Cyclization

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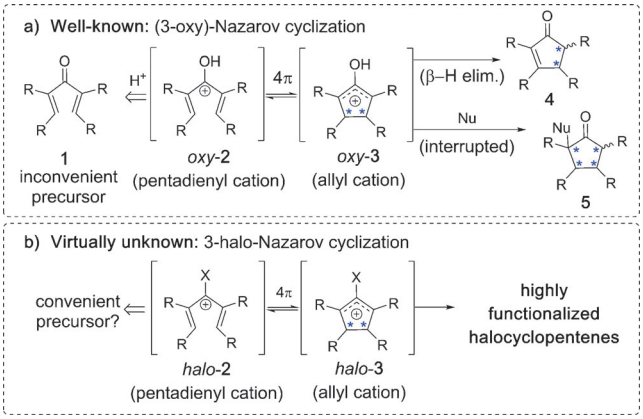
# Diastereoselective Construction of Densely Functionalized 1-Halocyclopentenes Using an Alkynyl Halo-Prins/Halo-Nazarov Cyclization Strategy

*Georgios Alachouzos and Alison J. Frontier**

***Abstract:*** *A diastereoselective two-step strategy for the synthesis of densely functionalized 1-halocyclopentenes with several chiral centers has been developed. In the first step, a multicomponent alkynyl halo-Prins reaction joins an enyne, a carbonyl derivative, and either a chloride, bromide, or iodide to produce a cyclic ether intermediate. In the subsequent step, the intermediate is ionized to generate a halopentadienyl cation, which undergoes an interrupted halo-Nazarov cyclization. The products contain three new contiguous stereogenic centers, generated with a high level of stereocontrol, as well as a vinyl halide allowing for additional functionalization. The strategy creates two new carbon–carbon bonds, one carbon–halide bond, and one carbon–oxygen bond.*

Many of the libraries available for lead identification in drug discovery programs contain molecules of low complexity, with achiral carbon scaffolds.[1] To increase the diversity of these libraries, chemists need new synthetic organic methods to access unusual carbon frameworks with both useful synthetic handles and dense arrays of $sp^3$ stereogenic centers.[1] For example, 4π cationic electrocyclizations are powerful reactions that occur stereospecifically (governed by orbital symmetry constraints)[2] to generate substituted allyl cation intermediates such as **3** from pentadienyl cations **2** (Scheme 1). Nazarov cyclizations (via *oxy*-**2** cation intermediates) have been studied extensively,[3] but a shortcoming of many of these methods is the requirement for a divinyl ketone precursor (see **1**), which can be difficult to synthesize and handle, particularly when terminally disubstituted vinyl groups are needed. Intermediates *oxy*-**3** can undergo elimination to deliver cyclopentenes **4** (up to two new stereogenic centers installed overall); alternatively, they can undergo trapping with a carbon[4] or heteroatom[5] nucleophile to afford cyclopentane rings **5** with installation of up to four stereogenic centers. Described here is a new cyclization method that capitalizes upon the stereospecificity of the electrocyclization through controlled capture of an allyl cation **3**. This method should simplify the synthesis of complex cyclopentanes with properties that are valuable for both drug discovery efforts and small-molecule synthesis.




***Scheme 1.*** Comparison of 3-oxy and 3-halo 4π electrocyclization pathways.

It has been observed that 4π electrocyclizations (see Scheme 1) of the analogous *hydrido*-**2** (X = H) and *carbo*-**2** ($X = CR_3$) pentadienyl cations are typically more favorable than *oxy*-**2** and *aza*-**2** ($X = NR_2$) cation cyclizations,[3] presumably because heteroatoms such as oxygen and nitrogen stabilize cation **2**, decreasing its reactivity and affecting the equilibrium between **2** and **3**.[6] Given these trends, one would expect electrocyclizations of pentadienyl cations *halo*-**2** to be facile as well as practical, affording products with a vinyl halide moiety. These halocyclopentene building blocks should be useful partners in various transition-metal-catalyzed cross-coupling reactions.[7] However, we are aware of only two isolated examples of 3-halo-Nazarov cyclizations,[8] and could find no studies dedicated to the subject. This is perhaps due to the fact that there is no straightforward method to prepare cationic intermediate *halo*-**2**.

