Published in final edited form as:

Org Biomol Chem. 2019 May 08; 17(18): 4406–4429. doi:10.1039/c8ob03178a.

Allylic azides: synthesis, reactivity, and the Winstein rearrangement

Angela S. Carlson and Joseph J. Topczewski

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA.

Abstract

Organic azides are useful synthetic intermediates, which demonstrate broad reactivity. Unlike most organic azides, allylic azides can spontaneously rearrange to form a mixture of isomers. This rearrangement has been named the Winstein rearrangement. Using allylic azides can result in low yields and azide racemization in some synthetic contexts due to the Winstein rearrangement. Effort has been made to understand the mechanism of the Winstein rearrangement and to take advantage of this process. Several guiding principles can be used to identify which azides will produce a mixture of isomers and which will resist rearrangement. Selective reaction conditions can be used to differentiate the azide isomers in a dynamic manner. This review covers all aspects of allylic azides including their synthesis, their reactivity, the mechanism of the Winstein rearrangement, and reactions that can selectively elaborate an azide isomer. This review covers the literature from Winstein's initial report to early 2019.

Introduction

Organic azides provide access to a wide range of nitrogenous compounds with an ever-expanding inventory of reactivity. In particular, the Huisgen cycloaddition, Staudinger reaction, Schmidt reaction, and Curtius rearrangement have been used extensively in organic synthesis.¹⁻¹⁰ Additionally, azides have classically been used as protected primary amine equivalents. The utility of organic azides has been further extended because of the bioorthogonality exhibited in several classic reactions with azides.^{11,12} For example, the Huisgen cycloaddition and Staudinger ligation are extremely selective and facile under biological conditions.¹² Because organic azides are useful synthetic intermediates, the general reactivity of organic azides has been reviewed several times.¹⁻¹⁰

The enormous breadth of azide reactivity can be divided into subclasses based on functionality adjacent to the azide. When additional functionality is proximal, the reactivity of an azide can change significantly. The resonance structures of simple aliphatic azides (Fig. 1a) demonstrate that the azide can act as a weak electrophile (generally attacked on the terminal nitrogen), or a weak nucleophile (generally attacking with the proximal nitrogen). When the azide is conjugated to other functionality, the azide's reactivity varies

jtopczew@umn.edu.

Conflicts of interest

There are no conflicts to declare.

significantly. Aryl azides, for instance, have extra resonance into the adjoining π -system (Fig. 1b).^{13,14} This class of azide is less nucleophilic and commonly loses nitrogen gas to form the corresponding nitrene. Vinyl azides exhibit enamine like reactivity due to a similar resonance effect, which is illustrated in the third resonance structure (Fig. 1c).¹⁵⁻¹⁹ Acyl azides are electron deficient due to the carbonyl's withdrawing ability (Fig. 1d).^{20,21} These resonance structures help explain why acyl azides tend to lose N_2 and form isocyanates, which is the key feature in the Curtius rearrangement. Benzylic azides demonstrate enhanced reactivity due to weak α -C—H bonds (Fig. 1e).²²⁻²⁴ Additionally, benzylic azides can undergo an aryl shift in the presence of strong acids or Lewis acids.²⁵⁻²⁷ This review will describe the synthesis and reactivity of allylic azides, a unique azide subclass (Fig. 1f).

Allylic azides are unique because the proximal double bond enables a reversible rearrangement. This process has been termed the Winstein rearrangement.²⁸ Because of this rearrangement, allylic azides frequently exist as an equilibrating mixture of structural isomers. While other classes of organic azides have been reviewed, allylic azides and applications of the Winstein rearrangement have been mostly overlooked.²⁹ This contrasts with other allylic functional groups (*e.g.* allylic boronates or allylic acetates) that are used extensively in synthesis by virtue of the enhanced reactivity attained by being allylic. Synthetically, using an equilibrating mixture of allylic azide isomers can result in a low yield of the desired product. Furthermore, some chiral allylic azides have the propensity to racemize.³⁰⁻³² These factors have so far limited the synthetic applications of allylic azides.

Recently, the Winstein rearrangement has been investigated to take advantage of the dynamic nature of allylic azides. The equilibrium ratios of a wide variety of allylic azides have been measured, which can help predict substrates that will exist primarily as one isomer.³³ Other reports describe using an equilibrating mixture of azides to obtain high yields with high stereoselectivity of a functionalized product.^{32,34} This review covers all aspects of allylic azides starting with Winstein's original observation and concludes with work published in early 2019.

Azide safety

Organic azides are high energy molecules, which imparts synthetic utility. However, this also makes organic azides potentially explosive. A few very low molecular weight bis-azides have been synthesized and reported to explode.³⁵ General procedures for using azide reagents and handling azide waste have been developed.³⁶ Because of their potentially explosive nature, several guidelines have been established to help determine which azides are lower risk to synthesize. The carbon atom to nitrogen atom ratio (C/N ratio) should be greater than three for any target azide. Similarly, there is the "Rule of Six", which states that for every energetic functional group there should be six carbon atoms in the target molecule.³⁷ The higher molecular weight minimizes volatility and provides mass to lower the energy density. This tends to render the azide sufficiently stable to synthesize. In several instances, the thermal stability of the allylic azide has been similar to that of the corresponding alcohol as determined by thermo-gravimetric analysis.³² We rigorously follow the guideline of having at least nine carbons per azide functional group. To date, we have not encountered any issues when working with allylic azides.

There are several common reagents used to prepare organic azides (*e.g.* TMSN₃, DPPA, NaN₃, *vide infra*), which can be used with minimal risk if certain guidelines are followed. These reagents have been used on large scales.³⁸⁻⁴⁴ However, improper use has resulted in explosions.⁴⁵ Reactions involving nucleophilic azides (*e.g.* NaN₃ or DPPA) should avoid halogenated solvents because the azide anion can displace the halogen(s), generating very low molecular weight azides. Because NaN₃ is toxic,⁴⁶ skin permeable solvents (*e.g.* DMSO) should be avoided if possible. No acid should be used during the reaction or workup with these reagents because HN₃ could be formed accidentally. TMSN₃ is commonly used under Lewis acidic conditions. Because of its volatile nature and the potential for TMSN₃ to form HN₃, care must be taken to quench and basify excess TMSN₃. Once the azide reagent has been quenched, all azide-containing waste should be stored in a dedicated waste container to ensure that no compatibility issues arise. Given the high toxicity and explosivity of HN₃, this waste container should be kept strictly free of acid. Waste should also be kept free of halogenated solvents if nucleophilic azide has been used.

The Winstein rearrangement

In 1960, Winstein and co-workers reported that crotyl and prenyl azide spontaneously rearrange (Scheme 1).²⁸ A mixture of azide isomers was observed when crotyl chloride was treated with sodium azide (Scheme 1a). Based on this observation alone, it was unclear whether the mixture of products was due to competitive S_N2 and S_N2' substitution mechanisms (Scheme 1a) or by the rearrangement of the initially formed S_N2 product (Scheme 1b). Given this ambiguity, Winstein and co-workers isolated each azide isomer and stored the isomers at -80 °C to prevent isomerization. The pure samples were warmed to 25 °C and monitored. Upon warming, each pure isomer resulted in the same mixture of isomers, thus confirming an equilibrium-based rearrangement.

To investigate the rearrangement further, the equilibrium constant and the rate of isomerization were measured in several solvents. There was little variation in the equilibrium constant in solvents ranging from pentanes to 70% aqueous acetone. An average value is provided here (Scheme 1b and c).²⁸ There was a measurable but minor solvent dependence on the rate of rearrangement. The rate of isomerization increased by a factor of 10–20 when measured in 70% aqueous acetone relative to pentane. The observed rate enhancement is similar to that of a Diels–Alder reaction, indicating a concerted mechanism.⁴⁷ The observation that prenyl azide (Scheme 1c) rearranges faster than crotyl azide (Scheme 1b) supports a small build-up of positive charge in the transition state. This seminal contribution resulted in the rearrangement being termed the Winstein rearrangement. It should be noted that VanderWerf had contemplated the existence of such an allylic rearrangement six years prior to explain the mixture of azides obtained when opening butadiene monoxide.⁴⁸ Because of the Winstein rearrangement, allylic azides can equilibrate to all possible alkene isomers. The details of the mechanism and equilibrium are discussed below.

