ORGANIC LETTERS

2011
Vol. 13, No. 8
1952–1955

A Catalytic Homo-Nazarov Cyclization Protocol for the Synthesis of Heteroaromatic Ring-Fused Cyclohexanones

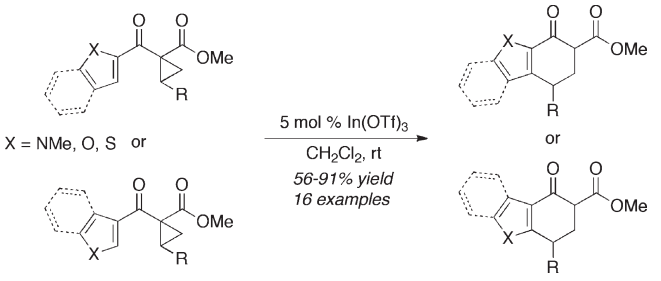
Lien H. Phun, Dadasaheb V. Patil, Marchello A. Cavitt, and Stefan France*

School of Chemistry and Biochemistry, Georgia Institute of Technology, 901 Atlantic Drive, Atlanta, Georgia 30332, United States

stefan.france@chemistry.gatech.edu

Received January 31, 2011

ABSTRACT



A general protocol for the catalytic homo-Nazarov cyclization of cyclopropyl heteroaryl ketones has been developed, which employs indium triflate as the promoter. A range of heteroaromatic ring-fused cyclohexanones was synthesized in 56−91% yield using this protocol. An example of a tandem cyclopropanation/homo-Nazarov cyclization is also reported in which the one-pot yield is greater than the overall yield of the two individual steps.

Heteroaromatic compounds fused to cyclohexyl rings are present in the core of many natural products and medicinally active molecules.[1] Furthermore, these ring-fused systems often serve as building blocks for complex chemical synthesis.[2] Given this utility, organic chemists have steadily explored the development of efficient methods for their synthesis.[3] One such method that has been relatively underexplored is the heteroaromatic homo-Nazarov cyclization,[4] an acid-promoted ring closure of a cyclopropyl heteroaryl ketone.[5]

Recently, we reported that $In(OTf)_3$ can effectively catalyze the homo-Nazarov cyclizations of alkenyl cyclopropyl ketones, furnishing cyclohexenones and methylene cyclohexanols under mild conditions.[6] The use of donor−acceptor cyclopropanes bearing a secondary electron acceptor (an ester group) was central to the observed reactivity because it allows for milder conditions for

(1) For some recent examples of naturally occurring or biologically active heteroaromatic ring-fused cyclohexyl rings: (a) Qu, Y.; Xu, F.; Nakamura, S.; Matsuda, H.; Pongpiriyadacha, Y.; Wu, L.; Yoshikawa, M. *J. Nat. Med.* **2009**, *63*, 102. (b) Wildeboer, K. M.; Zheng, L.; Choo, K. S.; Stevens, K. E. *Brain Res.* **2009**, *1300*, 41. (c) Barta, T. E.; Veal, J. M.; Rice, J. W.; Partridge, J. M.; Fadden, R. P.; Ma, W.; Jenks, M.; Geng, L.; Hanson, G. J.; Huang, K. H.; Barabasz, A. F.; Foley, B. E.; Otto, J.; Hall, S. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3517. (d) Ishiuchi, K. i.; Kubota, T.; Mikami, Y.; Obara, Y.; Nakahata, N.; Kobayashi, J. I. *Bioorg. Med. Chem.* **2007**, *15*, 413. (e) Li, X.; Vince, R. *Bioorg. Med. Chem.* **2006**, *14*, 2942. (f) Romeo, G.; Materia, L.; Pittala, V.; Modica, M.; Salerno, L.; Siracusa, M.; Russo, F.; Minneman, K. P. *Bioorg. Med. Chem.* **2006**, *14*, 5211.

(2) For representative examples as chemical building blocks: (a) Ohta, K.; Kobayashi, T.; Tanabe, G.; Muraoka, O.; Yoshimatsu, M. *Chem. Pharm. Bull.* **2010**, *58*, 1180. (b) Cadierno, V.; Diez, J.; Gimeno, J.; Nebra, N. *J. Org. Chem.* **2008**, *73*, 5852. (c) Martin, A. E.; Prasad, K. J. R. *Synth. Commun.* **2008**, *38*, 1778.