With these ideas in mind, we embarked upon a quest to develop a simple method for generating 3-halopentadienyl cations *halo*-**2** to study their reactivity and synthetic utility. This work has led to the development of a two-step stereoselective method for the synthesis of complex 1-halocyclopentenes **11** from simple, readily available precursors via cyclic ether intermediates **8** (Scheme 2).

We began by designing and optimizing an alkynyl halo-Prins reaction capable of generating ethers of type **8** (Table 1) via oxocarbenium intermediates **7**.[9] Benzaldehyde (PhCHO) was employed for an optimization screen, to be reacted with enyne **6a**. Bromide was used as a starting point for screening halides. Lewis acids were screened to effect the reaction, but ultimately failed to furnish the desired products.

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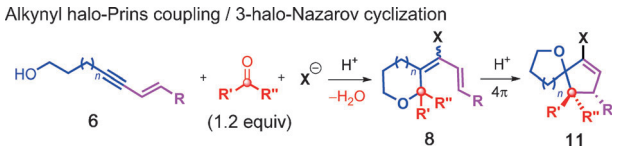
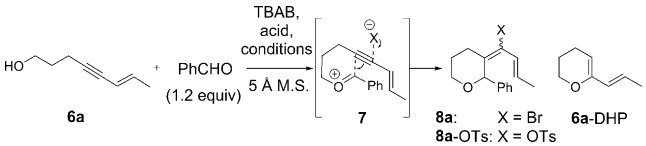


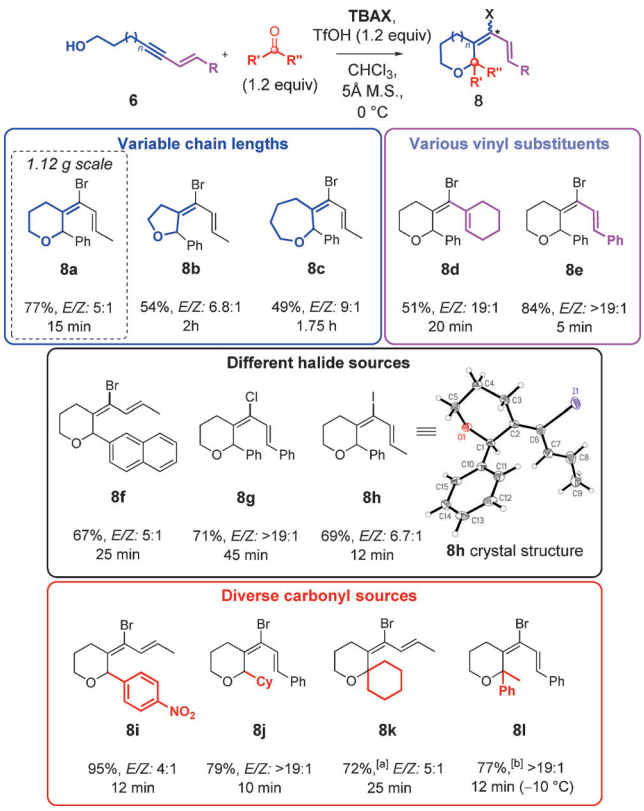

***Scheme 2.*** An overview of our method for synthesizing densely functionalized chiral halocyclopentenes **11** from enyne alcohols **6** and commercially available aldehydes or ketones.

***Table 1:*** Alkynyl halo-Prins optimization with enyne **6a**, PhCHO, and TBAB.




| Entry | Acid (equiv) | TBAB [equiv] | Solvent | *t* | *T* [°C] | Yield[a] **8a** |
|---|---|---|---|---|---|---|
| 1 | TsOH (1.2) | 1.2 | $CHCl_3$ | 16 h | reflux | 45%[b] |
| 2 | TsOH (0.3) | 1.5 | $CHCl_3$ | 30 h | reflux | 34%[c] |
| 3 | TfOH (1.2) | 1.2 | $CHCl_3$ | 45 min | 0 | 34%, *E*/*Z* 4:1 |
| **4** | **TfOH (1.2)** | **2** | **$CHCl_3$** | **20 min** | **0** | **78%, *E*/*Z* 7:1** |
| 5[d] | TfOH (1.2) | 2 | $CHCl_3$ | 24 h | RT | ca. 50% conv. |
| 6 | TfOH (1.2) | 2 | DCM | 1.5 h | 0 | 57%, *E*/*Z* 4:1 |
| 7 | TfOH (1.2) | 2 | THF | 24 h | RT | trace[e] |