Allylic azide synthesis

Substitution

The most well-established method to access allylic azides is through nucleophilic substitution with sodium azide (Schemes 1a and 2a).⁴⁹⁻⁵⁵ Allylic systems are typically activated for substitution and a wide range of electrophiles undergo substitution with azide anion including halogens, sulfonates, and some activated esters (Scheme 2a). As expected for a nucleophilic substitution, this reaction typically occurs with inversion of configuration. Scheme 2b⁵⁶ and c⁵⁷ provide examples of a substitution, with inversion, followed by a stereospecific Winstein rearrangement. It is noteworthy that the example in Scheme 2b occurs with inversion on a tertiary carbon.⁵⁶ The azide can be immediately reduced to generate the corresponding amine.⁵⁷ Electrophiles such as activated allylic acetates (Scheme 2d),⁵⁸ or allylic epoxides (Scheme 2e),^{29,59} can also be used for azide incorporation with NaN_3 . In all cases, the resulting allylic azide can equilibrate after substitution. When the alkene is conjugated to an aryl ring or carbonyl group, the conjugated isomer was observed as the major product (Scheme 2a, c, and d).

Other sources of inorganic azide anion can be utilized synthetically. Lithium azide (LiN_3) is scarcely used relative to NaN_3 , presumably because LiN_3 is commercially available as a solution in water, whereas NaN_3 is an easily weighable solid. In Trauner's synthesis of ioline alkaloids, LiN_3 was used to form an allylic azide (Scheme 3).⁶⁰ The allylic oxygen is more susceptible to substitution.⁶¹ Selective $\text{S}_{\text{N}}2$ attack, with inversion at the allylic position, explains the product's stereochemistry. The authors did not report a mixture of azide isomers. Since the substitution was conducted at 130 °C, it is likely that the product was isolated as the thermodynamically more stable isomer. It is possible that the observed isomer is the most stable isomer due to *gauche* interactions (*vide infra*).³³ It is also worth noting that cyclic allylic azides are generally slower to isomerize, which can sometimes minimize equilibration if the intermediate is promptly advanced.³¹

A variety of methods have been developed to convert allylic alcohols into the corresponding azide. Many of these methods use *in situ* generated HN_3 (Scheme 4a).^{62,63} Many methods mix NaN_3 with a strong proton source to generate HN_3 . It is important to note that HN_3 is a highly toxic and explosive gas; care should be taken when generating or handling it.⁴⁶ Spino and co-workers developed a method to convert alcohols into allylic azides using Mitsunobu style conditions (Scheme 4b).⁶⁴ The authors proposed an $\text{S}_{\text{N}}2$ reaction followed by Winstein rearrangement to account for the formation of the observed product.⁶⁵ When excess PPh_3 is added the azide can be reduced to the amine, providing a direct conversion from alcohols to amines.⁶⁶ Similar Mitsunobu conditions were used by Carell and co-workers in the synthesis of the nucleoside queuosine (Scheme 4c).³¹ In this case, the reaction was performed at 0 °C to suppress the Winstein rearrangement. A zinc azide bis-pyridine complex was described by Tanaka for azidation.^{67,68} Liu used this reagents to convert an enantiopure alcohol to the corresponding azide with inversion of the stereocenter (Scheme 4d).⁶⁷ Given that zinc azide complexes are reported to be relatively stable, this may be an attractive alternative to HN_3 .⁶⁹

Thompson developed a method to convert alcohols directly into azides using diphenylphosphoryl azide (DPPA) and a base (Scheme 5a).⁷⁰ This method generally

proceeds with clean inversion of the stereocenter. DPPA is generally considered a workhorse reagent for the direct installation of organic azides because DPPA is relatively inexpensive and stable. There is minimal risk of accidental HN_3 formation while using DPPA due to the basic reaction conditions. This reagent has been safely used on scale (>6 kg).⁷¹ Shioiri was able to convert allylic alcohols to allylic azides using bis-(*p*-nitrophenyl)phosphoryl azide, which is an activated version of DPPA (not shown).⁷² To make some allylic azides more readily accessible, Topczewski and co-workers developed a method to convert aldehydes and ketones directly into their corresponding azides (Scheme 5b).⁷³ Grignard addition generated an alkoxide *in situ* and subsequent addition of DPPA produced the azide without isolation of the intermediate alcohol or phosphate. The scope of this method includes the formation of allylic azides from vinyl magnesium chloride addition or addition to an enal/enone. A similar reaction can be performed with 2-azido-1,3-dimethylimidazolinium hexafluorophosphate.⁷⁴ Alkoxides can also be activated by triphosgene and displaced by NaN_3 .⁷⁵

TMSN_3 has been used to convert alcohols into the corresponding azides using an electrophilic activator (Scheme 6a). This reaction was first reported by Zwierzak, who reported using $\text{BF}_3 \cdot \text{OEt}_2$ and TMSN_3 .⁷⁶ Since then, a wide variety of Lewis acids have been used to catalyze this transformation.⁷⁷⁻⁷⁹ Rueping reported using catalytic AgOTf to convert primary, secondary, and tertiary allylic alcohols to the corresponding azide (Scheme 6b).⁸⁰ The authors proposed that the mechanism proceeds through a carbocation intermediate because using an enantiopure alcohol resulted in racemic azide. This seemingly straightforward substitution has created some unexpected products when coupled with the Winstein rearrangement. Srihari and co-workers attempted to generate chromanes by intramolecular substitution (Scheme 6c).⁸¹ However, the azide rearranged to the conjugated alkene isomer. This general reaction works with a wide variety of substrates. The optimal Lewis acid catalyst is likely substrate dependent. Zinc azide is significantly more stable than other metal azides, with copper or silver azide being reported as particularly explosive.^{82,83} Our lab has found $\text{Zn}(\text{OTf})_2$ to be highly effective across a range of substrates (Scheme 6d). We prefer this Lewis acid over AgOTf or $\text{Cu}(\text{OTf})_2$ for safety considerations.^{32,34,84}

Very recently, Burns and co-workers reported that bromonium ions could be opened selectively with TMSN_3 (Scheme 6e).⁸⁵ Here, the initial bromonium ion is formed regioselectively due to the directing ability of the allylic alcohol. Ligand **6.1** controls the absolute stereochemistry of the bromonium ion, which is opened with inversion to produce the distal azide after Winstein rearrangement.

Catalytic allylic substitution with palladium and gold

Multiple groups developed palladium catalyzed azidation reactions to convert allylic electrophiles into the corresponding azide (Scheme 7a).⁸⁶⁻⁸⁸ Chida used these conditions in the total synthesis of bengamide B.⁸⁹ Srivastava also found this reaction useful for the synthesis of 2- and 4-aminoglycosides.⁹⁰ Several other examples have been reported that will not be discussed here for brevity.⁹¹⁻⁹⁵ While the $\text{S}_{\text{N}}2$ reactions discussed above proceed with inversion of stereochemistry, these palladium catalyzed azidations generally occur with net retention of stereochemistry *via* a double inversion. This method is

complementary to the S_N2 conditions discussed above.⁹⁶ This stereoselectivity was demonstrated by Salaun and co-workers in the synthesis of (–)-(1*R*,2*S*)-norcoronamic acid (Scheme 7b).^{97,98} In this case, the other allylic azide isomer is disfavored because placing an sp^2 center in the cyclopropane ring is thermodynamically unfavorable. Schuster and co-workers also observed retention of stereochemistry when forming cinnamyl azide derivatives (Scheme 7c).⁹⁹ In this case, the allylic azide equilibrium is significantly biased toward the styrenyl alkene, so only one alkene isomer was observed.

