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Interrupted Nazarov Reactions Using Dichlorocyclopropanes: A Novel Mode of Arene Trapping

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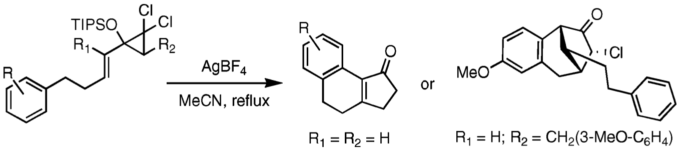
ABSTRACT



2-Siloxy-2-alkenyl-1,1-dichlorocyclopropanes with aryl-terminated side chains undergo silver-assisted electrocyclic opening/Nazarov cyclization. The resulting 2-siloxycyclopentenyl cations are intercepted by the pendant arenes to furnish tricyclic adducts in moderate to good yields. In cases where the arene trap was tethered through the cyclopropane unit, a new mode of trapping occurred to generate unique bridged carbon frameworks.

Tandem and domino-type reactions have found considerable utility in organic synthesis,[1] due to their potential formation of multiple carbon−carbon bonds and generation of multiple stereogenic centers in a single transformation. The Nazarov cyclization[2] can be used to initiate domino reactions involving capture by nucleophiles or 1,3-dienes of the 2-oxidocyclopentenyl cation resulting from electrocyclization. The “interrupted” Nazarov reaction can involve trapping of the oxyallyl cation in an intra-[3] or intermolecular[4] fashion, allowing the construction of complex ring systems from surprisingly simple starting materials.

Typically, the Nazarov cyclization is effected by treatment of a cross-conjugated dienone with stoichiometric Lewis acid.[5] We recently described an alternative route to the pentadienyl cationic intermediate starting from appropriately substituted *gem*-dichlorocyclopropane compounds, **1** (Scheme 1).[6] Silver(I)-mediated disrotatory ring opening furnishes pentadienyl cations, which then undergo the usual conrotatory electrocyclization and eliminative termination to give chlorocyclopentenones **2** and/or **3** analogous to those seen under more traditional conditions. During these initial studies, we observed that a substrate **1a** with a remote phenyl substituent surprisingly underwent intramolecular electrophilic aromatic substitution following electrocyclization to provide benzohydrindenone **4a**. Arene trapping in the Nazarov reaction using dienone substrates was known,[3b] but this result was

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[1] (a) Poli, G.; Gimabastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959−5989. (b) Padwa, A. *Pure Appl. Chem.* **2003**, *75*, 47−62. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551−564. (d) Tietze, L. F. *Domino Reactions in Organic Synthesis*; John Wiley: New York, 2006.

[2] Recent reviews: (a) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193−2206. (b) Pellisier, H. *Tetrahedron* **2005**, *61*, 6479−6517. (c) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577−7606.

[3] Recent examples: (a) Nair, V.; Bindu, S.; Sreekumar, V.; Chiaroni, A. *Org. Lett.* **2002**, *4*, 2821−2823. (b) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375−385. (c) Giese, S.; Mazzola, R. D., Jr.; Amann, C. M.; Arif, A. M.; West, F. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 6545−6549. (d) Rostami, A.; Wang, Y.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703−706.

[4] Recent examples: (a) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747. (b) Yungai, A.; West, F. G. *Tetrahedron Lett.* **2004**, *45*, 5445. (c) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629. (d) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472. (e) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312.

[5] Catalytic versions of the Nazarov reaction have recently been developed: (a) He, W.; Sun, X. F.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278−14279. (b) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927−4930. (c) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075−5078. (d) Liang, G. X.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544−9545. (e) Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R *J. Am. Chem. Soc.* **2004**, *126*, 6864−6865. (f) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661−5664.

[6] Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348−9349.