[a] Combined yield of the *E* and *Z* geometric isomers, where *E*/*Z* denotes the ratio of the two possible double-bond isomers of the tetrasubstituted vinyl halide (determined by $^1$H NMR analysis). [b] 22% of **8a**-OTs observed. [c] 20% **6a**-DHP observed. [d] Reaction carried out without 5 Å molecular sieves. [e] Full consumption of **6a** observed.




***Scheme 3.*** Scope of the alkynyl halo-Prins reaction. *E*/*Z* denotes the ratio of the two vinyl halide double-bond isomers as determined by $^1$H NMR spectroscopy. [a] 1,1-Dimethoxycyclohexane (1.5 equiv) was used as the carbonyl source. [b] α-Methoxystyrene (1.5 equiv) was used as the carbonyl source.

Attention was turned to Brønsted acids, with additive tetrabutylammonium bromide (TBAB) as the halide source, and 5 Å molecular sieves, to drive the dehydration/oxocarbenium formation necessitated by the first part of the reaction mechanism (see Table 1). Chloroform ($CHCl_3$) was found to be the best performing solvent for this reaction. Dichloromethane (DCM) as a solvent led to longer reaction times with diminished yields, and tetrahydrofuran (THF) as a solvent failed to produce the desired product. The strong Brønsted acid *para*-toluenesulfonic acid (TsOH) produced the desired vinyl bromide product **8a** when heated to reflux, but unfortunately led to generation of the corresponding vinyl tosylate adduct **8a**-OTs as a significant side product. As such, attention was turned to Brønsted acids with less nucleophilic conjugate bases.

A slight stoichiometric excess of trifluoromethanesulfonic acid (TfOH) and two equivalents of TBAB allowed for the reaction to be carried out in an ice bath instead of at reflux, resulting in full consumption of **6a** in 20 min, producing **8a** in excellent yield with an *E*/*Z* ratio of 7:1 (Table 1, entry 4). Any attempts to effect the alkynyl halo-Prins reaction with substoichiometric amounts of Brønsted acid did not go to completion.

Pleasingly, the optimized reaction conditions are effective for enynes with both shorter (**6b**) and longer (**6c**) carbon chains (Scheme 3). Different enyne substitution patterns are also tolerated, such as cyclohexenyl alkyne **6d** and styrenyl alkyne **6e** (see the Supporting Information), which both undergo efficient alkynyl halo-Prins coupling. Either tetrabutylammonium chloride (TBAC) or iodide (TBAI) can be employed instead of TBAB, producing the corresponding chlorovinyl and iodovinyl adducts **8g** and **8h**. Aryl aldehydes such as 2-napthaldehyde and *para*-nitrobenzaldehyde coupled smoothly, as well as the enolizable carbonyl partner cyclohexanecarboxaldehyde, giving the expected halovinyl ethers **8** in each case.

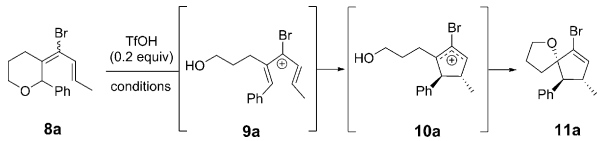
Unfortunately, the optimized conditions did not translate smoothly to the alkynyl halo-Prins reaction with cyclohexanone; only a trace amount of the desired product was observed. Fortunately, we discovered that the use of 1,1-dimethoxycyclohexane as a surrogate for cyclohexanone provides facile conversion into the desired product **8k**. Similarly, α-methoxystyrene is an effective surrogate for acetophenone, affording **8l**. These findings indicate that ketals or enol ethers are competent substrates for the coupling, and are in fact essential for the coupling of ketones. In these cases, the alkynyl halo-Prins coupling generates a tertiary ether, and represents a rare example of a Prins transformation that is effective for both aldehyde and ketone-equivalent partners.