Sinou and co-workers developed a similar palladium catalyzed azidation with $TMSN_3$ as the azide source (Scheme 8a).¹⁰⁰ Guo took advantage of the observed retention of stereochemistry during the synthesis of D- and L-swainsonine (Scheme 8b).¹⁰¹ In this case, the authors proposed that the other azide isomer was not observed due to the rigid structure and equatorial orientation of the azide. An alternate explanation could be that the OBn group of the acetal biases the equilibrium due to a steric interaction.^{34,102} If a *meso* compound is used as the substrate, then the catalyzed allylic substitution reaction can be made enantioselective (Scheme 8c). Trost and co-workers found that chiral phosphine ligand **8.1** can distinguish between the two enantiotopic sites of oxidative addition.¹⁰³ Using this ligand, the resulting azide could be generated in >95% ee. Trost and co-workers used this method in the total synthesis of (–)-epibatidine and (+)-pancratistatin.^{103,104}

In a related reaction, Krause and co-workers were able to generate allylic azides through a gold catalyzed ring opening reaction with $TMSN_3$ (Scheme 8d).¹⁰⁵ Based on the loss of stereochemical information, this process likely proceeds through a stabilized carbocation. Reddy developed a related palladium catalyzed method for generating cinnamyl azide derivatives from homoallylic alcohols that proceeded through alkene isomerization and substitution (Scheme 8e).¹⁰⁶

Allene hydroazidation

Munoz and co-workers developed a gold catalyzed method to transform allenes into allylic azides (Scheme 9a).¹⁰⁷ The reaction utilizes a cationic gold complex $[(PhO)_3PAu]^+$ that is generated *in situ* by halogen abstraction. The combination of TFA, water, and $TMSN_3$ likely generates HN_3 *in situ*, which is presumably the active reagent. This method works well for substituted allenes, though it is non-ideal if acid sensitive functional groups are present. The authors demonstrated that TFA/water could be substituted for NIS. The use of NIS results in an iodoazidation reaction (Scheme 9b). Incorporating iodine forms allylic azides with orthogonal functionality, which maximizes their potential synthetic utility. This method is also nice from the perspective of selectivity because the reaction regioselectively delivers iodine and an azide to only one of the two possible π -bonds. An enantioselective version of this reaction was recently developed by Toste and co-workers (Scheme 9c).¹⁰⁸ This reaction used 1-aryl-3-methyl-allenes and generates substituted cinnamyl azides. The Winstein rearrangement is suppressed because the arene stabilizes the conjugated azide isomer. Key to obtaining high enantioselectivity was the use of an acyclic diaminocarbene (ADC) ligand.

C—H activation

In 1992, Magnus and co-workers developed an oxidative C—H azidation to convert triisopropylsilyl enol ethers into the corresponding β -azido triisopropylsilyl enol ethers (**10.1**, Scheme 10a).^{109,110} The authors propose an ionic mechanism, which proceeds through a silyl oxocarbenium ion intermediate. A similar transformation can be accomplished using $\text{PhI}(\text{N}_3)_2$, which is possibly the active reagent formed when PhIO and TMSN_3 are combined.¹¹¹ The primary side product observed was 1,2-bis-azide **10.2**. This product was thought to arise *via* a competitive radical mechanism. When TEMPO was added as a radical initiator, the 1,2-bis-azido product was the major product. It is possible that product **10.1** was also the result of a radical reaction triggered by hydrogen atom abstraction instead of hydride abstraction. The synthetic utility of this method was demonstrated in White's total synthesis of (–)-huperzine.^{112,113}

Hartwig and co-workers developed a C—H azidation, which is viable on complex molecules (Scheme 10b).¹¹⁴ Rather than mix PhIO and TMSN_3 to form a hypervalent iodine reagent *in situ*, this work uses Zhdankin's reagent.¹¹⁵ Groves and co-workers contributed significantly to the field of C—H azidation (not shown).¹¹⁶ In 2014, Jiang developed a palladium catalyzed allylic oxidation to generate cinnamyl azides from the corresponding allyl benzene (Scheme 10c).¹¹⁷ The authors proposed oxidation to the π -allyl intermediate, which was intercepted by azide anion (as above under allylic substitution). A few other methods to generate azides through formal C—H activation have also been applied to allylic azides.

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Mechanism of the Winstein rearrangement

Four possible mechanisms have been considered for the Winstein rearrangement (Scheme 11).¹²¹ The rearrangement could proceed through a concerted mechanism (Scheme 11a and b), an ionic mechanism (Scheme 11c), or a diradical mechanism (Scheme 11d). Winstein originally proposed a cyclic concerted mechanism.²⁸ In VanderWerf's investigation, a two electron asynchronous mechanism with a cyclic transition state was proposed based on the solvent effects, measured entropy of activation, and substituent effects (Scheme 11b).³⁵ Subsequent studies confirmed that the Winstein rearrangement generally proceeds through a [3,3]-sigmatropic pathway.⁸⁴ However, at high temperatures or under Lewis acidic conditions, an ionic mechanism is possible.¹²² The following section discusses key experiments that illuminate the mechanism of this process.

Solvent effects

In Winstein's original report, the effect of solvent polarity on the rate of the rearrangement was investigated.²⁸ In a range of solvents with varying polarity, from pentane to 70% aqueous acetone, the rate of rearrangement increased by a factor of 10 or 20 for crotyl or prenyl azide, respectively. This is a smaller solvent effect than would be expected for an ionic mechanism. The rate of an $\text{S}_{\text{N}}1$ reaction on *tert*-butyl chloride increases by a factor of 10 000 when run in acetone as opposed to hexane.¹²³ For comparison, a Diels–Alder reaction between 1,3-cyclopentadiene and methyl vinyl ketone increases by a factor of 50 when run in formamide rather than isooctane.⁴⁷ Based on these solvent effects, it appears

that the build-up of charge in the transition state is similar to that of a concerted Diels–Alder reaction. These solvent effects, or lack thereof, are an important consideration when using allylic azides because the Winstein rearrangement occurs in a wide variety of solvents.

Additionally, no significant azide hydrolysis was observed in 70% aqueous acetone, which would be expected if an allylic cation was formed in the presence of water. In a separate experiment, it was determined that the rate of rearrangement was not affected by additional NaN_3 , which further suggests a unimolecular mechanism.^{28,124} Equilibration of the allylic azides in the dark had no effect on the rate of the rearrangement, which discourages, though does not eliminate, a radical mechanism.¹²⁴

Entropy of activation

Winstein and co-workers determined the entropy of activation for the azide rearrangement.²⁸ Values of -10 e.u. and -11 e.u. were reported for prenyl and crotyl azide, respectively (measured in pentane, diethyl ether, and 70% aqueous acetone). A negative entropy of activation supports a cyclic transition state. In a dissociative mechanism, a positive entropy of activation would be expected. In a concerted mechanism, a negative entropy of activation is expected because the two freely moving ends must come together. Noble and co-workers provided further support by measuring the effect of pressure on the rate of rearrangement.¹²⁵ The activation volume was measured in both directions with an average value of $-8.7 \text{ cm}^3 \text{ mol}^{-1}$. This value is consistent with a cyclic transition state. The activation volume of similar reactions is reported to be around $-10 \text{ cm}^3 \text{ mol}^{-1}$.¹²⁶

Substituent effects

Six years after Winstein's original observation, VanderWerf and Heasley reported an investigation of substituent effects for the rearrangement. They found that secondary and tertiary azides generally rearrange faster than the corresponding primary azide.³⁵ It was observed that allylic heteroatoms, in this case an additional azide group, slow the rearrangement. These observations appear to be consistent with a slight accumulation of positive charge in the transition state. Also suggestive of a cyclic transition state is the observation that *cis*-alkenes rearrange slower than *trans*-alkenes ($k = 2.6 \times 10^{-6}$ and $k = 8.5 \times 10^{-6}$ respectively), which was proposed to be due to steric hindrance in the transition state (Scheme 12a). The rate of rearrangement is reversed when both α and β substituents are present (Scheme 12b). These substituents hinder coplanarity in a concerted transition state but would likely facilitate an ionic mechanism because the substituent would stabilize the intermediate cation. In this case, prior examples would predict that the more substituted alkene isomer **12.2** would be favored at equilibrium; but in this instance, the reverse was observed with isomer **12.1** being dominant. These substituent effects, along with the solvent effects and entropy of activation, convinced VanderWerf to propose a concerted mechanism with a cyclic transition state.³⁵

¹⁵N-Labeling study

More recently, Topczewski and co-workers provided further support for the [3,3]-sigmatropic mechanism by selectively labelling one of the nitrogen atoms in the azide with an ¹⁵N atom (Scheme 13).⁸⁴ In this work, ¹⁵N-labeled amine **13.1** was synthesized and

converted to the azide through a diazo transfer reaction to afford azide **13.2**. This allylic azide spontaneously rearranged to generate ^{15}N -labeled cinnamyl azide **13.3**. If the [3,3]-sigmatropic mechanism is occurring, the ^{15}N label will be on the terminus. This azide was converted to phosphoramidate **13.4** and HRMS analysis showed that the ^{15}N labelled had been removed (>95%). This observation provides direct evidence for the [3,3]-sigmatropic mechanism.

