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Nazarov Reactions of Vinyl Cyclopropylamines: An Approach to the Imino-Nazarov Problem

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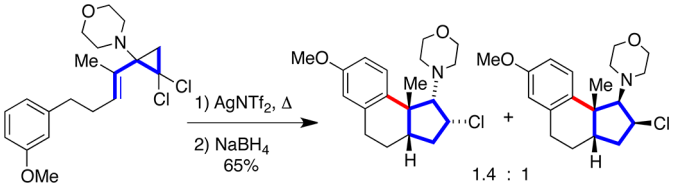
ABSTRACT



Dichlorocyclopropanation of 2-amino-1,3-dienes affords 1-alkenyl-1-amino-2,2-dichlorocyclopropanes which undergo silver-assisted 2-π electrocyclic opening to furnish 3-aminopentadienyl cations. Nazarov-type cyclization of these intermediates leads to cyclopentenone iminium salts, which provide allylic amines upon reduction. This process, the imino version of the traditional Nazarov reaction, can also be combined with an interrupted Nazarov domino process to give polycyclic amines.

In its traditional form, the Nazarov reaction entails the electrophilic activation of a cross-conjugated dienone and the electrocyclic closure of the resulting 3-oxygenated pentadienyl cation.[1] The resulting cyclopentenyl cation can undergo elimination to furnish a cyclopentenone or can be trapped with various functionalities to generate additional strategic bonds.[2] In contrast to these examples, there are relatively few cases of the analogous process employing a nitrogen in place of oxygen, termed the imino-Nazarov reaction (Scheme 1). The lack of general methods for the construction of the required divinyl imines, especially those with non-hydrogen substituents at C-2 and C-4, is one likely reason for the dearth of examples. Moreover, calculations by Smith and Ulmer have suggested that replacement of oxygen with nitrogen has a deleterious effect on the energetics of the process due to resonance stabilization of the 3-aminopentadienyl cation precursor to electrocyclization[3] (though it should be noted that these calculations were for the unsubstituted example).

Several successful approaches to the imino-Nazarov reaction have been described. Tius and co-workers reported the formation of 2-aminocyclopent-2-enones from the addition of an allenyllithium reagent to an unsaturated nitrile, presumably via an allenyl vinyl imine.[4a] González and co-workers obtained *N*-tosylcyclopentenone imines from treatment of propargyl tosylates with catalytic gold(I) and a tosyl imine and proposed an *N*-tosyldivinyl imine as the precursor.[4b] More recently, gold(I) was also used as a catalyst in the imino-Nazarov reaction of α-arylallenamides.[4c] The Tius group was able to effect Nazarov cyclization of enediones via activation by an enantioenriched diamine, with the likely involvement of a

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(1) (a) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *ChemCatChem* **2011**, *3*, 1. (b) Shimada, V.; Stewart, C.; Tius, M. A. *Tetrahedron* **2011**, *67*, 5851. (c) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discovery Dev.* **2009**, 12. (d) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676. (e) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (f) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (g) Habermas, K. L.; Denmark, S.; Jones, T. K. *Org. React.* **1994**, *45*, 1.

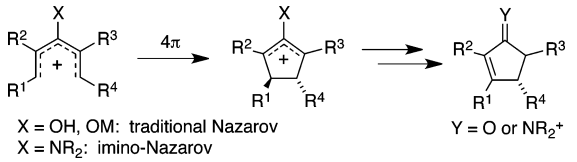
(2) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676–5688.

(3) Smith, D. A.; Ulmer, C. W., II. *J. Org. Chem.* **1997**, *62*, 5110–5115.

(4) (a) Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. *Tetrahedron Lett.* **2001**, *42*, 2419–2422. (b) Suárez-Pantiga, S.; Rubio, E.; Alvarez-Rúa, C.; González, J. M. *Org. Lett.* **2009**, *11*, 13–16. (c) Ma, Z.-X.; He, S.; Song, W.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 5736–5739. (d) Bow, W. F.; Basak, A. K.; Jolit, A.; Vicic, D. A.; Tius, M. A. *Org. Lett.* **2010**, *12*, 440–443.

