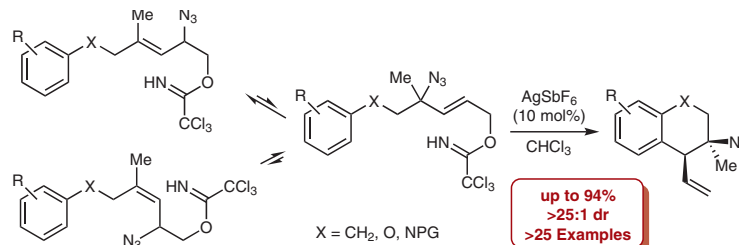J. J. Topczewski, M. R. Porter

# "It's a (Kinetic) Trap!" – Selectively Differentiating Allylic Azide Isomers

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X = CH₂, O, NPG

up to 94%
>25:1 dr
>25 Examples

**Abstract** Allylic azides are known to undergo the Winstein rearrangement and are often isolated as an equilibrating mixture of isomers. While this process has been known for almost 60 years, very few synthetic applications of this process have been reported. The absence of methods exploiting these intermediates likely stems from a paucity of approaches for gaining the required selectivity to differentiate the isomers. Our lab has made some progress in leveraging this unusual reaction into practical synthetic methodology. Presented herein is a summary of our lab's recent accomplishments in selectively trapping allylic azides.

**Joseph Topczewski** (left) grew up in Racine, Wisconsin and received his BSc degree from the University of Wisconsin at Parkside in 2007. After completing his PhD at the University of Iowa with Prof. David Wiemer in 2011, he conducted postdoctoral studies at Iowa with Prof. Hien Nguyen and Prof. Daniel Quinn until 2013. He then moved to the University of Michigan where he carried out postdoctoral studies with Prof. Melanie Sanford. He started his independent research career at the University of Minnesota in the summer of 2015.
**Matthew Porter** (right) was born in Portland, Oregon and received his BSc degree from Case Western Reserve University in 2014. In the fall of 2015, he joined the Topczewski lab to focus on organic synthesis with allylic azides.

## 1    Introduction

Organic azides are key synthetic intermediates with a storied history.[1–3] Azides are most generally recognized as protected primary amine equivalents and are typically installed by straightforward nucleophilic displacement using NaN₃, a commodity reagent. Many classic reactions utilize organic azides including the Staudinger reaction, aza-Wittig reaction, Huisgen cycloaddition, Curtius rearrangement, and Schmidt reaction. The combined utility of these transformations places organic azides in a unique arena of significance for synthesis.

Likewise, allylic systems are cherished in synthesis. Allylic electrophiles display enhanced reactivity, which is noted in most sophomore texts.[4] Allylic acetates, carbon-

ates, phosphates, and imidates are employed in transition-metal-catalyzed substitution reactions, such as the Tsuji–Trost reaction.[5–8] Allyl-vinyl ethers are substrates for the Claisen rearrangement.[9] Furthermore, allyl or crotyl metal reagents are central to many synthetic sequences.[10–13] These reagents have received as much attention as allylic electrophiles because they are functional equivalents to the aldol reaction. In light of the advantageous properties of allylic systems and the plethora of applications of azides, it is somewhat surprising that allylic azides are scarcely reported as synthetic intermediates.

One explanation for the noticeable underutilization of allylic azides is their spontaneous rearrangement (Scheme 1). This phenomenon was first fully documented by Winstein,[14] although others had speculated that the

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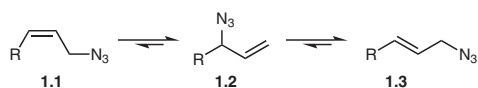
**Scheme 1** Equilibration of allylic azides by the Winstein rearrangement

rearrangement may exist.[15,16] In the first account of this process, Winstein thoroughly documented the rearrangement of crotyl and prenyl azide. The rate of this rearrangement is relatively slow at room temperature; however, it is facile enough that a mixture of azide isomers is commonly isolated.[17–20] Due to this complication, many authors have viewed the Winstein rearrangement as a nuisance. Several authors report immediate azide reduction to prevent isomerization.[21,22] However, a few promising reports demonstrate that allylic azides may be used in a dynamic process.

