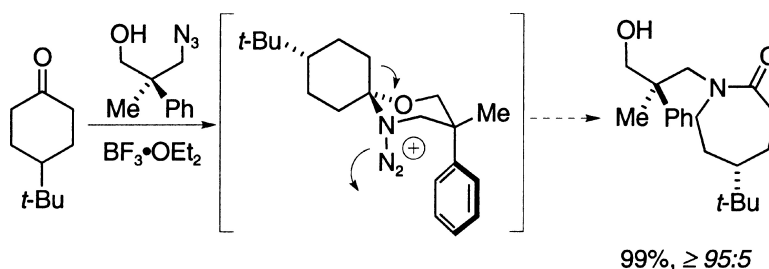Communication

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Unusual Tethering Effects in the Schmidt Reaction of Hydroxyalkyl Azides with Ketones: Cation−π and Steric Stabilization of a Pseudoaxial Phenyl Group

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Intramolecular reactions often benefit from greater control of stereoselectivity relative to their intermolecular counterparts. Specifically, the conformation of a "tether" connecting two reactive moieties often controls the ultimate diastereoselectivity of the process. Commonly, this stereoselectivity is ascribed to a reactive conformation in which the tether takes up a chairlike orientation, with a single substituent occupying the presumably more stable pseudoequatorial position on the linker.[1]

We have recently shown that Lewis acid-promoted reactions of hydroxyalkyl azides with substituted cyclohexanones can proceed with high levels of diastereotopic group-selectivity (Scheme 1).[2] In both potential intermediates **A** and **B**, the stereochemical relationship between the newly formed spirocyclic center and the *tert*-butyl group is established through pseudoequatorial addition of azide to an initially formed oxenium ion (not shown). The stereoselectivity of the reaction was proposed to result from (1) preferential reaction of the intermediate **A** bearing an equatorial substituent over **B** and (2) an axially oriented leaving N_2^+ substituent that permits antiperiplanar bond migration in the rearrangement step.[2b]

Herein, we report that the stereoselectivity of this reaction can be modulated by two unusual effects: one electronic (through-space cation−π stabilization) and one conformational (leading to superior selectivity in a substrate containing a geminally disubstituted tether).

In our initial study, we discovered that when R was Me or *i*-Pr, the products **1a,b** and **2a,b** were formed in 3−7:1 ratios, respectively (Scheme 1).[2b] In contrast, the replacement of either alkyl group with a phenyl substituent resulted in a substantially lower ratio (ca. 1.5:1 for **3a/3b**), despite the larger A value for this group.[3] This was surprising because hydroxypropyl azides bearing a phenyl group at either the 1- or 3-position afforded lactams with much higher selectivity (9→19:1 ratios). Two ways of explaining the apparently greater population of axial phenyl vs alkyl in these cases were immediately evident. First, noting that this intermediate placed the phenyl group and the positively charged N_2^+ group into a 1,3-diaxial relationship, it seemed prudent to consider through-space electronic effects. Although π−cation interactions are well established,[4] they have only rarely been invoked as a controlling feature in stereoselective reactions.[5] In addition, preferential axial placement of phenyl over alkyl has been noted in *gem*-disubstituted arylcyclohexanes.[6]

To probe the first point, we varied the electronic nature of a 2-aryl group in the reactions of three-carbon hydroxyalkyl azides with *tert*-butylcyclohexanone (Table 1).[7] In these experiments, isomer **a** arises from a transition structure resembling **A** in Scheme 1, bearing an equatorial phenyl group, whereas isomer **b** arises from a pathway involving an axial phenyl group (**B**).

The overall dependence of selectivity on the nature of arene substitution (from 1:1.3 to 3.2:1) is fully consistent with increased
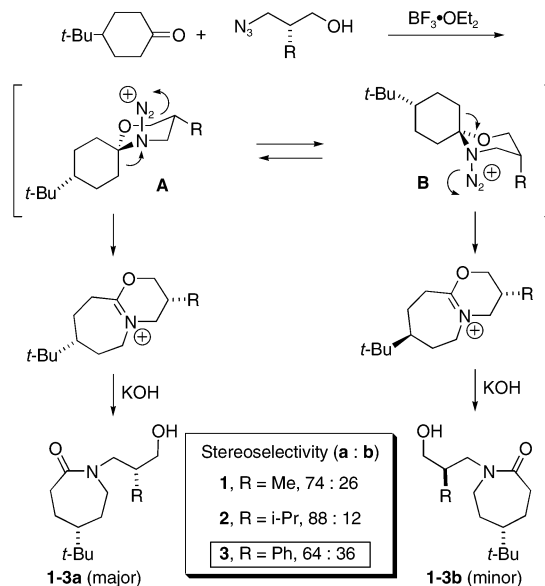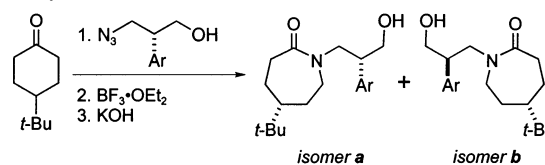
Scheme 1

