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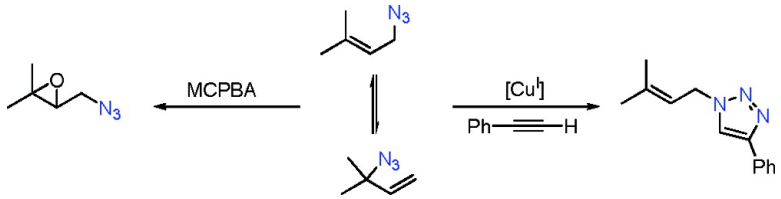

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The Allylic Azide Rearrangement: Achieving Selectivity

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Organic azides are most commonly used to introducte an amino group, and in this rather pedestrian role, their existence is barely noticed. Hence, the special reactivity features[1] of the azide functionality, as revealed in cycloadditions and pericyclic reactions, remain underappreciated, even though the latter are probably the most powerful and useful transformations involving azides.

Copper(I)-catalyzed cycloaddition with terminal alkynes, which results in 1,4-disubstituted 1,2,3-triazoles, is among the recent advances in the chemistry of organic azides.[2] The rare chemical orthogonality of the azide and alkyne functionalities (that is, inertness to acidic and basic conditions) has enabled unique applications of this process in chemical biology, organic synthesis, and materials science.[3] Since olefins, too, are stable in most acid/base environments, one expects that the special case of allylic azides might possess the familial reactivity profile, and it does, even though the azide and the olefin groups are engaged in the dynamic [3.3]-sigmatropic equilibration process[4] shown in Scheme 1.

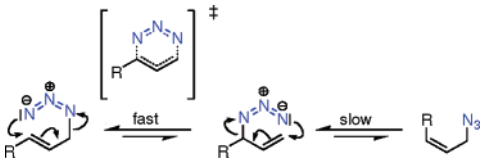
Since this rearrangement generally creates mixtures of the interconverting allylic isomers, it has been viewed as a liability.[5] The goal of our study was to achieve selective capture of one of these isomers. We envisioned that differences in their reactivity patterns could, in concert with their facile interconversion, prove advantageous. Reported here are the results from two model reactions: the Cu(I)-catalyzed azide−alkyne cycloaddition[2] and MCPBA epoxidation of olefins.[6]

Since both steric and electronic effects can influence reactivity of azides and olefins, the following allylic systems were studied in side-by-side experiments: primary vs tertiary, secondary vs tertiary, and primary vs secondary azides. Each of the three classes was represented by two members: the parent aliphatic azides (**1**, **5** and **9**) and their closely related hydroxylated derivatives (**3**, **7**, and **11**), selected to investigate the effect of the heteroatom and, in retrospect, the apparent hydrogen-bonding effects between the hydroxyl and the azide groups. As studies progressed, evidence grew that H-bonding effects could significantly modulate the equilibrium "set-points" in these dynamic systems.

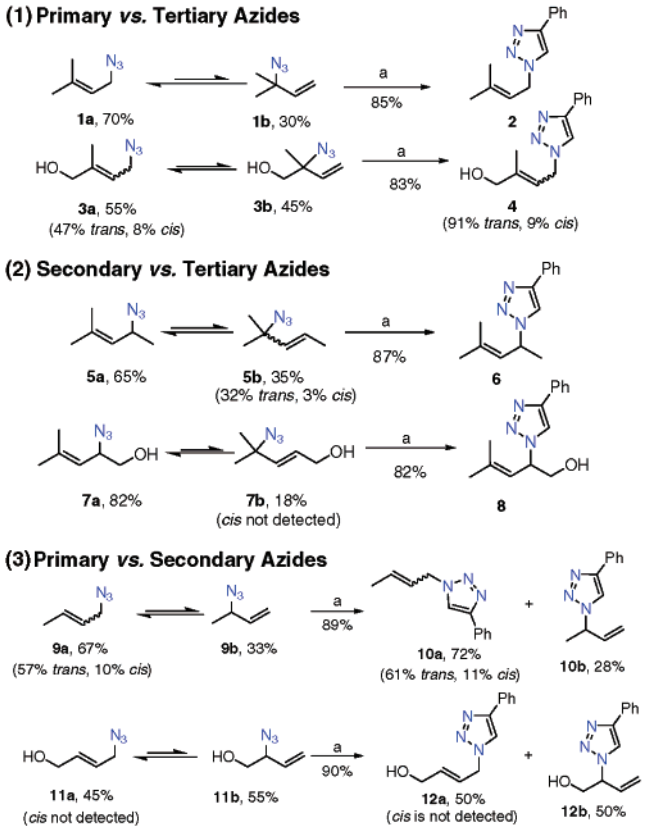
Having earlier noted that the Cu(I)-catalyzed triazole synthesis was somewhat sensitive to the steric environment of the azide,[7] we looked for such effects in the selectivity of product capture. Hence, a variety of allylic azides, all engaged in [3.3]-sigmatropy (albeit more or less facile for a specific case), were submitted to the Cu(I)-catalyzed cycloaddition with phenylacetylene as alkyne. The composition of the mixtures of triazole products was determined by ^{1}H and ^{13}C NMR and LC−MS. The results are summarized in Scheme 2.