With a variety of halovinyl ether adducts **8** in hand, we focused on identifying a viable ionization method for the generation of the cationic intermediates *halo*-**2**. Again, we chose **8a** for optimization studies. Various conditions with

catalytic amounts of a Brønsted acid were tested for inducing the ionization and obtaining **11a**, but most results were disappointing.[10] Serendipitously, we discovered that the reaction rates increased significantly with the addition of hexafluoroisopropanol (HFIP). Ultimately, two equivalents of HFIP in DCM with catalytic TfOH delivered **11a** cleanly at low temperature, with high diastereoselectivity (Table 2, entry 1). When the reaction was carried out with a large excess of HFIP (roughly 5 equiv; Table 2, entry 2), the reaction rate was comparable, but the observed diastereoselectivity was lower. Omission of HFIP (Table 2, entry 3) resulted in poor reaction performance, even at room temperature. Other protic solvents did not facilitate the desired reaction at all. When methanol was substituted for HFIP as the additive, no reaction was observed even after prolonged reaction at room temperature (Table 2, entry 4). HFIP alone does not facilitate ionization either: no reaction of ether **8a** was observed after 24 h in HFIP at reflux (Table 2, entry 5).

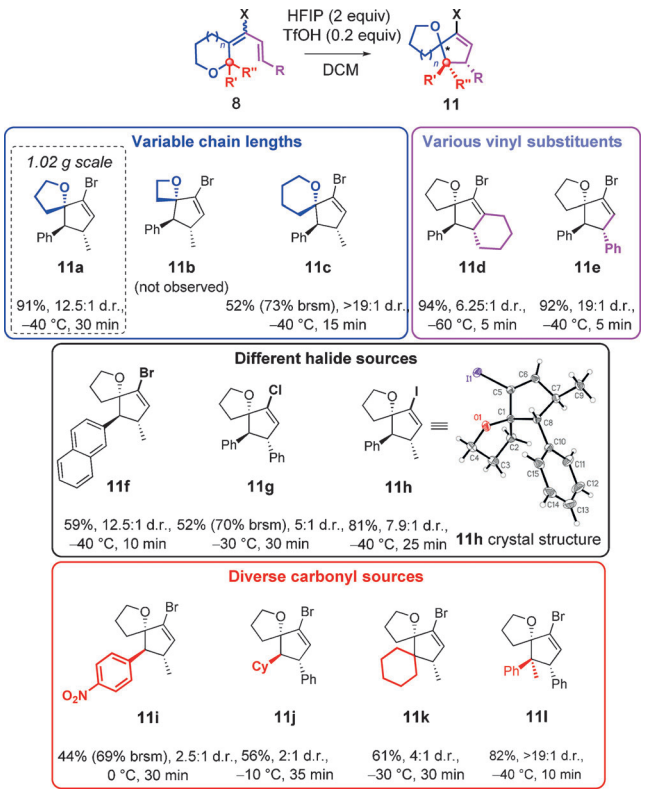
***Table 2:*** Optimization of the halo-Nazarov reaction with **8a**.




| Entry | Solvent (0.1 M) | *t* | *T* [°C] | Yield[a] **11a** |
|---|---|---|---|---|
| 1 | **2 equiv HFIP in DCM** | **25 min** | **−40** | **82%, >19:1 d.r.** |
| 2 | ca. 5 equiv HFIP DCM[b] | 20 min | −40 | 76%, 5.6:1 d.r. |
| 3 | DCM | 72 h | RT | trace[c] |
| 4 | DCM/MeOH 19:1 | 24 h | RT | no reaction |
| 5 | HFIP[d] | 24 h | reflux | no reaction |

[a] The d.r. refers to the *anti/syn* ratio of epimers at the spirocyclic ether center (determined by $^1$H NMR analysis). [b] 5 equiv HFIP in DCM is roughly equal to 19:1 DCM/HFIP. [c] Full consumption of **8a** observed (see the Supporting Information). [d] Without TfOH.