Stereoselectivity (**a** : **b**)
1, R = Me, 74 : 26
2, R = i-Pr, 88 : 12
3, R = Ph, 64 : 36

1-3a (major)   **1-3b** (minor)

Table 1. Effect of Aryl Group Substitution on Ring Expansion Selectivity

entry	azide[a]	Ar	lactam	yield, %	ratio a	ratio b
1	4	3,4,5-trimethoxyphenyl	10	99	43	57
2	5	4-methoxyphenyl	11	99	47	53
3	6	phenyl	3	85	64	36
4	7	4-bromophenyl	12	90	68	32
5	8	4-fluorophenyl	13	73	69	31
6	9	4-nitrophenyl	14	86	76	24

[a] Except for **4** and **8**, racemic hydroxyalkyl azides were used. See Supporting Information for details and structural assignments.

stabilization[5a] of the N_2^+ group in axial transition structures **B** by more electron-rich aryl rings (Figure 1). Interestingly, plotting the log[ratio **b/a**] of these reactions against the Hammett σ^+ parameter yields a correlation of $r = 0.91$ despite the lack of a discrete cation intermediate. The observed ρ value of -0.35 is consistent with a greater π stabilization of positive charge in intermediates **B** over **A**. Although modest (as expected for a through-space interaction), these data indicate a definite electronic effect.[8] In addition, this
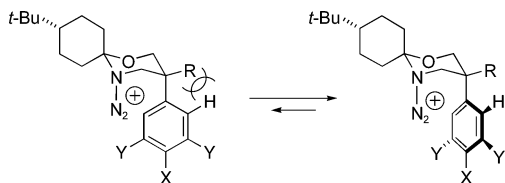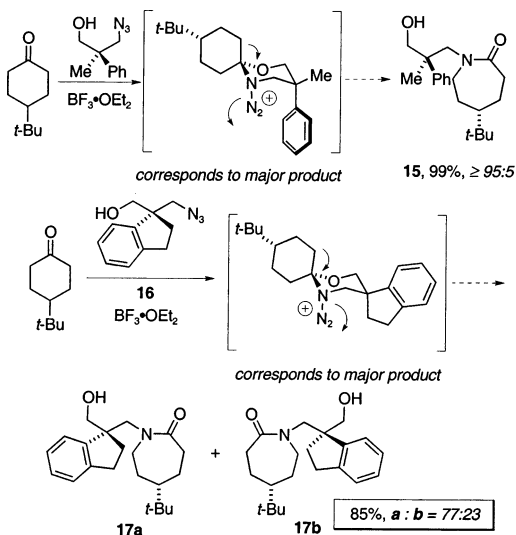
Figure 1. Proposed π−cation interaction in intermediates leading to isomers **b**.

Scheme 2

model suggests that the ability of the aromatic ring to pivot is necessary to both maximize stabilizing through-space electronic interactions and to minimize steric interactions with the hydrogen atom on the same carbon. This point was addressed through the experiments shown in Scheme 2.

Remarkably, when 3-azido-2-methyl-2-phenylpropanol was made to react with 4-tert-butylcyclohexanone, product lactam **15** *was isolated with ≥19:1 selectivity—by far the most lopsided of any encountered in this study.* Strikingly, the controlling center is a quaternary carbon, whereas conventional wisdom dictates that such centers ought to be ineffective purveyors of stereocontrol because of the need to place one group in an ostensibly disfavored axial position. Further, the intermediate leading to the major isomer places the phenyl group in an axial position and the methyl group equatorial. It is likely that the aromatic group adopts the axial position partially because it can minimize steric interactions through rotation and that this conformation is further favored by minimization of steric interactions between the ortho hydrogen and the methyl group (R = Me in Figure 1).[6]

To address this point, we synthesized conformationally constrained hydroxyalkyl azide **16** and subjected it to the reaction conditions. Here, a lower (ca. 3:1) ratio of lactams **17a,b** was obtained, favoring the intermediate with an equatorial phenyl group. This clearly establishes (1) that the conformational mobility of the phenyl group is key to the selectivity of these reactions and (2) that having a quaternary center per se is not solely responsible for

the enhanced selectivity of the methyl/phenyl case (i.e., by reaction rate acceleration through a *gem*-dialkyl effect[9]).

The exploration of this rearrangement reaction has uncovered two noteworthy effects that contribute to its stereoselectivity: the enhancement of selectivity by using a linker containing a quaternary carbon and electronic tuning of a through-space π−cation interaction. In addition to their interest from a fundamental perspective, both effects have the potential for broader application in a variety of stereoselective transformations. This work, along with further computational and experimental studies, is underway in this laboratory.

Supporting Information Available: Hammett plots, solvent studies, experimental procedures (PDF). CIF files for X-ray determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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