PRF# 56372-NDI1
Project Title: Titanium-Mediated Selective Dihalogenation for the Vicinal Difunctionalization of Simple Alkenes
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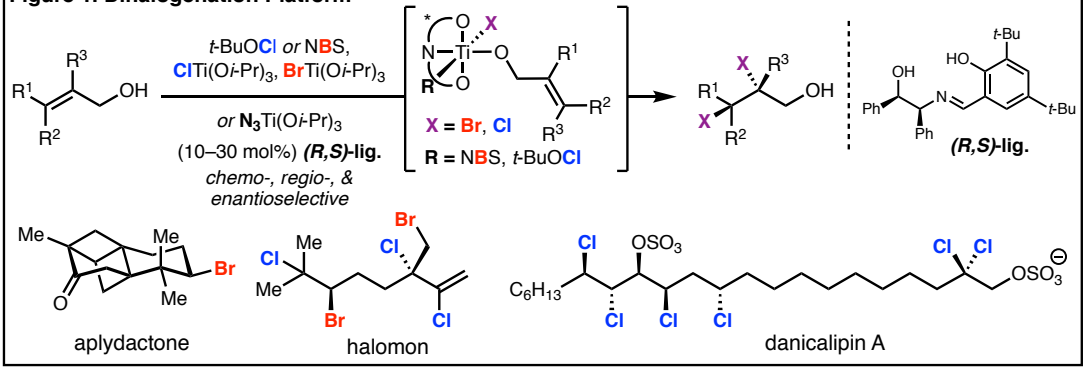
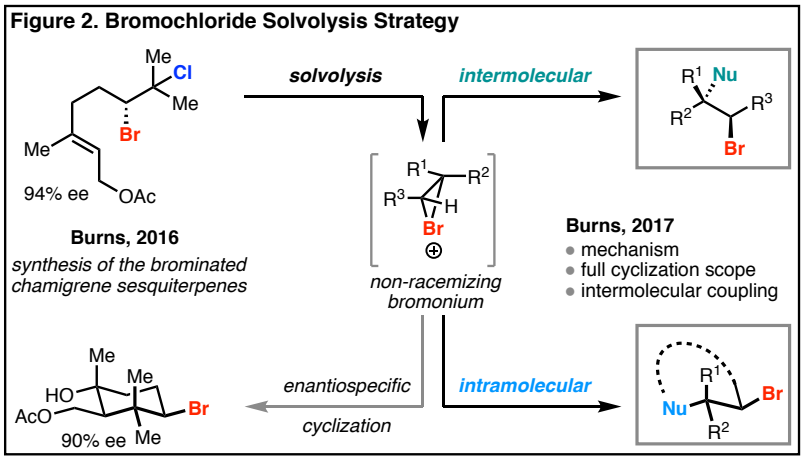
At the outset of our group's research, no general platforms existed to enable fully selective syntheses of relevant chiral organohalogenated motifs that recur in natural products and simple chiral small molecules. Inspired by mono- and polyhalogenated targets including halomon, danicalipin A, and aplydactone, we sought to develop practical methods to control the installation of bromine and chlorine in polyfunctionalized substrates. Our laboratory then disclosed a chemo-, regio-, and enantioselective Schiff base-catalyzed dihalogenation reaction of allylic alcohols, providing access to highly enantioenriched bromochlorides, dibromides, and dichlorides (**Figure 1**). The reaction is a chiral ligand-accelerated stoichiometric titanium(IV)-based system that operates on allylic alcohols and includes addition of an external oxidant. It strategically involves the use of separate electrophilic and nucleophilic halogen sources. We hypothesized that these individually inert species could become reactive in combination and in the presence of a chiral ligand to promote selective alkene dihalogenation. The modularity of our catalyst design then allowed us to approach other forms of selective vicinal difunctionalizations. Specifically, we have developed a catalytic enantioselective bromo- and chloroazidation reaction of allylic alcohols for the installation of nitrogen-bearing stereogenic centers with external control of regioselectivity. Funding from the ACS PRF has been critical for this ongoing development of selective alkene vicinal difunctionalizations and finding utility for the products therefrom.

**Figure 1. Dihalogenation Platform**



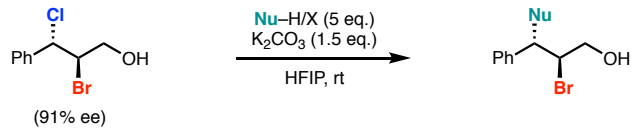

The majority of efforts funding by this ACS PRF went into subsequent derivatizations of the now readily accessible enantioenriched dihalide motifs. In the previous funding period efforts focused on various metal-mediated halide displacements including dialkyl zinc and silver reagents. Concomitantly, we foresaw that vicinal dihalides, and bromochlorides in particular, could be deployed under solvolytic conditions to effect further access to useful chiral small molecules from readily available petroleum feedstocks. We hypothesized a solvolytic approach could be a useful platform for the generation of an enantiopure bromonium ion from a vicinal bromochloride (**Figure 2**) which could then be captured in an intra- or intermolecular sense.