10.1021/ol4012663

Scheme 1. Nazarov and Imino-Nazarov Cyclization



divinyl iminium salt.[4d] In each of these examples, a unique structural feature can be invoked to explain successful cyclization. The involvement of allenes in the Nazarov cyclization is thought to provide additional conjugative stabilization of the cyclized product,[5] and in those cases a subsequent irreversible loss of a MOM group occurred, preventing back-reaction.[4a] The *N*-tosyl imines in the gold(I)-catalyzed examples are likely to have greatly reduced ability to stabilize the acyclic pentadienyl cation. Finally, the diamine adducts of enediones possess a 2,3-dinitrogen substitution on the pentadienyl framework, leading to resonance stabilization by one of the nitrogen atoms in both cyclized and uncyclized forms.

We have previously shown that 1-alkenyl-2,2-dichloro-1-siloxycyclopropanes serve as unconventional Nazarov substrates; these structures undergo sequential silver-assisted dehalogenative electrocyclic opening of the cyclopropane followed by 4π electrocyclization of the resulting 3-siloxypentadienyl cation (Scheme 2).[6] We speculated that a similar approach in which an amine was substituted for the siloxy group could provide direct access to 3-aminopentadienyl cations bearing a variety of substituents, allowing us to probe the generality of the imino-Nazarov reaction in the absence of the structural quirks that may have biased the previous examples. Here we describe the preparation of a series of aminocyclopropane substrates and their successful conversion to amine-substituted cyclopentanoid products via an imino-Nazarov process.

The requisite cyclopropanes could be obtained from the corresponding 2-dialkylamino-1,3-butadienes by standard dichlorocyclopropanation chemistry. We employed an aminomercuration/demercuration strategy with conjugated enynes,[7,8] modified by use of mercury(II) fluoride in place of mercury(II) acetate, and at elevated temperatures (Table 1).[9] The resulting dienes were found to be very labile, requiring immediate use in the subsequent cyclopropanation step without subjection to purification in most cases. The latter reaction was carried out under

Scheme 2. Dichlorocyclopropane Nazarov Substrates

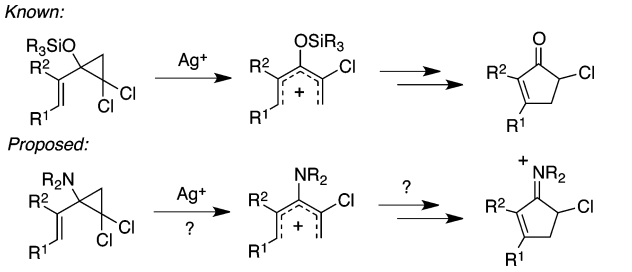
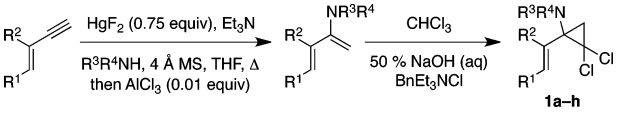


Table 1. Preparation of Aminocyclopropane Substrates[a]



entry	R^1	R^2	R^3	R^4	product	yield (%)[b]
1	Ph	Me	Bn	Me	**1a**	42
2	Ph	Me	$C_2H_4OC_2H_4$		**1b**	46
3	Ph	Me	Ph	Me	**1c**	14
4	H	Me	$C_2H_4OC_2H_4$		**1d**	34
5	$(CH_2)_4$		$C_2H_4OC_2H_4$		**1e**	44
6[c]	$Ar^1(CH_2)_2$	Me	$C_2H_4OC_2H_4$		**1f**	38
7[c]	$Ar^1(CH_2)_2$	Me	Bn	Me	**1g**	37
8[c]	$Ar^2(CH_2)_2$	Me	$C_2H_4OC_2H_4$		**1h**	26

[a] See Supporting Information for detailed procedures. [b] Overall yields for two steps, given for isolated **1** after chromatographic purification. Yields are unoptimized. [c] Ar^1 = 3-$MeOC_6H_4$; Ar^2 = 4-$MeOC_6H_4$.

standard phase-transfer conditions.[10] Complications associated with the aminodienes undoubtedly contributed to the modest two-step yields obtained in this process. However, this deficiency was mitigated by the simplicity of the reactants (simple enynes, secondary amines, and chloroform).