Stereospecific azide rearrangement and racemization

The [3,3] sigmatropic nature of the Winstein rearrangement should impart stereospecificity to rearrangement with chiral azides. Padwa and co-workers investigated a cyclization reaction that demonstrated the Winstein rearrangement is stereospecific (Scheme 14a and b).^{127,128} In this reaction, insertion of the metal carbene into the O—H bond formed five-membered ring **14.2**. Ketone tautomerization resulted in allylic azide **14.3**, which underwent the Winstein rearrangement to form enol **14.4**. A second tautomerization generated the observed product **14.5**. When a diastereomer of the starting material was used, the product was formed with the opposite relative configuration (Scheme 14b). This is consistent with stereospecific transfer, as expected for a concerted sigmatropic mechanism.

Panek observed stereospecificity during an asymmetric synthesis of γ -hydroxy- α -amino acid precursors and (–)-motuporin that involved allylation and rearrangement (Scheme 14c and d).^{129,130} In this sequence, the allylation proceeded to generate an intermittent allylic azide, which isomerized to the more stable conjugated isomer (Scheme 14c). Again, using an epimeric allylsilane starting material resulted in the opposite diastereomer, which is consistent with a stereospecific outcome. Spino and co-workers observed stereospecific rearrangement following $\text{S}_{\text{N}}2$ displacement (Scheme 14e).^{64,65} To confirm that the Winstein rearrangement is stereospecific with acyclic trisubstituted alkenes, Topczewski and co-workers isolated a single enantiomer of azide **14.6** and then let it equilibrate (Scheme 14f).⁸⁴ After equilibration, both alkene isomers **14.6** and **14.7** were still a single enantiomer, which confirmed that the alkene isomerization was independent from racemization.

These observations all indicate that the Winstein rearrangement is a concerted stereospecific process with a cyclic transition state. Computational studies also support this mechanism and demonstrate that the transition state is calculated to be a half-chair (TS, Scheme 15).^{84,121,131,132} In the calculated transition state, five of the six atoms are coplanar (C—N—N—N—C), with the central carbon atom forms a C—C—C “pucker”.⁸⁴ The *E* to *Z* stereospecific rearrangement of azide **15.1** to **15.3** is proposed to occur by one of two pathways that vary in the sequence of steps.⁸⁴ The pathway reproduced here occurs by (i) sigmatropic rearrangement of azide **15.1** into azide **15.2**, (ii) sigma bond rotation of azide **15.2**, and (iii) a second sigmatropic rearrangement of azide **15.2** into azide **15.3**.⁸⁴ Neither azide **15.4** nor azide **15.5** are accessible by the sigmatropic mechanism.

As described above, the Winstein rearrangement is generally stereospecific. Thus, when both of the isomers are chiral and have different substituents, typically no racemization is observed ($\text{R} \neq \text{R}'$, Scheme 16a).^{56,64,65,84,127-130} One exception to this is when the rearrangement's transition state is symmetric ($\text{R} = \text{R}$), which results in the enantiomer of the

starting material upon rearrangement (Scheme 16b).^{31,32} An illustrative example of this was encountered in the synthesis of queuosine by Carell and co-workers (Scheme 16c).³¹ The loss of stereochemical integrity was not due to an S_N1 like substitution but rather the fault of the Winstein rearrangement. The authors measured the rate of racemization and determined a half-life of about 10 h at 45 °C. Because racemization was relatively slow, the azide could be prepared and subsequently reduced at 0 °C to maintain high ee in the allylic amine product. The Winstein rearrangement can result in racemization when one of the isomers is achiral (Scheme 16d). Facile racemization can be enabling to dynamic kinetic resolution (*vide infra*).

While the Winstein rearrangement generally occurs *via* a [3,3]-sigmatropic mechanism, under certain conditions an ionic mechanism is possible (Scheme 17a).⁸⁴ Trisubstituted allylic azides **17.1** were heated to 100 °C for a week in hexanes, toluene, chloroform, or tetrahydrofuran with little or no racemization. However, when these azides were heated in methanol, significant racemization was observed after 1 h (from >99 : 1 er to 74 : 26 er) and the sample was completely racemic after 8 h. During this study, the formation of methyl ether **17.4** was observed and attributed to solvolysis. This product indicates that the racemization is likely occurring through ionic intermediate **17.2**. Once cation **17.2** is formed, it can either recombine with azide anion to provide either azide **17.1** or azide **17.3**. Alternatively, ion **17.2** can be trapped by methanol to form ether **17.4**. To further support the formation of a cationic intermediate, a Hammett plot was constructed based on initial rate data. The value σ^+ correlated with the rate of racemization ($R^2 = 0.99$, $\rho = -3.9$). These observations support the ionic mechanism.

While racemization is generally viewed as a problem to be avoided, it can be valuable in the context of dynamic kinetic resolutions (DKR). When performing a DKR, it is necessary to have a pathway for racemization. The ionic mechanism for racemization described above only proceeds in MeOH at high temperatures and produces a significant amount of the solvolysis by-product (Scheme 17a).⁸⁴ Thus, it is not a practical pathway for racemization to use for DKR. To address this issue, Topczewski and co-workers investigated Lewis acids to promote the racemization (Scheme 17b).¹²² A variety of Lewis acids were capable of racemizing activated organic azides, including allylic azides. Ideally, this observation could provide the racemization pathway for a DKR.

Equilibrium ratios

For most allylic azides, the Winstein rearrangement generates a mixture of alkene isomers. However, a variety of effects have been identified that bias the equilibrium. When one of the alkene isomers is conjugated to an aromatic ring, carbonyl, or sulfonyl group, then the equilibrium is significantly biased (Scheme 18a).^{129,133,134} Only the conjugated isomer is typically observed and this was noted in the synthesis section for these allylic azides. In contrast, if both alkene isomers are conjugated, then the thermodynamic stability of the isomers is brought closer together and a mixture of isomers is observed (Scheme 18b).⁸⁴

The equilibrium ratio of azide isomers can be affected by other allylic substituents (Scheme 19). Sharpless and co-workers observed that an allylic hydroxyl group shifted the equilibrium in favor of the isomer that places the hydroxyl group and azide proximal to each

other (Scheme 19a vs. 19b).¹³⁶ This was originally proposed to be due to a hydrogen bond between the hydroxyl and azide.^{121,136} More recently, Topczewski and co-workers demonstrated that a similar shift occurs when the hydroxyl is protected as the silyl ether (Scheme 19b vs. 19c).³³ This observation prompted a more detailed study to look at a variety of other allylic ethers and amines. The study found that the percentage of the branched isomer at equilibrium correlates to the DMSO pK_a of the allylic group. This effect was thought to be stereoelectronic in nature.³³

The equilibrium ratio of allylic azide isomers can be affected by *syn*-pentane interactions. The allylic azide in Scheme 20a exists as a 2 : 1 mixture of two structural isomers.³⁴ In the equilibrium of a related compound, one of the isomers is no longer observable by ^1H NMR (Scheme 20b). This observation was attributed to a destabilizing *syn*-pentane interaction in the unobserved isomer. It is important to note that even though this isomer was not observed, the Winstein rearrangement is still occurring based on the result of a subsequent intramolecular Friedel–Crafts alkylation.³⁴ A similar observation was made when working with pyranil azides (Scheme 20c and d).¹⁰² When the azide and OⁱPr groups are on opposite sides of the ring, both structural isomers were observed (Scheme 20c). However, when the two groups were on the same side of the ring, there was an additional destabilizing interaction in one of the isomers (Scheme 20d). This interaction disfavors the proximal isomer such that it was not observed by ^1H NMR. Spino and co-workers were able to use a menthone derived auxiliary to control both the stereochemistry and regiochemistry of the allylic azide (Scheme 20e). These combined examples show that the allylic azide equilibrium can be significantly biased due to conjugation, proximal heteroatoms, and steric effects.