## 2    Background

In a seminal study, Sharpless and co-workers reported that simple allylic azides could be used in click reactions or epoxidations (Scheme 2).[23] The mixture of crotyl or prenyl azide isomers could selectively afford a single product under appropriate conditions. In the mixture of prenyl azides (**2.1** and **2.2**), the primary azide **2.2** preferentially underwent copper-catalyzed click cycloaddition instead of the tertiary azide isomer **2.1**. The same azide isomer reacted preferentially with *m*-CPBA to afford the more substituted epoxide **2.3**. The selectivity is due to the known preference of *m*-CPBA to react with the more nucleophilic alkene.[24] For both reactions, the selectivity was not as high for crotyl azide. In both example reactions the predominant azide isomer was functionalized. Nevertheless, these results showed that it is possible to utilize the dynamic nature of allylic azides.
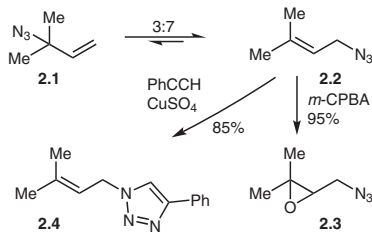


**Scheme 2** Seminal contribution by Sharpless and co-workers

For a generic internal allylic azide, the system is more complex than for prenyl azide (Scheme 3). Prenyl azide exists as a mixture of only two azide isomers (Scheme 2). However, in a general sense, up to eight isomers are possible (Scheme 3, enantiomers not shown). The azide can be proximal or distal to a specific group. The alkene can be *cis*

or *trans* and the absolute stereochemistry of the azide bearing carbon can be *R* or *S*. The complexity of this mixture necessitates exceptional selectivity in any reaction focused on resolving the azide isomers. A few strategies have been developed to accomplish this.
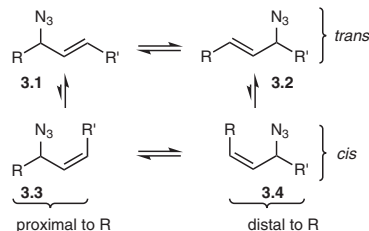


**Scheme 3** General equilibrium for an allylic azide

An initial success by Craig and co-workers was predicated on coupling the allylic azide rearrangement to an intramolecular [3,3] rearrangement (Scheme 4).[25] The authors recognized that only one isomer in the azide equilibrium was poised to undergo an irreversible second rearrangement. This insight enabled a high-yielding Johnson–Claisen rearrangement. While the yield of this process was generally high, it did suffer from minimal diastereoselectivity and a mixture of *syn* and *anti* azides was reported. This was the first example of using proximal functionality to lay a kinetic trap for the rearrangement.
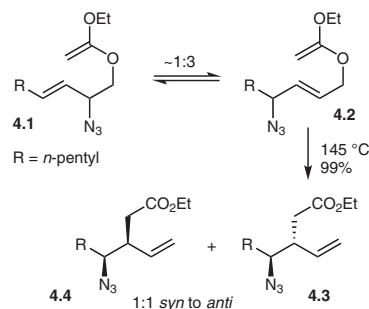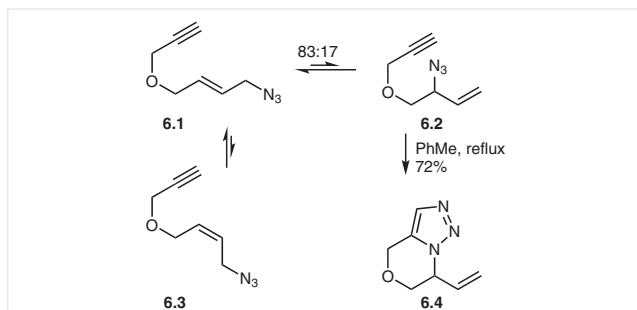