With substrates **1a**–**h** in hand, we were now ready to test the key question: will the 3-aminopentadienyl cations generated from these cyclopropane precursors undergo Nazarov cyclization despite the ground-state stabilization afforded by the 3-amino substituent? Using **1a** as a test case, we subjected it to 1 equiv of $AgNTf_2$ in acetonitrile at reflux (Scheme 3). The starting material was consumed after several hours, and two new polar products were formed, identified as the two iminium ion geometrical isomers **2a** and **2a′** resulting from imino-Nazarov cyclization and elimination. Although the isomers were inseparable, it was possible to assign related protons and carbons from each isomer in the NMR spectra, whose chemical

(5) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 1695–1689.

(6) (a) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348–9349. (b) Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789–3792.

(7) (a) Barluenga, J.; Aznar, F.; Liz, R.; Cabal, M.-P. *J. Chem. Soc., Chem. Commun.* **1985**, 1375–1376. (b) Barluenga, J.; Aznar, F.; Valdés, C.; Cabal, M.-P. *J. Org. Chem.* **1991**, *56*, 6166–6171.

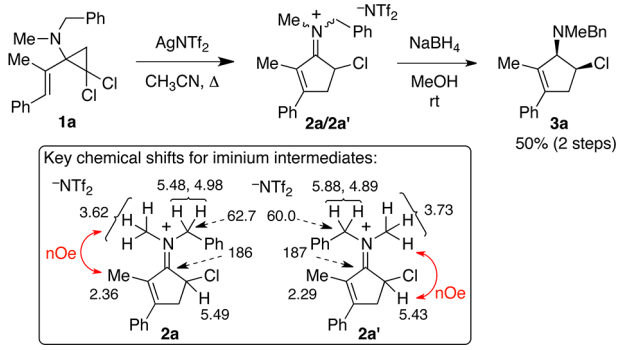
(8) Buchwald–Hartwig-type amination of 2-chlorodienes has also been reported, though not with nonhydrogen substituents at C-3: Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem. Commun.* **2004**, 1400–1401.

(9) Catalytic amounts of $AlCl_3$ were added to promote redistribution of mercury ligands: Calingaert, G.; Soroos, H.; Hnizda, V. *J. Am. Chem. Soc.* **1940**, *62*, 1107–1110.

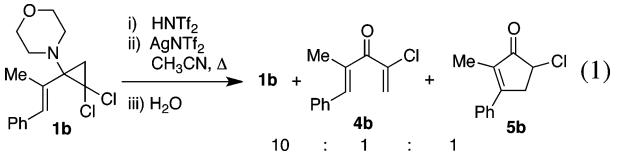
(10) (a) Makosza, M.; Wawrzyniewicz, M. *Tetrahedron Lett.* **1969**, 4659–4662. (b) Futugawa, T.; Mishiyama, N.; Tai, A.; Okuyama, T.; Sugimura, T. *Tetrahedron* **2002**, *58*, 9279–9287.

shifts were quite consistent with those reported for a related unsaturated iminium salt.[11] To simplify the isolation and characterization of the cyclization products, we explored the use of a subsequent reduction step to afford the neutral amines. On treatment with $NaBH_4$, iminium salts **2a**/**2a′** were cleanly converted to amino chlorocyclopentene **3a** with complete diastereoselectivity, and in 50% yield over two steps.[12]