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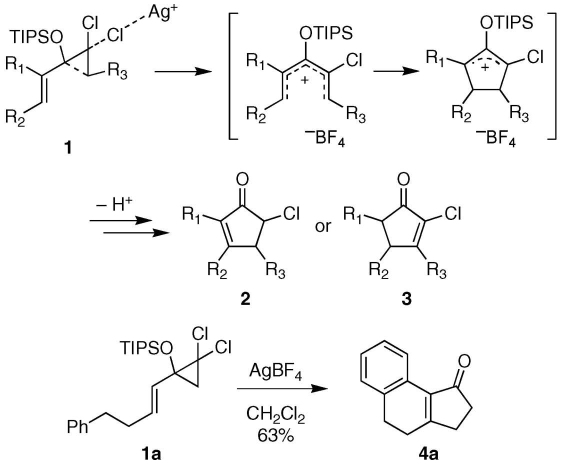
Scheme 1. Ring Opening/Ring Closure Sequence with *gem*-Dichlorocyclopropanes



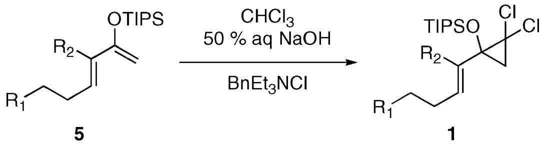
notable for the participation of an unactivated phenyl group under mild reaction conditions; previous examples had been limited to electron-rich arenes. Here we describe a preliminary study of this intriguing chemistry, in which simple siloxydienes with a variety of pendent aryl groups are converted in good yields via a two-step sequence to complex fused or bridged bicyclic products.

A number of substrates were synthesized to examine the effects of aromatic substitution, as well as the substitution pattern of the vinylcyclopropane precursor. The required siloxydiene substrates could be easily prepared by exhaustive reduction of the corresponding hydrocinnamic acids, followed by a one-pot Swern oxidation/Wittig olefination reaction[7] to provide the desired α,β-unsaturated ketones in moderate to good yield. The ketones were cleanly converted to the 2-triisopropylsiloxy dienes, **5a**−**i**, under standard conditions using triethylamine and triisopropylsilyl trifluoromethanesulfonate (see the Supporting Information).

Dichlorocyclopropanation of 2-triisopropylsiloxy dienes can be carried out under phase transfer catalysis conditions[6,8] in order to install the *gem*-dichlorocyclopropane moiety with complete regioselectivity (Table 1). Notably, the cyclopropanation of the 2-furyl-substituted compound (entry 7) could be accomplished in good yield after a very brief reaction time and without any evidence of over-cyclopropanation on the furan.

With the *gem*-dichlorocyclopropane substrates **1a**−**i** in hand, we could examine the tandem electrocyclic opening/electrocyclic closure/electrophilic aromatic substitution process. Unfortunately, application of the optimized conditions from the original study (1.5 equiv of $AgBF_4$, CH_2Cl_2, rt) to substrates **1b** and **1c** led to a complex mixture of inseparable products. Replacement of CH_2Cl_2 with the more polar CF_3CH_2OH failed to improve the outcome.[9]

Table 1. *gem*-Dichlorocyclopropanation of Siloxydienes[a]



entry	substrate	R1	R2	time (min)	product	yield (%)[b]
1	**5a**	Ph	H	30	**1a**	87
2	**5b**	3-MeO-Ph	H	30	**1b**	75
3	**5c**	4-MeO-Ph	H	20	**1c**	79
4	**5d**	2-Me-Ph	H	30	**1d**	71
5	**5e**	2-Br-Ph	H	40	**1e**	85
6	**5f**	4-TIPSO-Ph	H	45	**1f**	70
7	**5g**	2-furyl	H	7	**1g**	86
8	**5h**	Ph	Me	45	**1h**	91
9	**5i**	3-MeO-Ph	Me	75	**1i**	88

[a] Silyloxydienes **5** were dissolved in $CHCl_3$ (0.12M) and benzyltriethylammonium chloride (0.3 equiv) was subsequently added. To this solution was added 50% NaOH aq (190 equiv). The reaction was allowed to stir vigorously at room temperature and was monitored (TLC) for the disappearance of starting material. [b] Yields given are for isolated product after purification.