(3) For representative approaches to heteroaryl ring-fused cyclohexanones: (a) Albrecht, L.; Ransborg, L. K.; Gschwend, B.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 17886. (b) Bunce, R. A.; Nammalwar, B. *J. Heterocycl. Chem.* **2009**, *46*, 172. (c) Sridharan, M.; Beagle, L. K.; Zeller, M.; Prasad, K. J. R. *J. Chem. Res.* **2008**, 572. (d) Yadav, P. P.; Gupta, P.; Chaturvedi, A. K.; Shukla, P. K.; Maurya, R. *Bioorg. Med. Chem.* **2005**, *13*, 1497. (e) Amat, M.; Perez, M.; Llor, N.; Martinelli, M.; Molins, E.; Bosch, J. *Chem. Commun.* **2004**, 1602.

(4) For the earliest examples of an aromatic homo-Nazarov cyclization: (a) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 271. (b) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1029.

(5) For early usage of the term 'homo-Nazarov cyclization', see: Tsuge, O.; Kanemasa, S.; Otsuka, T.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2897.

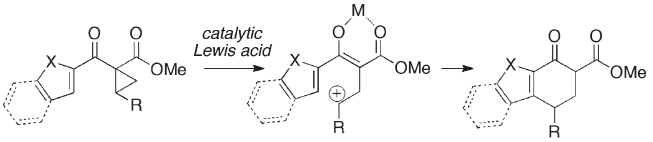
(6) Patil, D. V.; Phun, L. H.; France, S. *Org. Lett.* **2010**, *12*, 5684.

10.1021/ol200305n
Published on Web 03/18/2011

cyclopropyl ring-opening.[7] Furthermore, a catalytic amount of Lewis acid was sufficient to promote the reaction.

With this concept in mind, we envisioned employing these donor–acceptor–acceptor (D–A–A) cyclopropanes with heteroaromatics as reactive π-systems in order to generate heteroaryl ring-fused cyclohexanones.[8] This communication describes the development of a catalytic procedure for their synthesis using the homo-Nazarov cyclization of cyclopropyl heteroaryl ketones (Scheme 1).

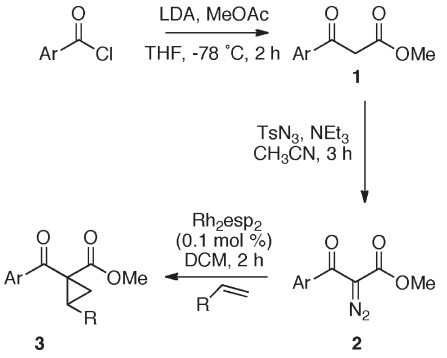
Scheme 1. Heteroaromatic Homo-Nazarov Cyclization of Donor–Acceptor–Acceptor (D–A–A) Cyclopropanes



To date, there have only been two examples of heteroaromatic homo-Nazarov cyclizations reported in the literature. In the earliest report, Yadav[9] reported the synthesis of 4-silylmethyl/hydroxymethyl-substituted 2,3-heteroaromatic ring-fused cyclohexanones. Although Yadav's method offers good to high yields (70–90%) and broad substrate scope, there are some key drawbacks, including the use of stoichiometric amounts of $SnCl_4$ (4 equiv), elevated temperatures (80 °C), and long reaction times (12 h) which were necessary for the cyclization to occur. Along the same line, Waser[10] recently reported a catalytic homo-Nazarov cyclization of activated cyclopropanes using *p*-TsOH. Despite this innovation, the successful cyclization of only one heteroaryl substrate was shown. Thus, a need remains for a general heteroaromatic homo-Nazarov method that will generate heteroaromatic ring-fused cyclohexanones rapidly and under mild conditions. This prompted us to disclose a protocol we have developed for a facile catalytic homo-Nazarov cyclization of heteroaromatic compounds.

The homo-Nazarov substrates **3** were synthesized according to Scheme 2. Addition of the enolate of methyl acetate to the appropriate 2- or 3-substituted heteroaromatic acid chloride provided β-ketoesters **1**. Diazo transfer then provided α-diazo esters **2**. Finally, treatment of **2** with

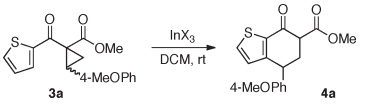
Scheme 2. Substrate Synthesis



Rh_2esp_2 (dirhodium $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzene dipropanoate)[11] in the presence of the requisite alkene provided cyclopropanes **3** as the homo-Nazarov precursors.