**Scheme 4** Double rearrangement of allylic azides

The Aubé lab contributed to the area of allylic azide differentiation by recognizing that the azide isomers could be resolved through a cyclization reaction. The azido-Schmidt reaction has been a central theme to the Aubé lab's research program and this reaction was extended to allylic azides (Scheme 5).[26–28] A mixture of allylic azide isomers was reported and the azide proximal to the ketone (branched) reacted preferentially. The tether controls the ring size of the intermediate adduct and subsequently controls the relative rate of ring closure. The five-membered ring forms preferentially over the seven-membered ring, which could arise from the *cis* isomer. Several examples of this process were reported as was a full discussion of the stereochemical out-

comes (not shown). This process was used to complete a formal synthesis of pinnaic acid. In a second study, the Aubé lab reinforced these findings and showed that allylic azides with a pendent alkyne could selectively undergo an intramolecular Huisgen cycloaddition (Scheme 6).[28] These examples were the first instances where a minor azide isomer (ca. 20% at equilibrium) preferentially formed the major product.
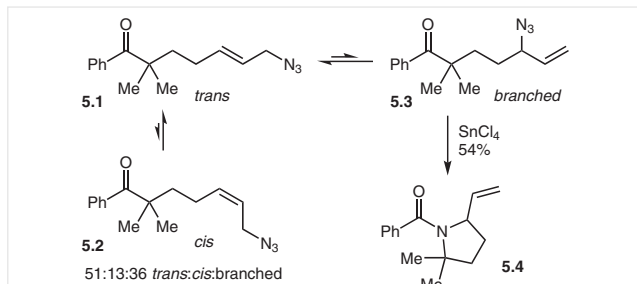


**Scheme 5**   Intramolecular azido-Schmidt reaction



**Scheme 6**   Intramolecular Huisgen cycloaddition of allylic azides

Our lab became interested in allylic azides because we envisioned that the Winstein rearrangement could be used as the racemization pathway in a dynamic kinetic resolution (DKR). Dynamic kinetic resolution is a well-established area in enantioselective synthesis.[29–33] However, only a few mechanisms of racemization are widely used. We achieved a DKR by coupling the Sharpless asymmetric dihydroxylation to the Winstein rearrangement (Scheme 7).[34] Key to the success of this process was using azides that provide the enantiomer upon rearrangement. The process achieved excellent stereoselectivity (up to 99:1 er). Of the eight possible stereoisomers that could arise from this reaction, one was predominantly formed.
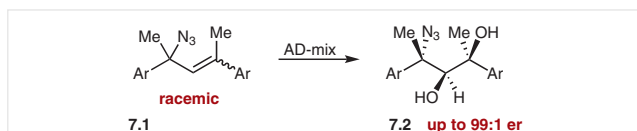


**Scheme 7**   First enantioselective allylic azide DKR

## 3   Dynamic Cyclization of Imidates

We turned our attention to more complex systems featuring proximal functionality.[20,35] We designed a system that could take advantage of the lessons learned from the studies of Craig and Aubé with an additional twist. It is well-known that allylic electrophiles react faster in substitution reactions.[36] We hypothesized that this difference in rate could be exploited to differentiate the azide isomers if a specific nucleophile and electrophile combination was identified (Scheme 8). An additional element of complexity must be noted. A substitution reaction could occur by an $S_N2$ or $S_N2'$ pathway and this could result in a mixture of products (Scheme 8, linear, *syn* and *anti*). If the substitution reaction provided the linear product, the azide would still be allylic and would likely form a new mixture of isomers.
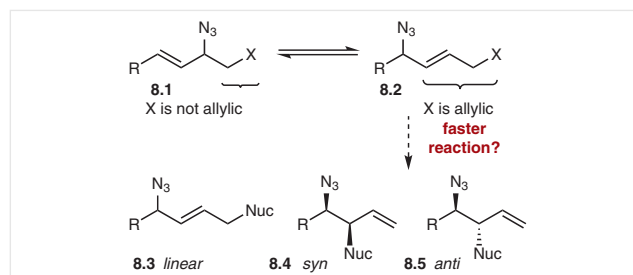


**Scheme 8**   Allylic leaving group and possible products. X = generic leaving group; R = generic carbon group; Nuc = generic nucleophile

Allylic trichloroacetimidates were investigated because prior experience indicated that these groups are quite versatile and can be activated under electrophilic conditions.[37,38] A classic nucleophile to intercept the putative allylic electrophile could be an arene by a Friedel–Crafts reaction. Borrowing from Aubé's cyclization strategy, tethering the arene to the allylic system would provide control for the site of nucleophilic capture. Therefore, we focused our initial attention on azides such as **9.1** (Scheme 9). After screening a variety of catalysts, it was found that cationic silver salts were effective at promoting the desired cyclization in high yield and diastereoselectivity. Control experiments and several qualitative observations indicate that general acid catalysis likely facilitates the cyclization.[39]
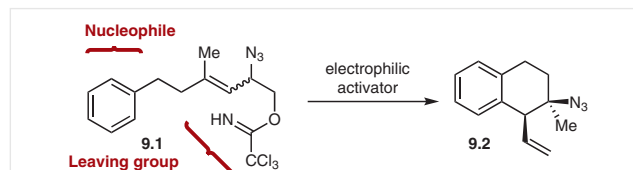