Scheme 3. Preliminary Imino-Nazarov Experiment

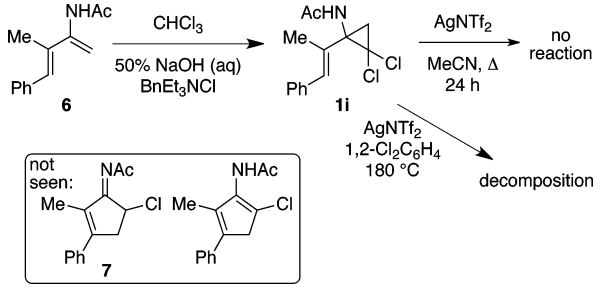


This two-step protocol was applied to the other simple substrates (**1b**–**e**), affording cyclopentenes **3b**–**e** in moderate yields (Table 2). In some cases, complete consumption of starting material was not possible, leading to diminished yields (entries 4 and 5). This may be a result of substrate deactivation via amine protonation by $HNTf_2$ inadvertently formed during the reaction. Evidence for this can be seen from the isolation of mostly starting **1b** upon its treatment with 1 equiv of $HNTf_2$, followed by extended heating with $AgNTf_2$ and aqueous workup (eq 1). Only small amounts of dienone **4b** and cyclopentenone **5b** were isolated, these products coming presumably from hydrolysis of the aminopentadienyl cation and the cyclized iminium salt, respectively. From this, we infer that the presence of a Brønsted acid suppresses the opening of the cyclopropane. When this experiment was carried out in the presence of the hindered base 2,4,6-tri-*tert*-butylpyridine, **1b** was rapidly consumed, though with no apparent conversion to Nazarov cyclization products.



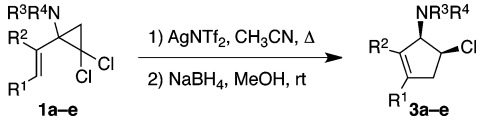
The effect of electron availability on nitrogen was also probed using acetamide **1i**, which was prepared via dichlorocyclopropanation of 2-acetamido diene **6** (Scheme 4).[13] Successful Nazarov cyclization in this case would afford unsaturated *N*-acylimine **7** or its enamide tautomer, either of which could be applied to a variety of subsequent transformations. However, in the event **1i** proved to be inert to the standard conditions, and when the temperature was increased to 180 °C, an intractable mixture was obtained. Given this result and the previously noted effect of the added Brønsted acid, it appears that an electron-rich amino group is required in the initial electrocyclic opening of the cyclopropane.

Scheme 4. Acetamidocyclopropane



Finally, substrates **1f**–**h** bearing pendent aryl groups were examined (Scheme 5). We were gratified to find that morpholino substrate **1f** underwent an efficient imino-Nazarov reaction with subsequent arene trapping, affording after borohydride reduction the two diastereomeric chloroamines **8f** and **8f′**. The mixture of isomers results from unselective protonation of the intermediate

Table 2. Combined Imino-Nazarov/Reduction[a]



entry	substrate	R^1	R^2	R^3	R^4	yield **3** (%)[b]
1	**1a**	Ph	Me	Bn	Me	50
2	**1b**	Ph	Me	$(CH_2)_2O(CH_2)_2$		50
3	**1c**	Ph	Me	Ph	Me	48
4	**1d**	H	Me	$(CH_2)_2O(CH_2)_2$		22
5[c]	**1e**	$(CH_2)_4$		$(CH_2)_2O(CH_2)_2$		12

[a] See Supporting Information for detailed procedures. Reaction time varied from 2–8.5 h. [b] Overall yields for two steps, given for isolated **3** after chromatographic purification. [c] Reaction time = 10 min.

(11) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335–7347.

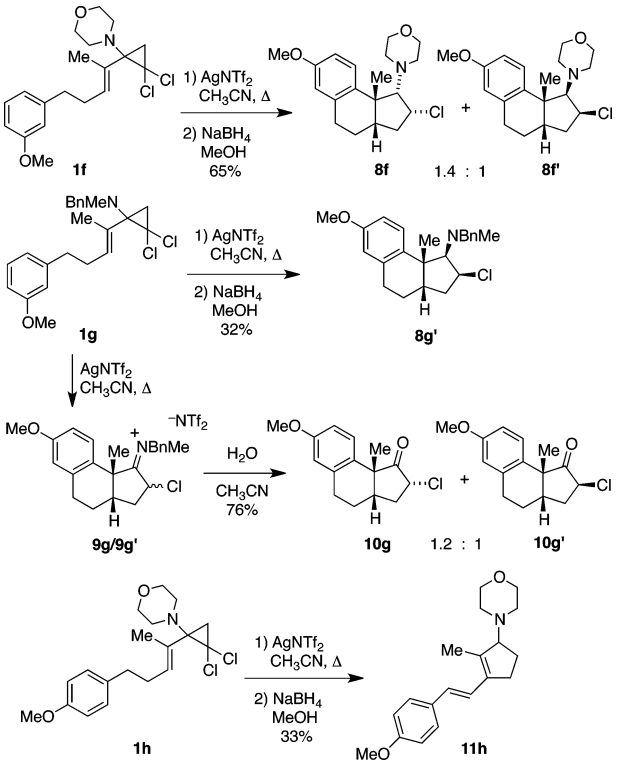
(12) The *syn* relative configuration assigned to **3a** and analogous products in Table 2 derives from selective attack by hydride from the sterically more accessible face and is supported by the observation of vicinal coupling constants in the range of 7.1–7.5 Hz.