Selectivity principles

In general, organic azides have been extensively used in organic synthesis. In contrast, allylic azides have largely been avoided because of the Winstein rearrangement and because allylic azides can exist as a mixture of isomers. Using the mixture of isomers has resulted in a mixture of products. One example of this undesirable outcome can be seen in Rydzewski's synthesis of 4'-azido carbocyclic nucleosides (Scheme 21).¹³⁷ Allylic ether **21.1**, a single isomer, formed multiple equilibrating azides upon displacement. Subsequent epoxidation resulted in the formation of all four possible epoxide isomers, with a low yield of the desired product.

The formation of an allylic azide mixture complicates the use of these intermediates in synthesis. However, two general approaches have been developed to overcome this complication. The first is to use allylic azides that exist and react predominantly as a single isomer. The second approach is to develop reactions that are selective for one azide isomer in the mixture. If appropriate selectivity principles are employed, allylic azides can be very useful synthetic intermediates. A particularly exciting aspect of the Winstein rearrangement is to use the rearrangement as the racemization pathway for dynamic kinetic resolutions (DKR). A chiral catalyst can selectively functionalize one of the azide enantiomers.³²

Reactions that have utilized allylic azides will be described below. Methods that maximize selectivity will be highlighted. These reactions have been divided into three sections: (1) reactions on allyl azide, (2) reactions of the azide component of the allylic azide, and (3) reactions of the alkene component of the allylic azide.

Allyl azide

The simplest allylic azide is allyl azide. Due to the low molecular weight and high volatility, care should be taken when handling allyl azide. We would discourage isolating allyl azide or using it on a large scale. Allyl azide is symmetric upon Winstein rearrangement, so the azide positions are indistinguishable. The alkene is terminal, so no *E/Z* isomers are present. Allyl azide is achiral, minimizing stereochemical considerations. Since allyl azide exists as a single isomer, minimal selectivity is needed when using this molecule. Scheme 22 demonstrates many of the reactions that have been performed with allyl azide.

In 1908, Forster and Fierz showed that allyl azide could be dimerized in the presence of acid to form a fused bis-triazoline (Scheme 2a).^{138,139} Yang performed a cycloaddition with acrylonitrile (Scheme 2b).¹⁴⁰⁻¹⁴² The initially formed triazoline adduct rearranged to form the observed fused ring system. This rearrangement is particularly interesting because it requires a proximal alkene in the starting material. Several more traditional cycloadditions have also been performed on allyl azide which will be discussed later.¹⁴³⁻¹⁴⁶ Kabalka used allyl azide as an aryl aminating reagent (Scheme 22c).¹⁴⁷ An aryl Grignard or lithium reagent was added to the azide, generating a triazene. After acidic workup, this resulted in the aryl amine. Pietruszka used allyl azide to generate secondary amines (Scheme 22d). This method involved mixing a potassium organotrifluoroborate with SiCl₄ in the presence of allyl azide to generate the *N*-substituted allyl amine.^{148,149} Other reactions using allyl azide are known, but will not be discussed further.¹⁵⁰⁻¹⁵⁶ It is worth noting that low molecular weight azides, such as this one, are potentially explosive.¹⁵⁷ Organic azides with a carbon to nitrogen ratio greater than 3 to 1 are generally safer to handle.

While reactions on allyl azide do not address the selectivity issue, they are a useful starting point for determining the reactivity of allylic azides. Alkene functionalizations in particular can be sensitive to substitution patterns, electronics, and proximal functionality. Since azides are electron withdrawing, they can cause the alkene to be less nucleophilic. Also, organic azides are capable of acting as ligands on metal complexes, potentially interfering with metal catalyzed reactions.^{158,159} Since allylic azides possess two reactive functional groups (azide and alkene), the reactions discussed below have been organized based on the reactive group.

Reactions of allylic azides at the azide

Azide decomposition to imine or nitrile

Allylic azides can decompose to form imines. This was first demonstrated by heating allyl azide to release nitrogen gas (Scheme 23a).¹⁶⁰ Banert accomplished this same transformation using potassium *tert*-butoxide on a substituted allylic azide, presumably by deprotonation of the acidic α -C—H (Scheme 23b).¹⁶¹ Subsequent hydrolysis resulted in the

corresponding ketone. This azide is symmetric upon rearrangement, so no site selectivity was required. Ghorai and co-workers also used potassium *tert*-butoxide to generate imines from cinnamyl azides. Imine formation was followed by an allylation (Scheme 23c).⁵¹ In this case, the aryl group stabilizes the conjugated alkene isomer, which controls the Winstein rearrangement. A high yield of the allyl amine was attained for most substrates. In 2016, Park and co-workers used diruthenium catalyst **23.1** to convert allylic azides into α,β -unsaturated imines (Scheme 23d and e).¹⁶² The reaction proceeded in excellent yield when performed on allylic azides that are conjugated (Scheme 23d). Additionally, when geranyl azide was used the primary azide isomer was selectively consumed leading to high yield of the desired imine (Scheme 23e). While the reaction was capable of distinguishing between primary and tertiary azides it was unsuccessful at selectively differentiating between primary and secondary azides. This method was applied to the synthesis of pyridines (Scheme 23f). Catalyst **23.1** was used to generate the imine. Subsequent electrocyclozation and oxidation led to the pyridine.

Other methods to convert allylic azides into nitrogenous aromatic rings have been developed. In 2003, Sá and co-workers reported a Lewis acid catalyzed cyclization to form quinolines (Scheme 24a).⁵⁸ The substrates for this reaction exist as one observable isomer due to conjugation. Unfortunately, the yield was not optimized above 23% due to starting material decomposition. Yu and co-workers broadened the scope of this reaction by using NBS and visible light to initiate a radical cyclization (Scheme 24b).¹⁶³

Several groups demonstrated the oxidation of cinnamyl azide to the corresponding nitrile using TBHP or a ruthenium catalyst (Scheme 25a).^{22,164-166} In 2014, Jiang and co-workers made this same nitrile through a palladium catalyzed allylic azidation followed by oxidation to the nitrile (Scheme 25b).¹¹⁷ Allylic leaving groups have been displaced with NaN_3 and the resulting azide was subsequently oxidized to the nitrile (Scheme 25c-e).^{23,24,167} While these reactions generally proceed in high yields when the alkene is conjugated to an aryl or ester, the corresponding aliphatic substrates were less efficient.^{23,167} It should be noted that the combination of dichloroethane (DCE) and sodium azide may raise safety concerns due to the potential to accidentally form 1-azido-2-chloroethane or 1,2-diazido-ethane (Scheme 25c).⁴⁶

Azide reduction

The reduction of azides with PPh_3 (Staudinger reduction) or LiAlH_4 is well known. When these reductions are performed on allylic azides a mixture of isomeric products can result.¹⁶⁸ Methods have been developed for the direct conversion of allylic acetates and allylic bromides into the corresponding allylic amine *via* the azide intermediate (Scheme 26a).⁸⁶ The Staudinger reaction occurs faster on the primary azide relative to the tertiary azide. So, good selectivity was obtained for the primary amine even if the azide equilibrated (Scheme 26a).¹⁶⁹ The primary azide is likely to be the major component at equilibrium due to the increased stability of the more substituted alkene (~70 : 30, Scheme 1). Carell and co-workers took advantage of the slow relative rate of isomerization (Scheme 26b).³¹ By keeping the allylic azide at 0 °C, the rearrangement was slowed and a Staudinger reaction proceeded in good yield with minimal loss of enantiopurity. Trost and co-workers performed

the same reduction, but on a substrate that significantly favors one azide isomer at equilibrium (Scheme 26c).¹⁷⁰ Spino demonstrated another setting for selective azide reduction. This example used a menthone derived chiral auxiliary to bias the equilibrium (Scheme 26d).⁶⁴ Subsequent azide reduction proceeded with excellent yield. Spino later used this methodology in the total synthesis of (+)-lentiginosine, (+)-lentiginosine, and (+)-pumiliotoxin C.⁶⁵ In a related reaction, Zanatta and co-workers used an aza-Wittig reaction to form a variety of 2-trifluoromethyl pyrroles (Scheme 26e).¹⁷¹ Only one azide isomer was observed in this case due to conjugation in the starting materials. These azide reductions emphasize the value of biasing the azide equilibrium and using reductions that kinetically out compete the rearrangement.