Shown in Scheme 4 is an overview of the scope of the ionization/interrupted halo-Nazarov cyclization sequence. The optimized procedure furnished **11a** from **8a** at gram scale, with no notable impact on performance. Unfortunately, unstable spirooxetane **11b** was not obtained from **8b**; instead the formation of various unknown side products was observed. Ionization of **8c**, however, provided **11c** in slightly lower yield when compared to **11a**, demonstrating that the ring size has a significant impact on the efficiency of the process. Cyclohexenyl and β-styryl vinyl substituents both accelerate the reaction and increase its efficiency, producing **11d** and **11e** in excellent yields. The chloro and iodo variants **11g** and **11h** are also competent substrates for this reaction. Finally, a variety of R/R′ substituents are tolerated. Substrates with electron-withdrawing (see **8i** to **11i**) or monoalkyl-substituted ethers (**8j** to **11j**) react more sluggishly and lead to slightly decreased diastereoselectivity, but with decent yields. Finally, ketone-derived tertiary ethers (**8k** and **8l**) give satisfactory results. Product **11k** was formed in good yield, at slightly elevated temperatures compared to other substrates, whereas **11l** was formed rapidly, as a single diastereomer, in excellent yield.

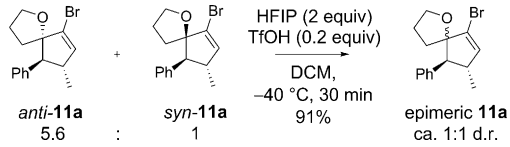



***Scheme 4.*** Scope of the halo-Nazarov reaction.

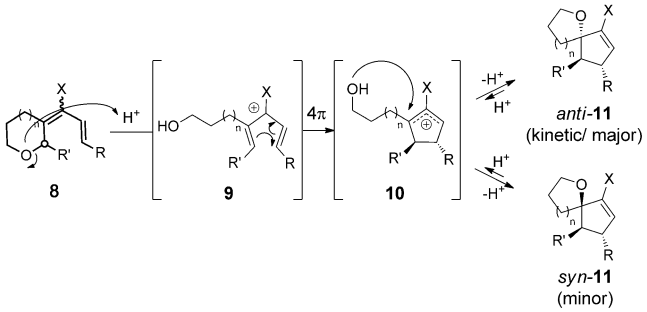
With regard to the observed reactivity of ethers **8**, we propose the formation of an HFIP/TfOH complex with enhanced Brønsted acidity and/or the ability to stabilize the critical cationic intermediate *halo*-**3**. HFIP has remarkable properties as a solvent, mainly owing to its electron-withdrawing trifluoromethyl substituents.[11] When compared to its non-fluorinated analogue isopropanol (*i*PrOH), it showcases higher polarity and density, a lower boiling point, a lower p$K_a$ value (9.3 compared to 17.1 for *i*PrOH), and lower nucleophilicity. Perhaps more importantly, it displays increased capacity for hydrogen-bond donation, yet diminished ability to accept hydrogen bonds. It has also been shown to be able to stabilize carbocations in ways that non-fluorinated alcohol solvents cannot.

To shed light on the factors controlling the diastereoselectivity during the formation of spirocycle **11a**, an experiment was conducted in which **11a** (*anti/syn* = 5.6:1) was resubjected to the typical HFIP/TfOH conditions (from Table 2, entry 1). Compound **11a** was recovered in near-quantitative yield after a 30 min reaction time but its diastereomeric ratio had eroded to roughly 1:1 (see Scheme 5). This finding implies that the major diastereomer in each case (*anti*-**11**) is formed under kinetic control, and suffers from epimerization under the reaction conditions.

With these experimental data in hand, a mechanistic hypothesis for the cyclization process was composed (Scheme 6). Upon protonation and ionization of ether **8**, halopentadienyl cation **9** is formed, giving haloallyl cation **10** after conrotatory electrocyclization. Haloallyl cation **10** is trapped with the pendant hydroxy group, affording spirocycle




***Scheme 5.*** An experiment is shown demonstrating the thermodynamic epimerization of **11a** after prolonged reaction times.