(13) Diene **6** was prepared from the corresponding enone: Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084–6085.

(14) Assignment of the relative stereochemistry for **8f** was based on TROESY correlations, while **8f′** was assigned by single crystal X-ray diffraction analysis. See Supporting Information for more details.

(15) (a) Kádár, Z.; Molnár, J.; Schneider, G.; Zupkó, I.; Frank, E. *Bioorg. Med. Chem.* **2112**, *20*, 1396–1402. (b) Bruno, R. D.; Vasaitis, T. S.; Gediya, L. K.; Purushottamachar, P.; Godbole, A. M.; Ates-Alagoz, Z.; Brodie, A. M. H.; Njar, V. C. O. *Steroids* **2011**, *76*, 1268–1279. (c) Vidma, L.; Cerny, I.; Pouzar, V.; Borovská, J.; Vyklicky, V.; Vyklicky, L., Jr.; Chodounská, H. *Steroids* **2011**, *76*, 1043–1050.

Scheme 5. Interrupted Imino-Nazarov Reactions



chloroenamine, followed by selective hydride delivery from the side opposite the chloride in each case.[14] Steroid derivatives bearing nitrogen functionality on the D-ring have shown a variety of promising biological properties,[15] including antiproliferative and antitumor activity,[15a,b] as well as inhibition of the glutamate-induced response of NMDA receptors,[15c] and these products may display similar activities. Surprisingly, *N*-benzyl-*N*-methyl analogue **1g** furnished only one of the cyclized products **8g′** in moderate yield. However, analysis of the crude mixture indicated that two diastereomers were present prior to chromatographic purification in an apparent ratio of 1.2:1, suggesting selective destruction of the major isomer during purification. If the cyclization step was followed by hydrolysis rather than reduction, chlorocyclopentanones **10g** and **10g′** were obtained in good yields and as a 1.2:1 mixture. Substrate **1h**, bearing an isomeric 4-methoxyphenyl trap, underwent Nazarov cyclization, but the subsequent arene trapping did not occur.[16] Instead, an unexpected dehydrohalogenation product **11h** was obtained in moderate yield. The mechanism by which this unusual product was formed is under study.

Silver-assisted electrocyclic opening of 1-amino-1-alkenyl-2,2-dichlorocyclopropanes provides a convenient route to the 3-aminopentadienyl cations required for imino-Nazarov cyclization. Despite concerns about the unfavorability of this electrocyclization due to preferential stabilization of the open pentadienyl form, these substrates underwent cyclization to give unsaturated iminium salts, which could then be stereoselectively reduced with borohydride. Nitrogen deactivation by protonation or acyl substitution severely inhibits the reaction, and pendent 3-methoxyphenyl groups permit a domino process that affords tricyclic products. Further applications of this new chemistry, including substitution of the amino group with trapping functionality or stereogenic centers, are under current study.

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Supporting Information Available. Experimental procedures for preparation, and characterization data for the substrates and products, including X-ray crystallographic data for **8f′**. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Similar reactivity issues based upon arene substitution have been observed in the interrupted Nazarov cyclizations of the related 1,1-dichloro-2-siloxy-2-vinylcyclopropanes. See ref 6b.

The authors declare no competing financial interest.