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Formation of halogenated cyclopent-2-enone derivatives by interrupted Nazarov cyclizations

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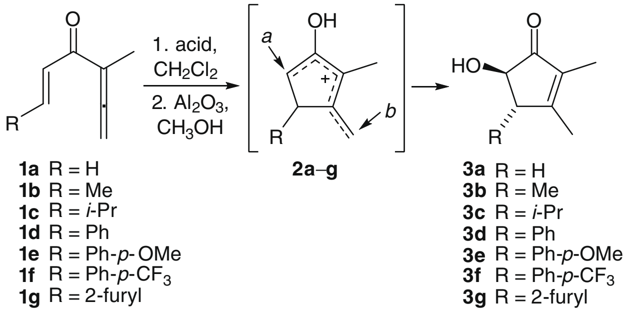
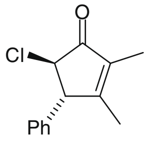
ABSTRACT

Allenyl vinyl ketones were exposed to titanium and indium halides in order to carry out Nazarov cyclizations. Whereas TiI_4 and InX_3 (X = Cl, Br, and I) led to cyclopentenones in which a halogen was trapped highly regioselectively, the reactions mediated by $TiBr_4$ gave mixtures of brominated isomers. When the allenyl vinyl ketones were treated first with Br_2 and then with $TiBr_4$, doubly brominated cyclopentenones resulted, and treatment with I_2 followed by TFA gave cyclopentenones bearing both hydroxyl and iodo groups.

There are examples in which the cyclized, cationic intermediate of a Nazarov cyclization[1] was intercepted, or 'interrupted,' by a nucleophile.[2–4] In the presence of protic or Lewis acids, allenyl vinyl ketones (AVK's) undergo Nazarov cyclizations particularly easily,[5–7] and work by Tius and co-workers[8] and ourselves[9] suggests that these substrates may be well suited for intermolecularly intercepted Nazarov cyclizations. The cationic intermediates (**2a**–**g**) from AVK's **1a**–**g** have two unencumbered positions (*a* and *b*) to which a nucleophile might add (Scheme 1). Our previous work involved mainly the trapping of **2a**–**g** by an oxygen function, and the products that were isolated (**3a**–**g**) had been intercepted only at position *a*.[9] A reaction of AVK **1d** in which $AuCl_3$ was used as the acid provided **4**, in which chloride had interrupted the Nazarov process at position *a*. The yield of **4** was only 32%, but prompted by this result, we explored whether halogens from other sources might intercept cationic intermediates **2a**–**g** more efficiently and whether a halogen might be captured at position *b*.



Scheme 1. Interrupted Nazarov cyclization of AVK's **1a**–**g** with trifluoroacetic acid (TFA).[8]



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Initially, we noted that treatment of **1d** with HCl yielded mainly products of Michael addition of chloride to the allene. White and West[3] had observed an interrupted Nazarov cyclization in which chloride was incorporated when a Lewis acid, $TiCl_4$, was used, but when we added $TiCl_4$ to **1d** the AVK was rapidly consumed and only intractable material was obtained.[9] However, retesting AVK **1d** with 5 M equiv[10] of $TiBr_4$ gave the brominated cyclopentenone **5d** in 80% yield. This was again the result of addition of bromide to position *a* of **2d**. The relative stereochemistry of **5d** and of subsequent Nazarov products was consistent with coupling constants in the ^{1}H NMR spectrum. This encouraging result led us to test AVK's **1a**–**g** with $TiBr_4$ (Scheme 2), but this $TiBr_4$ was from a different batch from the same commercial source. With this sample of $TiBr_4$ AVK's **1a**–**d** afforded modest yields of the brominated cyclopentenones **5a**–**d** and **6a**–**d** as 1:1 mixtures of compounds resulting from indiscriminate addition of bromide to positions *a* and *b* of intermediates **2a**–**d**. AVK's **1e**–**g** gave intractable material only. Purification of the $TiBr_4$ by sublimation led to frustrating results. With AVK **1d** as the substrate, the purer, pale yellow sublimate mediated the formation of the 1:1 mixture of **5d** and **6d**, but the impure, orange–brown residue elicited the highly regioselective process that yielded **5d** only.