**Scheme 9**   Initial substrate for dynamic cyclization

The scope of this reaction was explored, and the cyclization was facile with a wide range of substrates (Scheme 10). Several 3-azido-tetralins could be obtained. The possibility

of incorporating a heteroatom into the substrate's backbone was particularly interesting. These substrates afforded chromanes or tetrahydroquinolines after cyclization. Gratifyingly, the dynamic cyclization was generalizable and afforded a wide variety of these building blocks. This reaction is amenable to a variety of substituents on the arene as well as varied linkers. Qualitatively, the cyclization's rate was dependent on the aryl ring's substituents. As would be expected for an electrophilic aromatic substitution, donating groups accelerated the reaction. The rate of cyclization was decreased with strong withdrawing groups, representing a limitation of this reaction.

One interesting facet of this reaction is that the reactive azide isomer was less than 40% of the equilibrium mixture for almost all substrates. The percentage of the reactive isomer was highly dependent on the substrate's structure. At the extreme, the reactive isomer of substrate **11.3** was not detectable by $^1$H NMR analysis (Scheme 11). We speculate

that the geminal dimethyl motif causes a significant *syn*-pentane interaction in the branched isomer, shifting the equilibrium to the other isomers. Even though the reactive isomer is not easily detectible, the cyclization still proceeds in 72% yield and >25:1 dr. This example clearly demonstrates the dynamic nature of this reaction. Based on these combined observations, we propose that the system follows the Curtin–Hammett principle and that aromatic substitution is rate limiting.

To demonstrate potential synthetic applications of the dynamic cyclization, we performed a concise synthesis of hasubanan (Scheme 12). This scaffold represents the core of a natural product family that has been extensively studied.[40–46] The vicinal tetrasubstituted carbon stereocenters are a key challenge in the synthesis of these molecules. The allylic trichloroacetimidate precursor was synthesized in only a few steps from commercial materials. The allylic
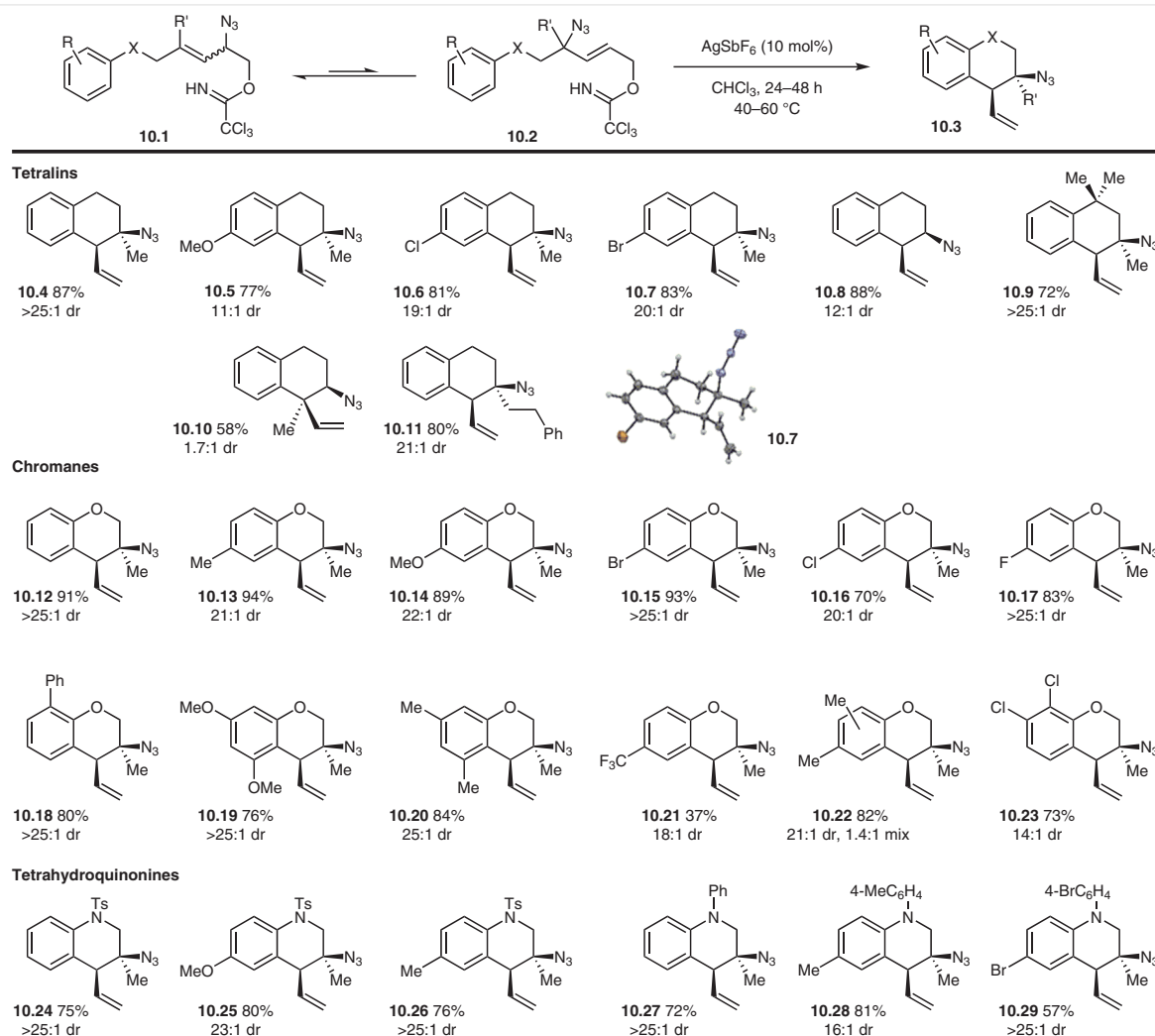