Ring-opening reactions of *gem*-dichlorocyclopropanes under strictly thermal conditions are known, leading to dichloroalkene products.[10] With this in mind, we examined higher temperatures together with halophilic silver(I) to sequester free chloride anions in the reaction mixture. We were gratified to find that treatment of **1b** and **1c** with 1 equiv of $AgBF_4$ in MeCN at reflux led to the production of tricyclic products **4b** and **4c** in 53% and 76%, respectively. These conditions were subsequently applied to the remaining substrates, including **1a** (Table 2).

Remarkably, an electron-poor aromatic ring (entry 5) can participate in this reaction, generating the desired tricyclic product, **4e**, albeit in a decreased yield of 48%. A silyl-protected phenol was also found to trap the cationic Nazarov intermediate to provide **4f**; however, the yield of this reaction was reduced and the reaction time required for complete conversion of starting material was substantially increased. Premature loss of the labile phenolic protecting group may have some detrimental effect upon the yield of this reaction, suggesting further investigation into the use of more robust protecting groups on these substrates (note the good yield obtained for methoxy counterpart **4c**, entry 3). In all of these cases (entries 1−6), the tricyclic products **4** had suffered dehydrochlorination, and possessed a ring-fusing alkene adjacent to the arene and the ketone.

Attempts to involve a furan moiety in the interrupted Nazarov reaction were unsuccessful (entry 7), leading to

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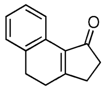
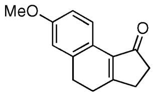
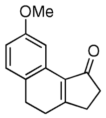
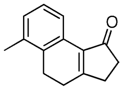
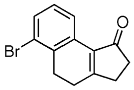
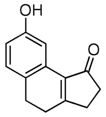
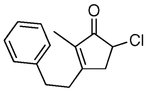
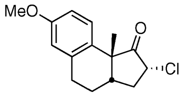
(7) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198−2200.

(8) (a) Makosza, M.; Wawryniewicz, M. *Tetrahedron Lett.* **1969**, 4659−4662. (b) Futugawa, T.; Nishiyama, N.; Tai, A.; Okuyama, T.; Sugimura, T. *Tetrahedron* **2002**, *58*, 9279−9287.

(9) CF_3CH_2OH has found some utility in the silver(I)-mediated Nazarov reaction, although its effectiveness was determined to be very substrate specific.

(10) (a) Kostikov, R. R.; Molchanov, A. P.; Hopf, H. Small Ring Compounds in Organic Synthesis. *Top. Curr. Chem.* **1990**, *155*, 41−80. (b) Banwell, M. G.; Reum, M. E. In *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press: Greenwich, CT, 1991; Vol. 1, pp 19−64. (c) Fedorynski, M. *Chem. Rev.* **2003**, *103*, 1099−1132.

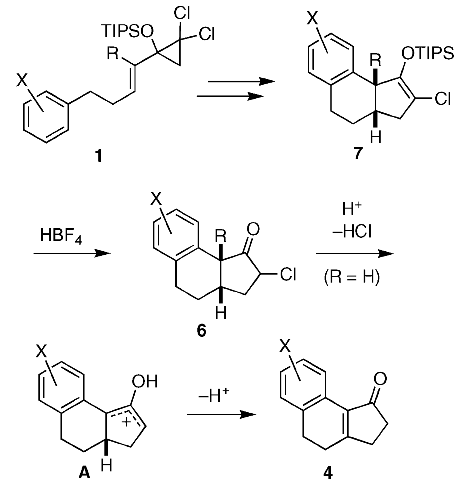
Table 2. Silver(I)-Mediated Interrupted Nazarov Reactions[a]

entry	substrate	product		yield (%)[b]
1	**1a**		**4a**	80
2	**1b**		**4b**	53
3	**1c**		**4c**	76
4	**1d**		**4d**	79
5	**1e**		**4e**	48
6	**1f**		**4f**	39
7	**1g**	Decomposition of S.M.		n/a
8	**1h**		**2h**	97[c]
9	**1i**		**6i**	89

[a] *gem*-Dichlorocyclopropanes **1** were dissolved in freshly distilled MeCN (0.05M) and stirred with $AgBF_4$ (1 equiv) at reflux. The reactions were monitored (TLC) for complete consumption of starting material (6−48 h). [b] Yields given are for isolated product after purification. [c] None of the tricyclic product was observed, even after prolonged reaction time.