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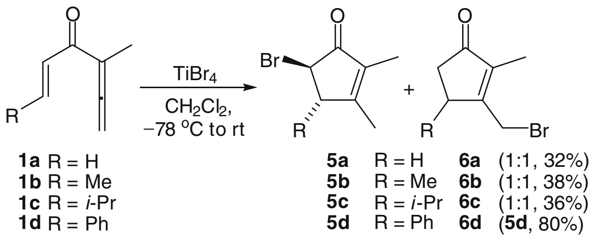
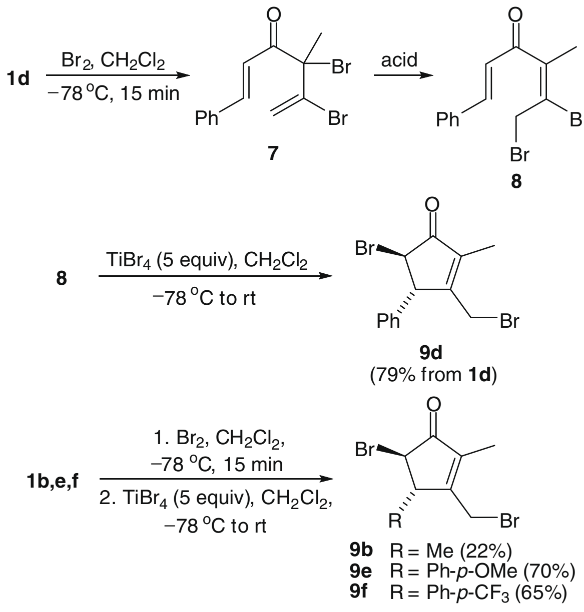


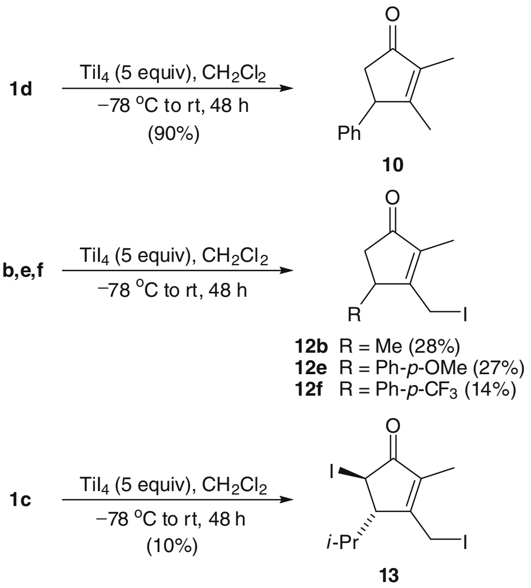
Scheme 2. Exposure of AVK's **1a**–**d** to $TiBr_4$.

It was not clear what the impurity was that led to the regioselective reaction, but the color of the residue suggested that it might have been molecular bromine. Dibromide **7** was formed when **1d** was treated with Br_2 at −78 °C. Exposure of **7** to $TiBr_4$ led first to the isomerized dibromide **8**[12] and then to the doubly brominated cyclopentenone **9d** in good overall yield (Scheme 3). It seems plausible that **9d** was the result of Nazarov cyclization of **8**, addition of bromide to the cyclic cationic intermediate, and then elimination of HBr to generate the conjugated double bond. It should be noted that neither **5d** nor **6d** was detected in the product mixture. Addition of Br_2 and then $TiBr_4$ to AVK's **1b**,**e**,**f** afforded the doubly brominated Nazarov products **9b**,**e**,**f**. Addition of TFA to **7** also gave the isomerized dibromide **8**, but **8** did not then undergo a Nazarov cyclization in the presence of TFA.