Cardillo and co-workers investigated the global reduction of allylic azides in work targeting 3(2'-amino)- β -lactams (Scheme 27a).⁵⁶ Using hydrogen gas and palladium on carbon, both the azide and the alkene were reduced in high yield. This reaction proceeded with good diastereoselectivity for the new endocyclic stereocenter, but the mixture of *Z* and *E* alkene isomers present in the starting material resulted in a mixture of diastereomers at the nitrogen center. The simultaneous reduction of the azide and alkene has also been used to synthesize lactams (Scheme 27b and c).¹⁷²⁻¹⁷⁴ In 2006, Sudalai and co-workers reported the enantioselective cyclization of an allylic azide conjugated to an ester (Scheme 27b).^{173,175,176} This work combines two reductions, which allowed lactamization. Sudalai and co-workers demonstrated the utility of this method by performing an enantioselective total synthesis of (*R*)-(-)-rolipram, in which the cyclization proceeded in 92% yield and 92% ee.¹⁷³ Tjeng developed a similar global reduction, which resulted in the formation of pyrrolidines.²⁹ Another lactamization of allylic azides was demonstrated by Murphy and co-workers in 2013 (Scheme 27c).¹⁷⁴ Homolytic cleavage of the aryl-iodide bond is thought to initiate a radical cascade to form the desired lactam. In this example, no selectivity is required with the 2-substituted allyl azide.

Amide formation from allylic azides

Cyclization reactions can enable selectivity when working with allylic azides. Selectivity can be attained because one isomer will react faster due to the relative rates of ring formation. In 2012, Aubé and co-workers developed a diastereoselective Schmidt reaction on an equilibrating mixture of allylic azides (Scheme 28a).¹³⁵ The azide that is in closer proximity to the ketone reacts preferentially despite, typically, being the minor isomer at equilibrium. The cyclization was mediated by SnCl₄ and proceeded in good yield with high diastereoselectivity for most substrates. This method's utility was demonstrated through a formal synthesis of pinnaic acid.¹⁷⁷ This example highlights the use of intramolecularity to enforce selectivity. Aubé and co-workers also demonstrated that this Schmidt reaction could be promoted by TiCl₄ in HFIP (Scheme 28b).¹⁷⁸ Reddy and co-workers expanded on this work by using substrates with a pendant hydroxyl group (Scheme 28c).¹⁷⁹ The hydroxyl group serves as a directing group to promote oxocarbenium ion formation. The oxocarbenium ion reacts preferentially with the proximal azide isomer. After hydrolysis, this reaction resulted in a selective formation of exocyclic amides.

Cycloadditions

Azides are well-known for their ability to undergo the Huisgen cycloaddition with alkynes.¹⁸⁰⁻¹⁸³ The Huisgen cycloaddition can occur thermally. Alternatively, the copper catalyzed azide–alkyne cycloaddition (CuAAC) is widely used both in organic synthesis and in biological applications.^{11,12,184} In addition to copper, a variety of other metals have been used to catalyze this cycloaddition.¹⁸⁵ The numerous examples of azide–alkyne cycloadditions on allylic azides have been divided into three sections based on the complexity of the substrate. Scheme 29 demonstrates the azide–alkyne cycloaddition on allylic azides that exist predominantly as one isomer due to conjugation. In this case, no additional selectivity is necessary to differentiate the azide isomers. Scheme 30 shows examples of the azide–alkyne cycloaddition on substrates that exist as an equilibrating mixture of isomers. In these cases, the least sterically hindered azide is selectively trapped. Scheme 31 is comprised of intramolecular cycloadditions with equilibrating substrates. In this case, the selectivity is driven by the rate of ring formation.

Lopez (Scheme 29a) and Evans (Scheme 29b) demonstrated intermolecular CuAAC on allylic azides that exist mainly as one isomer due to conjugation of the alkene with an aryl or sulfate functional group.^{134,186} Mishra performed a thermally promoted intramolecular cyclization with a variety of aryl groups in good to excellent yields (Scheme 29c).¹⁸⁷ A silver catalyzed azide–alkyne cycloaddition was developed and applied to allylic azides (Scheme 29d).¹⁸⁸ Several other examples have been developed that do not require selectivity.^{143-146,189,190} Methods have been developed to form the allylic azide and directly perform the azide–alkyne cycloaddition in one step.^{191,192} Fukuzawa found that Cu(OTf)₂ could act as a double catalyst (Scheme 29e).¹⁹¹ First, Cu(OTf)₂ was reported to catalyze the azide installation and then to catalyze the CuAAC. It should be noted that generally Cu(I) is thought to be the active species in CuAAC. Recently, Topczewski and Liu reported an enantioselective CuAAC (E-CuAAC) with allylic azides that proceeds by dynamic kinetic resolution (Scheme 29f).²⁴³ This reaction is noteworthy because the resulting triazole was isolated in high ee and high yield using the racemic azide as the limiting reagent. The authors provided several examples demonstrating that this reaction can proceed with good stereocontrol in a complex molecular environment.

The azide–alkyne cycloaddition has also been performed on equilibrating mixtures of allylic azides. Sharpless and co-workers made a significant advance in the area of selective allylic azide functionalization when they performed a CuAAC with an equilibrating mixture of azides (Scheme 30a).¹³⁶ In this case, the isomer with the primary azide reacted preferentially. The selectivity in this cycloaddition is thought to be a result of steric hindrance around the tertiary azide. When the CuAAC was performed on crotyl azide a mixture of triazoles was observed, indicating that the selectivity of a primary vs. secondary azide is minimal. Munoz and co-workers also performed a CuAAC on an equilibrating mixture of allylic azides (Scheme 30b).¹⁰⁷ Again, the isomer with the primary azide reacted preferentially. In 2014, Aubé and co-workers were able to obtain two different azide–alkene cycloaddition products depending on the reaction conditions (Scheme 30c). When the CuAAC was performed, dimerization of the linear isomer was observed.¹⁹³ When the same allylic azide was heated at reflux in toluene, an intramolecular cyclization was observed.

Aubé and co-workers investigated the thermally promoted intramolecular cyclization further (Scheme 31a).¹⁹³ An intramolecular cyclization was performed with good selectivity because the formation of a six-membered ring is significantly faster than cyclization to an eight-membered ring. Furthermore, the *cis* isomer, which would be the most likely to cyclize to an eight-membered ring, is a minor equilibrium component. Unfortunately, minimal diastereoselectivity was observed. Murphy improved upon this by taking advantage of stereocenters that were already set in the molecule to enforce diastereoselectivity (Scheme 31b).¹⁹⁴ The utility of this method was demonstrated by synthesizing C-glycosyl iminosugars. Mishra performed a similar reaction on a nitrile instead of the alkyne, which afforded tetrazoles (Scheme 31c).¹⁸⁷ This reaction was expanded to include a direct conversion of allylic acetates to the corresponding tetrazoles *via* an allylic azide intermediate.¹⁹⁵

While the azide–alkyne cycloaddition is more well-known, the azide cycloaddition is also viable with alkenes. Murphy demonstrated that a mixture of equilibrating allylic azides can be converted to a triazoline (Scheme 32a).^{194,196,197} Triazolines are not always stable and can extrude N₂, resulting in an aziridine. The fused aziridines were difficult to isolate and a nucleophile was used to form isolable products. Unfortunately, the aziridine intermediate has multiple electrophilic sites, which led to multiple products for most substrates in a low yield. More work is needed in this area to develop selective nucleophilic additions that take advantage of the aziridine intermediate. This aziridination has also been performed intermolecularly on a symmetric allylic azide (Scheme 32b).¹⁹⁸

Within an allylic azide, the azide's dipolar nature tends to make it more reactive in cycloaddition reactions. But, the alkene can also undergo cycloadditions. By using an electron deficient alkene, Quan was able to perform a cycloaddition between the alkene and an oximine to form the corresponding isoazole (Scheme 33).¹⁹⁹

The above examples illustrate that the azide portion of an allylic azide can undergo a number of reactions. The selectivity of these processes can be modest to excellent depending on the control elements used to differentiate the azide isomers.