rapid consumption of starting material with no discernible formation of the desired tricyclic product. A likely explanation for this is the instability of the furyl moiety in the presence of the HBF_4 that is generated during this process.[11] Finally, the effect of substitution at the α-position of the vinyl substituent was investigated. When a methyl substituent was added to the substrate with a pendant phenyl trap, only the product of the simple Nazarov reaction, **2h**, was isolated in excellent yield (entry 8). However, when the more nucleophilic 3-methoxyphenyl moiety was employed on a similar substrate (entry 9) the desired tricyclic product, **6i**, was isolated in very good yield. The relative stereochemistry of this product was confirmed by single-crystal X-ray crystallography. Retention of the chloro-substituent in **6i** suggests that a dehydrohalogenation process leading to benzohydrindenones **4a**−**f** requires the presence of a hydrogen atom at the bridgehead position of the initial tricyclic product, **6** (Scheme 2).

Scheme 2. Proposed Mechanism of Arene Trapping and Elimination



Product formation is presumed to involve silver-assisted opening of the dichlorocyclopropane and 4π electrocyclization of the resulting pentadienyl cation as in Scheme 1. Once the cyclopentenyl cation is formed, electrophilic aromatic substitution and rearomatization can proceed to give cyclization products **7**, which may suffer HBF_4-mediated desilylation under the reaction conditions to furnish α-chlorocyclopentanones **6**. In the absence of substitution at the α-position of the vinyl substituent, **6** can then undergo elimination of HCl to provide the cyclopentenones **4**. Notably, since methyl-substituted product **6i** does not undergo this process, we surmise that the elimination may proceed via a second oxyallyl cation (**A**), followed by elimination with the Zaitsev selectivity typically seen in the simple Nazarov reaction.[12]

In light of the possible intermediacy of a second cyclopentenyl cation, we envisaged a substrate with *two* pendent aryl groups capable of undergoing sequential trapping reactions. Substituted vinylcyclopropane **8a** was synthesized via Horner−Wadsworth−Emmons olefination[13] followed by formation of the triisopropylsiloxy diene using the previously outlined method (Scheme 3). Silyloxy diene **8a** was then subjected to phase transfer cyclopropanation conditions to generate the *gem*-dichlorocyclopropane intermediate **9a**. This more substituted cyclopropane substrate was found to be very sensitive to decomposition during attempted chromatographic purification (silica or alumina), and was submitted directly to $AgBF_4$ in refluxing MeCN without isolation. Under these

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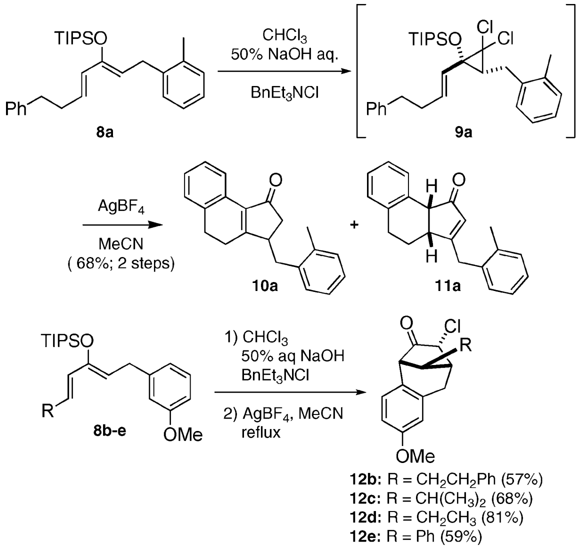
(11) Control experiments show that the enone precursor to diene **5g** is destructively consumed in the presence of HBF_4.

(12) Harmata has observed cyclopentenone elimination byproducts from the dehydrochlorination of chlorocyclopentanones during intramolecular [4+3]-cycloaddition reactions: Harmata, M.; Elomari, S.; Barnes, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 2860−2871.