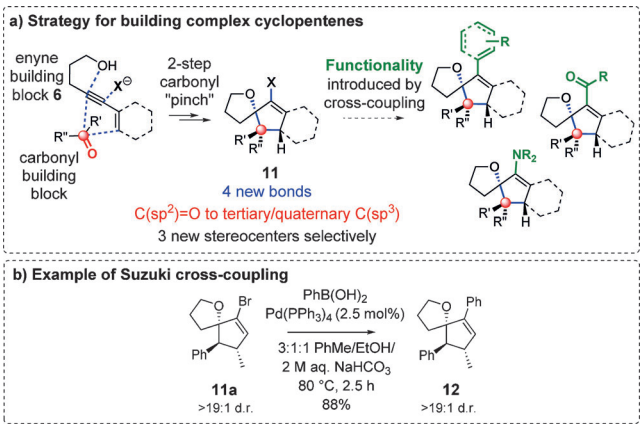



***Scheme 6.*** General mechanistic hypothesis for the ionization-induced halo-Nazarov reaction from **8** to **11**.

*anti*-**11** as the major diastereomer (kinetic control). However, under the reaction conditions, ring opening of *anti*-**11** can also occur, regenerating **10**, and thermodynamic equilibrium between *anti*-**11** and *syn*-**11** is reached after extended reaction times. This phenomenon is the predominant reason why substrates that were slower to ionize gave spirocycles with lower diastereomeric ratios (Scheme 4). These experiments required longer reaction times and, in some cases, were not run to completion to optimize the diastereoselectivity.

Scheme 7 shows a selection of hypothetical cross-couplings that could further diversify halocyclopentenes **11**, and potentially be used to help impart desirable biological activity to these complex small molecules. To test this idea, a Suzuki coupling of **11a** with phenylboronic acid was performed, affording cyclopentene **12** in high yield.

Overall, our two-step strategy provides a novel, facile synthetic disconnection for cyclopentene synthesis. The two building blocks **6** (easily accessible enyne alcohols) and a carbonyl partner (aldehyde, ketone) are coupled such that the carbonyl group is converted into an $sp^3$ carbon atom through the formation of two new C–C bonds (Scheme 7; critical carbon atom shown in red, new bonds shown in blue). The initial C–C coupling is facilitated by the oxocarbenium tether, which renders the alkynyl halo-Prins reaction intramolecular.[12] An acid-catalyzed cationic cascade completes the sequence. Future work in our laboratory will focus on developing new methods that employ this "carbonyl pinch" ring-building strategy, achieving enantioselective cyclizations, and applying the strategy to the synthesis of complex targets.




***Scheme 7.*** a) Using simple building blocks to build complex intermediates **11**, poised for further functionalization. b) An example of the synthetic utility of halocyclopentenes **11** in cross-coupling reactions.

## Acknowledgements

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** C–C bond formation · cyclization · electrocyclic reactions · multicomponent strategies · stereospecific reactions

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# Communications

**Cyclization**

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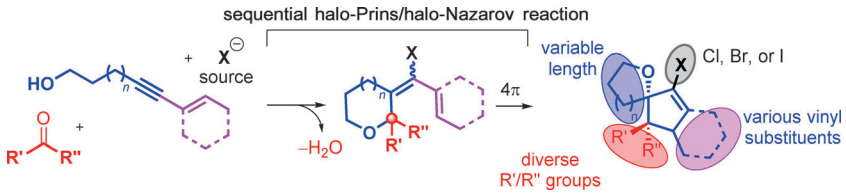


**A two-step strategy** has been developed for the synthesis of densely functionalized 1-halocyclopentenes with a high level of stereocontrol. First, a multicomponent alkynyl halo-Prins reaction joins an enyne, a carbonyl derivative, and either chloride, bromide, or iodide to produce a cyclic ether intermediate. Then, the intermediate is ionized to generate a halopentadienyl cation, which undergoes an interrupted halo-Nazarov cyclization.

  