Given thiophene's stability in the presence of Lewis acids,[12] it was chosen as the first heteroaromatic moiety examined for optimizing our protocol. The 2-substituted thienyl cyclopropane **3a** was synthesized and used as the substrate for catalyst screening (Table 1).[13] Influenced by

Table 1. Effects of Catalyst Loading



entry	Lewis acid	loading (mol %)	time (h)	% yield
1	$In(OTf)_3$	30	2.5	88%
2	$In(OTf)_3$	5	5	86%
3	$In(OTf)_3$	1	6.5	77%
4	$InCl_3$	5	4.5	78%

our earlier report, we began by screening $In(OTf)_3$. When subjected to 30 mol % catalyst, **3a** successfully cyclized to give the heteroaromatic 2,3-ring fused cyclohexanone **4a** in 88% yield in less than 3 h (entry 1). Next, the effects of lowering the amount of catalyst were examined. Starting from 30 mol %, the loading was gradually decreased to 1 mol %. As the catalyst loading was decreased, unsurprisingly, the reaction time increased. Ultimately, a loading of 5 mol % $In(OTf)_3$ provided the homo-Nazarov product in 86% yield (entry 2), which was highly comparable to the results with 30 mol % catalyst. It is notable that 1 mol % $In(OTf)_3$ can also be used to catalyze the reaction, albeit with a lower yield (entry 3). Similarly, $InCl_3$ catalyzes the

(7) (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.

(8) For representative examples of polarizing the classic heteroaromatic Nazarov cyclization: (a) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003. (b) For heteroaromatic: Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661.

(9) Yadav, V. K.; Kumar, N. V. *Chem. Commun.* **2008**, 3774.

(10) (a) De Simone, F.; Andres, J.; Torosantucci, R.; Waser, J. *Org. Lett.* **2009**, *11*, 1023. (b) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5767.

(11) González-Bobes, F.; Fenster, M. D. B.; Kiau, S.; Kolla, L.; Kolotuchin, S.; Soumeillant, M. *Adv. Synth. Catal.* **2008**, *350*, 813.

(12) Katritzky, A. R. *Advances in Heterocyclic Chemistry*, Vol. 78; Academic Press: San Diego, 2001.

(13) Electron-donating groups on the phenyl ring promote efficient homo-Nazarov cyclization due to their ability to stabilize the benzylic carbocation. To facilitate cyclopropane ring opening, a 4-methoxyphenyl substituent was employed.

cyclization in comparable time to $In(OTf)_3$, but with a significant decrease in yield (entry 4). Inspired by its successful use in $Sc(OTf)_3$- and $In(OTf)_3$-catalyzed Friedel–Crafts acylations[14] and Nazarov cyclizations,[8] $LiClO_4$ was explored as an additive. However, when 1 equiv of $LiClO_4$ was used with either In^{3+} salt, very low conversion was observed. Thus, $In(OTf)_3$ at 5 mol % loading in dichloromethane at room temperature was chosen as the final protocol.

With optimized conditions for the cyclization in hand, a diverse set of heteroaryl substrates was examined to determine the reaction scope and limitations (Table 2). In direct comparison to the 2-thienyl cyclopropane **3a** which afforded **4a** in 86% yield (entry 1), the 3-thienyl substrate **3c** provided cyclohexanone **4c** in 73% yield (entry 3). In contrast, the 3-furanyl substrate **3d** (entry 4) provided its product **4d** in a higher yield (73% vs 67%) than that of 2-substituted counterpart **3b**[15] (entry 2). The 2-indolyl cyclopropane **3e** afforded the cyclized product **4e** in 63% yield (entry 5), and the 3-indole **3f** gave product **4f** in 91% yield (entry 7). Similarly, the 2-benzofuran **3g** cleanly cyclized to give **4g** in 61% yield (entry 6) and the 3-benzofuran **3h** afforded the desired product **4h** in 71% yield (entry 8). This is noteworthy because benzofuran had been unsuccessful as a homo-Nazarov substrate due to issues with competing polymerization.[10]

To date, only 2,3-ring-fused heteroaromatics had been synthesized using homo-Nazarov cyclizations. As an expansion of the scope of this reaction, we were interested in trying to synthesize 3,4-ring-fused compounds as well. We envisioned employing a 3-substituted substrate with the 2-position blocked, as in the 2-bromo thienyl cyclopropane **3i**. With the 2-position unavailable, the only site for electrophilic attack would be the 4-position. Thus, cyclization of **3i** should produce the 3,4-fused heteroaryl cyclohexanone **4i**. As anticipated, when subjected to the reaction conditions, **3i** generated the desired product **4i** in 56% yield (entry 9).