Reactions of allylic azides at the alkene

Reactions that lead to alkene isomerization

Craig and co-workers took advantage of the Winstein rearrangement and designed a tandem Winstein rearrangement–Claisen rearrangement cascade (Scheme 34a).⁵⁹ In this cascade, an alcohol was converted to the corresponding vinyl ether (**34.1**). This intermediate can freely equilibrate by the Winstein rearrangement, but only one of the isomers can undergo the Claisen rearrangement. In this case, good site selectivity is enforced by the [3,3] mechanism of the Claisen rearrangement. Depending on the identity of R and R', these reactions proceeded with good to excellent yields but minimal diastereoselectivity, which is not uncommon for these types of Claisen rearrangements. Tjeng also worked on the Claisen rearrangement and then expanded the work to include Overman rearrangements (Scheme 34b).²⁹ Similar to Craig's work with the Claisen rearrangement, only one of the allylic azide isomers can undergo the Overman rearrangement. In Tjeng's work, the allylic azide is

attached to alkyl groups. Interestingly, when there is a pendant arene these substrates can undergo a Friedel–Crafts alkylation (Scheme 35).³⁴

Topczewski and co-workers successfully coupled the Winstein rearrangement with an intramolecular Friedel–Crafts alkylation to form highly substituted tetralins, chromanes, and tetrahydroquinolines with excellent diastereoselectivity (Scheme 35).³⁴ In this reaction, only azide isomer **35.2** can undergo the desired Friedel–Crafts alkylation reaction. As the reactive isomer **35.2** is consumed in the reaction, the unreactive isomer **35.1** will undergo the Winstein rearrangement to re-establish equilibrium. Through this dynamic equilibrium, all of the equilibrating isomers can be converted into the desired product. The reaction is thought to proceed by a chair like transition state, which may explain the high diastereoselectivity. The utility of this method was demonstrated by synthesizing the core of the hasubanan alkaloids.

In 2016, Tambar and co-workers reported on the [2,3] and [1,2]rearrangements of iodonium ylides (Scheme 36).²⁰⁰ In both of these reactions, the diazo is converted into the metal carbene and then is attacked by the iodide. This generates the iodonium ylide intermediate shown. At this point, the *cis* and *trans* isomers of the intermediate react differently. The *cis* isomer is aligned to undergo a [2,3]-sigmatropic rearrangement. This generates the terminal alkene shown in Scheme 36a. The *trans* isomer, on the other hand, undergoes a [1,2]-sigmatropic rearrangement to form the internal alkene (Scheme 36b). In this work, the individual azide isomers were separated by column chromatography and only the *cis* or *trans* isomers were subjected to the respective reaction conditions. This is likely necessary to obtain a high yield of a single product.

Trost and co-workers performed a diastereoselective allylic substitution on an allylic azide in the enantioselective total synthesis of (+)-pancratistatin (Scheme 37).¹⁰⁴ In this reaction, only one of the possible azide isomers contains an allylic carbonate. This difference in functionality is an important way to gain selectivity for the different azide isomers. As in many other copper catalyzed allylic substitutions, the nucleophile was added to the γ position (relative to the leaving group) with inversion of the stereochemistry.²⁰¹ Because of difficulty in purifying this product, it was immediately dihydroxylated to generate the diol in 62% overall yield.

Alkene oxidations

A highly utilized alkene oxidation is the Upjohn dihydroxylation.^{202,203} This reaction has been performed several times on allylic azides (Scheme 38).^{101,204,205} In the examples shown, the azide substrate exist primarily as a single isomer. Dihydroxylation proceeds with good yield. In these cases, good diastereoselectivity was observed with oxidation proceeding *anti* to the azide.^{32,102} Danishefsky and co-workers were able to obtain site selectivity on an equilibrating mixture of allylic azides during the total synthesis of *N*-acetylactinobolamine (Scheme 38d).²⁰⁶ In this case, vinyl ether **38.2** is significantly more nucleophilic than isomer **38.1**. The enol ether reacts preferentially and *syn*-dihydroxylation occurs *anti* to the azide.

More recently, Topczewski and co-workers performed a Sharpless asymmetric dihydroxylation on symmetric allylic azides (Scheme 38e).³² Given that the substrates are

symmetric upon rearrangement, site selectivity was not required. Good diastereoselectivity (up to 11 : 1 dr) and excellent enantioselectivity (up to 99 : 1 er) allowed this dihydroxylation to transform a racemic mixture of azides into products with three contiguous stereocenters. This dihydroxylation represented the first enantioselective DKR using the Winstein rearrangement as the racemization pathway. In this case, negative hyperconjugation was thought to contribute to the observed diastereoselectivity (*anti* to azide) and a chiral ligand was used to enforce enantioselectivity.

The dihydroxylation of allylic azides can be conducted with oxidants other than OsO₄. Ruthenium catalyzed dihydroxylations have been performed on several allylic azides that exist primarily as one isomer (Scheme 39a and b).²⁰⁷⁻²⁰⁹ In these examples, conjugation to an arene (Scheme 39a) or an ester (Scheme 39b) controls the azide equilibrium and leads to one major product. Product **39.2** arises from oxidation *anti* to the azide, as with OsO₄, and is a late stage intermediate for the synthesis of Tamiflu derivatives.²⁰⁹ The C₂ symmetric bis-azide 39.3 was oxidized to afford a fully substituted and stereo-defined cyclohexyl ring *en route* to *myo*-inositol derivatives (Scheme 39c).²¹⁰ A similar dihydroxylation was performed with KMnO₄ (Scheme 39d).^{211,212}

Epoxidations

Allylic azides also react with peracids, commonly *m*-CPBA, to form epoxides. One notable epoxidation of an allylic azide was performed by Sharpless and co-workers in 2005 (Scheme 40a).¹³⁶ In this work, an equilibrating mixture of allylic azides was exposed to *m*-CPBA. The more substituted alkene represented 70% of the original mixture, but was selectively oxidized, enriching the yield of this isomer to 85%. Trisubstituted alkenes are more electron rich and tend to undergo epoxidation faster than monosubstituted alkenes. Because the product was more abundant than the initial quantity of this isomer, one can conclude that the Winstein rearrangement occurred at a competitive rate with oxidation of the terminal alkene.

The electrophilic *m*-CPBA epoxidation has been performed on a variety of other allylic azides. The simplest systems are those which exist as a single isomer due to symmetry (Scheme 40b).²¹³ Please note that this bis-azide is likely explosive. The epoxidation of allylic azides has also been performed on a variety of substrates that exist primarily as one isomer due to a proximal hydroxyl group (Scheme 40c and d).^{214,215} Both Johnson and Altenbach used this epoxidation in the enantioselective synthesis of (–)-LL-C10037a from benzoquinone.^{216,217} In 2017, Salamci and co-workers synthesized the diazide shown in Scheme 40e.²¹⁸ By varying the temperature and solvent of azidation, the authors reported isolating a single isomer of the diazide. This isomer was subjected to *m*-CPBA epoxidation, which proceeded in excellent yield. Looper and co-workers performed an epoxidation on a cyclic allylic azide in the synthesis of pactmycin core (Scheme 40f).²¹⁹ In this case, only one azide regioisomer is reported. Another important class of allylic azides are those conjugated to ketones (Scheme 40g).²²⁰ In this case, nucleophilic epoxidation conditions are employed to oxidize the conjugated alkene.