Excellent selectivity was observed in the primary vs tertiary and secondary vs tertiary azides series (Scheme 2, entries 1 and 2). No products arising from tertiary azides were detected. Equilibration between the tertiary and the *trans*-primary allylic azides is faster than the Cu(I)-catalyzed reaction; however, the interconversion between the tertiary azide with the *cis* form of the primary azide is generally slower.[4c] As a result, the amount of product derived from the *cis* isomer of the azide approximated the amount of the *cis* azide found at equilibrium (as in triazole **4** derived from azide **3a**).

Scheme 1. Rearrangement of Allylic Azides



Scheme 2. Cu(I)-Catalyzed Cycloaddition of Allylic Azides with Phenylacetylene[a]



[a] Reagents and conditions: (a) azide (1 mmol), phenylacetylene (1 mmol), $CuSO_4 \cdot 5H_2O$ (0.05 mmol), sodium ascorbate (0.1 mmol), *t*BuOH/H_2O 1:1 (2 mL), room temperature, 12 h.

Interestingly, the Cu(I)-catalyzed cycloaddition reaction did not distinguish well between the primary and secondary azide regioisomers, with composition of the resulting mixture of triazole products being very similar to that of the starting materials (Scheme 2, entry 3).

To see if differential olefin reactivity would draw out similar selectivity, epoxidation with MCPBA, a reagent well known to

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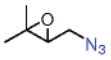
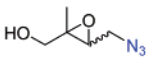
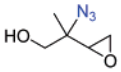
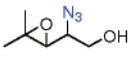
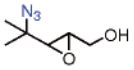
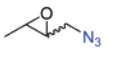
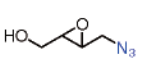
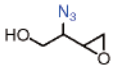
Table 1. Epoxidation of Allylic Azides

	allylic azide (regio ratio)	condi-tions[a]	epoxide products (ratio)		yield, (%)[b]
	Primary *vs.* Tertiary Azides				
1	**1a**:**1b** (70:30)	A			85
			>95	0	
			13a	**13b**	
2	**3a**:**3b** (55:45)	B			72
			>95	0	
			14a (81% *trans*, 9% *cis*)	**14b**	
	Secondary *vs.* Tertiary Azides				
3	**5a**:**5b** (65:35)	A			81
			90	10	
			15a	**15b**	
4	**7a**:**7b** (82:18)	B			83
			96	4	
			16a	**16b**	
	Primary *vs.* Secondary Azides				
5	**9a**:**9b** (67:33)	A			96
			>95	0	
			17a (87% *trans*, 8% *cis*)	**17b**	
6	**11a**:**11b** (45:55)	B[c]			44
			67	33	
			18a	**18b**	

[a] Conditions A:[6b] MCPBA (1.1 equiv), H_2O (0.3 M $NaHCO_3$), room temperature, 12 h. Conditions B: MCPBA (1.3 equiv), CH_2Cl_2, room temperature, 12 h. [b] Isolated combined yields. [c] Reaction time was 48 h.

be sensitive to the electronic properties of the olefin,[6b] was chosen. The epoxide product mixtures were analyzed by ^{1}H NMR,^{13}C NMR, and GC. Table 1 summarizes the results.

In general, good to excellent selectivity was realized. Aqueous conditions (A), which utilize buffered MCPBA, were preferred (see Supporting Information for details). However, for azido alcohols **3**, **7**, and **11**, nonaqueous conditions (B) were required to achieve complete conversion to the corresponding azidoepoxides. In the primary vs tertiary and primary vs secondary azide systems, excellent selectivity was observed for compounds **1** and **9** (cf. entries 1 and 5). As expected, more substituted olefins reacted faster. The more sluggish rearrangement rates noted with azido alcohols **3** and **11** appear to be due to the interplay of inductive electronic effects[8] and hydrogen bonding effects.[9] Although MCPBA reacts more slowly with less substituted olefins **3b** and **11b**, they appear to be sufficiently long-lived to produce noticeable amounts of the corresponding azidoepoxides **14b** and **16b**. In the secondary vs tertiary azide series, azido alcohol **7** performed slightly better than azide **5**, which lacks a hydroxyl group.

In summary, an allylic azide's existence as a dynamically equilibrating mixture of all possible [3.3]-isomers can be manipulated in interesting ways. By use of an appropriate capture trick, a given [3.3]-rearrangement family of allylic isomers is uniquely "siphoned off" through the isomer preferred by the "fixing" reaction. In the cases at hand, the rearrangement process was terminated by reactions selective for azide functionality and for olefin functionality, respectively. Given the wealth of useful olefin reactions with electrophiles and oxidants, allylic azides appear to offer many worthwhile selectivity refinements, in the already wide world of olefin transformations.

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Supporting Information Available: Typical experimental procedures and spectral characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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