Next, other donor substituents about the cyclopropane were examined (Table 3). Phenyl derivatives **3j** and **3k** provided the desired ring-fused cyclohexanones **4j** and **4k** in 81% and 83% yield, respectively (entry 1).[16] When α-methyl styrene was used to generate cyclopropane **3l**, product **4l** was obtained in 71% yield (entry 3). Similarly, the indanyl substrate **3m** gave tetracycle **4m** in 87% yield (entry 4). Inspired by Yadav's report, silyl derivative **3n** was synthesized and cyclized to afford **4n** in 72% yield (entry 5). When the donor group on the cyclopropane was changed to an oxygen donor (as in **3p**, derived from dihydropyran), no cyclization was observed (entry 7). Even at higher catalyst loading or elevated temperatures,

Table 2. Heteroaromatic Homo-Nazarov Cyclizations[a]

entry	substrate	product	% yield[b]	dr (trans/cis)[c]
1	**3a**: X = S	**4a**: X = S	86%	1.5/1
2[d]	**3b**: X = O	**4b**: X = O	67%	1.1/1
3	**3c**: X = S	**4c**: X = S	73%	1.7/1
4	**3d**: X = O	**4d**: X = O	73%	1.1/1
5	**3e**: X = NMe	**4e**: X = NMe	63%	1.2/1
6	**3f**: X = O	**4f**: X = O	91%	1.4/1
7	**3g**: X = NMe	**4g**: X = NMe	61%	1.2/1
8	**3h**: X = O	**4h**: X = O	71%	1.2/1
9	**3i**	**4i**	56%	--[e]

[a] Reactions run with 1 equiv of substrate **3** and 5 mol % $In(OTf)_3$ in CH_2Cl_2 at 25 °C and complete within 6 h. [b] Isolated yields after column chromatography. [c] Diastereoselectivities as determined by crude ^1H NMR. [d] Reaction performed in 1,2-dichloroethane at 80 °C. [e] 2:1 Mixture of keto and enol forms.

only starting material was recovered. This lack of reactivity can be rationalized if no chelation event was occurring at the two carbonyls. To support this hypothesis, we looked at the lowest energy conformers of **3o** based on MMFF calculations.[17] In each of these conformers, the two carbonyl oxygens are *anti* to one another, thus eliminating the ability to generate the requisite six-membered chelate. Without this activation, cyclopropane ring-opening does not occur. Furthermore, this effect seems to arise from the stereoelectronic influence of the methyl ester on the conformation of the fused pyran ring.[18] This effect can arguably be seen in the ^1H NMR spectrum of **3o** where the hydrogen at the fused ring junction adjacent to the oxygen is located at 6.5 ppm, which represents a ~3 ppm downfield shift from the analogous pyranyl derivative without the ester.[9,19] This downfield shift suggests the strong influence of the electron-withdrawing ester on the conformation of the fused ring. This hypothesis was further supported when the acyclic ether **3p** (derived from ethyl vinyl ether) was subjected to the standard reaction conditions and the substituted benzothiophene **5** was obtained in 51% yield (entry 8). This product

(14) (a) Chapman, C. J.; Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Tetrahedron Lett.* **2001**, *42*, 773. (b) Kawada, A.; Mitamura, S.; Kobayashi, S. *Chem. Commun.* **1996**, 183. (c) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* **1995**, *36*, 409.

(15) The 2-furanyl derivative **3c** readily cyclized at room temperature, but the yields (~28%) were fairly low due to byproduct formation. To circumvent this issue, **3c** was refluxed in DCE. No byproduct formation was observed.