**Figure 2. Bromochloride Solvolysis Strategy**

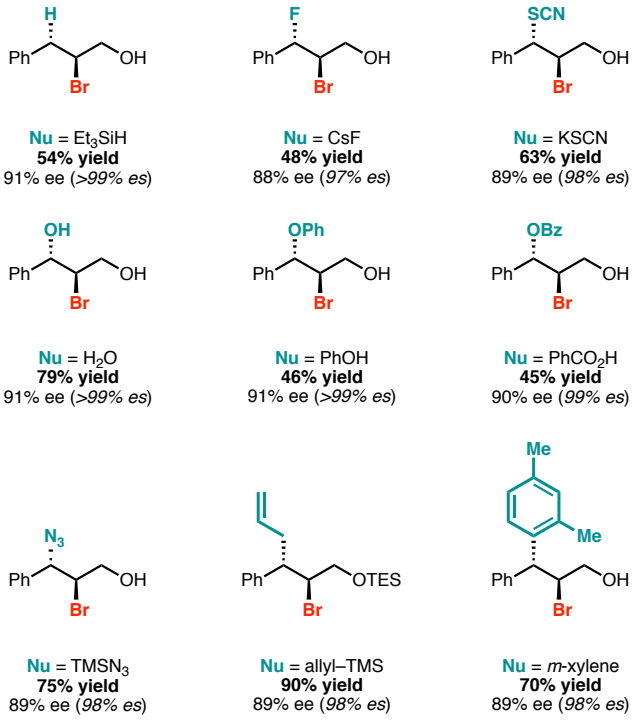



Such reactions saw initial success in the context of a natural product total synthesis effort that resulted in the enantioselective chemical synthesis of several brominated chamigrene sesquiterpenes including aplydactone and dactylone. We had envisioned that asymmetric bromopolyene cyclizations could be achieved by using enantioenriched bromochlorides as progenitors of chiral bromonium ions. This strategy was reduced to practice through use of basic hexafluoroisopropanol as a strongly ionizing medium for bromonium generation. Under these conditions a variety of enriched bromochlorides could be ionized and stereospecifically captured, providing access to valuable bromocyclic motifs for use in synthesis (e.g. bottom, Figure 2).

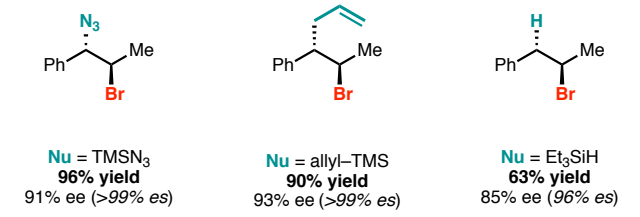
**Figure 3. Bromochloride Solvolysis Substrate Scope**



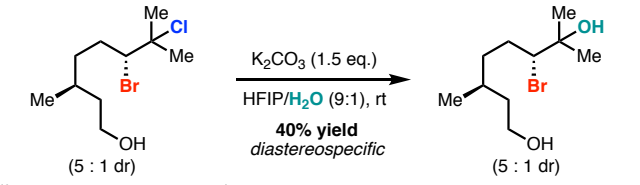

**A. Scope with cinnamyl bromochlorides**




**B. Scope with additional bromochlorides**




**C. Intermolecular coupling with a non-benzylic bromochloride**




Having demonstrated the utility of this approach in an *intramolecular* sense, as well as its utility in total synthesis, we set out to see if this methodology could be extended to *intermolecular* solvolytic couplings. Given the extensive use of alkyl halides as building blocks in chemical synthesis, we believed that developing a strategy for providing access to a diverse set of highly enantioenriched *anti*-functionalized alkyl bromides would be an enabling technology. After investigating an array of enantioenriched dihalides, we identified cinnamyl bromochloride as a versatile substrate which was observed to engage with a diverse set of exogenous nucleophiles in intermolecular coupling reactions. Our solvolysis conditions employed in the intramolecular cyclization were general for intermolecular coupling with some minor modifications. Running the reactions at a concentration of 0.1 M (versus cyclizations run at 0.05 M) at room temperature and employing 5 equivalents of a commercially available nucleophile proved optimal. Under these conditions, a variety of carbon–heteroatom bond formations can be effected and the scope of this reaction is highlighted in Figure 3A. Simple nucleophiles can be readily deployed to effect carbon–nitrogen, carbon–fluorine, carbon–sulfur, and carbon–oxygen bond formation in good yield, high levels of diastereoselectivity, and with excellent enantiospecificity (all >90%). Triethylsilane can be employed to effect stereospecific reduction of the bromochloride (Figure 3A). This methodology can also be extended to carbon–carbon bond formation using allyltrimethylsilane as nucleophile; triethylsilyl-protected cinnamyl bromochloride can be allylated in excellent yield producing the product in 12:1 dr with near perfect enantiospecificity. Simple arenes also serve as competent nucleophiles in this reaction for productive carbon–carbon bond formation. Deoxygenated cinnamyl bromochlorides were observed to be considerably more reactive than their alcohol-bearing counterpart and underwent clean reactivity with several distinct nucleophiles including azide, allyl, and hydride (Figure 3B). A current limitation of this methodology is the requirement of an arene to stabilize the bromonium resulting from the solvolysis of the bromochloride. Currently, most alkyl-derived bromochlorides do not engage in the solvolytic coupling, however citronellyl bromochloride can be diastereospecifically converted to its corresponding bromohydrin, a common motif found in halogenated natural products, under these conditions (Figure 3C). We are actively engaged in further exploring the substrate scope of this reaction, specifically with regard to non-benzylic substrates.

The ACS PRF funding was crucial for our development of the chemistry summarized here which all results in the conversion of inexpensive feedstocks into highly useful chiral small molecules. In the future, we foresee the selective halogenation reaction and subsequent functionalization serving as a general platform for a variety of other selective bond formations. Research along these lines is ongoing in our lab.