(13) Mitoshi, K.; Nakae, T.; Sakuyama, S.; Nishizaki, M.; Odagaki, Y.; Nakai, H.; Hamanaka, N. *Bioorg. Med. Chem.* **1997**, *5*, 1621−1647.

Scheme 3. A New Mode of Arene Trapping in the Interrupted Nazarov Reaction



conditions, **9a** was converted to benzohydrindenones **10a** and **11a** in a 2.7:1 ratio and a combined yield of 68% (2 steps). This result suggested that the nucleophilicity of the second arene moiety was insufficient to trap the putative intermediate carbocationic species. Bearing this in mind, we next prepared **8b** with a more electron-rich arene appended to the cyclopropane ring. After cyclopropanation and direct treatment with $AgBF_4$, we were surprised to observe clean conversion to the unexpected bridged bicyclic compound **12b** in 57% yield (Scheme 3).

Generation of **12b** appears to be the result of trapping of the initial cyclopentenyl cation by the more electron-rich arene unit, with complete regioselectivity in favor of 6-membered ring-closure on the unchlorinated terminus. The bridged architecture precludes elimination of HCl to generate a second cyclopentenyl cation in this case. To our knowledge, this trapping process is without precedent. To explore its generality, substrates **8c**−**e** were synthesized and the two-step cyclopropanation/silver(I)-mediated Nazarov procedure was applied. All three substrates were cleanly converted to bridged bicyclic products **12c**−**e**, respectively, in moderate to good yield over the two-step sequence. The silver(I)-mediated Nazarov reaction appears to proceed stereoselectively in each case, providing a single product as a result of conrotatory 4π electrocyclization, electrophilic aromatic substitution at the least hindered position on the aromatic ring (*para* to the MeO), and subsequent protiodesilylation from the *exo* face. The relative stereochemistry of these products was confirmed by single-crystal X-ray crystallography of **12d** and **12e**. Remarkably, the selectivity is also observed when the silyl enol ether portion of the diene exists as a mixture of *E*/*Z* isomers (**8d**, *E*:*Z* = 1:6.5). This observation suggests that under the reaction conditions the more substituted double bond experiences *E*/*Z* isomerization upon ring opening of the *gem*-dichlorocyclopropane, and equilibrates to the more stable *E*-isomer prior to 4π electrocyclization.[14] The unique carbon framework that is generated as a result of this reaction is inherent in the *Galbulimima belgraveana* family of alkaloids.[15] This novel mode of trapping offers a potential strategy toward advanced intermediates needed for the synthesis of these natural products.

In summary, we have found that *gem*-dichlorocyclopropane compounds undergo efficient interrupted Nazarov reaction with arene traps. Under these conditions, electron-rich, neutral, and electron-poor aromatic moieties can intercept the intermediate oxyallyl cationic species, providing an expedient route to benzohydrindenone skeletons. We have also developed a new mode of trapping using electron-rich aromatic rings tethered through the cyclopropane moiety. This new trapping pathway provides a stereoselective route to adducts possessing unique bridged bicyclic skeletons. Additional studies of the halocyclopropane-mediated Nazarov reaction involving other trapping modes are currently underway, and will be disclosed in due course.

Acknowledgment. We thank NSERC for support of this work, and T.N.G. gratefully acknowledges NSERC for a PGSD studentship and the University of Alberta for a Queen Elizabeth II scholarship. We also thank Dr. Bob McDonald and Dr. Michael Ferguson (X-ray Crystallography Lab, Department of Chemistry, University of Alberta) for the crystal structure determination of compounds **6i**, **12d**, and **12e**.

Supporting Information Available: Experimental procedures, physical data, and NMR spectra for all compounds and synthetic intermediates as well as CIF data for **6i**, **12d**, and **12e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) This phenomenon has previously been observed: (a) Denmark, S. E.; Wallace, M. A.; Walker, C. B. *J. Org. Chem.* **1990**, *55*, 5543−5545. (b) Giese, S.; West, F. G. *Tetrahedron Lett.* **1998**, *44*, 4043−4060. (c) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221−10228.

(15) Mander, L. N.; Wells, A. P. *Tetrahedron Lett.* **1997**, *38*, 5709−5712.