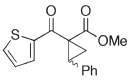
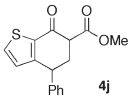
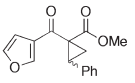
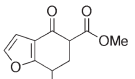
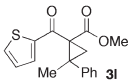
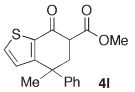
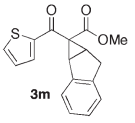
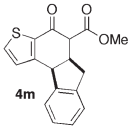
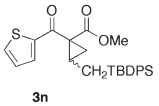
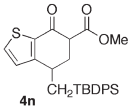
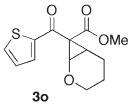
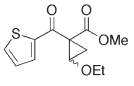
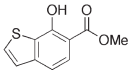
(16) We have observed that heating is required to achieve efficient cyclization for phenyl rings without substitution and those substituted with electron-withrawing groups.

(17) MMFF calculations were run using Trident software available from Wave function, Inc.

(18) It has been previously shown that cyclization readily occurs for the analogous pyran derivative without the methyl ester (see ref 9).

(19) See Supporting Information.

Table 3. Effects of Cyclopropyl Substituents[a]

entry	substrate	product	% yield[b]	dr (trans/cis)[c]
1[d]	 **3j**	 **4j**	81%	2.3/1
2[d]	 **3k**	 **4k**	83%	1.2/1
3	 **3l**	 **4l**	71%	2/1
4	 **3m**	 **4m**	87%	--[e]
5	 **3n**	 **4n**	72%	2.4/1
6	 **3o**	no reaction	--	--
7	 **3p**	 **5**	51%	--

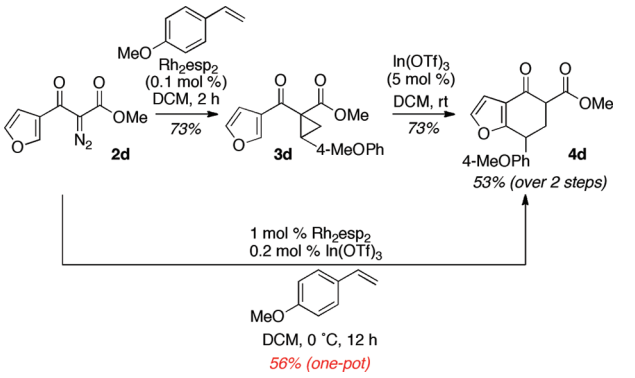
[a] Reactions run with 1 equiv of substrate **3** and 5 mol % $In(OTf)_3$ in CH_2Cl_2 at 25 °C and complete within 6 h. [b] Isolated yields after column chromatography. [c] Diastereoselectivities as determined by crude ^1H NMR. [d] Reaction performed in 1,2-dichloroethane at 80 °C. [e] Only one diastereomer visible by ^1H NMR.

seemingly arises from a rapid aromatization of the transient homo-Nazarov cyclization product through an indium-promoted elimination of EtOH.

Given that both the cyclopropanation and homo-Nazarov cyclization steps readily occurred in dichloromethane at room temperature, we envisioned the development of a one-pot procedure that would occur in the presence of both the rhodium (for cyclopropanation) and indium (for cyclization) catalysts (Scheme 3). To test the feasibility of this procedure, two key control reactions were conducted. First, the stability of α-diazoester **2d** in the presence of $In(OTf)_3$ (5 mol %) was established by monitoring a stirring mixture of the two components. Next, the stability of the alkene (4-methoxy styrene) was examined in the presence of both Rh_2esp_2 and $In(OTf)_3$. To achieve an active indium catalyst loading of ~20 mol %, 1 mol % of Rh_2esp_2 and 0.2 mol % of $In(OTf)_3$ in dichloromethane at 0 °C were employed as the initial reaction conditions. We were pleased to find that subjecting α-diazoester **2d** to these conditions provided the desired ring-fused cyclohexanone **4d** in 56% yield, which is higher than the yield for the two-step process and equates to an average of about 75% yield for each individual step.

(20) Preliminary studies have shown some transfer of chirality upon cyclization which suggests some degree of intimate ion pairing.

Scheme 3. Tandem Cyclopropanation/Homo-Nazarov Cyclization



In summary, a general protocol for the heteroaromatic homo-Nazarov cyclization has been reported. Further studies are underway to expand this method to other heteroaromatics, such as pyrrole and pyridine. Other activities include optimization and generalization of both the one-pot reaction as well as the aromatization reaction. Reactions examining the transfer of absolute chirality during the cyclization of a chiral cyclopropane are being conducted.[20] 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.