The Wacker oxidation of internal alkenes has proven to be challenging due to the lack of reactivity and regioselectivity.²²¹⁻²²³ Topczewski and co-workers recognized that the electron withdrawing property of allylic azides could induce selectivity in the Wacker

oxidation of cinnamyl azides (Scheme 41).⁵⁰ In this case, selective oxidation was attained at the benzylic position. Comparing the selectivity to the Wacker oxidation of β -methyl styrene indicates that the azide plays a critical role in the observed selectivity.²²³ This work emphasizes the electronic difference between allylic azides and unfunctionalized alkenes.

On a similar note, Zhang and co-workers were able to further oxidize cinnamyl azide to an α -hydroxy-ketone (Scheme 42a).²²⁴ This double oxidation reaction is noteworthy for its chemo- and regioselectivity. The reaction selectively oxidizes the alkene over the azide (*vide supra*, Scheme 25). Also, the ketone and alcohol are selectively added to the distal and proximal positions of the alkene, respectively. Murahashi demonstrated a similar transformation on a symmetric allylic azide using a different set of oxidants (Scheme 42b).²²⁵ The same regioselectivity was observed in this case.

Ozonolysis can be used to cleave the alkene in an allylic azide. Whitesides performed an ozonolysis on allylic azides to generate α -azidoaldehydes (Scheme 43a).⁴⁹ Originally, the ozonolysis was attempted on an equilibrating mixture and a mixture of aldehydes was generated. To solve this selectivity problem, a phenyl group was installed. This shifted the equilibrium so that there was only one observable isomer at equilibrium. Using this biased system, the ozonolysis successfully generated the desired aldehyde in moderate to good yield. Biasing the system through conjugation was clever in this context because the phenyl group is cleaved in the reaction. The ozonolysis of allylic azides has been performed on several other conjugated systems.^{99,226-228} Ozonolysis was used on cyclohexyl systems that exist as a single dominant azide isomer (Scheme 43b).²²⁹

A few other alkene oxidations are shown in Scheme 44. In Trauner's synthesis of ioline alkaloids, bromocyclization was performed on azide **44.1**.²³⁰ The bromonium ion intermediate was intercepted intramolecularly. After loss of the benzyl group, presumably through methanolysis, hydrobromide salt **44.2** was isolated. Wardrop and co-workers accomplished the formation of an aza-[2,2,2] bicyclic system through an intramolecular alkene difunctionalization (Scheme 44b).²³¹ This reaction proceeds with activation of the amide with PIFA generates an intermediate nitrene. The nitrene undergoes intramolecular aziridination and subsequent ring opening.²³¹ Winssinger and co-workers performed a phenyl selenium chloride mediated cyclization followed by oxidative elimination (Scheme 44c).²³² This was a key reaction in the synthesis of deguelin–biotin conjugates.

Propargyl azides

This review has focused on allylic azides and the Winstein rearrangement. A similar rearrangement occurs with propargyl azides (Scheme 45). The rearrangement of propargyl azides was originally reported by Banert and has since been termed the Banert cascade (Scheme 45a).^{4,161,233-238} Much like the Winstein rearrangement, the Banert cascade starts with a [3,3]-sigmatropic rearrangement. This is followed by a 6- π electrocyclization and a nucleophilic trap to generate NH-1,2,3-triazoles.²³⁹ Recently, Sharpless and co-workers explored this rearrangement and developed a general method for generating NH-1,2,3-triazoles (Scheme 45b).²⁴⁰ Substituted 1,2,3-triazoles can be generated *via* a CuAAC reaction, but using HN₃ would be unappealing to generate NH-1,2,3-triazoles. The Banert

cascade provides a complementary approach where the nitrogen is not substituted. This convenient synthesis has allowed NH-1,2,3-triazoles to be screened for inhibitory activity against VIM-2 Metallo- β -Lactamase.^{241,242} Few other applications of propargylic azides have been reported, which is likely due to the facile cyclization to triazoles *via* the Banert cascade.

Conclusions

Since 1960, significant progress has been made towards understanding the Winstein rearrangement and demonstrating how to take advantage of this spontaneous transformation. The Winstein rearrangement proceeds by a [3,3]-sigmatropic pathway in most situations, which imparts stereospecificity to the process. The stability of the azide isomers can be varied and conjugation or proximal functionality can bias the equilibrium. These biased substrates represent the clear majority of allylic azides that have been used as synthetic intermediates. Allylic azide isomers can be differentiated by a variety of functionalization reactions and or structural effects. While these selectivity principles have been applied to some of the common azide and alkene reactions (*e.g.* CuAAC reactions, epoxidation) more work is needed to expand the range of transformations. Ideally, through further development of selective reaction conditions, unbiased substrates can become reliable synthetic intermediates. Of particular significance is the use of the Winstein rearrangement as the racemization pathway in DKR. This represents a promising approach to the asymmetric synthesis of α,α -disubstituted amines. Further efforts are needed to expand this approach.

Acknowledgements

We thank other members of the Topczewski lab for their helpful discussions. This research was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number R35GM124718. Financial support was provided by the University of Minnesota.

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Fig. 1.
Classes of organic azides.

Scheme 1.

Mixture by the Winstein rearrangement not $\text{S}_{\text{N}}2'$.

Scheme 2.
Synthesizing allylic azides using sodium azide.

Scheme 3.

Use of LiN_3 in Trauner's synthesis of ioline alkaloids.

Scheme 4.
Conversion of alcohols directly to allylic azides.

Scheme 5.

Use of diphenylphosphoryl azide as an azide source.

Scheme 6.
Synthesis of allylic azides using TMSN₃.

Scheme 7.
Palladium catalyzed allylic substitution with NaN_3 .

Scheme 8. Palladium and gold catalyzed azidation with TMSN₃.

Scheme 9.
Gold catalysed hydroazidation of allenes.

Scheme 10.
Aziridination through C—H activation.

Scheme 11.

Possible mechanisms for the Winstein rearrangement.

Scheme 12.
Effect of substituents.

Scheme 13.
 ^{15}N -Labeling study.

Scheme 14.
Stereospecificity in the Winstein rearrangement.

Scheme 15.
Calculated transition state structures.

Scheme 16.
Racemization *via* the Winstein rearrangement.

Scheme 17.
Racemization *via* solvolysis or *via* catalysis.

A. Single Isomer Observed **B. Mixture Observed** **Scheme 18.**

Effect of conjugation on the allylic azide equilibrium.

Scheme 19.

Effect of allylic heteroatoms on the azide equilibrium.

Scheme 20.

Effect of steric interactions on the Winstein equilibrium.

Scheme 21.

Winsten rearrangement causes mixtures of isomers.

Scheme 22.
Reactions of allyl azide.

Scheme 23. Conversion of allylic azides to α,β -unsaturated imines.

Scheme 24.

Cyclization of allylic azides to form carboxyquinolines.

Scheme 25.
Oxidation of allylic azides to nitriles.

Scheme 26.
Chemoselective reduction of allylic azides.

Scheme 28.
Amide Formation from Allylic Azides.

Scheme 29.
CuAAC reactions using allylic azides.

Scheme 30.

Azide–alkyne cycloadditions on allylic azide mixtures.

Scheme 31.
Intramolecular cycloadditions with allylic azides.

Scheme 32.

Generating and trapping aziridines from allylic azides.

Scheme 33.
Alkene cycloaddition.

Scheme 34.
Tandem Claisen and Overman rearrangements.

Scheme 35.
Winstein rearrangement/Friedel–Crafts alkylation.

Scheme 36.
Copper-catalyzed [2,3]- and [1,2]-rearrangements.

Scheme 37.
Allylic substitution with an allylic azide.

Scheme 38.

Upjohn or sharpless dihydroxylations of allylic azides.

Scheme 39.
Dihydroxylation by RuCl_3 and KMnO_4 .

Scheme 40.
Epoxidation of allylic azides.

Scheme 41.

Wacker oxidation of internal alkenes.

Scheme 42.
Formation of α -ketols.

Scheme 43.
Ozonolysis of allylic azides.

Scheme 44.
Other alkene oxidations.

Scheme 45.
Banert cascade of propargyl azides.