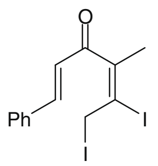
AVK's **1a**–**g** were mixed with 5 M equiv of TiI_4, and the result with **1d** was different from that with the other AVK's (Scheme 4). AVK **1d** was the only substrate that cyclized in high yield. Cyclopentenone **10** was the only product isolated, but this represented not only a Nazarov cyclization but also a reduction. In light of the TiI_4 products from the other AVK's, it seemed likely that **10** was derived from an iodinated cyclopentenone by de-iodination, a process for which there is precedence in work by West.[3] AVK **1a** reacted only by Michael addition of iodide, and **1g** was destroyed. Reaction of TiI_4 with **1b**,**c**,**e**,**f** led to complex mixtures of uncyclized, poly-iodinated Michael-addition products and di-iodinated compounds analogous to **11**, but, in addition, small amounts of iodinated cyclopentenones were isolated from the reaction mixtures. AVK's **1b**,**e**,**f** yielded **12b**,**e**,**f**, and **1c** gave the di-iodo compound **13**.



Scheme 3. Exposure of AVK's **1b**,**d**–**f** to Br_2 and then to $TiBr_4$.



Scheme 4. Exposure of AVK's **1b**–**f** to TiI_4.



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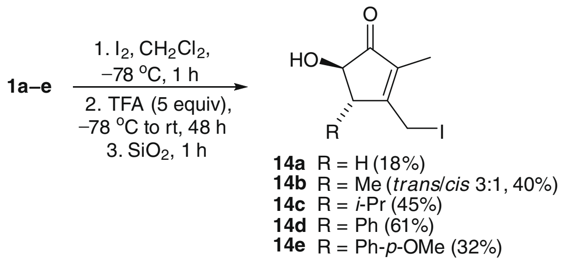
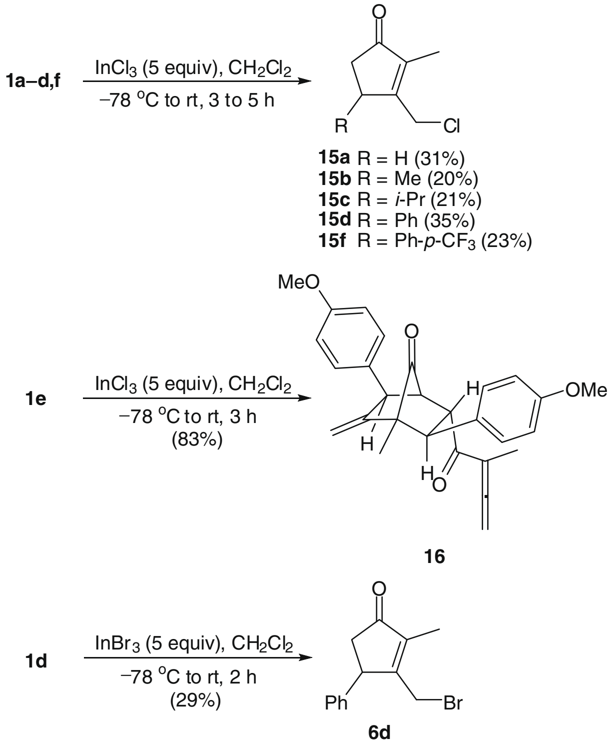
Addition of I_2 to **1d** provided **11**[12] directly, but subsequent addition of TiI_4 or $TiBr_4$ gave complex mixtures of products. However, in contrast with **8**, TFA did mediate the Nazarov cyclization of **11** to give the iodo-alcohol **14d**, following hydrolysis of an intermediate trifluoroacetate with silica gel. Then, the sequential treatment of **1a**–**c**,**e** first with I_2, then with TFA, and then with silica gel provided **14a**–**c**,**e** (Scheme 5) in low to modest yield.

$InCl_3$ has been shown to be similar to $TiCl_4$ in Lewis acidity,[13] but more recently it has been determined to be unlike $TiCl_4$ in the reactions that it preferentially mediates.[14] In addition, $InCl_3$ is much less soluble in the reaction medium, dichloromethane, than the titanium(IV) halides. In contrast with $TiCl_4$, cyclized products were obtained from AVK's **1a**–**f**, but the yields were generally low (Scheme 6). Nevertheless, in contrast with the reactions involving $TiBr_4$, the only cyclopentenones isolated, **15a**–**d**,**f**, were the result of addition of chloride to position *b* of intermediates **2a**–**d**,**f**. The product derived from **1e** was very different, and its structure, **16**, was confirmed by X-ray crystallography (Fig. 1).[15] This compound must have arisen by initial Nazarov cyclization, but then the intermediate carbocation **2e** underwent a regioselective, facially selective, and *endo*-selective cyclization with another



Scheme 5. Exposure of AVK's **1a**–**e** to I_2 and then to TFA.



