see the following review: Sankararaman, S.; Nesakumar, J. E. *Eur. J. Org. Chem.* **2000**, 2003.

(18) For accounts of scandium perchlorate catalysis, see: (a) Hachiya, I.; Kobayashi, S. *Tetrahedron Lett.* **1994**, *35*, 3319. (b) Nishikawa, T.; Kajii, S.; Wada, K.; Ishikawa, M.; Isobe, M. *Synthesis* **2002**, 1658.

(19) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons, Ltd.: New York, NY, 1976; Chapter 3, p 57.

(20) A novel synthetic route to acylbenzofuran **26** was developed in order to access benzofuran substrate **15**. Michael addition of *o*-iodophenol to ethyl propiolate gave a 12:1 *E*/*Z* ratio of vinyl ester **25**. Intramolecular Heck reaction (see Sakamoto, T; Nagano, T; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215 and references therein) afforded 3-subsitiuted benzofuran **26**. This represents a significant improvement over the previously reported strategy (see Chou, C.-H.; Trahanovsky, W. S. *J. Org. Chem.* **1986**, *51*, 4208).



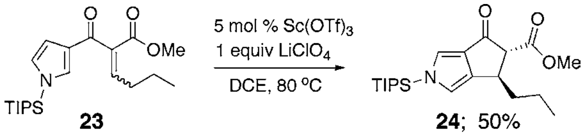
25; 12:1 E/Z; 95% **26**, 84%

Reaction Conditions: a) ethyl propiolate, N-methylmorpholine, THF, 2 h b) $Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN, 80 °C, 3.5 h furan **17** and the 2-substituted benzofuran **22** did not undergo Nazarov cyclization. Increasing temperature and catalyst loading only resulted in decomposition. Although these substrates were not expected to cyclize as readily as their 3-substituted counterparts, it was disappointing to find them inert to the standard reaction conditions.

In each case only one diastereomer was isolated after column chromatography, which was assigned as the diastereomer with a *trans* relationship between the α-carbomethoxy group and the *β*-alkyl group. This stereochemical assignment was made on the basis of earlier results from our laboratory[5,21] and was corroborated by an X-ray crystallographic study of representative compound **2** (see Supporting Information).

Whereas protection of the nitrogen was unnecessary for pyrrole and indole substrates, it was observed that the presence of a TIPS group on the pyrrole nitrogen blocked the normal Nazarov cyclization pathway (**23**, Scheme 3). Evidently, steric crowding precludes cyclization at the 2-position, leading instead to cyclization at the 3-position to give the regioisomeric product **24** (Scheme 3).

Scheme 3. Friedel−Crafts Ring Closure



23

24; 50%

In summary, a general catalytic system has been identified that allows the Nazarov cyclization of relatively unreactive aromatic heterocyclic substrates. This is the first such system that has been employed over a wide range of heterocycles and is the only procedure available that uses catalytic amounts of a mild Lewis acid activator. The reaction conditions should be compatible with a wide variety of distal functionality. In our laboratory, this methodology is being utilized in synthetic studies targeting bioactive natural products, and the exploration of methods for asymmetric Nazarov cyclization using chiral Lewis acid complexes is also underway.[22]

Acknowledgment. We thank the National Science Foundation (CAREER award CHE-0349045) and the University of Rochester for support of this work. The authors thank Mr. Wei He (University of Rochester) for initial experiments related to pyrrole **1** and for many helpful discussions. We also thank Dr. William Brennessel (University of Rochester) for carrying out an X-ray crystallographic study of compound **2** and Dr. Alice Bergmann (SUNY at Buffalo) for the collection of high-resolution mass spectra.

Supporting Information Available: Experimental procedures and spectral data for the intramolecuar Heck reaction of **25** and the synthesis of indole substrate **20**, as well as a general procedure for the Nazarov cyclization. Full characterization for new compounds, copies of ^{1}H and ^{13}C spectra, and crystallographic data for **2** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) (a) Janka, M.; He, W.; Frontier, A.; Eisenberg, R. *J. Am. Chem. Soc.* **2004**, *126*, 6864. (b) Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R.; Flaschenreim, C. *Tetrahedron* **2005**, *61*, 6193.

(22) Asymmetric catalysis of a number of reactions using chiral Lewis acidic scandium complexes has been fruitful: (a) Evans, D.; Sweeney, Z.; Rovis, T.; Tedrow, J. *J. Am. Chem. Soc.* **2001**, *123*, 12095. (b) Evans, D.; Wu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8006. For a study of Nazarov cyclization using chiral scandium complexes, see: (c) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544.