**Scheme 10**  Substrate scope of dynamic cyclization reaction

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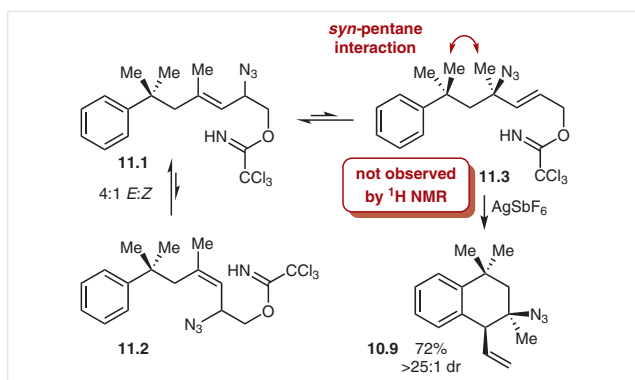
**Scheme 11** Dynamic cyclization from minor equilibrium component

azide cleanly cyclized to afford tetralin **12.4** as a single diastereomer in excellent yield. This reaction established both tetrasubstituted carbon centers in a single step with the required relative configuration. The final reaction used a protocol developed by Evans.[47] Here cyclohexyl borane triggered a hydroboration/cyclization sequence that established the final ring in hasubanan. This reaction illustrates the advantages of using an azide for this sequence.
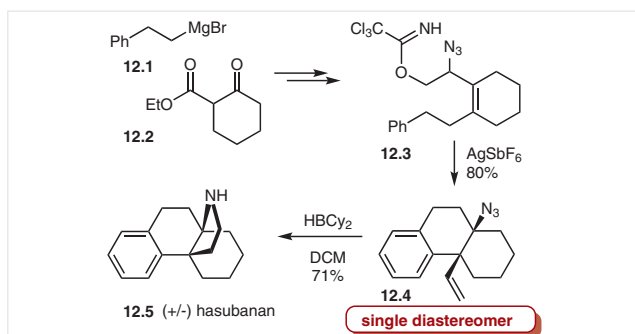


**Scheme 12** Synthesis of hasubanan via dynamic azide cyclization

## 4   Summary and Outlook

Herein, we have summarized known methods for the differentiation of allylic azides. Several successful and high-yielding strategies have been noted that attain site-, regio-, and stereocontrol. Future work will focus on identifying new approaches to gain selectivity as well as deploying these strategies in the context of new synthetic challenges.

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