Scheme 6. Exposure of AVK's **1a–f** to $InCl_3$ and $InBr_3$.

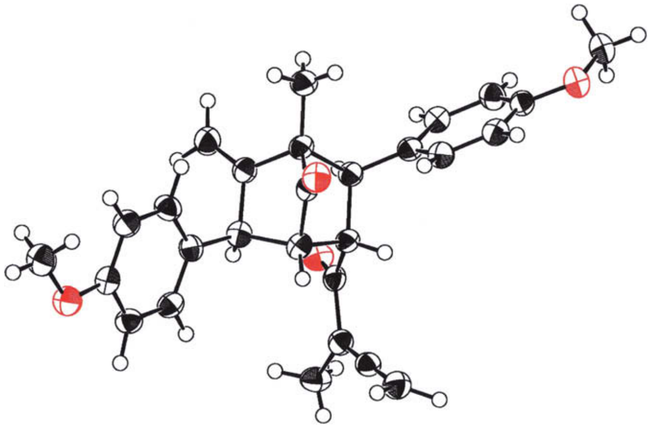
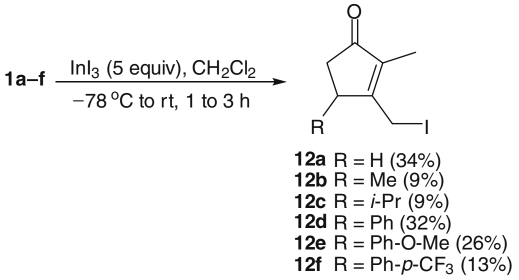


Figure 1. X-ray crystal structure of **16**.

molecule of **1e**. It is remarkable to note that even at a concentration of 0.01 M this reaction took place in good yield. Also, it seemed that electron donation by the *para*-methoxybenzyl substituent was crucial for this reaction to proceed because a re-examination of the ^{1}H NMR spectra of the crude reaction products from **1a–d**,**f** revealed no hint of any product resembling **16**. West[2b,11] had reported a cationic intermediate of a Nazarov cyclization undergoing formal [3+2] cycloaddition with electron-rich alkenes, but, to the best of our knowledge, **16** represented the first example of a dimerization as part of a domino process involving a Nazarov cyclization. $InBr_3$ was tested with AVK **1d** only, but the result paralleled that with $InCl_3$. Brominated cyclopentenone **6d** was isolated in only 29% yield. AVK's **1a–f** reacted with InI_3 as they had in the presence of $InCl_3$ to afford the iodo-cyclopentenones **12a–f** in low yield. With this reagent even **1e** gave the cyclopentenone (**12e**) instead of the dimerized product (Scheme 7).



Scheme 7. Exposure of AVK's **1a–f** to InI_3.

In summary, we have ascertained that AVK's can undergo Nazarov cyclizations in which the intermediate carbocation can be trapped by a halogen at either position *a* or position *b* in the cationic intermediate **2**. However, the efficiency of this process is very highly dependent on the Lewis acid and the substituent on the alkene, with yields ranging from very good to essentially zero. The AVK bearing a simple phenyl substituent (**1d**) is generally the best substrate. We observed the first instance of a formal [3+2] cycloaddition involving a carbocation intermediate being captured by unreacted substrate to generate the dimeric product.

Acknowledgments

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Supplementary data

Supplementary data (experimental details and characterization data for all identified products are available) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.052.

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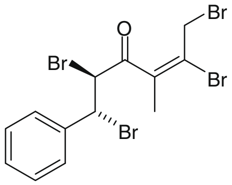
12. Addition of 2 equiv of Br_2 to **1d** gave the tetrabrominated compound below. The geometry of its double-bond was determined by X-ray crystallography,[15] and this geometry was then assumed for the structures of **8** and **11**.



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